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# Synthesis and $D_2$-Like Binding Affinity of New Derivatives of *N*-(1-Ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide and Related 4*H*-[1]Benzothiopyrano[4,3-*b*]pyrrole and 5,6-Dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxamide Analogues

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**Abstract**—Various new derivatives and structural analogues of *N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (**2a**), a representative term of a series of 2-aminomethylpyrrolidinyl derived 4,5-dihydrobenzo[*g*]indolcarboxamides with good $D_2$-like affinity, were synthesized and evaluated for their ability to bind to dopamine $D_2$-like receptors in vitro. The structural contribution to $D_2$-like receptor binding of the 4,5-dihydrobenzo[*g*]indole portion of the molecule was examined. From these studies, compound **2k**, 2-chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxamide, was found to possess a potent affinity for $D_2$-like receptors. Behavioural tests in rats have shown that this compound reduces the hyperactivity induced by amphetamine, a property shared by all antipsychotic drugs, at a dose which failed to induce catalepsy, an effect which is predictive of extrapyramidal side effects in humans. The other compounds demonstrated moderate (**2c**, **2h**, and **2j**) or no affinity for $D_2$-like receptors. 

## 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 activating 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, $D_2$ receptor antagonists can be used 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 $D_2$ 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 antipsychotics).[3] Therefore, the synthesis of novel antipsychotics with a better pharmacological profile remains a primary goal in the research for the therapy of psychoses.[3]

In previous papers,[4,5] we have reported the synthesis and structure–activity relationships of a series of 5-phenylpyrrole-3-carboxamides (**I**) and related 4,5-dihydrobenzo[*g*]indole-3-carboxamides (**II**) analogues whose most representative terms were **1a** and **2a**, respectively (Fig. 1).

Encouraged by these results, we carried out several modifications of **2a**. A first objective of this study was to seek correlations between the electronic and hydro-

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phobic properties of the benzene and pyrrole substituents as well as to evaluate the bioisosteric replacement $CH_2$ to S in the ethylenic bridge with a view to determine those physicochemical parameters which contribute to $D_2$-like binding affinity. Moreover, the spatial arrangement of the two aryl/heteroaryl rings of **2a** would be expected to influence bioactivity profoundly; thus, the preparation of 5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole analogues was also contemplated and their biological evaluation should permit some understanding of the importance of the relative positions of the aryl/heteroaryl rings. In summary, therefore, the synthesis of the new benzo[*g*]indole-3-carboxamide derivatives and related compounds, **2b–k** and their in vitro binding to the dopamine $D_2$-like receptors are reported in the present paper.

Finally, we performed a preclinical study on the potential antipsychotic activity of compound **2k**. To this end we studied the effect of **2k** on a behavioural test which is considered to be predictive of antipsychotic activity: the antagonism of amphetamine-induced hyperactivity in rats.[6] Moreover, since affinity for $D_2$-like receptors is related also to the ability of antipsychotics to cause extrapyramidal side effects, we compared the effect of different doses of compound **2k** to that of the classical antipsychotic haloperidol on the horizontal bar-inclined grid test in rats, a test which provides an index of catalepsy, an effect which is extrapyramidal in nature and is predictive of extrapyramidal side effects in humans.[7]

## Chemistry

Target compounds **2b–k** were prepared as shown in Scheme 1. The acids **6**, prepared via the esters **5** by saponification, were activated with 1,1′-carbonyldiimidazole, and without isolation, the intermediate *N*-imidazolides were reacted with a stoichiometric amount of the 2-aminomethyl-1-ethylpyrrolidine.

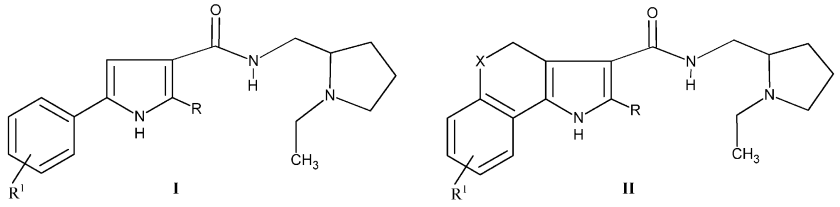
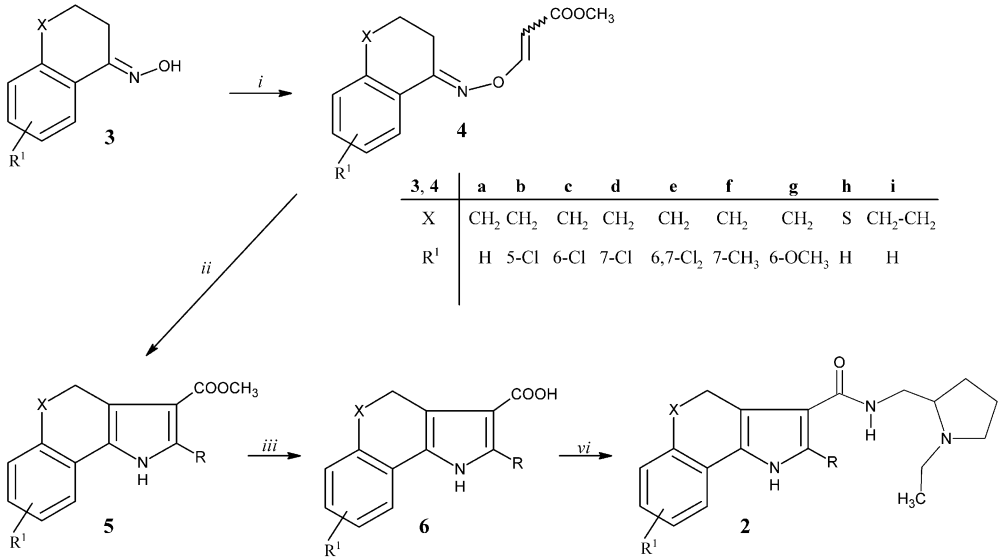



**Figure 1.** General structures of 5-phenyl-3-pyrrole carboxamide and related 4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide analogues **I** and **II**.




| 3, 4 | a | b | c | d | e | f | g | h | i |
|---|---|---|---|---|---|---|---|---|---|
| X | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | S | $CH_2$-$CH_2$ |
| $R^1$ | H | 5-Cl | 6-Cl | 7-Cl | 6,7-$Cl_2$ | 7-$CH_3$ | 6-$OCH_3$ | H | H |

| 2, 5, 6 | a | b | c | d | e | f | g | h | i | j | k |
|---|---|---|---|---|---|---|---|---|---|---|---|
| X | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | S | $CH_2$-$CH_2$ | $CH_2$-$CH_2$ |
| R | H | H | H | H | H | H | H | Cl | H | H | Cl |
| $R^1$ | H | 6-Cl | 7-Cl | 8-Cl | 7,8-$Cl_2$ | 8-$CH_3$ | 7-$OCH_3$ | H | H | H | H |

**Scheme 1.** Reagents: (i) methyl propiolate, TEA, anhydrous DMSO; (ii) Δ; (iii) 2.5 M NaOH, $H_2O$/EtOH; (iv) $SO_2Cl_2$, $CHCl_3$; (v) *N*-chlorosuccinimide, $CHCl_3$; (vi) *N*,*N*-carbonyldiimidazole, 2-aminomethyl-*N*-ethyl-pyrrolidine.

Esters **5b–f**, **5i–j** were prepared, as recently reported by us for **5a**[5] and **5g**,[5] via thermal cyclization of the *O*-vinyl oximes **4**,[8] in turn obtained by Michael addition of ketoximes **3** upon methyl propiolate. All oximes required, **3b**,[9] **3c**,[9] **3d**,[10] **3e**,[11] **3f**[10] **3h**,[12] **3i**,[13] were prepared by condensation of the appropriate benzocyclanones with hydroxylamine hydrochloride in the presence of sodium acetate in hydroalcoholic solution.

The 2-chloro substituted esters **5h**,**k** were prepared from the requisite esters **5a**,**j** by reaction with appropriate halogenating reagents (Table 1).

