LIPOPHILICITY OF SCHIFF BASES OF SUBSTITUTED THIAZOLYL BROMOCOUMARINS BY CHEMBIODRAW – PERKINELMER AND ALOGPS 2.1

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Lipophilicity is a well-known thermodynamical parameter with a major role in research of the structure-activity relationship caused by drug action and has been theoretically predicted for few proposed coumarin derivatives, using commercial software ChemBioDraw 3D Ultra - PerkinElmer and internet computational software called ALOGPS 2.1. The compounds analyzed for lipophilicity, using different QSAR predicting programs, present very appropriate data, based on the studied functional groups. The partition coefficient values of the compounds were found to lie within 3 and 6. Theoretical determination of lipophilicity reduces the time involved in calculation of lipophilicity by experimental methods.

Keywords: Lipophilicity, Coumarin derivatives, ChemBioDraw - PerkinElmer, ALOGPS 2.1

1. Introduction

Coumarin is a natural product identified as secondary metabolites from plants, bacteria, and fungi [1]. Different coumarins found in many plants, such as apricots, cherries, cinnamon, lavender, licorice, strawberries, sweet clover grass, Tonka bean etc., and have been used by many researchers to synthesize new derivatives [2-7]. Use of natural products as synthetic precursors to design new molecules with various interests has been of long standing demand [8]. Several of the coumarin derivatives have been reported for various pharmacological activity such as anti-inflammatory [9], anti-hypertensive [10], antibacterial [11], antifungal [12], anti-oxidant [13], anti-HIV [14], hepatoprotective [15], anti-thrombotic, anticonvulsant [16], antihyperglycemic [17], antitubercular [18], anti-viral [19], neuroprotective [20] and anti-cancer activities [21]. Aminothiazolyl

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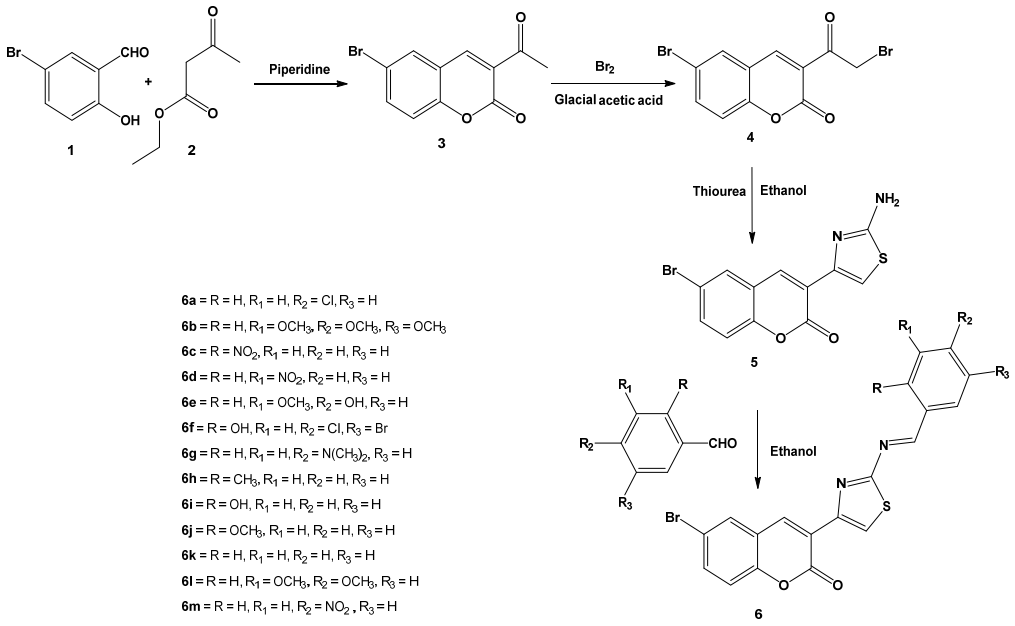
bromocoumarin and its Schiff bases exhibited promising *in-vitro* antimicrobial [22], *in-vivo* analgesic and anti-inflammatory activities [23]. The Schiff bases of coumarin are well known for their fluorescent properties and usefulness as laser dyes [24]. This has inspired us to calculate lipophilicity, which is a measure of the degree to which a given molecule prefers hydrophobic nonpolar environments to water. Since the concept of lipophilicity is so important in medicinal chemistry, many schemes have been developed to estimate this property as expressed by the partition coefficient Log P [25, 26]. Log P is closely related to the transport properties of drugs and their interaction with receptors. Scientific computation is not an end itself. It must be implemented in the context of problems to be solved. Determination of Log P values of organic compounds, including drugs, has special significance if standard substances are not available. This parameter can be either determined experimentally or calculated. Because experimental measurements are time consuming and difficult, computational methods are very valuable tools for calculation of Log Ps for large sets of compounds in quantitative structure activity relationship (QSAR) studies, particularly at the screening stage [27]. A number of different computer programs for prediction of lipophilicity have been recently developed. Since lipophilicity has been recognized for its importance in QSAR studies [28] efforts have been made to determine the Log P (logarithm of partition coefficient in *n*-octanol/water) values of few coumarin derivatives.

