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QSAR without arbitrary descriptors: the electron-conformational method

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Abstract The electron-conformational (EC) method in QSAR problems employs a unique (based on first principles) descriptor of molecular properties that incorporates the electronic structure and topology of the molecule and is presented in a digital-matrix form suitable for computer processing, the EC matrix of congruity (ECMC). Its matrix elements have clear-cut physical meanings of interatomic distances, bond orders, and atomic reactivity (interaction indices). By comparing these matrices for several active compounds of the training set a group of matrix elements is revealed that are common for these compounds within a minimum tolerance, the EC submatrix of activity (ECSA). The latter is the numerical pharmacophore for the level of activity and diversity of the tried compounds. The EC method was described in detail and used for pharmacophore identification and quantitative bioactivity prediction elsewhere. In this paper we give further general considerations of its uniqueness and emphasize its advantages as compared with traditional QSAR methods, outlining the following three novel points: (1) The unique, non-arbitrary descriptor employed in the EC method avoids the shortcomings of the arbitrary chosen descriptors and statistical estimation of their weight in the evaluation of the pharmacophore used in traditional QSAR methods. Arbitrary descriptors may be interdependent ("non-orthogonal") and their sets are necessarily incomplete, hence they may lead to chance correlations and artifacts. The EC pharmacophore is void of these failures, thus deemed to be absolutely reliable within the accuracy of the experimental data and the diversity of the molecules used in its evaluation; (2) The tolerances in the matrix elements of the ECSA play a special role reflecting the flexibilities of the pharmacophore parameters and the dependence of the activity on the latter quantitatively; they are obtained in a minimization procedure; by increasing the tolerances one can get pharmacophores for larger intervals of activity. An advanced formula is derived for the activity as a function of the drug–receptor bonding energy which handles also the multi-conformational problem, and a regressional procedure is suggested to represent the interaction energy and the activity by the ECSA matrix elements or tolerances; (3) The possibility of bimolecular activity is discussed when a single molecule of the active compound has no pharmacophore, but the latter is present in the bimolecular structure. Examples are given from the problem of aquatic toxicity to fish.

Keywords Biological activity · Descriptors · Drug design · Pharmacophore · QSAR

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Introduction

The quantitative structure–activity relationship (QSAR) and quantitative structure–property relationship (QSPR) methods reached a level of widespread use in a variety of problems from drug design to toxicity, screening and prediction, as well as prediction of other properties of molecular systems and solids. The main idea that underlies these methods is that there are several (or many) molecular features, *descriptors*, that represent the properties of the molecule in its interaction with other systems; by means of statistical comparison of the descriptors with the activities of a set of experimentally tried molecules (the training set)

and regression analysis one can reveal a limited number of relevant descriptors (with their weights), the *pharmacophore*. The latter represent the activity under consideration and can be used to screen other molecules from databases to reveal leads to more active compounds (see, e. g., [1, 2]).

Notwithstanding the success of the QSAR methods, in general, they have some aggravating failures that make them les reliable than expected. The main of them is in the *arbitrary choice of descriptors*. Indeed, there are no rules based on first principles that would allow one to choose the proper kind of descriptors for a given set of molecules. Note also that there are many cases when the molecular systems under consideration (drugs, toxicants, etc.) are not pure organic, and for them such widely used notions like connectivity are not reliable and not transferable from one molecule to another (especially when heavier atoms like transition and pre- and post-transition elements are present [3]). Although based on the intuition of the researcher and visual examination of the active molecules, but not based on first principles, such descriptors should be considered arbitrary chosen.

For arbitrary chosen descriptors there are several essential shortcomings. First, the number of descriptors is necessarily limited, they are not mutually "orthogonal" (meaning different descriptors may be interdependent), and their overlap is unknown. This means that the presentation of the activity by such descriptors is, in general, unreliable, and each of the descriptors separately has not necessarily the physical meaning that is implied. The situation here is somewhat similar to that in MO LCAO calculations of electronic structure of polyatomic systems where the calculated wavefunctions and energies depend on the chosen basis set. The latter is necessarily incomplete, so the addition of any function improves the results, but this does not mean that the added functions have unambiguous physical meaning. Dependent on the kind of added functions one can improve a specific part of the wavefunction on the expense of other parts.

