QSARs with Orthogonal Descriptors on Psychotomimetic Phenylalkylamines

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Abstract

Multiple linear regressions have been obtained for 49 psychotomimetic phenylalkylamines. The MTD method has been applied and the MTD parameter was used as steric descriptor. The energy of the lowest unoccupied molecular orbital and the net charges on the phenyl ring atoms (from AM1 calculations) have been used as electronic descriptors and $\log P_{ow}$, or average electrostatic field as lipophilicity descriptor. Hall and Kier electrotopological state indices were also tested. The descriptors have been scaled to unit and orthogonalized by Randic method. The predictability of the regressions obtained from MTD method have been checked by a method similar to cross-validation from CoMFA method. MTD has been identified as the dominant descriptor by Randic orthogonalization. The best model has been obtained with MTD and electrotopological state indices, showing the importance of the steric and electronic properties for the interaction at the receptor site level.

Key words: psychotomimetics, phenylalkylamines, MTD, AM1, orthogonal descriptors, electrotopological state indices.

Abbreviations and Symbols: MTD: Minimum Topological Difference; sMTD: single MTD (MTD descriptor optimized without supplementary descriptors); MTD – MTD optimized together with other descriptors.

1 Introduction

Amphetamine [phenyl-2-aminopropane] and mescaline [1-(3,4,5-trimethoxy-)-amino-ethane] derivatives are known as psychotomimetics with different actions from light stimulant to very strong hallucinogens. They act unselective on serotoninergic [1–4] or adrenergic receptors [5–7]. The mechanism of action at the receptor site level still remains unclear. It was supposed that the substituent at the 4-position of the phenyl ring is important in the orientation of the oxygen lone pairs of the neighbor methoxy group at 5-position so as to facilitate the electronic interaction ligand-receptor [8]. In a previous note [9] we applied the MTD method and parameter [10] in a QSAR study of a series of 31 psychotomimetic phenylalkylamine derivatives containing mostly 2-, 4-, 5-substituents. Good correlations obtained using the MTD parameter supported the importance of steric interactions. In the present study we apply Randic orthogonalization [11–13] of the descriptors and MTD method in a QSAR study of 49 psychotomimetic phenylalkylamines. This series contains besides 2-, 4-, 5-derivatives, a larger number of 3-, 4-, 5-derivatives.

MTD, LUMO energies, E_L, net atomic charges on the phenyl ring atoms, q_i, electrotopological state indices of Hall and Kier [14,15] for all atoms of the molecular core, S_i, and logP or average electrostatic field, F_i, for different substituents at the phenyl ring [16–18] are tested as descriptors in different monoparametric linear regressions. The descriptors showing significant correlations with the biologic activity have been associated with MTD descriptor and, applying the MTD connex optimization method [19], bi-, three or four parameter linear regressions have been obtained.

There are two sets of MTD values that can be used in orthogonalizations: (i) sMTD values and (ii) the values of MTD optimized together with supplementary descriptors. It is interesting to compare the effect of the orthogonalization in both cases.

We consider useful to scale to unit variance all descriptor variables before orthogonalization. This is done to avoid the possibility that different units of measurement of the descriptors distort the variance structure. The scalation has no effect on the statistic data, but allows a direct comparison of the regression coefficients in one model or in competing models.

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All the regression models resulted from MTD optimizations are cross-validated by a technique similar to the cross-validation used in CoMFA method. The cross-validated models have been compared with the ones resulted from the descriptor orthogonalization.

2 Methods

The phenylalkylamines evaluated here have been tested on human subjects [20–22]. Their structure is displayed in Table 1. The psychotomimetic activity is usually expressed in terms of mescaline units, MU, defined as the ratio of the effective dose of mescaline to the effective dose of tested compound. The mescaline effective dose is situated between 3.5 mg/kg [24] and 3.75 mg/kg [21,22]. In this study the dose of 3.75 mg/kg is considered and the potency is expressed as logMU, where MU is taken as mmol mescaline/mmol of tested phenylalkylamine. The potency values are listed in Table 1.

