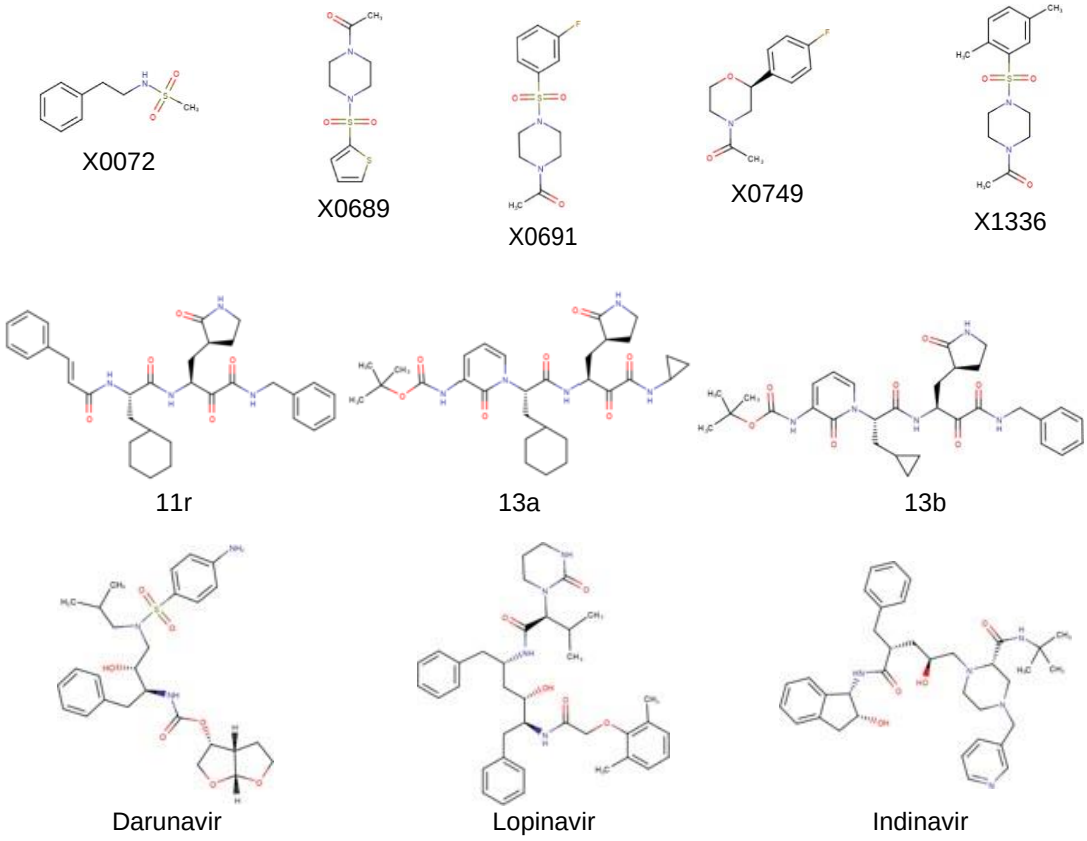


Figure S1. The used ligands in this work.

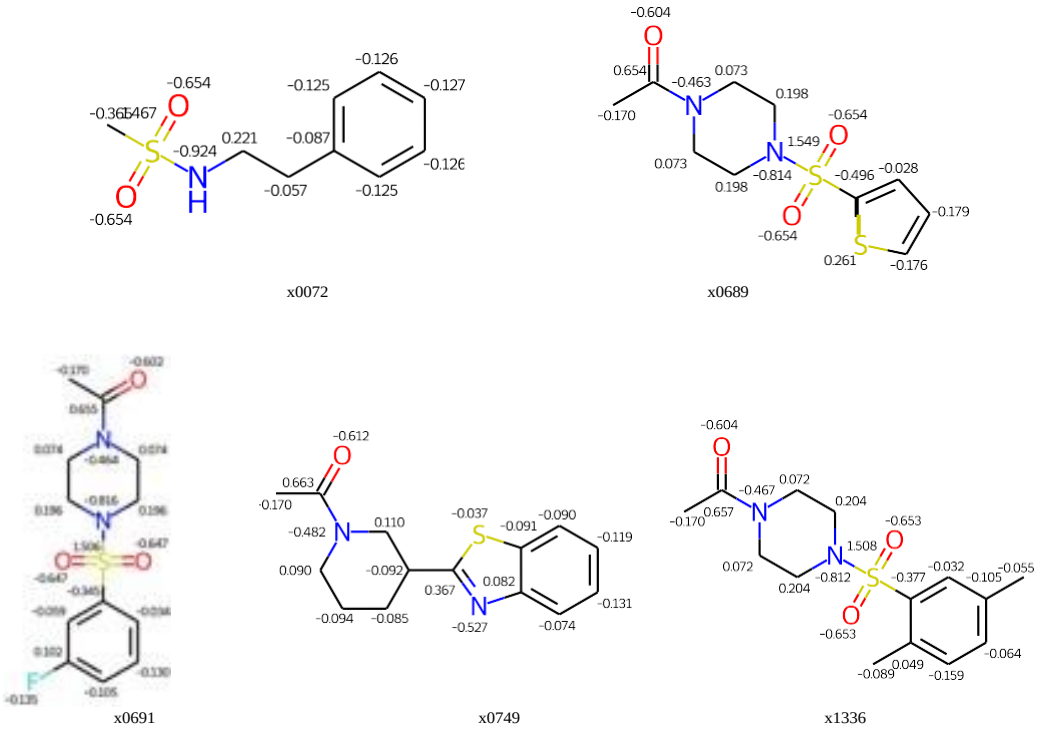
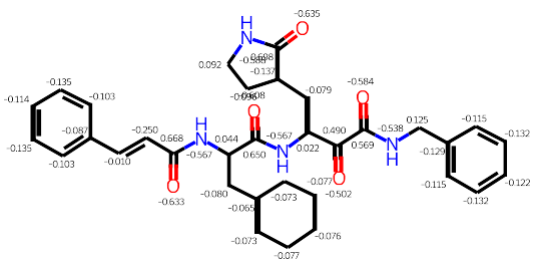
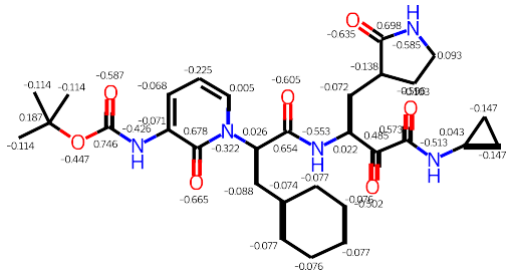


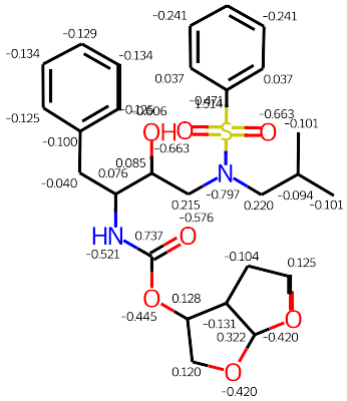
Figure S2. The partial charge represented ligand figures generated by gaff. Ligands are x0072, x0689,x0691, x0749, and x1336



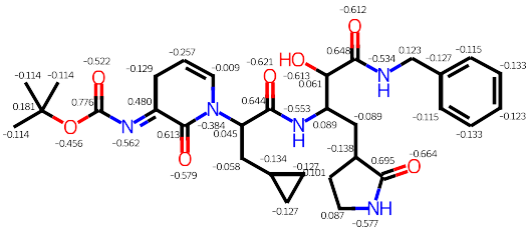
11r



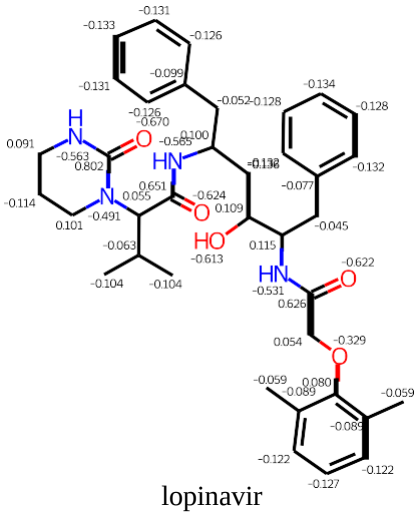
13a



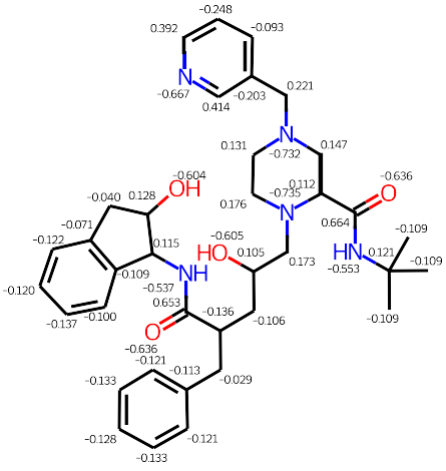
darunavir



13b



lopinavir



indinavir

Figure S3. The partial charge represented ligand figures generated by gaff. Ligands are 11r, 13a, 13b,darunavir, lopinavir, and indinavir

