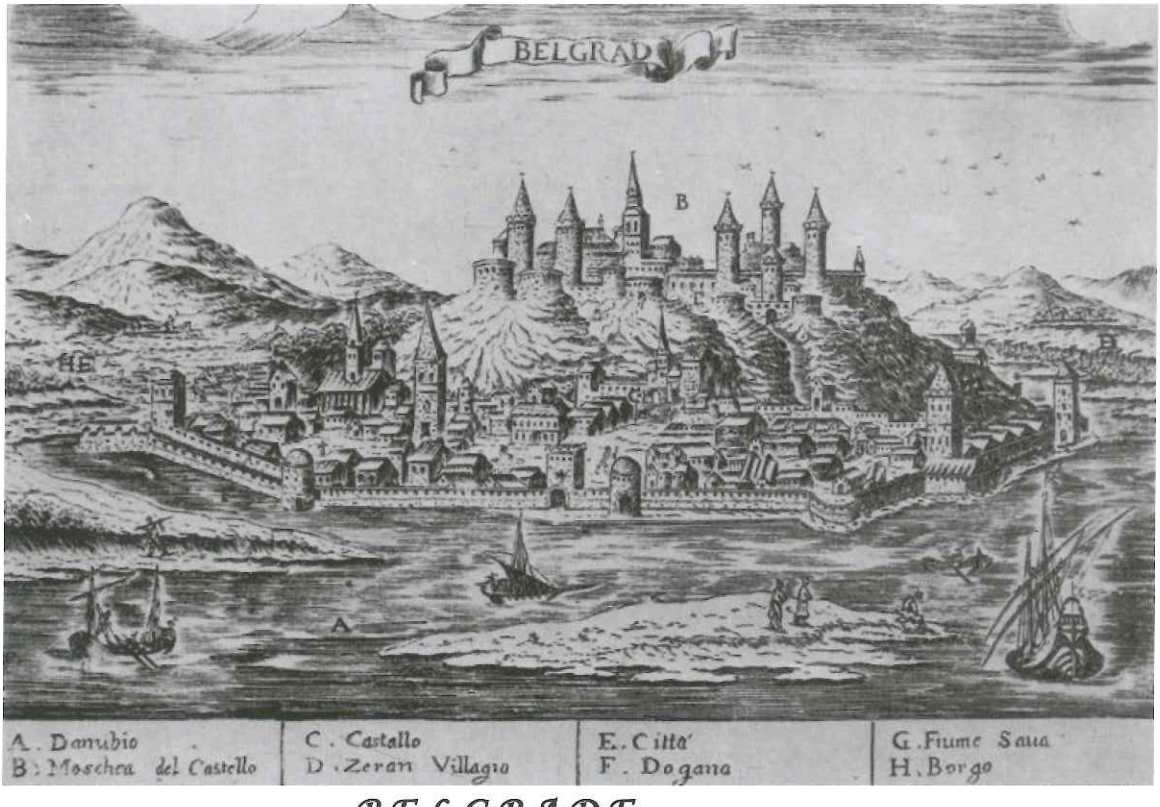
PHYSICAL CHEMISTRY 2016

13th International Conference on Fundamental and Applied Aspects of Physical Chemistry



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September 26-30, 2016

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LINEAR SOLVATION ENERGY RELATIONSHIP STUDY OF SELECTED IMIDAZOLINE RECEPTOR LIGANDSON α1-ACID GLYCOPROTEIN COLUMN

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ABSTRACT

The retention properties of 22 selected imidazoline receptor ligands were studied by high-performance liquid chromatography on α1-acid glycoprotein (AGP) column using 2-propanol as organic additive and Sørensen phosphate buffer (pH 7.0). Linear solvation energy relationships (LSER) were built using isocratic retention factors- log k_5, log k_8, log k_{10}, log k_{12}, log k_{15} obtained for (5, 8, 10, 12, 15)% of 2- propanol in mobile phase, respectively and extrapolated log K_w values as dependant variables. Independent variables (Abraham descriptors) for LSER analysis were calculated by ACD/i-Labsoftware. LSER analysis indicated on McGowan volume, hydrogen bond basicity and excess molar refraction as the most important parameters for all isocratic retention factors and log $K_w$values of 22 selected imidazoline receptor ligands.

