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QSAR analysis of coumarin derivatives as potent monoamine oxidases inhibitors

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Coumarins are a series of compounds with a variety of properties, one of which is the inhibitory activity against monoamine oxidases (MAOs), which are a pair of isoenzymes type A and B that regulate the levels of monoamines-neurotransmitters in the body. The disbalance in the levels of these neurotransmitters leads to a higher risk of neural cell death and causes neuro degenerative diseases, like Parkinson's and Alzheimer's diseases. A group of coumarin derivatives were used for a QSAR study in an attempt to clarify ways of searching for new drugs. The used descriptors were calculated on the base of semi-empirical quantum-chemical optimization of the molecular structures. Only the lipophilicity descriptor was calculated empirically. The found correlations show that the inhibitory activity against MAOs is connected to the polarizability, dipole moment, E_{HOMO}, E_{LUMO} and lipophilicity-index π.

Key words: QSAR, MAO inhibitors, coumarins.

INTRODUCTION

The monoamine oxidases (MAOs) are FAD-dependent enzymes that catalyze the deamidation of the monoamines dopamine, serotonin, adrenaline, noradrenaline, etc., which are important neurotransmitters.

Two types of MAOs - A and B are identified [1]. They differ by almost 30% in amino acid sequences. As a result, there is a significant difference in their properties. MAO-A has affinity for serotonin, norepinephrine and dopamine while MAO-B - for phenylethylamine and benzylamine [2]. These enzymes are a subject of many studies due to the effect they have on the metabolism of neurotransmitters and related diseases such as depression, Alzheimer's and Parkinson's disease.

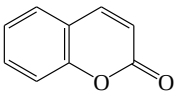

Figure 1. Coumarin

Coumarins (1-benzopyrane-2-one) are a large group of compounds, some of which can be found in the plants. Their clear inhibitory properties against MAOs have been of interest over the last decades. Due to differences in the two enzymes, it is possible to inhibit selectively and reversibly only one of them [3-5].

Coumarins also possess other biological activities, such as anticancer, antioxidant, anti-inflammatory, vasorelaxant, antimicrobial, antiviral activity [6]. They also inhibit other enzymes [7].

Modifications in coumarin at positions 4 and 7 have been found to improve activity and selectivity toward MAO-B [8].

EXPERIMENTAL

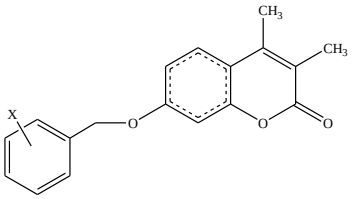

Figure 2. General structure of the tested compounds

It has been found in the literature that 71 compounds have been synthesized in order to find more effective MAO inhibitors [9]. 18 of them differ only by their substituents at the phenyl ring of the benzyl alcohol to which 3,4-dimethyl-7-hydroxycoumarin has been etherified (see Figure 2). This makes them a suitable group of congeners for QSAR analysis. Methyl groups at the 3th and 4th position serve for reducing the toxicity [10]. Modifications in the phenyl ring noticeably impact on the MAO inhibitory capabilities, and the close structures of the congeners in the group must ensure identical mechanism of interaction of all of them with the enzyme.

The main purpose of this work is to perform a QSAR analysis of the correlations between quantum-chemically and purely parametrically calculated descriptors and inhibitory activity against MAO of a series of coumarin derivatives.

CALCULATIONS

All calculations in this work were made with the program package Hyperchem 8.0 Professional edition [11]. This package was chosen for convenience: it enables the easy creation of molecular models for calculating important molecular descriptors. PM3 Hamiltonian was used [12] as it is adapted in HyperChem 8.0. We

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selected a boundary gradient norm from 0.01 kcal/Å. The same semi-empirical quantum-chemical method was used for the geometric optimization, as well as the HOMO and LUMO energies, dipole moment and polarizability.

Log P was calculated by using the atomic parameters of Ghose, Pritchett and Crippen [13].

The regression analysis was performed using the MS Excel program package.

The statistical significance of the found correlations was proven by the product–moment correlation coefficient [14,15].

RESULTS AND DISCUSSION

Our conclusions are based on the data from Table 1. pIC50 is a negative decimal logarithm of the inhibitor concentration that reduces the activity of the enzyme by 50%. It was used in all correlations below for the group of 18 compounds. The relationship between polarizability and pIC_{50} against MAO-B is presented schematically in Fig. 3.

