Three-dimensional Quantitative Structure–Activity Relationships of Hallucinogenic Phenylalkanamine and Tryptamine Derivatives: Studies using Comparative Molecular Field Analysis (CoMFA)

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Abstract

Investigations of the quantitative structure–activity relationships of a data set comprising 66 phenylalkanamines have been carried out using the CoMFA method. This yielded a cross-validated correlation coefficient (q^2 value) of more than 0.8. The target parameter used was the hallucinogenic effect on humans, since this variable is of particular importance for research into addictive substances. It was possible to confirm the reliability of the CoMFA analysis by using a second, independent phenylalkanamine data set. It was found that models with good predictive properties are obtained if up to ten components are taken into account. In a further step it was possible to include hallucinogenic tryptamine derivatives in a common QSAR analysis with the phenylalkanamines and this in spite of their differing basic structures. The final model from that the CoMFA plots were extracted is based on 148 compounds and permits precise inferences to be made concerning the relationships between structural elements and hallucinogenic effects.

Key words: QSAR, hallucinogens, amphetamines, mescaline units, components.

1 Introduction

Phenylalkanamines provoke a number of differing effects in humans, one result being that large numbers of these compounds are misused. Many members of this group of substances are synthesized in underground laboratories as "designer drugs" and solid illegally. Small, often arbitrary, structural variations of these designer drugs are frequently synthesized in an effort to produce compounds, that are just as active or even more active [1, 2]. Depending on the substitution pattern of the aromatic group and the side chain the phenylalkanamines can be classified more or less unequivocally as stimulants, entactogens or hallucinogens.

Alongside the phenylalkanamines, tryptamine derivatives such as psilocin and DMT, also produce hallucinations. The effect of both groups of substances is mediated by the 5-HT_{2A}-receptor [3, 4]. This has been demonstrated by means of radioligand binding studies [3, 5], drug discrimination tests [5, 6] and using other models [4]. It is known that the 5-HT_{2A}-receptor exists in a high affinity and a low affinity state [7, 8]; the hallucinogenic effect is brought about by an agonistic interaction at the high affinity state. The amino acid sequence of the receptor, which has been known since 1988 [9], has been presented as a three-dimensional model by means of molecular modelling studies [10]. However, this is only of limited applicability, since it was constructed in analogy to the bacteriorhodopsin receptor, which, in contrast to the 5-HT_{2A}-receptor, is not G protein-coupled. In order to obtain better understanding of why substances possess a particular activity, quantitative structure–activity relationships (QSAR) can be compiled without knowledge of the receptor topology. Attempts have long been made using classical methods to relate the steric, electrostatic and lipophilic properties of molecules to their biological effect. One of the most comprehensive studies in the field of phenylalkanamines was published by Clare in 1990 [11]. He succeeded in establishing a relationship between various structural parameters and the hallucinogenic effect using a data set of 50 molecules. It is now possible, with the availability of more computational power and appropriate molecular modelling software, to correlate the three-dimensional structure of these molecules with their effect. Cramer, Patterson and Bunce first used comparative molecular field analysis (CoMFA) in 1988 for the construction of a QSAR model [12].

This paper describes the construction of such a model for the hallucinogens, including tryptamines alongside the phenylalkanamines. As many substances as possible were included since the evidential value increases and the danger of random correlations is reduced as the number of molecules considered is increased [13]. In contrast to antagonists, that merely block the receptors in some manner or another, agonists are particularly suitable for CoMFA analyses, since their effect has to be exerted by a relatively uniform positioning of the pharmacophoric groups at the receptor [14].

In addition to addressing pharmacological questions the large amount of data used in the present study can be employed to estimate the predictive properties of a CoMFA analysis. An initial model is used to predict the activities of compounds in an independent data set. The comparison with experimentally determined data allows conclusions to be drawn concerning the number of components to be employed in the CoMFA model and the quality of the extrapolated predictions.

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2 Methods

2.1 Conformation of the Molecules of the Data Set

All molecules of data sets I, II and III were constructed on the basis of the X-ray structures of 1-(4-ethyl-2,5-dimethoxyphenyl)-propan-2-amine and of 5-hydroxy-N,N-dimethyltryptamine, whereby the substituents were assigned to the start conformations in accordance with the principle of the least possible steric hindrance. The structural optimization that followed was carried out using the Tripos Standard Force Field [15] without taking the Coulomb term into account and with a convergence criterion at gradients of 0.1 kcal/(mol × Å). After translation of the torsion angle given in Table 1 to the molecules the atomic charges were calculated by the Gasteiger-Hückel method [15]. The compounds were then superimposed with respect to the atoms of the six-membered aromatic ring in an RMS fit so that position 1 of the phenylalkanamines corresponded with position 4 of the tryptamines, position 2 of the phenylalkanamines with position 5 of the tryptamines etc. All operations and calculations were carried out at an Evans & Sutherland 3/32 graphics workstation using versions 6.0 and 6.03 of the SYBYL program packet.

2.2 Biological Data

The calculation of the hallucinogenic activity of the substances used was based on data published by Shulgin. The efficacy of a substance was expressed in mescaline units (MU), which are defined as the ratio of the effective dose of mescaline and the effective dose of the compound under consideration, both calculated as free bases. With the exception of molecules Hal 59 and Hal 61 [16] the MU of the phenylalkanamines used in the current investigation were calculated afresh from the data provided in one literature source [17]. Compounds, whose activities depended on an entactogenic effect rather than on a hallucinogenic effect ("MDMA like"), were not included. Since they were prodrugs two phosphate esters of 4-hydroxylated tryptamines were excluded from the 26 tryptamines tested by Shulgin [18]; the corresponding active forms were included in the data set in each case. A compound with a methyl group in position 4 was also omitted, because it was impossible to find an energetically acceptable conformation for the calculated torsion angles of the side chain. The fact that this molecule was also found to be inactive in Shulgin's investigations is consistent with our finding.

When recalculating the mescaline units the mean of the range was used when a mg range was quoted; when a lower limit for activity was quoted, then 1.5 times this dose was taken. In contrast to numerous earlier studies the quantities were converted to molar amounts before calculation. The activities so obtained are listed in Tables 2 to 4. Both the 2-phenylpropanamines and the α-methylated tryptamines exist in two stereoisomeric forms, in each case the more active structure (R for the amphetamine derivatives and S for the tryptamine derivatives) was included in the QSAR investigation. Since the biological data were basically all obtained with racemates a correction factor was included for these compounds. On the basis of affinity data for the two enantiomers of α-methyltryptamine [19], DOM [19] and DOB [20] it can be calculated that the mescaline units of the amphetamine derivatives must be multiplied by a factor of 1.7 while those of the α-methylated tryptamines must be multiplied by a factor of 1.8, in order to obtain the correct activities for the enantiomers included in the study. The mescaline units are concentration-dependent data. Since there is a logarithmic relationship between concentration and energy, e.g. interaction energy, the mescaline units were also converted to their logarithms before being subjected to QSAR analysis. In addition, this also yields a more even distribution of the data over the range observed [15].

2.3 CoMFA Parameters

A sp^3 hybridized carbon atom with a charge +1 was used for the calculation of the CoMFA fields. The steric (Lennard-Jones) and electrostatic (Coulomb) interaction energies were calculated each at a cut-off value of 30 kcal/mol at the grid points at a spacing of 2 Å in every case (except for the analysis reported in Table 8). The cross-validated PLS analyses were carried out using the leave-one-out method with up to 10 components and a minimum sigma value of 2.0. In accordance with a suggestion by Kubinyi and Abraham [21] the optimum number of components was determined by choosing the cross-validated analysis with the least possible standard deviation. Prescaling was carried out according to the CoMFA standard method. Standard values were also employed for all other QSAR-relevant parameters.

Table 1. Torsion angles of the structures used in the QSAR analyses.

