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IN-SILICO ADMET PROFILING OF VALPROIC ACID DERIVATIVES FOR THE TREATMENT OF EPILEPSY

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ABSTRACT

Epilepsy is a neurological disorder and can be threatening to life of an individual. Epilepsy is characterized by a long-term risk of recurrent seizures. These seizures may present in several ways depending on the part of the brain involved and the person's age. Approximately 80% of developing world leads the 80% of cases worldwide. In 2015, it resulted in 125,000 deaths up from 112,000 deaths in 1990.

Valproic Acid is the best first choice drug for seizures. But they have their short comings such as neural tube effects (NTDs), so there is a need for finding drugs which is effective with minor adversities.

In our present study we focused on calculating In-Silico ADMET properties, so that it can correlate biological properties (Pharmacokinetic / Pharmacodynamics parameters) and overcome the toxicity.

Our ligand based drug designing study explores the mechanisms while primarily focussing on the efficacy of the valproic acid derivatives as antiepileptic. In this study toxicity prediction has been done based on calculation of drug likeliness. During analysis we found that ADMET Predicted profile of several candidate compounds were better than valproic acid.

Keywords: Valproic acid, ADMETsar, Ligand based Drug Designing, Toxicity, ADME

INTRODUCTION

1.1. Epilepsy

Epilepsy is a disorder in which nerve cell activity in the brain is disturbed, causing seizures, which can be life threatening. Epilepsy is characterized by a long-term risk of recurrent seizures. These seizures may present in several ways depending on the part of the brain involved and the person's age. Epileptic seizures are vigorous shaking of body that can vary from brief (nearly undetectable) to long duration ones. These episodes can result in physical injuries, including occasionally broken bones. Epilepsy can have both genetic and acquired causes, with interaction of these factors in many cases **[1]**.

Genetics is believed to be involved in the majority of cases, either directly or indirectly (National Institute for Clinical Excellence, 2004). Some epilepsy are due to a single gene defect (1–2%); most are due to the interaction of multiple genes and environmental factors (National Institute for Clinical Excellence, 2004). Each of the single gene defects is rare, with more than 200 in all described **[2]**. Most genes involved affect ion channels, either directly or indirectly **[2]**. These include genes for ion channels themselves, enzymes, GABA, and G protein-coupled receptors **[3]**. About 60% of cases the cause is unknown **[6]**. Seizures may also occur as a consequence of other health problems, if they occur right around a specific cause, such as a stroke, head injury, toxic ingestion or metabolic problem.

1.2. Valproic acid

Valproate is primarily used to cure epilepsy and bipolar disorder to prevent migraine. It is also used for the prevention of seizures. It can be given as intravenous injection or oral tablets. It was created in year 1881 but came into medical use after 1962.

Valproic acid has several medical applications. It is primarily used to treat epilepsy, migraine and some mental illness issues. VPA shows broad spectrum of anticonvulsant activity, but it is used as first line treatment for several type of seizures. It is also proposed that this drug can show antipsychotic effects which are effective in treatment of Dopamine deregulation syndrome and Schizophrenia. It is one of the essential medicine in the list of World Health Organization as one of the most safe and effective medicine in health systems. Valproic acid (VPA) is an organic weak acid. The conjugate base is valproate.

Its therapeutic working is not well understood. It may act by increasing gamma-aminobutyric acid levels in the brain or by altering the properties of voltage dependent sodium channels as traditional anticonvulsant, by increasing the level of inhibitory synaptic neuro-transmitters and by inhibiting GABA degradative enzymes.

Valproic acid or valproate are typically supplied in the sodium salt form (valproate semi sodium or divalproex sodium). Like an every other drug Valproic acid has its side effects which include Nausea (22%), Drowsiness (19%), Dizziness (12), Vomiting (12%), and Weakness (10%). In patient it can cause some serious ill effects such as Bleeding, Low blood platelets counts, Encephalopathy, Low body temperature, Suicidal behaviour and thoughts etc. **[11]**. Medication can be potentially harmful to the fetus. Major abnormalities such as spina bifida can be seen **[12]**.

Children of mothers taking valproate during pregnancy are at risk for lower IQs.A study found that the 3-year-old children of pregnant women taking valproate had an IQ nine points lower than that of a normal group **[11, 12]**.

