ELSEVIER

Il Farmaco 53 (1998) 684–689

IL FARMACO

Synthesis and D_2-like binding affinity of 4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide derivatives as conformationally restricted 5-phenyl-pyrrole-3-carboxamide analogs☆

Gérard A. Pinna [a,*], Maria M. Curzu [a], Mario Sechi [a], Giorgio Chelucci [b], Paola Vianello [c], Elisabetta Maciocco [d]

[a] *Dipartimento Farmaco-Chimico-Tossicologico, Università di Sassari, Via Muroni 23, 07100 Sassari, Italy*
[b] *Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy*
[c] *Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, Viale Abruzzi 43, 20131 Milan, Italy*
[d] *Dipartimento di Biologia Sperimentale, Università di Cagliari, Via Palabanda 12, 09123 Cagliari, Italy*

Abstract

A series of 4,5-dihydro-1*H*-benzo[*g*]-indole-3-carboxamide derivatives **2a–g** were synthesized as conformationally restricted analogs of the dopamine D_2-like 5-phenylpyrrole-3-carboxamide ligands and evaluated for their affinity for the dopamine D_2-like receptors. In this series, *N*3-[(1-ethyltetrahydro-1*H*-2-pyrrolyl)methyl]-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (**2a**) showed the highest affinity for D_2-like receptors ($IC_{50} = 160$ nM). Replacement of the *N*-(1-ethyl-2-pyrrolidinyl)methyl side chain with a 2-(*N*,*N*-diethylamino)ethyl or a 1-benzyl-4-piperidinyl group (**2b**, **2d**) decreased affinity for the D_2-like receptor. The other compounds tested were found to be devoid of D_2-like binding affinity.

Keywords: D_2-like receptor binding affinity; 4,5-Dihydro-1*H*-benzo[*g*]indole-3-carboxamide derivatives; Structure–activity relationships

