SOME 4-SUBSTITUTED 1-(3-PYRIDYLMETHYL)PIPERAZINES WITH ANTIHISTAMINE ACTIVITY

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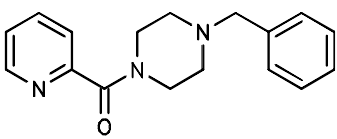
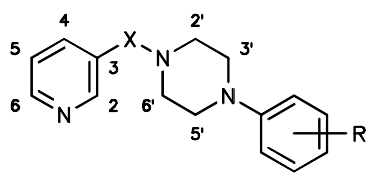
Several compounds derived from nicotinic acid were prepared within a more extensive programme aiming at the synthesis of new substances with expected antihistamine and antidepressant activity. Some of these compounds display certain structural resemblance with the antidepressant agent piberaline[1] (EGYT 475, Trelibet®, *I*) and its analogues[2]. The products were used as intermediates for the synthesis of further compounds

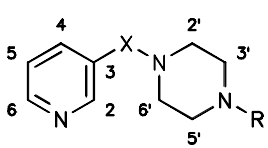


I



II, X = CO
III, X = CH_2

In formulae *II* and *III* :
a, R = H; *b*, R = 3-Cl; *c*, R = 3-CF_3; *d*, R = 4-OCH_3



IV, X = CO
V, X = CH_2
VI, X = CH_2CO

In formulae *IV* and *V* :
a, R = $CH_2C_6H_5$; *b*, R = $CH_2(4\text{-F-}C_6H_4)$; *c*, R = $CH(C_6H_5)_2$;
d, R = $CH(4\text{-F-}C_6H_4)_2$; *e*, 2-pyrimidinyl; *f*, R = $CH_2CH_2CONH_2$

and most of them were subjected to pharmacological testing. Substituted nicotinic acid piperazides *IIa – IId* and *IVa – IVe* were obtained by reactions of nicotinoyl chloride (prepared in situ) with the correspondingly substituted piperazines. Reduction of the piperazides *IIa – IId* and *IVa – IVd* with diborane "in situ" in tetrahydrofuran afforded corresponding 1-substituted 4-(3-pyridylmethyl)piperazines *IIIa – IIId* and *Va – Vd*. Whereas the alkylation of 1-(2-pyrimidinyl)piperazine[3] with 2-(chloromethyl)pyridine[4] in ethanol in the presence of triethylamine resulted in compounds *Ve*, compound *Vf* was obtained by the addition reaction of 1-(3-pyridylmethyl)piperazine[5] to acrylamide. The piperazides *VIe* and *VIf* were prepared by reactions of 2-(3-pyridyl)acetic acid[6] with 1-(2-pyrimidinyl)piperazine or 3-(1-piperazinyl)propionamide[7] in *N*,*N*-dimethylformamide in the presence 1,1′-carbonyldiimidazole. A similar procedure starting from nicotinic acid afforded the piperazide *IVf*.

Compounds *Vc* and *Vd* showed significant affinity for the histamine H_1-receptors (inhibition of binding of 2 nmol/l [^{3}H]mepyramine in membranes from the rat brain: *Vc*, IC_{50} = 28 nmol/l; *Vd*, IC_{50} = 148 nmol/l). They also proved active in test of histamine aerosol in guinea pigs (PD_{50} = 4.1 mg/kg p.o. for compound *Vc* and 2.4 for compound *Vd*). Results of a more detailed pharmacological testing of these compounds will be published elsewhere.

EXPERIMENTAL

The melting points were determined with the Mettler FP-5 melting point recorder or on the Kofler block. The analytical samples were dried in vacuo of about 40 Pa at a 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 with Unicam SP 2000 or Perkin–Elmer 298 spectrophotometers, NMR spectra on a Tesla BS 567A (^{1}H at 100 MHz, ^{13}C at 25.14 MHz), and Varian XL-200 (^{1}H at 200 MHz), chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The mass spectra 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 columns of silica gel (Fluka 60). The extracts were dried with Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

General Procedure for Preparation of Amides *IIa – IId* and *IVa – IVe*

A suspension of nicotinic acid (9.8 g, 0.08 mol) in dichloromethane (70 ml) was treated with pyridine (6.3 g; 6.2 ml; 0.08 mol) and then under stirring and cooling to 0 – 5 °C dropwise with $SOCl_2$ (9.5 g; 5.7 ml; 0.08 mol) over 20 min. The mixture was stirred at the temperature indicated for further 20 min, slowly warmed to 40 °C and stirred for 20 min. The solution obtained was cooled to 0 °C and added dropwise over 20 min to a solution of 0.08 mol of the corresponding piperazine (0.08 mol) and pyridine (6.3 g; 6.2 ml; 0.08 mol) in dichloromethane (50 ml) at 0 – 5 °C. It was then refluxed for 2 h under stirring. After cooling, the solution was washed with 50% NaOH (50 ml), water (2 × 20 ml), dried and evaporated.

