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Identification of Novel Anti-Heparanase Compounds Through Virtual Screening

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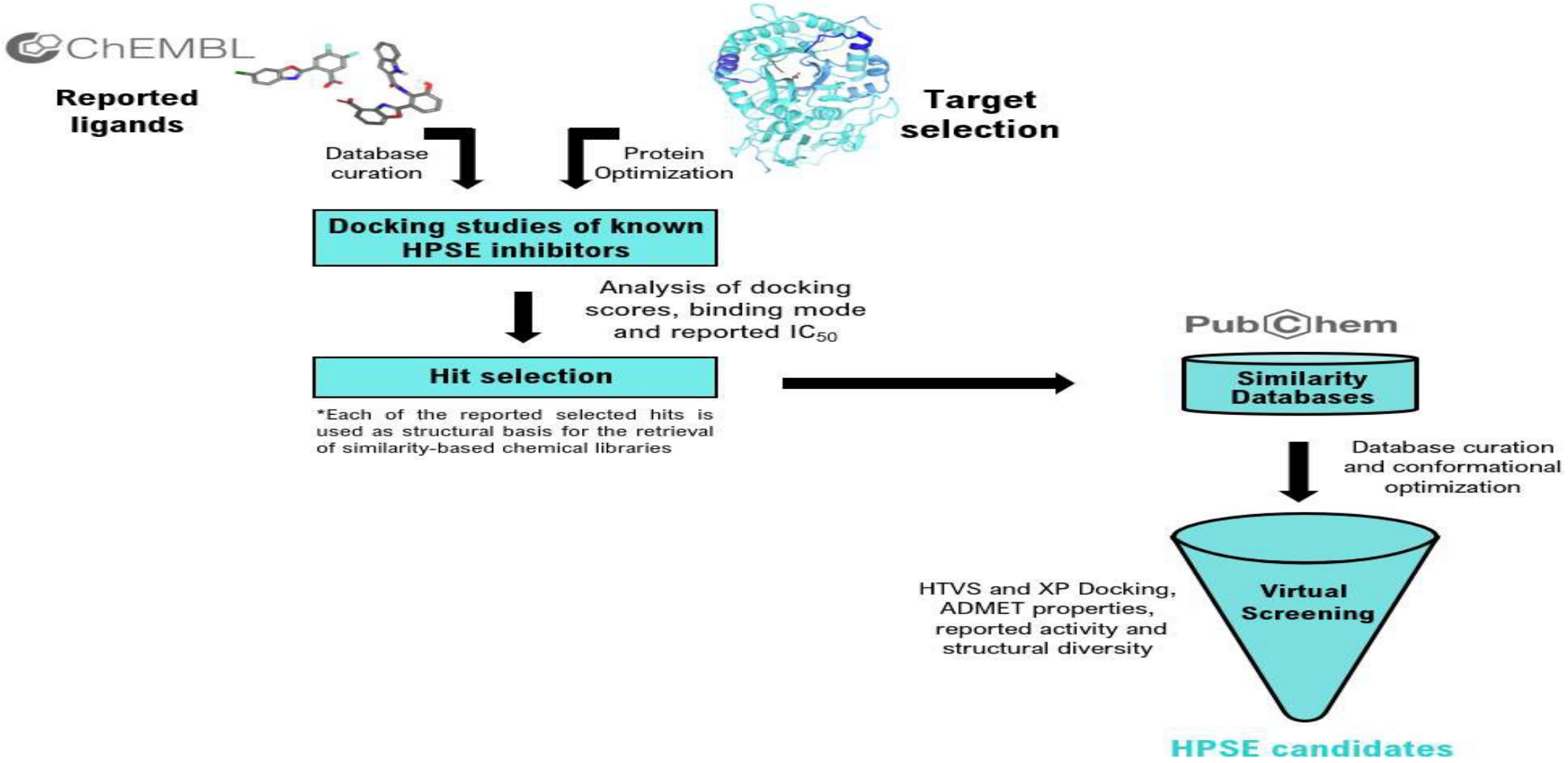
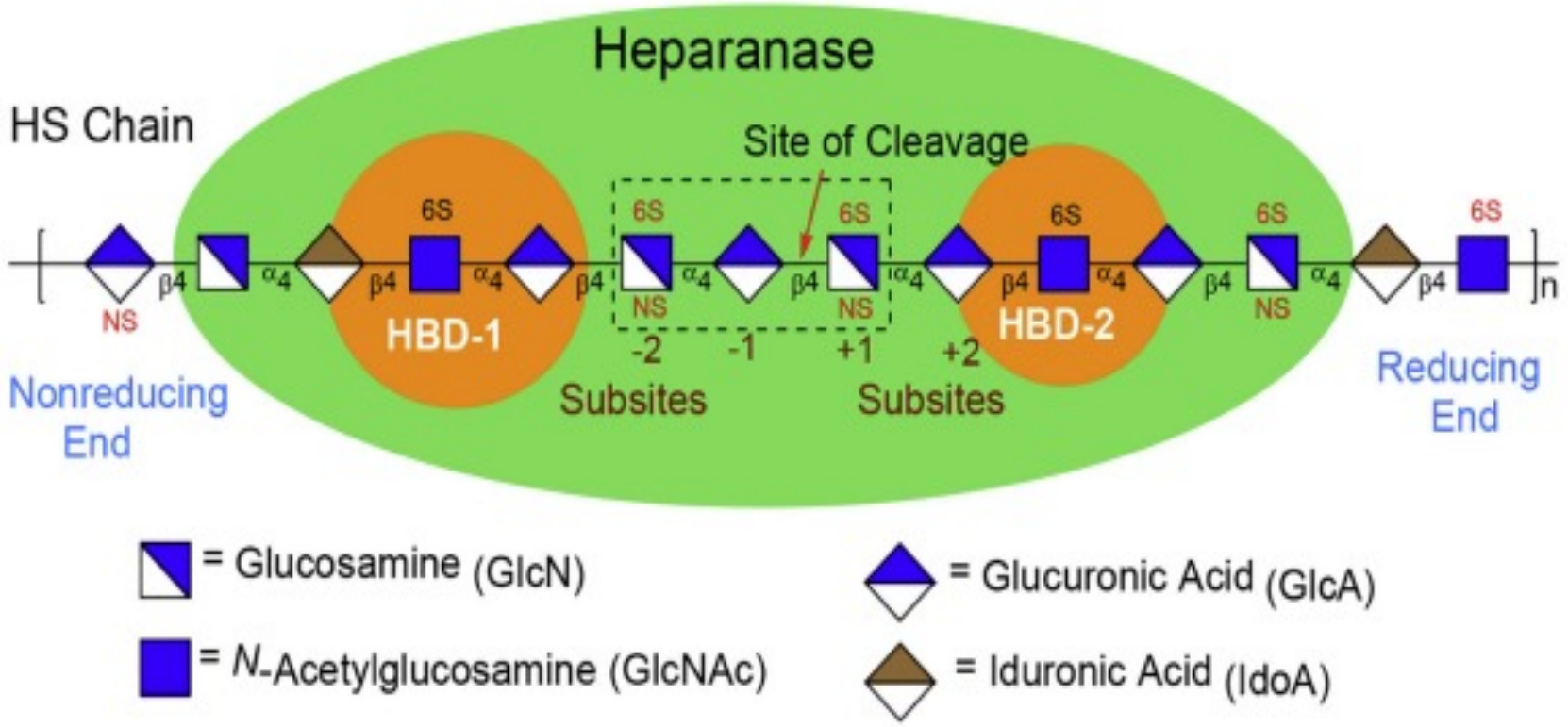
Identification of Novel Anti-Heparanase Compounds Through Virtual Screening



