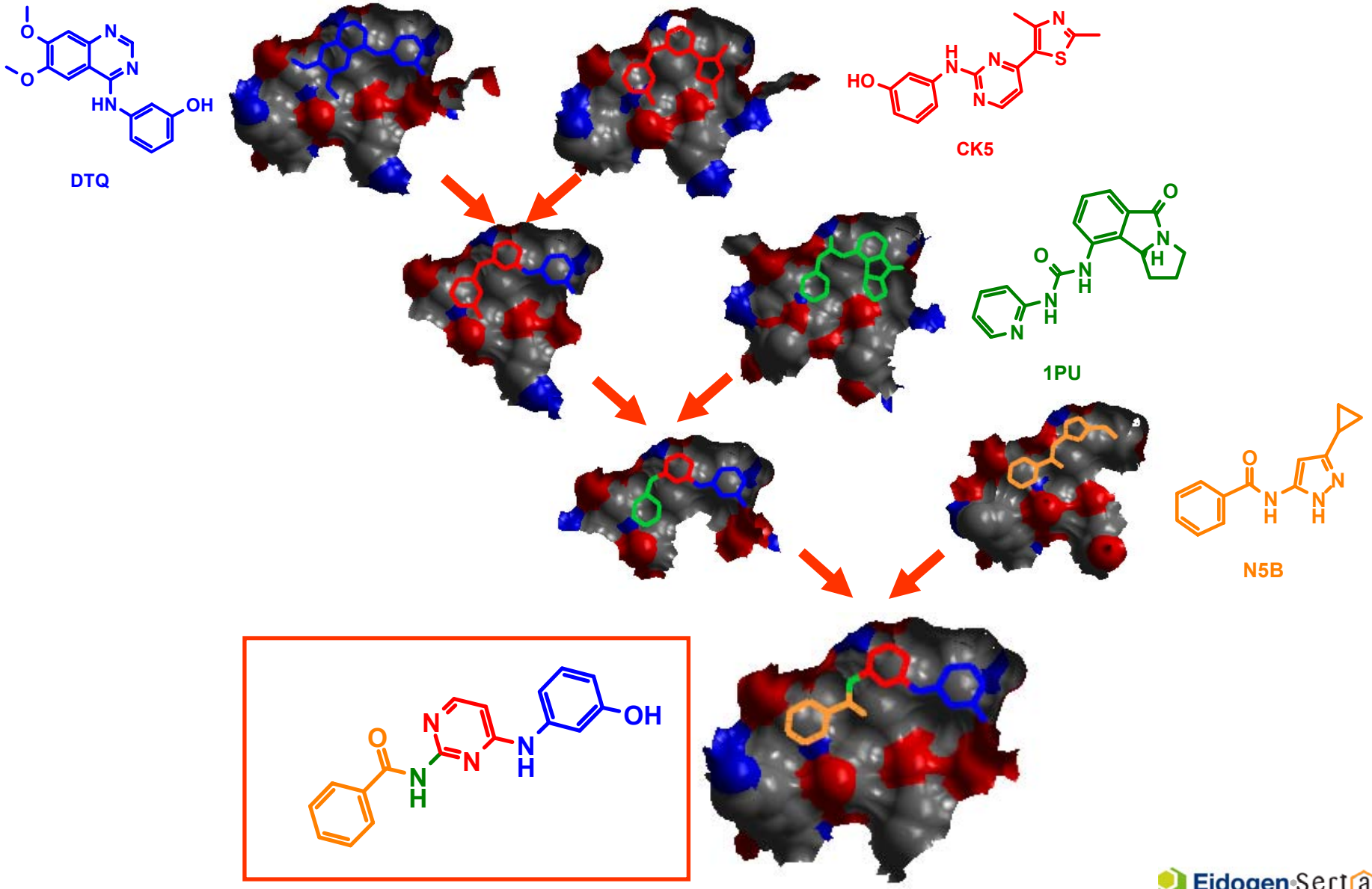
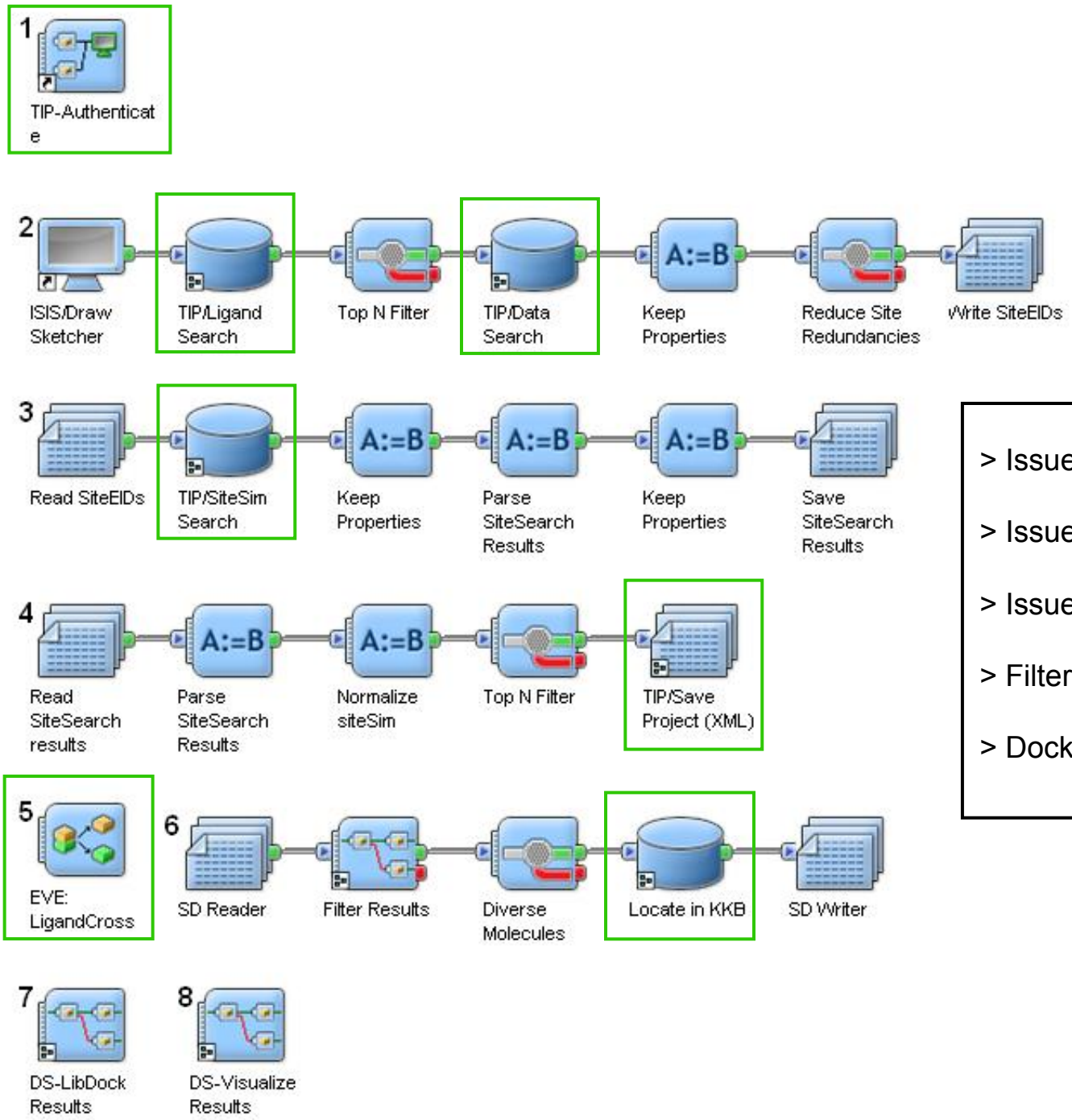
LigandCross: Shuffling Ligand Functionality

Similar to Vertex's BREED: J. Med. Chem. **47**, 2768 (2004)





> Issue TIP/LigandSearch

> Issue TIP/SiteSimSearch

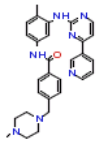
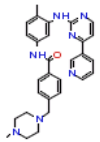
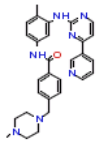
> Issue LigandCross

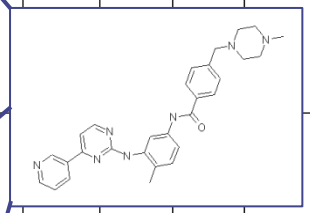
> Filter and locate results in KKB

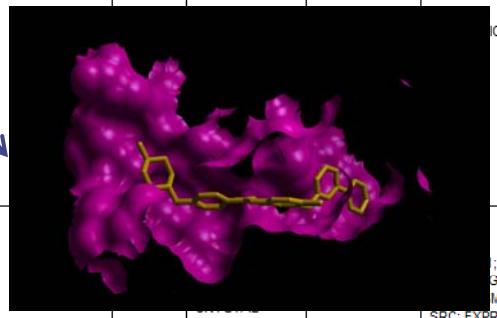
> Dock and visualize results

Eidogen Sertanty

Step 1: Find Co-complexes and Sites from Ligand-Structure-Search

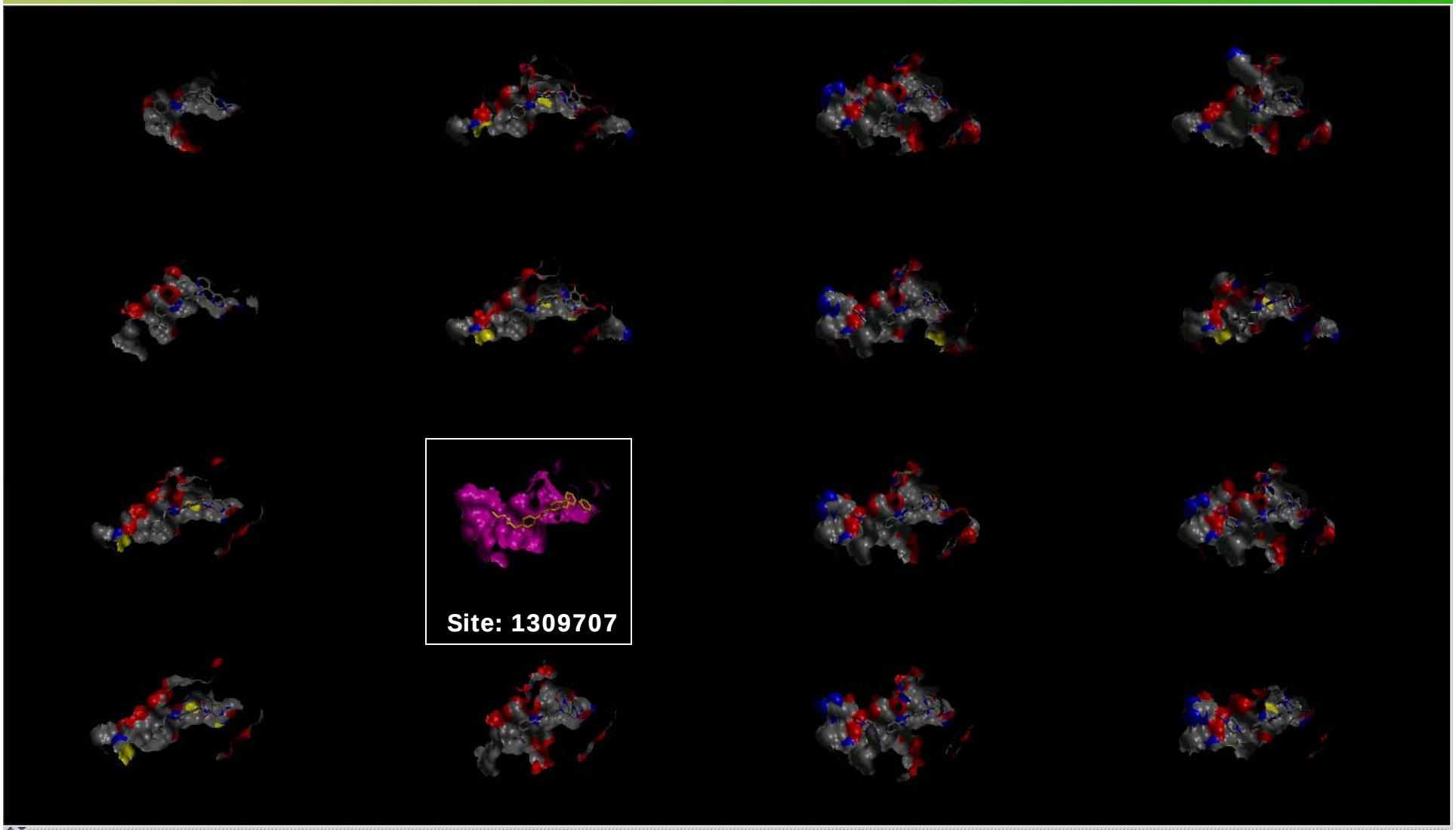
Molecule	ligname	similarity	pdbcode	siteeid	FourCode	pdbID	pdbBnxNumber	proteinId	title	classification	source	compound	releaseDate	journalTitle	journalReference	exptype
	STI	1	2pl0A	1309707	2pl0	2pl0	1305799	42526	LCK BOUND TO IMATINIB	TRANSFERASE	MOL_ID: 1; ORGANISM_SCIENTIFIC: HOMO SAPIENS; ORGANISM_COMMON: HUMAN; GENE: LCK; EXPRESSION_SYSTEM: SPODOPTERA FRUGIPERDA; EXPRESSION_SYSTEM_COMMON: FALL ARMYWORM; EXPRESSION_SYSTEM_VECTOR_TYPE: ION_SYSTEM_PLASMID:	MOL_ID: 1; MOLECULE: PROTO-ONCOGENE TYROSINE-PROTEIN KINASE LCK; CHAIN: A; FRAGMENT: PROTEIN KINASE; SYNONYM: P56-LCK, LYMPHOCYTE CELL-SPECIFIC PROTEIN-TYROSINE KINASE, LSK, T CELL-SPECIFIC PROTEIN-TYROSINE KINASE; EC: 2.7.10.2; ENGINEERED: YES	09-OCT-07	CLASSIFYING PROTEIN KINASE STRUCTURES GUIDES USE OF LIGAND-SELECTIVITY PROFILES TO PREDICT INACTIVE CONFORMATIONS: STRUCTURE OF LCK/IMATINIB COMPLEX	PROTEINS 2007	XRAY DIFFRACTION
	STI	1	2oiqA	1146914	2oiq	2oiq	1125109	26318	STRUCTURE OF CHICKEN C-SRC KINASE DOMAIN IN COMPLEX WITH THE CANCER DRUG IMATINIB.	TRANSFERASE	; ORGANISM_SCIENTIFIC: GALLUS; M_COMMON: CHICKEN; GENE: SRC; EXPRESSION_SYSTEM: ESCHERICHIA COLI; EXPRESSION_SYSTEM_COMMON: BACTERIA; EXPRESSION_SYSTEM_STRAIN: BL21DE3; EXPRESSION_SYSTEM_VECTOR_TYPE: PLASMID; EXPRESSION_SYSTEM_PLASMID: PET28	MOL_ID: 1; MOLECULE: PROTO-ONCOGENE TYROSINE-PROTEIN KINASE SRC; CHAIN: A, B; FRAGMENT: KINASE DOMAIN; SYNONYM: P60-SRC, C-SRC, PP60C-SRC; EC: 2.7.10.2; ENGINEERED: YES	20-MAR-07	C-SRC BINDS TO THE CANCER DRUG IMATINIB WITH AN INACTIVE ABL/C-KIT CONFORMATION AND A DISTRIBUTED THERMODYNAMIC PENALTY.	STRUCTURE V. 15 299 2007	XRAY DIFFRACTION
	STI	1	2hyyA	918207	2hyy	2hyy	904013	16961	HUMAN ABL KINASE DOMAIN IN COMPLEX WITH IMATINIB (STI571, GLIVEC)	TRANSFERASE	MOL_ID: 1; ORGANISM_SCIENTIFIC: HOMO SAPIENS; ORGANISM_COMMON: HUMAN; GENE: ABL1; EXPRESSION_SYSTEM: SPODOPTERA FRUGIPERDA; EXPRESSION_SYSTEM_COMMON: FALL ARMYWORM	MOL_ID: 1; MOLECULE: PROTO-ONCOGENE TYROSINE-PROTEIN KINASE ABL1; CHAIN: A, B, C, D; SYNONYM: P150, C-ABL, ABELSON MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1; EC: 2.7.10.2;	16-JAN-07	STRUCTURAL BIOLOGY CONTRIBUTIONS TO THE DISCOVERY OF DRUGS TO TREAT CHRONIC MYELOGENOUS LEUKAEMIA.	ACTA CRYSTALLOGR.,SECT.D V. 63 80 2007	XRAY DIFFRACTION





