Lipinski - CDD 10th Anniversary Thoughts on Drug Discovery

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CDD Vault - share chemical structures, talk about the data

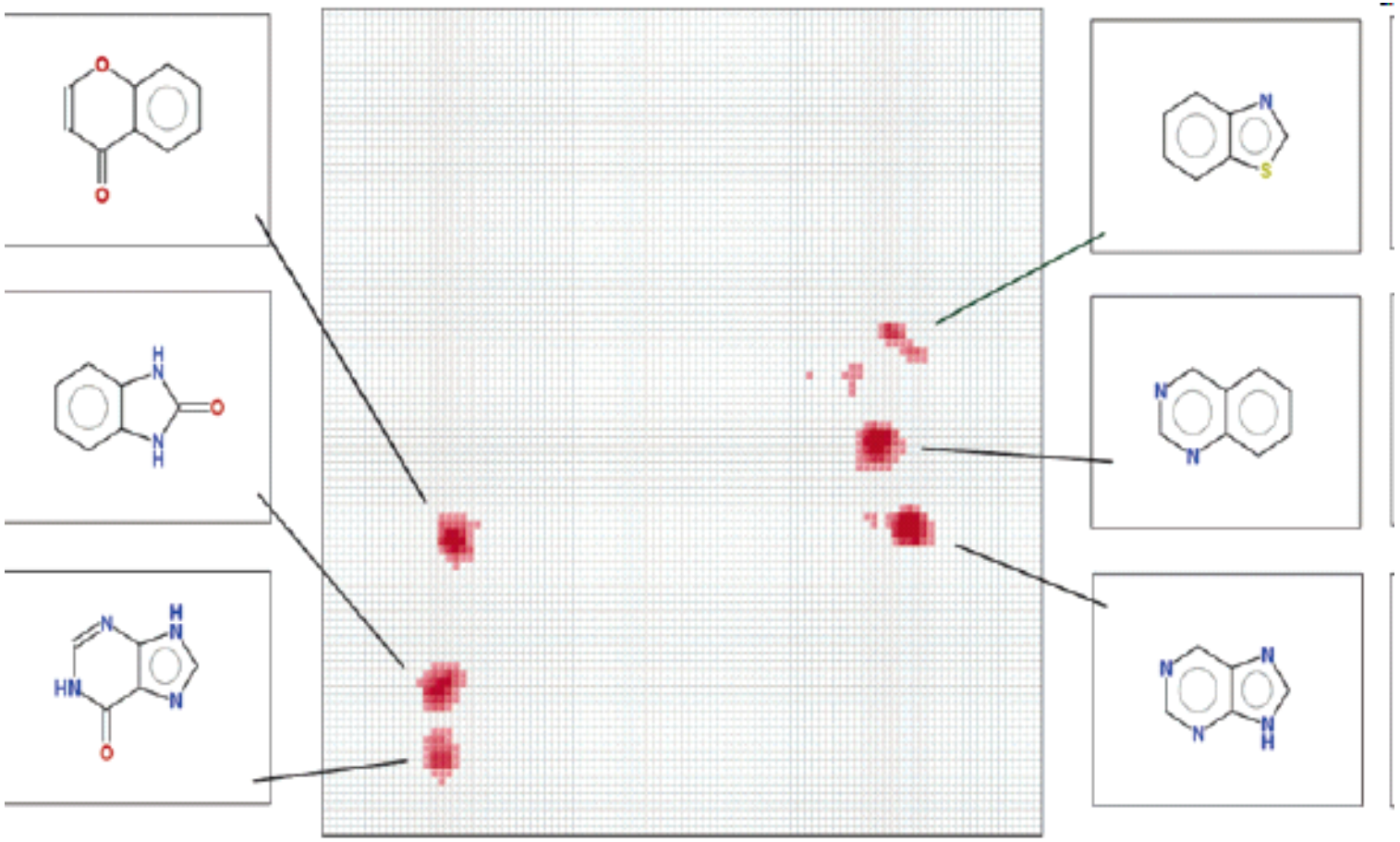
My topic: Two under appreciated aspects of sharing and talking about chemical structures

- Medicinal chemistry annotation
  - origins in target evolution
- Medicinal chemistry – chemical biology dialogue
  - target selectivity and ligand efficiency

