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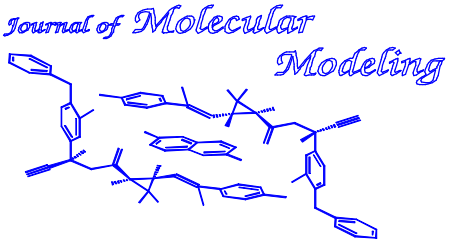

Structural Factors that Distinguish Dopamine D1 and D2 Agonists

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Abstract

To determine the structural features responsible for their selectivity as dopamine D1 agonists, a conformational analysis has been performed on an analog of nomifensine, dihydrexidine, a benzergoline, and an isochroman using the MM2-87 program. The preferred three dimensional structure of the hydroxylated phenyl ring of the nomifensine analog was found to differ from the other compounds with a substantial energy barrier to achieving the planar conformation of the other compounds which may explain its weak potency for D1 receptors. The preferred three dimensional structures of dihydrexidine and the benzergoline were found to differ significantly despite their molecular similarity. These conformational differences were also evident in crystal structures of the compounds or their analogs. The hypothesis that an equatorial ammonium hydrogen (or amine lone pair) is required for D1 agonist selectivity was tested by performing calculations on N-methyl equatorial and N-methyl axial analogs of the compounds. Calculations were also performed on nonselective dopamine agonists (apomorphine and 5,6-diOH- and 6,7-diOH aminotetralin) and dopamine D2-selective agonists ((+)-PHNO and an analog of quinpirole). The energy difference for the N-methyl axial conformations (or their equivalent) were found to be relatively small for the nonselective agonists and more substantial for the D2-selective agonists. This suggests that D2-selectivity may be associated with the relative unfavorability of the N-methyl axial conformation and provides an explanation for the decreased potency of tertiary amine analogs of the D1-selective agonists. In the benzergoline, where the energy difference is computed to be smaller, the addition of the N-methyl group appears to have a smaller deleterious effect on D1 activity. An N-methyl axial conformation has also been observed for the benzergoline in the crystal state suggesting that this conformation is energetically accessible.

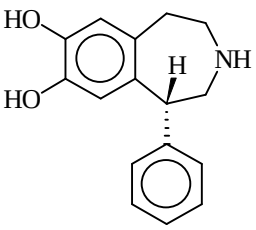
Keywords: D1 agonists; D2 agonists; molecular mechanics; conformation; pharmacophore
Running title: Dopamine D1 Agonists

Introduction

The major division in dopamine receptors is between the D1 and D2 subtypes which can readily be distinguished by selective agonists and antagonists [1,2]. More recently, with the cloning of five distinct dopamine receptors [3,4], this basic division has been preserved with the D1 and D5 receptors said to belong to the D1-like family and the D2, D3, and D4 receptors to the D2-like family. In general, the receptor subtypes within each family have closer amino acid homologies and are more difficult to distinguish pharmacologically with selective ligands, though this is beginning to change. The availability of amino acid sequences for dopamine receptors has lead to attempts to rationalize the detailed structure-activity relationships of agonist and antagonist ligands that bind to the receptor [5].

SKF38393 **1** and SCH23390 **2** (Scheme 1) were the first D1 selective agonist [6,7] and antagonist [8], respectively, of the D1-selective benzazepine family. The important struc-

D1-selective



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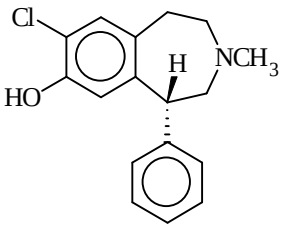

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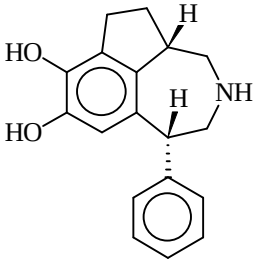

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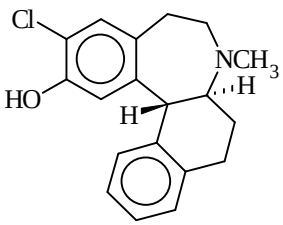

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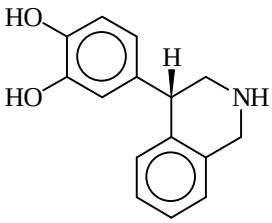

