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# A Three Dimensional Receptor Model of the Dopamine D2 Receptor from Computer Graphic Analyses of D2 Agonists

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**Abstract**—Four potent D2 agonists were employed to define a primary pharmacophore for the D2 receptor. Hypothetical receptor points, representing interaction points on a receptor were built on to each molecule. These points and the nitrogen atom were averaged to give the coordinates (Å) of the primary pharmacophore: R1 (0·00, 3·50, 0·00), R2 (0·00, -3·50, 0·00), R3 (5·79, 2·06, 0·00), and nitrogen (5·13, -0·63, 0·37). Eight structural classes of D2 agonists were then superimposed on to the primary pharmacophore to aid in the location of secondary binding sites. The secondary sites include two lipophilic clefts, an area of steric bulk, a region to hydrogen bond 'meta' hydroxy groups and a 'critical region' accepting methoxy and halogen substituents but not hydroxy substituents. The model has the potential to design and predict activity of novel D2 agonist compounds.

Research into the development of dopamine (DA) agonists has been prompted by the need for agents of low toxicity and high stability, whilst retaining clinical potency for the treatment of neurological and endocrinological disorders such as Parkinson's disease, schizophrenia, acromegaly and hyperprolactinaemia (Meltzer 1980; Schachter et al 1980; Stoof & Kebabian 1984; Seeman & Grigordiadis 1987). Two central dopamine receptors (D1 and D2) have been characterized, with the D2 subtype being particularly implicated in motor and endocrinological diseases (Stoof & Kebabian 1984; Seeman & Grigoriadis 1987). In recent years, several structure-activity relationship (SAR) studies have focused on DA agonists in attempts to define the molecular requirements essential for dopaminergic activity (Cannon 1985). Although a number of receptor models have been proposed, these have often been limited by the methods used to relate chemical structure to pharmacological activity. McDermed presented a receptor model from investigations into a series of 2-aminotetralins: binding sites for "meta" hydroxy and nitrogen (N) atoms, and a region of steric hindrance were hypothesized (McDermed et al 1979). Recently, Seeman et al (1985) used Drieding stereomodels of DA agonists to develop a tetrahedral receptor model, which contained two sites for agonist attachment and a series of steric obstacles to account for the activity of several structural classes of DA agonists. Liljefors & Wikstrom (1986) developed McDermed's model in their attempt to characterize the molecular requirements for centrally acting presynaptic DA agonists of the phenylpiperidine series. A shortcoming of such topographical DA receptor models is that they have generally not attempted to cover every class of DA agonist (for review see, Katerinopoulos & Schuster 1987).

From computer graphic analyses of centrally acting drugs, Lloyd & Andrews (1986) recently proposed a common structural model for drug action which consisted of two aromatic "receptor points", a N atom and a N "receptor point". The relative location of secondary binding groups determined pharmacological specificity and these could be mapped topographically to define the molecular requirements for individual receptor classes. In this present study, we have adopted similar techniques to examine the topographies of a number of potent, relatively conformationally rigid D2 agonists and have developed a primary pharmacophore and secondary binding sites of a receptor model for these compounds.

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## Methods

Molecular choice was based on the availability of atomic coordinates and pharmacological data indicating high potency, while compounds of low potency were chosen as either inactive stereoisomers or as compounds with minor substituent changes resulting in very low D2 agonist activity. Data from radioligand binding studies cited in Table 1 were employed as a guide to the potency of each compound for the D2 binding site (Seeman et al 1986; de Vries & Beart 1986; Beart et al 1987). In addition, data for compounds listed in Table 1 as being inactive, were taken from the review by Cannon (1985). The molecules R-(−)-*N*-n-propylnorapomorphine (8), LY 171555 (14), pergolide (16) and 2*S*-5-hydroxy-2-(di-n-propylamino)tetralin (18) were employed to define the primary D2 pharmacophore. These compounds had high affinity for the D2 receptor labelled by [$^3$H]spiperone: $K_H$ values were in the range 0·4–8·4 nM relative to a value of 4·9 nM for DA (de Vries & Beart 1986; Seeman et al 1986; Beart et al 1987). Many of the more potent compounds in Table 1 have been shown to give 'GTP-shifts' in the presence of guanosine-5′-triphosphate, consistent with them being agonists at a D2 receptor coupled to a guanine nucleotide regulatory protein (de Vries & Beart 1986; Seeman & Grigoriadis 1987).

A simple classical potential energy calculation procedure was used to find all low energy conformations for each molecule by varying up to three torsion angles labelled in Fig. 1 at a time. Potential energies were calculated at intervals of 15° for each variable with refinements at 1° intervals. These calculations pairwise sum the van der Waals interactions between non-bonded atoms (Andrews et al 1985). This method, however, holds molecular geometries rigid and tends to overestimate molecular energies. Because of these limitations, all thermally accessible conformations

within 5 kcal $mol^{-1}$ (21 kJ $mol^{-1}$) of the global minimum conformation were accepted. Molecular display, manipulation and superimposition were carried out using the computer graphics system 'MORPHEUS' at the Victorian College of Pharmacy Ltd., Parkville, Australia (Andrews & Lloyd 1982).

