The 4-Arylaminocoumarin Derivatives Log P Values Calculated According to Rekker's Method

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Abstract

In the QSAR (quantitative structure-activity relationship) and QSPR (quantitative structure-property-activity relationship) study physico-chemical property, lipophilicity is used, to predict bioactivity of the newly synthesized coumarin compounds. Lipophilicity is a property of a molecule which depends on and can be changed by modifications in molecular structure. The parameter of the lipophilicity, partition coefficient (log P), is commonly used in drug designing and it is a numeric characteristic of lipophilicity of the examined substance, potential drug.
The synthesis of 4-arylaminocoumarins derivatives from 4-hydroxycoumarin, has been carried out. In this work we described the fragmental method of calculation of partition coefficient according to the Rekker's method, because the best correlation between calculated and experimental values log P was determined according to the Rekker model.
4-Arylaminocoumarin has negative value of log P, but substitution with alkyl or allyl groups on the position 3 increases lipofilicity. Introduction of methyl or ethyl group into position 3 increases lipofilicity, suggesting that by increasing the chain length the values of log P become higher. The influence of allyl substituent in position three increases lipophilicity similar to methyl group. The aryl supstitent decreases lipoflicity, but a general relationship among them could not be established. The results obtained in this study enable further synthesis of new coumarin derivatives and predict their biological activity and properties.

Key words: lipophilicity, derivatives of 4-arylaminocoumarin, QSPR, QSAR.

Introduction

Search for new drugs is very difficult and expensive process. The experimental testing of many thousand compounds for their biological activity and medicinal potential is enormously expensive and time consuming process. Today we can employ some kind of modelling by which the most unpromising compounds can be sorted out , so that only 200-300 compounds out of, say 200 000 remain for experimental work (1). The QSAR (quantitative structure-activity relationship) and QSPR (quantitative structure-property-activity relationship) studies provide one such modelling framework for a cheep and fast search of biologically-active molecules. The main use of QSAR and QSPR is in the selection of compounds for preparation and biological, pharmaceutical and medicinal research(2). From this we can make conclusion that QSAR and QSPR methods can use to predict medicinal potential for synthetising and also for non synthetising compounds. Practically, before synthesis of some compound we can, using QSAR and QSPR, predict physico-chemical properties and biological activity of molecule.
The fundamental axiom of QSAR and QSPR modelling is that the structure of molecules is reflected in their biological activities and physico-chemical properties (3).
In QSAR approach, molecular structure is described by a number of parameters which can even be calculated. The representation of molecular structures by numbers is a way to encode the structural information in QSAR and QSPR studies. The modelling process reduced to a correlation between two sets of numbers, one sets of numbers representing the molecular bioactivity or property and the other set representing the molecular structure. This correlation is meaningful only if it is carried out for a larger set of molecules.
One of the goals in QSAR and QSPR research is to predict lipophilicity of molecule which is potential drug. Lipophilicity of drug have big influence on the drug disposition such as: pass trought the cellular membranes, binding on the plasma proteins, elimination. That means if we know value for lipophilicity for supstance we can predict her pass through the cellular membranes, binding on the receptors, elimination. It means that we can predict is it substance promising or unpromising as drug. Lipophilicity is a property of a molecule which depends on and can be changed by modifications in molecular structure. The parameter of the lipophilicity, partition coefficient (log P), is commonly used in drug desing and it is a numeric characteristic of lipophilicity of the examined substance, potential drug. The values of partition coefficient (log P) can be positive or negative. The higher log P value means the higher lipophilicity of the drug which penetrates easily through the cell membrane, while negative log P values indicate hydrophilic characteristics of the drug.
The partition coefficient describing the partitioning equilibrium of solute molecules between lipid organic solvent (octanol) and water:

$P = C_o / C_w$

were Co is concentration of a substance in the octanol phase and Cw is the concentration in the water phase. The partition of drugs between n-octanol and water reflects the process by which substances, potential drugs, are distributed between the aqueous biophase (intracellular and extracelular liquid) and lipophilic biophase (cellular membrane) (4).

