SRI VENKATESWARA INTERNSHIP PROGRAM
FOR RESEARCH IN ACADEMICS
(SRI-VIPRA)

SRI-VIPRA

Project of 2023: **Report**

SVP-2324

"QSAR study of Common Drugs Using Software Tools"

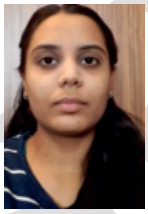
IQAC
Sri Venkateswara College
University of Delhi
Benito Juarez Road, Dhaula Kuan, New Delhi
New Delhi -110021

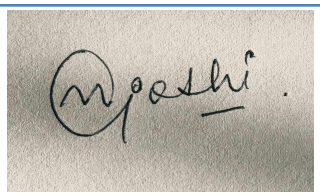
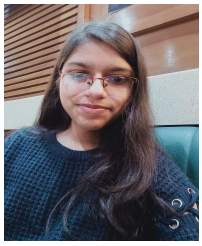
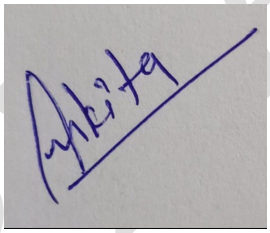
SRIVIPRA PROJECT 2023

Title: QSAR study of Common Drugs Using Software Tools

Name of Mentor: Dr. Vinita Kapoor **Name of Department:** Chemistry **Designation:** Assistant Professor	**Photo** 

List of students under the SRIVIPRA Project

S.No	Photo	Name of the student	Roll number	Course	Signature
1		Kanupriya Mahaur	1321001	Biological science Honors.	
2		Anusha K	1121053	BSc. Prog. Life Sciences	
3		Amish Mishra	1221004	B.Sc.(H) Biochemistry	

4		NUPUR JOSHI	1121088	BSc Life sciences	
5		Ankita kumari	1520072	Bsc Chemistry Hons.	

Signature of Mentor

Certificate of Originality

This is to certify that the aforementioned students from Sri Venkateswara College have participated in the summer project SVP-2324 titled "QSAR study of Common Drugs Using Software Tools**"**. The participants have carried out the research project work under

my guidance and supervision from 15th June, 2023 to 15th September2023. The work carried out is original and carried out in a hybrid mode.

Signature of Mentor

TABLE OF CONTENTS

1. INTRODUCTION

The process of drug discovery and development is a multidimensional process involving various disciplines of science and thus, is prone to error. The estimated time and money required for production of a single FDA approved drug is approximately 15 years and 2.6 billion dollars since the probability of failure is high at the level of clinical studies and pre-clinical trial.[1] Over the years, computer assisted drug design is becoming an integral part of pharmaceutical industry due to its high efficiency in collecting, optimizing and modifying data in in-silico manner before in-vitro and vivo testing.[2]

Computational drug designing can be categorized into 2 groups depending upon the target considered *i.e*., *structure based drug design* (SBDD) and *ligand based drug design* (LBDD). While SBDD focuses on the constitution of drug target to synthesize its inhibitor, LBDD mainly relies on the information of molecules that bind with the required biological target [3,4]. Structure Activity Relationship (SAR), a sub category under LBDD, is the study of changes in the biological activity of a drug due to change in its chemistry since changes in pharmacophore of a drug molecule can greatly affect its productivity. *Quantitative structure activity relationship* (QSAR) and quantitative structure-property relationship (QSPR), a sub-category under SAR, works with estimation and calculation of properties of molecules studied. These methods aim to optimize maximum biological, physio-chemical and structural activities by observing the change in variance of structure during the geometry optimization and predicting the properties of unavailable molecules or compounds [5] and thus, is an economic substitute of the medium throughput in vitro and low throughput in vivo assays. [6] Over time, QSAR techniques have undergone remarkable developments, from 0D QSAR to 6D QSAR, where addition of new parameters increases the complexity, dimensionality and application of the system [7].

