A Structure-Activity Study of Four Dopamine D-1 and D-2 Receptor Antagonists, Representing the Phenylindan, -Indene, and -Indole Structural Classes of Compounds

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Representatives of the phenylindan, -indene, and -indole classes of compounds (3–6) have been tested for affinity for the dopamine D-1 and D-2 receptors. The compounds all display high affinities for these receptors. Conformational analysis using MM2(87) and subsequent molecular least-squares superimpositions have been performed in order to determine if the affinities of the compounds can be rationalized by a recently proposed dopamine D-2 receptor–interaction model. In spite of the different geometric and conformational properties, the compounds can be well accommodated into the model in their calculated lowest energy conformations. The molecular superimpositions allow the absolute configurations of the active enantiomers of 4 and 5 to be predicted. The present structure–activity study extends the receptor–interaction model by suggesting that the receptor is not very sensitive to the orientation of the *p*-fluorophenyl ring in 1 and 3–6 or to the exact spatial location of the associated fluoro substituent.

Introduction

In 1987 Liljefors and Bøgesø[1] proposed a model for antagonistic dopamine (DA) D-2 receptor interaction. It was based on a comprehensive conformational study and subsequent molecular superimposition of the two potent DA D-2 antagonists (1*R*,3*S*)-tefludazine (1) and (*S*)-octoclothepin (2) (Chart I). A least-squares superimposition of the suggested biologically active conformations of 1 and 2 is shown in Figure 1. The superimposed conformers were selected as the only pair which had sufficiently low conformational energies to be likely to be responsible for the receptor affinity of the compounds. Compound 1 as well as 2 displays very similar affinities for DA D-1 and D-2 receptors (Table I). An analysis of the DA D-1 and D-2 receptor affinities of the enantiomers of octoclothepin (2) has been performed in the context of the receptor–interaction model described above.[2] This study concludes that 1 and 2 bind to the DA D-1 receptor in essentially the same way as proposed for DA D-2 binding in Figure 1.

The Liljefors–Bøgesø model was employed and strengthened in a recent work which focused on the structure–activity relationships of the two enantiomers of 2.[2] The model has also been successfully used by Froimowitz to rationalize the DA D-2 receptor affinity of two tetracyclic spiroamines and of cyproheptadine analogs.[3,4] Furthermore, the results of a study on the effect of aromatic substitution on the neuroleptic activity in 1-piperazino-3-phenylindans and 10-piperazino-10,11-dihydrodibenzo-[*b*,*f*]thiepins, by Bøgesø and Sommer, support the model.[5] Recently, it was demonstrated that low-energy conformations of four types of benzamides with high affinity for the DA D-2 receptor can be well accomodated into the receptor-interaction model.[6]

Tefludazine (1), being a potent neuroleptic,[7,8] has inspired the synthesis of a number of structural relatives including the phenylindene and -indole derivatives 4,[9] 5,[9] and 6[10] (Chart I). These compounds are progressively more conjugated and planar than 1. In 6-chloro-3-(4-fluorophenyl)-1-(1-methyl-4-piperidyl)-1-inden (4) the indan skeleton of 1 is transformed into a planar indene system and an sp^2 carbon atom connects to the piperidine ring in the plane of the phenylindene system. Furthermore, only the distal nitrogen atom of 1 is included in the six-membered nitrogen-containing ring of 4. In 6-chloro-3-(4-fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indene (5), the indene system forms a conjugated bond with the nitrogen containing ring forcing the nitrogen atom to be even closer to the indene plane in 5 than in 4 and, finally, in 5-chloro-1-(4-fluorophenyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (6) the tetrahydropyridyl ring as well as the *p*-fluorophenyl ring are conjugated with the bicyclic (indole) system which increases the coplanarity of the ringsystems.

The structural differences in 3–6 give these compounds different spatial relationships between molecular parts which are crucial for the receptor affinity.[1] Furthermore, the varying degree of conjugation should significantly

Table I. Dopamine D-1 and D-2 Receptor Binding Data for Compounds 1–6

	receptor binding (IC_{50}(nM))	
	D1([^{3}H]-SCH)[a]	D2([^{3}H]-SPI)[a]
1	19[b]	14[c]
2	2.2[d]	1.3[d]
3	9.5	12
4	12	19
5	23	5.1
6	9.8	1.1[e]

[a] Results are expressed as the logarithmic mean of at least two determinations. Two full concentration curves were measured by using five concentrations of test drug in triplicate (covering three decades). Standard deviation ratios were obtained by calculating the variance of repeated measures of ratios between the first and second IC_{50} determination for a series of 100 drugs. If the ratio was greater than 3 × SD (99% confidence interval), extra determinations were performed and outliers were discarded. The following 95% confidence ratios (2 × SD ratio) were calculated: D-1 2.13; D-2 2.26. [b] Data taken from ref 2a. [c] Data taken from ref 15. [d] Data taken from ref 2b. [e] Data taken from ref 10.

