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Solid State Conformations and Antidopaminergic Effects of Remoxipride Hydrochloride and a Closely Related Salicylamide, FLA 797, in Relation to Dopamine Receptor Models

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SUMMARY

The X-ray structures of two new 2,6-disubstituted benzamides, i.e., remoxipride hydrochloride monohydrate ((−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide hydrochloride monohydrate) and FLA 797 ((−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamide), have been determined as well as the distribution coefficients. The difference in dopamine receptor blocking activity is discussed in terms of lipophilicity and solid state conformations of the two benzamides. The major difference between the solid state conformations lies in the orientation of the carboxamide moiety. In remoxipride the carbonyl group is oriented almost perpendicularly to the benzene ring, thus preventing the formation of a hydrogen-bonded pseudo-ring between the amide hydrogen and the methoxy group found in other types of *o*-methoxybenzamides. In FLA 797, however, this pseudo-ring is present in the planar conformation of the salicylamide moiety. This conformation is further stabilized by a hydrogen bond between the phenol group and the carbonyl oxygen. The side chain in remoxipride adopts an extended conformation in contrast to FLA 797, where the side chain has a folded conformation. The crystal structures are related to current topographic dopamine receptor models developed from more rigid antidopaminergic compounds. Based on these comparisons, it is suggested that benzamides having an *N*-ethyl-2-pyrrolidinylmethyl side chain interact with the receptor in the folded conformation. The binding affinity is thought to be further increased by the planar conformation of the salicylamide moiety present in FLA 797, which permits an efficient π-π stacking interaction.

The substituted benzamides constitute a relatively new class of atypical antipsychotic compounds that have been shown to preferentially block dopamine D-2 receptors, i.e., dopamine receptors not coupled to or negatively coupled to adenylate cyclase (1, 2). Recently, the synthetic (3), pharmacological (3, 4), and clinical studies (5) of the new benzamide remoxipride (rINN) have been reported from our laboratories (Fig. 1). This compound is structurally related to sulpiride, which was the first benzamide found to possess antipsychotic effects in the clinic (6).

Remoxipride was found to be considerably more potent than sulpiride in blocking the apomorphine-induced syndrome in the rat (3, 4). Furthermore, remoxipride inhibits the hyperactivity component of the syndrome at much lower doses than the stereotypy component as shown in Table 1 (3, 4). This has been regarded to reflect a preferential effect in the limbic regions over the striatal regions, which in turn might indicate a low propensity to induce extrapyramidal side effects in man (4). However, the affinity of remoxipride for the ^{3}H-spiperone-binding site (D-2) was found to be unexpectedly low (cf. Table 1) (4). This discrepancy might be due to the formation of active metabolites in the rat. Incubation experiments in the supernatant fraction of rat liver homogenates revealed two such potential metabolites, FLA 797 and FLA 908 (Fig. 1).[2] Both of these 6-methoxysalicylamides were found to be considerably more potent than remoxipride in the spiperone binding assay (see Table 1 for FLA 797). Furthermore, minute amounts of the more potent metabolite FLA 797 were also found in rat urine after administration of remoxipride.[3]

The clinically used dose of sulpiride is relatively high (7), a fact which might be attributed to a limited bioavailability and penetration into the brain (8). This explanation is supported by the low octanol/water partition coefficient (log *P*) and distribution coefficient measured at pH 7.4 (log *D*) by the conventional shake flask procedure (9) (see Table 1). The log *P* values for remoxipride and FLA 797 have been determined by the same procedure and found to be nearly identical, i.e., about 2.0, and considerably higher than for sulpiride (Table 1). This, at first sight, anomalous observation is most likely due to formation of an internal hydrogen bond between the phenol hydrogen and the carbonyl oxygen in FLA 797, thus diminishing the tendency to associate with water. However, the distri-

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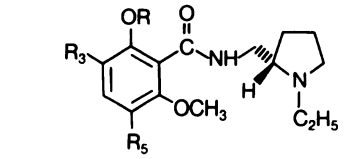
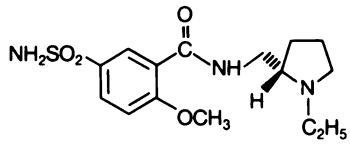
[2] M. Widman, B. Bryske, and B. Termander, manuscript in preparation.

