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Nonleadlikeness and leadlikeness in biochemical screening

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Biochemical assays have largely supplanted functional biological assays as drug screening tools in the early stages of drug discovery. The de-selection of compounds that are 'nonleadlike' binders (and bonders) and the proactive selection of those compounds that are 'leadlike' in their binding to the target are vital components of the screening effort. The physiochemical properties of leadlikeness and the surprising differences between those properties and the now classical definitions of druglikeness are becoming apparent.

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▼ Biochemical assays have largely supplanted functional biological assays as primary tier drug screening tools. However, the widespread misuse and misapplication of biochemical assays has resulted in a legacy of failure and compound attrition that requires the urgent attention of drug discovery scientists. Biochemical assays are far from biological systems. They are best described as ultra-sensitive molecular interaction assays, well-suited to generate structure–activity data in a leadlike series of compounds, but vulnerable to the artifact effects of nonleadlike compounds.

Enlightenment in drug discovery

In the recent medicinal chemistry literature Pharma scientists have offered insights into 'nondruglikeness' and 'druglikeness', doing well to define the physiochemical properties that determine the key issues of drug development such as solubility, membrane permeability and oral absorption. This important literature has been widely cited and reviewed and will not be covered in detail here [1–4]. This review will attempt to define the physiochemical properties of nonleadlike compounds and leadlike compounds, and to emphasize the central importance of these properties in the first stage of drug discovery. Special attention will be paid to the significant and important differences in the physiochemical properties that define leadlikeness as compared with those properties that define druglikeness. Much content will attempt to expose classes of nonleadlike compounds that result in artifact assay data.

Nonleadlikeness

The most desirable binding characteristics of a good leadlike compound to a protein target in a biochemical screen might be said to include the following:

- non-covalent high affinity ligand binding;
- reversible, time-independent competitive binding;
- tractability in structure–activity relationship (SAR) of a series of structural analogues of the binder.

These requirements depend largely on the physiochemical properties of the binder. An understanding of the physiochemical properties of leadlikeness has emerged largely from the increasing body of literature that has attempted to define nonleadlikeness. Many nonleadlike compounds are identifiable on the basis of structural class, functional group class, degree of ionic functionality and occurrence of 'warhead' chelators. It is imperative that drug discovery scientists distinguish between small molecules that bind to their protein targets in leadlike ways (for example non-covalent binding, H-bonding, hydrophobic binding and monoionic bonding), and those false binders (and bonders) that interact with their protein targets in nonleadlike ways (for example covalent bonding, chelate bonding and polyionic bonding).

Usual suspects

Nonleadlike compounds have been previously identified in the literature as reactive false positives [2], 'promiscuous inhibitors' [5], and characterized as 'frequent hitter' compounds [6].

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It is important at this time for drug discovery scientists to understand the structural classes and the mechanisms of nonleadlike false positives and, further, to overturn the bad dogma that rationalizes the development of nonleadlike compounds.

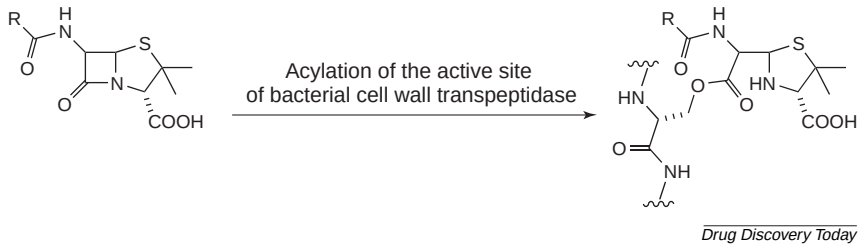


Figure 1. Industry dogma concerning penicillin has been mistakenly used to rationalize the development of reactive 'suicide inhibitor' agents when employing biochemical screens [7].

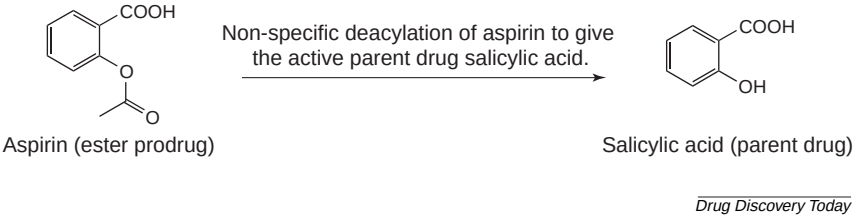


Figure 2. Industry dogma concerning aspirin has been mistakenly used to rationalize the development of reactive 'magic bullet' agents when employing biochemical screens.

Bad dogma!

Classical dogma from decades of medicinal chemistry has been misused to justify 'suicide inhibitor' approaches to the biochemical screening of human targets. For example, although penicillin and the many β-lactam antibiotics work by covalent modification of the bacterial cell wall transpeptidase (Fig. 1) [7], it is a misconception that this covalent suicide inhibitor approach might be applied generally to human enzymes and receptors studied in biochemical assays. The actions of these antibiotics (and the alkylating covalent antineoplastic agents) were discovered using biological assays and selective cytotoxicity assays, not by using biochemical assays. In biochemical assays the covalent-acting alkylating and acylating agents exhibit time-dependent covalent false positives. The inhibitor 'activity' being observed is actually a titration reaction resulting in protein poisoning. The false positive readout is reflective of chemical reaction kinetics. The covalent-acting agents are useless false positives in biochemical assays. They are nonleadlike and even 'nonhitlike'.

