

SUPPORTING INFORMATION

The effects of alternative one-point mutation on the resistance of New Delhi Metallo beta-lactamase-1 towards carbapenem antibiotics and β -lactamase inhibitors: an *in silico* systematically approach

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Table S1 Amino acid and atoms in binding site interacting with ligands

| Ligand | The interacted amino acids in the binding pocket of protein-ligand complexes | | | | | | | | | | | | | | | | |
|-------------|--|-----------|-----------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|-----------|-----------|------------|------------|------------|
| | Met 67 | Phe 70 | Val 73 | Trp 93 | His 120 | His 122 | Gln 123 | Asp 124 | His 189 | Gly 219 | Asn 220 | His 250 | Zn 301 | Zn 302 | HOH 405 | HOH 409 | HOH 500 |
| D-captopril | x | x | x | x | X | x | | x | x | | x | x | x | | x | x | x |
| L-captopril | x | x | x | | X | x | | | x | | x | x | x | | x | x | |
| Thiorphan | x | x | x | | | | | | | x | x | x | x | x | x | | x |
| Imipenem | x | | x | x | | x | x | x | | | | x | x | x | x | x | x |
| Meropenem | x | x | | x | | x | x | x | | | x | | x | x | | | x |

Table S2 The docking scores (kJ.mol⁻¹) of **d-captopril** with NDM-1 mutant structures

| D-captopril | Met67 | Phe70 | Val73 | Trp93 | His120 | His122 | Asp124 | His189 | Cys208 | Gly219 | Asn220 | His250 |
|-------------|--------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ala/A | | | -25.6 | | | | -23.5 | | | -24.09 | | |
| Arg/R | | | | -24.4 | -24.29 | -10.9 | | -24.43 | | | | -17.5 |
| Asn/N | | | | | -24.46 | -22.01 | -22.6 | -19.24 | | | | -15.59 |
| Asp/D | | | | | | | | | | | | |
| Cys/C | | | | | | | | | | | | |
| Gln/Q | | | | | -24.46 | -18.62 | | -10.33 | | | | -21.06 |
| Glu/E | | | | | | | -18.51 | | | | | |
| Gly/G | | | | | | | -22.12 | | | | -17.32 | |
| His/H | | | | | | | | | | | -18.22 | |
| Ile/I | -24.04 | | -25.6 | | | | | | | | | |
| Leu/L | -25.06 | -25.2 | | -24.7 | | | | | | | | |
| Lys/K | -24.31 | | | | | | | | | | -29.45 | |
| Met/M | | | | | | | | | | | | |
| Phe/F | | | | | | | | | | | | |
| Pro/P | | | | | | | | | | | | |
| Ser/S | | | | -24.7 | | | | | -25.05 | -25.88 | -26.53 | |
| Thr/T | | | | | | | | | | | -18.57 | |
| Trp/W | | | | | | | | | | | | |
| Tyr/Y | | -24.9 | | | | | | | | | | |
| Val/V | -25.06 | | | | | | | | | | | |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Table S3 The docking scores (kJ.mol⁻¹) of **l-captopril** with NDM-1 mutant structures

| L-captopril | Met67 | Phe70 | Val73 | Trp93 | His120 | His122 | Asp124 | His189 | Cys208 | Gly219 | Asn220 | His250 |
|-------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ala/A | | | -21.25 | | | | -16.78 | | | -17.23 | | |
| Arg/R | | | | -17.04 | -20.23 | -15.06 | | -17.39 | | | | -18.41 |
| Asn/N | | | | | -15.75 | -19.14 | -15.95 | -16.94 | | | | -12.66 |
| Asp/D | | | | | | | | | | | | |
| Cys/C | | | | | | | | | | | | |
| Gln/Q | | | | | -20.72 | -15.64 | | -12.93 | | | | -17.48 |
| Glu/E | | | | | | | -14.47 | | | | | |
| Gly/G | | | | | | | -16.33 | | | | -11.33 | |
| His/H | | | | | | | | | | | -13.10 | |
| Ile/I | -22.22 | | -20.98 | | | | | | | | | |
| Leu/L | -19.25 | -16.12 | | -20.75 | | | | | | | | |
| Lys/K | -16.16 | | | | | | | | | | -20.91 | |
| Met/M | | | | | | | | | | | | |
| Phe/F | | | | | | | | | | | | |
| Pro/P | | | | | | | | | | | | |
| Ser/S | | | | -17.33 | | | | | -17.68 | -18.15 | -13.23 | |
| Thr/T | | | | | | | | | | | -15.99 | |
| Trp/W | | | | | | | | | | | | |
| Tyr/Y | | -16.10 | | | | | | | | | | |
| Val/V | -19.08 | | | | | | | | | | | |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Table S4 The docking scores (kJ.mol⁻¹) of **thiorphan** with NDM-1 mutant structures

