Stereoelectronic Requirements of Benzamide $5HT_3$ Antagonists. Comparison with D_2 Antidopaminergic Analogues

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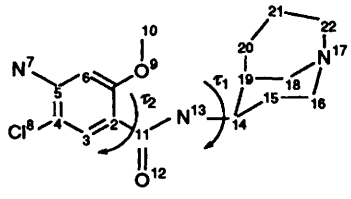
Renzapride (**I**) and Tropapride (**IV**) are very similar substituted benzamides but are distinguishable by their pharmacological profile: the former is a potent $5HT_3$ antagonist while the latter is a very active D_2 antidopaminergic drug. A combination of experimental methods (X-ray diffraction and ^1H NMR spectroscopy) and theoretical calculations (semiempirical molecular orbital AM1) were used to investigate the conformational space of three $5HT_3$ antagonists: Renzapride (**I**, BRL24924), DAU6215 (**II**) and Ondansetron (**III**, GR38032). The analysis of their solid state conformations as well as their isolated state structures allows us to propose a $5HT_3$ pharmacophoric model which is compared to the one previously reported for benzamide D_2 antagonists, represented by Tropapride (**IV**).

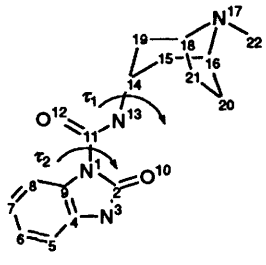
In the last decade, the discovery of multiple serotonin receptor subtypes has been reported. Today, there is much evidence for the existence of four groups classified as $5HT_1$, $5HT_2$, $5HT_3$ and $5HT_4$.[1,2] The $5HT_3$ subtype is a neuronal receptor coupled directly to a cation channel,[3] which is present within the central and peripheral nervous systems.[4] Many specific $5HT_3$ receptor antagonists are in clinical trials and are developed as antiemetics, gastrokinetics, or for central nervous system (CNS) disorders like anxiety and schizophrenia.[5–8] Among them, many substituted benzamides and analogues can be pointed out such as Renzapride (BRL24924), BRL24682 and Zacopride.[9–12]

Substituted benzamides are also known as a subclass of dopamine antagonists which act selectively on the D_2 receptor with a highly sodium-dependent binding.[13] The main stereoelectronic requirements for their affinity for the dopaminergic receptor have already been defined.[14,15] In particular, close three-dimensional and electrostatic analogies in all studied structures have been demonstrated. Three pharmacophoric elements—a basic nitrogen lone pair, a carbonyl group and a phenyl moiety—are oriented in exactly the same way in all the potent compounds.[14,16] This pharmacophoric model has been confirmed by quantitative structure–activity relationship (QSAR) analysis of a large orthopramide series.[16]

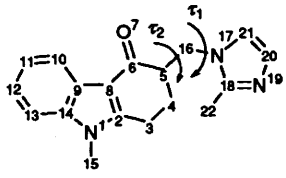
The present work is an attempt to explain why two very similar benzamidic structures: Renzapride (**I**) and Tropapride (**IV**) present opposite pharmacological activities ($5HT_3$ and D_2 antagonist activities, respectively). First, we determine the crystallographic structure of three very potent and structurally different $5HT_3$ ligands: Renzapride (**I**, BRL24924), **II** (DAU6215) and **III** (Ondansetron, GR38032). Second, for each compound we perform a conformational analysis, using ^1H NMR spectroscopy and/or molecular orbital AM1 calculations, in order to ascertain whether or not stable conformations other than the one observed in the crystalline state might exist. Hence, considering such structural information relative to compounds of very different chemical families will allow us to propose a $5HT_3$ pharmacophoric model which will be compared to the previously described D_2 model,



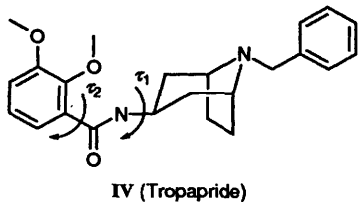
I (Renzapride, BRL24924)



II (DAU6215)



III (Ondansetron, GR38032)



IV (Tropapride)

Table 1 $5HT_3$ Activity in binding experiments (method described in experimental section; data represent the mean ± sem of at least three experiments)

Compound	*Ki*
I	6.77 ± 0.29 nmol dm^{-3}
II	3.75 ± 0.97 nmol dm^{-3}
III	4.31 ± 1.08 nmol dm^{-3}
IV	3×10^{-6} mol dm^{-3} [a]

[a] Value provided by the DELALANDE Research Laboratories.

