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Synthesis of New 2-(Aminomethyl)-4-phenylpyrrolo[1,2-a]-quinoxalines and their Preliminary In-vivo Central Dopamine Antagonist Activity Evaluation in Mice

J. GUILLON, M. BOULOUARD†, V. LISOWSKI*, S. STIEBING, V. LELONG†, P. DALLEMAGNE* AND S. RAULT*

*Synthéval, 5 Rue Vaubénard, 14032 Caen Cedex, *Centre d'Etudes et de Recherche sur le Médicament de Normandie, Laboratoire de Pharmacochimie, UFR des Sciences Pharmaceutiques, 1 Rue Vaubénard, 14032 Caen Cedex and †Laboratoire de Pharmacologie, UFR des Sciences Pharmacetiques, 1 Rue Vaubénard, 14032 Caen Cedex, France*

Abstract

In the search for antipsychotic agents that are not associated with extrapyramidal side effects, efforts have been focused on finding selective D_4-receptor antagonists and investigating their pharmacology. Our laboratory has developed a synthesis program for new pyrroloquinoxalines with therapeutic potential. We have described the synthesis of some new pyrroloquinoxalines with substituted arylpiperazino or aryltetrahydropyrido chain at position 3 of the quinoxaline ring (2-(4-phenylpiperazin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3a**), 2-[4-(2-methoxyphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3b**), 2-[4-(3-trifluoromethylphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3c**), 2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3d**), 2-(4-pyridin-2-ylpiperazin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3e**), and 2-(4-phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3f**)).

A preliminary pharmacological study of these products was conducted using climbing behaviour induced by apomorphine ($2{\cdot}5\,mg\,kg^{-1}$, s.c.) in mice. The derivatives were administered intraperitoneally 30 min before apomorphine. Haloperidol, chlorpromazine and clozapine were used as references.

Among this series, **3b**, **3c** and **3f** revealed a central dopamine antagonist activity. The most active derivative was **3b**, which exhibited a profile relatively close to clozapine.

Dopamine receptors are the primary targets in the treatment of schizophrenia. Most antipsychotic (neuroleptic) drugs like haloperidol block D_2 receptors in direct correlation with clinical potential but also with induction of substantial incidence of extrapyramidal symptoms such as neurological side effects (Tarsy 1983). In recent years, the term atypical neuroleptic has been used to describe antipsychotic agents that are not associated with extrapyramidal side effects. Clozapine is the principal example available for clinical use (Pickar & Hsiao 1995).

The atypical antipsychotic profile of clozapine is thought to result from its affinity for a multitude of receptors, including dopamine receptor subtypes, 5-hydroxytryptamine 5-HT_2 receptors and α_1-adrenoceptors (Meltzer 1992). In particular, it is suggested that the favourable effects of clozapine are derived from its relatively preferential blockade of D_4 over D_2 receptors (Lahti et al 1993). This observation indicates that selective D_4 antagonism may represent a novel and potent psychotropic mechanism and may have application as an atypical antipsychotic drug, which does not induce extrapyramidal symptoms (Taubes 1994).

Efforts have been focused on the search for selective D_4 receptor antagonists and to investigate their pharmacology. A few selective D_4 receptor antagonists have been described (Boyfield et al 1996; Hidaka et al 1996; Bristow et al 1997; Unangst et al 1997; Mansbach et al 1998). Thurkauf et al (1995) described a series of new 1-phenyl-3-(aminomethyl)pyrroles with high

Correspondence: J. Guillon, Synthéval, 5 Rue Vaubénard, 14032 Caen Cedex, France.

affinity for the D_4 receptor, particularly derivative **1** (Figure 1). Löber et al (1999) reported the synthesis of new azaindole derivatives like compound **2** with high affinity for the D_4 receptor. Thus it appeared possible to access new compounds with affinity for the D_4 receptor by binding a piperazino or phenylpiperazino chain on a different heterocycle-bearing chain or a chain with a few nitrogen atoms, for instance clozapine and derivatives **1** and **2** (Figure 1).

