

Topological Distance Based 3D Descriptors for Use in QSAR and Diversity Analysis

Christian T. Klein,* Dominik Kaiser, and Gerhard Ecker

Institute of Pharmaceutical Chemistry, University of Vienna, Universitätszentrum II,
Althanstrasse 14, A-1090 Wien, Austria

Received October 18, 2002

In topological autocorrelation approaches molecular descriptors are calculated by summing up properties located at given topological distances. Since the relationship between topological and Euclidean distance contains 3D structural information, in the present paper a modified version of an autocorrelation approach is proposed to include this type of information. Steric, electronic, and indicator-variable-type descriptors are calculated and used in QSAR studies with three different data sets. The results demonstrate that the descriptors can be efficiently used in cluster- and QSAR analysis. The models obtained are highly predictive and comparable to those obtained by other commonly used 3D-QSAR methods.

INTRODUCTION

With grid based methods in 3D quantitative structure–activity relationships (3D-QSAR) a new generation of molecular descriptors was introduced, with the facility to create virtual receptor sites (VRSs), thus giving insight into the interaction of active molecules with their biological targets, even if the spatial structure of the targets is unknown. The common philosophy of these methods is to place the superimposed molecules into a grid and to calculate energy contributions—mostly steric and electrostatic—at each grid point. The contributions can be interaction energies between a probe, placed at the grid point, and the considered molecule(s), as in CoMFA¹ or GRID.² In HASL³ the electric contribution is evaluated like in CoMFA, but the steric part is modeled by a binary code: 1 if the grid point lies inside the molecule and 0 in the contrary case. SOMFA⁴ uses the same binary description of steric contributions; however, the electrostatic contribution is the molecular electrostatic potential (MEP) at a grid point, rather than an interaction energy with a probe. Moreover, the concept of mean centered activity is introduced, a sort of variable weighting. In Compass⁵ the interaction points are placed at 2 Å from the common molecular surface of the molecules.

A major problem of these methods is the high sensitivity to the molecular alignment of the compounds of interest. Methods, which use the concept of similarity, are less sensitive to superposition. CoMSIA⁶ uses Gaussian functions to evaluate the similarity at a grid point to a given probe, the resulting similarity fields being smoother, i.e., less affected by superposition, than the interaction fields. Similarity matrix methods^{7,8} also give good results: $n \times n$ similarity indices between all pairs of the n compounds considered are evaluated.

To overcome the problem of molecular superposition CoMMA⁹ (Comparative Molecular Moment Analysis) calculates descriptors based on 3D structures without reference to a common orientation frame. Descriptors are the moments

of inertia (shape), magnitude of dipole and principal quadrupole moment (electrostatics), and additional parameters, which relate shape and charges.

The MS–WHIM (Weighted Holistic Invariant Molecular) approach¹⁰ overcomes the problem of molecular alignment by calculating statistical parameters (eigenvalue proportion, skewness and kurtosis) from the score matrix obtained from weighted principal component analysis (PCA).

Methods based on autocorrelation of certain molecular properties represent another type of approaches that are alignment insensitive. *Topological autocorrelation* descriptors have been first described by Broto et al.¹¹ Also in the Gasteiger group descriptors based on this concept have been successfully developed.¹² The descriptors are obtained by summing up the products of certain properties of two atoms, located at given topological distances. The topological distance T_{ij} represents the minimum number of bonds between two atoms i and j . Similarly, *spatial autocorrelation*¹³ considers properties on the molecular surface separated by a given Euclidean distance.

In a new variant of this approach molecular interaction fields (MIFs) are used as initial variables, but only the highest product of the autocorrelation sum is stored, while the others are discarded. In this way the descriptors can be back-transformed into the original variables, thus yielding grid independent descriptors (GRIND).¹⁴

Inspired by the idea of autocorrelation, in the present work descriptors which relate Euclidean to topological distances are introduced. Characterization of molecules via these descriptors—their calculation being very fast—turns out to be highly effective, reflected in reliable PLS models and cluster analysis.

METHODS

A relationship between topological (T_{ij}) and Euclidean distance (D_{ij}) contains important 3D-structural information. If a chain, for example, is in the extended conformation, the distance between two atoms separated by a given topological distance may be much larger than in another conformation. We thus consider the average Euclidean distance between all atoms located at a given topological distance d . It is

* Corresponding author phone: +43 1 80105-2573; fax: +43 1 80105-9573; e-mail: christian.klein@vie.boehringer-ingenheim.com. Present address: Boehringer Ingelheim Austria, Dr. Boehringer-Gasse 5-11, A-1121 Vienna, Austria.

included in a steric and an electronic descriptor via a quadratic form, in conjunction with covalent radii and sigma orbital electronegativities. The steric descriptors thus read

$$S(d) = \frac{1}{k(d)} \left[\sum_{i=1}^{n-1} \sum_{j=i+1}^n \text{rad}_i \cdot D_{ij} \cdot \text{rad}_j \right]_{T_{ij}=d} \quad (1)$$

where n is the number of atoms, rad_i , rad_j are the corresponding covalent radii, and $k(d)$ is the number of atom pairs located at a given topological distance d . The covalent radii used are taken from ref 15.

In a similar fashion electronic properties are described by the sigma orbital electronegativities χ_k :

$$X(d) = \frac{1}{k(d)} \left[\sum_{i=1}^{n-1} \sum_{j=i+1}^n \chi_i \cdot D_{ij} \cdot \chi_j \right]_{T_{ij}=d} \quad (2)$$

In the present paper the sigma orbital electronegativities¹⁶ are used. We have tested also electronic charges obtained from semiempirical methods. The improvement of the results is not significant and the computational costs are much higher (the electronegativities must not be calculated). Since the method is intended not only for QSAR but also for diversity analysis, i.e., for large(r) data sets, we have decided to go with electronegativities.

In addition to a steric and an electronic descriptor, an indicator-type variable discriminating between atom types is employed:

$$I(d) = \frac{1}{k(d)} \left[\sum_{i=1}^{n-1} \sum_{j=i+1}^n \delta_{\text{type}_i \text{type}_j} \right]_{T_{ij}=d} \quad (3)$$

$\delta_{\text{type}_i \text{type}_j}$ is the Kronecker delta, being 1 if *atom type*_{*i*} is equal to *atom type*_{*j*} and 0 in the contrary case.

Calculating these descriptors for different topological distances, vectors of the form

$$(S(1), X(1), I(1), \dots, S(k), X(k), I(k), \dots) \quad (4)$$

are obtained for each compound. The corresponding data matrix, resulting from all compounds, is correlated with the biological activity.

In what follows, the descriptors will be called 3D-TDB (3D-topological distance based) descriptors. Their calculation is performed with an in house program that uses the fast algorithm of Müller et al.¹⁷ for the computation of the topological distance matrix needed.

Unless noted, descriptors up to the topological distance of 13 are calculated, i.e., vectors of dimension 39 are computed. For molecules with less topological distance dimensionality the descriptor vectors are completed with zeros.

