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Computer-aided molecular modeling of a D_2-agonist dopamine pharmacophore

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SUMMARY

Using computer-aided molecular modeling techniques to analyze models recently proposed for the receptor binding sites of dopaminergic agonists, we superimposed the chemical structures of various compounds that mimic the pharmacological behavior of dopamine, as well as inactive enantiomers, on a postulated three-dimensional frame of reference. We analyzed the vector directionalities of the lone pairs of the nitrogen common to these molecules, and the acidic hydrogen of phenols (in aminoindanes, aminotetralins, apomorphines, *p*-phenol-piperazines, octahydrobenzo(g)quinolines, octahydrobenzo(f)quinolines, and benzazepines) or of nitrogen (in ergoline-type compounds and related structures). This model, when expressed as distances from that of the reference compound pergolide, correlates with the dopaminergic binding affinity observed in compounds previously reported to act on the dopaminergic system in the central nervous system (CNS). The regression analysis of log K_D with respect to the distances of the vectors of the acidic hydrogen support the hypothesis that these compounds bind to the receptor as donors in hydrogen bond formation.

INTRODUCTION

Efforts in recent years to determine receptor requirements for eliciting particular pharmacological responses have been due to the need of a better understanding of drug-receptor interactions in order to develop selective therapeutic agents. Such studies have served as a basis for the development of new, more selective compounds [1, 2], including dopaminergic compounds [3]. Some of the difficulties inherent in the studies of drug-receptor binding for these compounds are due (besides the lack of knowledge of the structure of the dopaminergic receptors) to the multiple classes of organic compounds interacting with the dopamine system [4, 5], and to the various subpopula-

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tions of the receptors, D_1, D_2 in the central nervous system (CNS), and D_{A1}, D_{A2} [6, 7] in the peripheral system. Currently, there is a strong trend for unifying the dopamine receptors to only the D_1 or D_2 subtype, where D_1 stimulates cyclic adenosine monophosphate (cAMP) synthesis and D_2 does not [8].

The antagonist structural requirements, also if far from being completed, have been satisfactorily modeled [9, 10]. This is not the case for the agonist dopaminergic pharmacophore for which various models have been proposed in the past [11, 12] and more recently [13, 14]. The most difficult aspect of determining the three-dimensional requirements for these receptors is the diversity in chemical structures interacting with the active site and eliciting agonistic effects. A classical question, not yet resolved, is what portions of ergolines should be considered in the pharmacophore: the pyrroloethylamine [3, 15, 16] or the indolethylamino [17] moieties.

Two models that unify the structural differences by a common universal pharmacophore for the dopaminergic receptor have been recently proposed [13, 14]. Wikstrom and coworkers [13] put the active compounds in a bidimensional model with the pharmacophore defined by nitrogen (always present in these molecules) and the heteroatom, which can be oxygen in compounds like dopamine, aminoindanes, 2-aminotetralins, and apomorphines, or nitrogen in the natural and synthetic ergolines or their substructures. Seeman et al. [14] qualitatively correlated many dissociation constants for the D_2 receptor to a tetrahedral model of the vectorial directions of the lone pairs of the nitrogen and the heteroatom. This correlation implies an interaction, by hydrogen bond with the drug as acceptor, with the receptor. Our attempt at matching the active and inactive dopaminergic compounds by this last model, using computer-aided molecular modeling, did not yield satisfactory correlations in finding structural differences for explaining the biological behavior of enantiomers. In Fig. 1, as an example, we illustrate the results we obtained by superimposing the enantiomers of 5,6-dihydroxy-2-aminotetralin (7R and 7S in Fig. 2) and *R*-apomorphine (8R in Fig. 2) in one of the low-energy conformations examined, using as reference points only the directionality of the lone pairs. All of the compounds show a good superimposition of the lone pair vectors, including the inactive *S*-5,6-dihydroxy-2-aminotetralin. In Fig. 1, the quasi planar structure of *R*-apomorphine must be seen perpendicular to the plane of the paper in contrast to the tetralin structures which lie in the plane.

In an attempt to gain better insight into the pharmacophore requirements for the D_2 receptor, we decided to try a tridimensional frame of reference similar to that of Wikstrom et al. [13], and then to check the relative importance of the vector directionality of the lone pairs of the nitrogen and the heteroatoms as well as the directions of the acidic hydrogens. In other words, we have attempted to combine the concepts of the two previous models into a hybrid model.

