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Structural requirements of Na^+-dependent antidopaminergic agents: Tropapride, Piquindone, Zetidoline, and Metoclopramide

Comparison with Na^+-independent ligands

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SUMMARY

Molecular graphic design coupled with PCILO and crystallographic results have been used to investigate the three-dimensional structure of Tropapride, Piquindone, Zetidoline, and Metoclopramide, four dopamine D-2 receptor antagonists showing Na^+-dependent binding. Three putative pharmacophoric elements, a nitrogen lone pair, a phenyl ring and a carbonyl moiety, are similarly oriented in all the Na^+-dependent drugs. Conversely, for Na^+-independent analogs, the two latter pharmacophoric elements play a subordinate role, but two Π-electron regions are systematically localized on the other side of the molecule: the first is a phenyl group while the second is a carbonyl function as in butyrophenones, a cyano group as in R48455, or a phenyl ring as in diphenylbutylpiperidines or tricyclics. The presence of a benzyl ring on this side in Tropapride might explain its weak extrapyramidal effects.

INTRODUCTION

Different families of compounds, including butyrophenones, diphenylbutylpiperidines, tricyclics, and various substituted orthopramides are used as antipsychotic drugs. These molecules show high affinity and selectivity mainly for dopamine receptors, usually subdivised into D-1 and D-2 subclasses [1]. Some compounds display selectivity towards D-1 receptors, such as Piflutixol (tricyclic), while others are highly selective towards D-2 receptors, as for example Sulpiride and Tropapride.

In recent years, a number of original structures including Piquindone (indolone) and Zetidoline (imidazolidinone) presenting a strong affinity for dopamine D-2 receptors have been found. These original compounds have been classified as atypical neuroleptics by analogy with the substituted benzamides, since they appeared to be devoid of extrapyramidal side effects. Moreover, it has been shown that their binding to dopamine receptors is highly sodium-dependent [2–5]. Stereochemical, conformational, electronic, and lipophilic properties should account for these pharmacological similarities. In that sense, stereoelectronic analogies have been previously reported by molecular electrostatic potential maps [6].

In this paper, we will attempt to define the three-dimensional requirements leading to the Na^+-dependent or -independent D-2 receptor binding. Structural results obtained from X-ray crystallography and conformational calculations will be used as starting point for molecular computer-aided comparisons. In a first step, we will verify whether Tropapride [7, 8] and Piquindone [9], two 'rigid' Na^+-dependent D-2 antagonists, may fit the same pharmacophoric pattern. The next logical step will compare these results with the ones obtained for 'flexible' atypical antipsychotics, Zetidoline [4, 10, 11] and Metoclopramide [12]. Finally, comparisons will be made between these four compounds and some Na^+-independent derivatives: R48455 [13], Pimozide [14], Spiperone [15], Dexclamol [16], and Chlorpromazine [17] (see Fig. 1).

METHOD

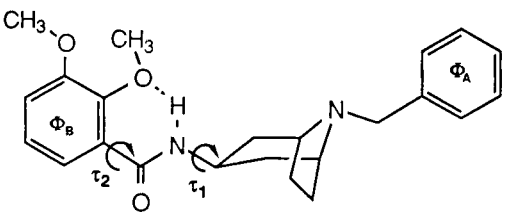
Structural data used for the theoretical conformational analysis and the subsequent molecular comparisons have been obtained in our laboratory by single crystal X-ray diffraction [6, 8, 18–25], or through the Cambridge Structural Database [26].

Conformational analysis has been performed with the largely tested PCILO (Perturbative Configuration Interaction using Localized Orbitals) method [27,28]. An enhanced version, DPCILO (Differential PCILO) [29], implemented on the IBM 4341-2 of the Namur SCF (Scientific Computing Facility) Center, has been used to produce a two-dimensional isoenergy values map by systematic variation – increment between successive calculations: 10° – of the freely rotating torsion angles.

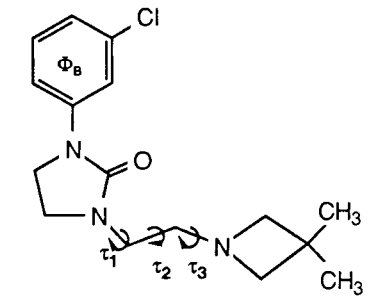
Comparisons of molecular models and searches for an optimal matching between the possible molecular conformations have been done using the in-house Molecular Graphic System (MGS) [30] developed on the IBM 4341-2 of the SCF Center. MGS is a highly interactive molecular modelling program (i) based on PHIGS (Programmer's Hierarchical Interactive Graphic System) as it is implemented by IBM in its GDDM/graPHIGS software, (ii) workstation-independent (IBM 3179-G terminal, IBM 5080 workstation, etc.). Real time interactivity is fully achieved on the IBM 5080 equipped with dials and the 5083 tablet.

Besides fully interactive three-dimensional visualization and manipulation of one or more molecular structures (eventually independently of each other), the MGS system allows intra- or intermolecular geometric calculations, generation of various conformers, link of preexistent fragments, comparison (fitting) of molecular models, dynamical simulations, etc. In the actual version, the molecular structures may be represented as wire frames and/or dot surfaces envelopes. The program is interfaced with the IBM Winchester Solid Modelling program, WINSOM [31], which allows to build raster pictures of any objects. For our purposes, WINSOM is mainly used for stick-and-ball and space-filling representations of molecules.

