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Charge-transfer interactions in the inhibition of MAO-A by phenylisopropylamines – a QSAR study

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Summary

The HOMO energies and the charges on the aromatic carbons of two sets of MAO-A-inhibiting phenylisopropylamines, one containing 4-amino substituents, were calculated by the AM1 method, in order to evaluate the importance of charge-transfer interactions between drug and enzyme. Multiple-linear regressions of the pIC_{50} values on the calculated descriptors were performed with 33 compounds from the two sets, and separately with each set. A poor correlation was obtained when the two sets were merged, as a result of opposing trends shown by the two separate sets. These opposing trends were reconciled by invoking a partial protonation of the basic 4-amino substituents by a hydrogen-bond-donor fragment of the enzyme. The resulting analysis indicated that electron-rich rings and higher HOMO levels tended to increase activity. This model received support from the evaluation of the IMAO activity of four new phenylisopropylamines.

Introduction

QSAR studies of MAO inhibitors constitute an active area of research. Various inhibitors of the MAO-A and MAO-B isoforms have been prepared and tested *in vitro*, in the search of the structural requirements for optimal activity and selectivity. Examples include, among others, pargylines [1], pyrazinocarbazoles [2], indole derivatives [3–5], oxazolidinones [6], coumarins [7] and xanthones [8]

Several QSAR studies have been published on the activity of phenylalkylamines as serotonergic agents [9–13]. Less studied is their activity as MAO inhibitors. A series of 4-aminophenylalkylamines have been shown to be selective MAO-A inhibitors [14, 15] and QSAR studies on these compounds have been published [16, 17]. To these data have been added more recently the IMAO activities of a series of phenylalkylamines exhibiting a wider structural variation [18].

In spite of these studies, the mechanisms by which these compounds inhibit both MAO isoforms remain poorly understood. A Phe-208 fragment in MAO-A and Ile-199 in MAO-B seem to be important for substrate selectivity [19]. A CoMFA analysis has suggested possible electrostatic interactions between pyrazinocarbazole inhibitors and the enzyme active site [2]. Charge-transfer interactions between electron-rich aromatic rings in various inhibitors and the FAD cofactor have also been suggested [6, 20, 21]. Such interactions have indeed been detected between harmane and xanthone derivatives and a flavin acceptor [8].

In the case of phenylalkylamines this suggestion remains to be tested. A regression analysis of a series of 4-substituted aminophenylalkylamines employing 56 physico-chemical parameters revealed a major (65%) contribution of electronic descriptors [17]. Nevertheless, these results added very little to our knowledge of the mode of interaction between drug and receptor, because they were restricted to a specific

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set of 4-aminophenylalkylamines. Also, because of the empirical nature of the principal electronic descriptors employed in the regression (Hammett σ values, or related Swain and Lupton parameters), they gave only a vague idea of possible charge-transfer interactions in the active site.

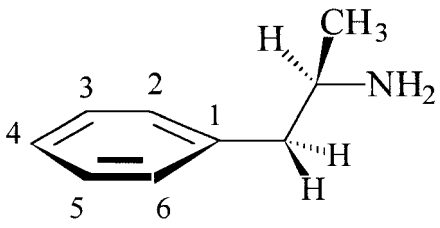
In the present communication we decided to investigate the contribution of electronic factors (charges and HOMO energies), calculated by the AM1 method, to the activity of ring-substituted amphetamine derivatives for which *in vitro* IMAO-A activities were available in the literature [17, 18]. It was hoped that the resulting analysis of the data might shed light on possible charge-transfer interactions between the aromatic ring of the inhibitors and the flavin cofactor, besides revealing some additional feature in the substrate-enzyme interaction. The resulting model might also be tested with four newly prepared sulfoxyl- and sulfonyl- phenylisopropylamines [22] for which *in vitro* MAO-A inhibition was evaluated.

