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QSAR study with steric (MTD), electronic and hydrophobicity parameters on psychotomimetic phenylalkylamines

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Abstract

Multiple linear regression analysis has been used to identify the most important properties relevant to psychotomimetic activity displayed by 37 phenylalkylamines. Using the minimal topologic differences (MTD) parameter, lipophilicity (log P, calculated by using π Hansch substituent terms), average electrostatic field (AEF) and electronic descriptors, lowest unoccupied molecular orbital energies (E_{LUMO}) and net atomic charges (obtained from AM1 calculations), good correlations with biological activity were obtained (R^2 = 0.79–0.92). Cross-validation procedure was applied indicating a good predictability of the proposed models (R^2_{cv} = 0.67–0.81).

Keywords: Phenylalkylamine; Psychotomimetic; QSAR; MTD method; Steric parameter; AM1

1. Introduction

Psychotomimetics are still receiving the attention of researchers especially due to the unsolved question of the nature of their biological activity. These compounds have an important role both in the study of cognitive processes and as drugs used in psychiatry. A review regarding different aspects of the structure and mechanism of action of different classes of hallucinogens has been recently published [1]. Phenylalkylamines such as mescaline [1-(3,4,5-trimethoxy-)-aminoethane], amphetamine [phenyl-2-aminopropane] and their derivatives are intensely studied, having a notable but unselective affinity with serotoninergic [2–13] or adrenergic [14–17] receptors. The most important structural feature of the potent phenylalkylamines is the presence of the substituent in para-position (see Table 1 for the atom numbering). Mescaline derivatives with ethoxy, propoxy, isopropoxy, alkyl or alkylthio groups bonded at 4-position of the phenyl ring exhibit biological activities 5–30 times greater than mescaline [23]. The same groups at positions 3- or 3,5- do not significantly modify the potency. Similar results are obtained for 2,4,5-derivatives. The most active compounds have an alkyl, alkylthio, or halogen at the 4-position [24]. The presence of these groups at 2-,3-, or 5-positions leads to compounds with reduced

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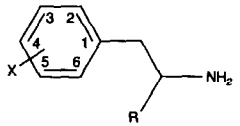
Table 1
First set of phenylalkylamines, their psychotomimetic potency (log MU), occupancy of the hypermolecule, values of the descriptors retained for biparametric correlations with MTD, and the values of the corresponding optimised MTD parameter



X	R	log MU	$j(x_{ii}=1)$	E_{LUMO}	log P	q_{para}	q_4	AEF	MTD	MTD+E_{LUMO}	MTD+log P	MTD+q_{para}	MTD+q_4
2,5-OMe,4-I	Me	2.73	1,2,4–6,9	–0.065	2.88	0.162	–0.263	–	1	3	1	2	1
2,5–OMe,4-Br	Me	2.66	1,2,4–6,9	–0.066	2.58a	0.072	–0.167	–	1	3	1	2	1
2,5-OMe,4-Et	Me	1.97	1,2,4–6,8,9	0.231	2.58	–0.115	–0.060	14.89	2	4	2	3	2
2,5-OMe,4-Pr	Me	1.90	1,2,4–6,8–10	0.226	3.08	–0.114	–0.060	14.65	2	4	2	3	2
2,5-OMe,4-SEt	Me	1.93	1,2,4–6,8–10	0.078	2.99	0.222	–0.211	14.75	2	4	2	3	2
2,5-OMe,4-Me	Me	1.84	1,2,4–6,9	0.231	2.08[a]	–0.169	–0.061	15.16	1	3	1	2	1
3,5-OMe,4-Br	Me	1.88	1,3–5,7,9	0.048	2.53	0.092	–0.229	–	2	5	2	3	3
2,5-OMe,4-S-i-Pr	Me	1.75	1,2,4–6,8–11	0.076	2.88	0.205	–0.208	14.54	2	4	3	4	3
2,5-OMe,4-Bu	Me	1.62	1,2,4–6,8–10,12	0.223	3.58	–0.118	–0.058	14.45	2	4	3	3	2
2,5-OMe,4-SMe	Me	1.60	1,2,4–6,8,9	0.055	2.49	0.240	–0.217	14.99	2	4	2	3	2
2,5-OMe,4-Br	H	1.63	2,4–6,9	–0.63	2.36	0.072	–0.166	–	2	4	2	3	2
2,5-OMe,4-Me	H	1.21	2,4–6,9	0.338	1.86	–0.173	–0.063	15.67	2	4	2	3	2
2,4,5-OMe	Me	1.27	1,2,4–6,8,9	0.185	1.74[a]	–0.212	0.072	15.97	2	4	2	3	2
2,5-OMe,4-Et	H	1.24	2,4–6,8,9	0.347	2.31	–0.114	–0.063	15.32	3	5	3	4	3
2,5-OMe,4-SMe	Me	1.12	1,2,4–6,8–10	0.224	2.24	–0.218	0.091	15.65	2	4	2	3	2
3,5-OMe,4-SMe	H	1.10	3–5,7–9	0.233	2.22	0.285	–0.279	15.43	4	7	4	5	5
2-OMe,3-OCH_2O-4	Me	1.06	1–4,6,14	0.248	1.66	–0.217	0.047	16.76	3	6	3	4	3
3,5-OMe,4-OEt	Me	1.00	1,3–5,7–10	0.308	1.90	–0.218	0.000	15.65	3	6	3	4	4
2,5-OMe,4-n-Pentyl	Me	1.04	1,2,4–6,8–10, 12,13	0.223	4.08	–0.118	–0.059	14.27	3	5	4	4	3
2,5-OMe,4-OPr	Me	0.92	1,2,4–6,8–10,12	0.234	2.74	–0.218	0.095	15.38	2	4	3	3	2
3,5-OMe,4-OEt	H	0.79	3–5,7–10	0.179	1.68	–0.216	–0.001	16.14	4	7	4	5	5
3,5-OMe,4-OPr	H	0.82	3–5,7–10,12	0.151	2.18	–0.215	0.002	15.80	4	7	5	5	5
4-OMe	Me	0.53	1,4,8	0.673	1.77[a]	–0.212	0.075	15.19	5	6	5	6	5
3-OCH_2O-4	Me	0.47	1,3,4,14	0.369	1.68	–0.219	0.007	16.63	4	6	4	5	4
3-OMe,4-OCH_2O-5	Me	0.36	1,3–5,7,15	0.333	1.66	–0.226	–0.078	16.76	4	7	4	5	5
3,5-OMe,4-$OCH_2C_6H_5$	Me	0.52	1,3–5,7–10,12, 13,16–18	0.247	3.53	–0.211	–0.042	15.23	4	7	6	5	5
3,4,5-OMe	Me	0.27	1,3–5,7–9	0.429	1.48	–0.195	–0.011	15.97	3	6	3	4	4
3,4,5-OMe	H	0.00	3–5,7–9	0.232	1.18	–0.216	–0.045	16.53	4	7	4	5	5
2,3,4-OMe	H	–0.06	2–4,6–8	0.215	1.21	–0.210	0.062	16.53	5	9	5	6	6
3,4-OMe	Me	–0.12	1,3,4,7,8	0.565	0.88[a]	–0.222	0.011	15.67	5	8	5	6	6
3,4-OMe	H	–0.67	3,4,7,8	0.420	0.66	–0.216	0.029	16.35	6	9	6	7	7