## Results and Discussion

### Receptor binding

The target carboxamide analogues of **2a, 2b–k**, 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[14] and (−)-raclopride as a specific displacer.[15] The dopamine $D_2$-like receptor binding affinities of the carboxamides **2b–k** are listed in Table 2. First we determined the effect of 4,5-dihydrobenzo[*g*]indole substituents in **2a** as well as the replacement of a $CH_2$ by a S. Substitution with various substituents (Cl, $CH_3$, $OCH_3$) in the benzene ring of the tricyclic portion of the ground term resulted in weak (**2c**, $IC_{50} = 681$ nM) or negligible affinity for $D_2$-like receptors. In general, chemical modulation of electronic and hydrophobic effects concerned with substitution on the 4,5-benzo[*g*]indole aromatic ring negatively influenced the affinity respect to the unsubstituted compound **2a**; this finding suggested that binding over $D_2$ receptors was extremely sensitive to the presence of any type of substituents. On the contrary in this series the 2-chloro substituted analogue **2h** had only a slight (1.38-fold) decrease in potency at $D_2$-like receptors, as previously[4] shown for **1a**, indicating that C-2 substitution with a lipophilic group was well tolerated.

Classical isosteric replacement of the $C_5$-methylene in **2a** with an atom of sulphur (**2i**) caused greater than an 18-fold decrease in $D_2$-like affinity.

The effect on receptor binding caused by homologation of the central carbocyclic ring of the 4,5-dihydrobenzo[*g*]indole framework from six atoms to seven was also studied. The 5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole analogue **2j** exhibited a level of activity comparable to that of the ground term (**2j**: $IC_{50} = 175$ nM).

Unexpectedly, the 2-chloro analogue of **2j**, **2k** resulted in a 5.3-fold increase in activity ($IC_{50} = 30$ nM) respect to the ground term **2a**, while **2h** was shown to be slightly less potent. Thus, the two structural changes of **2a**, homologation of central carbocyclic ring and chlorination at $C_2$ position, produced favourable features in terms of interaction with $D_2$-like receptors. Finally, these studies suggest that the $D_2$-like receptors have requirements for high binding affinity which are mutually satisfied by both the 2-aminomethylpyrrolidinyl motif and the 2-chloro-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta[*b*]pyrrolyl moiety of **2k**.

### Behavioural experiments

Compound **2k** was chosen for further study in behavioural models predictive of antipsychotic efficacy. Thus, we performed a preclinical study on the potential antipsychotic activity of compound **2k**. To this end we studied its effect on a behavioural test which is considered to be predictive of antipsychotic activity: the antagonism of amphetamine-induced hyperactivity in rats.[6]

Moreover, since affinity for $D_2$-like receptors is related also to the ability of antipsychotics to cause extrapyramidal side effects, we compared the effect of different doses of compound **2k** to that of the classical antipsychotic haloperidol on the horizontal bar and inclined grid tests in rats, which provide an index of catalepsy, an effect which is extrapyramidal in nature and is predictive of extrapyramidal side effects in humans.[7]

### Catalepsy

Haloperidol induced a strong cataleptogenic effect, as shown by the increase in the immobility time observed in the horizontal bar [*treatment* experiment 1: $F(5,42) = 60.3$, $p < 10^{-6}$; experiment 2: $F(5,51) = 8.02$, $p < 0.001$; *treatment*×*time* experiment 1: $F(10,84) = 4$, $p < 0.001$; experiment 2: $F(10,102) = 2.26$, $p < 0.05$] and in the inclined grid test [*treatment* experiment 1: $F(5,42) = 87.44$, $p < 10^{-6}$; experiment 2: $F(5,51) = 10.70$, $p < 0.001$; *treatment*×*time* experiment 1: $F(10,84) = 4.2$, $p < 0.001$; experiment 2: not significant]. Haloperidol effect was apparent at 10, 30 and 60 min (experiment 1) and 60, 90 and 120 min (experiment 2) after treatment. The remarkable difference in haloperidol-induced immobility at 60 min between the two experiments ($112 \pm 7.7$ s vs $30.9 \pm 15$ s, experiment 1 and 2, respectively) might be interpreted as an effect of habituation: indeed, in experiment 1 the 60 min test corresponded to the third experimental manipulation of the subjects, while in experiment 2 it corresponded to the first (Fig. 2).

Compound **2k**, at 10 mg/kg (Fig. 2) and at 2, 1 and 0.5 mg/kg (data not shown), at 10, 30 and 60 min (experiment 1) and 60, 90 and 120 min (experiment 2) after treatment, failed to induce any statistically significant increase in the immobility time with respect to the control groups both in the horizontal bar and in the inclined grid test.

### Amphetamine-induced hyperactivity

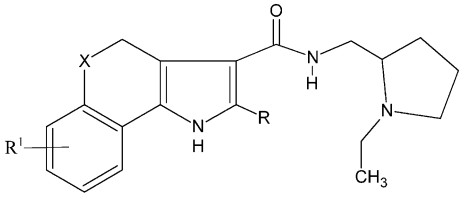
**Experiment 3.** The significant effect of the factor *time* in the long movements [$F(19,342) = 3.10$, $p < 0.001$], short movements [$F(19,342) = 6.3$, $p < 0.001$] and rearing

**Table 1.** Physicochemical data of the compounds **4**–**6**

| Compd | X | R | $R^1$ | Formula $M_r$ | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|---|
| **4b** | $CH_2$ | — | 5-Cl | $C_{14}H_{14}ClNO_3$ 279.72 | 77 (31/69)[a] | 68–70[b] |
| **4c** | $CH_2$ | — | 6-Cl | $C_{14}H_{14}ClNO_3$ 279.72 | 70 (29/71)[a] | 69–71[b] |
| **4d** | $CH_2$ | — | 7-Cl | $C_{14}H_{14}ClNO_3$ 279.72 | 79 (13/87)[a] | 82–85[b] |
| **4e** | $CH_2$ | — | 6,7-$Cl_2$ | $C_{14}H_{13}Cl_2NO_3$ 314.17 | 64 (30/70)[a] | 85–88[b] |
| **4f** | $CH_2$ | — | 7-$CH_3$ | $C_{15}H_{17}NO_3$ 259.30 | 37 (21/79)[a] | Colourless oil |
| **4h** | S | — | H | $C_{13}H_{13}NO_3S$ 263.31 | 84 (43/57)[a] | Colourless oil |
| **4i** | $CH_2CH_2$ | — | H | $C_{15}H_{17}NO_3$ 259.30 | 95 (26/74)[a] | Colourless oil |
| **5b** | $CH_2$ | H | 6-Cl | $C_{14}H_{12}ClNO_2$ 261.70 | 11 | 205–206[b] |
| **5c** | $CH_2$ | H | 7-Cl | $C_{14}H_{12}ClNO_2$ 261.70 | 21 | 208–209[b] |
| **5d** | $CH_2$ | H | | $C_{14}H_{12}ClNO_2$ 261.70 | 15 | 168–171[b] |
| **5e** | $CH_2$ | H | 7,8-$Cl_2$ | $C_{14}H_{11}Cl_2NO_2$ 296.15 | 34 | 90–91[b] |
| **5f** | $CH_2$ | H | 8-$CH_3$ | $C_{15}H_{15}NO_2$ 241.28 | 24 | 143–145[b] |
| **5h** | $CH_2$ | Cl | H | $C_{14}H_{12}ClNO_2$ 261.70 | 69 | 190–192[b] |
| **5i** | S | H | H | $C_{13}H_{11}NO_2S$ 295.30 | 26 | 190–192[b] |
| **5j** | $CH_2CH_2$ | H | H | $C_{15}H_{15}NO_2$ 241.28 | 25 | 124[c] |
| **5k** | $CH_2CH_2$ | Cl | H | $C_{15}H_{14}ClNO_2$ 275.73 | 79 | 163–165[b] |
| **6b** | $CH_2$ | H | 6-Cl | $C_{13}H_{10}ClNO_2$ 247.67 | 85 | 163–164[d] |
| **6c** | $CH_2$ | H | 7-Cl | $C_{13}H_{10}ClNO_2$ 247.67 | 87 | 153 d |
| **6d** | $CH_2$ | H | 8-Cl | $C_{13}H_{10}ClNO_2$ 247.67 | 66 | 125–127[d] |
| **6e** | $CH_2$ | H | 7,8-$Cl_2$ | $C_{13}H_9Cl_2NO_2$ 282.12 | 94 | 148–149 d |
| **6f** | $CH_2$ | H | 8-$CH_3$ | $C_{14}H_{13}NO_2$ 227.26 | 94 | 144–146[d] |
| **6g** | $CH_2$ | H | 7-$OCH_3$ | $C_{14}H_{13}NO_3$ 243.26 | 94 | 149–151[b] |
| **6h** | $CH_2$ | Cl | H | $C_{13}H_{10}ClNO_2$ 247.67 | 82 | 139–141[b] |
| **6i** | S | H | H | $C_{12}H_9NO_2S$ 231.27 | 95 | 176–178[d] |
| **6j** | $CH_2CH_2$ | H | H | $C_{14}H_{13}NO_2$ 227.26 | 96 | 165–167[d] |
| **6k** | $CH_2CH_2$ | Cl | H | $C_{14}H_{12}ClNO_2$ 261.70 | 78 | 170–172[d] |

[a]The ratio of *Z*/*E*:*E*/*E* mixtures was estimated from $^1$H NMR spectra of the crude product.
[b]Crystallized from ethanol.
[c]Triturated with diethyl ether.
[d]Triturated with petroleum ether.