Abstract:
Heparanase (HPSE) is a mammalian endo-β-D-glucuronidase. It cleaves heparan sulphate (HS) side chains of heparin sulphate proteoglycans (HSPG), which are composed of repeating polysulfated disaccharide units of glucosamine and hexuronic acid residues. By degrading HS into smaller fractions, heparanase controls the availability of chemokines, growth factors and a plethora of other bioactive molecules, thus enabling the release of saccharide fragments that end up activating multitude of signaling processes. When overexpressed, HPSE has been correlated with tumor growth and survival as well as chronic inflammation exhibited in several diseases, the latest of them being the COVID-19 pandemic caused by SARS-CoV-2. Thus, it has become increasingly important in clinic to search for compounds that may potentially inhibit HPSE. In this study, we combined virtual screening and molecular docking of publicly known chemical databases in order to identify small molecules that can be developed into novel HPSE inhibitors. We were able to identify promising new chemotypes through the structural rationalization of the interactions previously reported compounds. These novel potential HPSE inhibitors are shown to exhibit optimized in silico druggability and docking properties and can potentially serve as pharmacological tools to treat chronic and infectious diseases associated with chronic inflammation.

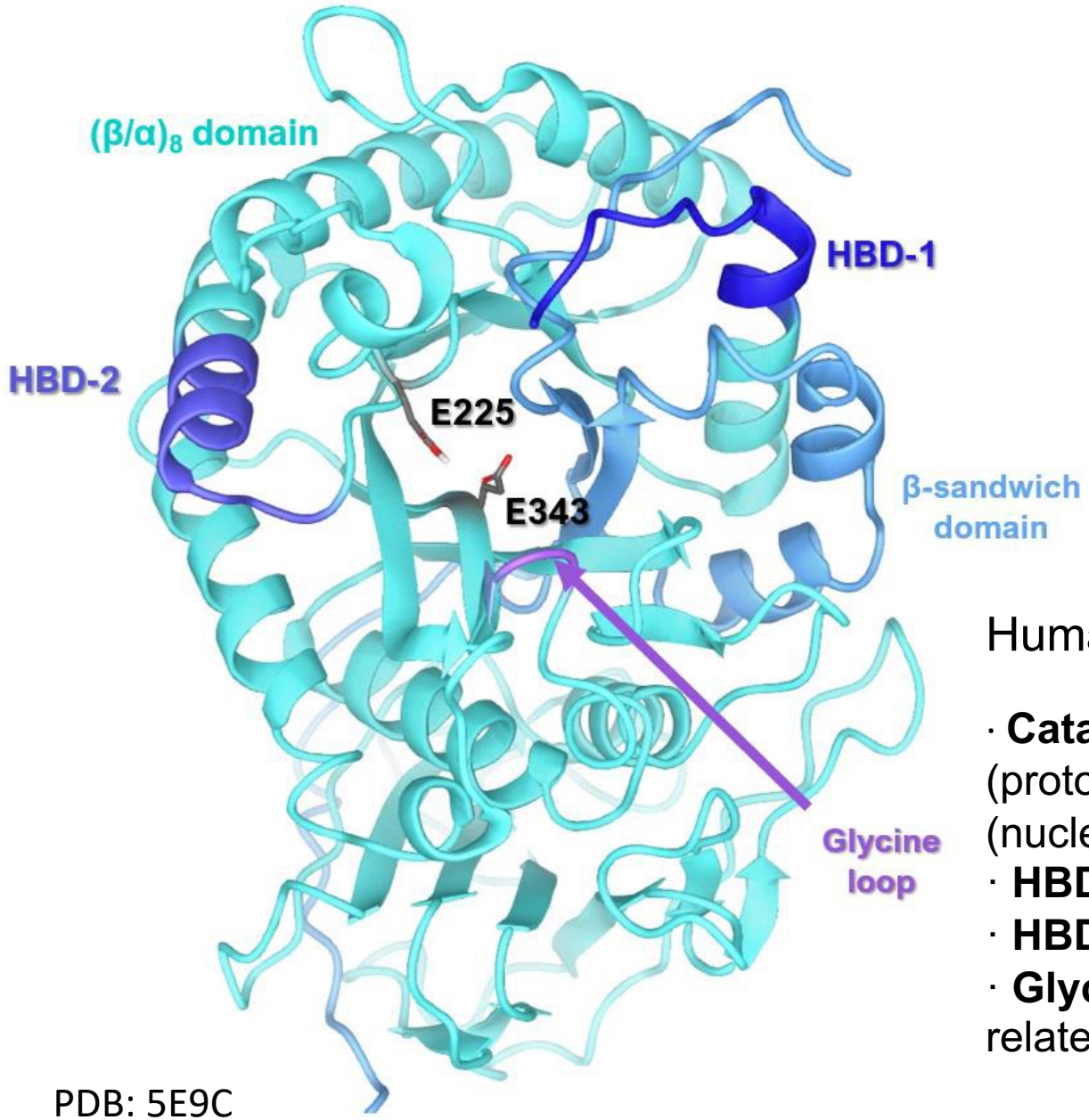
Keywords: COVID-19; docking; heparanase (HPSE); inhibitors; virtual screening

Introduction



- HPSE cleaves heparan sulphate (**HS**) side chains of heparin sulphate proteoglycans (**HSPG**).
- It controls the **availability of growth factors, chemokines, lipoproteins** and other bioactive molecules that interact with HS

