Drug Repurposing against SARS-CoV-2 Receptor Binding Domain using Ensemble-based Virtual Screening and Molecular Dynamics Simulations

Supplementary Information

Table S1: List of FDA approved drugs which are common in both top 50 XP-based and MM-GBSA-based shortlisted drugs. Receptor ID 1, 2 and 3 corresponds to the MD generated conformations of RBD. Receptor ID 4 is crystal conformation.

Sr. No	Generic name	Drug bank ID	XP score	MM-GBSA Score	Best Receptor ID	Description
1	Acarbose	DB00284	-11.53	-34.11	2 (XP), 3 (MM-GBSA)	Anti-Diabetic
2	FAD	DB03147	-10.69	-54.31	1	Dietary supplement
3	Rutin	DB01698	-10.30	-52.51	2	Dietary supplement
4	Gonadorelin	DB00644	-9.43	-53.12	1 (XP), 2 (MM-GBSA)	Synthetic female hormone
5	Hesperidin	DB04703	-8.85	-59.65	1	Antioxidant
6	Lactitol	DB12492	-8.53	-50.49	1	Sweetener and laxative. Used for the treatment of constipation
7	Diosmin	DB08995	-8.23	-47.06	2	Antioxidant. Used for the treatment of hemorrhoids and leg sores
8	Hyaluronic acid	DB08818	-10.55	-40.99	2	Anionic, nonsulfated glycosaminoglycan used to treat knee pain and reduce wrinkles on face during plastic surgery
9	Nystatin	DB00646	-9.49	-55.99	1	A polyene antifungal drug that has broad-spectrum fungicidal and fungistatic activity. Used to treat oral candidiasis

10	NADH	DB00157	-9.34	-43.17	4	Coenzyme. Dietary supplement
11	Framycetin	DB00452	-9.24	-33.48	3	**A**ntibiotic. For the treatment of bacterial blepharitis, bacterial conjunctivitis, corneal injuries, corneal ulcers and meibomianitis.
12	Fondaparinux	DB00569	-8.54	-32.06	3	Fondaparinux (Arixtra) is a synthetic anticoagulant agent.
13	Vidarabine	DB00194	-8.33	-31.30	1	**A** nucleoside antibiotic isolated from Streptomyces antibioticus. For treatment of chickenpox - varicella, herpes zoster and herpes simplex
14	Pralatrexate	DB06813	-8.02	-37.99	1	Pralatrexate is an antimetabolite for the treatment of relapsed or refractory peripheral T-cell lymphoma.
15	Gemcitabine	DB00441	-7.94	-32.90	1	Gemcitabine is a nucleoside analog used as chemotherapy.
16	Sucrose	DB02772	-7.61	-31.83	2	A nonreducing disaccharide composed of glucose and fructose linked via their anomeric carbons.
17	Glutathione Disulfide	DB03310	-7.51	-36.47	4	Glutathione is an antioxidant. After oxidation of GSH, glutathione disulfide forms.
18	Atrovastatin	DB01076	-7.36	-39.16	2	Atorvastatin (Lipitor®), is a lipid-lowering drug included in the statin class of medications.

Table S2: Known Side effects of repurposed drugs from the literature.

Drug Name	Drug bank ID	Major side effects	Reference
Gonadorelin	DB00644	Difficulty in breathing, flushing (continuing) and rapid heartbeat	1
Fondaparinux	DB00569	Pale skin, troubled breathing with exertion, unusual bleeding or bruising, unusual tiredness or weakness	2
Atrovastatin	DB01076	Type 2 diabetes mellitus, myopathy, persistent liver enzyme abnormalities	3
FAD	DB03147	No adverse effects	4
Hyaluronic acid	DB08818	Allergic reactions	5
Pralatrexate	DB06813	Abdominal pain, backpain, bloody nose, itching skin, rash and loss of strength	6

1. https://www.mskcc.org/cancer-care/patient-education/gonadorelin
2. https://www.mskcc.org/cancer-care/patient-education/fondaparinux
3. https://www.mskcc.org/cancer-care/patient-education/atorvastatin
4. https://lpi.oregonstate.edu/mic/vitamins/riboflavin
5. https://www.mskcc.org/cancer-care/patient-education/hyaluronate-and-derivatives
6. https://www.mskcc.org/cancer-care/patient-education/pralatrexate

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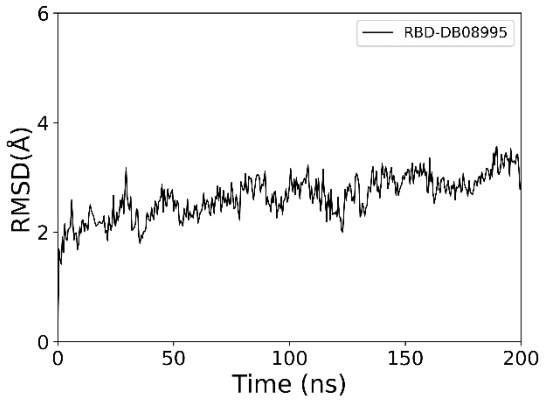

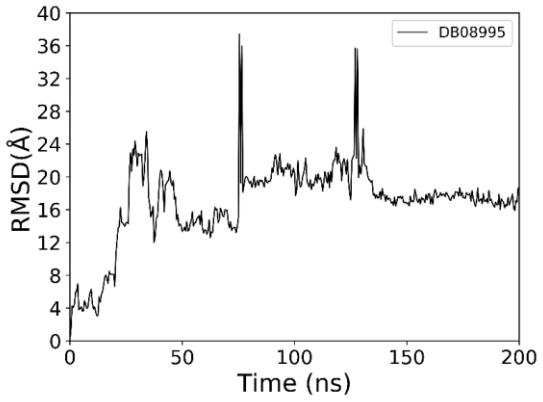

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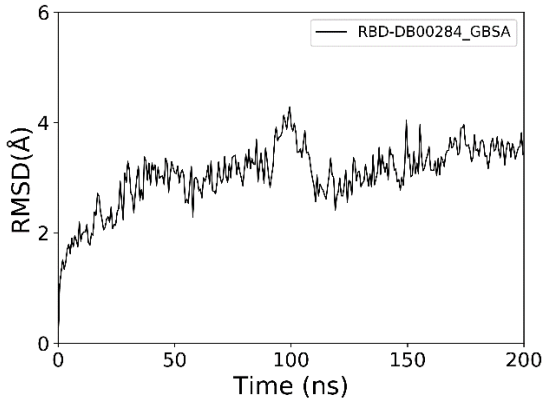

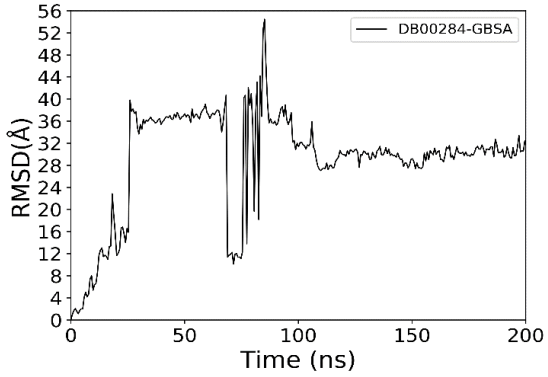

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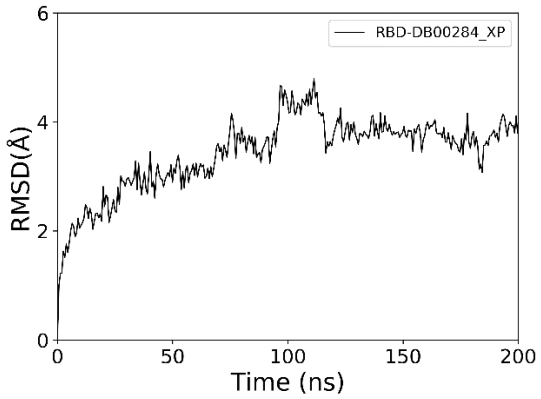

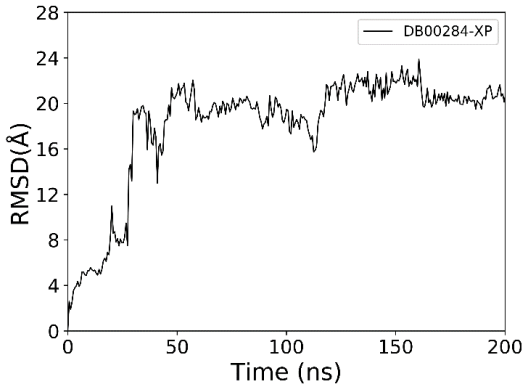

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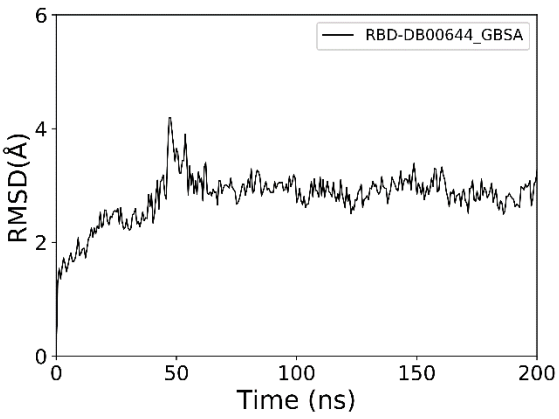

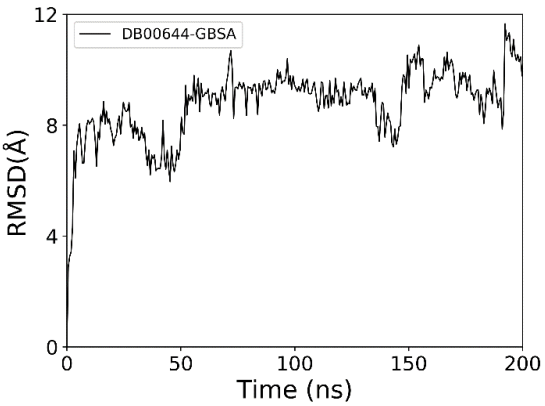

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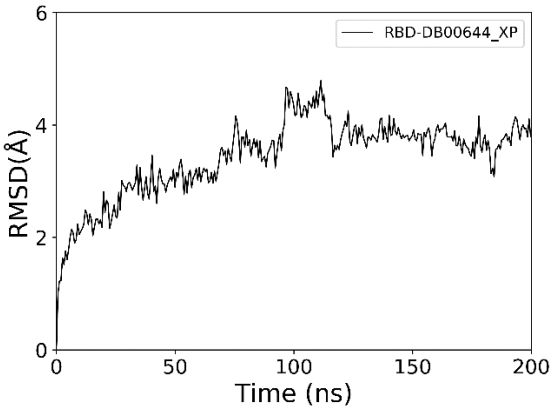

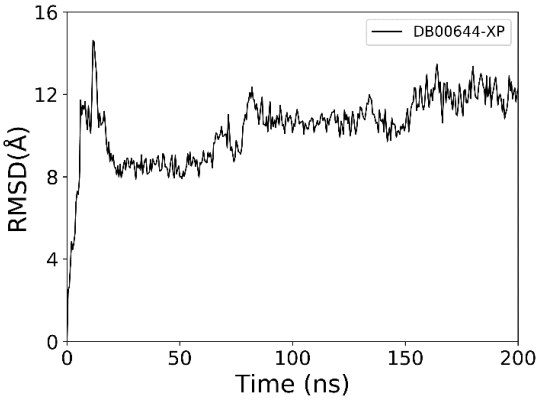

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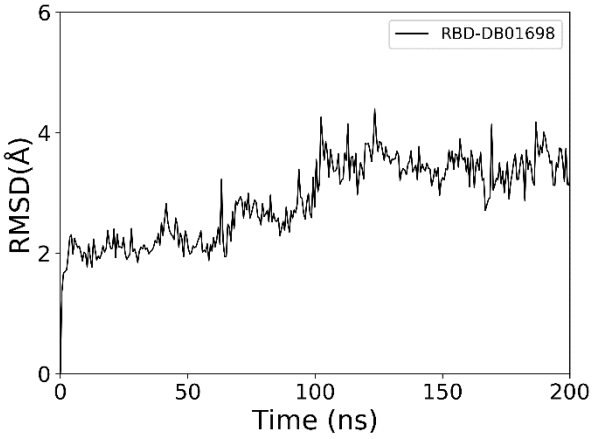

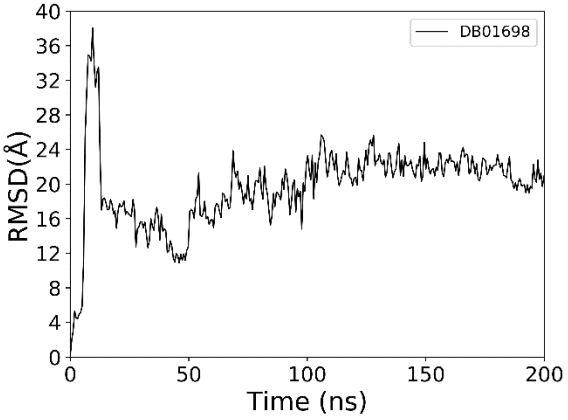

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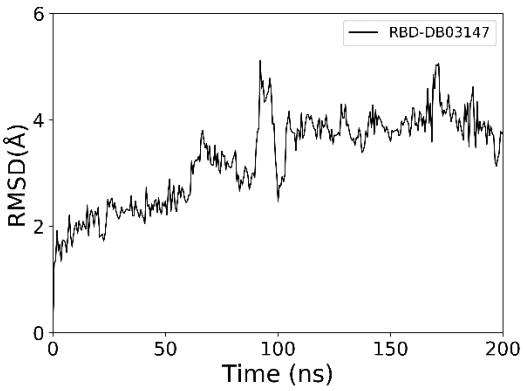

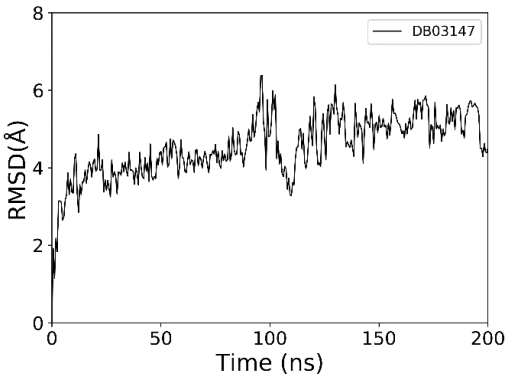

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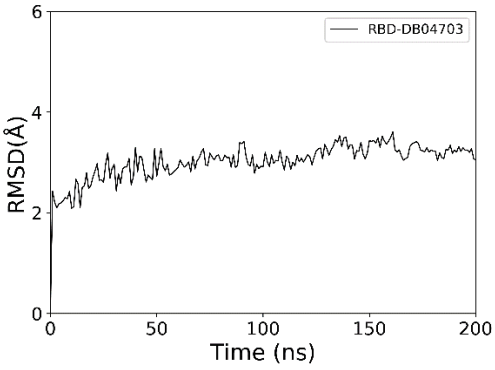

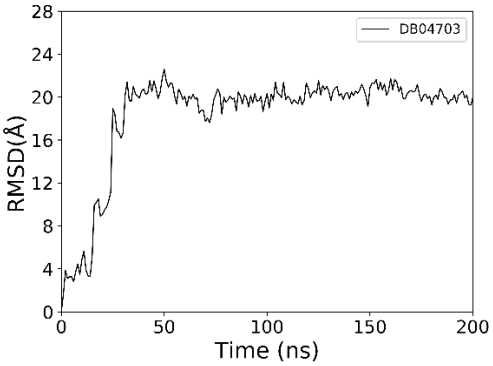

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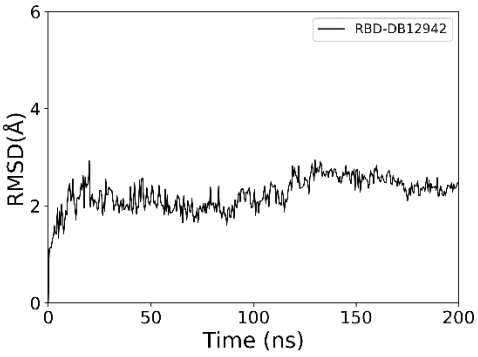

