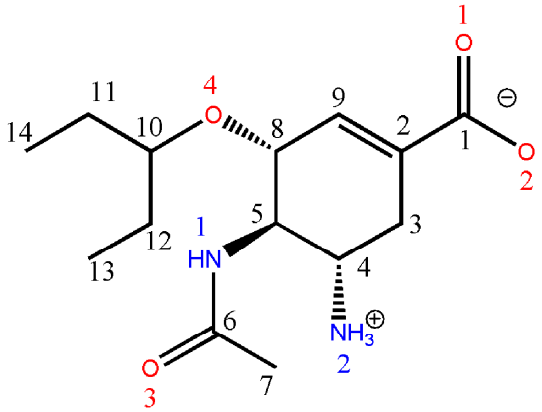
Supporting Materials

Table S1. The atom types and partial charges for oseltamivir



Atom name	Atom type	Partial charge
C1	c	0.7932
O1	o	-0.7572
O2	o	-0.7572
C2	ce	-0.0646
C3	c3	-0.1311
H1	hc	0.0861
H2	hc	0.0861
C4	c3	0.1775
H3	hx	0.1050
C5	c3	0.0864
H4	h1	0.1574
N1	n	-0.7729
H5	hn	0.3718
C6	c	0.8378
O3	o	-0.6502
C7	c3	-0.3473
H6	hc	0.1045
H7	hc	0.1045
H8	hc	0.1045
C8	c3	0.0738
H9	h1	0.0958
C9	c2	-0.2897
H10	ha	0.1966
O4	os	-0.3281
C10	c3	0.0614
H11	h1	0.0464
C11	c3	-0.0896
H12	hc	0.0599

H13	hc	0.0599
C12	c3	-0.0896
H14	hc	0.0599
H15	hc	0.0599
C13	c3	-0.1167
H16	hc	0.0448
H17	hc	0.0448
H18	hc	0.0448
C14	c3	-0.1167
H19	hc	0.0448
H20	hc	0.0448
H21	hc	0.0448
N2	n4	-0.6984
H22	hn	0.4039
H23	hn	0.4039
H24	hn	0.4039

Table S2. Binding free energy contributions of the key binding-site residues calculated from the binding energy decomposition (kcal/mol).

System	WT				
Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
R118	-0.36	10.80	-9.56	-0.04	0.84
E119	-1.00	-67.26	60.98	-0.30	-7.58
D151	-1.76	-40.68	36.52	-0.30	-6.22
R152	-2.54	-14.20	9.34	-0.32	-7.72
R156	-0.86	26.40	-22.70	-0.02	2.82
W178	-1.82	-2.20	2.84	-0.08	-1.26
S179	-1.14	2.62	-1.62	-0.08	-0.20
I222	-1.78	0.04	0.12	-0.24	-1.86
R224	-1.76	0.34	0.64	-0.14	-0.92
E227	-1.02	2.72	-1.06	-0.08	0.54
S246	-0.12	-0.50	0.74	-0.02	0.10
Y252	-0.02	0.10	-0.08	0.00	0.00
H274	-0.08	0.26	-0.16	0.00	0.04
E276	-0.88	5.30	-3.78	-0.04	0.60
E277	-1.82	-0.60	2.98	-0.18	0.38
R292	-1.54	-27.10	24.28	-0.42	-4.80
N294	-0.52	1.16	-0.86	-0.04	-0.26
N347	-0.16	-0.90	1.02	-0.02	-0.06
R371	-0.08	-18.48	16.66	-0.14	-2.04
Y406	-0.60	-1.08	1.26	-0.06	-0.48

