# A novel drug with a known mechanism that is superbly selective against a single target: Is this a contributor to reduced drug discovery productivity?

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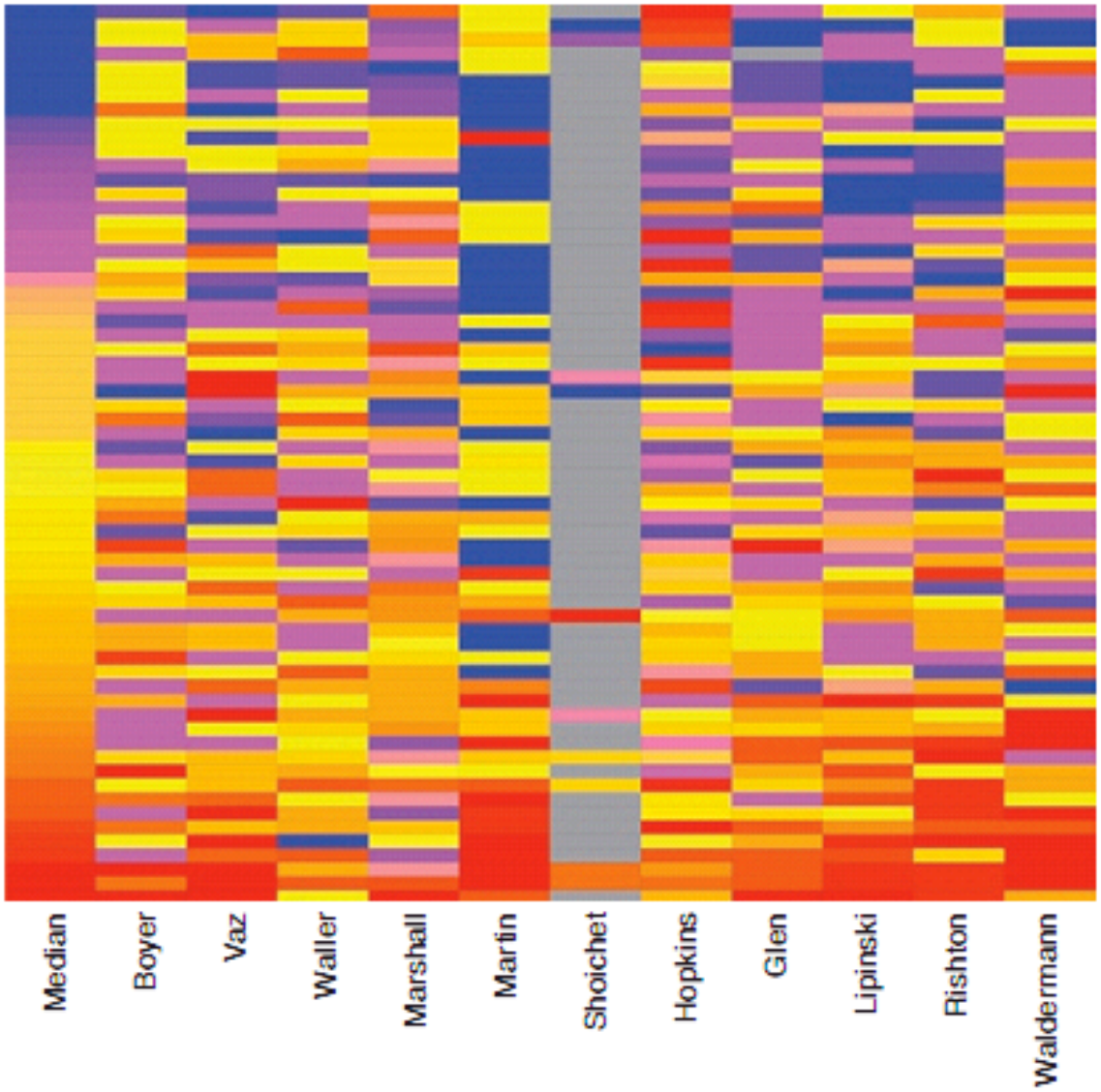
# Outline

- How a medicinal chemist looks at drugs
  - annotation
- Beautiful biology ruined by bad chemistry
- Target tractability can change
  - protein – protein interactions as an example
- Rules and filters: why “sharing” is important
  - thiol traps and FDA drugs
  - thiol traps and the Lopac1280 screening library
- Drug repurposing: why “mine” drugs?
  - MLR-1023 as an example
- Enhancing biology chemistry collaboration

