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QSAR STUDY FOR CLASSES WITH A BROAD RANGE OF BIOLOGICAL ACTIVITY USING ELECTRONEGATIVITY DESCRIPTORS FOR OMO – UMO QUANTUM STATES. CLOTRIMAZOLE IMIDAZOLE DERIVATIVES WITH ANTIFUNGAL ACTIVITY

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The class of clotrimazole imidazole derivatives having a broad spectrum of antimycotic activity has been studied using fingerprint descriptors based on electronegativity of the occupied molecular orbitals (OMO) and unoccupied molecular orbitals (UMO).
The Hansch equation $Kd = a_0 + a_1X_1$, where X_1 = OMO / UMO electronegativity allows us to identify the nature of the atoms involved in ligand (drug) – receptor interactions, as well as the nature of those interactions.

INTRODUCTION

The QSAR studies are usually performed[1] in order to obtain a linear equation $A = a_0 + \Sigma_k a_k X_k$ (Hansch equation) between the biological activity "A" values for a class of molecules and the descriptors X_k representing their chemical structures. Such an equation is useful for CADD (Computer Assisted Drug Design) techniques, where new candidates with predictable "A" activity can be designed by chemical modulation.

Due to the linear form of the Hansch equation, the molecules from a class must have their activity "A" comprised in a reasonable domain of values. The molecules from the class are chosen in such a way that their chemical structures do not differ too much.

The aim of the present paper is the study of a class of drugs having on one hand quite different chemical structures and on the other hand a broad range o values for their biological activity. As we shall see in the following, the use of fingerprint - descriptors for the valence shell of the molecules (electronegativity, hardness) allows us to get information regarding the nature of interactions taking place between ligand (drug) and biological receptor. In addition, the descriptors presented in this paper allow the identification of the atoms contributing to these interactions. The localization of these atoms on each chemical structure makes possible the identification of those molecular fragments or chemical groups which are involved in the biological response. A new way in CADD technique can be opened for the design of chemical structures incorporating the found fragments or chemical groups.

RESULTS AND DISCUSSION

For the set of 22 clotrimazole derivatives, their antifungal activity (see Table 1) by inhibition of the P450 enzyme is already known.[2]

As may be seen in Table 1, the activity –logKd assumes very broad range of values comprised between –logKd = 7.7 – 4.6 (*i.e.* Kd= 20 – 25,000 nM). The chemical structures of these derivatives are quite different.

The chemical structures contained in Table 1 have been modelled and their molecular geometries optimized using the Molecular Mechanics (MM+) and MOPAC 7 [3] packages. The descriptors have been obtained using original programs and the output data from quantum molecular ab initio calculations using GAMESS (RHF, STO 6, MP=4).[4]

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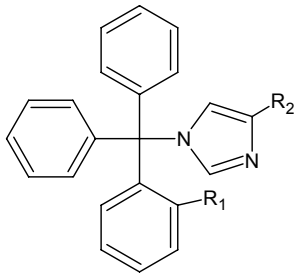
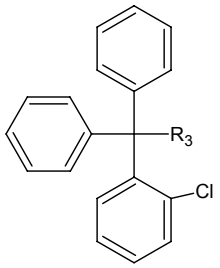
Table 1

The antifungal activity of 22 clotrimazole derivatives

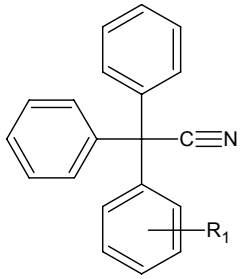
Derivative	R_1	R_2	R_3	$-\log K_d$
1a	Cl	H		7.1549
1c	Cl	CH_3		5.9208
2a			OH	6.2840
3a			NH_2	6.0000
3e			$NHCOCH_3$	5.9208
3h			$NHNONH_2$	5.3010
3m			$CH(COOC_2H_5)_2$	6.3979
5a	o-Cl			7.2218
5b	o-Fl			7.1549
5c	p-Cl			6.1249
5d	p-Fl			6.0969
6a	H	H	H	5.6021
6b	o-Cl	H	H	7.6990
6c	o-Fl	H	H	7.3979
6d	p-Cl	H	H	7.0458
6e	p-Fl	H	H	6.6990
6f	o-CF_3	H	H	5.4202
6g	p-CF_3	H	H	5.8239
6h	o-Cl	CH_3	H	5.9586
6i	o-Cl	CH_3	CH_3	4.9208
6j	o-Cl	CF_3	H	5.6990
6k	o-CF_3	CF3	H	4.6021



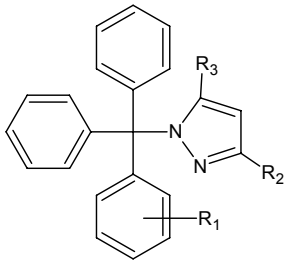
1a-c



2a, 3a, 3e, 3h, 3m



5a-d



6a-k

The fingerprint descriptors used in this paper regard the valence shell of the molecule, i.e. OMO (Occupied Molecular Orbitals) and UMO (Unoccupied Molecular Orbitals).