1.3. ADMET

Many drugs fail to enter the market due to their poor ADMET profile. It is very important now a day to bring in such a drug which is easily absorbed by the body at different stages. Easily transported to the target site through circulatory system and easily eliminate from the body after use. All of the above properties are characterized as ADMET properties. The concept behind the *in-silico* ADMET profiling is reduction of cost and timing when compared to wet lab ADMET profiling. As an example, it only takes a minute in an *in-silico* model to screen 20,000 molecules, but takes more than 20 weeks in the "wet" laboratory to do the same test on same molecules **[4, 5]**.

This paradigm shift has therefore spurred up the development of several theoretical methods for the prediction of ADMET parameters **[7]**. A set of these methods are implemented in various software. The software tools currently used to predict the ADMET properties of potential drug candidates often make use of quantitative structure-activity relationships, QSAR and data mining techniques **[8]**.

Several rules such as Lipinski rule of five are used to find the drug likeliness. The 5 mostly considered drug likeliness filters are The Lipinski (Pfizer), The Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods. These methods allow early screening of molecules from the large data set **[9]**.

Several molecular descriptors such as Blood-Brain Barrier Permeability, Human Intestinal Absorption, P-glycoprotein Inhibition, model organism toxicity, Carcinogenicity and CYP P450 inhibition *etc*. are used to predict the potential of a molecule to be a good drug **[8]**.

Here we adopted the method of consensus screening of molecule. This allowed us to individually study each candidate molecule on several molecular descriptors. Data sets of each descriptor were made. Intersection of all the dataset was verified **[10]**.

MATERIALS AND METHODS

In ADMET profiling of Valproic acid, Structure search was conducted on the basis of structural similarity using drug bank (https://www.drugbank.ca/). The information of the compounds was obtained in smiles format. In total 21 molecules were obtained at the similarity of 75 % as shown in **Table 1**.

The evaluation of drug likeliness was conducted on the basis of "Lipinski rule of five" using Swiss ADME. All 21 molecules were further selected for ADMET profiling.

A set of ADMET related properties (32 computed physicochemical properties or molecular descriptors) was calculated by ADMETsar. (http://lmmd.ecust.edu.cn/admetsar1/predict/). ADMETsar is an online server used for predicting ADMET properties. ADMETsar uses data mining and QSAR modeling technique for ADMET prediction. Several preformed models are used to generate probability data.

Spread sheet was made to enter and analyse the data from ADMETsar.Filters were applied to the descriptors. Screening was done according to these properties. Here we adopted the method of consensus screening of molecule.

2.1. Screening of molecules

The parameters considered for screening of molecules are detailed in **Table 2**.The screening of molecule was done on the basis of these properties:

1. Aqueous solubility was use to analyze the solubility of compound. It is one of the key factors in determining the bioavailability of the chemical compound. This property affects the absorption and distribution characteristics of the compound. Generally, low solubility goes along with a bad absorption. So we try to avoid poorly soluble compounds. Generally compounds with value of LogS greater the -4 are appreciable. **[2, 7]**.
2. The Caco-2 cell line is a continuous line of heterogeneous human epithelial colorectal adenocarcinoma cells, developed by the Sloan-Kettering Institute for Cancer Research through research conducted by Dr. Jorgen Fogh **[12]** this line of heterogeneous cells allow us to perform various invasion, infection and transfection studies visually **[12]**. Various mathematical models are developed to predict Permeability of compound in them **[7]**.
3. Rat Acute Toxicity, Fish Toxicity and Tetrahymena Pyriformis Toxicity are predicted on the basis of toxicology endpoints discovered in QSAR studies of these model organisms. This is done to predict dose of toxicity in an organism **[7, 13]**.

