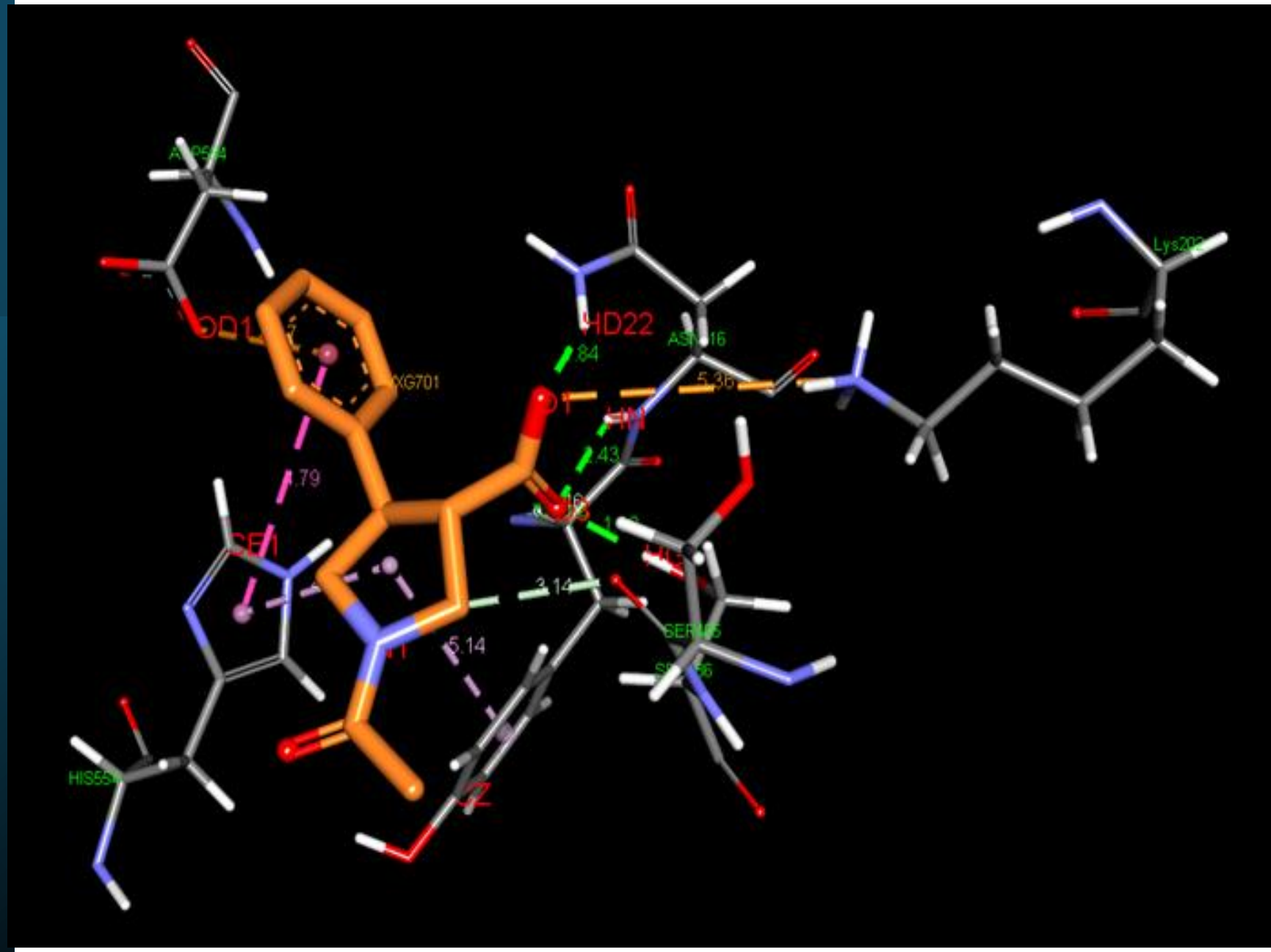
SARS-CoV-2 Nsp13 5’ RNA Site

pdb ID 5RMM fragment growing approach

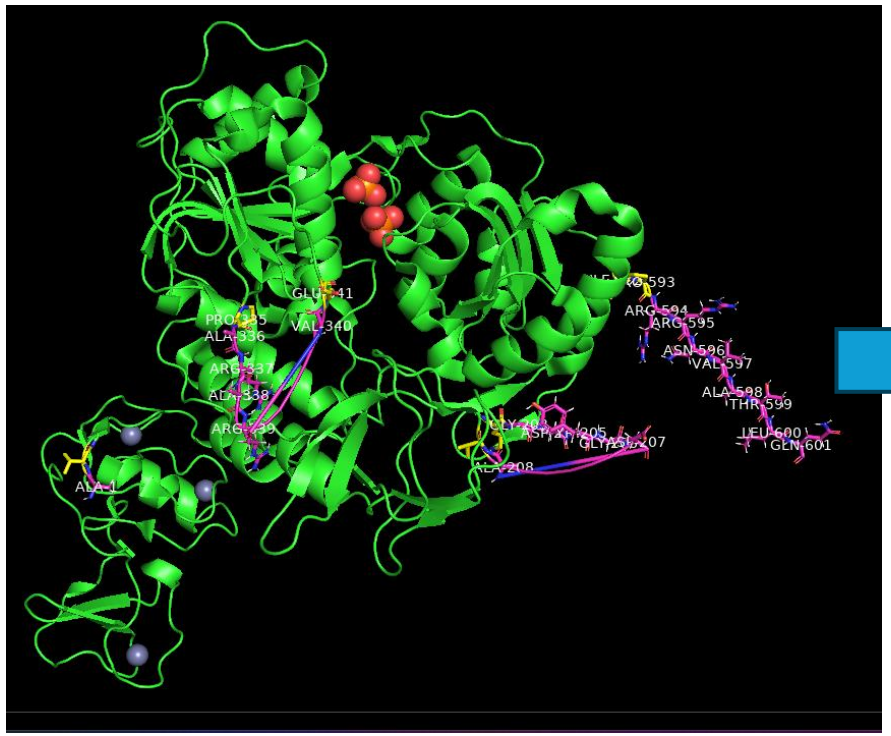
fragment-based combinatorial (SNAr) library and virtual screening

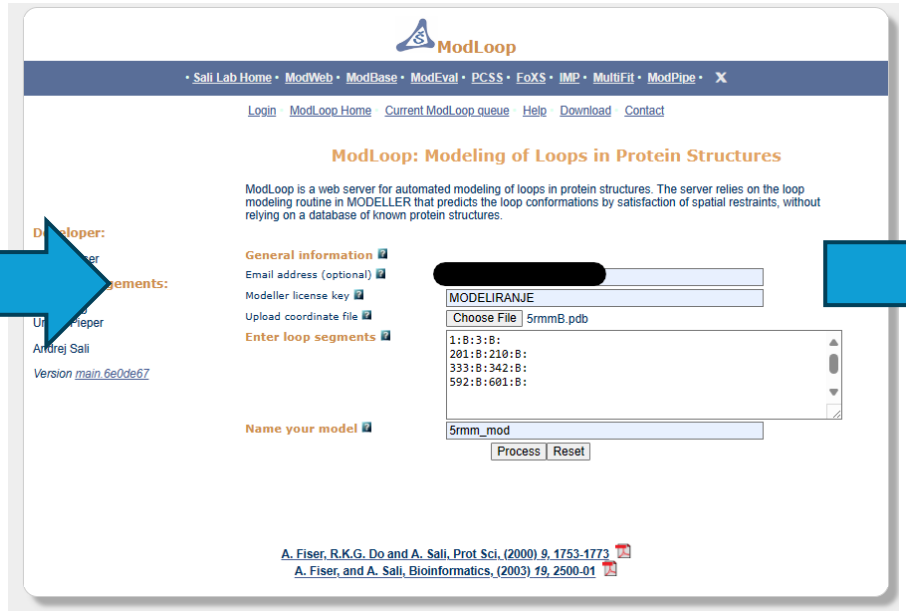
confirm by ligand-observed 19F NMR

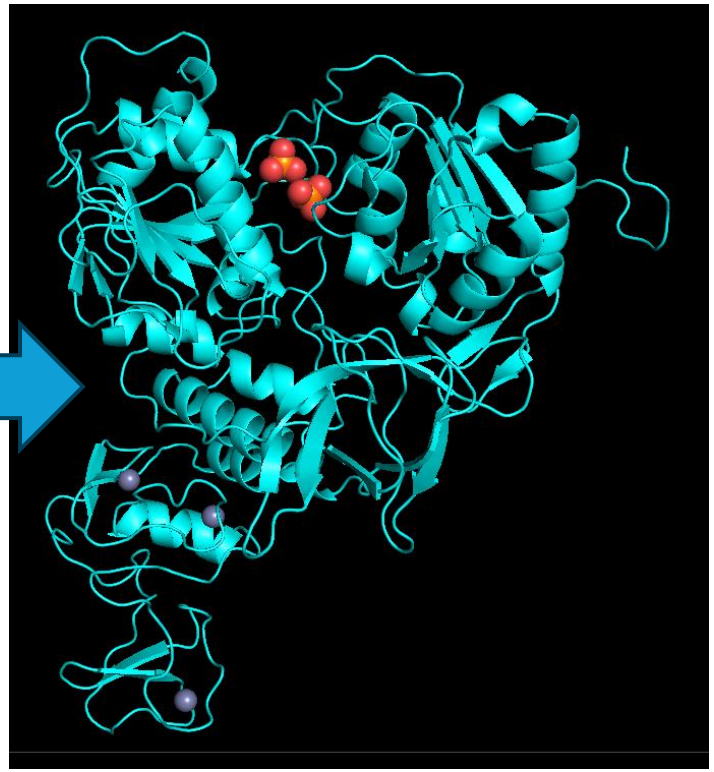


1. PDB 5RMM Missing Residues Added in ModLoop / PyMol

- Used the original protein crystal structure of the positive control compound (PDB ID 5RMM) for the virtual screen, having filled in the missing residues/loops using modelling software.





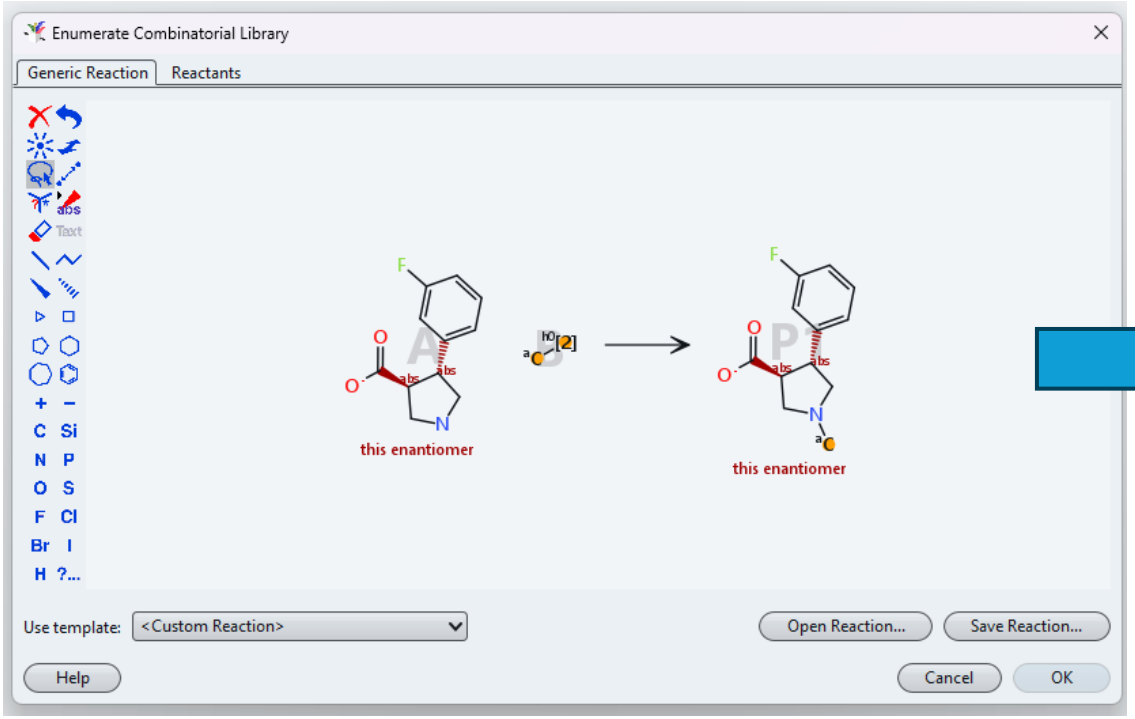


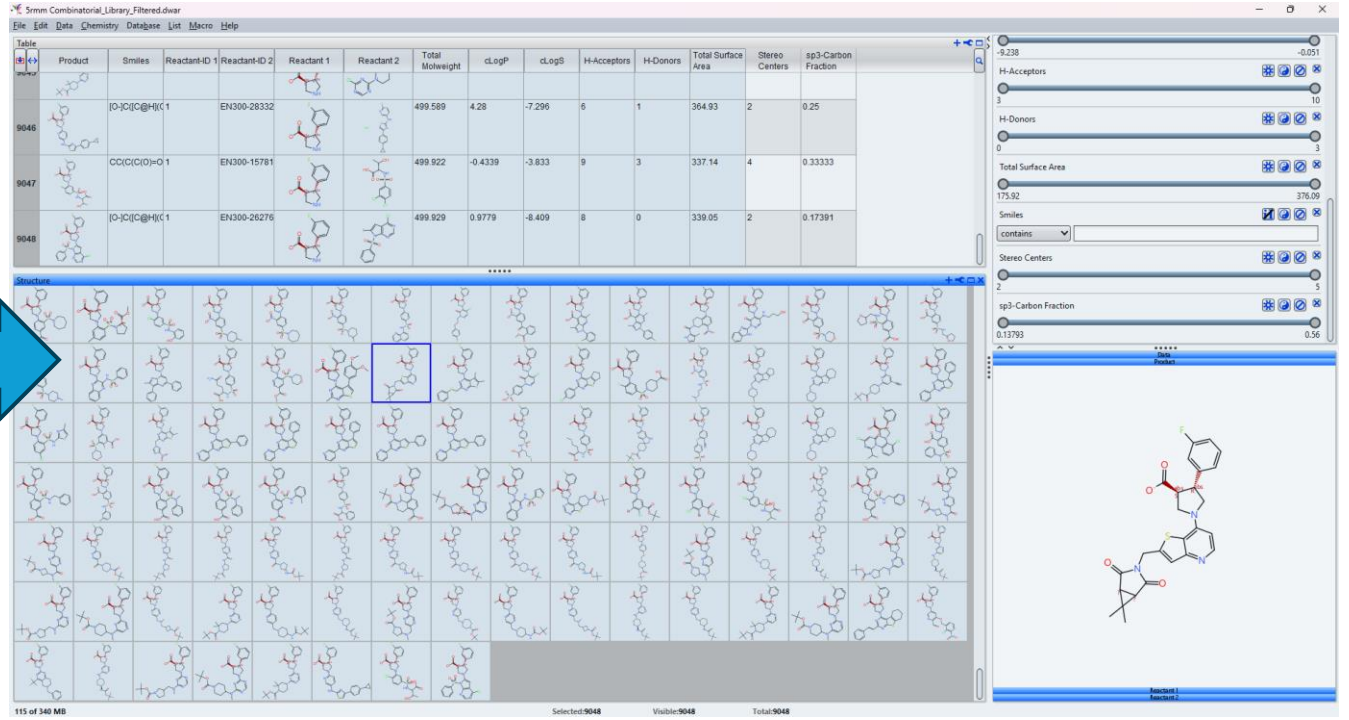
2. Generate SNAr Combinatorial Library in DataWarrior:

Enamine_Aryl_halides_SN_**10882cmps**_20240305

- Created an amine vector-based combinatorial library based on the fluorinated analogue of pdb ID 5RMM and the SNAr building block library (10’882 compounds) from Enamine using DataWarrior.

