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Synthesis and analgesic activity of *N*-aryl/arylalkyl 3-(1-pyrrolidinyl/piperidinyl)butyramides*

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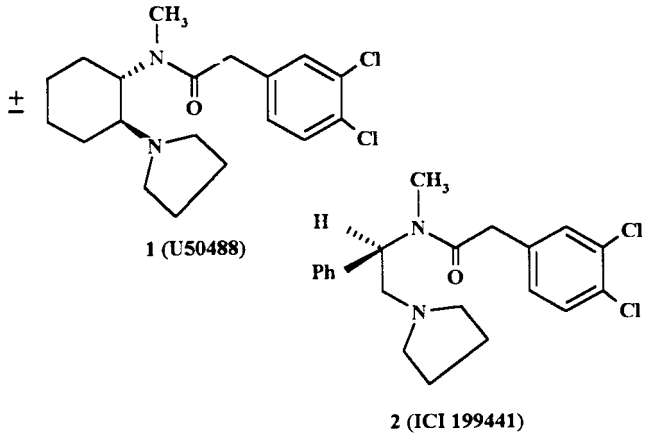
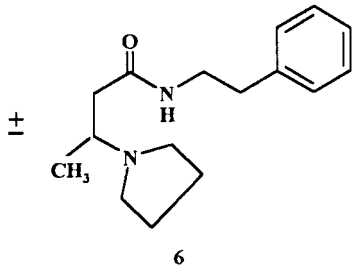
Conjugate addition of pyrrolidine or piperidine to methyl crotonate, and hydrolysis of the resulting methyl butyrates gave the (±)-3-pyrrolidino or piperidinobutyric acids **17** and **18**, respectively. Coupling of these racemic acids to arylalkylamines, L-phenylalaninamide or L-phenylalanine methyl ester gave the *N*-substituted butyramides **3**–**14** which were tested as analgesics using the hot-plate method. (±)-*N*-(2-Phenethyl)-3-(1-pyrrolidinyl)butyramide (**6**) showed naloxone-attenuated analgesia but was considerably less potent than morphine and of shorter duration of action. Diastereomeric butyramides containing Phe residue (**11**–**14**) were less active than **6**, but unlike *N*-arylalkylsubstituted derivatives, showed no toxic effects on locomotor activity at the high doses (30–60 mg/kg) used for testing. In all cases, analgesia was accompanied by an inhibition of spontaneous motor activity and sedation.

1. Introduction

Studies show that κ-opioid agonists may induce potent analgesia without some of the undesirable effects of μ or morphine-like agonists (respiratory depression, physical dependence...) [1–6]. Several arylacetamides, e.g. U50488 (**1**) [1] and ICI199441 (**2**) [2], have been identified as selective κ-opioid ligands and potent analgesics *in vivo*. These arylacetamides have a common pharmacophore characterized by a tertiary basic nitrogen separated by two carbon atoms to the amidic nitrogen [3]. The cyclohexane ring in **1** may serve to direct pharmacophoric groups to *trans*-positions for optimum binding. Conformational studies showed that the torsional $N^+-C-C-N$ angle in the truncated derivative **2** (60°) is nearly equal to that in U50488 (**1**) [3].

The objectives of this study were to synthesize *N*-aryl/arylalkyl 3-(1-pyrrolidinyl) or 3-(1-piperidinyl)butyramides **3**–**14** (Table 1), and to examine whether they have antinociceptive activity against noxious thermal stimulus in mice (hot-plate test) [7]. Compounds **3**–**14** possess common pharmacophores of κ agonists, however, the amide linkage in these derivatives is reversed relative to arylacetamide ligands. The distance between the amidic (or basic) nitrogen and the aromatic residue, which appears to be critical for opioid activity and selectivity was varied using methylene units (**3**–**9**) or Gly-CH_2CH_2 (**10**) as spacers. L-Phe residue is incorporated as in dipeptides **11**–**14** because of its crucial role in the activity of opioid peptides including the κ ligand *Dynorphin* and its analogues [8]. At this stage, no attempts were made to separate possible stereoisomers and compounds were tested as racemates (**3**–**10**) or mixtures of diastereomers (**11**–**14**).





