POTENTIAL ANTAGONISTS OF EXCITATORY AMINO ACIDS AND ANTICONVULSANTS: SOME HETEROCYCLIC (±)-PYRROLIDINE-2-CARBOXAMIDES

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The benzylpyrrolidine amides **1a–1d**, **3a–3e**, **5a**, and **5b** were prepared from *N*-benzyl-L-proline methyl ester with corresponding diamines. Compounds **2a–2d**, **4b**, and **4e** have similarly been synthesized from L-proline methyl ester and the corresponding diamines in refluxing methanol. In both cases, the reactions were accompanied by racemization. Prepared amides were transformed to salts, suitable for pharmacological testing (hydrogen maleates, hydrogen oxalates and hydrochlorides). The products were tested by selected methods of biochemical and behavioural pharmacology.

Key words: Excitatory amino acids; Anticonvulsants; Pyrrolidine-2-carboxamides.

In foregoing papers we described series of 2-oxopyrrolidine-1-acetic piperazides[1], some further amides and choline derivatives[2] and some other compounds of this type[3] as potential nootropic agents. This program is being continued with the aim at finding substances having positive action on memory and learning processes or neuroprotective effects with possible usefullness in ischemic, hypoxic or traumatic brain damages. Antagonists of excitatory amino acids may also be useful in these therapeutic areas and are, therefore, also the object of our interest.

Mechanisms of action based on interaction with excitatory amino acid receptors have recently been proven with some "classical" 2-pyrrolidinone-derived nootropic agents (cf. aniracetam, 1-(4-methoxybenzoyl)pyrrolidin-2-one, refs[4–7]). Until now, a number of nootropic agents, derived not only from pyrrolidin-2-one but also from proline and its derivatives, have been described in publications and patents[8–13]. The present paper deals with basic amides of racemic proline and related compounds with expected neuroprotective effects and influence on learning and memory.

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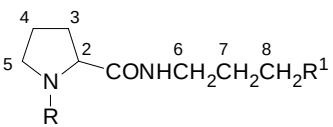
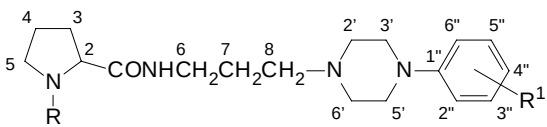
The benzylpyrrolidine amides **1a–1d**, **3a–3e**, **5a**, and **5b** were prepared by heating *N*-benzyl-L-proline methyl ester[14] with corresponding diamines (cf. Experimental). Compounds **2a–2d**, **4b**, and **4e** have similarly been synthesized from L-proline methyl ester[15] and the corresponding diamines in refluxing methanol. In both cases, the reactions were accompanied by racemization. Compound **4e** prepared in another way in optically pure L- and D-forms did not show different pharmacological effects[16]. Homogeneous amides were isolated by chromatography on silica gel and transformed to salts, suitable for pharmacological testing (hydrogen maleates, hydrogen oxalates and hydrochlorides).

The products were tested by selected methods of biochemical and behavioural pharmacology. Inhibition of binding of 1 nM [^{3}H]MK-801 (per cent of inhibition of the original binding by compounds in concentrations of 100 μM or IC_{50} values in μM are given) to receptors in rat brain cortex membranes: **1a**, 73; **2b**, IC_{50} = 11.3; **3a**, 67; **3b**, 66; **4b**, IC_{50} = 19.4; **4e**, IC_{50} = 5.8; for remaining compounds, IC_{50} > 100. Inhibition of binding of 50 nM [^{3}H]glycine (per cent of the original binding by compounds in concentrations of 100 μM), to neuronal membranes from rat brain cortex: **1a**, 50; **1b**, 38; **2a**, 95; **3a**, 89; **3b**, 73; **3c**, 75; **3d**, 46; **4b**, 125 (i.e. stimulation of binding); **4e**, 101; **5a**, 51. Inhibition of binding of 4 nM [^{3}H]5,7-dichlorokynurenic acid (per cent or IC_{50} values in