We remind that MTD_i is a measure of the steric misfit between the tested ligand "i" and the receptor cavity [10]. Beside an optimal regression equation, a receptor map is obtained from MTD optimization procedure [10].

The hypermolecule for the calculation of MTD values has been obtained by the superposition atom by atom of all molecules in the series. The vertices of the common molecular core have been considered as cavity vertices and they have been not numbered. A hypermolecule with 20 vertices drawn in Fig. 1 resulted. The occupancy of the molecular vertices in hypermolecule is displayed in Table 1. In all optimization runs the same starting receptor map has been used:

$$S^\circ \begin{cases} \varepsilon_j = -1 & 1, 2, 5, 9 \\ \varepsilon_j = 0 & 3, 4, 6, 7, 10-13, 16-18, 20 \\ \varepsilon_j = +1 & 8, 14, 15, 19 \end{cases}$$

The starting map is similar to the optimized map resulted from previous study [9], but it contains less detrimental vertices. The MTD version used to calculate the MTD descriptor is MTD connex [19], that takes into consideration the connectivity of every hypermolecule vertex and finally rejects the receptor maps containing insular beneficial vertices that are usually an artifact of the optimization process. The sMTD values and the ones resulted from the MTD optimization together with different descriptors are displayed in Table 1.

The electronic descriptors, E_L, are net charges on the phenyl ring atoms 2-, 3-, 4-, 5-, q_2, q_3, q_4, q_5 respectively, and on the atom occupying the vertex '4' of the hypermolecule, q_p (p-para), have been obtained from AM1 calculations. Using MM+ force field from HyperChem 2.0 package [23], molecular mechanics calculations have been performed for all molecules. The geometries resulted from MM+ optimisation have been fully optimized using the AM1 hamiltonian [24] from MOPAC 6.0 package [25] using keyword PRECISE. From the compounds having a chiral center, the R isomer is generally more active than the S isomer. Therefore, the geometry of the R isomer has been optimized.

The electrotopological state indices, S_i, have been calculated according to the Hall and Kier [14,15] algorithm with a program written by us in FORTRAN language.

The lipophilicity has been calculated using the experimental logP values of the phenylethylamine or amphetamine [26] to which π mean values of different substituents were added, according to Anderson *et al.* [27].

The average electrostatic field, F_i, for 2-, 3-, 4-, and 5-substituents, F_2, F_3, F_4, F_5, respectively and the alkylamine average electrostatic field, F_a, have been calculated by the bond increment method [16–18]. From the series of 49 compounds, four compounds contain I and Br atoms. For these four derivatives the F_i values cannot be calculated because of the lack of bond increments for the Br and I atoms.

The values of all descriptors used in regression equations are available as supplementary material.

All descriptor values have been scaled in the arbitrary scale [0–1] by using our FORTRAN program. The orthogonalization of the descriptors has been performed with a program written by S. Muresan (in PASCAL language) according to the algorithm proposed by Randic [14,15].

3 Results and discussions

The correlation and intercorrelation coefficients for the monoparameter linear regressions of some selected descriptors are listed in Table 2. The optimized receptor maps for the best models contain the vertices from the legend of Fig. 1.

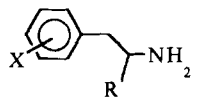
A good correlation is obtained with sMTD. From the receptor map corresponding to sMTD regression one can see that the atoms directly bonded at the phenyl ring at the positions 2-, 4-, and 5- are cavity vertices ($\varepsilon_j = -1$), while the atom of the substituent bonded at 3-position is a wall vertex ($\varepsilon_j = 1$). Thus, according to this model the active compounds should not contain a substituent at the 3-position of the phenyl ring.

