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Synthesis of substituted *N*-(4-piperidyl)-*N*-(3-pyridyl)amides with antiarrhythmic activity. Note 1

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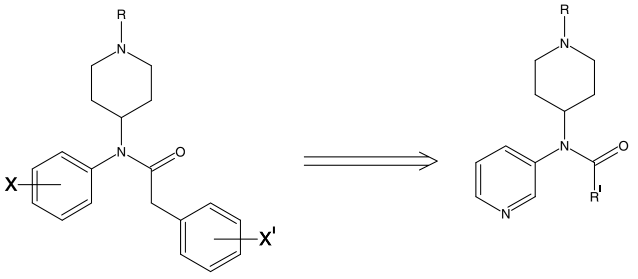
The synthesis of analogues of *N*,2-diphenyl-*N*-(4-piperidyl)acetamide endowed with antiarrhythmic activity is reported. Benzoyl, cinnamoyl, acetyl and propionyl groups replace the phenacyl group as *N*-acyl substituent, while pyridine replaces benzene as aromatic ring bound to the amide nitrogen. The title compounds were evaluated for antiarrhythmic activity on experimenthal arrhythmias induced by aconitine in rats. The presence of a *n*-propyl chain and an unsubstituted cinnamoyl moiety (**1j**) gives the highest protection against aconitine induced extrasystoles while the best efficacy against lethal effects is due to the presence of a *n*-propyl chain and an acetyl moiety (**1m**).

1. Introduction

Arrhythmias are abnormalities of cardiac rhythm where ion channel function can be perturbed by factors such as acute ischemia, sympathetic stimulation or myocardial scarring and can cause severe adverse effects including death. Antiarrhythmic drugs generally suppress arrhythmias by blocking flow through specific ion channels or by altering autonomic function [1]. Singh and Vaughan Williams based their classification on the results of microelectrode studies that suggested the existence of four main classes of antiarrhythmic activity [2, 3]. Antiarrhythmic drugs have several adverse events, especially during long-term treatment, including proarrhythmic effects which can cause increased mortality [1] and therefore the synthesis of antiarrhythmic drugs with high efficacy and low potential danger is the major goal in the search for arrhythmia therapy.

The alkaloid aconitine has been widely used as a tool in models of calcium overload [4], cardiac arrhythmias [5–7], and evaluation of effects of compounds against ischemia/reperfusion injury or against cardiac arrhythmias.

As part of our program for new antiarrhythmic compounds with a better pharmacological profile, we designed a new series of *N*-(4-piperidyl)-*N*-(3-pyridyl)-amides of the general formula **1**, related to the known *N*,2-diphenyl-*N*-(4-piperidyl)acetamides **A** and their derivatives [8, 9] exhibiting antiarrhythmic activity. In an attempt to elucidate the structure-activity relationships of this class of compounds, some structural modifications were made replacing the phenacyl moiety of the lead compound **A** with an (un)substituted aromatic (benzoyl and cinnamoyl) or an aliphatic (acetyl and propionyl) acyl moiety, and replacing the benzene ring with a pyridine ring as classical isoster. In our structures, R is represented by some of the previously experimented alkyl chains (i.e. methyl, ethyl, *n*-propyl, *i*-propyl), also including a benzyl group.



A

R = $C_{1\text{-}10}$alkyl

X = halo, alkyl

X' = halo, alkyl, hydroxy, alkoxy

1

R = $C_{1\text{-}3}$alkyl, benzyl

R' = $C_{1\text{-}2}$alkyl, phenyl, 4-halo-phenyl, 4-nitro-phenyl,cinnamyl,4-halo-cinnamyl, 4-alkyl-cinnamyl

We report herein the synthesis of substituted *N*-(4-piperidyl)-*N*-(3-pyridyl)amides **1** and their antiarrhythmic activity, evaluated as protection index against ecgraphic and lethal effects by aconitine in rats.

2. Investigations, results and discussion

2.1. *Synthesis of compounds*

Compounds **1a–p** (see Table) were prepared as outlined in the Scheme.

Condensation of conveniently substituted 4-piperidones **2** with 3-pyridinamine **3** in p-toluenesulfonic acid provided the Schiff bases **4**, which were reduced to the diamines **5a–d** with sodium borohydride in satisfactory yields. Acylation of **5a–d** was then performed, using either an acid chloride or an anhydride to give the target compounds **1a–o** in 30–72% yield. Compound **1p** was obtained starting from **1d**, after debenzylation of the piperidine ring in the presence of α-chloroethyl chloroformate (ACE-Cl) [10], followed by methanolysis, obtaining the secondary aminoamide **6**. The alkylation of **6** with 2-bromopropane and potassium carbonate provided the target compound **1p** in 75% yield.

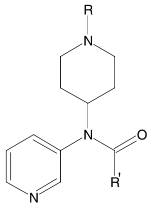
The intermediates **5a–d** and the target compounds **1a–p** were purified after recrystallization. The assigned structures were supported by IR, ^{1}H NMR, GC/MS and elemental analysis.

