COMPOUNDS INTERACTING WITH THE NEUROEXCITATORY AMINO ACIDS: SYNTHESIS OF 2-(4-ARALKYLPIPERAZINE-1-YL)-1-ARYLETHANOLS

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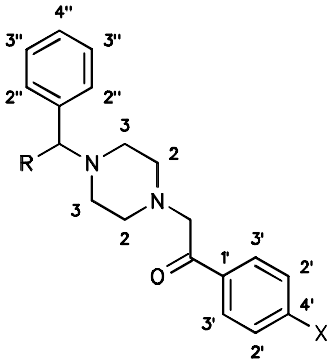
Amino ketones *Ia – If* and *III* were synthesized. Their reduction gave corresponding alcohols *IIa – IIf*, *IVa* and *IVb*. These were evaluated by methods of biochemical and behavioural pharmacology.

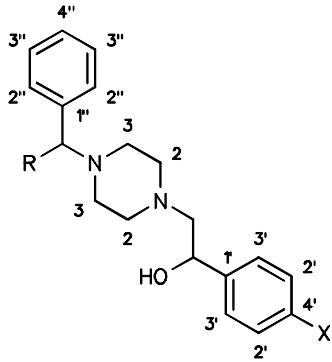
Within the program of synthesis of agents with neuroprotective action, the work was concentrated to compounds interacting selectively with the individual subtypes of neuroexcitatory amino acid receptors. In addition to substances with affinity to the quisqualate receptor, for which neurotropic effects against consequences of ischemia are assumed[1], also compounds having affinity to the glycine binding site on the NMDA receptor complex were searched after. For the last type of compounds one could expect anticonvulsant activity, a positive influence on memory and learning processes, and even antipsychotic effects[2,3,4]. In connection with a broader program of preparation of agents of this type, 2-(4-aralkylpiperazine-1-yl)-1-arylethanols were investigated which are the object of this communication.

The amino ketones *Ia – If* and *III* were obtained by alkylation reactions of 1-benzylpiperazine, 1-benzhydrylpiperazine[5,6] and 1-(6,11-dichydrodibenzo[*b,e*]thiepin-11-yl)-piperazine[7] with 4-fluorophenacyl chloride, 4-chloro- and 4-bromophenacyl bromide in tetrahydrofuran in the presence of triethylamine. Their reduction with sodium borohydride in ethanol resulted in the desired amino alcohols *IIa – IIf*, *IVa* and *IVb* obtained in yields of 71 – 93%. For pharmacological testing, the bases were transformed into water-soluble salts with pharmacologically acceptable acids (hydrochlorides, methanesulfonates, fumarates) and these were evaluated by methods of biochemical and behavioural pharmacology.

The following biochemical methods were used: (i) inhibition of binding of [^{3}H]5,7-dichlorokynurenic acid in rat brain cortex membrane protein (the glycine binding site of the NMDA receptor complex), (ii) inhibition of binding of [^{3}H]MK-801 in the rat brain cortex (the ionic channel coupled with the NMDA receptor), and (iii) inhibition

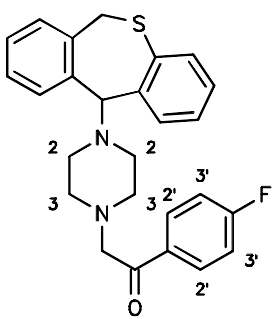


I

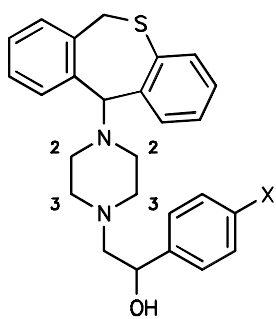


II

In formulae *I* and *II*: ***a***, X = F; R = H
b, X = Cl; R = H
c, X = Br; R = H
d, X = F; R = C_6H_5
e, X = Cl; R = C_6H_5
f, X = Br; R = C_6H_5



III



IVa, X = F
IVb, X = Cl

of binding of [^{3}H]mepyramine in the guinea pig cerebellum (interaction with the H_1 receptor).

