Bulgarian Chemical Communications, Volume 52, Issue A (pp. 93-100) 2020 DOI: 10.34049/bcc.52.A.330

QSAR analysis of coumarins, flavones and their bicyclo ethers as monoamine oxidases inhibitors

A. Zh. Rizakov, M. K. Kolev, Zh. A. Velkov*

South-West University "Neofit Rilski", 66 Ivan Mihajlov Str., Blagoevgrad 2700, Bulgaria

Received August 11, 2019 Revised February 15, 2020

Due to their role in the metabolism of monoamine-neurotransmitters, monoamine oxidases (MAO) represent a significant pharmacological interest in the treatment of different neurodegenerative disorders. Various observations highlight the need of novel, reversible MAO inhibitors as Parkinson's disease drugs. In this work we use parametrically and quantum-chemically calculated electronic descriptors. All the labor in this work was performed by the software package Hyperchem 8.0 Professional edition and the anchored therein PM3 semi-empirical quantum-chemical method and QSAR-empirical module. Significant linear correlations of the inhibitory activity against the MAO enzymes have been found with molecular surface, polarizability, dipole moment and lipophilicity descriptor. The found correlations clarify the requirements for MAO inhibitor candidates and will guide future synthetic efforts.

Key words: MAO inhibitors, QSAR, coumarins, flavones

INTRODUCTION

Coumarins (1,2-benzopyrone) and flavones (1,4-benzopyrone) are cognate classes of compounds containing condensed benzene and pyrone rings [1,2]. Their chemical structure is presented schematically in Fig. 1. These compounds are enzyme inhibitors, growth hormones, participate in respiratory control, photosynthesis, and protection against infections. They have also been found to possess anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, antithrombotic, antiviral and anti-carcinogenic activities [3,4].

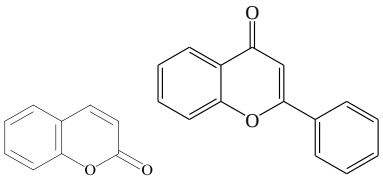


Figure 1. Coumarin and flavone

Monoamine oxidases (MAOs) are FAD-containing enzymes linked to the mitochondrial outer membrane of neuronal, glial and other cells. The MAO's functions include regulation of the biogenic amines levels in the brain and peripheral tissues by catalysing their oxidative deamidation. MAO preferentially deamines serotonin, norepinephrine and epinephrine, and is irreversibly inhibited by low concentrations of clorgillin [5]. Two types of MAOs – A and B can be identified [5], which differ significantly in their amino acid sequence and substrate specificity.

Due to their role in the metabolism of monoamine-neurotransmitters, MAO-A and MAO-B represent a significant pharmacological interest in the treatment of Parkinson's disease. Dopamine-replacement therapy is the most commonly used treatment in clinical practice of this neurodegenerative disorder. However, the rapid metabolic transformation of dopamine requires its use in combination with selective and irreversible MAO-B inhibitors [6].

Various observations highlight the need for novel, possibly reversible MAO-B inhibitors in Parkinson's disease therapy and require further research into the possible role of MAO-A and B inhibitors. Unfortunately, the rational design of the new MAO inhibitors is severely hampered by the lack of reliable three-dimensional structural information of the active sites of the two isoenzymes. For this reason, indirect studies [7-11] of structurally distinct compounds as MAO inhibitors have been conducted. However, the molecular structure requirements for selective inhibitors of MAO have only been partially elucidated.

In order to gain a better understanding of the relations between inhibitory activity against MAO and the compounds structure, and as a consequence to improve their activity, various 3-, 4-, 6-, and 7-substituted coumarins, flavones and their bicyclo ethers have been synthesized and tested *in vitro* [12]. The structure of the investigated coumarins, flavones and bicyclo ethers is schematically presented in Fig. 2. The obtained results reveal interesting features for the topography of the MAO-A and MAO-B active site.

