Chemocentric Informatics Strategy to Study the Polypharmacology of Kinases

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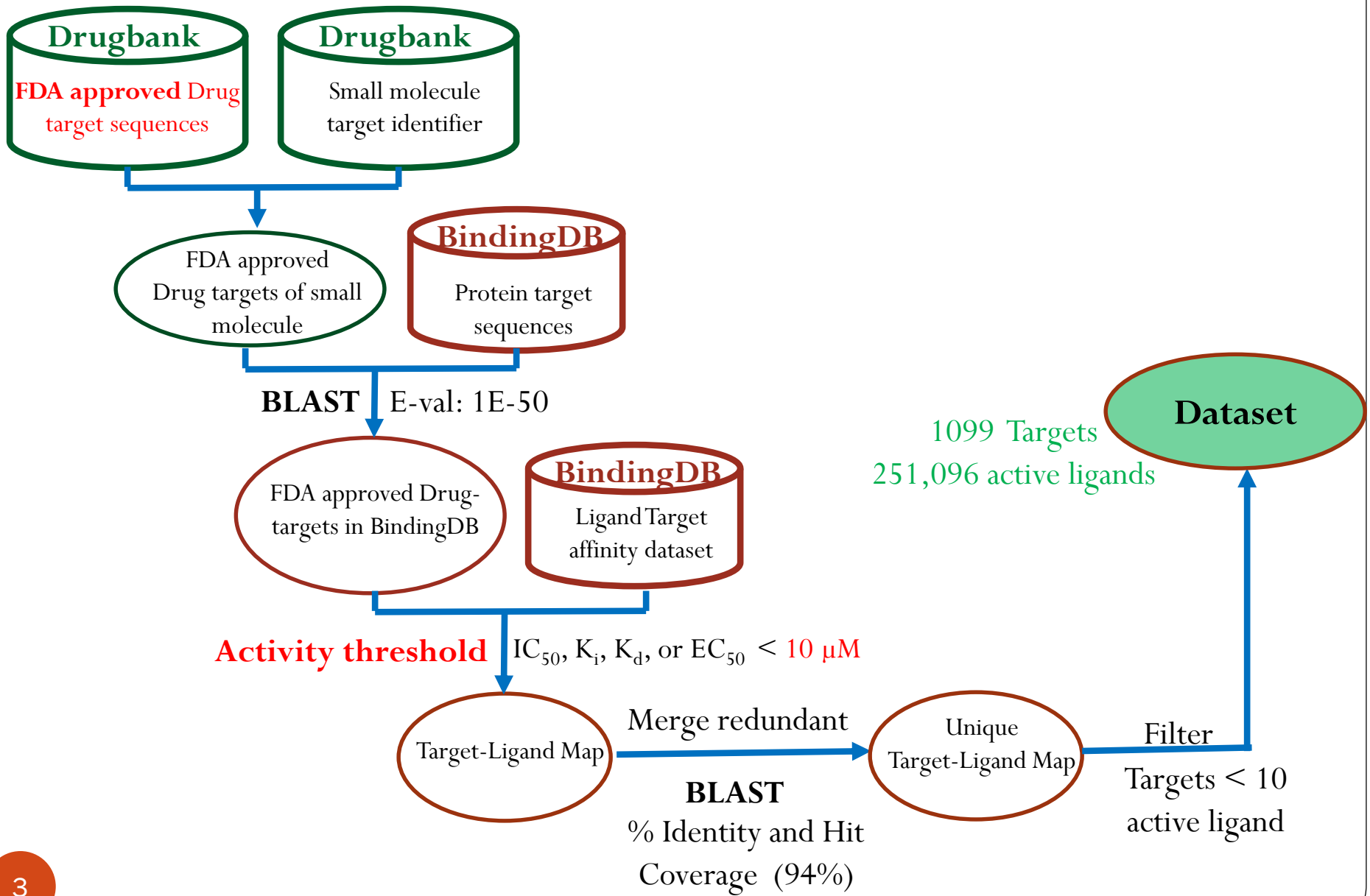
AIM

Build an in-house dataset of **active ligands of FDA-approved drug targets** for the purpose of:

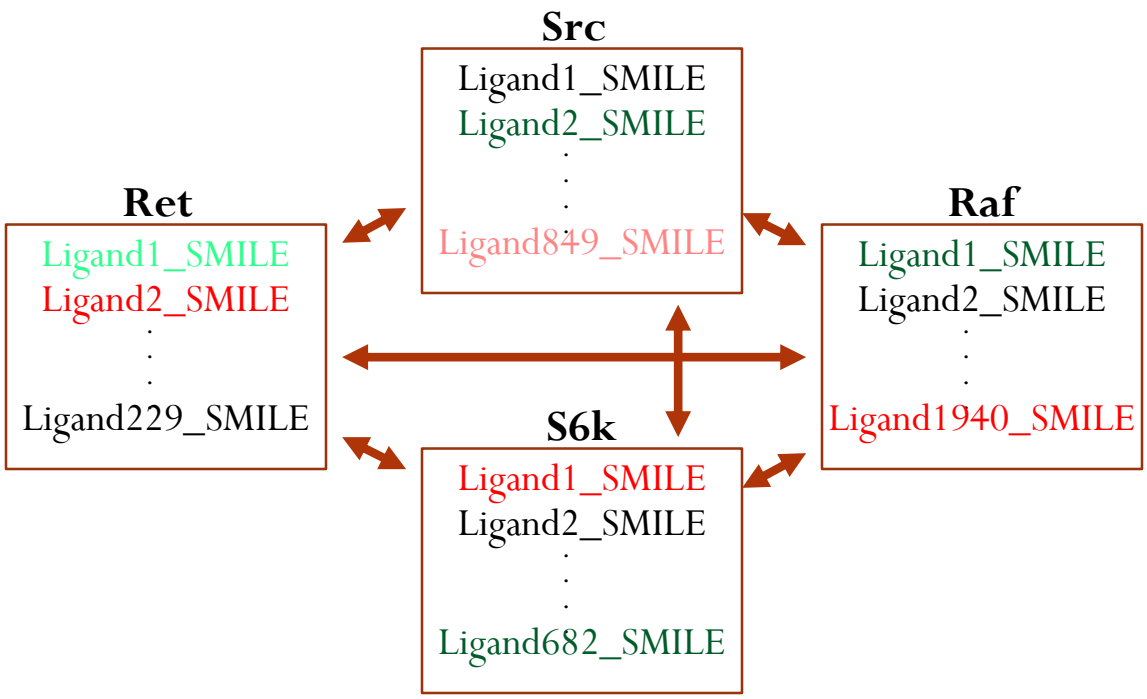
1. Discovering novel ligands that may efficiently inhibit Ret, Src, S6k, and Raf but not mTor.

2. In silico target fishing for kinase inhibitors.

Dataset Preparation Workflow



Strategy for obtaining Polypharmacology profile



2D Binary Fingerprint Tanimoto Similarity

0 — **1**

Complete dissimilarity — Identical

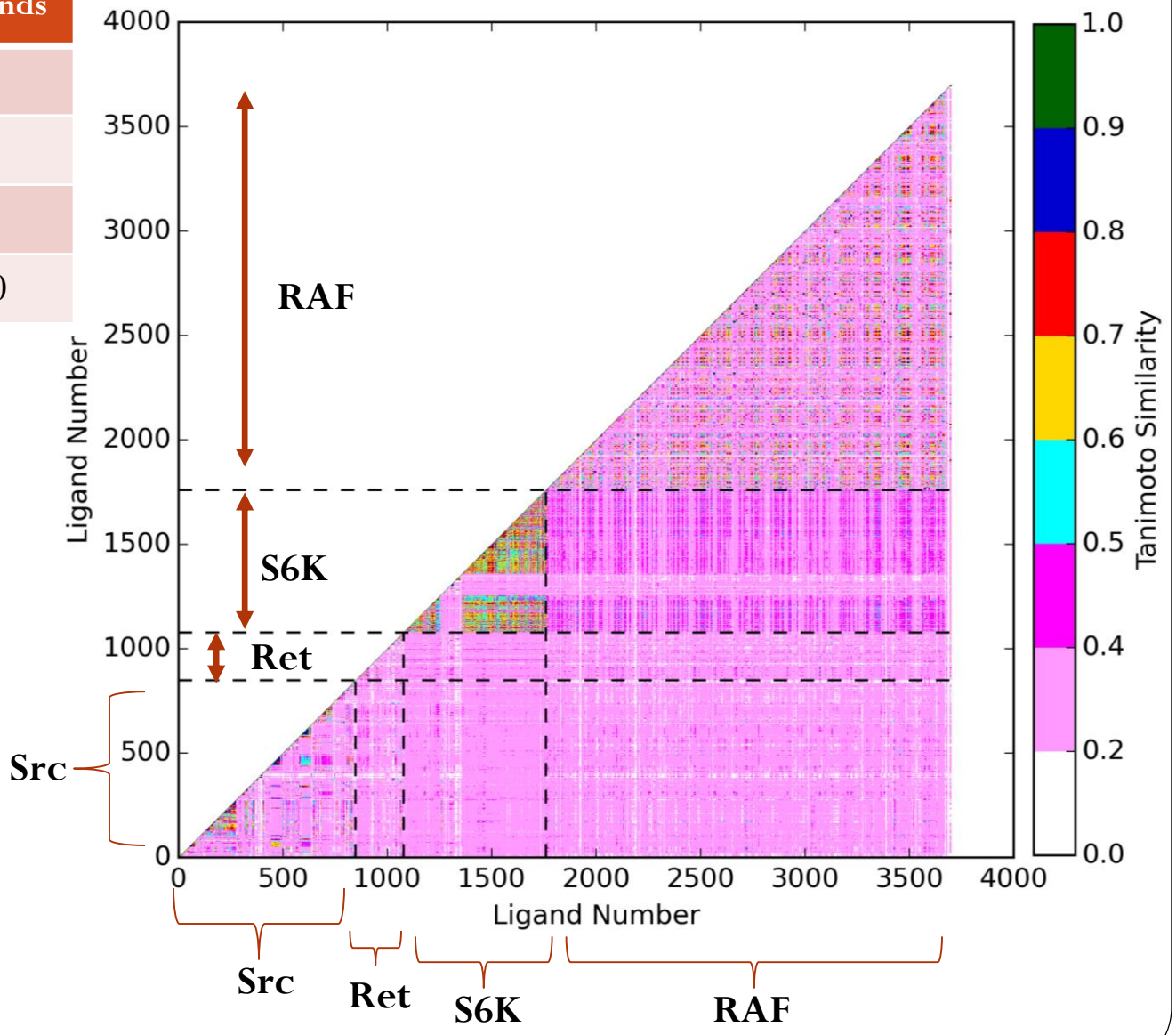
Tanimoto Cutoff (TC)
(free parameter)