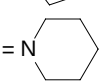
1, R = $CH_2C_6H_5$
2, R = H

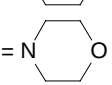


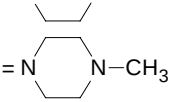
3, R = $CH_2C_6H_5$
4b, R = H
4e, R = H

In formulae **1** and **2** :

a, R^1 = 

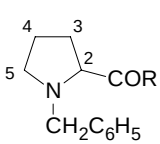
b, R^1 = 

c, R^1 = 

d, R^1 = 

In formulae **3** and **4** :

a, R^1 = 2-OCH_3; **b**, R^1 = 3-OCH_3
c, R^1 = 4-OCH_3; **d**, R^1 = 4-CH_3; **e**, R^1 = 3-Cl



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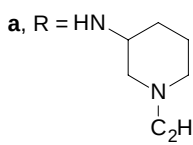
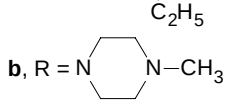
a, R = 

b, R = 

μM given; compounds in concentrations of 100 μM) to 100 μM of membrane proteins from rat brain cortex: **1c**, 60; **1d**, 60; **3a**, IC_{50} = 4.9; **3b,** IC_{50} = 6.7; **2c**, 29; **2d**, 48; **3e**, 217 (stimulation of binding); **4b**, 32; **4e**, IC_{50} = 4.9; glycine, IC_{50} = 2.7.

Anticonvulsant effect in the electroshock test in female mice (dose of 20 mg/kg i.p., effect in groups by 6 animals) : **1a**, 6/6; **2d**, indication of effect; **3a**, 6/6; **3b**, 5/6; **4e** 5/6. Protection of mice from acute anoxia elicited by intravenous administration of KCN (tested compounds in doses of 20 mg/kg i.p., survival time in s): **2a**, 45; **2b**, 45; **2c**, 40; **2d**, 54; **3a**, 270; **3b**, 217 (in 50% of animals more than 5 min); **3c**, 182; **3d**, 208; **3e**, 150 (with 2 animals in the group more than 5 min); **4b**, 112 (with 2 animals in the group more than 5 min); **4e**, 44; control, 30–36 s). Compounds **2a**, **2c**, **3a**, **3e**, and **4e** in doses of 10 and 20 mg/kg brought about significant prolongation of the duration of pentobarbital sleeping time in mice. Compound **4e** proved effective in the test of "social memory" in rats; in i.p. doses of 2.5 and 5 mg/kg it increased the efficiency of the animals (the optimum effect after the dose of 10 mg/kg was, however, accompanied by central depression). A more detailed report on the pharmacological testing will be the object of a special paper.

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. IR spectra were recorded (mostly in Nujol, ν in cm^{-1}) with Unicam SP 2000 or Perkin–Elmer 298 spectrophotometers; NMR spectra on a Tesla BS 567A (^1H at 100 MHz, ^{13}C at 25.14 MHz; chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz); 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 a columns of silica gel (Fluka 60, 0.063–0.20 mm).

General Procedure for Preparation of the Amides **1a–1d**, **3a–3e**, **5a**, and **5b**

A mixture of *N*-benzyl-L-proline methyl ester[14] (3.3 g, 15 mmol) and the corresponding diamine (15 mmol) was heated to 145–155 °C under stirring for 3 h. After cooling, the mixture was dissolved in dichloromethane (50 ml), the solution was washed with water (4 × 30 ml), dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of silica gel (60 g). The oily bases were transformed to the corresponding salts.

N-[3-(1-Pyrrolidinyl)propyl]-1-benzylpyrrolidine-2-carboxamide (Ia): Reaction of 1.92 g *N*-(3-aminopropyl)pyrrolidine[17] gave 2.95 g (47%) of the crude oily base **1a**. ^1H NMR spectrum ($CDCl_3$): 7.28 s, 5 H (Ar-H); 3.88 d and 3.48 d, 2 H, *J* = 13.0 (AB system, Ph-CH_2); 3.00–3.40 m, 3 H (H-2, H-6). ^{13}C NMR spectrum ($CDCl_3$): 174.27 s (C=O); 138.34 s (C-1 of benzyl); 128.48 d (C-3 and C-5 of benzyl); 128.10 d (C-2 and C-6 of benzyl); 126.98 d (C-4 of benzyl); 67.23 d (C-2); 59.61 t (**C**H_2-Ph); 54.23 t (C- 8); 53.93 t (C-2 and C-5 of pyrrolidine); 53.63 t (C-5); 37.50 t C-7); 30.40 t (C-6); 28.23 t (C-3); 23.75 t (C-4); 23.17 t (C-3 and C-4 of pyrrolidine).

