

The Qsar Study of Azole Derivatives Using Molecular Descriptors for Quantum Molecular States

M.O. AMZOIU¹, OANA MARIANA CRISTEA²

¹University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania, PhD student

²Department of Microbiology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Azoles are the main antifungal agents currently used in systemic therapy and local mycoses. The class of azole derivatives has been studied using fingerprint descriptors based on electronegativity of the occupied molecular orbitals (OMO) and unoccupied molecular orbitals (UMO). The Hansch equations that correlates partition coefficient with chemical structure allows us to identify the nature of the atoms involved in ligand (drug) – receptor interactions, as well as the nature of those interactions. The results indicate that in the most reactive molecular states, such as states HOMO and LUMO, the oxygen atoms are actually involved in the interaction of the ligand - receptor by the transfer of electrons from the biological receptor to the oxygen atoms.

KEYWORDS: azole derivatives, fingerprint descriptors, correlation regression

INTRODUCTION

Mycoses are commonly found in medical practice and their frequency is increased, mainly as a result of broad-spectrum antibiotic therapy [1].

Azoles are the main antifungal agents currently used in systemic therapy and local mycoses [2,3]. They are synthetic compounds that include imidazoles and triazoles.

To understand how these compounds can penetrate the skin several mathematical models have been proposed. The rate of penetration into the skin is dependent on various factors including partition coefficient between the vehicle and skin, log P.

Unlike an atom, "the valence shell" of a molecule may be considered as a layer filled with electrons (OMO), and the other layer unoccupied with electrons (UMO).

The interaction of a molecule with a biological receptor or other molecule may take place through electron transfer some on UMO or OMO molecular state, as it can be seen by the arrows [4]. The use of fingerprint descriptors for the valence shell of the molecules (electronegativity) allows us to get information regarding the nature of interactions taking place between ligand (drug) and biological receptor (Fig. 1) [4].

Skin is an elastic organ with multiple functions. Most remarkable is a shield for wounds, maintains body fluids and receives signals from the environment [3]. To understand how materials can penetrate several mathematical models have been proposed.

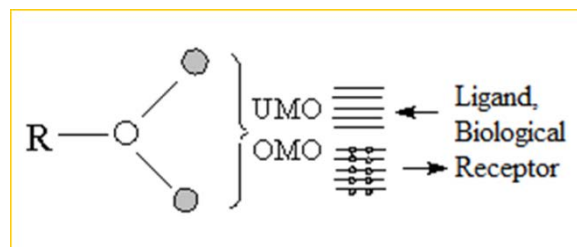


Fig.1. Ligand – receptor interaction by electron transfer

In general, these mathematical models consider that the skin is composed of three sections called: the stratum corneum, epidermal and dermal. These layers have different properties, but between each barrier the function is assumed to be constant. Penetration rate into the skin is dependent on factors such as the coefficient of diffusion of the compounds in the stratum corneum, the partition coefficient between the vehicle and the skin, concentration of the compounds and the thickness of the skin [2]. The second factor, the partition between the vehicle and the skin has the greatest influence.

MATERIALS AND METHODS

Chemicals which have been studied in this paper are 16 azole derivatives for which the partition coefficient octanol / water was determined and the results are shown in Table 1.

For molecular descriptors calculation that is involved in the partition process, the chemical design of the structure was studied with MM+ Molecular Mechanics [5] and RHF and PM3 semi-empirical method (MOPAC 7.0) [6].

Table 1. The partition coefficient of the azole derivatives

Compound	log P	Compound	log P
Azaconazole	2,32	Ketoconazole	3,55
Bifonazole	4,84	Luliconazole	3,98
Butoconazole	6,88	Miconazole	5,93
Clotrimazole	5,44	Metronidazole	-0,013
Econazole	5,32	Omoconazole	6,53
Fenticonazole	6,96	Oxiconazole	5,83
Flutrimazole	4,95	Sertaconazole	7,49
Isoconazole	5,93	Sulconazole	5,66

The evaluation was made with original programs for the fingerprint descriptors. These are electronegativity descriptors obtained from MOPAC program, *.mno.