QSAR studies have predictive ability regarding properties like surface area, volume, hydration energy, log P, refractivity, polarizability, mass, total energy, HOMO- LUMO, binding energy, enthalpy (heat of formation), electronic energy, nuclear energy and dipole moment of the molecules by formulating suitable QSAR model via preparation of molecules by geometry optimization, an important property for identification of the energetically most stable three-dimensional arrangement of atoms within a molecule, calculating values of all the descriptors in the training sets, selecting the suitable descriptor, implementing training sets to design the model, internal and external validation [8,9] using empirical and semi empirical methods in its calculations [9].

Empirical and semi empirical methods differ on the basis of Hamiltonian operator used and assumptions and approximations made to calculate the results. Thus, in order to improve the speed and accuracy of results, both methods are employed together to generate required data. Force fields are a type of empirical energy functions used to understand complex biodynamics at molecular level by calculating potential energy as a function of molecular coordinates. [8,10,11] For organic or drug-like molecules and compounds having elements of periodic table or complex geometry, class II force fields are used i.e., MMFF94 and UFF respectively [12]. On the other hand, most common type of Semi-empirical methods is Modified Neglect of Diatomic Differential Overlap or MNDO type which is further developed into

Austin Model 1 (AM1) and Parametric Method 3 (PM3) which differ in empirical core repulsion function [13].

Development of computational chemistry has revolutionised the field of Pharmaceuticals**,** material chemistry, nano chemistry and environmental studies as molecular modelling allows us to generate properties influencing interactions of receptors and compare structure of different molecules[14]. It cuts down time and money invested in research by eliminating hit and trial approach used during experimental chemistry and can generate results for large and diversified experimental sets in a short span of time [15, 16]. It compares and screens multiple data sets for generation of accurate results and adds it into the result window followed by utilisation in future calculations. Its major limitations are its highly descriptive data and graphics interpretation because of which information is widely spread in multiple variables and can results in omission of important in the middle of data, its inability to analyze the diverse data with regards to the genetic and physiological variation existing in human population. It's also important to consider relevant molecular descriptors for prediction of data as the predicted results are generated based on similarities in the present and previously generated data [15,17].

Our report focuses on calculation, compilation and cross checking of QSAR data generated by us for over-the-counter drugs such as Phenylephrine, Paracetamol and Ascorbic acid using ChemDraw and Argus lab.

2. METHODOLOGY AND OUTCOMES

In silico approach was utilised to elucidate the structures of commonly used over the counter drugs such as phenylephrine, ascorbic acid, and paracetamol on windows-based computer by using two software programs, Chem draw and Argus lab[18,19] respectively. ChemDraw Pro was used to import the structure of the drug from its trusted library into the Argus Lab application. Initially, the geometry optimization was performed using quantum mechanical method, austin model 1(AM1) parameterization utilizing 200 iterations with a total of 500 cycles to ensure that the geometry reaches maximum convergence. After optimization, further calculations were performed to determine various molecular properties such as dipole moment, Wiberg Bond order, ZDO (Zero Differential Overlap) charges, and Mulliken charges for each drug molecule. Using single point energy calculations, surfaces were created to visualize critical molecular properties such as the Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied

Molecular Orbital (LUMO), and Electron Potential Surface (ESP) map. The outcomes of the calculations and optimizations were compiled, cross checked and presented in results.

Table 1: Molecular Properties of Ascorbic Acid using ACD/ChemSketch

Sno.	Properties	Values
1	Molecular weight	$C_6H_8O_6$
2	Formula weight	176.124
3	Composition	C(40.92%)H(4.58%)O(54.50%)
4	Molar refractivity	35.26±0.3cm³
5	Molar volume	90.1±3.0cm³
6	Density	1.954±0.06g/cm³
7	Average mass	176.124 g/mol

Table 2: Molecular properties of Ascorbic acid using Arguslab Software

Sno.	**Properties**	**Value**	**Unit**
1	Final Geometric optimization value	-102.9344749311	au
		-64592.4165	kcal/mol