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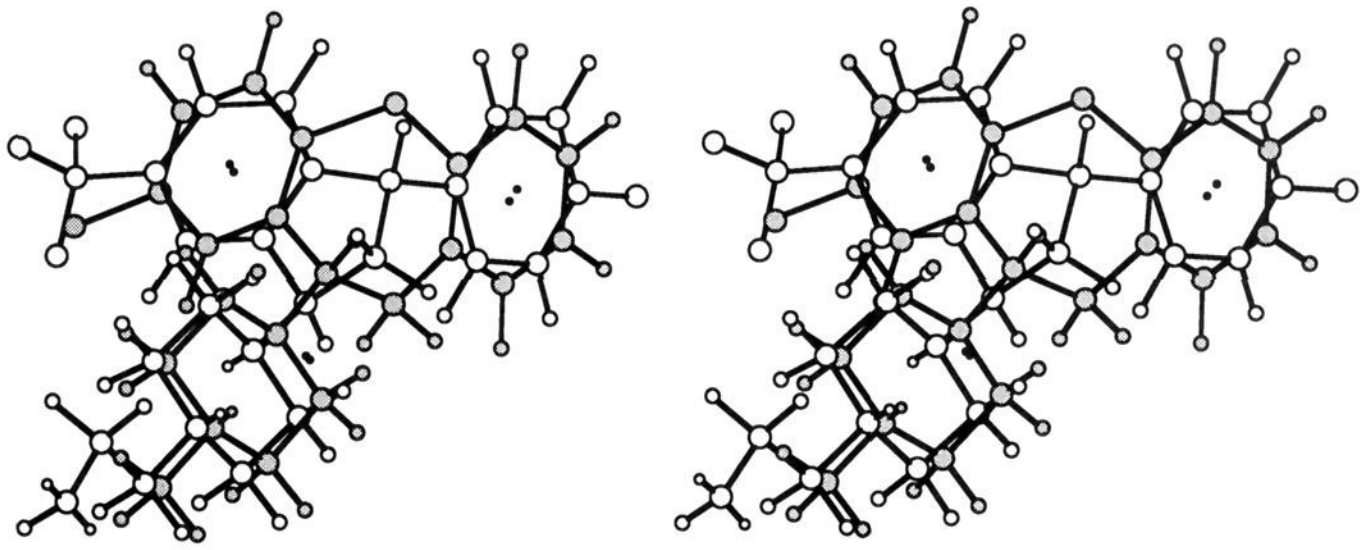
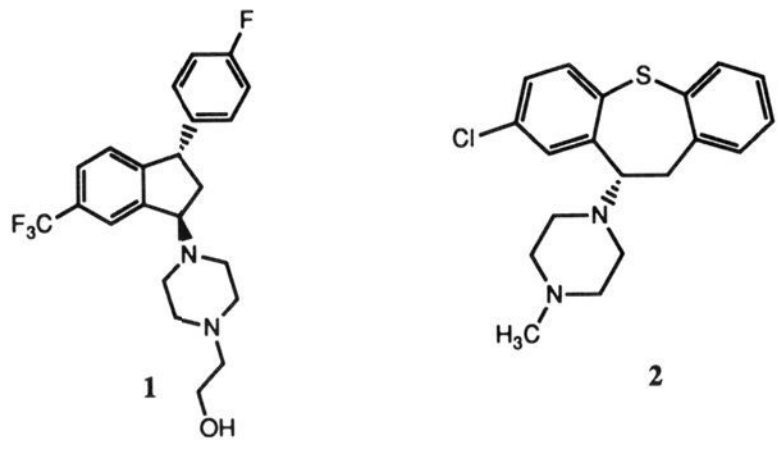


Figure 1. Least-squares superimposition of **1** and **2** (filled atoms). The black dots are fitting points used for the superimposition.

Chart I



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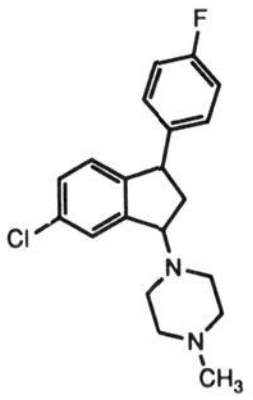

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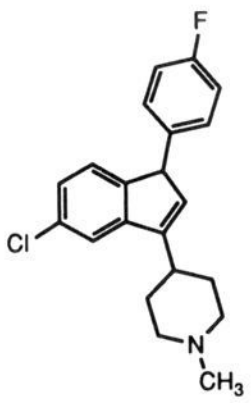

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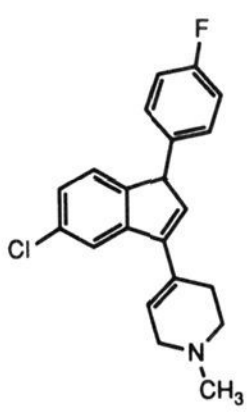

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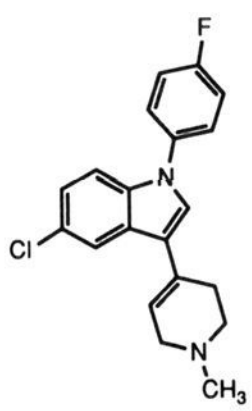


6

affect the conformational properties of the compounds. In addition, the replacement of the indan system in **1** and **3** by an indene or indole system have effects on the electronic properties of the systems.

In this study we present receptor binding data for the studied compounds for binding to the DA D-1 and D-2 receptors. These data are discussed on the basis of conformational analysis of **3–6**, performed using molecular mechanics calculations (MM2(87). Molecular least-squares superimpositions of **1** in its proposed biologically active conformation and **4–6** have been performed. In particular, we wish to establish whether compounds **4–6** can assume conformations compatible with the Liljefors–Bøgesø receptor–interaction model.

All affinities and conformational properties of **4–6** are compared to those of *trans*-4-[6-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-methylpiperazine (**3**),[11] a close relative to **1**, in order to ensure that differences in receptor affinity and conformational properties are not caused by differences in substitution pattern.

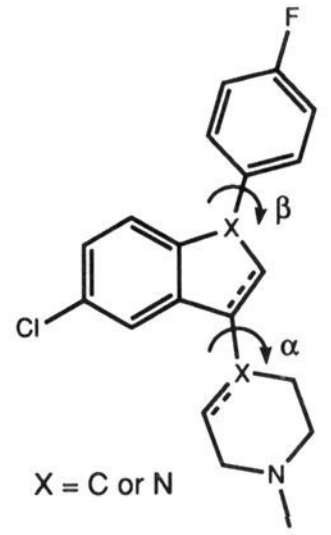


Figure 2. Definition of the α- and β-bonds employed in the calculations of conformational energies by dihedral driving.

Computational Methods

Conformational energies and energy-minimized geometries have been calculated using the molecular mechanics program MM2(87) developed by Allinger and co-workers.[12,13] The dihedral angle vs conformational energy curves were calculated using the dihedral driver option of MM2(87). Rotations about the α-bond (Figure 2) were performed from 0 to 360° and about the β-bond from 0 to 180°. Dihedral angles were driven in 10° steps. The actual dihedral angles employed in the calculations are shown in Figures 3–6. All calculations were as in our previous studies[1,2] performed for the nonprotonated amines. While it seems reasonable to assume that the amine is involved in hydrogen bonding, it is still not clear whether the receptor acts as an acceptor or donor in such a hydrogen bond.[14] As the nitrogens are situated on the rotational axis of the α-bond, the relative conformational energies should be relatively unaffected by the presence of a positive charge.