More bad dogma!

A second example of bad dogma used to justify covalent-acting reactive lead compounds is the example of aspirin as an anti-inflammatory or analgesic agent, which works by the 'magic bullet' acylation of the cyclooxygenase (COX) enzymes. This is untrue. Aspirin was developed in 1899 by the Bayer Company as a prodrug form of salicylate (Fig. 2). The intention of the prodrug approach was to attenuate the acidity of salicylate to reduce the nausea experienced by some patients on the oral administration of salicylate. In reality, aspirin, once absorbed through the gut and intestine, is non-specifically cleaved to produce salicylate which is the non-covalent ligand inhibitor of the COX enzymes. Aspirin is uninvolved. Clearly, the 'acylating agent hypothesis' which has surrounded aspirin is bad dogma. In fact, Nobel laureate John R. Vane has addressed this issue. It was his comparative studies of aspirin and salicylate using cell-free extracts in 1971 that initiated the hypothesis of the acylation mechanism of aspirin [8]. Vane himself retracted the acylation hypothesis in two subsequent papers, giving his support instead to the prodrug hypothesis based on the clinical pharmacokinetic data [9,10].

The initial cell-free extract data on aspirin was probably one of the first *in vitro* false positives caused by a reactive agent. Reactive prodrugs and protein-reactive compounds in general should not be studied in biochemical assays. Only a parent drug or a chemically stable ligand will give meaningful data *in vitro*.

Dead dogma

In summary, covalent-acting drugs can be effective as antibiotics and as anti-neoplastic agents when developed using biological assays. The reactive 'magic bullet' covalent inhibitor approach cannot be extended to human enzymes and receptors studied biochemically. Alkylating agents, acylating agents, prodrugs and covalent inhibitors in general are simply protein-reactive time-dependent false positives in biochemical assays.

The protein-reactive electrophilic false positives

Compounds containing electrophilic functional groups are the most common protein-reactive covalent-acting false

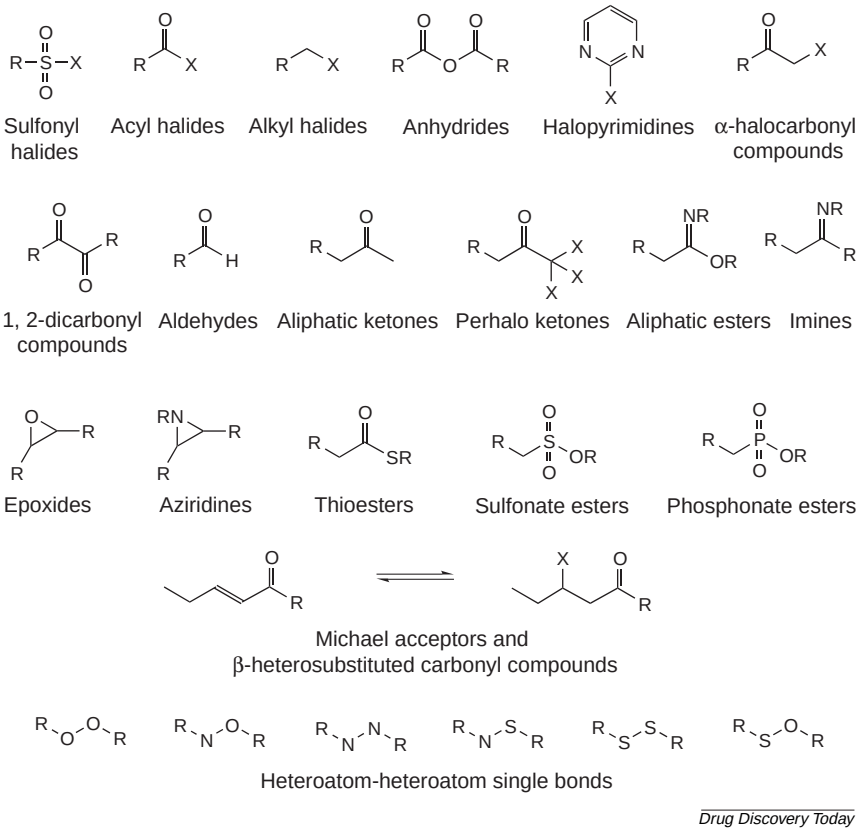


Figure 3. An abridged list of the functional groups responsible for electrophilic protein-reactive false positives [2].

positives in biochemical assays. An abridged summary of these commonly occurring electrophilic functional groups has been published (Fig. 3) [2]. This provides a useful guide but it is non-comprehensive and in the final analysis we need to depend on the good judgement of a medicinal chemist and a molecular pharmacologist. As a 'rule of thumb' a compound should be characterized as a false positive if it exhibits chemical reactivity over the time course and under the conditions of a biochemical assay. Generally, electrophilic false positives are prone to decomposition by solvolysis or hydrolysis and are characteristically reactive towards biological nucleophiles including target protein, serum protein and glutathione.

