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Articles

Comparison of 5-HT_{1A} and Dopamine D_2 Pharmacophores. X-ray Structures and Affinities of Conformationally Constrained Ligands

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Conformational and molecular mechanics studies of a new series of tricyclic ligands with affinity for either the dopamine D_2 receptor or the 5-HT_{1A} receptor, or both, has enabled us to elaborate considerably on previous pharmacophore models for these receptors. The new tricyclic ligands are either angular, 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole derivatives, or linear, 2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]indole derivatives; they have either cis or trans ring junctions, and many of the ligands are resolved. In order to have X-ray crystal coordinates for every structural type, two additional crystal structures were determined: **14a**, the *trans*-(±)-6-hydroxy-3-(*n*-propyl) angular derivative as the hydrochloride, and (±)-1,2,2a,3,4,8b-hexahydro-8-methoxy-2-(2-propenyl)-naphth[2,1-*b*]azetidine hydrochloride (**16d**). Several recently reported imidazoquinolinones with dopaminergic and serotonergic activities were also used in developing the models as were other known ligands which are conformationally constrained. A new method for determining intrinsic activity at the D_2 receptor made consistent and reliable estimates of dopamine agonist, partial agonist, and antagonist activities available. The models explain these activities in terms of the 3-dimensional structural features of the ligands and their probable orientations at the D_2 receptor site. They also explain why allyl and propyl analogs of some structures have very different affinities while affinities are quite similar for allyl and propyl analogs of other structures; at both receptors a particular orientation of the amine substituent in the binding site correlates with preference for allyl over propyl derivatives. Suggestions are made for enhancing selectivity at the 5-HT_{1A} receptor or at the dopamine D_2 receptor. An angular, *cis*, (3a*R*,9b*S*), 2-propyl, 9-hydroxy, 3-(*n*-propyl) analog should be selective for the 5-HT_{1A} receptor. A linear, trans, (3a*R*,9a*S*), 7-hydroxy, 1-(2-propenyl) analog should be selective for the dopamine D_2 receptor, and would be predicted to be an antagonist.

Introduction

Both the 5-HT_{1A} and the dopamine D_2 receptors belong to the guanine nucleotide-binding regulatory protein (G-protein) superfamily. Receptors in this family, which also includes the β-adrenergic receptor, the muscarinic cholinergic receptors, and rhodopsin, have seven hydrophobic transmembrane domains linked by hydrophilic loops. An agonist ligand binds to the receptor and activates it to interact with a G protein, initiating a cascade of events leading to a physiological change. D_2 activation results in inhibition of adenylyl cyclase;[1] 5-HT_{1A} activation has been reported both to inhibit and to stimulate adenylyl cyclase.[2]

There are as yet no X-ray crystal structures available for any of the neurotransmitter receptors. Although considerable effort has gone into modeling some of the

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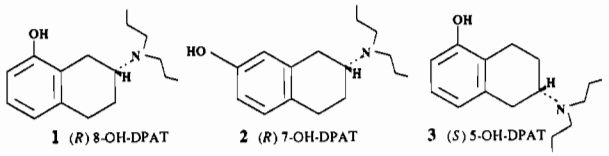
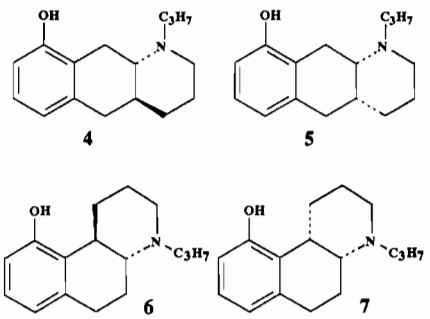
receptors,[3-6] the most detailed pharmacophore models have been based on studies of receptor ligands. Considering the ligands that bind with specificity to the various receptors, there are remarkable similarities between the 5-HT_{1A}-specific ligand, 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT), 1,[7] and the dopamine D_2 specific ligands **2**[8] and **3**.[9]



1 (*R*) 8-OH-DPAT **2** (*R*) 7-OH-DPAT **3** (*S*) 5-OH-DPAT

A model for the dopamine D_2 pharmacophore with considerable detail was developed in 1986 by Liljefors and Wikström[10] and further elucidated in 1990.[11] Parts a and b of Figure 1 show features of this agonist pharmacophore model: an "aromatic plane", a protonated nitrogen positioned slightly above this plane with proton pointing down from the plane and substituent propyl group above the plane and to the right in the "propyl cleft". The hydroxy substituent on the aromatic ring is positioned to form a hydrogen bond. The propyl cleft cannot accommodate a group larger than propyl; the area at top right in Figure 1a, however, can accommodate larger N-substituents.

Models for the 5-HT_{1A} pharmacophore[12-14] were less detailed until in 1991 Mellin and co-workers described a model based on linear and angular tricyclic fused rings, **4–7**, having both cis and trans ring junctions.[15] For all these structures, the four-carbon chain between the amine and the oxygen has the same geometry as that in **1**.



4 **5**

6 **7**

The Mellin model has an aromatic plane as in the D_2 pharmacophore and features a "dummy" atom, as shown in Figure 2, which is located 2.1–2.6 Å below the aromatic plane at a distance of 5.2–5.7 Å from the normal of the aromatic center. It is positioned so as to minimize the nitrogen–dummy atom distance for the ligands in this series with the highest affinities, i.e. the enantiomers of **6**.

Recently an analogous series of linear and angular tricyclic fused rings **8–11** (four-carbon amine-to-oxygen link as in **1**), and also the series **12–15** which has a longer amine-to-oxygen distance (the five-carbon link is either as in **2** or as in **3**), have been synthesized and tested for both 5-HT_{1A} and D_2 affinity and for agonist and antagonist activities.[16,17] In **8–15**, the nitrogen-bearing ring has five members instead of six, and consequently the molecules are considerably more constrained conformationally than the series **4–7**.

We include in this report the synthesis and affinities of new azetidine ring analogs of **11**, i.e. **16b–d**. These ligands

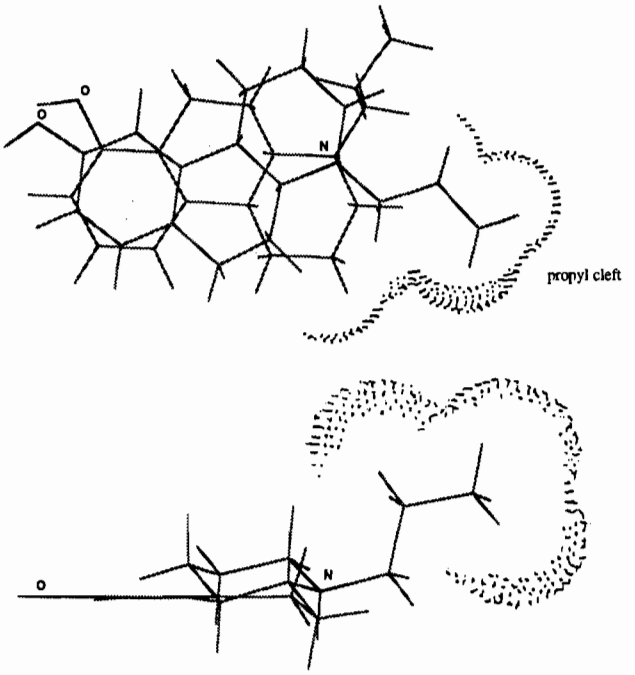


Figure 1. (a) Liljefors and Wikström[10] model for dopamine D_2 agonist pharmacophore (superposition of **22** and **23**). (b) **23** shown in an edge view. In the 1990 refinement of their model, Liljefors and co-workers[11] proposed that the conformation of the propyl group in the "propyl cleft" in part a is anti relative to the nitrogen lone pair, rather than the gauche conformation shown in a. The propyl cleft in this case would be almost entirely above the plane of the aromatic ring.

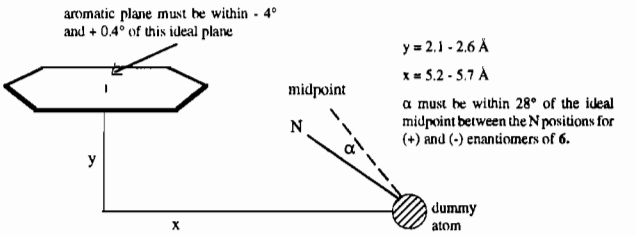
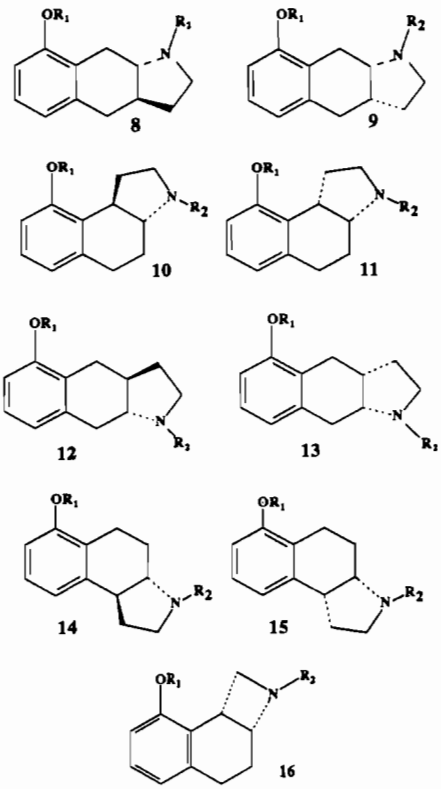


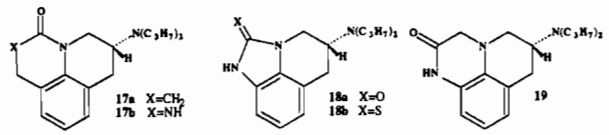
Figure 2. Model for 5HT_{1A} pharmacophore proposed by Mellin and co-workers.[15]

are quite rigid, except for side-chain motions, and have exceptionally high affinity for the 5-HT_{1A} receptor. Although the pattern of affinities for **8–11** is somewhat similar to the affinities of **4–7** on which the Mellin model was based, there are some notable differences. In particular, **7** was reported as a low-affinity ligand,[15] but the **11** and **16** analogs of **7** have at least 1 order of magnitude greater affinities than the enantiomers of **6**, which were reported by Mellin and co-workers to have the best affinities in the **4–7** series.

