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WEBLEM 6
Introduction to SWISS ADME, a free web-based tool to support pharmacokinetics optimization for drug discovery

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 synthetize, 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. In turn, these ADME parameters (for Absorption, Distribution, Metabolism and Excretion) can be evaluated separately by dedicated methods. 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 (i.e. the drug-likeness). This so-called *Rule-of-five* delineated the relationship between pharmacokinetic and physicochemical parameters.

The SwissADME web tool is freely accessible and meant for user-friendly submission and easy analysis of the results, also for nonexpert in CADD. Compared to the state-of-the art of free web-based tools for ADME and pharmacokinetics (e.g. pk-CSM and admetSAR) and apart from unique access to proficient methods (e.g. iLOGP or the BOILED-Egg), 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. Finally, SwissADME is integrated in the SwissDrugDesign workspace. One-click interoperability gives access to various CADD tools developed by the Molecular Modeling Group of the SIB Swiss Institute of Bioinformatics, e.g. ligand-based virtual screening (SwissSimilarity), biotarget prediction (SwissTargetPrediction), molecular docking (SwissDock), bioisosteric design (SwissBioisostere), or molecular mechanics (SwissParam). Applications of SwissADME web tool are in the design and development of anticancer, antitubercular and antimicrobial agents.

Submission Web page

- Accessing SwissADME 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.