Our laboratory has developed a synthesis program for new pyrroloquinoxalines with therapeutic potential (Guillon et al 1998a, b). As part of this program, we have described the synthesis of new pyrroloquinoxalines **3a–f** with a substituted arylpiperazino or aryltetrahydropyrido chain at position 3 of the quinoxaline ring (Figure 1). A preliminary pharmacological study of these products was conducted using climbing behaviour induced by apomorphine in mice (Protais et al 1976; Costall et al 1978), a model which has been described to reveal central dopamine antagonist properties.

Materials and Methods

Chemical procedures

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Genesis Series FTIR spectrometer. ^1H,^{13}C and 2D-COSY NMR spectra were recorded on a JEOL JNM-LA 400 spectrometer (400 MHz) using d_6-DMSO as the solvent. Chemical shifts refer to tetramethylsilane, which was used as an internal reference. The following abbreviations were used: s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were recorded on a JEOL GC mate instrument using a direct inlet system and electron impact ionization. Elemental analyses (C, H, N) were performed by INSA, Rouen, France, and agreed with the proposed structures within ±0·3% of the theoretical values.

*General procedure for preparation of 2-(aminomethyl)-4-phenylpyrrolo[1,2-a]quinoxalines (**8a–f**).* The pH of a solution of 4-phenylpyrrolo[1,2- *a*]quinoxaline-2-carboxaldehyde (**7**) (0·5 g, 1·8 mmol) and secondary amine (2·2 mmol) in 35 mL methanol was adjusted to 6 by the dropwise addition of acetic acid. Powdered sodium cyanoborohydride (0·32 g, 5·05 mmol) was then added and the resultant mixture was refluxed for 5 h. After removal of the methanol by rotary evaporation, the residue was triturated in water and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulphate and evaporated to dryness. Solids were recrystallized from propan-2-ol.

*2-(4-Phenylpiperazin-1-ylmethyl)-4-phenylpyrrolo-[1,2-a]quinoxaline (**8a**).* White crystals (69%); mp 150°C; ^1H NMR (d_6-DMSO) δ: 2·49 (4H, m, 2 CH_2), 3·04 (4H, m, 2 CH_2), 3·60 (2H, s, CH_2), 6·67 (1H, t, J = 7·65, *H*-4″), 6·81 (2H, d, J = 7·65, *H*-2″ and *H*-6″), 6·88 (1H, s, *H*-3), 7·10 (2H, t, J = 7·65, *H*-3″ and *H*-5″), 7·42 (1H, t, J = 7·80, *H*-7), 7·51 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·86 (1H, d,

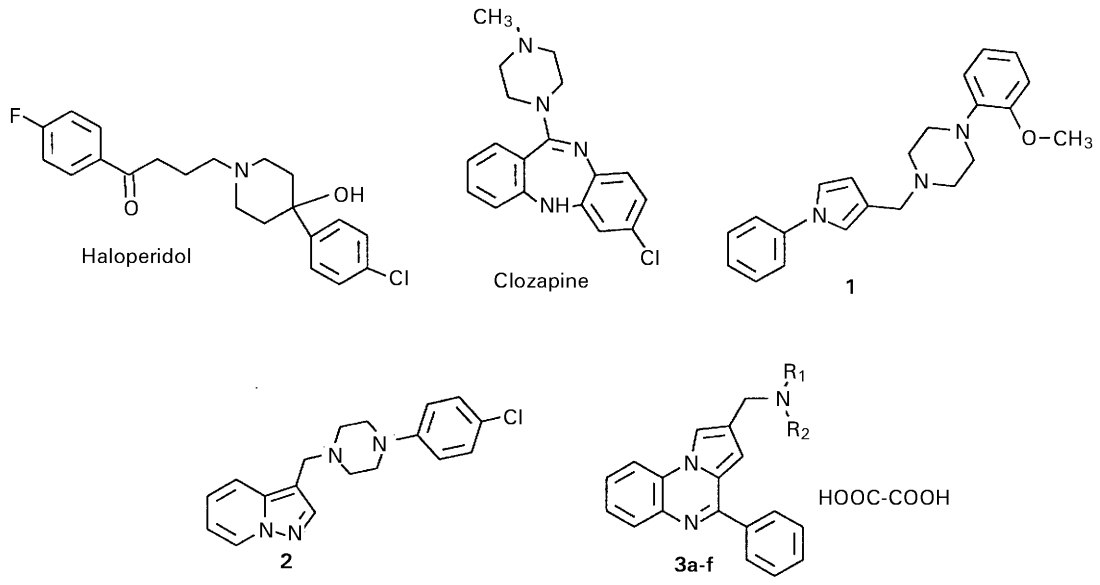

Figure 1. Structures of haloperidol, clozapine, **1**, **2** and the general structure of 2-(aminomethyl)-4-phenylpyrrolol[1,2-*a*]quinoxalinium oxalates **3a–f**.