1-Phenyl-4-nicotinoylpiperazine (IIa). Processing of 1-phenylpiperazine (13.0 g) by the general procedure gave 18.8 g (88%) of the crude base *IIa* which was transformed to the dihydrochloride,

m.p. 179 – 182 °C (methanol–ether). IR spectrum: 697, 769 (5 adjacent Ar-H); 1 489, 1 539, 1 600, 3 025, 3 040 (Ar); 1 643 (ArCON–R); 2 000, 2 118, 2 320 (NH^+). ^{1}H NMR spectrum (CD_3SOCD_3): 9.10 bs, 1 H (H-2); 9.00 bd, 1 H (J = 5.0, H-6); 8.56 bd, 1 H (J = 8.0, H-3); 8.05 dd, 1 H (J = 8.0, J' = 5.0 H-5); 7.40 m, 5 H (Ar-H); 3.20 – 4.00 bm, 8 H (H-2′, H-3′, H-5′, H-6′). For $C_{16}H_{19}Cl_2N_3O$ (340.3) calculated: 56.48% C, 5.63% H, 20.84% Cl, 12.35% N; found: 56.84% C, 5.82% H, 20.73% Cl, 12.66% N.

1-(3-Chlorophenyl)-4-nicotinoylpiperazine (IIb). Similar processing of 1-(3-chlorophenyl)piperazine[8] (15.7 g) gave 20.5 g oily base *IIb*, which was transformed to the dihydrochloride. Crystallization from ethanol afforded 11.5 g (47%) of *IIb* dihydrochloride melting at 168 – 170 °C. IR spectrum : 690, 800 (3 adjacent Ar-H); 886, 908 (solitary Ar-H); 1 485, 1 500, 1 550, 1 594, 1 604, 3 030 (Ar); 1 649 ($ArCONR_2$); 1 995, 2 105, 2 370, 2 495 (NH^+); 3 400 (H_2O). UV spectrum: 253 (4.26); 290 infl. (3.31). ^{1}H NMR spectrum (CD_3SOCD_3): 9.88 bs, 1 H (H-1); 9.05 bd, 1 H (J = 5.0, H-6); 8.59 bm, 1 H (H-4); 8.20 m, 1 H (H-5); 7.00 – 7.40 m, 4 H (Ar-H); 3.70 bm, 4 H (H-2′, H-6′); 3.42 bm, 4 H (H-3′, H-5′). Mass spectrum, *m/z* (%): 301 (M^+, $C_{16}H_{16}ClN_3O$, 7), 166 (86), 148 (35), 106 (24), 78 (37), 56 (100). For $C_{16}H_{18}Cl_3N_3O$ (374.7) calculated: 51.28% C, 4.84% H, 28.39% Cl, 11.22% N; found: 51.32% C, 4.98% H, 28.73% Cl, 10.93% N.

1-(3-Trifluoromethylphenyl)-4-nicotinoylpiperazine (IIc). Similar processing of 1-(3-trifluoromethyl)piperazine[9] (17.3 g) gave 20.5 g oily base which afforded 21.8 g (65%) of *IIc* dihydrochloride hemihydrate, m.p. 184 – 186 °C. IR spectrum: 693, 814 (3 adjacent Ar-H); 900, 909 (1 solitary Ar-H); 1 122, 1 171, 1 323 ($ArCF_3$); 1 582, 1 547, 1 604, 3 015, 3 028, 3 050 (Ar); 1 650 ($ArCONR_2$); 1 980, 2 100, 2 370, 2 475 (NH^+); 3 470, 3 520 (H_2O). ^{1}H NMR spectrum (base, CD_3SOCD_3): 8.70 m, 2 H (H-2, H-6); 7.80 m, 1 H (H-4); 7.00 – 7.50 m, 5 H (H-5, Ar-H); 3.80 bm, 4 H (Ar-H); 3.42 bm, 4 H (H-2′, H-6′); 3.30 bm, 4 H (H-3′, H-5′). Mass spectrum, *m/z* (%): 335 (M^+, $C_{17}H_{16}F_3N_3O$, 14), 316 (3), 229 (7), 200 (100), 188 (7), 172 (24), 148 (36), 145 (15), 106 (34). For $C_{17}H_{18}Cl_2F_3N_3O$ + 0.5 H_2O (417.3) calculated: 48.95% C, 4.59% H, 17.00% Cl, 13.66% F, 10.07% N; found: 49.11% C, 4.50% H, 17.36% Cl, 13.51% F, 10.11% N.

1-(4-Methoxyphenyl)-4-nicotinoylpiperazine (IId). Similar processing of 1-(4-methoxyphenyl)piperazine[10] (15.4 g) resulted in 19.9 g (84%) of crystalline *IId*, m.p. 85 – 87 °C. Analytical sample melted at 96 – 98 °C (benzene–ether). IR spectrum: 710, 800, 885, 827 (3 and 1 adjacent and solitary Ar-H); 1 013, 1 037, 1 248 (ArOMe); 1 511, 1 589, 3 030, 3 050, 3 075, (Ar); 1 622 ($ArCONR_2$); 3 420 (H_2O). UV spectrum: 241 (4.23); 289 (3.30). ^{1}H NMR spectrum ($CDCl_3$): 8.70 m, 2 H (H-2, H-6); 7.32 bd, 1 H (H-4); 7.40 bdd, 1 H (H-5); 6.90 s, 4 H (Ar-H); 3.90 bs and 3.65 bs, 2 × 2 H (H-2′ and H-6′); 3.78 s, 3 H (CH_3O); 3.10 bs, 4 H (H-3′, H-5′). ^{13}C NMR spectrum ($CDCl_3$): 167.69 s (C=O); 154.55 s (C-4 of aryl); 150.89 d (C-6); 147.97 d (C-2); 145.06 s (C-1 of aryl); 135.05 d (C-4); 131.46 s (C-3); 123.47 d (C-5); 118.99 d (C-2 and C-6 of aryl); 114.51 d (C-3 and C-5 of aryl); 55.50 q (OCH_3); 51.17 t (C-3′, C-5′); 48.21 bt and 42.96 bt (C-2′, C-6′). For $C_{17}H_{19}N_3O_2$ + 0.5 H_2O (306.4) calculated: 66.64% C, 6.58% H, 13.71% N; found: 66.83% C, 6.35% H, 13.63% N.