Di(hydrogen maleate), m.p. 114–118 °C. IR spectrum (KBr): 706, 755 (5 adjacent ArH); 1 360, 1 380, 1 574 (COO^-); 1 484, 1 612, 3 020, 3 085 (Ar); 1 584, 1 682 (CONH); 2 500, 2 640 (NH^+); 3 260 (NH). For $C_{27}H_{37}N_3O_9$ (547.6) calculated: 59.22% C, 6.81% H, 7.67% N; found: 59.01% C, 6.89% H, 7.52% N.

N-[3-(1-Piperidinyl)propyl]-1-benzylpyrrolidine-2-carboxamide (**1b**): Reaction with 2.1 g *N*-(3-aminopropyl)piperidine[18] afforded 3.6 g (55%) of oily base **1b**. ^{13}C NMR spectrum ($CDCl_3$): 174.34 s (C=O); 138.41 s (C-1 of benzyl); 128.55 d (C-3 and C-5 of benzyl); 128.25 d (C-2 and C-6 of benzyl); 127.06 d (C-4 of benzyl); 67.30 d (C-2); 59.68 t (**C**H_2-Ph); 56.99 t (C-8); 54.53 t (C-2 and C-6 of piperidyl); 53.78 t (C-5); 37.50 t (C-7); 30.55 t (C-6); 26.44 t (C-3); 25.77 t (C-3 and C-5 of piperidyl); 24.20 t (C-4 of piperidyl); 23.83 t (C-4).

Di(hydrogen maleate), m.p. 146.5–147.5 °C (acetone–ethanol). IR spectrum (KBr): 701, 747 (5 adjacent Ar-H); 1 364, 1 383, 1 570 (COO^-); 1 497, 3 054 (Ar); 1 570, 1 676 (RCONHR); 2 687 (NH^+); 3 222, 3 407 (NH). Mass spectrum, *m/z* (%): 329 (M^+, $C_{20}H_{31}N_3O$, 1.5), 238 (2), 169 (7), 160 (100), 91 (73), 54 (63). For $C_{28}H_{39}N_3O_2$ (561.6) calculated: 59.88% C, 7.00% H, 7.48% N; found: 59.77% C, 7.04% H, 7.28% N.

N-(3-Morpholinylpropyl)-1-benzylpyrrolidine-2-carboxamide (**1c**): Reaction using 2.16 g *N*-(3-aminopropyl)morpholine[19] resulted in 2.4 g (49%) of oily base **1c**. ^1H NMR spectrum ($CDCl_3$): 7.50 bm, 1 H (NH); 7.28 s, 5 H (Ar-H); 3.84 d and 3.50 d, 2 × 1 H, J = 13.0 (AB system, **C**H_2-Ph); 3.70 m, 4 H (H-3 and H-5 of morpholinyl); 2.42 m, 4 H (H-2 and H-6 of morpholinyl).

Di(hydrogen maleate), m.p. 138–139 °C (acetone–ethanol). IR spectrum (Nujol): 700, 751 (5 adjacent Ar-H); 1 100 (R–O–R); 1 480, 1 612, 3 010, 3 082 (Ar); 1 580, 1 677 (NHCO); 3 255 (NH). Mass spectrum, *m/z* (%): 331 (M^+, $C_{19}H_{29}N_3O_2$, 0.5), 301 (1), 240 (1), 228 (0.7), 210 (1.5), 200 (2), 171 (3), 160 (100), 91 (74), 73 (24), 60 (22). For $C_{27}H_{37}N_3O_{10}$ (563.6) calculated: 57.54% C, 6.62% H, 7.45% N; found: 57.25% C, 6.73% H, 7.39% N.