J = 7·80, *H*-6), 7·91 (2H, m, *H*-2′ and *H*-6′), 8·23 (1H, d, J = 7·80, *H*-9), 8·43 (1H, s, *H*-1). Anal. calc. for $C_{28}H_{26}N_4$: C, 72·94; H, 4·59; N, 12·76. Found: C, 72·75; H, 4·29; N, 12·70%.

*2-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxaline (**8b**)*. White crystals (62%); mp 84°C; ^{1}H NMR (d_6-DMSO) δ: 2·58 (4H, m, 2 CH_2), 2·97 (4H, m, 2 CH_2), 3·68 (2H, s, CH_2), 3·76 (3H, s, CH_3O), 6·86 (2H, m, *H*-3″ and *H*-4″), 6·92 (2H, m, *H*-2″ and *H*-5″), 6·98 (1H, s, *H*-3), 7·51 (1H, t, J = 7·95, *H*-7), 7·61 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·95 (1H, d, J = 7·95, *H*-6), 8·02 (2H, m, *H*-2′ and *H*-6′), 8·32 (1H, d, J = 7·95, *H*-9), 8·51 (1H, s, *H*-1); ^{13}C NMR ($CDCl_3$) δ: 50·0 (*C*H_2), 52·7 (*C*H_3), 54·6 (*C*H_2), 55·2 (*C*H_2), 109·0 (*C*-6″), 111·8 (*C*-3), 114·6 (*C*-3″), 115·9 (*C*-4″), 117·8 (*C*-1), 120·7 (*C*-3a), 122·3 (*C*-2), 124·0 (*C*-5″), 125·3 (*C*-9), 126·1 (*C*-6), 126·5 (*C*-7), 127·8 (*C*-8), 128·4 (*C*-3′ and *C*-5′), 128·5 (*C*-2′ and *C*-6′), 129·5 (*C*-4′), 129·9 (*C*-1″), 135·4 (*C*-9a), 137·8 (*C*-1′), 141·2 (*C*-5a), 151·9 (*C*-2″), 152·7 (*C*-4); m/z (EI) 449 ($M^+ + 1$), 448 (M^+) other major fragments; 312, 285, 258, 218, 203, 191, 136. Anal. calc. for $C_{29}H_{28}N_4O$: C, 77·65; H, 6·29; N, 12·49. Found: C, 77·53; H, 6·43; N, 12·60%.

*2-[4-(3-Trifluoromethylphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxaline (**8c**)*. White crystals (49%); mp < 50°C; ^{1}H NMR (d_6-DMSO) δ: 2·49 (4H, m, 2 CH_2), 3·13 (4H, m, 2 CH_2), 3·60 (2H, s, CH_2), 6·88 (1H, s, *H*-3), 6·97 (1H, d, J = 7·80, *H*-4″), 67·05 (1H, s, H-2″), 7·10 (1H, d, J = 7·80, *H*-6″), 7·31 (1H, t, J = 7·80, *H*-5″), 7·41 (1H, t, J = 7·55, *H*-7), 7·51 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·86 (1H, d, J = 7·55, *H*-6), 7·92 (2H, m, *H*-2′ and *H*-6′), 8·22 (1H, d, J = 7·55, *H*-9), 8·42 (1H, s, *H*-1). Anal. calc. for $C_{29}H_{25}F_3N_4$: C, 72·94; H, 4·59; N, 12·76. Found: C, 72·75; H, 4·29; N, 12·70%.

