

QUANTUM MECHANICAL AND CONFORMATIONAL STUDIES OF A SERIES OF THIOSEMICARBAZONE AND THIOSEMICARBAZIDE DERIVATIVES ON THEIR TOXICITY

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Abstract

In this study, an effective method named Electron Topological Method (ETM) developed in order to overcome some shortcomings of other methods related to Structure Activity Relationships (SAR) investigation is introduced. The method uses both conformational data obtained after geometry optimization by using different optimization programs and electronic data obtained from semi-empirical Quantum Mechanical calculations. The results of the ETM application to the study of dermal toxicity in a series of thiosemicarbazone and thiosemicarbazide derivatives is given and discussed.

1. Introduction

The problem of a biological activity prediction and of new compounds design with the activity given beforehand is extremely important in molecular sciences. Direct solution of this problem is to reveal micro-mechanisms of interaction of an active molecule with bio-receptor. Since this way is quite difficult and time consuming, interaction of molecules with bio-receptor may be considered as a black box analyzed just relative to its input and output. The input to that black box is the constitution and structure of the compounds that are to be tested on a bio-receptor. The outcome is the biological effect obtained experimentally, which is called biological activity. The answer to the question on which parts or features of compounds depends this or that biological activity is generally unknown.

There are many experimental data accumulated on different biological activities of compounds with known molecular constitution and structure. The practical way to solve the problem is to use these data. Supposing that there is a direct correlation between molecular structures of compounds and their biological activities, all the active compounds under consideration can be compared with the inactive ones in order to reveal similarities and differences between them. As a result, the molecular features responsible for the activity demonstration is found and the result obtained can be used for the estimation of the biological activity of new compounds. The methods based on these concepts are known Structure-activity Relationships (SAR) in literature.

2. Method

There are many methods for SAR study, and practically all of them have some disadvantages. The purpose of the Electron Topological Method (ETM) is to overcome the shortcomings of the molecular descriptions of the previously developed quantitative and/or qualitative SAR (QSAR) methods.

ETM pays attention to both electronic and conformational characteristics of the compounds, while previously developed QSAR methods use just integral characteristics of the molecules mainly. The compounds whose skeletons differ can be processed simultaneously by ETM, while other methods can handle just the compounds having similar skeletons. However, the results of the ETM applications can also be used in quantitative calculations with best outcome.

Compound structure description language (CSDL) used in the ETM is $n \times n$ matrices called Electron Topological Matrices of Conjunction (ETMC), where n is the number of atoms in the molecule. Conformational, quantum-chemical and physical-chemical data

used to form ETMCs. Since each ETMC is symmetric with respect to its diagonal, only upper part of the matrix is kept in the memory of computer and processed. Diagonal elements a_{ii} where i is the i -th atom in the molecule, are represented by one of the atomic parameters such as atomic charges, valence activities, HOMO or LUMO energies, etc. Off-diagonal elements a_{ij} are of two kinds. Namely, for chemically bonded atoms a_{ij} is one of the electronic parameters of the i - j bond such as Wiberg's index, bond energy (total, covalent or ionic), polarizability and so on, while for non-bonded atoms a_{ij} is the interatomic distance between i and j atoms (R_{ij}). Some of the atomic and bond parameters that are considered to be the most important for the given activity demonstration are fixed, and their values are used to form ETMC for each molecule under consideration.

After forming the ETMCs, one of the most active compound is chosen as a template, and ETMC of this molecule is compared with all other ETMCs to reveal matrix elements which are present in all the active compounds but absent in the inactive ones. The revealed submatrix is called Electron Topological Submatrix (ETS) of activity. That matrix representing both structural and electronic fragments of molecular structures is considered as the feature responsible for the activity demonstration.

When comparing the ETMCs, flexibility of the compounds is taken into account by introducing some parameters labeled Δ_1 and Δ_2 that are used for diagonal and nondiagonal elements, respectively, as allowable limits for their variations. Sometimes, another variation Δ_3 for distances is used instead of Δ_2 .