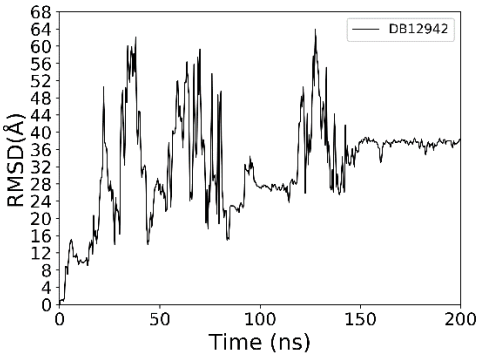

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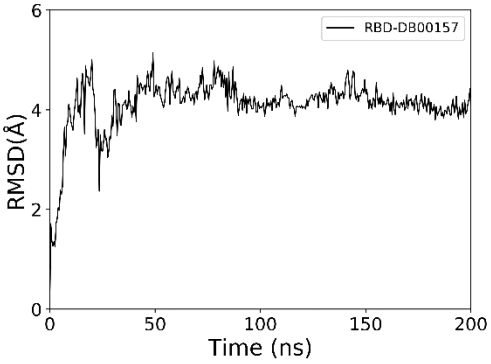

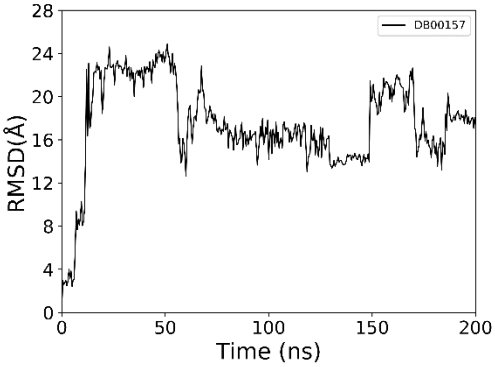

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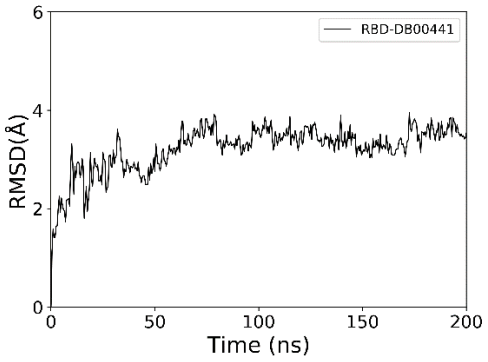

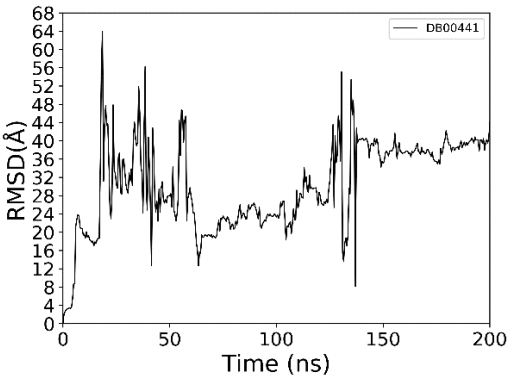

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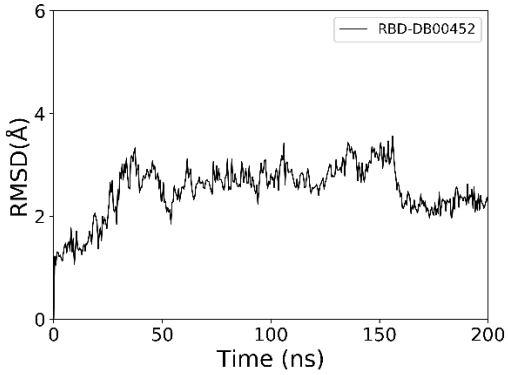

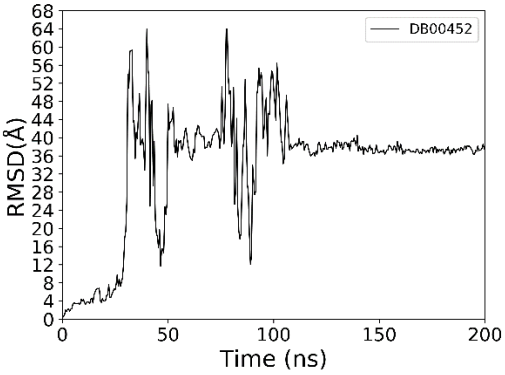

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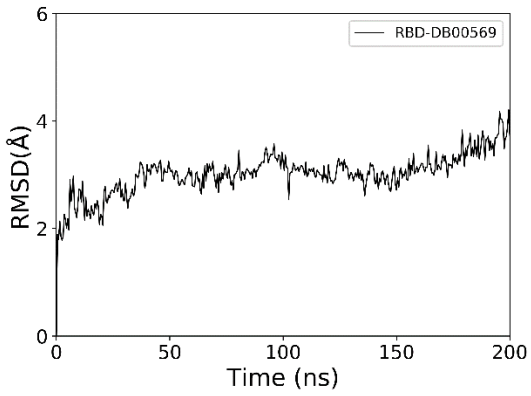

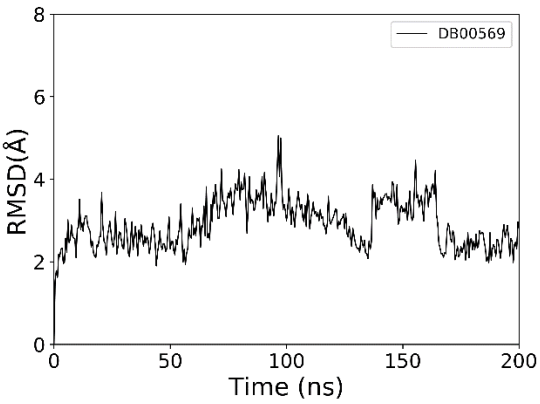

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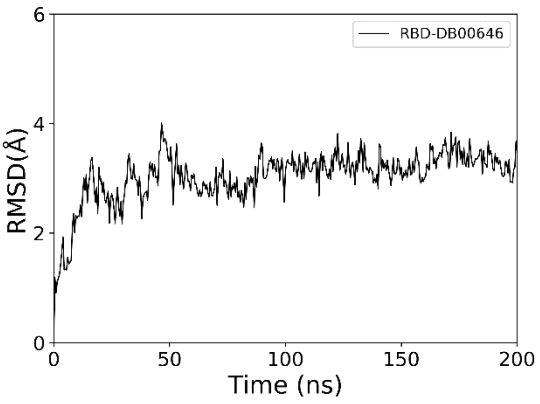

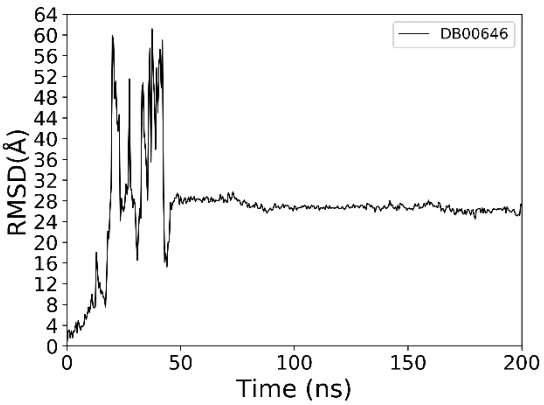

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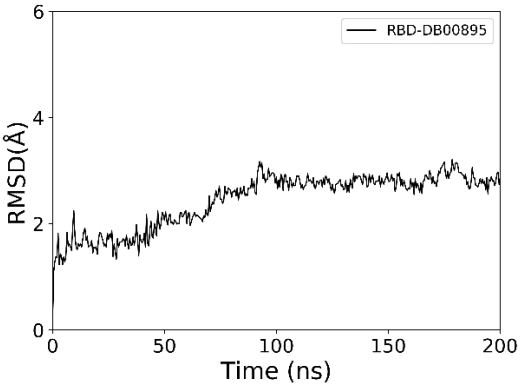

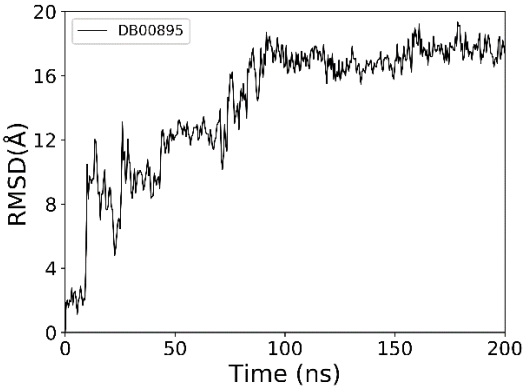

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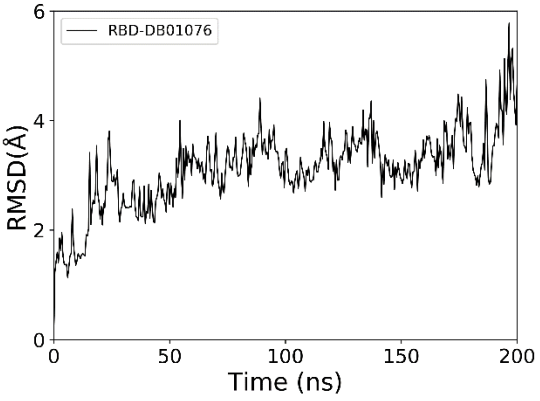

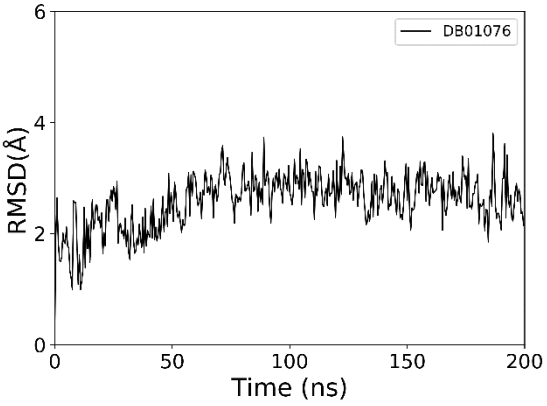

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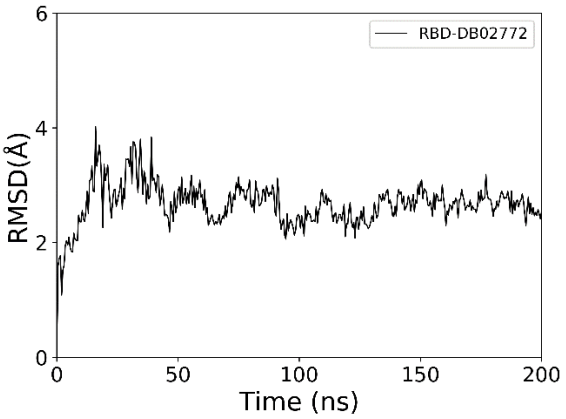

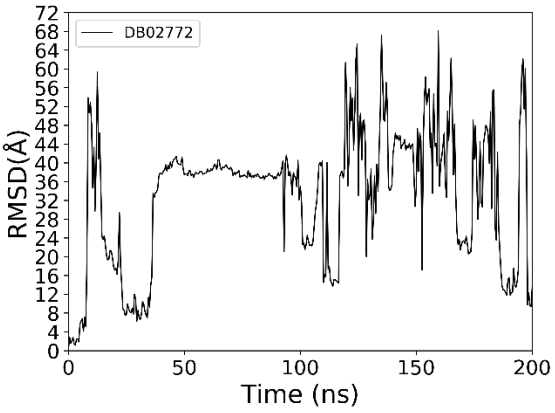

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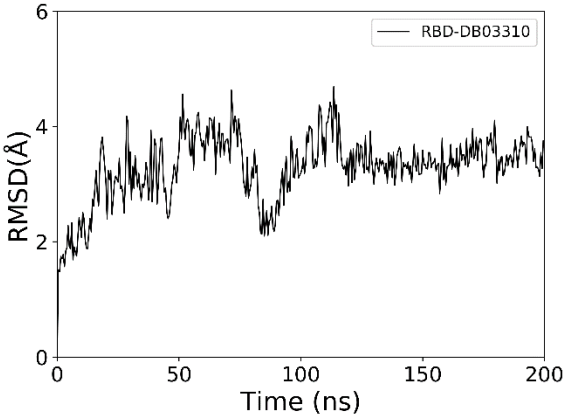

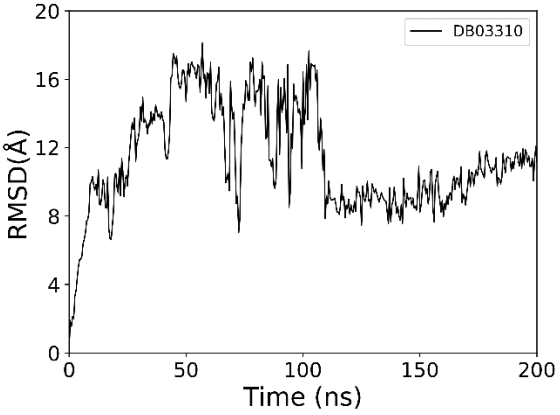

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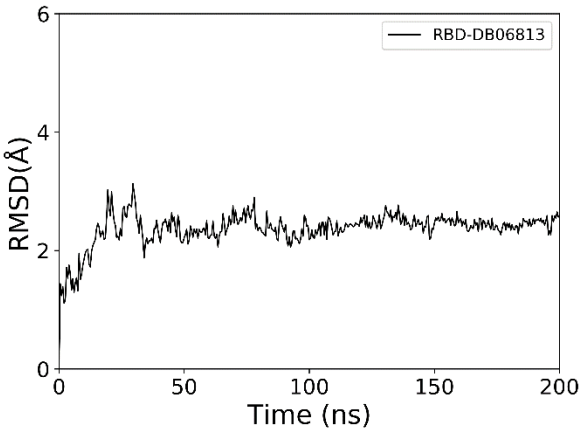

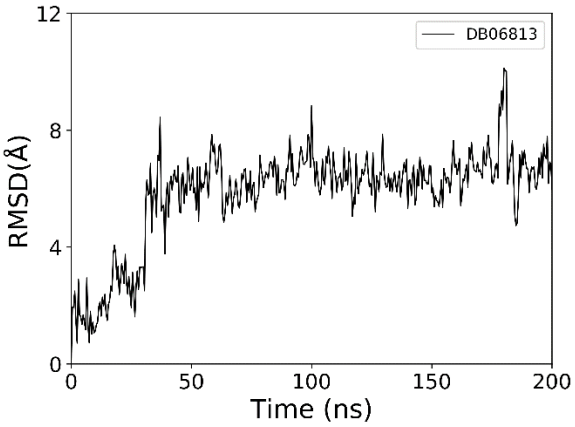

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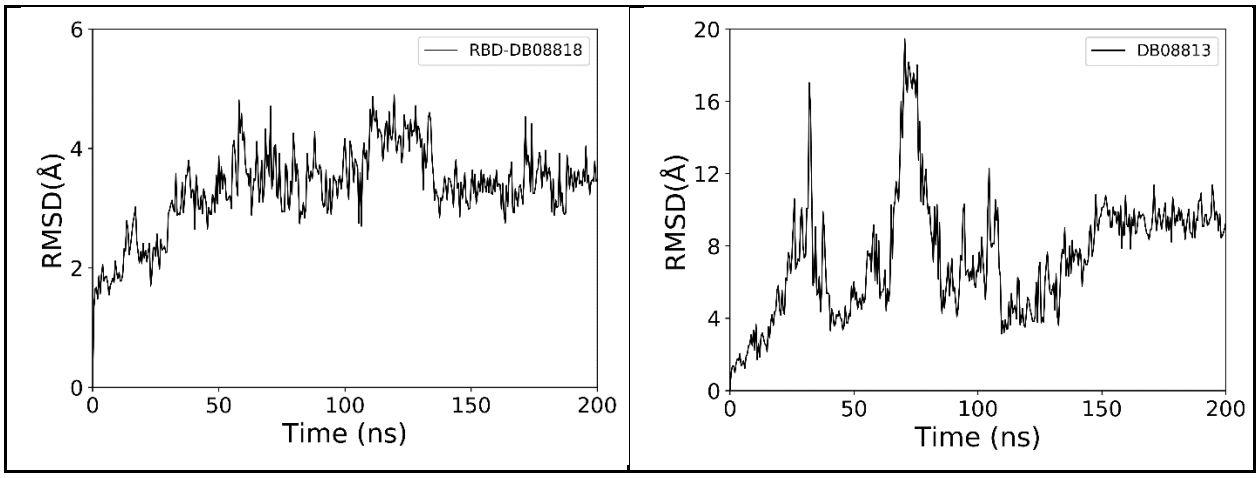

Figure S1: RMSD plots of SARS-CoV-2 RBD (left column) and drugs (right column) in 21 RBD-Drug complexes.