Similarly, by adding descriptors of a certain kind one can enhance the presence of a particular feature in the correlation with the activity, but with arbitrary and non-independent descriptors this may be an artifact. Added variables improve the correlation but diminish the physical meaning of each of them. This situation is especially important in QSAR where the goal is to identify the main descriptors that represent the activity, and to use them for screening and prediction of activity of new compounds. With arbitrary chosen non-orthogonal (mutually dependent) and incomplete set of descriptors the results of regression analysis may be either incorrect or at least unreliable. Arbitrary descriptors may result in chance correlations making some of them artifacts, meaning that such descriptors do not necessarily represent the activity in spite of being well represented in the statistical correlation.

In ab initio MO LCAO calculations the choice of basis sets got most attention during the latest decades, and a fairly good understanding of the problem was reached with basis sets that tend to the exact solution limit (which is a mathematical problem). The easy part of it is due to the fact that the functions in the basis set, distinguished from the descriptors in the QSAR problems, are not required to have a physical meaning directly transferable to other systems. Therefore the methodology of searching for the best set of descriptors cannot follow that employed in electronic structure calculations.

Can we avoid the arbitrariness in the choice of descriptors? The present contribution is aimed at this problem. We show that the electron-conformational (EC) method of pharmacophore identification and bioactivity prediction, suggested earlier (see the reviews [4, 5]), provides for an effective solution of this problem. It employs a unique, based on first principles, non-arbitrary descriptor of molecular systems that allows one to reveal the pharmacophore of activity avoiding statistical weighting arbitrary descriptors (that may lead to chance correlations and artifacts) and with the same reliability as the experimental data used in the training set. The unique descriptor is the full electronic structure and topology of the molecule in a given conformation presented in a digital (matrix) form, and all the low energy conformations are taken into account. We discuss some consequences of the uniqueness of this matrix description and the role of its flexibility (matrix element tolerances) in the quantitative evaluation of the activity, as well as some hints on the possible bimolecular mechanism of drug–receptor interaction with examples from the problem of aquatic toxicity to fish.

A unique non-arbitrary descriptor of molecular properties

The best description of molecular properties including their interaction with bioreceptors is given by their full electronic structure and topology in the ground and some excited states. It contains the whole information about the possible action of the molecule. Theoretically, nothing better than full electronic structure and topology can be suggested to represent the molecular ability to interact with other systems. All the particular descriptors used in the QSAR methods may be regarded as particular cases of this full description which is thus the upper limit that can be reached in the accuracy of this approach.

With the goal of QSAR problems, we suggested earlier to present the electronic structure of the molecule in a given conformation by means of the electron- conformational matrix of congruity (ECMC) (see in [4]). Figure 1 shows an example of such a matrix (the matrix is

symmetric, so only its upper part is shown). The rank of the matrix equals the number of atoms in the molecule. The diagonal matrix elements stand for the electronic properties of the atom in the molecule described by the so-called *interaction index* (*II*) (see below), while the off-diagonal elements are of two types: *bond orders* for near-neighbor (chemically bonded) pairs of atoms and *interatomic distances* for all the other pairs. The interaction index is derived approximately from the Fukui-Clopman theory of interatomic interactions to serve as a measure of relative electron-donor (proton acceptor) property of the atom-in-molecule, and it is given by the formula [6]:

$$II = g_m \exp[-\sqrt{21_m R_0}] \quad (1)$$

where g_m is the occupation number of the outermost atomic orbital, I_m is the energy of ionization of the atomic m orbital of the atom in its valence state in the molecule (the so-called *valence state ionization energy*), and R_0 can be regarded as a normalization parameter (usually we take $R_0 \sim 2$ a.u. [6]). Both g_m and I_m can be obtained directly from the data of electronic structure calculations.

In this way the topology (interatomic distances) and electronic structure (interaction indexes and bond orders) are fully represented in the ECMC. The latter should be calculated for all the low-energy conformations (taking into account the solvation effects) deemed to be populated at room temperature.

