DFT-based QSAR and Action Mechanism of Phenylalkylamine and Tryptamine Hallucinogens

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DFT/B3LYP/6-311G＋(d,p) basis set including solvent effect was first used to calculate a set of molecular descriptors of 55 phenylalkylamine and 20 tryptamine compounds with hallucinogenic activity. Four quantitative structure-activity relationship (QSAR) models of the ha llucinogenic activity for phenylalkylamines and tryptamines were obtained by employing multiple linear regression (MLR) method. The QSAR analysis indicated that electron-related descriptors were major contributors to the hallucinogenic activities of phenylalkylamines and tryptamines. In addition, electron-unrelated descriptors have some impact on the hallucinogenic activities of phenylalkylamines. Based on the results of QSAR study, a novel Conformation Complementary Judgement, Transformation and Induction (CCJTI) model had been proposed to explain different action mechanisms of phenylalkylamines and tryptamines with their target receptors. It was concluded that phenylalkylamines might combine with receptor by electronic effect, but steric factor could affect it also, whereas tryptamines could act only through the electronic effect.

Keywords phenylalkylamines, tryptamines, hallucinogens, action mechanism, structure-activity relationships, density functional calculations

Introduction

Hallucinogens commonly refer to the substances that provoke strong mental and psychic changes including disorientation, derealization and depersonalization, giving rise to a variety of abnormal phenomena. [1] In some countries, they are used as components of drugs. Some people, especially the ones who show special interest, may be addicted to these drugs for stimulation and self realization effects. The study of quantitative structure-activity relationships (QSARs) of hallucinogens and their action mechanism is important for classifying and controlling abused drugs as well as developing clinical therapeutic drugs.

According to their chemical structures, hallucinogens are usually divided into two categories, one are phenylalkylamines (phenylethylamines and amphetamines), and the other indolealkylamines such as tryptamines, lysergic acid diethylamide (LSD) and their derivatives. Understanding hallucinogens' action mechanism with their corresponding receptors may provide information about the nature of human behaviour affected by these agents. However, the three-dimensional (3D) structures of the corresponding receptors have not been fully known as yet, so most studies were based on homologous compounds of neurotransmitters. Some knowledge on the activity of hallucinogens at molecular level and their QSARs had been reported, and several QSAR models also established with different approaches.[2-7]

In this work, we carried out accurate calculations for the first time for selected hallucinogens on various electronic descriptors based on density functional theory (DFT) method using B3LYP hybrid functional[8] together with the 6-311 ＋G(d,p) basis set by Gaussian 03 package of programs.[9] We have established four new QSAR models for hallucinogenic activity by multiple linear regression (MLR) method. Based on the results of QSAR study, here we have proposed a new rule, i.*e*. Conformation Complementary Judgement, Transformation and Induction (CCJTI) model to explain the action mechanism of the drugs with their target molecules.

Activity data and computational details

Activity data

The structure and the hallucinogenic activity of 55 phenylalkylamine and 20 tryptamine compounds were shown in Table 1. The biological activity data were originated from Shulgin *et al*. and were cited from the

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Table 1 The structures of phenylalkylamines and tryptamines, with the hallucinogenic activity values in parentheses

