Swiss ADME predictions for anti cancer drug molecules prior In Vitro In Vivo Correlations (IVIVC)

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Abstract

Background: IVIVC is usually developed for in vivo absorption when drug dissolution is a rate-limiting step. Two key mechanisms, drug dissolution and permeation, rely on the absorption and thus the bioavailability of the oral solid dosage form. The key parameters influencing dissolution are the physicochemical properties of a substance, such as solubility and the gastrointestinal setting. The dissolution of in vitro drugs will be used as a substitute for in vivo absorption. **Objective:** The main objective of the study was to identify the physicochemical properties, pharmacokinetics, drug-likeness **Methods:** Swiss ADME tool was used to find out the in silico properties. Drug release and/or dissolution from the dosage form is the only factor governing drug absorption. In connection to that a potent molecule must meet its target in the body in adequate quantities to be successful as a drug, and remain there in a bioactive state long enough for the required biological events that exist. Drug development provides a comprehensive picture of absorption, distribution, metabolism and excretion (ADME) early these days in the process of discovery, at a time when there are multiple compounds considered, but access to physical samples is limited. **Results and Disscussion:** In our study which have used as model anticancer drugs Axitinib, Ibrutinib,Icotinib, Nilotinib and Dasatinib were evaluated. Computer simulations represent legitimate alternatives to experiments in that regard. **Conclusion:** During IVIVC drug development program chemical compound or drug molecules prior do the insilico model for promising analysis for drug development process.

Key words: *In* silico, IVIVC, SwissADME, solubility, permeability and anticancer agents

1. Introduction

Nowadays, the pharmaceutical industry is trapped between the rising pressure on costs and the growing expense of identifying and producing successful products. The average cost and time

needed for a new chemical entity to establish is much greater (approximately $500 million and 10-12 years) than those required for the development of a Novel Drug Delivery System (NDDS) ($20-50 million and 3-4 years) [1]. A new life may be granted to an available drug molecule in the form of an NDDS, thus improving its market value, competition and extending its patent life. The entire pharmaceutical industry today focuses on designing and improving innovative and improved drug distribution approaches through small formularies, patent expiry with eventual introduction of generic competition and vertical integration. During the last couple of years, there has been a substantial rise in NDDS permits, and this is projected to continue at striking rate in the future [2].

In the last few decades, with the development of novel dosage formulations, important medical developments have been made in the field of drug delivery. However, owing mainly to their short half-lives, low membrane permeability and related toxicity in the doses prescribed, the delivery of some types of drugs appears to be a concern. Today, the relationship between the chemical properties of drugs and their movement through the body is best understood. Drug research scientists are however, far earlier in the drug production process, recognising the pharmacokinetic properties of agents [3].

A delivery system's logical implementation is sensible and costly. The development and optimization of formulation includes differing amounts of excipients, manufacturing processes, detection of discriminating methods of dissolution and eventual scale-up of the finished product. As quantitative and qualitative changes in a formulation can alter the release and in vivo quality of drugs, it is often beneficial to develop tools that promote product production by reducing the need for bio studies [4]. In this respect, it is possible to consider the use of in vitro data to model in vivo results as a rational production of sustained release formulations. As part of the formulation design, a regulatory guide has recently been developed to mitigate the need for additional bioavailability studies. This guideline, referred to as the In vitro In vivo Correlation (IVIVC) Guidance, was developed and is focused on scientifically sound studies by the Food and Drug Administration (FDA) [5].

a) *In vitro in vivo* correlation

FDA has described IVIVC as a predictive mathematical model describing the relationship between a dosage form's in vitro property and an in vivo response [6]. The in vitro property is usually the rate or extent of dissolution or release of drugs, whereas the in vivo response is a concentration of plasma material or the amount of drug ingested and the United States Pharmacopoeia (USP) defined as forming a connection between a biological property or parameter derived from a biological property formed from a form of dosage and a physicochemical property of the same form of dosage [7]. The limitation derived from the biological property is usually AUC or Cmax, while the in vitro dissolution profile is the physicochemical property. As the dissolution profile is a representative of the absorption profile, a linear relationship with the slope of unity is desired, if possible. Non-linear correlation may also, however be appropriate [8].

IVIVC plays an essential role in the advancement of drugs in that it first serves as an in vivo surr ogate and helps to facilitate biowaivers; second, encourages and/or validates the use of dissolutio n methods and specifications; and third, assists in the development and selection of suitable form ulations in quality control [9]. The first and key function of developing IVIVC is to use the dissolution test for human trials as a substitute. The drawback of this is that the amount of bioequivalence tests done during the initial approval period and during improvements in scaling up and post approval was reduced. The IVIVC's further advantage is to assist in validating or determining dissolution conditions. This is because the IVIVC provides in vivo significance for the specification of in vitro dissolution. In other words, based on the performance of a bio batch in vivo, dissolution specifications are set. ±10% deviation from the mean dissolution profile obtained from the bio batch is the general dissolution time point specification [10].

