

# QSPR modeling of molecular lipophilicity of some formyl- and acetylpyridine-3-thio-semicarbazones by topological descriptors

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(Received April 28, 2008)

**Abstract:** Retention indices for formyl- and acetylpyridine-3-thiosemicarbazone derivatives were determined by RP-HPTLC experiments.

Multivariate regression analysis was used to describe the relationship between the chromatographic retention indices of tested compounds ( $R_{M0}$ ,  $b$ , and scores corresponding to PC1) and the calculated topological descriptors. The scores of the first principal component (PC1) appeared to be the best solution for the lipophilicity scale derived from the retention data.

The results of these investigations also indicate that the density and the molecular radius of the molecules are basic descriptors for the QSPR of formyl- and acetylpyridine-3-thiosemicarbazone derivatives; the model was improved by the use of topological descriptors.

## 1 Introduction

The partition coefficient of solutes between octanol and water,  $P$ , is extensively used in environmental and biomedical sciences as a descriptor of the lipophilicity properties of molecules [1, 2].

From the magnitude of the  $\log P$  of a compound, one can infer its ease of transport through the cell membrane and other related events. The lipophilicity of a substance affects its biological activity. As such, relationships between biological activities and  $\log P$  can be demonstrated [3-6].

Reversed-phase thin-layer chromatography is an alternative method to estimate the lipophilicity [7].

Correlation between thin layer chromatographic retention indices and molecular structures can provide insight into interactions between eluents and stationary phases, and give information about retention, adsorption and elution as well. A large number of structure–retention index correlations have been developed but among molecular descriptors, topological indices are of particular interest because they can be easily calculated directly from the molecular structures [8-12].

Molecular structure of a compound can be expressed by means of various graph matrices, polynomials, sequences counting distances, paths, and walks, or single number topological indices [13-16].

Topological indices are widely used as structural descriptors in quantitative structure–property relationship (QSPR) and quantitative structure–activity relationship (QSAR) models [13] and in the first steps of trial in data mining and finally in drug design [4].

Considerable attention has been devoted to thiosemicarbazones and their complexes with the first row transition metals, due to their interesting biological activities, e.g., antibacterial, anti-HIV, antiviral, antifungal, antitumour, antiinflammatory, tuberculostatic, and antileukemic properties [17-21].

The main goal of this work is to derive a correlation model of the chromatographic retention indices of a set of formyl- and acetylpyridine-3-thiosemicarbazone derivatives ( $R_{M_0}$ ,  $b$ , and scores corresponding to PC1) with topological descriptors calculated by two different software programs.

Another goal is to use the correlating results in understanding the molecular mechanism of interaction between eluents and stationary phases of various polarity.

## **2 Experimental**

### **2.1 Chemicals**

The formyl- and acetylpyridine-3-thiosemicarbazone derivatives and their palladium and zinc complexes (Table 1) were synthesized in the Department of Chemistry, Section of Inorganic and Analytical Chemistry, University of Ioannina, (Greece).

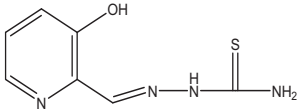
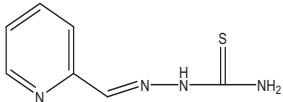
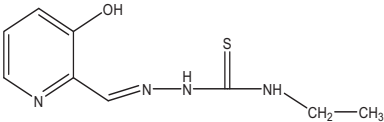
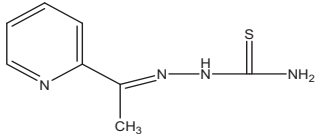
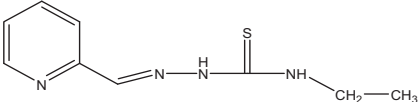
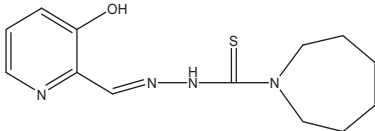
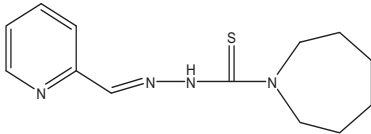
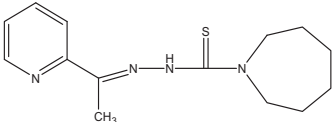
### **2.2 Chromatography**