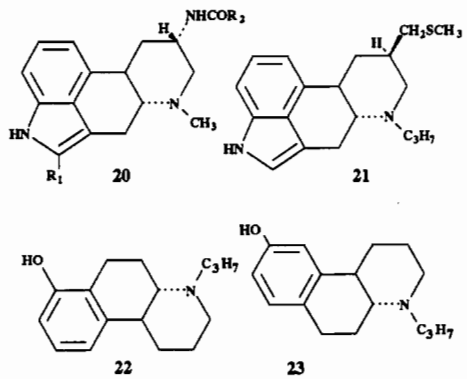
In general, the affinities in the new series **8–16** do not have the pattern that ligands with shorter (~5.2 Å) N–O distances (carbon linkage as in **1**) have specificity for the 5-HT_{1A} receptor, and ligands with longer (6.5–7.5 Å) N–O linkage as in **2** or **3** have specificity for the D_2 receptor. Moreover, other new ligands that bind to 5-HT_{1A} and/or to D_2 receptors, **17–19**, have contributed useful new information about pharmacophore requirements.[18] It seems likely that the D_2 receptor prefers a hydrogen bond donor (i.e. hydroxyl, amine) in a particular spatial relationship to the protonated amine but that a hydrogen-bond acceptor (i.e. carbonyl, hydroxyl, *O*-methyl) in a slightly different location would have affinity for the 5-HT_{1A} receptor. This hypothesis is supported by the



observation that in the series **8–15**, the D$_2$ receptor has a strong preference for hydroxyl over *O*-methyl substituents on the aromatic ring, but *O*-methyl ligands bind to the 5-HT$_{1A}$ receptor almost as well as their hydroxyl analogs.[16,17]

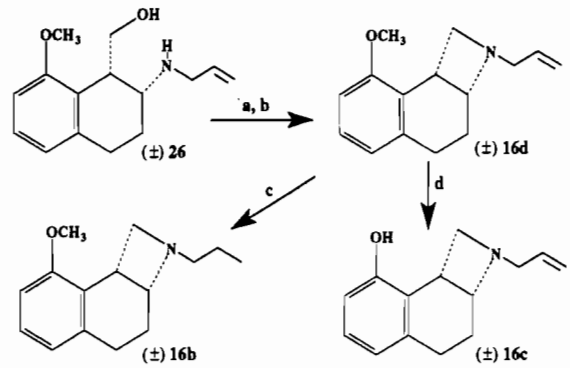


Other conformationally constrained ligands have been well characterized. The Sandoz compounds, **20a** (SDZ 208-911; $R_1 = CH_3$, $R_2 = C(CH_3)_3$) and **20b** (SDZ 208-912; $R_1 = Cl$, $R_2 = C(CH_3)_3$),[19] and the ergolines, **20c** (terguride; $R_1 = H$, $R_2 = N(C_2H_5)_2$),[19] and **21**, pergolide,[20] are known to have strong affinity for both D$_2$ and 5-HT$_{1A}$ receptors. The tricyclic ligands (*S,S*)-7-hydroxy- and (*R,R*)-9-hydroxy-*N*-*n*-propyloctahydrobenzoquinoline, **22** and **23**,[21] bind to the D$_2$ receptor but not to the 5-HT$_{1A}$ receptor.



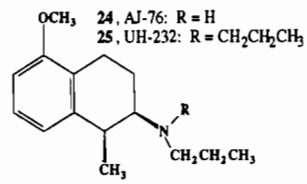
The *cis*-methyl-substituted, mono- and di-*n*-propylamino tetralins, **24** and **25**, AJ-76 and UH-232, are also quite constrained, except for rotation of the propylamino group,

Scheme I[a]



[a] Reagents and conditions: (a) *p*-TsCl/Py, CH_2Cl_2; (b) NaH/DMF; (c) H_2, 10% Pd/C, MeOH; (d) Ph_2PH, *n*-BuLi/THF, Δ.

and these ligands have been reported to be selective antagonists at the D$_2$ receptor.[22]



It seemed that by considering data already known together with the information on this new series **8–16**, it should be possible to elaborate considerably on the D$_2$ and 5-HT$_{1A}$ pharmacophore models already mentioned. Our goal was to arrive at models detailed enough to answer some questions important to drug design: How do the structural requirements differ for D$_2$ and 5-HT$_{1A}$ pharmacophores, so that ligands can be designed to have specificity for one or the other? What structural characteristics correlate with agonist, partial agonist, and antagonist behavior? Why are some ligands agonists at 5-HT$_{1A}$ and antagonists at D$_2$? Why do allyl and propyl analogs of some structures have very different affinities while allyl and propyl analogs of other structures have similar affinities?

In order to have available reliable low-energy conformations of all the structural types, two additional X-ray structures were determined, **14a** and **16d**. Only minor changes were needed to build all the structures from these and X-ray coordinates of structures previously reported.[16–21] Molecular mechanics calculations were used to verify that the conformations postulated to fit the models were reasonable and to exclude unlikely conformations of ligands.

Chemistry

The syntheses of the analogs **8–15** have already been described.[16,17] The azetidine analog **16d** was prepared from the readily available intermediate **26**.[23] As shown in Scheme I, the synthesis of **16d** was carried out by selective tosylation of the hydroxymethyl group in **26** followed by treatment with sodium hydride in DMF. Hydrogenation gave **16b** and demethylation gave **16c** (see Experimental Section). No attempt was made to resolve these racemates. The X-ray structure determination of **16d** confirmed the structures.

Development of the Pharmacophore Models

Molecule Building. All the tricyclic molecules were constructed from the appropriate crystal structures so as

to have *O*-methyl substituents and methyl-substituted protonated amines hydrogen bonded to chlorine ions. Coordinates from crystal structures of pergolide[20] and of **22** and **23**[21] were obtained from the Cambridge Crystallographic Database. The X-ray structures of racemic **14a** and **16d** are reported in the Experimental Section; 2α-methyl-**9b**, 2α-methyl-**11b**, (3a*R*,9b*S*)-**11d**, and (3a*S*,9b*R*)-**15d**, (3a*R*,9a*S*)-**12d**, and (5*R*)-2-OH-**18a** were reported by us previously.[16-18]

Molecular Mechanics. The program CONFOS[24] was used to calculate relative energies of the various conformers of each molecule. The basic nitrogen was protonated in all molecules, and a chlorine ion hydrogen bonded to the nitrogen was always included. The available crystal structures were all protonated molecules with a chlorine or bromine counterion (except pergolide is as the mesylate salt). The conformation observed in the crystal was always one of those minimized. Frequently the nitrogen was found, in the energy-minimized conformations, to be in approximately the same plane as the aromatic ring and oxygen atom. Because previous models for the D_2 pharmacophore have the nitrogen above the plane, the extra potential option in CONFOS was used to calculate the energy cost to force the nitrogen to be above the plane. The protonated nitrogen has tetrahedral geometry, so for all structures in which the nitrogen is part of a ring, with two bonds to ring carbons fixed, two possible configurations for the hydrogen and methyl substituents were evaluated. Since the point of attachment of the *O*-methyl substituent on the aromatic ring was found not to affect the relative energies of the conformations, analogous calculations (**8** and **12**, for example) could be compared to check the consistency of the calculations.

D_2 and 5-HT_{1A} Pharmacophore Models. The objective of this study was to generate a map of the receptor site by overlaying common features in the bound ligands. All of the ligands **1–26** have in common an aromatic ring and a protonated amine group; the hydrogen bond between this amine and a receptor atom is considered the most essential feature in either the D_2 or the 5-HT_{1A} pharmacophore. Except for the ergolines, the structures also have in common an aromatic ring substituent: OH, *O*-methyl, carbonyl, or NH, with potential to form a hydrogen bond we will designate the "secondary" hydrogen bond. The observation previously cited[18] for the secondary hydrogen bond was an important consideration: i.e. that the D_2 receptor prefers a hydrogen bond donor but a hydrogen bond acceptor will have affinity for the 5-HT_{1A} receptor providing it is in a different location relative to the aromatic ring and the protonated amine. The process of overlaying structures was strongly influenced by prior modeling studies;[10-15] a problem was encountered, however, in attempting to accommodate the new series of structures **8–16** to prior models. Affinities of these new ligands do not in general follow the pattern observed for 8-OH-DPAT and 7-OH- and 5-OH-DPAT: i.e. that shorter (~5.2 Å) amine-to-oxygen distance ligands bind to the 5-HT_{1A} receptor and longer (6.5–7.5 Å) amine-to-oxygen distance ligands bind to the D_2 receptor. The strategy used to solve this problem was to overlay the chlorine ions rather than the nitrogen atoms. The chlorine ions, then, are viewed as substitutes for whatever atom in the receptor is the hydrogen bond acceptor (with the caveat that the usual N–O hydrogen bond distance is about 2.8 Å and the N–Cl distance is a little longer, about 3.1 Å). The 5-HT_{1A} pharmacophore model proposed by Mellin and co-workers[15] used a "dummy" atom in a similar manner, although all of the amine-to-oxygen distances in their ligands were of the shorter variety. It was judged desirable to use, as much as possible, X-ray coordinates of ligands with their associated chlorine ions rather than low-energy conformers calculated using molecular mechanics together with a "dummy" atom, because it seemed a natural way to show a range of possibilities for the location of the primary hydrogen-bond acceptor.

