Eur. J. Med. Chem. 33 (1998) 975–983

Synthesis, hypotensive and antiarrhythmic activities of 3-alkyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)ureas or thioureas and their guanidine analogues

Elena G. Chalina[a]*, Lidia Chakarova[b]

[a]*Department of Organic Chemistry, Faculty of Pharmacy, Medical University, 2 Dunav St., BG-1000 Sofia, Bulgaria*
[b]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Medical University, 2 Dunav St., BG-1000 Sofia, Bulgaria*

(Received 27 January 1998; accepted 12 March 1998)

Abstract – A series of new 3-alkyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)ureas or thioureas and their guanidine analogues was synthesized from corresponding 3-amino-1,2,3,4-tetrahydronaphthalenes. Pharmacological tests showed that compounds 3-ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)urea **2a** and 3-ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-3-morpholinomethylurea **3a** possessed pronounced hypotensive and antiarrhythmic activities, as tested in anesthetized rats.

ureas / thioureas /guanidines /antiarrhythmic activity / hypotensive activity

1. Introduction

It is known that 3-amino-1,2,3,4-tetrahydronaphthalenes (aminotetralins) have shown to be biologically active agents. They have manifested a considerable activity on adrenergic receptors [1–4]. The 2,3-dihydroxytetralin analogue of Propranolol (Nadolol) is potent β-adrenergic antagonist [5]. It has been established that 3-amino-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene and its N-substituted derivatives possess β-adrenergic and hypotensive effects [6, 7]. These compounds are bicyclic analogues of the natural biogenic catecholamines in which the two hydroxyl groups are alkylated.

Some urea derivatives have exhibited antihypertensive [8] or antiarrhythmic [9] activities. Arylaminoguanidines [10, 11], benzimidazolylguanidines [12], thiadiazolylguanidines [13] and cyanoguanidines [14] have shown a strong antihypertensive effect. It has been reported that piperazineguanidines [15] and aminoguanidines [16] are promising antiarrhythmics. Among the guanidine derivatives Pinacidil is an antiarrhythmic and antihypertensive agent [17].

In earlier investigations we established that 1-cycloalkyloxy-3-guanidino-2-propanols [18] and their ureido analogues [19] have marked hypotensive and antiarrhythmic activities.

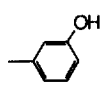
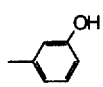
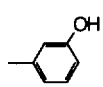
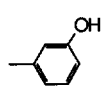
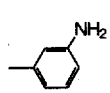
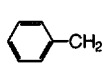
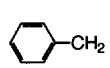
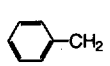
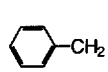
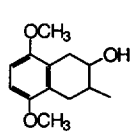
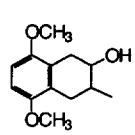
Following these observations, it appeared to be of interest to prepare new compounds which contain both 1,2,3,4-tetrahydronaphthalene and either ureido or guanidine moieties and to test them for antiarrhythmic and hypotensive activities.

2. Chemistry

The synthetic pathway followed for the preparation of ureas or thioureas **2a–q** (*tables I, II*) is represented in *figure 1*. 3-Amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalenes **1a–f**, which was obtained by the reaction of 2,3-epoxy-5,8-dimethoxy-1,2,3,4-tetra-hydronaphthalene with primary amines in ethanol [20], reacted with the appropriate isocyanate or isothiocyanate in anhydrous THF to afford substituted 1,2,3,4-tetrahydronaphthalenylureas or thioureas **2a–q**. N-Aminomethylation [21]

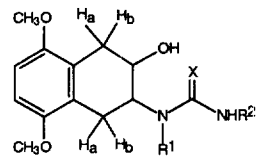
*Correspondence and reprints

Table I. Physical properties of ureas and thioureas **2a–q**.

Compound	R1	R2	X	M.p. (°C)	Yield (%)	Molecular formula	Analysis (Calc./Found) C, H, N, S
2a	H	Et	O	196–198 [a]	85	$C_{15}H_{22}N_2O_4$ (294.4)	61.18, 7.53, 9.51 61.00, 7.31, 9.29
2b	H	Et	S	169–171 [c]	69	$C_{15}H_{22}N_2O_3S$ (310.4)	58.04, 7.14, 9.02, 10.33 57.79, 7.01, 9.24, 10.02
2c	Ph	Et	O	147–149 [a]	79	$C_{21}H_{26}N_2O_4$ (370.4)	68.09, 7.07, 7.56 68.28, 7.31, 7.69
2d	Ph	Bu	O	151–153 [b]	80	$C_{23}H_{30}N_2O_4$ (398.5)	69.32, 7.59, 7.03 69.11, 7.38, 6.82
2e	Ph	c-C_6H_{11}	O	165–166 [b]	81	$C_{25}H_{32}N_2O_4$ (424.5)	70.72, 7.60, 6.60 71.00, 7.41, 6.89
2f	Ph	Ph	O	159–161 [b]	82	$C_{25}H_{26}N_2O_4$ (418.5)	71.75, 6.26, 6.69 71.62, 6.12, 6.50
2g		Et	O	162–164 [a]	71	$C_{21}H_{26}N_2O_5$ (386.4)	65.27, 6.78, 7.25 65.01, 6.53, 7.02
2h		Et	S	157–159 [c]	76	$C_{21}H_{26}N_2O_4S$ (402.5)	62.66, 6.51, 6.96, 7.96 62.32, 6.25, 6.68, 7.83
2i		Bu	S	171–173 [c]	70	$C_{23}H_{30}N_2O_4S$ (430.3)	64.20, 7.02, 6.50, 7.45 64.41, 7.29, 6.78, 7.31
2j		c-C_6H_{11}	S	192–193 [c]	71	$C_{25}H_{32}N_2O_4S$ (456.5)	65.78, 7.06, 6.13, 7.02 65.51, 6.82, 6.01, 7.29
2k		Et	S	138–140 [c]	72	$C_{21}H_{27}N_3O_3S$ (401.4)	62.84, 6.78, 10.46, 7.97 62.49, 6.41, 10.22, 8.11
2l		Et	O	147–148 [a]	80	$C_{22}H_{28}N_2O_4$ (384.5)	68.72, 7.34, 7.28 68.63, 7.28, 7.34
2m		Bu	O	155–156 [a]	82	$C_{24}H_{32}N_2O_4$ (412.5)	69.88, 7.82, 6.79 69.71, 7.63, 6.61
2n		c-C_6H_{11}	O	159–161 [c]	79	$C_{26}H_{34}N_2O_4$ (438.5)	71.22, 7.81, 6.38 71.01, 7.60, 6.21
2o		Ph	O	182–184 [a]	77	$C_{26}H_{28}N_2O_4$ (432.5)	72.20, 6.52, 6.47 72.31, 6.42, 6.28
2p		Et	O	163–165 [d]	74	$C_{27}H_{36}N_2O_7$ (500.6)	64.78, 7.25, 5.60 64.49, 7.12, 5.42
2q		Ph	O	152–153 [d]	66	$C_{31}H_{36}N_2O_7$ (548.6)	67.87, 6.61, 5.10 67.99, 6.79, 4.94

[a] Ethylacetate; [b] ethylacetate/ethanol, 3:1; [c] ethylacetate/hexane, 4:1; [d] ethanol.

