2-Phenylpyrroles as Conformationally Restricted Benzamide Analogues. A New Class of Potential Antipsychotics. 2

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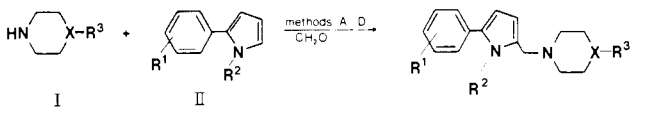
A series of 2-phenylpyrrole Mannich bases was synthesized and screened in pharmacological models for antipsychotic activity and extrapyramidal effects. Structure modifications of 5-(4-fluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (1), the prototype of a new class of sodium-independent atypical dopamine D-2 antagonists, resulted in 2-[[4-(7-benzofuranyl)-1-piperazinyl]methyl]-5-(4-fluorophenyl)pyrrole (15), which was an even more potent and selective D-2 antagonist than the parent compound. The excellent oral activity in the apomorphine-induced climbing behavior and the conditioned avoidance response tests and the absence of catalepsy make this compound particularly promising as a potential antipsychotic with a low propensity to induce acute extrapyramidal side effects.

Since the discovery of the antipsychotic properties of chlorpromazine,[1] a variety of neuroleptic drugs, belonging to different chemical classes, e.g., phenothiazines, butyrophenones, and benzamides, have been introduced in psychiatry.[2] All these agents interfere, mainly via a blockade of dopamine D-2 receptors, with dopaminergic transmission in the brain.[3] This characteristic is responsible not only for reducing the symptoms of schizophrenic disorders, but also for producing neurological side effects, including parkinsonism and tardive dyskinesia.[4] The class of the substituted benzamides, with sulpiride as the prototype, however, differentiates from the other (classical) neuroleptic drugs by a large separation between the dose that is effective in inhibiting apomorphine-induced behavior patterns (index for antipsychotic activity) and the doses inducing catalepsy (index for acute extrapyramidal side effects).[5] Since this atypical pharmacological profile of sulpiride seems to have been confirmed in humans,[6] the search for new substituted benzamides has been intensified.[7] Recently, potent and more lipophilic analogues of sulpiride have been synthesized as potential antipsychotics with a low propensity to induce extrapyramidal side effects, e.g., eticlopride,[8a] raclopride,[8b] tropapride,[8c] and YM 09151-2.[8d] The differences in pharmacological profile between the atypical and typical neuroleptics cannot simply be attributed to differences in pharmacokinetics. Both types penetrate the central nervous system (CNS) and are selectively bound to dopamine D-2 receptors in dopamine-rich areas.[9]

As the in vitro binding of the benzamides, in contrast to the classical neuroleptics, is strongly dependent on the presence of sodium ions, an interaction with a sodium-dependent subpopulation or conformation of the dopamine D-2 receptors has generally been accepted to explain the atypical pharmacological profile.[10] In a previous paper we have described the synthesis and pharmacological properties of a series of substituted 2-phenylpyrroles as conformationally restricted analogues of the benzamides and the butyrophenones.[11] Whereas dopaminolytic activity and sodium dependency were maintained in the 2-phenylpyrrole analogues of sultopride, the Mannich base of 2-(4-fluorophenyl)pyrrole with the pharmacophoric 4-(2-methoxyphenyl)piperazine moiety of fluanisone also displayed an atypical pharmacological profile, but the D-2 binding was only marginally sodium dependent.[11] This compound was further characterized by a high affinity and selectivity for the D-2 receptors and an excellent oral activity. We now report the structure–activity relationship of a series of Mannich bases of substituted 2-phenylpyrroles with a variety of substituted arylpiperazines and piperidines.

Scheme I



The compounds **1–22**, together with reference compounds, were screened in pharmacological models relevant for antipsychotic activity: affinity for dopamine D-2 receptors, inhibition of the apomorphine-induced climbing behavior in mice, and the suppression of the conditioned avoidance response in rats (Table III). Compounds **1** and **15**, together with their benzamide (**23** and **24**, respectively),

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(2) (a) Gschwend, H. W. In *Industrial Pharmacology*; Fielding, S., Lal, H., Eds.; Futura Publishing: New York, 1974; Vol. I, pp 1–51. (b) Enna, S. J.; Coyle, J. T. In *Neuroleptics: Neurochemical, Behavioral, and Clinical Perspectives*; Coyle, J. T., Enna, S. J., Eds.; Raven: New York, 1983; p 1.
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(7) Vinick, F. J.; Kozlowski, M. R. *Annu. Rep. Med. Chem.* **1986**, *21*, 1.
(8) (a) De Paulis, T.; Hall, H.; Ögren, S.-O. *Eur. J. Med. Chem.* **1985**, *20*, 273. (b) De Paulis, T.; Kumar, Y.; Johansson, L.; Rämsby, S.; Hall, H.; Sällemark, M.; Ängeby-Möller, K.; Ögren, S.-O. *J. Med. Chem.* **1986**, *29*, 61. (c) Rumigny, J.-F.; Benedetti, M. S.; Dostert, P. *J. Pharm. Pharmacol.* **1984**, *36*, 373. (d) Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224.
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(10) (a) Stefanini, E.; Marchisio, A. M.; Devoto, P.; Vernaleone, F.; Collu, R.; Spano, P. F. *Brain Res.* **1980**, *198*, 229. (b) Theodorou, A. E.; Hall, M. D.; Jenner, P.; Marsden, C. D. *J. Pharm. Pharmacol.* **1980**, *32*, 441. (c) Garau, L.; Govoni, S.; Stefanini, E.; Trabucchi, M.; Spano, P. F. *Life Sci.* **1978**, *23*, 1745. (d) Jenner, P.; Marsden, C. D. *Neuropharmacology* **1981**, *20*, 1285.
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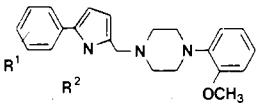
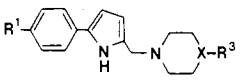
Table I. Structures and Physical Constants of Substituted 2-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]-5-phenylpyrroles 1–12



compd	R^1	R^2	method[a]	yield,[b] %	mp, °C	formula	anal.
1	4-F	H	A	66	116–118.5[c]		
2	H	H	A	75	125–127[d]	$C_{22}H_{25}N_3O$	H, N, C[e]
3	4-CF_3	H	B	81	55–60[d]	$C_{23}H_{24}F_3N_3O$	C, H, F, N
4	4-$CH(CH_3)_2$	H	A	63	129–131	$C_{25}H_{31}N_3O$	C, H, N
5	3-Cl	H	A	75	114–116	$C_{22}H_{24}ClN_3O\cdot H_2O$	C, H, N
6	2-OCH_3	H	A	70	107–108	$C_{23}H_{27}N_3O_2\cdot 0.5H_2O$	C, H, N
7	2-OCH_3, 5-$SO_2C_2H_5$	H	B	79	122–124[c]		
8	2,6-F_2	H	A	30	oil[d]	$C_{22}H_{23}F_2N_3O$	
9	4-F	CH_3	B	60	111–113	$C_{23}H_{26}FN_3O$	C, H, F, N
10	4-F	n-C_3H_7	D	33	oil[d]	$C_{25}H_{30}FN_3O$	
11	4-F	$(CH_2)_2OH$	D	61	139–140	$C_{24}H_{28}FN_3O_2$	C, H, F, N
12	H	C_6H_5	D	65	100–102[d]	$C_{28}H_{29}N_3O\cdot 0.5H_2O$	C, H, N

[a] See the Experimental Section. [b] After chromatographic purification. [c] Taken from ref 11. [d] Spectroscopic details are given in the Experimental Section. [e] C: calcd, 76.05; found, 75.45.