In this paper, the partition coefficients of the synthesized compounds were predicted theoretically by using commercial software like ChemBioDraw - PerkinElmer and an internet based computational software ALOGPS 2.1.

The title compounds have been synthesized, characterized and studied for analgesic and anti-inflammatory properties [23]. The intermediate 5 was subjected for single crystal X-ray method and found C-H----O intermolecular interactions [29]. The synthetic scheme of the molecules studied is given in Scheme 1.



Scheme 1: Synthesis of Schiff bases of aminothiazolyl bromocoumarins (**6a-6m**)

2. Materials and Methods

2.1. Prediction of lipophilicity

Thirteen Schiff bases of aminothiazolyl bromocoumarin derivatives (**6a-m**) have been chosen for the study (Figure 1).

2.1.1. ChemBioDraw Ultra 13 from PerkinElmer

The computer program ChemBioDraw - PerkinElmer predicts Log P values using the atom-additive method according to Ghose, Prichett and Crippen [30]. Their approach avoids correction factors and calculates lipophilicity on an individual atom basis by employing a large number of atom types. The following equation (1) is used to calculate the *n*-octanol-water partition coefficient:

$$\text{Log P} = \sum_{i=1}^{n} (n_i a_i) \quad (1)$$

where: - n_i is the number of atoms of type i, and - a_i is the contribution of the corresponding atom type.

The program lists atom contributions for each atom type and calculates the Log P value by summing up all atom contributions.

2.1.2. ALOGPS 2.1

The ALOGPS 2.1 package includes routines to predict lipophilicity and aqueous solubility of chemical compounds. A method for predicting Log P values based on atom-type electro-topological-state (E-state) indices and associative neural network modeling was developed by Tetko *et al*. [31]. This method combines electronic and topological characters to predict lipophilicity of the analyzed molecules. After E-state indices are assigned to each atom type according to the neighboring atoms, the estimated Log P value of the target compound is obtained.

2.2. Prediction of toxicity

In addition to lipophilicity computational calculation, we have undertaken toxicity prediction also with the following programs:

2.2.1 Software used for toxicological parameters

For the estimation of the parameters of new proposed compounds we have used the latest version of QSAR software VegaNIC [32] which provides prediction and applicability domain analysis for the following models:

2.2.2. Mutagenicity model (CAESAR) (version 2.1.10)

QSAR classification model for Mutagenicity based on a Support Vector Machine combined by a set of ToxTree rules developed by Benigni/Bossa. The model extends the original CAESAR Mutagenicity model 1.0 developed by Politecnico di Milano, Italy. Reference to the original model are found on the CAESAR Project website [33].

2.2.3. Mutagenicity SarPy model (version 1.0.5-BETA)

QSAR classification model for Mutagenicity based on a set of rules built with SarPy software. Developed by Instituto Mario Negri, Italy, SarPy software developed by Politecnico di Milano, Italy [32]. Model developed inside the VEGA platform.

2.2.4. Carcinogenicity model (CAESAR) (version 2.1.6)

QSAR classification model for carcinogenicity based on a Neural Network has been developed by Kemijski institute Ljubljana, Slovenija. The model extends the original CAESAR Carcinogenicity model 1.0 [33]. Results are given as membership function values of class Positive and Non-Positive, compound is assigned to the class having value >0.5. Furthermore, structural alerts from ToxTree are searched, providing useful additional information.

2.2.5. Developmental Toxicity model (CAESAR) (version 2.1.4)

QSAR classification model for Developmental Toxicity based on a Random Forest classification is the model extends the original CAESAR DevTox model 1.0 developed by Istituto Mario Negri, Italy. Reference to the original model are found on the CAESAR Project website [33].

