Ester Derivatives of 2,6-Bis(1-pyrrolidinylmethyl)-4-benzamidophenol as Short-Acting Antiarrhythmic Agents. 1

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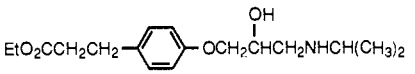
In an effort to find a replacement for the iv antiarrhythmic drug lidocaine having reduced systemic and central nervous system effects, activity against supraventricular as well as ventricular arrhythmias, and a biological half-life of less than 15 min, derivatives of the orally active class Ic clinical agent 2,6-bis(1-pyrrolidinylmethyl)-4-benzamidophenol, 1 (ACC-9358), were synthesized and tested. Compounds with ester groups attached to the phenyl ring were either weakly active or toxic. Replacement of the formanilide function with alkyl esters afforded compounds with antiarrhythmic activity in the range of 1. When the ester carboxyl was separated from the bis(aminomethyl)phenol by methylene units, very short half-lives were observed in human blood. In general, these compounds also had low lipophilic character.

Lidocaine is the most commonly used first line agent for the treatment of all ventricular arrhythmias. The drug is rapidly metabolized, having a biological half-life of 108 min upon iv administration in normal patients.[1] Indeed, liver metabolism of lidocaine is so rapid that the drug is ineffective when administered orally. Unfortunately, a large pharmacokinetic variability exists among patients, resulting in a more than 4-fold difference in lidocaine serum concentrations under identical dosing regimen.[2-4] Also, the metabolites, as well as lidocaine, have been implicated in a variety of potentially lethal cardiovascular and central effects.[5-7] As a consequence of the interpatient pharmacokinetic variability and the toxicity problems, dosing strategies have at times failed to achieve effective therapeutic serum concentrations, especially during prophylactic use in suspected acute myocardial infarction where the risk of toxicity must be low.[8]

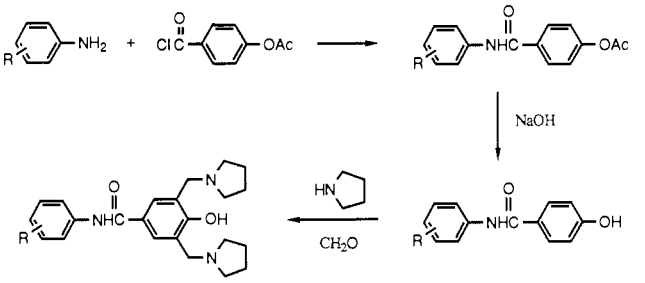
We perceived that an ideal intravenous antiarrhythmic agent would have the following characteristics. It would possess a short biological half-life (less than 15 min). In the event that a toxic level was reached, discontinuation of the infusion would result in the rapid elimination of the drug effect. Moreover, because diseases can alter the organs responsible for the metabolism of blood-borne substances, the rapid metabolism of drug would be more reliably carried out by serum esterases. This concept of controlling plasma drug levels by rapid metabolism via serum esterases has been elegantly demonstrated with the ultrashort acting β-blocker esmolol.[9] In addition, since



esmolol

the metabolism of the therapeutic agent would be rapid, a critical criterion for the drug would be the formation of inactive metabolites so as not to prolong activity by secondary-species formation. Efficacy against supraventricular arrhythmias, where lidocaine is not efficacious, as well as ventricular arrhythmias, would also be a desirable characteristic. The drug should not penetrate the central nervous system (CNS). Finally, the existence of an orally active analogue of the intravenous drug which possesses a long biological half-life would allow transferring the patient from short-term to long-term antiarrhythmic therapy.