METHODS

We have chosen the compounds listed in Fig. 2 from a large homogeneous set of affinity data for the prototype of the D_2 receptor [14]. Compounds 13, 14, and 15 are the natural substances bromocriptine, α-ergocriptine, and α-dihydro-ergocriptine. The structures of the polypeptide chains for these compounds have been omitted for clarity. We chose different classes of conformationally restrained organic structures with known affinities for the pure enantiomers. The dissociation constants of the resolved enantiomers for many compounds of potential interest have often not been determined, but only the affinity of the racemic mixture; and this precluded their use in con-

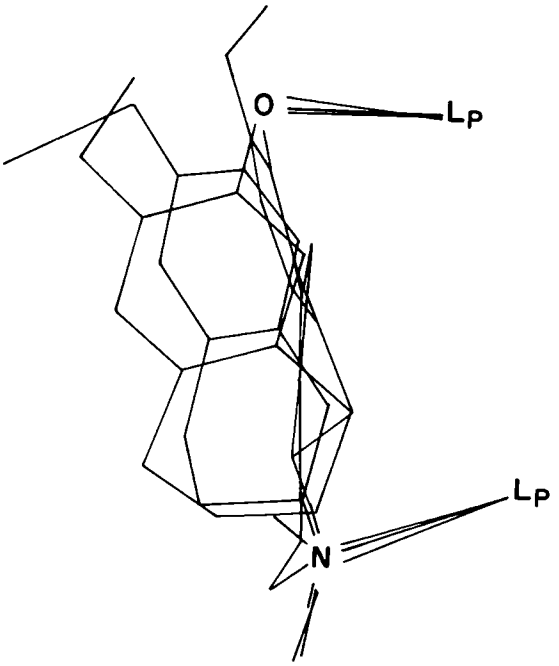
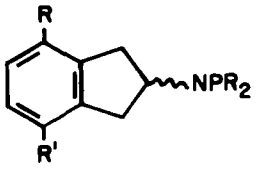


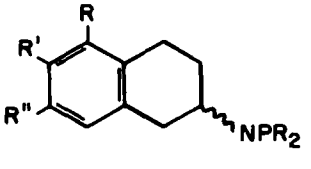
Fig. 1. Alignment of *R*-apomorphine (compound 8, perpendicular to page) and *R*- and *S*-aminotetralin-5,6-diol-dipropyl (compound 7, in plane of page) according to Seeman et al. [14].

struction of the model. When the molecules of Fig. 2 are given with the configurations of two chiral centers, the first assignment always refers to the atom near the nitrogen. The compounds were modeled on the MICROVAX II computer with the SYBYL program [18] using standard geometries. Apomorphine [19], compound 8, and bromocriptine [20], compound 13, were reconstructed on the basis of X-ray data, which were also used for building their analogs. All of the structures were adjusted and minimized using SIMPLEX [21], and the energy calculations were based on the force field of Vinter et al. [22], omitting the electrostatic terms. Compounds 1-7 were in their equatorial form, which is the most stable conformation as previously reported [5, 23]. The seven-bond ring structures of the benzazepine-7,8-diol-1-phenyl, 20R and 20S, used for matching the model described below were obtained by RING SEARCH [18], a program which allows the calculation of the sterically allowed conformations of the rings. Each conformer type was minimized and all conformers with relatively low energies were examined. The conformers which best fit the pergolide template were selected. The lowest energies for the enantiomers 1-12 and 19-29 were calculated and expressed as E_{min}, after scanning all of the rotatable bonds with angle increments of 30°, excluding the CH_3 terminals. The regression analyses were calculated using the statistical software package DABYL [24].