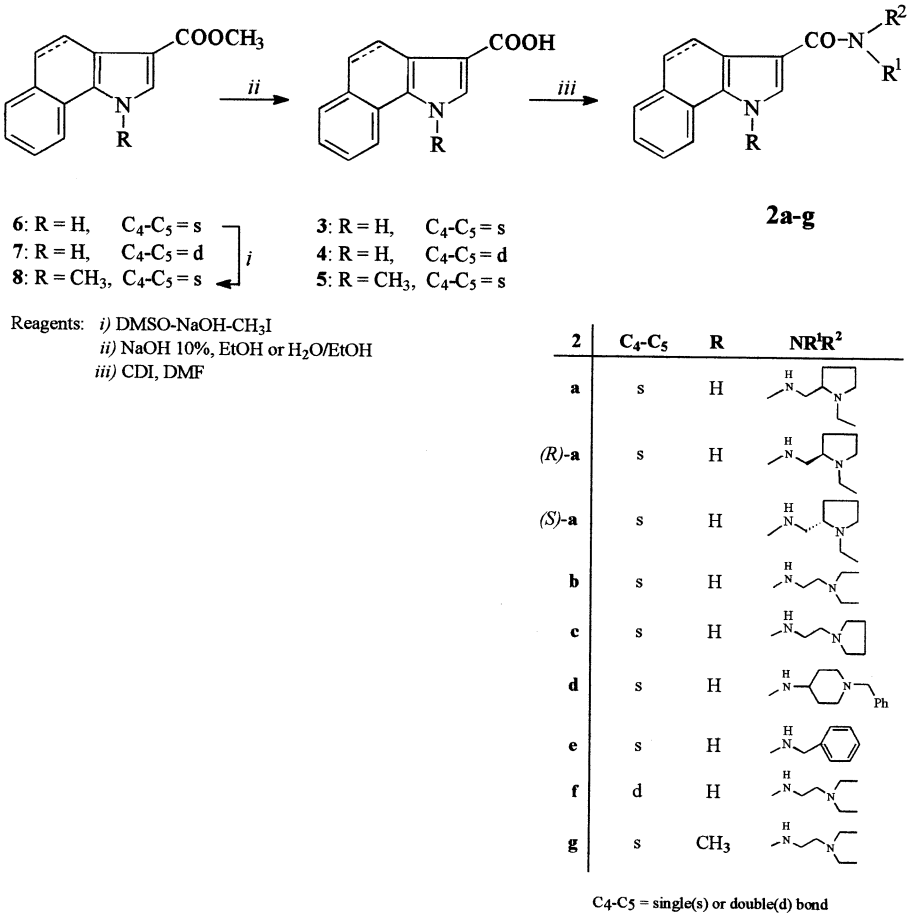
1. Introduction

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 D_1 and D_5 receptors, both of which activate adenylate cyclase, while the D_2-like family is divided into 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 overactivity of dopamine-secreting neurons in the 'limbic brain', rich in D_2-like 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 antipsychotic with a better pharmacological profile remains a primary goal in the research for the therapy of psychoses [3]. In a previous paper [4], we have reported on a series of substituted 5-phenylpyrrole-3-carboxamides which displayed poor affinity at dopamine D_2-like receptors, *N*3-[(1-ethyltetrahydro-1*H*-2-pyrrolyl)methyl]-5-phenyl-1*H*-3-pyrrolecarboxamide **1** being the best representative term. In search of compounds with a better in vitro pharmacological profile, we undertook structural modification of **1** by incorporating the 5-phenylpyrrole backbone into the tricyclic framework of 4,5-dihydrobenzo[*g*]indole, and varying the *N*-(1-ethyl-2-pyrrolidinyl)methyl moi-

☆ Dedicated to Professor Antonio Maccioni.

* Corresponding author.

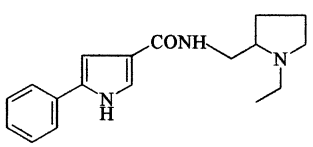
0014-827X/98/$ - see front matter
PII: S0014-827X(98)00087-1



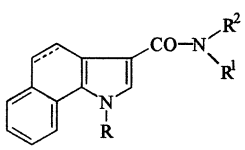
Scheme 1.

ety with 2-(*N*,*N*-diethylamino)ethyl, pyrrolidinylethyl, 1-benzyl-4-piperidinyl and benzyl groups.

The synthesis of benzo[*g*]indole-3-carboxamide derivatives **2** (see below) and their in vitro binding to the dopamine D_2-like receptors are reported in the present paper.



1



2

2. Chemistry

The synthesis of target compounds **2a–g** was prepared by amination of the suitable benzo[*g*]indole-3-carboxylic acids **3–5** with the requisite amines in the presence of 1,1′-carbonyldiimidazole (CDI) (Scheme 1). Acids **3–5** [5] were obtained by the hydrolysis of esters **6**, **7** [5] and **8**. The enantiomers of **2a** were prepared by coupling the carboxylic acid **3** with, (*S*)- and (*R*)-2-(aminomethyl)-1-ethylpyrrolidine, respectively [6].

3. Pharmacology

3.1. Receptor binding

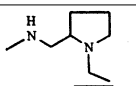
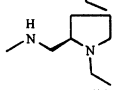
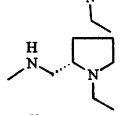
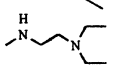
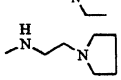
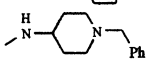
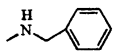
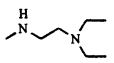
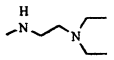
The target 4,5-dihydro-benzo[*g*]indole-3-carboxamide derivatives **2a–g** were examined in vitro for their binding affinities to dopamine D_2-like receptors. Affinities for the dopamine sites were determined via standard competitive displacement assay using D_2-like receptors isolated from caudate nucleus of male Sprague–Dawley rats with [^{3}H]YM-09151-2 (nemonapride) as a specific ligand [7] and (−)-sulpiride as a specific displacer [8].

4. Results and discussion

The dopamine D_2-like receptor binding affinities of the carboxamides **2a–g** are listed in Table 1.

Among the compounds synthesized **2a** displayed appreciable affinity at D_2-like receptors indicating the favorable effect of the replacement of the 5-phenylpyrrole backbone of the model compound **1** with a 4,5-dihydrobenzo[*g*]indole moiety (**2a**, $IC_{50} = 160$ nM versus **1**, $IC_{50} = 1.03$ μM).

Table 1
D_2-like receptor binding affinity[a] of compounds **2a–g**

Compound	C_4–C_5	R	NR^1R^2	Receptor binding[b] IC_{50} (nM)
2a	s	H		160
(*R*)-**2a**	s	H		1060
(*S*)-**2a**	s	H		120
2b	s	H		400
2c	s	H		>5000
2d	s	H		900
2e	s	H		>5000
2f	d	H		>5000
2g	s	CH_3		>5000
Raclopride				39

[a] [^{3}H]YM-09151-2 has been used as the specific ligand.
[b] The IC_{50} for binding is the average of three experiments. The S.E.M. for all values was <10%.