Coumarin derivatives have been found to be reliable, reversible, competitive inhibitors of MAO

* To whom all correspondence should be sent.
E-mail: jivko_av@abv.bg

and usually have high selectivity against MAO-B. Their important feature is the lipophilicity. The presence of a polar functional group increases the activity. This implies the presence of a polar pocket in the active center of the isozymes. In addition, the importance of the electronic effects has been evaluated, represented by Swain-Lupton F and R constants [13].

In this work we will use parametrically calculated and electronic density descriptors obtained by quantum-chemical calculations. Despite the proven utility of the field constant (F) and the resonance effect constant (R) of the substituents in the aromatic ring, they are obtained purely parametrically as a linear combination of Hammett σ_p and σ_m parameters, which could be the reason for the lack of statistically more reliable QSAR models.

Table 1. Substituents in coumarin derivatives (according to Figure 2).

Compounds	X_1	X_2	X_3	X_4
1	H	H	H	H
2	H	H	H	$OCH_2C_6H_5$
3	H	H	H	$CH_2OC_6H_5$
4	H	H	H	$CH_2NHC_6H_5$
5	H	H	OCH_3	$OCH_2C_6H_5$
6	H	H	$OCH_2C_6H_5$	OH
7	H	H	glucosyl	OH
8	H	H	glucosyl	$OCH_2C_6H_5$
9[c]	H_2	H_2	H	$OCH_2C_6H_5$
10	H	CH_3	H	$OCH_2C_6H_5$
11	H	CH_3	H	$OCH_2C_6H_4$-3'-NO_2
12	H	C_6H_5	H	$OCH_2C_6H_5$
13	H	CF_3	H	$OCH_2C_6H_5$
14	H	OH	H	$OCH_2C_6H_5$
15	CH_3	CH_3	H	$OCH_2C_6H_5$
16	CH_3	CH_3	H	$NHCH_2C_6H_5$
17	CH_3	CH_3	H	$O(CH_2)_2C_6H_5$
18	CH_3	CH_3	H	$OCH(CH_3)C_6H_5$
19	$(CH_2)_3$		H	$OCH_2C_6H_5$
20	$(CH_2)_4$		H	$OCH_2C_6H_5$
21	(-CH=CH-)$_2$		H	$OCH_2C_6H_5$
22	C_6H_5	CH_3	H	$OCH_2C_6H_5$
23	CH_3	CH_3	H	$NHCOC_6H_5$
24	CH_3	CH_3	H	$OSO_2C_6H_5$
25	CH_3	CH_3	H	$OSO_2C_6H_4$-4'-CH_3
26	CH_3	CH_3	H	$OSO_2C_6H_4$-4□-OCH_3
27	CH_3	CH_3	H	$OSO_2C_6H_4$-4□-NO_2
28	CH_3	CH_3	H	$NHSO_2C_6H_4$-4□-CH_3
29	CH_3	CH_3	H	*trans*-$CH=CHC_6H_5$
30	CH_3	CH_3	OH	$OCH_2C_6H_5$
31	CH_3	CH_3	$OCH_2C_6H_5$	OH
32	CH_3	CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$
33[e]	CH_3	CH_3	H	$OCH_2C_6H_5$
34	CH_3	CH_3	H	OH

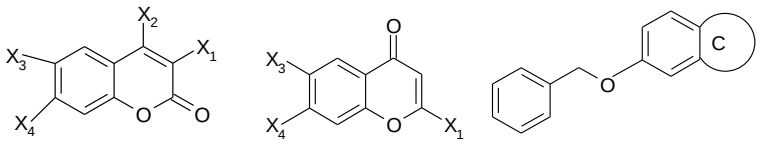
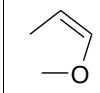
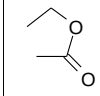
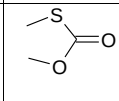
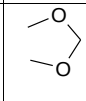
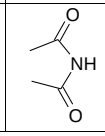
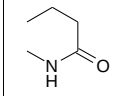
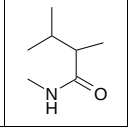


Figure 2. General structure of the investigated coumarins, flavones and bicyclo ethers.

