Available online at www.sciencedirect.com

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 14 (2004) 5611–5617

Bioorganic & Medicinal Chemistry Letters

QSAR modeling of the MAO inhibitory activity of xanthones derivatives

M. B. Núñez,[a,†] F. P. Maguna,[a] N. B. Okulik[a] and E. A. Castro[b,*]

[a]*Facultad de Agroindustrias, UNNE, Cdte. Fernández 755, Sáenz Peña 3700, Chaco, Argentina*
[b]*INIFTA, Departamento de Química, Facultad de Ciencias Exactas, UNLP, Diag. 113 y 64, Suc. 4, C.C. 16, La Plata 1900, Argentina*

Received 16 June 2004; accepted 26 August 2004
Available online 28 September 2004

Abstract—This work presents a study QSAR among the MAO A inhibitory activity (IMAO A) of a xanthones series correlated with descriptors like the E-state index (S_i), molecular connectivity (χ) and shape (k) descriptors. The xanthones group (9-H-xanton-9-onas) are of natural or synthetic origin, they present eight positions for the substitution and their MAO A inhibitory activity is reported in the work from Gnerre et al. The descriptors included in the adjusted model were selected to describe the molecular structure of the compounds. The model was selected using the leave-one-out method, the cross-validation statistics indicate a model useful for prediction: $r^2 = 0.847$ and $s = 8.069$, calculated by multiple linear regression.

1. Introduction

Classically, the design of new drugs was based on the search of some first compound opposing leaders 'fortuitously' or by means of a random screening of natural and synthetic products. These new drugs evolved toward a second series of leaders based on synthetic modifications and experimental evaluation of their activity. At the present time the rational design of the medication is the most frequent method used to look for such compounds. A first approach toward a rational design comes from the ideas of QSPR/QSAR (quantitative structure–property/activity) theory.

A variety of QSPR/QSAR models has been studied using various model parameters including several well known physicochemical properties and other molecular descriptors such as geometric, electronic or electrostatic, polar, steric, and graph-theoretical topological indices. Among these descriptors, the recently developed three-dimensional (3D) descriptors are particularly interesting because they take into account the geometric conformation and the nature of the bonding of groups in a molecule compared with the two-dimensional (2D) descriptors.[1–3]

In Chemical Graph Theory, molecular structures are normally represented as hydrogen-suppressed graphs, whose vertex and edges act as atoms and covalent bonds, respectively. Graph-theoretical indices, also known as topological indices, are descriptors that characterize a molecular graph and they are capable to give account of their structural properties in order to obtain the connective functions used in discrimination and prediction studies. They have shown their usefulness in classification analysis, and in general, in the modeling of biological activities.[4] The conventional 2D and 3D topological indices characterizes a molecule as a whole, that is, molecular size or shape, such as molecular connection index (χ), Hosoya's index (Z), Balaban's index (J), Schulz's index (MTI), etc. Among the most important topological descriptors describing the molecular characteristics, it is particularly noteworthy the connective index or Randíc index (χ), defined as the sum of weighted edges in a molecular graph.[5–9]

The shape profile index (κ) is determined principally by the shape of the molecule rather than its connectivity features. Most topological indices would fail to detect the apparent similarity between two compounds because most of the indices are derived from molecular connectivity or, in the case of 3D, forms from the molecular spatial bonding model. However, the internal bonds

Keywords: MAO inhibitory activity; Xanthones; QSAR theory; Pharmacological activities.
* Corresponding author. Tel.: +54 221 4214037; fax: +54 221 4259485; e-mail addresses: castro@quimica.unlp.edu.ar; jubert@arnet.com.ar
† E-mail: nora@fai.unne.edu.ar

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.08.066

do not participate in defining the shape, yet make contribution to computed graph or structural invariants, unless explicitly excluded. One can arrive at molecular shape profiles by considering only the contributions from atoms, which are located on the molecular periphery.[8]