[a] Experimental values according Ref. [18]. For the definition of MU see Section 2; $j(x_{ij}=1)$ = the hypermolecule vertices occupied by the atoms of the "i"th molecule, for the vertices numbering see Fig. 1; E_{LUMO} = the energy of the lowest unoccupied molecular orbital; log P = Hansch lipophilicity (experimental or calculated by using fragmental contributions); q_{para} = net charge on the atom bonded to the phenyl ring at para-position with respect to the alkylamine substituent; q_4 = net charge on the atom 4 of the phenyl ring, AEF = average electrostatic field (in V/nm) calculated from bond increments [19–22].

activities or to inactive compounds [25–27]. It has been thought that the role of the substituent at 4-position is to orient 5-methoxy group anti with respect to para-substituent [1]. This orientation could favour an easier access of the receptor(s) to the para region of the phenyl ring and to the lone pairs of 5-methoxy substituent. Gomez-Jeria et al. [28] have suggested that the receptor has a region controlling the size of the para-substituent, but not its lipophilicity. They have suggested that the electronic effect of the atom bonded at the para-position of the phenyl ring is important for the affinity. In order to obtain information about the mechanism(s) of action at the receptor site level, besides experimental work, many QSAR studies have been performed [9,17,29–47]. The aim of this note is to carry out QSAR studies using minimum topologic differences (MTD) [48] as steric parameter, either single or associated with lipophilicity or/and electronic descriptors and to evaluate the prediction ability of the deduced models by the cross-validation technique. MTD method seems to have similar performances in cross-validation tests with the CoMFA method [49].

Before starting an MTD optimisation, monoparametric linear regressions have been carried out between psychotomimetic potency [log MU (mescaline units)] and some 'local' steric substituent constants as ν Charton [50,51] and L, B_1, B_2, B_3, B_4, STERIMOL parameters [52] for the substituents bonded at 2-,3-,4-, and 5-positions of the phenyl ring. Other simple linear correlations have been performed with electronic descriptors obtained from AM1 calculations. The electronic descriptors used here are HOMO and LUMO energies, molecular hardness, η [53] (defined as $(I-A)/2$, I and A have been taken as AM1 HOMO and LUMO energies), molecular heat of formation, ΔH_f, dipole moment, μ, total net charge of substituents, Σq, and net charges on: (i) nitrogen atom, q_N, (ii) ring atoms 2, 3, 4, 5 (see Table 1 for the atom numbering), q_2, q_3, q_4 and q_5, respectively, (iii) the atom bonded at para-position with respect to the alkylamine substituent, q_{para}. Monoparametric linear regressions between lipophilicity and biological activity were also performed. As lipophilicity descriptors, either log P or average electrostatic field (AEF) have been used. AEF has been proposed as a candidate to substitute π hydrophobic parameter of Hansch [19–22]. The electrostatic field on the van der Waals surface of a certain molecular region can characterise its polarity. Regions with a large field strongly attract water molecules, while small field regions do not attract them and therefore can be considered hydrophobic. The value AEF is proportional to the overall hydration ability of the molecule, and thus this descriptor can be used as a proportional measure of the hydrophobicity either of a certain region or of the whole molecule [19–22].

The descriptors showing significant correlations with biological activity (except classical steric parameters) have been associated with MTD descriptor and, applying the MTD optimisation method, biparametric linear regressions have been obtained. Using the same optimisation procedure, some triparametric linear correlations, for log MU, have been performed with MTD, log P and one of the E_{LUMO}, q_4 or q_{para} electronic descriptors.

2. Methods

In this study thirtyseven phenylalkylamines that exhibit psychotomimetic activity in human subjects [23] were evaluated. The compounds are divided into two sets: one of thirtyone compounds, listed in Table 1 and the second of six compounds having only a superior limit for biological activity. The linear regressions resulting from the correlations corresponding to the first set of compounds have been used to calculate the biological activities of the compounds from the second set. The psychotomimetic potency is usually expressed in terms of MU — the ratio of the effective dose of mescaline (3.5 mg/kg) to the effective dose of the tested compound. In this study, the potencies are expressed as log MU, where MU is taken as mmol mescaline/mmol of tested phenylalkylamine. The potency values are listed in Table 1.