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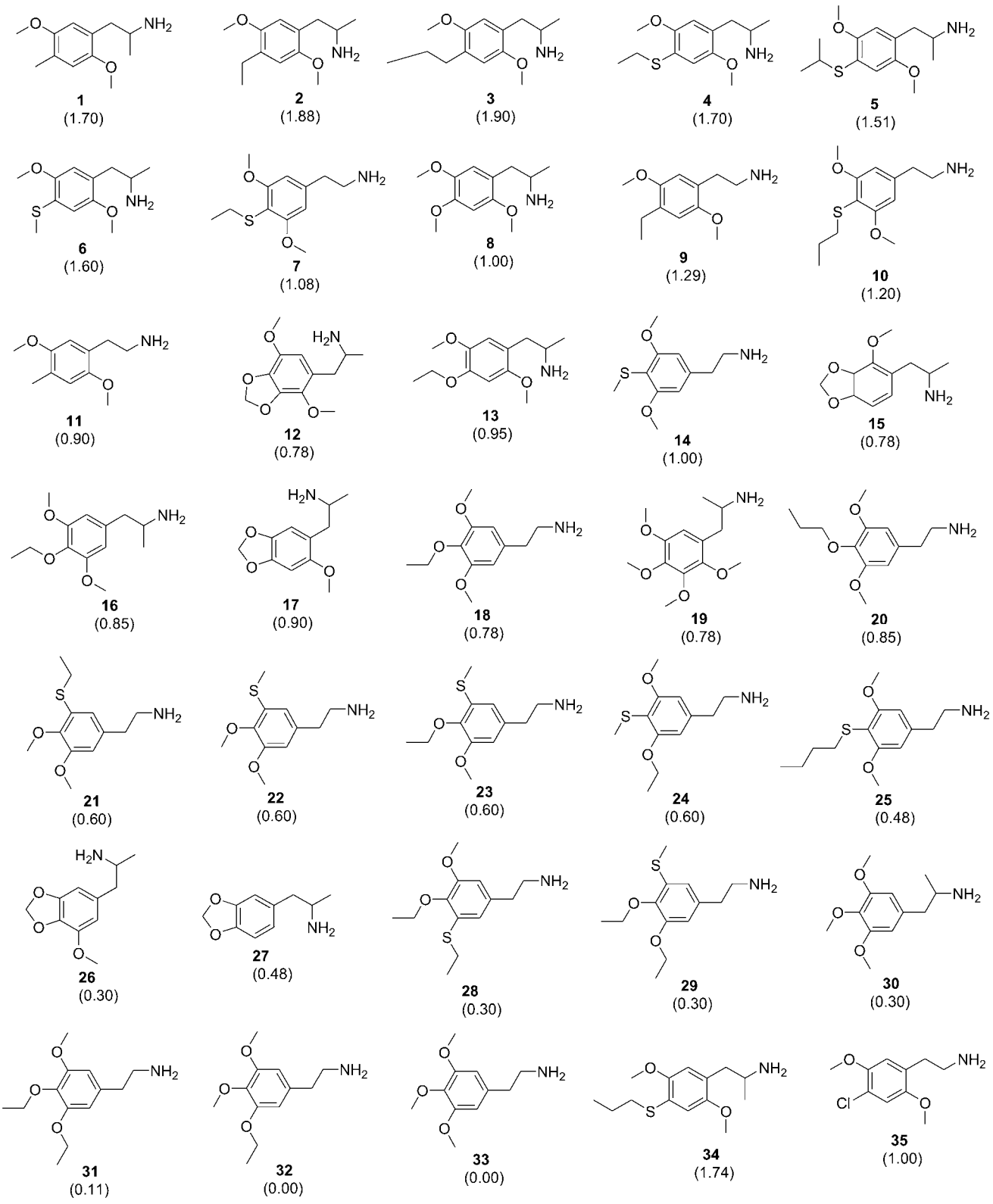

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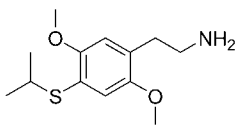
(a) Phenylalkylamines



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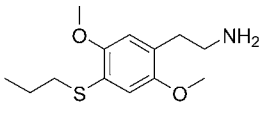

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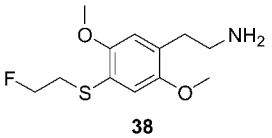

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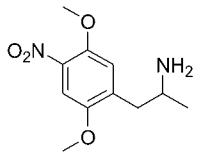

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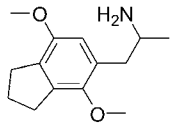

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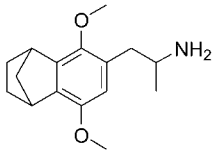

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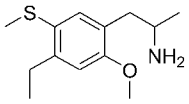

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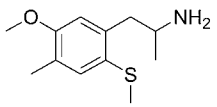

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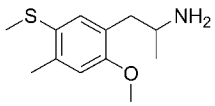

