

Lecture Sept. 6 and 11, 2018

Where Do Recent Small Molecule Clinical Development Candidates Come From? | Journal of Medicinal Chemistry

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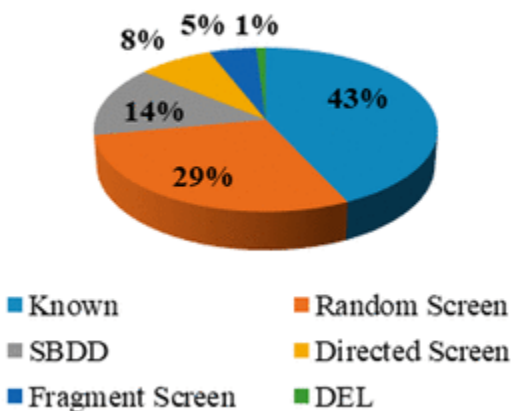
J. Med. Chem. **2018**, 61, 21, 9442–9468

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 ($\Delta MW = +85$) but no change in lipophilicity ($\Delta clogP = -0.2$), 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.

Key concepts

Lead generation strategies:



Target classes:

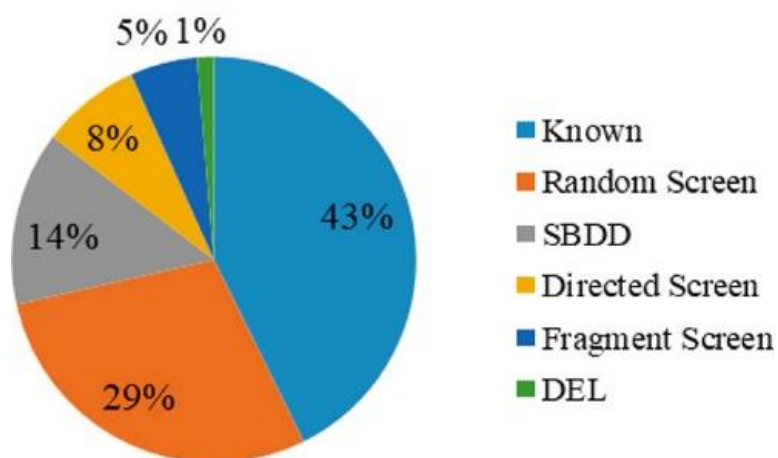
- Kinases (30%)
- Other enzymes (23%)
- GPCR's (17%)
- Epigenetic (9%)

Disease areas:

- Oncology (30%)
- CNS/Pain (18%)
- Infection (14%)
- Metabolic (12%)

[Epigenetics=the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.]

Lead Generation Strategy (%)



Explain:

(1) Random screen or high throughput screen (HTS): _____

(2) Directed screen: _____

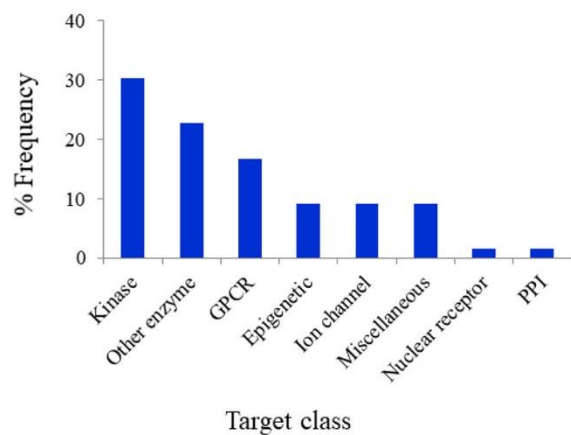
(3) Structure-based drug design (SBDD): _____

(4) Fragment screen or Fragment based lead generation (FBLG): _____

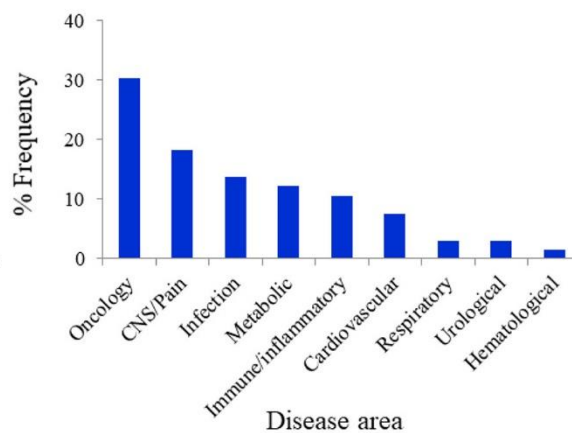
(5) DNA-encoded library screening (DEL): _____

