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Lead optimization in the nondrug-like space

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Drug-like space might be more densely populated with orally available compounds than the remaining chemical space, but lead optimization can still occur outside this space. Oral drug space is more dynamic than the relatively static drug-like space. As new targets emerge and optimization tools advance the oral drug space might expand. Lead optimization protocols are becoming more complex with greater optimization needs to be satisfied, which consequently could change the role of drug-likeness in the process. Whereas drug-like space should usually be explored preferentially, it can be easier to find oral drugs for certain targets in the nondrug-like space.

Introduction

Identifying the chemical space most likely to produce drug molecules is crucial in lead generation (LG) and lead optimization (LO). It is believed that certain sections of chemical space (i.e. drug-like space), defined by molecular properties such as molecular weight (MW), lipophilicity, hydrogen bonding capability, among others, is more likely to contain oral small-molecule drugs. In his seminal paper, Lipinski [1] concluded that a compound that complies with Rule-of-Five (RO5) is less likely to carry absorption and solubility liabilities. This association between simple molecular features and the pharmacokinetic (PK) profile has been expanded over the past decade by multiple analyses [2–4] to establish the concept of drug-likeness. It is now widely accepted that drug-like compounds tend to possess certain favorable PK properties such as aqueous solubility and cell permeability. Some experts have cautioned, however, not to follow these rules too strictly [5,6] and it has been recognized that 'many valuable discoveries can be made at the margins or even outside areas considered mainstream' [7]. Recent analyses showed that 20% of oral drugs violate at least one RO5 rule [8]. Among the top ten best-selling oral drugs in 2008: two are RO5 violators; three require metabolic activation to produce irreversible ligands to exert their pharmacological effects; and one contains a dienenone and a thioester group. It is clear that the drug-like space, as currently defined, and the oral drug space where the oral drugs were actually found do not completely overlap. The drug-like space is relatively static, whereas the oral drug space is more dynamic.

The nature of the emerging targets, untreated diseases, modern optimization tools and regulatory requirements constantly evolves, which consequently leads to the changes of molecular features of drugs. Historically, LO has been a complex process and is becoming increasingly more sophisticated as new assays are incorporated in the LO protocols on a regular basis. Most preclinical tests attempt to eliminate 'losers', but the ultimate goal of LO is to identify and develop 'winners'.

Given the limited annual first-in-class NCEs, even a small number of false positives and/or negatives could significantly impact productivity. It has long been a concern that the 'search for quicker and cheaper tests' might 'add to the obstacles, uncertainties and expense of developing drugs', as articulated by Weatherall 29 years ago [9]. Assigning an appropriate weight to drug-likeness in the ever changing LO protocols requires proper judgment. Every year, millions of compounds are screened and hundreds, maybe thousands, of advanced compounds with good potency, selectivity and PK are produced. This huge effort only generated 2–6 first-in-class NCEs per annum over the past decade. Clearly, readily measurable properties such as PK might not be the bottleneck in LO. It is an open question as to whether more faithful compliance to the drug-likeness rules will improve R&D output significantly.

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Drug-likeness: what does it mean?

The term 'drug-likeness' signifies different things to different people within the pharmaceutical industry [10]. It is literally a measure of how similar a compound is to a drug, and can only be determined when the compound to be measured and drugs targeting the same mechanism are characterized. A truly drug-like compound should capture most of the essential features of the drug molecule targeting the biological target of interest, and should carry only minor liabilities that can be fixed by medicinal chemistry techniques. Drug-like compounds clearly can, and marketed drugs do, have drastically different chemical characteristics depending on the nature and location of their biological target(s) and anti-target(s), the PK profile needed, the nature of the disease to be treated, and so on. A universal molecular definition of drug-likeness in this sense is impossible because, for example, vancomycin and aspirin share few structural similarities. The term 'drug-likeness' in medicinal chemistry literature is more narrowly defined by several molecular parameters (e.g. MW, *c*log*P*, polar surface area (PSA), rotatable bonds, etc.) that appear to influence PK properties by retrospective analyses. Therefore, 'drug-like' can be more appropriately termed as 'PK-friendly'.

