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QSPR STUDY ON THE CHROMATOGRAPHIC BEHAVIOR OF A SET OF THIAZOLE DERIVATIVES BY AUTO-CORRELATION ANALYSIS

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ABSTRACT. A set of twenty six thiazole derivatives, synthesized in our laboratory and measured for chromatographic retention was submitted to a QSPR study by auto-correlation analysis on the hypermolecule model. As predictor variables, mass fragments, Cluj indices and the HOMO energy, computed at the Hartree-Fock level of theory, are used. Several QSPR models were derived while the leave-one-out procedure was used to evaluate the predictive ability of the main model.

Key words: *thiazoles, hypermolecules, QSPR, topological descriptors*

INTRODUCTION

Quantitative structure-property relations (QSPR) have become a fundamental tool for property prediction in various scientific fields including chemistry, biology, pharmacology, and chemical engineering. Accordingly, relations between molecular structure and macroscopic quantities have been established in diverse areas ranging from thermophysics [1−7] carcinogenicity and toxicity, [8−10] and catalytic activity [11] up to combustion kinetic properties [12−15] and lubricity [16] of biofuels. Quantitative structure-activity relations (QSAR) are employed in drug design to identify molecules with high binding affinity to receptors in order to maximize biological activity.[17−20] A recent review about theory and applications of QSPR was provided by Katritzky et al. [21].

Any QSPR and QSAR approach assumes that a macroscopic property of a chemical compound depends on the molecular structure, as described,

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e.g. by the topological indices TIs, which are derived from the molecular topology or geometry. In the last years, thousands of TIs have been proposed and used in predicting various molecular properties. Among these, the Cluj indices play an important role [22], even we cannot hide a sentimental relation with them. They have been defined by Diudea at the end of the 2nd millennium [23,24], as shown below.

A Cluj fragment $CJ_{i,j,p}$ collects vertices *v* lying closer to *i* than to *j*, the endpoints of a path *p*(*i*,*j*). Such a fragment collects the vertex proximities of *i* against any vertex *j*, joined by the path *p*, with the distances measured in the subgraph $D_{(G-p)}$, as shown in the following equation:

$$CJ_{i,j,p} = \left\{ v \middle| v \in V(G); D_{(G-p)}(i,v) < D_{(G-p)}(j,v) \right\} \quad (1)$$

In graphs containing rings, more than one path could join the pair (*i, j*), thus resulting more than one fragment related to *i* (with respect to *j* and a given path *p*). The entries in the Cluj matrix are taken, by definition, as the maximum cardinality among all such fragments:

$$\mathbf{[UCJ]}_{\boldsymbol{i,j}} = \max_{p} \left| CJ_{i,j,p} \right| \quad (2)$$

Indices I_e and I_p are calculated, from the Cluj topological matrices $\mathbf{UCJ}_e$, and $\mathbf{UCJ}_p$, respectively (see above), as half sum of matrix entries. In the above symbols, *e* refers to edge-calculated matrix while *p* refers to the path-calculated ones.

The chromatographic behavior of a molecule reflects its interaction with two phases: a mobile phase (i.e., the eluent) and a stationary one. This interaction is a function of more than one factor, polarity, lipophylicity and the size of the molecule being included. Lipophilicity is related to the chromatographic behavior and controls the passive transport of a medicinal molecule through the cell membranes (of lipidic nature) [25].

AUTO-CORRELATION METHOD

In order to achieve the QSPR, the structure is encoded in a numerical form. The arrangement of substituent groups, on the Thiazole derivatives herein discussed, can be accounted for by the *hypermolecule* HM concept [26], viewed as the union of the molecules forming the correlating space. In the construction of the hypermolecule, a property *row-vector* P_i is attached to each molecule *i*:

$$\boldsymbol{P}_i = \left\{ \boldsymbol{P}_{ij}; \boldsymbol{j} = 1, 2, ..., \boldsymbol{n}_{\mathbf{HM}} \right\} \quad (3)$$

where n_{HM} is the number of vertices in the hypermolecule. The molecules of the set are superimposed according to their maximal common substructures.

This superposition is indicated by an associated vector X_i, in which the matching positions take $X_{ij} = 1$ while for the non-matching ones $X_{ij} = 0$.