Table II. ^{1}H-NMR spectral data of ureas or thioureas **2a–q**.



Compound	^{1}H-NMR δ (ppm; *J* in Hz)	MS (*m/z*)
2a	0.83 (t, *J* = 7.1, 3H, CH_3), 1.19 (q, *J* = 7.0, 2H, CH_2), 2.34 (dd, *J* = 17.5, 5.1, 1H, H_a-1), 2.83 (dd, *J* = 17.5, 4.8, 1H, H_b-1), 2.92 (dd, *J* = 17.5, 3.1, 1H, H_a-4), 2.92–3.06 (m, 1H, H_b-4), 3.55–3.80, 3.70 and 3.73 (m, s and s, 8H, H-2, H-3, 2 × OCH_3), 4.96 (d, *J* = 3.4, 1H, OH), 5.73 (d, *J* = 6.0, 1H, NH), 5.84 (t, *J* = 5.4, 1H, NH), 6.7 (s, 2H, H-6, H-7).	294
2b	0.80 (t, *J* = 7.1, 3H, CH_3), 1.20 (q, *J* = 7.0, 2H, CH_2), 2.34 (dd, *J* = 17.5, 5.1, 1H, H_a-1), 2.83 (dd, *J* = 17.5, 4.8, 1H, H_b-1), 2.92 (dd, *J* = 17.5, 3.1, 1H, H_a-4), 3.18 (dd, *J* = 17.0, 5.9, 1H, H_b-4), 3.37–3.60 (m, 1H, H-3), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.11–4.36 (m, 1H, H-2), 4.96 (d, *J* = 3.4, 1H, OH), 5.73 (d, *J* = 6.0, 1H, NH), 5.84 (t, *J* = 5.4, 1H, NH), 6.7 (s, 2H, H-6, H-7).	310
2c	0.83 (t, *J* = 7.1, 3H, CH_3), 1.17 (q, *J* = 7.1, 2H, CH_2), 2.25–2.52 (m, 2H, H_a-1, H_a-4), 2.90 (dd, *J* = 17.0, 5.4, 1H, H_b-1), 3.11 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.36–3.57 (m, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.25–4.48 (m, 1H, H-2), 4.97 (d, *J* = 5.9, 1H, OH), 6.02 (t, *J* = 5.6, 1H, NH), 6.67 (s, 2H, H-6, H-7), 7.32–7.52 (m, 5H, ArH).	370
2d	0.85 (t, *J* = 7.0, 3H, CH_3), 1.24 (m, 4H, $(CH_2)_2$), 2.12–2.60 (m, H_a-1, H_a-4), 2.82 and 2.90–3.11 (dd, *J* = 17.4, 5.8, m, 3H, H_b-1, NCH_2), 3.10 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.61 (s, 3H, OCH_3), 3.70 (s, 4H, OCH_3, H-3), 4.02 (m, 1H, H-2), 4.82 (d, *J* = 4.0, 1H, OH), 6.12 (t, *J* = 6.0, 1H, NH), 6.70 (s, 2H, H-6, H-7), 7.30 (s, 5H, ArH).	398
2e	0.98–1.84 (m, 10H, $(CH_2)_5$), 2.24–2.50 (m, 2H, H_a-1, H_a-4), 2.89 (dd, *J* = 17.0, 5.3, 1H, H_b-1), 3.11 (dd, *J* = 16.9, 5.7, 1H, H_b-4), 3.45 (m, 2H, H-3 and CH of C_6H11), 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.41 (m, 1H, H-2), 4.95 (d, *J* = 5.7, 1H, OH), 5.00 (t, *J* = 5.4, 1H, NH), 6.60 (s, 2H, H-6, H-7), 7.30–7.51 (m, 5H, ArH).	424
2f	2.40–2.51 (m, 2H, H_a-1, H_a-4), 2.98 (dd, *J* = 17.3, 5.7, 1H, H_b-1), 3.15 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.65 (m, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.48 (m, 1H, H-2), 5.18 (d, *J* = 15.7, 1H, OH), 6.68 (s, 2H, H-6, H-7), 6.91 (t, *J* = 7.3, 1H, H-para of Ar), 7.19 (t, *J* = 7.3, 2H, 2 × H-meta of Ar), 7.50 and 7.30–7.50 (d, *J* = 7.3 and m, 8H, 2 × H-ortho of Ar, NH, ArH).	418
2g	0.81 (t, *J* = 7.1, 3H,CH_3), 1.19 (q, *J* = 7.1, 2H, CH_2), 2.27–2.50 (m, 2H, H_a-1, H_a-4), 2.89 (dd, *J* = 17.0, 5.4, 1H, H_b-1), 3.15 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.31–3.53 (m, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.15–4.41 (m, 1H, H-2), 5.37 (d, *J* = 5.9, 1H, OH), 6.70 (s, 2H, H-6, H-7), 6.98 (s, 1H, OH), 7.42–7.61 (m, 4H, ArH), 7.91 (t, *J* = 5.6, 1H, NH).	386
2h	0.79 (t, *J* = 7.1, 3H,CH_3), 1.20 (q, *J* = 7.1, 2H, CH_2), 2.30–2.55 (m, 2H, H_a-1, H_a-4), 2.90 (dd, *J* = 17.0, 5.4, 1H, H_b-1), 3.15 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.31–3.50 (m, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.15–4.41 (m, 1H, H-2), 5.47 (d, *J* = 5.9, 1H, OH), 6.70 (s, 2H, H-6, H-7), 6.98 (s, 1H, OH), 7.42–7.61 (m, 4H, ArH), 7.80 (t, *J* = 5.6, 1H, NH).	402
2i	0.95 (t, *J* = 7.0, 3H, CH_3), 1.22 (m, 4H, $(CH_2)_2$), 2.16–2.58 (m, H_a-1, H_a-4), 2.92 and 3.01–3.19 (dd, *J* = 17.4, 5.8, m, 3H, H_b-1, NCH_2), 3.31 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.61 (s, 3H, OCH_3), 3.72 (s, 4H, OCH_3, H-3), 4.02 (m, 1H, H-2), 5.40 (d, *J* = 5.9, 1H, OH), 6.75 (s, 2H, H-6, H-7), 7.05 (s, 1H, OH), 7.35 (s, 4H, ArH), 7.85 (t, *J* = 5.6, 1H, NH).	430
