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Electron-Conformational Study for the Structure–Hallucinogenic Activity Relationships of Phenylalkylamines

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Abstract—The structure–hallucinogenic activity relationships of a series of phenylethylamine and phenylisopropylamine derivatives have been investigated in the frameworks of electron-conformational method. The calculated geometry and electronic structure parameters accompanying to each atom and bond of each molecule in view were arranged as a matrix called electron-conformational matrix of contiguity (ECMC). The features that are responsible for strong and weak activity demonstrations have been found as submatrices of ECMCs belonging to some template compounds. Two electron-conformational features present in non-hallucinogenic compounds have been revealed. A quantitative model has been improved for predicting hallucinogenic activity numerically. A test series was used to verify the results obtained.

Introduction

Hallucinogens are defined as those that produce changes in thought, mood, and perception with little memory or intellectual impairment, and that produce little stupor, narcosis, or excessive stimulation, minimal autonomic side effects, and that are nonaddicting.[1] The hallucinogenic drugs used by mankind for many centuries are still objects of substantial research, and the source of numerous questions as to the nature of their biological activity. There are a number of different classes of hallucinogenic agents which show behaviorally dissimilar effects in humans, such as lysergic acid derivatives, phenylalkylamines, indolealkylamines, piperidyl benzilate esters and phenylcyclohexyl compounds, and so on.[1] That is, hallucinogenic agents are a pharmacologically diverse and heterogenous group of agents.

Understanding of the action mechanism of the hallucinogens with the corresponding receptors can supply information about the nature of human behaviours affected from the agent. Although 5-HT_2 and 5-HT_{1C} receptors have been implicated as playing a major role and are currently the primary mechanistic focus of many investigations, the mechanism of action of classical hallucinogens is not fully understood.[2]

Different properties of phenylalkylamine derivatives, which are known to display hallucinogenic, central stimulant or empathogenic activity, or a combination of activities, have been studied with different approaches so far.[1–3] In this study, structure–hallucinogenic activity relations have been investigated for the phenylalkylamine hallucinogens by using the electron-conformational method (ECM). The training set compounds and their potencies A measured on human being as mescaline units (MU), that is, the ratio of the effective dose of mescaline to the effective dose of the substance in question, were taken from Clare's study[4] (see Table 1). Although different structure–activity relationships (SAR) studies were performed for these compounds (see refs 3 and 4, the research monographs given with the refs 2 and 5, and the references therein), they mainly focused on the estimation of activity intensities, A, by some quantitative SAR (QSAR) equations. We present a more elaborate study by considering both geometry properties and internal electronic parameters accompanying to each atom and bond in the molecules under consideration.

Electron-Conformational Method

Electron-conformational method (ECM),[6–13] which is also known as electron-topological method (ETM), was developed for pharmacophore (a group of specific atoms in a given geometric arrangement which are

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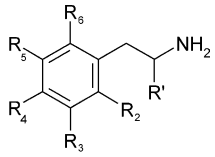
considered responsible for the activity demonstration) identification and pharmacophore-based bioactivity prediction. Bersuker et al.[12,13] have changed the term 'topological' in the method's name with the one 'conformational' to emphasise that all significantly populated conformations of molecules under consideration are taken into account. Considering their point of view, we present the method's name as ECM. The main steps followed by ECM are the following.

Choose the training set of molecules with the known bioactivity and divide the set into activity classes, such

Table 1. The training set (the compounds N1 to N20 are strongly active; the compounds N21 to N45 are weakly active; the compounds N46 to N57 are inactive)



