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Perspective

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Where Do Recent Small Molecule Clinical Development Candidates Come From?

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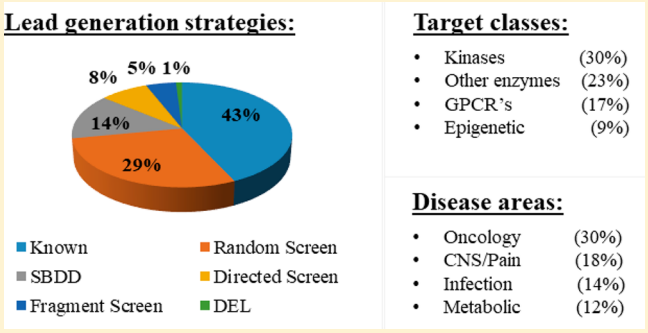
Supporting Information

ABSTRACT: An analysis of 66 published clinical candidates from *Journal of Medicinal Chemistry* has been conducted to shed light on which lead generation strategies are most frequently employed in identifying drug candidates. The most frequent lead generation strategy (producing a drug candidate) was based on starting points derived from previously known compounds (43%) followed by random high throughput screening (29%). The remainder of approaches included focused screening, structure-based drug design (SBDD), fragment-based lead generation (FBLG), and DNA-encoded library screening (DEL). An analysis of physicochemical properties on the hit-to-clinical pairs shows an average increase in molecular weight (ΔMW = +85) but no change in lipophilicity (ΔclogP = −0.2), although exceptions are noted. The majority (>50%) of clinical candidates were found to be structurally very different from their starting point and were more complex. Finally, several reports of noncovalent scaffolds modified by a covalent warhead using SBDD approaches are discussed.



INTRODUCTION

One of the most important decisions a drug discovery team can make is the choice of lead generation strategy to identify chemical starting points.[1−3] Traditional lead generation strategies have been random high throughput screening (HTS),[4] fragment-based lead generation (FBLG),[5] structure-based drug design (SBDD),[6] utilization of known literature such as fast-follower or knowledge-based programs,[7] and more recently DNA-encoded library screening (DEL).[8] The choice of which strategy to employ is dependent on multiple factors such as the technical demands for each approach, overall costs, and access to appropriate screening libraries or chemical starting points for each technology. Decisions and factors related to which biological assays to be used will dictate the direction of the program. For example, is a specific mode-of-action (MoA) desired? Is a biochemical screen or a cell-based screen or both considered to be required? What is the assay throughput? Can the inherent low signal-to-noise ratio in a large-scale HTS be justified, or should a higher quality but lower throughput screen be opted for? It should also be noted that where the technology allows, and if the resources are available, multiple lead generation strategies can be run together in an integrated fashion, termed "integrated lead generation". The decision to start a lead generation campaign sets the wheels in motion toward unknown chemical starting points that may or may not lead to a successful clinical candidate. The quality of the starting point influences the way forward since a high-quality hit will inevitably shorten the discovery phases. Conversely, if the initial hit structure is low-quality (e.g., poor physical properties and pharmacokinetics, the presence of structural motifs known to cause problems, off-target liabilities, and, of course, poor potency), a long and complex multiparameter optimization will be required. Given the competitive nature of the pharmaceutical industry, many biological targets are being pursued in parallel by different groups, perhaps even using the same lead generation strategy or even working on the same chemical starting points. Given the endless possibilities of molecules to make and the fact that drug discovery is a multiparameter optimization process colored by subjectivity, the odds that two different research groups will end up with the same final compound is negligible. As described recently by Murcko, great medicinal chemists know the competitive landscape but "don't panic over IP" since these endless possibilities of what can be made are not a frequent deterrent when embarking on a hit-to-lead program.[9] However, broad patent claims can influence the freedom to operate and are a factor of consideration for selecting a scaffold for lead generation.

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A literature study was undertaken to understand which approaches and the types of hit molecules associated with the delivery of clinical candidates. To obtain an understanding on structural modifications required when optimizing a hit to clinical candidate, molecular properties were compared. For example, were there significant discrepancies in physicochemical properties such as molecular weight (MW) and lipophilicity? Were any clinical candidates derived from just a one or two atom change from the lead starting point? Or do most clinical candidates reflect such significant lead optimization that they would be structurally unrecognizable from the initial hit? The aim of this study is to help address these types of questions and gain a better understanding of emerging lead generation strategies and possible impact on future drug discovery programs.

METHODS

The examples and data used in this analysis of hit-to-clinical pairs were generated by manually extracting case studies from the *Journal of Medicinal Chemistry* between 2016 and 2017. Efforts were made to include as many reported clinical candidates as possible in this two-year time span. However, a few caveats should be noted. First, the definition of a clinical candidate is likely to differ between organizations. Second, no effort was made to distinguish between examples that just entered clinical development versus those that had achieved a first-in-human (FIH) or eventually obtained regulatory approval. Third, once a clinical candidate was identified, the original hit that provided the genesis of the chemistry campaign was determined; however, this was not always possible (i.e., information not available). The lead generation method was assigned to one of six categories (see Figure 1 and Table 1), based on the descriptions used in the original manuscript. The categories were defined as the following.

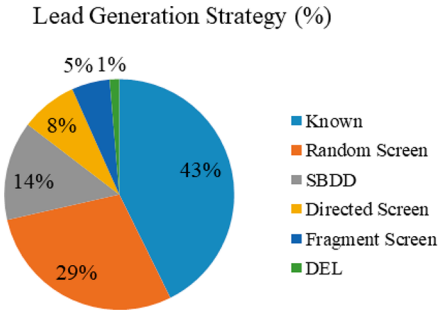

Figure 1. Distributions of the six sources of lead generation strategies: Known compounds, Random screen or high throughput screen (HTS), Fragment screen or Fragment based lead generation (FBLG), DNA Encoded Libraries (DEL), Structure based drug design (SBDD), Directed Screen for the 66 hit-to-candidate pairs in *J. Med. Chem.* 2016–2017.

(1) Random screen or high throughput screen (HTS): screening of small-molecules through collections of random compounds that can be large compound databases (10^5–10^6) for a large pharmaceutical organization but may also be smaller sets.
(2) Directed screen: screening of smaller sets of compounds that are selected based on prior knowledge of the target or chemical class. Also known as focused, targeted, or biased screening.
(3) Structure-based drug design (SBDD): in silico screening of compound collections, including the use of the target protein 3D structure, in this context used to generate novel chemical equity in a hit-finding campaign. Note that in general in silico project support in driving a hit-to-lead program from random screening efforts was not counted in this regard as "hit-finding".
(4) Fragment screen or Fragment based lead generation (FBLG): typically libraries with a few thousand compounds of low molecular weights (<200 Da), screened at high concentrations.
(5) DNA-encoded library screening (DEL): screening of very large collections (typically >10^8) of small molecule compounds, using a technology that involves the conjugation of chemical compounds to DNA fragments.
(6) Known compounds: project started based on a prior disclosure of an active compound, endogenous ligand or previous program.

If multiple lead-generation methods were used, those were assigned as multiple entries. It was observed that many programs used integrated SBDD in the context of advancing hit or lead compounds to candidate drugs. These examples were not counted as the initial hit-finding source. Structure-based drug design (SBDD) was consequently only assigned to those projects where it was used to identify novel hit starting points. The hit-to-clinical pairs were analyzed for their target class and disease area distribution. The pairs of molecules were evaluated against calculated physicochemical properties widely used in medicinal chemistry (clogP, log *D*, molecular weight, and the number of rotatable bonds).[10] Similarities based on maximum common substructures were calculated as described by Boström et al.[11] and molecular complexity according to the seminal description by Bertz.[12]

RESULTS

The 66 hit-to-clinical pairs were collected and summarized in Table 1. For each example, the "hit" or advanced lead is shown along with the clinical compound as well as the disease area and lead generation approach used. Overall, the most widely used lead generation approach was based upon utilization of a previously known compound ("Known") (Figure 1). See Discussion section for specific examples. A little less than half (43%) of the clinical candidates described were derived from known starting points. This was followed by screening approaches, subdivided into random screening (29%), focused screening (8%), FBLG (5%), and DNA-encoded library screening (1%). Structure based drug design was used as an integral part of the hit-finding strategy for 14% of the cases examined in this study.

The target class and disease area distribution for hit-to-clinical pairs are shown (Figure 2). Approximately 30% of these case studies came from kinases as targets, followed by other enzymes (such as phosphodiesterases, transferases, proteases, etc.). GPCRs as targets made up 17% of this set, followed by epigenetic targets (9%). Although epigenetic targets may technically be called "other enzymes", they were kept separate to highlight their emergence as a target class area. Other classes of targets were ion channels (9%), miscellaneous (9%), nuclear receptors (~1.5%), and protein–protein interactions (~1.5%). The disease area distribution (Figure 2b) was led by oncology (30%) followed by CNS/pain (18%), infection (13%), and metabolic diseases (12%).

