Development of a Receptor-Interaction Model for Serotonin 5-HT$_2$ Receptor Antagonists. Predicting Selectivity with Respect to Dopamine D$_2$ Receptors

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A receptor-interaction model for serotonin 5-HT$_2$ receptor antagonists has been developed by conformational analysis with molecular mechanics (MM2(91)) and superimposition studies of serotonin 5-HT$_2$ receptor antagonists. Substituted 3-(4-piperidinyl)-, 1-(4-piperidinyl)-, 3-(1,2,3,6-tetrahydropyridin-4-yl)-, and 1-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles, substituted 3-(4-fluorophenyl)-1-(4-piperazinyl)indans, cyproheptadine derivatives, ritanserin, and danitracene have been used as bases for the model. Other serotonin 5-HT$_2$ receptor antagonists, such as ketanserin and MDL 11,939, are well accommodated into the model. Comparison of the model with a recently described receptor-interaction model for dopamine D$_2$ receptor antagonists suggests a common pharmacophore for dopamine D$_2$ and serotonin 5-HT$_2$ receptor antagonists. Important steric differences between 5-HT$_2$ receptor antagonists with additional high affinity for dopamine D$_2$ receptors and serotonin 5-HT$_2$ receptor antagonists with high selectivity versus D$_2$ receptors are described. The geometry of the receptor-interaction model described is significantly different from that of a recently reported receptor-interaction model for 5-HT$_2$ receptor agonists and antagonists developed by use of (+)-LSD as a template, suggesting the existence of two binding modes at the 5-HT$_2$ receptor.

Introduction

The involvement of serotonin receptors in the pathology of a number of psychiatric disorders has recently been reviewed.[1,2] Centrally acting serotonin 5-HT$_2$ receptor antagonists are active in animal models predictive of anxiolytic and antidepressant activity.[3] Several clinical studies with the 5-HT$_2$ antagonist ritanserin have suggested improvements in dysthymic disorders,[4] negative symptoms in schizophrenia,[5] and quality of sleep.[6] Coadministration of ritanserin with classical neuroleptics in the treatment of schizophrenic patients reduces the incidence of extrapyramidal symptoms compared to treatment of patients with neuroleptics alone.[7] In addition, it has been proposed that the strong serotonin 5-HT$_2$ receptor blockade combined with the dopamine D$_2$ receptor blockade is responsible for the low incidence of acute extrapyramidal side effects produced by the atypical neuroleptic clozapine, compared to classical neuroleptics such as chlorpromazine and haloperidol.[8]

A receptor-interaction model for 5-HT$_2$ receptor agonists and antagonists, developed by comparison of the conformationally quite rigid molecules (+)-LSD and butaclamol, has recently been published by Glennon et al.[9] The model has been supported by superimposition of (+)-mianserin and several very flexible compounds such as (−)-DOB and 1-phenyl-5-HT. In the comprehensive model, the distance between the center of a benzene ring, which seems to be essential to obtain binding to 5-HT$_2$ receptors (e.g., the A ring in (+)-LSD), and the basic nitrogen atom is determined to be approximately 5.1 Å.

Liljefors and Bøgesø have reported a receptor-interaction model for dopamine D$_2$ receptor antagonists.[10] This model is based on a conformational study of the two D$_2$ receptor antagonists (1*R*,3*S*)-tefludazine (1) and (*S*)-octoclothepin (2). Recently, the model was further supported by a study of both enantiomers of octoclothepin.[11] The model has been used to rationalize the affinity for D$_2$ receptors for compounds from different chemical classes such as dexclamol,[10] butaclamol,[12] benzamides,[13] thioxanthenes,[14] phenothiazines,[14] cyproheptadine derivatives,[15] and tetracyclic spiroamines.[15] Recently, it was shown that phenylindans, -indenes, and -indoles with high affinity for D$_2$ receptors can also be well accommodated into the model.[16] Since the key compounds (1 and 2) used in the development of the D$_2$ model are also highly potent antagonists of 5-HT$_2$ receptors,[11,17] we decided to use this model as a basis for the development of a receptor-interaction model for 5-HT$_2$ receptor antagonists.

A series of noncataleptogenic 3-(4-piperidinyl)indoles, with high affinity for both 5-HT$_2$ and D$_2$ receptors, and α_1 adrenoceptors has recently been described.[18] Sertindole (**3a**, Chart 1), a potential antipsychotic with high limbic selectivity, is a member of this class of compounds.[19-21] Extensive structure affinity investigations on these compounds have led to indoles with high selectivity for 5-HT$_2$ receptors versus D$_2$ receptors and α_1 adrenoceptors (e.g., **3d** and **5d**, Chart 1).[22,23] These results prompted us to study the spatial relationships of the pharmacophoric elements (the two benzene rings and the distant basic nitrogen atom) known to be important in order to obtain binding to D$_2$ receptors according to the Liljefors–Bøgesø model. The spatial relationships are studied for low-energy conformations of these compounds to show whether the high selectivity with respect to D$_2$ receptors is a result of changes in these spatial relationships or a result of the introduction of substituents into forbidden areas at the D$_2$ receptors.

We describe conformational analysis by molecular mechanics calculations and subsequent structural comparisons by least-squares superimpositions of the indoles

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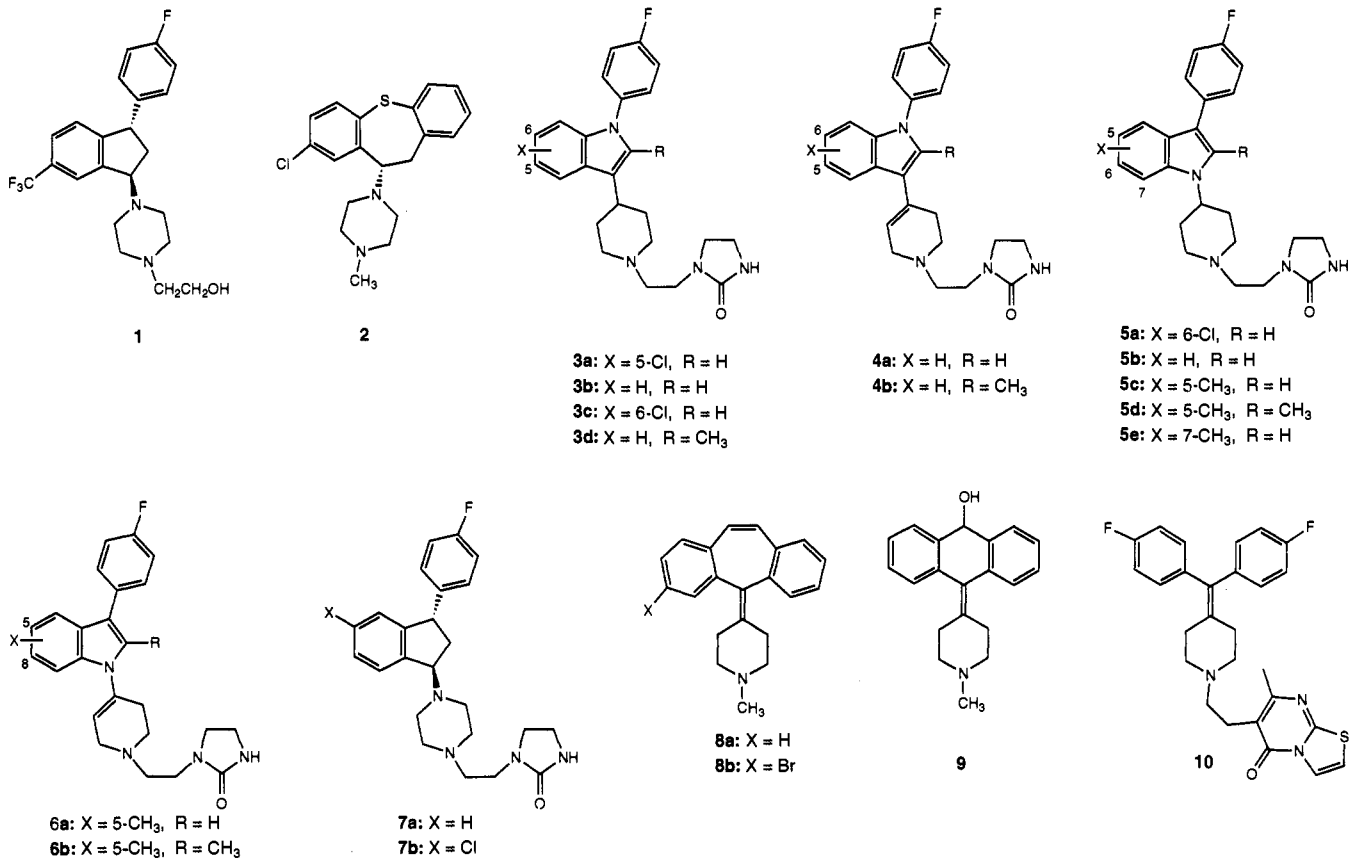
Chart 1



described above and other structural classes of high-affinity serotonin 5-HT$_2$ receptor antagonists. The structural comparisons will be discussed in relation to receptor-binding affinities for 5-HT$_2$ and D$_2$ receptors.

