**Supplementary Material 1.**

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

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Receptor  protein | 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 | Gln292  Arg305  Asp484  Lys641  Lys641 | O58  O52  H77  N20  O8 | 5 | 2.3  2.7  2.6  2.0  2.6 |
| Mutant type  A4489V | -8.7  -9.0  -9.2  -8.7  -9.0 | -8.92±0.19 | 0 | 317 | Gln292  Lys641  Lys641  Thr644 | O14  N20  O8  O58 | 4 | 2.6  2.0  2.3  2.8 |
| Mutant type  P4715L | -8.9  -9.0  -9.1  -8.9  -9.0 | -8.98±0.07 | 0 | 287 | Ser68  Lys143  Glu144  Lys160 | O13  O52  H89  O58 | 4 | 2.0  2.2  2.7  2.3 |
| Mutant type  A4489V & P4715L | -9.3  -9.0  -8.7  -9.2  -8.9 | -9.02±0.21 | 0 | 268 | Tyr129  Thr710  Lys714  Arg555 | O52  O57  O58  O33 | 4 | 2.2  2.8  3.5  3.9 |
| Nsp12/RdRp | Remdesivir | Wild type | -8.5  -8.5  -8.5  -8.6  -8.5 | -8.52±0.04` | 0 | 620 | Lys47  His133  Ser709  Ser709  Asn781  Ser784 | O8  O6  N4  N2  O2  O3 | 6 | 3.4  2.4  4.0  3.2  5.5  2.1 |
| Mutant type  A4489V | -8.0  -8.1  -7.9  -8.0  -8.1 | -8.02±0.07 | 0 | 1435 | Lys47  Lys47  Asp135  Ser709  Ser709  Asn781 | O8  O7  O6  N4  N2  O2 | 6 | 3.4  1.9  3.4  3.0  3.3  2.5 |
| Mutant type  P4715L | -8.1  -7.2  -7.8  -7.9  -7.9 | -7.78±0.30 | 0 | 2147 | Lys47  Tyr129  Tyr710  Ser709  Ser709  Ser784 | O6  O8  H20  N4  N2  O3 | 6 | 2.7  2.4  2.4  2.0  3.4  2.0 |
| Mutant type  A4489V & P4715L | -7.5  -7.5  -7.9  -7.9  -7.5 | -7.66±0.19 | 0 | 2626 | Lys47  His133  Asn138  Ser709  Ser784 | O8  O6  H10  N4  O3 | 5 | 3.4  2.4  4.4  5.5  2.1 |
| Nsp12/RdRp | Methylprednisolone | Wild type | -8.3  -8.0  -8.3  -8.3  -8.0 | -8.18±0.14 | 0 | 1097 | His133  Asp208  Asn781 | O6  H37  O10 | 3 | 2.2  2.8  2.3 |
| Mutant type  A4489V | -8.0  -8.0  -8.0  -7.9  -7.9 | -7.96±0.048 | 0 | 1587 | His133  Asp208  Asn781 | O6  H37  O10 | 3 | 2.3  2.8  2.3 |
| Mutant type  P4715L | -8.0  -7.6  -8.3  -7.6  -7.8 | -7.86±0.26 | 0 | 1877 | His133  Asn781 | O6  O10 | 2 | 2.2  2.3 |
| Mutant type  A4489V &P4715L | -7.7  -8.1  -7.9  -7.8  -7.7 | -7.84±0.14 | 0 | 1941 | His133  Asn209  Asn209 | O6  O10  O8 | 3 | 2.3  2.7  2.0 |
| Nsp12/RdRp | Azithromycin | Wild type | -8.2  -8.2  -7.7  -8.0  -8.0 | -8.02±0.18 | 0 | 1435 | Arg249  Arg249  Arg249  Phe396 | O27  O27  O13  O67 | 4 | 2.6  2.0  2.8  4.2 |
