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Application of Comparative Molecular Field Analysis to Dopamine D_2 Partial Agonists

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Abstract—Comparative molecular field analysis (CoMFA) has been applied to novel D_2 partial agonists. Due to the predictability of the CoMFA model across different series of D_2 partial agonists, we believe these compounds are binding to the D_2 agonist receptor in the conformation and alignment described herein.

Introduction

Numerous dopamine agonists with various levels of intrinsic activity have been prepared and concomitantly used to explore the pharmacophoric and topographical requirements of the dopamine D_2 receptor.[1] Traditionally, dopamine agonists and partial agonists have been designed to access the D_2 agonist pharmacophore by tethering the vital 3-OH group and basic nitrogen in an almost coplanar arrangement, by means of the phenethyl scaffold (Fig. 1).

In our laboratories, novel compounds have been synthesized which access the D_2 agonist pharmacophore using 2-aminomethyl chromans, 3-OH-phenoxyethylamines, 3-OH-*N*[1]-phenylpiperazines, and 2-aminomethyl-3,4,7,9-tetrahydro-2*H*-pyrano[2,3-*e*]indoles and indolones.[2–5] A representative set of the aforementioned compounds was selected to develop the CoMFA analysis and their affinity and selectivity for both the high (D_2^{High}, agonist) and low (D_2^{Low}, antagonist) affinity states are listed in Table 1. All experimental D_2^{High} K_i and D_2^{Low} K_i values were obtained from the references referred to in Table 1.

Results

A crossvalidated r^2 of 0.73 for an optimum number of 4 components and a non-crossvalidated r^2 of 0.953 were determined.[11] The crossvalidated and non-crossvalidated r^2 values for a 1 component model are 0.591 and 0.762, 0.674 and 0.849 for a 2 component model, and 0.712 and 0.905 for a 3 component model. The electrostatic and steric CoMFA fields are depicted in Figures 3 and 4. Furthermore, the predicted $-\log(K_i)$ values are listed in Table 1. After the CoMFA model had been established, a test set consisting of four compounds was utilized to ascertain the predictability of the derived CoMFA model (Table 2). The test set was chosen to reflect compounds with similar molecular features as represented in the training set.

Discussion

The CoMFA electrostatic fields depicted regions surrounding the superimposed molecules where interactions with the receptor may be present. In the region around the carbonyl of the oxindole compounds, a potential hydrogen bond acceptor was evident as increased negative charge (hydrogen-bond accepting CoMFA field; Fig. 3). Furthermore, a hydrogen bond donor about the indole hydrogen was also present (hydrogen-bond donating CoMFA field; Fig. 3). Since the oxindole also contains the most potent K_i binding for the D_2 receptor (Table 1), it is expected to see hydrogen-bond accepting and donating CoMFA fields about the oxindole molecules.

Unlike the rotationally promiscuous hydroxyl group of the phenols (structures 1–3, 4, 5–7, and 10–12), indoles and indolones contain a 'fixed geometry' hydrogen bonding group due to their rigid colinear NH bond. It was no surprise to see a CoMFA field in that area suggesting a hydrogen bond donor would increase binding (hydrogen-bond donating CoMFA field, Fig. 3). The

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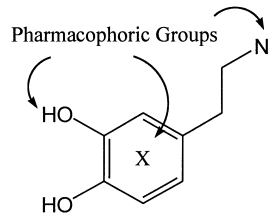


Figure 1. Dopamine pharmacophore.

directionality of the phenolic hydrogen could be established by superimposing the phenolic hydrogen on the indole and oxindole moieties (or analogues).

Finally, a hydrogen-bond donating CoMFA field centered about the protonated nitrogen is seen. Subtle conformational changes in the molecules led to subtle differences in the directionality of the lone pair nitrogens in the aligned molecules. Therefore, a CoMFA field close

