

# **Chemocentric Informatics Strategy to Study the Polypharmacology of Kinases**

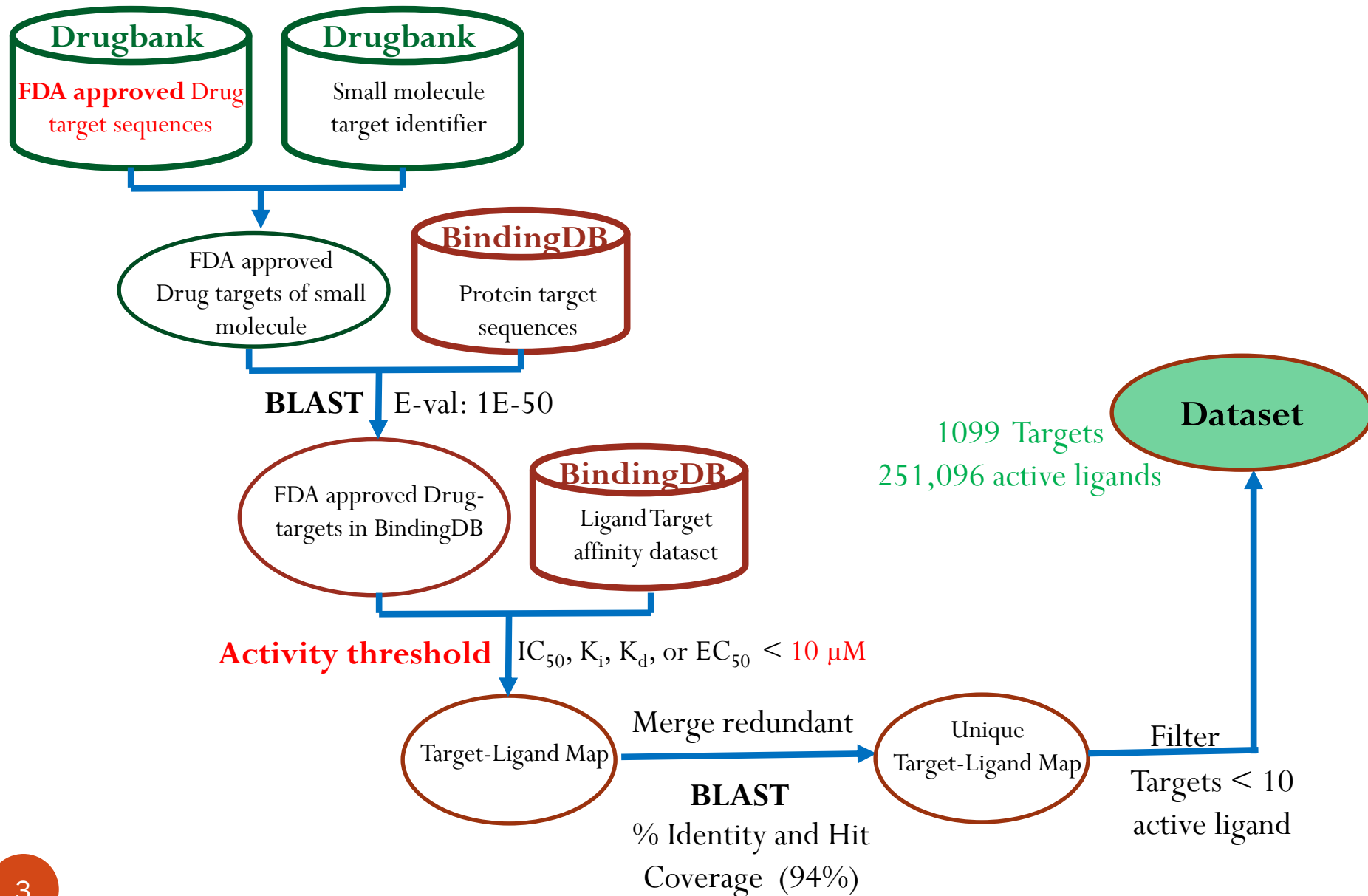
Abhijeet Kapoor

