Supporting Information

Interaction analysis of the spike protein of Delta and Omicron variants of SARS-CoV-2 with hACE2 and eight monoclonal antibodies using fragment molecular orbital method

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Figure S1. The predicted structure of the wild type, the Delta variant, and the Omicron variant containing Q493R. Crystal structure of the ACE2 and the RBD of (a) wild type (PDB ID: 6M0J), (b) Delta variant (PDB ID: 7V8B), and (c) Omicron variant containing Q493R (PDB ID: 7T9L). Predicted RBD structures of (d) wild type, (e) Delta variant, and (f) Omicron variant containing Q493R superimposed in crystal structure.
**Figure S2.** $\pi-\pi$ stacking interactions between Tyr41 in hACE2 and Tyr501 in S protein of (a) wild type and (b) Omicron variant.
Figure S3. RMSD changes in 9 complexes of ACE2 and spike protein of wild type during production time using molecular dynamics.
Figure S3. (continue)
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Figure S4. RMSD changes in 10 complexes of ACE2 and spike protein of delta variant during production time using molecular dynamics. RMSD is not shown in the chart when calculated over 9Å.
Figure S4. (continue)
Figure S4. (continue)
Figure S4. (continue)
Figure S4. (continue)
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Figure S5. (continue)
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Figure S5. (continue)
Figure S6. Distribution plots of pair interaction energy (a) between regdanvimab and four variants of spike protein and (b) between regdanvimab and each residue of spike protein of wild type and two Omicron variants. Asterisks indicate statistically significant variation (Student’s t-test, ns: P-value > 0.05, *: P-value < 0.05, **: P-value < 0.01, ***: P-value < 0.001).
Figure S7. Distribution plots of pair interaction energy (a) between bamlavimab and four variants of spike protein and (b) between bamlavimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S8. Distribution plots of pair interaction energy (a) between etesivimab and four variants of spike protein and (b) between etesivimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S9. Distribution plots of pair interaction energy (a) between casirivimab and four variants of spike protein and (b) between casirivimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S10. Distribution plots of pair interaction energy (a) between imdevimab and four variants of spike protein and (b) between imdevimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S11. Distribution plots of pair interaction energy (a) between cilgavimab and four variants of spike protein and (b) between cilgavimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S12. Distribution plots of pair interaction energy (a) between tixagevimab and four variants of spike protein and (b) between tixagevimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
Figure S13. Distribution plots of pair interaction energy (a) between sotrovimab and four variants of spike protein and (b) between sotrovimab and each residue of spike protein of wild type and two Omicron variants. The dashed red lines were described to median of total interaction energy for spike protein of wild type and Delta variant.
### Table S1. List of eight monoclonal antibodies

| Name           | Company                  | Code name  | PDB ID |
|----------------|--------------------------|------------|--------|
| Regdanvimab    | Celltrion                | CT-P59     | 7CM4   |
| Bamlavimab     | Eli Lilly and Company    | LY-CoV555  | 7L3N   |
| Etesivimab     | Eli Lilly and Company    | LY-CoV016  | 7C01   |
| Casirivimab    | Regeneron                | Regn10933  | 6XDG   |
| Imdevimab      | Regeneron                | Regn10987  | 6XDG   |
| Cilgavimab     | AstraZeneca              | AZD1061    | 7L7E   |
| Tixagevimab    | AstraZeneca              | AZD8895    | 7L7E   |
| Sotrovimab     | GlaxoSmithKline Pharmaceuticals Ltd | -       | 6WPS   |
Table S2. Median electrostatic energy of residues in receptor binding domain interacting with hACE2 using pair interaction energy decomposition analysis (PIEDA)

| Residue   | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|-----------|----------------------------------|-----------------|-----------------|
|           | Energy                           | P-value         | Energy          | P-value         |
| G339D     | 1.4                              |                 |                 |
| S371L*    | -1.4                             |                 |                 |
| S373P     | 1.2                              |                 |                 |
| S375F     | -4.7                             |                 |                 |
| K417N     | -287.7                           |                 |                 |
| N440K     | 5.3                              |                 |                 |
| G446S     | 1.7                              |                 |                 |
| S477N     | 3.0                              |                 |                 |
| T478K     | -4.7                             |                 |                 |
| E484A     | 201.5                            |                 |                 |
| Q493K/R   | -5.9                             |                 |                 |
| G496S     | -1.1                             |                 |                 |
| Q498R     | -5.4                             |                 |                 |
| N501Y     | -11.8                            |                 |                 |
| Y505H     | -6.8                             |                 |                 |

Bold residues and values indicate significantly stronger pair interactions energy in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median pair interaction energy for the Omicron variant was lower than that for the wild type.

Underlined residues and values indicate significantly stronger electrostatic energy in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median electrostatic energy for the Omicron variant was lower than that for the wild type.