Eidogen-Sertanty

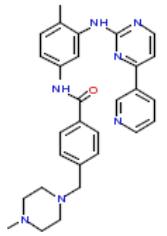
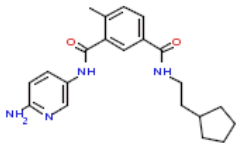
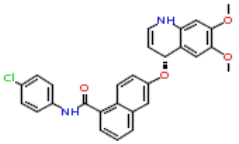
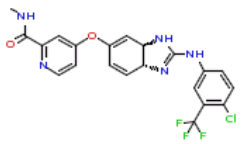
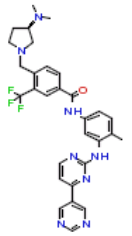
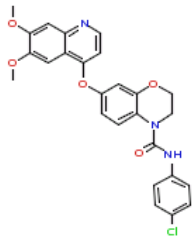
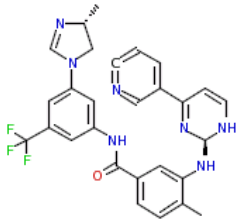
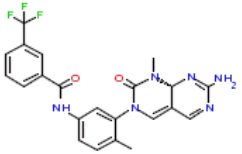
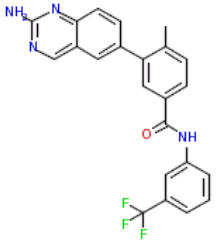
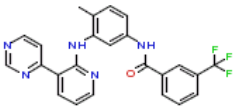
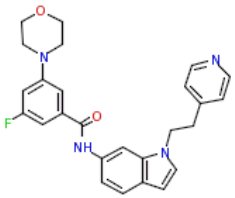
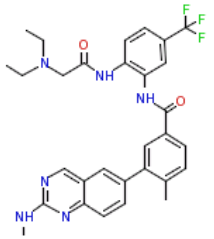
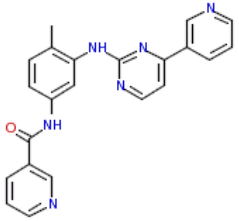
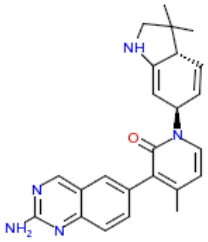
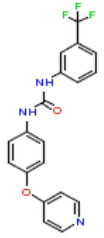
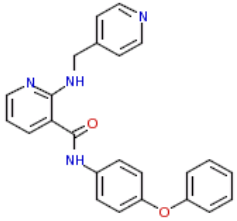
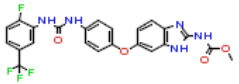
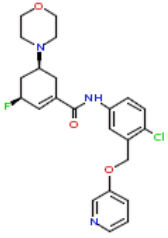
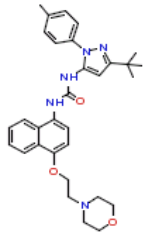
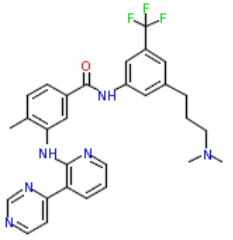
Step 2: Find Other Receptor Sites from Site-Similarity Search



Chains | Chain Alignments | Sites | Site Alignments

Site Name	Locus	Ligand	%Conf	Sequence Positions
pdb2pl0/s1309707 (chain A)	LCK	STI	100	.L.V.AVK.E.LM.L.LV.I.TEYM.GS.I.YIHR.L.IADF
pdb2ofw/s916548 (chain B)	LCK	242	100	.L.V.AVK.E.LM.L.LV.I.TEYM.G.I.Y.H.L.IADF.I
pdb2rl5/s1396160 (chain A)	-	2RL	100	.LG.V.AVK.L.E.LL.L.VV.V.TEFCKFGN.L.CIH.L.ICDF
pdb2e2b1/s1284639 (chain B)	ABL	406	100	.L.Y.V.A.K.E.VM.L.LV.I.TEFMT.G.L.FIHRD.L.VADF

Example Ligands Extracted from Similar Sites

 STI	 C92	 900	 276	 406
 2RL	 NIL	 7MP	 242	 MUH
 WBT	 1N8	 PRC	 C19	 KIN
 608	 GIG	 L11	 B96	 RAJ

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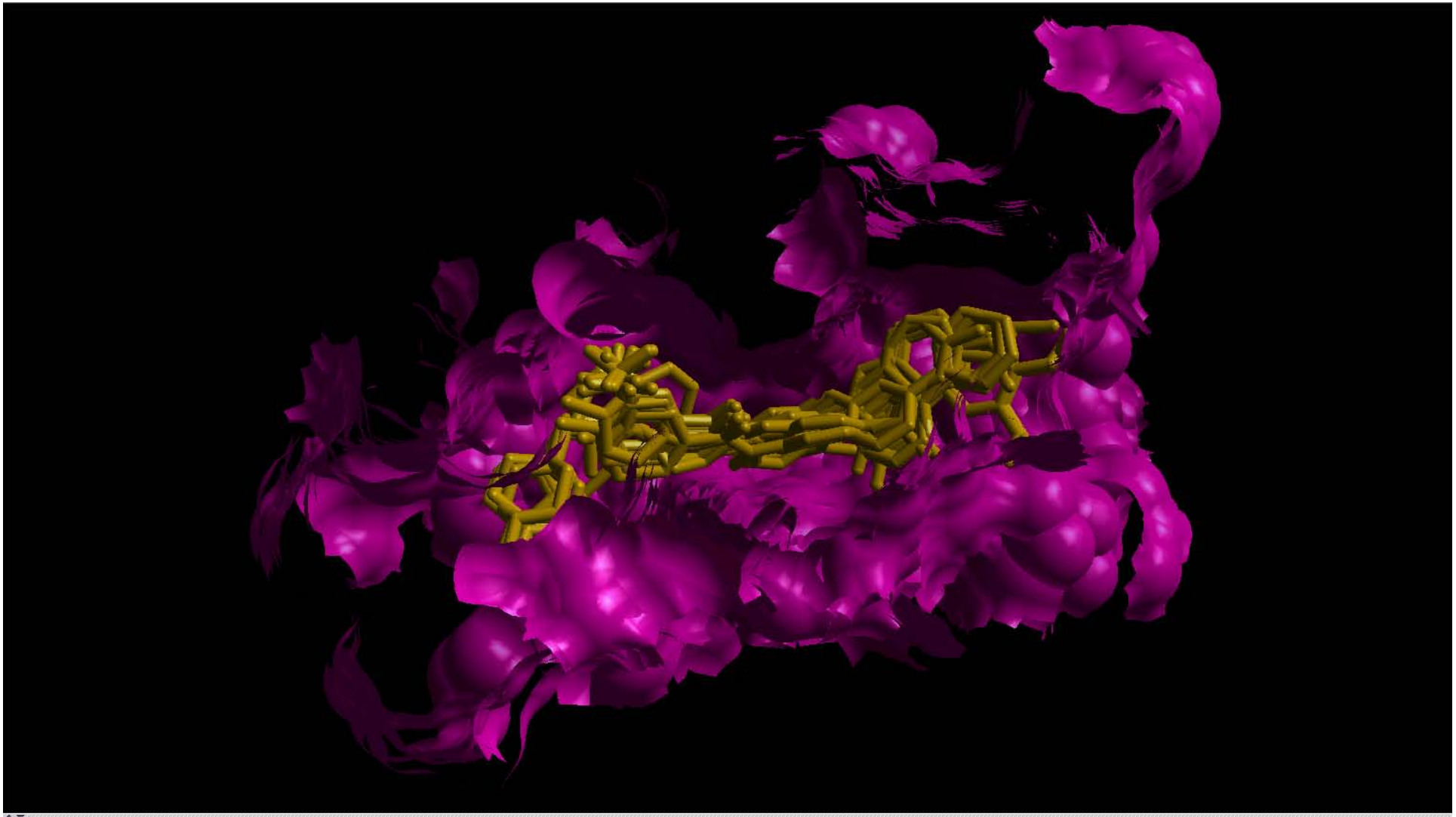
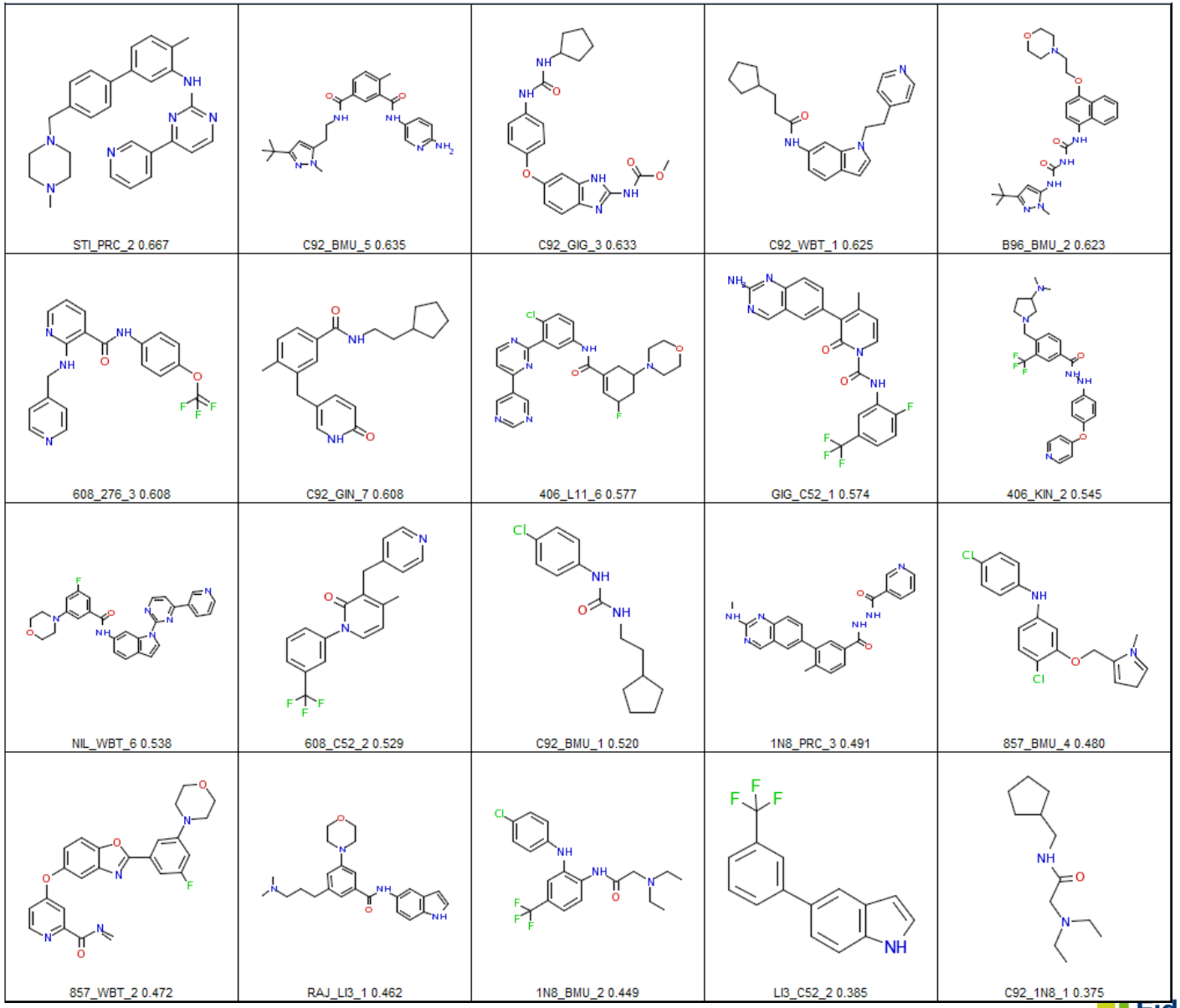
Step 3: LigandCross – Mixing Ligand Features from Aligned Sites