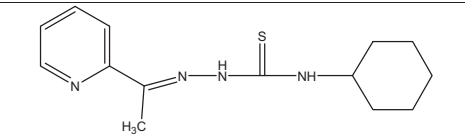
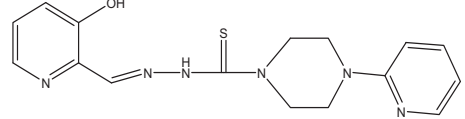
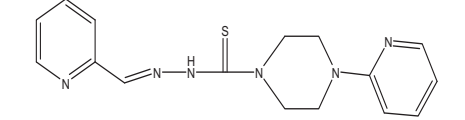
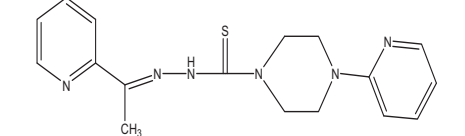
The chromatographic behavior of the formyl- and acetylpyridine-3-thiosemicarbazone derivatives was studied on two stationary phases: RP-C<sub>18</sub>/UV<sub>254</sub> (20x20 cm) and RP-C<sub>18</sub>W/UV<sub>254</sub> (10x20 cm) silica gel bounded plates from Merck (Darmstadt, Germany). RP-C<sub>18</sub>

stationary phases are the most widely used phases for RP-HPTLC, due to their ability to separate a wide range of solutes with good resolution, selectivity and efficiency.

**Table 1**

**Molecular structure of formyl- and acetylpyridine-3-thiosemicarbazone derivatives**

Cpd	Molecular formula	Molecular structure
1	$C_7H_8N_4SO$	
2	$C_7H_8N_4S$	
3	$C_9H_{12}N_4SO$	
4	$C_8H_{10}N_4S$	
5	$C_9H_{12}N_4S$	
6	$C_{13}H_{18}N_4SO$	
7	$C_{13}H_{18}N_4S$	
8	$C_{14}H_{20}N_4S$	

9	$C_{14}H_{20}N_4S$	
10	$C_{16}H_{18}N_6SO$	
11	$C_{16}H_{18}N_6S$	
12	$C_{17}H_{20}N_6S$	

RP-C<sub>18</sub>W plate differs from the RP-C<sub>18</sub> plate by the inclusion of a polar end-capping agent, which increases the polarity near the surface of the silica, and therefore allows better penetration of mobile phase into the stationary phase [22].

The formyl- and acetylpyridine-3-thiosemicarbazone of Zn and Pd complexes were separated in the above presented stationary phases. The solutions (1 $\mu$ L) were applied manually to the origin of the plates by means of a 10 $\mu$ L Hamilton (Switzerland) microliter syringe. Chromatography was performed in a normal developing chamber at room temperature (~20°C), the developing distance being 8.5 cm in both cases. A standard mobile phase (methanol-water) was used: methanol in the concentration range 25-45% (v/v) for RP-C<sub>18</sub> plate and 35-15% for RP-C<sub>18</sub>W plate, in steps of 5% in each case, as the studied compounds differed considerably in their retention.

Colored fluorescent blue-orange zones appeared on a colorless background under UV lamp ( $\lambda = 254$  nm).

### 2.3 Topological descriptors

The molecular structures were drawn by HyperChem Program (HyperCube Inc.) [23] and optimized by using the MM+ molecular mechanics force field and next by the

semiempirical AM1 procedure. The optimized geometries were sent into the DRAGON Plus version 5.4 [24] and TOPOCLUJ 3.0 [25] software packages.

A total set of 246 topological descriptors were calculated, from which 74 by Dragon and 172 by TOPOCLUJ.

The decision of which indices have to use was based on the possible physical interpretation of the descriptor, ease of calculation, or usefulness in the past studies [26].

## 2.4 RP-HPTLC

RP-HPTLC provides a variety of data that can be used as lipophilicity estimators. The lipophilicity indices measured by RP-HPTLC are derived from the retardation factor,  $R_F$  [27]:

$$R_M = R_{M0} + bC \quad (1)$$

where

$$R_M = \log(1/R_F - 1) \quad (2)$$

The lipophilicity scale was obtained by applying Principal Component Analysis directly to the matrix of retention data provided by various combinations of methanol-water as eluents [29].

## 2.5 Correlating study

Multilinear regression was used in view of deriving the best model of chromatographic retention of the compounds in Table 1.

## 3 Results and Discussion

A QSPR study was performed on the molecular lipophilicity of a number of formyl- and acetylpyridine-3-thiosemicarbazone derivatives, as measured by retention factors provided by RP-HPTLC. The lipophilicity was correlated with a series of topological descriptors and the results are adequate to explain the relationship between the structure of the molecules and the molecular lipophilicity.