**Table 2.** Physicochemical data and binding affinity to dopamine $D_2$-like receptors of 4,5-dihydrobenzo[*g*]indole-3-carboxamides **2a**–**h** and related derivatives **2i**, **2j** and **2k**




| Compd | X | R | $R^1$ | Formula $M_r$ | Yield (%) | Mp (°C) | $IC_{50}$ (nM)[a] |
|---|---|---|---|---|---|---|---|
| **2a** | $CH_2$ | H | H | $C_{20}H_{25}N_3O$ 323.43 | 33 | 160–163[b] | 160 |
| **2b** | $CH_2$ | H | 6-Cl | $C_{20}H_{24}ClN_3O$ 357.88 | 76 | 179–181[c] | 1370 |
| **2c** | $CH_2$ | H | 7-Cl | $C_{20}H_{24}ClN_3O$ 357.88 | 64 | 142–145[c] | 681 |
| **2d** | $CH_2$ | H | 8-Cl | $C_{20}H_{24}ClN_3O$ 357.88 | 58 | 148–150[c] | 2730 |
| **2e** | $CH_2$ | H | 7,8-$Cl_2$ | $C_{20}H_{23}Cl_2N_3O$ 392.32 | 22 | 180–182[d] | 5600 |
| **2f** | $CH_2$ | H | 8-$CH_3$ | $C_{21}H_{27}N_3O$ 337.46 | 56 | 160–162[c] | 3610 |
| **2g** | $CH_2$ | H | 7-$OCH_3$ | $C_{21}H_{27}N_3O_2$ 353.46 | 60 | 177–179[c] | 4000 |
| **2h** | $CH_2$ | Cl | H | $C_{20}H_{24}ClN_3O$ 357.88 | 51 | 172–174[b] | 220 |
| **2i** | S | H | H | $C_{19}H_{23}N_3OS$ 341.47 | 55 | 182–184[b] | 2900 |
| **2j** | $CH_2CH_2$ | H | H | $C_{21}H_{27}N_3O$ 337.46 | 70 | 147–149[c] | 175 |
| **2k** | $CH_2CH_2$ | Cl | H | $C_{21}H_{26}ClN_3O$ 371.90 | 62 | 140–141[c] | 30 |
| **Raclopride** | | | | | | | 39 |

[a][$^3$H]YM-09151–2 has been used as the specific ligand; the $IC_{50}$ for binding is the average of three experiments. The SEM for all values was $<10\%$.
[b]Triturated with diethyl ether.
[c]Triturated with hexane.
[d]Triturated with diisopropyl ether.

counts [$F(19,342)=6.36$, $p<0.001$], is due to the increase in activity observed after amphetamine (1 mg/kg b.w.) treatment. **2k**, at 10 mg/kg, injected 60 min before amphetamine treatment, failed to influence the long movements motility counts [*treatment* $F(1,18)=0.52$, n.s.; *treatment*×*time* $F(19,342)=1.06$, n.s.], while it induced a statistically significant decrease in the short movements motility counts 10 and 15 min after amphetamine challenge [*treatment*×*time* $F(19,342)=2.42$, $p<0.001$], and in rearing counts 10 min after amphetamine challenge [*treatment*×*time* $F(19,342)=1.85$, $p<0.05$] (Fig. 3).

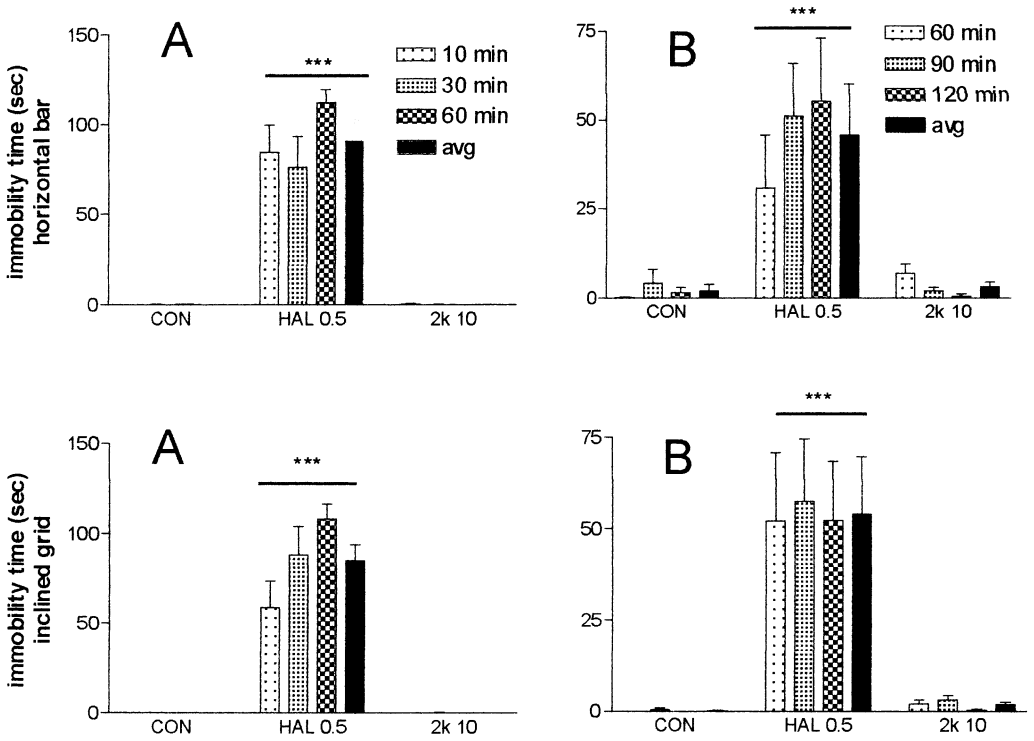



**Figure 2.** Horizontal bar-inclined grid test. Avg: mean from the three observations; HAL: haloperidol. A: experiment 1. B: experiment 2. Drug doses are expressed in mg/kg b.w. Each value represents the mean ± SEM from 8–11 subjects per group. ***$p < 0.001$ (ANOVA followed by Newman–Keuls test).

**Experiment 4.** Challenge with 0.5 mg/kg amphetamine increased the long movements [$F(1,36) = 5.69$, $p < 0.05$], the short movements [$F(1,36) = 19{,}79$, $p < 0.0001$] and the rearing counts [$F(1,36) = 6.65$, $p < 0.01$] with respect to controls. **2k** failed to influence amphetamine effect in short movements [$F(1,36) = 0.40$, n.s.] and in rearing counts [$F(1,36) = 1.53$, n.s.] (data not shown). However, ANOVA of long movements data revealed a statistically significant three ways interaction between *amphetamine*, ***2k*** and *time* [$F(23,828) = 1.65$, $p < 0.05$]. Further analysis (F tests for contrasts) showed that **2k** influenced in a statistically significant manner the activity of amphetamine-treated rats, inducing an increase in activity in the first 5 min, and a decrease in activity 60 and 85 min after amphetamine injection (Fig. 4).

The results show that compound **2k**, at a dose devoid of extrapyramidal side effects in rats, attenuates the hyperactivity induced by amphetamine. This effect, which is not particularly dramatic, is apparent one hour after the administration. Such attenuation of amphetamine-induced hyperactivity suggests that compound **2k**, which shows affinity for $D_2$-like receptors, act as an antagonist at these receptors. Moreover, such an effect is considered to be predictive of antipsychotic activity.[6] The observation that the effect on amphetamine-induced hyperactivity is apparent at a dose devoid of extrapyramidal side effects, supports the hypothesis that **2k** might show a profile similar to that of atypical antipsychotics. Therefore, further studies are needed to test this possibility. The ability of **2k** to potentiate locomotor activity in the first 5 min following amphetamine administration is consistent with the suggested antagonist profile: the blockade of dopamine autoreceptors by low drug levels in the synaptic cleft may result in an increased dopamine release.

## Experimental

### Chemistry

General information. Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Anhydrous solvents such as ethanol (EtOH), tetrahydrofuran (THF) and dimethyl-formamide (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).