N	R′	R_2	R_3	R_4	R_5	R_6	A (MU)	SF	WF	I_{Me}	IF1	IF2	E_{LUMO} (eV)	log P_p	log A (obs.)	log A (pred.)
1	Me	MeO	H	Et	MeO	H	100	1	0	1	0	0	0.212	1.046	2	1.696
2	Me	MeO	H	Pr	MeO	H	80	1	0	1	0	0	0.161	1.443	1.903	1.825
3	Me	MeO	H	Me	MeO	H	80	1	0	1	0	0	0.225	0.649	1.903	1.456
4	Me	MeO	H	MeS	MeO	H	40	1	0	1	0	0	−0.177	0.535	1.602	1.730
5	Me	MeO	H	iPrS	MeO	H	40	1	0	1	0	0	−0.273	2.870	1.602	1.309
6	Me	MeO	H	MeO	MeO	H	20	1	0	1	0	0	0.044	0.191	1.301	1.176
7	Me	MeO	H	EtO	MeO	H	20	1	0	1	0	0	0.061	0.535	1.301	1.513
8	Me	MeO	H	iBu	MeO	H	20	1	0	1	0	0	0.205	1.774	1.301	1.742
9	H	MeO	H	Me	MeO	H	20	1	0	0	0	0	0.184	0.649	1.301	0.950
10	H	H	MeO	EtS	MeO	H	20	0	1	0	0	0	−0.317	0.879	1.301	0.941
11	H	MeO	H	Et	MeO	H	18	1	1	0	0	0	0.166	1.046	1.255	1.009
12	H	H	MeO	PrS	MeO	H	16	0	1	0	0	0	−0.304	1.348	1.204	1.083
13	H	H	MeO	MeS	MeO	H	12	0	1	0	0	0	−0.353	0.535	1.079	0.731
14	Me	MeO	–OCH$_2$O—		MeO	H	12	0	1	1	0	0	0.025	0.301	1.079	0.702
15	Me	MeO	–OCH$_2$O—		H	H	10	0	1	1	0	0	−0.011	0.301	1.000	0.734
16	Me	MeO	H	–OCH$_2$O—		H	10	1	0	1	0	0	0.073	0.301	1.000	1.274
17	Me	–OCH$_2$O—		H	H	MeO	10	1	0	1	0	0	0.004	0.334	1.000	1.372
18	Me	MeO	MeO	H	H	MeO	10	1	1	1	0	0	0.052	0.334	1.000	1.142
19	Me	MeO	H	MeO	H	MeO	10	0	0	1	0	0	0.179	0.191	1.000	0.623
20	Me	MeO	H	H	MeO	H	8	1	0	1	0	0	0.181	0.334	0.903	1.211
21	H	H	MeO	EtO	MeO	H	7	0	1	0	0	0	−0.023	0.535	0.845	0.430
22	H	H	MeO	PrO	MeO	H	6	0	1	0	0	0	0.124	1.004	0.778	0.600
23	H	H	MeO	MeO	EtS	H	6	0	1	0	0	0	−0.208	0.191	0.778	0.246
24	H	H	MeO	EtO	MeS	H	6	0	1	0	0	0	−0.257	0.535	0.778	0.643
25	Me	MeO	MeO	MeO	MeO	H	6	0	1	1	0	0	−0.061	0.191	0.778	0.655
26	Me	H	H	MeO	H	H	5	0	0	1	0	1	0.330	0.191	0.699	0.486
27	Me	MeO	H	MeO	H	H	5	0	0	1	0	1	0.335	0.191	0.699	0.481
28	Me	MeO	MeO	–OCH$_2$O—		H	5	0	1	1	0	0	−0.124	0.301	0.699	0.837
29	Me	MeO	MeO	H	MeO	H	4	0	1	1	0	0	0.164	0.334	0.602	0.610
30	H	H	EtO	MeS	MeO	H	4	0	1	0	0	0	−0.277	0.535	0.602	0.662
31	H	H	MeO	BuS	MeO	H	3	0	1	0	0	0	−0.294	1.745	0.477	1.045
32	Me	H	–OCH$_2$O—		H	H	3	0	1	1	0	0	0.131	0.301	0.477	0.605
33	Me	–OCH$_2$O—		MeO	H	H	3	0	1	1	0	0	0.142	0.191	0.477	0.470
34	Me	H	MeO	–OCH$_2$O—		H	2.7	0	1	1	0	0	0.123	0.301	0.431	0.612
35	H	H	MeO	BuO	MeO	H	2	0	1	0	0	0	0.124	1.401	0.301	0.698
36	H	H	EtS	EtO	MeO	H	2	0	1	0	0	0	−0.102	0.535	0.301	0.502
37	H	H	EtO	EtO	MeS	H	2	0	1	0	0	0	−0.130	0.535	0.301	0.528
38	Me	H	MeO	MeO	MeO	H	2	0	1	1	0	0	0.030	0.191	0.301	0.572
39	Me	MeO	MeO	MeO	H	H	2	0	1	1	0	0	0.045	0.191	0.301	0.559
40	Me	H	Me	BzlO	MeO	H	2	0	0	1	1	0	0.005	1.873	0.301	0.426
41	H	H	EtO	EtO	MeO	H	1.5	0	1	0	0	0	0.047	0.535	0.176	0.366
42	H	H	MeO	MeO	MeO	H	1	0	1	0	0	0	0.030	0.191	0.000	0.029
43	H	H	EtO	MeO	MeO	H	1	0	1	0	0	0	−0.008	0.191	0.000	0.064
44	H	H	MeO	–OCH$_2$O—		H	1	0	1	0	0	0	0.111	0.301	0.000	0.080
45	H	H	–OCH$_2$O—		H	H	1	0	1	0	0	0	0.118	0.301	0.000	0.074
46	H	H	H	MeO	H	H	<1	0	0	0	0	1	0.344	0.191	<0	−0.070
47	H	MeO	MeO	MeO	H	H	<1	0	0	0	0	1	0.077	0.191	<0	0.173
48	H	MeO	H	MeO	MeO	H	<1	0	0	0	0	1	0.047	0.191	<0	0.200
49	H	H	EtO	MeO	EtO	H	<1	0	0	0	1	0	0.056	0.191	<0	−0.843
50	H	H	EtO	EtO	EtO	H	<1	0	0	0	1	0	0.045	0.535	<0	−0.481
51	H	H	EtO	MeO	MeS	H	<1	0	0	0	0	1	−0.198	0.191	<0	0.424
52	H	H	EtS	MeO	EtO	H	<1	0	0	0	1	1	−0.209	0.191	<0	−0.602
53	H	H	EtO	MeS	EtO	H	<1	0	0	0	1	0	−0.254	0.535	<0	−0.208
54	H	H	EtS	EtO	EtO	H	<1	0	0	0	1	0	−0.125	0.535	<0	−0.326
55	H	H	EtO	EtS	EtO	H	<1	0	0	0	1	0	−0.169	0.879	<0	−0.043
56	Me	H	MeO	MeO	H	H	0.5	0	0	1	1	0	0.194	0.191	−0.301	−0.426
57	H	H	MeO	MeO	H	H	<0.2	0	0	0	0	1	0.203	0.191	<−0.7	0.058

as strongly active, weakly active, and inactive or, at least, active and inactive.