Medicinal Chemistry Annotation

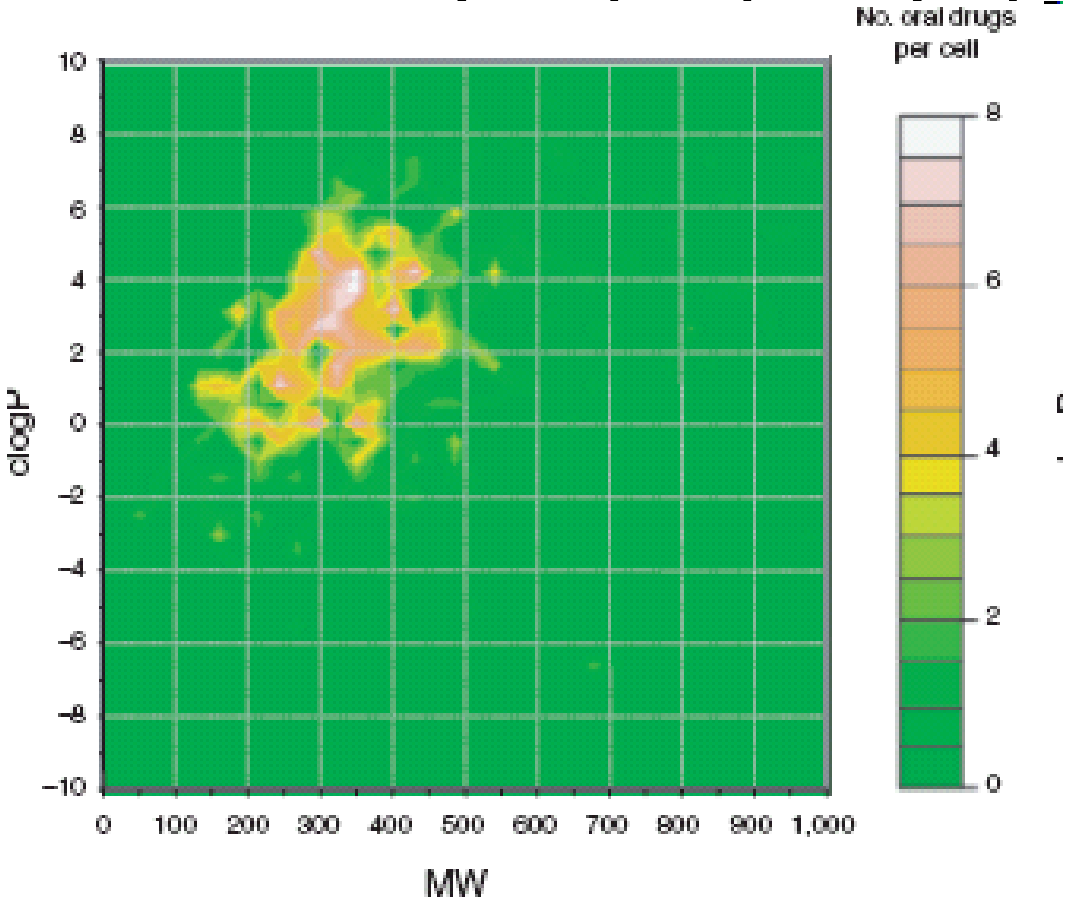
- Every publication I know of argues that biologically active compounds are not uniformly distributed through chemistry space
- Screening diverse compounds is the worst way to discover a drug
- Literature chemical searches on leads have value even if the prior art biology has nothing in common with the new biology

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 signaling
- Critical pathways are limited

Do drug structure networks map on biology networks?

