ADMET Predictor – An overview of prediction and evaluation of ADMET properties of drugs and chemicals

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Abstract- **Chemical absorption, distribution, metabolism, excretion and toxicity (ADMET) play key roles in the drug discovery and development. This covers the physicochemical properties of drugs, PH and solubility and approaches to improving aqueous solubility as well as drug metabolism and drug interactions. Followed by recent development on databases particularly related to the ADMET profiling and prediction. We consider advances in statistical modelling techniques, molecular descriptors and sets of data used for model building and changes in the way in which predictive ADMET models are being applied in drug discovery. The largest pharmaceutical companies have developed large in house databases containing consistently measured compound properties. A Computer Aided Drug Design (CADD) approach involving virtual screening was used to obtain binding scores and inhibiting efficiencies of previously known antibiotics. ADMET analysis carried out using ADMET SAR–2 software. Various experimental and computational methods have been developed to obtain ADME properties in an economical manner in terms of time and cost. As in vitro and in vivo experimental data on ADME have accumulated the accuracy of in silico models in ADME increases. In silico ADME analysis is not dangerous, simpler and quicker. One main reason for R and D failures is the efficacy and safety deficiencies which are largely related to absorption, distribution, metabolism and excretion (ADME) properties and various toxicities. Therefore rapid ADMET evaluation is urgently needed to minimize failures in drug discovery process. It also includes Swiss ADME which is a free web tool to evaluate pharmacokinetics, drug likeness and medicinal chemistry friendliness of small molecules.**

Keywords: **Computational tools, Risk, Score, Validation, ADMET properties, Computer Aided Drug Design (CADD), Swiss ADME.**

INTRODUCTION

ADMET stands for absorption, distribution, metabolism, excretion and toxicity. These are key processes and phenomenon occurring. When chemical substances are transported and transformed inside living organisms. ADME modelling and calculations are critical in developing new drugs and evaluating the risks and side effects of chemical substances such as food additives, pesticides and environmental pollutants which may contact or enter the humans body. Drug release is the system through which drug leaves a drug product and is allotted to ADME which includes absorption, circulation, metabolism and excretion of drug product eventually leading to pharmacologic action. In vivo drug disposition is dependent on the interactions between drug and the body. During drug discovery phase, chemical synthesis is guided toward potent compounds with physicochemical and absorption, distribution, metabolism and excretion properties that allow drug to reach effective concentration at the target (Ballard et al.,2012; Sohlenius-Sternbeck et al., 2016). The use of commercial software for prediction of chemical and ADMET properties is convenient, since such tools can be used with virtual compounds and do not require any user data while measured data are needed for local model building. Various open source and commercial software tools are available for ADMET modelling. These tools can be applied to virtual screening of chemical compound libraries and databases. The typical goal is to identify candidate compounds for further investigations, including synthesis and characterization of new compounds and structural refinement of existing ones. Several commercial software types or online prediction tools are available for ADME, pharmacokinetic, pharmacokinetic- pharmacodynamics, drug-drug interactions and toxicity predictions. We have previously successfully used Gastroplus from simulations plus, Inc. as part of strategy to identify risks for drug-drug interactions in drug discovery. ADMET Predictor from simulations plus, Inc. is a commercially available software for prediction of physical chemistry, ADME and toxicity parameters from compound structures.

ADMET covers pharmacokinetic issues determining whether a drug molecule will get to the target protein in body and how long it will stay in bloodstream. Parallel evaluation of efficiency and biopharmaceutical properties of drug candidates has been standardized and exhaustive studies of ADMET processes are nowadays routinely carried out

at early stage of drug discovery to reduce attrition rate. This is because majority of clinical trial failures have been due to ADMET issues, not from lack of efficiency. ADMET related in silico models are commonly used to provide a fast and preliminary screening of ADMET properties before compounds are further investigated in vitro (8-11). There are several free and commercial computational tools for predicting ADMET properties. However, these tools are not yet very accurate. In order to facilitate ADMET evaluation, we developed web platform called ADMET lab based on comprehensively collected database which integrates the existing ADMET and basic physicochemical related end points as many as possible. Compared with other online platforms, our proposed ADMET Lab incorporated more ADMET endpoints and improved model performance for some endpoints based on large and structurally diverse data sets.

