Date:

Weblem 6: SwissADME

(http://www.swissadme.ch)

Aim:

Introduction to SwissADME, a free web server tool

Introduction:

A large number of molecular structures are evaluated based on a wide range of criteria during the time- and resource-intensive processes of drug discovery and development in order to guide the choice of which chemicals to synthesise, test, and promote, with the ultimate goal of identifying those with the best potential to become a medicine that works for patients. The compounds must exhibit both a high level of biological activity and low toxicity. Equally crucial is the availability to and concentration at the therapeutic target in the body. The conventional approach to thinking about pharmacokinetics (i.e., what happens to a medicinal chemical in the body) is to separate the numerous effects that affect the target's access into separate parameters.

It has been shown that early ADME calculation during the discovery phase significantly lowers the percentage of clinical failures attributable to pharmacokinetics. In the early stages, when there are many researched chemical structures but few available compounds, computer models have been promoted as a viable alternative to experimental approaches for the prediction of ADME. The goal of many in-silico techniques is to predict ADME parameters from molecular structure. It is noteworthy that Lipinski et algroundbreaking .'s research looked at orally active chemicals to identify physicochemical ranges with a high likelihood of being an oral medication. The link between pharmacokinetic and physicochemical characteristics was defined by the so-called Rule-of-Five.

Substructure searches can directly describe molecules whereas physicochemical characteristics provide a more general description of the structure. Structural Alert, PAINS, and Lilly MedChem filters, which are used to rid chemical libraries of compounds that are expected to be unstable, reactive, poisonous, or likely to interfere with biological tests due to generalised frequent hits, dyes, or aggregators, are all based on these approaches. The SwissADME web tool described here is freely available at http://www.swissadme.ch and designed for easy submission and result analysis, even for those unfamiliar with CADD. SwissADME's strong points include, non-exhaustively: many input ways, computation for multiple compounds, and unique access to proficient methodologies when compared to the state-of-the-art of free web-based ADME and pharmacokinetics applications.

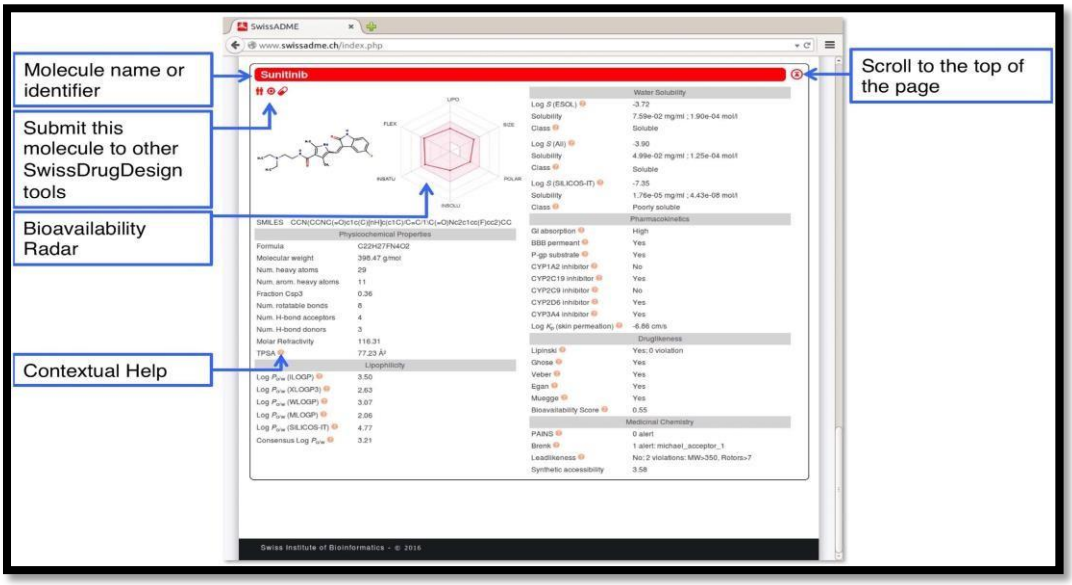
SIB Swiss Institute of Bioinformatics, including molecular docking (SwissDock), bioisosteric design (SwissBioisostere), ligand-based virtual screening (SwissSimilarity), and molecular mechanics.

Submission Web Page:

- Accessing http://www.swissadme.ch in a web browser displays directly the submission page of SwissADME, where molecules to be estimated for ADME, physicochemistry, drug-likeness, pharmacokinetics and medicinal chemistry friendliness properties can be input.
- A black toolbar at the top of the Webpage allows the user to navigate within the different SwissDrugDesign tools.
- A second bar gives access to different information regarding SwissADME, among which the FAQ and Help pages as well as legal disclaimer and contacts.
- The input zone itself comprises a molecular sketcher based on ChemAxon's Marvin JS that enables the user to import (from a file or an external database), draw, and edit a 2D chemical

structure, and to transfer it to a list of molecules.

- This list, on the right-hand side of the submission page, is the actual input for computation.
- It can be edited as a standard text, allowing for typing or pasting SMILES. The list is made to contain one input molecule per line, defined by SMILES and optionally a name separated by a space.
- If name is omitted, SwissADME will automatically provide an identifier.
- Noteworthy, both buttons for transferring the sketch to SMILES list and for running the computation are dynamic, in the sense that they are active only if the action is possible.
- At the time of writing, one can expect a result in 1 to 5 seconds for a drug-like molecule.
- Examples can be loaded in the SMILES list by clicking on the "Fill with an example" button.



One-panel-per-molecule Output

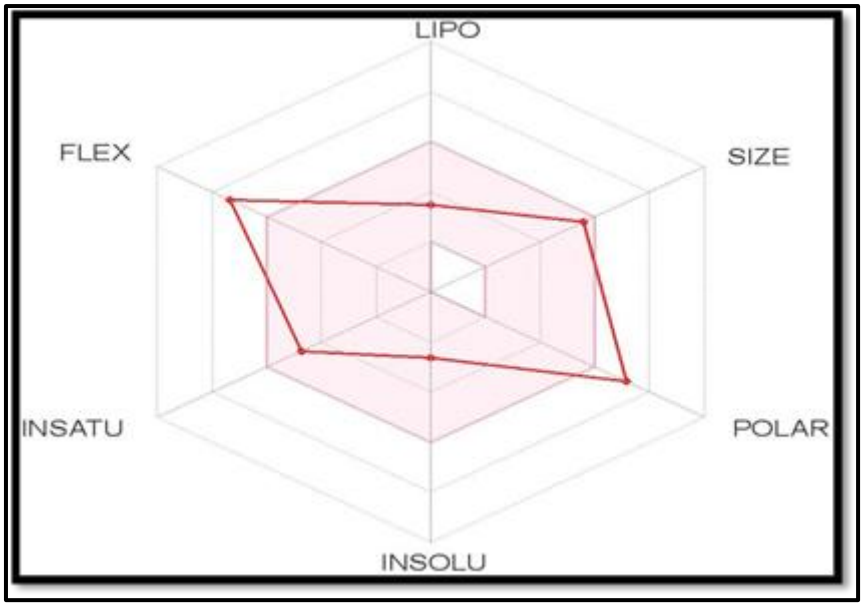
- The output panels are loaded in the same Web page.
- There is one panel compiling all values for each molecule. It is filled immediately after calculation completion, one molecule after the other.
- This way it is possible to inspect the results for the first compounds without waiting for the whole list to be treated.
- This one-panel-per-molecule is headed by the molecule name and divided into different sections.

Chemical Structure and Bioavailability Radar

- The first section, including two-dimensional chemical structure and canonical SMILES, is located below the title.
- It shows on which chemical form the predictions were calculated (refer to Computational Methods).
- Moreover, our Bioavailability Radar is displayed for a rapid appraisal of drug- likeness.
- Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation
- A physicochemical range on each axis was defined by descriptors and depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered drug-like.
- Leaving the mouse over the radar gives further information about the descriptors (see also Physicochemical Properties and Computational Methods).

Physicochemical Properties:

This section compiles straightforward molecular and physical descriptors such molecular weight (MW), molecular refractivity (MR), count of particular atom kinds, and polar surface area (PSA). OpenBabel, version 2.3.0, is used to calculate the values. By treating sulphur and phosphorus as polar atoms, the topological polar surface area (TPSA), a fragmental method, is used to determine the PSA. This has demonstrated to be an effective descriptor in many models and rules to quickly estimate some ADME properties, particularly with regards to biological barrier crossing like absorption and brain access.



Lipophilicity:

- The partition coefficient between n-octanol and water (log Po/w) is the classical descriptor for Lipophilicity.
- It has a dedicated section in SwissADME due to the critical importance of this physicochemical property for pharmacokinetics drug discovery.
- Many computational methods for log Po/w estimation were developed with diverse performance on various chemical sets.
- Common practice is to use multiple predictors either to select the most accurate methods for a given chemical series or to generate consensus estimation.
- The models behind the predictors should be as diverse as possible to increase the prediction accuracy through consensus log Po/ 28.
- The consensus log Po/w is the arithmetic mean of the values predicted by the five proposed methods.