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 δ (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; dd, doublet of doublets; t, triplet; m, multiplet), number of protons, and coupling constants in Hz. IR spectra were recorded as

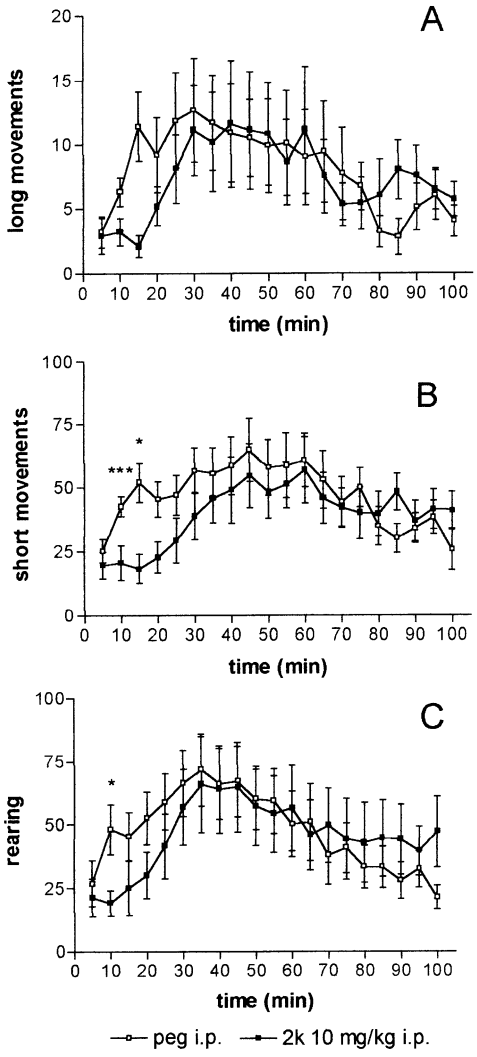



**Figure 3.** Effect of **2k** (1 h before amphetamine challenge) on amphetamine-induced hyperactivity (experiment 3). Each value represents the mean ± SEM from 10 subjects per group. After 60 min habituation to the motility cages, motor activity was recorded for 100 min following a 1 mg/kg ip amphetamine sulphate injection. **2k** (or PEG) was injected immediately before commencing habituation. $*p < 0.05$, $***p < 0.001$ (ANOVA followed by F-test for contrasts).

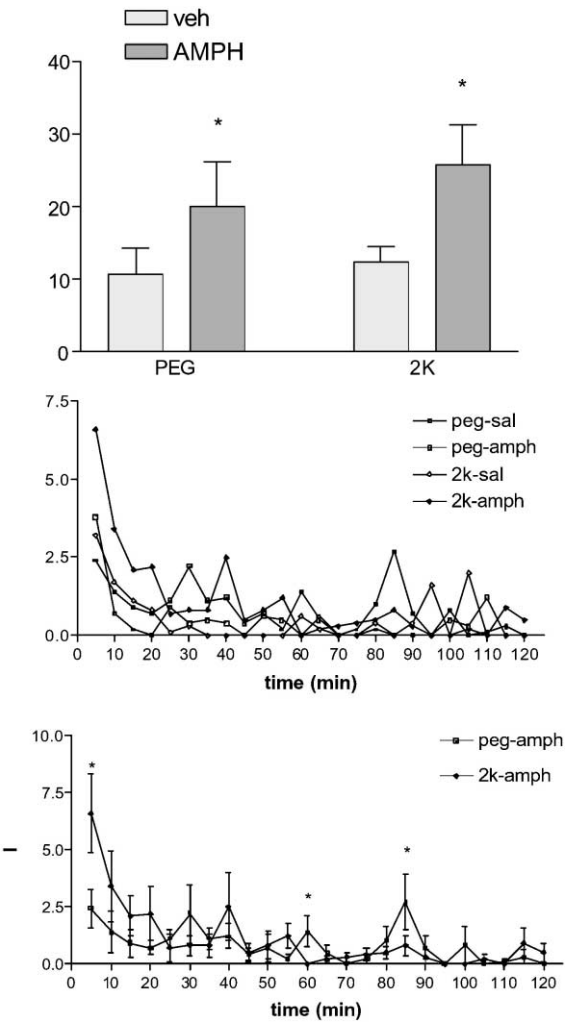



**Figure 4.** Effect of **2k** (immediately before amphetamine challenge) on amphetamine-induced hyperactivity (experiment 4) — long movement counts. Top panel: mean total values. Mid panel: time course data of the four groups. Low panel: effect of **2k** on amphetamine-treated rats. Each value represents the mean ± SEM from 10 subjects per group. After 60 min habituation to the motility cages, motor activity was recorded for 120 min following a 0.5 mg/kg ip amphetamine sulphate (or saline) injection. **2k,** (or PEG) was injected immediately before amphetamine. $*p < 0.05$ (ANOVA followed by F-test for contrasts).

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 solutions with a Perkin-Elmer Lambda 5 spectrophotometer and the absorption wavelenghts are expressed in nm followed by (log ε). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Benzocycloalkanones were both purchased from Aldrich Chemical Co. or prepared as reported in the literature: 1,2,3,4-tetrahydro-1-naphthalenone, 6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one, 4-thiochromanone, 6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one, 6-chloro-3,4-dihydro-2*H*-naphthalen-1-one,[9] 5-chloro-3,4-dihydro-2*H*-naphthalen-1-one,[9] 7-chloro-3,4-dihydro-2*H*-naphthalen-1-one,[16] 6,7-dichloro-3,4-dihydro-2*H*- naphthalen-1-one,[10] 7-methyl-3,4-dihydro-2*H*-naphthalen-1-one.[17]

*O*-Vinyl oxime ethers **4b**, **c**, **d**, **e**, **f** were obtained as inseparable mixtures of (*E*, *E*) (*Z*, *E*); the *O*-vinyl oxime ethers **4a**, **4g**, and esters **5a** and **5g** were synthesized by us elsewhere.[5] Final compounds **2b**–**k** were biotested as chlorohydrate salts which melted with decomposition.

**Procedure for chlorohydrate salts.** To a solution of amine in diethyl ether ($Et_2O$), was added an excess of an ethereal HCl solution. The mixture was stirred at room temperature for 1 h. Then the solvent was evaporated and the resulting salt was triturated with anhydrous ether and dried on vacuum.

**General Michael-type addition procedure for compounds 4b–f, h, i.** To a solution of the oxime **3** (6.2 mmol) in anhydrous DMSO (6 mL), a solution of methyl propiolate (12.4 mmol) in anhydrous DMSO (2.5 mL) was added dropwise at room temperature (at 0 °C for **3i**) and