Na^+-dependent compounds



Tropapride



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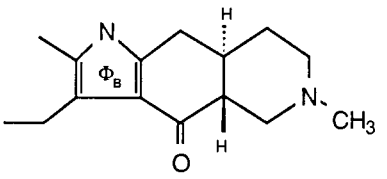
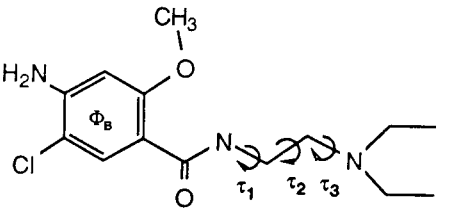
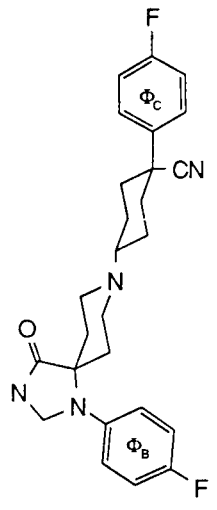


Piquindone

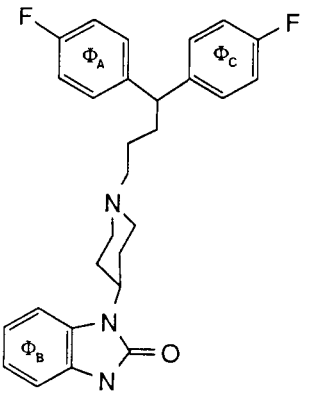


Metoclopramide

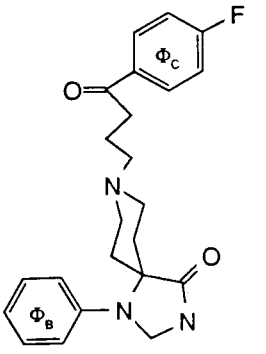
Na^+-independent compounds



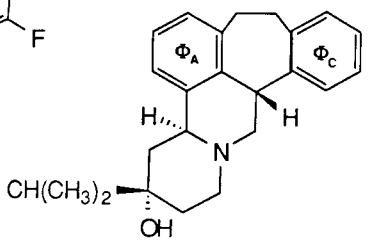
R48455



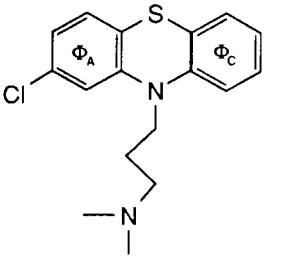
Pimozide



Spiperone



Dexclamol



Chlorpromazine

Fig. 1. Structural formulae of the Na^+-dependent and Na^+-independent compounds studied.

Comparisons of the molecular structures were performed by using a molecular least-squares fitting between the atomic coordinates or particular points (lone pairs, centroids, etc.) of each molecule with the IFMFIT (Improved or Interactive Molecular Fitting) [32] based on the Distance Matrix algorithm [33]. The quality of the superimposition might also be viewed in terms of volumes comparisons by taking into account the differences of the van der Waals envelopes built with the WINSOM software [31].

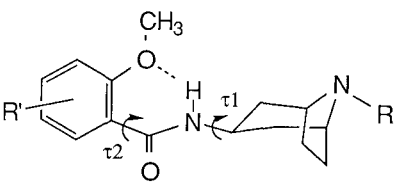
RESULTS AND DISCUSSION

Comparison between Tropapride and Piquindone, two 'rigid' Na^+-dependent D-2 antagonists

Tropapride is a very potent antidopaminergic agent belonging to a well-known neuroleptic class, the benzamide nortropanes, whose main particularity is a selective binding to D-2 receptors in a highly Na^+-dependent manner [2]. Tropapride is composed of two phenyl rings, one amide function, and one piperidinic ring blocked by an ethylene bridge; two freely rotating interatomic bonds (τ_1 and τ_2) may be considered in the 4-benzamido nortropane moiety (see Fig. 1).

The crystal structures of two polymorphic forms of Tropapride and those of several Tropapride analogs previously published show the relative structural rigidity of this family (see Table 1). The two constitutive groups of the benzamide moiety, phenyl Φ_B and amide, are nearly coplanar ($-19° < \tau_2 < 20°$). This geometry results from the existence of an intramolecular hydrogen bond between the oxygen atom of the *ortho* methoxy group and the amide nitrogen. In order to minimize the steric hindrance with the nortropane group, the carbonyl function is always oriented quasi antiparallel (ca. $180° \pm 40°$) to the piperidinic nitrogen lone pair ($75° < \tau_1 < 161°$ in Table 1) (see also Fig. 2).