2j	0.80–1.90 (m, 10H, $(CH_2)_5$), 2.20–2.64 (m, 2H, H_a-1, H_a-4), 2.84 (dd, *J* = 17.5, 5.6, 1H, (H_b-1), 3.13 (dd, *J* = 17.5, 5.5, 1H, H_b-4), 3.35–3.51 (m, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.80–4.24 (m, 2H, H-2, CH of C_6H11), 5.46 (d, *J* = 5.9, 1H, OH), 6.68 (s, 2H, H-6, H-7), 7.01 (s, 1H, OH), 7.30 (s, 4H, ArH), 7.89 (d, *J* = 7.0, 1H, NH).	456
2k	0.80 (t, *J* = 7.0, 3H, CH_3), 1.19 (q, *J* = 7.1, 2H, CH_2), 2.28–2.50 (m, 2H, H_a-1, H_a-4), 2.89 (dd, *J* = 17.0, 5.5, 1H, H_b-1), 3.20 (dd, *J* = 17.0, 5.9, 1H, H_b-4), 3.35–3.56 (m, 1H, H-3), 3.70 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.19–4.40 (m, 1H, H-2), 5.39 (d, *J* = 5.9, 1H, OH), 5.82 (s, 2H, NH_2), 6.72 (s, 2H, H-6, H-7), 7.40–7.62 (m, 4H, ArH), 7.90 (t, *J* = 5.6, 1H, NH).	401
2l	0.82 (t, *J* = 7.1, 3H, CH_3), 1.17 (q, *J* = 7.1, 2H, CH_2), 2.38–2.63 (m, 2H, H_a-1, H_a-4), 2.94 (dd, *J* = 17.0, 5.2, 1H, H_b-1), 3.16 (dd, *J* = 17.1, 5.5, 1H, H_b-4), 3.62 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.01 (m, 1H, H-3), 4.22 (m, 1H, H-2), 4.41 (d, *J* = 17.0, 1H, CHHPh), 4.87 (d, *J* = 17.0, 1H, CHHPh), 5.09 (d, *J* = 5.3, 1H, OH), 6.69 (s, 2H, H-6, H-7), 7.40–7.62 (m, 5H, ArH), 8.35 (s, 1H, NH).	384
2m	0.80 (t, *J* = 7.0, 3H, CH_3), 1.28 (m, 4H, $(CH_2)_2$), 2.16–2.64 (m, H_a-1, H_a-4), 2.82 and 2.86–3.11 (dd, *J* = 17.4, 5.8, m, 3H, H_b-1, NCH_2), 3.10 (dd, *J* = 17.0, 5.8, 1H, H_b-4), 3.61 (s, 3H, OCH_3), 3.70 (s, 4H, OCH_3, H-3), 4.02 (m, 1H, H-2), 4.32 (d, *J* = 17.0, 1H, CHHPh), 4.71 (d, *J* = 17.0, 1H, CHHPh), 4.82 (d, *J* = 4.0, 1H, OH), 6.09 (t, *J* = 6.0, 1H, NH), 6.70 (s, 2H, H-6, H-7), 7.35 (s, 5H, ArH).	412
2n	0.80–1.90 (m, 10H, $(CH_2)_5$), 2.20–2.64 (m, 2H, H_a-1, H_a-4), 2.84 (dd, *J* = 17.5, 5.6, 1H, H_b-1), 3.13 (dd, *J* = 17.5, 5.5, 1H, H_b-4), 3.40 (m, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.80–4.24 (m, 2H, H-2, CH of C_6H11), 4.31 (d, *J* = 17.0, 1H, CHHPh), 4.68 (d, *J* = 17.0, 1H, CHHPh), 4.83 (d, *J* = 5.0, 1H, OH), 5.65 (d, *J* = 7.0, 1H, NH), 6.68 (s, 2H, H-6, H-7), 7.30 (s, 5H, ArH).	438
2o	2.38–2.63 (m, 2H, H_a-1, H_a-4), 2.94 (dd, *J* = 17.0, 5.2, 1H, H_b-1), 3.16 (dd, *J* = 17.1, 5.5, 1H, H_b-4), 3.62 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.01 (m, 1H, H-3), 4.22 (m, 1H, H-2), 4.41 (d, *J* = 17.0, 1H, CHHPh), 4.87 (d, *J* = 17.0, 1H, CHHPh), 5.09 (d, *J* = 5.3, 1H, OH), 6.69 (s, 2H, H-6, H-7), 6.89 (t, *J* = 7.2, 1H, H-para of Ar), 7.20 and 7.16–7.34 (dd, *J* = 7.2, 8.1 and m, 7H, 2 × H-meta of Ar and 5H, ArH), 7.43 (d, *J* = 8.1, 2H, 2 × H-ortho of Ar), 8.35 (s, 1H, NH).	432
2p	0.85 (t, *J* = 7.1, 3H, CH_3), 1.23 (q, *J* = 7.1, 2H, CH_2), 2.18–2.41 (m, 4H, 2 × H_a-1, 2 × H_a-4), 2.80–3.15 (m, 4H, 2 × H_b-1, 2 × H_b-4), 3.62 (s, 6H, 2 × OCH_3), 3.75 (s, 6H, 2 × OCH_3), 3.62–3.81 (m, 2H, 2 × H-3), 4.18–4.31 (m, 2H, 2 × H-2), 5.18 (s, 2H, 2 × OH), 6.11 (t, *J* = 5.6, 1H, NH), 6.70 (s, 4H, 2 × H-6, 2 × H-7).	500
2q	2.40–2.65 (m, 4H, 2 × H_a-1, 2 × H_a-4), 2.90–3.16 (m, 4H, 2 × H_b-1, 2 × H_b-4), 3.60 (s, 6H, 2 × OCH_3), 3.72 (s, 6H, 2 × OCH_3), 3.99 (m, 2H, 2 × H-3), 4.20 (m, 2H, 2 × H-2), 5.05 (d, *J* = 5.3, 2H, 2 × OH), 6.65 (s, 4H, 2 × H-6, 2 × H-7), 6.90 (t, *J* = 7.2, 1H, H-para of Ar), 7.18 and 7.22–7.38 (dd, *J* = 7.2, 8.2 and m, 2H, 2 × H-meta of Ar), 7.45 (d, *J* = 8.1, 2H, 2 × H-ortho of Ar), 8.33 (s, 1H, NH).	548