*2-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxaline (**8d**)*. Pale yellow crystals (74%); mp 81°C; ^{1}H NMR (d_6-DMSO) δ: 2·67 (4H, m, 2 CH_2), 3·20 (4H, m, 2 CH_2), 3·42 (2H, s, CH_2), 6·97 (2H, d, J = 8·05, *H*-3″ and *H*-5″), 7·04 (1H, s, *H*-3), 7·26 (2H, d, J = 8·05, *H*-2″ and *H*-6″), 7·56 (1H, t, J = 7·75, *H*-7), 7·64 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 8·00 (1H, d, J = 7·75, *H*-6), 8·05 (2H, m, *H*-2′ and *H*-6′), 8·37 (1H, d, J = 7·75, *H*-9), 8·58 (1H, s, *H*-1). Anal. calc. for $C_{28}H_{25}ClN_4$: C, 72·94; H, 4·59; N, 12·76. Found: C, 72·75; H, 4·29; N, 12·70%.

*2-(4-Pyridin-2-ylpiperazin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxaline (**8e**)*. White crystals (62%); mp 86°C; ^{1}H NMR (d_6-DMSO) δ: 2·49 (4H, m, 2 CH_2), 3·44 (4H, m, 2 CH_2), 3·64 (2H, s, CH_2), 6·59 (1H, m, *H*-5″), 6·74 (1H, d, J = 8·55, *H*-6″), 6·94 (1H, s, *H*-3), 7·47 (1H, t, J = 7·60, *H*-7), 7·57 (5H, m, *H*-3′, *H*-4′, *H*-5′, *H*-4″ and *H*-8), 7·92 (1H, d, J = 7·60, *H*-6), 7·98 (2H, m, *H*-2′ and *H*-6′), 8·07 (1H, m, *H*-3″), 8·28 (1H, d, J = 7·60, *H*-9), 8·47 (1H, s, *H*-1). Anal. calc. for $C_{27}H_{25}N_5$: C, 72·94; H, 4·59; N, 12·76. Found: C, 72·75; H, 4·29; N, 12·70%.

*2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxaline (**8f**)*. Pale yellow crystals (61%); mp 153°C; ^{1}H NMR (d_6-DMSO) δ: 2·75 (2H, m, 2 CH_2), 3·04 (2H, m, 2 CH_2), 3·18 (2H, s, CH_2), 3·78 (2H, s, CH_2), 6·11 (1H, m, =C*H*), 6·96 (1H, s, *H*-3), 7·21 (1H, t, J = 7·30, *H*-4″), 7·30 (2H, t, J = 7·30, *H*-3″ and *H*-5″), 7·39 (2H, d, J = 7·30, *H*-2″ and *H*-6″), 7·48 (1H, t, J = 7·70, *H*-7), 7·57 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·93 (1H, d, J = 7·70, *H*-6), 8·00 (2H, m, *H*-2′ and *H*-6′), 8·24 (1H, d, J = 7·70, *H*-9), 8·41 (1H, s, *H*-1). Anal. calc. for $C_{29}H_{25}N_3$: C, 72·94; H, 4·59; N, 12·76. Found: C, 72·75; H, 4·29; N, 12·70%.

*General procedure for preparation of 2-(aminomethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalates (**3a–f**)*. To a solution of 2-(aminomethyl)-4-phenylpyrrolo[1,2-*a*]quinoxalines (**8a–f**) (1·2 mmol) in propan-2-ol (30 mL) was added oxalic acid (2·4 mmol). The reaction mixture was heated under reflux for 30 min. The precipitate was filtered, washed with diethyl ether and recrystallized from a mixture of propan-2-ol/water (60 : 40).

*2-(4-Phenylpiperazin-1-ylmethyl)-4-phenylpyrrolo-[1,2-a]quinoxalinium oxalate (**3a**)*. White crystals (58%); mp 245°C; ^{1}H NMR (d_6-DMSO) δ: 3·09 (4H, m, 2 CH_2), 3·31 (4H, m, 2 CH_2), 4·24 (2H, s, CH_2), 4·66 (H, bs, O*H* and NH^+), 6·80 (1H, t, J = 7·05, *H*-4″), 6·93 (2H, d, J = 7·05, *H*-2″ and *H*-6″), 7·13 (1H, s, *H*-3), 7·21 (2H, t, J = 7·05, *H*-3″ and *H*-5″), 7·53 (1H, t, J = 7·60, *H*-7), 7·61 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·95 (1H, d, J = 7·60, *H*-6), 7·97 (2H, m, *H*-2′ and *H*-6′), 8·26 (1H, d, J = 7·60, *H*-9), 8·61 (1H, s, *H*-1). Anal. calc. for $C_{30}H_{28}N_4O_4$: C, 70·85; H, 5·55; N, 11·02. Found: C, 70·90; H, 5·62; N, 11·03%.

