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APPLICATION OF THE CHROMATOGRAPHIC PARAMETERS IN THE ASSESSMENT OF AMIDE DERIVATIVES' BIOLOGICAL POTENTIAL

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Abstract: *In silico* approach is increasingly used in modern design to establish the qualitative / quantitative dependence between structure, physico-chemical properties and biological activity of the new molecule. The selection and application of appropriate molecular descriptors are important step in this process. Given the presence of the amide group in numerous pharmacologically and biologically active molecules, in the pharmaceutical and chemical industries its formation represents an eternal challenge and a significant transformation in the design of the synthetic plan. Evaluation of the biological potential of selected amide derivatives included theoretical and experimental determination of their lipophilicity, analysis of their bioavailability, study of their pharmacokinetic predictors and ecotoxicity parameters. The parameters (R_M^0, m and C_0) obtained by applying reversed-phase thin layer chromatography (RP TLC18 F_{254s}) in the presence of two organic modifiers, as assumed measures of lipophilicity of the examined amide derivatives were correlated with the studied parameters of biological activity by the linear regression method. The quality of the obtained mathematical models was confirmed by the values of statistical validation parameters.

Keywords: amide derivatives, lipophilicity, bioavailability, biological activity parameters.

1. INTRODUCTION

The synthesis of a new biologically active compound has always been a great challenge in chemistry. In modern molecule design, however, more attention is paid to the stages that precede synthesis in order to achieve time and financial viability. Namely, the primary task of modern pharmaceutical chemistry is to establish qualitative and quantitative dependencies between the structure, physicochemical properties and biological/ pharmacological behavior of a new molecule. *In silico* approach provides theoretical insight into the properties of the future molecule and in the early stages of design significantly contributes to the forming QSAR (Quantitative Structure-Activity Relationship) and QSPR (Quantitative Structure-Property Relationship) models [1]. The earliest stages of assessing the biological / pharmacological activity of a new molecule include the application of drug-likeness rules. The bioavailability of a compound is closely related to its lipophilicity [2]. By definition, lipophilicity represents the affinity of molecules for a lipophilic environment [3]. With this in mind, the lipophilicity of the compound determines its passage through the cell membrane, and thus significantly defines its ADMET (absorption, distribution, metabolism, excretion and toxicity) properties [4]. It is quantitatively most commonly described by the logarithmic value of the partition coefficient, log*P*, (1-octanol/ water system) [5,6]. Also, as reliable alternative measures of lipophilicity, the parameters, R_M^0, m and C_0, obtained by reversed phase thin-layer chromatography (RPTLC) are used [7–10]. The efficacy of a bioactive compound is conditioned by its pharmacokinetics. Most often, bioactive substances are applied orally, so their reaching the systemic circulation depends on the levels of intestinal absorption. The pharmacokinetic predictor that indicates the percentage of compounds that reach the bloodstream is the human effective permeability in the jejunum, P_{eff} (Human effective permeability in the jejunum). Better permeability through the phospholipid bilayer of enterocytes is characteristic for the molecules with higher lipophilicity, so the level of permeability is directly conditioned by the lipophilicity of the molecules [11]. Plasma protein binding, PPB, represents the ratio of the concentration of a protein-bound compound to its total plasma concentration and

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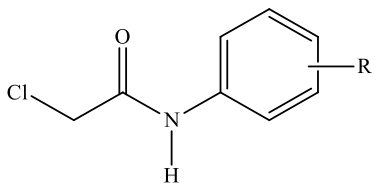
is expressed as a percentage. High binding capacity for plasma proteins is possessed by molecules with PPB > 90% [12]. The possibility of the action of the compound in the central nervous system is conditioned by its passage through the blood-brain barrier (BBB). This barrier controls the passage of substances from the blood into the cerebrospinal fluid, and thus into the brain and spinal cord. A compound can cross the blood-brain barrier if it fulfills „Rule 2", i.e. if its molecular weight (MW) is less than 500 and the total number of donors (NHBD) and hydrogen bond acceptors (NHBA) are less than 8-10 [13]. On the other hand, literature data indicate that compounds with values of the pharmacokinetic parameter logBBB > 0.3 have a good predisposition to cross the brain barrier, while a value of logBBB < -1 indicates a blockade of this passage [14]. In addition to knowledge of the lipophilicity and pharmacokinetic properties preliminary assessment of the biological potential of a compound requires the prediction of its ecotoxicity [15].