Introduction



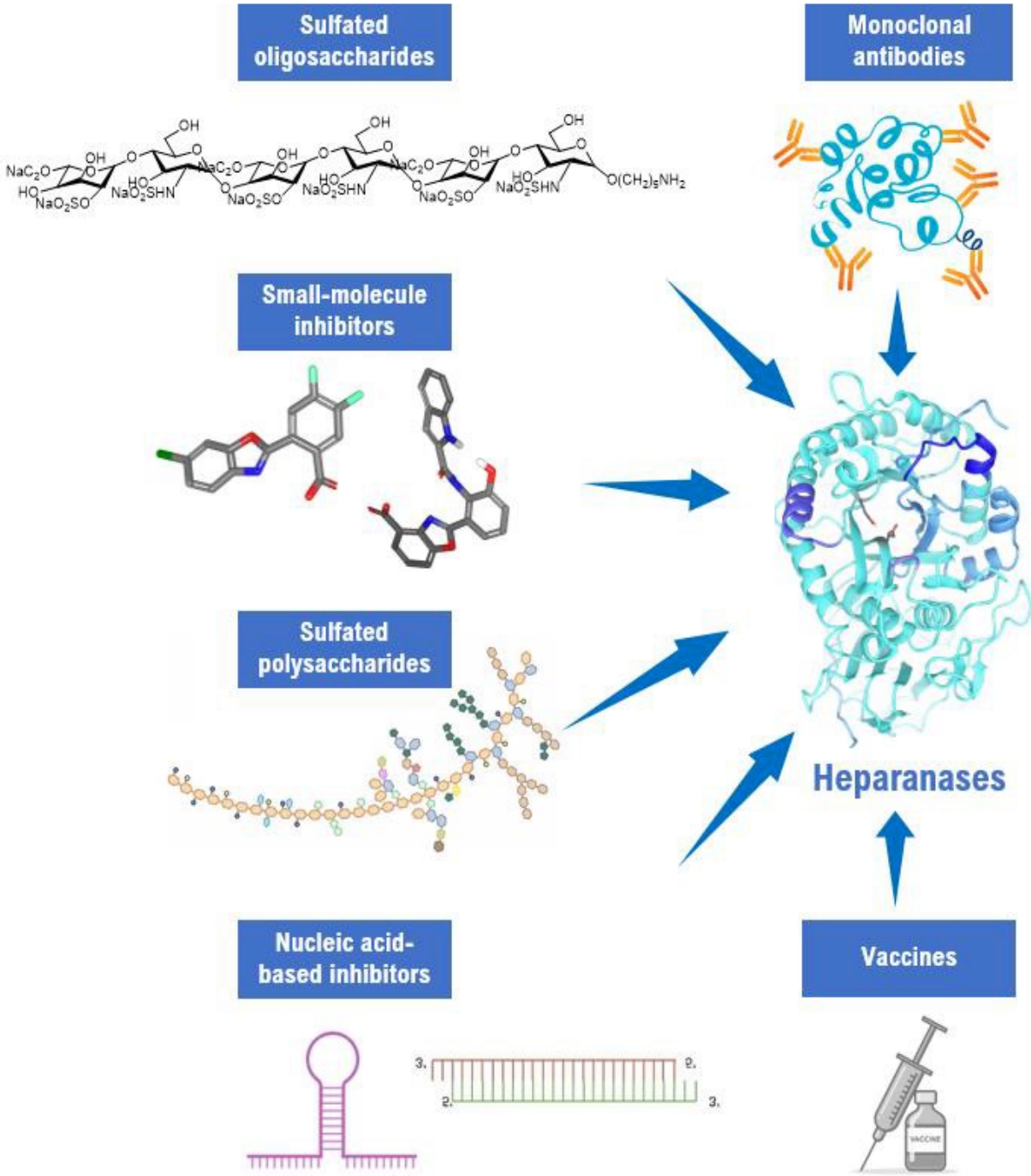
PDB: 5E9C

Human Heparanase **(HPSE)**

· **Catalytic Residues**: *Glu225* (proton donor*) and *Glu343* (nucleophile).
· **HBD-1**: Rich in basic residues.
· **HBD-2**: Rich in basic residues.
· **Glycine loop**: Ligand stability-related area.

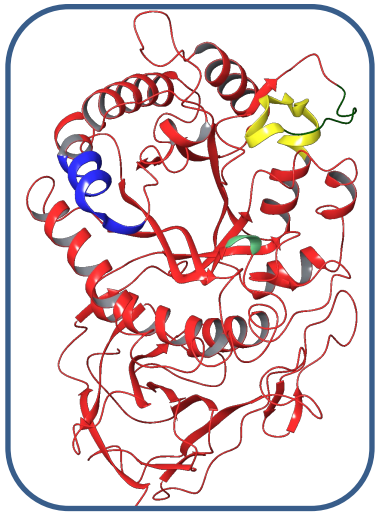
Introduction

Multiple strategies to inhibit HPSE

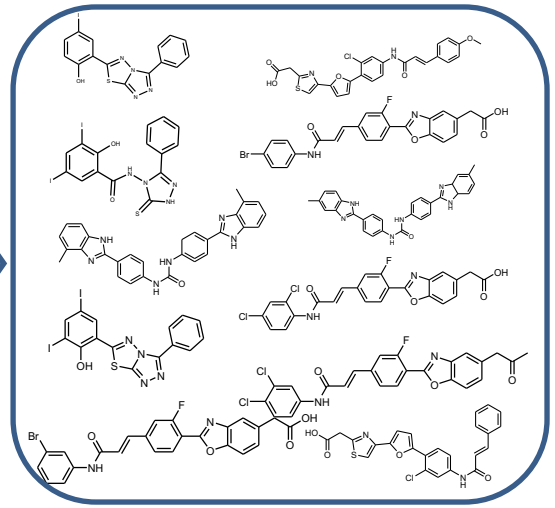


Results and discussion

Target selection



Ligands in Databases



Virtual Screening Workflow

573 known ligands

PubChem, ChEMBL & Pharos Databases

282 chemotypes

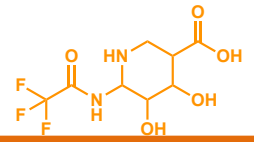
Limit: IC_{50} < 0.50 µM

4*

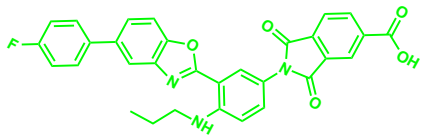
Docking studies

*Compounds drawn from Chemical Library 4 were discarded due to poorer docking values.