Table 2

Regression data of the compounds for RP-C<sub>18</sub> and RP-C<sub>18</sub>W silica gel bounded plates

RP-HPTLC Phases Molecule	RP-C <sub>18</sub>				RP-C <sub>18</sub> W			
	R <sub>M0</sub>	<i>b</i>	PC1	R?	R <sub>M0</sub>	<i>b</i>	PC1	<b>r</b>
<b>1</b>	0.92	-0.03	0.57	<b>0.9660</b>	1.47	-0.06	0.55	<b>0.9304</b>
<b>2</b>	1.33	-0.05	0.56	0.8352	1.34	-0.05	0.54	<b>0.9878</b>
<b>3</b>	2.16	-0.06	0.59	<b>0.9442</b>	2.20	-0.07	0.60	<b>0.9519</b>
<b>4</b>	1.61	-0.05	0.57	0.8736	1.52	-0.06	0.56	<b>0.9738</b>
<b>5</b>	2.30	-0.06	0.60	<b>0.9449</b>	2.07	-0.07	0.60	<b>0.9712</b>
<b>6</b>	3.41	-0.08	0.64	<b>0.9712</b>	2.80	-0.07	0.67	<b>0.9776</b>
<b>7</b>	3.20	-0.07	0.65	<b>0.9567</b>	2.49	-0.06	0.66	<b>0.9534</b>
<b>8</b>	2.95	-0.06	0.65	0.8842	2.37	-0.07	0.63	<b>0.9317</b>
<b>9</b>	3.86	-0.09	0.66	<b>0.9859</b>	3.30	-0.09	0.66	<b>0.9875</b>
<b>10</b>	3.47	-0.08	0.66	<b>0.9725</b>	2.17	-0.04	0.66	<b>0.9516</b>
<b>11</b>	3.08	-0.07	0.65	<b>0.9698</b>	3.08	-0.08	0.66	<b>0.9885</b>
<b>12</b>	2.85	-0.06	0.65	<b>0.9534</b>	2.76	-0.06	0.67	0.8623

Table 2 shows that the correlation coefficients obtained on the RP-C<sub>18</sub>W stationary phase are somewhat higher than those obtained on the RP-C<sub>18</sub> plates (see the **r** bolded values). This means that these molecules stronger interact with the more nonpolar RP-C<sub>18</sub> stationary phase. Also, from the larger variation in R<sub>M0</sub> on the RP-C<sub>18</sub> stationary phase, one can say that the structure of the formyl- and acetylpyridine-3-thiosemicarbazone derivatives as well as the methanol concentration in the mobile phase have a higher influence on the interactions of the compounds with the RP-C<sub>18</sub> stationary phase than with the RP-C<sub>18</sub>W one.

All the computed descriptors seem to be highly inter-correlated (R>0.9). Lower inter-correlation (R<0.50) was shown by the SPI-superpendentic index, MAXDN-maximal electro-topological negative variation, MAXDP-maximal electro-topological positive variation, BLI-Kier-benzene likeliness index (Dragon descriptors) and Charges, VEA1 and VEA3-incidency matrices, X[Sh[Connectivity]]-shell matrix and C[LM[Atomic radius]]-layer matrix (TOPOCLUJ descriptors).

Topological descriptors, computed by the both software packages, correlate well (R between 0.70 and 0.89) with the lipophilicity indices (R<sub>M0</sub>, *b*, and PC1 scores) of the studied compounds, better to RP-C<sub>18</sub> stationary phase as compared to RP-C<sub>18</sub>W.

Lower correlation was shown (R in the range 0.11 to 0.41) by the following descriptors: SPI-superpendentic index, MAXDP-maximal electrotopological positive variation, DELS-molecular electrotopological variation, and PW2-path/walk 2-Randić shape index (computed by Dragon software) and C[LM[Density]]-layer matrix, VEA1 and VEA3-

incidency matrices and X[Sh[Conectivity]]-shell matrix (computed by TOPOCLUJ software), in the case of RP-C<sub>18</sub> and RP-C<sub>18</sub>W plates and R<sub>M0</sub>.

Much lower values of correlation were found for *b* than for the other lipophilicity indices. This suggests that the polarity of stationary phase is more important to retention behavior of solutes in case of polar stationary phase than in case of weakly polar one.

