Assessing the Target Differentiation Potential of Imidazole-Based Protein Kinase Inhibitors

D. Dimova, P. Iyer, M. Vogt, F. Totzke, M. Kubbutat, C. Schächtele, S. Laufer, J. Bajorath

J. Med. Chem. **2012**, 55, 11067-11071.

Celeste Alverez

Wipf Group Current Literature

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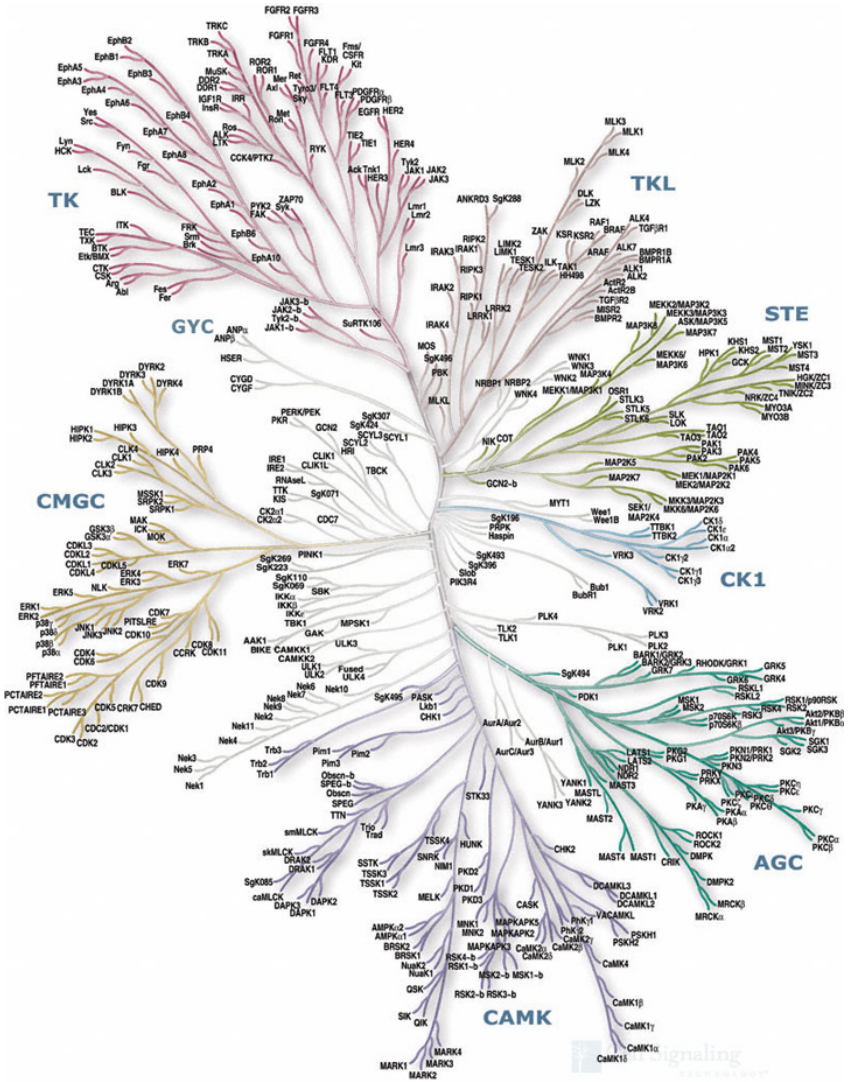
Kinome



- Consists of 518 kinases identified as genes by the Manning et. al
  - 478 are ePKs
  - 40 are aPKs that have little catalytic domain sequence similarity to ePKs
  - In 2002, 71 of the 518 were hypothetical, unknown entirely, or unknown as kinases

Manning, G. *Science*, 298, 1912-1934.

Target Profiling

- Can utilize both known drugs and experimental compounds
  - Can find new uses for known drugs
- Establishes ligand-based characterization of a class/ family of proteins
  - Identifies new active compounds/leads
  - Develops SAR
  - Establishes selectivity patterns
- Can be very useful in designing and developing drugs

Target Profiling - Advantages

- Establish a general SAR for the panel used
- Can explain and expose off target effects especially useful for important and challenging target classes such as kinases and GPCRs
  - Examples exist in the literature: kinases
    - 2005 study found off target effects of preclinical compounds as well as approved and developing drugs when screened against a panel of kinases from various families
  - SAR derived can be used to decrease interactions (increase selectivity)
  - Or multiple interactions can be utilized

Fabian et al. *Nat. Biotech.* **2005**, 23, 329-336.