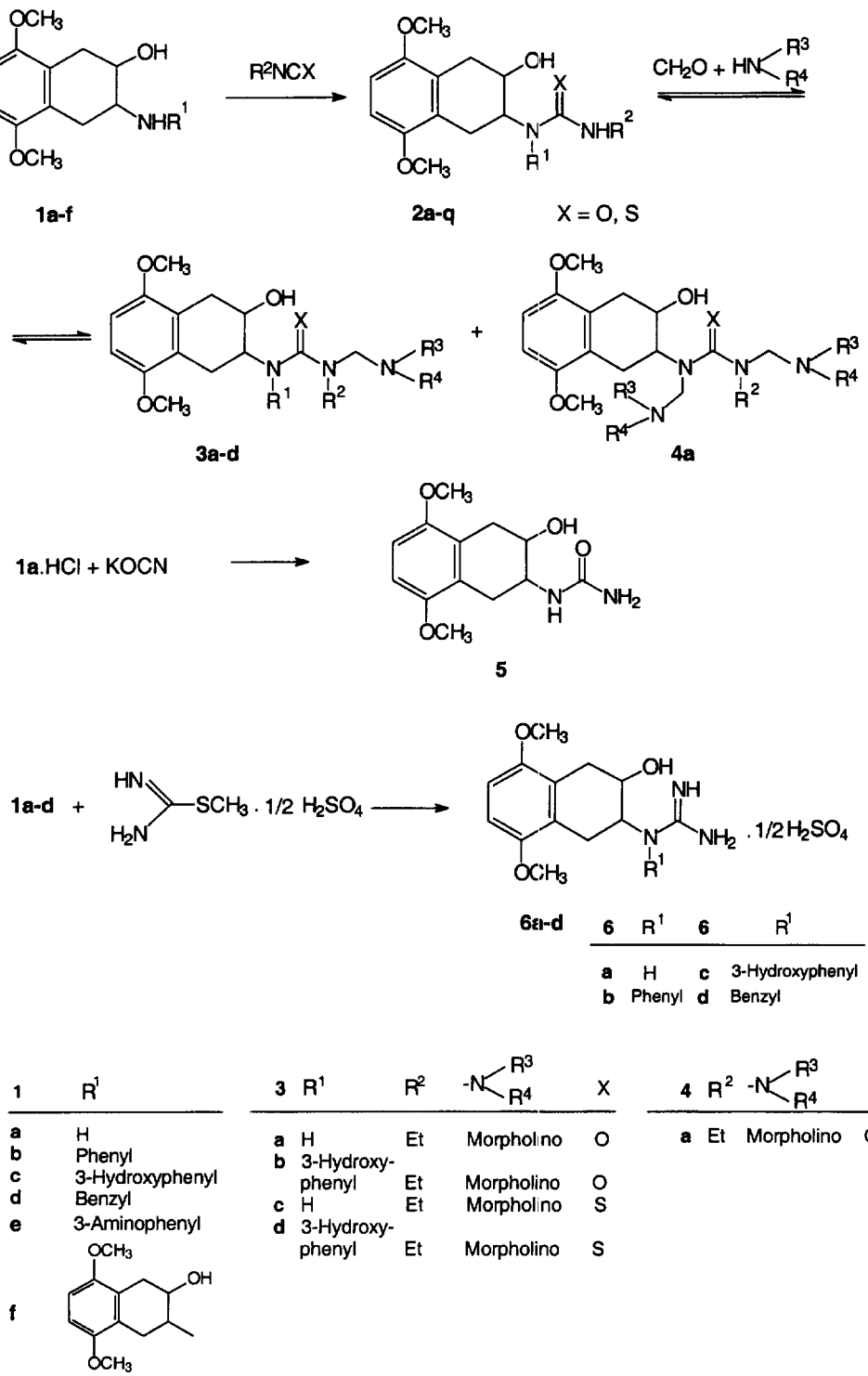

1a-f
2a-q
X = O, S
3a-d
4a
1a.HCl + KOCN
5
1a-d
6a-d
1 R1
a H
b Phenyl
c 3-Hydroxyphenyl
d Benzyl
e 3-Aminophenyl
f
3 R1 R2 X
a H Et Morpholino O
b 3-Hydroxyphenyl Et Morpholino O
c H Et Morpholino S
d 3-Hydroxyphenyl Et Morpholino S
4 R2 X
a Et Morpholino O
6 R1 6 R1
a H c 3-Hydroxyphenyl
b Phenyl d Benzyl

Figure 1.

of the latter with 33% formalin and morpholine resulted in the corresponding Mannich bases **3a–d** and **4a** (*figure 1*, experimental protocols). Mannich condensation was carried out in water or ethanol. In an aqueous solution the results obtained are unsatisfactory because of the reversibility of the process. The yields of N-mono- and N,N′-bismorpholinomethyl compounds depend mainly on the molar ratio of the initial reagents. In an excess of **2a** the process runs with a higher yield of the N-monomorpholinomethyl derivative **3a**. The yields of sulphur compounds **3c,d** are lower than those of the oxygen analogues **3a,b**. The molar ratio **2b,h**/CH_2O/morpholine, 1:2:2 was optimal for preparation of the N-monomorpholinomethyl derivatives **3c,d**. It was not possible to obtain N,N′-bismorpholinomethyl derivatives of the thioureas. This fact can be explained by a decreased nucleophilicity of the nitrogen atoms connected with thiocarbonyl group [22,23]. In the spectrum of **3c** in comparison to that of **3a** the proton of NH group appears in a weaker field. This result was in agreement with the data specified by Silverstein et al. [24]. The unsubstituted tetrahydronaphthalenylurea **5** was prepared from aminotetrahydronaphthalene **1a** hydrochloride by treatment with potassium cyanate. In order to obtain 1,2,3,4-tetrahydro-3-naphthalenyl guanidine sulphates **6a–d** the reaction of **1a–d** with 2-methylisothiourea sulphate was used [18] (*figure 1*, experimental protocols).

3. Pharmacology

The compounds were examined for acute toxicity on mice by intraperitoneal administration. They were screened with the norepinephrine arrhythmia test in rats, with the control group treated simultaneously with each compound. The effect of the compounds on arterial blood pressure was investigated. These studies were carried out on anesthetised rats. Propranolol was used as reference compound.

4. Results and discussion

Analysis of the experimental data for the acute toxicity (LD_{50}) showed that the tested compounds, except for **2f,k,o**, have lower toxicity compared to Propranolol ($p \leq 0.05$, *table III*). Compounds **2h,i,q** exhibited a toxicity similar to Propranolol.

The results of the hypotensive and antiarrhythmic activities are presented in *tables IV* and *V*, respectively. Compounds **2a,l,m,n**, **3a**, **4a** and **6a** all reduced the blood pressure in the rats by more than 30% after i.v. administration in doses of one hundredth of the LD_{50}. The highest activity was displayed by compound **3a** (NR_2 = morpholino). Its hypotensive activity is comparable to that of Propranolol.

Table III. Acute toxicity (LD_{50}) of the compounds.

Compound	LD_{50} (mg/kg, i.p.) and 95% confidence interval
Propranolol	102.8 (82.9–116.1)
2a	302.8 [a] (226.7–387.6)
2b	355.7 [a] (301.4–389.9)
2c	135.6 [a] (110.3–209.8)
2d	130.8 [a] (112.9–148.7)
2e	160.7 [a] (129.1–172.8)
2f	96.7 (83.8–112.1)
2g	171.2 [a] (160.8–179.2)
2h	109.8 (81.8–123.5)
2i	101.4 (88.6–112.6)
2j	155.2 [a] (123.7–177.8)
2k	99.2 (87.8 –120.7)
2l	132.7 [a] (115.8–150.1)
2m	138.1 [a] (117.6–147.9)
2n	151.8 [a] (127.1–179.2)
2o	97.8 (91.2–109.6)
2p	160.2 [a] (121.7–204.8)
2q	119.8 (86.2–187.7)
3a	287.8 [a] (231.7–391.6)
3b	184.7 [a] (140.6–304.1)
3c	204.7 [a] (150.8–318.7)
3d	156.3 [a] (129.1–247.7)
4a	251.9 [a] (202.1–307.6)
5	205.2 [a] (138.4–267.3)
6a	187.9 [a] (130.8–303.4)
6b	152.4 [a] (116.6–263.4)
6c	141.8 [a] (119.6–197.3)
6d	148.9 [a] (120.2–218.7)

[a] $p \leq 0.05$, statistically significant differences compared to Propranolol.

Compounds **2a**, **3a,b**, **4a** and **6d** inhibited distinctly norepinephrine-induced arrhythmia in the rats after i.v. application. The activity was statistically significant ($p \leq 0.05$) in comparison to the control group. Among these compounds **3a** manifested the greatest activity. The antiarrhythmic effect of this compound is similar to the effect of Propranolol.

