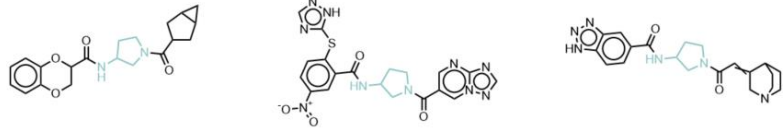


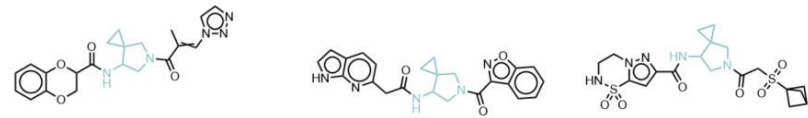
De-Novo Generated Top 100 Scoring Compounds: *Moving away from Pyridine N-oxides*

- 316 diverse acids available from Enamine Building Blocks and created 10 libraries of about 93,000 compounds each.
- 10 diamine core libraries, 93'026 molecules per library = ~ 1 million compounds.

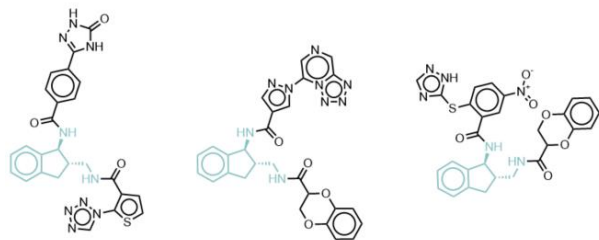
Core 1



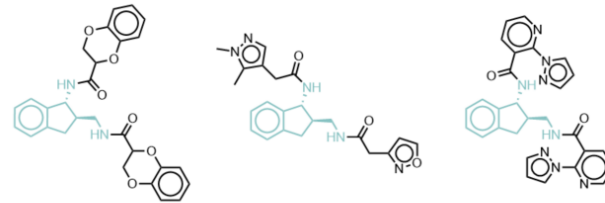
Core 2



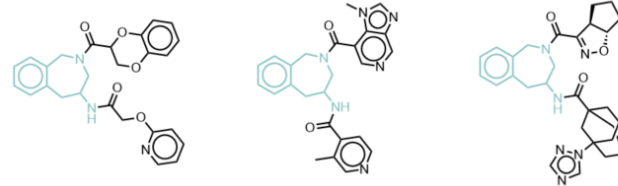
Core 3a



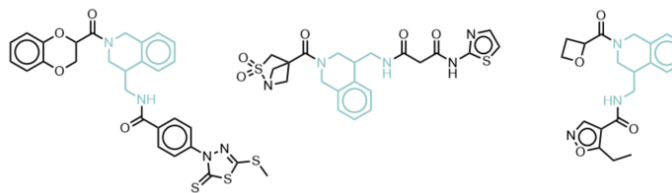
Core 3b



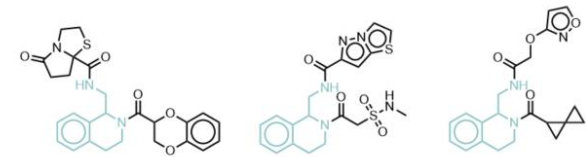
Core 4



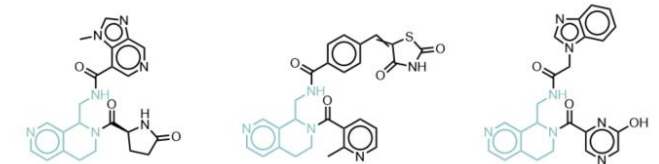
Core 5



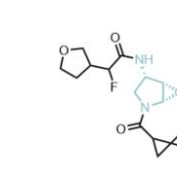
Core 6



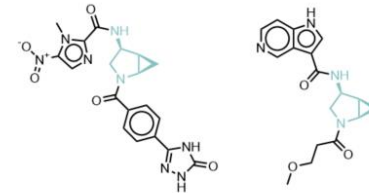
Core 7



Core 8a

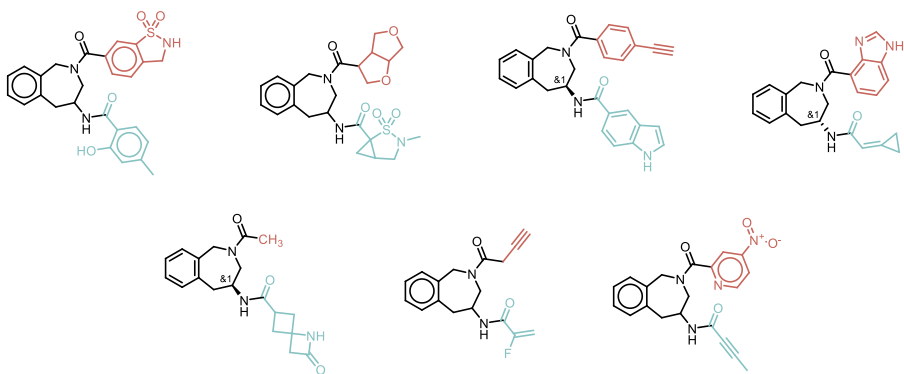


Core 8b



De-Novo Generated Top 100 Scoring Compounds: Moving away from Pyridine N-oxides whilst retaining cores

1) Diversification of the amine cores with commercially available and diverse Enamine carboxylic acids afforded 93'026 compounds, which were sent for virtual screening (Maestro Glide).