Perform 3-D geometry optimization and electronic structure calculations for all the compounds in view.

For each molecule in the set, form the $n \times n$ matrices called electron-conformational matrices of contiguity (ECMC) from the output file of electronic structure calculation program used, where n represents the number of atoms in the molecule considered.

The ECMC, which is being the specific language of ECM for compound structure description, is a square matrix that is symmetric with respect to the diagonal elements. Hence, only upper part of each ECMC is kept in the memory of computer and processed. The diagonal elements a_{ii} in the ECMC, where i represents the ith atom in the molecule, are one of the electronic atomic characteristics, such as atomic charges, valence activities, atomic polarizabilities, HOMO or LUMO contributions, etc. The off-diagonal elements a_{ij} are of two kinds, one of which is for chemical bonds and the other is for chemically non-bonded atoms. If i and j label chemically bonded atoms, then a_{ij} is one of the electronic parameters of the i–j bond such as bond order, Wiberg index, bond energy (total, covalent or ionic), bond polarizability and so on. If i and j label non-bonded atoms, then a_{ij} is the interatomic distance between ith and jth atoms (R_{ij}). Under fixed atomic and bond parameters that are deemed most important for activity demonstration, ECMC of each molecule under consideration is to be formed.

As understood from the description of ECMC, both geometry parameters and electronic characteristics accompanying to each atom and bond of a molecule are taken into account in the ECM. The classical QSAR methods use global characteristics of molecules, such as molecular weight, lipophilicity, hydrophobicity, solubility, molar volume, dipole moment, HOMO and LUMO energies, etc. One can also encounter to some studies in which the local properties of an atom or a group in the molecule are handled, by intuition, as a QSAR parameter. Hence, the electronic and conformational properties arising from the atoms and bonds are partially or completely ignored in QSAR applications, causing great information losses, in most cases.

Since numerical values of electronic characteristic of each atom, but not their sorts, are used in the ECMC, ECM can process the compounds having different kinds of atoms and skeletons, simultaneously. In the classical SAR studies, the compounds under investigation must be similar in structure.

Choose the ECMC of one of the active compounds as a template and compare it with the rest of ECMCs within some tolerance limits to reveal those matrix elements that are present in all active compounds but are absent in the inactive ones. The revealed submatrix is called Electron-conformational submatrix of contiguity (ECSC) for activity. In this way, the pharmacophore, which can also be called as activity feature, is identified as a submatrix containing both electron structural parameters (charges on atoms, bond orders, etc.) and interatomic distances.

Since it is impractical to enter different tolerances for all matrix elements [$n(n+1)$ matrix elements], only three variations, one of which for diagonal elements (Δ_1), one for bond parameters (Δ_2) and one for interatomic distances (Δ_3), are entered while searching ECSC for activity. After determining the ECSC, that is, with the reduced number of matrix elements, flexibility of each parameter can be easily determined.

If the submatrices found are not representative enough, change the tolerance limits, the template compound, the parameters chosen to form ECMCs, or all of them at once, until appropriate fragments are found.

After obtaining satisfactory results, test the features found over some compounds outside the training set. If the features obtained give again satisfactory results, the submatrices are considered appropriate for the activity prediction. If not, then the more profound study of the activity feature's violation is to be undertaken, and all the steps are to be repeated again.

The antagonist activity feature can also be determined by following the steps listed above. But, the template compound is to be selected among the inactive class of compounds.

Conformational analysis and ECSC searching steps are the most labor-intensive and time-consuming ones among the others listed above.

Results and Discussion

The training set molecules given in Table 1 were arbitrarily divided into three classes according to A (hallucinogenic potency) values. Substances less active than mescaline (activity less than 1 MU) were classified as inactive (12 compounds labelled N46-N57 in Table 1). Substances having activities in the range from 1 to less than 8 MU were classified as having weak activity (25 compounds labelled N21-N45 in Table 1) and those having activity of 8 MU or more were classified as strong active (20 compounds labelled N1-N20 in Table 1).

The semiempirical PM5 method implemented in the CAChe WorkSystem Pro Version 5.04 package program[14] were used for conformational analyses on each group attached to the aromatic ring and for electronic structure calculations on fully minimized conformations. Some conformational preferences of some phenylalkylamines were previously discussed.[3] However, we determined the conformations that are populated significantly at room temperature and included each of them to the training set as a separate molecule since it is not necessary for a molecule being in its lowest energy conformation while interacting with the bioreceptor. After feature searching process, the conformers

containing the activity feature are supposed to be active conformers.

