



Redefining the Human Kinome Tree

A Local Sequence & Structure-Based Selectivity Analysis

Peter Schmidtke, Gabriella Jonasson, Daniel Alvarez Garcia - Discngine SAS, Paris, France



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Background

Drug discovery on kinases is accompanied by selectivity issues. The Manning Kinome tree [1] was published in 2002 and became an important reference in drug design to map known kinase inhibitors and evaluate their selectivity. However, the initial tree was built using a global sequence alignment and comparison amongst all human kinase domains [2-4].

Here we propose a paradigm shift with binding site specific selectivity trees allowing for quick lookup of kinases to monitor during compound optimization.

Methods

- Refined Sequence Alignment
- Selection of Amino Acids in contact with ligand
- Tree generation & substitution matrix evaluation
- Validation vs HMS LINCScan Kinomescan

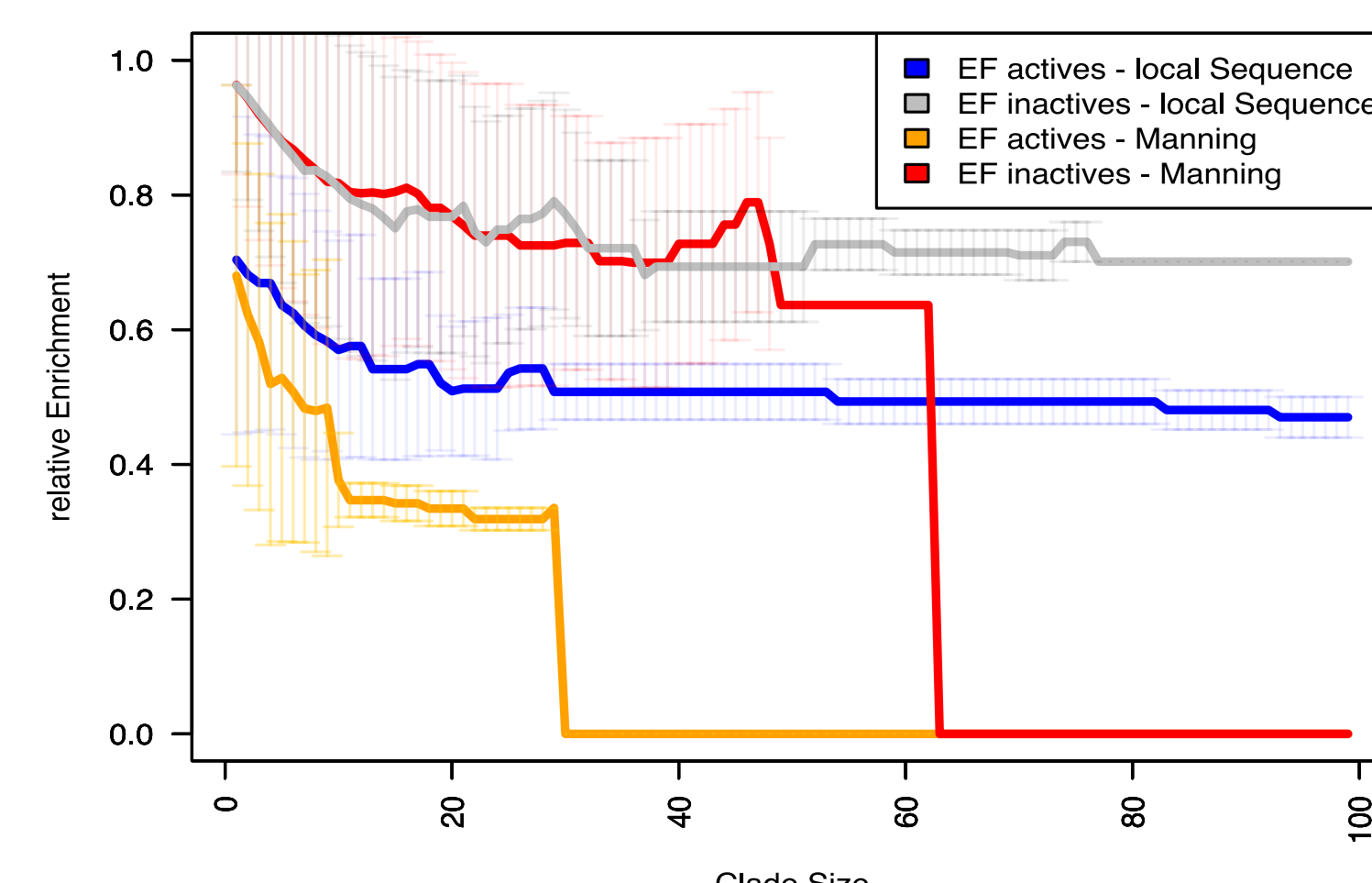
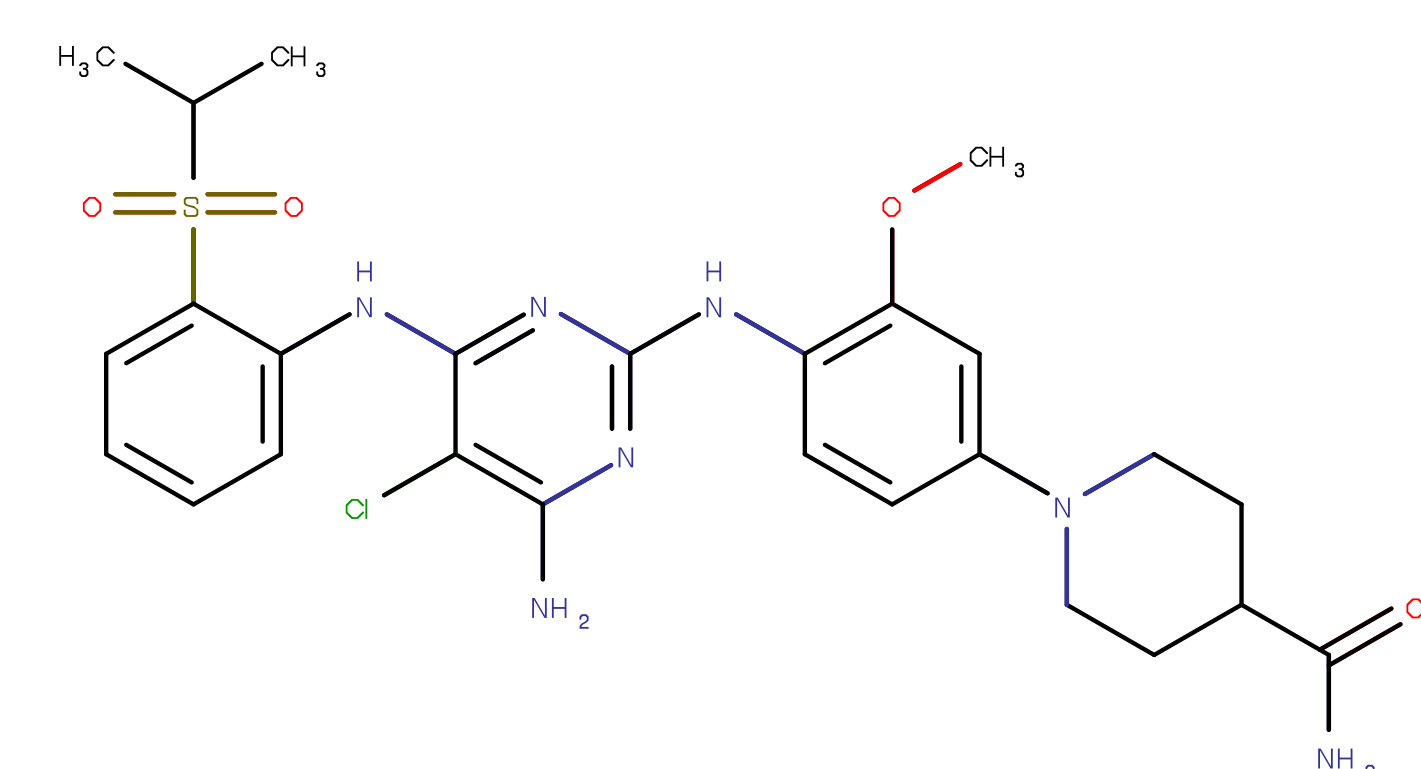
Conclusions

We obtain significant enrichment on large clades for type I inhibitors compared to the Manning tree. This supports that the type I tree might be already used for selectivity assessment. The type II tree does not result in significant enrichment in inhibited and non-inhibited kinases compared to the Manning tree and thus highlights the sensitivity to the initial sequence alignment.

