Rules, filters, pharmaceutical principles and future trends in drug discovery

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Outline

- How a medicinal chemist looks at drugs
  - annotation
- Target druggability and target choice
- Target tractability can change
  - “Stapled Peptides” as an example of new structures
- Do we have tools for larger ligands?
- Redox and thiol filters
  - FDA drugs
- Diversity in screening, good or bad?
- General rules and filters
- Biologically active chemistry space
- Academic drug discovery

Medicinal chemistry annotation

- Start with the structure of a hit. Is it known?
- What do you see in a substructure search?
- Try to understand the chemistry. How were the compounds made and how might they react?
- What is the pattern in the literature for compounds at about 85% similarity
- Look at 10 – 20 compounds and references.
- This type of annotation is almost impossible to do using public domain tools.

Hedgehog screening – chemistry blog

CORANTE

Home > Weblog Columns > In the Pipeline

ABOUT THIS AUTHOR

In the Boston area?: Join us on June 11 for insights from Intuit founder Scott Cook and

In the Pipeline

Dealing With Hedgehog Screening Results

Posted by **Derek**

I was looking over a paper in PNAS, where a group at Stanford describes finding several small molecules that inhibit Hedgehog signaling. That's a very interesting (and ferociously complex) area, and the more tools that are available to study it, the better.

But let me throw something out to those who have read (or will read) the paper. (Here's the PDF, which is open access). The researchers seem to have done a screen against about 125,000 compounds, and come up with four single-digit micromolar hits. Characterizing these against a list of downstream assays showed that each of these acts in a somewhat different manner on the Hedgehog pathway.

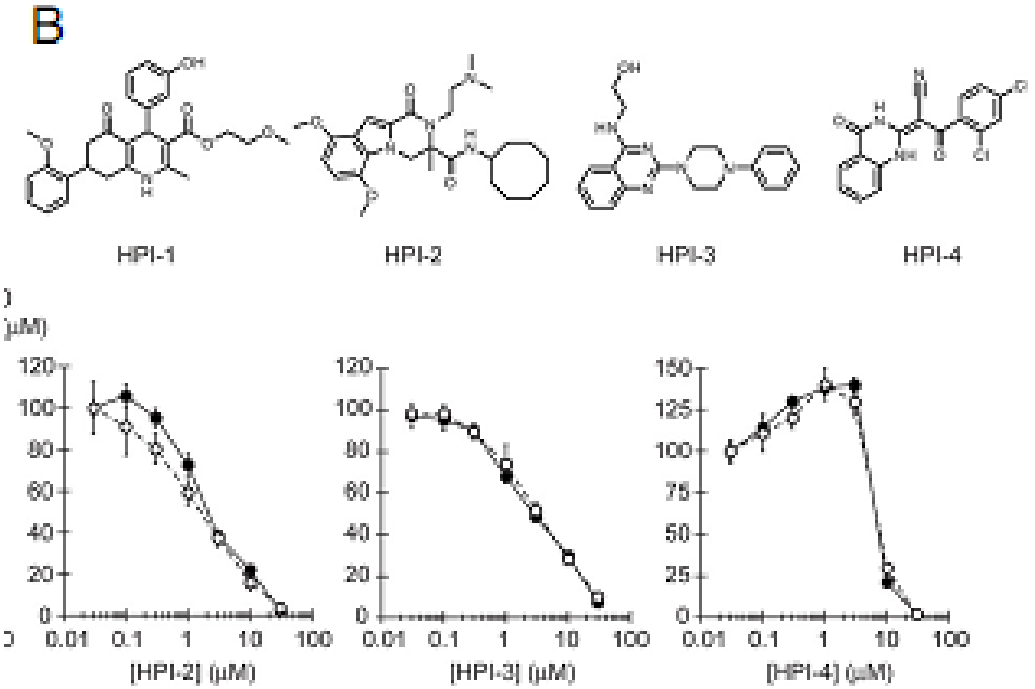
Hedgehog screening -PNAS

Small-molecule inhibitors reveal multiple strategies for Hedgehog pathway blockade

Joel M. Hyman[a,1], Ari J. Firestone[a,1], Vivi M. Heine[b], Yun Zhao[c,d], Cory A. Ocasio[a], Kyuho Han[a], Mark Sun[a], Paul G. Rack[a], Surajit Sinha[a,2], Jason J. Wu[e], David E. Solow-Cordero[e], Jin Jiang[c], David H. Rowitch[b], and James K. Chen[a,3]

[a]Department of Chemical and Systems Biology and [e]Stanford High-Throughput Bioscience Center, Stanford University School of Medicine, Stanford, CA 94305; [b]Institute for Regenerative Medicine, Howard Hughes Medical Institute, University of California, San Francisco, CA 94143; [c]Department of Developmental Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390; and [d]Laboratory of Molecular Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

Communicated by Matthew P. Scott, Stanford University School of Medicine, Stanford, CA, June 29, 2009 (received for review January 9, 2009)



Hedgehog screening - my comment

4. Chris on August 12, 2009 2:18 AM writes...

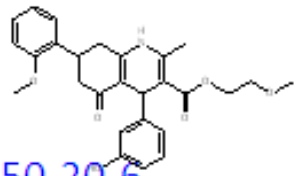
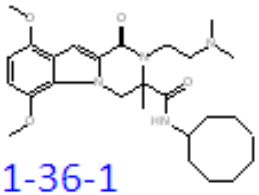
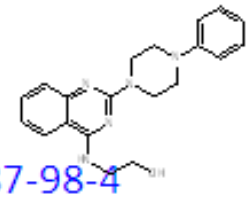
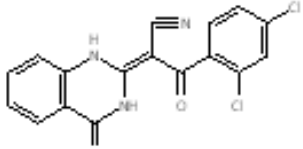
There is a common theme to the four "actives" identified in this paper. They are all commercially available compounds with a CAS registry number and (almost) no literature references. In each case there are commercially available analogs at high similarity again with CAS registry numbers and again no references. I frequently see this pattern in "actives" and it makes me deeply suspicious. What do you think is the probability that a vendor would make a totally novel series just to hit in my new screen? If I were suspicious I might think that the origin of each series was a compound with a flaw that hit enough screens to warrant preparing a flawed analog series. I particularly do not like HPI-4 with a push pull polarized double bond crying out "I am a Michael acceptor please interact with me".

"actives" all commercially available compounds …. no literature references ……. suspicious

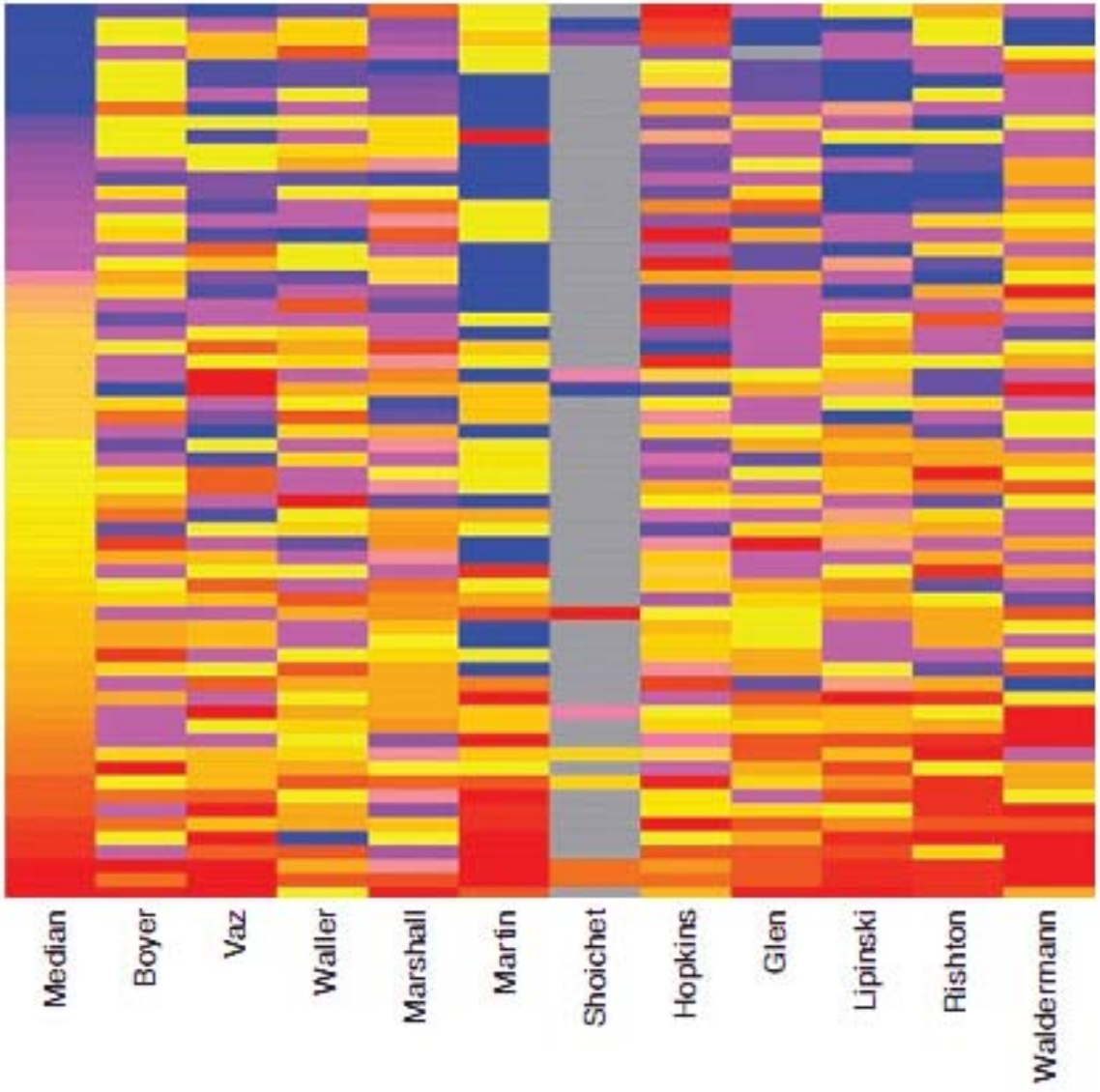
A profile to avoid

- The structure of a hit appears in CAS SciFinder
- It is a commercial compound with a CAS Registry Number but no references
- There are multiple compounds at 85% or better similarity
- All the similar compounds are commercially available with no literature references
- WARNING FLAG
- This could be a problematic series that proliferates because it is a flawed HTS hit series