Molecular geometries were obtained from X-ray crystal data or from crystal data of related compounds (see Table 1), to which extra groups were constructed using standard bond lengths and angles (Sutton 1958, 1965). The crystal structures of the semirigid molecules *R*-(−)-apomorphine (6), LY 171555 (14) and the backbone structure employed to construct pergolide (16) were considered to be their biologically active conformations. For each molecule, dummy atoms or receptor points R1 and R2 were built 3·5Å above and below the centre of a phenyl ring as origin, and in the case of the ergolines (16 and lergotrile, 17), above and below a point midway between atoms C15 and C2, and for the tricyclic partial ergolines (14 and LY 156525, 15), between atoms N1 and C3 to represent hydrophobic bonding to a receptor. A point R3 was placed 2·8Å tetrahedrally from N atoms to represent a hydrogen bond to an electronegative atom on a receptor (Lloyd & Andrews, 1986). Compound 18 was fitted to the dummy atoms R1, R2, R3 and N for each of the three semirigid molecules 8, 14 and 16 by varying the torsion angle $\tau$(C1, C2, N, R3). The three torsion angles calculated for $\tau$(C1, C2, N, R3) were averaged to give the final conformation chosen for 18. The tetralin inversion angle ($\phi$) is defined by equation 1 which is used to describe the conformation of the non-aromatic ring in the 2-aminotetralin series (Johansson et al 1987). A $\phi$ value of 180° for (2R)-2-aminotetralin and 0° for (2S)-2-aminotetralin correspond to half chair conformations with pseudoequatorial amino groups. The parameter $\phi$ is usually calculated using equation 1 with $\tau_{obsd}$ being the

$$\phi = \arccos(\tau_{obsd}/\tau_{max}) \quad (1)$$

observed value for the torsion angle $\tau$(C1, C2, C3, C4) and $\tau_{max}$ is the maximal value (64·73) for this torsion angle. In cases where this equation is not applicable, the $\phi$ angle is estimated from the relevant unsubstituted 2-aminotetralin conformation.

Using the dummy atoms R1, R2, R3 and N, the molecules 8, 14, 16 and 18 were superimposed using these points as guides to minimize the root mean square (RMS) of the distances between these points and the corresponding points on the other atom. The points R1, R2, R3, N and 'meta' oxygen were averaged to give the coordinates (in Å) of the primary pharmacophore and used for subsequent superimpositions. Three calculations were then performed on each compound. The first calculation gave the energy in kcal $mol^{-1}$ above the global minimum conformation. The second calculated the root mean square distance between the points R1, R2, R3 and the N atom to the corresponding points on the test compound, and where relevant the 'meta' oxygen was included to give a five point comparison. The third calculation, employed the programme 'OVALAP' to determine the percentage molecular overlap volume of representative compounds from each drug class with 8 (Hughes & Andrews 1986).

## Results

*Basic pharmacophore for D2 agonist receptor interactions*

Compounds 8, 14, 16 and 18 were used to define the coordinates of the receptor points R1, R2, R3 and the position of N and 'meta' oxygen. Much debate has been generated as to how the ergoline series of drugs should be superimposed on to the structure of 8. Camerman et al (1979) and Cannon (1979) suggested that the A ring of pergolide coincided with the dihydroxy (A) ring of apomorphine. This superimposition would lead to the 'pyrrole' ring being placed in a region that has been demonstrated to be unfavourable to bulky groups (Freeman & McDermed 1981). In yet another superimposition, Camerman & Camerman (1981) placed the A ring of the ergoline structure close to the C ring of apomorphine. In this view, the 'pyrrole' N of the ergoline is isosteric with the important 11 hydroxy atom of 8. The weakly acidic pyrrole N of the ergoline could therefore accept/donate a hydrogen bond with the same group on the

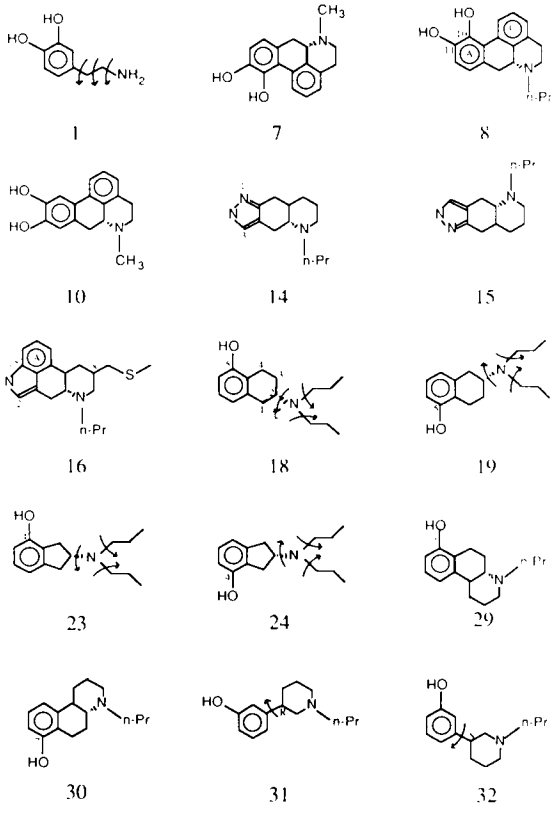


FIG. 1. Representative compounds from each of the eight drug classes examined in this study: dopamine (1), *S*(+)-apomorphine (7), *R*-(-)-*N*-n-propylnorapomorphine (8), isoapomorphine (10), LY 171555 (14), LY 156525 (15), pergolide (16), 2*S*-5-hydroxy-2-(di-n-propylamino)tetralin (18), 2*R*-5-hydroxy-2-(di-n-propylamino) tetralin (19), 2*R*-4-hydroxy-2-(di-n-propylamino)indan (23), 2*S*-4-hydroxy-2-(di-n-propylamino)indan (24), 4a*S*,10b*S*-7-hydroxy-4-n-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (29), 4aR,10b*R*-7-hydroxy-4-n-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (30), *R*(+)-3-(3-hydroxyphenyl)-*N*-n-propylpiperidine (31) and S(-)-3-(3-hydroxyphenyl-*N*-n-propylpiperidine (32). Torsion angles varied throughout this study have been indicated with arrows.