The following results were obtained: Inhibition of binding of 3.5 nM [^{3}H]5,7-dichlorokynurenic acid (100 μg of the membrane protein from the rat brain cortex, the compounds used in a concentration of 100 nM; inhibition of the original binding in % is given): *IIa*, 42; *IIb*, 33; *IIc*, 19; *IIf*, 25; the remaining compounds were inactive. Inhibition of binding of 1 nM [^{3}H]MK-801 in the rat brain cortex (compounds used in a concentration of 1 000 nM; inhibition of the original binding in % or the IC_{50} values in μM given): *IIb*, 51; *IIc*, 89; *IId*, IC_{50} = 52.7; *IIe*, IC_{50} = 73.7; *IIf*, IC_{50} = 43.9; *IVa*, IC_{50} = 35; *IVb*, IC_{50} = 43; the remaining compounds were inactive. Inhibition of binding of 2 nM [^{3}H]mepyramine in the guinea pig cerebellum (IC_{50} values in μM given): *IIb*, 8.7; *IIc*, 15.5; *IId*, 0.17; *IIf*, 0.04; *IVb*, 1.3.

Pharmacological tests in vivo evaluated the neuroprotective effect in the state of acute ischemia in mice (gasping reflex) where in the i.p. doses of 20 mg/kg compounds *IIa – IId* proved significant activity, and further in the state of histotoxic anoxia (KCN) in mice where in the same doses compounds *IIe*, *IIf*, *IVa* and *IVb* were significantly active. Anticonvulsant effect (test of electroshock in mice) was observed with compound *IIa* in the dose of 20 mg/kg. The general anaesthetic effect (potentiation of the barbiturate sleep) did not achieve with any of the compounds the level of the effect of ketamine.

Acute toxicity of the compounds in mice (approximate LD_{50} values in mg/kg): *IIa*, *IIb*, *IIc*, 45 – 50 i.v.; *IId*, *IIe*, > 75 i.p.; *IIf*, 80 i.v.; *IVa*, > 150 i.p.; *IVb*, > 75 i.p.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and they are not corrected; the samples were dried in vacuo of about 40 Pa at room temperature or at a suitably elevated temperature. UV spectra (in methanol), λ_{max} in nm (log ε) were recorded with the Unicam SP 8000 spectrophotometer; IR spectra (Nujol, wavenumbers in cm^{-1}) with Unicam SP 2000 or Perkin–Elmer 298 spectrophotometers; NMR spectra (in $CDCl_3$ unless stated otherwise) on a Tesla BS 567A (^{1}H at 100 MHz, ^{13}C at 25.14 MHz; chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz); mass spectra (*m*/*z*, %) were measured on a Varian-MAT 44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol UV_{254}). Preparative chromatographic separations were carried out on a columns of silica gel (Fluka 60).

1-Benzyl-4-(4-fluorophenacyl)piperazine (*Ia*)

A solution of 1-benzylpiperazine (7.04 g, 0.04 mol), 4-fluorophenacyl chloride (6.9 g, 0.04 mol) and triethylamine (5.3 ml, 0.04 mol) in tetrahydrofuran (100 ml) was stirred for 5 h at room temperature and allowed to stand overnight. The precipitated triethylamine hydrochloride was filtered off and washed with tetrahydrofuran. The filtrate was evaporated in vacuo; the oily residue (13.5 g) crystallized after cooling. Crystallization from pentane afforded 10.9 g (88%) of *Ia* as a slightly yellowish crystalline substance melting at 50 – 52 °C, unstable on air. ^{1}H NMR spectrum: 2.60 bs, 8 H (4 × H-2,

4 × H-3); 3.52 s, 2 H (N–CH_2–Ar); 3.75 s, 2 H (N–CH_2–CO); 7.10 t, 2 H (2 × H-3′, *J*(HH) = *J*(HF) = 8.5); 7.30 s, 5 H (2 × H-2″, 2 × H-3″, H-4″); 8.02 dd, 2 H (2 H-2′, *J*(HH) = 8.5, *J*(HF) = 6.0). For $C_{19}H_{21}FN_2O$ (312.4) calculated: 73.05% C, 6.78% H, 6.08% F, 8.97% N; found: 72.75% C, 6.79% H, 6.26% F, 8.65% N.