1-Benzyl-4-nicotinoylpiperazine (IVa). The general procedure applied to 1-benzylpiperazine (14.1 g) gave 18.2 g (81%) of crystalline base *IVa*, m.p. 74 – 76 °C (cyclohexane). ^{1}H NMR spectrum ($CDCl_3$): 8.70 m, 2 H (H-2, H-6); 7.76 m, 1 H (H-4); 7.40 m, 1 H (H-5); 7.32 s, 5 H (Ar-H); 3.80 bm, 2 H and 3.45 bm, 2 H (H-2′, H-6′); 3.55 s, 2 H (CH_2Ph); 2.50 bs, 4 H (H-3′, H-5′). ^{13}C NMR spectrum ($CDCl_3$): 167.69 s (C=O); 150.81 d (C-1); 148.05 d (C-6); 137.51 s (C-1 of benzyl); 135.05 d (C-4); 131.76 s (C-3); 129.15 d (C-3 and C-5 of benzyl); 128.40 d (C-2 and C-6 of benzyl); 127.36 d (C-4 of benzyl); 123.47 d (C-5); 62.82 t (**C**H_2Ph); 52.96 t (C-3′, C-5′); 47.73 t and 42.2 t (C-2′, C-6′). For $C_{17}H_{19}N_3O$ (281.4) calculated: 72.57% C, 6.81% H, 14.94% N; found: 72.34% C, 6.87% H, 14.74% N.

1-(4-Fluorobenzyl)-4-nicotinoylpiperazine (IVb). Similar processing of 1-(4-fluorobenzyl)piperazine[11] (15.5 g) afforded 12.3 g (82%) of oily *IVb* which was converted to the dihydrochloride, m.p.

244 – 246 °C (ethanol–water). IR spectrum: 685, 770, 821, 831, 899 (Ar-H); 1 510, 1 601, 3 000, 3 040, 3 075 (Ar); 1 629 ($ArCONR_2$); 1 995, 2 110, 2 385, 2 608, 2 680, 2 710 (NH^+); 3 320, 3 440 (H_2O). ^1H NMR spectrum (CD_3SOCD_3): 8.90 m, 2 H (H-2, H-6); 8.36 bd, 1 H (J = 9.0, H-4); 7.90 dd, 1 H (J = 9.0, J' = 5.0, H-5); 7.78 dd, 2 H (J(HH) = 9.0, J(HF) = 5.0 Hz, H-2 and H-6 of 4-FC_6H_5); 7.27 t, 2 H (J(HH) = J(HF) = 9.0, H-3 and H-5 of 4-FC_6H_5); 4.40 s, 2 H (**C**H_2Ar); 3.70 bm, 4 H (H-2′, H-6′); 3.30 bm, 4 H (H-3′, H-5′). Mass spectrum, *m/z* (%): 299 (M^+, $C_{17}H_{18}FN_3O$), 193, 164, 152, 150, 109 (100%), 106, 78. For $C_{17}H_{20}Cl_2FN_3O$ (372.3) calculated: 54.84% C, 5.42% H, 19.05% Cl, 5.10% F, 11.28% N; found: 54.82% C, 5.53% H, 19.19% Cl, 5.21% F, 11.09% N.

1-Benzhydryl-4-nicotinoylpiperazine (IVc). Similar processing of 1-benzhydrylpiperazine[12] (14.1 g) gave 14.3 g (80%) of crystalline *IVc* melting at 131 – 133 °C; analytical sample, m.p. 134 – 136 °C (ethyl acetate–light petroleum). IR spectrum: 710, 752 (5 adjacent Ar-H); 823 (3 adjacent H in pyridine); 896 (1 solitary H in pyridine); 1 482, 1 490, 1 566, 1 583, 1 600, 3 020, 3 060, 3 080 (Ar); 1 627 (Ar–CO–N); UV spectrum: 254 (3.96), 224 infl. (4.22). ^1H NMR spectrum ($CDCl_3$): 8.87 m, 2 H (H-2, H-6); 7.74 dt, 1 H (H-4); 7.00 – 7.50 m, 11 H (H-5 and ArH); 4.28 s, 1 H (C**H**Ph_2); 3.77 bs, 2 H and 3.46 bs, 2 H (H-3′, H-5′); 2.44 bs, 4 H (H-2′, H-6′). For $C_{23}H_{23}N_3O$ (357.4) calculated: 77.28% C, 6.48% H, 11.76% N; found: 77.06% C, 6.61% H, 11.61% N. Succinate hemihydrate, m.p. 176 – 178 °C (ethanol–ether). For $C_{27}H_{29}N_3O_5$ + 0.5 H_2O (484.5) calculated: 66.92% C, 6.24% H, 8.67% N; found: 66.97% C, 6.33% H, 8.43% N.

