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Synthesis and Class III Type Antiarrhythmic Activity of 4-Aroyl (and Aryl)-1-aralkylpiperazines

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Abstract—The synthesis and in vitro Class III antiarrhythmic activity of several 4-aroyl (and aryl)-1-aralkylpiperazine and piperidine derivatives are described. Among several potent compounds identified in the series, RWJ-28810 (**3**), with its EC_{20} of 3 nM, ranks as one of the most potent (in vitro) compounds reported.

Sudden cardiac death (SCD), a primary cause of mortality in patients with cardiovascular diseases, is caused by the loss of regular cardiac rhythm resulting from electrical instability of the cardiac muscle. These malignant ventricular arrhythmias leading to the lethal event are recognized as ventricular tachycardia (VT) and ventricular fibrillation (VF).[1] Although therapeutic interventions are available for VF, they are unsatisfactory from the view point of safety and general efficacy[2] Since the first observation of antiarrhythmic activity of a cinchona alkaloid preparation in a malaria patient in 1914, the alkaloid quinidine, subsequently identified as the most potent ingredient of such natural product preparation, remains an important antiarrhythmic therapeutic agent.[3] However, quinidine and other conventional[4] Class I antiarrhythmic agents, such as encainide and flecainide, with ionic mechanism of that action include interference with sodium channels in the cell membrane, are effective against simple ventricular, and in some cases, supraventricular arrhythmias, but are ineffective for the prevention of sudden cardiac death by VF. Moreover, the recent results of the Cardiac Arrhythmia Suppression Trial (CAST)[5] have raised concerns about the safety of the Class I type agents focusing attention on Class III agents. These provide antiarrhythmic protection by selectively prolonging the cardiac action potential and thereby increasing the *effective refractory period* (ERP).[6] d-Sotalol (**35**),[7] Dofetilide (**36**),[8] E-4031 (**37**),[9] Amiodarone,[10] and Azimilide[11] are a few representative examples of Class III antiarrhythmic agents.

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Herein we describe the synthesis and potent in vitro ERP activity of a series of 4-aroyl-1-aralkylpiperazines (Table 1), 4-aryl-1-aralkylpiperazines (Table 2), and a few piperidine derivatives (Table 3).

Chemistry[12]

Various 4-aroyl-1-aralkylpiperazines **I** (**3**–**11**, Table 1) were prepared according to Scheme 1. Acylation of piperazine with 4-nitrobenzoyl chloride afforded monoacylated product **2**,[13] separated from the diacylated product **1** by chromatography. 4-Nitroaralkylation of **2** with the various 4-nitroaralkyl halides (or sulphonate **IIe**) in refluxing MeCN in the presence of anhydrous K_2CO_3 and NaI gave **3** (70%), **6** (94%), **9** (80%), **10** (63%), and **11** (70%). Reduction of NO_2 to NH_2 followed by *N*-mesylation gave, respectively, **4** and **5** from **3** and a mixture of **7** and **8** from **6**. Compounds **12**–**21** (**V**, Table 1) were obtained according to Scheme 2 by first aralkylating mono-*t*-Boc protected piperazine to give **IIIa** (52%) and **IIIb** (33%), the latter converted sequentially to NH_2 (**IIIc**) and $NHSO_2Me$ (**IIId**) followed by deprotection to **IV** and then acylation to give **V** (**12**–**21**). 4-Aryl-1-aralkylpiperazines **22**–**30** (**VII**, Table 2) were similarly prepared according to Scheme 3 by aralkylating commercially available 4-arylpiperazines **VI** to **VIIa** (**27**, 50%), **VIIb** [**22**, (80%), **23** (70%), and **26** (80%)] and **VIId,e**, [**28** (48%) and **31**(88%), respectively], reduction of NO_2 to NH_2 (**VIIc**, **24**, **25**; **VIId**, **29**), and then N-mesylation of **29** to **30**. Three piperidine derivatives **32**–**34** (**IX**, Table 3) were similarly obtained according to Scheme 4.

