Chemical predictive modelling to improve compound quality

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Abstract | The 'quality' of small-molecule drug candidates, encompassing aspects including their potency, selectivity and ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics, is a key factor influencing the chances of success in clinical trials. Importantly, such characteristics are under the control of chemists during the identification and optimization of lead compounds. Here, we discuss the application of computational methods, particularly quantitative structure–activity relationships (QSARs), in guiding the selection of higher-quality drug candidates, as well as cultural factors that may have affected their use and impact.

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Reducing attrition rates remains a major challenge in drug development. Recent estimates indicate that the chances of a drug candidate successfully reaching the start of Phase II trials, where the role of the target biology in the disease can be tested, are only ~37%[1]. Moreover, the probability of success in Phase II trials is only ~34%. Although a substantial proportion of failures in Phase II trials may be due to flaws in the underlying biological hypothesis, the physicochemical properties of small-molecule drug candidates also have an important impact, through their influence on ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics and on the effectiveness of the compounds at selectively engaging their targets in humans[2].

Given such issues, there has long been interest in the use of computational approaches to help guide the selection and optimization of compounds for synthesis and testing in order to reduce the risks of failure related to their physicochemical properties[3]. Many papers have been published that discuss the properties of a 'quality compound' — a compound that is more likely to robustly test the biological hypothesis in the clinic.

Such computational approaches can be broadly divided into physics-based and empirically based methods. Physics-based methods encompass, for example, molecular dynamics and the prediction of binding affinity by methods such as free energy perturbation and quantum chemical calculations. Empirical methods are based on observed patterns in existing data, which are used to guide the design of future compounds; examples of such methods include quantitative structure–activity relationships (QSARs), rule-based systems and expert systems. They do not rely on any understanding of the physics of the system, although they can indicate what the controlling physical properties might be. QSAR methods use statistical regression and classification-based approaches to identify quantitative patterns that are present within the existing data. The rules in rule-based methods may be either manually or automatically generated. Physics-based approaches are often used in conjunction with QSAR methods, but the large scale of data sets available can limit the degree to which a physics-based approach may be rigorously applied owing to limitations in computational resources. Empirical methods, however, are particularly suited for the analysis of the large volumes of data that are now available from the routine use of high- and medium-throughput *in vitro* biological and ADMET assays in drug discovery. We term the suite of available empirically based methods 'chemical predictive modelling' (TABLE 1).

In this Review, we describe the development of some of the most important chemical predictive modelling tools that are currently used in the industry and discuss some of their limitations as well as the cultural aspects that may prevent these approaches from realizing their potential.

What defines compound quality?

A universally accepted definition of compound quality has not been established. However, multiple landmark publications over the past 15 years or so have indicated the importance of various physicochemical properties, particularly lipophilicity.

The pioneering 'rule of five' guidelines published by Lipinski *et al.* in 1997 proposed simple physicochemical property-based guidelines for drug permeability[4] (BOX 1). By analysing a set of drugs that had entered clinical trials,

Table 1 | **Selected commonly used tools for chemical predictive modelling**

Tool or toolkit	URL
Cheminformatics toolkits	
Daylight toolkit	http://www.daylight.com
OpenEye Scientific Software toolkit	http://www.eyesopen.com
ChemAxon	http://www.chemaxon.com
The Chemistry Development Kit[102]	http://sourceforge.net/projects/cdk/files/cdk
RDkit	http://www.rdkit.org
Dragon descriptors[103]	http://www.talete.mi.it
Batch Modules for ACD/Percepta	http://www.acdlabs.com/products/percepta/batch.php
Statistical tools and toolkits	
The R Project for Statistical Computing	http://www.r-project.org
Bioclipse[59]	http://bioclipse.net
JMP statistical discovery software	http://www.jmp.com
Pipelining tools	
Pipeline Pilot (Accelrys)	http://accelrys.com/products/pipeline-pilot
Knime[104]	http://www.knime.org
Data visualization tools	
Spotfire	http://spotfire.tibco.com
Vortex (Dotmatics)	http://www.dotmatics.com/products/vortex

it was found that the following rules pertained to a large proportion of the compounds: molecular mass ≤500 Da; calculated LogP (cLogP) ≤5; number of hydrogen-bond donors ≤5; and number of hydrogen-bond acceptors ≤10. It was suggested that compounds that violate any two of the 'rule of five' conditions are unlikely to be oral drugs[4].

The recognition that lead optimization often resulted in increased lipophilicity and molecular size prompted the definition of the 'lead-like' concept[5,6]. This suggested that screening libraries should be preferentially populated with smaller and less lipophilic compounds than those described by Lipinski's 'drug-like' definitions. Leads that are smaller and less lipophilic than drug-like compounds would provide 'headroom' for lead optimization. These publications had a huge impact on how medicinal chemists defined compound quality and led to an increase in the use of *in silico* approaches for drug design; for example, medicinal chemists would computationally filter compound collections and compounds proposed for synthesis to only include those with calculated physiochemical properties that were sufficiently lead- or drug-like.

Over the past 15 years, many developments on these guidelines have been published[7,8] to supplement and fine-tune recommended molecular property ranges for fragments[9], target classes, disease areas[10] and ADMET characteristics[11,12]. Some of the guidelines have been challenged and new ones proposed. Based on studies of the temporal invariance of physicochemical properties, it has been questioned whether the focus on molecular mass is justified, as lipophilicity is the more fundamental controlling property[13]. The importance of lipophilicity has been reaffirmed in multiple studies, such as a study of the toxicological outcomes of 245 compounds in development at Pfizer, which found that compounds with cLogP >3 and total polar surface area <75 Å^2 were six times more likely to show an adverse event in a rat or dog *in vivo* safety study than a compound with cLogP <3 and total polar surface area >75 Å^2 (REF. 12). Flexibility, molecular complexity and shape are additional properties that have received attention from some in the field[14,15].

Where potency information is available, the most recent evolution of these guidelines is the proposal of various ligand efficiency concepts that that build on the concepts of lead-likeness and of discriminating between optimal and non-optimal binders, as first suggested by Andrews[16]. Ligand efficiency[17], ligand lipophilic efficiency (LLE)[18] and LogP divided by ligand efficiency (LELP)[19] are size-, lipophilicity- and size-plus-lipophilicity-corrected measures of potency that help to identify compounds that are maximizing the use of their chemical structure in desirable binding and are therefore likely to be better leads.

For example, scientists at Astex have reported that companies focusing on leads with ligand efficiency and lipophilic efficiency find more robust SARs and produce candidate drugs with a more acceptable compound property profile[20]. Similar findings were reported by Leeson and St Gallay[21]; in their target-by-target comparison, companies that applied rigorous ligand efficiency and LLE optimization produced candidate drugs that were smaller and less lipophilic. Finally, Keserü and colleagues analysed data on the ADMET properties of compounds published by Pfizer and showed that LELP can discriminate between compounds with acceptable ADMET profiles and those with significant ADMET liabilities[22,23].

cLogP
The calculated logarithm of the 1-octanol–water partition coefficient of the non-ionized molecule.

Box 1 | **Rule-based models for compound quality**

Rule-based models that are based on calculated molecular properties and structural features are simple, intuitive and easy to compute and interpret.