| Thiorphan | Met67 | Phe70 | Val73 | Trp93 | His120 | His122 | Asp124 | His189 | Cys208 | Gly219 | Asn220 | His250 |
|-----------|--------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ala/A | | | -22.2 | | | | -13.73 | | | -24.31 | | |
| Arg/R | | | | -21.5 | -27.65 | -34.22 | | -25.71 | | | | -30.62 |
| Asn/N | | | | | -27.65 | -25.15 | -24.98 | -25.63 | | | | -22.95 |
| Asp/D | | | | | | | | | | | | |
| Cys/C | | | | | | | | | | | | |
| Gln/Q | | | | | -27.65 | -19.55 | | -19.16 | | | | -21.38 |
| Glu/E | | | | | | | -24.87 | | | | | |
| Gly/G | | | | | | | -24.18 | | | | -24.78 | |
| His/H | | | | | | | | | | | -25.59 | |
| Ile/I | -24.62 | | -26.9 | | | | | | | | | |
| Leu/L | -25.49 | -26.4 | | -24.9 | | | | | | | | |
| Lys/K | -27.9 | | | | | | | | | | -23.71 | |
| Met/M | | | | | | | | | | | | |
| Phe/F | | | | | | | | | | | | |
| Pro/P | | | | | | | | | | | | |
| Ser/S | | | | -27.6 | | | | | -24.97 | -26.54 | -22.74 | |
| Thr/T | | | | | | | | | | | -25.31 | |
| Trp/W | | | | | | | | | | | | |
| Tyr/Y | | -26.6 | | | | | | | | | | |
| Val/V | -25.65 | | | | | | | | | | | |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Table S5 The docking scores (kJ.mol⁻¹) of **imipenem** with NDM-1 mutant structures

| Imipenem | Met67 | Phe70 | Val73 | Trp93 | His120 | His122 | Asp124 | His189 | Cys208 | Gly219 | Asn220 | His250 |
|----------|--------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ala/A | | | -28 | | | | -20.13 | | | -27.8 | | |
| Arg/R | | | | -29.2 | -28.57 | -16.55 | | -18.62 | | | | -22.77 |
| Asn/N | | | | | -26.14 | -20.74 | -17.8 | -16.28 | | | | -24.96 |
| Asp/D | | | | | | | | | | | | |
| Cys/C | | | | | | | | | | | | |
| Gln/Q | | | | | -28.6 | -14.55 | | -18.21 | | | | -23.63 |
| Glu/E | | | | | | | -19.33 | | | | | |
| Gly/G | | | | | | | -14.98 | | | | -27.54 | |
| His/H | | | | | | | | | | | -29.39 | |
| Ile/I | -22.06 | | -30.1 | | | | | | | | | |
| Leu/L | -28.02 | -28.1 | | -28.7 | | | | | | | | |
| Lys/K | -22.06 | | | | | | | | | | -25.16 | |
| Met/M | | | | | | | | | | | | |
| Phe/F | | | | | | | | | | | | |
| Pro/P | | | | | | | | | | | | |
| Ser/S | | | | -28.8 | | | | | -23.19 | -19.35 | -22.37 | |
| Thr/T | | | | | | | | | | | -25.67 | |
| Trp/W | | | | | | | | | | | | |
| Tyr/Y | | -28 | | | | | | | | | | |
| Val/V | -22.87 | | | | | | | | | | | |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Table S6 The docking scores (kJ.mol⁻¹) of **meropenem** with NDM-1 mutant structures