Potential Active against all

Ligand1_SMILE_Ret
Ligand849_SMILE_Src

Chemical similarity within and among target ligands

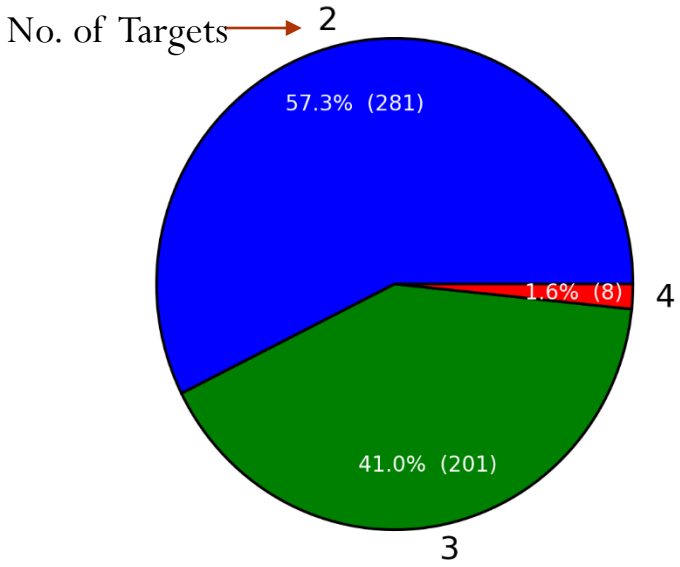
Target	Target_ID	No_ligands
Src	63	849
Ret	147	229
S6K	392	682
Raf	591	1940



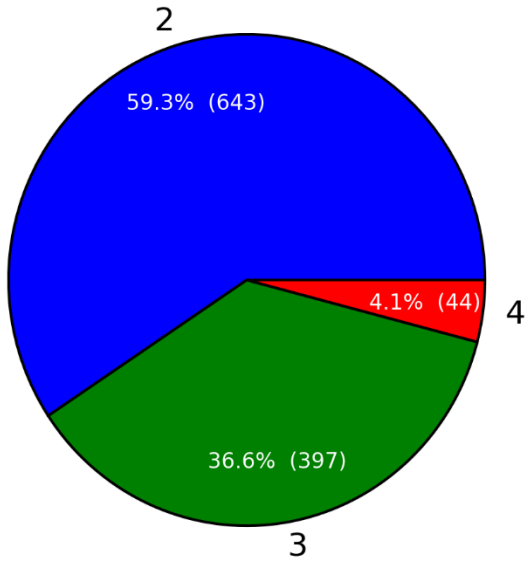
Polypharmacology profile of identified similar ligands

Target profile of similar ligands in Ret, Src, S6k, and Raf with no exact match in mTor

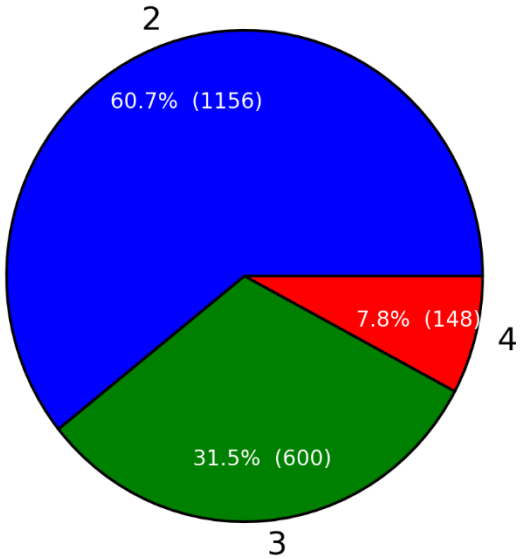
TC = 0.7



TC = 0.6



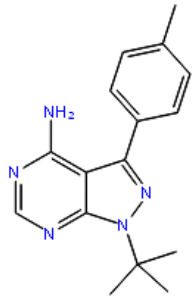
TC = 0.55



8 similar ligands at TC 0.7

Target	ID
Src	63
Ret	147
S6K	392
Raf	591

Ligands predicted to target 4 kinases (Src, Ret, S6k, and Raf)