Dihydrochloride hemihydrate, m. p. 216 – 219 °C (ethanol–water 9 : 1). IR spectrum: 700, 746 (5 adjacent Ar–H); 831, 841 (2 adjacent Ar–H); 1 235 (Ar–F); 1 509, 1 596, 3 015 (Ar); 1 700 (COAr); 1 627, 3 100, 3 280 (H_2O); 2 200, 2 240, 2 430, 2 530 (NH^+). ^{13}C NMR spectrum: 190.85 s (CO), 165.11 s (C-4′, *J*(FC) = 256), 136.00 (C-1″), 131.02 d (C-3″), 130.78 d (C-2′, *J*(FC) = 7.5), 129.22 s (C-1′), 129.00 d (C-4″), 128.25 d (C-2″), 115.03 d (C-3′, *J*(FC) = 21), 59.76 t (Ar–CH_2–N), 58.11 t (N–**C**H_2-CO), 48.25 t and 47.13 (C-2 and C-3). Mass spectrum: 312 (M^+, $C_{19}H_{21}FN_2O$, 3), 189 (80), 146 (14), 98 (14), 91 (100), 70 (57), 42 (29). For $C_{19}H_{23}Cl_2FN_2O$ + 0.5 H_2O (394.3) calculated: 57.87% C, 6.14% H, 17.98% Cl, 4.82% F, 7.10% N; found: 57.97% C, 5.97% H, 18.24% Cl, 5.21% F, 6.88% N.

2-(4-Benzylpiperazine-1-yl)-1-(4-fluorophenyl)-ethanol (*IIa*)

A stirred solution of *Ia* (10.9 g, 0.035 mol) in ethanol (150 ml) was treated over 30 min with a suspension of $NaBH_4$ (2.64 g, 0.07 mol) in ethanol (100 ml) at 10 – 15 °C. The clear solution obtained was stirred for 2 h at room temperature and allowed to stand overnight. Ethanol was evaporated in vacuo, the residue was diluted with water and extracted with chloroform (3 × 100 ml). The extract was dried with $MgSO_4$; processing afforded *IIa* (10.0 g, 91%) as colourless crystals, m.p. 123 °C (ethanol). IR spectrum: 698, 741 (5 adjacent Ar–H); 833 (2 adjacent Ar–H); 1 090 (CH–OH); 1 223 (Ar–F); 1 509, 1 600, 3 028, 3 060 (Ar); 2 778, 2 820 (N–CH_2); 3 100 (OH). ^{1}H NMR spectrum: 7.30 m, 7 H (2 × H-2′, 2 × H-2″, 2 × H-3″, H-4″); 7.00 t, 2 H (2 × H-3′, *J*(HH) = *J*(HF) = 8.5); 4.65 dd, 1 H (CH–O); 4.04 bs, 1 H (OH); 3.52 s, 2 H (Ar–CH_2–N); 2.40 – 2.80 m, 10 H (N–**C**H_2–CH, 4 × H-2, 4 × H-3). ^{13}C NMR spectrum: 162.39 s (C-4′, *J*(FC) = 250), 138.19 s (C-1″), 138.04 s (C-1′), 129.30 d (C-3″), 128.33 d (C-2″), 127.73 d (C-4″), 127.32 d (C-2′, *J*(FC) = 6), 115.25 d (C-3′, *J*(FC) = 24), 68.27 d (CH–OH), 66.25 t (N–**C**H_2–CH–OH), 63.12 t (Ar–CH_2–N), 53.26 t (C-2, C-3). For $C_{19}H_{23}FN_2O$ (314.4) calculated: 72.58% C, 7.37% H, 6.04% F, 8.91% N; found: 72.90% C, 7.54% H, 6.06% F, 9.31% N.

Dihydrochloride, m.p. 221 – 223 °C (ethanol–water 9 : 1). IR spectrum: 702, 760 (5 adjacent Ar–H); 835 (2 adjacent Ar–H); 1 075 (CH–OH); 1 212 (Ar–F); 1 510, 1 603, 3 010, 3 060 (Ar); 2 265, 2 450, 2 540, 2 630 (NH^+); 3 300 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 7.40 – 7.80 m, 7 H (2 × H-2′, 2 × H-2″, 2 × H-3″, H-4″); 7.24 t, 2 H (2 × H-3′, *J*(HF) = *J*(HH) = 9.0); 5.20 m, 1 H (CH–O); 4.40 s, 2 H (Ar–CH_2–N); 3.50 bm, 10 H (4 × H-2, 4 × H-3, N–C**H**$_2$–CH). For $C_{19}H_{24}ClFN_2O$ (387.3) calculated: 58.92% C, 6.50% H, 18.31% Cl, 4.91% F, 7.23% N; found: 59.12% C, 6.61% H, 18.34% Cl, 5.16% F, 7.23% N.