Target Profiling

Drawbacks

- Expensive
  - Time and materials
- Large scale assays needed for significant results
- Large amounts of data produced which need to be processed
- HTS frequently utilized but not available for all targets (GPCRs)

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How to Ameliorate

- Computationally can model to eliminate some of the *in vitro* assays to be run
- Computer programs can analyze available data to help guide which compounds to screen
- Programs also can speed up and ease the processing of the data generated

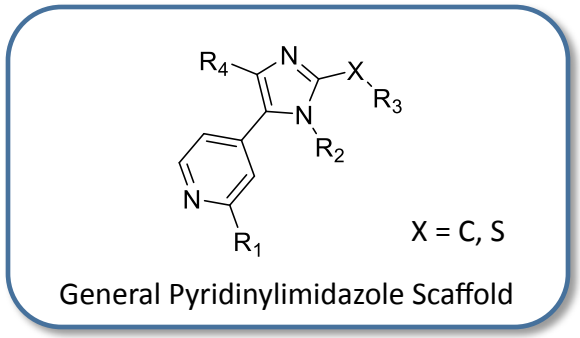
Differentiation Potential vs. Selectivity

- Ability of a compound to bind with varying potencies against different members of a family of proteins
- Will bind various proteins with high, moderate, and low potencies
- High differentiation potential indicates large activity differences between many kinase pairs

- Ability of a compound to bind with high potency to one protein over one or more other proteins
- If binds other proteins, it does so weakly to be considered selective

Panel Design

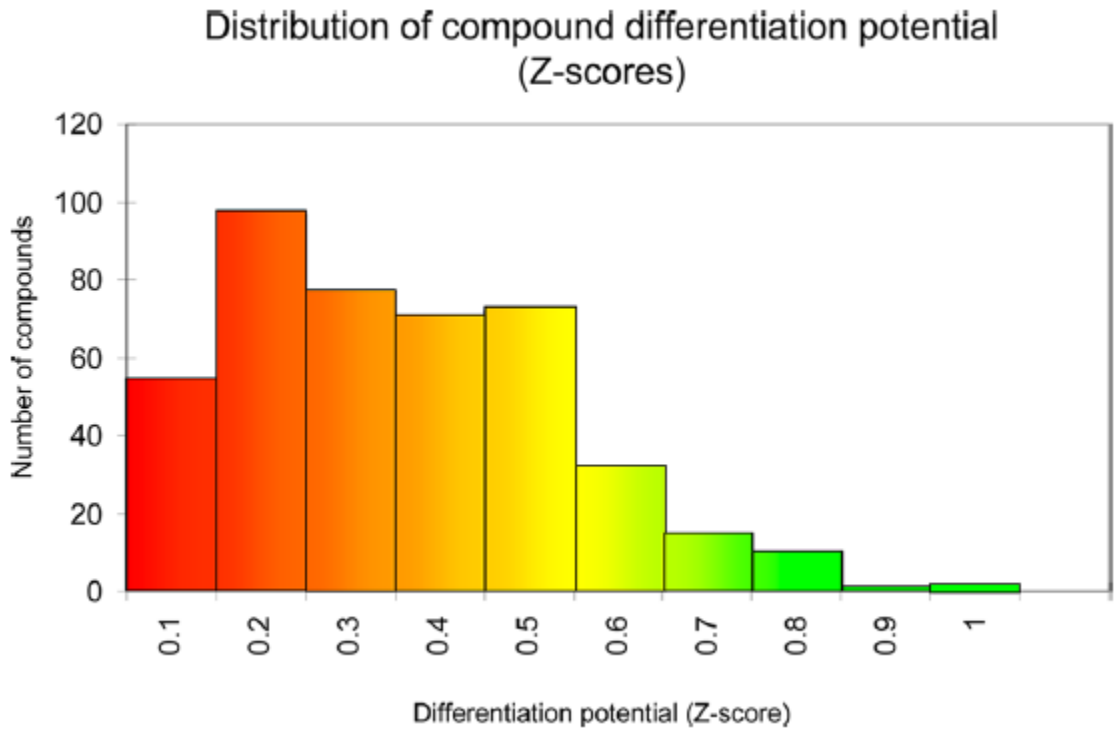
- Screened 484 known, structurally related compounds