Table II. Structures and Physical Constants of Substituted 2-[(1-Piperazinyl)methyl]- and 2-[(1-Piperidinyl)methyl]-5-phenylpyrroles (13–18 and 19–22, Respectively)



compd	R^1	X	R^3	method[a]	yield,[b] %	mp, °C	formula	anal.
13	F	N	3-$CF_3C_6H_4$	A	66	88–92	$C_{22}H_{21}F_4N_3$	C, H, F, N
14	F	N	4-FC_6H_4	A	71	89–93	$C_{21}H_{21}F_2N_3$	C, H, N
15	F	N	7-Bzf[c]	C	90	118–119[d]	$C_{23}H_{22}FN_3O\cdot 0.33(i\text{-}Pr)_2O$	C, H, N
16	H	N	6-Bdp[e]	A	55	151–155	$C_{24}H_{27}N_3O_2\cdot 1.1HCl\cdot 0.5H_2O$	C, H, Cl, N
17	F	N	4-FC_6H_4CO	C	70	121–122	$C_{22}H_{21}F_2N_3O$	C, H, F, N
18	F	N	$(CH_2)_2OH$	A	62	oil[d]	$C_{17}H_{22}FN_3O$	
19	H	CH	2-$MeOC_6H_4$	A	60	117–122	$C_{23}H_{26}N_2O\cdot 0.5H_2O$	H, N, C[f]
20	F	CH	C_6H_5	A	66	102–103	$C_{22}H_{23}FN_2\cdot 0.4H_2O$	C, H, F, N
21	F	C(OH)	4-ClC_6H_4	B	82	180.5–182.5[g]		
22	F	CH	4-FC_6H_4CO	A	68	135–139	$C_{23}H_{22}F_2N_2O$	C, H, F, N

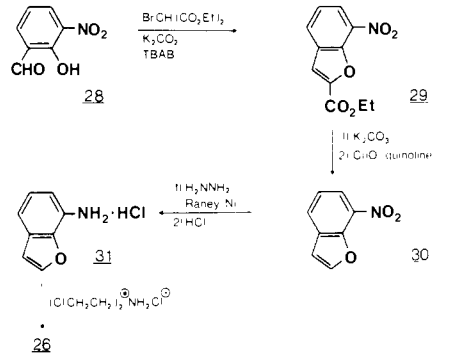
[a] See Table I, note *a*. [b] See Table I, note *b*. [c] 7-Benzofuranyl. [d] See Table I, note *d*. [e] 3,4-Dihydro-2*H*-1,5-benzodioxepin-6-yl. [f] C: calcd, 77.71; found, 78.43. [g] See Table I, note *c*.

and butyrophenone (fluanisone and **25**, respectively) analogues were screened for their potential to induce catalepsy (index for extrapyramidal side effects). The presence of sodium dependency as well as selectivity for the dopamine D-2 receptors in these compounds was assayed by in vitro radioligand displacement experiments (Table IV).

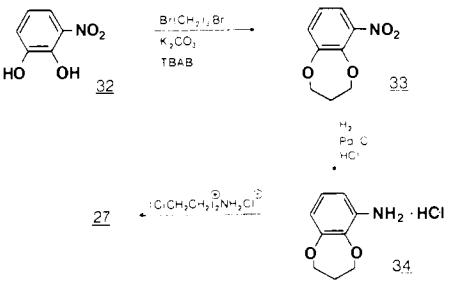
Chemistry. 2,5-Disubstituted pyrroles **1–22** were conveniently synthesized by Mannich type reactions. Secondary amines I were treated with formaldehyde and 2-phenylpyrroles II (Scheme I). The reaction could be performed either in refluxing ethanol (method A) or in the presence of acetic acid (1–2 equiv) in ethanol at room temperature (methods B and C). In the case of the less reactive 1-substituted pyrroles (II; $R^2 \neq H$), the coupling reaction was preferably carried out with acetic acid in refluxing ethanol (method D). The results for 1-(2-methoxphenyl)piperazine (I; X = N, R^3 = 2-methoxyphenyl) are given in Table I. The products derived from other 1-substituted piperazines (I; X = N) and 4-substituted piperidines [I, X = CH or C(OH)] are presented in Table II. In general, the yields ranged from 60 to 80% and only 2,5-disubstituted products were obtained, confirming the known preference for free α-positions in electrophilic substitution reactions of pyrroles.[12] Physical and spectroscopic properties of the compounds **1–22** are collected in Tables I and II and in the Experimental Section.

(12) Gossauer, A. In *Die Chemie der Pyrrole*; Springer: Berlin, 1974.

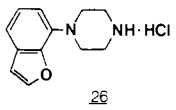
Scheme II



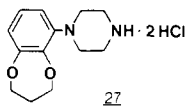
Scheme III



The synthetic routes for the unknown 1-(7-benzofuranyl)piperazine (**26**) and 1-(3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazine (**27**) are presented in Schemes II and III, respectively.



26



27

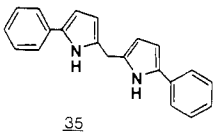
A key intermediate for the synthesis of **26** is 7-nitrobenzofuran (**30**). The scarce data in the literature on **30**[13] suggest a synthetic route starting from 3-nitrosalicylaldehyde (**28**). Alkylation of this strongly acidic phenol with diethyl bromomalonate could be accomplished under phase-transfer conditions with powdered K_2CO_3 in toluene.[14] By prolonged heating at reflux temperature ethyl 7-nitrobenzofuran-2-carboxylate (**29**) was formed in a one-step process in excellent yield (see the Experimental Section). After saponification and decarboxylation with *catalytic* amounts of cuprous oxide in quinoline,[15] **30** was obtained. Chemoselective reduction of the nitro group to **31** could be achieved nearly quantitatively with hydrazine/Raney nickel.[16,17] Finally, aniline **31** was converted into arylpiperazine **26** by reaction with bis(2-chloroethyl)ammonium chloride in refluxing chlorobenzene.[18]

The preparation of **27** started with the cycloalkylation of 3-nitrocatechol (**32**) with 1,3-dibromopropane, again proceeding efficiently under phase-transfer conditions.[14] Subsequent conversion of **33** into aniline **34** and piperazine **27**[18] proceeded conveniently.

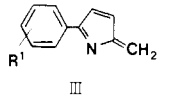
Unknown 2-phenylpyrroles II were prepared by ring closure of the corresponding 4-oxo-4-phenylbutanals, according to the method described by Berner.[19]

The benzamides **23** and **24** were prepared according to the literature by reaction of the appropriate piperazines with *N*-(4-fluorobenzoyl)aziridine.[20] Butyrophenone **25** was obtained by alkylation of **26** with 4-chloro-4′-fluorobutyrophenone.