The molecules under study can be numerically described by using a global molecular descriptor AD_i, calculated as a linear combination of the property descriptors $P_{ij}X_{ij}$, multiplied by the regression coefficients b_j performed on the all or most important positions j in the hypermolecule HM:

$$AD_i = \sum_j b_j P_{ij} X_{ij} \tag{4}$$

The above AD_i are called *auto-correlation* descriptors [27,28] and they are *ad-hoc* ones, depending on the chosen set of molecules.

The general regression equations are of the form:

$$Y_i = a + \sum_{j=1}^{m} b_j \cdot Z_{ij} \tag{5}$$

where Y_i is the dependent variable, Z_{ij} are the predictor variables, $m < n$, n being the number of structures in the set.

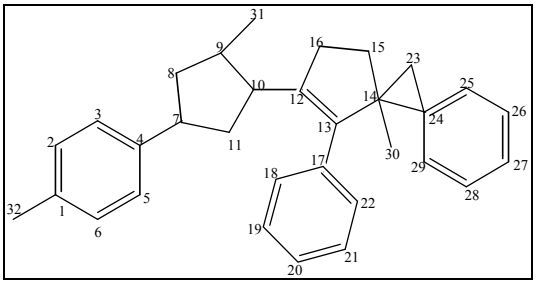
The correlating algorithm followed the steps:

1. generate the *hypermolecule*
2. calculate the molecularl descriptors by using a chosen property P_i
3. find the best regression equations
4. test the predictive capability of the model

In this paper, the property P_i was taken the mass fragment M_i while the correlated property was the measured chromatographic retention.

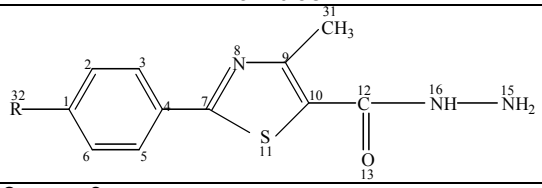
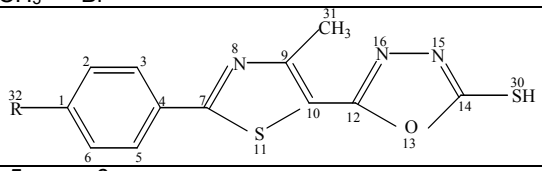
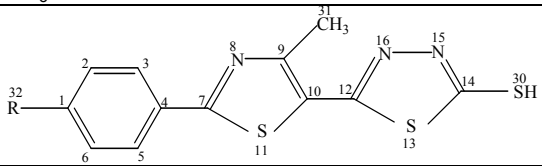
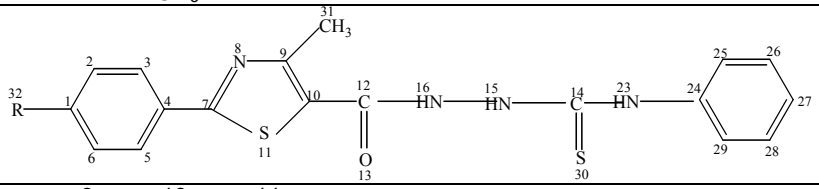
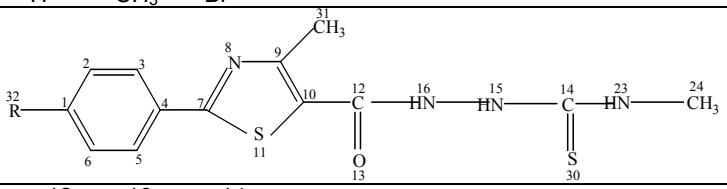
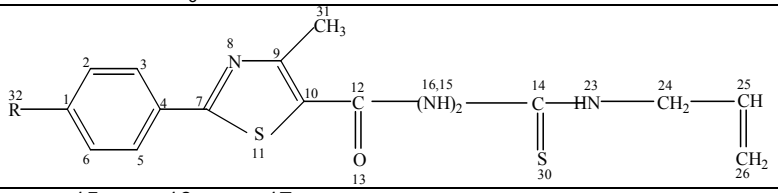
STRUCTURAL DATA

Statistics were done on the set of 26 thiazole derivatives illustrated in Table 1 (see also the experimental part). Numbering refers to the numbering of the hypermolecule, built up as the union of all molecules in the studied set. Cromatographic retention index is listed in Table 2, for each faze F_k, k=1 to 5. Details are given in the Experimental section.