- 9048 novel compounds remained after applying Lipinski filters.





3. Using Gypsum-DL for preparing small-molecule libraries for structure-based virtual screening

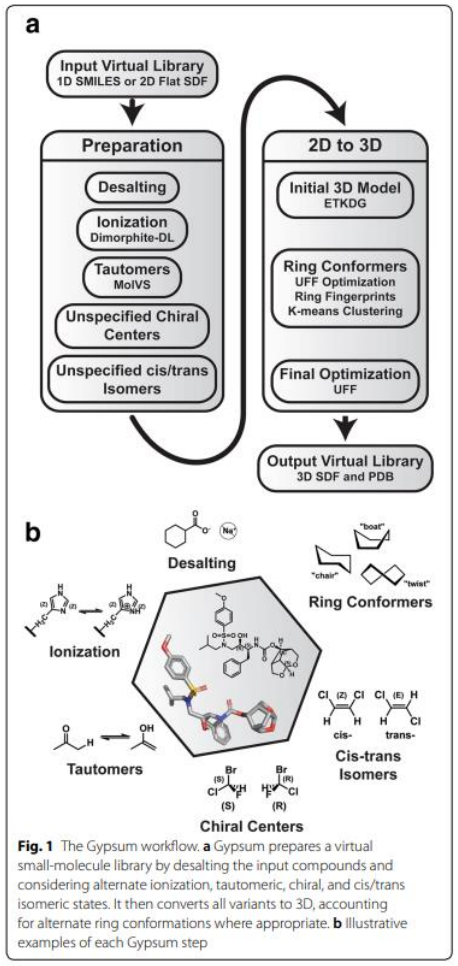
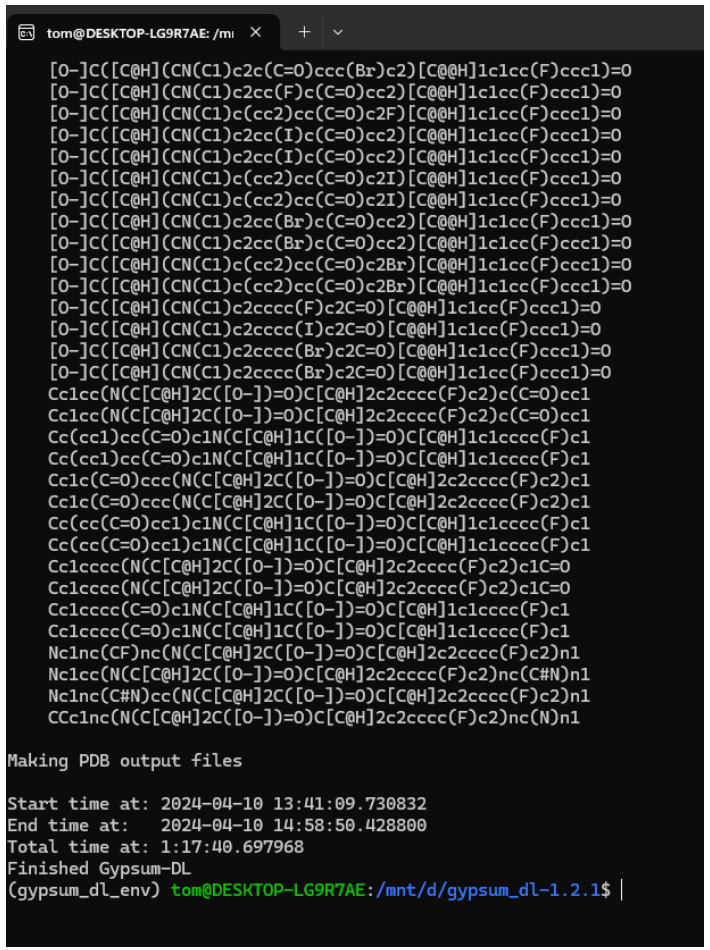
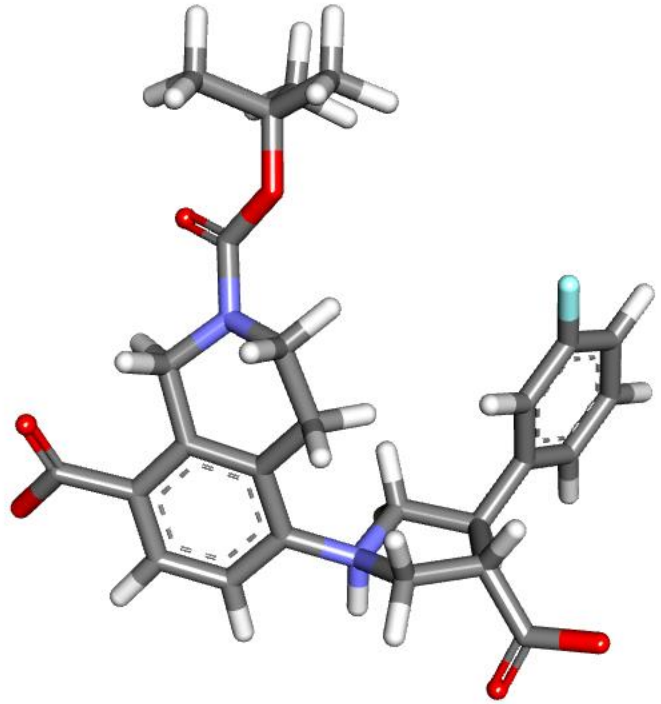


Fig. 1 The Gypsum workflow. **a** Gypsum prepares a virtual small-molecule library by desalting the input compounds and considering alternate ionization, tautomeric, chiral, and cis/trans isomeric states. It then converts all variants to 3D, accounting for alternate ring conformations where appropriate. **b** Illustrative examples of each Gypsum step



Gypsum allows a tunable number of enantiomers, E/Z regioisomers, tautomers, epimerizable centers, and ring conformations and accounts for pH and salts.



Limited Gypsum to 1 model selected per molecule for the initial virtual screen (9000+ compounds).

Ropp et al. J Cheminform (2019) 11:34 https://doi.org/10.1186/s13321-019-0358-3

4. Virtual screen with AutoDock Vina v1.2.3 in Batch Mode (WSL)

- Created a custom Perl script for running Vina in serial batch mode (WSL).

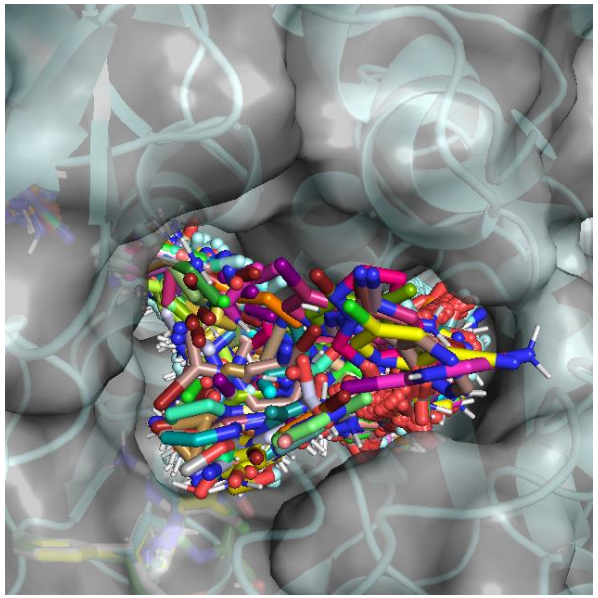
```
File  Edit  Selection  View  Go  Run  Terminal  Help
Restricted Mode is intended for safe code browsing. Trust this window to enable all features.  Manage  Learn More
Untitled-1  5rmm_filters.json  5rmm_snar_conf.txt  vina_vs.pl
D: > 5RMM_VS > vina_vs.pl
$SIG{INT} = \&sigint_handler;

# Prompt user to input directory containing ligand files
print "Enter the directory pathway containing the ligand .pdbqt files: ";
my $ligand_dir = <STDIN>;
chomp $ligand_dir;

# Retrieve list of ligand filenames in the directory
opendir(my $DH, $ligand_dir) or die "Cannot open directory $ligand_dir: $!";
my @ligand_files = grep { /\.pdbqt$/ } readdir($DH);
closedir($DH);

# Directory for log files
my $log_directory = "docked_lig_log_files";

# Create directory if it doesn't exist
unless (-d $log_directory) {
    make_path($log_directory) or die "Error creating directory $log_directory: $!";
}

# Prompt user for AutoDock Vina parameters
print "\nEnter the receptor filename (including extension): ";
my $receptor_file = <STDIN>;
chomp $receptor_file;

print "Enter the output filename for docking results (including extension): ";
my $output_file = <STDIN>;
chomp $output_file;

print "\nEnter the coordinates of the center of the search space (X Y Z): ";
my ($center_x, $center_y, $center_z) = split ' ', <STDIN>;
chomp($center_x, $center_y, $center_z);

print "Enter the size of the search space (X Y Z): ";
my ($size_x, $size_y, $size_z) = split ' ', <STDIN>;
chomp($size_x, $size_y, $size_z);

print "Enter the number of output poses per ligand: ";
my $num_modes = <STDIN>;
chomp $num_modes;

print "Enter the energy range for the search: ";
my $energy_range = <STDIN>;
chomp $energy_range;

print "Enter the exhaustiveness (amount of computational effort used during a docking experiment): ";
my $exhaustiveness = <STDIN>;
chomp $exhaustiveness;

# Number of CPUs to use
my $num_cpus = 8;

# Open results file for writing
open my $RESULTS, '>', "vinaresults_log.txt" or die "Cannot create vinaresults_log.txt: $!";
```

- Vina running in serial batch mode in WSL (~48 h).

```
(base) tom@DESKTOP-LG9R7AE:~$ cd /mnt/d/5RMM_VS
(base) tom@DESKTOP-LG9R7AE:/mnt/d/5RMM_VS$ perl vina_vs.pl
Enter the directory pathway containing the ligand .pdbqt files: 9125_snar_ligands

Enter the receptor filename (including extension): 5rmm_mod.pdbqt
Enter the output filename for docking results (including extension): vinaresults_log.txt

Enter the coordinates of the center of the search space (X Y Z): -30.601 14.036 -23.796
Enter the size of the search space (X Y Z): 40 40 40
Enter the number of output poses per ligand: 1
Enter the energy range for the search: 3
Enter the exhaustiveness (amount of computational effort used during a docking experiment): 8
Running Vina for untitled_line_1000__input1000__variant1...
Running Vina for untitled_line_1001__input1001__variant1...
Running Vina for untitled_line_1002__input1002__variant1...
Running Vina for untitled_line_1003__input1003__variant1...
Running Vina for untitled_line_1004__input1004__variant1...
Running Vina for untitled_line_1005__input1005__variant1...
Running Vina for untitled_line_1006__input1006__variant1...
Running Vina for untitled_line_1007__input1007__variant1...
Running Vina for untitled_line_1008__input1008__variant1...
Running Vina for untitled_line_1009__input1009__variant1...
Running Vina for untitled_line_100__input100__variant1...
Running Vina for untitled_line_1010__input1010__variant1...
Running Vina for untitled_line_1011__input1011__variant1...
Running Vina for untitled_line_1012__input1012__variant1...
Running Vina for untitled_line_1013__input1013__variant1...
Running Vina for untitled_line_1014__input1014__variant1...
Running Vina for untitled_line_1015__input1015__variant1...
Running Vina for untitled_line_1016__input1016__variant1...
Running Vina for untitled_line_1017__input1017__variant1...
Running Vina for untitled_line_1018__input1018__variant1...
Running Vina for untitled_line_1019__input1019__variant1...
Running Vina for untitled_line_101__input101__variant1...
Running Vina for untitled_line_1020__input1020__variant1...
Running Vina for untitled_line_1021__input1021__variant1...
Running Vina for untitled_line_1022__input1022__variant1...
Running Vina for untitled_line_1023__input1023__variant1...
Running Vina for untitled_line_1024__input1024__variant1...
Running Vina for untitled_line_1025__input1025__variant1...
Running Vina for untitled_line_1026__input1026__variant1...
Running Vina for untitled_line_1027__input1027__variant1...
Running Vina for untitled_line_1028__input1028__variant1...
Running Vina for untitled_line_1029__input1029__variant1...
Running Vina for untitled_line_102__input102__variant1...
Running Vina for untitled_line_1030__input1030__variant1...
Running Vina for untitled_line_1031__input1031__variant1...
Running Vina for untitled_line_1032__input1032__variant1...
Running Vina for untitled_line_1033__input1033__variant1...
Running Vina for untitled_line_1034__input1034__variant1...
Running Vina for untitled_line_1035__input1035__variant1...
```

- 9048 docking poses generated (1 top-scoring pose per ligand).

```
AutoDock Vina v1.2.3
###################################################################
# If you used AutoDock Vina in your work, please cite:          #
#                                                                 #
# J. Eberhardt, D. Santos-Martins, A. F. Tillack, and S. Forli  #
# AutoDock Vina 1.2.0: New Docking Methods, Expanded Force      #
# Field, and Python Bindings, J. Chem. Inf. Model. (2021)       #
# DOI 10.1021/acs.jcim.1c00203                                  #
#                                                                 #
# O. Trott, A. J. Olson,                                        #
# AutoDock Vina: improving the speed and accuracy of docking    #
# with a new scoring function, efficient optimization and       #
# multithreading, J. Comp. Chem. (2010)                         #
# DOI 10.1002/jcc.21334                                         #
#                                                                 #
# Please see https://github.com/ccsb-scripps/AutoDock-Vina for  #
# more information.                                             #
###################################################################

oring function : vina
gid receptor: 5rmm_mod.pdbqt
Ligand: 9125_snar_ligands/untitled_line_1879__input1879__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size   : X 40 Y 40 Z 40
Grid space  : 0.375
Exhaustiveness: 8
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1597215380) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1         -7.4         0          0
```

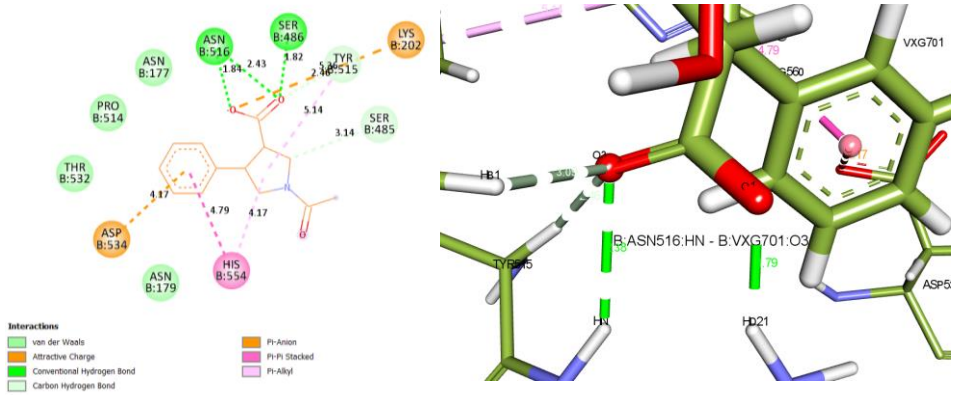


AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings

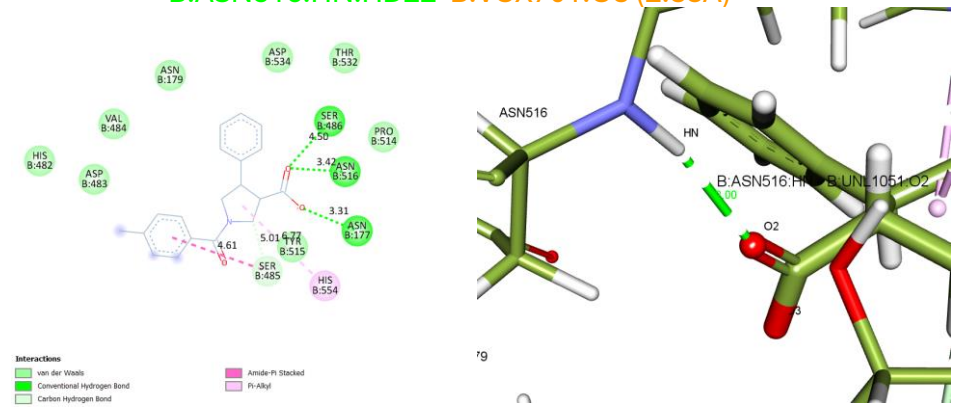
. Chem. Inf. Model. 2021, 61, 8, 3891–3898

5. Pose Filtration using LigGrep

- Identified key residue/ligand interactions in crystal structures of PDB 5rmm + analogue (unpublished).