*Omicron variant containing Q493K showed no significantly stronger interaction, but the Omicron variant containing Q493R showed a significantly stronger interaction than that observed in the wild type.
**Table S3.** Median exchange energy of residues in receptor binding domain interacting with hACE2 using pair interaction energy decomposition analysis (PIEDA)

| Residue | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|---------|----------------------------------|-----------------|-----------------|
|         | Energy | P-value | Energy | P-value |
| G339D   | 0.0     | -       | 0.0    | -       |
| S371L   | 0.0     | -       | 0.0    | -       |
| S373P   | 0.0     | 3.0 x 10^{-1} | 0.0 | 1.0 x 10^{-0} |
| S375F   | 0.0     | 7.2 x 10^{-2} | 0.0 | 3.4 x 10^{-4} |
| K417N   | 0.0     | 4.9 x 10^{-1} | 0.0 | 2.6 x 10^{-1} |
| N440K   | 0.0     | 6.2 x 10^{-1} | 0.0 | 2.9 x 10^{-1} |
| G446S   | 0.0     | 1.5 x 10^{-1} | 0.0 | 5.9 x 10^{-2} |
| S477N   | 0.0     | 1.5 x 10^{-1} | 0.0 | 8.6 x 10^{-2} |
| T478K   | 0.0     | 2.5 x 10^{-1} | 0.0 | 7.4 x 10^{-1} |
| E484A   | 0.0     | 2.7 x 10^{-2} | 0.0 | 6.0 x 10^{-2} |
| Q493K/R | 0.4     | 3.2 x 10^{-3} | 0.6 | 7.3 x 10^{-1} |
| G496S   | 0.0     | 1.6 x 10^{-1} | 0.0 | 1.1 x 10^{-1} |
| Q498R   | 0.1     | 3.2 x 10^{-1} | 0.0 | 9.6 x 10^{-1} |
| N501Y   | 0.2     | 3.2 | 2.7 x 10^{-2} | 1.0 | 3.6 x 10^{-2} |
| Y505H   | 23.5    | 12.3 | 8.8 x 10^{-1} | 8.9 | 8.4 x 10^{-1} |

Bold residues and values indicate significantly stronger pair interactions energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 x 10^{-2} and the median pair interaction energy for the Omicron variant was lower than that for the wild type.

*a* All exchanged energy were calculated to 0.0 kcal/mol.

*b* Omicron variant containing Q493K showed no significantly stronger interaction, but the Omicron variant containing Q493R showed a significantly stronger interaction than that observed in the wild type.
Table S4. Median charge transfer energy of residues in receptor binding domain interacting with hACE2 using pair interaction energy decomposition analysis (PIEDA)

| Residue   | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|-----------|---------------------------------|----------------|----------------|
|           | Energy                          | P-value        | Energy         | P-value        |
| G339D     | 0.0                             | -              | 0.0            | -              |
| S371L     | 0.0                             | -              | 0.0            | -              |
| S373P     | 0.0                             | 2.0 × 10⁻²     | 0.0            | 1.0 × 10⁻⁰     |
| S375F     | 0.0                             | 6.3 × 10⁻¹     | 0.0            | 7.4 × 10⁻¹     |
| K417N     | -0.1                            | 1.7 × 10⁻³     | 0.0            | 7.1 × 10⁻³     |
| N440K     | 0.0                             | 1.3 × 10⁻²     | 0.0            | 3.9 × 10⁻¹     |
| G446S     | 0.0                             | 3.2 × 10⁻¹     | 0.0            | 6.2 × 10⁻¹     |
| S477N     | 0.0                             | 4.0 × 10⁻¹     | 0.0            | 6.2 × 10⁻¹     |
| T478K     | 0.0                             | 2.6 × 10⁻¹     | 0.0            | 5.7 × 10⁻¹     |
| E484A     | 0.0                             | 8.4 × 10⁻⁵     | 0.0            | 9.8 × 10⁻⁴     |
| Q493K/R   | 0.0                             | 2.7 × 10⁻²     | 0.0            | 3.4 × 10⁻¹     |
| G496S     | 0.0                             | 1.5 × 10⁻³     | 0.0            | 4.4 × 10⁻³     |
| Q498R     | 0.0                             | 2.2 × 10⁻²     | 0.0            | 1.9 × 10⁻³     |
| N501Y     | 0.0                             | 7.9 × 10⁻¹     | 0.0            | 1.4 × 10⁻²     |
| Y505H     | 0.0                             | 7.6 × 10⁻¹     | 0.0            | 5.1 × 10⁻¹     |

Bold residues and values indicate significantly stronger pair interactions energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10⁻² and the median pair interaction energy for the Omicron variant was lower than that for the wild type.

*All charge transfer energy were calculated to 0.0 kcal/mol.

