QSAR Studies on Hallucinogens

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I. Introduction

Hallucinogens commonly refer to the drugs that act at central nervous system (CNS) to produce changes in thought, perception, and mood, sense of time and place, memory, and accustomed patterns of outer and inner universe of "normal" individuals. Such drugs have also been called psychedelic (mind manifesting)[1] agents to express the general activation of psychic phenomena without connotation of negative or morbid components. Another term commonly used for these CNS agents is "psychotomimetic" which implies disturbances of memory, hyperexcitability, deep depressive withdrawal, or even violent behavior resembling psychoses.[2] However, since the extraordinary, unexpected, colorful, world-encompassing, or frightening visions conjured up by these agents are comparable to autogeneous hallucinations, the term "hallucinogen" appears to be most appropriate for them.

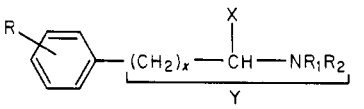
Although the general medical consensus is that there is little potential for medical utility in hallucinogens, some psychiatrists consider that they are a valuable adjunct to psychotherapy in carefully selected patients who possess neuroses and display obsessive or compulsive manifestations or have other disorders that are thought to be of a similar type (e.g., alcoholism, sexual deviation, autism).[3] The intention is to use the effects of hallucinogens to overcome inhibitions and repressions, and release the thoughts and memories that have been repressed from consciousness. Hofmann[4] described the psychotherapeutic values of these psychomimetic drugs in the following terms:

(1) They are able to release the patient from his austic fixation and isolation by shattering and transforming his customary setting. As a result the patient can obtain a more satisfactory relationship with the therapist.

(2) Following the general psychic activation elicited by these drugs, the resistance of the ego disappears, and forgotten and repressed memories may be evoked. Even experiences of early childhood are often remembered. This is of major importance for the success of psychotherapy, particularly when the experiences cornered are those which have led to psychic trauma.

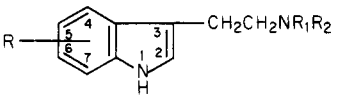
One of the earliest bases for the research interest in hallucinogens was, however, the assumption that the drug-induced hallucinatory state provided a model for schizophrenia and that the model psychosis produced by these drugs might be used to a certain extent as an aid in psychotherapy.[5] Though this assumption never gained favor in experimental psychiatric circles, the "altered state of consciousness" that results from the application of these drugs has, besides a purely hedonistic value, a potential for enhancing creativity and self-analysis.[6] These two properties, the one as prosaic as the other is audacious, would seem to guarantee a continuing fascination with these drugs in the research community.

Presently several compounds are known which cause psychoses.[7] However, the true hallucinogens, which



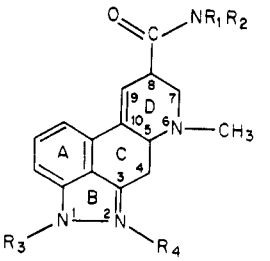
1

1a, Y = $CH_2CH_2NH_2$; R = H
1b, Y = $CH_2CH(CH_3)NH_2$; R = H
1c, Y = $CHOHCH_2NH_2$; R = 3,4-$(OH)_2$
1d, Y = $CH_2CH_2NH_2$; R = 3,4-$(OH)_2$



2

2a, R, R_1, R_2 = H
2b, R_1, R_2 = H; R = 5-OH



3

3a, R_1, R_2 = C_2H_5; R_3, R_4 = H
3b, R_1, R_2 = C_2H_5; R_3 = H; R_4 = Br
3c, R_1, R_2, R_3, R_4 = H
3d, R_1 = H, R_2 = $CH(C_2H_5)CH_2OH$; R_3 = CH_3; R_4 = H

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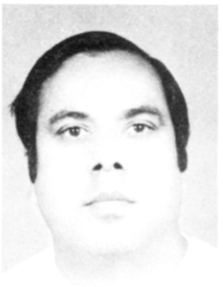
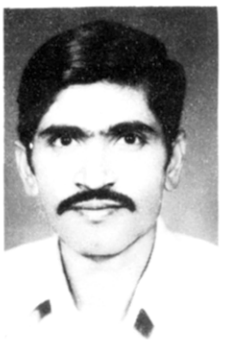


Born in 1945, Satya P. Gupta received his M.Sc. degree in Physical Chemistry from the University of Allahabad in 1967. After obtaining his D.Phil. degree in 1971 from the same university for his work on molecular orbital (MO) theories with Prof. Balkrishna, he moved to Tata Institute of Fundamental Research (TIFR), Bombay, where he associated himself with the group of Dr. G. Govil and worked on the use of MO theories to study the conformations of biologically important molecules such as phospholipids. He joined Birla Institute of Technology and Science (BITS), Pilani, in 1973 as an Assistant Professor of Chemistry. He continues there as an Associate Professor and is working on theoretical aspects of drug design. He is also interested in the use of MO theories to study other biochemical and biophysical phenomena of interest.



Prithvi Singh was born in 1951. He received his M.Sc. (Chemistry) in 1974 and his Ph.D. in 1978 from BITS, Pilani. For his Ph.D. he worked with Dr. Gupta and after spending another year with him as a postdoctoral fellow he joined the faculty of BITS. His main interests lie in the study of the correlation of electronic structures of drugs with their biological activity.

Mahesh C. Bindal was born in 1948. He received his M.Pharm. in 1972 from Punjab University, Chandigarh. After receiving his M.Pharm. he served in a few medical colleges until he was appointed as an Appraising Officer, Drugs and Pharmaceuticals, in 1976. He left this post after a few months to pursue his academic interests, and joined the staff at BITS, Pilani, where he remained until the end of 1981. During this period he worked with Dr. Gupta and obtained his Ph.D. degree. He then joined L.L.R.M. Medical College, Meerut, as a Reader in Pharmacy, and from there he reentered the administrative world to occupy the chair of Drugs and Food Controller of Uttar Pradesh.

have been used deliberately to produce psychosis and which have been extensively studied, belong to the following chemical classes: (a) phenylalkylamines (**1**), (b) indolealkylamines (**2**), and (c) lysergic acid derivatives (**3**).

II. Basic Postulates Concerning Mode of Action of Hallucinogens

Since the presumed brain neurohumors norepinephrine (**1c**) and serotonin (5-hydroxytryptamine, 5-HT; **2b**) are structurally similar to phenylethylamine (**1a**) and tryptamine (**2a**), respectively, it was thought that hallucinogens might effect synaptic transmission in the brain. One theory postulated that hallucinogens might act in the brain as antimetabolites of serotonin,[8,9] and was based on the finding that LSD (lysergic acid diethylamide) in low concentration antagonized the contractile effect of serotonin on smooth muscle.[10] However, 2-Br-LSD (**3b**), which has 50% more antiserotonin activity than LSD on isolated rat uterus and which readily enters the brain, has no hallucinogenic activity.[11] Mescaline (3,4,5-trimethoxyphenylethylamine), an effective hallucinogen, is devoid of antiserotonin activity on rat uterus.[12] However, when attempts were made to relate the electronic structure of hallucinogens with their activity, it was pointed out that these drugs exert their biological effects through the formation of charge-transfer complexes with the receptors.[13-17] However, as the study progressed, much confusion arose regarding this idea.

III. Recent Developments

As the interest was aroused in the mechanism of action of hallucinogens, people started making studies on their structure–activity relationships. The results of such studies were mostly expressed in terms of the correlations of the potency of action with chemical structure, functional group identity and physics, kinetics of body dynamics, organ and tissue distribution, agonist or antagonist efficacy in competition with other drugs or normal biochemicals, and for that matter, any phenomenon that can be measured or computed. If hallucinogenic phenylalkylamines, indolealkylamines, and lysergic acid derivatives form a class, it is natural to ask what is the common structural feature among them and how is it related with the activity. This line of enquiry led Snyder and Richelson[18,19] to suggest that hallucinogenic potency depends in part upon the degree to which a molecule tends to mimic the ring structure of LSD. An implication of this theory was that lysergic acid derivatives, indolealkylamines, and phenylalkylamines act upon the same central receptors. Recently strong arguments have been made to support a serotonin receptor as a site of action.

After Wooley and Shaw[8] made the suggestion that hallucinogens might act as antimetabolites of serotonin, various authors examined the ability of tryptamines and related components to interact as agonists or antagonists with serotonin receptors of various isolated tissue preparations.[20-24] Using a somewhat different approach Glennon and co-workers[25-28] investigated the binding affinities of *N*,*N*-dialkyltryptamines and related analogues for the serotonin receptors of isolated rat stom-

ach fundus preparation. Aghajanian and Haigler[29] employing a microinotophoretic technique have demonstrated that low doses of hallucinogenic tryptamines act preferentially upon presynaptic serotonin receptors to inhibit rapheneurons. Bennett and Snyder[30,31] have investigated the binding of tryptamines to calf brain membrane preparations and have suggested that the binding sites involved might be postsynaptic serotonin receptors. Similarly phenylalkylamines have been found to have direct actions on serotonin receptors, both as agonists[32-35] and as antagonists.[36] Glennon et al.[26,37,38] measured their binding affinity with these receptors of rat fundus preparation and found that certain phenyl-substituted derivatives possess an affinity greater than that of some indolealkylamines. The chemical similarities between the indolic hallucinogens and serotonin were apparent, but some successful studies of cross-tolerance (vide reviews by Brawley and Duffield[39] and by Brimblecombe[7]) had suggested that chemically unrelated drugs might also act there. Smythies et al.[40] catagorically suggested that mescaline, *N,N*-dimethyltryptamine, and LSD all act on serotonin receptors.

Thus, although the serotonin hypothesis appears to be attractive, the mechanism of hallucinations at receptor level is still not clear. The hallucinogenic potency of phenylalkylamines, a widely studied class of hallucinogens, has been found to have no direct correlation with their binding affinity for serotonin receptors. Many review articles on this subject have been written,[6,7,39,41-48] but none of them have been able to present any unified theory.

At molecular level some molecular orbital parameters, such as energy of the highest occupied molecular orbital (E_{HOMO}),[13-15] and certain physicochemical properties, such as ultraviolet absorption,[49] stability of charge-transfer complexes,[50] and native fluorescence,[51] all suggestive of charge-transfer processes were found to have significant correlations with hallucinogenic potencies. This simply suggested that electronic factors are relevant to the mechanism of pharmacological actions of hallucinogenic compounds. However, this suggestion could also not be generalized, as such correlation studies had been mostly made on only one class of hallucinogens, i.e., phenylalkylamines.