The OMO and UMO quantum states are characterized (LCAO approach) by the molecular orbitals $\Psi_i = \sum_j c_{ij}\varphi_j$ built from atomic orbitals φ_j, c_{ij} being their mixing coefficients. These molecular wavefunctions are useful to calculate the partition of the electron population as well as the electric charges on atoms in the molecule. One may in this way calculate the molecular electronegativity EL_i from the contribution of each atom to the corresponding quantum state (atomic electronegativity χ_j, weight p_{ij}), according to the expression:

$$EL_i = \langle \Psi i | \mathbf{EL} | \Psi_i \rangle = \sum \chi_j p_{ij} \quad (1)$$

The atomic electronegativity can be estimated from the following formulas derived from the Slater Type Orbitals and the Parr's definition of the atomic electronegativity[5]:

$$\chi(Q) = \chi_0 + \eta(Q)Q \; ; \; \eta(Q) = \eta_0 + \frac{3}{2}\frac{b^2 Q}{n^2}, \quad (2)$$

where Q is the electric charge of the atom in molecule, "n" the principal quantum number and b= 0.3 a screening constant. Formulas 1 and 2 allow us to define the following fingerprint descriptors:

For OMO states: OELN = $\sum_i^{occ} EL_i$ is the electronegativity of all OMO states.

As one can see, OELN = OELAT + OELH, where OELAT represents the sum of all electronegativities of the "heavy" atoms, other than the hydrogen ones and OELH the contributions of the hydrogen atoms. In the same way, OELAT = OEC + OEO + OEN + OEX, where the four terms represent the contributions to OELAT from different heavy atoms: OEC (carbon), OEO (oxygen), OEN (nitrogen) and OEX the contribution of the heavy atoms other than C, O and N.

For UMO states: LELN = $\sum_i^{unocc} EL_i$ is the electronegativity of the UMO quantum states. One may define in the same way the following quantities:

LELN = LELAT + LELH, where LELAT = LEC + LEO + LEN + LEX, the meaning of these quantities being the same as for OMO states substituting the prefix O by L.

The use of these descriptors in the QSAR analyses can give valuable information about the nature of the atoms involved in ligand (drug) – receptor interaction. The values of these descriptors summarized in Table 4, have been estimated from MOPAC and GAMESS outputs by using our own programs.

Table 2

OMO electronegativity descriptors

Derivative	-logKd	OELN	OELAT	OELH	OEC	OEN	OEX
1a	7.1549	141.229	81.373	59.856	65.108	9.534	6.731
1c	5.9208	151.586	84.523	67.063	68.257	9.557	6.710
2a	6.2840	121.111	68.246	52.865	56.965	0.000	6.706
3a	6.0000	124.259	67.712	56.548	56.741	4.344	6.627
3e	5.9208	142.564	78.905	63.659	63.274	4.296	6.919
3h	5.3010	140.389	80.283	60.105	60.382	8.827	6.742
3m	6.3979	193.180	104.589	88.591	79.751	0.000	6.649
5a	7.2218	120.433	71.044	49.390	59.941	4.347	6.756
5b	7.1549	122.715	73.315	49.400	60.277	4.345	8.693
5c	6.1249	120.318	70.938	49.380	59.965	4.333	6.640
5d	6.0969	122.610	73.239	49.371	60.223	4.338	8.678
6a	5.6021	138.044	74.593	63.452	65.338	9.255	0.000
6b	7.6990	141.209	81.305	59.904	65.340	9.247	6.717
6c	7.3979	143.467	83.567	59.900	65.630	9.255	8.682
6d	7.0458	141.116	81.226	59.891	65.334	9.246	6.645
6e	6.6990	143.401	83.520	59.881	65.594	9.249	8.678
6f	5.4202	163.667	103.789	59.877	69.328	9.128	25.334
6g	5.8239	163.711	103.838	59.873	69.267	9.233	25.338
6h	5.9586	151.518	84.416	67.102	68.475	9.230	6.710
6i	4.9208	161.808	87.512	74.296	71.576	9.214	6.723
6j	5.6990	167.208	110.845	56.364	69.152	9.652	32.040
6k	4.6021	189.710	133.373	56.337	73.109	9.572	50.691