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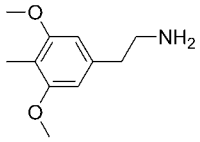

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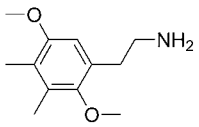

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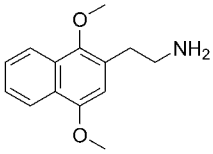

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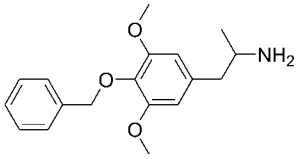

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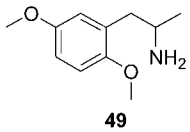

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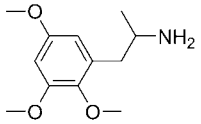

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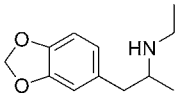

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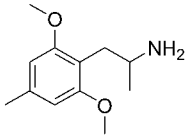

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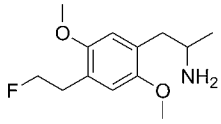

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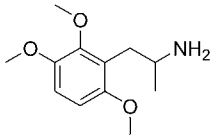

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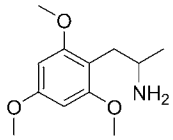

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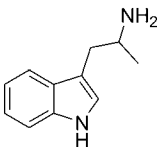

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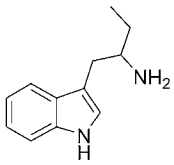

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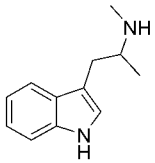

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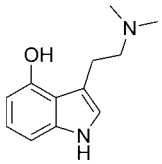

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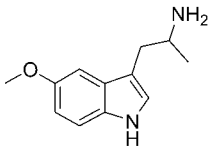

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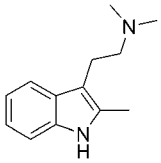

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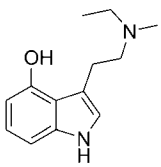

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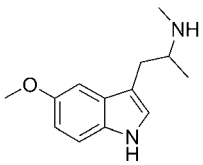

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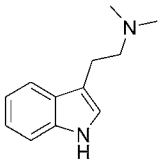

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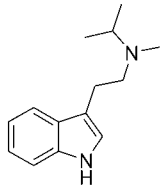

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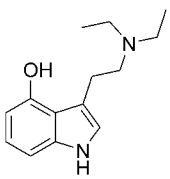

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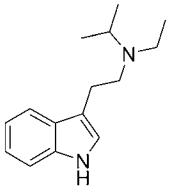

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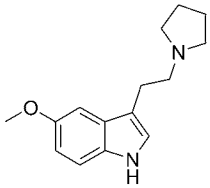

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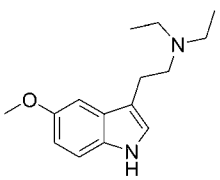

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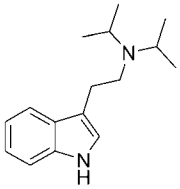

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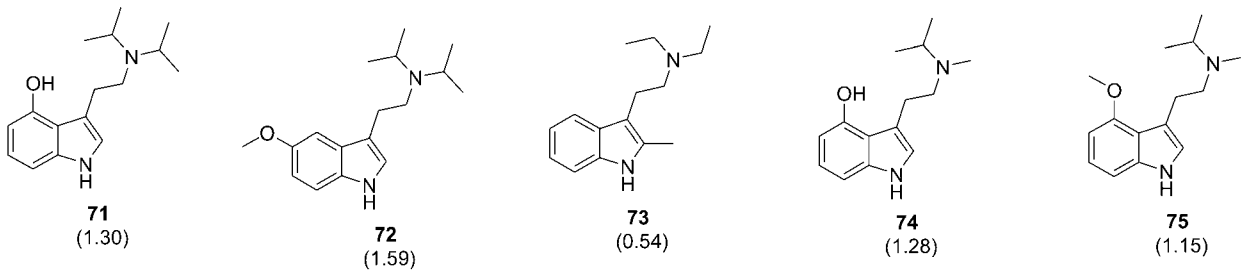
(b) Tryptamines



literatures.[10,11] The activity (in Mescaline Unit, MU) was the ratio of the effective dose of mescaline to the mean of the threshold dose of the trial drug and the dose required to obtain the full effect. In the following discussion, the logarithm of hallucinogenic activity value, expressed as lg A, was applied in the process of modeling.