Results and Discussion

Structures of selected high-affinity 5-HT$_2$ antagonists are shown in Charts 1 and 2. Receptor-binding affinities for serotonin 5-HT$_2$ receptors and dopamine D$_2$ receptors are reported in Table 1. The 5-HT$_2$ antagonists included in the present study are divided into two groups on the basis of structural features.

In Chart 1 are shown structures of compounds **1** and **2** used for the D$_2$ receptor model, the rather flexible indoles **3–6** and indans **7**, the antihistaminergic cyproheptadine (**8a**), the potential antidepressant danitracen (**9**), and the prototype of selective serotonin 5-HT$_2$ receptor antagonists ritanserin (**10**). These compounds belong to very different chemical classes but have important structural features in common. They all contain two benzene rings which are spatially close to each other and are separated by either a third aliphatic or aromatic ring or an aliphatic spacer. A basic nitrogen atom is separated from the two benzene rings by an aliphatic ring.

The compounds shown in Chart 2 differ from the compounds in Chart 1 by having only one benzene ring which is separated from the basic nitrogen atom by an aliphatic ring. The basic nitrogen atom is linked by an alkyl chain to either a phenyl group or a heterocyclic ring system. Examples of compounds with these structural features are the antihypertensive ketanserin (**11**)[24] and the highly selective serotonin 5-HT$_2$ receptor antagonist MDL 11,939 (**12**).[25]

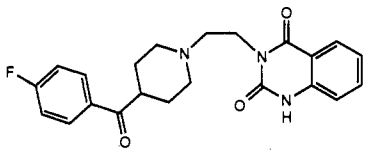
Indoles and Indans. The structure affinity relationships for indole derivatives[18,22,23] **3–6** and indan derivatives[17,26–28] **7** have previously been described. Regarding the indan derivatives, a substituent in the 6-position, such as trifluoromethyl (**1**), is necessary to obtain high affinity for dopamine D$_2$ receptors. Indans which are unsubstituted in the benzene part of the indan nucleus, such as

Table 1. Substituents and Receptor-Binding Affinities for Compounds 1–11

	substituents		receptor binding[a]	
compd	X	R	serotonin 5-HT$_2$[b]	dopamine D$_2$[c]
1			3.1[c,d]	14[d]
2			0.48[e]	1.3[e]
3a	5-Cl	H	0.39[f]	4.1[f]
3b	H	H	0.72[f]	18[f]
3c	6-Cl	H	1.4[g]	56[g]
3d	H	CH$_3$	0.59[g]	380[g]
4a	H	H	1.7[h]	5.1[h]
4b	H	CH$_3$	1.1[g]	160[g]
5a	6-Cl	H	1.9[i]	37[i]
5b	H	H	3.1[i]	120[i]
5c	5-CH$_3$	H	1.6[i]	920[i]
5d	5-CH$_3$	CH$_3$	3.4[i]	6900[i]
5e	7-CH$_3$	H	3.6[i]	370[h,i]
6a	5-CH$_3$	H	1.5[i]	280[i]
6b	5-CH$_3$	CH$_3$	2.8[i]	6300[i]
7a	H		3.4[j]	400[j]
7b	5-Cl		2.6[h]	360[h]
8a	H		3.1[h]	140[h]
8b	Br		NT	4.0[j]
9			2.6[h]	1600[h]
10			0.4[g]	12[g]
11			2.0[j]	1800[j]

[a] Binding affinities are expressed as IC$_{50}$ values in nM (logarithmic means). [b] [^{3}H]Ketanserin binding. [c] [^{3}H]Spiperone binding. [d] Reference 45. [e] Reference 11. [f] Reference 18. [g] Reference 22. [h] Hyttel, J. Unpublished results, H. Lundbeck A/S. [i] Reference 23. [j] Reference 46. [k] Receptor-binding affinities were reported for the racemate of the trans isomers in ref 27. [l] [^{3}H]Spiperone binding reported as K_i value in nM in ref 32.

Chart 2



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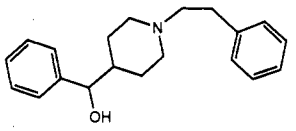

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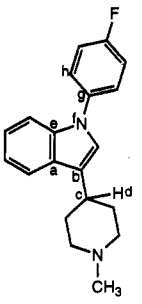
irindalone (**7a**), or are substituted in the 5-position in the indan ring system (e.g., **7b**) are high-affinity 5-HT_2 receptor antagonists with high selectivity with respect to D_2 receptors.

In the indole series, interchange of the C-3 atom and the nitrogen atom in the 3-(4-piperidinyl)indoles **3** results in the 1-(4-piperidinyl)indoles **5**. The result of this interchange is retained high affinity for 5-HT_2 receptors and enhanced selectivity with respect to D_2 receptors. The affinities for 5-HT_2 and D_2 receptors are independent of replacement of the 4-piperidinyl ring with 1,2,3,6-tetrahydropyridin-4-yl ring within both 3-(4-piperidinyl)- and 1-(4-piperidinyl)indoles **3** and **5**. In contrast to what is observed in the indan series, the affinity for dopamine D_2 receptors is only slightly weakened for indoles **3b** and **5b**, which are unsubstituted in the benzene part of the indole nucleus, compared to indoles **3a** and **5a**, which are substituted in the position corresponding to the 6-position in the indan derivatives. As for the indan derivatives, the affinity for 5-HT_2 receptors is not affected by these replacements. Substitution in the position corresponding to the 5-position of the indan ring system, like in the 6-chloro-substituted 3-(4-piperidinyl)indole **3c** and the 5-methyl-substituted 1-(4-piperidinyl)indole **5c**, results in retained affinity for 5-HT_2 receptors and reduced affinity for D_2 receptors. Similarly, the 7-methyl-substituted 1-(4-piperidinyl)indole **5e** has high affinity for 5-HT_2 receptors and high selectivity versus D_2 receptors. Methyl substitution in the 2-position of the indole nucleus results in high affinity for serotonin 5-HT_2 receptors and very low affinity for dopamine D_2 receptors within both (4-piperidinyl)indoles **3d** and **5d** and (1,2,3,6-tetrahydropyridin-4-yl)indoles **4b** and **6b**.

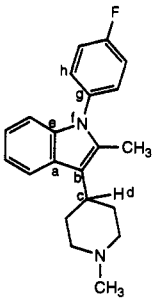
For simplicity, the conformational analyses of the indoles are performed on the corresponding compounds for which the 2-(2-oxoimidazolidin-1-yl)ethyl substituent at the basic nitrogen atom is replaced by a methyl group. The 2-(2-oxoimidazolidin-1-yl)ethyl substituent is excluded in the receptor model, since it is difficult to handle due to its high flexibility. It seems that replacement of the 2-(2-oxoimidazolidin-1-yl)ethyl substituent with a methyl group does not influence the affinity for 5-HT_2 and D_2 receptors, whereas the *in vivo* activity is highly influenced by this replacement.[18] Consequently, the only two degrees of conformational freedom of relevance for the present study are the internal rotation about the bond connecting the 4-fluorophenyl group to the indole nucleus and the internal rotation about the bond connecting the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring to the indole nucleus.

The conformational analyses are performed with the 4-piperidinyl and 1,2,3,6-tetrahydropyridin-4-yl rings in chair and half-chair conformations, respectively, and with the 1-methyl substituent in an equatorial position. These conformations have been shown to be the energetically most stable conformations.[29] For 2-unsubstituted indoles, the internal rotation about the bond connecting the 4-fluorophenyl group to the indole nucleus and the internal rotation about the bond connecting the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring to the indole nucleus are treated independently. Because of the large inter-

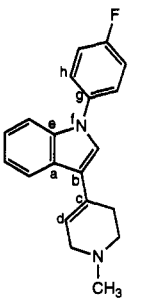
Chart 3



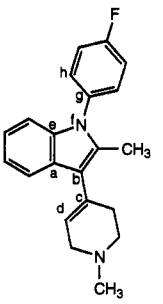
3b'



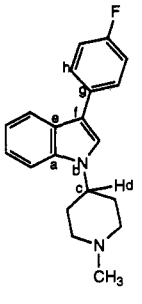
3d'



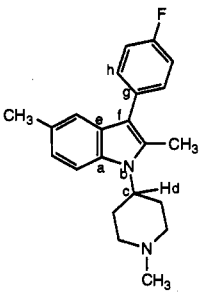
4a'



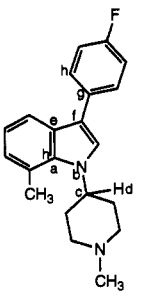
4b'



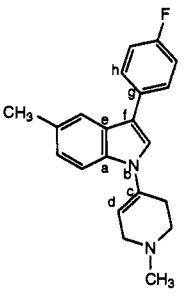
5b'



