ELSEVIER

Journal of Pharmacological and Toxicological Methods 44 (2000) 235–249

Journal of Pharmacological and Toxicological Methods

Original articles

Drug-like properties and the causes of poor solubility and poor permeability

Christopher A. Lipinski

Exploratory Medicinal Sciences, Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA

Received 21 September 2000; accepted 25 September 2000

Abstract

There are currently about 10 000 drug-like compounds. These are sparsely, rather than uniformly, distributed through chemistry space. True diversity does not exist in experimental combinatorial chemistry screening libraries. Absorption, distribution, metabolism, and excretion (ADME) and chemical reactivity-related toxicity is low, while biological receptor activity is higher dimensional in chemistry space, and this is partly explainable by evolutionary pressures on ADME to deal with endobiotics and exobiotics. ADME is hard to predict for large data sets because current ADME experimental screens are multi-mechanisms, and predictions get worse as more data accumulates. Currently, screening for biological receptor activity precedes or is concurrent with screening for properties related to ''drugability.'' In the future, ''drugability'' screening may precede biological receptor activity screening. The level of permeability or solubility needed for oral absorption is related to potency. The relative importance of poor solubility and poor permeability towards the problem of poor oral absorption depends on the research approach used for lead generation. A ''rational drug design'' approach as exemplified by Merck advanced clinical candidates leads to time-dependent higher molecular weight, higher H-bonding properties, unchanged lipophilicity, and, hence, poorer permeability. A high throughput screening (HTS)-based approach as exemplified by unpublished data on Pfizer (Groton, CT) early candidates leads to higher molecular weight, unchanged H-bonding properties, higher lipophilicity, and, hence, poorer aqueous solubility.

Keywords: Chemical diversity; Drug-like; ADME; Absorption; Permeability; Solubility; Clinical candidate; Merck; Pfizer

1. Introduction

The literature emphasis on combinatorial chemistry and the screening of up to million(s) of compounds tends to obscure the fact that the world of drug-like compounds is quite limited, and that most of the information content related to desirable drug-like properties is contained in relatively small numbers of compounds. Filters for selecting drug-like compounds (Brennan, 2000), or schemes for differentiating between nondrug and drug-like compounds are based on analysis of libraries of a few thousand to 50 000 compounds (Sadowski & Kubinyi, 1998; Shah et al., 1998). The ability to construct large experimental screening libraries and the very large estimates of chemistry space accessible to low molecular weight compounds has been coupled with the concept of ''maximal chemical diversity'' (Martin et al., 1995). This coupling results in the argument that screening efficiency and the probability of a useful screening active will be increased if screening libraries span as large a volume of chemistry space as possible. For example, a recent chemical diversity analysis suggests that ''in order to ensure nanomolar ligands to any given target, a library of at least 24 million molecules will be required'' (Wintner & Moallemi, 2000). In contrast to this estimate, current experience suggests that clinically useful drugs exist as small tight clusters in chemistry space. For example, the estimated number of drug targets is only about 500 (Drews, 2000). Maximal chemistry diversity is an inefficient library design strategy, unless there are vast numbers of useful undiscovered targets. Moreover, while maximal chemistry diversity is possible in-silico, it remains to be seen whether it is possible in an experimental setting. The theme of large chemistry space and small target space applies to the screening arenas of absorption, distribution, metabolism, and excretion (ADME). The author contends that ADME chemistry space is much simpler than pharmacological target chemistry space. The result is that simple filters and rules work for ADME (Clark, 1999; Lewis, 2000; Lipinski, Lombardo, Dominy, & Feeney, 1997), but not

1056-8719/00/$ – see front matter
PII: S1056-8719(00)00107-6

for pharmacological targets. Acceptable ADME space may be considered as a smaller subset of pharmacology target space, which is in turn likely a very small subset of chemistry space. Paradoxically, for large data sets, pharmacological target SAR prediction is easier than for ADME prediction. Much of the reason lies in the multi-mechanism nature of current ADME screens, as opposed to the typical single mechanism of pharmacological target screens. The theme of information content related to desirable drug-like properties in relatively small numbers of compounds applies to the question of the relative importance of poor solubility or poor permeability in the problem of poor oral absorption. The time-dependent analysis of simple properties from Merck and Pfizer clinical candidates illustrates that the research approach to lead generation strongly influences solubility and permeability. As targets become more complex, a Merck-like "rational drug discovery" approach tends to poorer permeability, while a Pfizer (Groton, USA)-like high throughput screening (HTS) approach tends to poorer solubility.

2. Drugs and chemistry space

The world of drug-like compounds is limited in that there are currently only about 10 000 drug-like compounds. Drug-like is defined as those compounds that have sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of human Phase I clinical trials. Compounds that survive through Phase I and into Phase II clinical efficacy studies are conveniently identified by the presence of a United States Adopted Name (USAN), International Non-Proprietary Name (INN). Some of these may be New Chemical Entities (NCE) that have been approved for marketing by a regulatory agency in at least one country. As an illustration, there were about 9500 USAN names in the last compilation of the United States Pharmacopeia. Regulatory approval does not imply commercial success. For example, in the early 1970s, it was common for a drug to receive early approval in one or two countries, and then to encounter problems in the large market regulatory bodies and to never be actually marketed.

Drugs and their targets are sparsely distributed through chemistry space (Drews, 2000), and the members of a structural chemotype can be thought of as small tight clusters in the vastness of chemistry space. The combinatorial chemistry focus on chemical libraries with very large numbers of compounds tends to hide the fact that the majority of information on drug-like properties is contained in a very small number of compounds. This fact, in turn, raises the issue of the distribution of drugs in chemistry space. Chemistry space for reasonably sized molecules, i.e., those up to about molecular weight 600, and containing the common atoms found in drugs is very large. Estimates range widely from 10^{40} to 10^{100} with 10^{62} as a commonly quoted middle-range estimate. Given the small number of known drug-like compounds and the vastness of chemistry space, there are only several possibilities on the distribution of drugs in chemistry space. At the extremes, either drugs are found in small, infrequently distributed clusters in the vastness of chemistry space (the authors view). Alternatively, drugs are uniformly distributed through the vastness of chemistry space, and, so far, the pharmaceutical companies have only found an incredibly small proportion of the possible drugs that might exist.

The number of possible drugs acting at receptors can be over-estimated from a simple reduction to absurdity argument working backward from the number of possible targets. The basic idea is that there cannot be more drugs than there are drug receptor targets and that we can set an upper limit on the number of drug targets. The argument is as follows. The size of a large human might be 100 kg. From the "rule of five" (Lipinski et al., 1997), we know that the upper size range for orally acting drugs is about molecular weight 500, corresponding to about the upper 90th percentile in drug size distribution. The minimum size of a drug target cannot be smaller than that of its ligand. Therefore, the maximum number of possible drug targets of MWT 500 in a human can be estimated from Avogadro's number of 6.02×10^{23} molecules/mol. For a minimum target molecular weight of 500, a 100-kg human can contain only $100/0.5 \times 6.02 \times 10^{23}$ targets. This is about 10^{26} targets. If we were able to screen against all possible targets in a purely random manner, and given a chemistry space at the lower estimate of 10^{40}, we would still have only one chance in 10^{14} of finding a hit. In actuality, most receptor targets will have a molecular weight much larger than 500, so the number of targets will be smaller than 10^{26}. Also, it seems highly unlikely that one could screen against all possible targets at the same time, so the actual probability of finding a hit would be much smaller than one in 10^{14}. The odds of finding a hit is even worse if one takes one of the estimates of chemistry space larger than 10^{40}. The hit rate would be far lower than one in 10^{14}. This is a truly miserable prediction for success. A number of about 10^{14} chemical compounds far exceeds the number of compounds (low tens of millions) that have historically been abstracted by the Chemical Abstracts Service. The chance of a hit is somewhat increased because there are very likely to be multiple actives at any one target. However, the improvement in probability of a hit because of multiple actives is likely to be masked by the conservative assumptions as to drug target number and by the conservative estimates on the numbers of accessible small molecular weight compounds. Further masking may arise from the very conservative estimate based on screening