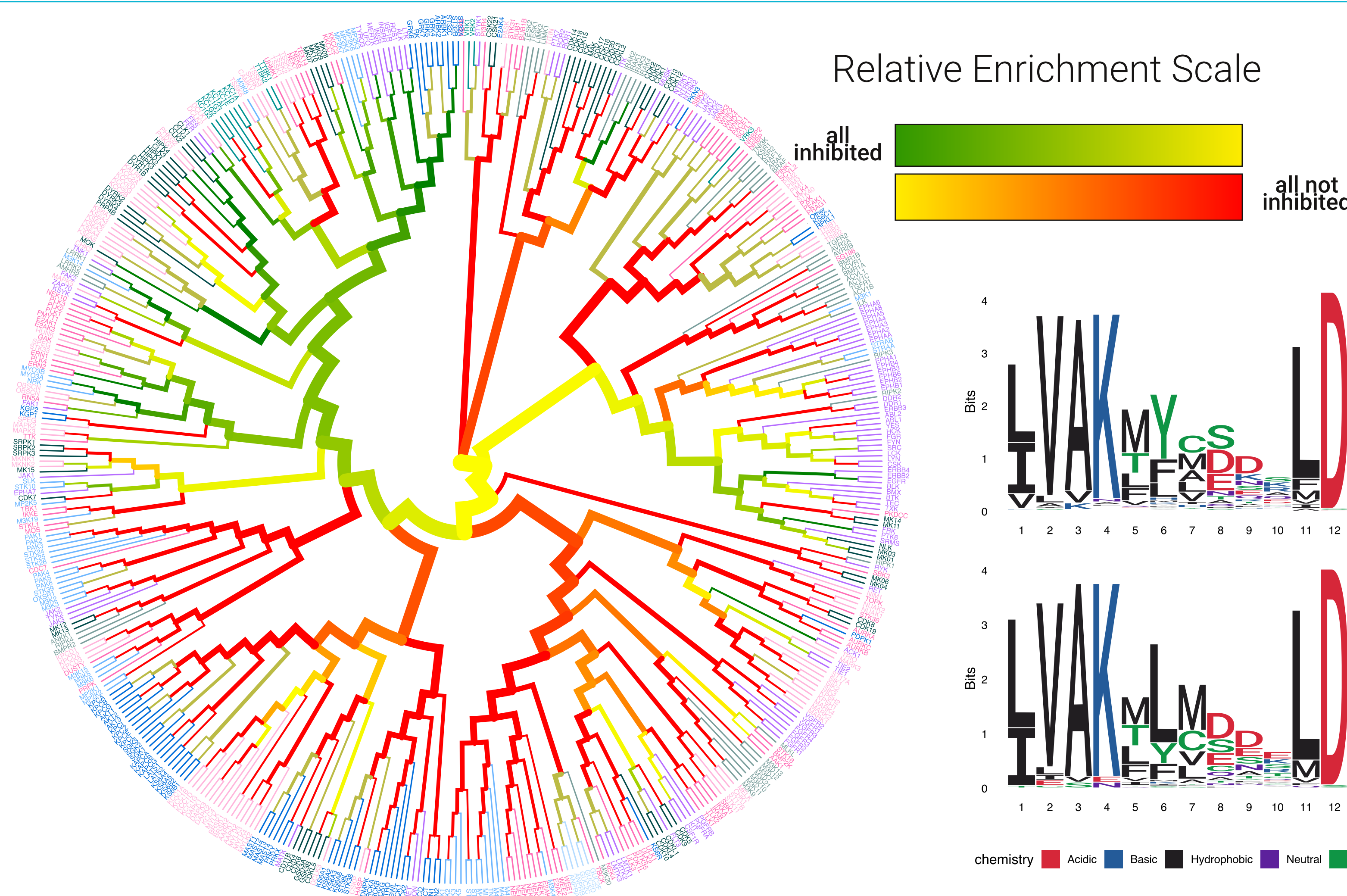
References

- [1] Manning et al. Science. 2002
- [2] Hanson et al. Cell Chem Biol. 2018
- [3] Kooistra & Volkamer, Ann Rep Med Chem, 2017
- [4] Christmann-Franck et al. JCI, 2016