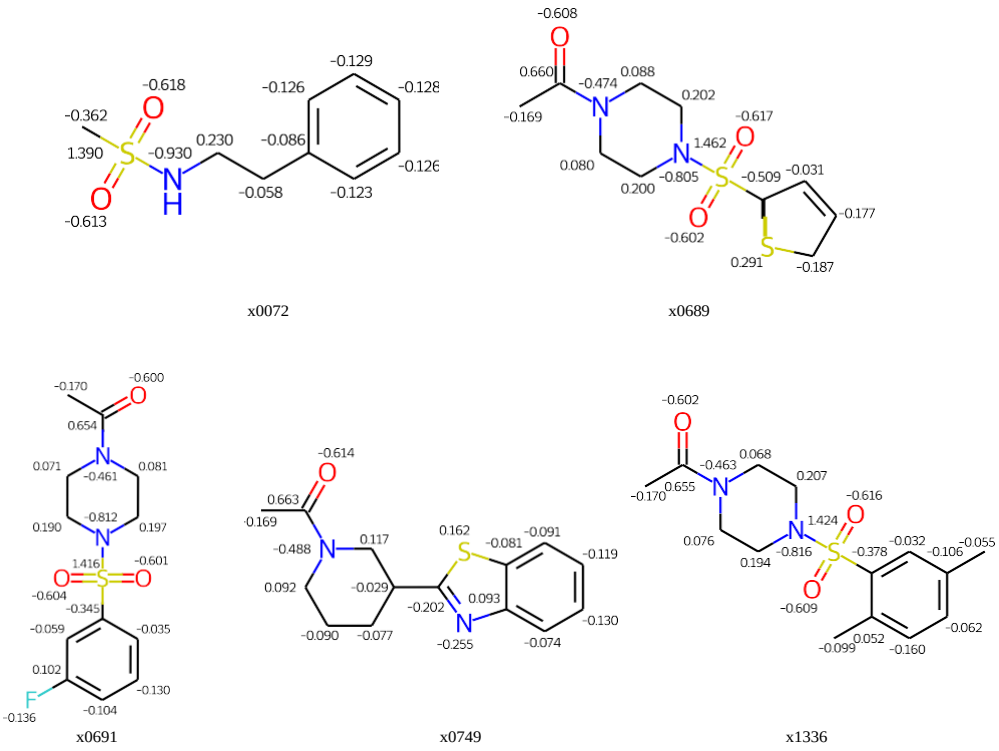
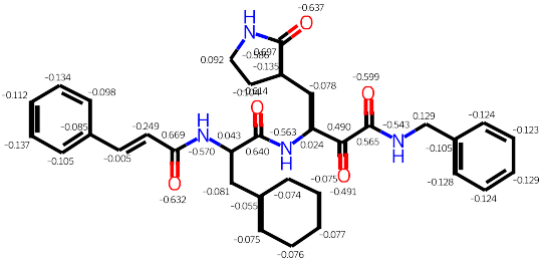
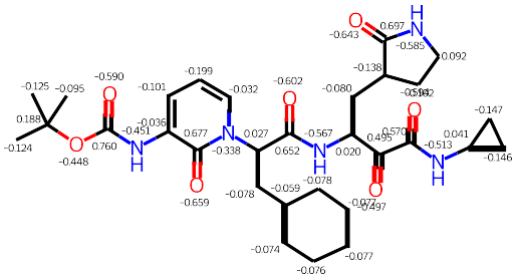


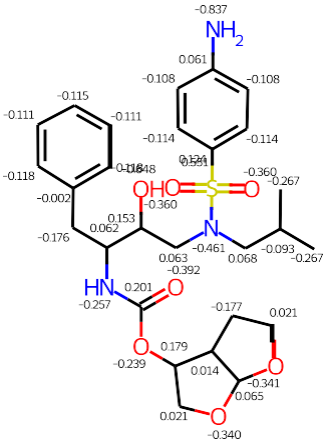
Figure S4. The partial charge represented ligand figures generated by charmm-gui. Ligands are x0072,x0689, x0691, x0749, and x1336



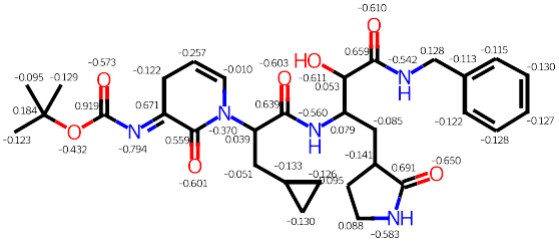
11r



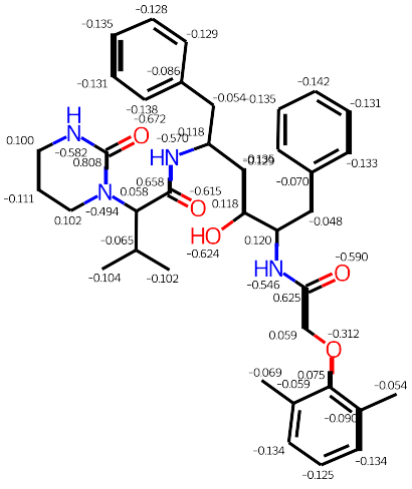
13a



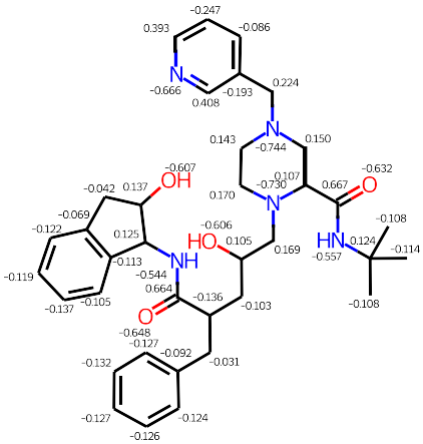
darunavir



13b



lopinavir



indinavir

Figure S5. The partial charge represented ligand figures generated by charmm-gui. Ligands are 11r, 13a,13b, darunavir, lopinavir, and indinavir

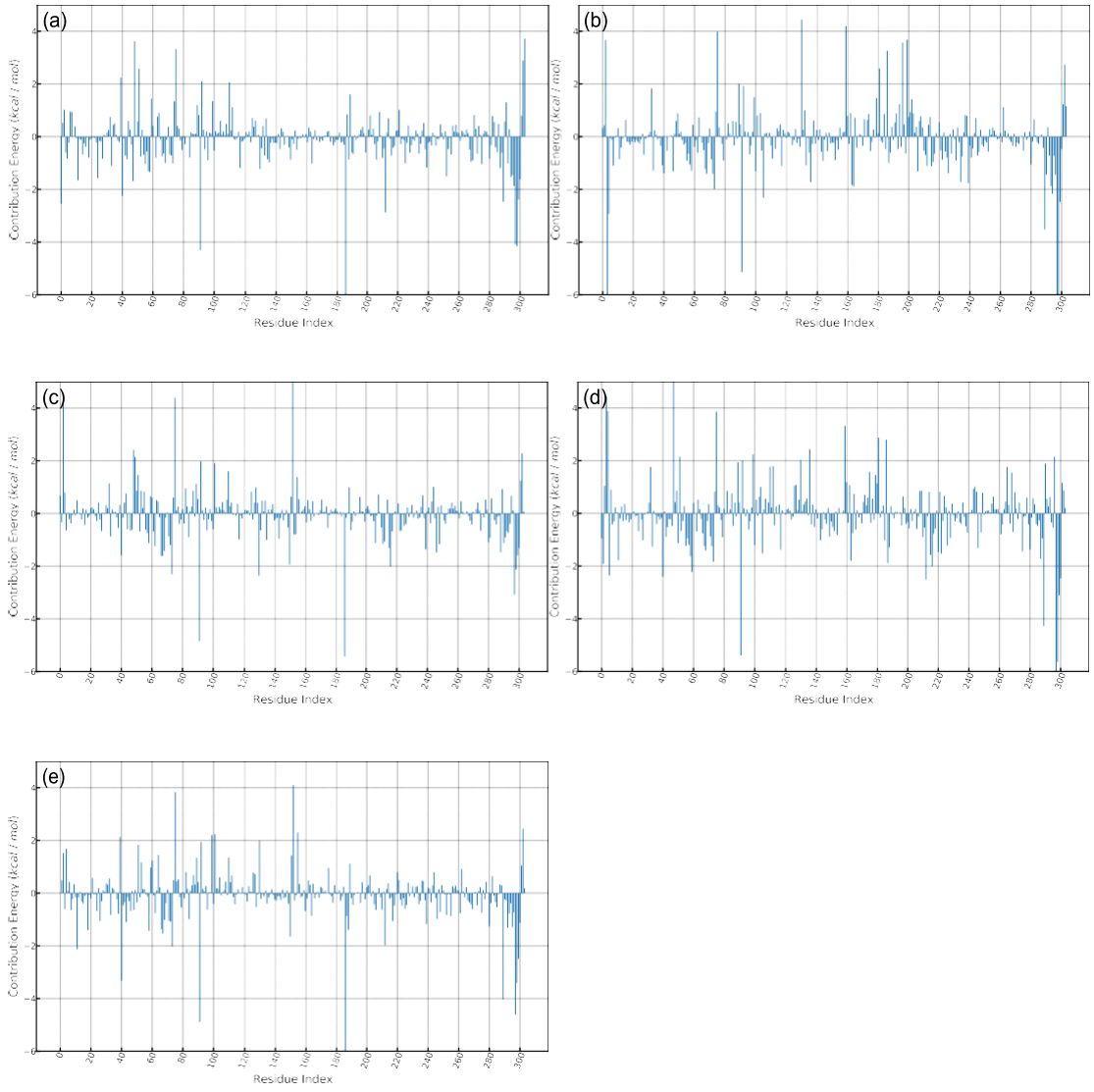


Figure S6. MM-PBSA decomposed energy per-reisdue with ff99SB (a) X0072 (b) X0689 (c) X0691 (d)X0749 (e) X1336

