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# Synthesis and dopamine $D_2$-like receptor binding affinity of substituted 5-phenyl-pyrrole-3-carboxamides

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**Abstract**

A series of 5-*p*-substituted phenyl-pyrrole-3-carboxamide derivatives was designed as hybrid analogs of the dopamine $D_2$-like 5-phenyl-pyrrole and heterocyclic carboxamide antipsychotics. The title compounds were synthesized and evaluated for dopamine $D_2$-like receptor by means of [$^3$H]YM-09151-2 receptor binding assay. The compound bearing a 1-ethyl-2-methyl-pyrrolidine moiety as the basic part of 5-phenyl-pyrrole-3-carboxamide derivative **1a** together with its 2-chloro analog **1f** were found to possess affinity in the low micromolar range. Substituted phenyl-pyrrolecarboxamides containing groups such as F, Cl, $NO_2$, $CH_3$, at the 4-position of the phenyl ring, gave ligands with lower $D_2$-like affinity. 

*Keywords:* $D_2$-like receptor binding; Substituted 5-phenyl-pyrrole-3-carboxamides; Structure–activity relationship

## 1. Introduction

Dopamine receptors can be divided into two major families: the $D_1$-like and $D_2$-like receptors based on their pharmacological profiles and coupling with the enzyme adenylate cyclase [1]. Molecular cloning techniques have shown that the $D_1$-like family is further divided into the $D_1$ and $D_5$ receptors, both of which activate adenylate cyclase, while the $D_2$-like family is divided into the $D_2$, $D_3$, and $D_4$ receptors, which either inhibit cyclic adenosine monophosphate (cAMP) production or are not coupled to adenylate cyclase [2]. Psychotic disorders such as schizophrenia seem to be characterized by an overreactivity of dopamine-secreting neurons in the 'limbic' brain, rich in D2 receptors [3]. From a pharmacological point of view, D2 receptor antagonists have been shown to treat these diseases effectively; however, a long-term treatment is associated with the induction of disabling side effects such as extrapyramidal syndrome (EPS) and irreversible tardive dyskinesia.

The therapeutic benefit of D2 antagonists in treating psychotic disorders has been fully accepted with the discovery of more effective antipsychotic drugs characterized by minimal induction of extrapyramidal effects (atypical antipsychotic) [3].

Therefore, the synthesis of novel antipsychotics with a better pharmacological profile still remains a primary goal in the search for the therapy of psychoses [3]. Thus, we have undertaken a research program aimed at the discovery of potential antipsychotic agents, taking as lead compounds the known aryl-pyrroles (**I**) and related heterocycles displaying high affinity for D2 receptors [4a–e]. Recent reports [5a,b] about heterocyclic carboxamides (**II**) exhibiting interesting binding affinity towards both $D_2$ and 5-$HT_{1a}$ receptors induced us to design a new series of 5-phenyl-pyrrole-3-carboxamides of general formula **1** (Scheme 1), whose 3-amidic side-chain was selected taking as reference known D2 blockers.

In this article, we report on the synthesis of substituted 5-phenyl-pyrrole-3-carboxamides (**1**) and the results of the binding affinities for the $D_2$-like receptors.

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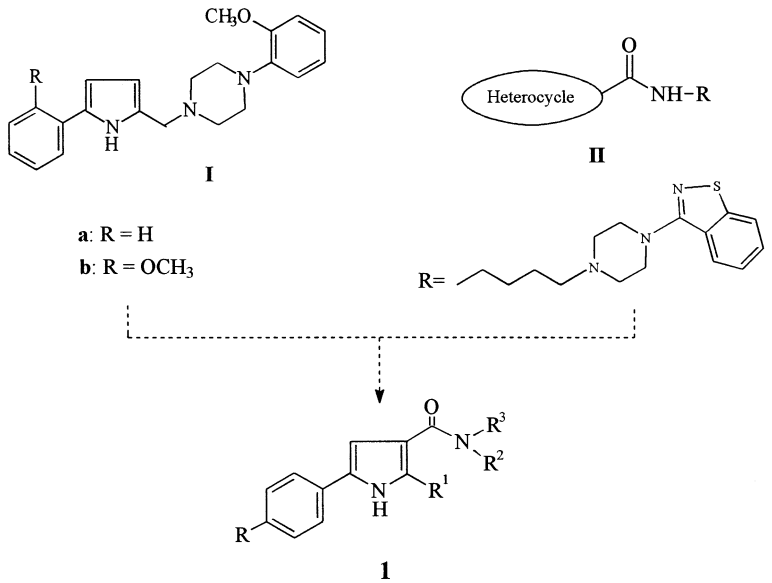



Scheme 1. Design of 5-phenyl-pyrrole-3-carboxamides.

## 2. Chemistry

Preparation of the substituted 5-aryl-3-carboxamides (**1a–l**) is outlined in Scheme 2. Alkylation of the sodium salt of the ethyl cyanoacetate [6] with suitable α-haloacetophenones (**2–6**) [7,8], afforded mixtures of monoalkyl (**7–11**) [6] and dialkyl (**12–15**) derivatives, with the exception of **5** that gave only the monoalkylated product **10**.

The desired cyanoketoesters **7–11** were separated either by trituration with ether of the crude alkylation mixtures or by flash chromatography in 50–82% yields. The structures assigned to **7–11** and **12–15** were supported by $^{1}H$ and $^{13}C$ NMR analyses. Esters of 5-phenyl-pyrrole (**16–20**) were obtained in satisfactory yield treating ethereal solution of **7–11** with gaseous HCl at room temperature (r.t.) for 18–24 h.

The formation of the pyrroles **16–20** most likely involved a Pynner-type cyclization as reported by Foley [9]. Compounds **21–23** were obtained in nearly quantitative yields by catalytic (10% Pd–C) hydrogenolysis of the 2-Cl substituted **16–18**. Saponification of **16–23** with hydroalcoholic NaOH provided carboxylic acids **24–31** which were condensed, as mixed anhydrides (Method A) or acid chlorides (Method B), with appropriate amines to give **1a–l**.

## 3. Pharmacology

### 3.1. Receptor binding

The target aryl-pyrrolecarboxamides **1a–l** were examined in vitro for their binding affinities to dopamine $D_2$-like receptors. Affinities for the dopamine sites were determined via standard competitive displacement assays using $D_2$-like receptors isolated from caudate nucleus of male Sprague–Dowley rats with [$^{3}H$]YM-09151-2 (nemonapride) as a specific ligand [10] and (−)-sulpiride as a specific displacer [11].