# 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.

# Annotation on 64 NIH 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)

# How do we judge biology value?

- New biology appears in the literature
- Initially the biology looks interesting
- Chemistry in the biology has problems
- How to judge value if the chemistry tools illustrating the biology have potential flaws

# Biology enthusiasm, but chemistry questions

## 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]

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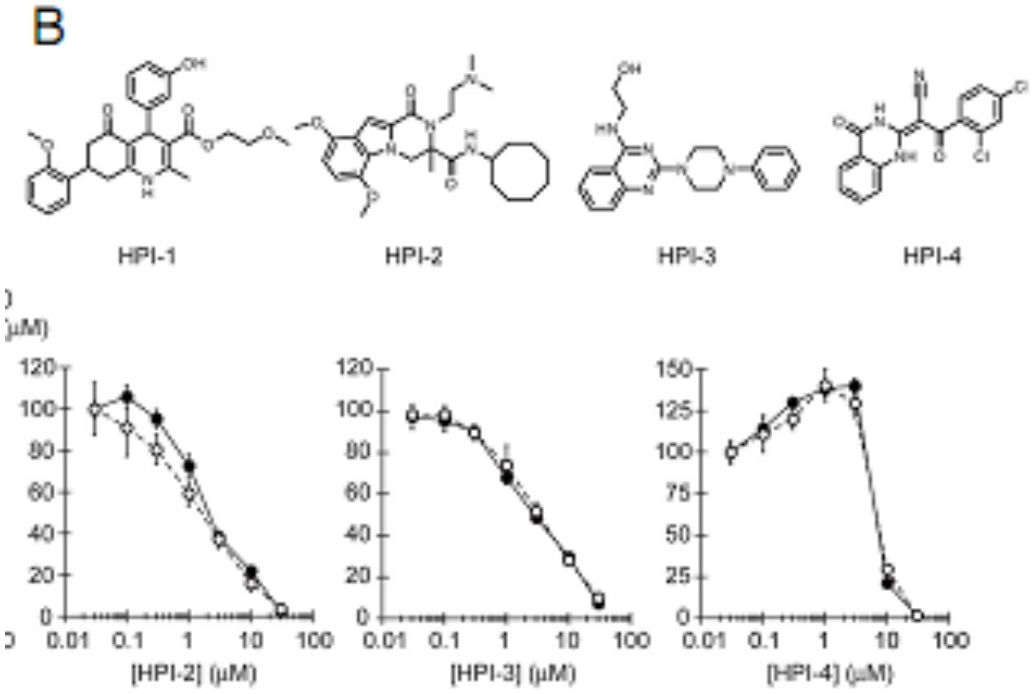
Communicated by Matthew P. Scott, Stanford University School of Medicine, Stanford, CA, June 29, 2009 (received for review January 9, 2009)



# Hedgehog screening - my comment

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

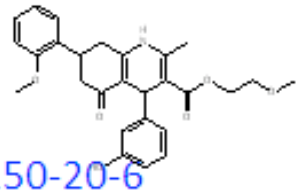
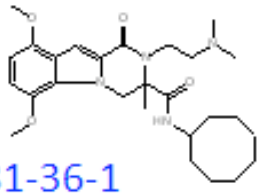
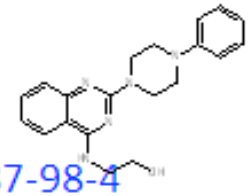
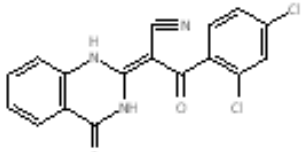
There is a common theme to the four "actives" identified in this paper. They are all commercially available compounds with a CAS registry number and (almost) no literature references. In each case there are commercially available analogs at high similarity again with CAS registry numbers and again no 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 – thiol trap filters

| CHEMISTRY | NAME | Alarm | smartsfilter_matches |
|---|---|---|---|
|  599150-20-6 | HPI-1 | **failed** | C=CC(=O)O[c,C] ()<br>C=CC(=O)[c,C] ()<br>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] () |