Table 2. Substitutes in the flavone (accordting to Figure 2).

Compound	X_1	X_3	X_4
35	H	H	$OCH_2C_6H_5$
36	H	$OCH_2C_6H_5$	H
37	CH_3	$OCH_2C_6H_5$	H
38	C_6H_5	H	$OCH_2C_6H_5$
39	C_6H_5	$OCH_2C_6H_5$	H

Table 3. Bicyclo-benzyl ethers (according to Figure 2).

Compound	40	41	42	43	44	45	46	47	48
C									

CALCULATIONS

All calculations in this work were performed by the software package Hyperchem 8.0 Professional edition [14]. This package was chosen for convenience: it enables the easy creation of molecular models and the calculation of important molecular descriptors. PM3 Hamiltonian was used [15] as it is built into HyperChem 8.0. The optimization procedure was performed at a boundary convergence limit of 0.01 kcal/Å. The calculation of HOMO and LUMO energy, dipole moment and polarizability was done at the same semi-empirical quantum-chemical level. The regression analysis was performed using the MS Excel program package.

The other descriptors used in the QSAR analysis were calculated on a parametric level using atomic parameters derived from Ghose, Pritchett and Crippen [16,17]. The obtained results are presented in Table 4.

We have investigated the possible linear correlation between the inhibitory activity (pIC_{50}) with respect to MAO-A and the surface of the compounds belonging to a group of 28 coumarins. Not all compounds listed in Table 4 were included in the study. The reason some compounds to be removed is their low solubility and unclear inhibitory activity.

It turned out that there is a significant linear correlation between both variables (see Figure 3). For these 28 compounds the correlation coefficient $R_{pIC,SA}$ is 0.6236. It is higher than the critical value $R^* = 0.374$ for significant correlation for sample size 28 at 95% confidence level [18]. The correlation is described by the regression equation:

$$pIC_{50} = 0.0116\ (\pm 0.0059) \times SA + 0.5746\ (\pm 2.5787),\ R_{pIC,SA} = 0.6236,\ s = 0.8472,\ F = 16.5480,$$

where the standard deviation s of the regression and the F-test statistic are also shown.

As the molecule surface area increases, the pIC_{50} increases, which means that the activity against MAO-A increases. Therefore, more active substances from these groups can be sought among the candidates with a surface area of about 530 $Å^2$ and more.

The surface of the compounds does not correlate with the inhibitory activity with respect to MAO-B.

All the extensive descriptors like volume and molecular mass also correlate well with the inhibitory activity of the compounds against MAO-A, but with lower correlation coefficients.

It was found, however, that the increase in polarity of the compounds results in an increase in the inhibitory activity against MAO-A (see Figure 4). We have found a significant linear correlation between the pIC_{50} against MAO-A and the dipole moment of a group consisting of 20 compounds. Besides the compounds with low solubility we have also excluded nitro- and sulfur-containing compounds for which the dipole moment is overestimaded by the PM3 semi-empirical method [19].

RESULTS AND DISCUSSION

Table 4. Calculated descriptors of the molecules presented in Tables 1, 2 and 3.

