PHARMA SCIENCE MONITOR
AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

LIPOPHILICITY OF FEW CHROMEN-2-ONES AND CHROMENE-2-THIONES BY HYPERCHEM 7.0 AND ALOGPS 2.1

P. Jayanthi* and P. Lalitha

Department of Chemistry, Avinashilingam Deemed University for Women, Coimbatore-641 043

ABSTRACT

Lipophilicity which plays an important role in research into the structure-activity relationship of drug action has been theoretically predicted for few chromen-2-ones and chromen-2-thiones using commercial software HyperChem 7.0 and an internet computational software ALOGPS 2.1. In the compounds analyzed for lipophilicity using HyperChem, the compounds possessing $-NO_2$ group showed a negative log *P* value. The log *P* values of all the other compounds were found to lie within 3. Theoretical determination of lipophilicity reduces the time involved in calculation of lipophilicity by experimental methods. ALOGPS 2.1 was comparatively greater than that calculated using HyperChem.

Key words: Lipophilicty, Coumarins, Thiocoumarins, HyperChem 7.0, ALOGPS 2.1

INTRODUCTION

Coumarins (chromen-2-ones) have long been recognized to posse's anti-inflammatory, anti-oxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral and anti-carcinogenic activities. Thiocoumarins (chromen-2-thiones) show apoptogenic effect [1], anti-coagulant [2], anticancer activity [3], anti-HIV activity [4] and inhibits TNF-α induced ICAM-1 expression on human umbilical vein endothelial cells (HUVECs) and microsomal lipid peroxidation [5].

Lipophilicity 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 chemistry, many schemes have been developed to estimate this property as expressed by the partition coefficient log *P*. Log *P* is closely related to the transport properties of drugs and their interaction with receptors. Determination of log *P* values of organic compounds, including drugs, has special significance if standards 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 *P*'s for large sets of compounds in QSAR studies, particularly at the screening stage. 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, efforts have been made to determine the log *P* (logarithm of partition coefficient in *n*-octanol/water) values of few coumarins and thiocoumarins.

In this paper, the partition coefficients of the synthesized compounds were predicted theoretically by using commercial softwares like HyperChem 7.0 and an internet computational software ALOGPS 2.1.

MATERIALS AND METHODS

Prediction of lipophilicity: Eighteen chromen-2-ones and chromene-2-thiones [6] have been chosen for the study.

HyperChem 7.0. – The computer program HyperChem 7.0 predicts log *P* values using the atom-additive method according to Ghose, Prichett and Crippen [7]. Their approach avoids correction factors and calculates lipophilicity on an individual atom basis by employing a large number of atom types. The following equation is used to calculate the *n*-octanol-water partition coefficient:

$\log P = {}^{n}_{i}\Sigma n_i a_i$

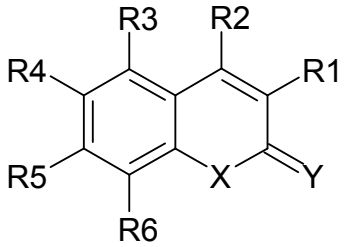
where n_i is the number of atoms of type *i*, and a_i is the contribution of the corresponding atom type. The program lists atom contributions for each atom type and calculates the log *P* value by summing up all atom contributions.

ALOGPS 2.1. – The ALOGPS 2.1 package includes programmes to predict lipophilicity and aqueous solubility of chemical compounds. A method for predicting log *P* values based on atom-type electrotopological-state (E-state) indices and associative neural network modelling was developed by Tetko *et al.* [8-10]. 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 neighbouring atoms, the estimated log *P* value of the target compound is obtained.

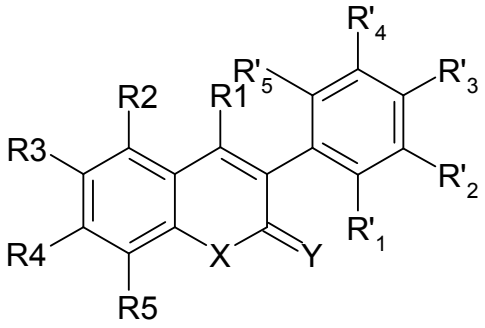
RESULTS AND DISCUSSION

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 both the softwares. Our analysis demonstrates a slight variation between the log *P* value predicted by the commercial software HyperChem 7.0 and internet computational software ALOGPS 2.1.

Table 1. Log P values from HyperChem 7.0 and ALOGPS 2.1



S.No	Structural formula	HyperChem 7.0	ALOGPS 2.1
1	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=H;X=0; Y=S	0.53	2.50
2	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=H;X=S; Y=S	0.81	2.98
3	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=H;X=S; Y=O	0.23	2.10
4	R1=H;R2=Me;R3=H;R4=NO_2; R5=OH; R6=H; X=0;Y=S	-2.10	-
5	R1=H;R2=Me;R3=H;R4=NO_2;R5=OH;R6=H; X=S; Y=S	-1.76	-
6	R1=H;R2=Me;R3=H;R4=NO_2;R5=OH;R6=H; X=S; Y=O	-2.10	-
7	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=OH;X=O;Y=S	1.04	2.51
8	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=OH;X=S;Y=S	1.38	1.81
9	R1=H;R2=Me;R3=H;R4=H;R5=OH;R6=OH;X=S;Y=O	1.02	2.11
10	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H;X=O; Y=S	0.55	2.72
11	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H;X=S; Y=S	0.89	4.77
12	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H;X=S; Y=O	0.24	4.21
13	R1=C_6H_5;R2=OH;R3=H;R4=H;R5=H;R6=H;X=O;Y=S	1.06	3.29
14	R1=C_6H_5;R2=OH;R3=H;R4=H;R5=H;R6=H;X=S;Y=S	1.40	3.74
15	R1=C_6H_5;R2=OH;R3=H;R4=H;R5=H;R6=H;X=S;Y=O	0.75	3.14