The calculation of ECMC is straightforward. The low energy conformations are obtained from conformation analysis, while the electronic structure in the fixed geometry and hence the electronic matrix elements are obtained by some simple ab initio or even semiempirical calculations dependent on the problem. The values and positions of the numbers in this matrix are unique for the molecule under consideration forming its *unique descriptor* evaluated according to the first principles of quantum mechanics.

How to use these ECMC unique descriptors for solving QSAR problems?

Revealing the pharmacophore—role of tolerances—bimolecular activity

With the ECMC as a unique non-arbitrary descriptor we can proceed to reveal the common features (meaning in this case common matrix elements of the ECMC) of active compounds, the pharmacophore, without involving statistics. Assume that there is a unique bioreceptor for the activity under consideration, and hence a unique pharmacophore, and we have a training set of molecules that were

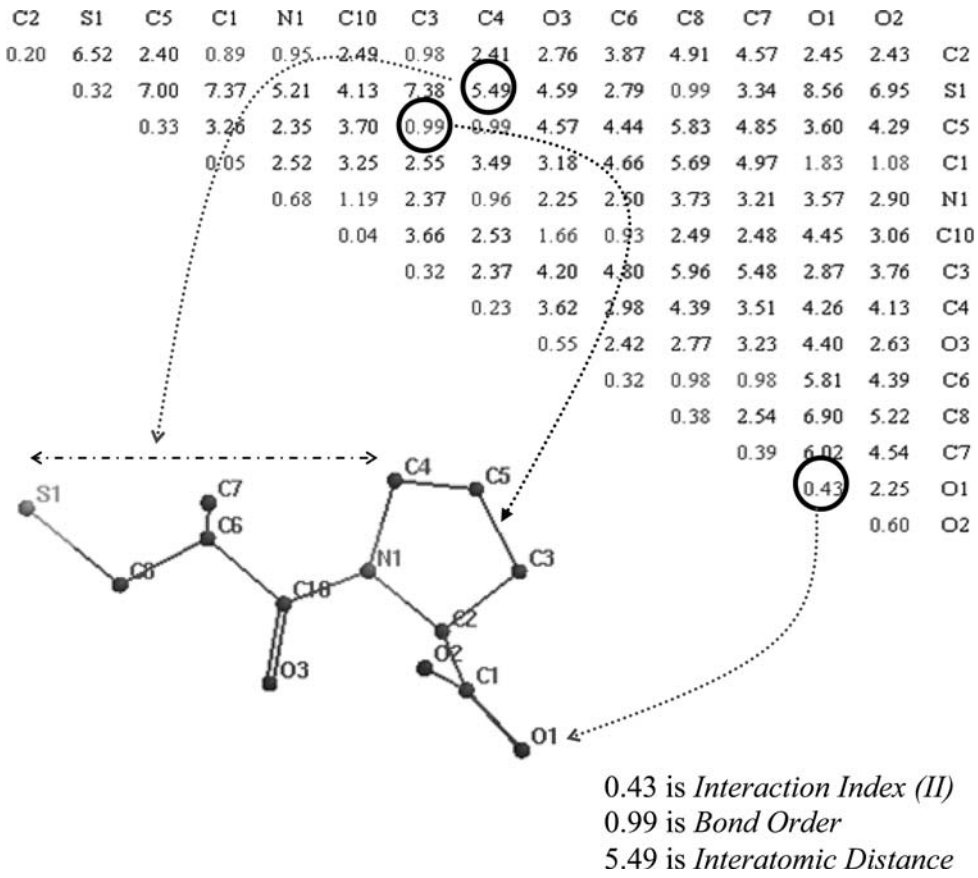

Fig. 1 A unique descriptor of molecular properties, the electron-conformational (EC) matrix of congruity (ECMC) for captopril taken as an example. The three types of matrix elements are outlined in the text

tried experimentally on this activity. Calculate their ECMC's by means of a conformational analysis and electronic structure calculations for low-lying conformations. Start with a small number of most active and simpler in structure compounds in the sense of less conformations (see, however, the note below about diversity) and compare their ECMC's by means of existing programs to find common matrix elements in all of them, meaning common interaction indices, bond orders and interatomic distances, *within a given tolerance*. In this way a common submatrix of activity, the ECSA is revealed which is the numerical picture of the pharmacophore. Figure 2 shows an example.