1-(4,4′-Difluorobenzhydryl)-4-nicotinoylpiperazine (IVd). Similar preparation starting from 1-(4,4′-difluorobenzhydryl)piperazine[13] (23.1 g) gave 30.8 g (95%) of oily base *IVe* which was used for the further step in crude state.

1-Nicotinoyl-4-(2-pyrimidinyl)piperazine (IVe). Similar processing of 1-(2-pyrimidinyl)piperazine[3] (13.3 g) afforded 14.9 g (69%) of crystalline *IVe* melting at 125 – 135 °C. Analytical sample, m.p. 136 – 138 °C (benzene–hexane). IR spectrum: 709, 801 (3 adjacent and 1 solitary Ar-H); 1 508, 1 550, 1 583, 3 038, 3 060, 3 100 (Ar); 1 627 ($ArCONR_2$). UV spectrum: 242 (4.47); 295 (3.63). ^1H NMR spectrum ($CDCl_3$): 8.74 m, 2 H (H-2, H-6); 8.36 d, 2 H (J = 5.0, H-3 and H-5 of pyrimidine); 7.83 td, 1 H (J = 7.0, H-4); 7.40 m, 1 H (H-5); 6.58 t, 1 H (J = 5.0, H-4 of pyrimidine); 3.40 – 4.00 bm, 8 H (H-2′, H-3′, H-5′, H-6′). ^{13}C NMR spectrum ($CDCl_3$): 167.92 s (CO); 161.42 s (C-1 of pyrimidine); 157.76 d (C-3 and C-5 of pyrimidine); 150.89 d (C-6); 147.97 d (C-2); 135.05 d (C-4); 131.39 s (C-3); 123.47 d (C-5); 110.62 d (C-4 of pyrimidine); 43.70 t (C-3′, C-5′); 47.73 bt, 42.96 bt (C-2′, C-6′). For $C_{14}H_{15}N_5O$ (269.3) calculated: 62.44% C, 5.61% H, 26.00% N; found 62.35% C, 5.73% H, 25.89% N. Fumarate, m.p. 146 – 148 °C (ethanol). For $C_{18}H_{19}N_5O_5$ (385.4) calculated: 56.10% C, 4.97% H, 18.18% N; found 56.29% C, 5.11% H, 18.33% N.

General Procedure for Preparation of Amines *IIIa* – *IIId* and *Va* – *Vd*

A solution of the corresponding amide (22.5 mmol) in tetrahydrofuran (60 ml) was treated with $NaBH_4$ (2.5 g; 66 mmol), the mixture was cooled to 5 °C and then treated under stirring and cooling in nitrogen atmosphere over 20 min with boron trifluoride etherate (9.0 g; 8.0 ml; 63 mmol). The mixture was stirred for 2 h at room temperature and then refluxed for 4 h. After cooling, the stirred mixture was slowly decomposed by addition of 50 ml dilute hydrochloric acid (1 : 1), refluxed for 2 h and evaporated in vacuo. The residue was dissolved in 20 ml ethanol, the mixture was made alkaline with a solution of KOH (25 g) in ethanol (35 ml) and refluxed for another 1 h. The solid was filtered off, washed with 2 × 20 ml ethanol and combined ethanolic solutions were evaporated in vacuo. The residue was distributed between toluene (20 ml) and water (20 ml). The toluene solution was evaporated in vacuo to dryness.

1-Phenyl-4-(3-pyridylmethyl)piperazine (IIIa). Reduction of 6.0 g amide *IIa* using the general procedure led to 3.3 g (52%) of the crude base *IIIa*, m.p. 70 – 75 °C (the literature[14] gave the value of

74 – 76 °C). Treatment of the methanolic solution of the base with a solution of HCl in ether afforded the dihydrochloride, m.p. 213 – 215 °C (methanol–ether). IR spectrum: 694, 769 (5 adjacent Ar-H); 1 491, 1 555, 1 595, 3 027 (Ar); 2 017, 2 100, 2 310 (NH^+). For $C_{16}H_{21}Cl_2N_3$ (326.3) calculated: 58.90% C, 6.49% H, 21.74% Cl, 12.88% N; found: 58.68% C, 6.64% H, 22.02% Cl, 12.87% N.

1-(3-Chlorophenyl)-4-(3-pyridylmethyl)piperazine (IIIb). Reduction of the amide *IIb* (6.8 g) gave 6.9 g crude base *IIIb* which was transformed to the trihydrochloride monohydrate (5.2 g, 56%), m.p. 126 – 135 °C; analytical sample, m.p. 135 – 137 °C (ethanol–ether). IR spectrum: 693, 713, 779, 869 (3 and 1 adjacent and solitary Ar-H); 1 535, 1 591, 1 604, 3 010, 3 045, 3 060 (Ar); 1 930, 2 040, 2 070, 2 110, 2 390 (NH^+); 3 220 (H_2O). ^{1}H NMR spectrum (CD_3SOCD_3): 9.34 bs, 1 H (H-2); 9.02 bd, 1 H (J = 5.0, H-6); 7.03 bm, 1 H (H-4); 7.29 t, 1 H (J = 5.0, H-5); 7.00 m, 4 H (H-2, H-4, H-5, H-6 of 3-ClC_6H_4); 4.78 bs, 2 H (CH_2); 3.62 bm, 4 H (H-3′, H-5′); 3.40 bm, 4 H (H-2′, H-6′). Mass spectrum, *m/z* (%): 287 (M^+, $C_{16}H_{18}ClN_3$), 195, 147, 139, 120 (100), 92. For $C_{16}H_{21}Cl_4N_3 + H_2O$ (415.2) calculated: 46.28% C, 5.58% H, 34.16% Cl, 10.12% N; found: 46.08% C, 5.62% H, 34.44% Cl, 9.86% N.