Furthermore, a structure–reactivity relationship (SRR) results where observed 'potency' is dependent on electrophilic functional group reactivity. An SRR is certainly indicative of a covalent-acting false positive (Fig. 4) [2]. There are hundreds of papers and patents that describe medicinal chemistry programs based on protein-reactive covalent-acting electrophilic false positives, all of which describe SRR not SAR. These programs are usually enzyme inhibitor programs touted as 'mechanism-based' and 'rational inhibitor design' approaches. The consistent failure of these covalent-acting electrophilic inhibitor programs has finally come under scrutiny [11], and the overall viability of the approach is now in question [12,13].

An important point to be made here is that a protein-reactive covalent-acting electrophilic false positive might easily pass the established druglikeness filters. The so-called 'rule of five' [1] considers the important physiochemical properties that impact drug development, but makes no comment on the chemical reactivity that might lead to *in vitro* false positives and overall nonleadlikeness in biochemical screening at the earliest stages of discovery.

The 'promiscuous inhibitors'

An excellent recent paper by Shoichet has described classes of compounds that when studied as inhibitor 'hits' in enzyme screening programs appear to be nondruglike and promiscuous in that they act noncompetitively, show no meaningful SAR and little target selectivity (Table 1) [5]. Industry efforts to optimize and subsequently develop these compounds in various programs have consistently met with failure, calling into question the nature of the 'activity' observed in the assay. To study this phenomenon, 45 structurally diverse promiscuous inhibitors that had previously been reported as inhibitors of various enzyme targets were tested against model enzymes. Time-dependent but reversible inhibition was observed across the assays. The inhibition was dramatically attenuated by additives such as albumin, guanadinium or urea. Furthermore, increasing the concentration of the target enzymes gradually eliminated the inhibitory effect of these promiscuous compounds. It was proposed that the active form of these promiscuous inhibitors might be an aggregate of many individual molecules. Light scattering and electron microscopy experiments observed aggregate particles of 30–400 nm diameter that appeared to be responsible for the inhibitory 'activity' of the promiscuous inhibitors. Among the structures in Table 1, an experienced medicinal chemist will quickly recognize the usual suspects. Compounds such as quercetin, the sulfonate

dyes and the various lipophilics appear again and again in screening hit lists. Polyphenols, polyionics, extended lipophiles and extended conjugation are among the common structural and functional group motifs of these aggregate-forming molecules.

One probable contributor to the observation of aggregates in biochemical assays is our use of aqueous protein-free, membrane-free media. A great many of the organic compounds found in our screening collections have little or no water solubility, and so it is not surprising that they would likely form aggregates in this artificial environment and, particularly, over increasing concentration ranges typical of IC_{50} studies. Such a significant technical difficulty demands further study of the co-solvents (DMSO, etc.) and the additives (albumin, lipid, glutathione, DTT, etc.) that molecular pharmacologists might employ to minimize insolubility and aggregation effects which lead to artifact *in vitro* data.

The 'frequent hitters'

Schneider recently reported the identification of 'frequent hitters' [6] employing a virtual screening approach [14]. Frequent hitters are compounds that show up as hits in many different assays. Two possible reasons for the artifactual behavior of a frequent hitter have been suggested: (i) the activity of the compound is not specific for the target ('promiscuous inhibitor'); and (ii) the compound perturbs the assay or detection method; for example colored or fluorescent molecules. In either case these compounds exhibit false *in vitro* data and offer no value as leads for medicinal chemistry. A virtual screening method to identify potential frequent hitters in several compound databases [the Available Chemicals Directory (ACD), the World Drug Index (WDI) and the MedChem Database] has been described. Fractions of 'druglike' compounds and fractions of frequent hitters in each of these databases are reported. An interesting observation resulting from the virtual screening of frequent hitters described above was the identification of certain known drug molecules as frequent hitter-type compounds (Fig. 5). This is described in the paper as a 'twilight zone' in the frequent hitter definition where known drugs might act as artifact-generating agents in biochemical screens against other targets. Polyaromatic, polyphenolic, highly lipophilic and highly conjugated compounds are represented in this group.

The authors remind us that the term 'frequent hitter' is not a synonym for 'undesired structure'. This subtle point is truly important and deserves further discussion. Drug databases are full of known drug compounds that have undesirable nonleadlike properties and promiscuous inhibitor or frequent hitter characteristics that cause artifact