What is ADMET Predictor?

ADMET predictor is a commercially available software for prediction of physical chemistry, ADME and its toxicity parameters from compound structures.

ADMET predictor is a machine learning software tool that quickly and accurately predicts over 175 properties, including solubility, log P, Pka and sites of CYP metabolism. It is an advanced computer program that enables researchers to rapidly estimate no. of ADMET properties of new chemical entities from their molecular structure.

Computational Tools

Softwares	**Description**
DSSTox	Distributed Structure-Searchable Toxicity public database
PK Tutor	Free Exel tools for PK and ADME research and education
Pre ADMET prediction	Predict permeability for BBB, Human intestinal absorption, skin permeability and plasma protein binding
Pre ADMET toxicity prediction	Predict toxicological properties from chemical structures such as mutagenicity and carcinogenicity
Molinspiration	Calculation of molecular properties and drug likeness
chemTree	Predict ADMET properties
Moka	In-silico computation of pka values
Shop	Useful to guide the scaffold hopping procedure during the drug discovery process
ADMET property calculator	In-silico screening based on known ADMET knowledge base
TOPKAT	Predictive toxicology
ADMET	Allow to eliminate compounds with unfavourable ADMET characteristics to avoid expensive reformulation

ADMET Risk

The original rule of 5 is widely considered to be an important development in modern drug discovery (Lipinski, et al;1997). The rule of 5 takes on numeric values from 0 to 4 as a measure of the compounds potential of absorption liability. As such, rule of 5 is a useful computational filter in drug candidate screening. In terms of ADMET predictor descriptors and models, the rule of 5 model rules can be formulated as follow the following set of conditions:

- MlogP >4.15 (excessive lipophilicity)
- MWt >500 (large size)
- HBDH> 5 (too many potential hydrogen bond donors)
- M_No >10 (too many potential hydrogen bond accepters)

Most commercial drugs suitable for oral dosing violate no more than one of the rules these conditions represent.

As an extension of that concept, simulations plus has created a series of ADMET Risk rule sets and calibrated them against our own ADMET models. They are parameterized to include thresholds for a wide range of calculated and predicted properties that represent potential obstacles to a compound being successfully developed as an orally bioavailable drug. These thresholds were obtained by focussing in on a specific subset of drugs in World Drug Index (WDI). Similar to methodology used by Lipinski et al, we removed irrelevant compounds from 2008 version of the WDI. In particular, we removed phosphates, antiseptics, insecticides, emollients, etc. as well as any compound that did not have an associated United States Adopted Name (USAN). The structure of principle component in salts was extracted and neutralised, after which duplicate structures were removed. This left us with a data set of 2,316 molecules, 8.3% of which violated more than one of Lipinski's rule.

The overall ADMET risk is the sum of three risk's:

- Absn risk – risk of low fraction absorbed (PCB module models)
- CYP risk – risk of high CYP metabolism (MET module models)
- TOX risk – toxicity related risk (TOX module models)

ADMET Score

The ADMET related properties were used to define the scoring function named the ADMET score. The predicted value of each property was employed in the score with weight. Instead of using positive and negative to represent the property, we used beneficial/positive (q=1) and harmful/negative (q=0) here. Therefore we transformed the predictive values of harmful properties into q=0. For instance, the prediction of hERG- would be transferred to beneficial and the prediction of hERG+ would be transferred to harmful. These harmful endpoints included Ames, AO, CARC, CYP inhibiters, CYPPRO, hERG blocker, OCT2 inhibiter, and p-gp inhibiter. Finally the ADMET score value was adjusted between 0 and 1 according to scores of oral drugs in drug bank, in which 1 indicates best and 0 means worst. When ADMET score of a compound is less than 0, we makes ADMET score zero. When ADMET score of drug is greater than 1, we makes ADMET score 1.