in the presence of some drops of triethylamine. The reaction mixture was heated to 65–70 °C (to room temperature for **3i**) for 24 h. The cooled reaction solution was poured into crushed ice and the aqueous layer was extracted with $CH_2Cl_2$. The organic phase was collected, washed with water, dried ($Na_2SO_4$) and concentrated to yield a brown coloured residue. Purification by flash chromatography [$SiO_2$, ethyl acetate/petroleum ether (for reaction of **3b**, **d**, **h**, **i** 1:4; **3c**, **e**, **f** 1:9)] afforded the desired *O*-vinyl oxime ether **4** as an inseparable mixture of (*E*,*E*) and (*Z*,*E*) isomers.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[5-chloro-(3,4-dihydro-1(2*H*)-naphthalenylidene)amino]oxy-2-propenoate (4b).** IR: 1720 (C=O), 1640 (C=N); UV: 275.2 (4.23), 232.0 sh (4.11), 212.0 (4.18); $^1$H NMR δ 1.86–2.01 (m, 2H, $CH_2$), 2.86 (t, 2H, $J$ = 5.8 Hz, $CH_2$), 3.00 (t, 2H, $J$ = 5.8 Hz, $CH_2$), 3.74 (s, 3H, $CH_3$), 6.23 and 6.88 (dd AB×2, 2H, $J$ = 7.40 and 12.40 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.18 (t, 1H, $J$ = 7.80 Hz, Ar–H), 7.44 (d, 1H, $J$ = 3.80 Hz, Ar–H), 7.97 (d, 1H, $J$ = 8.00 Hz, Ar–H). Anal. calcd for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; Cl, 12.67; N, 5.01. Found: C, 59.98; H, 5.26; Cl, 12.44; N, 5.07.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[6-chloro-(3,4-dihydro-1(2*H*)-naphthalenylidene)amino]oxy-2-propenoate (4c).** IR: 1720 (C=O), 1650 (C=N); UV: 275.3 (4.21), 232.0 (4.11); $^1$H NMR δ 1.80–2.00 (m, 2H, $CH_2$), 2.79 (t, 2H, $J$ = 5.8 Hz, $CH_2$), 2.85 (t, 2H, $J$ = 5.8 Hz, $CH_2$), 3.74 (s, 3H, $CH_3$), 6.24 and 6.87 (dd AB×2, 2H, $J$ = 7.40 and 12.40 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.18 (d, 1H, $J$ = 7.8 Hz, Ar–H), 7.22 (d, 1H, $J$ = 7.8 Hz, Ar–H), 7.96 (s, 1H, Ar–H). Anal. calcd for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; Cl, 12.67; N, 5.01. Found: C, 60.15; H, 5.10; Cl, 12.40; N, 5.02.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[7-chloro-(3,4-dihydro-1(2*H*)-naphthalenylidene)amino]oxy-2-propenoate (4d).** IR: 1714 (C=O), 1643 (C=N), 1614 (C=C); UV: sh 311.0 (3.73), sh 300.0 (3.90), 272.2 (4.27), 218.8 (4.35); $^1$H NMR δ 1.80–1.95 (m, 2H, $CH_2$), 2.75 (t, 2H, $J$ = 6 Hz, $CH_2$), 2.84 (t, 2H, $J$ = 6.8 Hz, $CH_2$), 3.73 and 3.74 (s×2, 3H, $CH_3$ of (*Z*,*E*) and (*E*,*E*) isomers), 6.24 and 6.88 (dd AB×2, 2H, $J$ = 6.0 and 12.60 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.14 (d, 1H, $J$ = 7.8 Hz, Ar–H), 7.28 (d, 1H, $J$ = 7.8 Hz, Ar–H), 7.99 (s, 1H, Ar–H). Anal. calcd for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; Cl, 12.67; N, 5.01. Found: C, 59.89; H, 5.22; Cl, 12.67; N, 5.01.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[6,7-dichloro-(3,4-dihydro-1(2*H*)-naphthalenylidene)amino]oxy-2-propenoate (4e).** IR: 1710 (C=), 1640 (C=N), 1620 (C=C); UV: 265.0 (4.08), 223.7 (4.11); $^1$H NMR δ 1.83–1.95 (m, 2H, $CH_2$), 2.74 (t, 2H, $J$ = 6.4 Hz, $CH_2$), 2.84 (t, 2H, $J$ = 6.6, $CH_2$), 3.73 and 3.75 (s×2, 3H, $CH_3$ of (*Z*,*E*) and (*E*,*E*) isomers), 6.23 and 6.88 (dd AB×2, 2H, $J$ = 6.6 Hz and 12.4 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.29 (s, 1H, Ar–H), 8.09 (s, 1H, Ar–H). $C_{14}H_{13}Cl_2NO_3$. Anal. calcd for $C_{14}H_{13}Cl_2NO_3$: C, 53.52; H, 4.17; Cl, 22.57; N, 4.46. Found: C, 53.67; H, 4.12; Cl, 22.26; N, 4.60.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[7-methyl-(3,4-dihydro-1(2*H*)-naphthalenylidene)amino]oxy-2-propenoate (4f).** IR: 1715 (C=O), 1644 (C=N), 1592 (C=C); UV: 273.8 (4.51), 209.6 (4.44); $^1$H NMR δ 1.79–1.95 (m, 2H, $CH_2$), 2.35 (s, 3H, $CH_3$), 2.75 (t, 2H, $J$ = 5.8 Hz, $CH_2$), 2.84 (t, 2H, $J$ = 6.6 Hz, $CH_2$), 3.74 (s, 3H, $CH_3$), 6.23 and 6.89 (dd AB×2, 2H, $J$ = 6.0 and 12.60 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.02–7.21 (m, 2H, Ar–H), 7.84 (s, 1H, Ar–H). Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.33; H, 6.74; N, 5.47.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[(2*H*-thiochroman)-4-yliden)amino]oxy]-2-propenoate (4h).** IR: 1714 (C=O), 1644 (C=N), 1602 (C=C); UV: 333.0 (3.55), 277.6 (4.18), 258.4 (4.24), 233.0 (4.15), 210.0 (4.00); $^1$H NMR δ 2.92–3.08 (m, 2H, $CH_2$), 3.17–3.42 (m, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 6.25 and 6.88 (dd AB×2, 2H, $J$ = 7.4 and 12.60 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.07–7.22 (m, 2H, Ar–H), 7.97–8.08 (m, 1H, Ar–H). Anal. calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.21; H, 4.76; N, 5.44, S, 12.33.

**Methyl (*E*,*E*)/(*Z*,*E*) 3-[(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yliden)amino]oxy]-2-propenoate (4i).** IR: 1740 (C=O), 1644 (C=N), 1602 (C=C); UV: 257.8 (4.50), 206.4 (4.38); $^1$H NMR δ 1.57–1.87 (m, 4H, $CH_2$×2), 2.68–2.84 (m, 4H, $CH_2$×2), 3.72 and 3.74 (s×2, 3H, $CH_3$, of (*Z*,*E*) and (*E*,*E*) isomers), 6.23 and 6.90 (dd AB×2, 2H, $J$ = 7.4 and 12.80 Hz, C2-H and C3-H of (*Z*,*E*) and (*E*,*E*) isomers), 7.14–7.44 (m, 4H, Ar–H). Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.31; H, 6.73; N, 5.26.

**General ring closure procedure to compounds 5b–f, i, j.** A neat mixture of the appropiate (*E*,*E*)/(*Z*,*E*) 4 (3.6 mmol) was heated to 110–130 °C for 10–24 h (for reaction of **4b**, 120 °C/24 h; **4c** and **4e**, 120 °C/20 h; **4d**, 110 °C/24 h; **4f**, 130 °C/12 h; **4i**, 130 °C/15 h; **4j**, 110 °C/10 h and 150 °C/10 min) to give a brown residue. Purification by flash chromatography [$SiO_2$, ethyl acetate/petroleum ether (for reaction **4b**, **c**, **e**, **f**, 1:9; **4d**, **i**, **j**, 1:4)] afforded desired product **5**.

**Methyl 6-chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (5b).** IR: 3320 (NH), 1685 (C=O), 1600 (C=C); UV: 348.0 (4.15), 312.8 (4.27), 236.4 (4.23), 222.0 (4.22), 212.0 sh (4.19); $^1$H NMR δ 2.78 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.09 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.89 (s, 3H, $CH_3$), 6.76 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.13–7.30 (m, 3H, Ar–H), 9.32 (br s, 1H, NH exch. with $D_2O$). $C_{14}H_{12}ClNO_2$. Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.12; H, 4.84; Cl, 13.81; N, 5.21.

**Methyl 7-chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (5c).** IR: 3300 (NH), 1700 (C=O), 1605 (C=C); UV: 341.7 (4.13), 306.0 (4.11), 227.1 (4.15); $^1$H NMR δ 2.75 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.92 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 3.88 (s, 3H, $CH_3$), 6.76 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.15–7.33 (m, 3H, Ar–H), 9.40 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.20; H, 4.59; Cl, 13.50; N, 5.29.

**Methyl 8-chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (5d).** IR: 3320 (NH), 1680 (C=O), 1600 (C=C); UV: 338.8 (4.13), 325.2 (4.21), 240.6 (3.99), 213.6 (4.20), 204.0 (4.06); $^1$H NMR δ 2.72 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.91 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 3.92 (s, 3H, $CH_3$), 6.77 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.06–7.22 (m, 2H, C6-H and C7-H), 7.44 (d, 1H, $J$ = 2.0 Hz, C9-H), 9.90 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.12; H, 4.39; Cl, 13.40; N, 5.52.

**Methyl 7,8-dichloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (5e).** IR: 3310 (NH), 1700 (C=O), 1600 (C=C); UV: 342.6 (4.11), 328.6 (4.19), 310.5 (3.97), 254.4 (4.18), 224.5 (3.98); $^1$H NMR δ 2.66 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.92 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 4.09 (s, 3H, $CH_3$), 6.77 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.39 (s, 1H, C6-H), 8.09 (s, 1H, C9-H), 9.41 (br s, 1H, NH exch. with $D_2O$). $C_{14}H_{11}Cl_2NO_2$. Anal. calcd for $C_{14}H_{11}Cl_2NO_2$: C, 56.78; H, 3.74; Cl, 23.94; N, 4.73. Found: C, 56.80; H, 3.77; Cl, 23.81; N, 4.91.

