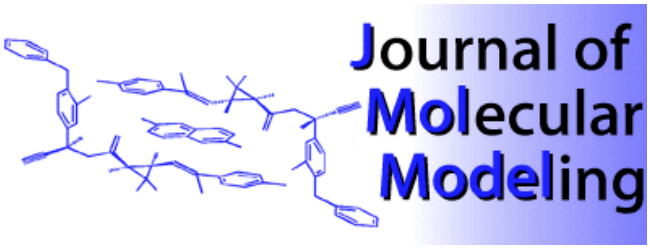
J. Mol. Model. **2000**, *6*, 425 – 432



FULL PAPER

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Ab initio Molecular Electrostatic Potential Grid Maps for Quantitative Similarity Calculations of Organic Compounds

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Received: 4 January 1999/ Accepted: 9 February 2000/ Published: 28 April 2000

Abstract The program MolSim designed to calculate the similarity of different molecules quantitatively in a fast and easy way is described. The molecular similarity is estimated for the molecular shape as well as for the electrostatic potentials of the molecules derived from *ab initio* calculations. A grid-based method is used to determine the steric and electrostatic similarities between a lead compound and the corresponding test set by calculating the Spearman correlation coefficient. The superpositioning of the molecules was accomplished with the SEAL algorithm incorporating a Monte Carlo simulated annealing approach while preserving the conformational flexibility of the calculated structures.
The ability of the program was tested on a set of Sandalwood odour compounds, a class of substances that is difficult to analyse with respect to its structure-activity relationship because of the structural diversity of Sandalwood odour compounds, in contrast to their high selectivity and pronounced structural specificity. The application of the program on a small test set of these compounds showed that the program is able to explain the Sandalwood odour activity correctly.

Keywords Sandalwood odour, Molecular similarity, Molecular shape, Molecular electrostatic potential, SAR

Introduction

The importance of theoretical investigations on structure-activity relationships is increasing strongly. Therefore, a broad variety of methods has been developed in recent years and applied successfully to different molecular systems [1]. The applicability of a method depends on the information available about the interaction of the biologically active compounds with the receptor site. If the structure of the receptor protein is known, docking simulations [2, 3] and at least *de novo* design methods [4-6] can be used. The possibility of determining a biological effect quantitatively enables the application of various QSAR procedures [7, 8], including also 3D methods such as CoMFA. [9-11]

For systems, where this concrete information is not available, molecular similarity methods [1, 12] only can be used. The basic idea of such investigations is that two or more molecules have the same biological activity if they share certain chemical or physico-chemical characteristics. The general approach is to superimpose the active molecules in

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order to find common structural subunits that might be important for the biological effect. Some problems are evident for such a procedure. One problem deals with the selection of relevant chemical features. A wide range of structural and topological descriptors, as well as electronic properties like electron density, net atomic charges or electrostatic potentials, are available for such a choice. A second group of difficulties is related with the type of mathematical analysis that is carried out with the data matrix. Finally, many measures of molecular similarity depend dramatically on the relative positions and the conformations of the molecules.

In the present work we have developed a fast and simple method that allows us to perform molecular similarity studies taking into account molecular shape as well as electrostatic potentials. We have tested this method on a class of sandalwood odour molecules, a system where high selectivity and a rather large diversity of chemical structures make the development of a good prediction model difficult.

The oil of the East Indian sandalwood, Santalum album L. possesses a very pleasing, sweet-woody, animalic and milky-nutty scent with excellent fixative properties. In the early 80ies Brunke and Naipawer studied structure-odour-correlations for the sandalwood scent by working out some molecular features postulated to be necessary for sandalwood scent [13-17]. Although different calculation methods have been applied in continuation of this study, and although some models for some groups of sandalwood odour compounds have been found, [18-22] it was not possible to define a general SAR model valid for all known sandalwood analogues. Therefore, this class of compounds was selected to test the developed program.

Similarities of the molecules were computed on the basis of molecular electrostatic potential distributions (MEP),[23] which are widely considered as relevant to characterise molecular interaction capabilities. There are many successful examples of the use of MEP distributions to study the relationships between molecular characteristics and biological activities.[24]

It should be noted that the present study deals with a small set of sandalwood odour compounds because the accent has been put on the testing of program performing a quantitative and accurate comparison of this test set, rather than on the evaluation of a general model for Sandalwood odour molecules.