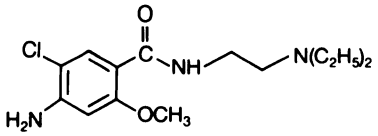
[3] M. Widman, personal communication.



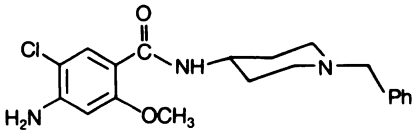
	R	R_3	R_5
Remoxipride	CH_3	Br	H
FLA 797	H	Br	H
FLA 908	H	H	Br
Eticlopride	H	C_2H_5	Cl



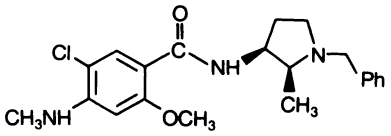
Sulpiride



Metoclopramide



Clebopride



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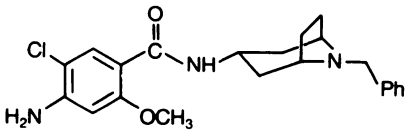

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Fig. 1. Structural formulas of substituted benzamides.

bution coefficients at physiological pH 7.4 are markedly different. The salicylamide FLA 797 was found to be more lipophilic (log D = 1.7) than remoxipride (log D = 0.7), a fact which is attributed to their different dissociation constants (Table 1).

It is not likely that the 100-fold increase in the *in vitro* activity of FLA 797 compared to remoxipride can be rationalized on the basis of lipophilicity arguments only, in particular if one regards the partition coefficient log P as more relevant for the receptor interaction. It is also unlikely that electronic differences in the aromatic moieties of remoxipride and FLA

TABLE 1

Comparison of pharmacological, physicochemical, and crystallographic characteristics of the 2-methoxybenzamides remoxipride, FLA 797, and sulpiride

	Remoxipride	FLA 797	(S)-Sulpiride[a]	
			I	II
^{3}H-Spiperone binding,[b] IC_{50}	1570	12	210	
Inhibition of hyperactivity,[c] ED_{50}	0.86	0.055	28	
Inhibition of stereotypy,[c] ED_{50}	6.5	0.32	162	
Partition coefficient,[d] log P	2.1	2.0	0.50, 0.64[e]	
Distribution coefficient,[d] log D	0.70	1.7	−1.3, −1.1[e]	
Dissociation constant(s), pK_a	8.9	7.4, 9.8	9.0[e]	
Torsion angles,[f] deg				
τ_1 C(6)C(1)-C(7)N(8)	−73	−4	−14	11
τ_2 C(1)C(7)-N(8)C(9)	−176	177	−171	−175
τ_3 C(7)N(8)-C(9)C(10)	116	−160	−111	114
τ_4 N(8)C(9)-C(10)N(14)	−178	−51	171	166
τ_5 C(9)C(10)-N(14)C(15)	−69	−75	−102	−121
N(14) distances,[g] Å				
to benzene ring	7.3	6.0	8.0	7.5
to pseudo-ring		3.6	5.0	5.2
above benzene ring	2.7	0.5	1.1	0.7
Angle between benzene and pyrrolidine rings,[h] deg	27	90	15	60

[a] Crystallographic data on (−)-(S)-sulpiride, which crystallizes in two conformations, I and II, taken from Ma *et al.* (16). Pharmacological data refer to racemic material.
[b] ^{3}H-Spiperone binding in rat brain; IC_{50} is in nM (4, 10).
[c] Inhibition of apomorphine-induced hyperactivity and stereotypy in the rat; ED_{50} is in μmol/kg, intraperitoneally (4, 10).
[d] Distribution coefficients in octanol/water were determined by the shake flask technique at various pH levels between 6 and 9 (9).
[e] Data taken from Ref. 9.
[f] Positive torsion angles (degrees) for clockwise rotation.
[g] Distances are calculated to the center of the benzene ring and the center of the hydrogen-bonded pseudo-ring.
[h] Dihedral angles between least squares planes through the rings.