All other descriptors used for comparison are calculated with the Tsar 3.3 software.¹⁸ All of the descriptors available are considered: molecular volume, surface, mass and refractivity, logP, dipole moment, all possible Kier and Hall χ^- , ${}^v\chi^-$, κ^- , and κ_α indices,¹⁹ shape flexibility,¹⁹ the sum of electrotopological indices,¹⁹ the Balaban²⁰-, Randic²¹-, and Wiener²² topological index, the number of hydrogen bond donors and acceptors, and the number of individual heteroatoms and halogens. They will be referred to as Tsar descriptors.

The quality of the obtained models are estimated by the correlation coefficient (r), the cross-validated (leave-one-out) correlation coefficient (q^2), by the statistical significance and by the standard deviation of errors of prediction, *SDEP*, obtained from external test sets

$$SDEP = \sqrt{\frac{\sum_{i=1}^n (y_{i,pred} - y_{i,exp})^2}{n}} \quad (5)$$

where $y_{i,pred}$ is the predicted and $y_{i,exp}$ the experimental value of the dependent variable.

Three data sets are used to study the new descriptors. The benchmark steroid set¹, originally compiled by Cramer et al.¹, was obtained from the Gasteiger group homepage.²³ In this set several bugs from other versions were fixed.¹⁴ The structures of the steroids are given in Chart 1; their binding affinities to the corticosteroid binding globulin are shown in Table 1.

As usual the steroids 1–21 are used as training set and the steroids 22–31 as test set.

The second set consists of 70 guest compounds from diverse classes that form 1:1 host–guest complexes with β -cyclodextrin. The free energies of complexation correlate well with molecular properties, as described previously.^{24–26} The free energies of complexation of the compounds are shown in Table 2. A set of 20 structures (compounds 51–70) was randomly picked out from the data set and is used as external test set.

The third data set consists of 70 TIBO-based HIV-1 reverse transcriptase (RT) inhibitors described in ref 27. Their general structure is shown in Figure 1, the activities in Table 3.

This set was chosen because the biological activities strongly depend on the stereochemistry of the compounds. The molfiles were generated with IsisDraw 2.3²⁸ and subsequently converted to 3D structures with CORINA,²⁹ as implemented in the Tsar package. The stereochemistry of the structures was checked and corrected where needed. Compounds 1–50 are used as a training set, compounds 51–70 as a test set.

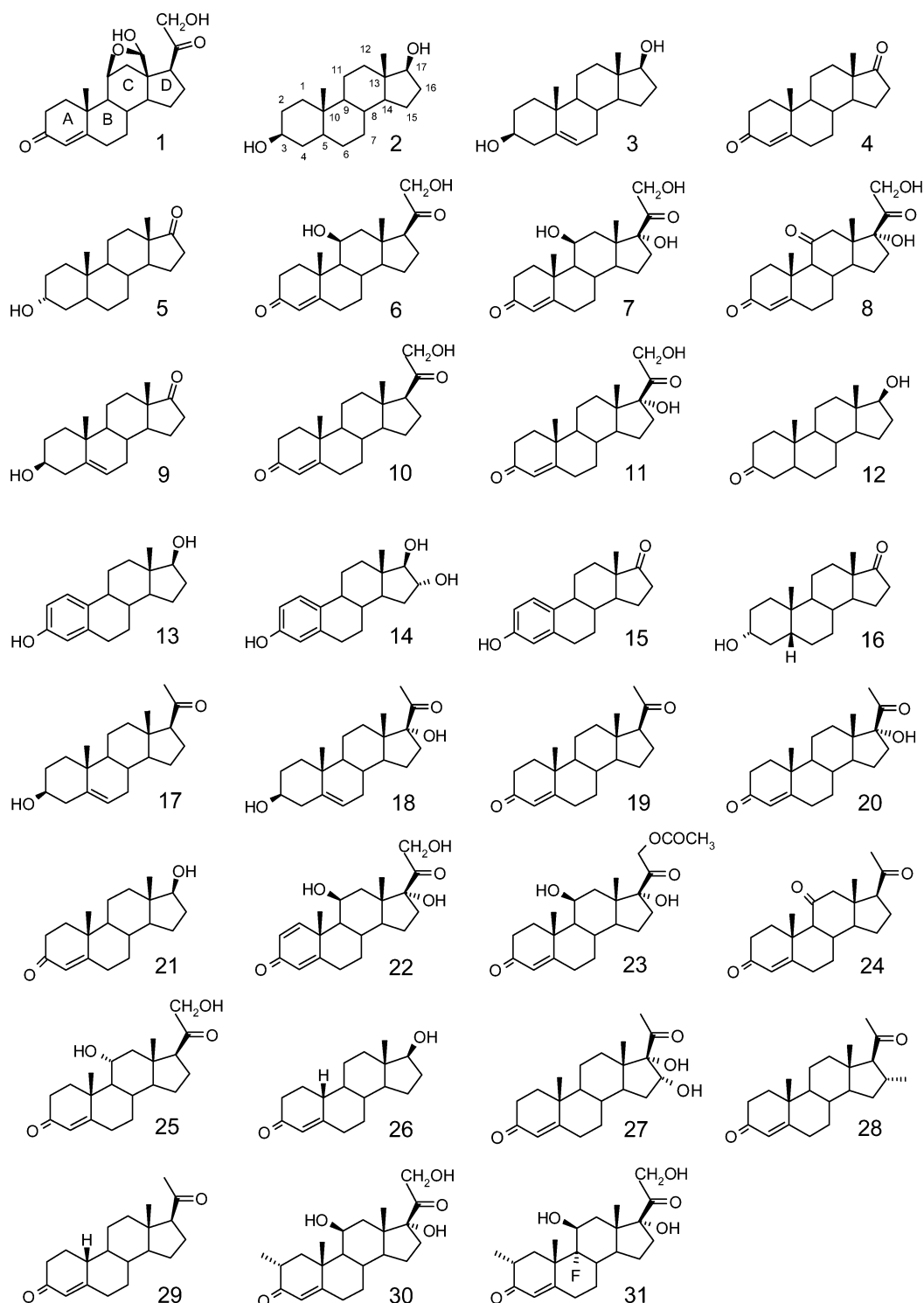
The PLS³⁰ facility from Tsar is used to correlate the descriptors with the biological activities.

RESULTS AND DISCUSSION

The best predictions of the test sets using 3D-TDB descriptors and the available descriptors from Tsar, respectively, are presented in Table 4 for all three data sets.

It can be seen that with 3D-TDB descriptors the obtained PLS models are more reliable, reflected by the statistical parameters, as well as by the *SDEPs*. The *F*-values for all models exceed the $F_{0.95,k,n-k-1}$ percentage points (n -number of substances data set, k -number of PLS components) at least five times, indicating that the models are significant at 95% level. According to some authors³¹ the *F*-ratio should exceed the percentage point at least four times. For the $F_{0.99,k,n-k-1}$ percentage points this condition is fulfilled for all models except for the model of benchmark steroids obtained with Tsar descriptors, indicating that these are significant even at 99% level of confidence.