If the formulation(s) comes between the upper and lower limits of the standard, bioequivalence between formulations will be expected. It is also possible to use the IVIVC based dissolution specification environment as a quality check for product results. However, since it focuses on the bioavailability of the substance, this quality management can often be more strict than the normal control level. However, the use of IVIVC is limited to a specific drug product. Only the same formulation can be used. IVIVC cannot be used for all products especially drug products with various release mechanisms [11].

IVIVC is typically designed for in vivo absorption when drug dissolution is a rate-limiting step. Two key mechanisms, drug dissolution and permeation, rely on the absorption and thus the bioavailability of the oral solid dosage form. The method in which the drug is released and available in solution and ready to be absorbed is drug dissolution. The key parameters influencing dissolution are the physicochemical properties of a substance, such as solubility and the gastrointestinal setting [12,13]. Drug permeability is the drug's ability to penetrate into the bloodstream circulation through a membrane. The level of permeation and eventually absorption also depends on the drug and blood perfusion's physicochemical properties. In a short time, the total penetration of an extremely permeable drug exists. Thus, drug release and/or dissolution from the dosage form is the only element regulating drug absorption. The dissolution of in vitro drugs will then be used as a replacement for in vivo absorption. It is very quick, contrary to the breakdown rate of immediate release drug products. The rate of absorption is likely to be a function of the rate of gastric emptying or the permeability of the stomach. IVIVC could not be accessed in this situation [14].

IVIVC have been documented for different drugs [15]. The experiments were carried out of all species, such as rodents, rabbits, dogs and humans. Much of the experiments concentrated on establishing associations between level B and level C. Rate B is a correlation in which the mean dissolution in vivo is compared to the mean dissolution in vitro. Whereas the level C association defines the relationship between one pharmacokinetic parameter and the volume of substance dissolved at one time. Level C is often known as the lowest correlation level. All Level B and C IVIVCs were established for so many purposes in the development of the formulation, e.g. for the selection of suitable excipients and the optimization of production processes, for quality control purposes, and for the characterization of release patterns relative to the reference for newly formulated immediate release (IR) and modified release (MR) products. Present IVIVC experiments, however have concentrated on the establishment and validity of a connection with level A. It is a point-to-point interaction between in vitro and in vivo release of drugs. While a non-linear association problem has been addressed, no official guidance on non-linear drug absorption regulated by IVIVC has been explored [16].

The IVIVC is set up to trigger the dissolution test to be utilized as a substitute for bioequivalency. It is advantage for drug manufacturers due to limiting the time and cost put

resources into the bioavailability studies. Moreover, IVIVC is typically expected for highly permeable drugs. This assertion is additionally upheld by the regulatory biopharmaceutical drug classification, which anticipates the effective IVIVC for highly permeable drugs [17-22].

The IVIVC is designed to make it easier to use the dissolution test as a bioequivalence proxy. It is an asset for pharmaceutical manufacturers because the time and costs invested in bioavailability trials are minimised. Furthermore under dissolution rate-limiting conditions, IVIVC is usually expected for extremely permeable drugs.

b) Biopharmaceutics Classification System (BCS)

BCS is a basic guideline for the evaluation of the conditions where in vitro in vivo correlations are predicted. It is also used as a method for improving the specification of in vitro dissolution. The drug dissolution and absorption model is correlated with the category, which defines the main parameters as a dimensionless number: the number of the absorption, the number of the dissolution, and the number of the dosage. The ratio of the mean residence time to the absorption time is the absorption number [23, 24]. The dissolution number is the ratio between the mean time of residence and the mean time of dissolution. The dosage number is the mass divided by the absorption volume of 250 ml and the solubility of the material. Here the mean time of residence is the average time of residence in the liver, small intestine, and colon. Based on these three factors, the percentage of the dosage absorbed can be estimated. A drug is classified as one of four classes in the BCS based exclusively on its solubility and intestinal permeability, high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability (Class III) (Class IV). A high soluble pharmaceutical drug is usually defined on the basis of the greatest dosage strength soluble in 250 ml or less of water over a pH spectrum of 1-8. In fact, considering that the drug is stable in the gastrointestinal setting, if the level of drug absorption is greater than 90%, it would be known to be a highly permeable drug [25]. Fig.1

c) *In vitro* dissolution

In the early stage of drug development, the aim of in vitro dissolution studies is to choose the optimal formulation, evaluate the active ingredient and the excipient, and evaluate any slight adjustments in drug products. Dissolution, however is hypothesised to be a surrogate of drug

bioavailability for the IVIVC viewpoint. For the in vivo waiver, however, a more rigorous dissolution requirement might be required.

In general, a method of dissolution that can distinguish between the formulations of the sample and that accurately reflects the in vitro activity will be chosen. The USP defines four specific forms of dissolution apparatus, i.e. rotating basket, paddle method, reciprocating cylinder, and cell flow, and suggests, in particular, the FDA guideline for modified release dosage form21.

