Corelatii structura – retentie in cromatografia de lichide de inalta performanta si aplicatii pentru compusi de importanta farmaceutica

Contractul PN2_Idei 55/28.09.2007 (Cod ID_957/2007)

Director Proiect: **Profesor Dr. Victor David**

Institutia: **Universitatea din Bucuresti, Facultatea de Chimie**.

- **Proiect interdisciplinar (analitica, organica, chimie-fizica; farmacie);**
- **Directie fundamentala, dar si cu aplicatii concrete;**
- **De mare interes in domeniul separarilor;**
- **Foarte discutat in literatura de specialitate;**
- **Cu mare potential pentru cercetari si publicatii;**
- **Se bazeaza pe instrumentatie moderna;**
- **S-au realizat colaborari, printre care si studenti sau tineri cercetatori.**

Membrii echipei:

Prof. Dr. Victor David
Lect. Dr. Emilia-Elena Iorgulescu
Lect. Dr. Florentin Tache
Drd. Medeea Radulescu
Masterand Alina Cristian

Colaborari:

Prof. Dr. Andrei Medvedovici
Prof. Dr. Mihaela Hillebrand
Conf. Dr. C. Mihailciuc
Lect. Dr. Sorana Ionescu
Dr. Iulia Sora
Drd. Toma Galaon
Drd. Stefan Udrescu
Drd. Jana Petre
Student Edvin Caiali

Rezumatul proiectului:

PROIECTUL PROPUNE O TEMA FUNDAMANTALA DE CERCETARE IN DOMENIUL CROMATOGRAFIEI DE LICHIDE: MODELAREA SI CORELAREA INTRE REZULTATELE EXPERIMENTALE ALE SEPARARILOR HPLC SI STRUCTURA COMPUSILOR INVESTIGATI, CU APLICATII PE COMPUSI DE IMPORTANTA FARMACEUTICA (QSRR). VOR FI STUDIATE CELE MAI IMPORTANTE MECANISME DE SEPARARE HPLC (FAZA INVERSA, FAZA NORMALA SI CHIRALA) SI SE VOR PROPUNE MODELE SI ABORDARI ORIGINALE PENTRU DESCRIEREA INTERACTIEI DINTRE ANALIT SI FAZA STATIONARA. VOR FI CERCETATE EXPERIMENTAL SI CLASE NOI DE COMPUSI FARMACEUTICI DIN PUNCT DE VEDERE AL COMPORTARII CROMATOGRAFICE SI SE VOR CORELA DESCRIPTORI MOLECULARI CU PARAMETRII EXPERIMENTALI. DINTRE DESCRIPTORII MOLECULARI, HIDROFOBICITATEA ANALITILOR STUDIATI VA FI CEA MAI UTILIZATA IN STUDIILE QSRR. SE VA PROPUNE O MODALITATE DE ATRIBUIRE A UNEI MARIMI DE HIDROFOBICITATE SI FAZEI STATIONARE. SE DORESTE CA REZULTATELE OBTINUTE SA FIE VALORIFICATE PRIN PUBLICARE A MINIMUM 6 ARTICOLE IN REVISTE ISI DIN STRAINATATE.

Proiectul nu este unul pur teoretic. Studiile de corelație proprietati-structura se bazează in primul rând pe o cantitate mare de informație experimentala. In cazul de fata, partea experimentala este decisiva; in plus, un sistem cromatografic trebuie calificat, verificat, iar rezultatele obținute de cele mai multe ori sunt prelucrate statistic, pentru care sunt necesare seturi de determinări paralele. Aşadar, proiectul isi propune atât o abordare experimentala pentru obținerea de rezultate experimentale in diverse condiții de separare cromatografica si pentru o gama mare de compuşi organici, cat si una de interpretare, pe baza literaturii si a propriilor realizări, parte din ele recunoscute in literatura de specialitate prin citarea lor.

In principiu, tema aleasă va fi îndreptată pe următoarele direcții:
a) Alegerea claselor de compuşi de importanta farmaceutica vor fi investigate atât in cadrul a doua teme de doctorat, cat si in afara pregătirii doctorale;
b) Dezvoltarea unui cadru teoretic original, bazat pe experiența si realizările anterioare;
c) Studii practice de retenție, în diverse condiții de separare: compoziții de faza mobila (pH-ul fazei mobile, natura modificatorului organic), temperatura din coloană, tipul de fază staționară, parametrii constructivi ai coloanei cromatografice, pe un număr mare de reprezentanți ai claselor de compuşi organici;
d) Studii experimentale privind volumele de injecție si parametrii care influențează aceasta etapa;
e) Studii şi metodologii de corelație între rezultatele obținute si structura compuşilor aleşi.

Rezultate:

Articole publicate in reviste ISI cu F.I., avand *acknowledgements*:

1. A.Medvedovici, D.I.Sora, S.Ionescu, M.Hillebrand, V.David, *Characterization of a new norfloxacin metabolite monitored during a bioequivalence study by means of mass-spectrometry and quantum computation*. **Biomedical Chromatography**, 22 (10), 1100-1107 (2008). **F.I. = 1.505**

2. St.Udrescu, A.Medvedovici, V.David, *Effect of large volume injection of hydrophobic solvents on the retention of less hydrophobic pharmaceutical solutes in RP-LC*. **Journal of Separation Science**, 31 (16-17), 2939-2945 (2008). **F.I. = 2.746**

3. J.Petre, V.Iancu, V.David, *Benzene/water partition constants and thermodynamic parameters estimated from liquid chromatography retention of some herbicides using phenyl-silica stationary phase*. **Revue Roumaine de Chimie**, 54 (4), 261-266 (2009). **F.I. = 0.284**

4. T.Galaon, F.Tache, V.David, *Retention behaviour of two biguanidines in liquid chromatography based on cyano stationary phase*. **Revue Roumaine de Chimie**, 54 (5), 361-364 (2009). **F.I. = 0.284**

5. A.Medvedovici, F.Albu, I.D.Sora, S.Udrescu, T.Galaon, V.David, *Assay of free captopril in human plasma as monobromobimane derivative, using RPLC/(+)ESI/MS/MS: validation aspects and bioequivalence evaluation*. **Biomedical Chromatography**, 23 (10), 1092-1100 (2009). **F.I. = 1.505**

6. M.Albu, V.David, F.Tache, A.Medvedovici, *HPLC/DAD assay of related impurity ethyl-4-oxopiperidine-1-carboxylate in loratadine through derivatization with 2,4-dinitrophenylhydrazine*. **Journal of Liquid Chromatography and Related Technologies**, 32 (17), 2569-2583 (2009). **F.I. = 1.026**

7. V.David, T.Galaon, E.Caiali, A.Medvedovici, *Competitional hydrophobicity driven separations under RP-LC mechanism: application to sulphonylurea congeners*. **Journal of Separation Science**, 32 (18), 3099-3106 (2009). **F.I. = 2.746**

8. V.Voicu, A.Medvedovici, M.Radulescu, E.E.Iorgulescu, V.David, *Unusual retention behavior of some cationic-type aldoximes used as AChE reactivators under ion-pairing liquid chromatographic mechanism*. **Analytical Letters**, 43, in press, (2010). **F.I. = 1.135**

9. A.Cristian, E.E.Iorgulescu, C.Mihailciuc, *Electrochemical study of meloxicam using activated glassy carbon*. **Revue Roumanie de Chimie,** 55, in press (2010). **F.I. = 0.284**

10. A.Cristian, E.E.Iorgulescu, C.Mihailciuc, *Electrochemical study of piroxicam using activated glassy carbon*. **Revue Roumanie de Chimie,** 55, in press (2010). **F.I. = 0.284**

11. J.Petre, S.Ionescu, M.Hillebrand, V.David, *Quantitative correlations between chromatographic data and molecular parameters for some weakly related pesticides*. **Journal of Liquid Chromatography and Related Technologies**, 33, in press (2010). **F.I. = 1.026**

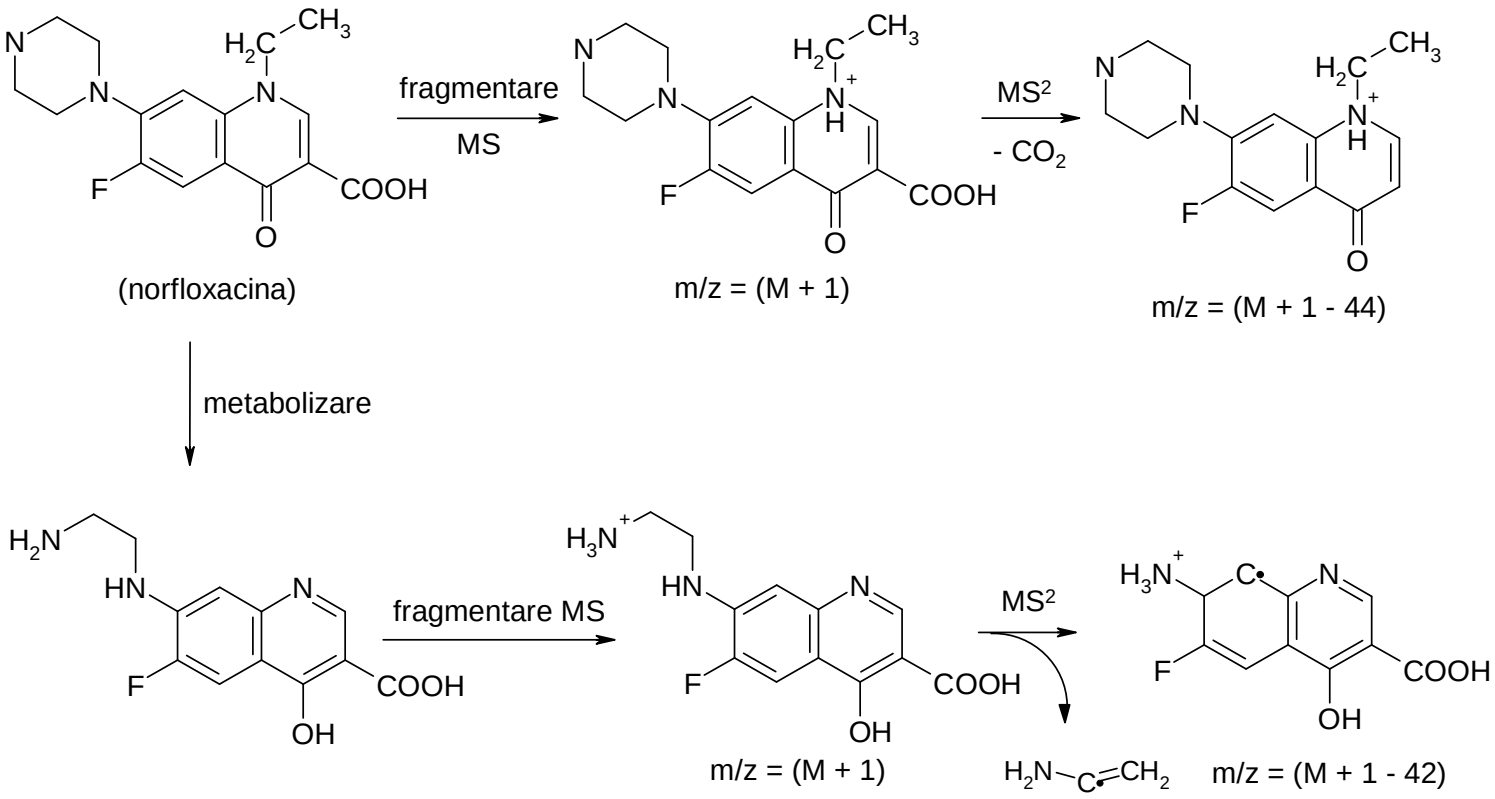
12. V.Voicu, I.Sora, C.Sarbu, V.David, A.Medvedovici, *Hydrophobicity/hydrophilicity descriptors obtained from extrapolated chromatographic retention data as modeling tools for biological distribution: application to some oxime-type acetylcholinesterase reactivators.*
Journal of Pharmaceutical and Biomedical Analysis, 52 (4), 508-516 (2010). **F.I. = 2.629**