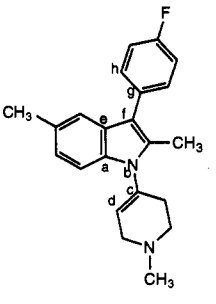
5d'



5e'



6a'



6b'

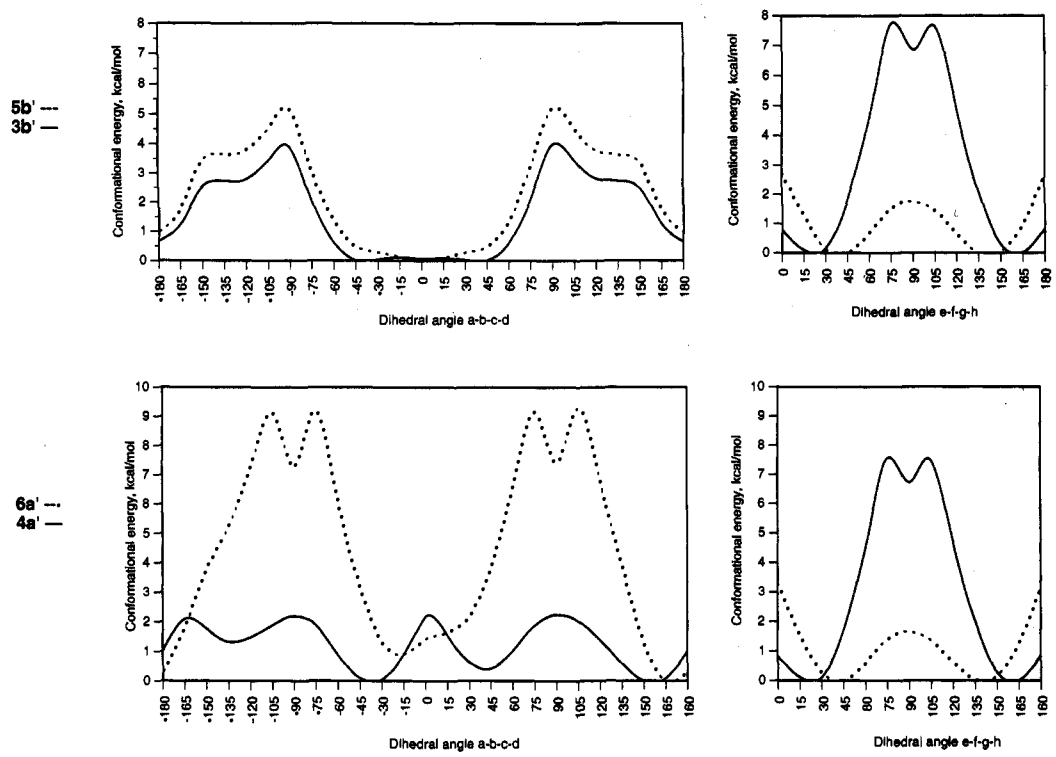


Figure 1. Calculated conformational energy curves for internal rotation about the bond connecting the indole nucleus and the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring and the bond connecting the indole nucleus and the 4-fluorophenyl ring in 2-unsubstituted indoles. Definitions of dihedral angles a–b–c–d and e–f–g–h are given in Chart 3.

atomic distance between the two groups, they do not interact during the internal rotations. The calculations are performed on indoles **3b′**, **4a′**, **5b′**, and **6a′** (Chart 3). They are *N*-methyl analogues of indoles **3b**, **4a**, **5b**, and **6a**, and since the interaction between the substituents in the 5- and 6-positions of the indole nucleus and the two rotatable groups seems negligible, the calculations are representative for the indoles **3a–c**, **4a**, **5a–c**, and **6a**, respectively. The calculated conformational energy curves for the internal rotation of the 4-fluorophenyl group and the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring for indoles **3b′**, **4a′**, **5b′**, and **6a′** are shown in Figure 1. The definitions of the dihedral angles and the structures of the compounds used in the calculations are shown in Chart 3.

The indoles **3d**, **4b**, **5d**, and **6b** are substituted by a methyl group in the 2-position, and it is obvious that both the 4-fluorophenyl group and the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring interact with the 2-methyl group during their internal rotations. To handle this problem, the internal rotations about the bonds connecting the 4-fluorophenyl group to the indole nucleus and the bond connecting the 4-piperidinyl or 1,2,3,6-tetrahydropyridin-4-yl ring to the indole nucleus are treated independently, and because of the symmetry of the methyl group, it is plausible that this group will find its optimal position during these internal rotations. The conformational analyses of these compounds are consequently performed by calculation of conformational energy curves for the internal rotations of the 4-fluorophenyl group and the 4-piperidinyl or the 1,2,3,6-tetrahydropyridyl ring for the compounds **3d′**, **4b′**, **5d′**, and **6b′**, which are *N*-methyl analogues of the compounds **3d**, **4b**, **5d**, and **6b**. The global minimum-energy conformations of corresponding compounds, which are unsubstituted in the 2-position, were used as input structures for all calculations for **3d′**, **4b′**, **5d′**, and **6b′**. The calculated conformational energy curves for the 1-(4-piperidinyl)indole **5d′** are shown in Figure 2.

For the 7-methyl-substituted compound **5e**, it was assumed that internal rotations about the bond connecting the 7-methyl group to the indole nucleus and the bond connecting the 4-piperidinyl ring to the indole nucleus are independent of the internal rotation about the bond connecting the 4-fluorophenyl group to the indole nucleus. The calculated conformational energy curve for the internal rotation about the bond connecting the 4-piperidinyl group to the indole nucleus for **5e′**, which is the *N*-methyl analogue of **5e**, is shown in Figure 2.

The conformational analyses indicate several minimum-energy conformations for each of the compounds. These conformations were further minimized without any conformational restrictions. The geometries and conformational energies of the conformers thus obtained are summarized in Table 2. For conformers, which are mirror images, only one of the two mirror images is included in the table.

Conformational Analysis of Indoles 3 and 5. Global minimum-energy conformations for 3-(4-piperidinyl)-indole **3b′** are found for values of angles a–b–c–d and e–f–g–h at 38° and 22°, respectively, and 34° and 161°, respectively (Figure 1; Table 2). A local minimum-energy conformation (0.7 kcal/mol) is found for values of angles a–b–c–d and e–f–g–h at 180° and 22°, respectively. The conformational analysis of the 3-(4-piperidinyl)indole **3b′** is in agreement with the crystal structures of sertindole (**3a**). For **3a**, two crystal structures have been determined, corresponding to polymorphic crystal forms (personal communication, S. Larsen et al., Department of Chemistry, University of Copenhagen, 1992). The conformation of the 4-piperidinyl ring and the 4-fluorophenyl group relative to the indole nucleus within the low-melting crystal form is highly similar to that of the local minimum-energy

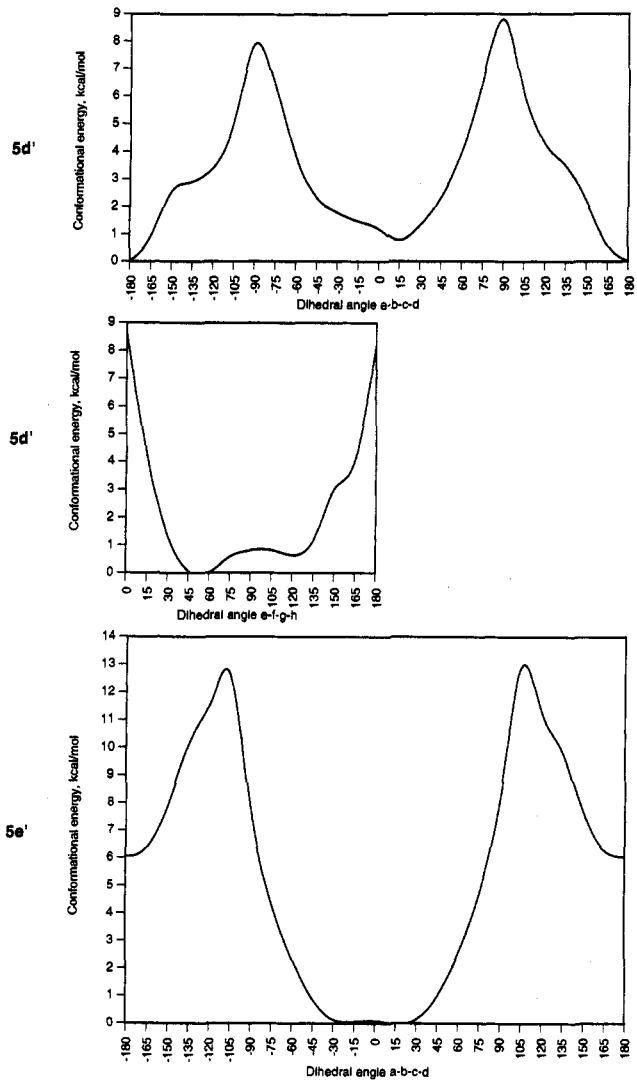


Figure 2. Calculated conformational energy curves for the internal rotation about the bond connecting the indole nucleus and the 4-piperidinyl ring in indoles **5d'** and **5e'** and the bond connecting the indole nucleus and the 4-fluorophenyl ring in indole **5d'**. Definitions of dihedral angles a–b–c–d and e–f–g–h are given in Chart 3.

conformer calculated for **3b'** and for the high-melting crystal form and to that of one of the two global minimum-energy conformers calculated for **3b'**.