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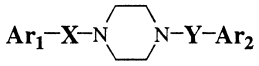
Table 1. 4-Aroyl-1-aralkylpiperazines

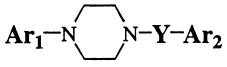


I, V

#	Ar_1-X	Y	Ar_2	Emperical formula	Mol. Wt.	Mp °C	Antiarrhythmic activity	
							EC_{20} μM	Tension% Δ
1	4-O_2N-PhCO–	CO	–Ph-4-NO_2	$C_{18}H_{16}N_4O_6$	384.34	>300	7	−6
2	4-O_2N–PhCO–	H	—	$C_{11}H_{13}N_3O_3$	235.24	149–50	20	−33
3	4-O_2N–PhCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{19}H_{20}N_4O_5/0.25H_2O$	384.38/388.88	123–25	0.003	−3
4	4-O_2N–PhCO–	$(CH_2)_2$	–Ph-4-NH_2	$C_{19}H_{24}N_4O/0.25\ H_2O$	324.41/333.41	154–56	1.40	−14
5	4-MeO_2SNH–PhCO–	$(CH_2)_2$	–Ph-4-$NHSO_2Me$	$C_{21}H_{28}N_4O_5S_3/0.25H_2O$	480.59/485.09	130–135	2.0	+1
6	4-O_2N–PhCO–	$(CH_2)_2O$	–Ph-4-NO_2	$C_{19}H_{20}N_4O_6/0.5H_2O$	400.38/404.88	160–61	0.060	0
7	4-MeO_2SNH–PhCO–	$(CH_2)_2O$	–Ph-4-$NHSO_2Me$	$C_{21}H_{28}N_4O_6S_2/0.5H_2O$	496.50/505.58	107–09	15	−13
8	4-MeO_2SNH–PhCO–	$(CH_2)_2O$	–Ph-4-$N(SO_2Me)_2$	$C_{22}H_{30}N_4O_8S_3$	674.67	212–13	25	−14
9	4-O_2N–PhCO–	CH_2CONH	–Ph-4-NO_2	$C_{19}H_{19}N_5O_6$	413.38	192–93	0.035	+5
10	4-O_2N–PhCO–	CH_2	–Ph-4-NO_2	$C_{18}H_{18}N_4O_5/0.25H_2O$	370.36/374.86	211–12	3.5	−44
11	4-O_2N–PhCO–	$(CH_2)_2$	–Th[a]-5-NO_2	$C_{17}H_{18}N_4O_5S$	390.41	137–38	0.01	−17
12	4-O_2N–PhCO–	$(CH_2)_2$	–Ph	$C_{19}H_{21}N_3O_3$	339.38	101–02	0.16	−8
13	PhCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{19}H_{21}N_3O_3$	339.38	138–39	0.14	−7
14	4-O_2N–PhCO–	$(CH_2)_2$	–Ph-4-$NHSO_2Me$	$C_{20}H_{24}N_4O_5S/0.25H_2O$	432.48/436.96	186–87	0.16	+13
15	4-MeO_2SNH–PhCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{20}H_{24}N_4O_5S$	432.48	170–71	0.06	1
16	4-MeO_2SNH–PhCO–	$(CH_2)_2$	–Ph	$C_{20}H_{25}N_3O_3S$	387.48	155–56	0.68	5
17	5-O_2N-Th[a]–	$(CH_2)_2$	–Ph-4-NO_2	$C_{17}H_{18}N_4O_5S$	390.42	101–02	0.012	0
18	5-O_2N-Fu[b]–	$(CH_2)_2$	–Ph-4-NO_2	$C_{17}H_{18}N_4O_6$	374.35	91–92	0.14	−2
19	4-PyrCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{18}H_{20}N_4O_3/0.25H_2O$	340.37/344.87	145–46	1	+19
20	3-O_2N–PhCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{19}H_{20}N_4O_5/0.25H_2O$	384.38/393.38	145–46	0.27	−7
21	4-O_2N–$PhSO_2$–	$(CH_2)_2$	–Ph-4-NO_2	$C_{18}H_{20}N_4O_6S$	420.43	154–55	1.0	−24

[a]Th = Thiophene.
[b]Fu = Furan.