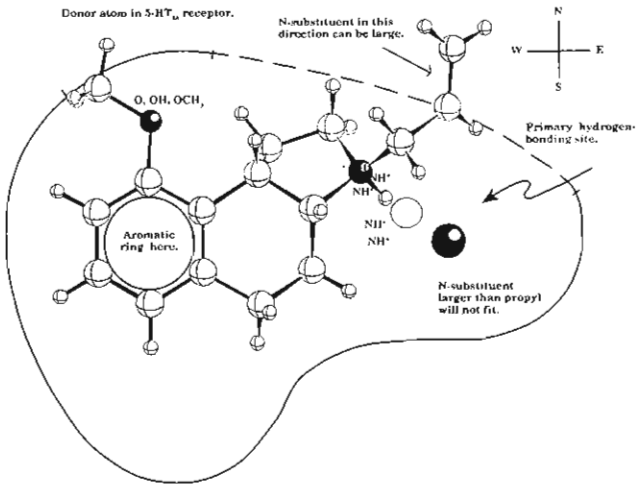


Figure 3. Model for 5-HT_{1A} pharmacophore. O, OH, and OCH_3 are possible ligand substituents. NH^+ shows position of protonated amine in several ligands. Gray circle is consensus Cl position.

In deciding how to orient the overlays, there were several other considerations: the aromatic rings were made to overlay, as has been done with all the earlier models. Although ligands **17–19** and the ergolines have two possible aromatic rings, the apparent ambiguity can be resolved by knowing which enantiomer the receptor prefers. Knowledge of the preferred enantiomer for the various structural types was very useful. The enantiomeric preference is known to be (*R*) for the 5-HT_{1A} agonist 8-OH-DPAT.[7,25] The dopamine D_2 receptor has the same enantiomeric preference, based on the related D_2 ligands, (*S*)-5-OH-DPAT and (*R*)-7-OH-DPAT.[25] (*S*,*S*)-7-hydroxy- and (*R*,*R*)-9-hydroxy-*N*-*n*-propylbenzoquinoline, **22** and **23**, are also known to be the enantiomers preferred by the D_2 receptor.[26] In the new series **8–16**, many of the structures have been resolved; in some cases both enantiomers bind and in others there is a strong preference for one of the enantiomers. In building up the overlays, the highest affinity compounds were studied first, and only the low-energy conformers as identified by X-ray structures or molecular mechanics calculations were considered.

Figures 3 and 4 are schematic pharmacophore models made from overlaying all the ligands with affinity for the respective receptors and outlining their combined van der Waals surface. Each figure is shown with the ligand with highest affinity for the receptor in the proposed orientation for binding. Other ligands are shown in Tables I–X in exactly the same orientations they would have in the models, with the consensus position of the chlorine ion (gray circle) as a reference. The orientations chosen are certainly not the only possible interpretation of the evidence. The way in which previously known ligands are fitted to the models is similar to previous work and is not especially controversial, but for some of the new structures the fitting process was not so straightforward. For trans

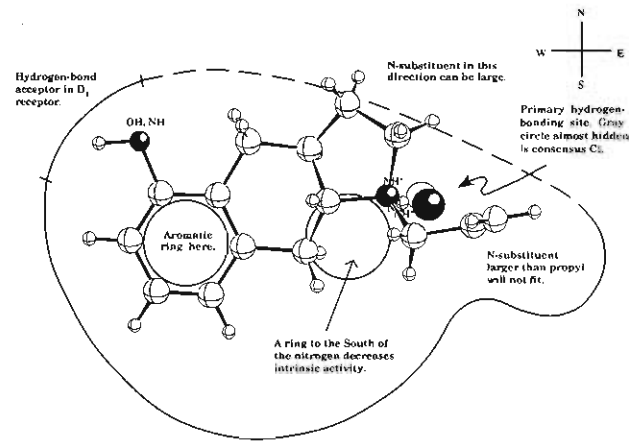


Figure 4. Model for D$_2$ pharmacophore. OH and NH are possible donors. NH$^+$ shows protonated amine locations in various ligands.

ring junction molecules, when the molecules are oriented as in the chemical drawings, with the aromatic ring and oxygen substituent in the plane of the paper and the hydrogen on the asymmetric carbon bonded to the nitrogen *up*, the basic nitrogen is presumed to be equatorial and is *above* the plane of the paper. The cis ring junction ligands with angular structures, however, do not have a low-energy conformation in which the nitrogen is above the plane when the hydrogen on the asymmetric carbon is up. For some of these ligands, the overlay in which the molecule is flipped 180° seemed to fit best, although in this orientation the secondary hydrogen bond from the aromatic substituent must be to a receptor atom in a different location than the one specified by the model. When a "flipped" orientation is suggested, the rationale that it "fits" better is that this choice allows a more consistent explanation of affinities, of agonist/antagonist activities and of differences between propyl and allyl analogs. Analogs of **11** and (3a*R*,9b*S*) analogs of **12** are predicted to have this "flipped" orientation at the dopamine D$_2$ receptor. Possibly, analogs of **10** at the D$_2$ receptor and analogs of **15** at the 5-HT$_{1A}$ receptor may also have this orientation.

Pharmacology

Intrinsic Activity. A method for determining intrinsic activity at the dopamine D$_2$ receptor was recently developed and reported.[27] The displacement of an antagonist, [^{3}H]raclopride, in the presence of high concentrations of GTP measures the ability of the ligand to bind to the "low-affinity agonist" (LowAg) state of the receptor, and the displacement of an agonist, [^{3}H]U-86170, in the absence of GTP measures the ability of the ligand to bind to the "high-affinity agonist" (HighAg) state of the receptor. Intrinsic activity is predicted using the ratio of LowAg/HighAg affinities; predicted values were shown to have good correlation with agonist, partial agonist, and antagonist activities determined by other means.[27] One of the advantages of this method is that it provides a reliable estimate of partial agonist activity; formerly, a ligand with intrinsic activity somewhere between 100% (pure agonist) and 0% (pure antagonist) would sometimes be characterized as an agonist and sometimes as an antagonist, depending on the assay.

Results and Discussion

There are several differences between the pharmacophore models in Figures 3 and 4 and previous models:

(1) Figures 3 and 4 indicate how the 5-HT$_{1A}$ and D$_2$ pharmacophores differ with respect to the spatial relationship of the secondary hydrogen bond to the aromatic ring and to the consensus position of the primary hydrogen bond acceptor, and with respect to the donor or acceptor nature of the secondary hydrogen bond.

(2) In each model, the shape of the ligand binding site along its "south" side (solid line) is postulated based on overlays of all the ligands having affinity for the receptor.

(3) Figure 4 shows an area to the south of the amine, occupation of which is proposed to confer antagonist or partial agonist activity at the dopamine D$_2$ receptor.

(4) The conformation of the amine substituent of ligands in the Figure 4 model is less constrained than in the most recent model of Liljefors and co-workers.[11] They propose (Figure 1b) that the conformation of the (downward in Figure 1a) propyl group is anti with respect to the lone pair on the nitrogen, with the result that the "propyl cleft" is almost entirely above the plane of the aromatic ring. However, in all of the 11 X-ray structures used to develop the models in Figures 3 and 4, the propyl and allyl substituents were found to be in the gauche conformation relative to the N–H bond. The geometry of the propyl cleft in Figure 4 is therefore more like the earlier Liljefors–Wikström model[10] (Figure 1a). The X-ray structures certainly do not prove that the gauche conformation of the allyl or propyl would fit the receptor better than the anti conformation, but since the Figure 4 model would accommodate either conformation, judgment can be reserved until more compelling evidence from less flexible analogs is available.

In order that orientations of the ligands in the Figures 3 and 4 schematic models can be compared along with their activities and affinities, Tables I–X are organized by structural type with the corresponding drawings of the molecules oriented exactly as they would fit in Figures 3 and 4, and also in edge views with (providing the molecule was not "flipped"), the aromatic substituent in back. For reference, the consensus position for the chlorine ion (gray circle) is shown with each drawing. This is very important for ligands that do not fit, to show the discrepancy. The protonated nitrogens in structures **17–19** are not constrained as they would be in a ring, so the conformers shown in Tables I–X are the appropriate low-energy conformers from molecular mechanics calculations. With some exceptions, the new structures, **8–16** are shown as they were found in the X-ray structure determinations; some were modified from X-ray coordinates by changing only the position of the aromatic substituent. (In the modified structures side chains are truncated to methyl groups.) Structures of type **8** did not have affinity for either receptor and did not have any low-energy conformers that fit the models; a representative low-energy conformer is shown. Two low-energy conformers of type **13** are shown: a conformer which did fit the D$_2$ model, and a conformer representative of several that do not fit either model. Considering structures of type **9**, most did not have affinity and did not fit the models (the X-ray structure shown is representative of these); one methyl-substituted structure does have 5-HT$_{1A}$ affinity and a low-energy conformer that does fit the model is shown. In every case the X-ray structure was one of the lowest energy conformers determined by the molecular mechanics calculations.

Although not many of the conformers calculated by

molecular mechanics are shown in Tables I–X, the calculations provided valuable information about probable configuration at the protonated amine and about likelihood that the amine would be above or below the aromatic plane. Comparing 39 low-energy conformers of all structural types, energy differences between the two possible configurations at the amine ranged from 0.5 to 3.8 kcal. Configurations found in the X-ray structures were in complete agreement with the predictions from molecular mechanics. Except for structures of types 11, 15, and 16 (angular structures with cis ring junctions), the energy cost to force the nitrogen to be on the opposite side of the plane to that found in the X-ray determination was calculated to be ≤2 kcal, not unreasonably high. Molecular mechanics were also useful in understanding ligands which did not bind, because these did not have low-energy conformers that fit the models.