In recent years, focus has been turned to the second type of topological indices, that is, the atomic-level-based topological indices. In contrast with the above-mentioned conventional indices, the atomic level topological indices characterize the structural environment of each atom type in a molecule and offer the possibility of understanding the role of individual atomic types or groups in a molecule, particularly special functional groups, such as OH, COOH, NH_2, etc.[5,10–14] In this sense, the most important topological index is the electrotopological state (E-state) introduced for Kier and Hall.[13]

Our research group is working in the study of some series of compounds to define groups of indices that allow one to predict biological activities in a rather acceptable form. Particularly the interest has been centered in topological indices such as the E-state, the connectivity and shape indices.[15,16] In this work the correlation is analyzed between topological descriptors and the biological activity of interest, centered in the MAO inhibitory activity of a group of xanthones molecules. The monoamine oxidase (MAO) is an FAD-containing enzyme of the outer mitochondrial membrane that exists as two isoenzymes (MAO-A and MAO-B), which differ in substrate specificity, sensitivity to inhibitors and differences in the amino acid sequences. Monoamine oxidase (MAO) is an important enzyme in the metabolism of several neurotransmitters including dopamine and serotonin. The main function of MAO enzyme is to catalyze the degradation of these monoamines by the *oxidative desamination*. In cases of deficiencies of any monoamine, the inhibition of the metabolizing enzyme leads to the preservation of the transmitter, producing a clinical effect equivalent to their direct use.

The xanthones (9*H*-xanthen-9-ones) of natural and synthetic origin are of biological and pharmacological interest. These natural compounds have deserved a high recognition of scientists and researchers, who have proposed a series of pharmacological properties, as the potent one to be able to antioxidating, maintenance of the balance at microbiological level and of the health of the immunologic system. Also, these molecules are of importance in the quimiotaxonomy like systematic markers and in the systematic classification. On the other hand, they have valuable pharmacological properties, xanthone-containing plant extracts being used in traditional medicine.[17]

The purpose of this article is to report results derived from the study of the correlation between topological descriptors and the inhibitory activity on the MAO A, of a series of xanthones derivates that are statistically significant to describe the biological property.

2. Method

The MAO A inhibitory activity of 42 xanthones derivates was obtained from Gnerre et al.[18] The values are reported in the form of IC_{50}, where C is the effective concentration of the compound to achieve 50% MAO A inhibitors in a micromolar range.

The series of molecules consists of invariant 15 atoms skeletal and the numbering is illustrated in Table 1, showing the eight positions substitutions (R_i).

All structures were constructed using the HyperChem structure format and were saved as .hin files.[19] Initially, physiochemical, topological and structural describers were calculated.

The values of the selected indices for the adjusted model are presented in Table 2.

Using the set of 42 xanthones derivates, multiple linear regression models were developed with the Statgraphics Plus package.[20] The quality of the model was considered as statistically satisfactory on the basis of squared correlation coefficient (r^2), standard deviation (s), and F-statistics (F) when all the parameters in Eqs. 1 and 2 were significant at 90% confidence level.

Molecular descriptors were selected with better adjustment to the MAO inhibitory activity, including the electrotopological states (E-state) for each atom level of the studied molecules, the molecular connectivity and shape indices. The E-state (S_i) were calculated with E-calc software package[21], the diverse order the molecular connectivity (χ) and shape (κ) indices were calculated with Dragon Web software package.[22]

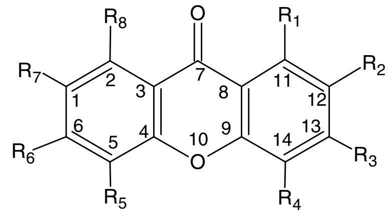
The predictive ability in the set was carried out cross-validation using the method of LOO (leave-one-out), through the defined values for ${r_{cv}}^2$ and ${s_{cv}}^2$, according to the following equations:

$$r^2_{cv} = 1.0 - \frac{\sum (yi - \hat{y}i)^2}{\sum_{i=1}^{n} (yi - \bar{y})^2} \quad (1)$$

$$ys^2_{cv} = \sqrt{\frac{\sum_{i=1}^{n} (yi - \hat{y}i)^2}{N - M - 1}} \quad (2)$$

where in Eq. 1, yi and $\hat{y}i$ are the experimental and predicted value, respectively. $\bar{y}$ is the mean value of yi. In Eq. 2, N is the number of samples used for model building. M is the number of descriptors.[5] The predictive capability in the training set was carried out using the jackknife r^2 (r_j^2) values.[23] For any given compound, C_j, its corresponding r_j^2 values can be determined by deleting this compound from the regression analysis and computing the resulting squared correlation coefficient, r^2, from the original model using $n-1$ data points. The unduely high r_j^2 values might indicate outliers and/or