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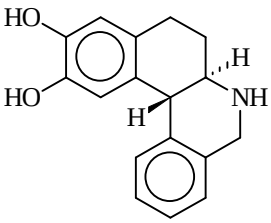

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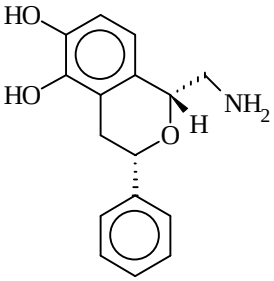

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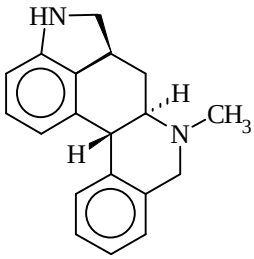

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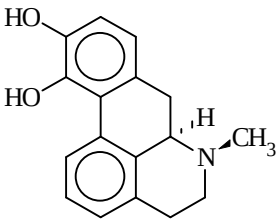
Nonselective



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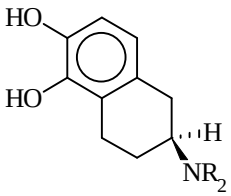

(–)-5,6-diOH

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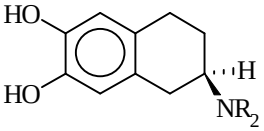

(+)-6,7-diOH

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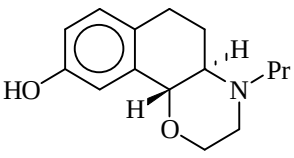
D2-selective



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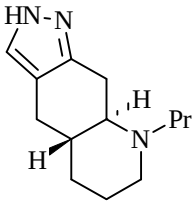

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Scheme 1

tural feature for D1 selectivity in the benzazepines is the second pendant phenyl ring since its omission leads to nonselective compounds [9]. The two-fold effect of the second ring is to increase affinity for D1 receptors and to decrease affinity for D2 receptors. This has lead to the suggestion that the D1 receptor contains a phenyl accessory site important for D1 selectivity [10]. More recent evidence has generally been in agreement with this since a second phenyl or other aromatic ring is important in all D1-selective classes of agonists including nomifensine analogs such as **5** [11-13], dihydrexidine **6** [14,15], isochromans **7** [16-18], and benzergolines **8** [19,20]. The only exception to this is in the isochroman series **7** where large saturated hydrocarbon groups such as cyclohexyl and 1-adamantyl are almost as effective as a phenyl ring for producing potent D1-selective agonists.

Highly detailed pharmacophores for dopamine agonist activity have been developed and are quite successful in explaining the agonist activity of a variety of compounds of different structural classes. These models are based on the work of Cannon, who proposed the idea of rigid analogs of the α- and β-rotamers of dopamine [21], and McDermed, who provided a model consistent with the activity of the active stereoisomers in each class [22,23]. This model has been further developed and provides a consistent picture of the structural requirements of dopamine agonists [24-27].

The above model is primarily concerned with agonists at D2-like receptors though it is also clear that the structural requirements of D1 and D2 agonists are similar [28,29]. In this work, we are attempting to determine a common pharmacophore for D1 agonists and how D1- and D2-selective agonists differ. The conformational properties of D1-selective agonists were calculated using the MM2-87 program for compounds where this has not been previously done. Low energy conformers of the compounds that appear to be the biologically active forms were then superimposed to determine if D1-selective agonists show structural similarities that can account for their common properties. The benzazepines 1 and 2 are quite flexible as shown in a number of studies [30-33]. For that reason, we have focused on the more rigid analogs 3 [30] and 4 [31] that maintain high affinity for D1 receptors. While the focus of this work is D1-selective agonists and 4 is the rigid analog of a D1-selective antagonist, it has been included in the discussion since it provides important structural information. Agonists that are nonselective toward D1-like and D2-like receptors such as apomorphine 9 [34] and aminotetralins 10 and 11 [28,29,35-37] were also examined. Finally, the structures of highly selective agonists for the D2 receptor such as (+)-PHNO 12 [38,39] and quinpirole 13 [40,41] were examined as well. For quinpirole, which contains an unusual pyrazole moiety for which MM2-87 parameters were not available, the equivalent ergoline structure was used.

