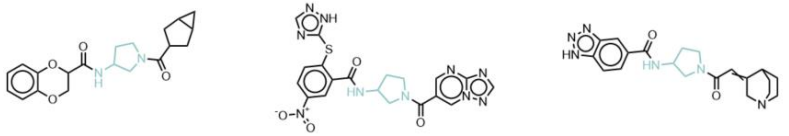
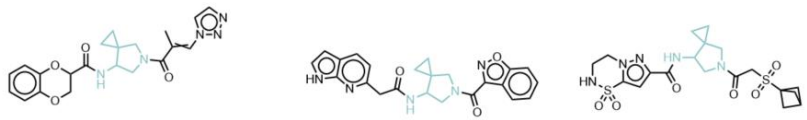
# De-Novo Generated Top 100 Scoring Compounds:
*Moving away from Pyridine N-oxides*

- 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.

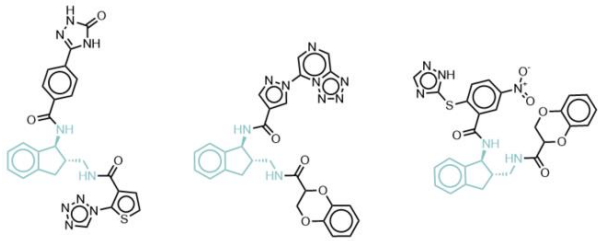
Core 1



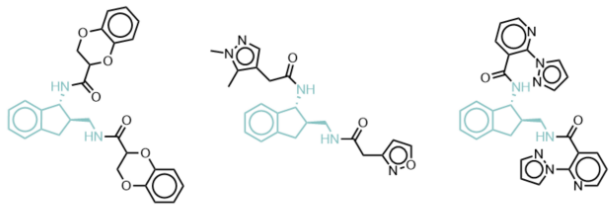
Core 2



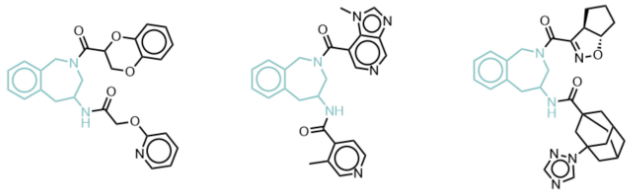
Core 3a



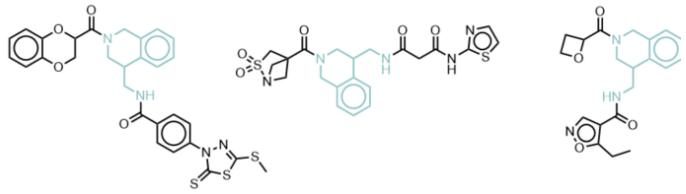
Core 3b



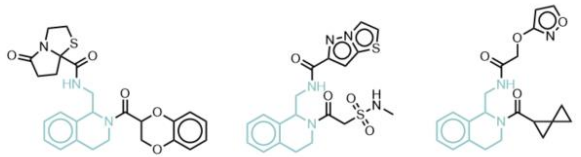
Core 4



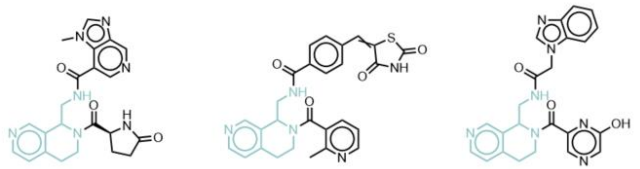
Core 5



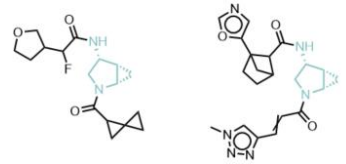
Core 6



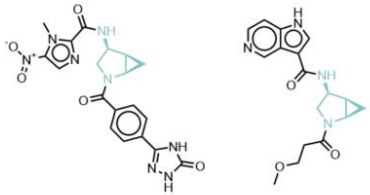
Core 7



Core 8a

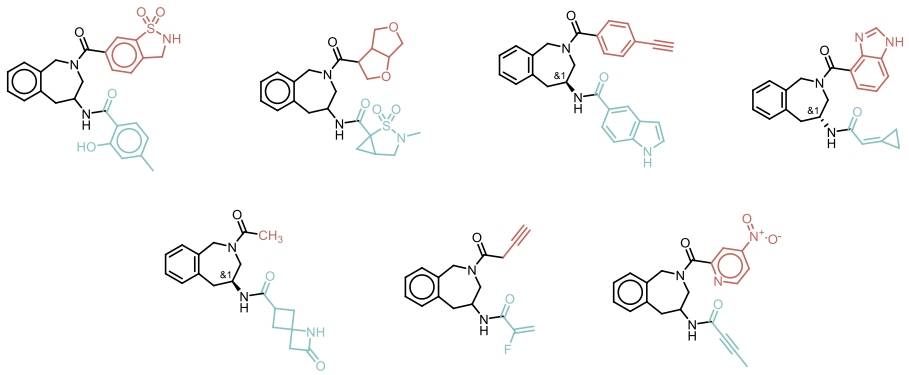


Core 8b



# 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).

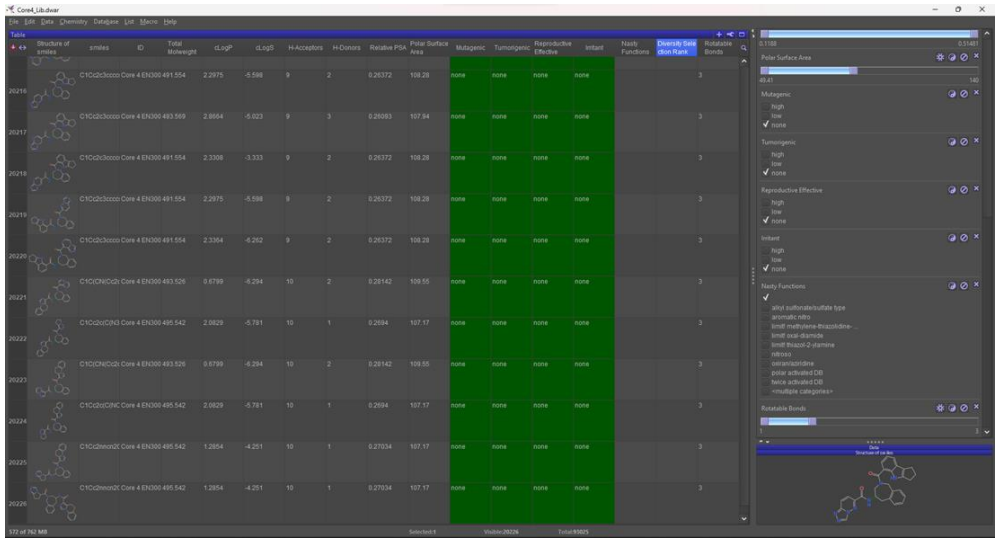


***2) DataWarrior triage***

*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***

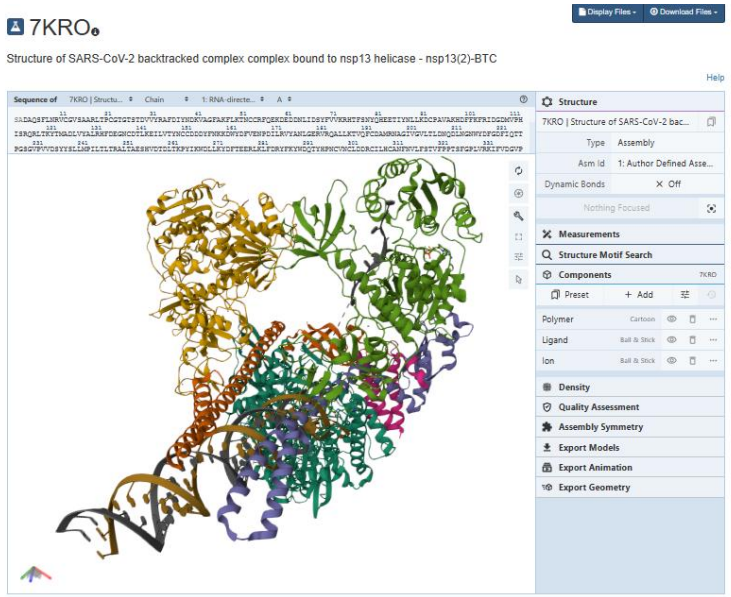
***3) Virtual Screening with PyRx 0.8 / AutoDock Vina 1.2***

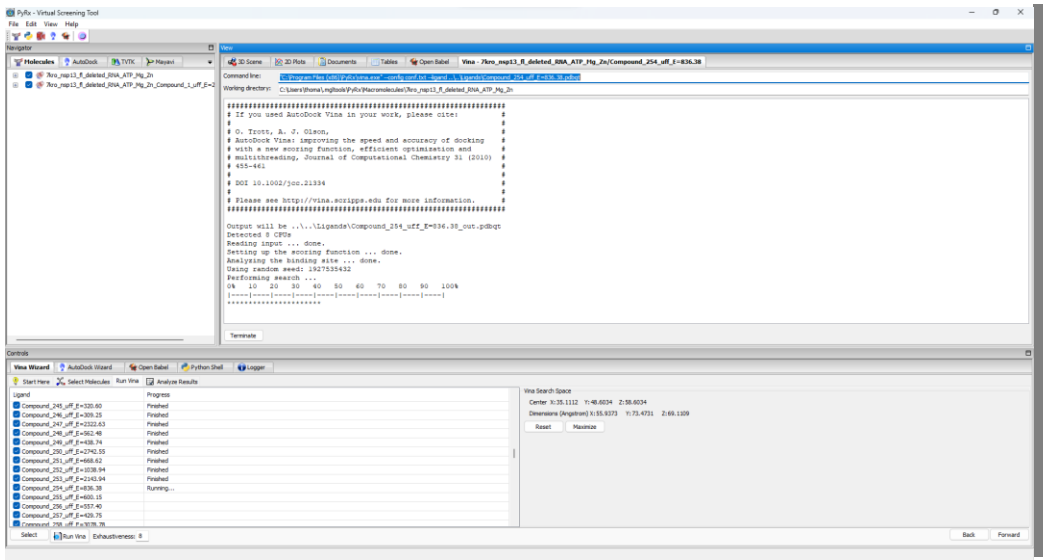