To facilitate the development of correlation, the in vitro dissolution release of a formulation may be changed. The dissolution profile can be changed by modifying dissolution test conditions, such as stirring speed, equipment choice, medium pH and temperature. Appropriate dissolution testing conditions should be chosen, as previously mentioned, so that the formulation works in the same way as in vivo dissolution.

d) In vivo evaluation

For a new drug application, the FDA requires in vivo bioavailability studies to be carried out (NDA). Bioavailability studies are usually done in certain restrictive conditions such as fasting, non-smoking, and no consumption of other drugs in young healthy male adult volunteers. The drug is generally given in a crossover mode with a minimum half-life of five washout periods. The bioavailability analysis can be evaluated using the following parameters via plasma or urine data:

- Area under the plasma time curve (AUC), or the cumulative amount of drug excreted in urine (D_u^{∞})
- Maximum concentration (C_{max}), or rate of drug excretion in urine ($dD_u\backslash dt$)
- Time of maximum concentration (T_{max}).

Numerous approaches can be applied for decisive the in vivo absorption. Wagner-Nelson, Loo-Riegelman, and numerical de convolution are such methods. Both model-dependent strategies are Wagner Nelson and Loo Riegelman, of which the prior is used for a one-compartment model and the latter is for a multi-compartment design.

e) Factors affecting performance of sustained release dosage forms

The physicochemical effects of the drug and the physiological influences of the body. Oral absorption of a drug is a complex process dependent on these variables and their interactions with each other. In addition, other physicochemical properties still demonstrate their influence on drug absorption by influencing solubility and permeability as the main physicochemical factor affecting the rate and degree of oral drug absorption.

f) Regulatory affairs perspective on new drug development:

Novel drug discovery is the identification process on compounds that have the potential to become useful new therapies. The potential should be adequate to legitimize further innovative work and development. A crucial step in the drug development process is the submission of nonclinical and clinical data and information in a New Drug Application (NDA) to the food and drug administration (FDA) by the sponsor for seeking marketing authorization. A distinctive new molecular entity (NME) has most picked studies in pre clinical side and has been in clinical trials. The International Conference on Harmonisation (ICH) Guidelines is available for providing a common format for regulatory submissions incase of new drug. The process of new drug development is to evaluate the risk or benefit which is affected by many of the conflicting factors. All aspects of drug studies which are related with their procedures of clinical trials are examined before the approval of drug. Scrutiny process will be done by the FDA, until the drug releases to the market.

g) Swiss ADME

A vast variety of molecular structures are tested according to very complex criteria during the time- and resource-consuming processes of drug discovery and development, in order to direct the collection of chemicals to synthesise, analyse and facilitate, with the end aim of finding those with the best chance of becoming a successful drug for patients.

The molecules, together with low toxicity, must exhibit higher biological activity. Access to concentration of the remedial target in the organism is equally significant. The standard method of understanding pharmacokinetics (i.e. the fate of a therapeutic agent in the organism) is to split the different effects into individual parameters that influence access to the target. Computer

models have been fostered as a valid alternative to ADME prediction experimental procedures, especially at initial steps, where there are various chemical structures investigated but compound availability is restricted.

From the point of view of drug development, bioavailability and pharmacokinetics are becoming more relevant for the study of effective potential drug molecules in silico calculation of molecular physicochemical parameters. In producing accurate data in a fast and easy way, theoretical studies have a fundamental role. Many free online portals have recently been established for quicker screening, to reduce the time and expense of drug candidate testing (no animal testing). Swiss ADME is a latest inclusive tool run by the Swiss Institute of Bioinformatics (SIB) that enables drug candidate parameters to be estimated for ADME (absorption, distribution, metabolism and excretion). At the initial stage of the drug discovery process, the ADME properties which determine either the access of the potential drug to the target or its elimination by the organism are necessary. In-silico experiments based on measured physicochemical requirements will validate these parameters. The latter emphasize lipophilicity, water-solubility, molecule size, polarity, saturation or flexibility. As the first, Lipinski et al. introduced a drug-likeness connected to the pharmacokinetics-physico-chemical characteristics relationship. In other words, drug-likeness is an involves the improvement of molecular properties and structural characteristics that decide whether the molecule being tested is like the drugs that are known. Christopher Lipinski described the 'Rules of 5' (Ro5), known as Pfizer's or Lipinski's rules, in 1997. The drug-likeness assessment is based on the following factors: molar mass (which should be ≤ 500 g mol-1), log P (≤ 5), number of acceptors of hydrogen bonds (≤ 10; accounted for in the molecule function of N or O atoms) and number of donors of hydrogen bonds (≤ 5, accounted for in the molecule function of NH or OH groups). In addition, SwissADME provides 'BOILED-egg evaluation' to provide insight into the permeability of human gastrointestinal absorption (HIA) and blood-brain-barrier (BBB) [26].

The goal of predicting ADME limitations from molecular structure is performed by a wide range of in silico methods. 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). The correlation between pharmacokinetic and physicochemical parameters was clearly defined by this so-called Rule-of-five. Whereas physicochemical parameters give the

structure a global description, substructure searches will specifically describe molecules. The PAINS6 or Lilly MedChem7 used to clean chemical libraries of substances most likely to be unstable, reactive, hazardous, or likely to interact with biological assays due to unidentified regular hitters, dyes or aggregators are at the root of Structural Alerts. Cheminformaticians developed different molecular descriptors mined from chemical structures. A molecular fingerprint (FP) composed of a series of bits defining the presence or absence in the molecule of chemical characteristics. The FP2 approach is one topological (or path-based) FP archetype that considers all molecular structure fragments following a linear path up to a given number of bonds. To generate the bit string, each potential path is hashed to (i.e. the FP).