D1-selective agonists of different structural classes show consistent structure-activity relationships. In benzazepine agonists such as **1**, secondary amines generally have higher affinities for the D1 receptor and/or higher potency in the adenylate cyclase assay than the corresponding tertiary amine [9]. A similar result was found for nomifensine analogs **5** [13], dihydrexidine **6** [14] and benzergolines **8** [19] in which the amine group is part of a ring system. In the isochroman series **7**, where the amine is not part of a ring, most of the synthesized compounds were primary amines [16]. While the addition of an N-methyl group (secondary amine) decreases D1 receptor affinity slightly, an N,N-methyl,allyl group (tertiary amine) results in a large drop in D1 affinity [16]. This differs considerably from the situation in D2 receptors where, depending on whether the compound is a rigid analog of the α- or β-rotamer of dopamine, the optimal N-alkyl group is N-propyl or larger [24,27]. The preference of the D1 receptor for secondary amines has been interpreted as being due to its requirement for an ammonium hydrogen (or amine lone pair) in the equatorial position which would preferentially be occupied by an N-alkyl group in a tertiary amine analog [42]. An alternate hypothesis is that the D1 receptor is more sensitive to steric bulk in the vicinity of the ammonium group than D2 receptors. These hypotheses will be tested by evaluating the energy difference between N-methyl equatorial and N-methyl axial or the equivalent conformations in D1-selective, D2-selective, and nonselective agonists.

With respect to the effect of phenyl hydroxy groups, various structural classes show similar trends. To achieve maximum agonist efficacy, a catechol group is generally required. This is true for the benzazepines **1** and nomifensine analogs **5** [9,13]. For a partial agonist like apomorphine **9**, the monohydroxy equivalent produces D1 antagonists [43]. While D1-selective benzergolines **8** are somewhat anomalous in that they do not contain any hydroxyl groups, these compounds do not appear to be fully efficacious agonists [19].

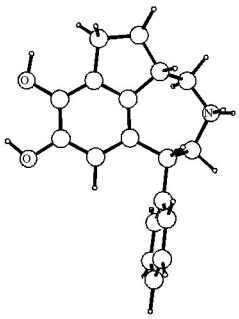
Results and Discussion

Benzazepines

Benzazepines such as **1** and **2** are quite flexible conformationally [30-33]. The seven-membered ring can be in a chair or twist conformation with the phenyl ring either equatorial or axial with little energy difference. Rigid analogs such as **3** and **4** have fewer conformational possibilities but, nevertheless, have several low energy forms within about 1 kcal·mol^{-1} [30-32]. Based on an analysis of a variety of benzazepines with differing pharmacological potencies, it was concluded that the biologically active form in this entire series is likely to be a chair conformation with an equatorial phenyl ring [32] and this was the conformation (Figure 1) used for compound **3** in the superposition studies.

*Nomifensine Analogs **5***

The catechol-containing phenyl ring can rotate and the optimal conformation is when the phenyl ring is perpendicular to the piperidine ring (Figure 2). The energy barrier for rotation of the phenyl ring is shown in Figure 3 and the conformation



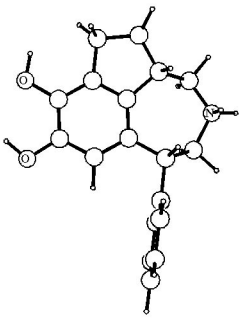
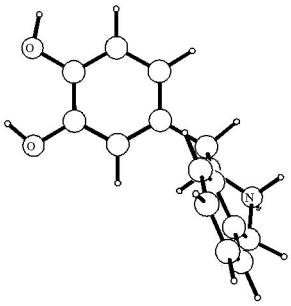


Fig. 1 *Energy minimized conformation of benzazepine **3** that is believed to be the biologically active form.*



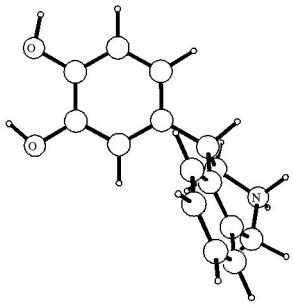


Fig. 2 *Energy minimized structure of the preferred conformation of the nomifensine analog **5**. This conformation does not match that of other D1-selective agonists and may be responsible for the weak activity of the compound.*

in which the hydroxylated phenyl ring is coplanar with the piperidine ring is close to a maximum in the energy surface. Thus, these compounds are clearly different from compounds such as dihydrexidine and benzergolines is which the two rings are constrained to be approximately coplanar. In the N-methyl derivative, the N-methyl group prefers the equatorial position by 3.9 kcal·mol^{-1} (Table 1).

