1-Phenyl-3-(aminomethyl)pyrroles as Potential Antipsychotic Agents. Synthesis and Dopamine Receptor Binding

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A series of 1-phenyl-3-(aminomethyl)pyrroles were prepared in two steps from aniline and their affinities for D_2, D_3, and D_4 dopamine receptor subtypes determined. A 15-fold selectivity for cloned human D_4 receptors over cloned African Green monkey D_2 receptors was observed with 1-(2-pyridyl)-4-[[3-(1-phenylpyrrolyl)]methyl]piperazine.

Schizophrenia is a complex psychological disorder of unclear etiology. Afflicted individuals may demonstrate a wide range of behavioral patterns characterized at one extreme by hallucinations, paranoia, and bizarre, disorganized behavior (positive symptoms) and at the further extreme by social withdrawal, catatonia, and affective "flattening" of the personality (negative symptoms).[1-3] Although the hypothesis that symptoms of schizophrenia result from a malfunctioning of dopaminergic pathways in the brain was suggested in 1963,[4] only two structural classes of clinically effective antipsychotic agents presently in use have been shown to be specific in their affinity for dopamine receptors. These are the butyrophenones, represented in Figure 1 by haloperidol (1),[5] and the benzamides, represented by remoxipride (**2**).

van Wijngaarden et al. prepared a series of 2-phenyl-5-(aminomethyl)pyrrole derivatives as conformationally restricted butyrophenones and tested their ability to bind to D_2 receptors in rat corpus striatum.[6] One of the best representatives of this series, **3a**, displayed high affinity for the D_2 receptor (0.8 nM). This study demonstrated that a heteroaromatic pyrrole system could be used as an isosteric substitute for the phenone linkage in the butyrophenones. It is interesting that the *N*-methylpyrrole derivative **3b** displayed 20-fold less affinity for the D_2 receptor. This would indicate either that the NH of the pyrrole is involved in an essential hydrogen bonding interaction with the receptor protein or that the methyl group is sterically disadvantageous to binding. The fact that haloperidol has no hydrogen-bonding interaction in its tail lends credence to the latter possibility.

As part of an ongoing study to examine possible rotational restriction within the butyrophenone antipsychotics, we have prepared a series of 1-phenyl-3-(aminomethyl)pyrroles (**4**) and tested them for their ability to bind to cloned dopamine D_2, D_3, and D_4 receptor subtypes. These compounds are isomeric to the 2-phenylpyrroles described by van Wijngaarden and, although retaining the same "six-five" aromatic ring structure, lack the NH functionality. The chemical structures of the compounds contained within this study are shown graphically in Figure 2. In order to limit the number of possible aminomethyl "tails", most of the amines were selected on the basis of either being subunits of known dopaminergic ligands or close analogs thereof. Thus, compounds **4a–g** have amino tails corresponding to unique amine subunits associated with the antipsychotic drugs haloperidol, spiperone, pim-

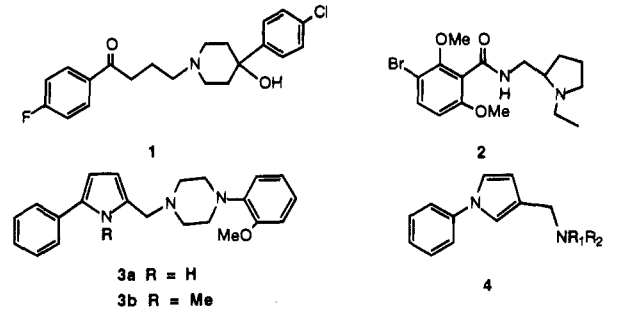

Figure 1. Structures of haloperidol, remoxipride, and (aminomethyl)pyrroles.