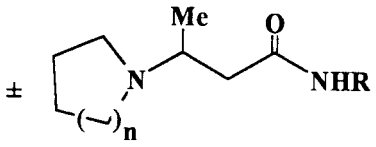
2. Investigations and results

2.1. Chemistry

Conjugate addition and pyrrolidine or piperidine to methyl crotonate afforded (±)-aminoester **15** and **16**, respectively (Scheme). Excellent yields of the addition products were obtained by carrying out the reaction in methanol at room temperature. Alkaline hydrolysis of these aminoesters gave the corresponding acids **17** and **18** which were coupled to the appropriate amine using HOBt/DCC. The amino component of **10** ($PhCH_2CH_2NHCOCH_2NH_2$) [9] was prepared by DCC coupling of phenethylamine to *N*-benzyloxycarbonylglycine (Z-Gly-OH) followed by removal of the Z group by catalytic transfer hydrogenation [10]. L-Phenylalaninamide or L-phenylalanine methyl ester were used as the amino components for the preparation of **11**–**14**. ^{1}H NMR spectra of **11**–**14** indicated that each compound consists of two diastereomers in equal quantities as was shown by their methyl signals (doublets, $J = 6.8$ Hz) which exhibited as much as 0.27 ppm difference in chemical shifts. The HCl salts of **6**–**10** and of **13** and **14** were extremely hygroscopic and suitable solvents for crystallization were not identified, neither were alternative acceptable salts found.

The ^{1}H NMR spectrum of aminoester **15** · HCl in $CDCl_3$ (Fig. 1) showed that the two diastereotopic methylene protons α to the carbonyl group (H_A and H_B, Fig. 2) appeared as two sets (4 lines each) of absorptions at δ 2.73 and 3.13 ppm, of $J_{gem} = 16.7$ Hz. Each of these two protons showed different coupling ($J_{vic} = 4.1$ and 8.85 Hz) to the C-3 methine proton (H_X). The H_X signal appeared as a multiplet at δ 3.5 (overlapping with other absorptions)

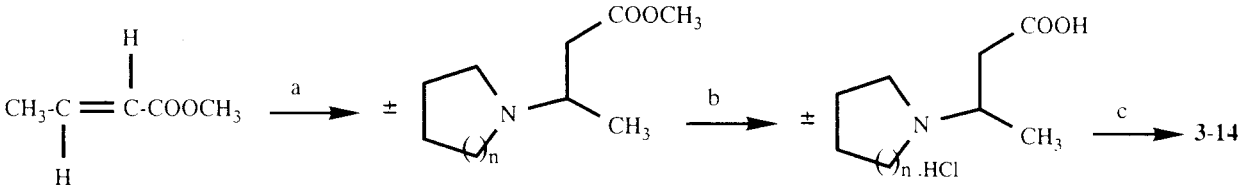
Table 1: Physical properties of *N*-substituted 3-(1-pyrrolidinyl or piperidinyl)butyramides



Compd.	R	n	mp, °C (cryst solv)	TLC[a], R_f	Formula[b]
3[c]	p-ClC_6H_4	1	86–90 (CH_2Cl_2)	0.47	$C_{14}H_{19}ClN_2O$
4 · HCl	CH_2Ph	1	121–125 (Me_2CO)	0.53	$C_{15}H_{22}N_2O \cdot HCl$
5 · HCl	CH_2Ph	2	163–165 (Me_2CO)	0.53	$C_{16}H_{24}N_2O \cdot HCl$
6	CH_2CH_2Ph	1	52–55	0.53	$C_{16}H_{24}N_2O$
7	CH_2CH_2Ph	2	oil	0.55	$C_{17}H_{26}N_2O$
8	$CH_2CH_2CH_2Ph$	1	oil	0.45	$C_{17}H_{26}N_2O$
9	$CH_2CH_2CH_2Ph$	2	oil	0.51	$C_{18}H_{28}N_2O$
10	$CH_2CONHCH_2CH_2Ph$	1	oil	0.17	$C_{18}H_{27}N_3O_2$
11[d,e]	$CH(CONH_2)CH_2Ph$	1	123–125 (Et_2O)	0.14	$C_{17}H_{25}N_3O_2$
12[d,e]	$CH(CONH_2)CH_2Ph$	2	110–112 (Et_2O)	0.25	$C_{18}H_{27}N_3O_2$
13[d]	$CH(COOCH_3)CH_2Ph$	1	oil	0.72	$C_{18}H_{26}N_2O_3$
14[d]	$CH(COOCH_3)CH_2Ph$	2	oil	0.74	$C_{19}H_{28}N_2O_3$