The tolerances are among the most important parameters of activity. The procedure of their evaluation is to start with larger values gradually reducing them until a ECSA with the smallest values of tolerances that still includes all the active compounds under consideration is reached (the tolerances may be different for different matrix elements). The absolute values of these tolerances are a measure of flexibility (maximum allowed deviation from an average position) of different atoms in the docking to the bioreceptor. Usually the lowest energy conformation fits the pharmacophore. If some of the active compounds have no ECSA in the ground state, the higher energy conformations should be tried.

Moving to the compounds with lower activity one may find out that this ECSA (revealed for the most active compounds) does not work for them, but they can be accommodated within this ECSA by allowing larger tolerances. In this way one can get slightly different ECSA's and hence *pharmacophores for different levels of activity*. The activity is thus quantitatively a function of the tolerances. The dynamics of change of the tolerances of different atoms when moving from more active to less active compounds reveals also the role of their flexibility in the change of activity.

Let us illustrate this important feature by an example of recently considered *aquatic toxicity to fish* [7]. By taking the first four most active compounds (from the 51 in the training set) shown in Fig. 3 with $\log LC_{50} = -0.30$,

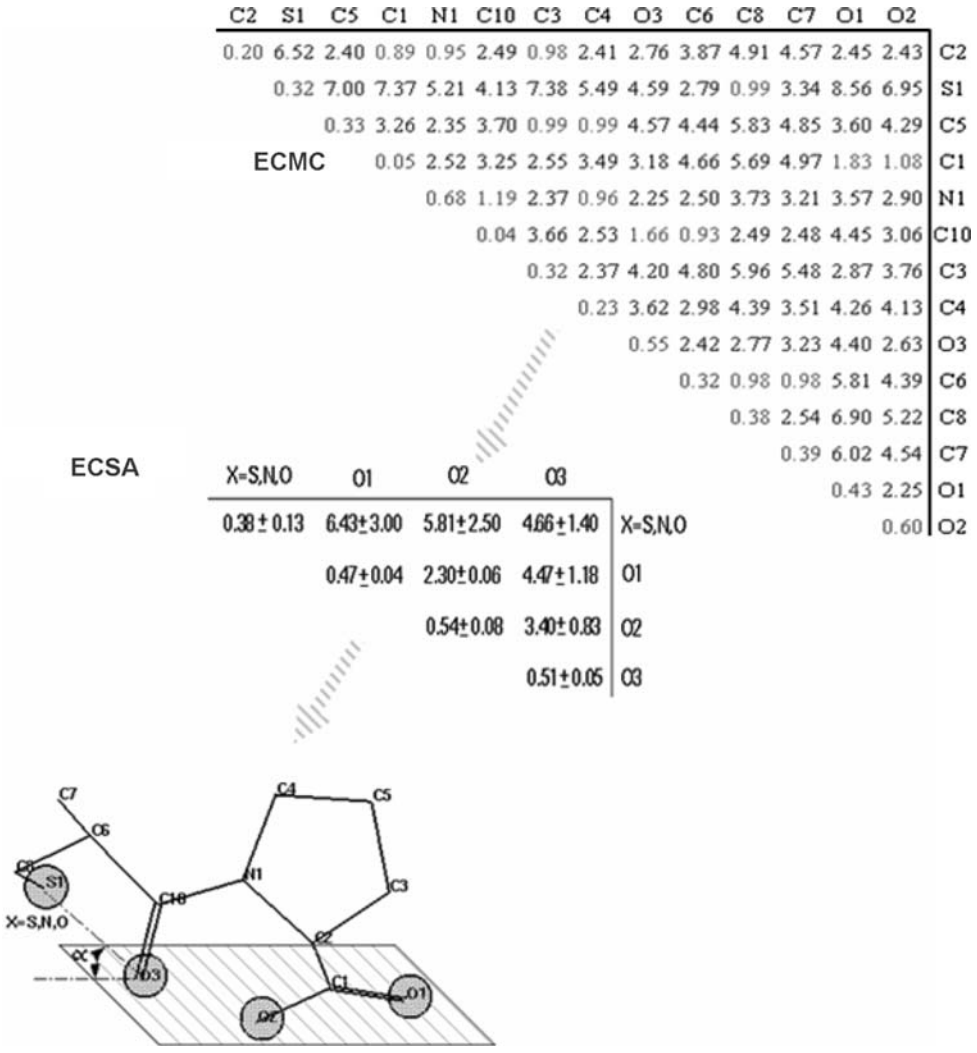

Fig. 2 The EC submatrix of activity ECSA obtained for angiotensin converting enzyme inhibitors with indication of the pharmacophore sites in the captopril molecule [6]. The tolerances in the matrix elements of the ECSA stand for the flexibility of the corresponding pharmacophore parameters, their variation being responsible for the changes in the activity quantitatively

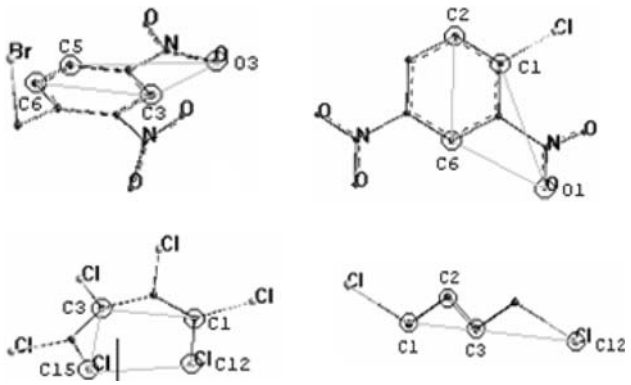

Fig. 3 Four most active toxicants of the 51 compounds tried on the aquatic toxicity to fish [7]. The pharmacophore obtained by applying the EC method to these molecules proved to be valid for 17 most active compounds

−0.20, −0.19, and −0.16, respectively, and performing the procedure of the EC method outlined above we got the following ECSA, the pharmacophore of the most active compounds (the indicated atoms are from the first, most active compound):