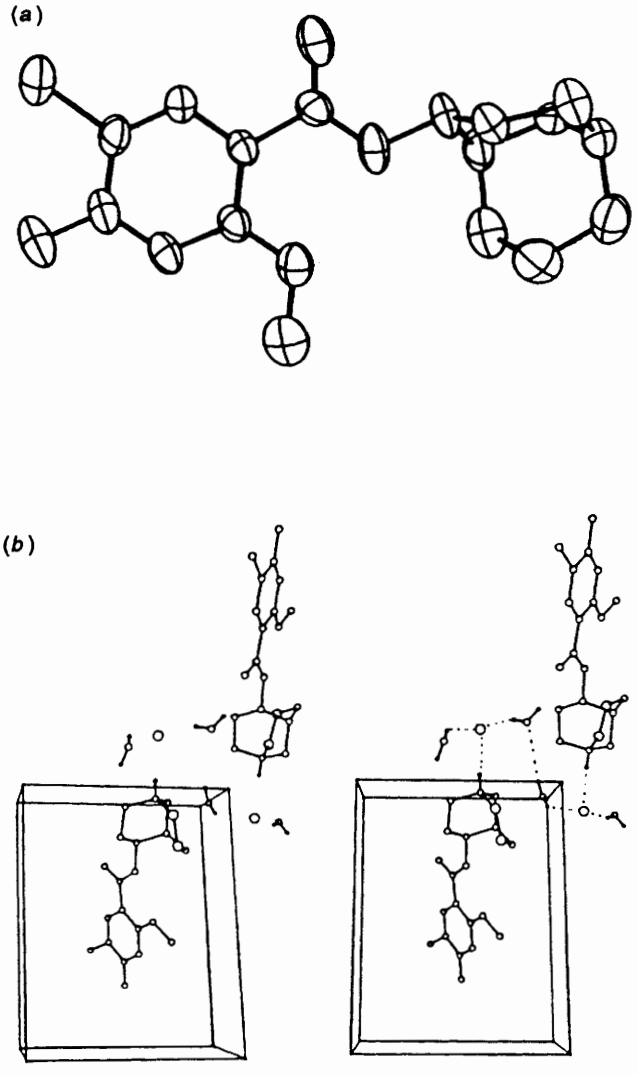


Fig. 1 (*a*) Crystal conformation and (*b*) stereoscopic view of crystal packing of compound **I**. Dotted lines represent intermolecular hydrogen bonds.

represented by Tropapride (**IV**). The $5HT_3$ activity data for all four compounds are reported in Table 1.

Results and Discussion

Structural Analysis of **I**.—*Mono-crystal structure of* **I**. The crystal conformation and crystal packing of compound **I** is shown in Fig. 1. Main bond lengths, bond angles and torsion angles are presented in Table 2. The existence of an intramolecular hydrogen bond between N(13) and O(9), [N(13)···O(9) = 2.623(5), H(13)···O(9) = 1.842 Å, N(13)–H(13)···O(9) = 122.1°], leads to the formation of a virtual six-membered ring [τ_2 = C(1)–C(2)–C(11)–N(13) = 2.8(7)°]

Table 2 Main bond lengths (Å), bond angles (°) and torsion angles (°) for structure **I** with esds in parentheses

C(1)–O(9)	1.352(6)	N(13)–C(14)	1.460(6)
O(9)–C(10)	1.437(7)	C(5)–N(7)	1.367(7)
C(2)–C(11)	1.497(6)	C(4)–Cl(8)	1.744(5)
C(1)–O(9)–C(10)		117.9(4)	
C(11)–N(13)–C(14)–C(15) τ_1		102.2(6)	
H(13)–N(13)–C(14)–H(14)		171.4	
C(1)–C(2)–C(11)–N(13) τ_2		2.8(7)	
C(2)–C(1)–O(9)–C(10)		−176.1(4)	
H(71)–N(7)–C(5)–C(4)		177.9	
H(72)–N(7)–C(5)–C(4)		28.9	
N(17)–C(22)–C(21)–C(20)		44.0(8)	
C(19)–C(20)–C(21)–C(22)		−46.3(8)	
C(18)–N(17)–C(22)–C(21)		−54.3(7)	
C(18)–C(19)–C(20)–C(21)		55.7(7)	
N(17)–C(18)–C(19)–C(14)		62.4(6)	
N(17)–C(16)–C(15)–C(14)		−46.9(6)	
N(13)–C(14)–C(15)–C(16)		169.9(4)	

similar to those observed for all active antidopaminergic benzamides.[15] Such a similar intramolecular bridge has already been shown in solution by ^1H NMR spectroscopy on a series of nortropane benzamides, differently substituted.[16]

The *ortho*-methoxy substituent O(9)–C(10) is quasi coplanar with the phenyl ring: C(2)–C(1)–O(9)–C(10) = −176.1(4)°. This planar arrangement has been observed in all the orthopramides including only one methoxy substituent on the phenyl moiety.[17] It would appear that the tendency of the Ph–O(9)–C(10) moiety towards planarity results from a partial sp^2 hybridization of the oxygen atom as revealed by the C(1)–O(9) bond length of 1.352(6) Å and by the valence angle: C(1)–O(9)–C(10) = 117.9(4)°.

The C(5)–N(7) distance, 1.367(7) Å, the sum of valence angles around N(7), 353.0°, and the torsion angles, H(71)–N(7)–C(5)–C(4) = 177.9° and H(72)–N(7)–C(5)–C(4) = 28.9°, indicate that the nitrogen N(7) is sp^2 hybridized.

The two twinned piperidine rings adopt a chair conformation. The sum of valence angles around N(17), 318.8°, indicates an sp^3 hybridization. This basic nitrogen atom is protonated by the HCl cocrystallized molecule: N(17)···H(17) = 0.885 Å [Fig. 1(*b*)]. The C(20)–C(21)–C(22) bridge induces an equatorial disposition of the N(17) lone pair. As we will see later, this equatorial orientation of the basic nitrogen lone pair will explain the $5HT_3$ profile of compound **I**. Only one isomer was crystallized from the racemic solution; the C(19) configuration in this isolated isomer is *R*.