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Table 1. Analysis of Hit-to-Clinical Pairs Reported *in J. Med. Chem.* 2016−2017

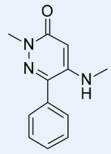
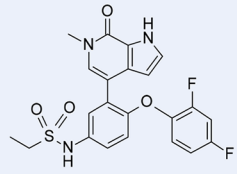
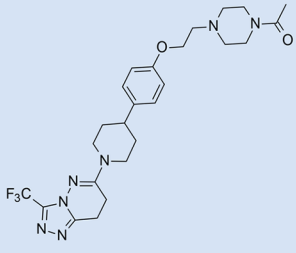
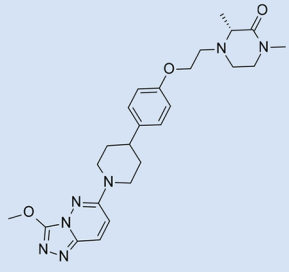
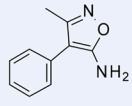
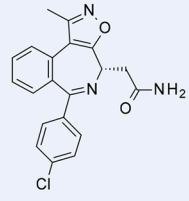
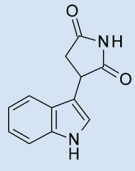
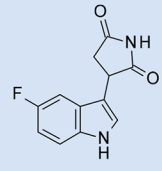
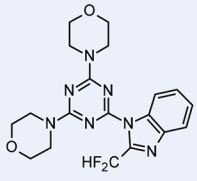
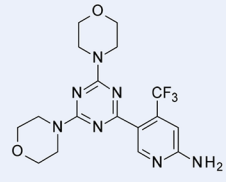
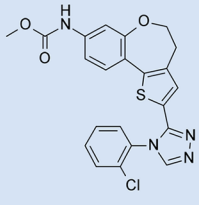
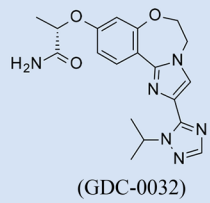
Entry	*Hit*	*Clinical candidate*	*Hit finding method*	*Target*	*Disease area*	*Ref*
1		 (ABBV-075, mivebresib)	Fragment Screen	BRD4	Oncology	13,14
2	 (AZD3514)	 (AZD5153)	Known	BRD4	Oncology	15
3		 (CPI-0610)	Fragment Screen	BRD4	Oncology	16
4		 (EOS200271, PF-06840003)	Random Screen	IDO-1 inhibitor	Oncology	17
5		 (PQR 309)	Known	PI3K/ mTOR	Oncology	18
6		 (GDC-0032)	Known; SBDD	PI3kα	Oncology	19

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Table 1. continued

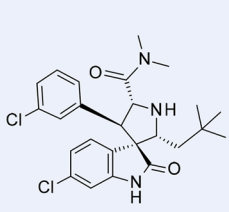
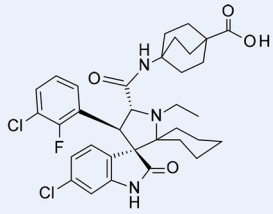
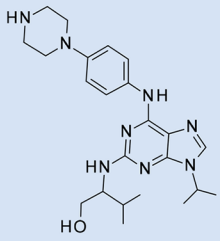
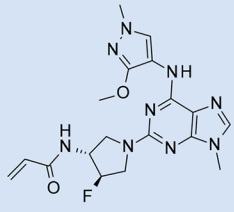
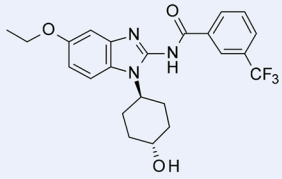
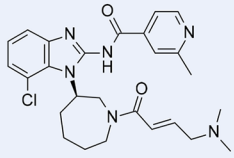
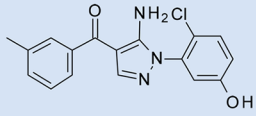
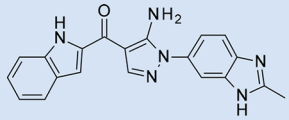
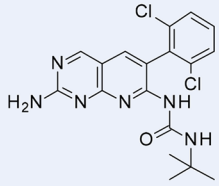
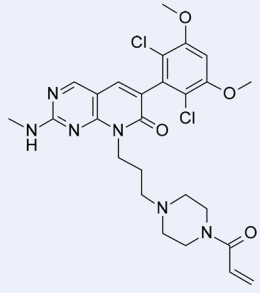
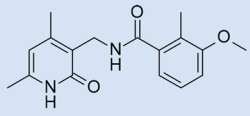
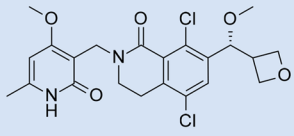
7		 (AA-115, APG-115)	SBDD	MDM2	Oncology	20, 21, 22
8		 (PF-06747775)	Directed Screen; SBDD	EGFR (mutant)	Oncology	23
9		 (EGF816, nazartinib)	Random Screen	EGFR (mutant)	Oncology	24
10		 (CH5183284, Debio1347)	Random Screen	FGFR	Oncology	25
11		 (PRN1371)	Known; SBDD	FGFR	Oncology	26, 27
12		 (PF-06821497)	Directed Screen	EZH2	Oncology	28

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Table 1. continued

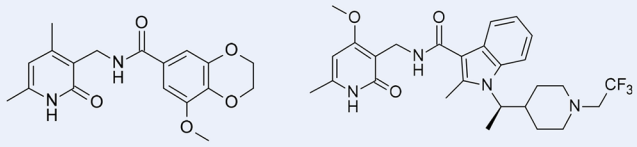
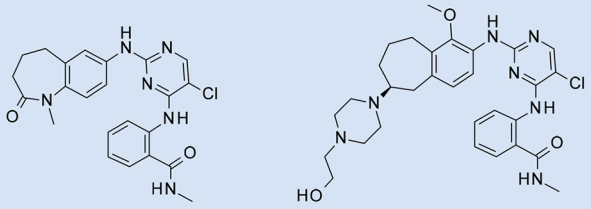
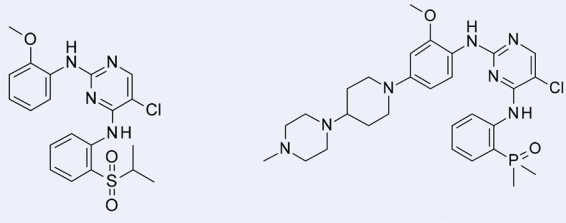
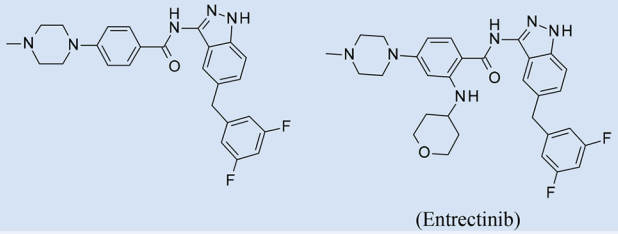
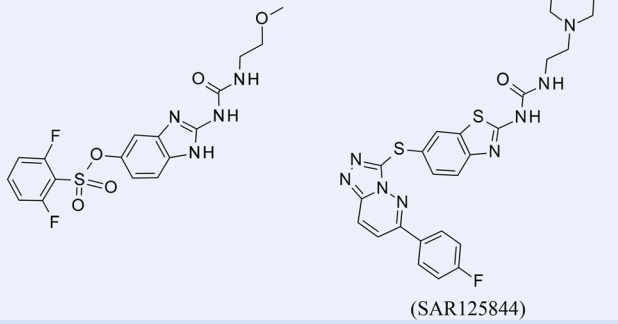
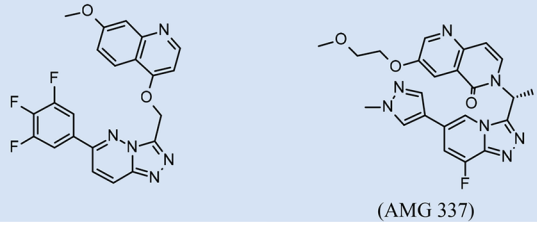
13	 (CPI-1205)		Random Screen; Known	EZH2	Oncology	30, 31
14	 (CEP-37440)		Known	FAK/ ALK	Oncology	32, 33
15	 (Brigatinib, AP26113)		Known	ALK	Oncology	34
16	 (Entrectinib)		Random Screen	ALK, ROS1, Pan-TRK	Oncology	35
17	 (SAR125844)		Directed Screen	MET	Oncology	36
18	 (AMG 337)		Known	MET	Oncology	37

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Table 1. continued

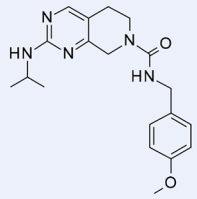
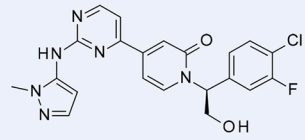
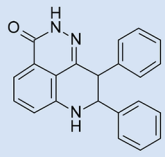
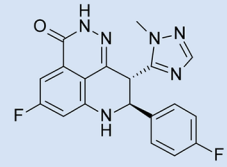
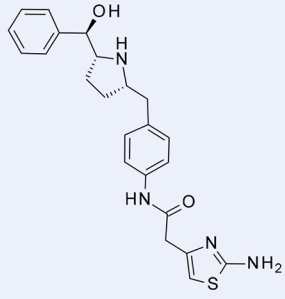
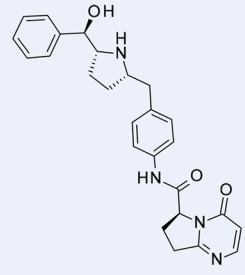
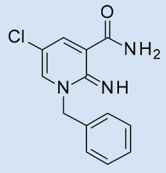
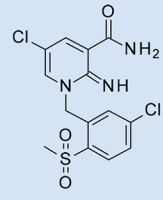
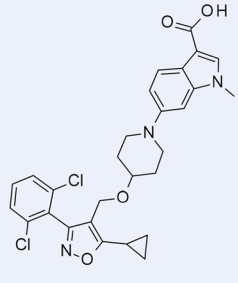
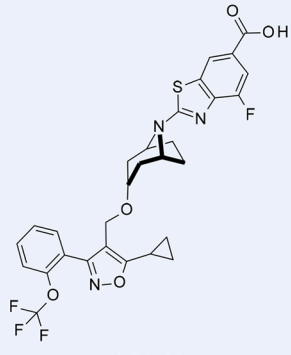
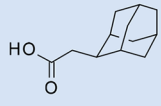
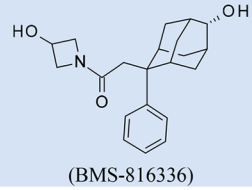
19		 (GDC-0994)	Random Screen	ERK1/2	Oncology	38,39
20		 (BMN-673, Talazoparib)	Known	PARP	Oncology	40
21		 (vibegron)	Known	β3-adrenergic	Urinary	41
22		 (TAK-259)	Random Screen	α_{1D}	Urinary	42
23		 (LJN452)	Known	FXR agonist	Liver disease	43, 44
24		 (BMS-816336)	Random Screen	11β-HSD-1	Diabetes; metabolic syndrome	45, 46