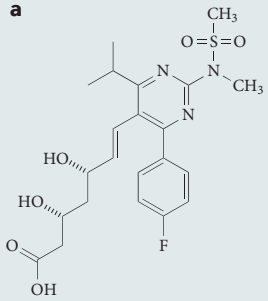
Physicochemical properties

Physicochemical properties, which are easily calculated from molecular structures, can be used to define guidelines for compound quality. They usually include properties related to molecular size (such as molecular mass and the number of heavy atoms), molecular complexity (such as the number of rotatable bonds, the number of aromatic rings and the number of chiral centres), lipophilicity (such as LogP and LogD) and polarity (such as polar surface area, the number of hydrogen-bond donors and the number of hydrogen-bond acceptors), as illustrated for the compound in the figure, part **a.**

Chemical filters and alerts

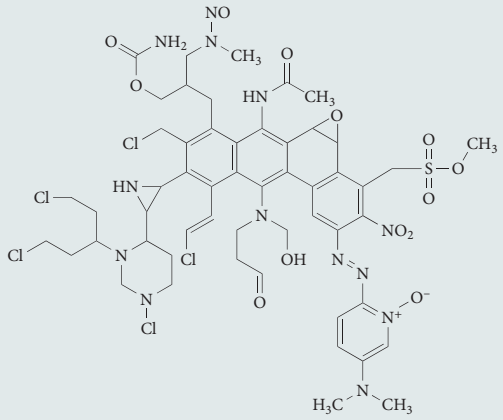
Computational filters and alerts are developed to assist drug design teams in identifying compounds with undesirable chemical features. Substructural elements 'to be avoided' in the hypothetical compound below (see figure, part **b**) include arylamines, epoxides and aziridines, alkane sulphonate esters, arylnitro functions, azo groups, heteroatom–heteroatom single bonds and chloramines. Data from REF. 100.

a



Property	Value
AZ filters	CORE
Molecular weight	481.538
cLogP	1.898
cLogP error	All fragments measured
Polar surface area	144.835
Heavy atom count	33
Rotatable bonds	9
Hydrogen-bond donors	2
Hydrogen-bond acceptors	8
Positive charges	0
Basic charges	0
Acid centres	1

b



Structure-based chemical filters

Computational structural filters were developed to assist drug design teams in identifying compounds with undesirable chemical features[24]. They rely on knowledge of medicinal chemistry and retrospective analysis of high-throughput screening (HTS) outputs or analysis of highly annotated compound subsets (such as hits, leads, clinical candidates and marketed drugs). Such filters usually include unattractive chemical features, known toxicophores, metabolically labile compounds and functionalities that could potentially generate false positives in HTS or interfere with biochemical assays (for example, fluorescent and coloured compounds or aggregate-forming compounds)[25] (BOX 1).

For example, AZFilters (see BOX 2 and Supplementary information S1 (box)) include both physicochemical properties and chemical filters[26]. The chemical filters are largely exclusion filters for 'ugly' functionality, but they are also complemented by inclusion filters; for example, compounds should have at least one polar atom and at least one single bond.

One drawback of such compound quality rules is that most of them use hard cut-offs for molecular properties and pass/fail assignments for the chemistry filters, and so they cannot be used for compound ranking; all compounds that comply with the rules are treated equally, as are all that violate them. Consequently, various scoring models for lead- and drug-likeness have been suggested, which are often derived by machine learning methods[27]. These have proved to be useful for compound prioritization but they lack the intuitiveness, transparency and ease of implementation associated with simple filters. To address this problem, Hopkins *et al.*[28] used the concept of desirability to provide a quantitative metric for assessing drug-likeness, known as the quantitative estimate of drug-likeness (QED); values can range from zero (all properties unfavourable) to one (all properties favourable). This metric combines the simplicity of rule-based methods with the ranking output of scoring models.

QSAR models

The next step from simple structure-based filters is the application of QSAR models, which offer more quantitative predictions. These can be used in large-scale library filtering but are particularly suitable for lead optimization, where more precise prediction of properties is required.

QSAR models are empirical models in which a quantitative description of a chemical structure is related to biological activity through an algorithm to guide future drug design. The emergence of the QSAR field was driven by the work of Hansch, Fujita and colleagues in the early 1960s, who — in a series of landmark papers — developed predictive models for potency and ADMET end points based on physicochemical properties, often in congeneric series[29].

In recent years, the growth in the study of ADMET properties has resulted in data sets that span chemical series, as compounds that are designed for many drug targets are screened through a limited number of assays, providing the opportunity to build cross-project 'global' ADMET models. However, the term 'global' is misleading in this context; although the aspiration is that if the model is built on enough compounds then it can effectively predict the properties of any future compound, owing to the nature of QSAR models they are unlikely to ever fulfil this aspiration. These models are not based on an understanding of the underlying physics of the system; rather, they are simply attempts to describe the SARs observed in the data set used to train the model. It is unlikely that a few thousand compounds — or even tens of thousands of compounds — in a training data set will confidently represent the entire pharmaceutical chemistry space. Nevertheless, based on either in-house

Congeneric series
A set of molecules belonging to the same class, usually with chemical changes limited to changes in substituents on a fixed chemical core.

Box 2 | **AZFilters**

AZfilters are computational structural filters that have been developed to assist drug design teams in identifying compounds with undesirable chemical features. They include both physicochemical properties and chemical filters. Illustrative examples of the filters in the ten classes are provided below; for a full list, see Supplementary information S1 (box). 'Core' compounds hit no chemical filters and fulfil the following property filters: molecular mass between 100 and 550 Da, cLogP between −2 and 6, and polar surface area between 1 and 160 $Å^2$. 'Backup' compounds fail on one property filter, and 'ugly' compounds fail on two or more property filters or hit at least one chemical filter. The AstraZeneca screening collection was split into 'core', 'backup' and 'ugly' sets, based on these filters. Only 'core' and 'backup' compounds are solubilized for high-throughput screening, and usually only 'core' compounds are purchased from external vendors.

Class 1: bland structures
- Compounds containing atoms other than hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine, chlorine, bromine and iodine
- Fewer than four carbon atoms
- Fewer than 12 heavy atoms
- No polar atoms (nitrogen, oxygen, sulphur)
- Straight or unbranched structures
- Positively charged atoms (for example, quaternary nitrogen)
- Compounds with three or more acidic groups
- Alkyl or aryl amine (with no other heteroatom)
- Hydroxyl or thiol (with no other heteroatom)
- Only hetero atom is one acid or derivatives

Class 2: reactive structures
- Michael acceptors: C=C-C=O, C=C-CN, C=C-SO_2, C=C-NO_2
- Reactive ester or thioester
- Anhydride
- Alpha halo ketone
- Halo methylene ether
- Acid halide and thio acid halide
- Aliphatic and aromatic aldehyde
- Peroxide
- Epoxide, aziridine, thiirane or oxazirane
- Thiocyanate
- Isocyanate, isothiocyanate
- Isocyanide, isonitrile

Class 3: frequent hitters
- More than two nitro groups
- Dihydroxybenzene
- Nitrophenols

Class 4: dye-like structures
- Two nitro groups on same aromatic ring, including naphthalene
- Diphenyl ethylene cyclohexadiene

Class 5: unlikely drug candidates or unsuitable fragments
- Large ring ≥ C_9
- C_9 chain not in any rings
- Crown ethers
- Multi-alkene chain: C=CC=CC=C or *N*=CC=CC=C
- Diyne: -C≡C-C≡C-
- Annelated rings such as phenanthrene, anthracene and phenalene
- Two sulphur atoms (not sulphones) in 5-membered rings or 6-membered rings
- Triphenylmethyl

Class 6: difficult series or natural compounds
- Steroids
- Penicillin or cephalosporin
- Prostaglandins

Class 7: general 'ugly' halogenated structures
- Di- or trivalent halogens
- *N*-, *S*-, *P*- and *O*-halogens
- Sulphonyl halides
- Triflates: SO_3CX_3

Class 8: general 'ugly' oxygen
- Five or more hydroxyl groups
- p-,p′-dihydroxybiphenyl
- p-,p′-dihydroxystilbene
- Formic acid esters

Class 9: general 'ugly' nitrogen
- Hydrazine (not in ring)
- Three or more guanidines
- Two or more *N*-oxides
- Azo (*N*=N) or diazonium (N≡N)
- Carbodiimide
- *N*-nitroso groups
- Aromatic nitroso groups
- Cyanohydrin or (thio)acylcyanide
- Nitrite
- Nitramine
- Oxime

Class 10: general 'ugly' sulphur
- Five or more sulphur atoms
- Disulphide
- Sulphate
- Sulphonic acid
- Thioketone
- Sulphonic ester (except for aryl or alkyl-SO_3-aryl groups)
- Sulphanylamino groups
- 1,2-thiazol-3-one
- Dithiocarbamate
- Thiourea, isothiourea, thiocarbamic acid or thiocarbonate
- Isocyanate or isothiocyanate
- Thiocyanate
- Thiol
- Dithioic or thioic acid

data or literature data, these 'global' models have been almost universally adopted in industry as a method for guiding compound property design.