Chart 1



Benchmark Steroids. For the benchmark steroids the *SDEPs* of the test set are larger when Tsar descriptors are used; in the case of 3D-TDB descriptors the predictions of the test set are comparable to those obtained with other 3D-QSAR methods (for comparison see ref 4).

We often have observed that the best predictions of external test sets are not necessarily made with the models that have the highest q^2 values.²⁶ This finding is confirmed in a recent paper,³² showing that for various data sets q^2 does not correlate with the predictive ability of external data sets. The authors point out that the real predictive power of a

model can only be established using an external test set that was not used for building the model. This situation is once again confirmed in the present study. While the 2 component model for the benchmark steroids—obtained with 3D-TDB descriptors—with q^2 of 0.558 leads to a *SDEP* of 0.583 (Table 4), the 5 component model (not shown in Table 4) with $q^2 = 0.831$ gives a *SDEP* of 0.886.

For both, the 3D-TDB- and Tsar descriptors, the models with more than 2 (3D-TDB) or 1 (Tsar) component(s) have improved statistical parameters but notably lower predictive power of the external test set.

Table 1. Steroid Benchmark Set with the Corresponding CGB Affinities^a

compound	steroid	CGB affinity (logK)
1	aldosterone	6.279
2	androstanediol	5.000
3	5-androstenediol	5.000
4	4-androstenedione	5.763
5	androsterone	5.613
6	corticosterone	7.881
7	cortisol	7.881
8	cortisone	6.892
9	dehydroepiandrosterone	5.000
10	11-deoxycorticosterone	7.653
11	11-deoxycortisol	7.881
12	dihydrotestosterone	5.919
13	estradiol	5.000
14	estriol	5.000
15	estrone	5.000
16	etiocholanolone	5.255
17	pregnenolone	5.255
18	17 α -hydroxypregnenolone	5.000
19	progesterone	7.380
20	17-hydroxyprogesterone	7.740
21	testosterone	6.724
22	prednisolone	7.512
23	cortisol-21-acetate	7.553
24	4-pregnene-3,11,20-trione	6.779
25	epicorticosterone	7.200
26	19-nortestosterone	6.144
27	16 α ,17 α -dihydroxy-4-pregnene-3,20-dione	6.247
28	16 α -methyl-4-pregnene-3,20-dione	7.120
29	19-norprogesterone	6.817
30	2 α -methylcortisol	7.688
31	2 α -methyl-9 α -fluorocortisol	5.797

^a In many publications the affinities are given as pK values; however, logK's are more obvious, since an increased value indicates increased binding affinity.

Molecular descriptors should be correlated as less as possible, since redundancy increases the noise in the data and can lead to misinterpretation of the importance of individual descriptors. Comparing the correlation matrices of 3D-TDB- and Tsar descriptors reveals that 3D-TDB descriptors are throughout less correlated among each others than Tsar descriptors. For the benchmark steroid set the percentage of correlation higher than 0.9, between 0.7 and 0.9, and below 0.7 is shown in Table 5.

The lower predictive power of the models obtained with the Tsar descriptors could be explained, on one hand, by the much higher correlation between variables. On the other hand, much of the Tsar descriptors describe rather overall properties of the molecules (molecular mass, volume, surface, dipole moment, logP, molecular refractivity, number of hydrogen bond donors and acceptors). Since the benchmark steroids are homologous, differences in the biological activity result from (small) local structural changes, as a consequence of highly specific interactions with the corticosteroid binding globulin. Such local structural variations are only poorly explained by overall properties. In the case of the 3D-TDB vectors the situation is somewhat different. The summation over pairs of properties is also done for the whole molecule; however, the descriptors obtained for small topological distances retain local structural information. The X(2) descriptor, for example, is calculated from pairs of distances and electronegativities of all atoms in the molecule, separated by a topological distances of 2, i.e., by 1 atom (or 2 bonds,

respectively). Higher X(2)-values will thus reflect higher local "densities" of electronegative atoms in the molecule.

We have also compared our approach with the spatial autocorrelation method developed by Wagener et al.¹³ The descriptors were calculated as described in the paper using the program Surface,³³ developed in the Gasteiger group. SNNS³⁴ was used to train a neuronal net as described. Although q^2 is improved for the spatial autocorrelation approach (0.689 versus 0.558 for the 3D-TDB method), the SDEP is higher (0.639 versus 0.583 for the 3D-TDB method).

TIBO Derivatives. A similar situation is encountered with the TIBO data set, i.e., the 3D-TDB descriptors give rise to models with better predictivity than the Tsar descriptors, as can be seen from Table 4. The compounds are homologous, and their biological activities strongly depend on their stereochemistry.

Again, the model with the highest q^2 of 0.712 (not shown in Table 4) has a reduced predictive ability of the test set ($SDEP = 0.754$), compared to the model with $q^2 = 0.613$ (shown in Table 4), leading to a $SDEP$ of 0.610 for the test set.

To check out whether the 3D-TDB descriptors are capable to discriminate between differences in stereochemistry, three pairs of diastereoisomers [compounds (23, 25), (28, 29) and (30, 32)] were excluded from the training set and used for external prediction. Comparing the experimental log(1/IC₅₀) values of (5.65, 4.84), (7.38, 5.94), and (6.64, 5.30) with the predicted ones, viz., (5.78, 5.43), (6.65, 6.68), and (6.14, 5.74), shows that for the first and the third pair of diastereoisomers the (S,S) isomers are correctly predicted as less active. The (R,R) and the (R,S) isomers of the second pair have the same predicted activities. The $SDEP$ of 0.565 for these 6 compounds is slightly lower than the $SDEP$ for the entire test set, which is 0.609 (Table 4).

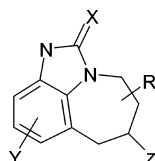
In the original paper²⁷ the TIBO data set is taken from the three pairs of diastereoisomers included in the training set which comprises 47 compounds. To be comparable to the CoMFA results published there, we also used the same training set. The best PLS model obtained with the 3D-TDB has a $SDEP$ of 0.656 for the test set. The best CoMFA model published has better external predictivity, with a $SDEP$ of 0.527. It is clear that grid-based descriptors such as those used in CoMFA have increased structural resolution than descriptors where certain properties are summed up over the whole molecule, as in the case of 3D-TDB. It is therefore not surprising that CoMFA gives superior results for this data set, where stereochemistry is so important for the biological activity.

Inclusion Compounds. In the case of the guest molecules that form inclusion complexes with β -cyclodextrin the situation is different: for both Tsar- and 3D-TDB descriptors models with approximately the same predictive quality are obtained. Although the statistical parameters are better for the 3D-TDB descriptors models, the external predictivities are nearly the same (Table 4). The reason for this situation stems from the fact that the cyclodextrin cavity is nearly symmetrical and the driving force of inclusion is, besides van der Waals forces, the hydrophobic effect.^{24,25} In other words, the host-guest interaction is much less specific than a receptor-ligand interaction and can thus be modeled well by Tsar and 3D-TDB descriptors.