13. T.Galaon, C.Mihailciuc, A.Medvedovici, V.David, *Estimation of thermodynamic parameters for some polar compounds using different mobile phase flow-rates in RP-LC*. **F.I. = 1.026**
Journal of Liquid Chromatography & Related Technologies, trimis spre publicare, (2010).

14. A.Medvedovici, V.Voicu, I.D.Sora, M.Radulescu, V.David, *Discontinuous double mechanism for the retention of some cation-type oximes on hydrophilic stationary phases in liquid chromatography*, **Chromatographia**, in curs de redactare. **F.I. = 1.312**

15. T.Galaon, A.Medvedovici, C.Mihailciuc, V.David, Deviation from van't Hoff dependence in RP-LC induced by tautomeric inter-conversion observed for three compounds.
Journal of Separation Science, in curs de redactare. **F.I. = 2.746**

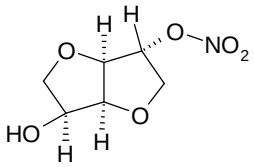
1. A.Medvedovici, D.I.Sora, S.Ionescu, M.Hillebrand, V.David, *Characterization of a new norfloxacin metabolite monitored during a bioequivalence study by means of mass-spectrometry and quantum computation*.
Biomedical Chromatography, 22 (10), 1100-1107 (2008).



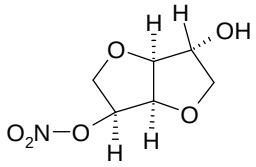
Articol citat în:

1. N.R.Srinivas, **Biomedical Chromatography**, 23 (6), 674-675 (2009).
2. N.R.Srinivas, **Arzneimittel-Forschung/Drug Researsch,** 59 (4) 155-165 (2009).

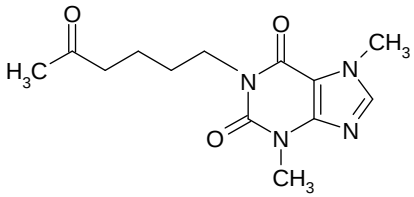
2. St.Udrescu, A.Medvedovici, V.David, *Effect of large volume injection of hydrophobic solvents on the retention of less hydrophobic pharmaceutical solutes in RP-LC*. **Journal of Separation Science**, 31 (16-17), 2939-2945 (2008).



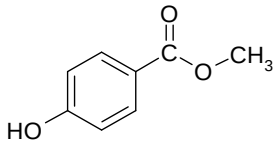
Isosorbide 2-nitrate (log P = -0.40)



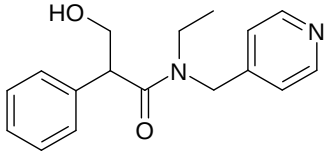
Isosorbide 5-nitrate (log P = -0.15)



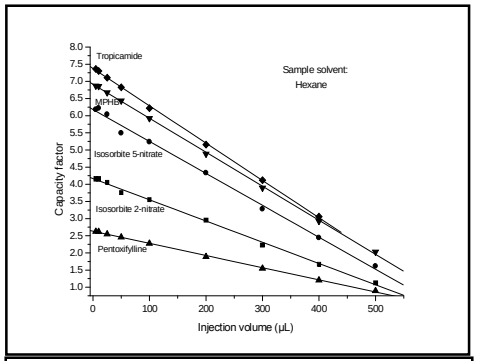
Pentoxifylline (log P = 0.56)

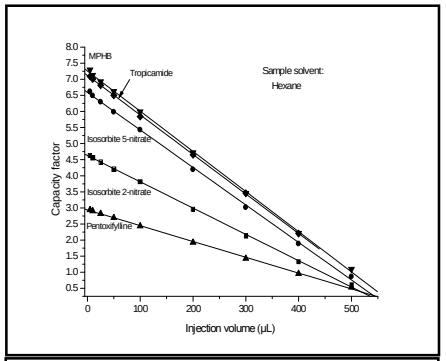


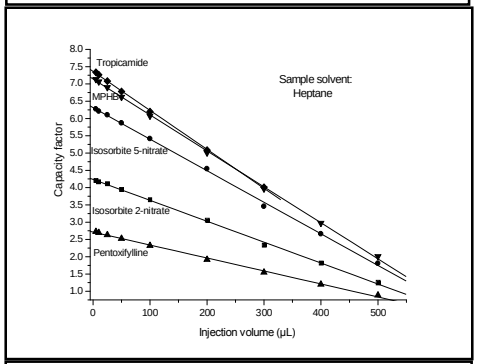
Methyl p-hydroxybenzoate (log P = 1.96)

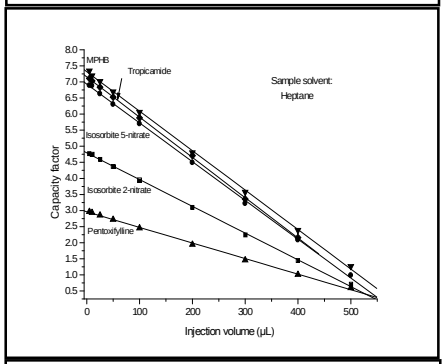


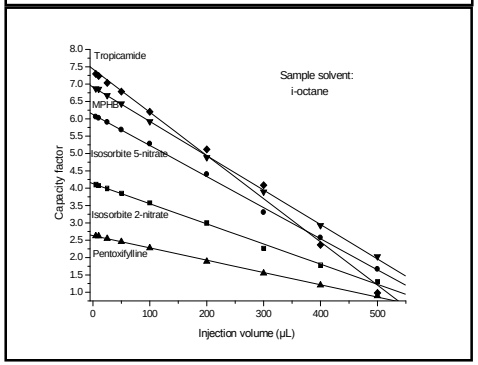
Tropicamide (log p = 1.19)

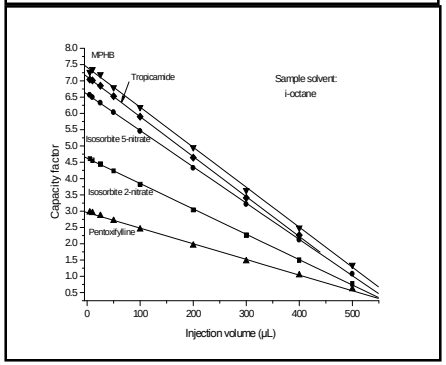








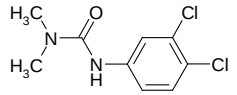
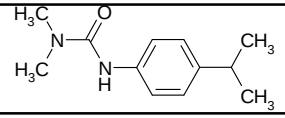
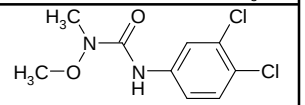
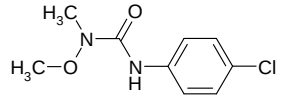
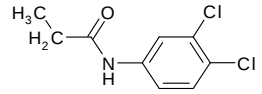




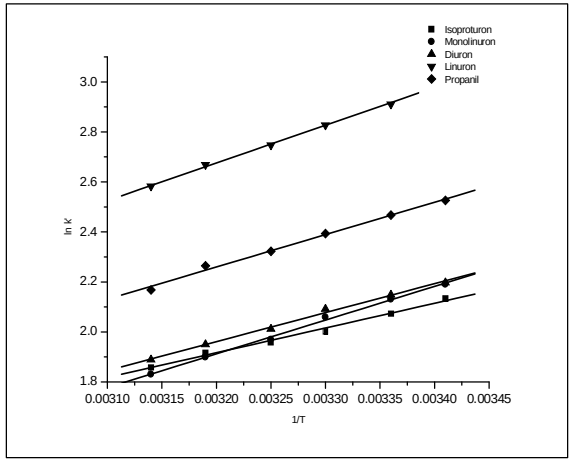
C8 – stationary phase **C18 – stationary phase**

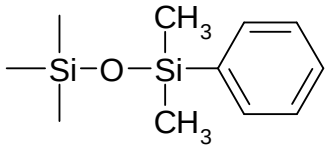
Articol citat si discutat pe larg în:
E.Loeser, S.Babiak, P.Drumm, **J. Chromatogr. A**,
1216 (15), 3409-3412 (2009).

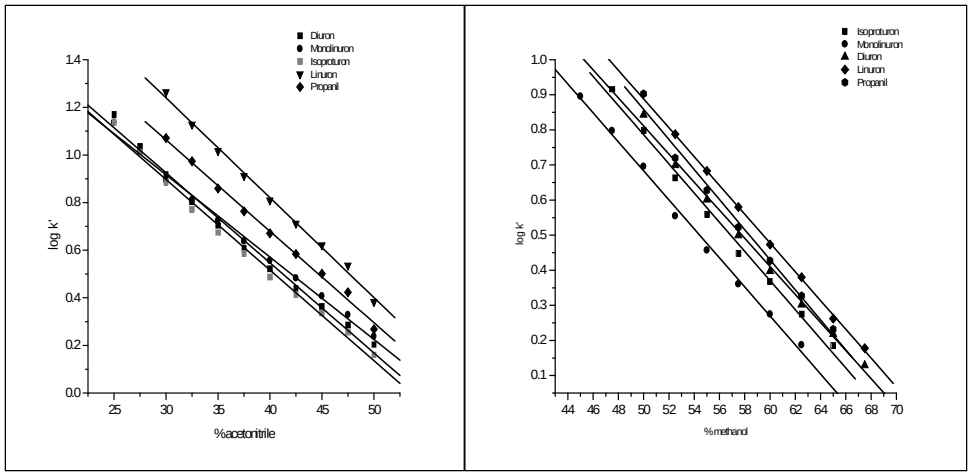
3. J.Petre, V.Iancu, V.David, *Benzene/water partition constants and thermodynamic parameters estimated from liquid chromatography retention of some herbicides using phenyl-silica stationary phase*. **Revue Roumaine de Chimie**, 54 (4), 261-266 (2009).