*Dihydrexidine **6***

Due to close contacts between the two phenyl rings, one phenyl ring can be either above or below the plane of the other and both are stable conformations. Energy minimization indicated that the conformer shown in Figure 4 is preferred by 2.5 kcal·mol^{-1} and this is also the conformer observed in the crystal state of a dihydrexidine analog [15]. For the optimal orientation of the phenyl rings in the N-methyl derivative, the N-methyl group prefers the equatorial position by 2.9 kcal·mol^{-1} (Table 1).

Table 1. *Computed conformational energies (kcal·mol^{-1}) of N-methyl equatorial and N-methyl axial conformers of N–methyl analogs of the listed compounds.*

	N-methyl equat	**N-methyl axial**	**difference**
D1-selective			
dihydrexidine 6	8.9	11.8	2.9
benzergoline 8	18.9	19.5	0.6
nomifensine 5	-1.5	2.4	3.9
nonselective			
apomorphine 9	-1.5	3.8	1.3
5,6-diOH–aminotetralin 10[a]	5.1	5.9	0.8
7,8-diOH–aminotetralin 11[a]	5.9	6.3	0.4
D2-selective			
(+)-PHNO 12	11.8	14.4	2.6
analog of quinpirole 13	22.0	25.7	3.7

[a] while N-methyl equatorial and axial do not exist for these open chain compounds, the corresponding three dimensional conformation was used.

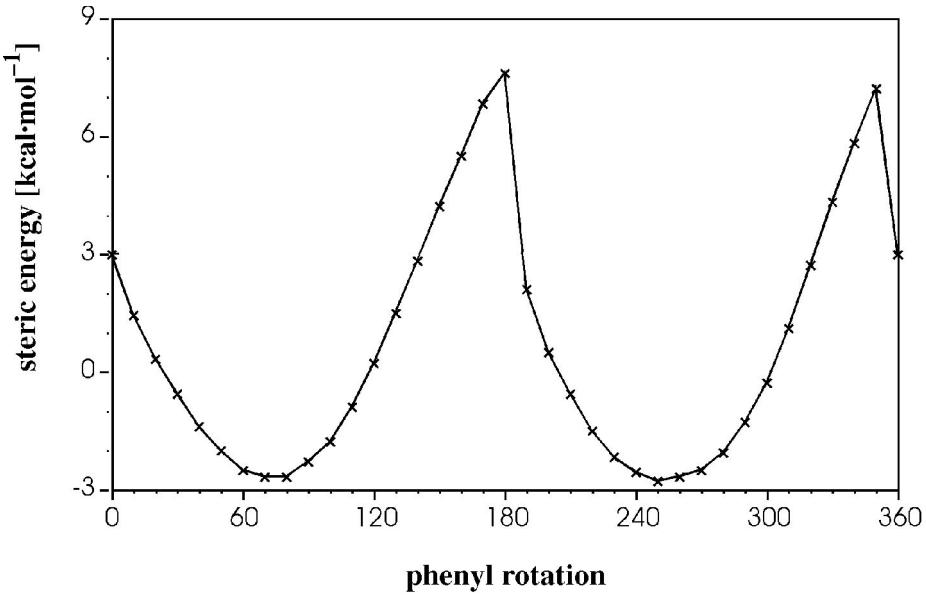


Fig. 3 *Energy barrier to rotation of the phenyl ring in the nomifensine analog* ***5****.*

Benzergolines ***8***

As with dihydrexidine, one phenyl ring can be either above or below the plane of the other and both are stable conformations. Energy minimization indicated that the conformer shown in Figure 5 is preferred by 2.1 kcal·mol^{-1} and this is also the conformer observed in the crystal state of two benzergoline derivatives [20]. Note that the preferred conformer is the opposite of that in dihydrexidine despite their close structural similarities. This potentially important structural difference was traced to the sp^2 hybridization present in the six carbon ring of benzergoline since sp^2 hybridization of the equivalent atom in dihydrexidine produces a similar calculated result. This unexpected result shows how a relatively minor change in one end of a molecule can have a profound impact on its overall three dimensional structure. For the optimal orientation of the phenyl rings in a benzergoline with an N-methyl group, the N-methyl prefers the equatorial position by 0.6 kcal·mol^{-1} which is a significantly smaller difference than in dihydrexidine (Table 1).