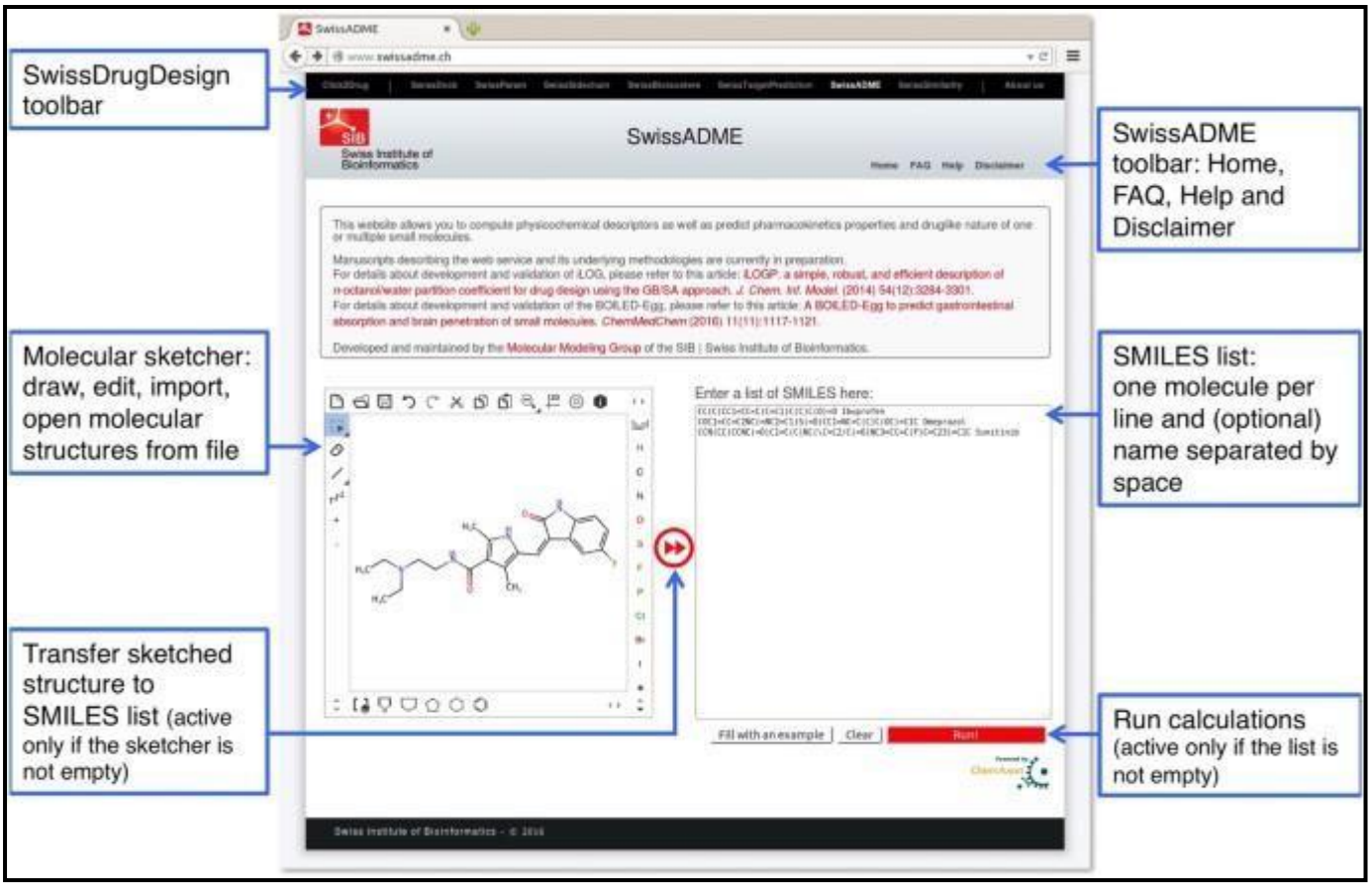

FIG 1: SwissADME submission page.

- 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.

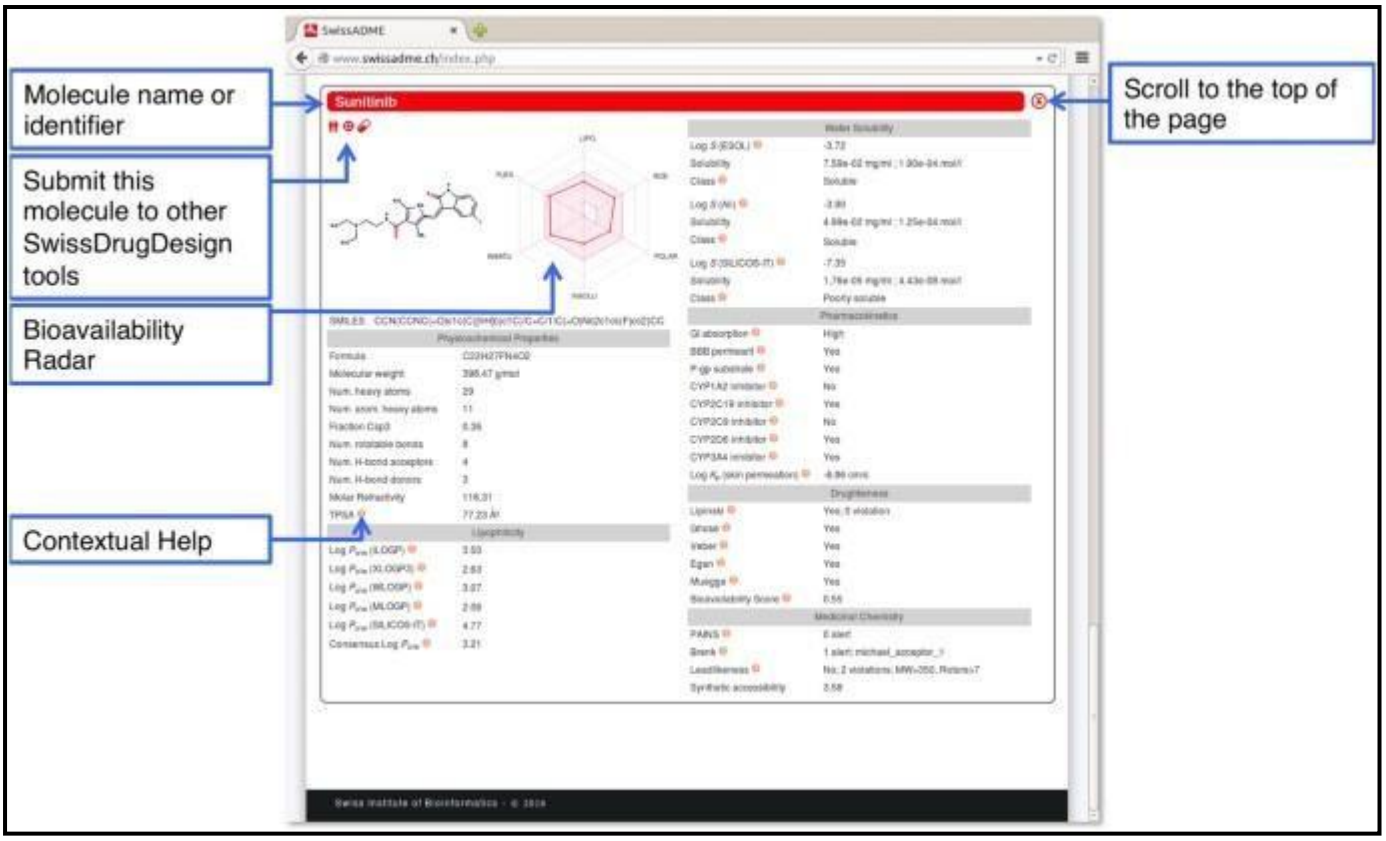

FIG 2: Computed parameter values are grouped in the different sections of the one-panel-par-molecule output (Physicochemical Properties, Lipophilicity, Pharmacokinetics, Drug-likeness and Medicinal Chemistry).