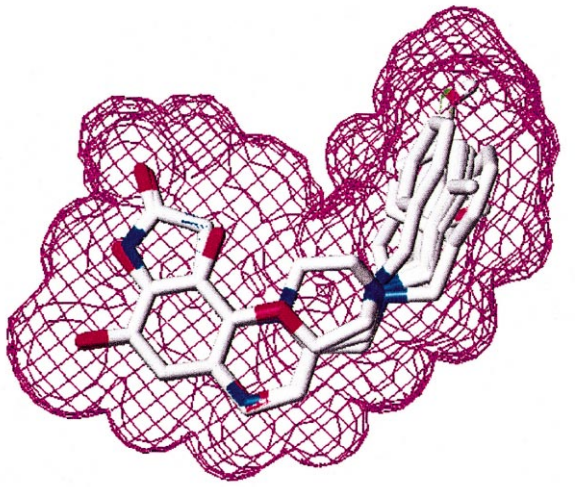
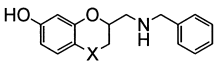
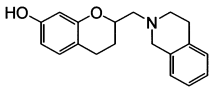
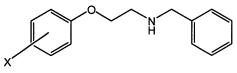
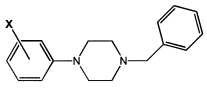
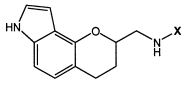
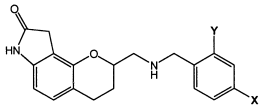


Figure 2. Alignment of training set molecules used in CoMFA study.

Table 1. D_2 partial agonists used in the training set



Compound	D_2^{High} K_i (nM),(exp)	$-\log(D_2^{High}K_i)$ (nM),(exp)	$-\log(D_2^{High}$ $K_i)$ (nM),(pred)	D_2^{Low} K_i (nM),(exp)
1 X = CH_2(R)-(−)[4]	0.16 ± 0.1	9.80	9.498	3.3 ± 0.8
2 X = O(S)-(−)[4]	0.35 ± 0.2	9.46	9.702	4.8 ± 3.7
3 X = NH[4]	6.7 ± 0.6	8.17	8.405	130 ± 0.0
				
4 [6]	0.63	9.2	9.018	3.16
				
5 X = 4-OH[3]	113	6.95	6.928	Not tested
6 X = 3-OH[3]	3.55	8.44	8.362	115.07
7 X = 2-OH[3]	9.58	8.02	7.696	191.07
8 X = H[3]	68.38	7.16	7.603	240.56
9 X = 3-NH_2[3]	237	6.63	6.585	Not tested
				
10 X = 2-OH[3]	64.70	7.19	7.480	1176
11 X = 3-OH[3]	5.5	8.26	8.237	95.1
12 X = 4-OH[3]	120	6.92	6.894	Not tested
13 X = H[3]	16.2	7.79	7.550	124
				
14 X = Bn(R)-(−)[5]	1.9 ± 0.8	8.72	8.919	35.9 ± 4.7
15 X = n-Pr[5]	40.1 ± 10.4	7.38	7.308	468 ± 20
				
16 X = H,Y = H(RS)-(±)[5]	0.37 ± 0.05	9.43	9.290	12.0 ± 0.9
17 X = OMe,Y = H[5]	0.43 ± 0.06	9.36	9.453	23.1 ± 2.7
18 X = Me,Y = H[5]	0.23 ± 0.02	9.63	9.262	8.1 ± 1.3
19 X = F,Y = H[5]	0.41 ± 0.05	9.38	9.566	24.3 ± 1.4
20 X = Me,Y = Me[5]	1.3 ± 0.17	8.88	9.023	30.7