Scheme I

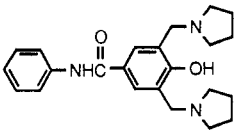


3 R = 2-$CO_2C_2H_5$

4 R = 4-$CO_2C_2H_5$

5 R = 4-CH=$CHCO_2C_2H_5$

We have described the antiarrhythmic agent 1 (ACC-9358),[10,11] which is currently in clinical trials. It is an orally



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active class Ic agent with a profile similar to that of flecainide but with reduced negative inotropic activity and an absence of the CNS side effects that accompany flecainide. We therefore chose 1 as our model compound with the goal of retaining the beneficial characteristics of this

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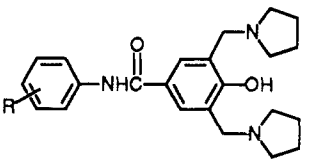
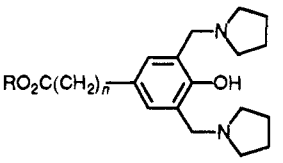
Table I. Antiarrhythmic Activity of Aryl Esters



compd	R	mp, °C	formula	ouabain dog:[a] active dose, mg/kg	N^b
3	2-$CO_2CH_2CH_3$	214–215	$C_{25}H_{33}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$	1.75	3
4	4-$CO_2CH_2CH_3$	137	$C_{25}H_{33}N_3O_4 \cdot 2HCl \cdot H_2O$	19.0 ± 2.6	3
5	4-$CH{=}CHCO_2CH_2CH_3$	151–152	$C_{27}H_{35}N_3O_4$	17.5	1
6	4-$CH_2CH_2CO_2CH_2CH_3$	227–230	$C_{27}H_{37}N_3O_4 \cdot 2HCl$	10.9 ± 5.8[d]	4

[a] Means of experimental values plus or minus the standard error of the mean. [b] Number of experiments. [c] Arrhythmogenic in two dogs at 2.5 mg/kg. [d] One dog died in asystole at 7.5 mg/kg.

Table II. Chemistry, Antiarrhythmic Activity, Ester Hydrolysis, and Lipophilicity of Alkyl Esters



compd	R	n	mp, °C	formula	GPRA[a,b] ED_{50}, μg/mL	N^c	ouabain dog:[b] active dose, mg/kg	N^c	human-blood[d] metabolism $t_{1/2}$, min	N^c	dist coeff
1					11	3	2.5 ± 0.6	6	NM		0.42
flecainide					6	5	2.3 ± 0.5	6			13.71
lidocaine					6	4	10.1 ± 3.2	6			19.19
7	H	0	227–229 dec	$C_{17}H_{24}N_2O_3 \cdot 2HCl$	>30	7	>60	7			
8	$(CH_3)_2CH$	0	218–220 dec	$C_{20}H_{30}N_2O_3 \cdot 2HCl$	11.4 ± 6.9	3			NM		0.37
9	$(CH_3)_2CHCH_2$	0	226–229	$C_{21}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	2.3 ± 1.1	9			NM		1.47
10	$CH_3CH_2CH(CH_3)$	0	170–172	$C_{21}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	6.7 ± 1.7	3	6.8[e]	2	NM		1.12
11	H	1	188	$C_{18}H_{26}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	>200	7					
12	CH_3CH_2	1	197–200	$C_{20}H_{30}N_2O_3 \cdot 2HCl$	17.2 ± 15.2	3	>7.5	2	NM	2	0.18
13	$(CH_3)_2CH$	1	210	$C_{21}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	1.0	1			NM	4	0.39
14	$CH_3(CH_2)_2$	1	165–168	$C_{21}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	10.3 ± 6.7	4	8.8 ± 1.8	3	18.5 ± 4.4	4	0.43
15	$CH_3(CH_2)_2$	1	166–167	$C_{22}H_{34}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	13.3 ± 3.3	3	7.3 ± 2.6	3	9.5 ± 0.3	4	1.50
16	$(CH_3)_2CHCH_2$	1	172–174	$C_{22}H_{34}N_2O_3 \cdot 2HCl$	5.0, 5.0	2	11.8 ± 2.5	5	8.7 ± 2.1	5	1.25
17	H	2	81–83	$C_{19}H_{33}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$	>1000	7					
18	$CH_3(CH_2)_2$	2	133–136	$C_{22}H_{34}N_2O_3 \cdot 2HCl \cdot 0.25H_2O$	7.0 ± 4.2	3	3.0	1	36.1 ± 14.3	3	0.78
19	$(CH_3)_2CH$	2	162–164	$C_{22}H_{34}N_2O_3 \cdot 2HCl$	4.0 ± 1.0	3			NM	6	0.62
20	$CH_3(CH_2)_3$	2	136–137	$C_{23}H_{36}N_2O_3 \cdot 2HCl$	2.5 ± 0.9	4	11.0	2	22.1 ± 5.3	6	2.00
21	$(CH_3)_2CHCH_2$	2	115–123	$C_{23}H_{36}N_2O_3 \cdot 2HCl \cdot 0.25H_2O$	14.0± 4.1	4	5.0 ± 1.2	3	25.9 ± 3.0	6	1.54
22	$CH_3(CH_2)_2$	3	139–140	$C_{23}H_{36}N_2O_3 \cdot 2HCl$					2.1 ± 0.5	3	
23	$CH_3(CH_2)_3$	3	123–126	$C_{24}H_{38}N_2O_4 \cdot 2HCl \cdot 1.5H_2O$	0.33, 10.0	2			0.77 ± 0.20	3	12.8
24	$(CH_3)_2CHCH_2$	3	140–141	$C_{24}H_{36}N_2O_3 \cdot 2HCl$	2.0, 10.0	2			1.96 ± 0.57	3	7.24

