Journal of Computer-Aided Molecular Design, **12:** 525–532, 1998.
KLUWER/ESCOM

Molecular moment similarity between clozapine and substituted [(4-phenylpiperazinyl)-methyl] benzamides: Selective dopamine D4 agonists

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Received 11 December 1997; Accepted 23 February 1998

Key words: clozapine, dopamine D4 agonists, molecular moment similarity

Summary

Moment descriptors of the molecular charge and mass distributions are investigated within the context of molecular similarity. Euclidean distances in the moment descriptor space are shown to yield molecular proximities in accord with chemical intuition for a substituted [(4-phenylpiperazinyl)-methyl] benzamide series of dopamine D4 agonists. The proximity of the dopamine D4 antagonist clozapine to the molecules of this series is also examined in the moment space.

Introduction

Molecular moments have previously been utilized in correlating biological data [1–3] as well as characterizing data obtained from a molecular dynamics simulation [4]. Recently, moments up to and inclusive of second order in the molecular mass and charge distributions have been utilized as descriptors for three-dimensional quantitative structure-activity relationships (3D-QSAR) [5] as well as descriptors for the assessment of three-dimensional molecular similarity [6]. Such characterization presumably captures at an elemental level certain molecular features involved in the delivery of a drug to its targeted receptor site as well as features involved in ligand-receptor binding. Quadrupole moments of a molecule with zero net charge and finite dipole moment can be used in molecular similarity assignments when referenced to the appropriate center, namely the center-of-dipole [7].

One objective of the present study is to examine issues involved in the use of the moment descriptors in ranking the similarity or proximity of molecules in the moment descriptor space. Such molecular similarity or proximity assignments necessarily involve a number of assumptions, whether explicit or implicit. Consequently, several of these will be the subject of comment or discussion in the present paper. These include selection of the descriptors, assignment of molecular charge, sensing of the principal inertial or quadrupolar axes, choice of a similarity metric, and conformer selection.

The demonstration of these aspects of calculation in a meaningful manner requires a set of molecules with essentially two characteristics. First, they must consist of a sufficient number of heteroatoms so that the charge distribution over the molecular set is modulated in an interesting manner. The descriptor set that will be chosen predominantly emphasizes molecular electrostatic character. Second, examination of conformer selection as will be described requires a reasonable but not overwhelming number of rotatable bonds. For large molecules with numbers of rotatable bonds greater than the number of descriptors, there will be a loss of discrimination generally associated with underdetermined systems.

Optimization of the affinity for the dopamine D4 receptor site by substituted analogs of [(4-phenylpiperazinyl)-methyl]benzamide (PPMB) yielded a compact series of 15 molecules that showed consistent partial agonist activity [8]. This series is of interest since clozapine, a clinically potent antipsy-

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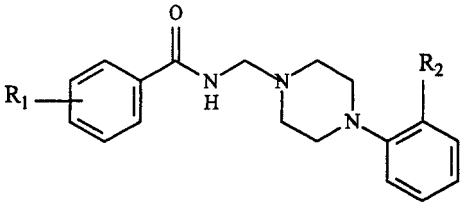
chotic drug that lacks certain of the disabling side effects associated with antipsychotic drugs having significant affinity for the D2 receptor site, has apparently reduced affinity for this site, while exhibiting enhanced affinity for the D4 receptor site. Identification of D4 receptor subtype selective antagonists and agonists is therefore of interest. The PPMB series satisfy the previously stated requirements with respect to an interesting distribution of heteroatom substituents and limited number of rotatable bonds, the maximum number being five.

The Methods section describes the methods used in assigning molecular similarity between molecules. The similarity between the molecules within the PPMB series is examined in the section entitled 'Similarity within the PPMB series'. It will be shown that the small number of moment descriptors is capable of selecting correspondences generally consistent with what one would intuitively expect for this series. Our experience with a wider range of molecular structures has shown the moment descriptors to be capable of distinguishing subtle differences in the structural and electrostatic features of molecules within a closely related structural series.

