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Investigating the extension of pairwise distance pharmacophore measures to triplet-based descriptors

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Summary

Distances between key functional groups have been used for some time as molecular descriptors in 3D database screening and clustering calculations. More recently, a number of groups have explored triplets of molecular centers to describe key ligand features in terms of the properties of triangles. Three-body distances are attractive, since they retain more information than pairwise representations. In most applications, the triangular descriptors have been used to detail molecular shape, using all the constituent atoms or molecular surface points as descriptor centers. As a consequence, the database keying times were such that only single conformers could be considered during molecular descriptor calculations. In this paper we reduce the points used in the molecular description down to the key functional centers, as applied in 3D pharmacophore database searches. Molecular triplets can then be calculated which describe the relative dispositions of differing functional groups, made up from multiple molecular conformations of a given molecule. The new triplet descriptors are compared with classical pairwise distance measures using a variety of pharmacophores, and their potential in database screening, clustering and pharmacophore identification is discussed.

Introduction

Rapidly evaluable geometric molecular descriptions are of central importance in many 3D database applications. Prime examples of descriptor utility include their use as filters in 3D pharmacophore database searches [1], and their application as similarity measures in database clustering calculations [2,3]. Such applications thus play an important role in direct lead generation, both directly within the discovery process [1,4], and indirectly in problems such as maximizing database molecular diversity to increase the effectiveness of random screening.

Many examples of 3D geometric descriptors have been given in the literature [1–3,5–9,11]. Pepperell and Willett considered a number of 3D similarity measures involving interatomic distance measures for the purpose of database clustering [3,5]. Bemis and Kuntz represented molecular shape utilizing histograms of atom triangle perimeter data, again applying the resulting shape descriptors to database clustering calculations [2]. Fisanick et al. have developed descriptors which employ the geometric features of atom triangles and other shapes, in order to describe molecular shape [6]. These descriptors (along with many others) were applied to similarity searches of the Chemical Abstracts Service (CAS) registry substances. Nilakantan et al. also investigated shape measures based on the distribution of atom triplet distances within a molecule, using the resulting descriptors as filters, both in DOCK [7] database searches and stand-alone ligand shape similarity screens [8]. The comparison of a number of these and other molecular descriptors has been made by Bath et al. [9].

Of particular interest for this work is the approach taken by the ChemDBS-3D database software [1,10]. ChemDBS-3D defines ligands in terms of chemical centers (hydrogen bond donors, hydrogen bond acceptors, charged positive centers, aromatic ring centroids and lipophilic centers – see Fig. 1). One of the features of the

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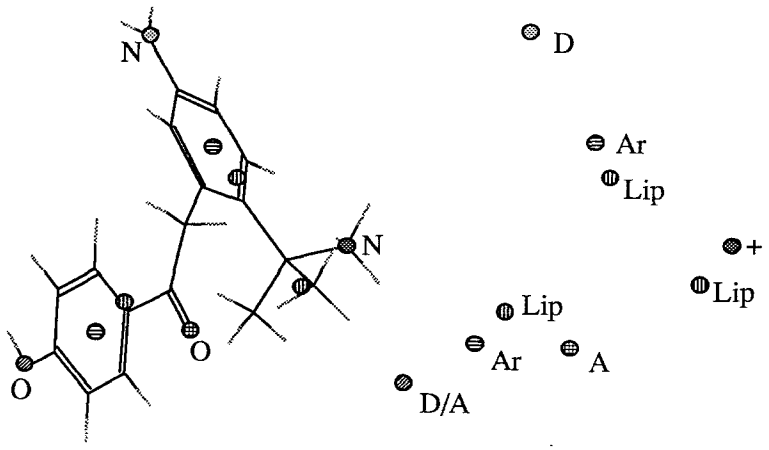

Fig. 1. Example of how ChemDBS-3D breaks molecules down into key functional centers. A = hydrogen bond acceptor, D = hydrogen bond donor, Ar = aromatic ring centroid, Lip = lipophilic centroid (center of group of atoms with ~0 charge), + = charged positive.

software is its generation of 3D distance keys. The program determines the location of all centers within the molecule, identifies the rotatable bonds within the structure, and initiates a conformational analysis of the structure. During the search, each conformer is checked for the pairwise distances among all the centers present in the molecule. These distances are stored within a one-word (32 bits) screen set. Each bit within the word represents a distance range bin. For example, if a particular conformer were found to have a donor–donor distance of 5.5 Å, using the default bin settings the 20th bit of the donor–donor word key would be switched on. Bin sizes are selected to reflect the general size of uncertainties in known pharmacophores. The final word values calculated after completion of the ligand conformational analysis are used as the geometric descriptors.