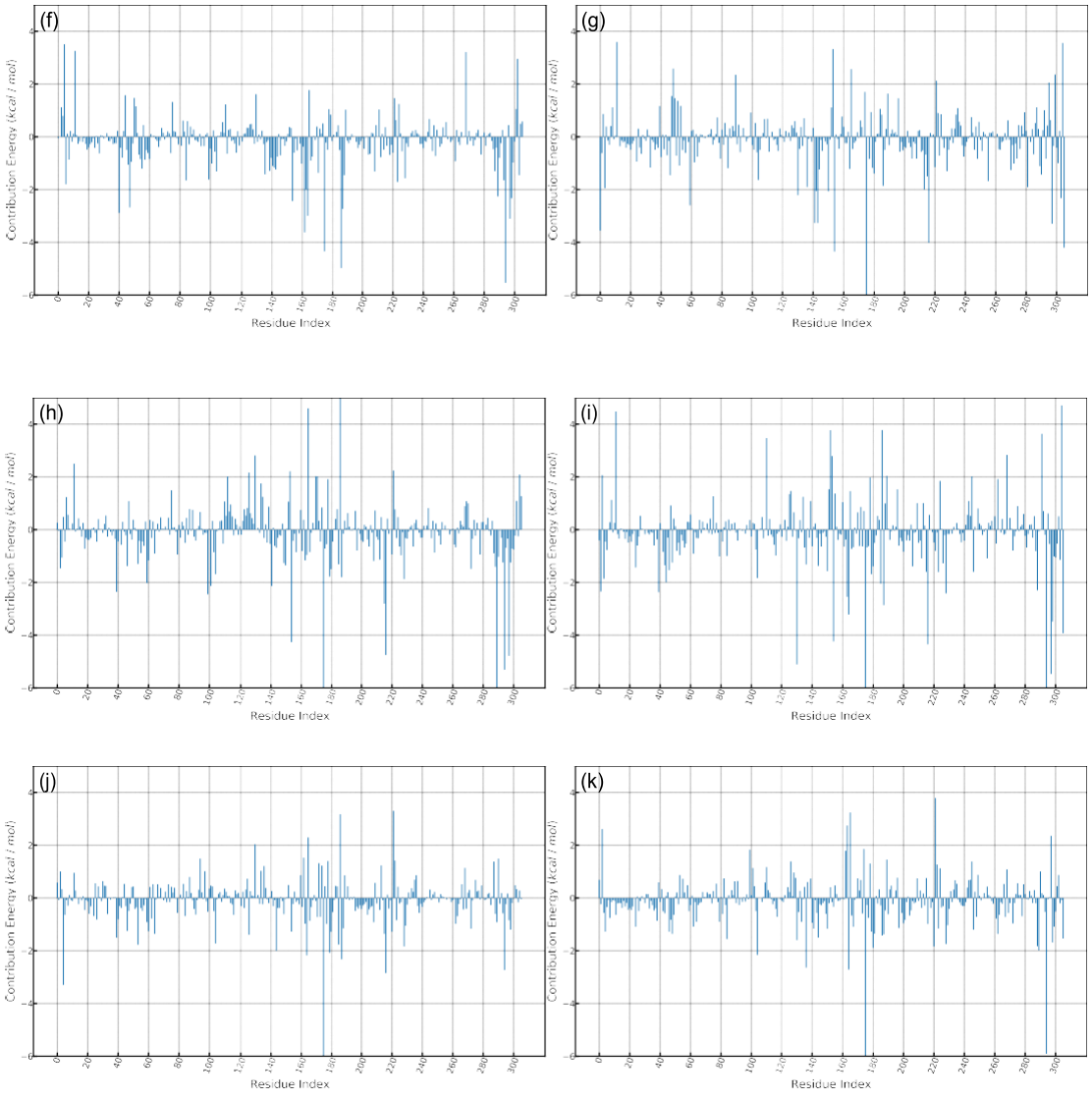


Figure S7. MM-PBSA decomposed energy per-residue with ff99SB (f) 11r (g) 13a (h) 13b (i) darunavir (j) lopinavir (k) indinavir

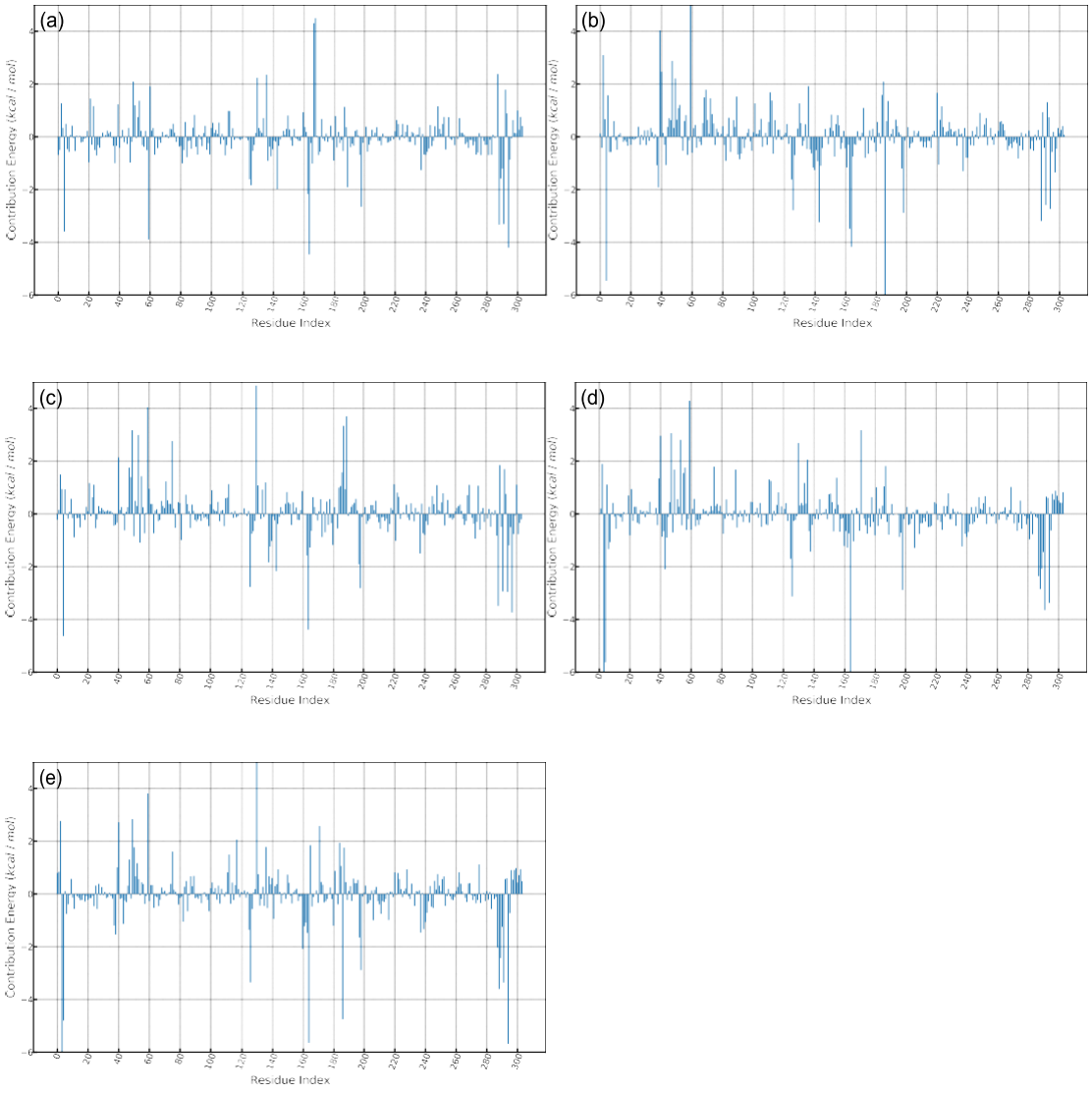


Figure S8. MM-PBSA decomposed energy per-reisdue with c36 (a) X0072 (b) X0689 (c) X0691 (d)X0749 (e) X1336