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

3. Maximal chemical diversity. Fact or fiction?

From HTS experience, we know that for the more tractable targets, i.e., g-protein coupled receptors, ion channels, and kinases, we can reliably detect hits from screening "diverse" chemical libraries in the size range of 10^5–10^6 (Spencer, 1999). How do we reconcile the experimental finding that HTS works in finding hits with the dismal prediction for screening success from the aforementioned thought experiment? The answer is that our "diverse" screening libraries are anything but diverse. True diversity can indeed possibly be attained in-silico in a virtual chemical library. However, as of today, diversity disappears as soon as one tries to translate the computational design into experimental reality. The rules of chemistry synthesis effectively eliminate huge realms of chemistry space. For example, there are no general reliable and predictable methods to construct carbon–carbon bonds between unactivated reaction centers. Only a subset of chemical synthesis technology is currently accessible to robotic chemistry high throughput methodology. The supply of available chemical building blocks severely constrains the construction of a truly diverse library. Apparently trivial problems, such as reagent solubility in organic solvents, conspire to limit robotic synthesis. Chemical vendors sell compounds that are likely to be purchased. Hence, there is an inherent bias towards available compounds that are likely to have agrochemical or pharmaceutical applications. Even the chemistry synthetic literature has a bias. Academics require funding to carry out research, and one of the best strategies to achieve funding is to work on chemistry related to known biomedical needs. In fact, one can make the argument that screening truly diverse libraries for drug activity is the fastest way for a company to go bankrupt because the screening yield will be so low. In the author's opinion, what has saved some companies is the impossibility of experimentally constructing a truly diverse chemical screening library. The current disillusionment with screening of large "diverse" libraries (Tapolczay & Cush, 2000), and the trend towards smaller more focused screening libraries (Borman, 2000; Martin & Wong, 2000) reflects both the sparse distribution of drugs in chemistry space and the realization that ADME/toxicity properties are as, or even more, important than purely biological receptor optimization in the search for drugs with real therapeutic potential potency (Darvas, Dorman, & Papp, 2000; Lipinski et al., 1997; Pickett, McLay, & Clark, 2000; Wagener & Van Geerestein, 2000).

4. ADME and pharmacological target dimensionality in chemistry space

ADME and chemical reactivity-related toxicity is very different from biological receptor activity in its occupancy of chemistry space. Compounds with biological receptor activity exist in small, tight clusters. The actual number of existing in-vivo drug targets is very small, and has been estimated at 417 in total (Drews, 1996). However, the chemistry space they occupy is very large. Hence, the chemical descriptor space can be very large. For example, the dimensionality of chemistry drug space has been estimated to lie in the range of 7–12 (Spencer, 1999). By way of contrast, the chemical space is much simpler and is of low order for the description of ADME and some of the chemical reactivity components of toxicity. The chemical space for ADME is less complex in the sense that it is of lower dimensionality. For example, the descriptors that describe almost all ADME variability are relatively few and simple. A principal component analysis can be used to identify descriptors that are unique, i.e., that are really different from each other. This type of analysis on a range of possible descriptors typically generates only five or, perhaps, six orthogonal (unique) descriptors. These might, for example, be descriptors related to size, lipophilicity, polarity, H-bonding status, and charge status. As a result, even simple rules and filters (like the rule of five) work remarkably well (Lipinski et al., 1997; Pickett et al., 2000).

The differences in dimensionality between ADME and chemistry drug space could be an inherent property of ADME and chemistry drug space or could be related at least in part as to whether the space is inclusionary or exclusionary. An inclusionary space defines those compounds that include a certain property, for example those compounds that are antagonists for a particular receptor subtype. This type of space tends to be higher dimensional. An exclusionary space defines those compounds that exclude a certain property, for example those compounds that are not drug-like. This type of space tends to be lower dimensional. For example, algorithms for the distinction between drug-like and non-drug-like tend to be fairly simple. (Sadowski & Kubinyi, 1998; Shah, Walters, & Murcko, 1998; Wagener & Van Geerestein, 2000). Currently, many experimental ADME assays tend to be exclusionary, for example a compound is not soluble, not permeable, or not metabolically stable, and so this exclusionary character could be responsible for at least some of the lower dimensionality of current ADME data.

Chemical reactivity-related toxicity can also be of low dimensionality in chemistry space. Simple chemical rules can be used as filters for mutagenicity and carcinogenicity. While numerical predictivity still remains a formidable challenge, the methods we currently have are

operationally useful. Rule-based programs, such as the "Derek" program from Lhasa, UK at the University of Leeds, and fragment-based correlation programs, such as the Multicase software developed by Giles Klopman, and the Topkat software currently distributed by Oxford Molecular, all find use at some level in the pharmaceutical industry. Very simple rules for mutagenicity prediction, such as "nitro-aromatics are bad" or "stay away from Michael acceptors" have no counterpart in the prediction of biological receptor affinity.

4.1. ADME and evolutionary pressure

Part of the difference between ADME chemistry space and biological receptor chemistry space is explainable by evolutionary pressures. Biological receptors evolved with a high degree of selectivity towards a ligand so as to minimize receptor cross-talk between agonists, thereby enhancing signal to noise ratio. This evolutionary trend translates into a high dimensional occupancy of biological receptors in chemistry space. There is another evolutionary trend that is seldom mentioned. There must also be a selection pressure against antagonists. It is hard to believe that evolutionary fitness would be enhanced by the indiscriminate activity of xenobiotics acting as antagonists of important signal transduction pathways. Perhaps this is one of the reasons for the frequent presence of nonnaturally occurring chemical motifs, such as the benzhydryl moiety or 1,4-disubstituted piperazine moiety among signal transduction antagonists. Natural products are frequently extolled as sources of drug leads. However, frequently occurring natural product motifs are seldom found in drugs. An example of this can be found in a very simple structural motif that is amazingly effective as a structural query to define natural products from nonnatural products. Searching a library with the structural query OCCOCCOCC pulls out almost exclusively natural products and only a very few, mostly cytotoxic, drugs, such as spermicides.

ADME properties evolved to deal with both endobiotics and exobiotics. The hallmark is, in general, much greater latitude in structural specificity, and this translates into a low dimensional occupancy of chemistry space. The low dimensionality of ADME properties may also reflect that most current ADME experimental data reflects a multiplicity of mechanisms. More on this point follows.

4.2. ADME predictivity and multi-mechanism screens

In theory, ADME should be easier to predict than biological receptor affinity. In practice it is not quite as easy as one might expect. Why is this so? Screening systems for biological receptor affinity are typically single mechanism systems. A biologist screens for a single mechanism, for example, a dopamine D-4 antagonist or a muscarinic M-1 agonist. Computational models are much easier to develop, and the resulting predictions are much more robust for single mechanism experimental data. Think how difficult it would be to develop a model for a biological screen run against a mixture of receptors in which, a priori, the contribution of each receptor type to activity was unknown. Currently, many experimental screens for ADME properties are multi-mechanism rather than single mechanism systems. Examples of multi-mechanism screens are aqueous solubility, metabolic stability to microsomal incubation, and membrane permeability as measured in Caco-2 cell culture systems. As a specific example, aqueous solubility is a multi-mechanism system. Solubility is affected by lipophilicity, compound H-bonding to solvent, intramolecular H-bonding, intermolecular H-bonding (crystal packing), and by ionic charge status. For a charged compound, solubility is even affected by the counter ion. This effect occurs primarily as a result of solution microequilibria between the ionic partners and not as commonly thought because of an effect on crystal packing forces. The multi-mechanism nature of aqueous solubility makes predictions very difficult. In the author's experience, filters for prediction of the most poorly soluble and most highly soluble are operationally useful. Numerical prediction of aqueous solubility works (within about a half log unit) only for neutral compounds, and usually within a structurally similar series.

Computational models for multi-mechanism assays (such as ADME) typically get worse as more data is accumulated. By contrast, computational models for single mechanism assays (biological receptor affinity) typically get better as more data is accumulated. The reason is that as more and structurally more diverse compounds are screened in a multi-mechanism system more data is obtained on more mechanisms, and the noise level for each individual mechanistic component rises. The result of this is a cause of much frustration to workers measuring and trying to predict multi-mechanism systems. Very nice correlations are obtained on small (usually mechanistically homogeneous) data sets. As the data set size increases (and the mechanistic range increases), the ability of the parameters used to predict the experimental data sets decline markedly. Typically, the same factors that worked so well in the small data sets are still highly statistically significant in the larger data set, but the predictivity is very low, perhaps too low to have any operational value. In this type of scenario, one often can only construct filtering algorithms (often based on clustering methods) to identify the compounds at the extremes of the property ranges. The solution to this dilemma is to carry out single mechanism ADME experimental assays and to construct single mechanism ADME computational models. The ADME area is at least 5 or more years behind the biology therapeutic target area in this respect. Most of the main line ADME

screens are still multi-mechanism. However, the landscape is changing just as it did a decade ago for biological target identification. Today, we already have early models for the position of transformation for substrates of some of the most widely studied cytochrome *P*450 metabolism systems and for a few transporters (both influx and efflux). Perhaps 10% of the human genome codes for the pumps and transporters so important in ADME. So we should expect a proliferation of single mechanism ADME assays akin to what we have experienced in the last decade in the biology therapeutic target area.