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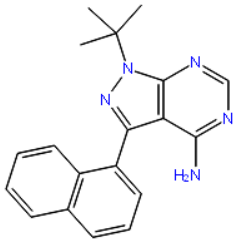


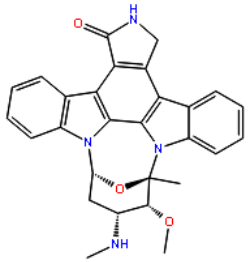
50229961_63

50142887_63

0.75

0.75

0.73



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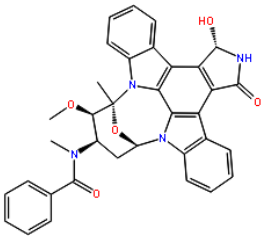

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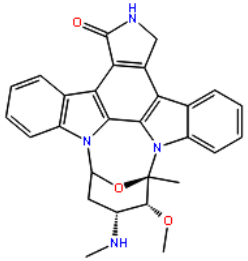

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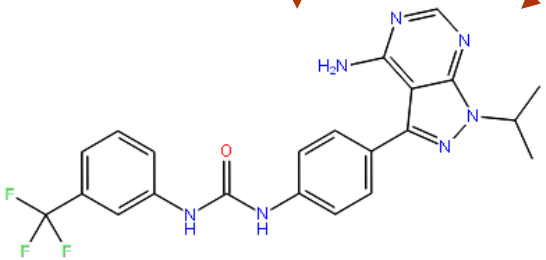
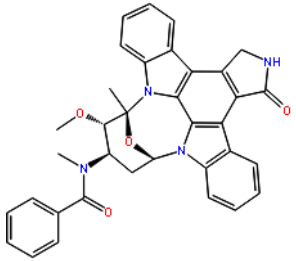


Same scaffold as AD57



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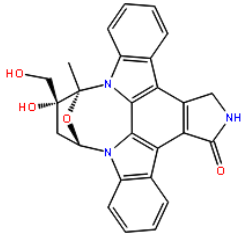

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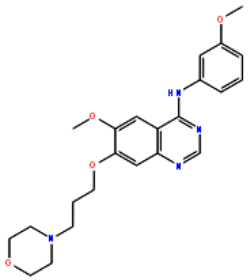
36 additional ligands at TC 0.6

Target	ID
Src	63
Ret	147
S6K	392
BRaf	591

Ligands predicted to target 4 kinases (Src, Ret, S6k, and Raf)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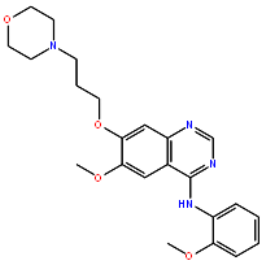
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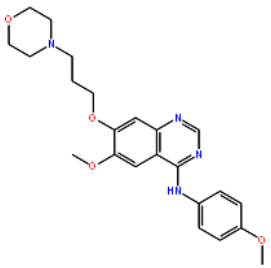
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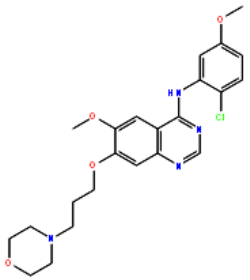
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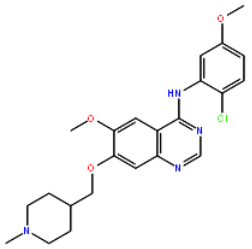
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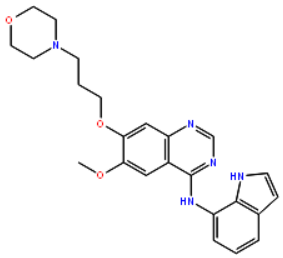
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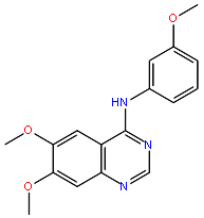
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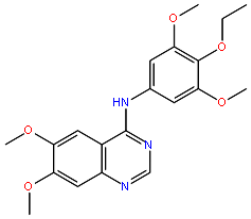
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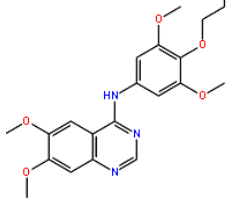
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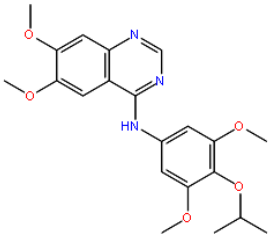
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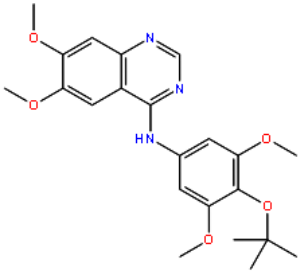
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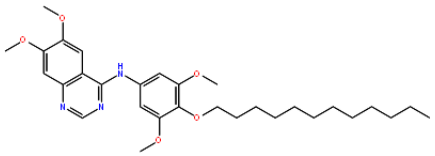
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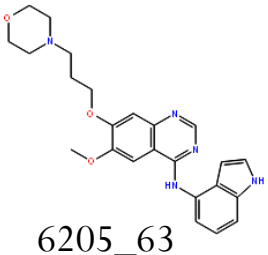
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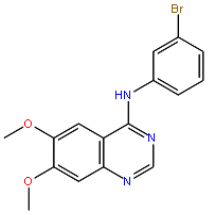
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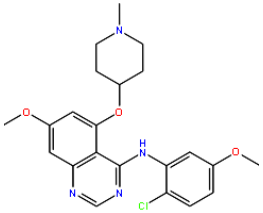
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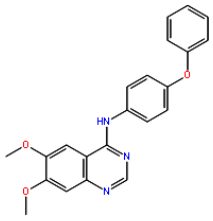
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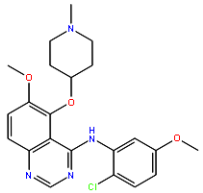
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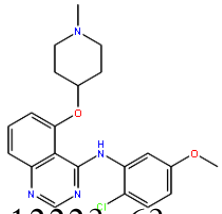
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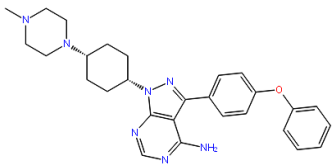
36 additional ligands at TC 0.6