In the ECMC formation, effective charges on atoms Q_i (in the electron charge unit e) were taken as diagonal elements whereas the bond orders (B_{ij}) and optimized distances in Å (R_{ij}) were used as off-diagonal elements for chemically bonded and unbonded atoms, respectively. Throughout this study, charges on atoms and bond orders are shown on ECMCs and ECSCs as italic and bold, respectively, to be able to separate the type of matrix elements. In addition to that, the atoms entering the ECSCs revealed are shown on molecules in black in this study.

To determine strong activity feature in the form of matrix elements that are common in the ECMCs of all the strongly active compounds and are absent in the ECMCs of both weakly active and inactive compounds, we have selected different strongly active compounds as templates and compared their ECMCs with all the other ECMCs. As a result of this comparison procedure, we revealed a feature formed by five atoms. The feature responsible for strong activity (SF) is shown in Figure 1 on the most active compound N1 in the series. Since the comparisons of ECMCs are performed without noting the atom types, we denote five atoms entering SF as A, B, C, D and E in Figure 1, arbitrarily.

To help imagination of the meanings of ECMC and ECSC, the ECMC of N1, as an example, is given in Figure 2 without matrix elements representing hydrogens bonded to carbon atoms. Elements of ECSC forming SF are enclosed by solid lines in the ECMC of N1.

As seen from Figures 1 and 2, the R_2 and R_5 substituents play very important role for strong activity demonstration of N1. However, this does not mean that SF is realized via R_2 and R_5 substituents in all compounds. For example, the SF appears in N17 and N18 via R_3 and R_6 substituents. The fragments constituting SF are demonstrated on different compounds in Figure 3.

The SF includes half of the aromatic ring system that is in contact with the alkylamine chain (1, 2 and 3 or 1, 6 and 5 portion) at one end and does not have any substituent other than hydrogen at the other end (at 3- or 5-position of the ring). Inclusion of a substituent to the furthest end of the ring portion entering the SF from alkylamine chain reduces hallucinogenic activity. For example, compare N20 and N29.

Two electronegative atoms attached to the aromatic ring at the trans positions (at 2 and 5 positions if 1, 2 and 3 positions of the ring is related to SF, or at 3 and 6 positions if 1, 6 and 5 positions of the ring is related to SF) exist in all strong activity fragments. Disappearance of any of these electronegative groups abolishes or reduces hallucinogenic activity. For example, compare N6 and N27.

It is to be kept in mind that rough checking of the groups needed for strong activity demonstration may cause wrong estimations (for example, see inactive compound N48). Instead, one must search the presence or absence of the ECSC responsible for strong activity demonstration within the given limits in Figure 1 in the ECMC belonging to the compound in view.

Flexibility limits are quite important for the realization of features. For example, the further growth of the upper limit of any elements of SF causes weakly active and inactive compounds to include the SF. Hence, if the variation of any parameter in the SF were taken greater than its upper limit, we would classify some weakly active and inactive compounds as if they were strongly active. If one goes beyond the lower limit of any parameter in the SF, the number of strongly active compounds including the feature is decreased.

We have selected different weakly active compounds as templates and compared their ECMCs with all the other ECMCs within some limits in order to find weak activity feature in the form of matrix elements that are present in the ECMCs of all the weakly active compounds and are absent in the ECMCs of both strongly active and inactive compounds. After this comparison proce-

C1 (A)	C2 (B)	C3 (C)	O13 (D)	O17 (E)	
-0.04 ± 0.06	**1.33 ± 0.12**	2.44 ± 0.16	2.36 ± 0.16	3.69 ± 0.10	A
	0.08 ± 0.07	**1.35 ± 0.12**	**0.98 ± 0.18**	4.14 ± 0.15	B
		-0.20 ± 0.06	2.43 ± 0.14	3.62 ± 0.14	C
			-0.33 ± 0.10	5.50 ± 0.15	D
				-0.32 ± 0.10	E

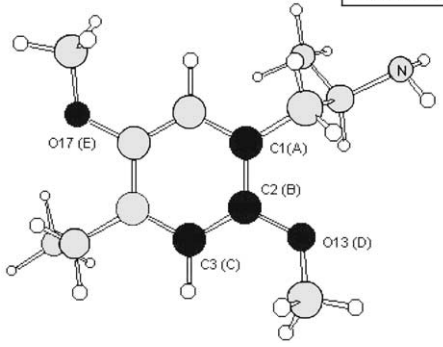


Figure 1. The feature of strong activity SF and the corresponding ECSC found relative to the compound N1.

