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Original article

Synthesis and antifibrillatory activity of nibentan and its analogues

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Abstract – A series of 1,5-diaminopentane derivatives, structurally related to nibentan, was synthesized and tested for antifibrillatory activity. Improved modifications of some known chemical syntheses were proposed. (±)-N-[5-(Diethylamino)-1-(4-nitrophenyl)pentyl]-benzamide hydrochloride, (±)-N-[5-(diethylamino)-1-(4-nitrophenyl)pentyl]-4-nitrobenzamide hydrochloride and (±)-N-[5-(diethylamino)-1-(4-hydroxyphenyl)pentyl]-4-nitrobenzamide hydrochloride were more potent than nibentan and possessed a longer duration of action (up to 5 h in comparison with 60–90 min for nibentan). The antifibrillatory activity of (±)-N-[5-(diethylamino)-1-(4-methoxyphenyl)pentyl]-4-nitrobenzamide hydrochloride was comparable to that of nibentan but exceeded the potency of D-sotalol and sematilide. © 2000 Éditions scientifiques et médicales Elsevier SAS

synthesis / antifibrillatory activity / nibentan / 1,5-diaminopentane derivatives / structure–activity relationships

1. Introduction

(±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-nitrobenzamide hydrochloride (nibentan, **1a**) is known as the representative of new class III antiarrhythmic drugs which is highly effective and well tolerated in patients with atrial flutter and fibrillation or supraventricular tachycardia [1, 2].

The aim of this work was to obtain compounds more active than nibentan and to study the structure–activity relationships in the series of 1,5-diaminopentane derivatives by way of chemical and structural variations on the molecule whose antiarrhythmic activity has been already shown.

In this paper we report the synthesis and the antifibrillatory activity of a new series of 1,5-diaminopentane derivatives which can be considered as structural analogues of nibentan *(table I*).

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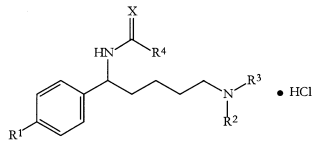
2. Chemistry

The synthetic route utilized for the preparation of nibentan (**1a**) and the majority of its analogues **1b**–**j** is shown in *figure 1*.

Condensation of phenylacetonitrile (**2a**) or (4-methoxyphenyl)acetonitrile (**2b**) with diethyl carbonate by means of sodium ethylate in toluene gave ethyl arylcyanoacetate sodium salts **3a** or **3b**, respectively.

Alkylation of sodium salts **3a** and **3b** with 1,4-dibromobutane yielded the corresponding bromides **4a** and **4b**. Treatment of the compounds **4a** and **4b** with the amines **5a**–**c** gave the amino derivatives **6a**–**d** which were decarbethoxylated with aqueous potassium hydroxide in the presence of triethylbenzylammonium chloride to the corresponding cyano derivatives **7a**–**d**. Reaction of **7a**–**d** with hydrogen peroxide in dimethylsulfoxide gave the 1-carbamoyl derivatives **8a**–**d** which were rearranged to the corresponding urethanes **9a**–**d** according to the Hoffman reaction by means of bromine and sodium methylate in methanol. Hydrolysis of urethanes **9a**–**d** with sodium hydroxide in ethanol afforded the amines **10a**–**d** which

Table I. 1,5-Diaminopentane derivatives **1a**–**p**.



Compound	R^1	R^2	R^3	R^4	X	Yield, %	M.p. °C	Formula**
1a	H	Et	Et	$C_6H_4NO_2$-4	O	92.6	165–167	$C_{22}H_{29}N_3O_3 \cdot HCl$
1b	H	Me	$(CH_2)_2C_6H_3(OMe)_2$-3,4	$C_6H_4NO_2$-4	O	23.0	73–75	$C_{29}H_{35}N_3O_5 \cdot HCl$
1c	MeO	Et	Et	$C_6H_4NO_2$-4	O	96.6	110–112	$C_{23}H_{31}N_3O_4 \cdot HCl$
1d	H	Et	Et	$C_6H_4NO_2$-3	O	72.0	104–106	$C_{22}H_{29}N_3O_3 \cdot HCl$
1e*	H	Et	Et	3-pyridyl	O	51.7	65–66	$C_{21}H_{29}N_3O$
1f*	NO_2	Et	Et	Ph	O	29.0	51–53	$C_{22}H_{29}N_3O_3$
1g	NO_2	Et	Et	$C_6H_4NO_2$-4	O	55.8	160–162	$C_{22}H_{28}N_4O_5 \cdot HCl$
1h	H	Et	CH_2Ph	Ph	O	68.8	71–72	$C_{27}H_{32}N_2O \cdot HCl$
1i	H	Et	Et	C_6H_4COOEt-4	O	52.0	116–117	$C_{25}H_{34}N_2O_3 \cdot HCl$
1j	H	Et	Et	$C_6H_4SO_2Me$-4	O	46.6	102–103	$C_{23}H_{32}SN_2O_3 \cdot HCl$
1k*	H	Et	Et	$C_6H_4NH_2$-4	O	68.5	56–57	$C_{22}H_{31}N_3O$
1l	H	Et	Et	C_6H_4OH-4	O	50.0	101–103	$C_{22}H_{30}N_2O_2 \cdot HCl$
1m	OH	Et	Et	$C_6H_4NO_2$-4	O	37.0	130–135	$C_{22}H_{29}N_3O_4 \cdot HCl$
1n	H	Et	H	Ph	O	55.6	194–195	$C_{20}H_{26}N_2O \cdot HCl$
1o	H	Et	Et	$C_6H_4CONH_2$-4	O	71.0	108–109	$C_{23}H_{31}N_3O_2 \cdot HCl$
1p	H	Et	Et	$C_6H_4NO_2$-4	NH	25.7	105–107	$C_{22}H_{30}N_4O_2 \cdot 2HCl$

*As a base, **C, H, N analyses were within ± 0.4% of the calculated values.

were coupled with the appropriate chlorides of acids **11a**–**f** in acetonitrile to yield the final products **1a**–**j** (*figure 1*).

The 1,5-diaminopentane derivatives **1k**–**o** were synthesized starting from the corresponding compounds **1a**, **1c**, **1h** and **1i** as illustrated in *figure 2*.

Reduction of the nitro-group in **1a** with iron in water in the presence of ammonium chloride gave the amino compound **1k**. Diazotization of **1k** in sulfuric acid and subsequent hydrolysis afforded N-[5-(diethylamino)-1-phenylpentyl]-4-hydroxybenzamide which was converted to the hydrochloride **1l** by treatment with hydrogen chloride solution in isopropyl alcohol. Reaction of **1c** with boron tribromide in dichloromethane and subsequent treatment of the resulting compound with hydrogen chloride solution in isopropyl alcohol gave the hydroxy derivative **1m**. Compound **1h** was reduced with catalytic hydrogenation in the presence of 20% palladium (II) hydroxide on carbon to obtain the hydrochloride **1n**. Reaction of ester **1i** with formamide and sodium methylate in methanol and subsequent treatment with hydrogen chloride solution in isopropyl alcohol provided amide **1o** (*figure 2*).