With regard to structure–activity relationships, several points are worth noting. Disubstituted urea **2a** (R^1 = H) or thiourea **2b** (R^1 = H) and the corresponding Mannich bases **3a,c** (R^1 = H) showed a low toxicity. Trisubstituted ureas **2c–g,l–o** or thioureas **2h–k** and Mannich bases **3b,d**, which contain phenyl, substituted phenyl or benzyl as R^1, were more toxic.

A precondition of the favourable hypotensive activity is that R^1 should be hydrogen (**2a**, **3a**, **6a**). When R^1 was

Table IV. Hypotensive effect of the compounds.

Compound	Dose one hundredth of LD_{50} (mg/kg, i.v.)	X ± SD [a] ($n = 6$)	Duration of the hypotensive effect (min)
Propranolol	1.03	45 ± 1.4	21 ± 2.6
2a	3.03	44 ± 2.1	20 ± 2.1
2b	3.56	11 ± 1.8	18 ± 1.8
2c	1.35	26 ± 2.3	15 ± 1.6
2d	1.31	20 ± 1.9	14 ± 1.7
2e	1.61	18 ± 1.4	9 ± 1.5
2f	0.97	10 ± 2.1	11 ± 1.7
2g	1.71	22 ± 1.1	17 ± 1.3
2h	1.10	9 ± 2.3	7 ± 1.2
2i	1.01	8 ± 1.7	15 ± 1.4
2j	1.55	9 ± 2.4	13 ± 2.3
2k	1.00	8 ± 1.9	10 ± 1.8
2l	1.32	38 ± 2.2	16 ± 1.4
2m	1.38	32 ± 1.7	20 ± 1.9
2n	1.51	40 ± 1.1	21 ± 2.4
2o	0.98	15 ± 2.4	7 ± 1.1
2p	1.60	5 ± 2.7	12 ± 1.2
2q	1.20	4 ± 3.1	10 ± 1.1
3a	2.88	46 ± 2.1	22 ± 2.3
3b	1.85	30 ± 1.5	19 ± 1.4
3c	2.05	14 ± 1.9	25 ± 1.7
3d	1.56	18 ± 2.7	5 ± 1.1
4a	2.52	36 ± 2.2	18 ± 1.2
5	2.05	11 ± 1.7	11 ± 1.5
6a	1.88	14 ± 1.9	12 ± 1.4
6b	1.52	19 ± 2.3	8 ± 1.5
6c	1.42	20 ± 2.8	10 ± 1.8
6d	1.49	35 ± 3.1	18 ± 2.1

[a] Mean percentage decrease of lowering blood pressure ± SD, compared with the initial value; n = number of determinations.

benzyl (**2l,m,n**), the activity was weaker. The hypotensive effect was decreased additionally when R^1 was phenyl or hydroxyphenyl (**2c–g**).

Introduction of a morpholinomethyl group at the second urea N-atom gave a product with a promising activity (**3a**; R′ = H). However, a decrease in activity was noted when two nitrogen atoms of urea moiety was substituted by morpholinomethyl groups (**4a**). All sulphur analogues showed a lower hypotensive activity.

5. Conclusion

The results of the screening tests showed that the introduction of the 1-alkyl- or 1-alkyl-1-morpholinomethylurea moiety at the 2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene afforded agents with pronounced hypotensive and antiarrhythmic effects. The most promising members were compounds **2a** and **3a**. Their hypotensive effects were comparable to that of Propranolol at equitoxic doses, when tested in anesthetized rats. However, they inhibited considerably norepinephrine-induced arrhythmia in the rats and showed lower toxicity compared to Propranolol. Compounds **2a** and **3a** were selected for further evaluations as antiarrhythmics or antihypertensives.

6. Experimental protocols

6.1. Chemistry

Melting points were determined using a Boetius hot plate microscope and are uncorrected. IR spectra (nujol, $CHCl_3$) were recorded on a UR 20, Karl Zeiss, Jena apparatus. ^{1}H-NMR spectra were recorded on a Brucker 250 WM (250 MHz) spectrometer in deuteriated dimethylsulphoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a LKB 2091 mass spectrometer. Microanalyses were performed by Microanalytical Unit, Chemical and Pharmaceutical Research Institute, Sofia and the results obtained were within ±0.4% of the theoretical values.

*6.1.1. 1,1,3-Trisubstituted ureas or thioureas **2a–q***

A solution of the appropriate isocyanate or isothiocyanate (20 mmol) in anhydrous THF (15 mL) was added dropwise to a solution of the appropriate amine (20 mmol) in anhydrous THF (25 mL). The resulting mixture was refluxed for 3–4 h and the solvent was evaporated in vacuum to give the crude ureas or thioureas **2a–q**, which were purified by recrystallization from the solvents indicated in *table I*.

*6.1.2. 3-Ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-3-morpholinomethylurea **3a***

A solution of 2.6 mL (30 mmol) of 33% formalin and 2.58 g (30 mmol) of morpholine in 20 mL of ethanol was added dropwise to a solution of 8.83 g (30 mmol) of **2a** in 30 mL ethanol with stirring over a period of 30 min. The stirring was continued for 2 h at 50 °C. The solvent was evaporated in vacuum. The residue was boiled with ethylacetate. The undissolved **2a** was filtered, **3a** precipitated at addition of hexane and was recrystallized from an ethylacetate/hexane mixture. Yield 8.14 g (69%), m.p. 148–151 °C. IR (cm^{-1}, nujol): 3380–3220 (νOH, NH), 1670 (νC=O), 1110 (νC–O–C). ^{1}H-NMR δ: 0.97 (t, J = 7.1, 3H, CH_3), 1.20 (q, J = 7.1, 2H, CH_2), 2.26 (dd, J = 17.3, 5.0, 1H, H_a-1), 2.49–2.64 (m, 4H, NCH_2 morpholine), 2.75 (dd, J = 17.3, 4.8, 1H, H_b-1), 2.80 (dd, J = 17.5, 3.1, 1H, H_a-4), 2.91–3.02 (m, 1H, H_b-4), 3.52–3.78 (m, 8H, H-2, H-3, 2 × OCH_3), 3.92–4.08 (m, 4H, OCH_2 morpholine), 4.25 (s, 2H, NCH_2N), 4.98 (d, J = 3.4, 1H, OH), 5.79 (s, 1H, NH), 6.9 (s, 2H, H-6, H-7). Anal. $C_{20}H_{31}N_3O_5$ (393.5). Calc.: C, 61.04; H, 7.94; N, 10.67. Found: C, 61.29; H, 8.12; N, 10.43.

*6.1.3. 3-Ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-1-(3-hydroxyphenyl)-3-morpholinomethylurea **3b***

The title compound was prepared in a similar way as described for **3a** starting from **2g**. Yield 65%; m.p. 136–138 °C (acetonitrile).

Table V. The effect of the compounds on norepinephrine-induced arrhythmia.