Table 1. MAO Inhibitory activities of xanthone derivatives[18]



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	IC_{50} MAO A (μM)
1	H	H	H	H	H	H	H	H	0.84 ± 0.08
2	OH	H	H	H	H	H	H	H	0.31 ± 0.05
3	MeO	H	H	H	H	H	H	H	0.9 ± 0.1
4	H	OH	H	H	H	H	H	H	3.8 ± 0.3
5	H	MeO	H	H	H	H	H	H	5.3 ± 0.4
6	H	H	OH	H	H	H	H	H	1.1 ± 0.3
7	H	H	MeO	H	H	H	H	H	0.18 ± 0.03
8	H	H	H	OH	H	H	H	H	1.3 ± 0.1
9	H	H	H	MeO	H	H	H	H	30 ± 3.2
10	OH	H	H	H	OH	H	H	H	0.73 ± 0.1
11	H	H	OH	H	OH	H	H	H	4.5 ± 0.2
12	H	H	OH	H	MeO	H	H	H	23 ± 1.4
13	OH	H	MeO	H	H	H	H	H	0.11 ± 0.01
14	MeO	H	MeO	H	H	H	H	H	20.2 ± 0.48
15	H	H	MeO	H	MeO	H	H	H	36 ± 2.9
16	MeO	H	H	H	OH	H	H	H	51 ± 7.8
17	H	H	MeO	OH	H	H	H	H	18 ± 3.1
18	H	H	OH	MeO	H	H	H	H	65 ± 6.8
19	H	H	MeO	MeO	H	H	H	H	31 ± 4.8
20	OH	H	OH	H	OH	H	H	H	3.8 ± 0.25
21	OH	H	MeO	H	OH	H	H	H	0.04 ± 0.005
22	OH	H	MeO	H	MeO	H	H	H	29 ± 4.3
23	MeO	H	MeO	H	MeO	H	H	H	58 ± 6.8
24	OH	H	OH	Me	H	H	H	H	4.3 ± 0.4
25	OH	Me	OH	H	H	H	H	H	3.7 ± 0.2
26	OH	Me	OH	Cl	H	H	H	H	27 ± 1.1
27	OH	Me	OH	Br	H	H	H	H	14.9 ± 0.6
28[a]	OH	H	OH	$C_{10}H_{17}$	OH	H	H	H	37 ± 5.5
29[b]	OH	C_5H_9	H	OH	OH	H	H	H	3.3 ± 0.2
30[c]	OH	H	C_5H_9	OH	OH	H	H	H	40 ± 3.7
31	OH	MeO	OH	H	OH	H	H	H	2.7 ± 0.4
32	OH	MeO	OH	H	MeO	H	H	H	51 ± 11
33	MeO	MeO	MeO	H	MeO	H	H	H	37 ± 2.0
34	OH	H	OH	H	H	H	OH	H	8 ± 1.2
35	OH	H	OH	H	OH	H	H	OH	13 ± 1.4
36	OH	H	MeO	H	OH	H	H	OH	0.66 ± 0.06
37	OH	H	OH	H	H	H	OH	OH	24 ± 4.6
38	OH	H	MeO	H	H	H	OH	OH	8.5 ± 0.8
39	OH	H	MeO	H	H	H	MeO	MeO	19 ± 1.0
40	OH	H	OH	H	H	OH	OH	H	25 ± 3.4
41	MeO	H	H	Me	OH	H	MeO	H	24 ± 7.0
42	OH	MeO	OH	H	MeO	OH	H	H	32 ± 5.0

[a] $C_{10}H_{17}$ is $Me_2C{=}CH–CH_2–CH_2–C(Me){=}CH–CH_2$.
[b] C_5H_9 is $CH_2{=}CH–CMe_2$.
[c] C_5H_9 is $Me_2{=}CH–CH_2$.

biases, and those with low r_j^2 values might be considered the influential points in the data set, respectively.