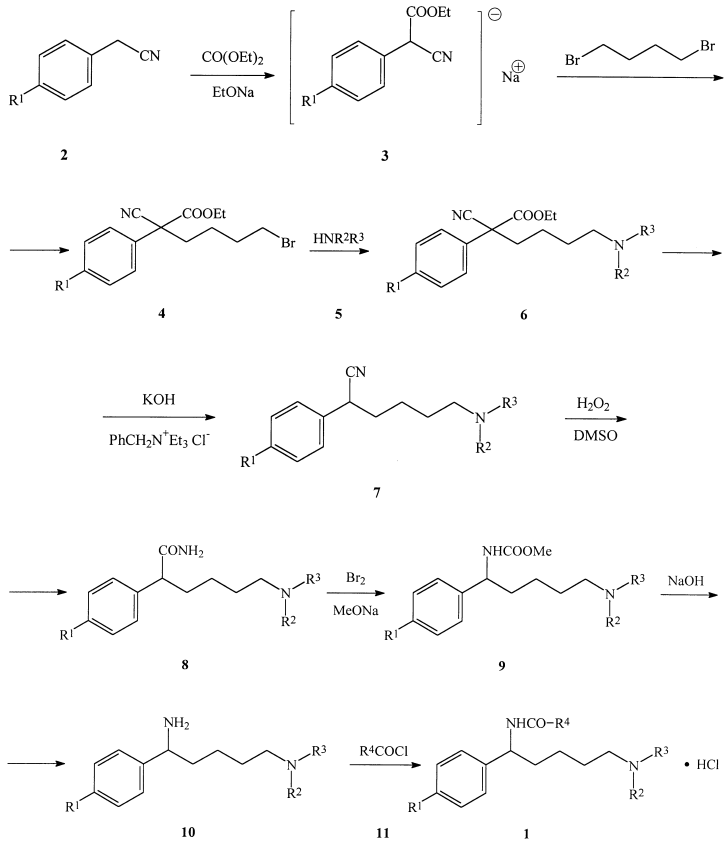
Diamine **10a** was coupled with the iminoester **14** to yield the desired compound **1p** (*figure 3*).

Nitro-substituted diamine **10e** was synthesized starting from non-substituted diamine **10a** for the preparation of nitrophenyl substituted final products **1f** and **1g**.

Diamine **10a** was acetylated by acetic anhydride to give the intermediate acetylated derivative **12** which was nitrated with fuming nitric acid in concentrated sulfuric acid to afford the compound **13** with a touch of the 3- and 2-nitro isomers in a 20:4:1 ratio, respectively. Treatment of **13** with aqueous hydrochloric acid gave 4-nitrophenyl substituted diamine **10e** (*figure 3*).

3. Results and discussion

We have recently described the preparation of the substituted phenylacetonitriles **7a**–**d** starting from the corresponding aryl substituted α-cyano esters **6a**–**d** by a phase-transfer catalysis method [3]. Hydrolysis of the cyano-group to the amide function using hydrogen peroxide in dimethylsulfoxide has been previously reported [4]. Our attempts to convert the amides **8a**–**d** to the amines **10a**–**d** according to the Hoffman reaction by alkaline sodium hypochlorite were not satisfactory because of side reactions and low yields of desired products. To obtain the amines **10a**–**d** as their carbomethoxy derivatives in good yields we have used our own variant



1 a–j: see table I; **2–4 a** R^1=H; **b** R^1=OMe; **5 a** R^2=R^3=Et; **b** R^2=Me, R^3=$(CH_2)_2C_6H_3(OMe)_2$-3,4; **c** R^2=Et, R^3=CH_2Ph; **6–10 a** R^1=H, R^2=R^3=Et; **b** R^1=H, R^2=Me, R^3=$(CH_2)_2C_6H_3(OMe)_2$-3,4; **c** R^1=OMe, R^2=R^3=Et; **d** R^1=H, R^2=Et, R^3=CH_2Ph; **10 e** R^1=NO_2, R^2=R^3=Et; **11 a** R^4=$C_6H_4NO_2$-4; **b** R^4= $C_6H_4NO_2$-3; **c** R^4=Ph; **d** R^4=3-pyridyl; **e** R^4=C_6H_4COOEt-4; **f** R^4=$C_6H_4SO_2Me$-4

Figure 1. Synthesis of nibentan **1a** and its analogues **1b–j**.

of the modification of the Hoffman rearrangement with bromine and sodium methylate in methanol [5, 6]. The order of the reagent mixing was changed. To carry out this reaction at 0 °C instead of –45 °C [6] bromine was added to the solution of sodium methylate and the amide **8** in methanol. It is known that acid hydrolysis of urethanes is very slow. Alkaline hydrolysis of urethanes in alcoholic solution also requires a long reaction time [7]. Thus, carbomethoxy derivatives **9a** and **9b** were converted to the amines **10a** and **10b** with sodium hydroxide in ethanol for 17–24 h by the above-mentioned method [7]. We have found that the addition of triethylbenzylammonium chloride to the reaction mixture decreased the reaction time to 5–6 h and gave the higher yields of desired amines **10**. Coupling of the amines **10a–e** with the chlorides of acids **11a–f** in acetonitrile directly provided the corresponding final products **1a–j** as hydrochlorides.

3.1. Structure–activity relationships

It was shown that the most of new 1,5-diaminopentane derivatives possessed the antifibrillatory activity (*table II*). The level of antifibrillatory activity depends on the nature of the substituents R^1, R^3, R^4 and X in the compounds **1a–p**. The presence of the nitro- or hydroxy-groups (R^1) in the 4- position of the phenyl ring in combination with the diethylamino function (R^2, R^3) and the 4-nitrophenyl or phenyl substituents (R^4) increased the antifibrillatory activity. Thus, the compounds **1f, 1g**

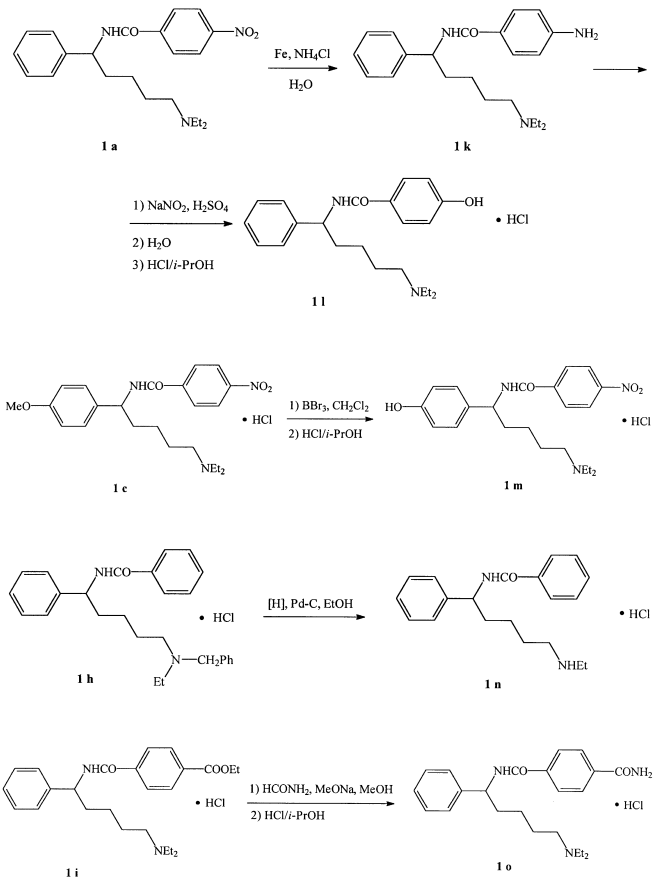


Figure 2. Synthesis of 1,5-diaminopentane derivatives **1k**–**o**.

and **1m** were more active than nibentan (**1a**) and possessed a longer duration of action. For example, the principal metabolite of nibentan (**1m**) [8] kept its antifibrillatory activity level for at least 5 h. The antifibrillatory activity of the 4-methoxy (R^1) derivative **1c** was comparable to that of nibentan (**1a**).