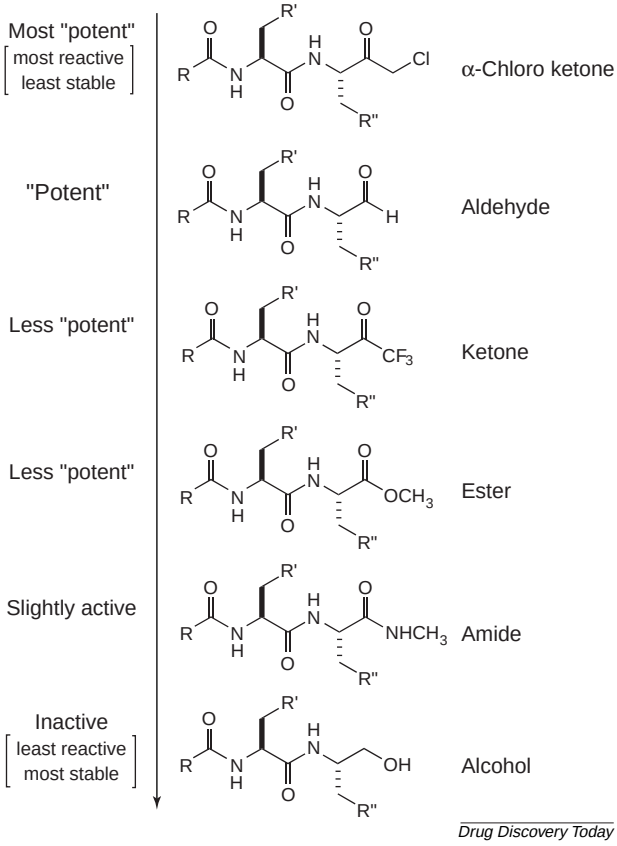


Figure 4. The fingerprints of the protein-reactive false positive: the structure–reactivity relationship (SRR) [2].

data in biochemical screens. Furthermore, many known drugs are chemically reactive (antineoplastic alkylators, reactive antibiotics, prodrugs, etc.), exceedingly lipophilic (steroids, terpenes, etc.), or in some way or another nonleadlike (cyclosporin, taxol, FK-506, vancomycin, etc.) by the definitions forwarded in this review. This is a reflection of the fact that most drugs found in the compiled databases were classically discovered and developed using biological assays, selective cytotoxicity assays and animal models of disease, not using biochemical assays. This dichotomy underscores the reasons that the definition of leadlikeness in the context of biochemical screens will differ significantly from the current definitions of druglikeness applied in biological systems. Leadlikeness and druglikeness are complementary and should be applied separately in the arenas of drug discovery and drug development, respectively.

The 'warhead' agents

In addition to the electrophilic false positives there are other reactive 'warhead' functional groups that are argued

Table 1. The promiscuous inhibitors [see 5]

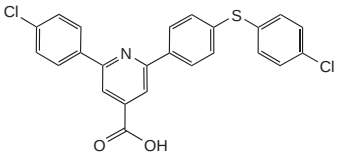
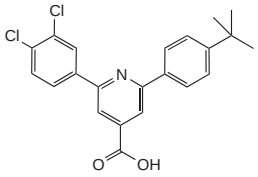
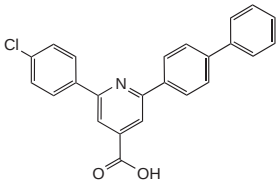
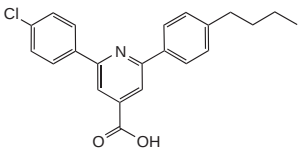
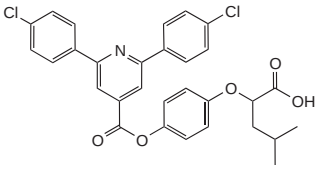
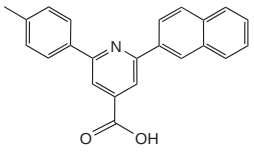
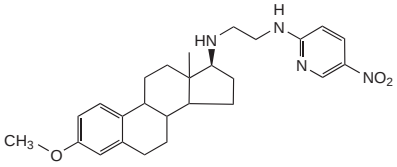
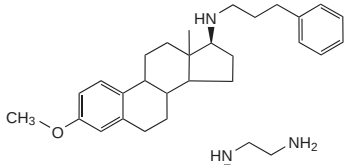
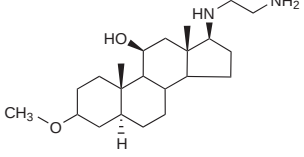
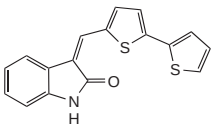
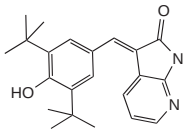
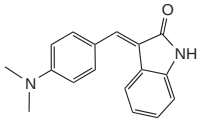
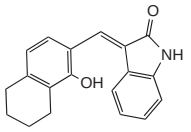
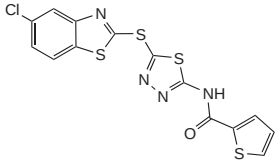
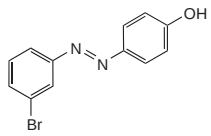
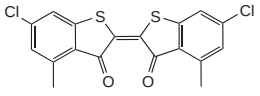
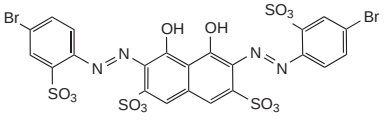
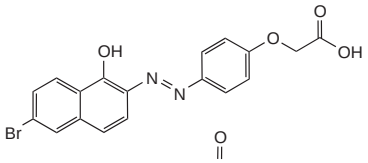
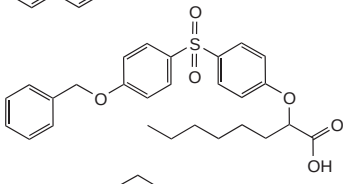
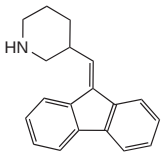
Structure	IC_{50} vs.β–lactamas (μM)	↓ IC_{50} with Incubation	↑ IC_{50} vs. 10x β–lactamase	IC_{50} vs. chymo. (μM)	DLS		
					Conc. (μM)	Intensity (kcps)	Diameter (nm)
	2	12-fold	4-fold	2	50	54.3 ± 5.5	100.4 ± 5.1
	4	> 50-fold	12-fold	13	50	24.4 ± 2.6	97.1 ± 2.5
	5	35-fold	10-fold	8	80[a]	19.2 ± 4.7	171.8 ± 35.8
	8	24-fold	20-fold	15	50	11.1 ± 2.4	106.9 ± 6.3
	15	> 50-fold	5-fold	3	50	30.4 ± 2.5	108.5 ± 5.1
	50	> 50-fold	4-fold	50	500[a]	13.5 ± 3.4	201.2 ± 44.4
	5	14-fold	> 50-fold	13	40[a]	20.2 ± 0.8	381.0 ± 30.4
	5	> 50-fold	> 50-fold	200	100	8.0 ± 0.6	297.4 ± 19.9
	10	4-fold	4-fold	40	100	10.0 ± 1.9	N.D.