Omicron variant containing Q493K showed no significantly stronger interaction, but the Omicron variant containing Q493R showed a significantly stronger interaction than that observed in the wild type.
Table S5. Median dispersion energy of residues in receptor binding domain interacting with hACE2 using pair interaction energy decomposition analysis (PIEDA)

| Residue   | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|-----------|----------------------------------|----------------|-----------------|
|           | Energy | P-value | Energy | P-value |
| G339D     | 0.0     | 0.0     | 3.8 × 10^{-2} | 0.0 | 4.3 × 10^{-3} |
| S371L*    | 0.0     | 0.0     | 1.9 × 10^{-3} | 0.0 | 4.6 × 10^{-4} |
| S373P     | 0.0     | 0.0     | 1.5 × 10^{-3} | 0.0 | 7.4 × 10^{-3} |
| S375F     | 0.0     | 0.0     | 9.6 × 10^{-3} | 0.0 | 3.9 × 10^{-3} |
| K417N     | -0.5    | -0.5    | 4.9 × 10^{-1} | -0.3 | 3.1 × 10^{-1} |
| N440K     | 0.0     | 0.0     | 3.7 × 10^{-1} | 0.0 | 6.5 × 10^{-1} |
| G446S     | 0.0     | 0.0     | 9.1 × 10^{-1} | 0.0 | 2.7 × 10^{-1} |
| S477N     | -0.2    | -0.1    | 9.4 × 10^{-1} | -0.1 | 2.0 × 10^{-1} |
| T478K     | -0.2    | -0.2    | 5.7 × 10^{-1} | -0.1 | 1.8 × 10^{-1} |
| E484A     | -0.2    | -0.1    | 6.9 × 10^{-4} | -0.1 | 1.9 × 10^{-4} |
| Q493K/R   | -0.5    | -1.2    | 4.9 × 10^{-3} | -0.7 | 9.2 × 10^{-1} |
| G496S     | -0.3    | -0.2    | 8.0 × 10^{-1} | -0.3 | 6.6 × 10^{-1} |
| Q498R     | -0.7    | -0.7    | 5.6 × 10^{-1} | -0.5 | 3.8 × 10^{-1} |
| N501Y     | -1.5    | -0.6    | 5.6 × 10^{-2} | -0.5 | 2.5 × 10^{-2} |
| Y505H     | -0.9    | -0.1    | 2.9 × 10^{-2} | -0.4 | 2.3 × 10^{-2} |

Bold residues and values indicate significantly stronger pair interactions energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10^{-2} and the median pair interaction energy for the Omicron variant was lower than that for the wild type.

Underlined residues and values indicate significantly stronger dispersion energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10^{-2} and the median electrostatic energy for the Omicron variant was lower than that for the wild type.

*Omicron variant containing Q493K showed no significantly stronger interaction, but the Omicron variant containing Q493R showed a significantly stronger interaction than that observed in the wild type.
**Table S6.** Median solvation energy of residues in receptor binding domain interacting with hACE2 using pair interaction energy decomposition analysis (PIEDA)

| Residue | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|---------|---------------------------------|-----------------|-----------------|
|         | Energy                          | P-value         | Energy          | P-value         |
| G339D   | 11.1                            | -115.3          | 5.4 × 10⁻³²     | -113.6          | 4.3 × 10⁻³¹     |
| S371L   | -11.6                           | -11.1           | 1.0 × 10⁻¹      | -9.7            | 6.1 × 10⁻⁴      |
| S373P   | -12.6                           | -0.1            | 4.8 × 10⁻³⁰     | 1.1             | 3.8 × 10⁻²⁹     |
| S375F   | **0.6**                         | **8.3**         | **4.1 × 10⁻²³** | **-6.6**        | **1.3 × 10⁻²³** |
| K417N   | 191.6                           | 12.9            | 5.4 × 10⁻³²     | 14.1            | 4.3 × 10⁻³¹     |
| N440K   | **18.3**                        | **200.2**       | **5.4 × 10⁻³²** | **201.2**       | **4.3 × 10⁻³¹** |
| G446S   | -2.2                            | 4.5             | 6.5 × 10⁻¹²     | 6.3             | 2.7 × 10⁻⁷      |
| S477N   | 9.9                             | 12.5            | 1.1 × 10⁻⁴      | 12.0            | 3.4 × 10⁻⁴      |
| T478K   | **-1.2**                        | **173.7**       | **5.4 × 10⁻³²** | **181.4**       | **4.3 × 10⁻³¹** |
| E484A   | **-174.4**                      | 7.1             | 5.4 × 10⁻³²     | 7.1             | 4.3 × 10⁻³¹     |
| Q493K/R | **1.2**                         | **191.3**       | **5.4 × 10⁻³²** | **188.1**       | **4.3 × 10⁻³¹** |
| G496S   | -0.5                            | 2.6             | 8.3 × 10⁻²      | -11.0           | 6.0 × 10⁻¹      |
| Q498R   | **-2.8**                        | **194.0**       | **5.4 × 10⁻³²** | **194.3**       | **4.3 × 10⁻³¹** |
| N501Y   | -8.9                            | -7.4            | 9.1 × 10⁻¹      | -6.4            | 6.0 × 10⁻¹      |
| Y505H   | 4.4                             | 0.8             | 7.7 × 10⁻²      | -1.9            | 1.8 × 10⁻⁴      |

Bold residues and values indicate significantly stronger pair interactions energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10⁻² and the median pair interaction energy for the Omicron variant was lower than that for the wild type.