Compound **1b** with the 3,4-dimethoxyphenylethyl and methyl groups (R^2, R^3) was less potent than nibentan (**1a**). Replacement of the 4-nitrophenyl group (R^4) in **1a** by 3-nitrophenyl, 3-pyridyl, 4-carboethoxyphenyl or 4-hydroxyphenyl ones decreased the antifibrillatory activity of the compounds **1d**, **1e**, **1i** and **1l.** Similar results were noted by replacement of the oxo- group in **1a** by an imido- group (compound **1p**). Compounds **1h**, **1n** with the benzylethylamino and ethylamino functions (R^2, R^3) and phenyl substituent (R^4) possessed only weak antifibrillatory activity. No detectable antifibrillatory activity was found for derivatives with the $C_6H_4SO_2Me$-4 and $C_6H_4CONH_2$-4 substituents (R^4; compounds **1j** and **1o**).

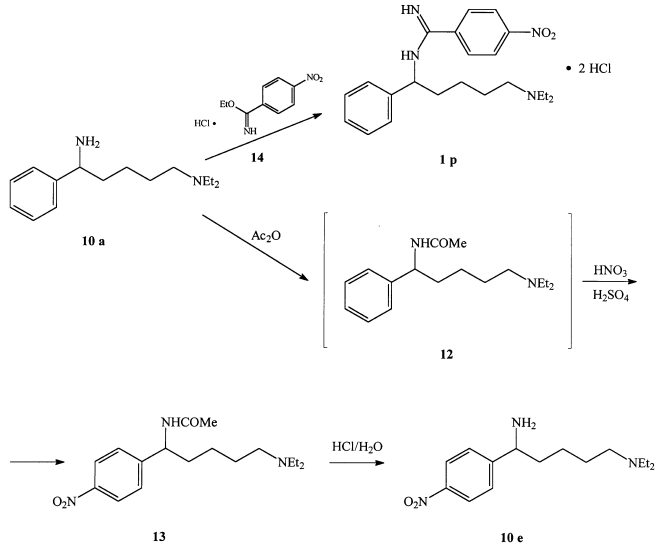


Figure 3. Synthesis of compounds **1p** and **10e**.

Thus, replacement of the 4-nitrophenyl group (R^4) in **1a** by the different substituents cited above, except for compound **1f**, was unfavourable. On the contrary, introduction of the nitro- and hydroxy- groups (R^1) in the 4-position of the phenyl ring increased the antifibrillatory activity. So, the search of new substituents in this position is the way to obtain the analogues of nibentan with higher antifibrillatory activity.

4. Experimental protocols

4.1. Chemistry

Melting points were determined in open capillaries and are uncorrected. Yields of products were not optimized. The structures of all the compounds were determined by IR, ^{1}H-NMR, mass-spectra and microanalyses. Chemical purity of the final products was checked by TLC on Silufol UV 254 plates and the location of spots was detected by illumination with a UV lamp. The analytical results (C, H, N) for pure compounds were within ± 0.4% of the theoretical values. Infrared (IR) spectra were recorded on a Perkin Elmer 599 spectrophotometer as nujol mulls or as liquid film.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Unity + 400 Varian spectrophotometer in $CDCl_3$ or $(CD_3)_2SO$ or CD_3OD using tetramethyl silane as the internal standard. All values of chemical shifts (δ) are reported in ppm. Signals are designated as follows: s, singlet; br.s, broad singlet;

Table II. Antifibrillatory activity of 1,5-diaminopentane derivatives **1a**–**j** and **l**–**p**.

Compound	Doses, μg/kg	Number of experiments	Number of cats[a]	Left ventricular fibrillation threshold (mA)[b]								
				Baseline	Time after compound administration							
					5 min	15 min	30 min	60 min	90 min	120 min	180 min	240 min	300 min
1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	Saline	6	6	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.4 ± 0.4	1.4 ± 0.4		
1a	25	16	16	1.3 ± 0.1	7.3 ± 1.6*	5.9 ± 0.9*	3.3 ± 0.4*	1.2 ± 0.2					
(Nibentan)	100	16		1.2 ± 0.1	18.7 ± 0.9*	20.0 ± 0.7*	13.2 ± 1.6*	8.5 ± 1.6*	7.4 ± 1.9*				
1b	25	5	5	1.4 ± 0.2	6.2 ± 1.1*	5.4 ± 0.9*	1.8 ± 0.2	1.3 ± 0.1					
	100	5		1.3 ± 0.2	12.3 ± 2.1*	10.7 ± 2.0*	3.3 ± 0.7*	2.4 ± 0.4					
1c	25	7	7	1.6 ± 0.2	12.3 ± 2.2*	12.0 ± 2.6*	8.2 ± 1.2*	4.1 ± 0.7*	1.6 ± 0.3				
	100	7		1.5 ± 0.2	15.2 ± 2.6*	20.0 ± 1.9*	18.2 ± 1.8*	4.4 ± 0.9*					
1d	25	6	6	1.6 ± 0.2	2.6 ± 0.3*	2.4 ± 0.3*	3.7 ± 0.2*	1.6 ± 0.2					
	100	6		1.5 ± 0.2	19.0 ± 0.7*	18.0 ± 1.1*	12.0 ± 1.5*	8.0 ± 2.3*	1.7 ± 0.2				
1e	25	7	7	2.0 ± 0.4	4.0 ± 1.2*	3.3 ± 0.7*	1.9 ± 0.3						
	100	7		1.9 ± 0.3	8.6 ± 2.7*	8.8 ± 2.8*	5.9 ± 3.4*	2.5 ± 0.4					
1f	25	5	5	1.9 ± 0.4	20.0 ± 1.4*	20.0 ± 1.4*	20.0 ± 1.4*	13.4 ± 3.0*	8.3 ± 5.9	6.0 ± 1.0			
1g	25	6	6	1.4 ± 0.1	20.0 ± 1.7*	20.0 ± 1.7*	10.0 ± 3.2*	8.4 ± 3.7*	8.2 ± 3.7*	8.0 ± 0.6*			
1h	100	6	6	1.2 ± 0.2	7.2 ± 0.8*	1.3 ± 0.3							
	500	6		1.3 ± 0.2	20.0 ± 1.1*	20.0 ± 1.2*	1.5 ± 0.2						
1i	500	4	4	1.6 ± 0.3	20.0 ± 1.8*	20.0 ± 1.8*	14.0 ± 2.2*	1.8 ± 0.4					
1j	500	3	3		Nonactive								
1l	500	4	4	2.0 ± 0.3	20.0 ± 0.8*	20.0 ± 0.8*	17.0 ± 1.3*	10.5 ± 2.0*	8.3 ± 2.0*	1.4 ± 0.2			
1m	25	9	9	1.5 ± 0.2	7.7 ± 1.7*	4.7 ± 1.0*	8.7 ± 1.9*	8.1 ± 2.7*	2.8 ± 0.3*	1.9 ± 0.4			
	100	9		1.9 ± 0.2	20.0 ± 1.0*	20.0 ± 1.1*	20.0 ± 1.1*	20.0 ± 1.0*	19.3 ± 0.9*	20.0 ± 0.9*	20.0 ± 0.8*	20.0 ± 0.8*	18.0 ± 0.6*
1n	100	6	6	1.4 ± 0.2	3.0 ± 0.6*	4.0 ± 1.0*	1.5 ± 0.5						
	500	6		1.5 ± 0.2	20.0 ± 1.3*	20.0 ± 1.0*	12.8 ± 1.3*	2.2 ± 0.4					
1o	500	3	3		Nonactive								
1p	500	5	5	1.1 ± 0.1	20.0 ± 1.4*	7.5 ± 1.0*	1.5 ± 0.4						
D-Sotalol	500	6	6	1.1 ± 0.4	2.2 ± 0.7	1.8 ± 0.3	3.1 ± 0.6	1.5 ± 0.3	0.9 ± 0.1				
	1 000	6		0.9 ± 0.1	13.5 ± 5.2*	11.1 ± 1.0*	10.9 ± 2.4*	5.9 ± 1.1*					
Sematilide	100	6	6	2.0 ± 0.4	4.9 ± 2.4	5.5 ± 1.8*	6.8 ± 2.8*	5.0 ± 1.7*	2.9 ± 0.5*	2.2 ± 0.4			
	500	6		2.2 ± 0.2	9.6 ± 3.3*	12.2 ± 3.0*	12.4 ± 3.4*	9.4 ± 1.9*	10.0 ± 4.3	6.5 ± 3.5	3.7 ± 1.0		