LO in the nondrug-like space

The drug-like and nondrug-like spaces are not clearly separated because all components of drug-likeness are not accurately defined [11]. MW and rotatable bonds can be accurately counted and hydrogen bond donors and acceptors can be readily identified, but their strengths are influenced by the local environment and are difficult to evaluate. Log*P* and PSA as measurements of lipophilicity and polarity, respectively, cannot be calculated reliably [12].

The most convincing liability associated with nondrug-like compounds is the poor PK properties, but PK-related attrition has been comparatively insignificant in recent years [13] and 'over optimization' of PK might increase other types of attrition. The weak correlation of PK properties across species further complicates the association between drug-likeness and human PK [14]. It has also been observed that high clog*P* can increase the promiscuity of a molecule and thus be linked to toxicity [15]. For most targets, however, the more lipophilic compounds also tend to be more-potent ligands and might not result in a reduced therapeutic window. In addition to Lipinski's analysis on the physicochemical properties of experimental drugs, Wenlock [3] and Vieth [16] have demonstrated that drugs have lower MW and clog*P* than discontinued candidates and highly active ligands, respectively. Although these observations indicate drug-like compounds can contain other superior qualities in addition to PK properties, several investigators have observed that final drugs are often larger and greasier than their lead compounds [17], which paradoxically implies drugs are less 'drug-like' than the lead compounds. Taken together, it can be concluded that drug-like space might be more densely populated with orally available compounds, but how productive this space is in generating oral drugs remains to be determined.

Given the associated PK advantages, the drug-like space should generally be explored preferentially but some caveats exist. The distribution of orally available compounds on the chemical space has not been determined and the difference between the drug-like space and the remaining chemical space has not been quantified. Although 80% marketed oral drugs share drug-like physicochemical profiles, they might not be representative of drug-like compounds because other confounding factors (efficacy, safety, etc.) are involved. Assuming the drug-like space contains 80% of the oral compounds, this 4-times enrichment might not be an overwhelming advantage when weighed up against the risks (e.g. inadequate potency, selectivity, targeted tissue distribution, etc.) that can cause problems for certain programs. Depending on the target of interest, other optimization needs could prevail and future discoveries should not be confined solely in the drug-like space. When the desired properties require conflicting molecular features, some properties might need to be in the suboptimal zone to maximize the overall molecular quality.

Newer classes of targets such as proteins with binding pockets that are large and shallow (e.g. protein–protein interactions, PPI) or highly hydrophilic (e.g. protein phosphatases, PPs) or highly lipophilic (e.g. cholesterol ester transfer protein, CETP) often require nondrug-like ligands. New strategies such as rational design of multiple ligands also demand large molecules to achieve dual activity. These targets and strategies represent new therapeutic opportunities, define the limit of state-of-the-art science, drive the invention of useful technologies and should be investigated intensively to expand the oral drug space.

Other forces can contribute to the production of nondrug-like candidates. For example, no screening compound collection is complete and the drug-like scaffolds might not be currently available even though they theoretically exist. Larger and more-complex molecules can also provide higher selectivity [18]. More-lipophilic compounds, although less soluble in water and less metabolically stable, also tend to have a larger volume of distribution [19] and longer exposure and can be useful under certain circumstances. Finally, the skills of the medicinal chemists can influence the quality of the compounds that they produce, but it is a fine line between designing compounds with no 'taste' and following rules with no discipline.

Proteins with large and shallow binding pockets

Potency against the desired target is crucial for a drug to exert therapeutic effects. At a tolerable dose the drug compound must achieve adequate exposure to modulate the target of interest to an appreciable degree. For some targets, however, it has proved challenging to achieve sufficient potency with drug-like compounds [20]. For example, protein–protein interactions often involve large, shallow and featureless binding pockets that are difficult to bind with drug-like molecules [21]. Biologically, however, protein–protein interactions are central to several key cellular signaling pathways and represent potential drug targets [22].