N-[3-(4-Methyl-1-piperazinyl)propyl]-1-benzylpyrrolidine-2-carboxamide (**1d**): The use of 2.34 g 1-(3-aminopropyl)-4-methylpiperazine[20] led to 2.9 g (56%) of oily base **1d**. ^{13}C NMR spectrum ($CDCl_3$): 174.19 s (**C**ONH); 138.19 s (C-1 of benzyl); 128.48 d (C-3 and C-5 of benzyl); 128.10 d (C-2 and C-6 of benzyl); 126.98 d (C-4 of benzyl); 67.15 d (C-2); 59.53 t (**C**H_2-Ph); 56.02 t (C-8); 54.75 t (C-3 and C-5 of piperazinyl); 53.63 t (C-5); 52.88 t (C-2 and C-6 of piperazinyl); 45.71 q (**C**H_3); 37.20 t (C-7); 30.33 t (C-6); 26.22 t (C-3); 23.68 t (C-4).

Tri(hydrogen maleate) monohydrate, m.p. 162–165 °C (acetone–ethanol). IR spectrum (Nujol): 699, 746 (5 adjacent Ar-H); 1 072, 1 355, 1 569 (COO^-); 1 473, 1 617, 3 026 (Ar); 1 569, 1 675 (RCONHR); 2 387, 2 550 (NH^+); 3 222, 3 407 (NH). Mass spectrum, *m/z* (%): 344 (M^+, $C_{20}H_{32}N_4O$, 0.6), 288 (0.9), 274 (2), 253 (4), 184 (5), 160 (100), 98 (6), 91 (65). For $C_{32}H_{44}N_4O_{13}$. H_2O (701.7) calculated: 54.77% C, 6.46% H, 7.98% N; found: 54.98% C, 6.42% H, 7.85% N.

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl}-1-benzylpyrrolidine-2-carboxamide (**3a**): Reaction with 3.8 g 1-(3-aminopropyl)-4-(2-methoxyphenyl)piperazine[21] gave 3.2 g (49%) of oily base **3a**. ^1H NMR spectrum ($CDCl_3$): 7.55 bm, 1 H (NH); 7.28 s, 5 H (Ar-H of benzyl); 6.90 m, 4 H (H-3″, H-4″, H-5″, H-6″); 3.88 d and 3.52 d, 2 × 1 H, J = 13 (AB system, CH_2 of benzyl); 3.88 s, 3 H (CH_3O); 3.10 m (H-3′ and H-5′); 2.65 m, 4 H (H-2′ and H-6′).

Di(hydrogen maleate), m.p. 135–138 °C (ethanol–ether). IR spectrum (Nujol): 700 (5 adjacent Ar-H); 750 (4 adjacent Ar-H); 1 025, 1 249 (ArOR); 1 500, 3 010, 3 050 (Ar); 1 580, 1 685 (CONH); 2 495, 2 620 (NH^+); 3 240 (NH). Mass spectrum, *m/z* (%): 436 (M^+, $C_{26}H_{36}N_4O_2$, 0.2), 421 (0.3), 345 (2), 286 (2.5), 160 (52), 98 (26), 91 (38), 54 (100). For $C_{34}H_{44}N_4O_{10}$ (668.7) calculated: 61.06% C, 6.63% H, 8.38% N; found: 60.99% C, 6.71% H, 8.32% N.