2	Final SCF value	-102.9344748986	au
		-64592.4165	kcal/mol
3	Heat of formation	-237.9895	kcal/mol
4	Dipole moment length	2.22764985	Meter

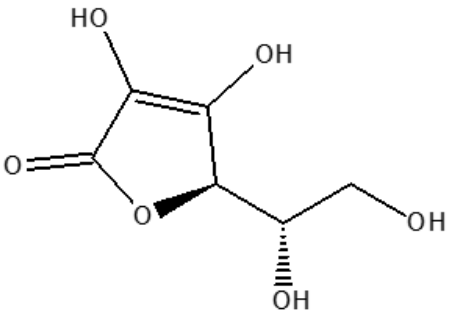


Figure 1.1 2D structure of Vitamin-C (Ascorbic Acid) obtained from ACD/ChemSketch

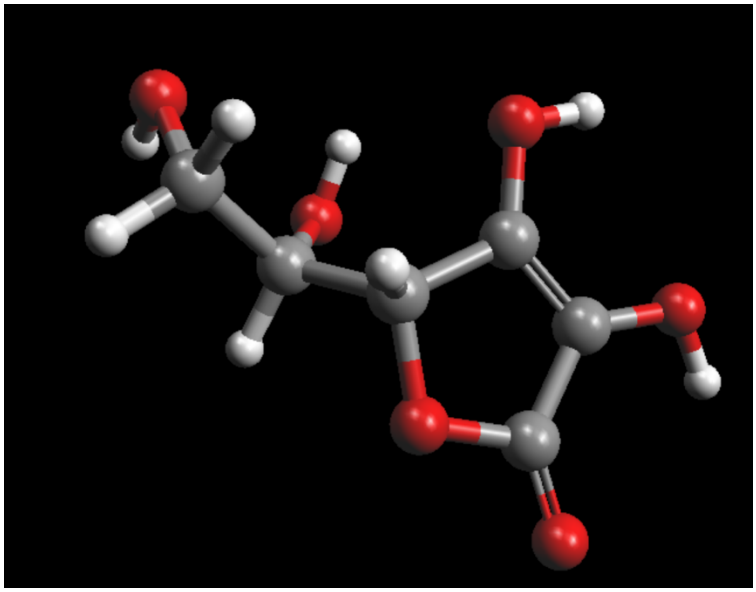


Figure 1.2 3D optimised structure of Vitamin-C (Ascorbic Acid) obtained from Arguslab

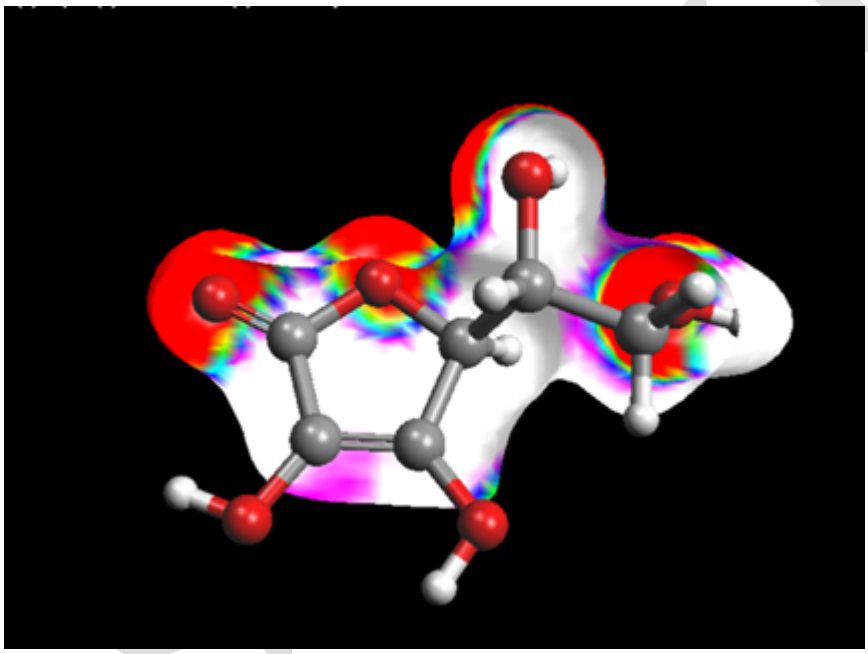


Figure 1.3 Electron potential mapped density for Vitamin-C (Ascorbic acid) obtained from Arguslab

