A COMPARATIVE STUDY OF MOLECULAR LIPOPHILICITY INDICES OF SOME FORMYL- AND ACETYLPYRIDINE-3-THIOSEMICARBAZONE DERIVATIVES ESTIMATED BY RP- HPTLC AND CALCULATED *LOG P* VALUES

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QSAR/QSPR/QSRR

- **QSAR** - Quantitative Structure-Activity Relations

- relates molecular structure to biological activity

- **QSPR** - Quantitative Structure-Property Relations

- correlates molecular information with different properties

- **QSRR** - Quantitative Structure-Retention Relations

- explains chromatographic retention by molecular information

Lipophilicity

- **Log P** estimated by direct equilibration method or by calculation according to different mathematical models
- Octanol - water partition coefficient (Log P)

$$P = C_o / C_w$$

- The "**flask shaking**" method has some disadvantages:
- it is tedious
- time consuming
- may be applied in a limited range on the lipophilicity scale

Estimation of Lipophilicity by RPTLC

- RPTLC method based on the assumed linear relationship between the molecular parameter R_M and **Log*P***

$$R_M = \log (1/ Rf - 1)$$

- R_M (related to molecular lipophilicity) depends linearly on the concentration of the organic modifier of the mobile phase

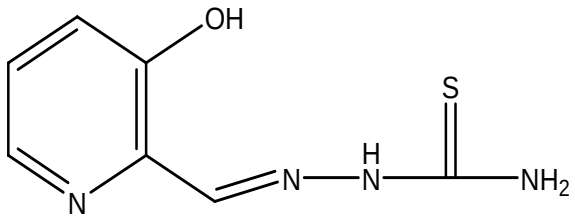
$$R_M = R_{Mo} + bC$$

- $\varphi_0 = R_{Mo}/b$

Principal Component Analysis

- Principal component analysis (**PCA**) is a favorite tool in chemometrics for data compression and information extraction.
- **PCA** finds linear combinations of the original measurement variables that describe the significant variations in the data.
- **PCA** represents in an economic way the location of the compounds in a reduced coordinate system describing the data set with maximum possible information.
- **PCA** gives both coordinates (**scores**) of the studied compounds and the **loadings** of variables on the principal components.

Structure of the studied compounds



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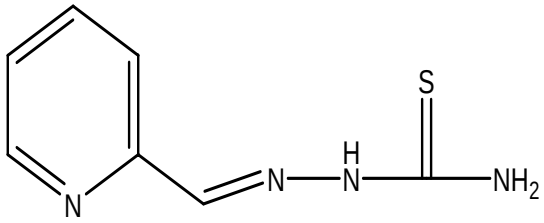

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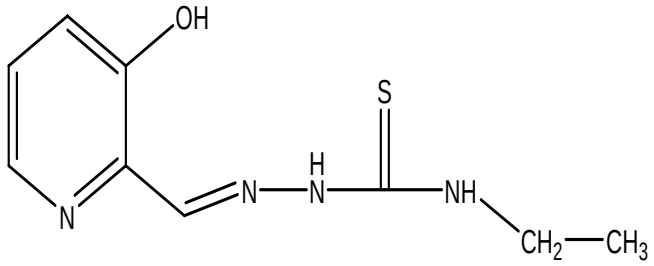

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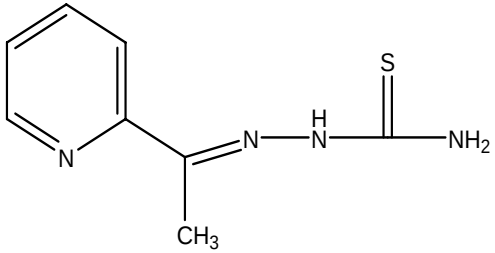

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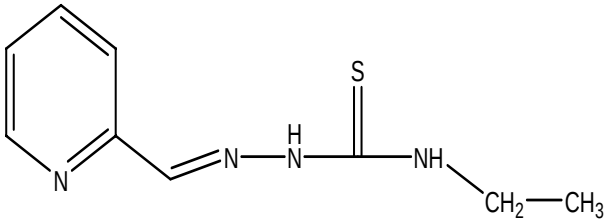

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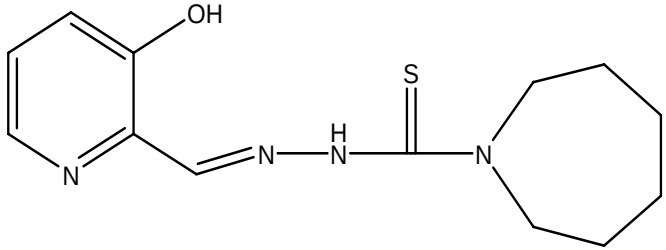