Chains | Chain Alignments | Sites | Site Alignments

Site Name	Locus	Ligand	%Conf	Sequence Positions
pdb2pl0/s1309707 (chain A)	LCK	STI	100	.L.V.AVK.E.LM.L.LV.I.TEYM.GS.I.YIHR.L.IADF
pdb2of/s916648 (chain B)	LCK	242	100	.L.V.AVK.E.LM.L.LV.I.TEYM.G.I.Y.H.L.IADF.I
pdb2rl5/s1396160 (chain A)	-	2RL	100	.LG.V.AVK.L.E.IL.I.VV.V.TEFCKFGN.L.CIH.L.ICDF
pdb2e2b1/s1284639 (chain B)	ABL	406	100	.L.Y.V.A.K.E.VM.I.LV.I.TEFMT.G.L.FIHRD.L.VADF

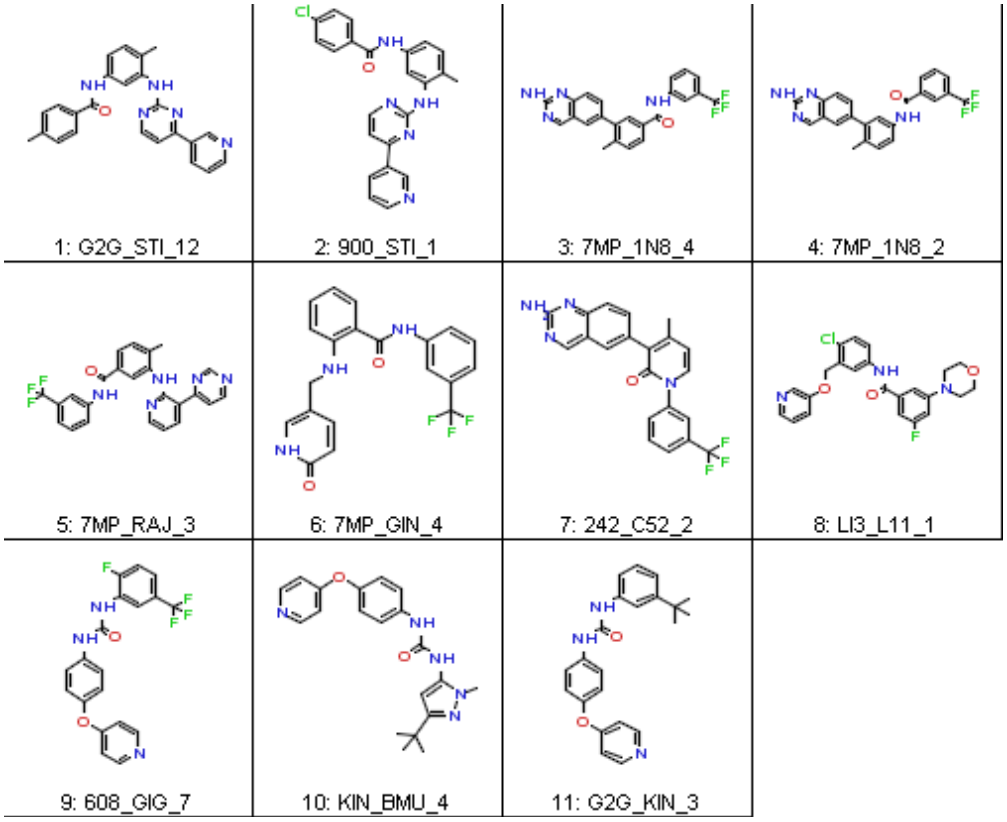
Example LigandCross Results



Eidogen-Sertanty

Step 4: LigandCross Ligands with Reported Biological Activity

	Kinase Knowledgebase (pIC50)										Bayesian Model Predictions (PP)									
LC-ID	ABL	PDGFR	PDGFRB	JAK3	KDR	LCK	MAPK14	TEK	KIT	RAF1	ABL	PDGFR	PDGFRB	JAK3	KDR	LCK	MAPK14	TEK	KIT	RAF1
G2G_STI_12	6.7	8	8								0.40	0.90	0.76	0.81	0.59	0.15	0.89	0.45	0.70	0.37
900_STI_1	6.1	8	8								0.38	0.91	0.76	0.72	0.55	0.16	0.88	0.42	0.71	0.55
7MP_1N8_4				7.8	9	9.5	8.7				0.36	0.49	0.34	0.32	0.94	1.00	0.95	0.67	0.86	0.39
7MP_1N8_2				6.8	8.3	9.5	9				0.37	0.46	0.31	0.44	0.92	1.00	0.92	0.69	0.84	0.45
7MP_RAJ_3					8.4			8.4			0.35	0.73	0.50	0.49	0.92	0.81	0.86	0.94	0.74	0.37
7MP_GIN_4					7.6						0.16	0.50	0.40	0.82	0.95	0.67	0.70	0.41	0.76	0.51
242_C52_2									7.9		0.30	0.28	0.29	0.74	0.80	0.66	0.74	0.31	1.00	0.43
LI3_L11_1							7.2				0.31	0.73	0.55	0.84	0.74	0.69	0.62	0.36	0.76	0.85
608_GIG_7										6.1	0.28	0.61	0.57	0.69	0.93	0.50	0.60	0.68	0.85	0.50
KIN_BMU_4										6.1	0.31	0.43	0.45	0.78	0.75	0.57	0.77	0.33	0.81	0.25
G2G_KIN_3										6.1	0.25	0.51	0.52	0.75	0.89	0.59	0.64	0.43	0.84	0.43



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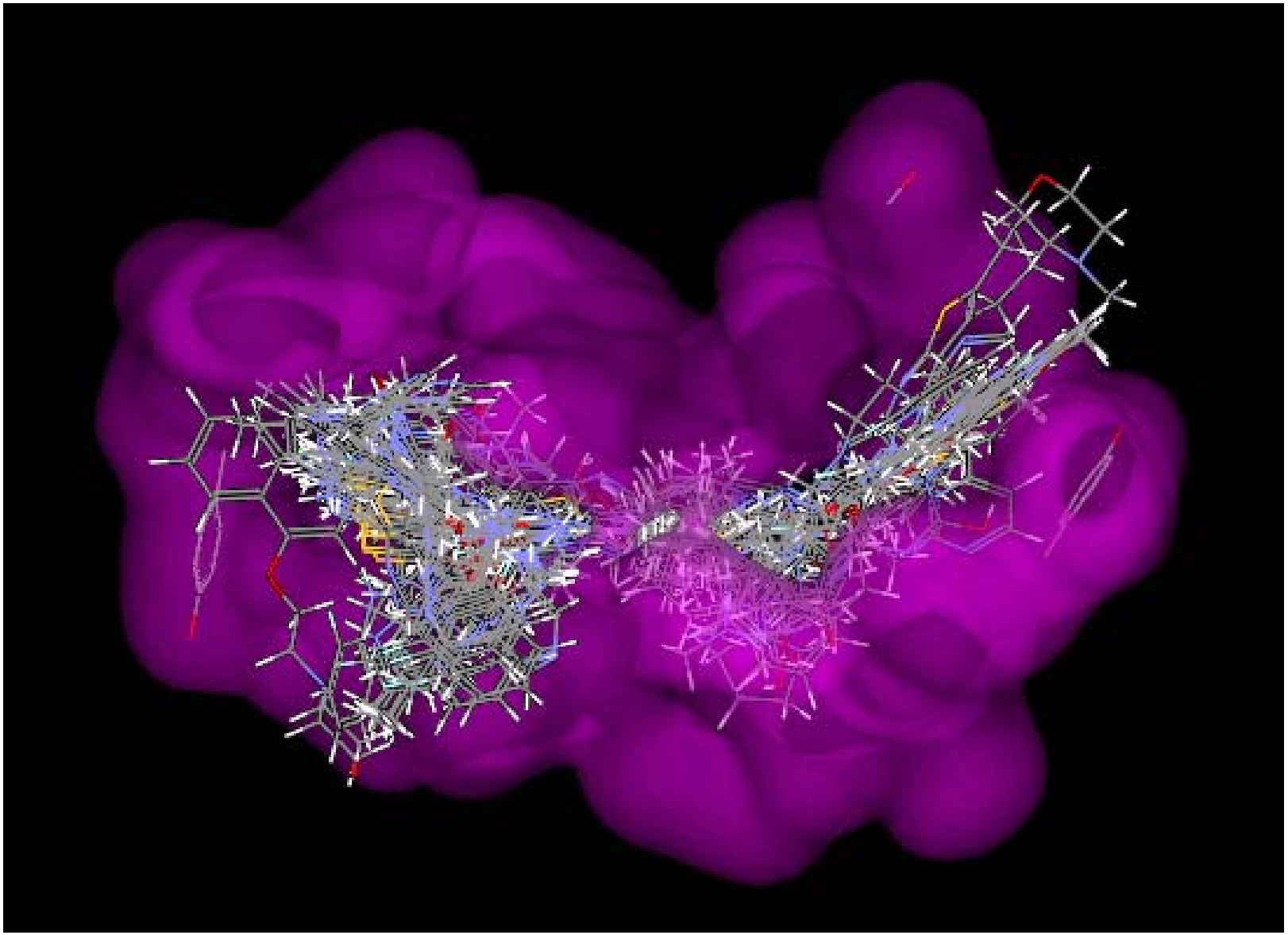
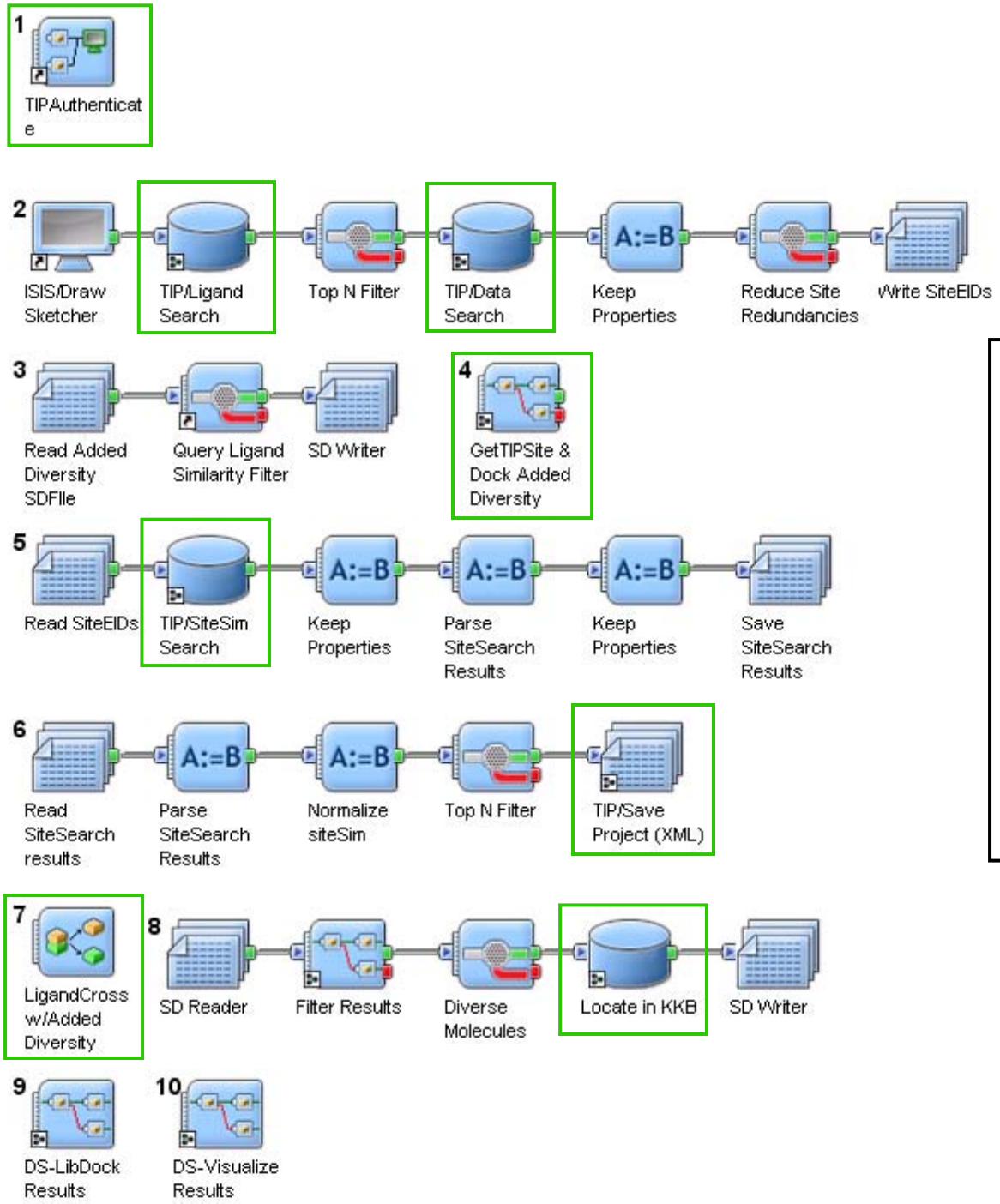
Step 5: LigandCross Ligands reDocked into s1309707