[a] GPRA = Guinea pig right atria. [b] Means of experimental values plus or minus the standard error of the mean. [c] Number of experiments. [d] NM = not metabolized. [e] Both dogs died in asystole at this dose.

agent while imparting a short duration of action.

Chemistry. Compounds 3–5 were prepared from the corresponding aniline derivatives as shown in Scheme I. Compound **6** was prepared from **5** by catalytic hydrogenation of the olefin. Esters **8–10**, **12–16**, and **18–24** were prepared by dissolving the phenol acid in the appropriate alcohol, saturating the solution with hydrogen chloride, and heating the solution to reflux. The esters were then aminomethylated with formaldehyde and pyrrolidine (Scheme II).

Pharmacology. Antiarrhythmic activity was determined in vitro in the guinea pig right atrium and in vivo in the ouabain-intoxicated dog. Metabolism of the compounds was determined in human blood.

Results and Discussion

In order to evaluate our compounds relative to the characteristics described, the following tests were carried out. Antiarrhythmic activity was assessed initially in the guinea pig atrium and, for compounds with good activity, the ouabain-induced-arrhythmia model. Biological half-life was evaluated in whole human blood. The lipophilic character of drugs has been associated with penetration of the blood–brain barrier and concomitant CNS effects.[12] Therefore, distribution coefficients were evaluated for test compounds.

At the outset we expected our goal for an ideal intravenous antiarrhythmic agent to be met by the simple addition of an ester group to the phenyl ring of **1**, since we found that aromatic substitution with groups other than esters had little effect on antiarrhythmic potency[10,13] and, in the case of esmolol, such a substituent afforded a compound that was rapidly metabolized.[14] However, as shown

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Scheme II

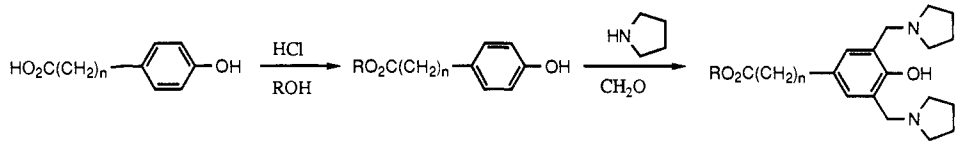
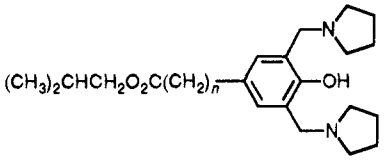


