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Short communication

2-Oxo-2-(phen-2-ylpyrrol-2-yl)acetamides as potential anxiolytic agents: Synthesis and affinity at the central benzodiazepine receptor

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Abstract – A series of *N*-substituted 2-hydroxy and 2-oxo-2-(phen-1-ylpyrrol-2-yl)acetamides were synthesized and their affinity at the benzodiazepine receptor tested. Isosteric replacement of the indolyl ring in previously described derivatives by a phen-1-ylpyrrole led to the synthesis of seven compounds **8–9**, **12–14**, **23** and **26** with benzodiazepine affinity ($K_i \leq 0.90$ µM). Among these, **26** exhibits an interesting anxiolytic activity and weak lateral effects. © Elsevier, Paris

benzodiazepine receptor affinity / phenylpyrrolylacetamide / anxiolytic activity

1. Introduction

Benzodiazepine receptors (BZR) ligands do not only belong to the benzodiazepine series. Besides these, a wide variety of various structural classes of agonists, antagonists or inverse agonists has been described [1–6] and all the molecular features responsible for receptor binding have not been completely established. In a large programme of original psychotropic heterocyclic compounds synthesis [7, 8] our laboratory had already described the preparation of new phen-1-ylpyrroles [9–11]. Moreover, we had undertaken the systematic biological evaluation of BZR ligands and pharmacological studies of several new coumpounds we had previously synthesized [12]. On the other hand, some *N*-(indol-3-yl), *N*-(benzothien-3-yl) and *N*-(benzofur-2-yl) 2-oxacetamides derivatives with BZR affinity have recently been described [13, 14]. In this double context, a series of new 2-oxo-2-(phen-1-ylpyrrol-2-yl)acetamide derivatives has been prepared, postulating that isosteric replacement of the indolyl ring by the phen-1-ylpyrrole nucleus could lead to compounds with potential BZR activity (*figure 1*). Synthesis and results obtained in their preliminary pharmacological screening are included in this present report.

2. Results and discussion

2.1. Chemistry

Synthesis of 2-oxo-(phen-1-ylpyrrol-2-yl)acetamide derivatives **1–27** involves the condensation of oxalyl chloride with the appropriate phen-1-ylpyrrole. These were previously synthesized from the corresponding anilines using 2,5-dimethoxytetrahydrofuran in acetic acid according to the Clauson-Kaas procedure [15, 16]. After adding oxalyl chloride and a 6 h period stirring at room temperature in acetonitrile, the (phen-1-ylpyrrol-2-yl)acyl chloride is used without further purification in a one-pot procedure in which the appropriate amine, benzyl ($n = 1$, compounds **1–4**) or phenethylamine ($n = 2$, compounds **5–27**), is added by a simple slow addition to the reactant mixture (*figure 2*). Using sodium borohydride in methyl alcohol allows the selective reduction of the α-carbonyle moiety and leads to the synthesis of 2-hydroxyacetamide derivatives **28–31** [17]. The structures of all the resulting products **1–31** purified by recrystallization and reported in *table I*, are supported by analytical, IR and NMR spectral data (*table II*).

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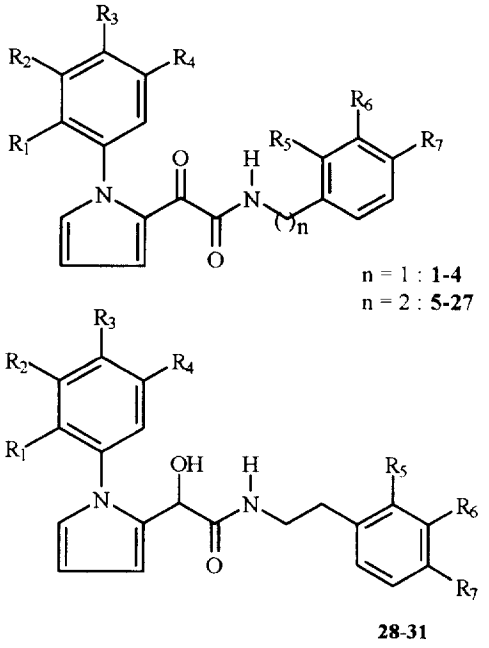


Figure 1.