Target	ID
Src	63
Ret	147
S6K	392
BRaf	591

Ligands predicted to target 4 kinases (Src, Ret, S6k, and Raf)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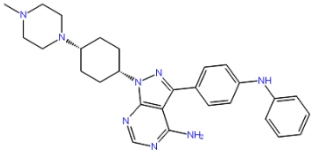
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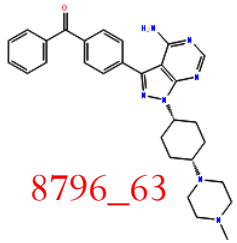
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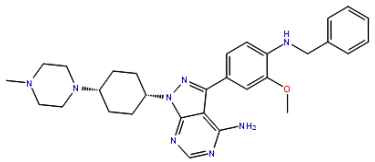
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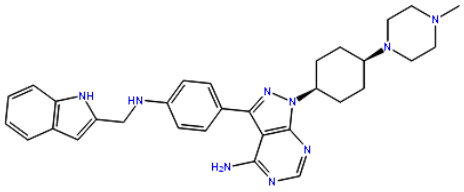
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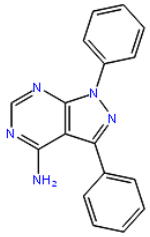
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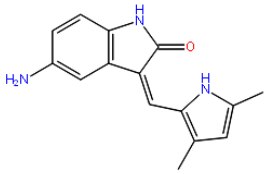
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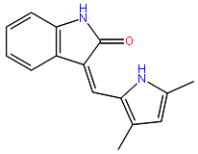
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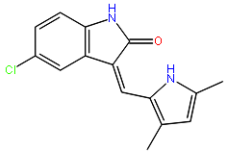
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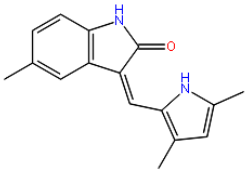
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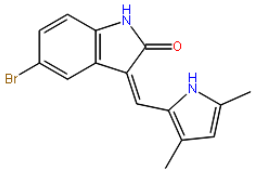
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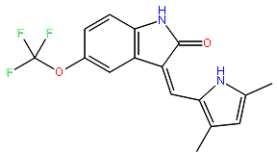
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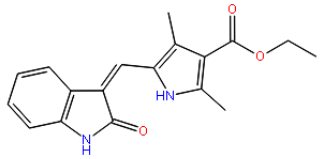
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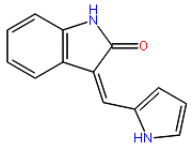
The 6 ligands also show similarity to AD57 with Tanimoto in range 0.63-0.74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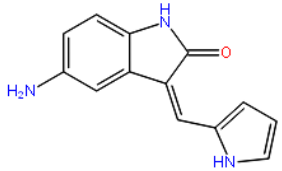
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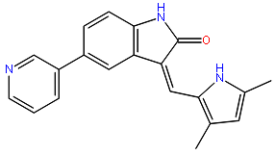
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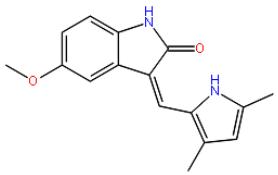
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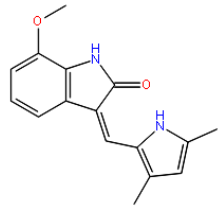
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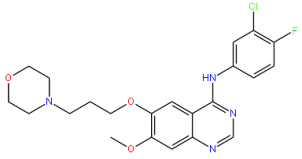
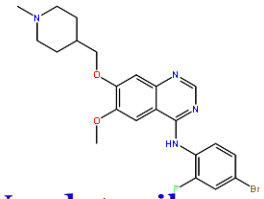
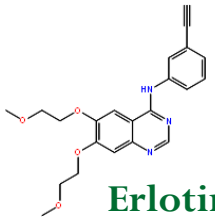
Similarity of 44 ligands (TC 0.6) with known inhibitors