## 4. Results and discussion

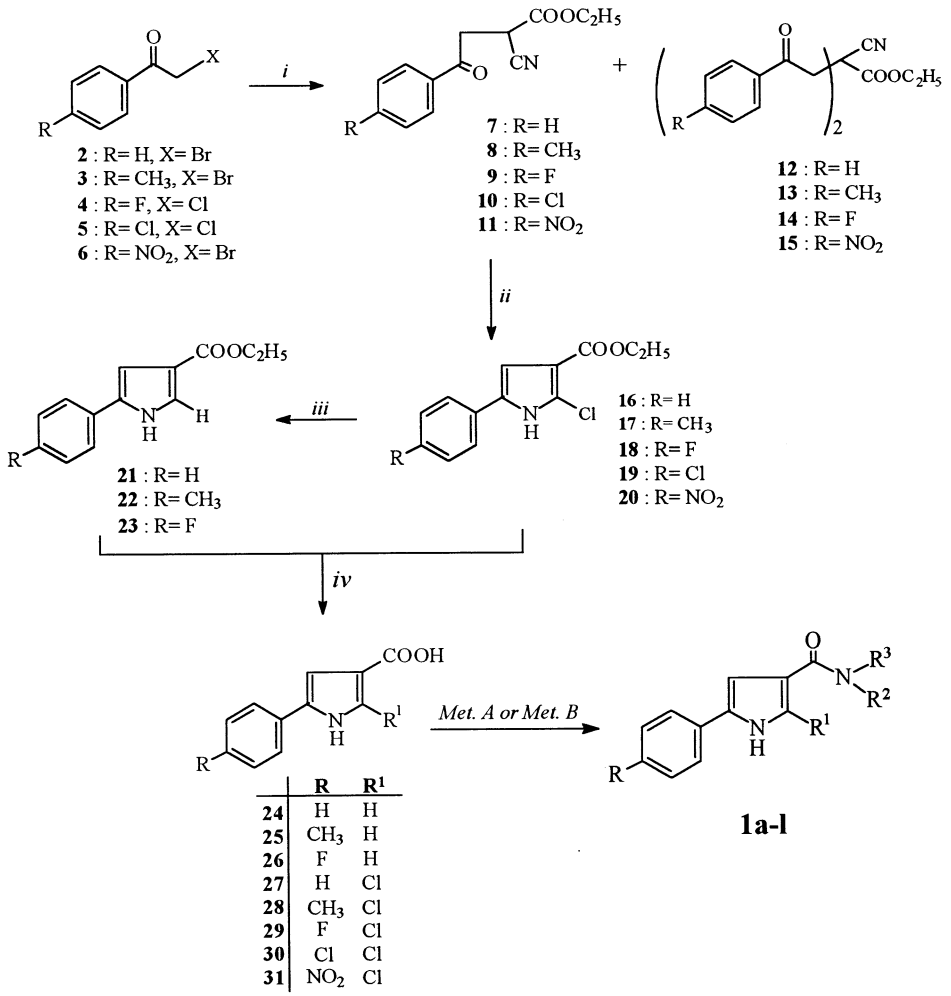
The $D_2$-like receptor binding affinity data for substituted phenyl-pyrrolecarboxamides **1** are presented in Table 1.

Compounds **1a–l** showed a marked decrease in $D_2$-like binding affinity with respect to the reference drug raclopride. However, it is worth noting that the presence of a 2-chloro substituent on the pyrrole moiety kept the affinity in the low micromolar range of the ground term (**1f** versus **1a**), while it significantly improved affinity of the *p*-phenyl substituted derivatives (**1j** versus **1g**, **1i** versus **1h**).

## 5. Chemical experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Anhydrous solvent such as ethanol (EtOH) tetrahydrofuran (THF) and dimethylformamide (DMF) were obtained from Aldrich in sure-seal bottles.

All reactions involving air- or moisture-sensitive compounds were performed under an argon 'S' atmosphere. Flash chromatography was performed using Merck Silica gel 60 (230–400 mesh ASTM).




| | R | $R^1$ |
|---|---|---|
| 24 | H | H |
| 25 | $CH_3$ | H |
| 26 | F | H |
| 27 | H | Cl |
| 28 | $CH_3$ | Cl |
| 29 | F | Cl |
| 30 | Cl | Cl |
| 31 | $NO_2$ | Cl |

Reagents : *i)* Ethyl cyanoacetate, Na ; *ii)* HCl, $Et_2O$ ; *iii)* $H_2$, 10% Pd/C; *iv)* NaOH, $H_2O$/EtOH
*Met. A)* BtOH, DCC/THF, *Met. B)* $(COCl)_2$/ DMF, $CH_2Cl_2$

Scheme 2.

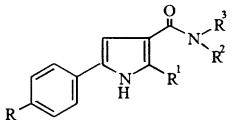
Thin layer chromatography (TLC) was performed with Polygram® SIL N-HR-/$HV_{254}$ precoated plastic sheet (0.2 mm). $^1H$ and $^{13}C$ NMR spectra were determined in $CDCl_3$ with superconducting FT-NMR using a XL-200 Varian apparatus at 200 MHz.

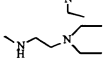
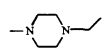
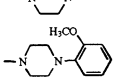
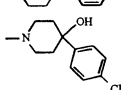
Chemical shifts are expressed in $\delta$ (ppm) downfield from internal TMS and coupling constants in Hz. Significant $^1H$ NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hz. IR spectra were recorded as thin films or Nujol mulls on NaCl plates with a Perkin–Elmer 781 IR spectrophotometer and are expressed in $\nu$ ($cm^{-1}$). UV–Vis spectra were recorded as ethanolic solutions with a Perkin–Elmer Lambda 5 spectrophotometer and the absorption wavelengths are expressed in nm followed by ($\log \varepsilon$). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed at Laboratorio di Microanalisi, Dipartimento di Scienze Farmaceutiche, Università di Padova (Italy), and are within $\pm$ 0.4% of the calculated values. For the binding studies [$^3H$] YM-09151-2 was purchased from NEN-DuPont (Boston, MA, USA).

### 5.1. General cyan(ethoxycarbonyl)methyl-alkylation procedure for compounds **7–15**

To a suspension of Na (16 mmol) in 4 ml of dry ethanol was added dropwise ethyl cyanoacetate (16 mmol) at 0–5°C. The reaction mixture was stirred until sodium dissolution was complete and then was evaporated in vacuo to give a solid residue, which was added portionwise to a solution of appropriate haloacetophenone (**2–6**) (16 mmol) in 10 ml of THF. The resulting suspension was stirred at r.t. (0.5–1 h) then concentrated in vacuo and the residue suspended in water. The

Table 1
$D_2$-like receptor binding affinity [a] of compounds **1a–l**



| Comp. 1 | R | $R^1$ | $NR^2R^3$ | Receptor binding[b] $IC_{50}$, μ M, mean ± SEM |
|---|---|---|---|---|
| **a** | H | H |  | 1.03 ± 0.15 |
| **b** | H | H |  | 6.99 ± 0.96 |
| **c** | H | H |  | 3.09 ± 0.25 |
| **d** | H | H |  | > 50 |
| **e** | H | H |  | > 50 |
| **f** | H | Cl |  | 1.04 ± 0.08 |
| **g** | F | H | " | 24.0 ± 1.1 |
| **h** | $CH_3$ | H | " | > 50 |
| **i** | $CH_3$ | Cl | " | 5.50 ± 0.58 |
| **j** | F | Cl | " | 3.21 ± 0.63 |
| **k** | Cl | Cl | " | 2.53 ± 0.59 |
| **l** | $NO_2$ | Cl | " | 16.6 ± 1.1 |
| **Raclopride** | - | - | - | 0.039 |

[a] [3H] YM-09151-2 has been used as the specific ligand
[b] The $IC_{50}$ for binding is the average of three experiments.

aqueous mixture was extracted twice with $CH_2Cl_2$, and the combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was triturated with ether isolating the dialkylated derivatives (**12–15**) by filtration and the monoalkylated compounds (**7–11**) by evaporation of the solvent.