Minimum steric (topologic) difference, MTD_i, is a measure of the steric misfit between the tested ligand "i" and the receptor cavity. Through atom by atom superposition (hydrogen atoms neglected) a hypermolecule is obtained, with $j = 1,2,...,M$ vertices. For each molecule "i" from the series a vector x_{ij} is constructed ($x_{ij} = 1$ for occupied and $x_{ij} = 0$ for unoccupied vertices). The MTD_i values are calculated according

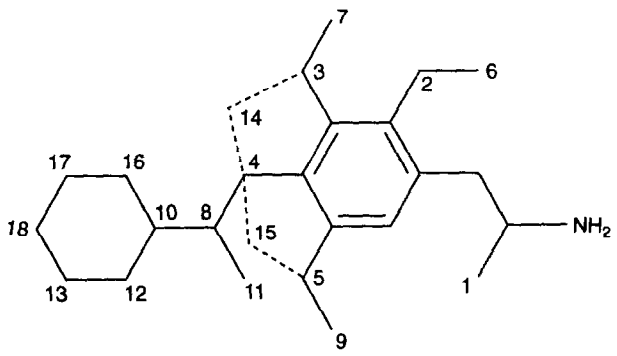


Fig. 1. The hypermolecule, the numbering of vertices and the maps corresponding to Eqs. 1–5 (Table 5).

	Beneficial vertices		Detrimental vertices	Indiferent vertices
Eq. 1	$\{\epsilon_j = -1$:	1,2,5,9,18;	$\epsilon_j = 1$: 8,13,15,17;	$\epsilon_j = 0$: 3,4,6,7,10,11,12,14,16}
Eq. 2	$\{\epsilon_j = -1$:	1,2,5,9;	$\epsilon_j = 1$: 3,6–8,13,15,17;	$\epsilon_j = 0$: 4,10–12,14,16,18}
Eq. 3	$\{\epsilon_j = -1$:	1,2,5,9;	$\epsilon_j = 1$: 8,10,13,15,17;	$\epsilon_j = 0$: 3,4,6,7,11,12,14,16,18}
Eq. 4	$\{\epsilon_j = -1$:	1,2,5,9,18;	$\epsilon_j = 1$: 8,11,13,15,17;	$\epsilon_j = 0$: 3,4,6,7,10,12,14,16}
Eq. 5	$\{\epsilon_j = -1$:	1,2,5,9,18;	$\epsilon_j = 1$: 7,8,11,13,15,17;	$\epsilon_j = 0$: 7,8,11,13,15,17}

to the formula:

$$MTD_i = s + \sum_{j=1}^{M} \epsilon_j x_{ij}$$

where s is the number of cavity vertices within the receptor map (hypermolecule vertices with $\epsilon_j = -1$); $\epsilon_j = -1$, 0, +1 for cavity (c), external (e) or wall (w) vertices. The values of ϵ_j are attributed through an optimisation procedure, maximising the "r" correlation coefficient of the equation:

$$\hat{A}_i = \alpha + \alpha_i \sigma_{i1} + \alpha_2 \sigma_{i2} + \ldots - \beta MTD_i$$

σ_{i1}, σ_{i2}... are other parameters, α and β values are regression coefficients. Thus, beside an optimal regression equation, the attributions of vertices ϵ_j are also obtained (beneficial, indifferent or detrimental, respectively) [48].

Experimentally unknown lipophilicities have been calculated using Hansch hydrophobic fragmental constants. Barfknecht et al. [18] have measured log P for a series of phenylalkyl amines and have pointed out the non-additivity of π values of metoxy groups bonded at different positions of polymetoxyphenylalkylamines. Therefore, the lipophilicity has been calculated using the experimental log P values of phenylethylamine or amphetamine [54] to which π values of different substituents were added, according to Anderson et al. [55]. These authors have analysed the π values of the various positional mono-, di-, and tri-methoxy configurations in a number of model compounds and compared the π mean values for different methoxy groups.

The AEF_i values corresponding to the set of 31 compounds have been calculated by bond increment method [19–22]. The rest of descriptors have been obtained from AM1 calculations. Using HyperChem 2.0 package (Autodesk Inc.), molecular mechanics calculations have been performed for all molecules by using MM+ force field. The geometries resulted from MM+ optimisation have been fully optimised using the AM1 Hamiltonian [56]. The optimisation algorithm was Polak-Ribiere conjugate gradient with the gradient norm set to 0.01 kcal/A mole. For the molecules containing Br and I, for which there are no parameters in the HyperChem 2.0 AM1 program, AM1 calculations have been carried out by using the MOPAC 6.0 package [57]. There are no significant differences between the values of different electronic descriptors given by the AM1 methods included in the two packages. HyperChem 2.0 has been preferred for its facilities offered by the presence in the same package of the two programs (MM+ and AM1) used for geometry optimisation. For the compounds having a chiral centre, R is generally more active than S isomer. Therefore, in the geometry optimisation process the R isomer has been considered.

The hypermolecule for the MTD calculation has been obtained by maximum atom by atom

superposition of all molecules in the first set, resulting in a hypermolecule with 18 vertices (Fig. 1). The vertices of the common molecular core have been considered as cavity vertices and they have not been numbered in the hypermolecule. The start map has been the same for all regressions and it has been chosen on a statistical basis. The vertices preferentially occupied by the very active compounds have been considered as cavity vertices ($\epsilon_j = -1$) and those occupied by the low activity compounds ($\epsilon_j = 1$) as wall vertices, and the rest of them were considered to be irrelevant ($\epsilon_j = 0$).

3. Results and discussions

From the full set of tested descriptors only five with the best statistic parameters have been further considered in this study: E_{LUMO}, log P, AEF, q_4 and q_{para}. The values of the five selected descriptors are presented in Table 1 and the corresponding statistical results in Table 2. Although the statistical parameters of these five descriptors have rather low values, suppositions can be made regarding the implication of different factors of steric, lipophilic and electronic nature in the mechanism of action of phenylalkylamines. The correlation of log MU with E_{LUMO} could be an argument in the favour of a charge transfer (CT) mechanism in which the psychotomimetics play the role of the acceptor. A similar correlation has been recently obtained by Clare from CNDO/2 calculations [44].