**Methyl 4,5-dihydro-8-methyl-1*H*-benzo[*g*]indole-3-carboxylate (5f).** IR: 3300 (NH), 1680 (C=O), 1600 (C=C); UV: 337.6 (4.12), 327.2 (4.12), 302.0 (3.84), 242.0 (3.78), 239.4 (3.79), 207.8 (4.07); $^1$H NMR δ 2.34 (s, 3H, $CH_3$), 2.72 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.90 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 3.87 (s, 3H, $CH_3$), 6.77 (d, 1H, $J$ = 2.2 Hz, C2-H), 6.93–7.21 (m, 3H, Ar–H), 9.39 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.39; H, 6.51; N, 5.57.

**Methyl 4*H*-[1]benzothiopyrano[4,3-*b*]pyrrole-1-carboxylate (5i).** IR: 3330 (NH), 1660 (C=O); UV: 339.0 (4.07), 332.0 (4.06), 313.0 (4.12), 304.0 (4.04), 287.0 (3.91), 267.4 (4.01), 243.0 (3.98), 220.4 (4.16), 207.5 sh (4.09); $^1$H NMR δ 3.89 (s, 3H, $CH_3$), 3.95 (s, 2H, $CH_2$), 6.74 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.10–7.47 (m, 4H, Ar–H), 9.42 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71, S, 13.07. Found: C, 63.51; H, 4.38; N, 5.74, S, 13.22.

**Methyl 5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxylate (5j).** IR: 3300 (NH), 1680 (C=O), 1600 (C=C); UV: 309.8 (4.15), 235.2 (3.81), 231.0 (3.79), 204.8 (4.01); $^1$H NMR δ 1.97–2.15 (m, 2H, $CH_2$), 2.76–2.86 (m, 4H, $CH_2$×2), 3.86 (s, 3H, $CH_3$), 6.81 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.16–7.50 (m, 4H, Ar–H), 9.11 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.50; H, 6.06; N, 5.85.

### General chlorination procedures for compounds (5h), k

**Methyl 2-chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (5h).** To a solution of **5a**[5] (0.2 g, 0.88 mmol) in chloroform (10 mL) a solution of sulfuryl chloride (0.125 g, 0.92 mmol) in chloroform (5 mL) was added keeping the whole in the dark. The reaction solution was stirred at room temperature for 1 h and then washed ($H_2O$), dried ($Na_2SO_4$) and concentrated to give a brown coloured residue. The crude product was purified by flash chromatography eluting with a solution of ethyl acetate/petroleum ether, 1:4 to afford the desired **5h**. IR: 3305 (NH), 1670 (C=O); UV: 334.0 sh (4.09), 313.1 (4.25), 300.0 (4.15), 275.0 (3.93), 254.0 (3.75), 245.0 sh (3.75), 230.0 (4.08), 211.7 (4.17); $^1$H NMR δ 2.73 (t, 2H, $J$ = 6.8 Hz, $CH_2$), 2.97 (t, 2H, $J$ = 6.8 Hz, $CH_2$), 3.94 (s, 3H, $CH_3$), 7.18–7.46 (m, 4H, Ar–H), 9.33 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.51; H, 4.52; Cl, 13.57; N, 5.38.

**Methyl 2-chloro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxylate (5k).** A solution of **5j** (0.2 g, 0.88 mmol) and *N*-chlorosuccinimide (0.13 g, 0.97 mmol) in chloroform (4 mL) was heated at reflux for 3 h, allowed to cool to room temperature, and then washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($Na_2SO_4$) and concentrated to yield a brown coloured residue which was purified by triturating with ether to give the desired **5k**. IR: 3315 (NH), 1680 (C=O), 1610 (C=C); UV: 304.8 (4.28), 246.0 sh (3.87), 234.0 (4.00), 226.0 (3.99), 205.8 (4.17); $^1$H NMR δ 1.98–2.12 (m, 2H, $CH_2$), 2.70–2.90 (m, 4H, $CH_2$×2), 3.92 (s, 3H, $CH_3$), 7.18–7.50 (m, 4H, Ar–H), 9.01 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; Cl, 12.86; N, 5.08. Found: C, 65.21; H, 5.33; Cl, 12.75; N, 5.12.

### General ester hydrolysis procedure for compounds 6b–k

A mixture of appropriate ester **5** (1 mmol) in hydroalcoholic solution (1 part of water, 2 of ethanol, 10.5 mL) of 2.5 M NaOH was refluxed for 12 h and poured into ice-water. The basic solution was acidified with concd hydrochloric acid 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 **6** which was used without further purification.

**6-Chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylic acid (6b).** IR: 3460 (NH), 1660 (C=O), 1600 (C=C); UV: 335.0 (4.06), 328.0 (4.16), 317.4 (4.19), 277.0 sh (3.71), 236.0 (4.12), 222.0 (4.14); $^1$H NMR δ 2.76 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.06 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.10–4.50 (br s, 1H, COOH exch. with $D_2O$), 6.78 (s, 1H, C2-H), 7.15–7.41 (m, 3H, Ar–H), 10.42 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66. Found: C, 63.22; H, 4.20; Cl, 14.18; N, 5.84.

**7-Chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylic acid (6c).** IR: 3290 (NH), 1680 (C=O); UV: 337.0 (4.14), 322.4 (4.23), 252.5 (3.79), 240.0 sh (3.94), 233.0 sh (4.06), 209.0 (4.15); $^1$H NMR δ 2.73 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 2.90 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.85 (br s, 1H, COOH exch. with $D_2O$), 6.77 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.05–7.65 (m, 3H, Ar–H), 10.62 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66. Found: C, 63.21; H, 4.21; Cl, 14.07; N, 5.51.

**8-Chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylic acid (6d).** IR: 3442 (NH), 3160 (OH), 1660 (C=O); UV: 338.0 (4.10), 321.8 (4.21), 308.0 (4.17), 240.0 (4.06), 215.8 (4.22); $^1$H NMR δ 2.71 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.85 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 3.85 (br s, 1H, COOH exch. with $D_2O$), 6.67 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.00–7.20 (m, 2H, Ar–H), 7.90 (s, 1H, Ar–H), 11.79 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66. Found: C, 63.31; H, 4.05; Cl, 14.28; N, 5.88.

**7,8-Dichloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylic acid (6e).** IR: 3420 (NH), 1650 (C=O); UV: 341.6 (4.05), 327.6 (4.06), 310.0 (3.97), 282.0 (3.78), 241.5 (3.94), 209.4 (4.19); $^1$H NMR δ 2.65 (t, 2H, $J$ = 6.6 Hz, $CH_2$), 2.86 (t, 2H, $J$ = 6.6 Hz, $CH_2$), 3.82 (br s, 1H, COOH exch. with $D_2O$), 6.62 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.46 (s, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 12.71 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_9Cl_2NO_2$: C, 55.34; H, 3.22; Cl, 25.13; N, 4.96. Found: C, 55.58; H, 3.15; Cl, 25.40; N, 4.78.

**4,5-Dihydro-8-methyl-1*H*-benzo[*g*]indole-3-carboxylic acid (6f).** IR: 3310 (NH), 1670 (C=O); UV: 335.2 (4.06), 322.6 (4.15), 303.2 (4.00), 276.1 (3.71), 237.0 (3.94), 212.6 (4.11); $^1$H NMR δ 2.38 (s, 3H, $CH_3$), 2.74 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 2.90 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 5.85 (br s, 1H, COOH exch. with $D_2O$), 6.80–7.30 (m, 4H, Ar–H), 9.50 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.21; H, 5.86; N, 6.02.

**4,5-Dihydro-7-methoxy-1*H*-benzo[*g*]indole-3-carboxylic acid (6g).** IR: 3300 (NH), 1650 (C=O); UV: 326.4 (4.14), 277.1 (3.78), 225.0 (3.97), 206.6 (4.11); $^1$H NMR δ 2.68 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 2.85 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 3.78 (s, 3H, $CH_3$), 4.02 (br s, 1H, COOH exch. with $D_2O$), 6.32–6.42 (m, 2H, Ar–H), 6.61 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.80 (d, 1H, $J$ = 8.6 Hz, Ar–H), 11.69 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{13}NO_2$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.21; H, 5.48; N, 5.55.

**2-Chloro-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylic acid (6h).** IR: 3260 (NH), 1700 (C=O); UV: 326.0 (4.24), 314.6 (4.26), 300.0 sh (4.17), 273.4 (3.99), 252.0 (3.81), 227.1 (4.08), 210.0 (4.20); $^1$H NMR δ 2.74 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 2.98 (t, 2H, $J$ = 7.4 Hz, $CH_2$), 3.80 (br s, 1H, COOH exch. with $D_2O$), 7.20–7.50 (m, 4H, Ar–H), 9.48 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; Cl, 14.31; N, 5.66. Found: C, 63.01; H, 4.22; Cl, 14.63; N, 5.38.