2.2. *Pharmacological assay*

All compounds **1a–p** were examined *in vivo* for their antiarrhythmic activity against ventricular extrasystoles and lethal effects induced by aconitine hydrochloride in rats narcotized with ethyl urethan. Quinidine was included in all tests as reference drug.

The antiarrhythmic activity data for *N*-(4-piperidyl)-*N*-(3-pyridyl)amides **1a–p** are shown in the Table.

Table: Activity against ventricular extrasystoles and lethal effects induced by aconitine in rats



Compd.	R	R'	Dose (mg/kg/i.v.)	Appearance time (sec ± s.e.) of extrasystoles	Death time (sec ± s.e.)
1a	CH_3	C_6H_5	50	206 ± 26.3	697 ± 12.8
1b	C_2H_5	$4Cl\text{-}C_6H_4$	50	189 ± 27.5	697 ± 19.1
1p	$CH(CH_3)_2$	$4Cl\text{-}C_6H_4$	50	213 ± 24.1	716 ± 23.9
1c	$CH_2\text{-}C_6H_5$	C_6H_5	50	294 ± 21.3**	746 ± 34.3**
			25	275 ± 19.6*	706 ± 28.6*
			12.5	198 ± 17.4	659 ± 32.3
1d	$CH_2\text{-}C_6H_5$	$4Cl\text{-}C_6H_4$	50	261 ± 16.3**	812 ± 19.4**
			25	280 ± 16.8**	700 ± 31.3*
			12.5	241 ± 18.3*	751 ± 27.3*
1e	$CH_2\text{-}C_6H_5$	$4Br\text{-}C_6H_4$	50	207 ± 23.6	701 ± 17.4
1f	$CH_2\text{-}C_6H_5$	$4F\text{-}C_6H_4$	50	196 ± 25.3	709 ± 23.6
1g	$CH_2\text{-}C_6H_5$	$4NO_2\text{-}C_6H_4$	50	226 ± 28.3*	740 ± 31.3
1h	CH_3	$4CH_3\text{-}C_6H_4{-}CH{=}CH$	50	207 ± 21.7	658 ± 27.1
1i	CH_3	$4Cl\text{-}C_6H_4{-}CH{=}CH$	50	215 ± 19.6*	723 ± 27.5
1j	C_3H_7	$C_6H_5{-}CH{=}CH$	50	403 ± 31.6**	723 ± 31.3**
			25	370 ± 26.5**	709 ± 24.7**
			12.5	265 ± 21.3*	680 ± 17.4*
1k	$CH_2\text{-}C_6H_5$	$C_6H_5{-}CH{=}CH$	50	210 ± 18.5	648 ± 25.3
1l	$CH_2\text{-}C_6H_5$	$4Cl\text{-}C_6H_4{-}CH{=}CH$	50	256 ± 18.7**	815 ± 23.7**
1m	C_3H_7	CH_3	50	282 ± 19.3**	819 ± 20.7**
			25	259 ± 16.3*	801 ± 19.3**
			12.5	220 ± 19.6	746 ± 17.3**
1n	$CH_2\text{-}C_6H_5$	CH_3	50	254 ± 20.6	660 ± 27.2
1o	$CH_2\text{-}C_6H_5$	C_2H_5	50	202 ± 20.3	689 ± 18.6
Quinidine			25	344 ± 28.7**	990 ± 32.1**
Control (Aconitine · HCl)			15 μg/kg/i.v.	170 ± 21.4	630 ± 21.3

* $P < 0.05$: Statistically significant value calculated in comparison with the test performed with aconitine only
** $P < 0.01$: Statistically significant value calculated in comparison with the test performed with aconitine only

2.2.1. Influence of the substituents on the piperidine nitrogen (R) in the (un)substituted benzamide series **1a–g**, **p**

In these series, the highest activity was observed for the *N*-benzyl derivatives **1c**, **d**, which at a dose of 50 mg/kg showed a remarkable protection against ventricular extrasystoles and aconitine lethal effects (**1d**), slightly lower than that of quinidine (25 mg/kg), with a dose-dependent effect exhibited by **1c**. The introduction of a NO_2, Br and F substituent in the benzoyl moiety (**1g**, **f**, **e**) led to a progressive disappearance of activity. Compounds **1a**, **b**, **p** were essentially inactive.

2.2.2. Influence of the substituents on the piperidine nitrogen (R) in the (un)substituted cinnamamide series **1h–l**

The *N*-propyl derivative **1j** showed the highest protection against aconitine ventricular extrasystoles, superior to that of quinidine at the same dose (370 ± 26.5 vs 344 ± 28.7 s prior to extrasystoles appearance; n.s.). Even in this case, the effect was dose-dependent. In the *N*-benzyl derivatives of this series **1k**, **l**, compound **1l**, bearing a Cl substituent in the cinnamoyl moiety, exhibited a remarkable protection especially against aconitine lethal effects at a dose of 50 mg/kg, as shown by **1d** in the previous series. Nevertheless in these series, the unsubstituted cinnamoyl moiety was detrimental for activity (**1l** versus **1k** and **1d** versus **1c**).