B:ASN516:HN:HD22 B:VGX701:O3 (2.38A)



B:ASN516:HN:HD22 B:UNL1051:O2 (2.00 A)

- Ligand carboxylate O---HN bond with ASN516 is conserved in two 5RMM analogues.
- Interaction believed to be conserved with fluorinated analogue.

- Created .JSON filter file specifying only poses where ligand ‘O’ atom is with 3.0 Angstroms of ‘HD22’.

Receptor atom name from .pdbqt file

```
[
    {
        "receptorAtom": {
            "chain": "B",
            "resid": 516,
            "atomname": "HD22"
        },
        "ligandSubstructSMARTS": "[#8]",
        "distance": 3.0
    }
]
```

Distance cutoff = 3.0 Angstroms

‘O atom’ SMARTS = [#8]

5i. Pose Filtration using LigGrep

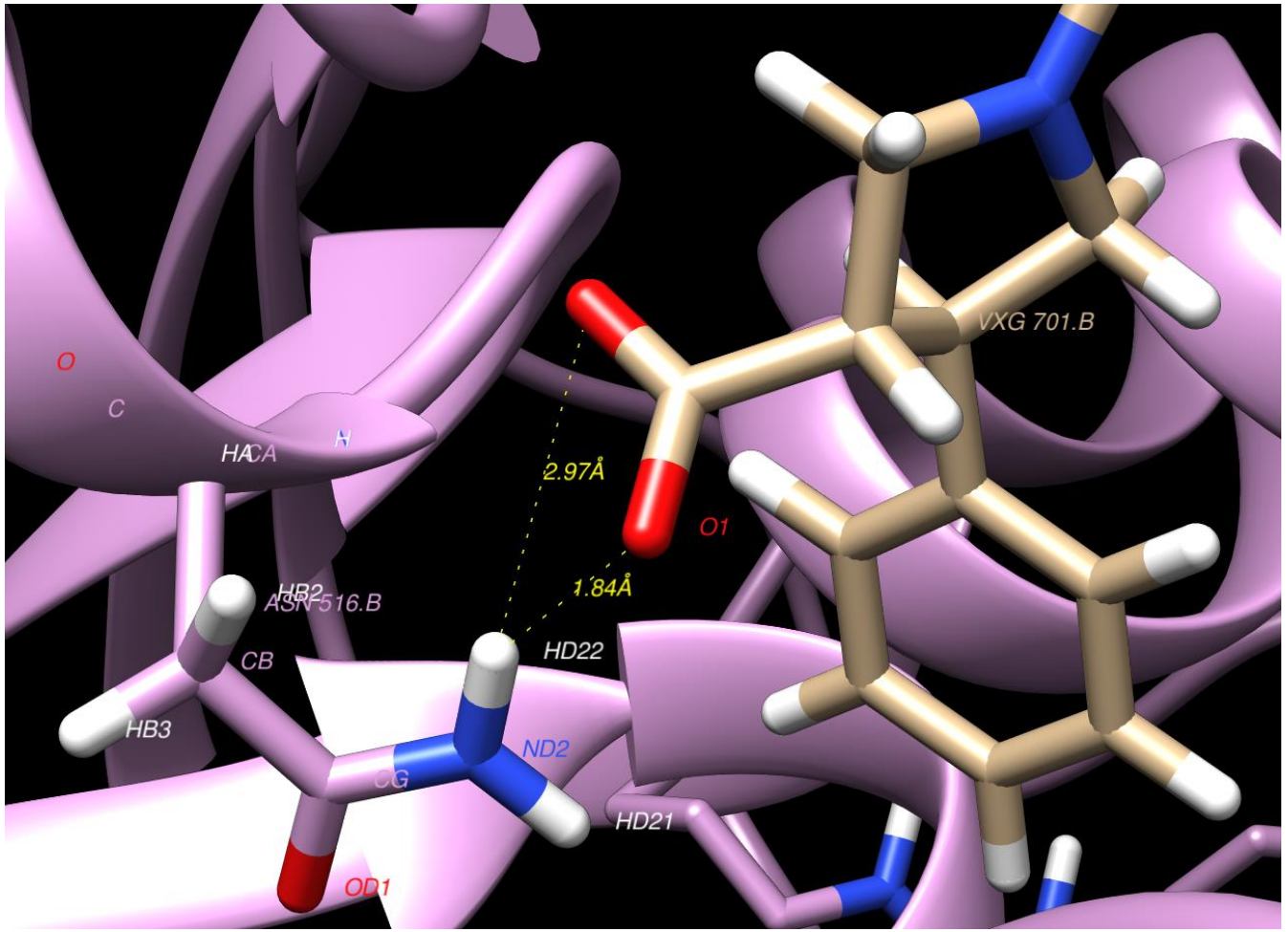
- Run a positive control first to check that crystal pose (pdb ID 5rmm) satisfies the .json filters:

Ligand = VGX.pdbqt

Receptor = 5rmm_mod.pdbqt

Result: ***Molecule VGX.pdbqt (pose 1) passes all filters.***

```
(Project_env) (base) tom@DESKTOP-LG9R7AE:/mnt/d/liggrep_project/project_env_1/liggrep$ python3 liggrep.p
y /mnt/d/5RMM_VS/5rmm_mod.pdbqt /mnt/d/5RMM_VS/docked_ligands/*.pdbqt /mnt/d/liggrep_project/5rmmJSO
N.json -m NONE --num_processors 1 --job_manager multiprocessing --verbose

PARAMETERS:

{
    "receptor": "/mnt/d/5RMM_VS/5rmm_mod.pdbqt",
    "ligands": "/mnt/d/5RMM_VS/docked_ligands/VGX.pdbqt",
    "filters": "/mnt/d/liggrep_project/5rmmJSON.json",
    "mode": "NONE",
    "babel_exec": null,
    "file": "output.txt",
    "verbose": true,
    "num_processors": 1,
    "job_manager": "multiprocessing",
    "test": false,
    "internal_test": false
}


MESSAGE: Molecule VGX.pdbqt (pose 1) passes all filters.

Output saved to "output.txt"
```



Ha et al. J Cheminform (2020) 12:69 https://doi.org/10.1186/s13321-020-00471-2

5ii. Pose Filtration using LigGrep

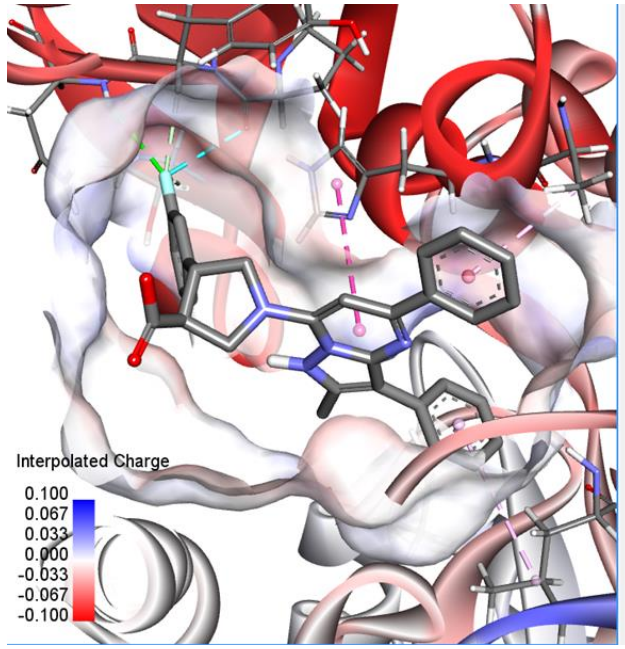
- **Then run a negative control to confirm filters work (e.g. good scoring ligand with wrong pose):**

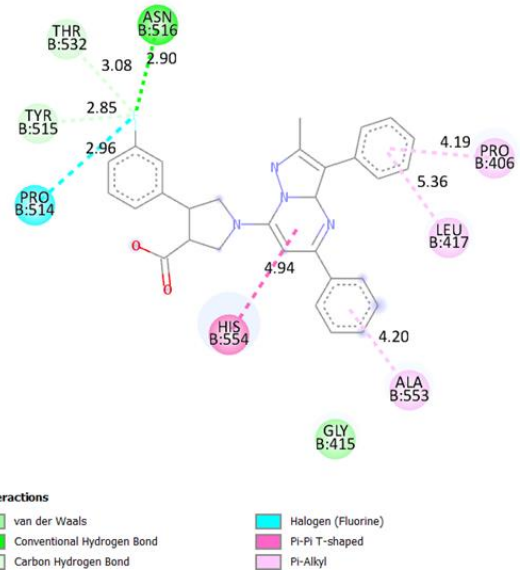
Ligand = untitled_line_9126__input9126__variant1_minvina_-9.843kcal_mol.pdbqt

Receptor = 5rmm_mod.pdbqt

Result = ***WARNING: Molecule "untitled_line_9126__input9126__variant1.pdbqt" (pose 1) has substructure "[#8]" more than 3.0 Å from the filter query point.***

```
This message is shown once a day. To disable it please create the
/home/tom/.hushlogin file.
(base) tom@DESKTOP-LG9R7AE:~$ cd /mnt/d/liggrep
(base) tom@DESKTOP-LG9R7AE:/mnt/d/liggrep$ cd environment
(base) tom@DESKTOP-LG9R7AE:/mnt/d/liggrep/environment$ source bin/activate
(Project_env) (base) tom@DESKTOP-LG9R7AE:/mnt/d/liggrep/environment/liggrep$ python3 liggrep.py /mnt/d/5RMM_VS/5rmm_mod.pdbqt /mnt/d/5RMM_VS/9125_snar_ligands/untitled_line_9126__input9126__variant1.pdbqt/mnt/
d/liggrep/5rmmJSON.json -m NONE --num_processors 1 --job_manager multiprocessing --verbose
usage: liggrep.py [-h] [-m MODE] [-o BABEL_EXEC] [-f FILE] [-v] [--num_processors N] [--job_manager {serial,multiprocessing,mpi}] [-t] [-i] receptor ligands filters
liggrep.py: error: the following arguments are required: filters
(Project_env) (base) tom@DESKTOP-LG9R7AE:/mnt/d/liggrep/environment/liggrep$ python3 liggrep.py -m NONE --verbose --num_processors 1 --job_manager multiprocessing /mnt/d/5RMM_VS/5rmm_mod.pdbqt /mnt/d/5RMM_VS/9
125_snar_ligands/untitled_line_9126__input9126__variant1.pdbqt /mnt/d/liggrep/5rmmJSON.json

PARAMETERS:

{
    "receptor": "/mnt/d/5RMM_VS/5rmm_mod.pdbqt",
    "ligands": "/mnt/d/5RMM_VS/9125_snar_ligands/untitled_line_9126__input9126__variant1.pdbqt",
    "filters": "/mnt/d/liggrep/5rmmJSON.json",
    "mode": "NONE",
    "babel_exec": null,
    "file": "output.txt",
    "verbose": true,
    "num_processors": 1,
    "job_manager": "multiprocessing",
    "test": false,
    "internal_test": false
}


WARNING: Molecule "untitled_line_9126__input9126__variant1.pdbqt" (pose 1) has substructure "[#8]" more than 3.0 Å from the filter query point.

Output saved to "output.txt"
```