TABLE 1
τ_1 AND τ_2 TORSION ANGLES (DEG) OBSERVED IN CRYSTAL STRUCTURES OF TROPAPRIDE ANALOGS. E.S.D.'s IN PARENTHESES



Tropapride analogs	Refs.	τ_1	τ_2
Tropapride $P2_1/n$	8	152.7(6)	15.3(9)
Tropapride Pbca	23	80.9(3)	20.4(4)
MD320083	22	103.9(6)	−19.1(8)
MD320634	25	159.7(4)	14.0(5)
MD790403	24	75.0(4)	−13.5(5)
MD320829	24	161.3(2)	9.1(3)
MD320389	18	116.6(3)	− 1.2(5)
MD320047	19	129.5(9)	− 9 (1)

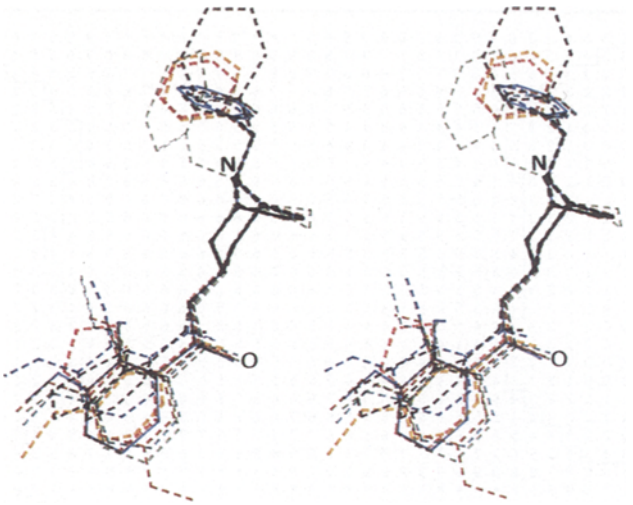


Fig. 2. Stereoscopic view of the molecular 'rigid' fitting of the crystalline conformations of Tropapride $P2_1/n$ (blue solid line), Tropapride Pbca (blue dotted line), MD320083 (beige dotted line), MD320634 (green dotted line), MD790403 (black dotted line), MD320829 (red dotted line), MD320389 (turquoise dotted line) and MD320047 (brown dotted line), obtained by superimposition of the nortropane rings.

PCILO calculations applied on Tropapride confirm this relative rigidity (Fig. 3); the phenyl ring Φ_B is maintained relatively coplanar versus the amide function, $-60° < \tau_2 < 60°$, while the amidic hydrogen is preferentially oriented in anti versus the axial nortropane hydrogen, $10° < \tau_1 < 230°$. Concerning the τ_1 torsion angle, PCILO calculations show a larger allowed low-energy region; moreover, a small allowed area appears around $\tau_1 = 300°$ corresponding to a perfect alignment of the amidic and nortropane hydrogen atoms. These conformations have, however, never been observed in any of the published crystal structures of nortropane benzamides [26]. It has to be pointed out that the two observed crystalline state geometries of Tropapride, marked by A and B symbols in Fig. 3, correspond to theoretical stable conformations ($\Delta E = 1$ kcal/mol).

These results lead us to suggest a model of three pharmacophoric elements for benzamide ligands at the D-2 receptor [34] (Fig. 4):

- the endocyclic nitrogen lone pair;
- the phenyl ring Φ_B of the benzamido group presenting a quasi parallel orientation as compared to the direction of the piperidinic nitrogen lone pair;
- the carbonyl group oriented in an antiparallel direction to the nitrogen lone pair. This orientation is particularly observed if a pseudo-six-membered ring is formed by an intramolecular hydrogen bond (dotted line in Fig. 4) between the lone pair of the *ortho* methoxy oxygen atom and the amide hydrogen, resulting in the coplanarity between the amide group and the phenyl ring.

At this step, we do not know if the drug interacts with the receptor in a protonated or a neutral form. The pKa values [34] are in agreement with the first hypothesis while the receptor lipophilic environment [35] is consistent with the former. Nevertheless, this problem is more apparent than real because the proton points in the same direction as the lone pair.

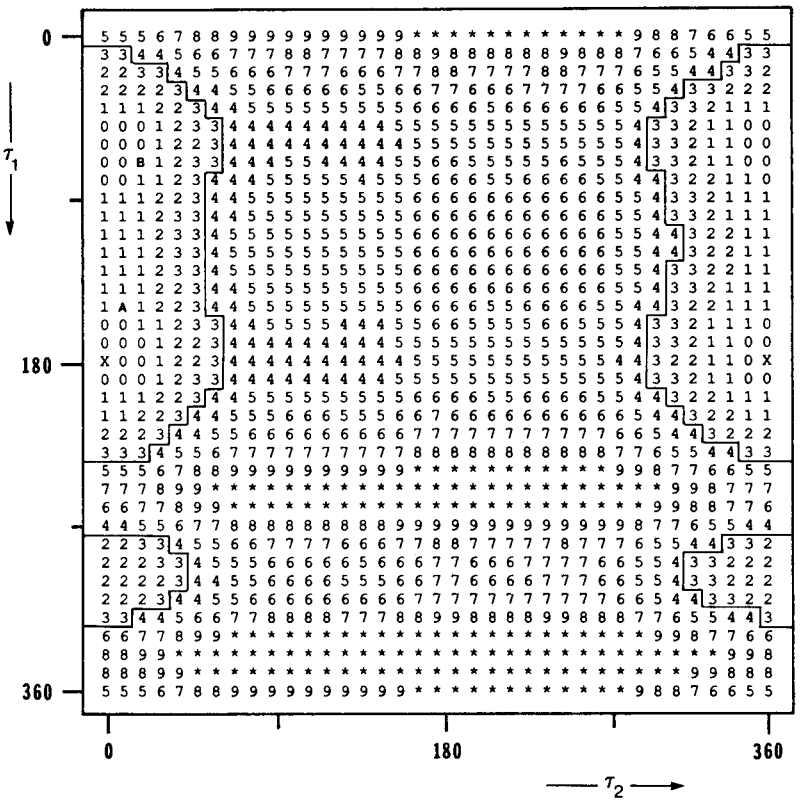


Fig. 3. PCILO conformational isoenergy values map (ΔE in kcal/mol) of Tropapride. The × symbol corresponds to the calculated absolute minimum energy. The * symbol indicates ΔE values = 10 kcal/mol. A and B correspond to the crystalline state conformation of Tropapride in the $P2_1/n$ and Pbca space groups, respectively.