Since clozapine and the PPMB series exhibit affinity for the dopamine D4 receptor it is of interest to examine their structural and electrostatic similarity. This is the subject of the section 'Similarity of the PPMB series to clozapine'. Comparable values of molecular weight for clozapine and the molecules of the PPMB series suggested that the conformational flexibility of the latter series might yield moments-of-inertia comparable with that of clozapine. Comparison between dissimilar molecules lacking an apparent common substructural unit is possible with the moment descriptors, since they are internal to the molecule and require no molecular structural superposition or alignment for similarity comparison.



Molecule	R_1	R_2
1	H	OMe
2	H	Cl
3	H	CN
4	$3-Me$	OMe
5	$3-Me$	Cl
6	$3-Me$	CN
7	$4-Me$	OMe
8	$4-Me$	Cl
9	$4-Me$	CN
10	$3-Cl$	OMe
11	$3-Cl$	Cl
12	$3-Cl$	CN
13	$4-Cl$	OMe
14	$4-Cl$	Cl
15	$4-Cl$	CN

Figure 1. Substituted [(4-phenylpiperazinyl)-methyl]benzamides.

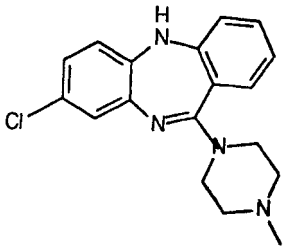


Figure 2. Clozapine.

Methods

Figures 1 and 2 illustrate the two-dimensional structures of the PPMBs and clozapine, respectively. Initial three-dimensional structures have been obtained with standard bond lengths and bond angles. The piperazine ring has been chosen to be in a chair conformation. The structures were then force-field optimized and subjected to a systematic search to obtain the conformer of lowest force-field energy [9]. A final force-field optimization was then performed on the extracted low energy conformers. Not surprisingly, the conformations of all molecular scaffolds of this series were found to be almost identical and differences in the moments of the molecules were then predominantly due to differences induced by the substituents. These structures were then used in the calculations of molecular similarity.

The 15 PPMB molecules constitute a compact combinatorial set consisting of five different groups of three molecules, each determined by the R_1 substituent. The first three groups consist of the nine structures, molecules 1 through 9, with either no substituent or an R_1 alkyl substituent. The remaining six structures, molecules 10 through 15, contain R_1 chlorine substituents. Differences within each group of three molecules are then distinguished by differences

induced by the R_2 substituent; namely the methoxy, chlorine or cyano substituent. The series, therefore, consists of a set of substituents yielding diversified electrostatic molecular character.

Dipole and quadrupole moments have been obtained from rapid charge assignments at the molecular atomic sites utilizing Gasteiger and charge equilibration procedures [10]. While one might have obtained moments of greater reliabilty from quantum chemistry calculations, the use of rapid procedures provides feasibility with respect to scaling the present procedure to large structural databases. While calculated dipolar and quadrupolar values may not accurately reproduce the gas phase values of these moments, systematic variation among the values will be shown to lead to meaningful correspondences between the different molecules.

A previous investigation [5] utilizing molecular moments had projected dipolar and quadrupolar moments onto the principal inertial axes. Since the principal inertial axes are unsensed, i.e., positive and negative directions not assigned, vector component magnitudes were previously used as well as a limited set of quadrupolar descriptors. Descriptors may, however, be developed for sensed axes when a procedure is adopted to assign directions to the principal axes. For a series of structures with scaffolds or backbones closely related, the manner in which the axes should be sensed is apparent. For a set of molecules with diverse structures bearing little or no apparent relationship with one another one might use information obtained from higher order in the moment expansion. The inertial axes of each of the molecules of the present investigation were sensed with use of the common scaffold geometries of the molecular series.

The set of moment descriptors used in the present paper consists of the molecular weight, m, the moments of inertia, I_x, I_y, I_z, the magnitude of the dipole moment, p, and principal quadrupole moment, q, calculated at the molecular center-of-dipole. Other descriptors relating molecular charge and shape can be developed in a number of different ways. In the present work the dipolar components, p_x, p_y, p_z, and quadrupolar components, q_{xx}, q_{xy}, q_{xz}, q_{yy}, q_{yz}, are written in the principal inertial frame with origin at the center-of-dipole. There are 14 descriptors in all. Referring electrostatic moments to the principal inertial axes provides a succinct representation of the relationship between molecular charge and shape.