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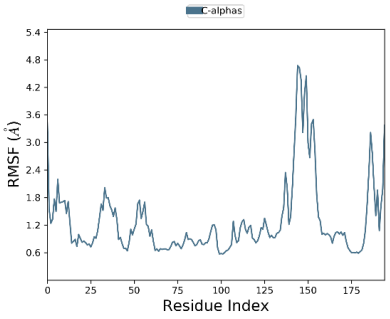

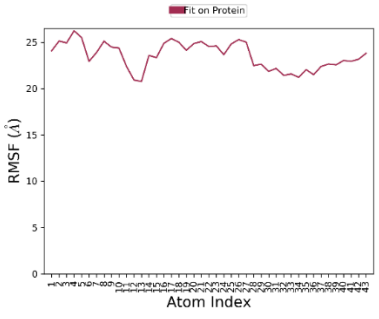

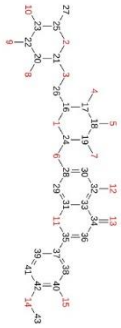

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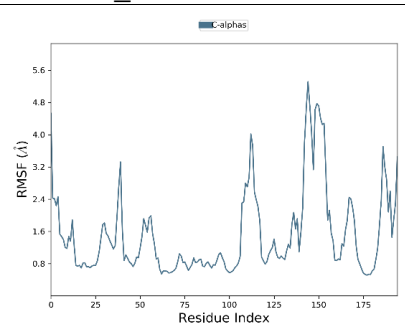

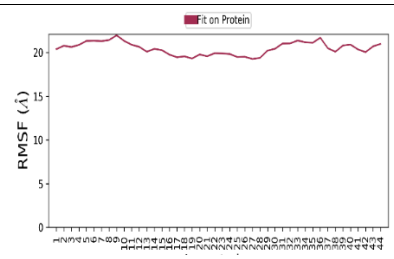

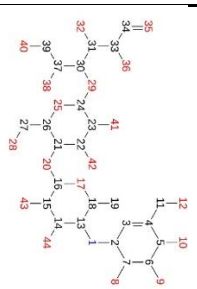

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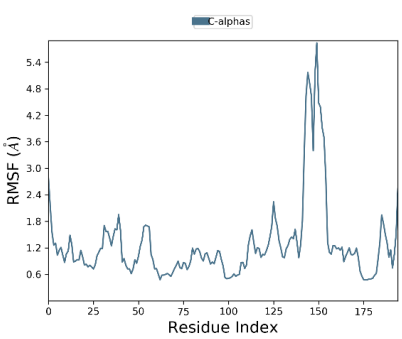

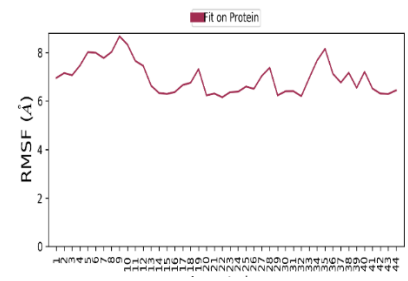

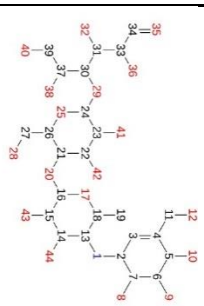

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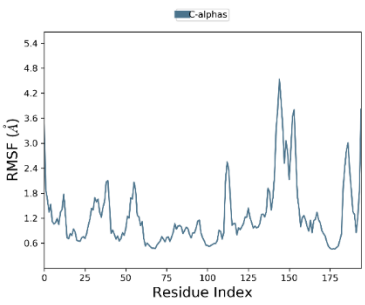

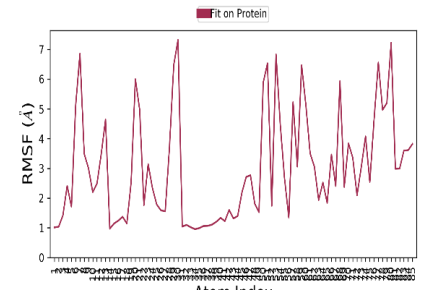

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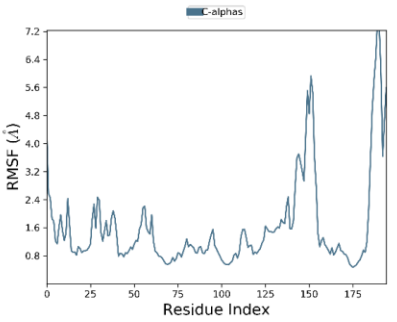

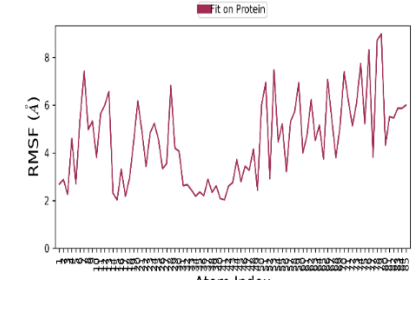

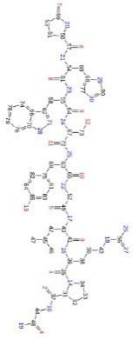

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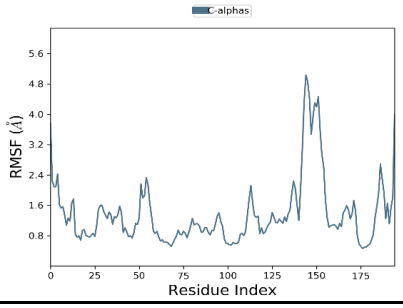

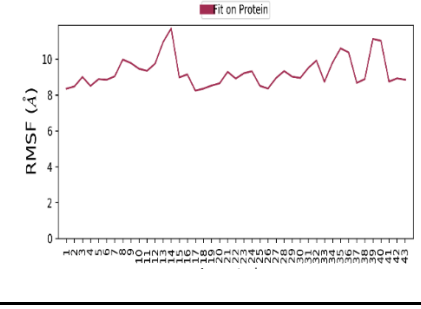

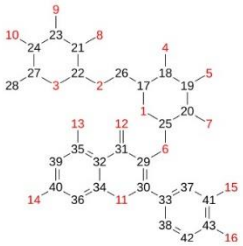

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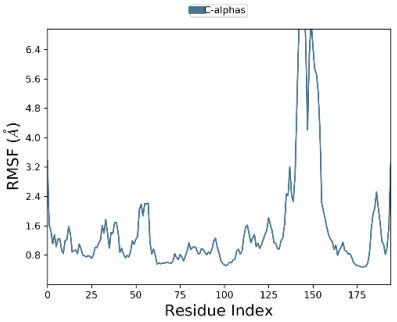

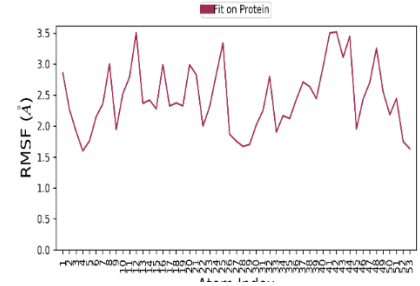

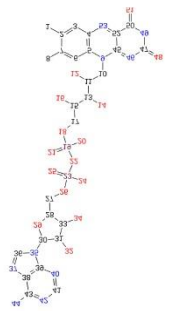

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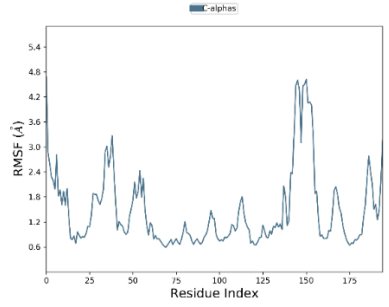

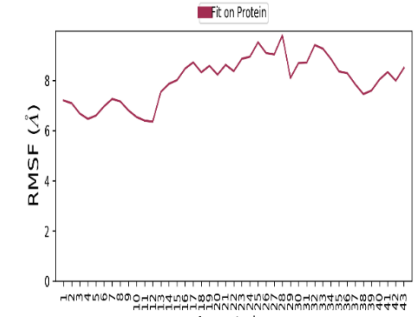

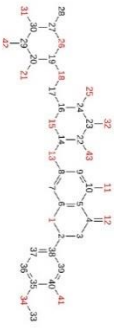

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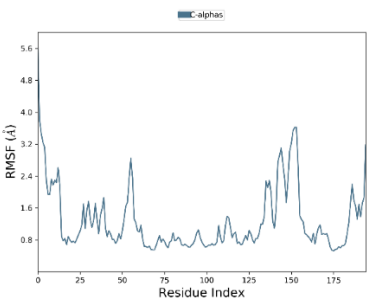

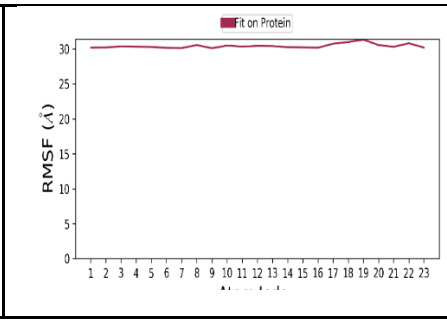

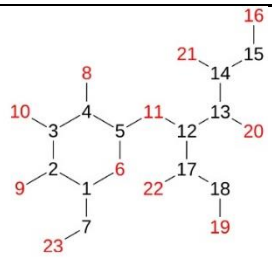

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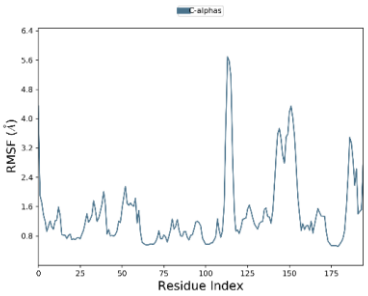

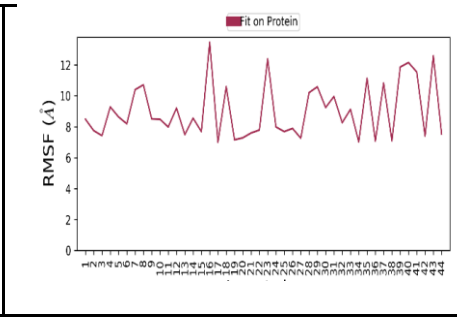

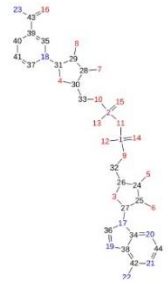

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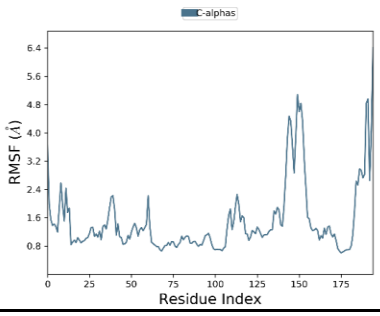

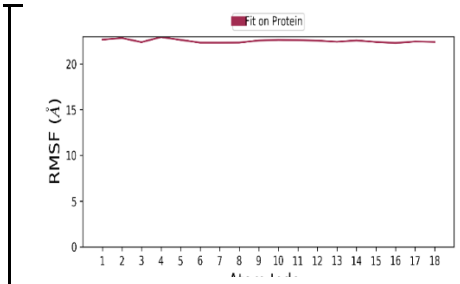

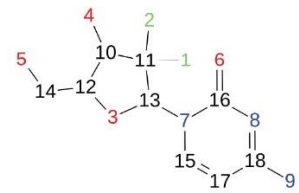

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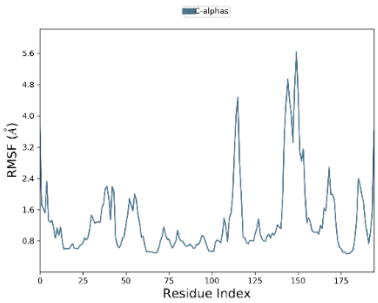

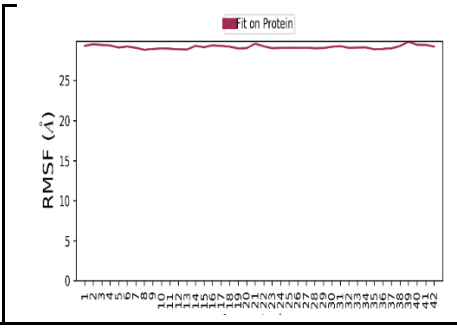

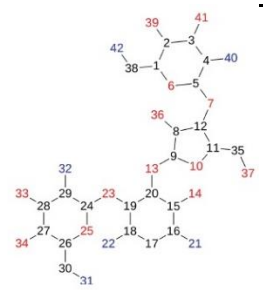

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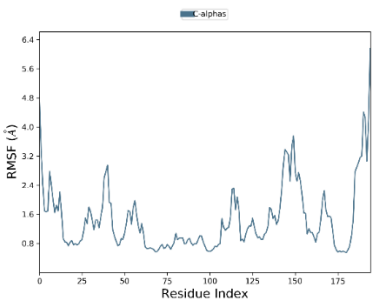

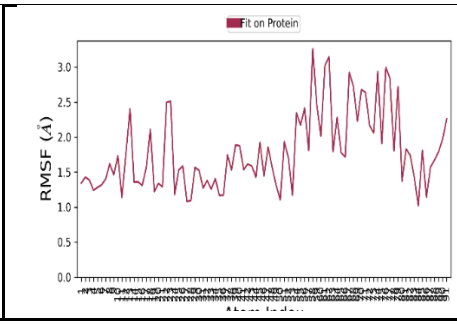

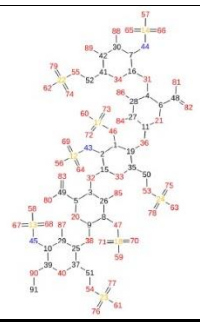

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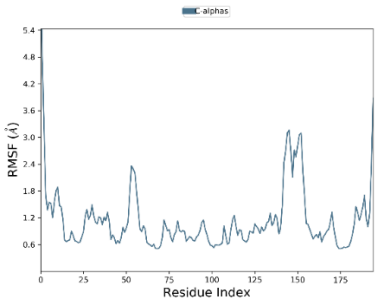

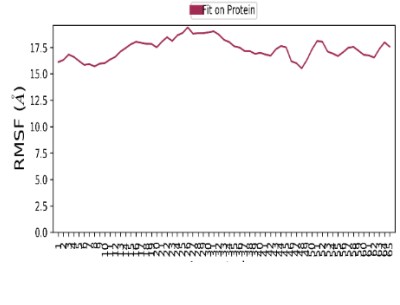

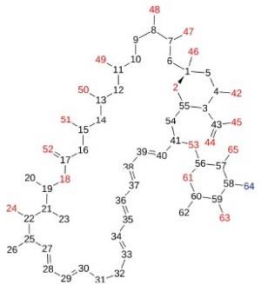

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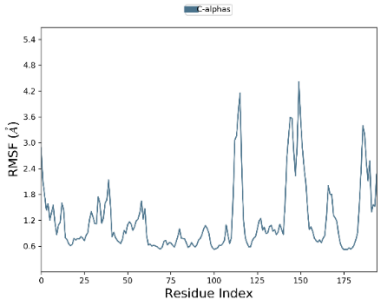

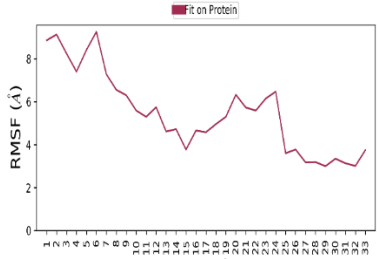

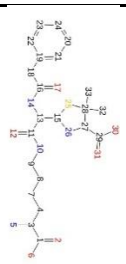

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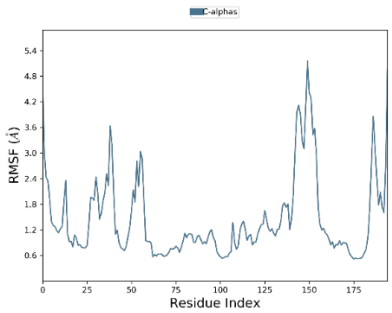

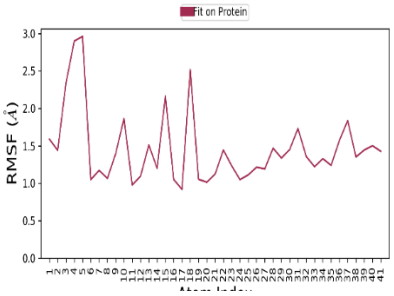

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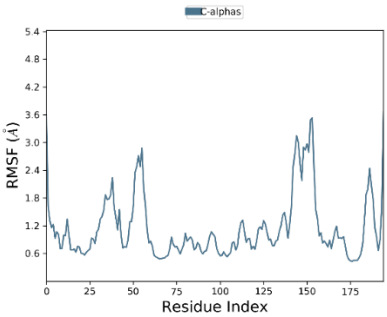