# 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

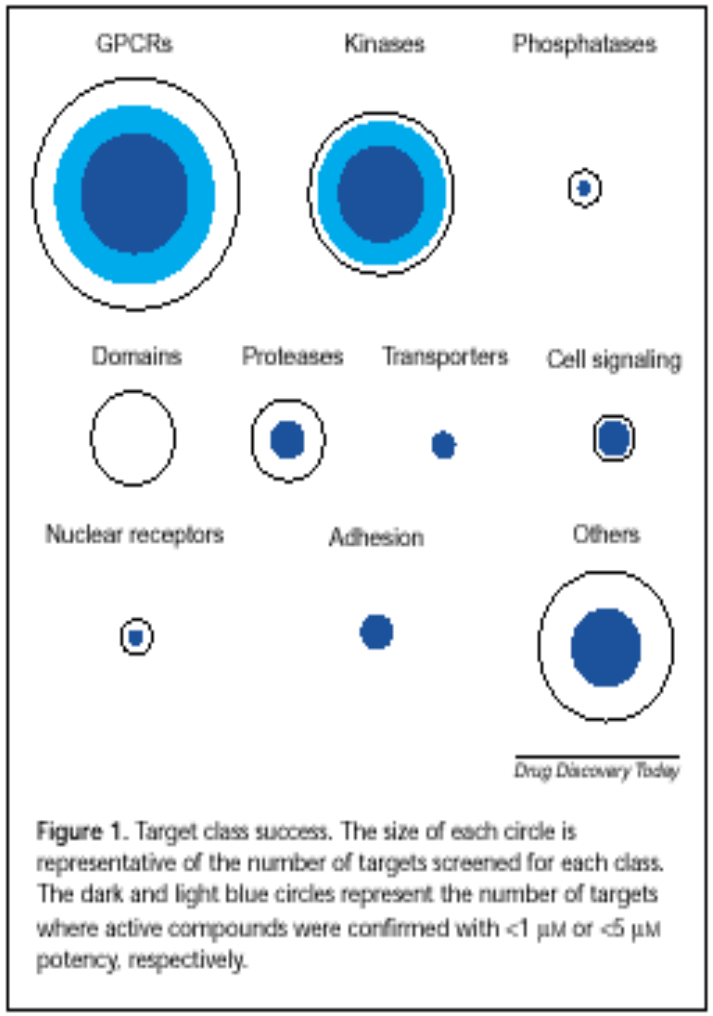



Figure 1. Target class success. The size of each circle is representative of the number of targets screened for each class. The dark and light blue circles represent the number of targets where active compounds were confirmed with <1 μM or <5 μM potency, respectively.

