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Synthesis and Biological Activity of KCB-328 and its Analogues: Novel Class III Antiarrhythmic Agents with Little Reverse Frequency Dependence

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Abstract: A series of 3,4-dimethoxyphenethylamine derivatives was prepared, and their prolongation effects on effective refractory period of contractile response (ERPc) and action potential duration (APD) in isolated guinea-pig papillary muscles at 1 Hz and 3 Hz were examined. SAR studies led to the identification of KCB-328 (**5l**) which is a novel class III antiarrhythmic agent with little reverse frequency dependence.

Keywords: Cardiovascular activity; Antiarrhythmic agent; Potassium channel blockers; Reverse frequency dependence

Antiarrhythmic agents have been classified according to their cellular electrophysiological properties by a modified Vaughan Williams classification system.[1] Almost all class III antiarrhythmic agents block outward repolarizing potassium currents, which result in the prolongation of APD and refractoriness in cardiac muscles.[2] Since the negative results of Cardiac Arrhythmia Suppression Trial (CAST) of class I antiarrhythmic agents,[3] class III drugs have become attractive due to their beneficial effect to life-threatening arrhythmia. Class III antiarrhythmic agents such as sotalol[4] and amiodarone[5] are in clinical use, however they block adrenergic receptors or other ion channels and exert other pharmacological effects besides as antiarrhythmics, which some-

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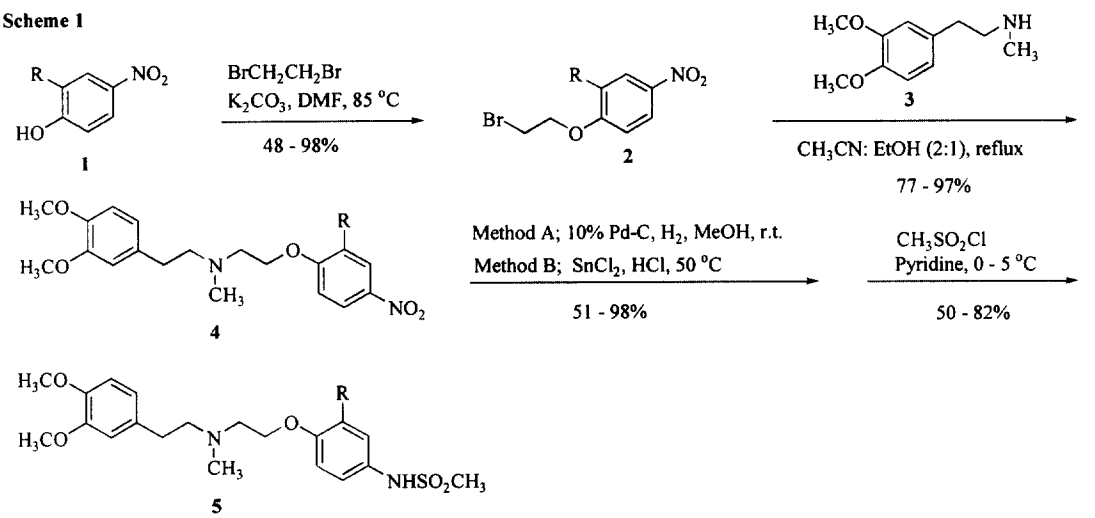
times cause side effects in patients. Number of class III agents, such as dofetilide,[6] E-4031[7] and sematilide[8] have been already studied clinically. They are pure potassium channel blockers which selectively act on the rapid component of delayed rectifier K^+ current, I_{Kr},[9] and have a pronounced prolongation effect on APD in cardiac muscles. However the prolongation effects of these selective I_{Kr} blockers on APD enhances at slow heart rates but reduces at higher rates. Because of such negative frequency dependence (i.e. reverse frequency dependence, RFD), the efficacy of class III agents decreases during tachycardias.[10] Conversely, during bradycardia, these agents produce the excessive prolongation of APD that may cause early afterdepolarization and resultant arrhythmia including triggered activity and torsade de pointes.[11] So, there is a need for novel class III agents without RFD or more ideally with positive frequency dependence.