Table 1. Continued

Structure	IC_{50} vs.β–lactamas (μM)	↓ IC_{50} with Incubation	↑ IC_{50} vs. 10x β–lactamase	IC_{50} vs. chymo. (μM)	DLS		
					Conc. (μM)	Intensity (kcps)	Diameter (nm)
	2	13-fold	8-fold	15	20	12.6 ± 4.3	N.D.
	4	> 50-fold	6-fold	10	10 [a]	14.2 ± 1.1	140.9 ± 9.0
	10	> 50-fold	3-fold	30	30 [a]	51.2 ± 7.2	288.6 ± 21.8
	15	3-fold	6-fold	40	40	14.0 ± 5.9	N.D.
	2	> 50-fold	3-fold	15	15	17.5 ± 1.8	172.5 ± 9.2
	15	5-fold	> 50-fold	220	500	10.5 ± 2.5	184.4 ± 25.6
	3	15-fold	3-fold	15	20	10.0 ± 0.3	205.8 ± 5.7
	80	2-fold	> 50-fold	110	—[b]	—[b]	—[b]
	30	> 50-fold	8-fold	80	20	19.6 ± 2.7	N.D.
	3	7-fold	9-fold	13	500[a]	3.0 ± 0.4	68.2 ± 7.6
	200	2-fold	> 50-fold	700	100	16.7 ± 1.2	221.0 ± 4.2

[a]DLS experiments in 5 mM KP_i; all others in 50 mM KP_i. [b]Compound absorbs significantly at 514.4 nm. Laser power was comparable in all experiments. chymo., chymotrypsin; N.D., not determined. Abbreviations: DLS, dynamic light scattering; kcps, kilocounts per second.