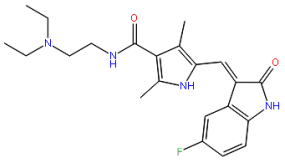
Gefitinib



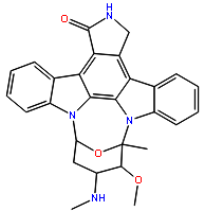
Vandetanib



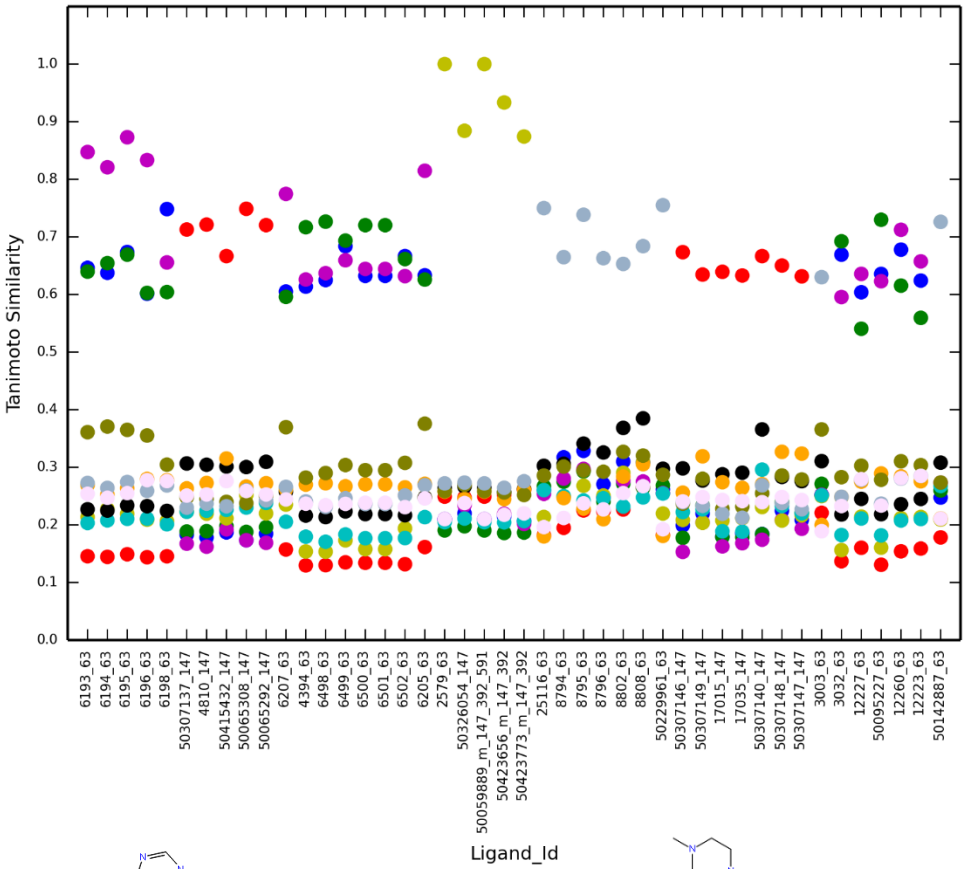
Erlotinib

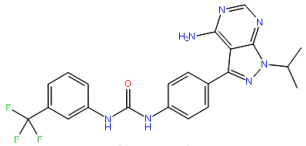


Sunitinib

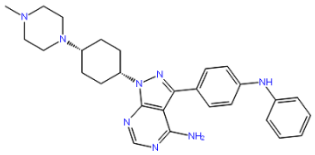


Straurosporine





AD57



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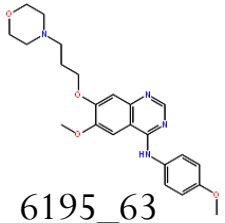

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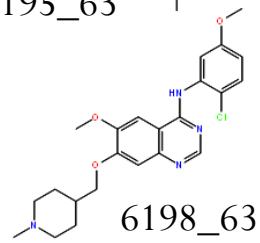

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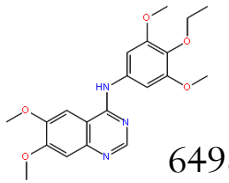

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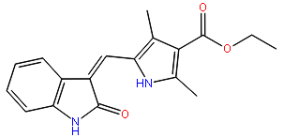

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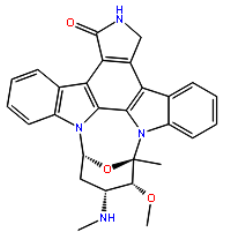