C1(A)	C2(B)	C3(C)	C4	C5	C6	C7	C8	N9	H10	H11	C12	O13(D)	C14	C15	C16	O17(E)	C18	
-0.04	**1.33**	2.44	2.83	2.42	**1.38**	**0.97**	2.51	3.78	4.54	4.04	3.05	2.36	3.61	4.33	5.08	3.69	4.24	C1
	0.08	**1.35**	2.42	2.77	2.40	2.54	3.27	4.54	5.22	4.57	4.00	**0.98**	2.39	3.79	4.59	4.14	5.03	C2
		-0.20	**1.40**	2.40	2.78	3.82	4.53	5.87	6.50	5.95	4.98	2.43	2.87	2.50	3.38	3.62	4.80	C3
			-0.06	**1.31**	2.44	4.33	5.10	6.51	7.14	6.76	5.21	3.69	4.25	**0.97**	2.49	2.35	3.65	C4
				0.10	**1.36**	3.79	4.63	5.99	6.64	6.40	4.49	4.14	5.02	2.54	3.27	**0.99**	2.40	C5
					-0.22	2.50	3.42	4.70	5.40	5.14	3.38	3.62	4.76	3.82	4.51	2.43	2.85	C6
						-0.15	**0.95**	2.45	3.33	2.71	2.53	2.80	4.12	5.83	6.53	4.93	5.18	C7
							0.00	**0.98**	2.05	2.05	**0.98**	3.25	4.61	6.55	6.96	5.72	5.97	C8
								-0.42	**0.95**	**0.95**	2.46	4.24	5.46	7.98	8.44	7.06	7.15	N9
									0.17	1.60	2.62	4.87	6.07	8.58	8.88	7.67	7.76	H10
										0.17	3.33	4.00	5.05	8.22	8.78	7.56	7.76	H11
											-0.30	4.35	5.75	6.56	6.71	5.32	5.40	C12
												-0.33	**0.95**	4.93	5.66	5.50	6.37	O13
													-0.11	5.20	6.02	6.35	7.34	C14
														-0.13	**0.98**	2.79	4.18	C15
															-0.28	3.26	4.58	C16
																-0.32	**0.95**	O17
																	-0.11	C18

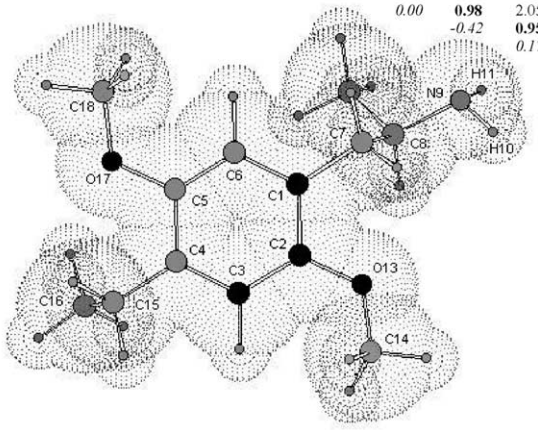


Figure 2. ECMC of the one of the active conformers of the compound N1 (due to its symmetry, only upper triangle is shown; the diagonal elements, which are shown as italic, are charges on atoms whereas the off-diagonal elements are interatomic distances for chemically nonbonded atoms and bond orders for bonded atoms; bond orders are demonstrated as bold; squared elements belong to the ECSC responsible for strong activty (SF); the atoms entering the feature are shown in black on N1).

dure, we revealed a feature formed by three atoms. The feature responsible for weak activity demonstration (WF) is shown in Figure 4 on the weakly active compound N44.

The weak activity fragment WF is formed of the amino group in the alkylamine side-chain and an electronegative atom directly attached to the ring at the position 3 or 5. Only one terminal H attached to N is enough for the realization of WF as seen in Figure 4.

For a more complete modeling, we have also investigated whether there are some features responsible for inactivity demonstration (anti-pharmacophores). For that purpose, we have chosen different inactive compounds as templates and compared their ECMCs with all the other ECMCs within some limits. This comparison procedure gave rise to reveal two features of inactivity.

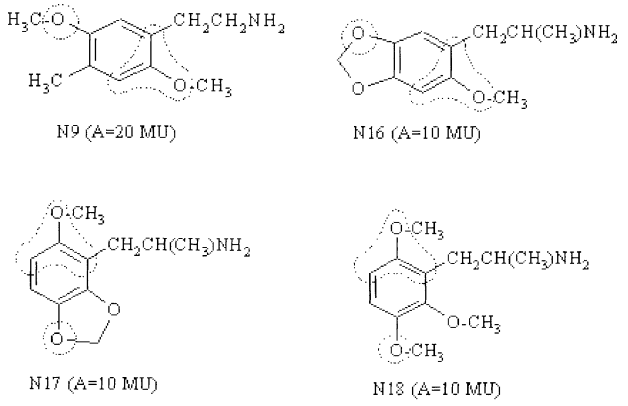


Figure 3. Demonstration of the strong activity fragment on different compounds.

Inactivity feature IF1 is shown in Figure 5 on the inactive compound N53. In addition to the parameters accompanying the carbon atoms placed at the 1 and 6 positions of the ring, the size of R_5 substituent is important for inactivity demonstration. For example, see the compounds N43 and N49. While N43 being weakly active (A = 1) has methoxy group at the 5 position, N49 being inactive (A < 1) has ethoxy group at the same position. The other substituents in N43 and N49 are the same. The presence of one additional carbon atom at the 5 position in N49 compared to N43 causes N49 to contain IF1 and abolishes hallucinogenic activity.