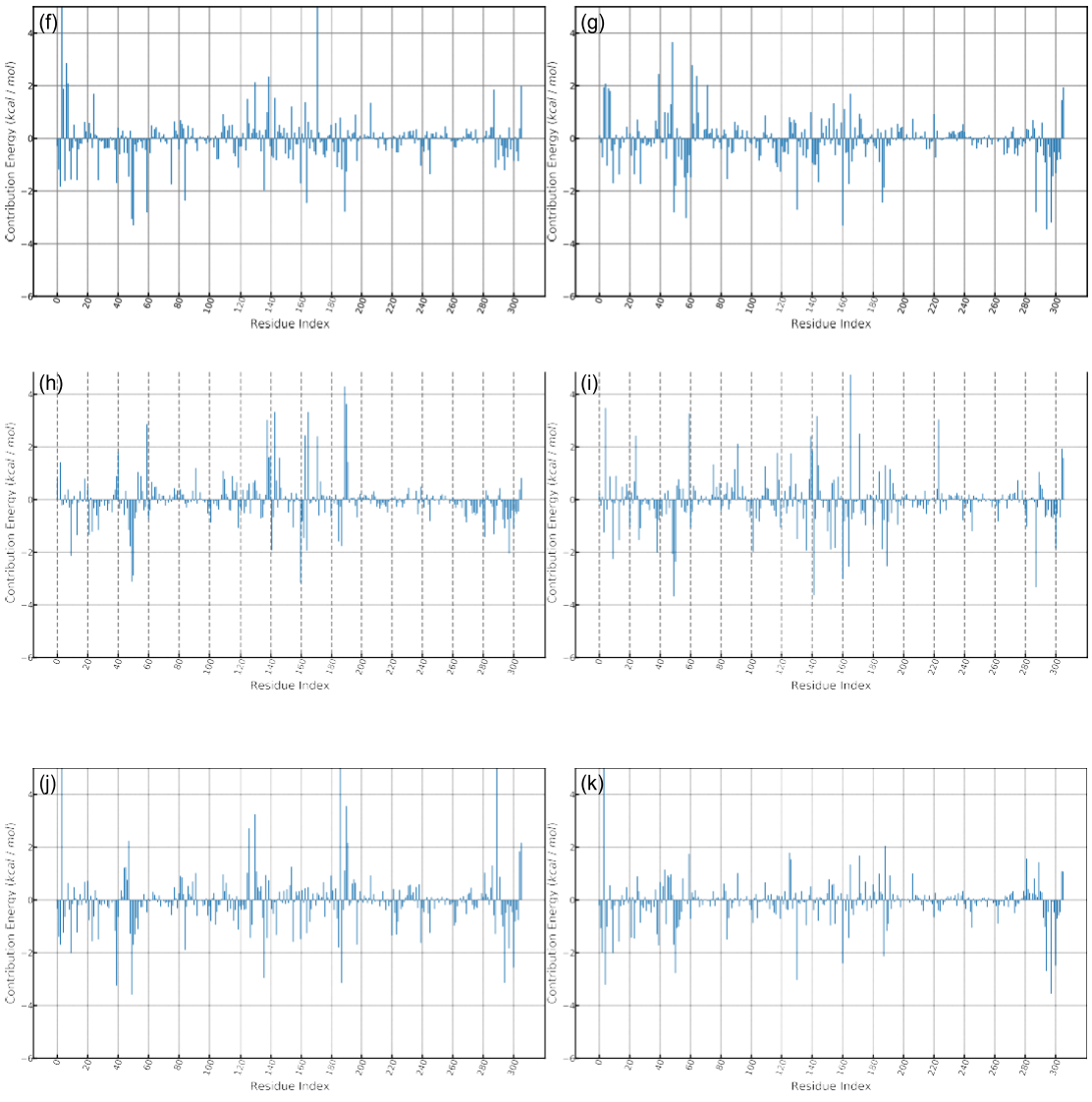


Figure S9. MM-PBSA decomposed energy per-residue with c36 (f) 11r (g) 13a (h) 13b (i) darunavir (j)lopinavir (k) indinavir

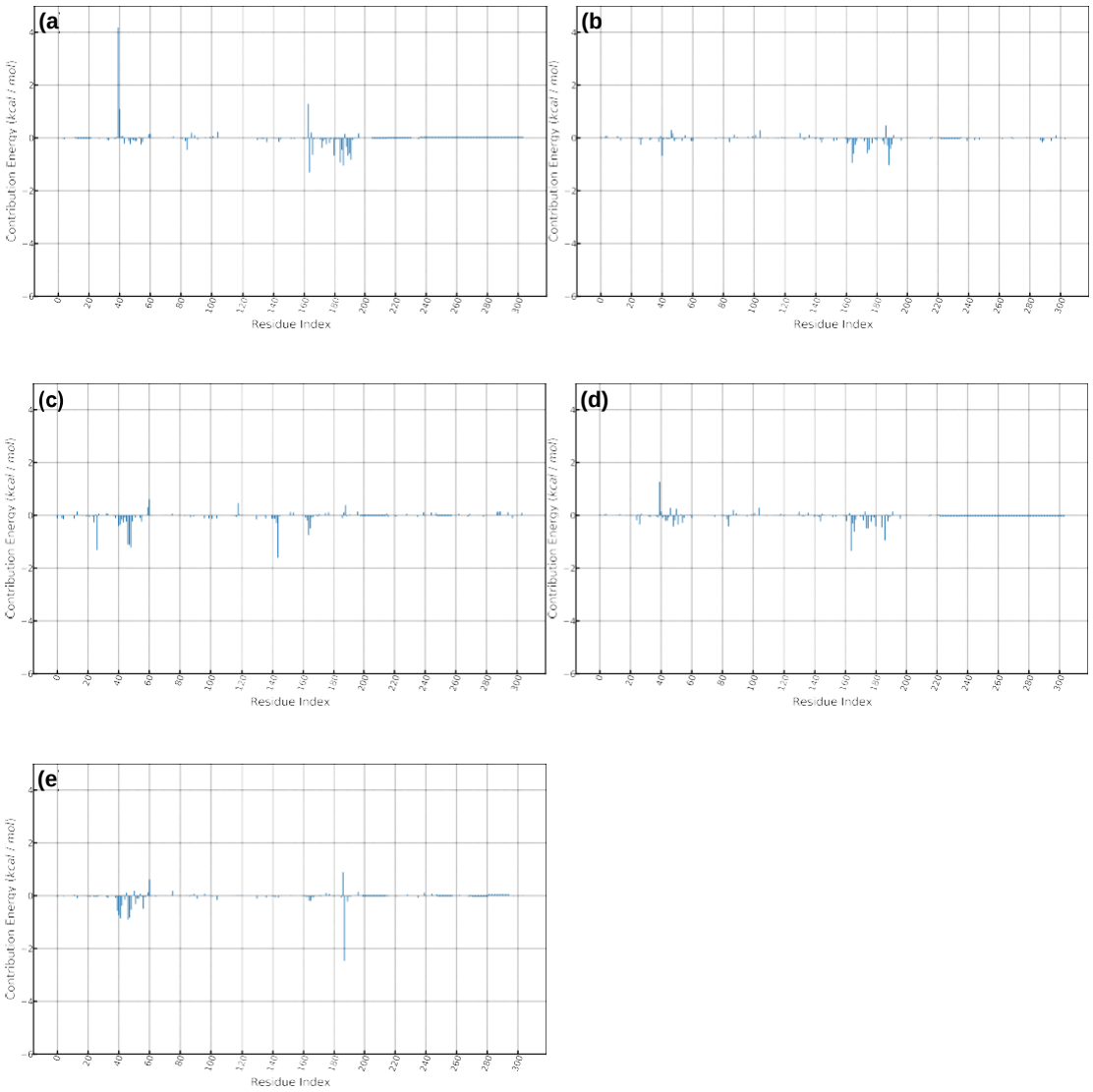


Figure S10. MM-PBSA Decomposed energy per-residue with g54a7 (a) X0072 (b) X06889 (c) X0691(d) X0749 (e) X1336

