A strategy to optimize the peptide-based inhibitor against different mutants of the spike protein of SARS-CoV-2

Prerna Priya[1], Abdul Basit[2], Pradipta Bandyopadhyay[2]

1. Department of Botany, Purnea Mahila College, Purnia, Bihar, India
2. School of Computational and Integrative Sciences, Jawaharlal Nehru University, New Delhi, India

Supporting Information

1. **Table S1:** List of the simulation performed for the MM-PBSA calculation using single trajectory method.
2. **Table S2:** List of the simulation performed for estimation of the change in the Entropy.
3. **Table S3:** Test to select the dielectric constant of solute.
4. **Table S4:** Change in the entropy obtained from separate simulation of complex, receptor, and ligand over 1 μs simulation.

Table S1: List of the simulated system with total sampling time used for the MM-PBSA calculations by single trajectory method

System	Total Simulation time (Simulation Length × No. of Independent Simulation)
S_{N501Y}-LCB3$_{D3F}$	100 ns (10 ns ×10)
S_{N501Y}-LCB3$_{D3Y}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{D3Y}$	100 ns (10 ns ×10)
S_{WT}-LCB3$_{D3Y}$	100 ns (10 ns ×10)
S_{N501Y}-LCB3$_{E4Y}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{T10D}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{T10E}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{T10Q}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{D11R}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{D11H}$	100 ns (10 ns ×10)
S_{K417N}-LCB3$_{D11HID}$	100 ns (10 ns ×10)
S_{N501Y}-LCB3$_{D11H}$	100 ns (10 ns ×10)
S_{WT}-LCB3$_{D11H}$	100 ns (10 ns ×10)

Table S2: List of the separate simulation of complex, receptor and ligand for quasi-harmonic approximation.

System	Simulation Length
S_{WT}	1μs
S_{N501Y}	1μs
S_{K417N}	1μs
LCB3	1μs
S_{WT}-LCB3	1μs
$LCB3_{D3Y}$	1μs
$LCB3_{D11H}$	1μs
S_{N501Y}- $LCB3_{D3Y}$	1μs
S_{K417N}- $LCB3_{D11H}$	1μs
S_{WT}- $LCB3_{D3Y}$	1μs
S_{WT}- $LCB3_{D11H}$	1μs
Total	11 μs

Table S3: Change in the binding free energy tested at the dielectric constant of protein 1, 2, 4 and 8. Values of binding energy are in kcal/mol. The calculations were performed over 10 trajectories each of 10 ns. 1000 frames were used in the calculations. Standard error is given in small parenthesis.

System	Dielectric Constant	Binding Energy
1. S_{WT}-LCB3[1]	1	+8.28 (1.4)
	2	-9.61 (0.8)
	4	-18.90 (0.6)
	8	-23.85 (0.6)
2. S_{N501Y}-LCB3[2]	1	+25.63 (2.0)
	2	+2.34 (1.0)
	4	-9.53 (0.6)
	8	-15.69 (0.6)
3. Difference $^{(2-1)}$	1	+17.35
	2	+11.95
	4	+9.37
	8	+8.16

Change in the binding affinity was tested using dielectric constants 1, 2, 4 and 8 for the protein. It was observed that the trend of the binding affinity of S_{WT}-LCB3 and S_{N501Y}-LCB3 remains the same in all the calculations i.e, the binding affinity of S_{N501Y} was reduced with LCB3 as compared to S_{WT}. The difference in the binding affinity at dielectric constant 8 is more similar (~+8.1 kcal/mol) to the already reported value (+7.1 kcal/mol) by Williams et al.[1]. Therefore, the dielectric constant of protein, 8 was selected for all the calculations.

Table S4: Change in Entropy at a given time, obtained from the separate, 1μs simulation of complex, receptor and ligand. Calculations were performed using 5 lakhs frames. TΔS was obtained by the subtraction of TS of receptor and ligand from the complex.

System	Time (μs)	TΔS (kcal/mol)
S_{WT}-LCB3	0.1	-134.8
	0.2	-103.6
	0.3	-89.2
	0.4	-80.2
	0.5	-72.7
	0.6	-66.7
	0.7	-63.2
	0.8	-60.4
	0.9	-57.7
	1.0	**-55.5**
S_{N501Y}-$LCB3_{D3Y}$	0.1	-130.4
	0.2	-98.5
	0.3	-82.7
	0.4	-72.9
	0.5	-66.2
	0.6	-60.7
	0.7	-56.1
	0.8	-53.1
	0.9	-51.6
	1.0	**-49.4**
	0.1	-130.2
	0.2	-103.7
	0.3	-88.2
	0.4	-78.6

S_{WT}-LCB3$_{D3Y}$	0.5	-73.6
	0.6	-69.2
	0.7	-65.2
	0.8	-61.5
	0.9	-58.6
	1.0	**-56.0**
S_{K417N}-LCB3$_{D11H}$	0.1	-131.5
	0.2	-104.6
	0.3	-85.9
	0.4	-73.4
	0.5	-55.5
	0.6	-45.2
	0.7	-37.6
	0.8	-34.2
	0.9	-29.5
	1.0	**-24.4**
S_{WT}-LCB3$_{D11H}$	0.1	-130.5
	0.2	-104.4
	0.3	-89.8
	0.4	-82.8
	0.5	-75.5
	0.6	-69.1
	0.7	-64.7
	0.8	-61.3
	0.9	-58.6
	1.0	**-56.2**

Reference:

1. Williams, A. H.; Zhan, C. G., Fast Prediction of Binding Affinities of the SARS-CoV-2 Spike Protein Mutant N501Y (UK Variant) with ACE2 and Miniprotein Drug Candidates. *J Phys Chem B* **2021,** *125* (17), 4330-4336.