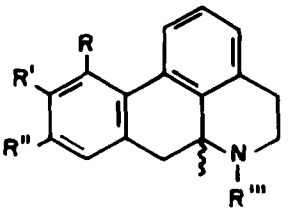
The frame of reference used for superimposing the molecules is shown in Fig. 3. For clarity, we show only pergolide, compound 17, and compounds 5R and 5S of the 2-aminotetralin series. We used pergolide as the reference compound, as it is the most active dopaminergic agonist in terms of its affinity while possessing relative structural rigidity. The superimposition of the molecules



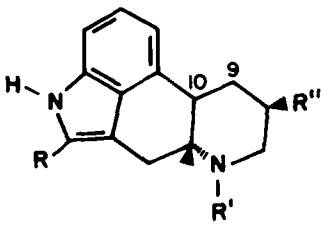
	R	R'
1	H	H
2R,2S	OH	H
3R,3S	OMe	H
4	OMe	OMe



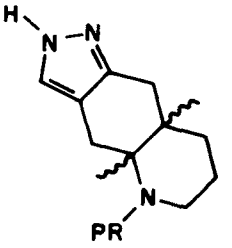
	R	R'	R''
5R,5S	OH	H	H
6R,6S	H	H	OH
7R,7S	OH	OH	H



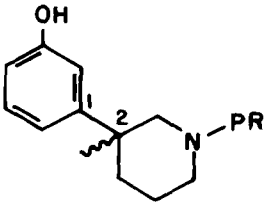
	R	R'	R''	R'''
8R,8S	OH	OH	H	CH_3
9R,9S	OH	OH	H	C_3H_7
10R	OH	H	H	C_3H_7
11R	OMe	H	H	C_3H_7
12R,12S	H	OH	OH	CH_3



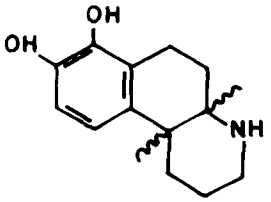
	9–10	R	R'	R''
13	Double Bond	Br	CH_3	Polypeptide Chain
14	,,	H	CH_3	,,
15	Single Bond	H	CH_3	,,
16	,,	Cl	CH_3	CH_2CN
17	,,	H	C_3H_7	CH_2SCH_3



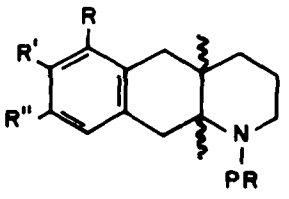
18RR,18SS TRANS



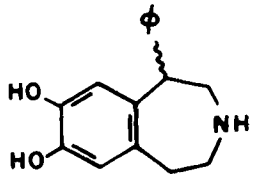
19R,19S



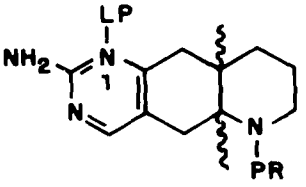
21RR,21SS TRANS
22RS,22SR CIS



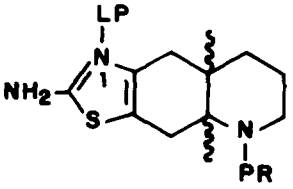
	R	R'	R''
23RR,23SS TRANS	OH	H	OH
24RR,24SS TRANS	H	OH	OH



20R,20S



25RR,25SS TRANS



26RR,26SS TRANS

Fig. 2. Compounds 1–24 correspond as follows to those listed in Table 1 of Seeman et al. [14]: 1 = aminoindan-dipropyl; 2 = aminoindan-4-OH-dipropyl, (−) = R, (+) = S; 3 = aminoindan-4-OCH_3-dipropyl, (−) = R, (+) = S; 4 = aminoindan-4,7-dimethoxy-dipropyl; 5 = aminotetralin-5-OH-dipropyl, (−) = S, (+) = R; 6 = aminotetralin-7-OH-dipropyl, (−) = S, (+) = R; 7 = aminotetralin-5,6-diol-dipropyl, (−) = S, (+) = R; 8 = apomorphine, (−) = R, (+) = S; 9 = aporphine-N-propyl-10,11-diol, (−) = R, (+) = S; 10 = aporphine-N-propyl-11-OH, (−) = R; 11 = aporphine-N-propyl-11-methoxy, (−) = R; 12 = aporphine-9,10-diol; 13 = bromocryptine; 14 = ergocryptine-α; 15 = ergocryptine-α-dihydro; 16 = lergotrile; 17 = pergolide; 18 = LY141865, (−) = R, (+) = S; 19 = 3-PPP, (−) = S, (+) = R; 20 = benzazepine-7,8-diol-1-Ph; 21 = benzo[f]quinoline-7,8-diol-*trans*; 22 = benzo[f]quinoline-7,8-diol-*cis*; 23 = benzo[g]quinoline-N-propyl-6,8-diol-*trans*; and 24 = benzo[g]quinoline-N-propyl-7,8-diol-*trans*. Compound 25 is LY137157 and 26 is LY163792 with the active isomers having the RR configuration [28].