N-{3-[4-(3-Methoxyphenyl)-1-piperazinyl]propyl}-1-benzylpyrrolidine-2-carboxamide (**3b**): Reaction with 3.8 g 1-(3-aminopropyl)-4-(3-methoxyphenyl)piperazine[21] resulted in 3.7 g (56%) of oily base **3b**. ^1H NMR spectrum ($CDCl_3$): 7.32 bs, 5 H (Ar-H of benzyl); 6.45 m, 3 H (H-2″, H-4″, H-6″); 3.85 d and 3.50 d, 2 × 1 H, J = 12 (AB system, CH_2 of benzyl); 3.77 s, 3 H (CH_3O). ^{13}C NMR ($CDCl_3$):

174.64 s (C=O); 160.60 s (C-3″); 152.60 s (C-1″); 138.56 s (C-1 of benzyl); 129.75 d (C-5″); 128.70 d (C-3 and C-5 of benzyl); 128.48 d (C-2 and C-6 of benzyl); 127.28 d (C-4 of benzyl); 108.76 d (C-6″); 104.42 d (C-4″); 102.41 d (C-2″); 67.45 d C-2); 59.83 t (**C**H_2-Ph); 56.25 t (C-8); 55.13 q (CH_3O); 53.93 t (C-5); 53.18 t (C-2′ and C-6′); 48.93 t (C-3′ and C-5′); 37.42 t (C-6); 30.62 t (C-7); 26.52 t (C-3); 23.98 t (C-4).

Di(hydrogen maleate), m.p. 160.5–161.5 °C (ethanol). Mass spectrum, *m/z* (%): 436 (M^+, $C_{26}H_{36}N_4O_2$, 0.3), 421 (0.3), 345 (2), 276 (2), 274 (2.5), 160 (100), 91 (74). For $C_{34}H_{44}N_4O_{10}$ (668.7) calculated: 61.06% C, 6.63% H, 8.38% N; found: 60.79% C, 6.73% H, 8.24% N.

N-{3-[4-(4-Methoxyphenyl)-1-piperazinyl]propyl}-1-benzylpyrrolidine-2-carboxamide (**3c**): The use of 3.8 g 1-(3-aminopropyl)-4-(4-methoxyphenyl)piperazine[22] afforded 3.7 g (56%) of crystalline base **3c**. ^{1}H NMR spectrum ($CDCl_3$): 7.28 s, 5 H (Ar-H of benzyl); 6.86 s, 4 H (H-2″, H-3″, H-5″, H-6″); 3.85 d and 3.50 d, 2 × 1 H, J = 13 (AB system, CH_2 of benzyl); 3.76 s, 3 H (OCH_3); 3.08 bt, 4 H (2 × H-3′ and H-5′); 2.58 bt, 4 H (2 × H-2′ and H-6′).

Di(hydrogen maleate), m.p. 125–128 °C (2-propanol–ether). IR spectrum (KBr): 701, 747 (5 adjacent Ar-H); 825 (2 adjacent Ar-H); 1 015, 1 245 (ArOR); 1 364, 1 383, 1 573 (COO^-); 1 508, 3 053 (Ar); 1 573, 1 674 (RCONHR); 2 585, 2 622, 2 685 (NH^+); 3 410 (NH). Mass spectrum, *m/z* (%): 436 (M^+, $C_{26}H_{36}N_4O_2$, 0.4), 421 (0.4), 345 (1.5), 276 (1.7), 274 (2), 160 (47), 98 (24), 91 (30), 72 (30), 54 (100). For $C_{34}H_{44}N_4O_{10}$ (668.7) calculated: 61.06% C, 6.63% H, 8.38% N; found: 61.29% C, 6.70% H, 8.33% N.

N-{3-[4-(4-Methylphenyl)-1-piperazinyl]propyl}-1-benzylpyrrolidine-2-carboxamide (**3d**): Reaction with 3.5 g 1-(3-aminopropyl)-4-(4-methylphenyl)piperazine[23] gave 4.85 g (77%) oily base **3d.** ^{1}H NMR spectrum ($CDCl_3$): 7.60 bm, 1 H (NH); 7.28 s, 5 H (Ar-H of benzyl); 7.08 d, 2 H, J = 9 (H-3″ and H-5″); 6.82 d, 2 H, J = 9 (H-2″ and H-6″); 3.88 d and 3.50 d, 2 × 1 H, J = 13 (AB system, CH_2 of benzyl); 3.12 m, 4 H (2 × H-3′ and H-5′); 2.58 m, 4 H (2 × H-2′ and H-6′); 2.28 s, 3 H (CH_3).