In the molecular least-squares superimpositions, the centers of the aromatic rings, the (distal) nitrogen atom and a point 2.8 Å from this nitrogen atom in the direction of the nitrogen lone pair, were used as fitting points. The 2.8 Å distance simulates a typical hydrogen bonding distance, which allows the fitting point to represent a corresponding hydrogen bonding group in the receptor.

All input structures were created using the molecular modeling program MacMimic,[15] as were the least-squares superimpositions.

Results and Discussion

DA D-1 and D-2 Receptor Binding. As mentioned in the Introduction, compounds **4–6** are, due to their structural differences, expected to have geometric, electronic, and conformational properties different from those of **1** (and the closely related compound **3**). In spite of this, it was found that **1** and **3–6** have remarkably similar affinities for the DA D-1 and D-2 receptors (Table I). The affinities for **4–6** are, with one exception, found to be within a factor of 2.4 of the corresponding affinities of the reference compound **3**. The exception is the D-2 receptor affinity of compound **6** which is ca. 10 times higher than that of **3**. The D-1/D-2 affinity ratio for **6** is ca. 10, while it is 0.8–4.5 for **3–5**. Thus, the D-1/D-2 selectivity is in general low for all compounds studied.

The nitrogen atom of **1** and **3** binding to the indan ring system is in **4–6** replaced by a carbon atom. The fact that these compounds have similar affinities for the DA D-1 and D-2 receptors further confirms that it is the distal nitrogen in **1** and **3** that is crucial for the receptor binding to these receptors.[1]

All activity of **1** resides in the 1*R*,3*S*-enantiomer. The affinity of the 1*S*,3*R*-enantiomer for the D-1 as well as for the D-2 receptor is negligible.[2a,16] The closely related compound **3** is in the present study tested as its *trans* racemate. Also **4** and **5** are tested as racemates. Due to the high enantioselectivity of **1** we may assume that the inactive enantiomers of **3**, **4**, and **5** contribute negligibly to the receptor affinities in Table I.

Conformational Analysis of 3–6. We have performed conformational analysis of **3–6** using the molecular mechanics program MM2(87) to investigate if each of these compounds can assume a conformation compatible with the Liljefors–Bøgesø receptor–interaction model. In order to determine the significance of such a conformation, we have to ensure that the conformational energy of the compatible structure is low enough so that it can be considered likely to be responsible for the receptor affinity of the compound. Furthermore, if a compound in a conformational energy minimum cannot produce a good fit to the model, it may be capable of assuming a more compatible shape by moving somewhat away from the energy minimum. Such flexibility of the compounds can be estimated from dihedral angle drives.

Compounds **3–6** mainly have two degrees of freedom of interest in this context, rotations about the α- and β-bonds defined in Figure 2. The rotations about these bonds have in the conformational analysis been treated as independent. The validity of this approach has been verified using sparse two-dimensional dihedral drives. Inversion(s) at the aliphatic nitrogen(s) does not need to be considered in the present context. Such an inversion causes an energy penalty of more than one kcal/mol according to MM2(87)

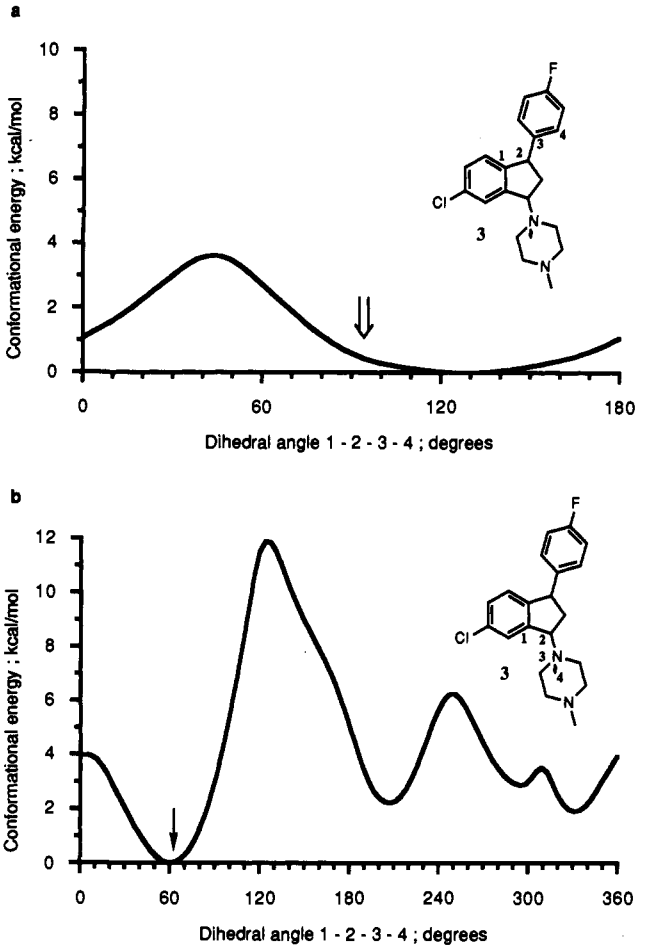


Figure 3. Calculated conformational energy curves for compound **3**. The arrows denote dihedral angles in the proposed biologically active conformation of **1**. The dihedral angle values refer to the 1*R*,3*S*-configuration.

calculations and, more importantly, yields conformers which are geometrically incompatible with the Liljefors–Bøgesø receptor-interaction model. In the calculations, the six-membered nitrogen-containing ring has the chair conformation (**3** and **4**) or the half-chair conformation (**5** and **6**). Other ring conformations are of much higher energy.

The conformational properties of the reference compound **3** are, as expected, virtually identical to those of **1** which was studied in ref 1. A more recent version of the molecular mechanics program was used in the present study (MM2(87) vs MM2(85)), but the calculated results are nevertheless very similar. In **3**, as in **1**, there are two envelope forms of the five-membered ring.[1] Both possibilities have been considered in the present study, but only the results for the conformer with a pseudoequatorial piperazine ring as in the proposed biologically active conformation of **1**, shown in Figure 1, is reported in this study. The other five-membered ring conformer is thoroughly discussed in ref 1.