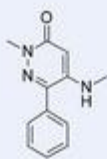
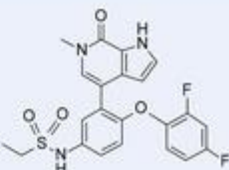
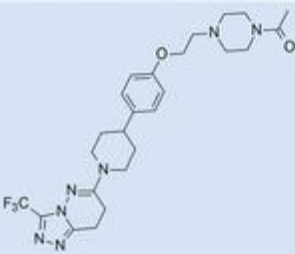
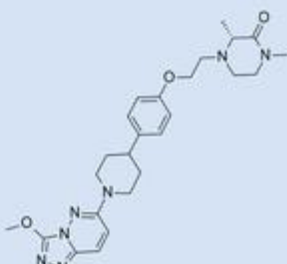
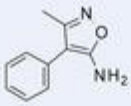
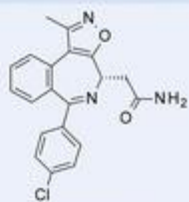
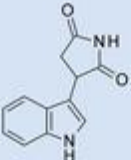
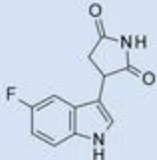
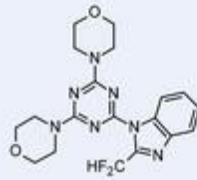
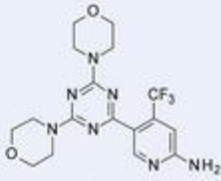
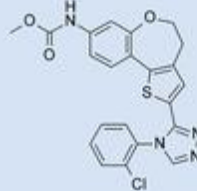
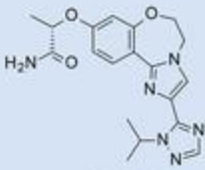
(6) Known compounds: _____

a) Target class distribution of hit-to-clinical pairs

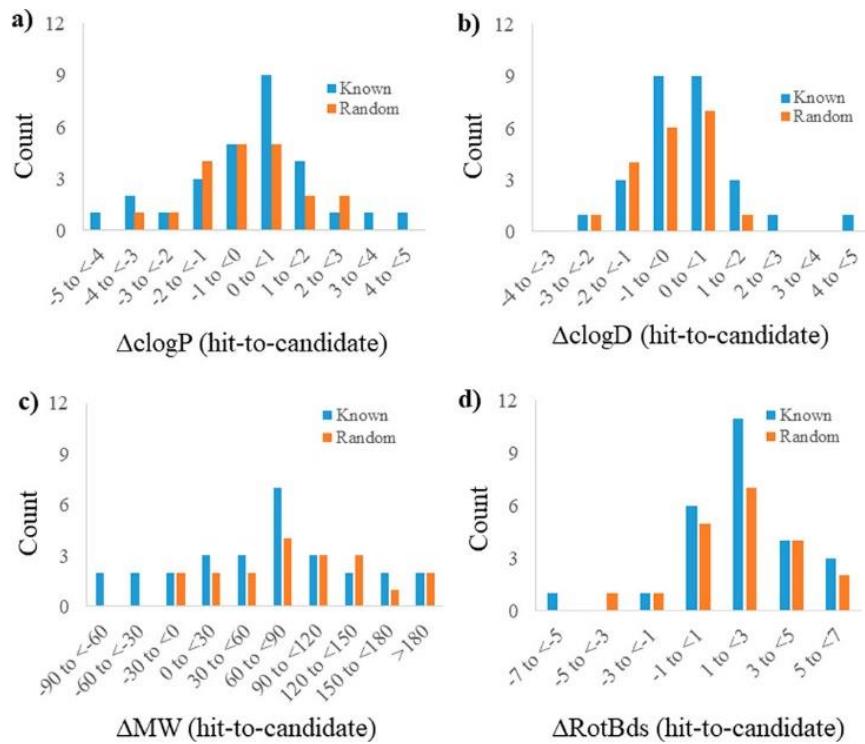


b) Disease area distribution of hit-to-clinical pairs



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)	 (PQR 309)	Known	PI3K/mTOR	Oncology	18
6		 (GDC-0032)	Known; SBDD	PI3ka	Oncology	19