Di(hydrogen maleate), m.p. 145–147 °C (ethanol–ether). IR spectrum (KBr): 703, 749 (5 adjacent Ar-H); 812 (2 adjacent Ar-H); 1 366, 1 385, 1 572 (COO^-); 1 511, 3 031, 3 056 (Ar); 1 572, 1 676 (CONH); 2 581, 2 677 (NH^+); 3 416, 3 417 (NH). Mass spectrum, *m/z* (%): 420 (M^+, $C_{26}H_{36}N_4O$, 0.4), 405 (0.6), 329 (3), 274 (3.5), 260 (3.5), 160 (100), 91 (60). For $C_{34}H_{44}N_4O_9$ (652.7) calculated: 62.56% C, 6.81% H, 8.79% N; found: 62.41% C, 6.81% H, 8.79% N.

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}-1-benzylpyrrolidine-2-carboxamide (**3e**): The use of 3.8 g 1-(3-aminopropyl)-4-(3-chlorophenyl)piperazine[23] resulted in 4.1 g (58%) of oily base **3e.** ^{1}H NMR spectrum ($CDCl_3$): 7.30 s, 5 H (Ar-H of benzyl); 6.70–7.20 m, 4 H (H-2″, H-4″, H-5″, H-6″); 3.85 d and 3.50 d, 2 × 1 H, J = 13 (AB system, CH_2 of benzyl); 3.15 bt, 4 H (2 × H-3′ and H-5′); 2.52 bt, 4 H (2 × H-2′ and H-6′).

Di(hydrogen maleate), m.p. 170–171.5 °C (ethanol). IR spectrum: 702, 748, 769 (5 adjacent Ar-H); 702, 841 (3 adjacent Ar-H); 886 (solitary Ar-H); 1 360, 1 382, 1 579 (COO^-); 1 481, 3 012 (Ar); 1 579, 1 674 (RCONHR); 1 572, 2 621, 2 684 (NH^+), 3 200 (NH). Mass spectrum, *m/z* (%): 440 (M^+, $C_{25}H_{33}ClN_4O$, 0.4), 349 (0.7), 274 (3), 160 (100), 91 (58), 88 (11), 54 (40). For $C_{33}H_{41}ClN_4O_9$ (673.1) calculated: 58.88% C, 6.14% H, 5.27% Cl, 8.32% N; found: 58.65% C, 6.22% H, 5.37% Cl, 8.04% N.

N-(1-Ethylpiperidin-3-yl)-1-benzylpyrrolidine-2-carboxamide (**5a**): The use of 2.25 g 3-amino-1-ethylpiperidine[24] led to 5.1 g (81%) of oily base **5a**.

Dihydrochloride monohydrate, m.p. 227–229 °C (2-propanol–ether). IR spectrum: 702, 753 (adjacent Ar-H); 1 365, 1 384, 1 579 (COO^-); 1 491, 2 999 (Ar); 1 656 ($RCONR_2$); 2 447, 2 584, 2 666 (NH^+). Mass spectrum, *m/z* (%): 287 (M^+, $C_{17}H_{25}N_3O$, 0.4), 160 (94), 91 (100), 65 (8), 54 (12), 91 (99). For $C_{19}H_{31}Cl_2N_3O$. H_2O (406.4) calculated: 56.15% C, 8.18% H, 17.45% Cl, 10.34% N; found: 55.82% C, 7.96% H, 17.34% Cl, 10.04% N.

1-(1-Benzylpyrrolidine-2-carbonyl)-4-methylpiperazine (**5b**): Reaction with 1.5 g of 1-methyl- piperazine gave 1.0 g (23%) of oily base **5b**. ^{1}H NMR spectrum ($CDCl_3$): 7.30 s, 5 H (Ar-H of benzyl); 3.94 d and 3.44 d, 2 × 1 H, J = 13 (AB system, CH_2 of benzyl); 3.60 bt, 4 H (2 × H-2′ and H-6′); 2.34 bt, 4 H (2 × H-3′ and H-5′); 2.28 s, 3 H (CH_3).