Hypermolecule

Table 1. Structural formulas for the studied thiazoles

	Formulas
1	
Struct.	1 2 3 R H CH_3 Br
2	
Struct.	4 5 6 R H CH_3 Br
3	
Struct.	7 8 R H CH_3
4	
Struct.	9 10 11 R H CH_3 Br
5	
Struct.	12 13 14 R H CH_3 Br
6	
Struct.	15 16 17 R H CH_3 Br

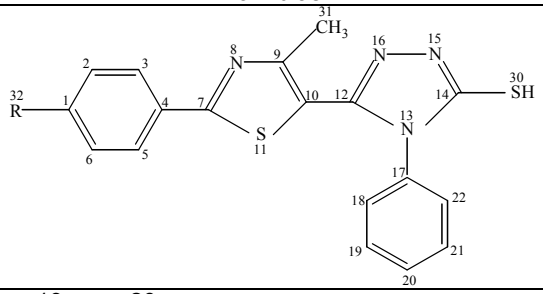
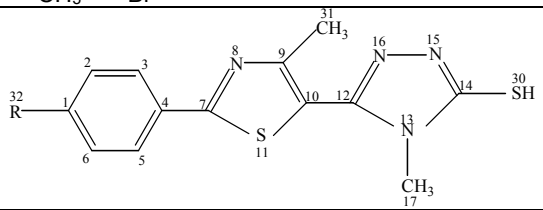
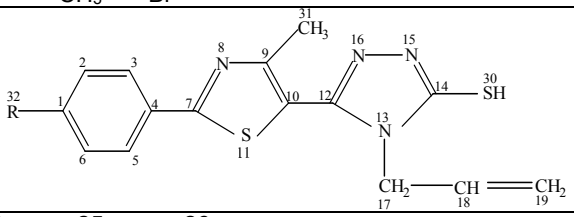
	Formulas
7	
Struct.	18 19 20 R H CH_3 Br
8	
Struct.	21 22 23 R H CH_3 Br
9	
Struct.	24 25 26 R H CH_3 Br

Table 2. Chromatographic retention values R_f for the Thiazoles in five mobile fazes F_i

Structure	i-propanol:water ratio				
	45:55:00	50:50:00	55:45:00	60:40:00	65:35:00
	F_1	**F_2**	**F_3**	**F_4**	**F_5**
1	0.400	0.510	0.588	0.552	0.694
2	0.352	0.482	0.529	0.576	0.670
3	0.247	0.376	0.458	0.470	0.611
4	0.658	0.729	0.723	0.764	0.835
5	0.600	0.682	0.676	0.711	0.729
6	0.576	0.670	0.658	0.694	0.729
7	0.470	0.540	0.517	0.547	0.647
8	0.410	0.470	0.482	0.470	0.576
9	0.376	0.494	0.552	0.600	0.688

Structure	i-propanol:water ratio				
	45:55:00	50:50:00	55:45:00	60:40:00	65:35:00
	F_1	**F_2**	**F_3**	**F_4**	**F_5**
10	0.305	0.435	0.505	0.541	0.647
11	0.282	0.400	0.458	0.494	0.611
12	0.529	0.635	0.670	0.705	0.788
13	0.458	0.588	0.623	0.664	0.752
14	0.388	0.517	0.564	0.611	0.717
15	0.435	0.564	0.600	0.635	0.735
16	0.376	0.505	0.541	0.588	0.705
17	0.329	0.447	0.482	0.529	0.658
18	0.317	0.447	0.482	0.517	0.647
19	0.247	0.400	0.423	0.464	0.611
20	0.153	0.305	0.294	0.435	0.435
21	0.329	0.505	0.482	0.611	0.600
22	0.247	0.447	0.435	0.552	0.553
23	0.211	0.388	0.376	0.482	0.505
24	0.258	0.435	0.429	0.552	0.494
25	0.200	0.376	0.376	0.494	0.505
26	0.152	0.317	0.305	0.670	0.458

RESULTS AND DISCUSSION

The local property P_{ij} chosen here was the hydride fragment mass M_{ij} (listed in Table 3, for each j-position of the hypermolecule). It will be used in the calculation of the auto-correlation property descriptor *AD* (see below).