As described in earlier papers, this proposed model explains the total D-2 inactivity of a large number of Tropapride analogs such as the anilide [36], the thioamide [37], the sulphonamide [38], the 4-axial isomer [8], the two 3-substituted isomers [39], the di*ortho* methoxy benzamide [8], etc.

The molecular superimposition presented in Fig. 5 shows that the three pharmacophoric elements proposed for the 4-benzamido-nortropanes are similarly localized in Piquindone, another Na^+-dependent dopamine antagonist.

The more basic nitrogen of Piquindone corresponds to the piperidinic one; the phenyl moiety is here replaced by a pyrrolidyl ring. Both carbonyl moieties and both aromatic rings are well fitted but no perfect superimposition of the nitrogen lone pairs is observed (distances between the two nitrogen atomic centers and between their lone pairs extremities are 1.9 and 1.0 Å, respectively). We believe that the weak difference of nitrogen lone pair orientations is only of minor importance for good receptor binding and that the receptor flexibility could certainly accommodate to small differences in orientation. Most probably, it is the orientation of the lone pairs (or of the hydrogen atoms) to an identical receptor site rather than their perfect fitting which plays the most important role [40].

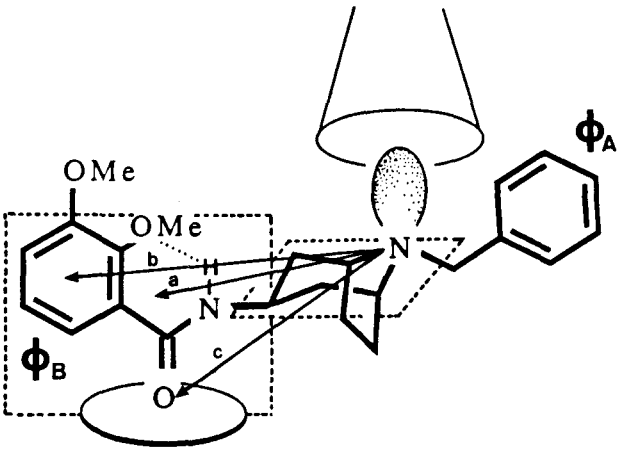


Fig. 4. Pharmacophoric model proposed for the 4-benzamido-nortropane ligands for the D-2 receptor ($5.3 \leq a \leq 5.7$ Å, $7.7 \leq b \leq 7.9$ Å, $5.4 \leq c \leq 5.6$ Å).

We might also suggest that poorly basic compounds, such as Piquindone (pKa = 7.90 [34]), will cause a minor perturbation on the complementary site of the receptor. Consequently, such molecules may have an optimal orientational position of the N atom with respect to the other elements of the pharmacophoric model. According to this hypothesis, we might suppose that more strongly basic compounds such as Tropapride (pKa = 8.91 [34]) would perturb more easily the receptor topography to orient the three receptor sites in an adequate way.

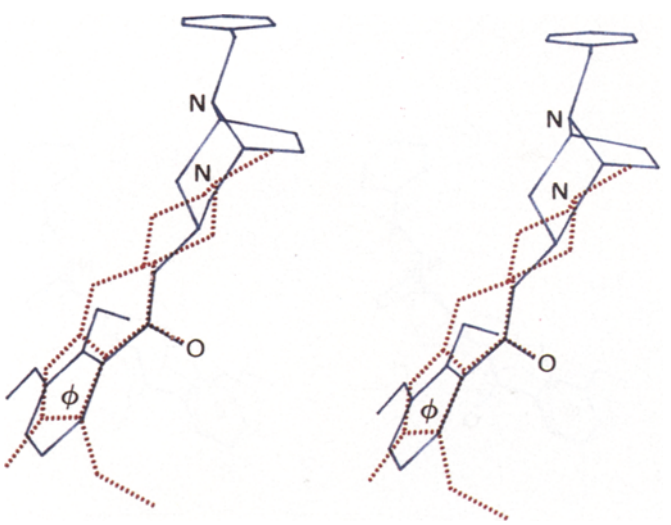


Fig. 5. Stereoscopic view of the molecular 'rigid' fitting of the Tropapride (blue solid line) and Piquindone (red dotted line) crystalline conformations obtained by superimposition of the carbonyl functions and the aromatic rings.

Comparison between Tropapride and a 'flexible' derivative: Zetidoline

Since Zetidoline is a highly flexible molecule (three single bonds) we compared its X-ray structure to Tropapride allowing conformational variations around the single bonds. Crystallographic and ab initio theoretical results have previously shown that the phenyl moiety of Zetidoline is coplanar to the imidazolidinone ring while the side chain is completely free [6].

