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INVIVO PREDICTION OF PHARMACOKINETIC PARAMETERS USING DIFFERENT SOFTWARES

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ABSTRACT

SWISS ADME is a free webtool which gives physicochemical properties of a drug in a one click. Molinspiration Cheminformatics Software also gives bioactive score, galaxy 3D structure and molecular properties of a drug. But when compared to molinspirationcheminformatics Swiss ADME in easily accessible by experts and non-experts in the field.It helps in the drug discovery. Applying software tools is the new and best approach in the present days. In the future, these approaches may grow rapidly.

INTRODUCTION

ADME is the abbreviation for absorption, distribution, metabolism and excretion. ADME studies are designed to investigate how a chemical [example: a drug compound] is processed by a living organism

Absorption

Absorption describes how a chemical enters the body. Absorption Relates to the movement of a chemical from the administration site to the blood stream.[1]

Distribution

Once a drug has been Absorbed, it moves from the absorption site to tissues around the body to around the Body, the distribution from one part of the body to another is typically accomplished via the bloodstream and it also across from cell to cell *Metabolism* Drug metabolism is the bio transformation of a drug by organ/tissue so that the drug can be excreted.

Excretion

Is the process by which the metabolized drug compound is eliminated from the body.

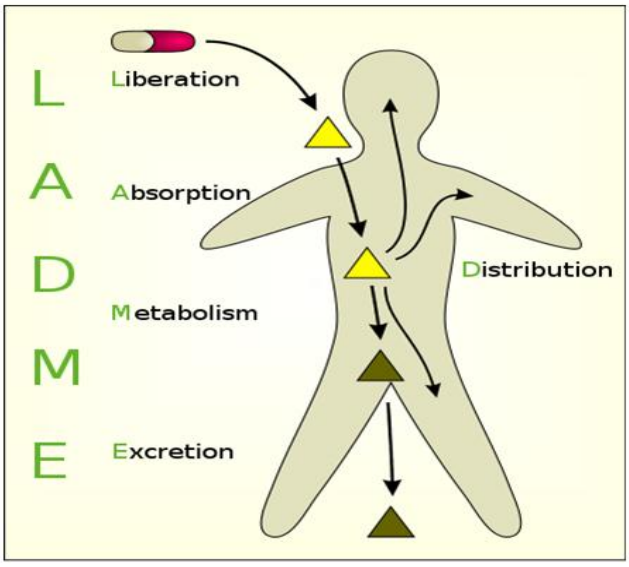

Figure 1: Most drug excretion occurs as feces/urine.[2]

To find out ADME parameters following software's are available: -

- ❖ SWISS ADME
- ❖ ADME PREDICTOR
- ❖ MOLINSPIRATION CHEMINFORMATICS

Swiss ADME

SWISSADME is online web tool used for the prediction of physicochemical pharmacokinetic properties of different molecules in graphical way like boiled egg, bioavailability radar, drug likeness by Lipinski rule veber rules.

It gives complete picture of molecules of their pharmacokinetic properties. These pharmacokinetic properties give the complete drug data and its GIT absorption in a graph plotted against ALOGP VS PSA respectively. Egan egg is called as BOILED EGG (brain or intestinal estimated permeation predictive model) which gives the complete absorption pattern in GIT and prediction for brain access for present in the white region of boiled egg it describes about absorption in GIT. If a drug molecule is present in yellow region, it describes then the drug has high permeability to cross blood passive diffusion and it has two regions white region and yellow region. If a drug molecule is brain barrier.

SWISSADME gives physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness, and medicinal chemistry properties.[3]

SWISSADME is the online website opened freely at http://www.swissadme.ch and its also user friendly. SWISSADME is most important part in the Swiss Drug Design and it has various CADD tools which are implemented by Molecular Modeling Group of SIB Swiss institute of bioinformatics, eg. ligand based virtual screening (Swiss similarity), bio target prediction (Swiss target prediction), molecular docking (Swiss dock), bio isosteric design (Swiss bio isostere), or molecular mechanics (Swiss Param).