An obvious concern with the use of triplet-type descriptors is the n^3 dependence (n = number of centers per molecule) when a large database is keyed. As a consequence, database keying using such descriptors can be CPU intensive, generally limiting the molecules keyed to single conformations (this is the case, for example, for all the triplet shape descriptors considered by Bath et al. [9]). In this work we exploit the features of ChemDBS-3D in order to break molecular structure down into just a few discrete points which describe both general molecular shape and critical chemical functionality (see Fig. 1). The distance keys used by ChemDBS-3D are then extended to encompass triplet descriptors. In this way we hope to gain the improved descriptive power of triplet measures, while still incorporating chemistry, shape and conformational flexibility into a single, rapidly calculable molecular descriptor.

Materials and Methods

Triplet descriptors

In a previous paper on molecular descriptors, Good et al. studied various ways to describe triangles, in an attempt to find the best compromise between keying accuracy and storage requirements [11]. Descriptors used included the individual triangle side lengths, triangular perimeter and area. In this work we have employed one of the two-dimensional triplet descriptors used by Good and co-workers. The first dimension corresponds to the perimeter P of a given center triplet triangle. The second dimension corresponds to the deviation of that triangle from equality, employing the fact that, for a given perimeter P, the area of a triangle is given by:

$$\text{Area} = (P/2\,(P/2 - \text{Side1})(P/2 - \text{Side2})(P/2 - \text{Side3}))^{1/2} \quad (1)$$

and that the maximum area for a given perimeter P is made by an equilateral triangle:

$$\text{Max Area} = (P^4/432)^{1/2} \quad (2)$$

The deviation of the area for a given triangle perimeter from the maximum possible area thus gives a measure of the triangle's deviation from equality, and hence an indirect measure of its shape. We store the ratio of the triangle area to the maximum possible area for a given perimeter according to the following equation:

$$\text{Ratio} = \frac{\text{Area}}{\text{Max Area}} \exp -(((P/3 - \text{Side1})^2)^{1/2} + ((P/3 - \text{Side2})^2)^{1/2} + ((P/3 - \text{Side3})^2)^{1/2}/2P/3) \quad (3)$$

The exponential function is used to increase the ratio sensitivity for triangles approaching equality. This descriptor was deemed to provide the best compromise between the high storage costs of storing side-length information for individual triangles in a 3D descriptor, and using the somewhat ambiguous 1D measure of perimeter alone.

In order to maximize the speed of triplet comparisons, it is important to store the triplet shape data in bit form. It was decided that the division of possible perimeter ranges should be restricted to one 32-bit word in order to maintain storage efficiency. The next stage was to determine perimeter range assignments to particular bits. This was accomplished by determining the integer values for the perimeters (round real perimeter value down and add 1) of all possible triplets between ChemDBS-3D centers for the first 50 000 compounds of the Available Chemicals Database (ACD) [12]. Individual 3D conformers were created for each compound by the program CONCORD [13]. Figure 2 shows the resulting triplet perimeter distribution. This distribution was then applied to make perimeter-bit assignments according to the following procedure:

(i) Assign the perimeter value of 1 to the first bit.

(ii) Assign each successive perimeter value to the same bit, until the accumulated total of triplets for the set of perimeter values for a bit exceeds 2% of the total number of triplets found.

(iii) Once the 2% barrier is exceeded, assign the ensuing largest perimeter value to the next bit.

(iv) Repeat process (ii) until all triplets have been assigned.

Applying this procedure to the perimeter distribution depicted in Fig. 2 generated the bin assignments shown in Table 1.

In order to complete the triplet shape descriptor, the area ratio information has to be encoded with the perimeter data. This was done by dividing the area ratio into 10 sections (0.1–1.0). Each triplet can thus be assigned to any one of 10 words depending on its area ratio, with the actual bit switched on being dependent on its perimeter. A sample set of bit assignments is shown in Fig. 3, which depicts the bits turned on for all possible triplets of a pharmacophore comprising three aromatic ring/lipophilic centroids.