	Torsion angles (numbers in Figure 1)		
Phenylalkanamine	2-1-1′-2′	1-1′-2′-3′	1′-2′-3′-4′
Hal 1–66, Hal 90–119, Hal 121–132, Hal 134–155	−120°	−130°	180°
Hal 120	−120°	—	180°
Hal 133	−120°	−130°	170°

	Torsion angles (numbers in Figure 1)					
Tryptamine	3a-3-1′-2′	3-1′- 2′-3′	1′-2′-3′-4′	2′-3′-4′-6′	2′- 3′-5′-7′	5-4-1″-2″
Hal 67–68, Hal 73–75, Hal 78, Hal 83, Hal 86	−55°	120°	70°	—	—	—
Hal 69–71, Hal 77, Hal 79, Hal 81, Hal 84–85, Hal 87–89	−55°	120°	60°	—	—	—
Hal 72, Hal 76	−55°	120°	60°	100°	−70°	—
Hal 80	−55°	120°	60°	—	—	30°
Hal 82	−55°	120°	60°	100°	−70°	30°

Table 2. QSAR dataset I.

Compound	Structure	R_a	R_b	R_2	R_3	R_4	R_5	R_6	$R_{N1} = R_{N2}$	Activity of racemates (MU)	Activity used in CoMFA [log(MU)]
Hal 1	a	–H	–H	–H	–H	–O–CH_3	–H	–H	–H	< 0.5	−0.60
Hal 2	a	–H	–H	–H	–O–CH_3	–O–CH_3	–H	–H	–H	< 0.2	−1
Hal 3	a	–H	–H	–H	–O–CH_3	–O–CH_3	–O–CH_3	–H	–H	1	0
Hal 4	a	–H	–H	–O–CH_3	–O–CH_3	–O–CH_3	–H	–H	–H	< 0.7	−0.46
Hal 5	a	–H	–H	–O–CH_3	–H	–O–CH_3	–O–CH_3	–H	–H	< 0.9	−0.35
Hal 6	a	–H	–H	–H	–O–C_2H_5	–O–CH_3	–O–CH_3	–H	–H	1	0
Hal 7	a	–H	–H	–H	–O–CH_3	–O–C_2H_5	–O–CH_3	–H	–H	5.6	0.75
Hal 8	a	–H	–H	–H	–O–CH_3	–O–C_3H_7	–O–CH_3	–H	–H	6.6	0.82
Hal 9	a	–H	–H	–H	–O–CH_3	–O–C_4H_9	–O–CH_3	–H	–H	< 2.1	−0.30
Hal 10	a	–H	–H	–H	–O–C_2H_5	–O–C_2H_5	–O–CH_3	–H	–H	1.2	0.08
Hal 11	a	–H	–H	–H	–O–C_2H_5	–O–CH_3	–O–C_2H_5	–H	–H	< 1.2	−0.30
Hal 12	a	–H	–H	–H	–O–C_2H_5	–O–C_2H_5	–O–C_2H_5	–H	–H	< 1.3	−0.30
Hal 13	a	–H	–H	–H	–O–C_3H_7	–O–CH_3	–O–CH_3	–H	–H	< 1.2	−0.30
Hal 14	c	–H	–H	–H			–O–CH_3	–H	–H	0.7	−0.15
Hal 15	c	–H	–H	–H			–H	–H	–H	< 0.7	−0.46
Hal 16	a	–H	–H	–O–CH_3	–H	–C_2H_5	–O–CH_3	–H	–H	15	1.18
Hal 17	a	–H	–H	–O–CH_3	–H	–CH_3	–O–CH_3	–H	–H	6.2	0.79
Hal 18	a	–H	–H	–H	–O–CH_3	–O–CH_3	–S–CH_3	–H	–H	3.6	0.56
Hal 19	a	–H	–H	–H	–O–CH_3	–S–CH_3	–O–CH_3	–H	–H	9.5	0.98
Hal 20	a	–H	–H	–H	–O–CH_3	–O–CH_3	–S–C_2H_5	–H	–H	3.7	0.57
Hal 21	a	–H	–H	–H	–O–C_2H_5	–S–CH_3	–O–CH_3	–H	–H	3.7	0.57
Hal 22	a	–H	–H	–H	–O–C_2H_5	–O–CH_3	–S–CH_3	–H	–H	< 1.5	−0.30
Hal 23	a	–H	–H	–H	–O–CH_3	–O–C_2H_5	–S–CH_3	–H	–H	4.3	0.63
Hal 24	a	–H	–H	–H	–O–CH_3	–S–C_2H_5	–O–CH_3	–H	–H	12	1.08
Hal 25	a	–H	–H	–H	–O–CH_3	–O–C_2H_5	–S–C_2H_5	–H	–H	2	0.30
Hal 26	a	–H	–H	–H	–O–C_2H_5	–S–C_2H_5	–O–CH_3	–H	–H	3.9	0.59
Hal 27	a	–H	–H	–H	–O–C_2H_5	–O–CH_3	–S–C_2H_5	–H	–H	< 1.6	−0.30
Hal 28	a	–H	–H	–H	–O–C_2H_5	–S–CH_3	–O–C_2H_5	–H	–H	< 1.3	−0.30
Hal 29	a	–H	–H	–H	–O–C_2H_5	–O–C_2H_5	–S–CH_3	–H	–H	2	0.30
Hal 30	a	–H	–H	–H	–O–C_2H_5	–O–C_2H_5	–S–C_2H_5	–H	–H	< 2.1	−0.30
Hal 31	a	–H	–H	–H	–O–C_2H_5	–S–C_2H_5	–O–C_2H_5	–H	–H	< 1.6	−0.30
Hal 32	a	–H	–H	–H	–O–CH_3	–S–C_3H_7	–O–CH_3	–H	–H	14	1.15
Hal 33	a	–H	–H	–H	–O–CH_3	–S–C_4H_9	–O–CH_3	–H	–H	3.7	0.57
Hal 34	a	–CH_3	–H	–H	–H	–O–CH_3	–H	–H	–H	3.3	0.75
Hal 35	a	–CH_3	–H	–O–CH_3	–H	–H	–O–CH_3	–H	–H	2.1	0.55
Hal 36	a	–CH_3	–H	–O–CH_3	–H	–O–CH_3	–H	–H	–H	2.8	0.68
Hal 37	a	–CH_3	–H	–H	–O–CH_3	–O–CH_3	–H	–H	–H	0.4	−0.17
Hal 38	a	–CH_3	–H	–H	–O–CH_3	–O–CH_3	–O–CH_3	–H	–H	1.6	0.43
Hal 39	a	–CH_3	–H	–O–CH_3	–H	–O–CH_3	–O–CH_3	–H	–H	9.4	1.20
Hal 40	a	–CH_3	–H	–O–CH_3	–O–CH_3	–O–CH_3	–H	–H	–H	< 2.8	−0.30
Hal 41	a	–CH_3	–H	–O–CH_3	–O–CH_3	–H	–O–CH_3	–H	–H	2.4	0.61
Hal 42	a	–CH_3	–H	–O–CH_3	–O–CH_3	–H	–H	–O–CH_3	–H	6.3	1.03
Hal 43	a	–CH_3	–H	–O–CH_3	–H	–O–CH_3	–H	–O–CH_3	–H	7.5	1.11
Hal 44	a	–CH_3	–H	–O–CH_3	–H	–O–C_2H_5	–O–CH_3	–H	–H	8.5	1.16
Hal 45	a	–CH_3	–H	–O–CH_3	–H	–O–C_3H_7	–O–CH_3	–H	–H	6.9	1.07
Hal 46	a	–CH_3	–H	–H	–O–CH_3	–O–CH_2–C_6H_5	–O–CH_3	–H	–H	3.2	0.74
Hal 47	a	–CH_3	–H	–O–CH_3	–O–CH_3	–O–CH_3	–O–CH_3	–H	–H	6.3	1.03
Hal 48	c	–CH_3	–H	–H			–H	–H	–H	1.9	0.51
Hal 49	b	–CH_3	–H			–O–CH_3	–H	–H	–H	2.2	0.57
Hal 50	c	–CH_3	–H	–H			–O–CH_3	–H	–H	1.5	0.41
Hal 51	c	–CH_3	–H	–H			–H	–O–CH_3	–H	7.1	1.08
Hal 52	c	–CH_3	–H	–O–CH_3			–H	–H	–H	5.3	0.95
Hal 53	b	–CH_3	–H			–H	–H	–O–CH_3	–H	8.8	1.17
Hal 54	c	–CH_3	–H	–O–CH_3			–O–CH_3	–H	–H	5.7	0.99
Hal 55	c	–CH_3	–H	–H			–O–CH_3	–O–CH_3	–H	5.9	1.00
Hal 56	a	–CH_3	–H	–O–CH_3	–H	–CH_3	–O–CH_3	–H	–H	41	1.84
Hal 57	a	–CH_3	–H	–O–CH_3	–H	–C_2H_5	–O–CH_3	–H	–H	70	2.08
Hal 58	a	–CH_3	–H	–O–CH_3	–H	–C_3H_7	–O–CH_3	–H	–H	79	2.13
Hal 59	a	–CH_3	–H	–O–CH_3	–H	–C_4H_9	–O–CH_3	–H	–H	24	1.61