- Reduced to 20'226 molecules.
- DataWarrior's 'diversity selection rank' in order of structural diversity.
- Selected the top 1000 most diverse compounds for virtual screening using PyRx 0.8/AutoDock Vina 1.2. PyRx - Virtual Screening Tool download | SourceForge.net

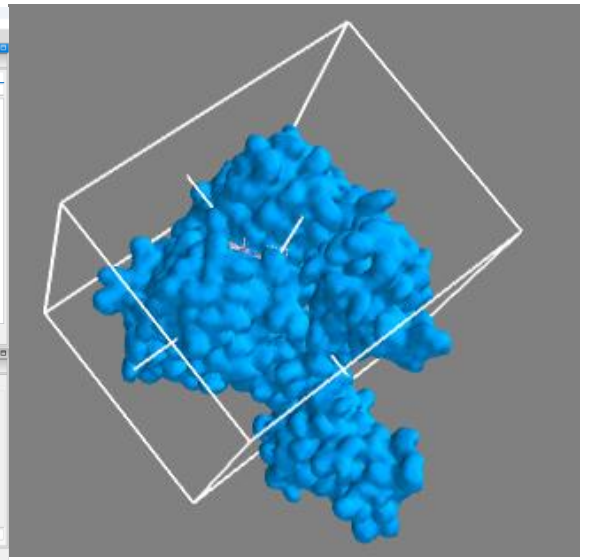


# De-Novo Generated Top 100 Scoring Compounds:
## *Virtual Screen with PyRx 0.8 / AutoDock VINA*

- Docked to pdb 7kro (ATP/(+)ssRNA bound state as part of replicase-transcriptase complex (RTC) cryo-EM structure.
- Backtracking ssRNA ; counteracting the RdRp/nsp12.
- Part of replicase-transcriptase complex (RTC) cryo-EM structure.
- Used **PyRx 0.8** to run virtual screen using **AutoDock Vina v1.2 scoring function** > protein prepared via DockPrep in **Chimera 1.16** with hydrogens added. All ligands energy minimised before running.
- Unbiased virtual screen (RecA domains, ATP site + RNA channel protein grid) using energy-minimised ligands and exhaustiveness = 8 conformers.