The correlation with S_3, the electrotopological state index of the atom '3' of the phenyl ring leads to the same conclusion. S_3 partial correlation coefficient (see Table 2) is positive (0.67), e.g. the highest values of the S_3 index correspond to the most active compounds. Within this series, the highest S_3 values are characteristic to the compounds unsubstituted at 3-position of the phenyl ring.

From the correlation of S_p, the electrotopological state index for the vertex '4' of the hypermolecule would result that an active compound should contain an alkyl C atom at the site of the vertex '4' of the hypermolecule. The positive partial correlation coefficient of logP would suggest that compounds with high hydrophobicity must be more active than those with low hydrophobicity.

The monoparametric regression of the F_i descriptor for different substituents suggest that the substituents at 3- and 4-position should be hydrophobe and the substituents at the positions 2- and 5

Table 1. Phenylalkylamine structure, psychotomimetic potency, logMU, occupancy of the hypermolecule and MTD values resulted by MTD optimization together with other descriptors



No	X	R	logMU	j ($x_{ij}=1$)	sMTD	MTD_1	MTD_2
1	2,5-OMe, 4-I	Me	2.78	1,2,4–6,9	1	2	
2	2,5-OMe,4-Br	Me	2.72	1,2,4–6,9	1	2	
3	2,5-OMe,4-SEt	Me	1.96	1,2,4–6,8–10	2	3	3
4	2,5-OMe,4-Et	Me	2.02	1,2,4–6,8,9	2	3	3
5	2,5-OMe,4-Pr	Me	1.95	1,2,4–6,8–10	2	3	3
6	3,5-OMe,4-Br	Me	1.91	1,3–5,7,9	3	2	
7	2,5-OMe,4-Me	Me	1.90	1,2,4–6,9	1	2	3
8	2,5-OMe,4-S-i-Pr	Me	1.71	1,2,4–6,8–11	2	4	3
9	2,5-OMe,4-Br	H	1.69	2,4–6,9	2	3	
10	2,5-OMe,4-Bu	Me	1.68	1,2,4–6,8–10,12	2	3	3
11	2,5-OMe,4-SMe	Me	1.66	1,2,4–6,8,9	2	3	3
12	3,5-OMe,4-SEt	H	1.36	3–5,7–10	4	4	4
13	2,4,5-OMe	Me	1.33	1,2,4–6,8,9	2	3	3
14	2,5-OMe,4-Et	H	1.25	2,4–6,8,9	3	4	4
15	3,5-OMe,4-SPr	H	1.29	3–5,7–10,12	4	4	4
16	2,5-OMe,4-Me	H	1.27	2,4–6,9	2	3	4
17	2,5-OMe,3-OCH_2O-4	Me	1.14	1–6,9,13	2	1	3
18	2,5-OMe,4-OEt	Me	1.36	1,2,4–6,8–10	2	3	3
19	3,5-OMe,4-SMe	H	1.11	3–5,7–9	5	4	4
20	2-OMe,3-OCH_2O-4	Me	1.00	1–4,6,13	4	3	5
21	2,5-OMe,4-n-Pentyl	Me	1.10	1,2,4–6,8–10,12,15	3	4	4
22	3,5-OMe,4-OEt	Me	1.05	1,3–5,7–10,12	4	3	3
23	2-OMe,4-OCH_2O-5	Me	1.00	1,2,4–6,14	3	4	3
24	2,5-OMe,4-OPr	Me	1.38	1,2,4–6,8–10,12	2	3	3
25	3,5-OMe,4-OEt	H	0.87	3–5,7–10	4	4	4
26	2,3,4,5-OMe	Me	0.86	1–9	3	2	4
27	3,5-OMe,4-OPr	H	0.83	3–5,7–10,12	4	4	4
28	3,4-OMe,5-SEt	H	0.84	3–5,7–9,16	4	3	3
29	3-OMe,4-OEt,5-SMe	H	0.84	3–5,7–10	4	4	4
30	3,4-OMe,5-SMe	H	0.81	3–5,7–9	5	4	4
31	2,3-OMe,4-OCH_2O-5	Me	0.76	1–7,14	4	3	4
32	3-OEt,4-SMe,5-OMe	H	0.66	3–5,7–9,17	5	5	5
33	3-OEt,4-SEt,5-OMe	H	0.68	3–5,7–10,17	4	5	5
34	2,4-OMe	Me	0.67	1,2,4,6,8	4	5	5
35	4-OMe	Me	0.59	1,4,8	5	6	4
36	3,5-OMe,4-SBu	H	0.58	3–5,7–10,12,15	4	5	5
37	3,5-OMe,4-$OCH_2C_6H_5$	Me	0.46	1,3–5,7–10,12,15,18–20	5	4	5
38	3-OMe,4-OCH_2O-5	Me	0.43	1,3–5,7,14	5	4	3
39	3-OCH_2O-4	Me	0.41	1,3,4,13	5	4	4
40	3,5-OMe,4-OBu	H	0.38	3–5,7–10,12,15	4	5	5
41	3-SEt,4-OEt,5-OMe	H	0.38	3–5,7–10,17	4	5	5
42	3,4-OEt,5-SMe	H	0.38	3–5,7–10,17	4	5	5
43	3,4,5-OMe	Me	0.33	1,3–5,7–9	4	3	3
44	3,4-OEt,5-OMe	H	0.23	3–5,7–10,17	4	5	5
45	3-OEt,4,5-OMe	H	0.03	3–5,7–9,17	5	5	5
46	3,4,5-OMe	H	0.00	3–5,7–9	5	4	4
47	2,3,4-OMe	H	−0.03	2–4,6–8	6	5	7
48	3,4-OMe	Me	−0.06	1,3,4,7,8	6	5	5
49	3,4-OMe	H	−0.67	3,4,7,8	7	6	6