2.2. Pharmacology

All the compounds **1–31** reported in this work were originally evaluated at 10^{-5} M for their ability to displace the ^{3}H-flunitrazepam (3H-FLU) from its specific binding in rat brain. Then, inhibition constants K_i were calculated for the more active ones (inhibition percentage superior at 75%) (*table I*). Derivatives **8**, **14** and **26** having stronger affinity at BZR, were submitted for acute toxicity and behavioral studies in mice, using the method of Morpugo [18]. Effects on spontaneous activity, proconvulsant and anticonvulsant activities were studied in mice at doses not greater than approximately 0.40 LD_{50}. Morever, anxiolytic activity of these three title compounds were evaluated with the Black and White test box [19].

For in vivo studies, the compounds were administrated i.p. Some reference standards, such as diazepam, methyl β-carboline-3-carboxylate (β-CCM) and chlorazepate were included in the tests for comparison purposes.

Inhibition percentages of 3H-FLU binding for derivatives **1–31** are also reported in *table I*. Among these, seven compounds **8**, **9**, **12–14**, **23** and **26** exhibited a good affinity at BZR. K_i values range from 0.054 to 0.875 μM.

First affinity data and activity profile results reveal that *N*-benzyl derivatives **1–4** demonstrated a low affinity at the benzodiazepine receptor. Condensed amine should be a phenethyl amine. Interestingly, reduction of a carbonyle moiety (2-hydroxyacetamides **28–31**) lowers this affinity.

N-phenethyl 2-oxo-2-(phen-1-ylpyrrol-2-yl)acetamides identified as compounds **5–27** exhibited some affinity at BZR especially when the phenyl nucleus of the phenethyl moiety is substituted with a chloro or a methoxy in the 4-position. On the other hand, affinity seems to be enhanced if compounds possess a methoxy in the 2 and/or 3-positions and in the 4-position of the phenyl linked to the pyrrole nucleus (compounds **14**, **23** and the most potent **26**), but a halogen (i.e. chloro, fluoro) or even a hydroxy allows a good binding activity (compounds **8–9**, **12–13**).

Concerning the behavioral effects evaluated in mice with the procedure of Irwin–Morpugo, subtoxic doses of compounds **8**, **14** and **26** only produce hypoactivity and relaxation effect. These effects were increased after 3 h. No ataxic effects occured even at high doses. Moreover, the compounds produced a spontaneous motility decrease with a dose at least five times higher than diazepam. On the other hand, the tested compounds did not show neither proconvulsant nor anticonvulsant activity (*table III*).

Behavioral effects of compounds **8**, **14** and **26** were investigated with the Black and White test box. Crawley and coworkers have used the number of transitions performed by mice between two experimental chambers as an index of anxiety. One of the chambers is large and brighty lit, and the other one is smaller and under a low level of illumination. This test exhibits a degree of face validity in that light serves as an anxiogenic stimulus, and there is an apparent conflict between the desire to explore and the desire to avoid the brighty lit part of the apparatus. Drugs which increase the number of light–dark transitions at doses that do not increase locomotor activity, are presumed to have anxiolytic properties [19]. In this work, the three title compounds **8**, **14** and **26** were tested with doses inferior to the minimal dose known to induce a significative decrease of spontaneous activity in the photoactimeter test (doses ≤ 50 mg/kg for derivatives **8** and **14**; doses ≤ 10 mg/kg for **26**). Compounds **8** and **14** failed to demonstrate either anxiolytic or anxiogenic activity (no increase or decrease of transition number compared to the control lot) but **26** exhibited anxiolytic activity with in particular a significative increase of the transitions at 5 mg/kg (*figure 3*).

3. Conclusion

In summary, isosteric replacement of the planar indolyl ring by phen-1-ylpyrrole leads to the disco-