# AIM

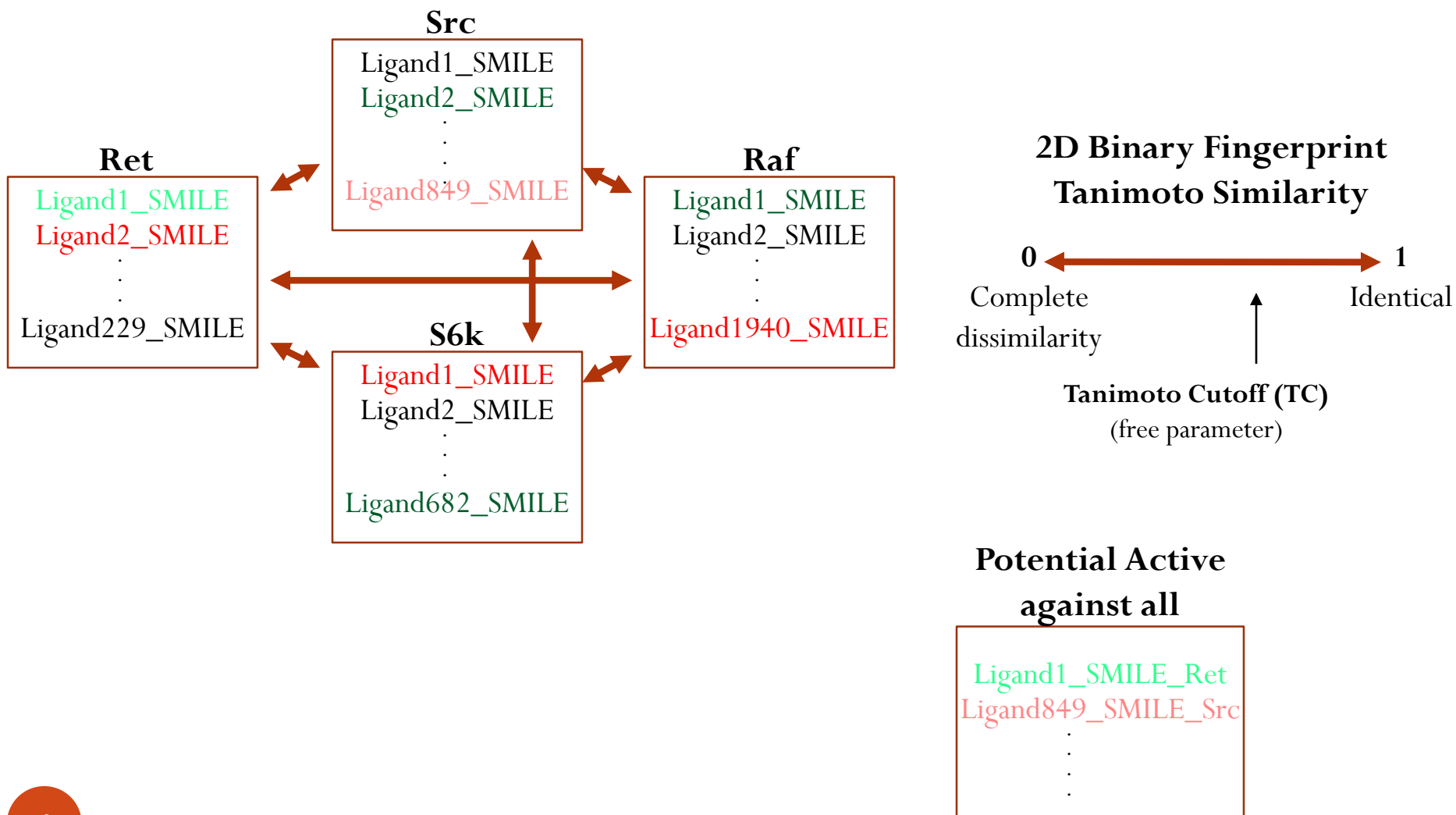
Build an in-house dataset of **active ligands of FDA-approved drug targets** for the purpose of:

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

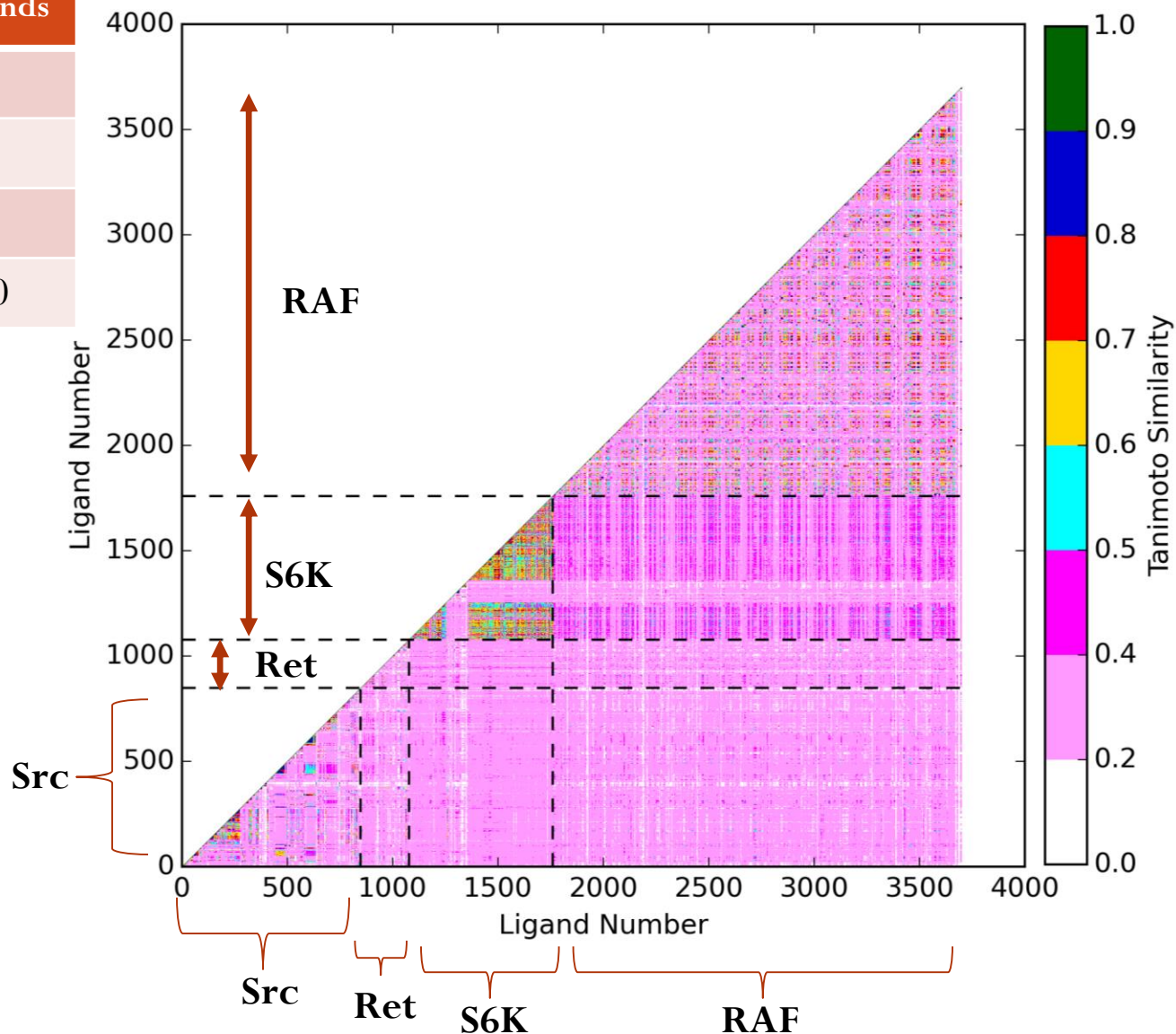


# Strategy for obtaining Polypharmacology profile



# 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

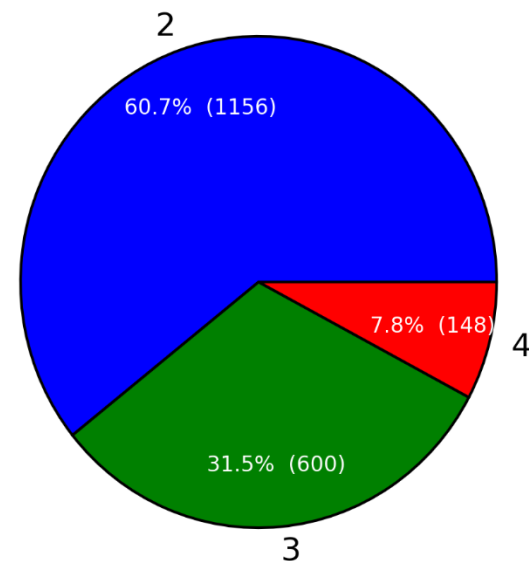
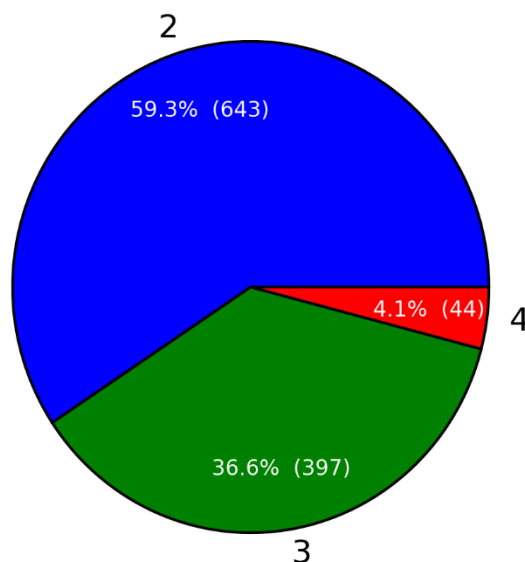
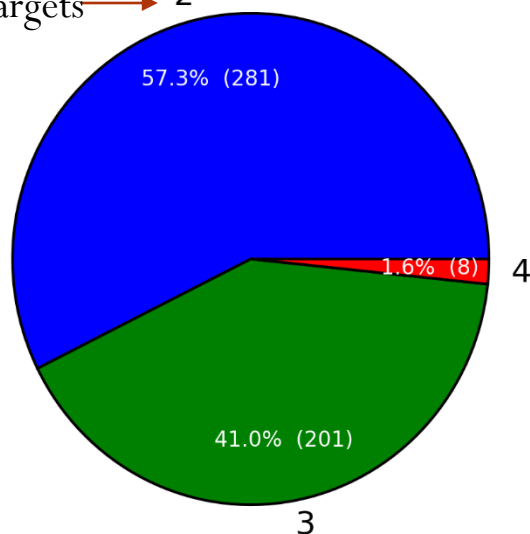
Target profile of similar ligands in Ret, Src, S6k, and Raf with no exact match in mTor

TC = 0.7

TC = 0.6

TC = 0.55

No. of Targets → 2



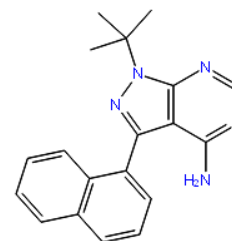
Target	ID
Src	63
Ret	147
S6K	392
Raf	591

# 8 similar ligands at TC 0.7

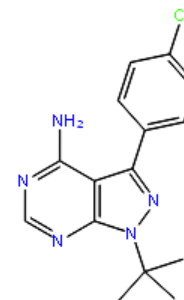
Ligands predicted to target 4 kinases (Src, Ret, S6k, and Raf)