Incorporation of triplet keying into ChemDBS-3D

As described above, ChemDBS-3D can determine the distance keys of a given molecule through conformational analysis. During the search, all distances between all centers of each acceptable molecular conformer are collected and stored in the form of a bit key. In order to implement our new triplet descriptors, we needed the possibility to incorporate triplet key calculations directly into the standard ChemDBS-3D keying process [1].

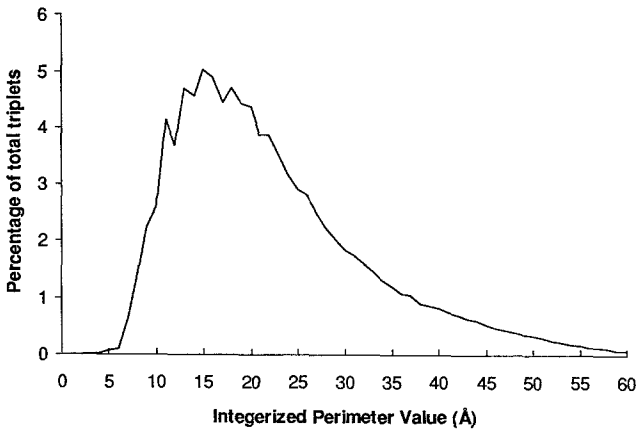

Fig. 2. Distribution of digitized triplet perimeters (INT(PERIMETER)+1) across the first 50 000 compounds of the ACD database.

ChemDBS-3D is part of a suite of molecular modeling programs known as Chem-X [10], which also provides a module called Chem-LIB. The latter module allows users to interface custom programs directly with Chem-X subroutines. One particular function allows users to define their own custom energy calculation routines. In this way, it is possible to force Chem-X to access a user-defined routine each time an acceptable conformer is determined during conformational analysis. For our purposes, rather than calculating energies (for faster database keying, rule-based conformational analyses are undertaken which do not include explicit energy calculations [1,14]), the geometry of each acceptable conformer is used to determine the accessible molecular center triplets for the given structure. Other Chem-LIB routines are used to access the center coordinate data required for triplet calculation. In this way, it has been possible to tie triplet keying directly with the ChemDBS-3D conformational keying procedures using our own custom FORTRAN programs.

These Chem-LIB keying programs have been incorporated into the standard Chem-X log files used in database keying. Thus, when undertaking ChemDBS-3D keying on a particular database of molecules, a parallel set of triplet keys is automatically created. As shown in Fig. 1, the current release of ChemDBS-3D supports five molecular center types. In triplet terms, this translates into 35 possible combinations of centers (donor–donor–donor, donor–donor–acceptor, etc.). Our triplet keying procedure has been designed to interpret the centers and assign the resulting shape to the appropriate triplet word. As a

TABLE 1
BIN ASSIGNMENT FOR DIGITIZED (INT(PERIMETER)+1) TRIPLET PERIMETER VALUES, BASED ON THE PERIMETER DISTRIBUTION SHOWN IN FIG. 2

	Integerized triplet perimeter bit assignments										
Word bit	1	2–22	23	24	25	26	27	28	29	30	31
Perimeter (Å)	1–8	9–29	30–31	32–33	34–35	36–37	38–40	41–43	44–47	48–54	>54

consequence, each molecule has 35 separate triplet descriptors, each with 10 associated words (to discriminate area ratio). Figure 3 shows a sample aromatic–aromatic–aromatic triplet assignment. Each molecule thus requires $35 \times 10 \times 4$ (1400) bytes for triplet descriptor storage. For the tests described in this paper, we used an earlier version of Chem-X (July 1994) that employs only four center-type assignments. We applied an expanded version of the standard extended.mmp parameter set provided by Chem-X, with lipophilic centers treated as being identical to aromatic ring centroids (center type 4). As a consequence, all triplet types which incorporate the fifth center will have zero assignments until our databases are re-keyed using a newer version of ChemDBS-3D. For the purpose of testing, however, this is not of particular importance.