*2-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3b**)*. White crystals (57%); mp 249°C; ^{1}H NMR (d_6-DMSO) δ: 3·04 (4H, m, 2 CH_2), 3·15 (4H, m, 2 CH_2), 3·77 (3H, s, CH_3O), 4·16 (2H, s, CH_2), 6·88 (2H, m, *H*-3″ and *H*-4″), 6·94 (2H, m, *H*-2″ and *H*-5″), 7·10 (1H, s, *H*-3), 7·20 (H, bs, O*H* and

N*H*$^+$), 7·51 (1H, t, J = 7·55, *H*-7), 7·60 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·94 (1H, d, J = 7·55, *H*-6), 8·02 (2H, m, *H*-2′ and *H*-6′), 8·22 (1H, d, J = 7·55, *H*-9), 8·52 (1H, s, *H*-1). Anal. calc. for $C_{31}H_{30}N_4O_5$: C, 69·14; H, 5·57; N, 10·41. Found: C, 68·99; H, 5·84; N, 10·35%.

*2-[4-(3-Trifluoromethylphenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3c**)*. White crystals (61%); mp 185°C; ^{1}H NMR (d_6-DMSO) δ: 3·06 (4H, m, 2 C*H*$_2$), 3·42 (4H, m, 2 C*H*$_2$), 4·21 (2H, s, C*H*$_2$), 4·56 (H, bs, O*H* and N*H*$^+$), 7·09 (1H, d, J = 7·65, *H*-4″), 7·12 (1H, s, H-2″), 7·19 (1H, s, *H*-3), 7·21 (1H, d, J = 7·65, *H*-6″), 7·42 (1H, t, J = 7·65, *H*-5″), 7·52 (1H, t, J = 7·70, *H*-7), 7·59 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·95 (1H, d, J = 7·70, *H*-6), 8·00 (2H, m, *H*-2′ and *H*-6′), 8·26 (1H, d, J = 7·70, *H*-9), 8·60 (1H, s, *H*-1). Anal. calc. for $C_{31}H_{27}F_3N_4O_4$: C, 64·58; H, 4·72; N, 9·72. Found: C, 64·43; H, 4·66; N, 10·01%.

*2-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3d**)*. White crystals (82%); mp 203°C; ^{1}H NMR (d_6-DMSO) δ: 3·13 (4H, m, 2 C*H*$_2$), 3·32 (4H, m, 2 C*H*$_2$), 4·29 (2H, s, C*H*$_2$), 4·71 (H, bs, O*H* and N*H*$^+$), 6·95 (2H, d, J = 7·15, *H*-3″ and *H*-5″), 7·14 (1H, s, *H*-3), 7·24 (2H, d, J = 7·15, *H*-2″ and *H*-6″), 7·54 (1H, t, J = 7·75, *H*-7), 7·61 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·96 (1H, d, J = 7·75, *H*-6), 7·99 (2H, m, *H*-2′ and *H*-6′), 8·27 (1H, d, J = 7·75, *H*-9), 8·62 (1H, s, *H*-1). Anal. calc. For $C_{30}H_{27}ClN_4O_4$: C, 66·36; H, 5·01; N, 10·32. Found: C, 66·49; H, 4·81; N, 10·09%.