Molecular descriptors and classification

Quantum chemical parameters The structure and atomic number of phenylalkylamines and tryptamines were given in Figure 1. The geometries of all 75 molecules selected have been fully optimized using the DFT/B3LYP/6-311＋G(d,p). The lowest energy conformation of molecules was used to calculate descriptors. All the computation was performed for single ground state of molecules.

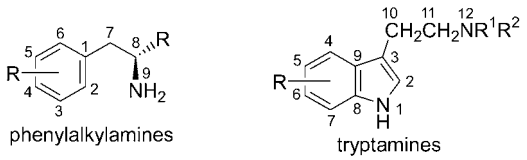


Figure 1 Structure and atomic number of phenylalkylamines and tryptamines.

Some quantum mechanical descriptors were calculated. They are as follows: dipole moment (μ) of molecule, polarizability (p), energies of the highest occupied (E_{HOMO}) and lowest unoccupied (E_{LUMO}) molecular orbitals, the difference between E_{HOMO} and E_{LUMO} energy (ΔE_{HL}), energy of the next highest occupied molecular orbital (E_{SHOMO}), energy of the next lowest unoccupied molecular orbital (E_{SLUMO}), the difference in energy between HOMO and SHOMO (ΔE_H), the diffe rence in energy between SLUMO and LUMO (ΔE_L). For phenylalkylamines, net charges of some important atoms (Q_i) include: sum of net charges on the *ortho* carbon atoms (Q_o) and on the *meta* carbon atoms (Q_m), net charge on the *para* carbon atom (Q_p), sum of atomic charges on phenyl ring (Q_{r6}) and net charge on the nitrogen atom (Q_n). For tryptamines, Q_i are net charge of each atom on phenyl and pyrrole rings, sum of atomic charges on them (Q_{r6}, Q_{r5}), net charges of atoms carbon and nitrogen on side chain.

Other parameters Besides aforesaid descriptors, some physicochemical descriptors were also generated. They are Wiener index (expressed as lg W), Balaban index (lg B), molar refractivity index (lg MR), molecular radius (r), hydrophobicity of molecule (H) and the sum of hydrophobicity of the substituents on the o*rtho*-positions (H_o), *meta*-positions (H_m) and *para*-position (H_p) in phenylalkylamines which were obtained through manual calculation. Considering the presence or absence of α-methyl group, indicator variable I_{me} was used, which takes the value of 1 if there is an α-methyl group on the α carbon atom, and 0 otherwise. In tryptamines indicator variables I_{me}, I_4 and I_5 were introduced and they refer to an α-methyl group on the α carbon atom, 4-hydroxyl group and 5-methoxyl group on phenyl ring, respectively.

Classification of descriptors All the descriptors in this work can be divided into two categories: electron-related descriptors and electron-unrelated descriptors. Electron-related descriptors can be simply defined as what have correlation to a certain extent with electr o-static interaction, whereas electron-unrelated descriptors represent what have correlation with hydrophobic interaction and steric effect. Electron-related descriptors mainly refer to some quantum mechanical descriptors, such as dipole moment, polarizability, molecular orbital energy, atomic charge, and so on. While electron-unrelated descriptors stand for some physicochemical descriptors such as Wiener index, Balaban index, molar refractivity index, molecular radius and hydrophobicity, *etc*.

Statistical analysis and validation of QSAR models

To find out the relationship between the hallucinogenic activity and molecular descriptors, the multiple linear regression (MLR) analysis was carried out by taking the observed hallucinogenic activity (lg MU) as the dependent variables and the selected molecular descriptors as the independent variables. We have generated various QSAR models through different combinations of quantum mechanical descriptors and physicochemical descriptors as above described, keeping in mind that the number of descriptors should be as small as possible and they should produce maximal correlation coefficient (R) in the calculations. The quality of

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the models was considered as statistically satisfactory on the basis of correlation coefficient (R), standard deviation (S) and F-statistics.