Triplet pharmacophore query keying again uses Chem-LIB routines and Chem-X log files to allow direct incorporation into the ChemDBS-3D searching process. Pharmacophore queries are defined by reading center and geometry information from both sources directly within Chem-X and Chem-X query files. The query file is used to access pharmacophore distance data, while query center information is read from the query directly within the Chem-X program. For each possible center-type triplet combination, all possible triplets are calculated from the lowest to the highest distance values of each of the three sides making up the triplet. For example, for the three-center pharmacophore in Fig. 3, all side-length combinations from 5.0–5.0–5.0 through to 7.0–7.0–7.0 are tried. An increment of 0.1 Å was used in the triplet calculation (5.0–5.0–5.0, 5.0–5.0–5.1, 5.0–5.0–5.2, etc.). The resulting triangles are used to construct bit queries which parallel the molecular descriptors.

Using triplet keys in pharmacophore screening

The resulting triplet queries have been used as an additional screen on top of the formula and distance key screens applied by ChemDBS-3D [1]. For any given pharmacophore, once the ChemDBS-3D screens of a database have been carried out, screening is extended by searching the answer set (an answer set defines a group of molecules passing a particular search criterion) of molecules which passed the initial ChemDBS-3D key screens using the triplet screens. In the current implementation, each molecule in the database has a number as part of its name. A Chem-LIB program extracts the names of the answer set to be screened, and these names are used to select the required data from the triplet direct-access file associated with the currently open database. Once the triplet data for a given molecule has been extracted, it is compared with each of the pharmacophore triplet queries using a bit-wise AND calculation. For each query a non-zero result allows the molecule to pass through to the next query comparison. If all queries are passed, the molecule is added to a new answer set of molecules which have met the pharmacophore triplet requirements.

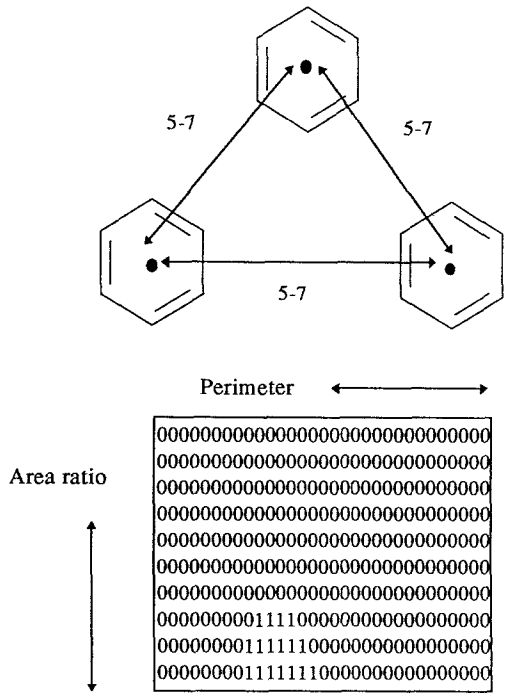

Fig. 3. Equilateral aromatic/lipophilic centroid pharmacophore and associated triplet bit assignment. The bit-perimeter assignments used are listed in Table 1. The pharmacophore triplet assignment is described in the text.

Triplet tests

To test the additional discrimination of triplet descriptors over pairwise distance measures, we decided to compare the ability of the descriptors to screen ligand databases using a variety of pharmacophores. A CONCORD converted 3D version of the Comprehensive Medicinal Chemistry (CMC) database [15] was keyed using both distance and triplet descriptors. Keyed molecules were restricted to those with less than 150 000 conformations, which resulted in a database of 5034 molecules. Rule-based conformational analysis was undertaken on each molecule using two (conjugated and double bonds), three (single bonds) and six (sp^2-sp^3 bonds) rotamers per bond, with the maximum CPU time limited to 1 min per molecule on a Silicon Graphics Indigo 2 (utilized for all calculations). Five pharmacophores were used in the descriptor comparison. These include the 'equilateral' pharmacophore shown in Fig. 3, together with the four pharmacophores illustrated in Fig. 4. The procedure used to screen the CMC has been described above. In addition, the answer set determined from the ChemDBS-3D key screens was also searched using the final geometry search with full conformational regeneration, fitting the molecules directly onto the pharmacophore [1]. The resulting molecular answer set was compared with the triplet