797 would account for the difference in their *in vitro* activities. Instead, the conformation of these benzamides seems to be of major importance. We therefore performed X-ray crystallographic determinations of the solid state conformations of remoxipride hydrochloride monohydrate and of the salicylamide FLA 797 in base form.

Materials and Methods

Crystal structure determination of remoxipride and FLA 797. Crystals of the two compounds, remoxipride hydrochloride monohydrate ((−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide hydrochloride monohydrate) (3) and FLA 797 ((−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamide) (10), were obtained from 95% aqueous acetone and hexane, respectively. X-ray data were collected at room temperature by the ω-2θ scan technique, $\theta \leq 67°$ on a Philips PW 1100 four-circle diffractometer utilizing graphite monochromatized CuK_α radiation (λ = 1.5418 Å). In each case, accurate unit cell parameters were obtained at 298° K from Guinier powder photographs, using strictly monochromatized $CuK(\alpha_1)$ radiation (λ = 1.5406 Å) with S_i (a = 5.4309 Å) as internal standard. The intensity data were corrected for Lorenz and polarization effects as well as for absorption. Some selected crystal data are listed in Table 2.

Direct methods, using the MULTAN 80 program system (11), gave reasonable models with 15 and 17 non-H atoms, respectively. These

TABLE 2

Selected crystal data for remoxipride hydrochloride monohydrate and FLA 797

	Remoxipride	FLA 797
Formula	$C_{16}H_{23}O_3N_2Br \cdot HCl \cdot H_2O$	$C_{15}H_{21}O_3N_2Br$
Space group	$P2_12_12_1$	$P2_1$
Cell dimensions		
a (Å)	27.185(5)	13.805(8)
b (Å)	9.972(2)	7.232(1)
c (Å)	7.137(1)	8.178(2)
		$\beta = 94.16(2)°$
μ $(cm^{-1})_{CuK\alpha}$	46.5	35.5
Number of unique reflections used $[F \geq 6\sigma(F)]$	1069	1261
Final R value (%)	4.17	3.84

molecular fragments were then completed and refined by a full matrix least squares technique in the SHELX 76 program system (12).

The H atom positions were generated after each cycle of the refinement from geometrical considerations, except for the two H atoms of the water molecule in the remoxipride salt and the amide hydrogen H(8) of the FLA 797 structure, which were located from difference electron density maps and isotropically refined in the subsequent calculations. The phenolic O(2)H atom of FLA 797, however, could neither be generated nor found in the maps.

In the last cycles of the refinement the positions of the non-H atoms were given anisotropic temperature factors. Isotropic group temperature factors were assigned to the hydrogens: one for the H atoms of the methyl groups and one for the remaining calculated H atoms.

The largest parameter shifts for remoxipride and FLA 797 were 0.15 and 0.31 times its estimated standard deviation, respectively, when the final R values of 0.0417 ($R_w = 0.0361$) and 0.0384 were reached. Three reflections (020, 001, and 317) were omitted from the last refinement of FLA 797 due to their abnormally high δ/σ ratio. The absolute configuration of remoxipride, confirming the (S)-form, was determined from the Bijvoet differences (13).

Fractional atomic coordinates and anisotropic temperature factors of the non-hydrogen atoms are deposited with and are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW, England.[4] Lists of calculated and observed structure factors and Bijvoet differences for remoxipride are available from the authors.

Determination of distribution coefficients and dissociation constants. Distribution coefficients in octanol/water were determined by the shake flask technique at various pH values between 6 and 9 (9). Solutions of 10 ml of aqueous saturated octanol and 10 ml of phosphate buffer (μ = 0.1) were shaken for 10 min with 60 shakes/min. After centrifugation for 10 min at 2000 rpm, the concentrations were determined spectrophotometrically, and the distribution coefficient at pH 7.4 (log D) and the partition coefficient for the un-ionized form (log P) were calculated. The pK_a value of remoxipride was determined by potentiometric titration in 0.1 M NaCl solution and that of FLA 797 was determined by photometric titration in 0.1 M KCl.[5]

Results

Solid state conformation of remoxipride hydrochloride monohydrate. Two different perspectives of the solid state conformation of remoxipride are shown in Fig. 2 and some selected crystallographic data are listed in Table 1. The molecular packing arrangement is depicted in Fig. 3.