Significant progress has been made in the past decade on this class of important but challenging targets. The most notable example is the B-cell lymphoma-2 (Bcl-2/xL) inhibitor ABT263 (**1**, Fig. 1), which is in Phase II clinical trials for cancer [23]. Although ABT263 has a MW of 974 Da, its PK profile is acceptable for oral dosing. Potent small-molecule ligands for several other PPI targets have also been discovered and some PPIs are now considered druggable targets [24].

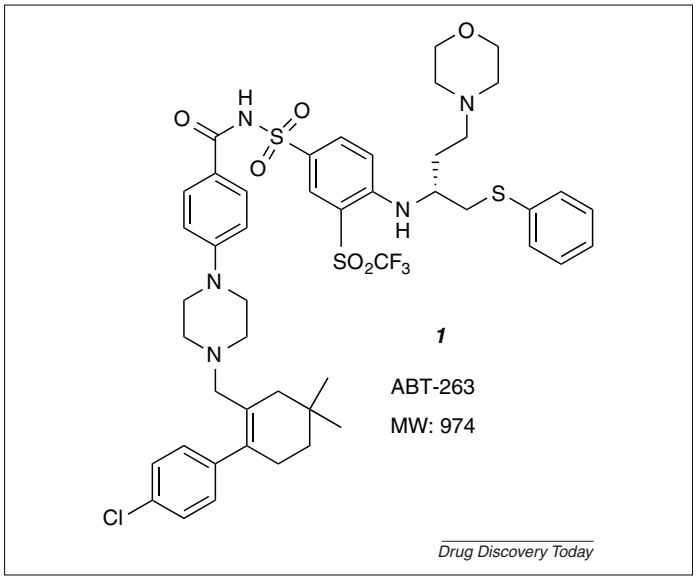

FIGURE 1

B-cell lymphoma-2 (Bcl-2/xL) inhibitor ABT263.

Proteins with highly lipophilic binding pockets

Proteins with extremely lipophilic binding pockets can usually only bind highly hydrophobic molecules. Marketed drugs targeting this type of protein, such as lipid GPCRs, are typically nondrug-like (high MW and clog*P*). CETP transports insoluble cholesterol ester and triglycerides, and has attracted much attention owing to its potential in preventing cardiovascular events [25]. CETP is soluble but nearly 50% of the amino acids in CETP are hydrophobic residues, which presumably form the binding pockets for its substrates. This hydrophobic nature of the CETP binding pocket determines the physicochemical properties of the ligands. The most advanced candidates are all highly lipophilic molecules (Fig. 2). A large Phase III trial (ILLUMINATE) revealed that torcetrapib (**2**, Fig. 2) caused more cardiovascular events than placebo and its development was terminated prematurely [26], whereas anacetrapib (**3**, Fig. 2) and dalcetrapib (**4**, Fig. 2) are currently being evaluated in late-stage clinical trials. These molecules are not drug-like, but their therapeutic potential warranted the medicinal chemistry effort and compounds with acceptable PK profiles have been successfully identified.

Proteins with highly hydrophilic binding pockets

Protein phosphatases catalyze the hydrolysis reactions of phosphoesters and, along with protein kinases, regulate protein phosphorylation—one of the most important cellular events. Unsurprisingly, PPs tend to form highly polar binding sites and their ligands often contain a large number of hydrogen bond donors, acceptors, and negatively charged groups. These features result in poor cell permeability and, thus, prevent the ligands from reaching their intracellular targets. No orally administrated phosphatase inhibitors have been approved for human use yet. Protein tyrosine phosphatase 1B (PTP1B) was probably the most intensely researched of the PPs [27]. PTP1B was considered a highly validated target for diabetes ten years ago and has been studied extensively by several major pharmaceutical companies. The protein can be crystallized and structure-based drug design was routinely used.