1-Benzyl-4-(chlorophenacyl)piperazine (*Ib*)

Title compound was prepared similarly like *Ia* but the reaction mixture was heated for 2 h to 50 – 60 °C (bath temperature); yield 80%, m.p. 61 – 62 °C (pentane). Reference[8] described the preparation of *Ib* by a similar reaction in ether in the presence of K_2CO_3; the base was isolated as an oil and characterized in the form of dihydrochloride. ^{1}H NMR spectrum: 7.94 d, 2 H (2 × H-2′, *J* = 8.5); 7.40 d, 2 H (2 × H-3′, *J* = 8.5); 7.38 s, 5 H (2 × H-2″, 2 × H-3″, H-4″); 3.74 s, 2 H (N–CH_2–Ar); 3.54 s, 2 H (N–CH_2–CO); 2.60 s, 8 H (4 × H-2, 4 × H-3). For $C_{19}H_{21}ClN_2O$ (328.8) calculated: 69.40% C, 6.44% H, 10.78% Cl, 8.52% N; found: 69.51% C, 6.38% H, 11.02% Cl, 8.46% N.

2-(4-Benzylpiperazine-1-yl)-1-(4-chlorophenyl)ethanol (*IIb*)

Title compound was prepared similarly like *IIa*; yield 92%, m.p. 148 – 151 °C. Reference[8] described the preparation from the corresponding ketone by reduction with aluminum isopropoxide, m.p. 152 °C. ^{1}H NMR spectrum: 7.35 s, 9 H (Ar–H); 4.68 dd, 1 H (CH–O); 3.52 s, 2 H (N–CH_2–Ar); 3.40 flat band (OH); 2.20 – 2.80 m, 10 H (4 × H-2, 4 × H-3, N–C**H**$_2$–CHOH).

Reduction of the ketone *Ib* with $LiAlH_4$ in ether at 0 °C gave *IIb* in the yield of 91%; it was necessary to isolate the product by extraction from the precipitated hydroxides in the Soxhlet apparatus.

Dihydrochloride, m.p. 209 – 213 °C (ethanol–water 19 : 1). IR spectrum: 696, 743 (5 adjacent Ar–H); 813 (2 adjacent Ar–H); 1 070 (CHOH); 1 490, 1 577, 1 596, 3 040 (Ar); 2 300, 2 435, 2 500, 2 605, 2 630 (NH^+); 3 270 (OH). For $C_{19}H_{25}Cl_3N_2O$ (403.8) calculated: 56.52% C, 6.24% H, 26.34% Cl, 6.94% N; found: 56.99% C, 6.31% H, 26.16% Cl, 6.68% N.

1-Benzyl-4-(4-bromophenacyl)piperazine (*Ic*)

The preparation was similar like with *Ia*, yield 73% of title compound *Ic*, m.p. 94 – 95 °C (cyclohexane); the compound was unstable on air. ^{1}H NMR spectrum: 7.88 d, 2 H (2 × H-2′, J = 8.5); 7.56 d, 2 H (2 × H-3′, J = 8.5); 7.28 s, 5 H (2 × H-2″, 2 × H-3″, H-4″); 3.73 s, 2 H (N–CH_2–CO); 3.52 s, 2 H (N–CH_2–Ar); 2.58 bs, 8 H (4 × H-2, 4 × H-3). For $C_{19}H_{21}BrN_2O$ (373.3) calculated: 61.13% C, 5.67% H, 21.41% Br, 7.50% N; found: 61.20% C, 5.69% H, 21.47% Br, 7.14% N.

Dihydrochloride, m.p. 214 – 216 °C (ethanol–water 10 : 1). For $C_{19}H_{23}BrCl_2N_2O$ (446.2) calculated: 51.14% C, 5.20% H, 17.91% Br, 15.89% Cl, 6.28% N; found: 50.95% C, 5.09% H, 17.94% Br, 15.91% Cl, 6.56% N.

2-(4-Benzylpiperazine-1-yl)-1-(4-bromophenyl)ethanol (*IIc*)