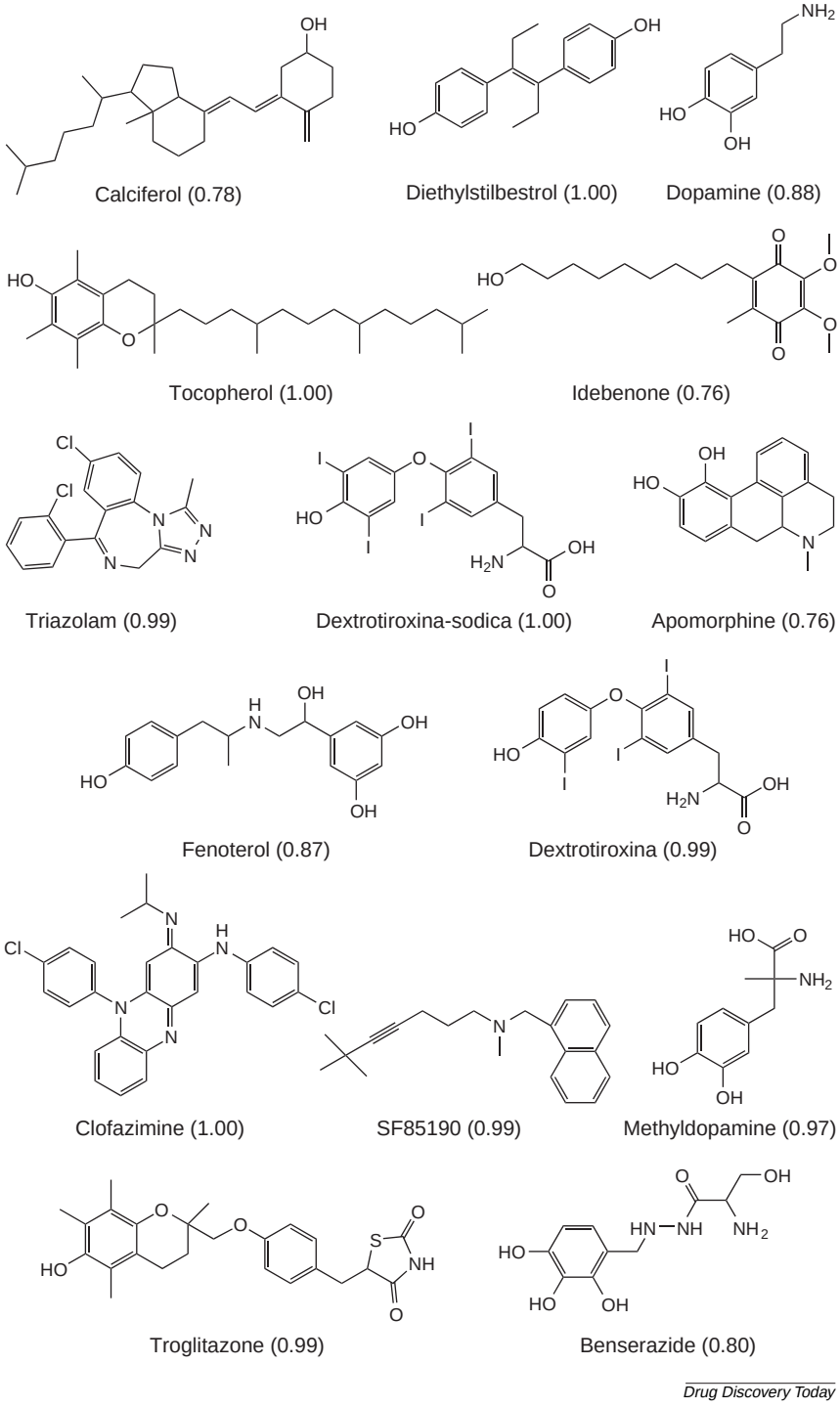


Figure 5. Structures of known drugs identified as 'frequent hitters' in biochemical screens and their prediction scores [6]. Reprinted, with permission, from the American Chemical Society.

to be non-covalent and reversible binders. Regardless of the debate over such subtle differences between binding and bonding at a protein target, these warhead agents exhibit SRR-like profiles and have resulted in extremely high failure rates in drug discovery and drug development. It is indeed debatable whether or not these chelator and polyionic 'warheads' are reactive in every sense of the word. However, it is time to include such classes of compounds in our analysis of nonleadlikeness if only to begin the discussion on whether or not warhead approaches yield relevant SAR in biochemical assays. It is altogether possible that the powerful interactions of warhead-type agents with their target proteins essentially constitute chemical reactivity over the time course and under the conditions of a biochemical assay and, thus, constitute a false positive. In any case, it is most likely that warhead agents will not appear on industry lists of leadlike and druglike compounds in the future. Examples of such warhead approaches include hydroxamate chelator binding (or bonding) to the metal ion in a matrix metalloproteinase assay, and the interactions of a polyionic phosphorylated substrate with the phosphoryl binding site in an SH2/SH3 domain assay. Although the logic and science of these inhibitor approaches is perfectly plausible, it is likely that the *in vitro* SAR data generated by warhead inhibitors in these assays is largely driven by chemical reactivity, not biological activity. The powerful interactions between a warhead and its target likely create an artificial situation whereby the observed relative 'potency' between analogues is actually a measure of relative reactivity resulting in an SRR. A summary of warhead agents has previously been presented [11](Fig. 6).

Leadlike molecules and leadlike binding

In summary, to be leadlike, compounds should generate meaningful SAR in biochemical screens, be chemically stable toward protein and not be the 'promiscuous inhibitor', 'frequent hitter' or 'warhead' compounds described here.