O_3	0.40 ± 0.06	4.80 ± 0.50	4.05 ± 0.58	3.05 ± 0.40
C_6		0.35 ± 0.05	1.21 ± 0.24	2.74 ± 0.33
C_5			0.30 ± 0.05	2.48 ± 0.58
C_3				0.39 ± 0.04

(2)

This pharmacophore came out to be valid for 17 most active compounds with $\log LC_{50} < 1.4$. Less active compounds don't fit in to this matrix. For example, the compound benzaldehyde with $\log LC_{50} = 1.57$ has the following ECSA:

O_1	0.51	4.79	50.6	2.89
C_3		0.35	1.45	2.79
C_4			0.31	2.41
C_6				0.31

(3)

We see that although this matrix does not fit to the above ECSA for the most active compounds (2), it fails just by some increase of the tolerances, mainly in the distance 5.06 Å between the oxygen atom and the carbon C4, which is out of the limits of the corresponding distance 4.05 ± 0.58 in the most active compounds. This dependence of the quantitative activity on the tolerances is employed below.

This picture of activity presented by ECSA as the pharmacophore and the dependence of the quantitative activity on the tolerances may be complicated by the presence of out-of-pharmacophore groups that influence the activity either by shielding of or competing with the pharmacophore in its interaction with the bioreceptor [3, 4, 8]. Therefore the presence of pharmacophore should be considered as just a *necessary condition of activity*, but not a sufficient one. Since based on first principles (quantum-chemical calculations) and not involving statistics to choose among arbitrary descriptors, the prediction of pharmacophore in the EC method has a potential of the same reliability as that of the experimental data of the training set, meaning 100% reliability if based on experimental data of highest accuracy. The latter are thus most important in getting the absolute reliable pharmacophore.

Another important feature that influences the pharmacophore in the EC method is the diversity of the training set. The ECSA (the pharmacophore) is valid for both levels of activity and classes of molecules the ECMC of which were used in its calculation. For the same mechanism of drug–receptor interaction different classes of compounds should have the same pharmacophore, but if the latter is obtained from one (or a limited number) of classes with active compounds, it may happen that it includes more active sites (atoms) than the minimal necessary which thus may be absent in active molecules from other classes.