The efficiency by which computers manage such bit strings is a major advantage of FP, allowing, for example large-scale virtual screening or the quick estimation of molecular synthetic accessibility. In classification models for ADME behaviours constructed by support vector machines (SVM) or Bayesian techniques, FP is often used. Computer-aided drug design (CADD) has, remarkably, been a pioneer in the implementation of such techniques for machine learning.

Although generalist ADME packages are commercial applications, we felt the need to collect what we consider the most important computational methods to include a global assessment of the pharmacokinetics profile of small molecules in silico ADME tools concentrate on one particular property or model only. The SwissADME web tool provided here is freely available at http:/www.swissadme.ch and is intended for user-friendly submission and simple outcome review, even for CADD non-experts. Compared to the state-of-the-art free web-based applications for ADME and pharmacokinetics, and aside from special access to qualified approaches, SwissADME's strengths are in a non-exhaustive way different input methods, multi-molecule computing, and the ability to view, store and exchange outcomes by molecule or by intuitive and interactive global graphs.

2. Material and methods

SwissADME online free tool was employed for the study. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules.

2.1. Chemical Structure and Bioavailability Radar

The two-dimensional chemical structure and canonical SMILES, is shown in (Fig. 2). It shows on which chemical form the predictions were calculated. In addition, our bioavailability radar is shown for a rapid drug-likeness evaluation (refer to Fig. 3). It calculates six physicochemical properties: lipophilicity, size, polarity, solubility, flexibility and saturation. On each axis, a physicochemical range was described by descriptors adapted from refs 23 and 24 and interpreted as a pink region where the molecule's radar plot needs to fall completely to be considered drug-like.

2.2 Physiochemical properties

The drug's physicochemical properties and the body's physiological influences. Based on these factors and their relations with each other the oral absorption of a drug is a complex process. In addition, other physicochemical properties still illustrate their effects on drug absorption by influencing solubility and permeability as the key physicochemical element affecting the rate and degree of oral drug absorption.

2.3 Lipophilicity

Lipophilicity is characterised as a drug's affinity for a lipid environment. In the pharmaceutical industry, it has been a critical parameter, suggesting a drug's interaction with its molecular, pharmacokinetic, and metabolic properties. Lipophilicity can be determined by the distribution of the substance between the organic form, which is typically water-pre-saturated with n-octanol, and the aqueous phase, which is usually n-octanol-pre-saturated with water. In a two-phase system composed of n-octanol and water, the partition coefficient (P) is referred to as the ratio of the balance concentrations (Ci) of the dissolved compound.

2.4 Water solubility

In a "simple" in vitro environment like a vessel agitated with a paddle, establishing an IVIVC is nothing more complicated than attempting to replicate all the dynamic phenomena that lead to the in vivo release and solubilisation of the API in the gut. In vitro approaches are less' systematic' in comparison to in vivo experiments, as USP Apparatus 1 to 4 may be used for

different media (HCl, clear buffer, surfactant or enzyme addition, etc and different technical parameters (e.g.,volume,rate).

2.5 Pharmacokinetics

Pharmacokinetics refers to the movement of the drug into, through, and out of the body, the time course of its absorption, bioavailability, distribution, metabolism, and excretion, often defined as what the body does to a drug. The pharmacokinetics of a drug relies on the conditions associated with the patient as well as the chemical properties of the drug. To predict the pharmacokinetic parameters of populations, several patient-related variables (e.g., renal function, genetic makeup, sex, age) may be used. For instance, in older persons, the half-life of certain medications, especially those that require both metabolism and excretion, can be surprisingly long.

2.6 Druglikeness

Based on chemical structures and physicochemical properties, drug-likeness is created. Most specifically, physicochemical properties are tested in terms of their lipophilicity, solubility, permeability, metabolic stability, and affinity. Molecular ADMET-associated properties, in addition to conventional physicochemical property-based drug-likeness laws and ratings.

2.7 "boiled egg model"

Apart from effectiveness and toxicity, poor pharmacokinetics and bioavailability are blamed for multiple drug discovery failures. Two pharmacokinetic activities important for estimating at different stages of the drug development process are gastrointestinal absorption and brain access. To this end, as an effective predictive model that operates by measuring the lipophilicity and polarity of small molecules, the Brain Or IntestinaL EstimateD permeation system (BOILED-Egg) is proposed. Due to the speed, accuracy, conceptual simplicity and consistent graphical performance of the model, concomitant predictions for both brain and intestinal permeation are derived from the same two physicochemical descriptors and directly converted through molecular architecture. From the filtering of chemical libraries at the early stages of drug research to the assessment of drug candidates for growth, BOILED-Egg can be used in a number of settings.