In general the stepwise multiple regression procedure was used for variable selection with the aim to overcome the shortage of multiple linear regression and to obtain the best regression equation. In order to avoid overfitting or difficulty in interpreting the resulting models, pairs of variables with $r \geqslant 0.7$ were classified as intercorrelated ones, and only one of the variables was included in the model.

We know that validation is a crucial aspect of any QSAR modeling. Most of the QSAR modeling methods implement the "leave-one-out" (LOO) cross-validated procedure.[12] Internal predictability of the models is characterized by the cross-validated squared correlation coefficient (R_{cv}^2). The R_{cv}^2 values are accepted as criteria of both robustness and the predictive ability of the QSAR model. Many authors consider higher $q^2 > 0.5$ as an indicator that the model is highly predictive.[13]

Results and discussion

QSAR models and residual analysis

Out of those generated QSAR models, four significant equations with the large predictive power are selected as models and summarized in Table 2. The threshold of all the descriptors entered the models is p-value < 0.05.

N represents the number of data points. The correlation coefficient R is a measure of the fit of the regression equation. S is the standard deviation of the regression. F, the Fisher test value, reflects the ratio of the variance explained by the model and the variance due to the error in the model. High values of F-test indicate the significance of the equation. The R_{cv}^2 values of the models (Eqs. 1 —4) are listed in Table 2. All the R_{cv}^2 values of these models are greater than 0.5. Therefore, these models are all acceptable and reliable.

From the four equations in Table 2 one can see that the hallucinogenic activities of phenylalkylamines and tryptamines are correlated with the electronic-related descriptors remarkably. Interestingly, for phenylalkylamines, electronic-unrelated descriptors (such as lg B in the Eq. 2) have some impact on their hallucinogenic activity, but for tryptamines, such an impact can be ignored. This shows that the two types of hallucinogens may perform via different mechanisms.

The difference between Eqs. 1 and 2 is the introduction of lg B, which is a good descriptor for the shape of molecule and usually is related to the size or polarizability of substituted group. [14] From Table 3, it can be concluded that when the number of C—C single bond in 4-substituted group R is less than 4, the value of lg B increased regularly with the increase of number of CH_2 (*e.g.* compounds **1**, **2** and **3**), and the electronic-unrelated descriptors have a little impact on the hallucinogenic activity. However, when the substituted group contains N, O, F or S atoms, the electronic-related descriptors will exert a significant impact on the activity of hallucinogens (as in **4**, **13**, **34**, **39** and **53**).

In contrast to Eq. 3, Eq. 4 demonstrates that Q_{r6} has an important correlation with the hallucinogenic activity. Eq. 4 also shows us that the smaller the value of Q_{r6}, the greater the value of lg A. Therefore, when the phenyl ring in tryptamines is connected with substituent group OH or OCH_3, for example compounds **60**, **68** and **69**, it will be more potent in their hallucinogenic activity.

The results of residual analysis show that these models can be used to predict the hallucinogenic activity of phenylalkylamines or tryptamines, most of them have small residual values. However, a few compounds

Table 2 QSAR models for phenylalkylamines (*a*) and tryptamines (*b*)

Compound	Model	N	R	R_{cv}^2	S	F
(a)	(1) $\lg A = -4.449 + 1.072E_{HOMO} - 0.516E_{LUMO} - 9.653Q_9 - 0.689Q_{r6}$	55	0.81	0.60	0.31	23.17
	(2) $\lg A = -6.454 + 1.165E_{HOMO} - 0.429E_{LUMO} - 8.993Q_9 - 0.575Q_{r6} + 0.678\lg B$	55	0.84	0.62	0.29	23.01
(b)	(3) $\lg A = -2.583 + 1.176Q_5 - 8.799Q_{r5}$	20	0.85	0.63	0.30	22.34
	(4) $\lg A = -4.091 + 1.479Q_5 - 11.591Q_{r5} - 1.141Q_{r6}$	20	0.89	0.68	0.27	21.15