Experience indicates that the application of QSAR models in drug discovery is fraught with difficulties, complications, confusion and failure, not least owing to limitations in the data, problems in combining data from multiple sources, limitations of the molecular descriptors, inappropriate use of machine learning models and the inherent limitation of empirical models to extrapolate beyond their domain of applicability (for further discussion, see REFS 30–33). Even more fundamentally, the structures need to be correct[34], and a call has recently been made for the accurate representation of chemical structures in publicly available SAR databases[35].

Regulatory authorities and the other international bodies such as the Organization for Economic Co-operation and Development (OECD) have also stepped in to provide guidance and tools to stimulate good QSAR modelling practice (see the OECD Quantitative Structure–Activity Relationships Project [(Q)SARs] for further information). To facilitate the consideration of a QSAR model for regulatory purposes, the OECD recommends that the model should be associated with the following properties: a defined end point; an unambiguous algorithm; a defined domain of applicability; appropriate measures of goodness of fit, robustness and predictivity; and a mechanistic interpretation, if possible. Some research journals have also imposed more rigorous acceptance criteria on QSAR papers to raise the quality of submitted articles as well as the transparency of the models in publication[36]. However, the requirement to publish all the data and molecular structures used to carry out the study can be problematic for pharmaceutical companies.

QSAR models will always have limitations, as noted above, but these papers and guidance documents give good advice on how to avoid common problems. When judiciously used, QSAR models can be the most accurate and precise prediction tools available, often exceeding the capability of physics-based models.

Domain of applicability of QSAR models. At present, a key problem that needs to be addressed in the application of QSAR models is estimating confidence in their predictions. Root mean squared errors of a chosen test set are the simplest estimate of the model's likely ability to predict the properties of an average set of compounds external to the model. It is a widely held belief that compounds that are 'close' to the model space (in terms of similarity to the training set) are likely to have their properties more accurately and precisely predicted than compounds that are more 'distant' from the model space. So, the problem then becomes quantification of the domain of applicability of the model, the distance of the new compound from it, and the relationship between that distance and error in prediction.

In its simplest sense, the applicability domain can be described by a Euclidean box defined by the descriptor properties of the training set, and a future compound can be within or outside that box. The distance of future compounds can be measured in the Euclidean space or, better, by probability-based distances that include information on the co-linearity of the descriptor set. Distance measures can be based on property-based distances or on structural descriptors such as molecular fingerprints. Descriptor-based distances can either be weighted according to the contribution of each descriptor in the QSAR model or given equal weight. It has been suggested that descriptor-based distances that are weighted according to their contribution to the model provide higher-quality applicability domain assessments than those obtained using the equally weighted descriptors of the training set molecules[37]. In situations where the QSAR model is an ensemble of models, the standard deviation of predictions of the model ensemble also outperformed descriptor-based distance measures as a measure of confidence in prediction[38].

In a recent review of many different definitions of applicability domains that were applied to bioconcentration factor models, developed according to the OECD guidelines under the EU project CAESAR (Computer Assisted Evaluation of Industrial Chemical Substances According to Regulations) with two test sets, it was found that the different approaches each had strengths and limitations. Although excluding compounds from prediction that were 'outside' the model's domain of applicability improved model statistics, applicability domain methods that excluded many compounds also limited the utility of the model[39]. There appears to be no universally successful method for describing the applicability domain of a QSAR model, nor a universal measure of the distance from the model space, and this topic remains a focus for QSAR scientists.

Some QSAR models, such as those used in the field of environmental toxicology, attempt to cover the chemical space of likely interest; that is, it is anticipated that the compounds being predicted will be either within the applicability domain of the model or not far from it. However, in drug discovery, the evolution of a compound series involves using prior data to predict the next compound to be synthesized, and hence compound optimization usually drives chemistry away from the domain of applicability of the QSAR model.

Within the global models used at AstraZeneca, we have observed that predictions for different chemical series have differing degrees of accuracy and precision. This may be due to: deficiencies in our descriptor set in identifying discriminating molecular features across chemical series or subseries; or the balance that the machine learning method needs to strike between different and perhaps conflicting SARs to minimize the unexplained error in prediction averaged across all chemical series in the training set; and/or the weight of representation of different chemical series in the training set itself. Maggiora described the concept "lack of invariance of chemical space" for instances where neighbourhood relationships may be significantly altered across chemical series or subseries; compounds that are nearest neighbours in one chemical space representation may not be nearest neighbours in another[40].

One approach to circumvent the local series description problem within a global QSAR model would be to build project-specific or chemical-series-specific

models. For each project, a decision could be made on which model is most appropriate for future predictions: the global model, the project model or even a chemical series-based model. This would maximize our ability to make accurate and precise predictions for all current structure optimizations. However, for a large pharmaceutical company with hundreds of ongoing projects, this might involve building thousands of project- or chemical-series-specific QSAR models and managing their comparisons with global models on a regular cycle. To minimize the distance between the current chemistry and the applicability domain of the model, QSAR scientists can manually update the global models, but this is a time-consuming activity. If possible, it would be ideal to automatically keep global QSAR models up to date.

Automated QSAR models. Although informatics technology has been capable of automatically building and maintaining QSAR models — as described above — for several years, the applications of such systems in drug discovery have only recently become apparent. The hurdle towards adoption is more psychological than technological; we need to become more confident that machines can build models of similar or superior quality to those built by computational chemistry specialists, and that the models will be stable and robust as the system evolves with time. Other fields have been more courageous in using machine learning and pattern recognition models in automated systems, particularly in automated online monitoring for fields as diverse as manufacturing, the food industry and in monitoring the reprocessing of nuclear fuel waste[41].

Nevertheless, there are some reported examples of automated QSAR model building for drug discovery. Oprea and colleagues[42] used an automated partial least squares (PLS) engine to build 1,632 QSAR models based on the WOMBAT (World of Molecular Bioactivity) database. The OCHEM database contains models and data sets, and offers automated generation of QSARs[43]. Leahy and coworkers[44] pioneered automated QSAR modelling with the development of the Discovery Bus technology. Discovery Bus is an automated machine learning environment based on "the competitive workflow", where new models are compared with old ones for their predictive ability on a common test set. Different machine learning agents and descriptor sets can compete to find the best model for a given data set, and a QSAR specialist can compete with the machine learning agents, which could help to build confidence in the automated system. ChemModLab provides a similar framework; it is a web-based automated QSAR platform that allows users to upload data sets, descriptor sets or modelling methods, which can then be compared with other data sets, descriptors or methods[45].

A few other groups have also reported investigations of automated QSAR modelling, including a study by Segall and colleagues[46] on ADME properties. Additionally, in an interesting development, automated modelling has become the basis for a published patent[47]. Wood, Rodgers and colleagues at AstraZeneca have attempted to answer some of the concerns over the automation of QSAR model development using real-world data to demonstrate the benefits of updating global and QSAR models[48,49]. Over a 2-year period, using in-house data for solubility, $LogD_{7.4}$ and protein binding, they showed that static models lose their predictive power over time, that different machine learning methods can be considered best as the criteria for decision-making change from a static model to an updating model, and that project- or series-specific models outperform global static models and even global updating models (FIG. 1).