2.2.6. Skin Sensitization model (CAESAR) (version 2.1.3)

QSAR classification model for Skin sensitization based on an Adaptive Fuzzy Partition is the model extends the original CAESAR Skin model 1.0. The original model was developed inside the CAESAR Project [33].

2.2.7. BCF model (CAESAR) (version 2.1.11)

QSAR model for fish BCF, based on a Radial Basis Function neural network is the model extends the original CAESAR BCF model 1.0, full reference to the model [34]. The original model was developed inside the CAESAR Project [33].

2.2.8. BCF model (Meylan) (version 1.0.0)

Full reference of QSAR model for fish BCF, based on Meylan approach, as implemented in EPI Suite can be found in the EPI Suite help [35, 36] and this model was developed inside the VEGA platform.

2.2.9. BCF Read-Across (version 1.0.0)

Read-Across for fish BCF is based on the similarity index developed in VEGA. The read-across is performed on a dataset of 860 compounds (this dataset is continuously updated), extending the original BCF dataset contained in the CAESAR model [32].

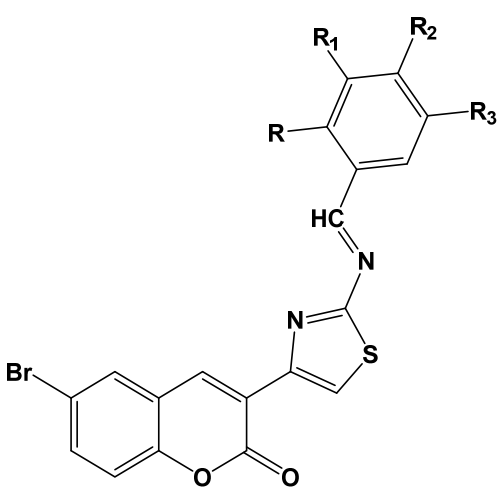
2.2.10. Ready Biodegradability model (version 1.0.6-DEV)

QSAR classification model for Ready Biodegradability based on fragments built by SarPy software was developed by Politecnico di Milano, Italy and Istituto di Ricerche Farmacologiche Mario Negri, Italy [32].

3. Results and Discussion

The results obtained are summarized in Table 1. The two computer programs showed to be relatively simple and applicable to QSAR studies. The widespread application of lipophilicity to QSAR studies easily explains the need for quick procedures to predict molecular lipophilicity. Routine application of computer programs demands a continuous check of their validity by comparison with other programs. We studied two commonly used calculation methods, based on different theoretical approaches, and correlated the calculated Log P values obtained from all used computational chemistry software. Our analysis

demonstrates a slight variation between the Log P value predicted by the commercial software ChemBioDraw – PerkinElmer and internet computational software ALOGPS 2.1.



6a = R = H, R_1 = H, R_2 = Cl, R_3 = H
6b = R = H, R_1 = OCH_3, R_2 = OCH_3, R_3 = OCH_3
6c = R = NO_2, R_1 = H, R_2 = H, R_3 = H
6d = R = H, R_1 = NO_2, R_2 = H, R_3 = H
6e = R = H, R_1 = OCH_3, R_2 = OH, R_3 = H
6f = R = OH, R_1 = H, R_2 = Cl, R_3 = Br
6g = R = H, R_1 = H, R_2 = $N(CH_3)_2$, R_3 = H
6h = R = CH_3, R_1 = H, R_2 = H, R_3 = H
6i = R = OH, R_1 = H, R_2 = H, R_3 = H
6j = R = OCH_3, R_1 = H, R_2 = H, R_3 = H
6k = R = H, R_1 = H, R_2 = H, R_3 = H
6l = R = H, R_1 = OCH_3, R_2 = OCH_3, R_3 = H
6m = R = H, R_1 = H, R_2 = NO_2 , R_3 = H

Fig. 1. Substitutions (R, R_1, R_2, and R_3) on phenyl ring which connects to thiazolyl bromocoumarin ring through azomethine group