Compound	Dose one hundredth of LD_{50} (mg/kg)	Latent time of arrhythmia [a] (s)	Duration of arrhythmia [a] (s)	Full recovery period [a] (s)
Control [b]		7.0 ± 1.2	59 ± 1.7	452 ± 9.5
Propranolol	1.03	16.2 ± 1.3 [c]	31.9 ± 2.6 [c]	117.3 ± 12.1 [c]
2a	3.03	12.7 ± 1.2 [c]	41.3 ± 3.8 [c]	138.1 ± 11.8 [c]
2b	3.56	9.1 ± 2.7	52.8 ± 1.5 [c]	447.1 ± 15.9
2c	1.35	10.7 ± 1.3 [c]	50.7 ± 1.9 [c]	385.1 ± 4.8 [c]
2d	1.31	10.3 ± 1.1 [c]	57.1 ± 2.1	401.9 ± 12.3 [c]
2e	1.61	9.5 ± 1.9	56.7 ± 2.7	448.7 ± 15.8
2f	0,97	11.1 ± 1.7 [c]	45.6 ± 1.9 [c]	391 ± 17.5 [c]
2g	1.71	8.5 ± 2.9	52.7 ± 4.7	438.1 ± 24.1
2h	1.10	9.8 ± 2.2	51.1 ± 5.7	421.9 ± 22.9
2i	1.01	8.7 ± 1.7	55.3 ± 2.4	432.7 ± 27.1
2j	1.55	7.9 ± 1.5	52.8 ± 1.6 [c]	449.1 ± 12.8
2k	1.00	7.2 ± 1.6	50.9 ± 2.8 [c]	399.2 ± 21.7
2l	1.32	11.8 ± 2.1 [c]	49.1 ± 3.1 [c]	256.1 ± 12.6 [c]
2m	1.38	11.4 ± 2.2 [c]	47.2 ± 2.8 [c]	287.1 ± 15.5 [c]
2n	1.51	10.1 ± 1.1 [c]	42.8 ± 3.5 [c]	307.9 ± 10.7 [c]
2o	0,98	9.8 ± 1.1 [c]	51.9 ± 5.2	441.8 ± 21.7
2p	1.60	7.2 ± 1.8	54.9 ± 3.9	431.2 ± 10.6
2q	1.20	7.6 ± 1.6	55.1 ± 4.1	429.9 ± 17.8
3a	2.88	15.8 ± 2.1 [c]	30.2 ± 1.8 [c]	116.4 ± 15.2 [c]
3b	1.85	12.2 ± 1.8 [c]	38.2 ± 2.5 [c]	140.5 ± 12.1 [c]
3c	2.05	10.8 ± 1.3 [c]	47.9 ± 2.1 [c]	398.2 ± 7.8 [c]
3d	1.56	10.7 ± 1.2 [c]	42.2 ± 1.8 [c]	415.8 ± 13.6 [c]
4a	2.52	11.8 ± 1.2 [c]	42.3 ± 1.9 [c]	155.1 ± 7.8 [c]
5	2.05	7.9 ± 2.2	57.1 ± 2.2	417.8 ± 12.8 [c]
6a	1.88	9.1 ± 1.9	56.1 ± 1.9	438.2 ± 25.2
6b	1.52	10.3 ± 2.5	50.2 ± 2.6 [c]	441.8 ± 15.6
6c	1.42	11.1 ± 1.1 [c]	50.1 ± 1.7 [c]	256.8 ± 12.1 [c]
6d	1.49	12.3 ± 2.1 [c]	40.2 ± 1.5 [c]	147.8 ± 7.9[c]

[a] n = number of determinations = 6; [b] for control experiments, saline with 1–2 drops of Tween 80 was used in equivalent volume; in the cases of water-soluble compounds **6a–d** only saline was used; [c] $p \leq 0.05$, statistically significant differences compared to the control group.

^{1}H-NMR (CD_3CN) δ: 0.83 (t, J = 7.1, 3H, CH_3), 1.21 (q, J = 7.1, 2H, CH_2), 2.25–2.50 (m, 2H, H_a-1, H_a-4), 2.50–2.62 (m, 4H, NCH_2 morpholine), 2.89 (dd, J = 17.0, 5.4, 1H, H_b-1), 3.14 (dd, J = 17.0, 5.8, 1H, H_b-4), 3.30–3.55 (m, 1H, H-3), 3.62 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.90–4.05 (m, 4H, OCH_2 morpholine), 4.15–4.30 (m, 3H, H-2, NCH_2N), 5.35 (d, J = 5.9, 1H, OH), 6.73 (s, 2H, H-6, H-7), 6.96 (s, 1H, OH), 7.45–7.64 (m, 4H, ArH). Anal. $C_{26}H_{35}N_3O_6$ (485.6). Calc.: C, 64.30; H, 7.26; N, 8.65. Found: C, 64.42; H, 7.09; N, 8.47.

6.1.4. 3-Ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-3-morpholinomethylthiourea ***3c***

A solution of 6.21 g (20 mmol) of **2b** in 20 mL of methanol was added to a solution of 3.4 mL (40 mmol) of 33% formalin and 3.44 g (40 mmol) of morpholine in 15 mL of methanol. The mixture was boiled for 3 h. The methanol was evaporated in vacuum. The product was recrystallized from ethanol. Yield 4.5 g (55%); m.p. 166–169 °C. ^{1}H-NMR δ: 0.83 (t, J = 7.1, 3H, CH_3), 1.19 (q, J = 7.1, 2H, CH_2), 2.29 (dd, J = 17.3, 5.1, 1H, H_a-1), 2.50–2.66 (m, 4H, NCH_2 morpholine), 2.71 (dd, J = 17.3, 4.8, 1H, H_b-1), 2.80 (dd, J = 17.5, 3.1, 1H, H_a-4), 2.90–3.10 (m, 1H, H_b-4), 3.52–3.83 (m, 8H, H-2, H-3, 2 × OCH_3), 3.90–4.05 (m, 4H, OCH_2 morpholine), 4.27 (s, 2H, NCH_2N), 5.01 (d, J = 3.4, 1H, OH), 6.95 (s, 1H, NH), 7.20 (s, 2H, H-6, H-7). Anal. $C_{20}H_{31}N_3O_4S$ (409.5). Calc.: C, 58.67; H, 7.63; N, 10.25; S, 7.83. Found: C, 58.51; H, 7.41; N, 10.11; S, 7.52.

6.1.5. 3-Ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-1-(3-hydroxyphenyl)-3-morpholinomethylthiourea ***3d***

The title compound was prepared in a similar way as described for **3c** starting from **2h**. Yield 53%; m.p. 158–160 °C (ethanol). ^{1}H-NMR (CD_3CN) δ: 0.82 (t, J = 7.1, 3H, CH_3), 1.20 (q, J = 7.1, 2H, CH_2), 2.26–2.42 (m, 2H, H_a-1, H_a-4), 2.50–2.64 (m, 4H, NCH_2 morpholine), 2.90 (dd, J = 17.0, 5.4, 1H, H_b-1), 3.14 (dd, J = 17.1, 5.9, 1H, H_b-4), 3.30–3.51 (m, 1H, H-3), 3.62 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.89–4.06 (m, 4H, OCH_2 morpholine), 4.15–4.40 (m, 3H, H-2, NCH_2N), 5.39 (d, J = 5.9, 1H, OH), 6.70 (s, 2H, H-6,

H-7), 6.98 (s, 1H, OH), 7.40–7.60 (m, 4H, ArH). Anal. $C_{26}H_{35}N_3O_5S$ (501.6). Calc.: C, 62.25; H, 7.03; N, 8.37; S, 6.38. Found: C, 62.49; H, 6.90; N, 8.18; S, 6.75.