For the 1-(4-piperidinyl)indole **5b'**, the global minimum-energy conformation is found for values of angles a–b–c–d and e–f–g–h at 1° and 39°, respectively. A local minimum-energy conformation (1.0 kcal/mol) is found for values of angles a–b–c–d and e–f–g–h at 180° and 39°, respectively.

The conformational energy curves for the internal rotation about the bond connecting the 4-piperidinyl ring to the indole nucleus show that the conformational energy is lower than 1 kcal/mol for values of angle a–b–c–d from −60° to 60° for both (4-piperidinyl)indoles **3b'** and **5b'** (Figure 1).

The conformational properties of the 2-methyl-substituted indoles **3d'** and **5d'** are very similar. Both compounds display two minima with the lowest one described by angles a–b–c–d close to 180° and by angles e–f–g–h of 35° and 51°, respectively (Table 2). The higher energy conformers (0.5 and 0.7 kcal/mol, respectively) differ from the lowest energy conformers by having a–b–c–d angles close to 15°. The conformational energy surface for internal rotation

Table 2. Conformations and Conformational Energies for Minimum-Energy Conformations for Indoles

compd	dihedral angles (deg) a–b–c–d	dihedral angles (deg) e–f–g–h	conformational energy (kcal/mol)
3b'	34	161	0.0
	38	22	0.0[a]
	180	22	0.7
3d'	177	35	0.0
	18	35	0.5[a]
4a'	156	23	0.0
	−35	23	0.1[a]
	−36	160	0.1
	154	159	0.1
	40	160	0.4
	40	23	0.5
	−136	23	1.4
	−136	160	1.4
4b'	−48	34	0.0[a]
	133	33	0.2
5b'	1	39	0.0
	180	39	1.0
5d'	178	51	0.0
	14	51	0.7[a]
5e'	19	40	0.0
	17	140	0.0
6a'	168	41	0.0
	169	140	0.0
	−17	141	1.0
	−17	41	1.0[a]
6b'	156	51	0.0
	−30	52	0.3[a]

[a] Conformers used in the superimpositions.

of the 4-piperidinyl ring is in both cases quite steep in the vicinity of the minima, as exemplified for **5d'** in Figure 2.

For the 7-methyl-substituted indole **5e'**, two global minimum-energy conformations are found for values of angles a–b–c–d and e–f–g–h at 19° and 40°, respectively, and 17° and 140°, respectively. The conformational curve for the rotation about the bond connecting the 4-piperidinyl ring to the indole nucleus in Figure 2 shows that the conformational energy is lower than 1 kcal/mol for values of angle a–b–c–d from −30° to 30°. It should be noted that the conformers of this compound with values of angle a–b–c–d at about 180° are high-energy conformers with a conformational energy higher than 6 kcal/mol (Figure 2).

The calculations show low-energy conformations of the 4-piperidinyl ring relative to the indole nucleus for the (4-piperidinyl)indoles **3b'**, **3d'**, **5b'**, and **5d'**, corresponding to values of angle a–b–c–d from 0° to 40° and at about 180°. Since the latter conformation is a high-energy conformation for the 7-methyl-1-(4-piperidinyl)indole **5e'**, the former conformers are the only low-energy conformations which are common for all the (4-piperidinyl)-indoles studied. These conformers are consequently possible receptor-active conformations for these compounds at the 5-HT_2 and D_2 receptors.

Conformational Analysis of Indoles 4 and 6. For the 2-unsubstituted 3-(1,2,3,6-tetrahydropyridin-4-yl)-indole **4a'**, four conformers with conformational energies lower than 0.1 kcal/mol are found for values of angle a–b–c–d close to −35° and 155° and for values of angle e–f–g–h at 23° and 160° (Figure 1). Additionally, four local minimum-energy conformations are found with conformational energies in the range 0.4–1.5 kcal/mol, as indicated in Table 2. The coplanarity of the π-system a–b–c–d is in these conformers hindered by strong repulsive interactions, as discussed in detail in ref 16. For the corresponding 1-(1,2,3,6-tetrahydropyridin-4-yl)indole **6a'**,

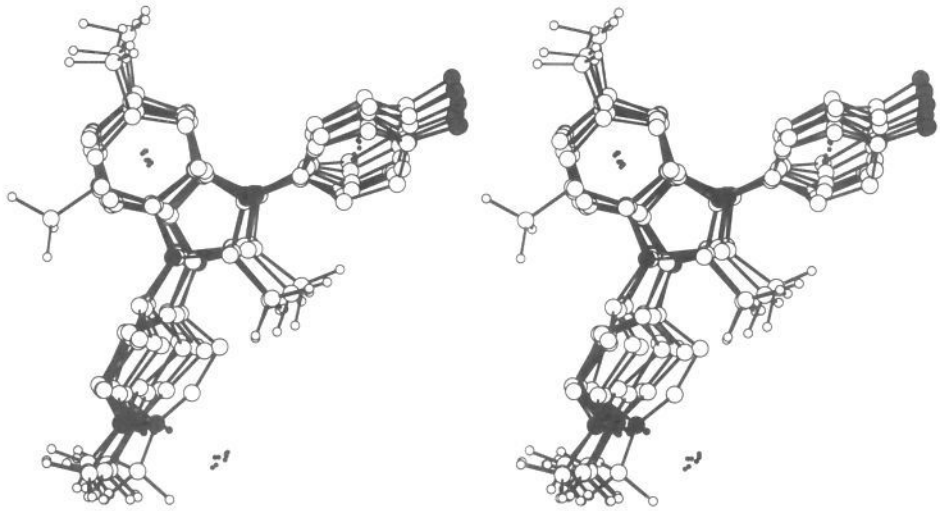


Figure 3. Least-squares superimposition of indoles **3b′**, **3d′**, **4a′**, **4b′**, **5d′**, **5e′**, **6a′**, and **6b′**. The rms values obtained are lower than 0.3 Å.

two conformers with conformational energies lower than 0.1 kcal/mol are found for a value of angle a–b–c–d at about 169° and for values of angle e–f–g–h at 41° and 140°, respectively. Two local minimum-energy conformers (1.0 kcal/mol) are found for a value of angle a–b–c–d at −17° and for values of angle e–f–g–h at 41° and 141°, respectively.

In addition to the minima described above for **6a′**, the conformational energy curve in Figure 1 displays high-energy minima at a–b–c–d equal to ±90° corresponding to orthogonality of the indole π-system and that of the double bond in the 1,2,3,6-tetrahydropyridin-4-yl ring. Similar minima are also displayed in the energy curves for the rotation about the bond connecting the indole ring system and the 4-fluorophenyl ring in **3b′** and **4a′** (Figure 1). We do not believe that these minima correspond to real high-energy conformers. The "minima" are most likely due to an improper balance of steric effects and torsional parameters for the atom combination C(sp2)–C(sp2)–N(sp2)–C(sp2) in the MM2(91) force field. The more recent MM3(92) program[30] gives results very similar to those of MM2(91) for the compounds discussed in the present work but gives maxima instead of minima for values of angle a–b–c–d at ±90° in **6a′** and values of angle e–f–g–h at ±90° in **3b′** and **4a′**.

For the 2-methyl-substituted 3-(1,2,3,6-tetrahydropyridin-4-yl)indole **4b′**, the global minimum-energy conformation is found for values of angles a–b–c–d and e–f–g–h at −48° and 34°, respectively, and a local minimum-energy conformation (0.2 kcal/mol) is found for values of angles a–b–c–d and e–f–g–h at 133° and 33°, respectively. For the corresponding 1-(1,2,3,6-tetrahydropyridin-4-yl)indole **6b′**, the global minimum-energy conformation is found for values of angles a–b–c–d and e–f–g–h at 156° and 51°, respectively, and a local minimum-energy conformation (0.3 kcal/mol) is found for values of angles a–b–c–d and e–f–g–h at −30° and 52°, respectively.

The calculations show low-energy conformations for the 1,2,3,6-tetrahydropyridin-4-yl ring relative to the indole nucleus for all four indoles studied, corresponding to two different ranges of angle a–b–c–d: −48° to −17° and 132° to 169°. Comparison of the two groups of conformers with the (4-piperidinyl)indoles described above shows that the former group of conformers fits better than the latter group on the suggested active conformations of the (4-piperidinyl)indoles.