PTP1B has a hydrophilic catalytic pocket, which is highly homologous with that of T-cell protein tyrosine phosphatase (TCPTP). All potent PTP1B inhibitors are highly polar compounds, few of which can penetrate the cell membrane. To achieve selectivity against TCPTP, even larger and more-hydrophilic ligands were needed to bind a second binding site of PTP1B, which is less homologous to that of TCPTP. Using fragment-based technology guided by X-ray crystallography scientists at Abbott discovered several potent and selective PTP1B inhibitors (Fig. 3). The doubly charged compound **5** (Fig. 3) was highly potent and moderately selective again TCPTP, whereas the monoacid **6** (Fig. 3) was less potent but more selective and showed cellular activity [28]. As a result of the daunting structural requirements, no PTP1B inhibitors have passed Phase II clinical trials—even with the assistance of powerful technologies and large investment from major pharmaceutical companies. This type of scientifically valuable research is the only way to define the (non)druggability of novel targets convincingly, as well as the limitations of the state-of-the-art drug discovery.

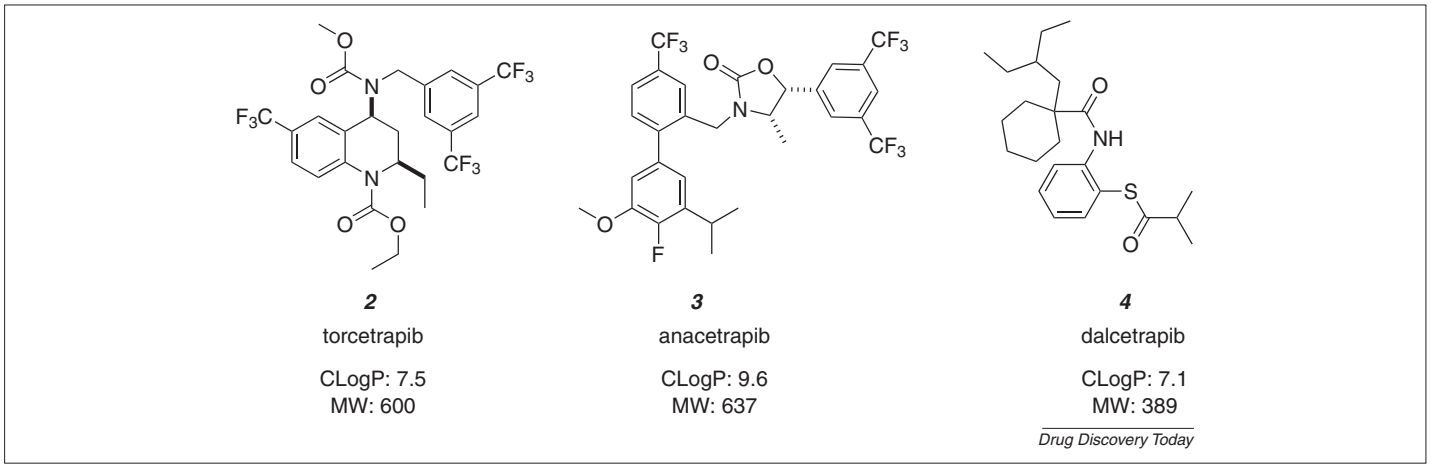

FIGURE 2

Advanced cholesterol ester transfer protein (CETP) inhibitors.

