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Discriminating D1 and D2 agonists with a hydrophobic similarity index

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Currently, methods for calculating molecular similarity indices have been developed for comparing steric, charge density, and molecular electrostatic potential (MEP) properties. Much of the existing technology may, however, be applied to the quantitative comparison of molecular hydrophobicities. In this article we present an empirical hydrophobic similarity index. We utilize atomic hydrophobic parameters derived from a quantum mechanical semiempirical wavefunction. Hydrophobicity at points on a grid is computed with a recently introduced "molecular lipophilicity potential." The overlap of pairs of molecules is calculated with the metric introduced by Carbó. This approach is applied to a case in which steric and electrostatic criteria have already been shown to be inadequate in rationalizing selectivity, namely, requirements for recognition at the dopamine D1 and D2 receptors. We demonstrate that, for a set of dopamine agonists, D1 ligands show higher similarity in this property than D2 analogs. This indicator of similarity is more successful at accounting for D1 selectivity than previous methods.

Keywords: molecular similarity, hydrophobicity, dopamines, molecular electrostatic potential

INTRODUCTION

In rational ligand design, it is becoming accepted that consideration should be given to a combination of steric, electrostatic, and hydrophobic factors.[1,2] Each of these plays its part in deciding the optimum arrangement of a ligand in a binding site. Steric factors are readily assessed by a number of methods, for example the intersection volume of a set of related molecules[3–5] or "sterimol" parameters,[6] but the study of physicochemical properties is more difficult.

The importance of the molecular electrostatic potential (MEP) in long-range ligand–receptor interactions has long been recognized.[7,8] The influence of the charge distribution of a molecule at long range is readily visualized by computing its MEP at points outside the van der Waals volume. Topological properties of the MEP, specifically the position, magnitude, and number of its minima, have often been used in rationalizing the relative activities of ligands for a given receptor. These quantities have also been used in the derivation of quantitative structure–activity relationships (QSARs).[9]

A natural extension of such studies has been the design of ways to compare MEPs quantitatively for series of molecules, that is, to assess molecular similarity.[10] The comparison of molecular property fields has received much attention, an approach with growing popularity being comparative molecular field analysis (CoMFA).[11] Pairwise molecular overlaps expressed as an index have also generated interest. Currently, a measure of overlap first introduced by Carbó et al.[12] has attracted interest and has enabled comparisons of charge densities with a number of theoretical methods,[13–20] steric features,[4] Coulombic repulsion effects,[21] and MEPs.[22–28] We note, however, that several other possible metrics have been considered.[22,29–31] Sanz et al., for example, used the Spearman rank correlation coefficient for MEP index calculations.[32–35]

The demonstrated utility of the MEP led people to consider ways of quantitatively representing hydrophobic properties so as to reflect the regional features of a molecule. Such techniques are entirely empirical but play their part in visualization. By analogy with the MEP, it was proposed that atom-centered functions that decay monotonically with distance can constitute useful descriptors of hydrophobicity. When computed for a whole molecule, these have been called molecular lipophilicity potentials (MLPs). It is important to stress that, in contrast with MEPs that have a real physical meaning, MLPs are entirely heuristic and are merely convenient devices for achieving the desired representation. The analytical form of an MLP has no connection at all with any physical quantity. The original motivation behind MLPs[36–38] was to allow a notional hydrophobicity to be computed at any point in space in the neighborhood of a molecule. The derivation of a number of newer MLPs[39–43] has largely been to facilitate the display of hydrophobic properties, for example, on a molecular surface.[38]

There now exist a number of parameter sets that quantify the contribution of fragments (or individual atoms in de-

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fined stereochemical environments) to the overall molecular hydrophobicity, expressed as log P, the logarithm of the partition coefficient between 1-octanol and water.[44–47] All of these, except for one,[47] can be described as conformationally independent because they do not require knowledge of the three-dimensional (3D) coordinates of the molecule. Any atomic parameters may be used in conjunction with MLPs, which, therefore, serve to modulate their behavior in space.