Table 2. Guest Compounds Used in This Study^a

	compound	$\Delta G_{\text{complex}}$		compound	$\Delta G_{\text{complex}}$
1	PGE1	-4.388	36	sulfamethomidine	-3.182
2	prostacyclin	-4.013	37	furosemide	-2.435
3	hydrocortison	-4.918	38	digitoxigenin	-5.588
4	beclomethasone diprop	-4.142	39	cinnarizine	-4.964
5	indomethacin	-3.365	40	chlorothiazide	-1.548
6	flurbiprofen	-5.036	41	carbutamide	-3.126
7	ketoprofen	-3.897	42	betamethasone valerate	-4.722
8	piroxicam	-2.654	43	sulfamonomethoxine	-3.384
9	thiopental	-4.472	44	sulfisoxazole	-3.167
10	phenytoin	-4.168	45	tolnaftate	-5.235
11	acetohexamide	-4.007	46	digitoxine	-5.747
12	menandion	-3.095	47	acenocumarol	-3.744
13	<i>p</i> -ethylaminobenzoat	-3.666	48	amobarbital	-3.735
14	<i>p</i> -butylhydroxybenzoat	-4.630	49	bendroflumethiazide	-2.589
15	medazepam	-3.280	50	barbital	-2.435
16	cortisone	-4.566	51	PGF2 α	-4.202
17	cortisone acetate	-4.915	52	fludiazepam	-3.182
18	triamcinolone acetonide	-4.767	53	fenbufen	-3.591
19	fluocinolone acetonide	-4.723	54	phenobarbital	-4.441
20	hydrocortisone acetate	-4.771	55	sulfaphenazole	-3.208
21	sulfadimethoxine	-3.080	56	clofibrate	-4.252
22	cyclobarbitol	-3.697	57	<i>p</i> -butylaminobenzoat	-4.360
23	hexobarbital	-4.206	58	<i>p</i> -ethylhydroxybenzoat	-4.109
24	mephobarbital	-4.315	59	prednisolone acetate	-5.109
25	nitrazepam	-2.692	60	dexamethasone	-4.980
26	<i>m</i> -methylcinamic acid	-4.003	61	sulfapyridine	-3.687
27	<i>p</i> -hydroxycinamic acid	-3.859	62	pentobarbital	-4.115
28	griseofulvine	-2.006	63	triamcinolone diacetate	-4.584
29	hydrochlorothiazole	-2.400	64	nimetazepam	-2.364
30	mefenamic acid	-3.403	65	hydroflumethiazide	-2.052
31	picotamide	-2.395	66	prostaglandin A1	-4.274
32	progabide	-3.461	67	dehydrocholic acid	-5.179
33	proscillaridine	-4.922	68	paramethasone	-4.625
34	prostaglandine B1	-3.928	69	sulfisomidine	-2.872
35	sulfanilamide	-3.774	70	allobarbitol	-2.705

^a $\Delta G_{\text{complex}}$ is the free energy of complexation, calculated from 1:1 host-guest complexation constants (refs 24 and 25).

**Figure 1.**

As for the QSAR models, clustering of the 70 compounds from the guest data set gives similar results for the 3D-TDB and the Tsar descriptors, respectively. The compounds are clustered on the basis of Euclidean distances between each other. These distances are measures of similarities between the molecules. Hence, the similar results of the cluster analysis indicate that both the Tsar and the 3D-TDB descriptors are able to describe overall similarities between the compounds.

The dendrograms for the cluster analysis are shown in Figures 2 and 3, respectively.

In both cases all 5 prostaglandines (cluster A, Figures 2 and 3) as well as all 16 steroids (cluster B, Figures 2 and 3) are found within the same clusters. A small clusters of eight-members (3D-TDB, cluster C Figure 3) and of six-members (Tsar, cluster C, Figure 2) contain mostly barbiturates. Out of 30 clusters, 14 clusters have the same centroids, for both the 3D-TDB and the Tsar descriptors.

To get a deeper insight into the relationship between the 3D-TDB descriptors and the other descriptors used, cluster analysis of *all descriptors* for the guest data set is per-

formed.³⁵ When clustering compounds, distances (in our case Euclidean distances) are computed for pairs of compounds using molecular descriptors. If distances are calculated for pairs of descriptors, clusters of descriptors are obtained, reflecting similar descriptorial properties. The dendrogram is shown in Figure 4.

The 3D-TDB descriptors tend to cluster mainly with other 3D-TDB descriptors. All steric $S(k)$ descriptors excepting $S(1)$ are found within the same cluster (D, Figure 4). D is a subcluster of B, which contains nearly all Kier-Hall χ - and κ -indices. The χ -indices represent weighted counts of sub-graphs of certain types (path, cluster, path/cluster, ring) in the molecule. κ -indices code for features concerning the shape of the molecules: the $^3\kappa$ -index, for example, is related to the degree and the centrality of branching. It is the larger when branching is nonexistent, or when it is located at the extremities of the graph.

The same cluster-membership of the Kier and Hall connectivity indices and of the steric 3D-TDB descriptors suggests that the latter also carry information on local structural features of molecules, as the connectivity indices do; yet, the steric 3D-TDB descriptors are found in different subclusters, thus suggesting that their information is unique.

The electronic 3D-TDB descriptors $X(k)$ are found in the same cluster (A) with the molecular refractivity and the sum of E-state indices. Both of the latter are related to electronic properties of a molecule. The molecular refractivity is a function of the polarizability of the molecule; the sum of