Compound	IUPAC name (CAS number)	Structure
Diuron	3-(3,4-dichlorophenyl)-1,1-dimethylurea (000330-54-1)	
Isoproturon	3-(4-isoprpylphenyl)-1,1-dimethylurea (034123-59-6)	
Linuron	3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (000330-55-2)	
Monolinuron	3-(4-chlorophenyl)-1-methoxy-1-methylurea (1746-81-2)	
Propanil	3’4’-dichloropropionanilide (000709-98-8)	

$$\ln k' = \ln \frac{V_{sp}}{V_{mp}} + \frac{\Delta S^0}{R} - \frac{\Delta H^0}{R} \cdot \frac{1}{T}$$

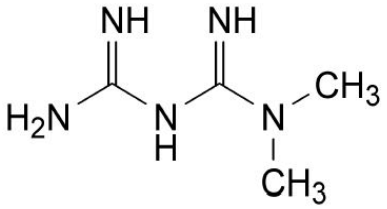




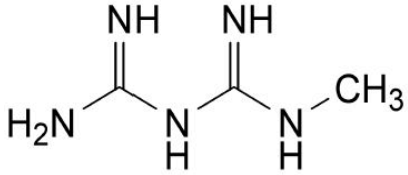


Analyte	log K_{ow}		log K_{bw} from retention data	
	theoretic	shake-flask	ACN	MeOH
Diuron	2.67	2.68	**2.30**	**3.05**
Monolinuron	2.20	2.30	**2.20**	**2.99**
Isoproturon	2.50	2.87	**2.25**	**3.11**
Linuron	2.91	3.20	**2.74**	**3.18**
Propanil	2.88	3.07	**2.46**	**3.25**

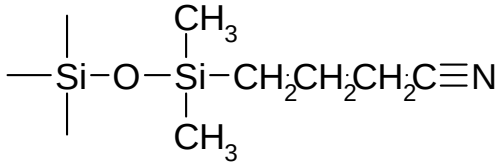
4. T.Galaon, F.Tache, V.David, *Retention behaviour of two biguanidines in liquid chromatography based on cyano stationary phase*. **Revue Roumaine de Chimie**, 54 (5), 361-364 (2009).



Metformin (log Kow = -2,64)



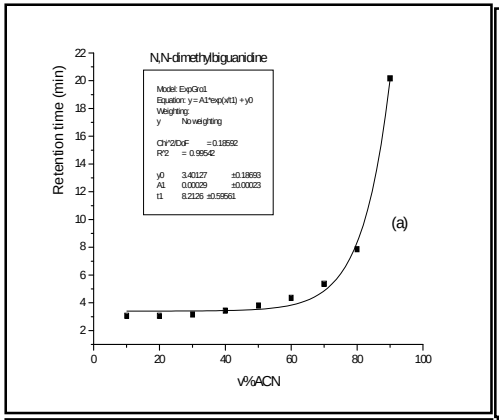
Metilbiguanidina (log Kow = -2,85)

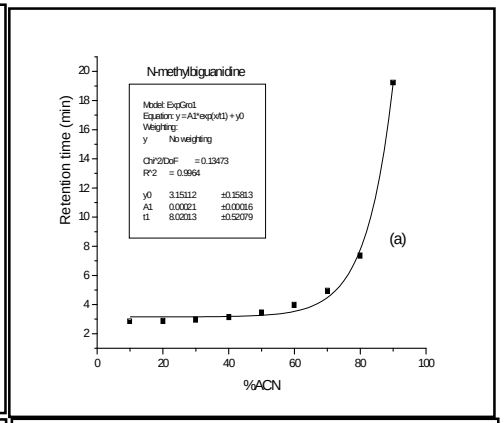


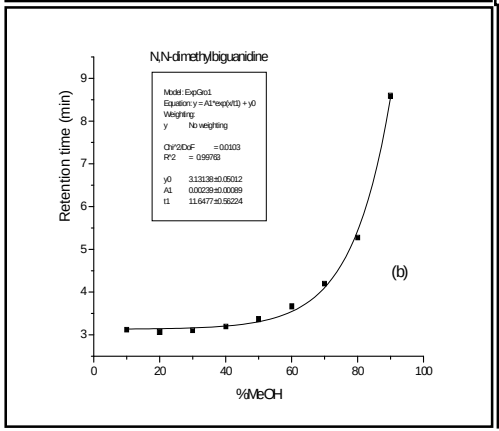
$$-C\equiv N^{\delta-} + H_3O^+ \rightleftarrows -C\equiv N^{\delta-}\cdot H_3O^+$$

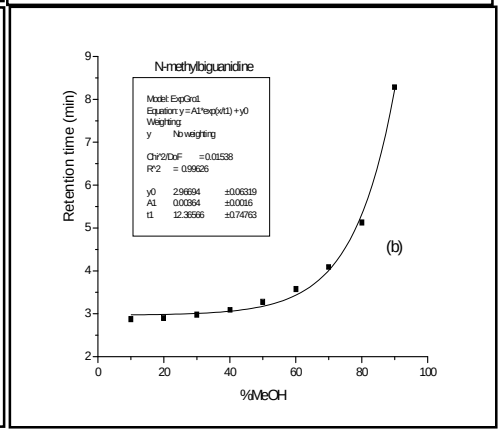
$$-C\equiv N^{\delta-} + Bg^+ \rightleftarrows -C\equiv N^{\delta-}\cdot Bg^+$$

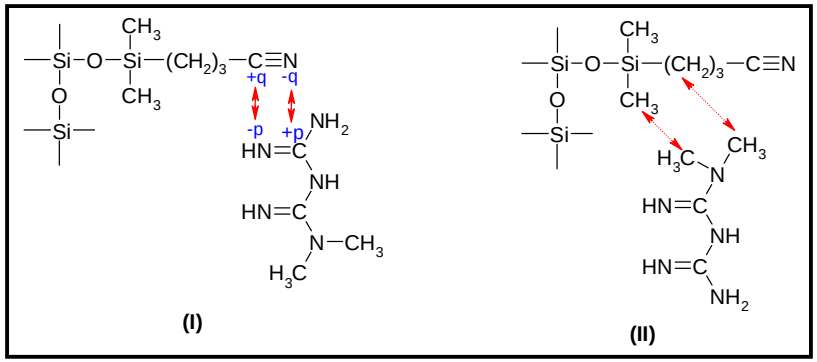
Mecanism mixt de retentie: NP + RP.











5. A.Medvedovici, F.Albu, I.D.Sora, S.Udrescu, T.Galaon, V.David,
Assay of free captopril in human plasma as monobromobimane derivative, using RPLC/(+)ESI/MS/MS: validation aspects and bioequivalence evaluation.
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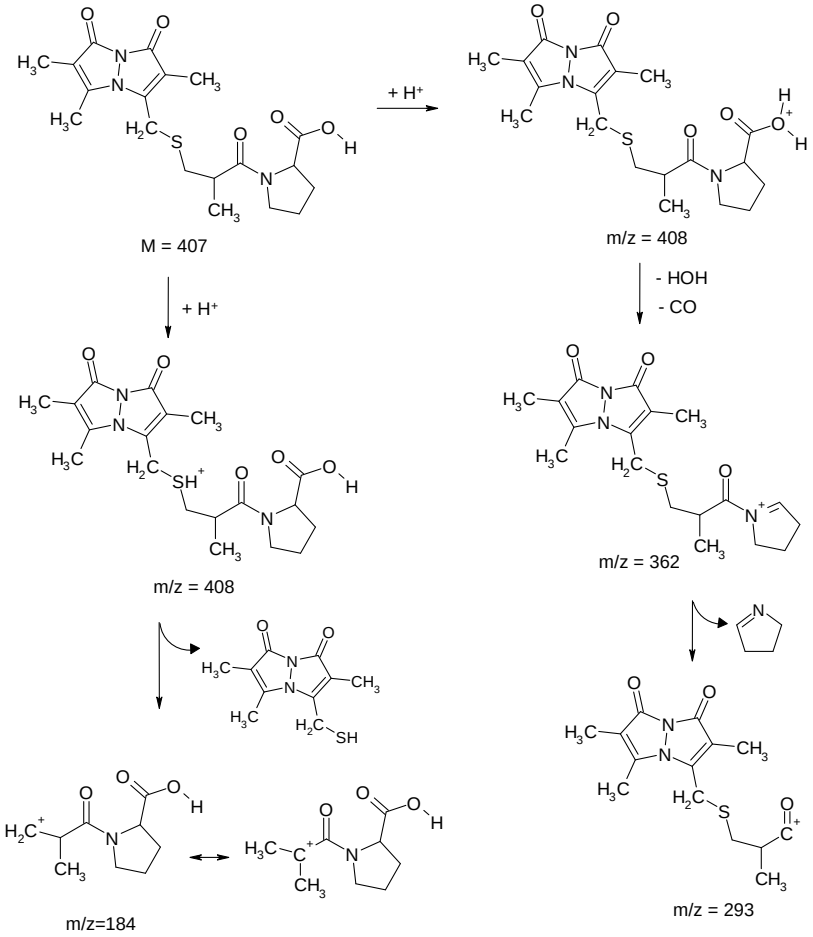
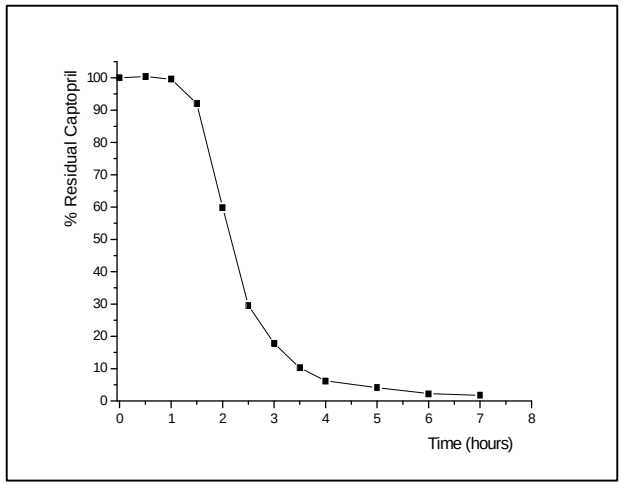
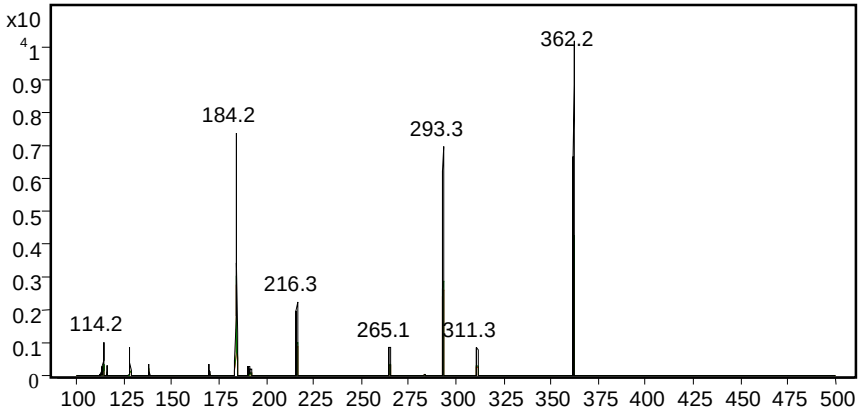
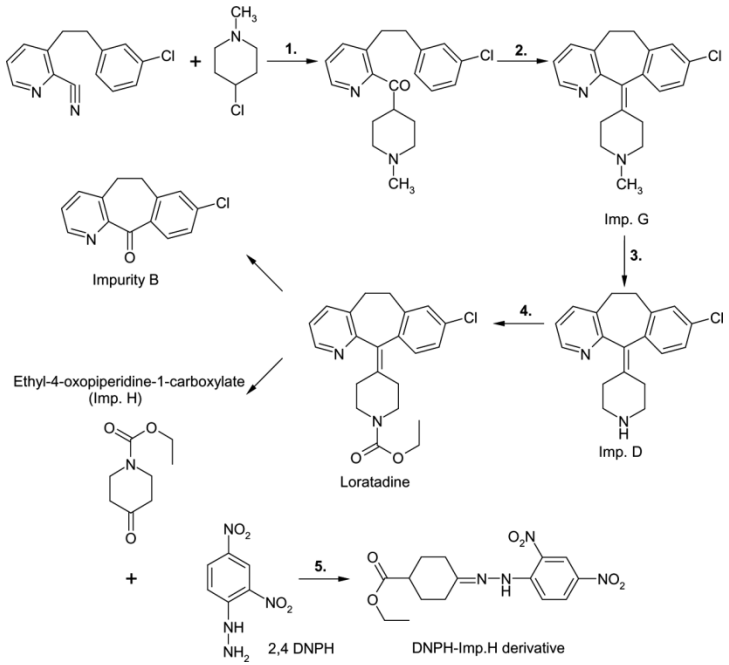