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Table 1. continued

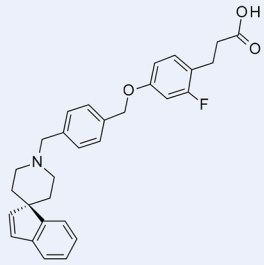
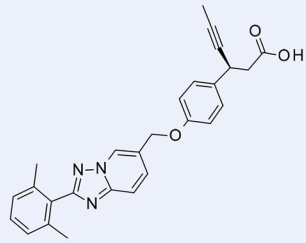
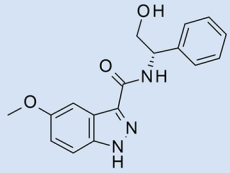
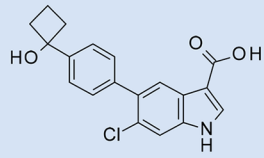
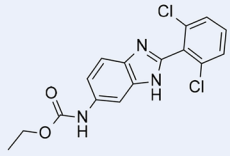
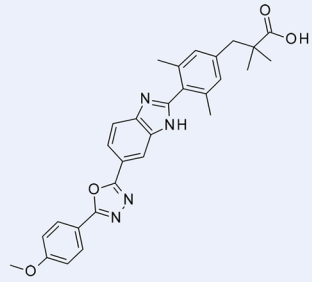
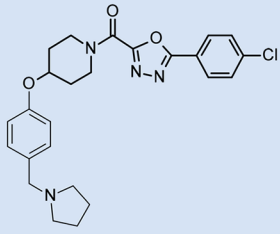
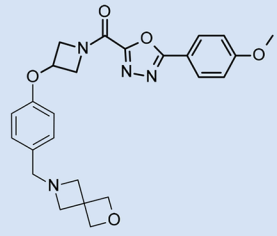
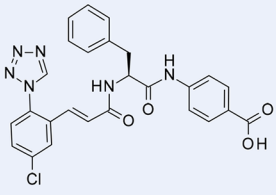
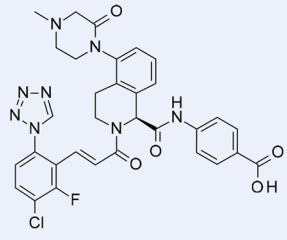
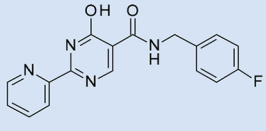
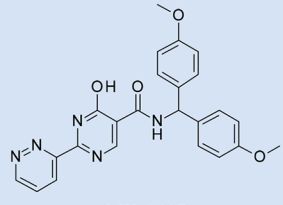
25		 (LY3104607)	Known	GPR40	Diabetes	47, 48
26		 (PF-06409577)	Random Screen	AMPK activator	Diabetic nephropathy	49
27			Random Screen	DGAT1	Obesity	50, 51
28	 (example advanced from HTS hit)	 (AZD1979)	Random Screen	MCHr1	Obesity	52
29		 (BMS-962212)	SBDD	Factor XIa inhibitor	Anticoag.	53
30		 (MK-8617)	Random Screen	HIF PHD1-3	Anemia	54

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Table 1. continued

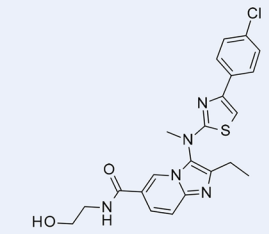
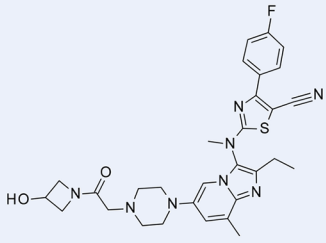
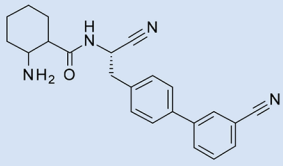
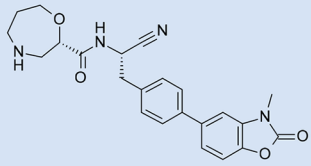
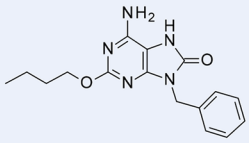
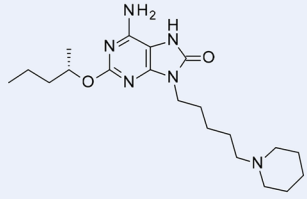
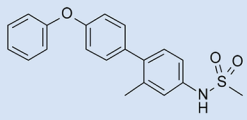
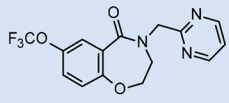
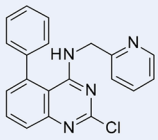
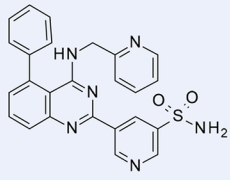
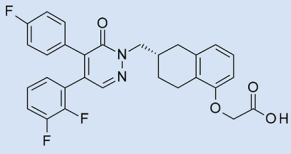
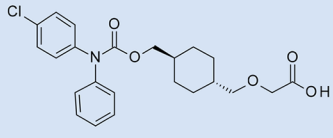
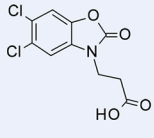
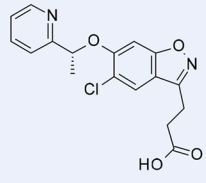
31	 (example advanced from HTS hit)	 (GLPG1690)	Random Screen	ATX	Idiopathic pulmonary fibrosis	55, 56
32		 (AZD7986)	Known	DPP1	COPD	57
33		 (GSK2245035)	Known	TLR7	Asthma	58
34		 (GS-6615)	Directed Screen	Late I_{Na}	Cardiovasc.	59, 60
35			Known	I_{Kur}	Atrial fibrillation	61, 62
36		 (Ralinepag)	Known	IP	Pulmonary arterial hypertension	63
37			Known	KMO	Acute pancreatitis	64

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Table 1. continued

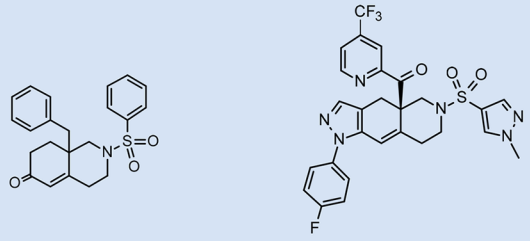
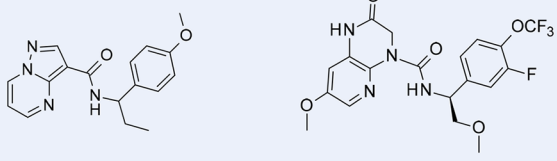
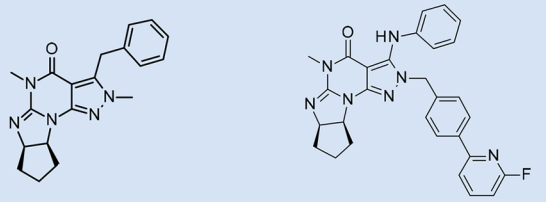
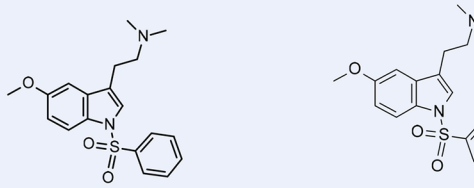
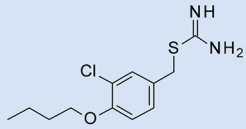
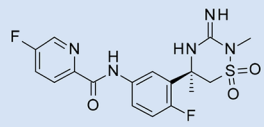
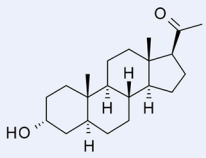
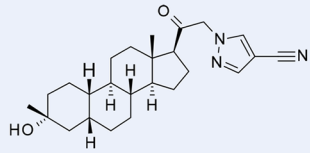
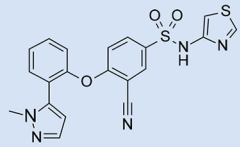
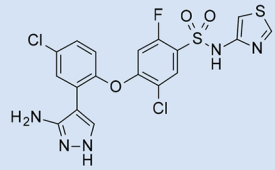
38	 (CORT125134)		Known	GR antagonist	Cushings syndrome	65, 66
39	 (TAK-915)		Random Screen	Phospho-diesterase 2A	Cognitive disorders	67, 68
40	 (ITI-214)		Known; SBDD	Phospho-diesterase 1A	Cognitive disorders	69, 70
41	 (SUVN-502)		Known	5HT6	Alzheimers disease	71
42	 (MK-8931; Verubecestat)		Fragment Screen	BACE	Alzheimers Disease	72
43	 (SAGE-217)		Known	$GABA_A$ PAM	Depression	73
44	 (example advanced from HTS hit)		Random Screen	NaV1.7	Pain	74