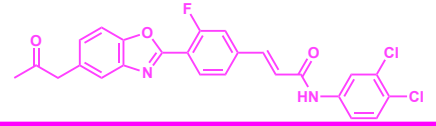
ChEMBL2349245



ChEMBL495255



ChEMBL2349247



Chemical Libraries from PubChem Databases

HTVS + XP-docks

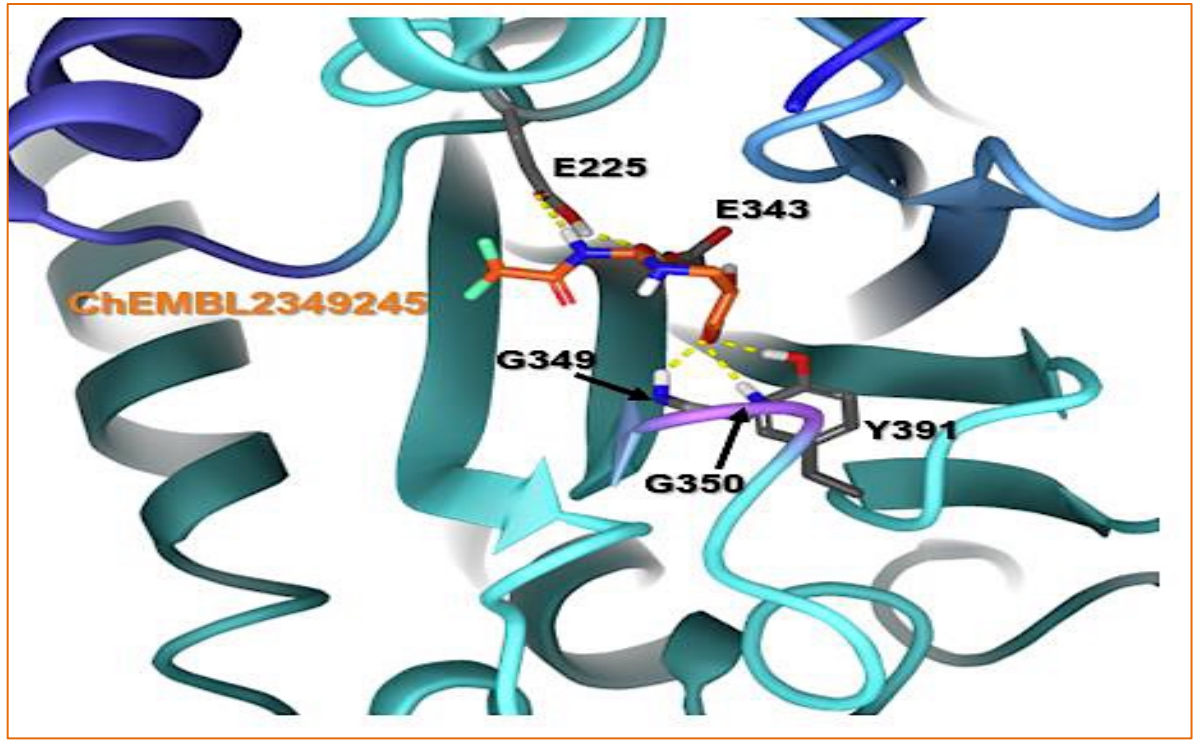
ADME + PAINS

HIT selection

4938 compounds	9923 compounds	34721 compounds
620 chemotypes	323 chemotypes	1352 chemotypes
1	1	1