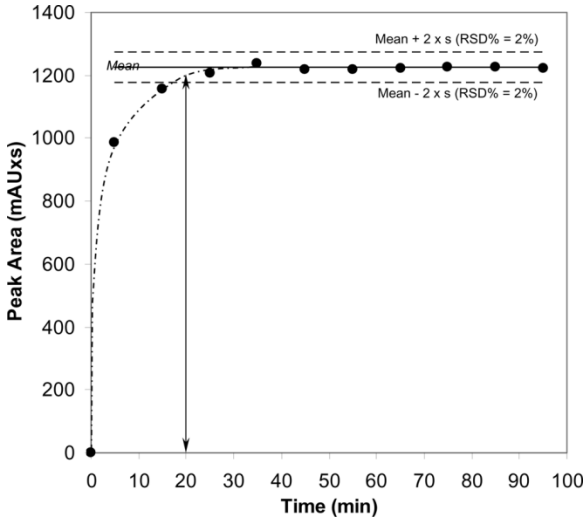


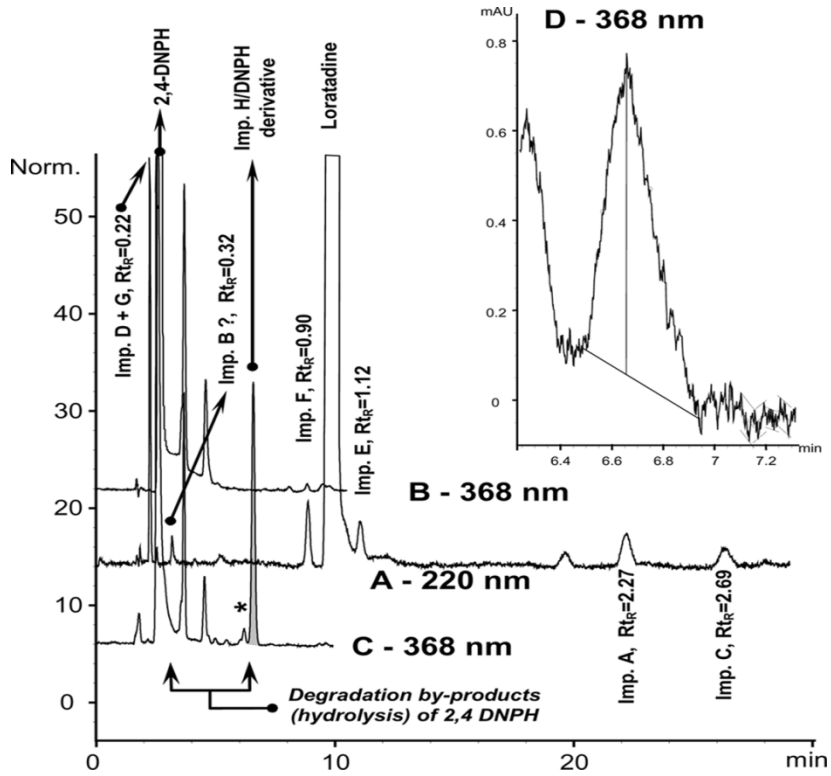
Oxidation kinetics of captopril to disulphide compound, determined by means of derivatization of free sulphide group with monobromobimane and MS detection.



6. M.Albu, V.David, F.Tache, A.Medvedovici, *HPLC/DAD assay of related impurity ethyl-4-oxopiperidine-1-carboxylate in loratadine through derivatization with 2,4-dinitrophenyl hydrazine.* **Journal of Liquid Chromatography and Related Technologies**, 32 (17), 2569-2583 (2009).

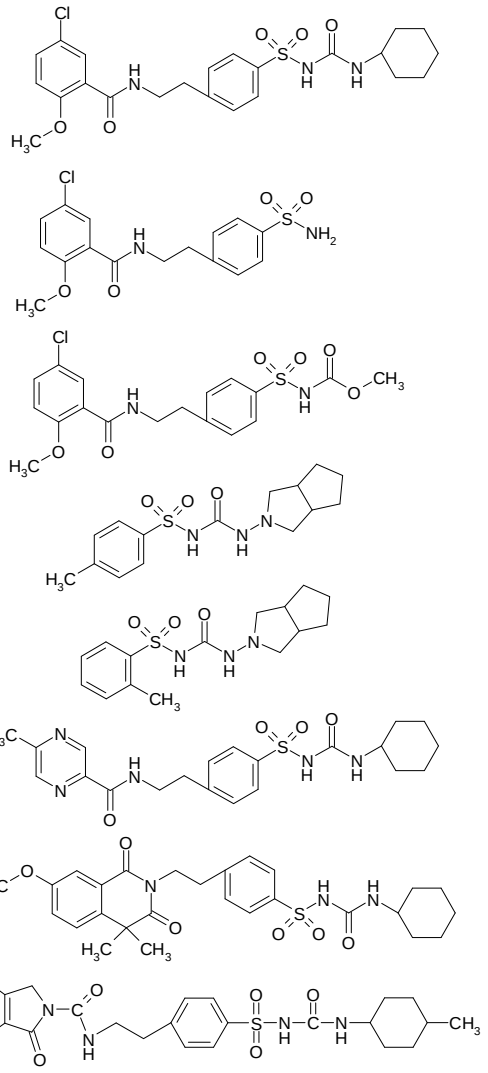


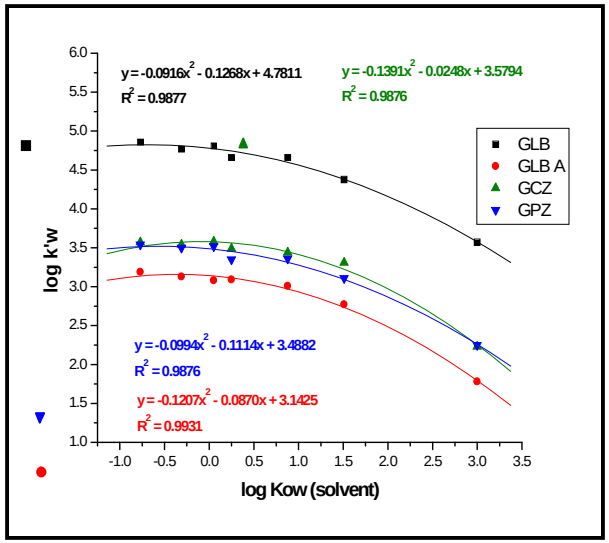


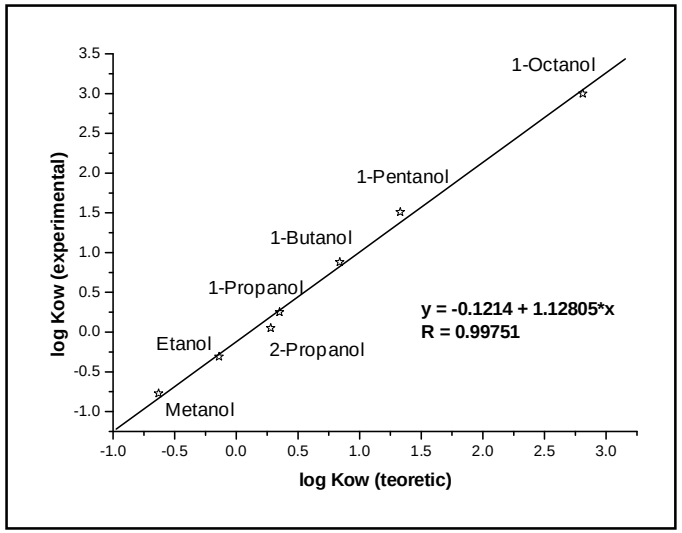


Typical chromatograms obtained on method application: A – loratadine and related compounds monitored at 220 nm, according to EP compendial method; B – derivatization reagent (2,4-DNPH), chromatogram monitored at 368 nm; C – chromatogram of a sample containing the derivatization product of impurity H with 2,4-DNPH, monitored at 368 nm; D – detail from a chromatogram corresponding to a sample having the concentration of impurity H at the LOQ level (0.1 mg=mL), monitored at 368 nm, used to evaluate the signal to noise ratio.

