scribed above. All peptides were at least 95% pure, as judged from the HPLC elution profiles. Analytical data are presented in Table III. The syntheses of peptides 1 and 9 have been reported elsewhere.[4]

Binding Assays and Bioassays. Receptor binding studies with rat brain membrane preparations were performed as reported in detail elsewhere.[22] [^{3}H]DAGO and [^{3}H]DSLET at respective concentrations of 0.72 and 0.78 nM were used as radioligands, and incubations were performed at 0 °C for 2 h. The calculation of the binding inhibition constants (K_i) was based on the equation by Cheng and Prusoff,[23] with values of 1.3 and 2.6 nM for the dissociation constants of [^{3}H]DAGO and [^{3}H]DSLET, respectively.[24,25]

The GPI[26] and MVD[27] bioassays were carried out as reported in detail elsewhere.[22,28] A log dose–response curve was determined with [Leu^5]enkephalin as standard for each ileum or vas preparation, and IC_{50} values of the compounds being tested were normalized according to a published procedure.[29] K_e values for naloxone as antagonist were determined from the ratio of IC_{50} values obtained in the presence and absence of a fixed naloxone concentration (5 nM).[30]

Acknowledgment. This work was supported by operating grants from the Medical Research Council of Canada (Grant MT-5655), the Quebec Heart Foundation, and the National Institute on Drug Abuse (Grant 1RO1 DA-04443-01). Naloxone hydrochloride was a gift from Endo Laboratories, Inc. We thank Drs. M. Evans and M. Bertrand, Department of Chemistry, University of Montreal, for the performance of the FAB mass spectroscopic determinations. Thanks are also due to H. Zalatan for typing the manuscript.

Registry No. 1, 96382-72-8; 2, 110172-15-1; 3, 110172-16-2; 4, 106818-61-5; 5, 106327-79-1; 6, 110116-73-9; 7, 110116-74-0; 8, 106327-80-4; 9, 97996-92-4; 10, 110116-75-1; 11, 110116-76-2.

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2-Phenylpyrroles as Conformationally Restricted Benzamide Analogues. A New Class of Potential Antipsychotics. 1

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Received May 18, 1987

2-Phenylpyrroles were synthesized as conformationally restricted analogues of the substituted benzamide sultopride and the butyrophenones haloperidol and fluanisone. Dopamine antagonistic activity is maintained if the 2-phenylpyrrole side chain is linked to the pharmacophoric *N*-ethylpyrrolidine moiety of sultopride or to the 4-substituted piperazine moiety of fluanisone but is lost if the 2-phenylpyrrole is combined with the 4-substituted piperidine moiety of haloperidol. The 2-phenylpyrrole analogue 1 of sultopride is in vitro 0.25 and in vivo 3 times as potent as the parent compound. Its binding to the dopamine D-2 receptors is, in analogy to the substituted benzamides, strongly sodium-dependent. The 2-(4-fluorophenyl)pyrrole analogue 5 of fluanisone is superior in vitro as well as in vivo to the corresponding benzamide 7 and the butyrophenone fluanisone. The increase in activity is not only due to a higher affinity for the D-2 receptors but also to an enhanced oral absorption (ratio po/ip = 4.5 vs 40 for the benzamide and 60 for fluanisone). Compound 5 is further characterized by a high selectivity for the D-2 receptors, in contrast to the benzamide and butyrophenone analogues (ratio D-2/α_1 = 60, 2.0, and 0.3, respectively). The binding to the D-2 receptors has little dependence on sodium. The 2-phenylpyrrole 5 shares with the benzamide 7 a low potential to induce catalepsy, which is in contrast to haloperidol. So, 5-(4-fluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (5) is the prototype of a new class of sodium-independent dopamine D-2 antagonists, which may be particularly useful as potential antipsychotics with a low propensity to induce acute extrapyramidal side effects.

The substituted benzamides have attracted considerable interest as potential antipsychotics with a lower propensity to induce extrapyramidal side effects (EPS) than the classical neuroleptics like haloperidol (I). The "atypical" neuroleptic profile is characterized by a large separation between the doses inhibiting apomorphine-induced behavior patterns (index for antipsychotic activity) and the doses inducing catalepsy (index for acute extrapyramidal side effects).[1] For sulpiride (IIa), the prototype of the substituted benzamides, the atypical neuroleptic profile could be confirmed in humans.[2] Sulpiride, however, is a rather weak antipsychotic drug[3] due to its low bioavailability [3a] and poor penetration into the brain.[3b]

Since the discovery of sulpiride, more lipophilic (sultopride, IIb)[3d] and highly potent [eticlopride (IIc)[4a] and ra-

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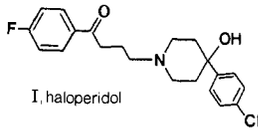
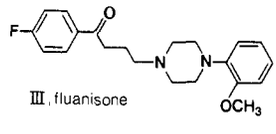
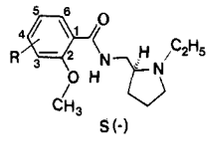
clopride (IId)[4b]] substituted benzamides have been synthesized. The atypical neuroleptic profile of these compounds was maintained notwithstanding a fast penetration into the CNS and a selective binding in dopamine-rich areas, similar to that of the butyrophenone spiperone.[4c,d]