Table 1. Congeners, calculated descriptors and inhibitory activity against MAO-A and MAO-B (Figure 2).

No.	Substituent	E_{HOMO} eV	E_{LUMO} eV	ΔE eV	logP	π	V Å^3	Polarizability a.u.	Dipole Moment Debye	MAO-A IC_{50} [μM]	MAO-B IC_{50} [μM]
0	-	-8.974	-0.841	8.132	0.77	0.00	840.07	172.5	5.761	6.16	8.36
1	o-CH3	-8.988	-0.846	8.142	0.92	0.15	876.65	179.5	5.752	5.64	8.06
2	o-CN	-9.144	-0.982	8.162	0.49	-0.28	882.27	187.7	6.628	6.38	7.64
3	m-CH3	-8.99	-0.845	8.144	0.92	0.15	883.76	179.2	5.759	5.48	8.36
4	m-OH	-9.024	-0.873	8.151	-0.26	-1.03	852.95	176.0	5.622	6.38	8.01
5	m-OCH3	-9.009	-0.862	8.148	-0.23	-1.00	908.09	185.7	5.687	5.82	8.44
6	m-OCF3	-9.122	-0.959	8.162	1.71	0.94	937.51	185.5	5.878	5.23	7.94
7	m-F	-9.091	-0.932	8.159	0.17	-0.60	839.58	171.6	5.847	6.24	8.55
8	m-Cl	-9.064	-0.910	8.153	0.54	-0.23	880.77	182.1	5.702	5.95	8.48
9	m-CF3	-9.167	-0.998	8.169	1.34	0.57	908.34	179.2	6.360	5.72	8.24
10	m-CN	-9.155	-0.992	8.163	0.49	-0.28	890.14	189.0	6.676	6.66	7.97
11	p-CH3	-8.97	-0.836	8.135	0.92	0.15	879.69	178.2	5.832	5.43	8.21
12	p-F	-9.085	-0.927	8.158	0.17	-0.60	838.55	171.6	5.672	6.91	8.52
13	p-Cl	-9.074	-0.919	8.155	0.54	-0.23	879.15	182.0	5.793	6.91	8.59
14	p-CN	-9.169	-1.007	8.162	0.49	-0.28	893.09	189.3	7.075	7.00	8.43
15	m,p-F,F	-9.179	-1.010	8.169	-0.43	-1.20	854.97	174.0	6.355	6.91	8.94
16	m,m-F,F	-9.153	-0.979	8.174	-0.43	-1.20	850.36	173.0	5.629	6.17	8.52
17	m,p-Oh,F	-9.105	-0.948	8.157	-0.86	-1.63	867.26	178.7	6.407	6.94	8.13

* Inhibitory activity is according to [9].