j ($x_{ij}=1$)—the hypermolecule vertices occupied by the atoms of the "i"th molecule, for the vertices numbering see Fig. 1; MTD_1—MTD optimized together with q_4 and S_3; MTD_2—MTD optimized together with F_4 and q_2.

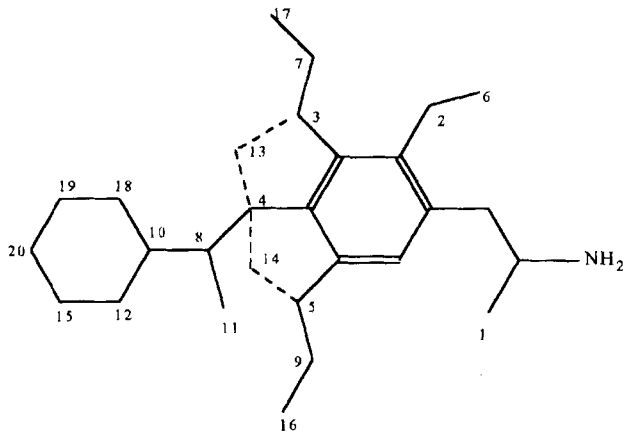


Figure 1. The hypermolecule, the numbering of vertices and the optimized receptor maps corresponding to different equations.

	Beneficial vertices	Detrimental vertices
sMTD	$\varepsilon_j = -1$: 1,2,5,9,16;	$\varepsilon_j = 1$: 3,8,14,15;
eq. 1	$\varepsilon_j = -1$: 1,2,3,5,9,16;	$\varepsilon_j = 1$: 8,11,14,15,17;
eq. 4	$\varepsilon_j = -1$: 1,5,9,14,16;	$\varepsilon_j = 1$: 6,7,15,17,19

hydrophile for high activity (see Table 2). The linear correlation with F_a reproduces the experimental trend i.e., compounds containing i-propylamine are more active than those containing ethylamine. This is also obtained from sMTD optimized receptor map where the vertex '1' corresponding to methyl group of i-propylamine is a cavity vertex.