Experimental

Biological Evaluation of the new compounds

The four new phenylisopropylamines were prepared following a described procedure. [22]. The (±) 4-methylsulfoxyl- (**43**) and the (±) 4-methylsulfonyl-phenylisopropylamine (**44**) were prepared by oxidation of (±) 4-methylthioamphetamine (MTA) (**2**) with trifluoroperacetic acid. Both amines were isolated as the corresponding hydrochlorides. Similarly, the (±)2,5-dimethoxy-4-ethylsulfoxyl- (**45**) and the (±) 2,5-dimethoxy-4-ethylsulfonyl-phenylisopropylamine (**46**), also isolated as the corresponding hydrochlorides, were obtained by oxidation of (±) 2,5-dimethoxy-4-ethylthioamphetamine (Aleph-2) (**18**).

The effects of the newly prepared phenylisopropylamine derivatives on MAO-A were measured *in vitro* following a protocol described previously [18]. The MAO-A isoform was obtained from a crude rat brain mitochondrial suspension. Serotonin (5-HT) was employed as a selective substrate. The MAO activities in the absence and presence of various concentrations of the inhibitor were assessed in triplicate by HPLC (Merck-Hitachi L-7110 pump with a Macrosphere KP300 C18 5μ column and a Labchrom L-3500A amperometric detector).



Scheme 1.

Theoretical calculations and statistical analysis

Calculations of charges and HOMO energies were performed with the MOPAC 6.0 package [23], employing the AM1 method. All molecules had their geometries fully optimized, keeping the side-chain in a constant, extended conformation, with the amino group pointing away from the aromatic ring. In order to minimize repulsive interactions between the α-methyl group and ring-substituents at the 2-position, the side chain was arbitrarily represented with the R configuration. All structures were drawn so as to ensure maximum superposition of common atoms or substituents in homologous series. Thus, for example, the 3,4-methylenedioxyphenyl ring was drawn with a 4,5-substitution pattern, because of the presence of homologous 2-bromo-, 2-nitro- and 2-chloro-4,5-methylenedioxyphenyl derivatives in the series. This procedure, which sometimes departed from the IUPAC numbering, rendered the ring carbon atoms strictly comparable across the series.

Protonation of the side-chain amino group was not considered in this study, since the emphasis was on the effect of the phenyl substituents upon possible charge-transfer interactions with an electron-accepting flavin ring. Whatever the effect may be of a free or a protonated side-chain amino group on these interactions, it should be fairly constant throughout the series of compounds, remaining undetected in the present study.

Multiple regression analyses of the data were performed with the aid of a program developed by Katritzky et al. [24]. The best multilinear regression (BMLR) method was employed, which searched for regression models with the maximum value of the Fischer criterion F and the highest cross-validated correlation coefficient, after a few initial constraints were defined. Default values were assumed for the upper limit of the square of the linear correlation coefficient for two descriptor scales to be considered orthogonal ($R^2_{\text{min}} = 0.1$) and for the probability level for the Fischer criterion ($F = 95\%$). In order to avoid

collinearity, a tighter value of 0.4 (default value $R^2_{nc} = 0.65$) was set for the lower limit of the square of the linear correlation coefficient, for two descriptor scales to be considered noncollinear. Cross-validated correlation coefficients, using a leave-one-out procedure, were calculated for all regressions, as a measure of the predictive power of the model.

Results and discussion

The structures of the studied amphetamine derivatives, with their corresponding IMAO-A activities, expressed as pIC_{50} values, are given in Table 1. The Table also includes the four new compounds evaluated in the present study.

Data for compounds **1–27** were taken from reference [18]. From these were extracted the set of active amines **1–18** (set A), all with accurate pIC_{50} values. Compounds **19–27**, with activities below the threshold value of 4.0 ($IC_{50} > 100\ \mu M$), were considered inactive. Since their pIC_{50} values had not been determined with accuracy, they were not included in the regression analyses.

Compounds **28–42**, taken from reference [17], constituted a second set of compounds (set B). All of them were racemic amphetamines substituted at the 4-position by an amino group.

The HOMO energies and the charges on the aromatic carbon atoms for all phenylisopropylamines are given in Table 2.

A multiple linear regression analysis was initially performed on all active compounds of Table 1 ($pIC_{50} > 4.0$), merging sets A and B, The resulting coefficients and other statistic parameters for the best regression model are given in Table 3.