In the present paper a Euclidean metric is used to rank the proximity of molecules in the molecular moment descriptor space. Prior to calculating the Euclidean distance in the descriptor space of 14 dimensions, the value of each descriptor is normalized by its standard deviation. The Euclidean distance is normalized by the total number of descriptors; namely, 14 in the present paper.

Since the descriptors are correlated it would seem reasonable to eliminate such correlations by transforming to an uncorrelated descriptor set and use the so-called Mahalanobis distance as a similarity metric [11]. Our experience with use of the Mahalanobis distance as a similarity metric has not provided assignments into different chemically recognized groups that are as consistent as obtained with the Euclidean metric, therefore, this metric has not been used in the present paper.

Clozapine, while of comparable molecular weight to the molecules of the PPMB series, is conformationally constrained, consisting of a single rotatable bond. In searching for similarities between clozapine and the PPMB series of molecules, conformer space will be examined as well. With clozapine as the query molecule, we will ramp through the conformers of each of the molecules of the PPMB set, removing sterically unstable conformers, to select the conformer nearest to the query molecule, clozapine, in the moment space of 14 dimensions.

Similarity within the PPMB series

In this section we will examine how the molecular moment descriptors sort out similarities among the different molecules of the PPMB series. It will be shown that molecules close to each other in the Euclidean space of the moment descriptors generally satisfy intuitive notions of chemical similarity. The consequences of using Gasteiger as well as charge-equilibration procedures for assigning molecular charge at the atomic sites will be exhibited. The moment descriptors can be thought of as three-dimensional structural tags which, with minimal information, can be used effectively to assign three dimensional molecular similarity between molecules.

Table 1 lists the neighbor rank and calculated distance of molecules of the PPMB series with respect to molecules 4, 5, and 6 of the series. Results for these three molecules are typical of the first three groups consisting of nine molecules with either no substituent or an R_1 alkyl substituent. Results are shown for moments obtained with the two different molecular

Table 1. Distances between molecules of the PPMB series

Neighbor	Proximity to Molecule 4				Proximity to Molecule 5				Proximity to Molecule 6			
	Gasteiger		Charge eq		Gasteiger		Charge eq		Gasteiger		Charge eq	
	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist
1	7	0.30	7	0.30	8	0.31	8	0.31	9	0.26	9	0.27
2	1	0.56	1	0.55	2	0.55	2	0.55	3	0.56	3	0.55
3	10	1.02	6	1.00	12	0.81	6	0.62	5	1.16	5	0.62
4	5	1.20	9	1.05	11	0.95	9	0.65	8	1.17	2	0.67
5	11	1.21	5	1.07	14	1.10	3	0.99	2	1.18	8	0.71
6	13	1.21	8	1.15	6	1.16	4	1.07	12	1.33	4	1.00
7	8	1.23	2	1.18	9	1.18	7	1.08	15	1.35	7	1.02
8	2	1.30	3	1.28	4	1.20	1	1.17	4	1.68	1	1.04
9	12	1.41	15	1.41	7	1.28	12	1.25	14	1.72	12	1.20
10	14	1.44	13	1.54	3	1.35	15	1.38	7	1.73	15	1.47
11	6	1.68	12	1.54	1	1.36	10	1.55	1	1.76	10	1.53
12	9	1.69	10	1.57	15	1.52	13	1.61	11	1.84	11	1.58
13	3	1.74	14	2.14	13	1.58	11	1.73	13	2.00	13	1.72
14	15	1.77	11	2.29	10	1.81	14	1.92	10	2.18	14	1.87

