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CONCEPT OF DRUG LIKENESS IN PHARMACEUTICAL RESEARCH

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ABSTRACT

The low success rate of converting lead compounds into drugs owing to unfavorable pharmacokinetic parameters has evoked a renewed interest in understanding more clearly what makes a compound drug-like. The concept of drug-likeness, established from the analyses of the physiochemical properties or/and structural features of existing small organic drugs or/and drug candidates, has been widely used to filter out compounds with undesirable properties. Present review summarise molecular property filters and the number of computational techniques for identifying drug-like molecules.

KEYWORDS: **Drug-likeness, pharmacokinetic parameters and molecular property filters.**

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INTRODUCTION

Lipinski's rule-of-five (ROF) was derived from an analysis of 2245 molecules of the Derwent World Drug Index (DWDI) that were believed to have entered phase II clinical testing .The rules encompassed by the ROF have been widely implemented throughout the industry and have generally served as a default measure of a drug- likeness, even though they were not originally intended for this purpose.

Properties that have been associated with oral drug- likeness include

(i) Oral bioavailability
(ii) Appropriate toxicity to pass phase I clinical trials
(iii) Minimal potency for interacting with a therapeutic target
(iv) Aqueous solubility
(v) Permeability
(vi) Synthetic accessibility
(vii) Pharmacokinetic viability
(viii) Blood brain barrier permeability(for Central Nervous System(CNS) drugs)

To proactively apply the above characteristics to drug discovery efforts, computational models would need to be developed for these individual properties. Alternatively, various molecular properties and/or calculated descriptors could be used in their place to identify those features that can discriminate between known oral drugs and presumed non-drugs[1]. In seeking to narrow the search space of chemically diverse candidate compounds, cheminformatic methods are used to constrain the compounds screened such that they tend to display 'lead-likeness'[4] or 'drug-likeness'. The same concepts hold true for drugs with multiple intended targets (promiscuous drugs or poly-pharmacology [2,3].The most common cheminformatic filter used to constrain pharmaceutical drug libraries is Lipinski and colleagues' celebrated 'rule of five' (Ro5)[6]. This states that poor absorption or permeation of a compound is more probable when there are more than five hydrogen-bond donors, the molecular mass is above 500 Da, the lipophilicity is high (clogP > 5) and when the sum of nitrogen and oxygen atoms is greater than 10. Other rules or filters consider generic and calculable properties such as the number of rotatable bonds and the polar surface area or the ligand efficiency, and a 'rule of three' has been proposed for fragment-based lead discovery. It was recognised explicitly in the original review that the Lipinski rules do not normally cover drugs that are derived from natural products, in which transporters are clearly involved in their disposition and it is, in fact, probable that this involvement of carrier molecules holds true for most other compounds too [7,8].

MOLECULAR PROPERTY-BASED DRUG-LIKENESS FILTERS[9]

It is believed that drugs or drug candidates tend to have similar distributions of physicochemical properties. Therefore, based on the analyses of simple molecular properties of existing drugs or/and drug candidates, simple rules/ filters that define acceptable boundaries for those properties can be developed. In 2007, Lipinski proposed the "Rule of Five" [10], the most famous drug-likeness filter, which provides four rules to determine whether a molecule is well orally absorbed or not: molecular weight (MW) ≤ 500, octanol/water partition coefficient (ClogP) ≤ 5, number of hydrogen bond donors (HBD) ≤ 5 and number of hydrogen bond acceptors (HBA) ≤ 10. If a compound violates two or more rules, it may not be orally active. For the 1543 drugs approved by the FDA deposited in Drug bank, 1318 (85.4%) of them obey the Rule of Five. Since then, a variety of "rules of thumb" in a similar spirit as the Rule of Five was developed. For example, by analyzing the 6304 molecules in the Comprehensive Medicinal Chemistry (CMC) database, Ghose et al. found that more than 80% of the compounds satisfy the following qualifying ranges: AlogP between –0.4 and 5.6, MW between 160 and 480, molar refractivity between 40 and 130, and total number of atoms between 20 and 70 [11]. By analyzing the compounds in drug-like databases (MDDR, Current Patents Fast-alert, CMC, PDR, and NCE) and non-drug-like database (ACD), Oprea and co-workers re-vealed that 70% of the drug-like molecules obey the following rules: 0 ≤ HBD ≤ 2, 2 ≤ HBA ≤ 9; 2 ≤ RTB (number of rotatable bonds) ≤ 8,