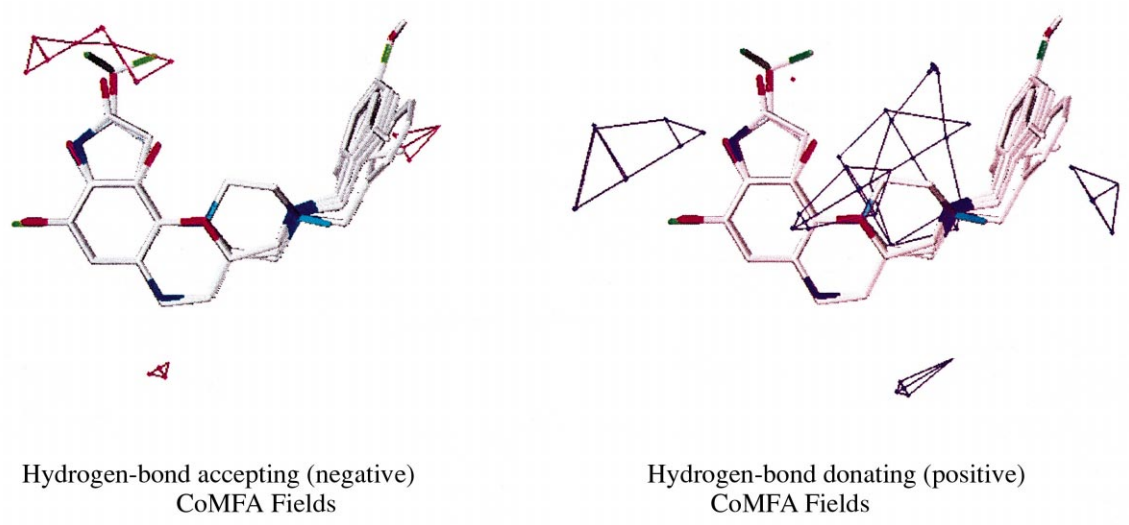


Figure 3. Electrostatic CoMFA results.

to the basic nitrogen is observed. The basic nitrogen is protonated at physiological pH for all of the molecules.

The steric CoMFA fields are depicted in Figure 4. Since the alignment was based on a 3 point pharmacophore (centroid of aromatic ring, basic nitrogen and carbon at the 3-OH position or indole hydrogen), the resulting alignment of the side chain on the basic nitrogen depended on the conformation of the molecules. In the case of the aryloxyethylamines, the conformation of the side chain was quite different than the arylpiperazines and angular indoles and oxindoles. Since the experimental binding data for the aryloxyethylamines was not optimal, the corresponding steric CoMFA field depicted this region as unfavorable (Disfavorable Steric CoMFA Field; Fig. 4). On the other hand, the resulting conformations of both the arylpiperazines and angular indoles and oxindoles were in a similar region in space. These molecules had more favorable D_2 binding in contrast to the aryloxyethylamines. Hence, this region was considered to be favorable (Favorable Steric CoMFA Field; Fig, 4).

This CoMFA model was used to predict activities of other compounds and could be used to prioritize synthesis. The $-\log(K_i)$ values (D_2^{High}) of the test set are shown in Table 2. The values are predicted well, but more importantly, the trend in activity is predicted correctly. Notice that both secondary and tertiary amines were used in the training (Table 1) and test set (Table 2). Even though 3-halogen substituted molecules are not present in the training set, the 3-Cl analog in the test set is less active than the hydrogen substituted analogue. The directionality of the Cl and increased steric hindrance over the hydrogen analogue could explain why the Cl analogue is less active. A hydrogen bond donor is the best substituent at the 3 position and Cl-substituted aryl molecules are poor hydrogen bond donors.

Conclusions

This study successfully integrates structural variability between different series of D_2 partial agonists and correlates these differences to binding. Due to the predictability of the CoMFA model across different series of D_2 partial agonists, we believe these compounds modulate agonist binding to the D_2 receptor in the conformation and alignment described herein (Fig. 2). Furthermore, the directionality of the OH and NH vector plays a pivotal role in binding to the D_2 receptor.

Experimental

A successful CoMFA model relies heavily on the conformation and alignment of the molecules in the training set. Thus, a Monte Carlo analysis of the partial D_2 agonist (structure 1, Table 1) using MM3* as implemented in Macromodel 6.0 was performed.[7] The first conformation that fulfilled the requirements outlined by the McDermed model existed within a Boltzmann energy distribution; this is the proposed bioactive conformation.[8,9] The McDermed model requires the directionality of the basic amine lone pair to be orthogonal to the plane of the aromatic ring containing the pharmacophoric phenol. Furthermore, the phenolic oxygen to basic nitrogen distance must reside between 6.4 and 7.8 Å. All other molecules were subsequently modified to reflect this proposed bioactive conformation. However, after torsion angles were modified to reflect the proposed bioactive conformation of structure 1, all bonds, angles and torsions were allowed to optimize to their local minimum conformation using the MM3* force field. Then, the alignment of the training set molecules was performed. The D_2 partial agonists were aligned based on a 3 point pharmacophore. All compounds were superimposed based on the carbon at the 3-OH position, the centroid of the corresponding aromatic ring and the basic amine. The vdW receptor volume mapped a much larger region than outlined in the McDermed volume. This led us to believe that the D_2 receptor is more accommodating than originally outlined (Fig. 2).