Drug properties:



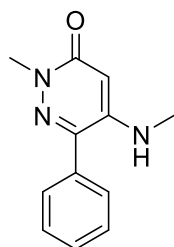
1. **c log P** = calculated log of the _____

(P) =

(note c = calculated versus experimentally determined)

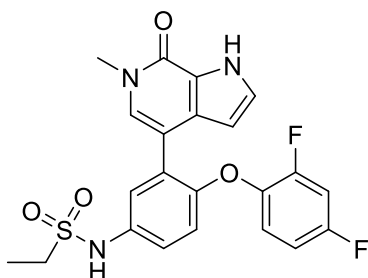
- measure of _____, one organic and one aqueous → mimicking experience of drug passing through....
- _____, and _____ in body.
- Drug form is _____

e.g. ChemDraw example....



initial hit

c log P = _____



mivebresib (ABBV-075)

c log P = _____

(references for compounds: J. Med. Chem. 2017, 60, 3828 and 2017, 60, 8369)

Note: final drug candidate _____ by more than one order of magnitude!

*most drugs have a log P = _____

-barbituates (sedatives) all have a log P ~ _____ (need _____ penetration)

2. log D = _____ coefficient, which is also the ratio of [Drug]octanol/[Drug]water, but it includes _____ of the drug (solute) so the pH of the aqueous solution matters. Note: most ionized form of drug will be in the _____ layer

-log P = log D at the _____

-e.g.

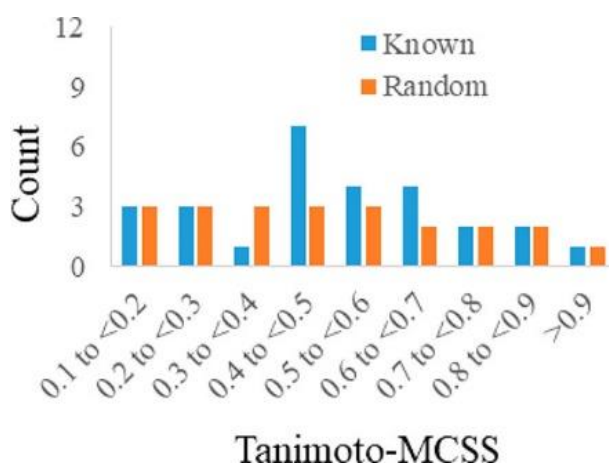
3. molecular weight...

4. rotatable bonds= _____

-measure of _____, but also _____

To understand this, consider...

In thermodynamic terms, what happens to a drug when it binds in a protein or enzyme? In particular, what effect does the binding have on entropy?



-Tanimoto MCS = measure of _____ (see J. Med. Chem. 2014, 57, 3186)

(MCS = maximum common substructure)

*Similar molecules have a Tanimoto number close to 1. Dissimilar molecules have a Tanimoto number close to 0.

LE = ligand efficiency = affinity of _____ →

(ΔG)/_____

[great reference: “The role of ligand efficiency metrics in drug discovery” Andrew L. Hopkins, György M. Keserü, Paul D. Leeson, David C. Rees & Charles H. Reynolds, *Nature Reviews Drug Discovery* **2014**, 13, pages 105–121]

-measure of how much _____ provides to overall

_____ for target

-affinity measured as ΔG in kcal from _____ or _____

-Note: ΔG = _____

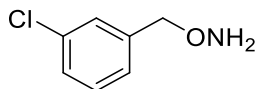
-the inhibition constant is a _____

-number of heavy atoms (HA)= number of non-H atoms

Therefore equation can be written as

LE = - _____ or _____ or

e.g.