and 1 ≤ RNG (number of rings) ≤ 4. Similar to the purpose of drug-likeness rules/ filters, the REOS (Rapid Elimination of Swill) program was developed at Vertex. Compared with Lipinski's "Rule-of-Five", the drug-likeness criteria used by REOS include six rules: MW (200 ~ 500), logP (–5 ~ 5), number of hydrogen bond donors (0 ~ 5), number of hydrogen bond acceptors (0 ~ 10), num- ber of formal charge (–2 ~ 2) and number of rotatable bonds (0 ~ 8). Besides, REOS also allows users to remove compounds with reactive, toxic, and undesirable fragments by using more than 200 functional groups fi lters. In 2012, Hopkins and co-workers proposed a concept of desirability: the quantitative estimate of drug-likeness (QED). The QED index was generated by fi tting the distributions of eight properties, including MW, AlogP, HBA, HBD, polar surface area (PSA), RTB, number of aromatic rings (AROM) and number of alerts for undesirable substructures (ALERTs), of 771 marketed oral drugs. Compared with most properties - based drug-likeness rules/ filters, the QED method is more fl exible by replacing the stiff cutoffs with a novel continuous index. Beyond as discussed above, the distribution pro fi les of the physicochemical properties for drug-like and non-drug-like datasets were also analyzed and compared. For example, Zheng and coworkers developed a series of size-independent molecular descriptors to discriminate drug-like from non-drug-like molecules, and a new chemistry space fi lter based on two descriptors, UNSATP (a representative of the molecular saturation-related descriptor) and NO_C3 (a heteroatom propor- tion descriptor), was proposed: a molecule is drug-like when 0 ≤ UNSATP ≤ 0.43 and 0.10 ≤ NO_C3 ≤ 1.8 are satisfied. Among the studied physicochemical properties, a size-independent descriptor, fractional negative accessible surface area (FASA–), has better performance to discriminate drug-like from non-drug-like molecules than the other descriptors.The linkages between drug discovery attritions and molecular physicochemical properties suggest that the drug-likeness filters based on physicochemical properties might be useful to speed up drug discovery and development. However, the reported studies have confirmed that the drug-likeness filters/rules based on physicochemical properties are not immobile and universal [12,13,14] and they should be used cautiously. For example, our studies showed that Rule-of-Five is not a good predictor to estimate intestinal absorption, and even less reliable than a simple molecular property, topological polar surface area (TPSA). In 2012, we evaluated the performances of Rule-of-Five and Oprea's filters to distinguish the drug-like molecules in MDDR from the non-drug-like molecules in ACD. Two MDDR and ACD subsets with similar MW distributions were generated artificially. When the violation number of Rule-of-Five less or equal to 1 was de fi ned as the criterion of drug-likeness, 86.8% of the ACD molecules and 88.3% of the MDDR molecules were identified to be drug-like. That is to say, when drug-like and non-drug-like compounds have similar MW distributions, Rule-of-Five does not have any prediction capability to distinguish drug-like from non-drug-like molecules. We also applied the Oprea's RNG and RGB filters to evaluate the ACD and MDDR subsets with similar MW distributions, and most non-drug-like molecules in ACD (59.5%) were identified to be drug-like. Recently, Ritchie et al. evaluated the correlations between the QED score and the actual pharmaceutical and pharmacokinetic (PK) profiles in humans for 300 oral drugs. It appears that the QED score shows acceptable performance in discriminating drug behaviors related to administration and absorption, but it is unable to discriminate drugs with respect to metabolism and elimination[15].