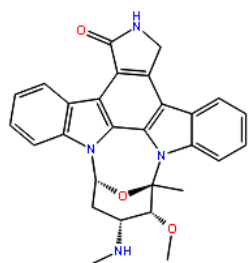
25116\_63



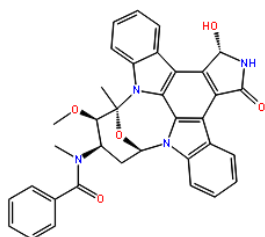
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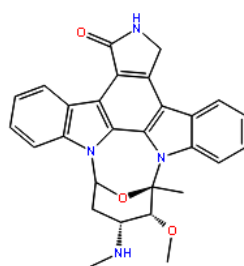
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2579\_63



50326054\_147

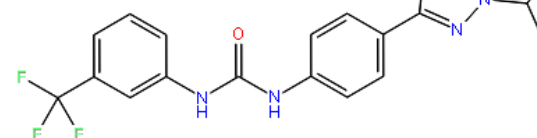


50059889\_m\_147\_392\_591

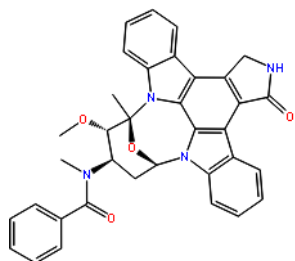
0.75

0.75

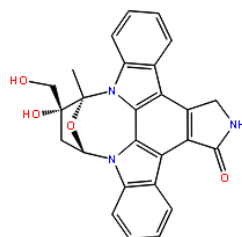
0.73



Similar scaffold as AD57



50423656\_m\_147\_392

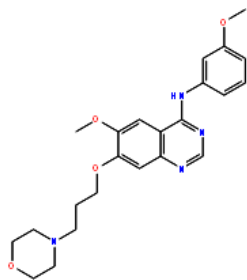


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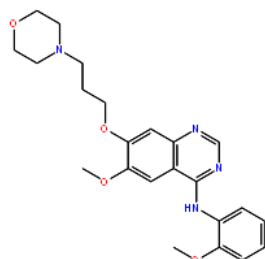
Target	ID
Src	63
Ret	147
S6K	392
BRaf	591

Ligands predicted  
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(Src, Ret, S6k, and  
Raf)

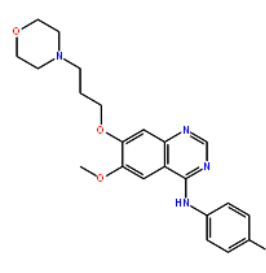
## 36 additional ligands at TC 0.6



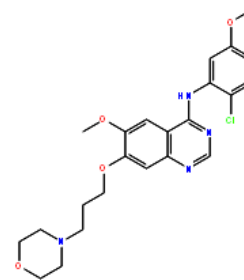
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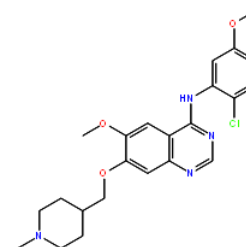
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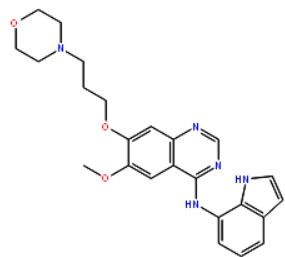
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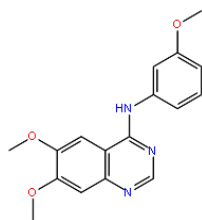
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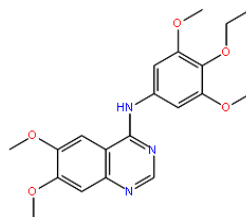
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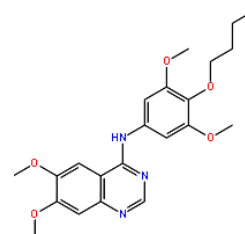
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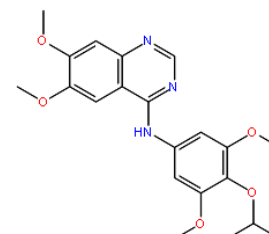
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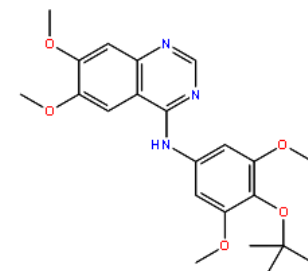
6498\_63