2.2.3. Influence of the substituents on the piperidine nitrogen (R) in the aliphatic acyl moiety series **1m–o**

Among these derivatives, compound **1m** carrying a *n*-propyl chain, at a dose of 50 mg/kg, exhibited remarkable protection either against ventricular extrasystoles (282 ± 19.3 s) or lethal effects (819 ± 20.7 s) from aconitine, comparable to that of quinidine (344 ± 28.7 s and 990 ± 32.1 s respectively), with a dose-dependent effect.

This preliminary screening carried out on *N*-(4-piperidyl)-*N*-(3-pyridyl)amides **1** has been useful to indicate that the reported pharmacological profile is greatly influenced by the substitution patterns. The presence of a *n*-propyl chain and an unsubstituted cinnamoyl moiety (**1j**) gives the highest protection against aconitine induced extrasystoles while the best efficacy against lethal effects is due to the presence of a *n*-propyl chain and an acetyl moiety (**1m**).

In order to fully evaluate the structure-activity relationships of this class of compounds, other derivatives will be synthesized and studied in the next future.

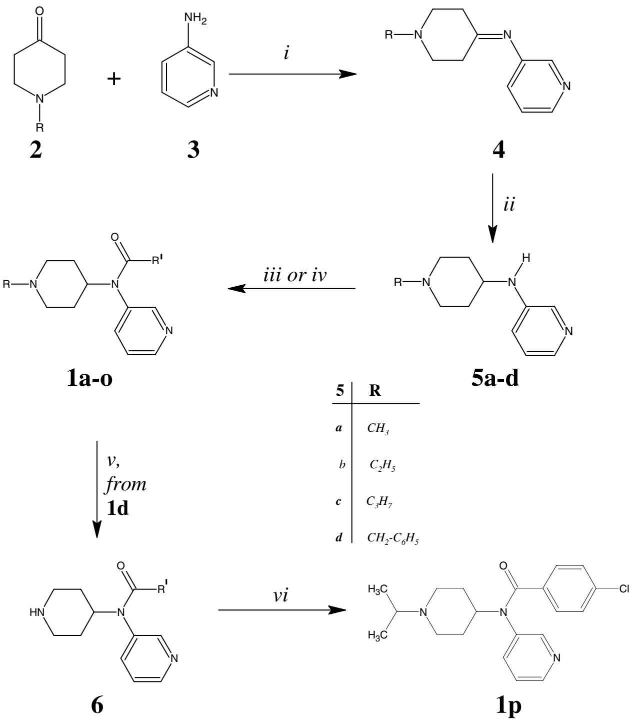
3. Experimental

3.1. Chemistry

3.1.1. Apparatus

Reactions were monitored by TLC on Polygram® ALOX N/UV_{254} precoated plastic sheets (0.2 mm), (eluant EtOAc/light petroleum 1 : 1); chromatogram sheets using UV light and/or iodine vapor for detection; the purified compounds each showed a single spot. Melting points were deter-

Scheme 1



Key: (i) p-TsOH, toluene; (ii) $NaBH_4$, dry C_2H_5OH; (iii) R′COCl, $N(C_2H_5)_3$, CH_2Cl_2; (iv) $(R'CO)_2O$, toluene; (v) a) ACE-Cl, CH_2Cl_2; b) dry CH_3OH; (vi) $(CH_3)_2CHBr$, K_2CO_3, CH_3CN. For R and R′ see Table

mined using a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a FT-IR Spectrophotometer Paragon 500 (Perkin-Elmer) and are expressed in ν (cm^{-1}), including solid samples in KBr pellets and analysing liquid samples as films.

Elemental analyses were obtained on all compounds and are within ±0.4% the theoretical values.

GC-MS spectra were obtained from an HP5970A Mass Selective Detector (MSD) equipped with a capillary column HP-5 (25 m × 0,2 mm I. D. × 0,11 μm film thickness). Programmed temperatures ranged from 100 to 300 °C (rate 10 °C/min) and the carrier gas was helium at a pressure of 10 psi. The detector mainframe includes the GC interface, an electron impact ion source with electron energy of 70 eV, hyperbolic quadrupole mass filter, electron multiplier detector; m/z value of diagnostic ions were reported followed by intensity in parentheses. The ^1H NMR measurements were performed on a Bruker AMX 500 MHz spectrometer equipped with a Bruker X-32 computer, using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane and coupling constants (**J**) are expressed in Hz.

3.1.2. Chemicals

Solvents were purified and dried [11]. The organic extracts were dried over anh. Na_2SO_4 prior to solvent evaporation. The 4-piperidinones commercially available were distilled prior to use on a Kugelrohr apparatus under vacuum. Most of the (un)substituted benzoyl chlorides and the unsubstituted cinnamoyl chlorides used were commercially available, whereas the substituted cinnamoyl chlorides were prepared according to the procedure described by Koo et al. [12].