The preparation was similar like with *IIa*, yield 93% of title compound *IIc*, m.p. 158.5 – 159 °C (ethanol). ^{1}H NMR spectrum: 7.45 d, 2 H (2 × H-3′, J = 8.5); 7.35 s, 5 H (2 × H-2″, 2 × H-3″, H-4″); 7.23 d, 2 H (2 × H-2′, J = 8.5); 4.66 dd, 1 H (Ar–C**H**–OH); 4.02 bs, 1 H (OH); 3.54 s, 2 H (Ar–CH_2–N); 2.30 – 2.80 m, 10 H (4 × H-2, 4 × H-3, N–C**H**$_2$–CHOH). ^{13}C NMR spectrum: 141.32 s (C-1′), 138.11 s (C-1″), 131.46 d (C-3′), 129.22 d (C-3″), 128.33 d (C-2″), 127.65 d (C-2′), 127.21 d (C-4″), 121.23 d (C-4′), 68.20 d (CH–OH), 65.96 t (N–**C**H_2–CHOH), 63.04 t (N–CH_2–Ar), 53.11 t (C-2, C-3). For $C_{19}H_{23}BrN_2O$ (375.3) calculated: 60.80% C, 6.18% H, 21.19% Br, 7.46% N; found: 60.69% C, 6.13% H, 21.28% Br, 7.61% N.

Dihydrochloride, m.p. unsharp till 224 °C (ethanol–water 7 : 1). For $C_{19}H_{25}BrCl_2N_2O$ (448.3) calculated: 50.91% C, 5.62% H, 17.83% Br, 15.82% Cl, 6.25% N; found: 50.80% C, 5.60% H, 18.00% Br, 15.97% Cl, 6.64% N.

1-Benzhydryl-4-(4-fluorophenacyl)piperazine (*Id*)

The preparation was similar like with *Ia*, yield 76.7% of title compound *Id*, m.p. 101 – 103 °C (2-propanol). IR spectrum: 705, 750 (5 adjacent Ar–H); 828, 831 (2 adjacent Ar–H); 1 223 (Ar–F); 1 491, 1 501, 1 597, 3 005, 3 050 (Ar); 1 689 (ArCOR); 2 753, 2 795 (N–CH_2). UV spectrum: 225 (4.18), 240 (4.11). ^{1}H NMR spectrum: 8.05 dd, 2 H (2 × H-2′); 7.10 – 7.60 m, 10 H (4 × H-2″, 4 × H-3″, 2 × H-4″); 7.10 t, 2 H (2 H-3′); 4.24 s, 1 H (N–$CHAr_2$); 3.76 s, 2 H (N–CH_2CO); 2.20 – 3.80 m, 8 H (4 × H-2, 4 × H-3). For $C_{25}H_{25}FN_2O$ (388.5) calculated: 77.29% C, 6.49% H, 4.89% F, 7.21% N; found: 77.12% C, 6.72% H, 4.73% F, 6.93% N.

Dihydrochloride, m.p. 199 – 202 °C (ethanol). For $C_{25}H_{27}Cl_2FN_2O$ (461.4) calculated: 65.08% C, 5.90% H, 15.37% Cl, 4.12% F, 6.07% N; found: 64.82% C, 5.92% H, 15.35% Cl, 4.02% F, 5.69% N.

2-(4-Benzhydrylpiperazine-1-yl)-1-(4-fluorophenyl)ethanol (*IId*)

The preparation was similar like with *IIa*, yield 71% of title compound *IId*, m.p. 110 – 111 °C (2-propanol). IR spectrum: 705, 748, 757 (5 adjacent Ar–H); 836 (2 adjacent Ar–H); 1 065, 1 095 (CH–OH); 1 221 (Ar–F); 1 490, 1 509, 1 600, 3 020, 3 056, 3 075 (Ar); 2 755, 2 805 (CH_2–N); 3 350 (OH). ^{1}H NMR spectrum: 7.30 – 7.50 m, 12 H (2 × H-2′, 4 × H-2″, 4 × H-3″, 2 × H-4″); 7.00 t, 2 H (2 × H-3′); 4.68 dd, 1 H (C**H**–OH); 4.22 s, 1 H ($CHAr_2$); 2.80 m, 2 H (N–C**H**$_2$–CH); 2.50 m, 8 H (4 × H-2, 4 × H-3). For $C_{25}H_{27}FN_2O$ (390.5) calculated: 76.89% C, 6.69% H, 4.87% F, 7.17% N; found: 76.72% C, 7.06% H, 4.67% F, 6.95% N.

Fumarate hemihydrate, m.p. 199 – 202 °C (ethanol). Mass spectrum: 390 (<0.1), 372 (0.1), 265 (26), 167 (100), 152 (10). For $C_{29}H_{31}FN_2O_5$ + 0.5 H_2O (515.6) calculated: 67.55% C, 6.26% H, 3.69% F, 5.43% N; found: 67.62% C, 6.20% H, 3.63% F, 5.34% N.