Table 3

The values of UMO electronegativity descriptors

Derivative	-logKd	LELN	LELAT	LELH	LEC	LEN	LEX
1a	7.1549	145.348	69.046	76.302	61.991	5.992	1.063
1c	5.9208	155.553	72.216	83.337	65.146	6.015	1.055
2a	6.2840	123.931	57.186	66.745	54.902	0.000	1.053
3a	6.0000	127.443	57.936	69.507	54.389	2.524	1.023
3e	5.9208	143.821	66.055	77.766	61.296	2.477	1.134
3h	5.3010	139.552	65.913	73.640	58.559	5.182	1.067
3m	6.3979	190.565	84.778	105.787	78.878	0.000	1.032
5a	7.2218	123.241	61.357	61.884	57.759	2.526	1.072
5b	7.1549	123.834	62.054	61.780	58.408	2.525	1.121
5c	6.1249	123.323	61.336	61.987	57.794	2.513	1.028
5d	6.0969	124.002	61.928	62.074	58.296	2.518	1.114
6a	5.6021	148.216	68.163	80.053	62.390	5.773	0.000
6b	7.6990	145.046	69.211	75.835	62.395	5.759	1.058
6c	7.3979	145.727	69.845	75.882	62.959	5.771	1.116
6d	7.0458	145.152	69.175	75.977	62.385	5.759	1.030
6e	6.6990	145.839	69.762	76.077	62.885	5.762	1.114
6f	5.4202	152.148	76.030	76.118	67.380	5.592	3.058
6g	5.8239	152.222	76.071	76.152	67.274	5.737	3.060
6h	5.9586	155.306	72.311	82.994	65.525	5.732	1.055
6i	4.9208	165.625	75.369	90.257	68.580	5.729	1.059
6j	5.6990	148.948	77.407	71.541	67.132	6.164	4.111
6k	4.6021	156.043	84.228	71.816	72.054	6.048	6.125

These descriptors have been individually correlated with -lokKd, according to the linear equation $-\log Kd = a_0+a_1X_1$. We can identify in this way the contribution of OMO – UMO electronegativities to the formation of the biological response. The regression data are summarized in Table 4, where $R^2\%$ is the correlation coefficient of the regression.

Table 4

Regression data for OMO- UMO electronegativities

Descriptor X_1:	$-\log Kd = a_0 + a_1X_1$	$R^2\%$
OELN	8.83 - 0.0180 OELN	21.1
OELAT	8.27 - 0.0242 OELAT	23.0
OELH	7.31 - 0.0185 OELH	4.1
OEC	9.08 - 0.0439 OEC	8.9
OEN	6.50 - 0.0417 OEN	2.6
OEX	6.60 - 0.0342 OEX	23.1
LELN	8.34 - 0.0148 LELN	8.6
LELAT	9.04 - 0.0409 LELAT	14.2
LELH	7.36 - 0.0153 LELH	3.6
LEC	9.14 - 0.0466 LEC	10.6
LEN	6.48 - 0.0640 LEN	2.5
LEX	6.66 - 0.292 LEX	23.1

As may be seen in Table 4, the total electronegativity OELN (21.1%) of the quantum states occupied with electrons (OMO) participate to a greater extent to the activity -logKd, than that of the unoccupied quantum states (UMO), LELN (8.6%). The result pleads for the existence of electrostatic interactions between ligand and receptor, inasmuch the electric charges of the atoms are due to the partition of the electron population on the OMO states.

Because the hydrogen atoms contribute almost equally in OMO and UMO states to –logKd

(OELH: 4.1%, LELH: 3.6%), the difference between OELN and LELN contributions must be due to the heavy atoms. Indeed, as may be seen in Table 4, the contribution of all heavy atoms to –logKd is different (OELAT: 23.0%, LELAT: 14.2%).

If the heavy atoms are taken separately, their contribution to -logKd is in the order: N: LEN (2.5%), OEN (2.6%); C: LEC (10.6%), OEC (8.9%); X= (halogen atoms, Figure 1): LEX (23.1%), OEX (23.1%).

Note that the halogen atoms have a significant and almost equal contribution to the biological activity: LEX (23.1%) ≈ OEX (23.1%). This result reveals the nature and the contribution of these atoms from the molecular quantum states able to donate (OMO) or to accept (UMO) electronic densities during their interactions with the receptor.

Such information can be helpful for rational drug design by chemical modulation of new chemical structures. The QSAR analysis performed using fingerprint descriptors herein presented allows the identification and localization of those atoms involved in the drug – receptor interaction. One may identify those fragments or chemical groups responsible for the biological activity. These groups or molecular fragments can be used to "build" new chemical structures with predictable activity.

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