Underlined residues and values indicate significantly stronger electrostatic energy in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10⁻² and the median electrostatic energy for the Omicron variant was lower than that for the wild type.

*Omicron variant containing Q493K showed no significantly stronger interaction, but the Omicron variant containing Q493R showed a significantly stronger interaction than that observed in the wild type.
### Table S7. Energy type and interaction energies with hACE2 by 15 mutant residues shown in Omicron variants using paired interaction energy decomposition analysis (PIEDA)

| Residue  | Wild type | Omicron (Q493R) |
|----------|-----------|-----------------|
|          | PIE<sup>a</sup> | ES<sup>b</sup> | EX<sup>c</sup> | CT<sup>d</sup> | DI<sup>e</sup> | SL<sup>f</sup> | PIE<sup>a</sup> | ES<sup>b</sup> | EX<sup>c</sup> | CT<sup>d</sup> | DI<sup>e</sup> | SL<sup>f</sup> |
| G339D    | 15.9      | 1.4             | 0.0           | 0.0           | 0.0           | 14.6          | 36.0         | 153.6         | 0.0           | 0.0           | 0.0           | -117.6        |
| S371L    | -21.9     | -2.1            | 0.0           | 0.0           | 0.0           | -19.7         | -12.0        | -1.7           | 0.0           | 0.0           | 0.0           | -10.2         |
| S373P    | -11.2     | -1.2            | 0.0           | 0.0           | 0.0           | -10.0         | 4.9          | -2.1           | 0.0           | 0.0           | 0.0           | 7.0           |
| S375F    | -4.8      | -6.0            | 0.0           | 0.0           | 0.0           | 1.2           | -7.9         | -5.6           | 0.0           | 0.0           | 0.0           | -2.3          |
| K417N    | -135.8    | -308.4          | 1.5           | -5.7          | -1.4          | 178.3         | 7.9          | -9.1           | 0.0           | 0.0           | -0.4          | 17.4          |
| N440K    | 21.0      | 6.5             | 0.0           | 0.0           | -0.1          | 14.6          | -7.0         | -252.6         | 0.0           | 0.0           | -0.2          | 245.7         |
| G446S    | -5.6      | -8.4            | 0.0           | 0.0           | -0.8          | 3.7           | 18.7         | 8.5            | 0.0           | 0.0           | -0.4          | 10.7          |
| S477N    | 15.3      | 0.7             | 0.0           | 0.0           | -1.0          | 15.6          | 14.3         | -5.0           | 0.3           | 0.0           | -2.5          | 21.4          |
| T478K    | -5.1      | -5.3            | 0.0           | 0.0           | -0.2          | 0.4           | -20.8        | -182.9         | 0.0           | 0.0           | -0.3          | 162.4         |
| E484A    | 39.9      | 203.0           | 0.0           | 0.0           | -0.7          | -162.4        | 4.1          | -5.1           | 0.0           | 0.0           | -0.2          | 9.3           |
| Q493R    | -5.2      | -20.3           | 0.9           | -0.1          | -3.4          | 17.8          | -125.0       | -274.1         | 3.9           | -3.2          | -6.7          | 155.1         |
| G496S    | 1.2       | -6.3            | -0.1          | 0.0           | -1.6          | 9.2           | -16.5        | -23.0          | -0.2          | -0.8          | -2.2          | 9.6           |
| Q498R    | -16.8     | -19.0           | 1.1           | 0.0           | -5.7          | 6.9           | -170.0       | -300.1         | 0.3           | -1.1          | -7.7          | 138.7         |
| N501Y    | -11.6     | 13.5            | -0.1          | 0.0           | -8.8          | -16.1         | -13.5        | 1.7            | 2.4           | -1.0          | -13.1         | -3.5          |
| Y505H    | 4.0       | -6.0            | 0.5           | 0.2           | -10.6         | 20.0          | 6.8          | -10.2          | 0.0           | 0.0           | -8.2          | 25.2          |

Bold residues and values indicate significantly stronger pair interactions energy in Omicron variant than wild type when using the structure via protein-protein docking simulation.

Underlined residues and values indicate significantly stronger electrostatic energy in the Omicron variants than those in the wild type when using the crystal structures.

<sup>a</sup>Pair interaction energy
<sup>b</sup>Electrostatic energy
<sup>c</sup>Exchange energy
<sup>d</sup>Charge transfer energy
<sup>e</sup>Dispersion energy
<sup>f</sup>Solvation energy
Table S8. Median interaction energy of residues in receptor binding domain interacting with regdanvimab