Dopamine D_2-like affinity was also affected by changes in the carboxamide basic side chain: the replacement of the *N*-(1-ethyl-2-pyrrolidinyl)methyl group of **2a** by a 2-(*N*,*N*-diethylamino)ethyl or 1-benzyl-4-piperidinyl chain resulted in an attenuation of D_2-like receptor binding (**2a** versus **2b** and **2d**) while the other compounds (**2c** and **2e**) lacked significant affinity.

Unexpectedly, oxidation or methylation of the tricyclic framework of **2b** led to compounds **2f** and **2g** devoid of D_2-like affinity suggesting that the 4,5-dihydrobenzo[*g*]indole nucleus is crucial for drug–receptor interaction. Finally, the most active compound **2a** was synthesized in the optically pure forms (*S*)-**2a** and (*R*)-**2a**, to examine the effects of stereochemistry on D_2-like binding affinity. The greater binding affinity for D_2-like receptors was found to reside in the (*S*)-isomer (IC_{50} 120 versus 1060 nM).

Aiming to improve the D_2 binding affinity of **2a**, further work is in progress involving structural modifications of the benzo[*g*]indole system.

5. Chemical experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification.

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).

Thin layer chromatography (TLC) was performed with Polygram® SIL N-HR-/HV_{254} precoated plastic sheet (0.2 mm). ^{1}H NMR 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 δ (ppm) downfield from internal TMS and coupling constants in Hz. Significant ^{1}H 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. Infrared (IR) spectra were recorded as thin films or Nujol mulls on NaCl plates with a Perkin–Elmer 781 IR spectrophotometer and are expressed in ν (cm^{-1}). UV–Vis spectra were recorded as ethanolic solution with a Perkin–Elmer Lambda 5 spectrophotometer and are the absorption wavelength expressed in nm followed by (log ε). Optical rotation (α) of the pure enantiomers was measured using a Perkin–Elmer 241 optical activity polarimeter. 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 Padova (Italy), and are within $\pm$0.4% of the calculated values (see Table 2). For the binding studies [^{3}H]YM-09151-2 was purchased from NEN-DuPont (Boston, MA, USA).

*5.1. Methyl 1-methyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (**8**)*

A suspension of powder KOH (8.80 mmol) in 5 ml of dry dimethylsulfoxide (DMSO) was stirred at room temperature for 5–10 min and then added to methyl 4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (**6**) [5] and the solution was stirred again for 45 min. To the reaction mixture was added 4.4 mmol of methyl iodide at 0–5°C which was then stirred for 45 min at room temperature. The mixture was diluted with water and the solid formed was filtered, washed with water, and air-dried to give the title compound **8**.

86.8% Yield; R_f 0.70 (AcOEt/light petroleum, 2:8); m.p. 98–100°C (EtOH); IR 1710 (CO); UV 218.0 (3.95), 224 (3.94), 2.38 (3.75), 263 sh (3.73), 303.9 (4.26); ^{1}H NMR 2.64 (t, 3H, $J = 6.10$, CH_2), 2.85 (t, 3H, $J = 6.10$, CH_2), 3.82 (s, 3H, CH_3), 4.18 (s, 3H, CH_3), 6.85 (s, 1H, C_2H), 7.14–7.65 (m, 4H, Ar-H).

Table 2
Elemental analysis

Compound	Required (%)			Empirical formula	Found (%)		
	C	H	N		C	H	N
2a	74.27	7.79	12.99	$C_{20}H_{25}N_3O$	74.38	7.95	12.83
2b	73.28	8.09	13.49	$C_{19}H_{25}N_3O$	73.09	8.22	13.57
2c	73.76	7.49	13.58	$C_{19}H_{23}N_3O$	73.88	7.24	13.51
2d	77.89	7.06	10.90	$C_{25}H_{27}N_3O$	77.95	7.28	10.99
2e	79.44	6.00	9.26	$C_{20}H_{18}N_2O$	79.62	6.25	9.33
2f	73.76	7.49	13.58	$C_{19}H_{23}N_3O$	73.89	7.55	13.76
2g	73.81	8.36	12.91	$C_{20}H_{27}N_3O$	73.69	8.20	12.87
4	73.92	4.29	6.63	$C_{13}H_9NO_2$	73.79	4.18	6.58
5	73.99	5.77	6.16	$C_{14}H_{13}NO_2$	73.82	5.72	6.36
8	74.67	6.27	5.80	$C_{15}H_{15}NO_2$	74.74	6.18	5.85