2) DataWarrior triage

Total molweight < 500 Da

cLogP < 5

cLogS < 1

H Acceptors < 10

H Donors < 5

Rotatable bonds < 3

Polar Surface Area < 140

Angstroms

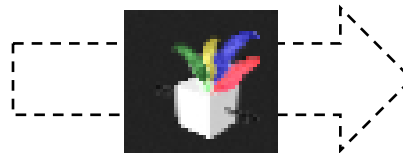
Mutagenic X

Tumorigenic X

Reproductive effective X

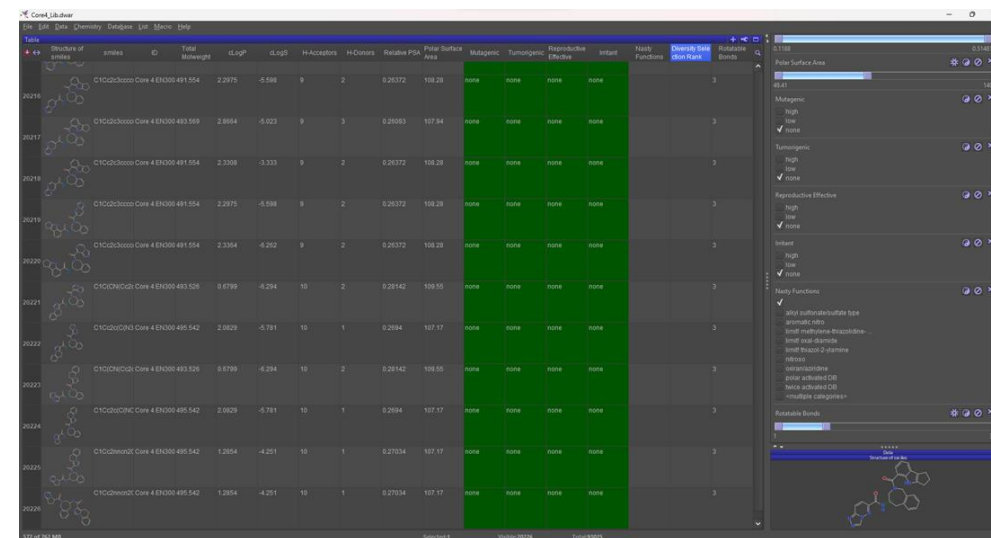
Irritant X

Nasty functions X



3) Virtual Screening with PyRx 0.8 / AutoDock Vina 1.2

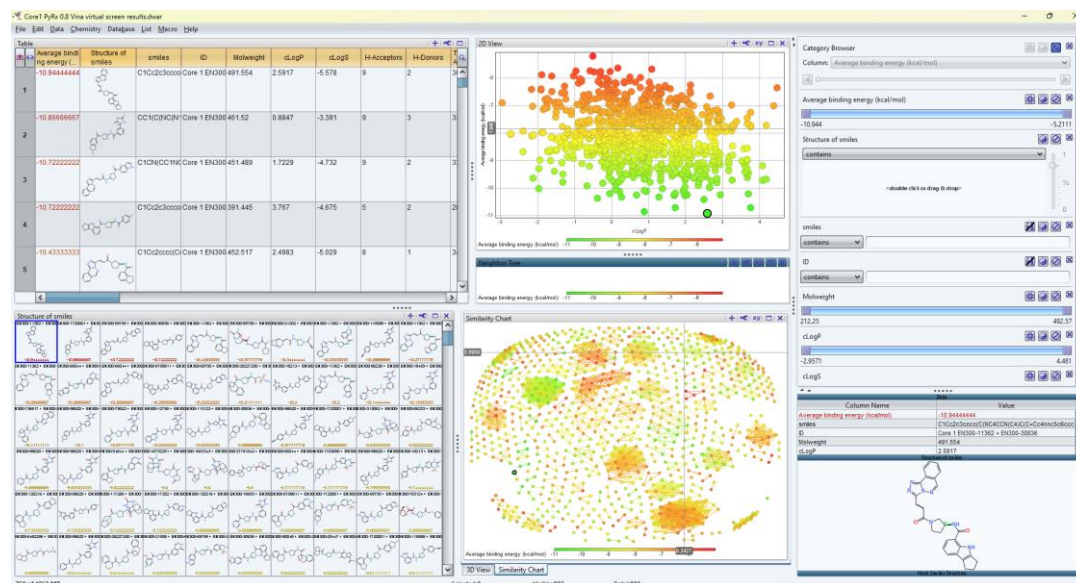
- Reduced to 20'226 molecules.
- DataWarrior's 'diversity selection rank' in order of structural diversity.
- Selected the top 1000 most diverse compounds for virtual screening using PyRx 0.8/AutoDock Vina 1.2. [PyRx - Virtual Screening Tool download | SourceForge.net](#)



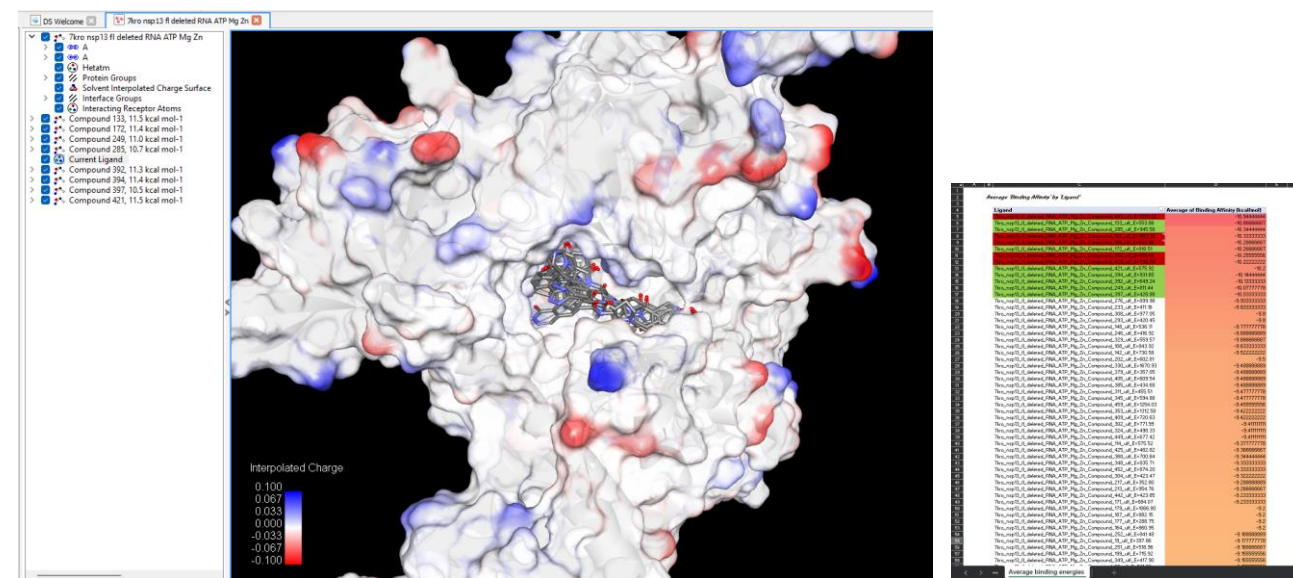
smiles	ID	Total Molweight	cLogP	cLogS	H-Acceptors	H-Donors	Relative PSA	Polar Surface Area	Mutagenic	Tumorigenic	Reproductive Effective	Irritant	Nasty Functions
OTG020000 Core 4 EN000 491 554	22975	-5.598	9	2	0.26372	108.28	none	none	none	none	none	3	
OTG020000 Core 4 EN000 493 569	23654	-5.023	9	3	0.26693	107.94	none	none	none	none	none	3	
OTG020000 Core 4 EN000 491 554	23008	-3.303	9	2	0.26372	108.28	none	none	none	none	none	3	
OTG020000 Core 4 EN000 491 554	22975	-5.598	9	2	0.26372	108.28	none	none	none	none	none	3	
OTG020000 Core 4 EN000 493 569	23654	-4.262	9	2	0.26372	108.28	none	none	none	none	none	3	
OTG020000 Core 4 EN000 493 526	9 8799	-6.294	10	2	0.28142	109.55	none	none	none	none	none	3	
OTG020000 Core 4 EN000 495 542	2 0829	-5.781	10	1	0.2694	107.17	none	none	none	none	none	3	
OTG020000 Core 4 EN000 493 526	9 8799	-6.294	10	2	0.28142	109.55	none	none	none	none	none	3	
OTG020000 Core 4 EN000 495 542	2 0829	-5.781	10	1	0.2694	107.17	none	none	none	none	none	3	
OTG020000 Core 4 EN000 495 542	1 2854	-4.251	10	1	0.27034	107.17	none	none	none	none	none	3	
OTG020000 Core 4 EN000 495 542	1 2854	-4.251	10	1	0.27034	107.17	none	none	none	none	none	3	