Table III. Effect of Methylene Extension of Blood Hydrolysis of Isobutyl Esters[a]

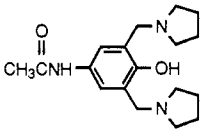


	$n = 0$	$n = 1$	$n = 2$	$n = 3$
$T_{1/2}$, min	NM	8.7	25.9	1.96

[a] Data from Table II for compounds **9** ($n = 0$), **16** ($n = 1$), **21** ($n = 2$), and **24** ($n = 3$). NM = not metabolized.

in Table I, compounds of this type were either weakly active or toxic.

Since alkyl amide **2** has been shown to be inactive,[15] we were surprised to discover that the replacement of the



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formanilide function of **1** with an alkyl ester afforded compounds that were very potent antiarrhythmic agents (Table II, where $n = 0$). However, when these compounds were incubated in human blood, no degradation was observed. We therefore employed the logic utilized by Erhardt in making β-blockers susceptible to enzymatic hydrolysis,[14] that is, separating the ester group from the bis(aminomethyl)phenol[16] with methylene units. Whereas Erhardt found a correlation between duration and distance of the aromatic group from the ester function in vivo,[14] we observed no such correlation in our in vitro assay. As shown in Table III for the isobutyl esters, when the ester was bonded directly to the ring (compound **9**), it was resistant to hydrolysis in human blood. Distancing the ester from the aromatic ring by two methylene groups afforded a compound (**21**) with a half-life ($t_{1/2}$) of 26 min. A one-carbon extension (**16**) resulted in a $t_{1/2}$ of 8.8 min, while with a three-carbon extension (**24**) the $t_{1/2}$ was an extremely short 2.0 min. Branching on the carbon bonded to the oxygen of the alkoxy functionality apparently inhibits ester hydrolysis. Isopropyl esters **13** and **19** were not metabolized, whereas the extension of the branching by one methylene group resulted in compounds that were readily hydrolyzed (**16** and **21**). It is interesting to note that none of the compounds were hydrolyzed in dog blood. Also, in the cases examined, the carboxylic acid products of hydrolysis, **7**, **11**, and **17**, were inactive as antiarrhythmic agents.

Because the lipophilicity of drugs has an effect on CNS penetration,[12] it is not surprising that marked central side effects are associated with the relatively lipophilic compound lidocaine, as well as the slightly less lipophilic drug flecainide.[17] No such CNS effects have been observed with **1**,[18] apparently due to its low lipophilic character. We assessed the octanol–water distribution coefficients for our standard agents and our test compounds (Table II). In most cases the test compounds were significantly less lipophilic than lidocaine or flecainide.

Summary

We have prepared ester analogues of the potent long-acting class Ic antiarrhythmic **1** (ACC-9358). Many of these agents also possess potent antiarrhythmic activity and low potential for CNS effects as well as short plasma half-lives. In addition, the primary carboxylic acid metabolites are devoid of antiarrhythmic activity.

Experimental Section

Pharmacological Evaluation. Guinea Pig Right Atrium. A guinea pig was killed by a blow to the head. The heart was rapidly removed and washed in Krebs solution, and the right atrium was removed from the heart. One end of the atrium was pierced with a platinum hook attached to a gold chain while the other end was pierced with a platinum hook fixed to a glass rod, and care was taken not to damage the SA node. The atrium was placed in a prewarmed (37 °C) Krebs solution. The glass rod was clamped in place and the chain was connected to an isometric force transducer. Tension was set at ca. 500 mg. After 1 h, acetylstrophanthidin solution (5 mg of acetylstrophanthidin in 1 mL of ethanol) was added to a concentration of 5.0 μg of solution/1 mL of Krebs solution. After 30 min, if arrhythmias had not developed, the concentration was increased to 7.5 μg/mL. After 45 min, test compound was added in incremental doses every 20 min. Once an arrhythmia was converted to normal sinus rhythm for at least 3 min the cumulative administered dose of test compound was recorded as its effective antiarrhythmic dose (ED).