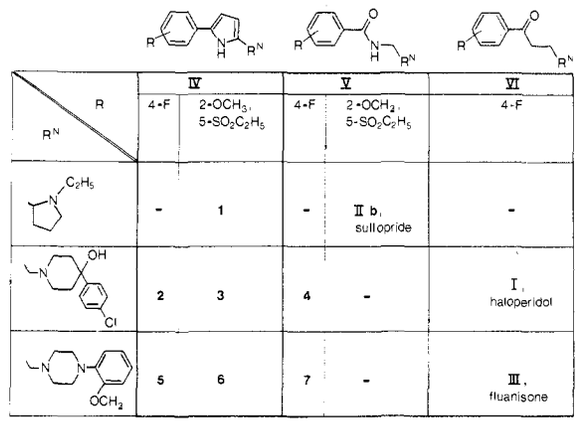


II a, sulpiride : R = 5-SO_2NH_2
b, sultopride : R = 5-$SO_2C_2H_5$
c, eticlopride : R = 3-Cl, 5-C_2H_5, 6-OH
d, raclopride : R = 3,5-diCl, 6-OH

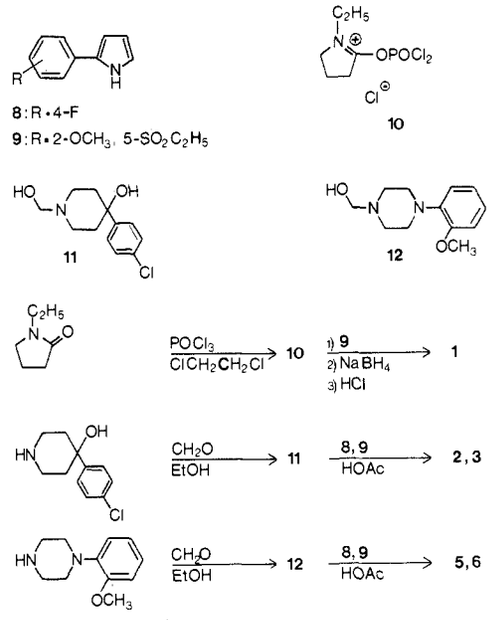
The substituted benzamides as well as the classical neuroleptics are in vitro and in vivo antagonists of the dopamine D-2 receptors.[5,1c] In contrast to the classical neuroleptics, however, the in vitro binding of the benzamides is strongly dependent on the presence of sodium ions.[6a,b] A selective interaction with a sodium-dependent subpopulation or conformation of dopamine D-2 receptors could explain the atypical neuroleptic profile of the substituted benzamides.[1b,6]

Differences in the structure–activity relationships between the substituted benzamides and neuroleptics of the butyrophenone series further support this hypothesis. First, in the substituted benzamide series, the presence of a 2-methoxy (or 2-ethoxy) group is essential for dopamine antagonistic activity.[7,4a] Combination with the appropriate substituents at the 3-, 4-, 5-, and 6-position of the benzene ring results in very potent dopamine D-2 receptor blockers.[4] Substitution of these benzamides with only a fluorine atom at the 4-position of the benzene ring reduces the activity dramatically.[7a] This is in contrast to the butyrophenone series, where optimal activity is obtained with a fluorine atom at the 4-position of the benzoyl group.[8] Second, the substituted benzamides are characterized by the presence of a simple tertiary amino moiety, substituted

Chart I



Scheme I



with lower alkyl or benzyl groups and maintained at a distance of two or three carbon atoms from the amide function. Optimal activity is achieved if the tertiary nitrogen atom is combined with one or two of the carbon atoms of the benzamide side chain to form a pyrrolidine or piperidine ring.[4a,9] In the butyrophenone series, however, high dopamine antagonistic activity is only observed if the butyrophenone moiety is linked to a more complex amine-containing ring system, e.g., 4-(4′-chlorophenyl)-4-hydroxypiperidine as in haloperidol.[8] Without a significant loss in affinity for the dopamine D-2 receptors, the piperidine moiety can be replaced by the 4-(2-methoxyphenyl)piperazine group as in fluanisone (III). In vivo, fluanisone is a rather weak neuroleptic with a strong sedative (α_1-adrenolytic) component.[8] A four-atom distance between the benzene ring and these tertiary amine functions is optimal for dopamine antagonistic activity. There is a dramatic fall in activity if the butyrophenone moiety is linked to simple tertiary amine containing groups.[8d] Third, the butyrophenone chain is more flexible than the pyrrolidinyl or piperidinyl type structures of the substituted benzamides.

To further investigate the structural requirements for the interaction with dopamine D-2 receptors, we have

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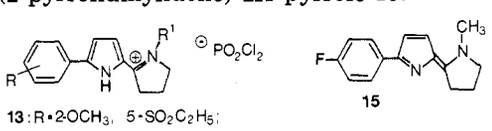
synthesized 2-phenylpyrroles of type IV as conformationally restricted analogues of the substituted benzamides V and butyrophenones VI (Chart I).