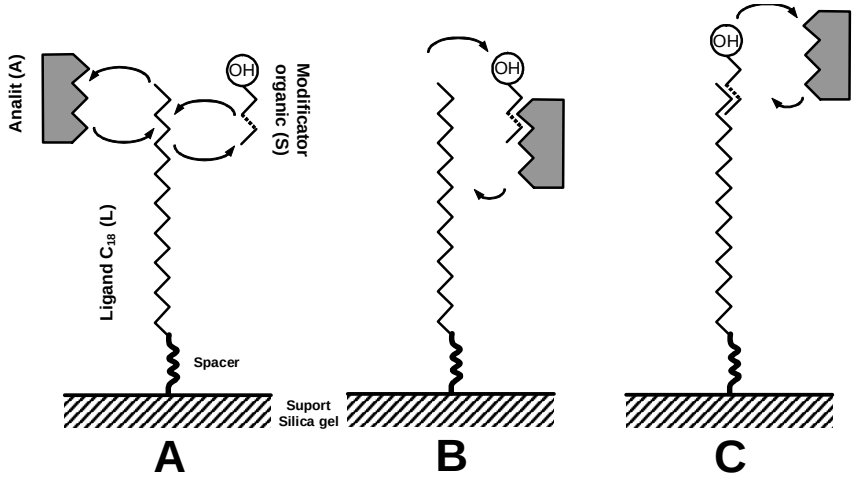
7. V.David, T.Galaon, E.Caiali, A.Medvedovici, *Competitional hydrophobicity driven separations under RP-LC mechanism: application to sulphonylurea congeners*. **Journal of Separation Science**, 32 (18), 3099-3106 (2009).







Metanol
Etanol
1-Propanol
2-Propanol
Butanol
Pentanol
Octanol



Modelul adsorbției (tratare matematică):

Echilibre competiționale de adsorbție-desorbție între analit, solvent şi ligand:

$$L + A \underset{\leftarrow}{\overset{\rightarrow}{}} LA \qquad K_{LA} = \frac{[LA]_s}{[L]_s \cdot [A]_m} = \frac{[A]_s}{[L]_s \cdot [A]_m} = \frac{1}{[L]_s} \cdot \gamma_1 \cdot K_{ow}^{A}$$

$$L + S \underset{\leftarrow}{\overset{\rightarrow}{}} LS \qquad K_{LS} = \frac{[LS]_s}{[L]_s \cdot [S]_m} = \frac{[S]_s}{[L]_s \cdot [S]_m} = \frac{1}{[L]_s} \cdot \gamma_2 \cdot K_{ow}^{S}$$

$$\log k'_A = \psi + \log K_{ow}^{A} - \log K_{ow}^{S}$$

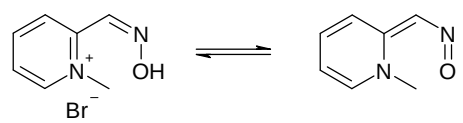
Alte echilibre competiționale:

$$L + nS \underset{\leftarrow}{\overset{\rightarrow}{}} LS_n \qquad K_{LS_n} = \frac{[LS_n]_s}{[L]_s \cdot [S]_m^n} = \frac{[S]^n{}_s}{[L]_s \cdot [S]^n{}_m} = \frac{1}{[L]_s} \cdot \gamma_2 \cdot (K_{ow}^{S})^n$$

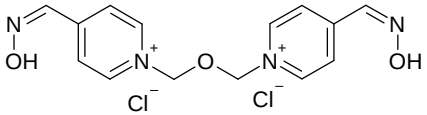
$$LS_n + A \underset{\leftarrow}{\overset{\rightarrow}{}} LS_{n-m}A + mS \qquad K_{LS_{n-m}A} = \frac{[LS_{n-m}A]_s \cdot [S]_m^m}{[LS_n]_s \cdot [A]_m}$$

$$\log k'_A = \psi + \log K_{ow}^{A} - \log K_{ow}^{S} - (\log K_{ow}^{S})^2$$

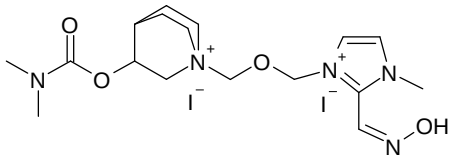
8. V.Voicu, A.Medvedovici, M.Radulescu, E.E.Iorgulescu, V.David, *Unusual retention behavior of some cationic-type aldoximes used as AChE reactivators under ion-pairing liquid chromatographic mechanism*. **Analytical Letters**, acceptat spre publicare, (2010).



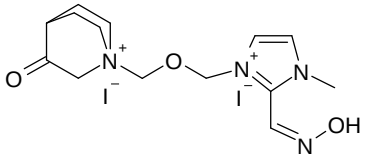
Pralidoxime (**PAM**)
2-[(hydroxyimino)methyl]-1-methylpyridin-1-ium



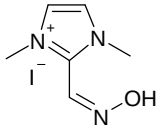
Obidoxime (**LuH-6**)
1,3-bis(4-hydroxyiminomethylpyridinium)
-2-oxapropane



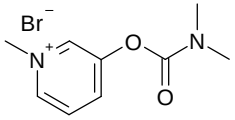
(**C2**)
Dimethyl-carbamic acid 1-[2-(hydroxyimino-methyl)
-3-methyl-3H-imidazol-1-ylmethoxymethyl]-1-aza-
bicyclo[2.2.2]octane-3-yl ester



Quinuclidinium derivative (**C3**)
1-Methyl-3-(3-oxo-1-aza-bicyclo[2.2.2]octane
-1-ylmethoxymethyl)-1H-imidazole-
2-carbaldehyde oxime

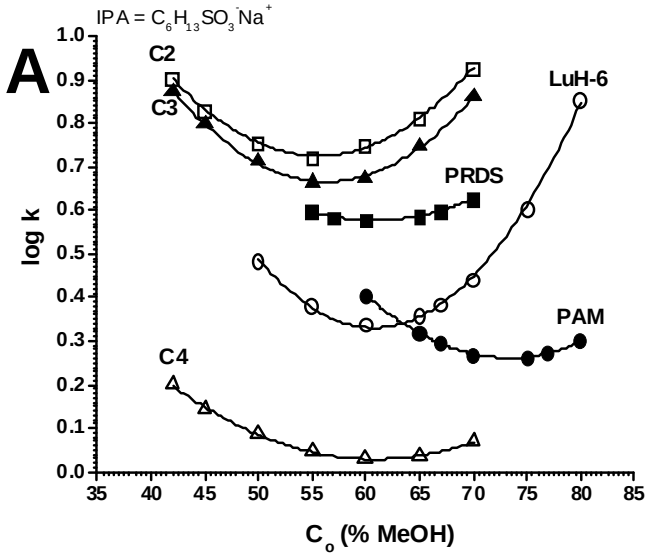


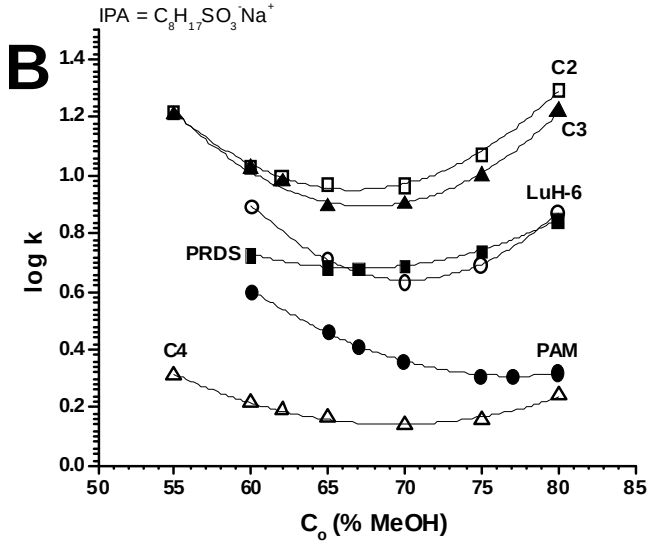
(**C4**)
2-(Hydroxyimino-methyl)-1,3
-dimethyl-3H-imidazol-1-ium



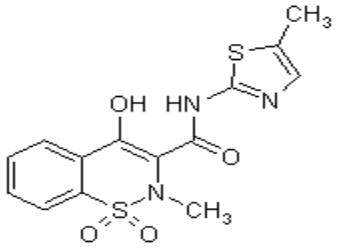
Pyridostigmine (**PRDS**)
Dimethyl-carbamic acid 1-methyl-
pyridin-3-yl ester

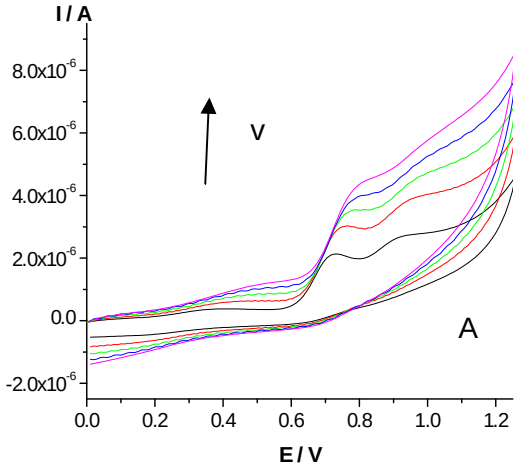
$$\log k = \log k_w + \sum_{i=1}^{2} \alpha_i C_0^i$$

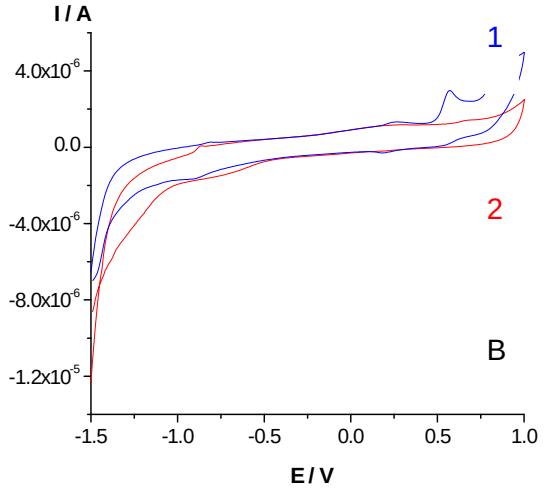




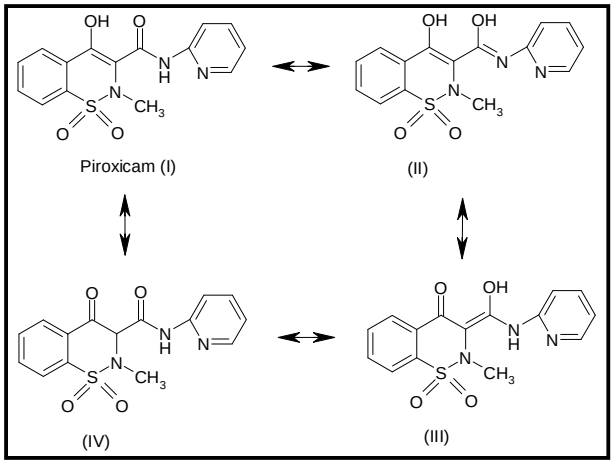
9. A.Cristian, E.E.Iorgulescu, C.Mihailciuc, *Electrochemical studies using activated glassy carbon. I Meloxicam*, **Revue Roumaine de Chimie,** in press (2010).