A QSAR study the correlation structure - activity involves, in fact, statistical correlation by regression processes of chemical activity (in this case partition coefficient log P) with physical-chemical quantities called descriptors, which represents chemical structure. These descriptors are "interface" with which chemical or biological activity is related to the chemical structure of substances [7].

RESULTS AND DISCUSSIONS

Descriptors can be of very different sizes and can be determined experimentally (dipole moments, enthalpy, polarizability, molecular weight, etc.) or, especially, theoretically predicted by quantum molecular semiempirical processes or accurate (ab initio) [8]. The descriptors can be also sizes that are not calculated or have not been determined experimentally (eg dipole moments, heat of formation, etc.), but especially sizes determinate

only in theory and that can characterize almost completely a chemical structure. Their nature is very different: geometric descriptors (eg. inertia), topological (indicated schematically describing how atoms in the molecule binding), electrostatic (dipole moments, electrical charge polarisability etc.), thermodynamic.

The reason why so many descriptors are used is explained by the fact that, in many cases, the connection between chemical structure and its activity to be studied is not known [8]. For this reason we use a large number of descriptors and link activity (property) - structure is realised statistically for a class of substances for which the property (activity) was determined experimentally. Another reason is that the mechanism of occurrence of a property is unknown. An example is the activity of biological, chemical or drug for a class of substances. In this case the activity of substances is obtained by their interaction with biological receptors (the active site) or by penetration of cellular membranes, such as those studied in this work.

The chosen descriptors for this paper refers to the ability of atoms in the molecule to release or accept electrons in their interaction with other atoms. By definition, the ease or the ability of an atom to release or accept electrons is described by electronegativity.

By using OMO - UMO fingerprint descriptors informations may be obtained on how the class molecules interacts with the active site of a biological receptor [4]. Fingerprint descriptors allow us to locate those atoms and identify those molecular fragments or chemical groups involved in the formation of biological response [9]. Can be designed in this way, new structures from identified fragments or chemical groups, for which biological activity is predictable.

The fingerprint descriptors allow the identification of the atoms contributing to partition process (Table 2).

Table 2. The OMO - UMO fingerprint descriptors

OMO-UMO descriptors:	
OMO: $OELN = \sum_i^{OMO} EL_i$	UMO: $UELN = \sum_i^{UMO} EL_i$
OEL = OELAT + OELH	UEL = UELAT + UELH
OELAT = OEC + OEO + OEN + ...	UELAT = UEC + UEO + UEN + ..

EL - the total electronegativity of the molecular state and the descriptors which refers to the contribution of the atom species to the electronegativity of a molecular states are:

ELAT - heavy atoms (other than hydrogen atoms), ELH - hydrogen atoms, EC - carbon atoms, EN - nitrogen atoms, EO - oxygen atoms.

The prefixes U- and O- refers to the sum of electronegativities for 1, 2, 3 ... OMO or UMO layers.

Because molecular states are described by molecular orbitals constructed with the contribution of the atoms in the molecule

$$\Psi_i = \sum_j c_{ij} \phi_j,$$

where ϕ_j are orbitals of the valence shell of atoms and c_{ij} are their contribution to the molecular orbital Ψ_i , then for each molecular

$$\text{Atomic descriptors: } \eta(Q) = \frac{1}{2} \frac{\partial^2 E_n}{\partial Q^2} = \frac{1}{2} \frac{\partial^2 E_n}{\partial N_n^2} = \eta_0 + \frac{3}{2} \frac{b^2 Q}{n^2} \quad (\text{Atomic rigidity})$$

$$\chi(Q) = \frac{\partial E_n}{\partial Q} = - \frac{\partial E_n}{\partial N_n} = \chi_0 + \eta(Q)Q$$

$$E_n(Q) = E_n^0 + \left(\frac{\partial E_n}{\partial N_n} \right)_{N_n=N_n^0} N_n + \frac{1}{2} \left(\frac{\partial^2 E_n}{\partial N_n^2} \right)_{N_n=N_n^0} N_n^2 + \dots$$

Statistical correlation of fingerprint descriptors with biological activity was made using Minitab. The results of these correlations are given in Table 3. As it can be seen in Table 3

state can be defined molecular electronegativity (ease of transfer or accept electrons) as the sum of the contributions electronegativity in accordance with the weight of these atoms that participate in the formation of the molecular state described by Ψ_i .