In order to decide whether the found features are good or bad ones, two probabilistic estimations known from literature are used. They are given as follows.

$$P_a = \frac{n_1 + 1}{n_1 + n_3 + 2} ; \quad \alpha_a = \frac{(n_1 \cdot n_4 - n_2 \cdot n_3)}{\sqrt{N_1 \cdot N_2 \cdot N_3 \cdot N_4}}$$

Here n_1 and n_2 are the numbers of molecules possessing and not possessing the features of activity found by the ETM in the class of active compounds respectively; n_3 and n_4 have the same meaning for the class of inactive compounds; N_1 and N_2 are the numbers of molecules in the classes of active and inactive compounds, respectively; $N_3 = n_1 + n_3$ and $N_4 = n_2 + n_4$. P_a is related just to compounds containing activity feature found by ETM, while α_a is related to all compounds, as seen from their definitions.

If the final features selected are not representative enough, the limits Δ_1 , Δ_2 and Δ_3 , the template compound, the parameters chosen to form ETMCs is to be changed until appropriate fragments are found. The following can be worked out with the ETS of activity.

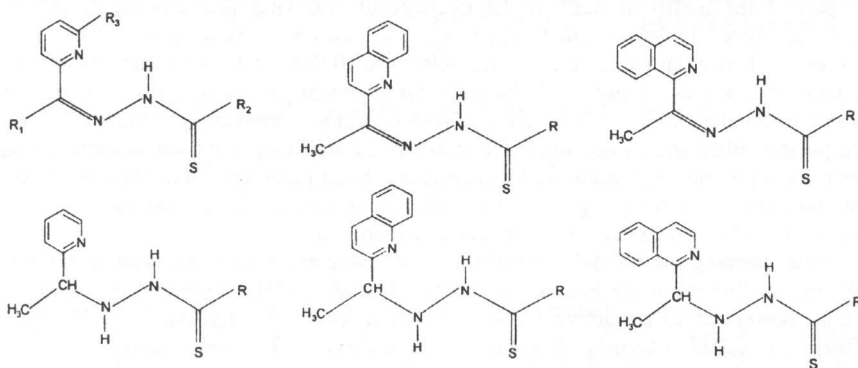
1. Molecular design of new active compounds.
2. Non-experimental computer screening of new molecules with respect to the activity.
3. Prediction of possible properties of the appropriate bio-receptor.

About 20 problems of prediction, screening and design of biologically active compounds, including drugs (anti-inflammatory and anti-allergic preparations, ferment inhibitors etc.), fragrances (musk, amber, sandal wood), plant growth regulators, defoliant, food flavorings (garlic, meat, etc.) and others have been successfully solved by ETM [1]. These applications show effectiveness of the ETM in a straight forward manner.

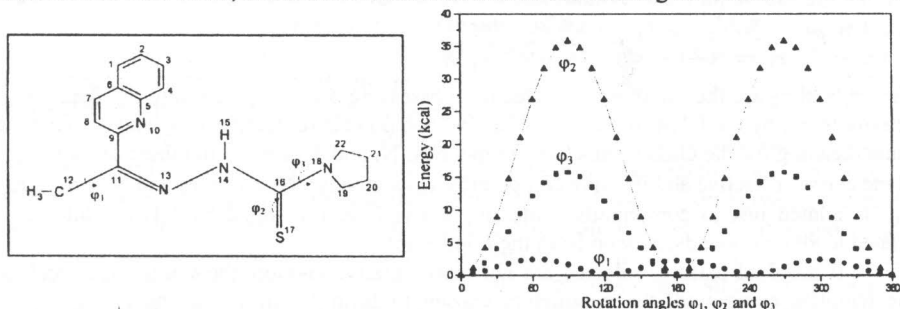
3. Results and Discussion

A series of thiosemicarbazone and thiosemicarbazide derivatives among which there are severe toxic (38 molecules) and non-toxic compounds (21 molecules) with skeleton types given in Table 1, has been investigated by means of the ETM on the subject of the SAR studies. Molecular mechanics program MMX was used for geometry optimization. After reaching optimized conformations, relative stability of each compound, as to its rotation around the bonds, was taken into account.