Affinities and intrinsic activities for 8–15 were reported in the companion papers,[16,17] but for convenience, Tables I–VIII also list again the K_i's for displacement of the 5-HT_{1A} agonist ligand [^{3}H]-8-OH-DPAT; the D_2 antagonist ligand [^{3}H]raclopride; the D_2 agonist ligand [^{3}H]U-86170; and intrinsic activity at the D_2 receptor. Some of the K_i's in Table X (DPAT and raclopride values for 17–19) have been published previously;[18] methods for the dopamine and serotonin binding assays used to determine the remaining values were the same as reported previously.[16,17] Note that since the values for displacement of raclopride were measured in the absence of added GTP, they were not the values used in the calculation of intrinsic activity. Intrinsic activity was not determined for all ligands; some were classified as dopamine agonists or antagonists according to their effects on locomotor activity in normal or reserpinized mice or on firing rates of dopaminergic neurons.[16,17]

In discussing the new structures 8–16, it is convenient to use a three-letter code with the first letter either L or A for *linear* or *angular*, the middle letter C or T for cis or trans ring junction, and the last letter T or A for ring closure *toward* the aromatic substituent or *away* from it.

LTT. In the (3a*S*,9a*R*) configuration these structures bind well to both receptors and are agonists; (3a*S*,9a*R*) **12c** is, in fact, the highest affinity D_2 ligand in the study and is shown in the Figure 4 model. Ligands with the opposite configuration, (3a*R*,9a*S*), bind to the D_2 receptor as antagonists but have no detectable binding at the 5-HT_{1A} receptor. The (3a*S*,9a*R*) ligands are the only ones that, according to the Figure 3 model, have their protonated nitrogens almost directly on top of the hydrogen bond acceptor at the 5-HT_{1A} receptor. The (3a*R*,9a*S*) configuration molecules have less propensity to bind in the same orientation because the nitrogen tends to be below the plane with the proton pointing up (or, in the higher energy configuration, the proton would be equatorial, pointing southeast). At the D_2 receptor, however, there apparently is room for the (3a*R*,9a*S*) molecules to bind in a 180° flipped orientation and in this case they have antagonist or partial agonist activity. The K_i's are considerably higher for (3a*R*,-9a*S*) molecules, perhaps because whatever interaction the oxygen substituent has in the flipped orientation is less stable than the usual secondary hydrogen bond. As previously mentioned, *O*-methyl ligands do not have high affinity for the D_2 receptor. The molecule drawings are of the X-ray crystal structure of (3a*R*,9a*S*)-**12d**[17] or its mirror image.

LTA. The lowest energy conformer from molecular mechanics calculations is similar to the LTT type X-ray structure shown in Table I (with oxygen substituent on the aromatic switched to the opposite side of the ring). Now, however, the orientation of the nitrogen is different relative to the oxygen and the acceptor atom, and the molecule does not fit either model very well (although a higher energy conformer could fit the 5-HT_{1A} model). This could explain the relatively low affinity observed.

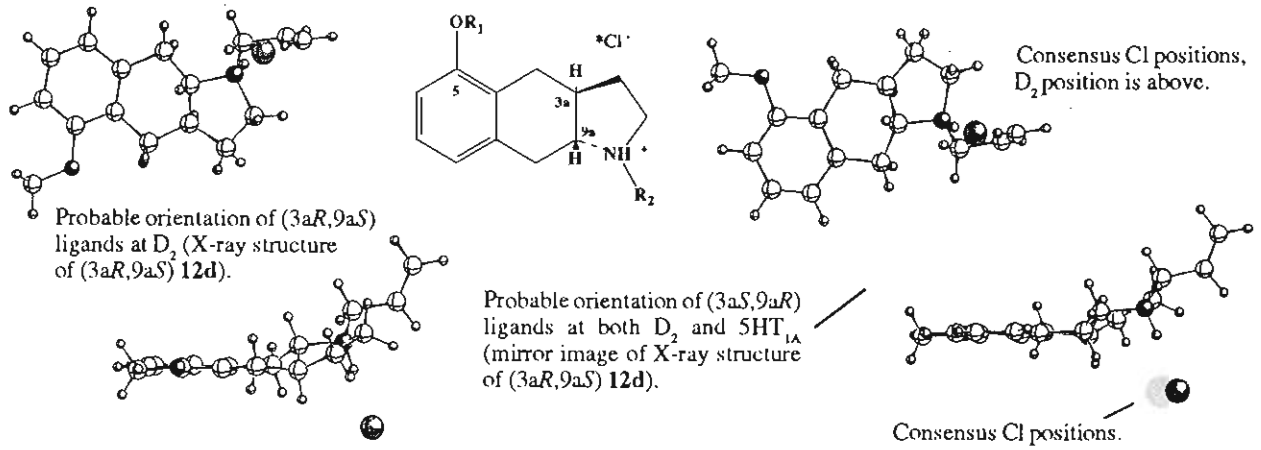
LCA. An X-ray structure[17] of 2α-methyl-**9b** shows that with this relative configuration at the methyl-substituted carbon on the five-membered ring, the conformation of the molecule is not ideal for binding at these receptors. This can be seen by trying to fit the molecule drawing of the X-ray structure in Table III into Figures 3 or 4, although the fit is somewhat better for the 5-HT_{1A} model than for the D_2 model. Molecular mechanics calculations indicate that the unsubstituted LCA type structures have many low-energy conformers in which the five-membered ring is bent away from the plane of the aromatic ring, and according to the models this conformation would not bind well. However, 2β-methyl-**9b**, which has the opposite relative configuration, has a low-energy conformer that fits the 5-HT_{1A} model but not the D_2 model. This low-energy conformer of 2β-methyl-**9b** is also shown in Table III.

LCT. There are no methyl-substituted structures in this category, and molecular mechanics calculations were similar to those for unsubstituted LCA molecules in Table III in that there are many low-energy conformers that are not well suited for binding at either receptor. However, one of the conformers shown in Table IV would fit the model for the D_2 pharmacophore and has the lowest energy of all. An example of a conformer that would not fit either model is also shown in Table IV.

ACT. Ligands of this type have the lowest K_i's at the 5-HT_{1A} receptor of any of the tricyclics in this study. (3a*R*,-9b*S*)-**11d** is the ligand with highest affinity for the 5-HT_{1A} receptor and is shown in Figure 3 as well as in Table V. The X-ray structure of this ligand is very similar to the lowest energy conformation from molecular mechanics calculations, and since this structure was one of the prototypes for developing the 5-HT_{1A} pharmacophore model, it fits the model very well indeed. Another X-ray structure, of 2α-methyl-**11b**,[16] also has a similar conformation. These cis ring junction ligands have a different conformation than their trans counterparts in that both the nitrogen and the carbon adjacent to the ring junction are forced to be on the opposite side of the plane from the ring junction hydrogens. One of the differences between 5-HT_{1A} and D_2 pharmacophores in Figures 3 and 4 is that in the D_2 model, the protonated nitrogens are almost directly above the chlorine ion whereas in the 5-HT_{1A} model the nitrogens are to the left (west) of it. This is probably the reason for the constraint in the D_2 pharmacophore model that the nitrogen must be above the plane of the aromatic ring; in the 5-HT_{1A} pharmacophore model the nitrogen can be below the plane (as it certainly is in a (3a*R*,9b*S*) molecule) and still have sufficient distance from the acceptor atom. It is likely that at least the ACT ligands with the best affinity for the D_2 receptor, (3a*R*,-9b*S*)-**11d** and (3a*R*,9b*S*)-**11b**, bind in an orientation that is flipped 180° about the horizontal. This is because they would then, except for their *O*-methyl substituents, exactly overlay the (3a*R*,9b*S*) ACA type molecules which have

Table I. LTT: Linear, Trans, Ring Closure toward O

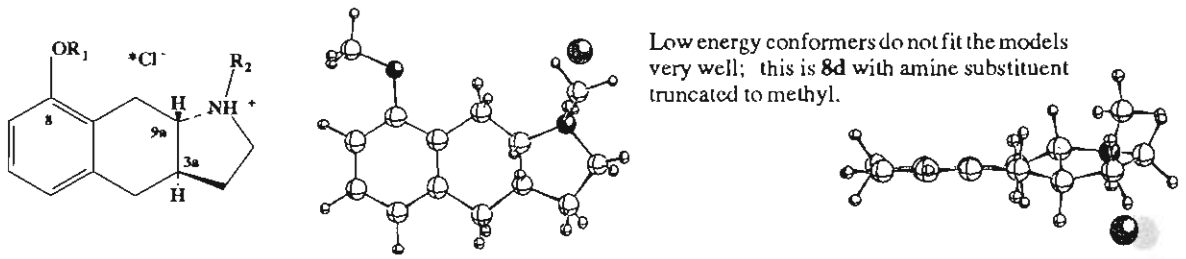
compound	R_1	R_2	binding data K_i, nM: 5HT$_{1A}$[a]	binding data K_i, nM: D$_2$ vs antagonist[b]	binding data K_i, nM: D$_2$ vs agonist[c]	intrinsic activity[d] or classification[e]
(3a*S*,9a*R*)-**12a**	H	propyl	36	2	0.5	109%
(3a*R*,9a*S*)-**12a**	H	propyl	>470	>630	917	18%
racemic **12a**	H	propyl	62	17	2.4	79%
(3a*S*,9a*R*)-**12b**	CH_3	propyl	38	IA[f]	75	37%
(3a*R*,9a*S*)-**12b**	CH_3	propyl	IA[f]		IA[f]	
racemic **12b**	CH_3	propyl	54	877	100	agonist
(3a*S*,9a*R*)-**12c**	H	allyl	56	3	0.3	106%
(3a*R*,9a*S*)-**12c**	H	allyl	>470	47	235	21%
racemic **12c**	H	allyl	105	25	1.4	91%
(3a*S*,9a*R*)-**12d**	CH_3	allyl	41	IA[f]		agonist
(3a*R*,9a*S*)-**12d**	CH_3	allyl	>1000	IA[f]		antagonist
racemic **12d**	CH_3	allyl	11	>1000		agonist



The mean SEM's for K_i's were approximately 30% of the K_i values. [a] [^{3}H]-8-OH-DPAT-labeled 5-HT$_{1A}$ sites in bovine hippocampus or in cloned CHO cells. [b] [^{3}H]Raclopride-labeled D$_2$ sites in rat striatum. [c] [^{3}H]U-86170-labeled D$_2$ sites in cloned CHO cells. [d] Determined using a ratio of affinities (see the Experimental Section); a value of 100% is the highest possible agonist intrinsic activity; a value of 0% the highest possible antagonist intrinsic activity. [e] Previously classified[16,17] as agonists or antagonists according to effects on locomotor activity in mice, effects on dopamine neuronal firing rates in rats, or on dopamine synthesis and metabolism in rats. [f] Found to display <50% inhibition of [^{3}H]-ligand displacement at 1 mmol/L concentration.