Molecular Comparisons of the Indoles. The indoles are compared in conformations corresponding to values of angles a–b–c–d and e–f–g–h from 14° to 40° and from 22° to 40°, respectively, for the (4-piperidinyl)indoles **3b′**, **3d′**, **5b′**, **5d′**, and **5e′** and from −48° to −17° and from 23° to 52°, respectively, for the (1,2,3,6-tetrahydropyridin-4-yl)indoles **4a′**, **4b′**, **6a′**, and **6b′**. Except for **5e′**, the conformers used in the comparison are minimum-energy conformations. These conformers are indicated in Table 2. For **5e′** is used a conformation corresponding to values of angles a–b–c–d and e–f–g–h of 45° and 40°, respectively, and with a conformational energy of 0.9 kcal/mol. The comparison is performed by least-squares superimpositions using **4a′** as a reference (Figure 3). The root mean squares (rms) for these superimpositions are lower than 0.3 Å, and the conformational energies of the conformers used are less than 1.0 kcal/mol.

Compounds 8a, 8b, 9, and 10. Cyproheptadine (**8a**) has, in addition to its antihistaminergic and anticholinergic properties,[31] high affinity for serotonin 5-HT$_2$ receptors with high selectivity with respect to dopamine D$_2$ receptors. Introduction of certain substituents in the 3-position of the dibenzocycloheptene nucleus, e.g., a bromine atom (**8b**), results in compounds with high affinity for dopamine D$_2$ receptors (Table 1),[32] suggesting that this position is equivalent to the 6-position within the indan derivatives. The conformational flexibility of these compounds is limited to inversion of the tricyclic dibenzocycloheptene ring system and inversion of the piperidine ring and the nitrogen atom. Piperidine chair conformers with an equatorial *N*-methyl group are significantly lower in energy than boat, twist-boat, and axial *N*-methyl conformers. For the unsubstituted derivative **8a**, there are two pairs of mirror image conformers that are identical. For the 3-substituted derivatives, the mirror image pairs are enantiomers that can be resolved due to the high barrier for inversion of the tricyclic ring system.[12,32] In Figure 4 are shown the two possible chair conformations of **8a** and **8b** with the *N*-methyl group in the equatorial position. The chiral sense of the tricyclic dibenzocycloheptene ring system in the two conformers corresponds to that of the crystal structure of the enantiomer of **8b** with highest

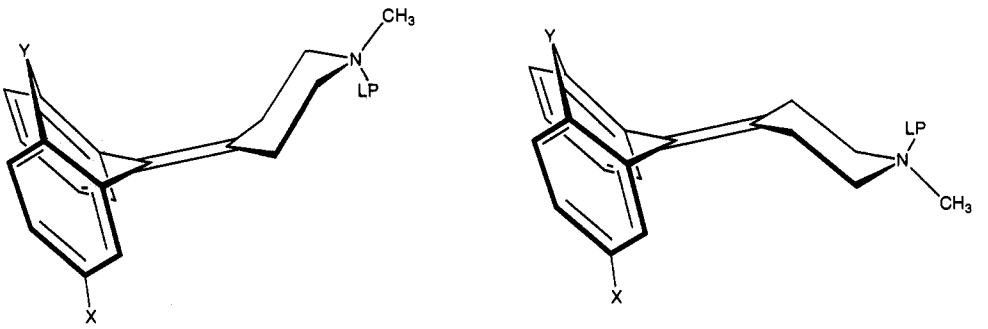


Figure 4. Two conformations of **8a**, **8b**, and **9** with the piperidine ring in a chair conformation and the *N*-methyl group in an equatorial position.

affinity for D_2 receptors.[32] MM2(91) minimization of the two conformers results in virtually identical energies. An NMR study of the hydrochloride of **8a** in chloroform suggests a ratio between the populations of conformers A and B to be 4:1, corresponding to a free-energy difference of 0.8 kcal/mol.[33] The crystal structure for both **8a** and **8b** determined by X-ray crystallography corresponds to conformer A.[32] The slight differences between the energy of the two conformers determined by both molecular mechanics and NMR analysis do not exclude any of them as possible receptor-active conformations of **8a** and **8b**. On the basis of conformational analysis of **8a**, using the semiempirical quantum mechanical method MNDO and structural comparisons with other antihistaminergics, it was suggested that the active conformation at the histamine H_1 receptor is a high-energy conformation with the piperidine ring in a boat conformation.[34] The energy of the suggested active conformation was determined to be 2.7 kcal/mol higher than the energy of the global minimum-energy conformation corresponding to conformer A.

Danitracen (**9**) has high affinity for 5-HT_2 receptors and potent anticholinergic properties.[35] **9** was minimized by MM2(91) with the hydroxy group in a pseudoequatorial position and the piperidine ring in the two possible chair conformations with the *N*-methyl group in equatorial positions. As for the cyproheptadine derivatives **8a** and **8b**, the two conformers have essentially the same conformational energies.

Conformational analysis of the prototype of selective serotonin 5-HT_2 receptor antagonists ritanserin[36] (**10**) is for simplicity performed on the corresponding compound **10′** in which the (oxothienopyrimidinyl)ethyl side chain is replaced by a methyl group. A conformational energy map representing the simultaneous internal rotation about the bonds connecting the 4-fluorophenyl groups to the 4-methylenepiperidine moiety is shown in Figure 5. The resulting global minimum-energy conformation corresponds to values of angles a–b–c–d and a–b–e–f at 126° and 123°, respectively. The flexibility of the two 4-fluorophenyl groups is rather high near the global minimum-energy conformation. Minimizations of structures in which the value of angle a–b–c–d is fixed at 120° and angle a–b–e–f is fixed at values in the range from 75° to 120° result in conformational energies lower than 0.8 kcal/mol.

A superimposition of compounds **9**, **10′**, and **8a** is shown in Figure 6. The conformations of **8a** and **9** used in the superimposition correspond to conformation B in Figure 4, and the conformation of **10′** corresponds to values of angles a–b–c–d and a–b–e–f at 120° and 75°, respectively.

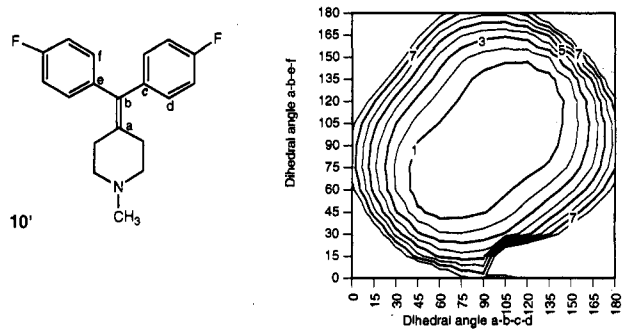


Figure 5. Conformational energy map for the simultaneous internal rotation about the bonds connecting the two 4-fluorophenyl groups to the 4-methylenepiperidine moiety in **10′**. The dihedral angles a–b–c–d and e–f–g–h are indicated in the molecular structure. Isoenergy curves in steps 1 kcal/mol are indicated from 1 to 8 kcal/mol.

The rms values obtained are below 0.1 Å, and the conformational energies of the conformers used are less than 0.8 kcal/mol.

Structural Comparison of 1, 4a′, 5d′, and 8a. The vector defined by the basic nitrogen atom and the point simulating the receptor site interacting with the basic nitrogen atom describes the direction between the basic nitrogen atom and the receptor site. The basic nitrogen atom was used as a fitting point in the development of the Liljefors–Bøgesø D_2 receptor-interaction model to simulate a similar direction of this interaction relative to the other two fitting points (the centers of the two benzene rings) in the superimpositions. The distances between the four fitting points used in the Liljefors–Bøgesø model (the two centers of benzene rings, the basic nitrogen atom, and a point 2.8 Å from the basic nitrogen atom in direction of the lone pair) are very similar for the compounds used in the present study, except for the distance between the basic nitrogen atom and the right benzene ring. The latter distance varies from 6.1 to 8.9 Å whereas the three other distances each vary within ±0.5 Å. This could indicate either that the site at the receptor, which interacts with these benzene rings, is highly flexible or that the geometry of the interaction between the basic amino group and the interaction site at the receptor is variable. It does not seem reasonable that the receptor can accommodate a group as large as the benzene ring in significantly different locations, whereas it seems more reasonable that the latter interaction can be obtained in different geometries. Consequently, the basic nitrogen atom is omitted as a fitting point in the present study, as explained in the description under Computational Methods.