In order to provide an aid to the understanding of mechanism of actions of this class of drugs, some workers became interested in the quantiative structure–activity relationships (QSAR) studies on these drugs. In the recent past, therefore, several QSAR studies were carried out. The aim of the present article is to compile all such studies and examine critically how far these studies have been able to help understand the mechanism of actions of hallucinogens.

IV. Results of QSAR Studies

QSAR studies could be started in the real sense only when Shulgin et al.[52] compiled the human data of hallucinogenic activity for a fairly large number of phenylalkylamines. Since then many investigators became interested in QSAR studies, and when the data became available on any kind of activity of hallucinogens of any class, attempts were made to correlate them, by regression analysis, with various physical, physicochemical, and electronic parameters. This section of the article will present the results of all such QSAR studies made until now. A few correlation equations involving only a topological parameter—the molecular connectivity index, have been recently discussed by Kier and Glennon.[53]

A. Phenylalkylamines

Phenylalkylamines are the most widely studied class of hallucinogens. They have been studied for a variety of actions, such as hallucinogenic activity in humans,[52] direct interaction with serotonin receptors (vide section III), and hyperthermic potency in rabbits.[54-58] Attempts were made to correlate these activities with electronic, topological, or physicochemical properties of the molecules. Results that were obtained are as follows.

1. Hallucinogenic Activity

Some of the human data (Table I) compiled by Shulgin et al.[52] was first correlated by Kang and Green[15] with the energy of highest occupied molecular orbital (E_{HOMO}) obtained by INDO (intermediate neglect of differential overlap) approximation[59] as

$$\log \text{MU} = 19.07 + 35.65E_{HOMO}$$

$$n = 13,\ r = 0.753,\ F_{1,11} = 14.36 \qquad (1)$$

where MU stands for the activity in mescaline units—the ratio of the effective dose of mescaline to that of drug. Among the statistical parameters, n represents the number of data points, r the correlation coefficient, and F the F ratio between the variances of calculated and observed activities. When the doses were expressed in moles, the equation obtained was

$$\log \text{mMU} = 18.07 + 35.10E_{HOMO}$$

$$n = 13,\ r = 0.756,\ F_{1,11} = 14.62 \qquad (2)$$

Correlations expressed by both the equations (eq 1 and 2) were however only moderately significant. E_{HOMO} is a measure of ionization potential (IP) or electron-donating capability of molecule. A little better correlation was therefore obtained when Domelsmith and Houk[60,61] used direct experimental ionization potential measured by photoelectron spectroscopy.[62] They treated compounds **7–11**, **14**, **15**, **24**, **30**, and **31** of Table I and (2,5-dimethoxy-4-(methylthio)phenyl)isopropylamine (**53** in Table III) with mMU = 49.1, and obtained the equation

$$\log \text{mMU} = 19.53 - 2.37\ \text{IP}$$

$$n = 11,\ r = 0.86 \qquad (3)$$

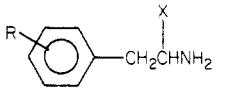
which was further improved by inclusion of 1-octanol–water partition coefficient (P) in the regression analysis, accounting for the role of hydrophobic character also of molecules in hallucinogenic activity.

$$\log \text{mMU} = 11.15 - 1.48\ \text{IP} + 0.78 \log P$$

$$n = 11,\ r = 0.94 \qquad (4)$$

For a small series of amphetamines (phenylisopropylamines), the data of Shulgin et al. were however found to be additionally correlated with other electronic

TABLE I. Hallucinogenic Activity and Related Electronic and Physicochemical Parameters for Phenylalkylamines



compd	R	X	MU[a]	E_{HOMO},[b] au	IP,[c] eV	log P[d]
4	3,4,5-$(OCH_3)_3$	H	1	−0.5226		1.18
5	2,4,5-$(OCH_3)_3$	H	1			1.44
6	3-OCH_3-4,5-(OCH_2O)	H	1			1.38
7	4-OCH_3	CH_3	5	−0.5262	8.16	1.77
8	2,4-$(OCH_3)_2$	CH_3	5	−0.5194	7.91	1.75
9	2,5-$(OCH_3)_2$	CH_3	8	−0.5012	7.70	1.88
10	3,4,5-$(OCH_3)_3$	CH_3	2.2	−0.5218	8.16	1.48
11	2,4,5-$(OCH_3)_3$	CH_3	17	−0.5001	7.66	1.74
12	2,3,5-$(OCH_3)_3$	CH_3	4	−0.5026		1.61
13	2,3,6-$(OCH_3)_3$	CH_3	13	−0.5112		1.73
14	2,4,6-$(OCH_3)_3$	CH_3	10	−0.5217	7.76	1.57
15	3,4-(OCH_2O)	CH_3	3		8.01	1.68
16	3-OCH_3-4,5-(OCH_2O)	CH_3	2.7			1.80
17	2-OCH_3-4,5-(OCH_2O)	CH_3	12			2.42
18	2-OCH_3-3,4-(OCH_2O)	CH_3	10			2.04
19	2,3-(OCH_2O)-4-OCH_3	CH_3	3			1.72
20	2,5-$(OCH_3)_2$-3,4-(OCH_2O)	CH_3	12			2.16
21	2,3-$(OCH_3)_2$-4,5-(OCH_2O)	CH_3	5			2.54
22	2,3,4,5-$(OCH_3)_4$	CH_3	6	−0.5126		1.48
23	2,5-$(OCH_3)_2$-4-OC_2H_5	CH_3	15			2.24
24	2,5-$(OCH_3)_2$-4-CH_3	CH_3	80	−0.4929	7.62	2.08
25	2,5-$(OCH_3)_2$-4-C_2H_5	CH_3	100			2.81
26	2,5-$(OCH_3)_2$-4-(n-C_3H_7)	CH_3	80			3.31
27	2,5-$(OCH_3)_2$-4-(n-C_4H_9)	CH_3	36			3.81
28	2,5-$(OCH_3)_2$-4-(n-C_5H_{11})	CH_3	10			4.31
29	2,5-$(OCH_3)_2$-4-Br	CH_3	400		7.94	2.58
30	3,4-$(OCH_3)_2$	CH_3	<1	−0.5238	8.03	1.00
31	2,3,4-$(OCH_3)_3$	CH_3	<2	−0.5274	8.09	1.36
32	3-OCH_3-4,5-(OC_2H_4O)	CH_3	<1			
33	2-OC_2H_5-4,5-$(OCH_3)_2$	CH_3	<7			
34	2,4-$(OCH_3)_2$-5-OC_2H_5	CH_3	<7			
35	3,4,5-$(OCH_3)_3$	C_2H_5	<2			
36	4-OCH_3	H	<1			
37	3,4-$(OCH_3)_2$	H	<0.2			
38	2-OCH_3-3,4-(OCH_2O)	H	<5			

[a] Reference 52, for compound 29 see: Shulgin, A. T.; Sargent, T.; Naranjo, C. *Pharmacology* **1971**, *5*, 103. [b] Reference 15. [c] Reference 60. [d] Reference 63.

properties also. For compounds **7–11** and **31**, Bailey and Verner[49] showed log MU to be correlated with UV absorption maximum (λ) and with molar absorptivity (ε) as exhibited by

$$\log \text{MU} = -9.96 + 0.038\lambda$$

$$r = 0.94,\ F_{1,4} = 28.15,\ p < 0.01 \qquad (5)$$

$$\log \text{MU} = 0.176 + 0.000213\epsilon$$

$$r = 0.94,\ F_{1,4} = 27.92,\ p < 0.01 \qquad (6)$$

respectively. To support the idea that hallucinogens exert their activity by the formation of charge-transfer complexes with the receptor, Sung and Parker[50] measured the association constant (K) for amphetamine–1,4-dinitrobenzene complexes (1,4-dinitrobenzene is an electron acceptor and can be used as serotonin receptor model) and showed MU of **7–9**, **11**, and **13–15** and unsubstituted amphetamine to be related as

$$\text{MU} = -3.798 + 7.918K$$

$$r = 0.97,\ F = 101.03 \qquad (7)$$

For these amphetamines native fluorescence was also shown qualitatively to be related with their MU values.[51]

However, for a bigger series of phenylalkylamines (**4–29**) Barfknecht et al.[63] found that there exists a quite satisfactory correlation between their hallucinogenic activity and hydrophobicity as shown by

$$\log \text{MU} = -3.17\ (\pm 1.61) + 3.15\ (\pm 1.33) \log P - 0.50\ (\pm 0.25)\ (\log P)^2$$

$$n = 26,\ r = 0.79,\ s = 0.41,\ \log P_o = 3.14(2.89\text{–}3.72) \qquad (8)$$

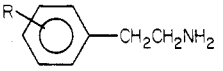
In eq 8, P_o is the partition coefficient corresponding to the optimum value of activity, and the additional statistical parameter s is the standard deviation, while quantities within parentheses are 95% confidence interval. Later, for almost the same series of compounds excluding only **4**, **5**, and **6** (taking only amphetamines), Kier and Hall[64] correlated MU (molar basis) with a topological parameter χ known as molecular connectivity index,[65] as shown by

$$\log \text{mMU} = 45.16\ (\pm 7.30)/{}^3\chi_p + 1.288\ (\pm 0.20)\ {}^6\chi_p - 4.298\ (\pm 0.19)/{}^4\chi_{pc}{}^v - 5.592\ (\pm 2.32)$$

$$n = 23,\ r = 0.920,\ s = 0.251,\ F_{3,19} = 35.0 \qquad (9)$$

where various χs are weighted counts of structural fragments and represent the complexity of skeletal branching in the molecule.[64,65] Obviously eq 9 expresses a more significant correlation than eq 8. The F value

TABLE II. Various Phenylethylamines and Their Hallucinogenic Activity



compd	R	MU[a]
4[b]	3,4,5-$(OCH_3)_3$	1
5[b]	2,4,5-$(OCH_3)_3$	1
6[c]	3-OCH_3-4,5-(OCH_2O)	2
36[c]	4-OCH_3	<1 (0.5)
37[b]	3,4-$(OCH_3)_2$	<1 (0.2)
38[c]	2-OCH_3-3,4-(OCH_2O)	<5 (2.5)
39[b]	3,5-$(OCH_3)_2$-4-OC_2H_5	7
40[b]	3,5-$(OCH_3)_2$-4-OC_3H_7	6
41[c]	2,5-$(OCH_3)_2$-4-CH_3	20
42[c]	2,5-$(OCH_3)_2$-4-Br	35
43[c]	3,4-(OCH_2O)	~1
44	2,3,4-$(OCH_3)_3$	<1
45	2,3,4,5,6-$(OCH_3)_5$	*d*
46[c]	2,5-$(OCH_3)_2$-4-I	44
47[c]	2,5-$(OCH_3)_2$-4-C_2H_5	18
48[b]	3,5-$(OCH_3)_2$-4-SCH_3	12

[a] See ref 68. [b] Used in eq 13. [c] Used in eq 14. [d] Effective human intoxication levels have not been evaluated fully.

in the former is significant at 99% level ($F_{3,19}$ (.01) = 5.01).