charge assignments. Molecules in the moment space that we will call close are approximately one-half a standard deviation or less from each other. It should be noted that the two nearest neighbors to molecules 4, 5, and 6 are molecules with the same R_2 substituent and either an R_1 alkyl substituent or no R_1 substituent. This result is independent of the charge assignment utilized. Furthermore, the two nearest neighbors of molecules 1 through 9 are ranked with respect to the R_1 substituent, e.g., the neighbor nearest to the molecule with a methyl group R_1 substituent will be the molecule with an R_1 methyl group substituent. Molecule 1, without the methyl R_1 substituent, is found to be equidistant from molecules 4 and 7; and a similar correspondence holds for molecules 2 and 3, namely they are equidistant from molecules 5 and 8 as well as from 6 and 9, respectively. As one examines more distant rankings, differences are noted for the two different charge assignments. For example, for the Gasteiger charge assignments the third nearest neighbor of molecule 5 is molecule 12; a molecule with different R_1 and R_2 substituents from molecule 5. The charge equilibration charges, on the other hand, place molecule 12 somewhat farther removed from molecule 5. Interestingly, all molecules with charge equilibration charge assignments and an R_1 chlorine substituent are the most distant from molecules 4 through 6, the molecules with an R_1 alkyl substituent. This is a consequence of the significant charge transfer assigned to the halogen atoms by this procedure.

Table 2 lists the ranking and calculated distances with respect to molecules 10, 11, and 12; molecules with an R_1 chlorine substituent. We again limit this listing since it is also representative of the rankings for molecules 13, 14, and 15 as well. Interestingly, the comparison of results that arises from the two different charge distributions exhibits greater differences than found for the first nine molecules. This is essentially due to two factors. First, the relatively small amount of charge transferred to the halogen atoms with the Gasteiger procedure compared with that of the charge equilibration procedure. Second, the significant emphasis on electrostatic character by the similarity metric we have chosen since 10 of the 14 descriptors are explicitly electrostatic in character. For charge equilibration results, relatively distant molecules in the moment space can be a consequence of simply shifting the location of the R_1 halogen substituent, e.g., molecules 11 and 14 as well as molecules 12 and 15. Close neighbors, such as molecules 10 and 12, arise from an identical R_1 halogen substituent.

Results from the Gasteiger charge assignments exhibit a greater diversity in the ranking of the series with respect to the molecules with an R_1 halogen substituent. This is one more consequence of the reduced charge transfer to the halogen atoms compared with that of the charge equilibration procedure. Ac-

Table 2. Distances between molecules of the PPMB series

Neighbor	Proximity to Molecule 10				Proximity to Molecule 11				Proximity to Molecule 12			
	Gasteiger		Charge eq		Gasteiger		Charge eq		Gasteiger		Charge eq	
	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist	Mol	Dist
1	13	0.99	12	0.53	12	0.87	12	1.06	5	0.81	10	0.53
2	4	1.02	13	1.04	14	0.91	10	1.48	14	0.87	11	1.06
3	7	1.10	15	1.28	5	0.95	9	1.58	11	0.87	6	1.20
4	11	1.32	11	1.48	8	1.02	6	1.58	8	0.94	9	1.22
5	1	1.44	6	1.53	4	1.21	8	1.73	2	1.23	5	1.25
6	14	1.57	9	1.54	13	1.25	5	1.73	15	1.29	13	1.25
7	12	1.63	5	1.55	7	1.30	3	1.85	6	1.33	15	1.29
8	5	1.81	4	1.57	10	1.32	15	1.92	9	1.39	8	1.30
9	8	1.85	8	1.57	2	1.39	14	1.95	4	1.41	4	1.54
10	15	1.96	7	1.58	1	1.60	2	1.98	13	1.45	2	1.54
11	2	2.06	2	1.83	15	1.75	13	2.00	7	1.52	7	1.55
12	6	2.18	1	1.83	6	1.84	7	2.26	10	1.63	3	1.57
13	9	2.20	3	1.89	9	1.86	4	2.29	3	1.66	1	1.76
14	3	2.38	14	1.99	3	2.13	1	2.46	1	1.73	14	1.83

cording to our definition of close, nothing is close to molecules 10 through 15. On the other hand, the neighbors nearest to molecules 10 and 11 do have one substituent in common. It is of interest to note that the molecule nearest molecule 12 is molecule 5. These two molecules have no substituent in common. This particular case highlights the ability of the molecular moment descriptors to identify, on occasion, molecular moment proximities unrelated to apparent molecular structural similarities.