(*continued*)

Table 2. *(continued)*

Compound	Structure	R_a	R_b	R_2	R_3	R_4	R_5	R_6	$R_{N1} = R_{N2}$	Activity of racemates (MU)	Activity used in CoMFA [log(MU)]
Hal 60	a	$-CH_3$	–H	$-O-CH_3$	–H	$-CH_2-CH(CH_3)_2$	$-O-CH_3$	–H	–H	25	1.63
Hal 61	a	$-CH_3$	–H	$-O-CH_3$	–H	$-C_5H_{11}$	$-O-CH_3$	–H	–H	10	1.23
Hal 62	a	$-CH_3$	–H	$-O-CH_3$	–H	$-S-CH_3$	$-O-CH_3$	–H	–H	40	1.83
Hal 63	a	$-CH_3$	–H	$-O-CH_3$	–H	$-S-CH(CH_3)_2$	$-O-CH_3$	–H	–H	35	1.77
Hal 64	a	–H	–H	$-O-CH_3$	–H	–Br	$-O-CH_3$	–H	–H	18	1.26
Hal 65	a	$-CH_3$	–H	$-O-CH_3$	–H	–Br	$-O-CH_3$	–H	–H	170	2.46
Hal 66	a	$-CH_3$	–H	$-O-CH_3$	–H	–I	$-O-CH_3$	–H	–H	170	2.46

Table 3. QSAR dataset II.

Compound	Structure	R_a	R_4	R_5	R_6	R_7	R_{N1}	R_{N2}	Activity of racemates (MU)	Activity used in CoMFA [log(MU)]
Hal 67	d	–H	–H	–H	–H	–H	–H	–H	< 1.7	−0.30
Hal 68	d	–H	–H	–H	–H	–H	$-CH_3$	$-CH_3$	3	0.48
Hal 69	d	–H	–H	–H	–H	–H	$-C_2H_5$	$-C_2H_5$	3.4	0.53
Hal 70	d	–H	–H	–H	–H	–H	$-C_3H_7$	$-C_3H_7$	1	0
Hal 71	d	–H	–H	–H	–H	–H	$-CH_3$	$-CH(CH_3)_2$	16	1.20
Hal 72	d	–H	–H	–H	–H	–H	$-CH(CH_3)_2$	$-CH(CH_3)_2$	10	1.00
Hal 73	d	–H	–H	–H	–H	–H	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$	3.7	0.57
Hal 74	d	$-CH_3$	–H	–H	–H	–H	–H	–H	7.6	1.4
Hal 75	d	–H	–H	$-O-CH_3$	–H	–H	$-CH_3$	$-CH_3$	34	1.53
Hal 76	d	–H	–H	$-O-CH_3$	–H	–H	$-CH(CH_3)_2$	$-CH(CH_3)_2$	33	1.52
Hal 77	d	–H	–H	$-O-CH_3$	–H	–H	$-CH_3$	$-CH(CH_3)_2$	61	1.79
Hal 78	d	$-CH_3$	–H	$-O-CH_3$	–H	–H	–H	–H	65	2.07
Hal 79	d	–H	–OH	–H	–H	–H	$-CH_3$	$-CH(CH_3)_2$	23	1.36
Hal 80	d	–H	$-O-CH_3$	–H	–H	–H	$-CH_3$	$-CH(CH_3)_2$	12	1.08
Hal 81	d	–H	–OH	–H	–H	–H	$-C_2H_5$	$-C_2H_5$	17	1.23
Hal 82	d	–H	–OH	–H	–H	–H	$-CH(CH_3)_2$	$-CH(CH_3)_2$	18	1.26
Hal 83	d	–H	–OH	–H	–H	–H	$-CH_3$	$-CH_3$	31	1.49
Hal 84	d	–H	–H	$-O-CH_3$	$-O-CH_3$	–H	$-CH_3$	$-CH(CH_3)_2$	< 5.6	−0.30
Hal 85	e	–H	–H			–H	$-CH_3$	$-CH(CH_3)_2$	< 5.3	−0.30
Hal 86	d	–H	–H	–H	–OH	–H	$-CH_3$	$-CH_3$	< 3.2	−0.30
Hal 87	d	–H	–H	–H	–F	–H	$-C_2H_5$	$-C_2H_5$	< 3.6	−0.30
Hal 88	d	–H	–H	–H	$-O-CH_3$	–H	$-CH_3$	$-CH(CH_3)_2$	< 6.1	−0.30
Hal 89	d	–H	–H	–H	–H	$-O-CH_3$	$-CH_3$	$-CH(CH_3)_2$	< 4.4	−0.30

2.4 PRESS Value

The press value is the sum of the squares of the deviation of the predictive values from the observed values. It is defined by means of the following formula:

$$PRESS = (y_{pred} - y_{obs})^2$$

y_{pred}: predictive target variable

y_{obs}: observed target variable

3 Results and Discussion

3.1 Determination of the Bioactive Conformation

The structures of amphetamines and tryptamines were compared in order to determine the relevant conformations for QSAR analyses. Appropriately substituted derivatives of both basic structures possess a high agonistic affinity for the 5-HT_{2A}-receptor. In accordance with Lyon et al. [22] and Kang, Johnson and Green [23] the planar six-membered ring systems were superimposed so that position 4 of the tryptamines corresponded to position 1 of the phenylalkanamines, position 5 of the tryptamines to position 2 of the phenylalkanamines etc. (Figure 1). This superimposition makes sense since similar effect-increasing or effect-diminishing influences have been observed at the corresponding places in the two structures in numerous investigations [22, 24, 25, 26].

All compounds were constructed and employed in their uncharged form. It is true that the molecules under consideration are largely in protonated form at physiological pH. However, there has been controversial discussion on the situation at the receptor [10, 27, 28].

Table 4. QSAR dataset III.