3.Results and discussion

3.1 Chemical Structure and Bioavailability Radar report

Axitinib and Dasatinib: 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 -0.7<XLOGP3 <+5.0, size: MW between 150g/mol <MW <500g/mol, polarity: Topological Polar Surface Area TPSA between 20 $Å^2$ < TPSA < 95.97 $Å^2$, Insolubility: 0 < log S < 6.0, Unsaturation: fraction of carbons in the SP^3 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 (Fig 2 a-f).

3.2 Physiochemical properties

Identifying an active lead molecule, identifying a suitable drug candidate, and designing a marketable product are deeply affected by molecular properties and dosage form design. Not only can physicochemical characterization direct the selection of formulation methods, but it can affect analogue selection and lead optimization if integrated into the lead selection process. The end effect of the physicochemical properties consideration is to minimise the risk of failure by encouraging the detection of suitable design alternatives for dosage type and at the same time allowing discovery chemists and drug development process to increase the chances of finding commercially viable leads. Using swiss ADME online free tool we found the physiochemical properties of drug molecules was described in Table 1

3.3 Lipophilicity

For the formulation of lipophilic drugs, lipid-based dosage formulations, which have a broad range of compositional and functional properties, can be used advantageously. Due to possible problems of chemical and physical instability, and a lack of information about formulation design algorithms and technology transition concerns, there has been a conventional reluctance to create lipid-based dosage types. However, due to potential commercial and pharmaceutical advantages, and the industry trend towards the discovery/development of increasingly hydrophobic (and potent) new chemical substances, there is a recent revival of interest in lipid-based dosage forms (Table :2).

3.4 Water solubility

Pure permeability through the intestinal membrane (mainly for Class III and IV of the BCS), release from the drug dosage material, or solubility of the active ingredient could be the limiting factor for the appearance of the drug in the blood in the case of oral administration of a solid dosage form. The absorption can be governed by the physico-chemical characteristics of the API (such as solubility, dissolution rate, particle size, crystal shape, polymorphism, pKa, GIT stability) and not by the permeability or formulation of the solubility-limited substance (Class II and IV of BCS). In the case of release-restricted formulations, the medication release from the drug dosage type is limited by absorption (Table 3)

3.5 Pharmacokinetics

Among novel drug delivery systems, Modified Release (MR) formulations have become an appealing alternative for improving the solubility and bioavailability of poorly soluble drugs due to their potential to hold the drug in the gastrointestinal tract in a solubilized condition. These formulations provide a range of benefits, such as a decrease in the impact of food and inter-individual variability, simplicity of preparation and the potential to produce using standard marketable excipients. Despite these benefits, relatively few drugs are present on the market today, possibly owing to insufficient awareness of in vitro experiments (for in vivo fate prediction) and a lack of comprehension of the pathways behind pharmacokinetic and biopharmaceutical aspects of MR formulations after oral administration (Table 4).

3.6 Druglikeness

Human intestinal absorption (HIA), blood-brain barrier (BBB) permeability, inhibition of the cytochrome P450 enzyme (CYP), acting as a substrate or receptor of P-gp, drug-induced liver damage (DILI), cardiotoxicity, and cytotoxicity are instances. The following elements should also be found in datasets that help drug-likeness research: chemical compositions, physicochemical properties, details correlated with ADMET, drug-likeness properties (rules and scores), and drug and drug-like collections (Table 5).

3.7 Boiled egg model prediction

The passive human gastrointestinal absorption (HIA) predictions and permeation of the blood-brain barrier (BBB) all consist of reading the BOILED-Egg model, an intuitive graphical classification model, which can be shown in fig 3. In our study shows we have selected aniticancer compounds except nilotinib other compounds have half life less than 6 hours. Icotinib shows that only compound that could able to cross the BBB, when compared with other compounds.

4. Conclusion

IVIVC plays a significant role during the drug development process. On other hand, any molecules which involves in the clinical trials such as chemical entity, orphan molecule and drug candidates need to undergo in silico modelling in order to confirm the physiochemical properties like solubility and permeability. In our study the anti cancer drug candidates Axitinib, Ibrutinib, Icotinib, Nilotinib and Dasatinib were evaluated for their physicochemical, pharmacokinetic and drug-likeness using the the SwissADME Web tool. By applying this method we could save the money, time and manpower. As per the results obtained we found that the solubility of said drug candidates needs to be improved the to enhance the efficacy of the drug.