J. Chem. Inf. Model. **2008,** *48,* 755–765

Quantifying the Relationships among Drug Classes

Jérôme Hert,[†] Michael J. Keiser,[†] John J. Irwin,[†] Tudor I. Oprea,[‡] and Brian K. Shoichet*,[†]

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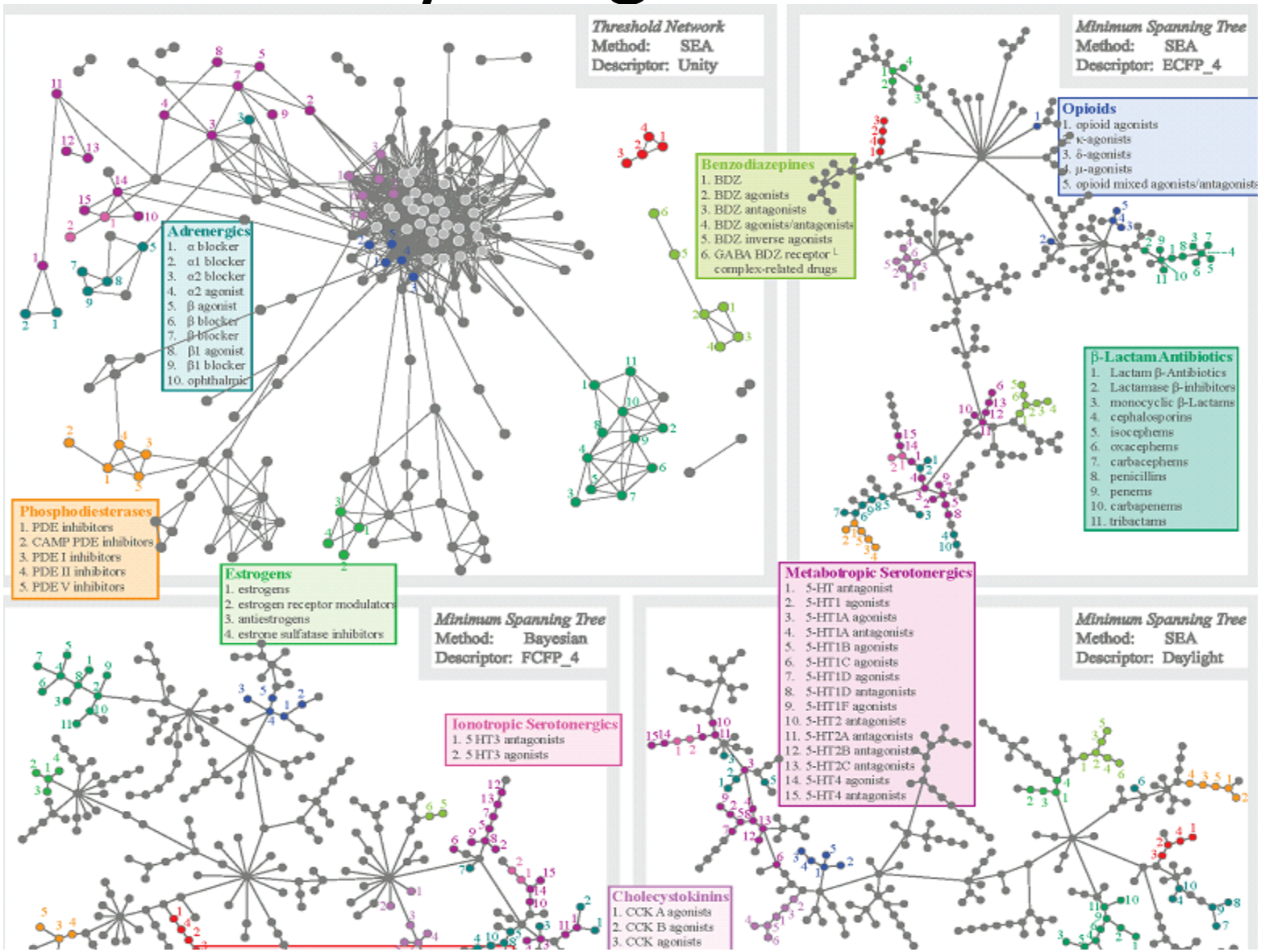
Chemistry drug class network



Network comparison conclusions

- “A startling result from our initial work on pharmacological networks was the observation that networks based on ligand similarities differed greatly from those based on the sequence identities among their targets.”
- “Biological targets may be related by their ligands, leading to connections unanticipated by bioinformatics similarities.”

What is going on?

- Old maxim: Similar biology implies similar chemistry
- If strictly true biology and chemistry networks should coincide

Network comparisons – meaning?