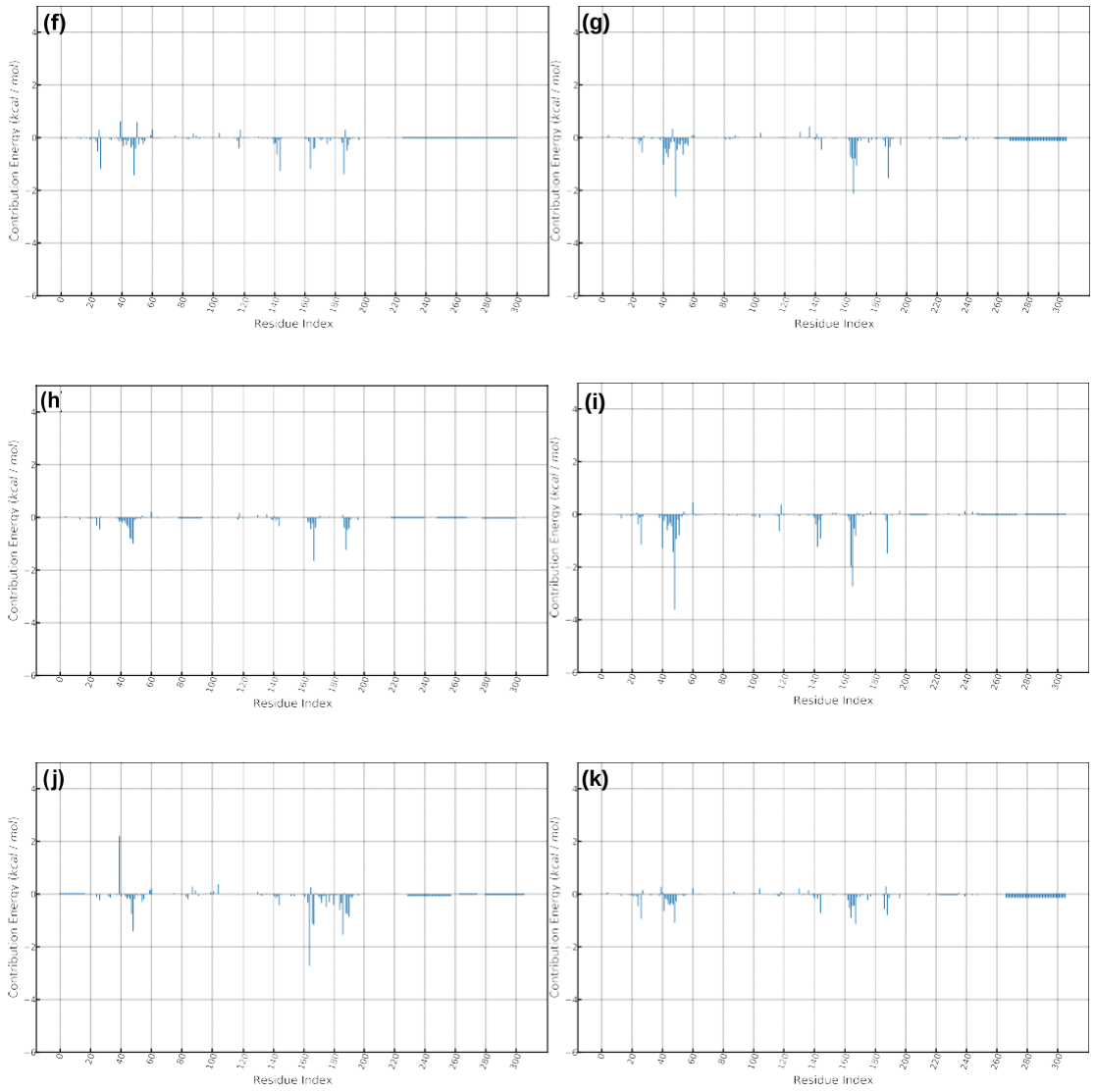
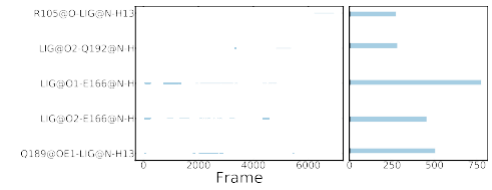
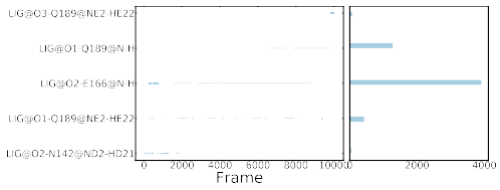


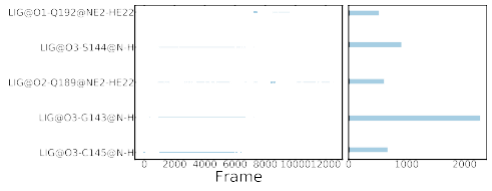
Figure S11. MM-PBSA Decomposed energy per-residue with g54a7 (f) 11r (g) 13a (h) 13b (i) darunavir (j) lopinavir (k) indinavir