Water Solubility:

- Having a soluble molecule greatly facilitates many drug development activities, primarily the ease of handling and formulation.
- Moreover, for discovery projects targeting oral administration, solubility is one major property influencing absorption.
- As well, a drug meant for parental usage has to be highly soluble in water to deliver a sufficient quantity of active ingredient in the small volume of such pharmaceutical dosage.
- Two topological methods to predict Water Solubility are included in SwissADME.
- The first one is an implementation of the ESOL model36 and the second one is adapted from Ali et al.

- Both differ from the seminal general solubility equation since they avoid the melting point parameter; the latter being challenging to predict.
- Moreover they demonstrate strong linear correlation between predicted and experimental values (R2 = 0.69 and 0.81, respectively).
- SwissADME third predictor for solubility was developed by SILICOS-IT.
- SwissADME also provides solubility in mol/l and mg/ml along with qualitative solubility classes.

Pharmacokinetics:

- Specialized models, whose predictions are compiled in the Pharmacokinetics section, evaluate individual ADME behaviors of the molecule under investigation.
- One model is a multiple linear regression, which aims at predicting the skin permeability coefficient (Kp).
- It is adapted from Potts and Guy, who found Kp linearly correlated with molecular size and lipophilicity (R2 = 0.67).
- The more negative the log Kp (with Kp in cm/s), the less skin permeant is the molecule.
- The predictions for passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation both consist in the readout of the BOILED-Egg model, an intuitive graphical classification model, which can be displayed in the SwissADME result page by clicking the red button appearing below the sketcher when all input molecules have been processed.
- Other binary classification models are included, which focus on the propensity for a given small molecule to be substrate or inhibitor of proteins governing important pharmacokinetic behaviors.
- The knowledge about compounds being substrate or non-substrate of the permeability glycoprotein is key to appraise active efflux through biological membranes, for instance from the gastrointestinal wall to the lumen or from the brain.
- One major role of P-gp is to protect the central nervous system (CNS) from xenobiotics. Importantly as well, P-gp is over expressed in some tumor cells and leads to multidrug-resistant cancers.
- Also essential is the knowledge about interaction of molecules with cytochromes P450 (CYP).
- This super family of isoenzymes is a key player in drug elimination through metabolic biotransformation.
- It has been suggested that CYP and P-gp can process small molecules synergistically to improve protection of tissues and organisms.
- Inhibition of these isoenzymes is certainly one major cause of pharmacokinetics- related drug-drug interactions leading to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites.
- SwissADME enables the estimation for a chemical to be substrate of P-gp or inhibitor of the most important CYP isoenzymes.
- We applied the support vector machine algorithm (SVM) on meticulously cleansed large datasets of known substrates/non-substrates or inhibitors/non-inhibitors.
- In similar contexts, SVM was found to perform better than other machine-learning algorithms for binary classification.
- The models return “Yes” or “No” if the molecule under investigation has higher probability to be substrate or non-substrate of P-gp (respectively inhibitor or non- inhibitor of a given CYP).
- SVM models rely merely on molecular and physicochemical descriptors generated by SwissADME.
- We believe that this improves robustness and sustainability of the underlying methodologies.

- In particular, not using molecular fingerprints, molecular graphs or other structural descriptions can be an handicap to generate high statistical values but should also limit over fitting biases and yield more generalist predictive models, not necessarily influenced by specific chemical scaffolds or moieties.
- In our practice, these well-performing models able to estimate important ADME behaviors are of great support for pharmacokinetics optimization and evaluation of small molecules.

Drug Likeness:

- As defined earlier, "drug-likeness" assesses qualitatively the chance for a molecule to become an oral drug with respect to bioavailability.
- Drug-likeness was established from structural or physicochemical inspections of development compounds advanced enough to be considered oral drug-candidates.
- This notion is routinely employed to perform filtering of chemical libraries to exclude molecules with properties most probably incompatible with an acceptable pharmacokinetics profile.
- This SwissADME section gives access to five different rule-based filters, with diverse ranges of properties inside of which the molecule is defined as drug-like.
- These filters often originate from analyses by major pharmaceutical companies aiming to improve the quality of their proprietary chemical collections.
- The Lipinski (Pfizer) filter is the pioneer rule-of-five implemented.
- The Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods were adapted.
- Any violation of any rule described here appears explicitly in the output panel.
- This semi-quantitative rule-based score relying on total charge, TPSA, and violation to the Lipinski filter defines four classes of compounds with probabilities of 11%, 17%, 56% or 85%.4

Medicinal Chemistry:

- The purpose of this section is to support medicinal chemists in their daily drug discovery endeavors.
- Two complementary pattern recognition methods allow for identification of potentially problematic fragments.
- PAINS (for pan assay interference compounds, a.k.a. frequent hitters or promiscuous compounds) are molecules containing substructures showing potent response in assays irrespective of the protein target.
- Such fragments, yielding false positive biological output, have been identified by Baell et al. in analyzing six orthogonal assays and breaking down the molecules active on 2 or more assays into 481 recurrent fragments, considered as potentially leading to promiscuous compounds.
- SwissADME returns warnings if such moieties are found in the molecule under evaluation.
- In SwissADME, it is possible to have a chemical description of the problematic fragments found in a given molecule by flying over the "question mark" icon appearing after the fragment list.
- This is implemented for both PAINS and Brenk filters.
- By applying these and other physicochemical filters to design screening libraries, Brenk et al.5 observed that most of the remaining compounds satisfy criteria for "leadlikeness".
- This concept is similar to drug-likeness, yet focusing on physicochemical boundaries defining a good lead, i.e. a molecular entity suitable for optimization.

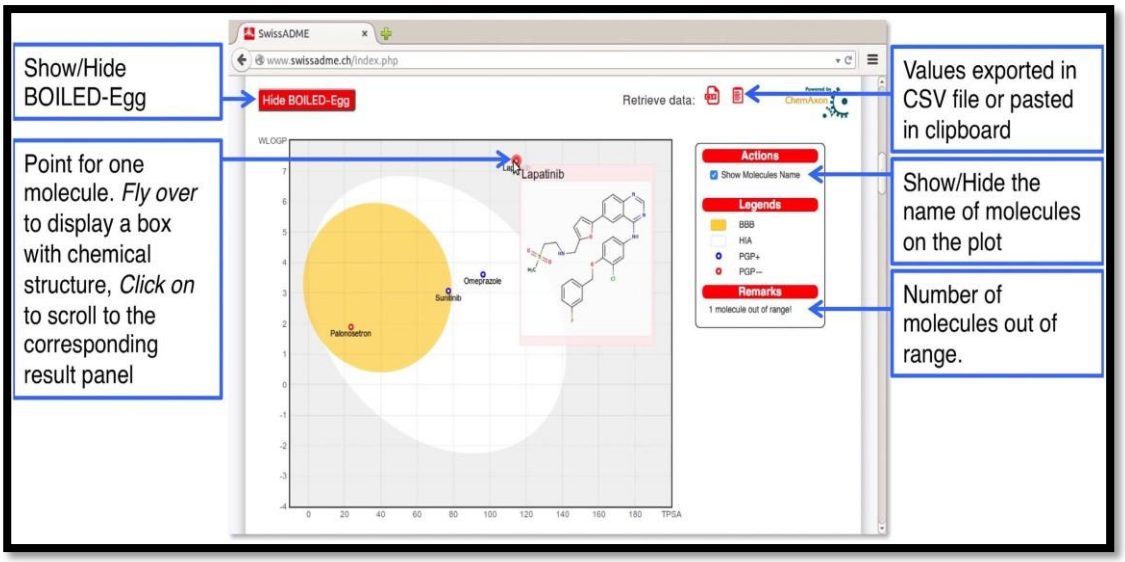
- By definition, leads are subjected to chemical modifications that will most likely increase size and lipophilicity.
- As a consequence, leads are required to be smaller and less hydrophobic than drug- like molecules.
- Synthetic accessibility (SA) is a major factor to consider in this selection process. Obviously, for a reasonable number of molecules, medicinal chemists are the best able to determine SA.
- However, when too many molecular structures prevent an expert evaluation, in silico estimation can be used for pre-filtering.
- Ertl & Schuffenhauer proposed a fingerprint-based approach for SA estimation but including closed-source information about fingerprint definition that prevents a straightforward implementation in our tool open to the scientific community.
- For a given molecule, the fragmental contributions to SA are summed and corrected by the terms describing size and complexity, such as macrocycles, chiral centers, or Spiro functions as defined by Ertl & Schuffenhauer.
- After normalization, the SA Score ranges from 1 (very easy) to 10 (very difficult).
- Human evaluation of synthetic complexity is undeniably subjective and relies on individual chemist's training and experience.
- However, significant linear correlation and small errors especially with SwissADME SA Score that outperformed the reference methods on both sets with smaller errors, and equal or higher linear correlation coefficients demonstrate how this simple and fast methodology can help prioritizing molecules to synthesize.

