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QSRR DESCRIPTORS AS A TOOL IN THE STUDY OF THE BARBITURIC ACID DERIVATIVES' BIOLOGICAL PROFILE

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Abstract: Thanks to the *in silico* approach in drug design, the identification of new molecules is enabled and facilitated, as well as the optimization of the pharmacokinetics and toxicity of compounds obtained from different sources. Chromatographic methods, on the other hand, provide accurate and reliable information on the influence of the nature of substituents and applied organic modifiers on the pharmacological behavior of compounds, relying on the existence of similarities between intermolecular interactions that determine compound behavior in biological and chromatographic media. Barbituric acid derivatives were subjected to QSRR analysis and the parameters obtained by reversed phase thin layer chromatography (RP TLC18 F254s) were correlated with selected software-derived predictors of permeability, pharmacokinetics and toxicity using the method of linear regression. Thus satisfactory mathematical models were obtained.

Keywords: barbituric acid derivatives, chromatography, permeability, pharmacokinetics, toxicity.

1. INTRODUCTION

Drug development is a complex, long-term and expensive process, goal is the identification and marketing of a safe and effective product with the desired pharmacological effect in the body. According to recent estimates, it takes an average of more than 12 years from the synthesis of a new drug to its arrival on the market, and development costs reach as much as 2.8 billion dollars [1]. The evaluation of each drug is a necessary step in its development, whereby out of about 5.000 – 10.000 potentially suitable compounds, 250 enter preclinical testing, five undergo clinical trials, and only one is approved and reaches the market [2].

The preclinical phase begins with the discovery of a new compound with the desired activity, which is most often achieved by modifying the structure of an existing drug, screening libraries of natural and synthetic compounds, or synthesizing a rationally designed molecule based on the application of QSAR (Quantitative Structure-Activity Relationship) knowledge [3]. Inadequate absorption, distribution, metabolism, elimination and toxicity (ADMET properties) of a potential drug are the main causes of failure of many late-stage studies. Bearing in mind that the evaluation of the efficacy and safety of the pharmacological effect of a new drug candidate must include in vivo experiments, the rationalization of research is increasingly achieved by an in silico approach to drug design [4]. Apart from the mentioned identification/de novo design of new molecules, this approach also enables the optimization of pharmacokinetics and toxicity of compounds obtained from different sources, as well as the elimination of unsuitable compounds in the preclinical phase and the prevention of unnecessary experiments on animals.

The study of lipophilicity, a physicochemical parameter closely related to bioavailability and ADMET properties of a biologically active compound (drug) is of great importance in QSAR and QSPR (Quantitative Structure-Property Relationship) studies during the definition of its pharmacokinetic and pharmacodynamic profile [5]. Thanks to the existence of similarities between intermolecular interactions that determine the behavior of compounds in biological and chromatographic environments, chromatographic parameters are applied as alternative measures of lipophilicity of compounds [6-11]. In addition, recent research has confirmed the possibility of applying chromatographic parameters in the assessment of pharmacokinetic and toxic properties of new compounds [12-16].

Based on the previous knowledge about the retention behavior of selected barbiturate derivatives in different chromatographic systems, as well as the established reliability of applying the parameters obtained by reversed phase thin-layer chromatography (RPTLC) in the assessment of their lipophilicity, the aim of this work was to study the dependence between of the mentioned chromatographic parameters of barbiturates (R_M^0 and m) and software-derived predictors of their pharmacokinetics and toxicity. The obtained linear dependencies indicated a wider and valid application of chromatographic parameters (R_M^0 and m) as QSRR (Quantitative Structure-Retention Relationship) descriptors in the evaluation of the biological profile of selected barbiturate derivatives.

2. EXPERIMENTAL

Selected barbituric acid derivatives (Table 1) were subjected to RPTLC C18/UV_{254s} in different systems of water - organic modifier, during which the values of the chromatographic parameters R_M^0 and m were determined [17,18].