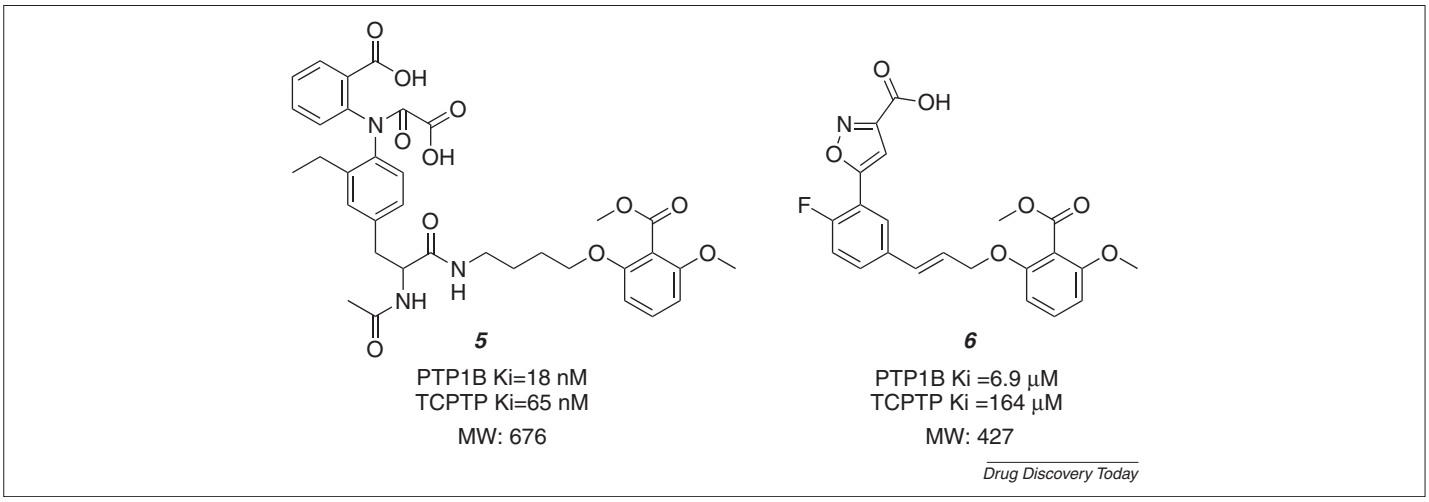

FIGURE 3

Selective protein tyrosine phosphatase 1B (PTP1B) inhibitors.

Multiple ligands

Some diseases are multifactorial and drugs targeting multiple biological targets can be more efficacious and less toxic than selective pharmaceuticals [29,30]. Several marketed drugs, especially CNS (central nervous system) drugs, are promiscuous but they were often discovered by serendipity rather than rational design [31].

Rational design of multiple ligands has emerged as an attractive strategy in recent years. Because multiple ligands aim to target more than one protein they tend to be large and nondrug-like [32]. A recent successful example is anticancer drug lapatinib (**7**, Fig. 4) [33]. The dual agent lapatinib inhibits epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) equipotently with an IC_{50} of ~10 nM. Although these two kinases share substantial homology, a large ligand was needed to achieve high potency against both with acceptable PK properties. Lapatinib has a MW of 581 Da and its water solubility is low, but it can be dosed orally although the absorption is incomplete and variable according to its label. This example demonstrates that, to give a novel therapeutic strategy a chance, using nondrug-like compounds is a risk worth taking and can be successful.

Other optimization needs can also escalate MW and lipophilicity. For example, most drugs targeting biogenic amine receptors are larger and greasier than the endogenous ligands such as dopamine and serotonin to achieve adequate selectivity. Owing to the small molecular size of the biogenic amines, most of these drugs are within drug-like range but selectivity can clearly be a driver for even larger compounds for certain targets (e.g. TCPTP-selective PTP1B inhibitor **5**, Fig. 3). Lipophilic compounds tend to distribute into tissues, which leads to longer exposure. Several lipophilic drugs (e.g. penfluridol, astemizole, pimozide) from Janssen Pharmaceutica have been designed to have long duration of actions. LO is complex and drug-likeness should be evaluated against other properties in the decision making.