3.1.3. Synthesis of substituted N,4-(3-pyridyl)-4-piperidinamines **5a–d**

Example: N,4-(3-pyridyl)-1-benzyl-4-piperidinamine **5d**

A mixture of 3-pyridinamine **3** (5.4 g, 57 mmol), 1-benzyl-4-piperidone **2** (10 g, 52 mmol), and a few crystals of p-toluensulfonic acid was refluxed in 60 ml of toluene, until removal of water was achieved by a Dean-Stark trap (7 h). Afterwards the solution was cooled to RT and 4Å molecular sieve was added (40 g). The resulting mixture was stirred for 12 h, filtered and the filtrate evaporated in vacuo yielded a brown oil which exibited a strong C=N absorption at 1662 cm^{-1} by IR analysis. The crude Schiff base (14 g) was dissolved in 70 ml of dry C_2H_5OH, and sodium borohydride (2.20 g, 58 mmol) was added portionwise during 30 min. (temperature rose to 26 °C). The reaction mixture was stirred under reflux for 2 h, cooled and concentrated in vacuo. H_2O was added, followed by extraction with CH_2Cl_2. The organic extract was dried over anh. Na_2SO_4 and evaporated in vacuo to give, after recrystallization (CH_2Cl_2) 10 g of **5d** as a white solid. Yield 72%, m.p. 131–134 °C; IR: 3250 (NH); ^1H NMR: 1.40 (m, 2 H, CH_2-5); 1.95 (m, 2 H, CH_2-3); 2.10 (m, 2 H, CH_2-6); 2.79 (m, 2 H, CH_2-2); 3.20 (m, 1 H, CH-4); 3.45 (s, 2 H, CH_2-Ar); 3.52 (br, 1 H, NH); 6.74 (d, 1 H, J = 4.7, CH-4′); 6.96 (t, 1 H, J = 3.6, CH-5′); 7.20 (m, 5 H, Ar–H); 7.81 (d, 1 H, J = 3.6, CH-6′); 7.93 (s, 1 H, CH-2′); GC-MS: 267, M^+ (12); 176, M^+-91(16); 147, M^+-91–29(17); 91, M^+-176(100).
$C_{17}H_{21}N_3$

5a: Yield 60%, m.p. 85–87 °C (diethyl ether); IR: 3240 (NH); ^1H NMR: 1.90 (m, 2 H, CH_2-5); 2.45 (m, 2 H, CH_2-3); 2.55 (m, 2 H, CH_2-6); 2.72 (s, 3 H, N–CH_3); 3.20 (m, 2 H, CH_2-2); 3.65 (m, 1 H, CH-4); 4.40 (br, 1 H, NH); 7.20 (d, 1 H, J = 4.7, CH-4′); 7.45 (t, 1 H, J = 3.6, CH-5′); 8.29 (d, 1 H, J = 3.6, CH-6′); 8.43 (s, 1 H, CH-2′); GC-MS: 191, M^+ (45); 162, M^+-29 (1); 147, M^+-29–15(10).
$C_{11}H_{17}N_3$

5b: Yield 65%, m.p. 78–83 °C (diethyl ether); IR: 3223 (NH); ^1H NMR: 1.07 (t, 3 H, J = 5.9, CH_2-$C\underline{H}_3$); 1.50 (m, 2 H, CH_2-5); 2.11 (m, 4 H, CH_2-3 and CH_2-6); 2.20 (q, 2 H, J = 5.9, $C\underline{H}_2$–CH_3); 2.90 (m, 2 H, CH_2-2); 3.30 (m, 1 H, CH-4); 3.63 (br, 1 H, NH); 6.84 (d, 1 H, J = 5.3, CH-4′); 7.11 (m, 1 H, CH-5′); 7.82 (d, 1 H, J = 4.0, CH-6′); 8.00 (s, 1 H, CH-2′); GC-MS: 205, M^+ (41); 176, M^+-29(1); 147, M^+-29–29(28).
$C_{12}H_{19}N_3$

5c: Yield 82%, m.p. 81–83 °C (diethyl ether); IR: 3270 (NH); ^1H NMR: 1.25 (t, 3 H, J = 5.9, CH_2–CH_2-$C\underline{H}_3$); 1.85 (m, 4 H, CH_2-$C\underline{H}_2$–CH_3 and CH_2-5); 2.40 (m, 4 H, CH_2-3 and CH_2-6); 2.70 (m, 2 H, $C\underline{H}_2$–CH_2–CH_3); 3.25 (m, 2 H, CH_2-2); 3.65 (m, 1 H, CH-4); 4.00 (br, 1 H, NH); 7.25 (d, 1 H, J = 4.7, CH-4′); 7.45 (t, 1 H, J = 3.6, CH-5′); 8.30 (d, 1 H, J = 3.6, CH-6′); 8.36 (s, 1 H, CH-2′); GC-MS: 219, M^+ (39); 190, M^+-29(27); 162, M^+-29–28(1); 147, M^+-29–28–15(100).
$C_{13}H_{21}N_3$