The benzamide moiety is in an equatorial position on the C(14)–C(15)–C(16)–N(17)–C(18)–C(19) six-membered ring. The torsion angle τ_1 = C(11)–N(13)–C(14)–C(15) = 102.2(6)° optimizes the alignment of the amidic hydrogen H(13) with H(14): H(13)–N(13)–C(14)–H(14) = 171.4°. This conformation leads to a quasi parallel disposition of C(14)–H(14) with the carbonyl function.

The crystal packing is mainly governed by intermolecular hydrogen bonds *via* the HCl and $2H_2O$ cocrystallization molecules [Fig. 1(*b*)].

Isolated state conformation of **I**. Starting from the crystallographic data, we performed semiempirical molecular orbital AM1 calculations in order to scan the conformational space and determine the main minimal energy conformations by allowing rotations around the τ_1 and τ_2 torsion angles, *i.e.*, the only two single bonds present in the molecule.

The two-dimensional iso-energy contour map presented in Fig. 2 clearly shows a relative stabilization (3–4 kcal mol^{-1}) resulting from the formation of the intrabenzamidic hydrogen

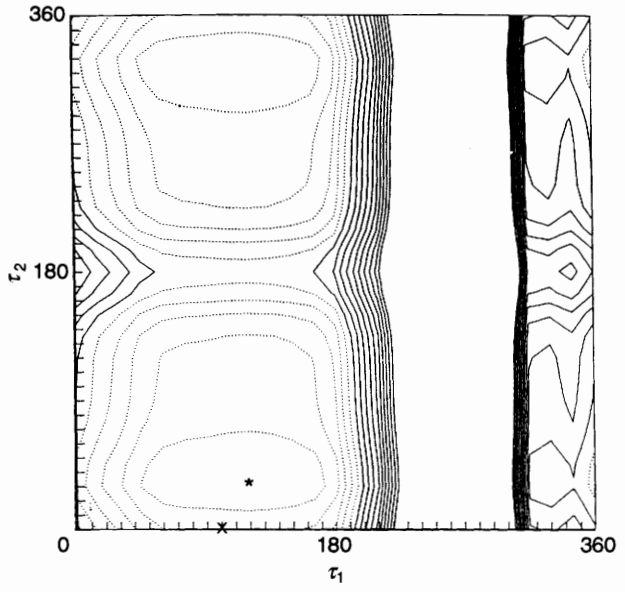


Fig. 2 AM1 Conformational iso-energy contour map (ΔE in kcal mol^{-1}) relative to the variations of τ_1 and τ_2 for compound **I**. The X and * symbols correspond to the crystalline and absolute minimum conformation, respectively. The contour-to-contour interval is 1 kcal mol^{-1}; dotted lines indicate iso-energies up to 5 kcal mol^{-1} and solid lines, contours from 6 to 15 kcal mol^{-1}.

(*a*)

(*b*)

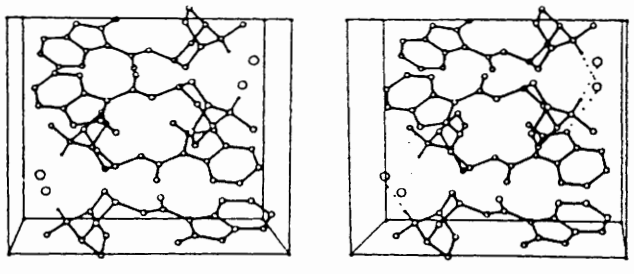


Fig. 3 (*a*) Crystal conformation and (*b*) stereoscopic view of crystal packing of compound **II**. Dotted lines represent intermolecular hydrogen bonds.

bond (τ_2 *ca.* 0°). Concerning the τ_1 torsion angle, a large energy barrier (> 15 kcal mol^{-1}) prevents the rotation of the benzamide moiety towards the twinned piperidinic heterocycle. It is interesting to note that the crystalline conformation, τ_1 = 102.4(6)° and τ_2 = 2.9(7)° (X in Fig. 2, ΔE = 1 kcal mol^{-1}), is located in the calculated absolute minimum region (* in Fig. 2).

Structural Analysis of **II**.—*Mono-crystal structure of* **II**. The crystal conformation and crystal packing of compound **II** is shown in Fig. 3. Main bond lengths, bond angles and torsion angles are presented in Table 3.

Table 3 Main bond lengths (Å), bond angles (°) and torsion angles (°) for structure **II** with esds in parentheses

N(1)–C(2)	1.413(2)	N(3)–C(4)	1.390(2)
N(1)–C(9)	1.410(2)	C(11)–O(12)	1.205(2)
N(1)–C(11)	1.433(2)	C(11)–N(13)	1.324(2)
C(2)–N(3)	1.358(2)	N(13)–C(14)	1.470(2)
C(2)–O(10)	1.217(2)		
C(2)–N(1)–C(9)	109.1(1)	C(9)–N(1)–C(11)	124.5(1)
C(2)–N(1)–C(11)	126.4(1)	C(2)–N(3)–C(4)	110.9(1)
C(11)–N(13)–C(14)–C(15) τ_1		−141.1(1)	
H(13)–N(13)–C(14)–H(14)		139.4(24)	
N(13)–C(14)–C(15)–C(16)		−90.3(1)	
C(15)–C(16)–N(17)–C(22)		−162.1(1)	
C(9)–N(1)–C(11)–N(13) τ_2		−172.0(1)	
C(8)–C(9)–N(1)–C(11)		1.1(2)	

Table 4 ^{1}H NMR chemical shift (δ) measured for compound **II** at various temperatures

T/K	δ[H(13)]
213	9.51
233	9.46
253	9.41
273	9.35
293	9.30
313	9.24
333	9.19

The N(1) and N(3) atoms are sp^2 hybridized as shown by the sum of valence angles, 360.0° for both atoms, and by the relatively short bond lengths: N(1)–C(9) = 1.410(2) and C(2)–N(3) = 1.358(2) Å (*ca.* 1.38 Å in imidazole). The benzimidazolone moiety is completely planar. The longer N(1)–C(11) bond length, 1.433(2) Å, suggests only a weak delocalization through the exocyclic amide function.