Hedgehog screening – Alarm filters

CHEMISTRY	NAME	Alarm	smartsfilter_matches
 599150-20-6	HPI-1	**failed**	C=CC(=O)O[c,C] () C=CC(=O)[c,C] () Oc1[a;R1][a;R1]a[a;R1][a;R1]1 ()
 868881-36-1	HPI-2	**passed**	
 796887-98-4	HPI-3	**failed**	[N;!$([N+]);!$(NC=[O,N])]c1[a;R1][a;R1]a[a;R1][a;R1]1 ()
 302803-72-1	HPI-4	**failed**	C=CC(=O)[c,C] ()

Annotation on 64 HIH tools and probes



Oprea et al. Nature Chemical Biology 2009, 5(7), 441-447.

Red is high dubiosity (low confidence), blue is low dubiosity (high confidence)

Chemical novelty and discovery success

- Biologically active compounds are not evenly distributed in chemical space
- Composition of matter patents drive chemistry toward greater novelty and away from precedented chemistry space
- Greater chemistry novelty tracks with decreasing success (greater attrition)
- Modest amount of literature background around an HTS hit is a positive

Not all targets are equal in screening

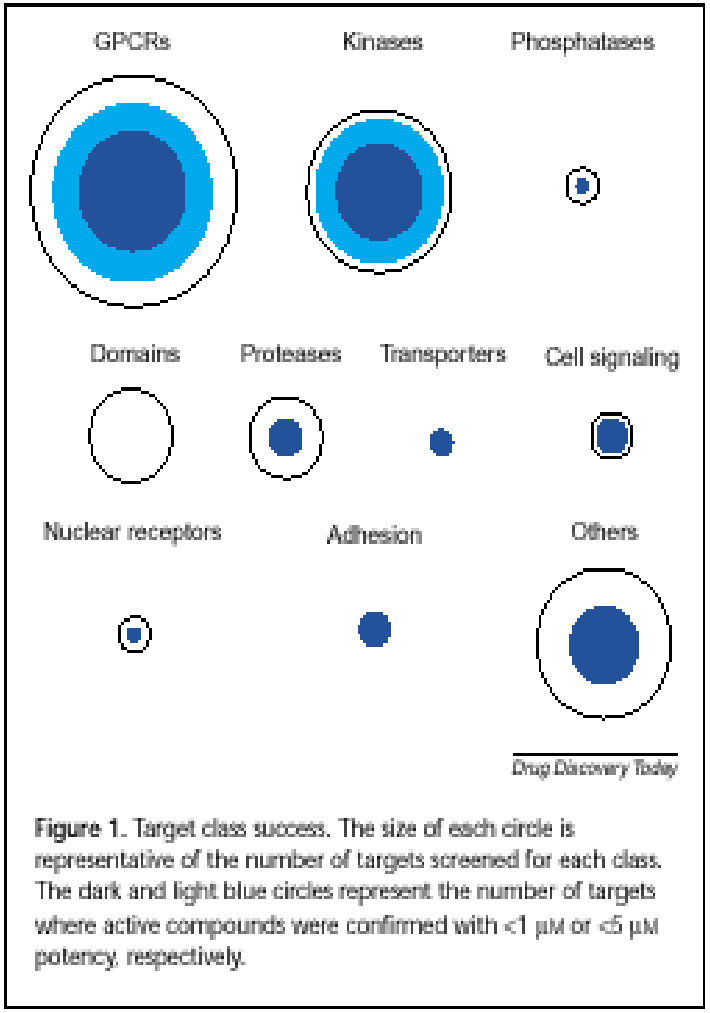


Figure 1. Target class success. The size of each circle is representative of the number of targets screened for each class. The dark and light blue circles represent the number of targets where active compounds were confirmed with <1 μM or <5 μM potency, respectively.

Size of colored graphic = screening success at Pharmacopeia

Reproduced with permission from "Targeting signal transduction with large combinatorial collections", D. S. Auld, D. Diller, K. Ho, Drug Discovery Today, 2002, 7(24) 1206-13.

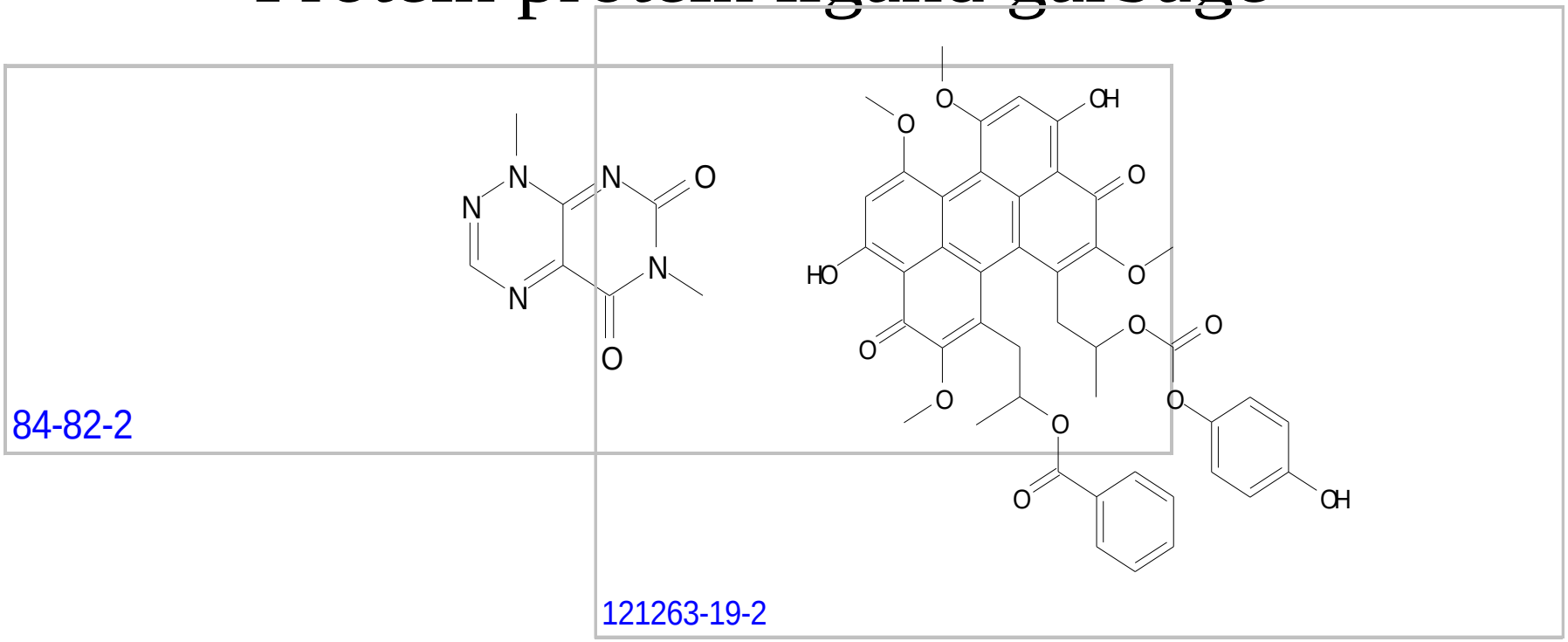
Targets, ligands and the rule of 5

- Beautiful targets and very do-able
  - GPCR's aminergic
  - phosphodiesterases
  - kinases
- Difficult targets but still do-able
  - GPCR's peptidergic
  - proteases
- Hopeless (or nearly so) targets
  - protein protein interactions
  - phosphatases