The standard CoMFA method available within SYBYL 6.4 was used.[10] All experimentally determined K_i values

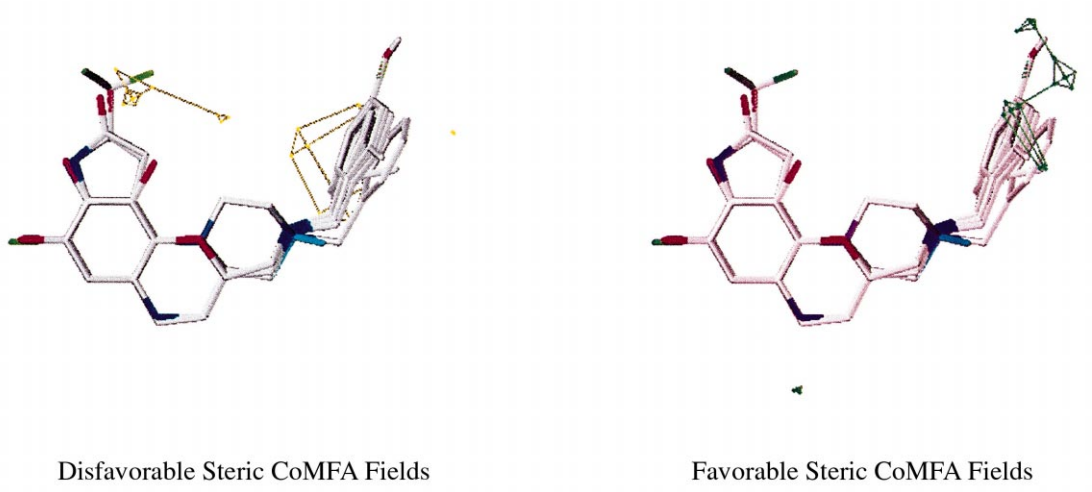
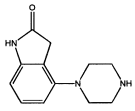
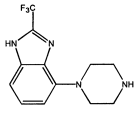
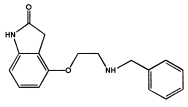
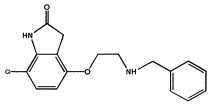


Figure 4. Steric CoMFA results.

Table 2. D_2 partial agonists used in test set

Compound	$-\log (D_2^{High}\ K_i)$ actual	$-\log (D_2^{High}\ K_i)$ predicted	D_2^{High} residual
	7.60	7.34	0.26
	7.52	7.10	0.42
	8.73	8.51	0.22
	8.44	8.26	0.18

were converted to $-\log(K_i)$ values before the CoMFA analysis was performed (Table 1). In this study, only the $-\log(D_2^{High})$ K_i values were used in the CoMFA model as our focus herein was to develop an agonist bound conformation. Consequently, the numerically larger values in Table 1 correspond to the more active agonists. Atomic point charges used in this study were calculated using the Gasteiger and Marsili method as implemented in SYBYL 6.4. Steric and electrostatic CoMFA fields at an energy cutoff of 30 kcal/mol were calculated using an sp^3 carbon probe atom with a charge of positive 1. A distance-dependent dielectric constant at all intersections of a regularly spaced 2.0 Å grid was used. The dimensions of the CoMFA lattice were determined through an automatic procedure featured by the SYBYL/CoMFA routine, which insured that the lattice walls extend beyond the dimension of each structure by 4.0 Å in all directions. All regression analyses were done using the partial least-squares (PLS) algorithm in SYBYL. Initial analyses were performed using full cross-validation (leave-one-out method). The analyses were performed with a scaling according to standard deviations (using the keyword CoMFA_STD). The optimal number of components used in the non-cross-validated analyses was defined as that yielding the lowest standard error.

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6. The K_i values are for $n=1$. The values, to date, are unpublished although patents have been filed.
7. All computations were performed using MM3 as implemented in Macromodel 6.0. The program MM3(93) is available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, IN 47401.
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11. The standard error for each crossvalidated and non-cross-validated r^2 value is listed in parentheses immediately following the r^2 value.