Table 3 Partial descriptors of 4-position R substituted phenylalkylamines

Compound (R)	lg A	E_{HOMO}	E_{LUMO}	ΔE_{HL}	Q_4	Q_{r6}	Q_9	p	lg B	H
1 (CH_3) 1.70		−5.59	−0.44	5.15	−0.02	−0.22	−1.21	9.29	4.91	1.91
2 (CH_2CH_3) 1.88		−5.59	−0.41	5.18	−0.17	−0.30	−1.21	9.97	5.04	2.33
3 ($CH_2CH_2CH_3$) 1.90		−5.58	−0.41	5.17	−0.13	−0.25	−1.21	10.67	5.17	2.75
4 (SCH_2CH_3) 1.70		−5.73	−0.58	5.15	0.04	−0.10	−1.19	11.49	5.17	2.20
13 (OCH_2CH_3)	0.95	−5.98	−0.52	4.93	0.23	−0.25	−1.20	10.19	5.17	1.64
34 ($SCH_2CH_2CH_3$)	1.74	−5.72	−0.58	5.14	0.14	−0.10	−1.18	12.21	5.18	2.69
39 (NO_2) 1.90		−6.26	−2.82	3.44	−0.17	−0.14	−1.19	10.21	5.16	1.62
53 (CH_2CH_2F) 2.04		−5.67	−0.53	5.14	−0.17	−0.22	−1.20	9.96	5.17	1.84

have larger residual values. The hallucinogenic activity of these compounds might be related to steric and electronic effects of meta substitution groups on phenyl ring or related to the formation of hydrogen bonds.[15]

Molecular descriptors in QSAR models

Molecular orbital energies It is understood that the strongest interaction between drug and receptor would occur when E_{HOMO} of drug is most coincided with E_{LUMO} of receptor. E_{HOMO} characterizes the susceptibility of attraction with the receptor, whereas E_{LUMO} refers to the capability of attraction with the donor.[16,17] The figures of HOMO and LUMO of compounds with the first three top activity (A, B and C) and the lowest one (D) were shown in Figure 2.

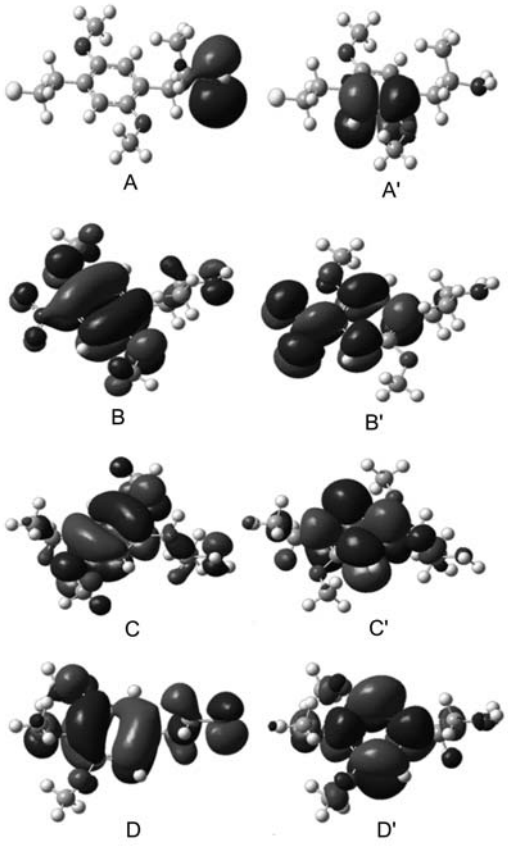

Figure 2 HOMOs and LUMOs of **53**, **39**, **2** and **33**. HOMOs and LUMOs are represented by A, B, C, D and A', B', C', D' respectively.