Formation of Dipyrrylmethanes. The formation of symmetric di(2-pyrryl)methanes as side products from hydroxymethylation and Mannich reactions on pyrroles is well documented.[12,21] The same products may be formed upon treatment of 2-(hydroxymethyl)pyrroles and 2-[(dialkylamino)methyl]pyrroles with acids.[12,21] Indeed, in the Mannich reactions with 1-unsubstituted pyrroles (II, R^2 = H) small quantities of apolar side products were observed. Isolation in the case of II, $R^1 = R^2$ = H yielded bis(5-phenyl-2-pyrryl)methane **35** (Experimental Section).[22] Apparently, azafulvene-type intermediates III are involved.[12,21]



35



III

We also studied the occurrence of these type of products by acid-catalyzed disproportionation reactions in aqueous solution of a number of representative Mannich bases (piperazines **1**, **15**, and **16**, and piperidines **19** and **21**).[23] At pH 5 no decomposition was observed, and at pH 2 only **1** and **16** were slowly converted into the corresponding dipyrrylmethanes and arylpiperazines I (about 50% and

Table III. Inhibition of [^{3}H]Spiperone-Striatum Binding (D-2 Receptors), Antagonism of Apomorphine-Induced Climbing Behavior in Mice, and Suppression of Conditioned Avoidance Behavior in Rats of Substituted 2-(Aminomethyl)-5-phenylpyrroles **1**–**22**

compd	D-2 [^{3}H]spiperone binding: K_i,[a] nM	apomorphine antag in mice: ED_{50},[b] mg/kg po	apomorphine antag in mice: ED_{50},[b] mg/kg ip	suppression of cond avoid. in rats: ED_{50},[c] mg/kg po	suppression of cond avoid. in rats: ED_{50},[c] mg/kg ip
1	0.96 ± 0.18	0.9	0.2	8.5	2.3
2	0.76 ± 0.12	3.0	0.4	13	1.9
3	25 ± 2.0	12		45	
4	59 ± 13	>100			>100
5	4.4 ± 1.3	5.7		>100	
6	6.5 ± 1.7	14			>100
7	7.0 ± 1.3	35			>20
8	1.1 ± 0.3	4.5		30	
9	20	34			
10	110 ± 14	76			>50
11	52 ± 8.0	>100		>100	
12	160 ± 20	>100		>100	
13	19 ± 3.2	2.0		21	
14	16 ± 2.3	22		40	
15	0.45 ± 0.05	2.3	2.3	2.5	5.4
16	0.68 ± 0.12	2.3	0.2	12	
17	120 ± 12	18		34	
18	31000 ± 8000	>100			>100
19	1.00 ± 0.05	9.6	1.7	100	
20	11 ± 2.1	8.4			>100
21	1100 ± 100	51	25	>50	>20
22	12 ± 3.5	1.0		34	
fluanisone	2.4 ± 0.8	25	0.4	>50	2.2
haloperidol	1.4 ± 0.05	0.24	0.08	0.80	0.45

[a] K_i (±SEM) values are based on three to six assays, each using four to six concentrations in triplicate; for **9** only one assay. [b] Test compounds were administered po 60 min or ip 30 min prior to apomorphine (1 mg/kg sc) to groups of five animals; the ED_{50} values are based on at least three dose levels. [c] Test compounds were administered po 60 min or ip 30 min before measurement to groups of 12 animals; the ED_{50} values are based on at least three dose levels.

(13) (a) Tanaka, S. *J. Chem. Soc. Jpn.* **1952**, *73*, 282; *Chem. Abstr.* **1953**, *47*, 9957*f*. (b) Rao, A. A.; Rao, N. V. S. *Symp. Syn. Heterocycl. Compounds Physiol. Interest* (Hyderabad, India 1964) 1966, 26; *Chem. Abstr.* **1968**, *69*, 18955*z*. (c) Brown, E. V.; Coleman, R. L. *J. Med. Chem.* **1973**, *16*, 717. (d) Royer, R.; Lamotte, G.; Demerseman, P.; Cavier, R.; Lemoine, J. *Eur. J. Med. Chem.-Chim. Ther.* **1978**, *13*, 411.

(14) This method has been developed for the alkylation of nonreactive phenols, see: Kruse, C. G.; Troost, J. J.; Bouw, J. P. *Book of Abstracts ESOC III* (Canterbury 1983), PC 20.

(15) The use of a catalytic amount of CuO is essential for obtaining high yields, since the starting carboxylic acid serves as a proton donor for the intermediate arylcuprate; see: Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229.

(16) By applying standard catalytic hydrogenation conditions (Pd/C or Raney Ni),[13,14] we observed partial reduction of the furan ring, resulting in the 2,3-dihydro derivative of **31**.

(17) Yuste, F.; Saldana, M.; Walls, F. *Tetrahedron Lett.* **1982**, *23*, 147.

(18) Standard methods for the conversion of anilines into arylpiperazines in protic solvents and in the presence of base gave very poor results; see, e.g., Brewster, K.; Coult, D. B.; Pinder, R. M. *Eur. J. Med. Chem.-Chim. Ther.* **1972**, *7*, 87.

(19) (a) Berner, H.; Schulz, G.; Reinshagen, H. *Monatsh. Chem.* **1977**, *108*, 285. (b) Full experimental details of the new methods applied for the synthesis of 4-oxobutanals have been published elsewhere: Kruse, C. G.; Bouw, J. P.; Van Hes, R.; Van de Kuilen, A.; Den Hartog, J. A. J. *Heterocycles* **1987**, *26*, 3141.

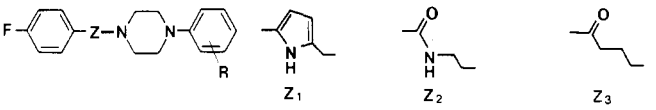
(20) Soudijn, W.; Van Wijngaarden, I.; Janssen, P. A. J. (to Janssen Pharm., N.V.) German Patent Appl. 2 636 614, 1977.

(21) Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles*; Academic: London, 1977.

(22) TLC spots and solutions of **35** and aryl-substituted derivatives rapidly developed a purple color, apparently due to air oxidation to the corresponding dipyrrylmethenes.[12,21]

(23) Solutions (0.1% by weight) in water–10% dimethylformamide with pH 5 and pH 2 were kept at 20 °C. Aliquots were quenched with 2 N KOH–ethyl acetate, and the organic layer was analyzed with TLC (dichloromethane–methanol, 95:5 as eluent); R_f values for dipyrrylmethanes, Mannich bases, and cyclic secondary amines I are about 0.8, 0.4 and 0.1, respectively).