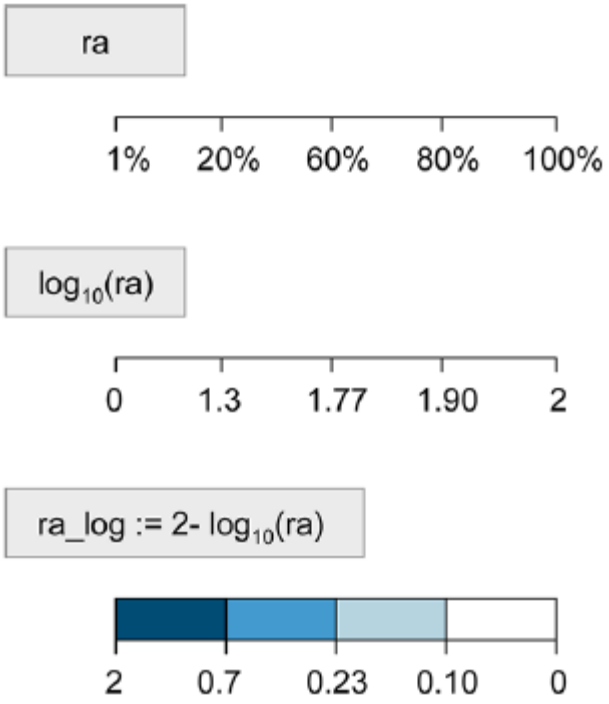
General Pyridinylimidazole Scaffold

  - ATP-binding site directed inhibitors
- Against 24 kinases all implicated in various cancers
  - AKT1, ARK5, Aurora-A, Aurora-B, BRAF VE, CDK2/CycA, CDK4/CycD1, COT, AXL, EGFR, EPHB4, ERBB2, FAK, IGF1R, SRC, VEGFR2, CK2-α1, JNK3, MET, p38- α, PDGFR-β, PLK1, SAK, TIE2