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Conflict of interest

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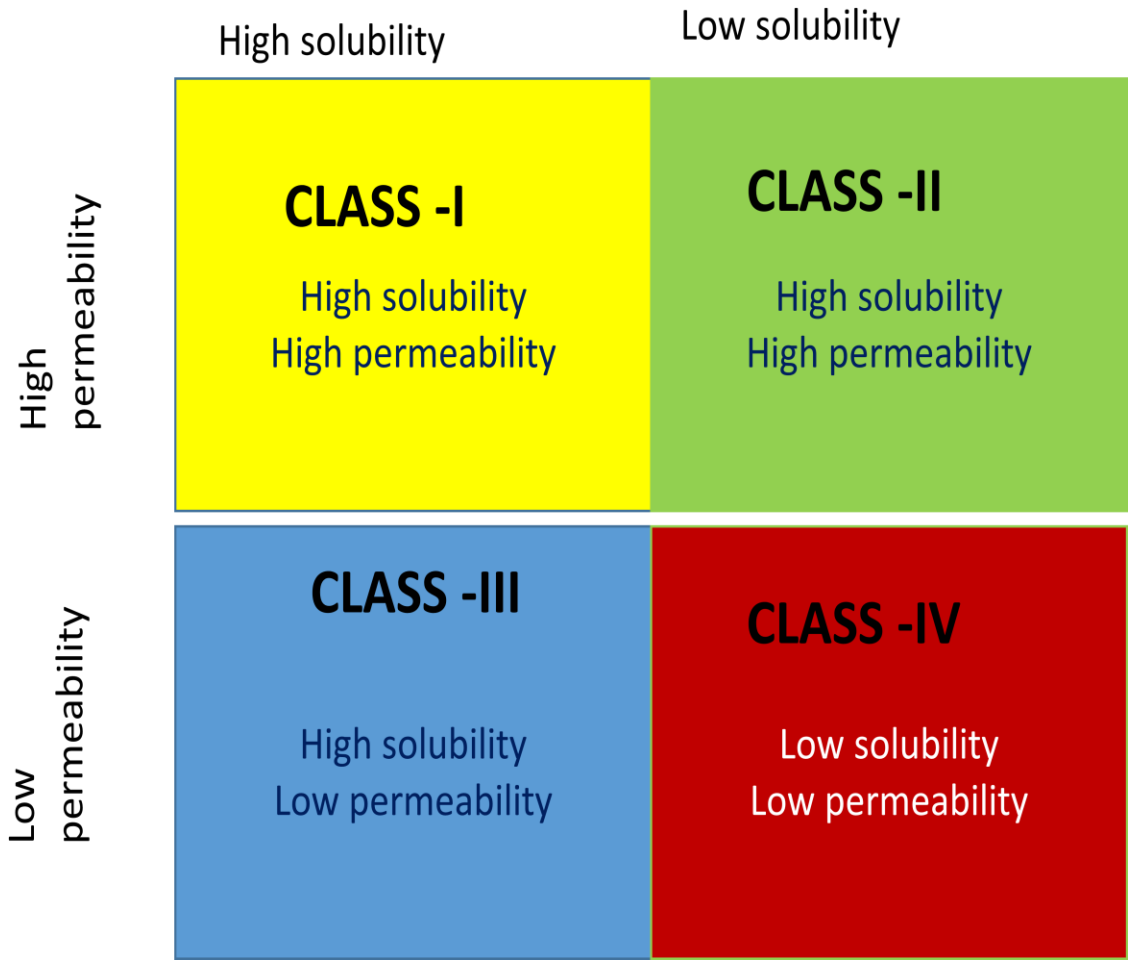

Figure 1. BCS classification.


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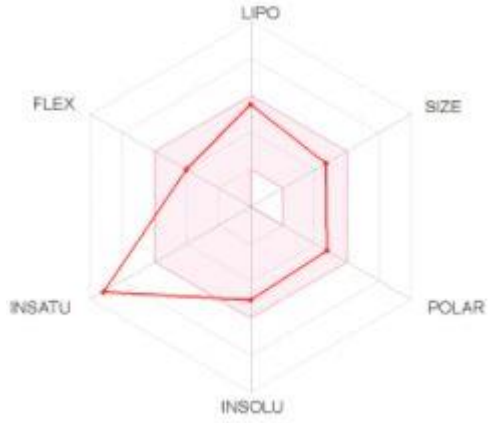
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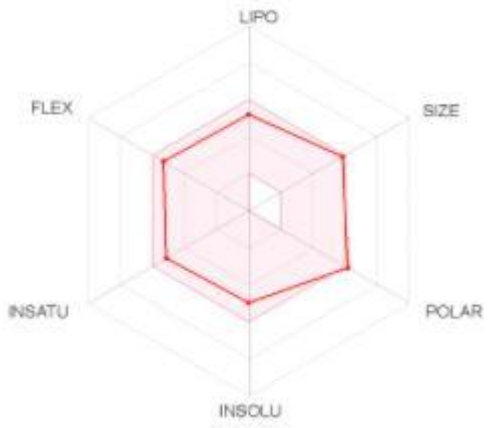
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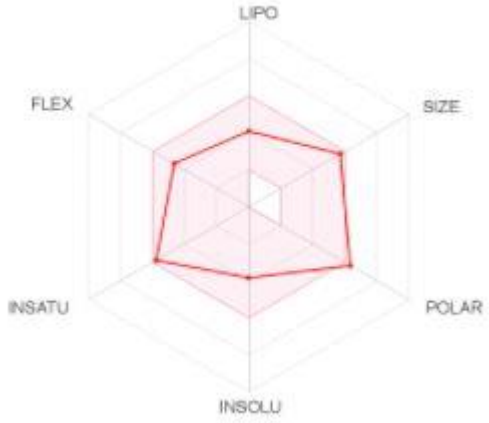
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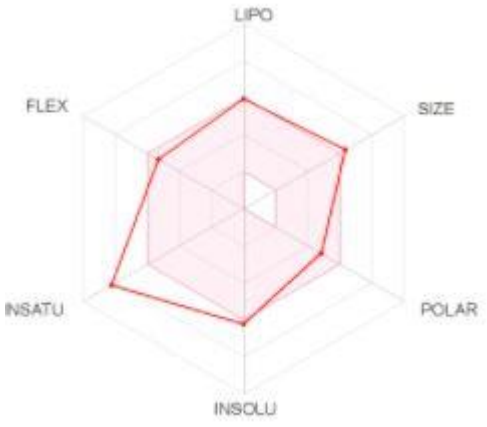
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[f]