Table IV. Structures and Pharmacological Profile of Substituted 2-[(4-Aryl-1-piperazinyl)methyl]-5-(4-fluorophenyl)pyrroles 1 and 15, Compared to the Corresponding Benzamides 23 and 24, and Butyrophenones Fluanisone and 25



compd	Z	R	D-2 [^{3}H]spiperone binding: K_i,[a] nM	D-2 [^{3}H]spiperone binding: Na^+ ratio[b]	α_1 [^{3}H]WB-4101 binding: K_i,[a] nM	5-HT_2 [^{3}H]spiperone binding: K_i,[a] nM	apomorphine antag in mice: ED_{50},[c] mg/kg po	apomorphine antag in mice: ED_{50},[c] mg/kg ip	suppression of cond avoid. in rats: ED_{50},[d] mg/kg po	suppression of cond avoid. in rats: ED_{50},[d] mg/kg ip	induct. of catalepsy in rats: ED_{50},[e] mg/kg ip
1	Z_1	2-OCH_3	0.96 ± 0.18	2.3 ± 0.5	57 ± 10	310 ± 40	0.9	0.2	8.5	2.3	>23
23	Z_2	2-OCH_3	4.3 ± 0.7	3.1 ± 0.5	9.0 ± 2.7	700 ± 150	15	0.4	30	0.7	>7.4
fluanisone	Z_3	2-OCH_3	2.4 ± 0.8	1.4 ± 0.3	0.87 ± 0.04	52 ± 11	25	0.4	>50	2.2	≥22[f]
15	Z_1	2,3-OCH=CH	0.45 ± 0.05	2.0 ± 0.4	220 ± 20	120 ± 24	2.3	2.3	2.5	5.4	>54
24	Z_2	2,3-OCH=CH	7.1 ± 1.9	2.5 ± 0.7	9.7 ± 0.2	29 ± 6	21	1.8	21	2.7	>30
25	Z_3	2,3-OCH=CH	5.1 ± 1.1	1.4	1.5 ± 0.2	8.2 ± 2.3	11	5	7.6	5.6	

[a] See Table III, note *a*. [b] Calculated as IC_{50} ($+Na^+$)/IC_{50} ($-Na^+$)(±SEM) from two to four experiments; for **25** only one experiment. [c] See Table III, note *b*. [d] See Table III, note *c*. [e] Test compounds were administered ip 4 h prior to measurement to groups of nine animals; the ED_{50} values are based on at least three dose levels. [f] In this dose 40% of the animals showed catalepsy.

25% conversion after 6 h, respectively).

These results underline the observation that no reproducibility problems have been encountered during in vitro and in vivo pharmacological testing of compounds **1–22**.

Pharmacology. The results of in vitro binding studies and in vivo dopamine-antagonistic activities of compounds **1–22**, representing a series of different structural modifications of the lead compound (**1**), are presented in Table III.

Compound **1** shows a high affinity for the D-2 receptors. The potency in displacing [^{3}H]spiperone from its binding sites is 2.5 times that of fluanisone and 1.5 times that of haloperidol. Omission of the 4-fluorine atom of compound **1** in **2** hardly influences the in vitro D-2 receptor affinity. Introduction at the 4-position of bulky groups such as the trifluoromethyl (**3**) or the isopropyl (**4**) substituent results in loss of affinity by a factor of at least 25, analogous with the butyrophenone series.[24] The 3-chloro (**5**) and the 2-methoxy (**6**), as well as the 2-methoxy-5-ethylsulfonyl (**7**), derivatives display rather good affinity. The 2,6-difluoro substituted derivative **8** shows a similar high affinity compared to the unsubstituted and 4-fluoro analogues. The high affinity of compounds **1**, **2**, and **8** is also reflected in the in vivo models for antipsychotic activity. After ip injection, compounds **1** and **2** are equipotent to fluanisone both in mice and rats. Orally, however, **1**, **2**, and **8** are superior to fluanisone. The improved oral absorption is most striking for **1**. The po/ip ratio of this compound in mice is about 4, similar to that of haloperidol (ratio = 3) and significantly better than that of fluanisone (ratio = 60). A similar increase in oral absorption is seen in the conditioned avoidance response test (CAR) in rats. The in vivo activity of **3** is significantly better than expected from the receptor binding data, but the results with **4–7** in the CAR are disappointing.

In analogy to the substituted benzamides,[25] alkylation of the nitrogen atom of the pyrrole ring is not favorable for dopamine antagonistic activity. Introduction of a methyl, propyl, or a 2-hydroxyethyl group in compounds **9–11**, respectively, lowers the affinity for the dopamine D-2 receptors by a factor of 20 (**9**) to 100 (**10**). Weak in vivo activity can be observed after oral administration of compounds **9** and **10** to mice. Dopamine antagonistic activity is also markedly reduced by N-arylation (**12**).

Replacement of the 2-methoxy group of the phenylpiperazine moiety of **1** by a 3-trifluoromethyl (**13**) or a 4-fluoro (**14**) substituent decreases the affinity for the D-2 receptors by a factor of about 20. Compound **13** shows a favorable oral activity in both species.

Fixation of the 2-methoxy group into a benzofuran (**15**) or a 3,4-dihydro-2*H*-1,5-benzodioxepine ring (**16**) results in highly potent compounds. The in vitro affinity of **15** is twice that of compound **1**. Both compounds are also very active in vivo. The oral absorption of **15** is optimal (ratio po/ip about 1).

Replacement of the 4-fluorophenyl substituent of the piperazine ring in **14** by a 4-fluorobenzoyl group in **17** decreases the affinity by a factor of 8. The in vivo potency of both compounds is comparable. Replacement of the aryl substituent at the piperazine ring by a 2-hydroxyethyl group (the amine-containing moiety in many tricyclic neuroleptics, e.g., fluphenazine), results in an inactive compound **18**.

The piperidine analogue (**19**) of compound **2** displays the same high affinity for the D-2 receptors as its piperazine congener. The activity in vivo, however, falls behind that of compound **2**. The unsubstituted 4-phenylpiperidine derivative **20** still has rather good affinity. This activity is also seen in vivo, but in mice only. Combining the 2-(4-fluorophenyl)pyrrole side chain with 4-(4-chlorophenyl)-4-hydroxypiperidine, the amine containing moiety of haloperidol, in compound **21** is detrimental for the activity in vitro. Weak in vivo activity is seen in mice only. On the other hand the combination of the 2-(4-fluorophenyl)pyrrole side chain with 4-(4-fluorobenzoyl)-piperidine, the amine containing part of lenperone, (compound **22**) shows high in vivo dopamine antagonistic activity. Except for the oral activity in rats, compound **22** is also more potent than its piperazine analogue **17**.

The compounds with nanomolar affinity of this series (**1**, **2**, **15**, **16**, and **19** in contrast to **13**, **14**, and **20**) all possess an oxygen atom at the ortho position of the piperazine aryl substituent, indicating an additional contribution of this structural feature to the thermodynamics of the receptor interaction.

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Table IV summarizes the pharmacological profile of the most potent 2-phenylpyrrole derivatives **1** and **15**, the corresponding benzamides **23** and **24**, and the butyrophenones fluanisone and **25**, respectively. In vitro, **15** is a more potent and selective dopamine D-2 antagonist than **1**. The potency to displace [^{3}H]spiperone from the dopamine binding sites is twice that of the 2-(methoxyphenyl)piperazine analogue **1**, whereas the affinity for the α_1-adrenergic receptors is decreased by a factor of 4. The affinity for the serotonin 5-HT_2 receptors of both phenylpyrrole compounds is rather weak in comparison to the affinity for the dopamine D-2 receptors (ratio 5-HT_2/D-2 about 300).