5. Screen for the target or ADME first?

Which is better to do first? Select for biological receptor activity or select for properties related to "drugability," i.e., ADME/toxicity. Currently, the industry practice is to screen for the receptor activity first, and then to follow with the "drugability" properties as a fast second. However, the order of this process could well change. Consider the problem faced when dealing with a new biological therapeutic target. A priori, in general, nothing will be known about the structural requirements for ligand binding to the target. Exceptions are a very high degree of structural similarity of the new target with a previous target on which there is an information base, or where there is some structural information on the new target itself. For example, from a single crystal X-ray structure or from NMR-based ligand affinity studies. For the most general case of a new biological target, one cannot de novo construct a computational model for the new target. The best that one can do is to carry out a series of library syntheses, then conduct assay screening, then computational model construction in an iterative sense with hopefully an improvement in the chemical hit rate, an improvement in the assay potency, and an improvement in the target computational models as one proceeds through the iterations. Contrast this process with the sequence where "drugability" precedes biological target affinity identification. For orally active drugs, we have a wealth of past history that we can apply to "drugability" properties, regardless of the nature of the new target. We know a great deal about requirements for the physicochemical factors, such as size, lipophilicity, and H-bonding, that are related to solubility and intestinal permeability. We can screen and in some cases predict for the structural moieties associated with the statistically most prevalent undesirable metabolic and toxicity processes. The starting knowledge base is inherently higher in the "drugability" prior to biological activity paradigm. The rate-limiting factor in the "drugability" before biological activity paradigm is screening capacity. Current

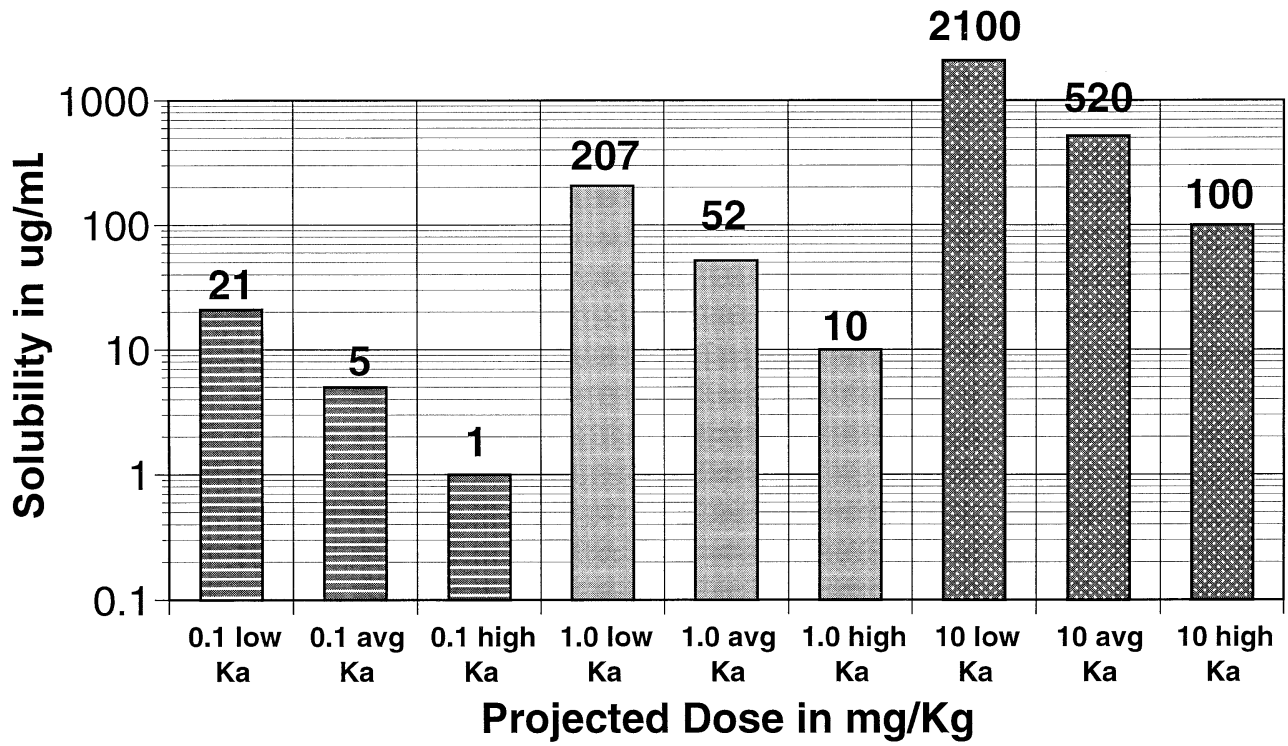

Fig. 1. Minimum acceptable solubility in μg/ml. Bars show the minimum solubility for low, medium, and high permeability (Ka) at a clinical dose. The middle three bars are for a 1-mg/kg dose. With medium permeability you need 52 μg/ml solubility.

Table 1
Merck advanced clinical candidates

CAS	MK-No.	Patent	Therapy	Mechanism
50-02-2	MK-125	1962	allergy	glucocorticoid
555-30-6	MK-351	1964	hypertension	alpha-agonist
4548-15-6	MK-915	1966	antiprotozoal	antiprotozoal
438-60-8	MK-240	1966	depression	cholinergic antagonist
113-597	MK-184	1966	psychosedative, neuroleptic	dopamine antagonist
148-79-8	MK-360	1966	antihelmintic	fumarate reductase inhibitor
50-48-6	MK-230	1966	antidepressant	parasympatholytic, antihistamine
58-54-8	MK-595	1966	hypertension, edema	sodium reabsorption–inhibition–renal
1458-11-3	MK-875	1967		diuretic, sodium hydrogen exchange inhibitor
1214-79-5	MK-685	1967	cardio-protection	GABA-antagonist, nhe1 na/h transporter inhibitor
3124-93-4	MK-665	1967	progestin	progestogen
2609-46-3	MK-870	1967	hypertension, edema	protein kinase C inhibitor
23456-71-5	MK-825	1968	inflammation	cyclo-oxygenase inhibitor
303-53-7	MK-130	1968	psychosedative	tricyclic
22662-39-1	MK-990	1968	antihelmintic (veterinary)	antihelmintic
98-96-4	MK-056	1968	antibacterial (tuberculostatic)	antituberculosis
22494-42-4	MK-647	1968	joint disease	HMG CoA reductase inhibitor
22494-27-5	MK-835	1968	pain	prostaglandin antagonist
26097-80-3	MK-905	1969	antihelmintic	ATP synthase inhibitor
3447-42-5	MK-410	1969	inflammation, pain	cyclo-oxygenase inhibitor
26718-25-2	MK-185	1969	atherosclerosis	platelet aggregation inhibitor
23155-02-4	MK-955	1969	antibacterial	protein synthesis inhibitor
28860-95-9	MK-486	1970	encephalopathy	dopa decarboxylase inhibitor
1110-40-3	MK-650	1970	corticosteroids	glucocorticoid
33468-84-7	MK-534	1971	hypertension	xanthine oxidase inhibitor
33450-08-7	MK-436	1971	protozoacide	NADH fumarate reductase inhibitor
31266-85-0	MK-316	1971	androgen antagonist	androgen antagonist
33564-30-6	MK-306	1971	antibacterial	cephalosporin
28875-92-5	MK-485	1971	neurological disorders	histidine decarboxylase inhibitor, dopa decarboxylase inhibitor
32579-36-5	MK-282	1971		renal glomerular filtration inhibitor
40396-83-6	MK-251	1972	anti-arrhythmic	
35523-45-6	MK-641	1972	antibacterial	gram-negative,-positive antibacterial
330-95-0	MK-075	1972	protozoacide	
33817-20-8	MK-191	1972	antibacterial	cell wall synthesis inhibitor
26538-44-3	MK-188	1972	anabolic	estrogen, contraceptive
42190-91-0	MK-356	1973	antibacterial	pivampicillin–probenecid salt
38194-50-2	MK-231	1973	joint disease	cyclo-oxygenase inhibitor
4204-99-3	MK-910	1974	amoebicides	
53108-00-2	MK-473	1974	hypertension, gout, glaucoma	chloride channel blocker, uricosuric diuretic
55779-18-5	MK-302	1975	coccidiostatics	hypoxanthine transport inhibitor
56592-32-6	MK-621	1975	antibacterial	elongation factor inhibitor
58456-91-0	MK-447	1975	inflammation	prostaglandin antagonist, diuretic
56049-88-8	MK-196	1975	hypertension	uricosuric loop diuretic, voltage-dependent chloride channel blocker
60200-06-8	MK-401	1976	antiparasitic	phosphoglycerate kinase inhibitor
26839-75-8	MK-950	1976	angina pectoris	beta-antagonist
60559-92-4	MK-761	1976	hypertension	sympatholytic beta-antagonist
65195-55-3	MK-936	1977	antihelmintic	GABA releaser
63463-51-4	MK-160	1977	psychosedative, neuroleptic	dopamine antagonist
64221-86-9	MK-787	1977	antibacterial	neutrophil activator
76547-98-3	MK-521, MK-522	1980	cardiopathy	angiotensin antagonist
76420-72-9	MK-422	1980	hypertension	angiotensin antagonist
75225-51-3	MK-819	1980	atherosclerosis	coenzyme A reductase inhibitor
75330-75-5	MK-803	1980	atherosclerosis	HMG CoA reductase inhibitor
77086-21-6	MK-801	1980	anticonvulsant	methyl-aspartate-*n*-antagonist
77236-35-2	MK-301	1980	acromegaly	somatostatin agonist
64022-27-1	MK-212	1981	anorectic	5-HT2c-agonist