receptor as the 11-hydroxy of apomorphine. This interpretation does not, however, explain the high potency of 13-hydroxy-lergotrile. Nichols (1976) employed a superimposition in which the pyrrole ring of the ergolines was placed on to the dihydroxy ring of apomorphine. In this orientation the 13-hydroxy derivatives of the ergolines could interact with the same group on the receptor as the 'meta' oxygen defined in our primary pharmacophore. We have adopted the superimposition suggested by Nichols (1976) for the ergoline structures and have assumed that the pyrazole ring of the tricyclic ergoline partial structures is bioisosteric with the dihydroxy (A) ring of apomorphine. The 'pyrazole' ring of the tricyclic ergoline partial structure 14 was assumed to be isosteric with the dihydroxy (A) ring of 8.

The conformation of 18 employed was determined by potential energy calculations after varying the three torsion angles shown in Fig 1. Compound 18 was fitted to each of the three semirigid molecules 8, 14 and 16 by altering the torsion angle $\tau$(C1, C2, N, R3) and plotting energy versus distance to the receptor points R1, R2, R3 and N. A related aminotetralin derivative (1R, 2S-UH-242: 1R, 2S-5-hydroxy-1-methyl-2-(di-n-propylamino)tetralin) was ultimately employed for the backbone structure of 18. By way of example, the energy/distance plot to 8 is shown in Fig 2. This average torsion angle $\tau$(C1, C2, N, R3) for the three 'best fit' conformations of 61° with a $\phi$ angle around 15° corresponded closely to the "D2-receptor agonistic conformation" defined by Johansson et al (1986, 1987). This conformation corresponds closely to the crystal structure of 18 (inversion angle 10°), and D2 receptor agonism in a series of aminotetralins has been shown to be critically dependent on a $\phi$ angle around 0° and a torsion angle $\tau$(C1, C2, N, R3) around 60° (Johansson et al 1986, 1987).

The coordinates of the receptor points R1, R2 and R3, and the N atom were averaged to give the primary D2 agonist drug-receptor model: R1 (0·00, 3·50, 0·00), R2 (0·00, -3·50, 0·00), R3 (5·79, 2·06, 0·00), and N (5·13, -0·63, 0·37). The distances from N to 'meta' oxygen and the centre of the aromatic rings were 6·53Å and 5·18Å, respectively. The angles R1-origin-N and origin-N-R3 were 97·0° and 96·1°, respectively and the dihedral angle R1-origin-N-R3 was -8·5°. The position of 'meta' oxygen was determined from the coordinates of the hydroxyl oxygen for molecules 11-hydroxy-*R*-(−)-*N*-n-propylnorapomorphine (11), 18 and

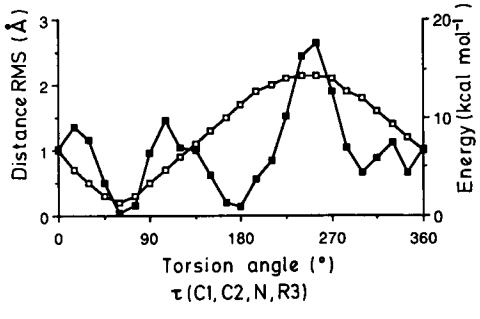


FIG. 2. Plot of potential energy (■) and RMS distance (□) versus the torsion angle $\tau$(C1, C2, N, R3) for 18 to the receptor points R1, R2, R3 and N of compound 8. The best fit and lowest energy conformation occur at a $\tau$ angle around 60°.

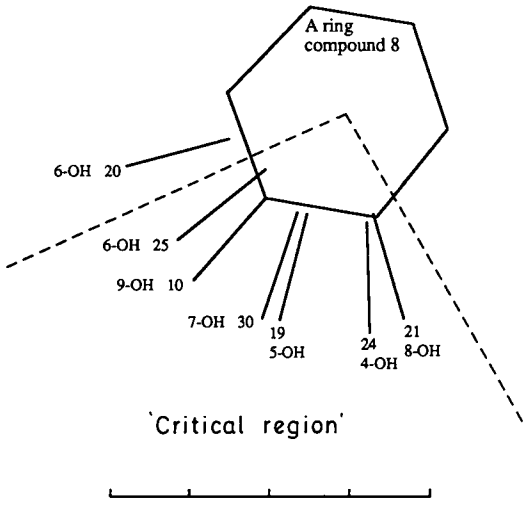


FIG. 3. Diagramatic representation of the 'critical region' (within dashed lines) which encompasses the hydroxyl groups of compounds 25 (6-OH), 10 (9-OH), 30 (7-OH), 19 (5-OH), 24 (4-OH) and 21 (8-OH). For reference purposes the A ring of 8 and the carbon oxygen bonds for each molecule are shown. The hydroxyl groups of the D2 agonist 20 do not fall within the 'critical region'. Each division on the scale bar represents 1 Å.

4aS,10b*S*-7-hydroxy-4-n-propyl-1,2,3,4,4a,5,6, 10b-octahydrobenzo[f]quinoline (29): 'meta' oxygen (0·99, 0·00, 2·57 Å).