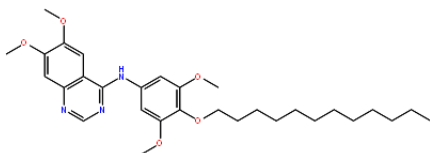
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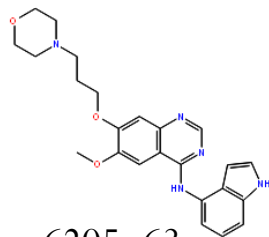
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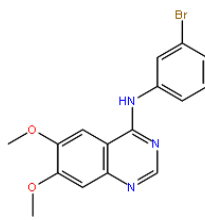
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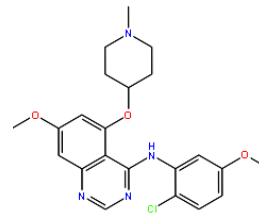
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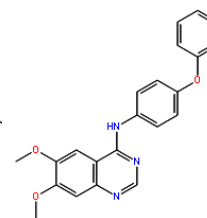
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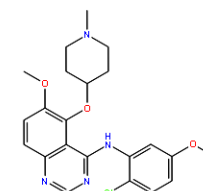
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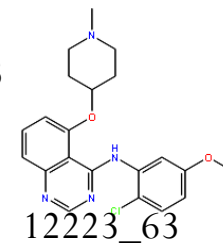
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50095227\_63



12260\_63

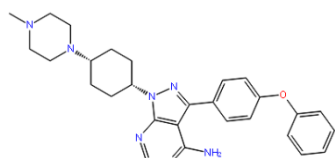


12223\_63

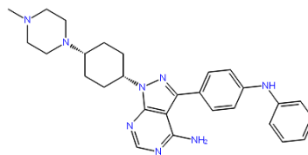


Target	ID
Src	63
Ret	147
S6K	392
BRaf	591

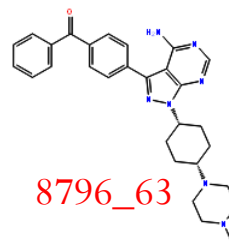
## 36 additional ligands at TC 0.6



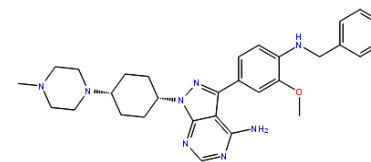
8794\_63



8795\_63

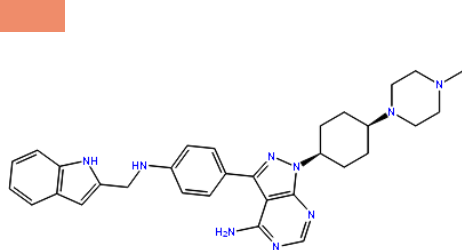


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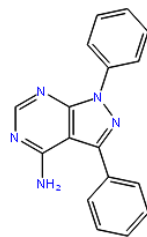


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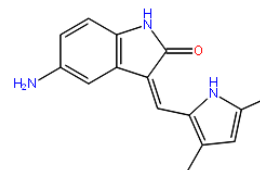
Ligands predicted  
to target 4 kinases  
(Src, Ret, S6k, and  
Raf)