Isochromans ***7***

In the isochromans, the amine side chain is free to rotate and three stable conformers were found. Relative to the ether oxygen, these are one trans and two gauche conformers. There is little energy difference (0.1 kcal·mol^{-1}) between the two gauche conformers while the trans conformer is 2.5 kcal·mol^{-1} above the global minimum due to close contacts with the catechol-containing phenyl ring. Of the two gauche conformers, the one shown in Figure 6, which is 0.1 kcal·mol^{-1} above the global minimum, is a better fit to the extended form of dopamine and to the other D1-selective compounds that are analyzed here.

Hydroxyl Groups

In general, there is a strong tendency of a phenyl hydroxyl to lie in the plane of the ring with little energetic preference for the hydroxyl hydrogen to point in one direction or the other. An example where this is not the case is apomorphine in which the proximity of the second phenyl ring sterically destabilizes

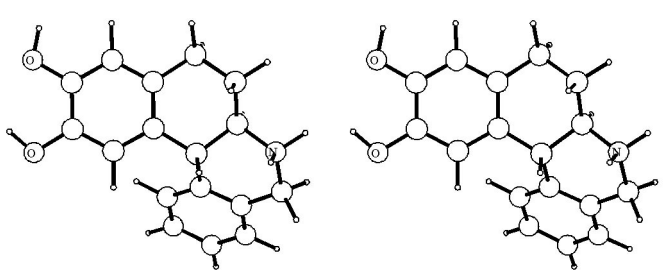


Fig. 4 *Energy minimized structure of the preferred conformation of dihydrexidine* ***6****.*

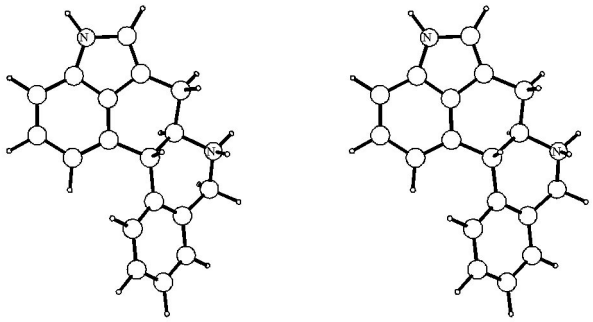


Fig. 5 *Energy minimized structure of the preferred conformation of benzergoline* ***8****.*

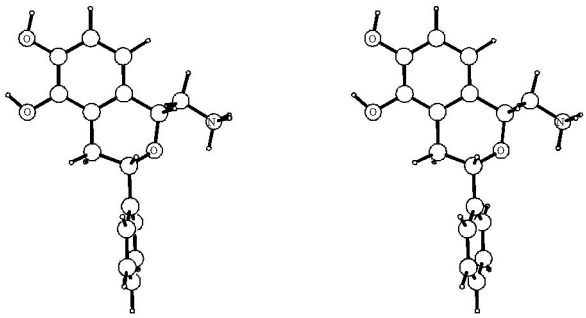


Fig. 6 *Energy minimized structure of isochroman* ***7*** *that appears to be responsible for the D1-selectivity of the compound.*

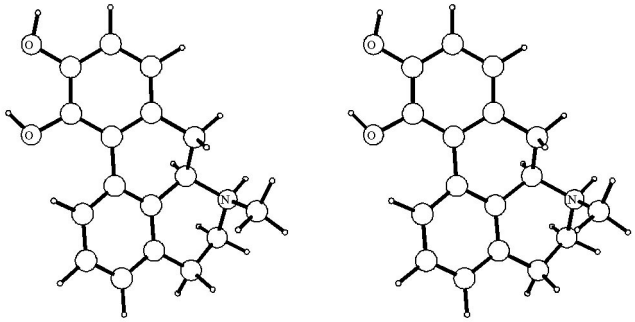


Fig. 7 *Energy minimized structure of the N-methyl axial conformation of the nonselective apomorphine* ***9****. This conformation is 1.3 kcal·mol*$^{-1}$ *above the preferred N-methyl*

the hydroxyls from pointing toward the second phenyl ring [25]. The same is true for a catechol group, except that both hydroxyls should optimally point in the same direction [32]. There would appear to be two distinct hydrogen bonding possibilities for a hydroxyl group on a ligand that binds to a receptor site. The hydroxyl hydrogen can interact with a negatively charged group in the receptor or a positively charged group in the receptor can interact with the hydroxyl oxygen. However, only the former possibility exists for a pyrrole group such as in the benzergolines and the viability of this compound and similar ones as dopamine agonists suggests that the role of the hydroxyl is to interact with a negative group in the receptor. The lack of conformational flexibility in ergolines also suggests that the appropriate position of the hydroxyls is as shown in the Figures since only then is the hydroxyl hydrogen pointing in the same direction as the pyrrole hydrogen and only then is it capable of making a similar hydrogen bond with a group in the receptor. This is the same direction as is sterically preferred in compounds such as apomorphine [25].