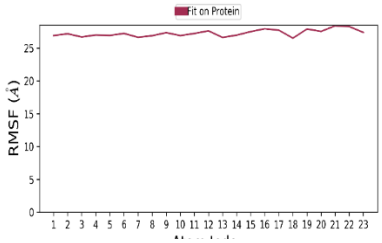

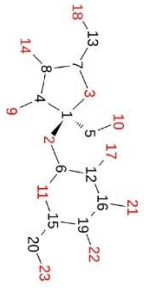

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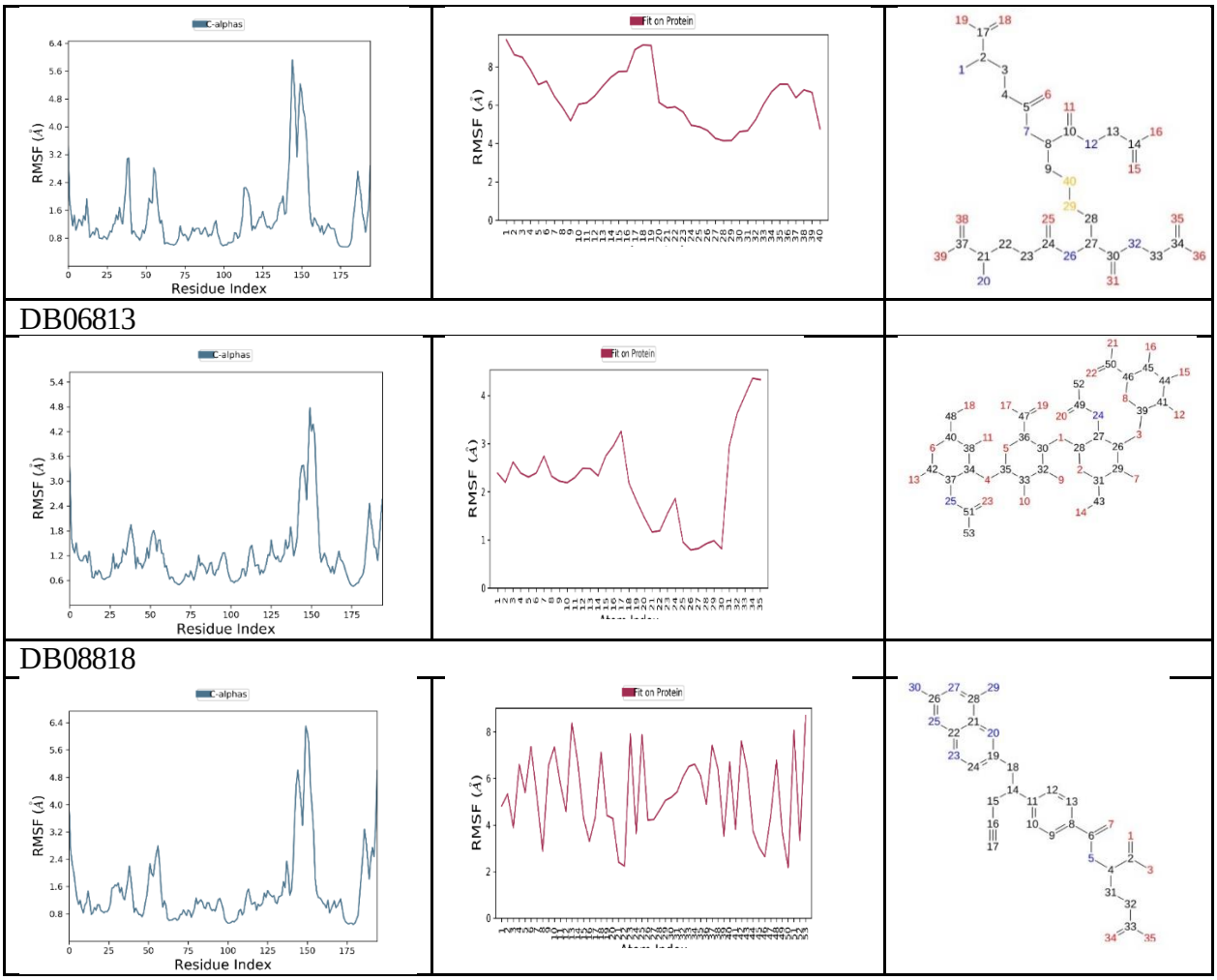
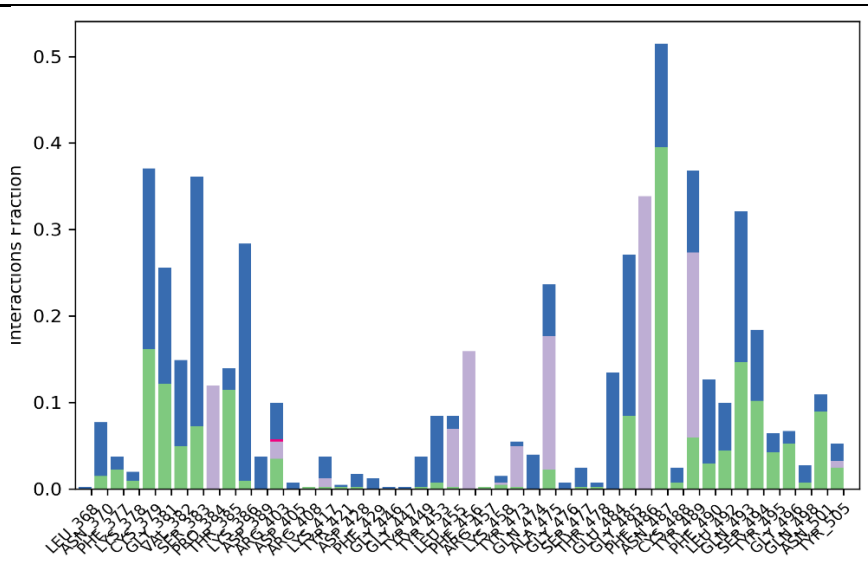
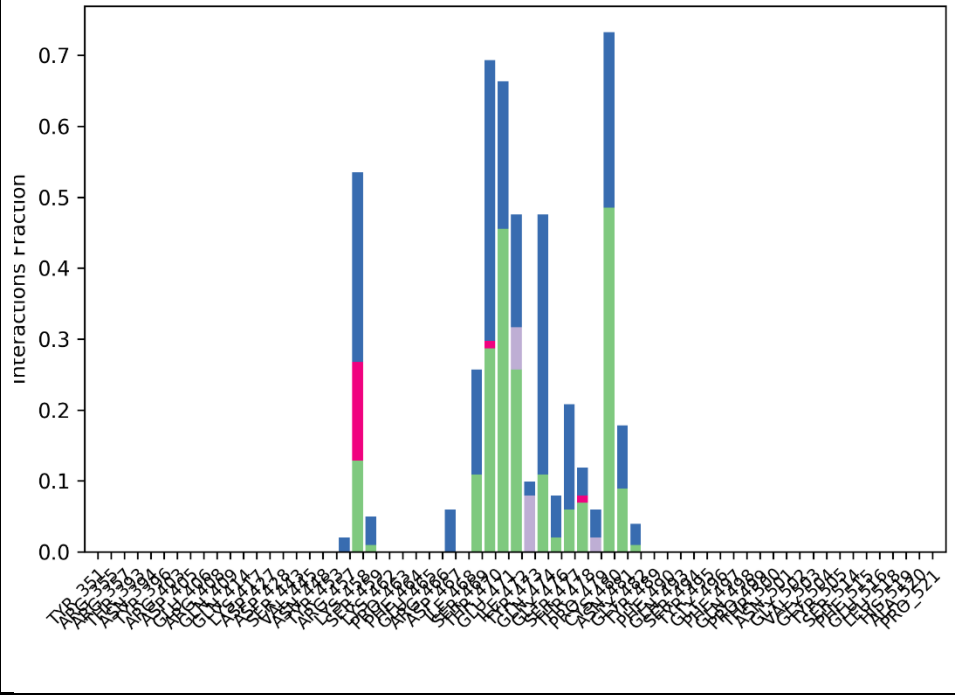
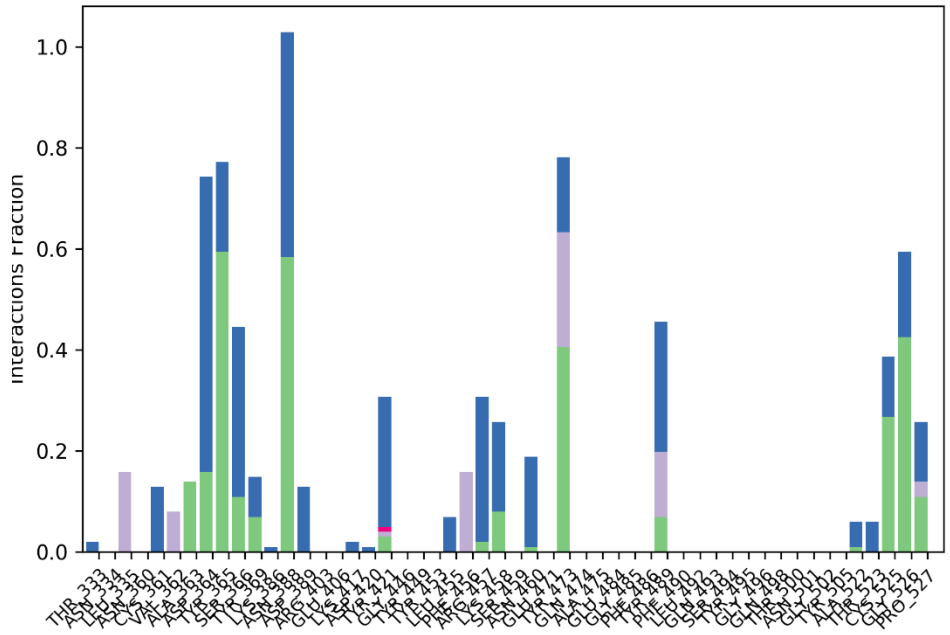
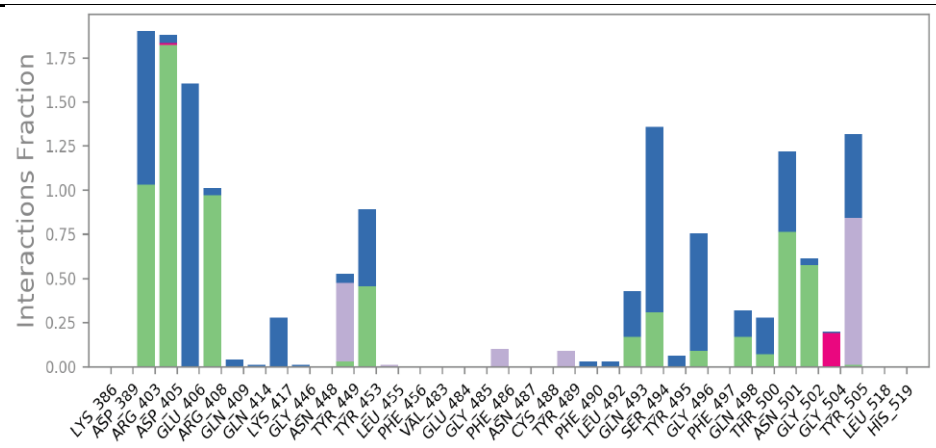
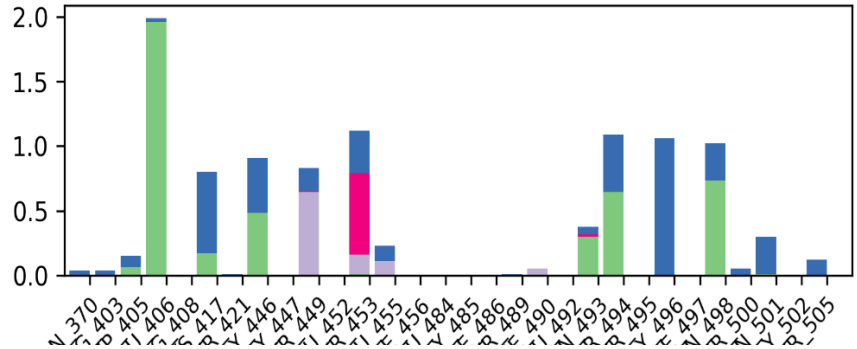
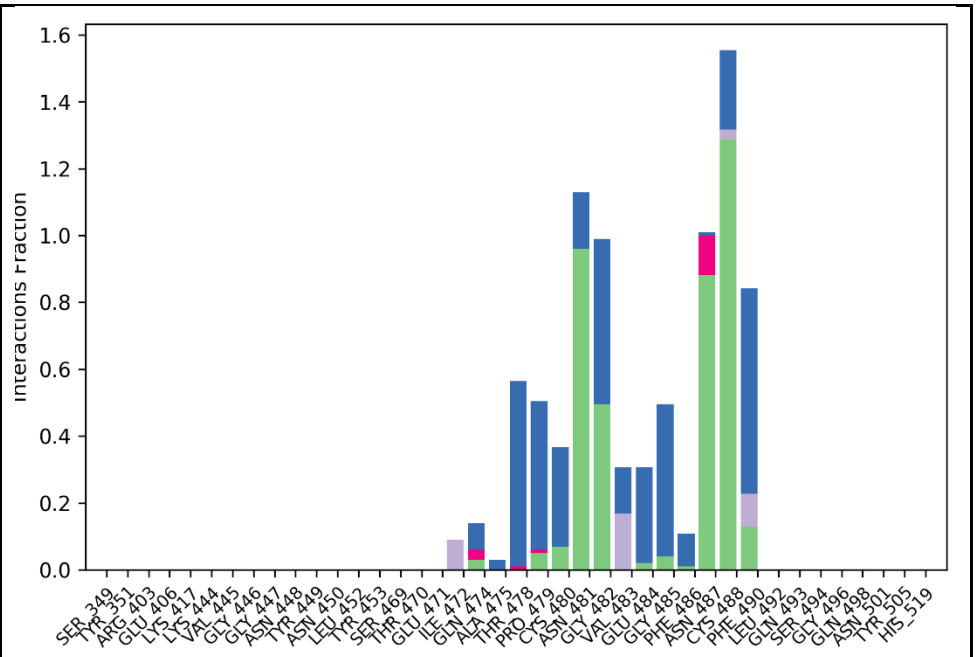
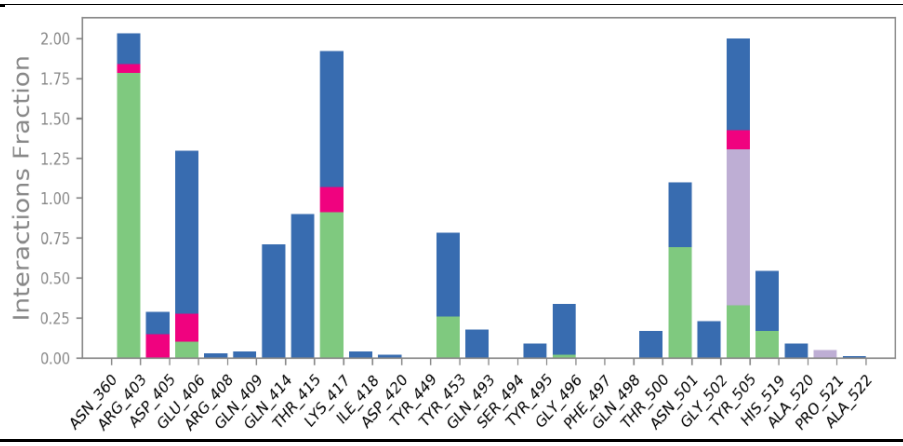
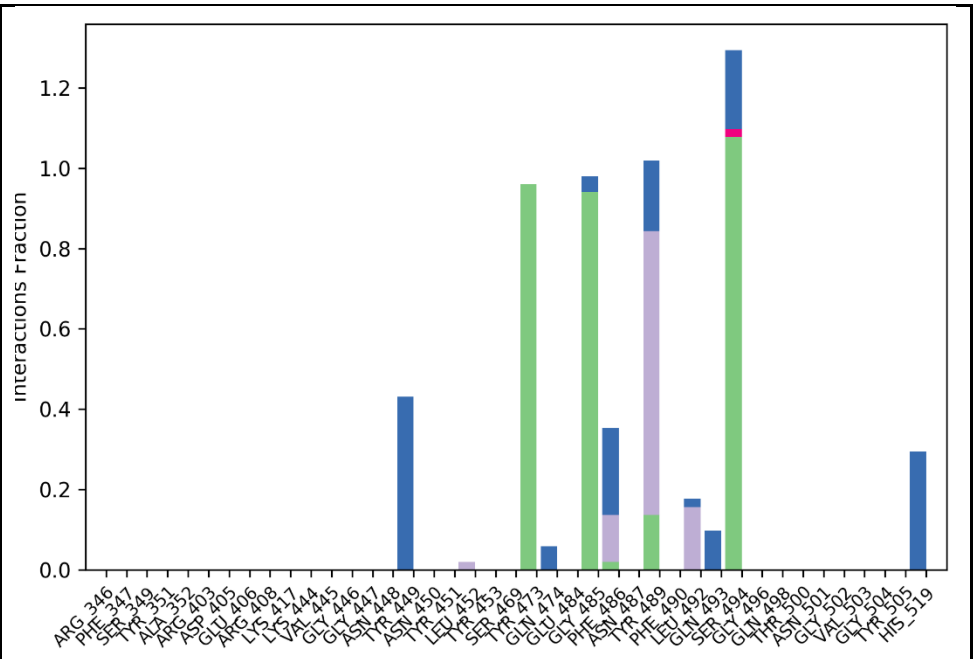
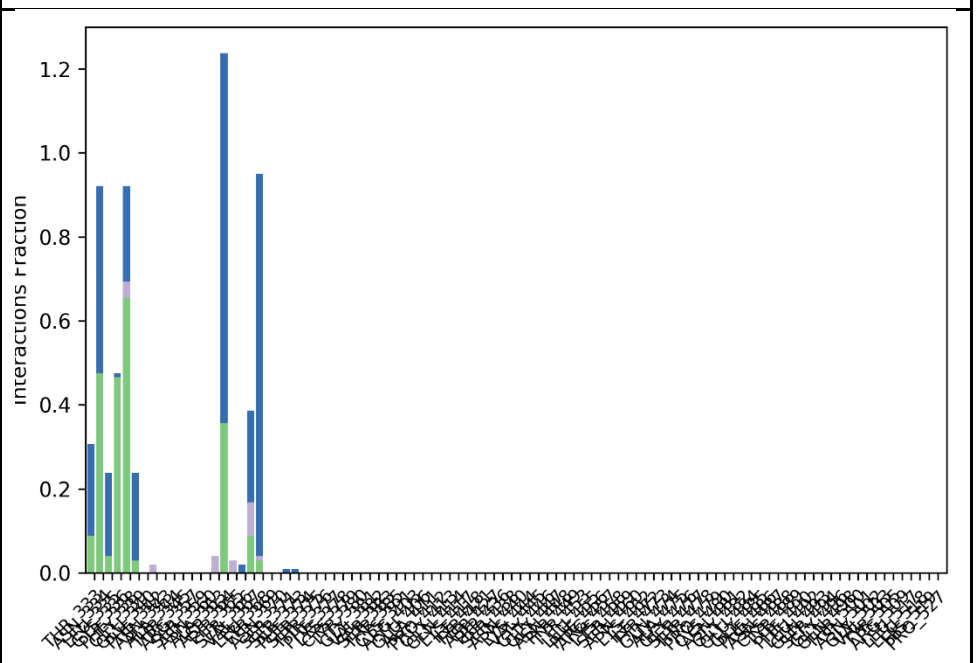