Differentiation Potentials of Compounds

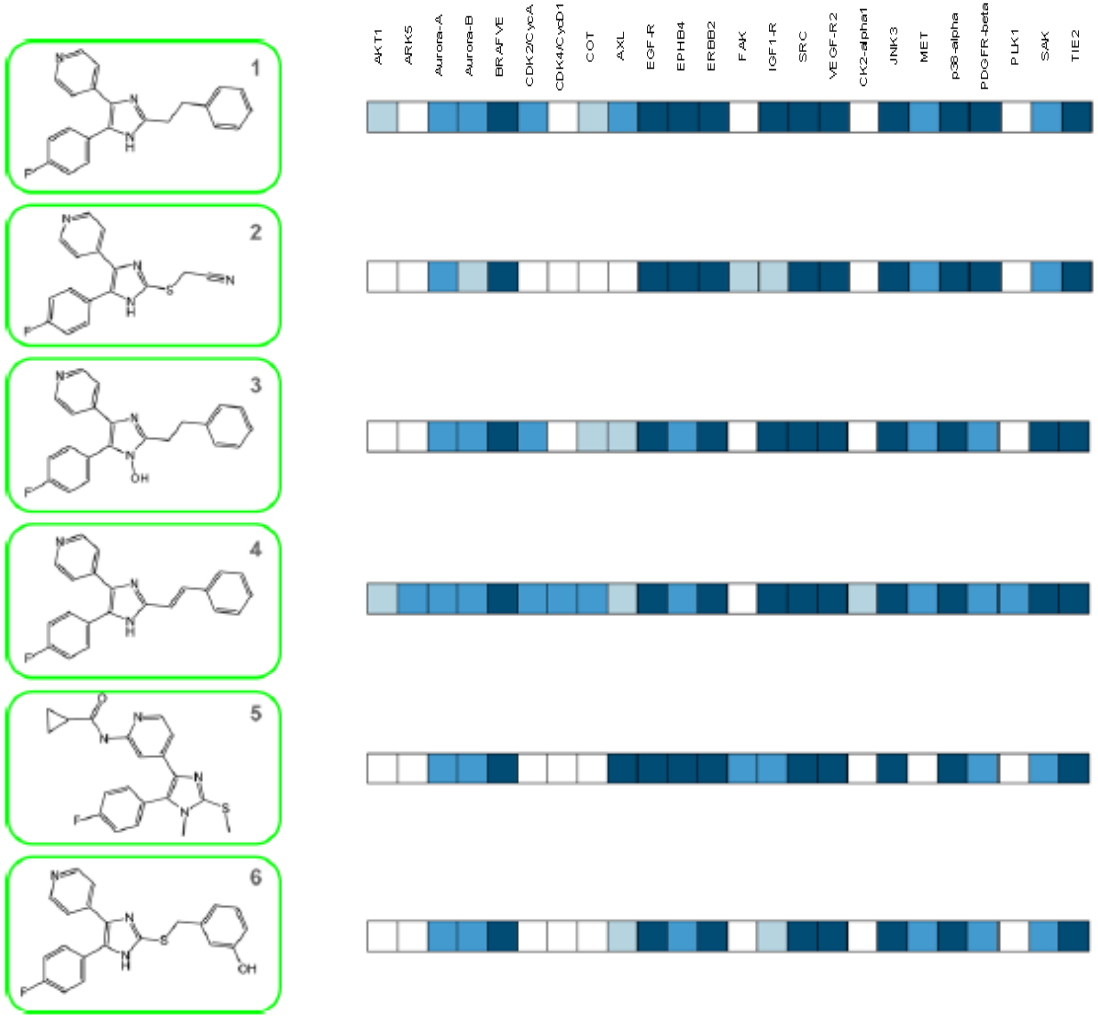


Scoring Scale

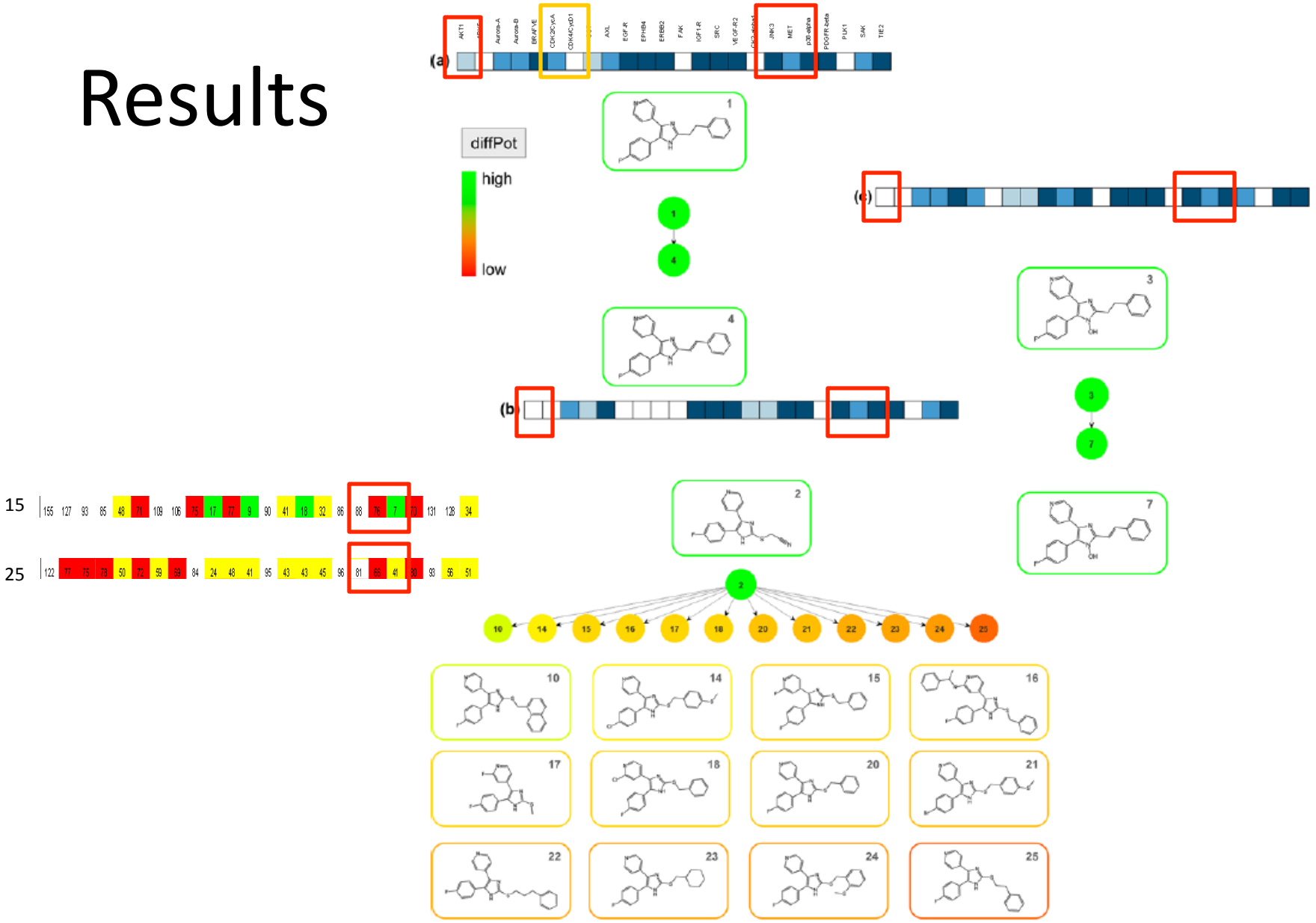


- Darker blue indicates >80% inhibition
- To white indicating <20% inhibition

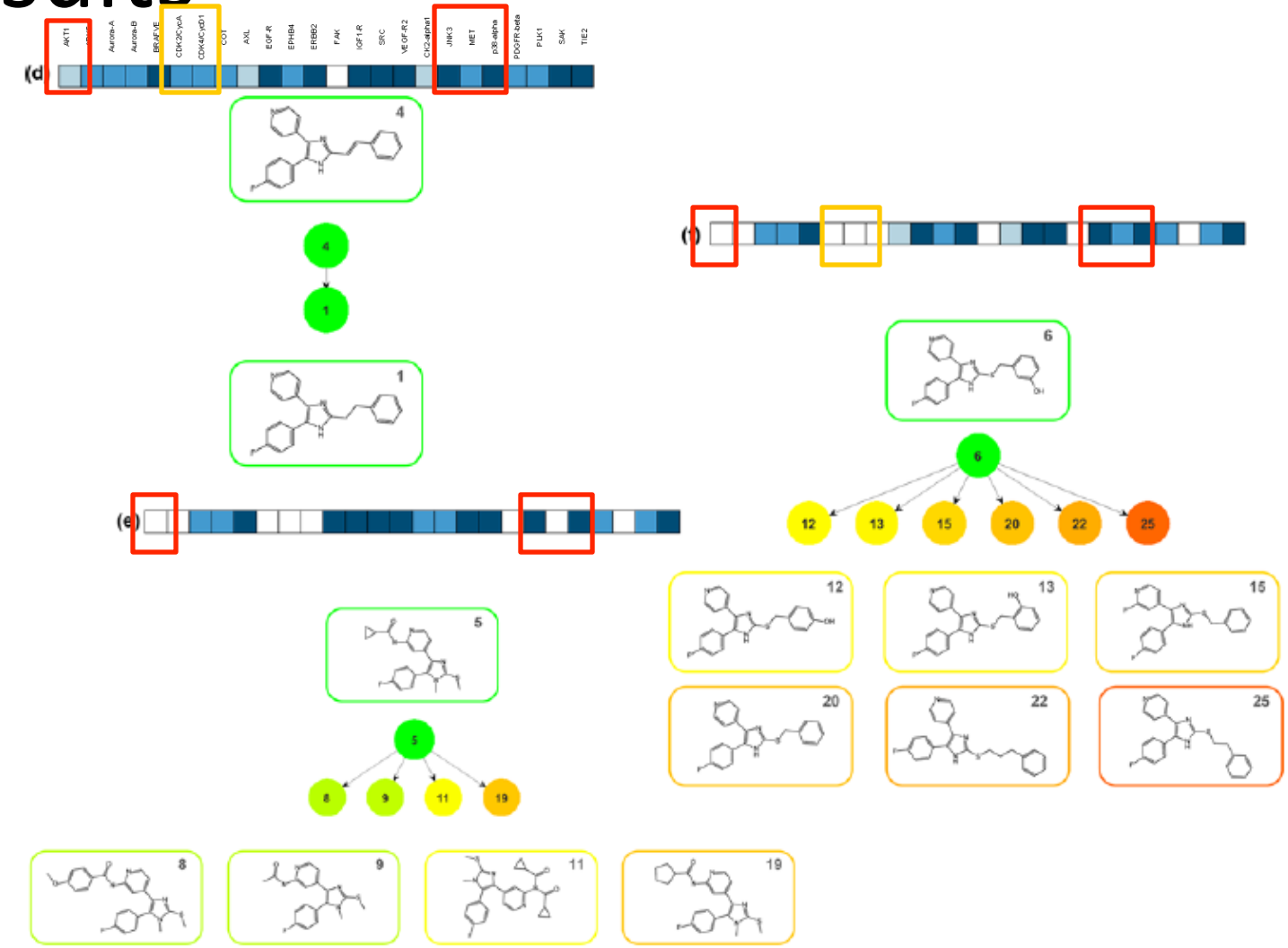
Results


1
2
3
4
5
6
AKT1
ARK5
Aurora-A
Aurora-B
BRAFV E
CDK2/CycA
CDK4/CycD1
COT
AXL
EGF-R
EPHB4
ERBB2
FAK
IGF1-R
SRC
VEGF-R2
CK2-alpha1
JNK3
MET
p38-alpha
PDGFR-beta
PLK1
SAK
TIE2

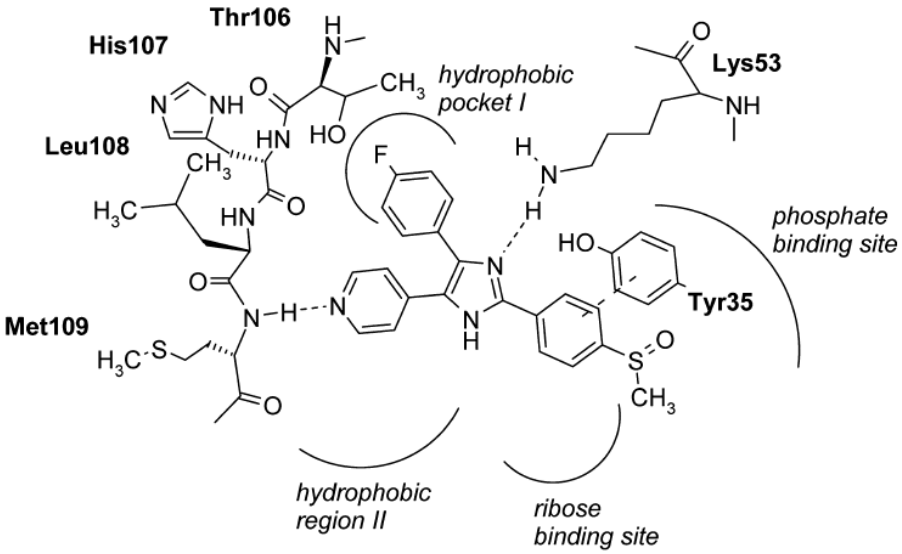
Results


(a)
AKT1
Aurora-A
Aurora-B
BRAFV6E
CDK3/cycA
CDK4/cyD1
AXL
EGFR
EPHB4
ERBB2
FAK
IGF1R
SRC
VEGFR2
JNK3
MET
p38-alpha
PDGFR-beta
PLK1
SAK
TIE2