*2-(4-Pyridin-2-ylpiperazin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3e**)*. White crystals (59%); mp 241°C; ^{1}H NMR (d_6-DMSO) δ: 2·90 (4H, m, 2 C*H*$_2$), 3·63 (4H, m, 2 C*H*$_2$), 4·07 (2H, s, C*H*$_2$), 5·00 (H, bs, O*H* and N*H*$^+$), 6·64 (1H, m, *H*-5″), 6·79 (1H, d, J = 8·30, *H*-6″), 7·06 (1H, s, *H*-3), 7·51 (1H, m, *H*-7), 7·57 (5H, m, *H*-3′, *H*-4′, *H*-5′, *H*-4″ and *H*-8), 7·94 (1H, d, J = 7·85, *H*-6), 8·00 (2H, m, *H*-2′ and *H*-6′), 8·10 (1H, m, *H*-3″), 8·22 (1H, d, J = 7·85, *H*-9), 8·49 (1H, s, *H*-1). Anal. calc. for $C_{29}H_{27}N_5O_4$: C, 68·36; H, 5·34; N, 13·74. Found: C, 68·36; H, 5·29; N, 13·69%.

*2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)-4-phenylpyrrolo[1,2-a]quinoxalinium oxalate (**3f**)*. White crystals (45%); mp 248°C; ^{1}H NMR (d_6-DMSO) δ: 2·72 (2H, m, 2 C*H*$_2$), 3·30 (2H, m, 2 C*H*$_2$), 3·71 (2H, s, C*H*$_2$), 4·18 (H, bs, O*H* and N*H*$^+$), 4·37 (2H, s, C*H*$_2$), 6·15 (1H, m, =C*H*), 7·19 (1H, s, *H*-3), 7·28 (1H, t, J = 6·70, *H*-4″), 7·35 (2H, t, J = 6·70, *H*-3″ and *H*-5″), 7·44 (2H, d, J = 6·70, *H*-2″ and *H*-6″), 7·53 (1H, t, J = 7·60, *H*-7), 7·59 (4H, m, *H*-3′, *H*-4′, *H*-5′ and *H*-8), 7·96 (1H, d, J = 7·60, *H*-6), 7·99 (2H, m, *H*-2′ and *H*-6′), 8·28 (1H, d, J = 7·60, *H*-9), 8·67 (1H, s, *H*-1). Anal. calc. for $C_{31}H_{27}N_3O_4$: C, 73·65; H, 5·38; N, 8·31. Found: C, 73·76; H, 5·38; N, 8·41%.

Pharmacological procedures

Animals. Male OF1 mice (20–25 g; Iffa Credo) were kept in conventional plastic cages in groups of 10 and had free access to food and water. They were housed in a well-ventilated room at an ambient temperature of 22°C on a 12-h light–dark cycle.

Apomorphine-induced climbing behaviour. Groups of eight mice were dosed with test compounds by the intraperitoneal route and placed individually into cylindrical wire mesh (height 15 cm, diameter 12 cm, mesh size 1 cm) 30 min before apomorphine administration. Climbing behaviour was assessed at 5-min intervals for 20 min, starting 10 min after the apomorphine (2·5 mg kg^{-1}, s.c.) administration. The following scoring system was used: 0, no paw on the cage; 1, one paw on the cage; 2, two paws on the cage; 3, three paws on the cage; and 4, four paws on the cage. An observer unaware of the specific drug treatments made all the observations. Climbing scores at each time interval were then summed and expressed as a climbing index; the maximum possible index was therefore 20.

Drugs and drug solutions of the new compounds to be tested and reference drugs (with the exception of haloperidol) were dissolved immediately before use in 0·9% saline. *R*(−)Apomorphine (HCl) and chlorpromazine (HCl) were purchased from RBI. Clozapine (HCl) was synthesized by Syntheval SA. Solutions of haloperidol were prepared by appropriate dilutions in 0·9% saline of a commercially available solution (Haldol, 2 mg mL^{-1}, Janssen-Cilag S.A.). Intraperitoneal or subcutaneous injections of drugs were given at a volume of 0·4 mL/20 g.