Graphical Output:

- After all calculations completed, the "Show BOILED-Egg" red button appears below the sketcher to display the graphical output on the same page.
- This consists primarily in the BOILED-Egg, an intuitive method to predict simultaneously two key ADME parameters, i.e. the passive gastrointestinal absorption (HIA) and brain access (BBB).
- Although conceptually very simple as it relies on two physicochemical descriptors only (WLOGP and TPSA, for lipophilicity and apparent polarity), this classification model was built with extreme care regarding statistical significance and robustness.
- The egg-shaped classification plot includes the yolk (i.e. the physicochemical space for highly probable BBB permeation) and the white (i.e. the physicochemical space for highly probable HIA absorption).
- Both compartments are not mutually exclusive and the outside grey region stands for molecules with properties implying predicted low absorption and limited brain penetration.
- In practice, the BOILED-Egg has proven straightforward interpretation and efficient translation to molecular design in a variety of drug discovery settings.
- Contrary to the one-panel-per-molecule concept for other parameters, the graphical output includes prediction for all molecules submitted to SwissADME, thus additional capacities were implemented to enable interactive navigation and easy evaluation.
- Flying over a specific point makes a semi-transparent box appear including the name and structure of the molecule.
- Clicking on a specific point makes the page scroll to the corresponding output panel including all predictions for the molecule.
- Getting back to the graphical output is achieved by clicking on the red up-arrow on the top-right corner of the panel.
- Moreover, on the right of the plot are displayed possible actions (at the moment, to show the name of

the molecules on the graph, only), legends and possible remarks (the number of molecules outside the range of the plot).

- The user may want to hide the plot by clicking the "Hide BOILED-Egg" red button.



Methodology:

1. Using Google search engine search Swiss ADME.
2. In Molecular Sketcher Add, Import or Draw a structure.
3. Transfer the sketched structure to SMILES list.
4. Run the calculations and observe the result page.
5. Browse through various parts of this result page.

Observations:

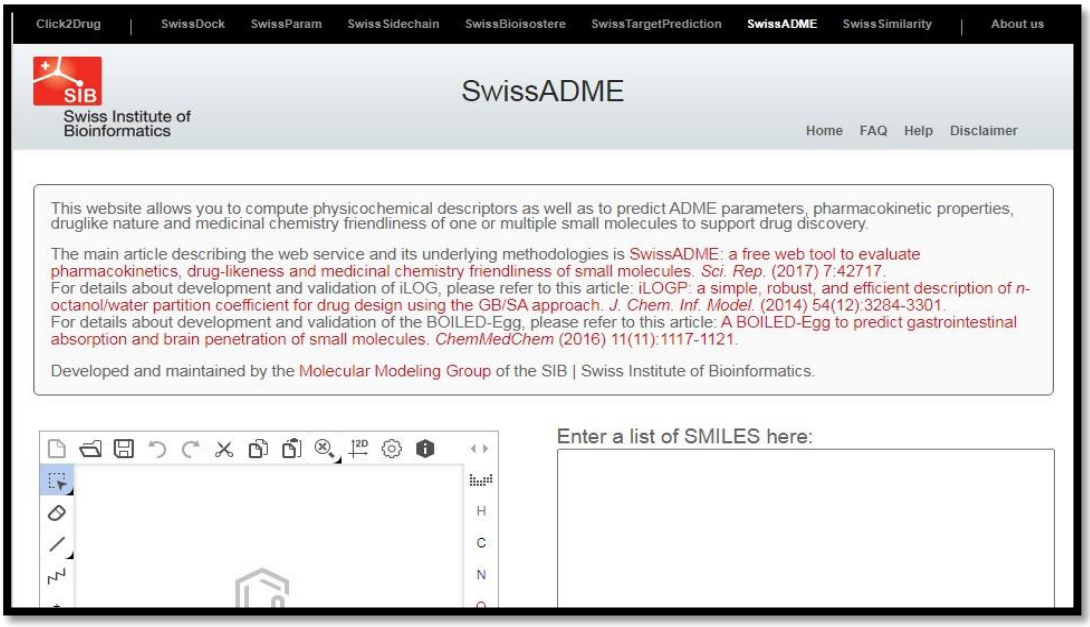


Figure 1: SwissADME Homepage

Figure 2: Molecular Sketcher and Smiles List

Figure 3: Smiles List filled with an example from the given option below

Figure 4: Run the example shown in Smiles Format

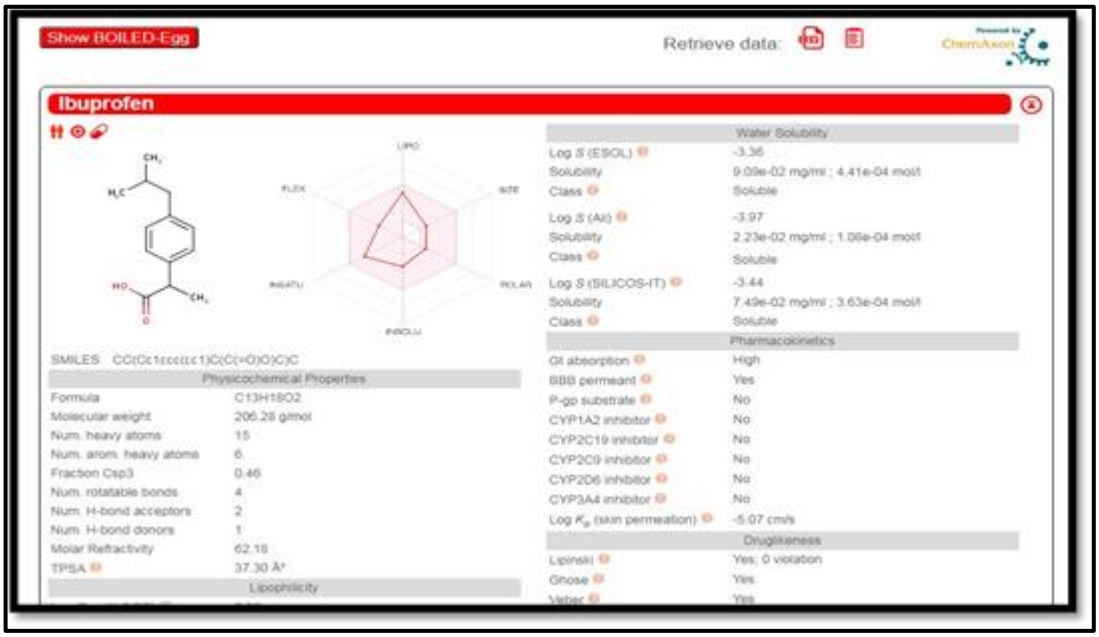


Figure 5: Result page of the given example

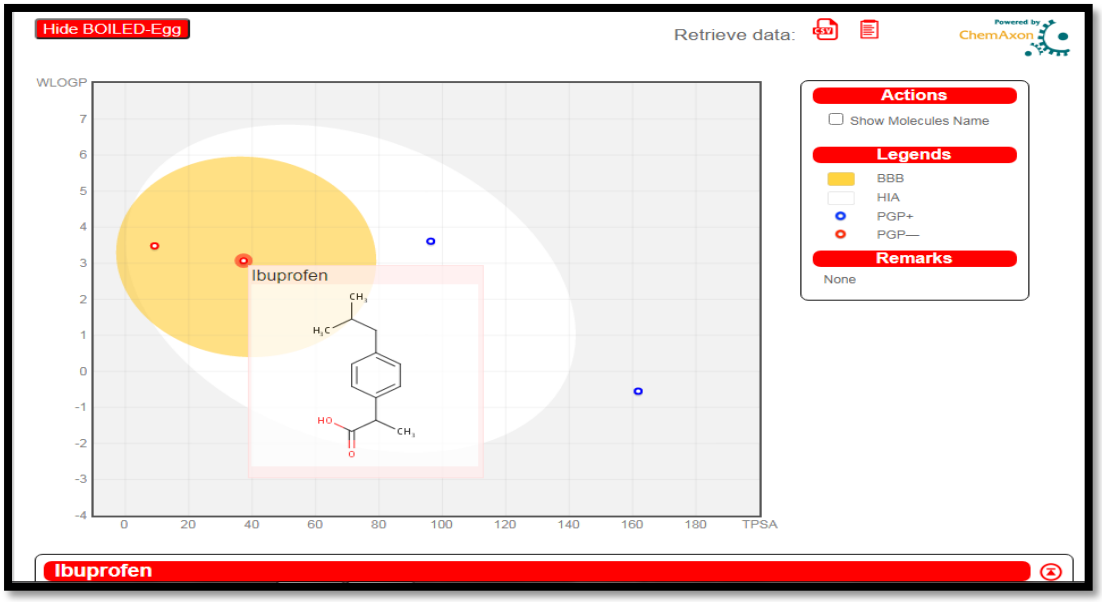


Figure 6: Graphical output of the example

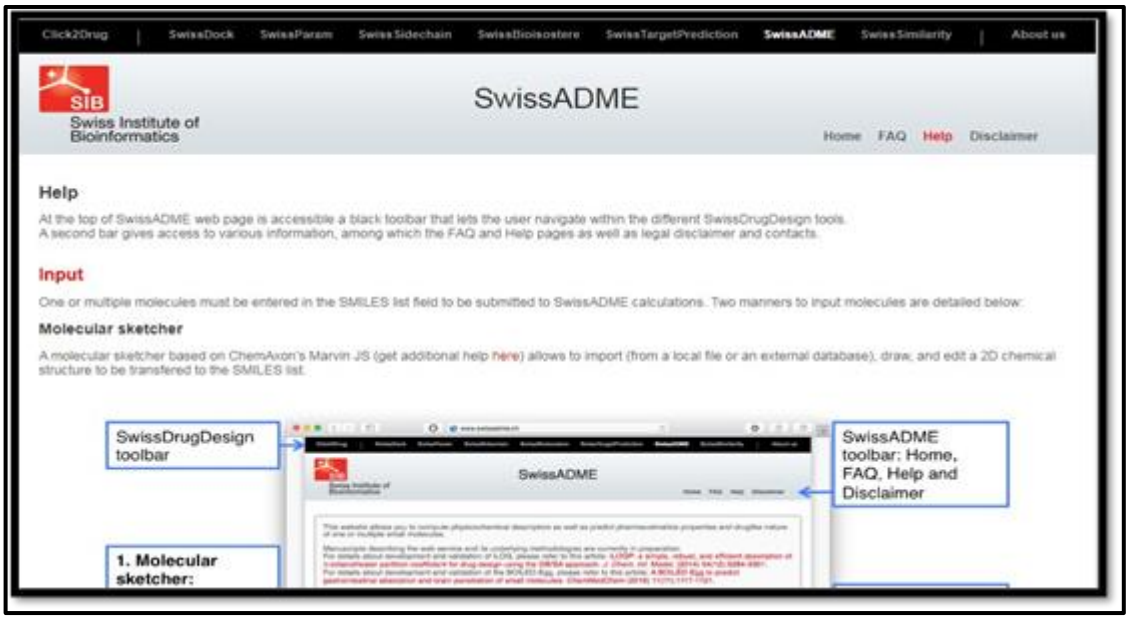


Figure 7: Help page on SwissADME

Result:

SwissADME server is used for studying properties of chemical compounds or drugs their permeability in blood, gastrointestinal tract, etc. Results stated physiochemical characteristics lipophilicity, drug likeliness, pharmacokinetics and water solubility also it showed a graphical view of the compound.

Conclusion:

For one or more molecules, the SwissADME Web tool enables the computation of physicochemical, pharmacokinetic, drug-like, and associated characteristics. Free open-access models were integrated that demonstrated statistical significance, predictive capability, and simple molecular design application. These models were modified from well-known published methods. Through interactive capabilities, simple input and effective output analysis are made possible. Additionally, direct access was provided to additional SwissDrugDesign web tools including SwissSimilarity (virtual screening), SwissBioisostere (ligand-based design), and SwissTargetPrediction (prediction of biotargets). SwissADME was developed as a result to aid the entire community in the development of new drugs.

References:

1. SwissADME Homepage (http://www.swissadme.ch)
2. SwissADME help manual (http://www.swissadme.ch/help.php)
3. SwissADME literature (https://www.nature.com/srep)

Date:

Weblem 6a SwissADME

(http://www.swissadme.ch)

Aim:

To evaluate pharmacokinetics and drug likeness using SwissADME server for query (PubChem ID- 5904)

Introduction:

Acetylsalicylic acid (ASA), popularly known as aspirin, is a drug used to treat inflammation, fever, and pain. Aspirin is used to treat a variety of inflammatory disorders, including Kawasaki disease, pericarditis, and rheumatic fever. When taken soon after a heart attack, aspirin reduces the risk of dying. Long-term usage of aspirin is also used to help those at high risk avoid further heart attacks, ischemic strokes, and blood clots. Additionally, it might make some cancers less likely, especially colorectal cancer. Effects often start within 30 minutes for pain or fever. Aspirin is a nonsteroidal anti-inflammatory medication (NSAID) that functions in a manner similar to other NSAIDs while also inhibiting platelet function. An uncomfortable stomach is a typical side effect. The exacerbation of asthma as well as stomach bleeding and ulcers are more serious adverse effects. People who are older, drink alcohol, use other NSAIDs, or are taking other blood thinners have a higher risk of bleeding. Taking aspirin during the final trimester of pregnancy is not advised. Due to the possibility of developing Reye syndrome, it is generally not advised for children who have infections. Ringing in the ears has been linked to high doses. One of the most often used drugs in the world is aspirin, which is taken in between 50 and 120 billion pills annually at an estimated 40,000 tonnes (44,000 tonnes) of weight. It is listed as one of the Essential Medicines by the World Health Organization.

Lipinski's rule of five:

- Lipinski's rule of five is a rule of thumb that describes the drugability of a determinate molecule.
- This rule helps to determine if a biologically active chemical is likely to have the chemical and physical properties to be orally bioavailable.
- The Lipinski rule bases pharmacokinetic drug properties such as absorption, distribution, metabolism and excretion on specific molecular properties such as:
    - No more than 5 hydrogen bond donors
    - No more than 10 hydrogen bond acceptors
    - Molecular mass less than 500 Da
    - Partition coefficient not greater than 5
- The violation of 2 or more of these conditions predicts a molecule as a non- orally available drug.

PubChem

PubChem is an open chemistry database at the National Institutes of Health (NIH). "Open" means that you can put your scientific data in PubChem and that others may use it. Since the launch in 2004, PubChem has become a key chemical information resource for scientists, students, and the general public. Each month our website and programmatic services provide data to several million users worldwide. PubChem mostly contains small molecules, but also larger molecules such as nucleotides, carbohydrates, lipids, peptides, and chemically-modified macromolecules. We collect information on chemical structures, identifiers, chemical and physical properties, biological activities, patents, health, safety, toxicity data, and many others. PubChem records are contributed by hundreds of data sources. Examples include:

government agencies, chemical vendors, journal publishers, and more. The amount of data in PubChem is ever- growing, please visit the PubChem Statistics page to find out what the latest data counts are.

SwissADME:

During the time and resource-consuming processes of drug discovery and development, a large number of molecular structures are evaluated according to very diverse parameters in order to steer the selection of which chemicals to synthesize, test and promote, with the final goal to identify those with the best chance to become an effective medicine for the patients. The molecules must show high biological activity together with low toxicity. Equally important is the access to and concentration at the therapeutic target in the organism. The traditional way to consider pharmacokinetics (i.e. the fate of a therapeutic compound in the organism) is to break down the various effects that impact the access to the target into individual parameters. It has been demonstrated that early estimation of ADME in the discovery phase reduces drastically the fraction of pharmacokinetics-related failure in the clinical phases. Computer models have been fostered as a valid alternative to experimental procedures for prediction of ADME, especially at initial steps, when investigated chemical structures are numerous but the availability of compounds is scarce. A large variety of in silico methods share the objective of predicting ADME parameters from molecular structure. Noteworthy, the pioneer work of Lipinski et al. examined orally active compounds to define physicochemical ranges for high probability to be an oral drug. This so-called Rule-of-five delineated the relationship between pharmacokinetic and physicochemical parameters. Whereas physicochemical parameters give a global description of the structure, molecules can be directly described by substructure searches. These techniques are at the root of Structural Alert, the PAINS or the Lilly MedChem filters applied to cleanse chemical libraries from compounds most likely unstable, reactive, toxic, or prone to interfere with biological assays because unspecific frequent hitters, dyes or aggregators. The SwissADME web tool presented here is freely accessible at http://www.swissadme.ch and meant for user-friendly submission and easy analysis of the results, also for non-expert in CADD. Compared to the state-of-the art of free web-based tools for ADME and pharmacokinetics and apart from unique access to proficient methods, SwissADME strong points are, non-exhaustively: different input methods, computation for multiple molecules, and the possibility to display, save and share results per individual molecule or through global intuitive and interactive graphs.

Methodology:

1. Using Google search engine search Swiss ADME.
2. In Molecular Sketcher Add, Import a structure.
3. The Structure will be from PubChem (ID- 2244).
4. Download the structure and save is SDF format.
5. Import the structure to the Molecular Sketcher in SwissADME.
6. Transfer the structure to SMILES list.
7. Run the calculations and observe the result page.
8. Browse through various parts of this result page.