No	SA1 Å^2	SA2 Å^2	V Å^3	EH Kcal/mol	logP	Ref. αÅ	Mass amu	E_{HOMO} eV	E_{LUMO} eV	ΔE eV	Dip. Mom. D	Mean Polar. a.u.	Charge$^-$	Charge$^+$	MAO A[a]	MAO B[a]
1	242.86	306.67	454.57	-4.09	0.32	45.60	146.15	-9.49	-0.99	8.49	4.42	83.80	-0.33	0.39	4.39	4.92
2	371.72	463.93	742.30	-6.15	0.34	80.72	252.27	-9.20	-0.95	8.25	3.91	149.50	-0.33	0.39	5.17	7.26
3	388.43	468.54	751.05	-6.30	0.34	80.72	252.27	-9.33	-1.06	8.27	3.94	152.40	-0.33	0.39	6.41	7.07
4	387.43	475.50	759.93	-6.94	0.02	82.67	251.28	-8.71	-1.06	7.65	5.03	157.10	-0.33	0.39	4.38	5.67
5	417.25	492.06	807.91	-7.40	-0.66	87.10	282.30	-9.20	-1.11	8.09	4.33	166.30	-0.33	0.39	-	5.17
6	370.66	471.52	760.81	-11.96	-0.69	82.33	268.27	-9.22	-1.06	8.15	2.93	159.70	-0.33	0.39	4.63	5.69
7[b]	395.36	505.74	835.82	-23.51	-2.88	79.56	324.29	-9.39	-1.47	7.92	2.76	158.60	-0.39	0.39	-	-
8	469.02	623.21	1078.95	-16.60	-1.83	113.08	414.41	-8.95	-1.09	7.86	6.48	215.90	-0.39	0.49	-	-
9[c]	401.90	489.29	787.14	-17.86	-1.59	84.01	284.27	-9.44	-1.08	8.36	4.65	151.20	-0.30	0.41	-	-
10	420.53	494.91	796.51	-5.35	0.49	85.01	266.30	-9.38	-1.05	8.33	5.03	159.10	-0.33	0.39	5.71	7.74
11	474.85	539.96	884.53	-21.7	-3.17	91.89	313.31	-9.28	-1.08	8.20	4.20	176.70	-0.33	0.39	6.90	7.88
12	464.50	579.79	959.97	-7.36	0.94	109.24	328.37	-9.31	-1.08	8.22	4.48	205.30	-0.33	0.39	-	-
13	438.57	506.73	822.48	-6.04	0.91	85.94	320.27	-9.56	-2.18	7.38	3.28	167.80	-0.31	0.40	-	5.86
14	396.48	471.44	768.29	-12.43	-0.69	82.33	268.27	-9.45	-1.11	8.35	5.93	155.40	-0.33	0.41	-	5.80
15	451.21	510.33	841.53	-4.71	0.77	89.36	280.32	-9.17	-0.97	8.21	5.06	169.90	-0.33	0.40	6.16	8.36
16	452.43	527.18	852.55	-5.27	0.45	91.31	279.34	-8.62	-0.82	7.79	5.11	180.10	-0.34	0.40	5.80	6.79
17	471.10	535.33	887.40	-4.95	1.02	94.12	294.35	-9.02	-0.87	8.15	5.78	177.60	-0.34	0.40	6.00	8.25
18	466.49	531.95	885.09	-3.97	1.18	93.78	294.35	-9.17	-0.97	8.20	4.41	176.20	-0.33	0.40	5.45	6.49
19	414.34	527.56	863.52	-4.90	0.66	92.16	292.33	-8.93	-0.88	8.04	3.70	176.20	-0.34	0.42	5.80	8.46
20	420.08	536.02	898.03	-4.77	1.06	96.76	306.36	-8.93	-0.80	8.13	3.61	180.40	-0.34	0.40	5.80	8.46
21	407.05	520.78	865.65	-7.00	0.54	99.00	302.33	-8.89	-0.87	8.03	3.18	186.70	-0.33	0.41	-	7.30
22	470.65	588.16	994.70	-6.97	1.22	113.60	342.39	-8.89	-0.98	7.91	3.80	216.00	-0.33	0.40		-
23	447.15	518.69	846.98	-5.80	0.01	91.54	293.32	-8.96	-0.93	8.03	7.00	181.50	-0.34	0.40	5.86	6.72
24	492.52	544.44	886.05	-8.07	-0.09	93.84	330.36	-9.03	-1.07	7.96	6.36	189.40	-0.84	2.39	7.12	5.28
25	526.12	566.95	935.50	-6.62	0.07	98.12	344.38	-9.00	-1.05	7.96	6.74	199.70	-0.84	2.39	7.33	-

