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CORRELATING STUDY ON PHISYCO-CHEMICAL AND BIOLOGICAL PROPERTIES OF THIOSEMICARBAZONE AND THIADIAZOLINE DERIVATIVES

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ABSTRACT. Thiadiazolines and Thiosemicarbazones represent classes of well-known molecular structures with important biological activities. The set of twenty structures, synthesized in our lab, was characterized about lipophilicity by reverse phase thin layer chromatography (RPTLC) and tested for their antimicrobial activities. These molecular properties were modeled by using topological and quantum descriptors, in the frame of a hypermolecule, with the meaning of a "mean molecule" in the set. A general procedure for developing and validating the models using the above concept is given. Within this frame, a method of data reduction (*i.e.*, selection of relevant descriptors) was exemplified.

Keywords: *thiosemicarbazone, thiadiazoline, hypermolecule, molecular descriptor,QSPR, QSAR*

INTRODUCTION

According to the literature, thiosemicarbazones are reported to possess various biological activities, as antimicrobial, anti-inflammatory, antiviral, antiparasitic, antimalarial, and antituberculosis [1-3].

Also, molecules containing nitrogen- and sulphur-related heterocycles (thiazole, thiazolidine, thiazolidinedione, thiadiazoline) are considered important pharmacophores as they can possess interesting biological activities too. For example, thiadiazolines have antihelmintic, antihypertensive, anticancer, anti-inflammatory, antibacterial, analgesic, and tyrosinase inhibitory activities [4].

Application of QSAR/QSPR techniques in order to elucidate the ways in which the structure can determine physical and/or biological properties has already become an essential tool in the area of medicinal chemistry [5-9]. These techniques combine the ability to predict physico-chemical properties of as yet unmeasured or unknown compounds with the ability to understand just how the structure influences a particular property.

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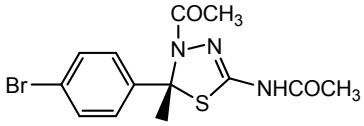
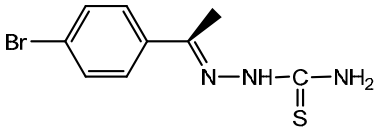
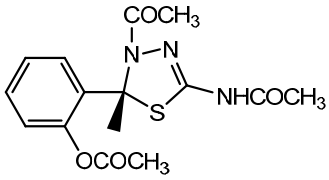
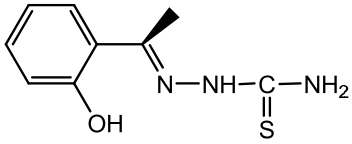
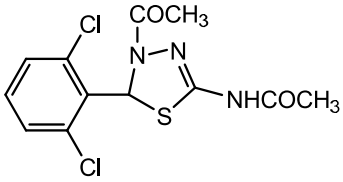
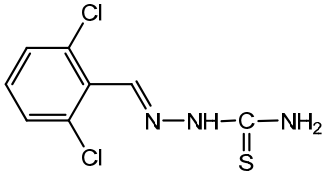
The retention chromatographic index, I_{CHR}, is a measure of the interaction between a given compound and two phases: a mobile phase (i.e., the eluent) and a stationary one. This interaction is function of more than one factor, polarity, lipophylicity and the size of the molecule being included. These factors are joined in a "global" molecular property, termed *chromatographic index* [10,11]. It is well known that the values of I_{CHR} vary with the chromatographic systems, pressure and temperature. This is the reason why, in correlating studies, values I_{CHR} from a single experiment are requested. Lipophilicity is related to I_{CHR} and controls the passive transport of a medicinal molecule through the cell membranes (of lipidic nature).