*5.2. General ester hydrolysis procedure for the preparation of compounds **4** and **5***

A mixture of appropriate ester (**7** or **8**) (2.48 mmol) in 26 ml of 10% hydroalcoholic (1:2 for **7** and 1:1 for **8**) NaOH was refluxed for 12 h and then poured into cold water. The resulting solution was acidified with conc. HCl and the resulting precipitate was collected, washed with water, and air-dried to give pure title acid (**4** and **5**) which was used without further purification in the next step.

*5.2.1. 1H-Benzo[g]indole-3-carboxylic acid (**4**)*

60.4% Yield; R_f 0.43 ($CHCl_3$/MeOH 7:3); m.p. 196–198°C; IR 3500 (NH), 1770 (CO); UV 195.5 (4.19), 206.0 (4.14), 231.5 (4.20), 255.7 (4.23), 278.0 (4.17), 290.0 (4.08), 304.0 (3.63), 318.0 (3.80), 333.8 (3.81); ^{1}H NMR 7.22 (d, 1H, $J = 1.98$, C_2H), 7.40–7.70 (m, 4H, Ar-H), 8.40 (ABq, 2H, C_4H and C_5H), 12.61 (br s, NH exch. with D_2O).

*5.2.2. 1-Methyl-4,5-dihydro-1H-benzo[g]indole-3-carboxlylic acid (**5**)*

84.2% Yield; R_f 0.47 ($CHCl_3$/MeOH 9:1); m.p. 260–261°C; IR 1650 (CO); UV 199.8 (4.25), 218.6 (4.27), 287.7 (4.23), ^{1}H NMR 2.64 (t, 2H, $J = 5.8$, CH_2), 2.87 (t, 2H, $J = 5.8$, CH_2), 4.19 (s, 3H, CH_3), 7.01 (s, 1H, C_2H), 7.18–7.70 (m, 4H, Ar-H).

*5.3. General acid amination procedure for the preparation of compounds **2a–g***

To a stirred solution of appropriate acid (**3–5**) (1.17 mmol) in 5.3 ml of DMF was added 1,1′-carbonyldiimidazole (1.3 mmol). After stirring the reaction mixture for 3 h, requisite amine (3.4 mmol) was added and stirring continued for 1 h. The reaction mixture was poured into water to give a crude solid which was filtered off or an oil which was extracted with CH_2Cl_2. The organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated to yield a crude brown oil. Crude product was purified by flash-chromatography (**2d**, **2g**) or by crystallization (**2a**, **2b**, **2c**, **2e**, **2f**) to give pure title compounds.

*5.3.1. N3-[(1-Ethyltetrahydro-1H-2-pyrrolyl)methyl]-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2a**)*

33% Yield; R_f 0.40 ($CHCl_3$/MeOH, 8:2); m.p. 160–163°C (Et_2O); IR 3400, 3260, 3200 (NH), 1660 (CO); UV 205.8 (4.38), 232.1 (4.11), 276.1 (4.06), 325.1 (4.48), 336.1 (4.40); ^{1}H NMR 1.13 (t, 3H, $J = 7.4$, CH_3), 1.55–1.96 (m, 2H, CH_2), 2.10–2.29 (m, 2H, CH_2), 2.59–3.00 (m, 6H, $3CH_2$), 3.10–3.40 (m, 2H, CH_2), 3.62–3.80 (m, 1H, CH), 6.43 (d, 1H, $J = 2.0$, C_2H), 6.60 (br s, 1H, NH exch. with D_2O), 7.10–7.52 (m, 4H, Ar-H), 10.36 (br s, 1H, NH exch. with D_2O).

*5.3.2. N3-[2-(Diethylamino)ethyl]-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2b**)*

34.4% Yield; R_f 0.40 ($CHCl_3$/MeOH 8:2); m.p. 166–167°C (DMF–H_2O); IR 3360, 3230 (NH), 1640 (CO); UV 217.8 (3.90), 236.2 (3.39), 260.4 (3.78), 306.1 (4.48), 318.5 (4.46); ^{1}H NMR 1.01 (t, 6H, $J = 7.2$, $2CH_3$), 2.40–2.70 (m, 8H, $4 \times CH_2$), 2.82 (t, 2H, $J = 8.0$, CH_2), 3.32 (t, 2H, $J = 8.0$, CH_2), 6.66 (s, 1H, C_2H), 7.09–7.79 (m, 4H, Ar-H), 7.88 (t, 1H, NH exch. with D_2O), 11.69 (br s, 1H, NH exch. with D_2O).