DRUGS AND CHEMISTRY SPACE[16]

The world of drug-like compounds is limited in that there are currently only about 10000 drug-like compounds. Drug-like is defined as those compounds that have sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of human Phase I clinical trials. Compounds that survive through Phase I and into Phase II clinical efficacy studies are conveniently identified by the presence of a United States Adopted

Name (USAN), International Non-Proprietary Name (INN). Some of these may be New Chemical Entities (NCE) that have been approved for marketing by a regulatory agency in at least one country. As an illustration, there were about 9500 USAN names in the last compilation of the United States Pharmacopeia. Regulatory approval does not imply commercial success. For example, in the early 1970s, it was common for a drug to receive early approval in one or two countries, and then to encounter problems in the large market regulatory bodies and to never be actually marketed. Drugs and their targets are sparsely distributed through chemistry space (Drews, 2000), and the members of a structural chemotype can be thought of as small tight clusters in the vastness of chemistry space. The combinatorial chemistry focus on chemical libraries with very large numbers of compounds tends to hide the fact that the majority of information on drug-like properties is contained in a very small number of compounds. This fact, in turn, raises the issue of the distribution of drugs in chemistry space. Chemistry space for reasonably sized molecules, i.e., those up to about molecular weight 600, and containing the common atoms found in drugs is very large. Estimates range widely from 10^{40} to 10^{100} with 10^{62} as a commonly quoted middle-range estimate. Given the small number of known drug-like compounds and the vastness of chemistry space, there are only several possibilities on the distribution of drugs in chemistry space. At the extremes, either drugs are found in small, infrequently distributed clusters in the vastness of chemistry space (the authors view). Alternatively, drugs are uniformly distributed through the vastness of chemistry space, and, so far, the pharmaceutical companies have only found an incredibly small proportion of the possible drugs that might exist. The number of possible drugs acting at receptors can be over-estimated from a simple reduction to absurdity argument working backward from the number of possible targets. The basic idea is that there cannot be more drugs than there are drug receptor targets and that we can set an upper limit on the number of drug targets.The argument is as follows. The size of a large human might be 100 kg. From the ‘‘rule of five’’ (Lipinski etal., 1997), we know that the upper size range for orally acting drugs is about molecular weight 500, corresponding to about the upper 90th percentile in drug size distribution. The minimum size of a drug target cannot be smaller than that of its ligand. Therefore, the maximum number of possible drug targets of MWT 500 in a human can be estimated from Avogadro’s number of 6.02×10^{23} molecules/mol. For a minimum target molecular weight of 500, a 100-kg human can contain only $100/0.5 \times 6.02 \times 10^{23}$ targets. This is about 10^{26} targets. If we were able to screen against all possible targets in a purely random manner, and given a chemistry space at the lower estimate of 10^{40}, we would still have only one chance in 10^{14} of finding a hit. In actuality, most receptor targets will have a molecular eight much larger than 500, so the number of targets will be smaller than 10^{26}. Also, it seems highly unlikely that one could screen against all possible targets at the same time, so the actual probability of finding a hit would be much smaller than one in 10^{14}. The odds of finding a hit is even worse if one takes one of the estimates of chemistry space larger than 10^{40}. The hit rate would be far lower than one in 10^{14}. This is a truly miserable prediction for success. A number of about 10^{14} chemical compounds far exceeds the number of compounds (low tens of millions) that have historically been abstracted by the Chemical Abstracts Service. The chance of a hit is somewhat increased because there are very likely to be multiple actives at any one target. However, the improvement in probability of a hit because of multiple actives is likely to be masked by the conservative assumptions as to drug target number and by the conservative estimates on the numbers of accessible small molecular weight compounds. Further masking may arise from the very conservative estimate based on screening of

all possible drug targets simultaneously, rather than separately. All in all, a random distribution of drugs in chemistry space suggests that the HTS of a maximally chemical diverse library should seldom, if ever, work