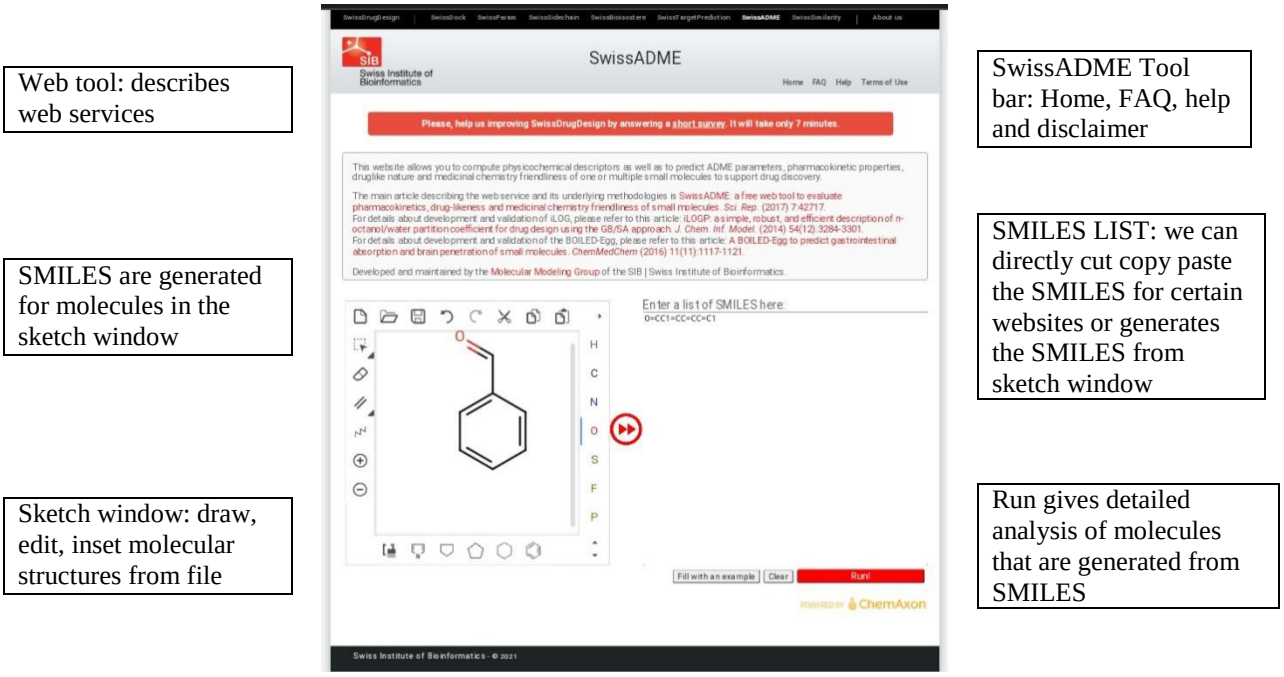

Figure 2.

Swiss ADME Submission Web Page

Submission page directly displays on the website http://www.swissadme.ch in which the pharmacokinetic and physicochemical properties of each and every molecule will be determined. The pharmacokinetic properties are like drug absorption {GIT} ADME Properties. As shown in the figure the black web tool bar gives the information regarding all other remaining web browsers in Swiss drug design tools and the second swissadme tool bar gives the information about swissadme, FAQ, Help pages, and contacts. And it also contains a window called molecular sketch window developed by chem Axon's marvin JS (http://www.chemaxon.com) that helps the users to insert a file from a database, draw and to edit a 2d structure.[4]

One panel per Molecule

Generated in one web page after run it contains the total information of drug molecule one by one in same web page. The one panel per molecule has various columns of different parameters of drug molecule.