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Table 1. continued

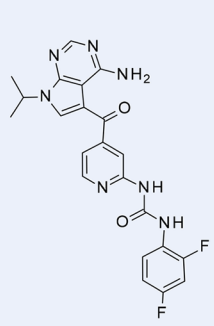
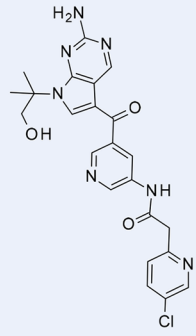
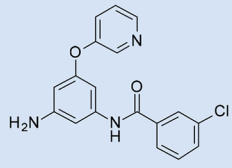
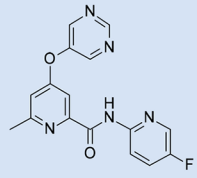
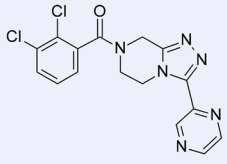
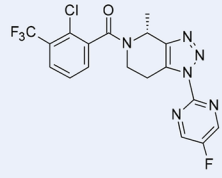
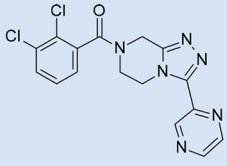
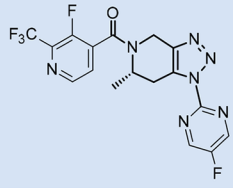
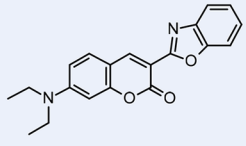
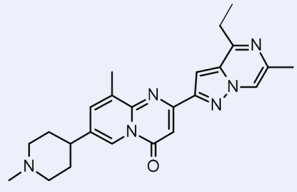
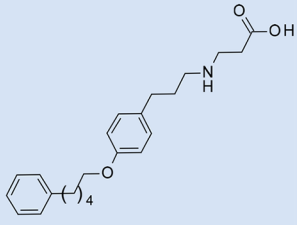
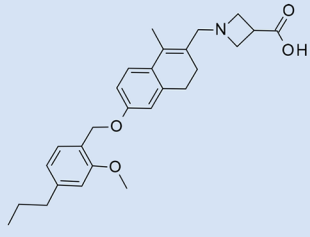
45		 (PF-06273340)	Random Screen	TrkA	Pain	75
46		 (VU0424238, Auglurant)	Random Screen	mGlur5	Mood disorders	76, 77
47		 (JNJ-54175446)	Known	P2X7	Mood disorders	78, 79, 80
48			Known	P2X7	Mood disorders	81, 82
49		 (RG7800)	Random Screen	SMN2 mis-splicing	Spinal muscular atrophy	83, 84, 85
50		 (Ceralifimod; ONO-4641)	Random Screen	S1P1 agonist	Autoimmune disease	86

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Table 1. continued

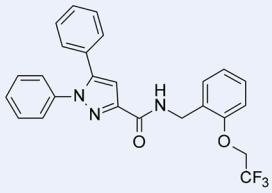
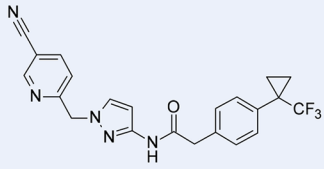
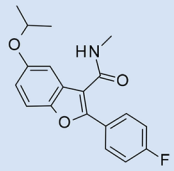
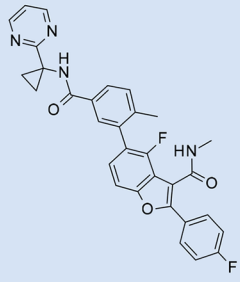
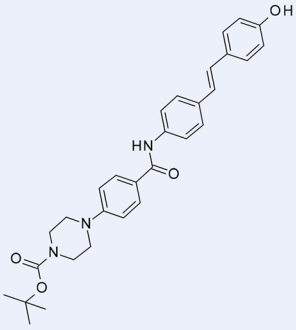
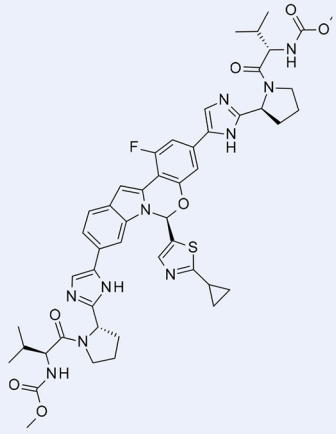
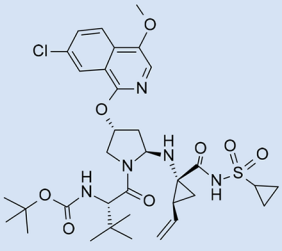
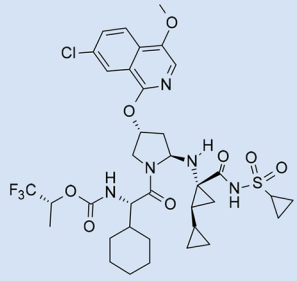
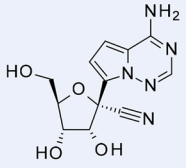
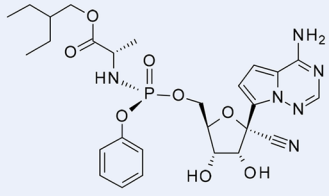
51		 (ACT-709478)	Random Screen	T-type calcium channel blocker	Epilepsy	87, 88
52		 (BMS-929075)	Random Screen; Known; SBDD	NSB5 replicase	Hepatitis C	89
53		 (Ruzasvir)	Random Screen; Known	NS5A	Antiviral	90, 91, 92
54	 (Asunaprevir)	 (BMS-605339)	Known	NS3 protease	Antiviral	93
55		 (GS-5734)	Directed Screen		Antiviral	94

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Table 1. continued

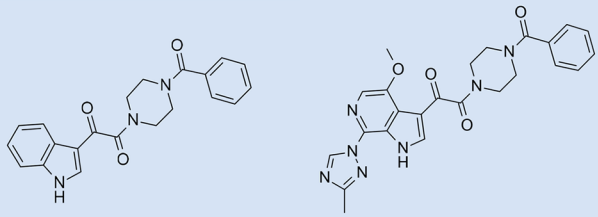
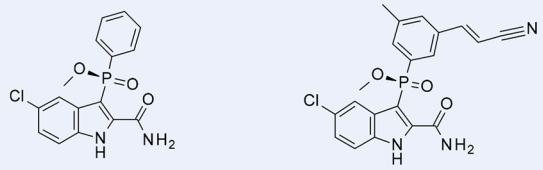
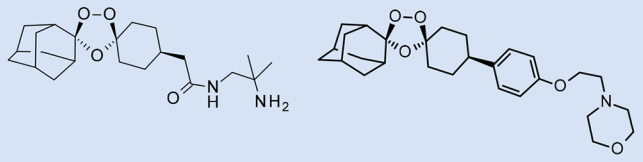
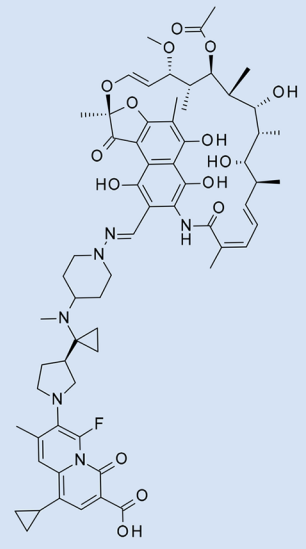
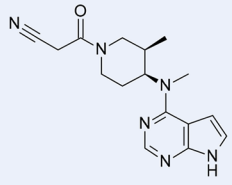
56	 (Temsavir)		Random Screen	HIV attach.	Antiviral	95
57	 (IDX899)		Known; SBDD	NNRTI	Antiviral	96, 97
58	 (OZ439)		Known		Antimalarial	98
59	 (GSK656)		Known	Leucyl-tRNA synth. inhibitor	Anti TB	99
60	Rifamycin and ABT-719	 (TNP-2092)	Known	Dual DNA gyrase/ RNA polymerase	Antibacterial	100
61	 (PF-06651600)		Known; SBDD	JAK3	Inflamm. diseases	101

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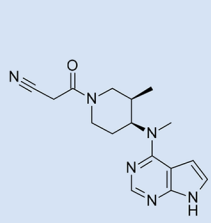
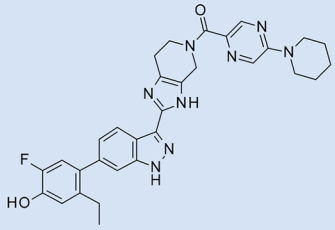
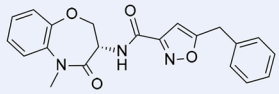
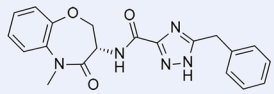
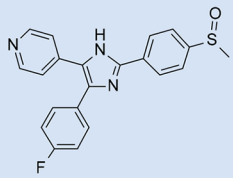
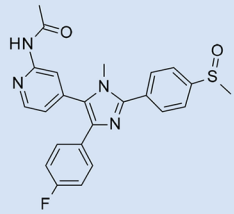
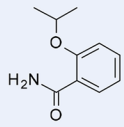
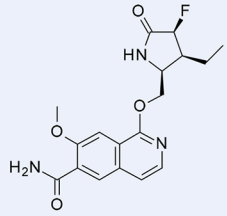
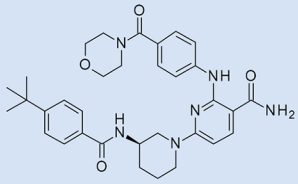
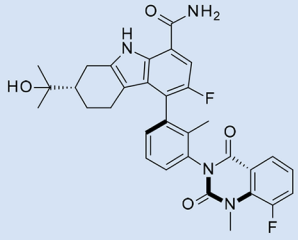
Table 1. continued

62		 (PF-06263276)	Known; SBDD	Pan-JAK	Inflamm. diseases (inhal./skin)	102
63		 (GSK 2982772)	DNA Encoded Library Screen (DEL)	RIPK1	Inflamm. diseases	103
64		 (CBS-3595)	Known; Directed screen	P38α MAPK/ PDE4	Inflamm. diseases	104
65		 (PF-06650833)	Fragment Screen	IRAK4	Inflamm. diseases	105
66		 (BMS-986142)	Known; SBDD	BTK	Rheumatoid arthritis	106, 107

PHYSICAL PROPERTY ANALYSIS

An analysis of clogP, clogD, MW, and rotatable bonds was conducted on the set of 66 hit-to-clinical pairs.[11] Only the categories "Known" compounds and "Random Screen" were analyzed due to smaller sample sizes of the other categories. The calculations were also restricted to those examples where a clear hit structure was identified (e.g., Table 1, entries 28, 44, and 60 excluded). Figure 3a–d contains the difference in a physical property for a given hit-to-clinical pair (e.g., ΔclogP, Δlog*D*, ΔMW and Δrotatable bonds), and changes are plotted as distributions. No significant change was observed in the ΔclogP when going from hit-to-clinical candidate for either of the two categories of "Known" compound or "Random Screen" (Figure 3a, ΔclogP = −0.2). However, both categories demonstrated an increase in MW (ΔMW = +63 Da) for the previously known compounds category and ΔMW = +95 for the Random screen category. The overall average for the 66 compounds was +84. The number of rotatable bonds also increased by 1 (average = +1.2) in going from hit-to-clinical candidate, as would be expected with the MW increase.