1-(3-Pyridylmethyl)-4-(3-trifluoromethylphenyl)piperazine (IIIc): Reduction of 6.7 g of the amide *IIc* gave 6.8 g of the crude base *IIIc* which was dissolved in ethanol (20 ml) and transformed by treatment with HCl in ether to the dihydrochloride monohydrate (4.1 g, 40%), m.p. 158 – 165 °C; analytical sample, m.p. 166 – 168 °C (ethanol–ether). ^{1}H NMR spectrum (CD_3SOCD_3): 9.30 bs, 1 H (H-2); 9.05 bd, 1 H (J = 5.0, H-6); 8.94 bd, 1 H (J = 8.5, H-4); 8.16 dd, 1 H (J = 8.5; J' = 5.0, H-5); 7.00 – 7.60 m, 4 H (3-$CF_3C_6H_4$); 4.77 s, 2 H (CH_2); 3.62 bm, 4 H (H-3′, H-5′); 3.40 bm, 4 H (H-2′, H-6′). Mass spectrum, *m/z* (%): 321 (M^+, $C_{17}H_{18}F_3N_3$), 229, 173, 172, 147, 120. For $C_{17}H_{20}Cl_2F_3N_3 + H_2O$ (412.3) calculated: 49.52% C, 5.38% H, 17.20% Cl, 13.83% F, 10.19% N; found: 49.36% C, 5.32% H, 17.18% Cl, 13.61% F, 10.21% N.

1-(4-Methoxyphenyl)-4-(3-pyridylmethyl)piperazine (IIId). Reduction of 6.7 g of the amide *IId* afforded 6.2 g (98%) of the crude oily base *IIId*, which was dissolved in ethanol and converted by treatment with a solution of 2.6 g maleic acid in ether to the hydrogen maleate monohydrate (6.7 g, 71%), m.p. 108 – 110 °C; analytical sample, m.p. 111 – 113 °C (ethanol–ether). Mass spectrum, *m/z* (%): 283 (M^+, $C_{17}H_{21}N_3O$, 75), 191 (23), 162 (15), 150 (18), 147 (24), 136 (40), 135 (38), 120 (100), 92 (58), 56 (73). For $C_{21}H_{25}N_3O_5 + H_2O$ (417.5) calculated: 60.42% C, 6.51% H, 10.07% N; found: 60.53% C, 6.31% H, 9.87% N.

1-Benzyl-4-(3-pyridylmethyl)piperazine (Va). Reduction of 6.3 g of the amide *IVa* gave 6.0 g (98%) of the crude oily base *Va* which was dissolved in methanol and converted by treatment with a solution of maleic acid (5.1 g) in methanol to dihydrogen maleate monohydrate (8.4 g, 72%), m.p. 195 – 197 °C; Analytical sample, m.p. 197 – 199 °C (methanol). ^{1}H NMR spectrum (CD_3SOCD_3): 9.24 d, 1 H (J = 1.5, H-2); 8.98 dd, 1 H (J = 1.5, J' = 5.5, H-6); 8.75 dd, 1 H (J = 1.5, J' = 8.2, H-4); 8.04 dd, 1 H (J = 5.5, J' = 8.2, H-5); 7.35 m, 5 H (Ar-H of benzyl); 6.91 s, 4 H (C**H**= of maleic acid); 6.14 bs, 4 H (COOH); 4.71 s, 2 H (CH_2-pyridine); 4.54 s, 2 H (CH_2 of benzyl); 3.58 m, 4 H (H-3′, H-5′); 3.29 m, 4 H (H-2′, H-6′). For $C_{25}H_{29}N_3O_8 + H_2O$ (517.5) calculated: 58.01% C, 6.04% H, 8.12% N; found: 58.33% C, 6.07% H, 8.25% N.

1-(4-Fluorobenzyl)-4-(3-pyridylmethyl)piperazine (Vb). Reduction of 6.7 g of the amide *IVb* resulted in 5.6 g (87%) of the crude base *Vb*. ^{1}H NMR spectrum ($CDCl_3$): 8.52 m, 2 H (H-2); 7.69 bd, 1 H (H-4), 7.30 m, 3 H (H-5; H-2 and H-6 of 4-FC_6H_4); 7.01 t, 2 H ((J(HH) = J(HF) = 9.0, H-3 and H-5 of 4-FC_6H_5); 3.57 s, 4 H (2 × CH_2); 2.58 s, 8 H (H-2′, H-3′, H-5′, H-6′). Mass spectrum, *m/z* (%): 285 (M^+, $C_{17}H_{20}FN_3$, 5), 193 (10), 176 (20), 109 (100), 92 (46), 72 (45). Dihydrogen maleate, m.p. 189 – 191 °C (aqueous ethanol). For $C_{25}H_{28}FN_3O_8 + H_2O$ (535.5) calculated: 56.07% C, 5.65% H, 3.54% F, 7.85% N; found: 55.94% C, 5.51% H, 3.27% F, 7.54% N.