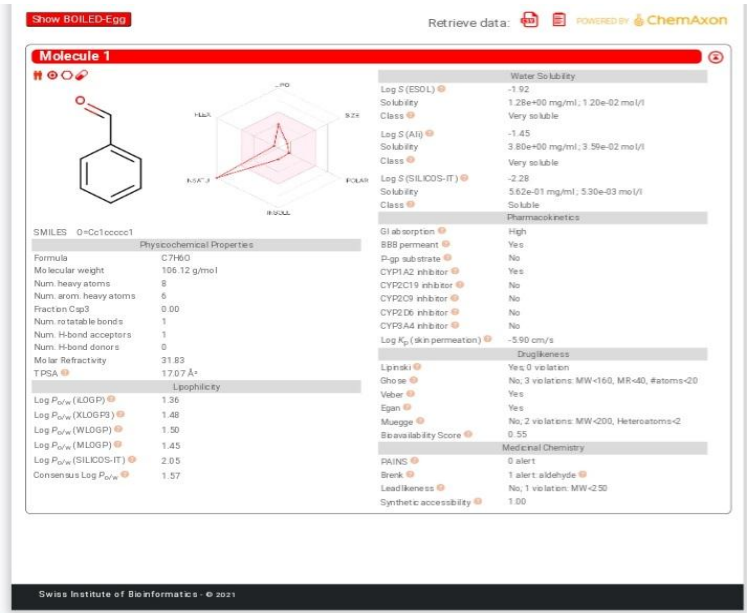

Figure 3.

Distribution of different physicochemical and pharmacokinetic parameters which are computed in one panel per molecule output. different parameters like physicochemical properties, lipophilicity, pharmacokinetics, Drug likeliness and medicinal chemistry. The one panel per molecule is started with name of molecule and divided into various section. The molecule is described as chemical structure and canonical SMILES along with bioavailability radar.

Chemical Structure and Bioavailability Radar

It includes canonical structures and SMILES present below the name of the molecule.it also comprises the bioavailability radar which describes about drug likeliness. Six physicochemical parameters are taken into consideration such as lipophilicity, size, polarity, solubility, flexibility, and saturation.[5]

Physicochemical Properties

It gives information regarding molecular weight, molecular refractivity, count of specific atom types and polar surface area are present in this section. The polar surface area is determined by fragmental technique called topological polar surface [TPSA] having Sulphur and phosphorus as polar atoms. As these properties will give faster results of ADME parameters like absorption and brain access.

The physicochemical properties column gives different parameters like: -

- Formula
- Molecular weight
- Number of heavy bonds
- Number of aromatic heavy bonds
- Fraction of csp3
- Number of rotatable bonds
- Number of H-bonds acceptors
- Number of H-bonds receptors
- Molar refractivity
- TPSA

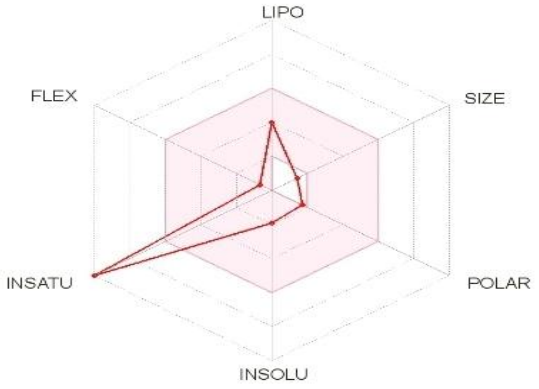

Figure 4.

The given figure bioavailability radar gives the drug likeliness of the molecule. The pink area represents the optimal ranges of each property like lipophilicity between -0.7 and +5.0, size molecular weight between 150 and 500g/mol, polarity: TPSA between 20 and 130 A^2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp^3 hybridization not less than 0.25, and flexibility not ≥9 rotatable bonds.[6]

Water solubility

Water solubility controls absorption and influences the processes formulation and handling.

General solubility equation is

$$\text{Log S} = 0.5\text{-}0.01\times (\text{MP °c} - 25)\text{-log p}$$

For orally administered drugs, solubility is one of the Major properties.

For parenteral use of drugs, the drug should be highly soluble. There are 2 methods to determine the water solubility.
1) ESOL model
2) Ali et al.