> Issue TIP/LigandSearch

> Identify/Dock “AddedDiversity”

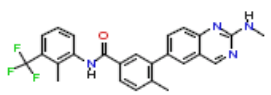
> Issue TIP/SiteSimSearch

> LigandCross w/AddedDiversity

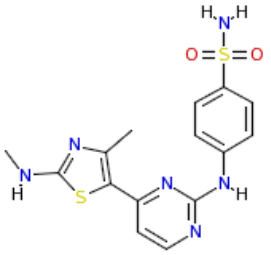
> Filter and locate results in KKB

> Dock and visualize results

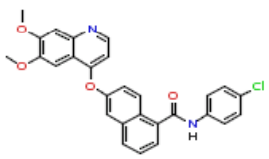
Example Potent Kinase Inhibitors ("Added Diversity")



4336533 LCK pval: 11.00



4302493 CDK9 pval: 10.54



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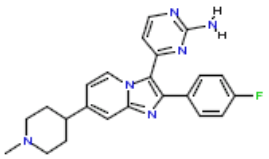

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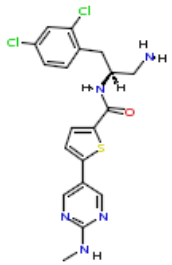
Chiral



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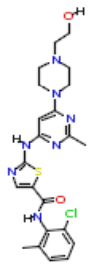
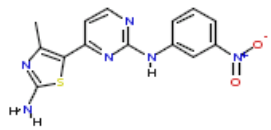
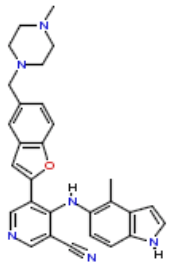


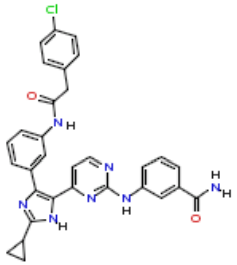
4272835 ABL1 pval: 10.00



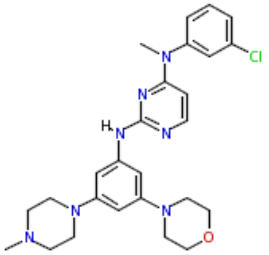
894611 CDK2 pval: 9.70



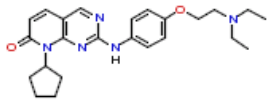
4358565 PRKCQ pval: 9.70



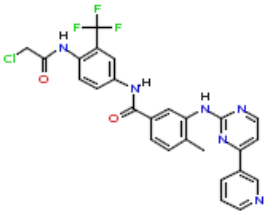
4363734 RAF1 pval: 9.30



4369892 EPHB4 pval: 9.24

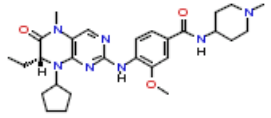


809 CDK4 pval: 9.15

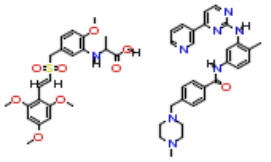


4374385 PDGFRA pval: 9.14

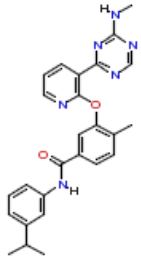
Chiral



4366691 PLK1 pval: 9.10

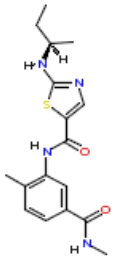


4301886 BCR_ABL pval: 9.08

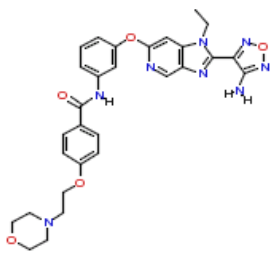


4307551 TEK pval: 9.00

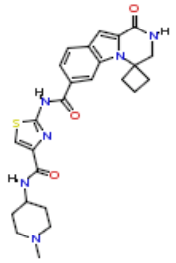
Chiral



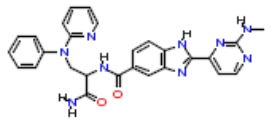
4363016 MAPK11 pval: 8.82



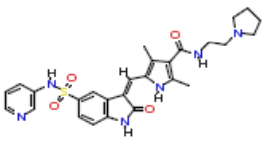
4343448 ROCK1 pval: 8.74



4363247 MAPKAPK2 pval: 8.70

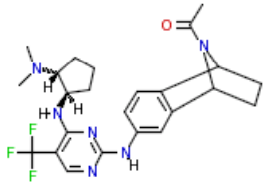


4291996 IKB pval: 8.70



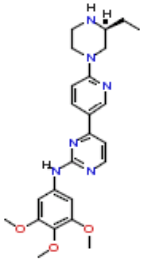
4208857 FAK2 pval: 8.22

Chiral

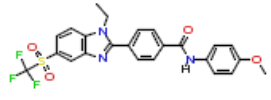


4373725 PTK2B pval: 8.22

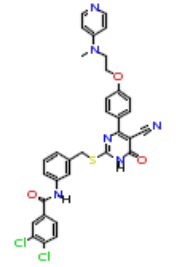
Chiral



1788 ZAP70 pval: 8.10

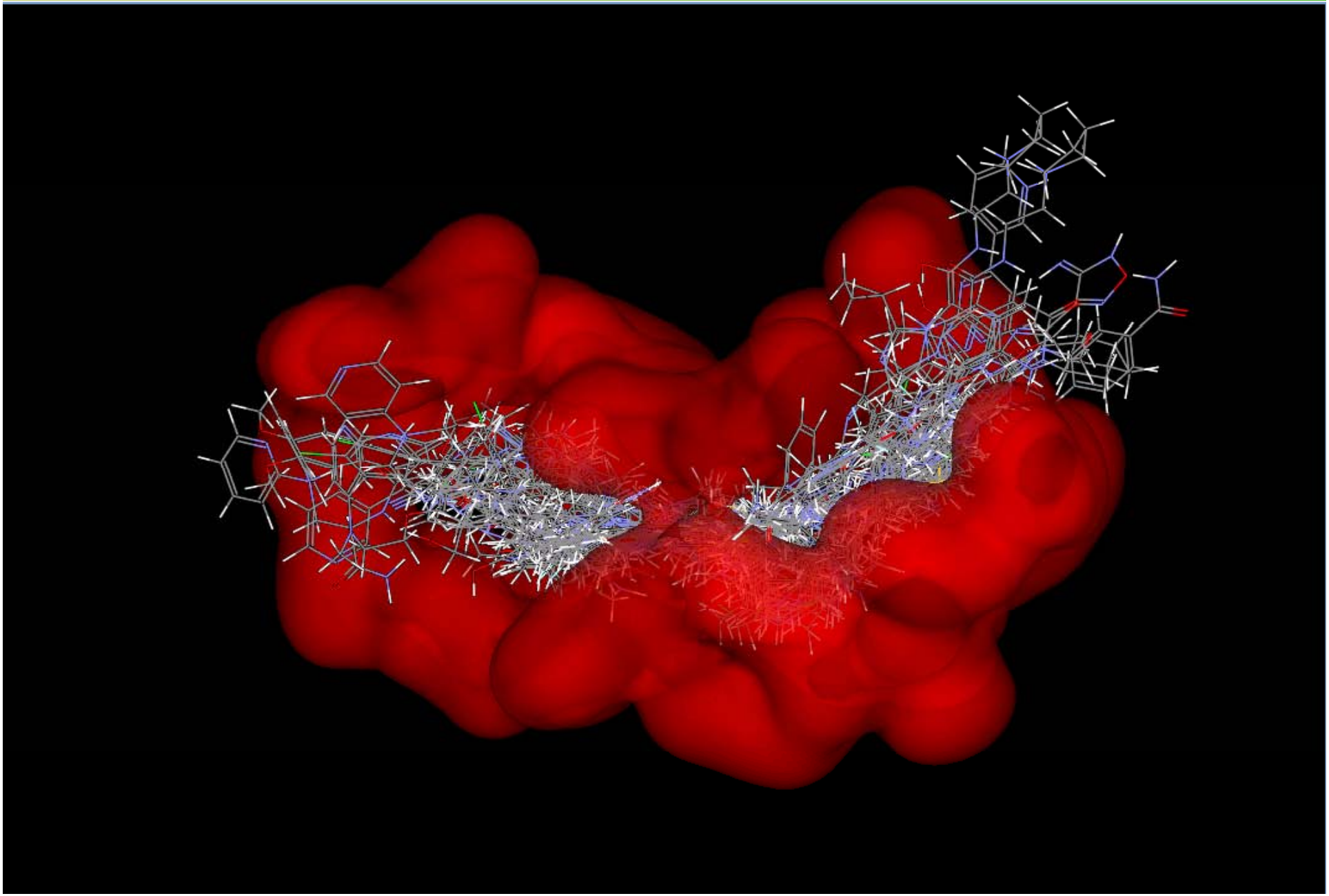


2425813 PTPN9 pval: 5.96

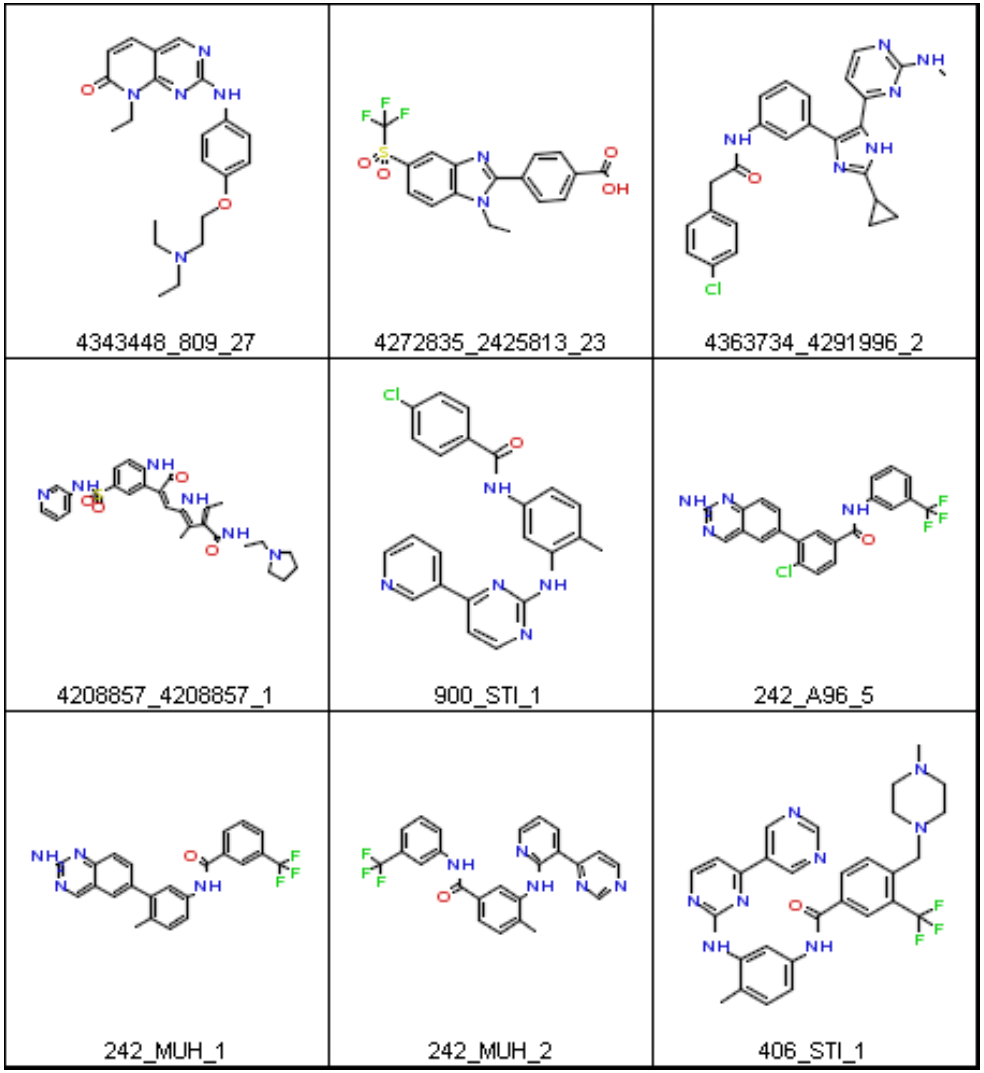


4303129 MAP3K2 pval: 4.70

Potent Kinase Inhibitors Docked (s1309707)