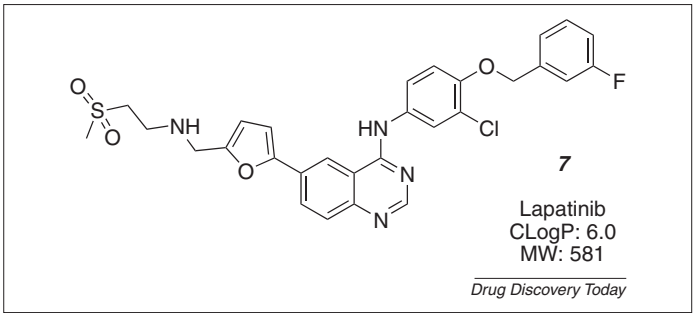

FIGURE 4

Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) dual inhibitor lapatinib.

First-in-class, best-in-class and withdrawn drugs

For several classes of drugs, the best-in-class drug is less drug-like than the first-in-class drug, suggesting LO should not always be directed toward making more-drug-like compounds. For instance, all follow-on statins have higher MWs than the first-in-class lovastatin, which is a RO5-compliant drug-like compound, and the best-in-class atorvastatin has a MW of 558 Da. Interestingly, the oral bioavailability of atorvastatin (14%) is higher than that of lovastatin (<5%). Had the LO been directed to designing more-drug-like compounds atorvastatin might not have been synthesized. In the field of anti-arrhythmics, the most effective agent is amiodarone, which is the least drug-like (MW = 645 Da, clog*P* = 8.9) and dirtiest of all anti-arrhythmics [34].

Similarly, the withdrawn drugs are not necessarily nondrug-like or less drug-like than the drugs remaining on the market from the same class. For example, among the 18 small-molecule drugs that have been withdrawn from the major markets between 2000 and 2010, four (22%) violate at least one RO5 rule while the other 14 are RO5 compliant. The RO5 compliance rate of these withdrawn drugs is almost identical to that (20%) of the marketed drugs. Among the four violators, troglitazone has two RO5-compliant analogs that remain on the market and rapacuronium has several analogs that violate the same rule but remain on the market. Among the RO5-compliant withdrawn drugs, ximelagatran and cerivastatin, each has one RO5-violating analog on the market (dabigatran etexilate and atorvastatin, respectively). Drug-likeness does not appear to correlate well with the fate of marketed drugs.

Compensating nondrug-likeness

Sometimes low oral bioavailability can be compensated by other PK properties or improved by novel formulation technologies. For example, the rennin inhibitor aliskiren has a low oral bioavailability of 3%, but it is sufficient to produce the desired therapeutic effect owing to a long half-life and a favorable distribution in the kidney [35]. The clog*P* for torcetrapib (**2**, Fig. 2) is 7.5, but the aqueous solubility can be improved by 100-fold with spray-dried dispersion formulation [36]. Using prodrug is another method that can enhance PK properties, particularly solubility and permeability [37]. For example, the clog*P* value (7.5) of anticancer agent miproxifene is high and the water solubility of this drug is low. Its phosphate prodrug increases the aqueous solubility by ~1000-fold [38] and a reasonable oral bioavailability was achieved. These options should be considered when making LO decisions. Finally, although oral administration is frequently preferred, other delivery methods can be acceptable and nearly 50% of FDA approved drugs are not oral drugs [39].

Closing remarks

Oral drug space is likely to expand in the future as optimization tools advance to allow the exploration of less druggable targets. Drug-likeness rules are helpful guidelines in finding orally available compounds, but appropriate application of these rules as LO becomes more complex can be subtle. Drugs are considered 'Black Swans' that do not follow the normal distribution and few breakthrough drugs would have succeeded if the drug hunters had not taken extraordinary risks. For example, when the anti-acid cimetidine project was initiated the existence of a H_2 receptor on parietal cells and the role of antihistamines in acid secretion were still a matter of controversy [40]. Without the assistance of HTS, the lead antagonists were generated from histamine, a nonselective histamine receptor agonist. The first clinical candidate metiamide induced agranulocytosis and it was unclear if this was a mechanism-based side effect. The backup candidate cimetidine was first given to a severely ill patient—a risky strategy that would have seriously delayed development if the patient had died upon treatment with cimetidine.