In order to remove RFD profile from class III antiarrhythmic agents, a series of 3,4-dimethoxyphenethylamine derivatives was synthesized, and their class III effects on ERPc and action potential duration at 90% repolarization (APD_{90}) were examined in isolated guinea-pig right ventricular papillary muscles at different pacing conditions (1 Hz and 3 Hz). In this report, we describe our SAR studies which led to the discovery of a novel class III antiarrhythmic agent with little RFD, KCB-328 (**5l**, 1-(2-Amino-4-methanesulfonamidophenoxy)-2-[*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino]ethane hydrochloride).[12]

Scheme 1



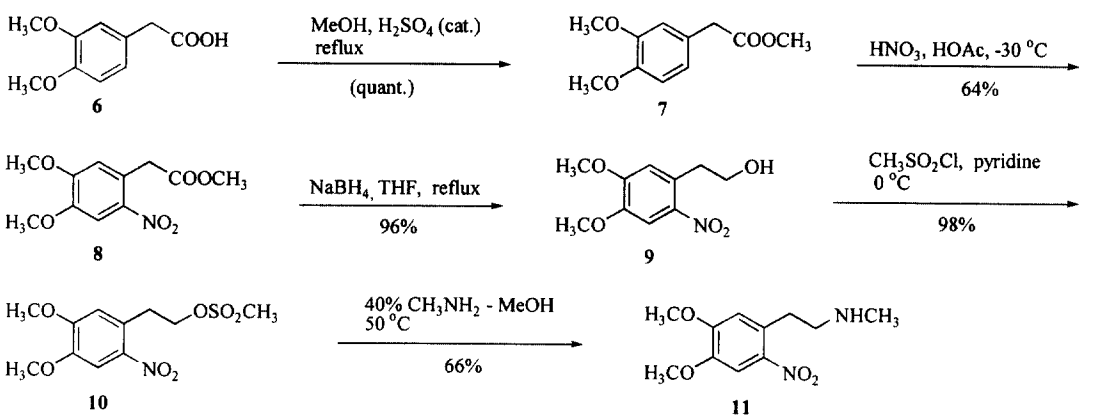
R = H, F, Cl, Br, I, CH_3, NO_2, $NHCOCH_3$, benzyloxy, 1-pyrrolyl,[13] 2- thiazolylamino.

Synthesis

The synthetic route to 3,4-dimethoxyphenethylamine derivatives is summarized in Scheme 1. Substituted 4-nitrophenol **1**, which is commercially available or synthesized by general methods, was converted to ether compound **2** by treatment with 1,2-dibromoethane at 85 °C. Condensation of ether **2** with commercially

available 3,4-dimethoxy-*N*-methyphenethylamine **3** gave compound **4**. Reduction of nitro group in compound **4** was performed by either of two methods, (1) treatment with 10% Pd-C catalyst in methanol under hydrogen gas (Method A), or (2) reaction with tin(II) chloride in conc. HCl (Method B). Reduced compound was reacted with methanesulfonyl chloride in pyridine at 0-5 °C to generate desired products **5a-k** (Table 1). Compound **5l** was prepared by acid hydrolysis of **5h** under reflux condition. If necessary, compound **5** was treated with saturated methanolic hydrochloric acid to give their HCl salt. Compounds **5m-5r** were obtained by the reaction of 2-methyl, 2-nitro or 2-chloro-4,5-dimethoxy-*N*-methylphenethylamine with ether **2** using a procedure similar to Scheme 1. For the synthesis of compounds **5o-5q**, intermediate **11** was used. The synthetic route of intermediate **11** is described in Scheme 2. Alcohol **9** was prepared by esterification of (3,4- dimethoxyphenyl) acetic acid **6**, nitration and subsequent reduction by $NaBH_4$. Treatment of alcohol **9** with methanesulfonyl chloride in pyridine gave mesylate **10**, which was reacted with 40% methylamine-methanol at 50 °C to afford the desired secondary amine **11** in 39% overall yield.

Scheme 2

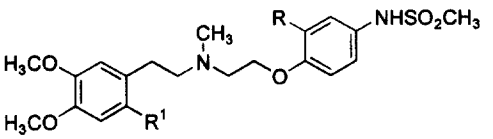


Results and Discussion

In our study on new class III agents, compounds with methanesulfonanilide group, which is commonly found in potent class III agents, were synthesized. Class III antiarrhythmic effects were evaluated by the prolongation effects on ERPc in isolated guinea-pig papillary muscles.[14] Dofetilide and E-4031 were also tested for comparison. 3,4-Dimethoxyphenethylamine derivative **5a** revealed pronounced ERPc prolongation, however it retained RFD profile. In order to select compounds with less RFD profile, ERPc was analyzed at two pacing frequencies (1 Hz and 3 Hz). Table 1 summarizes the efficacy of prolongation of ERPc, described as percent increase of ERPc (ΔERPc), by a series of **5a** derivatives.