Methods

Bonnacorsi et al. [25] first defined the molecular electrostatic potential (MEP) as the interaction energy between a molecule and a proton located in a specified distance *r*. The MEP is given by summing up the positive nuclear energy and the negative electronic one. Thus, the sign of the MEP depends whether the nuclear or the electronic interaction is dominant at a specific location *r*. With this information it is possible to detect regions of either hydrophilic interactions through MEP values which are positive or negative and hydrophobic interactions (VdW-Interactions, H-Bridges etc.) with MEP values near zero.[26]

$$V(r) = \sum_A \frac{Z_A}{|r - r_A|} - \int \frac{p(r')}{|r - r'|} dr' \quad (1)$$

In this equation Z_A represents the nuclear charges, r_A stands for the nuclear distances, and *p(r)* is the electron density distribution.

The basic idea behind the similarity calculations is to put the various molecules into a three dimensional grid containing the electrostatic potential at each grid point. The grid points which *touch* the molecule are therefore used as a good approximation of the molecular shape of the corresponding structure and represent the electrostatic potential on the molecular surface of the compound. These grid points are then used to calculate the steric and electrostatic similarity between two or more structures by superposing the structures and then through distance matching, selecting those grid points which lie at the same location in three dimensional space. The number of matching grid points is a good representation of the steric similarity between the compounds. The next step is to evaluate how much the electrostatic potentials differ at the matching grid points. It is therefore possible to detect regions of high and/or low steric as well as electrostatic similarity through this algorithm.

Methods for fitting the structures

Fitting is a very important task for the estimation of the similarity between two structures. The better the fit, the more accurate are the results obtained from similarity calculations. There exist many different methods for fitting two structures. The approach we used was the extended SEAL algorithm, which is preferred when the various structures have large structural differences, as in our investigation of sandalwood odour molecules. This method is based on the work of Smith et al.[27] Instead of superposing atom pairs, their steric and electrostatic fields are fitted. Another extension, which was introduced by Masek et al.,[28] favours similar atom types in the fit in addition to the steric and electrostatic fields. During the SEAL fitting process a fitting potential P_F is calculated to rank the different orientations. It consists mainly of overlapping energy and is defined as follows:

$$P_F = S_E + E_E + A_E \quad (2)$$

S_E defines the steric overlapping term. E_E is the electrostatic overlapping part and A_E means the atom type similarity. Lower potential values mean better structural and electrostatic fit between two structures.

The possibility to consider the conformational flexibility of the compounds *via* a Monte Carlo simulated annealing (MCSA) search algorithm has been found extremely useful. It is therefore not necessary to specify either atom pairs or the relative orientation of the fit, which would be rather dif-

Table 1 *Odour impression of the compounds used in this study*

No.	Compound	Odour impression	Reference
1	(+)-tert.-Butylbicyclo[4.4.0]decan-3-ol	clear sandalwood	[32,33]
2	(Z)-(-)-ß-Santalol	typical sandalwood, urinous, woody	[13,34]
3	Dihydro-ß-santalol	strong sandalwood	[35]
4	Desmethyldihydro-ß-santalol	typical sandalwood	[35]
5	Desmethyl-ß-santalol	typical sandalwood	[35]
6	(Z)-ß-santalal	sweaty, mild sandalwood	[36,37]
7	exo-Isocamphanylcyclohexan-3´-ol (ax)	sandalwood-like	[38-40]
8	exo-Isocamphanylcyclohexan-5´-ol (ax)	sandalwood-like	[38-40]
9	(-)-Madrol	unambiguously like sandalwood, animalic	[41,42]
10	nor-α-Santalenone	woody, sandalwood, ionone-like	[15,36]
11	nor-ß-Santalenone	sweaty, woody, green sandalwood	[15,36]
12	Osyrol®	typical sandalwood	[43,44]
13	1-Methyl 2-cis-methylcyclopropyl-5'hex 3-yl-cis-cyclopropylmethanol	sandalwood, creamy, warm, strong	[45]
14	(+)-(Z)-α-Santalol	woody, cedarwood and mild sandalwood	[15,45,46]
15	exo-Isocamphanylcyclohexan-2´-ol (ax)	odourless	[19,20,40,47]
16	exo-Isocamphanylcyclohexan-2´-ol (eq)	odourless	[19,20,40,47]
17	exo-Isocamphanylcyclohexan-3´-ol (eq)	odourless	[19,20,40,47]
18	exo-Isocamphanylcyclohexan-4´-ol (ax)	reminiscent of sandalwood	[19,20,40,47]
19	exo-Isocamphanylcyclohexan-4´-ol (eq)	odourless	[19,20,40,47]
20	exo-Isocamphanylcyclohexan-5´-ol (eq)	odourless	[19,20,40,47]
21	exo-Isocamphanylcyclohexan-6´-ol (ax)	odourless	[19,20,40,47]
22	exo-Isocamphanylcyclohexan-3´-ol (eq)	odourless	[19,20,40,47]
23	1-Methyl 2-trans-methylcyclopropyl-5'hex 3-yl-cis-cyclopropylmethanol	lactonic	[45]
24	(Z)-(-)-oxa-ß-Santalol	odourless	[21]
25	tetrahydro-ß-Santalol	odourless	[22]
26	(Z)-(-)-keto-ß-Santalol	woody, cedarwood	[48]