Inactivity feature IF2, which is shown in Figure 6 on N46, is formed by three charges situated at some specific distances. IF2 is realized in some compounds over the carbon atom placed at the position 6 of the ring (see N47 and N48), while it is realized over the carbon atom

O (F)	N (G)	H (H)	
-0.30 ± 0.02	6.67 ± 0.20	7.31 ± 0.20	F
	-0.41 ± 0.02	**0.95 ± 0.35**	G
		0.16 ± 0.02	H

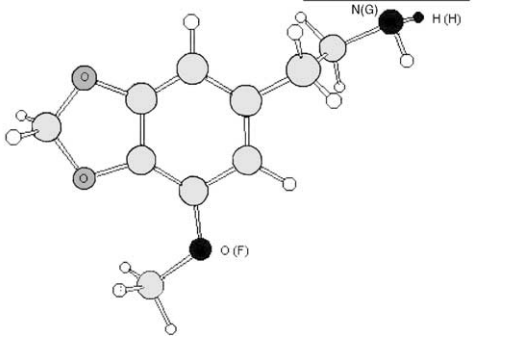


Figure 4. The weak activity feature WF and the corresponding ECSC found relative to the compound N44.

C (Q)	C (T)	C (V)	
-0.28 ± 0.13	**1.37 ± 0.16**	4.38 ± 0.11	Q
	0.02 ± 0.12	5.72 ± 0.10	T
		-0.31 ± 0.12	V

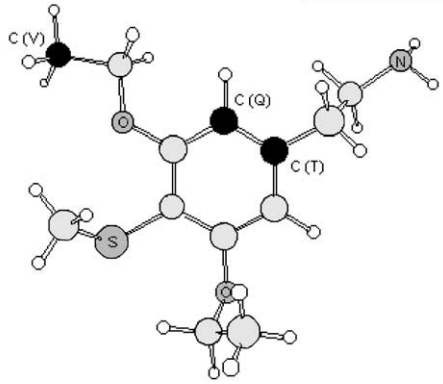


Figure 5. The inactivity feature IF1 on one conformer of N53 with the corresponding ECSC.

C (X)	H (Y)	C (Z)	
-0.12 ± 0.02	4.76 ± 0.34	4.79 ± 0.31	X
	0.16 ± 0.03	9.07 ± 0.37	Y
		-0.11 ± 0.02	Z

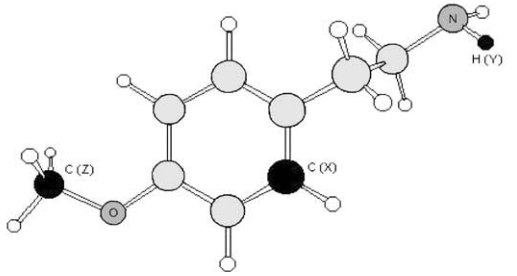


Figure 6. The inactivity feature IF2 revealed in the form of three directly nonbonded atoms on one conformer of N46 with the corresponding ECSC.

placed at the position 2 of the ring in some others (for example, see N46, N51, N52 and N57).

All the features emerged with this study appear quite insensitive to conformation. That does not mean that all conformers of a compound have the same potency. However, experimental data belonging to different conformers arising from different alignments of the substituents including alkylamine side chain are not available. That is why we included all possible conformers of a molecule to the same class (strongly active, weakly active or inactive) of our training set as a separate molecule.

When any of the phenylethylamine derivatives in the series is compared with a phenylisopropylamine derivative having the same ring substituents as the phenylethylamine derivative hold, it is seen that phenylisopropylamines are more potent than the corresponding phenylethylamines. Namely, the presence of a methyl group on the α carbon atom causes more appropriate alignment of the alkylamine side-chain for the proper docking with the corresponding bioreceptor and enhances the hallucinogenic activity. For example, see the couples of N45 (A = 1)–N32 (A = 3), N46 (A < 1)–N26 (A = 5), N57 (A < 0.2)–N56 (A = 0.5), N11 (A = 18)–N1 (A = 100) and N48 (A < 1)–N6 (A = 20), etc.

In Table 1, the presence of a feature revealed in a compound is demonstrated with 1 while its absence is indicated with 0. I_{Me} shown in Table 1 indicates the presence (1) or absence (0) of the α-methyl group, which strengthens the hallucinogenic activity.

If a compound contains just SF and/or the α-methyl group, it is then classified as strongly active. N19 do not contain any feature revealed. The presence of the α-methyl group makes N19 strongly active. The strongly active compound N9 contains just SF whereas, as an example, the most active compound of the series (N1) contains both SF and the α-methyl group.

Although the strongly active compounds N14 and N15 do not contain SF, they include WF. What makes these compounds strongly active instead of weakly active is the presence of the α-methyl group. Some weakly active compounds (N25, N28, N29, N32, N33, N34, N38 and N39) contain both WF and α-methyl group, as occurred in the strongly active compounds N14 and N15. Hence, if WF accompanies a compound along with α-methyl group, then WF causes some amount of activity decrease and the compound becomes either strongly or weakly active. The strongly active compound N11 contains both SF and WF. However, the activity decrease occurred with the presence of WF is not enough to make the compound as weakly active or inactive.

If a compound contains just WF, it is then classified as weakly active. For example, see N21, N35, N36 and N37, etc. If a compound contains any of the inactivity feature together with the α-methyl group, it then becomes weakly active (see N26, N27 and N40). As a result, presence of any of the inactivity feature in a compound causes activity decrease more than WF, remembering that the compound may demonstrate strong activity in the presence of both WF and α-methyl group. If a compound contains one or both of the inactivity features only, it is then classified as inactive.