| Residue | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|---------|---------------------------------|----------------|----------------|
|         | Energy | P-value | Energy | P-value | Energy | P-value |
| G339D   | -3.9   |         | -9.8   | $3.922 \times 10^{-26}$ | -8.7   | $1.262 \times 10^{-3}$ |
| S371L   | 3.9    |         | 3.5    | $3.247 \times 10^{-2}$  | 3.0    | $6.691 \times 10^{-3}$  |
| S373P   | 3.7    |         | 0.4    | $6.650 \times 10^{-32}$ | 0.4    | $1.588 \times 10^{-31}$ |
| S375F   | 1.0    |         | 2.4    | $1.787 \times 10^{-9}$  | 2.4    | $8.353 \times 10^{-14}$ |
| K417N   | 12.1   |         | -4.1   | $1.450 \times 10^{-10}$ | -3.7   | $1.924 \times 10^{-22}$ |
| N440K   | -7.2   |         | -2.8   | $1.999 \times 10^{-14}$ | -3.0   | $4.361 \times 10^{-14}$ |
| G446S   | 1.5    |         | -2.4   | $1.653 \times 10^{-8}$  | -2.4   | $4.843 \times 10^{-8}$  |
| S477N   | -6.3   |         | -7.7   | $1.629 \times 10^{-4}$  | -6.8   | $1.219 \times 10^{-3}$  |
| T478K   | 3.3    |         | 5.3    | $4.814 \times 10^{-3}$  | 4.2    | $2.901 \times 10^{-2}$  |
| E484A   | -19.6  |         | -0.5   | $6.083 \times 10^{-14}$ | -1.3   | $1.880 \times 10^{-12}$ |
| Q493K/R | 3.3    |         | 13.6   | $4.259 \times 10^{-2}$  | 24.3   | $4.457 \times 10^{-4}$  |
| G496S   | 3.2    |         | 1.6    | $6.106 \times 10^{-2}$  | 2.9    | $2.420 \times 10^{-1}$  |
| Q498R   | 0.4    |         | 11.5   | $2.303 \times 10^{-7}$  | 14.0   | $3.364 \times 10^{-11}$ |
| N501Y   | 2.2    |         | 1.0    | $8.775 \times 10^{-4}$  | 1.1    | $1.092 \times 10^{-3}$  |
| Y505H   | -0.3   |         | 1.5    | $3.332 \times 10^{-2}$  | 1.5    | $7.233 \times 10^{-3}$  |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median interaction energy for the Omicron variant was lower than that for the wild type.
**Table S9.** Median interaction energy of residues in receptor binding domain interacting with bamlavimab

| Residue | Energy with Wild type (kcal/mol) | Energy | P-value  | Energy | P-value |
|---------|---------------------------------|--------|----------|--------|---------|
| G339D   | -5.0                            | -15.8  | \(5.452 \times 10^{-34}\) | -16.0  | \(7.968 \times 10^{-34}\) |
| S371L   | 4.7                             | 4.5    | \(5.785 \times 10^{-1}\)  | 4.3    | \(1.252 \times 10^{-3}\)  |
| S373P   | 4.5                             | 0.5    | \(1.006 \times 10^{-32}\)| 0.4    | \(2.071 \times 10^{-32}\)|
| S375F   | 1.2                             | 3.1    | \(5.265 \times 10^{-11}\)| 2.9    | \(5.210 \times 10^{-15}\)|
| K417N   | 19.8                            | -1.9   | \(1.006 \times 10^{-32}\)| -1.5   | \(4.387 \times 10^{-30}\)|
| N440K   | -9.1                            | -1.9   | \(4.988 \times 10^{-28}\)| -1.2   | \(8.975 \times 10^{-30}\)|
| G446S   | 2.6                             | -3.3   | \(2.515 \times 10^{-9}\)  | -3.5   | \(9.721 \times 10^{-13}\)|
| S477N   | -6.8                            | -7.7   | \(1.499 \times 10^{-3}\)  | -8.0   | \(2.043 \times 10^{-5}\)  |
| T478K   | 3.2                             | 8.3    | \(8.430 \times 10^{-10}\)| 9.6    | \(4.764 \times 10^{-13}\)|
| E484A   | -24.0                           | 7.7    | \(5.493 \times 10^{-9}\)  | -1.6   | \(1.275 \times 10^{-7}\)  |
| Q493K/R | 6.4                             | 46.1   | \(5.886 \times 10^{-9}\)  | 65.7   | \(1.242 \times 10^{-9}\)  |
| G496S   | 2.7                             | 0.2    | \(8.939 \times 10^{-3}\)  | 4.0    | \(2.967 \times 10^{-1}\)  |
| Q498R   | 0.0                             | 18.3   | \(3.051 \times 10^{-30}\)| 19.8   | \(3.801 \times 10^{-30}\)|
| N501Y   | 1.6                             | 2.2    | \(2.622 \times 10^{-1}\)  | 2.2    | \(9.124 \times 10^{-1}\)  |
| Y505H   | -0.2                            | 2.0    | \(4.350 \times 10^{-16}\)| 2.6    | \(3.275 \times 10^{-18}\)|