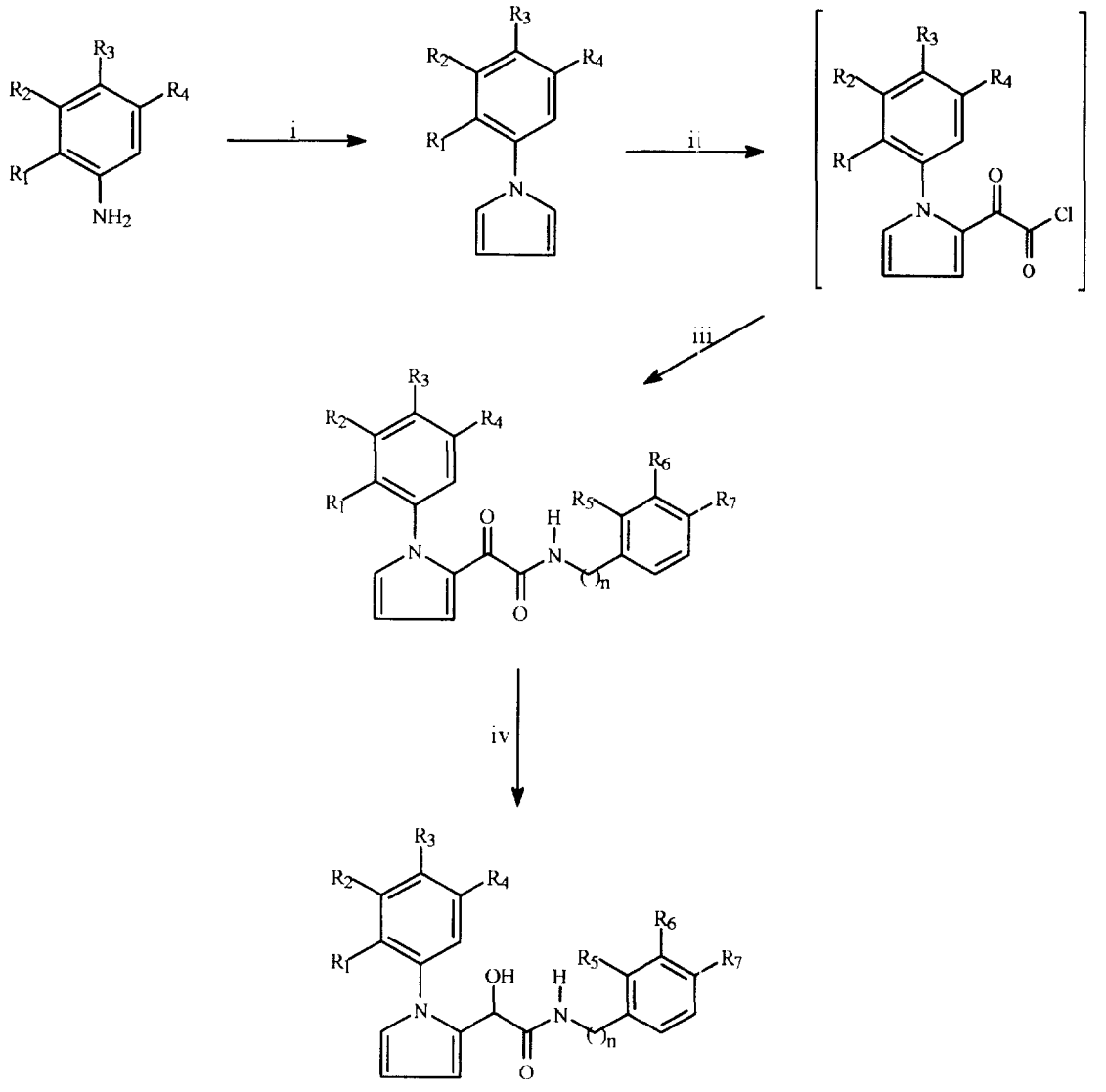


Figure 2. i: 2,5-dimethoxytetrahydrofuran, AcOH, μ.o. 8 min; ii: $(ClCO)_2$, CH_3CN, room temperature, 6 h; iii: amine, RT, 10 min; iv: $NaBH_4$, CH_3OH, reflux, 2h.

very of this new above-described compound which presents interesting BZR affinity data and pharmacological profile as partial agonist with a weak sedative and no anticonvulsant activity. Its anxiolytic effect as shown with the Black and White test box at a dose very close to the classical benzodiazepines ones, allows us to hope for synthesizing new anxiolytics with weak lateral effects in the phenylpyrrole series. Further investigations are currently in progress.

4. Experimental protocols

4.1. Chemistry

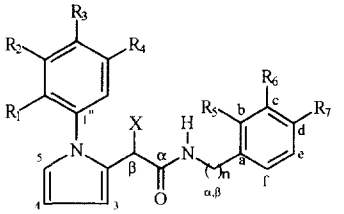
Melting points were determinated using a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. NMR spectra were recorded on a Jeol Lambda 400 using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Analyses were within ± 0.4% of the theoretical values.

Table I. Data for compounds **1–31**.