Table II. LTA: Linear, Trans, Ring Closure Away from O

compound	R_1	R_2	binding data Ki, nM: 5HT$_{1A}$[a]	binding data Ki, nM: D$_2$(antag[b])
racemic **8d**	CH_3	allyl	104	IA[f]



[a,b,f] See corresponding footnotes in Table I.

similar or better binding at the D$_2$ receptor and similar antagonist properties. Comparing a/b and c/d analogs for LTT and ATA types, it is apparent that *O*-methyl ligands have less favorable interactions in the usual orientation at the D$_2$ receptor, so molecules with *O*-methyl substituents would have little to lose by orienting this group in a different direction.

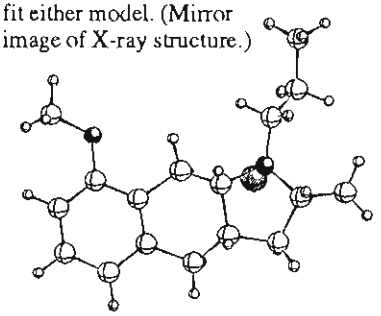
ATT. Only two racemic ligands have been synthesized, not enough data to be certain, but because the ligands bind fairly well to both receptors and have dopamine antagonist properties, we speculate that they would be oriented like the ACT structures (i.e. at the D$_2$ receptor the molecules would flip 180° about the horizontal).

ACA. The opposite configuration, (3a*R*,9b*S*), molecules bind very well to the D$_2$ receptor as antagonists. The protonated nitrogen is above the plane, as it is supposed to be at this receptor, but the energetically favored configuration at the nitrogen is the one shown in Table VII which has its proton pointing in the wrong direction to make the necessary hydrogen bond for agonist activity. Presumably, the hydrogen bond could still be made, but only if the molecule adopts a higher energy configuration at the protonated amine (molecular mechanics calculations indicate this would cost about 2 kcal). The molecule drawings of (3a*R*,9b*S*)-**15d** in Table VII are mirror images of the structure determined by X-ray crystallography. At

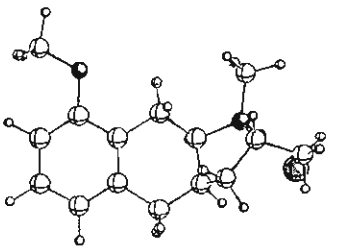
Table III. LCA: Linear, Cis, Ring Closure Away from O

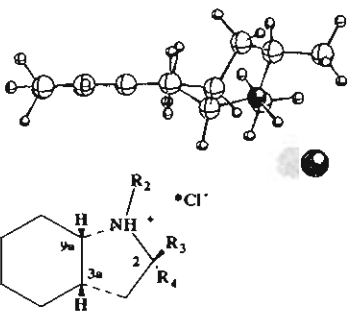
compound	R_1	R_2	R_3	R_4	binding data, K_i, nM: $5HT_{1A}$[a]	D_2(antag[b])	D_2(agonist[c])	intrinsic activity[d]
racemic **9d**	CH_3	allyl	H	H	145	IA[f]		
2β-methyl-**9b**	CH_3	propyl	CH_3	H	11	IA[f]	464	21%
2α-methyl-**9b**	CH_3	propyl	H	CH_3	384	IA[f]		

2α-methyl **9b** does *not* fit either model. (Mirror image of X-ray structure.)



A low energy conformer of 2β-methyl-**9b** does fit the $5HT_{1A}$ model.

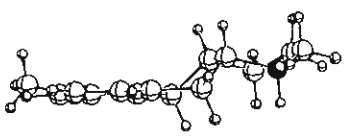




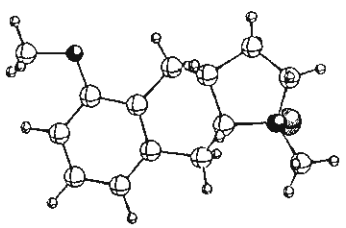
[a–d,f] See corresponding footnotes in Table I.

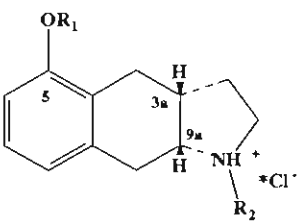
Table IV. LCT: Linear, Cis, Ring Closure toward O

compound	R_1	R_2	binding data, K_i, nM: $5HT_{1A}$	D_2(antag[b])	D_2(agonist[c])	intrinsic activity[d]
racemic **13a**	H	propyl	>1000	296	11	61%
racemic **13b**	CH_3	propyl	>5000	IA[f]		
racemic **13d**	CH_3	allyl	>1000	429		

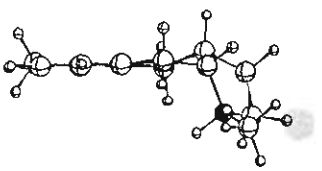


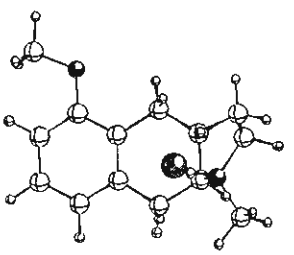
This low energy conformer would fit the D_2 model.





A low energy conformer which does not fit either model.





[b–d,f] See corresponding footnotes in Table I.

the 5-HT_{1A} receptor the molecules might bind in a 180° flipped orientation as well as in the standard orientation in which the aromatic substituent makes the usual secondary hydrogen bond. The flipped orientation is shown in Table VII; the standard orientation would look similar to the drawings shown for ATA types. The flipped (3a*R*,9b*S*) configuration molecules resemble the best ACT type 5-HT_{1A} ligands except that the aromatic substituent cannot make the same secondary hydrogen bond. Since in this orientation the oxygen substituent would overlay the NH of pergolide and the other ergolines, there may be an alternate secondary hydrogen bond made. Affinity, however, is much less than for the ACT type 5-HT_{1A} ligands, suggesting that this hypothetical alternate secondary interaction is less favorable.

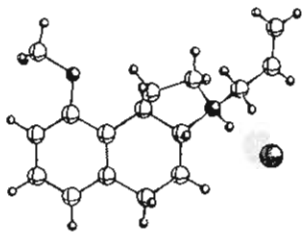
ATA. Since with trans ring junction molecules the nitrogen would tend to be above the plane in molecules with the (3a*S*,9b*S*) configuration, these ligands should have better affinity for the D_2 receptor than their enantiomers, although probably both enantiomers would bind. At the 5-HT_{1A} receptor, both enantiomers should also bind, and just as for the D_2 receptor, the (3a*S*,9b*S*) enantiomers should have better affinity. There are as yet no resolved ATA ligands to test this hypothesis, but one of the reasons for thinking that ATA ligands bind better in the standard orientation than in the flipped orientation is that the *N*-allyl ligands have better affinity than their *N*-propyl analogs. The rationale for this observation, which is discussed in the following section, is more consistent if the standard orientation for ATA molecules is assumed.

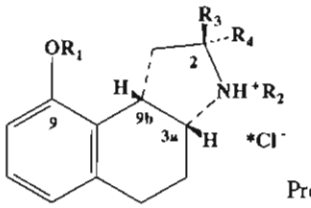
ACT Azetidine. These ligands are like the ACT ligands except that they have even fewer conformational options. Resolved enantiomers with the configuration shown should have even greater affinity.

Other Structures. These are included in Table X because they were used in the development of the pharmacophore models and because their affinities and intrinsic activities were determined in the same assays used for the new ligands in order to have a consistent basis for comparisons. (*R*)-**18a**, one of the highest affinity D_2

Table V. ACT: Angular, Cis, Ring Closure toward O

compound	R_1	R_2	binding data, K_i, nM: 5HT$_{1A}$[a]	D$_2$(antag[b])	D$_2$(agonist[c])	intrinsic activity[d] or D$_2$ class[e]
(3a*R*,9b*S*)-**11a**	H	propyl	0.1		IA/	
(3a*S*,9b*R*)-**11a**	H	propyl	3.0		IA/	0%
racemic **11a**	H	propyl	1.4	IA/		
(3a*R*,9b*S*)-**11b**	CH_3	propyl	0.2	67		37%
(3a*S*,9b*R*)-**11b**	CH_3	propyl	186	>1000		
racemic **11b**	CH_3	propyl	4.4	>1000		
racemic **11c**	H	allyl	0.3		153	7%
(3a*R*,9b*S*)-**11d**	CH_3	allyl	0.2	5.3	6.7	24%
(3a*S*,9b*R*)-**11d**	CH_3	allyl	74	270	77	17%
racemic **11d**	CH_3	allyl	0.8	IA/	7.0	15%
2α-methyl-**11b**	CH_3	propyl	1.0	IA/		
2β-methyl-**11b**	CH_3	propyl	16	IA/		

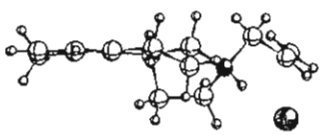


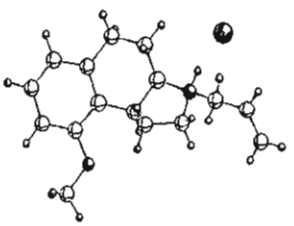


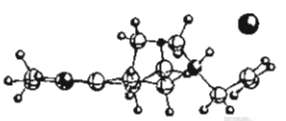
	R_3	R_4
α-methyl	H	CH_3
β-methyl	CH_3	H
all others	H	H

Probable orientation of (3a*R*,9b*S*) ligands at D$_2$; (molecules are flipped 180°).