Target tractability can change

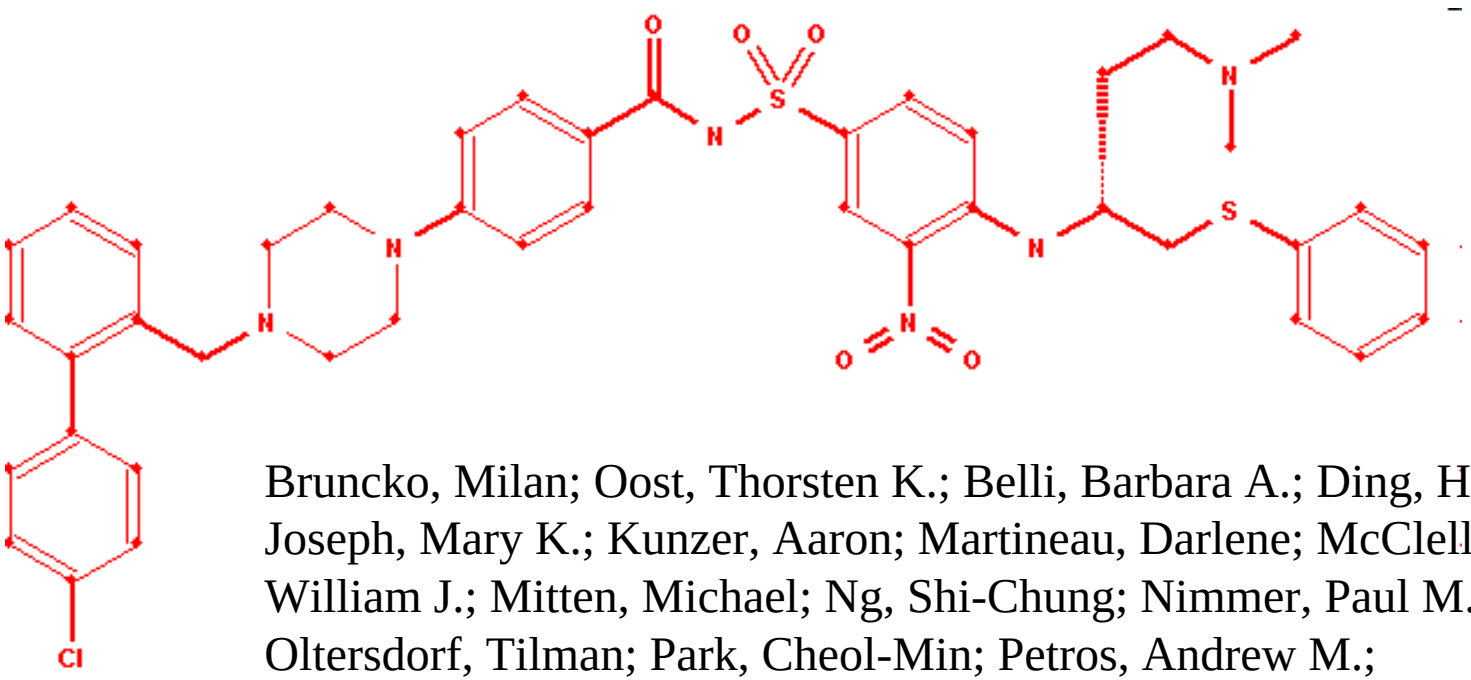
- Protein-protein interactions
  - hopeless from an HTS screening viewpoint
  - possible with structural biology information
- Scientific advances
  - fragment screening
  - SAR by nmr and x-ray
  - Bcl-2 family success from Abbott

Protein protein ligand garbage



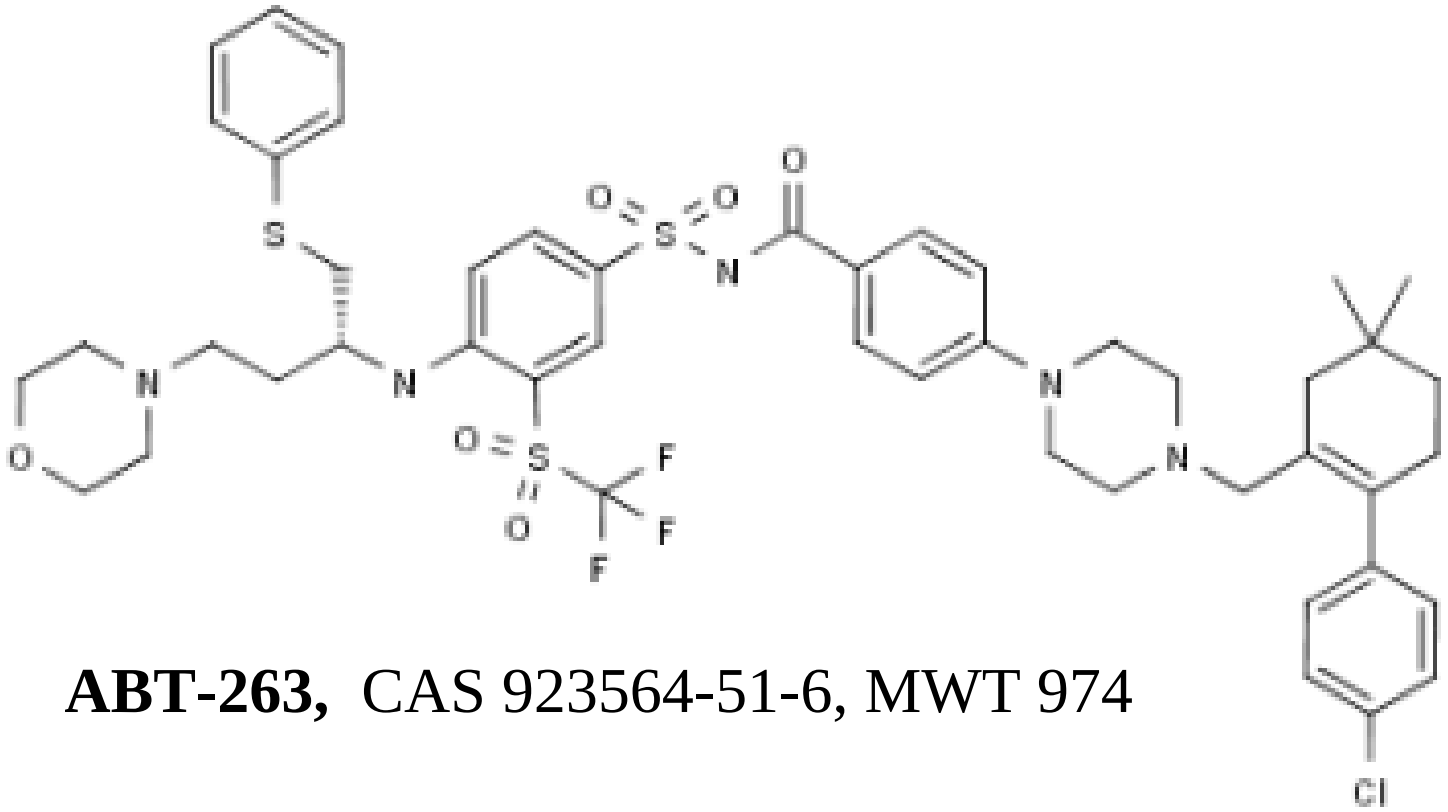
Lepourcelet, Maina; Chen, Ying-Nan P.; France, Dennis S.; Wang, Huisheng; Crews, Phillip; Petersen, Frank; Bruseo, Charles; Wood, Alexander W.; Shivdasani, Ramesh A. Small-molecule antagonists of the oncogenic Tcf/β-catenin protein complex. Cancer Cell (2004), 5(1), 91-102.

Protein protein ligand ABT-737



Bruncko, Milan; Oost, Thorsten K.; Belli, Barbara A.; Ding, Hong; Joseph, Mary K.; Kunzer, Aaron; Martineau, Darlene; McClellan, William J.; Mitten, Michael; Ng, Shi-Chung; Nimmer, Paul M.; Oltersdorf, Tilman; Park, Cheol-Min; Petros, Andrew M.; Shoemaker, Alexander R.; Song, Xiaohong; Wang, Xilu; Wendt, Michael D.; Zhang, Haichao; Fesik, Stephen W.; Rosenberg, Saul H.; Elmore, Steven W. **Studies Leading to Potent, Dual Inhibitors of Bcl-2 and Bcl-xL.** Journal of Medicinal Chemistry (2007), 50(4), 641-662.

BCL-2 inhibitor compound in phase II

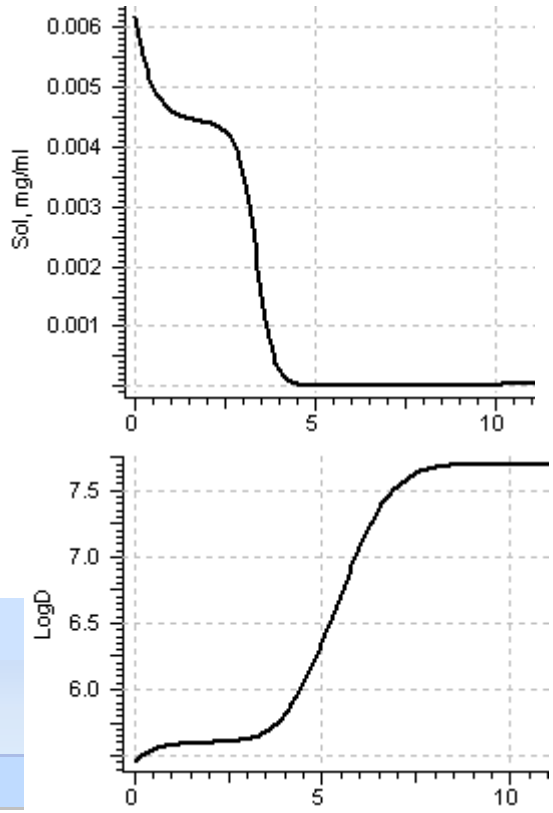


ABT-263, CAS 923564-51-6, MWT 974

Why is ABT-263 orally active???