An important structural feature of the hydrochloride monohydrate salt of remoxipride is the conformation of the carboxamide moiety. The torsion angle through atoms C(6)C(1)-C(7)O(7) is 109°. This almost perpendicular angle between the aromatic ring and the carbonyl group prevents the formation of an intramolecular hydrogen bond between the amide hydrogen atom H(8) and the methoxy oxygen O(6). Instead, the amide hydrogen is involved in intermolecular hydrogen bonding to the oxygen O(W) of the crystal water (cf. Fig. 2 and Table 3). This water molecule participates also as a donor in intermolecular hydrogen bonds to the carbonyl oxygen and to the chloride anion, thus linking the benzamide molecules together along the crystallographic c axis (Fig. 3). Furthermore, the intermolecular distance between the water oxygen and the bromide atom is notably short (3.15 Å). The protonated pyrrolidinyl nitrogen N(14) forms a hydrogen bond to the chloride ion.

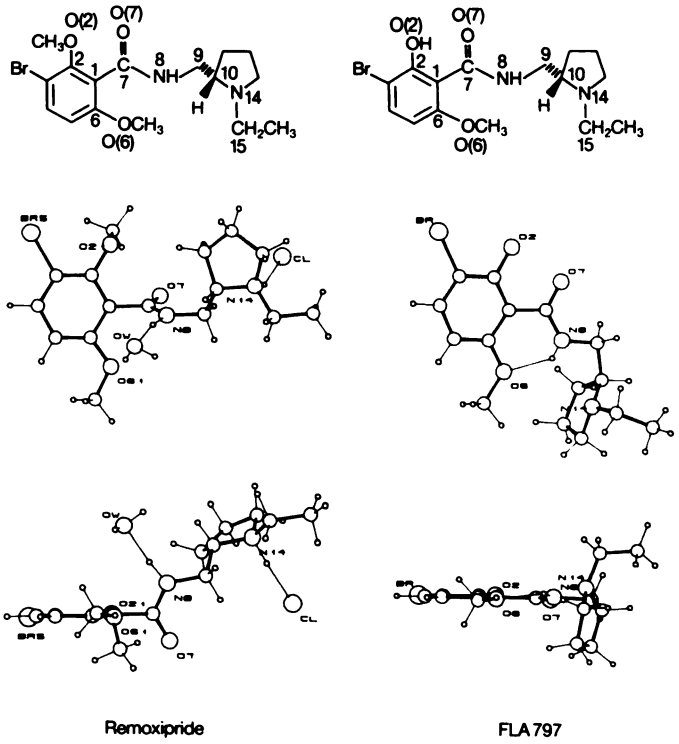


Fig. 2. The solid state conformations of remoxipride hydrochloride monohydrate and FLA 797 in base form shown from two different angles. *OW*, oxygen in crystal water.

In agreement with the crystal structure of sulpiride, the interchain NC-CN adopts a *trans* conformation (τ_4 shown in Table 1). The pyrrolidine ring conformation has a near half-chair form with the phase angle $P = -14(2)°$ calculated according to the method of Cremer and Pople (14), and with the 2-fold axis through the C(12) atom. The dihedral angle between the least squares planes of the benzene and the pyrrolidine rings is 27°, quite in agreement with the 28° found in racemic sulpiride (15), but different from the two solid state conformations of (S)-sulpiride shown in Table 1 (16).

Solid state conformation of FLA 797. The benzamide part of FLA 797 is planar, as shown in Fig. 2, with some minor deviations from 0° torsion angle [maximum is −5.1° for atoms C(2)C(1)-C(7)O(7)]. The r.m.s. atomic displacement from the least squares plane through the molecule, excluding the pyrrolidine moiety, is 0.04 Å. This planar conformation of the sali-

[4] Any request should be accompanied by the complete literature citation of this paper.