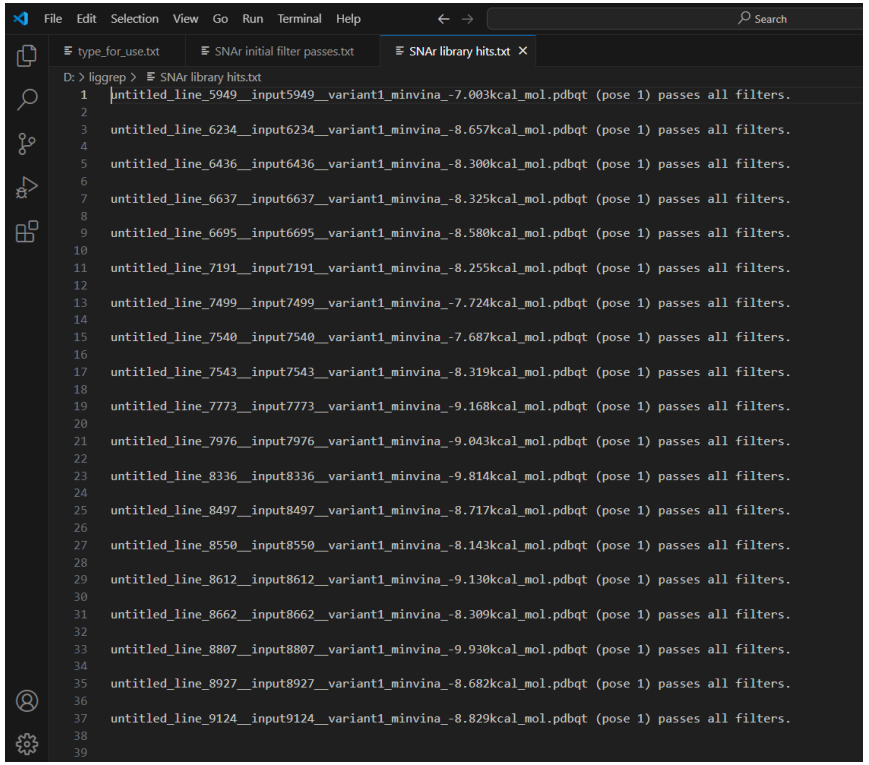


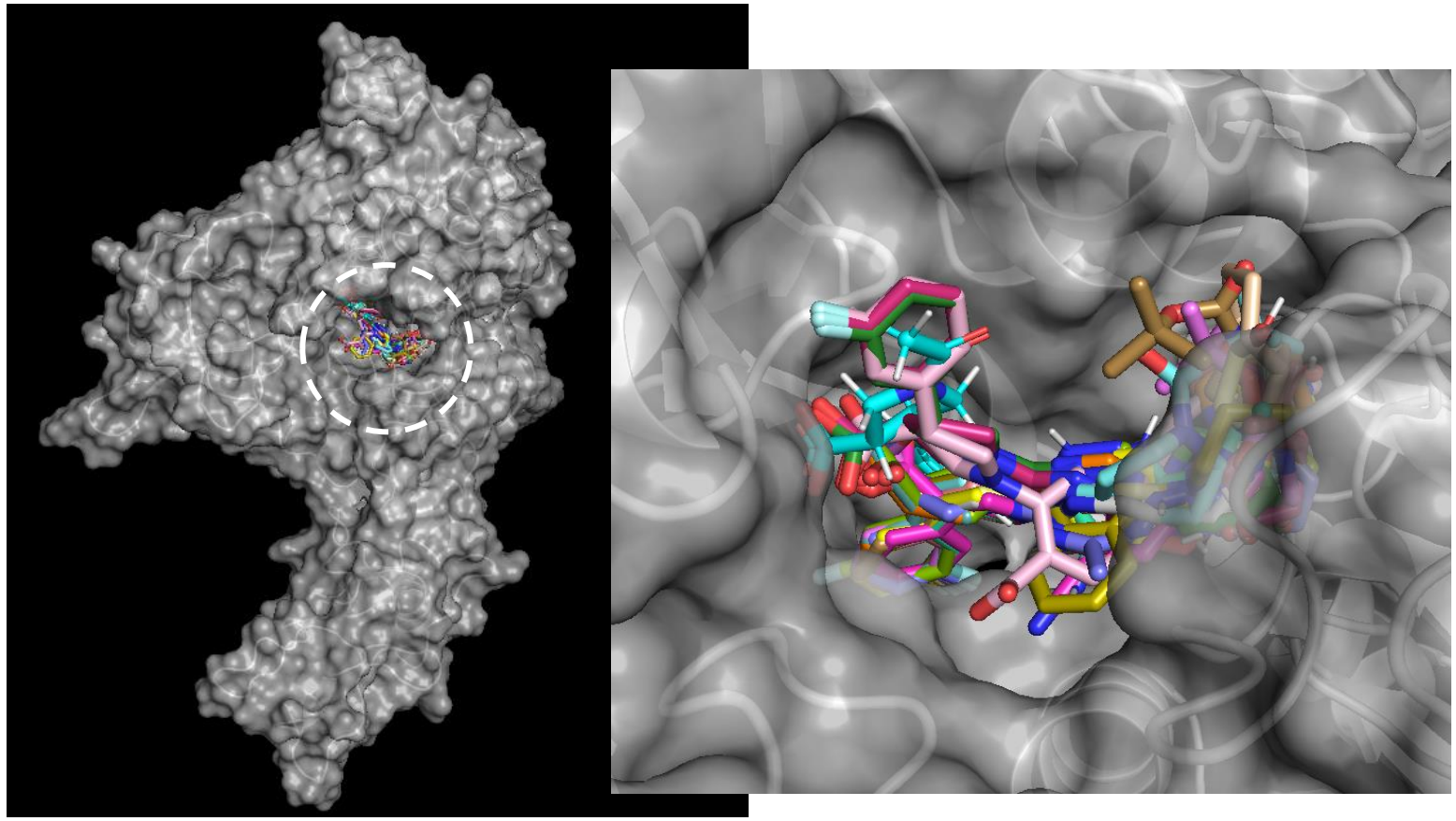


Ha et al. J Cheminform (2020) 12:69 https://doi.org/10.1186/s13321-020-00471-2

5iii. Pose Filtration using LigGrep

- 19 compounds fit criteria of satisfying .json filters with reasonable docking poses at the 5’ RNA site of Nsp13.





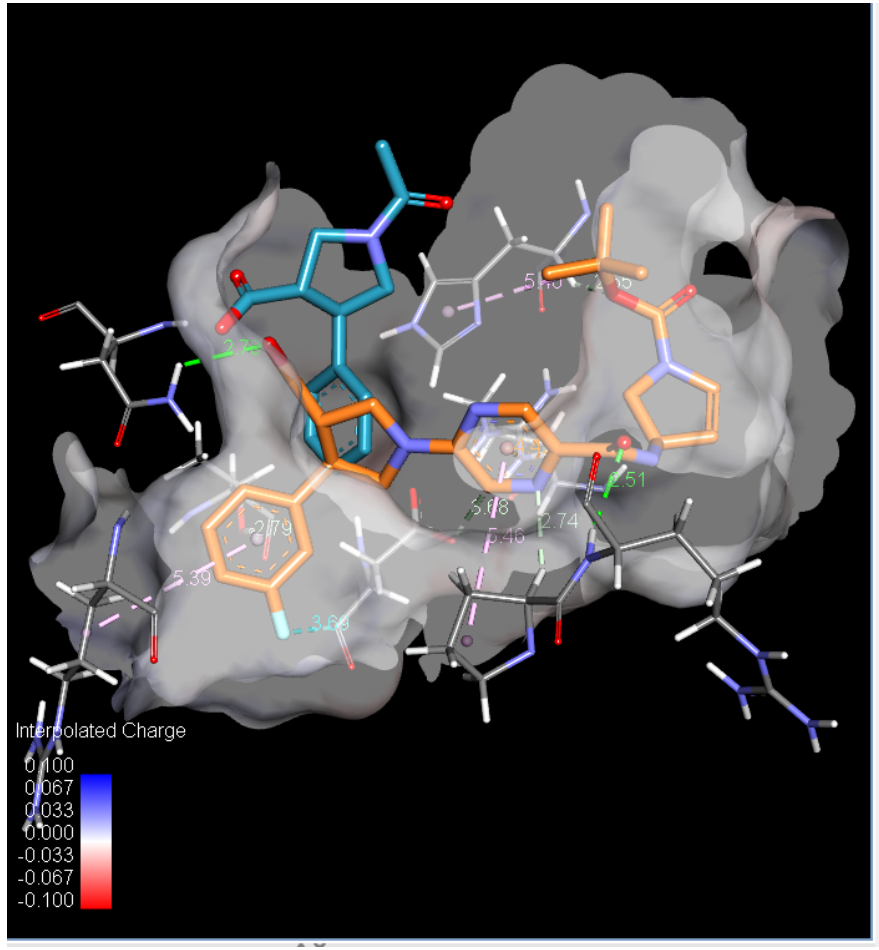
Ha et al. J Cheminform (2020) 12:69 https://doi.org/10.1186/s13321-020-00471-2

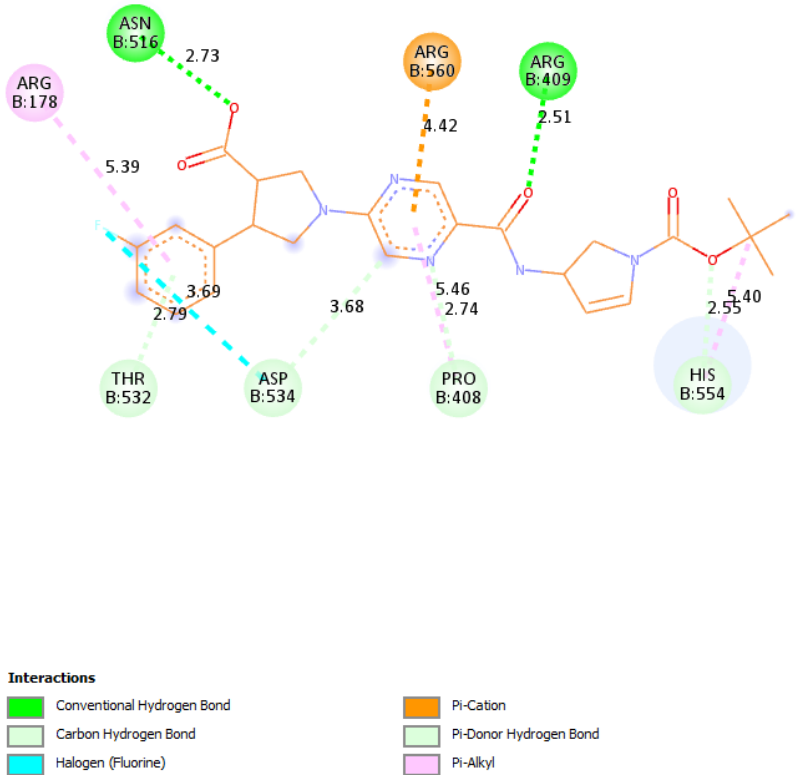
6. Second Virtual Screen

- Second round of virtual screening of round #1 compounds using a more computationally expensive run (exhaustiveness = 32 vs 8 in run #1).

```
(base) tom@DESKTOP-LG9R7AE:~$ cd /mnt/d/5RMM_VS
(base) tom@DESKTOP-LG9R7AE:/mnt/d/5RMM_VS$ perl vina_vs.pl
Enter the directory pathway containing the ligand .pdbqt files: vs_round_1_ligands

Enter the receptor filename (including extension): 5rmm_mod.pdbqt
Enter the output filename for docking results (including extension): round2vs_output.txt

Enter the coordinates of the center of the search space (X Y Z): -30.601 14.036 -23.796
Enter the size of the search space (X Y Z): 40 40 40
Enter the number of output poses per ligand: 10
Enter the energy range for the search: 3
Enter the exhaustiveness (amount of computational effort used during a docking experiment): 32


Running Vina for untitled_line_5949__input5949__variant1...
Running Vina for untitled_line_6234__input6234__variant1...
Running Vina for untitled_line_6436__input6436__variant1...
Running Vina for untitled_line_6637__input6637__variant1...
Running Vina for untitled_line_6695__input6695__variant1...
```

6. Second Virtual Screen



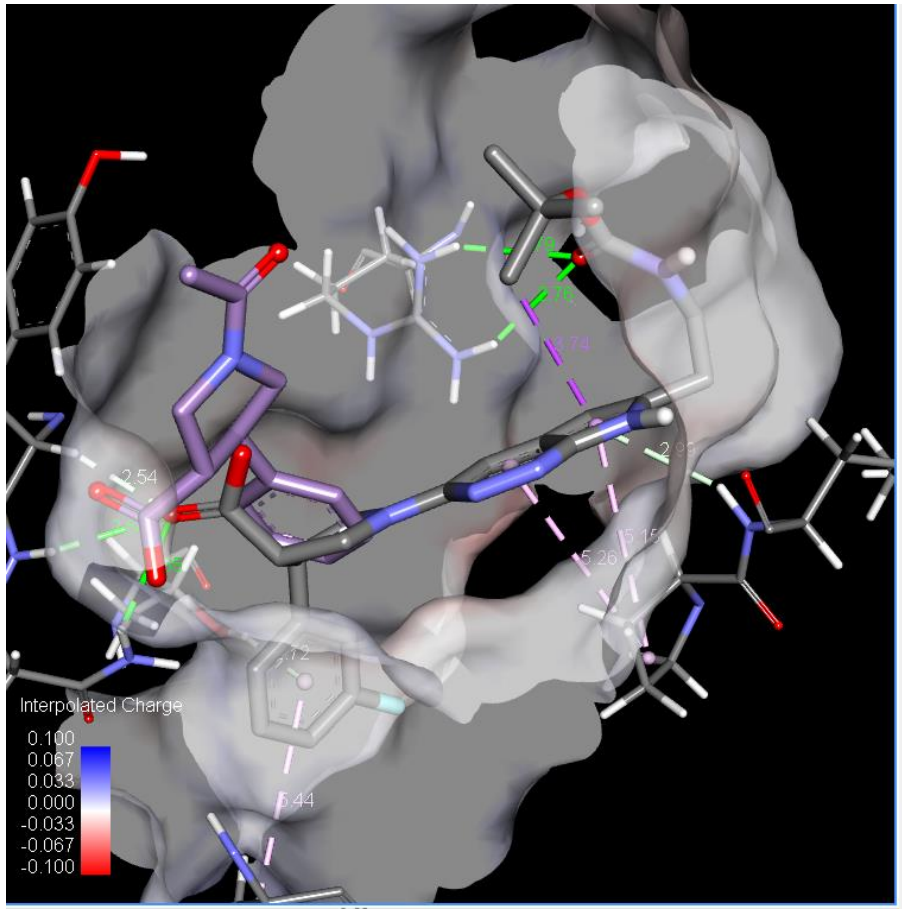


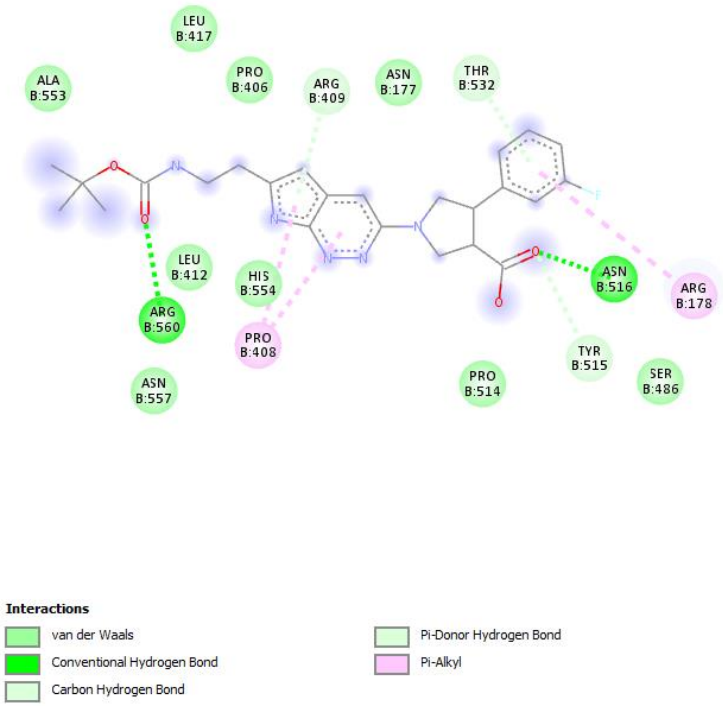
D: > 5RMM_VS > docked_lig_log_files > untitled_line_9124__input9124__variant1_log.log

```
AutoDock Vina v1.2.3
#################################################################
# If you used AutoDock Vina in your work, please cite:          #
#                                                               #
# J. Eberhardt, D. Santos-Martins, A. F. Tillack, and S. Forli  #
# AutoDock Vina 1.2.0: New Docking Methods, Expanded Force      #
# Field, and Python Bindings, J. Chem. Inf. Model. (2021)       #
# DOI 10.1021/acs.jcim.1c00203                                  #
#                                                               #
# O. Trott, A. J. Olson,                                        #
# AutoDock Vina: improving the speed and accuracy of docking    #
# with a new scoring function, efficient optimization and       #
# multithreading, J. Comp. Chem. (2010)                         #
# DOI 10.1002/jcc.21334                                         #
#                                                               #
# Please see https://github.com/ccsb-scripps/AutoDock-Vina for  #
# more information.                                             #
#################################################################

Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_9124__input9124__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1024407723) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -9.082          0          0
   2       -8.716      3.452      10.55
   3       -8.692      4.784      9.755
   4       -8.636      3.518      5.898
   5         -8.6      6.574      10.45
   6        -8.43      5.794      10.18
   7       -8.427      5.193      9.492
   8       -8.393      3.738      10.21
   9       -8.291      5.158       7.92
  10       -8.274      6.689      11.12
```

[AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)]