Single-valued Properties

Name	Value	Error
LogP	9.7	1.21
MW	974.61	-
PSA	170.42	-
FRB	15	-
HDonors	2	-
HAcceptors	11	-
Rule Of 5	3	-



pKa Results

Diss. Atom	Acidic/Basic	Exact Apparent pKa V...	Error
54	MB	7.24	0.1
3	B	6.32	0.7
30	MA	4.64	0.1

Bioavailability is 20-50% depending on formulation

Protein interaction targets: Stapled Peptides

Aileron closes $40M financing with four major pharmas

CAMBRIDGE, Mass.—Aileron Therapeutics, a biotechnology company discovering and developing a novel class of therapeutics called Stapled Peptides, announced in June a $40 million Series D financing round co-led by new investors SR One Ltd., the independent corporate venture fund of GlaxoSmithKline plc, and Excel Medical Fund. The round also included major participation by existing investors: Apple Tree Partners, the founding investor of Aileron, and Novartis Venture Fund. Lilly Ventures and Roche Venture Fund also participated in the offering.

Aileron Therapeutics was first funded in 2005 by Apple Tree Partners to develop and advance a therapeutic modality and class of drugs called Stapled Peptides that are based on discoveries made at Harvard University and the Dana-Farber Cancer Institute. Stapled Peptide drugs represent the first general solution for modulating intracellular protein-protein interactions. As such, Stapled Peptide drugs offer a unique opportunity

Aileron says.

Proceeds from the financing will be used to advance Aileron's lead Stapled Peptide program toward clinical trials in 2010 and to further advance the Stapled Peptide platform and programs in oncology, immune/inflammation, metabolic disease and infectious disease. In previous financings, Aileron has raised $20 million in funding.

According to Joseph A. Yanchik III, Aileron CEO, the company has demonstrated in multiple preclinical studies the powerful potential that Stapled Peptides represent in the treatment of cancer.

"The timing of the financing round and the caliber of the participants is further validation of the growing belief in the transformative potential of this novel class of therapeutics and the need for breakthrough technology platforms that will offer significant new growth avenues for the pharmaceutical industry," Yanchik says.

The program could represent a "fourth estate" in therapeutics, emerging as a major class akin to small molecules, antibodies and vaccines, says Dr. Michael Diem, partner at SR One.

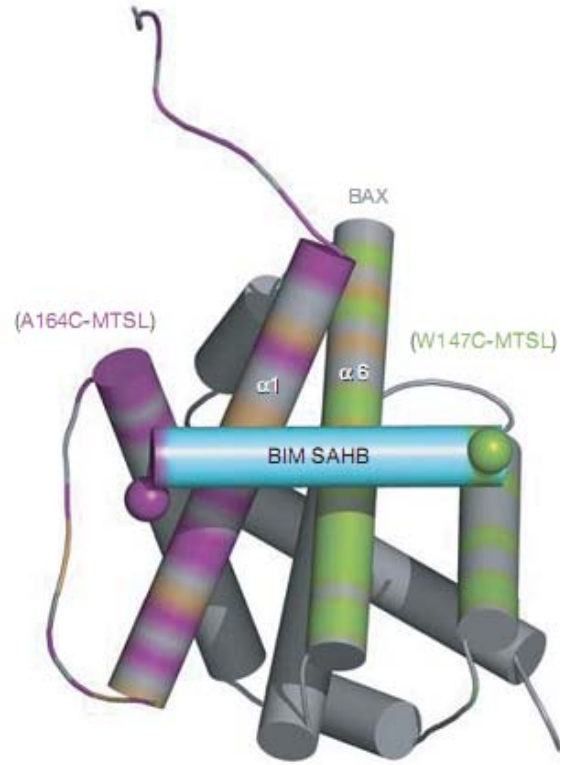
As part of the closing of this financing transaction, Diem and Dr. Enrico Petrillo, managing director of Excel Medical Fund, will join the board of directors of Aileron, joining Yanchik and existing board members Dr. Seth Harrison, chairman of Aileron and managing general partner of Apple Tree Partners, and Dr. Campbell Murray, managing director of Novartis Venture Funds. DDN

Stapled peptides - importance?

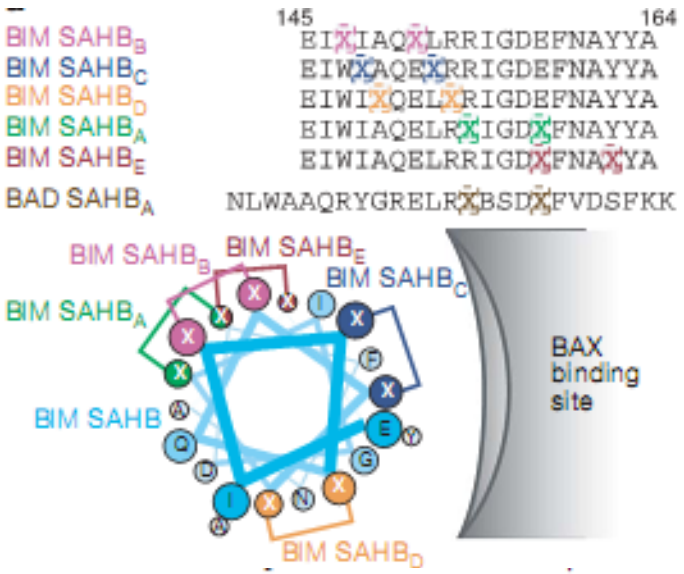
- “Stapled Peptide drugs represent the first general solution for modulating intracellular protein-protein interactions. As such, Stapled Peptide drugs offer a unique opportunity to exploit potentially thousands of currently “undruggable” targets across all human diseases, Aileron says”

Drug Discovery News, July 2009, page 3.

BIM SAHBA, biology & chemistry view



Orientation of BIM SAHB at the BAX binding site.



purified and characterized using methodologies previously described[33,46,47]. BIM SAHB$_A$ used in the NMR and *in vitro* studies is an *N*-acetylated, C-amidated 20-amino-acid peptide Ac-^{145}EIWIAQELRXIGDXFNAYYA^{164}-CONH$_2$, in which X represents the non-natural amino acid inserted for olefin metathesis. To

"BAX activation is initiated at a novel interaction site." Gavathiotis E. et al., Nature (London) 2008, 455 (7216) 1076-1081

BIM SAHBA in Prous Integrity®

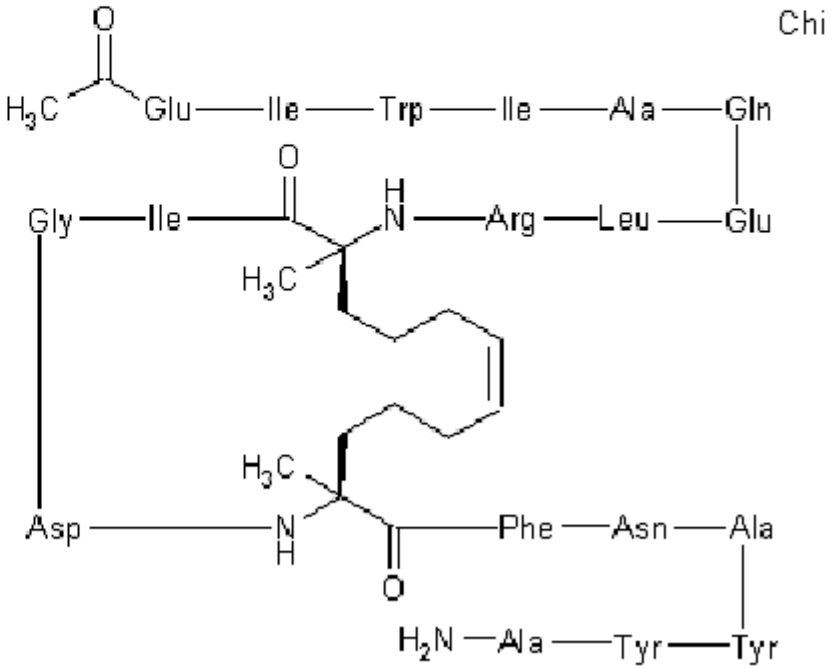
Records Retrieved 1 in Drugs & Biologics **Options**

Drugs & Biologics Search Results

Query > **Drug Name** = BIM SAHBA

Entry Number	643587
Molecular Formula	C118H171N27O31
Molecular Weight	2463.7826
Highest Phase	Biological Testing