Table 1

Prediction of Log P values for proposed compounds 6a-m

Compound code	*Structural formula (Molecular mass)*	*Log P*[1]	*Log P*[2]	*Log P*[3]
6a	$C_{19}H_{10}BrClN_2O_2S$ (445)	4.9583	4.19	5.16(± 0.49)
6b	$C_{22}H_{17}BrN_2O_5S$ (501)	3.9782	3.79	4.12 (± 0.90)
6c	$C_{19}H_{10}BrN_3O_4S$ (456)	3.9883	1.16	3.35 (± 0.88)
6d	$C_{19}H_{10}BrN_3O_4S$ (456)	3.9883	1.16	3.35 (± 0.87)
6e	$C_{20}H_{13}BrN_2O_4S$ (457)	4.3389	3.14	4.06 (± 0.70)
6f	$C_{19}H_{10}Br_2N_2O_3S$ (506)	5.4462	3.95	4.88 (± 0.60)
6g	$C_{21}H_{16}BrN_3O_2S$ (454)	4.9288	3.72	4.68 (± 0.53)
6h	$C_{20}H_{13}BrN_2O_2S$ (425)	4.7443	4.09	4.95 (± 0.42)
6i	$C_{19}H_{11}BrN_2O_3S$ (427)	4.4793	3.06	4.19 (± 0.54)
6j	$C_{20}H_{13}BrN_2O_3S$ (441)	4.5893	3.62	4.49 (± 0.53)
6k	$C_{19}H_{11}BrN_2O_2S$ (411)	4.2453	3.54	4.60 (± 0.42)
6l	$C_{21}H_{15}BrN_2O_4S$ (471)	4.3453	3.71	4.30 (± 0.76)
6m	$C_{19}H_{10}BrN_3O_4S$ (456)	3.9883	3.36	4.45 (± 0.44)

[1]ChemBioDraw 3D Ultra 13.0v
[2]VEGA NIC QSAR Model
[3]ALOGPS 2.1

LogP prediction (version 1.1.0 based on Meylan work [37] and implemented in EPI Suite software as KowWin. MLogP and ALogP descriptors are also calculated. Model developed inside the VEGA platform. Complete details on each model and on how to read results in the proper model's guide, are available online [32] or directly in the VegaNIC application [38].

According to the Lipinski's "rule of 5" [39, 40], the compounds with Log P values smaller than 5, have drug-likeliness potential and can be orally administered. A highly lipophilic compound will have low aqueous solubility comparing to bioavailability. In the compounds analyzed for lipophilicity using ChemBioDraw - PerkinElmer, the Log P values of all the other compounds were found to lie between 3.9883-5.4462. The Log P values calculated using ALOGPS 2.1 was comparatively greater than that calculated using ChemBioDraw - PerkinElmer.

T.E.S.T. (version 4.1) (Toxicity Estimation Software Tool), ©2012 U.S. Environmental Protection Agency, Todd Martin, PhD., Research Chemical Engineer.

Table 2

Predicted toxicity of compounds 6a-6m

Compound code	Mutagenicity[1]	Mutagenicity[2]	Carcinogenicity[3]
6a	NON-Mutagen	NON-Mutagen	NON-Carcinogen
6b	Mutagen	NON-Mutagen	NON-Carcinogen
6c	NON-Mutagen	NON-Mutagen	Carcinogen
6d	NON-Mutagen	NON-Mutagen	Carcinogen
6e	Mutagen	NON-Mutagen	NON-Carcinogen
6f	NON-Mutagen	NON-Mutagen	NON-Carcinogen
6g	Mutagen	Mutagen	NON-Carcinogen
6h	NON-Mutagen	NON-Mutagen	NON-Carcinogen
6i	Mutagen	NON-Mutagen	NON-Carcinogen
6j	Mutagen	NON-Mutagen	NON-Carcinogen
6k	Mutagen	NON-Mutagen	NON-Carcinogen
6l	Mutagen	NON-Mutagen	NON-Carcinogen
6m	NON-Mutagen	Mutagen	Carcinogen

Summary of prediction for models:

[1]Mutagenicity model (CAESAR) (version 2.1.10)

[2]Mutagenicity SarPy model (version 1.0.5-BETA)

[3]Carcinogenicity model (CAESAR) (version 2.1.6)

Table 2 continued

Compound code	Developmental Toxicity[4]	Skin Sensitisation[5]	BCF[6]	BCF[7]	BCF[8]
6a	Toxicant	Sensitizer	1.52	2.43	2.0
6b	Toxicant	Sensitizer	0.66	2.17	2.0

6c	Toxicant	Sensitizer	1.26	0.43	2.0
6d	Toxicant	Sensitizer	1.14	0.43	2.0
6e	Toxicant	Sensitizer	0.89	1.74	2.0
6f	Toxicant	Sensitizer	1.13	2.28	2.09
6g	Toxicant	Sensitizer	1.03	2.12	2.67
6h	Toxicant	Sensitizer	1.44	2.37	2.0
6i	Toxicant	Sensitizer	1.02	1.69	2.08
6j	Toxicant	Sensitizer	1.06	2.06	2.0
6k	Toxicant	Sensitizer	1.42	2.01	2.0
6l	Toxicant	Sensitizer	0.92	2.11	2.0
6m	Toxicant	Sensitizer	1.13	0.43	2.0