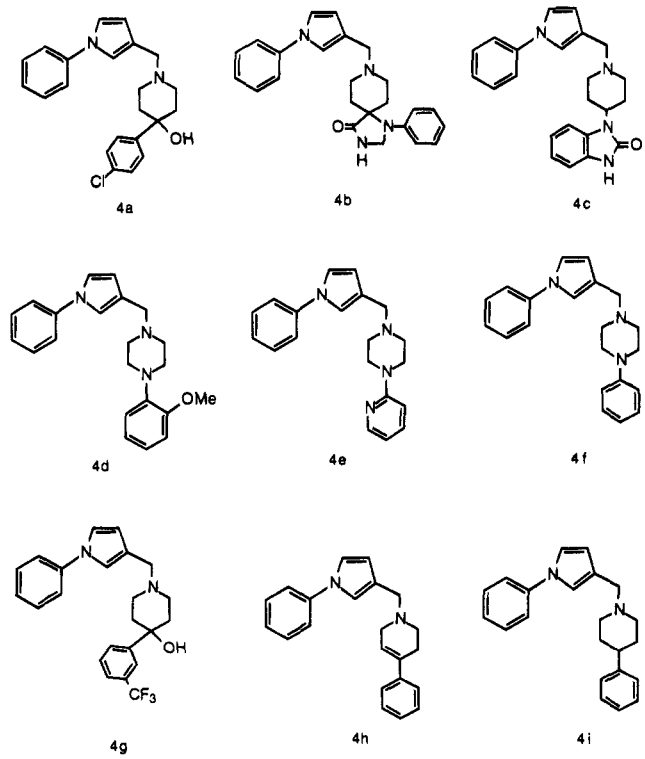

Figure 2. 1-Phenyl-3-(aminomethyl)pyrroles.

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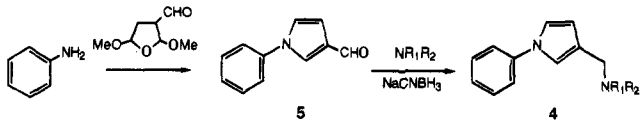
Scheme 1. of 1-Phenyl-3-(aminomethyl)pyrroles



ozide, fluanisole, azaperone, alpertine and trifluperidol, respectively. The 4-phenyl-1,2,3,6-tetrahydropyridine **4h** and its reduced analog **4i** are structurally related to precursors of the dopaminergic neurotoxin MPTP.

Chemistry. The preparation of the subject 1-phenyl-3-(aminomethyl)pyrrole compounds is described graphically in Scheme 1. Aniline was condensed with 2,5-dimethoxy-3-formyltetrahydrofuran to give 3-formyl-1-phenylpyrrole (**5**).[7] Reductive amination of **5** with selected secondary amines provided the desired tertiary 1-phenyl-3-(aminomethyl)pyrroles **4**.

Expression of Recombinant Dopamine Receptors. The recombinant African Green monkey (Cercopitecus Aethiops) D_{2A} and D_3 receptors (Genbank no. U18547 and no. U29296, respectively) were subcloned in the pcDNAI/Neo mammalian expression vector (Invitrogen). The recombinant human $D_{4.2}$ receptor was prepared from the $D_{4.2}$ minigene expression construct[8] by replacement of the NotI-KasI fragment containing two introns with a synthetic DNA fragment encoding the intron-deleted sequence (Genbank no. HSD4DOP). Stable clones expressing each receptor were isolated under G418 selection after calcium phosphate transfection of CHO-K1 cells (the human $D_{4.2}$ plasmid was cotransfected with pSV2Neo, Clontech). The membranes prepared from cell pellets were stored at −80 °C.

Receptor Binding. Affinity at D_2, D_3, and D_4 receptors was determined via standard competitive displacement assays using D_2 and D_3 receptors cloned from the African Green monkey and D_4 receptor cloned from human. The benzamide [^{3}H]YM 09151, which displays high affinity for each of these subtypes, was used as the competitive ligand in all three assays.[9] Binding data were analyzed with the nonlinear curve-fitting program RS/1 (BBN Software Products, Cambridge, MA). Calculated IC_{50} values were then converted to K_i values using the Cheng–Prusoff correction[10] with the following equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the radioligand concentration and K_d is the previously determined dissociation constant for [^{3}H]YM 09151 at the cloned primate D_2 receptor (0.070 nM), cloned primate D_3 receptor (0.38 nM), and cloned human D_4 receptor (0.37 nM).