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).

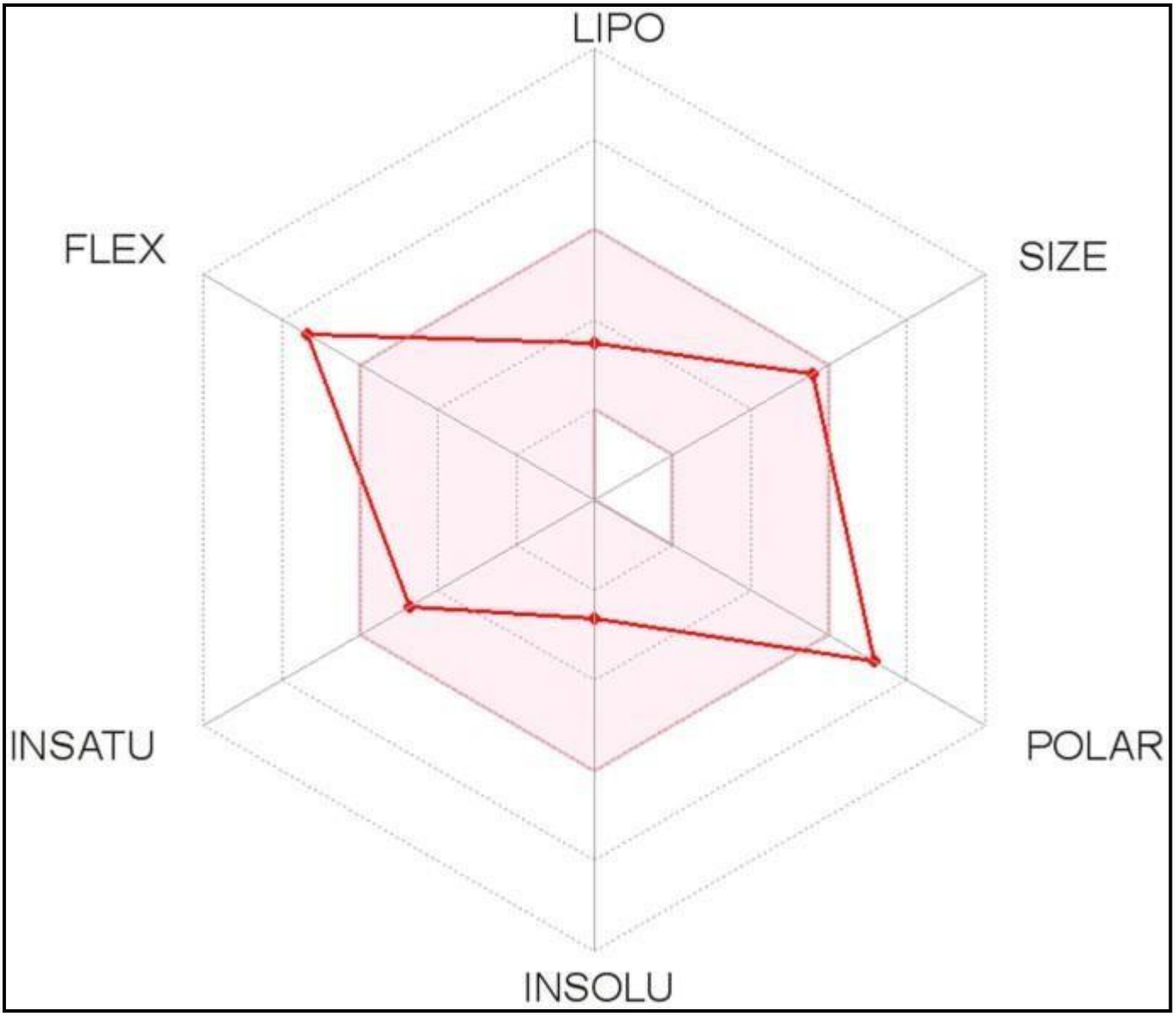

FIG 3: The Bioavailability Radar enables a first glance at the drug-likeness of a molecule.

The pink area represents the optimal range for each properties (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. In this example, the compound is predicted not orally bioavailable, because too flexible and too polar.