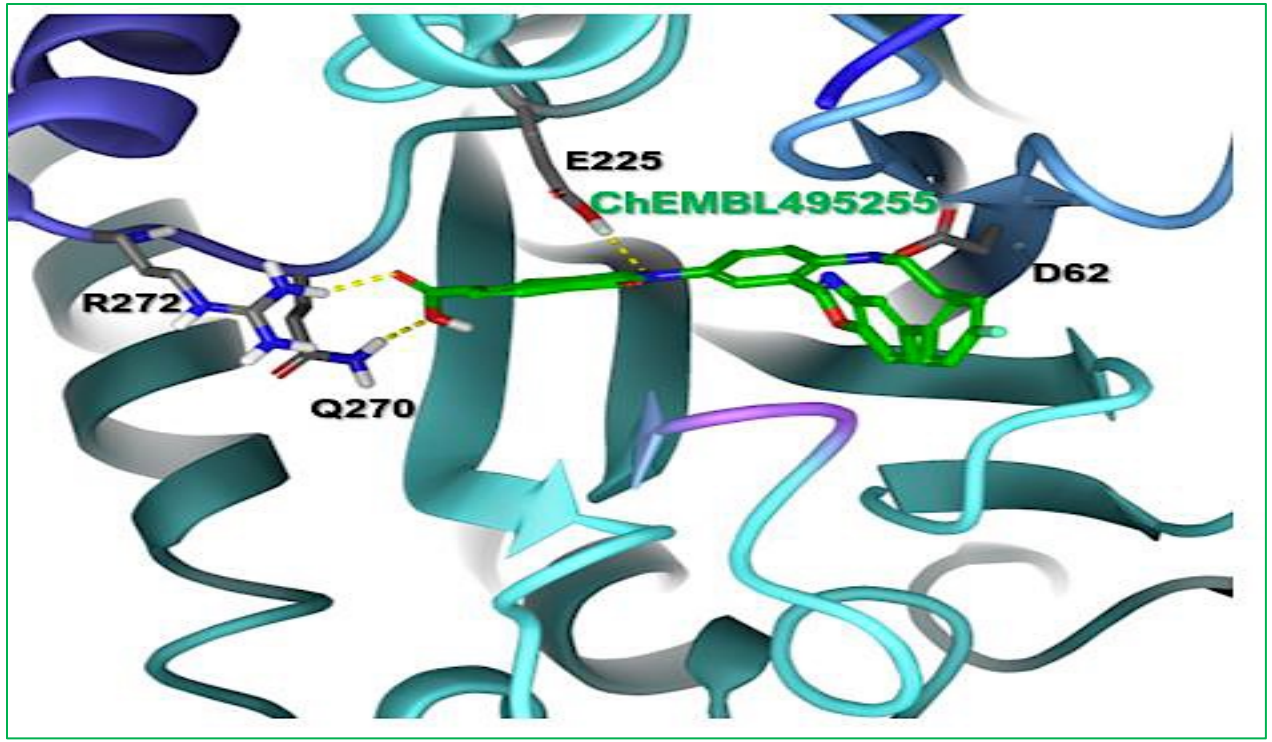
Results and discussion

ChEMBL2349245



IC_{50}: 1.00 μM
Glide Score: -7.86 kJ/mol

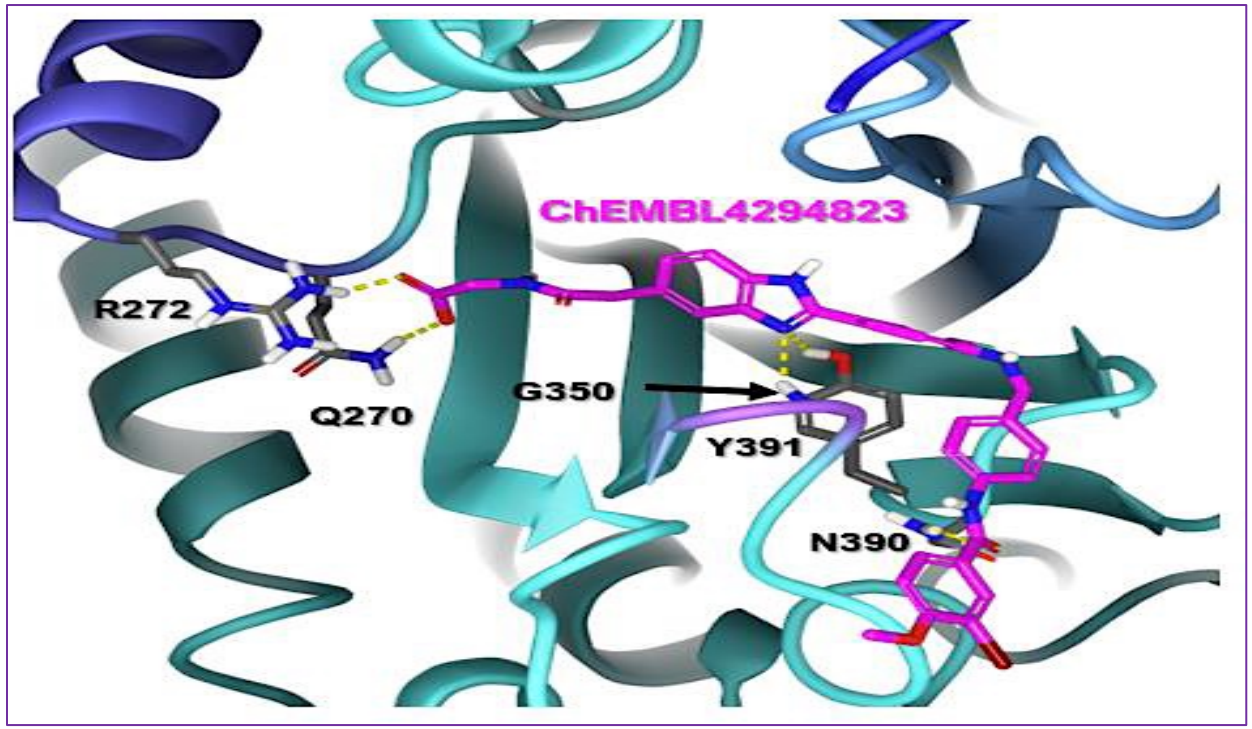
ChEMBL495255



IC_{50}: 0.50 μM
Glide Score: -5.79 kJ/mol

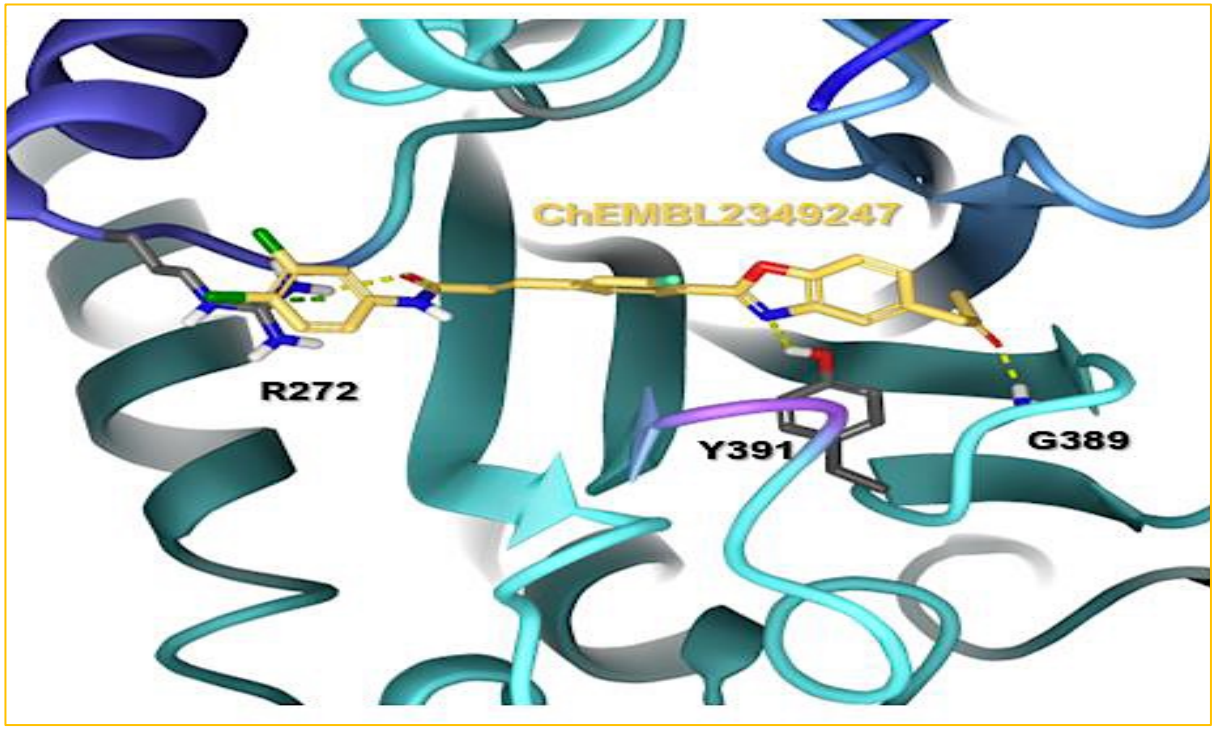
Results and discussion

ChEMBL2349247



IC_{50}: 0.20 μM
Glide Score: -5.60 kJ/mol

ChEMBL4294823



IC_{50}: 0.64 μM
Glide Score: -7.91 kJ/mol

Results and discussion

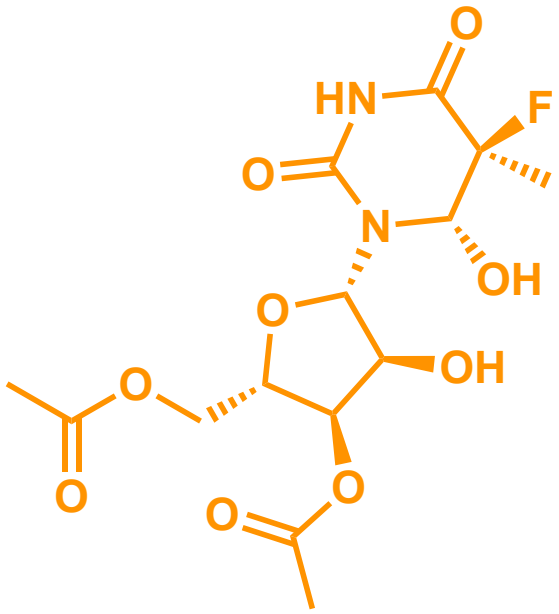
BEST HITS

Compound	QPlogS[a]	QPlogHERG[b]	QPPCaco[c]	QPlogBB[d]	% Human Oral Absorption[e]	PAINS[#]
ChEMBL2349245	-0.72	-0.97	1.90	-1.00	15	0
101687126	-2.53	-3.81	78.62	-1.66	44	0
61187649	-2.77	-0.67	57.15	-1.23	69	0
107828179	-2.83	-0.64	30.74	-1.11	63	0
66265156	-0.50	1.22	30.14	-0.89	52	0
113327907	-2.13	-0.47	36.73	-0.93	62	0
ChEMBL495255	-8.64	-6.24	23.02	-2.27	58	0