3.1.4. Synthesis of substituted N-(4-piperidyl)-N-(3-pyridyl)amides **1a–l**

Example: N-(1-benzyl-4-piperidyl)-N-(3-pyridyl)benzamide **1c**

A solution of benzoyl chloride (0.89 g, 6.3 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise to an ice-cold solution of **5d** (1.0 g, 3.7 mmol) and triethylamine (0.67 g, 6.3 mmol) in CH_2Cl_2 (10 ml). Following the addition, the ice bath was removed and the mixture stirred at room temperature and under nitrogen for 1 h.

Afterwards the resultant mixture was washed with a solution of saturated $NaHCO_3$ (4 × 10ml) and the organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude residue was triturated with ether and recrystallized from ethyl acetate to give 0.6 g of **1c** as a white solid. Yield 43%; m.p. 184–186 °C; IR: 1645 (CO); ^1H NMR: 1.35 (m, 2 H, CH_2-5); 1.89 (m, 2 H, CH_2-3); 2.03 (m, 2 H, CH_2-6); 2.79 (m, 2 H, CH_2-2); 3.32 (s, 2 H, CH_2-Ar); 4.61 (m, 1 H, CH-4); 7.10 (m, 12H, CH-4′, CH-5′ and Ar–H); 8.12 (s, 1 H, CH-2′); 8.25 (d, 1 H, J = 3.6, CH-6′); GC-MS: 371, M^+ (13); 266, M^+-105(93); 105, M^+-266 (48); 91, M^+-280(100).
$C_{24}H_{25}N_3O$

1a: Yield 40%, m.p. 141–143 °C (ethyl acetate); IR: 1643 (CO); ^1H NMR: 1.65 (m, 2 H, CH_2-5); 1.95 (m, 2 H, CH_2-3); 2.30 (s, 3 H, N–CH_3); 2.65 (m, 2 H, CH_2-6); 3.20 (m, 2 H, CH_2-2); 4.75 (m, 1 H, CH-4); 7.20 (m, 6 H, CH-5′ and Ar–H); 7.93 (d, 1 H, J = 3.7, CH-4′); 8.10 (s, 1 H, CH-2′); 8.42 (d, 1 H, J = 3.7, CH-6′); GC-MS: 295, M^+(3); 190, M^+-105(100); 147, M^+-105–43(7); 105, M^+-190(45).
$C_{18}H_{21}N_3O$

1b: Yield 30%, m.p. 129–131 °C (ethyl acetate); IR: 1634 (CO); ^1H NMR: 1.07 (t, 3 H, J = 5.8, CH_2-$C\underline{H}_3$); 1.58 (q, 2 H, J = 5.8, $C\underline{H}_2$–CH_3); 2.00 (m, 2 H, CH_2-5); 2.18 (m, 2 H, CH_2-3); 2.42 (m, 2 H, CH_2-6); 3.09 (m, 2 H, CH_2-2); 4.80 (m, 1 H, CH-4); 7.22 (m, 5 H, CH-5′ and Ar–H); 7.40 (d, 1 H, J = 5.1, CH-4′); 8.34 (s, 1 H, CH-2′); 8.50 (d, 1 H, J = 3.9, CH-6′); GC-MS: 343/345, M^+(3/1); 328/330, M^+-15(3/1); 204, M^+-139(100); 139/141, M^+-204(55/17).
$C_{19}H_{22}ClN_3O$

1d: Yield 59%, m.p. 140–141 °C (ethyl acetate); IR: 1646 (CO); ^1H NMR: 1.60 (m, 2 H, CH_2-5); 2.08 (m, 2 H, CH_2-3); 2.28 (m, 2 H, CH_2-6); 3.05 (m, 2 H, CH_2-2); 3.60 (s, 2 H, CH_2-Ar); 4.82 (m, 1 H, CH-4); 7.40 (m, 11H, CH-4′, CH-5′ and Ar–H); 8.40 (s, 1 H, CH-2′); 8.60 (d, 1 H, J = 3.4, CH-6′); GC-MS: 405, M^+(8); 266, M^+-139(49); 139, M^+-266(35); 91, M^+-314(100)
$C_{24}H_{24}ClN_3O$

1e: Yield 38%, m.p. 145–147 °C (ethyl acetate); IR: 1647 (CO); ^1H NMR: 1.50 (m, 2 H, CH_2-5); 1.90 (m, 2 H, CH_2-3); 2.18 (m, 2 H, CH_2-6); 2.98 (m, 2 H, CH_2-2); 3.43 (s, 2 H, CH_2-Ar); 4.66 (m, 1 H, CH-4); 7.02 (d, 2 H, J = 5.9, CH-4′, CH-5′); 7.13 (m, 9 H, Ar–H); 8.22 (s, 1 H, CH-2′); 8.43 (d, 1 H, J = 3.6, CH-6′); GC-MS: 450, M^+(1); 266, M^+-184(74); 183/185, M^+-266(19/19); 91, M^+-359(100).
$C_{24}H_{24}BrN_3O$