(continued on next page)

Table 1 (*continued*)

CAS	MK-No.	Patent	Therapy	Mechanism
79902-63-9	MK-733	1981	atherosclerosis	HMG CoA reductase inhibitor
70288-86-7	MK-933	1982	antiparasitic	microfilaricidal agent
81377-02-8	MK-678	1982	diabetes	releasing factor inhibitor, somatostatin agonist
63141-67-3	MK-711	1983	anorexia, appetite stimulant	5-HT antagonist
81129-83-1	MK-791	1983	infectious disease	leukotriene-d4 peptidase inhibitor — renal
70458-96-7	MK-366	1983	antibacterial	topoisomerase inhibitor
76095-16-4	MK-421	1984	hypertension	angiotensin antagonist, ACE inhibitor
98319-26-7	MK-906	1985	cancer	5-alpha reductase inhibitor
103497-68-3	MK-963	1985	alopecia, benign prostatic hypertrophy	5-alpha reductase inhibitor
76824-35-6	MK-208	1985	anti-ulcer	histamine-h2-antagonist
126453-94-9	MK-927	1986	glaucoma	carbonic anhydrase inhibitor
103420-77-5	MK-329	1986	obesity	CCK antagonist
120443-16-5	MK-679	1987	anti-asthmatic	leukotriene antagonist
115104-28-4	MK-571	1987	anti-asthmatic	leukotriene d4 antagonist, *p*-glycoprotein substrate
118414-82-7	MK-886	1988	inflammation	leukotriene b4 antagonist
72702-95-5	MK-538	1989	diabetes complications	aldose reductase inhibitor
130466 38 5	MK 467	1990	diabetes	alpha-antagonist
129318-43-0	MK-217	1990	osteopathy	chelator
113403-10-4	MK-233	1991	analgesic, anti-inflammatory	cyclo-oxygenase inhibitor
134067-56-4	MK-434	1991	benign prostatic hypertrophy	5-alpha reductase inhibitor
119271-78-2	MK-417	1991	glaucoma	carbonic anhydrase inhibitor
138199-64-1	MK-852	1991	vaso-occlusive disorders	fibrinogen receptor antagonist, gpiia/iiia antagonist, rgd-mimetic
145202-66-0	MK-462	1992	migraine	5-HT1d agonist
124750-99-8	MK-954	1992	vascular disease	angiotensin antagonist
135947-75-0	MK-287	1992	atherosclerosis	platelet-activating factor antagonist
123997-26-2	MK-397	1993	antihelmintic	
147030-01-1	MK-591	1993	inflammation	leukotriene b4 antagonist, flap inhibitor
130693-82-2	MK-507	1994	glaucoma	carbonic anhydrase II inhibitor
159752-10-0	MK-677	1994	frailty	grh secretagogue
155569-91-8	MK-244	1995	pesticide	GABA releaser
157810-81-6	MK-639	1997	AIDS	HIV-1 protease inhibitor
151767-02-1	MK-476	1997	anti-asthmatic	leukotriene antagonist

ADME/toxicity assays are limited by the bioanalytical analysis procedure. Biological target identification assays in HTS use a single assay endpoint that is independent of the compound that is screened. For example, a well-defined colorimetric or fluorometric endpoint. This assay design leads to true high throughput (in the hundreds of thousands per year and higher). ADME assays, such as metabolic stability or permeability, typically use a compound-specific endpoint. The compound disappears or is transferred from one compartment to another and the change in concentration is measured. Compound specific assays are currently medium throughput (in the low tens of thousands per year) even with the best MS/MS analytical equipment. I would argue that in the long term (the next 10 years), the technical ability to run ADME assays as single mechanism assays in true high throughput mode is likely to markedly increase. This is more probable than a marked increase in the detailed structural knowledge base for new target to ligand interactions. If I am correct in this supposition, we should see a reversal in the order of research activities, i.e., "drugability" will precede, not follow, target identification.

6. Solubility, permeability, and potency

What level of permeability or solubility is needed to minimize poor absorption? Fig. 1 shows a bar graph that we distribute to our medicinal chemists that answers this question. It depicts the minimum acceptable solubility in μg/ml that is required for an orally active drug. The vertical columns are grouped in sets of three and show the minimum thermodynamic aqueous solubility (at pH 6.5 or 7.0) that is required for low, medium, and high permeability values (K_a) at a particular clinical dose. The middle set of three bars is the required solubility for a 1-mg/kg dose for compounds with low, medium, and high intestinal permeability. To achieve oral absorption, a compound with medium intestinal permeability, and a projected human potency of 1 mg/kg, (the middle bar in the middle set of three) needs a minimum aqueous solubility of 52 μg/ml.

The General Pharmaceutics Laboratory in our pharmaceutical organization profiles all newly nominated clinical candidates. As part of the evaluation, a maximum absorbable dose (MAD) is calculated for oral dosage forms based on the expected clinical potency, solubility, and permeability (Cur-

Table 2
Merck candidate properties

MK-No.	Patent	MLOGP	HBND	MWT	No.	Alert
MK-125	1962	1.66	2	392.47	8	0
MK-351	1964	−1.72	5	211.22	5	0
MK-915	1966	2.18	1	251.22	6	0
MK-240	1966	4.14	1	263.39	1	0
MK-184	1966	4.41	0	315.87	1	0
MK-360	1966	1.53	1	201.25	3	0
MK-230	1966	4.37	0	277.41	1	0
MK-595	1966	3.01	4	303.14	3	0
MK-875	1967	0.74	9	244.65	9	0
MK-685	1967	1.32	6	257.68	8	0
MK-665	1967	3.96	1	330.86	2	0
MK-870	1967	0.67	8	229.63	8	0
MK-825	1968	3.42	1	370.84	5	0
MK-130	1968	4.29	0	275.4	1	0
MK-990	1968	5.07	2	626.02	4	1
MK-056	1968	−1.47	2	123.11	4	0
MK-647	1968	3.99	2	250.2	3	0
MK-835	1968	3.52	1	274.25	4	0
MK-905	1969	2.08	2	302.36	6	0
MK-410	1969	3.61	1	369.49	4	0
MK-185	1969	3.99	1	415.8	5	0
MK-955	1969	−0.68	2	138.06	4	0
MK-486	1970	0.53	6	226.23	6	0
MK-650	1970	3.71	2	530.67	7	0
MK-534	1971	1.49	1	213.16	3	0
MK-436	1971	1.08	0	250.26	7	0
MK-316	1971	5	0	388.5	2	0
MK-306	1971	0.79	4	427.46	10	0
MK-485	1971	0.53	6	226.23	6	0
MK-282	1971	2.6	1	458.52	7	0
MK-251	1972	5.42	2	311.32	1	0
MK-641	1972	−2.68	3	107.08	3	0
MK-075	1972	1.96	2	302.25	9	0
MK-191	1972	2.1	3	463.56	9	0
MK-188	1972	2.46	3	322.4	5	0
MK-356	1973	2.1	3	463.56	9	0
MK-231	1973	3.89	1	356.42	3	0
MK-910	1974	2.03	0	221.19	5	0
MK-473	1974	3.66	1	357.24	4	0
MK-302	1975	3.39	2	277.69	5	0
MK-621	1975	−2.52	8	1145.36	22	1
MK-447	1975	3.04	3	305.16	2	0
MK-196	1975	3.65	1	365.22	4	0
MK-401	1976	0.01	6	380.66	7	0
MK-950	1976	0.28	2	316.42	7	0
MK-761	1976	0.68	2	249.32	5	0
MK-936	1977	1.75	3	873.1	14	1
MK-160	1977	5.94	0	427.54	1	0
MK-787	1977	0.6	4	299.35	7	0
MK-521, MK-522	1980	1.11	5	405.5	8	0
MK-422	1980	1.18	3	348.4	7	0
MK-819	1980	3.02	3	422.57	6	0
MK-803	1980	3.8	1	404.55	5	0
MK-801	1980	3.51	1	221.31	1	0
MK-301	1980	0.35	9	806.97	15	1
MK-212	1981	0.67	1	198.66	4	0
MK-733	1981	4	1	418.58	5	0
MK-933	1982	1.35	3	835.05	14	1
MK-678	1982	0.62	9	808.99	15	1
MK-711	1983	4.1	1	333.43	3	0
MK-791	1983	−1.35	5	358.46	7	0
MK-366	1983	1.16	2	319.34	6	0
MK-421	1984	1.64	2	376.46	7	0
MK-906	1985	3.65	4	372.56	6	0
MK-963	1985	4.26	1	371.57	3	0
MK-208	1985	−0.18	8	337.45	9	0
MK-927	1986	−0.27	3	338.47	6	0
MK-329	1986	3.21	2	408.46	6	0
MK-679	1987	4.52	1	515.1	5	1
MK-571	1987	4.52	1	515.1	5	1
MK-886	1988	5.6	1	472.1	3	0
MK-538	1989	3.78	1	391.2	5	0
MK-467	1990	1.08	2	418.52	8	0
MK-217	1990	−0.98	7	249.1	8	0
MK-233	1991	3.23	1	206.29	2	0
MK-434	1991	4.48	1	377.53	3	0
MK-417	1991	0.78	1	337.48	5	0
MK-852	1991	−1.28	8	577.71	13	1
MK-462	1992	2.65	1	269.35	5	0
MK-954	1992	4.28	2	422.92	7	0
MK-287	1992	0.92	1	510.61	9	0
MK-397	1993	1.53	3	900.13	15	1
MK-591	1993	5.23	1	587.19	5	1
MK-507	1994	−0.57	3	324.44	6	0
MK-677	1994	1.18	3	528.68	9	0
MK-244	1995	1.59	3	859.07	14	1
MK-639	1997	1.72	4	613.81	9	0
MK-476	1997	5.66	2	586.2	4	1