$$\text{ADMET-score} = \frac{\sum_{i=1}^{n} w_i \times q}{\sum_{i=1}^{n} w_i}$$

Validation of ADMET Score

To compare the distribution of ADMET score for compounds in different data sets, the ADMET scores were calculated for the three data sets. The arithmetic mean and Mann-Whitney U test were then used to compare the different distribution of ADMET scores in the three data sets. The arithmetic mean is a sum of a collection of data divided by the number of data in the collection. The Mann-Whitney U test (49) is used to check whether the mean of two populations has a significant difference. It could also be used to determine whether two independent samples are selected from populations having the same distribution. In this study, we calculated the p-plus in the Mann-Whitney U test to distinguish the significant levels of any two data sets. In order to find the relationship between physicochemical and ADMET properties, the QED value was generated by fitting the MW, A log P, HBAs, PSA, ROTs, AROMs and ALERTs. We analysed the linear correlation between QED and ADMET score through linear regression. For the index of QBD values, we also calculated the arithmetic mean of three data sets and the p-value between any two data sets.

Computer Aided Drug Design (CADD)

Computer Aided Drug Design (CADD) provides several tools and techniques that helps in various stages of drug design thus reducing the cost of research and development time of drug. Drug discovery and developing a new medicine is a long, complex, costly and highly risky process that has few peers in the commercial world. This is why Computer Aided Drug Design (CADD) approaches are being widely used in the pharmaceutical industry to accelerate the process (50).

Drug Discovery Process:

Drug discovery is a series of processes which when followed identify the drug compounds for the effective treatment or control of disease targets. It starts with the screening of large number of chemical compounds to optimize the disease targets. It requires insight information about the structure of the drug receptor so that the drug molecules can be adjusted to the binding site.