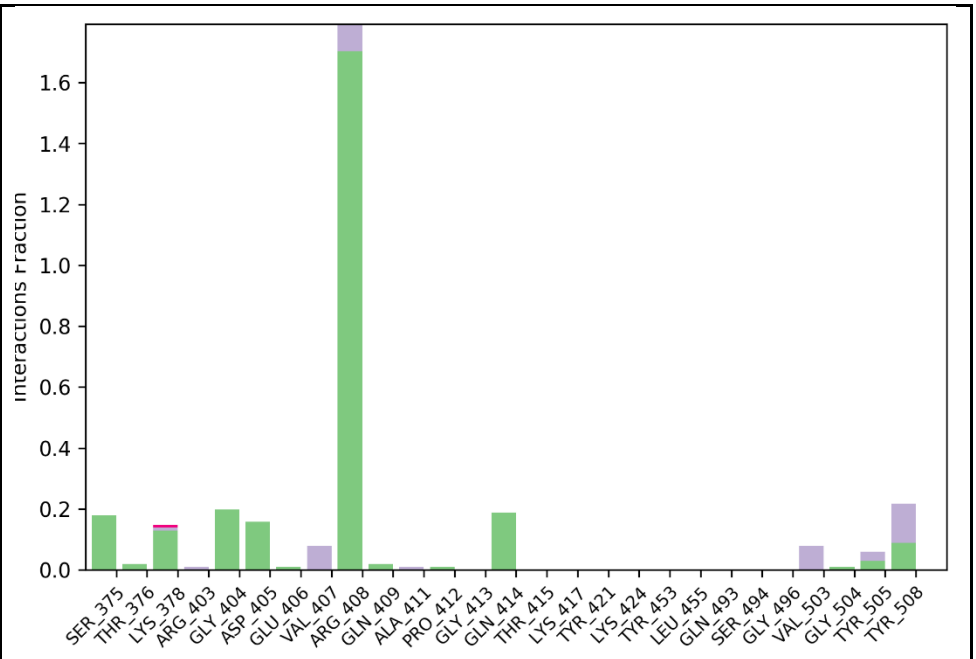
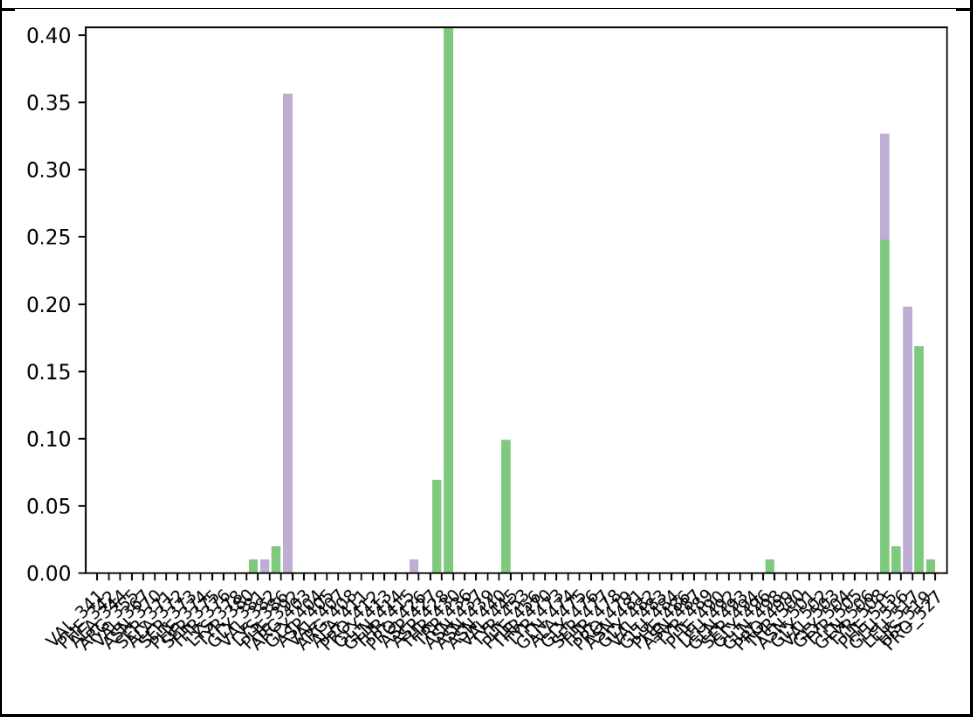
Figure S2: RMSF of SARS-CoV-2 RBD (first column) and drugs (second column) in 20 RBD-Drug complexes. 2D diagram of drugs are shown in third column.

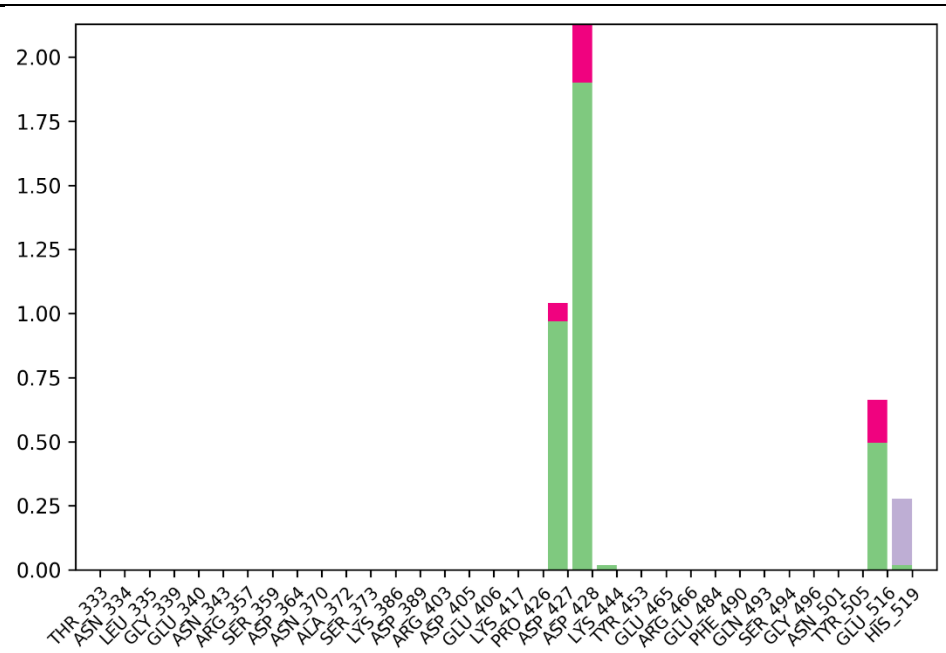
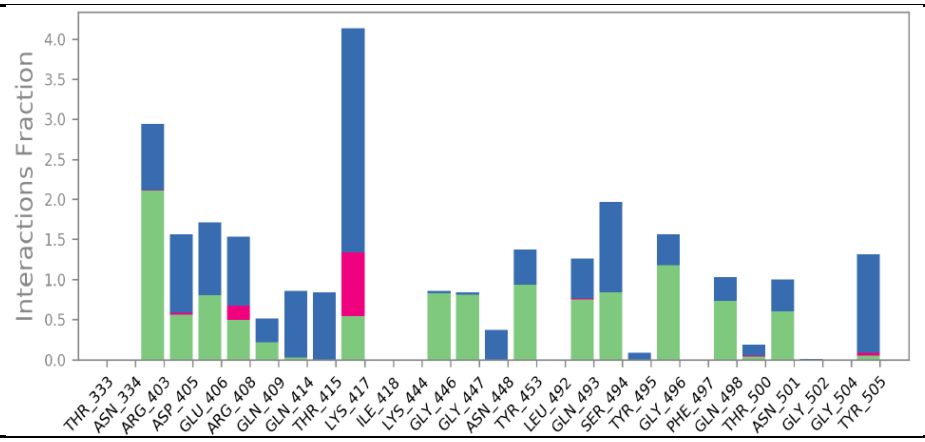
DB08995	
DB00284_MM GBSA	

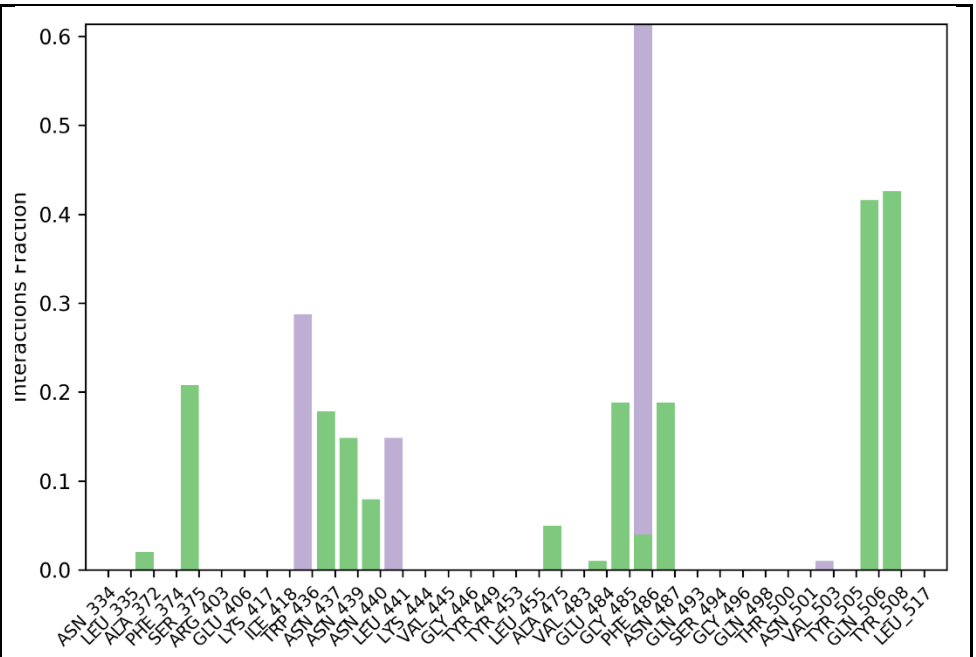
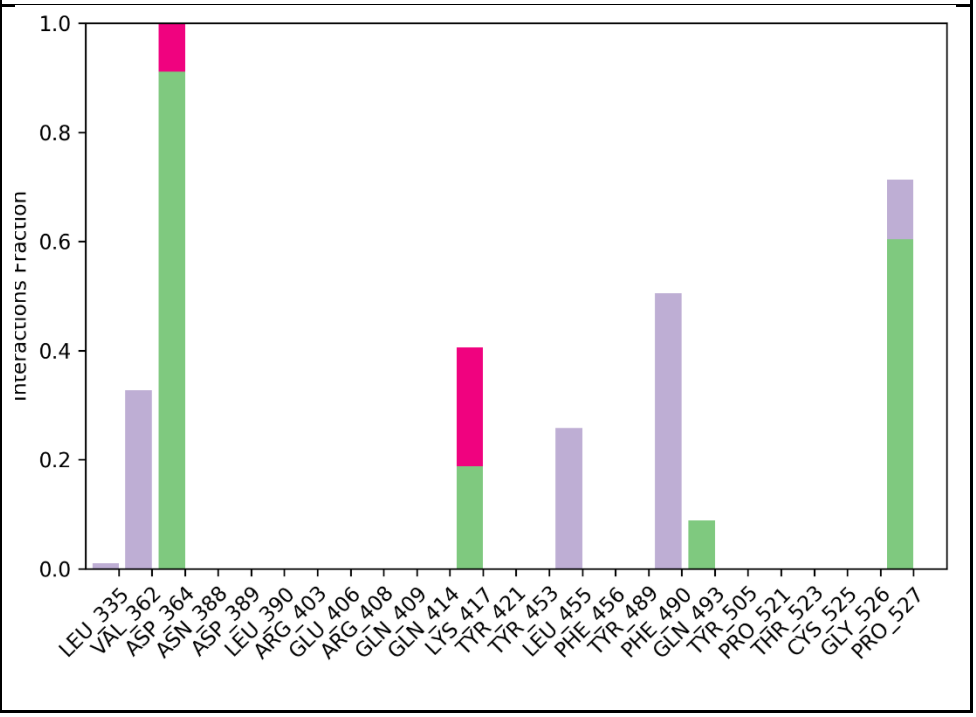
DB00284_XP	
DB00644_MM GBSA	
DB00644_XP	