De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)

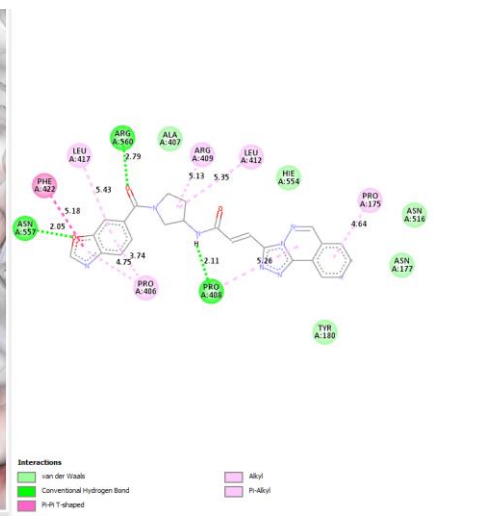
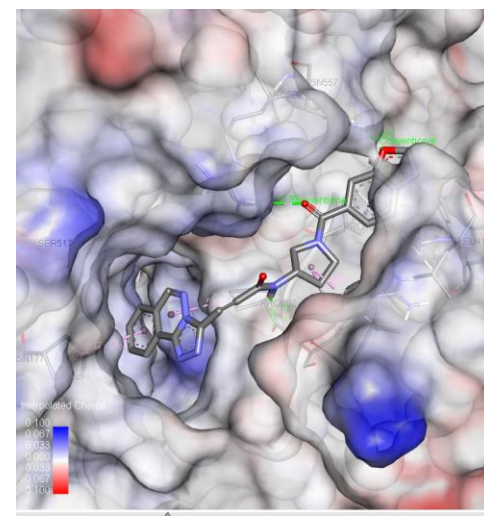
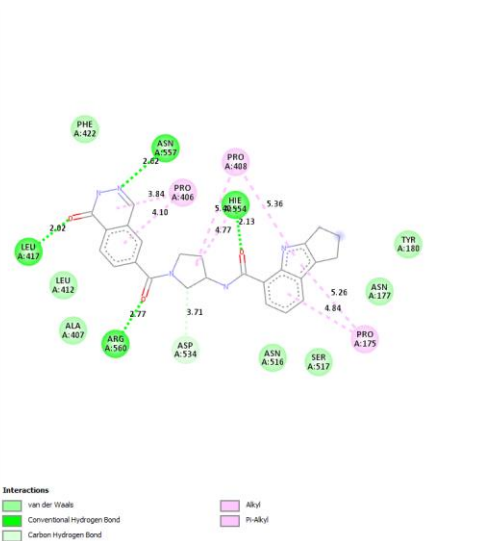
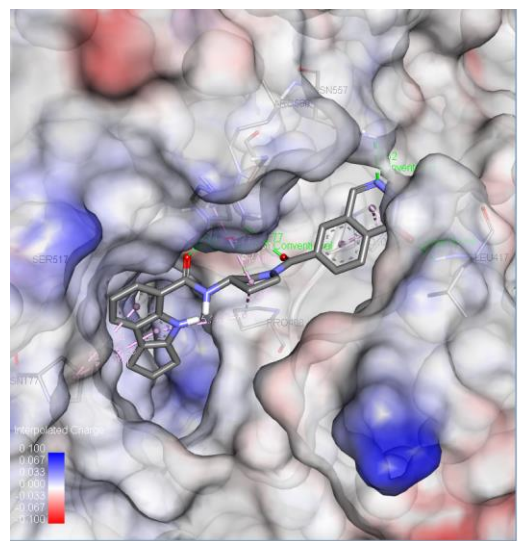
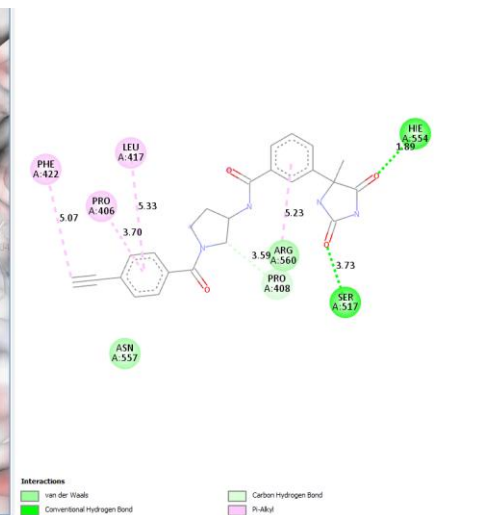
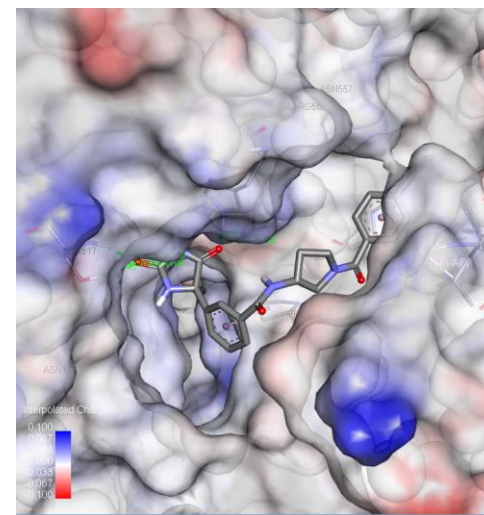
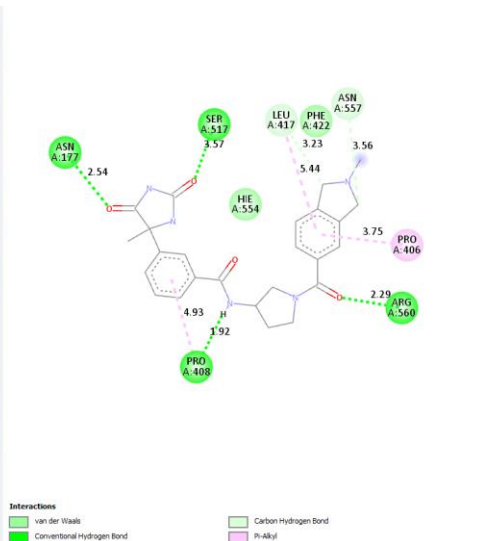
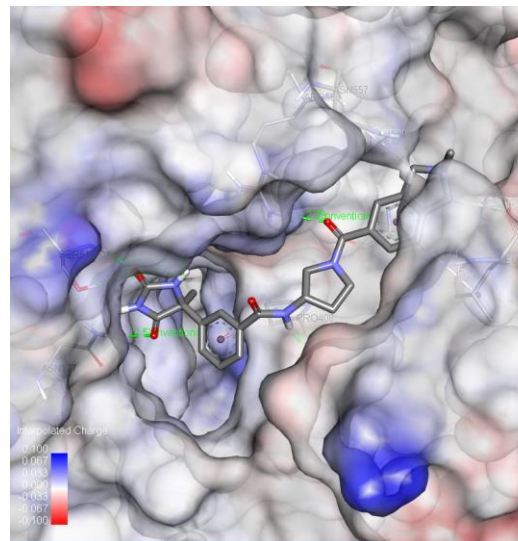
- Ranked average binding free energy scores, then applied cutoff at **-10.0 kcal/mol** (lead-like)