METHODS OF DRUG- LIKENESS PREDICTION

1. Simple counting method[17]

Many researchers over the years have attempted to show that drug-like molecules tend to have certain properties. For example log P, molecular weight, and the number of hydrogen bonding groups have been correlated with oral bioavailability. In principle, then, one should be able to very simply improve the 'odds of success' by biasing selections towards compounds that have certain properties. Researchers at Pfizer have extended this idea with the establishment of the 'rule of 5' which provides a heuristic guide for determining if a compound will be orally bioavailable [18]. The rules were derived from analysis of 2245 compounds from the WDI. Only those compounds with a USAN (United States Adopted Name) or INN (International Nonproprietary Name) and an entry in the 'indications and usage field' of the database were included in the analysis. The assumption is that compounds meeting these criteria have entered human clinical trials and therefore must possess many of the desirable characteristics of drugs. It was found that in a high percentage of compounds, the following rules were true: hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, molecular weight ≤ 500, and log P ≤ 5. The majority of the violations came from antibiotics, antifungals, vitamins and cardiac glycosides. The authors suggest that, despite their violations of the 'rule of 5', these classes of compounds are orally bioavailable because they possess groups which act as substrates for transporters. Ghose et al.[19] extended this work by characterizing 6304 compounds (taken from the Comprehensive Medicinal Chemistry Database) based on computed physicochemical properties. They established qualifying ranges which cover more than 80% of the compounds in the set. Ranges were established for A log P (20.4 to 5.6), molar refractivity (40 to 130), molecular weight (160 to 480), and number of atoms (20 to 70). A similar study was performed by Oprea[21], who carried out a Pareto analysis of compounds from MDDR, CMC, Current Patents Fast-alert, New Chemical Entities and ACD. The Pareto analysis was used to determine property ranges covering 80% of the compounds in a particular database. In addition to the properties discussed above, Oprea also considered counts of ring bonds, rigid bonds and rotatable bonds.

2.Knowledge-basedmethod[22]

Knowledge-based methods are based upon the concept of intrinsic binding energies and scoring of structural fragments. In this method mainly functional groups are used to classify drug and non-drug like molecules based on different scoring functional group fragment. Andrews *et al.*, used a set of 200 drug molecules to derive a set of intrinsic binding energies for the 10 functional groups as shown in [Table - 1] [23,24] . The inherent binding of small molecules was then estimated by summing the intrinsic binding energies and subtracting an entropic factor; the method had been widely used previously for the reagent selection rather than drug likeness prediction. On similar lines, Muegge *et al.*, in 2001 assigned a score to each molecule based on the presence of structural fragments typically found in drugs. The fragments used in this study were amines*, amides, alcohols, ketones, sulfones, sulfonamides, carboxylic acids*, carbamates, guanidine*, amidines*, urea, and esters. A molecule was given one point for each non-overlapping fragment. The molecules with a score between 2 and 7 were classified as drugs otherwise they were classified as non-drugs. Compounds containing a single pharmacophoric group would only be classified as drugs if they contained one of the groups marked with an asterisk in list of fragments. In order to create novel antidepressants without oxidative tissue damage, less side effects and good bioavailability, structurally simple selective

serotonin reuptake inhibitors with a isobenzofuran skeleton were designed based on the SAR of the target molecule - Citalopram and Talopram. As a result, designed molecules obey the Lipinski rule of 5 and also give moderate to good druglikness score[27].

Table 1
Functional Groups Used In the Scoring Scheme Developed by Andrews

Functional group	Score
Carboxylate	8.2
Phosphate	10
N+	11.5
N	1.2
OH	2.5
O or S ether	1.1
Halogens	1.3
CO	3.4
$C(SP^2)$	0.7
$C(SP^3)$	0.8