1-Benzhydryl-4-(4-chlorophenacyl)piperazine (*Ie*)

The preparation was similar like with *Ia*, yield 83% of title compound *Ie*, m.p. 99 – 102 °C (2-propanol). IR spectrum: 705, 745, 759 (5 adjacent Ar–H); 819 (2 adjacent Ar–H); 1 483, 1 590, 3 020, 3 060 (Ar); 1 684 (ArCOR); 2 655, 2 700 (N–CH_2). UV spectrum: 224 infl. (4.13), 254 (4.25). ^{1}H NMR spectrum: 7.94 d, 2 H (2 × H-2′); 7.00 – 7.50 m, 12 H (2 × H-3′, 4 × H-2″, 4 × H-3″, 2 × H-4″); 4.22 s, 1 H (N–$CHAr_2$); 3.72 s, 2 H (N–CH_2CO); 2.30 – 2.80 bm, 8 H (4 × H-2, 4 × H-3). Mass spectrum: 404 (M^+, $C_{25}H_{25}ClN_2O$, 0.6), 265 (24), 237 (6), 167 (100), 152 (12), 139 (4). For $C_{25}H_{25}ClN_2O$ + 0.25 H_2O (409.4) calculated: 73.36% C, 6.27% H, 8.66% Cl, 6.84% N; found: 73.19% C, 6.28% H, 9.00% Cl, 6.59% N.

2-(4-Benzhydrylpiperazine-1-yl)-1-(4-chlorophenyl)ethanol (*IIe*)

The preparation was similar like with *IIa*, yield 93% of title compound *IIe*, m.p. 138.5 – 140 °C (ethanol). ^{1}H NMR spectrum: 7.30 s, 4 H (2 × H-2′, 2 × H-3′); 7.00 – 7.50 m, 10 H (4 × H-2″, 4 × H-3″, 2 × H-4″); 4.70 dd, 1 H (C**H**–OH); 4.24 s, 1 H (N–$CHAr_2$); 2.80 m, 2 H (N–C**H**$_2$–CHOH); 2.50 m, 8 H (4 × H-2, 4 × H-3). For $C_{25}H_{27}ClN_2O$ (407.0) calculated: 73.78% C, 6.69% H, 8.71% Cl, 6.88% N; found: 73.44% C, 6.72% H, 8.87% Cl, 7.22% N.

Dihydrochloride hemihydrate, m.p. 234 – 236 °C (ethanol). Mass spectrum: 388 (0.2), 265 (25), 167 (100), 152 (8). The mass M 406 was confirmed by chemical ionization. For $C_{25}H_{29}N_2Cl_3O$ + 0.5 H_2O (488.9) calculated: 61.41% C, 6.19% H, 5.73% N; found: 61.36% C, 6.25% H, 5.64% N.

Dimethanesulfonate, m.p. 181 – 182 °C (2-propanol–ether). ^{1}H NMR spectrum: 7.20 – 7.60 m, 14 H (Ar–H); 5.10 dd, 1 H (C**H**–OH); 4.76 s, 1 H ($CHAr_2$); 3.48 bm, 4 H (4 × H-3); 3.30 m, 2 H (N–C**H**$_2$CH); 2.80 bm, 4 H (4 × H-2); 2.50 s, 6 H (2 × C**H**$_3$$SO_3$H). For $C_{27}H_{35}ClN_2O_7S_2$ (599.2) calculated: 54.12% C, 5.89% H, 5.92% Cl, 4.68% N, 10.70% S; found: 53.75% C, 5.85% H, 6.04% Cl, 4.94% N, 10.74% S.

Methanesulfonate hemihydrate was formed by crystallization of the dimethanesulfonate from water, m.p. 215 – 217 °C. For $C_{26}H_{31}ClN_2O_4S$ + 0.5 H_2O (512.1) calculated: 60.98% C, 6.30% H, 6.92% Cl, 5.47% N, 6.26% S; found: 61.19% C, 6.24% H, 7.09% Cl, 5.55% N, 6.19% S.

1-Benzhydryl-4-(4-bromophenacyl)piperazine (*If*)

The preparation was similar like with *Ia*, yield 68% of title compound *If*, m.p. 102 – 104 °C (2-propanol). Reference[9] gave the m.p. of 93 – 94 °C. ^{1}H NMR spectrum in accord with ref.[9]. IR spectrum: 703, 749, 755 (5 Ar–H in C_6H_5); 1 490, 1 581, 3 015, 3 015, 3 050 (Ar); 1 699 (ArCOR). UV spectrum: 225 infl. (4.12), 253 (4.08). ^{13}C NMR spectrum: 195.78 s (CO), 142.67 s (C-1″), 134.83 s (C-1′), 131.76 d (C-3′), 129.82 d (C-2′), 128.85 s (C-4′), 128.48 d (C-3″), 127.95 d (C-2″), 126.91 d (C-4″), 76.11 d (N–$CHAr_2$), 64.69 t (N–**C**H_2–CO), 53.71 t (C-2), 51.69 t (C-3).