HG-588-01 - type I inhibitor

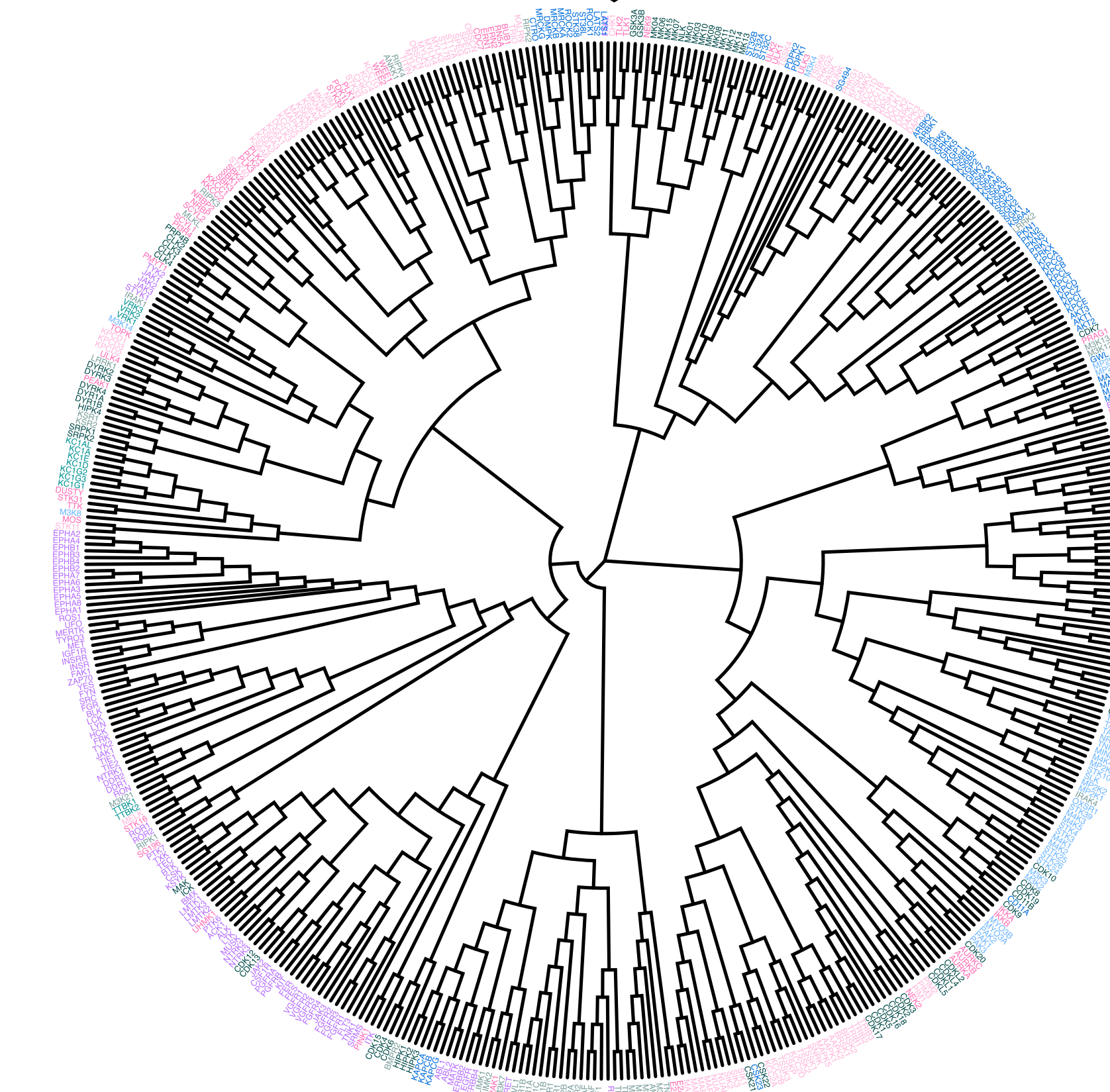
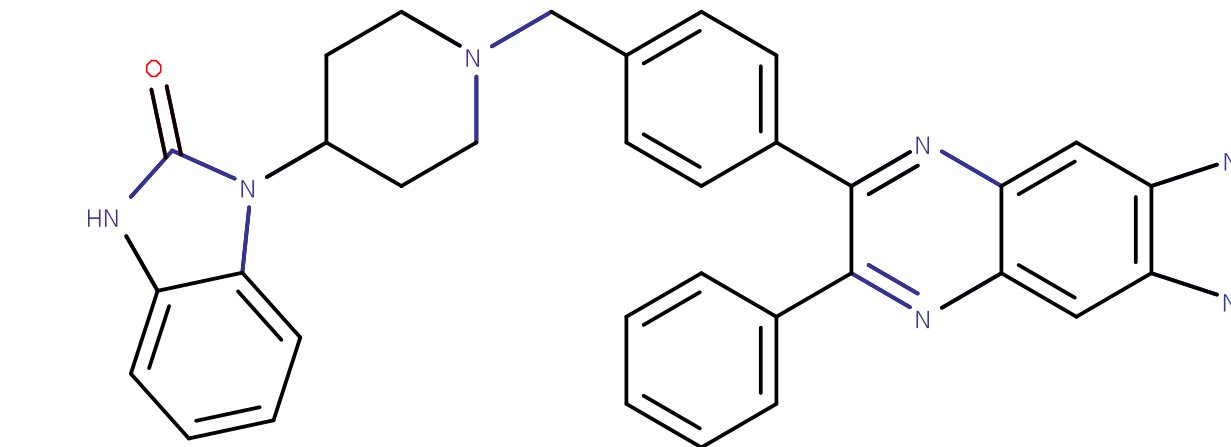