We explore in this article a new way in which some of the existing theory of MLPs and similarity indices can be extended to the quantitative comparison of hydrophobic properties. Many existing approaches to comparing molecules utilize a synthesis of just steric and electrostatic properties.[48–50] It could be expected that hydrophobic factors would lead to modulation and refinement of steric and electrostatic criteria for overlap because their origin is from weaker forces of interaction. Therefore they should have a useful place in combined application of molecular similarity calculations. To this end, we use atomic lipophilic parameters that are derived from a semiempirical wavefunction and computed explicitly for each molecular conformation.[47] We chose the most recent MLP in the literature, that of Heiden et al.,[40] and compute similarities with a Carbó index.

To test the effectiveness of this approach, we apply it to a case in which it has already been proven difficult to discriminate activity on the basis of steric and MEP considerations alone: the selectivity of a set of agonists for the D1/D2 receptor classes.[51] While a large number of pharmacophores have been developed, efforts to characterize D1/D2 selectivity to date have mainly been based on position of minima in the MEPs.[52] More recent investigations have revealed a steric component and highlighted the possibility that a lipophilic ring system may play a role.[53] A study of 10 agonists, a set that includes 3 D1-selective, 3 D2-selective, and 4 nonselective ligands,[54] suggested that, qualitatively, their MEPs were only slightly dissimilar. In that study, the molecules were aligned so as to approximately (i.e., visually) overlap maxima and minima in their MEPs. On the basis of visual comparison, little difference could be observed. While their commonalities probably pointed to a coherent requirement for receptor recognition, their differences would not be sufficient to explain their differing selectivities. On the other hand, we note that all the ligands considered have both polar and aromatic groups, with the latter adopting a range of dispositions and having a variety of bulks. Consequently their interaction with lipophilic regions of the receptors is likely to be markedly different. These molecules will usefully demonstrate that it is not the total molecular lipophilicity (as expressed by log P) that is important but its local distribution.

We aimed to investigate both the quantitative aspects of the MEP and the MLP using similarity indices, to ascertain if hydrophobic factors were responsible for modulating D1/D2 selectivity. The same 10 compounds were used in this study, and are shown in Figure 1.

METHODOLOGY

We adopt an approach that parallels previous efforts to define similarity indices for MEPs.[22,24,32,33] In essence, the property is computed at spatially fixed grid points uniformly spread through a box that contains the molecule pair. A number of aspects of the calculation need to be considered. Whereas for the calculation of MEPs the result is principally sensitive to choice of atomic charges, in the case of hydrophobic properties the issue is how to describe the regional distribution of hydrophobicity on a given molecule, that is, first, the choice of an atomic parameter set, and second, the way to transform such a representation into a field that is defined and computable at points in space around the molecule. Unlike with the MEP, which has a physical significance and which is dependent on the electronic density distribution, an MLP is purely a mathematical device that cannot be experimentally measured. Despite being a heuristic tool, comparisons between MLPs are most useful if calculated quantitatively, dictating choice of a metric.

Atom-based lipophilic parameters

The contribution, f_i, of each atom i to log P is calculated according to Eq. (1)[47]:

$$f_i = \alpha_i^N S_i + \beta_i^N S_i(\Delta q_i)^2 + \gamma_i^N q_i \quad (1)$$

Here, α, β, and γ are parameters that, for a given level of theory, depend only on the atomic number, N. S_i is the surface area of atom i; and q_i is its Mulliken charge. The last of these quantities comes from a semiempirical molecular orbital calculation. The parameters α, β, and γ were derived in Ref. 47 by least-squares fitting of expression (1) to experimental values of log P for a number of molecules at several levels of theory.