ficult with the structures we had to deal with in this work. During MCSA one of the to structures is kept rigid while the other is rotated and translated and rotatable bonds are varied. This yields to an enormous number of conformations of which the energies are calculated. The probability *P* of using one conformation is defined by the following equation:

$$P(\Delta E) = e^{-\left(\frac{\Delta E}{kT}\right)} \quad (3)$$

Where *k* is the Boltzmann constant, D*E* is the energy difference between two runs and *T* defines the absolute temperature.

Therefore, the number of conformations accepted is dependent on the temperature *T*. The higher the temperature, the more conformations are accepted and *vice versa*. This procedure consists of different cycles, whereas each cycle is defined at a given predefined temperature and number of accepted geometries. Using this technique we were able to find much better fitting solutions than using atom-pair based methods.

Surface generation methods

In this work a grid-based approach for describing both the molecular shape and the molecular electrostatic potential (MEP) of a compound was used. The various structures were therefore put into an evenly spaced three-dimensional grid surrounding the molecule. The grid points that describe the molecular shape can be selected with two implemented algorithms.

1. The van der Waals surface is calculated with spheres centred at the atom positions. The sizes of the spheres are atom-type-dependent and are taken from Gavezotti and Spackmann [29]. Grid points are then selected based on a distance criterion:

$$d \leq x \bullet 2 \quad (4)$$

Where *d* is the maximum allowed distance and *x* is the mean of grid spacing. The next step is to remove intersecting sphere parts buried in the molecular surface. The entity of these selected grid points forms the molecular shape described through points in three dimensional space.