The correlation between psychotomimetic activity of the considered compounds and log P supports the implication of transport phenomena in the biological effects of phenylalkylamines. The same supposition can be made based on the correlations of log MU and AEF. These results agree with those obtained by different authors [34,40,44,46,47].

The correlations between the ring net atomic charges (q_2, q_3, q_4, q_5) and biological activities could be due to a certain charge transfer between the ligand phenyl ring and the receptor site. This hypothesis is also supported by the correlation with E_{LUMO}. The correlation of log MU with q_{para}, suggests also the implication of charge transfer in the biological effects of phenylalkylamines.

Although a direct comparison between MTD and "classical" steric parameters is not quite correct (MTD is a global parameter representing the steric misfit of a certain compound with the receptor cavity, while the rest of steric parameters characterise the influence of steric properties of a certain substituent on the ligand–receptor interaction), Table 3 presents some linear correlations between biological activity

Table 2
Values of statistical parameters for all tested monoparametric linear regressions: log MU = b_0+b_1X; n = 31

X	b_0	b_1	r^2	s	F
E_{LUMO}	1.8918	-3.4077	0.500	0.567	14.0
log P	-0.3505	0.6575	0.416	0.613	9.96
q_{para}	1.4007	3.0015	0.396	0.624	9.17
q_4	0.8373	-4.5515	0.376	0.634	8.43
AEF*	11.1033	-0.6526	0.471	0.508	10.68
E_{HOMO}	6.5653	0.6365	0.068	0.774	1.03
ΔH_f	1.6717	0.0071	0.038	0.787	0.56
η	-0.5135	-0.3889	0.007	0.799	0.11
μ	2.0106	-0.4251	0.151	0.739	2.48
Σq	1.2733	0.1995	0.005	0.800	0.07
q_N	3.5328	7.2152	0.010	0.798	0.14
q_2	1.2414	3.3884	0.236	0.701	4.33
q_3	0.8775	-3.7739	0.335	0.654	7.07
q_5	1.0327	4.4583	0.294	0.674	5.84

* n = 27, n is the number of compounds; r = the correlation coefficient; s = the standard error in log MU; F = the F-test value; b_0 = model error plus measurement error; b_1 = regression coefficient; see for the significance of E_{LUMO}, log P, q_{para} and AEF; E_{HOMO} = the energy of the highest occupied molecular orbital (eV); ΔH_f = the heat of formation (kcal mol^{-1}); μ = the dipole moment (Debye units); η = the molecular hardness defined as $(I-A)/2$ (eV); Σq = the sum of the net atomic charges of the heavy atoms of all substituents; q_N = the net charge on nitrogen atom; q_2, q_3, q_4, q_5 = the net charges on the ring atoms 2, 3, 4 and 5, respectively.

Table 3
Mono and multiparametric QSARs for psychotomimetic activity of phenylalkylamines

Regressional equation	n	R^2	F	s
log (act) = $35.65E_{HOMO}$+19.07	13	0.567	14.4	–
log (act) = 0.78log P–1.48IP+11.15	11	0.884	–	–
act = 7.918K–3.798	7	0.941	101	–
log (act) = 45.16($^3\chi_n$)$^{-1}$–4.298($^4\chi^V_{PC}$)$^{-1}$+1.288 $^6\chi_p$ -5.592	23	0.846	35	0.251
log (act) = 0.668 $^1\chi^V$–1.298	8	0.904	57	0.251
act = 129 $^3\chi V_C$–4.45 $^4\chi_P$–14.54	10	0.941	–	3.02
log (act) = 0.28E–0.26$I_{3,4}$–0.63	17	0.689	15.5	0.17
log MU = –0.7065+1.3798$B_1$1*	28	0.172	2.60	0.748
log MU = –2.2874+2.8434$B_1$2	28	0.362	7.10	0.657
log MU = –4.6817–3.0958$B_1$3	28	0.429	9.40	0.621
log MU = –3.0076+2.7145$B_1$4	28	0.585	17.63	0.530
log MU = –4.2143+4.1342$B_1$5	28	0.393	8.09	0.641
log MU = –0.3833+2.6711ν4	28	0.392	8.06	0.641
log MU = 2.6077–0.5130MTD (a)	28	0.820	44.25	0.386
log MU = –5.8398+2.2203$B_1$4+2.7624$B_1$5	28	0.741	22.91	0.418
log MU = –6.5878+1.9134$B_1$4+1.4498$B_1$2+2.3479$B_1$5	28	0.820	26.25	0.349
log MU = –7.1690+0.7815$B_1$1*+1.2365$B_1$2+1.8881$B_1$4+2.2106$B_1$5 (b)	28	0.872	30.00	0.294

The first seven equations are from Ref. [41], and the rest are obtained in this work. The number of compounds taken in correlation is 28 (the 31 compounds from the first set (Table 1) except three compounds containing methylenedioxy group, for which no STERIMOL or Charton parameters are available); IP = ionisation potential; K = association constant with an electron acceptor; χ = molecular connectivity index; E = interaction energy to 3-methylindole; $I_{3,4}$ = indicator value for substituents at position 3 and 4; $B_1$2, $B_1$3, $B_1$4, $B_1$5 = STERIMOL parameters for the substituent bonded at positions 2-,3-,4-, or 5-, respectively; $B_1$1* = the B_1 parameter for the H or Me in alkylamine chain; ν4 = Charton steric parameter for para substituent; MTD = minimal topologic difference; n = the number of observables taken in correlation; for the meaning of statistic indices s and F see Table 2; R = the multiple correlation coefficient.

and "local" steric parameters. For three compounds containing a methylenedioxy-substituent there are no available STERIMOL and ν Charton parameters. Therefore, in these correlations only 28 compounds have been included. For comparison, Table 3 shows some equations obtained by different authors and collected by Gupta [41].