Appropriate pharmacokinetic predictors were calculated for the studied derivatives by using the SimulationPlus program:

$S+P_{eff}$ (human effective permeability in jejunum [10^{-4} cms^{-1}]) − human effective permeability in jejunum; *S+MDCK* (Madin-Darby canine kidney cell permeability line [10^{-7} cms^{-1}]) − permeability of Madin-Darby canine kidney epithelial cells;

$S+P_{Cornea}$ (Permeability Through The Rabbit Cornea [10^{-7} cms^{-1}]) – permeability of the rabbit cornea; $S+P_{Skin}$ (Permeability through human skin [10^{-7} cms^{-1}]) – permeability of human skin;

S+logBB (logarithm of the Blood-Brain Barrier Partition Coefficient ($\log(C_{brain}/C_{blood})$ – permeability of the blood-brain barrier;

hum fup, rat fup (Human and plasma protein binding as percent unbound [%]) − binding to plasma proteins in humans and rats expressed as a percentage of unbound compound;

Vd (Human volume of distribution [Lkg^{-1}]) – volume of distribution in humans;

RBP, RBP rat (Human and rat blood-to-plasma concentration ratio) – ratio of compound concentration in blood and plasma of humans and rats;

S+fumic (Fraction unbound in human liver microsomes) − unbound fraction in human liver microsomes;

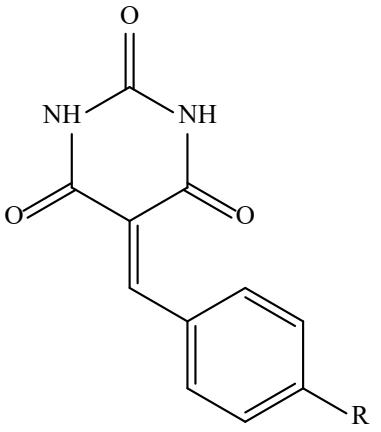
and predictors of toxicity:

TOX ATTP (the acute toxicity to *Tetrahymena pyriformis*, expressed as $Th\_pyr\_pIGC_{50}$ [$mmolL^{-1}$] − acute toxicity to Tetrahymena pyriformis expressed as $Th\_pyr\_pIGC_{50}$;

TOX FHM (the acute toxicity to *Pimephales promelas*, expressed as $Minnow\ LC_{50}$ [mgL^{-1}]) –

Table 1. *Structures of the tested barbituric acid derivatives*

Compound	*R*
1.	H
2.	OC_2H_5
3.	OCH_3
4.	CH_3
5.	F
6.	Br
7.	Cl
8.	OH
9.	NO_2
10.	$CH(CH_3)_2$
11.	CN



acute toxicity to Pimephales promelas expressed as *Minnow* LC_{50} value;

TOX DM (the acute toxicity to *Daphnia magna*, expressed as *Daphnia* LC_{50} [mgL^{-1}]) − acute toxicity to the species Daphnia magna expressed by the *Daphnia* LC_{50} value;

TOX BCF (the environmental toxicity based on bioconcentration factor (BCF) - environmental toxicity defined by the bioconcentration factor that describes the accumulation of pollutants that is distributed between the water and organic phases (aquatic organisms);

TOX RAT (the acute toxicity to rats, expressed as *Rat* LC_{50} [mgL^{-1}]) − acute toxicity to rats expressed as *Rat* LC_{50} *value*;

TOX BRM Rat (toxicity to rats, expressed as *Rat* TD_{50} [$mgkg^{-1}day^{-1}$] − toxicity to rats expressed by the value of an oral dose of a compound that causes a tumor in 50% of individuals in a rat population after their exposure during a standard lifetime, *Rat* TD_{50};

TOX BRM Mouse (toxicity to mice, expressed as *Mouse* TD_{50} [$mgkg^{-1}day^{-1}$] − toxicity to mice expressed by the value of an oral dose of a compound that causes a tumor in 50 % of individuals in a mouse population after exposure during a standard lifetime, *Mouse* TD_{50} [19]. The experimental results were processed using the computer program Origin 6.1.

3. RESULTS AND DISCUSSION

3.1. ADMET properties of the studied barbituric acid derivatives

The software calculated values of pharmacokinetic predictors and predictors of toxicity of the studied barbituric acid derivatives are shown in Table 2 and Table 3.