*Significantly different from baseline, $P < 0.05$. Absence of the asterisk indicates that $P > 0.05$. [a]The subsequent dose of the substance was administered to the same cat after restoration of the elevation of the left ventricular fibrillation threshold induced by the previous dose. [b]Values as mean ± SEM.

br.sign., broad signal; d, doublet; br.d, broad doublet; t, triplet; br.t, broad triplet; q, quadruplet; br.q, broad quadruplet; m, multiplet.

Mass spectra (MS) were recorded on an SSQ-710 chromatograph/mass spectrometer, electron impact 70 eV or chemical ionization; only significant m/z peaks are reported here.

4.1.1. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-nitrobenzamide hydrochloride **1a**

A solution of **11a** (14.97 g, 0.0807 mol) in dry acetonitrile (46 mL) was added to a stirred solution of **10a** [9] (18.0 g, 0.0768 mol) in dry acetonitrile (20 mL) cooled to 0–5 °C. The reaction mixture was stirred at 0–5 °C for 4 h. The precipitate was filtered off, washed with 2-propanol to give 29.81 g (92.6%) of **1a**. M.p. 165–167 °C (from 2-propanol).

4.1.2. (±)-[5-[N-Methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]amino]pentyl]-4-nitrobenzamide hydrochloride **1b**

A solution of **11a** (10.48 g, 0.0565 mol) in dry acetonitrile (33 mL) was added to a stirred solution of **10b** (19.18 g, 0.0538 mol) in dry acetonitrile (19 mL) cooled to 0–5 °C. The reaction mixture was stirred at 0–5 °C for 4 h, then at 50 °C for 1 h, cooled to room temperature and evaporated. The residual brown oil (13.7 g) was dissolved in water (260 mL) at 80 °C. The aqueous solution was treated with activated charcoal (3 g) under stirring. After filtration, the mother waters were passed through a short silica gel column. The aqueous solution was basified with aqueous ammonia to pH 9.0, extracted with $CHCl_3$ (2 × 100 mL), washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residual yellow oil was dissolved in dry diethyl ether and saturated with HCl gas. The yellow solid was collected by filtration and recrystallized from toluene to give 6.7 g (23%) of **1b**. M.p. 73–75 °C. The R_f value of the principal spot is 0.63 (200 μg was applied; chloroform-ethanol-ammonia 75:22:0.2 as mobil phase) and the total of all secondary spots is not more than 1.0% in comparison with the principal spot. IR (Nujol): 3 210 (NH), 2 680–2 560 (N^+H), 1 650 (C=O) cm^{-1}. MS, m/z: $[MH]^+$ 506. ^{1}H-NMR (CD_3OD): δ 1.49 (2H, m, 3-CH_2), 1.81 (2H, m, 4-CH_2), 2.01 (2H, m, 2-CH_2), 2.91 (3H, s, NMe), 2.90–3.50 (m, 5-CH_2, $(CH_2)_2$), 3.79 (3H, s, OMe), 3.83 (3H, s, OMe), 5.15 (1H, m, CH), 6.80–6.95 (3H, m, H arom.), 7.20–7.50 (5H, m, H arom.), 8.00–8.33 (4H, m, H arom.), 9.08 (1H, d, NH).

4.1.3. (±)-N-[5-(Diethylamino)-1-(4-methoxyphenyl)-pentyl]-4-nitrobenzamide hydrochloride **1c**

The compound **1c** was obtained in 96.6% yield from **10c** (10.73 g, 0.0406 mol), **11a** (7.61 g, 0.0410 mol) and dry acetonitrile (49 mL) using the same procedure described for compound **1a**. After cooling to 0–1 °C, acetonitrile was evaporated in vacuo. The residue was dissolved in 2-propanol (20 mL), treated with charcoal (2 g) and heated at reflux under stirring. After filtration, the mother liquor was cooled to 0–5 °C. The precipitate was filtered off, washed with 2-propanol (3 mL) to give 10.01 g of **1c**. The filtrate was evaporated in vacuo. The residue was recrystallized from 2-propanol to give 7.66 g of **1c**. The total yield was comprised 17.67 g (96.6%) of **1c**. M.p. 110–112 °C (from 2-propanol). IR (Nujol): 3 220 (NH), 2 680–2 090 (N^+H), 1 660 (C=O) cm^{-1}. MS, m/z: M^+ 413, $[M\text{-}Me]^+$ 398, $[M\text{-}(CH_2)_4NEt_2]^+$ 285, $^+O{\equiv}C\text{–}C_6H_4NO_2$ 150, $CH_2{=}N^+Et_2$ 86. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.17 (6H, t, Me_2), 0.95–1.60 (6H, m, $(CH_2)_3$), 2.97 (2H, m, 5-CH_2), 3.04 (4H, q, $N(CH_2)_2$), 3.76 (3H, s, OMe), 4.96 (1H, br.q, CH), 6.90 (2H, d, H arom.), 7.34 (2H, d, H arom.) 8.11 (2H, d, H arom.), 8.31 (2H, d, H arom.), 9.10 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.4 Hz).

4.1.4. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-3-nitrobenzamide hydrochloride **1d**

A solution of **11b** (5.54 g, 0.0299 mol) in dry acetonitrile (6 mL) was added to a stirred solution of **10a** [9] (7.0 g, 0.0299 mol) in dry acetonitrile (20 mL) at room temperature. The reaction mixture was stirred at 50 °C for 30 min, at 5–10 °C for 3 h. The solvent was evaporated in vacuo. The residue was triturated with 2-propanol at 0–5 °C. The precipitate was filtered off to give 9.0 g (72%) of **1d**. M.p. 104–106 °C. MS, m/z: $[MH]^+$ 384, $[M\text{-}Me]^+$ 368, $^+O{\equiv}C\text{–}C_6H_4NO_2$ 150, $CH_2{=}N^+Et_2$ 86. IR (Nujol): 3 230 (NH), 1 660 (C=O) cm^{-1}. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.19 (6H, t, Me_2), 1.20–2.05 (6H, m, $(CH_2)_3$), 3.00 (2H, m, 5-CH_2), 3.06 (4H, br.q, $N(CH_2)_2$), 5.04 (1H, m, CH), 7.20–7.47 (5H, m, H arom.), 7.79 (1H, t, 5-H arom.), 8.40 (2H, 2d, 4-,6-H arom.), 8.74 (1H, s, 2-H arom.), 9.31 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.1 Hz).