Chemical Structure STRUCTURE

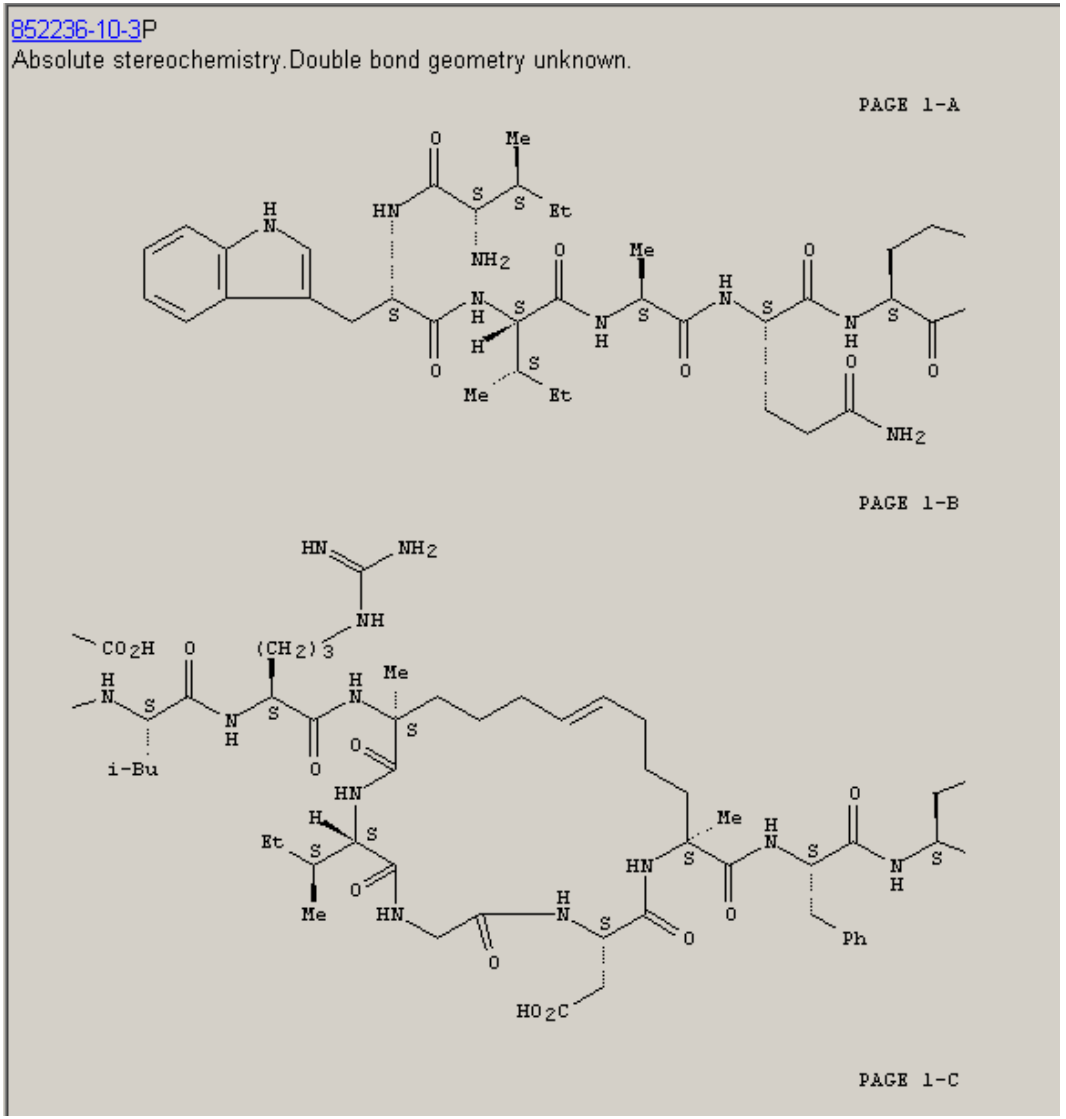


BIM SAHBA

*You can export data in *.sdf format from Prous Integrity®. The sdf file format allows import into software that reads in chemical structures. From the sdf file you can create an *.mol file that can be imported into CAS SciFinder®.*

Closest SciFinder match to BIM SAHBA

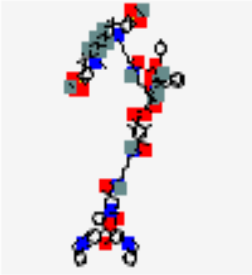
CAS SciFinder® has no exact match for BIM SAHBA.
CAS 852236-10-3 is the closest structure at 98% similarity to the BIM SAHBA structure retrieved from Prous Integrity®.



Nature Chemical Biology

SID: 26527391

Related Structures, Literature



nchembio.2007.26-comp8; 2-((1E,3E,5Z)-5-(1-((5S,8S)-5-benzyl-8-(2-(4-(6-(1-(2-((E)-6-(indolin-1-yl)-3-(indolinium-1-ylidene)-3H-xanthen-9-yl)phenylsulfonyl)piperidine-4-carboxamido)hexylcarbamoyl)-2,6-dimethylbenzoyloxy)acetyl)-3,6,14-trioxo-1-phenyl-2-oxa-4,7,13-triazanonadecan-19-yl)-3,3-dimethyl-5-sulfoindolin-2-ylidene)penta-1,3-dienyl)-1-ethyl-3,3-dimethyl-5-sulfo-3H-indolium

Compound ID: 16667342

Source: Nature Chemical Biology (nchembio.2007.26-comp8)

MW: 2020.471440 g/mol | **MF**: $C_{114}H_{126}N_{10}O_{18}S_3^{+2}$

Nature Chemical Biology directly deposits chemistry structures as SID's to PubChem. As of Aug 9 there were 3841 SID's. The highest MWT was 2020.

I easily downloaded all 3841 PubChem records as a machine readable *.sdf file. Batch mode operations are a big plus to the user but curation is likely to be an ongoing problem.

SiRNA there are no chemistry tools

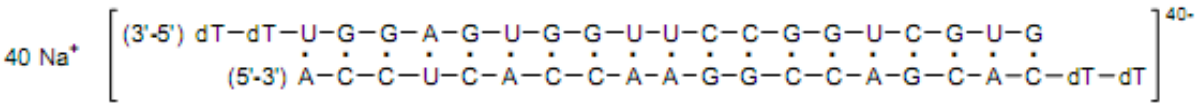
STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL

USAN	BEVASIRANIB SODIUM
PRONUNCIATION	be va" sir an' ib
THERAPEUTIC CLAIM	Treatment of wet age-related macular degeneration

CHEMICAL NAMES

1. RNA, (A-C-C-U-C-A-C-C-A-A-G-G-C-C-A-G-C-A-C-dT-dT), eicosasodium salt, complex with RNA (G-U-G-C-U-G-G-C-C-U-U-G-G-U-G-A-G-G-U-dT-

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{401}H_{463}N_{153}Na_{40}O_{290}P_{40}$
MOLECULAR WEIGHT	14224

Do we have the best tools?

- If chemistry drug discovery really moves more into structures with size in between small molecules and biologicals: Do we have the best tools?
- MWT 4000 tools OK, MWT 14000 hopeless
- Will more journals deposit structures?
- **My short experiment with BIM SAHBA points to the importance of user input?**

Industry filters vary a lot

- Pfizer –lint
  - likely the strictest filters in big pharma
- Glaxo
  - compounds to avoid – very loose
- Abbott – Alarm NMR
  - possible HTS problems due to Redox problems
  - a continuum rather than binary filter

Abbott Alarm NMR filters

Table S2. Structural Descriptors Used To Predict Thiol Reactivity

Smile	F (%)[a]	TRI[b]	#tested	Smart
O=C1C=CC(=O)C=C1	100	0.30	16	O=C1C=CC(=O)C=C1
c1oc(=S)sc1	85	0.30	21	c1oc(=[O,S])sc1
O=C1OCCS1	85	0.30	20	O=[#6]1[o,O][#6]@[#6][s,S]1
SC#N	66	0.30	19	SC#N
[OH]c1ccc(O)cc1	60	0.30	35	[OH]a1aaa(O)aa1
O=C1CCC(=O)C=C1	60	0.30	10	O=C1CCC(=O)C=C1
O=C1C=CCC=C1Br	55	0.30	14	O=C1C=CCC=C1[F,Cl,Br,I]
C=CS	50	0.30	12	C=[C;R0]S
C=CCl	48	0.30	57	C=C[Cl,Br,I]
c1cccc2nonc12	48	0.30	27	c1cccc2nonc12
Oc1ccc2nc(F)cnc2c1	47	0.30	20	[N,OH]c1ccc2nc([c,F])c[c,n]c2c1
[OH]c1ccc(N)cc1	44	0.30	60	[OH]a1aaa([n,N;R0])aa1
Nc1cccs1	44	0.30	30	[N;R0]a1caas1
Sc1ccccc1N	42	0.30	35	[s,S;R0;!$(S(=O)(=O)N)]a1a([n,N;R0])aaaa1
C(=S)S	42	0.30	18	[#6]C(=S)S
SC1=NCCS1	38	0.30	40	SC1=NCC[N,S]1
n1ncnc2C(=O)NC(=O)Nc	37	0.30	16	n1ncnc2c(=O)nc(=O)nc12
c1nsnc1	34	0.30	60	c1n[o,s]nc1
[SH]	34	0.30	37	[#6;!$(C=C);!$(CO);!$(CN)][SH]
CBr	33	0.30	62	[C;!$(C=C)][Br,I]
C1=CN=NC(=O)C1I	33	0.30	12	c1cnnc(=O)c1[Cl,Br,I]
NC=S	31	0.30	74	[n,N][c,C;R1]=S
C1CSCN1	30	0.30	81	C1CSCN1
Nc1nccs1	30	0.30	51	Nc1nccs1

Filters detect from 100% to 3% of compounds causing thiol perturbation problems.