Low bioavailability is the control point for further development of the drug. Taking into account that the ways of drug administration are numerous, and that oral administration would be the most desirable, optimization of its solubility, permeability through biological barriers in the body, as well as exposure to metabolism in the intestinal tract are of crucial importance for achieving appropriate bioavailability [20].

Bearing in mind the fact that the passage of compounds through biological barriers is largely determined by their lipophilicity, it is expected that lipophilic derivatives will show better permeability. In silico values of permeability predictors (Table 2) confirmed that derivatives with non-polar and halogen substituents penetrate better through kidney epithelial cells, skin and cornea, in contrast to derivatives with polar substituent.

The derivative with $-NO_2$ as a substituent could have the best permeability through the je-

Table 2. *The selected pharmacokinetic predictors of the studied barbituric acid derivatives*

R	*S+* P_{eff}	*S+ MDCK*	*S+ PCornea*	*S+ PSkin*	*S+ logBB*	*hum fup PPB*	*rat fup PPB*	*Vd*	*RBP*	*RBP rat*	*S+ fumic*
H	1.492	200.890	53.481	7.242	-0.604	12.665	20.202	0.262	0.772	0.781	0.903
OC_2H_5	0.956	190.896	41.137	12.090	-0.746	8.961	15.312	0.263	0.669	0.698	0.841
OCH_3	1.069	213.981	35.751	8.986	-0.728	10.773	18.011	0.244	0.650	0.708	0.888
CH_3	1.467	214.939	60.366	10.095	-0.642	11.091	15.301	0.278	0.666	0.790	0.872
F	1.991	259.259	66.929	11.909	-0.477	10.442	16.734	0.251	0.747	0.780	0.873
Br	1.918	201.699	70.311	20.091	-0.571	8.342	13.931	0.196	0.764	0.718	0.832
Cl	2.243	323.672	72.267	12.010	-0.527	8.606	10.375	0.243	0.755	0.789	0.832
OH	0.820	49.255	24.210	3.453	-0.683	15.718	23.881	0.220	1.061	0.706	0.928
NO_2	3.312	75.836	17.658	1.811	-0.644	19.084	30.104	0.286	0.785	0.832	0.917
$CH(CH_3)_2$	1.241	203.761	76.601	16.828	-0.560	8.225	12.601	0.327	0.638	0.799	0.745
CN	1.756	165.520	56.887	10.414	-0.878	10.457	18.850	0.225	0.587	0.796	0.912

Table 3. *The selected toxicity predictors of the studied barbituric acid derivatives*

R	*Th pyr* $pIGC_{50}$	*Minnow* LC_{50}	*Daphnia* LC_{50}	*Bioconc*	*Rat acute*	*Rat* TD_{50}	*Mouse* TD_{50}
H	-0.425	33.309	1.164	1.471	516.054	55.557	1128.951
OC_2H_5	-0.323	12.134	0.406	2.522	444.357	55.469	1370.685
OCH_3	-0.455	19.539	0.245	2.259	375.310	54.824	1314.966
CH_3	-0.243	26.452	0.505	1.698	413.500	38.164	1017.209
F	-0.351	32.706	0.897	2.242	200.001	90.379	1404.735
Br	0.040	15.645	0.773	2.405	190.041	81.648	1182.909
Cl	-0.015	10.328	0.286	2.388	426.045	80.138	1028.007
OH	-0.553	28.361	0.957	1.428	668.297	187.594	1713.516
NO_2	-0.302	3.030	3.932	1.432	454.761	30.735	1185.371
$CH(CH_3)_2$	0.138	14.417	0.577	2.043	425.246	33.453	1069.532
CN	-0.344	10.964	0.154	1.533	416.314	42.211	1104.849

junum wall, while the derivative with −OH group, as the least lipophilic, has the lowest $S+P_{eff}$ value. Given the primary use of barbituric acid derivatives, the values of the blood-brain barrier distribution parameter *logBB* were not surprising. Namely, they indicate the potential neuroactivity of all the tested derivatives, since they show a medium level of absorption into the central nervous system (log*BB* 0.3 ~ -1.0) [21].

It was also observed that the derivative with the −OH group as a substituent (*RBP* > 1) has an increased risk of accumulation in erythrocytes, and therefore potential hematotoxicity for humans [22].