LigandCross Examples using “Added Diversity”



4343448_809_27:
CDK4: 6.80 CDK2: 5.63 CDK2: 6.12 CDC2: 5.58 CSK: 5.99 CDK5: 6.81
CDK4: 6.80 CDK2: 5.63 CDK2: 6.12 CDC2: 5.58 CDK4: 6.80

4272835_2425813_23:
PTPN1: 4.24 PTPRA: 4.21

4363734_4291996_2:
RAF1: 9.00 MAPK1: 5.29 BRAF: 8.05 BRAF: 8.52

4208857_4208857_1:
FAK2: 8.22 KDR: 5.86 PDGFRB: 4.90 EGFR: 4.17 ERBB2: 5.23

900_STI_1:
PDGFR: 8.00 PDGFR: 8.00 ABL: 6.10 PDGFRB: 8.00 PDGFR: 8.00
ABL: 6.10

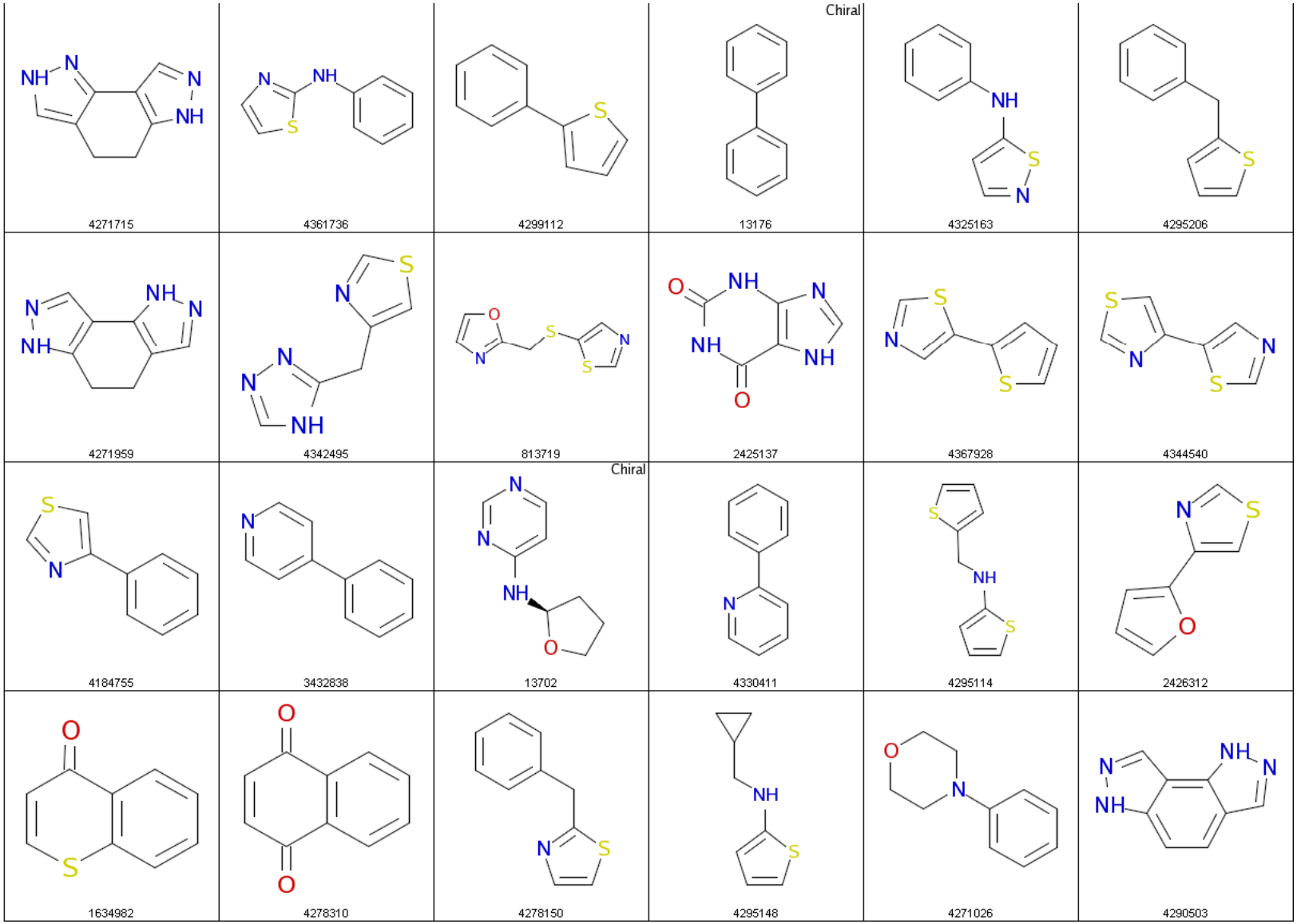
242_A96_5:
LCK: 9.40

242_MUH_1:
LCK: 9.40 TEK: 7.68 KDR: 8.22 MAPK14: 9.00 JAK3: 6.81

242_MUH_2:
KDR: 8.40 TEK: 8.40 TEK: 8.40 KDR: 8.40 TEK: 8.40 KDR: 8.40

406_STI_1:
BCR_ABL: 8.40 BCR_ABL: 5.30 LYN: 8.06 ABL1: 8.07 ABL1: 8.40

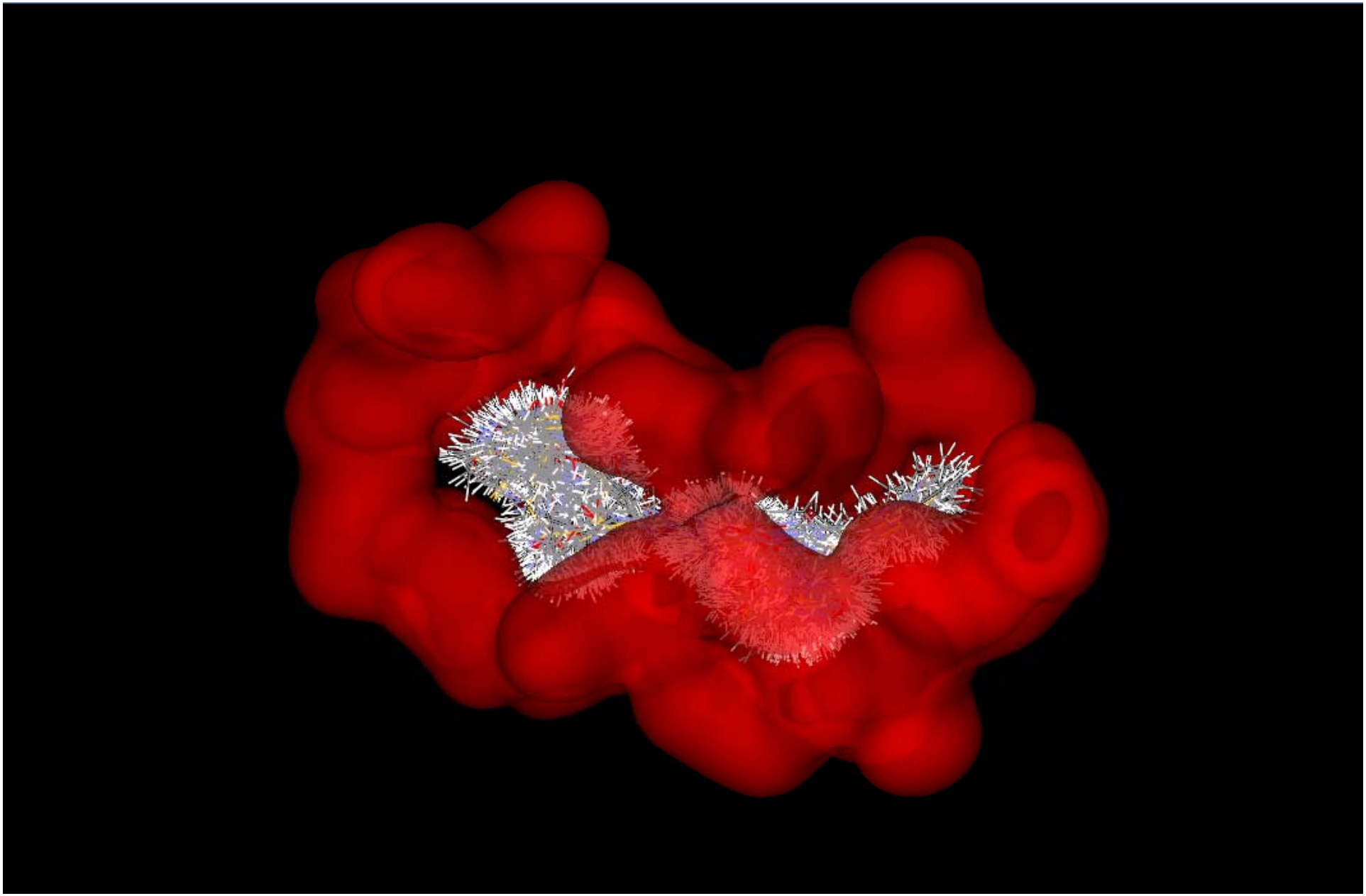
Murcko Assemblies Found in Kinase Inhibitors



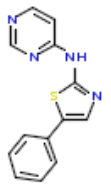
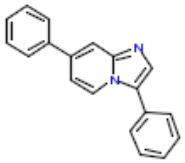
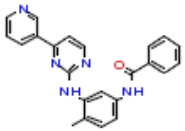
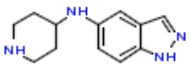
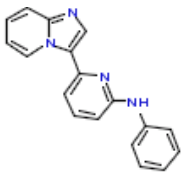
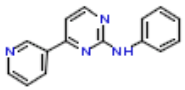
Murcko Assemblies: Contiguous ring systems plus chains that link two or more rings

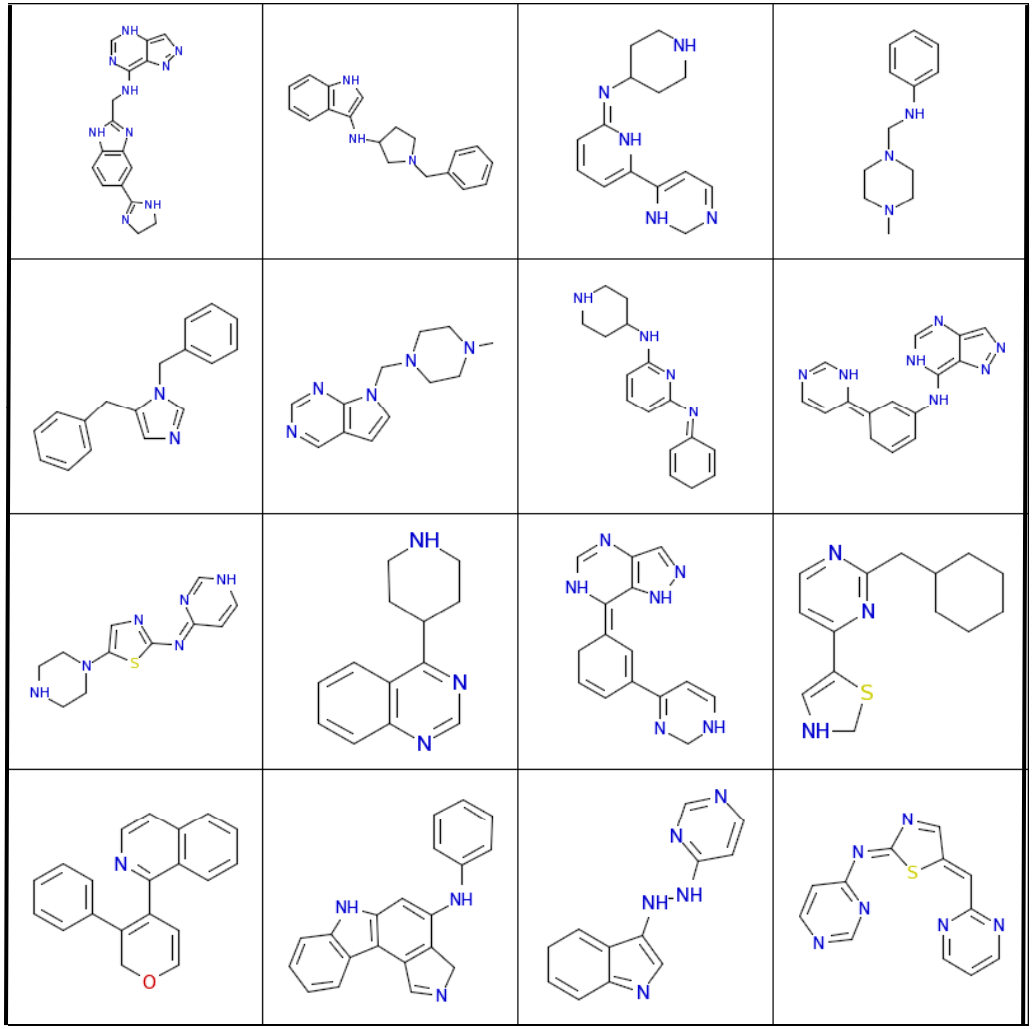
"The Properties of Known Drugs. 1. Molecular Frameworks", Guy W. Bemis and Mark A. Murcko, *J. Med. Chem.* 1996, 39, 2887-2893.