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than \(5.0 \times 10^{-2}\) and the median interaction energy for the Omicron variant was lower than that for the wild type.
Table S10. Median interaction energy of residues in receptor binding domain interacting with etesivimab

| Residue | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|---------|----------------------------------|-----------------|-----------------|
|         | Energy          | P-value     | Energy          | P-value     |
| G339D   | -0.5            | -1.9        | $2.144 \times 10^{-7}$ | -2.2        | $1.943 \times 10^{-16}$ |
| S371L   | 0.3             | 0.4         | $1.842 \times 10^{-1}$ | 0.4         | $6.313 \times 10^{-2}$ |
| S373P   | 0.2             | 0.0         | $1.660 \times 10^{-8}$ | -0.1        | $1.445 \times 10^{-10}$ |
| S375F   | -0.1            | 0.2         | $2.856 \times 10^{-2}$ | 0.2         | $1.189 \times 10^{-2}$ |
| K417N   | -0.8            | -0.9        | $1.747 \times 10^{-2}$ | 0.3         | $1.138 \times 10^{-3}$ |
| N440K   | -0.3            | 0.1         | $2.017 \times 10^{-2}$ | 0.6         | $5.733 \times 10^{-2}$ |
| G446S   | 0.1             | -0.3        | $4.407 \times 10^{-6}$ | -0.2        | $2.486 \times 10^{-4}$ |
| S477N   | -0.9            | -1.8        | $5.015 \times 10^{-1}$ | 1.6         | $1.339 \times 10^{-3}$ |
| T478K   | 0.3             | 1.0         | $2.276 \times 10^{-2}$ | 1.5         | $1.419 \times 10^{-3}$ |
| E484A   | -0.9            | -0.3        | $5.078 \times 10^{-2}$ | -0.3        | $2.356 \times 10^{-2}$ |
| Q493K/R | 0.0             | 3.5         | $1.184 \times 10^{-2}$ | 4.1         | $1.505 \times 10^{-6}$ |
| G496S   | 0.4             | 0.0         | $3.941 \times 10^{-1}$ | 0.5         | $9.251 \times 10^{-1}$ |
| Q498R   | -0.2            | 3.2         | $2.176 \times 10^{-2}$ | 2.9         | $2.187 \times 10^{-3}$ |
| N501Y   | 0.1             | 0.2         | $2.317 \times 10^{-1}$ | 0.1         | $8.286 \times 10^{-1}$ |
| Y505H   | -0.1            | 0.2         | $4.382 \times 10^{-1}$ | 0.4         | $7.705 \times 10^{-2}$ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median interaction energy for the Omicron variant was lower than that for the wild type.
| Residue | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|---------|---------------------------------|-----------------|-----------------|
|         | Energy | P-value | Energy | P-value |
| G339D   | -0.7   | 0.3     | 6.082 x 10⁻⁸ | 0.2     | 3.617 x 10⁻⁹ |
| S371L   | 0.7    | 0.7     | 3.510 x 10⁻¹ | 0.5     | 1.132 x 10⁻¹ |
| S373P   | 1.0    | 0.3     | 1.618 x 10⁻¹⁶ | 0.1     | 1.135 x 10⁻¹⁶ |
| S375F   | 0.3    | 0.7     | 5.142 x 10⁻³ | 0.4     | 3.609 x 10⁻²  |
| K417N   | -0.5   | -0.6    | 3.382 x 10⁻¹ | -1.0    | 6.142 x 10⁻¹ |
| N440K   | -1.8   | -3.4    | 3.745 x 10⁻⁶ | -2.3    | 1.729 x 10⁻² |
| G446S   | 0.3    | -0.6    | 5.582 x 10⁻¹⁶ | -0.4    | 1.091 x 10⁻¹⁶ |
| S477N   | 0.9    | 1.8     | 6.929 x 10⁻³ | 2.8     | 7.866 x 10⁻⁵ |
| T478K   | -0.1   | -6.5    | 3.412 x 10⁻⁹ | -4.1    | 3.257 x 10⁻⁵ |
| E484A   | 7.0    | 0.3     | 9.007 x 10⁻⁴ | 0.3     | 7.527 x 10⁻⁴ |
| Q493R   | 1.2    | -3.7    | 9.329 x 10⁻⁶ | -2.6    | 2.638 x 10⁻³ |
| G496S   | 0.3    | 0.2     | 2.793 x 10⁻¹ | 0.2     | 9.051 x 10⁻¹ |
| Q498R   | 0.0    | 1.2     | 1.540 x 10⁻² | 1.1     | 1.100 x 10⁻² |
| N501Y   | 0.8    | 0.3     | 2.908 x 10⁻² | 0.2     | 8.143 x 10⁻³ |
| Y505H   | -0.2   | 0.0     | 7.135 x 10⁻² | 0.0     | 1.483 x 10⁻¹ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than 5.0 x 10⁻² and the median interaction energy for the Omicron variant was lower than that for the wild type.
**Table S12.** Median interaction energy of residues in receptor binding domain interacting with imdevimab