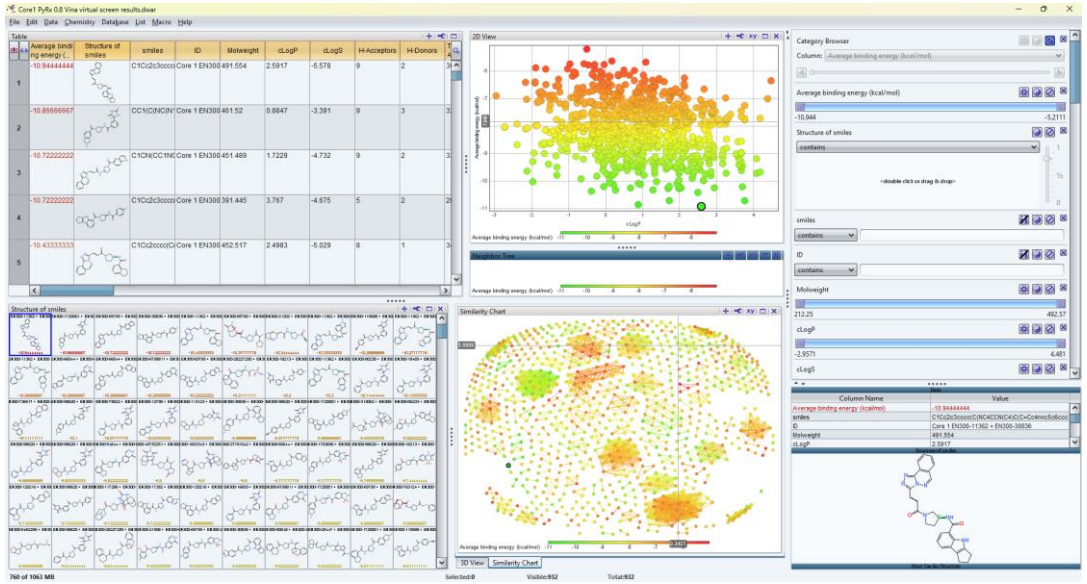


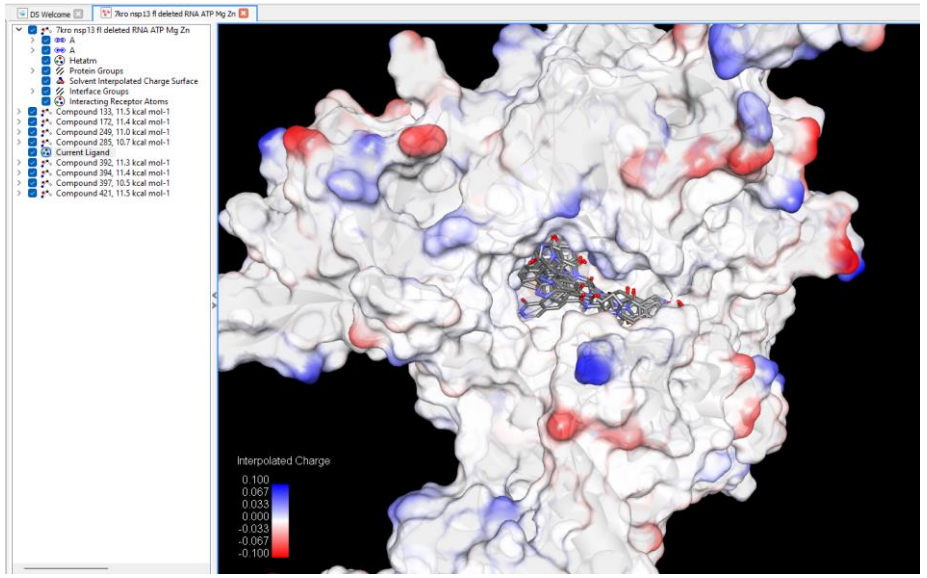


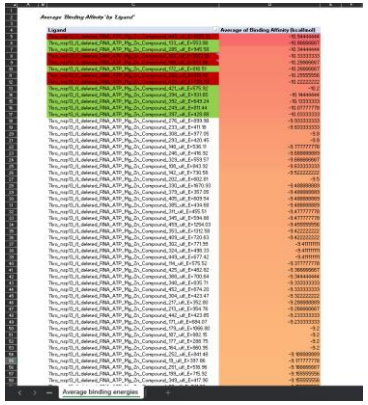
# De-Novo Generated Top 100 Scoring Compounds:
*Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)*

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

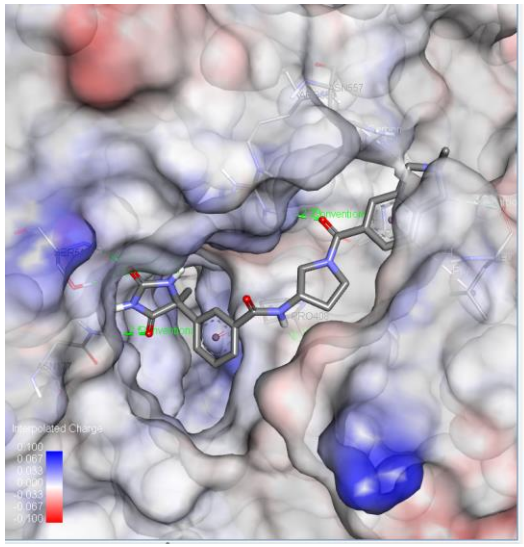


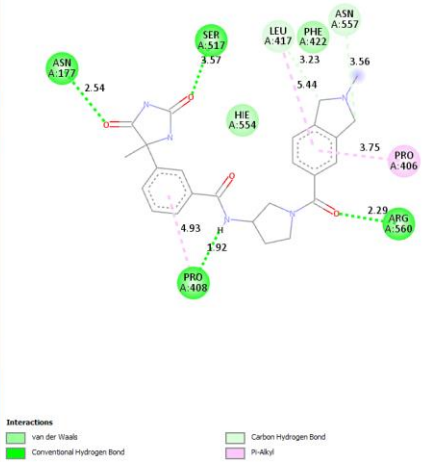
- **Visually inspected** minimum energy poses to validate, eliminating wrong geometries (cis-amides).

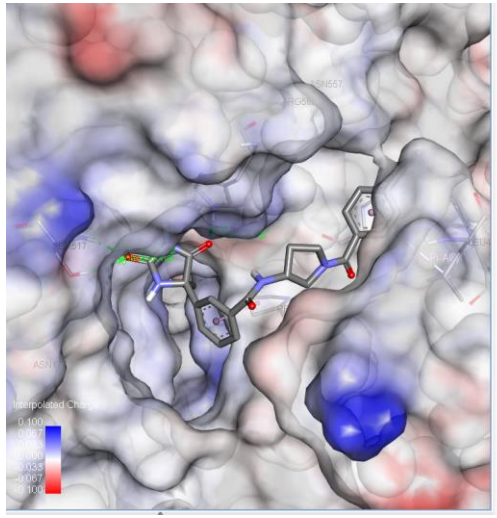


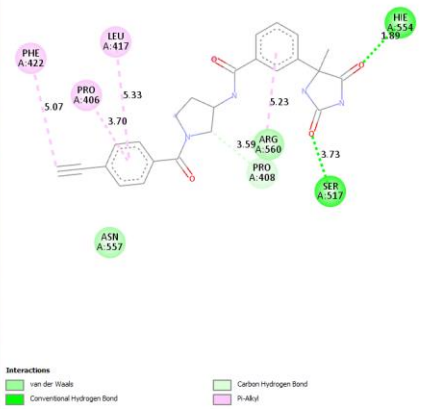



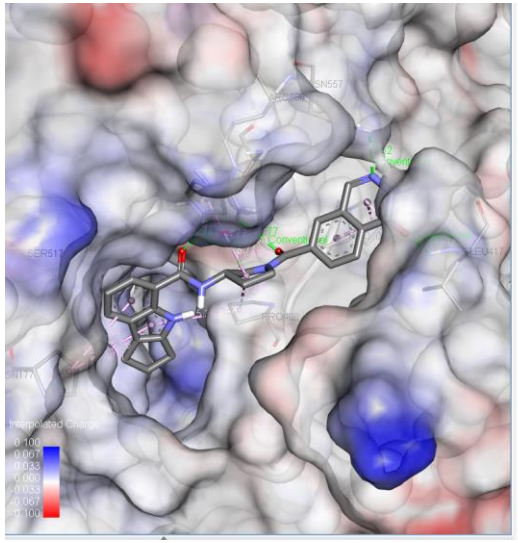
# De-Novo Generated Top 100 Scoring Compounds:
*Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)*