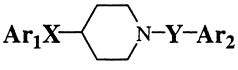
Table 2. 4-Aryl-1-aralkylpiperazine



VII

#	Ar_1	Y	Ar_2	Emperical formula	Mol. Wt.	Mp °C	Antiarrhythmic activity	
							EC_{20} μM	Tension% Δ
22	4-O_2N-Ph–	$(CH_2)_2$	–Ph-4-NO_2	$C_{18}H_{20}N_4O_4$	356.37	148–49	0.03	+5
23	4-O_2N–Ph–	$(CH_2)_2O$	–Ph-4-NO_2	$C_{18}H_{20}N_4O_5$	372.37	150–51	0.35	−27
24	4-H_2N–Ph–	$(CH_2)_2$	–Ph-4-NH_2	$C_{18}H_{24}N_4/0.8H_2O$	296.40/310.82	158–59	>100	−53*
25	4-H_2N–Ph–	$(CH_2)_2O$	–Ph-4-NH_2	$C_{18}H_{24}N_4O/0.75H_2O$	312.40/325.91	105–06	>100	−43*
26	4-O_2N–Ph–	$(CH_2)_2$	–Ph	$C_{18}H_{21}N_3O_2$	311.39	163–64	0.5	−6
27	Ph–	$(CH_2)_2$	–Ph-4-NO_2	$C_{18}H_{21}N_3O_2/0.125H_2O$	311.39/313.64	140–41	0.8	+10
28	4-Pyr–	$(CH_2)_2$	–Ph-4-NO_2	$C_{17}H_{20}N_4O_2/0.5H_2O$	312.36/321.36	146–48	0.03	+8
29	4-Pyr–	$(CH_2)_2$	–Ph-4-NH_2	$C_{17}H_{22}N_4/0.5H_2O$	282.38/291.38	184–85	15	+9
30	4-Pyr–	$(CH_2)_2$	–Ph-4-$NHSO_2Me$	$C_{18}H_{24}N_4O_2S/0.5H_2O$	360.46/369.46	202–03	0.22	+2
31	5-O_2N-2-Pyr–	$(CH_2)_2$	–Ph-4-NO_2	$C_{17}H_{19}N_5O_4/0.5H_2O$	357.36361.86	137–38	1.3	−21

Table 3. 4-Aryl(or aroyl)-1-aralkylpiperidines



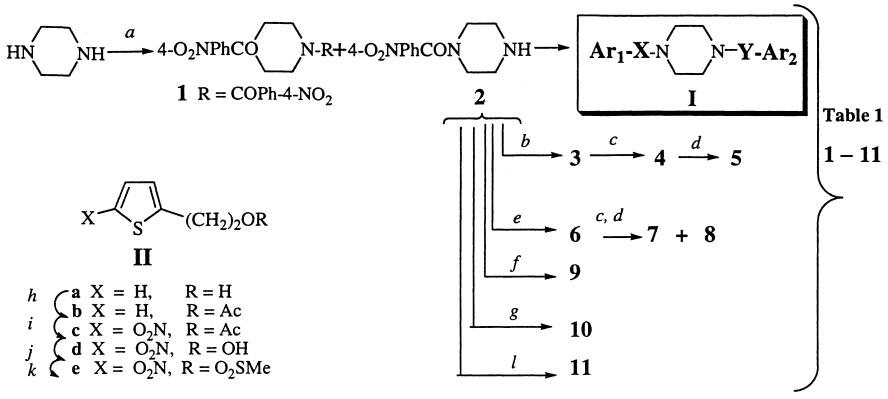
IX

#	Ar_1X	Y	Ar_2	Emperical formula	Mol. Wt.	Mp °C	Antiarrhythmic activity	
							EC_{20} μM	Tension% Δ
32	4-O_2N–Ph–	$(CH_2)_2$	–Ph-4-NO_2	$C_{19}H_{21}N_3O_4/0.25H_2O$	355.38/359.88	133–34	0.3	0
33	4-H_2N–Ph–	$(CH_2)_2$	–Ph-4-NH_2	$C_{19}H_{25}N_3/0.25H_2O$	295.43/299.91	140–42	2.0	+15
34	4-Cl–PhCO–	$(CH_2)_2$	–Ph-4-NO_2	$C_{20}H_{21}ClN_2O_3$	372.84	1501	0.3	−4