1-Benzhydryl-4-(3-pyridylmethyl)piperazine (Vc). Reduction of 8.1 g of the amide *IVc* afforded 6.5 g (84%) of the crude crystalline base *Vc* (m.p. 90 – 95 °C) which was transformed to the hydro-

chloride, m.p. 228 – 230 °C (ethanol). IR spectrum: 690, 710, 863 (5 and 3 adjacent and solitary Ar-H); 1 497, 1 552, 3 025, 3 045, 3 095 (Ar); 3 360, 3 420, 3 490 (OH, NH); 2 400, 2 500, 2 622 (NH^+). ^{1}H NMR spectrum (CD_3SOCD_3): 9.20 bs, 1 H (H-2); 8.96 bd, 1 H (*J* = 5.0, H-6); 8.80 bd, 1 H (*J* = 8.5, H-4); 8.05 m, 1 H (H-5); 7.95 m, 7.40 m, 10 H (2 × C_6H_5); 5.90 bs, 1 H (CH); 4.70 s, 2 H (CH_2); 3.64 bm, 4 H (H-3′, H-5′); 3.35 bm, 4 H (H-2′, H-6′). Mass spectrum, *m/z* (%): 343 (M^+, $C_{23}H_{25}N_3$, 4), 266 (2), 251 (9), 176 (98), 167 (66), 92 (100). For $C_{23}H_{28}Cl_3N_3$ + H_2O (470.9) calculated: 58.67% C, 6.42% H, 22.59% Cl, 8.92% N; found : 58.45% C, 6.18% H, 22.59% Cl, 8.93% N.

1-(4,4′-Difluorobenzhydryl)-4-(3-pyridylmethyl)piperazine (Vd). Reduction of 8.6 g of the amide *IVd* gave 7.8 g (91%) of the crude crystalline base *Vc*, m.p. 114 – 116 °C (ether–light petroleum). ^{1}H NMR spectrum ($CDCl_3$): 8.54 d, 1 H (*J* = 2.0, H-2); 8.50 dd, 1 H (*J* = 2.0, *J*′ = 5.0, H-6); 7.65 bd, 1 H (*J* = 8.0, H-4); 7.30 m, 5 H (H-5, 2 × H-2 and H-6 of 4-FC_6H_4); 6.95 t, 4 H (*J*(HH) = *J*(HF) = 9.0, 2 × H-3 and H-5 of 4-FC_6H_4); 4.22 s, 1 H (CH); 3.52 s, 2 H (CH_2); 2.43 bs, 8 H (H-2′, H-3′, H-5′, H-6′). ^{13}C NMR spectrum ($CDCl_3$): 161.87 s (*J*(F,C) = 244, 2 × C-4 from 4-FC_6H_4); 150.59 d (C-2); 148.64 d, (C-6); 138.19 s (2 × C-1 from 4-FC_6H_4); 136.69 d (C-4); 133.56 s (C-3); 129.30 d (*J*(FC) = 7.5, 2 × C-2 and C-6 from 4-FC_6H_4); 123.25 d (C-5); 115.37 d (*J*(FC) = 20.7, 2 × C-3 and C-5 from 4-FC_6H_4); 74.40 d (Ar_2**C**H); 60.13 t (CH_2); 53.26 t (C-2′ and C-6′); 51.69 t (C-3′ and C-5′). Trihydrochloride hemihydrate, m.p. 114 – 116 °C (ethanol–ether). IR spectrum: 690, 783 (3 adjacent Ar-H); 825 (2 adjacent Ar-H); 860 (solitary Ar-H); 1 231 (Ar-F); 1 510, 1 550, 1 603, 3 000, 3 045, 3 100 (Ar); 1 637 (H_2O); 3 420, 3 485 (OH, H_2O); 2 090, 2 400, 2 495, 2 620 (NH^+). ^{1}H NMR spectrum (CD_3SOCD_3): 9.00 bd, 1 H (H-2); 8.88 d, 1 H (H-6); 8.00 m, 6 H (2 × H-2 and H-6 from 4-FC_6H_4, H-4 and H-5); 7.30 t, 4 H (2 × H-3 and H-5 from 4-FC_6H_4); 5.98 bs, 1 H (CH); 4.75 s, 2 H (CH_2); 3.64 bm, 4 H (H-3′ and H-5′); 3.35 bm, 4H (H-2′ and H-6′). Mass spectrum, *m/z* (%): 379 (M^+, $C_{23}H_{23}F_2N_3$), 287, 244, 203, 176 (100), 133, 92. For $C_{23}H_{26}Cl_3F_2N_3$ + 0.5 H_2O (497.8) calculated: 55.49% C, 5.46% H, 21.37% Cl, 7.63% F, 8.44% N; found: 55.33% C, 5.25% H, 20.93% Cl, 7.69% F, 8.51% N.