1f: Yield 55%, m.p. 143–145 °C (ethyl acetate); IR: 1641 (CO); ^1H NMR: 1.95 (m, 2 H, CH_2-5); 2.38 (m, 2 H, CH_2-3); 2.61 (m, 2 H, CH_2-6); 3.42 (m, 2 H, CH_2-2); 3.95 (s, 2 H, CH_2-Ar); 5.19 (m, 1 H, CH-4); 7.21 (t, 2 H, J = 5.9, CH-4′ and CH-5′); 7.70 (m, 9 H, Ar–H); 8.61 (s, 1 H, CH-2′);

8.92 (d, 1 H, J = 4.7, CH-6′); GC-MS: 389, M^+(3); 266, M^+-123(52); 123, M^+-266(42); 91, M^+-298(100).

$C_{24}H_{24}FN_3O$

1g: Yield 46%, m.p. 161–163 °C (ethyl acetate); IR: 1642 (CO); ^{1}H NMR: 1.47 (m, 2 H, CH_2-5); 1.88 (m, 2 H, CH_2-3); 2.14 (m, 2 H, CH_2-6); 2.92 (m, 2 H, CH_2-2); 3.44 (s, 2 H, CH_2–Ar); 4.73 (m, 1 H, CH-4); 7.22 (m, 10H, CH-5′ and Ar–H); 7.98 (d, 1 H, J = 4.9, CH-4′); 8.23 (s, 1 H, CH-2′); 8.41 (d, 1 H, J = 3.6, CH-6′); GC-MS: 416, M^+(2); 266, M^+-150(43); 150, M^+-266(12); 91, M^+-325(100).

$C_{24}H_{24}N_4O_3$

1h: Yield 40%, m.p. 182–186 °C (ethyl acetate); IR: 1622 (CO); ^{1}H NMR: 1.60 (m, 2 H, CH_2-5); 2.00 (m, 2 H, CH_2-3); 2.33 (m, 2 H, CH_2-6); 2.42 (s, 3 H, N–CH_3); 2.51 (s, 3 H, Ar–CH_3); 3.10 (m, 2 H, CH_2-2); 4.95 (m, 1 H, CH-4); 6.10 (d, 1 H, J = 8.9, CO–CH=C$\underline{H}$); 7.18 (d, 2 H, J = 4.0, Ar–H); 7.32 (d, 2 H, J = 4.0, Ar–H); 7.55 (t, 1 H, J = 3.8, CH-5′); 7.64 (d, 1 H, J = 3.8, CH-4′); 7.85 (d, 1 H, J = 8.9, CO–C$\underline{H}$=CH); 8.60 (s, 1 H, CH-2′); 8.88 (d, 1 H, J = 3.8, CH-6′); GC-MS: 335, M^+(5); 190, M^+-145(91); 145, M^+-190(38).

$C_{21}H_{25}N_3O$

1i: Yield 30%, m.p. 178–181 °C (ethyl acetate); IR: 1622 (CO); ^{1}H NMR: 1.50 (m, 2 H, CH_2-5); 1.92 (m, 2 H, CH_2-3); 2.20 (m, 2 H, CH_2-6); 2.30 (s, 3 H, N–CH_3); 3.00 (m, 2 H, CH_2-2); 4.85 (m, 1 H, CH-4); 6.00 (d, 1 H, J = 11.9, CO–CH=C$\underline{H}$); 7.20 (d, 2 H, J = 4.8, Ar–H); 7.25 (d, 2 H, J = 4.6, Ar–H); 7.42 (t, 1 H, J = 3.6, CH-5′); 7.50 (d, 1 H, J = 4.9, CH-4′); 7.62 (d, 1 H, J = 11.9, CO–C$\underline{H}$=CH); 8.50 (s, 1 H, CH-2′); 8.77 (d, 1 H, J = 3.6, CH-6′); GC-MS: 355/357, M^+(3/1); 190, M^+-165(98); 165/167, M^+-190(24/7).