System	H274Y				
Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
R118	-0.42	-2.08	3.14	-0.06	0.58
E119	-0.20	-51.44	44.98	-0.22	-6.86
D151	-1.16	-42.50	39.42	-0.32	-4.58
R152	-2.18	-6.20	4.08	-0.32	-4.62
R156	-0.64	25.08	-21.42	-0.02	3.00
W178	-1.72	-3.24	3.42	-0.10	-1.62
S179	-0.56	2.24	-2.28	-0.04	-0.64
I222	-1.38	-0.52	0.52	-0.10	-1.50
R224	-2.86	10.34	-8.72	-0.20	-1.44
E227	-0.42	2.60	-2.50	-0.02	-0.34
S246	-1.20	-0.08	1.36	-0.24	-0.14
Y252	-0.02	0.14	-0.10	0.00	0.00
Y274	-0.36	0.48	-0.54	0.00	-0.42
E276	-1.62	-8.00	12.40	-0.12	2.66
E277	-1.34	3.84	-3.20	-0.16	-0.86
R292	-1.26	-29.88	25.56	-0.32	-5.90

N294	-0.76	2.00	-1.66	-0.10	-0.50
N347	-0.34	-0.24	0.58	-0.02	-0.02
R371	0.70	-49.24	38.50	-0.24	-10.28
Y406	-0.40	-0.54	0.60	-0.02	-0.36

System			N294S		
Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
R118	-0.70	-8.12	6.40	-0.16	-2.60
E119	0.56	-60.66	53.68	-0.14	-6.56
D151	-1.02	-46.42	41.88	-0.32	-5.86
R152	-2.08	-8.16	5.56	-0.26	-4.94
R156	-0.22	15.94	-14.78	0.00	0.96
W178	-1.56	-3.60	4.02	-0.12	-1.26
S179	-0.76	2.54	-2.48	-0.06	-0.74
I222	-1.98	-0.38	0.42	-0.22	-2.14
R224	-2.50	6.30	-5.18	-0.22	-1.60
E227	-0.72	3.62	-3.46	-0.02	-0.58
S246	-0.14	0.06	-0.06	0.00	-0.14
Y252	-0.02	0.06	-0.04	0.00	0.00
Y274	-0.12	0.36	-0.12	0.00	0.12
E276	-0.96	-2.54	5.20	-0.06	1.66
E277	-1.98	-1.82	2.86	-0.14	-1.08
R292	-1.68	-30.66	26.60	-0.36	-6.12
S294	-0.42	0.50	-0.08	-0.08	-0.08
N347	-0.14	0.02	0.16	-0.02	0.04
R371	-0.28	-19.98	19.82	-0.08	-0.54
Y406	-3.22	0.40	-0.40	-0.24	-3.46

System			Y252H		
Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
R118	-0.48	-1.02	1.94	-0.10	0.36
E119	0.16	-57.32	47.66	-0.12	-9.62
D151	-1.34	-39.74	35.64	-0.34	-5.78
R152	-1.74	-3.14	1.76	-0.22	-3.34
R156	-0.38	21.54	-18.92	0.00	2.22
W178	-1.24	-2.74	2.98	-0.08	-1.06
S179	-0.56	2.92	-2.82	-0.04	-0.50
I222	-1.74	-0.48	0.54	-0.20	-1.88
R224	-2.44	10.24	-8.18	-0.20	-0.56
E227	-0.94	4.96	-3.94	-0.04	0.04
S246	-0.82	0.04	0.50	-0.14	-0.42
H252	-0.02	0.18	-0.18	0.00	0.00
Y274	-0.12	0.22	0.08	0.00	0.18
E276	-0.86	-5.72	7.26	-0.02	0.66

E277	-3.06	-5.96	5.84	-0.26	-3.44
R292	-2.18	-24.02	20.88	-0.30	-5.62
N294	-0.66	1.76	-1.20	-0.08	-0.16
N347	-0.22	0.28	0.00	0.00	0.04
R371	1.10	-55.28	41.24	-0.22	-13.16
Y406	-3.50	5.18	-3.72	-0.18	-2.22