*5.1.1. Ethyl 2-cyano-4-oxo-4-phenylbutanoate (7) [6]*

50.3% Yield; $R_f$ 0.48 (AcOEt/light petroleum, 3:7); m.p. 53–55°C (EtOH); IR: 2260 (CN), 1740 (CO), 1690 (CO); UV: 238.7 (3.96), 208.7 (3.80); $^1$H NMR: 1.39 (t, 3H, $J = 7.2$, $CH_3$), 3.51–4.20 (ABXm, 3H, $J = 5.4$, 6.8 and 18.2, $CH_2CH$), 4.30 (q, 2H, $J = 7.2$, $CH_2$), 7.46–7.99 (m, 5H, Ar-H). *Anal.* $C_{13}H_{13}NO_3$ (C, H, N).

*5.1.2. Ethyl 2-cyano-4-(4-methylphenyl)-4-oxobutanoate (8)*

51% Yield; $R_f$ 0.46 (AcOEt/light petroleum, 3:7); m.p. 53–55°C (MeOH); IR: 2260 (CN), 1750 (CO), 1690 (CO); UV: 252.0 (3.88), 212.7 (3.80); $^1$H NMR: 1.34 (t, 3H, $J = 7.2$, $CH_3$), 2.34 (s, 3H, $CH_3$), 3.48–4.18 (ABXm, 3H, $J = 5.6$, 6.8 and 18.0, $CH_2CH$), 4.30 (q, 2H, $J = 7.2$, $CH_2$), 7.30 and 7.86 (2d, 4H, $J = 8.4$, Ar-H). *Anal.* $C_{14}H_{15}NO_3$ (C, H, N).

*5.1.3. Ethyl 2-cyano-4-(4-fluorophenyl)-4-oxobutanoate (9)*

55% Yield; $R_f$ 0.42 (AcOEt/light petroleum, 2:8); b.p. 140°C/0.05 mmHg; IR: 2260 (CN), 1750 (CO), 1690 (CO); UV: 227.8 (3.93), 194.8 (3.80); $^1$H NMR: 1.35 (t, 3H, $J = 7.2$, $CH_3$), 3.48–4.18 (ABXm, 3H, $J = 5.4$, 6.8 and 18.0, $CH_2CH$), 4.13 (q, 2H, $J = 7.2$, $CH_2$), 7.13 and 8.04 (m, 4H, Ar-H). *Anal.* $C_{13}H_{12}FNO_3$ (C, H, F, N).

*5.1.4. Ethyl 4-(4-chlorophenyl)-2-cyano-4-oxobutanoate (10)*

82% Yield; $R_f$ 0.42 (AcOEt/light petroleum, 2:8); bp 138–140°C/0.05 mmHg; IR: 2260 (CN), 1750 (CO), 1690 (CO); UV: 240.8 (3.97), 209.2 (3.84); $^1$H NMR: 1.35 (t, 3H, $J = 7.2$, $CH_3$), 3.47–4.17 (m, 3H, $J = 5.6$, 6.8 and 18.2, $CH_2CH$), 4.32 (q, 2H, $J = 7.2$, $CH_2$), 7.47 and 7.90 (2d, 4H, Ar-H). *Anal.* $C_{13}H_{12}ClNO_3$ (C, H, Cl, N).

*5.1.5. Ethyl 2-cyano-4-(4-nitrophenyl)-4-oxobutanoate (11)*

25% Yield; $R_f$ 0.39 (AcOEt/light petroleum, 3:7); m.p. 81–83°C (EtOH); IR: 2250 (CN), 1740 (CO), 1690 (CO); UV: 262.3 (4.00), 205.1 (3.97); $^1$H NMR: 1.36 (t, 3H, $J = 7.2$, $CH_3$), 3.55–3.90 (m, 3H, $J = 5.6$, 6.8 and 18.2, $CH_2CH$), 4.32 (q, 2H, $J = 7.2$, $CH_2$), 8.14 and 8.36 (2d, 4H, $J = 7.0$, Ar-H). *Anal.* $C_{13}H_{12}N_2O_5$ (C, H,, N).

*5.1.6. Ethyl 2-cyano-4-oxo-2-(2-oxo-2-phenylethyl)-4-phenylbutanoate (12)*

46% Yield; $R_f$ 0.34 (AcOEt/light petroleum, 3:7); m.p. 130°C (triturated with ether); IR: 2260 (CN), 1730 (CO), 1690 (CO); UV: 247.3 (4.34), 208.3 (4.25); $^1$H NMR: 1.33 (t, 3H, $J = 7.2$, $CH_3$), 3.82–4.02 (m, 4H, $2 \times CH_2$), 4.32 (q, 2H, $J = 7.2$, $CH_2$), 7.43–7.96 (m, 10H, Ar-H). *Anal.* $C_{21}H_{19}NO_4$ (C, H, N).

*5.1.7. Ethyl 2-cyano-4-(4-methylphenyl-2-[2-(4-methylphenyl)-2-oxoethyl])-4-oxobutanoate (13)*

48% Yield; $R_f$ 0.36 (AcOEt/light petroleum, 3:7); m.p. 148°C (triturated with ether); IR: 2260 (CN), 1740 (CO), 1680 (CO); UV: 247.0 (4.24), 207.7 (4.21); $^1$H NMR: 1.25 (t, 3H, $J = 8.0$, $CH_3$), 2.41 (s, 6H, $2 \times CH_3$), 3.78–4.03 (m, 4H, $2 \times CH_2$), 4.22 (q, 2H, $J = 8.0$, $CH_2$), 7.34 and 7.88 (2d, 8H, $J = 8.0$, Ar-H). *Anal.* $C_{23}H_{23}NO_4$ (C, H, N).

*5.1.8. Ethyl 2-cyano-4-(4-fluorophenyl-2-[2-(4-fluorophenyl)-2-oxoethyl])-4-oxobutanoate (14)*

43% Yield; $R_f$ 0.36 (AcOEt/light petroleum, 2:8); m.p. 138°C (triturated with ether); IR: 2260 (CN), 1740

(CO), 1680 (CO); UV: 247.0 (4.39), 208.5 (4.29); $^1$H NMR: 1.26 (t, 3H, $J = 8.0$, $CH_3$), 3.88–4.10 (m, 4H, $2 \times CH_2$), 4.20–4.32 (q, 2H, $J = 8.0$, $CH_2$), 7.28 and 8.13 (m, 8H, Ar-H). *Anal.* $C_{21}H_{17}F_2NO_4$ (C, H, F, N).