The potential energy curves resulting from dihedral angle drives of **3** are shown in Figure 3. It can be seen that the phenyl ring (Figure 3a) is very mobile as the energy minimum is very wide, making C(sp^2)–C(sp^3)–C(sp^2)–C(sp^2) dihedral angles in the range of 80–180° accessible with an energy penalty of less than 1 kcal/mol. The wide arrow in Figure 3 points at the dihedral angle that compound **1** assumes in the superimposition with compound **2** in Figure 1.

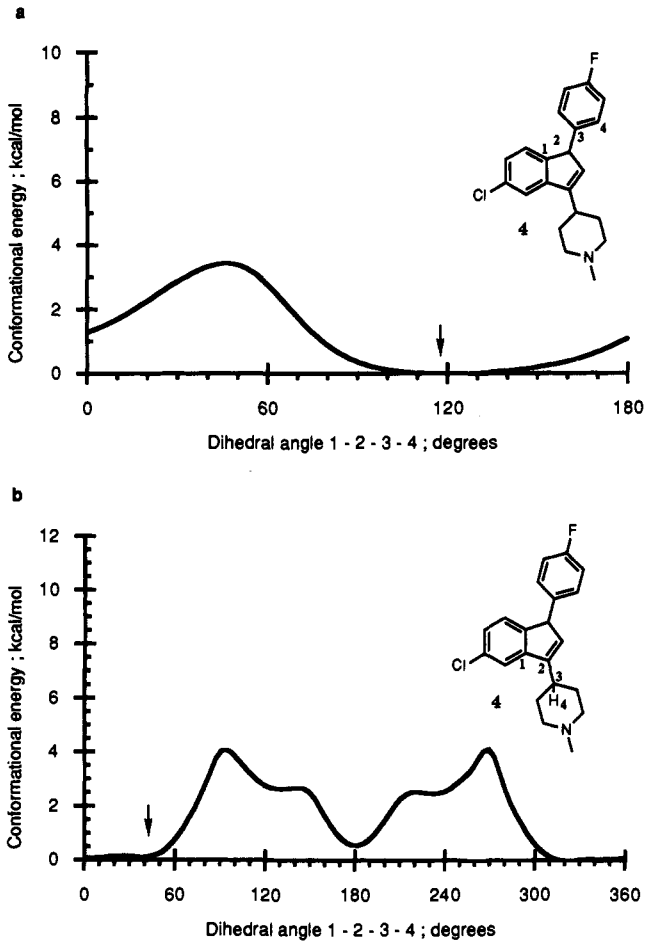


Figure 4. Calculated conformational energy curves for compound 4. The arrows denote dihedral angles corresponding to conformations used in the least-squares superimposition with 1. The dihedral angle values in a refer to the 3*S*-configuration.

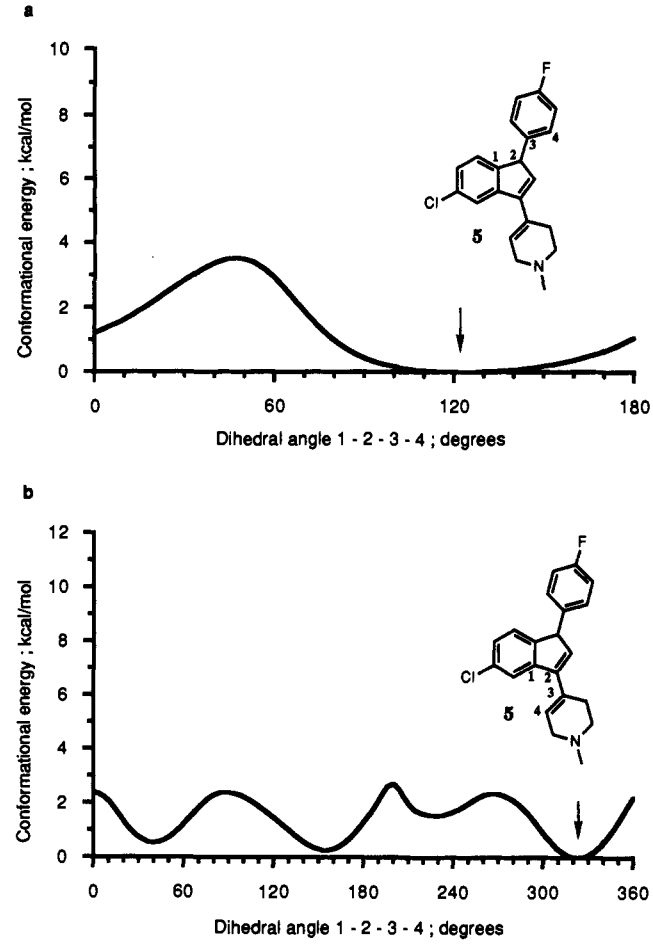


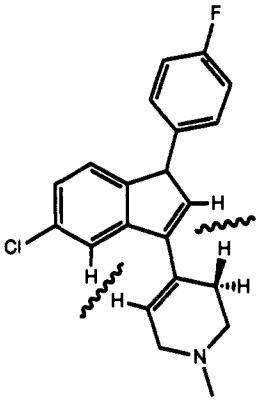
Figure 5. Calculated conformational energy curves for compound 5. The arrows denote dihedral angles corresponding to conformations used in the least-squares superimposition with 1. The dihedral angle values in a refer to the 3S-configuration.

The piperazine ring of 3 (Figure 3b) is significantly more conformationally restricted. The molecular mechanics calculations show four distinct minima. The minimum at a C(sp^2)–C(sp^3)–N–lone pair dihedral angle of ca. 60° is calculated to be 2 kcal/mol lower in energy than any of the others, and the energy rises relatively steeply around the minimum. This piperazine ring orientation (indicated by an arrow in Figure 3b) corresponds to the proposed biologically active orientation of the piperazine ring in 1[1] (Figure 1).