1-(3-Pyridylmethyl)-4-(2-pyrimidinyl)piperazine (*Ve*)

A solution of 1-(2-pyrimidinyl)piperazine[3] (3 g, 44.5 mmol) and 4.6 g (6.3 ml, 45 mmol) of triethylamine in ethanol (60 ml) was treated over 30 min under stirring with a suspension of 3-(chloromethyl)pyridine hydrochloride[4] (3 g, 44.5 mmol) in ethanol (40 ml). The mixture was stirred and refluxed for 6 h, evaporated in vacuo to dryness, the residue was dissolved in chloroform (100 ml) and made alkaline with a solution of NH_3 in chloroform. The separated NH_4Cl was filtered off and evaporation of the filtrate gave 8.8 g (76%) crude product melting at 100 – 104 °C; analytical sample, m.p. 102 – 104 °C (cyclohexane). IR spectrum: 718, 770, 792, 811 (3 adjacent Ar-H); 850 (solitary Ar-H); 1 480, 1 511, 1 540, 1 588, 3 028 (heterocyclic ring); 2 760, 2 775 (N-CH_2). ^{1}H NMR spectrum ($CDCl_3$): 8.60 bs, 1 H (H-2); 8.55 bd, 1 H (H-6); 8.30 d, 2 H (*J* = 5.0, H-3 and H-5 of pyrimidine); 7.28 bd, 1 H (H-5); 6.50 t, 1 H (*J* = 5.0, H-4 of pyrimidine); 3.84 bt, 4 H (H-3′ and H-5′); 3.58 s, 2 H (CH_2); 2.51 bt, 4 H (H-2′ and H-6′. ^{13}C NMR spectrum ($CDCl_3$): 161.72 s (C-1 of pyrimidine); 157.68 d (C-3 and C-5 of pyrimidine); 150.51 d (C-6); 148.79 d (C-2); 136.69 d (C-4); 133.48 s (C-3); 123.32 d (C-5); 109.88 d (C-4 of pyrimidine); 60.28 t (CH_2); 52.96 t (C-2′ and C-6′); 43.62 t (C-3′ and C-5′). For $C_{14}H_{17}N_5$ (255.3) calculated: 65.85% C, 6.71% H, 27.43% N; found: 65.85% C, 6.84% H, 27.25% N.

Dihydrogen maleate, m.p. 148 – 150 °C (ethanol). For $C_{22}H_{25}N_5O_8$ (487.5) calculated: 54.21% C, 5.17% H, 14.37% N; found: 53.99% C, 5.26% H, 14.27% N.

3-(4-(3-Pyridylmethyl)-1-piperazinyl)propionamide *(Vf)*

A solution of 1-(3-pyridylmethyl)piperazine[5] (12.3 g, 70 mmol) in ethanol (20 ml) was treated under stirring with a solution of acrylamide (5.0 g, 70 mmol) in ethanol (20 ml), the mixture was refluxed for 12 h, cooled to room temperature and treated with a solution of maleic acid (24.4 g, 0.21 mol) in ethanol (150 ml). The separated crystalline trihydrogen maleate was filtered, washed with ethanol (50 ml) and dried; yield 34.2 g (82%), m.p. 144 – 146 °C; analytical sample, m.p. 150 – 152 °C (aqueous ethanol–ether). ^{1}H NMR spectrum (CD_3SOCD_3): 8.60 bm, 2 H (H-2 and H-6), 7.82 bd, H (H-4), 7.45 bm, 1 H (H-5), 6.23 s, 6 H (=CH– of maleate), 3.72 s , 2 H (pyridyl-C**H**$_2$). Mass spectrum, *m/z* (%): 249 ($M^+ + 1$, $C_{13}H_{20}N_4O$), 177, 135, 92, 56, 44. For $C_{25}H_{32}N_4O_{13}$ (596.6) calculated: 50.33% C, 5.41% H, 9.39% N; found: 50.36% C, 5.55% H, 9.19% N.

1-(3-Pyridylacetyl)-4-(2-pyrimidinyl)piperazine *(VIe)*

A solution of 2-(3-pyridyl)acetic acid[6] (5.5 g, 40 mmol) in 70 ml dimethylformamide was treated over 20 min with 1,1′-carbonyldiimidazole (7.0 g, 45 mmol), added in parts, which was followed by 1-(2-pyrimidinyl)piperazine[3] (6.6 g, 40 mmol) in *N*,*N*-dimethylformamide (40 ml) and reaction mixture was stirred for 16 h at room temperature. The solution was evaporated in vacuo to dryness, the residue was mixed with ethanol (10 ml) and the crystalline solid was filtered; 7.1 g (63%) amide *VIe*, m.p. 127 – 133 °C; analytical sample, m.p. 133 – 135 °C (ethanol). ^{1}H NMR spectrum ($CDCl_3$): 8.52 bm, 2 H (H-2 and H-6); 8.32 d, 2 H (J = 5.0, H-3 and H-5 of pyrimidine); 7.65 bd, 1 H (J = 7.0, H-4); 7.28 dd (J = 5.0, J' = 7.0, H-5); 6.56 t, 1 H (J = 5.0, H-4 of pyrimidine); 3.50 – 3.90 bm, 10 H (H-2′, H-3′, H-5′, H-6′ and C**H**$_2$CO). ^{13}C NMR spectrum ($CDCl_3$): 168.74 s (CO), 161.49 s (C-1 of pyrimidine), 157.83 d (C-3 and C-5 of pyrimidine), 150.06 d (C-6), 148.42 d (C-2), 136.62 d (C-4), 130.72 s (C-3), 123.55 d (C-5), 110.62 d (C-4 of pyrimidine), 45.79 t (**C**H$_2$), 43.62 t (C-2′ and C-6′), 41.75 and 37.72 t (C-3′ and C-5′). IR spectrum: 709, 767, 793, 814 (3 adjacent ArH); 850 (solitary ArH); 1 480, 1 499, 1 542, 1 581, 3 000, 3 020, 3 045 (Ar); 1 641 ($RCONR_2$). UV spectrum: 203 (5.16), 241.5 (5.43), 303 (4.33). For $C_{15}H_{17}N_5O$ (283.3) calculated: 63.58% C, 6.05% H, 24.72% N; found: 63.30% C, 6.03% H, 24.52% N.