[a] Silica (EtOAc/methylcyclohexane/triethylamine, 7.5 : 3.5 : 0.4). [b] Compounds **3**–**5** were analyzed for C, H and N (within ±0.4%); compounds **6**–**14** were analyzed for N (within ±0.4%). [c] mp of HCl salt 168–170 °C (Me_2CO). [d] Mixture of two diastereoisomers (1 : 1) differ in configuration at C-(3) of the butyric chain and of the same L-configuration at R residue. [e] Purification from ether did not significantly alter isomeric ratio

Scheme



15, n = 1
16, n = 2

17.HCl, n = 1
18.HCl, n = 2

(a) pyrrolidine or piperidine, MeOH; (b) NaOH, H_2O then HCl; (c) HOBt, DCC, TEA, RNH_2 (see text)

from which the above J_{vic} values could be abstracted. These data suggested restricted rotation about the C(2)–C(3) bond with preferred torsional angles of nearly 50° and 155°, respectively, as in conformer **a** or **b** (or their mirror images) in Fig. 2 [11]. Conformer **a** is characterized by less *gauche* interactions to the methyl group, and by possible electrostatic stabilization between the positive nitrogen and the carbonyl oxygen.

Similar analysis of the corresponding acid **17** · HCl (in $CDCl_3$) showed that the chemical shift difference between the α methylene protons became less apparent. Their absorptions degenerated into a multiplet at 2.74 ppm. The C-3 methine signal (3.74 ppm) appeared, in this case, as a hextet of nearly equal spacings (6.6 Hz) which suggested equal coupling to the methylene protons, possibly due to free rotation. In that aspect, most of the amidic

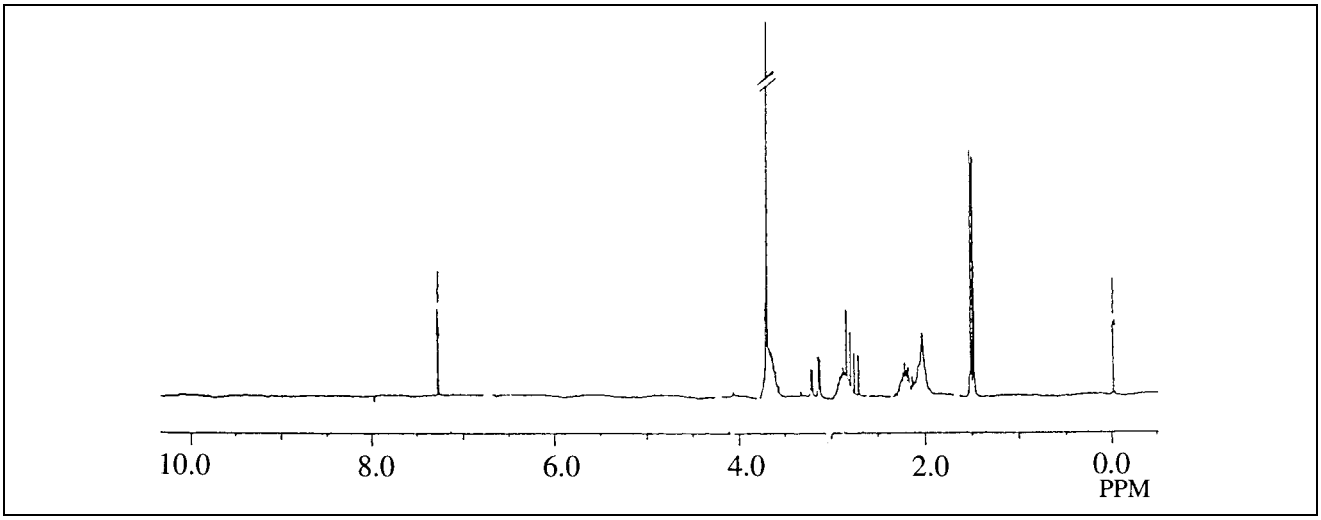


Fig. 1: 200 MHz ^1H NMR spectrum of aminoester **15** · HCl in $CDCl_3$

products **4**–**14** (whether as HCl or base forms) showed ^{1}H NMR characteristics similar or closer to that the of ester **15** than the acid **17** hydrochlorides. Most notably was the small methylene-methine coupling (~4 Hz) which was indicative of restricted rotation. It is likely, therefore, that an "**a**-like conformation" would prevail by these amides, particularly at physiological pH.

2.2. Pharmacology

Compounds **3**–**14** were investigated for antinociception using the mouse 55 °C hot-plate test [7, 12]. For each experiment, control paw-lick latency times (hot-plate latency; HPL) were collected prior to drug administration. Drug was administered i.p. at zero time and HPLs were redetermined at several time intervals up to 2 h. Selected data are presented in Table 2 as percentage changes in HPL for compounds **4**, **6**, **7**, **10**, **11**, **13**, **14** and morphine sulfate.