Probable orientation of ligands at 5HT$_{1A}$ (X-ray structure of (3a*R*,9b*S*) **11d**).



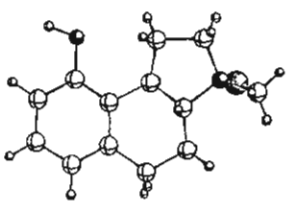


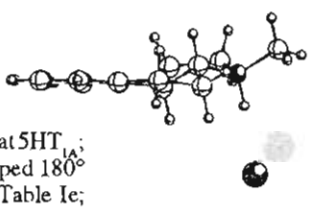


[a-f] See corresponding footnotes in Table I.

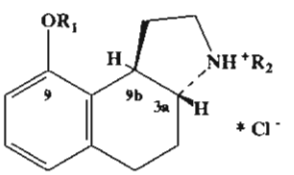
Table VI. ATT: Angular, Trans, Ring Closure toward O

compound	R_1	R_2	binding data, K_i, nM: 5HT$_{1A}$[a]	D$_2$(antag[b])	D$_2$(agonist[c])	intrinsic activity[d]
racemic **10c**	H	allyl	4.9		25	13%
racemic **10d**	CH_3	allyl	4.7	13	8.5	0%





Probable orientation of ligands at 5HT$_{1A}$; orientation at D$_2$ could be flipped 180° as for the ACT molecules in Table Ie; (modeled from X-ray structure of **14a**).



[a-d] See corresponding footnotes in Table I.

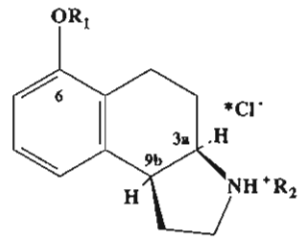
receptor agonists, is actually U-86170; K_i's for displacement of [^{3}H]-labeled U-86170 are listed in Tables I–X as a measure of D$_2$ receptor affinities. The properties of AJ-76 and UH-232 are discussed in the section on D$_2$ receptor antagonists. (*S*,*S*)-7-Hydroxy-*N*-*n*-propylbenzoquinoline, **22**, is shown in Table X, although binding data and intrinsic activity were obtained only for the NH analog. The (*R*,*R*)-9-OH analog, **23**, is not shown but would be oriented with the propyl group pointing southeast, into the "propyl cleft". Wikström and co-workers[26] supported the propyl cleft feature of their model with the observation that the *n*-butylamino analog of **22** has high affinity but the *n*-butylamino analog of **23** has very poor affinity for the D$_2$ receptor.

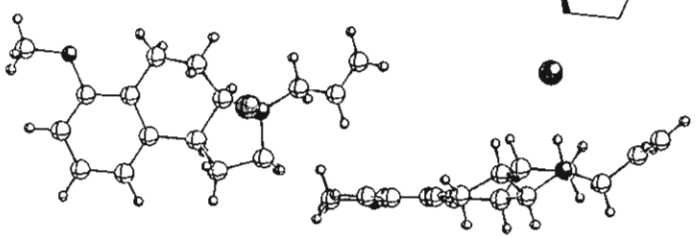
Allyl versus Propyl Substituents on the Nitrogen. Considering pairs of ligands that are identical except for the nitrogen substituent (allyl or propyl): sometimes the allyl ligands have much lower binding constants than their propyl analogs, sometimes there is no apparent difference, and sometimes there is a significant difference with regard to the D$_2$ receptor but not the 5-HT$_{1A}$ receptor. These rather confusing structure–affinity data can be rationalized in terms of the orientation of the molecules at the receptor sites; apparently the allyl group fits the receptor much better than the propyl group *when it is oriented in a certain direction*; when it is pointed another direction it makes no difference discernible from this data. In Figures 3 and 4, ligands that have a ring to the "south" of the nitrogen and have their allyl or propyl groups pointed up from the plane of the figure have this special orientation, and the receptor has a marked preference for allyl over propyl. According to our model, ATA type structures (Table VIII)

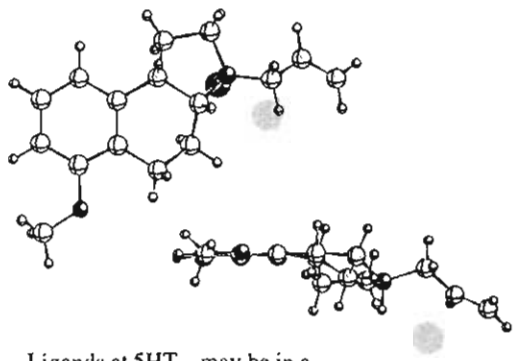
Table VII. ACA: Angular, Cis, Ring Closure Away from O

compound	R_1	R_2	binding data, K_i, nM: $5HT_{1A}$[a]	D_2(antag[b])	D_2(agonist[c])	intrinsic activity[d]
racemic **15a**	H	propyl	IA[f]	>1000	218	1%
racemic **15b**	CH_3	propyl	>1000	>1000		
(3a*R*,9b*S*)-**15c**	H	allyl	54	49	108	22%
(3a*S*,9b*R*)-**15c**	H	allyl	>1000	259	59	47%
racemic **15c**	H	allyl	923	198	75	29%
(3a*R*,9b*S*)-**15d**	CH_3	allyl	236	25	18	0%
(3a*S*,9b*R*)-**15d**	CH_3	allyl	>333	>1000	>339	
racemic **15d**	CH_3	allyl	252	42	78	0%

Probable orientation of ligands at D_2 (enantiomer of the X-ray structure of (3a*S*,9b*R*)**15d**); unless the molecule has the other (higher energy) configuration at the nitrogen, the NH - receptor hydrogen bond cannot form.





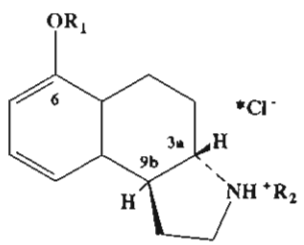


Ligands at $5HT_{1A}$ may be in a flipped orientation because the molecules would then be like the best ACT type ligands (except for the O-methyl substituent).

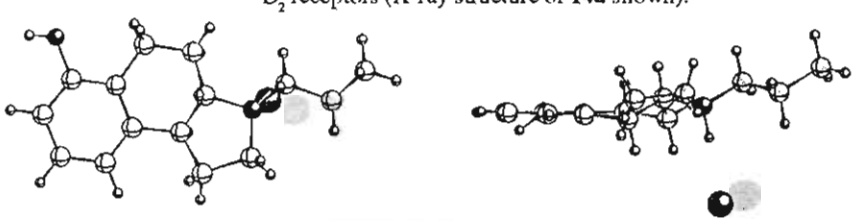
[a-d,f] See corresponding footnotes in Table I.

Table VIII. ATA: Angular, Trans, Ring Closure Away from O

compound	R_1	R_2	binding data, K_i, nM: $5HT_{1A}$[a]	D_2(antag[b])	D_2(agonist[c])	intrinsic activity[d]
racemic **14a**	H	propyl	338	33	93	28%
racemic **14b**	CH_3	propyl	66	63		0%
racemic **14c**	H	allyl	16	54	4.1	44%
racemic **14d**	CH_3	allyl	10	99	50	0%



Probable orientation of ligands at $5HT_{1A}$ and D_2 receptors (X-ray structure of **14a** shown).



[a-d] See corresponding footnotes in Table I.

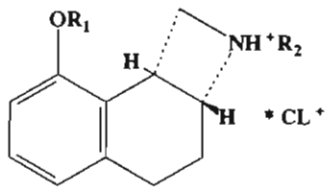
have this orientation at both receptors, and ACA (TableVII), ACT (Table V), and LTT with (3a*R*,9a*S*) configuration structures (Table I) have this orientation at the D_2 receptor. (The model suggests that ACT structures flip 180° to look like ACA structures at D_2.) The observed binding data is entirely consistent with this interpretation. We cannot be certain about ACA structures at the $5\text{-}HT_{1A}$ receptor; in any case affinities are low at this receptor. Pairs of allyl and propyl analogs of other types exhibit no significant difference in affinities.

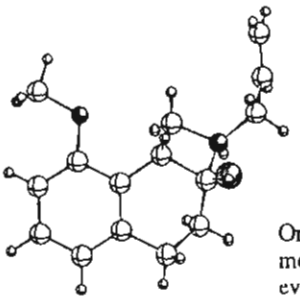
Agonists/Partial Agonists/Antagonists. We assume that agonist activity is correlated with efficient hydrogen bond formation from the protonated amine donor in the ligand to an acceptor atom in the receptor (perhaps an Asp carboxylate anion, as has been proposed for the β-adrenergic receptor and for the muscarinic receptor[28]). Probably some conformational change in the receptor is associated with the hydrogen bond, and providing this change lasts long enough, the ligand will behave as an agonist.

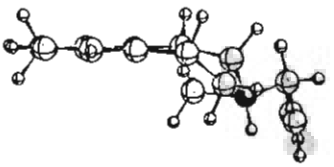
Partial agonist activity can result from any of several conditions: (a) the ligand is bound in alternate orientations and is able to form the hydrogen bond in only one of these; (b) even though the ligand is bound in only one orientation, it may be less efficient than other ligands in forming the hydrogen bond; (c) the ligand may form the hydrogen bond easily but lack the optimum hydrophobic interactions to fit the site and then the bound state is less stable. There is no reason that binding constants should correlate with the mean times that the ligands spend in the bound state. A molecule could have a rapid on/off behavior and still displace the radioactive ligand used to determine the K_i

Table IX. ACT: Azetidine: Angular, Cis, Ring Closure toward O

compound	R_1	R_2	binding data, K_i, nM: 5HT$_{1A}$[a]	binding data, K_i, nM: D$_2$(antagonist[b])
racemic **16b**	CH_3	propyl	4.8	329
racemic **16c**	H	allyl	0.3	
racemic **16d**	CH_3	allyl	5.9	







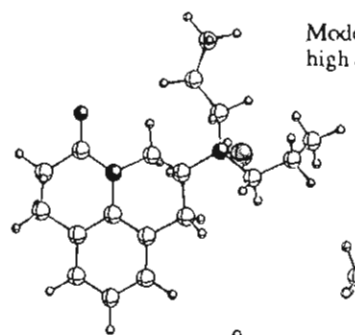
Orientation is probably similar to ACT 5-membered ring analogs, but this structure is even more rigid; (X-ray structure of **16d** shown).