3. Functional group filters[22]

A different approach is to identify functional groups that tend to be undesirable because of chemical reactivity and metabolic ability. Walter *et al.*, briefly described an approach REOS (Rapid Elimination of Swill) to eliminate undesirable reagent in combinatorial libraries . REOS is a hybrid method that combines some simple counting schemes similar to those in the RO5 with a set of functional groups filter to remove the reactive and otherwise under sizable moieties. The functional group filters implemented in REOS identify reactive, toxic, and otherwise undesirable moieties. Initial filtering is based on a set of seven property filters. Hydrogen bond donors, acceptors and charged groups are determined using a set of rules similar to those used in the PATTY program developed at Merck. Log P can be calculated based on a variety of schemes. A web-based interface makes it trivial to modify parameters to suit the needs of a particular drug discovery project. Examples of the functional group filters employed by REOS are listed in [Table - 2]. In REOS, the functional groups filters are specified using the SMARTS pattern matching language developed at Daylight Chemical Information Systems. SMARTS is extended version of the SMILES (Simplified Molecular Input Line Entry System) notation developed specifically for sub-structure searching. Steps involved in REOS analysis are as follows: In the first step reagents are filtered; reactive and toxic reagents are removed in addition to the reagents that clearly will create a product that violates the molecular weight limits. In the next step, reagents checked for compatibility with chemistry- for example, when synthesizing amide one can simplify the chemistry by removing acids containing basic amines and amines containing acidic functionality. Finally the product is filtered considering the properties such as log P. This step is also incorporates a maximum count cutoff for the functional groups. The major advantage of SMARTS patterns is that they are simple ASCII text, which can be easily modified and used by a variety of applications. However, writing such patterns takes a bit of practice and the notation may not be immediately accessible to medicinal chemists.

Table 2
Functional Group Filter Employed By Reos Program

Functional groups	SMARTS notation
Sulphonyl halide	S(=O)[F,Cl,Br,I]
Acid halide	C(=O)[Cl,Br,I]
Peroxide	OO
Aldehyde	[CH]=O

4.Multi-property optimization

When designing a combinatorial library, drug-like character refers to only as a small number of properties, which must be optimized; it may also be necessary to optimize diversity, potency, selectivity or a number of other properties. Simultaneous optimization of multiple properties of as combinatorial library involves selection of random subset of reagents, construction of a virtual library of compounds from these reagents, calculation of the properties of combinatorial products, making modifications to the reagent subset and accepting the changes if they improve the like character of the library. This process is repeated until a predetermined stopping condition has been reached. Gillet *et al.,* used a genetic algorithm to optimize both diversity and drug-like character of a combinatorial library. Libraries were scored by calculating the frequency distribution for each of the five properties (log P, MWT, HBD and HB-A) and comparing this distribution with that calculated from the CMC. The library whose frequency distribution most closely matched that of the CMC received the highest score.

5. Examination of building blocks in known drugs

This approach does not directly distinguish drugs from non-drugs but it helps chemists to identify preferred moieties for library design. Bemis and Murcko [5] developed a method for organizing drugs by decomposing molecules into framework [Figure - 1]. A successful examination of 5120 compounds from the CMC yielded 1170 scaffolds. This suggests that drugs are rather diverse. However, when atom and bonds were considered equivalent, only 32 frameworks described the shapes of half of the drugs in the set. These frameworks are shown in [Figure - 2]. Then the frequency of occurrence of a particular framework in the entire database is compared to its frequency in a specific toxicity subset, this allows the discrimination between composition frameworks which occurs in a variety of molecules and toxicity conferring framework which occur primarily in molecules with a specific toxicity. An automated technique that uses a highly connected network to model the toxicity-conferring frameworks can then be used to screen a database and identify potentially toxic molecules. Toxicity is a major cause of failure for the drugs in clinical trials and this will undoubtedly continue to be an area of active research. A similar approach to assess the occurrence of structural motifs in drug molecules has been presented by Wang and Ramnarayan who have developed the concept of multilevel chemical compatibility (MLCC) between drug databases and a test molecule as a measure for drug-likeness. In MLCC, local atom environments are defined using up to tetra centered groups. The occurrence of these topological features is then tested for 11 704 compounds from the CMC and MDDR. A compound is recognized as drug-like if all of its topological motifs occur in the other known drugs.