From all five STERIMOL parameters [48], B_1 correlates significantly with biologic activity. In Table 3 $B_1$1* represents B_1 parameter for H or Me in alkylamine chain, $B_1$2, $B_1$3, $B_1$4 and $B_1$5 are B_1 parameters for the substituents bonded at positions 2-, 3-, 4- and 5-, respectively. The most important correlation is obtained with $B_1$4 parameter. Significant correlations are obtained also with $B_1$3 and $B_1$5. There is a high intercorrelation (–0.8503) between $B_1$2 and $B_1$3 parameters. Regarding the ν Charton parameters, their correlations with log MU are inferior to those obtained with the STERIMOL B_1 parameters. The parameter ν4 in Table 3 represents the ν steric parameter for the substituent bonded at the position 4 of the phenyl ring. Correlations obtained with "local" steric parameters agree with the experimental observations regarding the steric influence of para-substituent on the biological effects of phenylalkylamines. Statistical parameters for the equation containing four B_1 parameters are better than those of the MTD equation. Using the best equation obtained with "local" steric parameters (Eq. (b), Table 3), and the equation obtained with MTD parameter (Eq. (a), Table 3), the log MU values for three molecules from the second set can be calculated. The results are shown in Table 4. The number of compounds is too small for a reliable comparison, however one can see that log MU values predicted by both equations are quite comparable. One could conclude that MTD is as good as STERIMOL parameters. However, MTD gives more specific information about the receptor map and allows predictions also for substituents like methylenedioxy, for which no STERIMOL parameters are available. Also, steric influences between two or more substituents on the phenyl ring can be taken

Table 4
Comparison between MTD (Eq. (a), Table 3) and B_1 STERIMOL parameters (Eq. (b), Table 3)

Compounds		Experimental (log MU)		Calculated activities with Eqs. (a) and (b) from Table 3					
X	R	[23]	[36]	Eq. (a)	$\Delta 1_a$	$\Delta 2_a$	Eq. (b)	$\Delta 1_b$	$\Delta 1_b$
2,5-OMe, 4-I	H	< 1.80	1.64	1.59	0.21	0.05	2.33	0.53	0.69
4-OMe	H	< -0.20	< 0.00	-0.50	0.30	0.50	-0.39	0.19	0.39
2,3,4,-OMe	Me	< 0.57	< 0.30	0.54	0.03	0.24	0.45	0.12	0.15

Calculated activities for three compounds from the second set. $\Delta 1_a$, $\Delta 1_b$ = differences between upper limits of Sulgin's data [23] and activity values calculated with Eqs. (a) and (b), respectively; $\Delta 2_a$, $\Delta 2_b$ = differences between Klopman's data [36] and activity values calculated with Eqs. (a) and (b), respectively.

into account within MTD method (via the set of vertices occupied by substituents), while no such influence can be revealed by using STERIMOL parameters.

Each one of the descriptors E_{LUMO}, log P, q_{para} and q_4 has been included in an optimisation process together with MTD parameter and a cross-validation-like test has been applied. The last columns of Table 1 contain the different MTD values resulted when the MTD parameter alone, or MTD and one of E_{LUMO}, log P, q_{para} and q_4 descriptors have been submitted to the optimisation process. Table 5 shows the receptor maps, statistic parameters and the equations resulted from the cross-validated optimisation procedure. As the AEF values for some of the most active compounds containing Br or I cannot be calculated,

Table 5
Optimised receptor maps and statistical parameters for mono and biparameter regression equations

	MTD (Eq. 1)	E_{LUMO}+MTD (Eq. 2)	log P+MTD (Eq. 3)	q_{para}+MTD (Eq. 4)	q_4+MTD (Eq. 5)	AEF∴ΠΣ–MTD* (Eq. 6)
$\epsilon = -1$	1,2,5,9,18	1,2,5,9	1,2,5,9	1,2,5,9,18	1,2,5,9,18	–
$\epsilon = 0$	3,4,6,7,10, 11,12,14,16	4,10–12,14,16, 18	3,4,6,7,11,12, 14,16,18	3,4,6,7,10, 12,14,16	3,4,6,10,12, 14,16	–
$\epsilon = +1$	8,13,15,17	3,6–8,13,15,17	8,10,13,15,17	8,11,13,15,17	7,8,11,13,15,17	–
b_0	2.7100	3.2279	1.4538	3.0922	2.1703	6.7842
	(± 0.1629)	(± 0.1893)	(± 0.2435)	(± 0.1809)	(± 0.1355)	(± 1.3875)
b_1(X)		-1.6575	0.4202	1.5665	-2.6706	-0.2900
		(± 0.4072)	(± 0.0731)	(± 0.3586)	(± 0.5130)	(± 0.0925)
b_2 (MTD)	-0.5454	-0.3246	-0.4036	-0.4615	-0.3639	-0.4120
	(± 0.0508)	(± 0.0393)	(± 0.0408)	(± 0.0463)	(± 0.0333)	(± 0.0516)
R^2	0.799	0.854	0.870	0.867	0.882	0.832
s	0.360	0.306	0.289	0.292	0.276	0.287
F	55.72	52.78	60.28	58.84	66.89	37.72
R^2_{cv}	0.672 (0.777)	0.714 (0.787)	0.781 (0.781)	0.766 (0.794)	0.788 (0.844)	
PRESS	4.31	4.11	4.23	3.98	3.01	

log MU = b0+b1X+b2 MTD; X is one of the descriptors E_{LUMO}, log P, q_{para}, $q4$ or AEF; $n = 31$; significance level = 99.5% for all equations; q_{para} = the atom bonded at the phenyl ring at para position with respect to the alkylamine substituent; q_4 = the atom 4 of phenyl ring; $\epsilon = -1,0,1$ = the optimised receptor map containing beneficial ($\epsilon = -1$), irrelevant ($\epsilon = 0$), and detrimental ($\epsilon = 1$) vertices, respectively, see Fig. 1; in parentheses are standard errors in the regression coefficients b_i; R = the multiple correlation coefficient; s = the standard error in logMU; F = the F-test value; R^2_{cv} = the value based on the residuals from the "leave-half-out" technique; the R^2_{cv} values in parentheses correspond to the optimised receptor map as start map for optimisation of the "half" series; PRESS = the sum of the squared differences between calculated (according to Eqs. (1)–(6)) and observed log MU values.