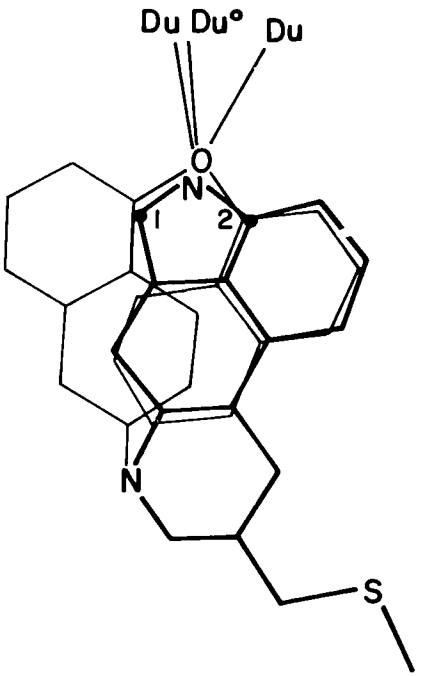


Fig. 3. Alignment of pergolide (compound 17 in bold) with *R*- and *S*-aminotetralin-5,6-diol-dipropyl (compound 7) by overlap of heteroatoms.

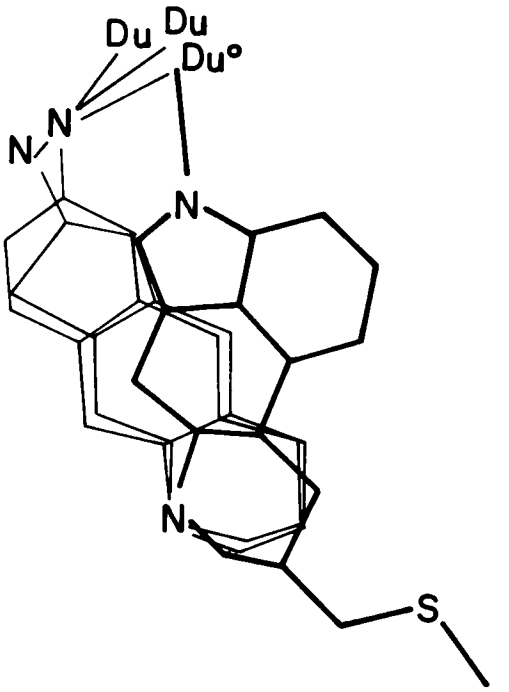


Fig. 4. Suggested alignment of pergolide (compound 17 in bold) with LY137157 (compound 25RR) and LY163792 (compound 26RR).

was performed on the basis of the root mean square (RMS) fitting for three points. We positioned molecules 2-29 in order to obtain the maximum superimposition between the basic nitrogens for each compound and the other corresponding heteroatoms; the latter can be nitrogens in ergoline-type compounds or oxygens for the others considered. The third point to superimpose was alternatively the carbon 1 or 2 of the reference compound (see Fig. 3) and an aromatic carbon of the fitted molecules to which is bound the heteroatom so as to always have the lone pair of the nitrogens directed downward toward [13] the plane of the paper, as in the structure of ergolines in Fig. 2. A direct consequence of this matching is also a general superimposition of the planes of aromatic moieties in all the molecules, which is considered one of the important requirements for dopaminergic activity [5, 25].

Dummy atoms were added to the nitrogens and heteroatoms on all of the molecules for simulating the vector directions of the lone pairs of nitrogen and heteroatoms. The heteroatoms may be acceptors or donors of hydrogen to the active site of the receptor. The distances of the lone pair vectors were set at 2.8 Å to represent the possible interaction distance with the receptor.

We have assumed binding to a receptor site by hydrogen bonding to accommodate compounds 1, 25, and 26, which lack a directly comparable position of the heteroatoms. These were matched to the heteroatoms of pergolide using the hydrogen in R for compound 1 and the lone pairs on the nitrogen 1 (see Fig. 2) for the compounds 25-26. The superimposition for 25RR and 26RR obtained is shown in Fig. 4, with the vector directionality of N-H bonds.