6. Second Virtual Screen

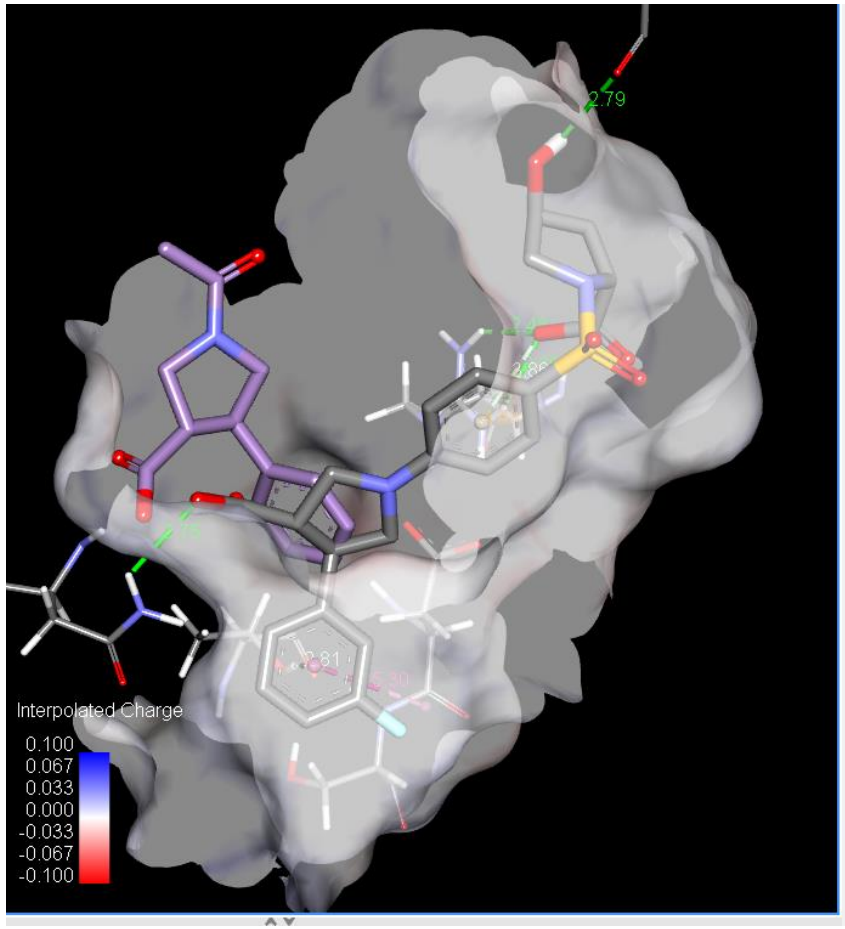


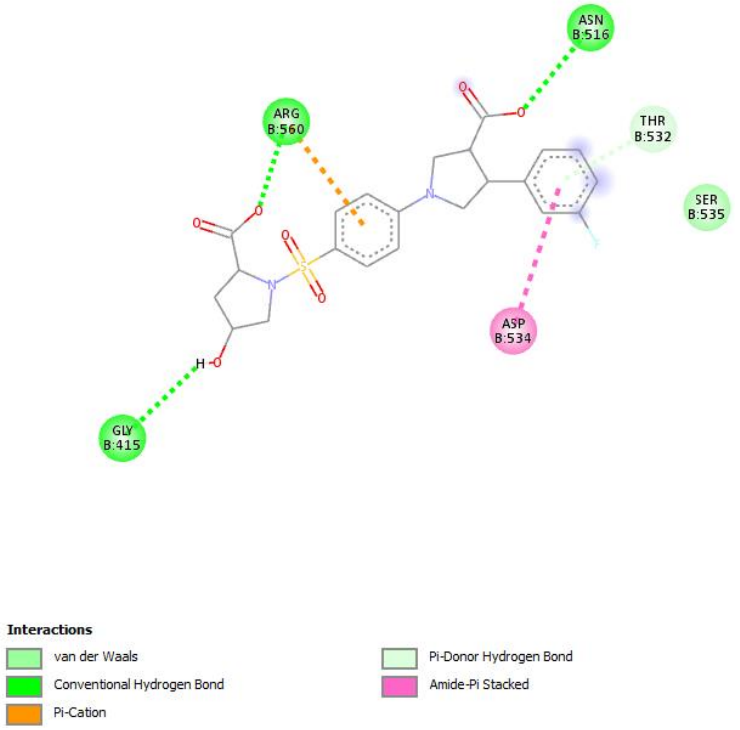



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_8927__input8927__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -186335468) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -9.001          0          0
   2       -8.477      3.108      4.796
   3       -8.349      4.473      5.797
   4       -8.311      7.078      10.56
   5        -8.31      3.058      3.988
   6       -8.302       4.59      6.297
   7       -8.198      3.837      5.539
   8       -8.196      5.605      9.316
   9       -8.192      2.813      4.524
  10       -8.084      15.54      22.41
```

AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)

6. Second Virtual Screen

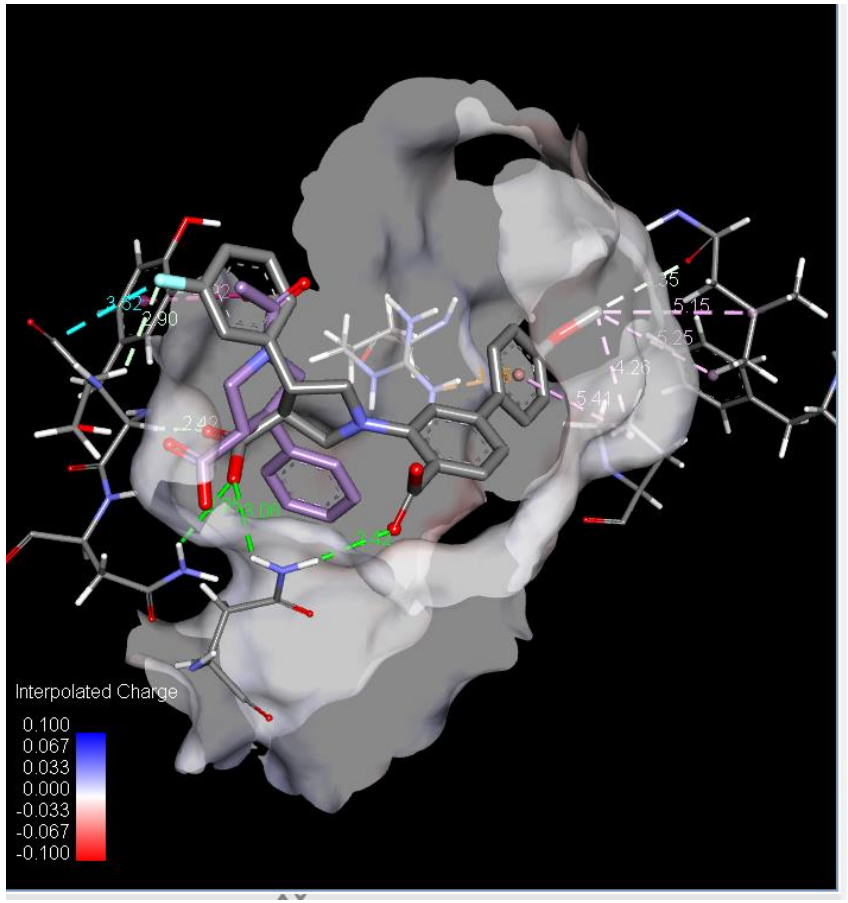


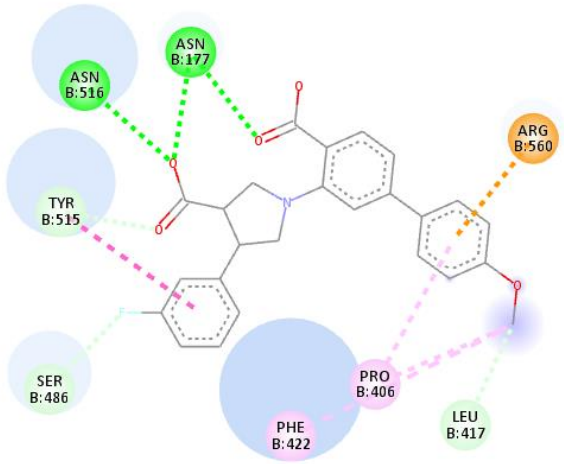


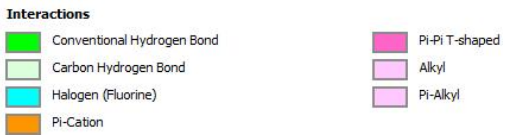

```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_8662__input8662__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -473328143) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.194          0          0
   2       -7.764      4.921      6.792
   3       -7.658      4.174      6.036
   4       -7.652          5      6.948
   5       -7.605      6.708       8.44
   6       -7.536      3.438      4.634
   7       -7.476      5.102      9.139
   8       -7.447      5.981      8.464
   9       -7.374      15.23       20.6
  10       -7.318      5.668      7.301
```

[AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)]

6. Second Virtual Screen








```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_8550__input8550__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1711439211) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -8.3          0          0
   2       -8.235      4.344       7.62
   3       -8.219      3.827      8.458
   4         -8.2      3.956      8.631
   5       -8.172       4.39      6.866
   6       -7.946       3.82       6.22
   7       -7.929      3.527      6.127
   8       -7.763      4.029      7.771
   9       -7.702      4.346      8.161
  10       -7.673      3.797       7.66
```

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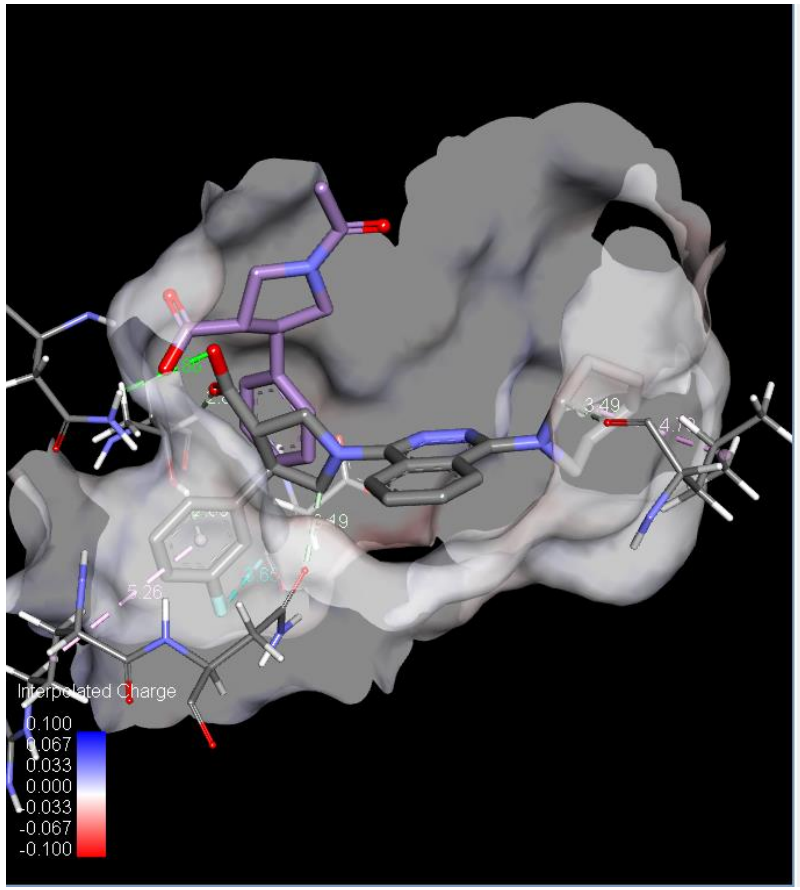
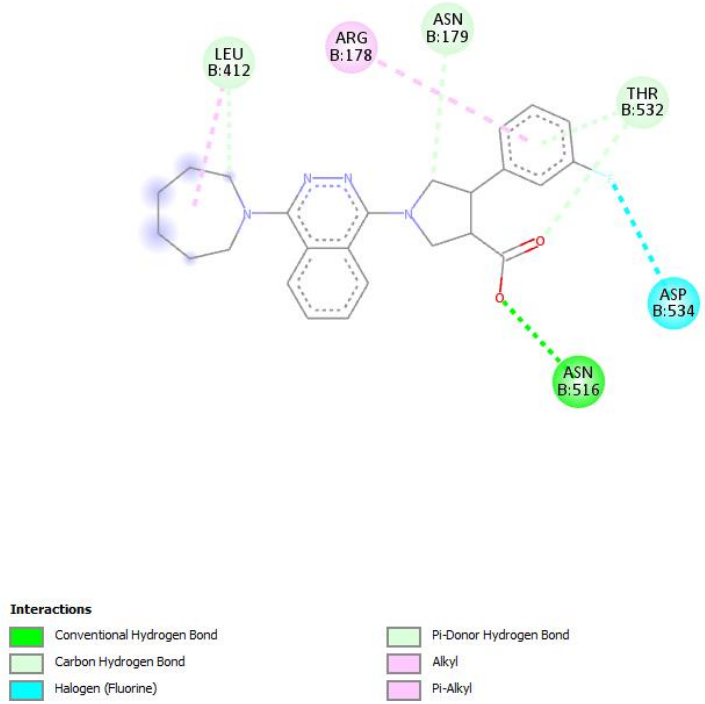
6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_8336__input8336__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 884673502) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -9.527          0          0
   2       -9.148      6.968       9.56
   3        -8.96      4.523      6.556
   4       -8.884      4.754      8.574
   5       -8.602      5.557      8.335
   6       -8.524      14.77      19.29
   7       -8.447       6.18      8.038
   8       -8.413      6.409      7.842
   9       -8.298      5.405      7.463
  10       -8.272      5.273      8.739
```

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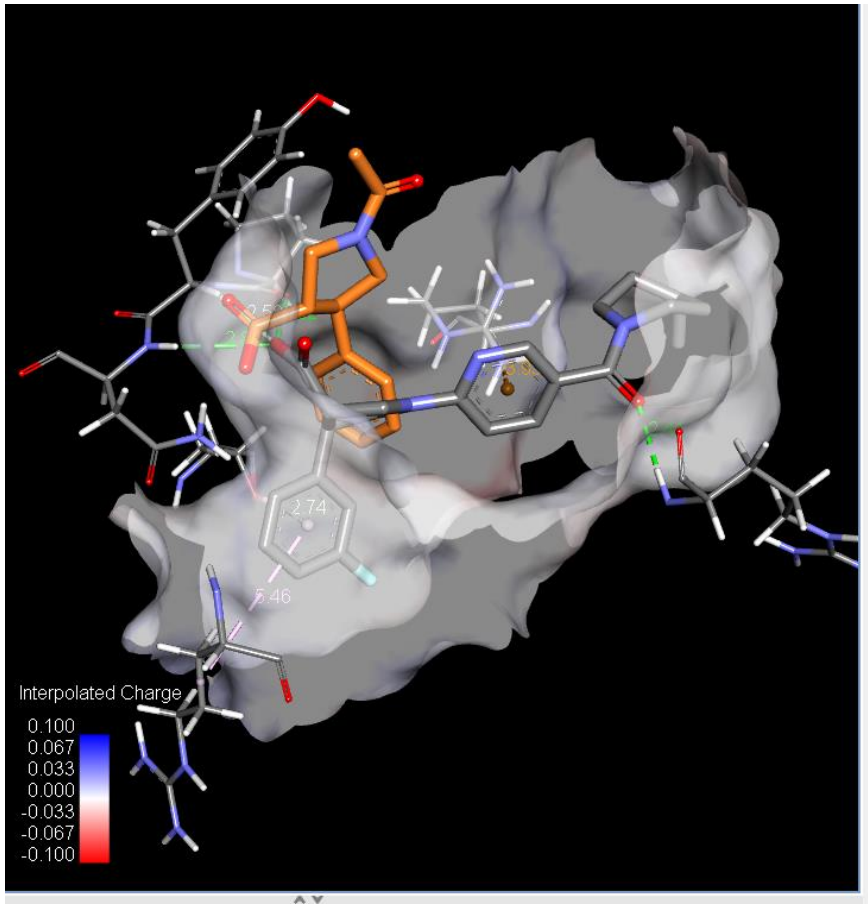
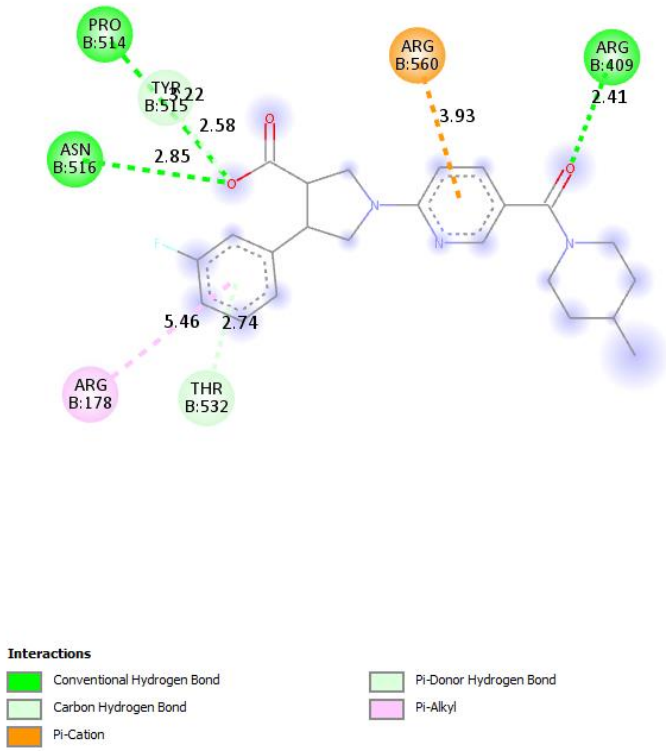
6. Second Virtual Screen