The coefficients obtained indicated a poor correlation between the experimental data and the electronic descriptors, The immediate conclusion was that no evidence of charge-transfer interactions could be gathered from the experimental data. This interpretation relied on the assumption that the merged sets behaved homogeneously, in which case regression analyses carried out independently on sets A and B would yield comparably poor correlations. An alternative explanation for the observed result might be the possibility that the two sets exhibited opposite trends for the employed descriptors. In this case, merging the two sets would lead to a poor correlation, although that the two sets, independently, might yield significant regression models.

In order to choose between the two alternative interpretations, multiple regression analyses were carried out independently on sets A and B. The resulting coefficients for the best models are given in Table 3.

Both sets, particularly set A, showed significant improvements of the obtained correlations. It also became apparent by inspection of the regression coefficients that the two sets exhibited opposite trends. For set A, the E_{HOMO} coefficient was positive, and all charge-descriptor coefficients were negative. Since the E_{HOMO} energies were all negative, decreasing in absolute value with the electron-donicity of a substituent, the model derived for set A predicted an increased activity for electron-rich phenyl rings, in agreement with the view that electron-donation should favor charge-transfer to the flavin ring.

The opposite was true of set B, where the signs of both the E_{HOMO} and the charge-descriptor coefficients pointed to a decrease of activity with increased electron-donation to the phenyl ring.

Neglecting the possible existence of systematic deviations between the experimental results originating from different laboratories, the causes for the opposing trends were sought in the structures of the phenylisopropylamines. All compounds had a substituent at the 4-position. This was a variable functional group in set A, and an amino group in all compounds of set B. The only two 4-amino-substituted phenylisopropylamines whose activity had been reported in reference [18], compounds (**22**) and (**23**), were not included in set A because they were inactive ($pIC_{50} < 4.0$). The unique feature that distinguishes the amino group from other functional substituents is its basicity. It was therefore hypothesized that the amino substituent in all compounds of set B might be partially protonated by some hydrogen-bond-donor fragment in the active site of the enzyme. This would affect the HOMO level and charges of the ring, bringing about a systematic deviation from the estimated activities, calculated in the absence of this effect. Such deviations should correlate with the basicity of the amino group, being larger for the more basic, and consequently, more extensively protonated compounds.

This anticipated deviation from the estimated activities was confirmed by a plot of the pIC_{50} values of all compounds of sets A and B, calculated with the regression model of set A, against the experimental activities (Figure 1). The compounds of set B did not deviate randomly from the regression line drawn for set A. Instead, the majority of them concentrated above this line, in an indication that their activities

