WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 2133-2141. Research Article ISSN 2277– 7105

SHORT COMMUNICATION: ESTIMATION AND QUANTITATIVE PREDICTION OF PARTITION COEFFICIENT OF SOME BENZOGLYCOLAMIDE ESTERS

Ansari Afaque Raza Mehboob[1*], Mourya Vishnukant[2], Gosavi Jairam Pramod[1], Mulla Saddamhusen Jahangir[1]

[1]Department of Quality Assurance, D.S.T.S. Mandal's College of Pharmacy, Solapur, India.
[2]Government College of Pharmacy, Amravati, India.

Article Received on
06 March 2015,

Revised on 29 March 2015,
Accepted on 19 April 2015

***Correspondence for Author**
Ansari Afaque Raza Mehboob
Department of Quality Assurance, D.S.T.S. Mandal's College of Pharmacy, Solapur, India.

ABSTRACT

A major goal of Quantitative Structure Property Relationship (QSPR) studies is to find a mathematical relationship between the activity and property under investigation e.g. solubility, LogP, pKa, molar refraction, dipole moment etc. which are related to the structure of the molecule. In the present communication an attempt was made to apply the concept of QSPR in determining and correlating one of the physicochemical properties of some drug molecules belonging to Benzoyloxyacetamide esters with that of *in-silico* methods. The descriptor of partition coefficient i.e. LogP of eight compounds was experimentally determined and the correlation of LogP values was done with the values obtained from software programs. LogP values obtained from Hyperchem 5.0® were found to correlate the best with experimental values.

KEYWORDS: QSPR, partition coefficient, Benzoyloxyacetamide, Computer-aided drug design, Molecular modeling.

1. INTRODUCTION

In the area of biological properties, the quantitative structure property relationship (QSPR) methodology has already become an essential tool in all parts of medicinal chemistry. All major pharmaceutical companies have considerable effort directed towards elucidating the effect of structure on particular biological properties, particularly of medicinally active compounds. By contrast, the application of similar Quantitative Structure Property Relationship (QSPR) techniques to the elucidation of the ways in which structure determines chemical and physical properties has been less developed. In the present era the structural

chemistry has become increasingly oriented towards elucidating in detail how the physicochemical properties are determined by the structure, such prior considerations thus enables subsequent experimentation to be concentrated in the most promising directions.[1] Molecular modeling or computational chemistry is the science of representing molecular structures numerically and stimulating their behavior with the equations of Quantum and classical physics. The development of the molecular program under application in pharmaceutical research has been formalized as a field of study known as" Computer Aided Drug Design (CADD) or Computer Assisted Molecular Design (CAMD)." The disciplines of molecular modeling include the computational chemistry which relates to the computation of energy of molecular system, energy minimization.[2]

The tools of CADD and CAMD are used to determine structural properties of existing compounds, to develop and quantify hypothesis which relates these properties to the observed activities or physical properties and utilize these rules to predict the properties and activities of new chemical entities.

The two most common models used in molecular modeling are Quantum mechanics and Molecular mechanics. Objective of Quantum mechanics is to describe the special positions of all the electrons and nuclei. Most commonly implemented is molecular orbital theory, where electrons flow around fixed nuclei until they reach self consisted field. This is where the attractive and repulsive forces of all the electrons with themselves and stationary nuclei are in a steady state. The nuclei are then moved iteratively until the energy of the entire system can go no lower. This is called as energy minimization or the geometric optimization and allows one to predict structural and electronic properties of the molecule under study. Molecular mechanics is the mathematical formalism which attempts to reproduce molecular geometrics, energies and other features by adjusting the bond lengths, bond angles, and torsion angles.

Molecular modeling program allows scientist to generate and present the molecular data including; *Geometrics* i.e. bond length, bond angle and torsion angle, *Energies* i.e. heat of formation and activation energy, *Electronic properties* i.e. moment charges, ionization potential and electronic affinity, *Spectroscopic Properties* i.e. vibration modes and chemical shifts, *Bulk Properties* i.e. volume, surface area, diffusion and viscosity.[2,3]

A major goal of QSPR studies is to find a mathematical relationship between the activity and property under investigation (e.g. LogP, pKa, etc.), and one or more descriptive parameters or

descriptors related to the structure of the molecule. While such descriptors can themselves be experimental properties of the molecule, it is generally more useful to use descriptors derived mathematically from either the 2D or the 3D molecular structure, since this allows any relationship so derived to be extended to the prediction of the property or activity for unavailable compounds. If an acceptable model of this type can be found, it can guide the synthetic chemist in the choice between alternative hypothetical structures.[4,5]