Similarly, fluoxetine did not show marked activity in the then-available animal models and even failed the first Phase II clinical trial [41]. The development of congestive heart failure (CHS) drug carvedilol was greeted with much criticism and skepticism because CHS was considered a contraindication for β-blockers at the time [42]. Several more-innovative drugs have also experienced severe technical problems in their discovery and development [43]. In all these cases, risks that are arguably greater than violating drug-likeness rules were taken.

Drug discovery has never been easy and will probably become more complex and involve tougher decision making. The fact that the concept of drug-likeness has quickly gained acceptance in the medicinal chemistry community reflects the desire to alleviate this burden. Sometimes, however, the complexity of LO is forgotten and drug-likeness rules are followed without proper care. Williams has opined that persistence might be the most crucial element in drug discovery [44], which appears to be agreed upon by other drug hunters [43,45]. New assays and filters do facilitate decision making, but 'good process will never be a substitute for good people or good science' [46]. Fundamentals and hard work remain the pillars of drug research.

References

1 Lipinski, C.A. *et al.* (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 23, 3–25
2 Veber, D.F. *et al.* (2002) Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* 45, 2615–2623
3 Wenlock, M.C. *et al.* (2003) A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* 46, 1250–1256
4 Lovering, F. *et al.* (2009) Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* 52, 6752–6756
5 Abad-Zapatero, C. (2007) A Sorcerer's apprentice and The Rule of Five: from rule-of-thumb to commandment and beyond. *Drug Discov. Today* 12, 995–997
6 Leeson, P.D. *et al.* (2004) Drug-like properties: guiding principles for design—or chemical prejudice? *Drug Discov. Today: Technol.* 1, 189–195
7 Fotouhi, N. *et al.* (2008) Lead generation: reality check on commonly held views. *Expert Opin. Drug Discov.* 3, 733–744
8 Overington, J.P. *et al.* (2006) How many drug targets are there? *Nat. Rev. Drug Discov.* 5, 993–996
9 Weatherall, M. (1982) An end to the search for new drugs? *Nature* 296, 387–390
10 Vistoli, G. *et al.* (2008) Assessing drug-likeness—what are we missing? *Drug Discov. Today* 13, 285–294
11 Muchmore, S.W. *et al.* (2010) Cheminformatic tools for medicinal chemists. *J. Med. Chem.* 53, 4830–4841
12 Waring, M.J. (2010) Lipophilicity in drug discovery. *Expert Opin. Drug Discov.* 5, 235–248
13 Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–715
14 Grass, G.M. and Sinko, P.J. (2001) Effect of diverse datasets on the predictive capability of ADME models in drug discovery. *Drug Discov. Today* 6 (Suppl. 1), 54–61
15 Hughes, J.D. *et al.* (2008) Physiochemical drug properties associated with in vivo toxicological outcomes. *Bioorg. Med. Chem. Lett.* 18, 4872–4875
16 Vieth, M. and Sutherland, J.J. (2006) Dependence of molecular properties on proteomic family for marketed oral drugs. *J. Med. Chem.* 49, 3451–3453
17 Oprea, T.I. *et al.* (2001) Is there a difference between leads and drugs? *J. Chem. Inf. Comput. Sci.* 41, 1308–1315
18 Hann, M.M. *et al.* (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* 41, 856–864
19 Lombardo, F. *et al.* (2002) Prediction of volume of distribution values in humans for neutral and basic drugs using physicochemical measurements and plasma protein binding data. *J. Med. Chem.* 45, 2867–2876
20 Lipinski, C.A. (2004) Lead- and drug-like compounds: the-rule-of-five revolution. *Drug Discov. Today: Technol.* 1, 337–341
21 Fuller, J.C. *et al.* (2009) Predicting druggable binding sites at the protein–protein interface. *Drug Discov. Today* 14, 155–161
22 Arkin, M.R. and Wells, J.A. (2004) Small-molecule inhibitors of protein–protein interactions: progressing towards the dream. *Nat. Rev. Drug Discov.* 3, 301–317
23 Tse, C. *et al.* (2008) ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. *Cancer Res.* 68, 3421–3428
24 Berg, T. (2008) Small-molecule inhibitors of protein-protein interactions. *Curr. Opin. Drug Discov. Dev.* 11, 666–674
25 Sikorski, J.A. (2006) Oral cholesteryl ester transfer protein (CETP) inhibitors: a potential new approach for treating coronary artery disease. *J. Med. Chem.* 49, 1–22
26 Barter, P.J. *et al.* (2007) Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* 357, 2109–2122
27 Johnson, T.O. *et al.* (2002) Protein tyrosine phosphatase 1B inhibitors for diabetes. *Nat. Rev. Drug Discov.* 1, 696–709
28 Liu, G. *et al.* (2003) Fragment screening and assembly: a highly efficient approach to a selective and cell active protein tyrosine phosphatase 1B inhibitor. *J. Med. Chem.* 46, 4232–4235
29 Hopkins, A.L. *et al.* (2006) Can we rationally design promiscuous drugs? *Curr. Opin. Struct. Biol.* 16, 127–136