atolo, 1998). This calculation serves to confirm that either the physicochemical properties of the candidate are easily within the acceptable range, or that the properties lie within a difficult range that will require more than the average pharmaceutics manning. We adapted this calculation to create the simple bar chart in Fig. 1. It answers the chemist's question of "how much solubility do I need?" The three middle bars describe the most common clinical potency that we encounter; namely that of 1 mg/kg. If the permeability is in the middle range, as for the average heterocycle, then a thermodynamic solubility of about 50 μg/ml at pH 6.5 or 7 is required. If the permeability is low (as in a typical peptidomimetic) the solubility should be about 200 μg/ml. The bar graph also nicely illustrates another point. It is very important to provide data to one's audience in a familiar format. In this particular example, the audience is a medicinal chemist with a highly developed appreciation for graphical presentations and little tolerance or interest in mathematical presentations. Showing essentially the same data to our chemists in an equation type format (a format that was quite suitable to our pharmaceutical scientists' needs) was not at all effective with our chemists.

7. Relative importance of poor solubility and permeability

What is the relative importance of poor solubility and poor permeability towards the problem of poor oral

Table 3
Pfizer candidate properties

Synthesis sequence	MLOGP	HBND	MWT	No.	Alert
1	1.83	2	277	5	0
2	1.73	3	246	4	0
3	2.29	0	206	2	0
4	2.82	2	329	7	0
5	2.58	4	167	3	0
6	3.43	2	389	9	0
7	2.57	0	220	2	0
8	2.05	2	383	9	0
9	2.66	1	497	6	0
10	1.64	1	409	6	0
11	−0.31	2	337	7	0
12	0.00	2	331	7	0
13	0.25	2	345	7	0
14	2.37	1	332	5	0
15	3.94	2	286	3	0
16	2.77	0	227	3	0
17	1.74	0	308	7	0
18	7.30	2	667	4	1
19	3.75	1	237	1	0
20	3.03	0	241	3	0
21	1.36	2	159	2	0
22	1.15	1	202	4	0
23	1.42	1	223	4	0
24	2.08	3	492	10	0
25	1.05	3	430	7	0
26	1.11	7	449	11	1
27	1.70	3	394	6	0
28	8.09	2	585	2	1
29	1.05	8	492	13	1
30	1.33	3	451	8	0
31	3.52	1	413	5	0
32	1.68	0	293	6	0
33	4.58	2	527	5	1
34	1.41	1	329	8	0
35	3.11	5	667	10	0
36	1.93	4	373	9	0
37	0.77	3	466	8	0
38	−0.57	0	245	2	0
39	1.47	5	389	10	0
40	5.27	1	451	3	0
41	4.05	2	385	6	0
42	1.98	5	424	10	0
43	1.58	9	532	16	1
44	1.47	6	388	10	0
45	1.05	1	284	6	0
46	3.97	1	383	6	0
47	2.55	1	275	8	0
48	1.59	1	266	5	0
49	1.37	2	202	4	0
50	2.34	2	343	10	0
51	1.64	5	562	14	1
52	3.89	2	438	5	0
53	1.30	2	904	16	1
54	0.34	2	875	16	1
55	0.16	1	233	6	0
56	1.16	2	247	4	0
57	5.18	2	545	4	1
58	5.35	1	453	3	0
59	1.37	5	761	15	1
60	1.30	2	847	15	1
61	1.51	0	347	8	0
62	4.54	2	333	2	0
63	0.51	2	889	16	1
64	3.53	1	280	2	0
65	0.65	1	169	2	0
66	0.91	5	869	15	1
67	2.19	4	204	6	0
68	2.15	2	317	9	0
69	3.89	2	438	5	0
70	0.40	4	611	14	1
71	4.08	1	452	5	0
72	−0.24	3	782	16	1
73	4.76	1	306	1	0
74	0.61	1	183	4	0
75	5.35	1	453	3	0
76	0.95	1	401	8	0
77	0.04	5	333	7	0
78	1.52	1	242	5	0
79	4.13	3	377	3	0
80	1.77	3	760	15	1
81	2.67	1	241	5	0
82	0.89	4	776	14	1
83	0.93	5	222	6	0
84	2.48	0	294	5	0
85	0.89	4	776	14	1
86	−0.28	3	262	7	0
87	0.77	1	377	10	0
88	1.30	3	753	17	1
89	1.24	3	681	15	1
90	2.85	6	307	7	0
91	1.52	1	417	10	0
92	0.14	5	749	14	1
93	1.94	1	374	7	0
94	1.03	2	376	9	0
95	1.72	2	262	5	0
96	2.49	1	345	6	0
97	0.14	5	749	14	1
98	2.81	1	245	5	0
99	0.02	4	699	12	1
100	1.34	1	447	10	0
101	1.95	2	321	5	0
102	2.39	4	292	6	0
103	1.77	1	480	9	0
104	1.56	1	462	10	0
105	2.67	4	312	6	0
106	1.80	2	927	16	1
107	0.63	2	349	6	0
108	4.03	2	299	4	0
109	3.05	1	430	6	0
110	2.34	2	339	5	0
111	2.58	1	353	4	0
112	1.99	2	291	4	0
113	3.27	1	419	6	0
114	2.60	1	316	5	0
115	0.24	5	401	10	0
116	2.09	1	371	6	0
117	1.86	2	275	4	0
118	2.82	1	369	6	0
119	3.24	0	400	7	0
120	3.02	0	384	7	0
121	2.60	2	316	5	0
122	4.11	0	416	4	0
123	3.24	1	386	7	0
124	1.59	4	512	10	0
125	2.29	0	215	2	0

(continued on next page)

Table 3 (*continued*)