*Secondary binding requirements*

A 'critical region' has been introduced to explain the low affinities of isoapomorphine (10), 2*R*-5-hydroxy-2-(di-n-propylamino)tetralin (19), 2*S*-8-hydroxy-2-(di-n-propylamino)tetralin (21), 2*S*-4-hydroxy-2-(di-n-propylamino)indan (24), 5,6-dihydroxy-2-(di-n-propylamino)indan (25) and 4a*R*,10b*R*-7-hydroxy-4-n-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (30). This region is located in the C9-C8 region of 8 and encompasses the hydroxy groups of 19, 21, 24, 30 and the C9 and C6 hydroxy groups of 10 and 25, respectively (Fig. 3). A hydroxyl group residing within this 'critical region' is proposed to result in a dramatic loss of activity. The proposed 'critical region' would not include the hydroxyl groups of 2*R*-6,7-dihydroxy-2-(di-n-propylamino)tetralin (20).

A cleft in the receptor that could accommodate optimally an n-propyl group in the 'downwards' direction (Fig. 4a, cf. Liljefors & Wikstrom 1986), would be sufficient to explain the activity of the listed compounds in Table 1. *N*-n-Propyl substituents were constructed employing low energy gauche conformations. Numerous SAR studies have established that the most active members of a series of dopaminergic agonists bear one or more n-propyl groups on the N atom (Goldman & Kebabian 1984).

Another secondary binding site for D2 agonist interaction is likely to involve a lipophilic cleft 'upwards' of the N atom capable of accommodating large substituents such as the thienyl moiety of 2-(*N*-n-propyl-*N*-2-thienylethylamino)-5-hydroxytetralin (22), which has been described as the most potent D2 agonist to date (Beaulieu et al 1984, Beart et al 1987). The proposed lipophilic region extends back to the 'meta' oxygen site to accommodate the C ring of the

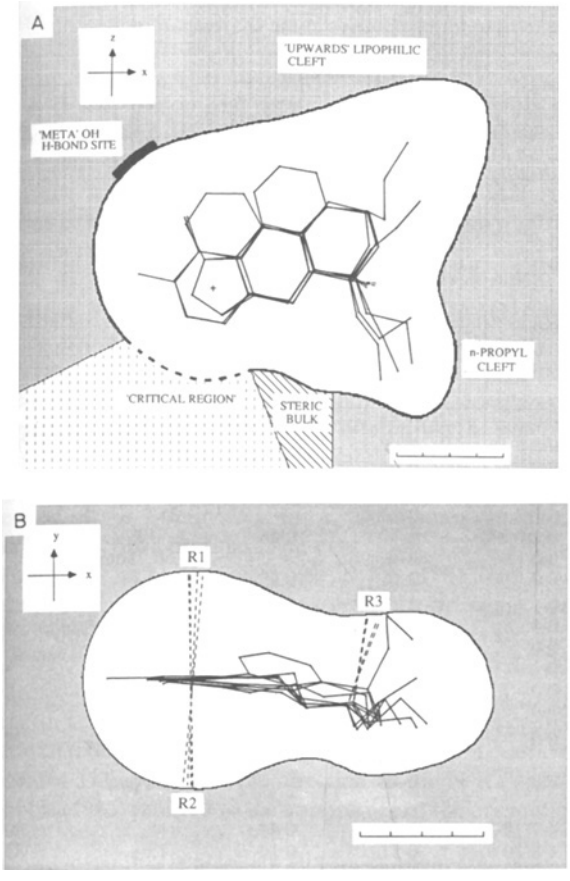


FIG. 4(a) Superimposition of compounds 8, 14, 16 and 18 in their best fit low energy conformations to the D2 primary pharmacophore. The secondary binding sites of the receptor model are shown viewed down the y-axis. For clarity, hydrogen atoms have been deleted. The N-R3 vector (dashed lines) points into the plane of the page. Each division on the scale bar represents 1 Å. (+)=origin. (b) Receptor model viewed down the z-axis showing compounds 8, 14, 16 and 18 in their best fit low energy conformations to the D2 primary pharmacophore. The hydrophobic receptor points R1 and R2 and, the hydrophobic receptor point R3 are detailed. Dashed lines indicate R1–R2 and N-R3 "bonds". Each division on the scale bar represents 1 Å.

aporphines and the A ring of the ergolines. In addition, substituents in the C8 position on the ergoline molecules also extend into this cleft.

The inactivity of *S*-(+)-apomorphine (7) and the low potency of 15 may be accounted for by the introduction of a region of steric bulk into the receptor model between the 'critical region' described above and the 'downward' *N*-propyl cleft. The A ring of 7 would interact with this inaccessible region of the receptor, resulting in a loss of activity. The low potency of 15 may be in part due to an interaction with this region of steric bulk or to the position of atom N1 which is directed into the 'critical region'.

*Miscellaneous SAR considerations*

Both isomers of 3-(3-hydroxyphenyl)-*N*-n-propylpiperidine (3-PPP, 31 and 32) fit our model exceedingly well, however, optimal fit is achieved with high energy conformations (at least 4·5 kcal $mol^{-1}$ (19 kJ $mol^{-1}$) above the global minimum conformation, see Table 1). This observation correlates with the observed low potency of these compounds for the D2 binding site (George et al 1985). The lower potency of 31 may be the result of the suboptimal fit of the 3-hydroxy substituent to the 'meta' oxygen site (Table 1).