- “Structure of the ligand reflects the target”
- Evolution selects target structure to perform a useful biological function
- Useful target structure is retained against a breadth of biology
- Conservation in chemistry binding motifs
- Conservation in motifs where chemistry binding is not evolutionarily desired
  - eg. protein – protein interactions

Hit / lead implications

- You have a screening hit. SAR on the historical chemistry of your hit can be useful even if it comes from a different biology area
- Medicinal chemistry principles outside of your current bioloogy target can be extrapolated to the ligand chemistry (but not biology) of the new target
- Medicinal chemistry due diligence is essential

Medicinal chemistry - chemical biology dialogue

CORANTE

Home > Weblog Columns > In the Pipeline

Weblog

In the Pipeline: Don't miss Derek Lowe's excellent commentary on drug discovery and the pharma industry in general at In the Pipeline

ABOUT THIS AUTHOR

Derek Lowe, an Arkansan by birth, got his BA from Hendrix College and his PhD in organic chemistry from Duke before spending time in Germany on a Humboldt Fellowship on his post-doc. He's worked for several major pharmaceutical companies since 1989 on drug discovery projects against schizophrenia, Alzheimer's, diabetes, osteoporosis and other diseases. To contact Derek email him directly: derekb.lowe@gmail.com Twitter: Dereklowe

Chemistry and Drug Data: Drugbank

In the Pipeline

« Predicting Toxicology | Main | Organic Synthesis: A Dead End For Graduate Students? »

June 13, 2012

Live By The Bricks, Die By The Bricks

Posted by **Derek**

I wanted to highlight a couple of recent examples from the literature to show what happens (all too often) when you start to optimize med-chem compounds. The earlier phases of a project tend to drive on potency and selectivity, and the usual way to get these things is to add more stuff to your structures. Then as you start to produce compounds that make it past those important cutoffs, your focus turns more to pharmacokinetics and metabolism, and sometimes you find you've made your life rather difficult. It's an old trap, and a well-known one, but that doesn't stop people from sticking a leg into it.

Take a look at these two structures from ACS Chemical Biology. The starting structure is a pretty generic-looking kinase inhibitor, and as the graphic to its left shows, it does indeed hit a whole slew of kinases. These authors extended the structure out to another loop of the their desired target, c-Src, and as you can see, they now have a much more selective compound.

Chemical basis of the dialogue

ACS chemical biology

Articles

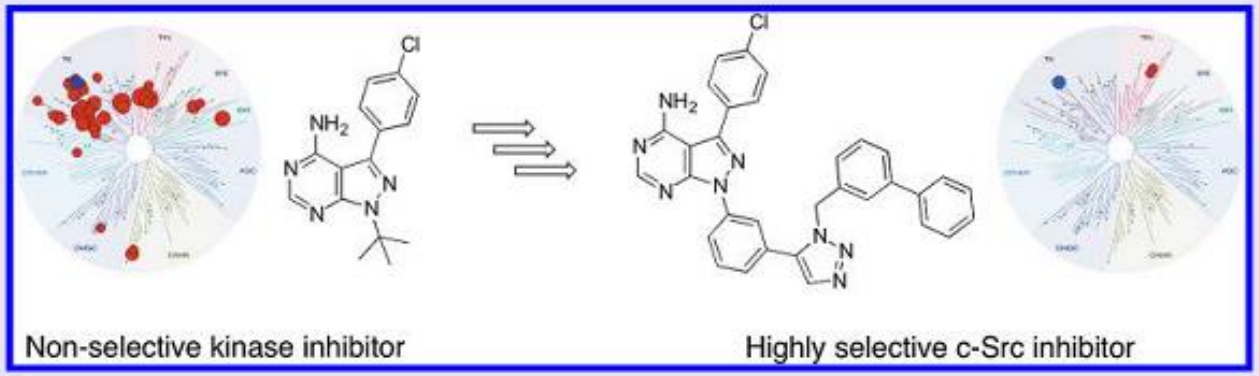
pubs.acs.org/acschemicalbiology

Development of a Highly Selective c-Src Kinase Inhibitor

Kristoffer R. Brandvold,[†] Michael E. Steffey,[†] Christel C. Fox,[†] and Matthew B. Soellner*[,†,‡]

[†]Department of Medicinal Chemistry and [‡]Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109, United States