Substitution of 3-position on the methanesulfonanilide ring in **5a** decreased ΔERPc at 1 Hz as retaining the efficacy on ΔERPc at 3 Hz, which result in the improved ratios of ΔERPc at 3 Hz against 1 Hz. Chloro (**5c**),

Table 1. ERPc prolongation effects of 3,4-dimethoxyphenethylamine derivatives in guinea-pig papillary muscle



Compound	R	R^1	ΔERPc (1 μM, %)[a]				ratio (%)[d]	Formula
			3 Hz	n[b]	1 Hz	n[c]		
5a	H	H	28.9 ± 2.85	5	60.1 ± 9.94	4	48	$C_{20}H_{28}N_2O_5S.HCl$
5b	F	H	25.9 ± 0.85	2	34.5	1	75	$C_{20}H_{27}FN_2O_5S.HCl$
5c	Cl	H	30.8 ± 2.76	5	32.2 ± 1.60	4	95	$C_{20}H_{27}ClN_2O_5S$
5d	Br	H	25.2 ± 1.32	3	32.8 ± 1.85	2	76	$C_{20}H_{27}BrN_2O_5S.HCl$
5e	I	H	21.2 ± 4.50	2	28.9 ± 5.75	2	73	$C_{20}H_{27}IN_2O_5S.HCl$
5f	CH_3	H	27.2 ± 1.15	3	28.9 ± 1.88	3	94	$C_{21}H_{31}ClN_2O_5S$
5g	NO_2	H	25.0	1	33.3	1	75	$C_{20}H_{27}N_3O_7S$
5h	$NHCOCH_3$	H	27.7 ± 1.41	7	39.3 ± 2.81	9	70	$C_{22}H_{31}N_3O_6S.HCl$
5i	benzyloxy	H	30.0 ± 2.07	4	26.3 ± 1.42	5	114	$C_{27}H_{34}N_2O_6S.HCl$
5j	1-pyrrolyl	H	40.1 ± 1.69	7	31.2 ± 1.57	8	128	$C_{24}H_{31}N_3O_5S.HCl$
5k	2-thiazolylamino	H	36.8 ± 1.93	10	43.4 ± 4.16	10	84	$C_{23}H_{30}N_4O_5S_2.HCl$
5l	NH_2	H	32.6 ± 2.31	10	31.0 ± 1.69	10	105	$C_{20}H_{29}N_3O_5S.HCl$
5m	Cl	CH_3	33.1 ± 1.93	6	28.0 ± 2.37	6	118	$C_{21}H_{29}ClN_2O_5S.HCl$
5n	Cl	Cl	17.8 ± 0.15	2	22.4 ± 0.95	2	79	$C_{20}H_{26}Cl_2N_2O_5S$
5o	Cl	NO_2	36.2 ± 2.08	6	29.4 ± 1.83	4	123	$C_{20}H_{26}ClN_3O_7S.HCl$
5p	Cl	NH_2	34.7 ± 1.38	7	27.5 ± 1.30	7	126	$C_{20}H_{28}ClN_3O_5S.HCl$
5q	1-pyrrolyl	NH_2	24.7 ± 4.70	2	39.4 ± 8.40	2	62	$C_{24}H_{32}N_4O_5S.HCl$
5r	1-pyrrolyl	CH_3	26.3 ± 1.91	4	32.1	1	81	$C_{25}H_{33}N_3O_5S.HCl$
E-4031[e]			30.2 ± 1.70	10	41.8 ± 1.67	10	71	
Dofetilide[e]			30.8 ± 7.08	6	49.9 ± 4.47	6	65	

Data expressed as percent change from predrug state (values are expressed as mean ± SEM).
[a] Percent change from predrug state on ERPc. [b] Number of experiments at 3 Hz. [c] Number of experiments at 1 Hz. [d] Ratio of ERPc prolongation (percent change at 3 Hz/1 Hz). [e] E-4031 and dofetilide were prepared in C&C Research Laboratories.

Table 2. APD_{90} prolongation effects on the action potential in guinea-pig papillary muscles

Compounds	Hz	ΔAPD_{90} (1 μM, %)[a]	n[b]	ratio (%)[c]
5j	3	26.2 ± 1.6	5	99
	1	26.4 ± 3.6	6	
5l	3	28.6 ± 1.4	6	86
	1	33.3 ± 2.1	9	
5m	3	22.2 ± 1.6	7	82
	1	37.8 ± 3.3	4	
Dofetilide	3	26.8 ± 2.8	6	59
	1	45.6 ± 4.1	10	

Data expressed as percent change from predrug state (values are expressed as mean ± SEM).
[a] APD_{90} was recorded under Krebs-Ringer solution at 34 ± 0.5 ℃. [b] Number of experiments. [c] Ratio of APD_{90} prolongation (percent change at 3 Hz/1 Hz).

methyl (**5f**) and amino (**5l**) derivatives showed almost no frequency dependence, and benzyloxy (**5i**) and pyrrolyl (**5j**) derivatives showed positive frequency dependence. In contrast, dofetilide and E-4031 prolonged ERPc more than those by our substituted methanesulphonanilide derivatives at 1 Hz, however the ratios of ΔERPc indicate both agents have RFD profile.