Table 3 shows results of hierarchical single linkage cluster analysis [10] for coalescence of the 15 molecules into eight clusters. Gasteiger charge assignments have been used for this analysis. As expected, molecules with either no substituent or an alkyl substituent at the R_1 position and an identical R_2 substituent are members of the same cluster. The proximity of molecule 5 to molecule 12 places these two molecules in the same cluster. Molecules with a chlorine substituent at the R_1 position are sufficiently removed from each other in the moment space and from the other molecules of the series to place them in single molecule clusters at the eight cluster level.

To conclude, the series distribute in moment space in a way that reflects the choice of substituents, and is therefore in accord with intuition. Therefore, when examining the consequences of different charge models on well-designed series, one should be able to assess how appropriate each charge model is for the series under investigation.

Table 3. Hierarchical single linkage clusters

Cluster number	Molecule membership
1	1, 4, 7
2	2, 5, 8, 12
3	14
4	11
5	13
6	10
7	3, 6, 9
8	15

Similarity of the PPMB series to clozapine

Since clozapine as well as the PPMB series exhibit binding affinity for the dopamine D4 receptor, it is of interest to investigate their similarity in the space of the molecular moment descriptors. Table 4 (upper part) lists the distances between clozapine and the molecules of the PPMB series using structures as found by the procedure described previously. Gasteiger charges were utilized in this calculation. One notes that the nearest neighbor to clozapine in this space is molecule 5 at a distance of 1.31, a value

Table 4. Distance to clozapine of molecules of the s4mb series

Neighbor	Molecule	Distance
Initial conformation		
1	5	1.31
2	2	1.34
3	11	1.48
4	8	1.53
5	12	1.57
6	4	1.59
7	1	1.62
8	7	1.79
9	6	1.91
10	3	1.95
11	14	1.96
12	9	2.03
13	10	2.06
14	13	2.20
15	15	2.33
Conformer optimized[a]		
1	4	0.54
2	1	0.64
3	7	0.65
4	5	0.68
5	2	0.72
6	8	0.76
7	6	0.78
8	9	0.83
9	10	0.83
10	12	1.05
11	11	1.05
12	13	1.06
13	3	1.13
14	14	1.14
15	15	1.36

[a]Eighteen rotations per bond; 20° increment

comparable with that between molecules of the PPMB series that differ by at least one heteroatom substituent.

Since the molecules of the PPMB series are conformationally flexible, the following search was performed. Treating clozapine as the query, its molecular moment descriptors were held fixed. Molecular moment descriptors for conformers of each of the molecules of the PPMB series were calculated at 20 degrees resolution, namely, 18 conformers per rotatable bond. The distance in the Euclidean space of the moment descriptors between each of the conformers and clozapine was calculated. Conformers with poor steric contacts were eliminated. For each molecule, only

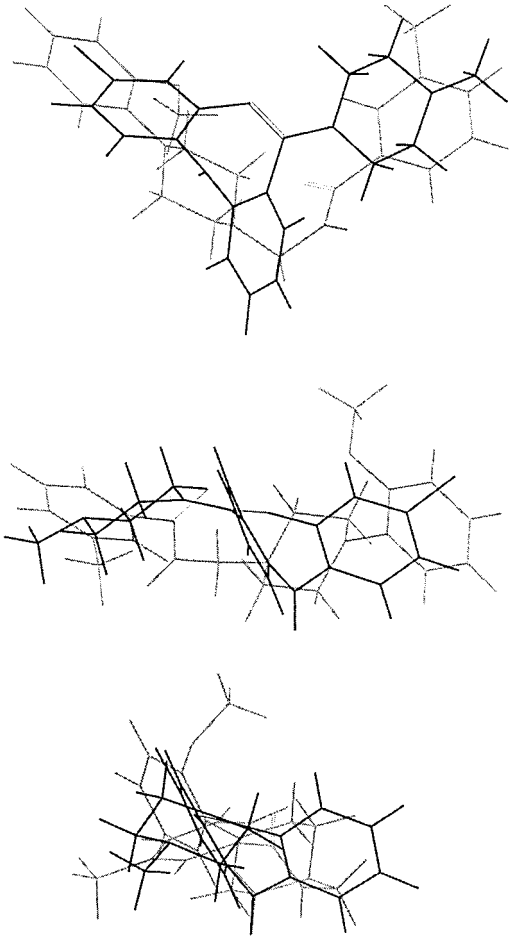


Figure 3. Three views of clozapine overlaid on molecule 4.