From Table 2 one can notice some very strong intercorrelations between descriptors, especially between net atomic charges, electrotopological state indices and average electrostatic fields for the same position of the phenyl ring. There are also intercorrelations between q_2 and q_3, S_2 and S_3. E_L descriptor is the only one that has low intercorrelation coefficients with all descriptors. For this reason it was associated in almost all multiple regressions with different descriptors. Statistical results for some tested regressions are listed in Table 3. By comparing the values from the left side with those from the right side of the Table 3 one can remark the positive effect obtained by adding E_L descriptor to different regressions.

The best correlation was obtained between logMU and MTD optimized together with the net charge on the atom 4 of the phenyl ring, q_4, and the electrotopological state index for atom 3 of the phenyl ring, S_3. The regression for the scaled descriptors is:

$$\log MU = 1.9925\ (0.1317) - 1.7802\ (0.1660)\ MTD + 0.9279\ (0.0969)\ S_3 - 0.7665\ (0.1226)\ q_4 \quad (1)$$

$n = 49 \quad R^2 = 0.885 \quad s = 0.241 \quad F = 84.72 \quad R^2_{cv} = 0.793$
$press = 5.02$

According to Eq. 1 the compounds having large negative net charges on atom '4' of the phenyl ring, large S_3 and low MTD values should be among the most active. These are compounds bonded by halogen or sulfur atoms at 4-position of the phenyl ring. The corresponding scaled descriptors of Eq. 1 have been orthogonalized. The order of orthogonalization is not important. All six possible regressions have statistically significant parameters. Eq. 2, with MTD as dominant descriptor and having a

Table 2. Correlation coefficients (diagonal elements) and intercorrelation coefficients (off diagonal elements) for monoparametrical linear regressions of some tested descriptors

	logP	MW	E_L	q_2	q_3	q_4	q_5	q_p	S_2	S_3	S_4	S_5	S_N	S_p	MF	F_2	F_3	F_4	F_5	F_a	MTD
logP	.56																				
MW	.64	.47																			
E_L	−.18	−.51	−.47																		
q_2	.17	−.09	−.28	.48																	
q_3	−.24	.08	.00	−.82	−.51																
q_4	−.56	−.50	.36	.19	−.21	−.51															
q_5	.42	.48	−.10	−.11	.09	−.58	.34														
q_p	.57	.45	−.31	−.11	.09	−.96	.50	.45													
S_2	−.17	−.06	.44	−.95	.70	−.11	−.02	.07	−.55												
S_3	.46	.05	−.03	.70	−.86	−.12	.07	.21	−.61	.67											
S_4	.67	.17	.02	.22	−.34	−.63	.19	.64	−.14	.64	.53										
S_5	−.30	−.58	.18	.12	−.10	.28	−.74	−.19	.05	−.01	.05	.33									
S_N	.42	.28	−.22	.55	−.47	.07	.13	−.05	−.56	.41	.08	−.15	.49								
S_p	−.65	−.23	.08	−.25	.26	.75	−.43	−.73	.24	−.58	−.93	.12	−.14	−.58							
MF	−.59	−.18	−.36	−.04	.38	.28	−.07	−.36	−.04	−.57	−.68	−.12	−.15	.57	−.41						
F_2	.23	−.01	−.37	.97	−.73	.13	.01	−.08	−.99	.66	.23	−.02	.62	−.32	−.05	.62					
F_3	−.36	.02	−.24	−.64	.87	−.04	−.05	−.06	.53	−.94	−.51	.08	−.40	.44	.50	−.62	−.58				
F_4	−.72	−.42	−.13	−.05	.20	.71	−.51	−.68	.06	−.52	−.85	.29	−.03	.87	.70	−.16	.44	−.59			
F_5	.40	.47	−.08	.06	−.07	−.40	.90	.31	−.19	.19	.13	−.87	.28	−.34	.04	.20	−.25	−.41	.41		
F_a	−.18	.05	.16	−.60	.54	−.26	.04	.19	.58	−.42	.04	−.07	−.93	.00	.08	−.57	.35	−.17	−.11	−.41	
MTD	−.48	−.43	.37	−.63	.64	.22	−.34	−.22	.68	−.71	−.39	.46	−.55	.44	.25	−.72	.66	.45	−.50	.44	−.88