Molecular lipophilicity potential

We used the most recent MLP, that of Heiden et al.,[40] which has the form

$$L_j = \left(\sum_{i}^{\text{all atoms}} f_i g(d_{ij}) \right) \Big/ \left(\sum_{i}^{\text{all atoms}} g(d_{ij}) \right) \quad (2)$$

where d_{ij} is the distance of atom i from the point j in question. In this case, $g(ij)$ is a Fermi-type function centered on each atom,

$$g(d_{ij}) = 1/[1 + e^{a(d_{ij} - d_{\text{cutoff}})}] \quad (3)$$

Whereas a function such as Eq. (3) decays rapidly over a short range, the effect of the denominator in Eq. (2) is to temper this decay, that is, it does not really serve as a "normalization factor" on L in the way suggested by Heiden et al.[40] In fact, the long-range behavior of Eq. (2) is rather similar to that of the simple inverse-distance dependence suggested by Audry et al.[36]

The atom-centered function in Eq. (3) has two adjustable parameters, a and d_{cutoff}, which, for simplicity, are taken to be the same for all atoms. The precise values of these parameters are somewhat arbitrary. We used a value of 1.5 for a, that is, that suggested by Heiden et al.[40] But we chose 2.0 Å for d_{cutoff} (a value that is closer to the van der Waals

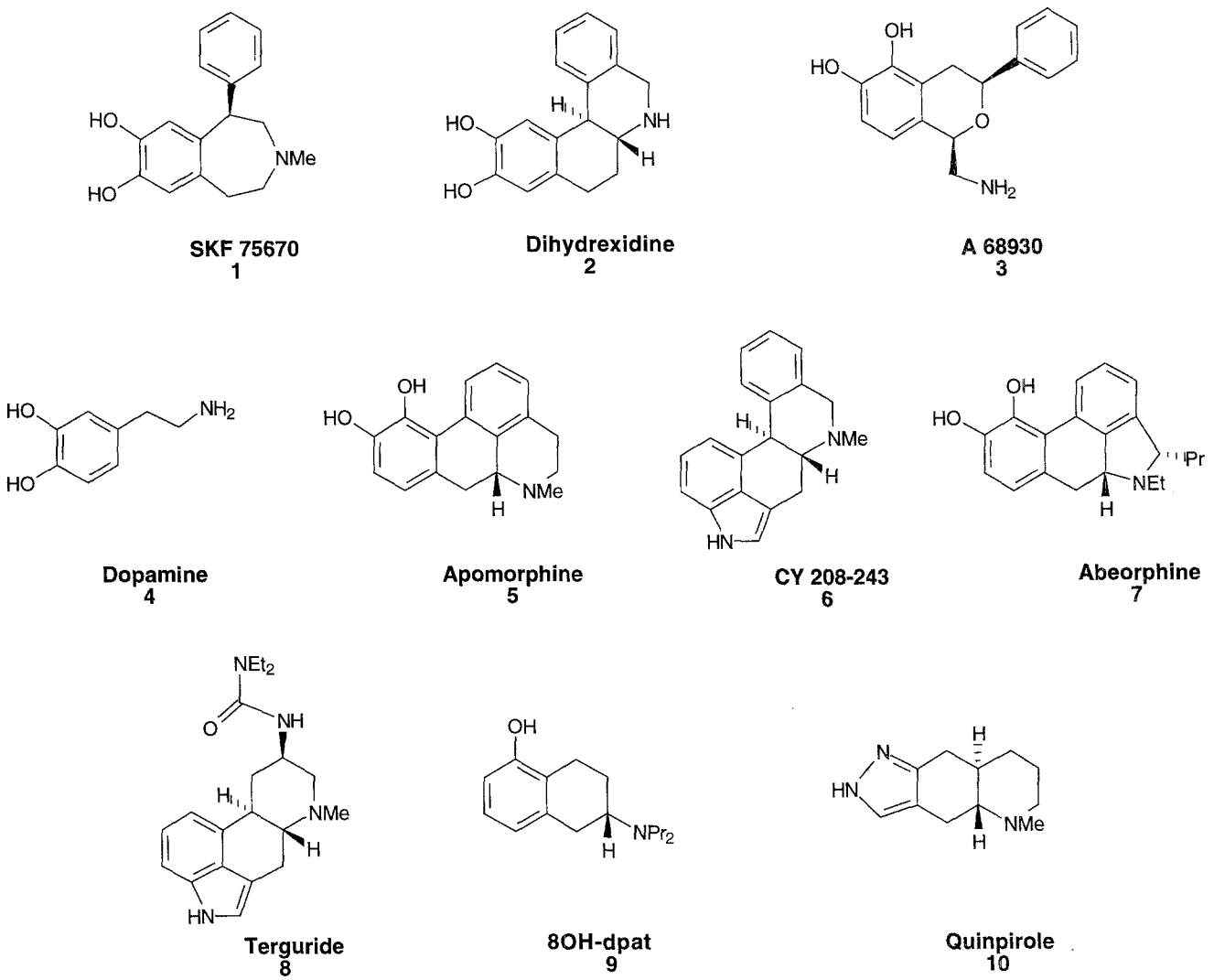

*Figure 1. Structures of dopamine agonists: **1–3**, D1 selective; **4–7**, nonselective; **8–10**, D2 selective.*