One area in which automation of QSAR model building may not help is where only a weak model can be built in the first place, which is often the case for potency end points in situations in which there is a high degree of molecular recognition between small molecules and the receptor. Maggiora described the concept of an "activity cliff", where molecules that are structurally highly similar can produce very different biological responses owing to subtle structural differences affecting receptor fit or lack of it[40]. In an attempt to define a universal confidence metric as well as one that is robust enough to potential problems due to activity cliffs, a group at Pfizer has included the 'activity landscape' of structural near neighbours within a QSAR confidence metric[50]. At the heart of the method is a weighted root mean square error estimation that combines the predicted value, the experimental values of the nearest neighbours and the relative distance of those neighbours within the model space. A calibration procedure based on a test set allows a method-independent confidence metric to be defined. It has been reported that this new approach has had a substantial impact on drug discovery efforts at Pfizer[50], which suggests it has been accepted by their medicinal chemists.

Automation may allow modellers to search through the model, descriptor and machine learning space to find where good models exist. The Discovery Bus methodology described above allows such exploration, which may be necessary to find the right descriptor data set combination for end points that are difficult to model. However, care must be exercised as such a tool could easily lead to another old problem: when multiple tests are carried out on the same data set, the likelihood of finding a model by chance alone increases. Demanding increased confidence in the robustness of the model before it is accepted is one approach for addressing this problem. Livingstone and Salt used an adjusted F-statistic to counter the misuse of the standard multiple regression algorithm to select important variables from a larger pool of available variables[51,52]. However, although adjusting the confidence level at which to accept or reject the model (when multiple comparisons are made) protects against false positives, it comes with the cost of increasing the chance of rejecting all models when a real one is present (false negatives).

Permutation tests can also provide confidence in the robustness of the model[53] but, depending on how they are executed, these tests can themselves lead to a biased estimate of the model's robustness. The full model generation procedure must be repeated, including variable selection, rather than just permuting the *y*-variables of the final model[54].

$LogD_{7.4}$
Log_{10} of the octanol–water partition coefficient of a molecule (for example, a drug) at pH 7.4.

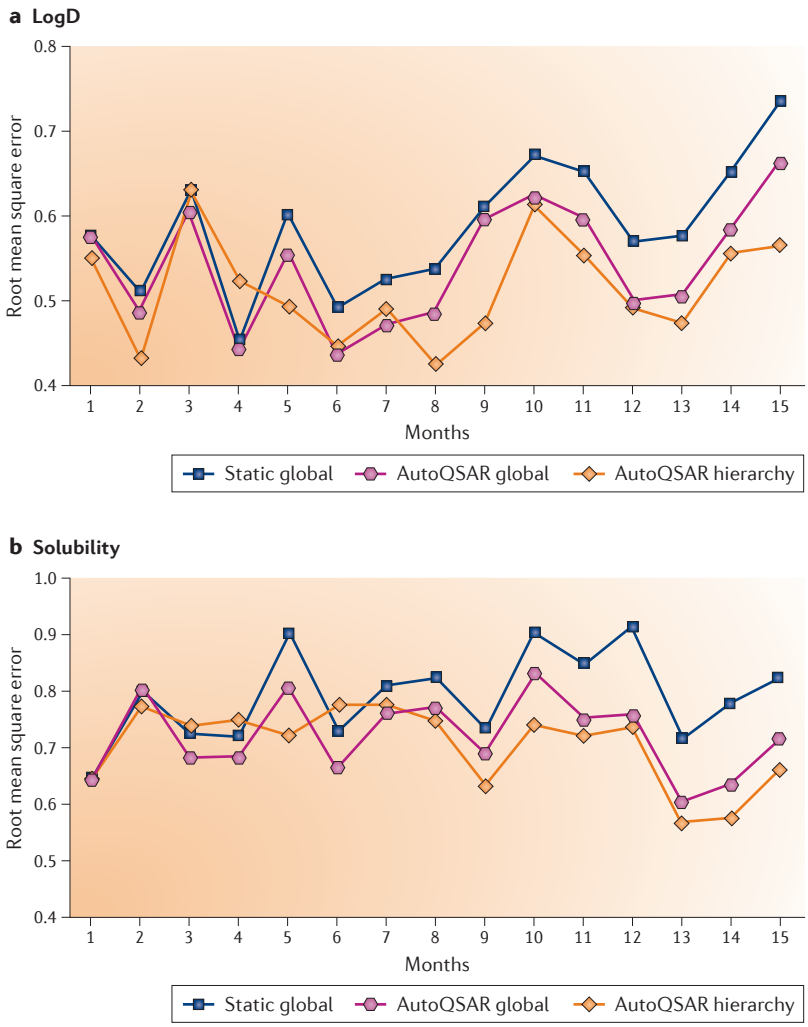


Figure 1 | **Performance of automated QSAR modelling.** Results of a 2-year performance comparison between models of $logD_{7.4}$ (panel **a**) and solubility (panel **b**) across ten active AstraZeneca projects are shown. The models compared were a static global model, an updating global quantitative structure–activity relationship (QSAR) model, and an automated QSAR (AutoQSAR) hierarchy model. The best model (static global, updating global or local project model) is selected on a project-by-project basis according to the latest month's test set performance. The graphs show that, as the models mature, month by month the AutoQSAR hierarchy outperforms the static or updating global model[48,49].

Support vector machine
A machine learning method that uses kernel functions to map input data into high-dimensional feature space. Support vector machines can be used for classification or regression.

Random forest
A machine learning method that constructs a multitude of decision trees with a random selection of features to split each node. Random forests can be used for classification or regression.

Further work is required to understand and quantify the risk of chance correlations. The iterative nature of drug discovery offers a further opportunity to test model robustness, as last week's predictions become next week's measurements, and so confidence in the model can be strengthened by real-world experience.

Interpretable QSAR models and inverse QSAR. An important limitation of the standard QSAR approach is that the medicinal chemistry designer must first generate an idea for a new compound before QSAR models are used to predict its properties. The designer is always looking for an answer to the question: "Which compound do I make next?" One way to address this issue is to improve the interpretability of QSAR models by helping the designer to understand the SAR that is encoded by the model[55]. The ability to do this depends on the nature of the descriptors and the modelling method used. Linear models that are built on familiar physicochemical descriptors are the most readily interpreted, whereas nonlinear models are generally viewed as opaque or 'black box' (that is, not amenable to interpretation). As nonlinear methods often lead to more accurate predictions, there is frequently a trade-off between interpretability and prediction accuracy.

Johansson *et al.*[56] compared the prediction accuracy of three ADMET and 13 potency classification end points using both interpretable and opaque modelling methods; they found that although the interpretable models — such as the decision list algorithm Chipper — performed less effectively than state-of-the-art ensemble methods, the loss of accuracy was relatively small (lower than 5%).

Carlsson *et al.*[57] have described a general method for the interpretation of nonlinear QSAR models. The method provides the most important model attributes in the context of a particular prediction molecule rather than the globally most important attributes. This helps the medicinal chemists to identify possible changes to their molecule that, according to the model, would be expected to have the greatest impact on the predicted property. The approach was illustrated using support vector machine and random forest models and applied to mutagenicity data. Signature descriptors[58] were used, although the authors say that their method can be used with other descriptors. In an extension of this work, a system was developed that colours the atoms of a predicted molecule according to whether they contribute positively or negatively to the property being predicted: in this case, mutagenicity, carcinogenicity and aryl hydrocarbon receptor activation[59]. A similar visual interpretation of ADMET QSAR models is implemented in the Glowing Molecule tool within the StarDrop software package[60].

Another way of tackling the interpretability issue is to use information embedded in the QSAR model to direct the transformation of a lead compound in an approach known as 'inverse-QSAR'. A general approach for automated, iterative, QSAR-driven compound optimization was described by Lewis[61]. In an extension of the work using the signature descriptors mentioned above, Helgee *et al.*[62] have described a method for automated optimization. Substructures that are identified by a QSAR model as significantly contributing to the prediction are systematically replaced, leading to the generation of new structures to improve the property being modelled. The approach was demonstrated using the Ames mutagenicity test but can be applied to any end point and in combination with other end points in a multi-objective optimization.