All the rigid compounds superimposed to pergolide share the same directions for the lone pairs of nitrogen. In the case of the more flexible compounds 1-7 and 19, we changed the rotatable bonds C(Cycle)-N until we obtained the minimum distance from the lone pair of pergolide. The same was done for those compounds where the X-LP and X-H bonds can freely rotate; in these latter cases, two different conformations are present. According to the dummy atom (representing X-LP or X-H) chosen, the minimum distances possible between the dummy atoms of the molecules and that of the reference compound pergolide were determined and formed the basis of the correlations.

RESULTS AND DISCUSSION

The data of distances and the log K_D for the high-affinity state of the D_2 receptor taken from Ref. 14 are reported in Table 1. $D_{du\text{-}du}$, $D_{(lp\text{-}lp')X}$, and $D_{(lp\text{-}lp')N}$ are the distances between the dummy atoms, representing the directionalities of X-H bonds, X-LP, and N-LP, respectively, in the molecules and the reference compound pergolide. For both compounds 19R and 19S, there are two ways of matching the model due to the flexibility of the bond 1-2 (see Figs. 2 and 5). In Fig. 5 are shown the two possible conformations of 19S. We chose the conformations of 19R and 19S on the basis of the shorter distance between the dummy atoms of 19 and pergolide, which were also the more energetically favorable. The energetic differences with respect to the minimum found were 2.134 kcal/mole for 19R and 2.129 kcal/mole for 19S compared to 5.480 kcal/mole

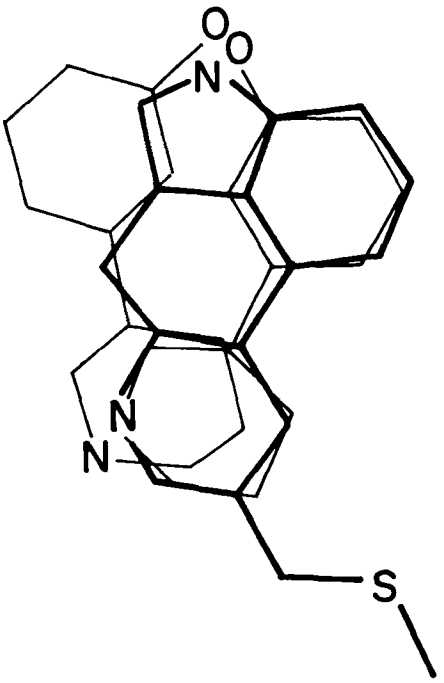


Fig. 5. Alignment of pergolide (compound 17 in bold) with two possible conformers of S-3PPP (compound 19) which allow heteroatom overlap.

TABLE I
AFFINITY DATA[a] FOR THE EXAMINED COMPOUNDS AND THE DISTANCE MEASUREMENTS AS DESCRIBED IN THE TEXT

Compound	Log K_D (10^{-5}M)	$D_{du\text{-}du}$ (Å)	$D_{(lp\text{-}lp)x}$ (Å)	$D_{(lp\text{-}lp)N}$ (Å)
1	2.93	–	–	0.34
2R	1.92	0.33	0.99	0.31
2S	3.02	0.99	0.83	1.33
3R	2.80	–	0.80	0.14
3S	2.30	–	0.86	1.07
4	1.71	–	0.84	0.38
5R	3.55	1.63	0.97	0.57
5S	1.49	0.45	1.11	0.36
6R	2.56	1.49	1.25	1.15
6S	4.13	2.60	1.27	0.19
7R	2.31	1.60	0.97	0.20
7S	1.32	0.58	1.00	0.24
8R	0.82	0.42	0.57	1.10
8S	3.69	1.64	1.33	0.21
9R	0.60	0.42	0.21	1.10
10R	1.15	0.56	1.04	1.10
11R	3.11	–	0.74	1.10
12R	5.27[b]	2.40	1.30	1.85
12S		1.50	0.40	1.38
13	1.68	0.13	0.45	0.15
14	1.46	0.09	0.11	0.04
15	1.49	0.03	0.03	0.02
16	1.74	0.04	0.09	0.02
17	0.15	0.00	0.00	0.00
18R	1.68	0.45	0.62	0.05
18S	2.95	1.31	0.95	0.17
19R	3.21	1.49	1.15	0.87
19S	2.20	0.39	1.08	0.92
20R	3.19[b]	2.13	0.55	1.05
20S		2.07	0.58	1.02
21RR	1.25[b]	1.27	1.33	1.63
21SS		0.07	1.50	1.01
22RS	2.99[b]	1.48	0.65	3.39
22SR		1.56	1.08	3.25
23RR	3.54[b]	0.21	1.91	1.19
23SS		1.53	1.08	1.00
24RR	5.23[b]	2.70	1.07	1.19
24SS		1.52	1.08	1.97
25RR	–	0.21	–	1.13
25SS	–	1.95	–	0.77
26RR	–	0.97	–	0.73
26SS	–	2.06	–	0.77