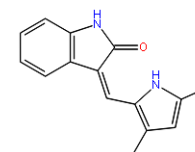
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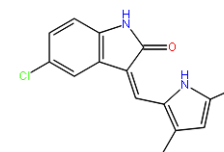
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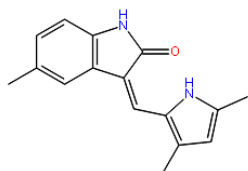
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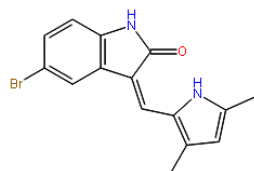
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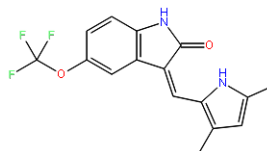
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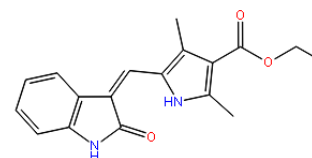
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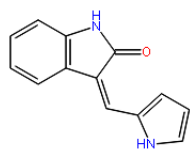


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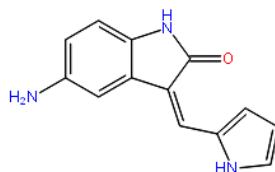


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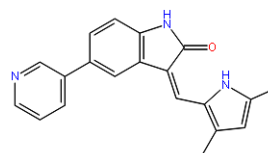
The 6 ligands also show  
similarity to AD57 with  
Tanimoto in range 0.63-0.74