Ouabain-Induced Arrhythmia. Adult male mongrel dogs (10–17 kg) were anesthetized with pentobarbital (30 mg/kg iv) and intubated for spontaneous respiration. Lead II of the ECG was recorded. Ouabain was administered intravenously in bolus doses: 40 μg/kg initially for 30 min, followed by 20 μg/kg for 15 min and additional 5–10 μg/kg doses at 15 min intervals as needed until a stable ventricular arrhythmia (>95% ectopic ventricular complexes) was present for 15 min.[19] Test compound was administered intravenously at 0.5 mg/kg per min until arrhythmia reverted to normal sinus rhythm for at least 10 min.

Human-Blood Metabolism. Freshly drawn heparinized blood from male volunteers and test compound in saline were preincubated separately at 37 °C for 5 min. The test compound (5 mL; final concentration, 25 μg/mL) was then incubated with 5 mL of human blood for 0, 1, 2.5, 5.0, 10, 20, 30, and 60 min at 37 °C in a Dubnoff shaking metabolic incubator. At the indicated times the incubation was stopped by the addition of 2 mL of acetonitrile and the combination was mixed vigorously for 30 s. Denatured blood proteins were sedimented by centrifugation at 1700*g* for 10 min. The clear supernatant was analyzed for test compound by HPLC with a Waters (Milford, MA) 3.9 mm × 30 cm μBondapak phenyl column packed with 10-μm particles. The mobile phase for analysis of samples containing the test compound

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(16) This group has been affectionately dubbed the "starship", due to its resemblance to the Starship Enterprise from Star Trek.
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(18) Brown, B. S. Unpublished results.
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consisted of 30% 0.01 M KH_2PO_4/30% 0.005 M K_2PO_4/40% acetonitrile, pH 6.6.

Quantitation of test compound was accomplished by using absolute peak-area response of the UV detector as integrated by the Hewlett-Packard Laboratory automated system model 3356 (Palo Alto, CA). The in vitro half-lives were determined by plotting the logarithm of the amount of test compound remaining against time. The time required to decrease the amount of test compound in the incubation mixture by 50% was defined as the half-life.

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A or EM-360 or an IBM NR-80 spectrometer in $CDCl_3$, Me_2SO-d_6, or CD_3OD with tetramethylsilane as internal standard or in D_2O with 4,4-dimethyl-4-silapentane-4-sulfonate as a standard.

2,6-Bis(1-pyrrolidinylmethyl)-4-(2-carbethoxybenzamido)phenol (3). The synthesis of **3** and **4** were carried out similarly. A solution of 9.1 g (58 mmol) of 4-acetoxybenzoyl chloride (prepared from 4-acetoxybenzoic acid and excess thionyl chloride) in 100 mL of methylene chloride was treated by dropwise addition with a solution of 8.9 mL (60 mmol) of ethyl 2-aminobenzoate and 25 mL (180 mmol) of triethylamine in 200 mL of methylene chloride. The reaction mixture was then heated to reflux for 2 h. Volatiles were removed under reduced pressure, and the resulting solid was washed with water, dilute HCl, and an aqueous solution of $NaHCO_3$. Crystallization from ethanol afforded 7.2 g (38%) of white, crystalline 4-(2-carbethoxybenzamido)acetylphenol: mp 124–129 °C.

The acetyl group was removed by dissolving the product in ethanol and saturating the solution with hydrogen chloride. Volatiles were removed, and the resulting product was washed with acetonitrile, affording 5.0 g (30%) of 4-(2-carbethoxybenzamido)phenol: mp 199–203 °C.