Supporting Information



Ligand Efficiency vs. IC_{50}

LE = $-\log_{10}(IC_{50})$/ no. heavy atoms

eg. IC50 is 7 nm ,37 heavy atoms

LE= $-\log_{10}(7 \times 10^{-9})$/ 37

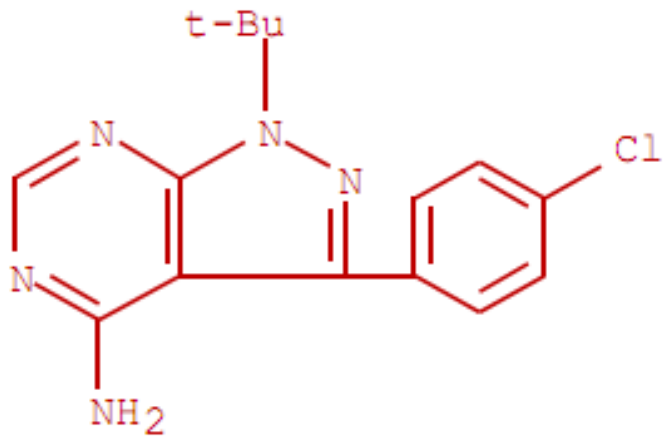
=-(0.85-9)/37 = 8.15/37= 0.22

LE a measure of how efficiently the ligand atoms are used in binding

<u>0.30 a drug discovery benchmark</u>

Ligand efficiency a useful metric for lead selection Hopkins et al. DDT 2004 9(10) 430-1