Recently Dipaola et al.[66] carried out model interaction energy calculations for some phenylethylamines using 3-methylindole as receptor model, and observed that there exists a correlation between the interaction energy (E) and the hallucinogenic activity of molecules. They obtained the quantitative correlations between E, calculated by Claverie and Rein procedure[67] for 17 compounds (**7–23**), and log MU, as shown by

$$\log \text{MU} = 0.31E - 0.89$$

$$n = 17,\ r = 0.73,\ s = 0.21,\ F_{1,15} = 16.70 \quad (10)$$

$$\log \text{MU} = 0.28E - 0.26I_{3,4} - 0.63$$

$$n = 17,\ r = 0.83,\ s = 0.17,\ F_{2,14} = 15.50 \quad (11)$$

In eq 11, $I_{3,4}$ is an indicator variable depicting the presence of substituents at positions 3 and 4 of the ring. The F values in eq 10 and 11 are significant at 99% level ($F_{1,15}$ (.01) = 8.68; $F_{2,14}$ (.01) = 6.51).

Kier's connectivity index (χ) was further found to be correlated with hallucinogenic activity of a small series of mescaline analogues also. For the first ten compounds of Table II, the correlation obtained by Glennon et al.[68] was

$$\text{MU} = 129\ {}^3\chi_c^v - 4.45\ {}^4\chi_p - 14.54$$

$$n = 10,\ r = 0.97,\ s = 3.02 \quad (12)$$

However, Gupta et al.[69] were able to correlate MU of these compounds with a single χ of low order with a little modification in the mode of its calculation in order to describe the structural influence on the activity more vividly. In this treatment, however, the whole series of Table II was found, when log MU was plotted vs. χ, to be distinctly separated into two groups: lower group comprising of compounds with superscript b, and upper group comprising of those with superscript c. For these two distinct groups, the correlations obtained were as shown by eq 13 and 14, respectively

$$\log \text{MU} = 0.758\ {}^1\chi^v - 2.70$$

$$n = 6,\ r = 0.962,\ s = 0.209,\ F_{1,4} = 49.20 \quad (13)$$

$$\log \text{MU} = 0.668\ {}^1\chi^v - 1.298$$

$$n = 8,\ r = 0.951,\ s = 0.251,\ F_{1,6} = 57.05 \quad (14)$$

Eq 13 and 14 both exhibit highly significant correlation. In both of them F values are significant at 99% level ($F_{1,4}$ (.01) = 21.20; $F_{1,6}$ (.01) = 13.74). Compounds **44** and **45** were not included in any equation, as the exact MU values for them were not known. The separation of the series into two groups in fact indicated that there may be two receptor sites possessing sterically quite dissimilar natures, and that the interaction of a molecule with a particular site might depend upon the conformation of the molecule. The idea of the presence of more than one receptor sites for a particular biological action, in fact, has not been new. The serotonin itself is supposed to act at two different receptor sites,[42,70–72] and Bridger and Mendel[73] have even suggested, based on their studies in intact animals, that mescaline, 3,4-dimethoxyphenylethylamine, and amphetamine have different sites of activity.

2. *Rabbit Hyperthermia and LSD-like Effects in Animals*

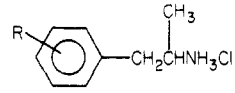
The rabbit hyperthermia assay has been employed in the pharmacological evaluation of a series of LSD analogues,[54] substituted tryptamines,[55] and phenylisopropylamines.[56,57] An excellent correlation has been found between hyperthermic and human potencies.[56–58,74] Table III compares the hyperthermic potency of some phenylisopropylamines in standard rabbit units (SRU)—activity expressed relative to 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, **24**), which is assigned the activity as 100—with hallucinogenic potency in MU. However, Anderson et al.[58] reported that hyperthermic potency could neither be well correlated with E_{HOMO} nor with log P. The correlation coefficient obtained for the correlation between log SRU and E_{HOMO} was only 0.65.

Gupta et al.[74] however recently analyzed the data obtained by Aldous et al.[56] (Table IV) in relation to hydrophobicity constant π and the steric parameter E_s (Taft constant). In their treatment also, no significant correlations were initially obtained when all the data points were included. However, when only (4-X-substituted-2,5-dimethoxyphenyl)isopropylamines (**9–11**, **24–26**, **29**, **58–60**) plus the 2,4,5-trichloro analogue (**61**) were treated, both HT_1 and HT_2 (hyperthermic potencies obtained by two different methods[56]) were found to be significantly correlated with $\sum\pi$ (sum of π values of substituents) as shown by eq 15 and 16, respectively.

$$\log HT_1 = 2.456\ (0.523)\ \textstyle\sum\pi - 1.563\ (0.282)\ (\sum\pi)^2 - 0.566$$

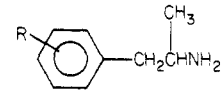
$$n = 10,\ r = 0.906,\ s = 0.468,\ F_{2,7} = 16.00 \quad (15)$$

TABLE III. Comparison of Rabbit Hyperthermic Potency of Some "Rearranged" Phenylisopropylamines with Human Psychotomimetic Potency and Electronic and Physicochemical Parameters[58]



compd	R	SRU	MU	E_{HOMO}, au	IP, eV	log P
8	2,4-$(OCH_3)_2$	3	5	−0.410	7.91	1.75
9	2,5-$(OCH_3)_2$	3	8	−0.409	7.70	1.72, 1.88
10	3,4,5-$(OCH_3)_3$	12	16	−0.397	7.66	1.10, 1.74
24	2,5-$(OCH_3)_2$-4-CH_3	100	80	−0.400	7.62	2.24, 2.08
29	2,5-$(OCH_3)_2$-4-Br	405	400	−0.375	7.94	2.54, 2.58
49	4,5-$(OCH_3)_2$	0.3	<1	−0.419	8.03	1.20, 1.00
50	2,4-$(OCH_3)_2$-5-CH_3	1		−0.403		2.24
51	2-CH_3-4,5-$(OCH_3)_2$	0.5		−0.407		1.76
52	2,4-$(OCH_3)_2$-5-SCH_3	3		−0.409		2.17
53	2,5-$(OCH_3)_2$-4-SCH_3	54	50	−0.405	7.64	2.17
54	2-SCH_3-4,5-$(OCH_3)_2$	2	4	−0.412		1.81
55	2,4-$(OCH_3)_2$-5-Br	2		−0.375		2.54
56	2-Br-4,5-$(OCH_3)_2$	3		−0.377		2.06
57	H	1		−0.473	8.99	1.63

TABLE IV. Hyperthermic and LSD-like Activities of Phenylisopropylamines[56] and Some Physicochemical Parameters



compd	R	HT_1[a]	HT_2[a]	LSD-like[b]	$\Sigma\pi$[c]	$E_s(4)$[d]
9	2,5-$(OCH_3)_2$	0.030	0.025	3.82	−0.21	0.00
10	3,4,5-$(OCH_3)_3$	0.036	0.030		0.20	−0.55
11	2,4,5-$(OCH_3)_3$	0.100	0.092		−0.25	−0.55
24	2,5-$(OCH_3)_2$-4-CH_3	1.000	1.000	0.44	0.31	−1.24
25	2,5-$(OCH_3)_2$-4-C_2H_5	2.290	2.220	0.38	0.76	−1.31
26	2,5-$(OCH_3)_2$-4-(*n*-C_3H_7)	2.370	2.440	0.073	1.34[e]	−1.60
29	2,5-$(OCH_3)_2$-4-Br	4.050	3.010	0.064	0.81	−1.16
58	2,5-$(OCH_3)_2$-4-Cl	3.770	3.910	0.75	0.49	−0.97
59	2,5-$(OCH_3)_2$-4-(*i*-C_3H_7)	0.160	0.080	1.83	1.19	−1.71
60	2,5-$(OCH_3)_2$-4-(*t*-C_4H_9)	0.142	0.130	6.96	1.77[e]	−2.78
61	2,4,5-Cl_3	0.006	0.002		2.05	−0.97
62	3-OCH_3-4-CH_3	0.052	0.019		0.64	−1.24
63	2-OCH_3-4-CH_3	0.078	0.051	23.20	0.19	−1.24
64	3-OCH_3-4-Cl	0.031	0.012	21.19	0.82	−0.97
65	2-OCH_3-4-Cl	0.165	0.078		0.37	−0.97
66	2,4-Cl_2	0.033		2.05	1.29	−0.97
67	4-CH_3			10.78	0.52	−1.24
68	4-Cl			4.85	0.70	−0.97
69	4-Br			2.00	1.02	−1.16

[a] Relative to DOM.[56] [b] Lowest dose (μmol/kg) producing desired effect.[56] [c] From Hansch, C.; Deutsch, E. W. *Biochim. Biophys. Acta* **1966**, *126*, 177 unless otherwise stated. [d] From Martin, Y. C. In "Drug Design"; Ariens, E. J., Ed.; Academic Press: New York, 1976; Vol. VIII, p 2. [e] From Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

$$\log HT_2 = 2.543\ (0.646)\ \Sigma\pi - 1.679\ (0.348)\ (\Sigma\pi)^2 - 0.600$$

$$n = 10,\ r = 0.884,\ s = 0.578,\ F_{2,7} = 12.55 \quad (16)$$

In both eq 15 and 16, the F value was significant at 99% level ($F_{2,7}$ (.01) = 9.55); the standard errors of the coefficients of variables were given within parentheses. The LSD-like effect exhibited by this small set of compounds in rats was also found to be significantly correlated with $\Sigma\pi$ but in combination with the steric parameter of the 4-substituent (eq 17).

$$\log (\text{LSD-E}) = 2.386\ (0.914)\ \Sigma\pi - 0.682\ (0.664)(\Sigma\pi)^2 - 1.383\ (1.047)\ E_s(4) + 0.556$$

$$n = 8,\ r = 0.813,\ s = 0.572,\ F_{3,4} = 2.59 \quad (17)$$

The steric factor did not affect in any way the correlations obtained between hyperthermic potencies and π. The treatment of this small group in isolation to others was due to the fact that the substitution at the 2- and 5-positions has been found to be very important in psychotomimetic activities of phenylisopropylamines[48,56-58] and that the substituent at the 4-position influences certain activities in a big way because of steric effect.[48,56]

