International Journal of Pharmacy Teaching & Practices 2013, Vol.4, Issue 1, 489-491.

Distribution Coefficient of Coumarin-Based Compounds Containing a Chalcone Moiety

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Research Article

Please cite this paper as: Selma ŠPIRTOVIĆ-HALILOVIĆ* [1], Davorka ZAVRŠNIK[1], Belma IMAMOVIĆ[2], Ervina BEČIĆ[2]. Distribution Coefficient of Coumarin-Based Compounds Containing a Chalcone Moiety. IJPTP, 2013, 4(1), 489-491.

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Abstract

Having in mind the results of our previous work, which suggested antimicrobial activity of 3-substitueted derivatives of 4-hydroxycoumarins containing a chalcone moiety, we carried out the synthesis of new derivatives. Those compounds are potential drugs and it is important to investigate their lipophilicity. We experimentally calculated the value of the distribution coefficient ($logD_{7.4}$) for two derivatives with satisfactory solubility and activity, 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one and 3-(3-(4-bromphenyl)prop-2-enoyl)-2H-1-benzopyran-2-one. logD at pH 7.4 ($logD_{7.4}$) is closely related to the transport properties of drugs and their interaction with receptors.

The results of experimental calculation of $logD_{7.4}$ value of by the shaking method, on pH = 7.40 using three different ratios of division phases (1:25, 1:50, 1:75), showed the medium $logD_{7.4}$ value of 1.78 for 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one and 2.15 for 3-(3-(4-bromphenyl)prop-2-enoyl)-2H-1-benzopyran-2-one. Investigated substances are have optimal value of $logD_{7.4}$ ($1 < logD_{7.4} < 3$) for good absorption per of and for good activity in CNS.

Keywords: *lipophilicity, coumarins, distribution coefficient, antimicrobial activity*

Introduction

Coumarins with chalcone as backbone have been reported to exhibit a wide variety of pharmacological effects, including antioncogenic, anti-inflammatory, antiviral and antibacterial activities. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of the substituent on the aromatic rings.[1-4]

From 3-Acetyl-4-hydroxy-2*H*-1-benzopyran-2-one acting on appropriate aromatic aldehydes with pyridin and piperidine as catalysts we carried out the synthesis of several new derivatives of this group. The course of the reaction and activity are presented in our previous work.[5]

Bearing in mind those compounds as potential drugs it is important to investigate their lipophilicity. Lipophilicity of drugs has been recognized for its importance in medicine and pharmacy, so efforts have been made to determine the logD (logarithm of distribution coefficient**)** values of a number of compounds.[6]

logD at pH 7.4 ($logD_{7.4}$) is the important factor affecting the distribution and fate of drug molecules in living organisms. It is closely related to the transport properties of drugs and their interaction with receptors. This parameter can be determined experimentally or calculated. Experimental measurements are time consuming and difficult, but they are very valuble tools for calculation of $logD_{7.4}$. The classical and most reliable method of $logD_{7.4}$ determination is the *shake-flask method.*[7]

Synthesized substances are almost insoluble in water, so we experimentally calculated the value of the distribution coefficient ($logD_{7.4}$) for two derivatives with satisfactory solubility and activity, 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one and 3-(3-(4-bromphenyl)prop-2-enoyl)-2H-1-benzopyran-2-one.

Material and Method

Experimental

»Shake-flask« method

Logarithm of distribution coefficient ($logD_{7.4}$) for investigated compounds between *n*-octanol and phosphate buffer was determined by the »shake-flask« method. Before the partitioning of substance the buffer (0.15 mol/L, pH = 7.4) and *n*-octanol p.a., Semikem, BiH.) were saturated with each other.[8] Investigated compound (1.4 mg) was dissolved in minimum amount DMSO i tranferre at the 40 mL saturated buffer (c = 0.035 mg/mL) to give the stock solution. Calibration was done in exactly the same manner as the partitioning, except that *n*-octanol was not used. Partitioning experiments were performed in the systems *n*-octanol/phosphate buffer 1:25, 1:50, 1:75 (*V/V*). All solutions were pipetted into glass vials; the *n*-octanol and stock solution were added . The phases were shaken together on a mechanical shaker (Heidolph Promax 1020, Schwabach, Germany) for 60 minutes 100 rpm, centrifuged 1500 rpm/15 minutes, (Tehnica Železniki LC-320) to afford complete phase separation, and the *n*-octanol phase was removed. Absorbance of the buffer phase was measured using Shimadzu UV/VIS spectrophotometer (Japan) at $\lambda = 339$ nm for 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one and $\lambda = 313$ nm for 3-(3-(4-bromophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one with buffer as blank solution.

The instrument was zeroed by the blank solution. The concentration was then calculated from a calibration graph of compounds. Calculation of $logD_{7.4}$ values for investigated compounds(Figure 1, Figure 2) was performed as follows:

$$\log D7.4 = \log \frac{C_o}{C_p} = \log \frac{\frac{m_o}{M_s V_o}}{\frac{m_p}{M_s V_p}} = \log \frac{\frac{m_o}{V_o}}{\frac{m_p}{V_p}}$$

Eq. (1)

C_o - concentration of substance in n-octanol phase;

C_p - concentration of substance in buffer phase;

m_o - mass of substance in n-octanol phase;

m_p - mass of substance in buffer phase;

V_o - volume of n-octanol phase;

V_p - volume of buffer phase;

M_s - molecular mass of substance.

