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

Suzana Apostolov[1], Borko Matijević[1], Gorana Mrđan [1], Đenđi Vaštag [1]
[1] University of Novi Sad, Faculty of Sciences, Departmant of Chemistry, Biochemistry and Environmental Protection, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia,
suzana.apostolov@dh.uns.ac.rs

Abstract

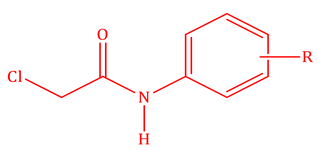
In silico approach is increasingly used in modern design to establish the qualitative/ quantitative dependence between structure, physico-chemical properties and biological activity of the new molecule. The selection and application of appropriate molecular descriptors are important step in this process. 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.

Figure 1 Application of amide derivatives

Methods

- Ethanol solutions of the studied amide derivatives were made in the concentration of 2 mg mL^{-1} (J.T. Baker, The Netherlands)
- Commercial plates RPTLC C18/UV254s Macherey-Nagel, were stationary phase
- Chromatograms were developed in water-*2*-propanol (J.T. Baker, Netherlands) and water-dioxan (J.T. Baker, The Netherlands) mixtures
- The volume fraction of the organic modifier, φ, in the mobile phase was varied in the range 0.36-0.52 v/v
- The chromatographic retention constant, R_M^0, chromatographic parameter, m, and parameter C_0, were calculated
- The processing of experimental results was done by the computer program Origin 6.1
- VCCLAB 2007, SimulationPlus and PreADMET were used to calculate the coefficients, log *P*, and selected pharmacokinetic parameters and parameters of toxicity

Table 1 Structures of the studied derivatives



Compound	Substituent	Compound	Substituent
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

$$R_M = R_M^0 + m\varphi$$

$$C_0 = R_M^0/m$$

Results and Discussions

Table 2 Chromatographic parameters R_M^0, m and C_o obtained in applied organic modifiers

R	modifier							
	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	-2.42	0.999	0.352	0.754	-1.931	0.999	0.39
4-OH	0.605	-1.974	0.999	0.306	0.617	-1.764	0.996	0.35
3-CN	0.775	-2.27	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

Table 3 logP values of the examined amide derivatives obtained by calculation

R	AClog*P*	Alog*P*	AlogP_s	Mlog*P*	milog*P*	*kowwin*	logPch.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

Table 4 Values of correlation coefficient, r, *for the obtained linear relationships R_M^0- log P, m- log P and C_0- logP*

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
Alog P_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
Xlog P_3	0.928	0.924	0.926	0.925	0.917	0.933

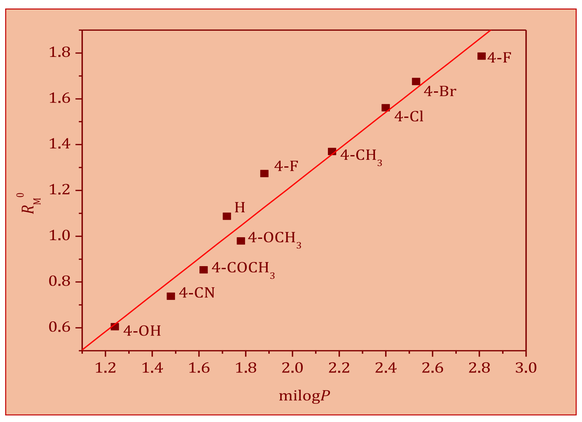


Figure 2 R_M^0- milog P obtained in 2-propanol

Table 5 Pharmacokinetic predictors of studied amides

R	P_{eff}	*PPB*	log*BBB*
H	3.536	45.46	0.20
4-CH_3	4.243	76.38	0.31
4-OCH_3	3.254	64.10	0.13
4-Cl	4.857	80.00	0.42
4-Br	5.213	84.80	0.47
4-F	4.559	63.51	0.24
4-I	5.579	91.06	0.58
4-$COCH_3$	3.679	61.70	0.14
4-OH	1.956	41.59	0.04
3-CN	2.366	62.42	0.03
4-CN	3.102	62.42	0.03
3-Br	4.546	84.80	0.47

Table 6 Values of the EC_{50} of the tested compounds for selected test organism

R	*Algae*	*Daphnia*	*Medaka*	*Minnow*
H	0.119	0.676	0.552	0.267
4-CH_3	0.075	0.410	0.213	0.143
4-OCH_3	0.103	0.618	0.479	0.279
4-Cl	0.067	0.284	0.113	0.082
4-Br	0.061	0.227	0.078	0.066
4-F	0.094	0.556	0.378	0.134
4-I	0.067	0.113	0.029	0.029
4-$COCH_3$	0.126	0.698	0.630	0.344
4-OH	0.101	0.701	0.614	0.262
3-CN	0.129	0.492	0.326	0.183
4-CN	0.129	0.506	0.342	0.182
3-Br	0.061	0.205	0.064	0.066

Table 7 Correlation matrix of the obtained models

EC_{50}	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

Conclusion

- The retention behaviour of the investigated amide derivatives is largely conditioned by the nature of the substituent *R* and less by the used organic modifier.
- Chromatographic parameters, R_M^0, m and C_0 of the examined compounds are in a linear dependence with partition coefficient log *P* and with their pharmacokinetic and toxicity parameters, also.
- Chromatographic parameters can be reliably applied to describe potential biological activity of the studied amides

Acknowledgment

The authors acknowledge financial support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 451-03-68/2020-14/ 200125).