To screen new compounds on the activity under consideration, their ECMC should be calculated, and then the presence of the ECSA should be checked taking into account the above class and activity level limits. If only very active compounds are looked for, say, in the problem of aquatic toxicity to fish, the ECSA (2) of the highly active ones should be tried, while for less active compounds another ECSA (with enlarged tolerances [7]) should be involved. We thus have a very flexible system of searching for leads of active compounds. Presently these procedures of matrix comparison are very fast.

The high reliability of pharmacophore identification by the EC method may serve as a basis for revealing novel knowledge. Indeed, if the pharmacophore is a necessary condition of activity, it should be present in all the active compounds. What if there are active compounds that have no pharmacophore? If the structure of the molecules, as well as the experimental measurement of activity are beyond doubt and the compound under consideration is within the diversity of the training set, the situation calls for a special investigation. The first time we encountered such a case was in the search of pharmacophore in musk odorant activity [9]. The pharmacophore that was present in several hundred compounds with musk odor from a variety of rather different classes failed in the case of a patented musk tibetan (a benzene derivative). The solution of this controversy was found in the suggestion that this molecule exhibits its odor properties in the form of a dimer formed by two stacking substituted benzene rings; the dimer has the pharmacophore.

In fact bimolecular activity does not require a priori dimerization before the interaction with the bioreceptor. Indeed, it is widely accepted that the drug–receptor

interaction, like any other substrate(S)–enzyme(E) interaction, follows the Michaelis–Menten mechanism [10] with pre-equilibrium in the formation of the complex SE before the transformation to the product P:

$$S + E \Leftrightarrow SE \Rightarrow P \tag{4}$$

This mechanism can be extended to the simultaneous action of two molecules. Indeed, if the first molecule S has no pharmacophore, there will not be transformation to the product. Then the equilibrium (Boltzman distribution) allows for the second molecule to enter the intermediate complex:

$$\begin{aligned} &S + E \Leftrightarrow SE \\ &SE + S \Leftrightarrow SSE \Rightarrow P \end{aligned} \tag{5}$$

If two molecules in a bimolecular docking to the receptor posses the pharmacophore, they may produce the necessary action that triggers the drug activity, albeit with lower probability than a single molecule with pharmacophore. We encountered such a situation in the mentioned above problem of aquatic toxicity to fish [7]. The molecule allyl chloride (II) with $\log LC_{50} = 1.20$ has no pharmacophore, while 1,4-dichloro-2-butene (I) with $\log LC_{50} = -0.16$ has the pharmacophore. Figure 4 shows how the stacking of two molecules II along their double bond (somewhat similar to the stacking of two benzene rings in the dimer of tibetan mentioned above) produce a structure III similar to I that has pharmacophore.

General formula of activity as a function of drug–receptor bonding energy

With the knowledge that the activity depends on the tolerances in the values of the matrix elements of ECSA (the parameters of the pharmacophore) we can proceed to find an approximate formula for the quantitative value of activity. Assume that:

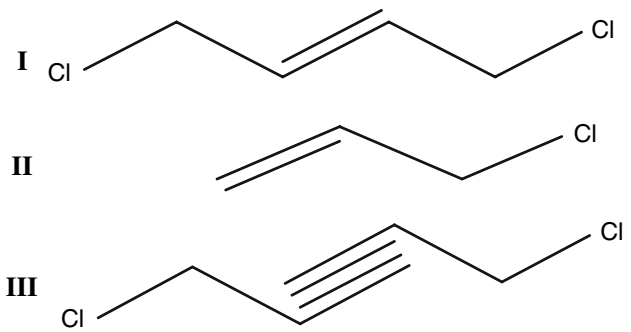

Fig. 4 Illustration to bimolecular activity: two active molecules of allyl chloride (II), which separately have no pharmacophore, by stacking along the double bond produce a bimolecular structure (III) which is similar to 1,4-dichloro-2-butene (I) and has the pharmacophore

(1) Enzyme–Substrate (drug–receptor) interaction takes place with the mentioned above *pre-equilibrium* (Michaelis–Menten mechanism [10]): $E + S \Leftrightarrow ES \Rightarrow P$;
(2) The activity A_n has an Arrhenius type dependence on an activation energy which is lowered by the enzyme–substrate *E–S bonding energy* Δ_n.