Table 1: Summary of all compounds selected for ADMET profiling and screening

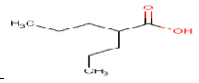
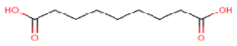
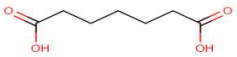
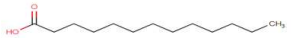
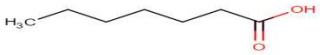
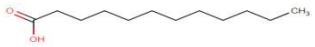
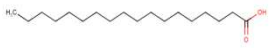
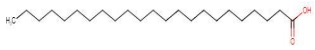
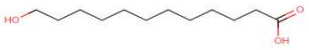
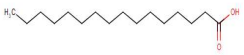
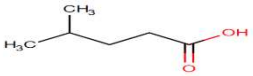
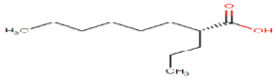
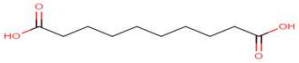
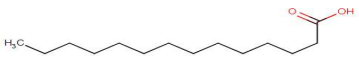
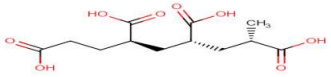
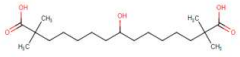
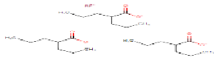
MOLECULE NUMBER	STRUCTURE	Molecule Name
molecule 1		Valproic Acid
molecule2		Azelaic Acid
molecule 3		Pimelic Acid
molecule 4		N-Valeric Acid
molecule 5		N-Tridecanoic Acid
molecule 6		Heptanoic Acid
molecule 7		Lauric Acid
molecule 8		Stearic acid
molecule 9		Tricosanoic Acid
molecule 10		Capric acid
molecule 11		12-Hydroxydodecanoic Acid
molecule 12		2-Methylbutanoic Acid
molecule 13		Palmitic Acid
molecule 14		4-Methyl Valeric Acid
molecule 15		Caprylic acid
molecule 16		Arundic acid
molecule 17		Sebacic acid
molecule 18		Myristic acid
molecule 19		Octane-1,3,5,7-Tetracarboxylic acid
molecule 20		Bempedoic acid
molecule 21		Valproate bismuth

Table 2: Summary of all the descriptors used for screening

Descriptors [a]	Unit [b]
Aqueous solubility	LogS
Caco-2 Permeability	LogPapp, cm/s
Rat Acute Toxicity	LD50, mol/kg
Fish Toxicity	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	pIGC50, ug/L

a) Descriptors [a] are those characters and properties of a chemical compound which can be quantized, here this column represent the properties selected from ADMETsar
b) Units of the properties in which they can be measured

RESULTS AND DISCUSSION

In the similarity search on Drugbank, 21 molecules were obtained at the similarity of 75 % as shown in **Table 1**. When these molecules were subjected to drug likeliness all of these molecules passed the Lipinski rule of 5 with minor violations as shown in **Table 3**.

Serial numbers of molecules their structure and molecular name is mentioned in **Table 1**, where molecule 1 represents valproic acid itself. All these molecules were used as query for their ADMET prediction using ADMETsar. It produces detailed profile of each compound for their ADMET properties. The data was saved in MS excel sheet and were further analysed for screening.

The absorption properties of these molecules were analysed on the basis of descriptors as shown in Table 4. All of them were found to be BBB+, HIA+,Caco2+ and non- inhibitors of p glycoprotein. Further on the analysis elimination properties they were found to be non-problematic. The metabolism data predicts that all these molecules have Low CYP Inhibitory Promiscuity. All this confirms that they all are suitable drug candidate.

During the screening of the molecules it was found that molecule 2, 3, 4, 11, 12, 14 and 17 were having better aqueous solubility (LogS) than Valproic acid (i.e. Molecule 1). Molecule4 was having better in Caco-2 permeability (LogPapp, cm/s) than valproic acid. Molecules 20 and 21 were having better result in rat acute toxicity (LD50, mol/kg) than Valproic acid. Molecules 2, 3, 4, 11, 12, 14, 17, 19 and 20 were having better result in Fish toxicity (pLC50, mg/L) than valproic acid and Molecules 9, 6, 7, 8, 9, 10, 13, 15, 16, 18, 19, 20, 21 were having better result in Tetrahymena Pyriformis Toxicity (pIGC50, ug/L) than valproic acid as shown in Table 7.