$C_{20}H_{22}ClN_3O$

1j: Yield 75%, m.p. 148–150 °C (ethyl acetate); IR: 1615 (CO); ^{1}H NMR: 0.70 (t, 3 H, J = 5.8, N–CH_2–CH_2-C$\underline{H}_3$); 1.20 (m, 2 H, N–CH_2-C$\underline{H}_2$–CH_3); 1.60 (m, 4 H, N-C$\underline{H}_2$–CH_2–CH_3 and CH_2-5); 1.90 (m, 2 H, CH_2-3); 2.40 (m, 2 H, CH_2-6); 3.20 (m, 2 H, CH_2-2); 4.80 (m, 1 H, CH-4); 6.30 (d, 1 H, J = 9.0, CO–CH=C$\underline{H}$); 7.15 (m, 6 H, CH-5′ and Ar–H); 7.40 (d, 1 H, J = 3.7, CH-4′); 7.62 (d, 1 H, J = 9.0, CO–C$\underline{H}$=CH); 8.37 (s, 1 H, CH-2′); 8.55 (d, 1 H, J =3.7, CH-6′); GC-MS: 320, M^+-29(1); 190, M^+-29–131(100); 131, M^+-218(29).

$C_{22}H_{27}N_3O$

1k: Yield 41%, m.p. 171–173 °C (ethyl acetate); IR: 1625 (CO); ^{1}H NMR: 1.42 (m, 2 H, CH_2-5); 1.89 (m, 2 H, CH_2-3); 2.23 (m, 2 H, CH_2-6); 2.86 (m, 2 H, CH_2-2); 3.52 (s, 2 H, CH_2-Ar); 4.80 (m, 1 H, CH-4); 6.00 (d, 1 H, J = 11.9, CO–CH=C$\underline{H}$); 7.29 (m, 10H, Ar–H); 7.43 (t, 1 H, J = 3.6, CH-5′); 7.57 (d, 1 H, J = 3.6, CH-4′); 7.69 (d, 1 H, J = 11.9, CO–C$\underline{H}$=CH); 8.48 (s, 1 H, CH-2′); 8.70 (d, 1 H, J = 3.6, CH-6′); GC-MS: 266, M^+-131(60); 131, M^+-266(32); 91, M^+-306(100).

$C_{26}H_{27}N_3O$

1l. Yield 48%, m.p. 188 °C (ethyl acetate); IR: 1620 (CO); ^{1}H NMR: 1.48 (m, 2 H, CH_2-5); 1.90 (m, 2 H, CH_2-3); 2.20 (m, 2 H, CH_2-6); 3.00 (m, 2 H, CH_2-2); 3.60 (s, 2 H, CH_2-Ar); 4.80 (m, 1 H, CH-4); 5.98 (d, 1 H, J = 8.9, CO–CH=C$\underline{H}$); 7.25 (m, 9 H, Ar–H); 7.45 (t, 1 H, J = 3.4, CH-5′); 7.52 (d, 1 H, J = 5.9, CH-4′); 7.60 (d, 1 H, J = 8.9, CO–C$\underline{H}$=CH); 8.48 (s, 1 H, CH-2′); 8.70 (d, 1 H, J = 3.6, CH-6′); GC-MS: 431, M^+(2%); 266, M^+-165(97); 165, M^+-266(19); 91, M^+-340(100).

$C_{26}H_{26}ClN_3O$

3.1.5. Synthesis of substituted N-(4-piperidyl)-N-(3-pyridyl)amides **1m–o**

Example: N-(1-benzyl-4-piperidyl)-N-(3-pyridyl)propanamide **1o**

5d (1.0 g, 3.7 mmol) was dissolved in 40 ml of anh. toluene. Excess propionic anhydride (2.28 ml, 17 mmol) in 2 ml of anh. toluene was added at RT and the reaction mixture refluxed for 19 h.

After cooling to room temperature, 12 ml of 20% NaOH was added and the resulting mixture stirred for 1 h. The organic layer was then washed with H_2O until pH 7 was achieved, dried over Na_2SO_4 and evaporated in vacuo. The crude residue obtained was crystallized from diethyl ether to give 0.8 g of **1o** as a white solid. Yield 66%, m.p 104–106 °C; IR: 1660 (CO); ^{1}H NMR: 1.20 (t, 3 H, J = 6.5, CH_2-C$\underline{H}_3$); 1.50 (m, 2 H, CH_2-5); 1.92 (m, 2 H, CH_2-3); 2.10 (m, 2 H, C$\underline{H}_2$–CH_3); 2.28 (m, 2 H, CH_2-6); 3.06 (m, 2 H, CH_2-2); 3.60 (s, 2 H, CH_2-Ar); 4.82 (m, 1 H, CH-4); 7.42 (m, 5 H, Ar–H); 7.52 (t, 1 H, J = 3.6, CH-5′); 7.60 (d, 1 H, J = 5.9, CH-4′); 8.50 (s, 1 H, CH-2′); 8.80 (d, 1 H, J = 3.5, CH-6′); GC-MS: 323, M^+(5); 294, M^+-29(1); 266, M^+-29–28(9); 232, M^+-91(3); 91, M^+-232(84).

$C_{20}H_{25}N_3O$

Compounds **1m**, **n** were synthetized according to the above described method in the presence of acetic anhydride.