Under these assumptions we can present the activity of the n-th compound as a function of the conformation energy E_{ni} and bonding energy Δ_{ni} using the Boltzman distribution formula:

$$A_n = A_0 \frac{\sum_i \delta_{ni}[Pha] \exp\left[-(E_{ni} - \Delta_{ni})/kT\right]}{\sum_i \exp\left(-E_{ni}/kT\right)} \tag{6}$$

where $\delta_{ni}[Pha]$ is the Kroneker index: $\delta_{ni}[Pha] = 1$ if the conformation has pharmacophore, and $\delta_{ni}[Pha] = 0$ if it has not. Now, if there is at least one conformation (p) with pharmacophore, *all* the other *conformations relax to the active one* in equilibrium of the ES bonding [6], and their energy is lowered to $E_{ni} - \Delta_{np} + E_{np}$, where E_{np} is the energy of the lowest conformation with pharmacophore read off the ground conformation with $E_{n0} = 0$ (since $\Delta_{np} \gg kT$, the relaxed and bonded state is the lowest in energy). By substituting this expression in the Boltzman formula we get:

$$\begin{aligned} A_n &= A_0 \frac{\sum_i \exp\left[-\left(E_{ni} - \Delta_{np} + E_{np}\right)/kT\right]}{\sum_i \exp\left(-E_{ni}/kT\right)} \\ &= A_0 \exp\left[-\left(E_{np} - \Delta_{np}\right)/kT\right] \end{aligned} \tag{7}$$

The constant A_0 is unknown, but it can be retrieved from the activity of a reference compound r: $A_r = A_0 \exp[-(E_{rp} - \Delta_{rp})/kT]$. Substituting A_0 from this formula in to Eq. (7) we get the final expression for the activity:

$$A_n = A_r \exp\left[\left(\Delta_{np} - \Delta_{rp} + E_{rp} - E_{np}\right)/kT\right] \tag{8}$$

Obviously, we can choose a reference compound which is active in the ground conformation with $E_{rp} = 0$ (which is the case for the overwhelming majority of active compounds).

Among other applications this formula can be used to express the relative value of the bonding energy as a function of the activity:

$$\Delta_{np} = \Delta_{rp} - E_{rp} + E_{np} + kT \ln \frac{A_n}{A_r} \tag{9}$$

The next step is to estimate the unknown bonding energy Δ_{np} in Eq. (8) as a function of pharmacophore matrix elements $a_n^{(j)}$ (or tolerances) plus parameters of out-of-pharmacophore influence with variational coefficients k_j (N is the number of parameters):

$$\Delta_n = \sum_{j=1}^{N} k_j a_n^{(j)} \qquad (10)$$

The coefficients k_j can be obtained from a regression procedure by minimizing the squares of expression, $kT(\ln A_n^{\exp} - \ln A_r^{\exp}) = \sum_{j=1}^{N} k_j(a_{np}^{(j)} - a_{rp}^{(j)})$, where A^{exp} are experimental values. Usually several parameters $a_n^{(j)}$, mostly ECSA matrix elements, are sufficient to get a good correlation with the experimental data. For example, for the above problem of aquatic toxicity to fish considered in Ref. [7] just three matrix elements from its pharmacophore (2) yield a very good cross-validation ($R^2 = 0.94$) for all the 17 most active compounds for which the pharmacophore was obtained [7]:

$$\log\left(LC_{50}\right)_i = 7.58\, II^i_{\max} - 14.74\, q^i_{\max} + 1.36\, C^i_{13} \qquad (11)$$

where $II^i_{\max}$is the largest interaction index, $q^i_{\max}$ is the largest atomic charge, and C^i_{13} is the largest interatomic distance. Figure 5 shows the cross-validation diagram.