Table 3: Molecular Properties of Paracetamol using ACD/ChemSketch

Sno.	Properties	Values
1	Molecular weight	$C_8H_9NO_2$
2	Formula weight	151.165
3	Composition	C(63.56%) H(6.00%)N(9.27%)O(21.17%)
4	Molar refractivity	42.4±0.3cm³
5	Molar volume	120.9±3.0cm³
6	Density	1.249±0.06g/ cm³
7	Average mass	151.165 g/mol

Table 4: Molecular properties of Paracetamol using Arguslab Software

Sno.	Properties	Value	Unit
1	Final Geometric optimization value	-73.3462457040	au
		-46025.5056	kcal/mol
2	Final SCF value	73.1697358529 au	au
		-45914.7439	kcal/mol

3	Heat of formation	-57.9127	kcal/mol
4	Dipole moment length	4.54433195	Meter

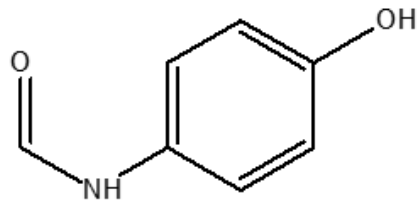


Figure 2.1 2D structure of Paracetamol obtained from ACD/ChemSketch

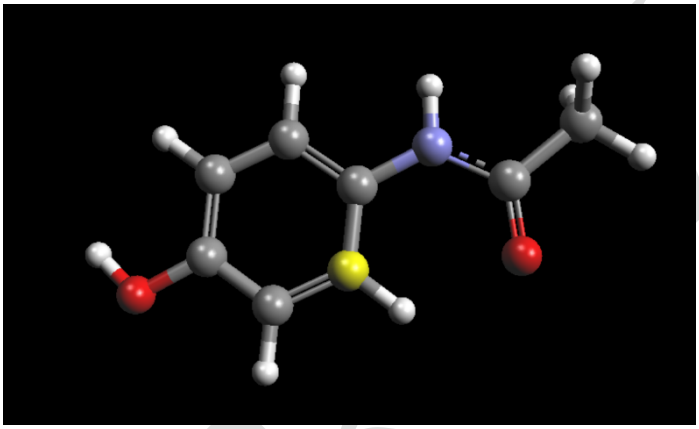


Figure 2.2 3D optimised structure of Paracetamol obtained from Arguslab

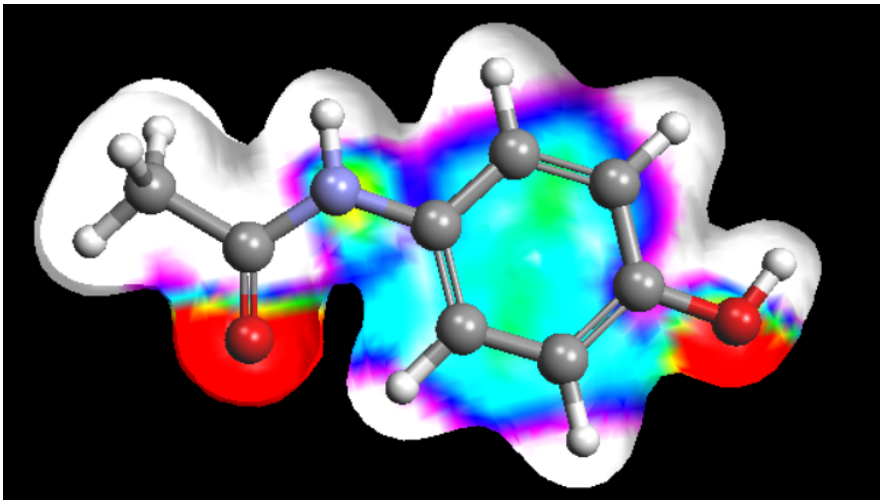


Figure 2.3 Electron potential mapped density of Paracetamol obtained from Arguslab