Dihydrochloride hemihydrate, m.p. 171 – 174 °C (ethanol). For $C_{25}H_{27}BrCl_2N_2O$ + 0.5 H_2O (531.3) calculated: 55.70% C, 5.41% H, 5.18% N; found: 55.42% C, 5.67% H, 4.80% N.

2-(4-Benzhydrylpiperazine-1-yl)-1-(4-bromophenyl)ethanol (*IIf*)

The preparation was similar like with *IIa*; yield 78% of title compound *IIf*, m.p. 147 – 151 °C (ethanol). ^{1}H NMR spectrum: 7.00 – 7.60 m, 14 H (Ar–H); 4.63 dd, 1 H (C**H**–OH); 4.22 s, 1 H (N–$CHAr_2$); 4.00 bs, 1 H (OH); 2.75 m, 2 H (N–C**H**$_2$–CH); 2.44 bs, 8 H (4 × H-2, 4 × H-3). For $C_{25}H_{27}BrN_2O$ (451.4) calculated: 66.52% C, 6.03% H, 17.70% Br, 6.21% N; found: 66.43% C, 6.03% H, 18.11% Br, 6.21% N.

Dihydrochloride monohydrate, m.p. 233 – 237 °C (ethanol–water 20 : 1). For $C_{25}H_{29}BrCl_2N_2O$ + H_2O (542.4) calculated: 55.36% C, 5.76% H, 14.73% Br, 13.07% Cl, 5.17% N; found: 55.37% C, 5.76% H, 15.01% Br, 13.30% Cl, 4.88% N.

Dimethanesulfonate, m.p. 187 – 189 °C (2-propanol–ether). For $C_{27}H_{35}BrN_2O_7S$ (643.6) calculated: 50.38% C, 5.48% H, 12.42% Br, 4.35% N, 9.96% S; found: 50.20% C, 5.53% H, 12.43% Br, 4.29% N, 9.74% S.

1-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4-(4-fluorophenacyl)piperazine (*III*)

The preparation of title compound *III* was similar like with *Ia*. The product obtained, which was not homogeneous (TLC), was separated by chromatography on silica gel (elution with chloroform and chloroform shaken with aqueous ammonia). There were obtained 72% of *III*, m.p. 82 – 84 °C (methanol–ethanol 1 : 1). IR spectrum: 751 (4 adjacent Ar–H); 835 (2 adjacent Ar–H); 1 223 (Ar–F); 1 501, 1 595, 1 611, 3 050 (Ar); 1 688 (COAr). ^{1}H NMR spectrum: 8.05 m, 2 H (2 × H-2′); 7.00 – 7.40 m, 10 H (2 × H-3′ and Ar–H of dibenzothiepin); 4.05 s, 1 H (N–CH); 3.72 s, 2 H (N–CH_2–CO); 2.50 bm, 8 H (4 × H-2, 4 × H-3); flat band belonging to S–CH_2 (shifting with temperature changes). Mass spectrum: 432 (M^+, $C_{26}H_{25}FN_2OS$, 1), 309 (0.5), 221 (4), 211 (38), 210 (100), 178 (44), 165 (6), 123 (8), 99 (7), 56 (14). For $C_{26}H_{25}FN_2OS$ + CH_3OH + 0.5 H_2O (473.6) calculated: 68.47% C, 6.38% H, 4.01% F, 5.91% N, 6.77% S; found: 68.72% C, 6.34% H, 4.15% F, 5.79% N, 6.83% S.