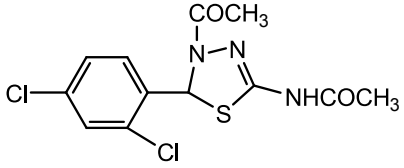
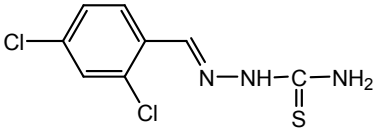
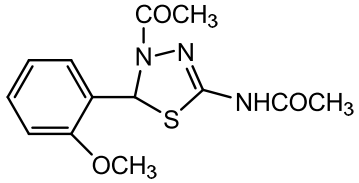
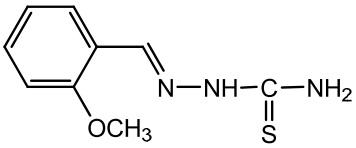
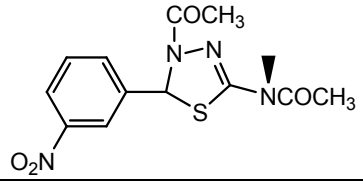
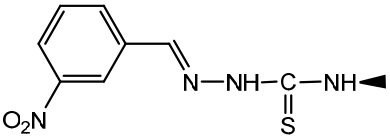
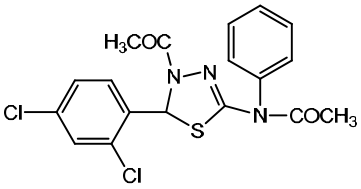
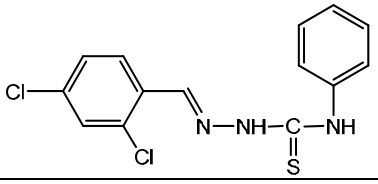
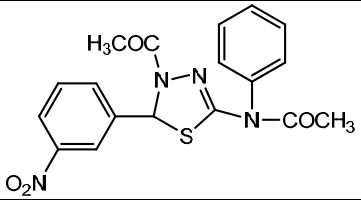
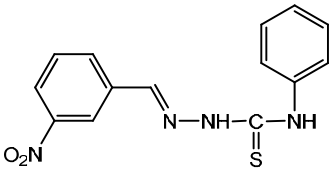
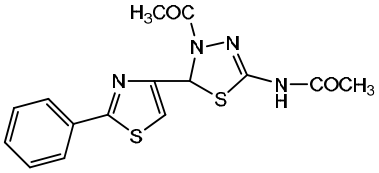
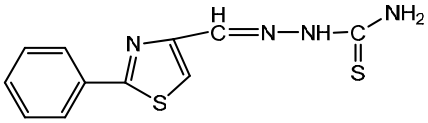
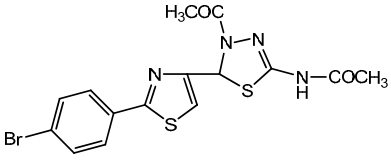
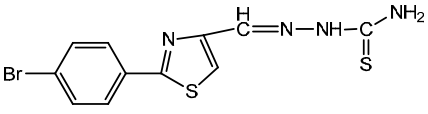
This paper is focused on the development of novel QSPR/QSAR models using quantum molecular and topological descriptors on the ground of available experimental physico-chemical and biological data.

DATA SETS

The molecular structures of thiadiazolines and thiosemicarbazones herein investigated are listed in **Table 1**.

Table 1. Chemical Structures of the Studied Thiadiazolines and Thiosemicarbazones

	Thiadiazolines		**Thiosemicarbazones**
1		**11**	
2		**12**	
3		**13**	

	Thiadiazolines		Thiosemicarbazones
4		**14**	
5		**15**	
6		**16**	
7		**17**	
8		**18**	
9		**19**	
10		**20**	

RESULTS AND DISCUSSION

The results of the correlating analysis are presented for both joint and separate sets: thiosemicarbazones (10) and thiadiazolines (10). Before starting the correlating analysis, let us introduce the concept of hypermolecule, as the "mean" molecule [12] within the investigated set of structures.

Hypermolecule Model

The *hypermolecule H* (**Figure 1**) was generated by superimposing all the common features of molecules under study [13,14]. On the already generated hypermolecule, we calculated the mass descriptors **M**, as groups of atoms, *e.g*. CH, Cl, *etc*. for any vertex of H and for all molecules in the set (see the **Appendix**) and used them as independent variables in the correlating study. **Table 2** includes selected mass descriptors along with other descriptors chosen to describe a given position in the hypermolecule, such as partial charges CH, and global descriptors including HOMO level of energy (in au, after Hartree-Fock optimization), HOMO-LUMO gap HL Gap and some global topological indices calculated by TOPO CLUJ program (on distance and detour, respectively).