The correlations obtained between hyperthermic potencies and LSD-like effect were as shown by

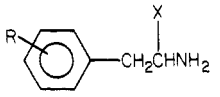
$$\log (\text{LSD-E}) = 0.901\ (0.184)\ \log HT_1 - 0.096$$

$$n = 11,\ r = 0.853,\ s = 0.482,\ F_{1,9} = 24.04 \quad (18)$$

$$\log (\text{LSD-E}) = 0.912\ (0.163)\ \log HT_2 - 0.071$$

$$n = 10,\ r = 0.892,\ s = 0.442,\ F_{1,8} = 31.18 \quad (19)$$

TABLE V. Serotonin Receptor Agonistic Activity of Phenylalkylamines



compd	R	X	log RBR[a]	log P[a]
4	3,4,5-$(OCH_3)_3$	H	0.00	0.78
24	2,5-$(OCH_3)_2$-4-CH_3	CH_3	1.00	2.24
25	2,5-$(OCH_3)_2$-4-C_2H_5	CH_3	1.59	2.76
26	2,5-$(OCH_3)_2$-4-*n*-C_3H_7	CH_3	1.84	3.37
27	2,5-$(OCH_3)_2$-4-*n*-C_4H_9	CH_3	1.62	4.00
28	2,5-$(OCH_3)_2$-4-*n*-C_5H_{11}	CH_3	0.88	4.43
29	2,5-$(OCH_3)_2$-4-Br	CH_3	1.57	2.54
39	3,5-$(OCH_3)_2$-4-OC_2H_5	H	0.31	1.11
40	3,5-$(OCH_3)_2$-4-O-*n*-C_3H_7	H	0.56	1.70
53	2,5-$(OCH_3)_2$-4-SCH_3	CH_3	1.31	2.17
60	2,5-$(OCH_3)_2$-4-*t*-C_4H_9	CH_3	1.39	3.91
70	3,5-$(OCH_3)_2$-4-Br	H	0.88	2.03
71	3,5-$(OCH_3)_2$-4-*i*-C_3H_7	H	0.45	1.52
72	2,5-$(OCH_3)_2$-4-Br	H	0.83	1.81
73	3,5-$(OCH_3)_2$-4-O-*n*-C_4H_9	H	0.10	2.32
74	3,5-$(OCH_3)_2$-4-$OCH_2C_6H_5$	H	0.48	2.40
75	2,5-$(OCH_3)_2$-4-NO_2	CH_3	0.67	1.74

[a] Reference 35.

3. Activity with Serotonin Receptors

Phenylalkylamines have been found to have direct actions on serotonin receptors. However, QSAR studies have been made only in very few cases. Their agonistic activity (Table V) on the serotonin receptors of isolated umbilical artery preparation was shown by Nichols et al.[35] to be related with log P as

$$\log \text{RBR} = 0.027 + 0.368 \log P$$

$$n = 17,\ r = 0.66,\ s = 0.44,\ F_{1,15} = 11.86 \quad (20)$$

This correlation was improved by inclusion of molar refraction of para substituents (MR_4) in the regression (eq 21) but still better correlation was obtained with the

$$\log \text{RBR} = 0.354 - 0.043MR_4 + 0.501 \log P$$

$$n = 17,\ r = 0.81,\ s = 0.39,\ F_{2,14} = 13.96 \quad (21)$$

use of an indicator parameter I_4—indicating number of atoms in para substituent—in place of MR_4 (eq 22). I_4

$$\log \text{RBR} = -0.265 - 0.539I_4 + 0.595 \log P$$

$$n = 17,\ r = 0.926,\ s = 0.23,\ F_{2,14} = 42.05 \quad (22)$$

was assigned a value of 0 for compounds **4**, **24–26**, **29**, **39**, **40**, **53**, **70–72**, and **75**, 1 for **27** and **60**, and 2 for **28**, **73**, and **74**.

With the exclusion of compounds **73** and **74**, which were much less active than predicted from their log P values, Nichols et al.[35] were however able to correlate this agonistic activity of phenylalkylamines with quite high degree of significance with log P alone, but the equation obtained was of third order (eq 23). In eq

$$\log \text{RBR} = 0.23 - 0.89 \log P + 0.95(\log P)^2 - 0.16(\log P)^3$$

$$n = 15,\ r = 0.98,\ s = 0.13,\ F_{3,11} = 77.86 \quad (23)$$

20–23, RBR stands for relative biological response, and represents the ratio of ED_{50} of mescaline to that of compound. This RBR could be found additionally, by Kier and Glennon,[75] to be well correlated with χ as

$$\log \text{RBR} = 11.07\ {}^3\chi_p^v - 2.78({}^3\chi_p^v)^2 + 6.89\ {}^4\chi_p^v - 21.19$$

$$n = 17,\ r = 0.95,\ s = 0.196,\ F_{3,13} = 39.6 \quad (24)$$

The data on serotonin receptor binding affinity (pA_2) for a small series of phenylalkylamines (Table VI) reported by Glennon et al.[26] were recently found[76] to be significantly correlated with steric factors, such as van der Waals volume V_w (eq 25) or molar refraction MR (eq 26). V_w and MR were however taken for ring

$$pA_2 = 2.174\ (0.378)\ \sum V_w + 5.196$$

$$n = 9,\ r = 0.909,\ s = 0.265,\ F_{1,7} = 33.15 \quad (25)$$

$$pA_2 = 0.079\ (0.013)\ \sum \text{MR} + 5.316$$

$$n = 9,\ r = 0.912,\ s = 0.260,\ F_{1,7} = 34.70 \quad (26)$$

substituents only. In fact, these parameters for side chain were not found to affect the correlation in any way. V_w was calculated as suggested by Moriguchi et al.[77] Compounds **4** and **80** were not included in the regression, as they fell quite far from the least-square line.

B. Indolealkylamines

Indolealkylamines are least studied for their hallucinogenic activity, but they are however comparatively well studied for their actions on serotonin receptors (vide section III). The data on binding affinity (pA_2) of several tryptamine analogues for serotonin receptors of rat stomach fundus strip have been obtained. Simultaneous attempts have been made to correlate them with molecular orbital (MO) and physicochemical parameters. Glennon and Gessner[25b] tried to correlate a few of the data obtained by themselves[25] with MO parameters calculated with the use of π (PPP-SCF) as well as all valence-electron (CNDO/2) methods.[59] For the data given in Table VII, the correlation equations obtained were

PPP–SCF results

$$pA_2 = 10.24f_4^E + 4.56$$

$$n = 9,\ r = 0.60,\ s = 0.496 \quad (27)$$

$$pA_2 = 15.47f_4^E + 3.90$$

$$n = 8,\ r = 0.96,\ s = 0.159 \quad (28)$$

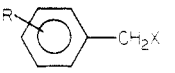
$$pA_2 = -16.87f_6^E + 7.54$$

$$n = 9,\ r = 0.94,\ s = 0.209 \quad (29)$$

$$pA_2 = 5.90f_6^N + 5.30$$

$$n = 9,\ r = 0.53,\ s = 0.525 \quad (30)$$

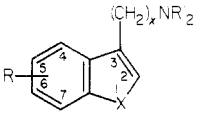
TABLE VI. Serotonin Receptor Binding Affinity of Phenylalkylamines and Steric Parameters



compd	R	X	$\Sigma V_w(R)$	$\Sigma MR(R)^a$	$pA_2{}^b$
4	3,4,5-$(OCH_3)_3$	CH_2NH_2	0.912	23.61	5.65
9	2,5-$(OCH_3)_2$	$CHCH_3NH_2$	0.664	16.77	6.83
11	2,4,5-$(OCH_3)_3$	$CHCH_3NH_2$	0.912	23.61	6.81
15	3,4-(OCH_2O)	$CHCH_3NH_2$	0.406	9.99	6.45
24	2,5-$(OCH_3)_2$-4-CH_3	$CHCH_3NH_2$	0.853	21.39	7.12
29	2,5-$(OCH_3)_2$-4-Br	$CHCH_3NH_2$	0.951	25.65	7.35
76	2,5-$(OCH_3)_2$	CH_2NH_2	0.664	16.77	6.85
77	H	CH_2NH_2	0.168	3.09	5.26
78	2,5-$(OCH_3)_2$	$CH_2N(CH_3)_2$	0.664	16.77	6.52
79	2,5-$(OCH_3)_2$	$CHCH_3N(CH_3)_2$	0.664	16.77	6.50
80	2,5-$(OCH_3)_2$	$CH_2CH_2N(CH_3)_2$	0.664	16.77	5.45

[a] From: Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. [b] References 26 and 53.

TABLE VII. Serotonin Receptor Binding Affinity of *N,N*-Dialkyltryptamines and Related Compounds[25]



compd	x	X	R	R′	$pA_2{}^a$
81	2	NH	H	CH_3	6.00
82	2	NH	5-OCH_3	CH_3	7.10
83	2	NH	4-OCH_3	CH_3	6.17
84	2	NH	5-$COCH_3$	CH_3	5.86
85	2	NH	6-OCH_3	CH_3	5.77
86	2	NH	7-OCH_3	CH_3	5.33
87	2	NH	5-OH	CH_3	7.41
88	3	NH	H	CH_3	6.00
89	2	S	H	CH_3	6.03
90	2	NH	H	C_2H_5	5.79
91	2	NH	5-OCH_3	C_2H_5	6.94
92	2	NH	5-OCH_3	n-C_3H_7	6.53
93	2	CH_2	H	CH_3	5.68

[a] Taken from ref 53.

CNDO/2 results

$$pA_2 = 11.46f_3^E + 1.25$$

$$n = 6,\ r = 0.82,\ s = 0.424 \quad (31)$$

$$pA_2 = 17.37f_4^E + 2.63$$

$$n = 6,\ r = 0.73,\ s = 0.499 \quad (32)$$

$$pA_2 = 14.99f_4^E + 3.29$$

$$n = 5,\ r = 0.76,\ s = 0.417 \quad (33)$$

$$pA_2 = -16.60f_6^E + 9.36$$

$$n = 6,\ r = 0.80,\ s = 0.457 \quad (34)$$

In the PPP–SCF results, however, were included only *N,N*-dimethyltryptamine (DMT, 81) analogues **81–89** and in the CNDO/2 results only methoxy derivatives of DMT (**81–86**) were included. Besides, **86** was not included in deriving eq 28 and 33. The MO parameters f_r^E and f_r^N (r = 1, 2, ...) occurring in these correlating equations are in general the electrophilic and nucleophilic frontier orbital electron densities at position r, respectively. No other parameters, not even the most expected ones—E_{HOMO} and E_{LUMO} (energy of the lowest unoccupied MO)—were found to be correlated with pA_2. However, eq 27–34 have also not been conclusive, as the number of data points used have been very small.