The restricted conformational flexibility of **1**[11] and **15** in comparison to the corresponding benzamides and butyrophenones is reflected by their pronounced selectivity for D-2 receptors. Whereas the phenylpyrroles show the highest affinity for D-2 receptors, the butyrophenone analogues display the highest affinity for the α_1-adrenergic receptor. For fluanisone and **25** the ratio α_1/D-2 is 0.3, which is in sharp contrast to the ratio of **1** (ratio α_1/D-2 about 60) and **15** (ratio α_1/D-2 about 500). The corresponding benzamides **23** and **24** show similar affinities for D-2 and α_1-receptors. The butyrophenones are also the most effective displacers of spiperone from the 5-HT_2 sites. The binding to the D-2 receptors of the two 2-phenylpyrrole derivatives as well as the corresponding benzamides and butyrophenones, does not appear to be significantly dependent on the presence of sodium ions in the incubation mixture.

The oral absorption of both 2-phenylpyrroles **1** and **15** is significantly better than that of the corresponding benzamides and butyrophenones.

When tested at a relatively high dose of 10 times the effective dose in the CAR, the compounds **1**, **15**, **23**, and **24** did not induce any catalepsy.

In conclusion, structural modification of 5-(4-fluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-pyrrole (**1**) resulted in 2-[[4-(7-benzofuranyl)-1-piperazinyl]methyl]-5-(4-fluorophenyl)pyrrole (**15**) being a more potent and selective compound. The high in vivo dopamine antagonistic activity and the low potential to induce catalepsy make the 2-phenylpyrrole benzofuranylpiperazine derivative an interesting member of this class of sodium-independent, atypical dopamine D-2 antagonists. It may be particularly useful as an antipsychotic with a low propensity to evoke acute extrapyramidal side effects. Further pharmacological evaluation of **15** is in progress.

Experimental Section

Chemistry. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP-200 or AM400 instrument in $CDCl_3$ (unless noted otherwise). Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (J) are in hertz. Elemental analyses were performed at the TNO laboratory of Organic Chemistry, Utrecht, The Netherlands, and were within 0.5% (C) and 0.4% (other elements) of the theoretical values. Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates in dichloromethane containing 1–5% methanol. For normal pressure and flash chromatography, Merck silica gel type 60 (size 70–230 and 230–400 mesh, respectively) was used. Unless stated otherwise, starting materials were used as high-grade commercial products. 4-(4-Fluorobenzoyl)piperidine,[26] 1-(4-fluorobenzoyl)piperazine,[27] 4-(2-methoxyphenyl)piperidine,[28] *N*-(4-fluorobenzoyl)aziridine,[29] substituted 2-phenylpyrroles IV,[19] and compound **23**[11] were prepared according to literature procedures.

General Procedures for Mannich Reactions. For each of the methods A–D one representative example will be given.

Method A. 2-[[4-(2-Methoxyphenyl)-1-piperazinyl]-methyl]-5-phenylpyrrole (2). To a solution of 1-(2-methoxyphenyl)piperazine (2.88 g, 0.015 mol) in absolute ethanol (60 mL) was added aqueous formaldehyde (37%, 1.13 mL, 0.015 mol). After 30 min of stirring at 20 °C, the 2-phenylpyrrole (II, R^1 = R^2 = H; 2.15 g, 0.015 mol)[19] was added, and the solution was refluxed for 4 h. TLC analysis showed complete conversion to product. The solvent was evaporated, and the crude product was purified by flash chromatography (dichloromethane–methanol, 98:2), yielding 3.90 g (75%) pure **2**. Crystallization was effected by stirring the product with petroleum ether (40–60 °C) (melting point and elemental analysis, see Table I): ^{1}H NMR δ 2.68 (m, 4 H, H-2′,6′), 3.06 (m, 4 H, H-3′,5′), 3.59 (s, 2 H, NCH_2), 3.83 (s, 3 H, OCH_3), 6.13 (m, 1 H, H-3), 6.43 (m, 1 H, H-4), 6.85–7.0 (m, 4 H, CH_3OAr H), 7.15 (tt, 1 H, Ar H-4, J = 7 and 1.5), 7.32 (m, 2 H, Ar H-3,5), 7.44 (m, 2 H, Ar H-2,6), 9.0 (br s, 1 H, NH); ^{13}C NMR δ 50.5 and 53.4 (C-2′,6′ and 3′,5′), 55.3 (OCH_3), 55.6 (NCH_2), 105.6, 109.8, 129.4 and 132.1 (C-4,3,2 and 5), 111.2, 118.2, 121.0, 123.0, 141.2 and 152.5 (OCH_3Ar C), 123.7, 125.9, 128.8 and 132.9 (Ar C).

Similarly the compounds **1**,[11] **4–6**, **8**, **13**, **14**, **16**, **18–20**, and **22** were prepared in the yields indicated in Tables I and II. In each case pure products were obtained by flash chromatography with dichloromethane containing 1–5% methanol as eluent. In all cases (except for **8** and **18**), the products slowly crystallized (as the free bases) upon standing at 20 °C under a nitrogen atmosphere or by treatment with an apolar organic solvent such as petroleum ether or diisopropyl ether. In the case of **16**, the HCl salt was prepared by treatment with 1 equiv of HCl in ethanol and subsequent crystallization from ethyl acetate.

5-(2,6-Difluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (8): ^{13}C NMR δ 50.7 and 53.4 (C-2′,6′ and C-3′,5′), 55.3 (OCH_3), 55.5 (NCH_2), 108.8, 112.2, 120.0 and 130.5 (C-4,3,5 and 2), 111.2, 118.2, 121.0, 122.9, 141.4 and 152.3 (OCH_3Ar C), 112.0, 112.3, 125.6 and 159.1 (FAr C).

5-(4-Fluorophenyl)-2-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]pyrrole (18): ^{13}C NMR δ 52.6 (C-2′,3′,5′,6′), 55.3 (NCH_2), 58.0, 59.8 (NCH_2CH_2OH), 105.3, 110.4, 128.0 and 131.7 (C-4,3,2 and 5), 115.5, 125.5, 128.5, 161.2 (FAr C).

Method B. 5-[4-(Trifluoromethyl)phenyl]-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (3). To a solution of 1-(2-methoxyphenyl)piperazine (1.54 g, 0.008 mol) in absolute ethanol (45 mL) was added aqueous formaldehyde (37%, 0.60 mL, 0.008 mol). After 30 min of stirring at 20 °C, 2-[4-(trifluoromethyl)phenyl]pyrrole (II, R^1 = 4-CF_3, R^2 = H; 1.69 g, 0.008 mol)[19] and then acetic acid (0.46 mL, 0.008 mol) were added, and stirring was continued at 20 °C for 16 h. After evaporation of the solvent, the residue was taken up in dichloromethane (25 mL). The solution was extracted with 2 N NaOH (2 × 10 mL) to remove the acid. Then the organic layer was dried (Na_2SO_4) and concentrated, giving crude **3**, which was obtained pure and crystalline after flash chromatography (dichloromethane–methanol, 99:1), 2.7 g (81%) (melting point and elemental analysis, see Table I): ^{1}H NMR δ 2.73 (m, 4 H, H-2′,6′), 3.10 (m, 4 H, H-3′,5′), 3.64 (s, 2 H, NCH_2), 3.85 (s, 3 H, OCH_3), 6.17 (m, 1 H, H-3), 6.53 (m, 1 H, H-4), 6.85–7.0 (m, 4 H, CH_3OAr H), 7.53 (s, 4 H, FAr H), 9.4 (br s, 1 H, NH); ^{13}C NMR δ 50.3 and 53.5 (C-2′,6′ and -3′,5′), 55.2 (OCH_3), 55.6 (NCH_2), 107.5, 110.8, 130.4 and 131.0 (C-4,3,2 and 5), 111.4, 118.2, 121.0, 123.1, 141.0 and 152.3 (OCH_3Ar C), 124.5 (CF_3), 123.7, 125.7, 127.3 and 136.3 (CF_3Ar C).