Up to the user to set an acceptable threshold

Huth J. R. et al. J. Am. Chem. Soc., 2005 127, 217-224

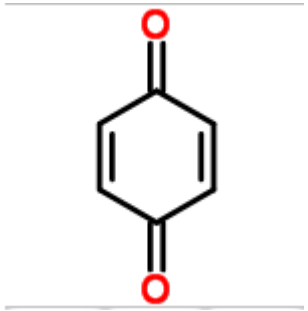
Alarm NMR fail on 740 FDA Drugs

CHEMISTRY	smartsfilter_matches	smiles	fail(#)	F (%)
ACEBUTOLOL	Oc1[a;R1][a;R1]a[a;R1][a;R1]1 ()	c1ccccc1O	46	10
Acetohexamide	S(=O)(=O)N ()	S(=O)(=O)N	44	8
Azithromycin	[o,O;R1][c,C]=O ()	O=C1CCCCO1	32	17
6alpha-Methylprednisolone	C=CC(=O)[c,C] ()	C=CC(=O)C	30	42
5-(N,N-dimethyl)-Amiloride	[N;!$([N+]);!$(NC=[O,N])]c1[a;R1][a;R1]a[a;R1][a;R1]1 ()	c1ccccc1N	29	10
Acetophenazine	[c,C;!$(C=O);!$(C=N);!$(C=S)][S;!$(S=O)][c,C;!$(C=O);!$(C=N);!$(C=S)] ()	CSC	26	23
(-)-Epinephrine	[OH]a1aaaaa1O ()	[OH]c1ccccc1O	21	22
Amlodipine	C=CC(=O)O[c,C] ()	C=CC(=O)OC	14	20
Ampicillin	C1CSCN1 ()	C1CSCN1	14	30
Almotriptan	csc ()	c1sccc1	14	19
AZTREONAM	Nc1nccs1 ()	Nc1nccs1	14	30
ANISINDIONE	c1ccccc1[C;R1](=O)[c,C] ()	c1ccc2C(=O)CCCc2c1	13	23
ACETYLCYSTEINE	[#6;!$(C=C);!$(CO);!$(CN)][SH] ()	[SH]	10	34

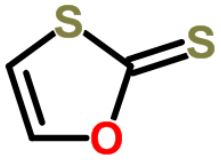
Adjusting Alarm NMR filters

- FDA approved 740 drug data set
- Most failures are where F(%) < 30
- Suggests using filters where F(%) > 30
  - ie. filter only the really bad actors
- Moiety thiol reactivity values exist
- Suggests idea generation for thiol proteases

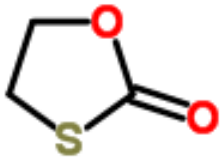
Worst Alarm NMR moieties



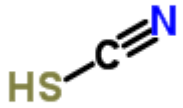
100%



85%



85%



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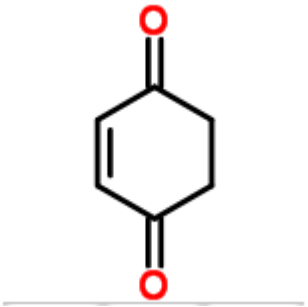

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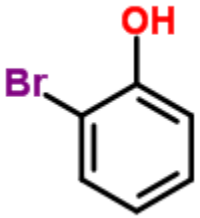

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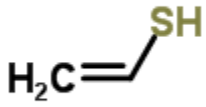
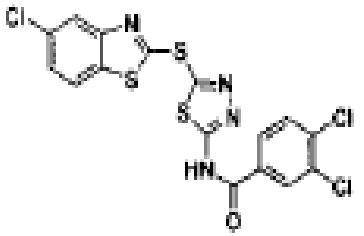
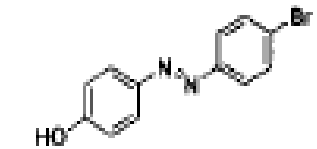
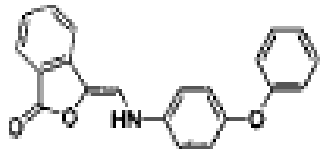


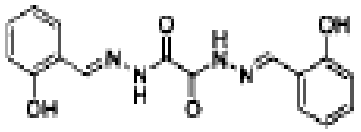
50%

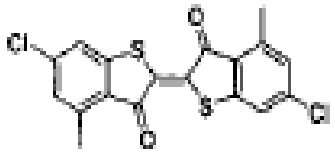
Bad chemistry: aggregation false positives in HTS assays

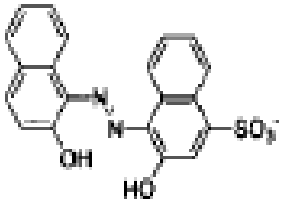


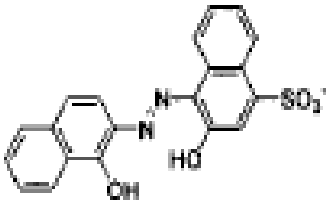


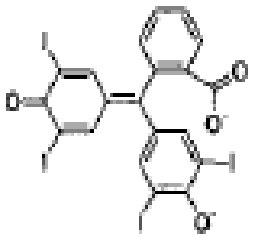


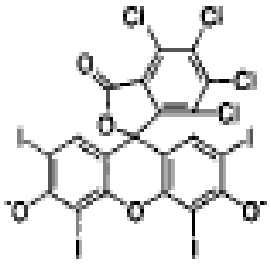


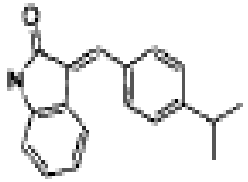


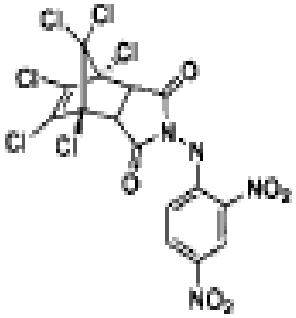








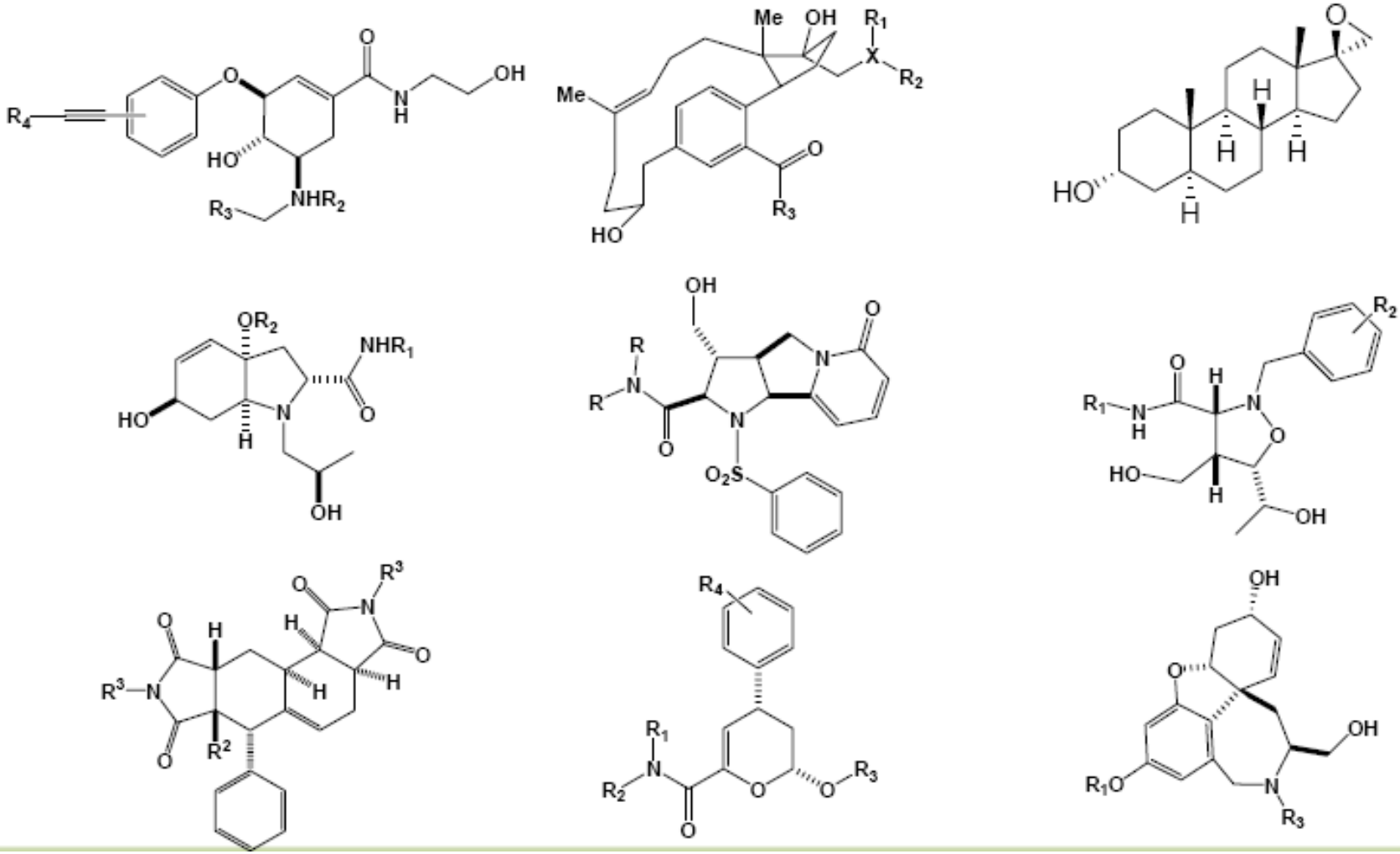




Remove these types of compounds from any assays

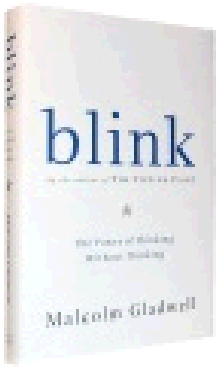
These looked good to PHARMACIA screeners

Nice chemistry: topology in DOS libraries



Chemistry pattern recognition

What is Blink about?