the conformer closest to clozapine in the Eucidean space was retained. In this manner, 10497600 conformers were investigated. The distance between each retained conformer of the PPMB series and clozapine is shown in Table 4 (lower part). In order to compare distances between the two parts of Table 4, the calculation involving the optimized conformers utilized the same descriptor normalization of Table 4 (upper part), namely, normalization by the standard deviation of molecular descriptors prior to conformer optimization with respect to clozapine.

One notes that the neighbor ranking with respect to clozapine gets shuffled as a consequence of conformer optimization. As expected, all distances to clozapine in the moment descriptor space become shortened. Molecule 4 which was the 6th neighbor in the original ranking, is now the nearest neighbor of clozapine. Of further interest is that its distance from clozapine

Table 5. Molecular moments

Moments	Initial conformer of molecule 4	Optimized conformer of molecule 4	Clozapine
m (amu)	339.4	339.4	326.8
I_x (amu. Å^2)	1137	1409	1445
I_y	6073	4414	3385
I_z	6606	4933	4327
p_x (e. Å)	−0.098	0.144	0.102
p_y	−0.162	−0.243	−0.338
p_z	−0.454	−0.174	−0.201
p	0.493	0.332	0.406
q (e. Å^2)	5.251	2.019	0.261
q_{xx}	4.645	1.415	−0.220
q_{xy}	−2.198	1.088	−0.105
q_{xz}	−0.223	−0.346	0.065
q_{yy}	−4.009	0.044	0.025
q_{yz}	1.913	0.840	−0.096

is now comparable to distances between molecules of the original PPMB set that involved the difference between the presence or absence of a single alkyl substituent.

Table 5 lists the values of the descriptors for clozapine and for molecule 4 before and after the conformer optimization was performed. One notes the significant difference between the set of values prior to and after conformer optimization. Differences between the moments-of-inertia and dipolar and quadrupolar components with respect to the principal inertial axes are significantly reduced. The only descriptor difference between clozapine and molecule 4 that increases with conformer optimization is that for q_{xz}. The dipolar components along the inertial axes are particularly well matched between the two molecules.

Figure 3 shows three different views of the superposition of the optimal conformer of molecule 4 and clozapine. Molecular alignment was performed by superposing the respective molecular centers-of-mass and principal inertial axes. It should be emphasized that, even though the alignment indicates that both molecules occupy a similar region of space, only three of the moment descriptors, namely the moments-of-inertia, optimize the type of visual superposition exhibited in the figure. Ten of the 14 descriptors are electrostatic in character so that the conformer has also been chosen to optimally align the molecular electrostatic moments. An attempt to interpret the subsequent alignment in terms of local electrostatic features is, however, difficult if not impossible since the electrostatic moments are global quantities involving detailed cancellations between the effects of charge redistribution at different locations of the molecule.

Conclusions

The present paper has attempted to illustrate several of the issues involved in using molecular moment descriptors to assign molecular similarity. One may view the utility of this assignment in one of two different ways. First, might the descriptors be used as tags for molecular structures? The representation and rapid identification of chemical structures is a subject of continued interest [12–14]. The molecular moments are an elemental approximation to detailed molecular structure and incorporate certain aspects of three-dimensional molecular shape and charge in an exceedingly compact manner. Our limited experience with such assignment indicates that the moment descriptors are capable of identifying subtle structural distinctions consistent with chemical intuition. Second, might the descriptors be utilized with regard to drug discovery? The moment descriptors are central to processes involving steric interactions as well as electrostatic interactions on a global molecular scale, e.g., the interaction of molecules with electric field and field gradients. Consequently they may be more descriptive of processes involving the alignment of a drug to its targeted receptor site prior to binding at the site, rather than descriptive of detailed features involving binding at the site. Details of such alignment, involving electrostatic interactions over relatively large separation distances, have been previously described [15].