A suspension of 4.9 g (17 mmol) of product in 100 mL of ethanol was treated with 3.1 mL (37 mmol) of pyrrolidine and 4.0 mL (53 mmol) of 37% aqueous formaldehyde. The mixture was heated to reflux for 48 h. Volatiles were removed under reduced pressure, leaving an oil. The oil was dissolved in ether/ethyl acetate and the solution was saturated with hydrogen chloride, causing the product to precipitate as a white solid. Crystallization of the solid from EtOH/EtOAc afforded 4.2 g of **3** as white crystals: mp 214–215 °C.

Compound **6** was prepared by the catalytic hydrogenation of the cinnamate used in the preparation of **5**. Thus, ethyl 4-(4-acetoxybenzamido)cinnamate (35.3 g, 0.100 mol) in 200 mL of ethanol was cooled in an ice bath and was treated with 1 g of 10% Pd/C. The mixture was saturated with hydrogen chloride and was placed in a Paar hydrogenation apparatus with a heating mantle. The mixture was shaken at 45 psi of hydrogen at ca. 80 °C for 18 h. The crude ethyl 4-(4-hydroxybenzamido)benzenepropionate, isolated by filtration, concentration under reduced pressure, and treatment with ethyl acetate/ethyl ether, was aminomethylated in the manner described for **3**.

2-Methyl-1-propyl 3,5-Bis(1-pyrrolidinylmethyl)-4-hydroxyphenylacetate (16). The synthesis of the esters in Table II is exemplified by **16**. Thus, a solution of 50 g (0.34 mol) of 4-hydroxyphenylacetic acid in 200 mL of 2-methyl-1-propanol was saturated with hydrogen chloride. The solution was heated to reflux for 24 h. Volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in ether and the solution was washed with dilute $NaHCO_3$ and water. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure, affording an oil.

A mixture of 62.5 mL (0.748 mmol) of cooled pyrrolidine and 76.5 mL (1.02 mol) of cooled 37% aqueous formaldehyde was stirred at ice-bath temperature for 10 min. This mixture was then added to a solution of the crude oil described above, in 250 mL of acetonitrile. The resulting solution was heated to reflux for 18 h. Volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in hexane and the solution was washed with water. The solution was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the resulting oil was dissolved in ether and the solution was saturated with hydrogen chloride. A thick oil precipitated and the ether was decanted. Crystallization of the oil from 2-propanol afforded 37 g (24%) of **16** as white crystals: mp 172–174 °C.

Acids **7**, **11**, and **17** were prepared by dissolving the methyl or ethyl esters in aqueous hydrochloric acid, heating the solutions to reflux for 3 h, removing all volatiles under reduced pressure, and crystallizing the products from methanol/ether.

Synthesis and Receptor Affinities of Some Conformationally Restricted Analogues of the Dopamine D_1 Selective Ligand (5*R*)-8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol

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The synthesis of a structurally novel series of 6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepines (**2**), conformationally restricted analogues of the dopamine D_1 antagonist (5*R*)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (SCH 23390, **1c**), is described. Affinity for D_1 receptors was determined by competition for rat striatal binding sites labeled by [^{3}H]SCH 23390; affinity for D_2 receptors was similarly determined by competition experiments using [^{3}H]spiperone. Compounds in this series having the B/C-trans ring junction (**2b** and related analogues), where the D ring is unequivocally fixed in an equatorial orientation, possess considerably more D_1 receptor affinity and selectivity vs the D_2 receptor than the conformationally mobile cis stereoisomers (**2a**), thus leading to the conclusion that axial substituents at the 4- or 5-positions of the benzazepine nucleus are detrimental to D_1 receptor affinity. Resolution and X-ray analysis demonstrated that D_1 receptor affinity was preferentially associated with the (−)-6a*S*,13b*R* enantiomer of **2b**.

Within the past several years, there has been considerable interest in the 2,3,4,5-tetrahydro-3-benzazepines as a result of their selective affinity for the D_1 subset[1] of dopamine receptors in the CNS and the periphery and the potential therapeutic utilities projected from these properties. Studies of substituent effects on activity of both agonist[2] and antagonist[3] members of this series have ap-

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