Green and Kang[17] analyzed the activity data obtained by Vane[21] for a series of ring-substituted tryptamines on the same LSD/serotonin receptor model in relation to MO parameters calculated by INDO approximation. The activity was expressed in terms of C_{50}, the concentration of the drug relative to serotonin giving a contraction of 50% maximum to the rat fundus. Later, however, Johnson and Green[78] extended the data set (Table VIII) and correlated them with MO parameters obtained by CNDO/2 method, and hydrophobicity constant π. The significant correlations that surfaced with exclusion of compounds **96** and **104** from regression analysis were as shown by eq 35–40. In these equations

$$\log (1/C_{50}) = 14.35f_1^E + 1.572\pi_7 - 3.734$$

$$n = 15,\ r = 0.926,\ s = 0.399,\ F_{2,12} = 43.1 \quad (35)$$

$$\log (1/C_{50}) = 10.55f_4^E + 1.948\pi_7 - 3.139$$

$$n = 15,\ r = 0.811,\ s = 0.618,\ F_{2,12} = 14.5 \quad (36)$$

$$\log (1/C_{50}) = 18.09f_1^E - 74.77q_1 + 1.182\pi_7 - 13.061$$

$$n = 15,\ r = 0.962,\ s = 0.288,\ F_{3,11} = 59.4 \quad (37)$$

$$\log (1/C_{50}) = 24.36f_4^E - 188.40q_1 + 1.410\pi_7 - 27.464$$

$$n = 15,\ r = 0.935,\ s = 0.375,\ F_{3,11} = 33.4 \quad (38)$$

$$\log (1/C_{50}) = 17.87f_1^E - 3.613q_7 + 1.157\pi_7 - 4.289$$

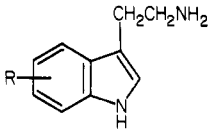
$$n = 15,\ r = 0.958,\ s = 0.304,\ F_{3,11} = 52.6 \quad (39)$$

$$\log (1/C_{50}) = 24.12f_4^E - 9.451q_7 + 1.300\pi_7 - 5.405$$

$$n = 15,\ r = 0.927,\ s = 0.395,\ F_{3,11} = 29.7 \quad (40)$$

q_r (r = 1, 2, ...) represents the net total charge on atom r and π_7 the hydrophobicity constant of the substituent at the 7-position. All these equations expressed significant correlations—the F value in all of them is significant at 99% level ($F_{2,12}(.01) = 6.93$; $F_{3,11}(.01) = 6.22$). However, since it was not clear to Johnson and Green how the ring carbon would be involved in electron do-

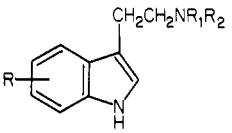
TABLE VIII. Potencies of Tryptamines on Isolated Rat Fundus Strip, MO Parameters, and Hydrophobicity Constant[78]



compd	R	log $(1/C_{50})^a$	q_1	q_6	q_7	f_1^E	f_4^E	π_7
2a	H	−1.17	−0.1188	−0.0138	−0.0231	0.1585	0.1505	
2b	5-OH	0.00	−0.1168	−0.0397	−0.0004	0.2384	0.2228	0.00
94	5-OCH_3	−0.06	−0.1167	0.0404	−0.0018	0.2325	0.2153	
95	5-OH-7-Cl	−0.16	−0.1131	−0.0331	0.0717	0.1951	0.2107	0.80
96	5,6-$(OH)_2$	−0.42	−0.1180	0.1535	−0.0665	0.0335	0.0360	
97	5-Cl	−0.88	−0.1181	0.0203	−0.0229	0.1901	0.1741	
98	5-CH_3	−0.95	−0.1180	−0.0042	−0.0169	0.1855	0.1743	
99	5-F	−0.98	−0.1162	−0.0415	−0.0015	0.1926	0.1767	
100	4-OH	−1.15	−0.1190	0.0371	−0.0521	0.1434	0.1454	
101	4-NH_2	−1.54	−0.1200	0.0297	−0.0460	0.1381	0.1498	
102	7-OCH_3	−1.70	−0.1089	−0.0588	0.1638	0.1761	0.2070	−0.21
103	5,7-$(OCH_3)_2$	−1.86	−0.1068	−0.1142	0.1843	0.1981	0.2452	−0.21
104	5,6-$(OCH_3)_2$	−2.17	−0.1194	0.1510	−0.0774	0.0206	0.0214	
105	6-OH	−2.50	−0.1216	0.1992	−0.0869	0.0866	0.0937	
106	6-OCH_3	−2.98	−0.1208	0.1991	−0.0963	0.0804	0.0862	
107	5,6,7-$(OH)_3$	−3.07	−0.1112	0.0862	0.1314	0.1390	0.1873	−1.07
108	5,7-$(OH)_2$	−3.09	−0.1081	−0.1151	0.1862	0.2010	0.2530	−1.07

[a] C_{50} is the concentration of the drug relative to serotonin giving a contraction of 50% maximum to the rat fundus strip.

TABLE IX. Serotonin Uptake Inhibition Activity of Tryptamine Derivatives



compd	R	NR_1R_2	$ED_{50}{}^a$	log P^a	E_T,[a] β
94[b]	5-OCH_3	NH_2	36.0	1.44	32.156
96[b]	5,6-$(OH)_2$	NH_2	22.5	0.72	32.422
100[b]	4-OH	NH_2	12.0	0.79	28.806
101[b]	4-NH_2	NH_2	12.5	0.23	26.298
103[c]	5,7-$(OCH_3)_2$	NH_2	9.5	1.42	40.510
105[b]	6-OH	NH_2	19.0	0.79	28.796
108[b]	5,7-$(OH)_2$	NH_2	48.5	0.12	32.426
109[b]	7-OH	NH_2	18.0	0.79	28.128
110[b]	4-NH_2	$NHCH_3$	35.4	0.79	30.410
111[c]	5-OH	$NHCH_3$	1.9	1.35	32.230
112[c]	7-OCH_3	$NHCH_3$	3.5	2.00	36.278
113[c]	5,7-$(OCH_3)_2$	$NHCH_3$	8.0	2.44	44.614
114[b]	7-OH	$N(CH_3)_2$	46.0	1.91	36.330
115[b]	4-NH_2	$N(CH_3)_2$	26.0	1.35	34.496
116[b]	5,7-$(OH)_2$	$N(CH_3)_2$	42.5	1.24	40.630
117[c]	5,7-$(OCH_3)_2$	$N(CH_3)_2$	9.3	2.54	48.704
118[c]	7-OH	NHC_2H_5	6.0	1.81	36.232
119[c]	7-OCH_3	NHC_2H_5	9.0	2.46	40.272
120[c]	5,7-$(OCH_3)_2$	NHC_2H_5	9.0	1.98	48.612
121[b]	5,7-$(OH)_2$	$N(C_2H_5)_2$	84.0	2.83	48.620
122[c]	4-NH_2	$N(C_2H_5)_2$	7.5	2.27	42.480
123[c]	7-OCH_3	$N(C_2H_5)_2$	18.0	3.48	48.356
124[c]	5,7-$(OCH_3)_2$	$N(C_2H_5)_2$	30.0	3.46	56.694

[a] Reference 71. [b] Forming upper group. [c] Forming lower group.

nation, they professed eq 37 to be the most meaningful,[78] though later Weinstein et al.[79] established the considerable contribution of C_4–C_5 and the importance of bridge region to the overall electrostatic reactivity pattern of biologically active indolealkylamines.

Kumbar et al.[71] studied the serotonin-uptake inhibition activity of a fairly large series of tryptamines in thrombocyte and correlated the ED_{50} (effective dose producing 50% inhibition) with total orbital energy (TOE) and the hydrophobicity factor log P. Later, Gupta et al.[72] correlated it with V_w. However, both groups of workers had found that on the plot (activity vs. relating parameters), the series as listed in Table IX was divided into two distinct groups:[71,72] the upper group comprising of compounds with superscript b and the lower group comprising of those with superscript c. For the upper group, the significant relating equations obtained by Kumbar et al.[71] were

$$\log ED_{50} = -2.952 + 2.908 \log TOE$$

$$n = 12,\ r = 0.851,\ s = 0.134 \qquad (41)$$

$$\log ED_{50} = 1.215 + 0.223 \log P$$

$$n = 12,\ r = 0.650,\ s = 0.190 \qquad (42)$$

$$\log ED_{50} = -3.581\ (\pm 0.038) + 3.368\ (\pm 0.939) \log TOE - 0.055\ (\pm 0.094) \log P$$

$$n = 12,\ r = 0.856,\ s = 0.132 \qquad (43)$$

That obtained by Gupta et al.[72] was

$$\log ED_{50} = 0.928 V_w + 0.826$$

$$n = 12,\ r = 0.791,\ s = 0.164,\ F_{1,10} = 16.73 \qquad (44)$$

Similarly for the lower group the corresponding equations were

$$\log ED_{50} = -5.539 + 3.954 \log TOE$$

$$n = 11,\ r = 0.893,\ s = 0.142 \qquad (45)$$

$$\log ED_{50} = 7.899 \times 10^{-2} + 0.361 \log P$$

$$n = 11,\ r = 0.801,\ s = 0.189 \qquad (46)$$

$$\log ED_{50} = -3.275\ (\pm 0.033) + 2.324\ (\pm 0.842) \log TOE + 0.226\ (\pm 0.092) \log P$$

TABLE X. Displacement of [^{3}H]Serotonin and [^{3}H]LSD from Rat Cerebral Cortex Membranes by Various Drugs and Log P Values[a]

no.	compd	log (1/IC$_{50}$) [^{3}H]-5HT	log (1/IC$_{50}$) [^{3}H]-LSD	log P
	Tryptamines			
2a	tryptamine	6.00	5.70	0.88
2b	5-HT	8.00	6.00	0.21
81	DMT	5.70[b]	5.70	1.78
87	5-HO-DMT	7.70	6.52	1.10
94	5-methoxytryptamine	7.30	6.00	0.81
96	5,6-dihydroxytryptamine	6.22	5.15	−0.37
108	5,7-dihydroxytryptamine	5.00	4.52	−0.45
	LSD Analogues			
3a	LSD	8.00	8.10	2.95
3b	2-Br-LSD	7.00	8.00	3.81
3c	isolysergic acid amide	7.00	6.70	0.95
3d	methylsergide	6.52	7.00	2.34
	Neurotransmitters and Analogues			
1c	norepinephrine	3.52	3.00	−1.24
1d	dopamine	4.40	4.22	−0.98
125	fluphenazine	5.70	7.00	4.36
126	chlorpromazine	4.30	7.00	5.35
127	promethazone		6.00	4.73
128	haloperidol		5.70[b]	4.30

[a] Reference 80. [b] Not used in regressions.

$$n = 11,\ r = 0.938,\ s = 0.109 \quad (47)$$

$$\log ED_{50} = 1.093V_w - 0.244$$

$$n = 11,\ r = 0.890,\ s = 0.152,\ F_{1,9} = 34.46 \quad (48)$$

On the basis of the separation of compounds into two distinct groups, it was therefore proposed that there might be involved two receptor sites of a sterically, if not electronically, dissimilar nature in uptake of serotonin.