radius of most atoms in organic molecules than to the solvent-accessible surface).

Measure of similarity

By paralleling work on the calculation of MEP similarity indices,[22–35] a hydrophobic similarity index can be defined. A box is constructed around the union of two superimposed molecules, A and B. Grid points are dispersed uniformly through the grid. The value of the MLP for each molecule may be calculated at every grid point.

There are three quantities to consider:

$$A = \sum_{j \in \text{grid}} (L_j^A)^2 \tag{4}$$

$$B = \sum_{j \in \text{grid}} (L_j^B)^2 \tag{5}$$

$$AB = \sum_{j \in \text{grid}} L_j^A \cdot L_j^B \tag{6}$$

We consider the metric proposed by Carbó and coworkers,[12] which is best interpreted as the scalar product of the two MLP distributions.

$$S = (AB)/([A \cdot B])^{1/2}) \tag{7}$$

It is thus normalized, and because, like the MEP, the lipophilicity function may take on both positive and negative values, it falls in the range $[-1,1]$ for each molecule pair.

A consideration in the calculation of MEP similarity indices, using a grid, is that points inside the molecular volume should not contribute at all.[23,24] There is no particular precedent for this with an MLP, however. In tests we carried out, blanking out of grid points that lie inside the union volume of each molecule pair has little effect on the qualitative trends observed in the similarity indices. This is largely because the MLP used [Eq. (2)] does not increase to a cusplike form at atomic nuclei (as the MEP does). We argue also that the shallow rate of decay of this MLP is convenient for a grid-based comparison because it truly smears the atomic contributions out into space and increases the chance that points on a relatively sparse grid will contribute effectively to the comparison.

Features of the grid used in the calculation of the molecular lipophilicity potential similarity index

An important parameter in the computation of similarity indices in this way is the dimension of the grid. Our calculations utilized a box whose sides extended 4 Å in each direction in each dimension beyond the maximum atomic coordinate in a given molecular union. Once again, we may look to MEP index calculations for comparison. Sanz et al.[32,35] used a 3-Å border around the molecule pair. It was shown in Ref. 23 that increasing the extent of the grid was less important than ensuring a fine enough grid-point density.

For the molecules in this study, the grid-point density was fixed at 30 points/dimension, a compromise between computational expense and numerical stability in the calculation. For the molecules studied here, such a point density translates into a typical spacing of 0.5–0.6 Å. A separation between grid points of at most 1 Å was deemed necessary for the MEP index calculations in Ref. 23, an observation subsequently confirmed by Richard.[24] Sanz and co-workers use a default fixed value of 0.5 Å[32,35] in MEP index calculations. With such a spacing, the use of an MLP that falls off too steeply with distance would be risky.

We chose to use a rectilinear grid, which represents a compromise between stability and detail of sampling. Several other types of grid have been proposed[24,32] to ensure a better sampling of fast-varying regions of the fields, but all have the disadvantage of depending on the union volume of the overlaid molecule pair and therefore changing during the course of an optimization. Recomputation of grid points in this way is undesirable because of the numerical instability that is introduced into an optimization. This would not be a factor in our present study but we emphasize the advantage of a fixed grid for the purposes of reliability.

Implementation

To test the MLP similarity index, a computer program, Match,[55] was written in standard Fortran77. Features of this program include the following: command file/keyword control, choice of input formats of molecular geometry, choice of starting alignments of molecule pairs, simplex optimizer in 6 degrees of freedom (three translation and three rotation), choice of metrics, MEP and MLP index calculation and user-defined weight sum, and automatic computation of similarity "matrix" for all input molecules. Not all of these features are explored in this article.