The 2-phenylpyrrole structure was linked to the different tertiary amine containing moieties present in sultopride (1), haloperidol (2 and 3), and fluanisone (5 and 6). These compounds, together with the corresponding substituted benzamides (4 and 7) and reference compounds (I, IIa, IIb, III), were tested in pharmacological models relevant for antipsychotic activity: affinity for dopamine D-2 receptors, inhibition of the apomorphine-induced climbing behavior in mice, and inhibition of the conditioned avoidance response in rats. The induction of catalepsy in rats was used as an index for their potential to evoke extrapyramidal side effects. Sodium dependency as well as selectivity for the dopamine D-2 receptors was assayed by in vitro radioligand displacement experiments.

Results

Chemistry. Benzamides 4 and 7 were prepared according to standard methods for the synthesis of *N*-[2-(dialkylamino)ethyl]benzamides[10] (see the Experimental Section). 2,5-Disubstituted pyrroles IV could be synthesized from the corresponding 2-phenylpyrroles 8 and 9 by regiospecific substitution reactions at position 5 of the pyrrole ring with Vilsmeier–Haack-type electrophiles (10) and Mannich-type (11 and 12) electrophiles (see Scheme I). In contrast to charge density MO calculations, electrophilic substitution reactions are known to prefer the free α-positions of the pyrrole nucleus, indicating late σ-complex transition states.[11]

The 2-(2-pyrrolidinyl)pyrrole 1 was obtained from 9 and 10 in good yield after sodium borohydride reduction of the iminium ion intermediate 13 and subsequent decomposition of the initially formed borane complex with acid.[12] To our knowledge, this is the first example of an aromatic aminoalkylation reaction with *tertiary* amides by the Vilsmeier-Haack/borohydride reduction sequence.[13] The presence of iminium salt intermediates was supported by the observation that attempted reduction of 14 with lithium aluminum hydride resulted in proton loss only, giving the 2-(2-pyrrolidinylidene)-2*H*-pyrrole 15.[14]



13: R = 2-OCH_3, 5-$SO_2C_2H_5$; $R^1 = C_2H_5$

14: R = 4-F; $R^1 = CH_3$

15

Mannich reactions of 8 and 9 with the hydroxymethylamines 11 and 12 (obtained by reaction of formaldehyde with norhaloperidol and norfluanisone, respectively) proceeded smoothly at room temperature with acetic acid as catalyst. No regioisomers could be detected in the NMR spectrum of the crude reaction products. The main side reaction was the formation of symmetric dipyrrylmethanes, which is a well-known phenomenon in this type of Mannich reactions.[11] The same products were detected (TLC) when the Mannich bases were kept in aqueous solution at low pH values (<3), especially in the case of the (2-methoxyphenyl)piperazines 5 and 6, apparently initiated by retro-Mannich reactions of the protonated molecules.[15] The methodology employed for the synthesis of the unknown 2-phenylpyrroles 8 and 9 is a modification of the method of Berner (see the Experimental Section) and will be published elsewhere.[16]

Pharmacology. The results of the in vitro binding studies and the in vivo pharmacological tests of the substituted 2-phenylpyrroles, benzamides, and reference compounds are presented in Table I. Fixation of the benzamide side chain of sultopride into the 2-phenylpyrrole analogue 1 is not detrimental for dopamine antagonistic activity. The ability of racemic 1 to displace [^{3}H]spiperone from its binding sites is 0.3 times that of (*S*)-sultopride. The binding of 1 is, in analogy with the substituted benzamides, strongly sodium-dependent. In the presence of sodium ions, the binding of 1, sultopride, and sulpiride is almost 10 times better than in the absence of sodium ions.

In vivo, the 2-phenylpyrrole 1 is superior to the corresponding benzamide (Table I). After oral administration, 1 is about 3 times more active than sultopride in inhibiting the apomorphine-induced climbing behavior (APO) in mice. Also, after ip injection, 1 is more active than sultopride. A similar increase in potency is observed in the conditioned avoidance test (CAR) in rats.

Combining norhaloperidol with the 2-(4-fluorophenyl)-pyrrole side chain (compound 2) causes a dramatic loss of the in vitro affinity for the dopamine D-2 receptors in comparison to haloperidol. A similar decrease is seen in the benzamide analogue 4. Introduction of the sultopride substitution pattern (compound 3) restores some of the affinity for the [^{3}H]spiperone binding sites, but 3 is still about 100 times less active than haloperidol. This low affinity for the D-2 receptors is reflected in the in vivo models for dopamine antagonistic activity. Only compounds 2 and 4 show some inhibition of the apomorphine-induced climbing behavior in mice (0.01–0.003 times haloperidol), whereas in the CAR no activity was observed at the doses tested.