In general, tested compounds showed weak to moderate analgesia. The *N*-phenethyl pyrrolidinobutyramide **6** was the most active analgesic. It showed a dose-related analgesic response which was attenuated by prior administration of naloxone. However, it was 2–3 times less potent than morphine or U50488 [6] in the hot-plate test and had a shorter duration of action. Analgesia was not accompanied by morphinomimetic effects (e.g., Straub tail), but with inhibition of spontaneous and exploratory motor activity, sedation and fast respiration. The *p*-chloroanilide **3** showed analgesic activity comparable to that of **6** (data not shown) but was apparently neurotoxic (tremors and jumping) at 20 mg/kg.

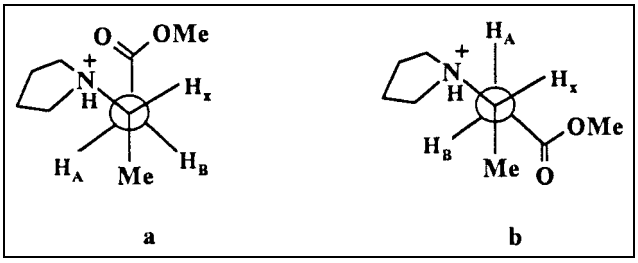


Fig. 2: Possible conformers of a (3*S*)-configuration of aminoester **15**

Animals treated with more than 40 mg/kg of **6** started to exhibit altered or impaired motor functions (most characteristically was a crawling and staggered movement with head and body close to the ground). Larger doses (100–120 mg/kg) resulted in tremors, convulsions and death from apparent respiratory depression. Other *N*-arylalkylamides (particularly **5** and **7**–**10**) were considerably less active than **6** and, except **10**, caused motor disfunctions at lower doses than **6**. Diastereomeric compounds containing a Phe residue **11**–**14** were less active than **4** or **6**. They also produced marked sedation, deminished spontaneous activity, but no motor impairments were observed at the high doses (up to 60 mg/kg) used for testing. As shown in Table 2, ester **14** exhibited a longer duration of analgesia than its amide counterpart **11**. At doses of 60–120 mg/kg of compounds **11**–**14**, animals appeared profoundly sedated, indifferent to non-painful stimuli and confined to hiding locations. However, at these doses they showed no motor dysfunctions, tremors, convulsions, catalepsy or lethality. Repeated administrations of naloxone (2–3 × 2 mg/kg) reduced the above effects.

Table 2: Analgesic response to butyramide derivatives in the mouse hot-plate test

		% Change in HPL[b]				
Time (min) n°	0 Dose[a] (mg/kg)	15	30	60	90	120
4	40	92 ± 20*	41 ± 16*	62 ± 13*[d]	55 ± 17*	17 ± 12
	40[c]	54 ± 6*	25 ± 22	33 ± 27	0 ± 13	–
6	20	86 ± 16*	71 ± 16*	32 ± 17	9 ± 9	−5 ± 9
	20[c]	42 ± 10*	23 ± 13	22 ± 13	0 ± 7	21 ± 12
	40	73 ± 22*	132 ± 14*	98 ± 27*	–	49 ± 18
	80	179 ± 12*	111 ± 7*[d]	86 ± 23*[d]	–	67 ± 34
7	40	78 ± 18*	18 ± 7	53 ± 11*	–	15 ± 7
10	40	62 ± 9*	33 ± 4*	16 ± 11	10 ± 8	4 ± 12
11[e]	30	68 ± 21*	45 ± 18*	10 ± 16	25 ± 6	0 ± 6
	60	94 ± 22*	91 ± 20*	63 ± 13*	–	16 ± 10
13[e]	60	42 ± 18*	65 ± 14*	65 ± 20*	54 ± 9*	40 ± 10*
14[e]	60	74 ± 16*	88 ± 19*	101 ± 18*	93 ± 15*	57 ± 13*
Morphine	20	123 ± 27*	150 ± 25*	108 ± 12*	72 ± 11*	52 ± 11*

[a] Solutions of compounds were prepared by adding equimolar amounts of citric acid to their base forms in H_2O; doses were calculated in mg (base)/kg, and administered by the i.p. route in a volume equivalent to 10 ml/kg. [b] calculated as T-To/To × 100, where T and To are the drug and control HPL in sec., respectively; values are expressed as the mean ± SE of the mean; 6–8 animals were used for each dose; asterisks (*) signify values statistically different from control (student t, $P < 0.05$). [c] Naloxone · HCl (4 mg/kg, s.c.) was administered 30 min prior to drug. [d] Signs of motor impairements. [e] Tested as an equal mixtures of two diastereomers (see text)