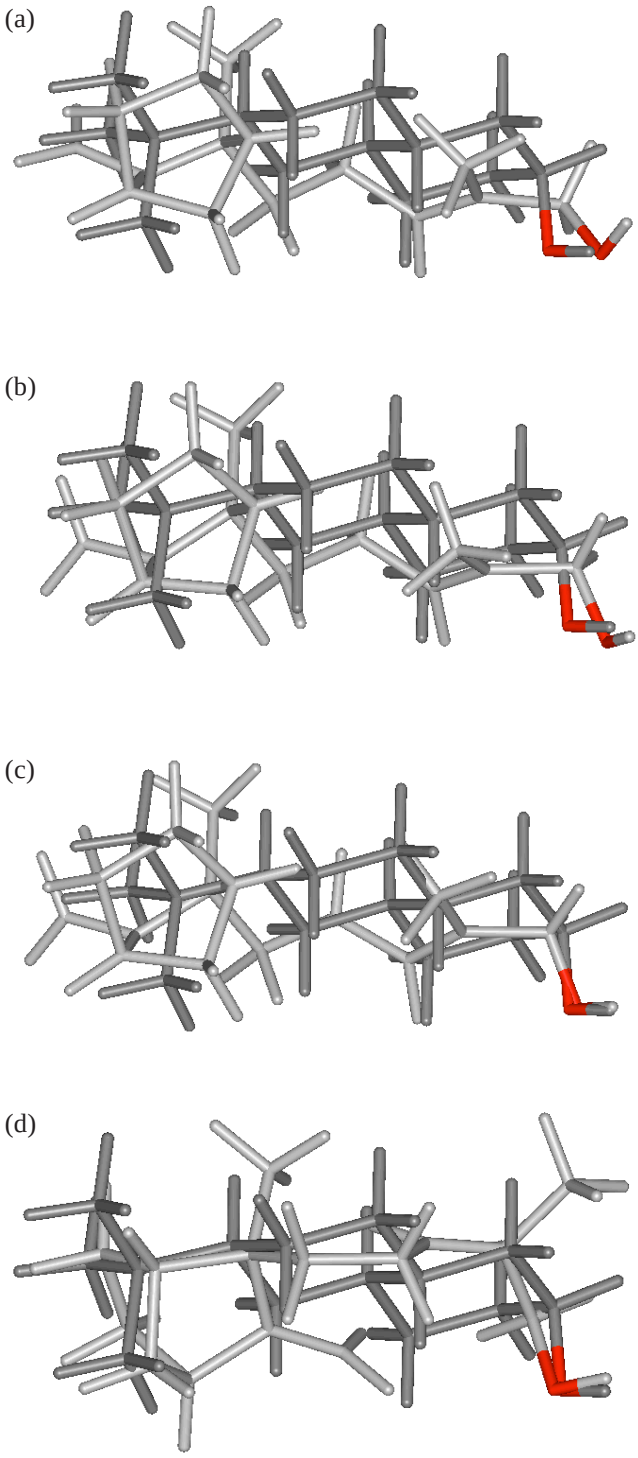

Figure 1 *Overlay of 1 and 2 after MCSA Seal fitting using a* (**a**) *O-O,* (**b**) *C-O,* (**c**) *O-H, and* (**d**) *C-O-H distance constraints. Dark Grey: Compound* ***1*** *Grey: Compound* ***2***

Table 2 *Enhancing the MEP similarity using distance constraints*

Fitting constraint between 1 and 2	Spearman rank correlation coefficient
O	0.6360
C-O	0.6453
O-H	0.6854
C-O-H	0.6856

2. The Electron Density Surface uses a second grid file containing the calculated electron density. The three dimensional isosurface generated at an isovalue of 0.001 Hartrees describes the molecular shape of a molecule very well. In contrast to the van der Waals surface, this molecular shape describes region of high electron accumulation (i.e. lone pairs, double bonds etc.) better through its quantum mechanical nature. A more detailed explanation of this surface description is given in [30].

These two algorithms have in common that they do not necessarily select a symmetric number of grid points for a symmetric molecule, even when so specified in the Cartesian coordinates. This results from the loss of accuracy when grid points are used with a relatively high grid spacing. The smaller the grid spacing specified, the better the symmetry of selected grid points will be.[9] One big advantage of a grid-based approach lies in the possibility of using the calculated grid points when forming logical operations with the molecular surfaces, including combination and subtraction of two or more molecular shapes.

Matching grid points – the marching squares algorithm

The grid points of two different structures are compared through a distance-matching algorithm, which is dependent on the grid width, as can be seen from the following formula:

$$d \leq \frac{stepx + stepy + stepz}{3} \tag{5}$$

Where d is the distance between two points and *stepx*, *stepy* and *stepz* are the grid stepping sizes.

Only if two points meet this criterion are the grid points considered to match sterically and count one complete point. A half point (0.5) count is used when the distance between two points is between $d \cdot 2$ and d.

The next step is to evaluate the total difference of the quantum mechanical MEP values between these two matching grid points. A maximum difference of 0.01 Hartrees was considered to be a useful value to evaluate regions of high and low similarity. The output from MolSim consists of both absolute grid point numbers as well as percentages in an atom-based manner. Along with the total number of grid points belonging to each atom of the structure, the number of

Table 3 *Politzer-Parameters calculated by various basis sets*

	3-21G		6-31G*	
Structure	**Polarity**	**Dispersion**	**Polarity**	**Dispersion**
1	0.005165	0.000101	0.004869	0.000089
5	0.006830	0.000148	0.006329	0.000129
9	0.007427	0.000147	0.006585	0.000121
23	0.007828	0.000157	0.007253	0.000137
26	0.009895	0.000249	0.009851	0.000243

sterically matching grid points is output as well as the number of MEP-matching grid points. This gives the possibility to examine steric and electrostatic similarity up to the atomic level instead of using index values or overall percentages for the whole molecule. These values can also be incorporated as hopefully relevant descriptors into QSAR studies.

Spearman rank correlation coefficient

Finally, the Spearman rank correlation coefficient is computed. The MEP values of the matching grid points are ranked to form a distribution of numbers from 1 to *n*. Where n is the number of point pairs.

$$r = 1 - 6\frac{\sum_{i=1}^{n} d_i^2}{n^3 - n} \tag{6}$$

The Spearman coefficient, where d_i is the difference in ranks between two matching grid points, ranges from 1.0 for 100% similarity to –1.0 for 0% similarity is scale-invariant and insensitive to normalisation of the data used. Note that this coefficient describes only the similarity of the MEP and not steric differences between two structures. Therefore, a similar coefficient for the steric similarity has been defined.

$$s = \frac{\sum_{i=1}^{n} d_i * 2}{n} \tag{7}$$

Lower values in this coefficient mean higher steric similarity, where d_i defines the distance between two matching grid points and n is the number of grid points in the structure with the higher number of grid points.