Table 3. TIBO Derivatives (See Figure 1) Used in This Study Are from Ref 27

compound	R	X	Y	Z	log(1/IC ₅₀)
1	H	S	8-Cl	DMA ^a	7.34
2	H	S	9-Cl	DMA	6.79
3	5-CH ₂ CH ₃ (R)	O	—	2-MA ^b	4.30
4	5-CH(CH ₃) ₂ (R)	O	—	2-MA	5.00
5	5-CH(CH ₃) ₂ (R)	O	—	DMA	5.00
6	5,5-di-CH ₃	O	—	2-MA	4.64
7	4-CH ₃ (R)	O	—	2-MA	4.49
8	4-CH ₃ (S)	S	9-Cl	2-MA	6.17
9	4-CH ₃ (R)	S	9-Cl	CH ₂ CH(CH ₂) ₂	5.66
10	4-CH(CH ₃) ₂ (R)	O	—	CH ₂ CH ₂ CH ₃	4.13
11	4-CH(CH ₃) (R)	O	—	2-MA	4.90
12	4-CH ₂ CH ₂ CH ₃ (R)	O	—	CH ₂ CH ₂ CH ₃	3.74
13	4-CH ₂ CH ₂ CH ₃ (R)	O	—	2-MA	4.32
14	7-CH ₃ (R)	O	—	CH ₂ CH ₂ CH ₃	4.08
15	7-CH ₃ (R)	O	—	DMA	4.92
16	7-CH ₃ (R)	O	8-Cl	DMA	6.84
17	7-CH ₃ (R)	O	9-Cl	DMA	6.79
18	7-CH ₃ (R)	S	—	CH ₂ CH ₂ CH ₃	5.61
19	7-CH ₃ (R)	S	—	DMA	7.11
20	7-CH ₃ (R)	S	8-Cl	DMA	7.92
21	7-CH ₃ (R)	S	9-Cl	DMA	7.64
22	4,5-di-CH ₃ (R,S)	O	—	DMA	4.25
23	4,5-di-CH ₃ (R,R)	S	—	DMA	5.65
24	4,5-di-CH ₃ (S,S)	S	—	CH ₂ CH(CH ₂) ₂	4.87
25	4,5-di-CH ₃ (S,S)	S	—	DMA	4.84
26	4-keto-5-CH ₃	S	9-Cl	CH ₂ CH ₂ CH ₃	4.30
27	4,5-benzo	S	—	CH ₂ CH(CH ₂) ₂	5.00
28	5,7-di-CH ₃ (R,R)	S	—	DMA	7.38
29	5,7-di-CH ₃ (R,S)	S	—	DMA	5.94
30	5,7-di-CH ₃ (R,R)	O	9-Cl	DMA	6.64
31	5,7-di-CH ₃ (R,R)	S	9-Cl	DMA	6.32
32	5,7-di-CH ₃ (S,S)	O	9-Cl	DMA	5.30
33	4,7-di-CH ₃ (S,R)	S	—	DMA	4.59
34	5,6-CH ₂ C(=CHCH ₃)CH ₂ (S)	S	9-Cl	—	5.42
35	6,7-(CH ₂) ₄	S	9-Cl	—	5.70
36	5-CH ₃ (S)	S	8-Cl	DMA	8.30
37	5-CH ₃ (S)	O	9-Cl	DMA	6.74
38	5-CH ₃ (S)	S	9-Cl	DMA	7.37
39	5-CH ₃ (S)	S	9-Cl	CH ₂ CH(CH ₂) ₂	7.47
40	5-CH ₃ (S)	S	—	CH ₂ CH(CH ₂) ₂	7.22
41	5-CH ₃ (R)	O	—	CH ₂ CH ₂ CH ₃	4.22
42	5-CH ₃ (R)	S	—	CH ₂ CH ₂ CH ₃	5.78
43	5-CH ₃ (R)	O	—	2-MA	4.46
44	5-CH ₃ (R)	S	—	DMA	7.01
45	5-CH ₃ (S)	O	—	DMA	5.48
46	5-CH ₃ (S)	S	—	2-MA	7.58
47	H	O	H	DMA	4.90
48	H	O	H	2-MA	4.33
49	H	O	H	CH ₂ CH ₂ CH ₃	4.05
50	H	O	H	CH ₂ C(C ₂ H ₅)=CH ₂	4.43
51	5-CH ₃ (S)	S	H	DMA	7.35
52	5-CH ₃ (S)	O	H	CH ₂ CH=CH ₂	4.15
53	5-CH ₃ (S)	O	H	CH ₂ CH ₂ CH ₂ CH ₃	3.99
54	5-CH ₃ (S)	S	8-F	DMA	8.23
55	5-CH ₃ (S)	O	8-Br	DMA	7.32
56	5-CH ₃ (S)	S	8-Br	DMA	8.52
57	5-CH ₃ (S)	S	8-CH ₃	DMA	7.86
58	5-CH ₃ (S)	S	8-OCH ₃	DMA	7.47
59	5-CH ₃ (S)	S	9,10-di-Cl	DMA	7.59
60	5-CH ₃ (S)	O	8-CN	DMA	5.94
61	5-CH ₃ (S)	S	8-CN	DMA	7.25
62	5-CH ₃ (S)	O	8-CH ₃	DMA	6.00
63	5-CH ₃ (S)	S	10-OCH ₃	DMA	5.33
64	5-CH ₃ (S)	O	10-OCH ₃	DMA	5.18
65	5-CH ₃ (S)	S	10-Br	DMA	5.97
66	5-CH ₃ (S)	S	8-CHO	DMA	6.73
67	5-CH ₃ (S)	O	8-I	DMA	7.06
68	5-CH ₃ (S)	S	8-I	DMA	7.32
68	5-CH ₃ (S)	O	8-CH=CH ₂	DMA	6.36
70	5-CH ₃ (S)	S	8-CH=CH ₂	DMA	7.53

^a DMA = 3,3-dimethylallyl. ^b 2-MA = 2-methylallyl. IC₅₀ is the inhibitory concentration of the substances required to achieve 50% inhibition.