Interestingly, dopamine antagonism is maintained if the phenylpyrrole moiety is linked to norfluanisone. High affinity is obtained if the 2-phenylpyrrole is substituted with a fluorine atom at the 4-position of the phenyl ring (compound 5). The potency of 5 in the [^{3}H]spiperone displacement studies is 3 times that of fluanisone and 1.5 times that of haloperidol. High potency is also seen in the in vivo models for antipsychotic activity. After ip injection to mice (APO test), 5 is twice as potent as the corresponding benzamide 7 and the butyrophenone fluanisone. The oral activity of 5 is enhanced by a factor of 15 and 25 with respect to 7 and fluanisone, respectively. The po/ip ratio of 5 in mice is 4.5, similar to that of haloperidol (ratio = 3) and significantly better than that of 7 and fluanisone (ratio $\approx$ 40 and 60, respectively). A similar increase in oral

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Table I. Inhibition of [^{3}H]Spiperone-Striatum (D-2 Receptors), [^{3}H]WB-4101 (α_1 Receptors), and [^{3}H]Spiperone-Cortex (5-HT_2 Receptors) Binding, Antagonism of Apomorphine-Induced Climbing in Mice, Suppression of Conditioned Avoidance Behavior in Rats, and Induction of Catalepsy in Rats of Substituted 2-Phenylpyrroles and Benzamides

compound	D-2 [^{3}H]spiperone binding		α_1 [^{3}H]WB-4101 binding:	5-HT_2 [^{3}H]spiperone binding:	apomorphine antag in mice: ED_{50},[c] mg/kg		suppression of cond avoid. in rats: ED_{50},[d] mg/kg		induct. of catalepsy in rats: ED_{50},[e]
	K_i,[a] nM	Na^+ ratio[b]	K_i,[a] nM	K_i,[a] nM	po	ip	po	ip	mg/kg ip
1[f]	29 ± 3	9.5 ± 1.6			11.4	4.7	35		
2	1100 ± 100		1600 ± 300	9300 ± 2300	51	25	>50	>20	
3	150 ± 12	5.7 ± 3.2			>100	>20			
4	480 ± 100		250 ± 90		20	9	>50		
5	0.91 ± 0.11	2.3 ± 0.5[g]	57 ± 10	310 ± 40	0.9	0.2	8.5	2.3	>24
6	7.3 ± 1.2	1.7 ± 0.2			35	>20	>50	>20	
7	5.0 ± 0.8	3.2 ± 0.5[g]	9.0 ± 2.7	700 ± 150	15	0.4	30	0.74	>7.4
(*S*)-sulpiride, IIa	39.0 ± 7.0	7.0 ± 2.0	15000 ± 1000	27000 ± 2000	195	>21	>220	>100	
(*S*)-sultopride, IIb	9.3 ± 1.7	8.4 ± 1.4	1100 ± 400	54000 ± 11000	36	>10	70		
haloperidol, I	1.4 ± 0.04	0.59 ± 0.12	31 ± 7	42 ± 12	0.24	0.08	0.80	0.45	2.0
fluanisone, III	2.9 ± 0.6	1.4 ± 0.3[g]	0.87 ± 0.04	52 ± 11	25	0.4	>50	2.2	≥22[h]

[a] K_i (±SEM) values are based on three to six assays, each using four to six concentrations in triplicate. [b] Calculated as $IC_{50}(+Na^+)/IC_{50}(-Na^+)$ (±SEM) from two to four experiments. [c] 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. [d] 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. [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] Racemic compound. [g] $p < 0.01$ (Student's two-tailed test) with respect to the sodium ratio of sultopride. [h] In this dose, 40% of the animals showed catalepsy.

absorption is seen in the CAR.

By introduction of the sultopride-substituent pattern into the 2-phenylpyrrole moiety (compound **6**), a decrease in potency in displacing [^{3}H]spiperone by a factor of 7 is observed with respect to **5**. Although the K_i value of this compound is still in the nanomolar range, in vivo dopamine antagonistic activity is weak. Compounds **5** and **7** are further characterized by a more than 10-fold (ip) separation between the dose that induces catalepsy (CAT) and the dose that is effective in the CAR test, which is significantly better than for haloperidol (ratio ca. 4.5).

Another interesting finding is the selectivity of **5** for dopamine D-2 receptors. In comparison to the corresponding benzamide analogue (**7**), **5** has a 5 times higher affinity for the dopamine D-2 receptors and a 6 times lower affinity for the α_1-adrenergic receptors. The affinity for 5-HT_2 receptors of both compounds is low. The selectivity of compound **5** is still more pronounced if it is compared with its butyrophenone analogue fluanisone, which displays a pronounced affinity for the α_1-adrenergic receptors (K_i = 0.87 nM) and has also a high affinity for the 5-HT_2 receptors. The receptor binding profiles of **5**, **7**, and fluanisone are shown in Figure 1. In contrast to **1**, sultopride, and sulpiride, the specific binding of **5**, **7**, and fluanisone is significantly less dependent on the presence of sodium ions.