30 Morphy, R. and Rankovic, Z. (2007) Fragments, network biology and designing multiple ligands. *Drug Discov. Today* 12, 156–160
31 Roth, B.L. *et al.* (2004) Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat. Rev. Drug Discov.* 3, 353–359
32 Morphy, R. and Rankovic, Z. (2006) The physicochemical challenges of designing multiple ligands. *J. Med. Chem.* 49, 4961–4970
33 Lackey, K.E. (2006) Lessons from the drug discovery of lapatinib, a dual ErbB1/2 tyrosine kinase inhibitor. *Curr. Top. Med. Chem.* 6, 435–460
34 Roden, D.M. (2003) Antiarrhythmic drugs: past, present, and future. *J. Cardiovasc. Electrophysiol.* 14, 1389–1396
35 Menard, J. and Azizi, M. (2007) The difficult conception, birth, and delivery of a rennin inhibitor: controversies around aliskiren. *J. Hypertens.* 25, 1775–1782
36 LaMattina, J.L. (2009) *Drug Truths: Dispelling the Myths About Pharma R&D.* John Wiley & Sons Inc.
37 Stella, V.J. and Nti-Addae, K.W. (2007) Prodrug strategies to overcome poor water solubility. *Adv. Drug Deliv. Rev.* 59, 677–694
38 Nomura, Y. *et al.* (1998) Phase I study of TAT-59 (a new antiestrogen) in breast cancer. *Gan To Kagaku Ryoho* 25, 553–561
39 Zhang, M.Q. and Wilkinson, B. (2007) Drug discovery beyond the ''rule-of-five''. *Curr. Opin. Biotechnol.* 18, 478–488
40 Molinder, H.K.M. (1994) The development of cimetidine: 1964–1976. A human story. *J. Clin. Gastroenterol.* 19, 248–254
41 Wong, D.T. *et al.* (2005) The discovery of fluoxetine hydrochloride (prozac). *Nat. Rev. Drug Discov.* 4, 764–774
42 Ruffolo, R.R. and Feuerstein, G.Z. (2006) Carvedilol case history: the discovery and development of the first β-blocker for the treatment of congestive heart failure. *Expert Opin. Drug Discov.* 1, 85–89
43 Cuatrecasas, P. (2006) Drug discovery in jeopardy. *J. Clin. Invest.* 116, 2837–2842
44 Williams, M. (2008) Perseverance furthers? The role of the drug hunter in the postgenomic era. *Curr. Opin. Investig. Drugs* 9, 21–27
45 Black, J. (2005) A personal perspective on Dr. Paul Janssen. *J. Med. Chem.* 48, 1687–1688
46 Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214