The presence of an intramolecular hydrogen bond between the carbonyl oxygen O(10) of the benzimidazolone and the amide nitrogen N(13), [N(13)···O(10) = 2.687(3), H(13)···O(10) = 1.999 Å, N(13)–H(13)···O(10) = 142.3°], leads to the formation of a virtual six-membered ring. A torsion angle τ_2 = C(9)–N(1)–C(11)–N(13) = −172.0(1)° evidences the coplanarity of the carboxamido and benzimidazolone systems.

The lateral chain is in an axial position on the piperidine ring. The torsion angle τ_1 = C(11)–N(13)–C(14)–C(15) = −141.1(1)° optimizes the alignment of the amidic hydrogen H(13) with H(14), [H(13)–N(13)–C(14)–H(14) = 139.4°] and with the hydrogens of the piperidine bridge. No particular comments are necessary regarding the tropane geometry. The N(17) basic atom is protonated by the HCl cocrystallized molecule: N(17)···H(17) = 0.915 Å [Fig. 3(*b*)]. The *N*-methyl group is orientated in an equatorial position as generally observed in *N*-substituted analogues.

The crystal packing is mainly governed by intermolecular hydrogen bonds *via* the HCl cocrystallization molecule [Fig. 3(*b*)].

Solution conformation of **II**. As shown by ^{1}H NMR analysis in a $CDCl_3$ solution at various temperatures (Table 4), the intramolecular hydrogen bond of compound **II** is maintained. When an X–H···Y hydrogen bond is created, the increasing X–H bond length induces a low field shift of the hydrogen atom as the proximity of Y leads to an additional diamagnetic effect. The first effect is always predominant so that the signal is shifted to low field when the hydrogen bond is reinforced.

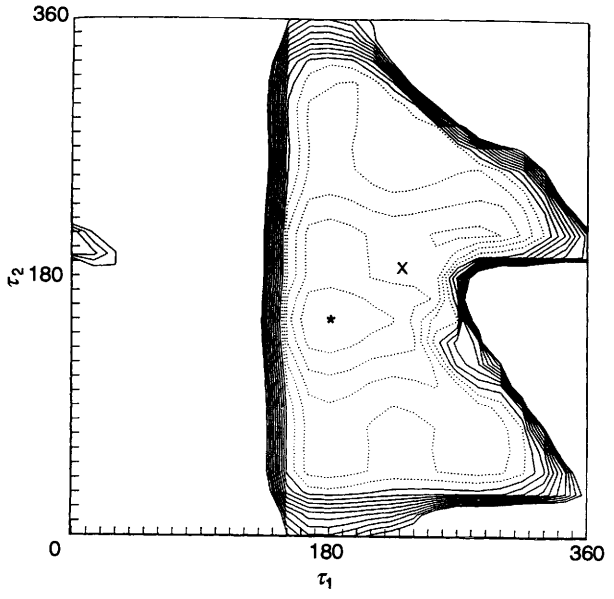


Fig. 4 AM1 Conformational iso-energy contour map (ΔE in kcal mol^{-1}) relative to the variations of τ_1 and τ_2 for compound **II**. The X and * symbols correspond to the crystalline and absolute minimum conformation, respectively. The contour-to-contour interval is 1 kcal mol^{-1}; dotted lines indicate iso-energies up to 5 kcal mol^{-1} and solid lines, contours from 6 to 15 kcal mol^{-1}.

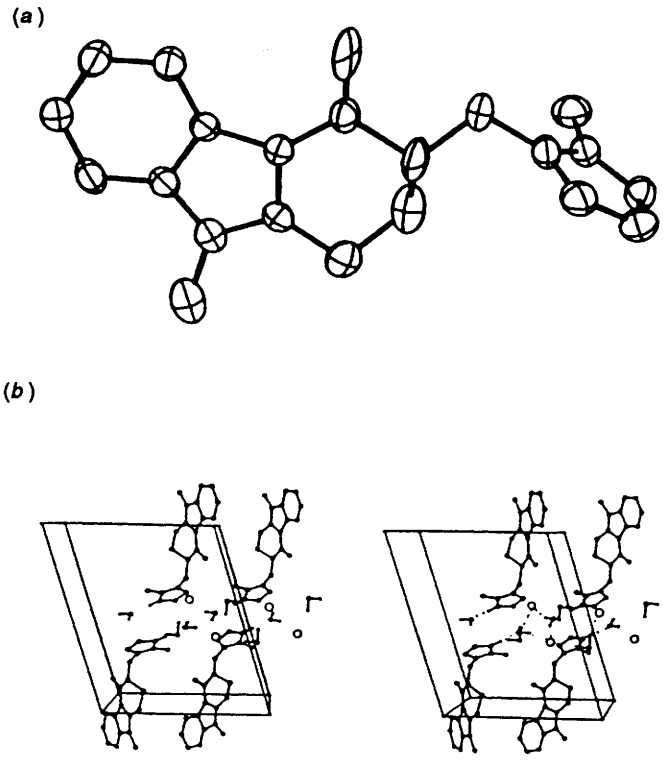


Fig. 5 (*a*) Crystal conformation and (*b*) stereoscopic view of crystal packing of compound **III**. Dotted lines represent intermolecular hydrogen bonds.