Strategies to improve solubility
1) Increase solubility
2) Structure modification
3) Carrier mediated
4) Drug complexation[7]

Drug likeliness

Drug likeliness along with bioavailability of the drug makes a molecule suitable for oral administration, structural similarities and physico-chemical properties forms the drug- likeliness
Drug- like properties
SAR for target potency and target selectivity
Receptry- drug interactions
Modifications to modulate metabolism, for bioavailability, to reduce toxicity
Scaffold- hopping to allow patentability
A drug - like molecule has a logarithm of partition coefficient (log p) between - o.4 and -5.6,molecular weight 160-480g/mol, molar refractivity of 40-130.

The Swiss ADME software tool provides access to five rule - based filters.
1) Lipinski (Pfizer)
2) The Ghose (Amgen)
3) Veber (GSK)
4) Egan(pharmacia)
5) Muegge (Bayer)

Medicinal chemistry plays a major role in the drug discovery endeavours[8]

Pharmacokinetics

Pharmacokinetic models are the mathematical tools that allow simulating drug concentration levels in the blood prior to real administration
For the evaluation and pharmacokinetics optimization of tiny molecules, ADME properties play a vital role
GI absorption
BBB permeation
PGT substrate
CYP inhibitors
The values of the above properties are determined in the pharmacokinetics

Types of Pharmacokinetic Models
1) Compartment Models
2) One compartment models
3) Two compartment models

Graphical Output

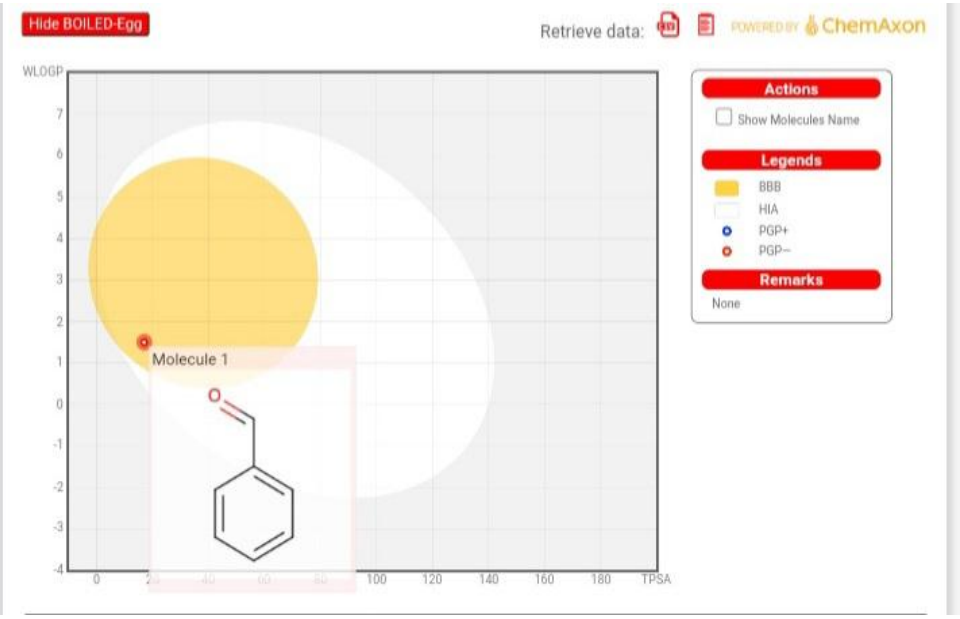

Figure 5.

The above-mentioned picture represents BOILED-Egg (Brain or Intestinal EstimateD Permeation Predictive Model which is also known as Egan Egg which gives the complete detailed absorption pattern in GI as well as brain access.

It has two regions
White region: - if a drug molecule present in this region, it describes about absorption in GIT

Yellow region: - if a drug molecule is present in this region, the drug has high permeability to cross blood brain barrier.[9]

Molinspiration Cheminformatics Software

Molinspiration is an independent research organization focused on development and application of modern cheminformatic techniques, especially in connection with the internet.