In 4 the indan moiety of 3 is transformed into an indene system which has considerable conformational and geometrical implications. The indene ring itself is planar, not puckered into envelope forms as the indan system of 1. Futhermore, the C(sp^2)–C(sp^3) bond connecting the indene and piperidine ring systems lies in the plane of the indene ring, which gives the molecule a significantly different angle between the piperidine ring and the indene moiety compared to the corresponding angle between the piperazine and indan ring systems of 3 (see Figure 7). The calculated potential energy curves resulting from dihedral drives about the α- and β-bonds in 4 are shown in Figure 4. The potential energy curve with respect to rotation about the β-bond (Figure 4a) is essentially identical to that of compound 3 (Figure 3a). However, the conformational properties of 4 with respect to rotation about the α-bond are drastically different from those of 3. The potential curve, shown in Figure 4b, displays a symmetrical behavior with the lowest energy minima at 40 and 320°. The energy barrier between these minima through 0° is very low, thus, the entire region from −50° through 0 to 50° can be regarded as a single very wide minimum with essentially free mobility of the piperidine ring. In contrast to the reference compound 3, 4 has another readily accessible energy minimum at 180°, with a conformational energy of less than 1 kcal/mol and two higher energy minima at 125 and 235° (+2.5 kcal/mol). A comparison of Figures 3a and 4a clearly shows that the energy barriers for the reorientation of the piperidine ring in 4 is significantly lower than those of 3. In particular the high barrier at ca. 120° in 3 (Figure 3a) is absent in the corresponding potential energy curve of 4. An analysis of the results of the MM2(87) calculations shows that the replacement of the proximate nitrogen atom in 3 with an sp^3 carbon in 4 does not cause any significant changes of the conformational behavior. Instead, the replacement of the indan methylene group in 3 by a C(sp^2)–H group in 4 with concomitant changes in bond angles about the carbon–carbon double bond causes the drastically lowered energy barriers and the displaced energy minima.

In 5 the indene moiety is conjugated with the nitrogen containing ring. Contrary to what might be expected, this conjugation *lowers* the energy barriers for rotation about the α-bond compared to the corresponding conformational interconversions in 4, as shown by the calculated potential energy curve in Figure 5b. There are three distinct energy minima with conformational energies lower than 1 kcal/mol. The entire potential energy curve in Figure 5b lies

Chart II



below 3 kcal/mol giving 5 a remarkable and unexpected conformational freedom. Note that in the lowest energy conformation the double bond in the tetrahydropyridyl ring is not coplanar with the indene ring system (see also Figure 7). The π-system is calculated to be twisted about the partial double bond by ca. 35°. The ideal coplanarity of the π-system is hindered by strong steric repulsive interactions between, in particular, the "peri"-type hydrogen atom of the indene system and olefinic and methylene hydrogens in the tetrahydropyridyl ring. These steric repulsions in the planar π-system are also responsible for the low-energy barriers for rotation about the partial double bond in 5 (Chart II).

As expected, the energy required for rotations about the β-bond in 5 is almost identical to that of compounds 3 and 4, making also the phenyl ring of 5 very flexible (Figure 5a).

The indole system of 6 causes the bond to the *p*-fluorophenyl ring as well as the bond to the tetrahydropyridyl ring to lie in the plane of the bicyclic ring system. This makes 6 even more flat than 5 (see Figure 7). Due to the conjugation of the *p*-fluorophenyl ring and the indole system, the energy barrier for rotation about the β-bond in 6 is much higher than those for 3–5, almost 10 kcal/mol (Figure 6a). The energy minima are also significantly more narrow, allowing the phenyl ring far less conformationl freedom in 6 than in 3–5. Due to steric repulsive interactions between the hydrogens in the phenyl ring in ortho positions to the indole nitrogen and hydrogens in the indole ringsystem, the *p*-fluorophenyl ring is not coplanar with the indole system in the energy minima.

In spite of the increased conjugation in 6, the energy required for rotation about the α-bond (Figure 6b) closely follows the somewhat surprising pattern established by 5. The energy minima and barriers are very similar to those of 5.

Structural Comparisons and Molecular Least-Squares Superimpositions. In Figure 7, compounds 3–6 are shown in their calculated lowest energy conformations using a projection along the central aromatic plane. This illustration shows how the compounds become progressively more planar with increasing conjugation. The nitrogen atom in the indenes 4 and 5 is closer to the aromatic plane than the corresponding nitrogen atom in 3. The indole 6 additionally has the phenyl ring close to the plane of the central aromatic moiety. Therefore, 4–6 have to be rotated about the projection axis in order to achieve a good fit to 1 and 3, using the fitting points described in the Computational Methods section. This

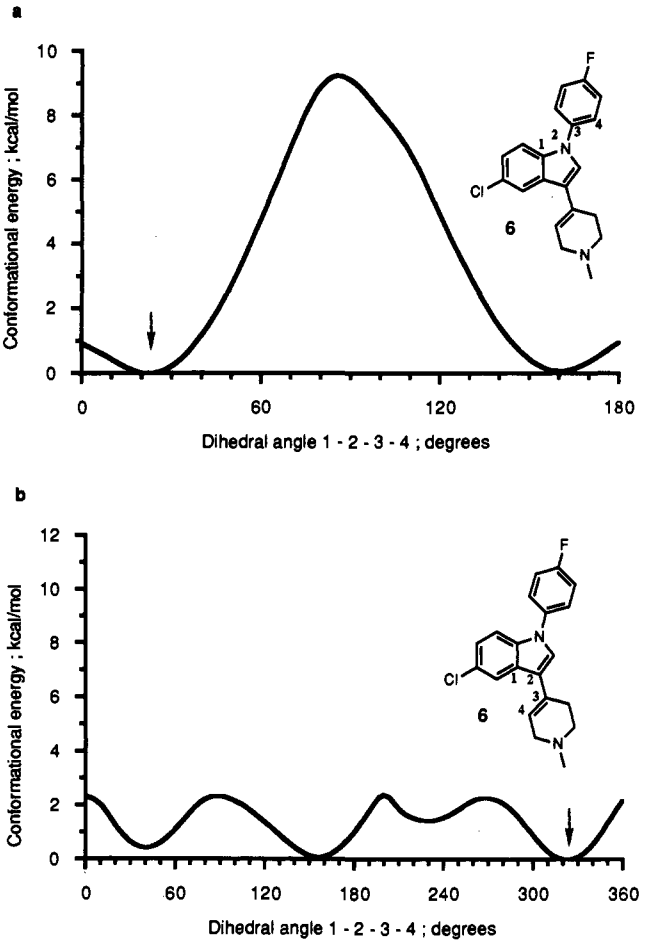


Figure 6. Calculated conformational energy curves for compound 6. The arrows denote dihedral angles corresponding to conformations used in the least-squares superimposition with 1.

in turn will cause the central aromatic moiety to be rotated with respect to the reference compound.