Positional Murcko Assemblies (parent inhibitors docked into s1309707)



LigandCross Results: Positional Murcko Assemblies
from docked Kinase inhibitors (s1309707)

	KDR KDR	Enzyme Assay Enzyme Assay	7.4437 7.4437
	KDR	Enzyme Assay	7.0088
	PDGFR PRKCA PRKCA ABL EGFR PDGFR PDGFR PDGFRB ABL PDGFRB PDGFRB PDGFRA ABL PDGFRB	Enzyme Assay Enzyme Assay Enzyme Assay Enzyme Assay Enzyme Assay Enzyme Assay Enzyme Assay Cell-Based Assay Enzyme Assay Cell-Based Assay Enzyme Assay Enzyme Assay Enzyme Assay Cell-Based Assay	7 4.1427 4.1427 6.3979 4.1871 7 7 7.1871 6.3979 6.2218 7 5.2218 6.3979 6.7696
	ROCK ROCK1	Enzyme Assay Enzyme Assay	6.5421 6.5229
	IRAK4	Enzyme Assay	5.9370
	PRKCA PRKCD ABL EGFR	Enzyme Assay Enzyme Assay Enzyme Assay Enzyme Assay	4.9788 4.4089 5.7447 4



Kinase Activity ????

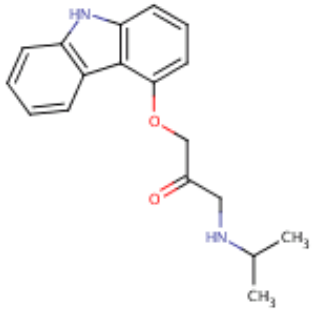
Eidogen-Sertanty

LigandCross CAU/siteSimilar Ligands w/Docked BioActives

- Extract CAU/2RH1 Site (siteEID: 1276810) from TIP
- Issue siteSimilarity Search against siteEID: 1276810
- LibDock 20-30 Bioactive Molecules (beta1-adrenergic active+ CAU similar)
- LigandCross CAU and siteSimilar Ligands w/Docked BioActives

TIP/SiteSimilarity Search – siteEID: 1276810 (CAU/2RH1)

Site Name	s1276810
Source	PDB Co-crystal
Confidence	100%
Resolution	XRAY
Description	CAU: (2S)-1-(9H-Carbazol-4-yloxy)-3-(isopropylamino)propan-2-ol
Parent	2rh1A



Query: 2rh1A/s1276810

Total Sites Found: 399

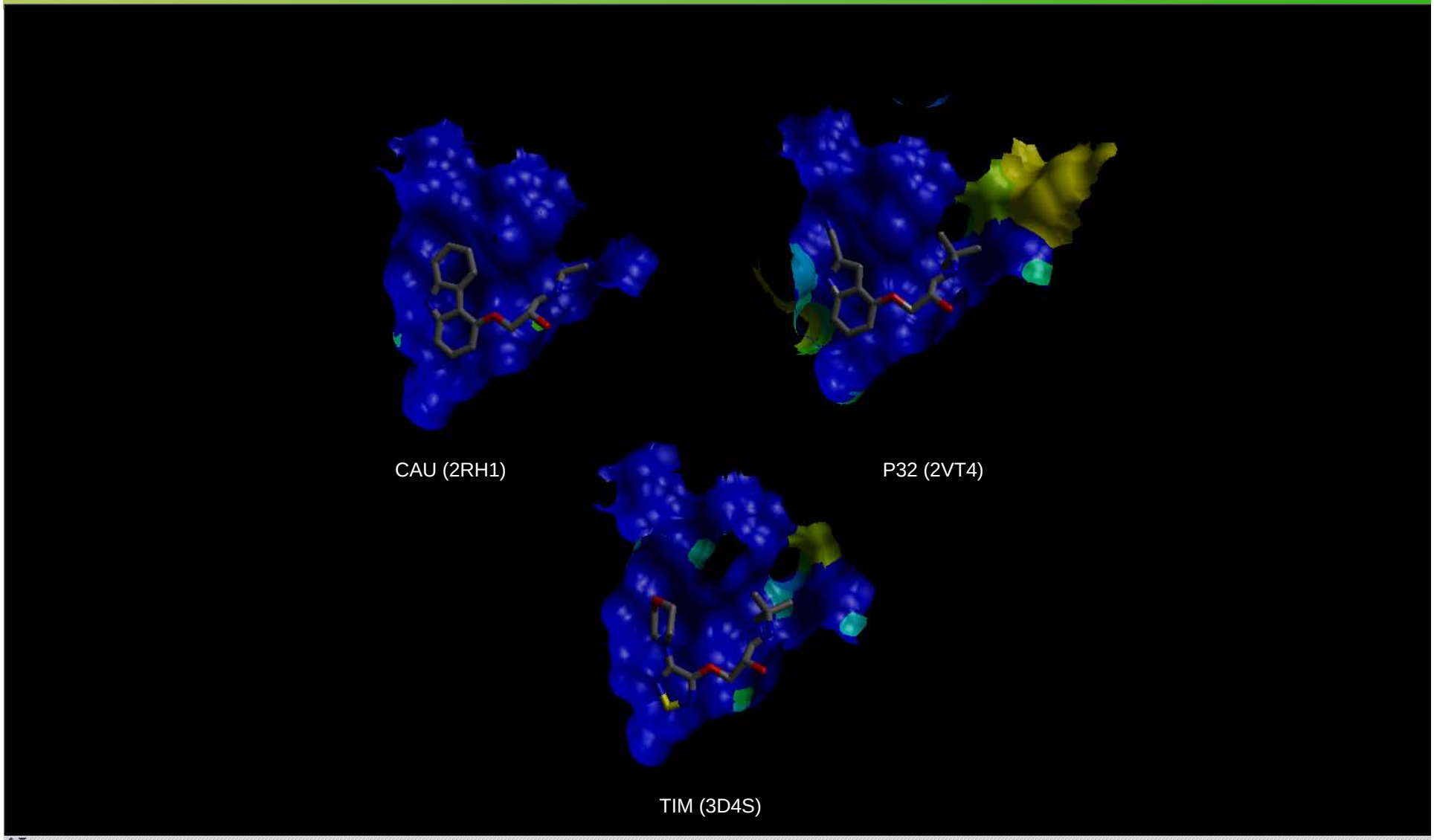
Same-Fold Sites:	358	(89.7%)	
Dissimilar-Fold Sites:	41	(10.3%)	
Ligands:	Predicted	354	(88.7%)
	MGD	15	(3.8%)
	NAD	11	(2.8%)
	ATP	4	(1.0%)
	Other	15	(3.8%)

Index	Superfamily Clusters	Family Clusters	Site Clusters	Sites	Description	Ligand Information	SiteSorter Range	%ID Range	Contact Range
1.	»	3	298	358	Beta-1 adrenergic receptor	Predicted: 350, P32: 4, RET: 3, TIM: 1	60-107	14-100	0.00-0.77
2.	»	1	2	15	PERIPLASMIC NITRATE REDUCTASE	MGD: 15	60-66	14-14	0.05-0.09
3.	»	1	2	4	PYRUVATE KINASE	ATP: 4	61-66	14-14	0.10-0.12
4.	»	1	2	2	4S-LIMONENE SYNTHASE	F3P: 1, FPG: 1	61-65	14-14	0.12-0.14
5.	»	1	11	11	PROTEIN (S-ADENOSYLHOMOCYSTEINE	NAD: 11	61-64	14-14	0.05-0.06
6.	»	1	1	2	BIOTIN BIOSYNTHESIS CYTOCHROME P4	Predicted: 2	63-64	14-14	0.00-0.00
7.	»	1	3	3	ALPHA-2,3/2,6-SIALYLTRANSFERASE/SIA	CSF: 3	60-63	14-19	0.09-0.12
8.	»	1	1	2	ARSENITE OXIDASE	Predicted: 2	61-62	14-14	0.00-0.00
9.	»	1	1	1	ASPARTATE AMINOTRANSFERASE	1ahgC: 1	62-62	14-14	0.06-0.06
10.	»	1	1	1	ACYL-COA OXIDASE	FAD: 1	60-60	14-14	0.06-0.06

Sequences | Chains | Sites | Binding Modes

Description						Site Residue Conservation
Site Name	Locus	Description	%Conf	SiteSorter	%ID	Non-polar Polar H-bond Polar/H-bond
pdb2rh1/s1276810 (chain A)	-	**CAU: (2S)-1-(9H-...**	100	-	-	.WT.DV.VT.F.T.YA.SS.SF.W.FF.N.Y.N.Y
pdb2vt4/s1421547 (chain B)	-	**P32: 4-[(2S)-3-(t...**	100	93.03	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2vt4/s1421552 (chain C)	-	**P32: 4-[(2S)-3-(t...**	100	93.81	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2vt4/s1421564 (chain C)	-	Predicted Site	78	104.37	95	WT DV VT F T YA SS SF W FF N F N Y
pdb3d4s/s1420913 (chain A)	-	Predicted Site	64	102.08	100	WT DV VT F t YA SS SF W FF N y N Y
pdb3d4s/s1420907 (chain A)	-	**TIM: (2S)-1-(tert-...**	100	97.93	100	WT DV VT F T YA SS SF W FF N Y N Y
pdb2vt4/s1421543 (chain A)	-	**P32: 4-[(2S)-3-(t...**	100	93.08	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2vt4/s1421560 (chain D)	-	**P32: 4-[(2S)-3-(t...**	100	91.69	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2vt4/s1421562 (chain A)	-	Predicted Site	64	101.26	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2vt4/s1421566 (chain D)	-	Predicted Site	65	99.89	95	WT DV VT F T YA SS Sf W FF N F N Y
pdb2z73/s1406997 (chain B)	**RHO**	**RET: RETINAL**	100	61.13	14	YG GG GF f y ni MF gF W YA A a V K
pdb2z73/s1406994 (chain A)	**RHO**	**RET: RETINAL**	100	61.76	14	YG GG GF f y ni MF gF W YA A a V K
pdb2z73/s1408905 (chain B)	**RHO**	Predicted Site	64	77.09	14	YG GG GF f y nI MF GF W YA a a V K
pdb2z73/s1408902 (chain A)	**RHO**	Predicted Site	77	70.81	14	YG GG GF f y ni MF GF W YA a a V K
pdb2ziy/s1406739 (chain A)	**RHO**	**RET: RETINAL**	100	62.56	14	YG GG GF f y ni MF GF W Ya a a V K
pdb3eml/s1491370 (chain A)	-	**ZMA: 4-{2-[(7-ami...**	100	49.29	14	ia VL Tq f p mv nf cv W LH N M I h
pdb2cbj/s824988 (chain B)	**NAGJ**	Predicted Site	71	-	-	
pdb2cbj/s824984 (chain A)	**NAGJ**	Predicted Site	92	-	-	
pdb2cbj/s824980 (chains A, B)	**NAGJ**	**OAN: O-(2-ACETA...**	100	54.72	19	W- NV V- - - -K -S -- - -- - - D V
pdb2cbj/s824983 (chains A, B)	**NAGJ**	**OAN: O-(2-ACETA...**	100	53.44	19	W- NV V- - - -K -S -- - -- - - D V
pdb2qk8/s1319712 (chain A)	-	**MTX: METHOTRE...**	100	53.66	14	-- EL VK L - -- -- -- M -F N - - T
pdb3e0b/s1504298 (chain B)	-	**N22: 5-[3-(2,5-di...**	100	45.21	14	-- EL VK L - -- -- -- M -F N - - -
pdb3e0b/s1504295 (chain A)	-	**N22: 5-[3-(2,5-di...**	100	43.71	14	L- EL V- L - -- -- -- M -F N - - -
pdb3e0b/s1504297 (chain B)	-	**NAP: NADP NICO...**	100	-	-	
pdb3e0b/s1504296 (chain A)	-	**NAP: NADP NICO...**	100	-	-	
pdb3e0b/s1504300 (chain B)	-	Predicted Site	70	-	-	
pdb3e0b/s1504299 (chain A)	-	Predicted Site	66	-	-	
pdb2qk8/s1319713 (chain A)	-	Predicted Site	76	-	-	
pdb1ith/s416096 (chain B)	**HBF1**	**HEM: PROTOPOR...**	100	45.54	14	-Q -V -L F - Y- LF -- K H- I M - -
pdb1ith/s416099 (chain B)	**HBF1**	Predicted Site	77	-	-	
pdb1ith/s416098 (chain A)	**HBF1**	Predicted Site	61	44.86	14	-Q -V -L F - Y- LF -- K H- - M - -
pdb1ith/s416094 (chain A)	**HBF1**	**HEM: PROTOPOR...**	100	43.93	14	-Q -V -L F - Y- LF -- K H- - M - -
pdb1lht/s1143974 (chain A)	**MB**	**HEM: PROTOPOR...**	100	47.88	14	-H -V -L F T -Y IL -- L H- I - - -
pdb1lhs/s1143884 (chain A)	**MB**	**HEM: PROTOPOR...**	100	47.69	14	-H -V -L F T -Y IL -- - H- I - - -
pdb1lhs/s1143885 (chain A)	**MB**	Predicted Site	94	46.66	14	-H -V -L F T -Y IL -- - H- I - - -
pdb1lht/s1143976 (chain A)	**MB**	Predicted Site	91	-	-	
pdb2nrm/s1298120 (chain A)	**MB**	Predicted Site	65	-	-	
pdb2nrm/s1298115 (chain A)	**MB**	**HEM: PROTOPOR...**	100	46.88	14	-- -V -L F T -- IF -- L H- - - - -
pdb1qkn/s484704 (chain A)	**ESR2**	**RAL: RALOXIFENE**	100	41.73	14	-- -L AT F I -H -L -- W M- G - - -