[5] A. Ohlberger, personal communication.

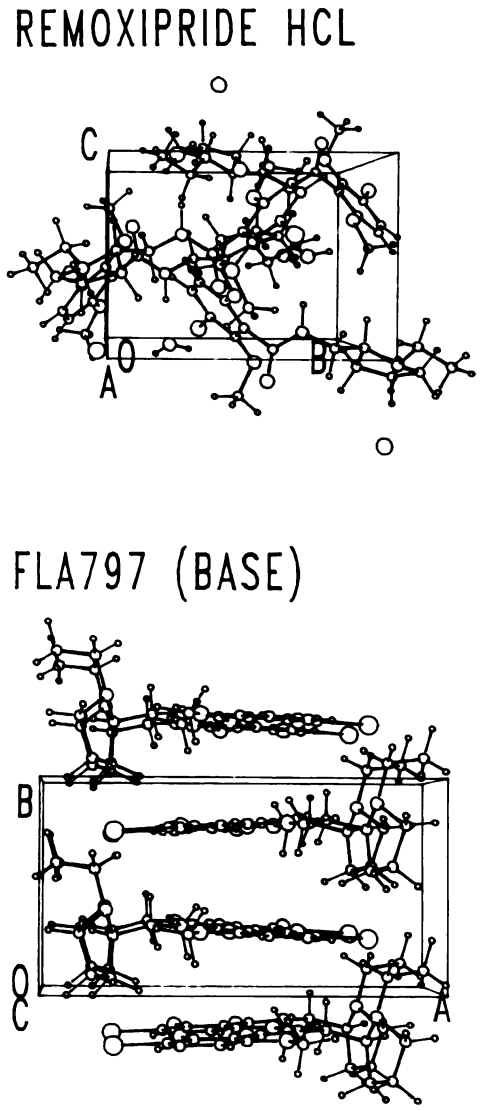


Fig. 3. The crystal packing arrangements of remoxipride hydrochloride monohydrate and FLA 797 in base form.

TABLE 3

Intra- and intermolecular hydrogen bond distances (Å) and angles (degrees) for remoxipride hydrochloride monohydrate and FLA 797

The estimated standard deviations, where given, are in parentheses.

Atoms	Donor.. Acceptor	Donor-H	H..Acceptor	Donor-H.. Acceptor
		Å		degrees
Remoxipride				
N(8)-H(8)..O(W)[a]	2.89(1)	1.08[b]	1.82	170
N(14)-H(14)..Cl[a]	3.06(1)	1.08[b]	2.07	151
O(W)-H(W2)..O(7)[c]	2.94(1)	0.64(13)	2.37(14)	150(14)
O(W)-H(W1)..Cl[c]	3.13(1)	0.95(9)	2.21(9)	161(8)
FLA 797				
N(8)-H(8)..O(6)[a]	2.588(5)	0.82(5)	1.95(6)	135(5)

[a] Symmetry operations: x,y,z.
[b] Standard distance.
[c] Symmetry operations: x,y,z^{-1}.

cylamide moiety is stabilized by intramolecular hydrogen bonds from the amide hydrogen H(8) to the methoxy oxygen O(6) atom and probably also another one between the O(2)H phenol group and the carbonyl O(7) atom. The hydrogen position in the latter interaction could not be determined, but the short non-bonded distance O(2)...O(7) = 2.46 Å and the comparison with the related salicylamide eticlopride (Fig. 1) strongly support the existence of this additional hydrogen bond (17, 18).

The dihedral angle formed by the calculated least squares planes through the benzene and pyrrolidine rings is 90° due to the interchain NC-CN *gauche* conformation (τ_4 shown in Table 1). As a consequence of this molecular conformation, the distance between N(14) and the center of the aromatic ring is shortened in FLA 797 in comparison to remoxipride (Table 1). The conformation of the pyrrolidine ring is intermediate between envelope and half-chair as shown by the phase angle $P = -48(2)°$ calculated according to the method of Cremer and Pople (14).