[a] Seeman et al. [14].
[b] Affinity data for the mixture of enantiomers.

and 4.942 kcal/mole for the conformers with longer distances between the dummy atoms of 19R and 19S, respectively, and the reference compound 17. We emphasize that these dual conformational properties of 19R and 19S may provide an explanation for the very interesting pharmacological behavior of 19S, which is an agonist for the autoreceptors and an antagonist for the postsynaptic receptors [26].

From the data in Table 1, only the nitrogen vectors N-LP are a common feature, while the compounds 1, 3, 4, and 11 do not have the possibility of reacting as a donor of a hydrogen bond to the receptor. From this point of view for the OMe derivatives 3, 4, and 11, there could be an electrostatic interaction at distance greater than the 2.8 Å between a hydrogen of OMe and a negative center of the receptor, considering that the hydrogen in a system O-C-H is partially charged positive. The existence of rather weak hydrogen bonding of this type O-C-H ...X, where X is an electron negative atom, was proposed in the past [27] for explaining the shorter distance observed for H...O, 2.3 Å, of this type with respect to the calculated 2.6 Å for van der Waals contact. Very surprisingly, the two methylated enantiomers 3R and 3S show an inversion of affinity with respect to the aminoindanes 2R and 2S in spite of the same substitution on the phenyl ring; in the case of 6R and 6S the inversion of affinity, with respect to the two other 2-aminotetralins, is due to the different aromatic substitution as noticed previously [13]. The compounds recently reported to have dopaminergic activity [28], 25 and 26, which do not have a heteroatom in the usual position for acting as acceptor in the postulated hydrogen bond with the receptor, could act as donors with different directions (see Fig. 4).

We performed a regression analysis of log K_D, with respect to $D_{du\text{-}du'}$ and $D_{lp\text{-}lp'}$, and we found a better linear correlation between log K_D and $D_{du\text{-}du}$ ($R = 0.717$, $S = 0.552$, $n = 21$) than between log K_D and $D_{lp\text{-}lp}$ ($R = 0.360$, $S = 0.608$, $n = 26$). In these statistical analyses, we considered only the compounds whose dissociation constants are known for the resolved enantiomers. No correlation was observed for $D_{(lp\text{-}lp')N}$, but the data in Fig. 2 suggest a range of optimal distance values of 0–1.3 Å for binding affinity. The combination of the distances $D_{du\text{-}du}$ and $D_{(lp\text{-}lp)N}$ may be considered one of the criteria for the three-dimensional structure-activity relationship in dopaminergic compounds binding to the D_2 receptor.