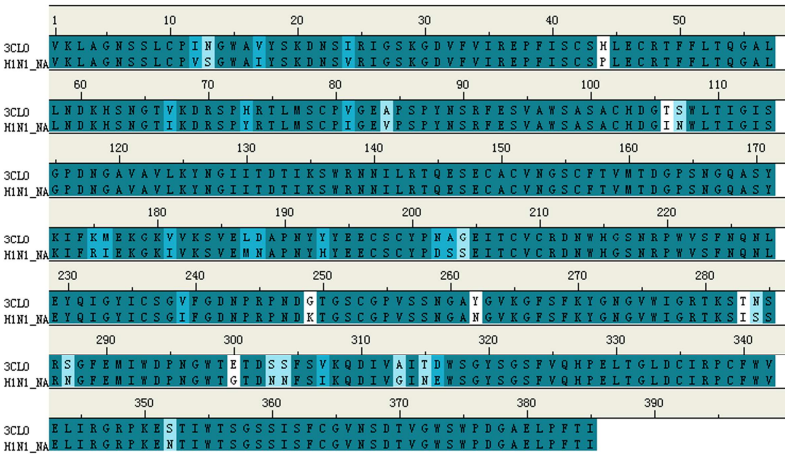


Figure S1. Sequence alignment of influenza A/H1N1 NA with 3cl0 (influenza A/H5N1 NA) used for homology modeling.

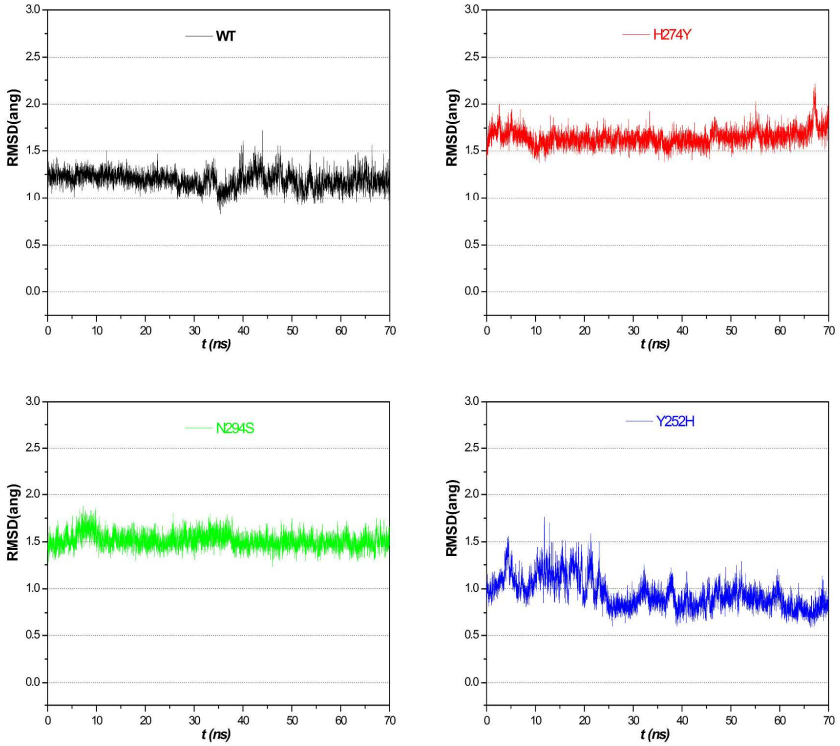


Figure S2. RMSD of the active site residues (the residues within 5 Å of oseltamivir) of NA with respect to the first snapshot as a function of time (black, red, green and blue lines represent WT, H274Y, N294S and Y252H, respectively).