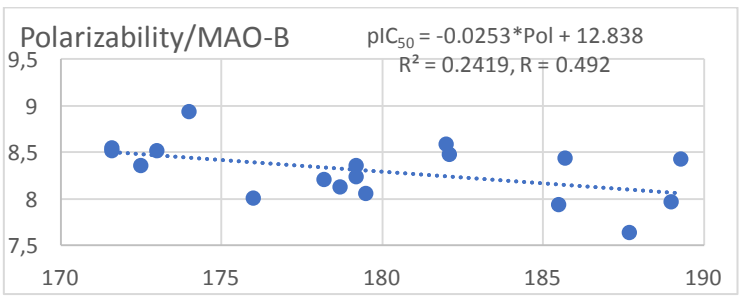

Figure 3. Relationship between polarizability and pIC_{50} against MAO-B

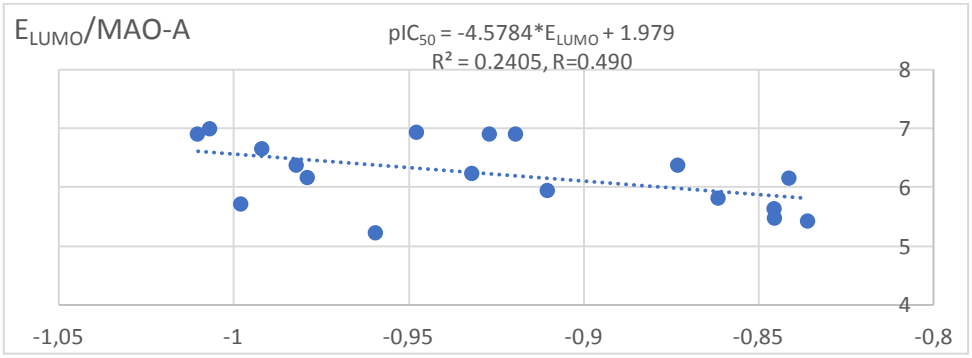

Figure 4. Correlation between the energy of LUMO and IC_{50} of MAO-A

We found that there is a significant linear correlation between both variables. The correlation coefficient RpIC,Pol is 0.492. It is higher than the critical value R* = 0.468 for significant correlation for sample size 18 at 95% confidence level [14,15]. The obtained linear correlation is described by the regression equation:

pIC50 = - 0.0253 (±0.0236) × Pol + 12.838 (±4.2607), RpIC,Pol = 0.492, s = 0.2741,

where s is the standard deviation of the regression.

The increase in polarizability of congeners leads to a decrease in inhibitory activity against MAO-B. Such dependence was not found for MAO-A.

The most active compound in this group is 7-(m,p-difluoro)-4-dimethylcoumarin (pIC50 = 8.94 μM), and the most inactive is 7-(o-cyano)-benzyloxy-3,4-dimethylcoumarin (pIC_{50} = 7.64 μM). The significant difference in the electronic effects of the substituents in the two compounds suggests that we need to seek correlation with the descriptors of the electronic properties of the congeners. Probably the volume of the investigated molecules is more substantial for the polarizability rather than the mobility of their electronic density.

Further, we studied the correlation between the pIC_{50} against MAO-A and the energy of LUMO (see Figure 4). The correlation coefficient RpIC,LUMO is 0.49, which is higher than the critical value R* = 0.468. Therefore, there is sufficient evidence to support the claim that there is a significant linear correlation between the pIC_{50} against MAO-A and the energy of LUMO [14,15]. The corresponding regression equation is:

pIC50 = - 4.5784 (±4.3123) × LUMO + 1.979 (±4.0021), RpIC,LUMO = 0.490, s = 0.5235.

An increase in LUMO energy leads to lowering of pIC50 and inhibitory activity against MAO-A. E_{LUMO} describes the oxidative and electron withdrawing properties of the molecules, which means that the lowering of these properties increases the activity against MAO-A. There is no similar dependence for MAO-B. Significant linear correlations were also found between pIC_{50} against MAO-A and the energy of HOMO (see Figure 5). The correlation coefficient RpIC,HOMO is 0.479, which is higher than the critical value R* = 0.468. The corresponding regression equation is:

pIC50 = - 3.8123 (±3.7055) × HOMO + 28.4021 (±33.6513), RpIC,HOMO = 0.479, s = 0.5279.

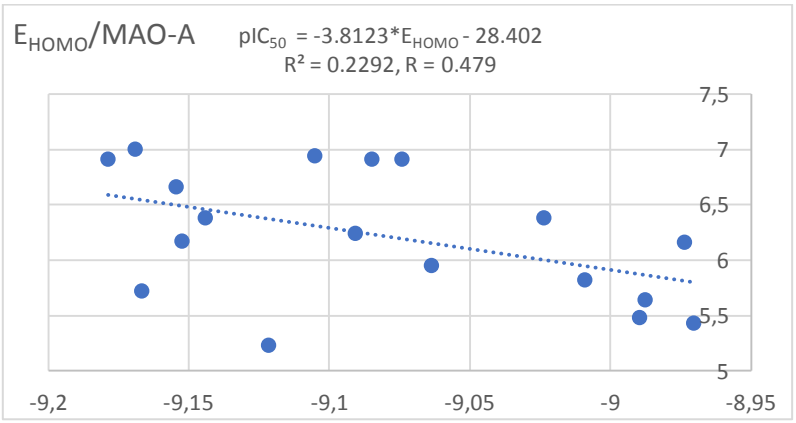

Figure 5. Correlation between the energy of HOMO and IC_{50} of MAO-A.