*5.1.9. Ethyl 2-cyano-4-(4-nitrophenyl-2-[2-(4-nitrophenyl)-2-oxoethyl])-4-oxobutanoate* ***(15)***

25% Yield; $R_f$ 0.24 (AcOEt/light petroleum, 3:7); m.p. 164–167°C (triturated with ether); IR: 2240 (CN), 1745 (CO), 1700 (CO); UV: 262.9 (4.17), 210.2 (3.62); $^1$H NMR: 1.36 (t, 3H, $J = 7.2$, $CH_3$), 3.88–4.18 (m, 4H, $2 \times CH_2$), 4.34 (q, 2H, $J = 7.2$, $CH_2$), 8.20 and 8.36 (2d, 8H, $J = 8.8$, Ar-H). *Anal.* $C_{21}H_{17}N_3O_8$ (C, H, N).

*5.2. General ring closure procedure for compounds* ***16–20***

A solution of the appropriate cyanoketoester **7–11** (4.3 mmol) in diethyl ether (30 ml) at 0–5°C was bubbled with an excess of gaseous HCl. After the HCl addition was completed the cooling bath was removed and the stirring continued at r.t. for 18–24 h and the progress of the reaction was monitored by TLC. Argon was then bubbled through the solution and the reaction mixture was concentrated to leave a solid which was purified by flash-chromatography eluting with ethylacetate/light petroleum to give phenyl-pyrroles **16–20**.

*5.2.1. Ethyl-2-chloro-5-phenyl-1H-3-pyrrolecarboxylate* ***(16)*** *[9]*

80% Yield; $R_f$ 0.46 (AcOEt/light petroleum, 2:8): m.p. 118–120°C ($MeOH/H_2O$); IR: 3300 (NH), 1700 (CO); UV: 252.4 (3.99), 213.1 (3.97); $^1$H NMR: 1.37 (t, 3H, $J = 7.0$, $CH_3$), 4.33 (q, 2H, $J = 7.0$, $CH_2$), 6.87 (d, 1H, $J = 3.2$, $C_4H$), 7.24–7.49 (m, 5H, Ar), 8.99 (br s, 1H, NH exch. with $D_2O$). $^{13}$C NMR 14.30 ($CH_3$), 60.32 ($CH_2$), 107.51 (C-4), 112.73 (C-3), 121.01 (C-2), 123.91 (C-3′ and C-5′), 127.13 (C-4′), 128.86 (C-2′ and C-6′), 130.85 (C-5), 131.12 (C-1′), 164.08 (C=O). *Anal.* $C_{13}H_{12}ClNO_2$ (C, H, Cl, N).

*5.2.2. Ethyl-2-chloro-5-(4-methylphenyl)-1H-3-pyrrolecarboxylate* ***(17)***

83% Yield; $R_f$ 0.60 (AcOEt/light petroleum, 2:8): m.p. 130–133°C (MeOH); IR: 3260 (NH), 1670 (CO); UV: 252.7 (4.10), 210.9 (4.07); $^1$H NMR: 1.37 (t, 3H, $J = 7.0$, $CH_3$), 2.35 (s, 1H, $CH_3$), 4.32 (q, 2H, $J = 7.0$, $CH_2$), 6.81 (d, 1H, $J = 3.2$, $C_4H$), 7.17 and 7.36 (2d, 4H, $J = 8.0$, Ar-H), 9.09 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{14}H_{14}ClNO_2$ (C, H, Cl, N).

*5.2.3. Ethyl-2-chloro-5-(4-fluorophenyl)-1H-3-pyrrolecarboxylate* ***(18)***

87% Yield; $R_f$ 0.49 (AcOEt/light petroleum, 2:8); m.p. 159–161°C (MeOH), IR 3290 (NH), 1680 (CO); UV: 255.7 (4.01), 210.4 (4.06); $^1$H NMR: 1.37 (t, 3H, $J = 7.2$, $CH_3$), 4.33 (q, 2H, $J = 7.2$, $CH_2$), 6.79 (d, 1H, $J = 3.0$, $C_4H$), 7.04–7.46 (m, 4H, Ar-H), 8.93 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{13}H_{11}ClFNO_2$ (C, H, Cl, F, N).

*5.2.4. Ethyl-2-chloro-5-(4-chlorophenyl)-1H-3-pyrrolecarboxylate* ***(19)***

82% Yield; $R_f$ 0.50 (AcOEt/light petroleum, 2:8); m.p. 178–179°C (MeOH); IR: 3300 (NH), 1690 (CO); UV: 259.0 (4.10), 209.1 (4.06); $^1$H NMR: 1.37 (t, 3H, $J = 7.6$, $CH_3$), 4.30 (q, 2H, $J = 7.6$, $CH_2$), 6.83 (d, 1H, $J = 2.6$, $C_4H$), 7.30 and 7.53 (2d, 4H, $J = 7.4$, Ar-H), 11.84 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{13}H_{11}Cl_2NO_2$ (C, H, Cl, N).

*5.2.5. Ethyl-2-chloro-5-(4-nitrophenyl)-1H-3-pyrrolecarboxylate* ***(20)***

72% Yield; $R_f$ 0.66 (AcOEt/light petroleum, 2:8); m.p. 249–252°C (MeOH); IR: 3250 (NH), 1690 (CO); UV: 369.3 (4.16), 264.4 (4.38), 199.9 (4.62); $^1$H NMR: 1.38 (t, 3H, $J = 7.2$, $CH_3$), 4.30 (q, 2H, $J = 7.2$, $CH_2$), 7.07 (d, 1H, $J = 2.2$, $C_4H$), 7.80 and 8.20 (2d, 4H, $J = 8.80$, Ar-H), 12.22 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{13}H_{11}ClN_2O_2$ (C, H, Cl, N).

*5.3. General dechlorination procedure for compounds* ***21–23***

A solution of the appropriate ethyl-2-chloro-5-phenyl-3-pyrrolecarboxylate (4.7 mmol) (**16–18**) in 60 ml of ethanol was hydrogenated over 10% Pd–C at 4 atm pressure and at r.t. After the theoretical amount of hydrogen had been adsorbed (ca. 2–6 h) the catalyst was removed by filtration through a bed of Celite and the filtrate concentrated in vacuo to give the title compound **21–23** as a solid product.

*5.3.1. Ethyl 5-phenyl-1H-3-pyrrolecarboxylate* ***(21)***

98% Yield; $R_f$ 0.34 (AcOEt/light petroleum, 2:8); m.p. 152°C (MeOH); IR: 3300 (NH), 1690 (CO); UV: 277.9 (4.29), 220.0 (4.39), 204.0 (4.35); $^1$H NMR: 1.36 (t, 3H, $J = 7.2$, $CH_3$), 4.31 (q, 2H, $J = 7.2$, $CH_2$), 6.90–6.93 (m, 1H, $C_4H$), 7.25–7.60 (m, 6H, Ar-H and $C_2H$), 9.15 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 14.42 ($CH_3$), 59.98 ($CH_2$), 106.45 (C-4), 117.65 (C-3), 124.04 (C-3′ and C-5′), 124.36 (C-2), 126.90 (C-4′), 128.90 (C-2′ and C-6′), 131.69 (C-5), 133.08 (C-1′), 165.38 (C=O). *Anal.* $C_{13}H_{13}O_2$ (C, H, N).