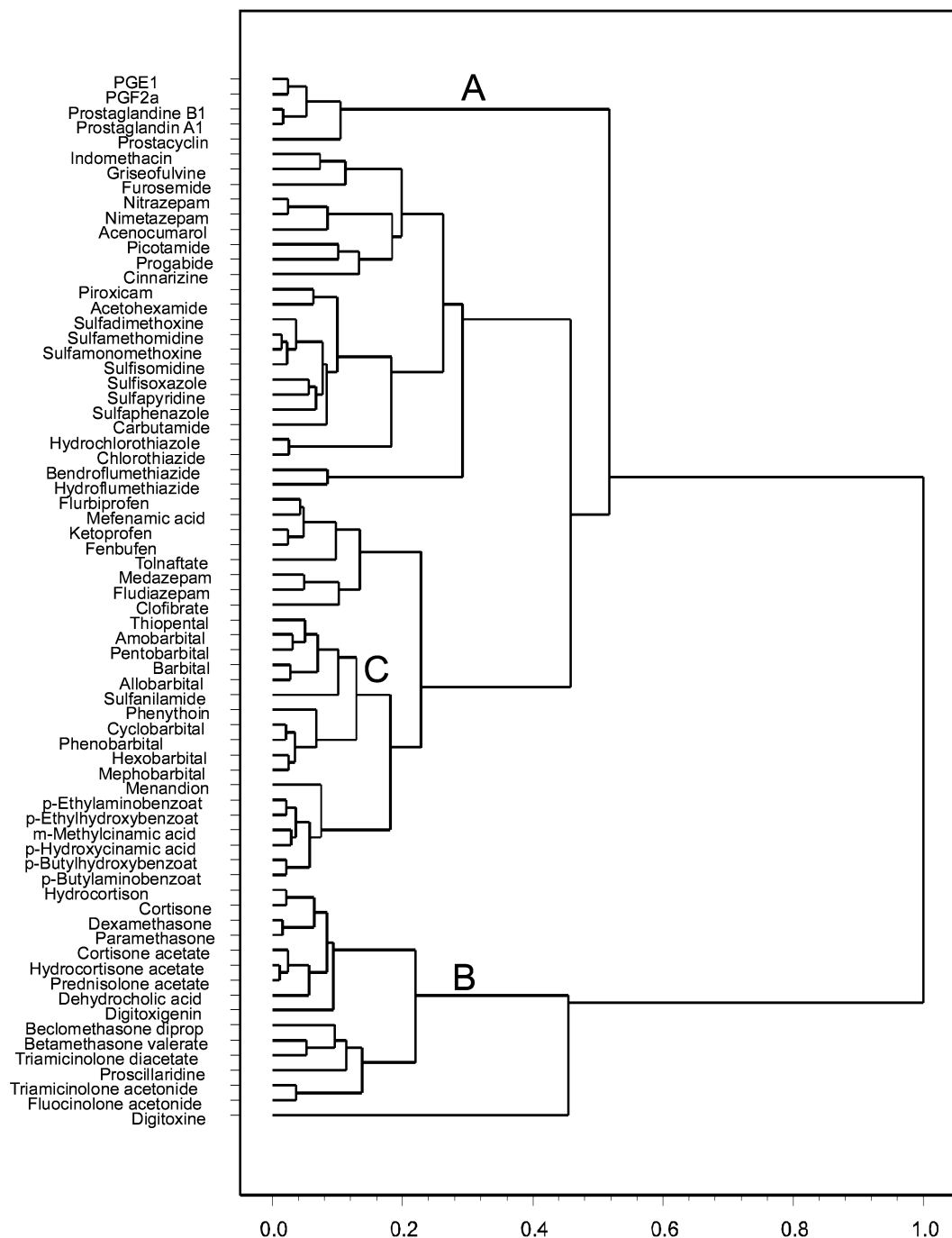


Figure 2. Dendrogram of the cluster analysis of the 70 inclusion compounds, performed with the Tsar descriptors.

Table 4. Models with Best External Predictivity for the Three Data Sets, as Judged by the *SDEP* of the Test Sets, Obtained with 3D-TDB Descriptors and the Descriptors from TSAR^a

data set	benchmark steroids		TIBO derivatives		guest compounds	
descriptors	3D-TDB	TSAR	3D-TDB	TSAR	3D-TDB	TSAR
Noc	2	1	10	1	9	6
<i>F</i>	26.99	22.72	47.37	43.13	52.51	54.00
<i>r</i>	0.866	0.738	0.943	0.623	0.942	0.915
<i>q</i> ²	0.558	0.505	0.613	0.350	0.734	0.665
<i>SDEP</i>	0.583	1.055	0.610	0.903	0.469	0.476

^a Noc is the number of components of the PLS model, *F* is the statistical significance, *r* is the correlation coefficient, *q*² is the cross-validated correlation coefficient (leave one out), and *SDEP* is the standard deviation of errors of prediction for the test sets.

E-state indices depends on the electronegativities and the local structural topologies of the atoms in the molecule, being decreased by less electronegative atoms buried in the skeleton

and increased by terminal atoms of high electronegativity. It is therefore plausible that the *X(k)* descriptors—like the sum of E-states—contain information on local electronic

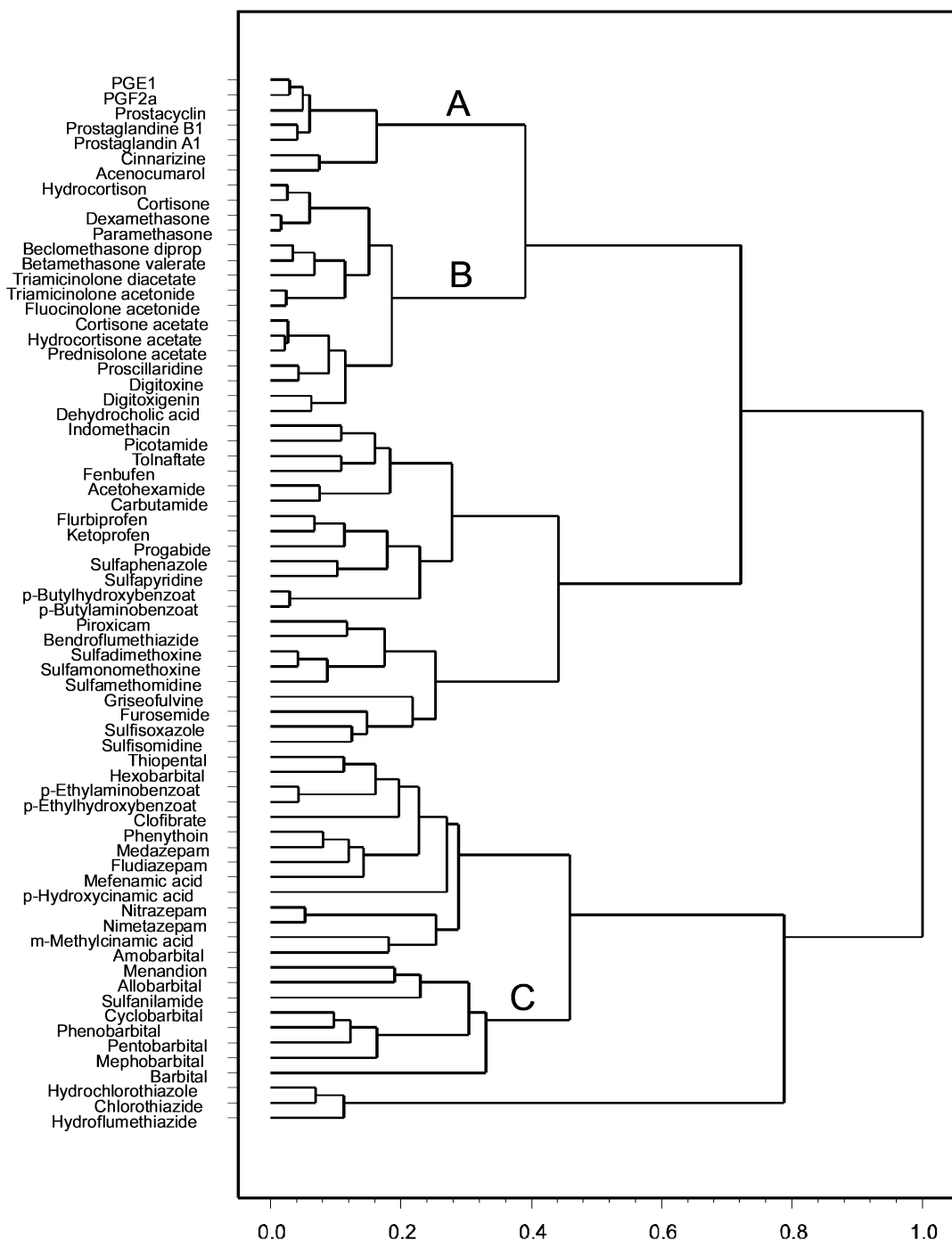


Figure 3. Dendrogram of the cluster analysis of the 70 inclusion compounds performed with the 3D-TDB descriptors.

Table 5. Percentage of Correlation below 0.7, between 0.7 and 0.9, and above 0.9 of TSAR and 3D-TDB Descriptors, Respectively

correlation level	<0.7	[0.7, 0.9)	≥0.9
3D-TDB	75.8	19.6	4.6
TSAR	41.1	33.1	25.8

features of the molecules. The same cluster-membership of the $X(k)$ descriptors with the molecular mass, surface, and volume results from the fact that for the most frequently occurring atoms (C, O, N) there exists a correlation between the electronegativities and both atomic masses and covalent radii.