By applying PCA to the obtained R<sub>F</sub> values, the eigenvalues of the covariance matrix were obtained. Thus, a significant one component PC1 model, explaining 99.997 % and 99.995 % of the total variance for RP-C<sub>18</sub> and RP-C<sub>18</sub>W stationary phases, was derived considering only the eigenvalues higher than one, the subsequent eigenvalues being just sampling noise. The scores corresponding to the first principal component (PC1) appeared to be the best solution for the lipophilicity scale derived from the retention data.

In MLR using a large set of molecular descriptors, variables reduction is needed. To find the best correlations, the sets were submitted to STATISTICA 7.0 software [30] and the statistical quality of the multivariate regressions was judged by parameters such as correlation coefficients (R), Fischer test (F), probability of error (p-level) and standard error of estimates (s).

Table 3

a) Regression equations using Dragon topological descriptors on RP-C<sub>18</sub> stationary phase data

Multivariate regression	$R_{M0} = -24.629 + 8.889GNar + 6.683BLI + 3.174PJI2$	R = 0.9414 F = 21 p < 0.0004 s = 0.367
	$b = 0.047 - 0.024S3K + 0.056PW2 - 0.509PW5$	R = 0.8969 F = 11 p < 0.0033 s = 0.008
	$PC1 = 0.509 - 0.012STN + 0.027S2K - 0.0262Lop$	R = 0.9923 F = 172 p < 0.0000 s = 0.006
Bivariate regression	$R_{M0} = -17.177 + 6.889GNar + 6.151BLI$	R = 0.9283 F = 28 p < 0.0001 s = 0.381
	$b = 0.075 - 0.024S3K - 0.439PW5$	R = 0.8968 F = 18 p < 0.0007 s = 0.008
	$PC1 = 0.498 + 0.021S2K - 0.015Lop$	R = 0.9808 F = 114 p < 0.0000 s = 0.008
Monovariate regression	$R_{M0} = -13.869 + 8.270GNar$	R = 0.8292 F = 22 p < 0.0009 s = 0.543
	$b = 0.056 - 0.028S3K$	R = 0.8679 F = 31 p < 0.0003 s = 0.008
	$PC1 = 0.429 + 0.028S2K$	R = 0.9651 F = 136 p < 0.0000 s = 0.011

The best regression equations are shown in the Table 3 (a, b, c, d) for the both stationary phases and the two groups of topological descriptors, as well. Lower correlations were obtained for R<sub>M0</sub> and *b*, and much higher values for the PC1 scores (Table 3a). The results show that the 2- and 3-path Kier alpha-modified shape index (S2K and S3K) seem to

be dominant in the retention model, best describing the lipophilicity in the case of RP-C<sub>18</sub> stationary phase.

Lower correlation coefficients were obtained for RP-C<sub>18</sub>W phase and the regression equations are given in Table 3b.

**Table 3**

**b) Regression equations using Dragon topological descriptors on RP-C<sub>18</sub>W stationary phase data**

Multivariate regression	$R_{M0} = -5.435 - 0.136S2K + 0.631PHI + 10.000PW2$	R = 0.8909 F = 10 p < 0.0041 s = 0.337
	$b = 0.121 + 0.194Xt - 0.115BLI - 0.139PJI2$	R = 0.7486 F = 3.4 p < 0.0739 s = 0.10
	$PC1 = 0.409 + 0.037S2K - 0.001VAR - 0.013Lop$	R = 0.9848 F = 86 p < 0.0000 s = 0.10
Bivariate regression	$R_{M0} = -0.382 - 0.089S2K + 0.661PHI$	R = 0.8800 F = 15 p < 0.0012 s = 0.332
	$b = 0.101 - 0.118BLI - 0.052PJI2$	R = 0.5899 F = 2.4 p < 0.1459 s = 0.11
	$PC1 = 0.434 + 0.029S2K - 0.012Lop$	R = 0.9786 F = 102 p < 0.0000 s = 0.11
Monovariate regression	$R_{M0} = -0.801 + 0.623PHI$	R = 0.8661 F = 30 p < 0.0003 s = 0.331
	$b = 0.029 - 0.095BLI$	R = 0.5068 F = 3.5 p < 0.0927 s = 0.11
	$PC1 = 0.378 + 0.036S2K$	R = 0.9721 F = 172 p < 0.0000 s = 0.12

As for RP-C<sub>18</sub>W stationary phase, the descriptor that brings a slightly higher contribution to the retention model is PW2-path/walk 2-Randic shape index.

All regression equations show high R values (except for *b*), which indicate satisfactory models provided by these topological descriptors and a definite physical meaning of them. The highest correlation coefficients shown by the scores of the first principal component, PC1, demonstrate this parameter as the best lipophilicity index derived from the retention data.