3. Results and discussion

The 36 physicochemical, topological and structural indices were calculated. The E-sate for atoms level, molecular connectivity χ and shape κ indices were selected for all xanthones derivates because they had bigger power in the prediction of the inhibitory activity. Pairwise correlations were examined for correlation coefficients, r^2, values greater than 0.80 were excluded. The descriptors were selected by their bigger predictive ability in the model.

Next Eq. 3 includes as the data X_i to 12 descriptors: E-state for atoms level (S_i), molecular connectivity (χ),

Table 2. MAO A inhibitory activity, molecular descriptors, residuals, and jackknife results

Molecule	$IC_{50\,obs.}$ [a]	C_5	C_7	O_{10}	C_{12}	C_{13}	C_{14}	R_1	R_4	R_6	R_7
1	0.84	1.809	0.035	5.627	1.841	1.861	1.809	1.367	1.371	1.255	1.256
2	0.31	1.736	−0.199	5.5478	1.480	1.648	1.669	9.651	1.419	1.273	1.281
3	0.9	1.787	−0.056	5.6895	1.758	1.804	1.769	5.197	1.424	1.276	1.283
4	3.8	1.75	−0.118	5.5709	0.065	1.500	1.596	1.500	1.446	1.269	1.274
5	5.3	1.792	−0.027	5.6709	0.653	1.778	1.752	1.513	1.454	1.272	1.277
6	1.1	1.736	−0.072	5.5478	1.480	0.0889	1.448	1.442	1.504	1.273	1.271
7	0.18	1.780	−0.027	5.724	1.785	1.778	0.574	1.450	1.517	1.276	1.272
8	1.3	1.711	−0.118	5.5078	1.628	1.500	−0.014	1.415	9.622	1.279	1.274
9	30	1.787	−0.009	5.6895	1.758	0.677	1.726	1.421	5.199	1.282	1.277
10	0.73	−0.093	−0.352	5.4286	1.424	1.576	1.572	9.658	1.452	1.407	1.355
11	4.5	−0.093	−0.225	5.4286	1.424	0.009	1.349	1.466	1.538	1.407	1.345
12	23	0.495	−0.134	5.6449	1.464	0.055	1.419	1.469	1.542	1.419	1.353
13	0.11	1.715	−0.243	5.6103	1.397	0.443	1.586	9.883	1.565	1.295	1.297
14	20.2	1.766	−0.101	5.752	1.675	0.586	1.686	5.259	1.570	1.297	1.301
15	36	0.541	−0.071	5.7865	1.741	0.643	1.697	1.477	1.554	1.422	1.355
16	51	−0.047	−0.209	5.5703	1.702	1.732	1.672	5.165	1.458	1.409	1.358
17	18	1.689	−0.162	5.5703	1.545	0.279	−0.155	1.498	9.976	1.300	1.291
18	65	1.708	−0.134	5.6449	1.423	−0.052	0.176	1.496	5.079	1.301	1.292
19	31	1.759	−0.071	5.7865	1.701	0.536	0.433	1.504	5.296	1.304	1.294
20	3.8	−0.172	−0.459	5.3494	1.063	−0.224	1.211	9.679	1.585	1.425	1.370
21	0.04	−0.126	−0.396	5.4911	1.341	0.3638	1.488	9.890	1.598	1.428	1.372
22	29	0.462	−0.305	5.7074	1.380	0.410	1.558	9.979	1.602	1.441	1.380
23	58	0.507	−0.162	5.849	1.658	0.552	1.658	5.285	1.608	1.443	1.383
24	4.3	1.677	−0.299	5.5994	1.156	−0.099	0.436	9.797	1.634	1.296	1.2981
25	3.7	1.671	−0.299	5.5237	0.269	−0.099	1.345	9.959	1.565	1.295	1.2981
26	27	1.625	−0.376	5.5225	0.153	−0.287	−0.076	10.025	5.982	1.312	1.312
27	14.9	1.663	−0.321	5.6076	0.238	−0.136	0.264	10.063	3.192	1.306	1.307
28	37	−0.168	−0.449	5.7867	1.1623	−0.156	0.399	10.227	0.338	1.456	1.3946
29	3.3	−0.212	−0.522	5.4849	0.365	1.341	−0.287	10.569	10.250	1.446	1.392
30	40	−0.19	−0.501	5.5362	1.364	0.439	−0.211	10.197	10.407	1.448	1.387
31	2.7	−0.198	−0.520	5.3934	−0.204	−0.365	1.154	10.032	1.669	1.442	1.391
32	51	0.390	−0.429	5.6096	−0.169	−0.319	1.224	10.121	1.673	1.455	1.399
33	37	0.482	−0.224	5.893	0.344	0.411	1.601	5.382	1.691	1.460	1.404
34	8	1.451	−0.459	5.4125	1.063	−0.193	1.253	9.679	1.571	1.425	9.357
35	13	−0.324	−0.692	5.2703	0.991	−0.285	1.138	9.688	1.610	1.501	1.503
36	0.66	−0.279	−0.630	5.4119	1.269	0.303	1.416	9.899	1.622	1.503	1.505
37	24	1.312	−0.692	5.3334	0.991	−0.254	1.180	9.688	1.595	1.501	9.361
38	8.5	1.363	−0.630	5.475	1.269	0.334	1.458	9.899	1.608	1.503	9.452
39	19	1.619	−0.396	5.7168	1.358	0.396	1.548	10.101	1.613	1.523	5.190
40	25	1.089	−0.566	5.3334	1.019	−0.254	1.180	9.684	1.595	9.379	9.394
41	24	−0.134	−0.263	5.745	1.723	1.802	0.792	5.245	1.830	1.559	5.079
42	32	−0.008	−0.537	5.5305	−0.218	−0.380	1.151	10.126	1.697	9.757	1.532

