**Supporting Information**

# Binding Mode Characterization of 6α- and 6β-*N*-Heterocyclic Substituted Naltrexamine Derivatives via Docking in Opioid Receptor Crystal Structures and Site-directed Mutagenesis Studies: Application of the "Message-Address" Concept in Development of Mu Opioid Receptor Selective Antagonists

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1. NTX docking – 10 best CHEM-PLP scored solutions

| MOR | KOR | DOR |
|---|---|---|
| 79.54 | 69.51 | 85.24 |
| 65.28 | 43.20 | 85.23 |
| 63.09 | 40.84 | 85.23 |
| 58.02 | 40.62 | 85.21 |
| 54.26 | 39.70 | 85.14 |
| 52.53 | 37.23 | 85.14 |
| 50.46 | 36.51 | 85.14 |
| 49.24 | 36.18 | 85.12 |
| 49.00 | 35.90 | 85.09 |
| 48.45 | 34.72 | 85.03 |

2. NAP docking – 10 best CHEM-PLP scored solutions

| MOR | KOR | DOR |
|---|---|---|
| 88.79 | 78.79 | 93.98 |
| 85.62 | 56.74 | 93.84 |
| 78.52 | 56.40 | 93.77 |
| 73.81 | 55.83 | 93.75 |
| 72.32 | 51.58 | 93.74 |
| 72.32 | 51.26 | 93.67 |
| 71.72 | 51.15 | 93.67 |
| 68.55 | 47.55 | 93.55 |
| 67.69 | 42.42 | 93.52 |
| 66.18 | 41.24 | 93.51 |

3. NAQ docking – 10 best CHEM-PLP scored solutions

| MOR | KOR | DOR |
|---|---|---|
| 82.63 | 56.46 | 75.7 |
| 80.6 | 50.21 | 73.21 |
| 77.54 | 46.49 | 72.86 |
| 75.66 | 45.88 | 71.58 |
| 72.86 | 44.22 | 64.78 |
| 71.99 | 43.99 | 62.56 |
| 71.07 | 43.43 | 59.46 |
| 67.81 | 43.07 | 58.28 |
| 65.78 | 42.43 | 57.07 |
| 65.22 | 41.92 | 55.23 |