Figure 2. [a] Acalabrutinib, [b] Axitinib, [c] Dasatinib [d] Ibrutinib, [e] Icotinib, [f] Nilotinib

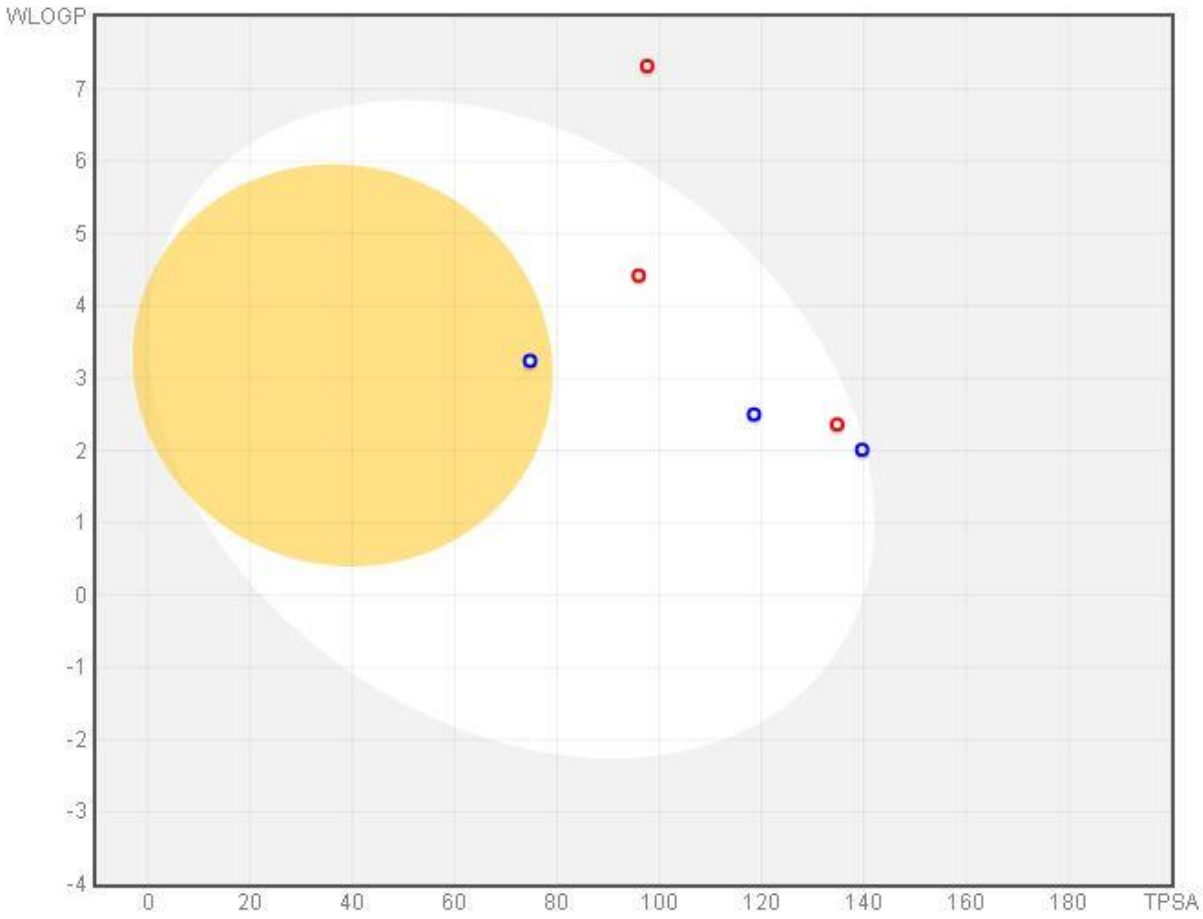

Figure 3 Boiled egg model predictions.