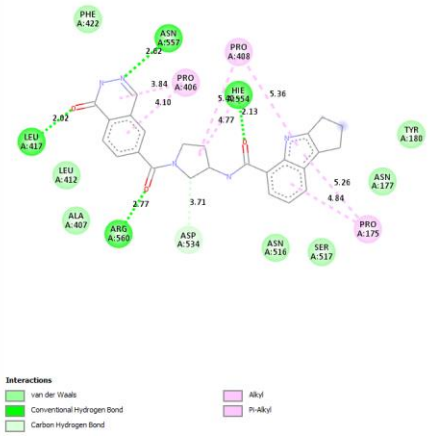


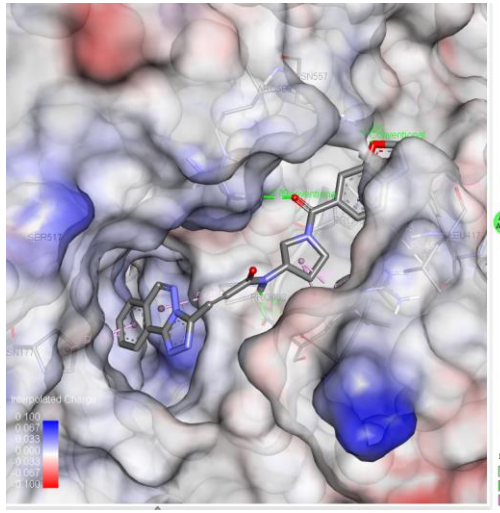


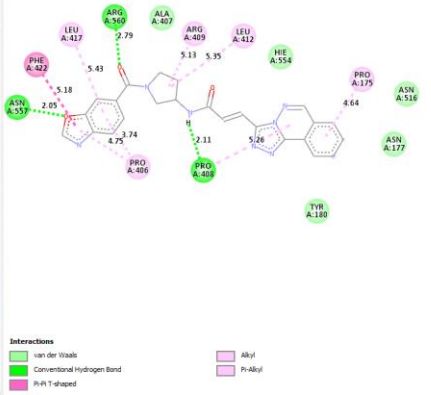





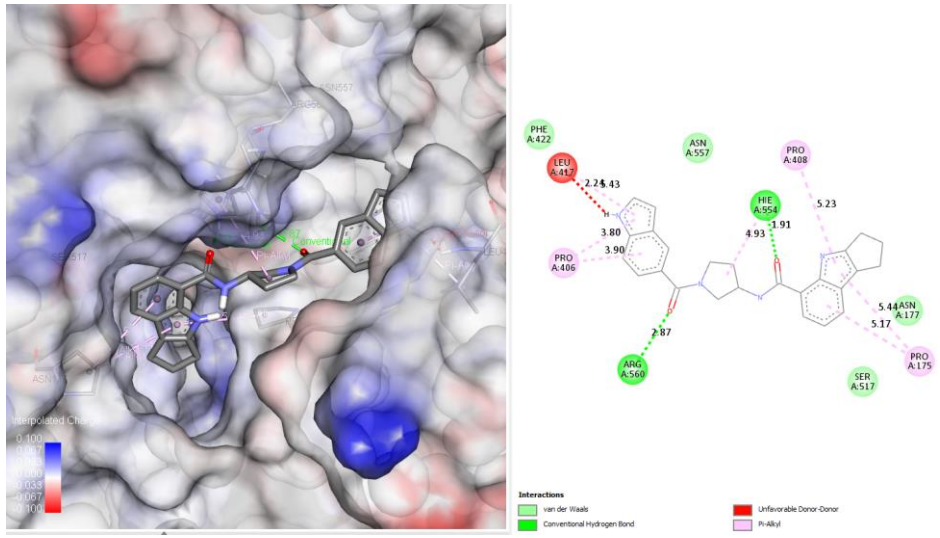



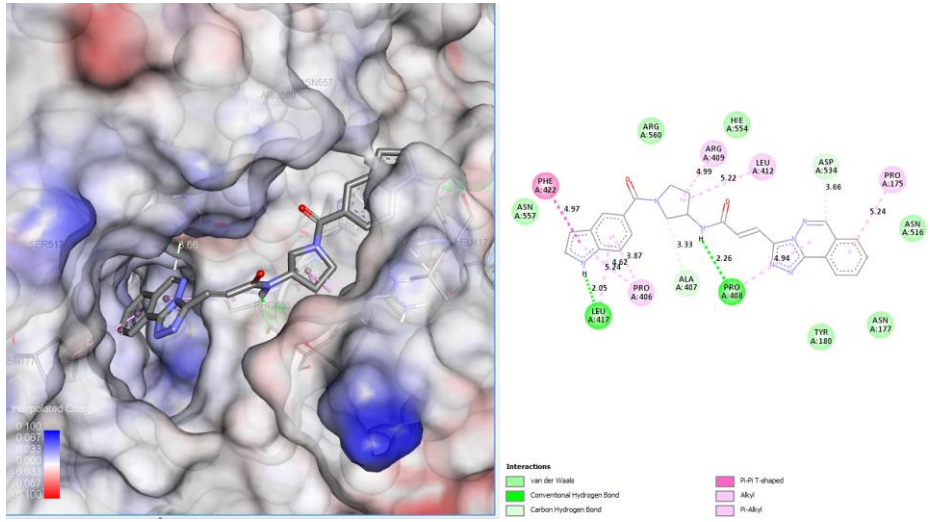


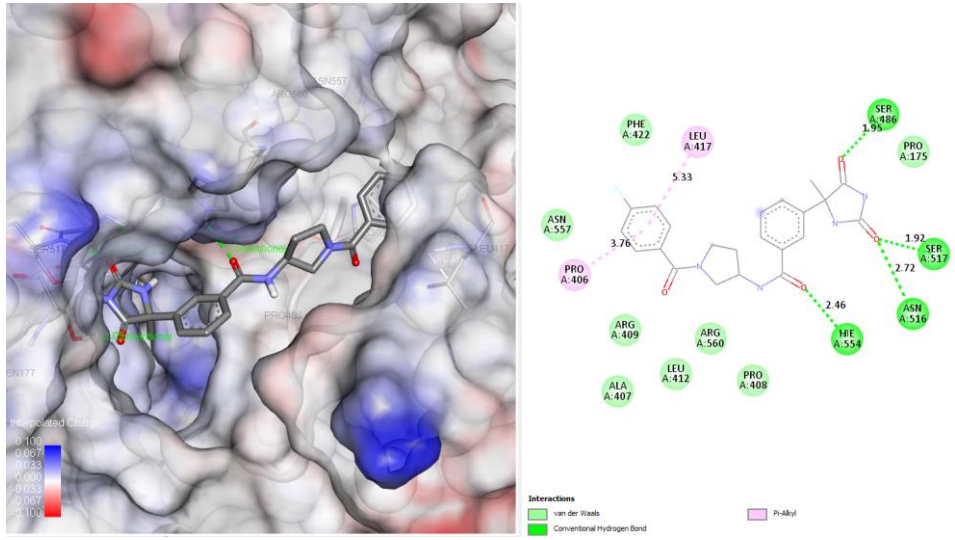



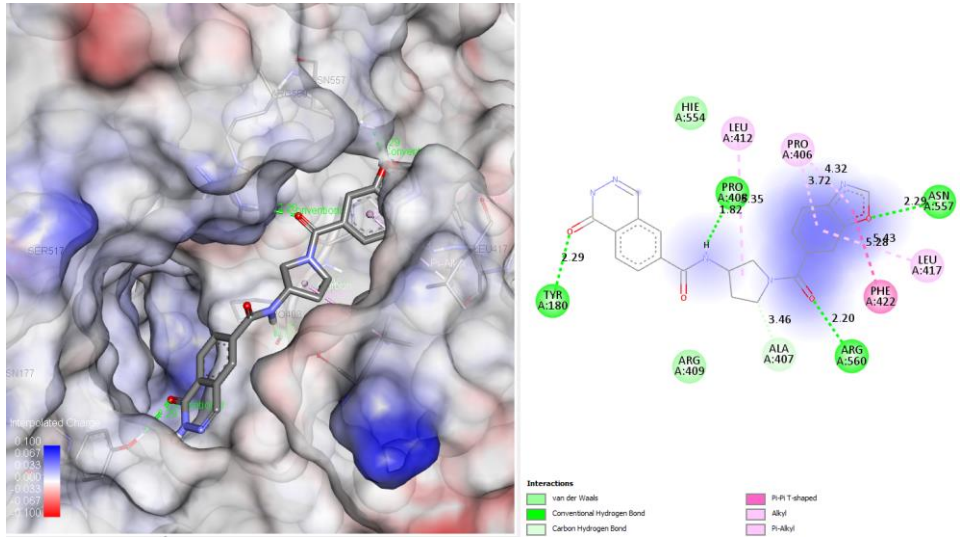


# De-Novo Generated Top 100 Scoring Compounds:
*Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)*