BLINK

1. What is "Blink" about?

It's a book about rapid cognition, about the kind of thinking that happens in a blink of an eye. When you meet someone for the first time, or walk into a house you are thinking of buying, or read the first few sentences of a book, your mind takes about two seconds to jump to a series of conclusions. Well, "Blink" is a book about those two seconds, because I think those instant conclusions that we reach are really powerful and really important and, occasionally, really good.

Screening - what is the goal?

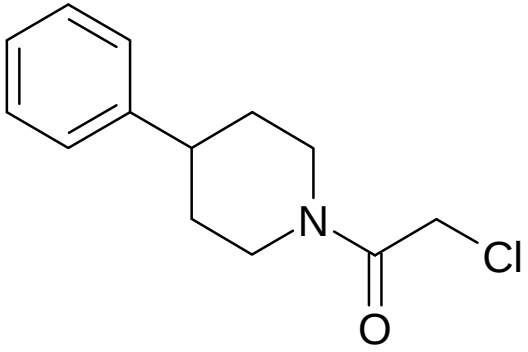
- Target validation
  - tool like compounds
  - relaxed chemistry criteria permissible
  - chemical biology
- Drug discovery
  - lead-like or drug-like compounds
  - strict chemistry criteria necessary
  - needs pharma skills

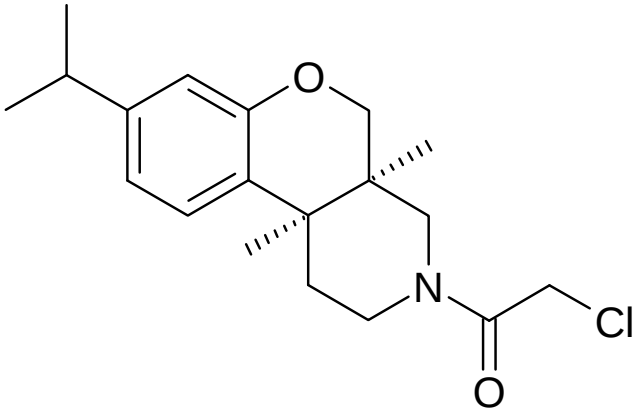
Target validation versus drug discovery

- Use a chemical tool to probe biology
  - relaxed chemistry criteria permissible
  - chemical costs go down
  - 50,000 or fewer compounds in HTS
- Drug discovery
  - strict chemistry criteria
  - cost as high as $200-400 for 15 mg compound
  - 500,000 compounds in an HTS

Tools for target validation

- Selectivity is paramount
- Covalent functionality can be OK
- But in a complex structure





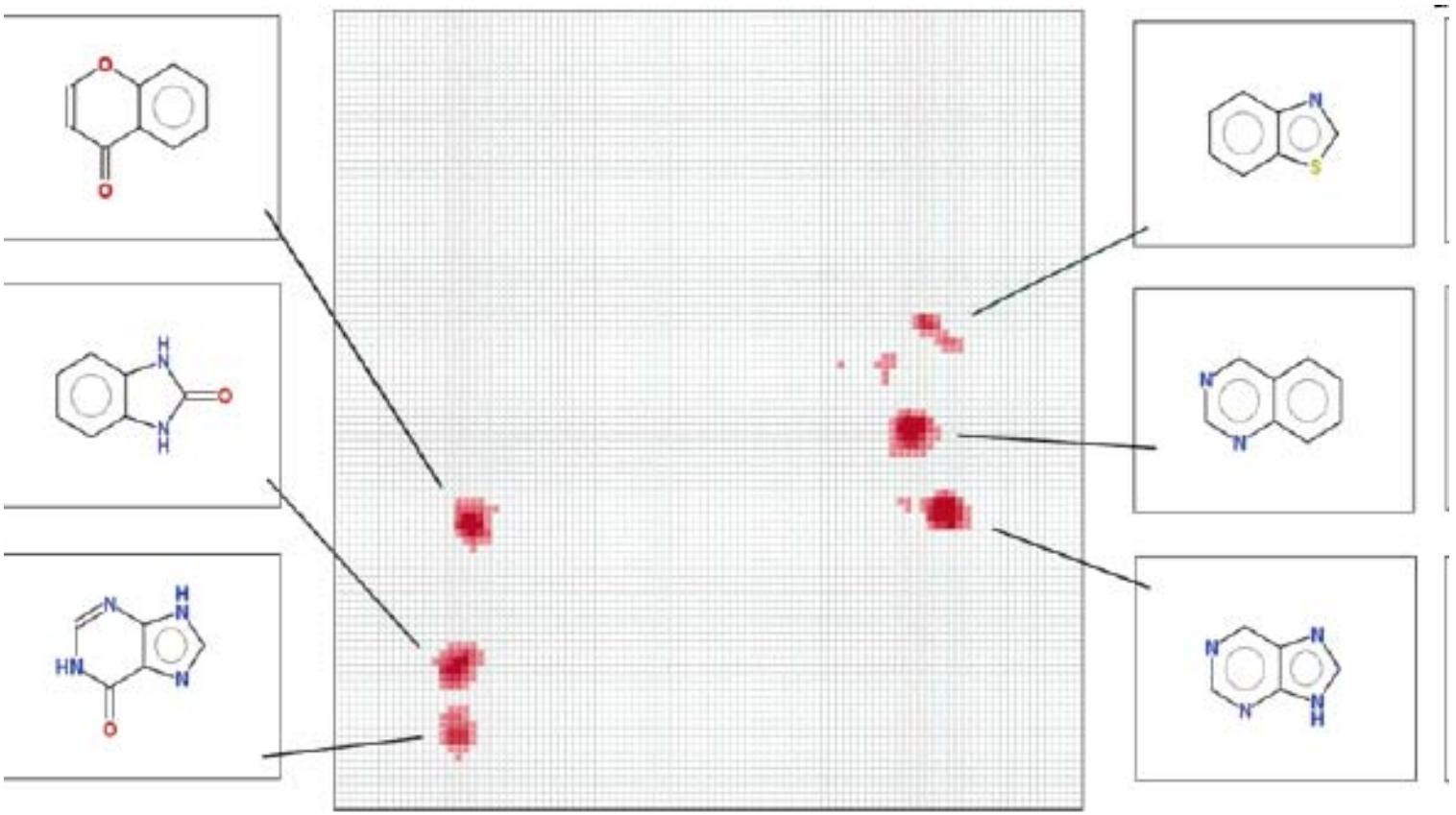
Questioning diversity

- How many targets are there?
- 20,400 genes, 10^6 proteins
- How many MWT 500 cpds in a human?
- 200 moles x 6.02 *10^{23} = 10^{26}
- Diverse compounds = 10^{60}
- Compounds / targets = 10^{-34} (1 hit / target)
- Compounds / targets = 10^{-25} (1 billion hits/ target)
- <u>Truly diverse library should never give a hit</u>

True diversity does not exist

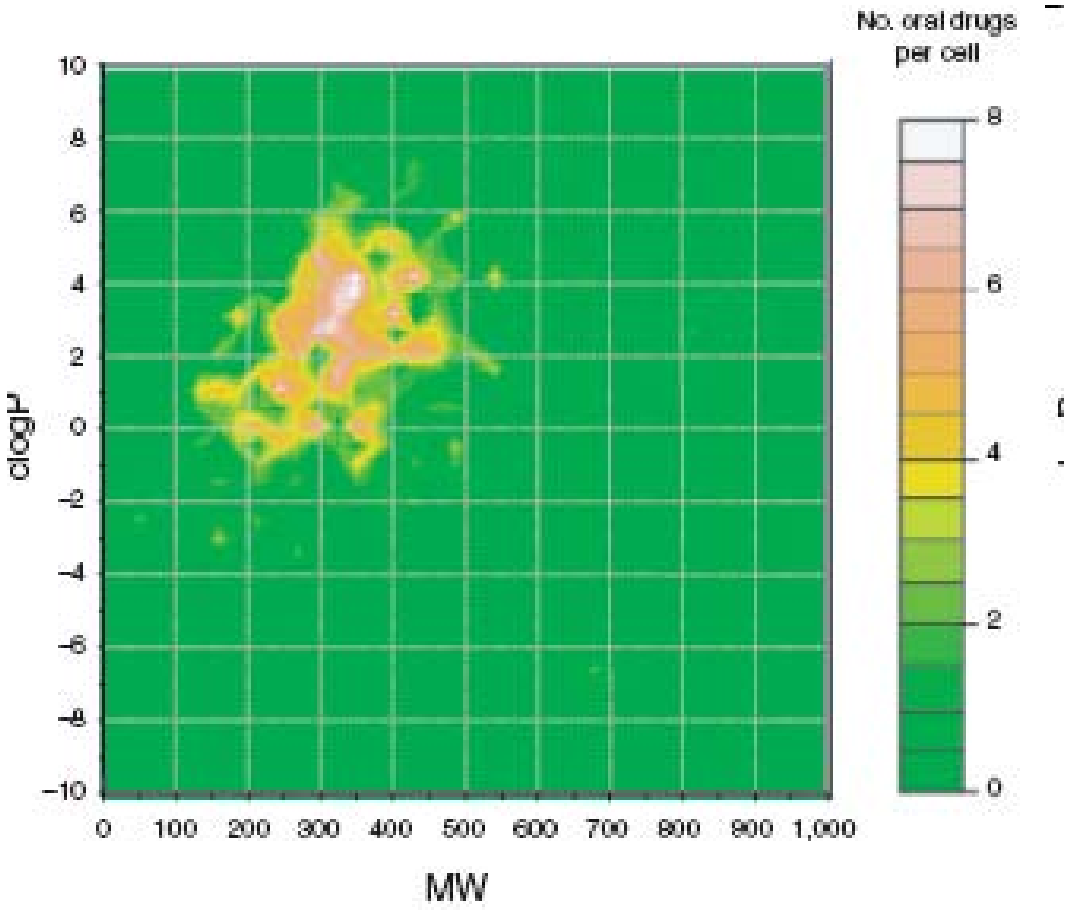
- HTS does indeed find hits
- True diversity does exist in silico
- True diversity does not exist experimentally
  - chemistry success bias
  - reagent access bias
  - people selection bias
- Involve medicinal chemists in screening library choices

Sparse activity in chemistry scaffold space



Quest for the Rings. In Silico Exploration of Ring Universe to Identify Novel Bioactive Scaffolds, Ertl et al. J. Med Chem., (2006), 49(15), 4568-4573.