26	541.73	577.57	958.51	-9.47	-1.08	100.22	360.38	-9.00	-1.02	7.98	5.97	206.80	-0.84	2.39	7.15	4.77
27	536.63	569.67	946.90	-12.8	-4.77	99.06	375.35	-9.27	-2.02	7.24	4.89	205.90	-0.84	2.39	7.90	-
28	534.77	575.79	944.49	-7.24	-0.25	100.07	343.4	-8.90	-1.00	7.90	8.31	203.60	-0.84	2.26	4.17	-
29	460.41	519.83	841.98	-3.94	1.89	93.07	276.33	-8.74	-1.21	7.53	4.72	199.00	-0.34	0.40	6.39	7.55
30	451.96	521.37	853.89	-8.64	-0.26	90.97	296.32	-9.02	-1.05	7.98	4.20	174.80	-0.34	0.40	5.03	7.55
31	447.70	524.79	853.04	-9.66	-0.26	90.97	296.32	-8.96	-0.92	8.04	6.13	176.50	-0.34	0.40	3.95	5.51
32	576.20	660.22	1133.10	-6.15	0.79	124.49	386.45	-8.71	-0.88	7.82	4.50	239.70	-0.34	0.40	-	-
33	466.25	534.59	874.92	-3.33	0.92	93.65	294.35	-8.96	-0.82	8.14	5.38	179.80	-0.34	0.40	6.25	5.48
34	319.31	362.24	563.85	-9.22	-0.28	55.84	190.2	-9.02	-0.89	8.13	3.53	108.20	-0.34	0.40	-	-
35	386.49	469.32	750.14	-6.85	0.31	80.40	252.27	-9.46	-0.55	8.91	2.70	147.40	-0.33	0.38	4.79	5.98
36	362.70	463.91	744.08	-7.05	0.31	80.40	252.27	-9.04	-0.58	8.46	3.99	142.50	-0.32	0.38	5.17	6.25
37	402.38	492.73	798.52	-5.59	0.34	86.19	266.3	-8.99	-0.55	8.44	4.17	151.60	-0.33	0.38	4.66	6.90
38	481.00	583.50	968.48	-7.11	1.01	110.19	328.37	-9.14	-0.98	8.16	3.69	205.30	-0.33	0.38	-	-
39	477.85	585.04	969.44	-7.20	1.01	110.19	328.37	-8.81	-1.17	7.64	3.03	216.50	-0.32	0.38		
40	386.23	473.88	753.81	-4.63	1.69	84.28	234.3	-8.69	-0.41	8.28	0.83	152.60	-0.19	0.12	-	5.59
41	345.43	439.33	707.06	-4.78	0.29	75.01	226.27	- 8.73	0.03	8.76	0.67	127.00	-0.21	0.12	4.40	6.30
42	360.39	449.03	707.29	-7.27	-0.04	75.13	224.26	-8.72	-0.11	8.61	0.66	128.90	-0.19	0.14	-	5.74
43	380.46	456.27	722.17	-5.32	0.45	74.65	240.26	-9.51	-0.70	8.81	5.65	135.60	-0.32	0.42	5.44	6.63
44	385.67	463.26	729.61	-7.11	0.24	78.82	258.29	-9.09	-0.94	8.15	3.91	146.70	-0.26	0.27	-	4.23
45	382.72	438.27	683.40	-8.67	-0.14	70.94	226.23	-9.54	-0.51	9.03	4.08	129.70	-0.18	0.12	-	5.62
46	386.45	469.60	740.21	-6.78	-0.31	76.82	253.26	-9.73	-1.15	8.58	3.63	146.80	-0.32	0.32	-	6.41
47	360.51	468.77	763.37	-5.53	-0.39	81.58	253.3	-8.81	-0.07	8.74	2.19	149.00	-0.37	0.24	3.99	5.98
48[e]	434.07	514.59	857.12	-4.90	0.50	90.70	281.35	-8.72	0.04	8.77	2.11	159.10	-0.36	0.24	-	6.20
34[f]	423.78	496.37	823.16	-4.12	0.77	89.36	280.32	-9.21	-0.88	8.33	5.25	168.90	-0.34	0.40	-	-