The indicator-variable-like $I(k)$ descriptors are clustered with the Chi4 (cluster)- Chi5 (ring)- and Chi6 (ring) indices (C). The latter code for the presence or absence of 4-clusters

and of 5- and 6-rings in the molecule. Since only part of the substances in the guest data set contain 4-clusters, 5- and/or 6-rings, the corresponding indices will be larger than zero only for these compounds. These indices thus resemble indicator variables and hence cluster with the $I(k)$ descriptors.

The results of the correlation analysis of the three data sets show that appropriate steric and electronic descriptions of the molecules are able to model their biological responses. Using 3D information included in an autocorrelation approach with only three types of descriptors gives equal or better results than the variety of descriptors from Tsar. For the benchmark steroids and the TIBO derivatives the predictive power of the models using 3D-TDB descriptors are superior because, as shown above, these descriptors retain

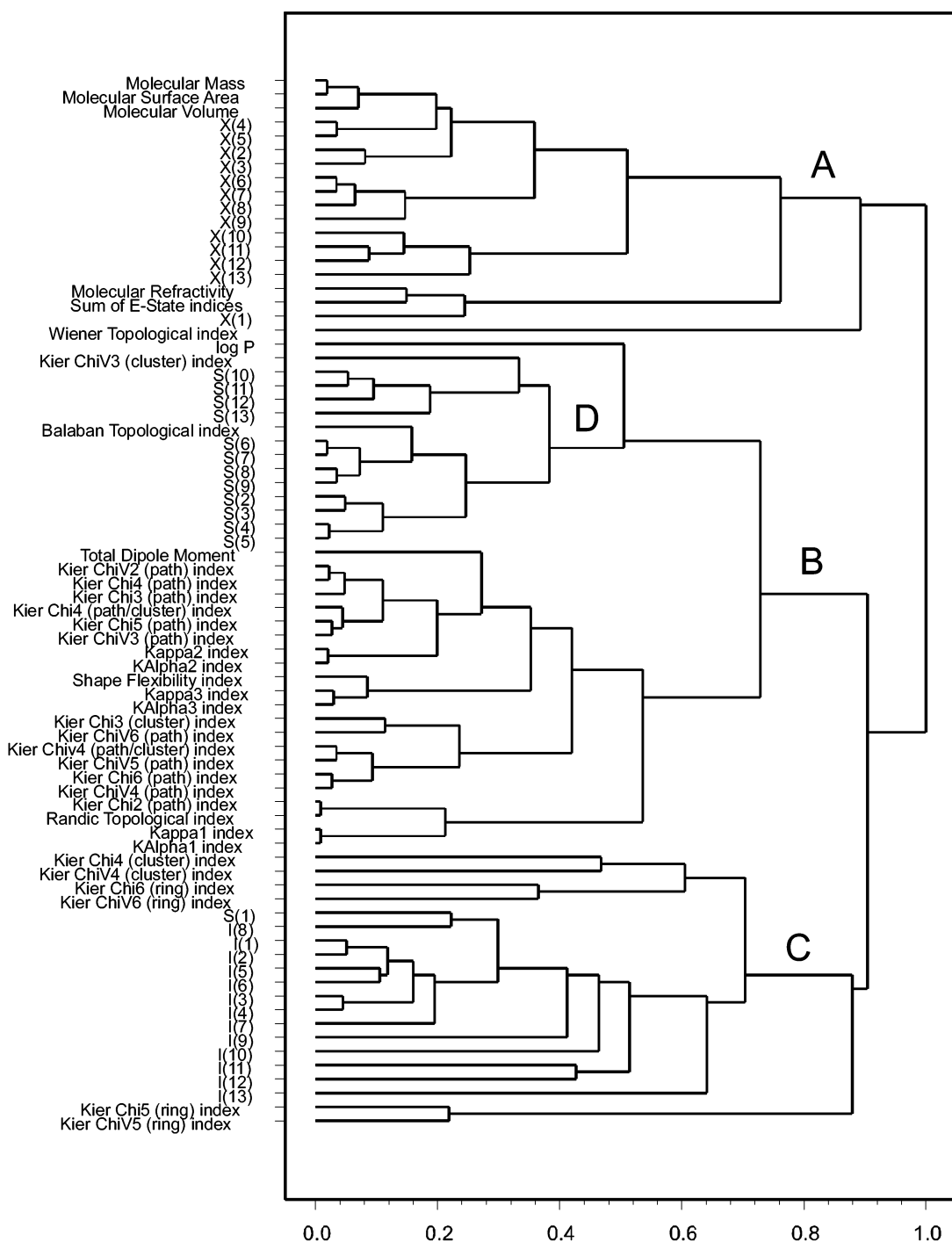


Figure 4. Cluster analysis of the descriptors used in the study.

local structural information: especially for small topological distances they reflect “local densities” of the employed properties. On the other hand overall properties of the molecules and the similarities (or dissimilarities), i.e., distances, to each other are described equally well as with both the variety of Tsar descriptors and the 3D-TDB descriptors, as shown by the cluster analysis of the second data set.

Finally, the calculation of the 3D-TDB descriptors is approximately 2 orders of magnitude faster than the calculation of the Tsar or the autocorrelation descriptors. For the 31 benchmark steroids (70 guest compounds) Tsar needs 35.1 (70.4) seconds on a SGI Octane for the calculation of the descriptors, whereas the 3D-TDB descriptors are calculated

in 0.30 (0.56) seconds. Surface needs 134.6 s for the calculation of the spatial autocorrelation descriptors. This makes the 3D-TDB descriptors particularly suitable for large data set.

CONCLUSIONS

The present paper introduces descriptors based on a modified autocorrelation approach (3D-TDB), for which 3D structural information is included in a simple and efficient way. The descriptors are tested with three different data sets: the benchmark steroids, a well characterized benzodiazepine set, and a set of β -cyclodextrin inclusion compounds. For comparison a variety of descriptors, implemented in the Tsar program are used. Analyzing the relationship between

the Tsar- and the 3D-TDB descriptors by means of cluster analysis suggests that the latter are able to retain information on local structural features of the described molecules.

The predictive abilities of models obtained with 3D-TDB descriptors compare well with those obtained from other 3D-QSAR methods. As their computation is very fast, the descriptors appear to be particularly suitable for large data sets.

ACKNOWLEDGMENT

The authors want to thank Prof. Gasteiger for helpful discussions and for providing them with the programs Petra and Surface. C.K. thanks Oliver Krämer for reading the manuscript carefully and for helpful comments and suggestions.