INTRODUCTION

Human serum albumin (HSA) and α_1-acidglycoprotein (AGP) are the most commonproteins of blood that are responsible for drug binding [1]. It is well describe dthat is o electric point of AGP (pI=2,7)at physiological conditions is lower then for HSA. AGP shows significant affinity to basic andneutraldrugs. Pathological processes like malignant disease, infection, other inflammatory diseases change the affinity and extent of AGP, therefore the variability of pharmacokinetic profile of basic and neutral drug scan be recognized [2].

The pharmacological effect of selected imidazoline derivatives is based on modulaton of imidazoline and alpha adrenergic receptors. These drug sach as centrally antihypertensives, diuretics (amiloride) and nasaldecongestives (xylometazoline, oxymetazoline) [3].

Early research showed that lipophilicity index of selected drug sis not the only parameter that correlates with protein binding [4]. Based on previous investigation, we extended this approach with linear solvation energy

relationships (LSER) study. The retention of 22 imidazoline receptor ligands on AGP column was examined under different chromatographic conditions (obtained under different percentages of 2-propanol in mobilephase - 5, 8, 10, 12, 15%, respectively). Imidazoline receptor ligands in this study have similar basic properties, thusit is expected that these compounds have affinity to serum AGP.

EXPERIMENTAL

The group of 22 selected imidazoline derivatives were purchased from Sigma–Aldrich, St. Louis, MO, USA as hydrochloride salts (Clonidine, moxonidine, guanfacine, brimonidine, efaroxan, idazoxan, rilmenidine, harman, harmine, tizanidine, xylometazoline, tetrahydrozoline, oxymetazoline, antazoline, phentolamine, benazoline, cirazoline, detomidine, metformin, and RX 821002) or provided by Zdravlje-Actavis, Leskovac, Serbia (trimazoline) and Galenika, Belgrade, Serbia (amiloride).

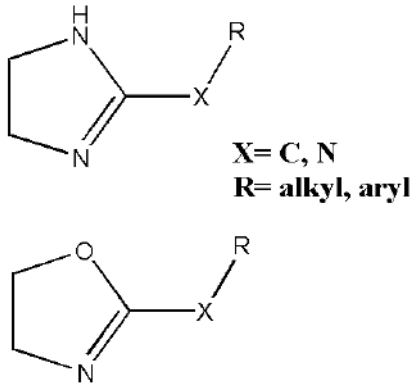

Figure 1. General structure of imidazolinereceptor ligands

Methanol (J.T. Baker, Deventer, Netherlands) and 2-propanol (Sigma–Aldrich, St. Louis, MO, USA) of HPLC grade and deionized water (TKA water purification system, Niederelbert, Germany) were used throughout this study.

The HPLC analysis was performed on a Dionex Ultimate 3000 system (Thermo Fisher Scientific, Germering, Germany) equipped with autosampler, Dionex Ultimate 3000 quaternary pump, and photodiode array detector. The retention behaviour of selected compounds were examined on CHIRALPAK®AGP column 100 mm × 2 mm I.D. packed with α_1-acid glycoproteinchemically bound to silica particles size of 5 μm (DAICEL CORPORATION, France). The mobile phases flow rate was set to 0.2 mL/min and temperature to 25 °C. The UV detection was performed at 225 nm.

RESULTS AND DISCUSSION

Isocratic retention factors (log *k*) calculated for different percentage of organic additive in mobile phase (from 5% to 15%) were linearly extrapolated to the lipophilicity index corresponding to 100% of buffered eluent (log K_w),following the Eq.1:

$$\log k = - S\varphi + \log k_w \quad \textbf{(1)}$$

where φ is the organic solvent fraction, and S is the slope of the regression curve.