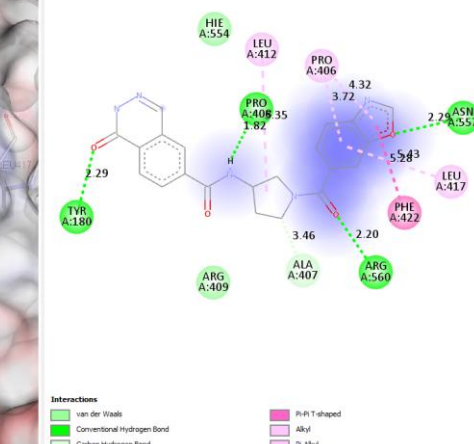
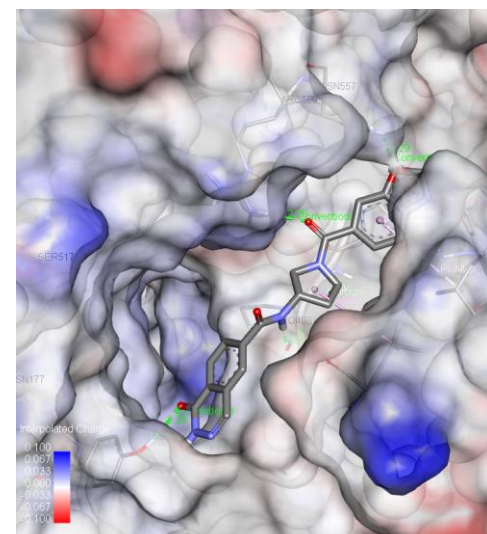
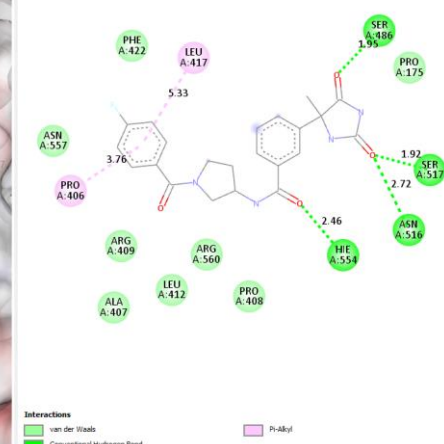
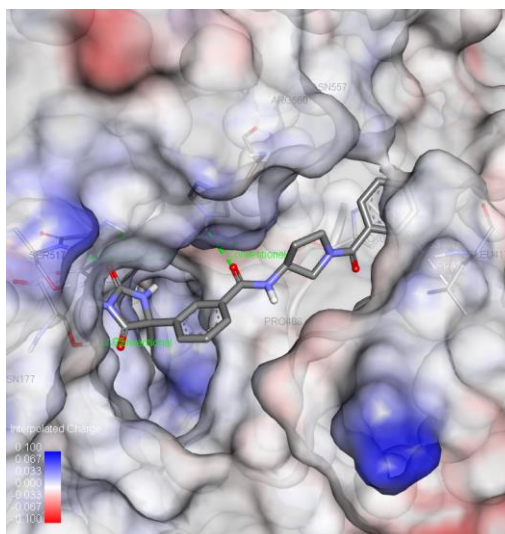
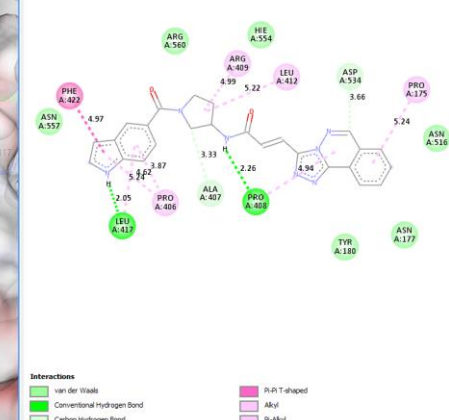
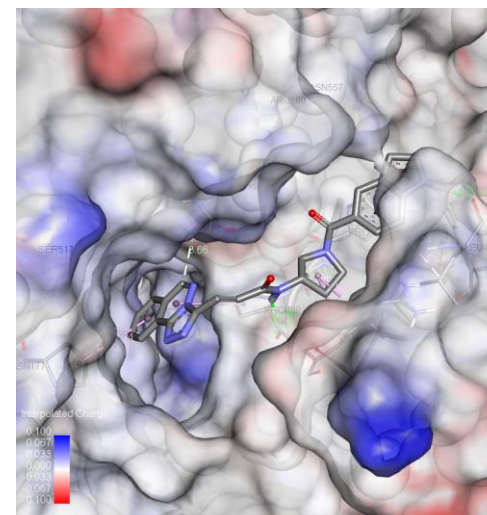
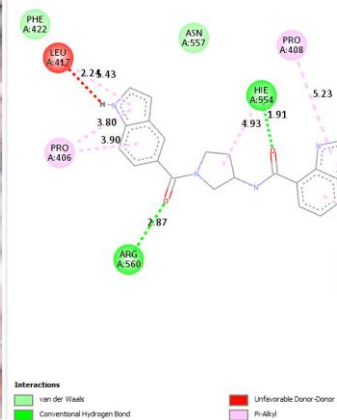
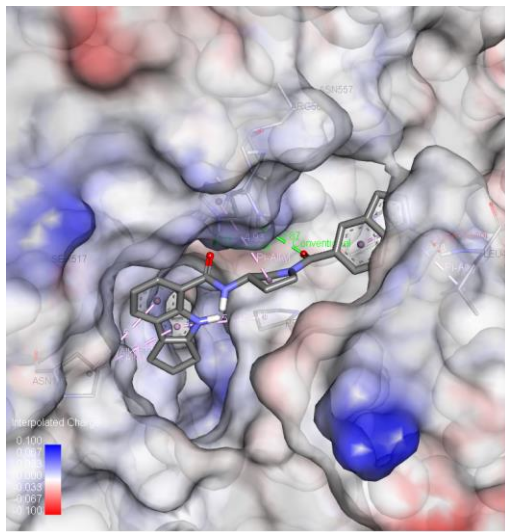
- Visually inspected** minimum energy poses to validate, eliminating wrong geometries (cis-amides).