4.1.5. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-3-pyridylamide **1e**

A solution of **11d** (0.48 g, 0.0034 mol) in dry acetonitrile (4 mL) was added to a stirred solution of **10a** [9] (0.8 g, 0.0034 mol) in dry acetonitrile (4 mL) at room temperature. The reaction mixture was refluxed for 30 min and cooled to room temperature. The solvent was evaporated in vacuo. The residue was dissolved in water (20 mL). The aqueous solution was basified with 40% aqueous NaOH to pH 9.0, extracted with ethyl acetate (2 × 20 mL), and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4, passed through a short silica gel column and evaporated. The residue was triturated with heptane. The precipitate

was filtered off to give 0.6 g (51.7%) of **1e**. M.p. 65–66 °C. MS, m/z: M^+ 339. ^{1}H-NMR ($(CD_3)_2SO$): δ 0.90 (6H, t, Me_2), 1.20–1.45 (4H, m, $(CH_2)_2$), 1.70–1.92 (2H, m, 2-CH_2), 2.32 (2H, t, 5-CH_2), 2.39 (4H, q, $N(CH_2)_2$), 5.00 (1H, m, CH), 7.18–7.42 (5H, m, H arom.), 7.47–9.04 (4H, m, H arom.), 8.96 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.4 Hz).

4.1.6. (±)-N-[5-(Diethylamino)-1-(4-nitrophenyl)pentyl]-benzamide **1f**

The compound **1f** was obtained from **10e** (2.8 g, 0.0100 mol), **11c** (1.4 g, 0.0100 mol) and dry acetonitrile (8 mL) using the procedure described for compound **1e**, but the reaction mixture was heated at 70 °C for 30 min. 40% aqueous NaOH was added to pH 8.0. The alkaline solution was extracted with toluene (2 × 30 mL) and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4. After evaporation, the residue was triturated with hexane and the precipitate filtered off to give 1.1 g (29%) of **1f**. M.p. 51–53 °C. MS, m/z: M^+ 383. ^{1}H-NMR ($CDCl_3$): δ 0.98 (6H, t, Me_2), 1.30–1.58 (4H, m, $(CH_2)_2$), 1.90 (2H, m, 2-CH_2), 2.37 (2H, m, 5-CH_2), 2.48 (4H, q, $N(CH_2)_2$), 5.17 (1H, m, CH), 6.66 (1H, br.d, NH), 7.42 (2H, t, H arom.), 7.50 (1H, t, 2H, d, H arom.), 7.76 (2H, d, H arom.), 8.17 (2H, d, H arom.).

4.1.7. (±)-N-[5-(Diethylamino)-1-(4-nitrophenyl)pentyl]-4-nitrobenzamide hydrochloride **1g**

A solution of **1a** (5.0 g, 0.0119 mol) in acetic anhydride was added to a stirred solution of fuming HNO_3 (15 mL) and concentrated H_2SO_4 (15 mL) cooled to 0–5 °C. The reaction mixture was stirred at 0–5 °C for 30 min, poured into ice water, basified with 40% aqueous NaOH to pH 8.0 and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The tarry residue was dissolved in a minimum of acetonitrile and HCl/EtOH was added to pH 1.0 at 0–5 °C. The precipitate was filtered off and recrystallized from acetonitrile to give 3.1 g (55.8%) of **1g** (p- isomer/o-, m- isomers, 95%/5%). In the ^{1}H-NMR spectral information the chemical shift values for the major isomer **1g** only are given. MS, m/z: M^+ 428. ^{1}H-NMR ($CDCl_3$): δ 1.35 (3H, t), 1.45 (3H, t) (Me_2), 1.60–2.43 (6H, m, $(CH_2)_3$), 2.84–3.36 (6H, m, $N(CH_2)_2$, 5-CH_2), 5.20 (1H, m, CH), 7.62 (2H, d, H arom.), 8.15 (2H, d, H arom.), 8.24 (2H, d, H arom.), 8.38 (2H, d, H arom.), 9.36 (1H, d, NH), 11.20 (1H, br.s, N^+H).

4.1.8. (±)-N-[5-(Benzylethylamino)-1-phenylpentyl]-benzamide hydrochloride **1h**

A solution of **10d** (2.96 g, 0.0100 mol) in dry acetonitrile (2 mL) was added to a stirred solution of **11c** (1.4 g, 0.0100 mol) in dry acetonitrile (2 mL). The reaction mixture was stirred at room temperature for 3 h and evaporated in vacuo. The oily residue was triturated with absolute diethyl ether (30 mL). The precipitate was filtered off, washed with absolute diethyl ether (10 mL) to give 3.0 g (68.8%) of **1h**. M.p. 71–72 °C. The base of **1h** was obtained by dissolution of **1h** (3 g) in 40% aqueous NaOH and extracting with benzene (2 × 25 mL). After evaporation, the residue was recrystallized from 2-propanol/water, 4:1 to give 2.2 g (80%) of the base of **1h**. M.p. 89–90 °C. IR (Nujol): 3 360 (NH), 1 630 (C=O) cm^{-1}. MS, m/z: M^+ 400, $[M\text{-}CH_3]^+$ 385, $[M\text{-}Et]^+$ 371, $[M\text{-}CH_2Ph]^+$ 309, $[M\text{-}NH(Et)CH_2Ph\text{-}H]^+$ 264, $[(CH_2)_4NEtCH_2Ph]^+$ 190, $[CH_2{=}NEtCH_2Ph]^+$ 148, $CH_3CH{=}NH^+CH_2Ph$ 134, $[PhCO]^+$ 105, $[PhCH_2]^+$ 91. ^{1}H-NMR (CD_3OD): δ 1.33 (3H, s, Me), 1.30–2.10 (6H, m, $(CH_2)_3$), 3.00–3.30 (4H, m, $CH_2N^+CH_2$), 4.33 (2H, s, CH_2), 5.13 (1H, m, CH), 7.20–7.60 (10H, m, H arom.), (3H, m, H arom.), 7.82 (2H, d, H arom.).

4.1.9. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-carboethoxybenzamide hydrochloride **1i**

The compound **1i** was obtained from **10a** [9] (1.1 g, 0.0047 mol), **11e** [10] (1.0 g, 0.0047 mol) and dry acetonitrile (5 mL) using the procedure described for compound **1e**. The alkaline solution was extracted with toluene (2 × 25 mL) and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4. After evaporation, the residue was dissolved in a minimum of acetonitrile and HCl/EtOH was added to pH 1.0 at 0–5 °C. The precipitate was filtered off to give 1.1 g (52%) of **1i**. M.p. 116–117 °C. IR (Nujol): 1 710, 1 635 (C=O) cm^{-1}. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.18 (6H, br.t, Me_2), 1.20 (3H, t, Me), 1.32 (1H, m), 1.42 (1H, m) (3-CH_2), 1.68 (2H, m, 4-CH_2), 1.78 (1H, m), 1.95 (1H, m) (2-CH_2), 2.96 (2H, br.t, 5-CH_2), 3.05 (4H, q, $N(CH_2)_2$), 4.33 (2H, q, CH_2), 5.02 (1H, m, CH), 7.21 (1H, t, H arom.), 7.33 (2H, t, H arom.), 7.44 (2H, d, H arom.), 8.03 (4H, m, H arom.), 9.12 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.4 Hz), 10.35 (1H, br.s, N^+H).

4.1.10. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-methylsulphonylbenzamide hydrochloride **1j**

The compound **1j** was obtained in 46.6% yield from **10a** [9] (1.0 g, 0.0043 mol), **11f** [11] (0.93 g, 0.0043 mol) and dry acetonitrile (20 mL) using the same procedure described for compound **1i**. M.p. 102–103 °C. IR (Nujol): 1 650 (C=O), 1 300, 1 150 ($MeSO_2$) cm^{-1}. ^{1}H-NMR

($(CD_3)_2SO$): δ 1.17 (6H, t, Me_2), 1.31 (1H, m), 1.42 (1H, m) (2-CH_2), 1.68 (2H, m, 4-CH_2), 1.78 (1H, m), 1.94 (1H, m) (2-CH_2), 2.96 (2H, q, 5-CH_2), 3.05 (4H, m, $N(CH_2)_2$), 3.26 (3H, s, Me), 5.03 (1H, m, CH), 7.23 (1H, t, H arom.), 7.33 (2H, t, H arom.), 7.42 (2H, d, H arom.), 8.0–8.14 (4H, m, H arom.), 9.15 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.0 Hz), 10.05 (1H, br.s, N^+H).