E_L – the energy of the lowest unoccupied molecular orbital; logP – experimental or calculated according Hansch π fragmental constants; MW – molecular weight; q_i – net charges on the phenyl ring atoms; S_i – electrotopological state indices for the phenyl ring atoms; S_N – the electrotopological state index for amine N; MF – average molecular electrostatic field (V/nm); F_i – average electrostatic field for the substituents at different positions of the phenyl ring; F_a – alkylamine average electrostatic field.

Table 3. Cross-validated results for the equations containing MTD optimized together with different descriptors; n = 49

Descriptor	R^2	R^2_{cv}	press	Descriptor	R^2	R^2_{cv}	press
MTD E_L	0.792	0.671	7.96				
MTD logP	0.839	0.760	5.81	MTD E_L logP	0.862	0.763	5.73
MTD q_2	0.806	0.695	7.38	MTD E_L q_2	0.833	0.715	6.91
MTD q_3	0.774	0.623	9.13	MTD E_L q_3	0.828	0.535	11.26
MTD q_4	0.853	0.718	6.82	MTD E_L q_4	0.863	0.733	6.46
MTD q_p	0.842	0.721	6.77	MTD E_L q_p	0.850	0.732	6.49
MTD S_2	0.782	0.607	9.52	MTD E_L S_2	0.810	0.690	7.52
MTD S_3	0.822	0.688	7.57	MTD E_L S_3	0.846	0.784	5.23
MTD S_4	0.832	0.741	6.29	MTD E_L S_4	0.855	0.786	5.18
MTD S_p	0.818	0.731	6.52	MTD E_L S_p	0.852	0.761	5.80
MTD S_N	0.770	0.639	8.75	MTD E_L S_N	0.831	0.675	7.87
MTD q_2 q_4	0.868	0.749	6.09	MTD E_L q_2 q_4	0.869	0.731	6.52
MTD q_2 q_p	0.871	0.728	6.60	MTD E_L q_2 q_p	0.873	0.745	6.19
MTD q_3 q_4	0.853	0.750	6.05	MTD E_L q_3 q_4	0.878	0.738	6.36
MTD q_3 q_p	0.862	0.730	6.53	MTD E_L q_3 q_p	0.874	0.751	6.03
MTD q_4 S_3	0.885	0.793	5.02	MTD E_L q_4 S_3	0.885	0.791	5.06
MTD S_2 S_4	0.836	0.688	7.56	MTD E_L S_2 S_4	0.866	0.776	5.43
MTD S_2 S_p	0.823	0.692	7.48	MTD E_L S_2 S_p	0.878	0.767	5.64
MTD S_4 S_N	0.837	0.693	7.44	MTD E_L S_4 S_N	0.868	0.765	5.70
MTD S_N S_p	0.826	0.693	7.44	MTD E_L S_N S_p	0.881	0.770	5.58

R^2_{cv}–the value based on the residuals from the "leave-half-out" technique; PRESS–the sum of the squared differences between calculated and observed logMU values

decreasing order of partial correlation coefficients of scaled and orthogonalized MTD, S_3, and q_4 descriptors, is:

$$\text{logMU} = 2.2527\ (0.0951) - 2.2948\ (0.1612)\ \Omega_1 - 0.9879\ (0.0975)\ \Omega_2 - 0.7665\ (0.1226)\ \Omega_3 \quad (2)$$

n = 49 R^2 = 0.885 s = 0.241 F = 84.72 $r_{\omega 1}$ −0.719 $r_{\omega 2}$ = −0.517 $r_{\omega 3}$ = −0.316