1.1 Property Prediction by using the Principles of Molecular Modeling

Although drug design constitutes the prime aspect of molecular modeling, a number of physical properties are also accessible with theoretical calculations. Molecular mechanics, semi empirical and *ab initio* methods can give rather reliable results on various molecular properties such as heat of formation, enthalpy, barriers and activation energies, dipole moments, reaction parts etc.Theoratical calculations can provide a number of indices that may not be directly related to experimental data but that can be very useful because they carry high physical information content (polarization, delocalization, atomic and bond population etc.) For example electron densities are useful because they provide a good basis for the analysis of the stereo-electronic properties of either isolated or interacting molecules. Molecular electrostatic potentials are usually generated from the partial atomic charges derived from quantum mechanical calculation. Most of the major software systems include facilities to calculate and display electrostatic potentials. Other properties can be calculated by empirical methods, the most are the prediction of log P (Octanol /water partition coefficient) and MR (molar refractivity).

1.2 Molecular Descriptors

Molecular descriptors are numerical values that characterize the properties of molecules. Descriptors are frequently divided into 1D, 2D, or 3D descriptors, depending on the dimensionality of the molecular representation from which they can be calculated. Specifically, 1D descriptors are based exclusively on the type of atoms which make up the molecule. In addition to the types of atoms, 2D descriptors also incorporate the bonding pattern of the molecule. 3D descriptors derived from the 3D molecular structure take the spatial arrangement of the atoms in the molecule into account.

A relationship between partition coefficients was proposed using a simple mathematical equation which theoretically allows the calculation of one partition coefficient if the others are known. Lipophilicity can also be estimated from models developed from studies of the

partitioning of compounds between octanol and water, LogP values were estimated using different software packages; these were compared with experimental values to assess the quality of the estimates.

2. MATERIALS

Benzoyloxyacetamide chloride, Benzoic acid, 2-Chloroacetamide, Dimethylformamide.

2.1 Selection of Software

2.1.1 HyperChem 5.0®-HyperChem 5.0® is a molecular modeling and simulation program that performs complex chemical calculations using desktop computers. HyperChem 5.0® functions include drawing molecules from atoms and bonds and converting them to 3D models as well as to rearrange the molecules by rotating and translating them. Changing display conditions including stereo, viewing, rendering models and structural labels is also possible. Setting up and directing chemical calculations including molecular dynamics by various molecular mechanisms or semi empirical methods is one of its important applications. Graphing results of various calculations and solvating molecules in a periodic box are some of its speciality.

HyperChem 5.0® provides following methods for chemical calculations;

a) MM+, AMBER, BIO+ and OPLS force fields for molecular mechanics calculations.

b) Extended Huckel, CNDO, INDO, MINDO, MNDO, AMI, PM3, ZINDO/1 for quantum mechanics (Semi-empirical calculations).

System requirements include 4 MB RAM (6 Mb for large systems), At least 20 MB storage disk and 500 MHZ, Pill or faster PC.

2.1.2 CAChe Pro® 5.0: CAChe Pro® 5.0 is computer aided molecular design software which visualizes the structural properties and which influences activity or properties. The structures were drawn using CAChe Pro® 5.0 drawing tool, by sketching the atoms in a molecule, connecting them with covalent bonds. The structure was converted from 2D to 3D by the Model Builder with realistic bond lengths, bond angles and torsion angles. The default element on the build menu was chosen; the skeleton was made with carbon atom and then changed to another element when needed.

System requirements include 128 MB RAM (512 for protein analysis), 10 GB storage drive and 500 MHz PIII or faster.