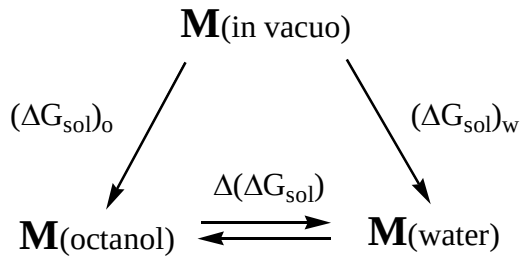


10. A.Cristian, E.E.Iorgulescu, C.Mihailciuc, *Electrochemical studies using activated glassy carbon.* II Piroxicam, **Revue Roumaine de Chimie,** in press (2010).

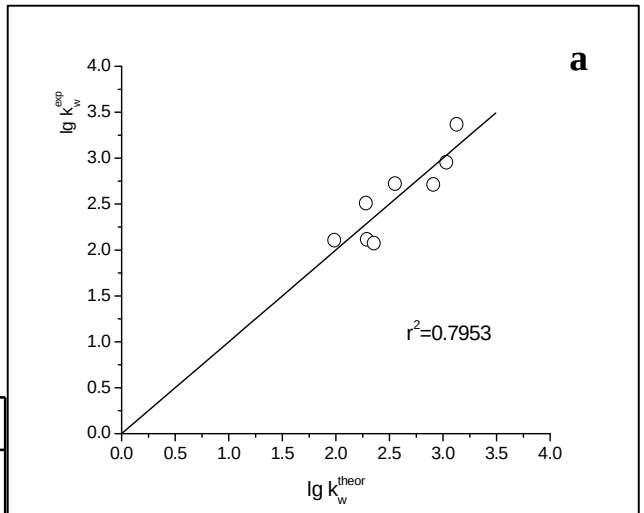


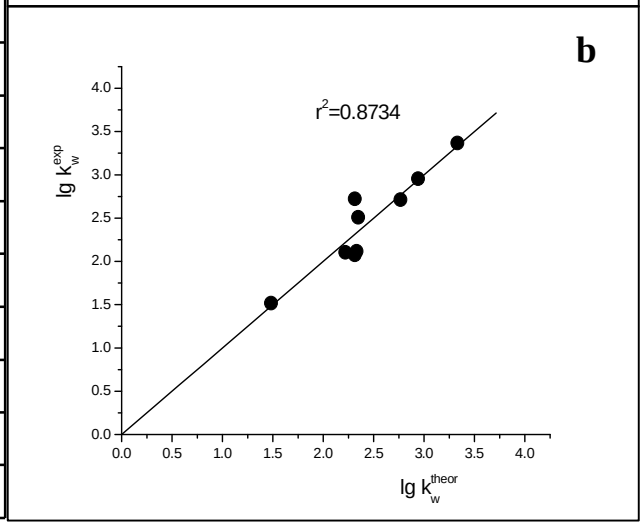
11. J.Petre, S.Ionescu, M.Hillebrand, V.David, *Quantitative correlations between chromatographic data and molecular parameters for some weakly related pesticides*. **Journal of Liquid Chromatography and Related Technologies**, spre publicare (2010).

$$\lg k = \sum_{i=0}^{n} \alpha_i C_m^i$$



Analyte	Shake-flask values	ACN		MeOH	
		lg K_{ow} from C8	lg K_{ow} from C18	lg K_{ow} from C8	lg K_{ow} from C18
Dichlorvos	0.706	1.270	1.370	2.114	2.086
Isoproturon	2.319	1.858	1.893	2.268	2.291
Diuron	2.784	1.869	1.917	2.648	2.666
Monolinuron	2.300	1.828	1.873	2.690	2.718
Propanil	3.179	2.263	2.358	3.057	3.075
Linuron	3.201	2.474	2.553	3.093	3.080
Fenitrothion	3.204	2.466	2.428	3.318	3.404
Coumaphos	3.857	2.707	2.900	4.236	4.291
Phoxim	4.390	3.120	2.962	4.348	4.549

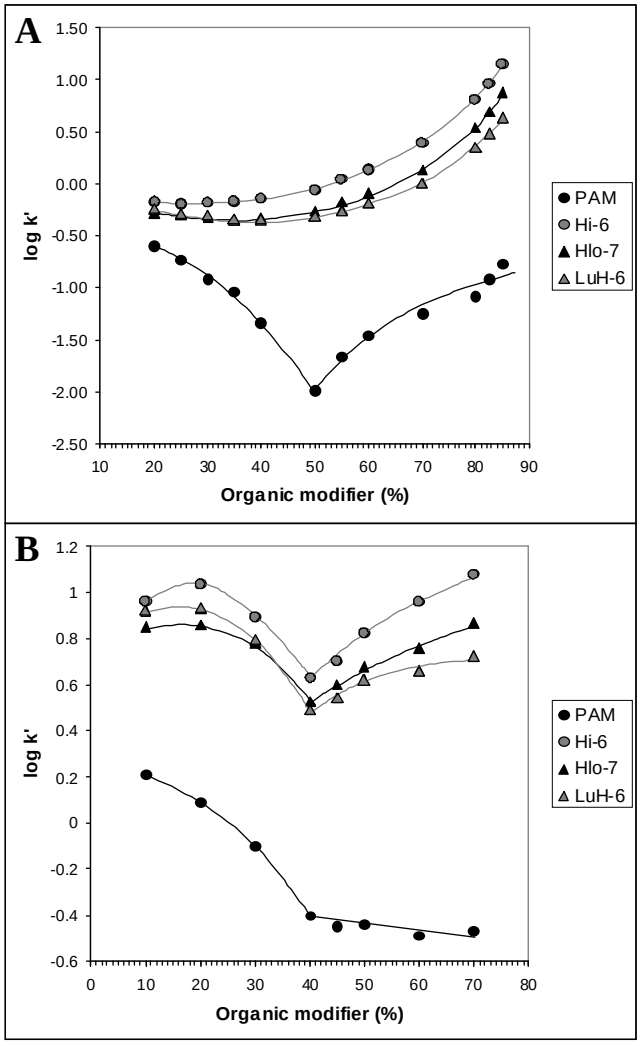




12. V.Voicu,, I.Sora, C.Sarbu, V.David, A.Medvedovici, *Hydrophobicity/hydrophilicity descriptors obtained from extrapolated chromatographic retention data as modeling tools for biological distribution: application to some oxime-type acetylcholinesterase reactivators.* **Journal of Pharmaceutical and Biomedical Analysis**, 52, 508-516 (2010).

Extrapolated retention at 100% organic solvent (χ) and parameters of the binomial and linear regressions, according to equations (1) and (2), relating retention data (log *k'*) to the content of the organic modifier in the mobile phase (φ), for analyte/stationary phase interactions accounting for hydrophilic mechanism.

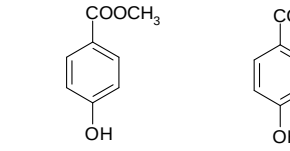
Analyte	**PAM**	**PRDS**	**HI-6**	**HLo-7**	**LuH-6**	**(1)**	**(2)**	**(3)**
Column HILIC (polyol)			analyte's H-bond donor interactions, dipole-dipole					
A	0.00131	0.00165	0.00362	0.00448	0.00353	-0.00026	0.00223	0.00219
B	-0.1959	-0.26584	-0.54862	-0.69362	-0.5398	0.12786	-0.32721	-0.32479
C	6.426	10.002	20.713	26.787	20.379	-9.574	11.614	11.645
χ_{bin}	**-0.064**	**-0.082**	**2.051**	**2.225**	**1.699**	**0.622**	**1.193**	**1.066**
S	0.0329	0.02262	0.08484	0.08965	0.07863	0.08252	0.06379	0.05814
I	-3.55129	-2.57672	-6.91034	-7.36951	-6.58931	-7.59667	-5.43685	-5.05365
χ_{lin}	-0.261	-0.315	1.574	1.595	1.274	0.655	0.942	0.760
Column ZIC-HILIC(*)			Electrostatic interactions, ion dipole					
A	0.07692	-0.03879	-0.06384	-0.07023	-0.06807	-0.06255	-0.06116	-0.06407
B	-0.00035	0.00040	0.00072	0.00075	0.00070	0.00069	0.00064	0.00066
C	-4.909	0.187	1.366	1.405	1.375	0.628	1.247	1.341
χ_{bin}	**-0.683**	**0.345**	**2.142**	**1.858**	**1.519**	**1.252**	**1.485**	**1.501**
S	0.02978	0.01613	0.03355	0.03147	0.02648	0.03102	0.02528	0.02527
I	-3.365	-1.612	-1.823	-1.925	-1.721	-2.435	-1.584	-1.585
χ_{lin}	-0.387	0.001	1.532	1.222	0.927	0.667	0.944	0.942
Column AGP			Protein binding ability					
A	0.00061	0.00054	0.00151	0.0016	0.00166	0.00059	0.00134	0.00135
B	-0.08661	-0.06948	-0.20023	-0.21814	-0.23023	-0.08332	-0.18537	-0.1876
C	2.491	1.435	6.927	7.813	8.261	2.288	6.513	6.604
χ_{bin}	**-0.050**	**-0.081**	**2.004**	**1.999**	**1.838**	**-0.061**	**1.376**	**1.344**
S	0.01437	0.02016	0.04887	0.04664	0.04336	0.0154	0.03564	0.0357
I	-1.65897	-2.24906	-3.31044	-3.06927	-2.98315	-1.76863	-2.56979	-2.57299
χ_{lin}	-0.222	-0.233	1.577	1.595	1.353	-0.229	0.994	0.997



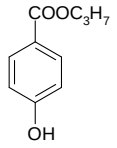
13. THE INFLUENCE OF MOBILE-PHASE FLOW-RATE IN RP-LC ON THERMODYNAMIC PARAMETERS STUDIED FOR SOME POLAR COMPOUNDS

T.Galaon, C.Mihailciuc, A.Medvedovici, V.David,

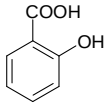
Journal of Liquid Chromatography and Related Technologies, spre publicare, 2010.