Numerous compounds with anticonvulsant, antioxidant, antipyretic, antimicrobial and antitumor activities have an amide fragment in their structure [16–20]. Therefore, in this paper, the assessment of the bioactive potential of selected amide derivatives included theoretical and experimental determination of their lipophilicity, assessment of their bioavailability, study of their pharmacokinetic properties and ecotoxicity. The parameters (R_M^0, m and C_0) obtained by applying thin layer chromatography on reverse phases in the presence of two organic modifiers, as assumed measures of lipophilicity of the tested amide derivatives, were correlated with the studied parameters of biological activity by linear regression.

2. EXPERIMENTAL

Structures of the studied derivatives are shown in Table 1.

Table 1. Structures of the studied amide derivatives



Compound	*R*	Compound	*R*
1.	H	7.	4-I
2.	4-CH_3	8.	4-$COCH_3$
3.	4-OCH_3	9.	4-OH
4.	4-Cl	10.	3-CN
5.	4-Br	11.	4-CN
6.	4-F	12.	3-Br

At the beginning of the chromatographic examination, solutions of the tested compounds were made in ethanol (J.T. Backer, Deventer, The Netherlands), at the concentration of 2mgcm^{-3}. RPTLC C18/ UV254s, (Macherey – Nagel, Germany) were used as the carrier of the stationary phase. After applying about 0.2 µl of the prepared solutions on the stationary phase, the plates were developed in mixtures: water–2-propanol (J.T. Backer, Deventer, The Netherlands) and water-acetonitrile (J.T. Backer, Deventer, The Netherlands). The volume ratios of organic modifiers varied in the range φ = 0.36–0.52. The chromatograms were developed about 15 minutes at room temperature with a one-dimensional ascending technique, without saturating the atmosphere of the chromatographic chamber with vapor modifiers. The identification of the developed compounds was performed under UV light of wavelength λ = 254 nm, with dark spots appearing on the fluorescent medium. Three chromatograms were developed for each modifier, and then the average R_f values were calculated. Based on these, R_M values were calculated [21]. Dependences of the obtained R_M values on the volume fraction of organic modifier, φ, as the intercept gave the chromatographic retention constant R_M^0, while the slope represented the value of the parameter m [22] (equation 1):

$$R_M = R_M^0 + m\varphi \quad (1)$$

Based on the obtained parameters, the hydrophobicity parameter, C_0 [23] (equation 2) was calculated:

$$C_0 = - R_M^0/m \quad (2)$$

The experimental results were processed using the Origin 6.1 computer program, while the Molinspiration, SimulationPlus, and PreADMET software packages were used for calculating the coefficients, log*P*, and selected toxicity parameters [24–27].

3. RESULTS AND DISCUSSION

3.1. Experimental and software determination of the lipophilicity of amide derivatives

The software obtained values of the partition coefficient, log*P*, as a standard measure of lipophilicity for the tested amide derivatives are shown in Table 2. The values of the chromatographic parameters R_M^0, m and C_0 of the tested derivatives are given in Table 3.

Table 2. logP values of the studied amide derivatives

R	AClog*P*	Alog*P*	AlogP_s	Mlog*P*	milog*P*	*kowwin*	log*P*ch.s	XlogP_3
H	1.77	1.70	1.73	1.95	1.72	1.68	1.64	1.63
4-CH_3	2.08	2.18	1.87	2.25	2.17	2.23	2.31	1.99
4-OCH_3	1.66	1.68	1.69	1.68	1.78	1.76	1.86	1.67
4-Cl	2.38	2.36	2.39	2.52	2.40	2.32	2.59	2.26
4-Br	2.47	2.44	2.42	2.66	2.53	2.57	2.79	2.32
4-F	1.83	1.90	2.00	2.37	1.88	1.88	1.91	1.73
4-I	2.70	2.72	2.94	2.81	2.81	2.85	3.21	2.28
4-$COCH_3$	1.69	1.43	1.59	1.89	1.62	1.36	1.65	1.86
4-OH	1.47	1.43	0.97	1.38	1.24	0.85	1.32	1.27
3-CN	1.58	1.57	1.53	1.59	1.45	1.78	1.50	1.82
4-CN	1.58	1.57	1.54	1.59	1.48	1.78	1.52	1.35
3-Br	2.47	2.44	2.42	2.66	2.51	2.57	2.78	2.94