The contribution to the retention model, on both stationary phases, was higher in case of S2K, BLI, PJI2, PW2 and Lop. The Kier benzene-likeness index (BLI) which is a measure of molecular aromaticity and 2D Petitjean shape index (PJI2) have a positive contribution on the RP-C<sub>18</sub> plate and a negative one upon RP-C<sub>18</sub>W. The 2-path Kier alpha-



modified shape index (S2K) which measures the disorder in the system and the path/walk 2-Randić<sup>123456789</sup> shape index (PW2) have a positive contribution in case of the both stationary phases.

The lopping centric index (Lop) is defined as the mean information content derived from the partition of acyclic graphs and it brings a negative contribution to the retention model, on both stationary phases.

The regression equations for the correlation of lipophilicity indices with the topological descriptors computed by TOPOCLUJ 3.0 software program, are presented in Table 3 (c).

**Table 3**

**c) Regression equations using TOPOCLUJ 3.0 topological indices on RP-C<sub>18</sub> stationary phase data**

Multivariate regression	$R_{M0} = 10.454 - 3.622C[LM[Density]] + 0.005VEA3 - 18.171X[LM[Density]]$	R = 0.9836 F = 79 p < 0.0000 s = 0.196
	$b = -0.091 + 0.00005PDS7[LM[Density]]$ $0.0002VEA3 + 0.337X[LM[Density]]$	R = 0.8988 F = 11 p < 0.0031 s = 0.008
	$PC1 = 0.428 + 0.0004PDS8[LM[Density]] - 0.0001PDS8[LM[Mass]] + 0.043VAD2$	R = 0.9926 F = 178 p < 0.0000 s = 0.006
Bivariate regression	$R_{M0} = 11.353 - 3.918C[LM[Density]] - 18.405 X[LM[Density]]$	R = 0.9427 F = 36 p < 0.0001 s = 0.342
	$b = -0.067 - 0.0001VEA3 + 0.209X[LM[Density]]$	R = 0.8815 F = 16 p < 0.0012 s = 0.008
	$PC1 = 0.560 + 0.0003PDS8[LM[Density]] - 0.00003PDS8[LM[Mass]]$	R = 0.9871 F = 172 p < 0.0000 s = 0.007
Monovariate regression	$R_{M0} = 3.405 - 14.074X[LM[Density]]$	R = 0.8893 F = 38 p < 0.0001 s = 0.445
	$b = -0.075 + 0.208X[LM[Density]]$	R = 0.7709 F = 15 p < 0.0033 s = 0.011
	$PC1 = 0.559 + 0.0002PDS8[LM[Density]]$	R = 0.9619 F = 124 p < 0.0000 s = 0.011

**Table 3**

**d) Regression equations using TOPOCLUJ 3.0 topological indices on RP-C<sub>18</sub>W stationary phase data**

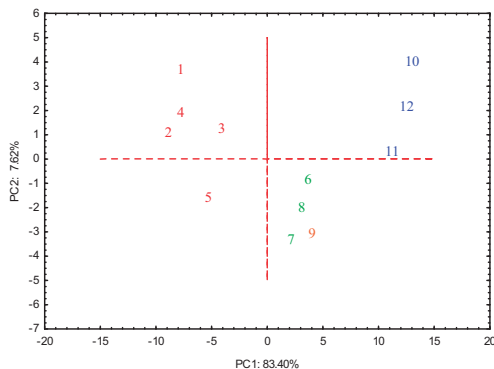
Multivariate regression	$R_{Mo} = -110.456 + 0.006PDS8[LM[Density]] - 0.016PRD^2S[Sh[Detour]] + 926.853X[LM[Atomic radius]]$	R = 0.9017 F = 12 p < 0.0028 s = 0.321
	$b = -0.997 - 0.0002VRA1 + 0.000W4[Atomic radius Detour] + 7.483X[Sh[Connectivity]]$	R = 0.7960 F = 4.6 p < 0.0372 s = 0.009
	$PC1 = 0.395 - 0.0001PDS6[Sh[Detour]] + 0.0002PDS8[LM[Density]] - 0.001VEA1 - 0.154VED3$	R = 0.9822 F = 48 p < 0.00004 s = 0.012
Bivariate regression	$R_{Mo} = 2.073 + 0.006PDS8[LM[Density]] - 0.007PRD^2S[Sh[Detour]]$	R = 0.8752 F = 15 p < 0.0015 s = 0.338
	$b = -1.268 - 0.0001VRA1 + 9.538X[Sh[Connectivity]]$	R = 0.6053 F = 2.6 p < 0.1283 s = 0.011
	$PC1 = 0.544 + 0.0002PDS8[LM[Density]] - 0.001VEA1$	R = 0.9602 F = 53 p < 0.2069 s = 0.012
Monovariate regression	$R_{Mo} = 1.476 + 0.002PDS8[LM[Density]]$	R = 0.8134 F = 20 p < 0.0013 s = 0.386
	$b = -0.747 + 5.357X[Sh[Connectivity]]$	R = 0.3925 F = 1.8 p < 0.0237 s = 0.461
	$PC1 = 0.544 + 0.0002PDS8[LM[Density]]$	R = 0.9541 F = 102 p < 0.0000 s = 0.016