Synthesis sequence	MLOGP	HBND	MWT	No.	Alert
126	2.93	1	387	6	0
127	2.60	2	316	5	0
128	2.10	1	398	5	0
129	3.22	1	379	5	0
130	1.13	2	252	5	0
131	1.79	4	633	11	1
132	3.05	2	466	6	0
133	2.80	1	420	6	0
134	3.66	0	407	5	0
135	2.20	3	355	5	0
136	3.71	1	413	5	0
137	2.20	3	355	5	0
138	−4.77	4	313	7	0
139	1.92	3	400	6	0
140	3.26	1	402	7	0
141	1.15	1	362	7	0
142	2.10	0	329	7	0
143	−0.51	5	283	8	0
144	3.39	1	407	5	0
145	3.52	0	380	4	0
146	4.33	0	493	5	0
147	4.06	1	436	5	0
148	5.25	1	420	3	0
149	4.74	0	503	5	1
150	0.37	2	275	5	0
151	2.81	3	416	7	0
152	3.38	0	389	4	0
153	3.75	0	491	6	0
154	2.77	2	296	3	0
155	2.59	2	373	5	0
156	2.19	3	327	4	0
157	−2.54	17	788	21	1
158	2.51	0	443	8	0
159	2.33	3	661	10	0
160	3.21	2	476	6	0
161	4.14	1	417	8	0
162	2.17	3	366	5	0
163	5.35	1	461	3	0
164	4.11	2	429	4	0
165	4.11	2	429	4	0
166	3.86	0	451	7	0
167	3.09	1	405	6	0
168	2.15	4	647	10	0
169	4.98	1	471	3	0
170	3.63	0	391	4	0
171	3.09	1	405	6	0
172	1.10	3	404	6	0
173	3.91	1	544	9	0
174	−0.09	7	755	14	1
175	4.91	1	447	3	0
176	1.78	5	559	11	1
177	3.93	1	381	5	0
178	3.52	1	388	4	0
179	−0.24	5	289	8	0
180	1.28	2	321	5	0
181	2.79	2	380	4	0
182	4.04	0	379	3	0
183	0.89	2	1064	20	1
184	2.69	4	697	9	0
185	4.22	1	439	5	0
186	2.87	2	351	7	0
187	3.59	1	447	5	0
188	3.73	2	378	4	0

Table 3 (*continued*)

Synthesis sequence	MLOGP	HBND	MWT	No.	Alert
189	2.88	1	340	4	0
190	1.83	1	321	6	0
191	2.42	3	437	8	0
192	4.72	2	455	4	0
193	3.31	1	424	6	0
194	2.16	4	440	8	0
195	2.67	2	579	7	0
196	3.90	3	527	7	0
197	2.62	2	587	7	0
198	2.09	2	395	8	0
199	3.23	1	355	5	0
200	1.35	4	723	12	1
201	2.49	3	398	5	0
202	4.63	1	388	3	0
203	2.89	0	339	5	0
204	4.53	1	375	5	0
205	4.01	3	505	7	0
206	3.99	1	394	5	0
207	4.41	2	428	4	0
208	4.41	2	428	4	0
209	2.38	2	609	8	0
210	2.07	2	617	8	0
211	4.25	3	533	7	1
212	0.77	2	314	6	0
213	3.18	7	1029	18	1
214	4.49	2	417	5	0
215	3.70	2	486	5	0
216	3.32	3	445	5	0
217	−1.84	18	848	22	1
218	1.78	3	359	5	0
219	4.24	0	360	5	0
220	3.71	4	549	9	0
221	1.81	2	298	5	0
222	4.57	0	327	3	0
223	1.97	3	416	7	0
224	3.18	2	481	5	0
225	2.72	3	444	6	0
226	−0.11	8	1029	23	1
227	0.12	7	1035	20	1
228	3.73	2	378	4	0
229	3.92	0	339	5	0
230	2.29	1	326	8	0
231	0.58	5	331	7	0
232	4.71	1	414	3	0
233	4.78	1	579	6	1
234	5.41	2	477	6	0
235	1.23	4	345	7	0
236	0.99	5	331	7	0
237	2.90	1	393	7	0
238	1.55	1	269	3	0
239	3.23	0	367	6	0
240	0.84	5	458	8	0
241	0.05	3	443	10	0
242	4.09	0	313	5	0
243	2.43	2	330	5	0
244	2.20	2	316	5	0
245	4.57	1	326	3	0
246	1.92	3	398	6	0
247	1.42	1	204	3	0
248	4.56	0	463	5	0
249	4.42	2	482	5	0
250	2.14	3	412	6	0
251	3.95	1	380	5	0

(continued on next page)

Table 3 (*continued*)

Synthesis sequence	MLOGP	HBND	MWT	No.	Alert
252	1.54	3	297	5	0
253	4.87	1	469	4	0
254	3.35	0	391	4	0
255	1.52	3	506	9	0
256	4.34	0	379	3	0
257	4.01	3	453	6	0
258	1.52	3	506	9	0
259	4.11	0	448	4	0
260	2.47	2	357	5	0
261	7.07	0	627	6	1
262	1.75	3	404	7	0
263	3.67	2	380	5	0
264	1.43	2	323	6	0
265	−4.43	8	5773	12	1
266	1.81	3	611	10	0
267	4.56	0	463	5	0
268	1.75	3	409	7	0
269	4.86	2	498	6	0
270	1.78	2	358	8	0
271	2.06	3	466	9	0
272	−0.04	7	806	15	1
273	1.67	5	483	8	0
274	0.13	5	820	15	1
275	1.1	1	211	3	0
276	6.69	0	600	6	1
277	6.88	0	615	6	1
278	2.39	1	469	7	0
279	3.04	2	311	4	0
280	1.38	3	410	8	0
281	1.44	2	324	6	0
282	3.08	4	532	8	0
283	2.71	2	359	5	0
284	3.52	4	337	6	0
285	2.19	4	320	7	0
286	1.84	3	436	8	0
287	3.67	1	227	1	0
288	1.86	2	842	17	1
289	4.21	1	300	2	0
290	1.33	5	529	13	1
291	4.1	1	480	5	0
292	2.12	3	373	6	0
293	5.01	2	537	4	1
294	4.54	1	430	5	0
295	2.27	3	341	6	0
296	2.03	2	856	17	1
297	4.77	2	603	6	0

absorption? In a global sense, the relative importance may depend at least in part on an organization's research approach. Specifically, it could depend on how leads are generated. Two extremes can be identified. In one extreme, leads are generated from an empirical HTS, and, in the other extreme, leads are generated in some type of "rational drug design" process. This could encompass a variety of techniques ranging from modification of a known compound to an approach where structural information exists as to target binding requirements, for example from target X-ray or NMR studies, or by analogy from target mechanistic information, or from information on similar previous targets. Whatever the mix of techniques, the hallmark is that the approach is "rational" in the sense that it is not based on empirical screening for in-vitro activity. Poor solubility will be viewed as the predominant problem if lead generation is heavily dependent on HTS. Poor permeability will be viewed as the predominant problem if leads arise from "rational drug design."

7.1. Merck and Pfizer clinical candidates

An analysis of published data on Merck advanced clinical candidates and the unpublished data on Pfizer early candidates illustrates the physical property trends with time that could result from these two extremes in lead generation. The limitations of this type of analysis should be kept in mind. The trends in clinical candidate profiles from two different research organizations are being compared without assurance that "apples are being compared with apples." For example, in the Pfizer clinical candidate data set, the criteria for candidate nomination evolved over a 30-year period, and this evolution in criteria might have affected the time-wise calculated property profiles. While one can identify the Merck clinical candidates over a 30-year period, it is not possible for this author to assess that organization's cultural preferences. For example, over the 30-year history of the Merck candidates, did the relative importance assigned to good permeability and good solubility change, and was the Merck relative importance the same as Pfizer? Despite these caveats, it is tempting to try to assign causality to the property trends with time.

Pfizer, at its Groton laboratories, has had a heavy reliance on HTS since 1987, and a more limited focus on "rational drug design." Merck has historically had a heavy reliance on "rational drug design" with significant efforts into combinatorial chemistry and high throughput synthesis only gradually increasing over the last 8 years.

Table 1 shows the publicly available data for Merck advanced clinical candidates. From a Chemical Abstracts Scifinder search, Merck candidates were identified by Chemical Abstracts registry number and by MK num-

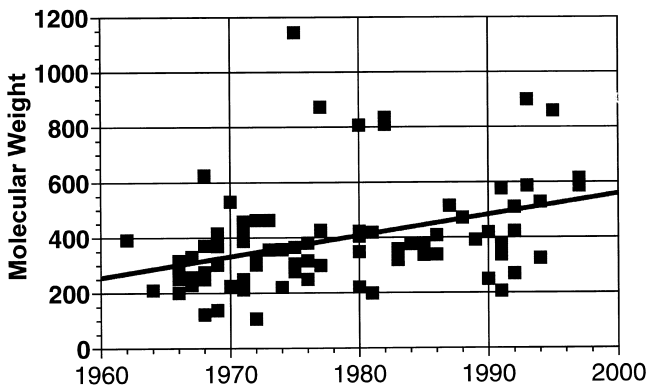

Fig. 2. Upwards molecular weight trend in Merck advanced candidates.