A chemical predictive modelling approach that is inherently interpretable is the automated matched molecular pair analysis (MMPA) of structure–property databases[63,64]. MMPA reveals the change in a measured property resulting from a specific small change in the structure (FIG. 2; TABLES 2,3). Hence, by applying the technique to local (project- or series-specific) or global

Ames mutagenicity test
A biological assay that uses *Salmonella* bacteria to test the mutagenic potential of compounds and thereby assess their potential to cause cancer.

(cross-project) sets of SAR data, rules can be derived that may be used to predict the properties of new analogues and to generate new compound suggestions in an inverse-QSAR fashion[65]. MMPA can be viewed as complementary to QSAR (TABLE 4). It is appealing to medicinal chemists because of its straightforward interpretability, but it is limited to molecular transformations that have previously been explored in a strict pairwise manner. The two approaches can be combined whereby MMPA-derived transformation rules are used to make prospective suggestions, and QSAR models are used to predict the properties of the proposed virtual compounds.

As an alternative to standard QSAR models, MMPA-derived rules can be used to predict the properties of the compounds that are proposed by these rules by applying the average change in property to a measured value — a strategy that is termed 'QSAR-by-MMPA'[66]. The authors used MMPA on a structurally diverse set of 322 inhibitors of the KCNQ1–KCNE1 potassium voltage-gated ion channel complex to predict prospectively the inhibitory potencies of 36 additional compounds. Comparison with predictions from a nearest-neighbour approach and a random forest QSAR model showed that the MMPA-derived predictions were superior[66]. These results suggest that QSAR-by-MMPA may be a successful approach for data sets for which useful QSAR models cannot be derived, because it identifies specific structural changes that control activity rather than attempting to fit a model to the whole data set.

The application of MMPA across large SAR databases for the optimization of ligand potency is problematic because the same structural transformation may increase potency against some targets, leave some targets unaffected and decrease potency against other targets[67]. How does one select those transformations from a global SAR data set that are most likely to increase (or maintain) potency against a given target? Mills *et al.*[68] have described one potential approach to address this bioisostere identification problem; they used pairwise analysis of chemical series to identify those with correlated SAR patterns and then applied MMPA to generate relevant transformation rules. The approach was successfully applied to the design of more potent antagonists of transient receptor potential cation channel, subfamily A, member 1 (TRPA1)[68].

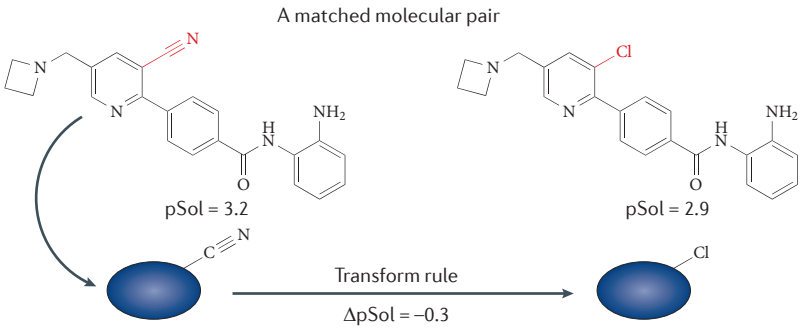


Figure 2 | **Matched molecular pair analysis.** Matched molecular pair (MMPA) analyses can be divided into two types: supervised and unsupervised. In supervised MMPA (TABLE 2), the chemical transformations are predefined, then the corresponding matched pair compounds are found within the data set and the change in end point computed for each transformation. With unsupervised (or automated) MMPAs (TABLE 3), an algorithm finds all possible matched pairs in a data set according to defined rules. This results in much larger numbers of matched pairs and unique transformations, which are typically filtered within the algorithm to identify those transformations that correspond to statistically significant changes in a property with a reasonable number of matched pairs. pSol, $-\text{Log}_{10}$(molar aqueous solubility).

Chemical predictive modelling in practice

Chemical predictive modelling is now a core part of drug discovery. For example, AstraZeneca's C-Lab platform[69] has been used to make over 2 billion calculations in the past 12 years. An internal analysis of the newly synthesized compounds registered in the AstraZeneca corporate database during the 2011–2012 period showed that for 55% of these compounds one or more properties had been predicted by C-Lab before synthesis. AstraZeneca's global HERG (a potassium voltage-gated channel; also known as KCNH2) QSAR model[70] has also contributed to the reduction in the synthesis of 'red flag' compounds (compounds that are measured to have an HERG potency of <1μM), from 25.8% of all compounds tested in 2003 to only 6% in 2010.

The true negative prediction rate of potentially genotoxic impurities by *in silico* models was recently surveyed across eight companies. The methods for prediction were given and the approaches used across the companies were very similar. The true negative prediction rate was found to be 94%, and this increased to 99% when expert evaluation of the results was included in the decision[71]. The results of this analysis are currently being written into guideline M7 of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on genotoxic impurities.

There are many published examples of the successful application of QSAR models, so we have just selected one illustrative example here. A QSAR model predicting the functional duration of a series of dopamine receptor D2 and β_2-adrenergic receptor agonists led to optimization of the *in vivo* duration of sibenadet and various other follow-on developmental compounds[72]. It also led to a more detailed understanding of the way these drugs interact with phospholipid bilayers and was cited in the development of long-acting β_2-adrenergic receptor agonists by Pfizer[73], as well as in the design of indacaterol — the recently approved long-acting β_2-adrenergic receptor agonist from Novartis[74]. Below, we discuss some important general issues in the application of QSAR models.

Commercial and public models versus in-house models. Commercial and public-domain predictive ADMET models are available, and one important issue for companies is the performance of these models compared with in-house models, given that the predictive ability of QSAR models is limited by the domain of applicability (see above). In an assessment of the success in genotoxic predictions, models that were based on data sets in the public domain were adequate in predicting compounds

Table 2 | **Published supervised matched molecular pair analyses**

Organization	End points	Data set size (approximate)	Transformations (N)	Number of matched pairs	Refs
AstraZeneca	• Solubility • Protein binding • Oral exposure (rat)	50,000	Ar-H → Ar-X (9)	4,588	105
GlaxoSmithKline	• CYP450 (five isoforms) • HERG • Solubility • PAMPA	500,000	R-H → R-X (50)	95,101	106
Pfizer	Human liver microsomes	150,000	Ar-H → Ar-X, Ar-X,Y (40)	4,380	107
AstraZeneca	Human liver microsomes	75,000	Ar-H → Ar-X (73)	5,321	108
AstraZeneca	Human liver microsomes	135,000	Ar → heterocycle (46)	2,323	109
AstraZeneca	Human liver microsomes	135,000	Ar-CH_2-R → Ar-X-R (24)	1,826	110

CYP450, cytochrome P450 enzyme; HERG, potassium voltage-gated channel subfamily H member 2 (also known as KCNH2); PAMPA, parallel artificial membrane permeability assay.

in the public domain but did not perform as well on proprietary active compound data sets from pharmaceutical companies, which tend to be more complex and generally do not contain obvious reactive functional groups[71].

Similarly, in an assessment of QSAR models of solubility, Bruneau found that a solubility model based on literature data was successful at predicting literature compounds, and an in-house solubility model was successful at predicting in-house compounds, but the cross-prediction of each model was markedly poorer[75]. Stouch, in his assessment of Bristol Myers Squibbs' search for useful global ADMET models, identified the same problem of the domain of applicability of even large literature data sets[32]. A model of Caco-2 permeability based on 800 literature compounds proved to have very little predictive ability on Bristol Myers Squibbs' compounds, and subsequent analysis found very little structural similarity between the literature compounds defining the Caco-2 model and the in-house compounds. A further weakness of literature data sets highlighted by Stouch is the diverse experimental methods that are used to collect the measured data[32].