Molecule	$IC_{50\,obs.}$ [a]	χ_5	κ_4	$IC_{50\,cal}$ [b]	Residuals [c]	Jackknife [d]
1	0.84	4.302	5.602	3.431	−2.591	57.685
2	0.31	4.472	5.662	−3.821	2.901	57.742
3	0.9	4.896	5.727	8.590	−3.231	58.205
4	3.8	4.685	5.806	2.560	11.490	57.954
5	5.3	4.814	6.328	−2.879	4.061	58.877
6	1.1	4.507	5.798	7.256	−7.079	58.026
7	0.18	4.703	6.324	3.963	6.336	57.761
8	1.3	4.601	5.661	13.922	5.083	59.435
9	30	4.851	5.876	28.862	42.623	58.151
10	0.73	4.774	5.801	−0.286	−0.407	57.621
11	4.5	4.808	5.861	12.600	3.484	58.748
12	23	5.058	5.9	35.999	31.100	60.104
13	0.11	4.973	6.209	4.4394	13.110	57.720
14	20.2	5.451	6.377	14.137	24.529	58.956
15	36	5.255	6.357	39.228	29.937	57.655
16	51	5.198	5.894	11.580	54.228	70.532
17	18	4.944	6.181	25.575	−21.421	59.208
18	65	5.002	6.017	29.423	72.575	64.373
19	31	5.341	6.289	35.719	−4.577	58.261
20	3.8	4.922	5.907	6.7063	8.519	58.0146
21	0.04	5.279	6.242	10.574	2.946	58.538
22	29	5.529	6.284	33.818	39.534	58.444

Table 2 (*continued*)

