PHYSICAL CHEMISTRY 2014

12th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

The Conference is dedicated to the
25. Anniversary of the Society of Physical Chemists of Serbia

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RP-TLC IN QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIPS OF SOME ALPHA ADRENERGIC AND IMIDAZOLINE RECEPTOR LIGANDS

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ABSTRACT

The chromatographic behavior of 16 alpha adrenergic and imidazoline receptor ligands has been studied by reversed-phase thin-layer chromatography (RP-TLC). Retention constant R_M^0 has been determined for all tested compounds in two different chromatographic systems (tetrahydrofuran-ammonia-water/RP-18, and tetrahydrofuran-ammonia-water/CN) and together with computed molecular parameters of the examined compounds further used for the quantitative structure–retention relationship (QSRR) study. The QSRR modeling was performed with use of the partial least squares regression (PLS). Obtained results from leave-one-out cross-validation (Q^2 values: 0.923 and 0.873 for RP-18 and CN stationary phase, respectively) and external test set prediction (root mean square error of prediction, RMSEP: 0.339 and 0.218, for RP-18 and CN stationary phase, respectively) were proved high predictive power of the proposed models.

INTRODUCTION

The concept of non-adrenergic imidazoline receptors (IR) and their ligands was proposed based on a discovery that antihypertensive drug clonidine and its analogues exert their effect on the central nervous system by interaction with both, the α_2-adrenoreceptors (α_2-AR) and the imidazoline receptors. Today it is well known that second generation of centrally acting antihypertensives, such as moxonidine and rilmenidine, is more selective for I_1-IR and have produced less side effects than clonidine and other nonselective imidazoline receptors ligands [1]. Therefore, design and synthesis of novel compounds with diverse activity and selectivity toward I_1-IR, I_2-IR, and I_3-IR, and the α-AR-receptors can instigate the development of promissing drug candidates with diverse pharmacological effects and reduced incidence of side effects. Significant interest in

developing of new IR/α-AR ligands requires fast and reliable methods for estimation of their physicochemical properties and retention behavior.
Application of thin-layer chromatography method in different quantitative structure–retention relationship (QSRR) studies provides valuable data which enable prediction of the retention behavior of the new compounds, understanding of the separation mechanism in a given chromatographic system, identification of important molecular descriptors, estimation of compounds' lipophilicity and prediction of biological activity [2].
The main objectives of this work were to investigate the chromatographic behavior of 16 alpha adrenergic and imidazoline receptor ligands by the RP-TLC and to develop the QSRR models enabling prediction of the retention behavior of the related guanidine and imidazoline derivatives.

EXPERIMENTAL

Chromatography was performed on the commercially available octadecyl silica plates (the TLC Silica gel 60 RP-18 F_{254s} pre-coated aluminium sheets, Merck, Darmstadt, Germany) and CN-modified silica plates (the HPTLC Silica gel 60 CN F_{254s}, Merck, Darmstadt, Germany). Two different mobile phase/stationary phase systems and different contents of organic modifier (φ) were used: tetrahydrofuran-ammonia-water/RP-18 (φ=0.6-0.8), and tetrahydrofuran-ammonia-water/CN (φ=0.55-0.75). The content of tetrahydrofuran was changed in the 5% steps, while the content of ammonia was kept constant at 5 vol%. The plates were developed in the ascending mode after 15 min pre-saturation with the mobile phase. Zone detection was performed in the UV light at 254 nm. The R_f values were calculated as an average from the three chromatograms. According to the obtained R_M values, $R_M=\log(1/R_f -1)$ retention parameter R_M^0 corresponding to pure water was obtained as an extrapolated value to 0% organic modifier in the mobile phase, using following linear equitation: $R_M=R_M^0+ m\times\varphi$; where m is slope and φ is the volume fraction of organic modifier in the mobile phase.
Theoretical studies including calculation of pK_a and selection of a predominant molecular/cationic/anionic form of the analyzed compounds at a given pH value of an aqueous phase, was performed using the Marvin 5.5.1.0 ChemAxon program. Geometry optimizations were performed on the B3LYP/3-21G (d,p) level of the density functional theory in the Gaussian 98 program. The Gaussian 98 (B3LYP/3-21G(d,p) basis set), the Chem3D Ultra 7.0.0, the Molinspiration Cheminformatics, and the Dragon programs were applied for the computation of molecular descriptors. The Soft Independent Modeling of Class Analogy SIMCA P+ 12.0 program was used for the Partial Least Squares (PLS) analysis and the QSRR modeling.