For the application of the developed analysis method a test set consisting of the following compounds representing different classes of sandalwood odourants has been selected. Table 1 lists the names of the above structures as well as their odour impression. The corresponding structures are given in the appendix. Compound **1** was chosen as the reference molecule because of its clear sandalwood odour. It shows very little conformational flexibility, in contrast to the other compounds considered. Therefore, all structures were compared to the molecular shape and electrostatic potential of **1**. The geometry of compound **1** was minimised with Gaussian 94 at the Hartree Fock level using the 3-21G basis set.[31]

For the superpositioning of the various molecules we used a MCSA enhanced SEAL algorithm, were **1** was kept rigid and all possible bonds of the structures to be fitted were allowed to rotate to achieve maximum steric and electrostatic field overlap as defined in the SEAL algorithm. The MCSA algorithm was set to begin at 1000 K, to have 250 steps at each temperature and 50 cycles in all. All weighting factors for the calculated fitting energy were set equal. It was found that the maximum MEP similarity between the sandalwood odour molecules can be increased dramatically by constraining the maximum distance of the aliphatic hydroxyl groups, one of the three known pharmacophoric regions, during the fitting process. For this purpose similarity calculations between compounds **1** and **2** using different techniques for constraining the hydroxyl groups have been performed. Table 2 shows the results using a different number of atoms per constraint. As can be seen in Table 2 and Figure 1, the best MEP similarity between the two structures is found when a distance constraint consisting of C-O-H of the aliphatic hydroxyl groups is used. Therefore, this approach was used in all further fittings.

Next to the superimposing procedure the Gaussian 94 [31] program package was used to minimise the fitted geometries, again at the HF/3-21G level, and to calculate the molecular electrostatic potential on the energy minimum located. Additionally, in order to preserve the optimal geometry obtained from the fitting process, the dihedral angles of the aliphatic sidechains were fixed. The main reason for using the relatively low quality HF/3-21G wavefunction was to save computational time when carrying out this high number of comparisons. On the other hand, the possible errors introduced by the use of such a basis set should be similar for all molecules of a series.[49] To justify the use of the 3-21G basis set, we calculated the geometries and MEP surfaces of five different compound using two different basis sets. Table 3 lists the well known *Politzer-Parameters*, local polarity and the MEP dispersion,[24] calculated with the data sets of the structures.

Table 3 shows that the values obtained from the more advanced 6-31G* wavefunction do not justify the much higher computational time compared to the 3-21G basis set, as both the MEP-sensitive local polarity and the dispersion of the MEP values at the corresponding molecular surfaces do not reveal great differences. The surrounding cube was defined so that all calculated structures would fit into the same three-

Table 4 *Overall molecular shape (OVS) and overall MEP similarity (OMS) of all structures with 1 as reference*

Structure	OVS%	OMS%
2	74	75
3	75	70
4	74	65
5	71	68
6	74	44
7	79	60
8	87	70
9	64	64
10	80	50
11	68	49
12	81	72
13	80	66
14	78	61
15	68	61
16	41	34
17	66	48
18	86	69
19	71	51
20	78	34
21	75	49
22	72	58
23	65	64
24	70	51
25	68	66
26	79	53

Table 5 *Spearman rank correlation coefficient (SCC) and Sterical Similarity Coefficient (SSC)*

Structure	SCC	SSC
2	0.6856	1.7
3	0.7037	1.9
4	0.5928	1.9
5	0.6062	1.9
6	0.3355	1.8
7	0.5907	2.0
8	0.5623	1.8
9	0.6764	2.3
10	0.0732	2.5
11	-0.1204	2.7
12	0.6831	1.8
13	0.6731	1.5
14	0.6060	1.6
15	0.4952	2.2
16	0.0334	4.9
17	0.1141	2.3
18	0.6154	1.9
19	0.3680	2.0
20	-0.3273	1.9
21	0.1450	2.0
22	0.4180	2.2
23	0.6233	2.0
24	0.3966	1.9
25	0.7103	2.2
26	0.3941	1.8

dimensional grid, which consisted of 50 points in every direction, giving a volume of 125,000 points for every molecule. The resulting numbers of points after the surface generation were between 2000 and 3000 points, depending on the size of the corresponding structure. The points were evenly spaced at 0.10 Å, resulting in about 100 points per atom.