Table 1. Ring substitution pattern of the phenylisopropylamines **1–46**

	Compound	R-2	R-3	R-4	R-5	R-6
1	ETA	H	H	SCH_2CH_3	H	H
2	MTA	H	H	SCH_3	H	H
3	ITA	H	H	$SCH(CH_3)_2$	H	H
4	4-EtOA	H	H	OCH_3CH_2	H	H
5	4-MetOA	H	H	OCH_3	H	H
6	PCA	H	H	C1	H	H
7	DOM	OCH_3	H	CH_3	OCH_3	H
8	MDA	H	$O–CH_2$	–O	H	H
9	3,4-DMA	H	OCH_3	OCH_3	H	H
10	5-Br-2,4-DMA	OCH_3	H	OCH_3	Br	H
11	DOB	OCH_3	H	Br	OCH_3	H
12	DOI	OCH_3	H	I	OCH_3	H
13	2-Br-4,5-DMA	Br	H	OCH_3	OCH_3	H
14	2-Br-4,5-MDA	Br	H	$O–CH_2$	–O	H
15	2-Cl-4,5-MDA	C1	H	$O–CH_2$	–O	H
16	2.4-DMA	OCH_3	H	OCH_3	H	H
17	Aleph-1	OCH_3	H	SCH_3	OCH_3	H
18	Aleph-2	OCH_3	H	SCH_2CH_3	OCH_3	H
19	TMA	H	OCH_3	OCH_3	OCH_3	H
20	2-TMA	OCH_3	H	OCH_3	OCH_3	H
21	2,5-DMA	OCH_3	H	H	OCH_3	H
22	DOA	OCH_3	H	NH_2	OCH_3	H
23	FLA527	OCH_3	H	$N(CH_3)_2$	OCH_3	H
24	DOTFM	OCH_3	H	CF_3	OCH_3	H
25	2-NO2-MDA	NO_2	H	$O–CH_2$	–O	H
26	2-NO2-DMA	NO_2	H	OCH_3	OCH_3	H
27	DON	OCH_3	H	NO_2	OCH_3	H
28	FLA289	H	H	$N(CH_3)_2$	H	H
29	FLA558	F	H	$N(CH_3)_2$	H	H
30	FLA314	C1	H	$N(CH_3)_2$	H	H
31	FLA405	Br	H	$N(CH_3)_2$	H	H
32	FLA336	CH_3	H	$N(CH_3)_2$	H	H
33	FLA365	C1	H	$N(CH_3)_2$	H	C1
34	FLA384	H	CH_3	$N(CH_3)_2$	H	H
35	FLA727	H	H	$NHCH_3$	H	H
36	RAN113	CH_3	H	$NHCH_3$	CH_3	H
37	FLA334	H	H	NH_2	H	H
38	FLA668	CH_3	H	NH_2	H	H
39	FLA1088	C1	H	NH_2	H	C1
40	NBFO27	F	H	NH_2	H	H
41	FLA1085	C1	H	NH_2	H	H
42	NBF006	CH_3CH_2	H	NH_2	H	H
43	MSOA	H	H	$SOCH_3$	H	H
44	MSO2A	H	H	SO_2CH_3	H	H
45	4-ESO-2,5-DMA	OCH_3	H	$SOCH_2CH_3$	OCH_3	H
46	4-ESO2-2,5-DMA	OCH_3	H	$SO_2CH_2CH_3$	OCH_3	H

Table 2. HOMO energies and charges on the aromatic carbon atoms of compounds **1–46**, calculated by the AM1 method

Compound	E_{HOMO}(eV)	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
1	−8.082	−0.076	−0.113	−0.118	−0.228	−0.142	−0.111
2	−8.105	−0.075	−0.114	−0.117	−0.234	−0.139	−0.112
3	−8.078	−0.077	−0.113	−0.119	−0.223	−0.142	−0.113
4	−8.785	−0.102	−0.098	−0.155	0.079	−0.203	−0.097
5	−8.827	−0.101	−0.099	−0.153	0.074	−0.201	−0.097
6	−9.334	−0.066	−0.121	−0.122	−0.065	−0.122	−0.123
7	−8.879	−0.05	0.025	−0.128	−0.072	0.06	−0.169
8	−8.862	−0.065	−0.112	0.012	0.007	−0.11	−0.131
9	−8.541	−0.065	−0.177	0.059	0.055	−0.177	−0.127
10	−9.243	−0.078	0.073	−0.175	0.086	−0.187	−0.087
11	−9.118	−0.031	0.02	−0.103	−0.178	0.09	−0.175
12	−9.139	−0.025	0.016	−0.095	−0.275	0.098	−0.18
13	−8.782	−0.035	−0.164	−0.111	0.062	0.031	−0.172
14	−9.025	−0.033	−0.169	−0.09	0.006	0.024	−0.119
15	−8.971	−0.058	−0.063	−0.108	0.015	0.012	−0.109
16	−8.904	−0.112	0.079	−0.164	0.086	−0.208	−0.088
17	−7.923	−0.051	0.041	−0.135	−0.231	0.058	−0.168
18	−7.897	−0.053	0.042	−0.138	−0.225	0.057	−0.168
19	−8.468	−0.042	−0.199	0.075	0.047	0.025	−0.182
20	−8.556	−0.077	0.057	−0.171	0.082	0.001	−0.151
21	−9.068	−0.048	0.022	−0.118	−0.138	0.059	−0.17
22	−8.341	−0.093	0.066	−0.197	0.062	−0.007	−0.129
23	−8.107	−0.099	0.071	−0.209	0.097	−0.012	−0.122
24	−9.464	−0.009	0.013	−0.076	−0.18	0.118	−0.189
25	−9.622	−0.001	−0.115	−0.071	0.007	0.045	−0.124
26	−9.914	−0.001	−0.113	−0.085	0.031	0.068	−0.146
27	−9.639	0.003	0.01	−0.069	−0.149	0.133	−0.197
28	−8.198	−0.11	−0.094	−0.183	0.076	−0.188	−0.094
29	−8.387	−0.143	0.127	−0.229	0.107	−0.204	−0.072
30	−8.388	−0.1	−0.022	−0.187	0.085	−0.185	−0.088
31	−8.401	−0.078	−0.123	−0.166	0.07	−0.177	−0.097
32	−8.172	−0.109	−0.031	−0.185	0.077	−0.19	−0.093
33	−8.534	−0.089	−0.017	−0.189	0.099	−0.189	−0.016
34	−8.482	−0.082	−0.119	−0.07	0.036	−0.167	−0.116
35	−8.319	−0.11	−0.092	−0.186	0.061	−0.185	−0.092
36	−8.204	−0.105	−0.033	−0.186	0.065	−0.128	−0.092
37	−8.418	−0.111	−0.09	−0.188	0.055	−0.189	−0.09
38	−8.374	−0.11	−0.027	−0.19	0.057	−0.192	−0.089
39	−8.798	−0.092	−0.014	−0.193	0.077	−0.192	−0.015
40	−8.608	−0.144	0.13	−0.234	0.088	−0.206	−0.068
41	−8.602	−0.101	−0.018	−0.191	0.067	−0.189	−0.084
42	−8.373	−0.105	−0.026	−0.189	0.056	−0.191	−0.091
43	−9.152	−0.033	−0.141	−0.052	−0.563	−0.06	−0.148
44	−10.121	0	−0.157	−0.018	−0.829	−0.015	−0.151
45	−8.733	−0.018	0.032	−0.1	−0.549	0.118	−0.196
46	−9.106	0.011	0.026	−0.082	−0.816	0.169	−0.205