A first molecular comparison might be done by considering the molecules as sticks and nodes. The two first pharmacophoric elements, the carbonyl groups and the phenyl rings, of Tropapride and Zetidoline can be fitted by 'rigid' superimposition (Fig. 6A). To reach a good matching of the third element, the endocyclic nitrogen lone pair, we need to pass to a 'flexible' step with successive rotations around the freely rotating bonds τ_1 and τ_2 in Zetidoline. Respective rotations of $-19.8°$ and $3.5°$ lead to an optimal geometric superposition as shown in Fig. 6B.

It can be stressed that the chlorine atom in Zetidoline corresponds to a position in benzamides

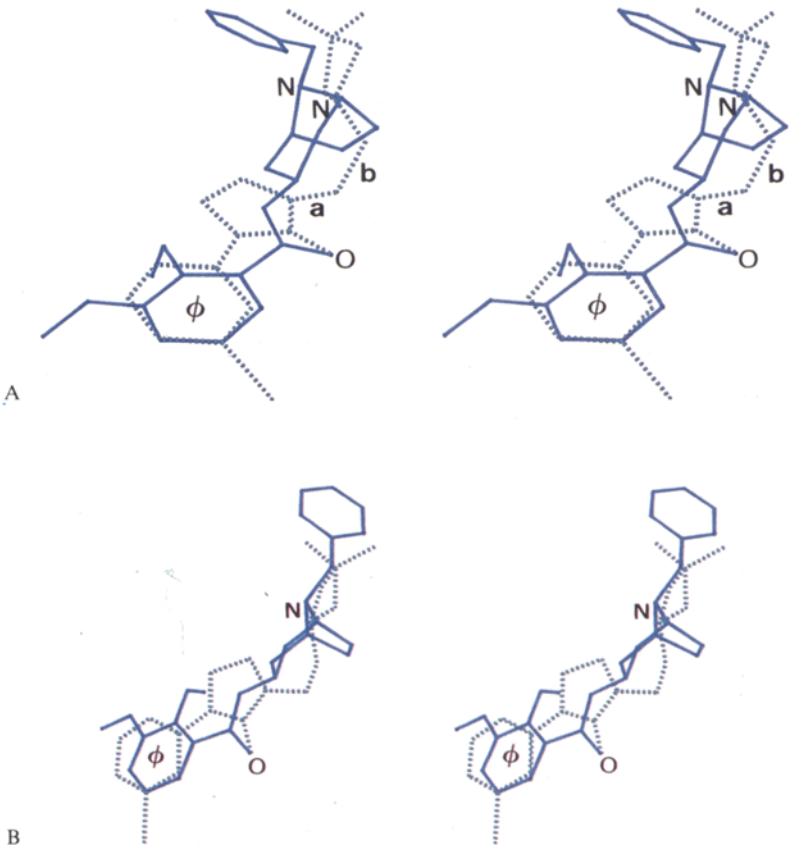


Fig. 6. Stereoscopic views of the molecular: (A) 'rigid' and (B) 'flexible' fittings between Tropapride (blue solid line) and Zetidoline (turquoise dotted line) obtained as detailed in the text.

often substituted by a similar atom, e.g., in Clebopride and Metoclopramide. As suggested for Tropapride, the Zetidoline strong basicity (pKa = 9.19 [34]) would induce an optimal disposition between the ligand nitrogen lone pair and the acceptor site of the receptor.

Alternatively, comparisons might be achieved by considering the molecular volumes available through the WINSOM solid modelling software [31]. Starting with fairly good superposable structures as described above, volume difference maps were generated (Fig. 7).

The empty space in the center of Fig. 7A, obtained by subtracting the Tropapride volume from the Zetidoline one, shows that the Zetidoline side chain is moving towards partially filling the spatial volume of the nortropane ring. The largely filled space on the left of Fig. 7A, on the other hand, indicates that the Zetidoline five-membered ring induces a larger steric hindrance than the one observed for the Tropapride amide group. The benzyl group of Tropapride has no correspondence in Zetidoline as represented by the filled space at the right of Fig. 7B, obtained by subtracting the Zetidoline volume from the Tropapride one. This last observation suggests that the N-substitution would not decrease the activity of Zetidoline if the transport and the distribution of the drug is not perturbed.

Comparison between previously studied compounds and the 'flexible' Metoclopramide

Metoclopramide presents a very flexible structure (three single bonds) [12]. By comparison with Tropapride, a first folded conformation corresponding to the crystalline structure shows the three proposed pharmacophoric elements, the basic nitrogen lone pair, the carbonyl moiety, and the phenyl ring, in a quasi similar orientation (Fig. 8A). In this superimposition, the phenyl rings are parallel oriented but not exactly superimposed (distance between the centroids of the phenyl rings is 1.4 Å).