Based on the data shown in Table 2, it can be seen that due to different calculation approaches, the values of the log*P* partition coefficient for the same compound differ from each other. Regardless of the calculation procedure, the lowest log*P* values were obtained for the derivative with the most polar group, –OH, and the highest values for the derivative with –I as a substituent. Also, no differences in log*P* values were observed for compounds with the same substituent at different positions.

Table 3.Values of chromatographic parameters of examined amides in applied modifiers

R	2-propanol				dioxane			
	R_M^0	*m*	r	C_0	R_M^0	*m*	r	C_0
H	1.087	-2.780	0.998	0.391	0.926	-2.190	0.996	0.423
4-CH_3	1.370	-3.179	0.999	0.431	1.192	-2.420	0.998	0.492
4-OCH_3	0.979	-2.632	0.999	0.372	0.865	-2.098	0.997	0.412
4-Cl	1.561	-3.408	0.997	0.458	1.433	-2.744	0.999	0.522
4-Br	1.675	-3.541	0.998	0.473	1.558	-2.897	0.996	0.538
4-F	1.273	-3.063	0.998	0.416	1.078	-2.333	0.997	0.462
4-I	1.786	-3.678	0.999	0.486	1.682	-3.096	0.998	0.543
4-$COCH_3$	0.853	-2.420	0.999	0.352	0.754	-1.931	0.999	0.390
4-OH	0.605	-1.974	0.999	0.306	0.617	-1.764	0.996	0.350
3-CN	0.775	-2.270	0.997	0.341	0.705	-1.869	0.998	0.377
4-CN	0.738	-2.200	0.999	0.335	0.694	-1.847	0.999	0.376
3-Br	1.686	-3.547	0.998	0.475	1.574	-2.915	0.997	0.540

The high values of the regression coefficient, r, shown in Table 3, indicate that the linear R_M-φ dependence is valid. It was expected that the same compound in different modifiers will have the same value of the chromatographic retention constant, R_M^0, since it represents the retention behavior of the compound in pure water (φ= 0). However, the data from Table 3 show that the obtained R_M^0 values for the same compound in the applied organic modifiers differ from each other, which is often registered during experimental work [28]. Higher R_M^0 values for all tested derivatives were obtained in the presence of protic and more polar 2-propanol.

By comparing the R_M^0 values of different amide derivatives in the same modifier, it is observed that derivatives with alkyl and halogen substituents have higher R_M^0 values compared to the unsubstituted derivative. In the case of halogen substituents, an increase in the R_M^0 value was observed in the series –F < –CH_3 < –Cl < –Br < –I, which has already been observed in the literature [29]. In both applied modifiers, the highest R_M^0 values were obtained for the derivative with –I as a substituent, and the lowest for the derivative with the most polar –OH group, which is in accordance with the previously theoretically obtained log*P* values. Also, no significant differences in R_M^0 values were obtained for compounds with the same substituent (–CN and –Br) in different positions (3 and 4).

Also, it is obvious that the values of slope, *m*, change as well as the R_M^0 value, in both modifiers for all tested derivatives. The correlation of the chromatographic retention constant R_M^0 and the parameter, *m* resulted in a linear dependence, which confirmed the assumption that both chromatographic parameters depend on the same physico-chemical properties. The equations of the obtained linear dependences and their regression coefficients are shown in Table 4.