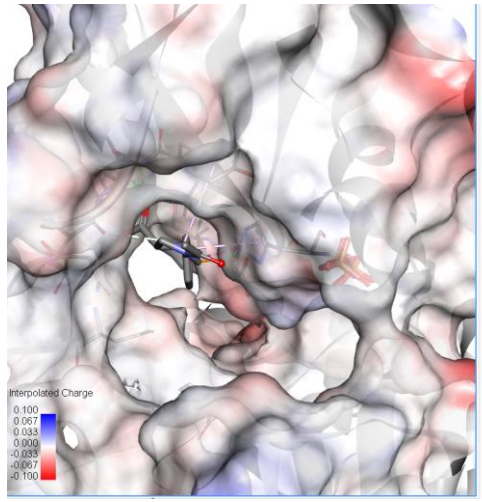



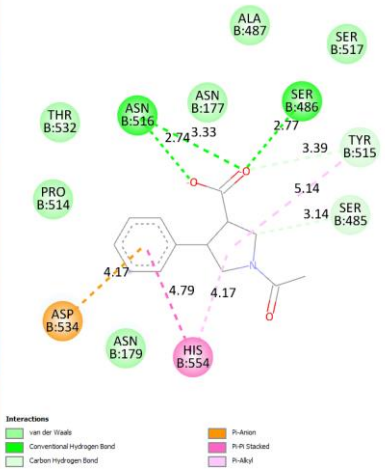



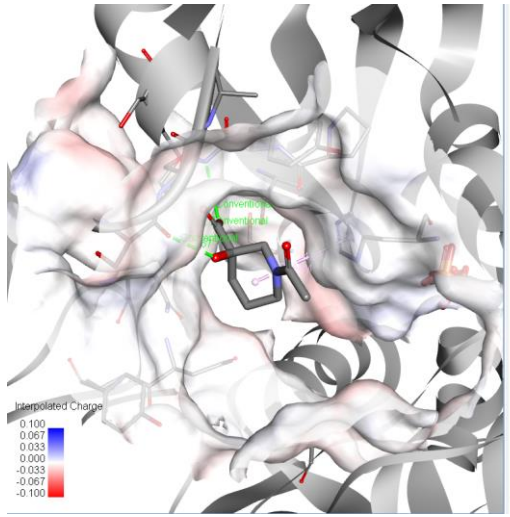



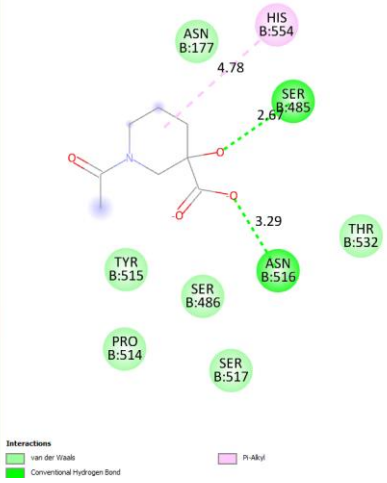
# De-Novo Generated Top 100 Scoring Compounds:
*Virtual Screen with PyRx 0.8 / AutoDock VINA (Core 1)*

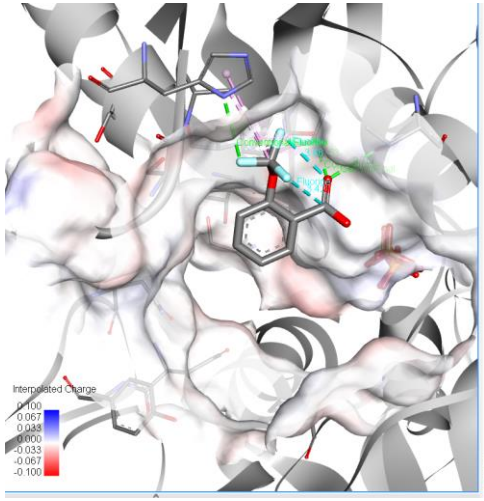
- PANDDA fragment interactions at 5’ RNA site