This compound could also be obtained in quantitative yield by hydrogenation of **19**.

*5.3.2. Ethyl 5-(4-methylphenyl)-1H-3-pyrrolecarboxylate* ***(22)***

100% Yield; $R_f$ 0.30 (AcOEt/light petroleum, 2:8); m.p. 160–163°C ($MeOH/H_2O$); IR: 3290 (NH), 1670 (CO); UV: 253.6 (4.02), 211.4 (4.01); $^1$H NMR: 1.35 (t,

3H, $J = 7.0$, $CH_3$), 2.34 (s, 3H, $CH_3$), 4.28 (q, 2H, $J = 7.0$, $CH_2$), 6.80–6.90 (m, 1H, $C_4H$), 7.17 and 7.48 (2d, 4H, $J = 8.0$, Ar-H), 7.39–7.45 (m, 1H, $C_2H$), 10.73 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{14}H_{15}NO_2$ (C, H, N).

*5.3.3. Ethyl 5-(4-fluorophenyl)-1H-3-pyrrolecarboxylate (**23**)*

67.5% Yield; $R_f$ 0.42 (AcOEt/light petroleum 2:8); m.p. 162–164°C (MeOH); IR: 3300 (NH), 1680 (CO); UV: 246.0 (4.01), 212.6 (3.99); $^1$H NMR: 1.36 (t, 3H, $J = 7.0$, $CH_3$), 4.29 (q, 2H, $J = 7.0$, $CH_2$), 6.81–6.83 (m, 1H, $C_4H$), 7.01–7.10 (m, 2H, Ar-H), 7.42–7.44 (m, 1H, $C_2H$), 7.51–7.56 (m, 2H, Ar-H), 10.65 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{13}H_{12}FNO_2$ (C, H, F, N).

*5.4. General ester hydrolysis procedures for compounds **24–31***

A mixture of appropriate ester (**16**, **17**, **20** and **21–23**) (4.65 mmol) in 48 ml of hydroalcoholic solution (1:2) of 10% NaOH was refluxed for 12 h and then poured into ice-water. The basic solution was acidified with conc. HCl and the solid precipitated was filtered off. The crude product was dissolved in 5% aqueous $NaHCO_3$ and the resulting mixture filtered. Concentrated HCl was added dropwise to the filtrate and the solid precipitated was filtered off to give the desired acid (**24–28**, **31**) which was used without further purification.

*5.4.1. 5-Phenyl-1H-3-pyrrolecarboxylic acid (**24**)*

85% Yield; $R_f$ 0.41 ($CHCl_3$/MeOH, 9:1): m.p. 176–178°C; IR: 3400 (NH), 1650 (CO); UV: 244.8 (3.89), 214.7 (3.88); $^1$H NMR: 3.05–5.00 (br s, 1H, COOH exch. with $D_2O$), 6.82–6.90 (m, 1H, $C_4H$), 7.16–7.80 (m, 6H, Ar-H and $C_2H$), 11.55 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_9NO_2$ (C, H, N).

*5.4.2. 5-(4-Methylphenyl)-1H-3-pyrrolecarboxylic acid (**25**)*

78% Yield; $R_f$ 0.59 ($CHCl_3$/MeOH, 8:2); m.p. 197–200°C; IR: 3420 (NH), 1680 (CO); UV: 246.7 (3.98), 213.7 (3.96); $^1$H NMR: 2.34 (s, 3H, $CH_3$), 5.20–6.10 (br s, 1H, COOH exch. with $D_2O$), 6.80–6.84 (m, 1H, $C_4H$), 7.17 and 7.48 (2d, 4H, $J = 8.0$, Ar-H), 7.40–7.46 (m, 1H, $C_2H$), 11.07 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{12}H_{11}NO_2$ (C, H, N).

*5.4.3. 5-(4-Fluorophenyl)-1H-3-pyrrolecarboxylic acid (**26**)*

94.5% Yield; $R_f$ 0.62 ($CHCl_3$/MeOH, 8:2); m.p. 190°C (dec.); IR: 3330 (NH), 1660 (CO); UV: 249.8 (3.93), 211.0 (3.91); $^1$H NMR: 2.66–4.20 (br s, 1H, COOH exch. with $D_2O$), 6.79–6.90 (m, 1H, $C_4H$), 7.01–7.62 (m, 5H, Ar-H and $C_2H$), 11.36 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_8FNO_2$ (C, H, F, N).

*5.4.4. 2-Chloro-5-phenyl-1H-3-pyrrolecarboxylic acid (**27**)*

78.3% Yield; $R_f$ 0.45 ($CHCl_3$/MeOH, 9:1): m.p. 193–195°C; IR: 3290 (NH), 1650 (CO); UV: 251.5 (3.96), 210.5 (3.92); $^1$H NMR: 6.88 (d, 1H, $J = 3.0$, $C_4H$), 7.20–7.69 (m, 5H, Ar-H), 9.80–10.60 (br s, 1H, COOH exch. with $D_2O$), 11.40 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_8ClNO_2$ (C, H, Cl, N).

*5.4.5. 2-Chloro-5-(4-methylphenyl)-1H-3-pyrrolecarboxylic acid (**28**)*

54% Yield; $R_f$ 0.60 ($CHCl_3$/MeOH, 8:2); m.p. 198–201°C (benzene); IR: 3300 (NH), 1680 (CO); UV: 253.2 (4.01), 211.0 (3.98); $^1$H NMR: 2.34 (s, 3H, $CH_3$), 2.36–3.40 (br s, 1H, COOH exch. with $D_2O$), 6.80 (d, 1H, $J = 3.0$, $C_4H$), 7.32 (ABq, 4H, Ar-H), 10.60 11.63 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{12}H_{10}ClNO_2$ (C, H, Cl, N).

*5.4.6. 2-Chloro-5-(4-nitrophenyl)-1H-3-pyrrolecarboxylic acid (**31**)*

57.6% Yield; $R_f$ 0.78 ($CHCl_3$/MeOH, 8:2); m.p. 278–279°C; IR: 3280 (NH), 1775 (CO); UV: 367.9 (4.06), 217.6 (4.11); $^1$H NMR: 3.02–4.10 (br s, 1H, COOH exch. with $D_2O$), 7.10 (d, 1H, $J = 2.8$, $C_4H$), 7.88 and 8.20 (2d, 4H, $J = 8.80$, Ar-H), 12.72 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_7ClN_2O_4$ (C, H, Cl, N).