Table 4. R_M^0-m equation for studied derivatives in used modifiers

modifier	equation	r
2-propanol	$R_M^0 = -0.824-0.700m$	0.997
dioxane	$R_M^0 = -0.839-0.824m$	0.998

High values of regression coefficients indicate the validity of the established R_M^0-*m* dependence, but also that the tested derivatives can be considered congeneric [30]. In line with expectations, the values of the parameter, C_0, follow the same trend of changes as the chromatographic parameters R_M^0 and *m*.

The reliability of the application of chromatographic parameters as alternative measures of lipophilicity of the tested amide derivatives was determined by their correlation with software log*P* values, using linear regression (Table 5). Derivatives with a substituent in position 3 are excluded from correlations, because the mathematical calculation procedure does not allow registering the influence of the substituent's different positions on the compounds' lipophilicity.

*Table 5. Correlation matrix for R_M^0- logP, m- logP and C_0- log*P*

log*P*	*r*					
	2- propanol			dioxane		
	R_M^0	*m*	C_0	R_M^0	*m*	C_0
AClog*P*	0.966	0.944	0.953	0.988	0.985	0.962
Alog*P*	0.971	0.953	0.960	0.987	0.982	0.972
AlogP_s	0.953	0.945	0.951	0.954	0.961	0.934
Mlog*P*	0.976	0.974	0.974	0.961	0.958	0.968
milog*P*	0.982	0.972	0.976	0.989	0.987	0.978
kowwin	0.935	0.928	0.938	0.932	0.929	0.935
log$P_{ch.s}$	0.960	0.941	0.947	0.991	0.978	0.957
XlogP_3	0.928	0.924	0.926	0.925	0.917	0.933

Based on the results shown in Table 5, it can be noticed that equally good dependencies were obtained in both applied modifiers. Among the divided coefficients, the best agreement with all chromatographic parameters (R_M^0, *m* and C_0) was shown by milog*P*, and the weakest by XlogP_3. Also, among the chromatographic parameters, the best agreement with all values of the partition coefficient was shown by the chromatographic retention constant R_M^0. High values of the regression coefficient r confirm that the established linear dependences are valid.

3.2. Relationship of chromatographic parameters with pharmacokinetic predictors and ecotoxicity parameters

The data in Table 6 show that the most lipophilic derivative (–I) has the highest P_{eff} value and the highest degree of binding to plasma proteins, while the weakest absorption and the highest percentage of free molecule in the blood was obtained for the most polar derivative (–OH). Also, all of the compounds studied can cross the blood-brain barrier because they meet „Rule 2". However, taking into account logBBB values, only derivatives with alkyl and halogen substituents (logBBB > 0.3) can be considered neuroactive.

The EC_{50} values of the studied amide derivatives for the selected test organisms shown in Table 8 show that the derivative with –I as a substituent is the most toxic among all tested amides, while all tested derivatives show the highest toxicity to Algae species. Using linear regression, the chromatographic parameters (R_M^0, *m* and C_0) of the tested amides were correlated with the values of their pharmacokinetic predictors and ecotoxicity parameters. The correlation matrix of the obtained linear dependences is shown in Table 7.

The high values of the regression coefficient r, given in Table 7, confirm the validity of the established linear dependences.

Table 6. Selected molecular descriptors, pharmacokinetic predictors and EC_{50} values of the studied amide derivatives for selected test organisms

R	MW	NHBD	NHBA	P_{eff} (cms^{-1})	PPB (%)	log BBB	*Algae*	*Daphnia*	*Medaka*	*Minnow*
H	169.611	1	2	3.536	45.460	0.20	0.119	0.676	0.552	0.267
4-CH_3	183.638	1	2	4.243	76.381	0.31	0.075	0.410	0.213	0.143
4-OCH_3	199.637	1	3	3.254	64.104	0.20	0.103	0.618	0.479	0.279
4-Cl	204.056	1	2	4.857	80.003	0.42	0.067	0.284	0.113	0.082
4-Br	248.507	1	2	5.213	84.802	0.47	0.061	0.227	0.078	0.066
4-F	187.601	1	2	4.559	63.506	0.24	0.094	0.556	0.378	0.134
4-I	295.507	1	2	5.579	91.062	0.58	0.067	0.113	0.029	0.029
4-$COCH_3$	211.648	1	3	3.679	61.698	0.14	0.126	0.698	0.630	0.344
4-OH	185.610	2	3	1.956	41.587	0.04	0.101	0.701	0.614	0.262
3-CN	194.621	1	3	2.366	62.242	0.03	0.129	0.492	0.326	0.183
4-CN	194.621	1	3	3.102	62.473	0.03	0.129	0.506	0.342	0.182
3-Br	248.507	1	2	4.546	84.933	0.46	0.061	0.205	0.064	0.066