Table 5: Molecular Properties of Phenylephrine using ACD/ChemSketch

S.no	Properties	values
1	Molecular weight	$C_9H_{12}NO_2$
2	Formula weight	167.208
3	Composition	C(64.65%)H(7.84%) N(8.38%) O(19.4%)
4	Molar refractivity	47.44 ± 0.3 cm^3
5	Molar volume	144.2 ±3.0 cm^3
6	Density	1.159±0.06g/ cm^3
7	Average mass	167.208 g/mol

Table 6: Molecular properties of Phenylephrine using Arguslab Software

Sno.	Properties	Value	Unit

1	Final Geometric optimization value	-80.0847203166	au
		-50253.9660	kcal/mol
2	Final SCF value	-80.0847202754	au
		-50253.9660	kcal/mol
3	Heat of formation	-71.8484	kcal/mol
4	Dipole moment length	1.77587318	Meter

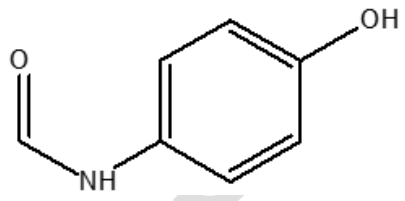


Figure 3.1 2D structure of Phenylephrine obtained from ACD/ChemSketch

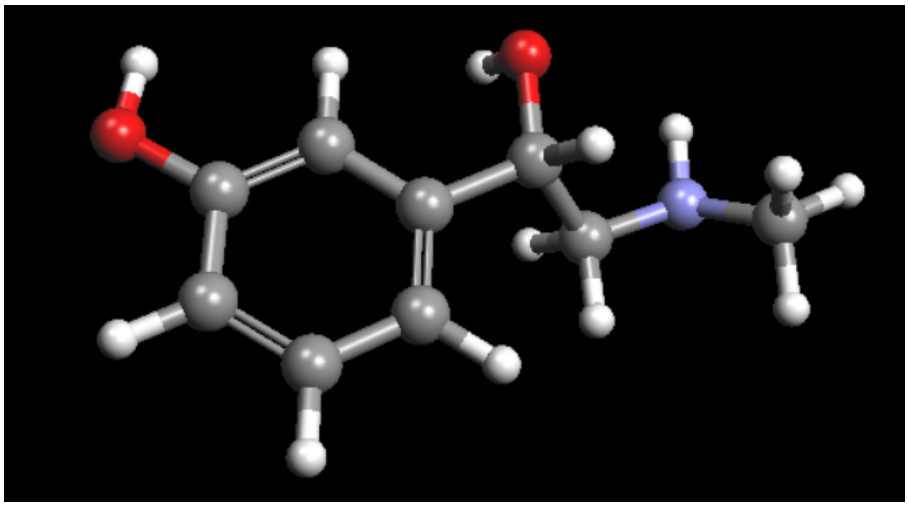


Figure 3.2 3D optimised structure of Phenylephrine obtained from Arguslab

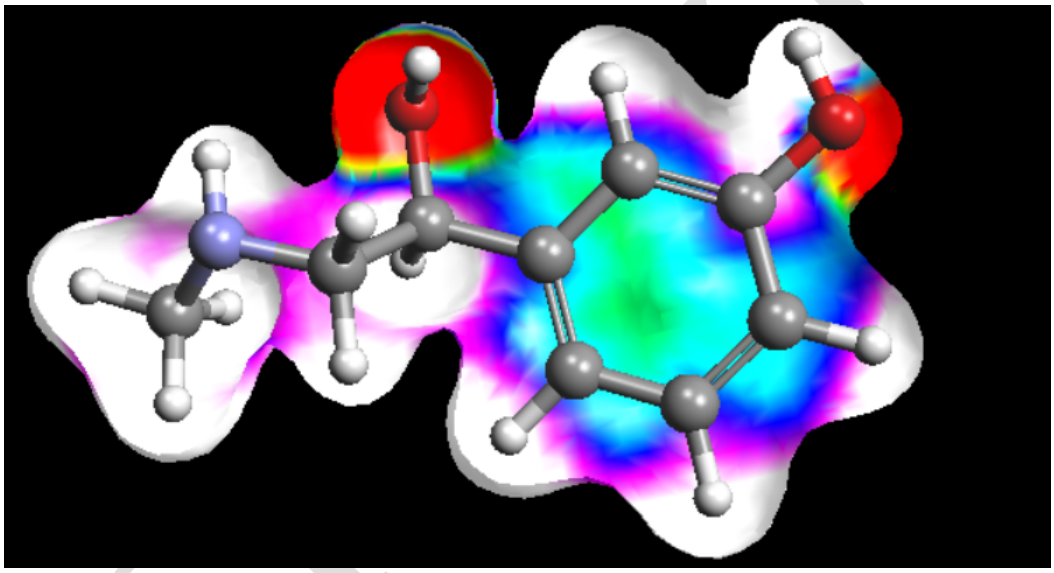


Figure 3.3 Electron potential mapped density of Phenylephrine obtained from Arguslab

3. CONCLUSIONS

Through this project we learnt about the ability of Arguslab software to reproduce a geometrically optimised molecular modelled structure and therefore use the experience and knowledge to produce unknown molecules. Arguslab software helped us in achieving the optimised structure with respective valuation of energies, viz. heat of formation, SCF energy and geometrical energy. This software provides values of initial and final geometrical energies which actually corresponds to energy of molecule before and after optimisation. The comparison and data computed by this software is quite apparent and self-explanatory. The data can be further used to improve understanding about the usability of the molecules for desired properties. The advantage of computational