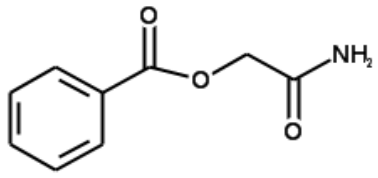
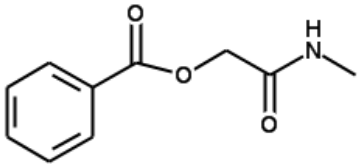
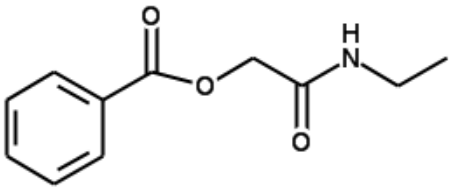
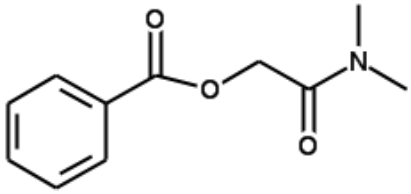
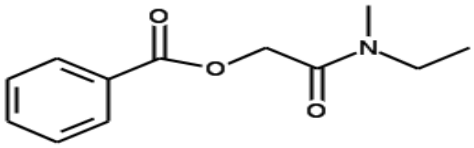
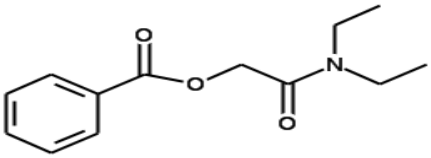
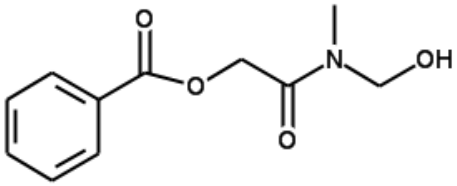
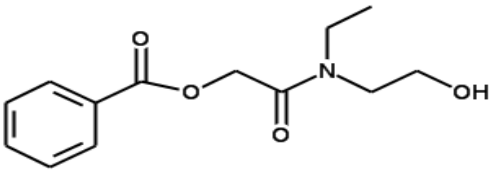
2.1.3 CLOGP®1.0.0: This program calculates the partition coefficient for the chemical moieties based on the SMILE codes for that compound. SMILE is a simple and comprehensive chemical nomenclature for calculating the LogP values of the compounds.

3. METHODS

3.1 Synthesis of Model Glycolamide Esters

The Glycolamide esters were synthesized by reacting Benzoyloxyacetyl chloride with appropriate amine in benzene and also it can be prepared by esterifying benzoic acid with the appropriate amine in Benzene and also it can be prepared by esterifying Benzoic acid with the appropriate 2-chloroacetamide in Dimethylformamide.The second method was used for synthesis of model Glycolamide esters because of the convenience and feasibility. [6, 7] The structures of prototype benzoglycolamide esters are shown in Table 1.

Table 1: Chemical Structure of Benzoglycolamide Esters

 **1. Benzoyloxyacetamide**	 **2. N-Methylbenzoyloxyacetamide**
 3. **N-Ethylbenzyloxyacetamide**	 4. **N,N-Dimethylbenzoyloxyacetamide**
 **5. N,N-Ethylmethylbenzoyloxyacetamide**	 **6. N,N-Diethylbenzoyloxyacetamide**
 **7.N-ethylhydroxyethylbenzoyloxyacetamide**	 **8.N-Ethylhydroxyethylbenzoyloxyacetamide**

3.2 GEOMETRY OPTIMIZATION

A molecule sketched in any molecular modeling program can be optimized for its geometry to settle it into a local minimum. Geometry optimization or energy minimization or

conformational research is done to find out the lowest energy conformation depending on the size and flexibility of the molecule.

3.3 Molecular Mechanics

The geometry optimization, energy minimization or conformational search is done to settle the molecule in local minimum among the many conformations it may exist in. A minimum energy conformation of molecule is the measure of stability of the molecule at which it is likely to exist. The molecular modeling programs optimize the geometry of the molecule depending upon the size and flexibility of the molecule. All the conformations were carried out using molecular modeling program HyperChem 5.0® on a Intel® Pentium Dual-Core 3.06 GHz computer system having 1GB RAM.

MM+ algorithm was used for molecular optimization. Polak-Ribiere minimization algorithm (conjugated gradient) was chosen as a numerical method for iterative calculations. Bond dipoles were selected for electrostatic potential and the cut-off point was set to "none".

The termination condition for energy gradient was set to 0.01 kcal/mol A^o. The process is repeated again if the energy gradient value does not cross the default. The total energy and its various components were stored in Microsoft Excel Worksheet using Dynamic Data Exchange concept.