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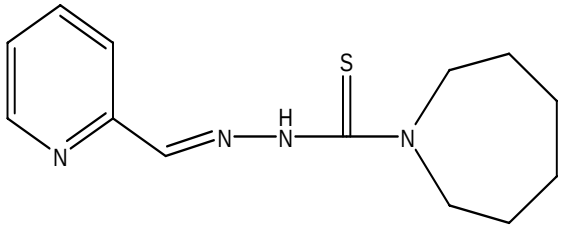
Structure of the studied compounds



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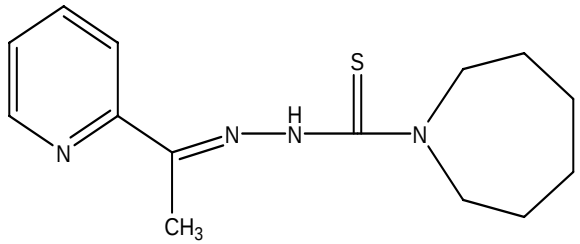

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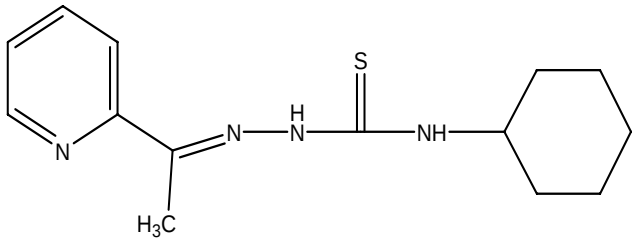

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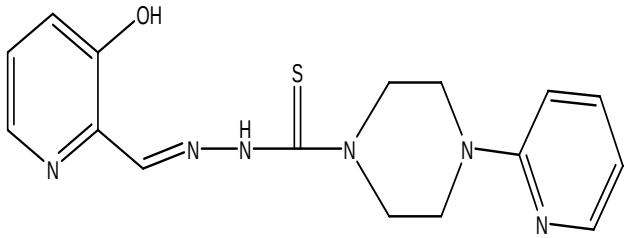

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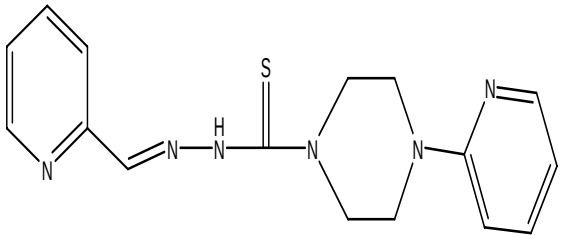

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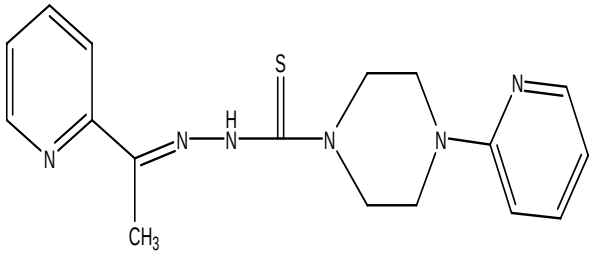

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Experimental

- ***Stationary phase*:** C_{18} silica gel bonded plates
- RP-C_{18}/UV_{254} (20x20 cm)
- RP-C_{18}W/UV_{254} (10x20 cm) Merck (Darmstadt, Germany)
- ***Mobile phase***: methanol-water (25-45 %; 15-35 v/v)
- **Colored zones** appeared on a colorless background
- **fluorescent blue-orange** zones under UV lamp (λ = 365 nm)

Lipophilicity indices based on retention data (RP-C_{18} silica gel)