In our view, models in the public domain should be used with caution and, wherever possible, they should be based on structures as close as possible to those for which predictions are desired, with experimental data obtained from a consistent, relevant assay. Even models that are based on data sets in the public domain and that contain many thousands of compounds may not be as useful as a model containing fewer compounds of relevant structural similarity.

Cultural aspects of chemical predictive modelling. Notwithstanding the explosion in available SAR data and the enormous progress in predictive modelling techniques, it is difficult to assess the real impact of these advances on the practice of drug design and on improvements in compound quality[76]. Although we can point to illustrative case studies of improvements in key compound quality indicators on a project-by-project basis, or even within a research site or company, the impact is less convincing across the industry overall.

In 2007, Leeson and Springthorpe reported that in the 10 years since the publication of the 'rule of five' guidelines, the drug-likeness concept had apparently not greatly influenced the design decisions of chemists in some major companies, as judged by the physicochemical properties of their patented compounds[18]. In a follow-up article in 2011, Leeson and St-Gallay

Table 3 | **Published unsupervised matched molecular pair analyses (approximate numbers)**

Organization (algorithm)	End point	Data set size	Number of matched pairs	Number of transformations	Refs
GlaxoSmithKline	HERG	76,000	1,400,000	1,000,000	111
	Solubility	94,000	1,400,000	900,000	
	Lipophilicity	180,000	4,400,000	3,200,000	
Pfizer (PairFinder)	Human liver microsomes	226,000	12,000,000	7,800,000	112
	Passive permeability	103,000	4,300,000	2,900,000	
	PGY1 efflux	75,000	2,600,000	1,900,000	
	Lipophilicity	30,000	930,000	760,000	
AstraZeneca (WizePairZ)	Not disclosed	35,000	Not disclosed	465,000	113

HERG, potassium voltage-gated channel subfamily H member 2 (also known as KCNH2); PGY1, P-glycoprotein 1 (also known as MDR1).

Table 4 | **Comparison of QSAR and MMPA**

QSAR	MMPA
Compounds are already proposed	Proposes new compounds
Prioritizes virtual compound sets for synthesis	Fixes specific issues on single compounds
Usually identifies general SAR trends	Explores SAR fine structure
Models can be abstract and lack clear interpretation	There is a clear link between transformations and the underlying data
Usually applicable to all chemistries represented in the training set	Limited to matched pair transformations that have previously been observed

MMPA, matched molecular pair analysis; QSAR, quantitative structure–activity relationship.

discussed the influence of organizational factors on compound quality, revealing some striking differences in the drug-likeness of synthesized compounds among organizations pursuing the same drug targets[21]. They proposed various cultural and organizational factors that could contribute to such differences, including varying tolerance of the companies to (or lack of awareness of) compound-related risks in clinical development; the lack of uptake or impact of computational tools; pressures on medicinal chemistry from proscribed project timelines and meeting corporate objectives; and a lack of innovation in the use of chemical templates and chemical synthesis. An example of the influence of organizational factors from AstraZeneca's experience is highlighted in FIG. 3.

All of the statistical studies on compound quality (many of which are cited in this Review) point to one key lesson: increasing potency without controlling lipophilicity (LogP) is detrimental to the chances of further progression for a medicinal chemistry project. So, it may be surprising that there is still continuing debate about whether drug-like concepts have improved compound quality or overly restricted compound design. However, Kenny and Montanari[77] have highlighted that the importance — or strength — of many of the reported relationships has been overstated because the approaches that are used to analyse and visually represent the data exaggerate trends in data. For example, one analysis highlighted the apparent overlooked importance of the fraction of sp^3 carbons[78]. In this analysis, binning of the fraction of sp^3 carbons as a function of Log(solubility) showed a high correlation ($r = 0.97$), which is indicative of a very strong relationship. As these data were publicly available, Kenny and Montanari were able to re-analyse them without the use of data binning, and found a correlation coefficient of only $r = 0.25$. The correlation of molecular weight with Log(solubility) for this series of molecules was actually much higher ($r = -0.62$), thus questioning the importance that the authors of the original analysis placed on the fraction of sp^3 carbons, which only described 6% of the variance in Log(solubility). Kenny and Montanari make some suggestions for good practice in data analysis[77], and in our view some of the most highly cited compound quality papers would benefit from reassessment following these recommendations.

A recent analysis of 150 of AstraZeneca's compounds in development showed that Pfizer's '3/75' rule and the fraction of sp^3 carbons did not discriminate between compounds that successfully reached Phase II trials and those that did not progress owing to toxicity[79]. The authors caution against using these simple guidelines as hard cut-offs, as many successful drugs would not pass them. Some chemists are even making a call to arms because more difficult targets may require us to step outside the drug-like space[80]. Nevertheless, despite challenges and even apparent opposing conclusions based on differing analyses of the same data sets, the weight of evidence indicates that compound quality guidelines have some value, and it would be foolish to ignore the potential of drug-likeness concepts harnessed from the successes and failures of hundreds of previous compounds in development. This is not to say that the definitions of drug-like space preclude discoveries in areas at the extremities, as some recent drug registrations have demonstrated[81,82]. The guidelines are based on statistical analyses (assuming that there is statistical validity) and therefore should be interpreted in a probabilistic manner. Projects working in the non-drug-like space should be prepared for a longer, higher-risk and more expensive journey. Some projects may be prepared for that risk, and for some it may be worth it, but it may not be wise to base a whole portfolio on the extremes of a probability distribution.

The organizational or cultural factor is also apparent in the definition of the chemical filters described above. Various validation exercises have shown that there can be little consensus among chemists on what constitutes a chemically attractive or unattractive structure. For example, Pharmacia evaluated how chemists selected and rejected compounds in lists of 2,000 compounds, seeded with 250 compounds that were previously rejected by a very senior medicinal chemist[83]. The average pairwise agreement among the 13 chemists in the study was only 28%. Nine of the chemists reviewed two lists of 2,000 compounds containing the same set of 250 probe compounds. The average consistency in rejection was only 51%, with the most consistent chemist only achieving a value of 71%. Based on an analysis of the full 2,000 compound sets, the average pairwise agreement was only 23%. The chemists who had been selected had experience ranging from 3 to 25 years, but it appeared that experience was not related to consistency of opinion; two of the reviewers had over 25 years of experience but they still showed very low consistency in their rejections.

In another example, Novartis gave 19 chemists 4,000 structures and asked them to identify desirable or undesirable fragments; only 8% of fragments were identified by more than 75% of chemists[84]. The consensus was uneven, with the agreement on good fragments being only 1%, whereas the consensus on bad fragments was 7%. Although still low, the higher consensus with 'bad' fragments suggests that chemists do a better job at carrying and sharing their bad experiences than they do with good ones.