The calculation of atomic values by Eq. (1) is achieved with a separate computer program, Q,[56] which takes as input the GRAPH binary output file from the semiempirical package MOPAC[57] and computes a number of properties, including atomic components, of the molecular surface area.

APPLICATION TO SELECTIVITY AT D1 AND D2 RECEPTORS

The method described above is applied to the D1/D2 selectivity of a set of dopamine agonists whose behavior could not be explained on the basis of the alignment of their MEPs alone.[54] Cluster analysis of the similarity matrix demonstrates that hydrophobic criteria are important for D1 selectivity.

Details of calculation

We carried out single-point AM1[58] energy calculations on each of the 10 molecules and derived the requisite atomic lipophilic parameters. The optimized geometries and relative alignments of each molecule pair were those obtained in an earlier study.[54] The matrix of similarity indices for both MLPs and MEPs were calculated at these orientations. We worked on the basic assumption that the MEP itself is a good primary quantity for determining recognition characteristics, but that it is not sufficient to explain selectivity. We looked to the MLP similarity to find an indication that hydrophobicity may discriminate between ligands of different selectivity.

Results

We see that the similarity indices (Table 1) based on both MEPs and MLPs display a substantial variation in values. The entries in the MEP matrix are all positive, except for the molecule pair **(4, 9)**, which is close to zero. By contrast, the MLP values span a wider range, from close to 1.0 to as low as −0.54. This suggests immediately that, in the configurations studied, the distribution of MEP overlaps is tighter than that of the hydrophobicity. This serves as rough numerical confirmation that the method of prealignment was primarily charge related.

A rigorous analysis of the similarity matrices is necessary if more detailed conclusions are to be drawn.[59,60] Hierarchical cluster analysis is a quick and convenient method of extracting proximities of entries in a distance matrix. Similarity indices of the form in Eq. (7) are larger for more similar molecules. By contrast, entries in a distance matrix are proportional to dissimilarity of the pairs of objects in the space in question, that is, the reverse of the case for entries in the similarity matrices. It is easy, however, to convert the similarity index into an index of dissimilarity in the following way[4]:

$$D_{AB} = 1 - S_{AB} \tag{8}$$

In the case of MEP and MLP, then, the range of D_{AB} will be [0, 2] and such quantities are amenable to hierarchical cluster analysis.

The dendrograms for the MEP and MLP dissimilarity matrices derived from the similarity matrices in Table 1 are shown on the same scale in Figure 2. For both properties we see that nonselective molecules **5** and **7** are clustered tightly together, which should not be surprising because of their close structural similarity. Of greater significance is the group of the D1-selective ligands **1–3** (which belong to different chemical families) by their MLP overlaps. On the basis of hydrophobicity those ligands are greatly separated from all other groupings of the ligands, except **5** and **7.** This is merely a graphical statement of the observation that compounds **1–3** all have MLP similarity indices that are (with respect to one another) >0.833, whereas their similarities with respect to the D2-selective ligands are all much smaller (as are those amongst other ligands and themselves). The

Table 1. Similarity Matrices for 10 Dopamine Agonists

a. MEP

	1	2	3	4	5	6	7	8	9	10
1	1.000	0.590	0.442	0.134	0.428	0.459	0.425	0.444	0.440	0.386
2	0.590	1.000	0.639	0.209	0.614	0.702	0.627	0.542	0.391	0.464
3	0.442	0.639	1.000	0.237	0.589	0.582	0.600	0.483	0.389	0.397
4	0.134	0.209	0.237	1.000	0.162	0.217	0.194	0.136	−0.008	0.050
5	0.428	0.614	0.589	0.162	1.000	0.598	0.880	0.555	0.579	0.391
6	0.459	0.702	0.582	0.217	0.598	1.000	0.627	0.727	0.426	0.679
7	0.425	0.627	0.600	0.194	0.880	0.627	1.000	0.549	0.581	0.435
8	0.444	0.542	0.483	0.136	0.555	0.727	0.549	1.000	0.460	0.659
9	0.440	0.391	0.389	−0.008	0.579	0.426	0.581	0.460	1.000	0.375
10	0.386	0.464	0.397	0.050	0.391	0.679	0.435	0.659	0.375	1.000