2-[4-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)-piperazine-1-yl]-1-(4-fluorophenyl)ethanol (*IVa*)

The preparation of title compound *IVa* was similar like with *IIa*. The crude product, which was obtained by extraction with chloroform, was triturated with cyclohexane and filtered after crystallization; 81% of *IVa*, m.p. 99 – 103 °C (ethanol). IR spectrum: 752 (4 adjacent Ar–H); 831 (2 adjacent Ar–H); 1 065 (CHOH); 1 212 (Ar–F); 1 504, 1 590, 1 613, 3 000, 3 010, 3 055 (Ar); 3 340 (OH). UV spectrum: 260 (4.88), 289 infl. (3.11). ^{1}H NMR spectrum: 7.00 – 7.50 m, 12 H (Ar–H); 4.70 m, 1 H (C**H**–OH); 4.12 s, 1 H (CH–N). For $C_{26}H_{27}FN_2OS$ (434.6) calculated: 4.37% F, 7.38% S; found: 4.15% F, 7.41% s.

Fumarate hemihydrate, m.p. 177 – 180 °C (ethanol–water 10 : 1). IR spectrum: 755 (4 adjacent Ar–H); 835 (2 adjacent Ar–H); 1 105 (CHOH); 1 360, 1 565 (COO^-); 1 220 (Ar–F); 1 455, 1 510,

1 600 (Ar); 2 640 (NH^+); infl. 3 070 (OH). Mass spectrum: 434 (M^+, $C_{26}H_{27}FN_2OS$, 1) 309 (6), 211 (84), 210 (100), 178 (47), 99 (19), 56 (20). For $C_{28}H_{29}FN_2O_3S$ + 0.5 H_2O (501.6) calculated: 67.04% C, 6.03% H, 5.58% N, 6.39% S; found: 67.37% C, 5.97% H, 5.42% N, 6.52% S.

1-(4-Chlorophenyl)-2-[4-(6,11-dihydrodibenzo[*b,e*]-thiepin-11-yl)piperazine-1-yl]ethanol (*IVb*)

A stirred solution of 1-(6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)piperazine[7] (14.8 g, 0.05 mol) in tetrahydrofuran (100 ml) was treated with a solution of 4-chlorophenacyl bromide (11.7 g, 0.05 mol) in tetrahydrofuran (50 ml) and with triethylamine (7.0 ml, 0.05 mol). The mixture was stirred for 10 h at room temperature, the precipitated triethylamine hydrochloride was filtered off, the filtrate was evaporated in vacuo and the oily residue was dried in vacuo. The remaining solid (22.6 g, m.p. 64 – 70 °C) could not be crystallized and was used in crude state.

Similarly like in the preparation of *IIb*, the above mentioned solid (10 g) was reduced with $NaBH_4$ (1.6 g) in ethanol. The oily residue, obtained after evaporation of the chloroform extract, was dissolved in ether. The solution was treated with HCl in ether, the suspension was diluted with 2-propanol, the hydrochloride was filtered and crystallized. The base was released by means of a solution of Na_2CO_3, extracted with ether and the extract was dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a solid which was crystallized from a mixture of cyclohexane and hexane (1 : 1), m.p. 102 – 106 °C. Even drying in vacuo for 10 h did not remove cyclohexane completely. IR spectrum: 750 (4 adjacent Ar–H); 817 (2 adjacent Ar–H); 1 090 (CHOH); 1 489, 1 589, 3 050 (Ar), 3 340 (OH). UV spectrum: 260 (3.55), 290 (2.77). ^{1}H NMR spectrum: 7.00 – 7.40 m, 12 H (Ar–H); 4.65 m, 1 H (C**H**–OH); 4.10 s, 1 H (CH–N); 2.75 bm, 2 H (N–C**H**$_2$–CH); 2.44 bm, 8 H (4 × H-2, 4 × H-3); 6.00 and 3.42, flat bands shifting with temperature changes (CH_2S). Mass spectrum: 450 ($M^+ - 1$, $C_{26}H_{27}ClN_2OS$, 1), 309 (6.5), 211 (82), 210 (100), 178 (46), 99 (17), 77 (9), 56 (20).

Hydrochloride, m.p. 237 – 239 °C (aqueous ethanol). IR spectrum: 754 (4 adjacent Ar–H); 821, 841 (2 adjacent Ar–H); 1 090 (CHOH); 1 490, 1 590 (Ar); 2 444, 2 560, 2 635 (NH^+); 3 220 (OH). Mass spectrum: 450 ($M^+ - 1$, $C_{26}H_{27}ClN_2OS$, 0.1), 432 (0.3), 212 (15), 211 (22), 210 (26), 197 (6), 179 (21), 178 (34), 44 (100). For $C_{26}H_{28}Cl_2N_2OS$ (487.5) calculated: 64.06% C, 5.79% H, 5.75% N, 6.58% S; found: 64.18% C, 5.74% H, 5.65% N, 6.75% S.

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