Results and Discussion

Chemistry

The 2-(aminomethyl)-4-phenylpyrrolo[1,2-*a*]quinoxaline oxalates **3a**–**f** were prepared according to the sequence as shown in Figure 2. Reaction of commercially available phenylenediamine with 1-phenylpropan-1,2-dione in acetic acid gave the methylphenylquinoxaline **4**. Treatment of ethyl

bromopyruvate in refluxing ethanol led to ethyl 4-phenylpyrrolo[1,2-*a*]quinoxaline-2-carboxylate (**5**). Reduction of the ester group of **5** with $LiAlH_4$ in anhydrous tetrahydrofuran gave the alcohol **6**, subsequently oxidized into the attempted aldehyde **7** using MnO_2 in refluxing chloroform (Guillon et al 1998a, b). The aldehyde **7** was then engaged in a reductive amination with $NaBH_3CN$ and secondary amines to give the quinoxalines **8a–f** (Borch et al 1971; Lane 1975; Thurkauf et al 1995). Treatment of **8a–f** with oxalic acid in refluxing propan-2-ol converted the compounds into their oxalate **3a–f**, respectively.

Pharmacology

Table 1 shows the dose-dependency of the climbing behaviour induced by apomorphine after intra-

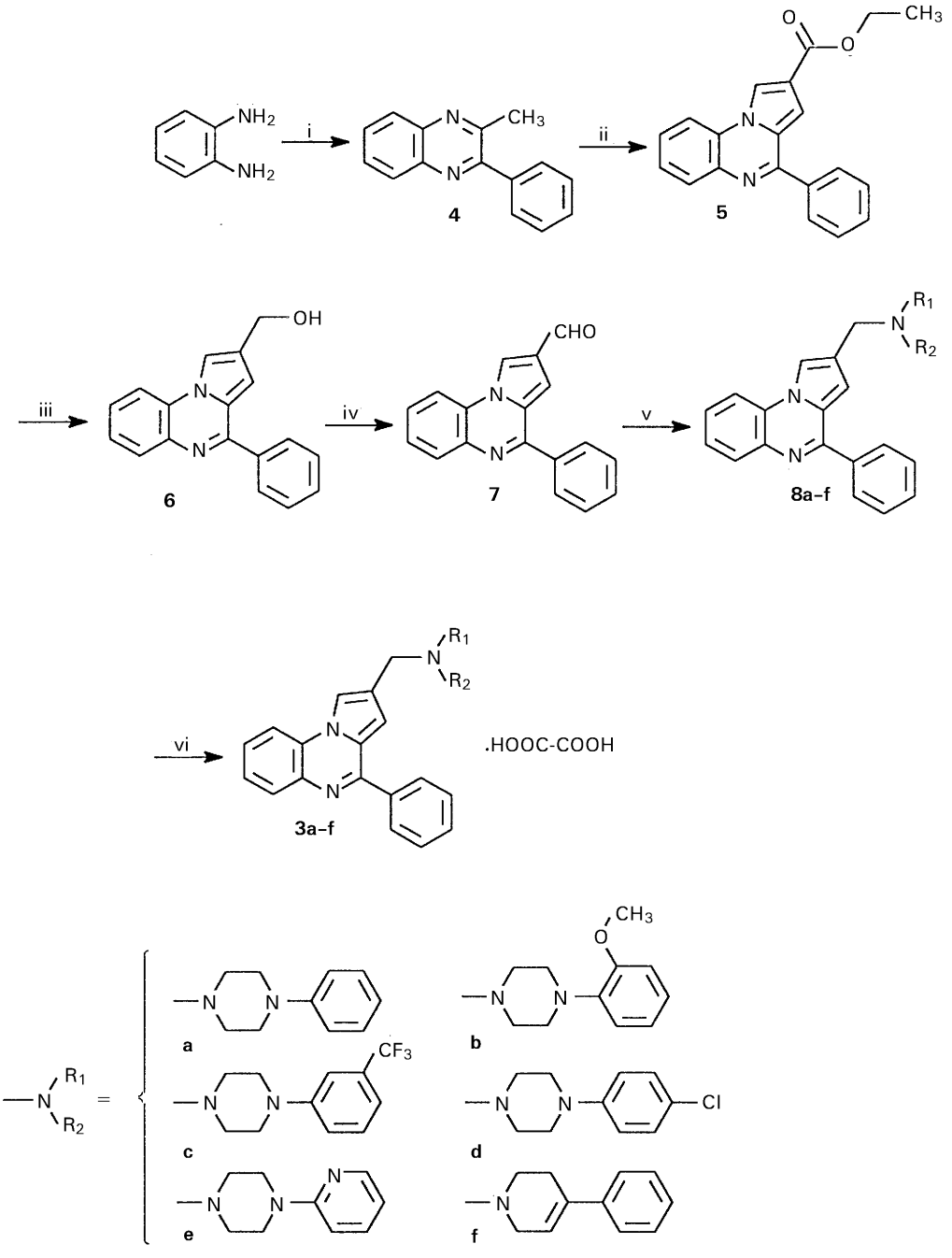

Figure 2. Preparation of the 2-(aminomethyl)-4-phenylpyrrolo[1,2-*a*]quinoxaline oxalates **3a–f**. Reagents: i. C_6H_5-CO-CO-CH_3, CH_3COOH; ii. Br-CH_2CO-$COOC_2H_5$, C_2H_5OH; iii. $AlLiH_4$, tetrahydrofuran; iv. MnO_2, $CHCl_3$; v. HNR_1R_2, $NaBH_3CN$, CH_3OH; vi. $(COOH)_2$, $(CH_3)_2CHOH$.

peritoneal administration of haloperidol, chlorpromazine, clozapine and quinoxalines **3a–f**.

Among the pharmacological references used, the two typical neuroleptics were the most effective, particularly haloperidol (1 mg kg^{-1}) which completely antagonized the apomorphine-induced climbing behaviour. Clozapine was also active in this model, but this effect was quantitatively less important. The present data corroborate the work of Protais et al (1976) and Costall et al (1978).