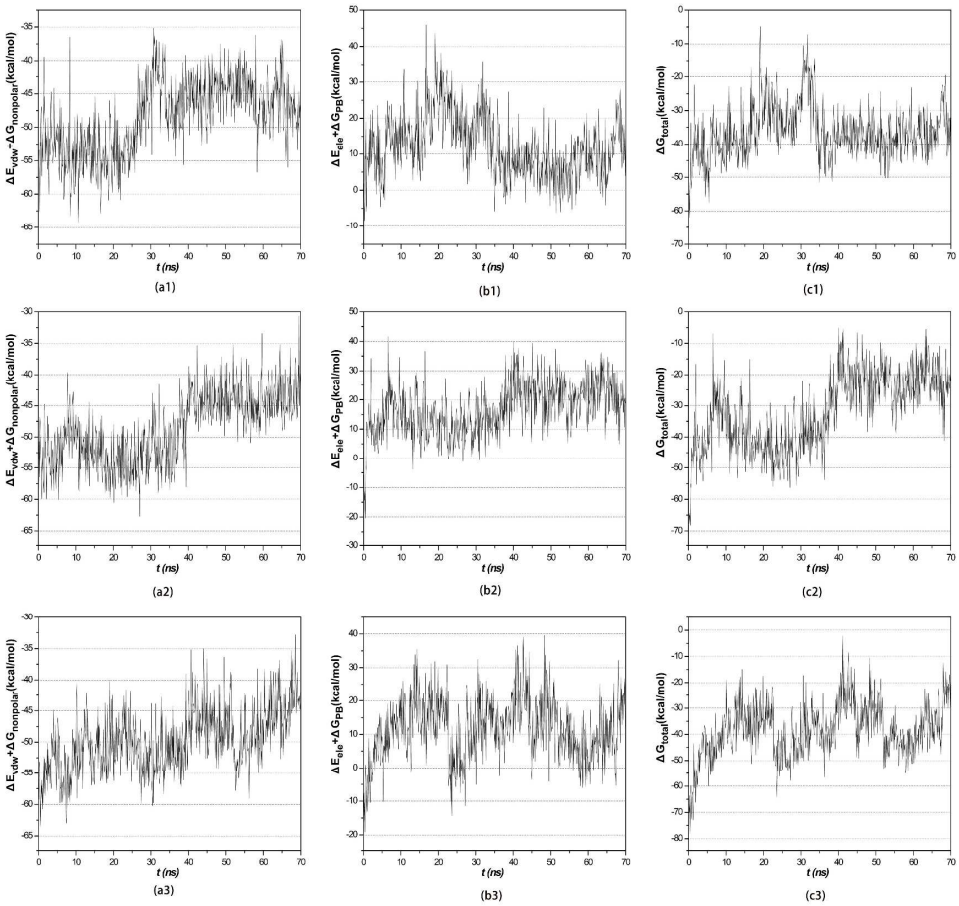


Figure S3. Fluctuations of the (a1) total non-polar ($\Delta E_{vdw}+\Delta G_{nonpolar}$), (b1) total polar ($\Delta E_{ele}+\Delta G_{PB}$), and (c1) total binding energy (ΔG_{total}) interactions between oseltamivir and the WT NA; fluctuations of the (a2) total nonpolar ($\Delta E_{vdw}+\Delta G_{nonpolar}$), (b2) total polar ($\Delta E_{ele}+\Delta G_{PB}$), and (c2) total binding energy (ΔG_{total}) interactions between oseltamivir and the N294S NA; fluctuations of the (a3) total non-polar ($\Delta E_{vdw}+\Delta G_{nonpolar}$), (b3) total polar ($\Delta E_{ele}+\Delta G_{PB}$), and (c3) total binding energy (ΔG_{total}) interactions between oseltamivir and the Y252H NA;