b. MLP

	1	2	3	4	5	6	7	8	9	10
1	1.000	0.933	0.833	0.285	0.915	0.218	0.887	−0.390	0.279	0.689
2	0.933	1.000	0.895	0.431	0.933	0.069	0.913	−0.382	0.403	0.566
3	0.833	0.895	1.000	0.346	0.828	0.021	0.790	−0.504	0.256	0.525
4	0.285	0.431	0.346	1.000	0.307	−0.543	0.363	−0.129	0.063	0.502
5	0.915	0.933	0.828	0.307	1.000	0.124	0.978	−0.355	0.497	0.464
6	0.218	0.069	0.021	−0.543	0.124	1.000	0.125	0.225	0.193	0.034
7	0.887	0.913	0.790	0.363	0.978	0.125	1.000	−0.352	0.547	0.448
8	−0.390	−0.382	−0.504	−0.129	−0.355	0.225	−0.352	1.000	0.149	−0.235
9	0.278	0.403	0.256	0.062	0.497	0.193	0.547	0.148	1.000	−0.406
10	0.689	0.566	0.525	0.502	0.464	0.034	0.448	−0.235	−0.400	1.000

MLP dissimilarities also cluster the remaining compounds into two families — **4** and **10;** and **6, 8,** and **9.** Not only are the D2-selective ligands separated from the D1s, but the nonselective ligands **4–7** are distributed amongst all the groupings.

For the MEP, by contrast, we observe a much flatter distribution in the dendrogram and molecules **1–3** are not segregated in the same way. In fact, the groupings of the ligands do not readily correspond at all with their selectivities for the dopamine receptors.

Visual confirmation of this result is obtained by the graphical display of the MLP on the solvent-accessible molecular surfaces (Color Plate 1). The value of d_{cutoff} in the MLP [Eq. (3)] was increased to 3.75 Å to make Color Plate 1, because the surface displayed is enlarged relative to the van der Waals surface. We printed out the value of the MLP on a grid of points in a format intelligible to the Insight/Discover package[61] and generated the "Solid_Connolly" surfaces with the software of Athay.[62] The coloring has been scaled so that the blue color corresponds to the lowest value on each surface, and red corresponds to the highest. The molecules are depicted in the alignment used in the study. The distribution of the hydrophobicity over the surfaces of the D1-selective agonists **1–3** is similar. There is a strong hydrophilic region around the two hydroxyl groups and a weaker region around the amine functionality. On the other hand, the distribution of the MLP on the surfaces of the three D2-selective ligands (also in the same orientation) is much less consistent.

We have tabulated the maximum and minimum values of the MLP on the solvent-accessible surface (Table 2). The range of (absolute) values of the maxima and minima of the MLP are remarkably similar for the D1-selective ligands whereas those for the D2 agonists have little in common. D1 selectivity appears to depend on local molecular hydrophobicity. Nevertheless, while similarity in the MLP appears to be required for D1 selectivity, it does not suffice to ensure selectivity. Two nonselective compounds show profiles similar to the D1-selective agonists in their MLPs.

DISCUSSION

We have shown how a quantitative measure of overlap of a pair of molecules may be defined in terms of their hydrophobic "fields." Our implementation uses a grid on which values of the field are calculated, much as other workers have done for both hydrophobic distributions[37,38,43] and MEPs.[22,24,33] Quantitative molecular comparisons are achieved with the use of a normalized overlap metric and patterns amongst a set of molecules are located with statistical analysis. This approach has some features in common with that of Kellogg and co-workers, who have developed HINT[63] for the use of molecular lipophilicity potentials in CoMFA[11] and ligand–receptor docking.[64] Their method also utilizes a grid but they employ the exponential form of the MLP by Fauchère et al.[37]

The overall approach can be looked on as a complement to existing similarity indices and has the strength that little extra coding is required to implement it in current software