The most accepted representation of the linear solvatation energy relationship (LSER) model, proposed by Abraham, is described by **Eq 2**:

$$\text{Log k} = c + e\text{E} + s\text{S} + a\text{A} + b\text{B} + v\text{V} \quad \textbf{(2)}$$

E – Excessivemolarrefraction, S - Polarity/polarizability, A - Hydrogen bond acidity, B - Hydrogen bond basicity, V - McGowan Volume

Since electrostatic interactions or ionization effects are not parameterized, positive and negative charged fractions,as F^+ and F^-have been calculated at pH 7.4.These additional parametersare included in **Eq.3**. in order to investigate the contribution of charge state in biomimetic retention of imidazolinereceptor ligands.

$$\text{Log k} = c + e\text{E} + s\text{S} + a\text{A} + b\text{B} + v\text{V} + f\text{F}^+ \quad \textbf{(3)}$$

Coefficients *c, e, s, a, b,v*and f^+ are derived by stepwise multiple linear regression (MLR) analysis. Coefficients with $p<0.05$ were determined as statistically significant and included in final equations (**Eq. 4-9**)

The significant coefficients (*c, e, s, a, b,v and* f^+) of the Abraham's parameters and statistical results presented in Table 1.From the data can be concluded:

Table. Linear Solvation Energy Relationship Equations

Eq.	log *k*	*a*	*b*	*s*	*e*	*v*	Intercept	f^+	r	r^2	SE	p
4	log K_w		-0.492 ± 0.148		0.384 ± 0.181	0.749 ± 0.177	0.567 ± 0.316	-0.007 ± 0.001	0.881	0.776	0.206	$2\cdot10^{-5}$
5	log k_5		-0.464 ± 0.117		0.208 ± 0.101	0.626 ± 0.155	0.325 ± 0.283	-0.004 ± 0.001	0.853	0.728	0.184	$3\cdot10^{-5}$
6	log k_8	0.379 ± 0.241	-0.521 ± 0.143		0.234 ± 0.097	0.451 ± 0.146	0.294 ±0.268	-0.002 ± 0.001	0.836	0.699	0.173	0.00031
7	log k_{10}	0.414 ± 0.246	-0.471 ± 0.146		0.235 ± 0.099	0.406 ± 0.149	0.192 ±0.273		0.803	0.645	0.176	0.00123
8	log k_{12}	0.473 ± 0.236	-0.511 ± 0.142	0.275 ± 0.099		0.363 ± 0.137	0.134 ±0.275		0.773	0.598	0.180	0.00117
9	log k_{15}		-0.400 ± 0.164			0.354 ± 0.163	-0.057 ± 0.325		0.685	0.469	0.209	0.0132

r - correlation coefficient, r^2 - adjusted for degrees of freedom, SE - standard error of the fit

1. Retention onAGP is mainly guided by McGowan volume, which *v*-coefficients show positive influence on retention behavior in all examined systems. Positive signs of coefficients of V parameters indicates on favourable interactions of bulky analytes with solvated AGP.

2. In all equations *b*-coefficients of Abraham basicity show negative influence on retention behavior, which indicates more intensively interaction of the neutral solutes with water/2-propanol then with solvated AGP.

3. Significant positive *a*-coefficient of Abraham's acidity parameters in equations (log k_8, log k_{10}, and log k_{12}, LSER equations **6-8**) indicated on influence of 2-propanol in concentration of 8 – 12% on hydrogen bond donating ability of solutes. The results indicate that bond donating groups of the analytes intensify interactions with AGPin this range of organic solvent fraction.

4. The positive *e*- and *v*- coefficients in our chromatography systems shown that increasing molar refractivity E and McGowan volume V facilitate partitioning of solute from mobile phase to stationary phase. This behaviour is explained with more easily formed cavities in solvated AGP phase.

5. The *f*-coefficientof F^+ parameter showed very modest influence (*f* : -0.007-0.002) on retention behavior of analytesin range of organic solvent fraction (0-8%). These results could be explained with very similar basicity and very narrow pKa interval of the analytes.

CONCLUSION

By designed LSER study of 22 selected imidazoline receptor ligands, Abraham's descriptors indicated on basicity, Mc Gowan volume and excess molar refractivity of solutes as the most significantparameters for all AGP chromatographicretentionfactorsand log Kw values. Described molecular factors represent valuable starting point for further development and prediction of biopharmaceutical properties of imidazoline derivatives.

Acknowledgement

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