Consequently, the observed high chemical shift of H(13) ($\delta > 9.1$), as compared to other amidic chemical shifts, ±7.3–9.4, for other substituted benzamides,[16] is a first argument in favour of an intramolecular hydrogen bond in solution. Moreover, the increase of the H(13) chemical shift at lower temperature (linear downfield shift of 0.05 ppm per 20°) must be related to the higher stability of this intramolecular hydrogen bond, the concentration-independent profile of the recorded spectra excluding the possibility of intermolecular associations (data not shown).

Isolated state conformation of **II**. Starting from the crystallographic data, we again performed semiempirical molecular orbital AM1 calculations allowing rotations around τ_1 and τ_2. The two-dimensional iso-energy contour map presented in Fig. 4 shows clearly a strong stabilization (around 15 kcal mol^{-1}) resulting from the formation of the intramolecular hydrogen bond (τ_2 *ca.* 180°). For the τ_1 torsion angle, a large energy barrier (> 15 kcal mol^{-1}) prevents the free rotation of the lateral chain towards the tropane ring. As for the preceding structure, the crystalline state conformation, $\tau_1 = -141.1(1)°$ and $\tau_2 = -172.0(1)°$ (X in Fig. 4, ΔE = 1 kcal mol^{-1}), is located in the calculated absolute minimum region (* in Fig. 4).

Structural Analysis of **III**.—*Mono-crystal structure of* **III**. The crystal conformation and crystal packing of compound **III** is shown in Fig. 5. Main bond lengths, bond angles and torsion angles are presented in Table 5.

The three nitrogen atoms of the molecule are sp^2 hybridized as shown by the sum of valence angles, 359.9°, 360.0° and 360.0° around N(1), N(17) and N(19), respectively. The protonation of N(19) by the HCl cocrystallization molecule indicates its more basic character: N(19)···H(19) = 0.935 Å [Fig. 5(*b*)].

The tricyclic moiety is coplanar except for the C(4) atom which is on the same side as the lateral chain on the C(5) atom (Fig. 5). The shorter C(6)–C(8) bond length, 1.434(3) Å (*versus ca.* 1.50 Å for a standard C_{sp^2}–C_{arom} bond), the longer C(2)–C(8) distance, 1.387(3) Å (*versus* 1.35 Å in pyrrole) and C(2)–C(8)–C(6)–O(7) = 179.4(3)° suggest a significant delocalization between the pyrrole ring and the carbonyl function.

The crystal packing is governed mainly by intermolecular hydrogen bonds *via* the HCl and $2H_2O$ cocrystallization molecules [Fig. 5(*b*)].

Isolated state conformation of **III**. In a similar fashion as for **I** and **II**, starting from the crystallographic data, we performed semiempirical molecular orbital AM1 calculations allowing rotations around τ_1 and τ_2. The crystalline state conformation, τ_1 = C(5)–C(16)–N(17)–C(18) = 109.2(3)° and τ_2 = C(6)–C(5)–C(16)–N(17) = 179.5(4)° (X in Fig. 6, ΔE = 2 kcal mol^{-1}), is located in a minimum energy region.

Molecular Superimpositions.—Comparison between compounds **I**, **II** *and* **III**. First, we tried to match the conformations of the three structurally different $5HT_3$ ligands [Fig. 7(*a*)]. The best least-squares flexible molecular superimposition between compounds **I**, **II** and **III** shows that the three pharmacophoric elements—*i.e.*, a basic nitrogen lone pair [N(17), N(17) and N(19) in **I**, **II** and **III**, respectively], a carbonyl group [C(11)–O(12), C(11)–O(12) and C(6)–O(7) in **I**, **II** and **III**, respectively] and an aromatic moiety (the phenyl ring in **I** and the annelated five-membered ring in **II** and **III**)—are similarly oriented in those three $5HT_3$ antagonists. Compounds **I** and **II** are presented in their crystalline structure while compound **III** is fitted taking into account a slightly modified conformation, *i.e.*, crystal structure except τ_1 = 140° (X_1 in Fig. 6); **II** was taken as the reference for the superposition. The role of the chlorine substituent in **I** is most probably to increase the polarizability in the region occupied by the large π-electron region in compounds **II** and **III**. We might thus believe that the $5HT_3$ antagonistic properties of compound **I** would be retained after replacement of the N(7) and Cl(8) atoms by another annelated polarizable ring.