[a] All inhibitory activities were taken from [12]. IC50 is the negative logarithm of the concentration reduced activity of the enzymes at half. All other compounds for which the % inhibition at maximum solubility was represented as inhibitory activity were excluded; [b] esculin (natural product); [c] 3,4-dihydrocoumarin derivative; [e] 8-methyl derivative; [f] 5-$OCH_2C_6H_5$ derivative.

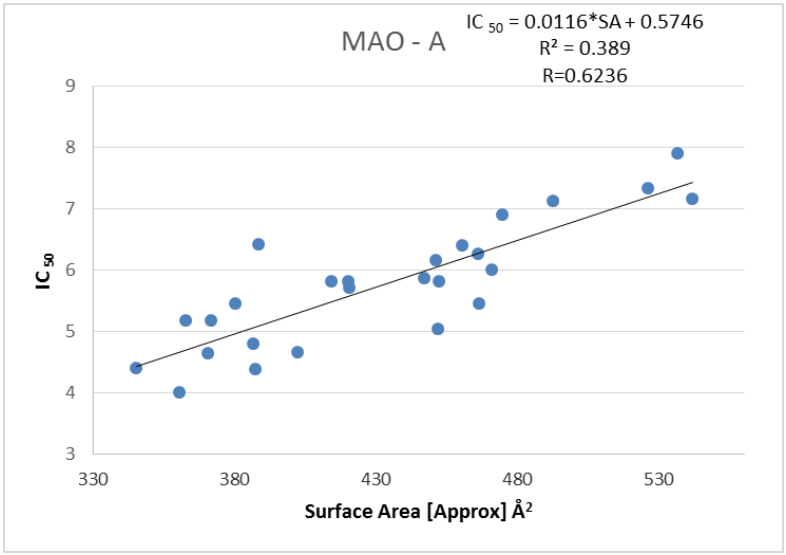


Figure 3. Relationship between surface and inhibitory activity

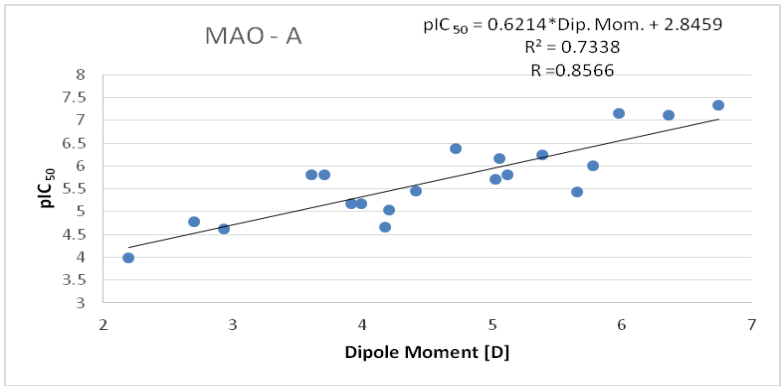


Figure 4. Correlation between polarity and pIC_{50}

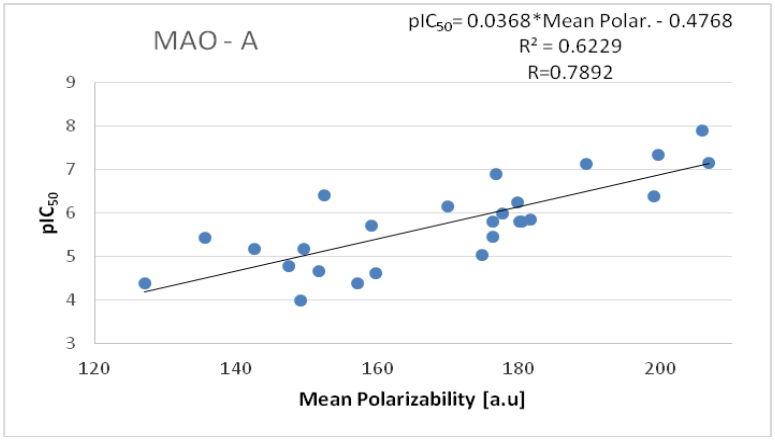


Figure 5. Correlation between polarizability and pIC_{50}

For these 20 compounds the correlation coefficient $R_{pIC,DM}$ is 0.8566. It is higher than the critical value $R^* = 0.444$ for significant correlation for sample size 20 at 95% confidence level [18]. The linear correlation is described by the regression equation:

$pIC_{50} = 0.6214\ (\pm 0.1853) \times DM + 2.8459\ (\pm 0.8772)$, $R_{pIC,DM} = 0.8566$, $s = 0.4711$, $F = 49.6188$.

The correlation is very reliable and the sensitivity of the inhibitory activity to changes in the dipole moment is good. Further, we studied the correlation between the pIC_{50} against MAO-A and

the mean polarizability of a group consisting of 26 compounds (Figure 5). The criteria for selecting the compounds included in the correlation are similar to those mentioned above.