Physicochemical Properties

Simple molecular and physicochemical descriptors like molecular weight (MW), molecular refractivity (MR), count of specific atom types and polar surface area (PSA) are compiled in this section. The values are computed with OpenBabel, version 2.3.0. The PSA is calculated using the fragmental technique called topological polar surface area (TPSA), considering sulfur and phosphorus as polar atoms. This has proven a useful descriptor in many models and rules to quickly estimate some ADME properties, especially with regards to biological barrier crossing such as 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 methodsWater 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 parenteral 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 model 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.

Pharmacokinetics

- Specialized models, whose predictions are compiled in the Pharmacokinetics section, evaluate individual ADME behaviours of the molecule under investigation.
- One model is a multiple linear regression, which aimsat predicting the skin permeability coefficient (Kp). It is adapted from Potts and Guy39, who found Kp linearlycorrelated 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 which is anintuitive graphical classification model and displayed on the SwissADME result page.
- The knowledge about compounds being substrate or non-substrate of the permeability glycoprotein (P-gp) is key to appraise active efflux through biological membranes, i.e. from the gastrointestinal wall to the lumen or from the brain.
- It is also important to know the interaction of molecules with cytochromes P450 (CYP) because CYP and P-gp can process small molecules synergistically to improve protection of tissues and organisms and thus various models are being studied by SWISSADME.

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 inspectionsof 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.
- The Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) methods are also used. Multiple estimations allow consensus views or selection of methods best fitting the end-user’s specific needs in terms of chemical space or project-related demands.
- Any violation of any rule described here appears explicitly in the output panel.
- The Abbot Bioavailability Score is similar but seeks to predict the probability of a compound to have at least10% oral bioavailability in rat or measurable Caco-2 permeability.
- 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%.
- Like the other methods in this section, it primary focuses on the fastscreening of chemical libraries, to select the best molecules to be purchased, synthetized or promoted at a further stage of a medicinal chemistry project.

Medicinal Chemistry

The purpose of this section is to support medicinal chemists in their daily drug discovery endeavours. 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 analysing 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.

Structural Alert, which consists in a list of 105 fragments identified by Brenk *et al*. to be putatively toxic, chemically reactive, metabolically unstable or to bear properties responsible for poor pharmacokinetics. n 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*. 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 of drug where SA Score ranges from 1 (very easy to synthesis) to 10 (very difficult for synthesis) and helps in 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 brainaccess (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 spacefor 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 moleculardesign in a variety of drug discovery settings. Whereas the predictive power of the BOILED-Egg is broad in term of chemical space, it is restricted to passive penetration through gastro-intestinal wall and BBB.
- We took benefit of its implementation within SwissADME to enrich the graphical output with the prediction of P-gp substrate, which is the most important active efflux mechanism involved in those biological barriers.
- As a result, the user conveniently obtains on the same graph a global evaluation about passive absorption (inside/outside the white), passive brain access (inside/outside the yolk) and active efflux from the CNS or tothe gastrointestinal lumen by colour-coding: blue dots for P-gp substrates (PGP+) and red dots for P-gp non-substrate (PGP−).