Compounds 4–6 have been least-squares superimposed on 1 as shown in Figures 8–10, using the fitting points described in the Computational Methods section. Compound 3 trivially gives a perfect fit to 1, as 3 differs from 1 only in substituents which do not influence relative conformational energies and spatial relationships between fitting points. This superimposition is therefore not shown. The conformation of 1 in these superimpositions is the proposed biologically active conformation shown in its superimposition with 2 in Figure 1. Note that in this conformation the *p*-fluorophenyl ring of 1 is rotated somewhat from its lowest energy conformation in order to achieve an optimal superimposition with 2.[1] This phenyl ring conformation is marked in Figure 3 with a wide arrow. The dihedral angles for 4–6 corresponding to the conformations used in the superimpositions in Figures 8–10 are marked with arrows in Figures 4–6. They are all lowest energy minima. For reasons which will be discussed below, no attempts have been made to obtain perfect coplanarity between the *p*-fluorophenyl rings in 4 and 5 and the corresponding ring in 1. Only those enantiomers of 4 and 5 that are analogous to the 1*R*,3*S*-enantiomer of 1 are shown, as the other enantiomers are unable to achieve reasonable superimpositions.

The molecular least-squares superimposition of 1 and the lowest energy conformer of 4 is shown in Figure 8. The rms error of the fit is low, 0.232 Å. In the superimposition, 4 has the 3*S*-configuration. The 3*R*-enantiomer cannot

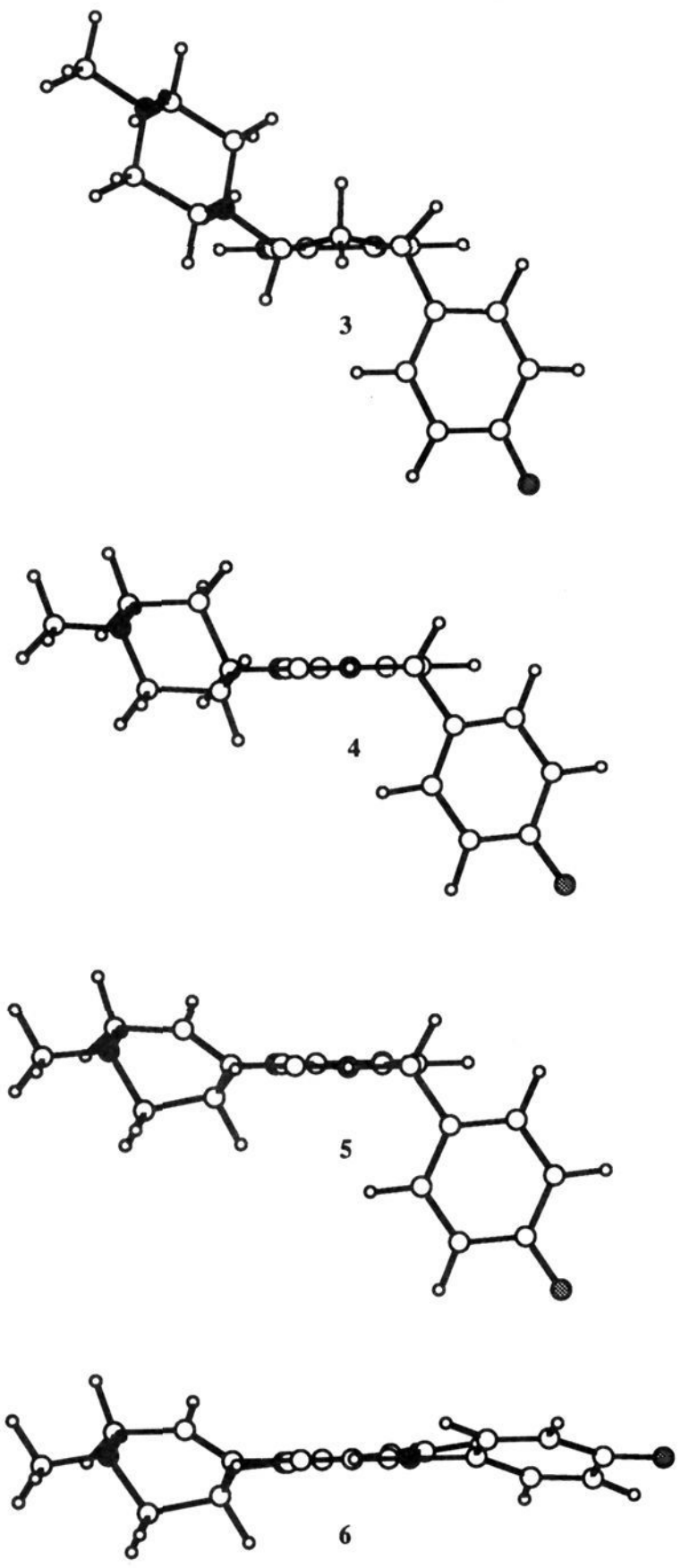


Figure 7. Compounds **3–6** in their calculated lowest energy conformations.

place its *p*-fluorophenyl ring in the same region of space as the corresponding ring in **1** and consequently gives a very bad fit to **1**. Thus, considering the similar receptor affinities of **1** and **4** (Table I) and the high enantioselectivity of **1**, it may be predicted that the active enantiomer of **4** has the 3*S*-configuration.