**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.**

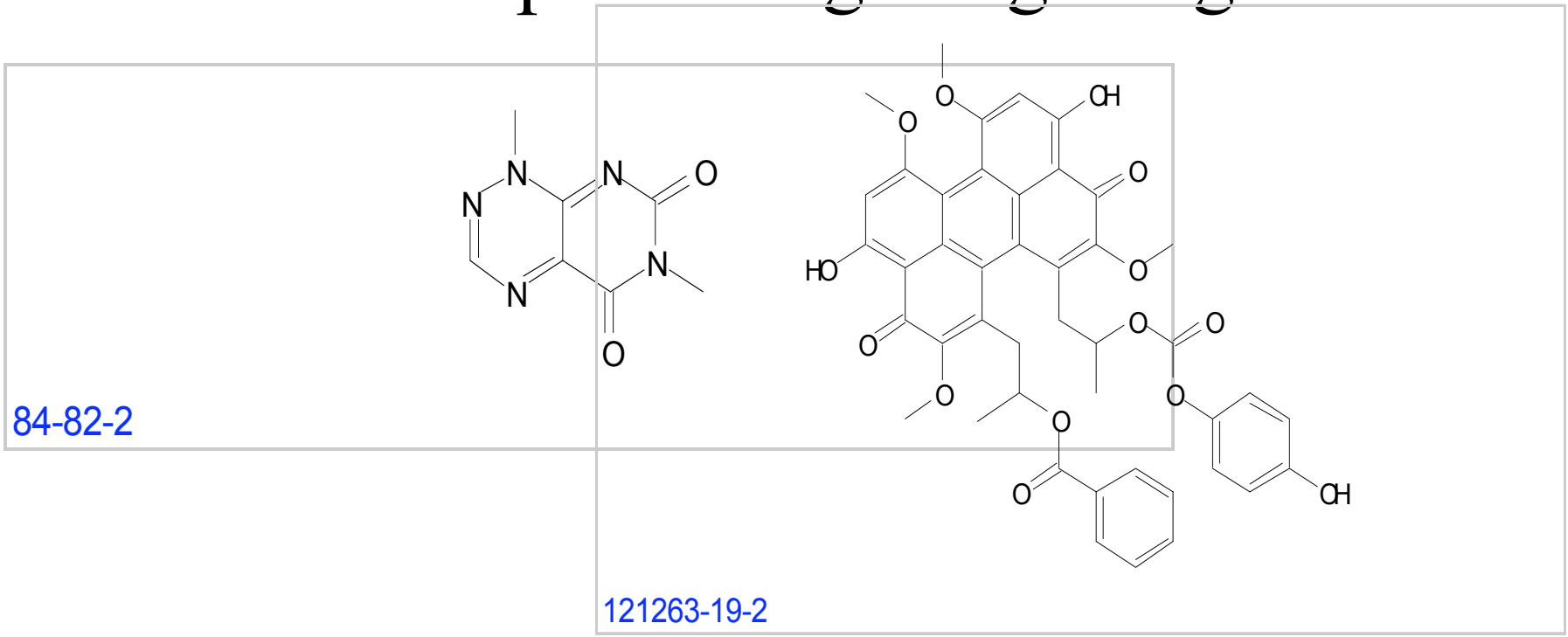
# Targets, ligands and the rule of 5

- 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

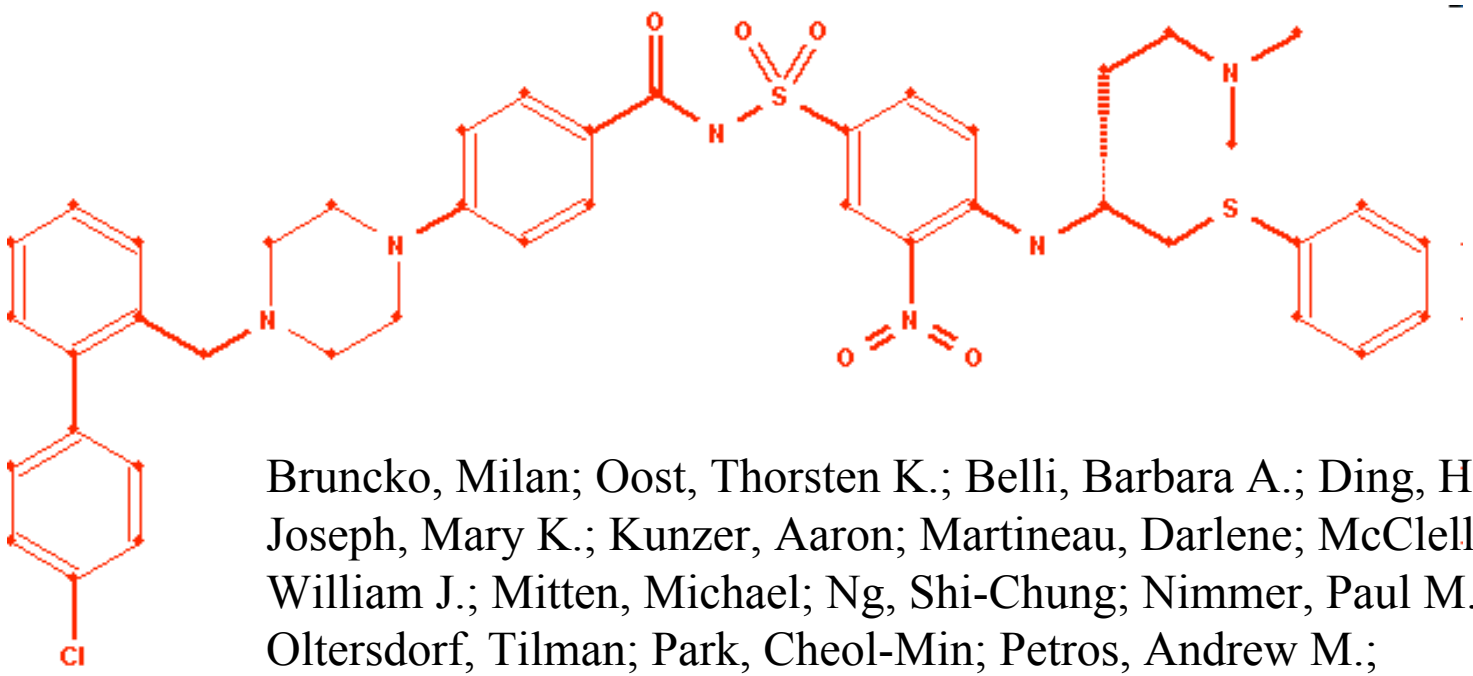
- Protein-protein interactions
  - hopeless from an HTS screening viewpoint
- Scientific advances
  - fragment screening
  - SAR by nmr and x-ray
  - Bcl-2 family success from Abbott