Sparse oral activity in property space



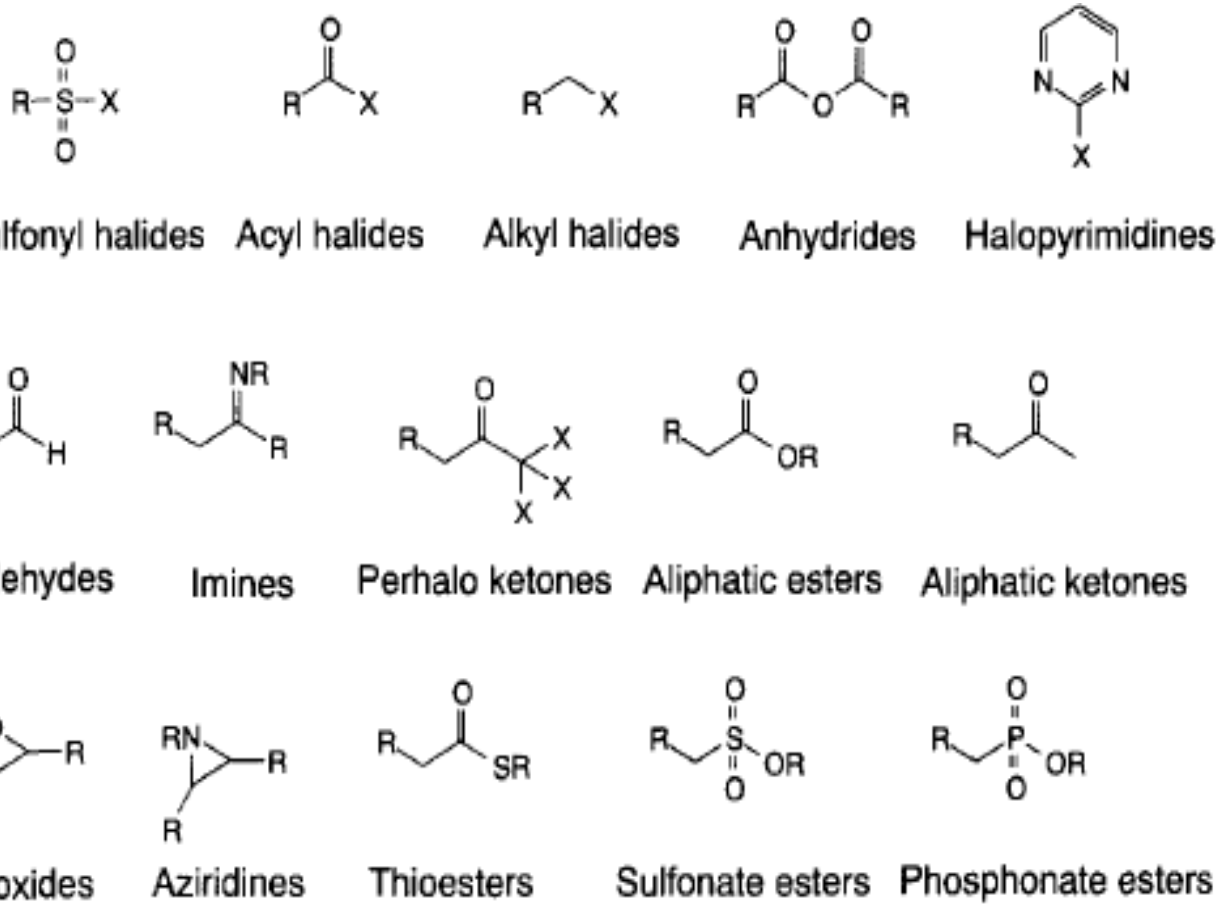
Global mapping of pharmacological space. Paolini et al., Nature Biotechnology (2006), 24(7), 805-815.

Why is biologically active medicinal chemistry space so small?

- Medicinal chemists are unimaginative?? **NO**
- Biological systems are designed to be robust and resistant to modulation
- Nature is conservative – motifs are re-used
- Protein folding motifs are limited
- Protein energetics are balanced for signalling
- Critical pathways are limited

Examples of structural filters

Reactive compounds and in vitro false positives in HTS. Rishton, Gilbert M. AMGEN, Thousand Oaks, CA, USA. Drug Discovery Today (1997), 2(9), 382-384. CODEN: DDTOFS ISSN: 1359-6446. Journal; General Review written in English. CAN 127:242708 AN



Filters for reactive functional groups

SMARTS for reactive functional groups

R1	Reactive alkyl halides	[Br,Cl,I][CX4;CH,CH2]
R2	Acid halides	[S,C](=[O,S])[F,Br,Cl,I]
R3	Carbazides	O=CN=[N+]=[N-]
R4	Sulphate esters	COS(=O)O[C,c]
R5	Sulphonates	COS(=O)(=O)[C,c]
R6	Acid anhydrides	C(=O)OC(=O)
R7	Peroxides	OO

American Chemical Society, J. Chem. Inf. Comput. Sci, Hann ci990423o Supporting Info

GSK compound quality filters

Filters for unsuitable natural products

SMARTS for unsuitable natural products

N1	Quinones	O=C1[#6]~[#6]C(=O)[#6]~[#6]1
N2	Polyenes	C=CC=CC=CC=C
N3	Saponin derivatives	O1CCCCC1OC2CCC3CCCCC3C2
N4	Cytochalasin derivatives	O=C1NCC2CCCCC21
N5	Cycloheximide derivatives	O=C1CCCC(N1)=O
N6	Monensin derivatives	O1CCCCC1C2CCCO2
N7	Cyanidin derivatives	[OH]c1cc([OH])cc2=[O+]C(=C([OH])Cc21)c3cc([OH])c([OH]
N8	Squalestatin derivatives	C12OCCC(O1)CC2

American Chemical Society, J. Chem. Inf. Comput. Sci, Hann ci990423o Supporting Info

GSK compound quality filters

Complete filters are publically available

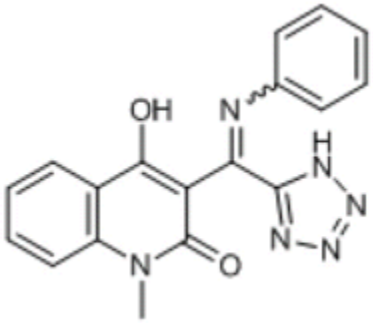
New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays

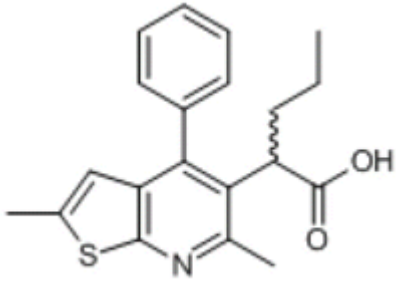
Jonathan B. Baell and Georgina A. Holloway

Baell, Jonathan B.; Holloway, Georgina A. **New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays.** Journal of Medicinal Chemistry (2010), 53(7), 2719-2740. CODEN: JMCMAR ISSN:0022-2623. CAN 152:326153 AN 2010:159922 CAPLUS

Filtering and HTS common sense

- Filter enough to avoid HTS false positives
- Allow “flawed” compounds in screen if:
  - compound is not an HTS false positive
  - compound flaw is fixable in chemistry
  - people discipline exists to fix the flaw





Rational design of small - molecule inhibitors of the LEDGF/p75 - integrase interaction and HIV replication. *Nature Chemical Bi ology* ***6, 442–448 (2010)***

Filtering and clinical common sense

- Clinical results are most important
  - drugs are used today that would fail filters
- Experimental results come next
  - drug-drug interactions
  - drug-transporter interactions
- Rules and filters are important early on especially if one has none of the above
- Efficacy versus safety balance is changing

Academic Drug Discovery

- Rapid growth in academic drug discovery
  - 10% academics at 2004 SBS meeting
  - 35% academics at 2009 SBS meeting
- Academic drug discovery proven success
  - academic biology is the core strength
  - competent medicinal chemistry
  - access to associated disciplines
  - competent project planning

Science + planning = success

- Wellcome Trust's Seeding Drug Discovery
- "A common element is that each project is supported by a research steering committee that includes a business development manager from the Trust, as well as independent advisors."

Nature Reviews Drug Discovery 9, 178-180 (March 2010)
News Feature: A Wellcome experiment in seeding drug discovery