25158919	-4.68	-4.76	66.73	-1.28	78	0
23794729	-4.34	-3.94	169.97	-0.78	87	0
103430682	-4.39	-3.21	411.40	-0.13	94	0
119243009	-4.82	-3.64	80.58	-1.38	84	0
ChEMBL2349247	-8.32	-7.43	818.21	-0.75	100	0
81421830	-4.63	-3.34	290.83	0.02	92	0
58743027	-6.07	-4.95	27.71	-1.51	73	0
155906206	-4.35	-4.08	387.64	-0.38	100	0
23886486	-4.35	-3.09	145.77	-0.66	85	0
6968873	-4.72	-4.77	58.63	-1.57	75	0

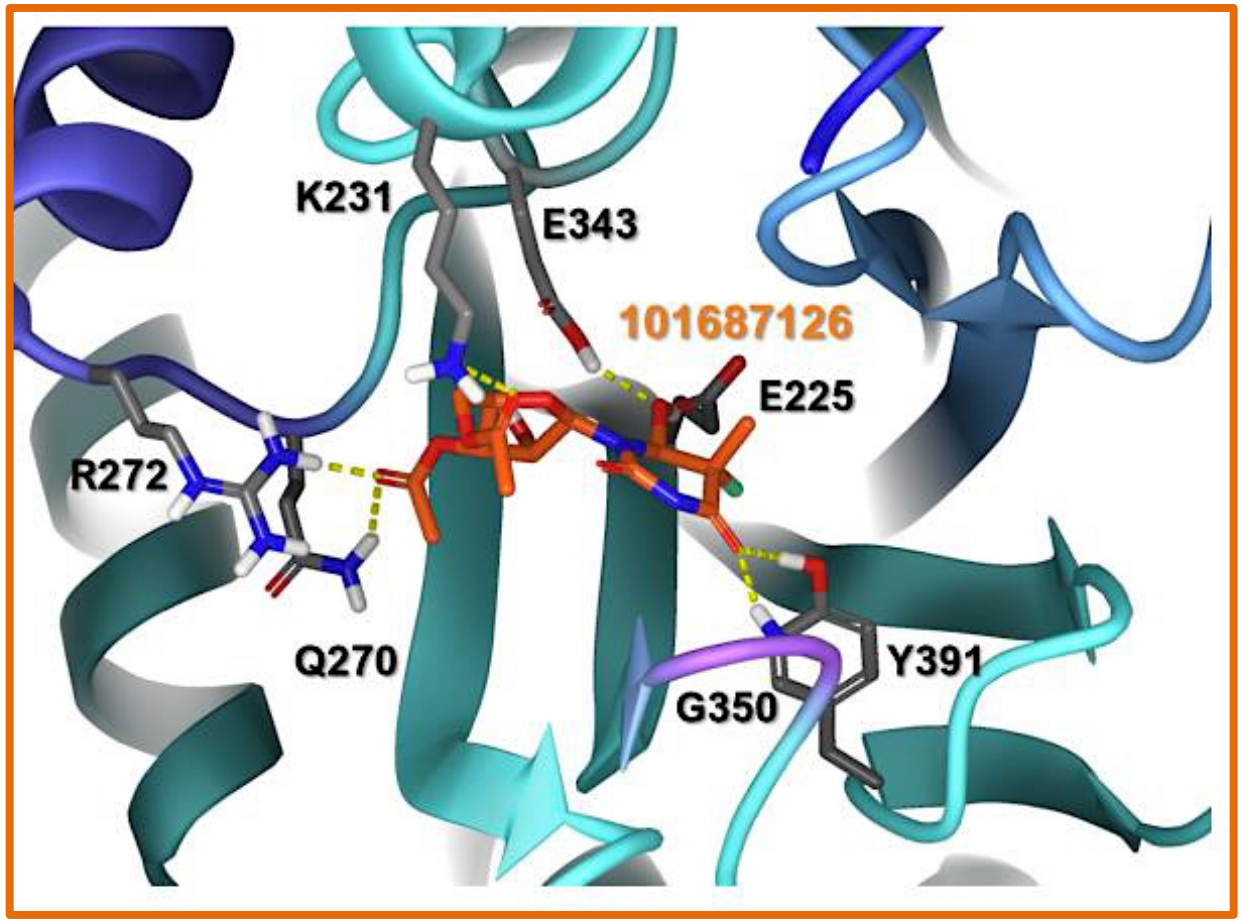
[a]Predicted aqueous solubility [-6.5/0.5]; [b]HERG K^+ Channel Blockage (log IC_{50}) [concern below -5]; [c]Apparent Caco-2 cell permeability in nm/s [<25 poor, >500 excellent]; [d]Predicted log of the brain/blood partition coefficient [-3.0/1.2]; [e]Human Oral Absorption in GI [<25% is poor]. [range of 95% of drugs]. [#]Number of structural alerts as calculated using the swissADME webserver.