3.4 Octanol–water partition coefficient (LogP) calculation

Three chemical modeling programs were used to obtain LogP values; a) Hyperchem® 5.0 b) CAChe Pro® 5.0 c) CLOGP® 1.0.0

4. RESULTS AND DISCUSSION

Table 2: Partition Coefficient –LogP (Calculated by the Experiment)

Sr. No	Compound	Log P
1.	Benzoyloxyacetamide	0.69
2.	N-methyl Benzoyloxyacetamide	0.99
3.	N-Ethyl Benzoyloxyacetamide	1.28
4.	N,N-Dimethyl Benzoyloxyacetamide	1.07
5.	N,N-Ethyl Methyl Benzoyloxyacetamide	1.27
6.	N,N-Diethyl Benzoyloxyacetamide	2.06
7.	N-methylhydroxyethylbenzoyl Benzoyloxyacetamide	0.58
8.	N-ethylhydroxy ethylbenzoyl Benzoyloxyacetamide	0.93

Table 3: Partition Coefficient –LogP (Calculated by the Software).

Sr. No	Compound	LogP (Hyperchem®)	LogP (CLOGP®)	LogP (CAChe Pro®)	LogP (Experimental)
1.	Benzoyloxyacetamide	0.508	0.508	0.45	0.69
2.	N-methyl Benzoyloxyacetamide	0.856	0.856	0.70	0.99
3.	N-Ethyl Benzoyloxyacetamide	1.385	1.385	1.04	1.28
4.	N,N-Dimethyl Benzoyloxyacetamide	1.286	0.475	-0.82	1.07
5.	N,N-Ethyl Methyl Benzoyloxyacetamide	1.815	1.286	0.95	1.27
6.		2.344	1.815	0.06	2.06
7.	N,N-Diethyl Benzoyloxyacetamide	1.812	0.525	0.50	0.58
8.	N-methylhydroxy ethylbenzoyl Benzoyloxyacetamide N-ethylhydroxy ethylbenzoyl Benzoyloxyacetamide	1.613	1.084	0.85	0.93

The LogP value obtained from the Hyperchem®5.0, CLOGP® 1.0.0 and CAChe Pro® 5.0 program (y-axis) shows the linear relationship between the LogP values obtained experimentally (x-axis).