Observations:

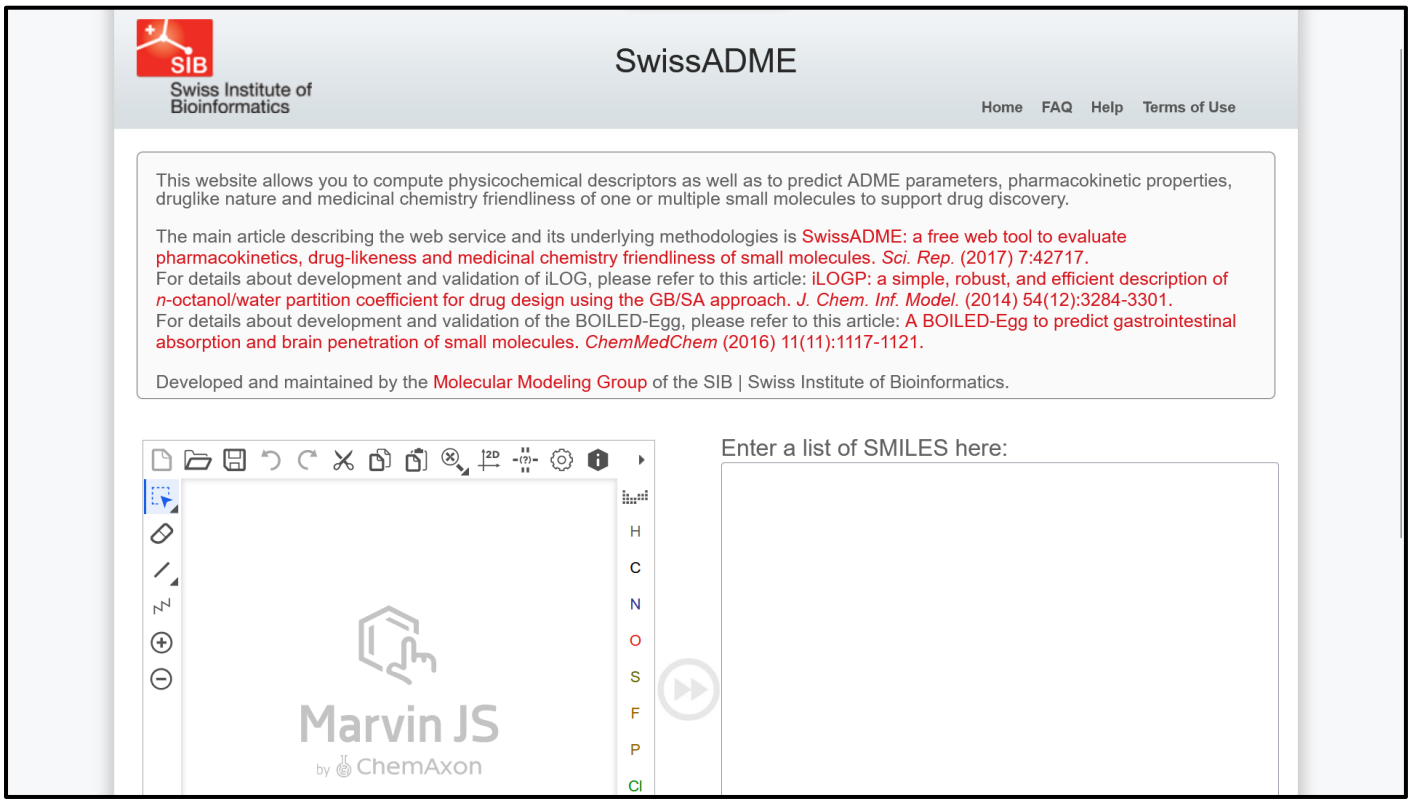


Figure 1: SwissADME Homepage

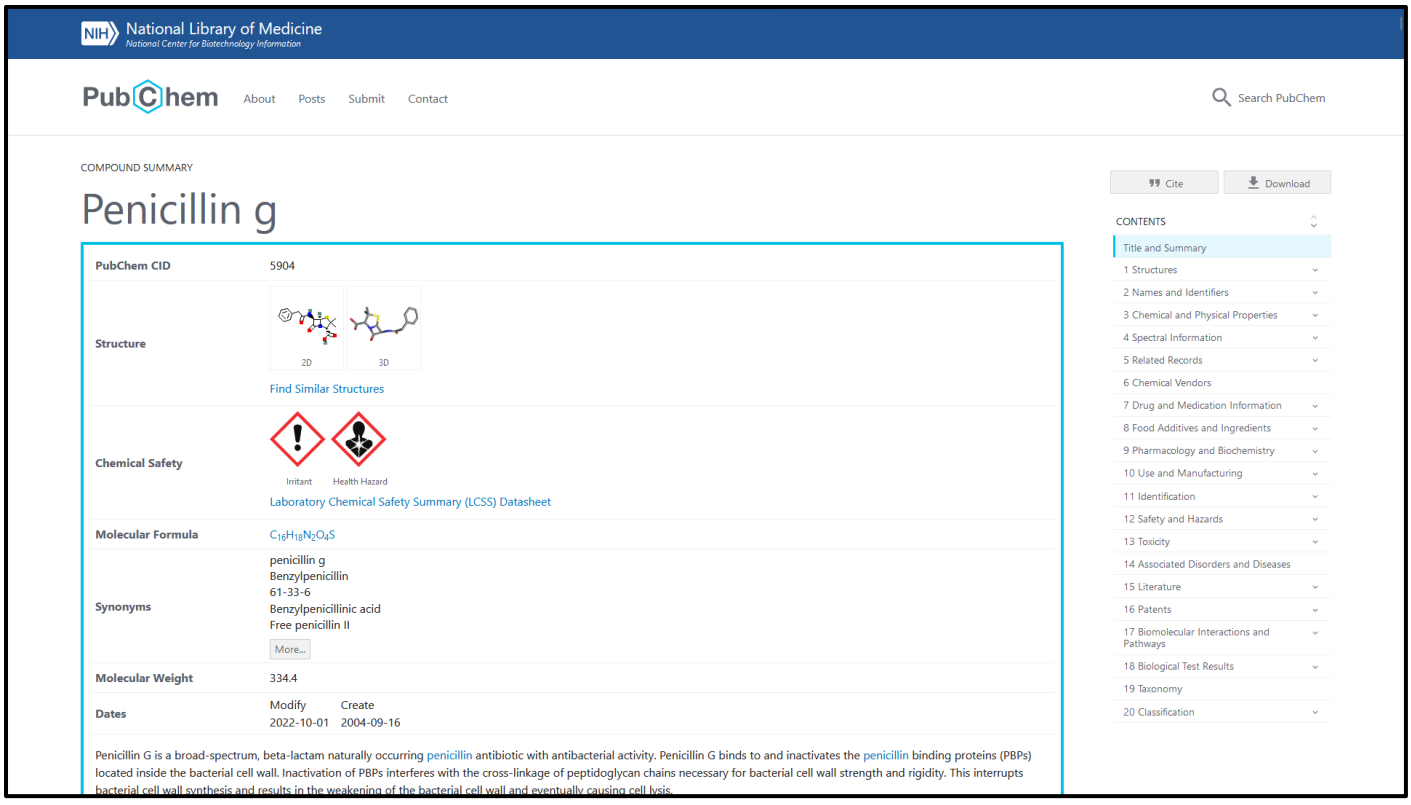


Figure 2: PubChem Compound ID

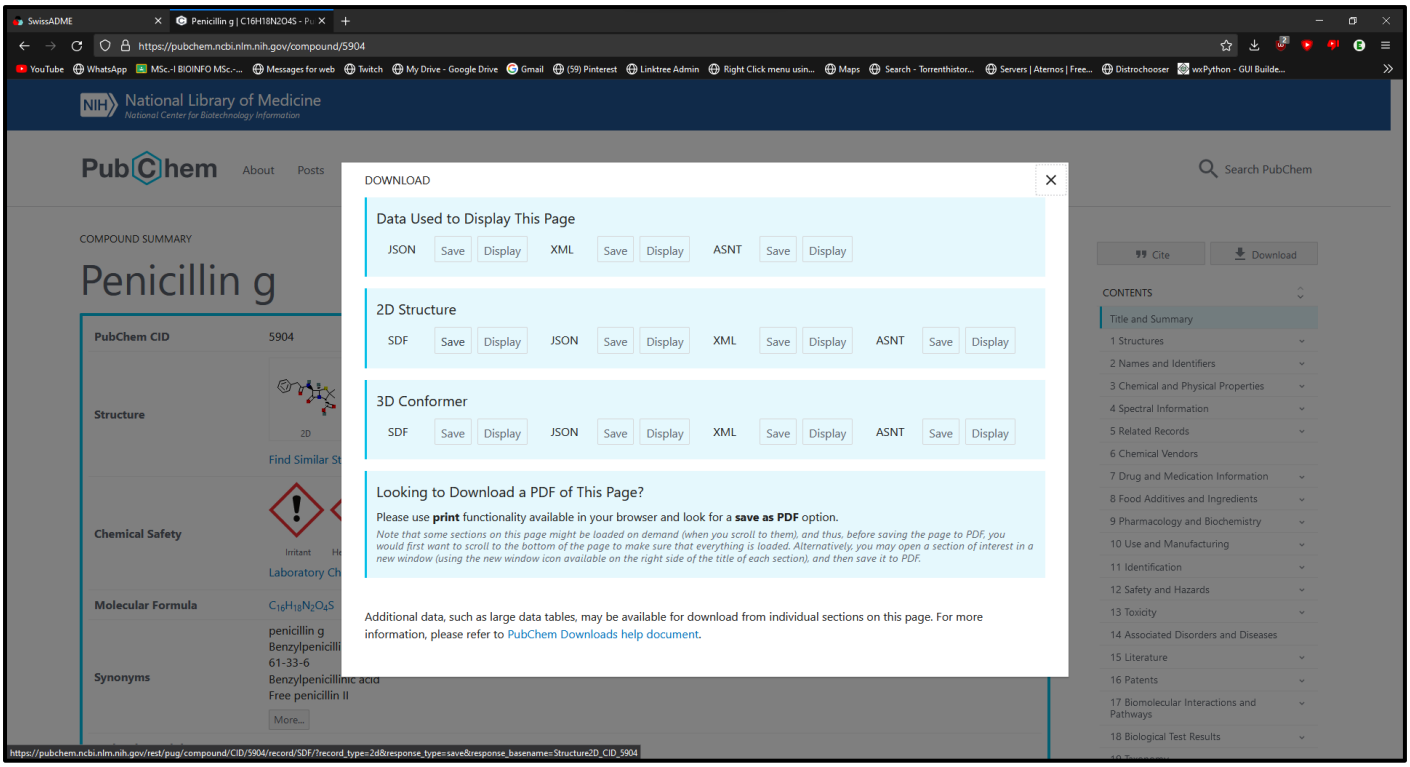


Figure 3: Compound structure, download in SDF format