Table 3: List of molecules and their Lipinski violation

S. No.	Number of Lipinski violations
Molecule 1	0
Molecule 2	0
Molecule 3	0
Molecule 4	0

Molecule 5	**0**
Molecule 6	**0**
Molecule 7	**0**
Molecule 8	**1 violation: MLOGP>4.15**
Molecule 9	**1 violation: MLOGP>4.15**
Molecule 10	**0**
Molecule 11	**0**
Molecule 12	**0**
Molecule 13	**1 violation: MLOGP>4.15**
Molecule 14	**0**
Molecule 15	**0**
Molecule 16	**0**
Molecule 17	**0**
Molecule 18	**0**
Molecule 19	**0**
Molecule 20	**0**
Molecule 21	**1 violation: MW>500**

Table 4: Summary of all descriptors used for determining absorption properties of compound

ABSORPTION PROPERTIES						
	Blood-Brain Barrier	**Human Intestinal Absorption**	**Caco-2 Permeability**	**P-glycoprotein Substrate**	**P-glycoprotein Inhibitor 1**	**P-glycoprotein Inhibitor 2**
molecule 1	**0.9626**	**0.9828**	**0.8866**	**0.7345**	**0.9695**	**0.7405**
molecule2	**0.7397**	**0.5731**	**0.6412**	**0.6969**	**0.9845**	**0.9229**
molecule 3	**0.7397**	**0.5731**	**0.6412**	**0.6969**	**0.9845**	**0.9229**
molecule 4	**0.9636**	**0.9898**	**0.7598**	**0.6725**	**0.9692**	**0.9803**
molecule 5	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 6	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 7	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 8	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 9	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 10	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 11	**0.7144**	**0.9418**	**0.5855**	**0.7351**	**0.9791**	**0.9252**
molecule 12	**0.9724**	**0.9946**	**0.7369**	**0.8093**	**0.9719**	**0.9582**
molecule 13	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 14	**0.9723**	**0.9869**	**0.7385**	**0.7084**	**0.9667**	**0.9804**
molecule 15	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 16	**0.9677**	**0.985**	**0.8856**	**0.6764**	**0.9748**	**0.7961**
molecule 17	**0.7397**	**0.5731**	**0.6412**	**0.6969**	**0.9845**	**0.9229**
molecule 18	**0.9488**	**0.9888**	**0.8326**	**0.6321**	**0.9598**	**0.9277**
molecule 19	**0.816**	**0.7398**	**0.5204**	**0.6014**	**0.9745**	**0.8458**
molecule 20	**0.9108**	**0.7676**	**0.5595**	**0.5785**	**0.9474**	**0.6092**
molecule 21	**0.9433**	**0.7536**	**0.6593**	**0.7457**	**0.941**	**0.6168**

- **This table contains values for the absorption properties which were used to for screening, these are the descriptors used in ADMET Predicted Profile --- Regression in ADMETsar**

Table 5: Summary of all the descriptors used for determining the elimination properties of the compound

ELIMINATION PROPERTIES	
MOLECULES	**RENAL ORGANIC CATION TRANSPORTER**
molecule 1	**0.9277**
molecule2	**0.9359**
molecule 3	**0.9359**
molecule 4	**0.9384**
molecule 5	**0.9266**
molecule 6	**0.9266**
molecule 7	**0.9266**
molecule 8	**0.9266**
molecule 9	**0.9266**
molecule 10	**0.9266**
molecule 11	**0.8989**
molecule 12	**0.9603**

molecule 13	**0.9266**
molecule 14	**0.9418**
molecule 15	**0.9266**
molecule 16	**0.9156**
molecule 17	**0.9359**
molecule 18	**0.9266**
molecule 19	**0.9427**
molecule 20	**0.9397**
molecule 21	**0.9532**

- **This table contains values for the elimination properties which were used to for screening, these are the descriptors used in ADMET Predicted Profile --- Regression in ADMETsar**

Table 6: Summary of all the descriptors used for determining the metabolism properties of the compound