The regression for scaled sMTD, S_3 and q_4 is

$$\text{logMU} = 2.2151\ (0.1769) - 2.1785\ (0.2543)\ \text{sMTD} - 0.6505\ (0.14)\ q_4 + 0.2116\ (0.1540)\ S_3 \quad (3)$$

n = 49 R^2 = 0.848 s = 0.277 F = 61.26

The correlation coefficient and the statistical tests corresponding to Eq. 3 are worse than the ones for Eq. 1. The orthogonalization of sMTD with S_3 and q_4 leads to only four statistical significant regressions from six possible. These contain as dominant descriptor either S_3 or q_4. When sMTD is considered dominant descriptor, S_3 has no more statistical significance (e.g. partial correlation coefficients for orthogonalization order sMTD, S_3, q_4 are −0.878, −0.067, −0.270. This means that almost all S_3 information is contained by sMTD and thus only MTD must be used in multiple regressions. The descriptor orthogonalization clarifies why the regression with S_3, q_4, and MTD is statistically significant and the regression with sMTD, S_3 and q_4 is not. When MTD is optimized with supplementary descriptors, the MTD values are chosen as to encode as much as possible from the information uncontained by its partner descriptors.

The addition of E_L to the descriptors of Eq. 1 has no positive effect on the cross-validated R^2_{cv} and R. The explanation is given by the descriptor orthogonalization. Partial correlation coefficients from orthogonalization in order MTD, q_4, E_L, S_3 (−0.774, 0.298, −0.087, −0.435) or q_4, MTD, E_L, S_3 (−0.459, 0.691, −0.087, −0.435) indicate that the pair MTD, q_4 extracts almost all information of E_L descriptor and consequently its partial correlation coefficient (−0.087) has no more statistical significance.

The optimization of F_4 and q_2 together with MTD gives comparable R^2, but better s and press than the corresponding values for Eq. 1. The equation for scaled descriptors is:

$$\text{logMU} = 1.3764\ (0.0776) - 1.3459\ (0.1446)\ \text{MTD} - 0.7908\ (0.0886)\ F_4 + 0.5628\ (0.0880)\ q_2 \quad (4)$$

n = 45 R^2 = 0.880 s = 0.209 F = 73.58 R^2_{cv} = 0.704 press = 4.71

Again by orthogonalization all six possible equations have statistic significance and the descriptor order in orthogonalization process is not important. Eq. 5 is chosen in decreasing order of partial correlation coefficients for the scaled and orthogonalized descriptors MTD, F_4, q_2:

$$\text{logMU} = 1.3496\ (0.0960) - 1.8219\ (0.2746)\ \Omega_1 + 0.7971\ (0.1791)\ \Omega_2 + 0.5628\ (0.1778)\ \Omega_3 \quad (5)$$

n = 45 R^2 = 0.880 s = 0.209 F = 73.58 $r_{\omega i,j}$ = 0.0 $r_{\omega 1}$ = −0.724 $r_{\omega 2}$ = 0.486 $r_{\omega 3}$ = 0.346,

From all possible descriptor orthogonalizations carried out for the set MTD, S_3, q_4, or for the set MTD, F_4, q_2, the highest partial correlation coefficients have been obtained for MTD. Thus, according to Randic orthogonalization, MTD can be considered the dominant descriptor and consequently the steric effects can be considered dominant for the mechanism of action of psychotomimetic phenylalkylamines. The electronic and lipophilicity properties have also their contribution to the activity.

4 Conclusions

From the regression equations obtained by correlation of the psychotomimetic activity of the phenylalkylamines with steric, electronic and lipophilicity descriptors it resulted that the steric and electronic properties of the ligand play the dominant role in the interaction with the receptor. The most correlations imply the 4 position of the phenyl ring where are probably concentrated both steric and electronic important effects.

The orthogonalization of the descriptors is a valuable criterion both for the identification of the descriptors that can be taken in a regression and for the selection of the dominant descriptor. This method proved that by optimization of MTD together with other descriptors, MTD becomes a 'more pure' steric descriptor and therefore it gives better regressions than sMTD.

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5 References

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