Molecule	$IC_{50\,obs.}$[a]	χ_5	κ_4	$IC_{50\,cal}$[b]	Residuals[c]	Jackknife[d]
23	58	6.007	6.314	46.824	62.819	54.132
24	4.3	5.084	5.903	16.166	−6.876	59.472
25	3.7	4.909	6.015	4.957	15.566	57.940
26	27	5.299	6.051	18.118	28.257	59.143
27	14.9	5.299	6.061	19.953	6.018	58.822
28	37	6.629	7.086	33.990	42.053	57.538
29	3.3	6.186	6.739	12.667	0.291	59.108
30	40	6.21	6.772	26.926	49.367	59.100
31	2.7	5.319	6.384	8.1423	−10.374	58.140
32	51	5.569	6.443	30.984	56.442	59.441
33	37	6.668	6.612	49.592	16.984	59.611
34	8	5.002	6.019	11.328	20.592	58.413
35	13	5.289	5.922	7.0168	16.328	58.990
36	0.66	5.646	6.251	11.003	−5.323	58.860
37	24	5.089	6.04	14.513	34.343	59.588
38	8.5	5.446	6.371	18.558	−0.987	59.566
39	19	6.135	6.792	17.449	29.058	58.624
40	25	5.169	6.192	17.461	23.449	59.640
41	24	6.183	6.346	33.003	16.461	59.660
42	32	5.721	6.591	39.117	41.003	59.154

[a] Observed IC_{50}.
[b] Calculated IC_{50}.
[c] Residuals in leave one out prediction.
[d] Jackknife results in test.

shape (κ) indices and finally, the term independent. The coefficients a_i of Eq. 3 are presented in Table 3

$$IC_{50} = \sum(a_i X_i) - 849.201 \tag{3}$$

$$n = 42 \quad r^2 = 0.586 \quad s = 13.736 \quad F = 3.42$$

where n is the number of compounds used in the fit, r^2 is squared correlation coefficient, s is standard deviation, F is the overall F-statistics for the addition of each successive term. The a_i values in Table 4 are at 90% confidence limit of each coefficient. The calculated IC_{50} and residual values of Eq. 3 are presented in Table 2.

The jackknife results were presented in Table 2, indicated eight data points higher than the limits of the mean r_j^2 values (58.975 ± 0.567). After excluding these data points (compounds 12, 16, 18, 33, 37, 38, 40, and 41), the following equation was obtained:

$$IC_{50} = \Sigma(a_i X_i) - 1071.22 \tag{4}$$

$$n = 34 \quad r^2 = 0.847 \quad s = 8.069 \quad F = 9.72$$
$$r^2_{cv} = 0.734 \quad s^2_{cv} = 1.558$$

The data X_i are the E-state for atoms level (S_i), molecular connectivity (χ), shape (κ) indices and finally the term independent. The coefficients a_i of Eq. 4 are presented in the Table 4. The values of calculated IC_{50} in Eq. 4 with the adjusted model and residuals ones are presented in Table 5.

The plot of calculated versus observed IC_{50} the adjusted model with Eq. 4 is shown in Figure 1.

A plot of residual versus observed IC_{50} in Figure 2, shows no trends and appears random.

The E-state index, calculated for all the atoms in the molecule, reflects structural information for each atom level. The molecular connectivity index (χ) is a simple value computed for the whole molecule, related with the sum of the edges of importance in the molecular

Table 3. Correlation matrix for the descriptors in Eq. 3

	χ_5	k_4	C_5	C_7	O_{10}	C_{12}	C_{13}	C_{14}	R_1	R_4	R_6	R_7
χ_5	1											
k_4	0.844	1										
C_5	0.492	−0.325	1									
C_7	0.344	−0.244	0.538	1								
O_{10}	0.383	0.396	0.253	0.650	1							
C_{12}	0.137	−0.137	0.164	0.448	0.272	1						
C_{13}	0.097	−0.019	0.180	0.555	0.316	0.427	1					
C_{14}	0.242	−0.262	0.0134	0.182	0.094	0.146	0.186	1				
R_1	0.338	0.251	−0.375	−0.823	−0.419	−0.447	−0.427	−0.083	1			
R_4	0.164	0.195	0.069	0.031	−0.058	0.027	0.071	−0.761	−0.131	1		
R_6	0.080	0.156	−0.143	−0.318	−0.230	−0.279	−0.264	0.022	0.215	−0.101	1	
R_7	0.040	0.040	0.106	−0.485	−0.340	0.017	−0.210	0.086	0.289	−0.170	0.303	1