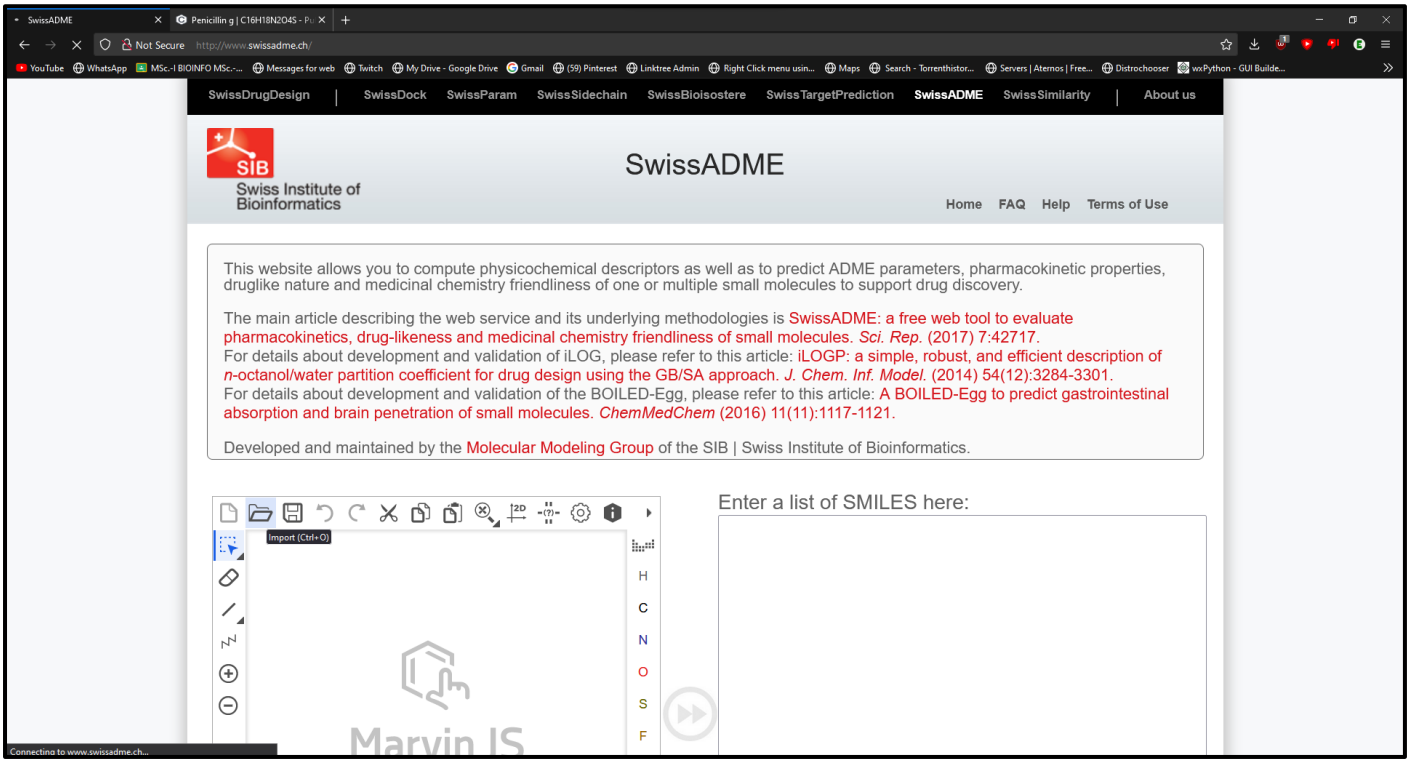


Figure 4: Import The structure in molecular structure

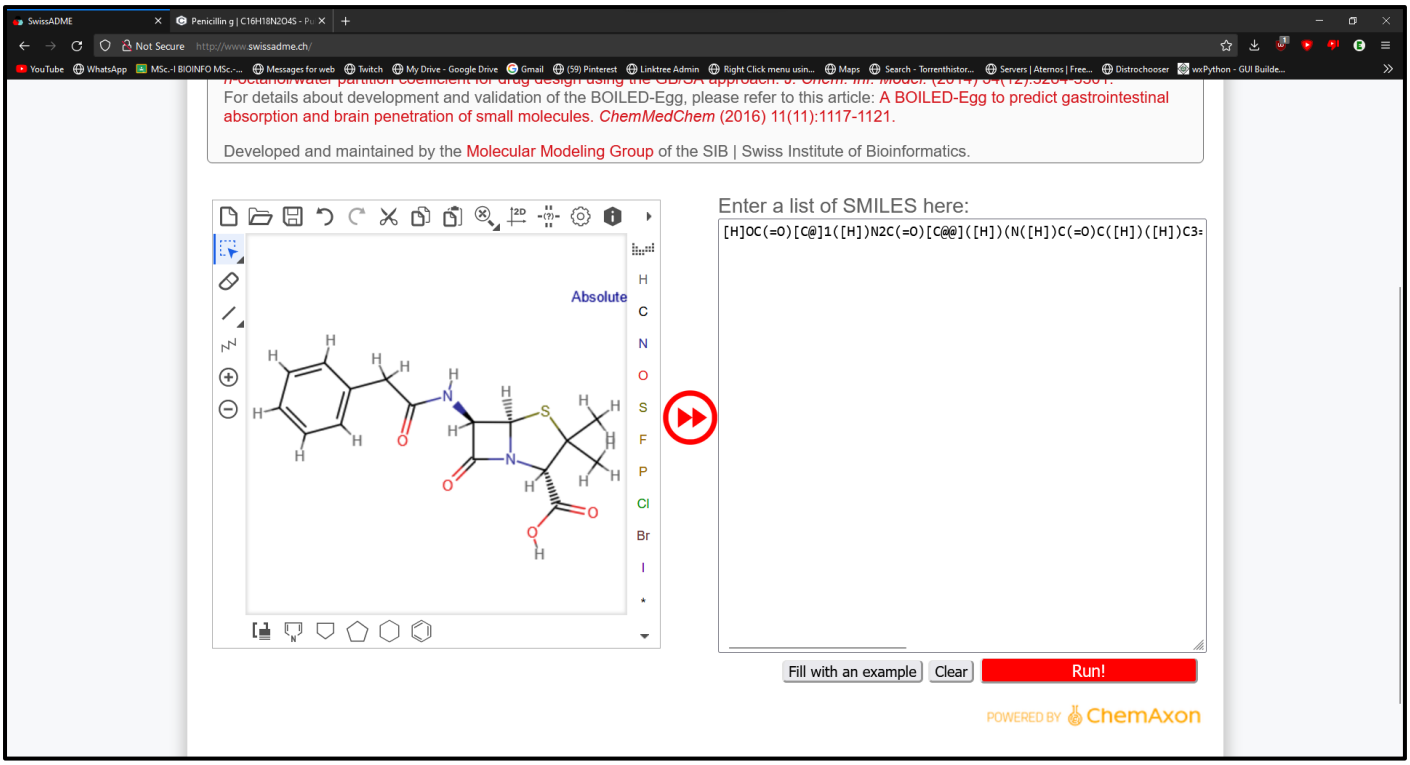


Figure 5: Transfer in to SMILES list

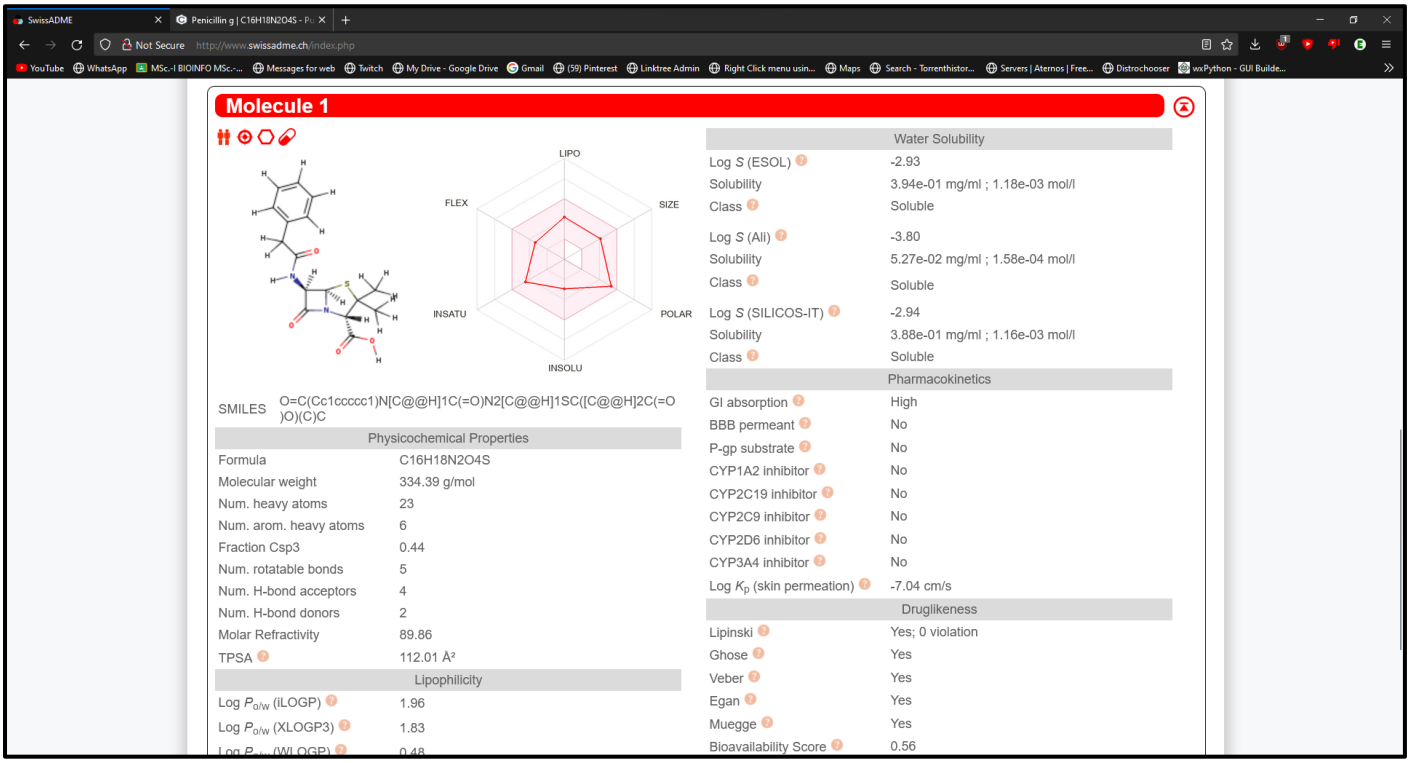


Figure 6: After running the calculations, Result page of the molecule