In the first series of similarity calculations that we carried out with the MolSim program, the similarity in terms of overall molecular shape and overall electrostatic potential was determined. Table 4 shows the results of this analysis were the overall molecular shape (OVS) and overall MEP similarity (OMS) is calculated with the following equations:

$$OVS = \sum_{i=1}^{n} \frac{p_i}{n}; p_i = \frac{N_m}{N_t} * 100 \quad (8)$$

Where P_i is the percentage of molecular shape similarity of atom *i*. N_m is the number of sterically matching points. N_t is the total number of points belonging to atom *i*. *n* is the total number of atoms in the reference structure.

$$OMS = \sum_{i=1}^{n} \frac{p_i}{n}; p_i = \frac{N_m}{N_s} * 100 \quad (9)$$

P_i is the percentage of MEP similarity of atom *i*. N_m is the number of potential matching points. N_s is the number of sterically matching points of atom *i*. *n* is the total number of atoms in the reference structure.

Results

Because the various calculated structures show a high degree of steric dissimilarity, it was necessary to increase the distance-matching value to 0.53 Å to achieve reasonable results in the distance-matching algorithm. The maximum difference of the corresponding MEP values was kept at a rather small value of 0.01 Hartrees as this was the main concern in this work.

Unfortunately, these overall values give only a very crude overview of steric and MEP similarities as only the OVS of **16** seems to be much lower than the OVSs of the other structures. This result was expected because of the rather high distance-matching value and the fitting technique used. Nevertheless, these overall values are useful in ”quick and dirty” screening procedures to compare a high number of structures in terms of steric and MEP similarities.

With the Spearman rank correlation coefficient (SCC) [Eq. 6] and a steric similarity coefficient (SSC) [Eq. 7] de-

veloped for these investigations, it is better possible to correlate the similarity with the odour impression between these structures and **1** by taking the degree of steric and MEP differences into account. Table 5 shows clearly the relationship of steric and electrostatic similarities to sandalwood odour. Each structure has a rather similar SSC value ranging from 1.5 to about 2.5. Only in the case of **16** is the steric similarity coefficient considerably higher at 4.9. The various SCC values give a much clearer picture. Every structure with sandalwood odour has a rather high SCC value of about 0.6. Note that structures **10**, **11** and **6** indeed show a very low SCC value, which would lead to the assumption that these three structures have no sandalwood odour. However, this is due to the fact that these three structures do not share an aliphatic hydroxyl group with the reference molecule as all the other structures do. Therefore the MEP at the location of the aliphatic keto group of these three compounds shows a rather high degree of dissimilarity when compared to the hydroxyl group of compound **1**, which results in a very low SCC value. All other compounds without sandalwood odour have an SCC value lower than 0.6, except compounds **14**, **18**, **23** and **25**. These structures have been found to be problematic in this field for many years as divergent odour impressions have been reported in the literature.[15, 19, 20, 41, 48]

Conclusion

Many aspects have to be considered to give a good prediction on the properties of non existing molecules created by molecular modelling and for the calculations of newly synthesised compounds with the goal to get more information about the olfactory mechanism and receptors. One of the most important questions for studies on odorous compounds is, which conditions such biologically active molecules have to follow. The class of sandalwood odour compounds seems to be somewhat inhomogeneous, which makes it difficult to find common structural elements responsible for this typical odour impression and could give more information about the nature of the responsible receptors. Therefore, the combination of different methods to compare both the molecular shape and the electronic properties of compounds was developed. With a reference molecule with rather limited conformational flexibility and the comparison of 25 different sandalwood odour molecules and related inactive compounds, it turned out that the combination of two calculated descriptors (SSC and SCC) reproduced the experimentally determined odour impression given in Table 1 for these structures very well. Further investigations are needed to incorporate more detailed descriptors into regression analysis and neural network techniques to extend the application possibility of MolSim to a much wider field.

Supplementary material The MEP-surfaces for all 26 calculated structures are provided in the form of three-dimensional VRML files.

Acknowledgements The authors would like to thank the Fonds zur Förderung der Wissenschaftlichen Forschung in Österreich (project No. 11349-CHE) for financial support.

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