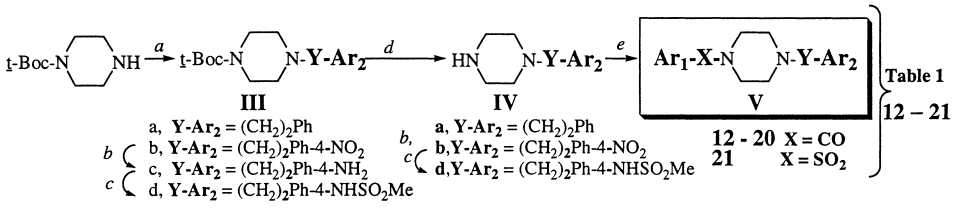
Biological Materials and Methods

Measurement of effective refractory period (ERP)

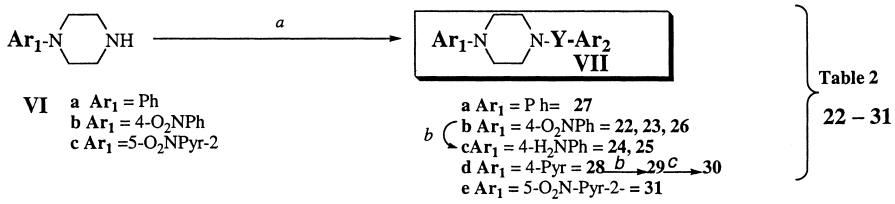
Papillary muscles were dissected from the right ventricle of anesthetized male ferrets, secured at one end and attached to a force transducer. Muscles were placed in a tissue bath containing Tyrode's solution of the following composition (mM): NaCl, 130; KCl, 4; $MgCl_2$, 1.0; $NaHCO_3$, 25; KH_2PO_4, 1.2; $CaCl_2$, 2; dextrose, 11; pH 7.3, gassed with 5% CO_2. 95% O_2 at 37 °C. Timolol (0.1 mM) was added to prevent variations in tension produced by spontaneous or stimulation-induced release of catecholamines. Isometric force was recorded during stimulation with constant current pulses (3 msec; 1.3×threshold) using platinum bipolar electrodes. The ERP was determined using the extra stimulus technique by applying trains of 20 basic stimuli (S_1) at cycle length of 300 msec (1 Hz), followed by application of an extra



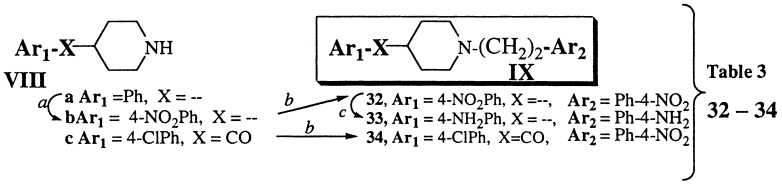
Scheme 1. Reagents: (a) 4-O_2NPhCOCl, acetone, HCl; (b) 4-O_2NPh$(CH_2)_2$-Br (Cl), K_2CO_3, NaI, MeCN, Δ; (c) Ra-Ni, H_2, EtOH; (d) $MeSO_2Cl$, Pyr, CH_2Cl_2; (e) 4-O_2NPhO$(CH_2)_2$Cl, K_2CO_3, NaI, MeCH, Δ; (f) 4-O_2NPhNHCOCH$_2$Cl, K_2CO_3, MeCN, Δ; (g) O_2NPhCH$_2$Cl, K_2CO_3, NaI, MeCN, Δ; (h) $(Ac)_2O$, H_2SO_4; (i) HNO_3, $(Ac)_2O$, −10 °C→0 °C; (j) 10% H_2SO_4/H_2O, Δ; (k) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; (l) **II**e, EtOH, Δ.



Scheme 2. Reagents: (a) **Ar$_2$-Y**-Br, K_2CO_3, NaI, MeCN, Δ; (b) Ra-Ni, H_2, EtOH; (c) $MeSO_2Cl$, Pyr, CH_2Cl_2; (d) CF_3CO_2H; (e) **Ar$_1$-X**-C, Et_3N, CH_2Cl_2.

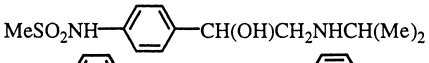
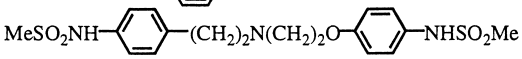
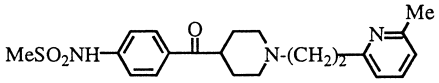


Scheme 3. Reagents: (a) **Ar$_2$-Y**-Cl (or Br), K_2CO_3, NaI, MeCN, Δ; (b) Ra-Ni, H_2, EtOH; (c) $MeSO_2Cl$, Pyr.