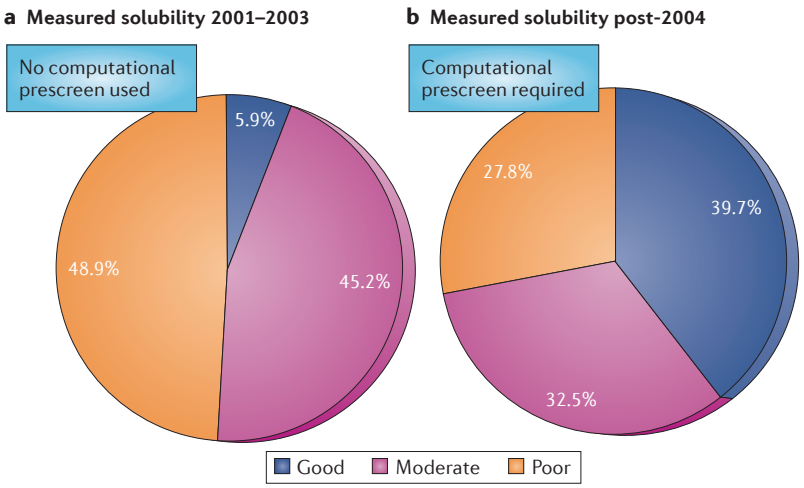


Figure 3 | **Example of the influence of organizational factors on the uptake of chemical predictive modelling. a** | The chart shows the distributions of the measured aqueous solubility of ~2,000 compounds synthesized at AstraZeneca's Södertälje site in the early 2000s (good compounds have a solubility higher than 100 μM; medium compounds have a solubility of 10–100 μM; poor compounds have a solubility lower than 10 μM). Managers at AstraZeneca's Södertälje site were tracking the solubility of synthesized compounds over time. Even though good computational models of aqueous solubility had been available from before 2001 (REF. 101), this did not result in an improvement in the solubility of the compounds synthesized. **b** | A marked improvement in the properties of compounds only occurred when management expectations on quality at the design stage were enforced in 2004; the chart shows the distributions for ~14,000 compounds synthesized between 2004 and 2012.

The lack of consistency among the same group of chemists, as highlighted by the Pharmacia research, supports the use of computational filtering methods, which can at least objectively apply defined rules (but only if we can agree on what they may be) with 100% accuracy. A lack of agreement among experts may demonstrate a lack of shared expertise. As highlighted by the Novartis group, chemists show higher consensus in assessing synthetic accessibility, where the correlation coefficient for the consensus was as high as 0.73–0.84 (REF. 84). It may be that although the underlying rules of chemical synthesis are mature and are the cornerstone of education in chemistry, the rules of medicinal chemistry are much less clear. This was further exemplified in an evaluation of 65 chemical probes identified from the US National Institutes of Health (NIH) molecular libraries programme, in which 11 experts were asked to rank the suitability of the identified probes as research tools for the elucidation of biological pathways (and not necessarily as lead compounds). The expertise of the panel was not in doubt; each expert was identifiable to many medicinal chemists by only their surname and reputation. The lack of general agreement among these 11 experts is obvious across the heatmap[85] shown in FIG. 4.

One conclusion is that chemists are all victims of their own experiences in medicinal chemistry projects. That experience is gained through several chemical series; most chemists experience a small number of projects, and many of the 'rules' derived may be specific to those chemical series explored. Those 'rules' then become their guiding principles in forthcoming projects. This is supported by Leeson's observations of organizational differences in drug optimization. It may be, as Leeson implies, that some companies are simply working in a less fruitful space, but from the chemist's point of view they are applying those optimization approaches that — based on their experiences — are more likely to succeed. Past success guiding behaviours that could lead to perceived future success is thought to be a strong driver for organizational culture[86]. Few cross-target rules have so far emerged or at least been accepted. This provides an opportunity for empirical predictive modelling to define the rules if we can overcome prejudices about using them.

From a statistical perspective, when trying to identify a weak signal it could be beneficial to increase the sample size, and this could be achieved with a crowdsourcing evaluation. AstraZeneca's AZFilters were initially defined in 2001 by a small group of chemists who were experienced in HTS hit evaluation. In 2003, AstraZeneca took a crowdsourcing approach to validate and refine AZFilters. Over 100 chemists from 9 sites were asked to vote on groups of 1,000 compounds taken randomly from more than 65,000 representatives from the internal AstraZeneca and external vendors' compound collections (including discontinued drugs) to assess for medicinal chemistry acceptability (whether the chemist would buy the compounds and would consider chemically modifying them). Statistical analysis led to 21 new chemical filters in addition to the original 150, a refinement of the existing filters and a tightening of the LogP window for the 'core' screening set (BOX 2).

In practice, medicinal chemistry experience and knowledge of the research area domain play an important part in the general assessment of compound quality and influence series prioritization for further development. Hence, instead of using structural filters as 'rules', a different approach is to present them as 'alerts' and rely on the medicinal chemistry design team's combined expertise to apply them appropriately. This is especially the case when evaluating the risk of reactive metabolites and undertaking safety or toxicity assessments, where the presence of certain functional groups should not automatically lead to the dismissal of compounds[87]. Alerts can also catalyse the 'frontloading' of a test for a liability to quantify the risk at an early stage.

Automated QSAR systems also impose good modelling practice on all models built and remove much of the subjectivity involved in QSAR model building, which is crucial if QSAR models are to achieve their potential utility. However, the introduction of automated QSAR methods to AstraZeneca generated some cultural challenges. The validation papers published by the AstraZeneca group were written as much to convince our own organization of the value, performance and safety of these procedures as to inform the wider research community of the value of automated modelling[48,49]. Internally, it required adjustments in the expectations of medicinal chemists, who are wary of predictions that potentially constantly change as the model is updated. Although completely automated model building is possible, including the definition of a project and chemical series, the majority of those decisions were left to the

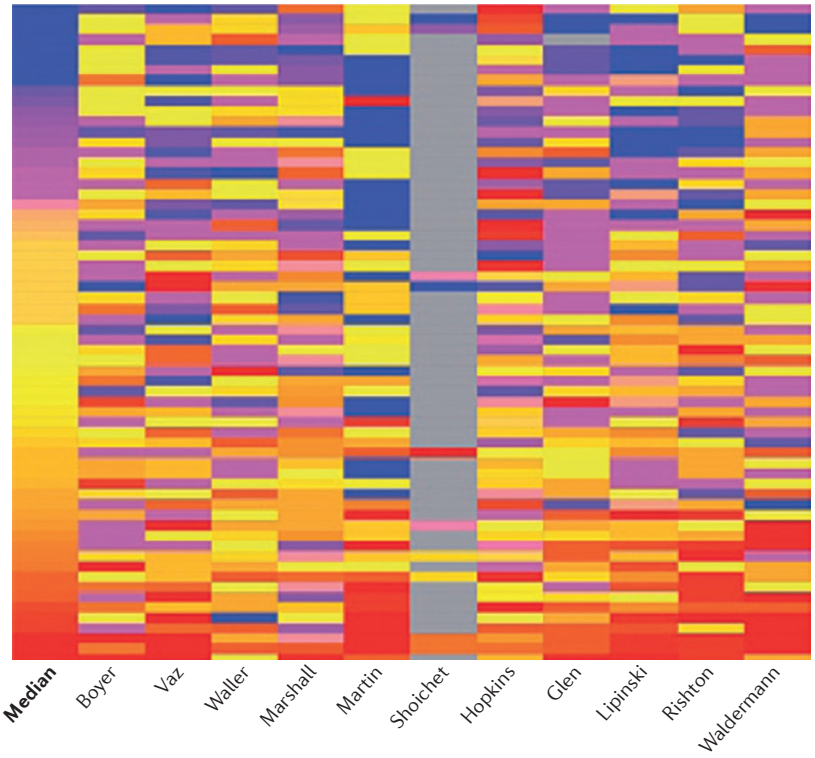


Figure 4 | **Lack of consistency in expert evaluations of chemical quality.** As part of an evaluation of the US National Institutes of Health (NIH) molecular libraries initiative, 11 experts were asked to rank the suitability of 65 chemical probe compounds as research tools for the elucidation of biological pathways (and not necessarily as lead compounds). The heatmap illustrates the confidence scores in the chemical probes (on the *y*-axis) for each of the 11 experts (listed on the *x*-axis). Red and orange indicate high dubiosity, whereas shades of blue indicate low dubiosity (that is, a good probe), with yellow indicating a median value. The probes are sorted by the median score on the *y*-axis. The *x*-axis is sorted by the research area of the voting experts: the two on the far left are pharmacokinetics and toxicology experts, the middle five are experts in chemoinformatics, whereas the last four are high-throughput screening and chemical experts. Image reproduced, with permission, from REF. 85 © (2009) Macmillan Publishers Ltd. All rights reserved.

project team. This made the system simpler and also meant that the models belonged to the project rather than being imposed on the team by an automated system. Automation also changes the role of computational chemists, as model building by the chemist is replaced. However, to ensure that automated methods succeed, computational chemists are still required to act as model evaluators and as model interpreters, which arguably demands more of their expertise. Furthermore, it is crucial that computational chemists provide medicinal chemists with confidence in the model in order for it to be applied[88].