This regression procedure is similar to those in the usual QSAR methods but, again, the parameters are not arbitrary, they are taken from the calculated electronic structure. This means that there is no chance correlation in (11) and the three parameters are no artifacts: the activity indeed depends on the interaction index of the most active atom (in our case oxygen or chlorine) and the most influential interatomic distance O–C4 (Fig. 3). If out-of-pharmacophore influence is significant, additional parameters should be introduced as shown in our previous publications (see in [4, 5, 8]). These additional parameters are in fact arbitrary too, but their role is essentially diminished. Again, this parameterization and regression analysis are not related to the pharmacophore identification above (which is fully quantum-chemical), but it is important for *quantitative* prediction of the activity

Conclusions

1. For QSAR and QSPR problems, a unique descriptor representing the electronic structure and topology of the molecule and given in a digital (matrix) form is provided by the electron-conformational method of pharmacophore identification suggested earlier. This descriptor is derived from first principles by quantum-chemical calculations, thus being devoid of the shortcomings of the traditional arbitrary descriptors that include incompleteness, "non-orthogonality" (interdependence), and overlap errors, as well as statistical evaluation of their relevance in the pharmacophore, which may result in chance correlation and artifacts.
2. With this descriptor the pharmacophore of activity is obtained as a matrix with physically meaningful matrix elements and tolerances that reflect the pharmacophore flexibility, their values affecting directly the activity quantitatively. By varying the tolerances one can obtain pharmacophores for different levels of activity. Based on the unique, non-arbitrary (first-principle) descriptor this pharmacophore is deemed to be most reliable.
3. The most reliable pharmacophore may serve as a basis for getting information about the mechanism of drug–receptor interaction. For one thing, the ECSA tolerances are directly related to the structure and flexibility of the receptor. A more important problem arises when there are well established active compounds (from

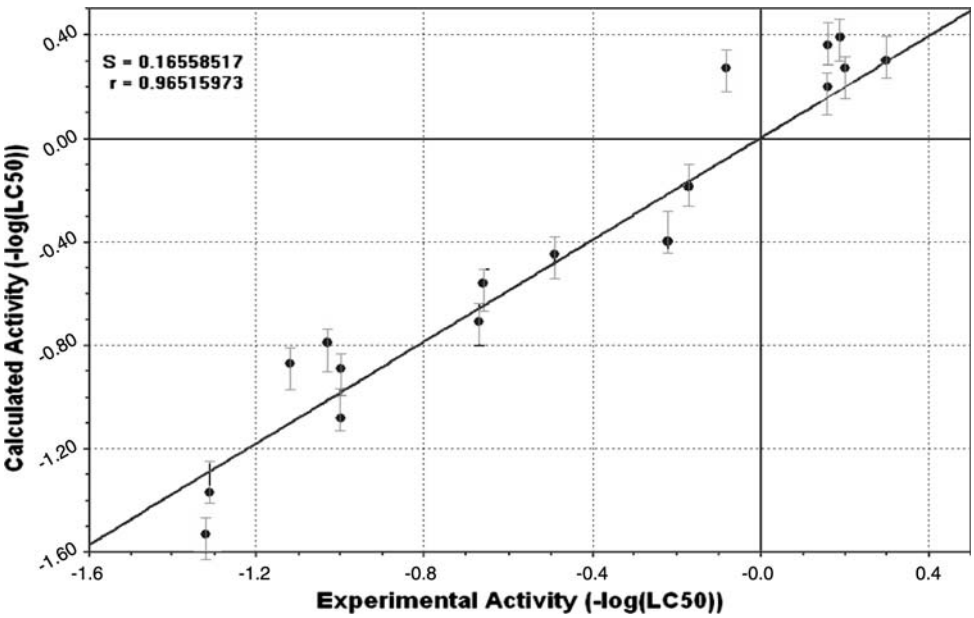

Fig. 5 The cross-validation diagram for the 17 most active compounds in aquatic toxicity to fish [7] that follows Eq. (11) with three parameters of the electronic structure and topology; $R^2 = 0.94$

within the diversity of the training set) which do not possess the pharmacophore. In these cases a bimolecular activity is assumed in which two molecules interact with the receptor simultaneously (this is feasible according to Michaelis–Menten mechanism of enzyme–substrate interaction), and they produce the pharmacophore action in such a bimolecular form.

4. Under these conditions a simple formula for the relative activity as a function of the interaction energy is derived, and by presenting the latter as a function of the pharmacophore parameters the activity can be predicted quantitatively. Examples from the problem of aquatic toxicity to fish are shown.

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