Molinspiration is a free online server which affords wide range of cheminformatics software tools assisting processing and manipulation of molecules, fragmentation of molecules, generation of tautomers, molecule normalization, SMILES and SDFile conversion, drug design, molecular properties calculation which are necessary in quantitative structure activity relationship, molecular modelling, depiction of high quality molecules, molecular database tools aiding substructure and similarity searches. Molinspiration also supports prediction of bioactivity, fragment – based virtual screening, visualization of data. Molinspiration software tools are written in java script, so it can be used on computer platform. This software is used for the calculation of molecular properties like number of hydrogen bond donors and acceptors, logP, polar surface area and also prediction of bioactivity scores like GPCR Ligands, nuclear properties, kinase inhibitors; ion channel modulators. It gives high quality scientific results. Molinspiration cheminformatics software is available on smart devices like android phones, I phones, tablets and desktop computers.[10]

Molinspiration Submission Page

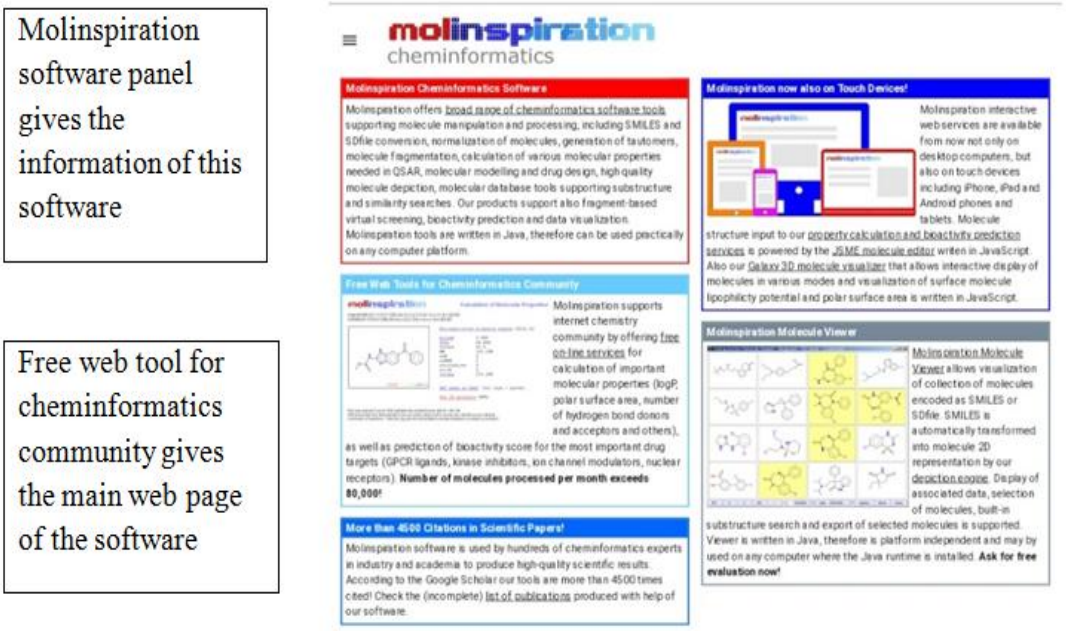

Figure 6.

Molinspiration cheminformatics software is directly displays on website https://www.molinspiration.com/ it gives detailed description of molinspiration software and also other information like:

1. Molinspiration products and services
2. Calculations of molecular properties and prediction of bioactivity
3. Galaxy 3D generator
4. Molecular databases
5. Molinspiration publications
6. Molinspiration FAQ
7. About molinspiration

Software Products Available In Molinspiration

1) Molinspiration depiction – molecules are depicted in high quality encoded as SMILES of MDL profile
2) Molinspiration property calculator – easy interactive calculation of molecular properties, QSAR table generation
3) Mib engine - molecular processing and calculation of molecular properties, molecular image generation
4) Molinspiration data viewer – visualization of QSAR datasets with interactive molecule display
5) Miscreen engine – screening and validation of large molecular libraries, virtual screening engine enabling development of pharmacophore models
6) Molinspiration molecular viewer – molecular visualization og large sets
7) Misearch engine – flexible molecular data base supporting substructure, similarity and pharmacophore similarity searches
8) Galaxy – generation of 3D structure from SMILES[11]

Molinspiration software

We can calculate different properties of molecules or compounds by generating the smiles or by copy paste the smiles from different websites or by drawing the molecular structure in sketch window.