De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)

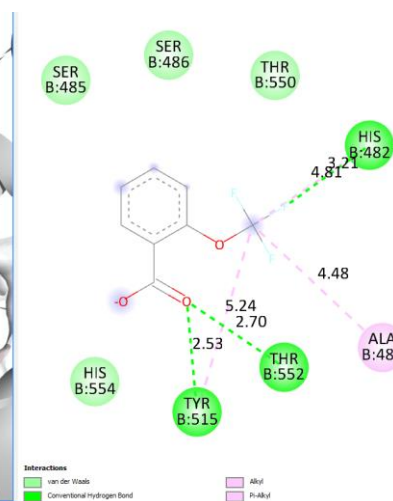
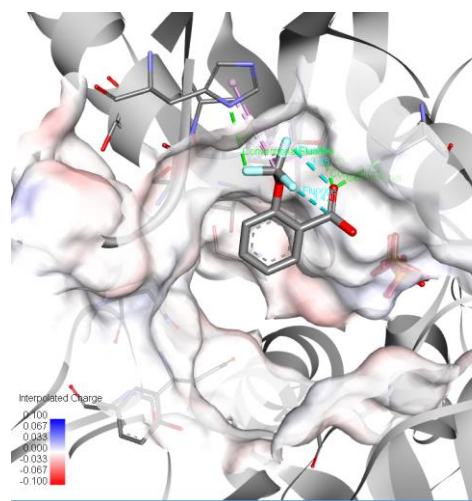
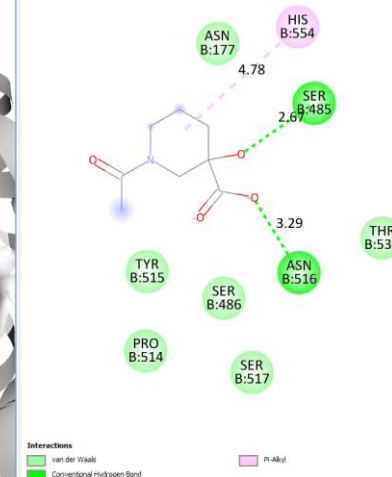
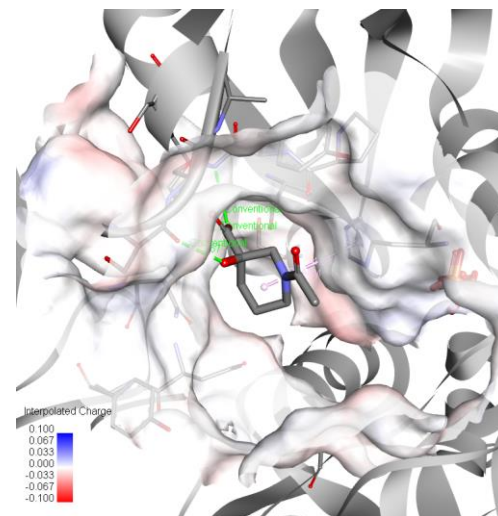
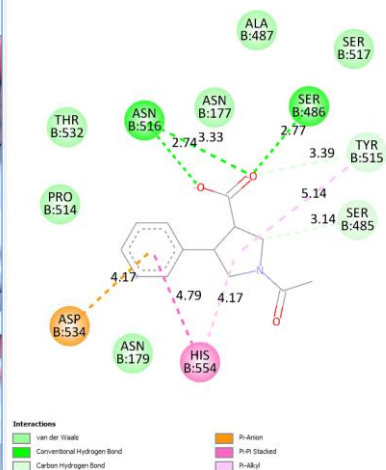
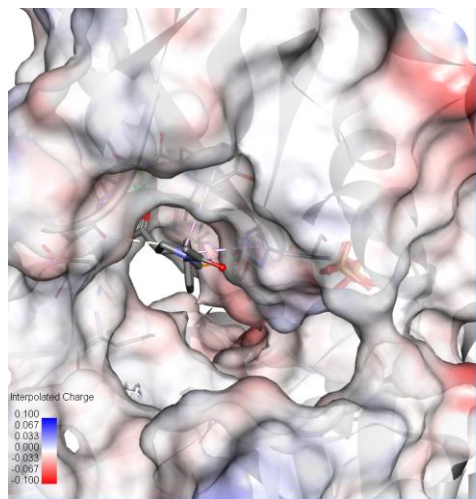


De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)



De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)