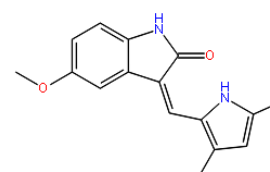
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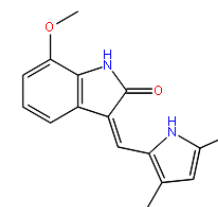
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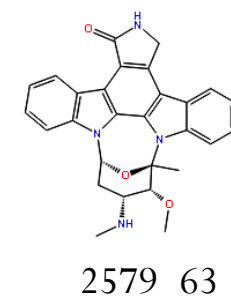
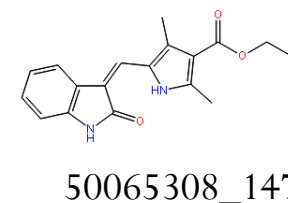
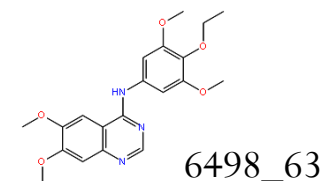
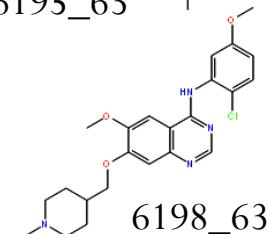
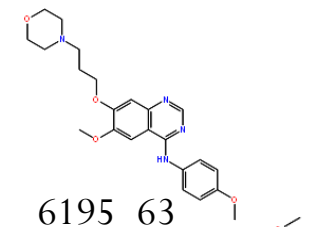
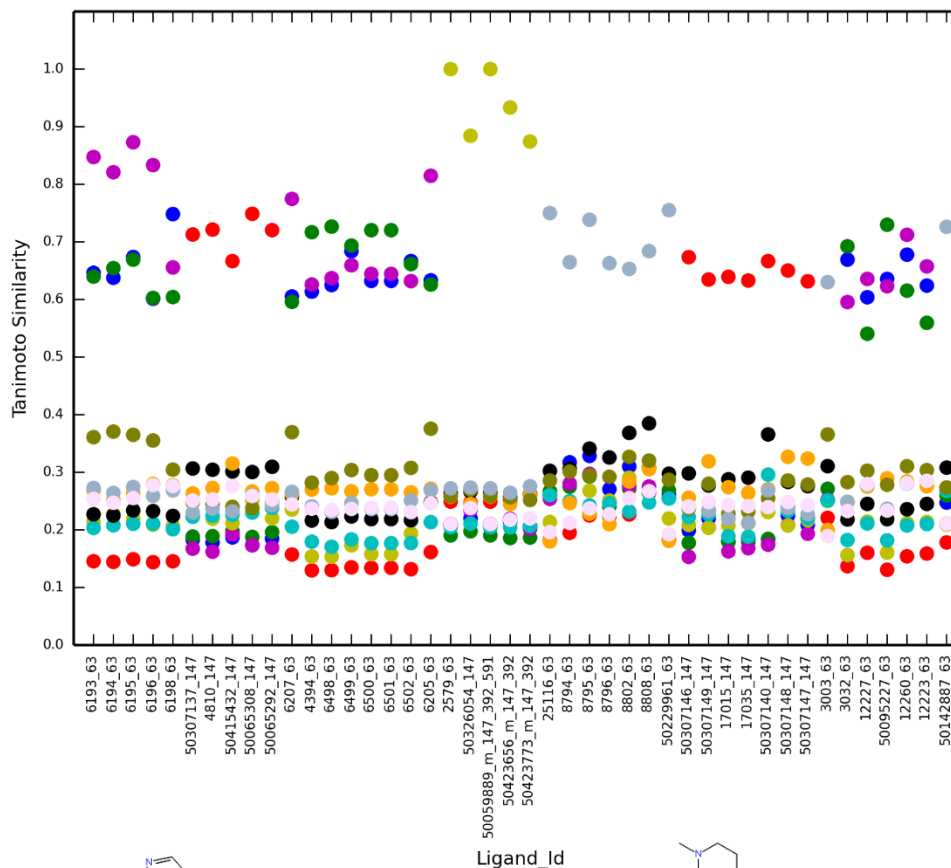
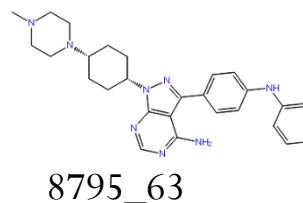
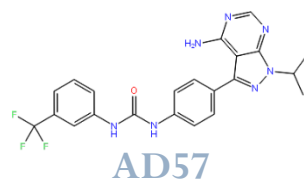
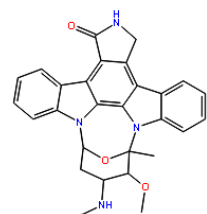
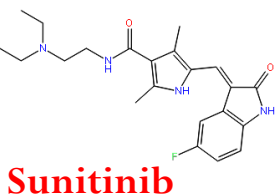
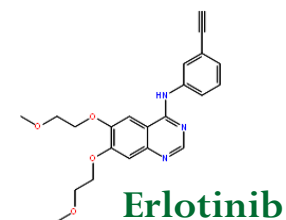
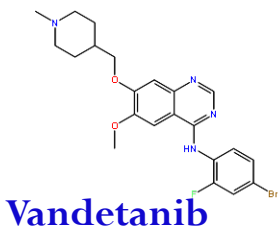
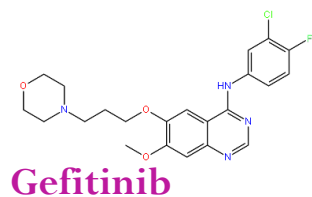


50307148\_147



50307147\_147

# Similarity of 44 ligands (TC 0.6) with known inhibitors



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

# 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	<b>Src, Ret, Raf</b> etc.
Doramapimod (BIRB796)	59	<b>Ret, Raf</b> , Map Kinase etc.
Erlotinib	59	<b>Src, Ret</b> , EGFR etc.
Gefitinib	44	EGFR, her-2 substrate etc.
Imatinib	46	<b>Src, Raf</b> , carbonic anhydrase etc.
SB-202190	24	<b>Raf</b> , p38-beta, jnk2 etc.
Sorafenib	70	<b>Ret, Raf</b> , vegfr etc.
Staurosporine	208	<b>Src, Ret, S6k, CRAF</b> etc.
Sunitinib	133	<b>Src, Ret, S6k</b> , fgfr1 etc.
Vandetanib	77	<b>Ret, S6k</b> , hiv-1 protease etc.