6.1.6. 3-Ethyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-1,3-bismorpholinomethylurea ***4a***

The title compound was prepared in a similar way as described for **3c** from 4.42 g (15 mmol) of **2a**, 2.87 mL (33 mmol) of 33% formalin and 2.84 g (33 mmol) of morpholine. Yield 5.39 g (73%); m.p. 131–133 °C (ethylacetate). IR (cm^{-1}, $CHCl_3$) 3420–3350 (νOH), 1680 (νC=O), 1115 (νC–O–C). ^{1}H-NMR (CD_3CN) δ: 0.83 (t, J = 7.1, 3H, CH_3), 1.19 (q, J = 7.1, 2H, CH_2), 2.31 (dd, J = 17.3, 5.1, 1H, H_a-1), 2.45–2.60 (m, 8H, NCH_2 morpholine), 2.73 (dd, J = 17.3, 4.8, 1H, H_b-1), 2.83 (dd, J = 17.5, 3.1, 1H, H_a-4), 2.91–3.04 (m, 1H, H_b-4), 3.54–3.80 (m, 8H, H-2, H-3, 2 × OCH_3), 3.92–4.06 (m, 8H, OCH_2 morpholine), 4.18 (s, 2H, NCH_2N), 4.30 (s, 2H, NCH_2N), 4.96 (d, J = 3.4, 1H, OH), 7.0 (s, 2H, H-6, H-7). Anal. $C_{25}H_{40}N_4O_6$ (492.6). Calc.: C, 60.95; H, 8.18; N, 11.37. Found: C, 60.81; H, 8.00; N, 11.62.

6.1.7. 1-(2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)urea ***5***

Aqueous solution of **1a** hydrochloride [20] (2.60 g, 10 mmol) was mixed with potassium cyanate (0.81 g, 10 mmol) under cooling. The mixture was stirred for 1 h at 20 °C. The precipitated urea **5** was filtered, washed with water and recrystallized from ethylacetate. Yield 2.4 g (90%); m.p. 175–178 °C. ^{1}H-NMR δ: 2.31 (dd, J = 17.2, 5.1, 1H, H_a-1), 2.88 (dd, J = 17.5, 4.8, 1H, H_b-1), 2.95 (dd, J = 17.6, 3.3, 1H, H_a-4), 3.20 (dd, J = 17.1, 5.9, 1H, H_b-4), 3.20 (dd, J = 17.1, 5.9, 1H, H_b-4), 3.40–3.61 (m, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.08–4.29 (m, 1H, H-2), 5.05 (d, J = 5.8, 1H, OH), 5.80 (d, J = 6.1, 1H, NH), 5.86 (t, J = 5.5, 2H, NH_2), 6.9 (s, 2H, H-6, H-7), IR (cm^{-1}, nujol) 3450–3350 (νOH, NH), 3300 and 3190 (νNH_2), 1670 (νC=O), 1050 (νC–O–C). Anal. $C_{13}H_{18}N_2O_4$ (266.3). Calc.: C, 58.63; H, 6.81; N, 10.51. Found: C, 58.41; H, 6.70; N, 10.37.

6.1.8. 1-(2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)guanidine sulphate ***6a***

A solution of 10 mmol of 2-methylisothiourea sulphate in 5 mL of H_2O was added to a solution of 10 mmol of **1a** in 5 mL of ethanol. The reaction mixture was refluxed for 2 h, then it was cooled to room temperature, acetone was added and the resulting solid was recrystallized from ethanol/water mixture to yield 2.01 g (64%) of **6a**; m.p. 181–184 °C. IR (cm^{-1}, nujol) 1690, 1650 ([–NH– (C=NH)–NH_3]$^+$. Anal. $C_{13}H_{19}N_3O_3 \bullet 1/2H_2SO_4$ (314.29). Calc.: C, 49.68; H, 6.09; N, 13.36; S, 5.09. Found: C, 49.41; H, 5.92; N, 13.11; S, 4.81.

Displacement of the sulphate salt by K_2CO_3 in water gave the free base **6'a**, m.p. 119–122 °C (ethylacetate/ethanol). ^{1}H-NMR δ: 2.18–2.50 (m, 2H, H_a-1, H_a-4), 2.83 (dd, J = 17.1, 5.4, 1H, H_b-1), 3.15 (dd, J = 17.0, 5.8, 1H, H_b-4), 3.28–3.51 (m, 1H, H-3), 3.62 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.20–4.45 (m, 1H, H-2), 5.02 (d, J = 5.8, 1H, OH), 6.10–6.32 (m, 3H, NH_2, NH), 6.52 (s, 1H, NH), 6.90 (s, 2H, H-6, H-7).

6.1.9. 1-(2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-1-phenylguanidine sulphate ***6b***

By analogy with **6a**, respectively **6'a**, from 10 mmol of **1b** and 10 mmol of 2-methylisothiourea sulphate. **6b**: yield 2.69 g (69%), m.p. 192–194 °C. IR (cm^{-1}, nujol) 1687, 1655 ([–NH–(C=NH)–NH_3]$^+$. Anal. $C_{19}H_{23}N_3O_3 \bullet 1/2H_2SO_4$ (390.39). Calc.: C, 58.46; H, 5.94; N, 10.76; S, 4.11. Found: C, 58.21; H, 5.70; N, 10.61; S, 3.93.

6'b: m.p. 139–141 °C (ethylacetate). ^{1}H-NMR δ: 2.20–2.48 (m, 2H, H_a-1, H_a-4), 2.85 (dd, J = 17.0, 5.4, 1H, H_b-1), 3.11 (dd, J = 17.0, 5.8, 1H, H_b-4), 3.30–3.51 (m, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.21–4.45 (m, 1H, H-2), 4.97 (d, J = 5.8, 1H, OH), 6.00–6.27 (m, 3H, NH_2, NH), 6.70 (s, 2H, H-6, H-7), 7.34–7.50 (m, 5H, ArH). MS (*m/z*) 341.

6.1.10. 1-(2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-1-(3-hydroxyphenyl) guanidine sulphate ***6c***

By analogy with **6a**, respectively **6'a**, from 10 mmol of **1c** and 10 mmol of 2-methylisothiourea sulphate. **6c**: yield 2.52 g (61%), m.p. 176–179 °C (ethanol/water, 3:1). IR (cm^{-1}, nujol) 1685, 1650 ([–NH–(C=NH)–NH_3]$^+$. Anal. $C_{19}H_{23}N_3O_4 \bullet 1/2H_2SO_4$ (406.39). Calc.: C, 56.16; H, 5.70; N, 10.33; S, 3.94. Found: C, 55.91; H, 5.61; N, 10.22; S, 3.78. **6'c**: m.p. 145–147 °C (ethylacetate/ethanol). ^{1}H-NMR δ: 2.21–2.51 (m, 2H, H_a-1, H_a-4), 2.81 (dd, J = 17.0, 5.4, 1H, H_b-1), 3.18 (dd, J = 17.2, 5.8, 1H, H_b-4), 3.25–3.52 (m, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.25–4.51 (m, 1H, H-2), 5.10 (d, J = 5.8, 1H, OH), 5.79 (s, 1H, OH), 6.09–6.28 (m, 3H, NH_2, NH), 6.85 (s, 2H, H-6, H-7), 7.35–7.52 (m, 4H, ArH).