It turned out that there is a significant linear correlation between both variables. For these compounds the correlation coefficient $R_{pIC,MP}$ is 0.7892. It is higher than the critical value $R^* = 0.388$ for significant correlation for sample size 26 at 95% confidence level [18]. The correlation is described by the regression equation:

$pIC_{50} = 0.0368\ (\pm 0.0121) \times MP - 0.4768\ (\pm 2.0595)$, $R_{pIC,MP} = 0.7892$, s = 0.6288, F= 39.6364.

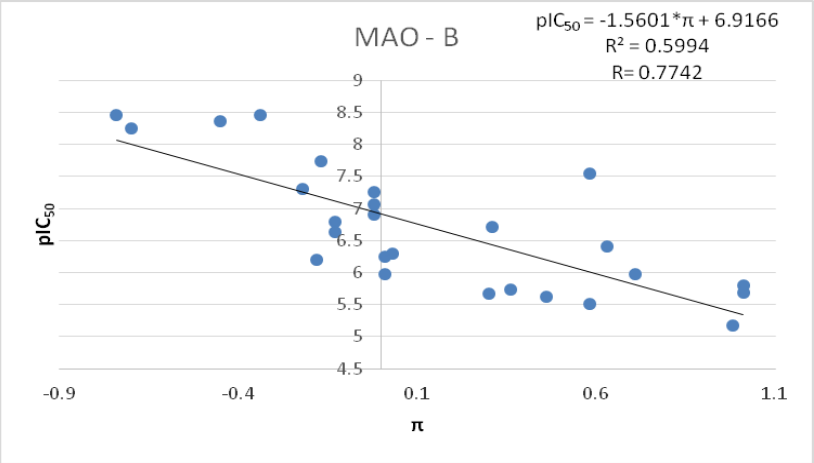


Figure 6. Correlation between lipophilicity and pIC_{50}

It is not surprising that the increase in the polarizability of the compounds results in an increase in inhibitory activity, which is easy to be explained by the the higher adaptability of the molecules in the active center of the enzyme (see Figure 5). Significant linear correlations between the lipophilicity index π (log P_{R-X} – log P_{R-H}) and the pIC_{50} relative to the two isoenzymes MAO-A and MAO-B were also found (see Figure 6). Within the range of compounds employed, the highest activity have the compounds with π above 0, which is very close to that found earlier [12].

Now then, 26 of the compounds with clearly defined inhibitory activity were included in the study. The linear correlation is described by the regression equation:

$pIC_{50\_B} = -1.5601\ (\pm 0.5373) \times \pi + 6.9166\ (\pm 0.2708)$, $R_{pIC\_B,\pi} = 0.7742$, s = 0.6393, F= 35.9097.