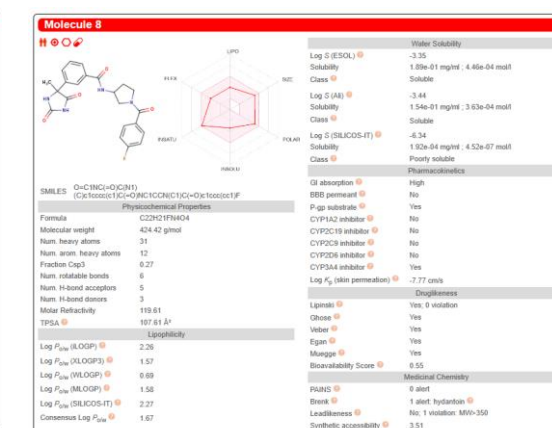
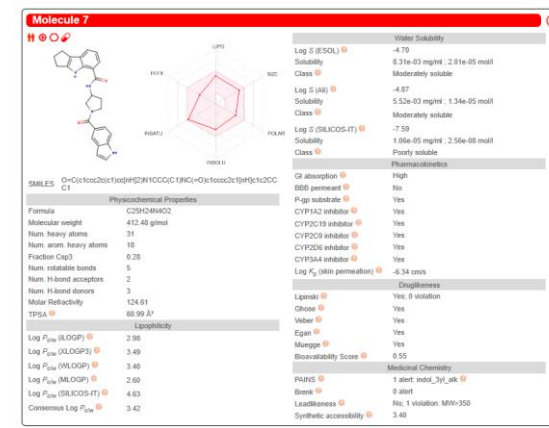
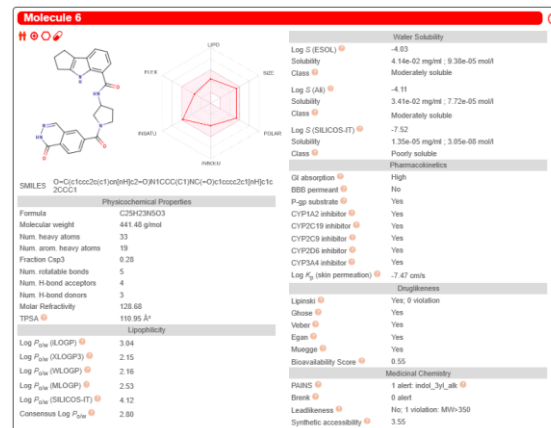
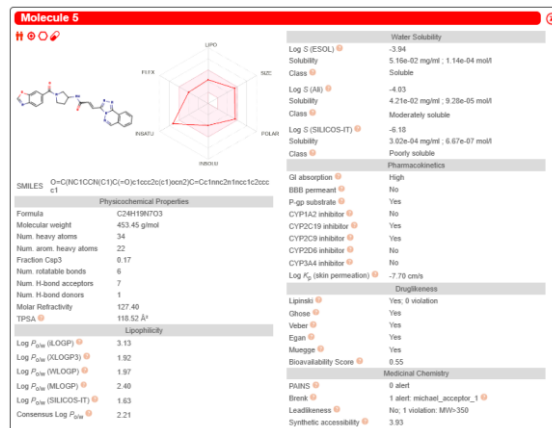
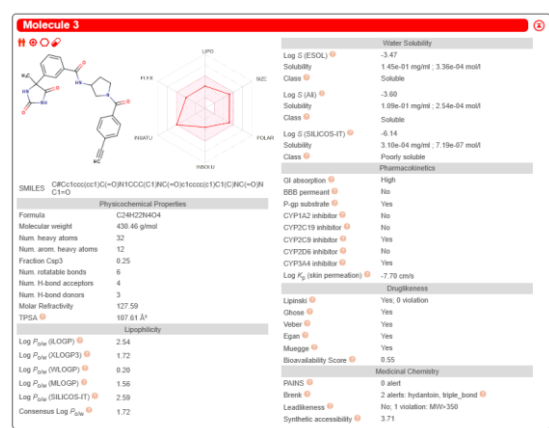
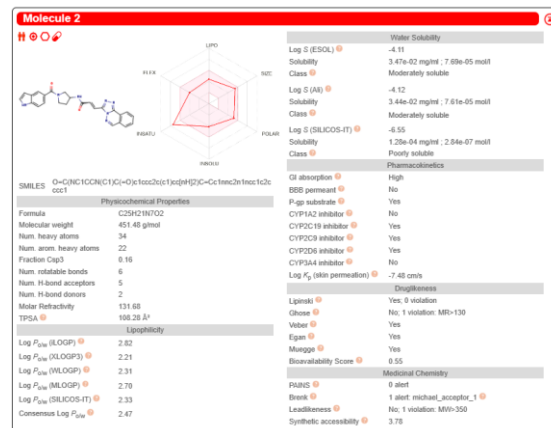
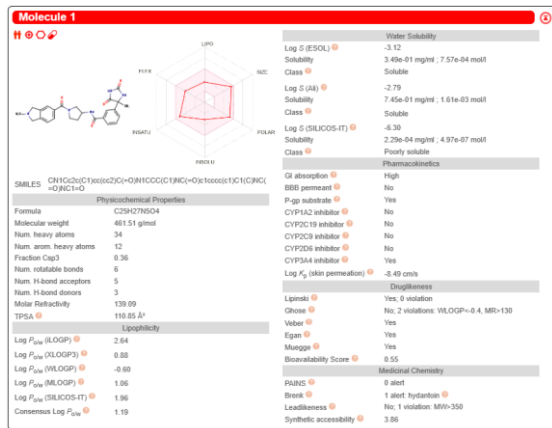
- PANDDA fragment interactions at 5' RNA site



De-Novo Generated Top 100 Scoring Compounds: Core1 compounds



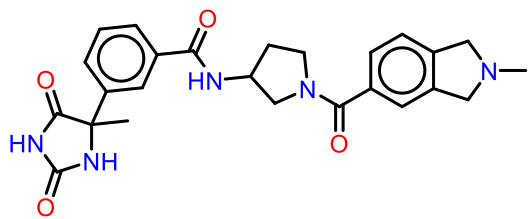
- PAINS filtering (SwissADME) cleared.