*5.4.7. 2-Chloro-5-(4-fluorophenyl)-1H-3-pyrrolecarboxylic acid (**29**)*

A solution of ethyl-2-chloro-5-(4-fluorophenyl)-1*H*-3-pyrrolecarboxylate (**18**) (7.5 mmol) in 7.5 ml of EtOH and 75 ml of 20% aqueous NaOH was refluxed for 5 h and then poured into ice-water. The mixture was acidified with conc. HCl and extracted with $CHCl_3$. The organic layers were combined, dried ($Na_2SO_4$), filtered and concentrated in vacuo to give a brown solid, which was dissolved in 5% $NaHCO_3$ solution. The basic mixture was extracted with $Et_2O$, acidified with conc. HCl and extracted with $CHCl_3$ which was dried ($Na_2SO_4$) and evaporated in vacuo to give compound **29**.

84% Yield; $R_f$ 0.42 ($CHCl_3$/MeOH, 9:1); m.p. 125–127°C; IR: 3300 (NH), 1690 (CO); UV: 248.0 (4.01), 211.6 (3.98); $^1$H NMR: 3.83 (br s, 1H, COOH exch. with $D_2O$), 6.76 (d, 1H, $J = 2.5$, $C_4H$), 7.01–7.61 (m, 4H, Ar-H), 11.88 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_7ClFNO_4$ (C, H, Cl, F, N).

*5.4.8. 2-Chloro-5-(4-chlorophenyl)-1H-3-pyrrolecarboxylic acid (**30**)*

A solution of ethyl-2-chloro-5-(4-chlorophenyl)-1*H*-3-pyrrolecarboxylate (**19**) (1.76 mmol) and KOH (9.5 mmol) in 10.6 ml of $CH_3OH$ and 0.35 ml of $H_2O$ was

heated at 75°C for 12 h, then concentrated in vacuo. Water was added to the residue and the suspension was acidified with concentrated HCl and filtered to give the title compound.

100% Yield; $R_f$ 0.40 (AcOEt/light petroleum, 4:6): m.p. 185–187°C; IR: 3300 (NH), 1680 (CO); UV: 250.0 (4.06), 209.1 (4.03); $^1$H NMR: 5.80 (br s, 1H, COOH exch. with $D_2O$), 6.86 (d, 1H, $J = 3.0$ $C_4H$), 7.31. and 7.53 (2d, 4H, $J = 8.6$, Ar-H), 11.55 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{11}H_7Cl_2NO_2$ (C, H, Cl, N).

### *5.5. General acid amination procedures for compounds **1a–l***

#### *5.5.1. Method A: for amides **1a–d**, **g–l***

A heterogeneous mixture of appropriate acid (2.67 mmol) (**24–26**, **28–31**), the requisite amine (2.94 mmol) and hydrate 1-hydroxybenzotriazole (BTOH, 2.94 mmol) in 15 ml of THF was cooled to 0°C and then dicyclohexylcarbodiimide (DCC, 2.94 mmol) in 3 ml of THF was added. The reaction was warmed to r.t. and stirred for 15 h. The solid was removed by filtration and rinsed with THF. The filtrate was concentrated under reduced pressure, and the oily residue was dissolved in $CH_2Cl_2$ and washed with 5% aqueous $NaHCO_3$ and then extracted with 2 M $H_3PO_4$. The acidic aqueous layer was made basic with 2 M NaOH and extracted with $CH_2Cl_2$, which was dried ($Na_2SO_4$) and concentrated in vacuo to afford a residue. The residue was dried under vacuum (60°C, 0.5 mmHg) or triturated with ether or acetone to give the title compound **1a**, **1i**, **1h**, **1k** as amorphous or **1g**, **1j**, **1b**, **1c**, **1d** and **1l**) as powder solids.

*5.5.1.1. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-5-phenyl-1H-3-pyrrolecarboxamide (**1a**).* 77.2% Yield; $R_f$ 0.22 ($CHCl_3$/MeOH, 8:2); m.p. 72–75°C (amorphous); IR: 3230 (NH), 1710 (CO); UV: 282.6 (4.15), 217.5 (4.32), 200.9 (4.44); $^1$H NMR: 1.14 (t, 3H, $J =$ 7.0, $CH_3$), 1.60–1.90 (m, 4H, $2 \times CH_2$), 2.20–2.31 (m, 2H, $CH_2$), 2.84 (m, 2H, $CH_2$), 3.21–3.90 (m, 2H, $CH_2$), 3.60–3.79 (m, 1H, CH), 6.71–6.73 (m, 1H, $C_4H$), 7.20–7.60 (m, 6H, Ar-H and $C_2H$), 10.25 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 13.82 ($CH_3$), 22.78, 27.92, 40.48, 48.20 and 53.49 ($5 \times CH_2$), 62.67 (CH), 120.52 (C-3), 122.18 (C-2), 124.09 (C-3′ and C-5′), 126.33 (C-4′), 126.61 (C-2′ and C-6′), 132.11 (C-5), 133.12 (C-1′), 165.78 (C=O). *Anal.* $C_{18}H_{23}N_3O$ (C, H, N).

*5.5.2. N3-[(2-(Diethylamino)ethyl]-5-phenyl-1H-3-pyrrolecarboxamide (**1b**)*

73.7% Yield; $R_f$ 0.22 ($CHCl_3$/MeOH, 8:2); m.p. 60–62°C (triturated with $Et_2O$); IR: 3260 (NH), 1730 (CO); UV: 282.2 (4.26), 218.5 (4.39), 202.2 (4.46); $^1$H NMR: 1.01 (t, 6H, $J = 7.4$, $2 \times CH_3$), 2.50–2.82 (m, 6H, $3 \times CH_2$), 3.49 (m, 2H, $CH_2$), 3.68 (br s, 1H, NH exch. with $D_2O$), 6.71–6.72 (m, 1H, $C_4H$), 7.16–7.56 (m, 6H, Ar-H and $C_2H$), 10.64 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 10.96 ($2 \times CH_3$), 36.50 ($CH_2$), 46.68 ($2 \times CH_2$), 51.73 ($CH_2$), 103.79 (C-4), 120.35 (C-3), 122.32 (C-2), 124.02 (C-3′ and C-5′), 126.36 (C-4′), 128.64 (C-2′ and C-6′), 132.06 (C-5), 133.09 (C-1′), 165.66 (C=O). *Anal.* $C_{17}H_{23}N_3O$ (C, H, N).