K_i = 154 nM has _____ heavy atoms, therefore

LE = _____ → LE = _____

Optimal values?

“LE > _____ kcal per mole per heavy atom

From *Nature Reviews Drug Discovery* **2014**, 13, pages 105–121

LLE = _____

=

-links _____ and _____ in an attempt to estimate
drug “likeness” (Wikipedia)

-c log P often substituted for log P; pIC₅₀ is the -log (IC₅₀)

e.g. IC₅₀ ~ 10⁻⁹ M (nM level) and log P around 2, then...

LLE = _____

Optimal values?

LLE > _____

based on a K_d <10 nM molecule having a heavy atom count of 38 (~500 Da) and a cLogP < 3.

Key point: You can drive your potency simply by making a drug _____, but that won't help in the long run with _____. Often greasy molecules have bad _____.

Important points highlighted in Results and Discussion section

Overall: MW increased and structural complexity increased (Tanimoto change significant)

1. Random HTS versus Known compound leads → _____

Message: Whether you start with a _____ or with a _____ compound, you have similar _____ happening.

2. More _____ atoms added on average: _____

3. 2/3rds of clinical candidates added _____

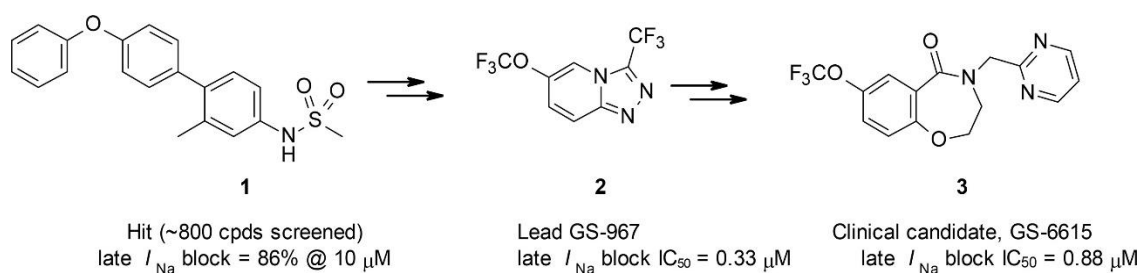
-properties of heterocyclic N? _____

4. 1/3rd of clinical candidates _____

-properties of _____? _____

5. _____ common, but _____ also worked:

Fig. 5. Example of hit-clinical success from small, directed screening set

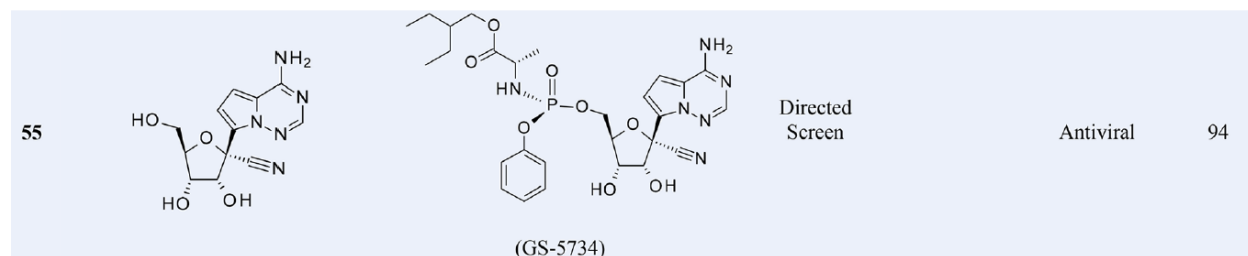


-not sure how the "hit" helped lead to the "lead" and then on to "clinical candidate"

- isolated enzyme or receptor _____
- less common, but interesting: phenotypic screens→ _____

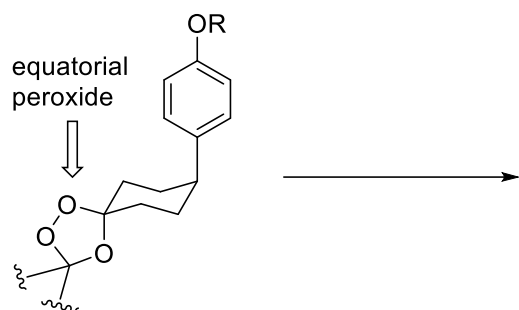
-prior to 2010, _____ AstraZeneca internal drug projects lacked a clear link between main target and disease