Axial or Equatorial Ammonium Hydrogen

As indicated above, N-alkylation generally decreases affinity of agonists for the D1 receptor unlike the effect it has for D2 agonists. There appear to be two possible explanations for this effect on D1 agonists. One hypothesis is that the D1 receptor requires an equatorial ammonium hydrogen (or amine lone pair for the free base) for agonist activity [42]. Since N-alkyl groups generally prefer the equatorial position of a six-membered ring, an N-alkyl group will preferentially occupy the position required for the ammonium hydrogen. For agonists such as the aminotetralins where the amine group is not part of a ring, the equivalent conformer would presumably be required. An alternate hypothesis is that an N-alkyl group directly interferes with the binding of an agonist to the D1 receptor. To attempt to answer this question, calculations were performed on D1-selective, D2-selective, and nonselective agonists with an N-methyl group (or N,N-dimethyl group for the aminotetralins) and the computed steric energies for N-methyl axial and N-methyl equatorial conformers are listed in Table 1.

In all of the compounds, the N-methyl equatorial (ammonium hydrogen axial), or equivalent in the case of the aminotetralins, is consistently preferred though by varying amounts. For the nonselective agonists (those that have substantial D1 and D2 agonist effects), the energy required to place the N-methyl axial (ammonium hydrogen equatorial) ranges from 0.4 kcal·mol^{-1} to 1.3 kcal·mol^{-1}. For the N-propyl analog of apomorphine, the energy difference is only 0.6 kcal·mol^{-1} [25]. It has previously been shown that there is little energy difference between possible conformers of the aminotetralins [27]. For the two D2-selective agonists (+)-PHNO and the analog of quinpirole, the energy difference is 2.6 and 3.7 kcal·mol^{-1}. This result appears to be consistent

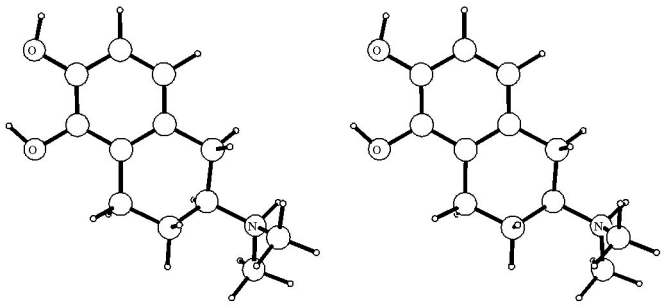


Fig. 8 *Energy minimized conformation of the nonselective 5,6-diOH,N,N-dimethyl aminotetralin that best matches the D1 pharmacophore. This conformation is 0.8 kcal·mol*$^{-1}$ *above the global minimum.*

with the hypothesis that an equatorial ammonium hydrogen is required for D1 agonist activity since this conformer is considerably more accessible in compounds that retain significant D1 agonist activity.

For the D1-selective agonists, the energy required to put the N-methyl axial varies from 0.6 kcal·mol^{-1} for the benzergoline **8** to 2.9 and 3.9 kcal·mol^{-1} for dihydrexidine **6** and the nomifensine analog **5**. The smaller energy difference for the benzergoline suggests that an N-methyl group should have a less drastic effect in this series. This appears to be the case since the N-methyl analog of the benzergoline is only slightly less potent on the adenylate cyclase assay than the des-N-methyl compound whereas the affinity of the N-methyl analog of dihydrexidine goes down by a factor of nine [14,19].

Comparing the D1-selective benzergolines **8** with the closely related D2-selective analog of quinpirole **13**, the energy difference between N-methyl axial and N-methyl equatorial is considerably smaller in the former. As was found previously in the aporphine series [25], this appears to be due to the proximity of the second phenyl ring which reduces steric interactions between an axial N-methyl group and nearby axial hydrogen atoms present in a fully saturated ring.