The correlations of partition coefficient, log P, with activity were studied and significant correlation was obtained (5). The log P value should be of practical use in developing new drugs, in optimizing the therapeutic index or toxicity.

To be able to predict the lipophilicity theoretical and experimental methods for the determination of partition coefficient (log P) values have been developed.

Methods of determination of the partition coefficient

a) Experimental way

Shake flask method is commonly used experimental method for the calculation of partition coefficient (log P) values. The basic procedure for obtaining a partition coefficient is to shake a weighed amount of chemical in a flask containing a measured amount of water//saturated octanol and octanol/saturated water. Partitioning system n-octanol/ water seems to mimic the lipid membranes /water systems found in the body. It must be remembered that the n/octanol water system is only an approximation of the actual environment found in the interface between the cellular membranes and the extracellular/intracellular fluids. Many times, the aqueous phase will be buffered with a phosphate buffer at pH 7,4 to reflect physiological pH. The determination of partition coefficients is tedious and time consuming. Some chemicals are too unstable and either degrade during the procedure, which can take several hours. Quantification of the amount of the substance in the two phases is performed by appropriate analytical method. This has led to attempts at approximating the partition coefficient. Second experimental way , perhaps the most popular approach has been high/ performance liquid chromatography HPLC or thin -layer chromatography TLC. This model has also limitations (6). In this chromatographic determination of the substances lipophilicity the retention time on Rf values in different mobile phases are discriminatory for it.

b) The calculation methods for calculation of log P

Hanch/Fujita's π-System and Rekker's f-System are methods for calculation of log P. It is expected for the drugs to have the same log P values obtained experimentally or by calculation, but in the practise this is not happened. If we compared experimental lipophilicity values to calculated values do not give identical values. The best correlation between calculated and experimental values log P determined according to Rekker model.
Rekker's f-System

Rekker and covockers choose following equation as the basis of a new approach to calculated lipophilicity(7,8):

$$P(o/w) = \sum_{i=1}^{n} a_n f_n$$

f- the hydrophobic fragmental constant, the lipophilicity contribution of a constituent part of a structure to the total lipophilicity.
a_n- numerical factor which indicating the incidence of fragment (f_n) in the structure.

Material and methods

Synthesis of derivatives of 4-arylaminocoumarin

The synthesis of 4-arylaminocoumarin and its derivatives, their spectral characteristics, elementary analysis were described in our previous investigation (9,10).

The calculation of partition coefficient logP (octanol/water)

Values the log P(o/w) for the series coumarines are calculated according to the method of Rekker:

$$P(o/w) = \sum_{i=1}^{n} a_n f_n$$

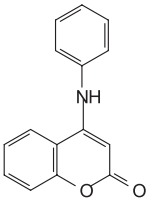
f- the hydrophobic fragmental constant, the lipophilicity contribution of a constituent part of a structure to the total lipophilicity.

a_n- numerical factor which indicating the incidence of fragment (f_n) in the structure.

Results and Discussion

In this work we shall describe the fragmental method of calculation of partition coefficient according to Rekker's method. This method is based on summing up convenient parameters. 4-arylaminocoumarin and its derivatives will serve as examples for calculation of log P.

Example 1: 4-arylaminocoumarin



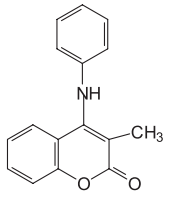
log P= ∑ a x f

log P= f (C_6H_5) + f (C_6H_4) + f (NH al) + f (C=O al) + f (-O- al) + f (=C=) + f (CH al)

log P= 1,886 + 1,688 + (-1,825) + (-1,703) + (-1,581) + 0,200 + 0,235

log P = -1,100

Example 2: 3-substituted-4-arylaminocoumarin



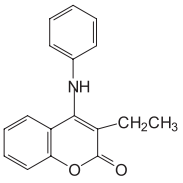
log P= ∑ a x f

log P= f (C_6H_5) + f (C_6H_4) + f (NH al) + f (C=O al) + f (-O- al) + 2f (=C=) + f (CH_3)