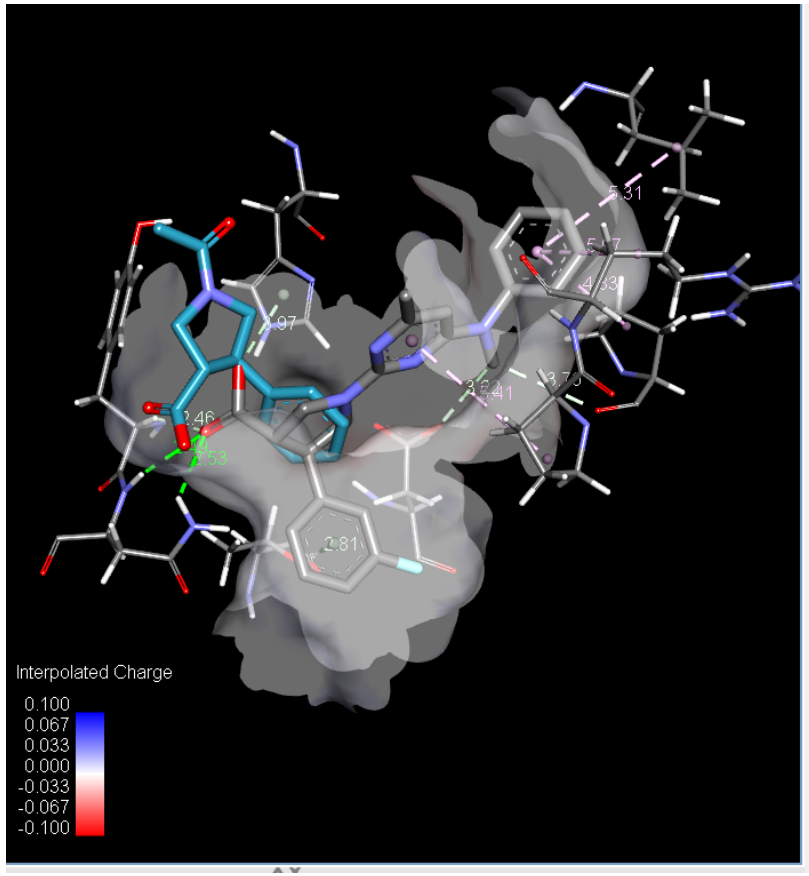


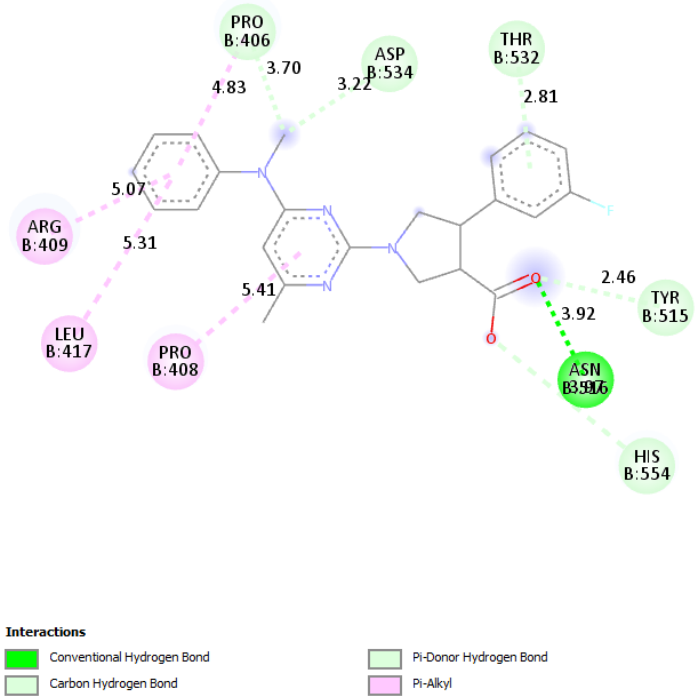



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7976__input7976__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 256786996) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -9.087          0          0
   2       -8.435      2.492      3.939
   3       -8.399      3.945      4.475
   4       -8.208      5.026       6.94
   5       -8.074      4.233      4.783
   6       -8.043      4.238      6.188
   7       -8.038      3.938      5.246
   8       -7.963        3.7      4.766
   9       -7.878      4.415      6.274
  10       -7.814      15.87      21.14
```

AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)

6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7773__input7773__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -682037403) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -9.19          0          0
   2      -8.477      4.272      5.228
   3       -8.35      4.649      5.835
   4      -8.242      4.673      5.884
   5      -7.989      5.547       9.32
   6      -7.921      4.446      6.439
   7       -7.59      4.066      5.228
   8      -7.467       13.2      15.15
   9      -7.461      4.791        8.5
  10      -7.416      5.354      6.737
```

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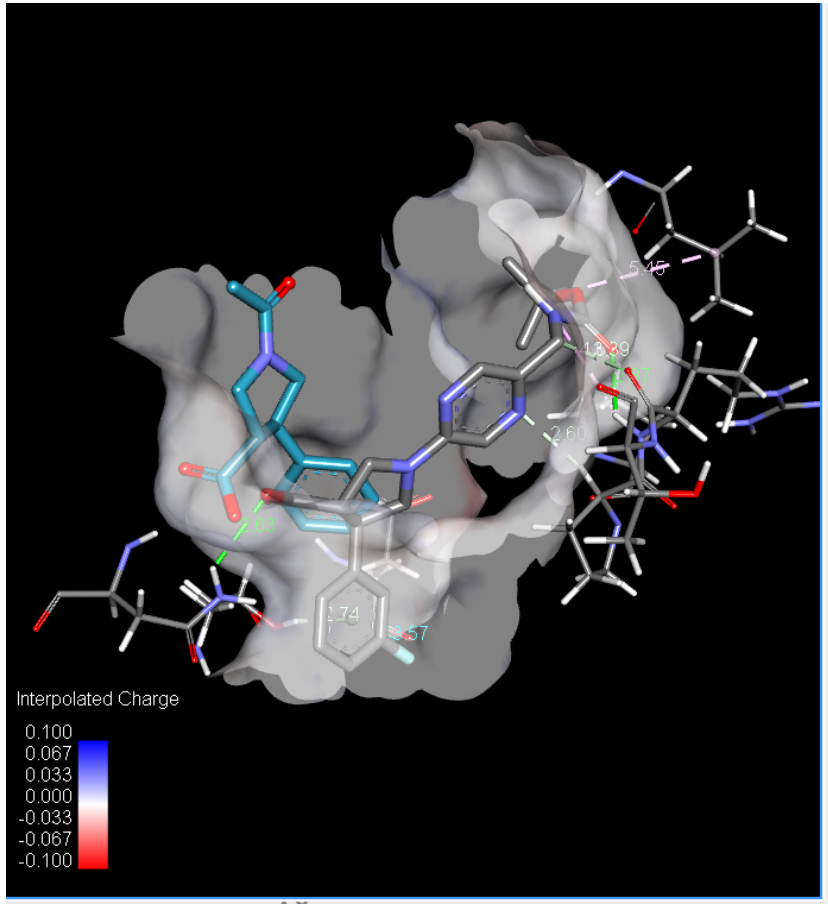
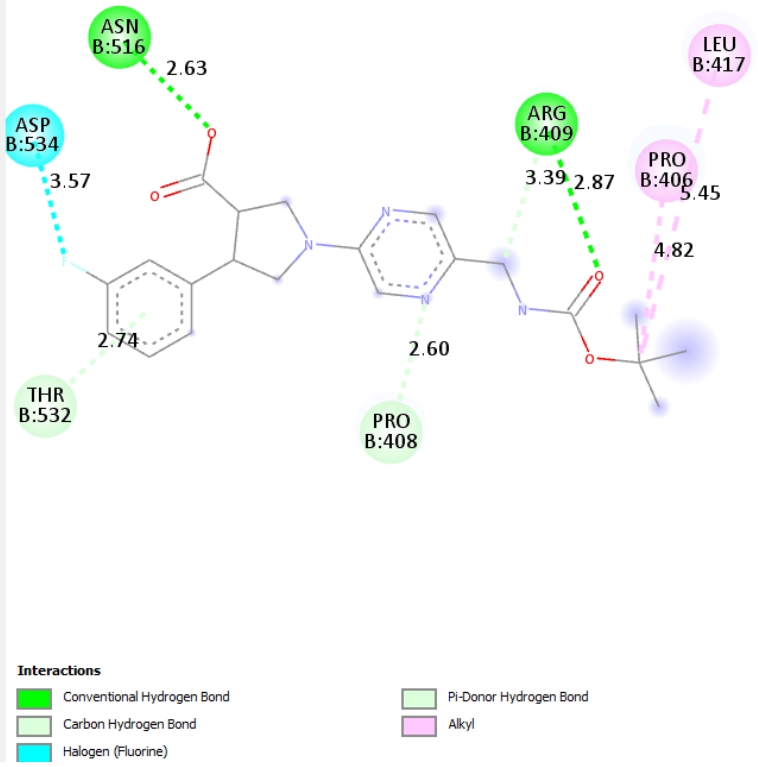
6. Second Virtual Screen