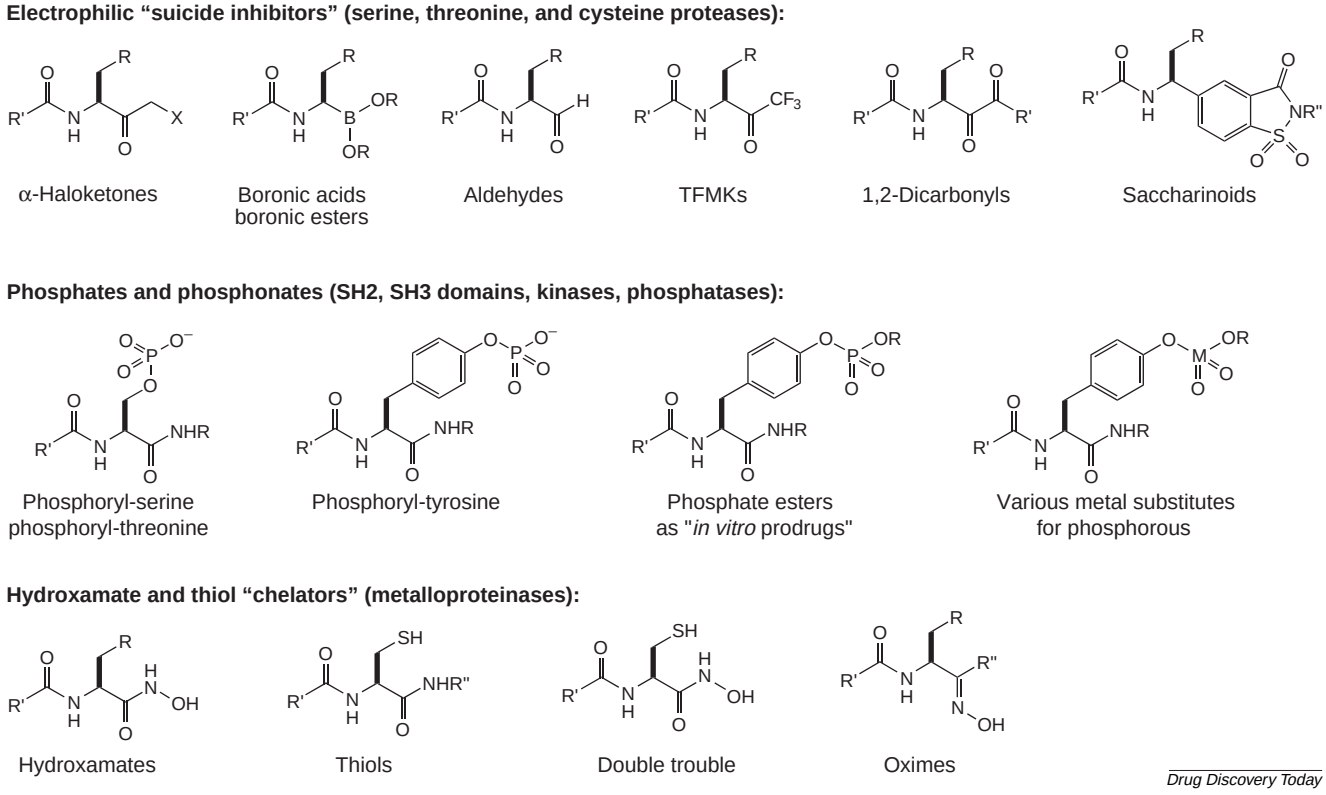


Figure 6. The commonly employed warheads responsible for artifact data in biochemical screens [11].

Biological assay tools versus biochemical assay tools

Future efforts to discover new chemically reactive drugs, large molecule antibiotics and reactive anti-neoplastics will require classical approaches employing biological assays such as selective cytotoxicity assays and disease models, not biochemical assays. The choice of appropriately employing biological assay tools versus biochemical assay tools depending on target class and on compound class for a given drug discovery project is a complex but vitally important decision that the pharmaceutical industry has yet to thoughtfully come to terms with.

Leadlikeness

The preceding discussion suggests that the evolving literature definition of 'leadlikeness' has depended significantly on the separate and complementary evolution of the definition of 'nonleadlikeness'. It would seem that 'likeness' filters are most practically defined by the implementation of more easily manageable 'nonlikeness' filters when dealing with the infinite terrain of chemical structural space.

Recent contributions to the leadlikeness literature suggest that the physiochemical properties that define druglike compounds, although well-suited for drug development issues such as oral absorption and bioavailability, are strikingly different from the physiochemical properties of compounds which should be considered leadlike in the early stages of drug discovery programs that employ biochemical screens. An important paper from Oprea and the AstraZeneca group addressed the design of leadlike combinatorial libraries and suggested that leads suitable for further optimization by medicinal chemistry are most likely to be relatively polar, low molecular weight (MW = 200–350) and of relatively low lipophilicity (clogP <1.0–3.0) [15]. The authors point out that when beginning from a tractable low MW lead molecule, subsequent optimization by medicinal chemistry increasing potency and selectivity will likely increase MW and lipophilicity to values on the order of the druglikeness parameters. In contrast, attempted optimization of a relatively high MW lipophilic lead compound is notoriously more difficult and often results in the generation of 'flat SAR' across series of analogues. In the words of the authors: 'Once a small polar molecule with affinity at micromolar levels has been found, more focused libraries can rapidly improve on it. This is often achieved by the introduction of lipophilic groups that simultaneously improve the affinity and the

Box 1. The properties of leadlikeness as compared with the properties of druglikeness

Leadlikeness[a]

Physiochemical properties typical of good lead compounds in target-driven drug discovery programs that employ biochemical assays [a,b]:

- Molecular weight (MW) = 200–350 (optimization might add ca. 100–200)
- clogP <1.0–3.0 (optimization might increase by 1–2 log units)
- Single charge present (secondary or tertiary amine preferred)
- Importantly, exclude chemically reactive functional groups [c], 'promiscuous inhibitors' [d], 'frequent hitters' [e] and warheads [f]
- Non-substrate peptides are suitable.

[a]Many known drugs are exceedingly lipophilic (steroids, terpenes, etc.), chemically reactive (antineoplastic alkylators, β-lactam antibiotics, prodrugs, etc.), and/or of relatively high MW (cyclosporin, taxol, FK-506, vancomycin, etc.). These agents are exempt from any analysis of leadlikeness because they were discovered and developed using biological assays not biochemical assays.

Druglikeness

Physiochemical properties that improve probability of success in drug development by addressing issues of absorption and bioavailability [g]:

- Presume discovery phase filtering of chemically reactive functional groups [c]; warheads [f]; 'promiscuous inhibitors' [d]; and 'frequent hitters' [e]
- MW <500
- clogP <5
- H-bond donors <5
- Sum of N and O (H-bond acceptors) <10
- Peptides unsuitable
- Polar surface area consideration ≤140A^2 [h–l]
- Number of rotatable bonds consideration ≤10 [l].