**4*H*-[1]Benzothiopyrano[4,3-b]pyrrole-1-carboxylic acid (6i).** IR: 3450 (NH), 1650 (C=O); UV: 337.6 (4.04), 332.0 (4.04), 312.8 (4.08), 267.4 (4.31), 244.2 (4.02), 220.0 (4.16); $^1$H NMR δ 3.05 (br s, 1H, COOH exch. with $D_2O$), 2.94 (s, 2H, $CH_2$), 6.73 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.05–7.80 (m, 4H, Ar–H), 11.02 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.06; S, 13.87. Found: C, 62.54; H, 4.04; N, 6.22; S, 13.83.

**5,6-Dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxylic acid (6j).** IR: 3465 (NH), 1650 (C=O); UV: 306.6 (4.18), 235.0 (3.90), 228.0 (3.88), 221.0 (3.85), 205.8 (4.05); $^1$H NMR δ 2.04–2.13 (m, 2H, $CH_2$), 2.70–2.90 (m, 4H, $CH_2$×2), 3.80 (br s, 1H, COOH exch. with $D_2O$), 6.95 (d, 1H, $J$ = 2.2 Hz, C2-H), 7.21–7.55 (m, 4H, Ar–H), 9.18 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.21; H, 5.94; N, 6.12.

**2-Chloro-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxylic acid (6k).** IR: 3450 (NH), 1660 (C=O), 1600 (C=C); UV: 308.4 (4.21), 300.6 (4.29), 246.0 (3.97), 234.0 (4.12), 225.0 (4.10); $^1$H NMR δ 1.98–2.28 (m, 2H, $CH_2$), 2.60–2.90 (m, 4H, $CH_2$×2), 3.89 (br s, 1H, COOH exch. with $D_2O$), 7.12–7.60 (m, 4H, Ar–H), 9.16 (br s, 1H, NH exch. with $D_2O$). Anal. calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.48; H, 4.39; Cl, 13.78; N, 5.22.

### General amidification procedure for compounds 2b–k

To a stirred solution of appropriate acid **6** (1 mmol) in DMF (4.5 mL) was added 1,1′-carbonyldiimidazole (1.11 mmol). After stirring the reaction mixture at room temperature for 3 h, 2-(aminomethyl)-1-ethylpyrrolidine (2.9 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 (**2b**,**c**,**d**,**g**,**k**) or an oil which was extracted with $CH_2Cl_2$ (**2e**,**f**,**h**–**j**). 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 or by triturating with an appropriate solvent to give pure title compounds **2**.

**6-Chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (2b).** IR: 3450 (NH), 3250 (NH), 1650 and 1630 (C=O), 1600 (C=C); UV: 337.0 (4.25), 332.0 (4.30), 321.3 (4.35), 237.0 (4.13), 211.2 (4.22); $^1$H NMR δ 1.13 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.57–1.96 (m, 4H, $CH_2$×2), 2.09–2.31 (m, 2H, $CH_2$), 2.78 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 2.80–2.92 (m, 2H, $CH_2$), 3.07 (t, 2H, $J$ = 7.2 Hz, $CH_2$), 3.16–3.33 (m, 2H, $CH_2$), 3.73–3.85 (m, 1H, CH), 6.42 (d, 1H, $J$ = 2.2 Hz, C2-H), 6.72 (br s, 1H, NH exch. with $D_2O$), 7.08–7.33 (m, 3H, Ar–H), 9.95 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{20}H_{24}ClN_3O$: C, 70.67; H, 7.06; Cl, 9.93; N, 7.85. Found: C, 70.90; H, 6.99; Cl, 9.96; N, 7.82.

**7-Chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (2c).** IR: 3400–3180 (2×NH), 1630 (C=O); UV: 339.0 (4.29), 324.8 (4.37), 277.0 (3.92), 253.0 (3.95), 208.6 (4.33); $^1$H NMR δ 1.18 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.60–1.94 (m, 4H, $CH_2$×2), 2.17–2.27 (m, 2H, $CH_2$), 2.68–2.94 (m, 6H, $CH_2$×3), 3.17–3.40 (m, 2H, $CH_2$), 3.64–3.79 (m, 1H, CH), 6.46 (d, 1H, $J$ = 2.2 Hz, C2-H), 6.71 (br s, 1H, NH exch. with $D_2O$), 7.16–7.42 (m, 3H, Ar–H), 10.15 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{20}H_{24}ClN_3O$: C, 70.67; H, 7.06; Cl, 9.93; N, 7.85. Found: C, 70.82; H, 6.91; Cl, 9.85; N, 7.88.

**8-Chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (2d).** IR: 3400–3100 (2×NH), 1630 (C=O); UV: 338.3 (4.25), 324.5 (4.34),

307.0 (4.22), 280.0 (3.85), 240.5 (4.10), 213.5 (4.31); $^1$H NMR δ 1.12 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.63–1.99 (m, 4H, $CH_2\times2$), 2.10–2.22 (m, 2H, $CH_2$), 2.63–3.00 (m, 6H, $CH_2\times3$), 3.16–3.42 (m, 2H, $CH_2$), 3.64–3.80 (m, 1H, CH), 6.45 (d, 1H, $J$ = 2.2 Hz, C2-H), 6.75 (br s, 1H, NH exch. with $D_2O$), 7.02–7.48 (m, 3H, Ar–H), 10.47 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{20}H_{24}ClN_3O$: C, 70.67; H, 7.06; Cl, 9.93; N, 7.85. Found: C, 70.59; H, 6.95; Cl, 9.99; N, 7.74.

**7,8-Dichloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (2e).** IR: 3400 (NH), 3200 (NH), 1640 (C=O); UV: 343.6 (4.30), 329.8 (4.33), 315.0 (4.22), 285.0 (3.87), 242.0 (3.96), 209.0 (4.34); $^1$H NMR δ 1.16 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.68–1.98 (m, 4H, $CH_2\times2$), 2.09–2.38 (m, 2H, $CH_2$), 2.68–2.92 (m, 6H, $CH_2\times3$), 3.20–3.48 (m, 2H, $CH_2$), 3.72–3.84 (m, 1H, CH), 6.51 (d, 1H, $J$ = 1.8 Hz, C2-H), 7.67 (s, 1H, Ar–H), 8.02 (s, 1H, Ar–H), 11.08 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{20}H_{23}Cl_2N_3O$: C, 64.45; H, 6.18; Cl, 18.12; N, 7.16. Found: C, 64.32; H, 6.24; Cl, 18.35; N, 7.02.

***N*-(1-Ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-8-methyl-1*H*-benzo[*g*]indole-3-carboxamide (2f).** IR: 3330 (NH), 3260 (NH), 1640 (C=O), 1600 (C=C); UV: 337.0 (4.22), 324.4 (4.30), 278.0 (3.76), 237.0 (3.98), 208.8 (4.24); $^1$H NMR δ 1.19 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.50–2.05 (m, 4H, $CH_2\times2$), 2.19–2.43 (m, 5H, $CH_3$ and $CH_2$), 2.68–2.93 (m, 6H, $CH_2\times3$), 3.23–3.43 (m, 2H, $CH_2$), 3.62–3.80 (m, 1H, CH), 6.51 (d, 1H, $J$ = 1.8 Hz, C2-H), 6.95–7.20 (m, 3H, Ar–H), 9.56 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{21}H_{27}N_3O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.39; H, 8.44; N, 8.07.

***N*-(1-Ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-7-methoxy-1*H*-benzo[*g*]indole-3-carboxamide (2g).** IR: 3360 (NH), 3240 (NH), 1660 (C=O); UV: 339.0 (4.25), 329.0 (4.29), 279.0 (3.89), 223.0 (4.10), 206.6 (4.26); $^1$H NMR δ 1.14 (t, 3H, $J$ = 7.4 Hz, $CH_3$), 1.65–1.80 (m, 2H, $CH_2$), 1.84–1.98 (m, 2H, $CH_2$), 2.13–2.32 (m, 2H, $CH_2$), 2.60–3.00 (m, 6H, $CH_2\times3$), 3.16–3.36 (m, 2H, $CH_2$), 3.81 (s, 3H, $CH_3$) 6.45 (d, 1H, $J$ = 1.8 Hz, C2-H), 6.60 (br s, 1H, NH exch. with $D_2O$), 6.70–6.85 (m, 2H, Ar–H), 7.36 (d, 1H, Ar–H), 9.89 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{21}H_{27}N_3O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.18; H, 8.26; N, 7.88.