[a,b] See corresponding footnotes in Table I.

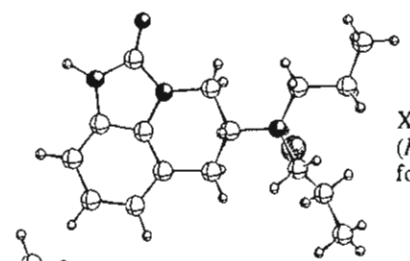
Table X. Other Structural Types

compound	binding data, K_i, nM: 5HT$_{1A}$[a]	D$_2$(antag[b])	D$_2$(agonist[c])	intrinsic activity[d] or D$_2$ class
racemic **17a**	6.4	18.8	3.5	79%
racemic **17b**	2.2	>1000	58	30%
(*R*)-**18a**	24.8	5.4	1.7	91%
racemic **18b**	80	39	0.6	agonist
racemic **19**	304	28		70%
20a (SDZ-208-911)	18.7	0.74	3.1	11%
20b (SDZ-208-912)	2.9	0.47	3.6	0%
20c (terguride)	5.4	0.95	0.8	22%
21 (pergolide)	1.8	1.0		66%
(±)-NH analog of **22***	>1000	38	11	53%
25 (AJ-76)	410	179	14	3%
26 (UH-232)	228	22	13	0%

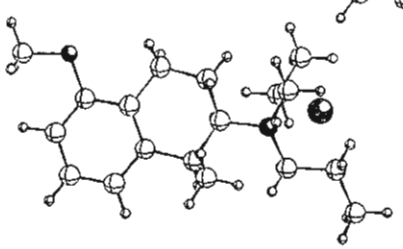
*N-Propylamino was not available for testing in this assay, but is reported[26] to have 2–3 times greater affinity for the D$_2$ receptor than its NH analog.



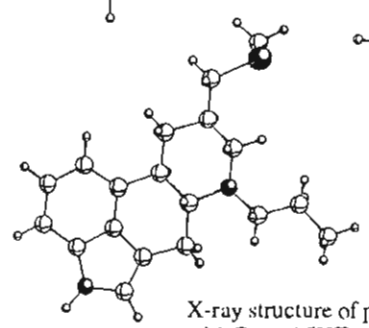
Modeled structure of **17b**; high affinity 5HT$_{1A}$ ligand.



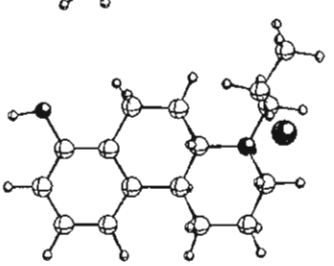
X-ray structure of (*R*) **18a**; high affinity for D$_2$.



Modeled structure of **26**; chlorine ion is above the plane, not close to the consensus position.



X-ray structure of pergolide (mesylate omitted) with D$_2$ and 5HT$_{1A}$ consensus chlorines.



(*S,S*)-7-OH-*n*-propylamino BQ, **22**, at the D$_2$ receptor.

[a–d] See corresponding footnotes in Table I.

as effectively as a different molecule that tended to be bound for longer times. However, the molecule having a longer duration of binding would have a higher intrinsic activity, a parameter that does correlate well with the agonist/antagonist spectrum.

An antagonist classification is the result of binding such that the agonist type conformational change does not take place. This can happen because the hydrogen bond is not formed, or is formed but lasts for a much shorter time, or is formed and other characteristics of the ligand block the

conformational change. An intrinsic activity close to 0% is a good indication that a ligand is a pure antagonist, but some assays are less reliable; a ligand could even be bound so that the hydrogen bond is formed and the conformational change takes place, but if all this happens with less frequency than when the endogenous ligand, e.g. dopamine or serotonin, is unopposed by the ligand being tested, the test ligand could be classified as an antagonist.

With respect to dopamine D_2 ligands, there are examples of all three types of activity, agonist, partial agonist, and antagonist, and this can be rationalized in terms of the way in which the ligands fit the pharmacophore model.

D_2 Antagonists and Partial Agonists. The tricyclics in this study that have been classified as antagonists or partial agonists all have the five-membered ring on the "south" side of the nitrogen in Figure 4. **22** has a six-membered ring to the south of the nitrogen. **25** and **26** have methyl groups cis to the nitrogen and have the same configuration as the ACA type structures with low K_i's. Their structures would overlay the ACA type in Figure 4. The constraint already discussed, that the D_2 receptor prefers that the nitrogen be above the plane of the aromatic ring, means that when the ring junction (or substituent relationship) is cis, and when the oxygen substituent of the aromatic ring is oriented so that it can make the secondary hydrogen bond, the proton on the nitrogen is up from the plane, in the wrong direction to form the agonist type hydrogen bond. This is consistent with the low intrinsic activities observed with these ligands, (0% and 22% for (3a*R*,9b*S*) and racemic ACA ligands; 3% and 0% for **25** and **26**). Some of the racemic ATA ligands have partial agonist activity (44% and 28%) because with a trans ring junction the nitrogen would tend to be above the plane in the (3a*S*,9b*S*) configuration, and in this case the lower energy protonation direction favors hydrogen-bond formation. None of the full agonists in this model have a ring on the south side of the nitrogen; it seems that a ring (or a methyl substituent) in this position somewhat hinders either the formation of the hydrogen bond to the amine or the conformational change associated with the hydrogen bond.

20a–c are ergolines having antagonist or partial agonist activity, and they have six-membered rings with ring closure on the north side of the nitrogen. Our rationale for the behavior of these ligands is somewhat different: because a propyl or allyl nitrogen substituent is the optimum size for a hydrophobic group oriented toward the east in this model, and because **20a–c** have only methyl in this position, the bound state for these ligands would be less stable. (Also, they cannot form the secondary hydrogen bond, although they may form a different hydrogen bond on the southwest side.) **21**, however, which has a propylamino substituent, is an agonist.[20]

Froimowitz and Baldessarini[29] proposed a model for dopamine antagonist activity that Liljefors and co-workers[11] have also adopted. In this model the direction of the N–H bond in antagonist ligands is *up* from the plane of the aromatic ring, opposite to the N–H direction for agonists. If the ligand orientations we have proposed are correct, several of the dopamine antagonists and partial agonists in this study would be in agreement with this model, with their N–H bonds directed upwards: two ACA ligands shown in Table VII (3a*R*,9b*S*)-**15c** and **15d**, which have 22% and 0% intrinsic activity, and (providing they adopt the "flipped" orientation) two ACT ligands shown in Table III, (3a*R*,9b*S*)-**11b** and **11d**, with 37% and 24% intrinsic activity. However, the enantiomers of these ACA and ACT ligands also have low intrinsic activity and would have N–H bonds directed downwards. The antagonist activity of the (3a*R*,9a*S*)-**12** LTT ligands in Table I could be rationalized using this model if the ligands are *not* flipped at the binding site, but then other structure–activity relationships (allyl compared with propyl, ring at the south of the amine in Figure 4) would be less consistent. In the previous section several scenarios for partial agonist and antagonist activity were discussed. Considering all the data we have at present, we suggest that having the N–H bond directed upwards from the aromatic plane should be a sufficient condition, but not a necessary condition for dopamine antagonist or partial agonist activity.

Specificity for the 5-HT_{1A} Receptor. Specificity for this receptor should be enhanced by eliminating aromatic substituents that are hydrogen bond donors if they fit the geometry for donors shown in Figure 3. Another way to enhance specificity would be to take advantage of two features of the D_2 pharmacophore: it is thought from previous studies[10,11,26] that amine substituents to the south cannot be larger than propyl, and in addition, there is an enantiomeric preference explained by the Figure 4 model. According to Figure 4, the nitrogen must be above the plane at the D_2 receptor; otherwise it would be too close to the hydrogen bond acceptor. An ACT type molecule (Table V) with an (3a*R*,9b*S*) configuration should have high affinity for the 5-HT_{1A} receptor, would not tend to bind at the D_2 receptor in the normal orientation because the nitrogen would be below the plane and the secondary hydrogen bond donor would be in the wrong location, and could be prevented from binding in a flipped orientation if it had a propyl or larger substituent at carbon 2. The substituent at 9 could be either hydroxy or carbonyl, and the amine substituent could be either propyl or allyl.

Specificity for Dopamine D_2 Receptor. (3a*R*,9a*S*) LTT molecules (Table I), which are proposed to bind at the D_2 receptor in a flipped orientation, do not bind to the 5-HT_{1A} receptor. The racemic analog of 7-hydroxy-*N*-*n*-propylbenzoquinoline, **22**, has been reported to be inactive at the 5-HT_{1A} receptor;[26] also, its racemic NH analog was tested in our binding assay and found to lack affinity. Steric hindrance may well be the reason for this, since according to Figure 4 rings to the south of the nitrogens in these molecules would occupy receptor space not occupied by any ligands known to have affinity for the 5-HT_{1A} receptor. Analogs having the ring geometry and configuration to overlay either of these molecules should be selective for the dopamine D_2 receptor; (3a*R*,9a*S*)-**12c** with, for higher affinity, the hydroxyl substituent at 7 instead of 5, is an example of an analog which should be specific but would be a dopamine antagonist or partial agonist.