By analyzing the structural differences between hit-and-clinical lead pairs using $Tanimoto_{MCS}$ as a measure of comparison, where it has been previously shown that compounds that have Tanimoto values of >0.8 disclose structurally similar ligand pairs, we could assess the degree of optimization required.[11] Both sets of "Known compounds" and "Random screen" were again compared, and the results are illustrated (Figure 4). In many cases, the optimized compound is structurally very different from the hit compound. Interestingly, the average was found to be around 0.5 for both sets. One might have assumed that the HTS hits should have required more structural changes, as compared to using a previously known compound as starting point. This was not the case as both sets are equally different from the initial

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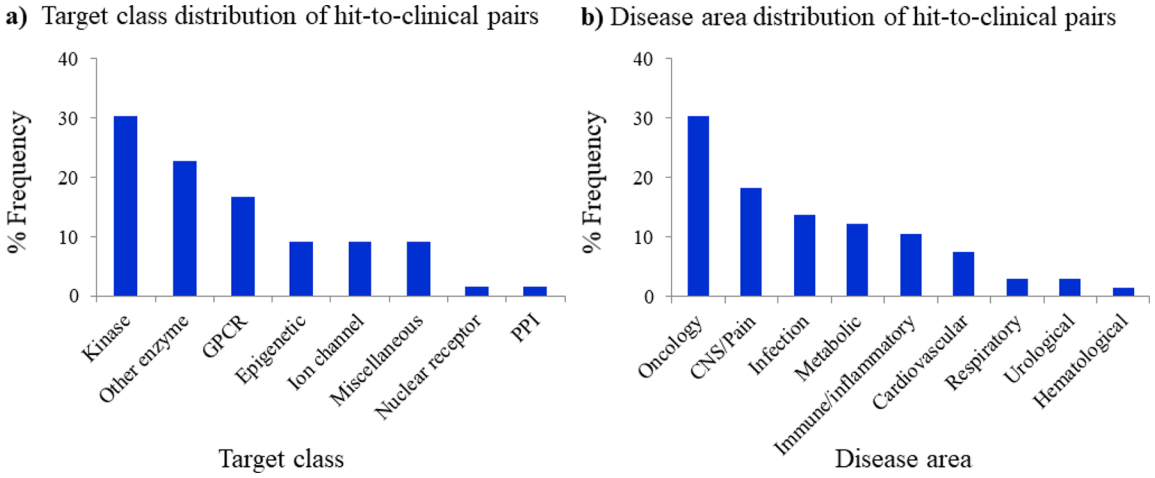

Figure 2. Target class analysis (a) and disease area (b) analysis for the 66 hit-to-candidate pairs in *J. Med. Chem.* 2016–2017.

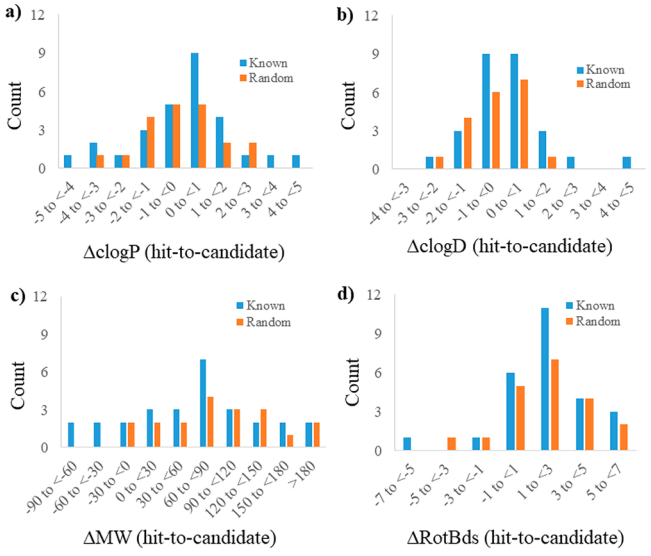

Figure 3. Analysis of calculated physicochemical property changes for the 66 hit-to-candidate pairs in *J. Med. Chem.* 2016–2017 in "Known" starting points and "Random" screening categories.

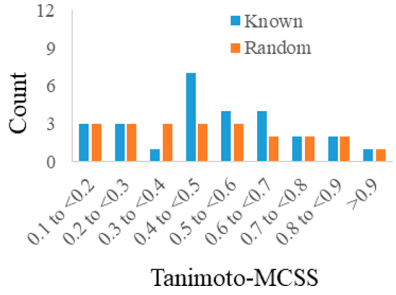

Figure 4. Comparison of the Tanimoto maximum common substructure (Tanimoto-MCCS) for hit-to-clinical lead pairs in the "Known" starting point and "Random" screening categories.

starting points. Finally, calculated molecular complexities show that clinical candidates are on average indeed more complex than their corresponding starting point (see Supporting Information). When analyzing simple counts for the pairs, several observations were made. The number of heavy atoms increase by 6, from 27 to 33. On average four aliphatic atoms are added, and two aromatic atoms. Two hydrogen-bond acceptors are added on average, and the polar surface increases. The number of hydrogen-bond donors and fraction-sp^3 remains unchanged. Strikingly, in two-thirds (43/65) of the cases at least one heterocyclic nitrogen is added when going from hit to lead. Similarly, in one-third of the pairs (20/65) at least one fluorine atom is added during this development phase.

DISCUSSION

Lead Generation from Screening Methods. High-throughput random screening strategies have been a cornerstone of successful drug discovery programs, harkening back to natural product screening success stories in the "golden era of drug discovery" leading to the discovery of many important antibiotics and other important drugs.[108,109] As has been well documented, the capability to screen increasingly large numbers of compounds continues to improve across the industry. This has now become a routine part of the drug discovery process, including the recent incorporation into academic screening centers as well.[107] Screening technologies can employ a vast range of compounds, from billions of molecules for DEL,[8] low millions for a typical HTS screen,[110] to hundreds or a few thousands for fragment screening.[5] Among some of the more interesting reports in this cohort are those that illustrate that successful campaigns can be done on relatively few compounds, illustrating that large screening libraries are not a requirement for finding quality hit starting points. For example, in a publication by Gilead, a small subset of 800 nonbasic heterocyclic compounds were screened to identify the hit molecule **1** (Table 1, entry 34, and Figure 5).[59,60] Subsequent efforts led to removal of the phenoxy phenyl groups as well as the para aniline groups resulting in lead structure **2** and ultimately to the clinical candidate GS-6615 (**3**). It should be noted that the clinical candidate in this example is quite distant from the initial hit structure ($Tanimoto_{MCS}$ = 0.17). This example illustrates that in some cases, a focused screening strategy, coupled with medicinal chemistry optimization, might be equally or perhaps even more effective than a large HTS, where costs of screening and time spent in triaging might offset the additional capacity. Maybe for this reason, focused screening sets (e.g., a few thousand compounds) are popular in practice, many of which can be purchased commercially.[110]

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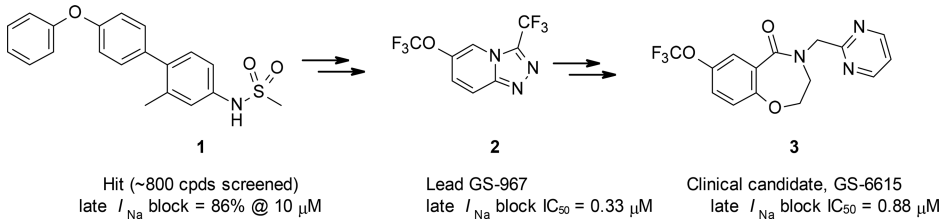

Figure 5. Example of hit-clinical success from small, directed screening sets.

Fragment-based lead generation has led to several successful examples of clinical candidates as evidenced in this analysis. Johnson and colleagues reviewed 27 recent examples of successful fragment-to-lead published case studies in 2015 as well as 28 in 2016.[111,112] On the basis of their analysis, kinases were by far the largest target class reported in fragment-to-lead examples (33%), with only 4% GPCRs most likely owing to the challenge of using structure-based drug design of these targets. Advances in technology to generate stabilized membrane proteins may increase the use of FLBG in GPCR as target classes, with a recent example of protease-activated receptor 2 (PAR2) as a good case study on how both FBLG and DEL can be applied to these targets.[113] A wide variety of screening techniques can be used in FBLG. For example, it was found that biochemical screens (28% of reported studies) followed by thermal shift (17%) and ligand observed NMR (17%) were the most frequently used techniques. Of the four cases documented in this report, three were identified by NMR methods (BET, BACE, and IRAK4)[13,14,72,105] and one was identified in a thermal shift assay (BET).[16]

Only one clinical candidate in this cohort was discovered by DNA-encoded library technology (Table 1, entry 63).[103] Of the lead generation technologies highlighted in this review, it is the most recent of the screening technologies[8] and, as such, might require time and development to truly come of age and demonstrate impact on drug discovery. At least one other example of a known successful clinical candidate from this technology has been reported, namely, the soluble epoxide hydrolase inhibitor GSK2256294).[114] Another factor owing to the limited impact is that only a few of the large pharmaceutical companies and contract research organizations currently have access to the technology. There are also limitations to the types of chemistry that can be used to construct libraries on DNA. A review by Franzini and Randolph highlighted this as a current challenge, coupled with the limitations on large libraries to low MW and low lipophilicity.[115] Advances in library design with more diverse and compatible chemistry may likely lead to an increased application and could provide similar impact to other lead generation strategies covered in this review.