Table 1. Main skeletons of the compounds under consideration



If a molecule was found in a few stable conformations, all of them were considered as a separate molecule and included into the set. After ETM processing, the conformation containing activity feature is considered as the active conformation. For the molecule given in Fig. 1, conformational energies taken as a function of rotation angles φ_1 , φ_2 and φ_3 , are seen below. The minima seen in the figure do not produce new conformations because of the symmetry. The rotations around other bonds require higher energy than the given conformation. As a result, this conformation is the most stable among the others.

Figure 1: Conformational energies depending on rotation angles φ_1 , φ_2 and φ_3

For electronic structure determination, Complete Neglect of Differential Overlap (CNDO/2) being a semi-empirical quantum mechanical method was used. Each ETMC was formed of effective charges on atoms, Wiberg's indices and optimized distances between chemically non-bonded atoms in the molecule. The electronic charges and distances are given in electron charge unit e and in Å, respectively.

To determine feature of non-toxicity, we selected one non-toxic compound from the series and compared its ETMC with the other ETMCs belonging to the rest of compounds demonstrating both severe and none dermal toxicity. One of the most informative features selected that is common for most of the none toxic molecules but absent in severe toxic ones is seen in Fig. 2.

Not only the part playing role for π - π interaction (the bond labelled 1-6) with the bio-receptor but also hydrophobic part in the form of aliphatic groups are necessary for the molecules to be non-toxic.

For the feature selection process, Δ_1 and Δ_2 are very important. To optimize them, one of them was fixed while the other changed.

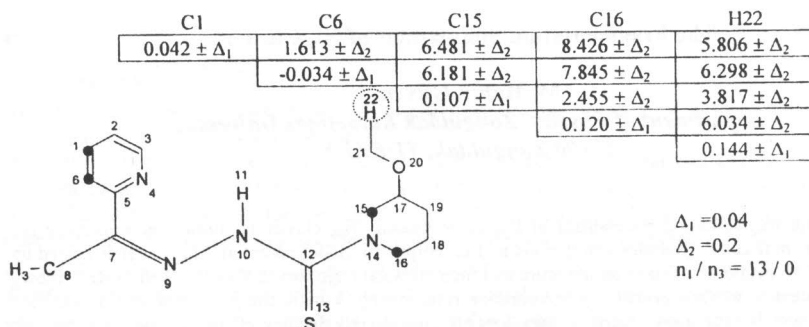


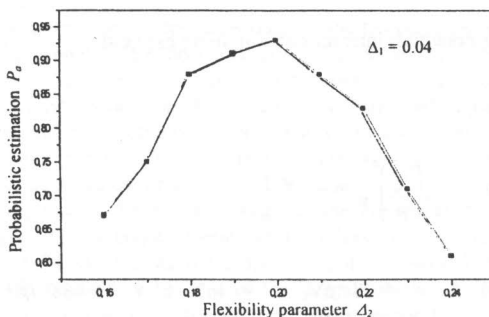
Figure 2: Template compound and corresponding ETS of non-toxicity.

After reaching optimum value of the changing flexibility parameter, it is hold and optimum value of the other is determined. The behavior of Δ_2 is seen in Table 2 and Fig. 3. for the non-toxicity feature selected

Table 2: Dependence of the probability of the non-toxicity feature realization on the Δ_2 choice (Δ_1 is affixed to 0.04)

Δ_2	0.16	0.17	0.18	0.19	0.20	0.21	0.22	*0.23	0.24
n_1 / n_3	1 / 0	2 / 0	7 / 0	10 / 0	13 / 0	13 / 1	14 / 2	14 / 5	15 / 9
P_a	0.67	0.75	0.88	0.91	0.93	0.88	0.83	0.71	0.61

If Δ_1 and Δ_2 are smaller or bigger than their optimum values, then there is no clear separation of compounds on active and inactive ones (both of them can contain the feature of activity), and P_a is decreasing.



Conclusion

Before carrying out experiments, people can search the feature of non-toxicity found in molecules under investigation and say that they are non-toxic without dealing with quite difficult and time consuming procedure mentioned if they contain the feature.

References

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2. Shipman C., Smith S.H., Drach J.C., Klayman D.L., *Antiviral Research*, No. 6, pp. 197-222, 1986.