Di(hydrogen maleate) hemihydrate, m.p. 164–167 °C (acetone–ether). Mass spectrum, *m/z* (%): 315 (M^+, $C_{19}H_{29}N_3O$, 0.7), 224 (0.5), 205 (3.5), 160 (100), 111 (31), 91 (99). For $C_{25}H_{33}N_3O_9$. 0.5 H_2O (528.5) calculated: 56.80% C, 6.48% H, 7.95% N; found: 56.57% C, 6.35% H, 7.79% N.

General Procedure for Preparation of the Amides **2a–2d**, **4b**, and **4e**

A mixture of L-proline methyl ester hydrochloride[15] (4.95 g, 0.03 mol), the corresponding amine (0.03 mol) and methanol (30 ml) was refluxed for 8 h. Methanol was evaporated in vacuo and the oily residue was chromatographed on a column of silica gel (150 g). Elution with chloroform removed the less polar components and the desired amides were then eluted with chloroform containing NH_3 (0.5 g per 100 ml). The obtained homogeneous bases were transformed to salts.

N-(3-(1-Pyrrolidinyl)propyl)pyrrolidine-2-carboxamide (**2a**): Reaction with 3.8 g *N*-(3-aminopropyl)pyrrolidine[17] gave 3.3 g (50%) oily base **2a**. ^{1}H NMR spectrum ($CDCl_3$): 8.00 bm (NH); 3.70 dd, 1 H (H-2); 3.32 m, 2 H (H-5); 2.95 m, 2 H (H-6).

Di(hydrogen oxalate) hemihydrate, m.p. 111–115 °C (ethanol). Mass spectrum, *m/z* (%): 225 (M^+, $C_{12}H_{23}N_3O$, 3), 155 (12), 84 (68), 70 (58), 44 (100). For $C_{16}H_{27}N_3O_9$. 0.5 H_2O (405.4) calculated: 46.37% C, 6.81% H, 10.14% N; found: 46.51% C, 6.61% H, 10.04% N.

N-[3-(1-Piperidinyl)propyl]pyrrolidine-2-carboxamide (**2b**): The use of 4.25 g *N*-(3-aminopropyl)piperidine[18] gave 4.3 g (60%) of oily base **2b**. ^{1}H NMR spectrum ($CDCl_3$): 8.00 bs (NH); 3.68 dd, 1 H (H-2); 3.30 m, 2 H (H-5); 2.95 m, 2 H (H-6). ^{13}C NMR spectrum ($CDCl_3$): 175.16 s (C=O); 60.58 d (C-2); 57.29 t (C-8); 54.59 t (C-2 and C-6 of piperidyl); 47.13 t (C-5); 37.95 t (C-6); 30.70 t (C-7); 26.14 t (C-3); 25.99 t (C-4); 25.77 t (C-3 and C-5 of piperidyl); 24.28 t (C-4 of piperidyl).

Di(hydrogen oxalate), m.p. 117–121 °C (ethanol). Mass spectrum, *m/z* (%): 239 (M^+, $C_{13}H_{25}N_3O$, 0.8), 169 (5), 98 (28), 84 (12), 70 (24), 44 (100). For $C_{17}H_{29}N_3O_9$ (419.4) calculated: 48.68% C, 6.97 H, 10.02% N; found: 48.84% C, 7.07% H, 9.96% N.

N-[3-(4-Morpholinyl)propyl]pyrrolidine-2-carboxamide (**2c**): Working up of 4.7 g of *N*-(3-aminopropyl)morpholine[19] gave 2.0 g (28%) of oily base **2c**. ^{1}H NMR spectrum ($CDCl_3$): 3.70 m, 5 H (H-3, H-5 of morpholinyl, H-2); 3.32 q, 2 H (C-6); 2.50 m, 4 H (H-2 and H-6 of morpholinyl). ^{13}C NMR ($CDCl_3$): 175.31 s (C=O); 66.85 t (C-3 and C-5 of morpholinyl); 60.65 d (C-2); 57.14 t (C-8); 53.78 t (C-2 and C-6 of morpholinyl); 47.28 t (C-5); 37.87 t (C-6); 30.77 t (C-7); 26.14 t (C-3); 25.99 t (C-4).