REFERENCES AND NOTES

- (1) Cramer, R. D., III; Patterson, D. E.; Bunce, J. D. Comparative Molecular Field Analysis (CoMFA). 1. Effect of Shape on Binding of Steroids to Carrier Proteins. *J. Am. Chem. Soc.* **1988**, *110*, 5959–5967.
- (2) Goodford, P. J. A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. *J. Am. Chem. Soc.* **1985**, *28*, 849–857.
- (3) Doweiko, A. The Hypothetical Active Site Lattice. An Approach to Modelling Active Sites from Data on Inhibitor Molecules. *J. Med. Chem.* **1988**, *31*, 1396–1406.
- (4) Robinson, D. D.; Winn, P.J.; Lyne, P. D.; Richards, G. W. Self-organizing Molecular Field Analysis: A Tool for Structure–Activity Studies. *J. Med. Chem.* **1999**, *42*, 573–583.
- (5) Jain, A. N.; Koile, K.; Chapman, D. Compass: Predicting Biological Activities from Molecular Surface Properties. Performance Comparisons on a Steroid Benchmark. *J. Med. Chem.* **1994**, *37*, 2315–2327.
- (6) Klebe, G.; Abraham, U.; Mietzner, T. Molecular Similarity Indices in a Comparative Analysis (CoMSIA) of Drug Molecules to Correlate and Predict their Biological Activity. *J. Med. Chem.* **1994**, *37*, 4130–4146.
- (7) Good, A. C.; So, S.-S.; Richards, W. G. Structure–activity Relationships from Molecular Similarity Matrices. *J. Med. Chem.* **1993**, *36*, 433–438.
- (8) Good, A. C.; Peterson, S. J.; Richards, W. G. QSARs from Similarity Matrixes. *J. Med. Chem.* **1993**, *36*, 2929–2937.
- (9) Silverman, B. D.; Platt, D. E. Comparative Molecular Moment Analysis (CoMMA): 3D-QSAR without Molecular Superposition. *J. Med. Chem.* **1996**, *39*, 2129–2140.
- (10) Bravi, G.; Gancia, E.; Mascagni, P.; Pegna, M.; Todeschini, R.; Zaliani, A. J. MSWHIM, New 3D Theoretical Descriptors Derived from Molecular Surface Properties: A Comparative 3D QSAR Study in a Series of Steroids. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 79–92.
- (11) Broto, P.; Vandycke C. Molecular Structures: Perception, Autocorrelation Descriptor and SAR Studies. *Eur. J. Med. Chem.-Chim. Ther.* **1984**, *19*, 66–70.
- (12) Bauknecht, H.; Zell, A.; Bayer, H.; Levi, P.; Wagener, M.; Sadowski, J.; Gasteiger, J. Locating Biologically Active Compounds in Medium-Sized Heterogeneous Data Sets by Topological Autocorrelation

- Vectors: Dopamine and Benzodiazepine Agonists. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 1205–1213.
- (13) Wagener, M.; Sadowski, J.; Gasteiger, J. Autocorrelation of Molecular Surface Properties for Modeling Corticosteroid Binding Globulin and Cytosolic Ah receptor. *J. Am. Chem. Soc.* **1995**, *117*, 7769–7775.
 - (14) Pastor, M.; Cruciani, G.; McLay, I.; Pickett, S.; Clementi, S. GRIND-Independent Descriptors: A Novel Class of Alignment-independent Three-dimensional Molecular Descriptors. *J. Med. Chem.* **2000**, *43*, 3233–3243.
 - (15) Kaye, G. W.; Laby, T. H. *Tables of Physical and Chemical Constants*; Longman: 1965; p 144.
 - (16) Hinze, J.; Jaffé, H. Orbital Electronegativities of Neutral Atoms. *J. Am. Chem. Soc.* **1962**, *84*, 540–546.
 - (17) Müller, W. R.; Szymanski, K.; Knop, J. V. An Algorithm for Constructing of the Molecular Distance Matrix. *J. Comput. Chem.* **1987**, *8*, 170–173.
 - (18) Tsar 3.3, Oxford Molecular Ltd., The Medawar Centre, Oxford Science Park, Oxford, 2000.
 - (19) Hall, L. H.; Kier, L. B. The Molecular Connectivity Chi Index and Kappa Shape Index in Structure–Property Modeling. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B, Eds.; VCH Publishers: New York, 1991; Vol. 1, pp 367–422.
 - (20) Balaban, A. T. Highly Discriminating Distance-Based Topological Index. *Chem. Phys. Lett.* **1982**, *89*, 399–404.
 - (21) Randic, M. J. On Characterization of Molecular Branching. *J. Am. Chem. Soc.* **1975**, *97*, 6609–6615.
 - (22) Wiener, H. Correlation of Heats of Isomerisation and Differences in Heats of Vaporization of Isomers among the Paraffin Hydrocarbons. *J. Am. Chem. Soc.* **1947**, *69*, 2636–2638.
 - (23) Dataset of 31 steroids binding to the corticosteroid binding globulin receptor. <http://www2.ccc.uni-erlangen.de/services/steroids/index.html>.
 - (24) Klein, C. T.; Polheim, D.; Viernstein, H.; Wolschann, P. A Method for Predicting the Free Energies of Complexation between β -Cyclodextrin and Guest Molecules. *J. Incl. Phenom.* **2000**, *36*, 409–423.
 - (25) Klein, C. T.; Polheim, D.; Viernstein, H.; Wolschann, P. Predicting the Free Energies of Complexation between Cyclodextrins and Guest Molecules: Linear versus Nonlinear Models. *Pharm. Res.* **2000**, *17*, 358–364.
 - (26) Klein, C. T.; Viernstein, H.; Wolschann, P. Free Energy Prediction of the Complexation between β -Cyclodextrin and Guest Molecules: External Predictivity of MR and PLS Models. *Sci. Pharm.* **2000**, *68*, 15–24.
 - (27) Hannongbua, S.; Pungpo, P.; Limtrakul, J.; Wolschann, P. Quantitative Structure Activity Relationships and Comparative Molecular Field Analysis of TIBO Derivatised HIV-1 Reverse Transcriptase Inhibitors. *J. Comput.-Aided Mol. Des.* **1999**, *13*, 563–577.
 - (28) ISIS/Draw 2.3, MDL Information Systems, Inc. 2001.
 - (29) CORINA Molecular Networks GmbH Computerchemie, Nögelsbachstrasse 25, 91052 Erlangen, <http://www.mol-net.de>.
 - (30) Dunn, W. J.; Wold, S. Edlund, U.; Hellberg, S. *Quant. Struct.-Act. Relat.* **1984**, *3*, 131.
 - (31) Drapper, N. R.; Smith, H. *Applied Regression Analysis*; J. Wiley & Sons: 1981; p 93.
 - (32) Goilbraikh, A.; Tropsha, A. Beware of q^2 ! *J. Mol. Graph. Model.* **2002**, *20*, 269–276.
 - (33) SURFACE Molecular Networks GmbH Computerchemie, Nögelsbachstrasse 25, 91052 Erlangen, <http://www.mol-net.de>.
 - (34) SNNS, Version 4.5, Stuttgarter-Neuronale-Netze-Simulator. Universität Stuttgart, 1995, <http://www-ra.informatik.uni-tuebingen.de/SNNS/>.
 - (35) Stanton, D. T. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 11–20.