Figure 1
Reducing a drug to molecule to framework

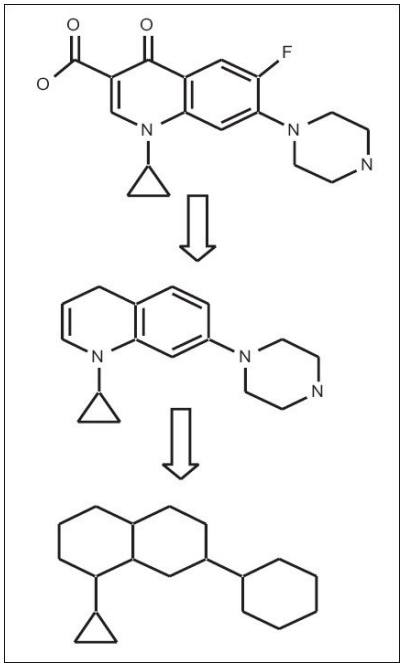
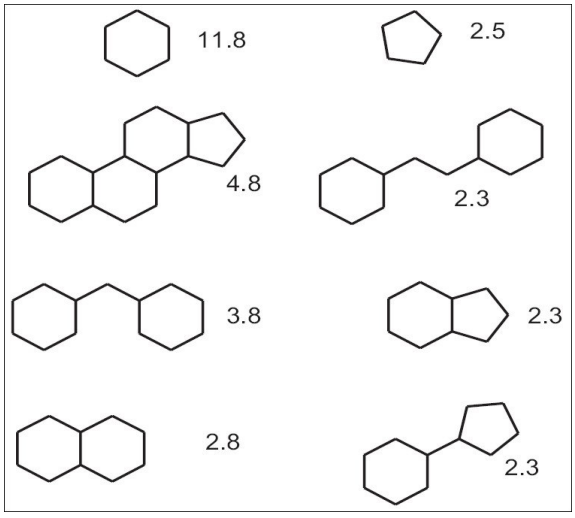


Figure 2
Most frequently occurring frameworks in drugs. The number indicates percentage of occurrence in the comprehensive medicinal chemistry (CMC) database.



OTHER METHODS

The majority of the methods discussed above were developed by translating the collected knowledge of scientists involved in drug discovery into a computer programs. An alternate approach is to design a computer program for a set of drugs and non-drugs and allow the program to learn to distinguish these set of drugs and non-drugs.

1) Machine learning programme

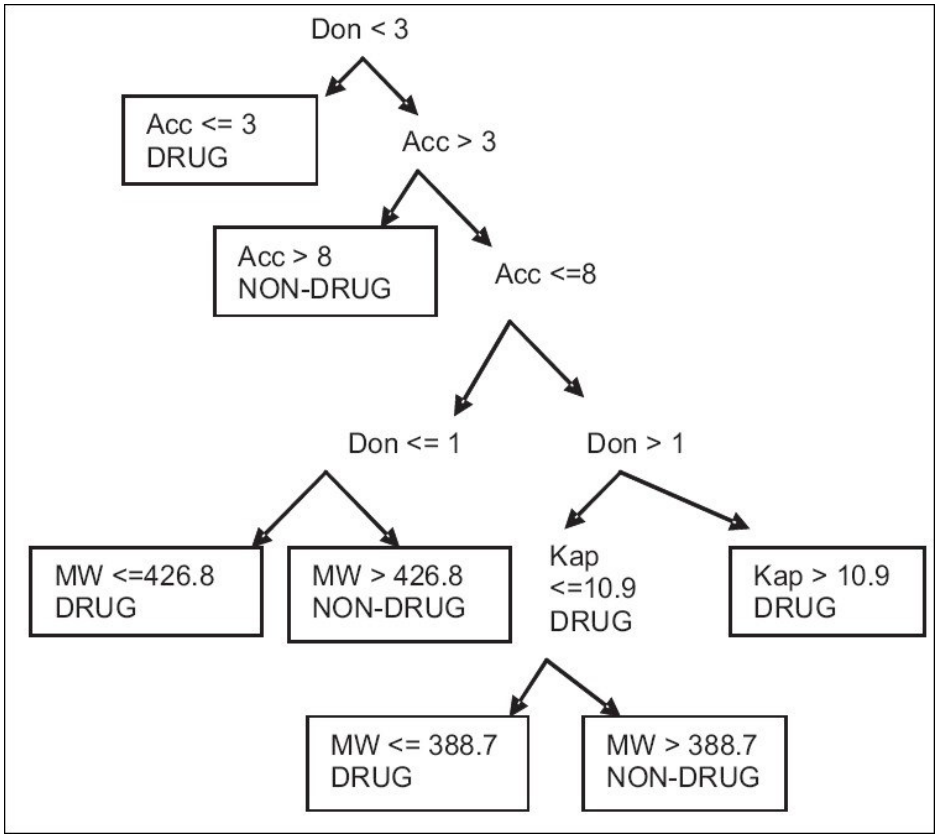
Machine-learning approaches have been applied most successfully today to distinguish between drugs and non-drugs. Assuming that compounds structurally similar to known drug molecules are potential drug candidates themselves. Databases of drugs such as the CMC or MDDR and reagent-like databases such as the ACD can be statistically analyzed