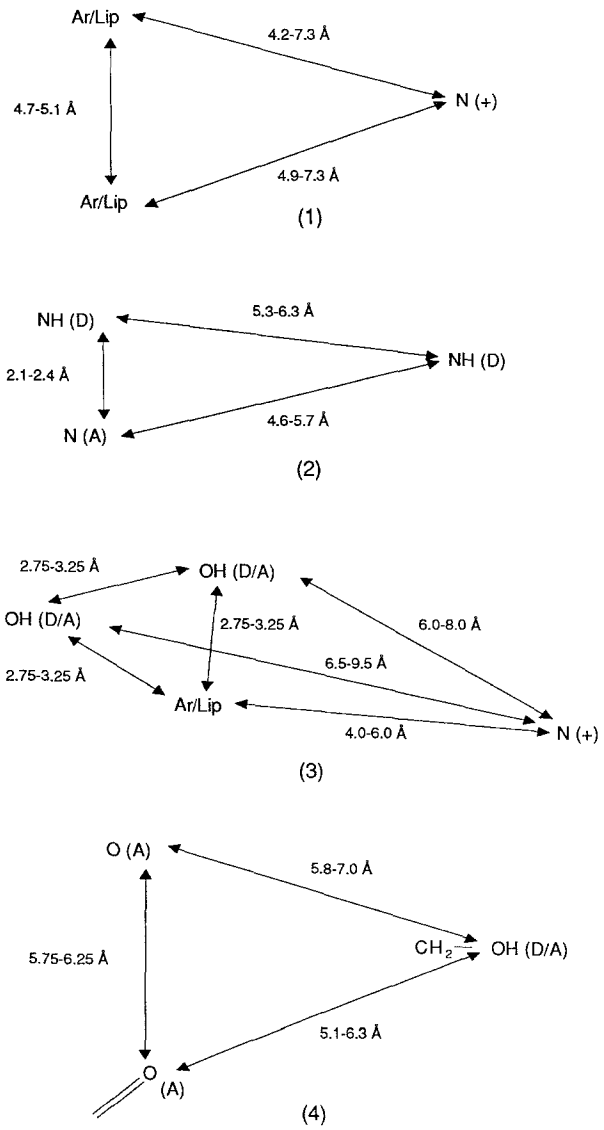

Fig. 4. Four of the five pharmacophores used in the triplet screening tests. (1) Histamine1 [16]; (2) histamine2 [17]; (3) dopamine (derived directly from the structure of dopamine); and (4) protein kinase C [4].

answer set to determine the degree of overlap. The results of these calculations are shown in Table 2.

The additional time required to key the triplets was studied using the first 100 molecules of the CMC containing less than 10 000 potential conformations. These molecules were keyed using the previously defined rotamer conditions, but with no CPU limits imposed on the keying time of each molecule. When only standard ChemDBS-3D distance keys were calculated for these molecules, the time required was 160 s. Addition of triplet keying calculations increased the time required to 282 s.

The speed of triplet screening was investigated through CPU timings of the 'equilateral' pharmacophore triplet screen. The CPU time required to screen the 2087 ChemDBS-3D key-screened answer set structures was 3 s.

Discussion

The results shown in Table 2 illustrate the additional discrimination provided by triplet descriptors under certain circumstances. The 'equilateral' pharmacophore of Fig. 3 was specifically engineered to show the potential advantages of triplet shape measures. Its symmetry and degeneracy are such that the shape is reduced to one Ar/Lip–Ar/Lip distance of 5–7 Å from the perspective of pairwise distance measures. As a consequence, filtering the ChemDBS-3D key-screened answer set using triplet descriptors produces an 82% reduction in its size. Similarly, the highly degenerate (based on ChemDBS-3D center positions) protein kinase C pharmacophore shows a significant (59%) reduction in answer set size on triplet filtering. However, this degree of filtering is not uniform. The histamine2 pharmacophore shows only 2% additional filtering when screened by triplets. Similarly, the histamine2 and dopamine pharmacophores show less dramatic filtering results (11% and 29%, respectively). The large variation in distances and atom types for the histamine2 pharmacophore could well explain why triplet filtering adds little to the screen-out, since the description contains essentially no degeneracy. Histamine1 does show some symmetry in its shape, so on first inspection it is a little surprising that more structures are not filtered out on triplet screening. Analysis of the molecules in the ChemDBS-3D key-screened answer set, together with the large number of structures that can actually fit the pharmacophore on regeneration (562 molecules in the fitted answer set), suggests, however, that the make-up of the CMC is such that many of the ChemDBS-3D key-screened molecules are in fact able to conform to the