diffPot
high
low
(c)
(b)
15
25

Results


(d)
AKT1
Aurora-A
Aurora-B
BRAF-V.E
CDK2/CyclA
CDK4/CyclD1
COT
AXL
EGF-R
EPHB4
ERBB2
FAK
IGF1-R
SRC
VEGF-R2
CK2-alpha1
JNK3
MET
p38-alpha
PDGFR-beta
PLK1
SAK
TIE2
4
1
(e)
5
8
9
11
19
(f)
6
12
13
15
20
22
25

Results



SAR for p38

- Based on the co-crystal structure with SB203580 (left) the SAR developed from the profiling and comparison studies can be justified

Conclusion

- This approach of computationally deriving differentiation potentials from large amounts of comparative data can be utilized for determining new lead compounds and directing the design of new inhibitors for various targets
  - Potentially accomplished by performing several profiling assays against cancer related kinases with a concentration of kinases from specific pathways important to the particular cancer(s) of interest
    - One utilizing a structurally diverse library
    - One utilizing 20-30 small diverse sets, with individual sets composed of structurally related compounds to develop a more specific SAR
- The novel computational approach of analyzing the data for differentiation potential can be used to gain large amounts of SAR
- Could be used to identify compounds that could have multiple targets and lead to a synergistic effect in tumors