Compound	Structure	R_a	R_b	R_2	R_3	R_4	R_5	R_6	R_{N1}	R_{N2}	Activity of racemates (MU)	Activity used in CoMFA [log(MU)]
Hal 90	a	$-CH_3$	–H	$-O-CH_3$	–H	$-NO_2$	$-O-CH_3$	–H	–H	–H	80	2.13
Hal 91	a	–H	–H	$-O-CH_3$	–H	–I	$-O-CH_3$	–H	–H	–H	21	1.32
Hal 92	a	$-CH_3$	–H	$-O-CH_3$	–H	$-S-C_2H_5$	$-O-CH_3$	–H	–H	–H	52	1.95
Hal 93	a	–H	–H	$-O-CH_3$	–H	–F	$-O-CH_3$	–H	–H	–H	< 1.0	−0.30
Hal 94	a	–H	–H	–H	$-O-CH_3$	$-O-CH_2-CH=CH_2$	$-O-CH_3$	–H	–H	–H	11	1.04
Hal 95	a	$-CH_3$	–H	$-O-CH_3$	–H	$-S-C_3H_7$	$-O-CH_3$	–H	–H	–H	60	2.01
Hal 96	a	–H	$-O-CH_3$	$-O-CH_3$	–H	–Br	$-O-CH_3$	–H	–H	–H	23	1.36
Hal 97	a	–H	$-O-CH_3$	$-O-CH_3$	–H	$-CH_3$	$-O-CH_3$	–H	–H	–H	14	1.15
Hal 98	a	–H	$-O-CH_3$	–H	$-O-CH_3$	$-O-CH_3$	$-O-CH_3$	–H	–H	–H	< 1.5	−0.30
Hal 99	a	$-CH_3$	–H	–H	$-O-CH_3$	–Br	$-O-CH_3$	–H	–H	–H	48	1.91
Hal 100	f	$-CH_3$	–H	–Br	–H			–H	–H	–H	1	0.23
Hal 101	a	–H	–H	$-O-C_2H_5$	–H	–Br	$-O-CH_3$	–H	–H	–H	10	1.00
Hal 102	a	–H	–H	–Br	–H	$-O-CH_3$	$-O-CH_3$	–H	–H	–H	0.8	−0.10
Hal 103	a	–H	–H	$-O-CH_3$	–H	–Cl	$-O-CH_3$	–H	–H	–H	9.1	0.96
Hal 104	a	$-CH_3$	–H	–H	$-O-CH_3$	$-O-C_2H_5$	$-O-CH_3$	–H	–H	–H	6.6	1.05
Hal 105	a	–H	–H	$-O-CH_3$	$-CH_3$	$-CH_3$	$-O-CH_3$	–H	–H	–H	9.6	0.98
Hal 106	g	–H	–H	$-O-CH_3$			$-O-CH_3$	–H	–H	–H	14	1.15
Hal 107	h	–H	–H	$-O-CH_3$			$-O-CH_3$	–H	–H	–H	24	1.38
Hal 108	i	–H	–H	$-O-CH_3$			$-O-CH_3$	–H	–H	–H	9.6	0.98
Hal 109	a	–H	–H	$-O-CH_3$	–H	$-C_3H_7$	$-O-CH_3$	–H	–H	–H	35	1.54
Hal 110	a	–H	–H	–H	$-O-CH_3$	$-O-CH_2$-(cyp)[a]	$-O-CH_3$	–H	–H	–H	4.4	0.64
Hal 111	a	–H	–H	$-O-CH_3$	–H	$-S-C_2H_5$	$-O-CH_3$	–H	–H	–H	16	1.20
Hal 112	a	–H	–H	$-O-CH_3$	–H	$-S-CH(CH_3)_2$	$-O-CH_3$	–H	–H	–H	22	1.34
Hal 113	a	–H	–H	$-O-CH_3$	–H	$-S-C_3H_7$	$-O-CH_3$	–H	–H	–H	16	1.20
Hal 114	a	–H	–H	$-O-CH_3$	–H	$-S-CH_2$-(cyp)[a]	$-O-CH_3$	–H	–H	–H	8.2	0.91
Hal 115	a	–H	–H	$-O-CH_3$	–H	$-S-C(CH_3)_3$	$-O-CH_3$	–H	–H	–H	4.1	0.61
Hal 116	a	–H	–H	$-O-CH_3$	–H	$-S-C_2H_4-O-CH_3$	$-O-CH_3$	–H	–H	–H	10	1.00
Hal 117	a	–H	–H	$-O-CH_3$	–H	$-S-CH(CH_3)-C_2H_5$	$-O-CH_3$	–H	–H	–H	4.1	0.61
Hal 118	a	–H	–H	$-O-CH_3$	–H	$-S-C_2H_4-F$	$-O-CH_3$	–H	–H	–H	32	1.51
Hal 119	a	–H	–H	–H	$-O-CH_3$	$-CH_3$	$-O-CH_3$	–H	–H	–H	3.1	0.49
Hal 120	k			$-O-CH_3$	–H	$-CH_3$	$-O-CH_3$	–H	–H	–H	15	1.18
Hal 121	a	–H	–OH	–H	$-O-CH_3$	$-O-CH_3$	–H	–H	–H	–H	< 2.2	−0.30
Hal 122	a	$-CH_3$	–H	$-O-CH_3$	–H	$-CH(CH_3)-C_2H_5$	$-O-CH_3$	–H	–H	–H	11	1.27
Hal 123	a	$-CH_3$	–H	$-O-CH_3$	–H	–Cl	$-O-CH_3$	–H	–H	–H	130	2.34
Hal 124	a	$-CH_3$	–H	$-O-CH_3$	–H	$-C_2H_4-F$	$-O-CH_3$	–H	–H	–H	110	2.27
Hal 125	a	$-CH_3$	–H	$-O-CH_3$	–H	$-CH_3$	–H	$-O-CH_3$	–H	–H	13	1.34
Hal 126	g	$-CH_3$	–H	$-O-CH_3$			$-O-CH_3$	–H	–H	–H	20	1.53
Hal 127	h	$-CH_3$	–H	$-O-CH_3$			$-O-CH_3$	–H	–H	–H	19	1.51
Hal 128	a	$-CH_3$	–H	$-O-CH_3$	$-CH_3$	$-CH_3$	$-O-CH_3$	–H	–H	–H	11	1.27
Hal 129	a	–H	–H	$-O-CH_3$	–H	$-S-C_2H_5$	$-O-CH_3$	–H	–OH	–H	23	1.36
Hal 130	a	–H	–H	$-O-CH_3$	–H	$-S-C_3H_7$	$-O-CH_3$	–H	–OH	–H	17	1.23
Hal 131	a	–H	–H	$-O-CH_3$	–H	$-S-CH(CH_3)-C_2H_5$	$-O-CH_3$	–H	–OH	–H	3.7	0.57
Hal 132	a	–H	–H	–H	$-O-CH_3$	$-O-CH(CH_3)_2$	$-O-CH_3$	–H	–H	–H	5	0.70
Hal 133	a	–H	–H	–H	$-O-CH_3$	$-O-CH_3$	$-O-CH_3$	–H	$-CH_3$	$-CH_3$	< 0.6	−0.52
Hal 134	a	–H	–H	–H	$-O-CH_3$	$-O-CH_2-C(CH_3)=CH_2$	$-O-CH_3$	–H	–H	–H	5.9	0.77
Hal 135	l	$-CH_3$	–H	–H			–H	–H	–H	–H	< 1.7	−0.30
Hal 136	c	$-CH_3$	–H	–H			–H	–H	–OH	–H	1.9	0.51
Hal 137	m	$-CH_3$	–H	–H	$-O-CH_3$			–H	–H	–H	< 1.5	−0.30
Hal 138	a	–H	–H	–H	$-O-CH_3$	$-O-C_2H_5$	–H	–H	–H	–H	< 0.8	−0.40
Hal 139	a	$-CH_3$	–H	$-O-CH_3$	–H	$-O-CH_3$	$-O-C_2H_5$	–H	–H	–H	5	0.93
Hal 140	a	–H	–H	–H	$-O-CH_3$	$-O-C_2H_4-C_6H_5$	$-O-CH_3$	–H	–H	–H	< 2.4	−0.30
Hal 141	a	–H	–H	–H	–H	–H	–H	–H	–H	–H	< 0.1	−1.30
Hal 142	a	–H	–H	–H	–H	–Cl	–H	–H	–H	–H	< 0.4	−0.70
Hal 143	a	–H	–H	$-S-CH_3$	$-O-CH_3$	$-O-CH_3$	–H	–H	–H	–H	< 1.2	−0.30
Hal 144	a	–H	–H	$-O-CH_3$	$-S-CH_3$	$-O-CH_3$	–H	–H	–H	–H	< 1.2	−0.30
Hal 145	a	–H	–H	$-O-CH_3$	$-O-CH_3$	$-S-CH_3$	–H	–H	–H	–H	< 1.8	−0.30
Hal 146	a	$-CH_3$	–H	$-O-CH_3$	–H	$-C_2H_5$	$-S-CH_3$	–H	–H	–H	16	1.43