Examining the alternate hypothesis that an N-alkyl group has a direct steric effect at the D1 receptor, this has some aspects that would require further explanation. For example, an N-propyl group in dihydrexidine **6** causes a 50-fold decrease in affinity for the D1 receptor [14]. However, in 5-OH aminotetralins, the affinity for D1 receptors and potency for stimulating the adenylate cyclase assay is *increased* 90-fold [28]. If the D1 receptor is sensitive to steric bulk on the nitrogen, how does one explain the greatly increased potency of the N,N-dipropyl derivative of 5-OH aminotetralins?

For the above reasons, it appears that the ammonium hydrogen equatorial hypothesis provides a somewhat better explanation for the effects of an N-alkyl group on D1 receptor affinity. While the hypothesis does not appear to provide a quantitative explanation, this may be the best that can be achieved with complex pharmacological effects. For example, while an added N-methyl group may have an overall deleterious steric effect on receptor binding, it is also likely to have a favorable hydrophobic effect that may partially counteract the unfavorable effects.

Superposition Studies

To determine a common D1-pharmacophore, the substituted phenyl ring of the energy minimized structures have been superimposed in Figure 10-12. In Figure 10, dihydrexidine **6** has been superimposed with benzergoline **8**. These two compounds are critical since they have little conformational flexibilty with substantial energy differences among possible conformers (see above). Because of the different curvatures of the molecules, there are clear differences in the position of the second phenyl ring. In Figure 11, the benzazepine **3** has been superimposed with the isochroman **7**. In this case, the second phenyl ring of the latter significantly protrudes compared with the second phenyl ring of the former. In Figure 12, all four compounds are superimposed simultaneously. Clearly, there is significant variation possible for the second phenyl ring which may explain some of the differences in structure-activity relationships in D1-selective agonists. Notably, the substitution of a cyclohexane ring for the second phenyl produces inactive compounds in the benzazepine series [9] but has little effect in the isochroman series [17].

An attempt to develop a D1 pharmacophore with many of the same compounds has recently been published [44]. Some of the features of that study are similar to the approach used here but there are also significant differences. While conformational analyses of the compounds were performed, the previous study emphasizes a common structure as the "bioactive" form regardless of their relative energies. For example, the bioactive form of dihydrexidine is reported to be 3.8 kcal·mol^{-1} above the global minimum. We believe that such an energetically unfavorable conformer could not be the biologically active form since the necessity of putting that much energy into a molecule to get it to bind would have a severely negative effect on the thermodynamics of the receptor-ligand complex. Instead, our approach has been to examine low energy forms that are within about 1 kcal·mol^{-1} of the global minimum as the biologically active form. While this means that the superpositions may not be as quantitative, we believe that more realistic conformations are being utilized. Despite this difference, that study came to a similar conclusion regarding the variability of the position of the second phenyl ring. Also, the previous study did not report preferred conformations so that we are unable to compare conformational results.

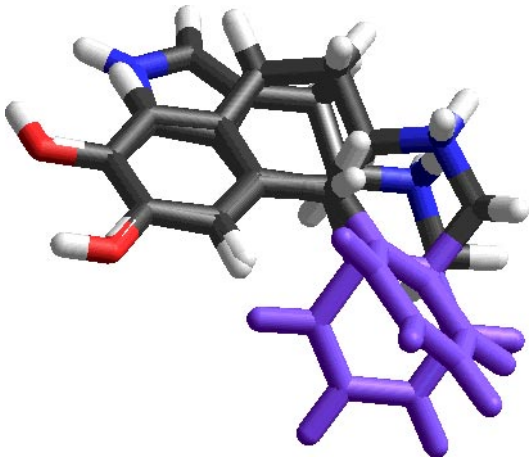


Fig. 10 *Superposition of the primary phenyl ring of dihydrexidine 6 with that of the benzergoline 8 showing the placement of the second phenyl ring (violet)*

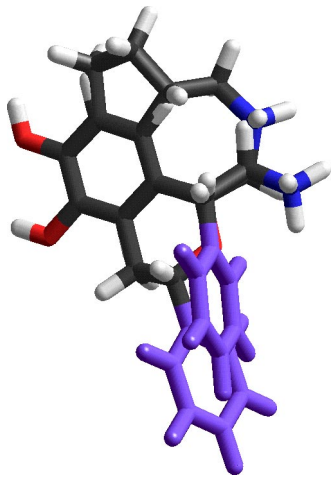


Fig. 11 *Superposition of the primary phenyl ring of the benzazepine 3 with that of the isochroman **7** showing the placement of the second phenyl ring (wiolet).*