The planarity of the salicylamide moiety and the lack of intermolecular hydrogen bonds result in a molecular packing shown in Fig. 3. The molecules, in a planar arrangement, are stacked along the crystallographic b axis. By virtue of the 2-fold screw axis, adjacent planes contain molecules with opposite orientations. The interplanar spacing is 3.6 Å and thus is of the same magnitude as common van der Waals contact distances.

Discussion

The major difference between the conformation of remoxipride and that of the salicylamide FLA 797 lies in the orientation of the carbonyl group and in the interchain NC-CN conformation. The planar conformation of the benzamide moiety in FLA 797 is stabilized by the intramolecular hydrogen bond between the amide and the methoxy group forming a pseudo-ring. Such a pseudo-ring has been found in the solid state conformations of other neuroleptic 2-methoxybenzamides including sulpiride (15, 16, 19), eticlopride (17, 18), metoclopramide (20), and YM-09151-2 (21) (Fig. 1). The presence of a pseudo-ring also in solution has been demonstrated for metoclopramide in $CDCl_3$ (22). This intramolecular hydrogen bond was not found in aqueous solution in contrast to $CDCl_3$, which lacks possibilities for efficient competing external hydrogen bonds. In the case of the salicylamide FLA 797, the planar conformation can be further enforced by an additional hydrogen bond between the phenol and carbonyl group. Such an additional hydrogen bond has been found in other related 6-methoxysalicylamides, e.g., eticlopride (17, 18).

Topographic models of the neuroleptic dopamine receptor have been developed based on distance and angle parameters from pharmacophores of rigid dopamine receptor blockers (23, 24). The crucial distances are between the center of the aromatic ring and the nitrogen atom and the distance of the nitrogen atom above a plane through the aromatic ring. These parameters found in the solid state conformations of remoxipride, FLA 797, and (S)-sulpiride are shown in Table 1. It is obvious that the torsion angles τ_3 and τ_4 largely determine these parameters as shown by the comparison of (S)-sulpiride and FLA 797, both having a planar pseudo-ring with almost identical torsion angles τ_1 and τ_2. The folded conformation of FLA 797 results in a considerably shorter distance (6.0 Å) between the aromatic center and the nitrogen atom compared to the extended conformations of remoxipride and (S)-sulpiride (about 7.5 Å). Varying side-chain conformations have been documented for other substituted benzamides as well. The distances between the aromatic ring and the nitrogen are in the range of 6–8 Å as shown in Table 4. As pointed out earlier,

TABLE 4

Topographical features derived from various antidopaminergic compounds

Distances from the nitrogen to the center of the aromatic ring (Ar-N) and above the aromatic ring plane (N-plane) are shown.

Compound	Ar-N	N-plane	Method	Ref.
	Å			
Remoxipride·HCl	7.3	2.7	X-ray	
FLA 797	6.0	0.5	X-ray	
(*S*)-Sulpiride				
mol I	8.0[a]	1.1[a]	X-ray	16
mol II	7.5[a]	0.7[a]		
(±)-Sulpiride	7.4[a]	0.8[a]	X-ray	15
(±)-Sulpiride·HCl	6.1[a]	2.3[a]	X-ray	19
Eticlopride·HCl	6.1	2.6	X-ray	17, 18
Metoclopramide	6.3	1.6	X-ray	20
YM-09151-2	6.3	0.9	X-ray	21
Clebopride	7.6[b]	0.0[b]	Theor.	25
	7.4[c]	0.0[c]		
BRL 25594	7.4[c]	0.0[c]		
(±)-Butaclamol·HBr	5.1[a]	0.5[a]	X-ray	30
(+)-Isobutaclamol·HBr	6.0[a]	1.1[a]	X-ray	26
Piquindone·HCl	5.9	0.1	X-ray	24

[a] Distances were calculated from the X-ray coordinates obtained from Cambridge Crystallographic Data File.

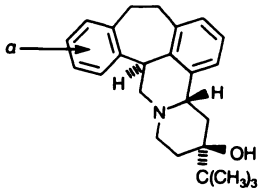
[b] Distances in the low energy conformation were derived from PCILO calculations of a model compound (25).