(*continued*)

Table 4. (*continued*)

Compound	Structure	R_a	R_b	R_2	R_3	R_4	R_5	R_6	R_{N1}	R_{N2}	Activity of racemates (MU)	Activity used in CoMFA [log(MU)]
Hal 147	a	$-CH_3$	–H	$-S-CH_3$	–H	$-CH_3$	$-O-CH_3$	–H	–H	–H	3.5	0.77
Hal 148	a	$-CH_3$	–H	$-O-CH_3$	–H	$-CH_3$	$-S-CH_3$	–H	–H	–H	7.1	1.08
Hal 149	c	$-CH_3$	–H	–H			–H	–H	$-O-CH_3$	–H	< 1.5	−0.30
Hal 150	f	$-CH_3$	–H	$-CH_3$	–H			–H	$-CH_3$	–H	< 0.9	−0.30
Hal 151	c	$-CH_3$	–H	–H			–H	–H	$-CH_2-CH=CH_2$	–H	< 1.5	−0.30
Hal 152	c	$-CH_3$	–H	–H			–H	–H	$-CH(CH_3)_2$	–H	< 1.1	−0.30
Hal 153	c	$-CH_3$	–H	–H			–H	–H	$-C_2H_4-O-CH_3$	–H	< 1.6	−0.30
Hal 154	c	$-CH_3$	–H	–H			–H	–H	$-C_3H_7$	–H	< 1.4	−0.30
Hal 155	a	$-CH_3$	–H	$-O-CH_3$	–H	–H	$-O-CH_3$	–H	$-CH_3$	–H	< 1.1	−0.30

[a] (cyp) = cyclopropyl-

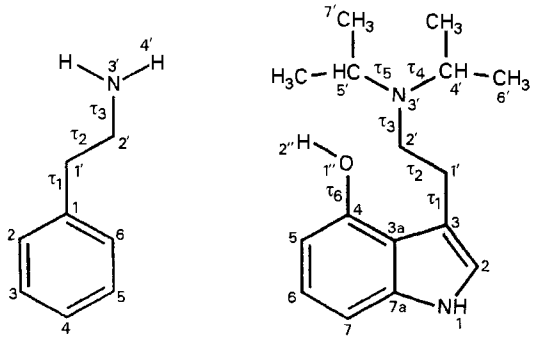

Figure 1. Phenethylamine and tryptamine derivative with relevant rotable bonds.

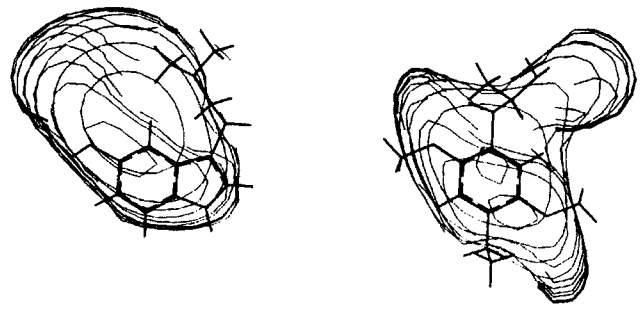

Figure 2. Negative isopotential lines of 5-Hydroxy-N,N- dimethyltryptamine and 4-ethyl-2,5-dimethoxyphenyl-2-propaneamine; contour level − 1 kcal/mol.

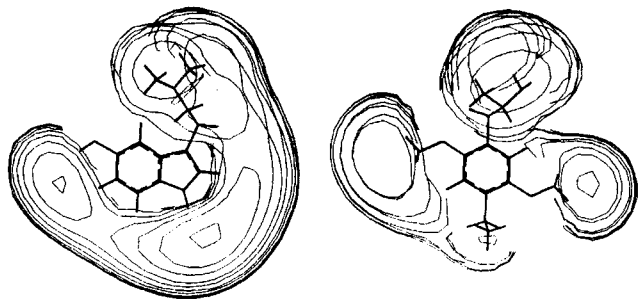

Figure 3. Positive isopotential lines of 5-Hydroxy-N,N-dimethyltryptamine and 4-ethyl-2,5-dimethoxyphenyl-2-propaneamine; contour level + 1 kcal/mol.

In the literature one can find models with ligands bound to the receptor in the protonated form [10, 27] as well as models in which you have a deprotonation before binding to the receptor [28]. So using the uncharged molecules in QSAR studies is justified even if a protonated substance binds to the receptor in reality, because the positive charge of the ligand would be neutralized by a negative charge on the receptor protein [27]. For example it was found that for histamine the distribution of charges on the aromatic ring is identical for unprotonated and for ionic bound protonated ligands [29].

A systematic conformational analysis was carried out on one derivative of the two basic structures to determine an energetically sensible conformation, in which the pharmacophoric nitrogen atoms of the side chain were almost superimposed in their fit. The molecules chosen were those named in the "Methods" section for which X-ray structures are available for the uncharged molecules [30, 31]. When the lone pair of electrons at the nitrogen atom were taken into account the torsion angles listed in Table 1 were obtained. The nitrogen atoms of the two basic structures are situated in practically the same position after both, molecular-mechanical and semiempirical geometry optimization (AM1), and the energy difference from the appropriate energetically-favourable conformer is acceptable for both amphetamine and tryptamine derivatives. Therefore this conformation of the molecules' respective basic structures was used for all the compounds of the dataset without additional geometry optimization. Höltje and Briem obtained similar results in a conformational analysis of other derivatives of the two groups of substances [32]. Comparison of isopotential lines (Figures 2 and 3) provides confirmation for the overall conformation determined in this manner. The distribution of positive and negative charges is very similar for the two structures in spite of their fundamental difference.

3.2 Investigations Utilizing the Initial Data Set

The basis for the present investigation was a data set with which a classical QSAR analysis was carried out in 1990 [11]. In that analysis 13 of the 63 molecules remained inactive up to the highest dose tested and were omitted from the investigation. These

Table 5. Results of the CoMFA-analyses, dataset I, different location of the grid (grid-shift 1 Å).

Grid shifted along	Cross-validated		Non-cross-validated		Number of components
	q^2	s_{pred}	r^2	s_{est}	
x-axis	0.744	0.421	0.923	0.230	7
y-axis	0.776	0.403	0.947	0.196	10
z-axis	0.778	0.398	0.933	0.218	9
x- and y-axis	0.785	0.392	0.938	0.211	9
x- and z-axis	0.813	0.366	0.934	0.217	9
y- and z-axis	0.765	0.410	0.935	0.216	9
x-, y- and z-axis	0.682	0.460	0.858	0.308	5
not shifted	0.803	0.375	0.943	0.202	9

Table 6. Results of the CoMFA-analyses, dataset I, different grid-spacing.

Grid-spacing	Cross-validated		Non-cross-validated		Number of components
	q^2	s_{pred}	r^2	s_{est}	
1 Å	0.798	0.380	0.944	0.200	9
2 Å	0.803	0.375	0.943	0.202	9

"inactive" molecules were included in the new CoMFA analysis; they were assigned an activity of half the mescaline units of the highest dose at which they were tested within an upper limit of 0.5 MU. In addition, three highly active substances, namely Hal 64, 65 and 66, were also included. The 66 molecules of the initial data set are listed in Table 2 together with their biological effects in log(MU) used in the CoMFA-analysis.