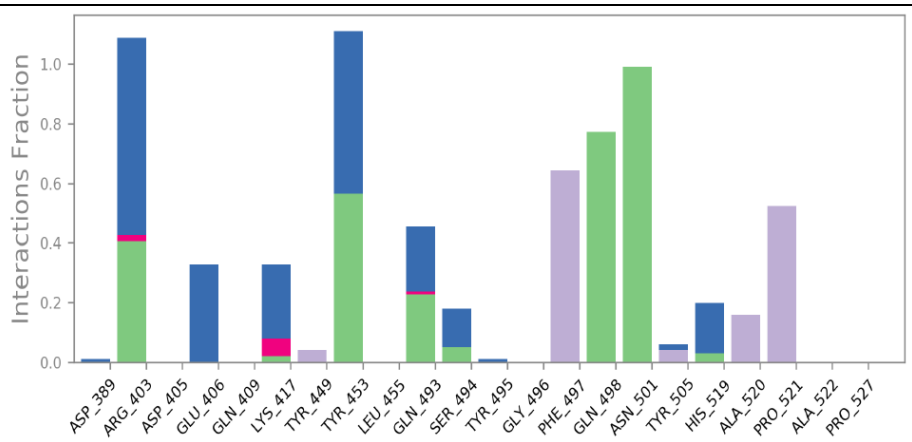
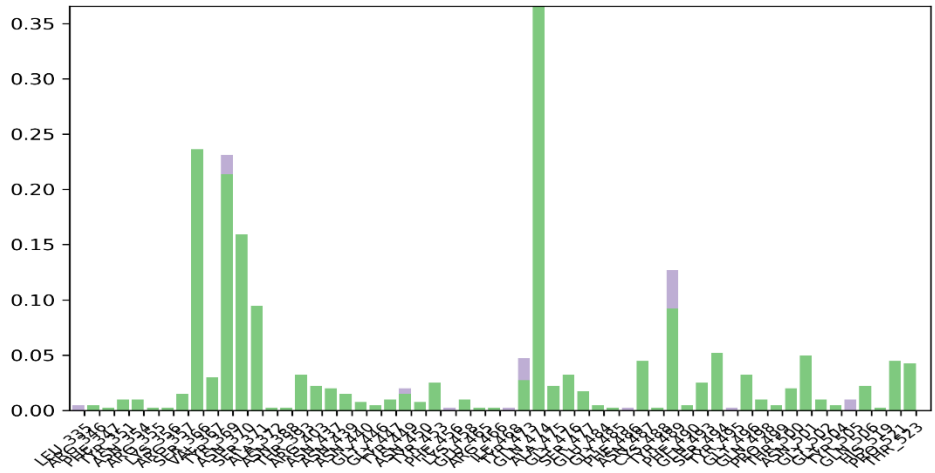
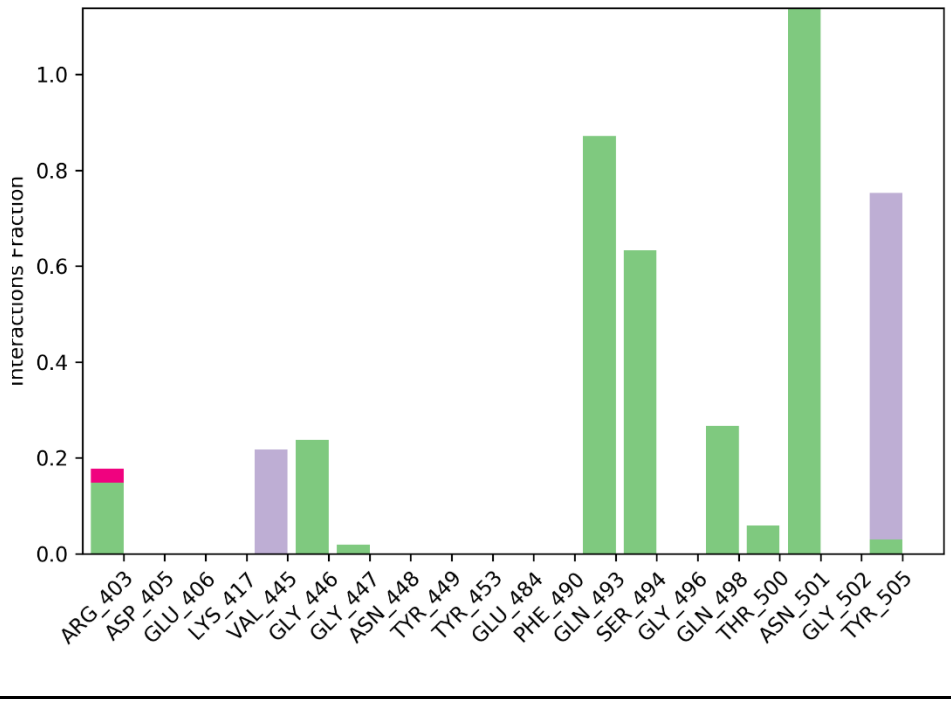
DB01698	
DB03147	

DB04703	
DB012942	

DB00157	
DB00441	

DB00452	
DB00569	

DB00646	
DB00895	

DB01076	
DB02772	
DB03310	

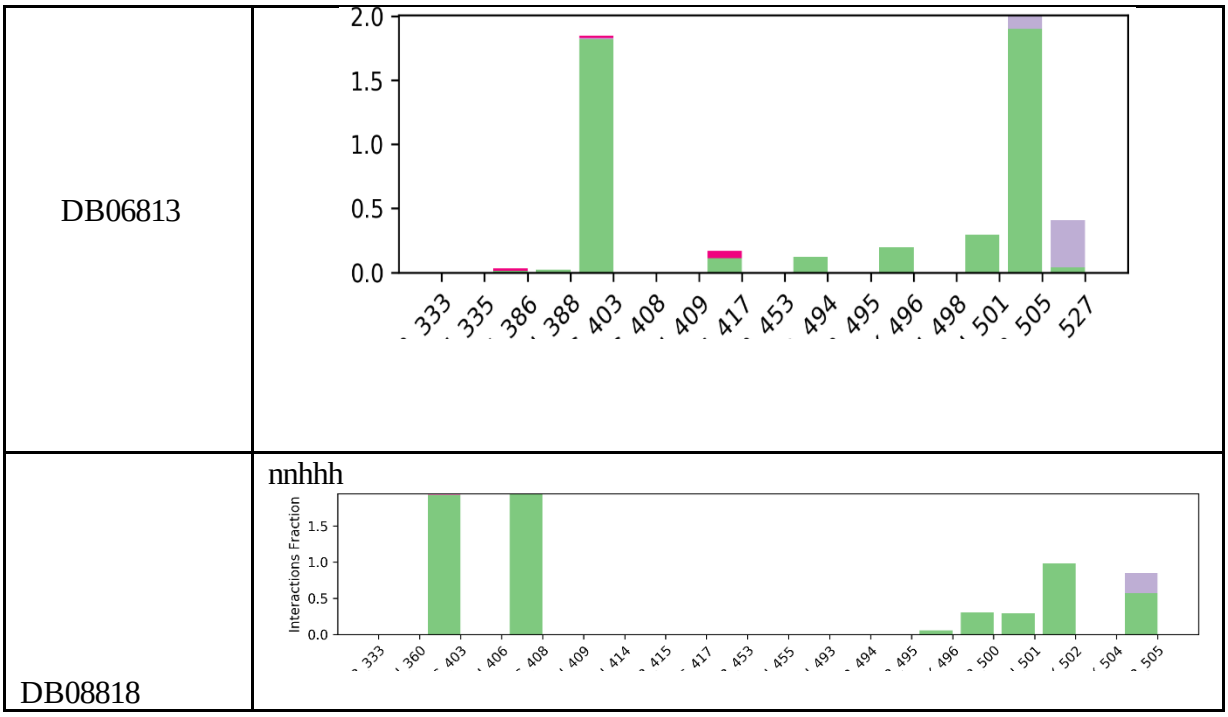
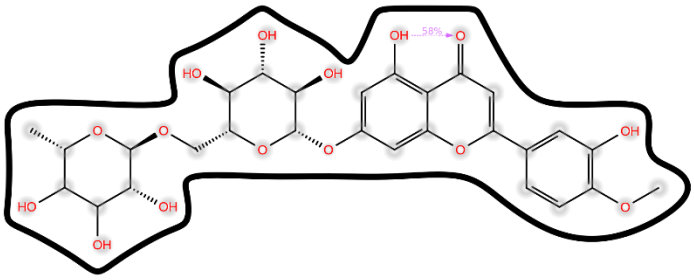
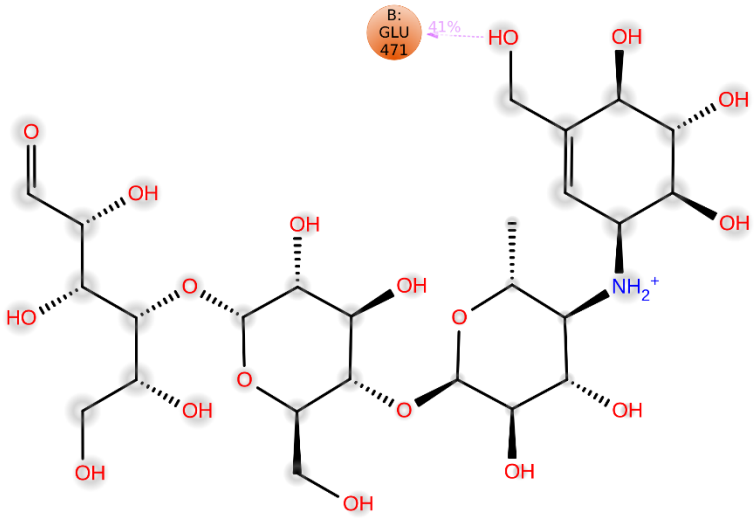
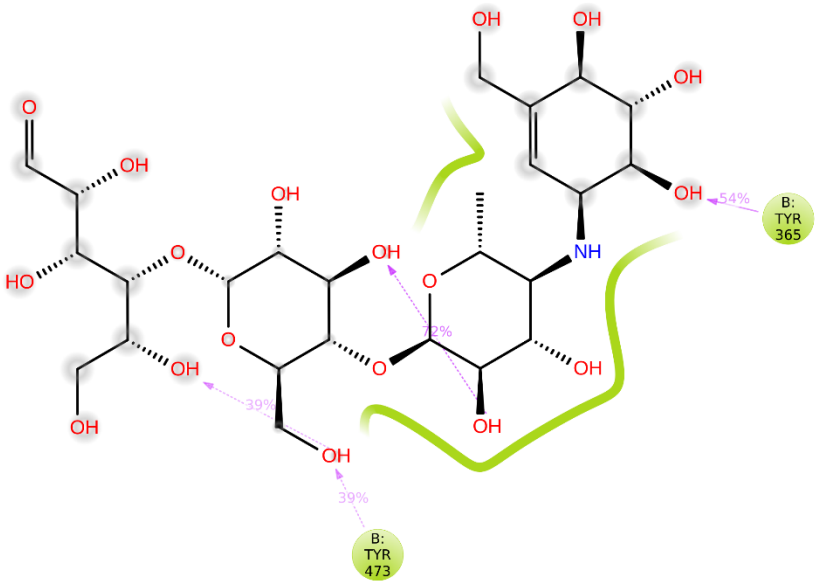
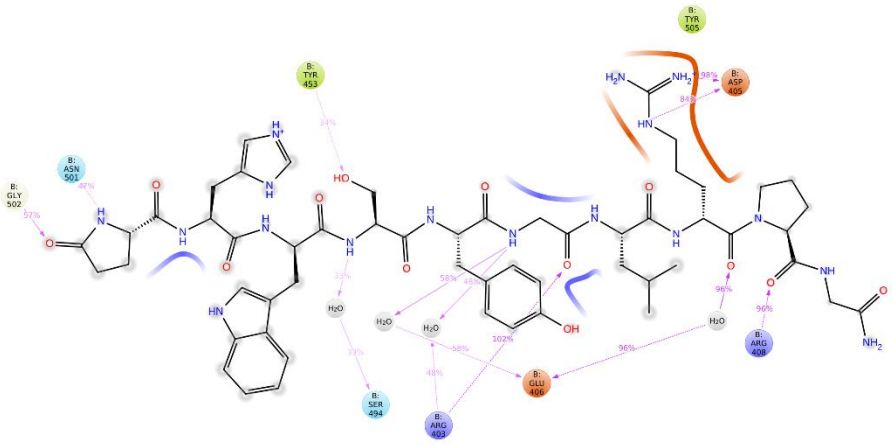
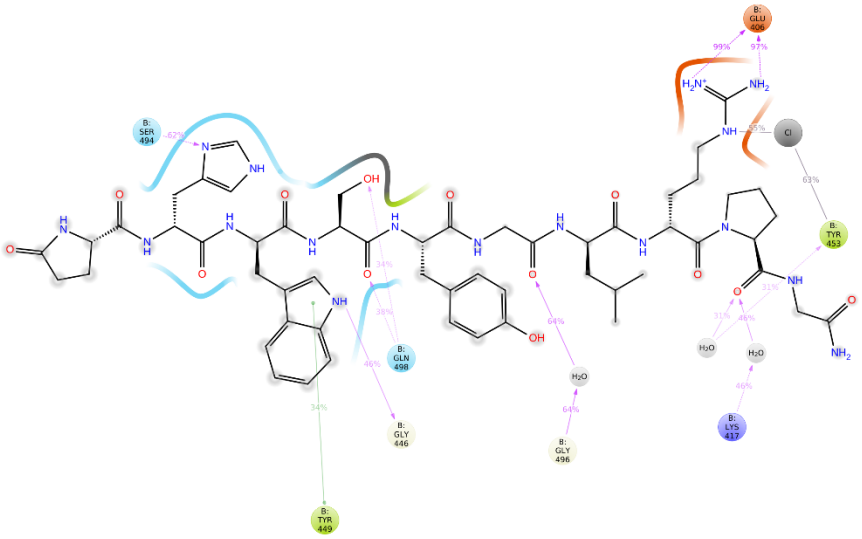
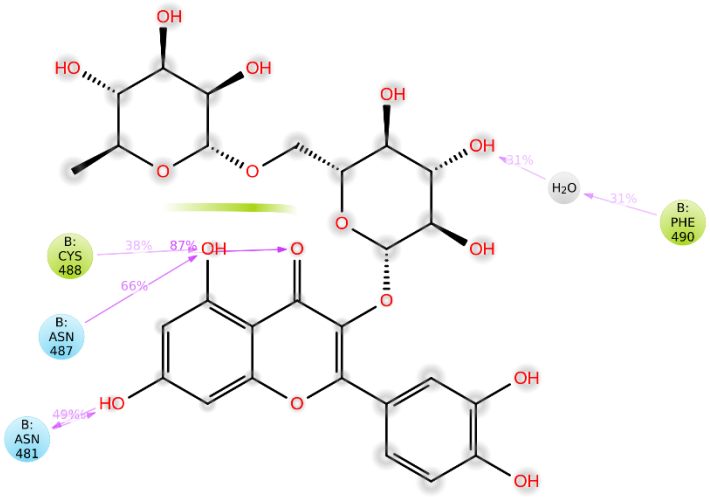
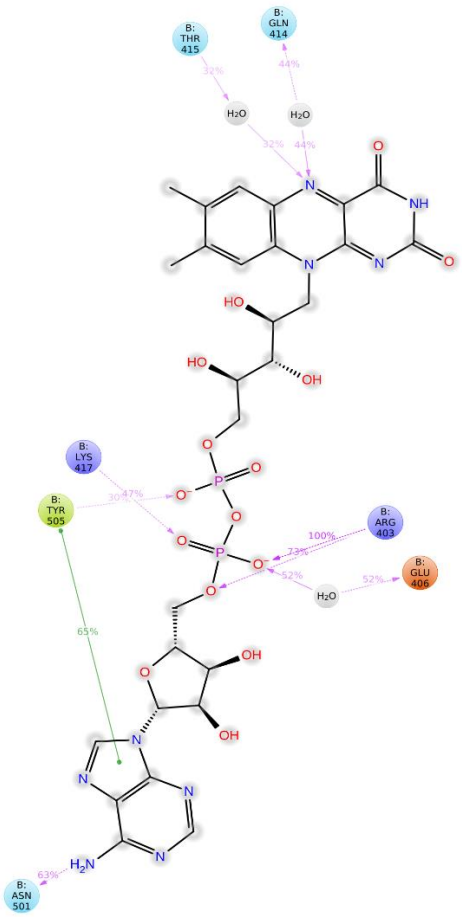


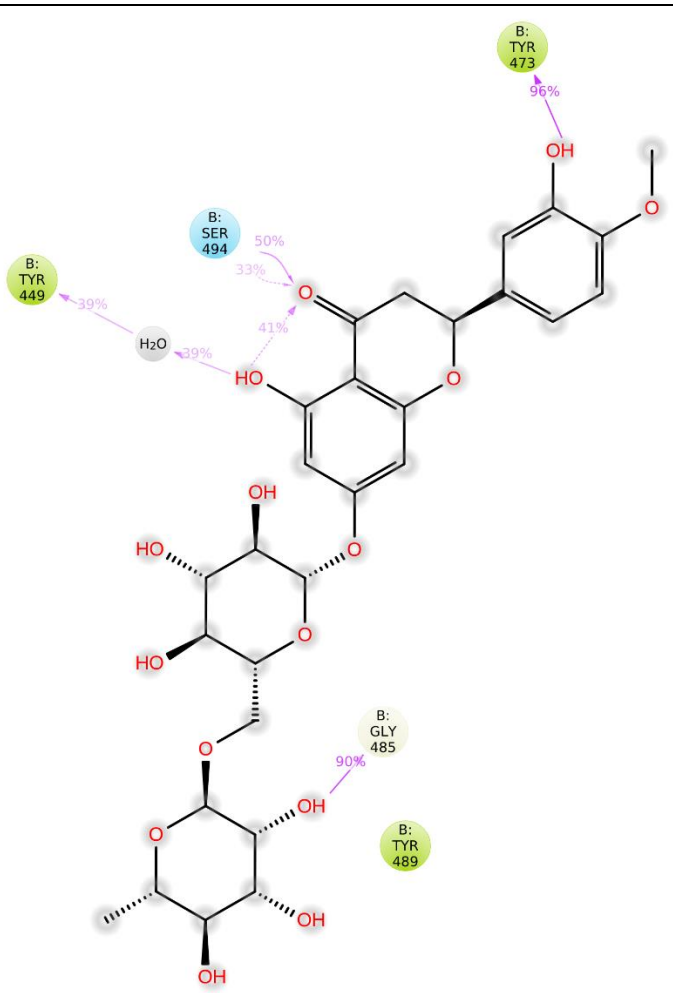
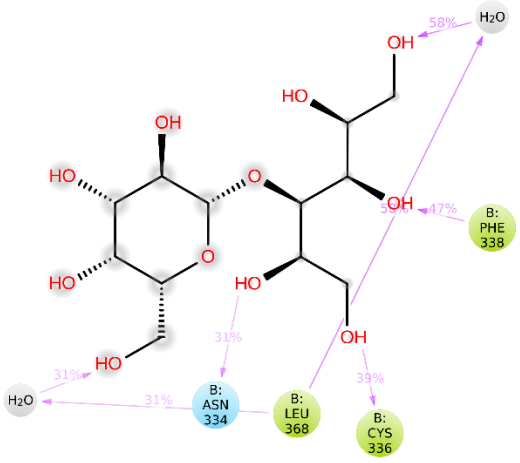
Figure S3: Histograms showing different types of interactions between drugs and spike RBD.