*5.5.3. (4-Ethylpiperazino)(5-phenyl-1H-3-pyrrolyl)-methanone (**1c**)*

72.3% Yield; $R_f$ 0.70 ($CHCl_3$/MeOH, 8:2); m.p. 176–178°C (triturated with $Et_2O$); IR: 3200 (NH), 1660 (CO); UV: 282.3 (4.35), 218.5 4.44), 203.8 (4.49); $^1$H NMR: 1.07 (t, 3H, $J = 6.8$, $CH_3$), 2.34–2.50 (m, 6H, $3 \times CH_2$), 3.70–3.90 (m, 4H, $2 \times CH_2$), 6.52–6.62 (m, 1H, $C_4H$), 6.88–6.98 (m, 1H, $C_2H$), 7.15–7.60 (m, 5H, Ar-H), 10.86 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 11.75 ($CH_3$), 52.11 ($3 \times CH_2$), 52.70 ($2 \times CH_2$), 105.51 (C-4), 118.70 (C-3), 122.38 (C-2), 124.07 (C-3′ and C-5′), 126.35 (C-4′), 128.64 (C-2′ and C-6′), 132.04 (C-5), 132.36 (C-1′), 166.98 (C=O). *Anal.* $C_{17}H_{21}N_3O$ (C, H, N).

*5.5.4. [4-(2-Methoxyphenyl)piperazino](5-phenyl-1H-3-pyrrolyl)methanone (**1d**)*

45% Yield; $R_f$ 0.53 ($CHCl_3$/MeOH, 9:1); m.p. 193–196°C (triturated with acetone); IR: 3310 (NH), 1630 (CO); UV: 281.0 (4.14), 207.5 (4.40); $^1$H NMR: 3.01–3.20 (m, 4H, $2 \times CH_2$), 3.89 (s, 3H, $OCH_3$), 3.97–4.10 (m, 4H, $CH_2$2x), 6.66–6.75 (m, 1H, $C_4H$), 6.91–7.70 (m, 10H, Ar-H and $C_2H$), 11.83 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{22}H_{23}N_3O_2$ (C, H, N).

*5.5.5. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-5-(4-fluorophenyl)-1H-3-pyrrolecarboxamide (**1g**)*

62% Yield; $R_f$ 0.30 ($CHCl_3$/MeOH, 8:2); m.p. 104–107°C (triturated with EtOH); IR: 3220 (NH), 1630 (CO); UV: 274.8 (4.17), 219.2 (4.48), 208.0 (4.22); $^1$H NMR: 1.17 (t, 3H, $J = 7.0$, $CH_3$), 1.63–1.91 (m, 4H, $2 \times CH_2$), 2.16–2.40 (m, 2H, $CH_2$), 2.78–2.97 (m, 2H, $CH_2$), 3.23–3.40 (m, 2H, $CH_2$), 3.64–3.80 (m, 1H, CH), 6.68 (br s, 1H, $C_4H$), 6.96–7.56 (m, 5H, Ar-H and $C_2H$), 10.41 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{18}H_{22}FN_3O$ (C, H, F, N).

*5.5.5.1. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-5-(4-methylphenyl)-1H-3-pyrrolecarboxamide (**1h**).*

67.53% Yield; $R_f$ 0.40 ($CHCl_3$/MeOH, 8:2); m.p. 130–134°C (as hydrochloride triturated with $Et_2O$); IR: 3280 (NH), 1630 (CO); UV: 281.8 (4.12). 218.8 (4.37); $^1$H NMR: 1.13 (t, 3H, $J = 7.2$, $CH_3$), 1.60–1.88 (m, 4H, $2 \times CH_2$), 2.32 (s, 3H, $CH_3$), 2.38–2.59 (m, 2H, $CH_2$), 2.75–2.92 (m, 2H, $CH_2$), 3.60–3.71 (m, 1H, CH), 6.65–6.71 (br s, 1H, $C_4H$), 6.86 (br s, 1H, NH exch. with $D_2O$), 7.13 and 7.44 (2d, 4H, $J = 8.2$, Ar-H), 7.39 (br s, 1H, $C_2H$), 10.19 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{19}H_{25}N_3O$ (C, H, N).

*5.5.5.2. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-2-chloro-5-(4-methylphenyl)-1H-3-pyrrolecarboxamide (**1i**).* 58.4% Yield; $R_f$ 0.39 ($CHCl_3$/MeOH, 8:2); m.p. 115–120°C (as hydrochloride, triturated with $Et_2O$); IR: 3240 (NH), 1630 (CO); UV: 281.8 (4.18), 218.8 (4.19); $^1$H NMR: 1.12 (t, 3H, $J = 7.0$, $CH_3$), 1.78–1.92 (m, 4H, 2 × $CH_2$), 2.10–2.28 (m, 2H, $CH_2$), 2.63 (s, 3H, $CH_3$), 2.65–2.98 (m, 2H, $CH_2$), 3.10–3.22 (m, 2H, $CH_2$), 3.52–3.75 (m, 1H, CH), 6.79 (s, 1H, $C_4H$), 7.15 and 7.49 (2d, 4H, $J = 8.0$, Ar-H), 7.18 (br s, 1H, NH exch. with $D_2O$), 11.80 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 13.15 ($CH_3$), 20.13 ($CH_2$), 21.93 ($CH_2$), 27.50 ($CH_3$), 40.07 ($CH_2$), 47.05 ($CH_2$), 52.57 ($CH_2$), 61.45 (CH), 105.03 (C-4), 114.09 (C-3), 115.01 (C-2), 123.40 (C-3′ and C-5′), 127.91 (C-4′), 128.48 (C-2′ and C-6′), 130.35 (C-5), 135.30 (C-1′), 162.54 (C=O). *Anal.* $C_{19}H_{24}ClN_3O$ (C, H, Cl, N).

*5.5.6. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-2-chloro-5-(4-fluorophenyl)-1H-3-pyrrolecarboxamide (**1j**)*

67.5% Yield; $R_f$ 0.40 ($CHCl_3$/MeOH, 8:2); m.p. 188–189°C (triturated with $Et_2O$); IR: 3360 (NH), 1630 (CO); UV: 277.3 (4.29), 216.5 (4.31), 207.5 (4.35); $^1$H NMR: 1.12 (t, 3H, $J = 7.4$, $CH_3$), 1.67–1.91 (m, 4H, 2 × $CH_2$), 2.16–2.30 (m, 2H, $CH_2$), 2.81–2.94 (m, 2H, $CH_2$), 3.20–3.27 (m, 2H, $CH_2$), 3.64–3.80 (m, 1H, CH), 6.80, (s, 1H, $C_4H$), 6.70–7.61 (m, 4H, Ar-H), 11.80 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 13.62 ($CH_3$), 22.37 ($CH_2$), 27.87 ($CH_2$), 40.35 ($CH_2$), 47.44 ($CH_2$), 53.01 ($CH_2$), 61.78 (CH), 106.04 (C-4), 114.83 and 115.26 (C-3′ and C-5′), 115.61 (C-3), 125.27 and 125.43 (C-2′ and C-6′), 127.48 (C-2), 129.87 (C-5), 158.63 (C-1′), 163.03 (C-4′), 163.52 (C=O). *Anal.* $C_{18}H_{21}ClFN_3O$ (C, H, Cl, F, N).