Results and Discussion

Affinity of the compounds of Figure 2 at D_2 and D_3 receptors was determined via standard competitive displacement assays using D_2 and D_3 receptors cloned from the African Green monkey with [^{3}H]YM 09151 as the competitive ligand. Affinity at D_4 receptors was determined via standard competitive displacement assays using human D_4 receptor clones with [^{3}H]YM 09151 as the competitive ligand. The results of these assays are displayed in Table 1. The reference compound remoxipride was prepared by condensation of commercially available 3-bromo-2,6-dimethoxybenzoic acid with (−)-(*S*)-2-(aminomethyl)-**1**-ethylpyrrolidine.[10]

Table 1. Binding Affinities of 1-Phenyl-3-(aminomethyl)-pyrroles at D_2, D_3, and D_4 Receptor Clones Expressed as K_i (nM)[a]

compd	D_2	D_3	D_4	mp (°C)	yield (%)
4a	151	477	325	116–118	78
4b	36	90	201	196–198	94
4c	176	398	646	226–228	72
4d	0.7	10	1.3	148–150	60
4e	25	150	1.6	223–225	72
4f	14	49	4	218–220	55
4g	237	420	492	100	46
4h	6	15	4	216–218	88
4i	21	61	9	192–194	83
haloperidol	5	3	7		
remoxipride	873	4603	3872		
clozapine	254	466	71		

[a] All data reported is an average of three experiments and SEM was <10%. Melting points are for oxalate salts. Yield refers to preparation of **4** from **5**.

The reference compounds haloperidol and clozapine were obtained from commercial sources.

While all of the compounds tested displayed significant binding at the receptor subtypes, only the compounds containing the aminomethyl tails of fluanisole (**4d**) and MPTP (**4h**) and their structural analogs **4f** and **4i** showed relatively high affinities (<100 nM) for these receptors. It is notable that **4d** is comparable, in both structure and affinity for D_2 receptors, to the isomeric pyrrole derivative **3a**. This indicates that an NH is not essential for binding to D_2 receptors in "five-six" type conformational restrictions of the butyrophenone series. While haloperidol and spiperone have been shown to have high affinity for D_2, D_3, and D_4 receptors, the analogous compounds within the 3-(aminomethyl)-biphenyl series, **4a** and **4b**, are undistinguished in this regard.

Selectivity of most of the described (aminomethyl)-pyrroles for the subtypes is relatively modest. Compounds **4a**, **4c**, and **4g** display relatively weak binding at all three receptor subtypes and no appreciable selectivity between the sites. Some selectivity for D_2/D_4 vs D_3 is observed in **4d**, **4f**, **4h**, and **4i**. The greatest subtype selectivity found within this series was observed for the 2-pyridinylpiperazine derivative **4e**, which displayed a D_4 subtype selectivity of 95-fold against D_3 and 15-fold against D_2. The latter selectivity for D_4 vs D_2 receptors is notable since this type of selectivity has been hypothesized to be the factor differentiating traditional neuroleptics, which often induce tardive dyskinesia after chronic use, from the "atypical" antipsychotic clozapine, which is free of these motor side effects.[11] While clozapine displays remarkable clinical efficacy as an antipsychotic agent, fatal hematological dyscratias have been observed within patient populations taking the medication.[13] The identification of the D_4 selective compound **4e**, which is structurally unrelated to the dibenzo[*b*,*e*][1,4]diazepine clozapine, provides a structural example which may lead to compounds possessing clinical efficacy similar to that of clozapine but devoid of the hematological toxicity.

The dopamine receptor subtype binding data obtained within this study serves to demonstrate that a 1-phenylpyrrole ring system may be used to conformationally restrict four-atom linkages in butyrophenone type dopaminergic ligands. While compounds with high affinity for the receptors have been identified, relatively high receptor subtype specificity was only observed within

the case of **4e**, which demonstrated 15-fold specificity for D_4 vs D_2 and 95-fold specificity for D_4 vs D_3 subtypes. In order to assess the pharmacological and behavioral attributes of a highly selective D_4 receptor compound, efforts to improve upon the D_4 selectivity of **4e** are presently underway.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were obtained for all compounds tested for binding. ^{1}H NMR and/or mass spectral analysis were carried out on all isolated intermediates and are available upon request. Elemental analyses were performed at Robertson Microlabs, Madison, NJ, and were within 0.4% of the theoretical C, H, and N unless otherwise noted. Electron ionization mass spectra were obtain using a Hewlett-Packard 5890 mass spectrometer. ^{1}H NMR spectra were recorded from DMSO-d_6 or $CDCl_3$ solutions using a Varian Unity 400 spectrometer; results are recorded as ppm downfield from the TMS signal. Spectral data for all amines are reported in the oxalate salt form. Haloperidol and clozapine were purchased from Research Biochemicals Inc., Natick, MA. [^{3}H]YM 09151 was purchased from NEN-DuPont, Boston, MA.