Summary of prediction for models:

[4]Developmental Toxicity model (CAESAR) (version 2.1.4)

[5]Skin Sensitization model (CAESAR) (version 2.1.3)

[6]BCF model (CAESAR) (version 2.1.11)

[7]BCF model (Meylan) (version 1.0.0)

[8]BCF Read-Across (version 1.0.0)

Lipophilicity is one of the most important characteristics connected to absorption, distribution, metabolism and excretion (ADME) properties. Since most of the drug-like molecules fail because of poor bioavailability, reliable predicted Log P value, based on the pre-selection of compounds, can dramatically decrease the drug research expenses. Moreover, the compounds chosen for the study obey Lipinski's "rule of 5", which is an obvious indication that these compounds can be further experimentally analyzed for them to be used as effective drugs. A consistent depiction on the applicability of calculation methods in lipophilicity studies can be obtained by studying numerous substances of variable lipophilicity.

To explain why we have started studying these compounds, let's see why plants produce a large variety of secondary products that contain a phenolic group, a chemically heterogeneous group. This could be an important part of the plants defense system against pests and diseases including root parasitic nematodes. As interesting aspects of plants cultivated in elevated ozone (mean 32.4ppb) have increased the total phenolic content of leaves and had minor effects on the concentration of individual compounds.

Coumarins are simple phenolic compounds, widespread in vascular plants and appear to function in different capacities in various plant defense mechanisms against insect herbivores and fungi. They derived from the shikimic acid common in bacteria, fungi and plants but absent in animals. Also, they are a highly active group of molecules with a wide range of antimicrobial activity against both fungi and bacteria. It is believed that these cyclic compounds behave as natural pesticide

defense compounds for plants and they represent a starting point for the exploration of new derivatives possessing a range of improved antifungal activity.

Halogenated coumarin derivatives work very effectively *in vitro* to inhibit fungal growth; hydroxylated simple coumarins may play a defensive role against parasitism of Orobanche cernua by preventing successful germination, penetration and connection to the host vascular system. Some coumarin derivatives have higher antifungal activity against a range of soil borne plant pathogenic fungi and exhibit more stability as compared to the original coumarin compounds alone.

Also a type of coumarin, Furanocoumarins, with special interest of phytotoxicity, abundant in members of the family Umbelliferae including celery parsnip and parsley. Normally, these compounds are not toxic, until they are activated by light (UV-A), causes some furanocoumarins to become activated to a high energy electronic state, which can insert themselves into the double helix of DNA and bind to the pyrimidine bases and thus blocking transcription and repair and eventually leading to cell death. Based on these we have synthetized modified coumarins and analyzed the resulted compounds. Even if they do not entirely satisfy the Lipinski rule they proved themselves as valuable compounds for future drugs.

Lipophilicity refers to the ability of a chemical compound to dissolve in fats, oils, lipids, and non-polar solvents such as hexane or toluene. Thus lipophilic substances tend to dissolve in other lipophilic substances, while hydrophilic (water-loving) substances tend to dissolve in water and other hydrophilic substances.

Lipophilicity, hydrophobicity, and non-polarity can describe the same tendency towards participation in the London dispersion force as the terms are often used interchangeably. However, the terms "lipophilic" and "hydrophobic" are not synonymous, as can be seen with silicones and fluorocarbons, which are hydrophobic but not lipophilic.

4. Conclusions

In this paper, the partition coefficients of some cumarine compounds were predicted theoretically by using commercial software like ChemBioDraw from Perkin-Elmer, VEGA Non-Interactive Client and an internet based computational software ALOGPS 2.1.

The title compounds have been analyzed in standard thermodynamically conditions. The results showed that predictions correlation is very tight in most of the aspects studied but in a few cases contradictory results are present. In future works we intend to do the experimental synthesis and analysis in order to establish the scientific values. The data will be supplied to all involved databases used in order to improve the accuracy of future predictions.

The computational chemistry provides a useful tool for organic chemistry synthesis and predictive evaluations of compounds. This can be also useful in reducing costs with classic synthesis and analysis, allowing the synthesis of valuable active compounds with minimum investments.

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