PP2 non selective c-SRC inhibitor



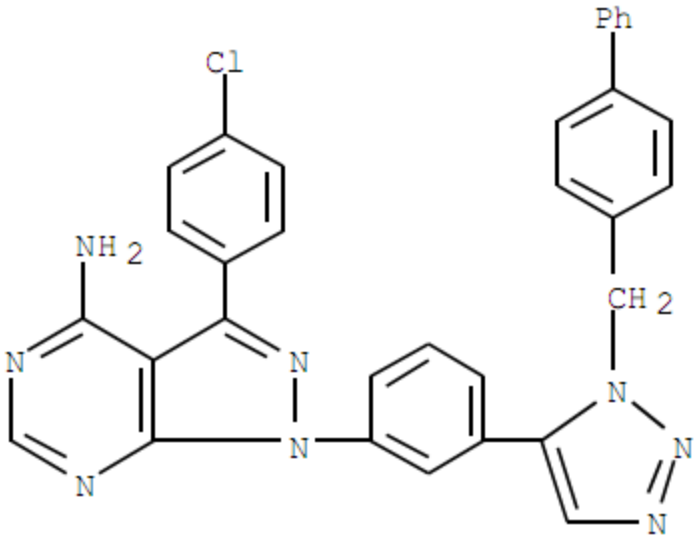
$C_{15}H_{16}Cl_1N_5$ 21 heavy atoms

0.033 x 10^{-6} versus c-SRC kinase

$-\log_{10}(3.3x10^{-8}) = 7.48$

Ligand efficiency = 7.48/21 = 0.36

Compound 4



$C_{32}H_{23}Cl_1N_8$ 41 heavy atoms

44 nm versus c-SRC kinase

$-\log_{10}(44 \times 10^{-9}) = 7.36$

Ligand efficiency = 7.36/41 = 0.18

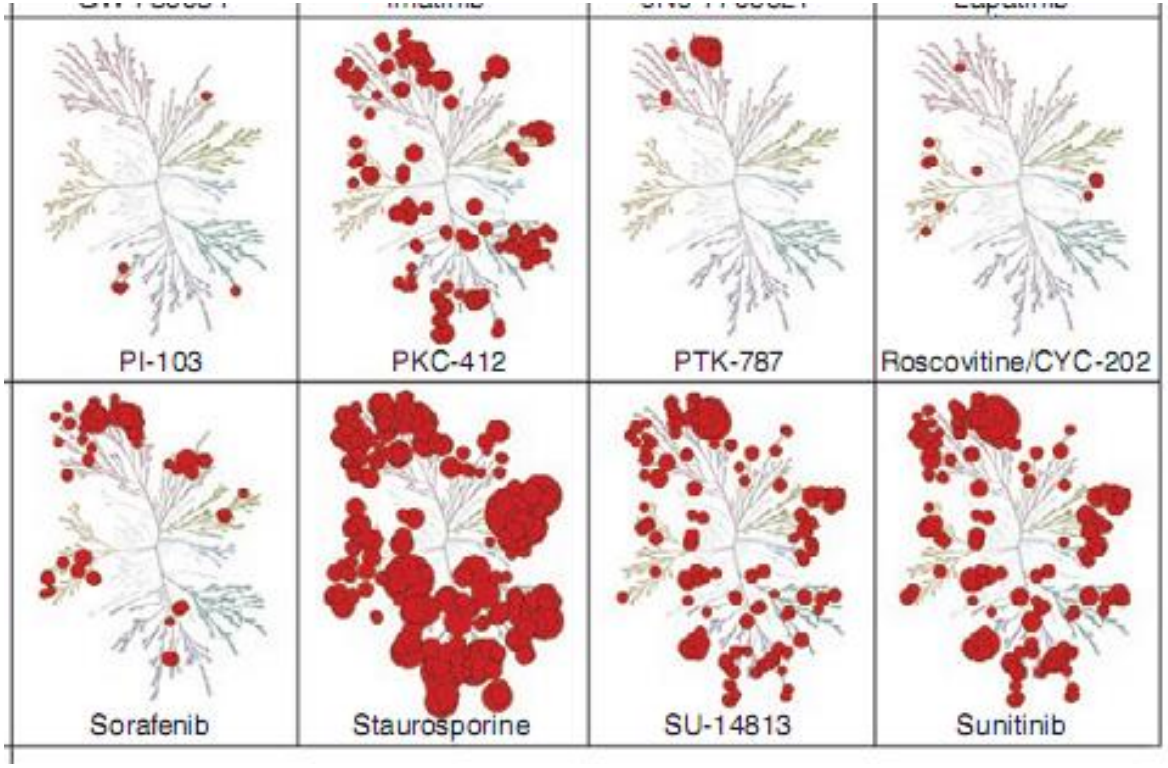
Compd 4 vs. PP2

- PP2 is non selective against cSRC kinase
- IC-50 is 33 nm
- Ligand efficiency is 0.36
- Compd 4 is very selective against cSRC kinase
- IC-50 is 44nm
- Ligand efficiency is 0.18
- Compound 4 likely is selective because of favorable entropy and not enthalpy

What is the relationship between selectivity and ligand efficiency?

- Find a data set of selectivity values
- For each compound calculate ligand efficiency
- Observe the relationship between selectivity and ligand efficiency

Kinase selectivity database



38 kinase inhibitors against 317 kinase targets

A quantitative analysis of kinase inhibitor selectivity. Zarrinkar P. P. et al. Nature Biotechnology (2008) 26(1) 127-132.