General Procedure for the Preparation of Compounds 4a–l. The following two-step preparation of **4a** represents a generalized experimental procedure which was utilized to prepare all of the new compounds described in this report.

3-Formyl-1-phenylpyrrole (5). A solution of aniline (9.31 g, 100 mmol) and 2,5-dimethoxy-3-formyl-2,3,4,5-tetrahydrofuran (20 g, 125 mmol) in acetic acid (100 mL) was heated at 90 °C for 2 h. The solvent was removed on a rotary evaporator. The residue was partitioned between ethyl acetate and 10% NaOH solution. The organic layer was further washed with water, filtered through a pad of silica, and concentrated to provide compound **5** as an oil (10.2 g, 58%): ^{1}H ($CDCl_3$) 9.86 (s, 1H), 7.68 (dd, J = 2, 2 Hz, 1H), 7.35–7.51 (m, 5H), 7.09 (dd, J = 3, 3 Hz, 1H), 6.81 (dd, J = 2, 3 Hz, 1H); mass spectra (CI) 172 (M + 1).

1-Phenyl-3-[[1-[4-hydroxy-4-(4-chlorophenyl)piperidinyl]]methyl]pyrrole Oxalate (4a). The pH of a solution of 0.5 g of 5 (2.9 mmol) and 0.62 g of 4-hydroxy-4-(4-chlorophenyl)piperidine in 10 mL of methanol was adjusted to 6.0 by the dropwise addition of acetic acid. Powdered sodium cyanoborohydride (0.5 g) was then added and the resultant mixture stirred for 3 h. After removal of the methanol by rotary evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The resulting oil was taken up in 5 mL of 2-propanol, mixed with a solution of 260 mg of oxalic acid in 3 mL of 2-propanol, and allowed to stand. After 30 min, the off-white crystals were filtered, washed with ice-cold 2-propanol, and recrystallized from 2-propanol to give **4a** (0.98 g, 78%): mp 116–118 °C; ^{1}H (DMSO) 7.55–7.60 (m, 3H), 7.37–7.49 (m, 7H), 7.28 (dd, J = 3, 3 Hz, 1H), 6.42 (dd, J = 3, 3 Hz, 1H), 4.36 (s, 2H), 3.30 (d, J = 12 Hz, 2H), 3.18 (d, J = 14 Hz, 2H), 2.22 (m, 2H), 1.76 (d, J = 14 Hz, 2H). Anal. ($C_{26}H_{27}N_2O_5Cl$) C, H, N.

1-Phenyl-8-[[3-(1-phenylpyrrolyl)]methyl]-1,3,8-triazaspiro[4.5]decan-4-one oxalate (4b): ^{1}H (DMSO) 9.0 (s, 1H), 7.4–7.6 (m, 6H), 7.28 (dd, J = 7, 7 Hz, 1H), 7.20 (dd, J = 8, 8 Hz, 2H), 6.92 (d, J = 8 Hz, 2H), 6.75 (dd, J = 7, 7 Hz, 1H), 6.44 (s, 1H), 4.60 (s, 2H), 4.20 (s, 2H), 3.62 (dd, J = 7, 7 Hz, 2H), 3.42 (d, J = 8 Hz, 2H), 2.83 (m, 2H), 1.85 (d, J = 15 Hz, 2H). Anal. ($C_{26}H_{28}N_4O_5$) C, H, N.