1m: Yield 72%, m.p. 88–90 °C (light petroleum); IR: 1665 (CO); ^{1}H NMR: 0.73 (t, 3 H, J = 5.9, CH_2–CH_2-C$\underline{H}_3$); 1.22 (m, 4 H, C$\underline{H}_2$-C$\underline{H}_2$–CH_3); 1.60 (s, 3 H, CO–CH_3); 1.63 (m, 2 H, CH_2-5); 1.92 (m, 2 H, CH_2-3); 2.12 (m, 2 H, CH_2-6); 2.78 (m, 2 H, CH_2-2); 4.50 (m, 1 H, CH-4) 7.20 (t, 1 H, J = 3.6, CH-5′); 7.23 (d, 1 H, J = 4.8, CH-4′); 8.22 (s, 1 H, CH-2′); 8.50 (d, 1 H, J = 3.6, CH-6′); GC-MS: 261, M^+(12); 232, M^+-29(100); 218, M^+-43(12); 189, M^+-43-29(34).

$C_{15}H_{23}N_3O$

1n: Yield 69%, m.p. 94–96 °C (diethyl ether); IR: 1662 (CO); ^{1}H NMR: 1.10 (m, 2 H, CH_2-5); 1.67 (m, 5 H, CH_2-3, CO–CH_3); 2.01 (m, 2 H, CH_2-6); 2.78 (m, 2 H, CH_2-2); 3.36 (s, 2 H, CH_2-Ar); 4.56 (m, 1 H, CH-4); 7.15 (m, 5 H, Ar–H); 7.28 (t, 1 H, J = 3.6, CH-5′); 7.34 (d, 1 H, J = 4.8, CH-4′); 8.29 (s, 1 H, CH-2′); 8.53 (d, 1 H, J = 3.6, CH-6′); GC-MS: 309, M^+(15); 266, M^+-43(19); 218, M^+-91(8%); 91, M^+-218(100).

$C_{19}H_{23}N_3O$

3.1.6. Synthesis of N-(1-isopropyl-4-piperidyl)-N-(3-pyridyl)-4-chloro benzamide **1p**

Step 1: A solution of α-chloroethyl chloroformate (0.58 ml, 5.4 mmol) in CH_2Cl_2 (4 ml), was added dropwise to a cooled (0–5 °C) solution of **1d** (2.0 g, 4.9 mmol) in CH_2Cl_2 (22 ml). After 30 min at 0 °C, the solution was allowed to warm to room temperature and stirred for 3 h. The solvent was evaporated and the residue was dissolved in anh. CH_3OH (22 ml) and the mixture was warmed with stirring at 55 °C for 1 h under N_2. After evaporation of the solvent, the resulting residue was taken up with H_2O (20 ml), washed with diethyl ether (5 ml), basified with 35% aqueous NaOH and extracted with CH_2Cl_2 (4×5 ml); the combined CH_2Cl_2 extracts were dried over anh. Na_2SO_4 and filtered. The solvent was removed in vacuo to give 0.8 g (51%) of the deprotected piperidine intermediate **6** which was used without further purification. IR (KBr): 3320 (NH) and 1643 (CO).

Step 2: 2-Bromopropane (0.25 g, 2 mmol) was added dropwise to a stirring mixture of **6** (0.5 g, 1.6 mmol) and powdered anh. K_2CO_3 (1.45 g) in CH_3CN (25 ml). The reaction mixture was refluxed for 36 h and then cooled, filtered and the filtrate evaporated in vacuo. The crude residue was triturated with ether to yield a solid which was recrystallized from ethyl acetate (0.42 g, 75%); m.p. 137–140 °C; IR: 1643 (CO); ^{1}H NMR: 1.11–1.09 (2s, 6 H, CH–(C$\underline{H}_3$)$_2$); 1.58 (m, 2 H, CH_2-5); 2.10 (m, 2 H, CH_2-3); 2.45 (m, 2 H, CH_2-6); 2.80 (m, 1 H, C$\underline{H}$–(CH_3)$_2$); 3.05 (m, 2 H, CH_2-2); 4.81 (m, 1 H, CH-4); 7.23 (m, 4 H, Ar–H); 7.30 (t, 1 H, J = 3.8, CH-5′); 7.42 (d, 1 H, J = 5.00, CH-4′); 8.40 (s, 1 H, CH-2′); 8.55 (d, 1 H, J = 3.8, CH-6′); GC-MS: 357, M^+(5); 342/344, M^+-15(100/33); 218, M^+-139(69); 139, M^+-218(73).

$C_{20}H_{24}ClN_3O$

3.2. Pharmacology

Antiarrhythmic activity was evaluated against ventricular extrasystoles and lethal effects induced by aconitine hydrochloride (15 μg/kg i.v.) in rats of both sexes (body weight 200–250 g), pregnant females excluded, narcotized with ethyl urethan (1 g/kg i.p.). Quinidine and test compounds were given i.v. to groups of ten animals at a dose of 25 and 50 mg/kg respectively, 15 min prior to aconitine. When activity was observed, then lower doses of test compounds were given (25 and 12.5 mg/kg) to evaluate a dose-dependent effect.

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