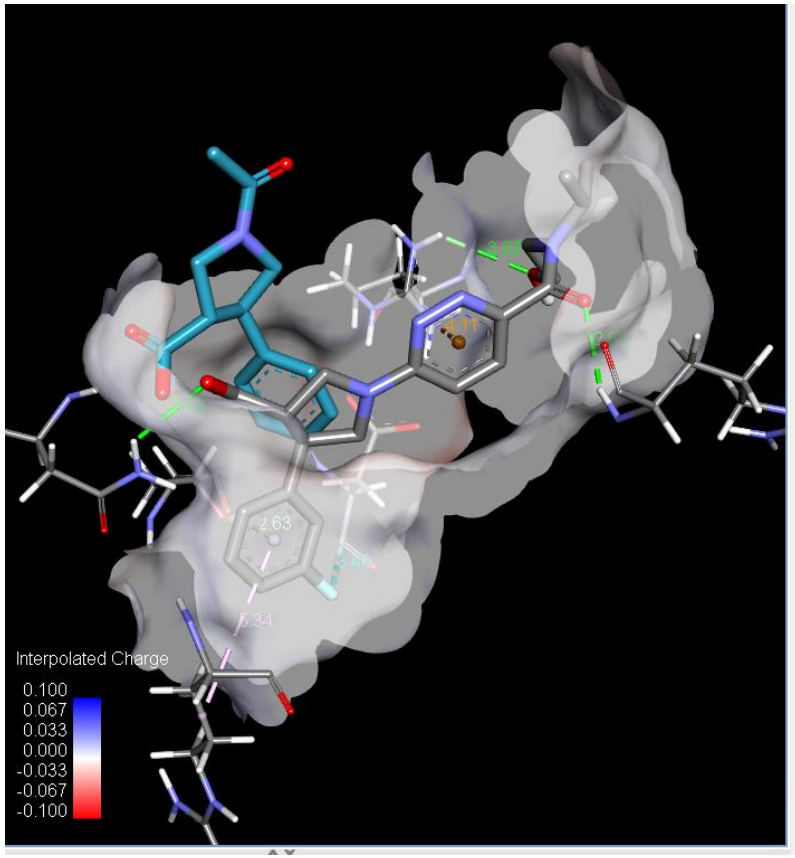


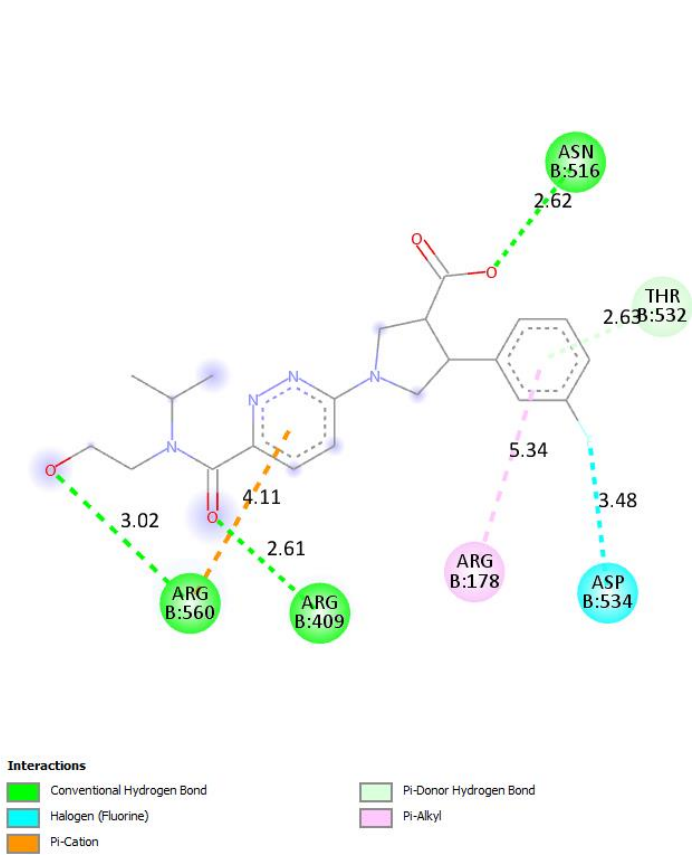



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7543__input7543__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -610634018) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.166          0          0
   2       -7.941      2.433       3.92
   3       -7.778      3.498      9.621
   4       -7.695      4.021      9.798
   5       -7.685      2.898      3.614
   6       -7.559      3.097      3.739
   7       -7.555      3.898      9.666
   8       -7.479       4.31      9.968
   9       -7.355      4.521      5.552
  10       -7.257      5.775      10.13
```

AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)

6. Second Virtual Screen

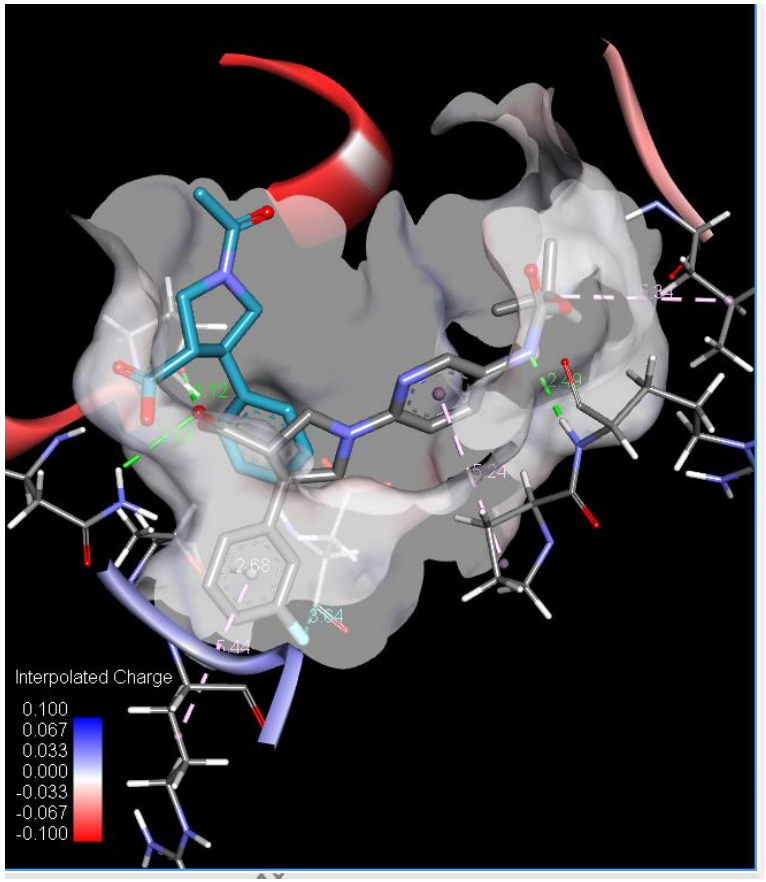


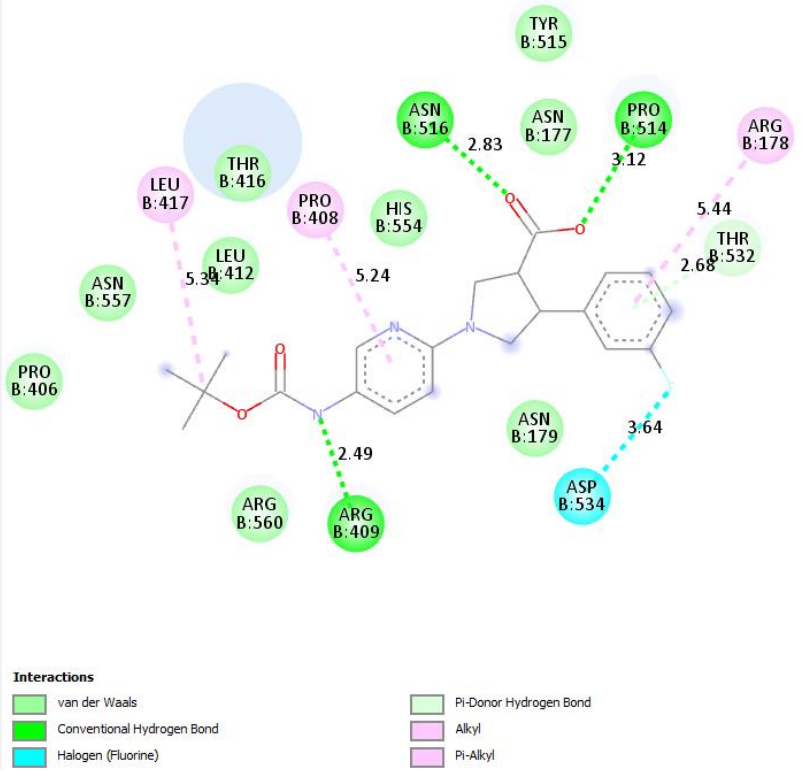



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7540__input7540__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 1937630652) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -7.735          0          0
   2       -7.462       4.86      6.714
   3       -7.262       5.12      7.004
   4       -6.813      3.595      4.312
   5        -6.78      15.65      20.76
   6       -6.716      6.224      8.283
   7         -6.7      5.779      7.429
   8       -6.683      4.808      6.565
   9        -6.68      5.598      9.284
  10       -6.653      5.591      9.061
```

AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)

6. Second Virtual Screen

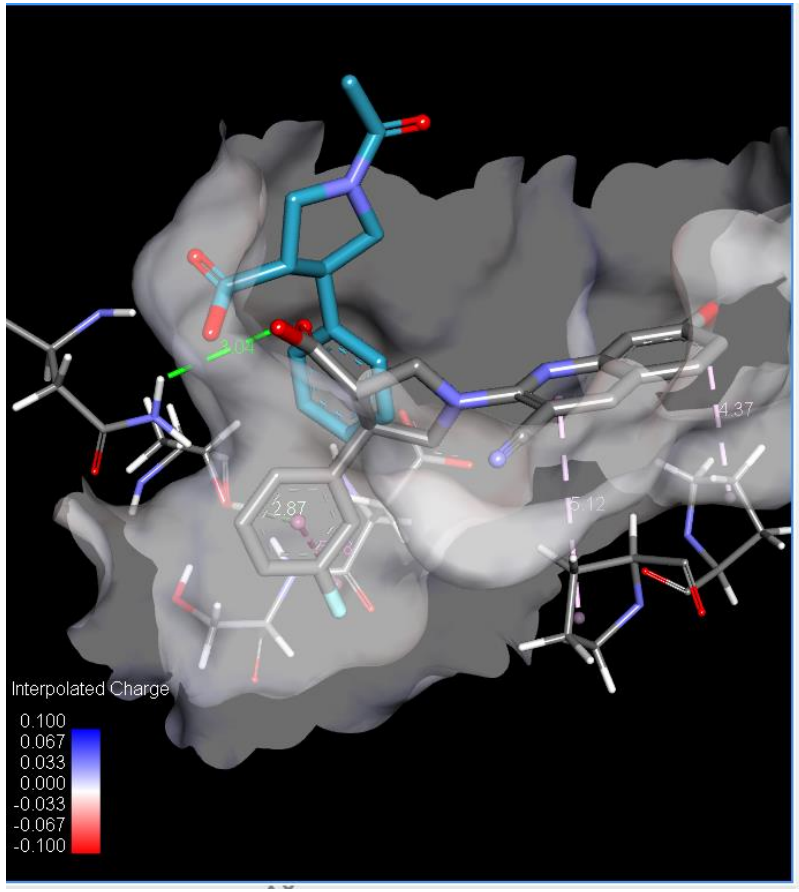


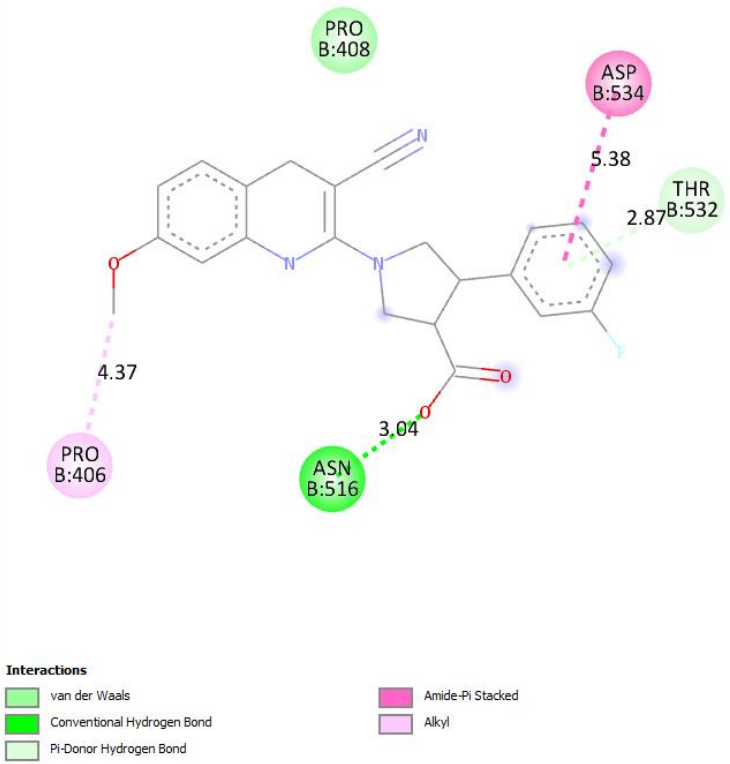



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7499__input7499__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 1988620525) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -7.512          0          0
   2       -7.423      2.569      4.037
   3       -7.264      3.534      9.517
   4        -7.26      2.654      3.299
   5       -7.253      3.292       9.48
   6       -7.222      3.851      9.505
   7       -7.184      2.857      3.859
   8       -7.143       4.56      9.093
   9       -7.132      2.654      3.443
  10       -6.957      2.983      3.815
```

[AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)]

6. Second Virtual Screen

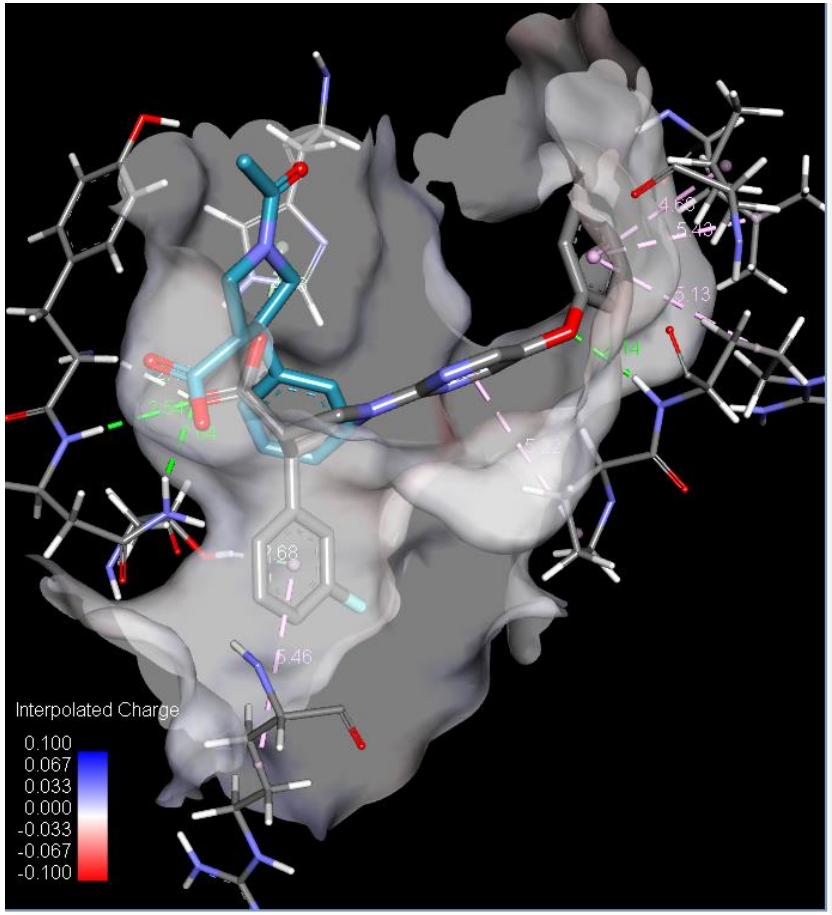


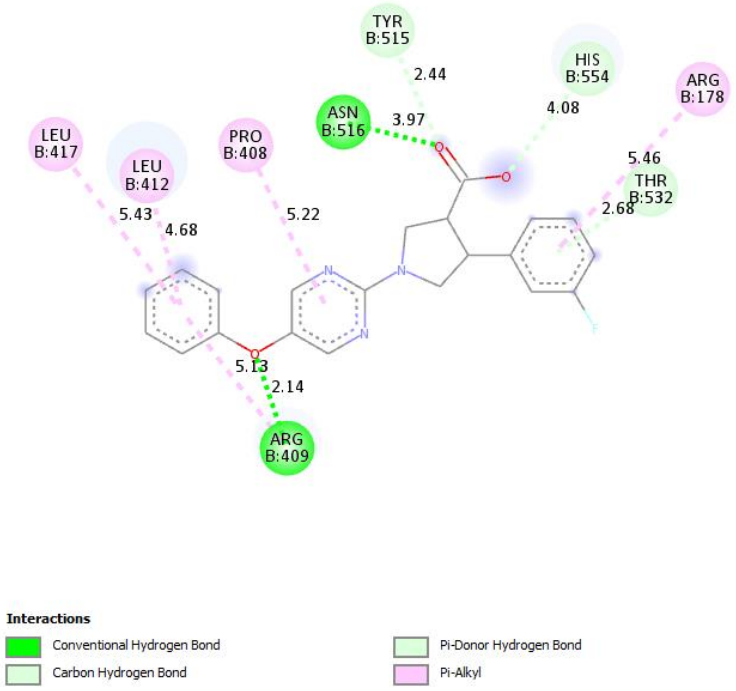



```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_7191__input7191__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1374365763) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.129          0          0
   2       -7.721      3.336      4.161
   3       -7.508      4.549      8.951
   4       -7.488      3.094       3.93
   5       -7.467      6.573      7.594
   6       -7.448      4.959      8.835
   7       -7.436      4.983      8.889
   8       -7.402      14.26      18.23
   9         -7.4       4.25      5.458
  10       -7.344      4.267      8.803
```

AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)

6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_6695__input6695__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 173653430) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.611          0          0
   2       -8.516      3.908      9.492
   3       -8.509      3.696      9.378
   4       -8.466      2.653      4.218
   5       -8.268      3.173      4.591
   6       -7.814      4.791      6.835
   7       -7.792      4.166      5.286
   8       -7.735      14.16      19.89
   9       -7.697      5.543      9.196
  10       -7.674      5.453      9.379
```