Phenotypic Screens. The opportunities and potential pitfalls of phenotypic based screening have been recently reviewed by Moffat et al.[116] Many successful drugs have been brought to the market through this approach.[117] However, very few examples are found in this set. Thus, most of the screens reported in this study utilize target-based biochemical screens. The Merck NS5A candidate is an exception (Table 1, entry 53),[90−92] where a viral replication assay not biased to any target or mechanism was used to identify a stilbene scaffold resulting in a lead series of compounds and clinical candidates. Another antiviral example comes from the HIV attachment inhibitor temsavir (Table 1, entry 56)[95] which was discovered by a phenotypic screen and later proposed to work via inhibition of HIV attachment. The Ebola compound discovered by Gilead and USAMRIID (Table 1, entry 55)[94] was also identified through a phenotypic cell based screen. Outside the infection therapeutic area, one compelling example was the discovery of small molecules that are splicing modifiers of the SMN2 gene. Implementation of a cell based (HEK293H) SMN2 mini-gene screen led to multiple chemical series, ultimately resulting in clinical candidate RG7800 after medicinal chemical optimization (Table 1, entry 49).[83−85] With the increased implementation of gene-editing technologies and access to patient-derived stem cells, phenotypic screening presents a very attractive method to more directly link the lead generation screen to the disease of interest. Since the clear majority of case studies in this article come from target-based biochemical screens, it does suggest that phenotypic screening, at the moment, is most beneficial to infection-based screens. Perhaps there are several reasons for this.[116] One of the primary bottlenecks of phenotypic screens may arise from deconvolution of these hits, which can be significantly complicated and resource-intense. If indeed target identification is required by management in the pharmaceutical company (it is not a requirement by regulatory authorities) before proceeding to lead optimization, it can take an indefinite amount of time. Project teams may have to embark on a tool compound campaign to build tagged molecules for target pull-down and chemoproteomics experiments. There are many drugs where the mechanism of action is still not known, and not all diseases can be sorted under the "one target, one disease" theory. Humans are complex, and drugs are likely to affect several biochemical responses simultaneously, which in turn can cause feedback reactions on the effected pathways. A lesson learned from the fate of AstraZeneca's drug pipeline prior to 2010 was that 40% of the AZ internal drug projects lacked a clear link between the main target and disease.[118] Without knowledge of (or claiming to know) the mode-of-action, publication can be challenging, possibly limiting the number of examples in the scientific literature.

Do New Drugs Come Directly from Existing Hits? There is one example in this analysis where the drug candidate appears to have been discovered directly in the screen, namely, the Ebola drug candidate GS-5734 (Table 1, entry 55)[94] which was discovered by a directed screen of nucleoside analogs. It should be noted that the final drug candidate was ultimately the phosphoramidate prodrug of the screening hit. This highlights the difficulty in identifying drugs or "near-drugs" (e.g., prodrugs) directly from a screen.

The concept to screen drug and drug-like molecules or "pharmacologically active" compounds is an area of current interest.[119] Related to this, drug repurposing is where current drugs or clinical compounds are screened to identify new therapeutic opportunities. A review by Baker et al. has shown that two-thirds of all drugs have been evaluated in at least one other disease area.[120] Not surprisingly many successful

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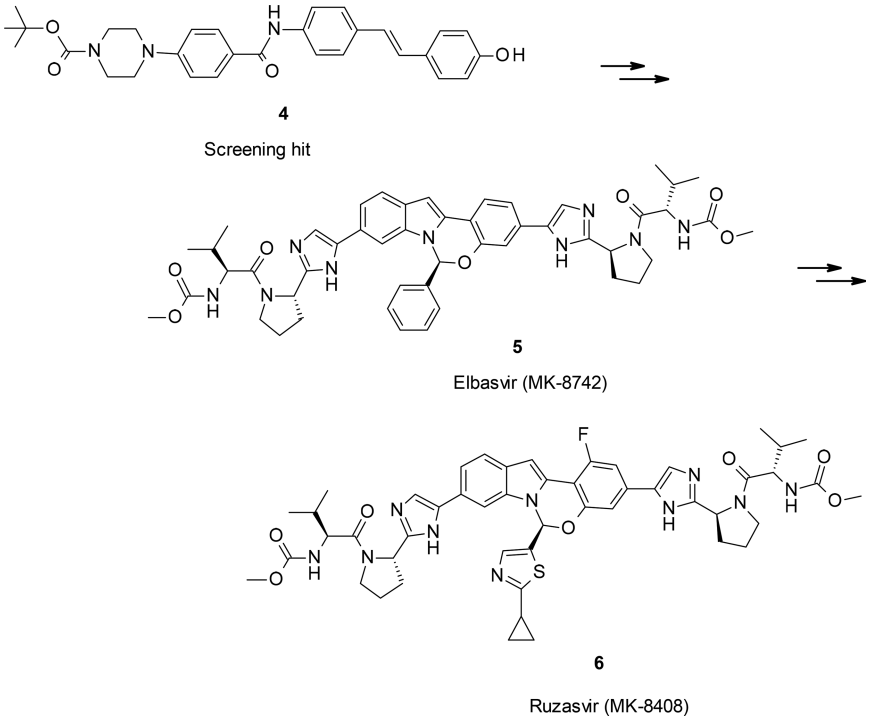

Figure 6. Example of hit-clinical success from known starting points.

examples are those where the disease area is related to the original one. However, there are cases where a drug has been repositioned for a completely different therapeutic area. For example, prednisolone from inflammatory disease to restless leg syndrome.[120] Although there are examples from the clinical setting of repurposing, it remains in question whether screening drug, drug-like, or pharmacologically active sets of compounds will lead to hits that can be optimized quickly into a clinical candidate. It is our belief that high-quality hits will shorten the discovery phases; however finding a "hit" derived from a clinical candidate will still require optimization of the target biology without loss of the drug-like properties in the process. In theory, drug and drug-like molecules will have been optimized for superior drug metabolism and disposition and as such, if hits are found from random screening, might progress much more quickly. However, to date, no comprehensive studies have been published on the advantages of screening these types of collections.

Lead Generation from Known Starting Points. Follow-on drugs or "fast-follower" type approaches have been a staple in the pharmaceutical industry.[7] Many successful follow-on drugs have come to the market, one-third of which surprisingly receive priority review from the FDA, thus indicating that many follow-on drugs are potential "best-in-class" options.[121] A fast-follower type approach often seeks to identify the minimal changes that provide both differentiation and opportunities to claim novelty and invention. To illustrate this, a review by Giordanetto et al. compared >50 structurally related first in class follow-on pairs and determined that there are frequently minimal differences in heavy atom counts (median, +2) between these pairs.[122] It should be noted that fast follower programs may not always appear in the literature, and this may be due to several potential reasons. First, even if the new drugs may be novel by a patent examiner, the "discovery story" might have already been told from the first-in-class molecule and perhaps less compelling for publication within the scientific community. The second reason might be due to the risk of compromising an intellectual property claim, since it is difficult to claim that a structure is novel while at the same time documenting that it was the competitor compound that led to this discovery. Thus, it should be pointed out that we did not attribute the designation of "fast follower" to any of these examples but kept the designation very broad and restricted to the category of "Known" in order to avoid any incorrect assumptions.

In some cases, the clinic candidate was immediately derived from another clinical candidate from the same company to improve on a particular profile. This is a common practice and backup strategy in many pharmaceutical R&D organizations. In these cases, the category was marked "Known", but efforts were made to try and trace back to the original starting point where possible. One example is highlighted below (Figure 6), where scientists at Merck first launched elbasvir as a NS5A inhibitor for HCV infections. This discovery was driven by knowledge of their screening hit **4**, along with emerging literature of others compounds in the field on the successful cyclization strategies to the advanced lead scaffolds.[90−92] A team at Merck recently reported ruzasvir **6** as a pan-genotype inhibitor, which was derived from the elbasvir scaffold **5**.[90−92]

Another example of improvement on an existing clinical is the antimalarial compound OZ439 (Table 1, entry 58),[98] which also demonstrated the importance of physicochemical and synthetic insight on a key liability of the original clinical candidate. In this case, the stability of the ozonide functional group was a long sought after but elusive improvement which would lead to better plasma stability and corresponding improved therapeutic efficacy for this class of drugs. A transformational change was the introduction of an 8′-aryl ring, proposed to shift the conformational equilibrium of the cyclohexyl ring system to a more stable axial-peroxide conformation. It should be noted that in this case the physical property changes led to a dramatic increase in lipophobicity

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(clogP of 2.8 of starting compound versus clogP of 5.5 for final compound), a change that is not typically conducive in going from the hit to clinical candidate. It is often the case that reducing lipophilicity may also reduce metabolic and other unwanted liabilities.[123−125] However, in this example, addition of the aryl group led to improved chemical stability and subsequently greatly improved plasma stability.