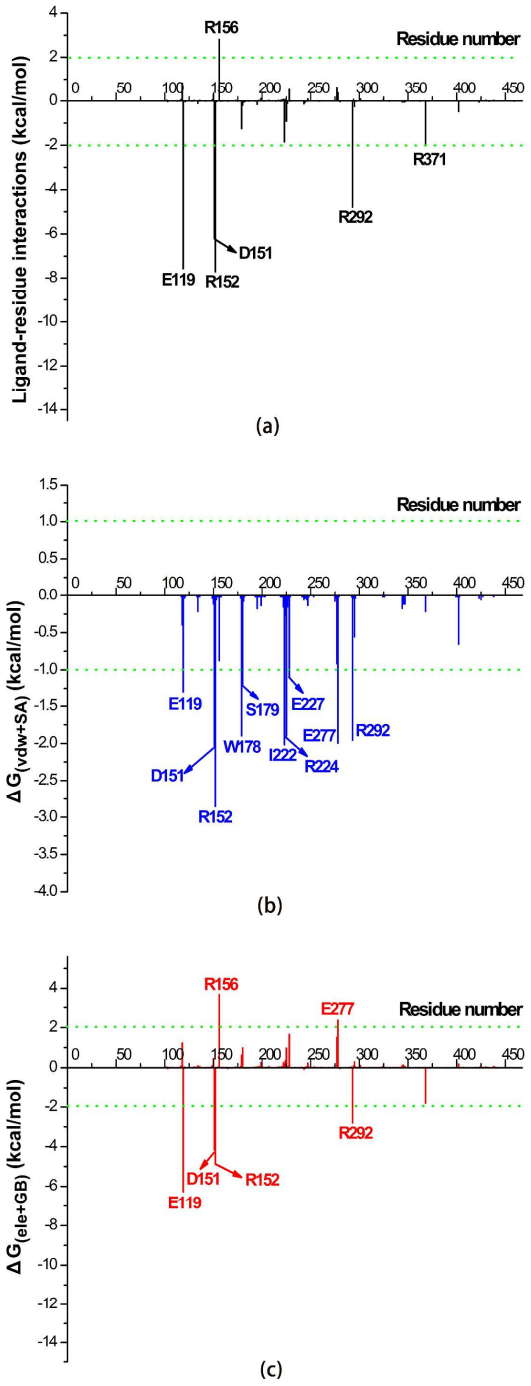


Figure S4. Inhibitor-residue interaction spectrums for the WT/mutation oseltamivir complexes: (a) the total energy for the WT/oseltamivir complex, (b) the non-polar energy (ΔG_{vdw}+ΔG_{SA}) for the WT/oseltamivir complex, and (c) the polar energy (ΔG_{ele}+ΔG_{GB}) for the WT/oseltamivir complex.