to identify criteria that distinguish drugs from non-drugs. Drug-classification models that are based on this idea include neural network approaches as well as recursive partitioning approaches.

2) Recursive partitioning approach

The machine-learning program (i.e. recursive partitioning approach) was used with a set of seven, one-dimensional descriptors to produce a decision tree which was able to correctly classify ~80% of CMC compounds and ~70% of ACD compounds. The rules for such trees can be identified by walking up the tree from bottom to top. An example of such a set of rules for a decision tree can be that if parameter like molecular weight (MW >388.7), kappa index (Kap <= 10.924), number of donor atoms (Don >1) and number of acceptor atoms (Acc >3) or number of acceptor atoms (Acc <=8) and a number of donor atoms (Don <=3), then Class is called as Drug [Figure - 3]. The primary disadvantage of this method is its tendency to over train and produce rules based on chance correlation in the data.

Figure 3
A portion of a decision tree used to distinguish drugs from non-drugs



3) Neural network approach

Neural network simulates the biological nervous system to create an output classification based on a set of input values. Simple neural networks use Ghose and Crippen atom types as topological descriptors. Ninety one statistically significant atom types correspond to 91 input neurons of the neural net. Typically, the hidden layer consists of five neurons which are used in the net design. The result from single neuron output layer can vary between 0.1 (non-drugs) or 0.9 (drugs). Trained on 5,000 drugs taken from the WDI and 5,000 compounds labeled as non-drugs taken from the ACD, the resulting neural net has been shown to correctly classify ~80% of other drugs/non-drugs. However the possible drawbacks of neural nets are that, discernible

rules as to why a given compound is classified as drug or non-drug cannot be derived, also the neural net will strongly reflect its database heritage.

LIMITATIONS OF THE GENERAL DRUG-LIKENESS CONCEPT[26]

Although physicochemical properties are widely used as general drug-likeness filters, there are several articles pointing to their limitations. As Walters et al. envisioned, instead of dealing with the complex problem of drug-likeness, a viable alternative is the prediction of the various pharmacokinetic properties (logP, half-life, plasma protein binding, etc.) that contribute to a drug's success. Remarkably, even the calculation and modeling of these properties themselves is rather complex and extremely difficult in many cases. The lack of validated sets of drugs and decoy sets of non-drugs also limits the usefulness of any drug-likeness filters as there are compounds, e.g., that can easily fall into either category. Moreover, the filters can only recognize those compounds that resemble existing drugs as drug-like – compounds from completely new classes could be misclassified. Remarkably, the original publication of Lipinski , root of many others in this field, addressed the prediction of only pharmacokinetic properties (absorption and permeation) and not general drug-likeness. However, collecting sets of good and bad pharmacokinetic properties remains a challenge for property filters due to the above mentioned complexity of the properties themselves. In addition, the final decision on drug-likeness is just further postponed if a filter can provide information only on one drug-likeness property. In fact, there are several properties to be predicted which can easily give controversial results in ranking of a compound or a library and it is still unclear which property should be prioritized for the final decision, etc. For example, Kubinyi finds that "inappropriate ADME (Absorption, Distribution, Metabolism, Excretion) characteristics have clearly made far less of a contribution to clinical failures than is widely supposed!". At the same time, he also accepts that the application of the Ro5 aimed at prediction of "A" of ADME significantly aided improving early combinatorial libraries which had included "many large and greasy, biologically inactive molecules". This example of the controversial judgment of the fairly well-studied ADME properties illustrates that it would be indeed very difficult to set the above-mentioned priority order of properties in a decision tree. The questions on the appropriate use of a property, i.e., "where and to which extent" seem to remain unanswered in general. Similarly, an important study by Feher and Schmidt analyzing properties of natural products concluded that: "Drug-like filters, such as the Lipinski rules, are very helpful in isolating likely problem molecules. However, overly strict adherence to it can have the adverse effect of restricting diversity …and hence also reducing similarity to natural products. … A large proportion of natural products are biologically active and has favorable ADME/T properties, despite the fact that they often do not satisfy 'drug-likeness' criteria." Furthermore, Ganesan analyzed a total of 24 unique natural products that led to an approved drug in the period 1970–2006. They found an identical success rate of 50% both for the classes conforming or violating the Ro5. It was also found that natural products are successful in maintaining favorable logP and intermolecular H-bond donating potential even with high MW and large numbers of rotatable bonds. Lajiness et al raise additional concerns regarding drug-likeness studies. They claimed that there are very few studies accompanied by the data sets used for analysis, and therefore, reproducibility of the results is questionable. Lajiness et al. mentioned that proprietary collections may be biased due to historical lead optimization efforts focused at particular chemical classes, such as steroids or benzodiazepines. They also concluded that comparing drug-likeness of groups instead of individual compounds was appropriate to achieve significant results. There are also methodological problems with the properties 'traditionally' used as filters. For example, Bhal et al. suggest the cautious use