Cpd	R_{Mo}	*b*	φ_o	$PC1_{RF}$	Mean RF	PC1 RM	Mean RM
1	0.922	-0.029	-31.893	-0.434	0.549	1.153	-0.090
2	1.332	-0.046	-29.275	-0.600	0.621	1.486	-0.262
3	2.160	-0.060	-36.063	-0.277	0.473	0.726	0.061
4	1.611	-0.050	-32.020	-0.495	0.570	1.227	-0.152
5	2.297	-0.062	-37.107	-0.217	0.445	0.568	0.129
6	3.407	-0.080	-42.485	0.180	0.273	-0.518	0.597
7	3.195	-0.071	-44.874	0.295	0.227	-0.715	0.702
8	2.951	-0.065	-45.747	0.276	0.224	-0.662	0.693
9	3.862	-0.086	-44.856	0.355	0.199	-1.083	0.846
10	3.465	-0.076	-45.593	0.352	0.197	-0.949	0.802
11	3.080	-0.068	-45.100	0.288	0.225	-0.671	0.687
12	2.850	-0.063	-45.244	0.278	0.235	-0.562	0.644

Lipophilicity indices based on retention data (RP-C_{18}W silica gel)

Cpd	R_{Mo}	*b*	φ_o	$PC1_{RF}$	Mean RF	PC1 RM	Mean RM
1	1.468	-0.056	-26.254	-0.523	0.469	1.414	0.069
2	1.345	-0.053	-25.615	-0.547	0.488	1.480	0.031
3	2.198	-0.071	-30.777	-0.241	0.334	0.646	1.069
4	1.519	-0.056	-27.269	-0.464	0.446	1.273	0.125
5	2.074	-0.067	-30.994	-0.222	0.333	0.657	0.399
6	2.801	-0.066	-42.313	0.363	0.099	-1.018	1.144
7	2.493	-0.059	-42.534	0.317	0.120	-0.767	1.025
8	2.371	-0.066	-35.703	0.084	0.214	-0.054	0.708
9	3.300	-0.090	-36.872	0.234	0.143	-0.820	1.062
10	2.169	-0.045	-48.296	0.372	0.100	-0.777	1.044
11	3.075	-0.081	-37.781	0.255	0.137	-0.779	1.039
12	2.755	-0.061	-45.544	0.372	0.095	-1.255	1.243

Computed different *Log P*

- **Computer programs based on atom contributions:**
  - SciQSAR: *LogP*[1]
  - SciLogP: *LogPc*
  - Chem3D Ultra 8.0: *LogP*[2], *PartCoeff*
  - XLOGP: *XLOGP*
- **Computer programs based on atom/fragment contributions:**
  - KOWWIN: *KOWWIN*
- **Computer programs based on fragmental contributions:**
  - cLogP: *cLogP*
- **Computer programs based on atom-type electrotopological--state indices and neural network modeling:**
  - ALOGPS: *ALOGPs*, *AB/LogP*, *miLogP*, *AvLogP*, *COSMOFrag*
  - IAlogP: *IAlogP*

Values of the computed *Log P*

Cpd	LogP[1]	LogPc	LogP[2]	Part Coeff	ALOGPs	AB/LogP	COSMO Frag	miLogP	KOWWIN	XLOGP	AvLogP
1	0.953	0.253	0.395	1.375	1.010	1.690	-0.130	0.830	1.310	0.080	0.800
2	1.279	2.382	0.785	1.088	1.090	1.090	0.130	0.710	0.790	0.490	0.720
3	1.273	2.765	1.254	1.513	1.690	3.050	1.340	1.580	2.270	1.020	1.820
4	1.468	2.345	0.350	1.324	1.320	0.790	0.790	0.630	1.950	0.630	1.020
5	1.530	1.755	1.643	1.113	1.720	2.450	1.690	1.460	1.750	1.430	1.750
6	2.624	2.804	2.443	2.769	2.780	3.110	1.920	2.860	3.840	1.960	2.750
7	2.459	3.694	2.832	2.482	2.830	2.510	2.220	2.740	3.320	2.370	2.670
8	2.948	2.388	2.397	2.278	2.940	2.600	2.880	2.660	4.480	2.510	3.010
9	2.967	3.037	2.418	3.241	3.120	3.150	3.980	2.900	4.690	2.980	3.470
10	1.361	2.669	2.502	1.408	2.370	3.210	2.550	2.140	3.160	2.030	2.580
11	2.929	2.545	2.892	1.121	2.430	2.610	2.800	2.020	2.640	2.430	2.490
12	2.825	2.262	2.457	0.917	2.540	2.700	3.450	1.930	3.800	2.580	2.830