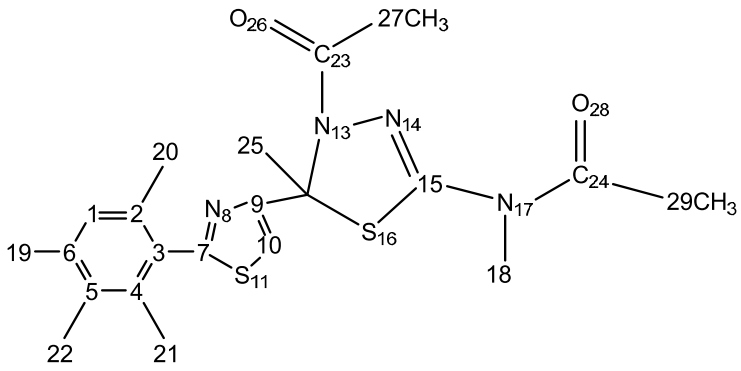


Figure 1. Hypermolecule H

Chromatographic Index I_{chr}.

The reverse phase thin-layer chromatography data, provided by six sets of experiments $\mathbf{P_1}$ to $\mathbf{P_6}$, for the set of 20 molecules in **Table 1** are listed in **Table 3**.

Table 2. Descriptors values for molecules and for relevant positions in the Hypermolecule

Structure	E_{tot} HF	HL Gap	HOMO (eV)	IE CJDE	IE CJDI	14CH	19CH
1	-3780.933	11.627	-8.988	232	526	0.001	-0.069
2	-1438.271	11.991	-9.024	391	723	-0.480	0.146
3	-2090.376	11.605	-9.003	247	515	-0.392	0.187
4	-2090.387	11.828	-9.341	241	539	-0.415	-0.096
5	-1286.481	11.708	-8.566	255	522	-0.468	0.172
6	-1415.089	10.938	-9.464	312	691	-0.437	0.212
7	-2168.147	10.891	-8.141	321	873	-0.369	-0.079
8	-1453.829	9.951	-8.376	367	984	-0.371	0.182
9	-1738.747	10.616	-8.342	337	812	-0.476	0.146
10	-4308.052	10.374	-8.393	374	938	-0.550	-0.054
11	-3477.391	10.815	-8.254	121	230	0.084	-0.042
12	-982.947	11.168	-8.328	124	216	0.229	0.163
13	-1786.829	10.824	-8.359	126	222	0.190	0.190
14	-1786.833	10.386	-8.46	123	234	0.259	-0.062
15	-982.928	10.648	-8.098	132	226	0.369	0.160
16	-1111.539	9.652	-8.526	190	336	0.135	0.200
17	-2016.375	10.262	-8.314	353	669	0.103	-0.062
18	-1302.051	9.522	-8.416	405	765	0.191	0.204
19	-1435.190	9.984	-8.3	188	397	0.034	0.149
20	-4004.494	9.809	-8.386	214	476	0.114	-0.036

Table 3. Chromatographic index I_{chr} values for the molecules in Table 1

Structure	P_1	P_2	P_3	P_4	P_5	P_6
1	0.317	0.376	0.470	0.588	0.635	0.682
2	0.576	0.588	0.658	0.747	0.770	0.817
3	0.364	0.423	0.505	0.623	0.670	0.717
4	0.305	0.364	0.458	0.582	0.635	0.682
5	0.476	0.541	0.611	0.717	0.753	0.788
6	0.388	0.458	0.541	0.647	0.694	0.729
7	0.070	0.105	0.164	0.270	0.341	0.388
8	0.264	0.352	0.447	0.576	0.641	0.682
9	0.352	0.447	0.529	0.647	0.694	0.741
10	0.235	0.341	0.429	0.552	0.623	0.670
11	0.282	0.376	0.447	0.576	0.635	0.682
12	0.470	0.558	0.594	0.705	0.752	0.788
13	0.300	0.140	0.441	0.588	0.647	0.688
14	0.223	0.305	0.352	0.517	0.564	0.605
15	0.400	0.482	0.535	0.623	0.705	0.752
16	0.352	0.429	0.488	0.623	0.670	0.694
17	0.210	0.294	0.337	0.498	0.531	0.586

Structure	P_1	P_2	P_3	P_4	P_5	P_6
18	0.164	0.247	0.311	0.470	0.535	0.576
19	0.247	0.341	0.417	0.552	0.611	0.652
20	0.270	0.235	0.411	0.558	0.623	0.658

Looking at the I_{chr} values in Table 3, one can see that these are inter-correlated, as shown in the matrix below (the highly correlated ones in bold characters):

Intercorrelating matrix for the Chromatographic index I_{chr}

	P_1	P_2	P_3	P_4	P_5	P_6
P_1	1	0.88168	**0.96396**	0.90565	0.87199	0.85756
P_2		1	0.89156	0.85531	0.8393	0.84362
P_3			1	**0.97806**	**0.96257**	0.95364
P_4				1	**0.99451**	**0.99071**
P_5					1	**0.99855**
P_6						1

It comes out that some statistical data will be very close for the highly inter-correlated chromatographic parameters P_n.