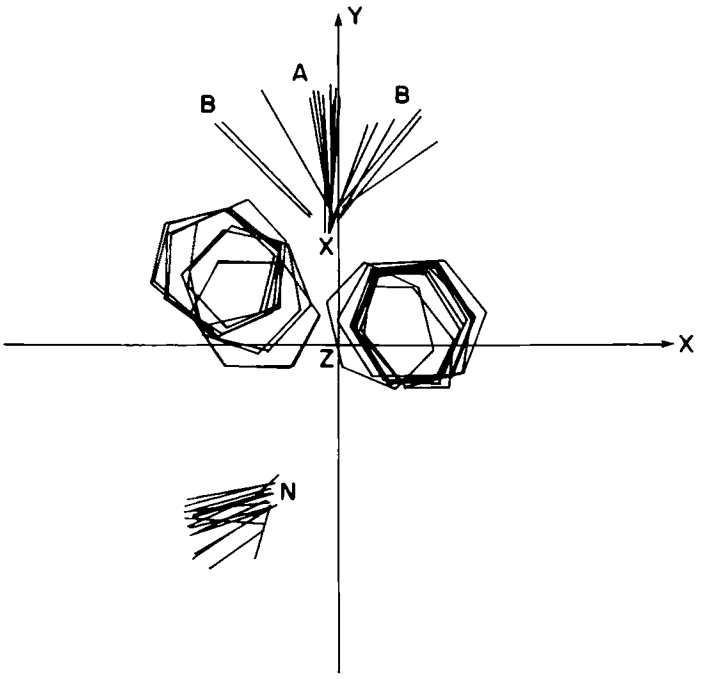
The data obtained from this model strongly support the hypothesis that the unsubstituted heteroatoms should serve as a donor in the hydrogen bond formation to the receptor for dopaminergic activity. The energies of the conformations used in the model E_{conf}, the energies of the respective global minima found, E_{min}, and the difference, $E_{conf} - E_{min}$, for the compounds showing flexibility for the atom matching the model are reported in Table 2. The E_{conf} are not energetically far from the minima calculated. In Fig. 6, we show the N-LP and X-Du vectors for the compounds with affinity data for both the enantiomers, as well as the phenyls of the aromatic moieties present in the molecules. Compounds 25-26 which 'see' the active site in a different orientation are excluded from this figure. Upon analyzing the different orientations of the X-Du vectors, a separation from active and inactive enantiomers is evident. As shown in Table 1, for each pair of separated enantiomers, the distance $D_{du\text{-}du'}$ is less in the enantiomer showing higher affinity and dopaminergic activity in vivo.

In the list of Table 1, there is a series of compounds whose affinity data are not known for the separated enantiomers, while some have the dopaminergic activity in vivo reported for the optically pure compounds [13]. The compounds 12R, 12S, and 24RR, 24SS are practically devoid of dopaminergic activity, but our model correlation for the two isomers 12S and 24SS would predict

TABLE 2
CONFORMATIONAL ENERGIES OF THE NONRIGID COMPOUNDS IN THE CONFORMATION MATCHING THE MODEL AND THE ENERGETIC MINIMA FOUND AS EXPLAINED IN THE METHODS SECTION

Compound	E_{conf} (kcal/mol)	E_{min} (kcal/mol)	$E_{conf} - E_{min}$ (kcal/mol)
1	5.058	2.665	2.393
2R	7.228	3.101	4.127
2S	3.764	2.911	0.853
3R	4.782	2.395	2.387
3S	6.292	2.695	3.597
4	6.926	2.980	3.946
5R	−2.374	−2.889	0.515
5S	1.012	−1.561	2.573
6R	−0.451	−3.143	2.692
6S	0.355	−2.929	1.284
7R	1.681	−1.285	2.966
7S	3.845	−1.088	4.933
8R	3.912	1.099	2.818
8S	4.674	1.932	2.742
9R	3.664	−0.169	3.833
10R	2.856	0.729	2.132
11R	1.034	0.759	0.275
12R	0.763	0.624	0.139
12S	2.115	0.175	2.040
19R	−3.092	−5.216	2.124
19S	−3.208	−5.144	1.936
20R	11.091	9.801	1.240
20S	7.620	5.312	2.308
21RR	2.559	1.541	1.018
21SS	0.183	−1.459	1.692
22RS	1.266	−1.693	2.959
22SR	11.856	8.615	3.241
23RR	−4.314	−5.792	1.378
23SS	4.614	1.479	3.135
24RR	3.597	−1.418	5.015
24SS	6.358	2.064	4.294

weak activity. We assume steric hindrance at the receptor site as previously postulated [11,12] for these compounds to rationalize their lack of activity. In the case of the enantiomers of *trans* 21 and *cis* 22, it is possible to anticipate, without invoking steric effects, no activity for the *cis* isomer on the basis of the large deviation of $D_{(lp\text{-}lp^{\circ})N}$ from that found in the active compounds, while for the *trans* enantiomers the activity should be retained in the 21SS. This has been reported for the resolved N-substituted n-propyl analogs of these structures [13]. The model also predicts for the compounds 25 and 26, which were not considered in the work of Seeman et al. [14]; the most active compounds expected are 25RR and 26RR as recently reported [28]. We do not know if the enantiomers of 23 have been resolved so far, but the higher affinity should reside in the compound



XA= Vectors X-Du for compounds with high affinity
XB= Vectors X-Du for compounds with low affinity

Fig. 6. Composite diagram showing alignment of nitrogen lone pair vectors and aromatic rings with high affinity heteroatom lone pair vectors (XA) and low affinity heteroatom vectors (XB).