Among the studied compounds, derivatives with polar substituents (–OH, $–NO_2$ and –CN) have a low binding capacity for plasma proteins. High values of predictor *Vd* are characteristic of lipophilic compounds, due to which they are widely distributed in tissues, especially in adipose tissue [23]. Accordingly, the highest *Vd* value has the most lipophilic derivative ($–CH_3$).

The fraction of unbound drug in human liver microsomes represents an important parameter for the assessment of internal clearance in the liver and drug-drug interactions (fumic fraction). It is determined by the lipophilicity of the compound, the degree of its ionization, the class of studied compounds and the concentration of microsomal proteins, i.e. it can be considered the result of a combination of two different processes – non-specific binding of the drug to neutral lipids and ionic binding to acidic phospholipids [24]. Among the tested compounds, the most polar derivative (−OH) has the highest fumic fraction value, which is in accordance with previous research [25].

Based on the data from Table 3, it can be noted that on average, the most polar derivative (–OH) would show the lowest toxicity to all test organisms, while the highest degree of accumulation in aquatic organisms would be derived from derivatives with non-polar and halogen substituents.

3.2. Quantitative relationship of chromatographic parameters and software-derived ADMET predictors

In order to make the results easier to understand, Table 4 and Table 5 list the chromatographic parameters of the studied barbituric acid derivatives, previously determined in mixtures of water and various organic modifiers [17,18].

Table 4. *Values of chromatographic parameters of tested derivatives in protic modifiers*

R	methanol			1-propanol			2-propanol		
	R_M^0	*m*	r	R_M^0	*m*	r	R_M^0	*m*	r
H	1.035	-1.331	0.997	0.390	-1.396	0.999	1.350	-3.465	0.998
OC_2H_5	1.335	-1.739	0.996	0.565	-1.662	0.996	1.586	-3.789	0.999
OCH_3	1.155	-1.465	0.996	0.451	-1.475	0.997	1.397	-3.510	0.999
CH_3	1.385	-1.815	0.997	0.658	-1.739	0.997	1.656	-3.907	0.997
F	1.269	-1.635	0.994	0.532	-1.607	0.995	1.438	-3.635	0.998
Br	1.646	-2.080	0.998	0.833	-1.985	0.999	1.843	-4.156	0.998
Cl	1.529	-1.955	0.999	0.735	-1.837	0.998	1.739	-4.054	0.999
OH	0.671	-0.936	0.994	0.115	-0.918	0.997	0.909	-2.705	0.999
NO_2	0.764	-1.148	0.998	0.222	-1.155	0.999	1.065	-2.920	0.999
$CH(CH_3)_2$	1.854	-2.348	0.998	0.951	-2.158	0.996	1.931	-4.278	0.997
CN	0.730	-1.107	0.998	0.185	-1.058	0.996	1.001	-2.803	0.999

Table 5. *Values of chromatographic parameters of tested derivatives in aprotic modifiers*

R	acetone			tetrahydrofurane			acetonitrile		
	R_M^0	*m*	r	R_M^0	*m*	r	R_M^0	*m*	r
H	1.269	-2.555	0.999	0.813	-2.385	0.994	0.985	-1.970	0.996
OC_2H_5	1.514	-2.775	0.999	1.055	-2.579	0.998	1.224	-2.280	0.998
OCH_3	1.304	-2.597	0.995	0.848	-2.439	0.996	1.106	-2.111	0.997
CH_3	1.556	-2.800	0.999	1.110	-2.605	0.998	1.331	-2.357	0.999
F	1.471	-2.748	0.998	1.025	-2.555	0.998	1.085	-2.085	0.996
Br	1.781	-3.009	0.999	1.335	-2.755	0.998	1.505	-2.503	0.997
Cl	1.652	-2.892	0.999	1.185	-2.648	0.997	1.413	-2.440	0.998
OH	0.858	-2.275	0.988	0.408	-2.085	0.994	0.654	-1.622	0.999
NO_2	1.069	-2.425	0.998	0.589	-2.233	0.998	0.810	-1.735	0.996
$CH(CH_3)_2$	1.839	-3.065	0.998	1.389	-2.860	0.999	1.593	-2.594	0.998
CN	0.955	-2.365	0.991	0.515	-2.163	0.996	0.737	-1.685	0.999