Tryptamines and some other drugs (Table X) were found to displace specifically bound [^{3}H]serotonin and [^{3}H]LSD from rat cerebral cortex membranes.[32] Chan et al.[80] reported the displacement of binding data (IC$_{50}$ – the molar concentration required for 50% displacement) to be significantly correlated with log P in the manner as shown by eq 49 for [^{3}H]serotonin and by eq 50 for [^{3}H]LSD. Some [^{3}H]LSD displacement data,

$$\log (1/IC_{50}) = 1.391 \log P - 0.330 (\log P)^2 + 6.181$$

$$n = 14,\ r = 0.873,\ s = 0.766,\ \log P_0 = 2.11\ (1.76 - 2.52) \quad (49)$$

$$\log (1/IC_{50}) = 1.222 \log P - 0.182 (\log P)^2 + 5.265$$

$$n = 16,\ r = 0.906,\ s = 0.613,\ \log P_0 = 3.36\ (2.77 - 4.83) \quad (50)$$

e.g., those of Green et al.[81] on mescaline, LSD, and a few amphetamine and tryptamine derivatives, and those of Bennett and Aghajanian[82] on a small series of similar compounds including some phenothiazine tranquilizers, were shown by Domelsmith and Houk[60] to be related with ionization potentials also (eq 51 and 52, respectively, where IP$_1$ represents first ionization potential and IP$_2$ second ionization potential, measured by photoelectron spectroscopy[62,83]). In these equations

TABLE XI. Relationship of Hallucinogenic Activity (MU) of Different Classes of Hallucinogens with E_{HOMO}[14]

no.	compd	MU	E_{HOMO},[a] β
3a	LSD	3700	0.2184
4	mescaline	1	0.5357
10	3,4,5-trimethoxyamphetamine	2.2	0.5357
11	2,4,5-trimethoxyamphetamine	17	0.4810
129	4-HO-DMT	31	0.4603
130	6-hydroxydiethyltryptamine	25	0.4700

[a] Hückel values.

$$-\log IC_{50} = 47.78 - 3.81IP_1 - 1.64IP_2$$

$$n = 10,\ r = 0.85 \quad (51)$$

$$-\log IC_{50} = 43.26 - 2.79IP_1 - 1.93IP_2$$

$$n = 7,\ r = 0.97 \quad (52)$$

IC$_{50}$ represents the inhibition constant for high affinity LSD binding in rat brain homogenates.

However, the scantly available human or animal qualitative data on psychotropic activity of these indolealkylamines were not found to have any relation with any electronic parameter reflective of either a general or localized charge-transfer process,[84] in spite of the fact that Karreman et al.[13] and Snyder and Merril[14] stressed that, irrespective of their class, the hallucinogens exert their psychomimetic effects through the formation of charge-transfer complexes with the receptors, and the qualitative observation of Snyder and Merril (Table XI) being well substantiated by quantitative analysis by Gupta and Singh[85] (eq 53).

$$\log MU = 5.956 - 10.259E_{HOMO}$$

$$n = 6,\ r = 0.972,\ s = 0.327,\ F_{1,4} = 68.81 \quad (53)$$

C. Lysergic Acid Derivatives

Lysergic acid derivatives or LSD analogues have been comparatively well studied for their antiserotonin and hallucinogenic activities,[11,54,70,86-90] and the data that were available was subjected to QSAR studies. However, as in the case of tryptamines, Kumbar and Siva Sankar[91,92] failed in their attempt to correlate them with any electronic parameter reflective of charge-transfer process apparently, rather they found a correlation with TOE. With the use of data as given in Table XII, these authors showed the hallucinogenic activity (H) to be related with TOE as[91]

$$\log H = -11.8596 + 7.3951 \log TOE$$

$$n = 12,\ s = 0.4003 \quad (54)$$

and antiserotonin activity (anti-S) and TOE are related as[92]

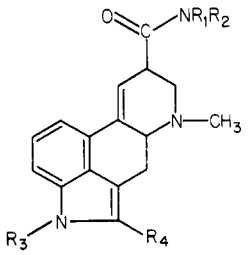
$$\log (\text{anti-S}) = -2.7092 + 0.07955TOE$$

$$n = 15,\ s = 0.2715 \quad (55)$$

$$\log (\text{anti-S}) = -16.2811 + 10.2838 \log TOE$$

$$n = 15,\ r = 0.889,\ s = 0.2709 \quad (56)$$

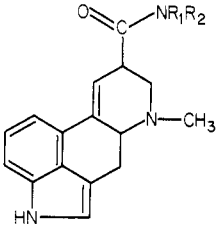
TABLE XII. Antiserotonin and Hallucinogenic Activities and Hückel's Total MO Energy of LSD and its Analogues



compd	NR_1R_2	R_3	R_4	anti-S[a]	H^a	TOE,[b] β
3a	$N(C_2H_5)_2$	H	H	100	100[d]	58.250
3b	$N(C_2H_5)_2$	H	Br	150	7.2,[d] <2	61.294
3c	NH_2	H	H	4.3	0	42.292
3d	$NH[CH(C_2H_5)CH_2OH]$	CH_3	H	400	0.6	63.294
131	$NHCH_3$	H	H	6.3		46.188
132	$N(CH_3)_2$	H	H	23.2	10[d,e]	50.262
133	NHC_2H_5	H	H	11.9	5,[d] 3.4[e]	50.180
134	NHC_2H_5	CH_3	H	835[c]	4,[d] 5[e]	54.228
135	NHC_2H_5	$COCH_3$	H	39	7[d,e]	59.756
136	$NH(iC_3H_7)$	H	H	22.2		51.024
137	$N(C_2H_5)_2$	CH_3	H	368	36,[d] 40[e]	62.294
138	$N(C_2H_5)_2$	OCH_3	H	58.9	66[d,e]	63.718
139	$N(C_2H_5)_2$	$COCH_3$	H	210	100,[d] 91[e]	67.824
140	$N(C_2H_5)_2$	H	I	57.4		59.516
141	$N(C_2H_5)_2$	CH_3	Br	533	<1	65.352
142	$N(-C_4H_8-)$	CH_3	H	130	<5	62.502
143	$N(-C_4H_8-)$	H	H	4.7[c]	5.3,[d] 10[e]	58.440
144	$N(-CH_2-CH=CH-CH_2-)$	H	H	4.1[c]	10[d,e]	52.968
145	$N(-C_5H_{10}-)$	H	H	8.5[c]		62.442
146	$N(-C_2H_4-O-C_2H_4-)$	H	H	8.0[c]	11[d,e]	62.728

[a] Data collected by Kumbar and Siva Sankar,[91,92] from ref 70a, 87, 88, and 90; all activities are relative to that of LSD taken as 100. [b] Reference 92. [c] Not included in regression analysis. [d] Used to obtain eq 54. [e] Used to obtain eq 58 and 60.

TABLE XIII. Antiserotonin Activity and Hydrophobicity of Side-Chain Only Substituted LSD Analogues



compd	NR_1R_2	log (anti-S)[a]	log P[b]
3a	$N(C_2H_5)_2$	2.00	2.16
3c	NH_2	0.63[c]	0.16
131	$NHCH_3$	0.81[c]	0.66
132	$N(CH_3)_2$	1.36	1.16
133	NHC_2H_5	1.08[c]	1.16
136	$NH(i\text{-}C_3H_7)$	1.35	
143	$N(-C_4H_8-)$	0.67	1.76
144	$N(-CH_2-CH=CH-CH_2-)$	0.61	1.56
145	$N(-C_5H_{10}-)$	0.93	2.16
146	$N(-C_2H_4-O-C_2H_4-)$	0.31	0.22
147	NHC_3H_7	1.60[c]	1.60
148	NHC_4H_9	1.81[c]	2.16
149	$NH(C_5H_{11})$	1.87[c]	2.66
150	$N(C_3H_7)_2$	1.62	3.16
151	$N(i\text{-}C_3H_7)_2$	1.37	
152	$N(C_4H_9)_2$	1.49	4.16

[a] Cereletti and Doepfner data[87] used by Dunn and Bederka[94] and Glennon and Kier.[95] [b] Reference 94. [c] Used by Kumbar and Siva Sankar to obtain eq 58.

The antiserotonin and hallucinogenic activity data were however also found to be significantly correlated with the size of the substituents accounted for by V_w,[93] and in their study Gupta et al.[93] found that both activities were, to a great extent, the function of the size of side-chain substituents (NR_1R_2) and thus the correlations expressed by eq 57 and 58 could be only slightly improved by inclusion of V_w of the R_3 substituent (compare eq 57 with 59, and eq 58 with 60) and were hardly affected by the inclusion of V_w of the R_4 substituent.

$$\log (\text{anti-S}) = 2.793\ (0.401)\ V_w(NR_1R_2) - 0.032$$

$$n = 15,\ r = 0.888,\ s = 0.311,\ F_{1,13} = 48.49 \quad (57)$$

$$\log H = 2.686\ (0.658)\ V_w(NR_1R_2) - 0.612$$

$$n = 10,\ r = 0.822,\ s = 0.289,\ F_{1,8} = 16.65 \quad (58)$$

$$\log (\text{anti-S}) = 2.536\ (0.388)\ V_w(NR_1R_2) + 1.120(0.581)\ V_w(R_3) - 0.056$$

$$n = 15,\ r = 0.916,\ s = 0.283,\ F_{2,12} = 31.17 \quad (59)$$

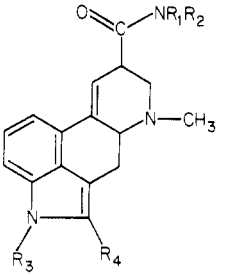
$$\log H = 2.474\ (0.503)\ V_w(NR_1R_2) + 1.267\ (0.477)\ V_w(R_3) - 0.716$$

$$n = 10,\ r = 0.916,\ s = 0.218,\ F_{2,7} = 18.14 \quad (60)$$

In agreement with the findings of Gupta et al., some of the Cereletti and Doepfner data[87] on antiserotonin activity of side-chain only substituted LSD analogues (Table XIII) were shown[91] to be related with number of carbon atoms N in the alkyl substituent as shown by

$$\text{anti-S} = 1/(0.01185 + 0.2207\ e^{-N}) \quad (61)$$

TABLE XIV. Toxicity and Pyretogenic Activity of Some LSD Analogues



compd	NR_1R_2	R_3	R_4	log TC[a]	log PG[a]
3a	$N(C_2H_5)_2$	H	H	2.000[b]	2.000
3b	$N(C_2H_5)_2$	H	Br	0.699	0.699
132	$N(CH_3)_2$	H	H	1.892	1.634
133	NHC_2H_5	H	H	1.532[b]	1.230
134	NHC_2H_5	CH_3	H	0.505	
135	NHC_2H_5	$COCH_3$	H	0.778	0.000[b]
137	$N(C_2H_5)_2$	CH_3	H	0.748	0.699
139	$N(C_2H_5)_2$	$COCH_3$	H	1.279	1.114[b]
141	$N(C_2H_5)_2$	CH_3	Br	0.301[b]	
142	$N(-C_4H_8-)$	CH_3	H	0.602	
143	$N(-C_4H_8-)$	H	H	1.863	1.000
146	$N(-C_2H_4-O-C_2H_4-)$	H	H	1.634	1.000

[a] See ref 91. [b] Not used to obtain correlating equations (eq 66 and 67).