Scheme 4. Reagents: (a) HNO_3, H_2SO_4; (b) **Ar$_2$**-$(CH_2)_2$-Br, K_2CO_3, NaI, MeCN, Δ; (c) Pd/C, H_2, EtOH.

Table 4. Class III antiarrhythmic standards

#			Antiarrhythmic activity	
			EC_{20} μM	Tension% Δ
35	d-Sotalol		3.5	−13
36	Dofetilide		0.015	+5
37	E-4031		0.02	+9

stimulus (S_2) at decreasing coupling intervals (S_1–S_2) in decrements of 2 ms until muscle activation failed. ERP was defined as the shortest S_1–S_2 interval producing muscle activation. Test compounds were dissolved in dimethylsulfoxide (DMSO) at a stock concentration of 1×10^{-2} M and added in appropriate amounts directly to Tyrode's solution to achieve the final concentrations. Following duplicate control measurements, compound concentrations were increased sequentially and ERP measurements were taken at steady state, usually 15 min after addition of each concentration. The mean dose that produced a 20% increase in ERP is defined as EC_{20} and is reported in μM (1×10^{-6} M), as a measure of Class III antiarrhythmic activity.

Measurement of tension

Tension was measured as peak isometric tension during the basic stimulus trains (S_1) during control, and compound induced changes in tension were expressed as a percent of control.

Results and Discussion

SAR highlights

In in vitro tests, the most potent compound of the series, RWJ-28810 (**3**), increased ERP ~5 times more potently than Dofetilide (**36**),[8] the most potent reference standard tested (Table 4). In the piperazine series, the general potency order for the 4,4′-substituents on the two terminal aromatic rings, keeping NO_2 constant on one end while varying the other is, for Ar_1CO (**I** and **V**): NO_2 (**3**) >$NHSO_2Me$ (**15**) > H (**13**); for Ar_2: NO_2 (**3**) > H (**12**) > $MeSO_2NH$ (**14**) > NH_2 (**4**) [3-NO_2 on Ar_1 (**20**) is much weaker than 4-NO_2 on Ar_1 (**3**)]; for arylpiperazines (**VII**), on Ar_1: NO_2 (**22**) > H (**27**); on Ar_2: NO_2 (**22**) > H (**26**) > NH_2 (**24**). Of the two possible regioisomeric mono-NO_2 analogues **12** and **13** of the di-NO_2 lead **3**, the 4-NO_2-aroyl analogue **12**, although 5 times less potent than **3**, is 10 times more potent than the 4-NO_2-aralkyl isomer **13**. With mixed functionality, present on different aryl moieties, the potencies are reversed in favor of $MeSO_2NH$-aroyl/NO_2-aralkyl (**15**) versus NO_2-aroyl/$MeSO_2NH$-aralkyl (**14**). For the aromatic ring Ar_1, potency order is: benzoyl (**3**) > thienoyl (**17**) >> furanoyl (**18**) > 4-pyridoyl (**19**); for Ar_2 potency order is: phenyl > thienyl. The non-basic amido nitrogen of aroyl-piperazine core (as in **I**) is replaceable by a CH group (e.g. piperidine derivative **34**) as also is the anilino nitrogen of **VII**, but with significant loss of potency (compare **22** with **32**). For the spacer group **X**, whereas CO is better than SO_2 (**21**), it is altogether dispensable (e.g. **22**). For the spacer group Y, $(CH_2)_2$ (**3**) is better than $(CH_2)_2O$ (**6**) or CH_2 (**10**). There were only two compounds showing significant decrease in tension (**24** and **25**, possibly **10**) and these were at high μM concentrations where vehicle (DMSO) is known to decrease tension. Others had little or no change in tension indicating selectivity of Class III action, since selective block of K channels is associated with no change or an actual increase in isometric tension in the absence of an effect on Na or Ca channels.

Summary

We have synthesized and identified a series of 4-aroyl (andaryl)-1-aralkylpiperazine derivatives as potent Class III Type antiarrhythmics as evidenced by in vitro ERP prolongation.

The lead compound RWJ-28810 (**3**) with its EC_{20} of **3 nM** represents ***one of the most potent (in vitro) compounds reported***.

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