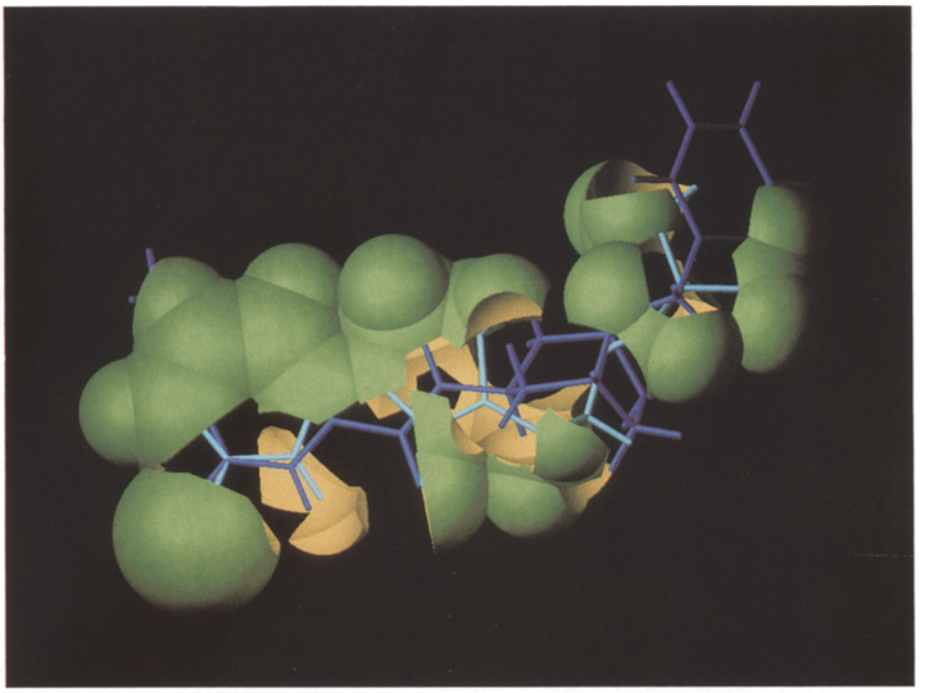
A second stable conformation [12] of Metoclopramide, more extended, is still better fitted to Tropapride or Zetidoline (Figs. 8B and C). However, the molecular superposition presented in Fig. 8D shows that Piquindone is very similar to the folded Metoclopramide. Further investigations are thus needed to discriminate between the two proposed conformations of Metoclopramide. In fact, the strong basicity of its nitrogen atom (pKa = 9.27 [34]) probably allows the binding of the two conformers to the receptor.

Figure 9, presenting the superimposition of the four studied Na^+-dependent antipsychotics with two other well-known Na^+-dependent derivatives, Sulpiride and YM-09151-2, shows again that the three proposed pharmacophoric elements are similarly oriented in all these compounds.

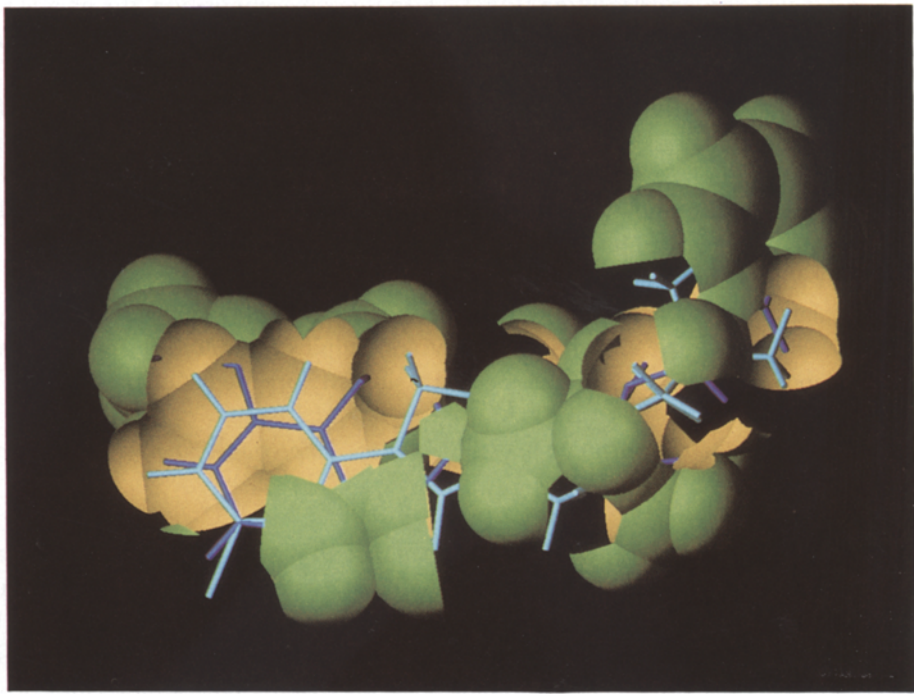
Comparison with the Na^+-independent compounds R48455, Spiperone, Pimozide, Chlorpromazine and Dexclamol

As described in earlier papers [13, 41], Fig. 10 shows that all the Na^+-independent D-2 antagonists are characterized by a nitrogen lone pair and two Π-electron regions quasi oriented in a same plane; the first (top arrow in Fig. 10, Φ_C in Fig. 1) is always a phenyl ring while the second (bottom arrow in Fig. 10, Φ_A in Fig. 1) may be a cyanide as in R48455, a carbonyl function as in Spiperone (butyrophenone), or a phenyl moiety as in Pimozide (diphenylbutylpiperidine), Chlorpromazine or Dexclamol (tricyclics).

When these compounds are compared to the Na^+-dependent antipsychotics studied here, it can



A



B

Fig. 7. Volume difference maps: (A) Zetidoline minus Tropapride, (B) Tropapride minus Zetidoline.