Data Reduction and Models

Data reduction was made in view of eliminating the irrelevant descriptors and/or inactive positions in the hypermolecule, either in chromatography or biological activity terms. The procedure implies the calculation of a first regression with as many as possible invariant descriptors followed by the stepwise elimination of the irrelevant ones.

The quality of statistics was monitored by Pearson correlation coefficient R, by Fischer ratio F (as higher value, as better quality regression) and also by the percentage variance CV%, expressing the accuracy of the prediction (particularly the non-explained part of the data variation). The correlating equations are listed in **Tables 4** to **6**.

As an example, data reduction dropped the initial 18 descriptors to only 4 ones (see **Table 4)**, with statistical relevance in the description of the chromatographic index. One can see that a same set of descriptors correlates differently with the different dependent variables.

Note that, among many, the mass descriptors **M** and partial charges **CH** have been successfully used. The best models also included the global molecular parameters such as HOMO-LUMO Gap **HL Gap** (**Table 5**), HOMO energy (**Table 6**) and topological descriptors, e.g., the **Cluj index** IECJDE (**Table 4, 6**) [15,16].

Table 4. Chromatographic index I_{chr} values P_1 to P_5 correlated by the same set of descriptors

Descriptors	Coeff	Const	R	CV%	F
P_1		-0.012	0.861	25.127	11.506
18M	-0.003				
19M	-0.002				
2M	0.027				
IECJDE	0.0003				
P_2		-1.186	0.786	24.13	6.068
18M	-0.003				
19M	-0.002				
2M	0.123				
IECJDE	0.0003				
P_3		-0.013	0.921	14.828	22.461
18M	-0.003				
19M	-0.002				
2M	0.038				
IECJDE	0.0003				
P_4		-0.009	0.945	10.624	33.465
18M	-0.003				
19M	-0.001				
2M	0.048				
IECJDE	0.0002				
P_5		-0.008	0.958	0.053	8.821
18M	-0.002				
19M	-0.001				
2M	0.053				
IECJDE	0.0002				

Table 5. High quality QSPRs for the P_6 set of I_{chr} data

Descriptors	Coeff	Const	R	CV%	F
P_6		-0.007	0.960	8.177	66.578
18(20)M	-0.002				
19(20)CH	-0.001				
2(20)M	0.058				
P_6		-0.011	0.970	7.303	63.947
18(20)M	-0.002				
19(20)CH	0.350				
2(20)M	0.037				
HL GAP	0.021				
P_6		-0.004	0.968	7.587	58.951
14(20)CH	-0.042				
18(20)M	-0.002				
19(20)CH	0.321				
2(20)M	0.054				

Model Validation

Despite the small number of experimental data concerning the antimicrobial activity (10 data), we could find that the prediction by QSAR was not "by chance": changing the order of data in the column "*B. cereus*" (**Table 7**), by "*B. cereus**" we could observe a large drop in R and F and an increase in the explained variance (**Table 7**, the bolded and underlined rows, respectively).

We could not split the data set in "training set" and "prediction set" in order to calculate the predictive power of the model. Our intention was only to give a methodology, rather than to offer the best model for a given property/activity.

Table 6. QSARs for the activity against *B.cereus*

Descriptors	Coeff	Const	R	CV%	F	*B.cereus*	*B. cereus**
B. cereus		18.633	0.879	3.005	11.859	**18**	18
14(10)CH	-4.660					**18**	18
18(10)M	-0.025					**18**	16
B. cereus		**10.659**	**0.951**	**2.105**	**18.877**	**18**	18
14(10)CH	**-5.407**					**16**	16
18(10)M	**-0.018**					**18**	18
HOMO	**-0.912**					**16**	16
*B. cereus**		11.388	0.529	5.771	0.776	**16**	18
14(10)CH	-4.458					**18**	18
18(10)M	-0.002					**18**	18
HOMO	-0.777						
B. cereus		8.512	0.968	1.884	18.299		
14(10)CH	-5.084						
18(10)M	-0.019						
HOMO	-1.039						
IECJDE	0.003						
B. cereus		8.124	0.968	2.100	11.784		
14(10)CH	-5.185						
18(10)M	-0.019						
HOMO	-1.022						
HL Gap	0.045						
IECJDE	0.003						
B. cereus		8.103	0.969	2.060	12.280		
14(10)CH	-4.837						
18(10)M	-0.019						
19(19)M	0.002						
HOMO	-1.066						
IECJDE	0.004						