Table 5 lists the q^2 values and the standard deviations of the cross-validated analyses as a function of the number of components and the position of the grid at which the CoMFA interaction energies were calculated. The excellent analysis results are largely independent of the grid position. Only in one case, involving considerable displacement of the grid in all three co-ordinate axes, there was an appreciable deterioration of the results. Reduction of the distance between the grid points to 1 Å (Table 6), thus increasing the data to be processed eight-fold, made practically no difference to the result. Hence, such an increase in the amount of computing is not justified. When a noncross-validated analysis is carried out with 9 components without grid displacement then the correlation coefficient is 0.943 with a standard deviation of 0.202.

3.3 Testing the Model and Determining the Optimum Number of Components

There is still a wide degree of disagreement concerning the criteria, that ought to be employed to decide on the optimum number of components to be extracted. Alongside selection methods maximizing q^2 or minimizing standard deviations, it has also been suggested that models with fewer components be employed when the increase in q^2 is "slight" [21]. In the analysis mentioned above 9 components were extracted since this model resulted in the lowest standard deviation with a higher correlation coefficient compared to the model with 7 components (Table 7). In any case this cross-validated analysis was a robust one, because the q^2-value obtained with more than 4 components changed only in a neglectable way. Nevertheless it had to be checked if consideration of up to 10 components is acceptable for this data set. Since Shulgin [17] has tested further biological compounds in addition to the substances in data set I, data set III was set up containing 66 further phenylalkanamines, whose effects were calculated in MU, as was done for data set I. These compounds can then be used to assess the predictive quality of the QSAR model that has been set up. Furthermore, it was intended to investigate, by varying the number of components extracted, which model produced the best predictions for comparison with the experimentally determined values. The substitution patterns of the aromatic ring and of the side chain were more varied in data set III, so that it was necessary to extrapolate a not inconsiderable proportion of the target variables in the case of some compounds. Thibaut et al. [33] considered these extrapolations to be very questionable. Hence, the problem of the reliability of extrapolated values was also investigated.

Table 7. Correlation coefficients and standard deviations with different number of components.

Components	1	2	3	4	5
q^2	0.539	0.621	0.715	0.766	0.774
s_{pred}	0.537	0.490	0.429	0.392	0.388
Components	6	7	8	9	10
q^2	0.784	0.797	0.799	0.803	0.800
s_{pred}	0.383	0.375	0.376	0.375	0.381

Table 8 lists the predictive values for compounds Hal 90 to Hal 155 as a function of the parameters described. Basically all models appear suitable for the approximate prediction of the experimentally determined activity data. Care is necessary in the case of substances whose predictive effect is less than 5 MU, since these are frequently compounds where no effect was observable in the experiment. The PRESS value (see Methods) is suitable for a precise comparison of the predictive performance of the various models. The target variable of the QSAR analysis, the logarithm of the mescaline units, must be used in this calculation. The PRESS values of the models with between five and nine components are very similar, but appreciably poorer for three components (Table 8). These results do not provide support for the theory that the model with the lower number of components is to be preferred when there is only a slight improvement in the correlation coefficients and standard deviation. It appears appropriate to consider the procedure involving up to ten components when carrying out QSAR analyses. The current data do not allow a decision to be made concerning whether extrapolated or nonextrapolated data are more to be trusted. In any case the predictive data should be reviewed critically if there is a great divergence between extrapolated and nonextrapolated values.

Table 8. Prediction of the activities of Hal 90 to Hal 155 using models with different numbers of components.

Compound	Predicted MU, with extrapolation			Predicted MU, without extrapolation			MU (R/S-corrected),
	3 comp.	5 comp.	9 comp.	3 comp.	5 comp.	9 comp.	experimental
Hal 90	64	190	360	60	140	220	140
Hal 91	10	21	40	9.3	19	34	21
Hal 92	98	130	96	98	130	96	88
Hal 93	5.3	5.6	3.1	4.8	3.9	1.7	< 1.0
Hal 94	2.0	2.6	3.0	2.1	2.3	2.2	11
Hal 95	110	97	120	110	96	120	100
Hal 96	10	18	24	8.6	15	20	23
Hal 97	13	13	13	10	11	11	14
Hal 98	1.6	2.4	1.8	1.3	1.8	1.1	< 1.5
Hal 99	7.0	23	26	7.0	15	14	82
Hal 100	6.3	5.7	3.7	4.9	4.8	3.6	1.7
Hal 101	8.6	17	23	7.9	15	20	10
Hal 102	0.7	0.7	1.2	0.5	0.5	0.8	0.8
Hal 103	9.1	15	15	8.4	13	14	9.1
Hal 104	9.3	20	24	9.3	20	24	11
Hal 105	1.4	2.3	3.5	1.4	2.2	4.0	9.6
Hal 106	1.3	1.9	2.8	1.1	1.7	2.5	14
Hal 107	1.8	3.0	4.2	1.2	1.8	2.7	24
Hal 108	1.4	2.2	3.3	1.3	1.7	2.2	9.6
Hal 109	17	13	13	17	13	13	35
Hal 110	2.3	2.2	3.4	2.7	1.8	1.6	4.4
Hal 111	20	18	12	20	18	12	16
Hal 112	20	12	7.8	16	8.8	6.0	22
Hal 113	23	14	15	23	14	15	16
Hal 114	17	10	8.4	16	9.4	7.5	8.2
Hal 115	15	8.7	5.5	12	6.7	4.8	4.1
Hal 116	14	4.7	4.1	16	5.5	4.0	10
Hal 117	19	11	6.9	15	7.8	5.9	4.1
Hal 118	19	14	11	21	14	8.8	32
Hal 119	2.1	3.3	2.7	2.2	3.4	2.7	3.1
Hal 120	24	28	27	16	18	18	15
Hal 121	0.2	0.2	0.2	0.2	0.2	0.2	< 2.2
Hal 122	34	41	71	30	35	64	19
Hal 123	45	98	110	45	96	110	220
Hal 124	110	280	400	77	130	160	190
Hal 125	180	120	370	127	110	390	22
Hal 126	6.2	13	22	4.4	8.9	15	34
Hal 127	9.3	20	33	6.0	12	20	32
Hal 128	7.0	15	26	7.0	15	29	19
Hal 129	19	18	13	20	18	13	23
Hal 130	22	14	16	22	14	15	17
Hal 131	17	9.8	6.3	18	9.8	6.4	3.7
Hal 132	2.2	2.8	1.9	4.2	4.9	4.2	5
Hal 133	1.5	2.6	2.4	4.7	4.8	1.6	< 0.6
Hal 134	2.6	2.3	4.3	6.7	3.1	2.7	5.9
Hal 135	1.9	1.2	2.2	2.2	1.5	2.8	< 2.9
Hal 136	3.1	2.0	2.5	3.6	2.5	3.0	3.2
Hal 137	1.3	1.1	0.4	1.7	1.8	0.8	< 2.6
Hal 138	0.3	0.4	0.4	0.8	0.8	0.9	< 0.8
Hal 139	3.6	1.8	2.0	7.6	2.9	4.2	8.5
Hal 140	2.7	1.4	1.9	2.4	1.2	1.2	< 2.4
Hal 141	1.7	0.6	0.3	1.8	0.7	0.4	< 0.1
Hal 142	2.5	3.2	9.3	2.4	2.8	7	< 0.4
Hal 143	0.2	0.2	0.1	0.2	0.1	0.1	< 1.2
Hal 144	0.2	0.3	0.3	0.3	0.3	0.3	< 1.2
Hal 145	2.0	2.6	1.9	1.8	2.1	1.6	< 1.8
Hal 146	58	69	70	38	47	60	27
Hal 147	26	74	120	24	71	130	6.0
Hal 148	74	82	82	57	62	61	12
Hal 149	3.6	2.3	2.9	3.6	2.4	3.1	< 2.6