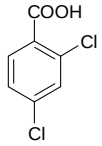
Methyl p-hydroxybenzoate



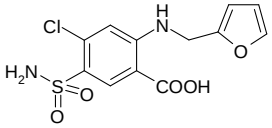
Propyl p-hydroxybenzoate



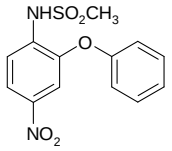
Salicylic acid



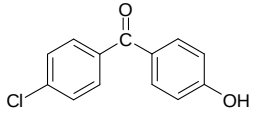
2,4-Dichlorobenzoic acid (impurity E of furosemide)



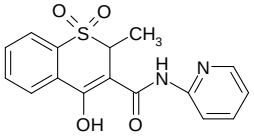
Furosemide



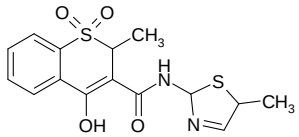
Nimesulide



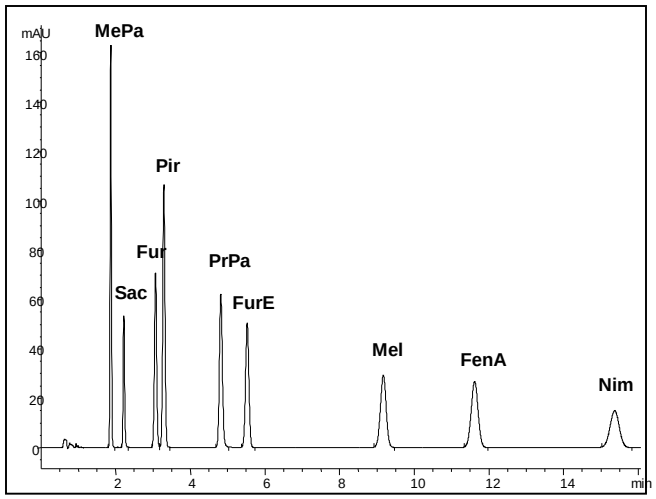
(4-chlorophenyl)(4-hydroxyphenyl) methanone
(impurity A of fenofibrate)



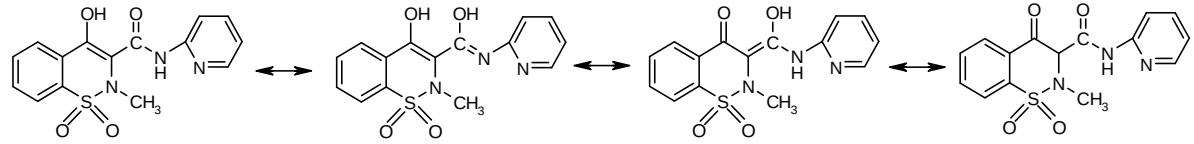
Piroxicam



Meloxicam



$$\ln k' = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} + \ln \phi$$

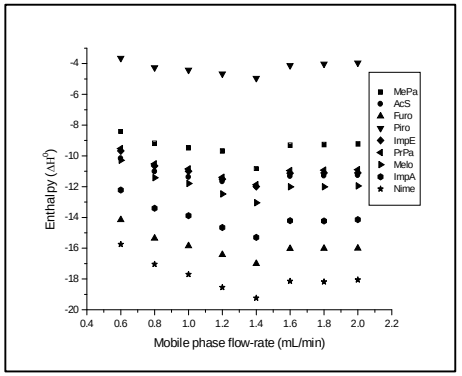


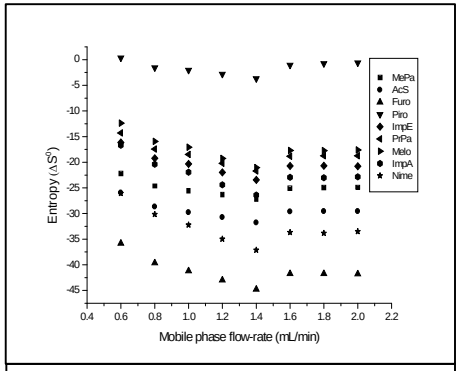
(I) log K_{ow} = 2.58

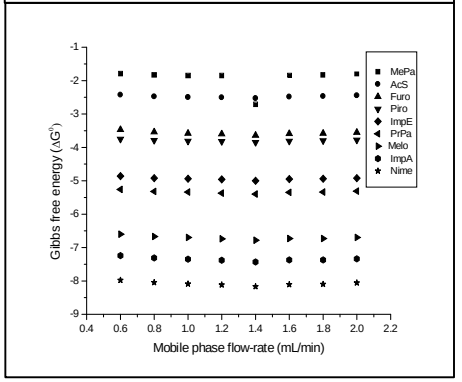
(II) log K_{ow} = 0.01

(III) log K_{ow} = 0.99

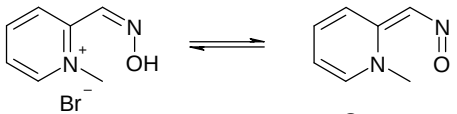
(IV) log K_{ow} = 1.53



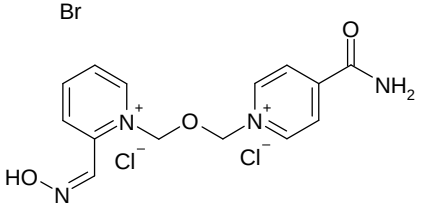




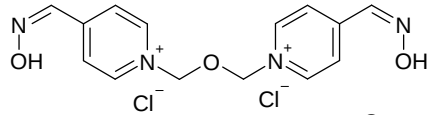
14. A.Medvedovici, V.Voicu, I.D.Sora, M.Radulescu, V.David, *Discontinuous double mechanism for the retention of some cation-type oximes on hydrophilic stationary phases in liquid chromatography*, **Chromatographia**, in curs de redactare.



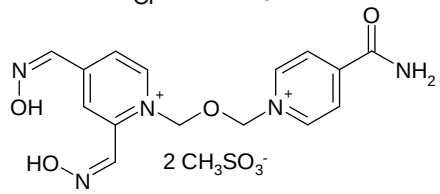
Pralidoxime (**PAM**)
2-[(hydroxyimino)methyl]-1-methylpyridin-1-ium



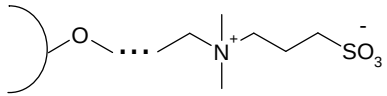
(**HI-6**)
2,1-(2-hydroxyiminomethylpyridinium)-3-(4-carbamoylpyridinium)-2-oxapropane



Obidoxime (**LuH-6**)
1,3-bis(4-hydroxyiminomethylpyridinium)-2-oxapropane



(**HLo-7**)
1-(4-aminocarbonylpyridinio)methoxymethyl-2,4-bis(hydroxyiminomethyl)pyridinium

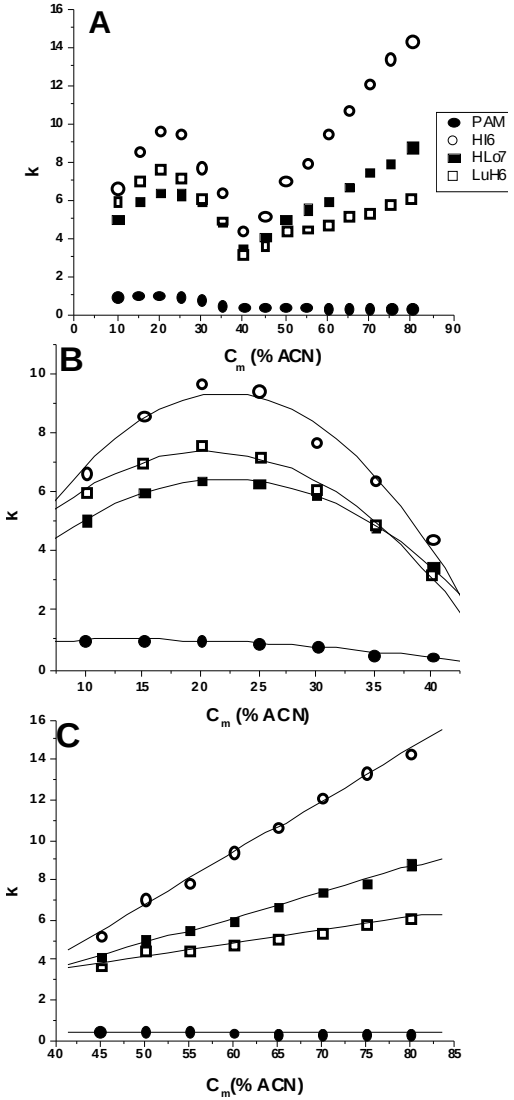


ZIC-HILIC stationary phase

$$k = \alpha_1 + \beta_1 \times C_m + \gamma_1 \times C_m^2$$

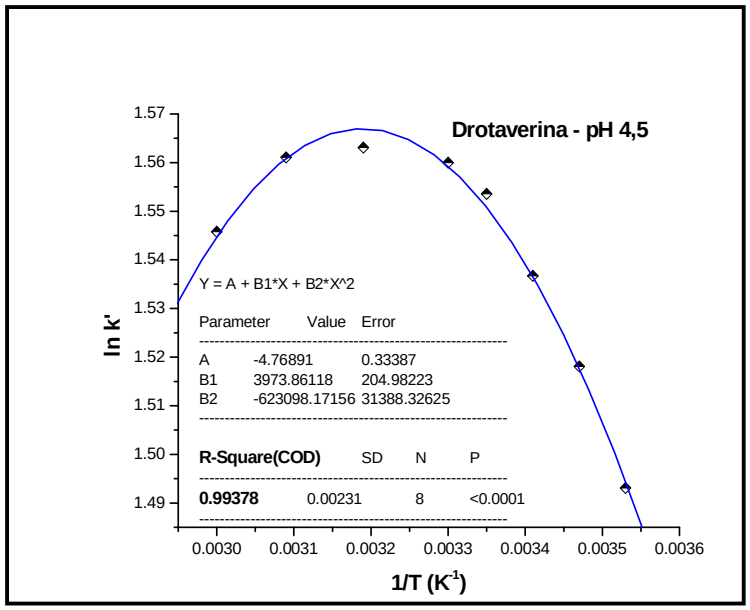
$$k = \alpha_2 + \beta_2 \times C_m$$

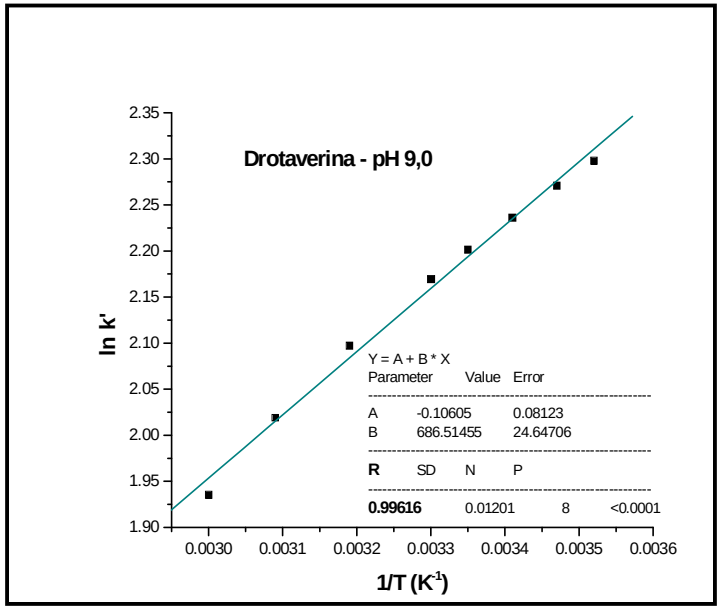
$$(C_m)_{1,2} = \frac{-(\beta_1 - \beta_2) \pm \left[(\beta_1 - \beta_2)^2 - 4 \times \gamma_1 \times (\alpha_1 - \alpha_2)\right]^{1/2}}{2 \times \gamma_1}$$