Hydrogen maleate, m.p. 132 – 134 °C (ethanol). For $C_{19}H_{21}N_5O_5$ (399.4) calculated: 57.13% C, 5.30% H, 17.54% N; found 57.01% C, 5.35% H, 17.68% N.

3-(4-(3-Pyridylacetyl)-1-piperazinyl)propionamide (*VIf*)

A similar reaction of 3-(1-piperazinyl)propionamide[7] (4.5 g, 29 mmol) with 2-(3-pyridyl)acetic acid[6] (4.0 g, 29 mmol) gave 5.2 g (66%) of the base *VIf*, m.p. 156 – 163 °C; analytical sample, m.p. 166 – 168 °C (ethanol–hexane). ^{1}H NMR spectrum ($CDCl_3$): 8.44 m, 2 H (H-2 and H-6); 7.64 dt, 1 H (J = 7.0, J' = 2.0, H-4); 7.38 bs, 1 H and 6.80 bs, 1 H (CON**H**$_2$); 7.35 dd, 1 H (J = 7.0, 5.0, H-5); 3.77 s, 2 H (C**H**$_2$CO); 3.50 bt, 4 H (H-2′ and H-6′); 2.54 t, 2 H (J = 7.0, NC**H**$_2$CH$_2$); 2.36 bt, 4 H (H-3′ and H-5′); 2.22 t, 2 H (J = 7.0, NCH$_2$C**H**$_2$). ^{13}C NMR spectrum ($CDCl_3$): 173.22 s (CO), 168.29 s (CH$_2$**C**O-piperazine), 150.36 d (C-6), 147.52 d (C-2), 136.92 d (C-4), 131.84 s (C-3), 123.25 d (C-5), 53.78 t (**C**H$_2$CH$_2$CONH$_2$), 52.66 t and 52.14 t (C-3′ and C-5′), 45.19 t (C-2′ and C-6′), 36.23 t (**C**H$_2$CO-piperazine), 32.79 t (**C**H$_2$CONH$_2$). For $C_{14}H_{20}N_4O_2$ (276.3) calculated: 60.85% C, 7.30% H, 20.28% N; found: 60.59% C, 7.34% H, 20.26% N.

3-(4-Nicotinoyl-1-piperazinyl)propionamide *(IVf)*

Reaction of 3-(1-piperazinyl)propionamide[7] (4.7 g, 30 mmol) with nicotinic acid (3.7 g, 30 mmol) and 1,1′-carbonyldiimidazole (5.6 g, 35 mmol), carried out similarly like in the two foregoing cases, afforded 5.2 g (67%) of the base *IVf*, m.p. 171 – 175 °C; analytical sample, m.p. 173 – 175 °C

(ethanol–hexane). ^{1}H NMR spectrum ($CDCl_3$): 8.70 bm, 2 H (H-2 and H-6); 7.80 bd, 1 H (J = 7.0, H-4); 7.30 dd, 1 H (J = 7.0, J' = 5.0, H-5); 7.20 bs and 5.75 bs, 2 × 1 H (NH_2); 3.62 bt, 4 H (H-2′ and H-6′); 2.70 t, 2 H (J = 7.0, C**H**$_2$CH$_2$CONH$_2$); 2.50 bt, 4 H (H-3′ and H-5′); 2.40 t, 2 H (J = 7.0, CH$_2$C**H**$_2$CONH$_2$). ^{13}C NMR spectrum ($CDCl_3$): 174.79 s ($CONH_2$), 167.62 s (CO), 150.89 d (C-6), 147.90 d (C-2), 134.98 d (C-4), 131.31 s (C-3), 123.47 d (C-5), 53.63 t (**C**H$_2$CH$_2$CONH$_2$), 52.59 t (C-3′ and C-5′), 47.23 t and 42.26 t (C-2′ a C-6′), 32.27 t (CH$_2$**C**H$_2$CONH$_2$). IR spectrum: 711, 821 (3 adjacent ArH); 898 (solitary ArH); 1 480, 1 490, 1 568, 1 590, 3 005 (Ar); 1 616 (ArCON); 1 684 ($RCONH_2$); 2 820 (NCH_2); 3 165, 3 330 (NH_2). UV spectrum: 253 (4.58), 259 (4.58). For $C_{13}H_{18}N_4O_2$ (262.3) calculated: 59.52% C, 6.92% H, 21.36% N; found: 59.38% C, 6.94% H, 21.39% N.

Hydrogen maleate, m.p. 157 – 159 °C (ethanol). For $C_{17}H_{22}N_4O_6$ (378.4) calculated: 53.96% C, 5.86% H, 14.81% N; found: 53.85% C, 5.87% H, 14.74% N.

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