Table 4. Coefficients a_i included in Eqs. 3 and 4

Descriptors	Eq. 3	Eq. 4
Independent term	−849.201	−1071.22
a S_{C5}	−11.276	−11.622
a S_{C7}	−74.301	−99.986
a S_{O10}	189.780	230.433
a S_{C12}	−2.307	−7.222
a S_{C13}	−9.384	−9.533
a S_{C14}	2.093	7.857
a S_{R1}	−1.174	−1.353
a S_{R4}	3.100	4.0754
a S_{R6}	1.821	0.029
a S_{R7}	1.847	1.731
a χ_5	−12.149	−14.589
a κ_4	−23.089	−23.046

Table 5. Predictive ability and residuals values in Eq. 4

Molecule No.	$IC_{50\,obs}$	$IC_{50\,cal}$	Residuals
1	0.84	−1.818	2.658
2	0.31	−7.136	7.446
3	0.9	6.300	−5.4
4	3.8	5.617	−1.817
5	5.3	−0.421	5.721
6	1.1	1.110	−0.01
7	0.18	−3.429	3.609
8	1.3	5.637	−4.337
9	30	29.750	0.25
10	0.73	−5.124	5.854
11	4.5	4.929	−0.429
13	0.11	3.784	−3.674
14	20.2	14.411	5.789
15	36	41.213	−5.213
17	18	20.232	−2.232
19	31	33.861	−2.861
20	3.8	1.1240	2.676
21	0.04	8.387	−8.347
22	29	37.450	−8.45
23	58	51.389	6.611
24	4.3	10.927	−6.627
25	3.7	6.587	−2.887
26	27	17.405	9.595
27	14.9	20.095	−5.195
28	37	35.276	1.724
29	3.3	13.987	−10.687
30	40	25.631	14.369
31	2.7	10.904	−8.204
32	51	39.581	11.419
34	8	6.862	1.138
35	13	3.202	9.798
36	0.66	10.579	−9.919
39	19	21.392	−2.392
42	32	31.974	0.026

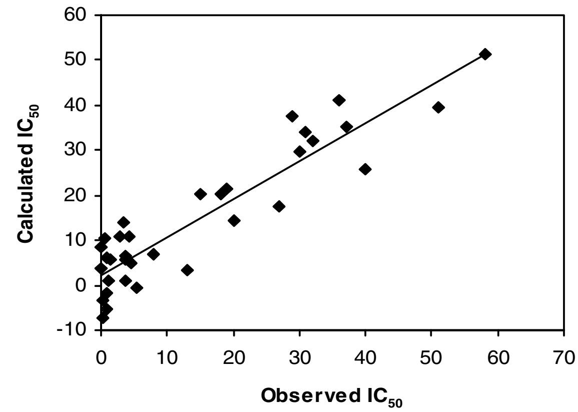


Figure 1. Plot of calculated versus observed IC_{50} for 34 xanthones based on Eq. 4.

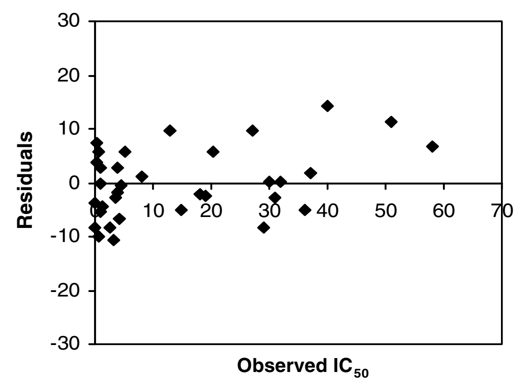


Figure 2. Plot of observed IC_{50} versus residuals for 34 xanthones based on Eq. 4.

graph. The shape index k is a value that describes certain molecular property mainly for the form of the molecule, presenting a reference on the contour in the molecular shape of a compound.