Recent studies has provided new insights into *N*-alkyl substitution in the downwards direction. Although initial evidence indicated that di-*N*-n-butyl derivatives were inactive (e.g. *N,N*-dibutyldopamine, (3) and *R*-(−)-*N*-n-butyl apomorphine, (9)), the *N*-n-butyl and *N*-*β*-phenethyl derivative of 31 whose *N*-substituents are directed into the N-propyl cleft, retain activity (Wikstrom et al 1984). Liljefors & Wikstrom (1986) demonstrated that the n-butyl group could adopt a folded conformation which could then be accommodated by the propyl cleft, but clearly the larger phenethyl substituent is too bulky to be accommodated by this site. We investigated whether an alternative explanation for this paradoxical activity might be that the derivatives of 31 undergo an *N*-inversion which would place the large substituents in a position away from the propyl cleft. Indeed, the potential energy difference between the crystal conformation of 31 and the best fit of its *N*-invertomer (33) to the receptor model is only 2 kcal $mol^{-1}$ (8·3 kJ $mol^{-1}$), although the degree of fit is reduced (RMS 0·79Å, see Table 1). More importantly, the large *N*-alkyl substituents would be placed into the upward lipophilic cleft and the oxygen atom is placed in a more favourable position; RMS 0·76 (5 point comparison).

In addition to the structures chosen to describe the primary and secondary pharmacophores, we have also examined potent D2 agonists from the phenylethylamine and aminoindan drug classes. For example, 2*R*-4-hydroxy-2-(di-n-propylamino)indan (23), dopamine (1), *N,N*-dipropyl dopamine (2) fit the model well (RMS 0·37, 0·27 and 0·3, respectively). The 2-aminoindan structure can adopt either an *N*-axial or an *N*-equatorial conformation. In this study we have employed the lower energy *N*-equatorial conformer which corresponds to the D2 active conformation predicted previously (Cannon et al 1982; Wikstrom et al 1987).

## Discussion

We have employed a computer graphics approach with energy, degree of fit and overlap procedures to develop a D2 agonist receptor model comprising of a primary pharmacophore and secondary binding sites. For D2 selectivity a compound must not only 'fit' the primary pharmacophore, but its secondary binding groups should also be in favourable locations. This model (Fig. 4a, b) describes all of the features outlined above for the compounds listed in Table 1.

Most receptor models for DA agonists have generally not attempted to cover every structural class of DA agonist. Our model has not discussed octahydrobenzo[g]quinolines (Cannon 1985), yet from observations using Dreiding molecular models these compounds (employing the same stereochemistry and substituents as *R*-apomorphine) would fit the model exceedingly well. In addition, we have not taken into account extremely 'floppy' molecules (e.g. indoleethylamine derivatives) where conformational freedom produces weaker receptor binding because of the cost in entropy (Andrews et

Table 1. The potential energy, degree of fit, receptor affinity and percentage overlap for compounds at the D2 receptor model

| Compound | Energy[a] | Distance[b] | Distance[c] | Potency[d] | Overlap[e] |
|---|---|---|---|---|---|
| 1. Dopamine | 1·6(6·7) | 0·27 | 0·31 | 4·9 | |
| 2. *N,N*-Dipropyldopamine | 2·0(8·4) | 0·30 | 0·34 | 5·4 | 78 |
| 3. *N,N*-Dibutyldopamine | 2·0(8·4) | 0·30 | 0·34 | inactive | |
| 4. Tyramine 'meta' | 1·6(6·7) | 0·27 | 0·31 | 84·3 | |
| 5. Tyramine 'para' | 1·6(6·7) | 0·27 | 0·68 | 1980 | |
| 6. *R*-(−)-Apomorphine | 0·0 | 0·17 | 0·16 | 1·2 | |
| 7. *S*-(+)-Apomorphine | 0·0 | 0·30 | — | 493 | |
| 8. *R*-(−)-*N*-n-Propylnorapomorphine | 0·0 | 0·17 | 0·16 | 0·4 | 100 |
| 9. *R*-(−)-*N*-n-Butyl-norapomorphine | 0·0 | 0·17 | 0·16 | inactive | |
| 10. Isoapomorphine | 0·0 | 0·17 | 0·89 | inactive | |
| 11. 11-Hydroxy-*R*-(−)-*N*-n-propylnorapomorphine | 0·0 | 0·17 | 0·16 | 1·4 | |
| 12. 10-Hydroxy-*R*-(−)-*N*-n-propylnorapomorphine | 0·0 | 0·17 | 0·89 | 7·3 | |
| 13. 11-Methoxy-*R*-(−)-*N*-n-propylnorapomorphine | 0·0 | 0·17 | 0·16 | 130 | |
| 14. LY 171555 | 0·0 | 0·22 | — | 8·4 | 85 |
| 15. LY 156525 | 0·0 | 0·32 | — | 89 | |
| 16. Pergolide | 0·0 | 0·11 | — | 0·43 | 71 |
| 17. Lergotrile | 0·0 | 0·11 | — | 5·5 | |
| 18. 2S-5-Hydroxy-2-(di-n-propylamino)tetralin | 0·0 | 0·16 | 0·15 | 2·9 | 74 |
| 19. 2*R*-5-Hydroxy-2-(di-n-propylamino)tetralin | 0·2(0·84) | 0·23 | — | 353 | |
| 20. 2*R*-6,7-Dihydroxy-2-(di-n-propylamino)tetralin | 0·2(0·84) | 0·23 | 0·46 | 12[f] | |
| 21. 2S-8-Hydroxy-2-(di-n-propylamino)tetralin | 0·0 | 0·16 | — | IC50 750nM | |
| 22. (±)2-(*N*-n-propyl-*N*-2-thienylethylamino)-5-hydroxytetralin | 0·0 | 0·16 | 0·15 | 0·14 | |
| 23. 2*R*-4-Hydroxy-2-(di-n-propylamino)indan | 0·0 | 0·37 | 0·49 | 8·3 | 72 |
| 24. 2*S*-4-Hydroxy-2-(di-n-propylamino)indan | 0·0 | 0·37 | — | 106 | |
| 25. 5,6-Dihydroxy-2-(di-n-propylamino)indan | 0·0 | 0·37 | 0·69 | inactive | |
| 26. 2*R*-4-Methoxy-2-di-n-propylamino)indan | 0·0 | 0·37 | 0·49 | 63 | |
| 27. 2S-4-Methoxy-2-di-n-propylamino)indan | 0·0 | 0·37 | — | 20 | |
| 28. 4,7-Dimethoxy-2-di-n-propylamino)indan | 0·0 | 0·37 | 0·49 | 5·1 | |
| 29. 4a*S*,10bS-7-Hydroxy-4-n-propyl-1,2,3,4,4a,5,6, 10b-octahydrobenzo[f]quinoline | 0·0 | 0·21 | 0·19 | g | 78 |
| 30. 4a*R*,10b*R*-7-Hydroxy-4-n-propyl-1,2,3,4,4a,5,6, 10b-octahydrobenzo[f]quinoline | 0·0 | 0·40 | — | inactive | |
| 31. *R*(+)-3-(3-Hydroxyphenyl)-*N*-n-propylpiperidine | 4·7(19·7) | 0·23 | 0·44 | 161 | 80 |
| 32. *S*(−)-3-(3-Hydroxyphenyl)-*N*-n-propylpiperidine | 4·8(20·0) | 0·11 | 0·10 | 15·8 | 82 |
| 33. *R*(+)-3-(3-Hydroxyphenyl)-*N*-n-propylpiperidine-(N-invert) | 2·0(8·4) | 0·79 | 0·76 | | |