Figure 7.

Calculate properties

Used to Calculate the properties of molecules which are pasted in smiles box or by the structure which is drawn on sketch window.

The Properties are like

- ❖ MiLog P
- ❖ TPSA (total polar surface area)
- ❖ Natoms
- ❖ Molecular weight
- ❖ Nohnh
- ❖ Nviolations[12]

Predict Bioavailability

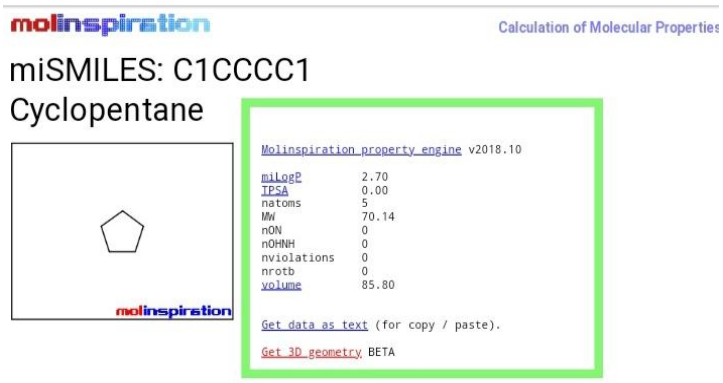

Figure 8.

The bioactivity score is defined as the measurement of the potency of a molecule.

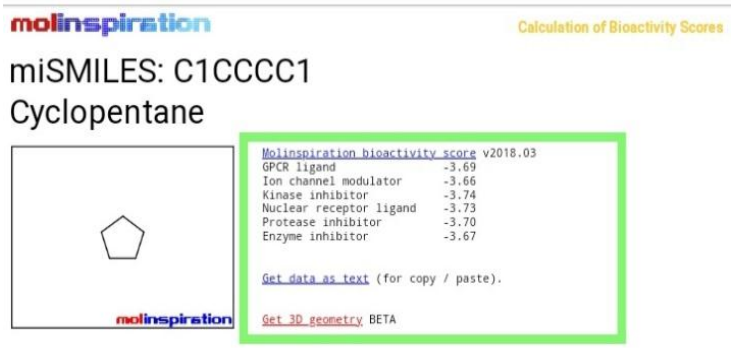

Figure 9.

VALUES FOR BIOACTIVE SCORE
>0.0=active
Between -5.0 and 0.0=moderately active

<0.0=inactive
By observing these values, benzene compound is good and meditatively active complex[12]

Galaxy 3d generator
Galaxy 3D generator gives complete 3D structure of the molecule which is given in the sketch draw window.

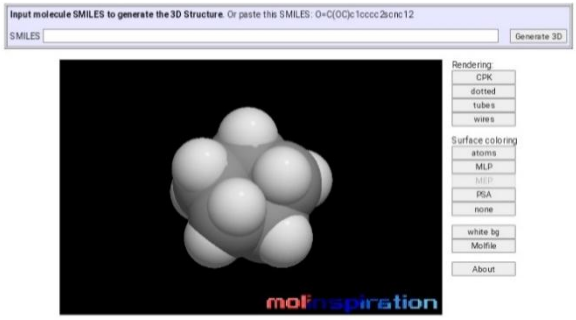

Figure 10.

ACCEPTABLE RANGE VALUES
Molecular weight =<500
Hydrogen bond donors=<5
Hydrogen bond acceptor=<10
High lipophilicity (expressed as logP) =<5
Molar refractivity=between 40-130

If the values are greater than the above-mentioned values, the molecule is not good for human consumption[13]

CONCLUSION
Therefore, comparing Molinspiration Cheminformatics with Swiss ADME free web tool, Swiss ADME has easily accessible interface and in one click we get all properties like lipophilicity, water solubility, pharmacokinetics, and drug likeliness in detail whereas by Molinspration Cheminformatics only bioactive score and molecular properties, galaxy 3D structure are known.

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