Kinase inhibitors sorted by selectivity

CHEMISTRY	CAS	NAME	FORMULA	HATM	TARGET	KdNM	LE(Kd)	SELECT
371935-74-9	371935-74-9	PI-103	C19 H16 N4 O3		26PIK3CA	1.5	0.34	0.0000
870483-87-7	870483-87-7	GW-2580	C20 H22 N4 O3		27CSF1R	1.8	0.32	0.0000
209410-46-8	209410-46-8	VX-745	C19 H9 Cl2 F2 N3 O S		28p38-alpha	2.8	0.31	0.0000
184475-35-2	184475-35-2	Gefitinib	C22 H24 Cl F N4 O3		31EGFR	1	0.29	0.0000
289499-45-2	289499-45-2	CI-1033	C24 H25 Cl F N5 O3		34EGFR	0.19	0.29	0.0000
257933-82-7	257933-82-7	EKB-569	C24 H23 Cl F N5 O2		33EGFR	0.44	0.28	0.0000
231277-92-2	231277-92-2	Lapatinib	C29 H26 Cl F N4 O4 S		40EGFR	2.4	0.22	0.0000
183321-74-6	183321-74-6	Erlotinib	C22 H23 N3 O4		29EGFR	0.67	0.32	0.0035
285983-48-4	285983-48-4	BIRB-796	C31 H37 N5 O3		39p38-alpha	0.37	0.24	0.0035
477600-75-2	477600-75-2	CP-690550	C16 H20 N6 O		23JAK3	2.2	0.38	0.0069
692737-80-7	692737-80-7	CHIR-258	C21 H21 F N6 O		29FLT3	0.64	0.32	0.0069
383432-38-0	383432-38-0	CP-724714	C27 H27 N5 O3		35ERB2	43	0.17	0.0069
869363-13-3	869363-13-3	MLN-8054	C25 H15 Cl F2 N4 O2		34AURKA	6.5	0.24	0.0104
301836-41-9	301836-41-9	SB-431542	C22 H16 N4 O3		29TGFBR1/ALK5	170	0.23	0.0104
387867-13-2	387867-13-2	MLN-518	C31 H42 N6 O4		41KIT	3	0.21	0.0104
796967-16-3	796967-16-3	ABT-869	C21 H18 F N5 O		28FLT3	0.63	0.33	0.0105
169939-94-0	169939-94-0	LY-333531	C28 H28 N4 O3		35PRKCQ	2.5	0.25	0.0138
152121-30-7	152121-30-7	SB-202190	C20 H14 F N3 O		25p38-alpha	9.8	0.32	0.0173
722543-31-9	722543-31-9	AZD-1152	C26 H31 F N7 O6 P		41AURKB	7.2	0.20	0.0173
627908-92-3	627908-92-3	SU-14813	C23 H27 F N4 O4		32PDGFRB	0.29	0.30	0.0174
557795-19-4	557795-19-4	Sunitinib	C22 H27 F N4 O2		29VEGFR2	1.5	0.30	0.0174
152459-95-5	152459-95-5	Imatinib	C29 H31 N7 O		37ABL1	12	0.21	0.0209
152121-47-6	152121-47-6	SB-203580	C21 H16 F N3 O S		27p38-alpha	12	0.29	0.0242
212141-54-3	212141-54-3	PTK-787	C20 H15 Cl N4		25VEGFR2	62	0.29	0.0242
444731-52-6	444731-52-6	GW-786034	C21 H23 N7 O2 S		31FLT1	14	0.26	0.0244
186692-46-6	186692-46-6	Roscovitine	C19 H26 N6 O		26CDK5	1900	0.22	0.0313
639089-54-6	639089-54-6	VX-680	C23 H28 N8 O S		33AURKA	4.1	0.25	0.0314
453562-69-1	453562-69-1	AMG-706	C22 H23 N5 O		28KIT	3.7	0.30	0.0383
630124-46-8	630124-46-8	AST-487	C26 H30 F3 N7 O2		38KIT	5.4	0.22	0.0417
345627-80-7	345627-80-7	BMS-387032	C17 H24 N4 O2 S2		25CDK2	69	0.29	0.0588
120685-11-2	120685-11-2	PKC-412	C35 H30 N4 O4		43FLT3	11	0.19	0.0764
443797-96-4	443797-96-4	JNJ-7706621	C15 H12 F2 N6 O3 S		27CDK2	23	0.28	0.0833
284461-73-0	284461-73-0	Sorafenib	C21 H16 Cl F3 N4 O3		32BRAF	540	0.20	0.0972
302962-49-8	302962-49-8	Dasatinib	C22 H26 Cl N7 O2 S		33ABL1	0.53	0.28	0.1042
927880-90-8	927880-90-8	CHIR-265	C24 H16 F6 N6 O		37BRAF	1200	0.16	0.1215
146426-40-6	146426-40-6	Flavopiridol	C21 H20 Cl N O5		29CDK2	23	0.26	0.1696
443913-73-3	443913-73-3	ZD-6474	C22 H24 Br F N4 O2		30EGFR	9.5	0.27	0.2613
62996-74-1	62996-74-1	Staurosporine	C28 H26 N4 O3		35PRKCH	4.8	0.24	0.5017

Most selective

Best ligand efficiency in green (0.30 or better)

Least selective

Kinase data from “A Quantitative Analysis of Kinase Inhibitor Selectivity.” Zarrinkar P. P. et al. Nature Biotechnology (2008) 26(1) 127-132.”

Summary

- CDD Vault is the collaboration tool
- Literature chemical searches on leads have value even if the prior art biology has nothing in common with the new biology
- Data shown as ligand efficiency instead of IC-50 leads to new insights
- Looking for selectivity – look for ligand efficiency