6.1.11. 1-Benzyl-1-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthalenyl)-guanidine sulphate ***6d***

By analogy with **6a,** respectively **6'a**, from 10 mmol of **1d** and 10 mmol of 2-methylisothiourea sulphate. **6d**: yield 2.83 g (70%), m.p. 168–170 °C (ethanol/water, 3:1). IR (cm^{-1}, nujol) 1690, 1655 ([–NH–(C=NH)–NH_3]$^+$. Anal. $C_{20}H_{25}N_3O_3 \bullet 1/2H_2SO_4$ (404.42). Calc.: C, 59.40; H, 6.23; N, 10.39; S, 3.96. Found: C, 59.29; H, 6.15; N, 10.25; S, 3.62.

6'd: m.p. 133–135 °C (ethylacetate). ^{1}H-NMR δ: 2.17–2.49 (m, 2H, H_a-1, H_a-4), 2.76 (dd, J = 17.0, 5.4, 1H, H_b-1), 3.20 (dd, J = 17.0, 5.8, 1H, H_b-4), 3.18–3.49 (m, 1H, H-3), 3.58 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.21–4.48 (m, 1H, H-2), 4.31 (d, J = 17.1, 1H, CHHPh), 4.69 (d, J = 17.0, 1H, CHHPh), 5.01 (d, J = 5.8, 1H, OH), 5.98–6.29 (m, 3H, NH_2, NH), 6.70 (s, 2H, H-6, H-7), 7.35–7.52 (m, 5H, ArH).

6.2. Pharmacology

6.2.1. Acute toxicity

The experiments were conducted on white male mice with body weight 20–25 g. Acute toxicity (LD_{50}) of water soluble compounds was assessed by dissolving them in saline (0.9% NaCl). The water insoluble compounds were dissolved in saline with 1–2 drops of Tween 80. The substances were administered to mice via intraperitoneal (i.p.) route. The percentage mortality within 7 days was noted. LD_{50} was evaluated for 5 different doses, each on the 6 animals and calculated by the method of Litchfield–Wilcoxon [25].

6.2.2. Antiarrhythmic effect

Cardiac arrhythmia was induced by intravenous (i.v.) administration of norepinephrine (0.01 mg) [26] into anesthetized (Nembutal 30 mg/kg, i.v.) male Wistar rats. The compounds were applied i.v. in dose one hundredth of LD_{50} 5 min before to application of

norepinephrine. The ECG-IInd lead was recorded on Transistor-Electrocardiograf-NEK 215 (Germany), starting immediately after norepinephrine injection. The substance-induced delay in the appearance of the arrhythmias was determined and compared to the control group of rats pretreated with physiological saline with 1 or 2 drops of Tween 80 or with saline only when water soluble compounds were investigated. The duration of arrhythmia and the full recovery period were also measured. Each group consisted of 6 animals.

6.2.3. Hypotensive effect

Male Wistar rats (body weight 265–290 g) were anesthetized with Nembutal. The compounds ($n = 6$ for each compound) were administered i.v. in dose one hundredth of LD_{50} and arterial blood pressure was measured indirectly on the tails of rats on 'Indirect Blood Pressure Meter LE 5002' (Hungary). The mean ($X \pm SD$) percentage decrease of blood pressure from the initial value was determined. The duration of lowered blood pressure were also measured.

6.2.4. Statistical analyses

The results of pharmacological experiments underwent statistical processing by the Student–Fisher t-test at $P \leq 0.05$.

References

[1] Itoh K., Lotohashi M., Sugihara H., Oka Y., Chem. Pharm. Bull. 11 (1977) 2917–2922.

[2] Itoh K., Mijake A., Hirata N., Oka Y., Chem. Pharm. Bull. 32 (1984) 130–135.

[3] Mijake A., Itoh K., Tada N., Tanabe M., Hirata N., Oka Y., Chem. Pharm. Bull. 31 (1983) 2329–2333.

[4] Schwender C., Faber S., Blaum C., Shavel I., J. Med. Chem. 13 (1970) 684–689.

[5] Condon M., Cimarusti Ch., Fox R., Narayanan V., Reid J., Hauck F., J. Med. Chem. 21 (1978) 913–920.

[6] Christova K., Dantchev D., Arch. Pharm. (Weinheim) 311 (1978) 948–952.

[7] Christova K., Dantchev D., Staneva D., Rainova L., Arch. Pharm. (Weinheim) 317 (1984) 829–834.

[8] Cleophas T., Van Der May N., Van Der Meulen J., Nilmeyer M., Int. J. Clin. Pharmacol. Ther. 34 (1996) 312–317.

[9] Ranise A., Bondavalli F., Schenone R., Angrisani M., Lisa M., Marrazo R., Marmo E., Farmacol. Ed. Sci. 43 (1988) 79–89.

[10] Augsheim J., Green S., Wrigley M., J. Med. Chem. 10 (1967) 391–396.

[11] Bream J., Picard C., White T., J. Med. Chem. 13 (1970) 1051–1057.

[12] Serafin B., Borkowska G., Glowczyk J., Kowalska I., Runp S., Pol. J. Pharmacol. Pharm. 41 (1989) 89–96.

[13] Turner S., Myers M., Gadie B., Hale S., Horsley A., Nelson A., Pape P., Saville J., Doxey J., Berridge I., J. Med. Chem. 31 (1988) 906–913.

[14] Eda M., Takemoto T., Okada T., Sakashita H., Matzo S., Gohda M., Hayashi J., Nakamura N., Fukaya Ch., Chem. Pharm. Bull. 44 (1996) 307–313.

[15] Pascal J.C., Pinhas H., Laure F., Dumez D., Poizot A., Eur. J. Med. Chem. 25 (1990) 81–85.

[16] Érczit I., Rablóczky G., Varró A., Somogy I.G., Kürthy M., Bódy I., Eur. J. Med. Chem. 28 (1993) 185–193.

[17] Alonzo D., Albert J., Hess T., Darbenzio R., Raymond B., Sewter J., J. Cardiovascular Pharmacol. 21 (1993) 677–683.

[18] Chalina E., Dantchev D., Georgiev A., Staneva D., Arch. Pharm. (Weinheim) 317 (1984) 63–69.

[19] Chalina E., Chakarova L., Staneva D., Eur. J. Med. Chem. 33 (1998) 985.

[20] Dantchev D., Christova K., Staneva D., Rainova L., Tchakarova L., Arch. Pharm. (Weinheim) 310 (1977) 369–371.

[21] Trippetta L., Orazi O., Corral R., An. Asoc. Quim. Argent. 51 (1965) 49–52.

[22] Kumber W.D., Fohlen G.M., J. Am. Chem. Soc. 64 (1942) 1944–1946.

[23] Lee C.M., Kumber W.K., J. Org. Chem. 27 (1962) 2052–2054.

[24] Silverstein R.M., Bassler G.C., In: Spectrometric Identification of Organic Compounds, 2nd ed., Wiley, New Jork, 1964, p. 74.

[25] Litchfield J.I., Wilcoxon F., J. Pharmacol. Exp. Ther. 96 (1949) 99–102.

[26] Szekeres L., Papp G., Experimental Cardiac Arrhythmias and Antiarrhythmic Drugs, Akademiai, Budapest, 1971.