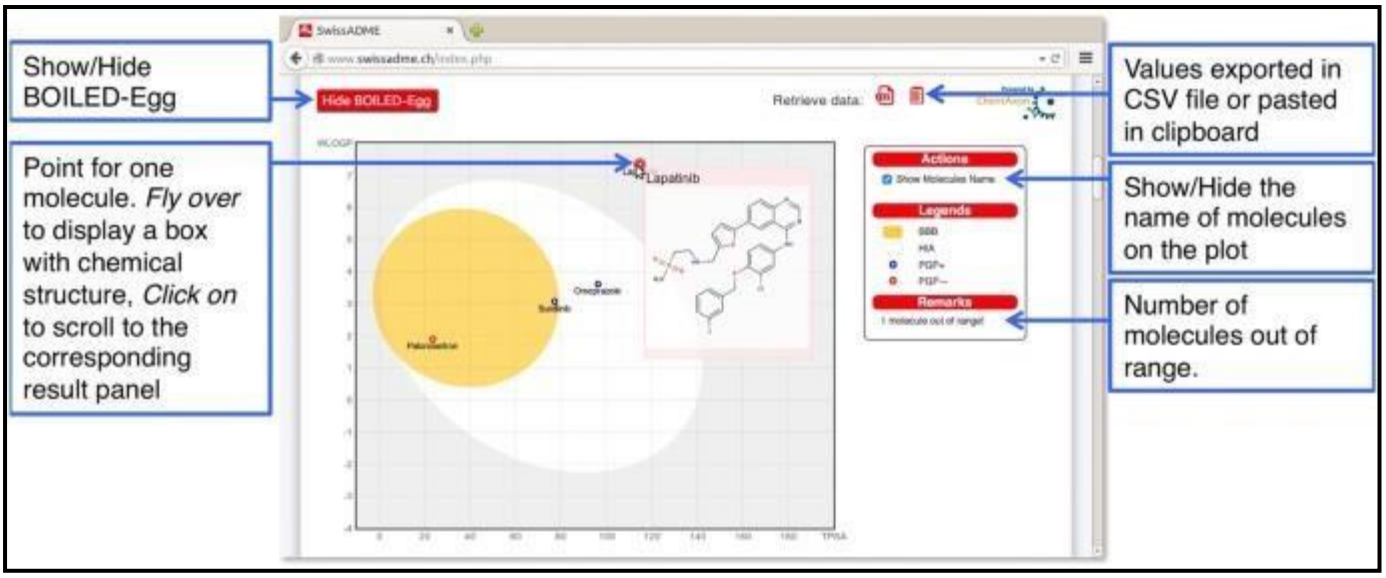

FIG 4: The BOILED-Egg

Allows for intuitive evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) in function of the position of the molecules in the WLOGP- *versus* -TPSA referential. The white region is for high probability of passive absorption by the gastrointestinal tract, and the yellow region (yolk) is for high probability of brain penetration. Yolk and white areas are not mutually exclusive. In addition the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP−). For an interactive analysis, the user can leave the mouse over a dot to show the structure of the molecule and click on the dot to scroll to the corresponding output panel.

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1. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, *7*(1). https://doi.org/10.1038/srep42717
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WEBLEM 6A
SwissADME Tool

(URL: http://www.swissadme.ch/)

AIM:

To evaluate pharmacokinetics and drug-likeness properties using the SwissADME server for Quercetin (PubChem Id- 5280343) molecule.

INTRODUCTION:

Quercetin is a flavonoid found in many foods and herbs and is a regular component of a normal diet. Extracts of quercetin have been used to treat or prevent diverse conditions including cardiovascular disease, hypercholesterolemia, rheumatic diseases, infections and cancer but have not been shown to be effective in clinical trials for any medical condition. Quercetin as a nutritional supplement is well tolerated and has not been linked to serum enzyme elevations or to episodes of clinically apparent liver injury.

Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. Here, we present the new SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar. Easy efficient input and interpretation are ensured thanks to a user-friendly interface through the login-free website. Specialists, but also nonexpert in cheminformatics or computational chemistry can predict rapidly key parameters for a collection of molecules to support their drug discovery endeavours.

METHEODOLOY:

- Open homepage of SwissADME tool. (URL: http://www.swissadme.ch/)
- Retrieve canonical SMILES for Quercetin from Pubchem database.
- Run the canonical SMILES in SwissADME.
- Observe and interpret the results.

OBSERVATION:

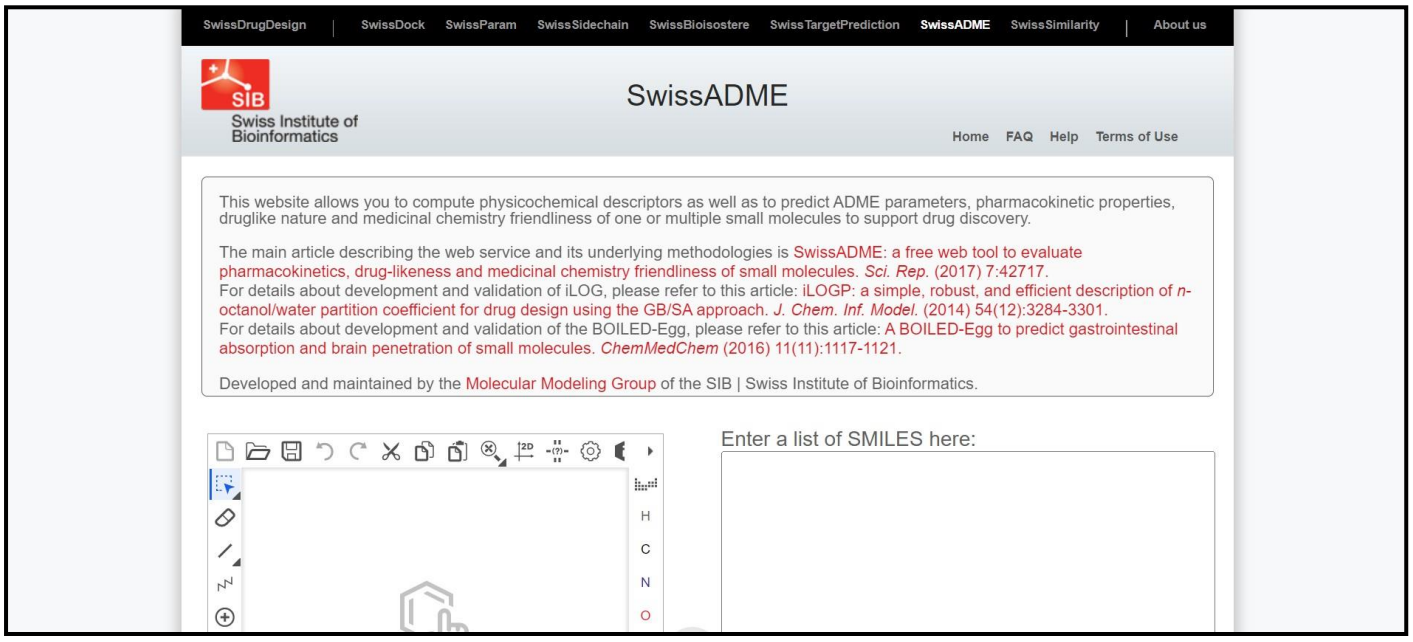

FIG 1. Homepage of SwissADME Server

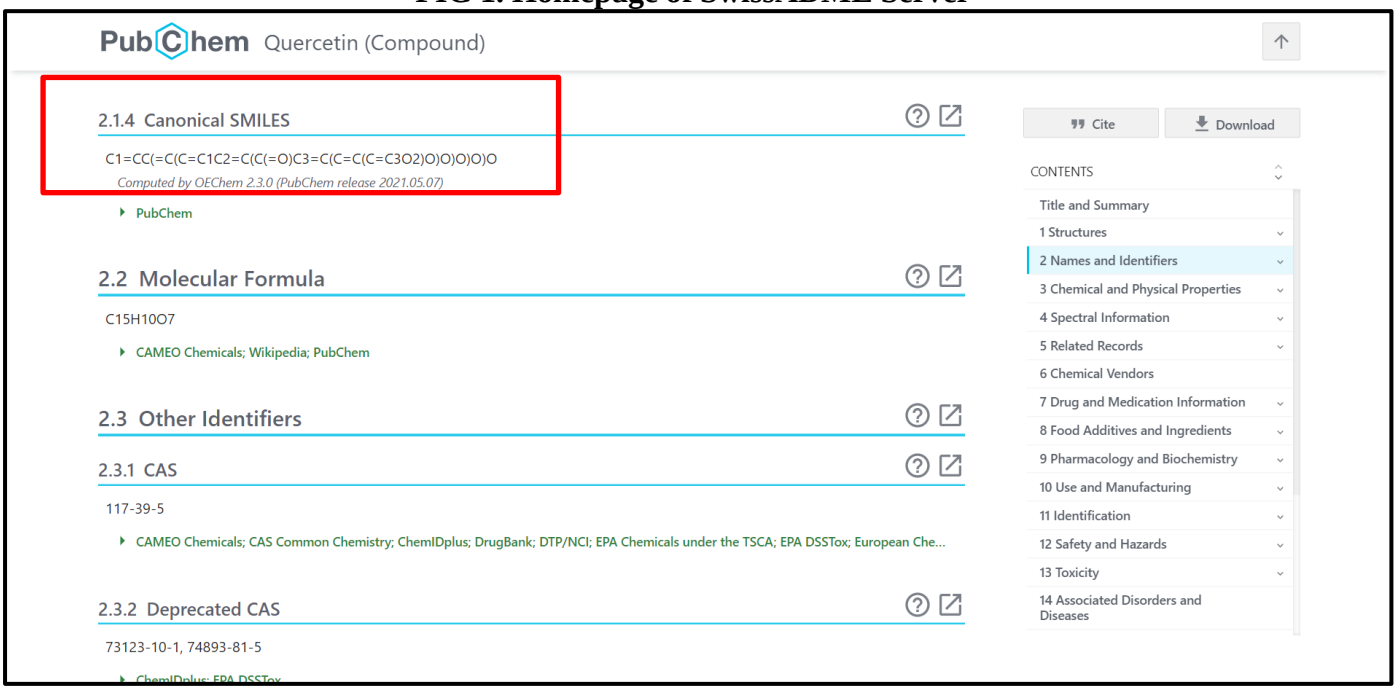

FIG 2. Canonical SMILES for Luteolin from PubChem database

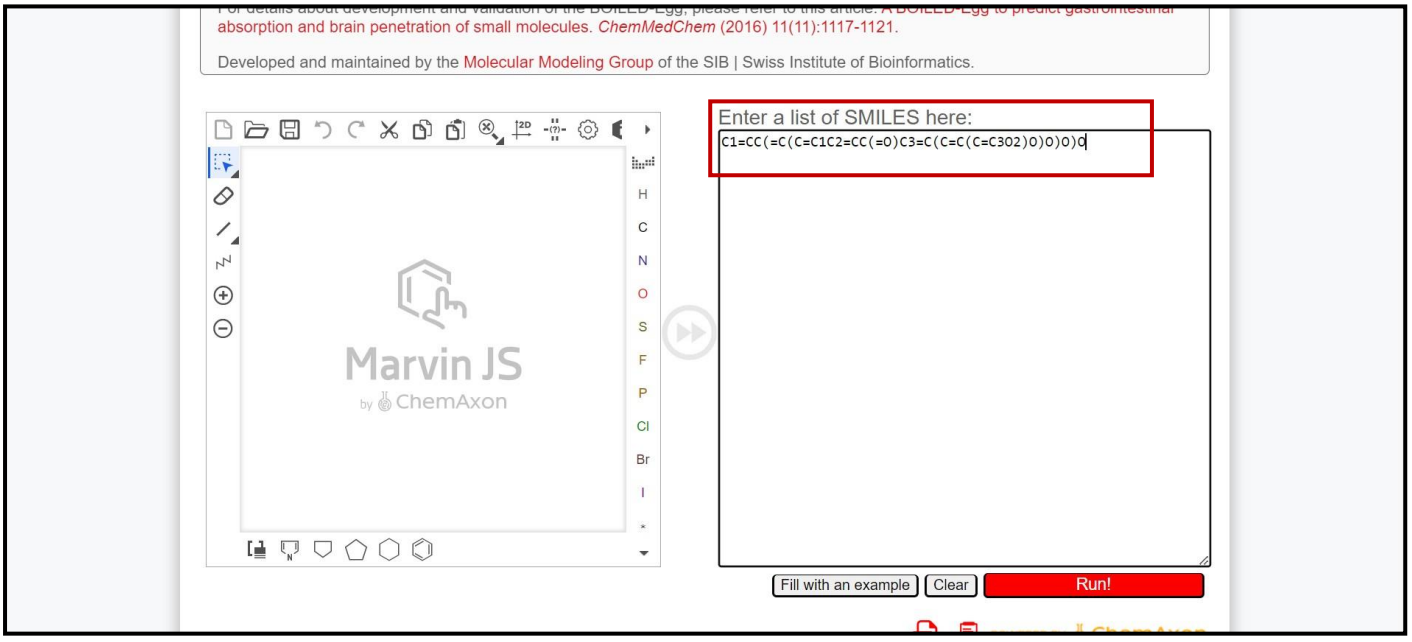

FIG 3. Submitting canonical SMILES to SwissADME server