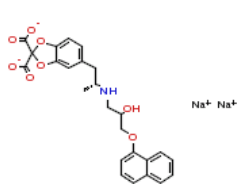
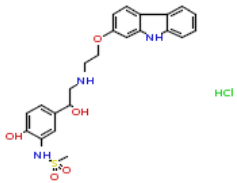
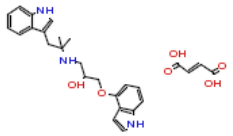
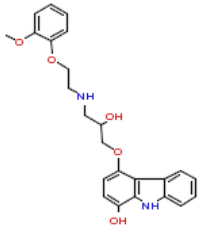
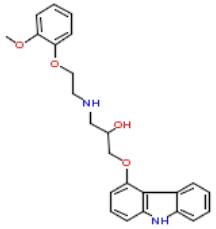
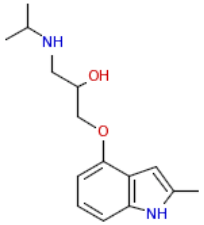
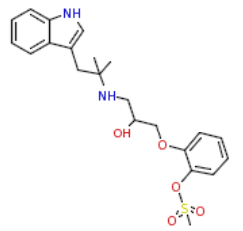
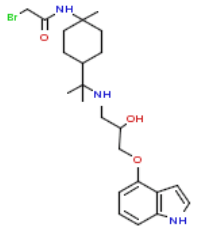
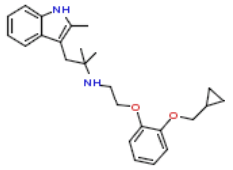
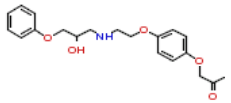
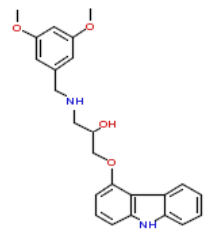
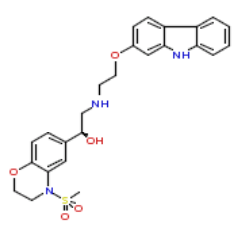
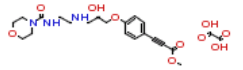
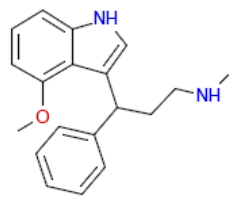
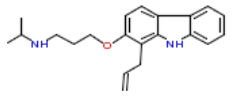
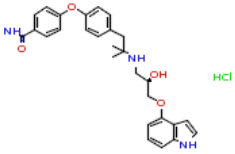
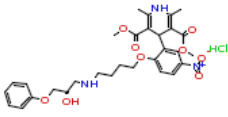
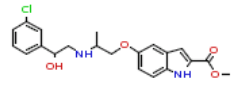
CAU (2RH1), P32 (2VT4), and TIM (3D4S)

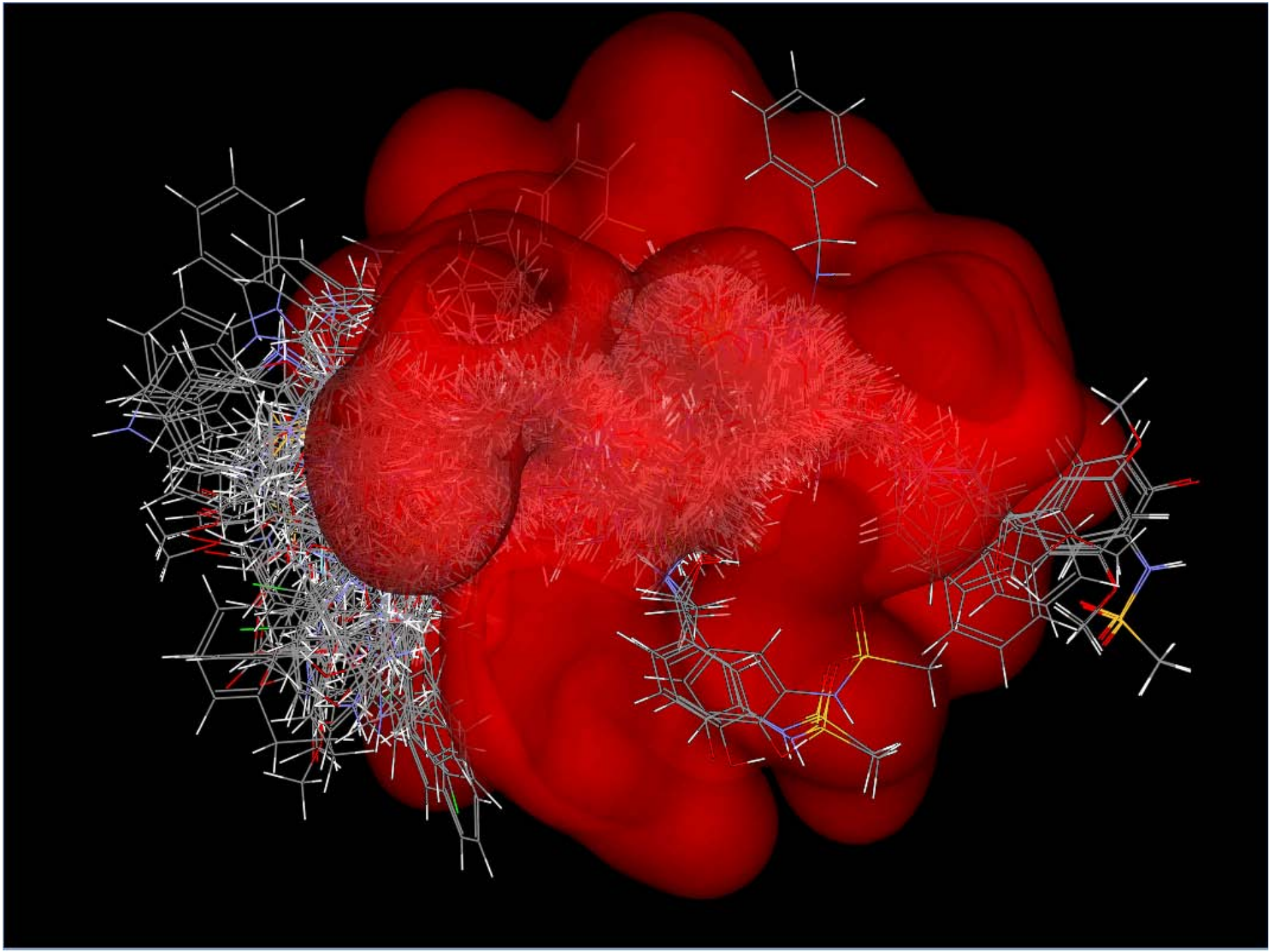


Chains | Chain Alignments | Sites | Site Alignments

Site Name	Locus	Ligand	%Conf	Sequence Positions
pdb2rh1/s1276810 (chain A)	-	**CAU**	100	.WT.DV.VT.F.T.YA.SS.SF.W.FF.N.Y.N.Y
pdb2vt4/s1421547 (chain B)	-	**P32**	100	.L.WT.DV.VT.S.C.F.T.YA.SS.S.W.FF.N.F.N.Y
pdb3d4s/s1420907 (chain A)	-	**TIM**	100	.WT.DV.VT.C.F.T.YA.SS.SF.W.FF.N.Y.N.Y

Example beta1-adrenergic blocker and CAU similar

Docked into siteEID: 1276810 (Bioactive Molecules)					
Groups					
NumQueries: 1					
Chiral 					
232315 Antiobesity and antidiabetic agent, a specifically claimed compound within a series of benzodioxole dicarboxylates that exerts its action by virtue of its beta3-adrenoceptor-agonist activity, as demonstrated by stimulati	254159 Agent for the treatment of obesity, diabetes and hyperlipidemia, a beta3-adrenoceptor agonist, as demonstrated by stimulation of cAMP in CHO cells transfected with the human beta3-adrenocepto r (EC50 = 0.18 nM) and by st	135771 Antihypertensive agent, which decreases stimulating effect of isoproterenol and norepinephine in anesthetized dogs and is active in spontaneously hypertensive rats; another related indoyloxyp ropanolamine is: 141474	217630 A human metabolite of carvedilol that shows more potent antioxidant activity than parent compound in various models including iron-catalyzed lipid peroxidation in rat brain homogenates (IC50 = 0.30 mcmol/l vs. 8.1 mcmol/	090701 Antihypertensive, beta1-adrenergic blocker with additional alpha1-blocking properties. INDICATION - Essential hypertension. PRESENTATION - Tablets, 25 mg.	159104 Transdermal delivery system for mepindolol via TSD patch that appeared to be well tolerated and to induce pharmacodynamic equivalents of stable, prolonged and quite pronounced beta-adrenergic blockade within 1 week after
					Chiral 
175562 Oral antidiabetic agent with insulinomimetic and hypoglycemic activities. In vitro it activated glucose uptake by lipidic cells (epididymic lipid tissue of male rats) by 256% at a concentration of 1 mcM. After i.p. admin	156471 Anxiolytic and antimigraine agent that strongly and selectively binds to 5-HT1A-receptors (IC50 = 0.71 +/- 0.02 nM, against [3H]-8-OH-DPAT binding), with remarkable specificity in comparison to other 5-HT-receptors, e.g.	226668 alpha1-Adrenoceptor antagonist whose activity was evaluated in a receptor binding assay using rat submaxillary gland and liver membrane preparations, as well as in functional assays in rat is olated aorta and rat isolate	172623 Antiobesity agent having thermogenic activity in standard tests, giving an ED50 value for GDP binding in mitochondrias of rat interscapular brown adipose tissue of 0.55 mg/kg s.c. or p.o. Com pound induces very slight ca	450766 pSTAT3/IL-6 inhibitor that suppressed the growth of NCI-H460 (GI50 = 0.78 mcM), HCT 116 (GI50=8.5 mcM) and MDA-MB-231/U-251 (GI50 = 5 mcM) cells and inhibited IL-6 production in NCI-H460 cells (IC50 = 5 mcM) and in mice	291422 Agent for the treatment of obesity, diabetes and hyperlipidemia, a beta3-adrenoceptor agonist, as demonstrated by stimulation of cAMP in CHO cells transfected with the human beta3-adrenocepto r (EC50 = 12 nM; 69% activat
Chiral 			Chiral 	Chiral 	
174322 beta1-Adrenergic blocker with high selectivity, short-term activity and low toxicity. Remedy for angina pectoris, myocardial infarction, cardiac insufficiency,hypertension and arrhythmia. Inh ibition was shown to be 51.5	414953 Monoamine (5-HT and norepinephrine) reuptake inhibitor that displayed pKi values of 8.90 and 8.19, respectively, when tested for affinity at human 5-HT (SERT) and norepinephrine (NET) transporters. It is considered to ha	263881 Hypolipidemic agent, a potent inhibitor of squalene synthase (IC50 = 32 nM in human hepatoma HepG2 cells). It reduced blood cholesterol levels in rats fed a cholesterol-enriched diet by 50% at a dose of 50 mg/kg p.o. Ano	250527 Agent for the treatment of obesity and type II diabetes, a selective beta3-adrenoceptor agonist with minimal or no beta1- and beta2-adrenoceptor-stimulatory effects. Other specifically claime d compounds include the foll	146217 Calcium antagonist and selective beta1-adrenergic blocker, the 2S-isomer of YM-16151-1. When orally administered to rats (3 - 30 mg/kg) and dogs (0.3 - 10 mg/kg), it produces dose-dependent hypotension without increasing	239356 Antidiabetic and antiobesity agent that acts by virtue of its beta3-adrenoceptor-agonist activity (EC50 = 85 nM for increasing cAMP levels in CHO cells expressing human receptor). Its activity was also determined by meas