of logP in drug design due to its inability to account for the ionization of compounds under physiological conditions. They conclude that the pH-dependent logD is a more realistic descriptor of lipophilicity under physiological pH's and, therefore, logD should be used preferentially over logP as the descriptor for lipophilicity, especially when working with ionizable compounds. Vistoli et al. also mention the problems of pH-dependent properties. In their seminal paper, Lipinski et al. already claimed that antibiotics, antifungals, vitamins, and cardiac glycosides fell outside their Ro5, possibly due to transporter effects. The results of the study of Good and Hermsmeier suggest further discontinuities in drug-like space, beyond those claimed by Lipinski et al., in the context of classification. Giménez et al. also concluded that Ro5 is very useful to select better compounds in chemical libraries, but it must be used carefully to avoid a possible exclusion of promising compounds. They evaluated the top pharmaceutical products in 2007. Among 60 drugs, 7 (atorvastatin, montelukast, docetaxel, telmisartan, tacrolimus, leuprolide and olmesartan) did not fit the Ro5, and 5 failed one of the threshold values. Zhang and Wilkinson summarized their criticism of the overemphasis of Ro5 of drug-likeness from two points of view. Firstly, they claim that only 51% of all FDA-approved small molecule drugs are both used orally and comply with the Ro5. This does not even include the increasing number of biologicals of which several have reached 'blockbuster' status. Secondly, the Ro5 does not cover natural product and semisynthetic natural product drugs, which constitute over one-third of all marketed small-molecule drugs (see also Feher and Schmidt). A further doubt arises from the finding (Dobson and Kell) that general drug-likeness properties such as MW or logP, adequate for passive diffusion, have decreased ability for prediction of carrier-mediated and active uptake of drugs that are more common forms of transport than is usually assumed. For drugs transported by carriers, general property filters are not normally effective in individual cases, and specific data on interactions of drugs and transporters would therefore accelerate research in this field. Similarly to drugs, naturally occurring intermediary metabolites may also require solute carriers to enter cells. Thus, an evaluation of metabolite-likeness (Dobson et al.) would be essential to understand the true physiological processes. However, estimation of metabolite-likeness is missing from most of the present drug likeness studies.

CONCLUSION

There are many research groups currently engaged in identifying drug-like and non-drug-like molecules. Consequently it is desirable to develop 'filters' that help to bias the drug discovery search in our favour. Lead-likeness, drug-likeness and the Ro5 have all been used to advantage, but as our knowledge of systems biology grows there is a need to move towards more mechanistic approaches. This will also require prediction of where and how drugs interact with metabolism, which can be addressed by cheminformatic methods to assess molecular similarity between putative drugs and metabolites. Future advances in the field shall involve the combination of general drug-likeness with specific properties of small molecules to hit specific gene families.

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