Among the new pyrroloquinoxalines, three compounds (**3b**, **3c** and **3f**) demonstrated activity in this test but at larger doses than the reference drugs. The most active derivative was **3b**, which exhibited a profile relatively close to clozapine. It seems difficult to deduce the structure–activity relatioship from these preliminary results. In terms of substitution on the phenyl group, the best results were obtained with the orthomethoxy substitutent (**3b**) and the metatrifluoromethyl substitutent (**3c**), which have almost different electronical behaviour.

Table 1. Test compounds antagonism of climbing behaviour. Climbing behaviour was induced in mice by 2·5 mg kg^{-1} subcutaneous apomorphine. The derivatives were given intraperitoneally 30 min before apomorphine. The climbing index (see experimental section) is expressed as the mean ± s.e.m. Eight mice were used at each dose of drug. Animals with doses designated 0 received saline 30 min before apomorphine.

Drugs	Dose (mg kg^{-1})	Climbing index
Haloperidol	0	14·12 ± 2·05
	0·1	3·50 ± 0·53*
	0·3	0·25 ± 0·02***
	1	0·00
Chlorpromazine	0	13·21 ± 1·35
	1	6·87 ± 1·25*
	2	4·25 ± 0·22**
	4	0·00
Clozapine	0	15·20 ± 1·65
	5	12·50 ± 1·25
	10	4·50 ± 0·46*
	20	1·50 ± 0·07***
3a	0	15·71 ± 1·06
	100	16·50 ± 1·55
3b	0	14·12 ± 1·56
	10	14·00 ± 1·65***
	33	2·75 ± 0·80***
	100	0·00
3c	0	15·11 ± 1·56
	100	9·87 ± 0·78*
	150	5·25 ± 0·45**
	225	0·00
3d	0	15·71 ± 1·06
	100	17·12 ± 1·01
3e	0	14·12 ± 1·55
	100	13·62 ± 1·70
3f	0	14·00 ± 1·51
	100	11·50 ± 1·44
	150	8·25 ± 0·74*
	225	3·25 ± 0·55**

*$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ vs vehicle-treated groups (Student's t-test).

The replacement of the piperazine ring (compound **3a**) by a 3,4-dehydropiperidine ring in compound **3f** led to an increase of activity, probably due to the absence of a basic amine. Substitution of the phenylpiperazine with a parachloro (compound **3d**) had no effect on activity.

Further biological characterization in-vitro (in particular selectivity towards dopamine receptor subtype studies) and in-vivo will be necessary to determine the real therapeutic potential of these new compounds as neuroleptics, and perhaps to aim structural arrangement in this chemical series from the leading compound **3b**.

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