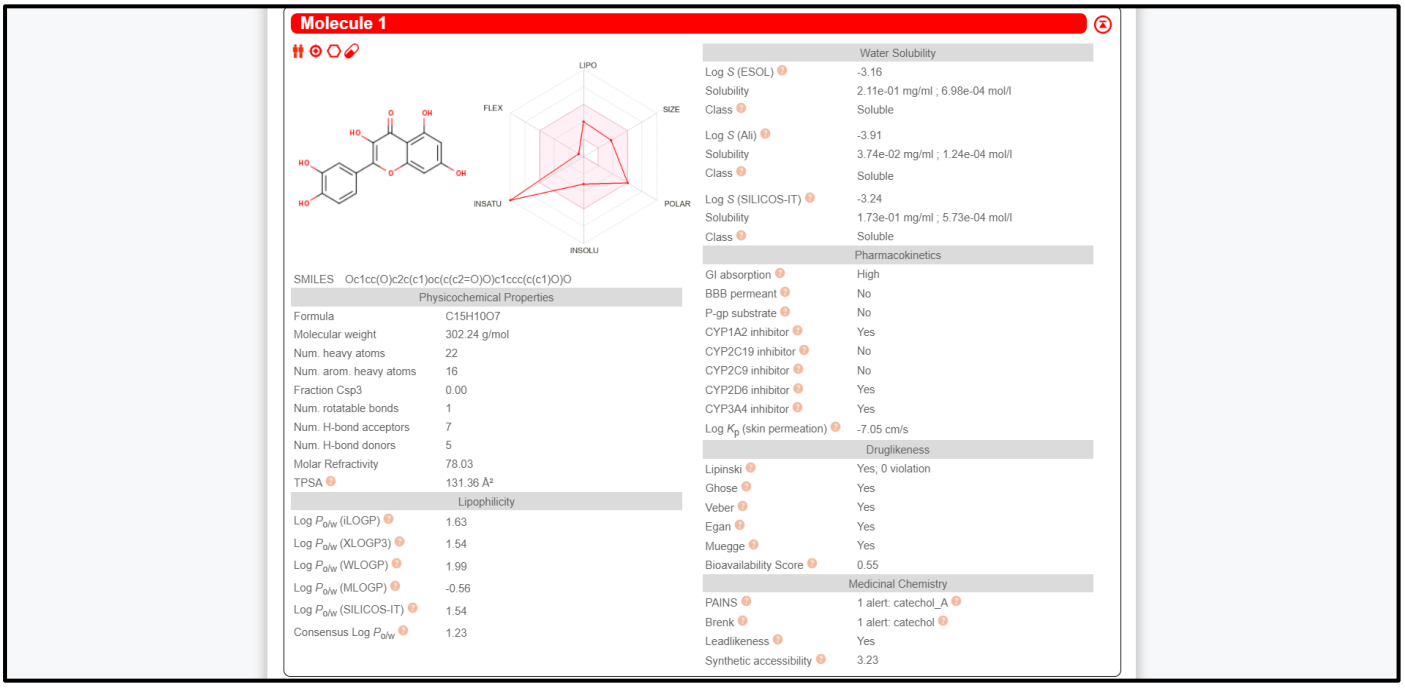

FIG 4. Result page for Quercetin

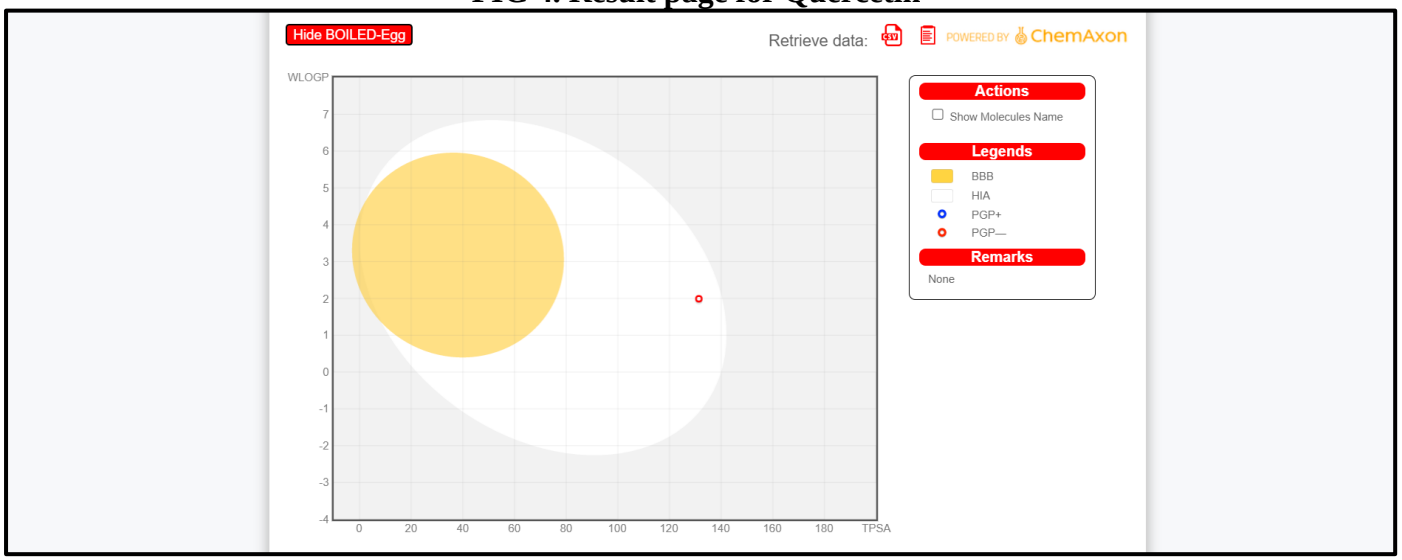

FIG 5. BOILED-EGG result for Quercetin

RESULTS:

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:

During the drug discovery process, to be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. SwissADME Web tool enables the computation of key physicochemical, pharmacokinetic, drug-like and related parameters for one or multiple molecules.

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