4.1.11. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-aminobenzamide **1k**

To a stirred mixture of iron (18.0 g, 0.3223 mol), ammonium chloride (2.25 g, 0.0421 mol) and water (55 mL) heated to 95 °C, was added a solution of **1a** (25.0 g, 0.0595 mol) in hot water (50 mL). The reaction mixture was refluxed for 30 min. The precipitate was filtered off and washed with a hot water. The filtrate was cooled to room temperature, basified with 40% aqueous NaOH to pH 9.0, extracted with ethyl acetate (3 × 150 mL) and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was triturated with hexane and a cream-coloured solid filtered off to give 15.0 g (68.5%) of **1k**. M.p. 56–57 °C. MS, m/z: M^+ 353. ^{1}H-NMR ($(CD_3)_2SO$): δ 0.88 (6H, t, Me_2), 1.16–1.46 (4H, m, $(CH_2)_2$), 1.66–1.88 (2H, m, 2-CH_2), 2.29 (2H, t, 5-CH_2), 2.40 (4H, q, $N(CH_2)_2$), 4.94 (1H, m, CH), 5.59 (2H, s, NH_2), 6.52 (2H, d, H arom.), 7.15–7.38 (5H, m, H arom.), 7.60 (2H, d, H arom.), 8.22 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.6 Hz).

4.1.12. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-hydroxybenzamide hydrochloride **1l**

To a stirred solution of **1k** (20.0 g, 0.0566 mol) in concentrated H_2SO_4 (10 mL) and H_2O (130 mL) cooled to 0 °C, was added dropwise a solution of $NaNO_2$ (4.5 g, 0.0652 mol) in H_2O (20 mL) at 0–5 °C. The reaction mixture was stirred at 0 °C for 30 min, poured into boiling water (300 mL), stirred at 95 °C for 15 min, and cooled to room temperature. 40% aqueous NaOH was added to pH 9.0 and the aqueous phase was extracted with ethyl acetate (2 × 150 mL) and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was dissolved in acetone and petroleum ether was added. The precipitate was filtered off, dissolved in a minimum of 2-propanol, and HCl/i-PrOH was added to pH 1.0. The solvent was removed in vacuo and the residue was triturated with acetone. The precipitate was filtered off to give 10.0 g (50%) of **1l**. M.p. 101–103 °C. MS, m/z: M^+ 354. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.17 (6H, t, Me_2), 1.20–1.48 (4H, m, 3-CH_2), 1.66 (2H, m, 4-CH_2), 1.70–1.95 (2H, m, 2-CH_2), 2.95 (2H, m, 5-CH_2), 3.02 (4H, m, $N(CH_2)_2$), 4.97 (1H, m, CH), 6.80 (2H, d, H arom.), 7.40 (1H, t, H arom.), 7.60 (2H, t, H arom.), 7.77 (2H, d, H arom.), 7.78 (2H, d, H arom.), 8.56 (1H, d, NH), 10.25 (1H, br.s, N^+H).

4.1.13. (±)-N-[5-(Diethylamino)-1-(4-hydroxyphenyl)-pentyl]-4-nitrobenzamide hydrochloride **1m**

Under a nitrogen atmosphere, to a stirred solution of **1c** (1.0 g, 0.0022 mol) in dry dichloromethane (60 mL) cooled to –70 °C, was added dropwise a solution of BBr_3 in the same solvent (18 mL). The reaction mixture was stirred for 3 h at –70 °C and for 2 h at room temperature, then poured into ice water. Saturated $NaHCO_3$ aqueous solution was added and stirred at room temperature for 1 h. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water, dried over $MgSO_4$ and evaporated in vacuo. The residue was dissolved in 2-propanol (2 mL) and HCl/i-PrOH was added to pH 2.0. The solvent was removed in vacuo. The residual oil was triturated with 2-propanol and diethyl ether. The precipitate was filtered off to give 0.36 g (37%) of **1m**. M.p. 130–135 °C. MS, m/z: M^+ 399. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.17 (6H, t, Me_2), 1.20–2.05 (6H, m, $(CH_2)_3$), 3.03 (2H, m, 5-CH_2), 3.05 (4H, m, $N(CH_2)_2$), 4.95 (1H, m, CH), 6.71 (2H, d, H arom.), 7.21 (2H, d, H arom.), 8.10 (2H, d, H arom.), 8.26 (2H, d, H arom.), 9.07 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.0 Hz), 9.33 (1H, s, OH), 9.74 (1H, br.sign, N^+H).

4.1.14. (±)-N-[5-(Ethylamino)-1-phenylpentyl]-benzamide hydrochloride **1n**

A mixture of **1h** (2.5 g, 0.0057 mol), absolute ethanol (100 mL) and 20% Pd–C (200 mg) was subjected to hydrogenation at room temperature. The catalyst was filtered, washed with absolute ethanol (2 × 20 mL), and the ethanol was evaporated in vacuo. The precipitate was triturated with absolute diethyl ether and recrystallized from EtOH/Et_2O to give 1.1 g (55.6%) of **1n**. M.p. 194–195 °C. IR (Nujol): 3 340, 3 285 (NH), 1 630 (C=O) cm^{-1}. MS, m/z: M^+ 310, $[M\text{-}CH_3]^+$ 295, $[M\text{-}NHEt]^+$ 266, $[M\text{-}(CH_2)_4NHEt]^+$ 210, $[M\text{-}NHCOPh]^+$ 190, $[190\text{-}Et\text{-}H]^+$ 160, $[190\text{-}CH_2NHEt]^+$ 132, $[PhCO]^+$ 105, $[CH_2{=}CH\text{-}CH{=}NH^+Et]$ 84, Ph^+ 77, $[CH_2{=}NHEt]^+$ 59. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.16 (3H, t, Me), 1.00–2.00 (6H, m, $(CH_2)_3$), 2.82–2.86 (4H, m, $CH_2N^+CH_2$), 5.00 (1H, m, CH), 7.20–7.60 (5H, m, H arom.), 7.20–7.60 (3H, m, H arom.), 7.90 (2H, d, H arom.), 8.85 (2H, m, N^+H_2), 8.87 (1H, d, NH).

4.1.15. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-carbamidobenzamide hydrochloride **1o**

Under a nitrogen atmosphere, to a stirred mixture of **1i** (0.6 g, 0.0013 mol), formamide (0.18 mL, 0.2 g,

0.0044 mol) and dry DMF (10 mL) was added a solution of sodium (0.03 g, 0.0013 g-a) in methanol (1 mL) at 100 °C. The reaction mixture was heated at 100 °C for 1 h, cooled to room temperature and water (20 mL) was added. The precipitate was filtered off, dissolved in a minimum of acetonitrile and HCl/EtOH was added to pH 1.0. After evaporation, the residue was triturated with diethyl ether. The precipitate was filtered off to give 0.4 g (71%) of **1o**. M.p. 108–109 °C. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.18 (6H, t, Me_2), 1.31 (1H, m), 1.42 (1H, m, 3-CH_2), 1.68 (2H, m, 4-CH_2), 1.78 (1H, m), 1.94 (1H, m) (2-CH_2), 2.96 (2H, q, 5-CH_2), 3.05 (4H, m, $N(CH_2)_2$), 5.03 (1H, m, CH), 7.22 (1H, t, H arom.), 7.33 (2H, t, H arom.), 7.42 (2H, d, H arom.), 7.50 (1H, br.s, NH), 8.12 (1H, br.s, NH), 7.95 (4H, m, H arom.), 8.97 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.4 Hz), 10.11 (1H, br.s, N^+H).