[c] Geometry was obtained from standard bond distances and angles with the molecular modeling subset of CHEMGRAPH, Chemical Design Ltd. version, October 1985.

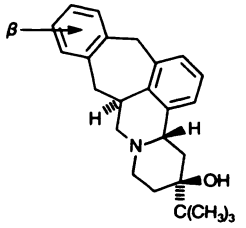
the benzamide moiety possesses a planar arrangement in the solid state in all cases examined with the exception of remoxipride (15–22). Thus, this low energy benzamide conformation is observed for compounds both in base and salt form (Table 4). However, it must be emphasized that the number of plausible side-chain conformations is large, mainly due to variations in τ_3 and τ_4. It has been calculated that the energy difference between the folded and extended conformers of pyrrolidinyl benzamides is only a few kcal/mol (22, 25).[6] Thus, FLA 797 could, without passing serious energy barriers, adopt an extended conformation on interacting with the dopamine receptor. The reverse applies for remoxipride and (*S*)-sulpiride. The X-ray conformation should certainly not *a priori* be regarded as the bioactive conformation, a fact which is further underlined in Table 4, showing three different X-ray studies on sulpiride revealing both extended and folded forms.

Further information about the conformers actually responsible for the dopamine receptor blocking activity can be obtained from comparisons with conformationally restricted compounds. Thus, butaclamol and isobutaclamol provided the basis for Humber's widely used dopamine receptor model (23) (Fig. 4). This model implies a flat phenyl ring binding site with the dimensions of at least two adjoining benzene rings (α and β regions) having their centers 5.1 and 6.4 Å, respectively, from the nitrogen. The nitrogen binding site was positioned 0.9 Å above the ring plane based on modeling studies of the assumed bioactive conformer B rather than on the conformer A. The former conformer was found in the crystal structure of (+)-isobutaclamol, whereas the latter was found in (±)-butaclamol and (+)-dexclamol (26) (cf. Table 4). It should be noticed that this model also predicts the presence of a lipophilic accessory

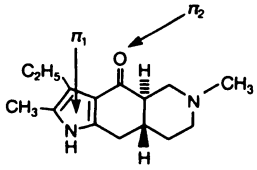
[6] T. Högberg, U. Norinder, S. Rämsby, and B. Stensland, manuscript in preparation.



Butaclamol



Isobutaclamol



Piquindone

Fig. 4. Conformationally restricted neuroleptics used in dopamine receptor mapping (23, 24).

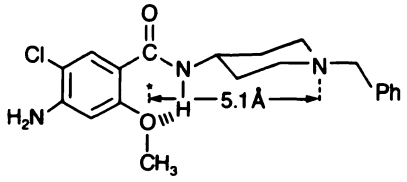


Fig. 5. Distance between the hydrogen-bonded pseudo-ring and the nitrogen atom which have been suggested to be essential for the binding of clebopride to the dopamine receptor (25). The conformation was derived from standard bond distances and angles with the molecular modeling subset of CHEMGRAPH.

binding site centered 4.5 Å away from the nitrogen-binding site.

Certain 2-methoxybenzamides exist almost exclusively in extended conformers, e.g. 4-piperidyl derivatives and bicyclic tropane derivatives exemplified by clebopride and BRL 25594 (see Table 4 and Fig. 1). In both series the N-benzyl substituent seems to be a prerequisite for high antidopaminergic activity, which suggests an accessory binding for this group (27, 28). The obvious problem, to accommodate extended 2-methoxybenzamide derivatives to Humber's receptor model, led van de Waterbeemd and Testa (25) to view the pharmacophore of these compounds differently. They proposed that the receptor model could be applied for the extended *o*-anisamides as well, if the hydrogen-bonded pseudo-ring is playing the role of the aromatic pharmacophore with affinity for the α region of the topographical dopamine receptor (Fig. 5). Such a model will be in accordance with the solid state conformations of (*S*)-sulpiride (5.0 and 5.2 Å) but not with the more potent salicylamide FLA 797 (3.6 Å). Conversely, if the aromatic ring in FLA 797 is regarded as the pharmacophoric group which binds to the α-β region, the folded solid state conformation of FLA 797 will

fit Humber's receptor model as shown in Fig. 6 (cf. Tables 1 and 4). However, the relevance of these comparisons of the *N*-ethyl-2-pyrrolidinylmethyl benzamides with butaclamol-isobutaclamol derivatives should be questioned. The former lack capabilities of efficient binding to the lipophilic accessory binding site required in the latter case. These discrepancies between the two structure classes make it desirable to relate benzamides like FLA 797 to other conformationally restricted compounds without this accentuated need for an accessory binding.