(*continued*)

Table 8. (*continued*)

Compound	Predicted MU, with extrapolation			Predicted MU, without extrapolation			MU (R/S-corrected), experimental
	3 comp.	5 comp.	9 comp.	3 comp.	5 comp.	9 comp.	
Hal 150	4.8	4.8	3.0	4.5	4.6	3.7	< 1.5
Hal 151	3.2	2.0	2.5	3.4	2.2	2.7	< 2.6
Hal 152	3.3	2.1	2.8	3.1	2.0	2.4	< 1.9
Hal 153	3.5	2.1	2.6	3.3	2.0	2.4	< 2.7
Hal 154	3.6	2.0	2.5	3.1	2.0	2.4	< 2.4
Hal 155	30	17	3.4	27	15	3.0	< 1.9
PRESS	26.49	20.28	20.16	27.12	20.72	19.96	

3.4 Inclusion of Data Set II

Like the amphetamines the hallucinogenic tryptamine derivatives exert their effect via the 5-HT_{2A}-receptor. Hence, the question of whether tryptamines can be included in a QSAR analysis with phenylalkanamines, in spite of their differing basic structure, is of interest. Initially all 23 compounds of data set II were included (Table 3). The inactive compounds were again assigned an activity of 0.5 MU. A further QSAR analysis was carried out with the enlarged data set of 89 molecules. Here it was found that the enlargement to include tryptamines was successful, although the correlation coefficient of 0.731 was somewhat poorer than in the analysis in which only phenylalkanamines were included (Table 9).

The tryptamine derivatives added to the data set included substances that had only been tested up to relatively high doses and had not been found to be active up to these levels. A not inconsiderable error can occur when these substances for which activity has not been found, are included in the analysis with the maximum activity assigned of 0.5 MU. In order to reduce the error as much as possible a further analysis was carried out where all compounds were excluded that had been found to be inactive up to the highest dose tested if this dose corresponded to more than 3 MU. This applied to the tryptamine derivatives Hal 84 to Hal 89; it also applied to the amphetamine derivative Hal 40. Exclusion of the compounds named before brought about an appreciable increase in the correlation coefficient, which was now of the order of magnitude of that obtained in the analysis carried out exclusively on phenylalkanamines (Table 9).

3.5 Inclusion of the QSAR Data Set III

It is advisable to include as many substances as possible in the construction of the QSAR model in order to obtain a description of the structure–activity relationships of the hallucinogens, that is as detailed and exact as possible. Hence, we have also included data set III in a further CoMFA model (Table 4). Inactive molecules were only included in this data set if they had been tested up to a dose that corresponded to 3 MU or less.

The following 148 compounds were included in the construction of the final QSAR model: Hal 1 to Hal 39, Hal 41 to Hal 83 and Hal 90 to Hal 155. The results of the analysis (Table 10) show that the correlation coefficient drops slightly. This is understandable in view of the multiplicity of new structural elements in data set III. However, the q^2 value is still excellent and the results are very similar if a smaller number of groups is used in the cross-validation process than with the leave-one-out method; hence, the inclusion of data set III can be regarded as an important and valuable extension of the analysis.

3.6 Interpretation of the CoMFA Plots

The steric and electrostatic results of the final CoMFA analysis are presented graphically in Figures 5 and 6. The colors make a semi-quantitative estimate of the appropriate influences in particular regions possible. Different contour levels were used in the figures in order to improve the visualization of the results. In the last analysis the steric field influenced the model to the extent of 56.6%. The evaluation of the CoMFA plots containing the whole information from all three data sets, reveals the relationships described below (the positions reported refer to the phenylalkanamines).

Effect-increasing steric regions (Figure 5) are to be found (1) in very pronounced form in position 4 at small to moderate distance from the aromatic ring, (2) at the α-methyl group of the side chain, also with a strong influence on the activity, and (3) in the form of a small region of slight influence at a moderate distance from position 6 of the aromatic ring. The side chain of the tryptamines also lies in this region.

Table 9. Results of the CoMFA-analyses, dataset I and II, different consideration of inactive compounds.

Inactive compounds	Cross-validated		Non–Cross-validated		Number of components
	q^2	s_{pred}	r^2	s_{est}	
all	0.731	0.428	0.920	0.233	6
only if < 3 MU	0.791	0.374	0.949	0.186	9

Table 10. Results of the CoMFA-analysis, dataset I, II and III.

Inactive compounds	Cross-validated		Non-Cross-validated		Number of components
	q^2	s_{pred}	r^2	s_{est}	
only if < 3 MU	0.730	0.427	0.893	0.269	8

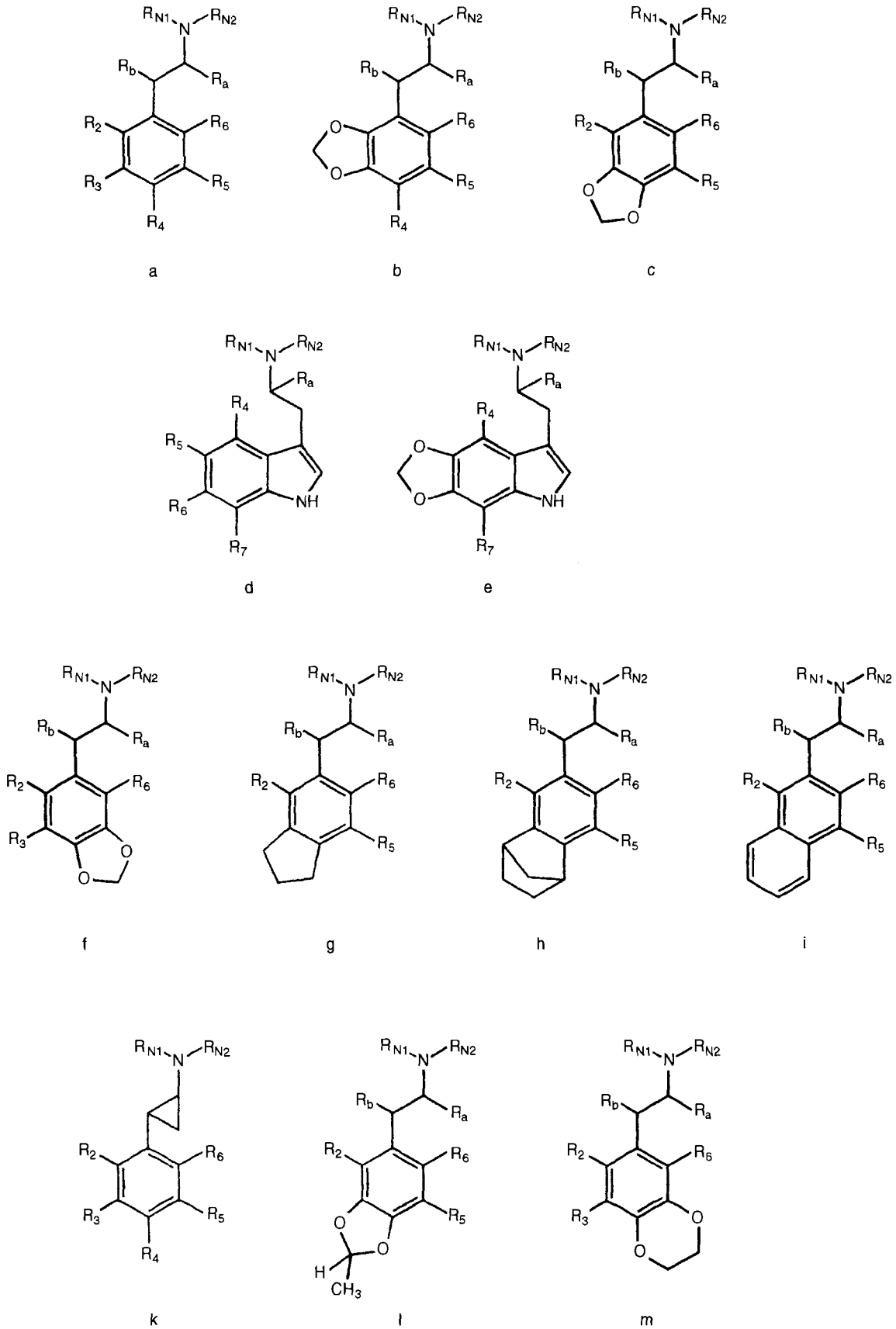

Figure 4. Basic structures of the compounds of data sets I, II, and III.