Table 7. Correlation matrix obtained for chromatographic parameters- EC_{50} values relationships

	r					
	2-propanol*			dioxane**		
	R_M^0	*m*	C_0	R_M^0	*m*	C_0
P_{eff}	0.957	0.959	0.961	0.937	0.935	0.948
PPB	0.863	0.848	0.857	0.880	0.864	0.879
log *BBB*	0.981	0.966	0.970	0.991	0.992	0.970
Algae	0.908	0.923	0.918	0.883	0.903	0.964
Daphnia	0.993	0.992	0.994	0.987	0.979	0.971
Medaka	0.968	0.976	0.974	0.973	0.958	0.989
Minnow	0.953	0.966	0.951	0.957	0.948	0.978

* derivatives with 4–OCH_3, 4–$COCH_3$, 4–OH and 4–CN are excluded from the correlation
** 4–OH and 4–CN derivatives are excluded from the correlation

4. CONCLUSION

The evaluation of the biological/ pharmacological potential of selected amide derivatives was performed by studying their lipophilicity, pharmacokinetic and ecotoxic properties. Chromatographic parameters (R_M^0, *m* and C_0) of the tested derivatives as reliable alternative measures of their lipophilicity were determined using RPTLC in the presence of two organic modifiers. It was found that lipophilicity, ADMET properties and ecotoxicity of the tested derivatives predominantly depend on the polarity of the benzene ring-bound substituent. Theoretically, derivatives with alkyl and halogen substituents have a predisposition for the best intestinal absorption, the highest degree of binding to plasma proteins, as well as the possibility of passing through the blood-brain barrier. They also show the greatest ecotoxicity to selected test organisms. The established linear dependences between chromatographic parameters (R_M^0, *m* and C_0) of the examined amide derivatives and their software obtained values of pharmacokinetic predictors, i.e. ecotoxicity parameters indicate that they can be accurately and reliably applied as alternative molecular descriptors of biological activity of studied derivatives.

5. ACKNOWLEDGEMENTS

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ПРИМЕНА ХРОМАТОГРАФСКИХ ПАРАМЕТАРА У ПРОЦЕНИ БИОЛОШКОГ ПОТЕНЦИЈАЛА ДЕРИВАТА АМИДА

Сажетак: У модерном дизајну новог молекула се, за успостављање квалитативне/ квантитативне зависности између његове структуре, физичко-хемијских својстава и биолошке активности, све више користи *in silico* приступ. Избор и примена одговарајућих молекулских дескриптора важан су корак у овом процесу. С обзиром на присуство амидне групе у бројним фармаколошки и биолошки активним молекулима, у фармацеутској и хемијској индустрији њено формирање представља вечити изазов и битну трансформацију у дизајну синтетског плана. Процена биолошког потенцијала одабраних деривата амида обухватала је теоријско и експериментално одређивање њихове липофилности, оцену њихове биорасположивости, проучавање њихових фармакокинетичких предиктора и параметара екотоксичности. Параметри (R_M^0, m и C_0) добијени применом танкослојне хроматографије на обрнутим фазама у присуству два органска модификатора, као претпостављена мерила липофилности испитиваних амидних деривата, корелисани су са проучаваним параметрима биолошке активности методом линеарне регресије. Квалитет добијених метематичких модела потврђен је вредностима валидационих статистичких параметара.

Кључне речи: деривати амида, липофилност, биорасположивост, параметри биолошке активности липофилност, токсичност.

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