* $n = 27$ (AEF for the compounds containing Br and I cannot be calculated by bond increment method).

Table 6
Intercorrelation coefficients for descriptors included in statistically significant equations

	log P	E_{LUMO}	q_4	q_{para}	AEF*
log P	1.000	−0.479	0.412	0.418	−0.818
AEF*	−0.818	0.264	0.449	−0.513	1.000
MTD	−0.574	0.658	0.428	−0.443	0.438
MTD(+log P)	−0.324	0.581	0.420	−0.440	0.343
MTD(+E_{LUMO})	−0.599	0.521	0.367	−0.421	0.624
MTD(+q_4)	−0.576	0.574	0.336	−0.386	0.536
MTD(+q_{para})	−0.558	0.640	0.397	−0.401	0.498
MTD(+log P+E_{LUMO})	−0.219	0.405	0.350	−0.400	0.333
MTD(+log P+q_4)	−0.184	0.480	0.3305	0.385	0.223
MTD(+log P+q_{para})	−0.324	0.581	−0.440	−0.402	0.343

* n = 27; MTD(+log P), etc, correspond to the MTD values obtained by optimisation for biparametric regressions (MTD with log P, etc).

the Eq. (6) from Table 5 has been obtained for only 27 compounds of the first set with MTD values used in Eq. (1) (Table 1, values under MTD column).

Starting from the following initial receptor map for all optimisation cases:

$$S^o\begin{cases}\epsilon=-1 & 1,2,5,6,9\\ \epsilon=0 & 3,4,7,8,10-12,14,16,18\\ \epsilon=+1 & 13,15,17\end{cases}$$

the optimised receptor maps shown in the rows 2-4 of Table 5 have been obtained (see also Fig. 1). Eq. (1) and statistical parameters corresponding to the optimised MTD values are shown in the second column of Table 5. The correlational Eq. (1) explains about 80% of the data variance. Due to the essentially steric nature of MTD descriptor, Eq. (1) strongly supports the hypothesis of the predominance of steric factors in the mechanism of action of the psychotomimetic compounds. The optimisation of MTD together with a supplementary descriptor yield the results from column 3–6 of Table 5. The intercorrelation coefficients for the descriptors used in bi- or triparametric linear correlations are presented in Table 6. The most important intercorrelation is shown by log P and AEF. The descriptors associated in bi- or triparametric equations are not significantly intercorrelated.

When MTD is optimised in combination with q_{para} or q_4, in every case the optimised receptor map contains the same cavity vertices (ϵ_j = −1) as the corresponding map resulted from MTD optimisation without supplementary descriptors (Table 5). Differences only appear for the irrelevant (ϵ_j = 0) vertices 7 and 11. When MTD is optimised together with

Table 7
Experimental and calculated psychotomimetic potencies for the six phenylalkylamines from the second set

Compounds		Experimental			Calculated activities with eqns (1)–(6) from Table 5					
X	R	[23]	[44]	[36]	I	II	III	IV	V	VI
2,5-OMe,4-I	H	< 1.80	–	1.64	1.62	2.04	1.76	1.52	1.55	–
3-OMe,4-OCH_2O-4	H	< 0.11	0.00	0.00	−0.02	0.36	0.03	0.02	0.07	−0.35
2-OMe,3-OCH_2O-4	H	< 0.73	–	0.70	0.53	0.65	0.44	0.44	0.59	0.06
3-OCH_2O-4	H	< 0.14	0.00	–	−0.02	0.64	0.04	0.02	0.33	−0.27
4-OMe	H	< −0.20	–	< 0.00	−0.56	0.17	−0.32	−0.47	−0.21	−0.17
2,3,4-OMe	Me	< 0.57	0.30	< 0.30	0.53	0.43	0.44	0.46	0.19	0.46
R^2 (Ref. [23])					0.902	0.788	0.949	0.893	0.895	
PRESS					0.25	0.53	0.13	0.27	0.26	
R^2 (Refs. [44,36])					0.812	0.645	0.902	0.844	0.910	
PRESS					0.40	0.75	0.21	0.33	0.19	

For the comparison of the calculated and the experimental potencies according to Ref. [23], the upper limit of the experimental values was considered.

Hansch lipophilicities or LUMO energies, a different receptor map is obtained. This map seems more realistic from a chemical viewpoint, due to the absence of the vertex 18 from the cavity vertices. For the biparametric correlations presented in Table 5 (Eqs. (1)–(5)) the following vertices are shared in common by the final receptor maps:

$$\begin{cases} \epsilon = -1 & 1,2,5,9 \\ \epsilon = 0 & 4,12,14,16 \\ \epsilon = +1 & 8,13,15,17 \end{cases}$$

For all biparametric optimisations the receptor maps are only slightly modified by the intervention of other than steric factors, emphasising the steric factor as important in psychotomimetics–receptor interaction.

Using Eq. (1), corresponding to MTD optimised without supplementary parameters, or biparametric Eqs. (2)–(6) (Table 5), one can calculate the psychotomimetic activity for the test series. The results of these calculations are presented in Table 7. Except for the data obtained with E_{LUMO}+MTD and AEF+MTD (Eqs. (2), () and (6)), the rest of the values reproduce the experimental trend quite well. Almost the same results are obtained with MTD+q_{para} (Eq. (4)) and MTD+q_4 (Eq. (5)), (columns 4 and 5 from Table 6). Good predicted values are also given by the model obtained from MTD optimisation without supplementary parameters (column 1 Table 6). The best values are obtained from MTD+log P (Eq. (3)).