Slight differences were observed comparing the correlation coefficients of the regression equations obtained using the two classes of software programs, but higher correlation coefficients were obtained for lipophilicity indices on RP-C<sub>18</sub> stationary phase, compared to the results obtained previously, so it seems that the topological descriptors (weighted by atomic properties) provided by TOPOCLUJ 3.0 program are more confident in describing the retention model.

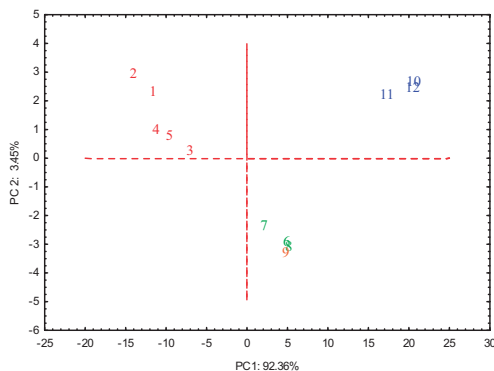
The retention model on RP-C<sub>18</sub> stationary phase is well described by the density and mass for all estimated lipophilicity indices, while on the RP-C<sub>18</sub>W, beside the density, other descriptors bring their contribution to the model, which means that the interactions between elutes and stationary phases differ in both cases and the compounds stronger interact with the more nonpolar RP-C<sub>18</sub> stationary phase. A high positive coefficient of X[LM[Atomic radius]] index shows that the molecular lipophilicity increases along with the atomic radii of the molecule components.

It was also shown that PC1 score plots can be used to search for structural similarity within groups of compounds, since similar structures are grouped. The scatterplot of scores shows interesting results (Figure 1 and 2). Three clusters appear to be well defined and in a good agreement to the structure of compounds for both classes of descriptors computed: one of them corresponds to the compounds 1, 2, 3, 4, and 5 (formyl- and acetyl- derivatives), the second includes the group of piperaziny- derivatives (10, 11 and 12), and the third group, the

hexamethylenimine- derivatives, (6, 7 and 8) with the exception of compound 9 (cyclohexyl-derivative).



**Figure 1**  
Scatterplot of scores given by Dragon descriptors



**Figure 2**  
Scatterplot of scores given by TOPOCLUJ indices

Much more, the scatterplot given by TOPOCLUJ descriptors shows a more compact classification of the compounds, compared to that given by Dragon descriptors.

## 5 Conclusions

In the present study, the relationship between chromatographic retention indices ( $R_{M0}$ ,  $b$ , and PC1 scores) studied experimentally by RP-HPTLC, and the calculated descriptors for the formyl- and acetylpyridine-3-thiosemicarbazone derivatives computed with Dragon and TOPOCLUJ software, has been investigated.

Good structure–retention index models show the efficiency of these indices in QSPR studies. Much higher correlation coefficients were obtained when the lipophilicity indices were estimated by the topological indices computed with TOPOCLUJ software than with Dragon software and higher correlation coefficients were obtained for molecular lipophilicity on RP-C<sub>18</sub> stationary phase compared to RP-C<sub>18</sub>W. The scores corresponding to the first principal component (PC1) appeared to be the best solution for the lipophilicity scale resulted from the retention data.

The shape of the molecules is an important index which should be taken into consideration because it plays a dominant role in the chromatographic behavior on both stationary phases with different polarities.

Much more, the scatterplot given by TOPOCLUJ descriptors shows a more compact classification of the compounds, compared to classification given by Dragon descriptors.

Also, the topological descriptors computed by TOPOCLUJ 3.0 program are the most important in QSAR/ QSPR on formyl- and acetylpyridine-3-thiosemicarbazone derivatives.

## References

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