LigandCross Diverse Examples

Groups

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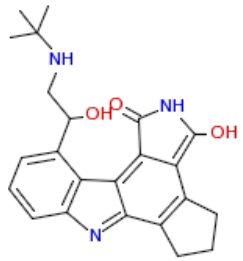
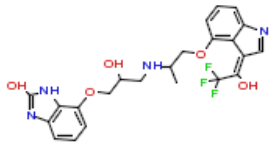
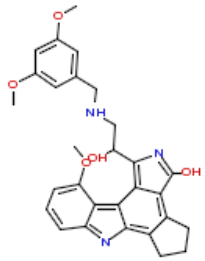
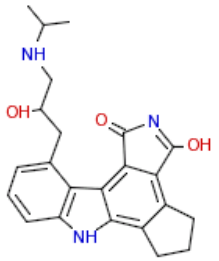
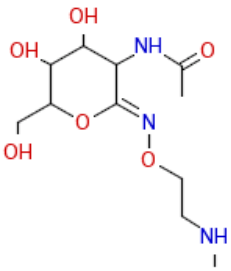
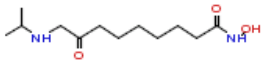
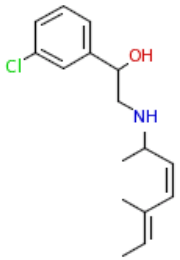
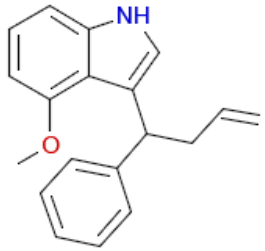
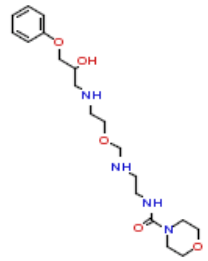
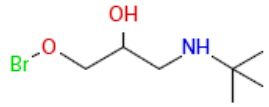
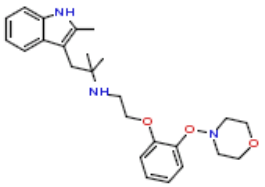
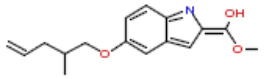
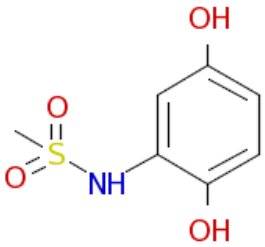
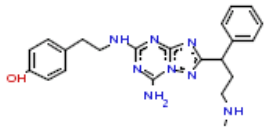
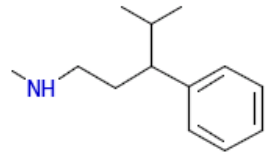
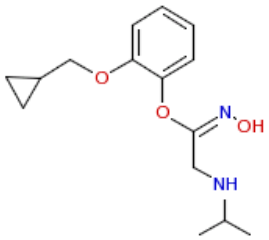
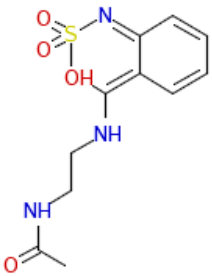
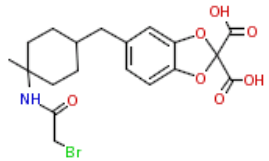
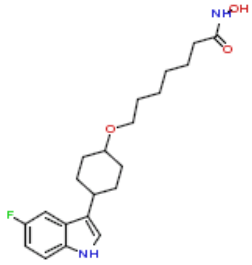
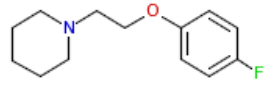
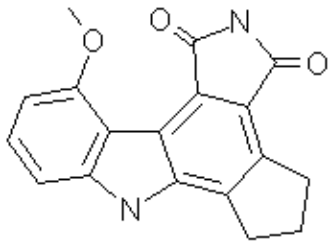
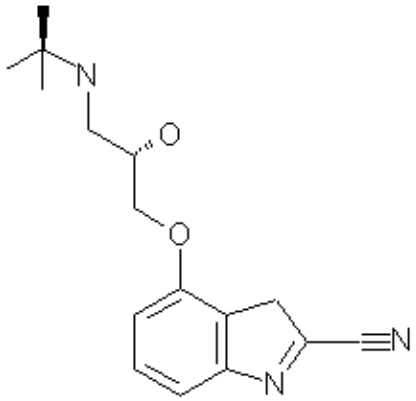
 396707_P32_20 LC: 0.818 DL: 16.41	 263341_257094_35 LC: 0.674 DL: 16.53	 450766_396707_3 LC: 0.818 DL: 13.02	 396707_257094_15 LC: 0.614 DL: 15.30	 414953_OAN_11 LC: 0.465 DL: 19.22
 328954_CAU_7 LC: 0.500 DL: 15.74	 239356_RET_7 LC: 0.511 DL: 14.83	 263881_414953_2 LC: 0.659 DL: 10.75	 172623_174322_26 LC: 0.313 DL: 21.04	 156471_TIM_4 LC: 0.452 DL: 14.33
 226668_TIM_3 LC: 0.400 DL: 15.82	 239356_387297_42 LC: 0.619 DL: 10.22	 254159_263341_3 LC: 0.558 DL: 11.24	 414953_ZMA_1 LC: 0.568 DL: 10.66	 414953_164327_1 LC: 0.568 DL: 10.45
 226668_164327_7 LC: 0.500 DL: 11.02	 284771_229728_2 LC: 0.457 DL: 10.29	 232315_156471_2 LC: 0.386 DL: 11.58	 281697_328954_1 LC: 0.383 DL: 10.75	 263341_RAL_11 LC: 0.205 DL: 13.50



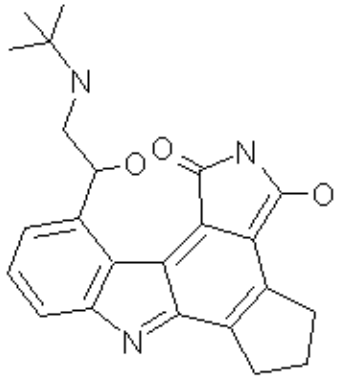
396707

Potent and selective poly(ADP-ribose) polymerase-1 (PARP-1) and PARP-2 inhibitor (IC50 = 20 and 6 nM, respectively) that demonstrated chemosensitizing properties at a concentration of 1 mcM when combined with temozolomid



P32 (2VT4)

2VT4: TURKEY BETA1 ADRENERGIC RECEPTOR WITH STABILISING MUTATIONS AND BOUND CYANOPINDOLOL



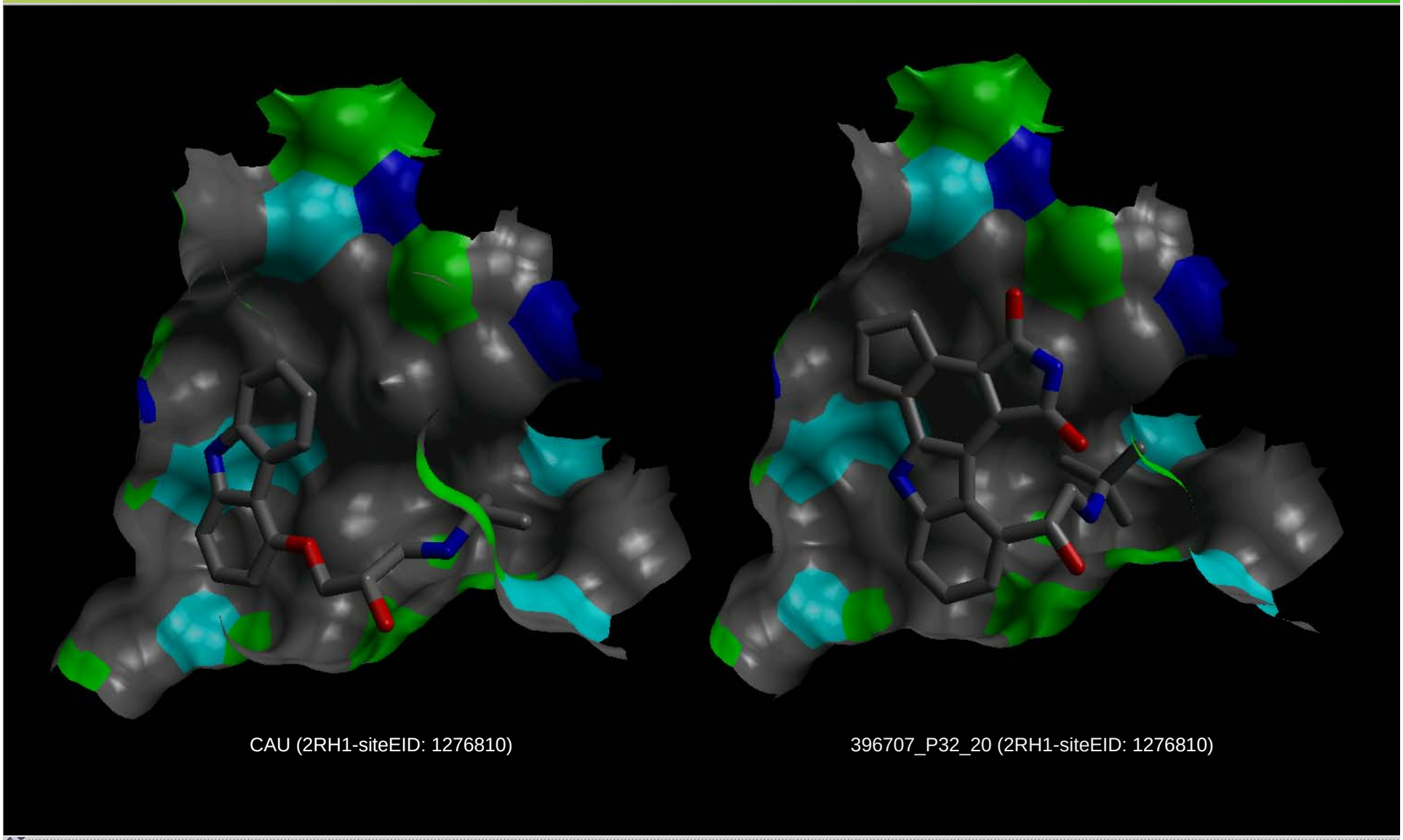
396707_P32_20

LigandCross result for siteEID:2RH1-siteEID: 1276810

Sequences | Chains | Sites | Binding Modes

Description				Binding Modes
Site Name	Locus	Description	Contact	Non-polar Polar H-bond Polar/H-bond
pdb2rh1/s1276810 (chain A)	-	**CAU: (2S)-1-(9H-Carba...**	-	.WT.DV.VT.F.T.YA.SS.SF.W.FF.N.Y.N.Y
pdb2rh1/s1276810_7 (chain A)	-	450766_396707_3	0.79	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_286 (chain A)	-	450766_396707_3	0.79	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_1 (chain A)	-	450766_396707_3	0.79	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_280 (chain A)	-	450766_396707_3	0.79	WT DV VT F T YA SS SF W FF N Y N Y
pdb2vt4/s1421543 (chain A)	-	**P32: 4-{[(2S)-3-(tert-bu...**	0.77	WT DV VT F T YA SS S- W FF N F N Y
pdb2vt4/s1421560 (chain D)	-	**P32: 4-{[(2S)-3-(tert-bu...**	0.77	WT DV VT F T YA SS S- W FF N F N Y
pdb2rh1/s1276810_13 (chain A)	-	396707_257094_15	0.74	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_292 (chain A)	-	396707_257094_15	0.74	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_67 (chain A)	-	414953_ZMA_1	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_346 (chain A)	-	414953_ZMA_1	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_18 (chain A)	-	263341_257094_35	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_31 (chain A)	-	414953_ZMA_1	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_297 (chain A)	-	263341_257094_35	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_310 (chain A)	-	414953_ZMA_1	0.73	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_17 (chain A)	-	414953_ZMA_1	0.72	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_296 (chain A)	-	414953_ZMA_1	0.72	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_107 (chain A)	-	263341_257094_35	0.71	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_386 (chain A)	-	263341_257094_35	0.71	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_42 (chain A)	-	263341_257094_35	0.71	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_321 (chain A)	-	263341_257094_35	0.71	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_3 (chain A)	-	450766_396707_3	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_24 (chain A)	-	450766_396707_3	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_282 (chain A)	-	450766_396707_3	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_303 (chain A)	-	450766_396707_3	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_19 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_27 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_29 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_298 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_306 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_308 (chain A)	-	396707_257094_15	0.70	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_164 (chain A)	-	226668_164327_7	0.69	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_211 (chain A)	-	263881_414953_2	0.69	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_443 (chain A)	-	226668_164327_7	0.69	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_490 (chain A)	-	263881_414953_2	0.69	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_138 (chain A)	-	239356_387297_42	0.68	WT DV VT F T YA SS SF W FF N Y N Y
pdb2rh1/s1276810_417 (chain A)	-	239356_387297_42	0.68	WT DV VT F T YA SS SF W FF N Y N Y
pdb3d4s/s1420907 (chain A)	-	**TIM: (2S)-1-(tert-butyla...**	0.67	WT DV VT F T YA SS SF W FF N Y N Y

Example Docked LigandCross Result (siteEID: 1276810)



CAU (2RH1-siteEID: 1276810)

396707_P32_20 (2RH1-siteEID: 1276810)

Chains | Chain Alignments | Sites | Site Alignments

Site Name	Locus	Ligand	%Conf	Sequence Positions
pdb2rh11/s1276810 (chain A)	-	**CAU**	100	.WT.DV.VT.F.T.YA.SS.SF.W.FF.N.Y.N.Y
pdb2rh1/s1276810_6 (chain A)	-	396707_P32_20	100	.WT.DV.VT.F.T.YA.SS.SF.W.FF.N.Y.N.Y

Conclusions

- Significant receptor-site similarities exist within and across target families

- The structurally resolved and modelable proteome is a very rich source for new matter ideas

- LigandCross can be an effective approach to generating novel, bioactive matter using co-complexes, known inhibitors, and/or fragment-based information.