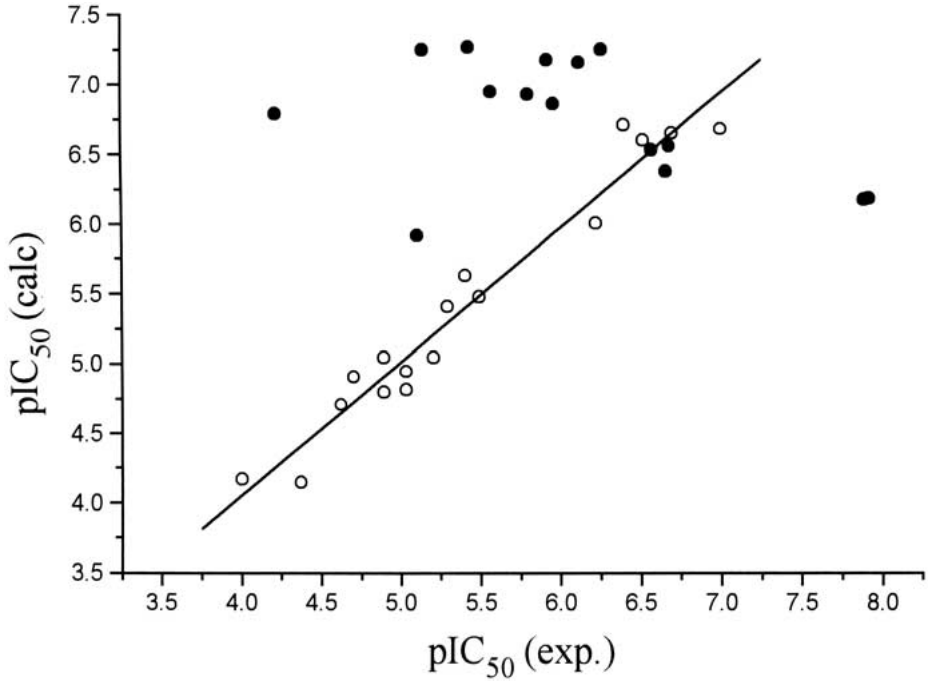


Figure 1. Plot of calculated *vs* experimental pIC_{50} values of amines **(1)–(18)** (open circles, set A) and **(28)–(42)** (full circles, set B). The regression model was derived for set A only.