RESULTS AND DISCUSSION

In the QSRR study, experimentally obtained retention parameters (R_M^0) in the two different chromatographic systems were used as dependent variables, while the computed molecular parameters of the examined compounds were used as independent variables. The examined data set of 16 compounds was divided into the training set consisting of 12 compounds (moxonidine, brimonidine, clonidine, amiloride, guanabenz, idazoxan, efaroxan, harmane, naphazoline, tramazoline, oxymetazoline, and xylometazoline), used for building of the models, and the test set consisting of 4 compounds (tizanidine, guanfacine, harmine, and tetrahydrozoline), used for an external validation. The distribution of the studied substances into the training and test set were randomly determined but taking into the account that each chemical group (i.e., the guanidine, 2-aminoimidazoline, 2-arylmethylimidazoline and β-carboline derivatives) has one representative in the test set. The statistical results and PLS-coefficients of the QSRR models are given in Table 1. High values of leave-one-out cross-validation parameter Q^2 (Q^2 >0.5) and low values of the root mean square error of estimation (RMSEE) for the training set and root mean square error of prediction (RMSEP) for the test set indicate good prognostic capacity of the obtained QSRR models (Table 1.). In all devised QSRR models, logarithm of the partition coefficient, log *P* is selected as the important property with positive influence on the retention in the tested chromatographic RP-TLC systems. Similar sets of descriptors were selected for both, the RP-18 (log *P*, nN, P_VSA_e_2) and the CN (log *P*, nON, P_VSA_e_2) stationary phases and tetrahydrofuran-ammonia-water as mobile phase. The P_VSA-like on Sanderson electronegativity, bin 2 (P_VSA_e_2) descriptor is defined as an amount of the van der Waals surface area (VSA), which in certain range has the P property (Sanderson electronegativity). In the both chromatographic systems, the P_VSA_e_2 descriptor exerts negative influence on the R_M^0. Therefore the compounds with higher P_VSA_e_2 values have lower retention on the two investigated stationary phases. The number of nitrogen atoms (nN) is a constitutional descriptor and in the tetrahydrofuran-ammonia-water/RP-18 system, it exerts negative influence on the retention constant (R_M^0). Thus the compounds with a higher number of the nitrogen atoms (nN) less efficiently interact with the C18-modified silica stationary phase, which results in a lower retention thereof.

Table 1. Statistical results of the developed PLS-QSRR models

RP-TLC systems	PLS-Coefficients	R^2Y	Q^2	RMSEE	RMSEP
THF-NH_3-H_2O (RP-18)	Constant: 2.431; log *P*: 0.953; nN: - 0.375; P_VSA_e_2: -0.364	0.96	0.92	0.171	0.339
THF-NH_3-H_2O (CN)	Constant: 2.162; log *P*: 1.078; nON: - 0.116; P_VSA_e_2: - 0.265	0.93	0.87	0.186	0.218

The number of the hydrogen bond acceptors (nON) negatively contributes to the R_M^0 values in the tetrahydrofuran-ammonia-water/CN system, so that the larger number of the nitrogen and oxygen atoms as the hydrogen accepting sites leads to the lower retention on the CN stationary phase.

CONCLUSION

Upon the results of the performed QSRR analysis, the log *P* values were selected in all the devised models as those indicating the importance of lipophilicity for the retention behavior of the investigated compounds. Moreover, constitutional descriptors (nN), P_VSA-like descriptors (P_VSA_e_2), and the number of the hydrogen bond acceptors (nON) contribute to an overall retention mechanism in RP-TLC systems. The developed QSRR models are very useful predictive tools for evaluation of the R_M^0 values for the related guanidine and imidazoline derivatives.

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