| Residue | Energy with Wild type (kcal/mol) | Energy | P-value | Energy | P-value |
|---------|---------------------------------|--------|---------|--------|---------|
| G339D   | -2.4                            | -0.5   | $3.929 \times 10^{-6}$ | -0.3   | $5.686 \times 10^{-10}$ |
| S371L   | 1.9                             | 1.8    | $8.054 \times 10^{-2}$ | 1.5    | $4.176 \times 10^{-6}$ |
| S373P   | 2.0                             | 0.4    | $4.979 \times 10^{-15}$ | 0.3    | $3.426 \times 10^{-16}$ |
| S375F   | 0.6                             | 0.3    | $5.214 \times 10^{-5}$ | 1.0    | $2.952 \times 10^{-3}$ |
| K417N   | -0.5                            | -1.8   | $6.797 \times 10^{-9}$ | -1.7   | $3.830 \times 10^{-8}$ |
| N440K   | -2.8                            | -9.3   | $1.563 \times 10^{-8}$ | -9.0   | $6.534 \times 10^{-4}$ |
| G446S   | 27.9                            | 9.3    | $5.408 \times 10^{-2}$ | 17.0   | $2.418 \times 10^{-1}$ |
| S477N   | -1.9                            | -2.3   | $1.652 \times 10^{-3}$ | -2.2   | $5.364 \times 10^{-3}$ |
| T478K   | 1.1                             | -1.9   | $3.804 \times 10^{-26}$ | -2.0   | $2.238 \times 10^{-27}$ |
| E484A   | 0.4                             | -0.8   | $1.299 \times 10^{-1}$ | -0.9   | $1.916 \times 10^{-1}$ |
| Q493R   | 1.1                             | -1.8   | $3.912 \times 10^{-4}$ | -2.2   | $4.041 \times 10^{-5}$ |
| G496S   | 0.4                             | -0.1   | $3.765 \times 10^{-1}$ | 0.5    | $6.277 \times 10^{-1}$ |
| Q498R   | 0.6                             | -0.2   | $9.456 \times 10^{-1}$ | 0.3    | $5.957 \times 10^{-1}$ |
| N501Y   | -0.6                            | 66.1   | $2.238 \times 10^{-12}$ | 52.6   | $1.363 \times 10^{-3}$ |
| Y505H   | -1.0                            | 3.0    | $2.030 \times 10^{-5}$ | -0.1   | $1.967 \times 10^{-2}$ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median interaction energy for the Omicron variant was lower than that for the wild type.
**Table S13.** Median interaction energy of residues in receptor binding domain interacting with cilgavimab

| Residue  | Energy with Wild type (kcal/mol) | Omicron (Q493K) | Omicron (Q493R) |
|----------|----------------------------------|------------------|------------------|
|          | Energy                           | P-value          | Energy           | P-value          |
| G339D    | 0.7                              | 5.3              | $4.911 \times 10^{-34}$ | 5.3              | $5.858 \times 10^{-34}$ |
| S371L    | -0.9                             | -0.8             | $3.142 \times 10^{-2}$ | -0.7             | $3.799 \times 10^{-4}$ |
| S373P    | -1.0                             | -0.2             | $2.428 \times 10^{-26}$ | -0.1             | $7.778 \times 10^{-25}$ |
| S375F    | -0.1                             | -0.3             | $1.195 \times 10^{-5}$ | -0.5             | $7.945 \times 10^{-10}$ |
| K417N    | -3.6                             | -0.1             | $1.128 \times 10^{-8}$ | -0.2             | $3.597 \times 10^{-8}$ |
| N440K    | 1.3                              | -4.4             | $3.500 \times 10^{-18}$ | -5.1             | $3.503 \times 10^{-12}$ |
| G446S    | 31.3                             | 3.1              | $9.055 \times 10^{-2}$ | 0.6              | $1.029 \times 10^{-1}$ |
| S477N    | 0.2                              | 0.3              | $1.997 \times 10^{-5}$ | 0.4              | $6.145 \times 10^{-10}$ |
| T478K    | -0.1                             | -2.5             | $4.144 \times 10^{-30}$ | -3.3             | $4.485 \times 10^{-34}$ |
| E484A    | 2.6                              | -0.3             | $3.405 \times 10^{-5}$ | -0.4             | $6.556 \times 10^{-6}$ |
| Q493R    | 0.0                              | -6.2             | $4.916 \times 10^{-17}$ | -7.9             | $1.161 \times 10^{-13}$ |
| G496S    | 0.3                              | 0.8              | $6.435 \times 10^{-1}$ | -1.1             | $2.443 \times 10^{-4}$ |
| Q498R    | 0.3                              | -4.3             | $6.905 \times 10^{-5}$ | -6.6             | $4.132 \times 10^{-7}$ |
| N501Y    | 0.5                              | 0.6              | $8.465 \times 10^{-2}$ | 0.0              | $2.755 \times 10^{-1}$ |
| Y505H    | 0.0                              | -0.5             | $3.489 \times 10^{-3}$ | -0.6             | $6.331 \times 10^{-6}$ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median interaction energy for the Omicron variant was lower than that for the wild type.
Table S14. Median interaction energy of residues in receptor binding domain interacting with tixagevimab