A case study reported by a group at ARIAD demonstrated that the incorporation of "nontraditional" structural motifs can be a useful approach to go from hit to clinical candidate based on known scaffolds (Table 1, entry 15).[34] In this case, a phosphine oxide was designed to interact in the hinge region replacing a sulfonamide, which led to brigatinib (AP26113), a potent and selective compound with favorable ADME properties. Although not directly identified in this cohort of examples, deuterium (with the first FDA approval given in 2017) and silicon are also potential nontraditional elements that have been used to try and advance existing clinical candidates and drugs.[126,127]

Another approach identified in the "Known" compound category was the strategy of combining two drug classes into one via tether as illustrated (Figure 7). The rationale behind

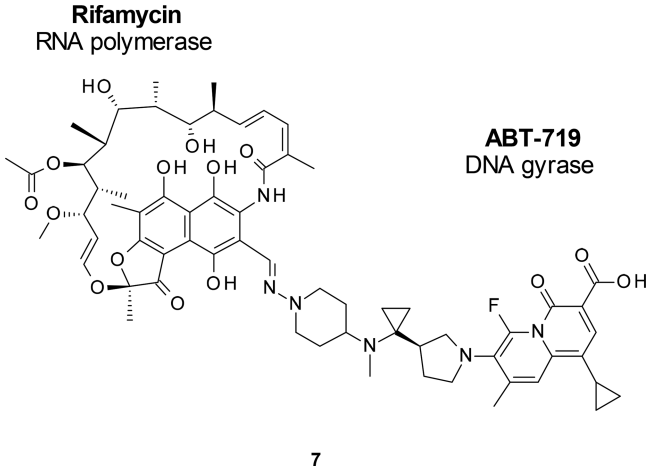

Figure 7. Example of hit-clinical success by building dual-acting compounds.

the dual-acting compound was primarily to provide an improved activity over resistant bacterial strains. However, TNP-2092 (Table 1, entry 60)[98] also demonstrated an unexpected synergy in vitro and in vivo, as compared to either of the two antibacterial agents. Ghasemi et al. have recently reviewed strategies and approaches to dual-acting compounds in this emerging area.[128]

A special class of dual-acting compounds utilizes the concept of targeted protein degradation (PROTACS); two target domains are tethered to one another in order to trigger protein degradation of the desired protein.[129] Although no examples were found in this cohort, the first clinical candidate was recently reported elsewhere.[130,131]

Endogenous ligands can also serve as useful starting points for lead generation. As an example, a research team at Eli Lilly has reported on three GPR40 agonists which are all clinical candidates. The most advanced compound is shown in Table 1 (entry 25, **11** in Figure 8)[47,48] along with the initial starting point **9** which served as the lead generation scaffold. This scaffold was ultimately inspired and initially designed based on the natural ligand DHA **8**, with conformational constraints leading to a potent GPR40 agonist series.

Back-Up Candidates. Very few cases of clinical candidate backups were identified in this analysis. One example is that by the group at BMS for a backup of the HCV compound asunaprevir (Table 1, entry 54).[93] This compound was discovered by an effort to find molecules with an improved cardiovascular profile of the original candidate using ex vivo models. There may be several reasons for the lack of backup clinical cases reported in the recent literature. One reason could be that these studies are not considered the most interesting publications by peer reviewers and/or journal editors (as discussed above) and perhaps do not receive the type of attention a first-time disclosure of a clinical candidate receives. It is also possible that publication of a backup candidate requires disclosing a flaw in the original compound which might be a competitive disadvantage once disclosed. Yet another reason is quite possibly a shift in pharmaceutical companies' strategies, prioritizing "novel" programs, as compared to investing in back up candidates.[118]

Integrated Lead Generation Approaches. Integrated lead generation approaches are those that utilize multiple lead generation campaigns in parallel and combine the knowledge from the various streams to identify the lead starting points. BMS-929075, a clinical candidate for hepatitis C virus, represents an example of a molecule derived from this "integrated lead generation" approach (Table 1, entry 52).[89] The project team utilized a random screening HTS hit (**13**)

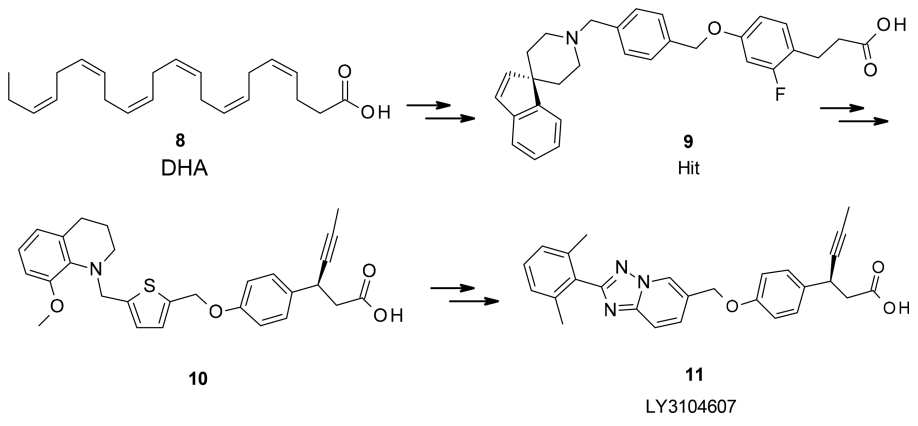

Figure 8. Example of hit-clinical candidate from endogenous ligand.

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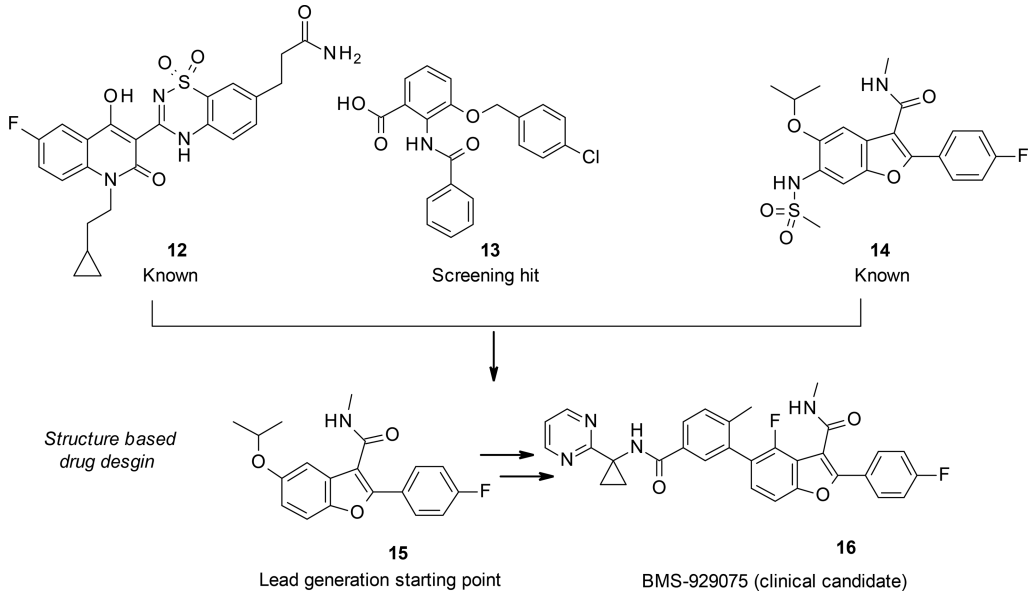

Figure 9. Example of integrated lead generation approach.

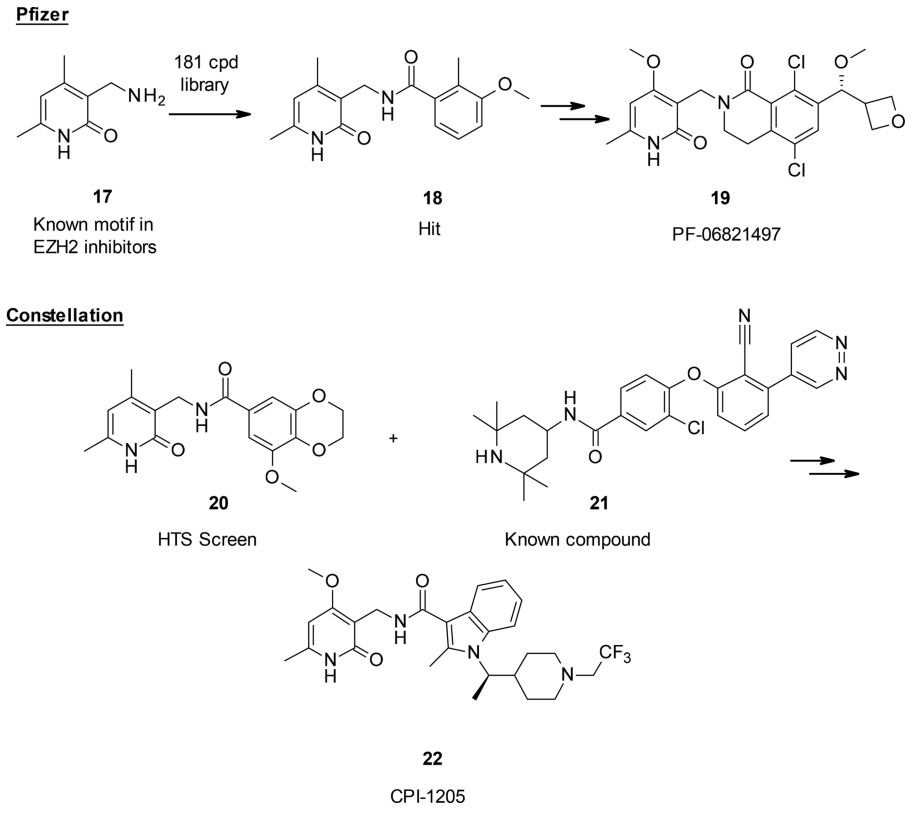

Figure 10. Examples of integrated lead generation strategies for EZH2 inhibitors.

and combined it with the known ligands **12** and **14** in a structure-based drug design approach giving the lead scaffold **15** (Figure 9). This highlights the value of having access to HTS hits and X-ray structures and exploiting this information together with previously known compounds/scaffolds.