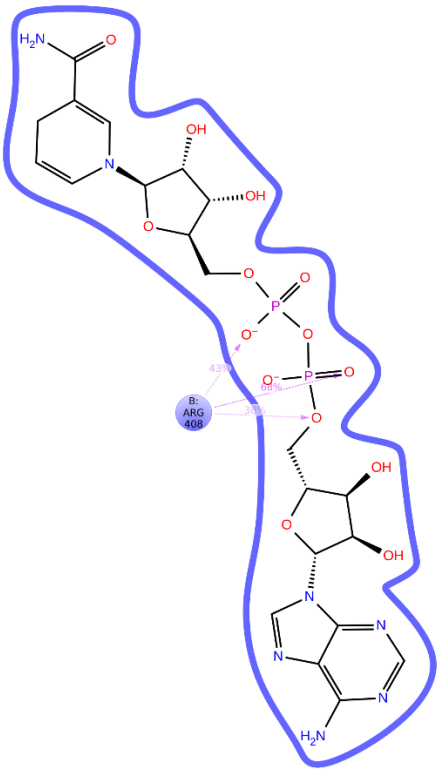
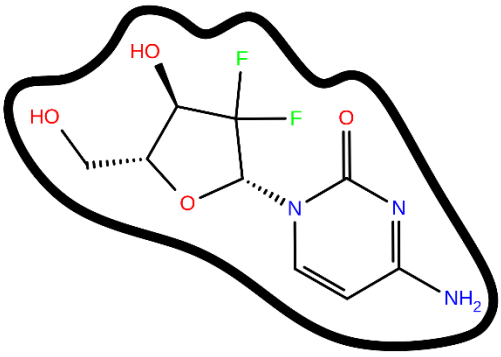
DB08995	
DB00284_MM GBSA	

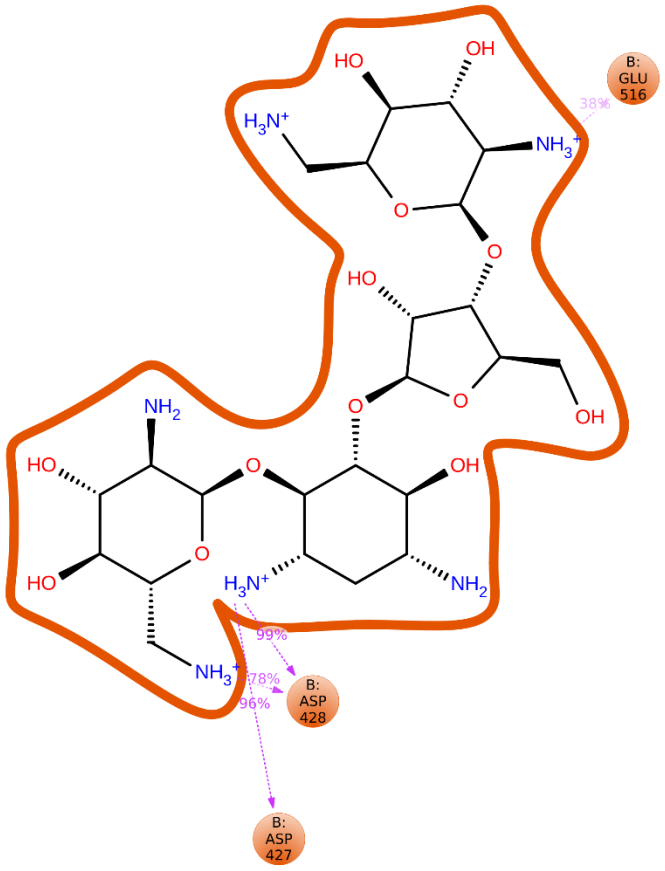
DB00284_XP	
DB00644_MM GBSA	

DB00644_XP	
DB001698	

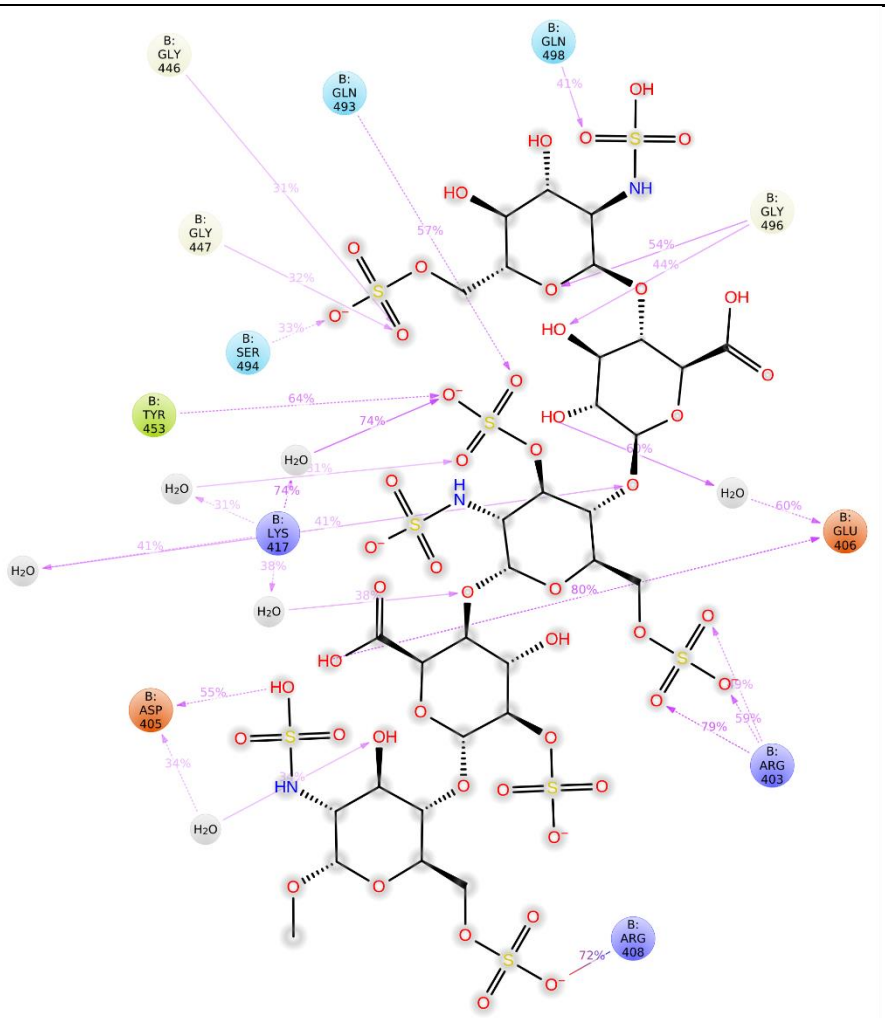
DB03147	

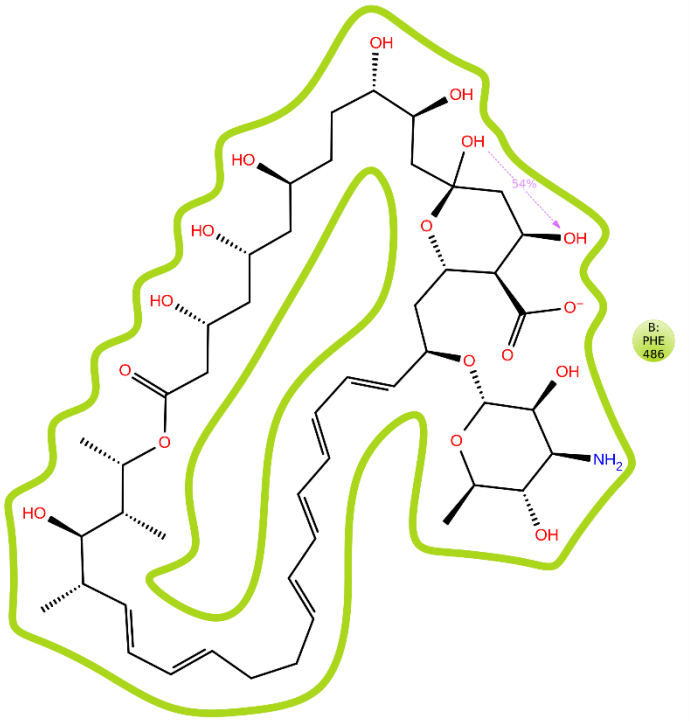
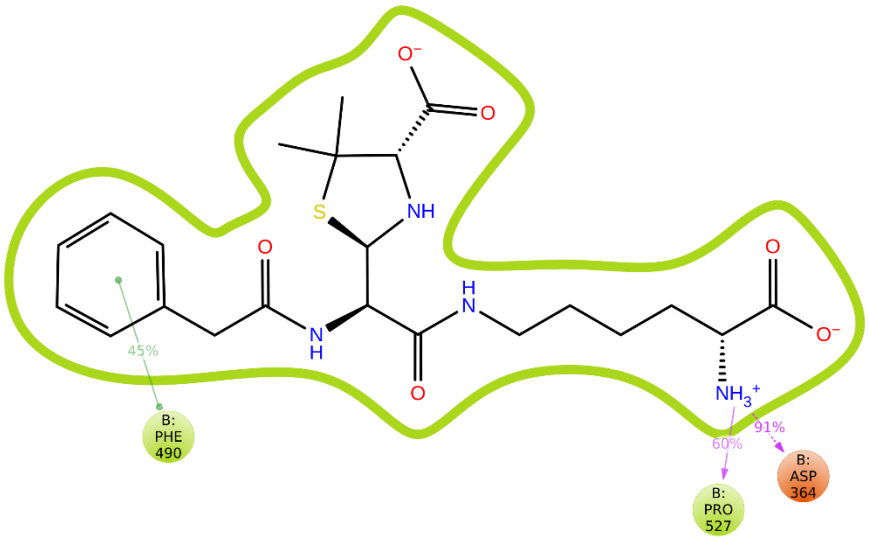
DB04703	
DB12492	

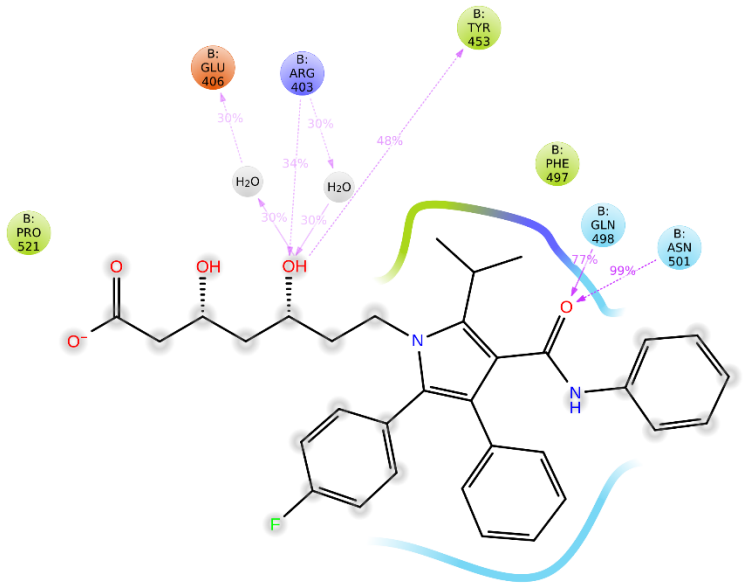
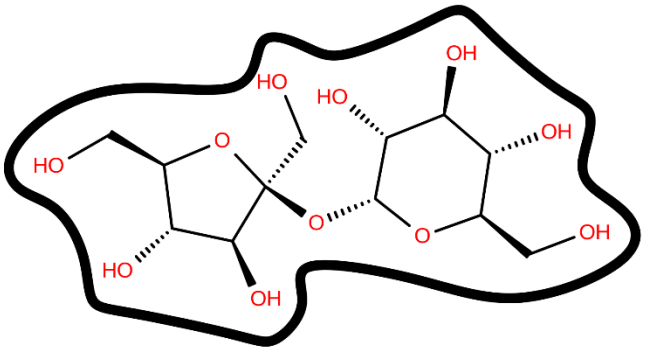
DB00157	
DB00441	

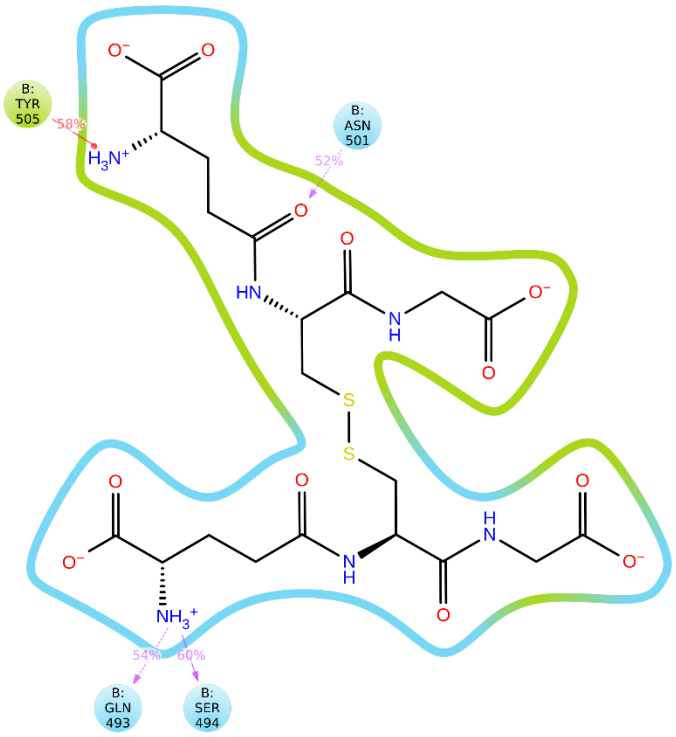
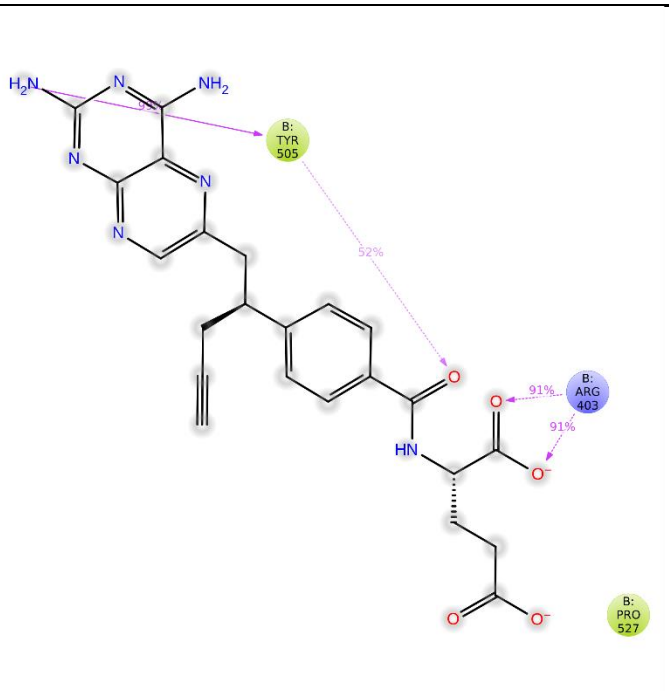
DB00452	