Relative enrichment from small clade sizes (2 leaf nodes) to large clade sizes (100 leaf nodes) of local pocket sequence vs original Manning tree in actives / inactives vs assay lincs kinomescan hms 20052.



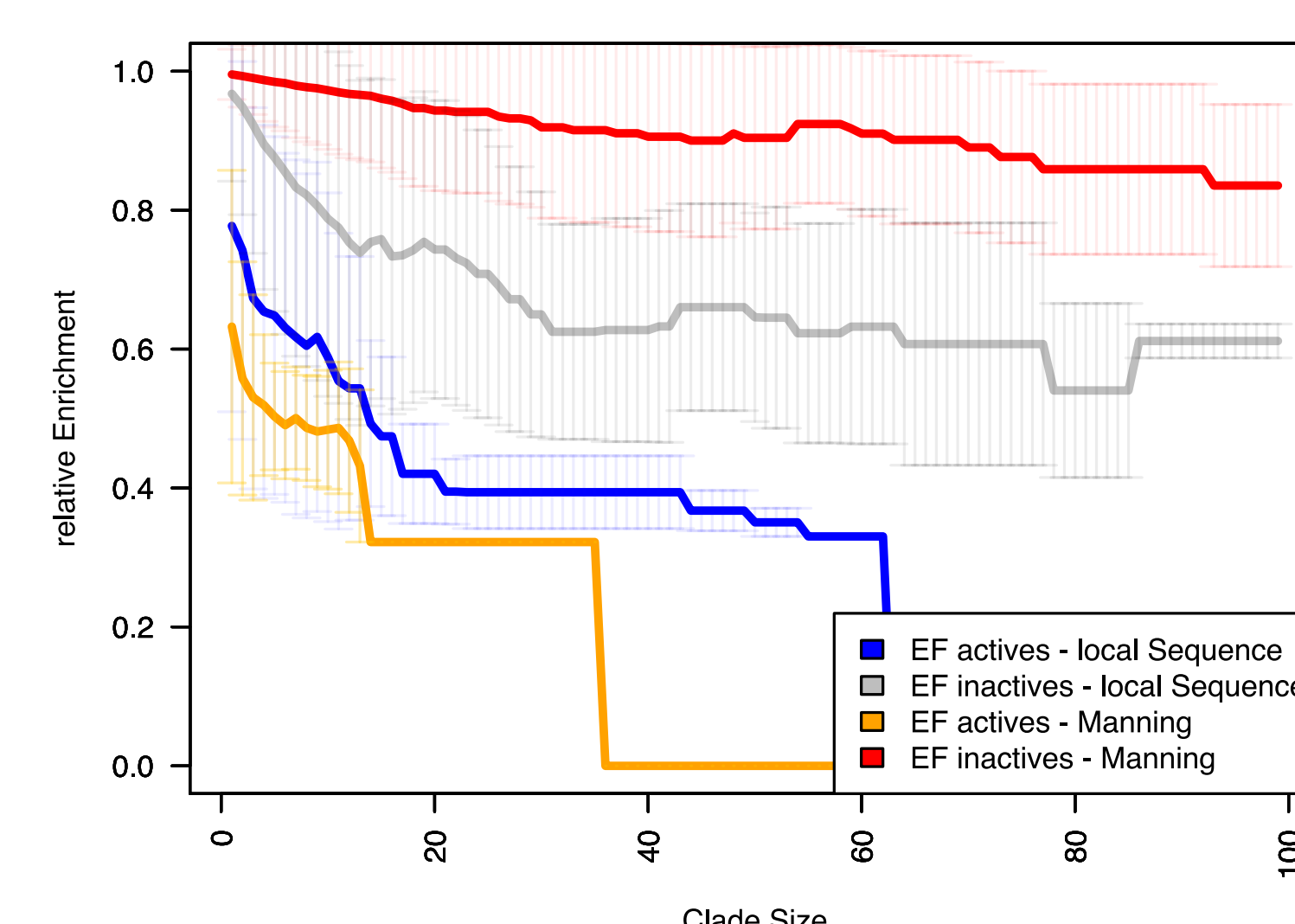
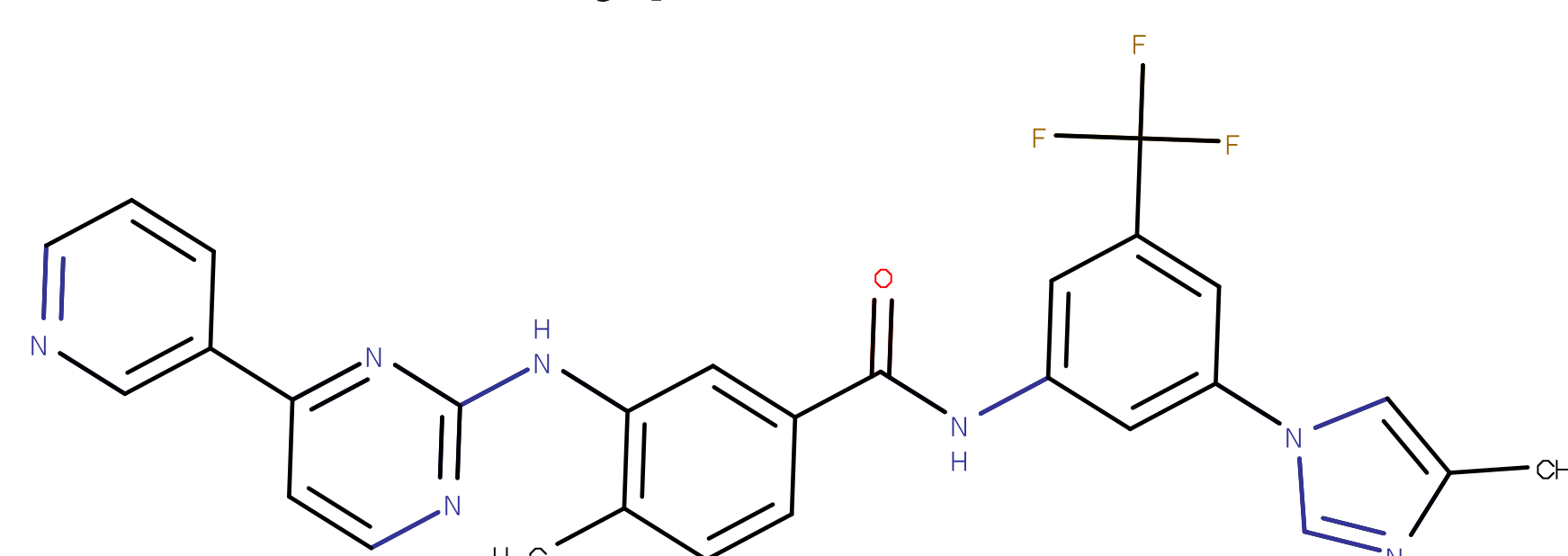
Kinome tree for type I inhibitor based on local pocket alignment and structure 2xb7. Branches are colored by relative enrichment in kinases the molecule is active (green) or inactive (red) against. Leaf nodes are colored by the original Manning classification.