Variable	R_{Mo}^{18}	b^{18}	φo^{18}	$PC1_{RF}^{18}$	$Mean_{RF}^{18}$	$PC1_{RM}^{18}$	$Mean_{RM}^{18}$	R_{Mo}^{18W}	b^{18W}	φo^{18W}	$PC1_{RF}^{18W}$	$Mean_{RF}^{18W}$	$PC1_{RM}^{18W}$	$Mean_{RM}^{18W}$
LogP[1]	0.75	-0.67	-0.79	0.79	-0.79	-0.78	0.78	0.86	-0.60	-0.56	0.75	-0.75	-0.78	0.65
LogPc	0.70	-0.77	-0.53	0.53	-0.53	-0.55	0.53	0.53	-0.24	-0.52	0.59	-0.59	-0.57	0.62
LogP[2]	0.92	-0.83	-0.96	0.95	-0.95	-0.95	0.94	0.86	-0.36	-0.86	0.95	-0.95	-0.94	0.84
PartCoeff	0.60	-0.62	-0.43	0.48	-0.48	-0.53	0.52	0.52	-0.44	-0.27	0.43	-0.43	-0.42	0.38
ALOGPs	0.95	-0.88	-0.94	0.94	-0.95	-0.95	0.95	0.88	-0.46	-0.78	0.91	-0.91	-0.90	0.81
AB/LogP	0.81	-0.77	-0.79	0.79	-0.79	-0.80	0.79	0.78	-0.42	-0.73	0.79	-0.81	-0.78	0.88
COSMOFrag	0.90	-0.82	-0.91	0.91	-0.91	-0.91	0.91	0.89	-0.53	-0.74	0.85	-0.86	-0.87	0.80
miLogP	0.92	-0.87	-0.89	0.90	-0.91	-0.92	0.91	0.84	-0.45	-0.75	0.88	-0.88	-0.86	0.81
KOWWIN	0.87	-0.79	-0.87	0.87	-0.88	-0.88	0.88	0.81	-0.43	-0.71	0.82	-0.83	-0.82	0.76
XLOGP	0.93	-0.85	-0.95	0.95	-0.95	-0.95	0.95	0.90	-0.50	-0.78	0.90	-0.91	-0.91	0.81
AvLogP	0.95	-0.88	-0.95	0.95	-0.96	-0.96	0.96	0.91	-0.50	-0.79	0.91	-0.92	-0.91	0.86
R_{Mo}^{18}	1.00	-0.97	-0.92	0.93	-0.94	-0.95	0.94	0.88	-0.43	-0.83	0.93	-0.94	-0.92	0.85
b^{18}		1.00	0.81	-0.82	0.82	0.85	-0.83	-0.83	0.46	0.74	-0.85	0.86	0.84	-0.81
φo^{18}			1.00	-0.99	1.00	0.98	-0.99	-0.85	0.34	0.88	-0.96	0.96	0.94	-0.85
$PC1_{RF}^{18}$				1.00	-1.00	-1.00	1.00	0.86	-0.35	-0.89	0.96	-0.97	-0.95	0.85
$Mean_{RF}^{18}$					1.00	1.00	-1.00	-0.86	0.35	0.88	-0.96	0.96	0.95	-0.85
$PC1_{RM}^{18}$						1.00	-1.00	-0.86	0.37	0.88	-0.96	0.96	0.94	-0.84
$Mean_{RM}^{1}$							1.00	0.86	-0.36	-0.87	0.96	-0.96	-0.94	0.83
R_{Mo}^{18W}								1.00	-0.73	-0.67	0.85	-0.86	-0.88	0.86
b^{18W}									1.00	-0.02	-0.26	0.29	0.32	-0.40
φo^{18W}										1.00	-0.95	0.95	0.93	-0.84
$PC1_{RF}^{18W}$											1.00	-1.00	-0.99	0.90
$Mean_{RF}^{18W}$												1.00	0.99	-0.92
$PC1_{RM}^{18W}$													1.00	-0.91
$Mean_{RM}^{18W}$														1.00

Conclusions

- The lipophilic character of of formyl- and acetylpyridine-3-thiosemicarbazone derivatives has been investigated using TLC retention data and and various calculated *log P*
- Statistically significant correlations were found between lipophilicity indices, R_{Mo}, φo, scores corresponding to PC1 and a new scale based on the mean of retention indices
- The scores corresponding to PC1 and the mean of retention indices appeared to be the best solution for the lipophilicity scale resulted from the retention data
- $LogP^2$, AvLogP and XLOGP have been appearing to be the most appropriate for chromatography

QSAR/QSPR/QSRR and the Bright Future of TLC

The responsibility for change ...
lies within us. We must begin with ourselves, teaching ourselves not to close our minds prematurely to the novel, the surprising, the seemingly radical.

Alvin Toeffler

Thank you for your attention!