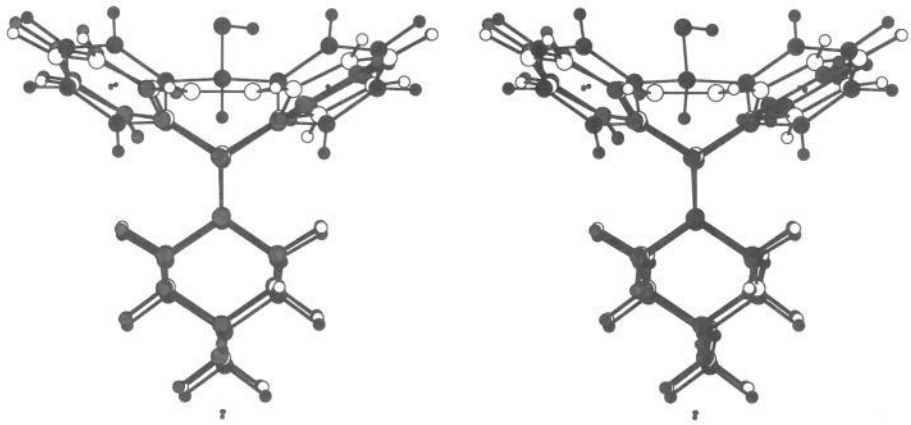


Figure 6. Least-squares superimposition of **9** (black) and **10′** (shaded) on **8a** (white). The rms values obtained are lower than 0.1 Å.

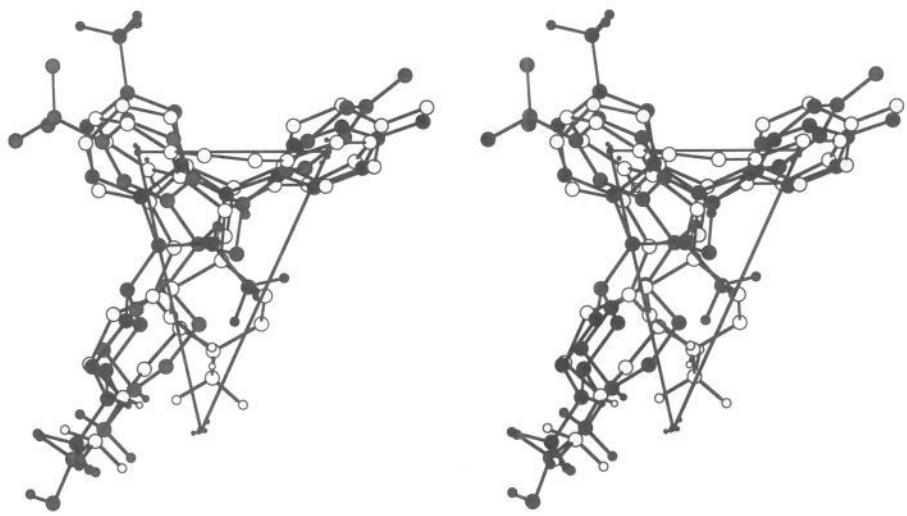


Figure 7. Least-squares superimposition of tefludazine **1** (dark shaded), **4a′** (light shaded), **5d′** (black), and **8a** (white) on three points describing the 5-HT$_2$ receptor-interaction model. The rms values obtained are lower than 0.3 Å.

To study the differences and similarities of the pharmacophores obtained by the two structural comparisons described above and the previously described pharmacophore for D_2 receptor antagonists, selected compounds used in the two comparisons and in the development of the D_2 receptor model were compared. The indole derivative **4a′** and cyproheptadine (**8a**) which were used as references in the two superimpositions described above, the indole **5d′** which had the poorest fit (highest rms value) in the comparison of the indoles, and tefludazine as a representative for the D_2 receptor model were chosen for the comparison. In Figure 7 are shown the superimpositions of these four compounds using three points describing the 5-HT$_2$ receptor-interaction model as a reference. The distances between the three points were calculated as average values of the distances between the three fitting points in the four structures used in the superimpositions. The average values for the distance between the centers of the two benzene rings, for the distance between the left benzene ring (e.g., the benzene part of the indole nucleus) and the point simulating a receptor site hydrogen bonding to the basic nitrogen atom, and for the distance between the right benzene ring (e.g., the 4-fluorophenyl group in the indole derivatives) and the point simulating a receptor site hydrogen bonding with the basic nitrogen atom are calculated to 5.1, 7.5, and 8.1 Å, respectively. The rms values obtained in the superimpositions are lower than 0.3 Å indicating that the relative positions of the important pharmacophoric elements are highly similar for the compounds studied. The left benzene rings in the superimposition are not highly coplanar indicating that the recognition site for this moiety at D_2 and 5-HT$_2$ receptors has some flexibility. The pharmacophore thus described is applicable to 5-HT$_2$ receptor antagonists that have or lack high affinity for dopamine D_2 receptors.

Structural Comparisons of Compounds with High Affinity for Both D_2 and 5-HT$_2$ Receptors. In Figure 8, superimpositions of selected antagonists of 5-HT$_2$ receptors with additional affinity for D_2 receptors are shown, using the three fitting points described. These compounds are tefludazine (**1**), the *N*-methyl analogue (**3a′**) of sertindole (**3a**), and the 3-bromo analogue (**8b**) of cyproheptadine. The superimpositions indicate that the substituents, which have been shown to be essential to obtain affinity for D_2 receptors within the indans (i.e., 6-substitution) and the cyproheptadine derivatives (i.e., 3-substitution) and which have been shown to only slightly increase the affinity for D_2 receptors within the series of 3-(4-piperidinyl)indoles (i.e., 5-substitution), interact with the same region of space.

Structural Comparisons of Compounds with High Affinity and High Selectivity for 5-HT$_2$ Receptors. Figure 9 shows superimpositions of 5-HT$_2$ receptor antagonists with high selectivity with respect to D_2 receptors using the three fitting points described above. The

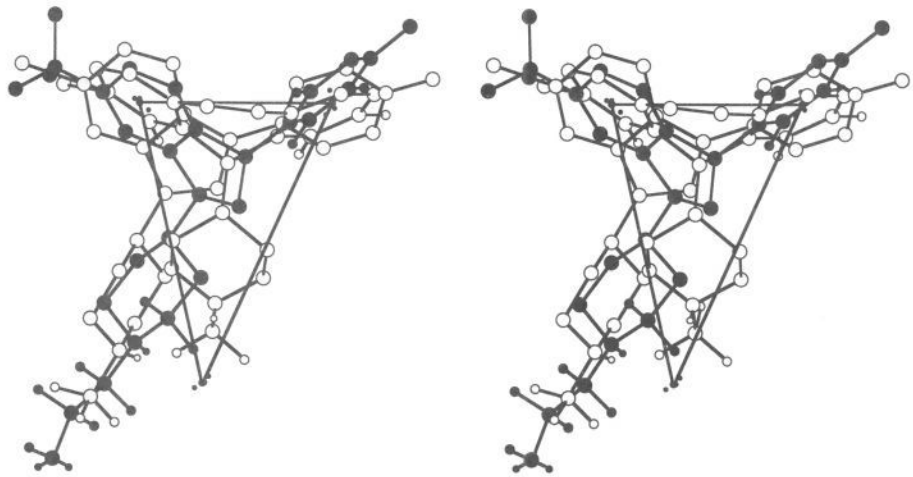


Figure 8. Least-squares superimposition of antagonists of 5-HT_2 receptors with additional affinity for D_2 receptors at three points describing the 5-HT_2 receptor-interaction model. The compounds superimposed are **1** (dark shaded), **3a′** (light shaded), and **8b** (white).

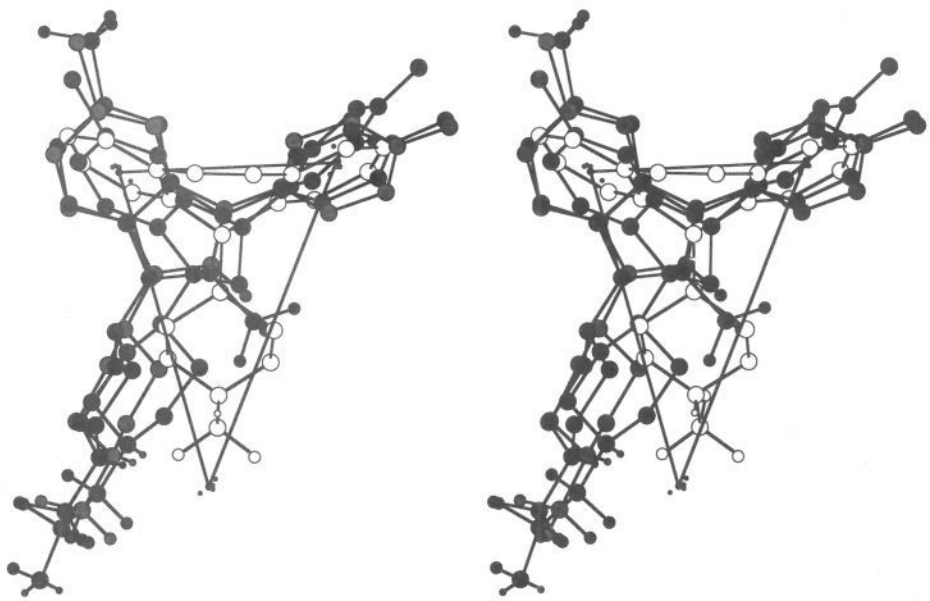


Figure 9. Least-squares superimposition of antagonists of 5-HT_2 receptors with high selectivity with respect to D_2 receptors at three points describing the 5-HT_2 receptor-interaction model. The compounds superimposed are **3c′** (light shaded), **5d′** (black), **7b′** (dark shaded), and **8a** (white).

compounds superimposed are cyproheptadine (**8a**) and the *N*-methyl analogues of the indoles **3c** and **5d** and of the indan **7b**. The superimposition indicates that substituents shown to significantly reduce the affinity for D_2 receptors, such as the 6-chloro atom in **3c**, the 5-methyl group in **5d**, and the 5-chloro atom in **7b**, interact with the same region of space. The 2-methyl group in **5d** occupies the same region of space as a part of the piperidine ring in **8a** indicating that steric bulk in this region reduces the affinities for D_2 receptors, whereas the affinities for 5-HT_2 receptors are not affected. The high affinity for dopamine D_2 receptors obtained for the 3-bromo analogue (**8b**) of cyproheptadine which contains the same steric bulk as does cyproheptadine (**8a**) may be explained by a compensatory dopamine D_2 receptor affinity-enhancing effect from the 3-substituent in **8b**.