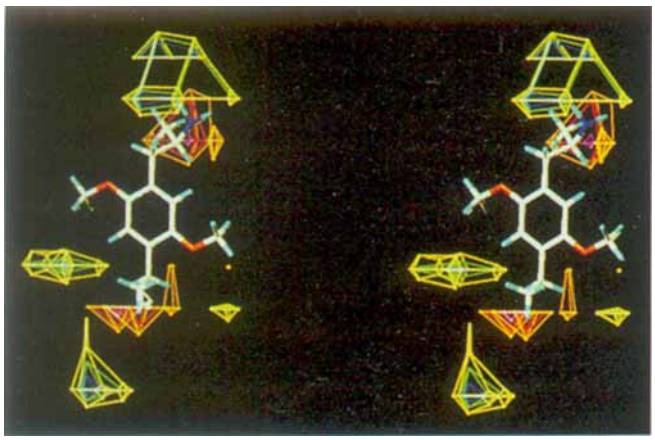

Figure 5. Stereoview of the steric CoMFA plot; contour levels (contribution) 75% (orange), 85% (red), 90% (purple), 20% (yellow), 15% (green), 10% (blue).

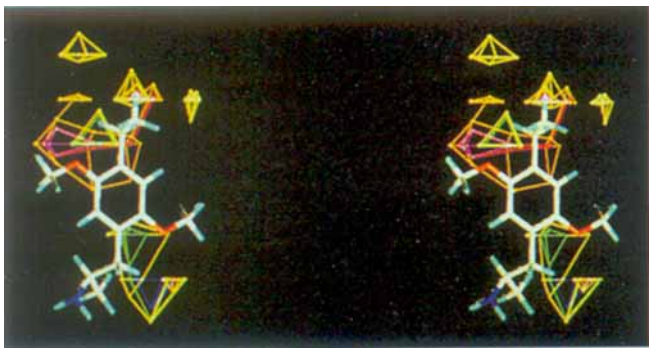

Figure 6. Stereoview of the electrostatic CoMFA plot; contour levels (contribution) 80% (orange), 85% (red), 90% (purple), 25% (yellow), 20% (green), 17% (blue).

Effect-diminishing steric areas (Figure 5) are to be found (1) at the side chain nitrogen, where voluminous substituents lead to appreciable reductions in activity (2). An important region lies at the aromatic ring near position 3; there should not be any substitution here. Further effect-diminishing areas (3) lie at a greater distance from the aromatic ring starting from position 4, hence, a substituent in this position must not be too large and (4) as small region moderately distant from the aromatic ring and between positions 4 and 5; a substituent in position 4 should not be coplanar and should not point in the direction of position 5.

Areas which are effect-increasing when they exhibit a partial positive charge (Figure 6) are to be found (1) near the aromatic ring at position 4 with a clear extension in the direction of positions 3 and 5, the centre of this region with the greatest influence lies between positions 4 and 5 and in addition (2) very weakly marked close to the β-position of the side chain.

Areas which are effect-increasing when they are partially negatively charged (Figure 6) lie (1) at position 2 of the aromatic ring with appreciable extension to the area of the side chain, where the influence of a charge is greatest, and (2) at a moderate distance from position 4 of the aromatic ring (these weaker regions are immediately outside the region in which a positive charge possesses effect-increasing influence).

The results of the steric CoMFA plots are readily interpreted on the basis of the structural elements; naturally it is necessary to remember that the Lennard-Jones potential also exerts an influence up to a certain distance from the molecular structure.

It is more difficult to understand the electrostatic plots. Here it is helpful to consider the isopotential lines of chosen molecules (Figures 2 and 3). For instance, the results of the CoMFA analysis make a negative charge on position 2 of the phenylalkanamines or 5 of the tryptamines advantageous. In fact, the oxygen-containing substituents cause a negative partial charge or an interruption of the positive isopotential lines to be observed in this position in Figures 2 and 3. Both amphetamine and tryptamine derivatives exhibit the necessary positive potential near position 4 of the aromatic rings to differing degrees depending on their substitution pattern.

However, final conclusions concerning the influence of the two fields on the effect can only be drawn if new molecules are synthesized, which should be brought into the correct conformation like those of the data set and then predictions about them are possible on the basis of the existing model.

4 Conclusion

The interpretation of the CoMFA contour plots showed that the three-dimensional QSAR studies discussed here allow an appreciably more exact description of the structural elements of the molecules and, hence, yield more detailed results than the classical analyses carried out previously. It was possible to construct a useful QSAR model from data set I consisting of 66 phenylalkanamine derivatives. Although the CoMFA method was originally designed to describe the interactions of a ligand with an unknown receptor [14], it has also proved possible to use the hallucinogenic effect on humans very successfully as target variable. This is shown by the comparison of the predictive values from the model with the experimentally determined effects of the compounds of data set III. The present results reveal that by three-dimensional description of the molecules the model can accommodate pharmacokinetic influences as well as receptor binding. Since the relevant target parameters for investigation of designer drugs are the effects on humans, these biological data should also be employed in the construction of the QSAR model.

Furthermore, it also proved possible to include the hallucinogenic tryptamine derivatives in a common analysis with the phenylalkanamines in spite of the different basic structures of the two groups. Here it was found that inactive substances should only be included in the analysis if they had been tested up to a relatively high dose. Data set III was then included in the final model. Thus, a comprehensive CoMFA model could be constructed taking into account 148 compounds.

On the basis of this model it is possible to predict the effects of other hallucinogens not included in the data set. However, it should be remembered that quantitative predictions can only be taken as guides for the effects of substances. The standard

deviation of 0.427 logarithmic units means, if normal distribution is assumed, that 68% of the predictive values will be subject to a deviation of less than the factor 2.67 in mescaline units, 32% will lie outside this range.

The substance 1-(2,5-dimethoxy-4-trifluoromethylphenyl)propan-2-amine, whose synthesis and receptor affinity data were published in December 1994 [34], can be used to test the model. Comparison of the receptor affinities of DOI [3, 35] reveals that the effect of this substance is of the same order of magnitude as that of DOI, which itself, together with DOB, is the strongest known hallucinogen of the phenylalkanamine class. The affinity of the new compound at the [^{3}H]-ketanserin-labelled receptor is 0.6 times that of DOI and at the [^{125}I]-DOI labelled receptor, which labels the high affinity state and, thus, provides more relevant data, the affinity is 2.4-fold that of DOI. This caused the authors to suspect that the hallucinogenic effect of the new compound might be greater than that of either DOB or DOI. When the molecule is included in the 3D-QSAR model the predictive value obtained is 180 MU without extrapolation and 850 MU with extrapolation. Hence, an effect is predicted for the new compound which is 0.6-fold or 2.9-fold that of the effect of DOI. These values are in good agreement with the results obtained in the radioactive ligand binding studies and provide further evidence of the excellent predictive power of the CoMFA model.

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