**Supplementary Material 1.**

**Binding affinity and interactions of selected drugs against nsp 12 or RdRp of Indian viral strain(s) (Full Table)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Receptorprotein | Ligand | Receptor type | Binding affinity(kcal/mol) | Mean standard deviation(kcal/mol) | RMSD | Ki(expressed in terms of nM) | Interacting residues(Receptor) | Interacting residues(Ligand) | Polar bonds number | Bond length(Angstrom) |
| Nsp12/RdRp | Elbasvir | Wild type | -9.1-8.3-8.9-8.9-9.0 | -8.84±0.28 | 0 | 363 | Gln292Arg305Asp484Lys641Lys641 | O58O52H77N20O8 | 5 | 2.32.72.62.02.6 |
| Mutant typeA4489V | -8.7-9.0-9.2-8.7-9.0 | -8.92±0.19 | 0 | 317 | Gln292Lys641Lys641Thr644 | O14N20O8O58 | 4 | 2.62.02.32.8 |
| Mutant typeP4715L | -8.9-9.0-9.1-8.9-9.0 | -8.98±0.07 | 0 | 287 | Ser68Lys143Glu144Lys160 | O13O52H89O58 | 4 | 2.02.22.72.3 |
| Mutant typeA4489V & P4715L | -9.3-9.0-8.7-9.2-8.9 | -9.02±0.21 | 0 | 268 | Tyr129Thr710Lys714Arg555 | O52O57O58O33 | 4 | 2.22.83.53.9 |
| Nsp12/RdRp | Remdesivir | Wild type | -8.5-8.5-8.5-8.6-8.5 | -8.52±0.04` | 0 | 620 | Lys47His133Ser709Ser709Asn781Ser784 | O8O6N4N2O2O3 | 6 | 3.42.44.03.25.52.1 |
| Mutant typeA4489V | -8.0-8.1-7.9-8.0-8.1 | -8.02±0.07 | 0 | 1435 | Lys47Lys47Asp135Ser709Ser709Asn781 | O8O7O6N4N2O2 | 6 | 3.41.93.43.03.32.5 |
| Mutant typeP4715L | -8.1-7.2-7.8-7.9-7.9 | -7.78±0.30 | 0 | 2147 | Lys47Tyr129Tyr710Ser709Ser709Ser784 | O6O8H20N4N2O3 | 6 | 2.72.42.42.03.42.0 |
| Mutant typeA4489V & P4715L | -7.5-7.5-7.9-7.9-7.5 | -7.66±0.19 | 0 | 2626 | Lys47His133Asn138Ser709Ser784 | O8O6H10N4O3 | 5 | 3.42.44.45.52.1 |
| Nsp12/RdRp | Methylprednisolone | Wild type | -8.3-8.0-8.3-8.3-8.0 | -8.18±0.14 | 0 | 1097 | His133Asp208Asn781 | O6H37O10 | 3 | 2.22.82.3 |
| Mutant typeA4489V | -8.0-8.0-8.0-7.9-7.9 | -7.96±0.048 | 0 | 1587 | His133Asp208Asn781 | O6H37O10 | 3 | 2.32.82.3 |
| Mutant typeP4715L | -8.0-7.6-8.3-7.6-7.8 | -7.86±0.26 | 0 | 1877 | His133Asn781 | O6O10 | 2 | 2.22.3 |
| Mutant typeA4489V &P4715L | -7.7-8.1-7.9-7.8-7.7 | -7.84±0.14 | 0 | 1941 | His133Asn209Asn209 | O6O10O8 | 3 | 2.32.72.0 |
| Nsp12/RdRp | Azithromycin | Wild type | -8.2-8.2-7.7-8.0-8.0 | -8.02±0.18 | 0 | 1435 | Arg249Arg249Arg249Phe396 | O27O27O13O67 | 4 | 2.62.02.84.2 |
| Mutant typeA4489V | -7.4-8.2-8.2-7.7-7.8 | -7.86±0.31 | 0 | 1877 | Thr394Arg249Phe396 | O7O27O67 | 3 | 2.72.23.9 |
| Mutant typeP4715L | -7.6-7.8-8.2-7.8-7.6 | -7.8±0.22 | 0 | 2076 | Leu49Arg249Phe396 | H84O27O67 | 3 | 5.32.03.8 |
| Mutant typeA4489V & P4715L | -7.7-7.4-7.6-7.4-7.5 | -7.52±0.12 | 0 | 3321 | Leu49Arg249Phe396 | H84O27O67 | 3 | 5.32.03.8 |
| Nsp12/RdRp | EIDD 2801 | Wild type | -7.2-7.2-6.8-6.8-6.9 | -6.98±0.18 | 0 | 8216 | Lys47Tyr129Asn781 | O6O10O25 | 3 | 2.52.02.4 |
| Mutant typeA4489V | -6.6-7.1-7.2-6.6-7.0 | -6.9±0.25 | 0 | 9396 | Lys47Tyr129Asn781 | O5O10O25 | 3 | 2.02.22.2 |
| Mutant typeP4715L | -7.0-6.3-6.8-6.7-6.8 | -6.72±0.23 | 0 | 12708 | Arg33Asn52Lys73Thr206 | O27H37O18O5 | 4 | 2.42.52.02.0 |
| Mutant typeA4489V & P4715L | -6.6-6.7-6.6-6.6-6.7 | -6.64±0.05 | 0 | 14533 | Asn52Lys73Asn781 | O25O27O25 | 3 | 4.12.52.2 |