HO
OH
B:
GLU
516
38%
H_3N^+
NH_3^+
O
O
HO
O
O
OH
NH_2
HO
O
OH
O
HO
H_3N^+
NH_2
99%
NH_3^+
78%
96%
B:
ASP
428
B:
ASP
427

DB00569	

DB00646	
DB00895	

DB01076	
DB02772	

DB03310	
DB06813	

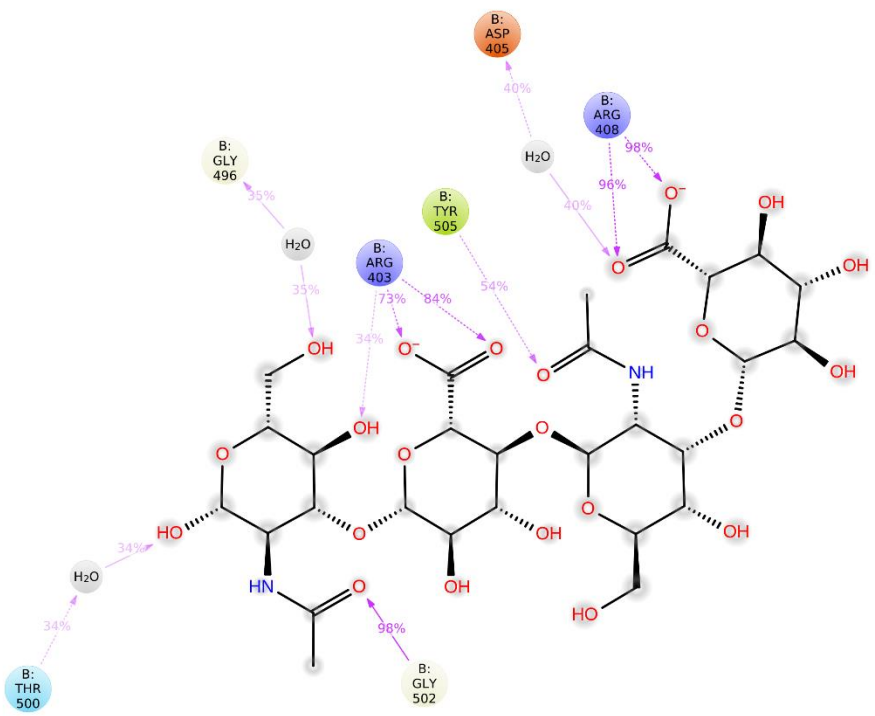
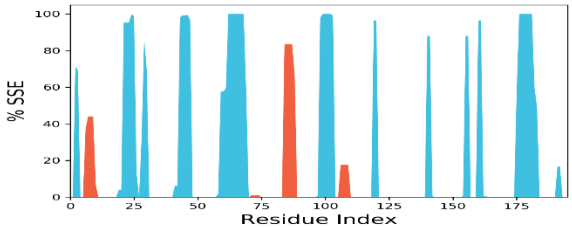
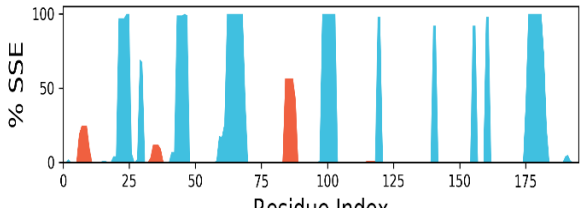
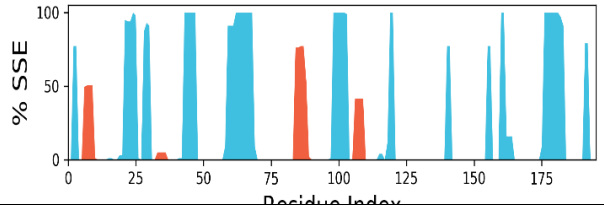
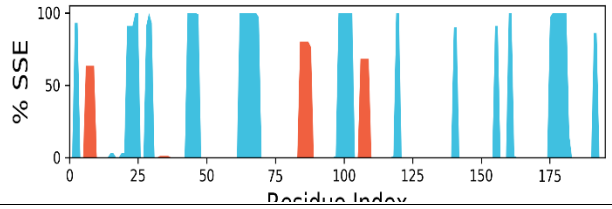
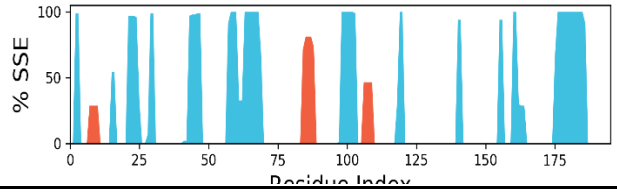
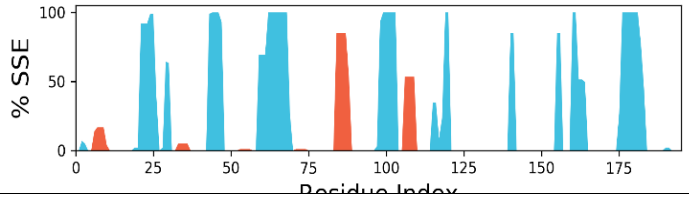
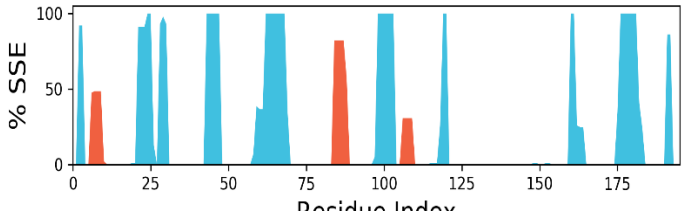
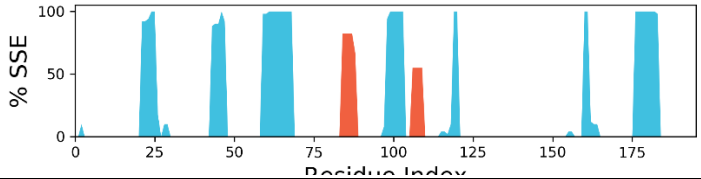
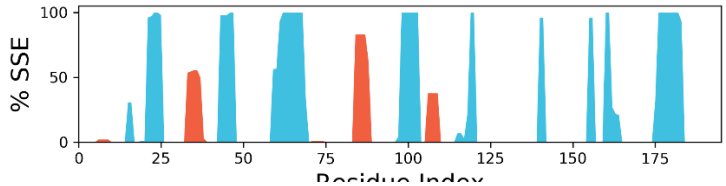
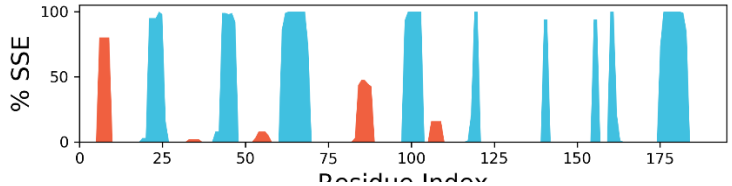
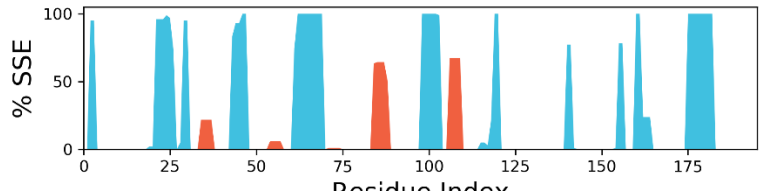
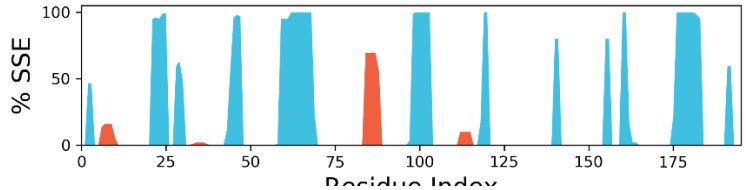
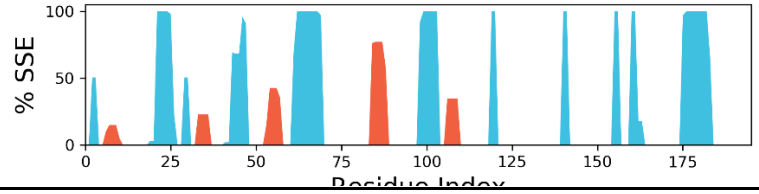
DB08818	

Figure S4: Interactions which occur more than 30 % of the simulation**.** Last 50 ns of the trajectories was considered for the generation of images.

DB08995	
DB00284_GBSA	
DB00284_XP	
DB00644_GBSA	
DB00644_XP	

DB01698	
DB03147	
DB04703	
DB12942	
DB00157	
DB00441	
DB00452	
DB00569	

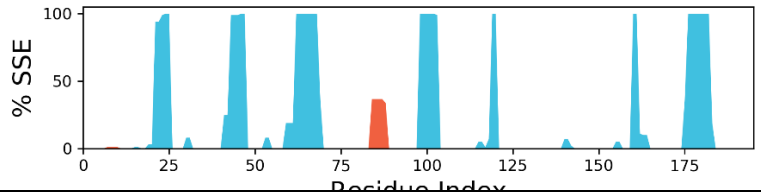
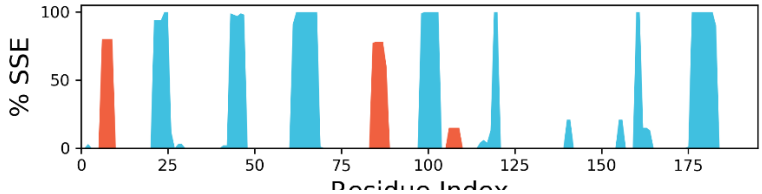
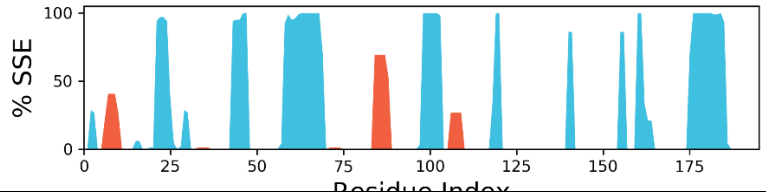
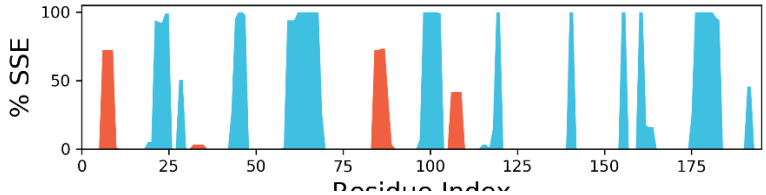
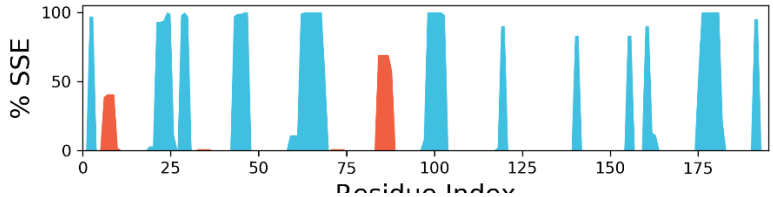
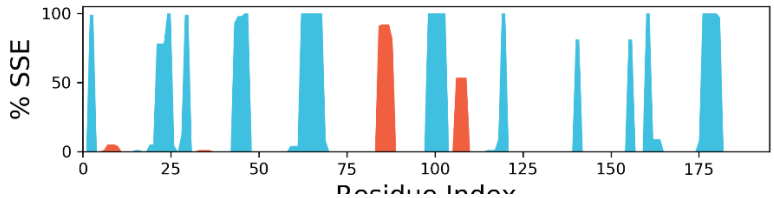
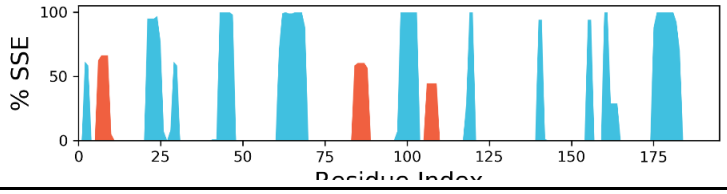
DB00646	
DB00895	
DB01076	
DB02772	
DB03310	
DB06813	
DB08818	
	Residue Index

Figure S5: SSE of RBD during last 50 ns of trajectories.

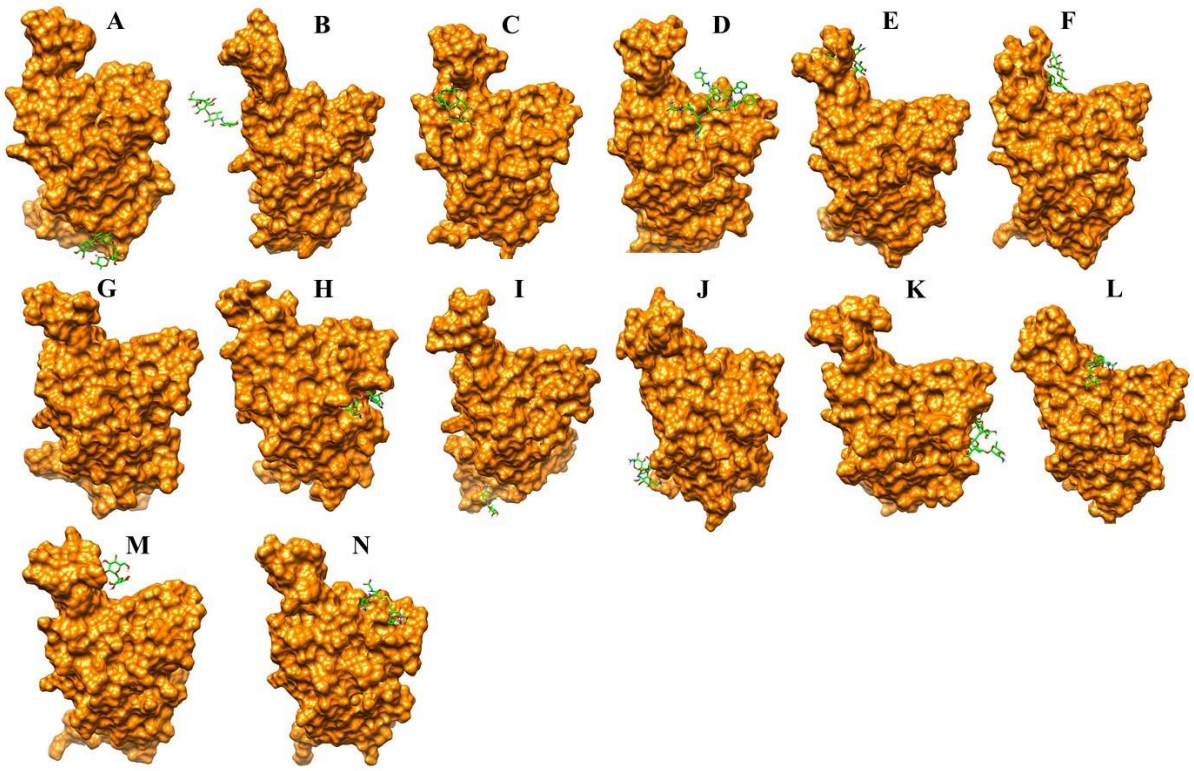


Figure S6: Drugs which show high RMSD from the initial docked conformations. (A) DB08995 (B) DB00284_MMGBSA (C) DB00284_XP (D) DB00644_XP (E) DB01698 (F) DB04703 (G) DB12942 (H) DB00157 (I) DB00441 (J) DB00452 (K) DB00646 (L) DB00895 (M) DB02772 and (N) DB03310. RBD is shown in surface representation (Orange) and bound drugs are shown in stick representation (Green). Last frames of drug-RBD complexes were used to generate the images. Note: DB00644_XP also showed RMSD less than 10 Å but other pose (DB00644_MMGBSA) has been mentioned in main text. DB00644_MMGBSA showed lower RMSD than DB00644_XP.