chemistry being, in case of discrepancies needed reformations can be done easily and results and conclusion can be drawn without undergoing hectic and tedious iterations of testing and experimentation. The ESP density mapping also gives a very good picture of the charge distribution on the molecules. Charge distribution on molecules helps to draw conclusions regarding the reactivity of molecules towards nucleophiles and electrophiles. The preferred solvent and attacking reagents can also be accordingly selected for further reactions.

4. REFERENCES

[1] Sadybekov, A., & Katritch, V. (2023). Computational approaches streamlining drug discovery. *Nature*, *616*(7958), 673–685. https://doi.org/10.1038/s41586-023-05905-z

[2] Cherkasov, A., Muratov, E., Fourches, D., Varnek, A., Baskin, I. I., Cronin, M. T., Dearden, J. C., Gramatica, P., Martin, Y. C., Todeschini, R., Consonni, V., Kuz'min, V. E., Cramer, R. D., Benigni, R., Yang, C., Rathman, J. F., Terfloth, L., Gasteiger, J., Richard, A. M., & Tropsha, A. (2014). QSAR modeling: Where have you been? Where are you going to? *Journal of Medicinal Chemistry*, *57*(12), 4977–5010. https://doi.org/10.1021/jm4004285

[3] Aparoy, P., Reddy, K. K., & Reddanna, P. (2012). Structure and ligand based drug design strategies in the development of novel 5- LOX inhibitors. *Current Medicinal Chemistry*, *19*(22), 3763–3778. https://doi.org/10.2174/092986712801661112

[4] Yu, W., & MacKerell, A. D. (2016). Computer-Aided drug design methods. In *Methods in molecular biology* (pp. 85–106). https://doi.org/10.1007/978-1-4939-6634-9_5

[5] Pathan, S., Ali, S.M. and Shrivastava, M. (2016) Quantitative Structure Activity Relationship and Drug Design: A Review. International Journal of Research in BioSciences, 5, 1. http://www.ijrbs.in