# Protein protein ligand garbage



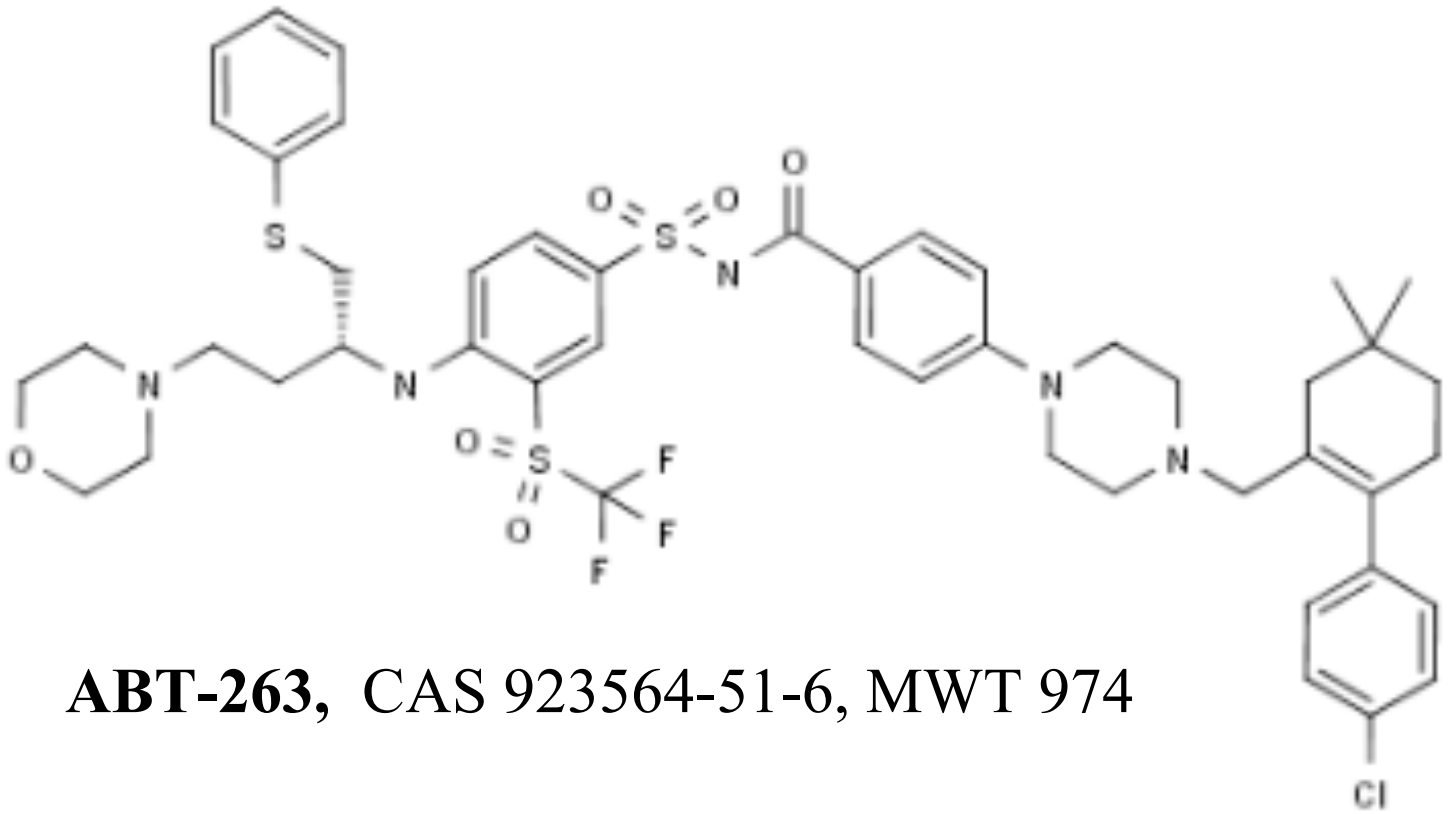

**Lepourcelet, Maina; Chen, Ying-Nan P.; France, Dennis S.; Wang, Huisheng; Crews, Phillip; Petersen, Frank; Bruseo, Charles; Wood, Alexander W.; Shivdasani, Ramesh A. Small-molecule antagonists of the oncogenic Tcf/β-catenin protein complex. Cancer Cell (2004), 5(1), 91-102.**