| Meropenem | Met67 | Phe70 | Val73 | Trp93 | His120 | His122 | Asp124 | His189 | Cys208 | Gly219 | Asn220 | His250 |
|-----------|--------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| Ala/A | | | -30.7 | | | | -26.68 | | | -28.16 | | |
| Arg/R | | | | -30.1 | -26.02 | -13.03 | | -30.88 | | | | -38.58 |
| Asn/N | | | | | -27.43 | -33.18 | -22.97 | -30.71 | | | | -28.94 |
| Asp/D | | | | | | | | | | | | |
| Cys/C | | | | | | | | | | | | |
| Gln/Q | | | | | -27.43 | -24.83 | | -26.37 | | | | -28.95 |
| Glu/E | | | | | | | -16.5 | | | | | |
| Gly/G | | | | | | | -29.59 | | | | -28.37 | |
| His/H | | | | | | | | | | | -29.03 | |
| Ile/I | -29.54 | | -30.8 | | | | | | | | | |
| Leu/L | -29.68 | -28.3 | | -30.1 | | | | | | | | |
| Lys/K | -30.18 | | | | | | | | | | -25.83 | |
| Met/M | | | | | | | | | | | | |
| Phe/F | | | | | | | | | | | | |
| Pro/P | | | | | | | | | | | | |
| Ser/S | | | | -30.2 | | | | | -29.83 | -28.79 | -28.35 | |
| Thr/T | | | | | | | | | | | -30.75 | |
| Trp/W | | | | | | | | | | | | |
| Tyr/Y | | -24.2 | | | | | | | | | | |
| Val/V | -29.02 | | | | | | | | | | | |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Table S7 Percentage increase in docking score (%) between NDM-1 mutants and ligands

| Acid amin | Mutant | Ligand | | | | |
|-----------|--------|-------------|-------------|-----------|----------|-----------|
| | | D-captopril | L-captopril | Thiorphan | Imipenem | Meropenem |
| Met67 | M67L | 2.69 | 7.23 | 8.32 | 7.89 | 3.58 |
| | M67V | 2.69 | 8.06 | 7.21 | 26.28 | 5.73 |
| | M67I | 2.66 | -7.07 | 10.96 | 29.17 | 4.04 |
| | M67K | 5.6 | 22.13 | -0.94 | 29.17 | 1.95 |
| Phe70 | F70L | 2.29 | 22.35 | 4.40 | 7.78 | 7.91 |
| | F70Y | 3.18 | 22.44 | 3.85 | 8.06 | 21.27 |
| Val73 | V73A | 0.47 | -2.373 | 19.74 | 8.06 | 0.27 |
| | V73I | 0.64 | -1.09 | 2.56 | 0.32 | 0.09 |
| Trp93 | W93R | 5.34 | 17.89 | 22.07 | 3.57 | 2.32 |
| | W93L | 4.09 | 0.027 | 10.04 | 5.64 | 2.32 |
| | W93S | 4.09 | 16.47 | 0.00 | 5.10 | 1.77 |
| His120 | H120R | 5.69 | 2.52 | 0.00 | 5.95 | 15.47 |
| | H120N | 5.03 | 24.09 | 0.00 | 14.61 | 10.89 |
| | H120Q | 5.03 | 0.15 | 0.00 | 5.85 | 10.89 |
| His122 | H122R | 57.67 | 27.45 | -23.78 | 48.81 | 57.68 |
| | H122N | 14.54 | 7.77 | 9.02 | 33.87 | -7.80 |
| | H122Q | 27.7 | 24.62 | 29.30 | 55.98 | 19.34 |
| Asp124 | D124A | 8.77 | 19.15 | 50.35 | 36.07 | 13.30 |
| | D124N | 12.24 | 23.15 | 9.65 | 44.36 | 25.38 |
| | D124E | 28.12 | 30.29 | 10.03 | 38.91 | 46.38 |
| | D124Q | 14.12 | 21.29 | 12.55 | 54.43 | 3.87 |
| His189 | H189R | 5.15 | 16.22 | 7.01 | 41.45 | -0.32 |
| | H189N | 25.29 | 18.36 | 7.30 | 49.79 | 0.23 |
| | H189Q | 59.89 | 37.68 | 30.69 | 42.89 | 14.33 |
| Cys208 | C208S | 2.79 | 14.81 | 9.66 | 25.12 | 3.07 |
| Gly219 | G219A | 6.477 | 16.99 | 12.06 | 8.67 | 8.50 |
| | G219S | -0.47 | 12.54 | 4.01 | 38.84 | 6.47 |
| Asn220 | N220G | 32.76 | 45.42 | 10.38 | 9.61 | 7.81 |
| | N220H | 29.25 | 36.89 | 7.44 | 3.00 | 5.70 |
| | N220K | -14.36 | -0.74 | 14.25 | 18.11 | 16.07 |
| | N220S | -3.01 | 36.25 | 17.73 | 28.06 | 7.89 |
| | N220T | 27.89 | 22.93 | 8.46 | 16.29 | 0.09 |
| His250 | H250R | 32.04 | 11.27 | -10.77 | 26.64 | -25.36 |
| | H250N | 39.48 | 39.01 | 17.00 | 18.83 | 5.97 |
| | H250Q | 18.22 | 15.79 | 22.68 | 23.56 | 5.95 |