[6] Santos-Filho, O. A., Hopfinger, A. J., Cherkasov, A., & De Alencastro, R. B. (2009). The Receptor-Dependent QSAR Paradigm: An overview of the current state of the art. *Medicinal Chemistry*, *5*(4), 359–366. https://doi.org/10.2174/157340609788681458

[7] Lill, M. A. (2007). Multi-dimensional QSAR in drug discovery. *Drug Discovery Today*, *12*(23–24), 1013–1017. https://doi.org/10.1016/j.drudis.2007.08.004

[8] Laxmi, K. (2013). A study on Structural aspects of Indoline-2, 3-Dione-3-Oxime: Experimental and Theoretical approach. *International Journal of Computational and Theoretical Chemistry*, *1*(2), 11. https://doi.org/10.11648/j.ijctc.20130102.12

[9] Peng, C., Ayala, P. Y., Schlegel, H. B., & Frisch, M. J. (1996). Using redundant internal coordinates to optimize equilibrium geometries and transition states. *Journal of Computational Chemistry*, *17*(1), 49–56. https://doi.org/10.1002/(sici)1096-987x(19960115)17:1

[10] Laxmi, K.(2014) Theoretical Approach on structural aspects of antiepileptic agent indoline-2,3- dione-3-oxime by arguslab 4 software *Journal of Applied Chemistry*, 2(1):92-101.

[11] Martín-García, F., Papaleo, E., Gómez-Puertas, P., Boomsma, W., & Lindorff-Larsen, K. (2015). Comparing molecular dynamics force fields in the essential subspace. *PLOS ONE*, *10*(3), e0121114. https://doi.org/10.1371/journal.pone.0121114

[12] O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. (2011). Open Babel: An open chemical toolbox. *Journal of Cheminformatics*, *3*(1). https://doi.org/10.1186/1758-2946-3-33

[13] Dral, P. O., Wu, X., Spörkel, L., Koslowski, A., Weber, W., Steiger, R., Scholten, M., & Thiel, W. (2016). Semiempirical Quantum-Chemical Orthogonalization-Corrected Methods: Theory, Implementation, and Parameters. *Journal of Chemical Theory and Computation*, *12*(3), 1082–1096. https://doi.org/10.1021/acs.jctc.5b01046.

[14] Braja, E.J., Corpe, B.T., Marinho, M.M., & Marinho, E.S. (2012). Molecular electrostatic potential surface, HOMO– LUMO, and computational analysis of synthetic drug Rilpivirine. *International Journal of Scientific Research & Engineering*, *7*(7), 315- 319.

[15] Olier, I., Sadawi, N., Bickerton, G. R. J., Vanschoren, J., Grosan, C., Soldatova, L. N., & King, R. D. (2017). Meta-QSAR: a large-scale application of meta-learning to drug design and discovery. *Machine Learning*, *107*(1), 285–311. https://doi.org/10.1007/s10994-017-5685-x

[16] Marion, A., Monard, G., Ruiz-López, M. F., & Ingrosso, F. (2014). Water interactions with hydrophobic groups: Assessment and recalibration of semiempirical molecular orbital methods. *Journal of Chemical Physics*, *141*(3). https://doi.org/10.1063/1.4886655

[17] Cruciani, G., Clementi, S., & Pastor, M. (1998). GOLPE-guided region selection. *Perspectives in Drug Discovery and Design*, *12*, 71–86. https://doi.org/10.1023/a:1017069619333

[18] Thompson, M. A. (1996). *QM/MMpol: A Consistent Model for Solute/Solvent Polarization. Application to the Aqueous Solvation and Spectroscopy of Formaldehyde, Acetaldehyde, and Acetone* (Vol. 6).

[19] Thompson, M. A. (1996). *QM/MMpol: A Consistent Model for Solute/Solvent Polarization. Application to the Aqueous Solvation and Spectroscopy of Formaldehyde, Acetaldehyde, and Acetone* (Vol. 6).