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	n	I%[a] (10^{-5} M)	K_i[b] (μM)
1	H	H	H	H	H	H	Cl	1	+ 24%	
2	H	H	H	H	Cl	H	H	1	+ 8%	
3	H	H	OCH_3	H	H	H	H	1	+ 19%	
4	H	H	OCH_3	H	H	H	Cl	1	+ 14%	
5	H	H	H	H	H	H	Cl	2	+ 26%	
6	H	H	H	H	H	H	OCH_3	2	+ 43%	
7	H	H	H	H	OCH_3	H	H	2	+ 6%	
8	H	H	OH	H	H	H	Cl	2	**+ 77%**	**0.248 ± 0.120**
9	H	H	OH	H	H	H	OCH_3	2	**+ 76%**	**0.875 ± 0.025**
10	H	H	OH	H	H	OCH_3	OCH_3	2	+ 56%	
11	H	H	OH	H	Cl	H	Cl	2	+ 58%	
12	H	H	Cl	H	H	H	Cl	2	**+ 80%**	**0.667 ± 0.032**
13	H	H	F	H	H	H	Cl	2	**+ 75%**	**0.580 ± 0.021**
14	H	H	OCH_3	H	H	H	Cl	2	**+ 90%**	**0.212 ± 0.018**
15	H	H	OCH_3	H	H	H	OCH_3	2	+ 23%	
16	H	H	OCH_3	H	OCH_3	H	H	2	+ 27%	
17	H	H	OCH_3	H	H	OCH_3	OCH_3	2	+ 2%	
18	H	H	OCH_3	H	Cl	H	Cl	2	+ 54%	
19	H	H	CF_3	H	H	H	OCH_3	2	+ 31%	
20	Cl	H	H	H	H	H	OCH_3	2	+ 8%	
21	Cl	H	H	H	H	H	Cl	2	+ 8%	
22	Cl	H	H	H	H	OCH_3	H	2	12.5%	
23	OCH_3	H	H	H	H	H	Cl	2	**+ 93%**	**0.400 ± 0.028**
24	CH_3	H	H	CH_3	H	H	Cl	2	+ 38%	
25	CH_3	H	H	CH_3	H	H	OCH_3	2	+ 4%	
26	H	OCH_3	OCH_3	H	H	H	Cl	2	**+ 98%**	**0.054 ± 0.070**
27	H	OCH_3	OCH_3	OCH_3	H	Cl	Cl	2	+ 1%	
28	H	H	OCH_3	H	H	H	Cl	2	+ 15%	
29	H	H	CF_3	H	H	H	Cl	2	+ 1.5%	
30	H	H	CF_3	H	OCH_3	H	H	2	– 3%	
31	OCH_3	H	H	CH_3	OCH_3	H	H	2	– 3%	

[a]Percentage of inhibition (I%) of 3H-FLU binding at 10 μM concentration; [b]K_i values are means ± SEM of three experiments.

Table II. Analytical data for compounds **1–31**.



X : =O n=1 **1-4**
X : =O n=2 **5-27**
X : OH n=2 **27-31**

Compound	Formula	Yield (%) (M.p. (°C))	Compound	Formula	Yield (%) (M.p. (°C))
1	$C_{19}H_{15}N_2O_2Cl$	98 (194)	**17**	$C_{23}H_{24}N_2O_5$	76 (97)
2	$C_{19}H_{15}N_2O_2Cl$	92 (168)	**18**	$C_{21}H_{18}N_2O_3Cl_2$	82 (92)
3	$C_{20}H_{18}N_2O_3$	81 (113)	**19**	$C_{22}H_{19}N_2O_3F_3$	86 (141)
4	$C_{20}H_{17}N_2O_3Cl$	86 (154)	**20**	$C_{21}H_{19}N_2O_3Cl$	90 (132)
5	$C_{20}H_{17}N_2O_2Cl$	92 (212)	**21**	$C_{20}H_{16}N_2O_2Cl_2$	78 (149)
6	$C_{21}H_{20}N_2O_3$	94 (176)	**22**	$C_{21}H_{19}N_2O_3Cl$	94 (134)
7	$C_{21}H_{20}N_2O_3$	82 (171)	**23**	$C_{21}H_{19}N_2O_3Cl$	81 (109)
8	$C_{20}H_{17}N_2O_3Cl$	95 (159)	**24**	$C_{22}H_{21}N_2O_2Cl$	71 (116)
9	$C_{21}H_{20}N_2O_4$	88 (128)	**25**	$C_{22}H_{24}N_2O_3$	94 (142)
10	$C_{22}H_{22}N_2O_5$	86 (102)	**26**	$C_{22}H_{21}N_2O_4Cl$	72 (100)
11	$C_{20}H_{16}N_2O_3Cl_2$	92 (159)	**27**	$C_{23}H_{22}N_2O_5Cl_2$	69 (113)
12	$C_{20}H_{16}N_2O_2Cl_2$	90 (67)	**28**	$C_{21}H_{21}N_2O_3Cl$	82 (250)
13	$C_{20}H_{16}N_2O_2FCl$	88 (100)	**29**	$C_{21}H_{18}N_2O_2F_3Cl$	71 (69)
14	$C_{21}H_{19}N_2O_3Cl$	85 (113)	**30**	$C_{22}H_{21}N_2O_3F_3$	88 (144)
15	$C_{22}H_{22}N_2O_4$	96 (128)	**31**	$C_{23}H_{26}N_2O_3$	86 (108)
16	$C_{22}H_{22}N_2O_4$	92 (116)			