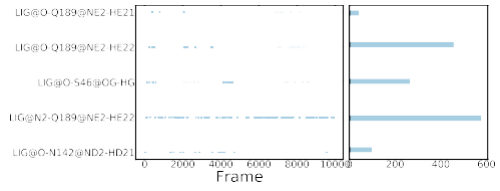
(a) X0072



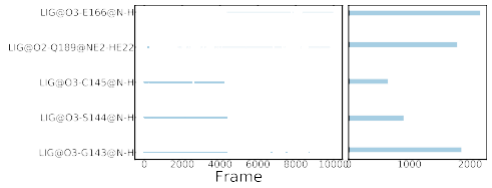
(b) X0689



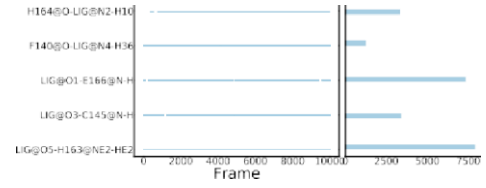
(c) X0691



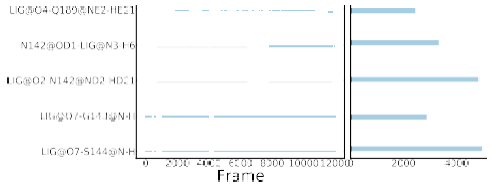
(d) X0749



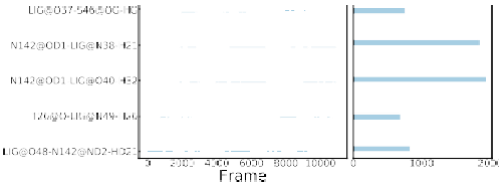
(e) X1336



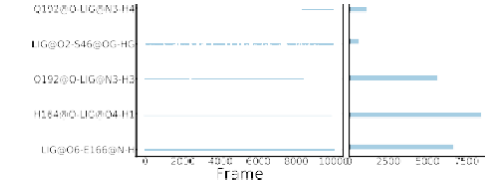
(f) 11r



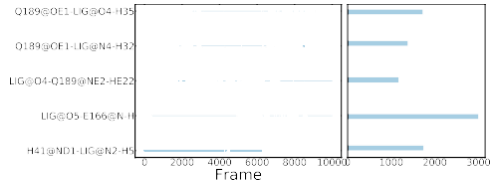
(g) 13a



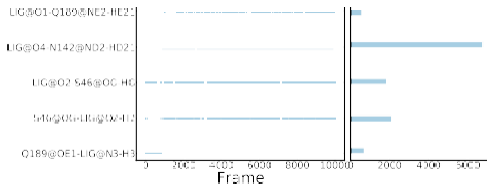
(h) 13b



(i) darunavir

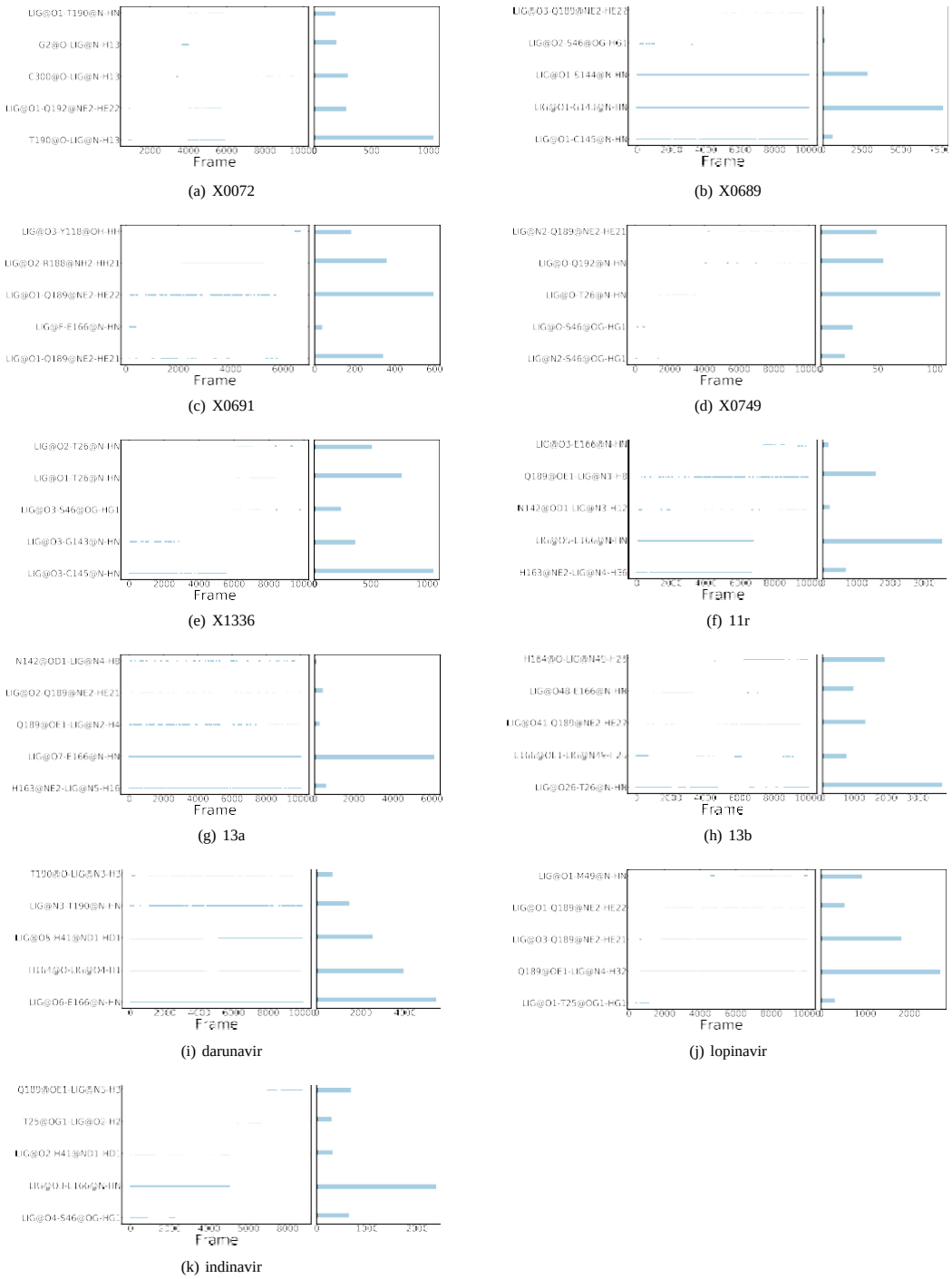


(j) lopinavir



(k) indinavir

Figure S12. Hydrogen bond existence map with ff99SB



(a) X0072 (b) X0689

(c) X0691 (d) X0749

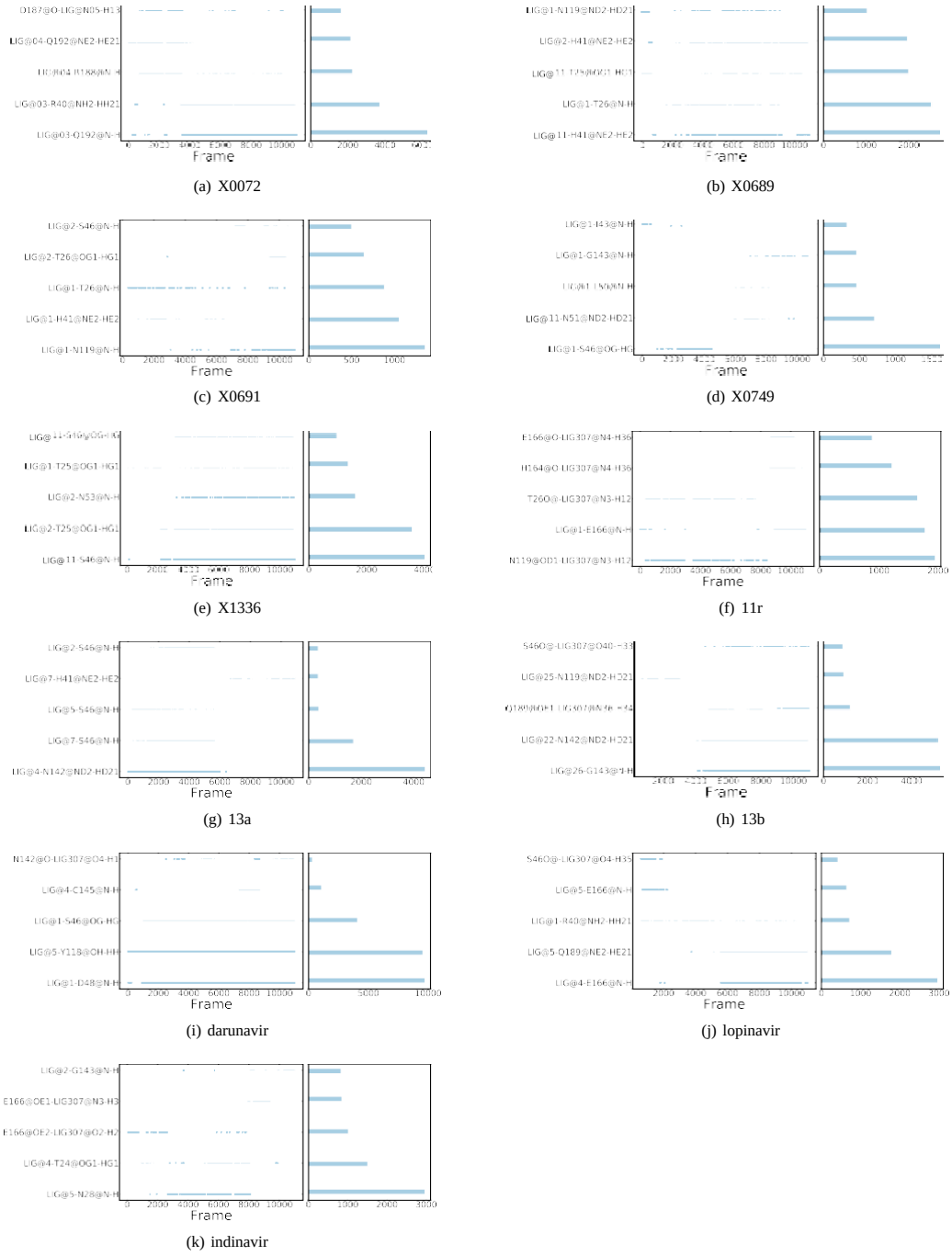
(e) X1336 (f) 11r

(g) 13a (h) 13b

(i) darunavir (j) lopinavir

(k) indinavir

Figure S13. Hydrogen bond existence map with c36



(a) X0072 (b) X0689

(c) X0691 (d) X0749

(e) X1336 (f) 11r

(g) 13a (h) 13b

(i) darunavir (j) lopinavir

(k) indinavir

Figure S14. Hydrogen bond existene map with g54a7

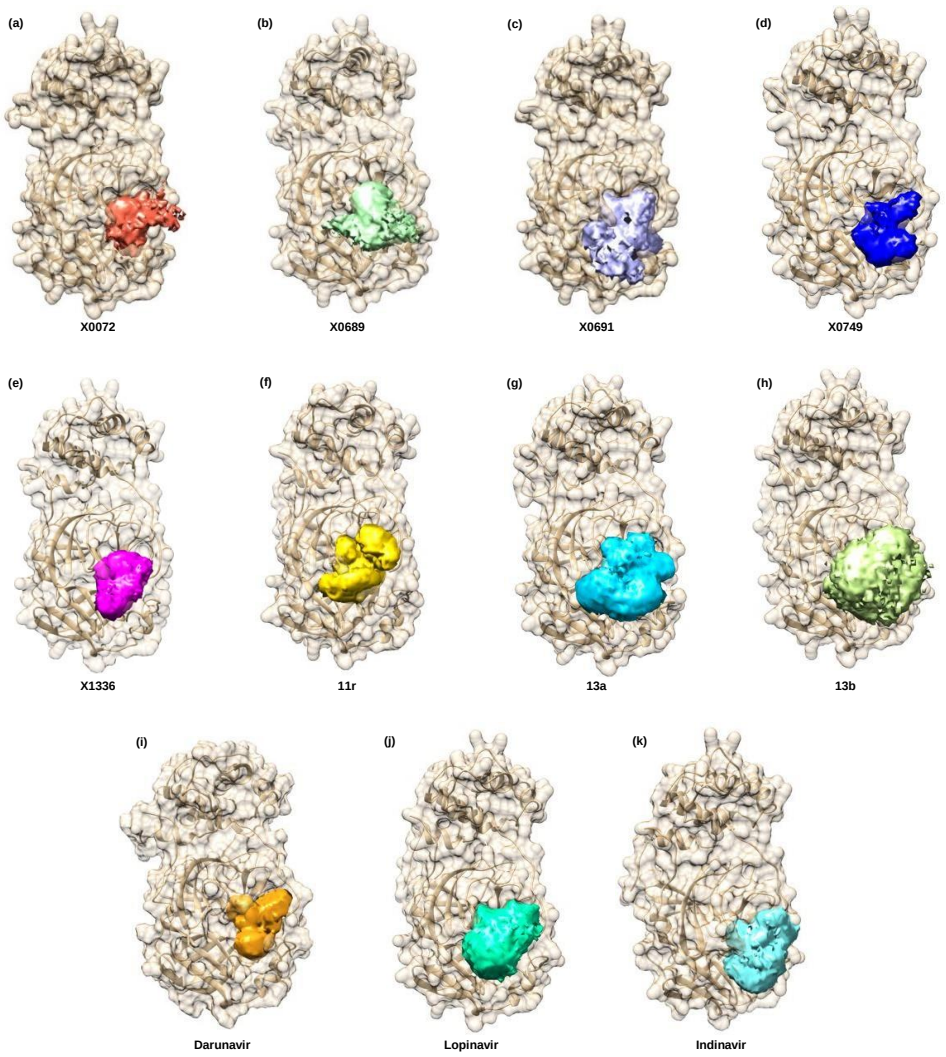


Figure S15. 3D histogram from the production trajectories with ff99SB

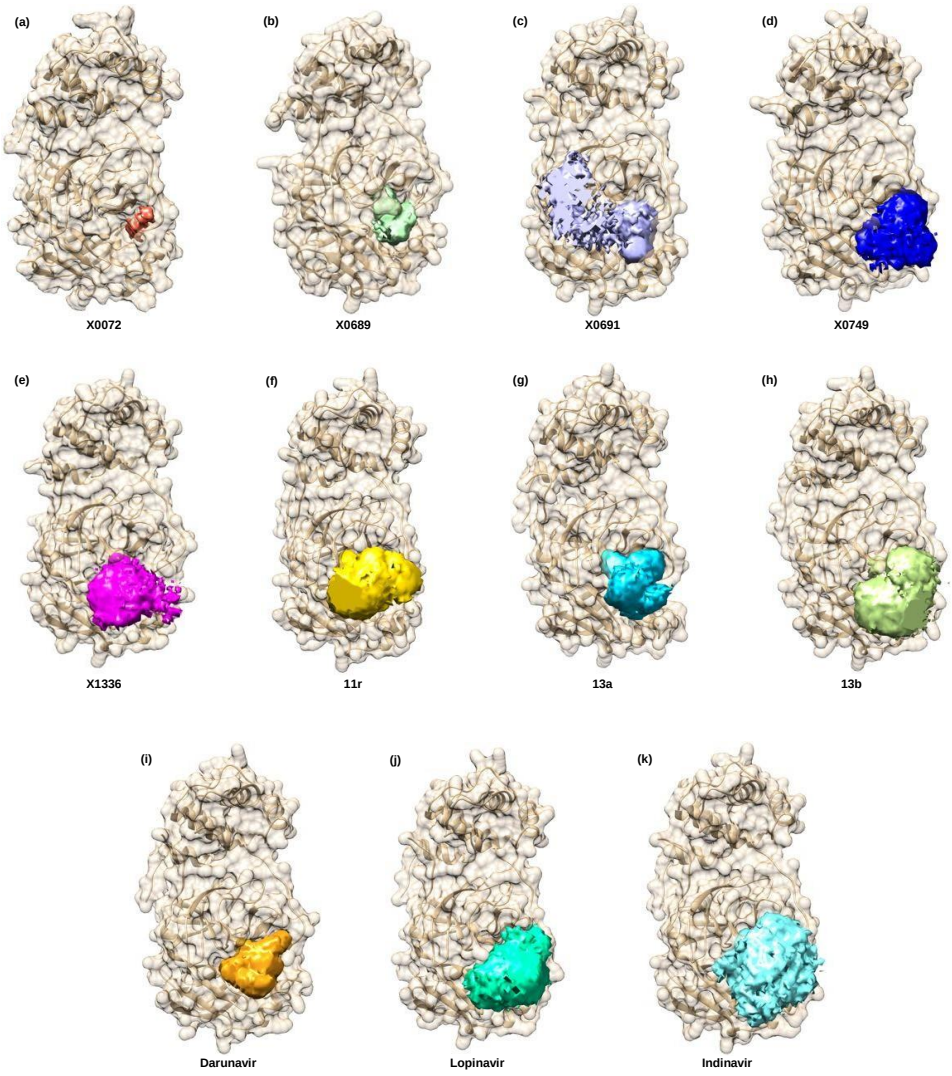


Figure S16. 3D histogram from the production trajectories with c36

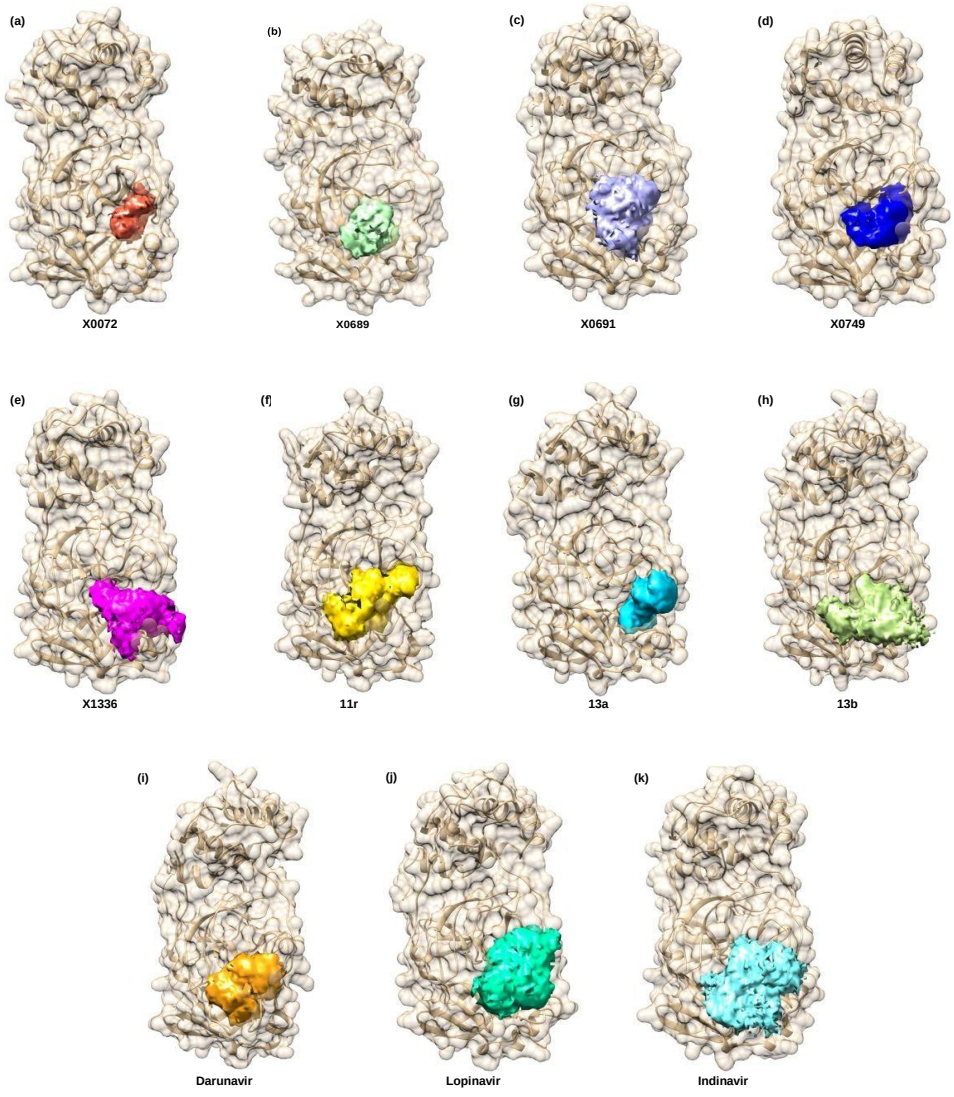