Compounds 11 and 12. In Figure 10 are shown conformational energy maps for simultaneous internal rotation about the two flexible bonds in the 4-(4-fluorobenzoyl)piperidine part of ketanserin (**11**) and the α-phenyl(4-piperidinyl)methanol part of MDL 11,939 (**12**). For simplicity, the calculations are performed on compounds **11′** and **12′** in which the (dioxoquinazolinyl)ethyl and phenylethyl substituents at the piperidine nitrogen atom are replaced by a methyl group.

For **11′**, the global minimum-energy conformation is found for values of angles a–b–c–d and b–c–d–e at 13° and 31°, respectively, and a local minimum-energy conformation with similar energy is found for values of angles a–b–c–d and b–c–d–e at 171° and 48°, respectively. For **12′**, the global minimum-energy conformation is found for values of angles a–b–c–d and b–c–d–e at 107° and 61°, respectively. Two local minimum-energy conformations are found for values of angles a–b–c–d and b–c–d–e at 80° and −59°, respectively, with a conformational energy of 0.8 kcal/mol and for values of angles a–b–c–d and b–c–d–e at 92° and 178°, respectively, with a conformational energy of 1.1 kcal/mol.

Tollenaere et al. have published a conformational analysis of ketanserin (**11**) concerning both the very flexible ethylene chain connecting the piperidine ring to the quinazolinedione group[37] and the bonds connecting the

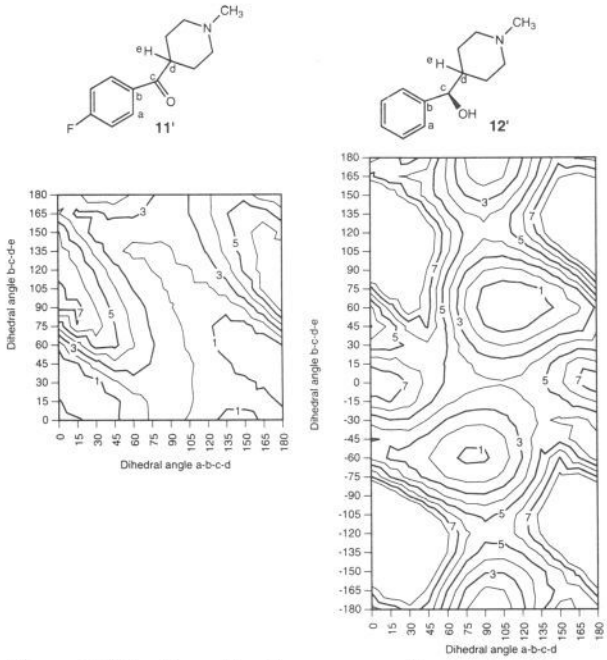


Figure 10. Conformational energy maps for the simultaneous internal rotation about the two flexible bonds in the (4-fluorobenzoyl)piperidine part of ketanserin (**11**) and the α-phenyl-(4-piperidinyl)methanol part of the *S*-enantiomer of MDL 11,939 (**12**). Isoenergy curves in steps of 1 kcal/mol are indicated from 1 to 8 kcal/mol.

4-fluorobenzoyl part to the piperidine ring.[38] The results of the latter study correspond qualitatively to the results of the conformational analysis shown in Figure 10. A crystal structure of **11** has been reported[39] in which the conformation of the piperidine ring relative to the benzoyl moiety corresponds to values of a–b–c–d and b–c–d–e at −8.9° and 35°, respectively. This conformation is very similar to the calculated global minimum-energy conformation.

Bøgesø et al. have suggested that the benzene part of the benzoyl group in **11** binds to the same site at the receptor as the benzene ring of the indan nucleus in **1**. The 4-fluorophenyl substituent of the indan derivatives **7**, which is absent in ketanserin, is assumed to bind to an auxiliary binding site at the 5-HT$_2$ receptors.[17] To evaluate this hypothesis, the global minimum-energy conformations of **11'** and the two enantiomers of **12'** are superimposed on tefludazine (**1**) in its proposed receptor-active conformation. For these superimpositions, the fitting point in the center of the 4-fluorophenyl group in **1** is replaced by a fitting point 1 Å above the center of the benzene plane in the indan nucleus. For **11'** and for the enantiomers of **12'** are, in addition to the fitting point in the center of the benzene ring and the point simulating a receptor site hydrogen bonding with the basic nitrogen atom, added a further fitting point 1 Å above the center of the benzene planes. This fitting point substitutes the third fitting point in the superimpositions described above. The superimpositions result in rms values lower than 0.4 Å, which supports the hypothesis and suggests that a similar hypothesis for the phenyl part of the benzyl alcohol in **12** is plausible. The superimpositions are shown in Figure 11.

Several compounds have been made to evaluate these suggestions. Bøgesø et al. have prepared analogues of irindalone (**7a**) in which the 4-fluorophenyl group has been removed and analogues in which the (4-fluorophenyl)-indan has been replaced by a benzyl group. These modifications result in compounds without any significant affinity for 5-HT$_2$ receptors.[17] Within the 5-HT$_2$-selective indoles **4**, it has been described that removal of the 4-fluorophenyl group results in reduced affinity for 5-HT$_2$ receptors by a factor of 40.[22] These results suggest that the presence of the 4-fluorophenyl group within the indan derivatives is essential to obtain affinity for 5-HT$_2$ receptors, whereas the absence of the 4-fluorophenyl group results in reduced affinity for 5-HT$_2$ receptors within indole derivatives and high affinity for 5-HT$_2$ receptors for ketanserin. These observations might suggest an additional hydrogen-bond interaction between the receptor and the keto group in ketanserin and the pyrrole part of the indoles. Such a potential hydrogen-bonding group is not present in the indan analogues described above. This hypothetical interaction could compensate for the loss of interaction energy by the absence of the 4-fluorophenyl group within indoles and ketanserin but not within the indan analogues.

It has been shown that replacement of the 2-(2-oxoimidazolidin-1-yl)ethyl substituent by a methyl group within the indan derivatives results in retained affinity for 5-HT$_2$ receptors.[17] In contrast, replacement of the side chain in ketanserin by a methyl group results in affinities for 5-HT$_2$ receptors reduced by a factor of 40.[40]

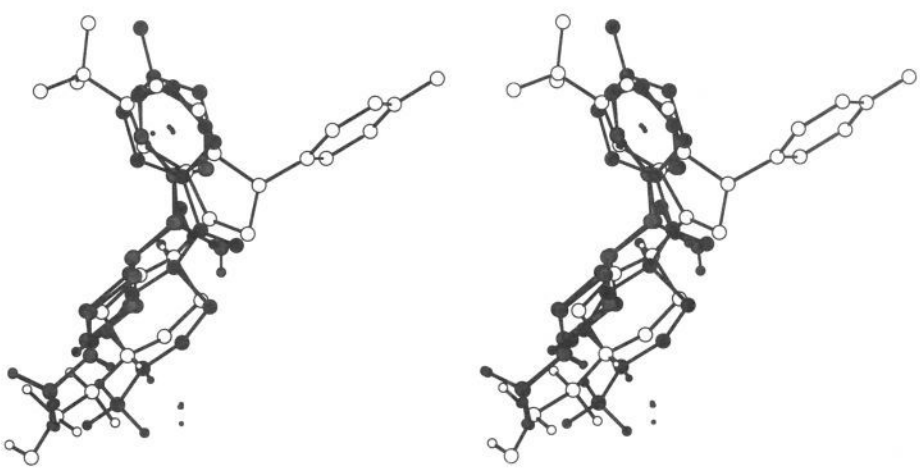


Figure 11. Least-squares superimposition of **11'** and the two enantiomers of **12'** on **1**. The rms values obtained are lower than 0.4 Å.