METABOLISM PROPERTIES								
MOLECULE	**CYP450 2C9 Substrate**	**CYP450 3A4 Substrate**	**CYP450 1A2 Inhibitor**	**CYP450 2C9 Inhibitor**	**CYP450 2D6 Inhibitor**	**CYP450 2C19 Inhibitor**	**CYP450 3A4 Inhibitor**	**CYP Inhibitory Promiscuity**
molecule 1	**0.8247**	**0.7033**	**0.5447**	**0.8174**	**0.9397**	**0.957**	**0.9583**	**0.9364**
molecule2	**0.8447**	**0.7534**	**0.9046**	**0.939**	**0.9729**	**0.9762**	**0.96**	**0.9927**
molecule 3	**0.8447**	**0.7534**	**0.9046**	**0.939**	**0.9729**	**0.9762**	**0.96**	**0.9927**
molecule 4	**0.7575**	**0.7201**	**0.7049**	**0.9059**	**0.946**	**0.9396**	**0.9653**	**0.9713**
molecule 5	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 6	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 7	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 8	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 9	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 10	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 11	**0.8418**	**0.7786**	**0.9088**	**0.9043**	**0.9707**	**0.9622**	**0.9543**	**0.9759**
molecule 12	**0.8331**	**0.7858**	**0.8933**	**0.9082**	**0.9398**	**0.9721**	**0.9763**	**0.9809**
molecule 13	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 14	**0.7952**	**0.6606**	**0.6446**	**0.9498**	**0.9577**	**0.9718**	**0.9819**	**0.9896**
molecule 15	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 16	**0.8125**	**0.6953**	**0.5793**	**0.8225**	**0.9384**	**0.9531**	**0.9524**	**0.9326**
molecule 17	**0.8447**	**0.7534**	**0.9046**	**0.939**	**0.9729**	**0.9762**	**0.96**	**0.9927**
molecule 18	**0.7886**	**0.6982**	**0.8326**	**0.8808**	**0.9554**	**0.9578**	**0.9484**	**0.9647**
molecule 19	**0.8072**	**0.6804**	**0.7114**	**0.9457**	**0.9688**	**0.9772**	**0.9463**	**0.9918**
molecule 20	**0.8307**	**0.555**	**0.723**	**0.8863**	**0.9669**	**0.9472**	**0.8829**	**0.9776**
molecule 21	**0.8581**	**0.6586**	**0.8273**	**0.8514**	**0.9245**	**0.9207**	**0.9569**	**0.9434**

Table 7: Summary of all the descriptors used for determining ADMET Predicted Profile of the compound

ADMET Predicted Profile --- Regression					
MOLECULES	**Aqueous solubility**	**Caco-2 Permeability**	**Rat Acute Toxicity**	**Fish Toxicity**	**TetrahymenaPyriformis Toxicity**
molecule 1	**-1.9225**	**1.4551**	**1.8543**	**1.9458**	**-0.0948**
molecule2	**-1.8273**	**0.3625**	**1.3577**	**2.3886**	**-0.385**
molecule 3	**-1.8273**	**0.3625**	**1.3577**	**2.3886**	**-0.385**
molecule 4	**-1.0568**	**1.5044**	**1.5194**	**2.6457**	**-0.3949**
molecule 5	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 6	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 7	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 8	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 9	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 10	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 11	**-1.6845**	**0.9866**	**1.3311**	**3.1761**	**-0.659**
molecule 12	**-0.2759**	**1.407**	**1.7348**	**3.2018**	**-0.3569**
molecule 13	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 14	**-1.2366**	**1.4302**	**1.7842**	**2.5027**	**-0.1446**
molecule 15	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 16	**-2.8186**	**1.4249**	**1.7694**	**1.5237**	**0.201**
molecule 17	**-1.8273**	**0.3625**	**1.3577**	**2.3886**	**-0.385**
molecule 18	**-3.5022**	**1.395**	**1.3275**	**1.892**	**0.3852**
molecule 19	**-2.2069**	**0.4763**	**1.6551**	**2.1283**	**0.0364**
molecule 20	**-2.2903**	**0.6199**	**2.0513**	**2.089**	**0.5336**
molecule 21	**-3.0368**	**0.8025**	**1.9075**	**0.6405**	**0.0083**

- **This is ADMET Predicted Profile , produced by ADMETsar online server of all the 21 molecule**

CONCLUSION

Valproic acid (VPA) or Valproate is primarily used to cure epilepsy and bipolar disorder to prevent migraine. It is also used for the prevention of seizures. It is one of the drugs of choice for preventing convulsions because of its seizure prevention in wide range of epileptic types. VPA suffers from several long term and short term toxicity, including teratogenicity. Therefore, search for new VPA type drug is a constant endeavour for pharmaceutical companies. The present study was a primitive attempt to evaluate a few VPA analogues for their ADME and toxicity.