CONCLUSIONS

In the present paper, we used (local) molecular descriptors for encoding a hypermolecule, as the "mean molecule" in the set. Next, we have calculated quantum molecular and topological indices/descriptors to model the chromatographic retention index $\mathbf{I_{chr}}$ in reversed phase, having the meaning of molecular lipophilicity and being involved in the transport of drugs through membranes to the biological receptors. The biological activity against *Bacillus cereus* was also modeled. Even the work didn't provide the best predictive model, it has a methodological value.

EXPERIMENTAL

Computational

The QSPR study was performed on a series of 20 structures, 10 thiadiazolines and 10 thiosemicarbazones, vs the chomathographic retention index $I_{CHR,}$ while the QSAR study was realized only on the 10 thiadiazolines.

The molecular graphs have been optimized by the Molecular Mechanics MM+ procedure and next at the Hartree-Fock HF level of theory. From the outputs, the HOMO energy, HOMO_LUMO Gap, and the partial charges of all the atoms have been collected. The calculations have been done on Gaussian G09 [17].

Thin-layer chromatography

The reverse phase thin-layer chromatography of the set of 20 molecules, listed in Table 1, was performed using a mixture of *i*-propanol-water as mobile phase, in six different ratios. This experiment provided data, with the meaning of molecular lipophilicity, for multi-linear regression. The chromatographic experimental data were listed in **Table 3**.

Appendix

Mass descriptors **M**, according to the hypermolecule H

	Positions in the Hypermolecule H																							
Structure	**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**
1	13	13	12	13	13	12	0	0	0	0	0	12	14	14	12	32	14	1	0	0	0	0	43	43	15
2	13	13	12	12	13	13	0	0	0	0	0	12	14	14	12	32	14	1	0	0	59	0	43	43	15
3	13	12	12	12	13	13	0	0	0	0	0	13	14	14	12	32	14	1	0	35.5	35.5	0	43	43	0
4	13	12	12	12	13	13	0	0	0	0	0	13	14	14	12	32	14	1	35.5	0	35.5	0	43	43	0
5	13	13	12	12	13	13	0	0	0	0	0	13	14	14	12	32	14	1	0	0	31	0	43	43	0
6	13	13	12	13	12	13	0	0	0	0	0	13	14	14	12	32	14	15	0	0	0	46	43	43	0
7	13	12	12	13	13	12	0	0	0	0	0	13	14	14	12	32	14	77	35.5	35.5	0	0	43	43	0

	Positions in the Hypermolecule H																							
Structure	**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**
8	13	13	12	13	12	13	0	0	0	0	0	13	14	14	12	32	14	77	0	0	0	46	43	43	0
9	13	13	12	13	13	13	12	14	12	13	32	13	14	14	12	32	14	1	0	0	0	0	43	43	0
10	13	13	12	13	13	12	12	14	12	13	32	13	14	14	12	32	14	1	80	0	0	0	43	43	0
11	13	13	12	13	13	12	0	0	0	0	0	12	14	15	12	32	14	1	80	0	0	0	0	1	15
12	13	13	12	12	13	13	0	0	0	0	0	12	14	15	12	32	14	1	0	0	17	0	0	1	15
13	13	12	12	12	13	13	0	0	0	0	0	13	14	15	12	32	14	1	0	35.5	35.5	0	0	1	0
14	13	12	12	13	13	12	0	0	0	0	0	13	14	15	12	32	14	1	35.5	35.5	0	0	0	1	0
15	13	13	12	12	13	13	0	0	0	0	0	13	14	15	12	32	14	1	0	0	31	0	0	1	0
16	13	13	12	12	12	13	0	0	0	0	0	13	14	15	12	32	14	15	0	0	0	46	0	1	0
17	13	13	12	12	13	12	0	0	0	0	0	13	14	15	12	32	14	77	35.5	0	35.5	0	0	1	0
18	13	13	12	13	12	13	0	0	0	0	0	13	14	15	12	32	14	77	0	0	0	46	0	1	0
19	13	13	12	13	13	13	12	14	12	13	32	13	14	15	12	32	14	1	0	0	0	0	0	1	0
20	13	13	12	13	13	12	12	14	12	13	32	13	14	15	12	32	14	1	80	0	0	0	0	1	0

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