The nitrogen atoms and the lone pair vectors of **1** and **4** overlap almost perfectly. This causes the phenylindene moiety to be rotated somewhat relative to the phenylindan of **1**. The angle between the two bicyclic ring systems is slighly less than 20°. The *p*-fluorophenyl ring of **4** deviates from coplanarity with corresponding phenyl ring plane of **1** by some 30°. The orientation of the bond connecting to the phenyl ring is almost identical in the two compounds, which makes it possible to achieve a virtually perfect coplanarity of the phenyl rings by rotating the phenyl ring of **4** by 30°. As can be seen in Figure 4a, this may be done with a very small energy penalty.

A least-squares superimposition of **1** and the lowest energy conformer of **5** is shown in Figure 9. The rms error of this fit, 0.266 Å, is very similar to the one between **1** and **4**, described above. Also in this case, only the 3*S*-enantiomer of **5** can produce a good fit to **1**. Since both compounds have similar affinities (Table I), this enantiomer should be the active one for **5**. In **5** the indene moiety binds to the nitrogen-containing ring via conjugated sp^2 carbons. Nevertheless, all parts of the compound superimpose excellently with **1**. The *p*-fluorophenyl ring of **5** is in its energy minimum in Figure 9, and its orientation corresponds well to that of the corresponding ring of **1**. The nitrogen of **5** is somewhat closer to the plane of the indene ring system than is the nitrogen in **4** (Figure 7). Therefore, in the superimposition of **1** and **5**, the angle between the two bicyclic ringsystems is somewhat larger than in the superimposition of **1** and **4**.

A least-squares superimposition of **1** and the lowest energy conformer of the indole **6** is shown in Figure 10. The rms error of this fit with respect to the fitting points used, 0.278 Å, is very similar to those of the superimpositions described above. Compound **6** has a planar indole moiety in which the conjugated system is extended into the fluoro-substituted phenyl ring, placing the bond to the fluorosubstituted phenyl ring in the plane of the indole moiety (Figure 7). As with compound **5**, the bond to the tetrahydropyridyl ring is also in the plane of the indole moiety, which brings the aliphatic nitrogen close to this plane. Nevertheless **6** can achieve a remarkably good fit to **1**.

In the superimposition with **1** shown in Figure 10, the dihedral angle 1–2–3–4 in **6**, defined in Figure 6a, would have to be in the order of 75° to obtain an optimal coplanarity of the two *p*-fluorophenyl rings. As can be seen in Figure 6a, the barrier to rotation of the phenyl ring in **6** is high and a dihedral angle of 75° corresponds to an energy penalty of ca. 8 kcal/mol. This makes it improbable that **6** can achieve its high affinity to the DA D-1 and D-2 receptors (Table I) with its phenyl ring in such a high-energy orientation. As can be seen in Figure 10, the phenylindole moiety of **6** is rotated relative to the phenylindan ringsystem even more than in the cases of **4** and **5**, and the *p*-fluorophenyl ring is at an angle of some 20° relative to that of **1**. This places the corresponding fluorine atoms at a distance of 1.5 Å. This distance cannot be diminished by rotation about the β-bond. Therefore, the superimposition of **1** and **6**, in conjunction with the high affinities of both compounds for the DA D-1 and D-2 receptors, indicates that the receptors are relatively insensitive to the precise orientation of the *p*-fluorophenyl rings and to the precise spatial position of the fluorine atom. In particular, strict coplanarity with the *p*-fluorophenyl ring of **1**, as defined by the optimal overlap between corresponding rings in **1** and **2** (Figure 1), does not seem to be required for a high affinity to the DA D-1 and D-2 receptors. As the electrostatic potential of a phenyl ring is very anisotropic,[17] this further implies that the *p*-fluorophenyl ring most likely does not have important electrostatic interactions with the receptor.

Conclusions

Receptor binding studies of **3–6** show that these compounds have high and similar affinities for DA D-1 as well as D-2 receptors. The D-1/D-2 selectivity is in general low. Conformational analysis and molecular least-squares

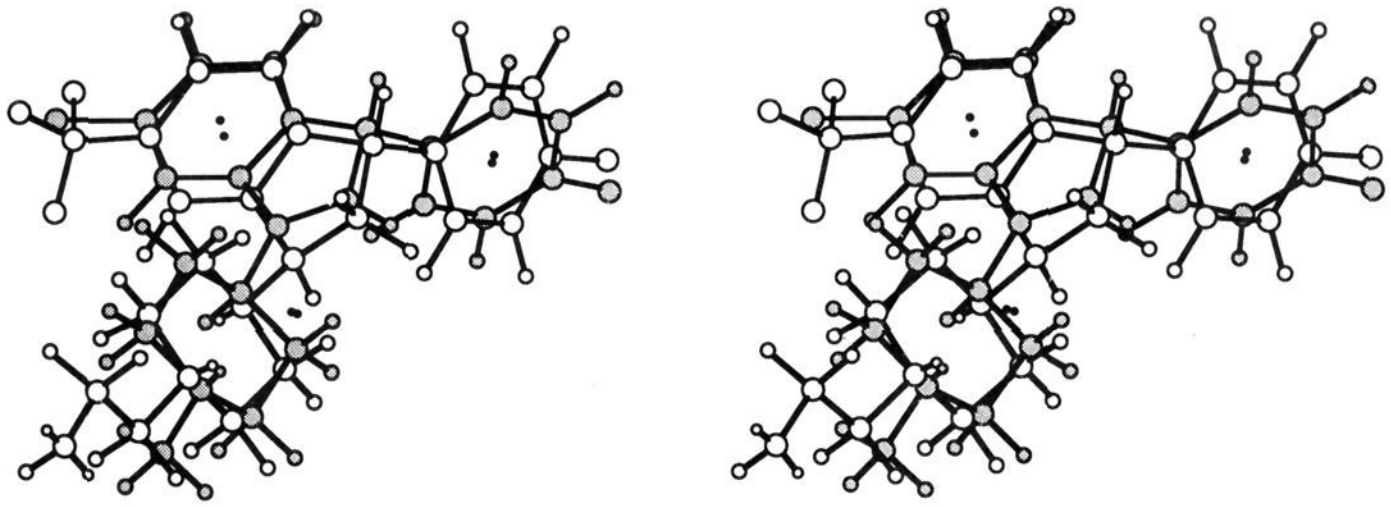


Figure 8. Least-squares superimposition of 1 and 4 (filled atoms).