Table 3. Hydride fragment mass M_{ij}, for each *j*-position of the hypermolecule

j |	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
1 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
2 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
3 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
4 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
5 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
6 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
7 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
8 |	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
9 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
10 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
11 |	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32
12 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
13 |	16	16	16	16	16	16	32	32	16	16	16	16	16	16	16	16	16	14	14	14	14	14	14	14	14	14
14 |	0	0	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12

j |	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
15 |	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
16 |	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
17 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	12	12	12	12	12	12
18 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	0	0	0	12	12	12
19 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	0	0	0	12	12	12
20 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0
21 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0
22 |	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0
23 |	0	0	0	0	0	0	0	0	14	14	14	14	14	14	14	14	14	0	0	0	0	0	0	0	0	0
24 |	0	0	0	0	0	0	0	0	12	12	12	12	12	12	12	12	12	0	0	0	0	0	0	0	0	0
25 |	0	0	0	0	0	0	0	0	12	12	12	0	0	0	12	12	12	0	0	0	0	0	0	0	0	0
26 |	0	0	0	0	0	0	0	0	12	12	12	0	0	0	12	12	12	0	0	0	0	0	0	0	0	0
27 |	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28 |	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29 |	0	0	0	0	0	0	0	0	12	12	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30 |	0	0	0	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32	32
31 |	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
32 |	0	12	80	0	12	80	0	12	0	12	80	0	12	80	0	12	80	0	12	80	0	12	80	0	12	80

Topological Cluj descriptors were computed by TOPOCLUJ sofware and listed in Table 4 along with the number of atoms *N* in molecules and the energy of the highest occupied molecular orbital HOMO, computed on the optimized molecules, at the Hartree-Fock level of theory (see the experimental part).

Table 4. Topological and energetic descriptors of the optimized molecules at the Hartree-Fock level of theory

Molecule	***N***	I_e	I_p	**HOMO** (au)
1	16	310	1400	-1778.65
2	17	380	1800	-1817.691
3	17	380	1800	-4347.955
4	18	430	2500	-1588.141
5	19	520	3000	-1627.187
6	19	520	3000	-4157.45
7	18	430	2500	-1665.028
8	19	520	3000	-1704.068
9	25	1100	7500	-1702.554
10	26	1300	8600	-1741.595
11	26	1300	8600	-4271.859
12	20	570	3000	-1512.092
13	21	670	3600	-1551.132
14	21	670	3600	-4081.396

Molecule	***N***	I_e	I_p	**HOMO** (au)
15	22	740	4200	-1588.973
16	23	860	5000	-1628.013
17	23	860	5000	-4158.278
18	24	930	6700	-1492.878
19	25	1100	7800	-1531.919
20	25	1100	7800	-4062.183
21	19	480	2900	-1815.518
22	20	580	3500	-1854.559
23	20	580	3500	-4234.319
24	21	620	3900	-1891.562
25	22	720	4600	-1930.602
26	22	720	4600	-1058.682

The best QSPR model, without auto-correlation descriptors are listed in Table 5. The descriptors named by numbers represent the mass fragments in the given positions of the hypermolecule. Even the models are statistically significant, the number of predictor variables is too large for the set of 26 thiazole derivatives, according to [29]. By this reason, we calculated the auto-correlation descriptors AD, cf. [4] (see below).

Table 5. Regressions without auto-correlation; the descriptors named by numbers represent the mass fragments in the given positions of the hypermolecule

		F_1		
Descriptors	**R^2**	**Adjus. R^2**	**St. Error**	**F**
IE, 13, 17, 24, 25, 30, 32	0.957	0.940	0.033	56.592
IE, IP, 13, 17, 25, 30, 32,HOMO	0.969	0.955	0.029	67.008
IE, 13, 17, 24, 30, 32	0.941	0.922	0.037	50.464
IE, IP, 13, 17, 25, 30, HOMO	0.954	0.936	0.034	53.425
		F_2		
IE, 13, 17, 24, 30, 32, HOMO	0.949	0.929	0.029	47.577
IE, 13, 17, 24, 30, 32	0.943	0.926	0.030	52.806
IP, 13, 17, 24, 30, 32	0.937	0.917	0.031	47.162
		F_3		
IE, 13, 17, 25, 30, 32, HOMO	0.947	0.926	0.030	45.614
IE, 13, 17, 25, 30, 32	0.938	0.919	0.032	48.169
IP, 13, 17, 25, 30, 32	0.932	0.911	0.033	43.432
		F_4		
IE, IP, 13, 17, 22, 25, 30, 32, HOMO	0.957	0.932	0.023	39.275
IE, 13, 17, 22, 25, 30, 32, HOMO	0.913	0.872	0.031	22.359
IE, 13, 17, 25, 30, 32, HOMO	0.913	0.879	0.031	27.044
		F_5		
IE, 13, 17, 22, 29, 30, 32	0.933	0.906	0.031	35.598
IP, 13, 17, 22, 29, 30, 32	0.937	0.913	0.030	38.378
IE, 13, 17, 22, 29, 30, HOMO	0.918	0.885	0.035	28.619