| Residue | Energy with Wild type (kcal/mol) | Energy | P-value   | Energy | P-value   |
|---------|---------------------------------|--------|-----------|--------|-----------|
| G339D   | -1.5                            | 0.3    | 1.098 × 10⁻¹³ | -0.2  | 5.355 × 10⁻⁴ |
| S371L   | 1.4                             | 1.2    | 6.998 × 10⁻³ | 1.2    | 1.421 × 10⁻³ |
| S373P   | 1.3                             | 0.2    | 2.750 × 10⁻³³ | 0.2    | 3.327 × 10⁻³³ |
| S375F   | 0.4                             | 0.9    | 9.748 × 10⁻⁶  | 1.0    | 3.732 × 10⁻²  |
| K417N   | 5.7                             | -2.0   | 9.501 × 10⁻⁸  | -1.8   | 1.935 × 10⁻⁷  |
| N440K   | -2.6                            | -5.5   | 5.521 × 10⁻²² | -4.3   | 2.012 × 10⁻¹⁰ |
| G446S   | 0.3                             | -1.1   | 2.588 × 10⁻¹⁷ | -1.3   | 8.860 × 10⁻¹² |
| S477N   | 4.8                             | -0.5   | 1.061 × 10⁻⁴  | 4.3    | 4.877 × 10⁻¹  |
| T478K   | 0.1                             | 1.5    | 6.199 × 10⁻¹  | 15.2   | 6.295 × 10⁻¹  |
| E484A   | 2.7                             | 1.1    | 3.923 × 10⁻¹  | 0.5    | 8.968 × 10⁻¹  |
| Q493R   | 0.4                             | -2.1   | 1.688 × 10⁻²  | 3.8    | 9.074 × 10⁻²  |
| G496S   | 0.7                             | 0.3    | 5.086 × 10⁻¹  | 1.3    | 6.188 × 10⁻¹  |
| Q498R   | 0.4                             | -1.4   | 7.616 × 10⁻⁵  | 0.0    | 7.196 × 10⁻¹  |
| N501Y   | 0.6                             | 0.8    | 6.043 × 10⁻¹  | 0.8    | 8.462 × 10⁻¹  |
| Y505H   | -0.3                            | 0.4    | 6.772 × 10⁻¹² | 0.7    | 2.481 × 10⁻¹⁵ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than 5.0 × 10⁻² and the median interaction energy for the Omicron variant was lower than that for the wild type.
Table S15. Median interaction energy of residues in receptor binding domain interacting with sotrovimab

| Residue | Energy with Wild type (kcal/mol) | Energy | P-value | Energy | P-value |
|---------|---------------------------------|--------|---------|--------|---------|
| G339D   | 2.4                             | 1.5    | $1.735 \times 10^{-1}$ | 5.6    | $7.750 \times 10^{-1}$ |
| S371L   | 0.3                             | 0.2    | $5.170 \times 10^{-1}$ | -0.1   | $8.189 \times 10^{-2}$ |
| S373P   | 0.1                             | -0.4   | $1.342 \times 10^{-2}$ | -0.6   | $4.951 \times 10^{-4}$ |
| S375F   | -0.4                            | -0.4   | $2.102 \times 10^{-1}$ | -0.6   | $2.655 \times 10^{-1}$ |
| K417N   | -2.7                            | 0.0    | $1.005 \times 10^{-2}$ | -0.1   | $1.344 \times 10^{-9}$ |
| N440K   | 0.1                             | 1.6    | $4.056 \times 10^{-2}$ | 1.7    | $1.179 \times 10^{-2}$ |
| G446S   | -0.1                            | 0.0    | $3.443 \times 10^{-1}$ | -0.2   | $6.503 \times 10^{-1}$ |
| S477N   | 0.2                             | 0.2    | $8.421 \times 10^{-1}$ | 0.2    | $7.663 \times 10^{-1}$ |
| T478K   | -0.2                            | 0.0    | $2.116 \times 10^{-1}$ | 0.2    | $2.997 \times 10^{-2}$ |
| E484A   | 2.3                             | 0.0    | $1.896 \times 10^{-13}$ | 0.0    | $1.866 \times 10^{-13}$ |
| Q493R   | -0.1                            | -1.0   | $1.458 \times 10^{-4}$ | -0.6   | $1.834 \times 10^{-2}$ |
| G496S   | -0.1                            | -0.3   | $7.110 \times 10^{-1}$ | -0.4   | $3.262 \times 10^{-1}$ |
| Q498R   | -0.1                            | -1.4   | $2.940 \times 10^{-6}$ | -1.1   | $1.617 \times 10^{-6}$ |
| N501Y   | 0.0                             | -0.0   | $3.675 \times 10^{-1}$ | -0.1   | $3.044 \times 10^{-1}$ |
| Y505H   | -0.1                            | -0.4   | $3.858 \times 10^{-11}$ | -0.4   | $2.725 \times 10^{-12}$ |

Underlined residues and values indicate significantly stronger interactions in the Omicron variants than those in the wild type for which the P-value less than $5.0 \times 10^{-2}$ and the median interaction energy for the Omicron variant was lower than that for the wild type.