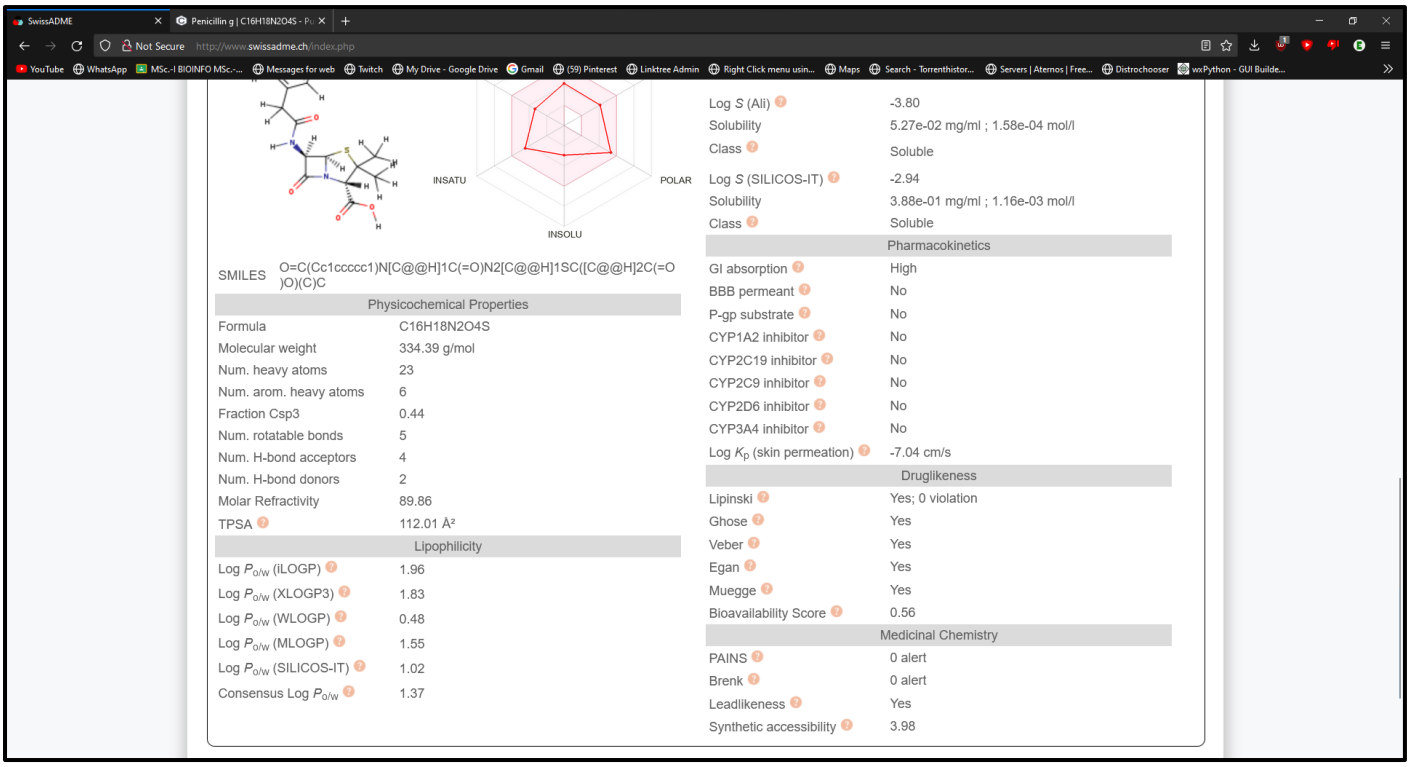


Figure 7: Properties, drug likeness, Pharmacoinetics, etc of the compound in the result

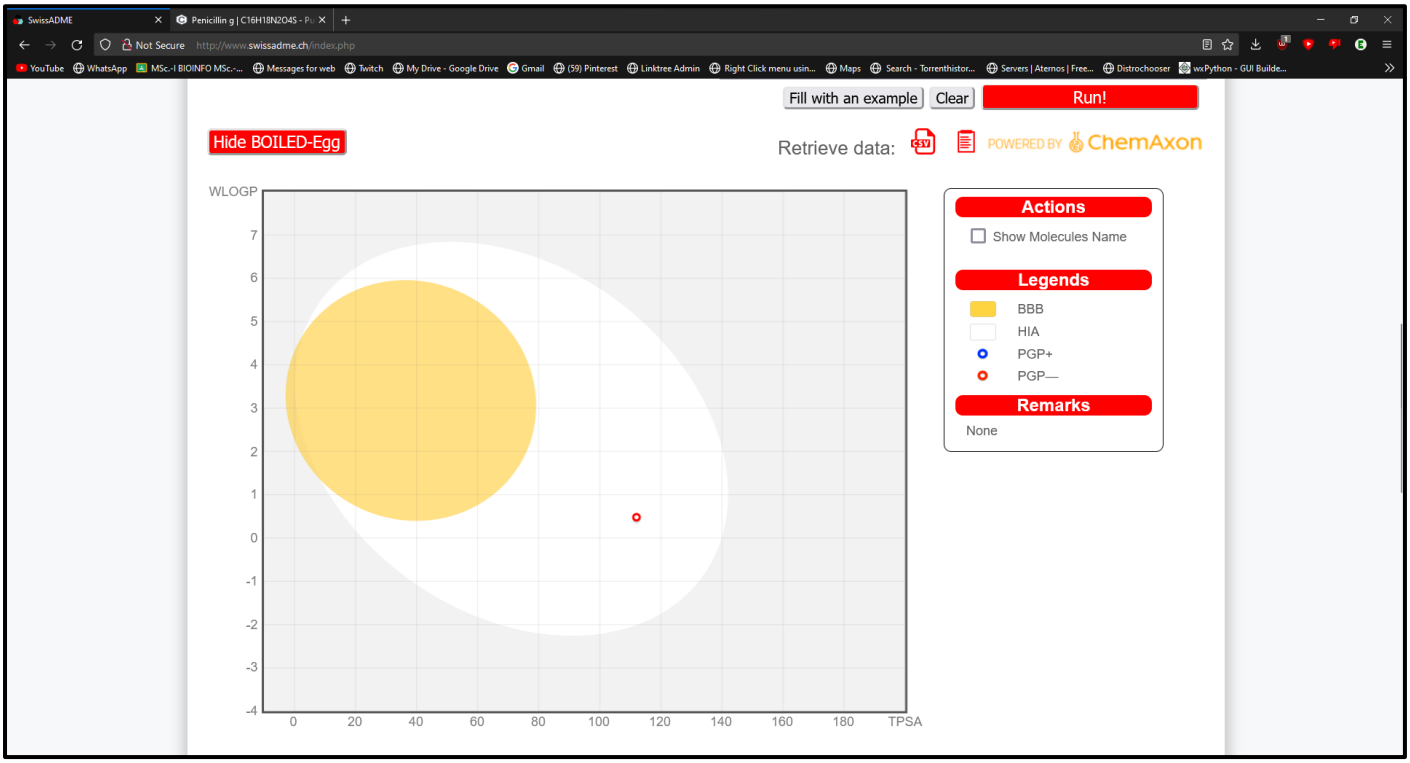


Figure 8: Boiled Egg view/ Graphical view/ Pharmacokinetic result of the compound