Automated MMPA and automated QSAR were introduced to AstraZeneca at around the same time, and in some senses this generated a conflict in their application. Which approach should medicinal chemists use to make predictions? As discussed above, MMPA appeals to medicinal chemists as the results are readily comprehensible structural features, whereas QSAR models are the domain of computational chemists and use descriptors that are often difficult to interpret. It is likely that the two approaches are complementary, as shown in TABLE 4, but the full evaluation of when and where to apply these methods is still being defined. Objective assessments of where particular tools fit into the 'design–make–test–analyse' cycle are critical, and medicinal chemists should consider multiple approaches when deciding what to make next.

Outlook

In general, there are relatively good models available for the prediction of *in vitro* ADMET end points owing to large data sets, sometimes with over 100,000 data points that have been collected in large screening centres and with high consistency in the assays. The predictivity is often sufficient for distinguishing among good, medium or bad compound quality profiles and can provide a solid basis for selecting which molecules to progress with. However, predictions for potency and efficacy are more challenging. Efficacy is distinct from potency and usually refers to a functional response in a more complex model; it can be as simple as an agonist response in a functional cellular assay or a change in the course of disease in an *in vivo* situation, and therefore embodies both potency and the pharmacokinetic/pharmacodynamic (PK/PD) relationship. In this case, there are far fewer data points available and the models need to perform well in predictions that are extrapolations beyond the chemical space of the compounds used to train the models.

QSAR models are effective when the property being modelled changes smoothly as the descriptors change. Many enzymes, transporters and receptors involved in ADMET are designed to recognize a broad range of substrates and so ADMET end points are largely controlled by bulk properties. For this reason, QSAR models based on physicochemical descriptors — such as LogP, molecular volume, hydrogen bond counts, and so on — have proved to be successful in modelling many ADMET end points.

However, to model potency end points embodying a substantial degree of molecular recognition, we would need to have descriptors that are able to capture subtle structural changes within chemical series that are relevant to the SAR. It is not so surprising, therefore, that in a recent study it was found that for six potency end points, described by two descriptor sets and modelled with three machine learning methods, the descriptor choice was much more important than the machine learning method[89]. In instances where a model could be built, results from the different machine learning methods were generally not substantially different from each other[89]. Fragment-based descriptors and molecular fingerprints have potential in modelling potency end points. As molecular recognition involves both bulk property control and specific molecular recognition, it likely that methods that are based on combining multiple types of descriptors will be required in the future if QSAR is to be valuable in modelling potency.

Many of the properties that medicinal chemists need to optimize are dependent on the configuration of chiral centres in the molecule[90]. However, QSAR

models typically use only achiral molecular descriptors and therefore cannot model these stereochemical effects. Three-dimensional QSAR methods such as comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) are available, and they have shown some promise in modelling potency end points[91]. They are dependent on the initial three-dimensional alignment, and results would be relative to this alignment of the molecular structures.

CoMFA appears to have maintained its popularity as a QSAR method. In our experience, three-dimensional QSAR methods are useful for understanding potential SAR patterns within the data set, but less useful in prediction. For example, a CoMFA analysis of the duration of action of dual dopamine D2 receptor and β_2-adrenergic receptor agonists suggested that the three-dimensional positioning of hydrogen-bond acceptors near a basic amine was important for the duration of action. This was indeed the case, but the correct positioning of hydrogen bond acceptors alone did not result in a long duration of action. The real role of those groups that positioned hydrogen bonds was their through-bond electronic effect on the pK_a of the basic amine, and the overall contribution to lipophilicity[72]. The CoMFA model was reporting SARs only indirectly. If we hope to build chirality into automated QSAR models for potency, we need models that require less manual intervention. There is a need for an approach to describe chirality in a way that can cross chemical series and be incorporated into global automated QSAR models. Carbonell *et al.*[92] have recently described a method for incorporating stereochemistry into the algorithm that generates the signature descriptors discussed above, and this method was applied to QSAR predictions.

The last step in any design workflow is to decide which compounds to actually synthesize. Having applied the available predictive modelling approaches, the medicinal chemist is subsequently faced with a large data set of more or less accurate predictions of all the individual properties of the candidate molecules. A common way to deal with this problem is to colour the different properties green, amber and red, and to select the optimal compounds manually. However, this approach is not practical for the selection of compounds from huge virtual libraries. There is also a need to take into account the uncertainties in the predictions and deal effectively with error propagation from the multitude of models applied to each virtual compound[60]. Simply applying the predictions as 'hard' filters is likely to remove potentially good compounds from consideration, or it may just eliminate every idea. Seeking a compromise in the potency, selectivity, pharmacokinetic and toxicological profiles to discover a safe and efficacious drug is a complex task and although several methods have been described for molecular multi-objective optimzation[93], this is a field that still merits further research. A more precise quantification of the uncertainty in any given prediction will also reap considerable benefits.

QSAR models of both potency and ADMET properties are increasingly becoming integrated in expert systems that aim to optimize an input compound against a given set of parameters in an iterative process. In addition to the inverse-QSAR systems discussed above, they are being applied as constraints alongside physics-based approaches in *de novo* drug design algorithms[94,95] and in approaches using general molecular transformations to generate new compounds[96]. In a recent article, Hopkins and colleagues described a successful proof of concept for using such algorithms to design ligands with different polypharmacological profiles[97]. First, using Bayesian probabilistic activity models built on data from the CHEMBL database, they identified donepezil — an acetylcholinesterase inhibitor — as a moderately potent inverse agonist of the D4 receptor with minimal D2 receptor activity. The activity was further improved using a multi-objective optimization approach. Using a set of acceptable medicinal chemistry transformations, guided by the QSAR models, they were able to optimize donepezil into a dual D2 receptor and D4 receptor agonist with blood–brain barrier permeability. They were also able to optimize donepezil into a brain-penetrant D4 receptor agonist, increase D4 receptor activity by 69-fold (with 95-fold selectivity over the D2 receptor) and retain high blood–brain barrier permeability[97]. Again, further advances in prediction accuracy, estimates of uncertainty and a description of the domain of applicability will be essential to improving such expert systems.

Various commentators have speculated on how far chemical predictive modelling may go in the future. Will it ever be possible to design a drug completely on a computer in the way that modern aeroplanes are designed?[98] In our view, this will probably not be possible until physics-based methods evolve to the same level as the mathematical equations of fluid dynamics and materials science; even then, the vast complexity and unpredictability of biological systems will always present a formidable challenge[99]. A more achievable goal in the short term is for the predictions of each of the assays in the first wave of a screening cascade to become sufficiently accurate and reliable that they can be used as a 'wave zero' virtual screening assay. This means that the predicted parameters are solely used as a basis for the next round of design and the method can be used to refine the ideas of molecules to be synthesized, resulting in a high probability that the project will synthesize a new 'best compound' in each round of optimization.

The advances in chemical predictive modelling over the past few years have provided an increased understanding of the relationship between chemical structure and compound quality. Automated approaches enable the extraction of information from huge compound property databases and its application to compound selection as well as the optimization of lead compounds to high-quality candidate drugs. Although scientific and cultural challenges remain, chemical predictive modelling approaches are leading to considerable improvements in both the quality of all compounds synthesized during each phase of the drug discovery process and in the efficiency of that process, which will have a beneficial impact on the productivity of the pharmaceutical industry.

pK_a
The pH at which a group would be protonated in 50% of molecules. More molecules will become protonated with decreasing pH, and vice versa.

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Competing interests statement
The authors declare no competing interests.

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