# 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

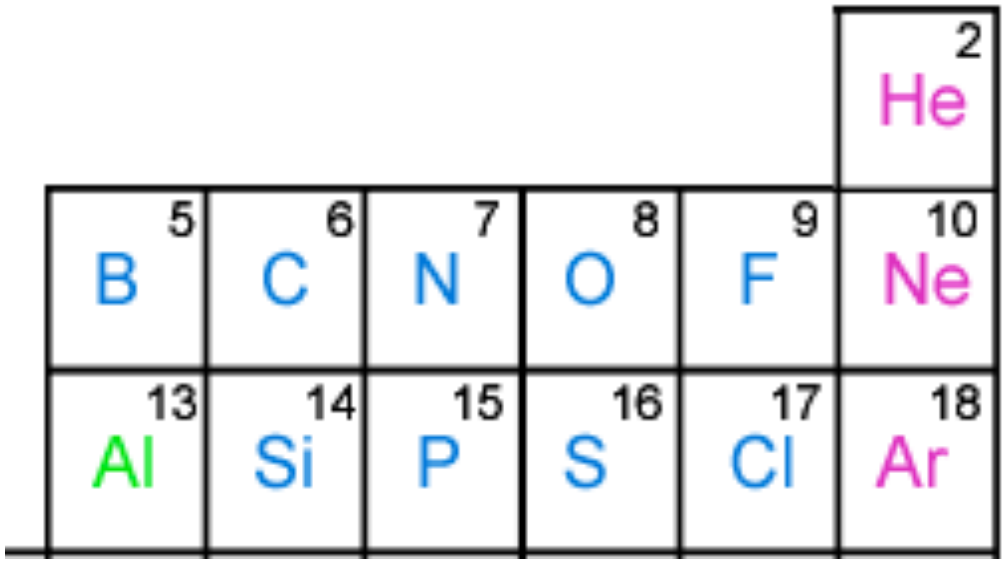



**ABT-263,** CAS 923564-51-6, MWT 974

# Industry filters vary a lot

- Pfizer –lint 2001
  - likely the strictest filters in big pharma
- Abbott – Alarm NMR - 2005
  - possible screening problems due to thiol traps and Redox problems
  - a continuum rather than binary filter
- BMS -2006
- Glaxo -2001
  - compounds to avoid – very loose

# Cysteine is the most nucleophilic AA




Nucleophilicity increases as you descend a column

Nucleophilicity increases as you move to the left in a row

First principles suggest that thiol traps are likely one of the most troublesome chemistry screening problems against protein targets