All oxacetamides **1–27** were prepared in a one-pot procedure from the corresponding phen-1-ylpyrrole. Synthesis of hydroxyacetamides **28–31** involved the reduction of the corresponding oxacetamide with sodium borohydride. All general procedures and analytical data of compounds **1**, **26** and **28** as examples are reported below. Abbreviations used are: Ph: phenyl, s: singlet, d: doublet, m: multiplet and t: triplet.

4.1.1. General procedure for the synthesis of N-substituted 2-oxo-2-(phen-1-ylpyrrol-2-yl)acetamides 1–27

The synthesis of phen-1-ylpyrroles is reported in the literature. The corresponding phen-1-ylpyrrole was dissolved in acetonitrile (50 mL) and the solution was cooled using an ice bath (T < 10 °C). Oxalyl chloride (1.1 equiv.) was then added dropwise. Thereafter, the reaction mixture was stirred at room temperature for 4–6 h. The corresponding amine (2 equiv., benzylamines for compounds **1–4** and phenetylamines for **5–31**) was directly added. After stirring for 15 min, the solvent was concentrated and the residue dissolved in diethyl ether (30 mL). The solution was washed twice with brine (2 x 20 mL), dried over $MgSO_4$ and removed under reduced pressure. Recrystallization from alcohol (ethyl alcohol or isopropyl alcohol)/water gave analytically pure **1–27**.

Analytical data for compound **1**: IR (KBr, cm^{-1}) 3260 (NH), 1640 (2CO); ^1H NMR (δ-TMS, DMSO-d_6) 9.51 (s, 1H, NH), 7.34–7.78 (m, 9H, 2Ph), 7.17 (dd, 1H, $J_{H5\,H4}$ = 2.38 Hz, $J_{H5\,H3}$ = 1.16 Hz, H_5), 7.11 (dd, 1H, $J_{H3\,H4}$ = 3.14 Hz, $J_{H3\,H5}$ = 1.16 Hz, H_3), 6.62 (dd, 1H, $J_{H4\,H3}$ = 3.14 Hz, $J_{H4\,H5}$ = 2.38 Hz, H_4), 4.32 (d, 2H, CH_2); ^{13}C NMR (δ-TMS, $CDCl_3$) 175.8 (β-CO), 158.4 (α-CO), 138.2 ($C_{1''}$), 134.6 (Ca), 130.4 (C_2), 129.4 (Cd), 128.1 ($C_{3'}$ and $C_{5'}$), 127.7 (Cb and Cf), 126.9 (Cc and Ce), 125.1 (C_5), 124.2 ($C_{4''}$), 118.1 ($C_{2''}$ and $C_{6''}$), 117.6 (C_3), 111.8 (C_4), 47.2 (CH_2).

Analytical data for compound **26**: IR (KBr, cm^{-1}) 3400 (NH), 1650 and 1690 (2CO); ^1H NMR (δ-TMS, DMSO-d_6) 8.61 (s, 1H, NH), 8.01 (dd, 1H, H_5), 6.89–7.04 (m, 7H, 2Ph),

Table III. Pharmacological data for the tested compounds.