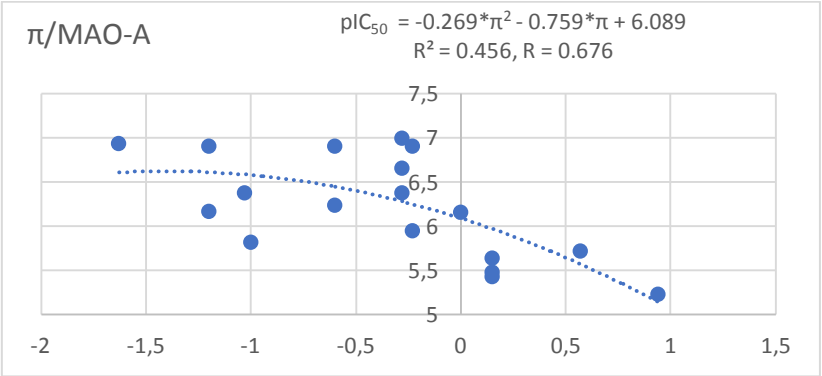

Figure 6. Parabolic correlation between lipophilicity descriptor of substituents (π) and pIC_{50} of MAO-A

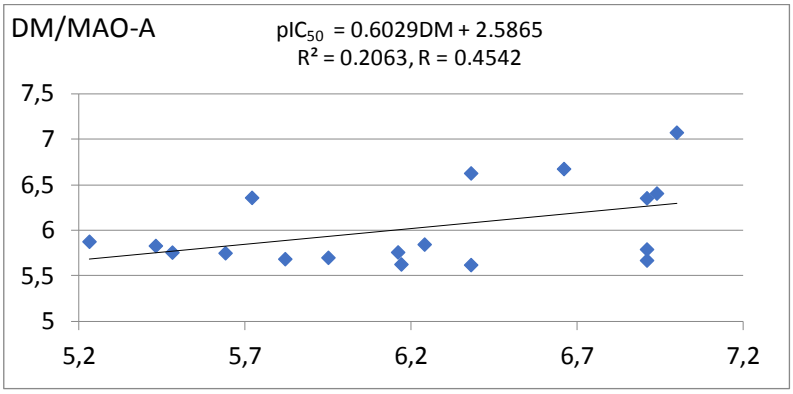

Figure 7. Relationship between dipole moment and IC_{50} against MAO-A

Lowering of E_{HOMO} in fact increases the reductive and electron donating properties of the molecules. Therefore, the best reductors are the weakest inhibitors against MAO-A.

When we studied the relationship between the lipophilicity descriptor (π=log$P_{R\text{-}X}$-log$P_{R\text{-}H}$) of the substituents in the phenyl ring of the benzyl ethers and their MAO-A inhibitory activity, we found a significant linear correlation with a correlation coefficient of 0.6311, but also a parabolic correlation with an even higher correlation coefficient $R_{pIC,\pi}$=0.676. The corresponding parabolic dependence is described by the equation:

$pIC_{50} = -0.269 \times \pi^2 - 0.759 \times \pi + 6.089$, $R_{pIC\_B,\pi} = 0.676$.

This parabolic correlation is natural and has a maximum at π = -1.411. Close to this lipophilicity among the congeners can be obtained with substituents OH group or F atom.

Finally, we present a significant linear correlation between pIC_{50} against MAO-A and the dipole moment of the compounds, which is not so confident as the above results. Namely, the correlation coefficient $R_{pIC,DM}$ is 0.454. It is higher than the critical value R^* = 0.400 for significant correlation for sample size 18 at 90% confidence level [14,15]. The linear correlation is described by the regression equation:

pIC_{50} = 0.6029 (±0.6268) × DM + 2.5865 (±3.7852), $R_{pIC,DM}$ = 0.4542, s = 0.5354.

An increase in pIC_{50} values was observed when the dipole moment increased. This leads to the conclusion that a higher dipole moment is more favorable for the inhibitory activity among the selected group of compounds for MAO-A inhibitors.

CONCLUSIONS

- In this group of congeners the volume changes are insignificant to permit drawing a conclusion, but a decrease in inhibitory activity against MAO-B with an increase in polarizability can be explained as this: the increase in volume leads to a decrease in inhibitory activity;
- the lowering of oxidative and electron withdrawing properties increases the activity against MAO-A;
- the best reducers are the weakest inhibitors against MAO-A;
- the best lipophilicity within this congeners group is π = -1.411;
- the higher dipole moment is more favorable for the inhibitory activity among the selected group of compounds for MAO-A inhibitors.

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