The value of each E-state index shows the influence of the environment on an atom, observing that the C_5 and C_{14} present negative values when the substituent is OH and positive values with MeO, although minor compared with the positive value when is H. The C_7 present negative values influenced by the group O=. The C_{12} presents small positive or negative values in presence of groups MeO and Me, not observing is influenced if the alkylic chain consists of a large number of C atoms, as that observed in C_{12}, C_{13} and C_{14} with C_5H_9, C_5H_9, and $C_{10}H_{17}$, respectively. The C_{14} presents negative values when chlorine is the substituent and low positive value when the substituent is bromine. The positive coefficients the E-states are of O_{10}, C_{14} and of the groups R_4, R_6, and R_7. On the other hand, the negative coefficients of E-states in C_5, C_7, C_{13}, R_1 show that when diminishing their values the activity is increased.

The χ_0 values are increased fundamentally when the ramified chain of the substituent increases, when increases the number of MeO substituents and in smaller measure with increases the number of OH. The coefficient χ_5 in the adjusted model is negative presenting an inverse relationship with the activity. The κ_4 values is increased when the ramified chain of the groups increases, when increases the number MeO or in smaller measure when increases the number of OH groups in the molecule. The κ_4 coefficient is negative in inverse relationship with the prediction of the activity.

In the adjusted model is observed that the r^2_{cv} value is smaller and next to the value of r^2, the s^2_{cv} value is smaller that s^2 and F-statistic values is bigger than that of initial model, this demonstrates that the final pattern is good statistically.

4. Conclusions

The best adjusted model of prediction of activity proposed was constituted by the E-state, molecular connectivity and shape indices as molecular descriptors presenting a good statistical result. This model presents an appropriate ability to predict the MAO A inhibitory activity expressed as IC_{50} of the xanthones.

The results of the present study, the prediction of MAO A inhibitory activity of a set of xanthones derivates, gives new evidence of the importance of atom level E-state, molecular connectivity and shape indices as descriptors in QSAR studies.

References and notes

1. Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
2. Consonni, V.; Todeschini, R.; Pavan, M. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 682–692.
3. Puri, S.; Chickos, J. S.; Welsh, W. J. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 109–116.
4. Murcia-Soler, M.; Pérez-Giménez, F.; Garcia-March, F. J.; Salabert-Salvador, M. T.; Diaz-Villanueva, W.; Medina-Casamayor, P. *J. Mol. Graph. Model.* **2003**, *21*, 375–390.
5. Ren, B. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 161–169.
6. Mut-Ronda, S.; Salabert-Salvador, M. T.; Duart, M. J.; Antón-Fos, G. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2699–2702.
7. Gough, J. D.; Hall, L. H. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 356–361.
8. Randic, M. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 672–687.
9. Mihalic, Z. *J. Chem. Educ.* **1992**, *69*(9), 701–712.
10. Hall, L. H. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 784–791.
11. Huuskonen, J. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 425–429.
12. Huuskonen, J.; Livingstone, D.; Tetko, I. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 947–955.
13. Kier, L. B.; Hall, L. H. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 548–552.
14. Hall, L. H.; Story, C. T. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 1004–1014.
15. Marinich, J. A.; Maguna, F. P.; Okulik, N. B.; Castro, E. A. *Polish J. Chem.* **2002**, *76*, 589–600.
16. Maguna, F. P.; Nuñez, M. B.; Okulik, N. B.; Castro, E. A. *Russ. J. Gen. Chem.* **2003**, *11*, 1792–1798.
17. Hostettmann, K.; Hostettmann, M. In *Methods in Plant Biochemistry*; Harborne, Y. B., Ed.; Academic: New York, 1989; 493–508.
18. Gnerre, C.; Thull, U.; Gaillard, P.; Carrupt, P. A.; Testa, B.; Fernandes, E.; Silva, F.; Pinto, M.; Pinto, M. M.; Wolfender, J.-L.; Hostettmann, K.; Cruciani, G. *Helv. Chim. Acta* **2001**, *84*, 552–570.
19. HyperChem. Version 6.03 - **2001**. Hypercube, Inc. http://www.hyper.com.
20. StatGraphics Plus. Versión 4.0, **1999**. Statistical Graphics Corp.
21. ChemPlus: Extensions for HyperChem. Version 1.1 **1994**. Hypercube, Inc.
22. Dragon Web software 3.0 **2003**. http:www.disat.unimib.it/chm/Dragon.htm.
23. Huuskonen, J. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 425–429.