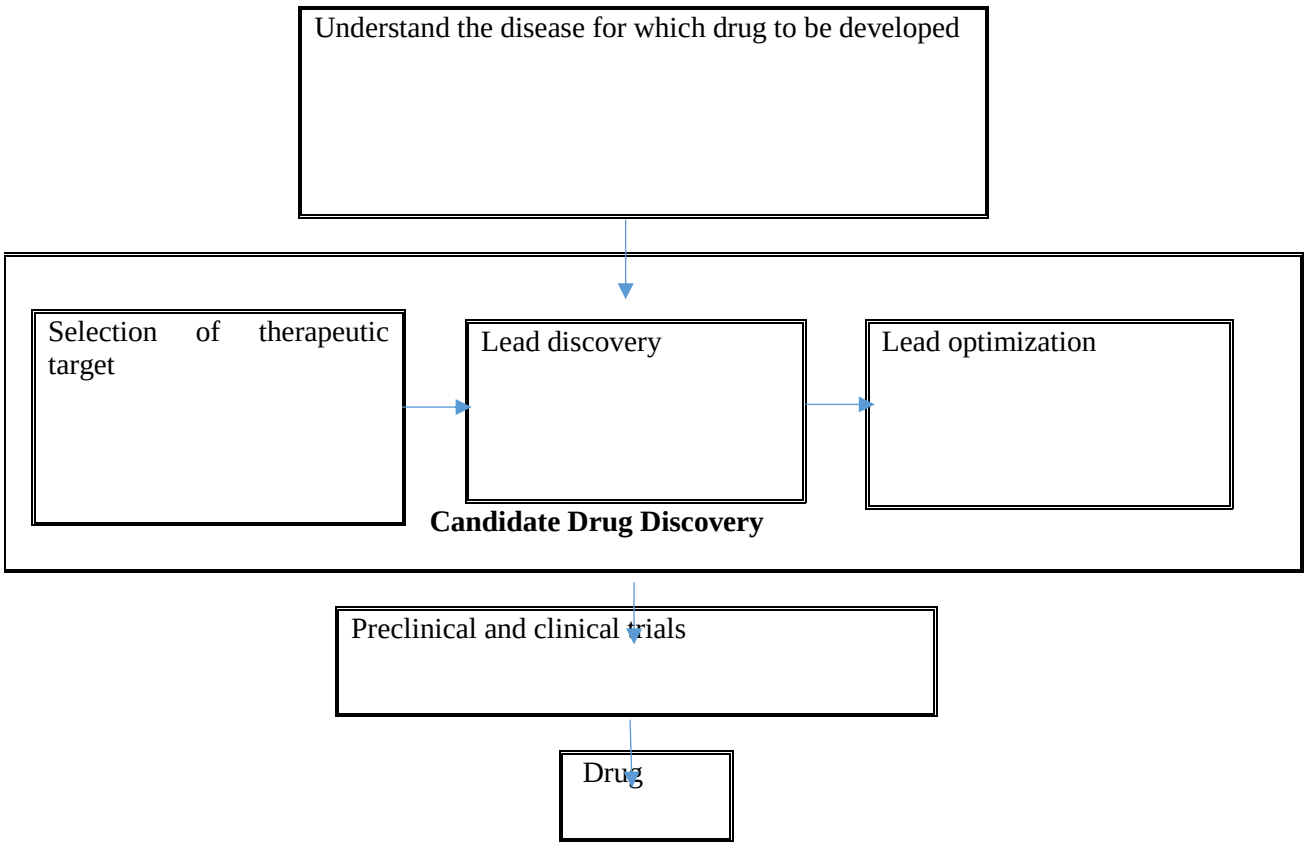
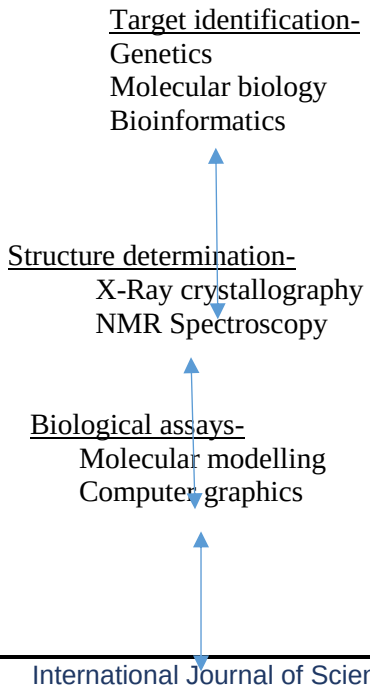


Fig. Drug Discovery Process

Working of CADD:



Synthetic chemistry
Peptidomimetics
Combinatorial chemistry

Objectives of CADD:

To change from-

- Random screening against disease assays
- Natural products, synthetic chemicals

To-

- Rational drug design and testing
- Speed up screening process
- Efficient screening
- De Novo design
- Integration of testing into design process
- Fail drugs fast

Advantages of CADD:

1. Time
2. Cost
3. Accuracy
4. Information about the disease
5. Screening is reduced
6. Database screening
7. Less manpower

Draw tools:

1. Chemdraw
2. Marvinsketch
3. Chemsketch
4. Marvin molecular editor and viewer
5. Chemwriter
6. UCSFchimera
7. Pymol

Swiss ADME

Swiss ADME is a free web tool to evaluate pharmacokinetics, drug likeness and medicinal chemistry friendliness of small molecules (36).

Parameters:

Rotatable bonds	≤ 7
Molecular weight	< 500
Polar surface area	< 120
Lipophilicity	Lop < 5

H-bond donors	< 5
H-bond acceptor	< 10

Solubility Criteria:

Description terms	**Parts of solvent required per parts of solute**
Very soluble	Less than 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10000
Practically insoluble	10000 and over

Computational methods:

1. Programing and scripting
2. Submission page
3. One panel per molecule output
4. Graphical output

Smiles code of artimisinin:

1.Artemisinin- CC1CCC2C[C(=O)OC3C24C1CC C(O3)(OO4)C]C

2.Artemether- CC1CCC2C[C(OC3C24C1CCC(O3)(OO4)C)OC]C

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