Figure1. 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one

Figure 2. 3-(3-(4-bromophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one

Results and Discussion

Since lipophilicity has been recognized for its importance in pharmacy and medicine, efforts have been made to determine the $logD_{7.4}$ values of a number of compounds.

$logD_{7.4}$ is closely related to the transport properties of drugs and their interaction with receptors. Determining the value of this constant for ivestigated substances, which are potential drugs, is very important–namely, its can serve for predicting distribution of them from blood (pH 7.4) to surrounding tissues and vice versa.

The results of experimental calculation of $logD_{7.4}$ are summarized in Table 1 and Table 2. Each value is the average of five determinations.

Table1. The results of experimental calculation of $logD_{7.4}$ value for compound I (3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one)

Compound I				
ratio	**C_1**	**Ā**	**C_2**	**log $D_{7.4}$**
1:25	2.96 x 10^{-3}	0.436	3.65 x 10^{-5}	1.75
	3.56 x 10^{-3}	0.528	0.11 x 10^{-5}	1.74
	5.04 x 10^{-3}	0.591	5.00 x 10^{-5}	1.87
	7.11 x 10^{-3}	0.974	8.34 x 10^{-5}	1.78
1:50	2.96 x 10^{-3}	0.310	2.56 x 10^{-5}	1.82
	3.56 x 10^{-3}	0.405	3.38 x 10^{-5}	1.74
	5.04 x 10^{-3}	0.437	3.56 x 10^{-5}	1.94
	7.11 x 10^{-3}	0.802	6.84 x 10^{-5}	1.73
1:75	2.96 x 10^{-3}	0.248	2.02 x 10^{-5}	1.86
	3.56 x 10^{-3}	0.355	2.95 x 10^{-5}	1.66
	5.04 x 10^{-3}	0.398	3.32 x 10^{-5}	1.88
	7.11 x 10^{-3}	0.701	5.96 x 10^{-5}	1.64

C_1 – concentration (mol L–1) of substance in n-octanol before partitioning;

Ā – arbitrary absorbance in buffer solution after partitioning;

C_2 – concentration (mol L–1) in buffer solution after partitioning;

log $D_{7.4}$ - logarithm of distribution coefficient at pH 7.4.

Table 2. The results of experimental calculation of $logD_{7.4}$ value for compound II (3-(3-(4-bromphenyl)prop-2-enoyl)-2H-1-benzopyran-2-one)

Compound II				
ratio	C_1	Ā	C_2	log $D_{7.4}$
1:25	3.23 x 10^{-3}	0.316	1.95 x 10^{-5}	2.15
	4.58 x 10^{-3}	0.513	3.65 x 10^{-5}	2.03
	6.46 x 10^{-3}	0.558	4.03 x 10^{-5}	2.13
	7.00 x 10^{-3}	0.560	4.05 x 10^{-5}	2.17
1:50	3.23 x 10^{-3}	0.309	1.89 x 10^{-5}	2.08
	4.58 x 10^{-3}	0.371	2.43 x 10^{-5}	2.14
	6.46 x 10^{-3}	0.546	1.89 x 10^{-5}	2.06
	7.00 x 10^{-3}	0.592	4.33 x 10^{-5}	2.05
1:75	3.23 x 10^{-3}	0.274	1.49 x 10^{-5}	2.15
	4.58 x 10^{-3}	0.293	1.76 x 10^{-5}	2.27
	6.46 x 10^{-3}	0.364	2.37 x 10^{-5}	2.29
	7.00 x 10^{-3}	0.370	2.42 x 10^{-4}	2.33

C_1 – concentration (mol L–1) of substance in n-octanol before partitioning;
Ā – arbitrary absorbance in buffer solution after partitioning;
C_2 – concentration (mol L–1) in buffer solution after partitioning;
$logD_{7.4}$ - logarithm of distribution coefficient at pH 7.4.

The results of experimental calculation of $logD_{7.4}$ value, by the shaking method, on pH = 7.40 using three different ratios of division phases (1:25, 1:50, 1:75), showed the medium $logD_{7.4}$ value $logD_{7.4}$ = 1.78 for 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one and $logD_{7.4}$ = 2.15 for 3-(3-(4-bromphenyl)prop-2-enoyl)-2H-1-benzopyran-2-one.

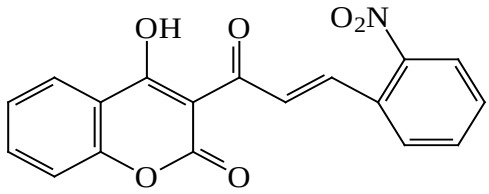

Figure 1. 3-(3-(2-nitrophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one

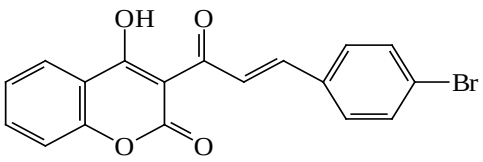

Figure 2. 3-(3-(4-bromophenyl)prop-2-enoyl)-2H-1-benzopyran-2-one

Conclusion

Bearing in mind those compounds as potential drugs it is important to their lipophilicity have good values. Investigated substances are have optimal value of logD7.4 (1 < logD < 3) for good absorption per os and for good activity in CNS. In our next investigation more similar substances will be included.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

Not commissioned; externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.