| Nsp12/RdRp | Galidesivir | Wild type | -6.4-6.5-6.5-6.3-6.4 | -6.42±0.07 | 0 | 21021 | Asn52Lys73Arg116 | N21O7N21 | 3 | 2.42.42.8 |
| Mutant typeA4489V | -6.2-6.2-6.7-6.1-6.3 | -6.3±0.21 | 0 | 25708 | Arg583Asn600Thr604 | O7N19H33 | 3 | 2.42.42.1 |
| Mutant typeP4715L | -6.2-6.4-6.2-6.3-6.2 | -6.26±0.08 | 0 | 27493 | Phe48Ser784Ser784 | H33O7O10 | 3 | 5.52.52.7 |
| Mutant typeA4489V & P4715L | -6.1-6.3-6.3-6.1-6.3 | -6.22±0.09 | 0 | 29401 | Asp760Asp761 | H29H34 | 2 | 3.02,7 |
| Nsp12/RdRp | Umifenovir | Wild type | -6.1-6.1-6.5-6.1-6.3 | -6.22±0.16 | 0 | 29401 | Lys47Tyr129 | O23O5 |  | 2.22.3 |
| Mutant typeA4489V | -6.5-6.1-6.4-6.4-6.5 | -6.38±0.15 | 0 | 22480 | Lys47Tyr129 | O23O5 |  | 2.22.3 |
| Mutant typeP4715L | -6.0-6.5-6.5-6.3-6.3 | -6.32±0.18 | 0 | 24860 | Lys47Tyr129 | O23O5 |  | 2.22.3 |
| Mutant typeA4489V & P4715L | -6.5-6.4-6.4-6.6-6.5 | -6.48±0.75 | 0 | 19008 | Ser709Lys780 | O5O9 | 2 | 2.32.9 |
| Nsp12/RdRp | N4 hydoxycytidine | Wild type | -6.0-6.0-6.2-6.0-6.1 | -6.06±0.08 | 0 | 38453 | Tyr129Asn781Asn781 | H27H31O19 | 3 | 3.92.42.2 |
| Mutant typeA4489V | -6.9-6.2-6.0-6.2-6.7 | -6.4±0.34 | 0 | 21738 | His133Asn781Asn781 | O22H23O5 | 3 | 2.71.92.2 |
| Mutant typeP4715L | -5.7-6.0-6.2-5.7-6.0 | -5.92±0.19 | 0 | 48632 | His133Asn781Asn781 | O19N20O19 | 3 | 2.22.62.4 |
|  |  | Mutant typeA4489V & P4715L | -6.0-6.2-6.1-5.9-6.0 | -6.04±0.10 | 0 | 39765 | Arg583Asn600 | O1N20 | 2 | 2.52.5 |
| Nsp12/RdRp | Fingolimod | Wild type | -5.1-6.1-5.7-5.7-5.3 | -5.58±0.35 | 0 | 86027 | Asn52Arg116Tyr217 | H52O20H46 | 3 | 2.52.62.2 |
| Mutant typeA4489V | -4.8-5.3-5.3-5.1-5.1 | -5.12±0.18 | 0 | 186112 | Asn52Arg116 | H52O18 | 2 | 2.42.2 |
| Mutant typeP4715L | -5.9-5.7-5.5-5.7-5.5 | -5.56±0.15 | 0 | 88963 | Asn52Asn52Arg116 | H46O18O18 | 3 | 2.32.12.4 |
| Mutant typeA4489V & P4715L | -5.8-5.5-5.0-5.5-5.2 | -5.4±0.28 | 0 | 116353 | Thr206Asn209Asn209 | H46O18O20 | 3 | 2.22.52.2 |
| Nsp12/RdRp | Hydroxychloroquine | Wild type | -5.6-5.4-5.5-5.5-5.4 | -5.48±0.75 | 0 | 101740 | Tyr38Asn52Asn209 | O6N21H44 | 3 | 4.22.52.3 |
|  |  | Mutant typeA4489V | -5.9-5.5-5.6-5.5-5.6 | -5.62±0.14 | 0 | 80444 | Tyr38Asn52Asn209 | O6N21H44 | 3 | 4.22.52.3 |
| Mutant typeP4715L | -5.7-5.9-5.5-5.5-5.6 | -5.64±0.15 | 0 | 77790 | Ile37Asn52Asn209 | O6N21H44 | 3 | 3.52.52.3 |
| Mutant typeA4489V & P4715L | -5.5-5.6-6.0-5.6-5.7 | -5.68±0.17 | 0 | 72741 | Tyr38Asn209 | O6H44 | 2 | 3.72.7 |
| Nsp12/RdRp | Favipiravir | Wild type | -5.0-5.0-5.1-5.0-5.1 | -5.04±0.05 | 0 | 212843 | Lys789Trp800 | H3O1 | 2 | 2.52.1 |
| Mutant typeA4489V | -4.9-5.1-5.1-5.1-5.0 | -5.04±0.08 | 0 | 212843 | Tyr129His133Ser784 | O1O1O2 | 3 | 2.52.52.8 |
| Mutant typeP4715L | -5.2-5.6-5.3-5.3-5.5 | -5.38±0.15 | 0 | 120323 | Tyr129His133Ser784 | H1O1O2 | 3 | 2.22.82.8 |
| Mutant typeA4489V &P4715L | -5.0-5.3-5.1-5.1-5.0 | -5.1±0.11 | 0 | 192462 | Tyr129Ser709Ser784 | O2H3H1 | 3 | 2.52.12.6 |
| **Negative control** |
| Nsp12/RdRp | Cinnamaldehyde | Wild type | -4.9-4.9-4.9-4.9-4.9 | -4.9 | 0 | 269189 |  |  |  |  |
| Nsp12/RdRp | Thymoquinone | Wild type | -4.9-5.0-5.0-4.9-4.9 | -4.94±0.048 | 0 | 251718 |  |  |  |  |