Discussion

The 2-phenylpyrroles are bioisosteric to the corresponding benzamides with respect to dopamine D-2 antagonists properties. Activity is maintained if the 2-phenylpyrrole side chain is combined with the tertiary amine containing moieties of sultopride (**1** vs IIb) and of fluanisone (**5** vs **7**), whereas the phenylpyrrole as well as the benzamide moiety in combination with norhaloperidol are both weak dopaminolytics (**2** vs **4**). In vitro, the binding of the 2-phenylpyrroles to the D-2 receptors is influenced by sodium ions in a similar way as for the corresponding benzamides, only in the sultopride series, the binding is strongly sodium-dependent. Quantitatively, the 2-phenylpyrroles and the benzamides are different. In vitro, the affinity to the D-2 receptors of **1** and **2** is somewhat less than for the corresponding benzamides

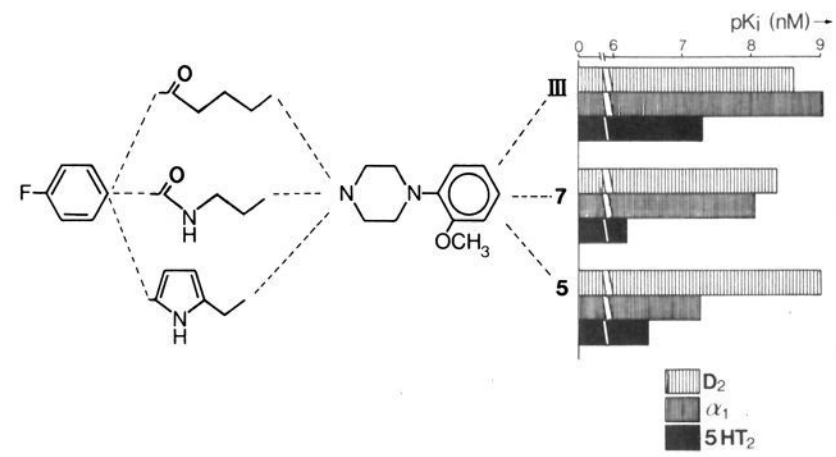

Figure 1. Receptor binding profiles of the butyrophenone, benzamide, and 2-phenylpyrrole derivatives from the 4-(2-methoxyphenyl)piperazine series (fluanisone, **7**, and **5**, respectively) showing the pronounced selectivity of **5** toward D-2 receptors in contrast to **7** and fluanisone.

sultopride and **4**, respectively, but the 2-phenylpyrrole **5** has a 5 times higher affinity than the corresponding benzamide **7**. In the in vivo models for dopamine antagonistic activity, the 2-phenylpyrroles of the sulpiride and fluanisone series are superior to the corresponding benzamides, especially after po administration. The high oral activity of **5** in the APO and the CAR tests is not only due to a better fit on the dopamine D-2 receptors but also to an enhanced oral absorption. The po/ip ratio in both tests for dopamine antagonistic activity is only 4.5, which is significantly better than the corresponding benzamide **7** and the butyrophenone fluanisone. The 2-phenylpyrrole **5** shares with the benzamide **7** an extremely low potential to induce cataleptic behavior.

In the fluanisone series, the selectivity for the D-2 receptor of the 2-phenylpyrrole **5** is improved with respect to the benzamide **7** and especially to the butyrophenone fluanisone (see Figure 1). It is obvious that fixation of the side chain into the 2-phenylpyrrole structure is unfavorable for the interaction with α_1-adrenoceptors. This conformational restriction in the 2-phenylpyrrole, however, is favorable for the interaction with D-2 receptors. Previous attempts to restrict the number of conformations of the butyrophenone side chain were less successful. Incorporation of the β and γ carbons of the propyl chain of flua-

nisone into a cyclohexane ring is unfavorable for dopamine antagonistic activity[17] just as including the propyl chain in a cyclopropane ring in a series of substituted piperidines is unfavorable.[18] Introduction of double bonds in the butyrophenone side chain is in general accompanied by a loss in activity. Only in combination with properly 4-substituted piperidine moieties could high dopamine antagonistic activity be maintained.[8a] Activity is lacking completely if these unsaturated side chain modifications are combined with substituted piperazines.[19]

In the 2-phenylpyrroles 1 and **5**, however, neither the lack of saturation nor the absence of a carbonyl function is detrimental for dopamine antagonistic activity. This finding fits the recently described semiaromatic character of the amide bond in the salicylamide compound eticlopride[20] and may support the hypothesis of Van de Waterbeemd et al., who suggested a coincidence of the aromatic ring of dopamine with the (semiaromatic) amide function of the benzamides, allowing the best possible fit between the regions of maximum positive potential, as well as between the regions of maximum negative potential.[21]

In the substituted benzamides, structure–activity relationship studies have shown that a coplanar benzamide group is a prerequisite for dopamine blocking activity.[4b,7b,22] In 1 the 2-phenylpyrrole moiety can fully adopt such a planar structure, and since the carbon-2 atom of the pyrrolidine ring is incorporated into the plane of the aromatic rings, the planarity of the total structure is extended with one carbon atom. Such a conformation is also possible in the substituted benzamides as was recently presented by Högberg et al., with molecular mechanics calculations.[23] An extended planar structure is also present in the solid-state conformation of FLA 797, the salicylamide analogue and active metabolite of remoxipride.[23] X-ray studies of two other salicylamides (eticlopride and raclopride) show a conformation in which the bond between the chain methylene carbon and the carbon-2 atom of the pyrrolidine ring is nearly perpendicular to the plane of the benzamide moiety.[20,23] However, the finding that the rigid structure of 1 still shows affinity for the D-2 receptors excludes this conformation as a candidate for studying the interaction with the receptor at the molecular level. Therefore, it is reasonable to assume that for the interaction with the D-2 receptors an extended planar structure is the most likely candidate. This finding is also supported by the high dopamine antagonistic activity of the conformationally restricted, semiplanar structure of the pyrrolo[2,3-*g*]isoquinoline derivative piquindone.[24]