**2-Chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxamide (2h).** IR: 3360 (NH), 3270 (NH), 1640 (C=O); UV: 328.0 (4.35), 315.6 (4.38), 273.0 (3.99), 254.0 (3.75), 232.0 sh (4.16), 209.4 (4.30); $^1$H NMR δ 1.13 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.60–2.01 (m, 4H, $CH_2\times2$), 2.13–2.40 (m, 2H, $CH_2$), 2.60–3.00 (m, 6H, $CH_2\times3$), 3.20–3.32 (m, 2H, $CH_2$), 3.70–3.84 (m, 1H, CH), 7.18–7.70 (m, 5H, Ar–H and NH exch. with $D_2O$), 10.31 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{20}H_{24}ClN_3O$: C, 70.67; H, 7.06; Cl, 9.93; N, 7.85. Found: C, 70.81; H, 6.98; Cl, 9.85; N, 7.70.

***N*-(1-Ethyl-2-pyrrolidinylmethyl)-4*H*-[1]benzothiopyrano[4,3-*b*]pyrrole-1-carboxamide (2i).** IR: 3340 (NH), 3240 (NH), 1640 (C=O), 1590 (C=C); UV: 331.8 (4.38), 313.8 (4.22), 306.0 (4.15), 285.0 (4.08), 268.6 (4.18), 244.6 (4.13), 215.8 (4.30); $^1$H NMR δ 1.13 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.58–1.95 (m, 4H, $CH_2\times2$), 2.12–2.36 (m, 2H, $CH_2$), 2.75–2.99 (m, 2H, $CH_2$), 3.16–3.38 (m, 2H, $CH_2$), 3.64–3.81 (m, 1H, CH), 3.94 (s, 2H, $CH_2$), 6.43 (s, 1H, C2-H), 6.68 (br s, 1H, exch. with $D_2O$), 7.06–7.60 (m, 4H, Ar–H), 10.41 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{19}H_{23}N_3OS$: C, 70.55; H, 7.10; N, 8.30, S 9.42. Found: C, 70.33; H, 7.22; N, 7.98, S, 9.39.

***N*-(1-Ethyl-2-pyrrolidinylmethyl)-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta[*b*]pyrrole-3-carboxa-mide (2j).** IR: 3340–3100 (NH×2), 1650 (C=O), 1600 (C=C); UV: 309.6 (4.62), 230.0 (4.34), 206.8 (4.52); $^1$H NMR δ 1.15 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.55–1.95 (m, 4H, $CH_2\times2$), 1.96–2.12 (m, 2H, $CH_2$), 2.13–2.39 (m, 2H, $CH_2$), 2.60–2.96 (m, 6H, $CH_2\times3$), 3.16–3.36 (m, 2H, $CH_2$), 3.63–3.78 (m, 1H, CH), 6.49 (d, 1H, $J$ = 2.6 Hz, C2-H), 6.66 (br s, 1H, exch. with $D_2O$ ), 7.18–7.52 (m, 4H, Ar–H), 9.31 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{21}H_{27}N_3O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.42; H, 8.12; N, 8.51.

**2-Chloro-*N*-(1-ethyl-2-pyrrolidinylmethyl)-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[*b*]pyrrole-3-carboxamide 2k.** IR: 3360 (NH), 3220 (NH), 1630 (C=O); UV: 305.4 (4.32), 232.0 (4.06), 226.0 (4.08), 206.4 (4.26); $^1$H NMR δ 1.12 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 1.50–2.45 (m, 8H, $CH_2\times4$), 2.60–2.90 (m, 6H, $CH_2\times3$), 3.17–3.35 (m, 2H, $CH_2$), 3.66–3.80 (m, 1H, CH), 7.10–7.60 (m, 5H, Ar–H and NH exch. with $D_2O$), 9.43 (br s, 1H, exch. with $D_2O$). Anal. calcd for $C_{21}H_{26}ClN_3O$: C, 71.24; H, 7.34; Cl, 9.56; N, 7.55. Found: C, 71.40; H, 7.21; Cl, 9.33; N, 7.51.

## Biology

**In vitro methods. 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).

**Binding assay.** [$^3$H]YM-09151–2 (nemonapride) was used as a specific ligand for $D_2$-like receptor[14] and raclopride as a specific displacer.[15]

[$^3$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.[18] with bovine serum as standard.

**In vivo experiments.** The experiments were performed on male Sprague–Dawley rats (Harlan, Italy), weight 200–250 g. They were housed two/three per cage in air-conditioned rooms. The rooms were lit between 08.00 and 20.00 h and maintained at a temperature of 22 °C and humidity of 60–70%. The animals had water and standard laboratory diet ad libitum.

**Drugs and treatments.** Compound **2k** 2-chloro-*N*-[(1-ethyl-2-pyrrolidinylmethyl]-5,6-dihydro-4*H*-benzo[6,7]-cyclohepta[*b*] pyrrole-3-carboxamide, was dissolved in PEG200. Haloperidol 1 mg/mL (Serenase) was diluted up to a concentration of 0.5 mg/kg. Amphetamine sulphate (Sigma, USA) was dissolved in distilled water. Vehicle treated animals received PEG200. All drugs were injected intraperitoneally at the volume of 1 mL/kg b.w.

**Catalepsy.** The effect of four different doses of **2k** (0.5, 1, 2 and 10 mg/kg) has been studied in the horizontal bar-inclined grid test. A group treated with the typical antipsychotic haloperidol (0.5 mg/kg) has been included in the experiment as a positive control group. The subjects have been allocated into six groups (vehicle, the four **2k** doses and haloperidol). Each subject was tested in the horizontal bar 10, 30 and 60 min (experiment 1) and 60, 90 and 120 min (experiment 2) after the treatment; after 2 min they have been tested in the inclined grid. The horizontal bar test has been performed placing each subject on a platform with its forepaws on a horizontal bar at a height of 12 cm. The inclined grid test has been performed placing each subject on a wire mesh grid tilted at 60°, with both forelimbs and hindlimbs in extension and in abduction. The immobility time was recorded in both test, for a maximum time of 120 s. Experiments were performed between 09.00 and 20.00 h.

**Amphetamine-induced hyperactivity.** Motor activity was measured by an apparatus consisting of a mobile rack (height 180 cm, width 100 cm and depth 60 cm) with eight compartments (h 40 cm, w 45 cm, d 50 cm), into which a transparent perspex cage (23×33 cm, h 19 cm) was placed (Imetronic, Pessac, France). Motor activity is detected by a system of photocell infrared beams, dividing the cage area into two sectors, rear and front sector. In particular, the interruption of two photocell beams belonging to two different sectors is recorded as a 'long movement' motility count. The interruption of two photocell beams belonging to the same sector is recorded as a 'short movement' motility count. A 'barrier' of infrared photocell beams, placed at the height of 15 cm, detects rearing activity. The apparatus was connected to a personal computer by an electronic interface.

Two experiments have been performed. In the first experiment (experiment 3) the subjects have been allocated into two groups: vehicle (PEG200 1 mL/kg) and **2k** 10 mg/kg. Immediately after treatment, they were individually placed into the motility cages, and, after 1 h habituation to the apparatus, treated with amphetamine sulphate at the dose of 1 mg/kg ip. In the second experiment (experiment 4) the subjects have been allocated in two groups: vehicle (PEG200 1 mL/kg) and **2k** 10 mg/kg. Half of the subjects from each group were challenged with amphetamine sulphate at the dose of 0.5 mg/kg. Amphetamine was administered after 1 h habituation to the motility cages. Compound **2k** (or PEG200) were administered immediately before amphetamine treatment. Immediately after amphetamine treatment activity was recorded for 100 min in experiment 3 and for 120 min in experiment 4. Data have been collected in 5-min time bins. Experiments were performed between 09.00 and 20.00 h.

**Statistics.** The results were analysed by analysis of variance (ANOVA), supplemented by F-tests for contrasts or Newman–Keuls test, using the appropriate ANOVA error term.[19] The analysis of the horizontal bar and inclined grid test data involved one between groups factors, *treatment* (with six levels), and one within group factor, *time* (with three levels, corresponding to the data collected at three different times). The analysis of the amphetamine-induced hyperactivity involved one between groups factor, **2k** (with two levels) and one within group factor, *time* (with 20 levels, experiment 3, and 24 levels, experiment 4, corresponding to the 5-min time bins). An additional between group factor, *amphetamine* (with two levels: amphetamine and vehicle) was considered in the analysis of data from experiment 4.

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