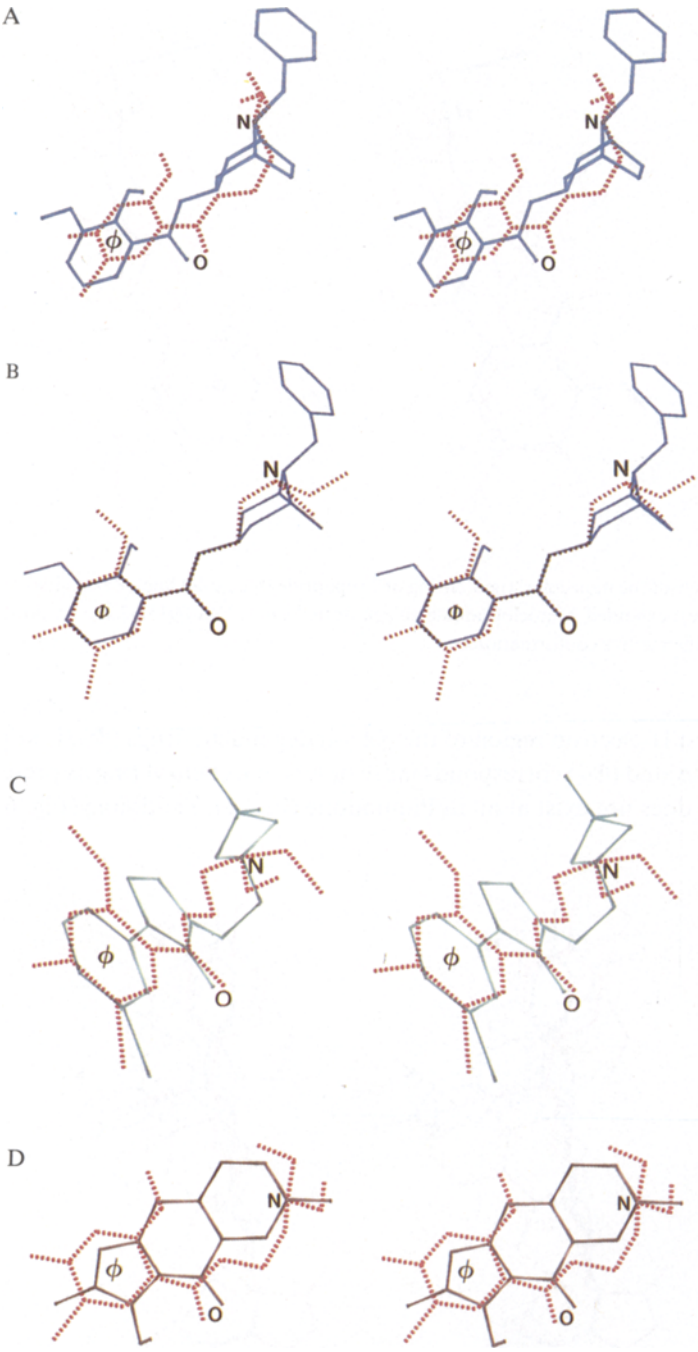


Fig. 8. Stereoscopic views of the molecular 'rigid' fitting between: (A) folded Metoclopramide (red dotted line) and Tropapride (blue solid line), (B) extended Metoclopramide (red dotted line) and Tropapride (blue solid line), (C) extended Metoclopramide (red dotted line) and Zetidoline (turquoise solid line), (D) folded Metoclopramide (red dotted line) and Piquindone (black solid line).

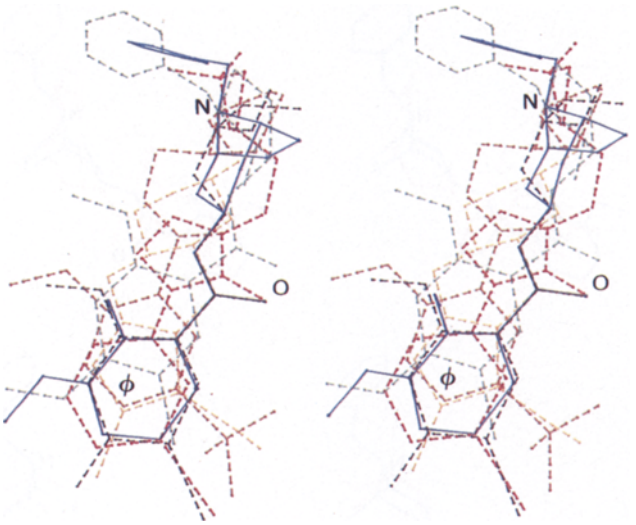


Fig. 9. Stereoscopic view of the molecular 'rigid' fitting of Tropapride (blue solid line), Zetidoline (red dotted line), Piquindone (beige dotted line), extended Metoclopramide (black dotted line), YM-09151-2 (green dotted line) and Sulpiride (brown dotted line) in their active conformations.

be seen that the first Π-electron region of the Na^+-independent drugs (Φ_C) is not occupied in Tropapride while the second (Φ_A) corresponds more or less to its benzyl ring as presented in Fig. 11.