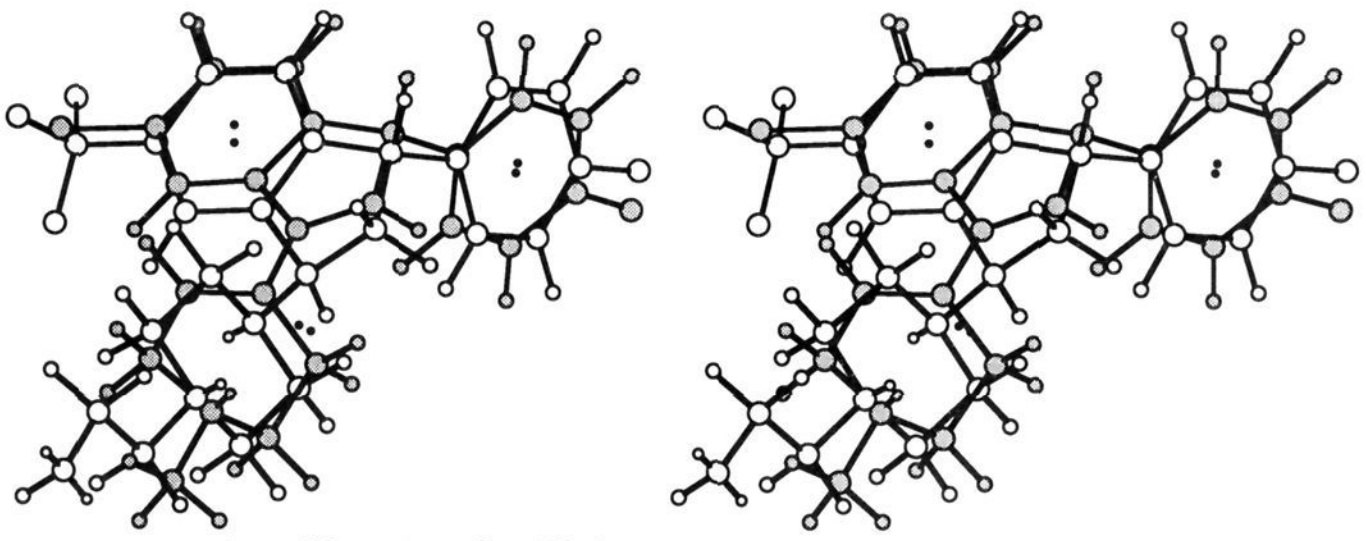


Figure 9. Least-squares superimposition of 1 and 5 (filled atoms).

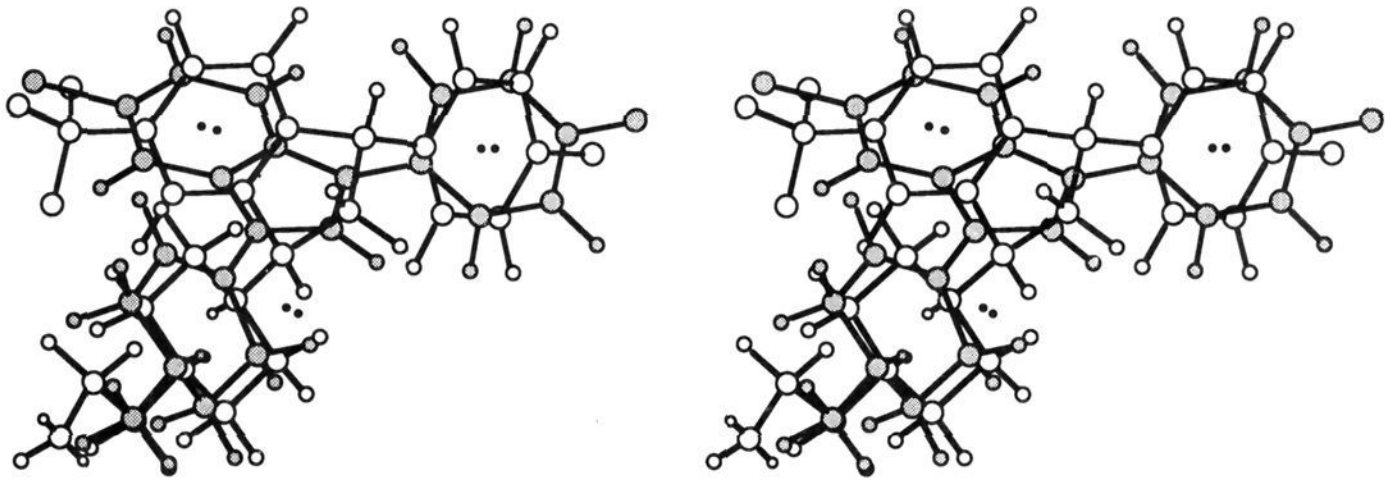


Figure 10. Least-squares superimposition of 1 and 6 (filled atoms).

superimpositions of the compounds show that these compounds can be accommodated in a recent DA D-2 receptor–interaction model. In spite of their very different geometrical and conformational properties they all fit well to the previously proposed biologically active conformation of 1 in their lowest energy conformations. Using the results of the superimpositions we predict that the affinities of **4** and **5** are confined to their 3*S*-enantiomers. The structure–activity study extends the receptor–interaction model in that it suggests that the receptor does not make strict demands on the precise orientation of the fluoro-substituted phenyl ring or the exact spatial location of the associated fluoro substituent.

Experimental Section

Receptor Binding Studies. DA D-1 Receptors. Inhibition of [^{3}H]SCH 23390 binding to DA D-1 receptors in rat striatal membranes was determined as described by Hyttel[18] and Hyttel and Arnt.[19]

DA D-2 Receptors. Inhibition of [^{3}H]spiperone binding to DA D-1 receptors in rat striatal membranes was determined as described by Hyttel.[20]

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