In the 2-phenylpyrrole derivative **5**, more conformational freedom is present than in 1, since two torsion angles are variable. Conformational energy calculations (PCILO method) of 1 and **5** and the corresponding benzamides and butyrophenones are in progress to gain more insight into possible bioactive conformations of these two types of dopamine antagonists.

In conclusion, 2-phenylpyrroles are bioisosteric to the dopamine antagonistic benzamides of the sultopride and fluanisone series. Activity and selectivity for the D-2 receptors were significantly enhanced if the 2-(4-fluorophenyl)pyrrole side chain was combined with the pharmacophoric 4-(2-methoxyphenyl)piperazine moiety of fluanisone. The excellent oral activity and the wide range between the doses that are effective in the apomorphine-mediated behavior patterns and the doses that induce catalepsy make compound **5**, the prototype of a new class of dopamine D-2 antagonists, particularly useful as a potential antipsychotic with a low propensity to induce acute extrapyramidal side effects. Structure–activity relationship studies are in progress to investigate the scope of our findings.[15]

Experimental Section

Chemistry. Melting points are uncorrected. NMR spectra were recorded on a Bruker WP-200 or AM400 instrument. 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 0.4% of the theoretical values. For normal-pressure and flash chromatography, Merck silica gel type 60 (size 70–230 and 230–400 mesh, respectively) was used. Unless stated otherwise, all starting materials were used as high-grade commercial products.

2-(1-Ethyl-2-pyrrolidinyl)-5-[5-(ethylsulfonyl)-2-methoxyphenyl]pyrrole (1). Under an atmosphere of dry nitrogen, phosphorus oxychloride (0.27 mL, 0.003 mol) was added dropwise to *N*-ethyl-2-pyrrolidinone (0.34 g, 0.003 mol) at ca. 10 °C with stirring. After 15 min at 20 °C, 1,2-dichloroethane (5 mL) was added, and the suspension of **10** was cooled to 0 °C. Then pyrrole **9** (0.80 g, 0.003 mol), dissolved in 1,2-dichloroethane (9 mL), was gradually added during 20 min. Stirring was continued first at 0 °C for 3 h and then at 20 °C for 16 h; hydrogen chloride gas was liberated. The purple solution of **13** was cooled to 0 °C, and sodium borohydride (1.0 g, excess) was added, followed by stirring at 20 °C for 2 h. Then the reaction mixture was hydrolyzed carefully at 0–5 °C by the addition of H_2O (5 mL) and methanol (5 mL).

After addition of H_2O (25 mL), the resulting mixture was extracted with methylene chloride (3 × 15 mL). The solution was dried ($MgSO_4$) and concentrated, giving the borane complex of 1 (1.3 g). This material was subsequently hydrolyzed by the addition of methanol (10 mL) and 12 N HCl (5 mL) and stirring at 20 °C for 3 h. After the addition of H_2O and 50% NaOH (6 mL), the basic solution was extracted with methylene chloride. The solution was dried ($MgSO_4$). After evaporation, crude 1 was obtained (1.1 g). Chromatography (dichloromethane–methanol, 85:15 as eluent) yielded pure 1: (0.60 g, 55%); mp 45 °C; NMR ($CDCl_3$) δ 1.11 (t, 3 H, NCH_2CH_3, J = 7), 1.27 (t, 3 H, $SO_2CH_2CH_3$, J = 7), 1.8–2.5 (m, 6 H, NCH_2CH_3 and H-3′,4′), 2.7–2.9 (m, 1 H, H-5′), 3.11 (q, 2 H, $SO_2CH_2CH_3$, J = 7), 3.4–3.7 (m, 2 H, H-2′,5′$_{eq}$), 4.07 (s, 3 H, OCH_3), 6.14 (br t, 1 H, H-3), 6.64 (br t, 1 H, H-4), 7.06 (d, 1 H, Ar H-3, J = 8), 7.65 (dd, 1 H, Ar H-4, J = 8 and 2), 8.08 (d, 1 H, Ar H-6, J = 2), 9.9–10.3 (br s, 1 H, NH). Anal. ($C_{19}H_{26}N_2O_3S \cdot 0.75H_2O$): C, H, N, S.

General Procedure for the Preparation of Mannich Bases 2, 3, 5, and 6. To a solution of the secondary amine (0.01 mol) in absolute ethanol (50 mL) was added aqueous formaldehyde (37%, 0.8 mL). After 30 min of stirring at 20 °C, a clear solution of reagents 11 or **12** was obtained. Then pyrrole **8** or **9**[16] (0.01 mol) was added followed by acetic acid (0.8 mL). Stirring was continued at 20 °C for 16 h, and then the solution was evaporated. After flash chromatography with dichloromethane or ethyl acetate containing 3–20% methanol as eluent, products **2**, **3**, **5**, and **6** were

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obtained: yields 80–95%. Crystallization gave the pure compounds.