The compounds **7**,[11] **9**, and **21**[11] (see Tables I and II) were prepared in a similar fashion.

Method C. 2-[[4-(7-Benzofuranyl)-1-piperazinyl]-methyl]-5-(4-fluorophenyl)pyrrole (15). A suspension of the piperazine **26**·HCl salt (1.03 g, 0.004 mol) and sodium acetate (0.44 g, 1.2 equiv) in absolute ethanol (30 mL) was stirred at 20 °C for

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15 min. Then aqueous formaldehyde (37%, 0.34 mL, 0.004 mol) was added, and stirring was continued for 30 min, followed by the addition of 2-(4-fluorophenyl)pyrrole (II, R^1 = 4-F, R^2 = H; 0.67 g, 0.004 mol).[19] After being stirred at 20 °C for 3 h, the reaction was complete (TLC); workup as described for method B gave product **15** (1.4 g, 90%). Crystallization was effected with diisopropyl ether (melting point and elemental analysis, see Table II): ^{1}H NMR δ 2.75 (m, 4 H, H-2′,6′), 3.35 (m, 4 H, H-3′,5′), 3.68 (s, 2 H, NCH_2), 6.14 (m, 1 H, H-3), 6.36 (m, 1 H, H-4), 6.74 (d, 1 H, Bzf H-3, J = 2.0), 6.73 (dd, 1 H, Bzf H-6, J = 8.5 and 1.0), 7.05 (t, 2 H, FAr H-3,5, J = 8.5), 7.14 (t, 1 H, Bzf H-5, J = 8.5), 7.22 (dd, 1 H, Bzf H-4, J = 8.5 and 1.0), 7.42 (dd, 2 H, FAr H-2,6, J = 8,5 and 5), 7.59 (d, 1 H, Bzf H-2, J = 2.0), 9.05 (br s, 1 H, NH).

Compound **17** (see Table II) was prepared in a similar way.

Method D. 2-[[4-(2-Methoxyphenyl)-1-piperazinyl]methyl]-1,5-diphenylpyrrole (12). To a solution of 1-(2-methoxyphenyl)piperazine (0.75 g, 0.004 mol) in absolute ethanol (10 mL) was added aqueous formaldehyde (37%, 0.34 mL, 0.004 mol). After being stirred at 20 °C for 30 min, 1,2-diphenylpyrrole (II, $R^1 = R^2 = C_6H_5$) (0.86 g, 0.004 mol)[19] and acetic acid (1.0 mL, excess) were added, and the resulting solution was stirred at reflux for 4 h. TLC analysis indicated complete conversion. After workup as described under method B and flash chromatography (dichloromethane–methanol, 99:1), pure crystalline **12** was obtained, 1.1 g (65%) (melting point and elemental analysis, see Table I): ^{1}H NMR δ 2.57 (m, 4 H, H-2′,6′), 3.01 (m, 4 H, H-3′,5′), 3.36 (s, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 6.28 (d, 1 H, H-3, J = 3), 6.39 (d, 1 H, H-4, J = 3), 6.85–6.95 (m, 4 H, CH_3OAr H), 7.10 and 7.30 (m, 10 H, Ar H); ^{13}C NMR δ 50.8 and 52.6 (C-2′,6′ and -3′,5′), 54.0 (NCH_2), 55.2 (OCH_3), 111.1, 118.1, 120.9, 122.3, 141,4 and 152.3 (OCH_3Ar C), 108.6, 110.3, 132.1 and 135.1 (C-4,3,5 and 2), 125.8, 127.2, 127.9, 128.4, 128.9, 133.3 and 139.2 (2- and 5-Ar C).

In a similar way compounds **10** and **11** were prepared (see Table I).

5-(4-Fluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-1-*n*-propylpyrrole (10): ^{13}C NMR δ 11.2 (CH_3), 24.5 (CH_2CH_3), 45.9 (CH_2CH_2N), 50.8 and 53.2 (C-2′,6′ and -3′,5′), 55.2 (NCH_2 and OCH_3), 107.8, 109.7, 129.7 and 130.5 (C-4,3,2 and 5), 111.3, 118.1, 121.0, 122.7, 141.5 and 152.3 (OCH_3Ar C), 115.2, 129.7, 130.6 and 161.8 (FAr C).

***N*-[2-[4-(7-Benzofuranyl)-1-piperazinyl]ethyl]-4-fluorobenzamide (24).** A solution of **26** (as free base; 0.99 g, 0.0049 mol) and *N*-(4-fluorobenzoyl)aziridine (0.85 g, 0.0052 mol)[29] in ethyl acetate (5 mL) was heated at reflux for 2 h. After being cooled to 20 °C and concentrated in vacuo, the residue was purified by flash chromatography (dichloromethane–methanol, 98:2); crystallization from cyclohexane yielded pure **24**: 1.28 g (71%); mp 157–158 °C; ^{1}H NMR δ 2.7–2.8 (m, 6 H, aliphatic NCH_2), 3.39 (m, 4 H, aromatic NCH_2), 3.60 (q, 2 H, $NHCH_2$, J = 6), 6.76 (d, 1 H, Bzf H-3, J = 2.5), 6.78 (dd, 1 H, Bzf H-6, J = 7 and 1), 6.84 (br t, 1 H, NH), 7.13 (t, 2 H, FAr H-3,5, J = 8), 7.16 (t, 1 H, Bzf H-5, J = 7), 7.24 (dd, 1 H, Bzf H-4, J = 7 and 1), 7.63 (d, 1 H, Bzf H-2, J = 2.5), 7.81 (dd, 2 H, FAr H-2,6, J = 8 and 5). Anal. ($C_{21}H_{22}FN_3O_2$) C, H, F, N.

1-(7-Benzofuranyl)-4-[3-(4-fluorobenzoyl)propyl]-piperazine Hydrochloride (25). A stirred suspension of **26** (1.79 g, 0.075 mol), 4-chloro-4′-fluorobutyrophenone (1.82 g, 0.009 mol), powdered K_2CO_3 (2.80 g, 0.02 mol), and NaI (0.10 g, catalytic) in ethyl methyl ketone (50 mL) was refluxed for 16 h. Then another portion of the butyrophenone (1.82 g) was added, and reflux was continued for 24 h. After being cooled to 20 °C, the mixture was filtered, and the solvent was removed by evaporation. Column chromatography (ethyl acetate) yielded the free base of **25**, 0.91 g (33%). This material was taken up in ethyl acetate (20 mL), and after addition of 1 equiv of HCl in ethanol (2 mL), **25** crystallized from the solution (0.80 g): mp 219–220 °C; ^{1}H NMR δ 2.40 (m, 2 H, $CH_2CH_2CH_2$), 3.2–3.3 (m, 4 H, NCH_2 and $C(=O)CH_2$), 3.3–3.8 (br m, 8 H, pip CH_2), 6.78 (dd, 1 H, Bzf H-6, J = 7 and 1), 6.79 (d, 1 H, Bzf H-3, J = 2.5), 7.15 (t, 2 H, FAr H-3,5, J = 8), 7.16 (t, 1 H, Bzf H-5, J = 7), 7.29 (dd, 1 H, Bzf H-4, J = 7 and 1), 7.61 (d, 1 H, Bzf H-2, J = 2.5), 8.01 (dd, 2 H, FAr H-2,6, J = 8 and 5). Anal. ($C_{22}H_{23}FN_2O_2$·HCl) C, H, F, Cl, N.