Results and discussion

101687126

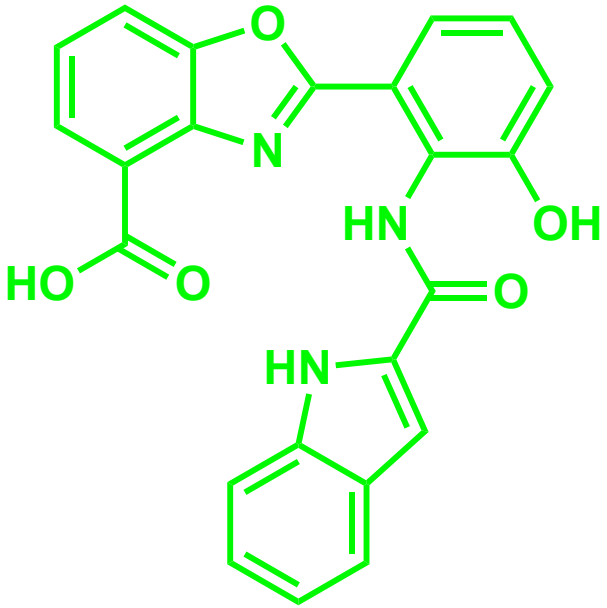


Glide Score:
-10.80 kJ/mol

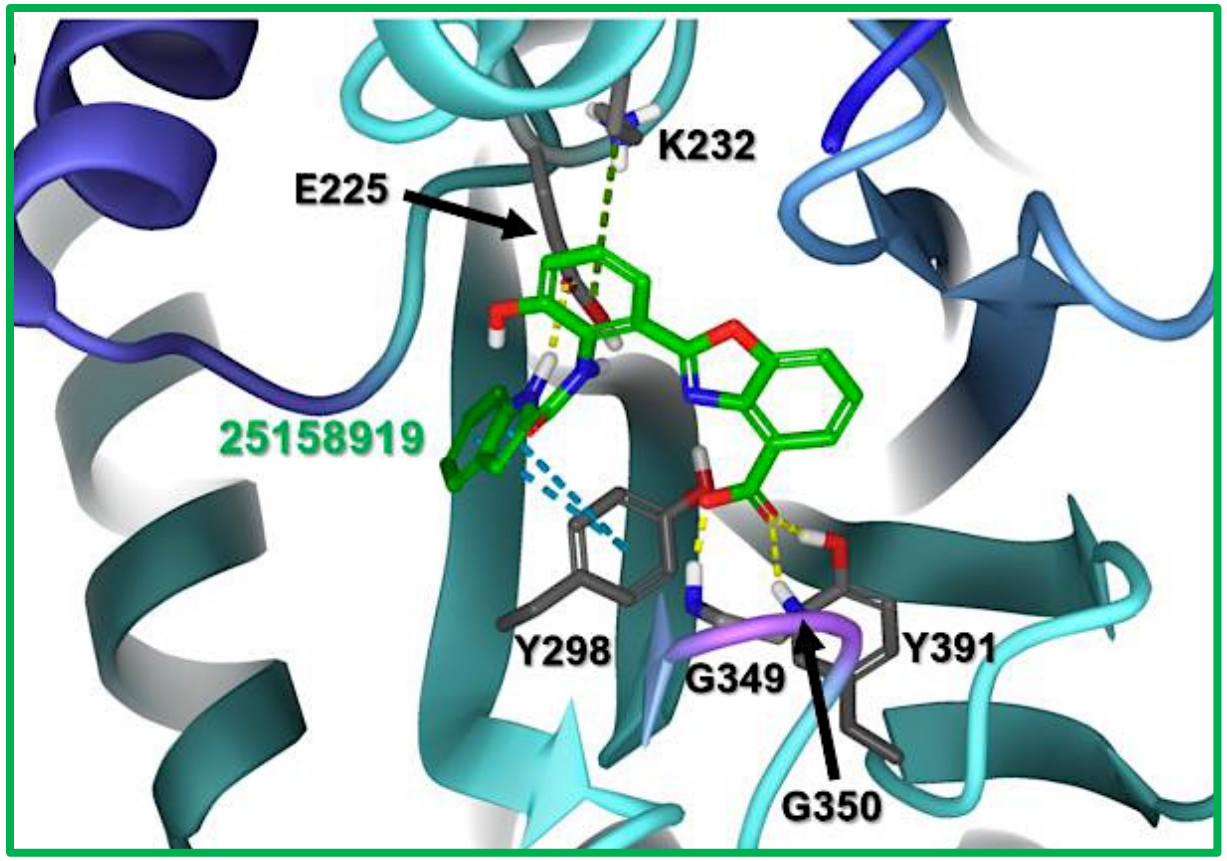


Results and discussion

25158919

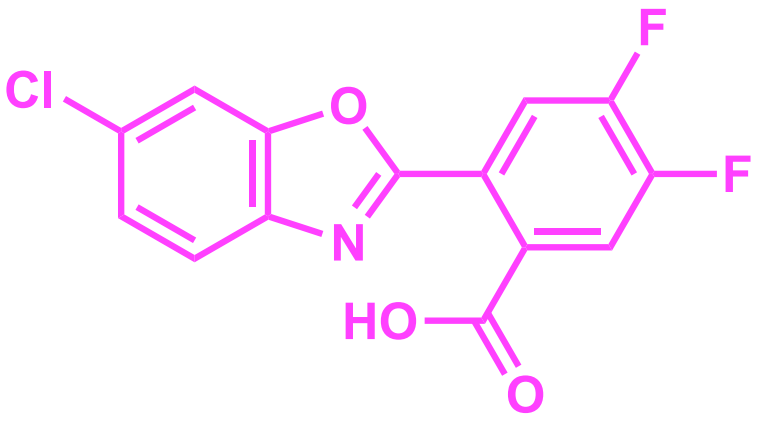


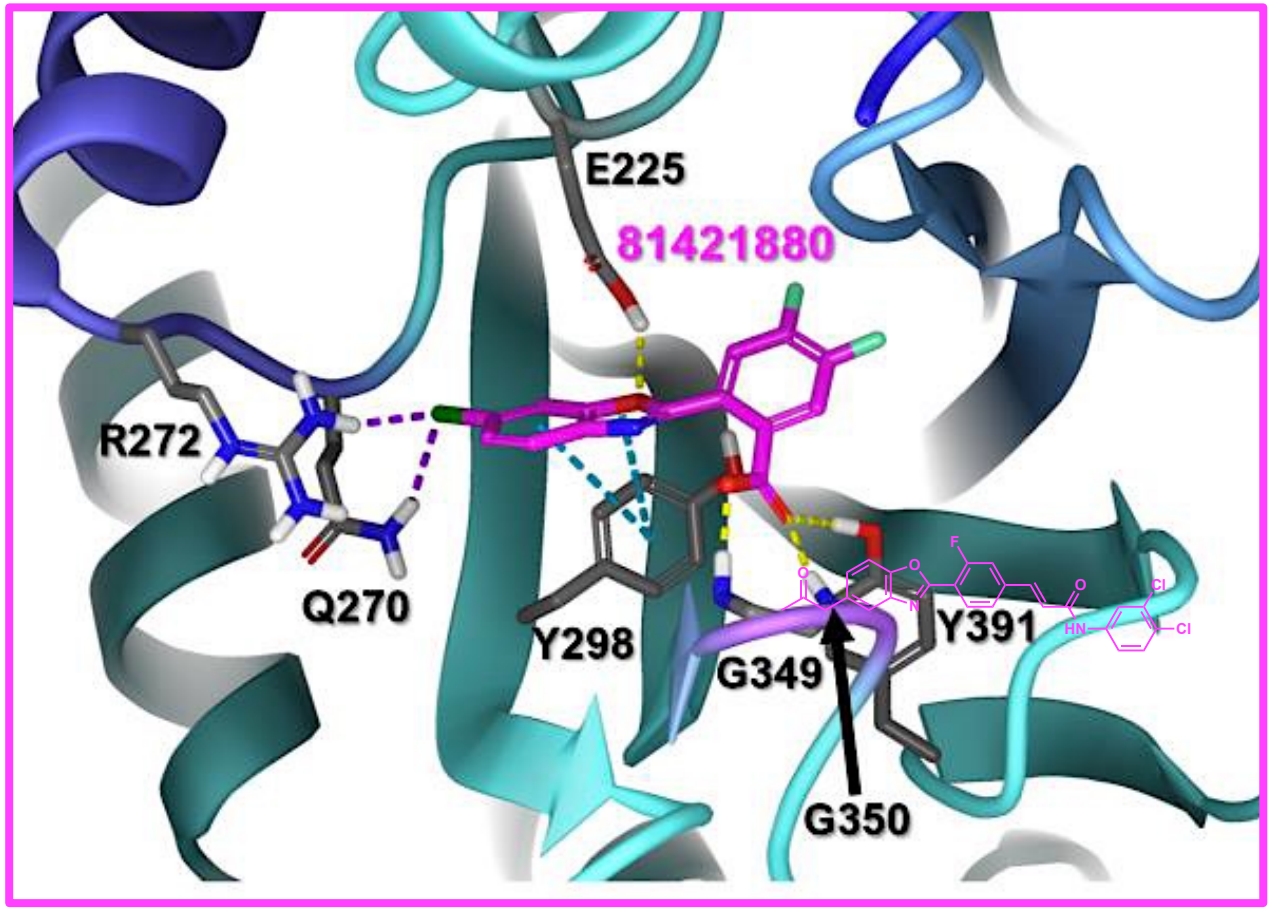
Glide Score:
-9.33 kJ/mol



Results and discussion

81421880

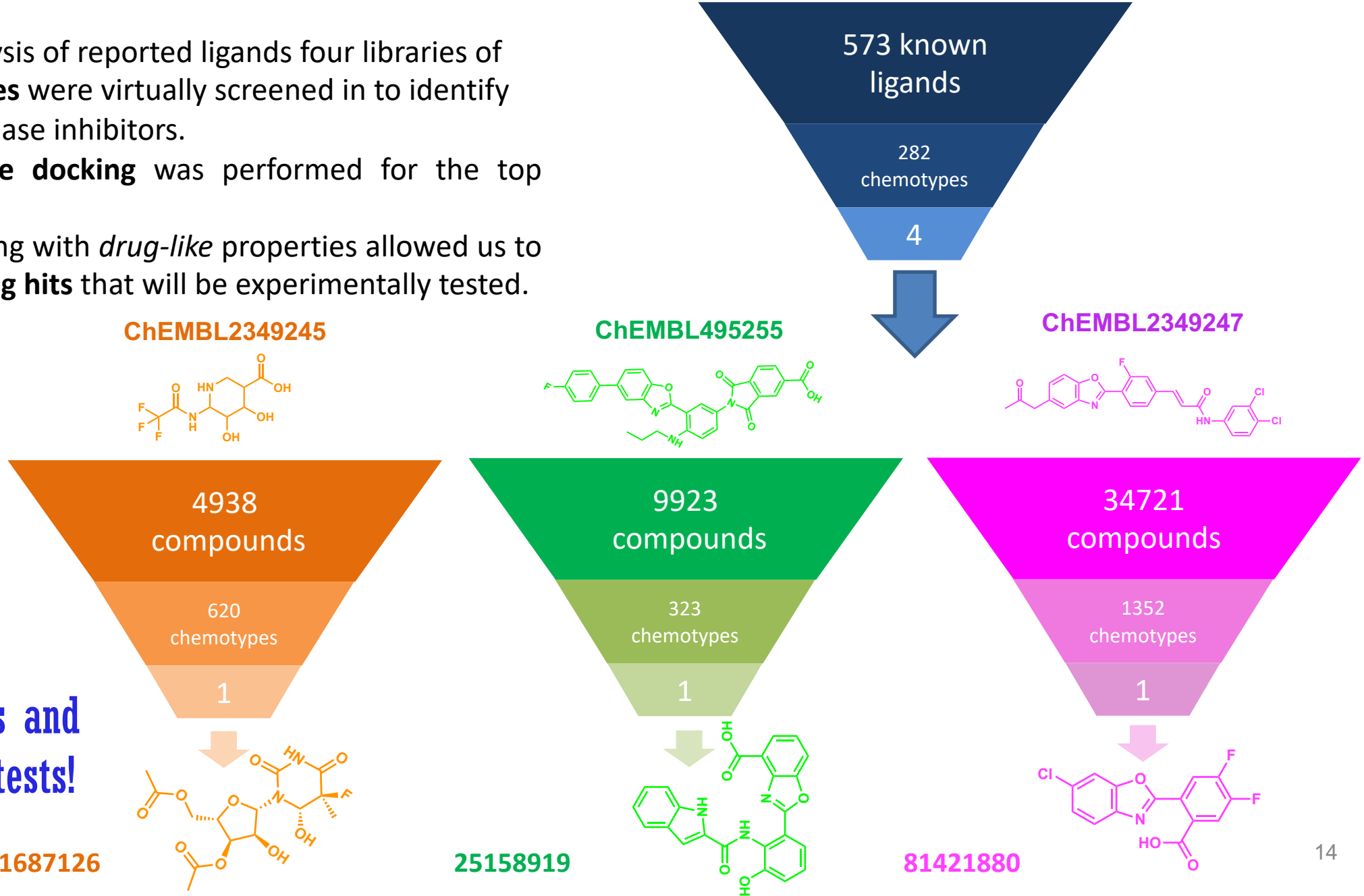




Glide Score:
-7.90 kJ/mol

Conclusions

- Upon structural analysis of reported ligands four libraries of **over 50,000 molecules** were virtually screened in to identify more potent heparanase inhibitors.
- **Extra precision Glide docking** was performed for the top ranked molecules.
- Docking energies along with *drug-like* properties allowed us to select **three promising hits** that will be experimentally tested.



Ready for synthesis and biological activity tests!

Thank you for your attention

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