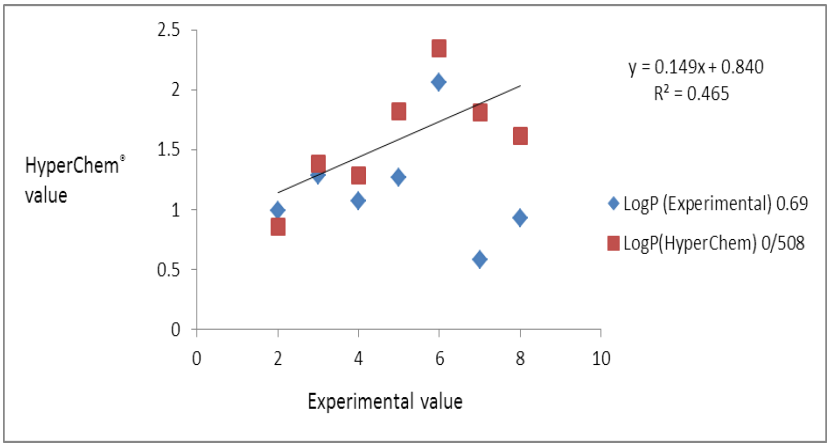


Fig. 1: Comparison of Experimental LogP and LogP calculated by Hyperchem® 5.0

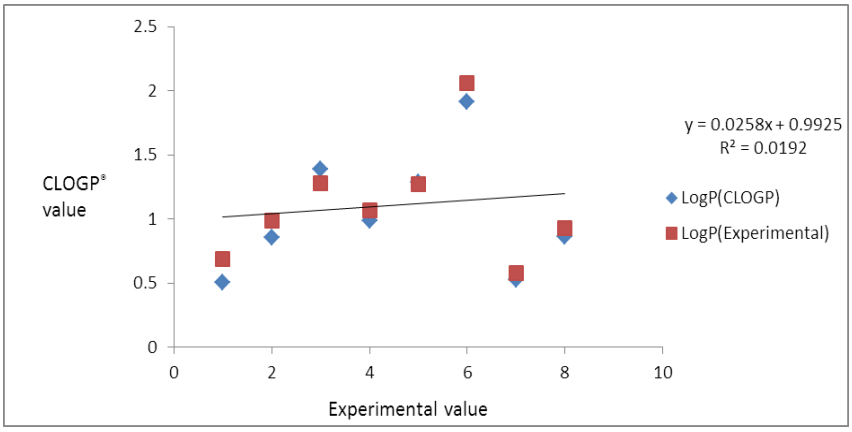


Fig. 2: Comparison of Experimental LogP and LogP calculated by CL0GP® 1.0.0

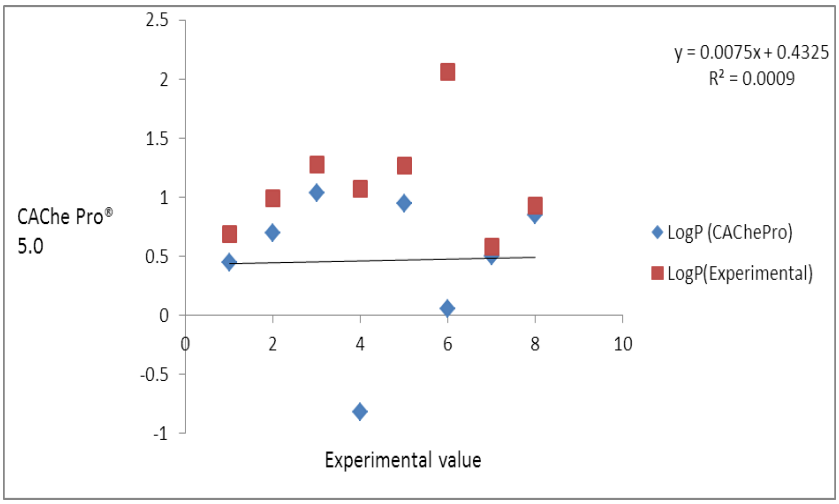


Fig. 3: Comparison of Experimental LogP and LogP calculated by CAChe Pro® 5.0

5. CONCLUSION

For the purpose of seeking reliable and reproducible compound lipophilicity values, experimental LogP values and data from the three computational programs were correlated with lipophilicity value estimates (LogP) from including Hyperchem® 5.0**,** CAChe Pro® 5.0, CLOGP® 1.0.0. The highest average R^2 value was 0.465 for the Hyperchem® 5.0 program, whereas the lowest R^2 was 0.0009 for the CAChe Pro® 5.0 program.

Thus the Quantitative structure-performance relationship (QSPR) makes it possible to predict the activities/properties of a given compound as a function of its molecular substituent. In this case from the observations in Table 2 we can say that increase in the alkyl group substitution on Benzoyloxyacetamide causes increase in the LogP value of the Molecule also substitution of the alcoholic groups causes decrease in the LogP value of Benzoyloxyacetamide.

The observations which have obtained from Table 3 helps to find out the correlation in between the LogP value obtained with the help of experiment and the LogP value obtained from the Hyperchem® 5.0, CLOGP® 1.0.0 and CAChe Pro® 5.0 program which shows that the relationship between the LogP value obtained experimentally has a more linear correlation with the values obtained by using Hyperchem® 5.0 program as compared to the CLOGP® 1.0.0 and CAChe Pro® 5.0 program.

6. REFERENCES

1. Alan A.Katritzi, Mati Kerelson, Victor S.Lobanov. QSPR as a means of predicting physical and chemical properties in terms of structure., 245-249.

2. Sonika Redhu, Anil Jindal. Molecular modeling: A New Scaffold for Drug Design. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5: 5-8.
3. Jacek Kujawski, Hanna Popielarska, Anna Myka, Beata Drabińska, Marek K. Bernard. The log *P* Parameter as a Molecular Descriptor in the Computer-aided Drug Design – an Overview, computational methods in science and technology,August., 2012; 18(2): 81-88.
4. Bachwani Mukesh, Kumar Rakesh. Molecular Docking: A Review. IJRAP, 2011; 2(6): 1746-1751.
5. Rama Rao Nadendla. Molecular Modeling. A Powerful Tool for Drug Design and Molecular Docking. Resonance, May 2004; 51-60.
6. Niels Mørk Nielsenw and Hans Bundgaard. Glycolamide esters as biolabile Prodrugs of carboxylic acid agents: Synthesis, stability, bioconversion, and physicochemical properties. Journal of Pharmaceutical Sciences, April 1988; 77(4): 285–298.
7. Balasubramanian Narasimhan, Afaque Mehboob Ansari, Nartaj Singh, Vishnukant Mourya, and Avinash Shridhar Dhake.A QSAR Approach for the Prediction of Stability of Benzoglycolamide Ester Prodrugs. Chem Pharm Bull (Tokyo) Aug 2006; 54(8): 1067-71.