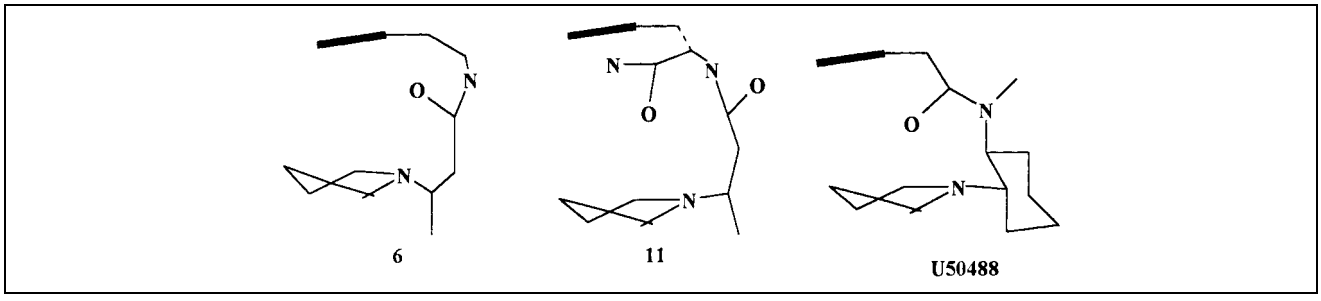


Fig. 3: Possible structural and conformational analogies between **6**, **11** and an active conformation of U50488 described in ref. [16]

3. Discussion

Attenuation of the antinociceptive effect of **6** by naloxone suggested that analgesia was mediated via opioid receptors. In addition, the associated behavioral effects in mice and the observed structure-activity changes were similar to that reported for κ agonists. However, radioligand binding studies should assess the nature of this opioid activity. SAR of the relatively rigid U-50488 showed stringent structural and conformational requirements for the amide linkage [13–15]. For example, reversing this linkage resulted in a dramatic loss of receptor affinity, which implied its possible involvement in hydrogen bonding interaction with the receptor in the proximity of the phenyl ring binding site [13]. In the more conformationally flexible secondary amides described in this study (e.g., **6**) it is likey that the amidic group may serve to enforce particular conformation of the molecule by intramolecular hydrogen bonding as suggested from NMR data, and as depicted in Fig. 3. Similar hydrogen bonding scheme to the carbonyl oxygen of Phe residue in compounds **11**–**14** should constrain the number of conformations available to these molecules possibly to a conformation which overlays that of U50488 (Fig. 3) [16].

Compounds **11**–**14** are of particular interest because of their low toxicity relative to **4** or **6**, probably due to limited accessibility to CNS. The introduction of polar groups to lipophilic opioids has been the goal of several studies to produce safer peripherally-acting analgesics [17]. In addition, higher analgesic scores for these potential κ ligands may be obtained using pressure than thermal stimulus [7]. Accordingly, it seems that separation and further testing of these isomeric compounds are worthwhile. The direct synthetic approach to these compounds from readily available materials can be advantageous.

4. Experimental

M.p. (uncorrected): Griffin apparatus. IR: Shimadzu-IR 345. ^{1}H NMR: Jeol FX 90 or Bruker 200, using tetramethylsilane as an internal standard. MS: Finnigan SSQ 7000. TLC: UV-fluorescent plastic-backed sheets with silica (Merck 60 F254). Elemental analysis were carried out at the Microanalytical Center at Cairo University, Cairo, Egypt. L-Phenylalanine methyl ester HCl $[\alpha]_D^{20} + 32.4$ (c =2, EtOH) was obtained from Aldrich; L-phenylalaninamide from Sigma; all other fine chemicals from Aldrich or Merch. Extracts of substances were dried over Na_2SO_4 and evaporations of solvents were carried out under reduced pressure.