Comparison between $5HT_3$ *and* D_2 *antagonists*. As compared now to the Na^+-dependent D_2 antagonists,[15] and in particular to Tropapride[18] (**IV**) including the benzamide moiety, the

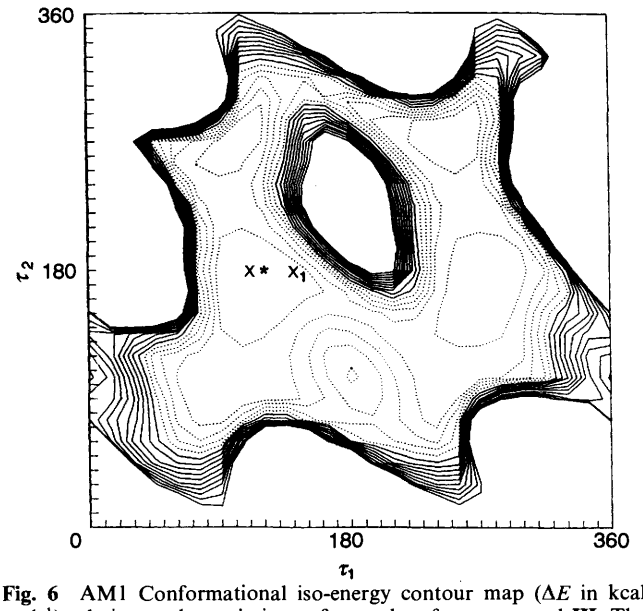


Fig. 6 AM1 Conformational iso-energy contour map (ΔE in kcal mol^{-1}) relative to the variations of τ_1 and τ_2 for compound **III**. The X and * symbols correspond to the crystalline and absolute minimum conformation, respectively; X_1 corresponds to the conformation used within the molecular superimposition. The contour-to-contour interval is 1 kcal mol^{-1}; dotted lines indicate iso-energies up to 5 kcal mol^{-1} and solid lines, contours from 6 to 15 kcal mol^{-1}.

Table 5 Main bond lengths (Å), bond angles (°) and torsion angles (°) for structure **III** with esds in parentheses

N(1)–C(2)	1.356(3)	N(17)–C(21)	1.388(3)
N(1)–C(14)	1.385(3)	C(18)–N(19)	1.329(3)
N(1)–C(15)	1.457(3)	N(19)–C(20)	1.381(3)
C(16)–N(17)	1.467(3)	C(20)–C(21)	1.342(4)
N(17)–C(18)	1.334(3)	C(18)–C(22)	1.476(3)
C(2)–N(1)–C(14)	108.9(2)	C(16)–N(17)–C(21)	123.9(2)
C(2)–N(1)–C(15)	127.3(2)	C(18)–N(17)–C(21)	108.7(2)
C(14)–N(1)–C(15)	123.7(2)	C(18)–N(19)–C(20)	109.6(2)
C(16)–N(17)–C(18)	127.4(2)		
N(1)–C(2)–C(3)–C(4)		157.2(3)	
C(2)–C(3)–C(4)–C(5)		48.8(3)	
C(3)–C(4)–C(5)–C(6)		−55.7(4)	
C(4)–C(5)–C(6)–C(8)		31.5(3)	
C(6)–C(5)–C(16)–N(17) τ_2		179.5(4)	
C(5)–C(16)–N(17)–C(18) τ_1		109.2(3)	
C(16)–N(17)–C(18)–C(22)		−0.2(4)	

spatial disposition of the $5HT_3$ π-electron region is completely different when the basic nitrogen lone pairs and the carbonyl oxygen atoms are superimposed in both structures [Fig. 7(*b*)]. Owing to the equatorial orientation of its N(17) nitrogen lone pair, **I** completely differs from its chemically related analogue **IV**. As information, two other very potent D_2 antagonists, Zetidoline and YM-09151-2,[15] have been added in Fig. 7(*b*) to illustrate the previously published D_2 pharmacophoric model.

Conclusions

The present work has shown that the $5HT_3$ and D_2 requirements are very similar in terms of chemical functions and distances between them. For both receptors, three elements, a basic nitrogen lone pair, a carbonyl group and an aromatic moiety are quasi coplanar. Also, for both receptors, the distance between the nitrogen lone pair and the centroid of the aromatic moiety is *ca.* 7.9 Å, the distance between the nitrogen lone pair and the carbonyl oxygen is *ca.* 5.6 Å and the distance between the carbonyl oxygen and the centroid of the aromatic moiety is *ca.* 3.6 Å. However, the spatial disposition between those three elements is different. Usually, the piperidinic derivatives substituted by the amidic moiety in equatorial position, as Tropapride (**IV**), fit the D_2 model, while the axial isomers, as DAU6215 (**II**), fill the $5HT_3$ requirements. Although it is an equatorial isomer at the C(14) position, Renzapride (**I**) adopts a conformation corresponding exactly to the $5HT_3$ model due to the particular orientation of the nitrogen N(17) lone pair.

Experimental

Syntheses.—Compound **I** [(±)-4-amino-5-chloro-2-methoxy-*N-endo*-(1-azabicyclo[3.3.1]non-4-yl)benzamide hydrochloride] was synthesized in the De Angeli Laboratories according to a known procedure.[19] Compound **II** [*N-endo*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide] was synthesized in the De Angeli Laboratories as recently described.[20] Compound **III** {9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydrocarbazol-4(4*H*)-one} was synthesized in the De Angeli Laboratories according to a known procedure.[21]

Biochemical Tests.—The $5HT_3$ serotonin receptor subtype of the rat cerebral cortex (P2 fraction, prepared essentially according to Peroutka and Snyder),[22] was labelled with [^{3}H]ICS 205–930 (82.7 Ci mmol^{-1}, Amersham). The final pellet was homogenized in 50 mmol dm^{-3} TRIS·HCl buffer, pH 7.4 containing 0.1% ascorbate, 4 mmol dm^{-3} $CaCl_2$ and 10 μm pargyline and then it was diluted to have a protein concentration of about 500 μg cm^{-3} (1:40 w/v). Experiments were performed by incubating the homogenate (450 mm^3) (1 mm^3 = 1 μl) in the presence of 0.2–2.0 mmol dm^{-3} [^{3}H]ICS 205–930 and different concentrations of the tested compounds dissolved in the assay buffer (50 mm^3), at 30 °C for 30 min. To separate bound from free radioligand, an automatic filtration technique (SKATRON harvester) was employed using a GF/8 filter (Whatman). Filters were introduced into plastic vials. 3.5 cm^3 of Filter Count (Packard) were added and the radioactivity present was counted by liquid scintillation spectrometry. All the experiments were performed at least three times and data were evaluated by computer fitting analysis.