Equation 61 was in fact obtained only for side-chain monoalkyl substituted analogues excluding **136**. For all such monoalkyl-substituted analogues including even **136**, the Cereletti and Doepfner data were found to be correlated with V_w as[93]

$$\log (\text{anti-S}) = 1.789\ (0.173)\ V_w(NR_1R_2) + 0.282$$

$$n = 7,\ r = 0.977,\ s = 0.113,\ F_{1,5} = 106.38 \quad (62)$$

However, for both mono- and dialkyl side-chain-substituted analogues, these antiserotonin data as mentioned in Table XIII were shown by Dunn and Bederka[94] to be significantly correlated with log P, and by Glennon and Kier[95] with χ, as shown by eq 63 and 64, respectively. In both eq 63 and 64, RBR stands for

$$\log \text{RBR} = -0.54\ (\pm 0.32) - 0.74\ (\pm 0.28)\ D + 0.84\ (\pm 0.35) \log P - 0.14\ (\pm 0.08)\ (\log P)^2$$

$$n = 14,\ r = 0.94,\ s = 0.20,\ \log P_0 = 2.90\ (2.40 - 4.32) \quad (63)$$

$$\log \text{RBR} = 24.94\ (\pm 3.9) - 0.835\ (\pm 0.033)\ {}^2\chi - 0.917\ (\pm 0.083)\ {}^6\chi_p - 1/0.0072\ (\pm 0.004)\ {}^0\chi^v$$

$$n = 16,\ r = 0.940,\ s = 0.196 \quad (64)$$

relative biological response and was used by these authors in place of anti-S. Further in eq 63, D is a dummy variable used to account for amide nitrogen being enclosed in a ring system. It was assigned a value of 1 if amide nitrogen was part of cyclic system, otherwise its value was 0. In the derivation of eq 63, however, compounds **136** and **151** were not included.

With the use of data of Table XII, a mutual correlation was shown to exist between hallucinogenic and antiserotonin activities of LSD analogues by Siva Sankar and Kumbar[92] as

$$\log (H/\text{anti-S}) = 1.1614 - 1.1093 \log (\text{anti-S})$$

$$s = 0.6499 \quad (65)$$

Finally, the toxicity (TC) and the pyretogenic activity (PG) of some LSD analogues (Table XIV) have also been reported to be correlated with V_w as shown by eq 66 and 67, respectively.[96]

$$0.996\ (\log \text{TC})^2 - 2.262 \log \text{TC} + V_w + 0.044 = 0$$

$$n = 9,\ r = 0.901,\ s = 0.103,\ F_{2,6} = 12.95 \quad (66)$$

$$0.960\ (\log \text{PG})^2 - 2.784\ (\log \text{PG}) - V_w + 2.628 = 0$$

$$n = 7,\ r = 0.973,\ s = 0.060,\ F_{2,4} = 36.23 \quad (67)$$

V. Discussion

From these QSAR studies, the first impression that is created is that among the various factors that may be responsible for physiological and pharmacological actions of hallucinogens the electronic properties play dominant role. However, the idea that these drugs exert their hallucinogenic activity through the formation of charge-transfer complexes with the receptors, in which they act as donor, could not be firmly established. The reasons are

(1) The correlations that have been obtained between the activity and the electronic factors reflective of charge-transfer processes have never been totally free from criticisms. For example, neither eq 1 nor 2, obtained by Shulgin et al.,[52] represents any highly significant correlation between the activity and E_{HOMO} even though only 13 compounds were treated, while activity data were available for a large series of compounds. Besides, E_{HOMO} was not able to account for the activity of all compounds treated.[52] Similarly eq 3, showing the correlation between activity and observed ionization potential, was obtained only for 11 compounds, excluding the most potent one, 2,5-dimethoxy-4-bromoamphetamine (**29**). The ionization potential was not able to account for the activity of this compound, and even for those compounds fitting eq 3,

there were some notable deviations, e.g., compounds **11** and **24** have almost equal ionization potentials but there is a large difference between their activities. In a recent communication also, Domelsmith and co-workers[97] showed that ionization potential alone was not sufficient to account for the hallucinogenic activity of amphetamine analogues. Anomalies were found in the data of Antun et al. on UV fluorescence,[51] in Bailey and Verner's data on UV absorption,[49] and in Sung and Parker's data on stability of charge-transfer complexes,[50] hence neither eq 5 and 6 nor eq 7 included all data points studied. Thus, they were obtained for a very small number of data points, such as 6 and 8, respectively, and on inclusion of all data points they showed very poor correlations.[49,50] Moreover, Sung and Parker made their study on charge-transfer complexes using a model receptor and not the true serotonin receptor, as did DiPaola et al.[66] in their model interaction energy calculation. The parameter E appearing in eq 10 and 11 represents, as already mentioned, interaction energy between a phenylalkylamine and 3-methylindole used as a receptor model.

(2) Correlations between hallucinogenic activity and electronic parameters reflective of charge-transfer phenomena were mostly obtained for only one class of hallucinogens, e.g., phenylalkylamines.

(3) Though the activities, like serotonin receptor binding affinity, and abilities to contract LSD/serotonin receptor and displace specifically bound [^{3}H]serotonin and [^{3}H]LSD from rat cerebral cortex membranes of indolealkylamines have been found to be related with electronic parameters (vide section IVB), they have not been shown to have any direct relation with their hallucinogenic activity.

(4) The validity of such structure–activity relationship studies is sometimes challenged on the basis that the biological data used for the correlations with molecular structure do not necessarily reflect the efficacy of the drug on its biological receptor but are a composite of many events including the various stages of drug transport, uptake, metabolism, and excretion.

However, the role of electronic factors in hallucinogenic drug–receptor interaction cannot be completely ruled out. But Glennon and Gessner[25b] pointed out, particularly in the case of indolealkylamines, that a general charge-transfer mechanism may not be involved, but rather a localized charge-transfer phenomenon may be implicated. These authors had failed in their attempt to correlate binding affinity data (pA_2) of tryptamines with E_{HOMO}, but obtained eq 27–34, on the basis of which they suggested that electron donation might occur in a localized manner from the 4-position of tryptamines. Although f_6^E (electrophilic frontier orbital electron density at the 6-position), obtained by PPP as well as CNDO/2, was also found to be significantly correlated with pA_2 (eq 29 and 34) but, since coefficient was negative in both the correlating equations and thereby implied that as electron-donating capability at the 6-position increased pA_2 would decrease, Glennon and Gessner did not assign any importance to this position, nor did they argue in favor of electron donation from the 3-position, as f_3^E obtained by CNDO/2 only was found to be correlated with pA_2.

However, as a matter of fact, none of the equations obtained by Glennon and Gessner was very convincing, since eq 27–30 were derived with the use of data obtained by the PPP method, which involves several approximations, and eq 31–34 were obtained for such a small number of data points that it was difficult to associate any significance to them, though electronic data were obtained by a refined method, i.e., CNDO/2. f_4^E alone was found to have no correlation with LSD/serotonin receptor contraction ability of tryptamines,[78] and although in combination with π_7 and q_1 or q_7, and with the exclusion of compounds **96** and **104** from Table XIII, some significant correlations were obtained (eq 38 and 40), it was not clear to Johnson and Green[78] how ring carbon would be involved in electron donation, nor could they find an explanation as to why potency would increase either by increasing the negative charge at the 7-position or by increasing the hydrophobic nature of the substituent at this position. Therefore, in their view eq 37 was the most meaningful. π_7, q_1, or q_7 individually were not found to be significantly correlated with the activity. However, Weinstein et al.[79] later established the importance of the entire C_4–C_5 bond region. According to these authors tryptamines form polarization-type complexes with the receptor, and the sites of maximal polarizability in the indole portion of the tryptamines form the reactivity criteria. These sites of maximal polarizability were shown to be directly related to the localization of the highest occupied molecular orbital (HOMO) in the molecules. The highest contribution to the polarization term in the interaction energy comes from the highest occupied molecular orbital (HOMO) and at the centers at which the density of HOMO is localized. However, the patterns of localization of HOMO's were found to be different in different tryptamine congeners, and that was one of the reasons for the apparent failure to find a direct correlation of biological activity with E_{HOMO}.

Further, Weinstein et al.[98,99] made studies on the complexes of some tryptamine congeners with imidazolium cation used as a model for secondary binding site in the LSD/serotonin receptor, and found that the interaction in the complexes was totally electrostatic in nature; the transfer of charge to the imidazolium cation was negligible and the mutual polarization of the molecule was the major component of the electron charge redistribution. The degree of polarization affected the stabilization energy of the complex and depended upon the mutual orientation of the molecules. A hypothesis for the interaction of tryptamine congeners with the LSD/serotonin receptor resulted from these findings: "the difference between the affinity of 5-HT and that of any other congener is related to the discrepancy between the preferred electrostatic orientation of 5-HT and that of congener in the field of the receptor."[99,100]

On the basis of their findings as to the electrostatic nature of complexes and the relative contribution of polarization, exchange repulsion, and "charge-transfer" terms to the stabilization energies, Weinstein et al.[99] also assumed that the charge redistribution accompanying complex formation would be mainly "intramolecular" in character: the polarization with each molecule will enhance the electrostatic interaction but there will be little "overlap" or actual transfer of charge.