# Abbott Alarm NMR alerts

***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 |

*Alerts 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

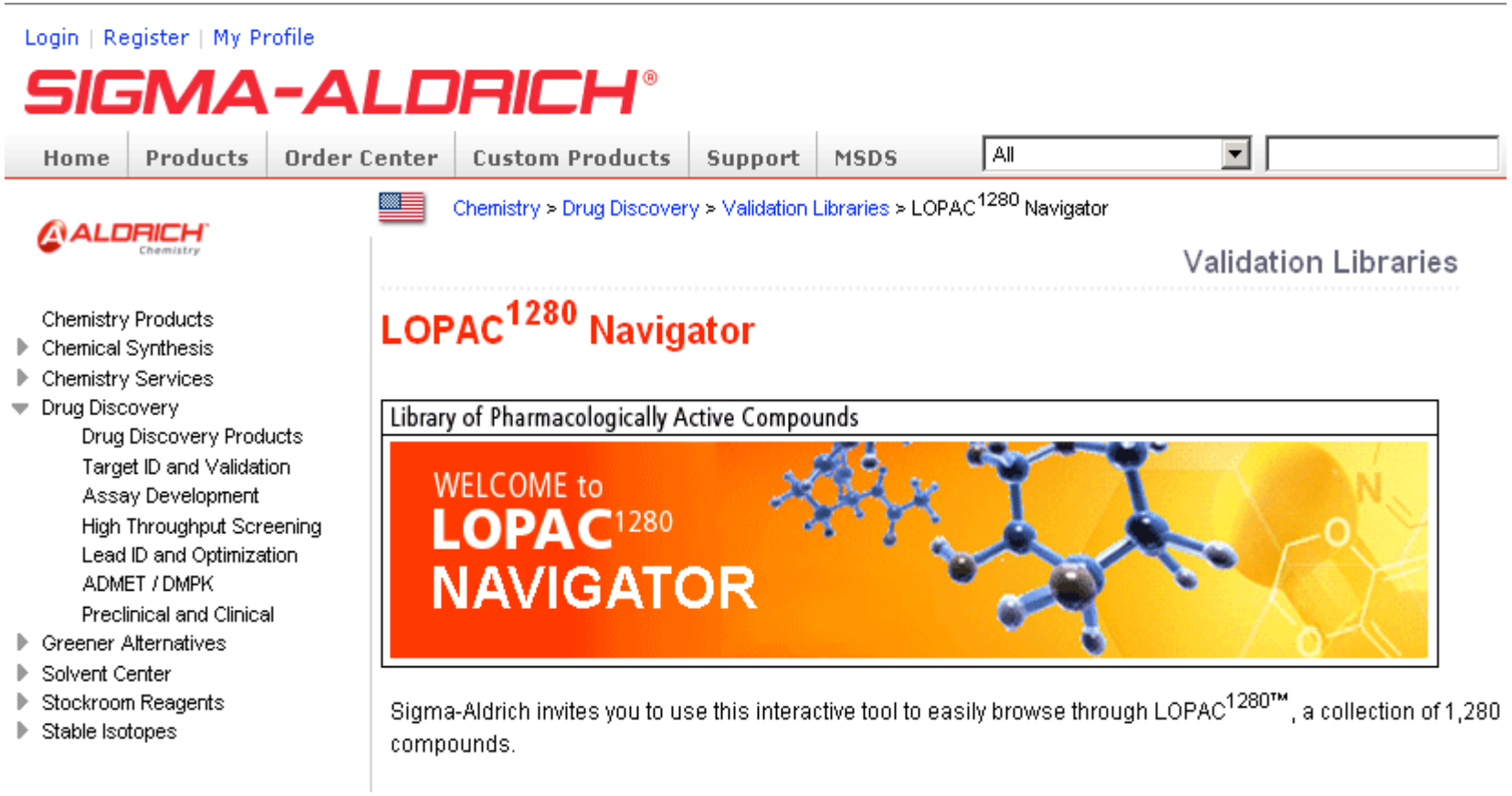
# Alarm NMR fail on 740 FDA Drugs

| 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 alerts

- FDA approved 740 drug data set
  - F(%) = 100 is 100% of the time a thiol trap
  - F(%) = 30 is 30% of the time a thiol trap
- Most FDA failures are where F(%) < 30
- Suggests using alerts where F(%) > 30
  - ie. focus mostly on the really bad thiol traps
- Filter out when a functionality fails both a thiol trap and a compound quality filter

# Screening starting point - LOPAC$^{1280}$ library of pharmacological actives

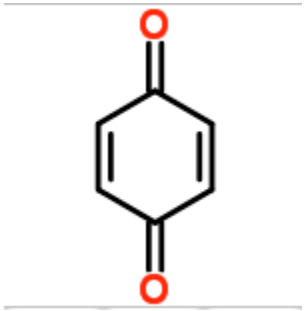


# Thiol reactivity is very prevalent

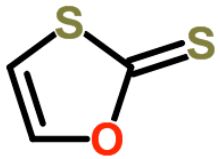
- Desalt Lopac1280 in ACS/Labs Chemfolder
- Export cleaned up compounds as an sdf file
- Run Abbott Alarm NMR and Pfizer lint alerts
- Alarm NMR Pfizer lint Numbers

| Alarm NMR | Pfizer lint | Numbers |
|---|---|---|
| Fail | Fail | 363 (28%) |
| Fail | Pass | 356 (28%) |
| Pass | Fail | 202 (16%) |
| Pass | Pass | 359 (28%) |

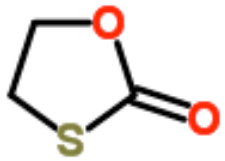
# Worst Alarm NMR moieties



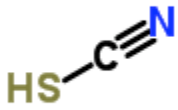

**100%**




**85%**

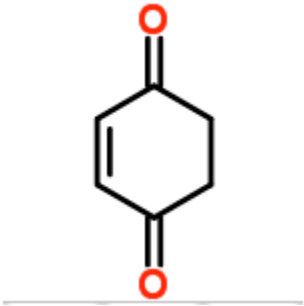



**85%**

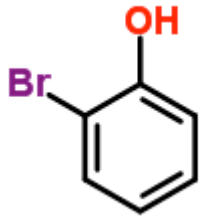



**66%**

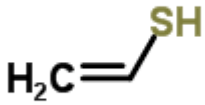

**60%**




**60%**




**55%**




**50%**

# Drug Repurposing Observations

- New uses for an old drug:
  - success rate is 10 – 90%
  - 70 – 90% is original mechanism
- Smaller drugs are better
  - properties change throughout clinical
  - MWT 347 mean for FDA approved drugs
  - merit in “back to the future” approach

# Drug repurposing examples

- Nelfinavir for cancer
- Tamoxifen for bipolar disorder
- Gleevec for rheumatoid arthritis
- Pentylenetetrazole for downs syndrome
- Minocycline for retinopathy
- Thioridazine for tuberculosis
- Astemizole for malaria
- Lipitor for alzheimers
- Lipitor for influenza mortality
- Metformin for cancer