Degree of fit, energy above the global minimum, potency and percentage overlap for dopamine agonists from eight drug classes. Molecular geometries were obtained using the following references: Anderson, J. B. (1978) Acta Crystallogr., Sect. B B34, 2344–2348; Camerman, N., Chan, L. Y. Y., Camerman, A. (1979) Mol. Pharmacol. 16: 729–736; Gentric, E., Le Borgne, G., Grandjean, D. (1978) J. Organomet. Chem. 155: 207–220; Giesecke, J. (1973) Acta Crystallogr., Sect. B B29: 1785-1791; Giesecke, J. (1977) Acta Crystallogr., Sect. B B33: 302–303; Johansson, A. M., Karlen, A., Grol, C. J., Sundell, S.,Kenne, L., Hacksell, U. (1986) Mol. Pharmacol. 30: 258–269; Thorberg, S.-O., Gawell, L., Csoregh, I., Nilsson, J. L. G. (1985) Tetrahedron 41: 129–139; Titus, R. D., Kornfeld, E. C., Jones, N. D., et al (1983) J. Med. Chem. 26: 1112–1116.

a. Energy above the global minimium conformation in kcal $mol^{-1}$ (kJ $mol^{-1}$).
b. Best fit distance measured as the root mean square (RMS) in angstroms using R1, R2, R3 and nitrogen as guide points.
c. Best fit distance (RMS) using R1, R2, R3, nitrogen and 'meta' oxygen as guide points.
d. Potency in nM from radioligand binding data (de Vries & Beart 1986 and Seeman et al 1985). Data for inactive compounds was obtained from the review by Cannon (1985).
e. Overlap expressed as a percentage of spatial overlap with 8.
f. Data for this compound is for the racemate, however, McDermed (1979) resolved the isomers and demonstrated that the *R* isomer was more active.
g. This compound was shown to be as potent as apomorphine in biochemical tests (Liljefors & Wikstrom 1986).

al 1984). Our model has attempted to explain the activity of eight different classes of D2 agonists basing our hypotheses largely on radioligand binding data.

The most favourable location of a hydroxyl group for optimal D2 activity is in the 'meta' position as defined in our primary model and deviation from this position generally leads to a reduction in activity (cf. 'meta' (4) vs 'para' tyrosine (5) and (11) vs 10-hydroxy-*R*-(−)-*N*-n-propylnorapomorphine (12)). The lack of a hydroxyl group in this region usually results in a loss of activity (Cannon 1985) and the same argument applies to methoxy derivatives such as 11-methoxy-*R*-(−)-*N*-n-propylnorapomorphine (13) and 2*R*-4-methoxy-2-di-n-propylamino)indan (26) which cannot donate a hydrogen bond. The importance of the 'meta' position is also exemplified by 14, which displays higher potency than its pyrrole isostere (Cannon 1983). The weakly acidic N1 atom of 14 is located in a position where it could donate or accept a hydrogen bond with the same group in the receptor as the 'meta' oxygen hence its appreciable affinity for the D2 receptor.

At first inspection, a region of steric bulk located in the position of the 'critical region' would be sufficient to explain the inactivity of 10, 19, 21, 24, 25, and 30, however, 2*S*-4-methoxy-2-(di-n-propylamino)indan (27) and 4,7-dimethoxy-2-(di-n-propylamino)indan (28) have methoxy groups in this region and retain reasonable affinity. This phenomenon is not unique, as Langer et al (1984) demonstrated a significantly higher affinity for the methoxy versus hydroxy

substituent in a series of tetrahydro-$\beta$-carboline derivatives at the [$^3$H]imipramine binding site on human platelets. In addition, lergotrile (17) and related ergolines have halogen atoms in this region and retain activity. Presumably the receptor will not accept a hydroxy group or an ionizable substituent, yet will allow a substituent that cannot donate a hydrogen bond. Further evaluation of compounds with various substituents on the phenyl rings is necessary to fully ascertain the nature of the 'critical region'.