A rigid pyrroloisoquinoline derivative, piquindone, shown in Fig. 4, served as a template for another receptor model proposed by Olson *et al.* (24). Piquindone appears to be a more suitable rigid model for the flexible benzamides than the butaclamol derivatives due to the closer chemical relationship. Thus, the pyrroloisoquinoline structure contains three pharmacophoric groups, namely, a π-excessive 3-pyrrole moiety (π_1-site), a keto function (π_2-site) and a tertiary amine nitrogen to be compared with the 2-hydroxy-6-methoxyphenyl group, the amide carbonyl, and the pyrrolidine nitrogen in FLA 797, respectively. The distance between the tertiary nitrogen and the aromatic group is practically identical for the two compounds as shown in Table 4. Also, in piquindone the nitrogen is close to the plane of the aromatic ring. Importantly, this receptor model does not require bulky lipophilic groups for interaction with the accessory binding site, but such groups are reported to be tolerated and even to enhance ^{3}H-spiperone binding potency in the piquindone series (24, 29).

The low *in vitro* dopamine receptor blocking activity of remoxipride is rationalized on the basis of the solid state conformation of the hydrochloride salt. The receptor models discussed above call for a relatively large planar aromatic pharmacophore which allows an efficient π-π stacking interaction. The difference in the packing behavior of FLA 797 and remoxipride is apparent in Fig. 3. These arrangements in the solid state may reflect the tendency of the molecules to participate in π-π stacking with the receptor. The planar salicylamide in FLA 797 provides for a perfect stacking with interplanar distances of ca. 3.6 Å. In contrast, no intermolecular stacking is observed for remoxipride. Except for the salt hydrogen bonding [N(14)-H···Cl] and ordinary intermolecular van der Waals forces, the crystal packing is affected by the hydrogen bonding to the crystal water [N(8)-H···O(W)-H···O(7)]. Thus, a π-π stacking at the receptor is rendered more difficult with remoxipride, having the carbonyl group forced out of planarity with the phenyl ring as indicated by the X-ray structure. However, it might be argued that this conformation in the crystal lattice could have been supported by the external hydrogen bonding of the carbonyl oxygen to the crystal water [cf. above-mentioned solvent effects on conformations of metoclopramide (22)]. Work is in progress to elucidate this factor.

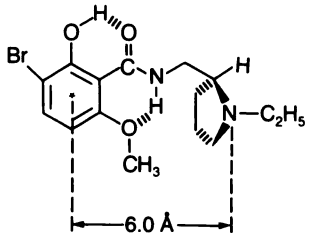


Fig. 6. Distance between the aromatic ring and nitrogen atom in the folded conformation found in the solid state of FLA 797. A conformation suggested to interact with the dopamine receptor.

The present work supports the view of the importance of the hydrogen-bonded pseudo-ring to provide the conformational constraint necessary for high binding affinity to the dopamine receptor. It also seems likely that the 2-methoxybenzamide derivatives having *N*-ethyl-2-pyrrolidinylmethyl side-chains exert their action via the folded conformation with the amine function close to the aromatic plane as found for the solid state structure of FLA 797 (Fig. 6). This means that the phenyl ring represents the aromatic pharmacophore (π_1-site) rather than the pseudo-ring in the topographical receptor models. The latter ring might, however, as originally suggested by van de Waterbeemd and Testa (25), be implied in the explanation of the pharmacophore of extended *N*-benzyl-4-piperidyl derivatives requiring an accessory lipophilic site (Fig. 5).

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