-prodrug=

[illegible]

-an example of “ _____ ” → _____ (IP)
is important

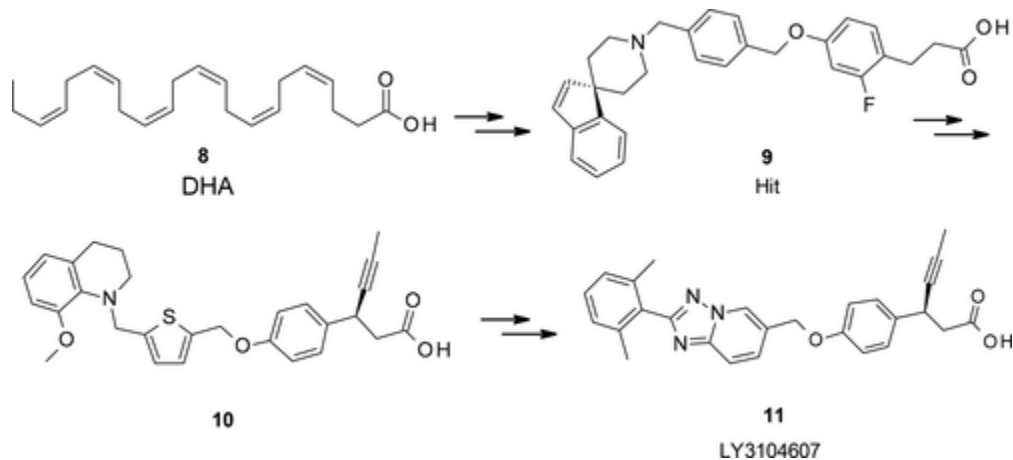
10. Table 1, entry 58: Chair _____ on peroxide structure



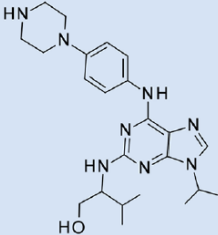
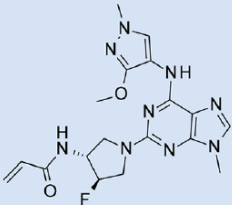
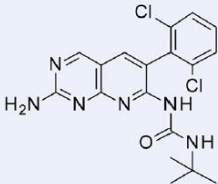
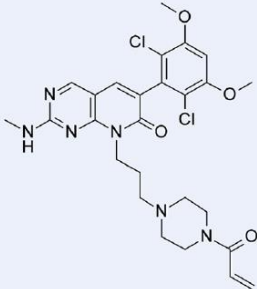
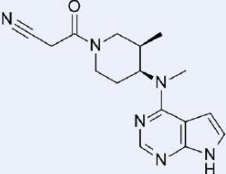
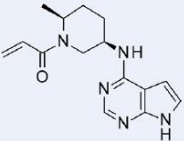
-better _____ for axial peroxide and improved _____

11. Table 1, entry 25 and Figure 8: natural substrate, DHA (docosahexanoic acid, an omega-3 fatty acid; a primary structural component of the human brain, cerebral cortex, skin and retina) is the natural ligand of GPR40 and was the _____.

-see similarity in _____ chain and benzene structures → both _____



12. IP issues _____! (p. Q, bottom right)

8			Directed Screen; SBDD	EGFR (mutant)	Oncology	23
11			Known; SBDD	FGFR	Oncology	26, 27
61			Known; SBDD	JAK3	Inflamm. diseases	101

Entry 61 lead is _____ (trade name: Xeljanz, a JAK1 and JAK3 inhibitor) →
clinical candidate (PF-06651600) is a JAK3 selective inhibitor. Development based on X-ray structure.
JAK=_____

-From Young and Leeson [Mapping the Efficiency and Physicochemical Trajectories of Successful Optimizations](#) | [Journal of Medicinal Chemistry](#)

1. seek necessary _____
2. _____
3. _____
4. _____