Two particular points pertinent to our study are worthy of comment. Firstly, care, must be exercised in the choice of atomic coordinates for this type of study as the crystal conformation may not necessarily be the active biological conformation. Thus all combinations of low energy conformers should be considered when attempting the superimposition of one molecule on to another. This study has employed low energy conformers for each drug class and in the case of the 2-aminotetralins a "D2 agonist conformation" as described by Johansson et al (1986, 1987). Various substitutions on to the non-aromatic ring of the 2-aminotetralins often result in the ring conformation being distorted away from the ideal $\phi$ and $\tau$(C1, C2, N, R2) angles around 0 and 60°, respectively. Indeed, the compound 1*R*,2*R*-5-hydroxy-1-methyl-2-(di-n-propylamino)tetralin, a D2-receptor antagonist, is unable to adopt a D2-agonist conformation (Johansson et al 1986). Another important consideration for D2 agonism is the direction of the N-R3 vector. Nichols (1983) referred to the importance of the orientation of this vector (see also Froimowitz et al 1986) and in subsequent studies (Liljefors & Wikstrom 1986; Johansson et al 1986, 1987) the N-H or N-lone pair vectors were used in superimposition routines. Lijefors & Wikstrom (1986) proposed that the antagonist properties of 32 may be in part due to this compound adopting an alternative (lower energy) conformation in which the N-lone pair vector differs from the N-R3 vector as defined in our primary D2 receptor model. This study is in accord with Froimowitz et al (1986) who demonstrated the difference between DA agonists and antagonists lay in the difference of N-lone pair vector orientations.

The model we have presented here is in accord with the previous studies of Johansson et al (1986, 1987) and the receptor models described by Liljefors & Wikstrom (1986), and McDermed et al (1979), however, it differs slightly from the tetrahedral model presented by Seeman et al (1985). McDermed's (1979) model was developed to explain the activity of a series of 2-aminotetralins and to account for the inactivity of isoapomorphine. The three dimensional model of Seeman et al (1985) placed importance on the direction of H-bonds arising from the 'meta' oxygen and N atoms, in addition to including three steric obstacles to explain D2 activity. Liljefors & Wikstrom (1986) recently updated the McDermed model by employing molecular mechanics and computer graphics to examine a number of non-ergoline dopamine agonists, although they concentrated mainly on the requirements for presynaptic agonist activity in a series of phenylpiperidines.

*Conclusions*

Our receptor model for the D2 receptor is somewhat more global than other quantitative SAR studies in that it takes account of ergolines, 2-aminotetralins, 2-aminoindans, aporphines, phenylethylamines, partial ergoline structures, octahydrobenzo[f]quinolines and phenylpiperidines. This model with its primary pharmacophore and secondary binding site locations can be used to design novel D2 agonists and to predict whether compounds will display D2 activity.

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## References

Andrews, P. R., Carson, J. M., Caselli, A., Spark, M. J., Woods, R. (1985) Conformational analysis and active site modelling of angiotensin-converting enzyme inhibitors. J. Med. Chem. 28: 393–399

Andrews, P. R., Craik, D., Martin J. L. (1984) Functional group contributions to drug-receptor interactions. Ibid. 27: 1648–1657

Andrews, P. R., Lloyd, E.J. (1982) Molecular conformation and biological activity of central nervous system active drugs. Med. Res. Rev. 2: 355–393

Beart, P. M., Cook, C. J., Cincotta, M., de Vries, D. J., Tepper, P., Dijkstra, D., Horn, A. S. (1987) Radioreceptor binding reveals the potencies of N,N-disubstituted 2-aminotetralins as D2 dopamine agonists. N. S. Arch. Pharmacol. 336: 487–493

Beaulieu, M., Itoh, Y., Tepper, P., Horn, A. S., Kebabian, J. W. (1984) N,N-disubstituted 2-aminotetralins are potent D-2 dopamine receptor agonists. Eur. J. Pharmacol. 105: 15–21

Camerman, N., Chan, L. Y. Y., Camerman, A. (1979) Stereochemical characteristics of dopamine agonists: molecular structure of bromocryptine and structural comparisons with apomorphine. Mol. Pharmacol. 16: 729–736

Camerman, N., Camerman, A. (1981) On the stereochemistry of dopaminergic derivatives. Ibid. 19: 517–519

Cannon, J. G. (1979) Dopamine congeners derived from the benzo[f]quinoline ring, in: Imbs, J.-L., Schwartz, J., (eds) Peripheral dopaminergic receptors, Advances in the Biosciences Vol. 20 Pergamon, New York, 20: pp 87–94

Cannon, J. G. (1983) Structure-activity relationships of dopamine agonists. Ann. Rev. Pharmacol. Toxicol. 23: 103–130

Cannon, J. G. (1985) Dopamine agonists: structure-activity relationships. Prog. Drug Res. 29: 303–414

Cannon, J. G., Perez, J. A., Bhatnagar, R. K., Long, J. P., Sharabi, F. M. (1982) Conformationally restricted congeners of dopamine derived from 2-aminoindan. J. Med. Chem. 25: 1442–1446

de Vries, D. J., Beart, P. M. (1986) Role of assay conditions in determining agonist potency at D2 dopamine receptor in striatal homogenates. Mol. Brain Res. 1: 29–35