TABLE 2
PHARMACOPHORE SEARCH RESULTS ON THE CMC DATABASE

Pharmacophore	Distance answer set	Triplet answer set	Fitted answer set	Triplet/fitted answer set overlap
(1) Histamine1	911	805	562	539
(2) Histamine2	303	295	9	9
(3) Dopamine[a]	136	96	32	32
(4) Protein kinase C	1039	426	7	7
Equilateral (Fig. 3)	2087	376	373	237

[a] This pharmacophore was derived directly from the structure of dopamine.

pharmacophore. It may well be that filtering would therefore be larger on different databases. The triplet filtering on the dopamine pharmacophore is reasonable, but the distance and formula screens of ChemDBS-3D are already good enough to reduce the molecular answer set size to 136 molecules, thus 25% triplet filtering translates into a saving of only 40 molecules.

One problem encountered during these studies is illustrated by the triple/fitted answer set overlap results of the 'equilateral' and histamine1 pharmacophores (Table 2). These numbers show that not all the structures deemed to be able to match the pharmacophore during ChemDBS-3D geometric fitting/conformer regeneration are found in the triplet filter answer set. The reason for this is that, in the final geometric search phase, ChemDBS-3D uses an additional fitting tolerance on top of the pharmacophore tolerances (1.0 Å in the experiments described above). This is done to minimize the potential for missed structures due to the approximations used in conformational analysis during database keying and searching [18]. As a consequence, molecules can be deemed to match the pharmacophore even when they do not strictly adhere to the pharmacophore tolerances. Because the triplet keys do not include this additional tolerance, these molecules are sometimes thrown out. Adjustment of this fitting tolerance illustrates its effects. Reduction of the tolerance to 0.1 Å in the case of the histamine1 search reduces the number of fitted hits to 65, all of which appear in the triplet filtered answer set. A similar increase in overlap can be obtained by increasing the triplet pharmacophore tolerance. When the triplet pharmacophore distances for the 'equilateral' pharmacophore are increased to 4–8 Å, the overlap with the fitted answer set increases from 237 to 342. Of course, the problem with increasing the tolerance is that the ability of the triplets to filter the search is reduced. In the 'equilateral' pharmacophore case, this additional 'tolerance' increased the size of the triplet answer set from 376 to 1082, reducing the filtering of the ChemDBS-3D key screens to around 50%. Even at this level, around 10% of the fitted molecules still had not been located by the triplet screen. A study of the missing molecules showed deviations from the pharmacophore even greater than the permitted tolerances. The reason for this turned out to be that ChemDBS-3D doubles the fitting tolerance when matching atoms to the query. As a consequence, in the 'equilateral' query the 1.0 Å fitting tolerance effectively results in a 2–10 Å pharmacophore distance. The utility of triplet screening is thus sensitive to the fitting tolerances defined as being acceptable at the start of the search, although the removal of poorly fitting structures may prove useful under certain circumstances.

The additional time requirement for triplet screening does not seem particularly exorbitant from the studies undertaken. The number of triplets that must be calculated varies as approximately the cube of the number of centers in the molecule being keyed. As a consequence, the keying time will vary widely depending on the number of centers present. For example, methotrexate, which is defined by ChemDBS-3D as having 18 centers (4896 triplets), takes five times longer (119 s versus 24 s) to key its 2970 acceptable conformations with triplets. The average number of centers per molecule in the CMC is only ~10 (720 triplets), however. One would thus expect only ~15% of the fivefold increase to manifest itself across the whole database, which is in keeping with the calculation time for the 100-molecule subset.

The search speed for triplet filtering was found to be ~700 molecules per second. The rate-limiting step of the calculation is the continuous access of the triplet data file. Faster calculations would be possible if the triplet data were stored in memory. This has not been implemented, because each molecule requires 1400 bytes of storage, which translates to >100 Mb of RAM for a database of 100 000 molecules. One would thus require either a more frugal use of resources in triplet description, or a significant amount of memory to store the triplet data on-line. For most purposes, however, a search speed of 700 molecules per second is fast enough.