References

a Teague, S.J. *et al.* (1999) The design of leadlike combinatorial libraries. *Angew. Chem. Int. Ed. Engl.* 38, 3743–3748

b Oprea, T.I. *et al.* (2001) Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comput. Sci.* 41, 1308–1315

c Rishton, G.M. (1997) Reactive compounds and *in vitro* false positives in HTS. *Drug Discov. Today* 2, 382–384

d McGovern, S.L. *et al.* (2002) A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. *J. Med. Chem.* 45, 1712–1722

e Roche, O. *et al.* (2002) Development of a virtual screening method for identification of 'frequent hitters' in compound libraries. *J. Med. Chem.* 45, 137–142

f Rishton, G.M. (1999) *Reactive Compounds and In Vitro False Positives*. Presented for Vision in Business, Integrated Drug Discovery, Geneva, Switzerland

g 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

h Palm, K. *et al.* (1997) Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm. Res.* 14, 568–571

i Clark, D.E. (1999) Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. *J. Pharm. Sci.* 88, 807–814

j Ertl, P. *et al.* (2000) Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.* 43, 3714–3717

k Yoshida, F. and Topliss, J.G. (2000) QSAR model for drug human oral bioavailability. *J. Med. Chem.* 43, 2575–2585

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pharmacokinetic properties of these molecules. However, if libraries of molecules of druglike size (relatively higher MW) are used at the outset, this opportunity is lost [15].'

These observations would suggest that combinatorial library design, and the composition of screening collections in general, should emphasize leadlikeness (as opposed to druglikeness) by incorporating low MW, relatively polar and densely functionalized molecules.

The definition of leadlikeness

On examination of the body of work that has addressed the issue of leadlikeness, it becomes apparent that it arises largely through a filtering process enabled by the definition of nonleadlikeness. It also becomes apparent that definitions of druglikeness are strikingly different from definitions of leadlikeness. Both definitions serve their own ends; druglikeness serving to identify compounds suitable for drug development and product candidacy, and leadlikeness serving to identify compounds that are tractable for optimization by medicinal chemistry. Leadlike compounds bind appropriately to their protein targets in biochemical assays and subsequently enable viable SAR development by medicinal chemistry.

Leadlikeness versus druglikeness

A summary of the published leadlikeness parameters is provided (Box 1) and offered in contrast to the druglikeness parameters. The leadlikeness summary is based primarily on the parameters suggested by Oprea and the AstraZeneca group [15,16]. I have added information to include the artifact false positives described in this review, commentary on peptide leads and a footnote addressing the many apparent exceptions to the leadlikeness criteria.

The now classical druglikeness parameters are derived mainly from the contributions of Lipinski and the Pfizer group [1], supplemented with more recent contributions citing polar surface area [17–19] and rotatable bond considerations [20]. Druglikeness definitions need also to operate under the presumption of discovery phase filtering of the artifact-generating false positives described above. Finally, a commentary on the nondruglikness of peptides has been added.

Yes, peptides are leadlike

The classification of peptides as leadlike deserves further discussion. Peptides have been poor performers in drug development. However, peptides should be considered as valuable leadlike compounds when used in biochemical assays in early discovery for the generation of SAR. Many screening and drug design programs have benefited significantly from peptide lead compounds and some have led to approved drugs, such as the ACE inhibitors and the HIV protease inhibitors. In fact, peptides meet the relatively low MW and relatively high polarity leadlikeness criteria uniquely. The densely functionalized and structurally diverse peptides are also well-suited for lead compound generation. The important caveat to the study of peptides in biochemical screens is that the peptides employed should not be substrates for the enzyme being studied. If proteolysis is occurring under the conditions of the assay then the data observed will be reflective of substrate saturation, not ligand inhibition. In such cases the scissile bond in the peptide backbone needs to be replaced as a non-cleavable surrogate such as a statine or a reduced amide. Further, the subsequent challenge of peptidomimetic chemistry in developing a product candidate with suitable druglike properties is formidable. Peptidomimetic chemistry is certainly a viable approach but tends to be time- and resource-intensive and remains as much an art as a science.

Moving forward and reducing compound attrition

Modern drug discovery efforts that employ biochemical assays have enjoyed significant successes, for example, in ACE inhibition, HIV protease inhibition and in COX-2 inhibition. However, one reason for the high frequency of compound attrition in the pharmaceutical industry over the past 15 years has been in the misuse of biochemical assays in such a way so as to pursue nonleadlike agents that generate artifact false positive data in these sensitive assays. Clearly, early attempts to establish criteria filters for nondruglikeness and druglikeness were in some respects unsuitable for the discovery phase selection of leadlike compounds and the de-selection of nonleadlike compounds in biochemical screening programs. Druglikeness criteria and leadlikeness criteria will be best applied separately in the context of development and discovery, respectively.

As we turn our collective attention to the identification of quality lead compounds that will enable the development of quality product candidates, we must recognize the scope and limitations of our assay tools and detection technologies. Nonleadlike compounds are useless artifact-generating agents in our biochemical screens. We should discard these false positives at the earliest possible stage. We should seek to populate our screening collections with appropriate leadlike compounds and take care in compound acquisition to purchase only leadlike compounds for our screening programs. Vendors worldwide should gain an understanding of these concepts so that the commercial collections will evolve to contain ever more leadlike compounds and fewer of the artifact false positives that have been reviewed here. Now, more than ever, it becomes important for medicinal chemists to apply their insights into the structure and reactivity of organic molecules and to help deliver quality compounds for drug development. It is imperative that chemists and molecular pharmacologists understand the subtle differences between ligand binding and time-dependent reagent bonding or artifact binding in a biochemical assay. This insight, applied along with the nonleadlikeness and leadlikeness criteria properly applied in the context of either the drug discovery or the drug development environment, will enable us to significantly decrease the high rate of compound attrition currently plaguing our industry.

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