*5.5.7. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-2-chloro-5-(4-chlorophenyl)-1H-3-pyrrolecarboxamide (**1k**)*

43% Yield; $R_f$ 0.32 ($CHCl_3$/MeOH, 8:2); m.p. 100–102°C (amorphous); IR: 3360 (NH), 1630 (CO); UV: 291.9 (3.26), 221.3 (3.34), 216.0 (3.49); $^1$H NMR: 1.26 (t, 3H, $J = 6.8$, $CH_3$), 1.82–2.15 (m, 4H, 2 × $CH_2$), 2.84–2.94 (m, 2H, $CH_2$), 3.24–3.49 (m, 2H, $CH_2$), 3.61–3.71 (m, 2H, $CH_2$), 3.74–3.83 (m, 1H, CH), 6.88–6.94 (m, 1H, $C_4H$), 7.27 and 7.47 (2d, 4H, $J = 8.2$, Ar-H), 8.45 (br s, 1H, NH exch. with $D_2O$), 11.90 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 12.40 ($CH_3$), 22.37 ($CH_2$), 27.62 ($CH_2$), 39.98 ($CH_2$), 48.30 ($CH_2$), 53.02 ($CH_2$), 63.18 (CH), 106.13 (C-4), 122.85 (C-3), 123.30 (C-2), 124.76 (C-3′ and C-5′), 128.15 (C-2′ and C-6′), 129.49 (C-5), 129.57 (C-1′), 131.31 (C-4′), 163.12 (C=O). *Anal.* $C_{18}H_{21}Cl_2N_3O$ (C, H, Cl, N).

*5.5.8. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-2-chloro-5-(4-nitrophenyl)-1H-3-pyrrolecarboxamide (**1l**)*

22% Yield; $R_f$ 0.33 ($CHCl_3$/MeOH, 8:2); m.p. 170–175°C (dec.) (triturated with $Et_2O$); IR: 3350 (NH), 1620 (CO); UV: 370.0 (4.03), 226.0 (4.02); $^1$H NMR: 1.23 (t, 3H, $J = 6.4$, $CH_3$), 1.98–2.20 (m, 4H, 2 × $CH_2$), 2.80–3.10 (m, 2H, $CH_2$), 3.22–3.42 (m, 2H, $CH_2$), 3.58–3.72 (m, 2H, $CH_2$), 3.82–4.01 (m, 1H, CH), 7.24 (s, 1H, $C_4H$), 7.68 and 8.13 (2d, 4H, $J = 8.0$ Ar-H), 8.60 (br s, 1H, NH exch. with $D_2O$), 12.43 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{18}H_{21}ClN_4O_3$ (C, H, Cl, N).

*5.5.9. Method B: for amides **1e**,**f***

To a solution of appropriate acid (0.534 mmol) (**24**, **27**) in 5 ml of $CH_2Cl_2$ at 0–5°C was added oxalyl chloride (1.34 mmol) followed by DMF (7.3 ml, 20 mol%). The reaction mixture was warmed to r.t. and stirred for 30 min, concentrated in vacuo. The corresponding acid chloride residue was dissolved in 5 ml of $CH_2Cl_2$ and added of the requisite amine (0.801 mmol). The solution was stirred at r.t. for 20 min, then concentrated in vacuo to give a crude residue which was triturated with acetone to afford title compound as a powder (**1e**, **f**).

*5.5.10. (4-Hydroxy-4-chlorophenylpiperidino)(5-phenyl-1H-3-pyrrolyl)methanone (**1e**)*

75% Yield; $R_f$ 0.46 ($CHCl_3$/MeOH, 8:2); m.p. 230–231°C (triturated with acetone); IR: 3305 (NH), 1630 (CO); UV: 281.80 (3.90), 220.0 (4.11), 204.8 (4.16); $^1$H NMR: 1.04–2.01 (m, 8H, 4 × $CH_2$), 4.20–4.50 (m, 1H, OH exch. with $D_2O$), 6.71 (br s, 1H, $C_4H$), 7.19 (br s, 1H, $C_2H$), 7.19–7.68 (m, 9H, Ar-H), 11.63 (br s, 1H, NH exch. with $D_2O$); $^{13}$C NMR: 22.64 ($CH_2$), 23.49 ($CH_2$), 31.53 ($CH_2$), 45.70 ($CH_2$), 68.29 (C–OH), 104.10 (C-4), 117.60 (C-3), 119.84 (C-2), 121.85 (2 × C), 124.10 (C-4′), 124.86 (2 × C), 125.85 (2 × C), 126.93 (2 × C), 129.28 (C-1′), 129.37 (C-5), 146.47 (C-1‴), 154.89 (C-4‴), 163.49 (C=O). *Anal.* $C_{22}H_{21}ClN_2O_2$ (C, H, Cl, N).

*5.5.11. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-2-chloro-5-phenyl-1H-3-pyrrolecarboxamide (**1f**)*

56% Yield; $R_f$ 0.34 ($CHCl_3$/MeOH, 8:2); m.p. 175–177°C (triturated with acetone); IR: 3360 (NH), 1630 (CO); UV: 282.0 (4.20), 218.5 (4.33), 200.6 (4.45); $^1$H NMR: 1.07 (t, 3H, $J = 7.2$, $CH_3$), 1.58–1.90 (m, 4H, $CH_2$x2), 2.11–2.29 (m, 2H, $CH_2$), 2.50–2.83 (m, 2H, $CH_2$), 3.08–3.32 (m, 2H, $CH_2$), 3.66–3.69 (m,1H, CH), 6.89 (s,1H, $C_4H$), 7.15–7.55 (m, 5H, Ar-H), 11.07 (br s, 1H, NH exch. with $D_2O$). *Anal.* $C_{18}H_{22}ClN_3O$ (C, H, Cl, N).

## 6. Pharmacological experimental

### 6.1. In vitro pharmacology

#### 6.1.1. Membrane preparation

Membranes for $D_2$-like receptor binding assays were prepared from caudate nucleus of Sprague–Dowley rats.

Tissue was homogenized in 200 volumes of ice-cold 50 mmol Tris–HCl buffer pH 7.7 (buffer A) and centrifuged at 50000 *g* at 4°C for 25 min. The pellet was resuspended in 50 mmol Tris–HCl buffer pH 7.7 containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM EDTA and 5.7 mmol ascorbic acid (buffer B).

*6.1.2. Binding assay*

[$^3$H]YM-09151-2 was used as a specific ligand for $D_2$-like receptors [10] and 50 μM (−)-sulpiride as a specific displacer [11]. [$^3$H]YM-09151-2 binding was determined in a final volume of 1000 μl, consisting of 400 μl tissue homogenate, 100 μl 0.4 nM [$^3$HY]YM-09151-2, 100 μl drugs (dissolved in dimethylsulfoxide and serial dilutions made up in buffer) or incubation buffer (total and non specific samples). The incubation (at 25°C, in the dark) was started by the addition of tissue homogenate and was terminated 60 min later by rapid filtration through glass-fiber filter strips (Whatman GF/B) with a filtration manifold (Model M-24, Brandel). The filters were rinsed three times with 4 ml of ice-cold Tris buffer B.

Protein concentration was assayed by the method of Lowry [12] with bovine serum as standard. $IC_{50}$ values were determined from displacement curves with the MEDUSA program.

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