| Mutant type  A4489V | -7.4  -8.2  -8.2  -7.7  -7.8 | -7.86±0.31 | 0 | 1877 | Thr394  Arg249  Phe396 | O7  O27  O67 | 3 | 2.7  2.2  3.9 |
| Mutant type  P4715L | -7.6  -7.8  -8.2  -7.8  -7.6 | -7.8±0.22 | 0 | 2076 | Leu49  Arg249  Phe396 | H84  O27  O67 | 3 | 5.3  2.0  3.8 |
| Mutant type  A4489V & P4715L | -7.7  -7.4  -7.6  -7.4  -7.5 | -7.52±0.12 | 0 | 3321 | Leu49  Arg249  Phe396 | H84  O27  O67 | 3 | 5.3  2.0  3.8 |
| Nsp12/RdRp | EIDD 2801 | Wild type | -7.2  -7.2  -6.8  -6.8  -6.9 | -6.98±0.18 | 0 | 8216 | Lys47  Tyr129  Asn781 | O6  O10  O25 | 3 | 2.5  2.0  2.4 |
| Mutant type  A4489V | -6.6  -7.1  -7.2  -6.6  -7.0 | -6.9±0.25 | 0 | 9396 | Lys47  Tyr129  Asn781 | O5  O10  O25 | 3 | 2.0  2.2  2.2 |
| Mutant type  P4715L | -7.0  -6.3  -6.8  -6.7  -6.8 | -6.72±0.23 | 0 | 12708 | Arg33  Asn52  Lys73  Thr206 | O27  H37  O18  O5 | 4 | 2.4  2.5  2.0  2.0 |
| Mutant type  A4489V & P4715L | -6.6  -6.7  -6.6  -6.6  -6.7 | -6.64±0.05 | 0 | 14533 | Asn52  Lys73  Asn781 | O25  O27  O25 | 3 | 4.1  2.5  2.2 |
| Nsp12/RdRp | Galidesivir | Wild type | -6.4  -6.5  -6.5  -6.3  -6.4 | -6.42±0.07 | 0 | 21021 | Asn52  Lys73  Arg116 | N21  O7  N21 | 3 | 2.4  2.4  2.8 |
| Mutant type  A4489V | -6.2  -6.2  -6.7  -6.1  -6.3 | -6.3±0.21 | 0 | 25708 | Arg583  Asn600  Thr604 | O7  N19  H33 | 3 | 2.4  2.4  2.1 |
| Mutant type  P4715L | -6.2  -6.4  -6.2  -6.3  -6.2 | -6.26±0.08 | 0 | 27493 | Phe48  Ser784  Ser784 | H33  O7  O10 | 3 | 5.5  2.5  2.7 |
| Mutant type  A4489V & P4715L | -6.1  -6.3  -6.3  -6.1  -6.3 | -6.22±0.09 | 0 | 29401 | Asp760  Asp761 | H29  H34 | 2 | 3.0  2,7 |
| Nsp12/RdRp | Umifenovir | Wild type | -6.1  -6.1  -6.5  -6.1  -6.3 | -6.22±0.16 | 0 | 29401 | Lys47  Tyr129 | O23  O5 |  | 2.2  2.3 |
| Mutant type  A4489V | -6.5  -6.1  -6.4  -6.4  -6.5 | -6.38±0.15 | 0 | 22480 | Lys47  Tyr129 | O23  O5 |  | 2.2  2.3 |
| Mutant type  P4715L | -6.0  -6.5  -6.5  -6.3  -6.3 | -6.32±0.18 | 0 | 24860 | Lys47  Tyr129 | O23  O5 |  | 2.2  2.3 |
| Mutant type  A4489V & P4715L | -6.5  -6.4  -6.4  -6.6  -6.5 | -6.48±0.75 | 0 | 19008 | Ser709  Lys780 | O5  O9 | 2 | 2.3  2.9 |
| Nsp12/RdRp | N4 hydoxycytidine | Wild type | -6.0  -6.0  -6.2  -6.0  -6.1 | -6.06±0.08 | 0 | 38453 | Tyr129  Asn781  Asn781 | H27  H31  O19 | 3 | 3.9  2.4  2.2 |