ADMET profiles of all the molecules predicted that all of them are eligible drug candidate. Also in ADMET Predicted Profile we found several candidate compounds which were better than valproic acid in some aspect as mentioned in Table 3, but none of the compound was consensus in all the descriptors. So, it can be inferred that none of the molecule investigated in present study is better than valproic acid in overall ADMET profiling, but are worth investigating further for their anti-convulsant properties.

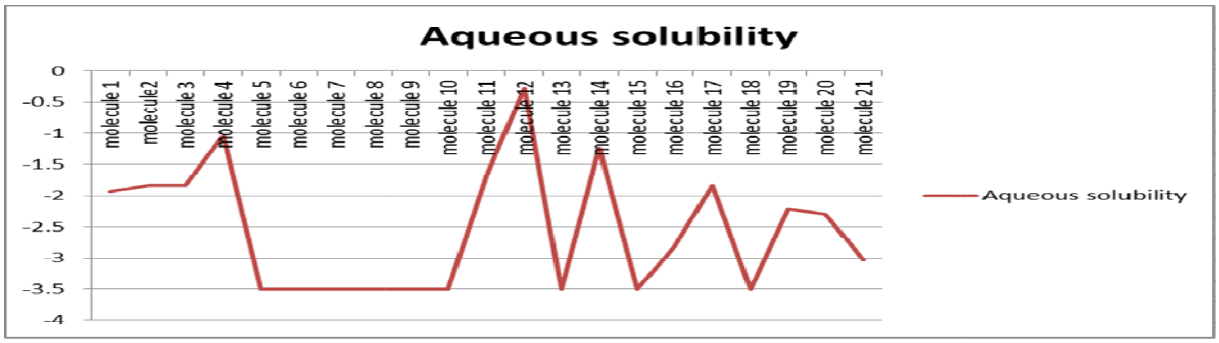


Fig 1: Graph showing the aqueous solublity (LogS) Value of all the molecules

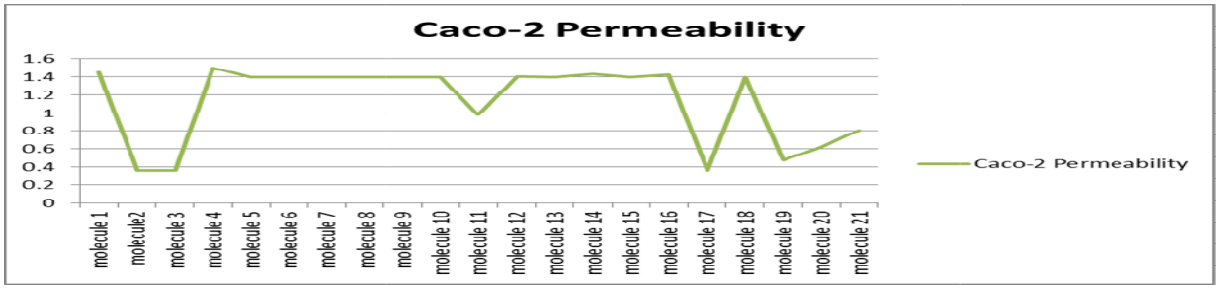


Fig 2: Graph shows the caco-2(LogPapp, cm/s)value of all the molecules

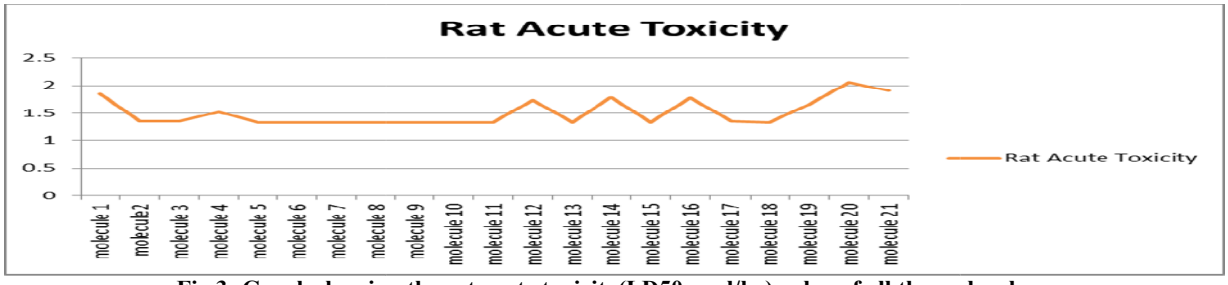


Fig 3: Graph showing the rat acute toxicity(LD50, mol/kg) value of all the molecules