Freeman, H. S., McDermed, J. D. (1981) Interactions of chiral agonists and dopamine receptors, in: Creighton, A. M. and Turner, S. (eds) *The chemical regulation of biological mechanisms.* The proceedings of the 1st medicinal chemistry symposium, Cambridge, England, Royal Soc. of Chem. London, Spec. publication No. 42 pp 154–166

Froimowitz, M., Neumeyer, J. L., Baldessarini, R. J. (1986) A stereochemical explanation of the dopamine agonist and antagonist activity of stereoisomer pairs. J. Med. Chem. 29: 1570–1573

George, S. R, Watanabe, M., Seeman, P. (1985) Dopamine D2 receptors in brain and anterior pituitary recognize agonist and antagonist actions of (−)-3-PPP. J. Neural Transm. 64: 13–33

Goldman, M. E., Kebabian, J. W. (1984) Aporphine enantiomers. Interactions with D-1 and D-2 dopamine receptors. Mol. Pharmacol. 25: 18–23

Hughes, R. A., Andrews, P. R. (1986) Structural and conformational analogy between cholecystokinin and ergopeptines. J. Pharm. Pharmacol. 39: 339–343

Johansson, A. M., Karlen, A., Grol, C. J., Sundell, S., Kenne, L., Hacksell, U. (1986) Dopaminergic 2-aminotetralins: affinities for dopamine D2-receptors, molecular structures and conformational preferences. Mol. Pharmacol. 30: 258–269

Johansson, A. M., Nilsson, J. L. G., Karlen, A., Hacksell, U., Sanchez, D., Svensson, K., Hjorth, S., Carlsson, A., Sundell, S., Kenne, L. (1987) C1- and C3-methyl-substituted derivatives of 7-hydroxy-2-(di-n-propylamino)tetralin: activities at central dopamine receptors. J. Med. Chem. 30: 1827–1837

Katerinopoulos, H. E., Schuster, D. I. (1987) Structure-activity relationships for dopamine analogues: a review. Drugs of the Future 12: 223–253

Langer, S. Z., Lec, C. R., Segonzac, A., Tateishi, T., Esnaud, H., Schoemaker, H., Winblad, B. (1984) Possible endocrine role of the pineal gland for 6-methoxytetrahydro-$\beta$-carboline, a putative endogenous neuromodulator of the [$^3$H]imipramine recognition site. Eur. J. Pharmacol. 102: 379–380

Liljefors, T., Wikstrom, H. (1986) A molecular mechanics approach to the understanding of presynaptic selectivity for centrally acting dopamine receptor agonists of the phenylpiperidine series. J. Med. Chem. 29: 1896–1904

Lloyd, E. J., Andrews, P. R. (1986) A common structural model for central nervous system drugs and their receptors. J. Med. Chem. 29: 453–462

McDermed, J. D., Freeman, H. S., Ferris, R. M. (1979) Enantioselectivity in the binding of (+)- and (−)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene and related agonists to dopamine receptors, in: Usdin, E., Kopin, I. J. and Barchas, J. (eds) Catecholamines: Basic and clinical frontiers Vol 1. Pergamon Press, New York, pp. 568–570

Meltzer, H. Y. (1980) Relevance of dopamine autoreceptors for psychiatry: Preclinical and clinical studies. Schizophren. Bull. 6: 456–475

Nichols, D. E. (1976) Structural correlation between apomorphine and LSD: Involvement of dopamine as well as serotonin in the actions of hallucinogens. J. Theor. Biol. 59: 167–177

Nichols, D. E. (1983) The development of novel dopmine agonists, in: Kaiser, C., Kebabian, J. W. (eds) Dopamine Receptors ACS Symposium Series 224, American Chemical Society: Washington, DC, pp. 201–218

Schachter, M., Bedard, P., Debono, A. G., Jenner, P., Marsden, C. D., Price, P., Parkes, J. D., Kennan, J., Smith, B., Rosenthaler, J., Horowski, R., Dorow, R. (1980) The role of D-1 and D-2 receptors. Nature 286: 157–159.

Seeman, P., Grigoriadis, D. (1987) Dopamine receptors in brain and periphery. Neurochem. Int. 10: 1–25

Seeman, P., Watanabe, M., Grigoriadis, D., Tedesco, J. L., George, S. R., Svensson, U., Nilsson, J. L. G., Neumeyer, J. L. (1985) Dopamine D2 receptor binding sites for agonists. A Tetrahedral model. Mol. Pharmacol. 28: 391–399

Stoof, J. C., Kebabian, J. W. (1984) Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 35: 2281–2296.

Sutton, L. E. (ed.) (1958) 'Tables of interatomic distances and configurations in molecules and ions', Chemical Society special publication No. 11.

Sutton, L. E. (ed.) (1965) 'Tables of interatomic distances and configurations in molecules and ions', Chemical Society special publication No. 18.

Wikstrom, H., Lii, J.-H., Allinger, N. L. (1987) Conformational analysis of 2-aminoindans and 2-(aminomethyl)indans in relation to their central dopaminergic effects and a dynamic receptor concept. J. Med. Chem. 30: 1115–1120

Wikstrom, H., Sanchez, D., Lindberg, P., Hacksell, U., Arvidsson, L.-E., Johansson, A. M., Thorberg, S.-O., Nilsson, J. L. G., Svensson, K., Hjorth, S., Clark, D., Carlsson, A. (1984) Resolved 3-(3-hydroxyphenyl)-N-n-propylpiperidine and its analogues: central dopamine receptor activity. J. Med. Chem. 27: 1030–1036.