It should be emphasized at this point that the screening studies described here were not performed just to test the utility of triplet searches in pharmacophore screens. They also provide an elegant way of showing how the use of triplets can enhance descriptive power when compared to pairwise distance-based pharmacophore descriptors. An example of the kind of structure that is filtered out by triplet screening is illustrated in Fig. 5. This structure passed ChemDBS-3D key screening for the protein kinase C pharmacophore. It is clear that the molecule contains all the individual distance requirements for matching the pharmacophore, but that no three distances together can form the required triangular shape. It is the ability of triplet descriptors to distinguish these shape features, together with their lower susceptibility to distance and atom-type degeneracy, that gives them their utility. It is easy to see how these features would be of great use in

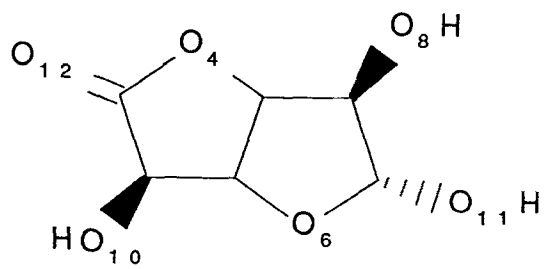

Fig. 5. Sample structure of a molecule passing the ChemDBS-3D key screens for the protein kinase C pharmacophore, but failing to clear the triplet filter. Distances between heteroatoms are: O6-O4: 3.2183 Å; O8-O4: 3.4424 Å; O8-O6: 3.5550 Å; O10-O4: 3.1891 Å; O10-O6: 3.6105 Å; O10-O8: 5.5657 Å; O11-O4: 4.4425 Å; O11-O6: 2.3549 Å; O11-O8: 3.2055 Å; O11-O10: 5.8775 Å; O12-O4: 2.2464 Å; O12-O6: 4.3535 Å; O12-O8: 5.6504: Å; O12-O10: 3.0341 Å; O12-O11: 5.9104 Å.

database clustering, since degeneracy (multiple donors, acceptors etc.) often abounds within molecules (for example the structure depicted in Fig. 5). Such triplet measures should thus prove extremely useful as molecular similarity descriptors.

ChemDBS-3D keys have also been used as descriptors to aid in pharmacophore identification [18]. Distance keys are calculated in the ChemDBS-3D/Chem-X software from the observed distances between all the pharmacophore centers in a group of active ligands. Common center–center distances are used to define potential three- and four-center pharmacophore descriptions, which can then be validated through their use as queries in 3D searches on the ligand database. One of the problems of such an approach is that many false positive models are generated due to ambiguity in the distance key descriptors. The application of triplet keys as an additional filter to these screens should reduce the number of incorrect binding models proposed.

ChemDBS-3D was chosen for this work because the 3D key generation function was suitable for conversion to triplet descriptor creation. There is no reason why the specific conformer storage methodology applied by the CATALYST package [19] could not be used to derive similar descriptors. The torsional tweak methodology available in ISIS [20], UNITY [21] and ChemDBS-3D is not suitable for pharmacophore-based descriptors generated in the manner described. This is because keying relies on explicit multiple conformation generation to define the molecular descriptors. Torsional tweak does not undertake conformational analysis to create distance screens, instead relying on simple minimum and maximum path lengths between centers [20]. Conformational flexibility is only taken into account during the search, and then only to force the molecule to conform to a specific pharmacophore*.

Conclusions

New triplet descriptors have been proposed which show enhanced discriminatory powers when compared to their pairwise distance counterparts. These measures show potential as molecular descriptors, both in database clustering and in pharmacophore identification, and should have some use as additional filters in pharmacophore database searches, although this is dependent on search tolerance and conformational keying accuracy.

*Alternative techniques are required to create similar pharmacophore-based descriptors using torsional tweaking. Since the submission of this paper, one such method, known as pharmacophore-derived queries, has been proposed [22]. An alternative method for exploiting rule-based conformational analysis to generate pharmacophore-based descriptors has also been presented [23].

Acknowledgements

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