However, the significance of general charge-transfer phenomenon is reinforced by the existence of good correlations between the ionization potentials and the

ability of some psychotropic drugs to inhibit high affinity LSD binding in rat brain homogenates (eq 51), and of a few to displace specifically bound LSD from the same (eq 52). The human data on hallucinogenic activity of a group of compounds that includes members from all different classes of hallucinogens were shown to be correlated with E_{HOMO} as significantly as shown by eq 53. E_{HOMO} was obtained by a very crude method (Hückel approximation), but for a comparative study on π-electron systems the importance of this method cannot be completely overlooked. Several authors have discussed that in the field of relative aromatic reactivity, the Hückel method is as good as any refined method.[101-106]

However, the correlations of total orbital energy (TOE) with serotonin-uptake inhibition activity of tryptamines (eq 41 and 43 or 45 and 47) or with hallucinogenic or antiserotonin activity of LSD analogues (eq 54–56) hardly convey any meaning, as no particular significance has been attached to this quantum chemical parameter.

The other parameter that appears to be important from these QSAR studies in the activities of hallucinogens is the hydrophobic character of molecules. The correlation of hallucinogenic activity of phenylalkylamines with log P as shown by eq 8 had led Barfknecht et al. to suggest that while drug action ultimately may be related to chemical or electronic factors, distribution and transport to the receptor may also be important in determining the activity of hallucinogens.[63] The same conclusion was drawn by Domelsmith and Houk[60,61] from eq 4. The low value of correlation coefficient (r) in eq 8 was attributed to the variability in biological data and the use of calculated log P values for certain compounds, nonetheless, it did not undermine the role of chemical or electronic effects in hallucinogenic potency of drugs.

Correlation of rabbit hyperthermia produced by a particular series of phenylalkylamines including mostly (4-X-substituted-2,5-dimethoxyphenyl)isopropylamines with hydrophobic parameter (eq 15 and 16) further add to the importance of hydrophobic nature of hallucinogens in their activity. Their LSD-like effect in rat, however, was found to be influenced also by steric effect of 4-substituent. The steric effects of 4-substituent has been well discussed by a few authors.[48,56] In any substitution series, the 4-substituent has been found to be of unique importance, and although eq 15–17 indicate the combined effect of hydrophobic nature of all substituents in the ring, π_4 has been found to be most significant.[97] Domelsmith et al.[97] have recently concluded that there are two significant indicators of hallucinogenic potency of phenylalkylamines: the hydrophobic nature of 4-substituent and for molecules without a hydrophobic 4-substituent, the first ionization potential. They showed π_4 and IP_1 significantly correlated with hallucinogenic potency and rabbit hyperthermia as well.

The correlation of in vitro activity data with log P and MR_4 or I_4 (eq 21 and 24) reaffirm the role of the hydrophobic nature of molecules and steric bulk of 4-substituent in the drug–receptor interaction of phenylalkylamines, although the MR_4 is a crude measure of the latter and I_4 is vaguely defined. If one does not theoretically justify a third-order relationship as expressed by eq 23, the first-order correlation between log RBR and log P (eq 20) shows very poor role of hydrophobicity. But Nichols et al.[35] claimed that a second order relationship in log P was greatly improved. These authors then pointed out that serotonin receptors may possess a specific hydrophobic site that accommodates the para substituent provided it is less than 5–6 Å in length.[34,35] Green et al.[107] also proposed a specific hydrophobic site approximately at this region of the serotonin receptor.

The importance of the length of the 4-substituent has been also argued by Kier and Glennon[75] who obtained eq 24. The parabolic correlation of activity with the $^3\chi_P^v$ term which increases by one subgraph as the length of the 4-substituent increases led them to suggest that a maximum potency will be obtained with an intermediate length of the 4-substituent chain. This suggestion is fully consistent with the finding that in (4-X-substituted-2,5-dimethoxyphenyl)isopropylamines the optimum activity is associated with an alkyl or halo group at the 4-position that is probably limited in bulk to n-propyl or bromo.

Further support for this aspect comes from eq 25 and 26 which correlate other "in vitro" activity data with steric factors. Although $\sum V_w$ or $\sum$MR represents the total sum of V_w or MR of all substituents in the phenyl ring, almost all the compounds that were included in deriving eq 25 or 26 (Table VI) belong to the series of (4-X-substituted-2,5-dimethoxyphenyl)alkylamines (exception is only 15 which is otherwise equivalent to 4,5-(methylenedioxy)-substituted analogue) where the variation occurs only at the 4-position. Correlations were linear due to the fact that the substitution at the 4-position in the entire series (Table VI) was limited in bulk only up to the bromo group.

If the assumption that the 4-position of phenylalkylamines corresponds to the 7-position of tryptamines[108,109] is really true, it removes all the doubt of the significance of π_7 in tryptamines activity as shown by eq 35–40.

The serotonin uptake inhibition activity of tryptamines also appear to be influenced by steric bulk of substituents in the phenyl ring as well as in the side chain (eq 44 and 48). They probably affect the conformations of the molecules that are required for interaction of compounds with two different receptor sites.[72] However, what is the exact nature of drug–receptor interaction in this case that cannot be fully explained, as the hydrophobic parameter was found to be significantly correlated only in one case and, as already mentioned, TOE is hardly any meaningful parameter. But since hydrophobicity is found to be important in determining the ability of tryptamines to displace specifically bound [^{3}H]serotonin and [^{3}H]LSD from rat cerebral cortex membrane (eq 49 and 50), the one possible reason for a good correlation not existing between the serotonin uptake inhibition activity and log P in the other case (upper group, eq 42) may be that only one of the two receptor sites involved would possess the hydrophobic character.

Hydrophobic character of molecules or steric bulk of the substituents appear to be most important in the activities of LSD analogues. Equation 63 obtained by Dunn and Bederka[94] for a series of side-chain only substituted LSD analogues shows very well the dependence of antiserotonin activity on log P. Further, this equation also shows that if the dummy parameter D has

a non-zero value, i.e., the substituent is cyclic, the activity would be lowered. A possible explanation for this effect given by Dunn and Bederka[94] is that a cyclic substituent brings about a conformational rigidity that impairs the receptor contact.

That the steric bulk of the substituent in the side chain is detrimental to the activity is shown by eq 57, 58, 61, and 62. Not only the antiserotonin activity but also the hallucinogenic activity of LSD analogues is found to be related to the size of the substituent in the side chain (eq 58) and neither of these activities appears to be significantly affected by the substituents in the phenyl ring (compare eq 59 with 57 and 60 with 58 and for details see ref 93). However, the steric bulk of the substituent in the side chain probably affects the activities by altering the hydrophobic nature of the moiety, as we found that log P of compounds in Table XIII is well correlated with V_w of their NR_1R_2 group (unpublished). But the activity (log term) is shown to have a parabolic correlation with log P and only linear relationship with the size of the substituent. This is not hard to explain. The value of log P corresponding to the optimum activity is calculated to be equal to 2.90 which corresponds to a greater size than that of the $-NHC_5H_{11}$ group (see Table XIII), for which the calculated V_w would be 0.955×10^2 Å^3, and no equation showing linear correlation between the activity and size of the substituent incorporates a molecule that has its NR_1R_2 group bigger than this.[93]

The steric effect in the antiserotonin activity of LSD analogues is also manifested by eq 64. This equation led Glennon and Kier[95] to suggest that a bigger substituent in the side chain would lead to enhanced activity, but the presence of a branched chain, a cyclic structure, a heteroatom, or an unsaturated bond in it would diminish its effect. However, all such factors of a substituent will have almost parallel effects on the hydrophobicity of the molecule. Thus, ultimately it appears, although the hallucinogenic activity could not be shown to be directly related with log P, that hydrophobicity of the molecules is very important in determining the activities of LSD analogues and that there would be a hydrophobic zone at the receptor which will accommodate the substituent of the side chain. The hallucinogenic activity is shown to be related with antiserotonin activity (eq 65). This supports the idea that hallucinogenic activity may be due to the antiserotonin action of drugs on the receptor.

The role of electronic factors in the activities of LSD analogues remains questionable. Kumbar and Siva Sankar[91,92] failed in their attempt to correlate their activity with E_{HOMO} or for that matter with any other electronic parameter reflective of general or localized charge-transfer process. With this reference, it is very difficult to explain how the degree of electron delocalization will influence any activity as claimed by these authors on the basis of their eq 54–56. Two other activities of LSD analogues—toxicity and pyrogenesis—were found to be related with V_w only (eq 66 and 67) and not with any electronic parameter even with TOE.

VI. Conclusions

Since the subjective nature of hallucinogenic activity in man leads to 20–25% error in the measurement[52] and the "in vitro" data are not completely free from errors, certain anomalies, discrepancies, and deviations occurring in the correlations may be excused, and it may be therefore concluded from the discussions in the preceding section that, at the molecular level, electronic, hydrophobic, and steric factors play a dominant role in various biological and pharmacological actions of hallucinogenic drugs. Correlations of activities with topological parameter such as χ accounted sometimes for steric effects, otherwise they have been more of predictive value than providing any understanding to the mechanism of drug–receptor interaction. However, while hydrophobicity and steric factors appear to be important in all types of hallucinogenic drugs, the electronic properties do not appear to be so important in the case of indolealkylamines and LSD analogues as in the case of phenylalkylamines. With this background, it is difficult to assume that all types of hallucinogens have exactly identical mode of actions. Rather, the finding that there can be two receptor sites for hallucinogens indicates that structurally and conformationally different molecules will interact with different receptor sites and that the binding at one site might involve totally electronic interaction and at the other totally hydrophobic. Because of the use of nonhuman experimental animals in most biochemical studies and in the correlations the biological data that do not necessarily reflect the efficacy of the drug on its biological receptor but are a composite of many events including various stages of drug transport, uptake metaboism, and excretion, it is difficult to say what is the exact mechanism of actions of hallucinogens at the receptor level. Because of these shortcomings QSAR studies should not be heavily relied upon. However, the distribution of hallucinogens in the intact body, the localization in specific organs or in specific sites of organs, the attempt to show agonistic or antagonistic action with specific regard to these neurotransmitters, the efforts to demonstrate degrees of cross-tolerance between one another, etc., also have not been uniformly so successful[45] that a unified theory of mechanisms can be drawn. Therefore, theory and experiment both have a long way to go to provide an unquestionable theory for the mechanism, mode, and site of actions of hallucinogens.

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