4.1. (±)-*3-(1-Pyrrodinyl)butyric acid methyl ester* (**15**) *and* (±)-*3-(1-piperidinyl) butyric acid methyl ester* (**16**)

To an ice-cold solution of methyl crotonate (0.1 mol) in MeOH (25 ml) was added portionwise a solution of pyrrolidine or piperidine (0.12 mol) in MeOH (10 ml). The mixture was flushed with N_2, stoppered and set aside in the dark for 7 d at ambient temperature. The mixture was evaporated and the oily residue was treated with ice-H_2O (50 ml), CH_2Cl_2 (50 ml) then with ice-cold 3 N HCl (15 ml). The aqueous layer was separated, washed with CH_2Cl_2 (2 × 50 ml), cooled in ice, basified with K_2CO_3, and extracted with CH_2Cl_2 (2 × 30 ml). The extract was dried and evaporated to give 85% yield of **15** or **16** as an oil.

15: IR (Neat) 1735–1740 cm^{-1}. **15** · HCl: m.p. 143–145 °C (hygroscopic); IR (KBr) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.24 (br, N^+H), 3.69–3.56 (m, 6 H, OCH_3, H-3 and CH_2N^+), 3.13 (dd, J = 16.7 and 4.01 Hz, 1 H, HCO), 2.88–2.66 (m, 3 H, HCO and CH_2N^+), 2.23–1.98 (m, 4 H, CH_2CH_2), 1.45 (d, H = 6.56 Hz, 3 H, CH_3); EIMS m/z 171 $(M)^+$ (13.7%), 156 $(M\text{-}CH_3)^+$ (28.1%), 98 $[(CH_2)_4NCHCH_3]^+$ (100%).
$C_9H_{17}NO_2 \cdot HCl$.

16: IR (Neat) 1735–1740 cm^{-1}. **16** · HCl salt: m.p. 124–126 °C (hygroscopic); IR (KBr) 1735 cm^{-1}.
$C_{10}H_{19}NO_2 \cdot HCl$.

4.2. (±)-*3-(1-Pyrrolidinyl)butyric acid hydrochloride (17 · HCl) and* (±)-*3-(1-piperidinyl)butyric acid hydrochloride (18 · HCl)*

Methyl ester **15** or **16** (0.02 mol) was added to an ice-cold 15% NaOH solution (20 ml, 0.06 mol) and the mixture was stirred for 4 h at ambient temperature and for 0.5 h at 50 °C. The mixture was cooled, acidified to litmus with 3 N HCl and evaporated to dryness. The residue was treated with isopropanol (30 ml) and the mixture was cooled, filtered and the filtrate was evaporated. This process was repeated 2–3 times to remove dissolved NaCl. The oily residue obtained was dried in vac. to give about 70% yield of the amino acid HCl as a gummy oily material.

17 · HCl: IR (Neat) 3600–2300, 1660–1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.14 (brs), 3.54 (sext, J ≈ 6.6 Hz, W_H = 15.42 Hz, 1 H, H-3), 3.37 (m, 4 H), 2.74 (m, 2 H, W_H = 15.42 Hz, CH_2CO), 2.14 (m, 4 H), 1.17 (d, J = 6.68 Hz, 3 H, CH_3); EIMS m/z 158 $(MH)^+$ (12.6%), 157 $(M)^+$ (15.3%), 142 $(M-CH_3)^+$ (31.8%), 98 $[(CH_2)_4NCHCH_3)]^+$ (100%), 70 $[(CH_2)_4N]^+$ (8.8%).
$C_8H_{15}NO_2 \cdot HCl$.

18 · HCl: IR (Neat) 3600–2300, 1660–1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.97 (brs), 3.71–0.68 (m, 16 H). EIMS m/z 172 $(MH)^+$ (2%), 171 $(M)^+$ (10.4%), 156 $(M\text{-}CH_3)^+$ (26.7%), 112 $[(CH_2)_5NCHCH_3]^+$ (100%), 84 $[(CH_2)_5N]^+$ (12%).
$C_9H_{17}NO_2 \cdot HCl$.

4.3. (±)-*N-Substituted 3-(1-pyrrolidinyl/piperidinyl)butyramides* **3**–**14**

To a stirred, ice-cold solution of **17** · HCl or **18** · HCl (0.25 g) in CH_2Cl_2 (20 ml) was added successively equimolar amounts of TEA, HOBt, DCC and a solution of the appropriate amine in CH_2Cl_2 (10 ml). The mixture was stirred at 0–5 °C for 1 h then at RT for 48 h. The precipitated DCU was filtered off and the filtrate was evaporated. The residue was treated with ice-H_2O, basified (K_2CO_3) and extracted with CH_2Cl_2 (25 ml). The extract was dried, evaporated, the residue was treated with 10% citric acid solution and extracted with CH_2Cl_2 (2 × 25 ml). The aqueous solution was cooled, basified (K_2CO_3) and extracted with CH_2Cl_2 (2 × 25 ml). The extract was dried and evaporated. In case of **11** and **12**, the resulting oily residue was washed with cold $(C_2H_5)_2O$ to remove a high R_f side product which showed a 2200 cm^{-1} (CN) absorption in the IR spectra. The yield of the isolated products (Table 1) was 60–70%. Hydrochloride salts of **3**–**5** (hygroscopic) were prepared in $(C_2H_5)_2O$ using ethereal-HCl. The following are the spectral properties of **3**–**14**. All ^{1}H NMR spectra were measured in $CDCl_3$; assigned NHs were D_2O-exchangeable.