Ethyl 7-Nitrobenzofuran-2-carboxylate (29).[14] A stirred mixture of **28**[30] (27.7 g, 0.166 mol), diethyl bromomalonate (43.4 g, 0.182 mol), powdered K_2CO_3 (34.4 g, 0.25 mol), and tetrabutylammonium bromide (5.35 g, 0.017 mol) in toluene (450 mL) was heated at reflux under dry nitrogen with a Dean–Stark trap (to remove water and ethanol) for 20 h. After the mixture was cooled to 20 °C, the solvent was evaporated and the residue was treated with dichloromethane (500 mL). After filtration, the filtrate was washed successively with water (3 × 300 mL) and 2 N KOH (100 mL) and dried (Na_2SO_4). The organic layer was then filtered over a short silica gel (250 g) column. After further elution with dichloromethane, pure **29** was obtained as light yellow crystals: yield 32.7 g (84%); mp 88–89 °C (lit.[13a] mp 90–91 °C); ^{1}H NMR δ 1.46 (t, 3 H, CH_3, J = 7.5), 4.49 (q, 2 H, CH_2, J = 7.5), 7.48 (t, 1 H, H-5, J = 8), 7.66 (s, 1 H, H-3), 8.05 (dd, 1 H, H-4, J = 8 and 1), 8.31 (dd, 1 H, H-6, J = 8 and 1).

7-Nitrobenzofuran (30).[13] To a suspension of **29** (14.6, 0.06 mol) in ethanol (60 mL) was added 2 N KOH (60 mL, 2 equiv). After being refluxed for 1 h, the solution was cooled and concentrated to a volume of about 60 mL. Then 12 N HCl (excess) was added, and the 7-nitrobenzofuran-2-carboxylic acid precipitated. This was filtered off, washed with water, and dried in vacuo over P_2O_5. The resulting white solid was dissolved in quinoline (100 mL). After the addition of cuprous oxide (0.20 g, catalytic)[15] the solution was heated at 180–200 °C under a dry nitrogen atmosphere. After heating for 30 min, the CO_2 production stopped, and the mixture was cooled to 20 °C and filtered. The filtrate was diluted with ether (250 mL), and then the solution was washed with 2 N HCl (5 × 250 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was extracted with hot petroleum ether (60–80 °C; 5 × 50 mL). After cooling, product **30** crystallized: yield 8.0 g (82%); mp 95.5–97 °C (lit.[13a] mp 96–97 °C); ^{1}H NMR δ 6.95 (d, 1 H, H-3), 7.38 (t, 1 H, H-5), 7.86 (d, 1 H, H-2), 7.94 (dd, 1 H, H-4), 8.16 (dd, 1 H, H-6); J_{23} = 2.5, J_{45} = J_{56} = 8, J_{46} = 1. Anal. ($C_8H_5NO_3$) C, H, N.

7-Aminobenzofuran Hydrochloride (31).[16] A stirred suspension of **30** (7.03 g, 0.043 mol) and Raney nickel catalyst (50 mg) in methanol (70 mL) was heated at about 50 °C. Then hydrazine hydrate (6.3 mL, 0.13 mol) was added dropwise, giving an exothermic reaction. The temperature was maintained at 55–60 °C by external cooling. When the addition was completed (1 h), the mixture was stirred at reflux for 1 h and then cooled to 20 °C. The catalyst was filtered off, and the solvent was evaporated. The residue was dissolved in ethyl acetate (60 mL), and 1 equiv of HCl in methanol (15 mL) was added. Product **31** crystallized and was collected by filtration and dried in vacuo: yield 6.75 g (92%); mp 212–213 °C; ^{1}H NMR (DMSO–$CDCl_3$, 4:1) δ 7.01 (d, 1 H, H-3), 7.23 (t, 1 H, H-5), 7.23 (dd, 1 H, H-4), 7.59 (dd, 1 H, H-6), 8.07 (d, 1 H, H-2); J_{23} = 2.5, J_{45} = J_{56} = 7.5, J_{46} = 1.

1-(7-Benzofuranyl)piperazine Hydrochloride (26).[18] In an atmosphere of dry nitrogen a suspension of **31** (6.75 g, 0.04 mol) and bis(2-chloroethyl)amine hydrochloride (7.20 g, 0.04 mol) in chlorobenzene (40 mL) was heated at reflux temperature under efficient stirring for 72 h. After the mixture was cooled to 20 °C, the solvent was evaporated and the residue was taken up in hot methanol (50 mL) and filtered. The filtrate was concentrated in vacuo, and the residue (8.7 g) was purified by column chromatography (tetrahydrofuran–methanol–ammonia, 85:15:2). The fractions containing pure **26** were collected and concentrated, giving the free base (6.1 g). Conversion into the HCl salt was carried out in ethyl acetate (150 mL) by the addition of 1 equiv of HCl in absolute ethanol (15 mL). Product **26** crystallized and was filtered off and dried in vacuo: yield 6.85 g (72%); mp 194.5–195 °C; ^{1}H NMR (DMSO–$CDCl_3$, 4:1) δ 3.33 and 3.54 (2 m, 8 H, H-2,3,5,6), 6.81 (dd, 1 H, Bzf H-6), 6.89 (d, 1 H, Bzf H-3), 7.14 (t, 1 H, Bzf H-5), 7.26 (dd, 1 H, Bzf H-4), 7.90 (d, 1 H, Bzf H-2), 9.5 (br s, 2 H, NH_2^+); J_{23} = 2.5, J_{45} = J_{56} = 7.5, J_{46} = 1. Anal. ($C_{12}H_{15}ClN_2O$) C, H, N.

3,4-Dihydro-6-nitro-2*H*-1,5-benzodioxepine (33).[14] A mixture of 3-nitrocatechol (**32**)[31] (15.5 g, 0.10 mol), powdered K_2CO_3 (41.4 g, 0.30 mol), 1,3-dibromopropane (15.3 mL, 0.15 mol), and tetrabutylammonium bromide (3.2 g, 0.01 mol) in toluene (500 mL) was heated under dry nitrogen in a water-trap equipment

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at 80 °C for 24 h. After the mixture was cooled to 20 °C, ether (50 mL) and water (300 mL) were added. The organic layer was separated and washed with 2 N NaOH (200 mL). After drying (Na_2SO_4), **33** was obtained quantitatively by filtration and evaporation of the solvents. Distillation afforded the pure product: bp 139–140 °C (0.04 mm); n^{20}_D 1.5612; ^{1}H NMR δ 2.28 (q, 2 H, $CH_2CH_2CH_2$, J = 5.5), 4.29 and 4.39 (2 t, 2 H, OCH_2, J = 5.5), 6.99 (t, 1 H, H-8, J = 8.5), 7.18 (dd, 1 H, H-9, J = 2 and 8.5), 7.38 (dd, 1 H, H-7, J = 2 and 8.5). Anal. ($C_9H_9NO_4$) C, H, N.