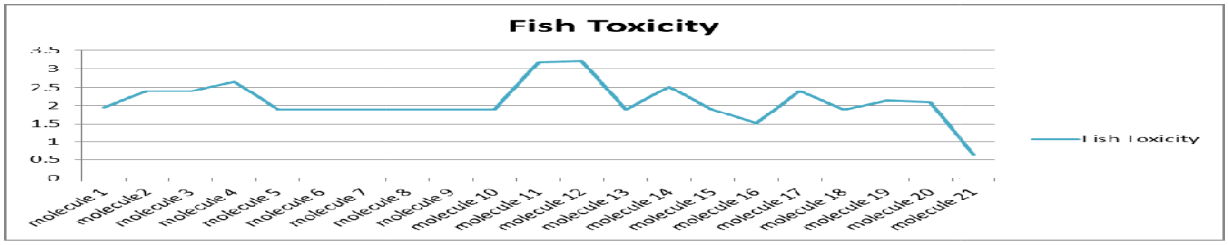


Fig .4: Graph showing the Fish toxicity (pLC50, mg/L) value of all the molecules

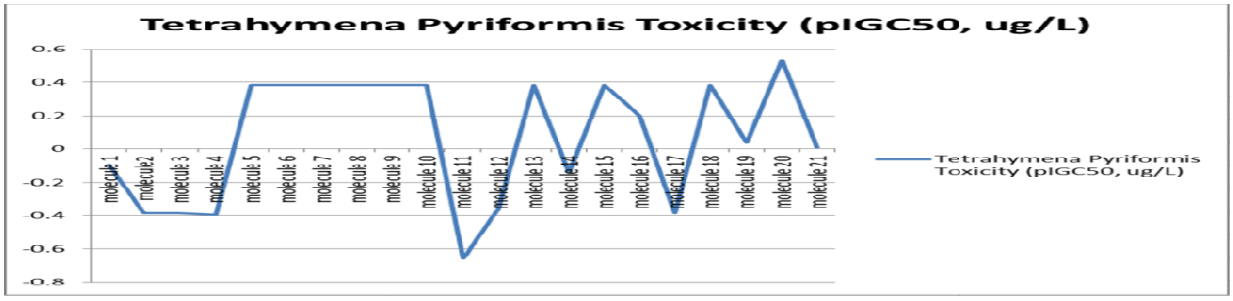


Fig 5: Graph showing the Tetrahymena Pyriformis Toxicity (pIGC50, ug/L) value of all the molecules

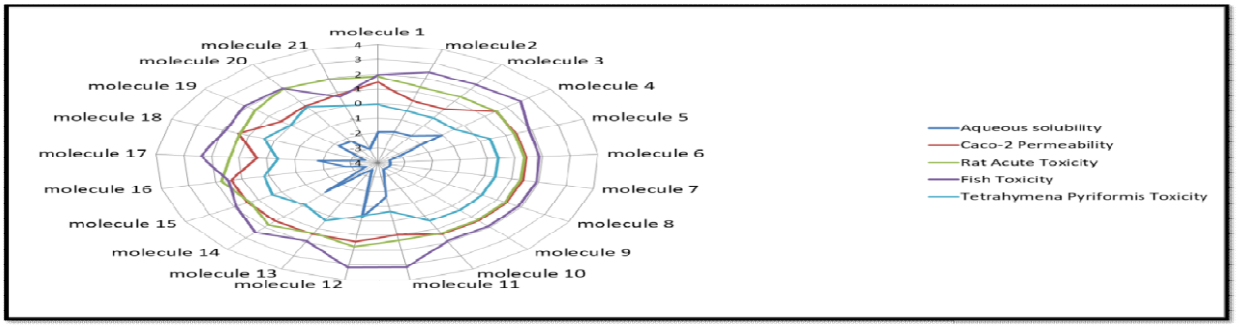


Fig 6: Graph showing Value of all the molecules in a single property radar graph

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