were in general overestimated by the model. This was reinforced by a comparison of the estimated pIC_{50} values for compounds (**22**) and (**23**) with their reported activities. Both compounds had been evaluated together with set A phenylisopropylamines, and found to be inactive ($pIC_{50} < 4.0$). Though extrapolations from a regression model are statistically dubious and should be regarded with caution, their qualitative significance may be taken *cum grano salis*. The estimated pIC_{50} values for (**22**) and (**23**), 6.06 and 6.48, respectively, also overestimated the activities of these 4-aminophenylisopropylamines.

These systematic deviations led us to search for a possible correlation between the residuals of the predicted pIC_{50} values of the compounds of set B and the basicity of the aromatic amino substituents. The latter was estimated from Hammett relationships [25], applied to substituted anilines, where the side-chain of the amphetamine was replaced by a methyl group. We employed for anilines the relationship $pK_a = 4.58 - 2.88.\Sigma\sigma$ [26], and for N,N-dimethylanilines the equation $pK_a = 5.06 - 3.46.\Sigma\sigma$ [27], where the pK_a values were a measure of the acidity of the protonated amine. The pK_a values for the two N-methylanilines of the set (compounds **35** and **36**) were estimated from those of the corresponding anilines, adding 0.2 pK_a units to the calculated values [25]. The estimated pK_a values thus obtained are given in Table 4.

Table 3. Results of the best multiple linear regressions of the pIC_{50} values of the two sets of phenylisopropylamines on the electronic descriptors of Table 2

	Data sets[a]		
	A+B	A	B
Number of data points	33	18	15
Intercept	12.81	6.42	−5.35
E_{HOMO} coefficient	0.615	0.43	−1.51
Coefficient of Q_1	–	−26.86	25.39
Coefficient of Q_2	–	−5.04	–
Coefficient of Q_3	–	−6.00	–
Coefficient of Q_4	–	−1.87	29.88
Coefficient of Q_5	–	–	–
Coefficient of Q_6	16.76	–	9.44
F value	18.34	56.89	8.33
R^2	0.55	0.96	0.77
Standard error of estimate, s^2	0.46	0.05	0.32
Crossvalidated coefficient, R^2	0.48	0.89	0.63

[a]Set A, data from reference [18]; set B, data from reference [17].

A plot of the predicted residuals, against the estimated pK_a values of Table 4 yielded the linear dependence $\Delta pIC_{50} = pIC_{50}^{calc} - pIC_{50}^{exp} = 1.22\ pK_a - 4.89$,

Table 4. Experimental and predicted pIC_{50} values of phenylisopropylamines **1–46**.