2-[[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]methyl]-5-(4-fluorophenyl)pyrrole (2). After chromatography (dichloromethane–methanol, 95:5) the HCl salt was obtained: yield 82%; crystallization from ethyl acetate; mp 180.5–182.5 °C; NMR (DMSO–$CDCl_3$, 4:1) δ 1.82 (br d, 2 H, H-3′$_{eq}$,5′$_{eq}$), 2.38 (br t, 2 H, H-3′$_{ax}$,5′$_{ax}$), 3.1–3.5 (br m, 4 H, H-2′,6′), 4.35 (br s, 2 H, NCH_2), 5.53 (br s, 1 H, OH), 6.34 (br t, 1 H, H-3), 6.48 (br t, 1 H, H-4), 7.16 (t, 2 H, FArH-3,5, J = 9), 7.39 and 7.47 (2 br d, 4 H, ClArH, J = 8), 7.69 (dd, 2 H, FArH-2,6, J = 6 and 9), 11.7 (br s, 1 H, NH). Anal. ($C_{22}H_{22}ClFN_2O\cdot0.9HCl$): C, H, F, N, Cl.

2-[[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]methyl]-5-[5-(ethylsulfonyl)-2-methoxyphenyl]pyrrole (3): yield 80%; crystallization from ethyl acetate–diisopropyl ether; mp 81–84 °C; NMR ($CDCl_3$) δ 1.27 (t, 3 H, $SO_2CH_2CH_3$, J = 7), 1.82 (br d, 2 H, H-3′$_{eq}$,5′$_{eq}$), 2.37 (dt, 2 H, H-3′$_{ax}$,5′$_{ax}$, J = 13 and 3), 2.90 (br t, 2 H, H-2′$_{ax}$,6′$_{ax}$), 3.08–3.22 (m, 4 H, $SO_2CH_2CH_3$ and H-2′$_{eq}$,6′$_{eq}$), 4.00 (s, 2 H, NCH_2), 4.07 (s, 3 H, OCH_3), 4.90–6.00 (br s, 1 H, OH), 6.24 (br t, 1 H, H-3), 6.65 (br t, 1 H, H-4), 7.06 (d, 1 H, H_3COArH-3, J = 8), 7.27 and 7.41 (2 br d, 4 H, ClArH, J = 8), 7.67 (dd, 1 H, CH_3OArH-4, J = 8 and 2), 8.09 (d, 1 H, CH_3OArH-6, J = 2), 11.2–11.3 (br s, 1 H, NH). Anal. ($C_{25}H_{29}ClN_2O_4S\cdot1.5HOAc$): C, H, N, S.

5-(4-Fluorophenyl)-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (5): yield 51%; crystallization from petroleum ether (40–60 °C); mp 116–118.5 °C; NMR ($CDCl_3$) δ 2.6–2.8 (m, 4 H, H-2′,6′), 3.1–3.2 (m, 4 H, H-3′,5′), 3.61 (s, 2 H, NCH_2), 3.85 (s, 3 H, OCH_3), 6.11 (br t, 1 H, H-3), 6.34 (br t, 1 H, H-4), 6.82–7.11 (m, 6 H, CH_3OAr and FArH-3,5), 7.38–7.50 (m, 2 H, FArH-2,6), 8.9–9.0 (br s, 1 H, NH). Anal. ($C_{22}H_{24}FN_3O$): C, H, F, N.

5-[5-(Ethylsulfonyl)-2-methoxyphenyl]-2-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]pyrrole (6): yield 79%; crystallization from diisopropyl ether; mp 122–124 °C; NMR ($CDCl_3$) δ 1.22 (t, 3 H, $SO_2CH_2CH_3$, J = 7), 2.6–2.7 (m, 4 H, H-2′,6′), 3.0–3.2 (m, 6 H, $SO_2CH_2CH_3$ and H-3′,5′), 3.59 (s, 2 H, NCH_2), 3.80 and 4.00 (2 s, 3 H, OCH_3), 6.10 (br t, 1 H, H-3), 6.60 (br t, 1 H, H-4), 6.8–7.0 (m, 4 H, CH_3OArH), 7.02 (d, 1 H, SO_2ArH-3, J = 8), 7.60 (dd, 1 H, SO_2ArH-4, J = 8 and 2), 7.99 (d, 1 H, SO_2ArH-6, J = 2), 9.7–9.8 (br s, 1 H, NH). Anal. ($C_{25}H_{31}N_3O_4S\cdot0.25HOAc$): C, H, N, S.

***N*-[2-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]ethyl]-4-fluorobenzamide (4).** Compound 4 was prepared by coupling of the 1-unsubstituted piperidine with *N*-(4-fluorobenzoyl)aziridine as described in ref 10b; mp 150–152 °C.