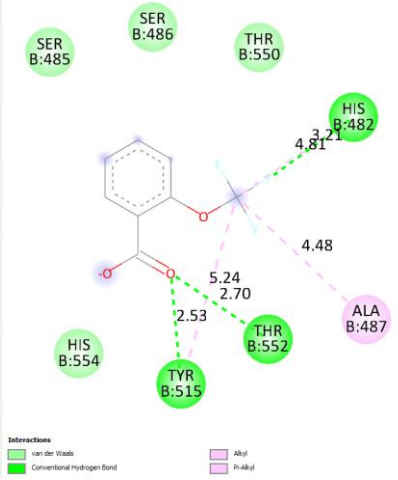


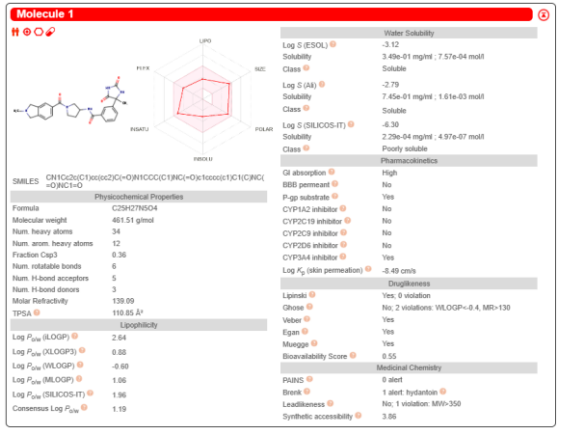



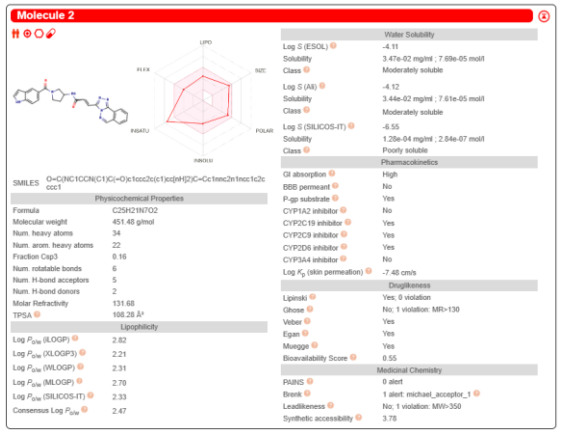



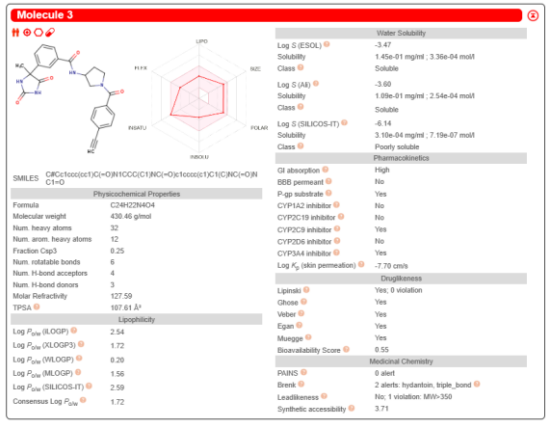



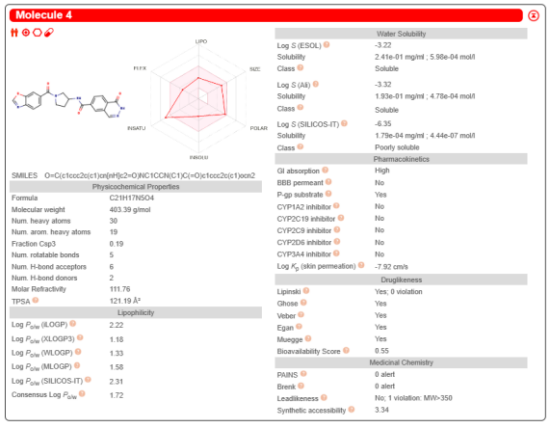
# De-Novo Generated Top 100 Scoring Compounds:
*Core1 compounds*

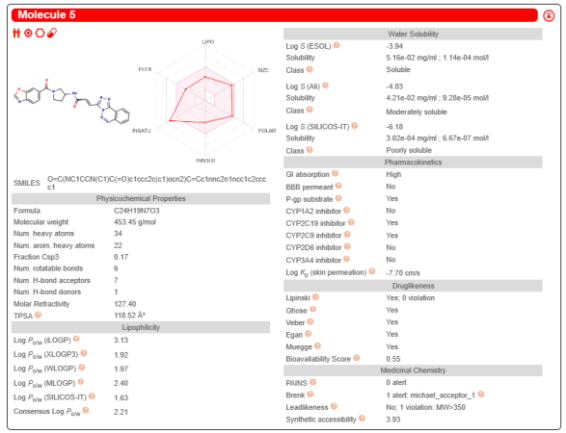
- PAINS filtering (SwissADME) cleared.