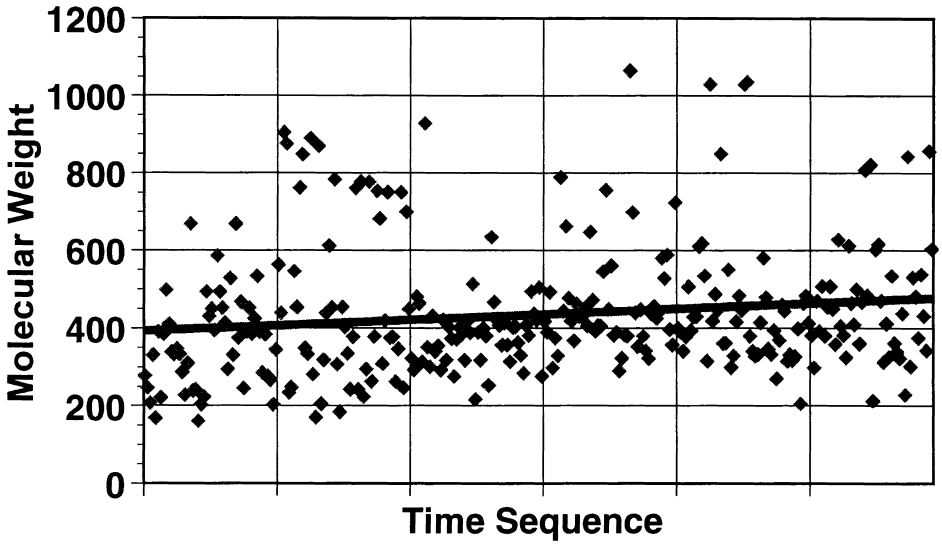

Fig. 3. Upwards molecular weight trend with time in Pfizer, Groton candidates.

ber. The intended therapy and mechanism of action are also listed. The year of the earliest Merck patent corresponding to the candidate is also listed. MK numbers exist that do not have corresponding patents. These appear to be mostly important biological standards and were not used in this analysis. Table 2 shows the "rule of five" calculated properties for the Merck candidates. Pfizer early candidates were taken from our historical list of candidate alert notices issued when a candidate is first identified, or from the list of candidates that were formally recommended for development. Table 3 shows the "rule of five" calculated properties for the Pfizer candidates. Unlike Merck, and some other pharmaceutical companies, Pfizer does not identify clinical candidates by a new or changed code number, and the list of candidates is not in the public domain. The year of the candidate is the year of the earliest patent for the Merck candidates, and the time sequence is the order of synthesis for the Pfizer early candidates. Only candidates from Pfizer's US Groton laboratories were used because the method of historical lead generation in Pfizer's UK laboratories is quite different and is not historically biased towards HTS. The number of candidates differs between Merck and Pfizer with more compounds listed for Pfizer. This does not reflect on research productivity, but, rather, the fact that the Pfizer candidates were identified from the historical record of those recommended for advancement at the earliest research stage and before any significant attrition had occurred. The Merck list is for those candidates at a more advanced stage.

7.2. The trend in molecular weight

Both the Merck advanced candidates and the Pfizer early candidates show an upward molecular weight trend with time. Fig. 2 illustrates the trend towards higher molecular weight in the Merck clinical candidates. The *x*-axis is the date of the earliest Merck patent covering the MK number candidate. Although there is considerable scatter, there is clearly an increase in molecular weight with time.

Fig. 3 illustrates the increase in molecular weight with time for Pfizer clinical candidates. The time sequence is roughly the same as for the Merck candidates and the *x*-axis corresponds to the date of candidate nomination. These are candidates at a very early stage, so there are more points in this graph than for the Merck advanced candidates. The main point of Figs. 2 and 3 is that the upward trend in molecular weight is seen in clinical candidates from companies with very different research strategies. In the case of Pfizer's discovery research, there is a very heavy reliance on leads from HTS with synthetic follow-up and compound optimization using small, highly interdisciplinary approach teams. In the case of Merck's discovery research (over the time frame of this analysis), there is almost no reliance on leads from HTS. Discovery is mostly a mixture of the tech-

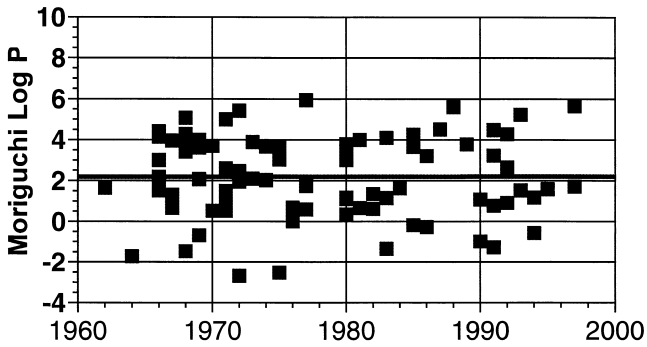

Fig. 4. No increase in lipophilicity in Merck advanced candidates.

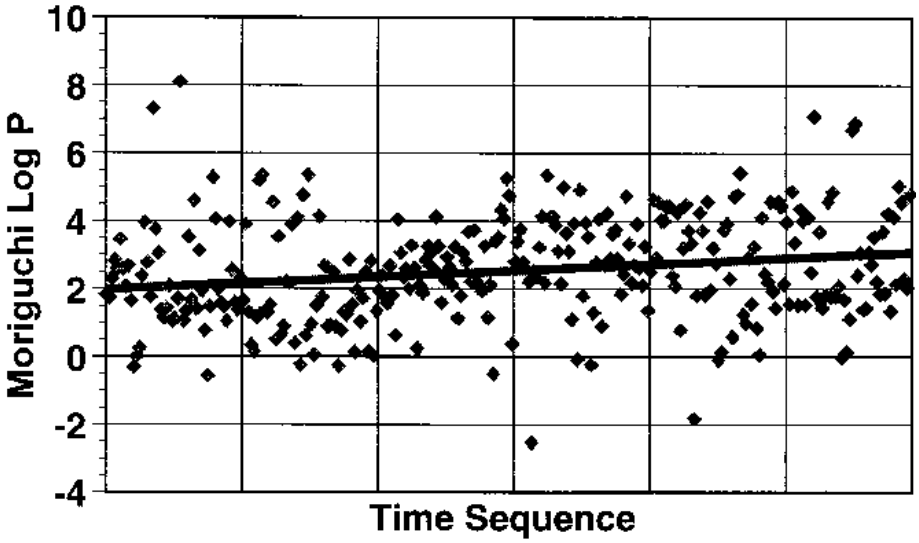

Fig. 5. Upwards lipophilicity trend with time in Pfizer candidates.

niques of "rational drug design" with large teams tackling targets that are sometimes very difficult from a physicochemical and PK/PD perspective.

7.3. The trend in lipophilicity

In contrast to molecular weight, there is no increase in lipophilicity with time in Merck advanced candidates (Fig. 4), but there is an upward lipophilicity trend with time in Pfizer early candidates (Fig. 5). Why is there no increase in lipophilicity with time among Merck candidates? HTS does not influence a "rational drug design" approach to drug discovery, and, therefore, there is no obvious trend towards increased lipophilicity. Among candidates from Pfizer's discovery research, there is an increase in lipophilicity with time. In recent years, about 50% of candidates from Pfizer have resulted from leads that were originally found by HTS. A drug discovery strategy that depends heavily on HTS will exhibit an inherent bias towards increased lipophilicity in drug leads and, to a lesser extent, in clinical candidates. The reason is based on fundamental medicinal chemistry principles. The most reliable method to increase in-vitro potency is with appropriately positioned lipophilic functionality. As a result, an HTS screen will in general select for hits that are more lipophilic (and larger). It should be noted that this occurred in Groton, even though our large screening library is overall very drug-like in calculated properties. One might anticipate an even greater trend towards higher lipophilicity in leads, if the library screened by HTS contained significant numbers of combinatorial chemistry compounds with high molecular weight or lipophilicity. In the very early days of HTS, many of our hits from HTS screens were in fact larger and more lipophilic. In a later time period, we minimized this problem by filtering HTS hits to remove those compounds with the least desirable drug-like properties.

7.4. The trend in H-bonding

The H-bond acceptor trend with time differs between the two companies, but now it is the Merck candidates that show a trend towards increasing number of H-bond acceptors (Fig. 6). This trend is what one might expect given the strong focus in "rational drug design" in recent years on peptido-mimetic like structures. Peptido-mimetics typically interact with three (or even four) peptide structural elements often through H-bonding arrays. By way of contrast there is no H-bond acceptor trend with time in Pfizer, Groton candidates (Fig. 7). The Pfizer, Groton screening library contains relatively few peptido-mimetic like structures and there is nothing in the HTS screening process to select for leads with high H-bond acceptor or donor number.