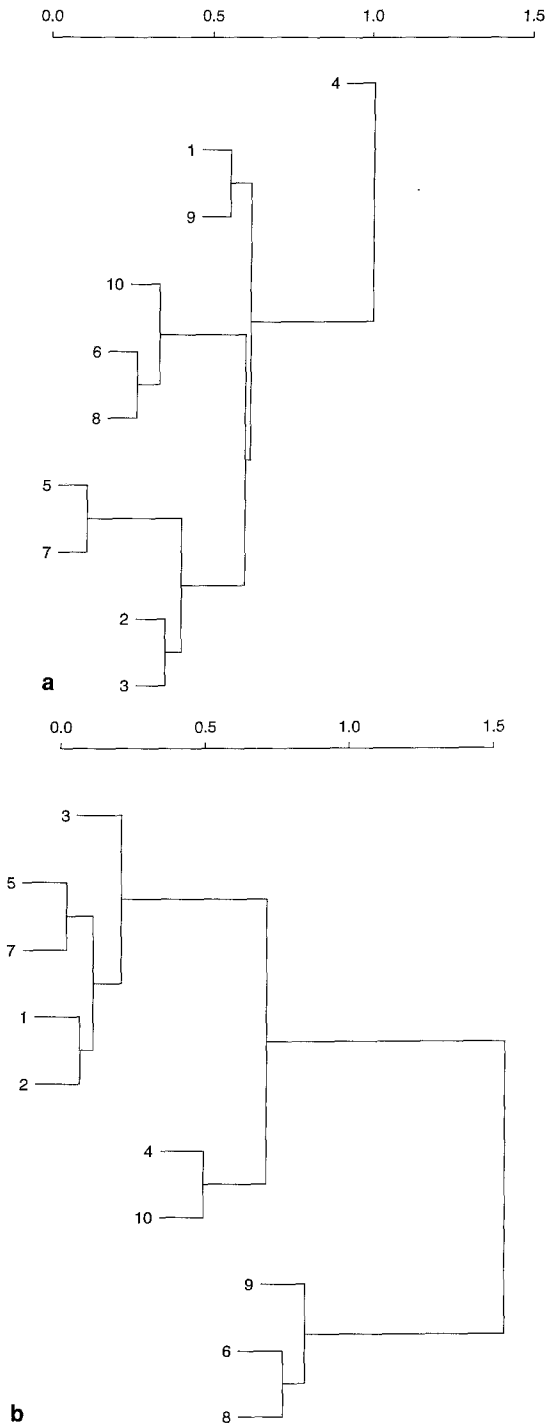

Figure 2. Cluster diagrams for dissimilarity matrices. (a) MEP; (b) MLP.

packages. It is worth noting that the calculation of steric and MEP similarity indices today can be rapid, owing to the Gaussian-fitting methods introduced by Good et al.[26,28] There is no reason per se, why a Gaussian fit to the MLPs may not be employed here, too, thus allowing not only efficient computation of the index, but analytical evaluation of it and its derivatives with respect to translation and rotation. We have not implemented that particular variant ourselves because it does not alter the basic underlying science of the approach presented here. We do note, however, that

Table 2. Values of the maximum and minimum values of the molecular lipophilicity potential on an approximate solvent-accessible surface

Ligand/selectivity	Minimum in MLP	Maximum in MLP
1/D1	−0.2760	0.1908
2/D1	−0.2979	0.1835
3/D1	−0.2679	0.1974
8/D2	−0.1499	0.1641
9/D2	−0.1506	0.1782
10/D2	−0.3658	0.0781

grid-based schemes suffer from several drawbacks: computational intensiveness, numerical instabilities, choice of an appropriate grid, and sensitivities to the positioning of the grid points. In general, the precision and resolution of the calculation are heavily dependent on grid-point density.[23]

We have shown that our MLP-based similarity index is capable of distinguishing between the properties responsible for D1 and D2 recognition, with a specific hydrophobic distribution being more important at the D1 receptor than at the D2 receptor. Visual representations confirm this result. We note also that the similarity index is able to reveal a wider variation in properties of the MEP than is obvious from a visual analysis. This approach therefore holds promise for future applications that might include QSAR-type studies in the manner presented by Good and coworkers.[59,60]

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