Sigma A6730 - allosteric inhibitor

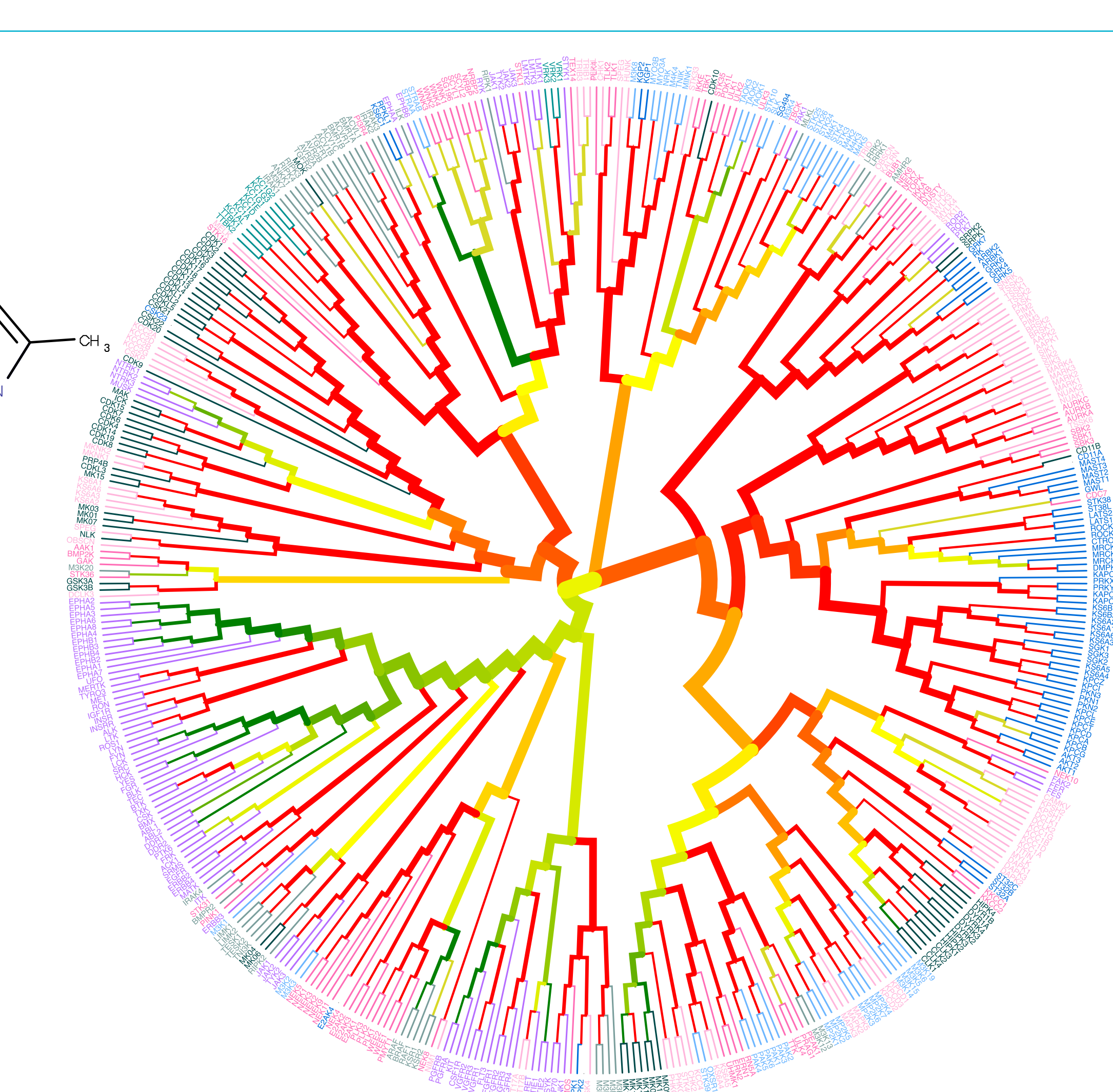


Kinome tree for allosteric binding site based on PDB structure 3o96

Nilotinib - type II inhibitor



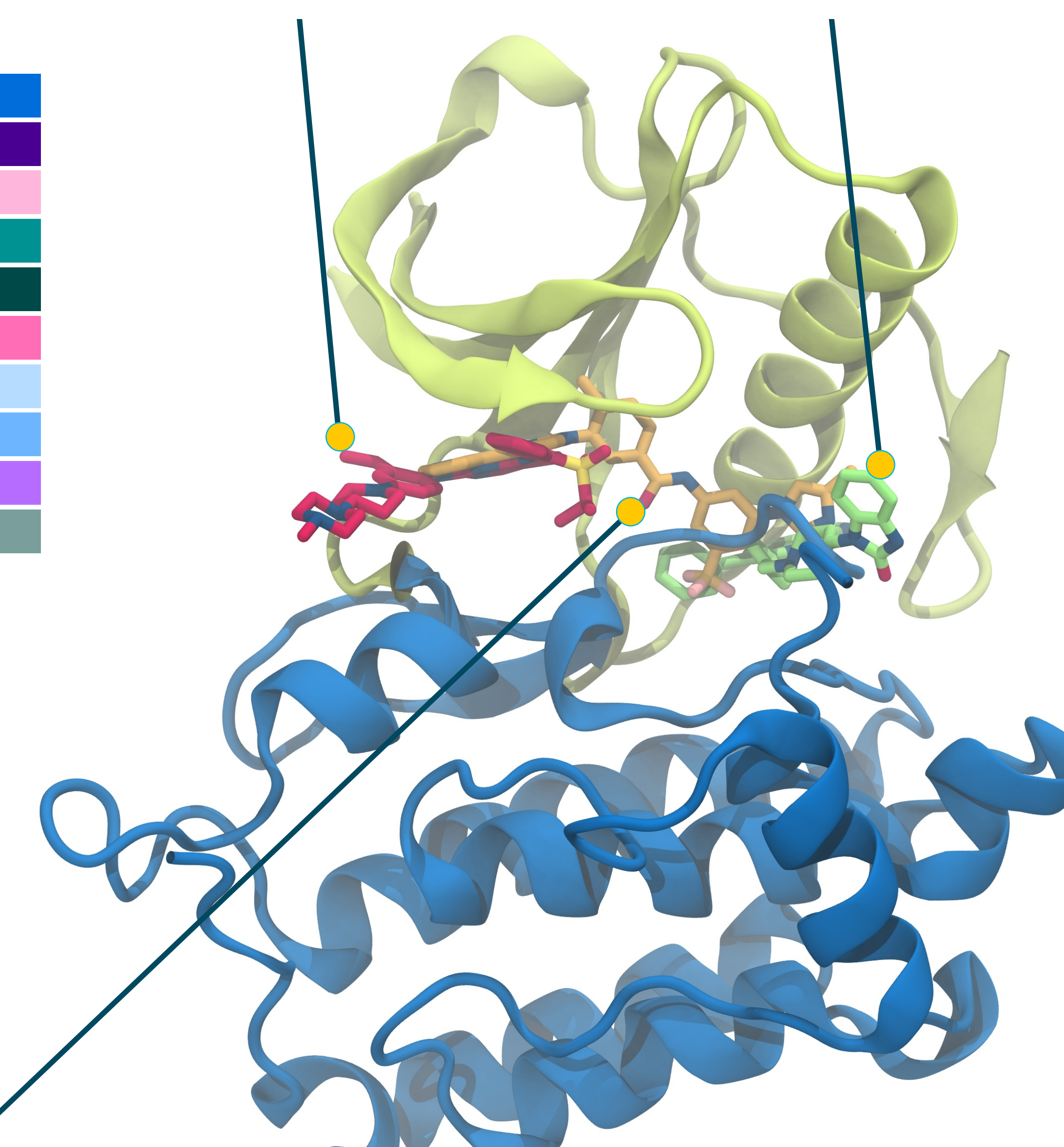
Relative enrichment from small clade sizes (2 leaf nodes) to large clade sizes (100 leaf nodes) of local pocket sequence vs original Manning tree in actives / inactives vs assay lincs kinomescan hms 20162.



Kinome tree for type II inhibitor based on local pocket alignment and structure 3cs9. Branches are colored by relative enrichment in kinases the molecule is active (green) or inactive (red) against. Leaf nodes are colored by the original Manning classification.

Considered Binding Modes

AGC
Atypical
CAMK
CK1
CMGC
Other
RGC
STE
TK
TKL



<https://github.com/Discngine/kinometree>