X-Ray Crystallography.—Compound **I** crystallized from a propan-2-ol solution at room temperature. A colourless prismatic crystal was used for all X-ray measurements. Lattice parameters were obtained from least-squares refinement of the angular settings of 25 well centred reflections. The X-ray intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SHELX86;[23] the best FOM E map showed all the non-hydrogen atoms. The structure was refined by full-matrix least-squares on F with the SHELX76 program.[24] All hydrogen atoms appeared in a difference Fourier map but were not refined. Anisotropic temperature factors were used for all non-H atoms and isotropic ones for H atoms (corresponding to the isotropic temperature factor of the carrier atom incremented by 0.02). Crystal and refinement data are given in Table 6. The XRAY76 program[25] was used for molecular geometry analysis.

Compounds **II** and **III** crystallized from a methanol solution. Their crystal structures were obtained using the same procedure as for **I**. The hydrogen atoms of **II** were refined.

Atomic coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme, see 'Instructions for Authors (1995)', *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1.

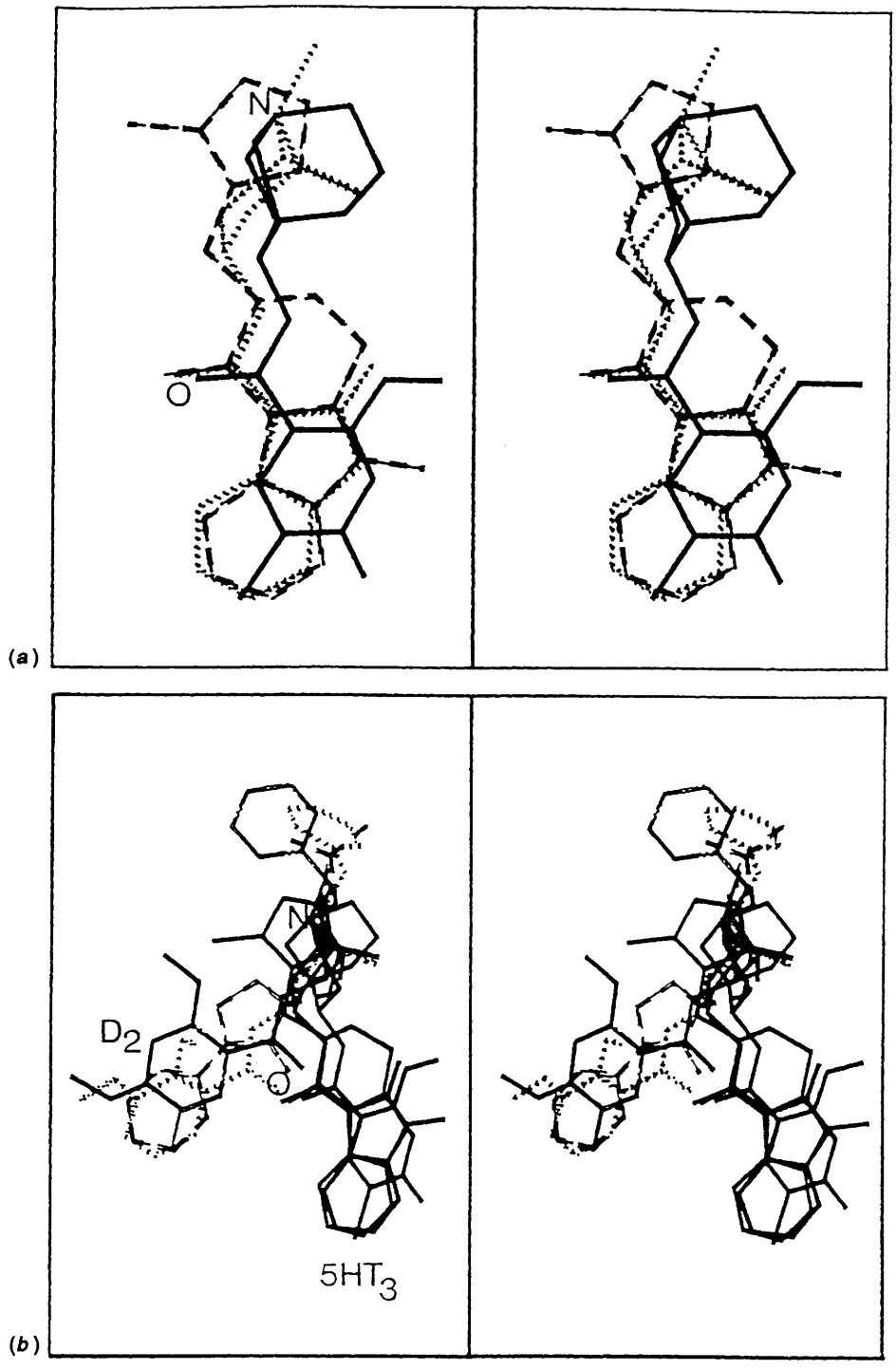


Fig. 7 (*a*) Stereoscopic view of the best least-square superimposition between three $5HT_3$ antagonists: **I** (solid line, X-ray crystal structure), **II** (dotted line, X-ray crystal structure) and **III** (dashed line, X-ray crystal structure except $\tau_1 = 140°$); (*b*) stereoscopic view of the best least-square superimposition between the $5HT_3$ antagonists: **I**, **II** and **III** (solid lines) and D_2 antagonists: **IV** (dotted line, X-ray crystal structure), Zetidoline[15] (dashed line) and YM-09151-2[15] (L-dashed line)