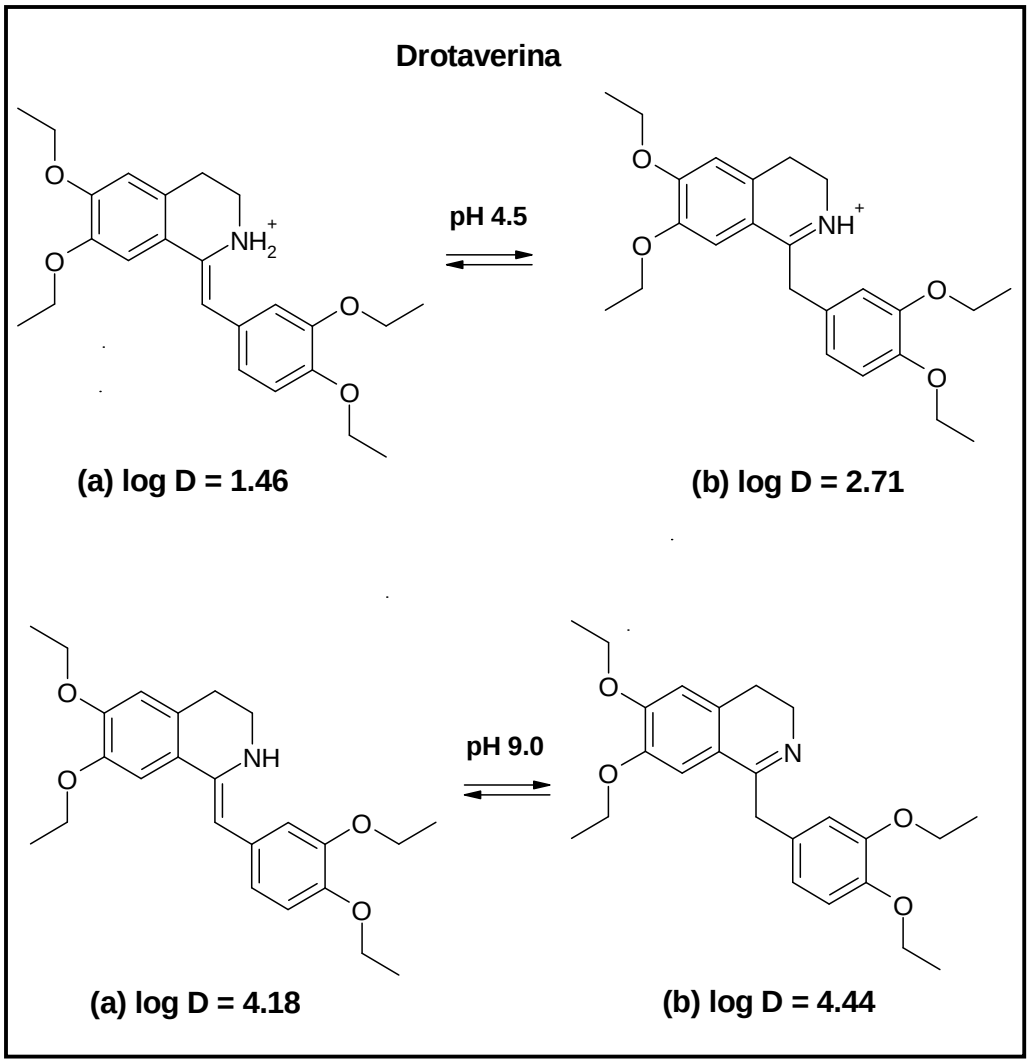


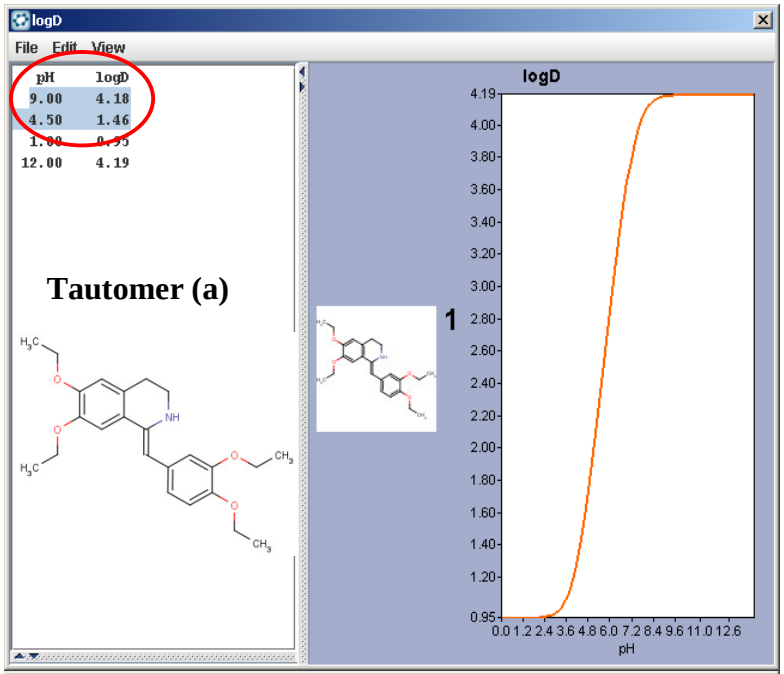
15. T.Galaon, A.Medvedovici, C.Mihailciuc, V.David, Deviation from van't Hoff dependence in RP-LC induced by tautomeric inter-conversion observed for three compounds. **Journal of Separation Science**, in curs de redactare.

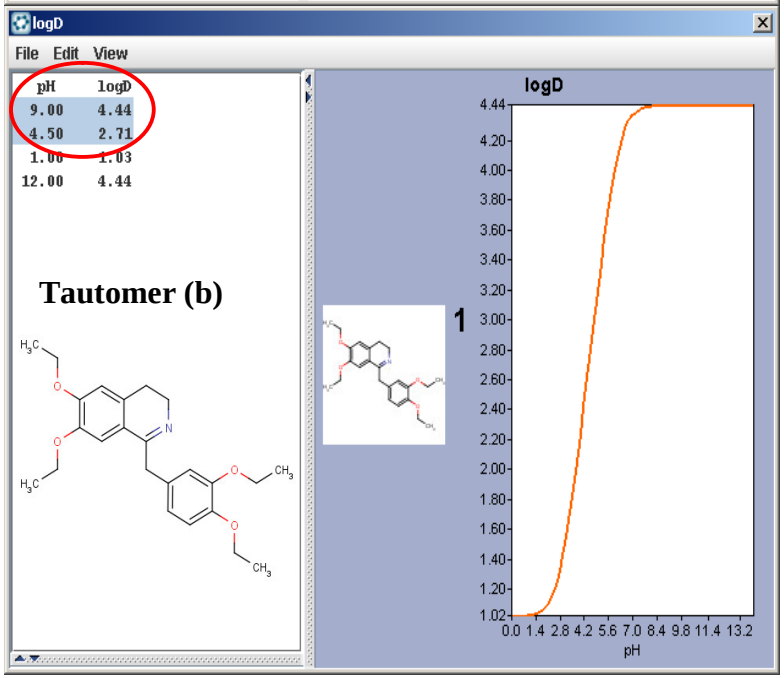
- **pH 4,5** – retenția creşte moderat cu temperatura în intervalul 10 – 40°C; după 40°C retenția scade; la acest pH molecula Drotaverinei este protonată în proporție de **99,9%**
- **pH 9,0** – retenția scade liniar cu creşterea temperaturii pe întreg domeniul studiat (conform ecuației van't Hoff); la acest pH molecula Drotaverinei se află în stare neprotonată în proporție de **97,6%**






Drotaverina
pH 4.5
(a) log D = 1.46
(b) log D = 2.71
pH 9.0
(a) log D = 4.18
(b) log D = 4.44


logD
File Edit View
pH logD
9.00 4.18
4.50 1.46
12.00 4.19
Tautomer (a)
logD
pH


logD
File Edit View
pH logD
9.00 4.44
4.50 2.71
12.00 4.44
Tautomer (b)
logD
pH

Capitole in monografii (fara acknowledegements):

1.V.David, A.Medvedovici, Chapter: *Sample Introduction Techniques for HPLC*, in **Encyclopedia of Chromatography** (Editor. J. Cazes), Francis & Taylor Publications, New York, Vol. 1, p. 2067-2076 (2009).

2.A.Medvedovici, A.Farca, V.David, *Chapter 8: Derivatization reactions in liquid chromatography for drug assaying in biological fluids*.
Advances in Chromatography (Editori: E.Grushka, N.Grinberg), CRC Press – Francis and Taylor Publications, Boca Raton, USA, vol. 47, 283-322 (2009).

Monografie in Editura Nationala cu mentionarea in Prefata a Proiectului de fata:

1. V.David, A.Medvedovici, **Metode de separare si analiza cromatografica**, Ed. Universitatii din Bucuresti (2008), ISBN: 978-973-737-590-2.

Conferinte:

1.V.David, **Aspecte extra-analitice in cromatografia de lichide**, Conferinta la Societatea de Chimie Analitica din Romania (SCAR), 27 feb. 2008.

2.V.David, **Modelare in cromatografia de lichide in faza inversa: partitie *versus* adsorbtie**, Conferinta la Universitatea Babes-Bolyai din Cluj-Napoca, 15 aprilie 2008.

3.A.Medvedovici, V.David, V.Voicu, **Prediction of the hydrophilic character (as molecular descriptor) for organic compounds from chromatographic retention data under HILIC partition mechanism**, *10th International Congress of Clinical Pharmacology, Therapeutics and Toxicology*, Sinaia, June 9-12 2009.

Teza de doctorat finalizata:

Mecanismul de retenție în cromatografia de lichide în fază inversă cu eluție izocratică. Modelare şi parametri extraanalitici. Drd. Toma Galaon (sustinuta in 26 martie 2010).

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