	Phenylisopropylamine	Experimental value[a]	Predicted value[b]	Estimated pK_a value[c]
1	ETA	7.00	6.68	
2	MTA	6.70	6.66	
3	ITA	6.40	6.71	
4	4-EtOA	6.70	6.65	–
5	4-MetOA	6.52	6.61	–
6	PCA	5.40	5.63	–
7	DOM	4.62	4.71	–
8	MDA	5.03	4.83	–
9	3,4-DMA	4.70	4.92	–
10	5-Br-2,4-DMA	4.89	5.05	–
11	DOB	4.00	4.17	–
12	DOI	4.37	4.16	–
13	2-Br-4,5-DMA	5.03	4.95	–
14	2-Br-4,5-MDA	4.89	4.80	–
15	2-Cl-4,5-MDA	5.20	5.05	–
16	2.4-DMA	6.22	6.02	–
17	Aleph-1	5.29	5.41	–
18	Aleph-2	5.49	5.48	–
19	TMA	<4.00	4.36	–
20	2-TMA	<4.00	5.39	–
21	2,5-DMA	<4.00	4.66	–
22	DOA	<4.00	6.06	4.66
23	FLA527	<4.00	6.30	5.16
24	DOTFM	<4.00	3.31	–
25	2-NO2-MDA	<4.00	3.29	–
26	2-NO2-DMA	<4.00	3.20	–
27	DON	<4.00	2.83	–
28	FLA289	5.43	7.27	5.54
29	FLA558	5.92	7.18	4.37
30	FLA314	6.68	6.57	4.26
31	FLA405	6.66	6.38	4.20
32	FLA336	5.57	6.95	5.75
33	FLA365	7.89	6.17	2.98
34	FLA384	5.10	5.92	5.20
35	FLA727	6.26	7.26	5.18
36	RAN113	5.96	6.87	5.07
37	FLA334	5.14	7.25	4.98
38	FLA668	5.80	6.94	5.16
39	FLA1088	7.92	6.19	2.85
40	NBF027	6.12	7.16	4.00
41	FLA 1085	6.57	6.54	3.92
42	NBF006	4.22	6.79	5.18
43	MSOA	<4.00	5.45	–
44	MSO2A	<4.00	4.52	–
45	4-ESO-2,5-DMA	<4.00	4.61	–
46	4-ESO2-2,5-DMA	<4.00	4.10	–

[a]Data from references [17] for compounds **28–42**, and [18] for compounds **1–27**.
[b]Calculated by the corresponding regression equation derived for set A.
[c]Estimated pK_a value of a toluidine with the same pattern of ring substitution of compounds **22**, **23** and **28–42**.

Table 5. MAO-A inhibition by sulfoxyl- and sulfonyl-derivatives (**43**), (**44**), (**45**) and (**46**), at different concentrations

Compound	% Inhibition		
	10^4 M	5×10^{-5} M	10^{-5} M
43	38	n.d.[a]	0
44	41	16	0
45	30	n.d.[a]	1
46	0	n.d.[a]	0

[a]Not determined.

with a significant correlation coefficient ($R^2 = 0.72$, $p = 0.00006$) . This lent support to the hypothesis that the observed deviations of set B should be ascribed to the partial protonation of the 4-amino group by a hydrogen-bond-donor fragment of the receptor.

The above interpretation, though plausible, could not be taken as conclusive, in our search for evidence of charge-transfer interactions in the MAO-A inhibition by phenylisopropylamines. It was hoped that the evaluation of novel derivatives of set A compounds with reasonable activities might be used to test the regression model. This expectation was only partially fulfilled, since the derivatives newly prepared by us, compounds (**43**), (**44**), (**45**) and (**46**), proved to have inhibitory activities below the threshold pIC_{50} value of 4.0. Their activities at concentrations higher than 10^{-6} M are given in Table 5. It is seen that the two oxidized derivatives of methylthioamphetamine, compounds (**43**) and (**44**), have similar inhibitory activities, whereas the IMAO activity of sulfoxide (**45**) is higher than that of its sulfonylated analog (**46**). From a qualitative point of view, it is clear that the conversion of two fairly active members of set A, MTA (**2**) and Aleph-2 (**18**), into four oxidized derivatives, where the electron-donor substituent at position 4 is replaced by electron-withdrawing groups, leads to a substantial decrease of their inhibitory activities. This is in agreement with the regression model and the hypothesis that electron-rich ring systems and higher HOMO levels favor the IMAO activity of phenylisopropylamines. It also agrees with the observation that compounds (**24**)–(**27**), variously substituted with an electron-withdrawing group (NO_2, CF_3), likewise exhibited some of the lowest HOMO energies of the set, and were all inactive.

In conclusion, the present analysis of two sets of MAO-A-inhibiting phenylisopropylamines supports the suggestion that electron-rich ring systems favor charge-transfer interactions with an isoalloxazine ring of the FAD cofactor, thereby increasing their IMAO activity. It also draws attention to the possibility of partial protonation of the basic 4-amino substituent in many of these compounds by some hydrogen-bond-donating fragment of the enzyme. At this stage, this suggestion lacks further experimental support. However, since the actual molecular drug-enzyme interactions in MAO inhibition are at present poorly understood, it should deserve consideration in the future.

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