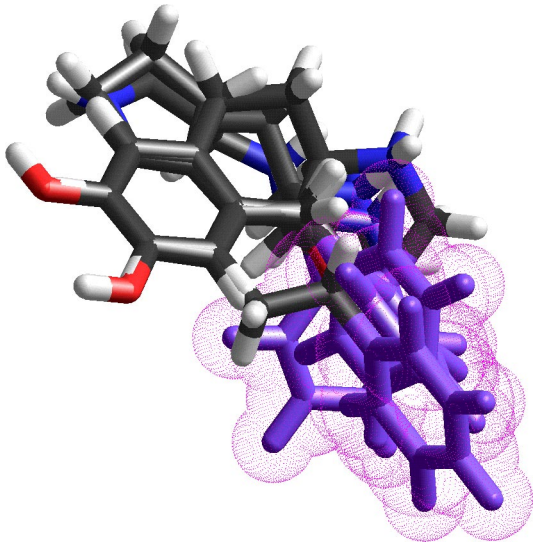


Fig. 12 *Superposition of the primary phenyl ring of the benzazepine **3**, dihydrexidine **6**, the isochroman **7**, and the benzergoline **8** showing the diverse positions occupied by the second phenyl ring.*

Conclusions

Conformational analysis of D1 selective agonists has produced some unexpected results. Despite the superficial similarity between the structures of dihydrexidine **6** and benzergolines **8**, the preferred three dimensional relationships between the two phenyl rings of the two compounds appear to be quite different. These differences also appear in the crystal structures of the compounds or their close analogs. The energy difference between an N-methyl equatorial and N-methyl axial conformation also appears to be much greater in dihydrexidine (2.9 kcal·mol^{-1}) than in benzergolines (0.6 kcal·mol^{-1}). It should be noted that one crystal structure of a benzergoline has an N-methyl axial conformation [20] suggesting that this conformer is readily accessible. Despite these different conformational preferences, both compounds are reported to be D1-selective agonists.

Conformational analysis of nomifensine analogs **5** indicates that the preferred orientation of the phenyl ring relative to the piperidine ring differs from other agonists in that the catechol-containing phenyl ring is perpendicular to the piperidine ring rather than in the same plane. To achieve a planar structure requires considerable energy and this appears to be associated with relatively weak potencies for these agonists.

Calculations of the relative preferences for an N-methyl axial or N-methyl equatorial conformation in D1-selective, nonselective, and D2-selective agonists provide evidence for the hypothesis that D1-selective agonists require the ammonium hydrogen (or amine lone pair) to be in the equatorial position. There is little energy difference for an N-methyl group to be either axial or equatorial (or the three dimensional equivalent) in aporphines such as apomorphine and in aminotetralins. In D2-selective agonists such as (+)-PHNO **12** and quinpirole **13**, however, the energy difference is more substantial. This provides an explanation for the potency decreasing effect of N-alkyl groups in D1-selective agonists. In benzergolines **8**, where the energy difference is smaller, the presence of an N-methyl group has a less deleterious effect on potency.

Superposition of the D1-selective agonists indicate that the second aromatic ring (or other groups) occupy similar regions of space. However, there appears to be considerable leeway in the exact positioning or orientations of the groups. This would account for the somewhat different structure-activity relationships for series such as the isochromans **7** where a cyclohexane ring produces the same result as a phenyl ring whereas only a phenyl ring produces D1-active agonists in the benzazepines.

Computational Methods

Energy minimization of the compounds in this study were performed with respect to all internal coordinates using the MM2-87 program and parameter set of Allinger and Yuh [45,46]. All calculations were performed for the protonated molecule. Initial Cartesian coordinates of the molecules were generated with the PCMODEL program [47] or the DRIVER option of the MM2-87 program. The dielectric constant was set to 80 and the hydrogen bonding terms involving the ammonium group was set to zero to approximate a water solution and to prevent intramolecular electrostatic forces from dominating the calculations in the absence of explicit water

molecules [48,49]. To ensure complete convergence of the calculations, the convergence criterion was set to 1/8 of its default value except for the energy barrier calculations where the default value was used.

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