2579_63

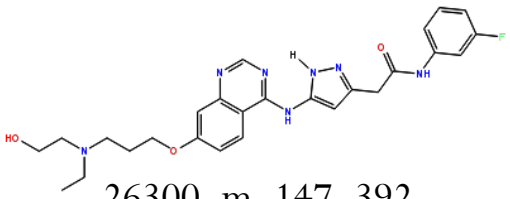
No significant similarity (Tanimoto < 0.4) with SB202190, Sorafenib, **Imatinib**, Doramapimod, and Dasatinib

104 additional ligands at TC 0.55

104 ligands were clustered based on chemical similarity (No. of Clusters = 18)

Target	ID
Src	63
Ret	147
S6K	392
BRaf	591

Ligands predicted to be target 4 kinases (Src, Ret, S6k, and Raf)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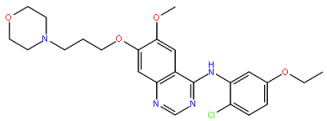
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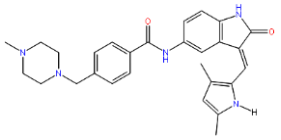
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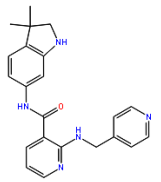
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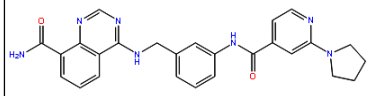
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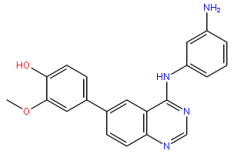
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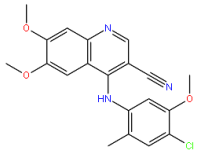
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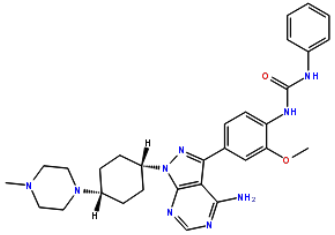
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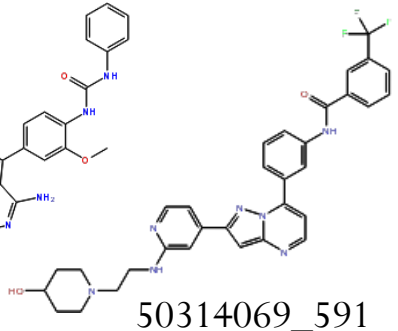
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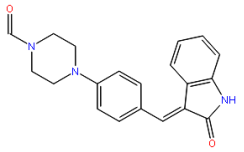
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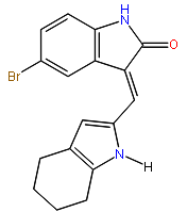
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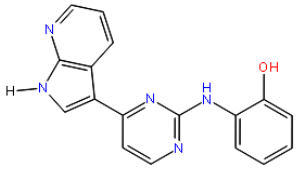
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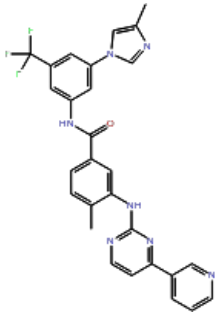
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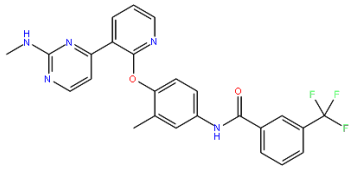
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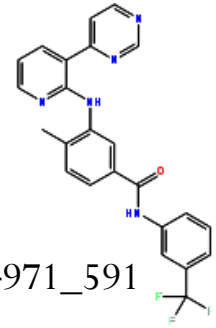
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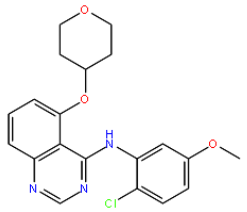
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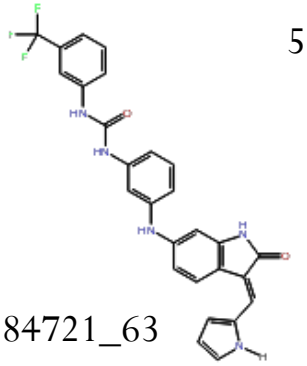
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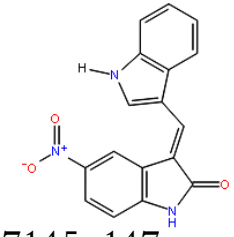
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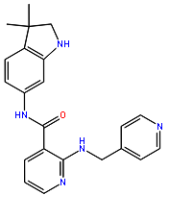
Structure of Cluster centroids

Similarity of cluster centroids with known inhibitors



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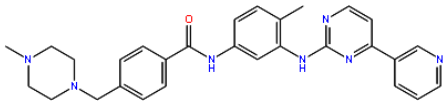
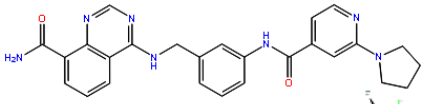