Compound	Approximate i.p. LD_{50} in mice (mg/kg)	Spontaneous motility i.p. ED_{50} and 95% confidence interval (mg/kg)	Proconvulsant activity[a]			Anticonvulsant activity[b] i.p. ED_{50} and 95% confidence interval (mg/kg)
			Dose[c]	nt[d]	nt[e]	
Solvent[f]	–	–		10	0	
8	> 800	185 (156–228)	100	10	0	Inactive 300 mg/kg[g]
			300	10	0	
14	> 800	178 (149–222)	100	10	0	Inactive 300 mg/kg[g]
			300	10	0	
26	700	50 (41–62)	100	10	0	Inactive 300 mg/kg[g]
			300	10	0	
Diazepam		10.2 (3.9–17.7)	–	–	–	5.5 (4.9–6.2)
β-CCM			0.3	10	7	

[a]Potentiation of PTZ (30 mg/kg) convulsion-induced (see Experimental protocols); [b]protection against pentylenetetrazole-induced lethal convulsions (see Experimental protocols); [c]mg/kg; [d]nt = total number of mice; [e]ns = number of convulsing mice; [f]1% carboxymethylcellulose suspension; [g]highest dose assayed.

6.86 (dd, 1H, H_3), 6.35 (dd, 1H, H_4), 3.89 (s, 3H, $2OCH_3$), 3.55 (t, 2H, α-CH_2), 2.80 (t, 2H, β-CH_2); ^{13}C NMR (δ-TMS, $CDCl_3$) 176.1 (β-CO), 159.4 (α-CO), 147.8 ($C_{3''}$), 143.9 ($C_{4''}$), 137.8 (Ca), 132.3 ($C_{1''}$), 131.4 (C_2), 130.8 (Cd), 128.6 (Cb and Cf), 127.8 (Cc and Ce), 125.6 (C_5), 119.0 (C_3), 114.6 ($C_{5''}$), 112.6 ($C_{6''}$), 111.8 (C_4), 105.7 ($C_{2''}$), 55.4 ($2OCH_3$), 43.8 (α-CH_2), 36.1 (β-CH_1).

4.1.2. General procedure for the synthesis of N-substituted 2-hydroxy-2-(phen-1-ylpyrrol-2-yl)acetamides ***28–31***

The corresponding N-substituted 2-oxo-2-(phen-1-ylpyrrol-2-yl)acetamide was dissolved in methyl alcohol (50 mL) and sodium borohydride (1.2 equiv.) is added. The mixture was refluxed for 2 h and the solvent was distilled off. The cooled residue was poured into water (100 mL) and extracted with diethyl ether. The pooled extracts were filtered, dried over $MgSO_4$ and concentrated. Recrystallization from isopropyl alcohol/water gave analytically pure **28–31**.

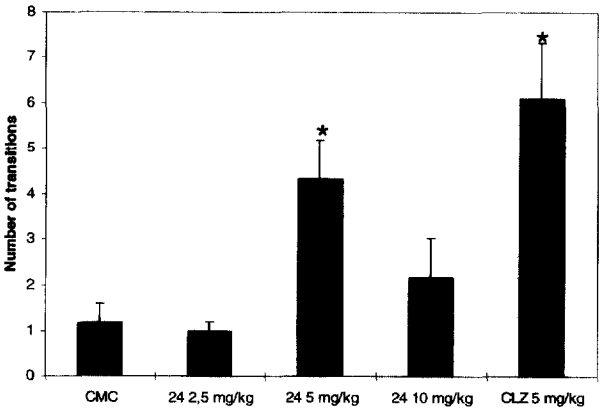


Figure 3. Effects of the solvent (CMC, n = 12), compound **26** (**26**; 2.5, 5 and 10 mg/kg, n = 12 for every dose) and chlorazepate (CLZ; 5 mg/kg, n = 12) on the number of transitions in the Black and White test; *: $p < 0.05$.

Analytical data for compound **28**: IR (KBr, cm^{-1}) 3600 (OH), 3200 (NH), 1650 (CO); ^1H NMR (δ-TMS, DMSO-d_6) 8.94 (s, 1H, NH), 6.97–7.46 (m, 8H, 2Ph), 6.77 (dd, 1H, H_5), 6.03 (dd, 1H, H_3), 5.94 (dd, 1H, H_4), 5.91 (d, 1H, OH), 4.71 (d, 1H, CH), 3.79 (s, 3H, OCH_3), 3.30 (t, 2H, α-CH_2), 2.71 (t, 2H, β-CH_2); ^{13}C NMR (δ-TMS, $CDCl_3$) 174.8 (CO), 159.1 ($C_{4''}$), 137.5 (Ca), 132.1 ($C_{1''}$), 131.9 (C_2), 131.1 (Cd), 128.8 (Cb and Cf), 127.6 (Cc and Ce), 120.6 ($C_{2''}$ and $C_{6''}$), 117.3 (C_5), 114.4 ($C_{3''}$ and $C_{5''}$), 110.3 (C_4), 108.2 (C_3), 81.2 (*C*H), 54.7 (OCH_3), 44.2 (α-CH_2), 36.3 (β-CH_2).