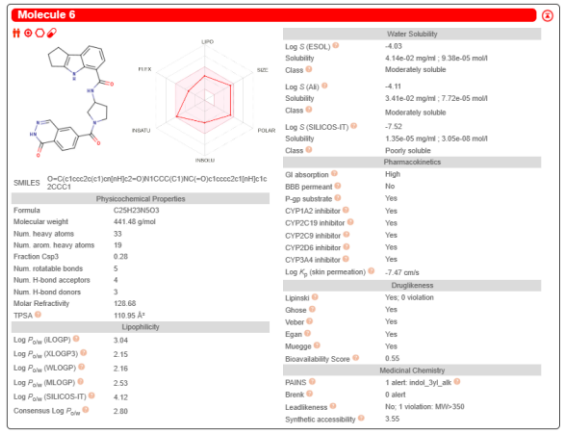


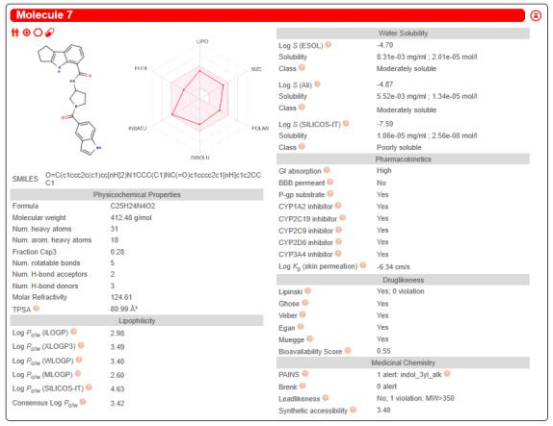



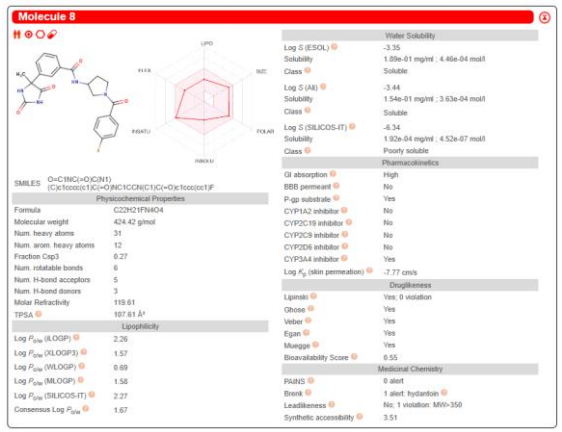



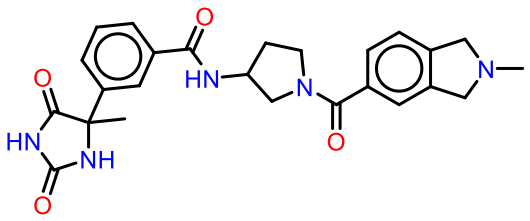



# De-Novo Generated Top 100 Scoring Compounds:
*Core1 compounds*

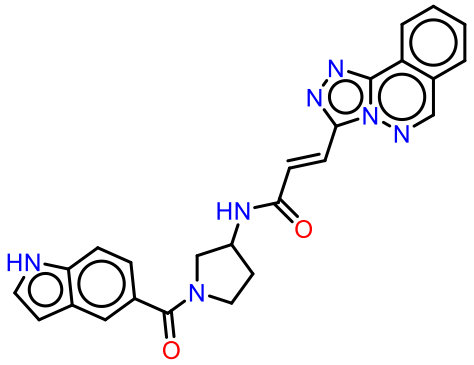
**Compound 133**

Core 1 EN300-1720001 + EN300-98620



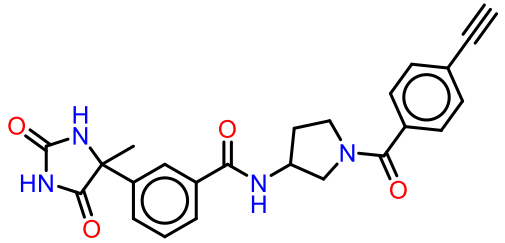
**Compound 285**

Core 1 EN300-69795 + EN300-11362



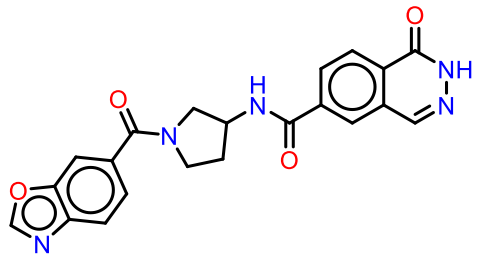
**Compound 172**

Core 1 EN300-115688 + EN300-98620



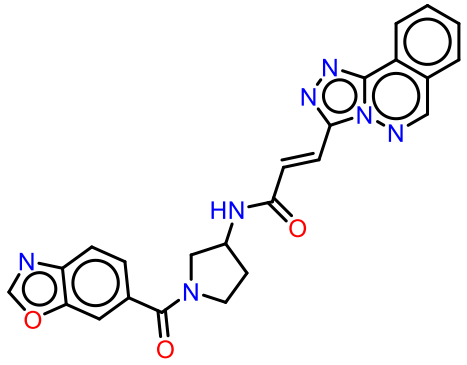
**Compound 421**

Core 1 EN300-66044 + EN300-6758811



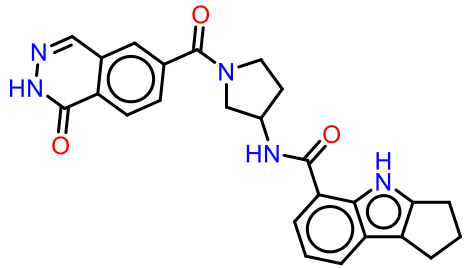