*5.3.3. N3-(2-Tetrahydro-1H-pyrrolylethyl)-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2c**)*

25.5% Yield; R_f 0.37 ($CHCl_3$/MeOH, 8:2); m.p. 75–77°C (DMF–H_2O); IR 3430 (NH), 1640 (CO); UV 214.7 (3.86), 232.0 (3.81), 248.2 sh (3.56), 280.0 sh (3.59), 318.3 (3.89); ^{1}H NMR 1.75–1.95 (m, 4H, $2CH_2$), 2.48–2.80 (m, 8H, $4CH_2$), 2.92 (t, 2H, $J = 8.0$, CH_2), 3.58 (t, 2H, $J = 8.0$, CH_2), 6.52 (s, 1H, C_2H), 6.85 (br s, 1H, NH exch. with D_2O), 7.10–7.52 (m, 4H, Ar-H), 10.10 (br s, 1H, NH exch. with D_2O).

*5.3.4. N3-(1-Benzyl-4-piperidyl)-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2d**)*

39% Yield; R_f 0.38 ($CHCl_3$/MeOH, 9:1); m.p. 98–99°C; IR 3250 (NH), 1640 (CO); UV 212.0 (4.64), 228.5 (4.52), 248.0 (4.34), 274.6 (4.54), 312.0 (4.45), 322.0 (4.52), 332.0 (4.49), 336.0 (4.55); ^{1}H NMR 1.52–1.68 (m, 2H, CH_2), 1.80–1.95 (m, 2H, CH_2), 2.02–2.20 (m, 2H, CH_2), 2.54–2.94 (m, 9H, $4CH_2$ and CH), 6.68 (s, 1H, C_2H), 7.12–7.68 (m, 9H, Ar-H), 7.90 (br s, 1H, NH exch. with D_2O), 11.49 (br s, 1H, NH, exch. with D_2O).

*5.3.5. N3-Benzyl-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2e**)*

40% Yield; R_f 0.35 (AcOEt/light petroleum, 4:6); m.p. 168–170°C (DMF–H_2O); IR 3260 (NH), 1630 (CO); UV 206.0 (4.41), 226.0 sh (4.10), 250.0 sh (3.68), 276.1 (3.80), 322.3 (4.45), 322.5 (4.48), 335.2 (4.44); ^{1}H NMR 2.69 (t, 2H, $J = 5.6$, CH_2), 2.91 (t, 2H, $J = 5.6$, CH_2), 4.67 (d, 2H, $J = 5.72$, CH_2), 6.26 (t, 1H, $J = 5.72$, NH exch. with D_2O), 6.44 (d, 1H, $J = 2.14$ C_2H), 6.99–7.60 (m, 9H, Ar-H), 10.73 (br s, 1H, NH exch. with D_2O).

*5.3.6. N3-[2-(Diethylamino)ethyl]-1H-benzo[g]-indole-3-carboxamide (**2f**)*

81.7% Yield; R_f 0.43 ($CHCl_3$/MeOH, 8:2); m.p. 131–133°C (DMF–H_2O); IR 3360, 3240 (NH) 1650 (CO); UV 195.0 (4.34), 224.0 (4.14), 232.3 (4.19), 254.0 (4.34), 280.0 (4.17), 292.2 (4.12), 316.5 (3.84), 332.4 (3.90); ^{1}H NMR 1.07 (t, 6H, $J = 7.1$, $2CH_3$), 2.60 (q, 4H, $J = 7.1$, $2CH_2$), 2.71 (t, 2H, $J = 6.0$, CH_2), 3.63 (q, 2H, $J = 6.0$, CH_2), 7.02 (d, 1H, $J = 1.2$, C_2H), 7.22 (br s, 1H, NH exch. with D_2O), 7.40–7.68 (m, 4H, Ar-H), 8.20 (ABq, 2H, C_4H and C_5H), 11.14 (br s, 1H, NH exch. with D_2O).