3: IR (KBr) 1665 cm^{-1} [HCl salt: IR (KBr) 1685 cm^{-1}]; ^{1}H NMR δ 12.0 (br, NH), 7.65 (d, 2 H), 7.42 (d, 2 H), 3.25–1.42 (m, 11 H), 1.14 (d, 3 H, CH_3).

4 · HCl: IR (KBr) 1640 cm^{-1}; ^{1}H NMR δ 10.0 (br, N^+H), 7.60 (s, 5 H, ArH), 4.63 (m, 2 H, CH_2Ph), 3.9–0.4 (m, 14 H).

5 · HCl: IR (KBr) 1640 cm^{-1}; ^{1}H NMR δ 11.1 (br, N^+H), 8.23 (br, NH), 7.32 (s, 5 H, ArH), 4.42 (s, 2 H, CH_2Ph), 3.8–3.1 (m, 3 H), 2.9–0.5 (m, 13 H).

6: IR (Neat) 1640 cm^{-1}; ^{1}H NMR δ 8.97 (br, NH), 7.54 (m, 5 H, ArH), 3.82–0.62 (m, 18 H); EIMS m/z 261 $(MH)^+$ (10.4%), 260 $(M)^+$ (3.1%), 258 $(M\text{-}2)^+$ (6.2%), 245 $(M-CH_3)^+$ (11.8%), 169 $(M\text{-}CH_2Ph)^+$ (5.9%), 112 $[(CH_2)_4NCHMeCH_2]^+$ (4.9%), 98 $[(CH_2)_4NCHMe]^+$ (100%), 70 $[(CH_2)_4N]^+$ (21%).

7: IR (Neat) 1640 cm^{-1}; ^{1}H NMR δ 7.7 (br, NHs), 7.3–7.1 (m, 5 H, ArH), 3.6–0.7 (m, 20 H).

8: IR (Neat) 1635 cm^{-1}; ^{1}H NMR δ 8.97 (br, NH), 7.54 (s, 5 H, ArH), 3.37 (m, 1 H, H-3), 3.19–0.8 (m, 19 H); EIMS m/z 275 $(MH)^+$ (17.5%), 274 $(M)^+$ (5.8%), 272 $(M\text{-}2)^+$ (13.6%), 259 $(M-CH_3)^+$ (20.8%), 203 $[M\text{-}(CH_2)_4NH]^+$ (26.2%), 98 (100%), 91 $(PhCH_2)^+$ (25.7%), 70 (18%).

9: IR (Neat) 1635 cm^{-1}; ^{1}H NMR δ 7.57 (m, 5 H, ArH), 3.88–0.91 (m, 22 H); EIMS m/z 289 $(MH)^+$ (55.6%), 288 $(M)^+$ (7.9%), 273 $(M\text{-}CH_3)^+$ (5.5%), 112 $[(CH_2)_5NCHMe]^+$ (100%), 91 (38.8%), 84 $[(CH_2)_5N]^+$ (38.5%).

10: IR (Neat) 1635–1640 cm^{-1}; ^{1}H NMR δ 9.47 (br, NH), 7.54 (m, 5 H, ArH), 6.57 (br, NH), 4.14–3.14 (m, 3 H), 3.08–0.68 (m, 17 H); EIMS m/z 317 $(M)^+$ (5.4%), 226 $(M-CH_2Ph)^+$ (2.6%), 98 (100%).

11: IR (KBr) 1635, 1670 cm^{-1}; ^{1}H NMR δ 9.42 (br, NH), 7.57 (s, 5 H, ArH), 6.94 (br, NH), 5.85 (br, NH), 4.89 (q, J = 7.71 Hz, 1 H, methine proton of Phe), 3.67–0.71 (m, 16 H); EIMS m/z 303 $(M)^+$ (1.8%), 288 $(M\text{-}CH_3)^+$ (1.4%), 259 $(M\text{-}CONH_2)^+$ (3.4%), 212 $(M\text{-}CH_2Ph)^+$ (4.2), 148 $(PhCH_2CHCONH_2)^+$ (100%), 98 (52.6%).