# Phenotypic Screens and Mechanism

- FDA doesn't require mechanism.
- Drug company attitude change
  - eg. Sanofi-Aventis, Eli Lilly
- Phenotypic screen gives an active but without mechanism.
- Progress on deciphering mechanism
  - antibacterials and antivirals
- Phenotypic screen for target validation

# Phenotypic screening leverage

- Phenotypic screening
  - enhanced target opportunity space
- Melior runs pan therapeutic in-vivo screens
  - finds activity in type II diabetes model
  - finds an in-vivo active in a clinically tested drug
  - literature unprecedented mechanism
- Wildly lucky or predictable in drug repositioning?
  - 97 mechanisms for type II diabetes in Prous' Integrity

# MLR-1023 aka Tolimidone

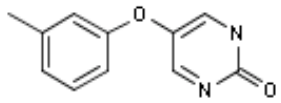
**Records Retrieved** 1 in Drugs & Biologics — Options

**Drugs & Biologics Search Results** 1

Query > **Drug Name** = MLR-1023

| | |
|---|---|
| **Entry Number** | 329565 UPDATES |
| **CAS Registry No.** | 041964-07-2 |
| **Molecular Formula** | C11H10N2O2 |
| **Molecular Weight** | 202.2094 |
| **Highest Phase** | IND Filed |
| **Under Active Development** | |

**Chemical Structure** — STRUCTURE FEATURES




Tolimidone

**Chemical Name/Description**

5-(3-Methylphenoxy)pyrimidin-2(1H)-one

| Code Name | Generic Name | Brand Name |
|---|---|---|
| CP-26154<br>MLR-1023 | Tolimidone | |

| Therapeutic Group | Cellular / Molecular Mechanism | Biological / Chemical Group |
|---|---|---|
| Antiulcer Drugs<br>Type 2 Diabetes, Agents for | | |

**Organization**

Melior Discovery
Pfizer (Originator)

# Melior MLR-1023

- Antiulcer compound phase 3 from 1970's Pfizer. New activity from phenotypic in-vivo mouse screens
- IND filed by Melior Discovery for type 2 diabetes/metabolic syndrome. Lyn kinase activator with EC-50 63 nm. MWT 202, LE 0.48 kcal/heavy atom
- How many other unrecognized kinase activators are there?

# Why does repurposing work?

- Negative viewpoint
- 85-90% novel targets fail
- Network bypasses the block
- 10% predictivity in clinical
- Unexpected clinical effects
- Pleiotropic effects
- Useful activity seen late
- Too late to be clinically optimized

- Positive viewpoint
- Phenotypic screening
- In-vivo screening
- Pathway screening
- Screen the 1-2% that become early clinical drugs
- Screen known drugs
- 30 – 90% success rate
- An active drug almost never has just a single activity

Caffeine – Collaborative Drug Discovery

file:///Users/moses/code/design-svn/templates/molecule.html

Google

CDD · Lipinski Group

Chris Lipinski: Your Account · Help · Log out

Dashboard | Group Data | Import Data | Share Data

Currently using **Lipinski Group** data and **6 shared data sets** Choose data sets ...

Back to Dashboard

# CAS 957217-65-1 PUBLIC MOLECULE

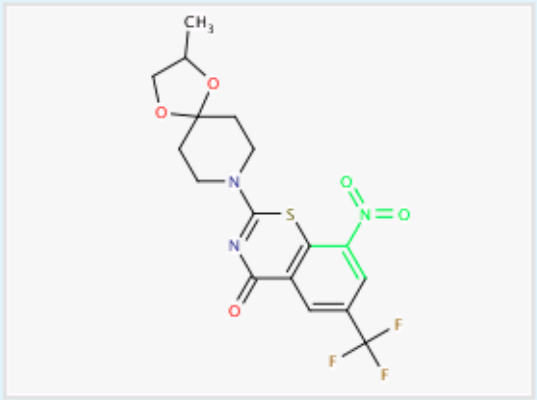
**Available in 3 data sets.** Now viewing:

TB MIC Prathipati NIAID – 37532

Overview | Batches 2 | Plates 1 | Protocols 3 | Associated Files 2 | Alerts 2

## 2 Alerts

Structure Match Preview



Alert

**Abbott Alarm NMR failed**

- csc
- Nc1cccc2aaaaa12

**Pfizer Lint failed**

- O~N(=O)-c(:*):* (aromatic NO2)

# Conclusion

- We need to “share” information
- We need to “mine” existing drugs
- We need mechanisms to enhance biology – chemistry “collaboration”
- We need diversity in our screening