23RR. In the case of 20R and 20S, the values of $D_{du\text{-}du}$ suggest low affinities for both for the D_2 receptor. These compounds are specifically active on the D_1 receptor, with 20R the most active compound of the enantiomers [8]. The requirements for D_1 activities could be due to slightly different orientations of N-LP and X-H for a best binding to the D_1 receptor. The distances for these latter compounds were taken from the conformation that geometrically had the best match with the proposed model.

CONCLUSIONS

In Fig. 7, we propose a general pharmacophore model for attaining D_2 dopaminergic activity from the data obtained. The most important part of the pharmacophore is N and X, which are the only pharmacophore moieties in compound 18R, which is known as the most specific for the D_2 receptor. Compound 18R has been demonstrated to be only a weak agonist of histamine H_2 receptor [28]. The corresponding inferred receptor binding points, drawn as balls, in Fig. 6, for hydrogen bonds and the corresponding vector directionalities could be considered important geometrical requirements for predicting dopaminergic activity; at the same time, we cannot exclude com-

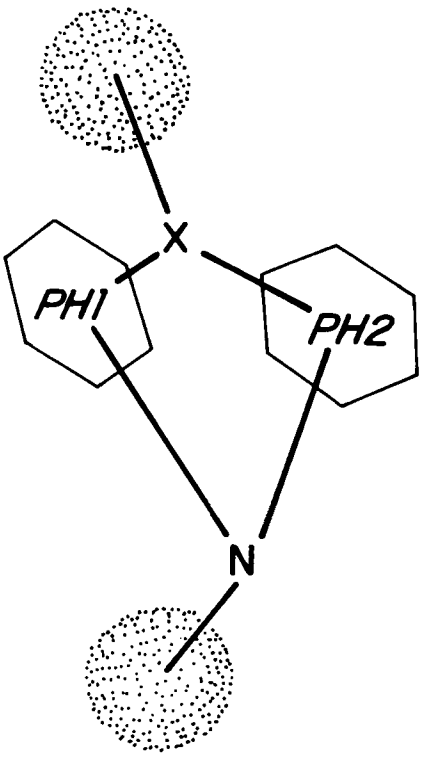


Fig. 7. Schematic presentation of pharmacophore model suggested by this study. PH1 and PH2 are postulated aromatic binding sites. Spheres are receptor sites interacting with critical heteroatoms.

pletely that X may be acting both as donor and acceptor in the hydrogen bond to the receptor. It is not established if the nitrogen interacts with the receptor in its protonated form or not, but in the unprotonated form, the vectorial direction of the lone pair would be a more important feature to be considered for binding to the receptor, which could trigger the pharmacological response.

The minimal requirements to bind fruitfully to the dopaminergic receptor is the N, when substituted with *n*-propyl and the unsubstituted phenyl ring, of Fig. 7, as is observed for compound 1 [29]. This corresponds to the recently proposed common structural pharmacophore model for the reported drugs [30] that are active in different pharmacological systems of the CNS, but which lacks specificity for the dopaminergic system. The PH1 position (see Fig. 7) of the phenyl group in the active compounds, even if they lie in the quasi same plane, may not be perfectly superimposable, as is seen in the left side of Fig. 6, suggesting possible accommodation for this structural moiety inside the receptor pocket. This could also explain the inversion of affinity of enantiomer 3S, with respect to 3R, in fact, as the compound 3S does not have the possibility of a strong hydrogen bond with the receptor and may bind by PH1 phenyl stacking interaction [31] with the receptor. The phenyl PH2 of Fig. 7 is present in the active ergoline compounds and may be considered a secondary binding site not sufficient for dopaminergic activity, but its importance for binding to the D_2 receptor could be better understood by the synthesis of new molecules containing this structural moiety. It should be recognized that many alternative models may be as consistent in

rationalizing the pharmacological data. Prediction and synthesis of new compounds should allow refinement or rejection of this model, whichever proves necessary.

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