A possibility for a dopamine D_2-selective ligand with greater intrinsic activity would be an analog of **13a** in Table IV, a (3a*R*,9a*R*) LCT ligand, with a 3-ethyl substituent to prevent binding in a flipped orientation. LTT and LCT types are the only ones having nitrogens more to the northwest of the consensus chlorine position in the D_2 model than in the 5-HT_{1A} model. This molecule should not bind to the 5-HT_{1A} receptor any more than a (3a*R*,-9a*S*) LTT molecule would, and molecular mechanics calculations indicate that even though the nitrogen would

tend to be below the plane, the energy cost for the amine to be above the plane is less than 2 kcal. This ligand should have agonist activity.

Conclusions. The models proposed for the 5-HT$_{1A}$ and dopamine D$_2$ pharmacophores have several features which allow us to rationalize enantiomeric differences and dopamine agonist, partial agonist, or antagonist behavior, as well as trends toward selectivity for one or the other receptor. Some suggestions were made for designing 5-HT$_{1A}$-selective ligands and dopamine D$_2$-selective agonist and antagonist ligands.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10- × 20-cm (250 μm) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. ^{1}H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Flash column chromatography and medium-pressure liquid chromatography were performed with 400 g to 1 kg silica gel 60 (230–400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under a nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine based products were converted into the HCl salts by dissolving the free base in a methanolic HCl solution.[31] The solvent was removed and azeotroped with toluene in vacuo followed by recrystallization from an appropriate solvent. Other physical data, such as IR (infrared spectra), MS (mass spectra), and elemental analyses, were performed by the Physical and Analytical Chemistry Unit of the Upjohn Laboratories. The elemental analyses reported are within 0.4% of the calculated values.

(±)-1,2,2a,3,4,8b-Hexahydro-8-methoxy-2-(2-propenyl)-naphth[2,1-*b*]azetidine Hydrochloride (16d). (1) A solution of *cis*-(±)-1,2,3,4-tetrahydro-8-methoxy-2-(2-propenylamino)-1-naphthalenemethanol, **24**[23] (4.95 g, 20 mmol), and pyridine (3.2 mL, 40 mmol) in chloroform (20 mL, Burdick and Jackson, passed through a layer of alumina)[32] was stirred at 0–5 °C under a nitrogen atmosphere. *p*-Toluenesulfonyl chloride (3.81 g, 20 mmol) was added over 5 min, and the resulting yellow solution was allowed to stand for 24 h in the refrigerator. To this mixture another portion of *p*-toluenesulfonyl chloride (3.81 g, 20 mmol) was added, and the reaction continued at 0–5 °C for additional 24 h. The reaction was then quenched with water (5 mL), and the mixture was stirred for 1 h at room temperature. The mixture was extracted with methylene chloride (2 × 500 mL), and the combined organic layers were washed with 5% sodium hydroxide, water, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. During the removal of the solvent, the bath temperature was maintained at <50 °C, and toluene was added to facilitate the removal of pyridine.

(2) A three-neck, round-bottomed flask, equipped with a dropping funnel and a magnetic stirring bar, was charged with sodium hydride dispersion (60% active, 2.4 g, 60 mmol). The hydride was washed with hexane (2 × 10 mL) and suspended in 20 mL of DMF. The tosylate prepared in step 1 dissolved in DMF (20 mL) was added slowly over a period of 1 h. The mixture was stirred at room temperature for 2 days. The reaction was quenched with water (5 mL) and extracted with 1 L of ethyl acetate–ether (4:1). The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/ethyl acetate (2:1), and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated in vacuo to give an off-white solid (1.94 g, 34.7%). This solid was converted into HCl salt and recrystallized from hexane/ethyl acetate to yield **16d** as a white solid: ^{1}H NMR 7.20 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.32–5.38 (m, 3H), 3.78 (s, 3H), 4.62–1.88 (m, 10H); IR (mull) ν_{max} 1603 and 1587 cm^{-1}. Note: About an equal amount of a more polar fraction was isolated and identified by ^{1}H NMR as the elimination product.

(±)-1,2,2a,3,4,8b-Hexahydro-8-methoxy-2-*n*-propylnaphth-[2,1-*b*]azetidine Hydrochloride (16b). A mixture of **16d** (0.8 g, 3.0 mmol) and 10% Pd/C (0.2 g) in methanol (100 mL) was hydrogenated in a Parr shaker under 30 psi of hydrogen atmosphere at room temperature for 2 h. The mixture was then filtered through a Celite pad and concentrated in vacuo. The product was recrystallized from ethyl acetate/methanol to yield **16b** as a white solid: ^{1}H NMR δ 7.20 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 5.05–3.92 (m, 4H), 3.79 (s, 3H), 3.62–1.60 (m, 8H), 1.04 and 0.99 (2 t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 1604 and 1519 cm^{-1}.

(±)-1,2,2a,3,4,8b-Hexahydro-8-hydroxy-2-(2-propenyl)-naphth[2,1-*b*]azetidine Hydrochloride (16c). A solution of diphenylphosphine (7.0 mL, 40.5 mmol) in THF[33] was treated with 1.6 M *n*-butyllithium in hexane (25.3 mL, 40.5 mmol) at 0 °C to give a red solution. To this solution, the starting material **16d** (3.1 g, 13.5 mmol) dissolved in THF (5 mL) was added and refluxed for 24 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The oil was purified by liquid chromatography on 400 g of silica gel, eluting with hexane/ethyl acetate (2:1), and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated in vacuo to give a colorless oil. This oil was converted into the HCl salt and recrystallized from ethyl acetate/methanol to give **16c** as a white solid: ^{1}H NMR δ 7.05 (t, J = 7.9 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.02–5.52 (m, 3H), 4.88–3.92 (m, 4H), 3.92–1.92 (m, 6H); IR (mull) ν_{max} 3101, 1614, and 1588 cm^{-1}.

Dopamine Intrinsic Activity Measurements. Intrinsic activity was determined using membranes from CHO cells stably transfected with the dopamine D$_2$ receptor as previously described by Lahti and co-workers.[34] Briefly, this method uses the normalized logarithm of the ratio of the affinity of a compound for the low- and high-affinity states of the receptor to determine the intrinsic activity. The affinity for the low-affinity agonist state is determined using [^{3}H]raclopride + GTP, and the affinity for the high affinity state is determined using the dopamine agonist ligand [^{3}H]U-86170.[27]

X-ray Crystallography of (±)-14a and (±)-16d. Intensity data were collected at low temperature, −120 °C, on a Siemens P2$_1$ diffractometer using graphite monochromatized Cu Kα radiation, (λ(Cu Kα) = 1.5418 Å), with $2\theta_{max}$ = 138°. $\theta/2\theta$ step scans were used with scan widths ≥3.4° and scan rates of 4 deg/min for **14a** and 2 deg/min for **16d**. Ten reflections periodically monitored showed no trend towards deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(dI)^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections and was 0.03 for **14a** and 0.015 for **16d**. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values ($\lambda_{K\alpha 1}$ = 1.5402) for 25 high 2θ reflections.[35] An Lp correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[36]

Trial solutions for both structures were solved using DIREC.[37] Hydrogens in both structures were found in difference maps close to generated positions; generated positions were used in the calculations for **14a** and updated after each refinement. Least-squares refinement of **14a** included coordinates and anisotropic thermal parameters for non-hydrogen atoms, except for a disordered methanol which was located close to the center of symmetry at 0, $^1/_2$, $^1/_2$; coordinates for the methanol oxygen and isotropic temperature factors for the oxygen and the carbon were refined, but coordinates of the methanol carbon were constrained to be in the position found in the difference Fourier map; methanol hydrogens were not found. The least-squares refinement of **16d** included coordinates (including hydrogen coordinates) and anisotropic thermal parameters for non-hydrogen atoms. Temperature factors for hydrogens in both structures were assigned as 0.5 unit higher than the equivalent isotropic temperature factors for the attached carbon. The function minimized in both

refinements was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. In the refinement for **16d**, F_c^2 was as defined by Larson.[38] Shifts in the final cycle of refinement were $\leq 0.25\sigma$ for **14a** and $\leq 0.1\sigma$ for **16d**. Atomic form factors were from Doyle and Turner,[39] and for hydrogen, from Stewart, Davidson, and Simpson.[40] The CRYM system of computer programs was used.[37]

Crystal data specific for 14a: $C_{15}H_{21}NO{\cdot}HCl{\cdot}0.5(CH_3OH)$; formula wt = 231.4 × 36.5 × 16.0; monoclinic; space group $P\bar{1}$; $Z = 2$; $a = 7.334(1)$, $b = 7.573(1)$, $c = 13.701(1)$ Å, $\alpha = 95.14(1)$, $\beta = 90.30(1)$, $\gamma = 99.20(1)°$; $V = 748.0(1)$ Å^3; calculated density = 1.26 g cm^{-3}, absorption coefficient $\mu = 2.1$ mm^{-1}. The data collection crystal was a clear needle 0.03- × 0.07- × 0.20-mm mounted on a glass fiber. The final agreement index R was 0.068 for all 2465 reflections, and 0.060 for the 2073 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 3.6. The amine nitrogen is protonated and makes a hydrogen bond with the chlorine; the N to Cl distance is 3.129(2) Å.

Crystal data specific for 16d: $C_{14}H_{19}NO{\cdot}HCl$; formula wt = 217.3 × 36.5; monoclinic; space group $P2_1/c$; $Z = 4$; $a = 9.269(2)$, $b = 7.262(2)$, $c = 22.304(10)$ Å, $\beta = 114.46(2)°$; $V = 1366.5(5)$ Å^3; calculated density = 1.29 g cm^{-3}, absorption coefficient $\mu = 2.3$ mm^{-1}. The data collection crystal was a clear needle 0.02- × 0.07- × 0.11-mm mounted on a glass fiber. The final agreement index R was 0.031 for 1543 reflections and 0.027 for the 1354 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 2.7. The amine nitrogen is protonated and is hydrogen bonded to the chlorine; the N to Cl distance is 3.073(2) Å.

Supplementary Material Available: The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. Tables of atomic coordinates, thermal parameters, bond lengths and angles, torsion angles, and close intermolecular contacts (12 pages). Ordering information is given on any current masthead page.

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