4.1.16. (±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-nitrobenzamidine hydrochloride **1p**

A solution of **10a** [9] (0.5 g, 0.0021 mol) in anhydrous 1,2-dichloroethane was added to a stirred mixture of **14** [12] (0.48 g, 0.0021 mol) and anhydrous 1,2-dichloroethane (20 mL). The reaction mixture was heated at 70–75 °C for 1.5 h, cooled to room temperature and evaporated in vacuo. The residue was chromatographed on a short silica gel column with 2-propanol as eluent. Appropriate fractions were combined and evaporated in vacuo. The residue was dissolved in water (10 mL), basified with 5% aqueous $NaHCO_3$ to pH 8.0, extracted with $CHCl_3$ (2 × 5 mL), and dried over $CaCl_2$. The solvent was removed in vacuo, the residue was dissolved in a minimum of 2-propanol, HCl/i-PrOH was added to pH 1.0. After evaporation, the residue was triturated with dry diethyl ether. The precipitate was filtered off to give 0.25 g (25.7%) of **1p** as a hygroscopic substance. ^{1}H-NMR ($(CD_3)_2SO$): δ 1.16 (6H, t, Me_2), 1.30–1.50 (2H, m, 3-CH_2), 1.75 (2H, m, 4-CH_2), 1.87 (1H, m), 2.13 (1H, m) (2-CH_2), 3.00 (2H, m, 5-CH_2), 3.01 (4H, q, $N(CH_2)_2$, 5.32 (1H, q, CH), 7.30–7.66 (5H, m, H arom.), 8.03 (2H, d, H arom.), 8.39 (2H, d, H arom.), 9.90 (1H, s), 9.95 (1H, s) (C=NH, N^+H), 10.45 (1H, br.s, N^+H), 10.72 (1H, d, NH, $^3J_{CH,\ NH}$ = 8.0 Hz).

4.1.17. (±)-6-[N-[2-(3,4-Dimethoxyphenyl)ethyl]-methylamino]-2-phenylhexanamide **8b**

Hydrogen peroxide, 30 wt.% solution in water (30 mL) was added dropwise to the mixture of **7b** [3] (38.5 g, 0.1051 mol), potassium hydroxide (3.5 g, 0.0624 mol) and DMSO (150 mL) under stirring at 5–10 °C. The reaction mixture was stirred at room temperature for 1 h, water was added and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with water (250 mL), dried over anhydrous Na_2SO_4 and passed through a short alimina column. The solvent was evaporated in vacuo to give 32.0 g of **8b** as an oil. 2.0 g of crude product was refluxed in hexane (40 mL) and cooled to room temperature. After decanting of the hexane layer, the treatment was reiterated to give 1.5 g of pure product **8b** as a white solid. M.p. 73–76 °C. IR (Liquid film): 3 400 (NH), 1 650 (C=O) cm^{-1}. MS, m/z: [MH^+] 385, [$PhCH(CONH_2)(CH_2)_4N(Me)CH_2]^+$ 233, [$CH_2Ph(OMe)_2$-3,4] 151, [$PhCH_2]^+$ 91.

4.1.18. (±)-Methyl-N-[5-[N-[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]-1-phenylpentyl]carbamate **9b**

A solution of **8b** (30.0 g, 0.0780 mol) in methanol (145 mL) was added to a stirred solution of sodium (5.95 g, 0.2588 g-a) in methanol (145 mL). Bromine (6.6 mL, 20.47 g, 0.1281 mol) was added dropwise to the reaction mixture at 0 °C. The mixture was refluxed for 20 min, cooled to room temperature, water (460 mL) was added and extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were washed with water (2 × 600 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 32.0 g of **9b** as an oil. The crude product was used for the next reaction. MS, m/z: M^+ 414.

4.1.19. (±)-1-Amino-5-[N-[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]-1-phenylpentane **10b**

The mixture of sodium hydroxide (36.66 g, 0.9165 mol), water (62 mL), ethanol (62 mL) and **9b** (32.0 g, 0.0772 mol) was refluxed under stirring for 24 h. The reaction mixture was cooled to room temperature, poured into water (1 200 mL) and extracted with toluene (2 × 300 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give 19.18 g of **10b** as an oil. The crude product was used for the next reaction. MS, m/z: M^+ 356.

4.1.20. (±)-6-Diethylamino-2-(4-methoxyphenyl)hexanamide **8c**

The compound **8c** was obtained from **7c** [3] (16.7 g, 0.0609 mol), potassium hydroxide (1.71 g, 0.0305 mol), hydrogen peroxide, 30 wt.% solution in water (16 mL) and DMSO (80 mL) using the procedure described for compound **8b**. The reaction mixture was stirred at room temperature for 6 h, water (90 mL) was added and extracted with diethyl ether (2 × 120 mL). The combined organic extracts were washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from heptane/benzene, 2:1 to give 12.95 g (72.8%) of **8c**. M.p. 53–55 °C. MS, m/z: [MH^+] 293, [293-$NH_2]^+$ 277, [293-$HCONH_2]^+$ 248, $CH_2{=}N^+Et_2$ 86. IR (Nujol): 3 450, 3 370 (NH), 1 660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.97 (6H, t, Me_2), 1.23

(2H, m, CH_2), 1.44 (2H, m, CH_2), 1.75 (1H, m), 2.16 (1H, m, 2-CH_2), 2.34 (2H, t, 5-CH_2), 2.46 (4H, q, $N(CH_2)_2$), 3.32 (1H, t, CH), 3.78 (3H, s, OMe), 5.55 (1H, br.sign.), 5.69 (1H, br.sign.) (NH_2), 7.13 (2H, d, H arom.), 7.21 (2H, d, H arom.).

4.1.21. (±)-Methyl-N-[diethylamino-1-(4-methoxyphenyl) pentyl]carbamate **9c**

The compound **9c** was obtained from **8c** (15.7 g, 0.0537 mol), sodium (3.8 g, 0.1653 g-a), bromine (3.5 mL, 10.86 g, 0.0679 mol) and methanol (140 mL) using the procedure described for compound **9b**. Water (240 mL) was added to the reaction mixture and extracted with toluene (2 × 200 mL). The combined organic extracts were washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 16.74 g of **9c** as an oil. The crude product was used for the next reaction. MS, m/z: M^+ 322, [M-HNCOOMe] 248, $CH=N^+Et_2$ 86. ^{1}H-NMR ($CDCl_3$): δ 0.98 (6H, t, Me_2), 1.27, 1.45 (4H, m, $(CH_2)_2$), 1.72 (2H, m, 2-CH_2), 2.36 (2H, m, 5-CH_2), 2.48 (4H, q, $N(CH_2)_2$), 3.62 (3H, s, COOMe), 3.78 (3H, s, OMe), 4.55 (1H, q, CH), 4.93 (1H, br.sign., NH), 6.85 (2H, d, H arom.), 7.18 (2H, d, H arom.).

4.1.22. (±)-1-Amino-5-diethylamino-1-(4-methoxyphenyl)pentane **10c**

The compound **10c** was obtained using the procedure described for compound **10b** from **9c** (14.16 g, 0.0439 mol), sodium hydroxide (19.0 g, 0.4750 mol), triethylbenzylammonium chloride (0.91 g, 0.0040 mol), ethanol (19 mL) and water (19 mL). The reaction mixture was refluxed for 5 h and treated as described above to give 10.73 g (92.4%) of **10c**. B.p. 165–170 °C/1 mm Hg. MS, m/z: M^+ 264, $CH=N^+Et_2$ 86. IR (Liquid film): 3 360, 3 280 (NH_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.98 (6H, t, Me_2), 2.18–2.65 (6H, m, $(CH_2)_3$), 2.48 (4H, q, $N(CH_2)_2$), 2.65 (2H, br.sign., NH_2), 3.55 (2H, m, 5-CH_2), 3.78 (3H, s, OMe), 3.82 (1H, t, CH), 6.85 (2H, d, H arom.), 7.21 (2H, d, H arom.).