The correlation coefficient $R_{pIC\_B,\pi} = 0.7742$ is higher than the critical value $R^* = 0.388$ for significant correlation for sample size 26 at 95% confidence level [18]. Therefore, the linear correlation is significant at 95% confidence level.

CONCLUSIONS

Important correlations were found. They clarify the requirements to the future MAO inhibitor candidates, namely:

- The surface area of the molecules should be about 530 Å^2 and more, the volume and molecular mass of the coumarin derivatives must be maximal for the coumarins, flavones and their bicyclo benzyl ethers from the type tested here;
- The polarity of the compounds must be about 6-7 D and the polarizability around 200 au;
- The lipophilicity of the candidates described by the π-descriptor should be about 1.

Acknowledgement: *The study was supported by intra-university project RP-B8/19 entitled "Theoretical and Spectral Methods for Organic Molecules Modeling".*

REFERENCES

1. G. J. Keating, R. O'Kennedy, in: The chemistry and occurrence of coumarins, R. O'Kennedy, R. D. Thornes (eds.), John Wiley & Sons, West Sussex, England, 1997, p. 23.
2. M. H. Vakarelska-Popovska, Zh. Velkov, *Comp. Theor. Chem.*, **1077,** 87 (2016).
3. I. Kostova, *Curr. Med. Chem. - Anti-Cancer Agents*, **5**, 29 (2005).
4. T.-Y. Wang, Q. Li, K.-Sh. Bi, *Asian J. Pharm. Sci.*, **13,** 12 (2018).
5. C. Binda, J. Wang, L. Pisani, C. Caccia, A. Carotti, P. Salvati, D. E. Edmondson, A. Mattevi, *J. Med. Chem.*, **50**, 5848 (2007).
6. S. Kirkiachiarian, R. Bakhchinian, H. Chidiak, M. Mazmanian, C. Planche, *Ann. Pharm. Fr.*, **57**, 251 (1999).

7. L. S. Forna, *J. Neuropathol. Exp. Neutol.*, **55**, 259 (1996).
8. J. Wouters, *Curr. Med. Chem.*, **5**, 137 (1998).
9. A. S. Kalgutkar, N. Castagnoli, Jr., B. Testa, *Med. Res. Rev.*, **15**, 325 (1995).
10. S. M. N. Efange, R. J. Boudreau, *J. Comput.-Aided Mol. Des.* **5**, 405 (1991).
11. S. Mabic, N. Castagnoli, Jr., *J. Med. Chem.*, **39**, 3694 (1996).
12. C. Gnerre, M. Catto, Fr. Leonetti, P. Weber, P. A. Carrupt, C. Altomare, A. Carotti, B. Testa, *J. Med. Chem.*, **43**, 4747 (2000).
13. S. G. Williams, F. E. Norrington, *J. Am. Chem. Soc.*, **98**, 508 (1976).
14. Hyperchem (Molecular Modeling System) Hypercube, Inc., 1115 Nw, 4th Street, Gainesville, Fl 32601; USA, 2007.
15. J. S. D. Michael, E. G. Zoebisch, E. F.Healy, J. J. P. Stewart, *J. Am. Chem. Soc.*, **107(**13), 3902 (1985).
16. A. K. Ghose, A. Pritchett, G. M. Crippen, *J. Comp. Chem.*, **9**, 80 (1988).
17. V. N. Viswanadhan, A. K. Ghose, G. N. Revankar, R. K. Robins, *J. Chem. Inf. Compt. Sci.*, **29**, 163 (1989).
18. M. Triola M, Elementary Statistics, 13th edn., Pearson, Boston 2018.
19. D. C. Young, Computational Chemistry, A Practical Guide for Applying Techniques to Real-World Problems, Wiley-Interscience, New York, 2001.