The size EL_i is the molecular electronegativity described by molecular orbital Ψ_i :

$$EL_i = \langle \Psi_i | EL | \Psi_i \rangle = \sum \chi_j c_{ij}^2$$

As molecular descriptors as function of the electric charge of atoms in the molecule we choose particularly atom rigidity (hardness) [6], which describes the opposition of an atom or molecule to the change in the electric charge (Q) or electron density (N).

for each chemical structure from the class of substances studied in this paper, the species of atoms contribute differently to molecular quantum states.

Table 3. Correlation coefficients (R2, %) for molecular states electronegativity

ATOM	HOMO	LUMO	O- MO	U-MO	OC-MO	UN-MO	OC-MO + UN-MO
H	5.9	4.4	7.3	1.8	5.8	5.8	5.8
C	1.9	0.4	4.7	4.6	0.3	0.5	0.4
O	23.5	25.7	11.8	26.2	18.8	26.0	28.2
N	0.4	22.5	6.7	11.4	2.3	14.2	9.0

HOMO = Highest occupied molecular orbital energy

LUMO = Lowest unoccupied molecular orbital energy

O-MO = three occupied orbitals with electrons

U-MO = three unoccupied orbitals with electrons

OC-MO/UN-MO = all occupied molecular orbitals and unoccupied with electrons

From the atom species involved, it can be observed the oxygen atoms in the HOMO / LUMO states which contributes with about 23.5% (HEO) or 25.7% (LEO) for the HOMO / LUMO states to the partition coefficient logP.

Also, the nitrogen atoms takes considerable part to the log P are being involved in the

transfer of electrons from the receptor to the nitrogen atoms (LEC 22.5%) and less in the donation of electrons (HEC 0.4%). Compared with the other atoms from chemical structures studied, oxygen atoms are most involved in the formation of the log P. Indeed, for all occupied or unoccupied molecular states, oxygen atoms

contribute by far the most to log P: occupied electron states (%): O-EO 11.8, OC-EO 18.8, for unoccupied states with electrons (%): U-EO 26.2, UN-EO 26.0 and for overall molecule the sum of molecular states of all occupied or unoccupied with electrons, ELO 28.2%.

It can be noted that the molecular states occupied with electrons are less involved in the interaction ligand - receptor than the molecular state unoccupied with electrons, which shows

that the electron transfer is made from the biological receptor atoms to oxygen and nitrogen atoms of derivatives azole, ie Receptor =>Ligand type (Fig.1).

The results obtained using fingerprint descriptors of quantum molecular states are in agreement with the results obtained using CODESSA descriptors. For 16 azole derivatives studied (Table 1) results of statistical correlation are presented in Table 4.

Table 4. Multilinear regression equation $\log P = a_0 + a_1X_1 + a_2X_2 + \dots$

best correlations	descriptors involved (X_i)
R2=0.8470 (3 descriptors)	157 - Atomic nucleoph. react. indecies 265 - Max e-e repulsion for a C-C bond 54 - LUMO+1 energy
R2=0.8367 (3 descriptors)	157 - Min electron-nuclear attraction for a H-O bond 265 - Max e-e repulsion for a C-C bond 54 - LUMO+1 energy
R2=0.8352 (3 descriptors)	157 - FHBCA Fractional HBSA (HBSA/TMSA) 265 - Max e-e repulsion for a C-C bond 55 - HOMO - LUMO energy gap
R2=0.7618 (2 descriptors)	55 - HOMO - LUMO energy gap 54 - LUMO+1 energy
R2=0.7572 (2 descriptors)	28 - Max bonding contribution of a MO 54 - LUMO+1 energy

In Hansch equation with 3 and 2 descriptors we can see the presence of the HOMO, LUMO and LUMO + 1 descriptors (descriptors 54, 55), which contributes significantly to the partition coefficient ($R^2 = 75 - 85\%$).