Figure S17. 3D histogram from the production trajectories with g54a7

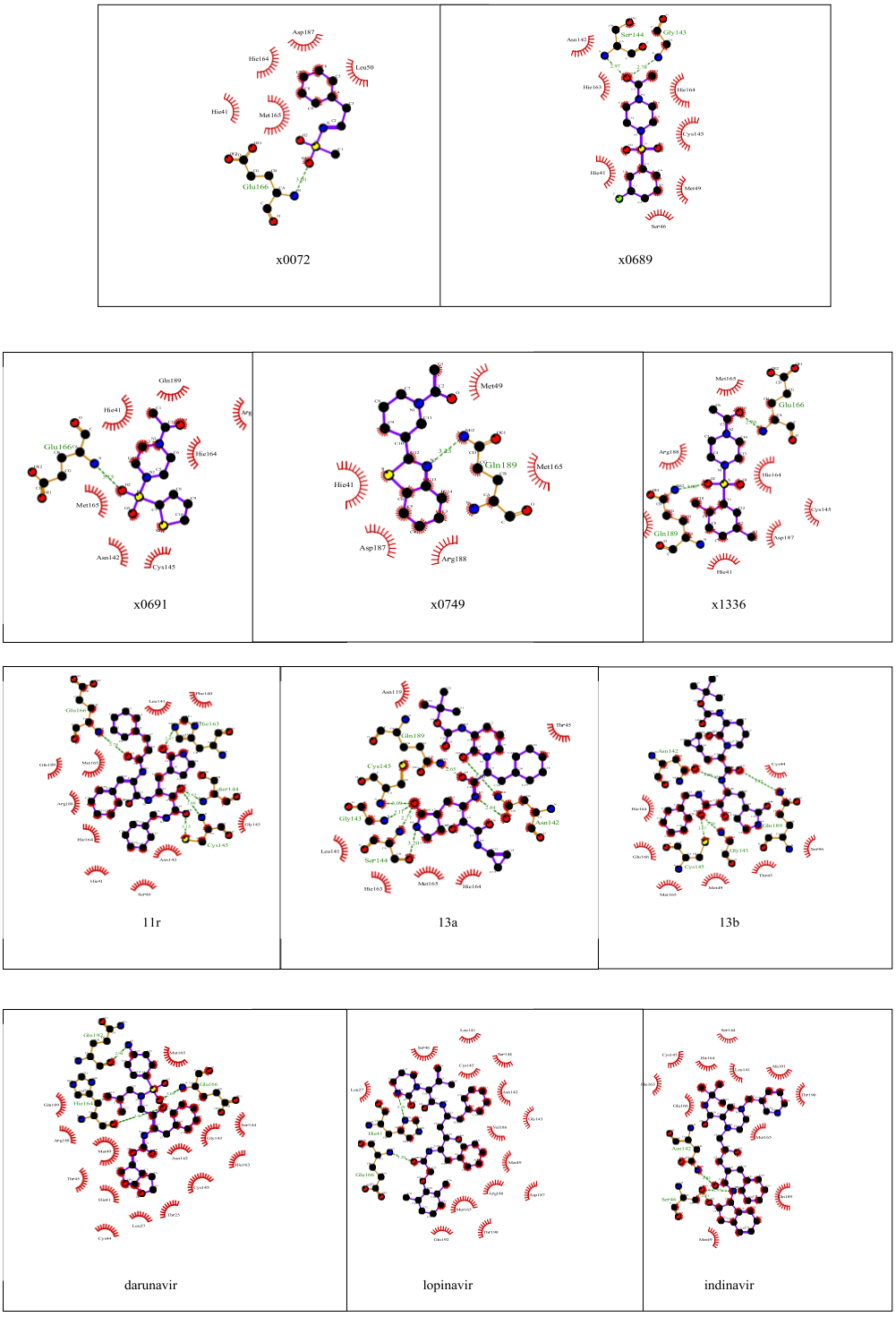


Figure S18. The protein-ligand interaction plot generated by ligPlot+ program with ff99sb force field

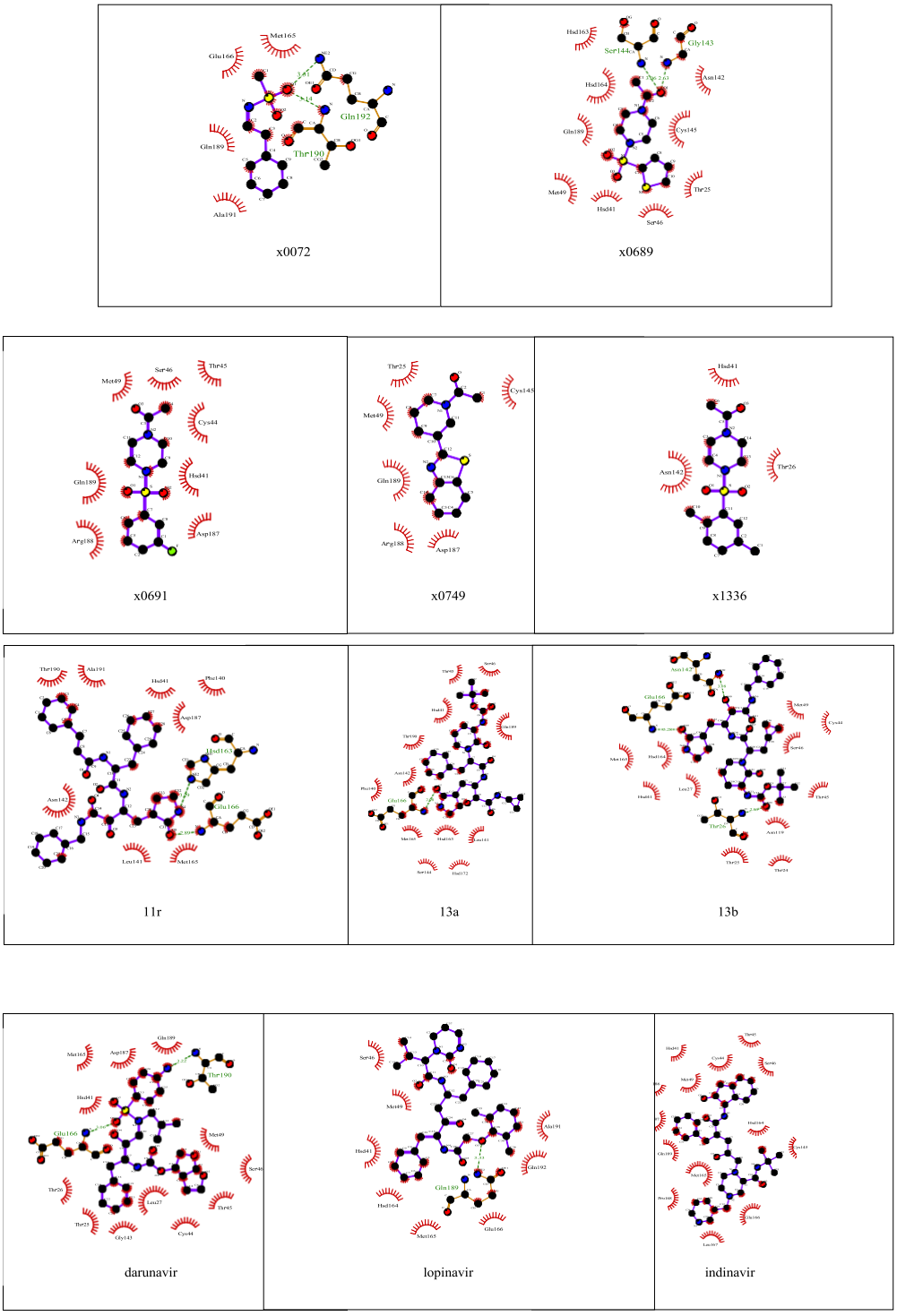


Figure S19. The protein-ligand interaction plot generated by ligPlot+ program with c36 force field

Table S1. Each energetic components of $\Delta G_{component}$ (kcal/mol) of each ligand-M^{pro} calculated by the MM-PBSA analysis.

Ligand	E_{vdw}	E_{elec}	E_{MM}	E_{PB}	E_{nonpol}	E_{sol}	E_{total}
X0072							
ff99SB	-34.56	-21.98	-55.91	-14.49	35.54	21.05	-34.86
c36	-12.54	-75.34	-83.03	35.95	30.18	66.13	-17.30
g54a7	-31.61	-17.17	-48.78	38.24	-3.12	35.12	-13.66
X0689							
ff99SB	-50.56	-111.34	-154.66	69.21	62.23	131.44	-23.22
c36	-20.07	38.12	12.66	-41.79	33.60	-8.19	3.94
g54a7	-30.54	-17.38	-47.92	28.61	-2.92	25.68	-22.24
X0691							
ff99SB	-26.76	-13.66	-47.07	3.85	34.14	38.00	-9.08
c36	-11.19	-2.63	-17.93	7.49	23.60	31.09	12.18
g54a7	-28.19	-14.32	-42.51	24.83	-2.87	21.96	-20.55
X0749							
ff99SB	-42.95	-20.21	-62.54	-8.86	53.23	44.37	-18.17
c36	-31.06	-53.27	-92.13	34.89	44.00	78.89	-13.24