Due to the low number of test compounds, as well as their uncertain activities, the experimental data of the second set compounds are not suited for statistical tests. We computed, nevertheless (Table 7), R^2 and PRESS values, using the upper activity limits given by other authors [23,44,36]. The results of Shulgin [23] yield higher R^2 and lower PRESS values. No comparison with the activities calculated with B_1 STERIMOL parameter (Eq. (b), Table 3) is possible, as such parameters are not available for methylenedioxy-substituents.

Three descriptor linear regressions between psychotomimetic activity and MTD, log P and q_4, or MTD, log P and q_{para} do not significantly improve the statistical values of resulted equations in comparison with the values of the biparametric equations. From the correlation of psychotomimetic potency with MTD, log P and E_{LUMO} the following equation and statistical indices result:

$$\log MU = 2.071(\pm 0.2364) - 1.3925(\pm 0.3293)E_{LUMO} + 0.3866(\pm 0.0655)\log P - 0.3751(\pm 0.0391)MTD \quad (7)$$

$n = 31$; $R^2 = 0.914$; $s = 0.235$; $F = 69.26$; $R^2_{cv} = 0.815$; PRESS = 3.576 (R^2cv = 0.851; PRESS = 2.885)The values of R^2cv and PRESS in parenthesis correspond to the final optimised receptor map. The intercorrelation coefficients are presented in Table 6. In this case the receptor map was much different in comparison with those obtained from biparametric regressions. Only two beneficial ($\epsilon = -1$) vertices, 1 and 5 resulted hereby, and more detrimental ones 3, 8, 10, 13, 15, 17, the rest of them being irrelevant. The predicted potencies have the following values: 2.06, 0.15, 0.50, 0.50, 0.14, 0.58.

4. Conclusions

Correlations using the MTD method yield a good predictability for psychotomimetic phenylalkylamines, checked by the cross-validated R^2_{cv} (Table 5, Eqs. (1)–(5)). This result indicates the dominance of steric effects in receptor–phenylalkylamine interactions. MTD combined with electronic or lipophilicity descriptor gives generally the same optimised receptor map (beneficial and detrimental vertices). MTD optimised without supplementary parameters can include some electronic and lipophilic interactions, i.e., without supplementary parameters MTD is not a "pure" steric descriptor. When a multiple linear regression (MLR) treatment is applied, lipophilicity and electronic descriptors extract transport and electronic effects from MTD and this becomes a "more pure" steric descriptor. Although the steric descriptors have a dominant effect on the phenylalkylamine potency, Hansch lipophilicity or AEF, and electronic descriptors (net charges on phenyl ring, or para-bonded atoms, LUMO energies) also contribute to the activity of these compounds. Moreover, electronic parameters support a possible CT mechanism of action, in which phenylalkylamines play the acceptor role.

A rough comparison between the MTD parameter and classical steric parameters for this series of

compounds revealed that the MTD parameter is at least as good as STERIMOL parameters, but it has some advantages regarding the information about the receptor map and interactions between neighbour substituents. MTD also allows the inclusion of polyanelated substituents, like methylenedioxy, for which no STERIMOL parameters are available.