The para substituent (R_4) plays a unique role on hallucinogenic activity. It is seen from Tables 1 and 2 that the hallucinogenic potency of the compounds increases as the group in the para position varies from H < OR < SR < R < X, where R and X stand for alkyl group and halogen, respectively.

Three strongly active compounds contain just WF. R_4 being—SR in these compounds [N10 (R_4 = EtS, A = 20), N12 (R_4 = PrS, A = 16) and N13 (R_4 = MeS, A = 12)] causes activity jumps compared to their—OR analogues [N21 (R_4 = EtO, A = 7), N22 (R_4 = PrO, A = 6) and N42 (R_4 = MeO, A = 1)]. When R_4 is ethylthio (−SEt), hallucinogenic potency appears to be strongest for the class of compounds in which R_4 = −SR. Smaller or longer alkyl chain in the para substituent of this class means lower potency.

Table 2. The test series (The compounds from N58 to N63 were taken from ref 4 whereas the compounds from N64 to N67 were taken from different parts of the research monograph[5])

N	R′	R_2	R_3	R_4	R_5	R_6	A (MU)	SF	WF	I_{Me}	IF1	IF2	E_{LUMO} (eV)	log P_p	log A (obs.)	log A (pred.)
58	Me	MeO	H	Bu	MeO	H	40	1	0	1	0	0	0.195	1.84	1.602	1.730
59	Me	MeO	H	PrO	MeO	H	20	1	0	1	0	0	0.053	1.004	1.301	1.824
60	Me	MeO	H	Am	MeO	H	10	1	0	1	0	0	0.157	2.237	1.000	1.555
61	H	H	MeO	MeO	MeS	H	6	0	1	0	0	0	−0.127	0.191	0.778	0.172
62	H	H	EtO	EtS	MeO	H	4	0	1	0	0	0	−0.169	0.879	0.602	0.806
63	H	H	PrO	MeO	MeO	H	<1	0	0	0	0	1	−0.015	0.191	<0	0.257
64	H	MeO	H	Br	MeO	H	35	1	1	0	0	0	−0.037	1.236	1.544	1.251
65	Me	MeO	H	Br	MeO	H	513	1	0	1	0	0	−0.039	1.236	2.710	1.983
66	H	MeO	—OCH_2O—		H	H	>5	0	1	0	0	0	0.039	0.301	>0.699	0.141
67	Me	EtO	H	—OCH_2O—		H	7	1	0	1	0	0	0.042	0.301	0.845	0.759

When the para substituent is an alkyl group in a hallucinogenic compound, its potency becomes greater than those of the compounds in which R_4 is −OR or −SR. For example, the hallucinogenic potency of N4 (R_4 = −SMe) is equal to half of the potency of N3 (R_4 = −Me). The ethyl group as the R_4 substituent is again optimal in the class of compounds in which the para substituent is an alkyl group. For example, see N1 (R_4 = −Et, A = 100), N2 (R_4 = −Pr, A = 80), N3 (R_4 = −Me, A = 80) and N8 (R_4 = −*i*Bu, A = 20).

After revealing the rules expressed above, one can also interest in determining hallucinogenic potency numerically. For that purpose, we take the presence or absence of each feature revealed as a QSAR parameter supposing that each feature has a certain contribution (positive or negative) to hallucinogenic activity. Without including the inactive compounds of the training set whose potencies are not known numerically to the regression analysis, the following equation has been found for determining hallucinogenic activity:

$$\log A = 0.430 \times SF + 0.543 \times I_{Me} - 0.187 \times WF - 1.036 \times IF1 + 1.362 \times \log P_p - 0.464 \times (\log P_p)^2 - 1.032 \times E_{LUMO}$$

Here $R^2 = 0.92$, S = 0.29 (R is the correlation coefficient, S is the standard error of log A estimate). Observed versus predicted log activity plot is given with Figure 7.

In deriving the equation, LUMO (lowest unoccupied molecular orbital) energy of the lowest energy active conformer has been taken into account. Since HOMO (highest occupied molecular orbital) energy is not statistically significant at the 90% confidence level, the equation of the fitted model does not include this term. The decrease in LUMO energy or equivalently the increase in electron affinity results in the increase of hallucinogenic potency of a compound.

Log P (the log of the octanol-water partition coefficient P) being a measure of hydrophobicity is a configuration independent variable. Although total log P does not appear statistically significant at the 90% confidence level, log P and squared log P of the para substituent, which are given with the subindex p, appear to make significant contribution to the hallucinogenic activity. In the case of the methylenedioxy compounds, log P value of $-OCH_2$ attached to the ring was assigned as log P_p.

The equation shows that the appearance of SF and the α-methyl group in a compound increases the hallucinogenic activity whereas appearance of WF and IF1 reduces the activity. This sentence was examined while discussing the features. We did not include the IF2 to the equation since it does not appear statistically significant at the 90% confidence level.

We have also examined the validation of the results on a test series given in Table 2. The features found by ECM and the regression equation are also found on the test series to be useful for predicting the potency of phenylalkylamine hallucinogens.