Substitution on 3,4-dimethoxyphenyl ring was also examined. 6-Methyl (**5m**), amino (**5p**) and nitro (**5o**) substitution in **5c** slightly increased ΔERPc at 3 Hz and decrease at 1 Hz, which result in positive frequency dependence. On the other hand, substitution on 3,4-dimethoxyphenyl ring in **5j** decreased ΔERPc at 3 Hz and lost positive frequency dependence profile of **5j**.

Three compounds (**5j**, **5l** and **5m**) were selected for further evaluation on electrophysiological studies in guinea-pig papillary muscles.[14] Percent changes of action potential duration at 90% repolarization (ΔAPD_{90}) from pre-drug state were shown in Table 2. These compounds prolonged APD_{90} at 3 Hz almost same potency as that by dofetilide, however ΔAPD_{90} at 1 Hz was less potent than dofetilide. The ratio of ΔAPD_{90} of **5j**, **5l** and **5m** indicate that these compounds have little frequency dependence compared with dofetilide.

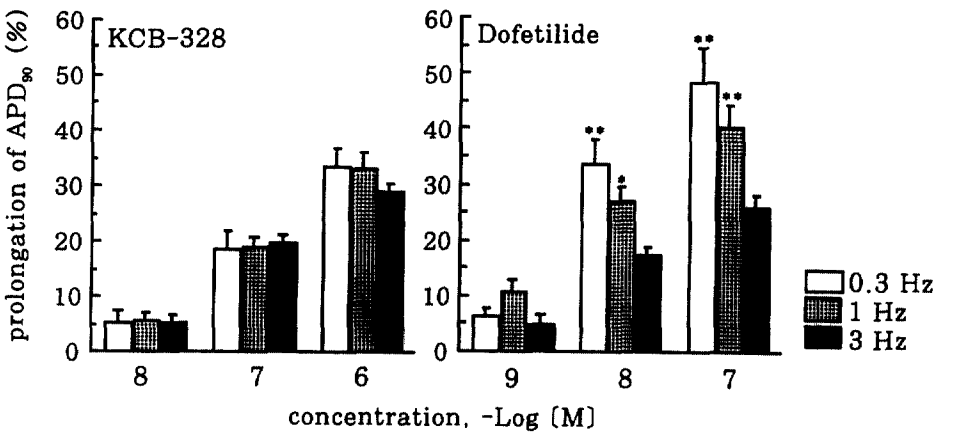


Figure 1. Concentration and frequency dependent effects of dofetilide and KCB-328 on APD_{90} recorded from isolated guinea-pig papillary muscles.

Each value represents mean ± SEM. (N = 5-10). *p<0.05, **p<0.01 in unpaired Student's *t* test between 3 Hz and 1 Hz or 0.3 Hz at each concentration, respectively.

KCB-328 (**5l**) was further evaluated for its concentration or frequency dependent effects on APD_{90} in isolated guinea-pig papillary muscles (Figure 1). KCB-328 increased APD concentration-dependently at three different stimulating paces as dofetilide did. At each concentration of KCB-328, ΔAPD_{90} between three pacing frequencies were almost same levels. In contrast, dofetilide significantly lowered ΔAPD_{90} at 3 Hz from those at

0.3 Hz and 1 Hz. These results suggest that KCB-328 is a novel class III antiarrhythmic agent with little RFD at therapeutic concentration. A study on arrhythmia animal models of KCB-328 was published recently,[15] which indicated that KCB-328 has powerful antiarrhythmic effects with fewer proarrhythmic potencies. Mechanisms of the improved frequency dependence profiles in 3,4-dimethoxyphenethylamine derivatives are not clear,[14] but the better profile may be resulted from appropriate kinetics of interaction with subtypes of outward potassium current, rapid component I_{Kr} and slow component I_{Ks}. Because dofetilide and E-4031 selectively block I_{Kr}, it would be interesting to examine whether KCB-328 has any effect on I_{Ks}.

In conclusion, we have discovered that 3,4-dimethoxyphenethylamine derivatives are novel class III antiarrhythmic agents with little reverse frequency dependence. SAR studies of these derivatives led to compound **5l** (KCB-328) which have shown a therapeutic benefit for suppression of arrhythmia.

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