E_{HOMO} was considered to be the dominant factor to the hallucinogenic activity, especially for phenylalkylamines.[18] The correlation coefficient R between E_{HOMO} and lg A was 0.612 (Eq. 5).

$$\lg A = 7.552 + 1.099E_{HOMO} \quad (5)$$

$$N=55,\ R=0.612,\ S=0.405,\ F=31.775$$

Here phenylalkylamines may act as donors to supply electrons in the charge transferring process, and the main acting sites are phenyl ring, atom N from amine group or atom O from the substituents (see A, B, C and D in Figure 2).

Unlike E_{HOMO}, there is not a credible correlation between E_{LUMO} and lg A ($R=0.194$). But the results of MLR models (Eqs. 1 and 2) indicated that the contribution of E_{LUMO} to hallucinogenic activity should not be ignored. Therefore, phenylalkylamines may also act as electron receptors and such actions occur mainly on phenyl ring (A', B', C' and D' in Figure 2).

Most researchers approved the opinion that E_{HOMO} has direct correlation with hallucinogenic activity of phenylalkylamines, but few were aware of the importance of E_{LUMO}.

ΔE_{HL}, the difference of E_{HOMO} and E_{LUMO}, is an important descriptor as well and it is used as a tool to understand the stability of molecules.[19] The larger the value of ΔE_{HL} is, the higher the stability of molecule is.[20] The regression Eq. 6 shows that the correlation coefficient between ΔE_{HL} and lg A is 0.569 for phenylalkylamines, and that the larger the value of ΔE_{HL} is, the lower the hallucinogenic activity is.

$$\lg A = 4.531 - 0.665\Delta E_{HL} \quad (6)$$

$$N=55,\ R=0.569,\ S=0.422,\ F=25.340$$

Nevertheless, when attempting to relate the E_{HOMO}, E_{LUMO} and ΔE_{HL} with hallucinogenic activity of tryptamines, we found that no obvious correlation existed with E_{HOMO} ($R=0.153$), E_{LUMO} ($R=0.114$) and ΔE_{HL} ($R=0.224$).

We think that such difference between phenylalkylamines and tryptamines might be attributed to the existence of a more electronegative atom N from the indole ring in the later.

Atomic charges In a molecule the atomic charges are the driving force of electrostatic interactions. Thus, charge-based descriptors are important indices in QSAR study. From Table 3, it is easily found that most of atomic charges are negative. This indicates that these hallucinogens mainly act as electron donors to the receptors. The results of MLR analysis in Table 2 have shown that electron-related descriptors are important contributors to hallucinogenic activity for both phenylalkylamines and tryptamines. Our results also showed that the atomic charges, especially for some key atoms, are significant to the hallucinogenic activity. For example, for tryptamines, the atomic charge of C atom (*i.e.* Q_5 in Eqs. 3 and 4) at 5-position on phenyl ring is important to their hallucinogenic activity, and once it is connected with an OCH_3 group, as in case of compounds **60**, **68**, **69** and **72**, the hallucinogenic activity will be increased dramatically.

Other descriptors Hydrophobicity of a molecule is another important descriptor in the QSAR study.[21] With checking molecular structures of phenylalkylamines, it is easy to notice that those compounds with α-methyl group in 8-position C atom have greater hallucinogenic activity than those without α-methyl group.

Such a difference can be attributed to hydrophobic effect reasonably.

Dipole moment of molecule, polarizability and Wiener index are suggested to be important descriptors in the QSAR study. But they have been ignored in present work because of the higher multiple collinearity among the independent variables.

Furthermore, other descriptors (*e.g.* Q_4, and Q_{12}) were not selected into our models with the consideration of their less significance ($P > 0.05$) in the statistical analysis.

Considerations to the action mechanism of hallucinogenic drugs

For a given drug molecule, as we known, its treating effects can be generated only when it interacts with or combines with its target. So it is very important for us to explore the action mechanism for a hallucinogenic drug. In this study based on the complementarity of combining-sites of molecules, we have tried to put forward a new model for the action mechanism for hallucinogenic drugs and we named it the Conformation Complementary Judgement, Transformation and Induction (CCJTI) model. To illustrate the model here we present a schematic diagram (Figure 3) of drug-receptor complex to explain the situation in the process of recognition-combination for them.