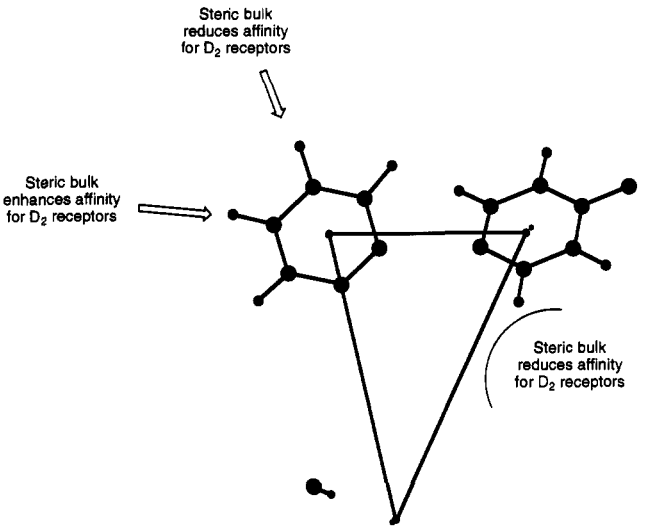


Figure 12. 5-HT_2 receptor-interaction model.

These results indicate that the hydrogen-bond interactions suggested above cannot alone compensate for the interaction with the auxiliary binding site for the 4-fluorophenyl group, which is absent in ketanserin, and that a further compensation by the quinazolinedione group present in ketanserin is necessary to obtain high affinity for 5-HT_2 receptors.

It has been shown that the (+)-enantiomer of **12** has a 20-fold higher affinity for 5-HT_2 receptors than the opposite enantiomer.[41] This difference is not reflected in the structural comparison shown above, since the fit of both enantiomers on **1** is very good. A possible explanation for the difference in affinity of the two enantiomers is that a secondary interaction exists between the benzylic hydroxy group and the receptor and that this interaction is more optimal for the (+)-enantiomer of **12**. Herndon et al. have described the differences in structure affinity relationship for the substituents at the piperidine nitrogen atom between **11** and **12**.[40] Replacement of the quinazolinedione group in **11** by a phenyl group results in retained affinity for 5-HT_2 receptors. In contrast, the reverse replacement of the phenyl group in **12** by a quinazolinedione group results in reduced affinity for serotonin 5-HT_2 receptors by a factor of 50.[40] These differences are in agreement with the fact that the substituents at the piperidine nitrogen atom in **11** and **12** occupy different regions of space in the superimposition shown.

(+)-LSD. The receptor-interaction model for 5-HT_2 receptor agonists and antagonists described by Glennon et al. was developed by using (+)-LSD as a template in the comparison of compounds acting at the 5-HT_2 receptor, such as mianserin and phenethylamines.[9] It was concluded that a common feature among the compounds studied is a distance from the center of an aromatic site to a basic nitrogen atom of approximately 5.1 Å. In contrast, corresponding distances for the compounds used in the present study in the proposed active conformations are determined to be significantly larger, 6.4 ± 0.4 Å.

As described above, the basic nitrogen atom is not used as a fitting point in the present study but is replaced by a fitting point simulating a receptor site hydrogen bonding with the basic nitrogen atom. To determine the distances from the center of the aromatic group to the latter fitting point in (+)-LSD, the structure of (+)-LSD was constructed on the basis of the crystal structure of its *o*-iodobenzoate[42] and subsequently minimized by MM2(91).

Table 3. Force-Field Parameters added to the MM2(91) Force-Field Parameters[a]

A. Torsional Parameters (kcal/mol)

	atom types	V1	V2	V3
C(sp3)–C(sp3)–N(sp2)–C(sp2)	(1–1–40–2)	–0.44	0.24	0.06
C(sp2)–C(sp2)–N(sp2)–C(sp3)	(2–2–40–1)	0	15	0
H-C(sp2)–N(sp2)–C(sp3)	(5–2–40–1)	0	15	0
H-C(sp3)–C(sp3)–N(sp2)	(5–1–1–40)	0	0	0.35
C(sp3)–C(sp3)–C(sp3)–N(sp2)	(1–1–1–40)	0	0	0.3
H-C(sp3)–N(sp2)–C(sp2)	(5–1–40–2)	0	0	0.46
C(sp3)–C(sp2)–C(sp2)–N(sp2)	(1–2–2–40)	0	15	0
C(sp3)–C(sp2)–N(sp2)–C(sp2)	(1–2–40–2)	0	15	0
H-C(sp3)–C(sp2)–N(sp2)	(5–1–2–40)	0	0	–0.24
C(sp3)–C(sp3)–C(sp2)–N(sp2)	(1–1–2–40)	–0.44	0.24	0.06
C(sp3)–C(sp2)–N(sp2)–C(sp3)	(1–2–40–1)	–0.1	10	0

B. Bond Length and Stretching Constant

	atom types	l_0 (Å)	k (mdyn Å^{-1})
C(sp3)–N(sp2)	(1–40)	1.48	5.00

C. Bond Angles and Bending Constants

	atom types	θ_0 (deg)	k_θ (mdyn Å rad^{-2})
C(sp3)–C(sp3)–N(sp2)	(1–1–40)	109.47	0.42
H-C(sp3)–N(sp2)	(5–1–40)	109.47	0.42
C(sp3)–N(sp2)–C(sp2)	(1–40–2)	121.4	0.55
C(sp3)–C(sp2)–N(sp2)	(1–2–40)	121.4	0.55
N(sp2)–C(sp3), out-of-plane	(0–40–1)		0.05

[a] The constants were chosen in analogy with parameters for similar combinations of atoms in a standard force-field parameter list.

The distance from the center of the aromatic group to the fitting point simulating the receptor site hydrogen bonding with the basic nitrogen atom is determined to be 6.2 Å for (+)-LSD which is significantly lower than that for the compounds used in the present study (7.5 ± 0.5 Å). The discrepancy between the geometry of the two models suggests either that one of the two models is incorrect or that two different binding modes exist at the serotonin 5-HT_2 receptor. Since it is not possible to accommodate the compounds used in the Glennon model in the present model and *vice versa*, the former suggestion is ruled out. The receptor-interaction model developed by Glennon accounts for the binding of 5-HT_2 receptor agonists, such as analogues of 5-HT, phenethylamines, and (+)-LSD, and structurally related antagonists, such as mianserin, whereas the present receptor-interaction model accounts for antagonists of 5-HT_2 receptors which are structurally unrelated to the agonists.

Conclusion

A receptor-interaction model for 5-HT_2 receptor antagonists has been developed. The model is described by the distance between the center of the two benzene rings present in the compounds studied and the distances from the centers of these rings to a point simulating the receptor site hydrogen bonding with the basic nitrogen atom. Compounds belonging to different chemical classes, such as indoles, indans, cyproheptadine, and ritanserin (Chart 1), are well accommodated into the model in low-energy conformations. Among these compounds are both 5-HT_2 receptor antagonists with additional high affinity for D_2 receptors and 5-HT_2 receptor antagonists with high selectivity with respect to D_2 receptors, suggesting a common pharmacophore for antagonists of the two re-

ceptors. A structural comparison of these two groups of 5-HT$_2$ receptor antagonists describes important steric differences between the receptor-interaction models for the D$_2$ and 5-HT$_2$ receptor antagonists as indicated in Figure 12. Ketanserin (11) and MDL 11,939 (12) are also accommodated into the model, suggesting that the benzene part of the benzoyl group in 11 and the benzene part of the benzyl alcohol in 12 bind to the same site at the 5-HT$_2$ receptor as the benzene part of the indan nucleus in 1.

The geometry of the developed receptor-interaction model is significantly different from the geometry of the receptor-interaction model described by Glennon et al., which was developed by using (+)-LSD as a template in the comparison of both 5-HT$_2$ receptor agonists and antagonists. The discrepancy suggests the existence of two binding modes at the 5-HT$_2$ receptor.

Computational Methods

Conformational energies and energy-minimized geometries were calculated using the molecular mechanics program MM2-(91) developed by Allinger and co-workers.[43] Full π-electron SCF calculations have in all cases been included in the computations. In addition to standard force-field parameters, constants listed in Table 3 were chosen in analogy with parameters for similar combinations of atoms in the MM2(91) force-field parameter list. As in previous work, all calculations were done on the unprotonated amines with unshared electron pairs represented by a pseudoatom.[10] Conformational energy curves and maps were calculated by using the driver option implemented in MM2-(91) with an angle increment of 15° and with full energy minimization except for the dihedral angle(s) used as driving angle(s). The construction of input structures for MM2(91) and the studies on molecular superimposition were done by means of the molecular modeling program MacMimic.[44] Fitting points used in the superimpositions were centers of two benzene rings (e.g., the benzene part of the indole nucleus and the 4-fluorophenyl group) and a point 2.8 Å from the basic nitrogen atom in the direction of the lone pair. The point is assumed to simulate a receptor site hydrogen bonding with the nitrogen atom.

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