12: IR (KBr), 1640, 1670 cm^{-1}; ^{1}H NMR δ 10.0 (br, NH), 7.54 (s, 5 H, ArH), 6.65 (br, NH), 5.54 (br, NH), 4.91 (quint, J = 7.7 Hz, 1 H, methine proton of Phe), 3.4–0.7 (m, 18 H); EIMS m/z 318 $(MH)^+$ (10.1%), 317 $(M)^+$ (8.3%), 302 $(M\text{-}CH_3)^+$ (1.4%), 273 $(M\text{-}CONH_2)^+$ (7.4%), 226 $(M\text{-}CH_2Ph)^+$ (20.4%), 112 (100%), 91 (9.4%), 84 (34.3%).

13: IR (Neat) 1645, 1730 cm^{-1}; ^{1}H NMR δ 9.9 (br, NH), 7.54 (s, 5 H, ArH), 5.14 (quint, J = 7.7 Hz, 1 H), 4.0–0.8 (m, 19 H).

14: IR (Neat) 1645, 1730 cm^{-1}; ^{1}H NMR δ 7.3 (m, 5 H, ArH), 4.9 (m, 1 H), 3.7–0.8 (m, 21 H); EIMS m/z 333 $(MH)^+$ (80.4%), 332 $(M)^+$ (11.1%), 317 $(M\text{-}CH_3)^+$ (4.7%), 273 (M-COOMe)$^+$ (2.6%), 241 $(M\text{-}CH_2Ph)^+$ (8.8%), 112 (100%), 91 (20.8%), 84 (17.8%).

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References

1 Aldrich, J. V.; in: Wolff, M. E. (Ed.): Berger's Medicinal Chemistry and Drug Discovery, 5th Ed., vol. 3, p. 321, John Wiley Inc., New York 1996
2 Szmuszkovicz, J.; Von Voigtlander, P. F.: J. Med. Chem. **25**, 1125 (1982)
3 Castello, F.; James, R.; Show, J. S.; Slater, A. M.; Stutchbury, N. C.: J. Med. Chem. **34**, 181 (1991)
4 Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D.: J. Med. Chem. **34**, 397 (1991)
5 Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. T. C.; Hayes, A. G.; Birch, P.: J. Med. Chem. **36**, 2075 (1993)
6 Holzgrabe, U.; Nachtsheim, C.; Siener, T.; Drosihn, S.; Brandt, W.: Pharmazie **52**, 4 (1997)
7 Piercey, M. F.; Einsparch, F. J.: J. Pharmacol. Exp. Ther. **251**, 267 (1989)
8 Lung, F.-D. T.; Meyer, J.-Ph.; Li, G.; Lou, B.-S.; Stropova, D.; Davis, P.; Yamamura, H. I.; Porreca, F.; Hruby, V. J.: J. Med. Chem. **38**, 585 (1995)
9 Essawi, M. Y. H.; Portoghese, P. S.: J. Med. Chem. **26**, 348 (1983)
10 Anwer, M. K.; Spatola, A. F.: Synthesis 929 (1980)
11 Eleil, E. L.; Wilen, S. H.; Mander, L. N.: Stereochemistry of Organic Compounds, p. 641, John Wiley Inc., New York 1994
12 Eddy, N. B.; Leimback, D.: J. Pharmacol. Exp. Ther. **107**, 385 (1953)
13 Halfpenny, P. R.; Hill, G. R.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Johnson, S.; Rees, D. C.: J. Med. Chem. **32**, 1620 (1989)
14 Fujimoto, R. A.; Boxer, J.; Jackson, R. H.; Simke, J. P.; Neale, R. F.; Snowhill, E. W.; Barbaz, B. J.; Williams, M.; Sills, M. A.: J. Med. Chem. **32**, 1259 (1989)
15 Brandt, W.; Drosihn, S.; Haurand, M.; Holzgrabe, U.; Nachtsheim, C.: Arch. Pharm. Pharm. Med. Chem. **329**, 311 (1996)
16 Froimowitz, M.; DiMeglio, C. M.; Makriyannis, A.: J. Med. Chem. **35**, 3085 (1992)
17 Chang, A.; Cowan, A.; Takemori, A. E.; Portoghese, P. S.: J. Med. Chem. **39**, 4478 (1996)

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