4.2. Pharmacology

4.2.1. Benzodiazepine receptor-binding assays [21, 22]

Male Wistar rat (220–240 g) whole brains were homogenized in 100 volumes of Tris-citrate buffer (50 mM, pH = 7.4), using a Brinkman Polytron (setting 6 for 15 s). Homogenates were centrifuged at 20 000 *g* for 20 min at 4 °C. Tissues were resuspended and washed five more times before final resuspension in 100 volumes of buffer. The incubation mixture consisted of 0.5–0.6 mg of protein, 0.1 mL of 3H-FLU (final concentration 1 nM), and varying amounts of the test compounds and buffer to a volume of 1 mL. The mixture was incubated at 0 °C for 60 min, and the incubations were terminated by rapid filtration through Whatmann GF/B fiber filters. The filters were washed three times with 5 mL of the buffer and placed in minivials containing 5 mL of Optiphase Highsaphe 2 (Wallac). After 12 h, the radioactivity was counted with a liquid scintillation counter. Non-specific binding (using 10 μM FLU) was consistently < 10% of the total binding. The protein content was determined by the method of Lowry using bovine serum albumine as standard [23]. Each value was determinated in duplicate, and IC_{50} values were estimated from semilogarythmic plots. K_i values were calculated from the following equation: $K_i = IC_{50}/(1 + L/K_d)$, where L is the ligand concentration (1 nM) and K_d is the dissociation constant for 3H-FLU, determined by parallel experiments. The data shown are the means of at least four individual experiments.

4.2.2. Pharmacological evaluation

Female OF-1 mice weighing 20–24 g were used for pharmacological studies. The animals were allowed free access to food and water and were housed at room temperature (20–22 °C). All the test compounds were administrated via intraperitoneal (i.p.) injection in a 1% carboxymethylcellulose suspension.

4.2.3. Gross behavioral effects and acute toxicity in mice

Morpugo's modification of Irwin's multidimensional screening procedure was used on groups of four mice to evaluate drug-induced behavioral alterations. The test compounds were administred in log-spaced doses, and detailed observations were made 1, 3 and 24 h after treatment. Perphenazine (50 mg/kg i.p.) and methylphenidate (50 mg/kg) were used for comparison. The approximate LD_{50} was obtained from the mortality observed during a 48 h period.

4.2.4. Anticonvulsant activity

Test compounds were given to groups of five mice, 30 min before an i.p. injection of 150 mg/kg pentylenetetrazole [18]. The protection against pentylenetetrazole-induced lethal convulsions was evaluated for a 15 min observation period.

4.2.5. Proconvulsant activity

Test compounds were given to groups of ten mice, 2 min before an i.p. injection of 30 mg/kg pentylenetetrazole. Animals were then observed for 5 min and the number of mice exhibiting convulsive behavior was noted.

4.2.6. Locomotor activity

Locomotor activity was recorded with a photocell activity meter for 15 min, beginning 30 min after i.p. administration of each test drug ($n = 12$ for every treatment group).

4.2.7. Light/dark exploration test [24]

The test boxes, entirely constructed of perspex, consist of two compartments with 270 mm high walls. The first of these, colored matt black, measures 270 x 180 mm; the other, matt white, measures 270 x 270 mm (interior dimensions). Both compartments are separated by a wall (470 mm high, to act as a light separator) with a 70 x 70 mm opening in its base. The box does not have a top cover. Each compartment is independently illuminated: the white one with a 100 W bulb (white) and the black one with a 40 W bulb (red). Both bulbs are 370 mm from the floor of the box.

Each mouse (12 mice for each dose treatment) was placed in the centre of the light compartment of the light dark box and over a 5 min period, 30 min after i.p. administration of test compounds and measurements were made of the number of transitions between light and dark compartments.

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