g54a7	-38.32	-6.22	-44.54	26.06	-3.56	22.50	-22.04
X1336							
ff99SB	-37.13	24.50	-18.83	-51.88	46.99	-4.89	-23.73
c36	-7.08	-47.02	-63.11	28.08	26.98	55.07	-8.93
g54a7	-31.97	-23.57	-55.55	35.98	-3.17	32.81	-22.73
11r							
ff99SB	-68.82	-24.22	-91.33	-37.34	73.68	36.34	-54.99
c36	-32.06	-14.22	-46.84	-12.54	49.77	37.23	-10.18
g54a7	-53.31	-11.87	-65.18	33.43	-6.16	27.27	-37.91
13a							
ff99SB	-43.84	-97.48	-146.15	51.74	56.44	108.18	-37.97
c36	-27.47	-53.46	-69.46	-3.84	44.60	40.76	-28.52
g54a7	-56.01	-14.01	-70.02	31.60	-5.19	26.41	-43.61
13b							
ff99SB	-35.98	-17.60	-52.33	-25.44	48.24	22.80	-29.54
c36	-35.20	-138.26	-171.51	116.50	60.66	177.16	5.58
g54a7	-38.31	-18.49	-56.80	29.35	-4.48	24.87	-31.93
DARUNAVIR							
ff99SB	-57.96	-50.70	-110.38	-0.73	60.82	60.10	-50.29
c36	-44.52	-90.10	-124.84	58.39	64.57	122.96	-1.56
g54a7	-52.76	-23.14	-75.90	34.72	-5.45	29.26	-46.64
INDINAVIR							
ff99SB	-67.49	11.94	-54.86	-49.95	75.58	25.62	-29.24
c36	-33.10	-20.36	-59.65	-3.66	42.03	38.37	-21.34
g54a7	-44.27	-13.41	-57.68	26.13	-4.59	21.54	-36.14
LOPINAVIR							
ff99SB	-53.21	10.14	-35.53	-47.76	66.23	18.47	-17.06
c36	-36.66	-33.91	-63.79	-1.39	52.52	51.13	-13.17
g54a7	-53.32	-11.17	-64.49	29.31	-5.57	23.74	-40.74