Di(hydrogen oxalate) hemihydrate, m.p. 119–122 °C (ethanol). Mass spectrum (chemical ionization), *m/z* (%): 241 (M^+, $C_{12}H_{23}N_3O_2$). For $C_{16}H_{27}N_3O_{10}$. 0.5 H_2O (430.4) calculated: 44.65% C, 4.55% H, 9.76% N; found: 44.78% C, 6.43% H, 10.04% N.

N-[3-(4-Methyl-1-piperazinyl)propyl]pyrrolidine-2-carboxamide (**2d**): Reaction of 4.7 g 1-(3-aminopropyl)-4-methylpiperazine[20] led to 4.2 g (55%) of oily base **2d**. ^{1}H NMR spectrum ($CDCl_3$): 3.70 m, 1 H (H-2); 3.30 dd, 2 H (H-5); 2.95 m, 2 H (H-3); 2.48 bs, 8 H (H-2, H-3, H-5 and H-6 of piperazinyl); 2.28 s, 3 H (CH_3). ^{13}C NMR ($CDCl_3$): 175.09 s (C=O); 60.58 d (C-2); 56.54 t (C-8); 54.98 t (C-3 and C-5 of piperazinyl); 53.11 t (C-2 and C-6 of piperazinyl); 47.13 t (C-5); 45.86 q (**C**H_3); 37.80 t (C-7); 30.70 t (C-6); 26.22 t (C-3); 25.99 t (C-4).

Tri(hydrogen oxalate) hemihydrate, m.p. 186–189 °C (aqueous ethanol). For $C_{19}H_{32}N_4O_{13}$. 0.5 H_2O (533.5) calculated: 42.77% C, 6.23% H, 10.50% N; found: 42.85% C, 6.23% H, 10.73% N.

N-{3-[4-(3-Methoxyphenyl)-1-piperazinyl]propyl}pyrrolidine-2-carboxamide (**4b**): General procedure applied to 7.5 g 1-(3-aminopropyl)-4-(3-methoxyphenyl)piperazine[21] produced 3.95 g (38%) of oily

base **4b**. ^{1}H NMR spectrum ($CDCl_3$): 7.18 bs, 1 H (H-5″); 6.46 m, 3 H (H-2″, H-4″, H-6″); 3.80 s, 3 H (OCH_3).

Di(hydrogen oxalate), m.p. 190–197 °C (aqueous ethanol). For $C_{23}H_{34}N_4O_{10}$ (526.5) calculated: 52.46% C, 6.51% H, 10.64% N; found: 52.97% C, 6.43% H, 10.37% N.

N-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}pyrrolidine-2-carboxamide (**4e**): Reaction of 7.6 g 1-(3-aminopropyl)-4-(3-chlorophenyl)piperazine[23] afforded 4.9 g (4 %) of oily base **4e**. ^{13}C NMR spectrum ($CDCl_3$): 175.24 s (C=O); 153.38 s (C-1″); 134.98 s (C-3″); 130.05 d (C-5″); 119.22 d (C-4″); 115.68 d (C-2″); 113.84 d (C-6″); 60.73 d (C-2); 56.69 t (C-8); 53.11 t (C-3′ and C-5′); 48.63 t (C-2′ and C-6′); 47.28 t (C-5); 37.87 t (C-7); 30.78 t (C-6); 26.37 t (C-3); 26.14 t (C-4). Mass spectrum, *m/z* (%): 350 (M^+, $C_{18}H_{27}ClN_4O$, 0.3), 335 (1), 280 (3), 209 (6), 198 (5), 184 (35), 167 (9), 113 (8), 86 (10), 84 (10), 70 (95).

Di(hydrogen oxalate), m.p. 100–107 °C (ethanol–ether). For $C_{22}H_{31}ClN_4O_9$ (531.0) calculated: 49.76% C, 5.88% H, 6.68% Cl, 10.55% N; found: 49.46% C, 6.18% H, 6.89% Cl, 10.41% N.

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