A group at Pfizer reported an integrated strategy to identify novel EZH2 starting points leading to a clinical candidate (Table 1, entry 12).[28,29] The strategy was built on the recognition of a known lactam motif (**17**) common to previously reported EZH2 inhibitors (Figure 10). This knowledge was used in the construction of a small focused library, wherein hit structures such as **18** were discovered as the key starting point for further optimization efforts. Careful attention was placed on synthesizing library members within a selected clogP range (−1 to 3). Further ring constraint and aromatic substitution led to the final clinical candidate **19**. Development and discovery of new synthetic routes during a drug discovery campaign can also be the genesis of new hit structures and clinical candidates. A similar starting point (**20**), this time derived from HTS screening but also incorporating

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integrated approach with a known inhibitor, led to another EZH2 clinical candidate (**22**) by Constellation (Table 1, entry 13).[30,31] These examples highlight that structurally different clinical candidates can be obtained by medicinal chemistry expansion by two different companies, arguably starting from very similar starting points.

New synthesis technologies can play an important role in advancing hits to leads and ultimately to clinical candidates. However, exploration of novel chemistry can also lead serendipitously to reasonable starting points. Wang et al. have described the search for novel PARP inhibitors, which resulted in the unexpected synthesis of the trans-diphenyl intermediate **24**, which upon cyclization led to extremely potent PARP inhibitors (Table 1, entry 20; Figure 11).[40]

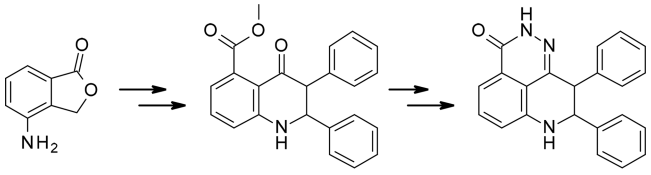

Figure 11. Synthesis and the role of serendipity in lead generation strategies.

Novel synthetic chemistry has played an important role in the history of medicinal chemistry, including those structures that were not originally intended by the chemists (e.g., discovery of benzodiazpines).[130]

Covalent Inhibitors. One strategy to leverage previously known compounds, which is gaining in popularity, is to introduce a covalent "warhead" with the aim to form a covalent bond to a neighboring cysteine or serine residue. Four examples of this strategy are shown in Table 1. Two examples are shown against the EGFR receptor (Table 1, entries 8 and 9)[23,24] and one against FGFR (Table 1, entry 11).[26,27] The first example from Pfizer was derived from known EGFR inhibitors using a SBDD approach, whereas the example from Novartis was derived from an HTS biochemical screen on the kinase domain. Another example published by Pfizer highlighted that selectivity could be built in with the covalent approach, in this case JAK3 over other JAK subtypes, by utilizing the known published X-ray coordinates of tofacitinib and building in the right covalent warhead (Table 1, entry 61).[101] An important design element in this strategy is the introduction of an electrophile that is not reactive to more biologically prevalent nucleophiles such as glutathione but is selective toward a thiol or a serine residue on the target protein. Important factors such as the kinetics of the reaction, steric considerations, and electronics, which govern the addition, all play an important role in deciding which electrophiles are most appropriate for a given electrophilic warhead.[132] It is notable that tofacitinib was used in the design of another Pfizer clinical candidate, in this case a pan-JAK compound. The molecular properties were also optimized toward inhaled or skin applications (Table 1, entry 62).[102]

It is interesting to note that there are no reported examples of clinical candidates emerging from a virtual screening approach. Computational methods were integrated into many of these programs, but none of these reported cases disclosed that the original hit was identified via a virtual screen such as docking approach or a ligand-based approach. We can speculate on several reasons for this observation. The first one is perhaps that the examples from "Known" compounds as starting points have benefited from virtual screening but it was not explicitly stated. Virtual screening techniques are also likely integrated into SBDD approaches once the lead has been identified as well.

Physical Properties. Keserü and Makara have reviewed a set of hit-to-lead pairs from 2000 to 2007.[133] In their analysis, more than 80% of hit-to-lead pairs originated from HTS and ∼15% from focused screens (which include FBLG and VS). This paper serves as a useful benchmark for comparison on how physical properties change from the initial hits. One observation noted was that lipophilicity (as measured by log*P*) of HTS hits was significantly higher than those of non-HTS hits. The authors also discuss the challenges in progressing HTS hits without increasing hydrophobicity to achieve potency. Other analyses have been reported previously around the evolution of physicochemical properties going from hits to leads and from leads to clinical candidates. Morphy has studied in detail across the various target classes and further stratified by pharmacological action (e.g., antagonists, agonists, etc.) and hits compared to leads.[134] They conclude from this paper that the nature of the endogenous ligand determines the physical property space of lead expansion. In all studies the median MW and clogP increase when optimizing hits to leads.

Analyzing the cohort of 66 hit-to-clinical candidate pairs reveals a slightly different picture. We see very little change on average in lipophilicity (as measured by clogP) when comparing "Random" screening and "Known" starting points with their corresponding candidate drug. In fact, the average clogP change was close to zero, with examples where it increased as well as decreased. Perhaps this is an indication that lead generation and screening collections have improved in quality since the previous analysis over a decade ago (2000−2007). However, it might also reflect the difference in hit-to-lead compared to hit-to-candidate profiles. If high MW and high log*P* lead to the closure of a lead series, and subsequent publication, this may lead an overabundance of these examples in the literature. Arguably the clinical candidates have passed a significant hurdle of multiparameter optimization and represent a unique set of molecules. Not all structural modifications from hit-to-clinical candidates were designed to improve potency and/or physical properties against a weak hit. Some cases are noted in Table 1 where the clinical candidate was derived from an already potent and/or optimized compound, but the key challenge was to either provide additional pharmacology (e.g., ALK/FAK inhibitor) or to remove a liability such as anti-target potency or metabolic stability. The molecular weight changes from hit-to-clinical candidate in this analysis are consistent with those hit-to-lead changes reported in the previous examples from Keserü and Morphy.[133,134] Finally, it should be noted that the use of ligand efficiency measures (e.g., LE and/or LLE) appears to have significant impact on the trajectory of lead generation programs, but these are target-specific and not necessarily generically applied, as recently reported by Young and Leeson.[135] The uptake of these efficiency metrics is becoming more widely used, and many of the examples of the hit-to-clinical pairs in this manuscript were optimized with an underlying strategy where these were included. Young and Leeson describe in detail many successful hit-to-lead and lead-to-clinical examples and outline four major strategies that enable project teams to achieve a successful trajectory (e.g., (a)

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seek "necessary" nitrogens,[136] (b) methylate, (b) fluorinate, and (d) hydroxylate) which benefited from the application.[135] Indeed several successful examples in this review have taken these general strategies (e.g., Table 1, entries 4, 14, 19, 20, 24, etc.).

CONCLUSIONS

In summary the recent literature (*J. Med. Chem.* between 2016 and 2017) was curated to obtain a set of 66 hit-to-clinical candidate pairs. These were categorized into specific lead-generation approaches and analyzed for changes in properties and structural diversity. We observed that approximately half (46%) of the clinical drug examples originated from previously known compounds. These clinical candidates were not always fast-follower or part of back-up programs, as there were examples of from endogenous ligands, including examples tethering known drugs. The second largest category of clinical candidates was derived from random screening approaches (31%). Examples were also identified from focused screening, fragment-based lead generation, and DNA-encoded library screening, although their prevalence was low. Furthermore, an area of increasing interest is design of covalent compounds derived from known noncovalent ligands. Very few examples of clinical candidates derived from phenotypic screening were reported and none from virtual screening. An analysis of physicochemical properties indicated that molecular weight was typically the only significant change in going from hit-to-clinical candidate. The additional molecular weight added was on average +63 Da for the "Known" categories of compounds and +95 Da for the "Random" screening set. On average one rotatable bond was added, but little change in lipophilicity was observed ($\Delta \log D = -0.2$). Lipophilicity, as calculated by clogP, did not seem to be a significant property change. There were an equal number of examples that increased vs decreased lipophilicity in going from hit to clinical candidate. Overall this analysis demonstrated that using previously known compounds as starting points is a successful strategy and led to most clinical candidate compounds for this set. However, random screening approaches also deliver clinical candidates, and the strategy is advantageous when no known compounds exist or if a specific mode-of-action is desired. Other strategies also have demonstrated impact (e.g., FBLG and DEL), and their full potential may yet be realized. It may be a coincidence that no examples come from virtual screening, but we find this to be a curious observation since it is relatively inexpensive method with significant potential. It is also noted that drugs are rarely found straight from screening hit-finding campaign, and most clinical candidates are the result of significant chemistry optimization campaigns. In conclusion, this study provides a retrospective analysis of past trends that have led to successful clinical candidates and hopefully provides the framework for the exploitation of future opportunities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.8b00675.

Tabulated changes in properties for entries 1−66 (PDF)

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Jonas Boström is currently working as Principal Scientist at AstraZeneca, Sweden. He obtained a M.Sc. in Chemistry at the University of Gothenburg in 1996 and a Ph.D. in Computational Medicinal Chemistry in 2000 at the University of Copenhagen, Denmark. Jonas has 20 years of experience in the pharmaceutical industry. He has coauthored 30+ publications, been named inventor on 15 patent specifications, and is a member in project teams delivering a number of clinic compounds, including one launched drug. Research interest includes all aspect of digitalizing chemistry, from synthetic methods, SAR, ultrafast virtual screening capabilities to the use of AI in drug design. Jonas is also Associate Professor at the University of Gothenburg and CEO of EduChem VR, a start-up gamifying chemistry education using virtual reality.

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ABBREVIATIONS USED

FBLG, fragment-based lead generation; CNS/pain, central nervous system and pain; DEL, DNA-encoded library screening; FIH, first-in-human; GPCR, G-protein-coupled receptor; HTS, high-throughput screening; MoA, mode of action; MW, molecular weight; SBDD, structure-based drug design; VS, virtual screening.

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