| Mutant type  A4489V | -6.9  -6.2  -6.0  -6.2  -6.7 | -6.4±0.34 | 0 | 21738 | His133  Asn781  Asn781 | O22  H23  O5 | 3 | 2.7  1.9  2.2 |
| Mutant type  P4715L | -5.7  -6.0  -6.2  -5.7  -6.0 | -5.92±0.19 | 0 | 48632 | His133  Asn781  Asn781 | O19  N20  O19 | 3 | 2.2  2.6  2.4 |
|  |  | Mutant type  A4489V & P4715L | -6.0  -6.2  -6.1  -5.9  -6.0 | -6.04±0.10 | 0 | 39765 | Arg583  Asn600 | O1  N20 | 2 | 2.5  2.5 |
| Nsp12/RdRp | Fingolimod | Wild type | -5.1  -6.1  -5.7  -5.7  -5.3 | -5.58±0.35 | 0 | 86027 | Asn52  Arg116  Tyr217 | H52  O20  H46 | 3 | 2.5  2.6  2.2 |
| Mutant type  A4489V | -4.8  -5.3  -5.3  -5.1  -5.1 | -5.12±0.18 | 0 | 186112 | Asn52  Arg116 | H52  O18 | 2 | 2.4  2.2 |
| Mutant type  P4715L | -5.9  -5.7  -5.5  -5.7  -5.5 | -5.56±0.15 | 0 | 88963 | Asn52  Asn52  Arg116 | H46  O18  O18 | 3 | 2.3  2.1  2.4 |
| Mutant type  A4489V & P4715L | -5.8  -5.5  -5.0  -5.5  -5.2 | -5.4±0.28 | 0 | 116353 | Thr206  Asn209  Asn209 | H46  O18  O20 | 3 | 2.2  2.5  2.2 |
| Nsp12/RdRp | Hydroxychloroquine | Wild type | -5.6  -5.4  -5.5  -5.5  -5.4 | -5.48±0.75 | 0 | 101740 | Tyr38  Asn52  Asn209 | O6  N21  H44 | 3 | 4.2  2.5  2.3 |
|  |  | Mutant type  A4489V | -5.9  -5.5  -5.6  -5.5  -5.6 | -5.62±0.14 | 0 | 80444 | Tyr38  Asn52  Asn209 | O6  N21  H44 | 3 | 4.2  2.5  2.3 |
| Mutant type  P4715L | -5.7  -5.9  -5.5  -5.5  -5.6 | -5.64±0.15 | 0 | 77790 | Ile37  Asn52  Asn209 | O6  N21  H44 | 3 | 3.5  2.5  2.3 |
| Mutant type  A4489V & P4715L | -5.5  -5.6  -6.0  -5.6  -5.7 | -5.68±0.17 | 0 | 72741 | Tyr38  Asn209 | O6  H44 | 2 | 3.7  2.7 |
| Nsp12/RdRp | Favipiravir | Wild type | -5.0  -5.0  -5.1  -5.0  -5.1 | -5.04±0.05 | 0 | 212843 | Lys789  Trp800 | H3  O1 | 2 | 2.5  2.1 |
| Mutant type  A4489V | -4.9  -5.1  -5.1  -5.1  -5.0 | -5.04±0.08 | 0 | 212843 | Tyr129  His133  Ser784 | O1  O1  O2 | 3 | 2.5  2.5  2.8 |
| Mutant type  P4715L | -5.2  -5.6  -5.3  -5.3  -5.5 | -5.38±0.15 | 0 | 120323 | Tyr129  His133  Ser784 | H1  O1  O2 | 3 | 2.2  2.8  2.8 |
| Mutant type  A4489V &P4715L | -5.0  -5.3  -5.1  -5.1  -5.0 | -5.1±0.11 | 0 | 192462 | Tyr129  Ser709  Ser784 | O2  H3  H1 | 3 | 2.5  2.1  2.6 |
| **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 |  |  |  |  |