Table 6 lists the global auto-correlating descriptor $AD_{(13, 17, 19, 24, 25, 30, 32)}$ calculated cf (4) (on the positions 13, 17, 19, 24, 25, 30, 32 of the hypermolecule), the F_1 values, observed and estimated, the corresponding residuals (i.e., the difference between the experimental and calculated F-values) for eq. (6) and the predicted *leave-one-out* $F_{1,loo}$-values cf (7).

$$F_1=0.575+\mathbf{AD}(F_1);\ n=26;\ R^2=0.950;\ s=0.031;\ F=454.567 \quad (6)$$

$$F_{1,loo}=0.002+0.994\mathbf{AD}(F_1)_{\boldsymbol{loo}};\ n=25;\ R^2=0.942;\ s=0.033;\ F=391.815 \quad (7)$$

One can see a good predictive ability of the $\mathbf{AD}(F_1)_{\boldsymbol{loo}}$ descriptors by the small drop of the correlation coefficient R^2 in a monovariate regression (eqs. 6 and 7). The subscript numbers in AD_i symbols represent the positions in hypermolecule and suggest these are responsible of the chromatographic retention. The large values of Fischer ratio F in (6) in comparison to the multivariate regressions listed in Table 5 suggest a higher level of (statistical) significance for the monovariate regression in comparison to that of multivariate ones. Table 7 lists the best modeld using the auto-correlating descriptors and some other molecular: Cluj indices and the energy of HOMO, for all the 5 mobile phases F_i. One can see a similar chromatographic behavior in all the phases except F_4, which is the worst one.

It is noteworthy the adjusted R^2 speaks clearly that the additional variables (i.e., Cluj indices and HOMO) are not necessary, thus proving the utility of the auto-correlating descriptors.

Table 6. Auto-correlating descriptors $AD_{(13, 17, 19, 24, 25, 30, 32)}$ in the learning (calcd) and predicting (*loo*) steps, respectively

Molecule *i*	AD_i	$F_{1,obs}$	$F_{1,calcd.}$	$Resid_{calcd}$	$F_{1,loo}$
1	-0.203	0.4	0.372	0.028	0.371
2	-0.218	0.352	0.357	-0.005	0.357
3	-0.305	0.247	0.270	-0.023	0.271
4	0.075	0.658	0.651	0.007	0.648
5	0.060	0.6	0.635	-0.035	0.645
6	-0.027	0.576	0.548	0.028	0.544
7	-0.128	0.47	0.448	0.022	0.446
8	-0.143	0.41	0.432	-0.022	0.434
9	-0.185	0.376	0.390	-0.014	0.39
10	-0.201	0.305	0.374	-0.069	0.377
11	-0.288	0.282	0.287	-0.005	0.288
12	-0.078	0.529	0.498	0.031	0.495
13	-0.093	0.458	0.482	-0.024	0.484
14	-0.180	0.388	0.395	-0.007	0.395
15	-0.185	0.435	0.390	0.045	0.388
16	-0.201	0.376	0.374	0.002	0.374

Molecule *i*	AD_i	$F_{1,obs}$	$F_{1,calcd.}$	$Resid_{calcd}$	$F_{1,loo}$
17	-0.288	0.329	0.287	0.042	0.285
18	-0.315	0.317	0.260	0.057	0.257
19	-0.330	0.247	0.245	0.002	0.245
20	-0.417	0.153	0.158	-0.005	0.159
21	-0.274	0.329	0.302	0.027	0.300
22	-0.289	0.247	0.286	-0.039	0.288
23	-0.376	0.211	0.199	0.012	0.198
24	-0.315	0.258	0.260	-0.002	0.261
25	-0.330	0.200	0.245	-0.045	0.248
26	-0.417	0.152	0.158	-0.006	0.159