S.No	Structural formula	HyperChem 7.0	ALOGPS 2.1
1	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H; R'1=NO2; R'2=H; R'3=NO2; R'4=H; R'5=H; X=O;Y=S	- 4.72	3.29
2	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H; R'1=NO2; R'2=H; R'3=NO2; R'4=H; R'5=H;X=S;Y=S	- 4.37	5.30
3	R1=C_6H_5;R2=H;R3=H;R4=H;R5=H;R6=H; R'1=NO2; R'2=H; R'3=NO2; R'4=H; R'5=H;X=S;Y=O	- 5.02	3.14

According to Lipinski's "rule of 5", the compounds with log *P*< 5 have drug-likeliness and can be orally administered. A highly lipophilic compound will have low aqueous solubility comparing to bioavailability. In the compounds analyzed for lipophilicity using HyperChem 7.0, the compounds possessing $-NO_2$ group showed a negative log *P* value. The log *P* values of all the other compounds were found to lie within 3. The log *P* values calculated using ALOGPS 2.1 was comparatively greater than that calculated using HyperChem 7.0.

CONCLUSION

Lipophilicity is one of the most important ADME properties. Since most of the drug-like molecules fail because of poor bioavailability, reliable predicted log *P* value based preselection of compounds can dramatically decrease 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 analysed experimentally for it to be used as an effective drug. A consistent depiction on the applicability of calculation methods in lipophilicity studies can be obtained by studying numerous substances of varying lipophilicity.

ACKNOWLEDGEMENT

The authors thank the authorities of the Avinashilingam Deemed University for Women, Coimbatore, for having providing the facilities to carry out this research work.

REFERENCES

1. Goel A, Prasad AK, Parmar VS, Balaram G and Saini N: Apoptogenic effect of 7,8-diacetoxy-4-methylcoumarin and 7,8-diacetoxy-4-methylthiocoumarin in human lung adenocarcinoma cell line: Role of NF-κB, Akt, ROS and MAP kinase pathway. Chemico- Biological Interactions 2009; 179(2-3): 363-374.
2. Woi Suk P, Jae Cheol J, Ju Cheon K and Bong Seok J: Improved manufacturing method of 2-hydroxythiocoumarin derivatives, anti-coagulant type rodenticide. Repub. Korean Kongkae Taeho Kongbo 2000.
3. Shalaby NMM and Elgamal MHA: Spectroscopic investigation of some biologically active coumarins and their thionated derivatives. Egyptian Journal of Chemistry 2001; 44 **(**4-6): 201-214.
4. Wu Jie, Zhen Y, Reza F and Qiang Z: Preparation of 4-thio substituted coumarin derivatives as anti-HCV agent. U.S. Patent 20040180950 2004.
5. Sarvesh K, Brajendra KS, Neerja K, Vineet K, Ajit K, Ashok KP, Hanumantharao GR, Parmar VS and Balaram G: Novel thiocoumarins as inhibitors of TNF-β induced ICAM-1 expression on human umbilical vein endothelial cells (HUVECs) and microsomal lipid peroxidation. Bioorganic & Medicinal Chemistry 2005;13(5): 1605-1613.
6. Jayanthi P, Lalitha P and Subhashini KS: A facile synthesis of few chromene-2-thiones using lawesson's reagent. Accepted for publication in Acta Ciencia Indica 2010
7. Ghose AK, Pritchett A and Crippen GM: Atomic physicochemical parameters for three-dimensional structure-directed quantitative structure- activity relationships. J. Comput. Chem. 1988; 9: 80-90.

8. Tetko IV: Neural Network Studies. 4. Introduction to Associative Neural Networks. J. Chem. Inf. Comput. Sci. 2002; 42: 717–728.
9. Tetko IV and Tanchuk VY: Application of Associative Neural Networks for Prediction of Lipophilicity in ALOGPS 2.1 program. J. Chem. Inf. Comput. Sci. 2002**;** 42: 1136–1145.
10. Tetko IV, Tanchuk VY, Kasheva TN and Villa AEP: Internet software for the calculation of the lipophilicity and aqueous solubility of chemical compounds. J. Chem. Inf. Comput. Sci. 2001**;** 41: 246-252.

For Correspondence:
P.Jayanthi
Research Scholar
Department of Chemistry
Avinashilingam Deemed University for Women, Coimbatore, Tamilnadu, India
Email:jayanthijns@gmail.com