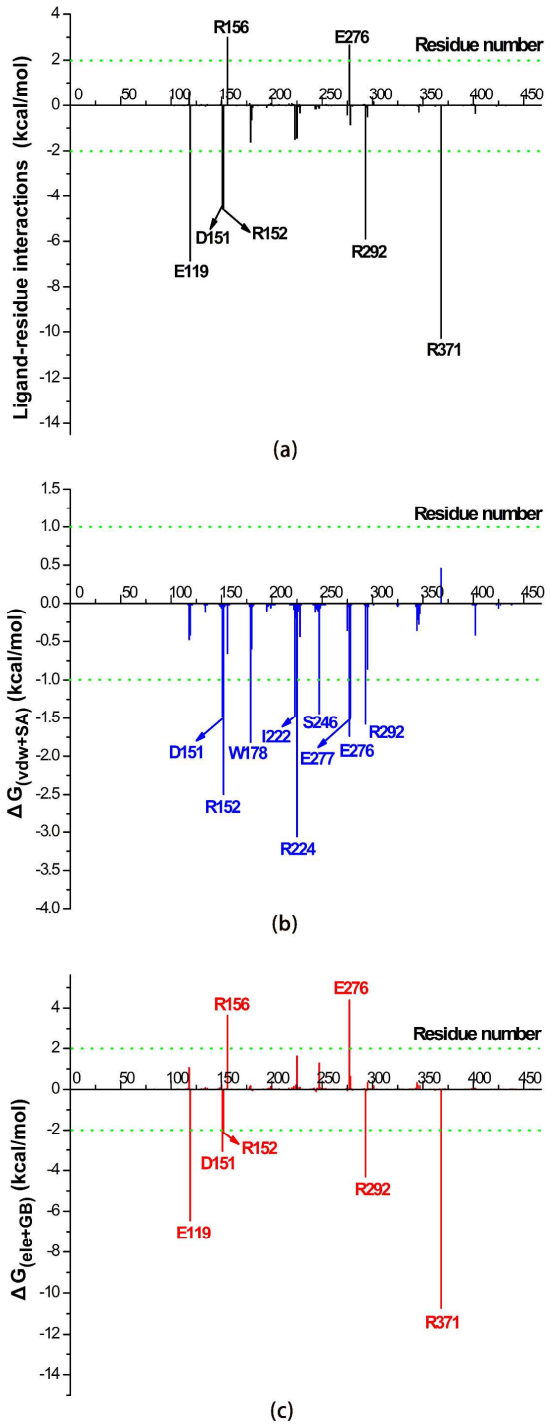


Figure S5. Inhibitor-residue interaction spectrums for the WT/mutation oseltamivir complexes: (a) the total energy for the H274Y/oseltamivir complex, (b) the non-polar energy (ΔG_{vdw}+ΔG_{SA}) for the H274Y/oseltamivir complex, and (c) the polar energy (ΔG_{ele}+ΔG_{GB}) for the H274Y/oseltamivir complex.