List of tables

Physiochemical properties						
	Axitinib	Dasatinib	Ibrutinib	Acalabrutinib	Icotinib	Nilotinib
Formula	$C_{22}H_{18}N_4OS$	$C_{22}H_{26}ClN_7O_2S$	$C_{25}H_{26}N_6O_4$	$C_{26}H_{23}N_7O_2$	$C_{22}H_{21}N_3O_4$	$C_{28}H_{22}F_3N7O$
Molecular weight	386.47 g/mol	488.01 g/mol	474.51 g/mol	465.51 g/mol	391.42 g/mol	529.52 g/mol
Num. heavy atoms	28	33	35	35	29	39
Num. arom. heavy atoms	21	17	21	21	16	29
Fraction Csp3	0.05	0.36	0.28	0.19	0.27	0.11
Num. rotatable bonds	6	8	7	6	2	8
Num. H-bond acceptors	3	6	7	5	6	8
Num. H-bond donors	2	3	3	2	1	2
Molar Refractivity	112.82	138.63	133.81	136.51	109.28	141.08
Topological Polar surface area	95.97 Å²	134.75 Å²	139.62 Å²	118.51 Å²	74.73 Å²	97.62 Å²

Table 1 Physiochemical properties of drug molecules

Lipophilicity						
	Axitinib	Dasatinib	Ibrutinib	Acalabrutinib	Icotinib	Nilotinib
Log $P_{o/w}$ (iLOGP)	2.62	3.37	3.22	3.10	3.60	3.36
Log $P_{o/w}$ (XLOGP3)	4.17	3.59	1.68	3.04	3.08	4.90
Log $P_{o/w}$ (WLOGP)	4.42	2.36	2.01	2.50	3.24	7.32
Log $P_{o/w}$ (MLOGP)	3.12	1.35	1.36	1.52	1.62	2.75
Log $P_{o/w}$ (SILICOS-IT)	4.80	3.33	1.21	2.02	3.53	4.83
Consensus Log $P_{o/w}$	3.82	2.80	1.90	2.44	3.01	4.63

Table 2: Lipophilicity of drug molecules.

Water Solubility						
	Axitinib	Dasatinib	Ibrutinib	Acalabrutinib	Icotinib	Nilotinib
Log *S* (ESOL)	-5.02	-4.98	-3.82	-4.69	-4.48	-6.32
Solubility	3.67e-03 mg/ml ; 9.50e-06 mol/l	5.10e-03 mg/ml ; 1.05e-05 mol/l	7.14e-02 mg/ml ; 1.51e-04 mol/l	9.52e-03 mg/ml ; 2.04e-05 mol/l	1.29e-02 mg/ml ; 3.28e-05 mol/l	3.10e-04 mg/ml ; 5.86e-07 mol/l
Class	Moderately soluble	Moderately soluble	Soluble	Moderately soluble	Moderately soluble	Poorly soluble
Log *S* (Ali)	-5.89	-6.11	-4.23	-5.19	-4.32	-6.69
Solubility	4.94e-04 mg/ml ; 1.28e-06 mol/l	3.82e-04 mg/ml ; 7.83e-07 mol/l	2.82e-02 mg/ml ; 5.94e-05 mol/l	2.97e-03 mg/ml ; 6.39e-06 mol/l	1.89e-02 mg/ml ; 4.82e-05 mol/l	1.09e-04 mg/ml ; 2.06e-07 mol/l
Class	Moderately soluble	Poorly soluble	Moderately soluble	Moderately soluble	Moderately soluble	Poorly soluble
Log *S* (SILICOS-IT)	-8.09	-6.88	-5.35	-6.51	-6.54	-10.86

Solubility	3.11e-06 mg/ml ; 8.05e-09 mol/l	6.46e-05 mg/ml ; 1.32e-07 mol/l	2.11e-03 mg/ml ; 4.45e-06 mol/l	1.44e-04 mg/ml ; 3.10e-07 mol/l	1.13e-04 mg/ml ; 2.90e-07 mol/l	7.29e-09 mg/ml ; 1.38e-11 mol/l
Class	Poorly soluble	Poorly soluble	Moderately soluble	Poorly soluble	Poorly soluble	Insoluble

Table 3: Water solubility predictions.

Pharmacokinetics						
	Axitinib	Dasatinib	Ibrutinib	Acalabrutinib	Icotinib	Nilotinib
GI absorption	High	High	High	High	High	Low
BBB permeant	No	No	No	No	Yes	No
P-gp substrate	No	No	Yes	Yes	Yes	No
CYP1A2 inhibitor	Yes	No	No	No	Yes	No
CYP2C19 inhibitor	Yes	Yes	No	Yes	No	Yes
CYP2C9 inhibitor	Yes	Yes	No	Yes	Yes	Yes
CYP2D6 inhibitor	Yes	Yes	No	Yes	Yes	Yes
CYP3A4 inhibitor	Yes	Yes	No	Yes	Yes	Yes
Log K_p (skin permeation)	-5.70 cm/s	-6.73 cm/s	-8.00 cm/s	-6.98 cm/s	-6.50 cm/s	-6.05 cm/s

Table 4: Pharmacokinetic predictions

Druglikeness						
	Axitinib	Dasatinib	Ibrutinib	Acalabrutinib	Icotinib	Nilotinib
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	No; 2 violations: MW>480, MR>130	No; 1 violation: MR>130	No; 1 violation: MR>130	Yes	No; 3 violations: MW>480, WLOGP>5.6, MR>130
Veber	Yes	Yes	Yes	Yes	Yes	Yes
Egan	Yes	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>131.6	Yes	Yes	No; 1 violation: WLOGP>5.88
Muegge	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55

Table 5. Drug-likeness predictions