1-[[3-(1-Phenylpyrrolyl)]methyl]-4-(2-keto-1-benzimidazolinyl)piperidine oxalate (4c): ^{1}H (DMSO) 10.9 (s, 1H), 7.58 (d, J = 7 Hz, 2H), 7.42–7.52 (m, 4H), 7.31 (m, 1H), 7.27 (dd, J = 7, 7 Hz, 1H), 6.96 (m, 3H), 6.40 (s, 1H), 4.42 (m, 1H), 4.05 (s, 2H), 3.42 (d, J = 12 Hz, 2H), 2.90 (m, 2H), 2.6 (dd, J = 12, 6 Hz, 2H), 1.82 (m, 2H). Anal. ($C_{25}H_{26}N_4O_5$) C, H, N.

1-(2-Methoxyphenyl)-4-[[3-(1-phenylpyrrolyl)]methyl]-piperazine oxalate (4d): ^{1}H (DMSO) 7.58 (d, J = 8 Hz, 2H), 7.42–7.50 (m, 4H), 7.26 (dd, J = 7, 7 Hz, 1H), 6.84–7.0 (m, 4H), 6.39 (s, 1H), 4.13 (s, 2H), 3.75 (s, 3H), 3.0–3.3 (b, 8H). Anal. ($C_{24}H_{27}N_3O5$) C, H, N.

1-(2-Pyridyl)-4-[[3-(1-phenylpyrrolyl)]methyl]piperazine oxalate (4e): ^{1}H (DMSO) 8.12 (dd, J = 4, 1 Hz, 1H), 7.4–7.58 (m, 7H), 7.26 (dd, J = 8, 7 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 6.70 (dd, J = 7, 5 Hz, 1H), 6.37 (s, 1H), 4.05 (s, 2H), 3.70 (m, 4H), 3.10 (m, 4H). Anal. ($C_{22}H_{24}N_4O_4$) C, H, N.

1-Phenyl-4-[[3-(1-phenylpyrrolyl)]methyl]piperazine oxalate (4f): ^{1}H (DMSO) 7.57 (d, J = 7 Hz, 2H), 7.42–7.49 (m, 4H), 7.27 (dd, J = 7, 7 Hz, 2H), 7.23 (dd, J = 7, 7 Hz, 2H), 6.95 (dd, J = 8 Hz, 2H), 6.82 (dd, J = 7, 7 Hz, 1H), 6.37 (s, 1H), 4.05 (s, 2H), 3.35 (m, 4H), 3.10 (m, 4H). Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

1-Phenyl-3-[[1-[4-hydroxy-4-[3-(trifluoromethyl)phenyl]-piperidinyl]]methyl]pyrrole oxalate (4g): ^{1}H (DMSO) 7.79 (m, 1H), 7.72 (m, 1H), 7.58–7.64 (m, 5H), 7.49 (d, J = 8 Hz, 2H), 7.45 (dd, J = 3, 1 Hz, 1H), 7.28 (dd, J = 7, 7 Hz, 1H), 6.44 (s, 1H), 4.22 (s, 2H), 3.2–3.4 (m, 4H), 2.25 (m, 2H), 1.80 (d, J = 13 Hz, 2H). Anal. ($C_{25}H_{25}N_2O_4F_3$) H, N; C: calcd, 61.22; found, 60.75.

4-Phenyl-1-[[3-(1-phenylpyrrolyl)]methyl]-1,2,3,6-tetrahydropyridine oxalate (4h): ^{1}H (DMSO) 7.58 (m, 3H), 7.44–7.50 (m, 5H), 7.36 (dd, J = 8, 8 Hz, 2H), 7.29 (dd, J = 12, 7 Hz, 2H), 6.42 (s, 1H), 6.18 (m, 1H), 4.20 (s, 2H), 3.78 (m, 2H), 3.30 (bm, 2H), 2.75 (m, 2H). Anal. ($C_{24}H_{24}N_2O_4$) C, H, N.

4-Phenyl-1-[[3-(1-phenylpyrrolyl)]methyl]piperidine oxalate (4i): ^{1}H (DMSO) 7.58 (d, J = 8 Hz, 2H), 5.54 (s, 1H), 7.43–7.50 (m, 3H), 7.18–7.32 (m, 6H), 6.41 (s, 1H), 6.12 (s, 2H), 3.45 (d, J = 12 Hz, 2H), 2.95 (m, 2H), 2.78 (m, 1H), 1.85 (m, 4H). Anal. ($C_{24}H_{26}N_2O_4$) C, H, N.

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