6-Amino-3,4-dihydro-2*H*-1,5-benzodioxepine Hydrochloride (34). To a solution of **33** (2.0 g, 0.01 mol) in ethanol (35 mL) was added 12 N HCl (0.85 mL, 0.01 mol) and Pd catalyst (0.25 g, 10% on C). Hydrogenation at 20 °C and 1 atm was complete after 1.5 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo, yielding a white solid, which was stirred with ether. After filtration and drying in vacuo, pure **34** was obtained: yield 1.78 g (89%); mp 227–230 °C dec; ^{1}H NMR (as free base) δ 2.18 (q, 2 H, $CH_2CH_2CH_2$, J = 5.5), 3.87 (br s, 2 H, NH_2), 4.19 (m, 4 H, OCH_2), 6.39 and 6.42 (2 dd, 1 H, H-7,9, J = 1.5 and 8), 6.72 (t, 1 H, H-8, J = 8). Anal. ($C_9H_{12}ClNO_2$) C, H, Cl, N.

1-(3,4-Dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazine Dihydrochloride (27).[18] In an atmosphere of dry nitrogen, **34** (5.64 g, 0.028 mol) and bis(2-chloroethyl)amine hydrochloride (5.0 g, 0.028 mol) were suspended in chlorobenzene (45 mL). This mixture was stirred at reflux temperature for 60 h. After the mixture was cooled to 20 °C, ether was added (40 mL) and the precipitate was filtered off. The solid was dissolved in boiling absolute ethanol (50 mL), and then excess HCl (5 equiv) in absolute ethanol (10 mL) was added. Crystallization was effected by cooling to 20 °C and addition of ether (50 mL); after filtration and drying in vacuo, **27** was obtained: yield 4.4 g (51%); mp 253–257 °C dec; ^{1}H NMR ($CDCl_3$, 5% trifluoroacetic acid) δ 2.30 (m, 2 H, $CH_2CH_2CH_2$), 4.25 (br m, 8 H, pip H-2,3,5,6), 4.33 and 4.48 (2 m, 4 H, OCH_2), 7.11 (t, 1 H, Bdp H-8, J = 8), 7.27 and 7.34 (2 dd, 2 H, Bdp H-7,9, J = 8 and 1.5), 8.55–9.0 (br m, 2 H, NH_2^+). Anal. ($C_{13}H_{20}Cl_2N_2O_2$) C, H, Cl, N.

Bis(5-phenyl-2-pyrryl)methane (35). From the Mannich reaction of 2-phenylpyrrole (II, R^1 = R^2 = H) with 1-(2-methoxyphenyl)piperazine (method A, 30 mmol of both reactants), chromatography fractions, containing the apolar side product, were collected and concentrated in vacuo. The residue was crystallized from ethyl acetate–petroleum ether (60–80 °C), giving **35** as white crystals (turning to purple very fast in contact with air):[22] yield 0.43 g (10%); mp 189–192 °C; ^{1}H NMR (DMSO–$CDCl_3$, 4:1) δ 3.94 (s, 2 H, CH_2), 5.86 (m, 2 H, H-3), 6.35 (m, 2 H, H-4), 7.09 (tt, 2 H, Ar H-4, J = 8 and 1), 7.31 (t, 4 H, Ar H-3,5, J = 8), 7.57 (dt, 4 H, Ar H-2,6, J = 8 and 1).

Biochemistry. Receptor Binding Assays. Binding assays were carried out as described previously.[11] Thus, [^{3}H]spiperone was used to label dopamine D-2 receptors in the rat corpus striatum[32] or 5-HT_2 receptors in the rat frontal cortex,[33] and [^{3}H]WB-4101 was used to label α_1-adrenergic receptors in the rat total brain.[34]

Pharmacology. The apomorphine-induced climbing behavior in mice,[35] the conditioned avoidance behavior in rats,[36] and the catalepsy in rats[37] were performed as described previously.[11]

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Registry No. 1, 110319-92-1; **2**, 114518-03-5; **3**, 114518-25-1; 4, 114518-26-2; **5**, 114518-02-4; **6**, 114518-07-9; **7**, 110319-93-2; 8, 114518-06-8; **9**, 114518-31-9; **10**, 115464-74-9; 11, 115464-75-0; **12**, 115464-76-1; **13**, 114518-08-0; 14, 114542-67-5; **15**, 115464-77-2; **16**, 114518-11-5; **16**·HCl, 115464-78-3; **17**, 114518-27-3; 18, 115464-79-4; **19**, 114518-15-9; **20**, 114518-32-0; **21**, 110319-90-9; **22**, 114518-17-1; **23**, 27227-14-1; **24**, 98224-13-6; **25**, 115464-80-7; **26**, 115464-81-8; **26** (free base), 98224-26-1; **27**, 115464-82-9; **28**, 5274-70-4; **29**, 110683-72-2; **30**, 18761-32-5; **31**, 115464-83-0; **32**, 6665-98-1; **33**, 115464-84-1; **34**, 115464-85-2; **34** (free base), 115464-86-3; **35**, 115464-87-4; **I** (X = N, R^3 = 2-$MeOC_6H_4$), 35386-24-4; **I** (X = N, R^3 = 3-$F_3CC_6H_4$), 15532-75-9; **I** (X = N, R^3 = 4-FC_6H_4), 2252-63-3; **I** (X = N, R^3 = $(CH_2)_2OH$), 103-76-4; **I** (X = CH, R^3 = 2-$MeOC_6H_4$), 58333-75-8; **I** (X = CH, R^3 = Ph), 771-99-3; **I** (X = C(OH), R^3 = 4-FC_6H_4CO), 56346-57-7; **I** (X = N, R^3 = 4-FC_6H_4CO), 102391-98-0; **II** (R^1 = H, R^2 = H), 3042-22-6; **II** (R^1 = 4-F, R^2 = H), 110319-94-3; **II** (R^1 = 4-CF_3, R^2 = H), 115464-88-5; **II** (R^1 = 4-Pr*i*, R^2 = H), 93971-52-9; **II** (R^1 = 3-Cl, R^2 = H), 115464-89-6; **II** (R^1 = 2-OMe, R^2 = H), 69640-32-0; **II** (R^1 = 2-OMe, 5-SO_2Et, R^2 = H), 110319-95-4; **II** (R^1 = 2,6-F_2, R^2 = H), 115464-90-9; **II** (R^1 = 4-F, R^2 = Me), 115464-91-0; **II** (R^1 = 4-F, R^2 = Pr), 115464-92-1; **II** (R^1 = 4-F, R^2 = $(CH_2)_2OH$), 115464-93-2; **II** (R^1 = H, R^2 = Ph), 837-56-9; *N*-(4-fluorobenzoyl)aziridine, 15257-81-5; 4-chloro-4′-fluorobutyrophenone, 3874-54-2; diethyl bromomalonate, 685-87-0; 7-nitrobenzofuran-2-carboxylic acid, 90483-98-0; bis(2-chloroethyl)amine hydrochloride, 821-48-7; 1,3-dibromopropane, 109-64-8.

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