De-Novo Generated Top 100 Scoring Compounds: Core1 compounds

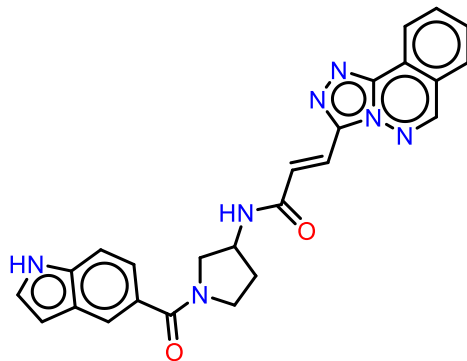
Compound 133

Core 1 EN300-1720001 + EN300-98620



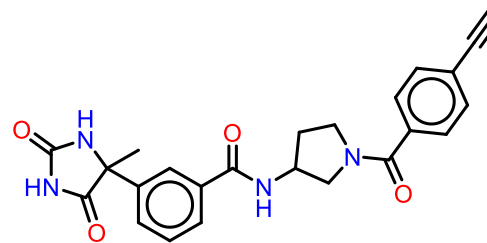
Compound 285

Core 1 EN300-69795 + EN300-11362



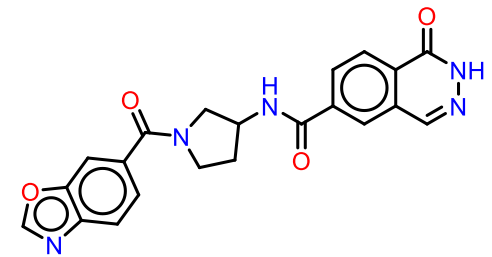
Compound 172

Core 1 EN300-115688 + EN300-98620



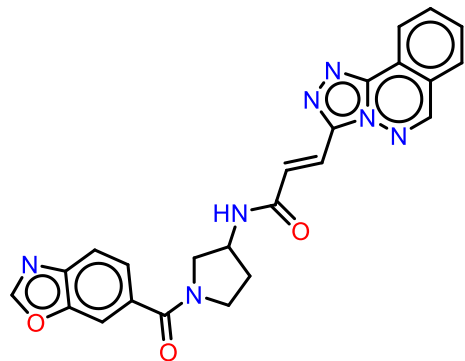
Compound 421

Core 1 EN300-66044 + EN300-6758811



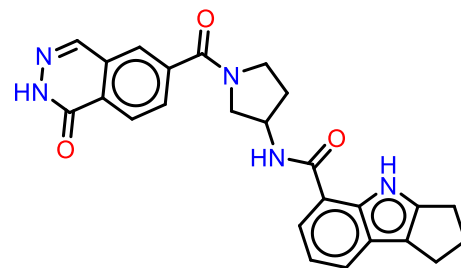
Compound 394

Core 1 EN300-66044 + EN300-11362



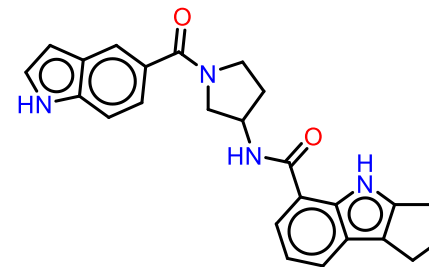
Compound 392

Core 1 EN300-6758811 + EN300-30836



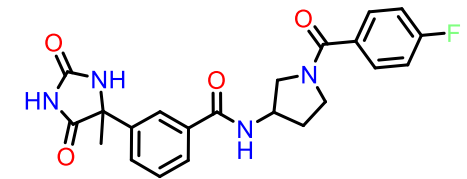
Compound 249

Core 1 EN300-69795 + EN300-30836



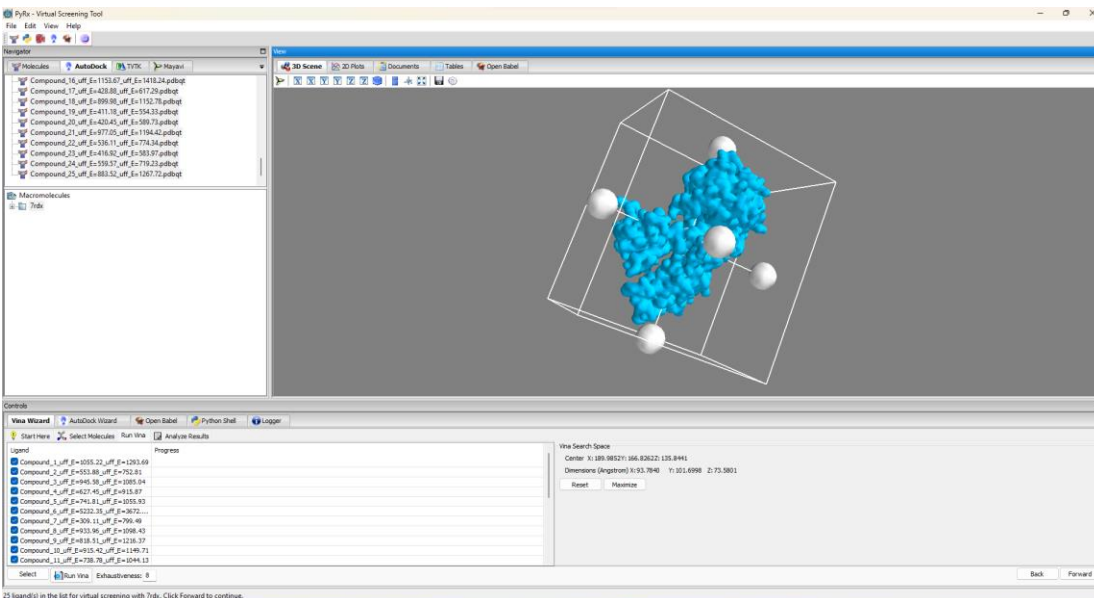
Compound 397

Core 1 EN300-18213 + EN300-98620



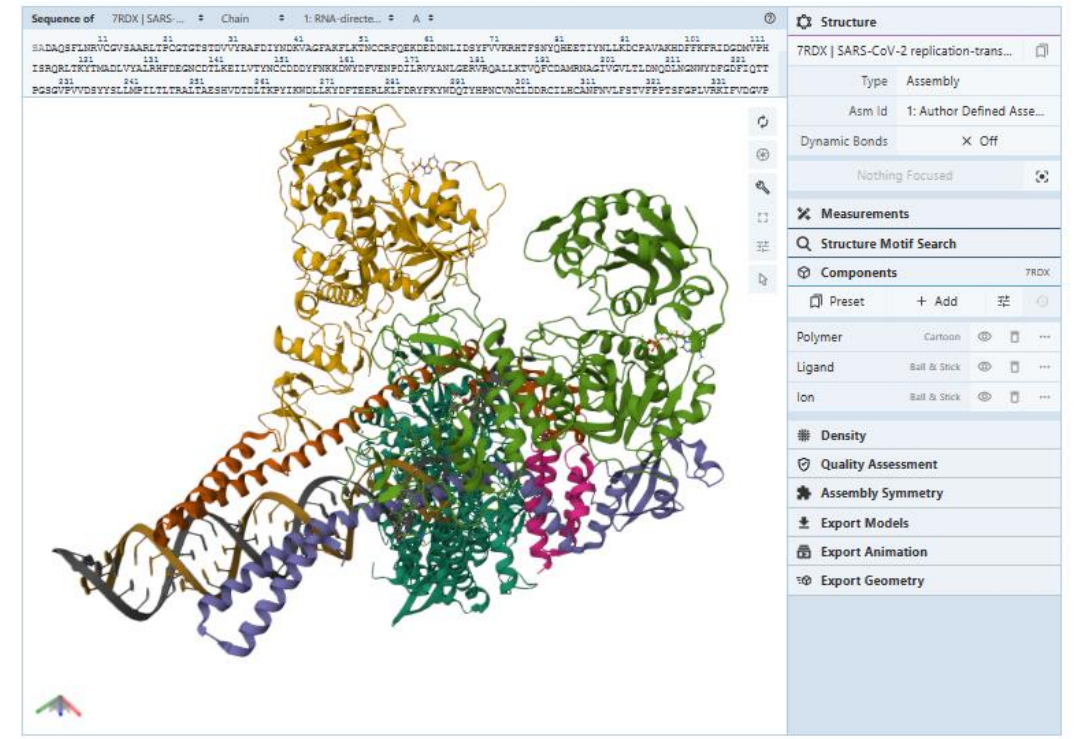
De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA

- Selected ligands with average binding scores of **-10 kcal/mol or below**.
- Docked to **pdb 7rdx (open state)** as part of replicase-transcriptase complex (RTC) cryo-EM structure.
- 1B domain fully open; RNA unbound, ATP bound.
- Unbiased virtual screen (full protein) using energy-minimised ligands and exhaustiveness = 8 conformers.



7RDX

SARS-CoV-2 replication-transcription complex bound to nsp13 helicase - nsp13(2)-RTC - open class



De-Novo Generated Top 100 Scoring Compounds: Virtual Screen with PyRx 0.8 / AutoDock VINA

PyRx - Virtual Screening Tool

File Edit View Help

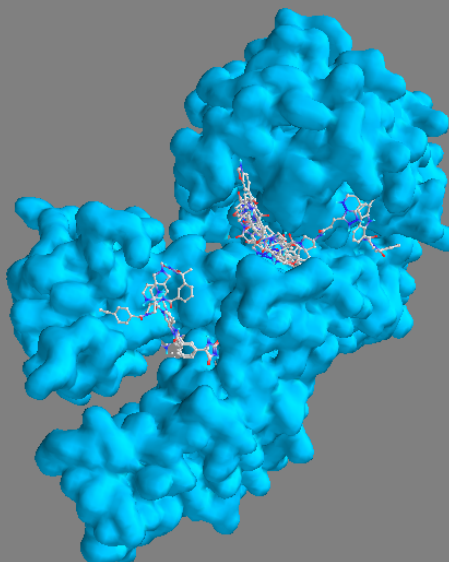
Navigator

Molecules AutoDock TVTK Mayavi

7rdx
 7rdx_Compound_1_uff_E=1055.22_uff_E=1293.69
 7rdx_Compound_5_uff_E=741.81_uff_E=1055.93
 7rdx_Compound_3_uff_E=945.58_uff_E=1085.04
 7rdx_Compound_13_uff_E=931.65_uff_E=1128.81