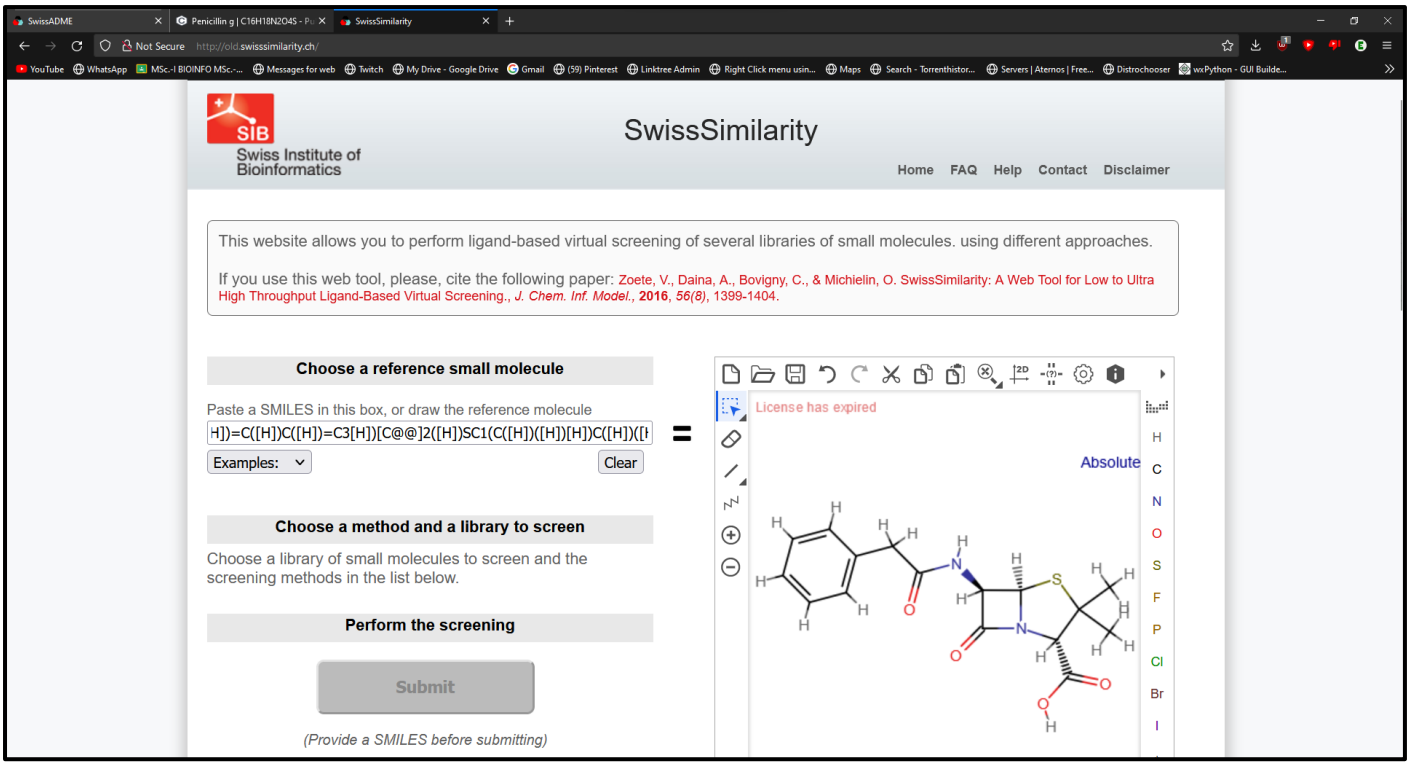


Figure 9: Similarities searched through SwissSimilarity

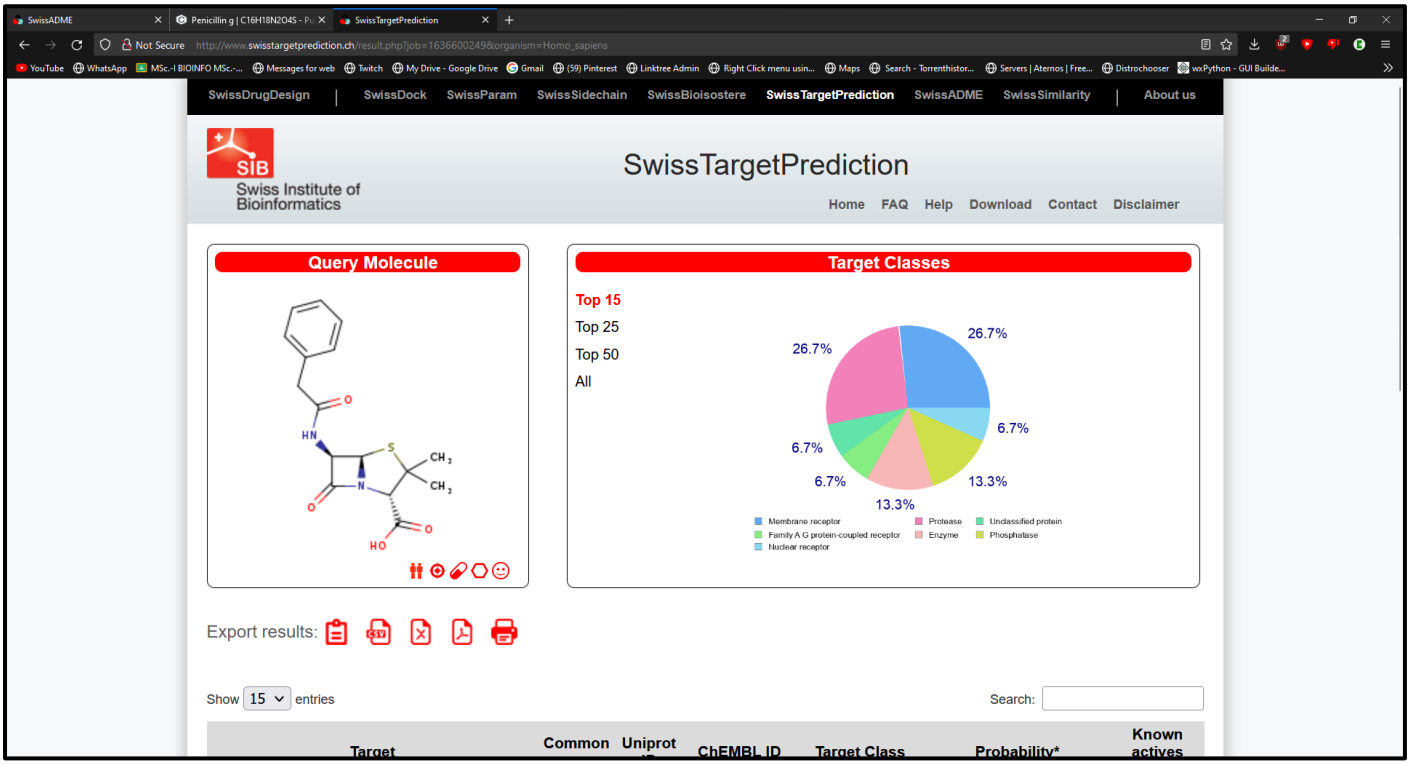


Figure 10: Target prediction of the compound in SwissTargetPrediction

Result:

In Boiled egg section molecule-1 is present in yellow section i.e. Boiled eggs yolk where molecules are predicted to passively permeate through the blood brain barrier and according to its physiochemical properties and lipophilicity the molecule also obeys the Lipinski 5 rule.

Lipinski 5 Rule:

1. Molecular weight less than 500 Dalton - Molecular weight (180.16g /mol).
2. High lipophilicity expressed as LogP less than 5 – LogP (1.30)
3. Less than 5 hydrogen bond donors - No. of H bonds donors (1)
4. Less than 10 hydrogen bond acceptors - No. of H bonds acceptors (4)
5. Molar refractivity should be between 40-130 – Molecular Refractivity (44.90)

Pharmacokinetics:

Gastrointestinal absorption – High

BBB Permeant –Yes

CYP1A2 inhibitor – NO

CYP2C9 inhibitor - NO

CYP2C19 inhibitor – NO

Drug likeness:

Lipinski – Yes; 0 Violation

Ghose - Yes

Veber -Yes

Egan - Yes

Muegge No; - 1 violation: MW<200

Bioavailability Score - 0.85

Conclusion:

The Pubchem ID of the query was taken &imported in SwissADME database and SMILES were generated. After generating SMILES and running calculations various results were obtained, where in Boiled egg section the molecule-1 was present in the yellow section which means that it can enter in the BBB i.e. Blood brain barrier but it cannot cross the (GI) Gastro intestinal track. In Drug likeness section, filters like Lipinski, Ghose, Veber, Egan was observed with 0 violations with bioavailability score 0.85.

References:

1. SwissADME Homepage (http://www.swissadme.ch)
2. SwissADME literature (https://www.nature.com/srep)
3. PubChem Compound (https://pubchem.ncbi.nlm.nih.gov/)
4. Compound literature (https://www.medicalnewstoday.com/articles/161255)
5. SwissSimilarity (http://www.swisssimilarity.ch/)
6. SwissTargetPrediction (http://www.swisstargetprediction.ch/)