The strongly active compounds N58, N59, N60 and N65 contain both SF and the α-methyl group. Hence, they are classified correctly by ECM. N64 contains both SF and WF. Since this compound is strongly active, it is concluded that activity reduction occurring with the appearance of WF is not enough to make the compound weakly active. The QSAR equation derived finds

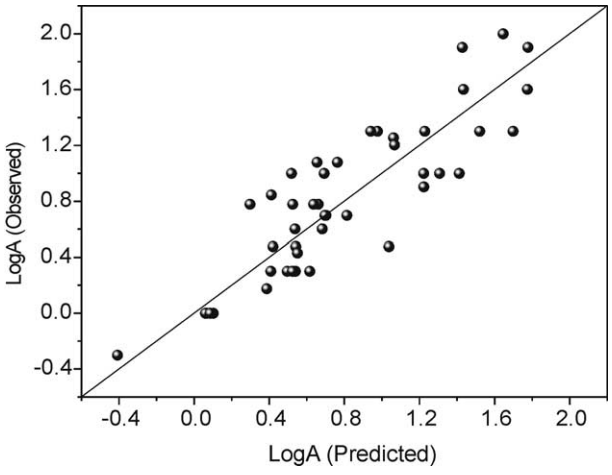


Figure 7. Plot of observed log activity against predicted log activity.

also N64 as strongly active proving the previous sentence. The compounds N61 and N62 contain only WF. Hence, ECM classifies these compounds in accordance with the experimental results as weakly active. Inactive compound N63 contains only IF2. Hence, ECM classifies it correctly as inactive. N66 whose potency is greater than 5 appears weakly active in terms of both ECM and QSAR equation. However, activity value obtained by using the QSAR equation is quite smaller than 5 for this compound. The activity value of N67 is near the transition value from weak activity to strong activity. ECM classifies N67 as strongly active. The regression equation estimates its potency quite close to experimental result.

Conclusions

The structure–hallucinogenic activity relationships for a series of phenylethylamine and phenylisopropylamine derivatives have been investigated by means of the ECM. Two feature, one is responsible for strong activity demonstration and the other is responsible for weak activity demonstration, have been found in the compounds belonging to active class. We observed that presence of the α-methyl group in the alkylamine sidechain makes positive contribution to the hallucinogenic activity. The effect of the para substituent on hallucinogenic activity has been discussed. Two features have been revealed by taking some nonhallucinogenic compounds as templates. If these features accompany also the active compounds, they make negative contribution to the activity intensity. We have also built a QSAR model by means of multiparameter regression analysis.

The features mentioned can be used when planning the synthesis of new hallucinogenic compounds as future drugs. They can also be found useful when predicting possible properties of the appropriate bioreceptor. The regression equation can be used to determine activity intensity within the given accuracy.

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References and Notes

1. Glennon, R. A. *Pharmacol. Biochem. Behav*. **1999**, *64* (2), 251.
2. Glennon, R. A. In *Hallucinogens: An Update, Research Monograph 146*, Lin, G. C., Glennon, R. A., Eds.; National Institute on Drug Abuse: Washington, DC, 1994; pp 4–32.
3. Taurian, O. E.; Contreras, R. H. *J. Mol. Struct. (Theochem)* **2000**, *504*, 119.
4. Clare, B. W. *J. Med. Chem*. **1990**, *33*, 687.
5. (a) Kier, L. B.; Glennon, R. A. In *Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists and Hallucinogens, Research Monograph 22*, Barnett, G., Trsic, M., Willette, R. E., Eds.; National Institute on Drug Abuse: Washington, DC, 1978; pp 159–185 (b) Anderson, G. M.; Castagnoli, N., Jr; Kollman, P. A. In *Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists and Hallucinogens, Research Monograph 22*, Barnett, G., Trsic, M., Willette, R. E., Eds.; National Institute on Drug Abuse: Washington, DC, 1978; pp 159–185.
6. Bersuker, I. B.; Dimoglo, A. S. In *Reviews in Computational Chemistry, Vol. 2*, Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1991; pp 423–461.
7. Altun, Ah.; Kumru, M.; Dimoglo, A. *J. Mol. Struct. (Theochem)*. **2001**, *535*, 235.
8. Altun, A.; Kumru, M.; Dimoglo, A. *J. Mol. Struct. (Theochem)*. **2001**, *572*, 121.
9. Dimoglo, A. S.; Chumakow, Y. M.; Dobrova, B. N.; Saraçodlu, M. *Drug Res*. **1997**, *47* (4), 415.
10. Shvets, N.; Terletskaya, A.; Dimoglo, A. *Chumakov, Yu. J. Mol. Struct. (Theochem)*. **1999**, *463*, 105.
11. Güzel, Y.; Saripinar, E.; Yilidrim, I. *J. Mol. Struct. (Theochem)*. **1997**, *418*, 83.
12. Bersuker, I. B.; Bahceci, S.; Boggs, J. E.; Pearlman, R. S. *J. Comput.-Aided Mol. Des*. **1999**, *13*, 419.
13. Bersuker, I. B.; Bahçeci, S.; Boggs, J. E. *J. Chem. Inf. Comput. Sci*. **2000**, *40*, 1363.
14. CAChe WorkSystem Pro Version 5.04, A computational chemistry package program, Fujitsu Limited, 2000–2002.