Note:

| Percentage of docking score increase | | | | | | |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <0% (Group 1) | 0-10% (Group 2) | 10-20% (Group 3) | 20-30% (Group 4) | 30-40% (Group 5) | 40-50% (Group 6) | 50-60% (Group 7) |

Figure S1 The total numbers of H-bonds forming in mutant and wild type complexes

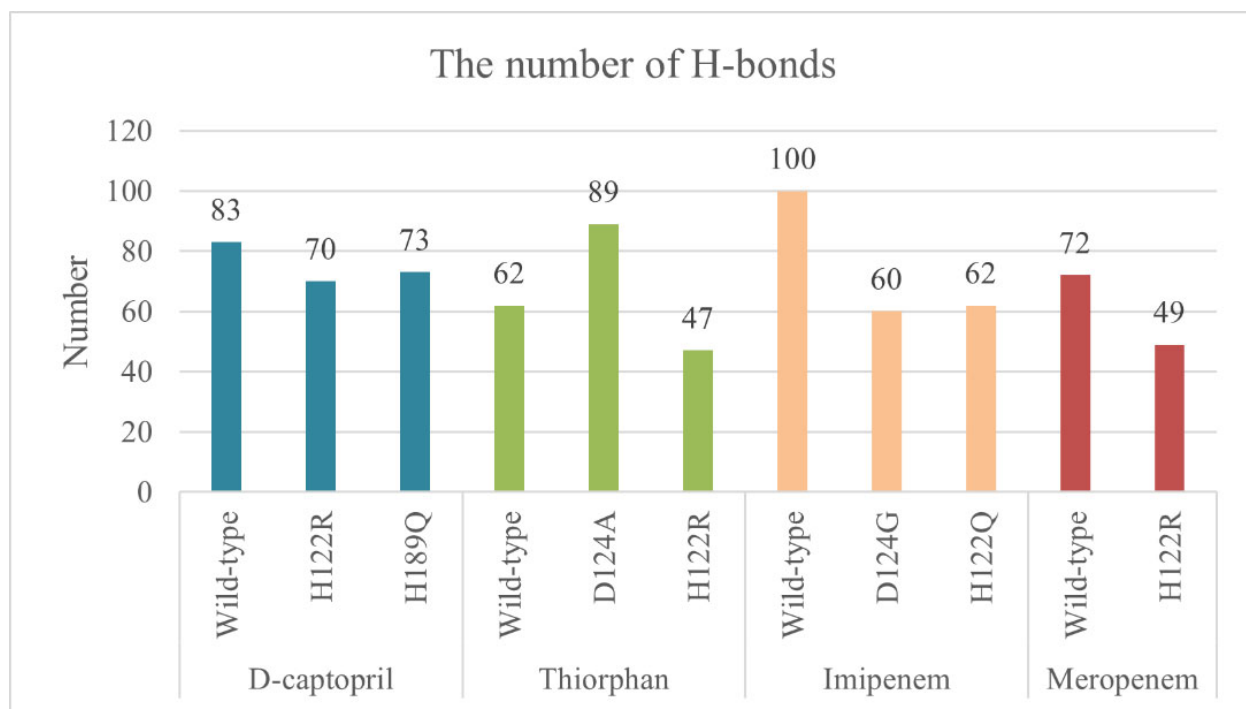


Figure S2 The average number of H-bonds formed by the ligands with mutant and wild type NDM-1 protein during MD simulations