*5.3.7. N3-[2-(Diethylamino)ethyl]-1-methyl-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2g**)*

35.7% Yield; R_f 0.62 ($CHCl_3$/MeOH, 8:2); yellow oil; IR 3300 (NH), 1670 (CO); UV 221.0 (3.92), 233.1 sh (3.37), 262.2 (3.78), 300.3 (4.44), 313.5 (4.41); ^{1}H NMR 0.98 (t, 6H, $J = 7.2$, $2CH_3$), 2.40–2.62 (m, 8H, $4CH_2$), 3.30–3.46 (m, 2H, CH_2), 4.08 (s, 3H, CH_3), 6.41 (s, 1H, C_2H), 6.82 (br s, 1H, NH exch. with D_2O), 7.03–7.50 (m, 4H, Ar-H).

*5.4. General procedure for the enantiomers of N3-[(1-ethyltetrahydro-1H-2-pyrrolyl)methyl]-4,5-dihydro-1H-benzo[g]indole-3-carboxamide (**2a**)*

To a stirred solution of the carboxylic acid **3** (1.17 mmol) in 5.3 ml of DMF was added 1,1′-carbonyldiimidazole (1.3 mmol). After stirring the reaction mixture for 3 h, (*S*)- or (*R*)-(aminomethyl)-1-ethylpyrrolidine [6] was added and stirring continued for 1 h. The reaction mixture was poured into water to give a crude solid. The resulting solid was recrystallized from AcOEt/Et_2O to give (*S*)- or (*R*)-**2a**. Physical data for (*S*)- or (*R*)-**2a** are as follows:

Compound (*R*)-**2a**:	Yield 33%; m.p. 168–170°C; $[\alpha]_D^{23} = +58$ ($c = 1.0$ CH_3OH)
Compound (*S*)-**2a**:	Yield 35%; m.p. 166–168°C; $[\alpha]_D^{23} = -55$ ($c = 1.0$ CH_3OH)

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–Dawley rats. Tissue was homogenized in 200 volumes of ice-cold 50 mM Tris–HCl buffer pH 7.7 (buffer A) and centrifuged at 50 000 × *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 (nemonapride) was used as a specific ligand for D_2-like receptor [7] and (−)-sulpiride as a specific displacer [8].

[^{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}H]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 et al. [9] with bovine serum as standard. IC_{50} values were determined from displacement curves with the Medusa program.

Acknowledgements

The authors acknowledge Professor G. Cignarella for his insightful comment on this work.

References

[1] J.W. Kebabian, D.B. Calne, Multiple receptor for dopamine, Nature 277 (1979) 93–96.

[2] O. Civelli, J.R. Bunzow, D.K. Grandy, Molecular diversity of the dopamine receptors, Ann. Rev. Pharmacol. Toxicol. 32 (1993) 281–307.
[3] M. Jaber, S.W. Robinson, C. Missale, M.G. Caron, Dopamine receptors and brain function, Neuropharmacology 35 (1996) 1503–1519.
[4] G.A. Pinna, M.M. Curzu, M. Sechi, G. Chelucci, E. Maciocco, Synthesis and dopamine D_2-like receptor binding affinity of substituted 5-phenylpyrrole-3-carboxamines, Farmaco, submitted for publication.
[5] G.A. Pinna, M.A. Pirisi, G. Paglietti, Addition reactions of acetylenic esters upon 6-substituted-α-tetralone oximes and conversion of the adducts into 4,5-dihydro-1*H*-benzo[*g*]indoles, J. Chem. Res. (M) (1990) 2773–2781.
[6] G. Boulteau, Resolution of 1-ethyl-2-(aminomethyl)pyrrolidine, S. African 68 02, 593, 18 Oct (1968), CA 303540, 71, 280 (1969).
[7] H.B. Niznik, D.E. Grigoriadis, I. Pri-Bar, O. Buchman, P. Seeman, Dopamine D_2 receptors selectively labeled by a benzamide neuroleptic: [^{3}H]YM-09151-2, Naunyn-Schmiedebergs Arch. Pharmacol. 329 (1985) 333–340.
[8] E. Stefanini, M. Frau, G.L. Gessa, Increase in D2 dopamine receptors in the substantia nigras after chronic (()-sulpiride treatment, Brain Res. 555 (1991) 340–342.
[9] O.H. Lowry, N.J.M Rosebrough, A.L. Farr, R.J. Randall, Protein measurement with the Folin phenol reagent, J. Biol. Chem. 193 (1951) 265–275.