Also, to the biological activity of the substances analysed contributes the descriptor repulsive electrostatic interactions for the C-C bonding (265), for which Fig.2 indicate the following distribution values:

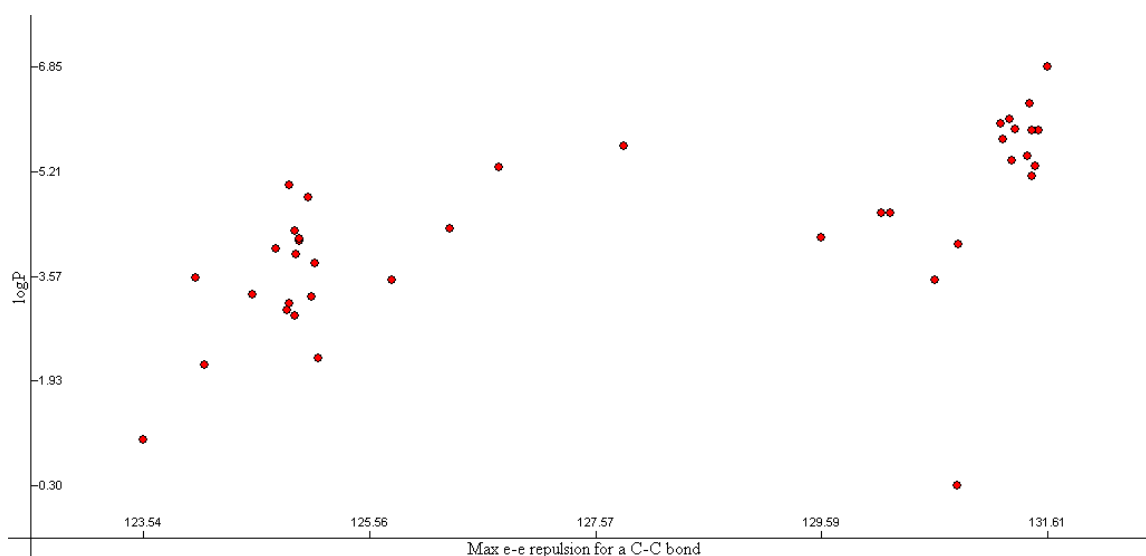


Fig.2. Distribution values for the 265 descriptor

Descriptor 55 (HOMO-LUMO energy gap) gives the following distribution of values (Fig.3) for a correlation $R^2 = 76,18\%$.

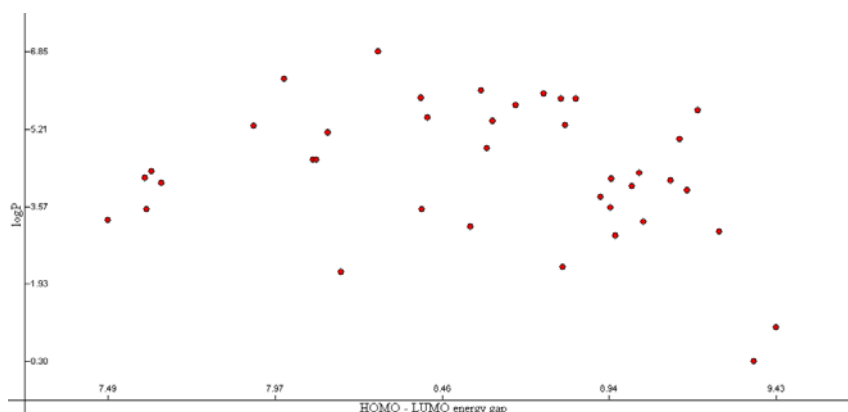


Fig.3. Distribution values for the 55 descriptor

CONCLUSIONS

With fingerprint descriptors can analyze better the contribution and role of each species of atoms in the molecule to the formation of the biological response. The use of molecular electronegativity type fingerprint descriptors suggest the participation of oxygen atoms to the antifungal activity. The results indicate that in the most reactive molecular states, such as states HOMO and LUMO, the oxygen atoms are actually involved in the interaction of the ligand - receptor by the transfer of electrons from the biological receptor to the oxygen atoms.

The location of the atoms using these descriptors open a new way of identifying groups or molecular fragments that contribute to the biological or medical response.

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Corresponding Author: Manuel Ovidiu Amzoiu, Faculty of Pharmacy, University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania. Tel. 0745160707; e-mail: m_amzoiu@yahoo.com