 7rdx_Compound_10_uff_E=915.42_uff_E=1149.71
 7rdx_Compound_15_uff_E=811.44_uff_E=1120.91
 7rdx_Compound_11_uff_E=738.78_uff_E=1044.13
 7rdx_Compound_8_uff_E=933.96_uff_E=1098.43
 7rdx_Compound_20_uff_E=420.45_uff_E=589.73
 7rdx_Compound_14_uff_E=649.24_uff_E=946.92
 7rdx_Compound_23_uff_E=416.92_uff_E=583.97
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 7rdx_Compound_18_uff_E=899.98_uff_E=1152.78
 7rdx_Compound_17_uff_E=428.88_uff_E=617.29
 7rdx_Compound_9_uff_E=818.51_uff_E=1216.37
 7rdx_Compound_24_uff_E=559.57_uff_E=719.23
 7rdx_Compound_2_uff_E=553.88_uff_E=752.81
 7rdx_Compound_12_uff_E=575.92_uff_E=851.26
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 7rdx_Compound_4_uff_E=627.45_uff_E=915.87
 7rdx_Compound_19_uff_E=411.18_uff_E=554.33
 7rdx_Compound_6_uff_E=5232.35_uff_E=3672.86_uff_E=3672.77
 7rdx_Compound_25_uff_E=883.52_uff_E=1267.72

View

3D Scene 2D Plots Documents Tables Open Babel



Controls

Vina Wizard AutoDock Wizard Open Babel Python Shell Logger

Start Here Select Molecules Run Vina Analyze Results

View: No filter Results: All 225 items

Ligand	Binding Affinity (kcal/mol) >>	Mode	RMSD lower bound	RMSD upper bound
7rdx_Compound_10_uff_E=915.42_uff_E=1149.71	-7.7	6	27.67	30.939
7rdx_Compound_12_uff_E=575.92_uff_E=851.26	-7.7	7	32.587	35.806
7rdx_Compound_12_uff_E=575.92_uff_E=851.26	-7.7	8	31.072	36.991
7rdx_Compound_25_uff_E=883.52_uff_E=1267.72	-7.6	1	27.198	30.519
7rdx_Compound_25_uff_E=883.52_uff_E=1267.72	-7.6	0	0.0	0.0
7rdx_Compound_19_uff_E=411.18_uff_E=554.33	-7.6	6	8.167	15.335
7rdx_Compound_19_uff_E=411.18_uff_E=554.33	-7.6	5	16.676	17.995
7rdx_Compound_9_uff_E=818.51_uff_E=1216.37	-7.6	5	19.659	22.06
7rdx_Compound_8_uff_E=933.96_uff_E=1098.43	-7.6	6	31.713	33.623

Finished Running Vina.