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References

[1] D.E. Nichols, R. Oberlender and D.J. McKenna, in R.R. Watson (Ed.), Biochemistry and Physiology of Substance Abuse, Vol III, CRC Press, Boca Raton, Boston, 1991, p. 9.
[2] R.A. Glennon, J. Med. Chem., 25 (1982) 393.
[3] R.A. Glennon, R. Young, F. Benington and R.D. Morin, J. Med. Chem., 25 (1982) 1163.
[4] A.P. DeJong, F. Huggins, D. Fournier and A. Makriyannis, Eur. J. Pharmacol., 83 (1982) 305.
[5] R.A. Glennon, M. Titeler and J.D. McKennedy, Life Sci., 35 (1984) 2505.
[6] J.S. Gomez-Jeria and D. Morales-Lagos, in M. Kuchar (Ed.), QSAR Des. Bioact. Compd., Prous, Barcelona, 1984, p. 145.
[7] M. Shannon, G. Battaglia, R.A. Glennon and M. Titeler, Eur. J. Pharmacol., 102 (1984) 23.
[8] R.A. Glennon, J.D. McKennedy, R.A. Lyon and M. Titeler, J. Med. Chem., 29 (1986) 194.
[9] R.A. Glennon and M.R. Seggel, ACS Symp. Ser., 413 (1988) 264.
[10] R.A. Glennon, A.M. Ismaiel, C. Chaurasia and M. Titeler, Drug Develop. Res., 22 (1991) 25.
[11] R.A. Glennon and M. Dukat, Pharmacol. Biochem. Behav., 40 (1991) 1009.
[12] R.A. Glennon, R. Reva, P. Bartyzel, M. Titeler and S. Leonhardt, J. Med. Chem., 35 (1992) 7342.
[13] R.A. Glennon, Med. Chem. Res., 3 (1993) 317.
[14] R.R. Ruffolo and J.E. Waddell, J. Pharmacol. Exp. Ther., 224 (1983) 559.
[15] R.R. Ruffolo, Neurotransm. Recept., 1 (1983) 1.
[16] V. Tarcisio, R. Meroni, R. Dagani, G. Baldi, M. Pagani, M. Bevilaqua and G. Norviato, J. Pharm. Pharmacol., 37 (1985) 593.
[17] T. Solmajer, M. Hodscek, D. Hadzi and I. Lukovits, QSAR Pharmacol. Chem. Biol., 3 (1984) 51.
[18] C.J. Barfknecht, D.E. Nichols and W.J. Dunn, J. Med. Chem., 18 (1975) 208.
[19] G. Náray-Szabó, Int. J. Quantum Chem. 16 (1979) 265.
[20] P. Nagy, J.G. Angyan, G. Náray-Szabó and G. Peinel, Int. J. Quantum Chem., 31 (1987) 927.
[21] G. Náray-Szabó, in H. van der Goot, G. Domány, L. Pallos and H. Timmerman (Eds.), Trends in Medicinal Chemistry '88, Elsevier, Amsterdam, 1989, p. 29.
[22] T. Balogh, G. Náray-Szabó, Croat. Chem. Acta, 66 (1993) 129.
[23] U. Braun, G. Braun, P. Jacob III, D.E. Nichols and A.T. Shulgin, in G. Barnett, M. Trsic and R. Villette (Eds.), QuaSAR Research Monograph 22, NIDA, Rockville, 1978, p. 27.
[24] A.T. Shulgin, in L.L. Iversen, S.D. Iversen and S.H. Snyder (Eds.), Handbook of Psychopharmacology, Vol. 11, Plenum Press, New York, 1978, p. 243.
[25] P. Jacobs III and A.T. Shulgin, J. Med. Chem., 24 (1981) 1348.
[26] P. Jacobs III and A.T. Shulgin, J. Med. Chem., 26 (1983) 746.
[27] P. Jacobs III and A.T. Shulgin, J. Med. Chem., 27 (1984) 881.
[28] J.S. Gomez-Jeria, B.K. Cassels and J.C. Saavedra-Aguilar, Eur. J. Med. Chem., 22 (1987) 433.
[29] I. Lukovits, Int. J. Quantum Chem., 20 (1981) 429.
[30] I. Lukovits, Magy. Kém. Lapja., 37 (1982) 26.
[31] S. Gupta, P. Singh and M.C. Bindal, Farmaco, 37 (1982) 566.
[32] S. Gupta, M.C. Bindal and P. Singh, Arzneim.-Forsch., 32 (1982) 1223.
[33] M.C. Bindal, P. Sing and S.P. Gupta, Arzneim.-Forsch., 32 (1982) 719.
[34] S. Gupta, A. Handa, M.C. Bindal and P. Singh, Arzneim.-Forsch., 33 (1983) 1089.
[35] S. Wold, W.J. Dunn and S. Helberg, in G. Jolles and K.R.H. Wooldridge (Eds.), Drug Des.: Fact Fantasy, Proc. 3rd Rhone-Poulenc Round Conf., 1984, Academic, London, p. 95.
[36] G. Klopman and O.T. Macina, J. Theor. Biol., 113 (1985) 637.
[37] R.A. Glennon, R. Young and A.E. Hauck, Pharmacol. Biochem. Behav., 21 (1984) 895; 22 (1985) 723.
[38] I. Lukovits, in M. Kuchar (Ed.), QSAR Des. Bioact. Compd., Prous, Barcelona, 1984, p. 359.
[39] J.S. Gomez-Jeria, D. Morales-Lagos and J.I. Rodriguez-Gatica, Acta Sud Amer. Quim., 4 (1984) 1.
[40] M. Mahmoudian, Acta Pharm. Suec., 25 (1988) 151.
[41] S.P. Gupta, Chem. Rev., 89 (1989) 1765.
[42] D. Lee Duewer, J. Chemometr., 4 (1990) 299.
[43] A.W. Schmidt, Mol. Pharmacol., 38 (1990) 511.
[44] B.W. Clare, J. Med. Chem., 33 (1990) 687; Chemometr. Intell. Lab. Syst., 18 (1993) 71.
[45] A. Cartier and J.L. Rivail, Chemometr. Intell. Lab. Syst., 1 (1987) 335.
[46] M. Medic-Saric, S. Rendic, V. Vestemar and S. Saric, Acta Pharm. (Zagreb), 43 (1993) 15.
[47] P. Caldirola, E. Coats, R. Mannhold, H. Van der Goot and H. Timmerman, Eur. J. Med. Chem., 28 (1993) 783.
[48] Z. Simon, A. Chiriac, S. Holban, D. Ciubotariu and G.I. Mihalas, Minimum Steric Difference, Res. Stud. Press, Letchworth, London, 1984; I. Niculescu-Duvăz, Z. Simon and N. Voiculet, in M. Dawson, W.H. Okanura (Eds.), Chemistry and Biology of Synthetic Retinoids, CRC Press, Boca Raton, 1990, p. 575; Z. Simon, in H. Kubinyi (Ed.), 3D-QSAR in Drug Design, Theory, Methods, Applications, ESCOM Leyden, 1993,

p. 307; S. Muresan, C. Bologa, M. Mracec, A. Chiriac, B. Jastorff, Z. Simon and G. Naray-Szabo, J. Mol. Struct., 342 (1995) 161.
[49] Z. Simon, D. Ciubotariu, T.I. Oprea and T.I. Sulea, Quant. Struct.-Act. Relat., 12 (1993) 21.
[50] M. Charton, Progr. Phys. Org. Chem., 10 (1973) 81.
[51] M. Charton, J. Am. Chem. Soc., 97 (1975) 1552, 3691, 3694, 6159, 6472.
[52] A. Verloop, W. Hoogenstraaten and J. Tipker, in E.J. Ariens (Ed.), Drug Design, Academic, New York, 1976, vol. VIII.
[53] R.G. Parr and R.G. Pearson, J. Am. Chem. Soc., 105 (1983) 7512.
[54] A. Leo, C. Hansch and D. Elkins, Chem. Rev., 71 (1971) 525.
[55] G.M. Anderson, N. Castignolli and P.A. Kollman, in G. Barnett, M. Trsic and R. Villette (Eds.), QuaSAR Research Monograph 22, NIDA, Rockville, 1978, p. 199.
[56] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy and J.J.P. Stewart, J. Am. Chem. Soc., 107 (1985) 3902.
[57] J.J.P. Stewart, QCPE Bull., 6 (1986) 43.