AM1 Molecular Orbital Calculations.—The semi-empirical quantum mechanical AM1 method[26] was used in order to scan the conformational space and determine the possible existence of other minima than the ones experimentally observed. The good performance of this method for conformational analysis problems has been pointed out widely and moreover, consideration of more sophisticated methods such as non-empirical ones would have been rather time consuming. The two-dimensional (2D) iso-energy contour maps were built by systematic variation (increment between two successive calculations: 10°) using the AM1 option with the standard parameters available within GAUSSIAN88.[27] The starting coordinates were taken from the X-ray analysis except for the hydrogen atoms placed at standard values depending on the type of carrier atom and hybridization. The 2D iso-contour maps were produced with an in-house device-independent, IBM 5080 workstation or IBM 31XX-G terminal, contouring program, CPS (Contouring Plotting System),[28] developed in Fortran and using the IBM graPHIGS software.[29] Dotted lines indicate iso-energies up to 5 kcal mol^{-1} and solid lines contour

Table 6 Crystallographic data and instrumental setting

	Compound I	Compound II	Compound III
Molecular formula	$C_{16}H_{22}ClN_3O_2$·HCl·2H_2O	$C_{16}H_{20}N_4O_2$·HCl	$C_{18}H_{19}N_3O$·HCl·2H_2O
Molecular weight	396.32	336.82	365.86
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1/c$	$P2_1/c$
Crystal dimensions/mm	0.24 × 0.18 × 0.20	0.32 × 0.32 × 0.28	0.39 × 0.29 × 0.15
a/Å	13.773(4)	13.345(2)	15.082(3)
b/Å	10.448(1)	11.392(1)	9.741(3)
c/Å	6.926(1)	10.698(1)	12.734(3)
β(°)	103.59(2)	91.45(1)	100.83(1)
V/Å^3	968.76	1625.86	1837.48
Z	2	4	4
F(000)	420	712	776
Measured density/g cm^{-3}	1.35	1.36	1.33
Calculated density/g cm^{-3}	1.36	1.37	1.32
Diffractometer	Enraf–Nonius CAD-4		
Radiation (λ/Å)	Graphite-monochromated Mo-Kα (0.710 73)	Cu-Kα (1.541 78)	Cu-Kα (1.541 78)
Unique data	2015 ($-17 \leqslant h \leqslant 17$, $0 \leqslant k \leqslant 12, 0 \leqslant l \leqslant 8$)	3191 ($-16 \leqslant h \leqslant 16$, $-12 \leqslant k \leqslant 14, 0 \leqslant l \leqslant 13$)	4891 ($-18 \leqslant h \leqslant 18$, $-10 \leqslant k \leqslant 12, 0 \leqslant l \leqslant 15$)
Unique data with $I \geqslant 2\sigma(I)$	1723	2967	3219
Absorpt. coeff./cm^{-1}	3.11	20.98	19.17
Final R value	0.05	0.04	0.07
Final R_w value [$w = 1/(\sigma^2(F) + xF^2)$]	0.05 ($x = 0.001$)	0.06 ($x = 0.007$)	0.10 ($x = 0.01$)
Max. and min. in final diff. Fourier map/e Å^{-3}	0.34 and −0.31	0.22 and −0.51	1.4 and −0.5

from 6 to 15 kcal mol^{-1}. The contour-to-contour interval is 1 kcal mol^{-1}. White zones correspond to energies greater than 15 kcal mol^{-1}. All calculations were performed on the IBM 9377/90-FPS 164 and 364 computer system of the Scientific Computing Facility Center of the University of Namur.

^{1}H *NMR Chemical Shifts' Measurement.*—^{1}H NMR spectra were recorded on the basic form with a Bruker CXP-200 spectrometer operating in the pulsed Fourier transform mode (pulse width: 4 μs, number of accumulations: 100, time interval between pulse sequence: 5 s; sweep width: 3.0 kHz, number of points: 4096, ppm relative to tetramethylsilane). The concentration of the solutions was *ca.* 0.1 mol dm^{-3} in $CDCl_3$. The recorded spectra were independent of solute concentration, excluding the possibility of intermolecular associations.

Molecular Superimpositions.—Real-time interactive comparisons of molecular models and searches for an optimal matching between the various conformations were done using KEMIT[30] developed on the IBM 9377/90 of the Scientific Computing Facility Center of the University of Namur. KEMIT is an in-house device-independent, IBM 5080 workstation or IBM 31XX-G terminal, molecular graphics system developed in Fortran and using the IBM graPHIGS software.[29] Molecular superimpositions are performed by molecular least-squares flexible (*i.e.*, allowing rotations around single bonds) fitting between the cartesian coordinates of particular points (atomic positions, lone pairs, centroids, *etc.*) of each molecule using the IFMFIT (Improved or Interactive Molecular FITting)[31,32] facility included in KEMIT.

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