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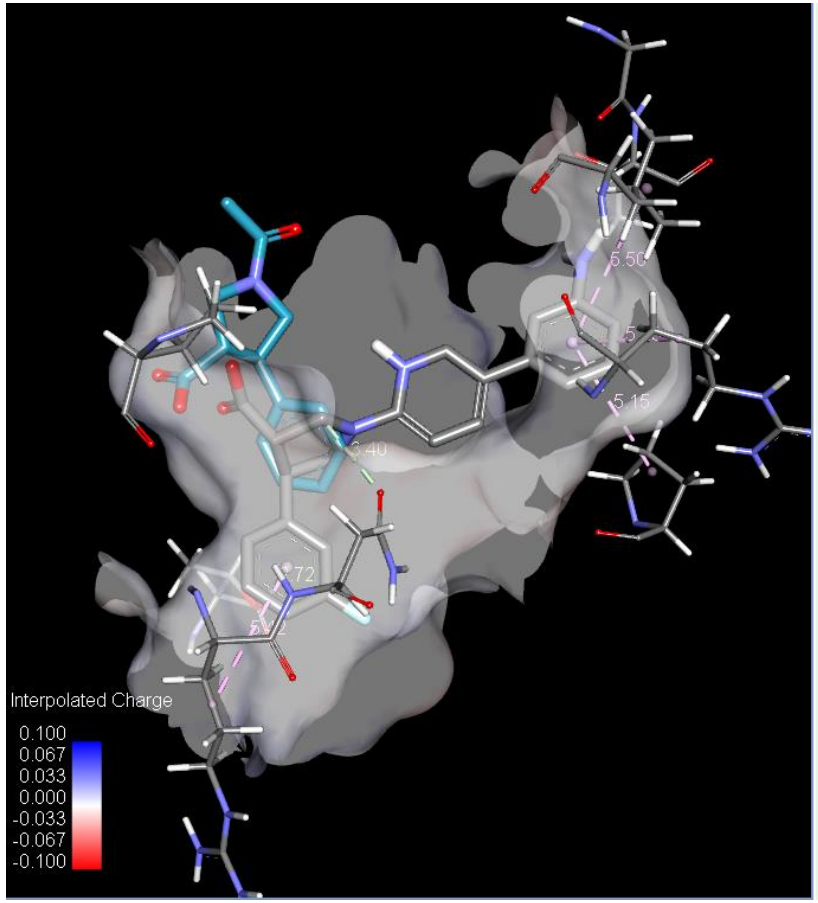
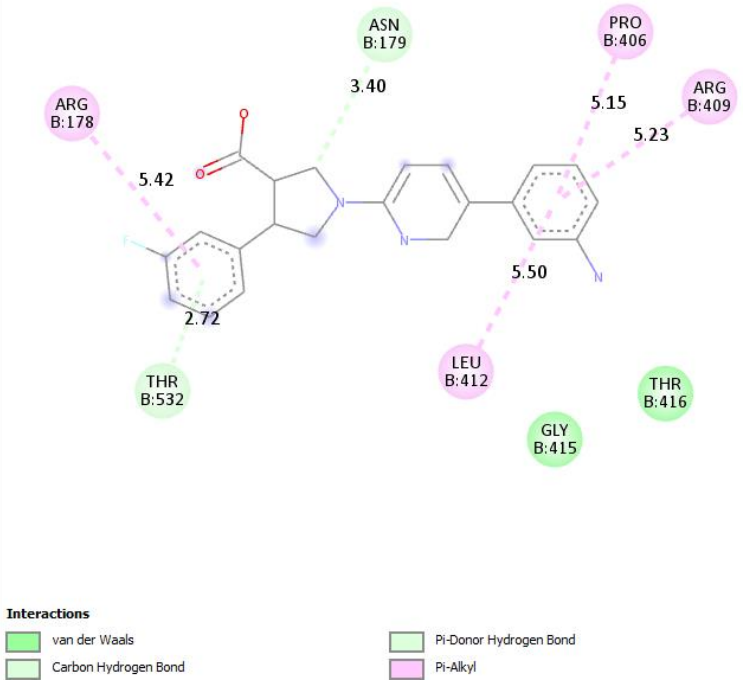
6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_6637__input6637__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1714726573) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.612          0          0
   2       -8.544      2.723      4.189
   3        -8.06      14.93      17.16
   4       -8.028      13.17      19.11
   5       -7.985      4.139      4.803
   6       -7.722      16.27      18.67
   7       -7.683      6.753      9.753
   8       -7.621      3.975      5.509
   9       -7.489      3.348      4.102
  10       -7.475      4.714      6.615
```

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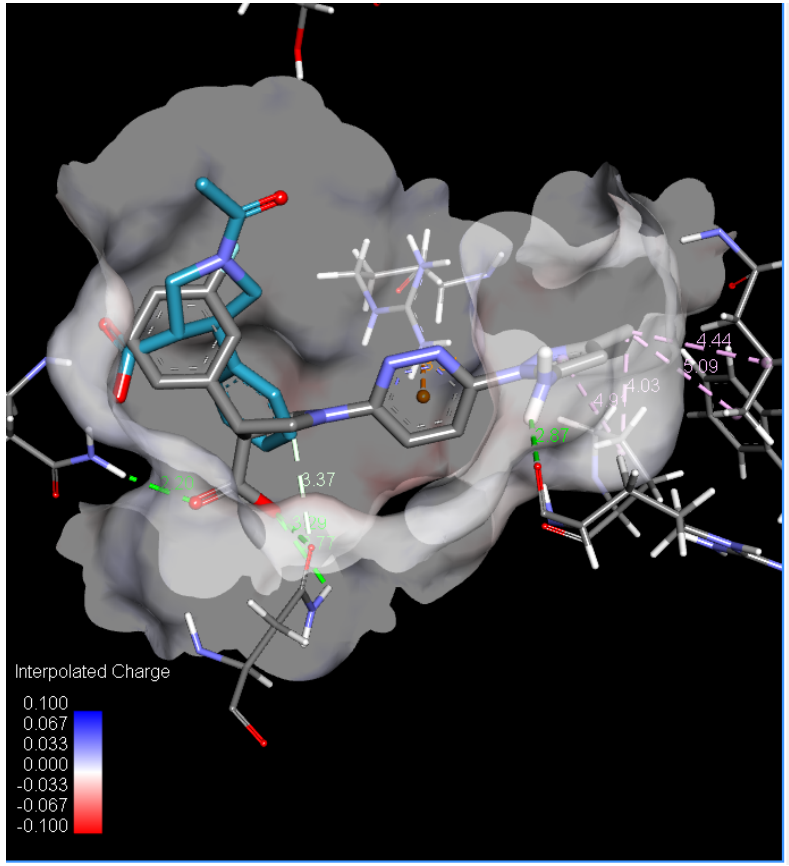
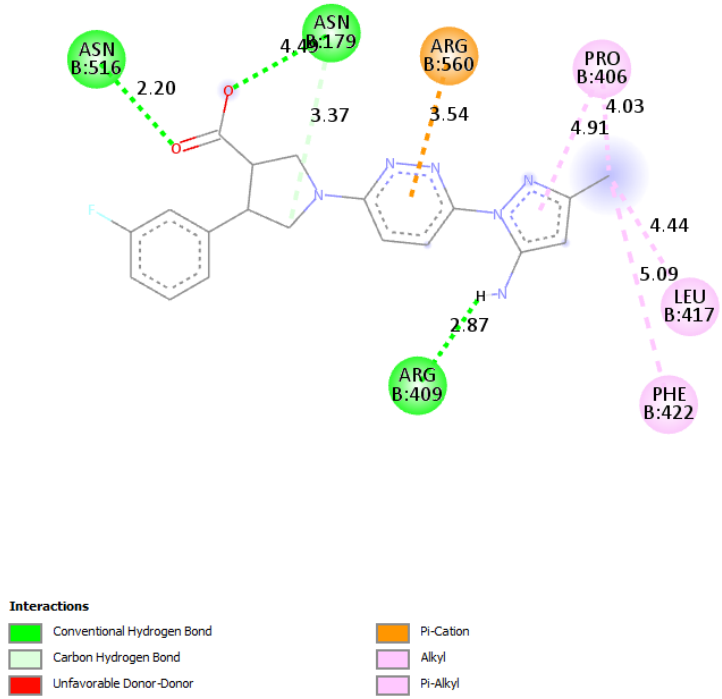
6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_6436__input6436__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: -1105417413) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.257          0          0
   2       -8.217      2.554      4.086
   3       -8.213       4.05      8.935
   4       -8.025       3.97      8.453
   5       -8.008      4.614       9.48
   6       -7.919      2.777      3.264
   7       -7.589       14.9      19.55
   8       -7.576      3.068      3.752
   9       -7.417      3.083      3.714
  10       -7.352      6.329      9.774
```

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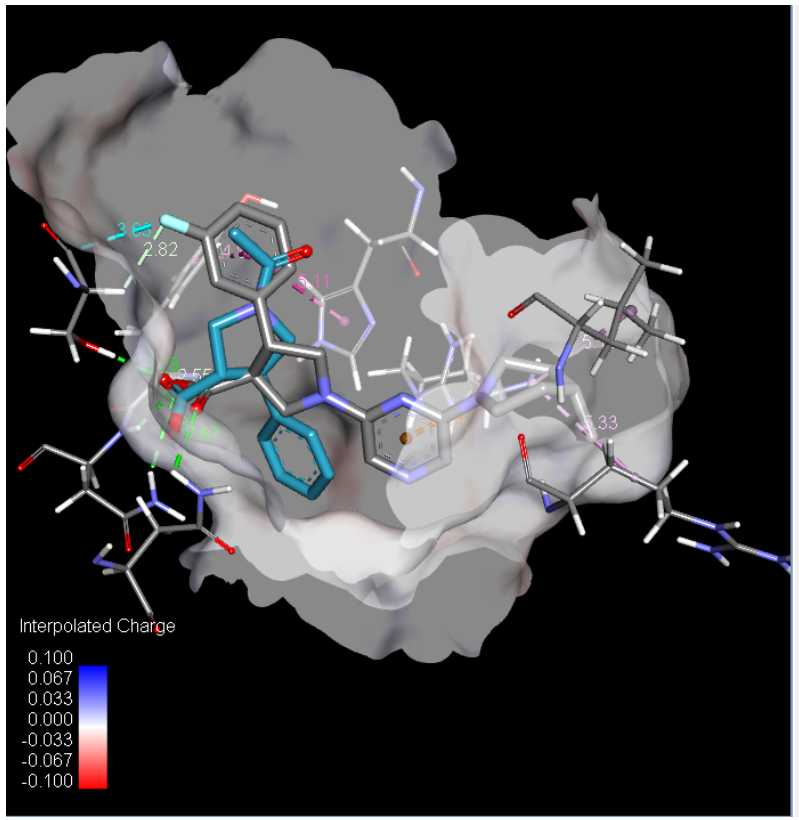
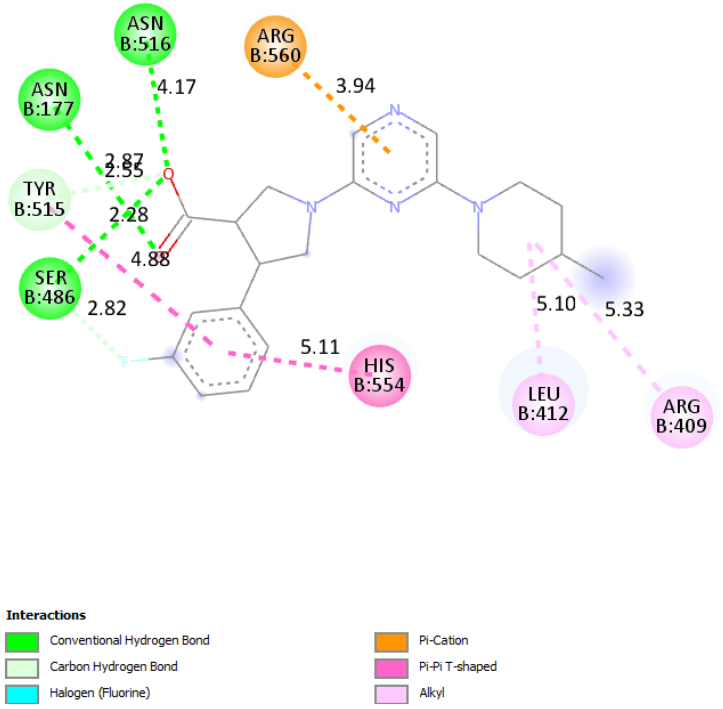
6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_6234__input6234__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 882193590) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.62          0          0
   2      -8.412       4.46      8.773
   3      -8.276      2.164      3.279
   4       -8.25      4.221      7.879
   5      -8.188      4.349       8.29
   6      -8.144      3.078       5.07
   7      -8.094      3.028      4.547
   8      -8.056      5.255       8.57
   9      -7.784      3.344      4.881
  10      -7.783       5.39      9.051
```

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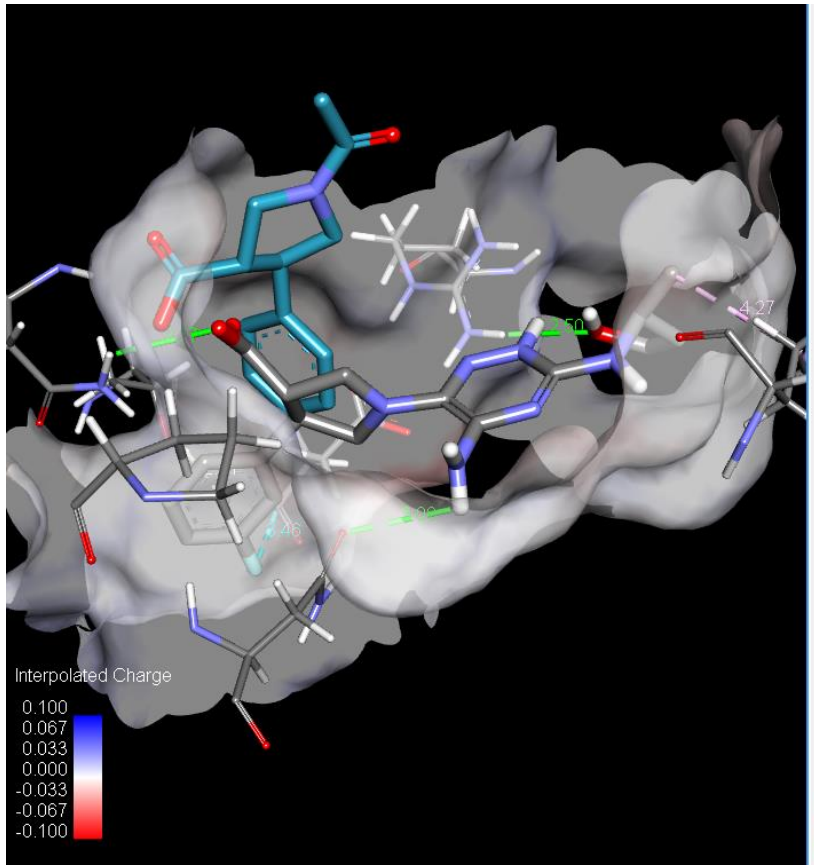
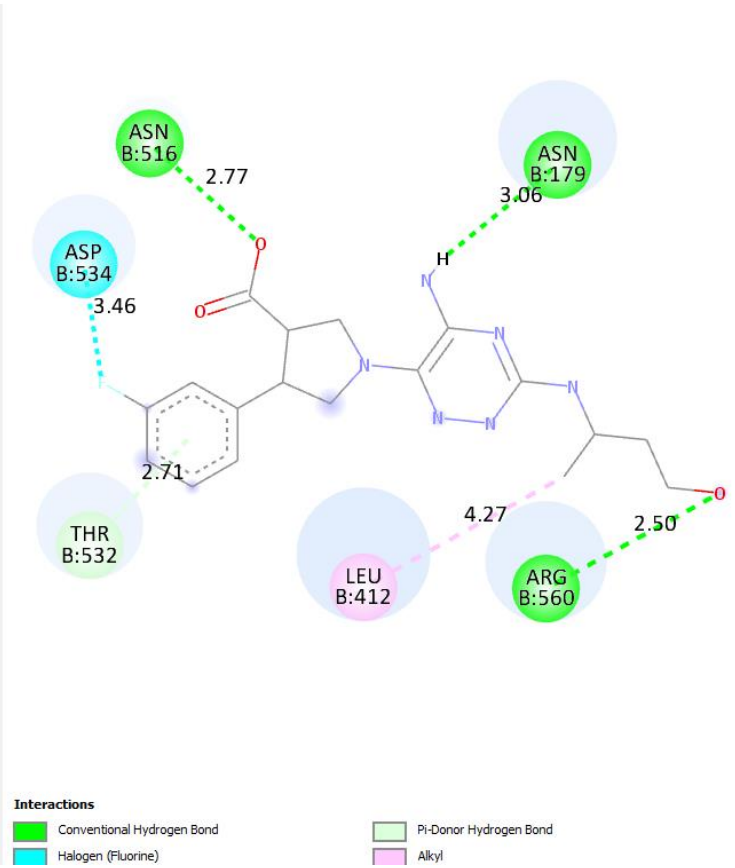
6. Second Virtual Screen






```
Scoring function : vina
Rigid receptor: 5rmm_mod.pdbqt
Ligand: vs_round_1_ligands/untitled_line_5949__input5949__variant1.pdbqt
Grid center: X -30.601 Y 14.036 Z -23.796
Grid size  : X 40 Y 40 Z 40
Grid space : 0.375
Exhaustiveness: 32
CPU: 8
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing Vina grid ... done.
Performing docking (random seed: 980427960) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -6.85          0          0
   2      -6.846      15.11      20.08
   3      -6.788       16.1      20.25
   4       -6.66         16      20.92
   5      -6.554      16.41      21.39
   6      -6.528      16.93      20.83
   7      -6.465      20.38      22.76
   8      -6.423      20.88      23.05
   9      -6.393      19.66      22.39
  10      -6.381      16.87      21.12
```

[AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)]

Virtual Screen References

- ccsb-scripps/AutoDock-Vina: AutoDock Vina (github.com)
- AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings | Journal of Chemical Information and Modeling (acs.org)
- AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading - Trott - 2010 - Journal of Computational Chemistry - Wiley Online Library
- Critical assessment of the automated AutoDock as a new docking tool for virtual screening
- Evaluation of AutoDock and AutoDock Vina on the CASF-2013 Benchmark | Journal of Chemical Information and Modeling (acs.org)

In the paper, Vina is compared to other scoring functions using the CASF-2013 benchmark:

- **Scoring Power**: Vina shows a strong correlation with experimental binding constants, with a Pearson correlation coefficient of 0.600 after local optimization, placing it close to the top methods.
- **Docking Power**: Vina excels in distinguishing the native ligand binding pose from decoys, achieving the best docking power success rates among all methods tested, with 85.6% in single-point model.
- **Screening Power**: Vina also performs well in distinguishing binders from nonbinders, with high success rates and enrichment factors, especially after local optimization.

- **Overall Performance**: Generally, Vina ranks in the first quarter of the 33 methods tested, indicating a robust and reliable scoring function for docking simulations.