Table 6. *Correlation matrix between ADMET predictor values of the tested barbituric acid derivatives and their chromatographic parameters, R_M^0 and m*

	r					
	S+*PCornea**	*S+Perm Skin**	*hum fup**	*rat fup**	*S+fumic*	*Th pyr pIGC50***
methanol						
R_M^0	0.883	0.930	0.890	0.888	0.930	0.965
m	0.864	0.911	0.853	0.858	0.940	0.957
1-propanol						
R_M^0	0.886	0.922	0.863	0.869	0.920	0.975
m	0.878	0.919	0.865	0.858	0.914	0.967
2-propanol						
R_M^0	0.870	0.913	0.887	0.887	0.890	0.967
m	0.891	0.910	0.906	0.907	0.867	0.974
acetone						
R_M^0	0.884	0.925	0.872	0.865	0.888	0.963
m	0.883	0.934	0.865	0.860	0.907	0.960
tetrahydrofurane						
R_M^0	0.891	0.932	0.879	0.871	0.888	0.957
m	0.876	0.924	0.874	0.859	0.907	0.943
acetonitrile						
R_M^0	0.847	0.903	0.862	0.871	0.898	0.957
m	0.844	0.902	0.892	0.900	0.888	0.936

Application possibility of parameters R_M^0 and *m* as QSRR descriptors in the assessment of pharmacokinetic and toxic properties of barbituric acid derivatives was examined by their correlation with software obtained ADMET predictors using the linear regression method. Table 6 shows the correlation matrix of obtained relationships.

* derivative with −CN group excluded from correlation

** derivatives with –OH, $–NO_2$ and –CN group excluded from correlation

4. CONCLUSION

Although barbituric acid derivatives were primarily considered as misused depressants of the nervous system that often led to fatal outcomes, today their application is very broad. Simpler identification of a new molecule (barbituric acid derivative), optimization of its pharmacokinetic and toxic properties in order to obtain an effective and safe drug, is possible with an *in silico* approach. In this work, the values of important ADMET predictors were calculated by software for selected barbituric acid derivatives, and it was confirmed that their pharmacokinetic and toxic properties are largely determined by their lipophilicity, that is, the type of substituent present in the molecule. Relying on the results of previous research, the chromatographic parameters R_M^0 and *m* obtained by thin-layer chromatography on reversed phases, as alternative measures of their lipophilicity, were correlated with software-derived ADMET predictors, and linear relationships were obtained ($r > 0.844$). The obtained results confirmed the possibility of applying chromatographic parameters as QSRR descriptors in the assessment of the toxicity of barbituric acid derivatives on different test organisms, but also established the reliability of their application in the evaluation of certain pharmacokinetic properties of these derivatives. From all of the above, it can be concluded that the chromatographic parameters can be considered a simply obtained, but reliable tool for assessing the existence of biological activity of the tested barbituric acid derivatives.

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QSRR ДЕСКРИПТОРИ КАО АЛАТ У ПРОУЧАВАЊУ БИОЛОШКОГ ПРОФИЛА ДЕРИВАТА БАРБИТУРНЕ КИСЕЛИНЕ

Сажетак: Захваљујући *in silico* приступу у дизајну лекова, омогућена је и олакшана идентификација нових молекула, као и оптимизација фармакокинетичких и токсичних својстава једињења добијених из различитих извора. Хроматографске методе, пак, обезбеђују тачне и поуздане информације о утицају природе супституента и примењених органских модификатора на фармаколошко понашање једињења, ослањајући се на постојање сличности између међумолекулских интеракција које одређују понашање једињења у биолошкој и хроматографској средини. Деривати барбитурне киселине подвргнути су QSRR анализи и параметри добијени танкослојном хроматографијом на обрнутим фазама (RP TLC18 F_{254s}) корелисани су са одабраним софтверски добијеним предикторима пермеабилности, фармакокинетике и токсичности применом методе линеарне регресије. Притом су добијени задовољавајући математички модели.

Кључне речи: деривати барбитурне киселине, хроматографија, пермеабилност, фармакокинетика, токсичност.

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