Table 7. Regressions with auto-correlation descriptors

Descriptors	R^2	Adjust. R^2	St. Error	F
	F_1			
$AD_{(13, 17, 19, 24, 25, 30, 32)}$	0.950	0.948	0.031	454.567
IE, AD	0.952	0.948	0.031	228.094
IE, IP, AD	0.952	0.946	0.031	146.168
IE, AD, HOMO	0.952	0.946	0.031	146.705
IE, IP, AD, HOMO	0.953	0.944	0.032	106.068
	F_2			
$AD_{(13, 17, 18, 24, 26, 30, 32)}$	0.944	0.942	0.026	403.468
AD, HOMO	0.944	0.939	0.027	194.442
IE, IP, AD	0.949	0.943	0.026	137.740
IP, AD, HOMO	0.950	0.943	0.026	138.406
IE, IP, AD, HOMO	0.950	0.940	0.027	99.095
	F_3			
$AD_{(13, 17, 24, 25, 30, 32)}$	0.940	0.937	0.028	372.732
AD, HOMO	0.942	0.937	0.028	186.190
IE, IP, AD	0.945	0.937	0.028	125.169
IE, AD, HOMO	0.947	0.940	0.027	131.604
IE, IP, AD, HOMO	0.947	0.937	0.028	94.370
	F_4			
$AD_{(13, 17, 22, 24, 25, 30, 32)}$	0.776	0.766	0.943	82.981
IE, IP, AD	0.781	0.751	0.044	26.084
AD, HOMO	0.805	0.788	0.041	47.424
IP, AD, HOMO	0.809	0.783	0.041	31.037
IE, IP, AD, HOMO	0.809	0.773	0.042	22.294
	F_5			
$AD_{(13, 17, 18, 22, 26, 29, 30, 32)}$	0.926	0.923	0.029	298.865
AD, HOMO	0.926	0.919	0.029	143.519
IE, AD, HOMO	0.926	0.916	0.030	92.332
IE, IP, AD	0.929	0.919	0.029	95.325
IE, IP, AD, HOMO	0.929	0.915	0.030	68.276

EXPERIMENTAL

Twenty six thiazole derivatives (thiazolyl-carbonyl-thiosemicarbazides and hybrid thiazolyl-1,3,4-oxadiazoles, thiazolyl-1,3,4-triazoles, and thiazolyl-1,3,4-triazoles - Table 1), synthesized in our laboratory, according to a previously described procedure [30,31], were investigated for chromatographic behavior. Chromatography was performed on 20 X 20 cm RP-18F_{254s} TLC precoated silica plates (Merck; Darmstadt, Germany). Solutions (1 mg mL^{-1}) of the tested compounds were prepared in *iso*-propanol, and 3 μl in duplicate were spotted on the plates by hand, 10 mm from the bottom edge and 20 mm apart. The mobile phases were composed of the *iso*-propanol-water binary mixtures, with a varying content of organic modifier between 45-65% (v/v) in 5% increments, as the study compounds differed considerably in their retention. Chromatography was performed in a normal developing chamber at room temperature, the developing distance being 10 cm. The chromatography chamber was saturated with the mobile phase for 30 minutes before use. After the development (30-60 minutes), the plates were air dried at room temperature and examined under UV lamp (λ= 254 nm) and the R_f (retardation factor) values were measured manually by a digital caliper. The experiments were made in triplicate. All components of the mobile phases used were of the analytical grade of purity. Table 2 lists the data for each faze F_k, k=1 to 5. The results were addressed to statistical correlational analysis.

Topological indices were computed by the TOPOCLUJ [32] software while the HOMO energy was computed by single point on the optimized molecules at the Hartree-Fock HF/6-31G(d,p) level of theory.

CONCLUSIONS

A set of twenty six thiazole derivatives, synthesized in the laboratory of Faculty of Pharmacy, “Iuliu Hatieganu” University of Medicine and Pharmacy, and measured for chromatographic retention was submitted to a QSPR study by auto-correlation analysis within the hypermolecule model. As predictor variables, mass fragments, Cluj indices and the HOMO energy, computed at the Hartree-Fock level of theory, have been used. Several QSPR models were derived while the leave-one-out procedure was used to prove the predictive ability of the main model. The auto-correlation descriptors behaved statistically better than the normal descriptors, according to the parameters of regression equations.

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