This last region does not exist at all in Piquindone (Fig. 5), Zetidoline (Fig. 6B), and Metoclo-

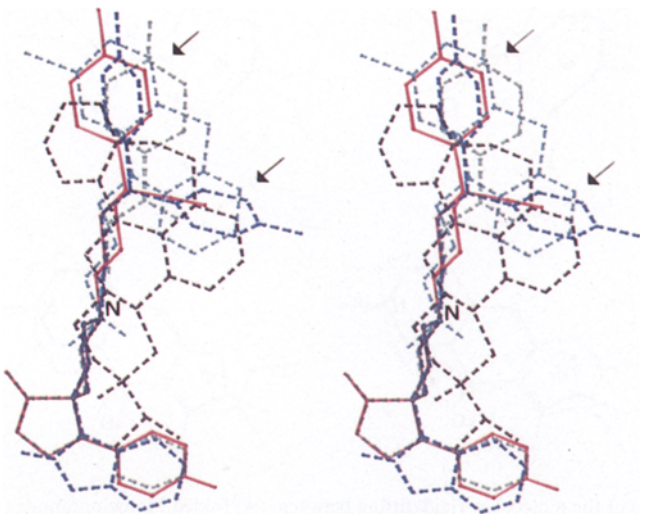


Fig. 10. Stereoscopic view of the molecular 'rigid' fitting of R48455 (red full line), Spiperone (blue dotted line), Pimozide (green dotted line), Chlorpromazine (black dotted line), and Dexclamol (yellow dotted line) in their active conformations.

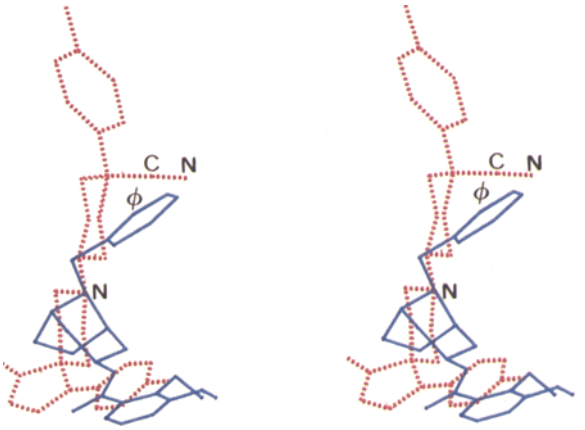


Fig. 11. Stereoscopic view of the molecular 'rigid' fitting of the Na^+-dependent Tropapride (blue solid line) and the Na^+-independent R48455 (red dotted line) compounds.

pramide (Fig. 8B). On the other hand, the pharmacophoric elements observed in all the Na^+-dependent derivatives, the nitrogen lone pair excepted, are not always present, e.g., in Chlorpromazine, or perfectly oriented, e.g., in Pimozide or Spiperone, in the classical antagonists. All these observations may be summarized by the pharmacophoric model presented in Fig. 12.

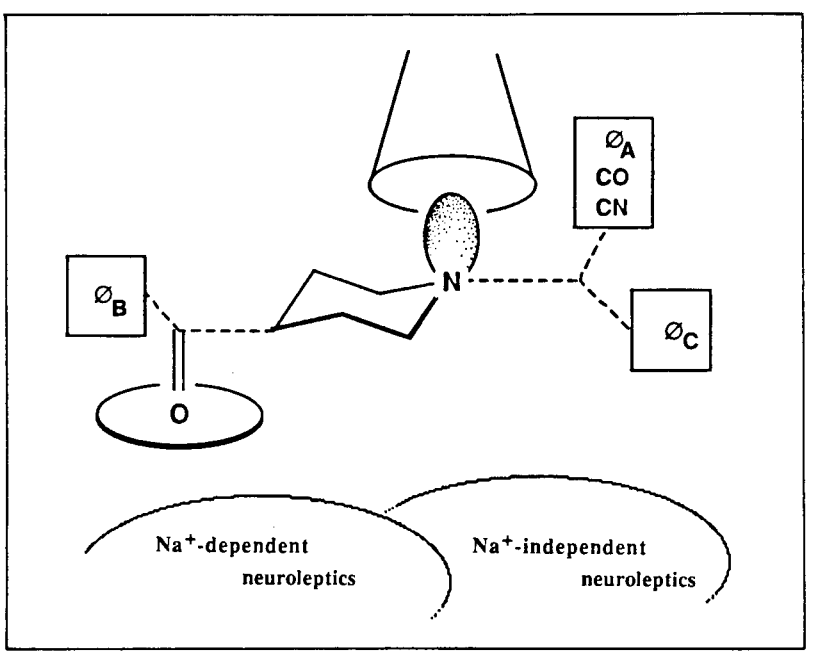


Fig. 12. Pharmacophoric model proposed for Na^+-dependent and Na^+-independent D-2 antagonist compounds.

CONCLUSIONS

The present investigations have shown that three pharmacophoric elements: a nitrogen lone pair, a phenyl ring, and a carbonyl moiety are oriented in the same way in all the Na^+-dependent antipsychotics. Most probably, these particular three-dimensional structural elements and associated properties explain their selectivity to D-2 receptor and, perhaps, the absence of extrapyramidal effects. Conversely, for the Na^+-independent analogs, the two latter pharmacophoric elements play a subordinate part, but two Π regions are always localized on the other side of the molecule. We might attribute the extrapyramidal effects of these compounds to the presence of these Π sites. The benzyl ring on this side in Tropapride might explain its slight cataleptic effect.

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