log P= 1,886 + 1,688 + (-1,825) + (-1,703) + (-1,581) + 0,400 + 0,702

log P = -0,433

Example 3: 3-substituted-4-arylaminocoumarin



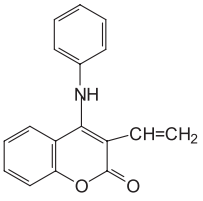
log P= ∑ a x f

log P= f (C_6H_5) + f (C_6H_4) + f (NH al) + f (C=O al) + f (-O- al) + 2f (=C=) + f (CH_2) + f(CH_3)

log P= 1,886 + 1,688 + (-1,825) + (-1,703) + (-1,581) + 2 x 0,200 + 0,503 + 0,702

log P = 0,070

Example 4: 3-substituted-4-arylaminocoumarin



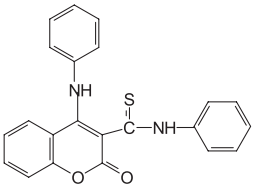
log P= ∑ a x f

log P= f (C_6H_5) + f (C_6H_4) + f (NH al) + f (C=O al) + f (-O- al) + 2f (=C=) + f ($CH=CH_3$)

log P= 1,886 + 1,688 + (-1,825) + (-1,703) + (-1,581) + 2 x 0,200 + 0,730

log P = -0,405

Example 4: 3-substituted-4-arylaminocoumarin



log P= ∑ a x f

log P= 2f (C_6H_5) + f (C_6H_4) + 2f (NH al) + f (C=O al) + f (-O- al) + 3f (=C=) + f (-S- al)

log P= 2 x 1,886 + 1,688 + (2 x -1,825) + (-1,703) + (-1,581) + 3 x 0,200 + (-0,510)
log P = -1,384

The regression analysis and experimentally or mathematical determined lipophilicity have been used to assess the effect of structural modification on these processes. Values of calculated or experimental log P can be positive or negative. The higher log P value means the higher lipophilicity of the drug which penetrates easily through the cell membrane, while negative log P values indicate hydrophilic characteristics of the drug.

The position 3 of coumarin ring is a very important site of molecular modification. The introduction of various substituens on the different sites on coumarin ring can change lipophilicity, properties and activity of coumarin derivatives.

The results of log P obtained of the synthetised 4-arylaminocoumarin derivatives show different values of partition coefficient. 4-Arylaminocoumarin (example 1) has negative value of log P. Our previous investigations showed that some derivatives of 4-arylaminocoumarin with supstituents CH_3, OCH_3, CH_2CH_3, OCH_3, Cl changed lipophilicity, but all values of log P were always negative.

The influence of substitution in position three of coumarin ring plays a role in modification of lipophilicity. Substitution with alkyl or allyl groups (example 2-4) increases lipophilicity. Introduction of methyl or ethyl group into position 3 increases lipophilicity, suggesting that by increasing the chain length the values of log P become higher. 3-ethyl-4-arylaminocoumarin is the only one that has a positive value of log P and this compound is the only one of lipophilic character.

The influence of allyl substituent (example 4) in position three increases lipophilicity similar to methyl group.

The aryl substituent (example 5) decreases lipophilicity, but a general relationship among them could not be established.

Conclusion

In this work we have investigated influence of different substituents in position three of coumarin ring on lipophilicity of derivatives of 4-arylaminocoumarins.

4-Arylaminocoumarin has negative value of log P, but substitution with alkyl or allyl groups increases lipophilicity. Introduction of methyl or ethyl group into position 3 increases lipophilicity, suggesting that by increasing the chain length the values of log P become higher. 3-ethyl-4-arylaminocoumarin is the only one that has a positive value of log P and this compound is the only one of lipophilic character The influence of allyl substituent in position three increases lipophilicity similar to methyl group.

The aryl substitent decreases lipophilicity, but a general relationship among them could not be established. The results obtained in this study enable further synthesis of new coumarin derivatives and predict their biological activity and properties.

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