***N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-4-fluorobenzamide (7).** Compound 7 was prepared by reaction of 1-(2-aminoethyl)-4-(2-methoxyphenyl)piperazine with 4-fluorobenzoyl chloride and subsequent conversion into the HCl salt as described in ref 10a; mp 234–238 °C.

Substituted 2-phenylpyrroles 8 and 9 were synthesized by Paal–Knorr cyclization of the corresponding 4-oxophenylbutanals according to Berner.[25] New methods were developed for the synthesis of these intermediates.[16]

2-(4-Fluorophenyl)pyrrole (8).[16] Compound 8 was prepared from 4-fluoroacetophenone by a three-step reaction sequence: yield 50%; mp 123–124 °C.

2-[5-(Ethylsulfonyl)-2-methoxyphenyl]pyrrole (9).[16] Compound 9 was prepared from 5-(ethylsulfonyl)-2-methoxybenzoyl chloride[4b] in two steps: yield 34%; mp 130–133 °C.

(*E*/*Z*)-5-(4-Fluorophenyl)-2-(1-methyl-2-pyrrolidinylidene)-2*H*-pyrrole (15). A solution of iminium salt 14 (0.0055 mol) in 1,2-dichloroethane was prepared from *N*-methyl-2-pyrrolidinone and 8 as described for 13 above. After addition of excess lithium aluminum hydride (0.8 g, 0.021 mol) at 0 °C, stirring was continued at 20 °C for 30 min. Then the reaction was worked up by addition of 5% $NaHCO_3$ and extraction with methylene chloride. The solution was dried ($MgSO_4$) and evaporated. Pure 15 was obtained after crystallization from 2-propanol: yield 0.85 g (76%); mp 164–165 °C; NMR (DMSO–$CDCl_3$, 4:1) δ 2.0–2.2 (m, 2 H, H-4′), 3.30 and 3.32 (2 s, 3 H, *Z*- and *E*-CH_3), 3.8–4.0 (m, 4 H, H-3′,5′), 6.7 (m, 1 H, H-3), 7.05–7.15 (m, 5 H, H-4 and FArH-3,5), 7.77 (dd, 2 H, FArH-2,6).

Biochemistry. Receptor Binding Assays. Binding assays were carried out as described in literature. Thus, [^{3}H]spiperone was used to label dopamine D-2 receptors in the rat corpus striatum[26] or 5-HT_2 receptors in the rat frontal cortex[27] and [^{3}H]WB-4101 was used to label α_1 adrenergic receptors in rat total brain.[28] In all displacement experiments, the drug solution was pipetted manually, the ^{3}H-labeled-ligand solution and the tissue suspension were pipetted automatically by a Filter Prep 101 (Ismatec, Zürich, Switzerland), which further performed the assays up to and including the addition of scintillation emulsifier-299 (Packard) to the glass fiber filters (Whatman GF/B) collected in plastic minivials (Packard). After overnight equilibration, the vials were counted for tritium in a liquid scintillation counter (Packard B-460).

Concentrations of unlabeled drugs causing 50% displacement of specific binding of a ^{3}H label (IC_{50} values) were obtained by computerized log-probit linear regression analysis of data obtained in experiments in which four to six different concentrations of the test compound were used. Inhibition constant (K_i) values were calculated with the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + S/K_d)$ in which S and K_d stand for concentration and dissociation constant of the ^{3}H label, respectively.

Average K_i values were calculated from at least three values obtained in independent experiments, that is, experiments performed on different days, with different membrane preparations. All incubations were done in triplicate. Sodium ratios were determined by also carrying out the spiperone-striatum assay in the absence of sodium ions and dividing both IC_{50} values ($+Na^+/-Na^+$).

Pharmacology. General. The test compounds were dissolved or suspended in a tragacanth solution (1% v/v) or a gelatin–mannitol mixture (0.5:5% v/v) for po and ip administration, respectively. ED_{50} values were estimated from linear regression analysis of the scores of at least three dose levels with the indicated number of animals per dose level.

Apomorphine-Induced Climbing Behavior in Mice. Male Swiss-derived mice (20–26 g) were used. The climbing behavior was scored 10 and 20 min after subcutaneous administration of apomorphine (1 mg/kg) as described by Protais et al.[29] Test compounds were injected to groups of five animals po 60 min or ip 30 min prior to apomorphine.

Conditioned Avoidance Behavior in Rats. Male Wistar rats (300–500 g) were used. The disruption of avoidance behavior was measured in animals previously trained to show high (>80%) and stable avoidance rates, according to a procedure developed by Van der Heyden and Bradford.[30] Test compounds were administered to groups of 12 animals either po 60 min or ip 30 min before measurement.

Catalepsy in Rats. Male Wistar rats (200–250 g) were used. The presence of cataleptic behavior was established by placing the animal with its front paws on a horizontal bar and measuring the time spent in this position according to the method described by Costall and Olley.[31] An animal was considered cataleptic if it maintained this position for more than 10 s. Test compounds were injected to groups of nine animals either po or ip 4 h prior to measurement.

Acknowledgment. We thank Dr. G. J. Katerberg for helpful comments and A. Gieling for the preparation of the manuscript.

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