One significant limitation in the calculation of the descriptors is the present ability to obtain reasonably accurate electrostatic molecular moments. The ability to calculate, for example, a local molecular region of high negative electrostatic potential is a very different problem from the ability to calculate quantities that result from the modulated molecular electronic charge over the entire molecule and its close cancellation with the charge of the positive nuclear cores. Presumably the ability to perform such calculations with increased accuracy and speed will improve with time. Nevertheless, the present as well as other investigations suggest that even with limited accuracy, systematic variations

in the moments from structure to structure yield useful results.

One might question the biological significance of the comparison made between the PPMB series and clozapine. The proximity between clozapine and its few proximate neighbors in the molecular moment space is striking. As mentioned, this is not only a consequence of the manner in which the molecules fill space but a consequence of the manner in which the charge distribution projects onto the inertial axes of the molecules as well. Does this suggest a similar mode of delivery to or local binding at the receptor site? Perhaps. Other structures of antagonists known to bind to the dopamine D4 receptor [161 would lead one to conclude that their moments-of-inertia would not exhibit values comparable with those calculated in the present paper. It will be of interest, however, to see if their moments of molecular mass and charge exhibit similar relationships to clozapine as found for the present series.

Finally, the assignment of molecular similarity involving a large molecular database of diverse structures can involve two difficult steps, namely, molecular superposition and conformer examination; the former poorly defined. The moment descriptors do not require the superposition step for such assignment.

References

1. Henry, D.R. and Craig, A.M., ACS Symposium Series 413 (1989) 70.
2. Inami, Y., Tomita, T. and Terada, Y., Chem. Pharm. Bull., 39 (1991) 1426.
3. Cardozo, M.G., Iimura, Y., Sugimoto, H., Yamanishi, Y. and Hopfinger, A.J., J. Med. Chem., 35 (1992) 584.
4. Lipkowitz, K.B. and Peterson, M.A., J. Comput. Chem., 16 (1995) 285.
5. Silverman, B.D. and Platt, D.E., J. Med. Chem., 39 (1996) 2129.
6. Silverman, B.D. and Pitman, M.C., manuscript in preparation.
7. Platt, D.E. and Silverman, B.D., J. Comput. Chem., 17 (1996) 358.
8. Glase, S.A., Akunne, H.C., Georgic, L.M., Heffner, T.G., MacKenzie, R.G., Manley, P.J., Pugsley, T.A. and Wise, L.D., J. Med. Chem., 40 (1997) 1771.
9. Systematic search and force-field optimizations were performed with SYBYL, available from TRIPOS Associates Inc., St. Louis, MO.
10. The Rappe-Goddard charge equilibration and Gasteiger charge assignments as well as the hierarchical single linkage cluster analysis were performed with the Cerius2 molecular modelling program distributed by Molecular Simulations, Inc., San Diego, CA.
11. See for example, Joliffe, I.T., Principal Components Analysis, Springer Verlag, New York, NY, 1986.
12. Willet, P., Similarity and Clustering in Chemical Information Systems, John Wiley & Sons Inc., New York, NY, 1987.
13. Johnson, M.A. and Maggiore, G.M. (Eds.) Concepts and Applications of Molecular Similarity, John Wiley & Sons Inc., New York, NY, 1990.
14. Dean, P.M. (Ed.), Molecular Similarity in Drug Design, Blackie Academic & Professional, Glasgow, 1995.
15. Dean, P.M. and Wakelin, L.P.G., Phil. Trans. R. Soc. London Ser. B, 287 (1979) 571.
16. Unangst, P.C., Capiris, T., Connor, D.T., Heffner, T.G., MacKenzie, R.G., Miller, S.R., Pugsley, T.A. and Wise, L.D., J. Med. Chem., 40 (1997) 2688.