The suggested mechanism contains two steps: (1) Judgement of Molecular Conformation Complementary (steric effect) and (2) Conformation Transformation and Induction (electronic effect). As a drug molecule, it should be able to 'recognize' the basic conformation of its receptor firstly, and then to judge whether it was suited to form a new complementary conformer. If the conformation complementarity is adapted ('Yes' in Figure 3), the drug molecule will combine with its receptor. This progress was easily done because both the drug and corresponding receptor retain their original lowest energy conformation; If not ('No' in Figure 3), the conformation of drug would be transformed to a certain extent according to the result of complementary judgement. At the same time, the conformation of receptor would be induced by electrostatic interaction to form a complementary conformation of the drug. This progress is relatively difficult because the conformations of the drug and corresponding receptor were transformed to higher energy conformations and ended up with reasonable conformations in order that they were able to combine well with each other.

Based on the results of our QSAR study and the CCJTI model above proposed, we could conclude that phenylalkylamines and tryptamines might perform different action mechanisms when they combine with the receptor. The most important difference is that, for phenylalkylamines they combine directly with the receptors to form a new complex by charge-transfer on the phenyl ring, but for tryptamines they will not adopt the same path. In addition, the hallucinogenic activity of phenylalkylamines is related to both steric and electronic effect of substitution groups on phenyl ring, whereas for tryptamines it is related only to electronic effect of substitution groups on indole ring. It shows that phenylalkylamines could combine with receptor by electronic effect, but steric factor could affect it also, while tryptamines could act only through the electronic effect.

Conclusions

In this paper, four QSAR models have been developed by means of MLR for a series of hallucinogenic phenylalkylamines and tryptamines. Several descriptors selected into QSAR models were discussed in detail. The results of QSAR study confirmed that the electron-related descriptors are major contributors to the hallucinogenic activity of phenylalkylamines and tryptamines. In addition, the electron-unrelated descriptors have some impact on the hallucinogenic activity of phenylalkylamines. Considering the complementarity of combining sites of molecules, we have put forward the CCJTI model of the action mechanism for hallucinogens. From these results we can derive the conclusion that phenylalkylamines and tryptamines may perform different action mechanisms. More specifically, for

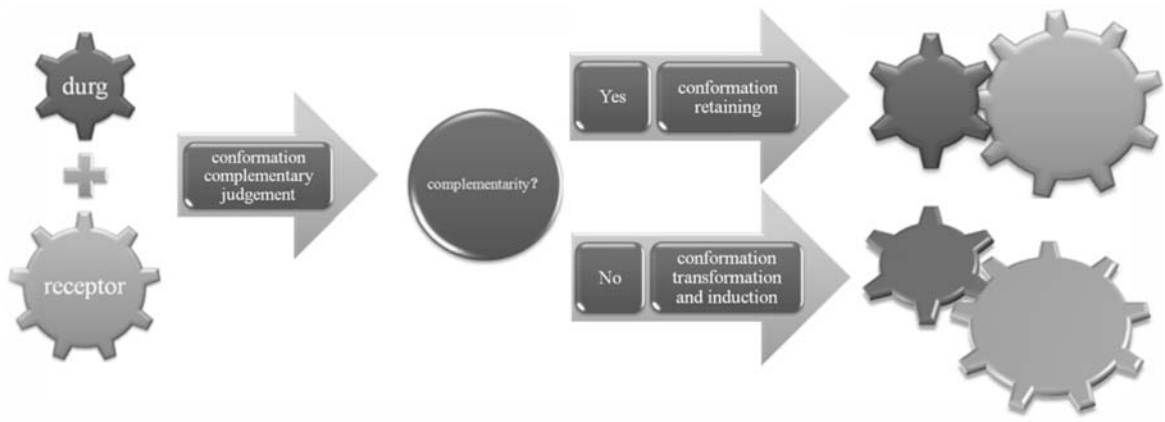

Figure 3 The action mechanism of drug and its receptor.

phenylalkylamines, they could combine with receptor by electronic effect, but steric factor could affect it also, while tryptamines could act only through electronic effect.

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