Imatinib



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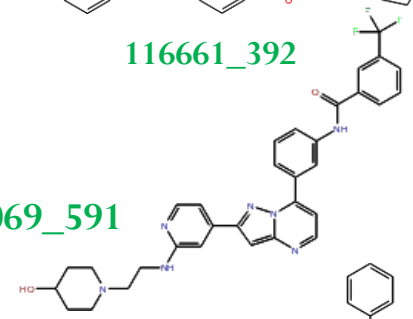

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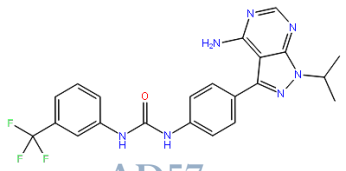
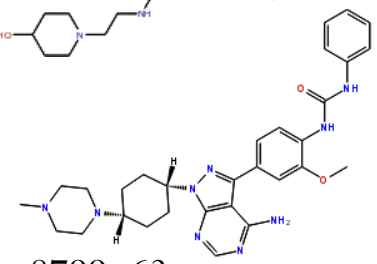


AD57



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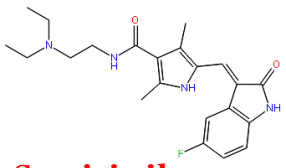
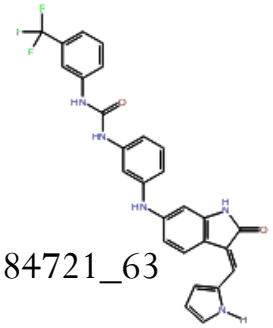


Sunitinib



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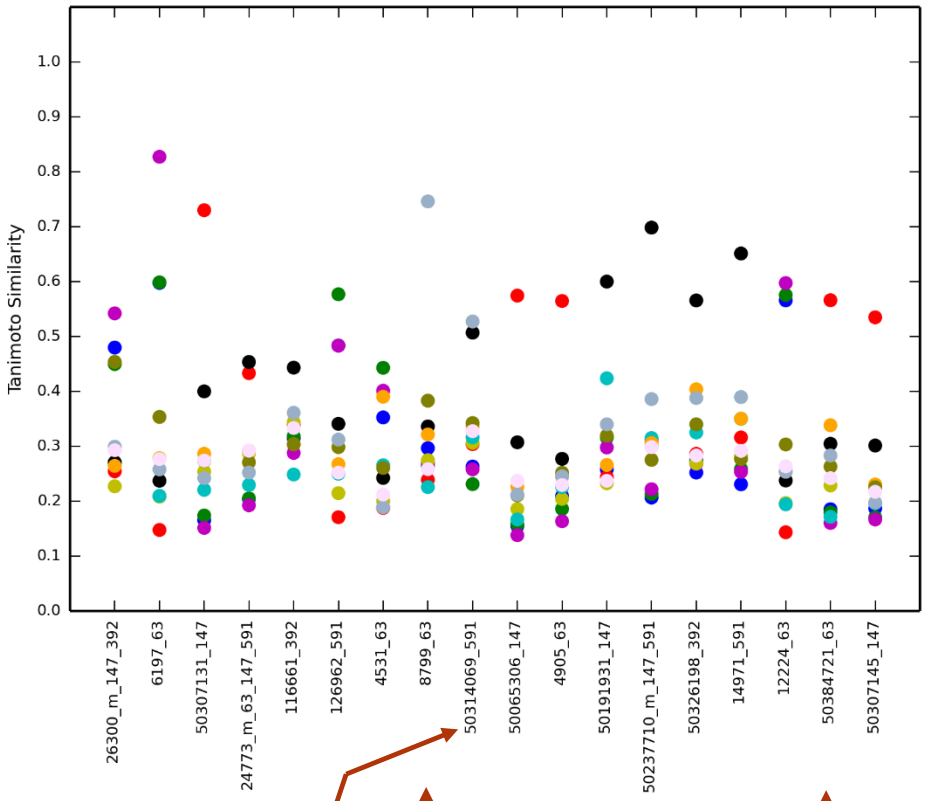

Different Scaffold

Similar to AD57

Similar scaffold as Sunitinib and AD57

Polypharmacology profile of known inhibitors

- Entire dataset was also screened with 15 known kinase inhibitors (Dar et al., Nature, 486 (2012)).

Inhibitor	#Targets (Exact Match)	Example Targets
AD Series (AD36, AD57, AD58, AD80 and AD81)	0	---
Dasatinib	78	**Src, Ret, Raf** etc.
Doramapimod (BIRB796)	59	**Ret, Raf**, Map Kinase etc.
Erlotinib	59	**Src, Ret,** EGFR etc.
Gefitinib	44	EGFR, her-2 substrate etc.
Imatinib	46	**Src, Raf,** carbonic anydrase etc.
SB-202190	24	**Raf,** p38-beta, jnk2 etc.
Sorafenib	70	**Ret, Raf,** vegfr etc.
Staurosporine	208	**Src, Ret, S6k, CRAF** etc.
Sunitinib	133	**Src, Ret, S6k,** fgfr1 etc.
Vandetanib	77	**Ret, S6k,** hiv-1 protease etc.