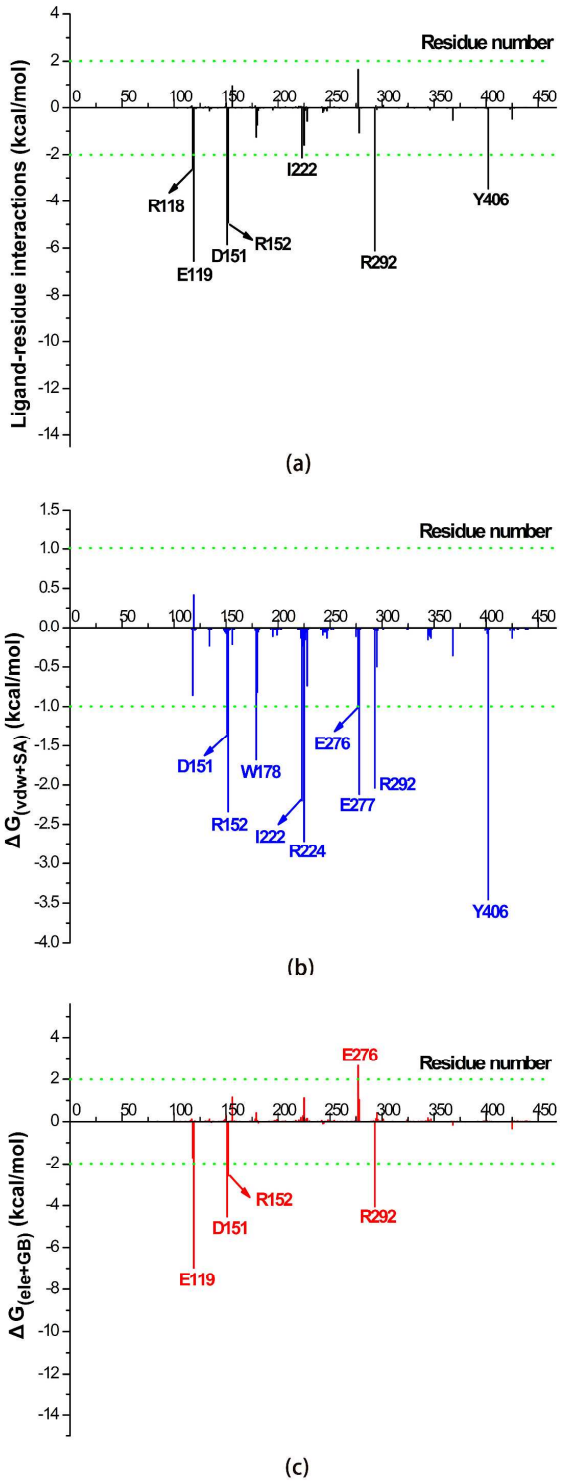


Figure S6. Inhibitor-residue interaction spectrums for the WT/mutation oseltamivir complexes: (a) the total energy for the N294S/oseltamivir complex, (b) the non-polar energy (ΔG_{vdw}+ΔG_{SA}) for the N294S/oseltamivir complex, (c) the polar energy (ΔG_{ele}+ΔG_{GB}) for the N294S/oseltamivir complex.

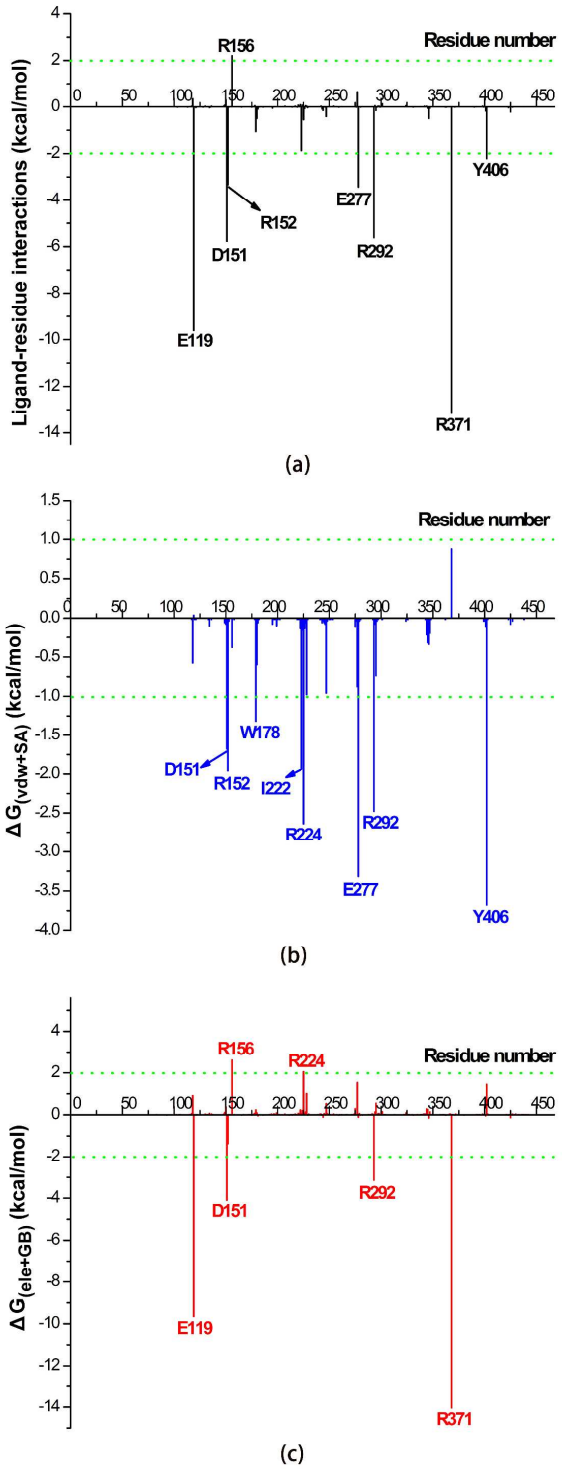


Figure S7. Inhibitor-residue interaction spectrums for the WT/mutation oseltamivir complexes: (a) the total energy for the Y252H/oseltamivir complex, (b) the non-polar energy (ΔG_{vdw}+ΔG_{SA}) for the Y252H/oseltamivir complex, (c) the polar energy (ΔG_{ele}+ΔG_{GB}) for the Y252H/oseltamivir complex.