**Compound 394**

Core 1 EN300-66044 + EN300-11362



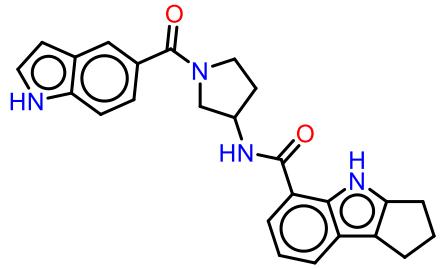
**Compound 392**

Core 1 EN300-6758811 + EN300-30836



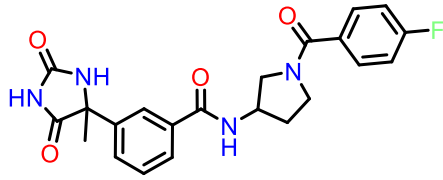
**Compound 249**

Core 1 EN300-69795 + EN300-30836



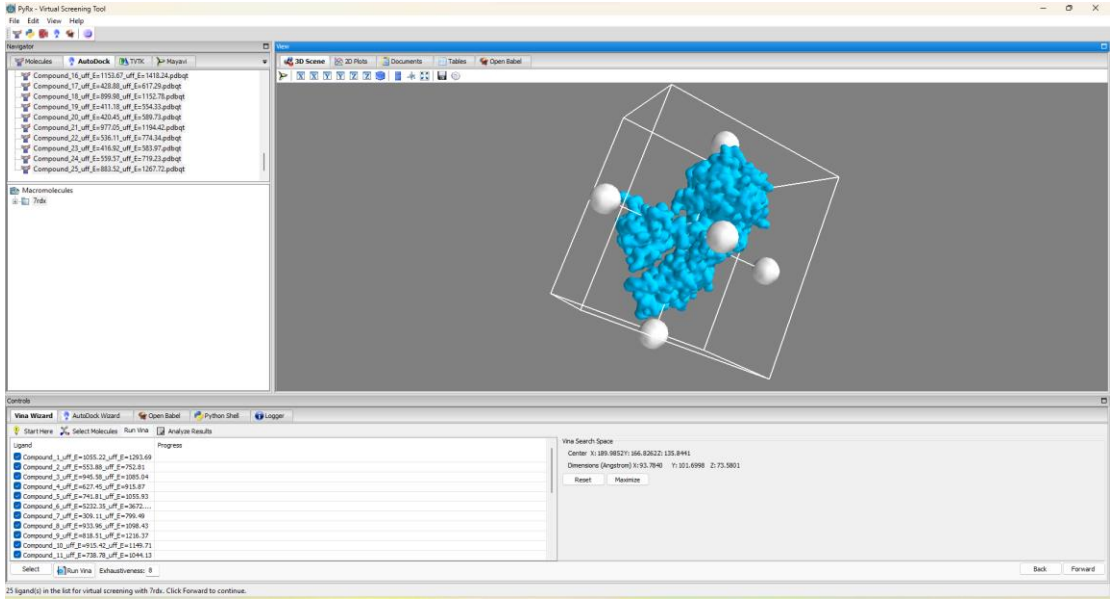
**Compound 397**

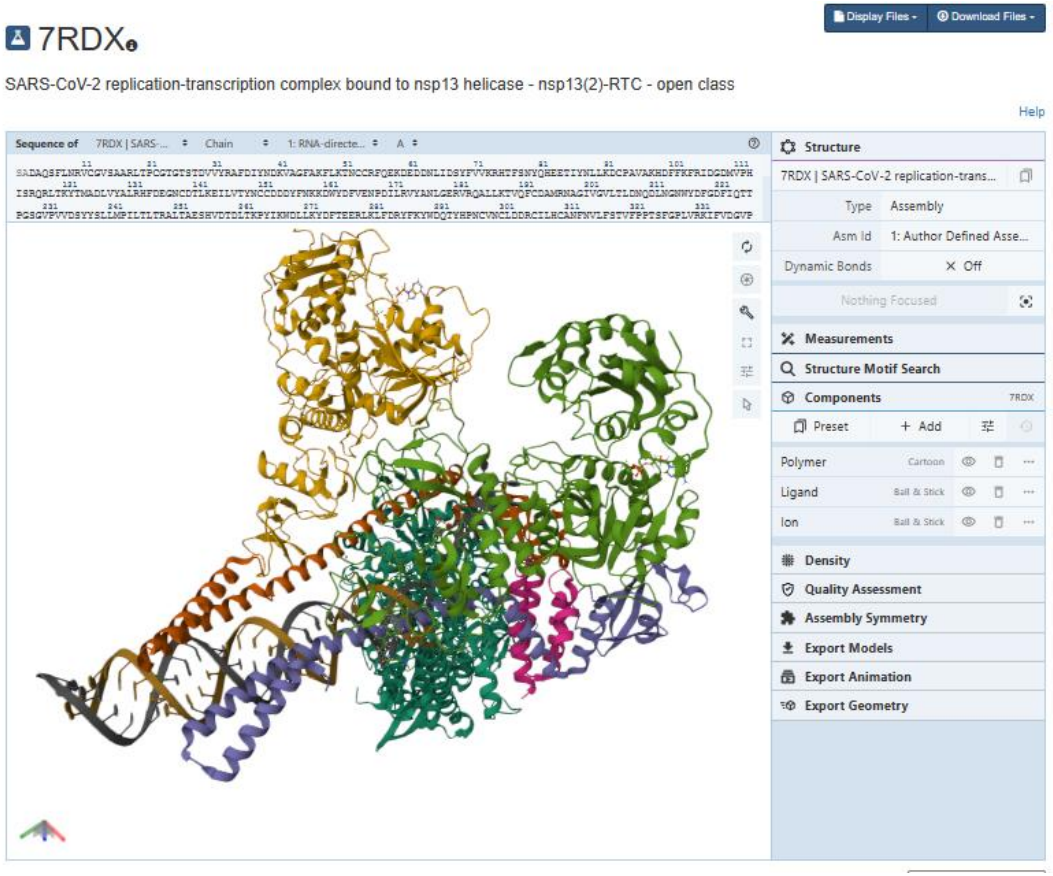
Core 1 EN300-18213 + EN300-98620



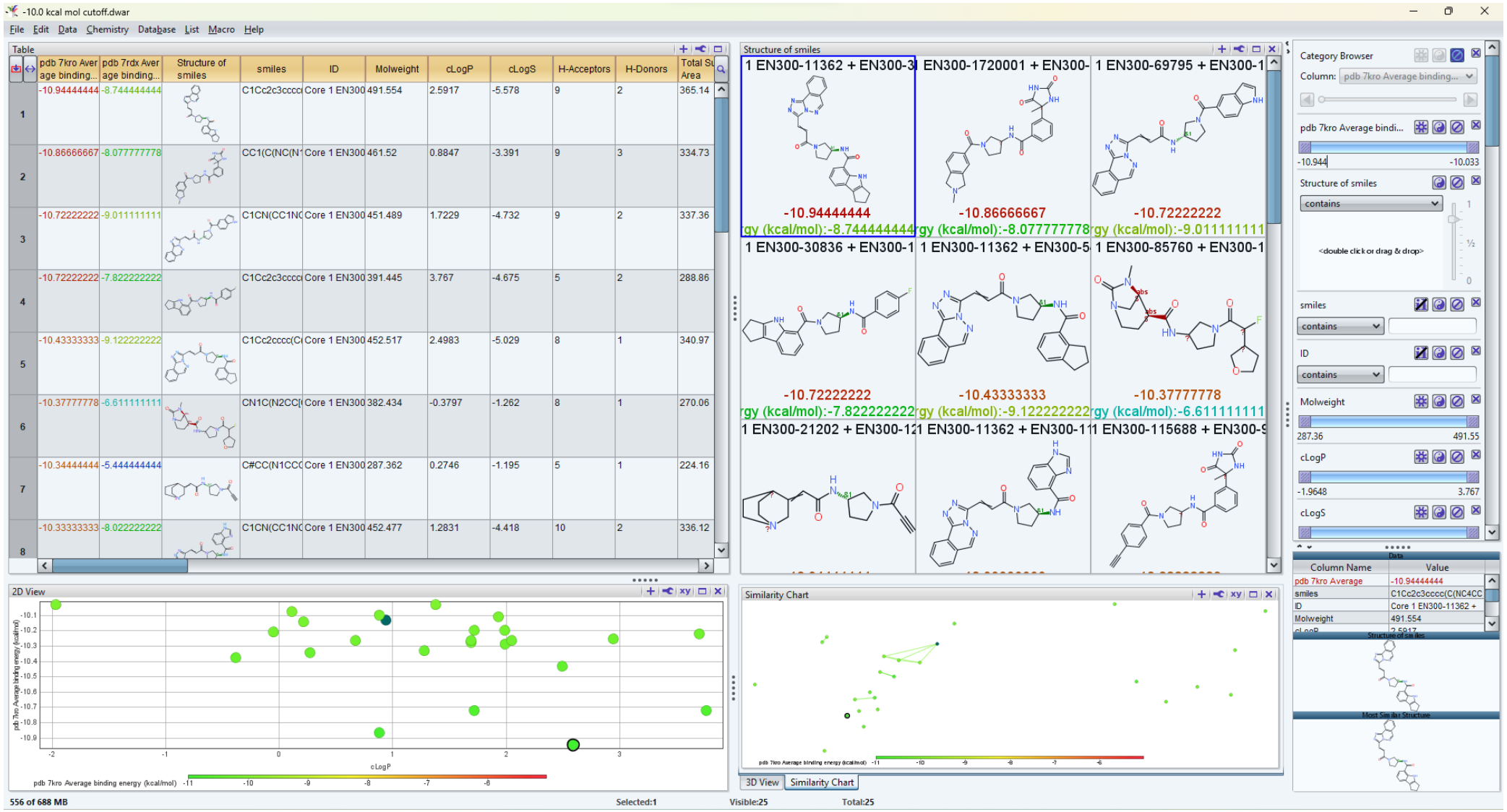
# De-Novo Generated Top 100 Scoring Compounds:
## *Virtual Screen with PyRx 0.8 / AutoDock VINA*

- 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.





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



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