4.1.23. (±)-6-N-Benzylethylamino-2-phenylhexanamide **8d**

The compound **8d** was obtained from **7d** [3] (12.38 g, 0.0404 mol), potassium hydroxide (1.20 g, 0.0214 mol), hydrogen peroxide, 30 wt.% solution in water (10 mL) and DMSO (25 mL) using the procedure described for compound **8b**. The reaction mixture was stirred at 30 °C for 1 h, cooled to room temperature, water (100 mL) was added and extracted with toluene (2 × 100 mL). The combined organic extracts were washed with water (2 × 50 mL) dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was triturated with hexane. The precipitate was filtered off to give 10.67 g (82.26%) of **8d**. M.p. 57–58 °C. IR (Nujol): 1 660 (C=O) cm^{-1}.

4.1.24. (±)-Methyl-N-[5-N-Benzylethylamino)-1-phenylpentyl]carbamate **9d**

The compound **9d** was obtained from **8d** (10.6 g, 0.0326 mol), sodium (2.24 g, 0.0978 g-a), bromine (2.0 mL, 6.1 g, 0.0382 mol) and methanol (45 mL) using the procedure described for compound **9b**. The reaction mixture was stirred at room temperature for 10 min, heated at reflux for 10 min and cooled to room temperature. Water (200 mL) was added to the reaction mixture and extracted with toluene (3 × 100 mL). The combined organic extracts were washed with water (3 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give 11.0 g of **9d** as an oil. The crude product was used for the next reaction. IR (liquid film): 3 310 (NH), 1 700 (C=O) cm^{-1}. MS, m/z: [MH^+] 355, [M-Ph]$^+$ 277, $CH_2=N^+EtCH_2Ph$ 148, [Ph CH_2]$^+$ 91.

4.1.25. (±)-1-Amino-5-(N-Benzylethylamino)-1-phenylpentane **10d**

The compound **10d** was obtained from **9d** (11.0 g, 0.0339 mol), sodium hydroxide (12.6 g, 0.3150 mol), triethylbenzylammonium chloride (0.6 g, 0.0264 mol), ethanol (15 mL) and water (15 mL) using the procedure described for compound **10b**. The reaction mixture was refluxed for 6 h and treated as described above to give 7.76 g of **10d**. The crude product was used for the next reaction. Dihydrochloride of **10d**: m.p. 205 °C (dec.). IR (Nujol): 1 610 (CH=CH arom.) cm^{-1}. MS, m/z: M^+ 296, [M-NH_3]$^+$ 279, [M-Et]$^+$ 267, [M-NH_3-Et]$^+$ 250, [M-CH_2Ph]$^+$ 205, [M-$PhCH_2$-NH_3]$^+$ 188, $CH_2=N^+EtCH_2Ph$ 148, [M-$(CH_2)_2NEt_2CH_2Ph$]$^+$ 134, [$PhCH^+NH_2$] 106. ^{1}H-NMR ($(CD_3)_2$ SO): δ 1.21 (3H, t, Me), 1.0–2.05 (6H, m, $(CH_2)_3$), 2.8–3.0 (4H, m, $CH_2N^+CH_2$), 4.20 (1H, m, CH), 4.25 (2H, s, CH_2), 7.35–7.65 (10H, m, H arom.), 8.60 (3H, s, N^+H_3).

4.1.26. (±)-1-Acetylamino-5-(N-diethylamino)-1-(4-nitrophenyl)pentane **13**

A solution of **10a** [9] (13.0 g, 0.0556 mol) in acetic anhydride (25 mL) was stirred at room temperature for 2 h, added to the mixture of concentrated H_2SO_4 (50 mL) and fuming HNO_3 (50 mL) and cooled to 0 °C. The reaction mixture was stirred at 0–5 °C for 1 h, poured into ice water, basified with 40% aqueous NaOH to pH 9.0 and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with water (100 mL), dried over $CaCl_2$ and evaporated to dryness in vacuo to give 13.0 g of **13** as a yellow oil. The crude product was used for the next reaction. MS, m/z: M^+ 321. ^{1}H-NMR ($(CD_3)_2$ SO): δ 0.89 (6H, t, Me_2), 1.10–1.40

(4H, m, $(CH_2)_2$), 1.65 (2H, m, 2-CH_2), 2.29 (2H, t, 5-CH_2), 2.34 (4H, q, N$(CH_2)_2$), 4.83 (1H, m, CH), 7.55 (2H, d, H arom.), 8.18 (2H, d, H arom.), 8.40 (1H, d, NH, $^3J_{NH,\ CH}$ = 7.8 Hz).

4.1.27. (±)-1-Amino-5-(N-diethylamino)-1-(4-nitrophenyl)pentane **10e**

A solution of **13** (9.0 g, 0.0280 mol) in concentrated HCl (120 mL) was refluxed for 6 h and cooled to room temperature. 40% aqueous NaOH was added to pH 8.0, extracted with ethyl acetate (3 × 50 mL), washed with water (100 mL), dried over anhydrous Na_2SO_4 and passed through a short silica gel column. The solvent was removed in vacuo to give 5.7 g of **10e** as a yellow oil. The crude product was used for the preparation of **1f** and **1g**. MS, m/z: M^+ 279. ^{1}H-NMR ($CDCl_3$): δ 0.98 (6H, t, Me_2), 1.10–1.70 (6H, m, $(CH_2)_3$), 1.76 (2H, br.s, NH_2), 2.36 (2H, t, 5-CH_2), 2.48 (4H, q, N$(CH_2)_2$), 4.02 (1H, t, CH), 7.48 (2H, d, H arom.), 8.17 (2H, d, H arom.).

4.2. Pharmacology

The experiments were carried out on 110 cats (body weights 2.5–3.5 kg) anaesthetized with pentobarbital sodium (40–50 mg/kg i.v.) under controlled ventilation. After opening of the pericardium, the left ventricle was stimulated by a series of squarewave pulses (400 ms, 50 Hz) of increasing intensity applied from the stimulator HSE-215 (Germany) until left ventricular fibrillation occurred [13]. If necessary, defibrillation was done by using a defibrillation discharge directly applied to the heart from the apparatus DI-3 (Russia). The left ventricular fibrillation threshold was measured before administration of the substances until it stabilized at a constant level (baseline), and then after intravenous administration of the substances at 5, 15, 30, 60 min and in some cases at 120, 180, 240 and 300 min. All substances including nibentan and known class III antiarrhythmics D-sotalol and sematilide were injected in the cumulative effective doses (25, 100, 500 and 1 000 μg/kg).

Only one substance was given to each cat. Each consequent dose of the same substance was administered only after restoration of the elevation of the left ventricular fibrillation threshold induced by the previous dose. In most cases duration of action of each substance was determined after administration of the most effective dose. The duration of each experiment was up to 6–7 h.

The left ventricular fibrillation threshold in the control group of animals receiving a placebo (1.0 mL of saline) did not change significantly throughout the experiment. Changes in left ventricular fibrillation threshold were tested for statistical significance by the *t*-test based on paired observation. Results are expressed as means ± SEM in terms of mA. A *P* value of 0.05 or less was considered statistically significant.

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