7.5. Understanding the trends

Merck and Pfizer exemplify two quite different approaches to drug discovery. Merck's approach is more based on a mixture of the techniques of "rational drug design," while Pfizer's is biased more towards empirical

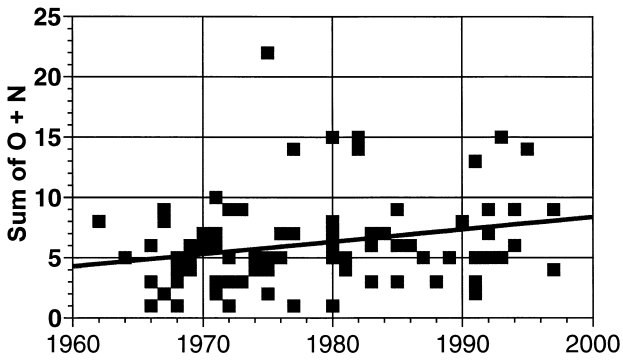

Fig. 6. Increasing H-bond acceptor trend with time in Merck candidates.

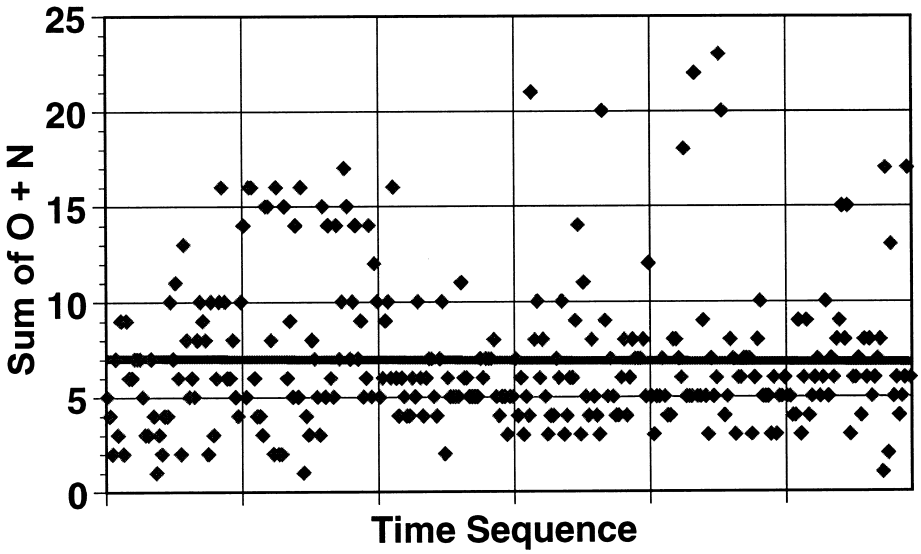

Fig. 7. No H-bond acceptor trend with time in Pfizer, Groton candidates.

HTS screening. Both approaches are successful in drug discovery, and both have led to increased molecular weight in recent years. The trend towards increased molecular weight worsens both aqueous solubility and intestinal permeability. The structure-based approach increases H-bond count for both acceptors and donors. This trend tends to worsen permeability, but has no consistent effect on solubility. For example, our extensive turbidimetric aqueous solubility screening shows that more than half of poor aqueous solubility ($\leqq 20$ μg/ml solubility in pH 7 phosphate buffer) is due to H-bonding considerations. The HTS screening-based approach tends towards producing more lipophilic leads, and could result in somewhat more lipophilic candidates (depending on the extent of property improvement in lead optimization). This trend towards increased lipophilicity, in general, worsens aqueous solubility, but has very little effect on permeability (provided the lipophilicity is not extremely high). To summarize, the approach used in lead generation leads to quite different physicochemical profiles in "rational" as opposed to HTS-based discovery approaches. In "rational" approaches, one might be working on enzyme inhibitors or peptidomimetics. Potency enhancement usually involves probing for at least three binding sites, for example in the P1, P1′, and P2 pocket. The binding pocket is often elongated. These considerations tend to lead towards larger size. H-bonding count tends to go up because one is often trying to satisfy multiple receptor H-bonding interactions. Often the natural ligand is a peptide. There is not much selection pressure for lipophilicity (log *P*) to increase because the lead generation is structure based — a lot is known about the target. It is not an empirical search for potency against a target as is HTS. Lipophilicity does not play a role in discovering the lead series as it does in the HTS-based discovery approach. Large size and increased H-bonding translates to a poorer permeability profile. HTS-based approaches tend to bias towards larger size and higher lipophilicity because these are the parameters whose increase is globally associated with an improvement of in-vitro activity. Larger size and higher lipophilicity translate to poorer aqueous solubility. Fortunately, for HTS-based approaches, this bias can be corrected by appropriate computational or experimental filtering based on a compound's physicochemical properties.

8. Conclusions

This article has focused on the themes of chemistry space and on the information content found in small data sets. Against these themes are portrayed the concepts of maximal chemical diversity in combinatorial chemistry and the differences in dimensionality between ADME and pharmacological screening. The author argues that drugs are not uniformly distributed in chemical space, and that true "maximal chemical diversity" is unobtainable in an experimental setting. The proposition is made that ADME is simpler in chemistry space so that simple rules and filters work, but that paradoxically SAR for large ADME data sets is harder to predict because of the multi-mechanism problem. An examination of the trend with time for molecular weight, H-bonding properties, and lipophilicity among Merck and Pfizer clinical candidates suggests a causal link to the method of lead generation. A trend towards higher molecular weight and higher H-bonding from a Merck-like "rational drug design" approach tends towards poorer permeability as target complexity increases. A trend towards higher molecular weight and higher lipophilicity from a Pfizer-like "HTS" approach tends towards poorer solubility as target complexity increases. Both types of approaches are successful in drug research, but the differences likely could dictate differences in the

relative importance of permeability vs. solubility screening in obtaining orally active compounds.

References

Borman, S. (2000). Combinatorial chemistry redefining the scientific method. *Chemical & Engineering News*, 53–65 (May 15).

Brennan, M. B. (2000). Drug discovery filtering out failures early in the game. *Chemical & Engineering News*, 63–73 (June 5).

Clark, D. E. (1999). Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena: 1. Prediction of intestinal absorption. *Journal of Pharmaceutical Sciences*, *88* (8), 807–814.

Curatolo, W. (1998). Physical chemical properties of oral drug candidates in the discovery and exploratory development settings. *Pharmaceutical Science & Technology Today*, *1* (9), 387–393.

Darvas, F., Dorman, G., & Papp, A. (2000). Diversity measures for enhancing ADME admissibility of combinatorial libraries. *Journal of Chemical Information and Computer Sciences*, *40* (2), 314–322.

Drews, J. (1996). Genomic sciences and the medicine of tomorrow. *Nature Biotechnology*, *14*, 1516–1518.

Drews, J. (2000). Drug discovery: a historical perspective. *Science*, *287* (5460), 1960–1963.

Lewis, D. F. V. (2000). On the recognition of mammalian microsomal cytochrome *P*450 substrates and their characteristics. Towards the prediction of human *P*450 substrate specificity and metabolism. *Biochemical Pharmacology*, *60* (3), 293–306.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *23* (1–3), 3–25.

Martin, E., & Wong, A. (2000). Sensitivity analysis and other improvements in tailored combinatorial library design. *Journal of Chemical Information and Computer Sciences*, *40* (2), 215–220.

Martin, E. J., Blaney, J. M., Siani, M. A., Spellmeyer, D. C., Wong, A. K., & Moos, W. H. (1995). Measuring diversity: experimental design of combinatorial libraries for drug discovery. *Journal of Medicinal Chemistry*, *38* (9), 1431–1436.

Pickett, S. D., McLay, I. M., & Clark, D. E. (2000). Enhancing the hit-to-lead properties of lead optimization libraries. *Journal of Chemical Information and Computer Sciences*, *40* (2), 263–272.

Sadowski, J., & Kubinyi, H. (1998). A scoring scheme for discriminating between drugs and nondrugs. *Journal of Medicinal Chemistry*, *41* (18), 3325–3329.

Shah, A. V., Walters, W. P., & Murcko, M. A. (1998). Can we learn to distinguish between "drug-like" and "nondrug-like" molecules? *Journal of Medicinal Chemistry*, *41* (18), 3314–3324.

Spencer, R. (1999). Search techniques used in identifying actives in a large HTS dataset. Book of abstracts, 217th ACS National Meeting, Anaheim, CA. Washington, DC: American Chemical Society.

Tapolczay, D., & Cush, S. (2000). Companies look to outsource chemistry. *Drug Discovery Development,* http://www.dddmag.com/ 44–48 (May 2000).

Wagener, M., & Van Geerestein, V. J. (2000). Potential drugs and nondrugs: prediction and identification of important structural features. *Journal of Chemical Information and Computer Sciences*, *40* (2), 280–292.

Wintner, E. A., & Moallemi, C. C. (2000). Quantized surface complementarity diversity (QSCD): a model based on small molecule–target complementarity. *Journal of Medicinal Chemistry*, *43* (10), 1993–2006.