**SUPPLEMENTARY MATERIAL**

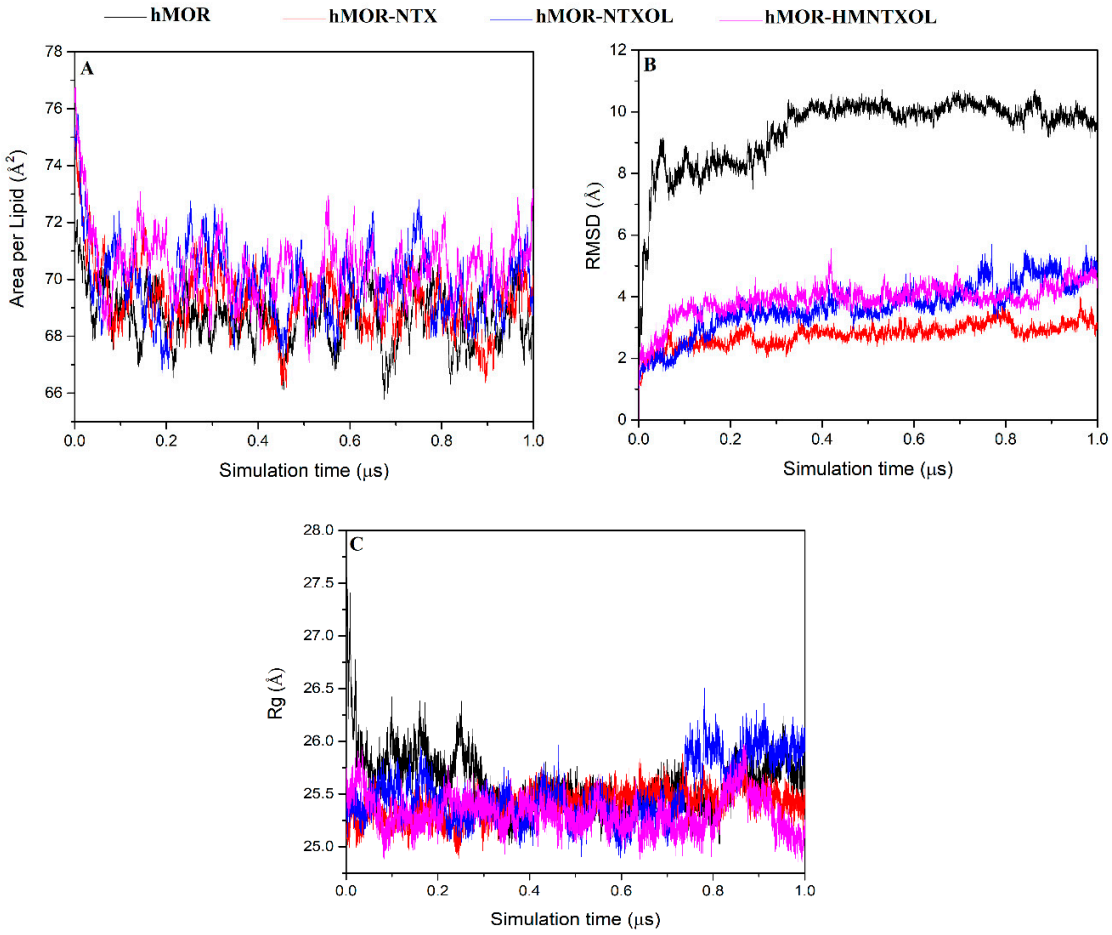


**Figure S1**. Area per lipid, root means squared deviation (RMSD), and radius of gyration (Rg) analysis of hMOR-ligand systems. Area per lipid (A), RMSD (B), and Rg (C) of hMOR-naltrexone, hMOR-NTXOL, and hMOR-HMNTXOL.

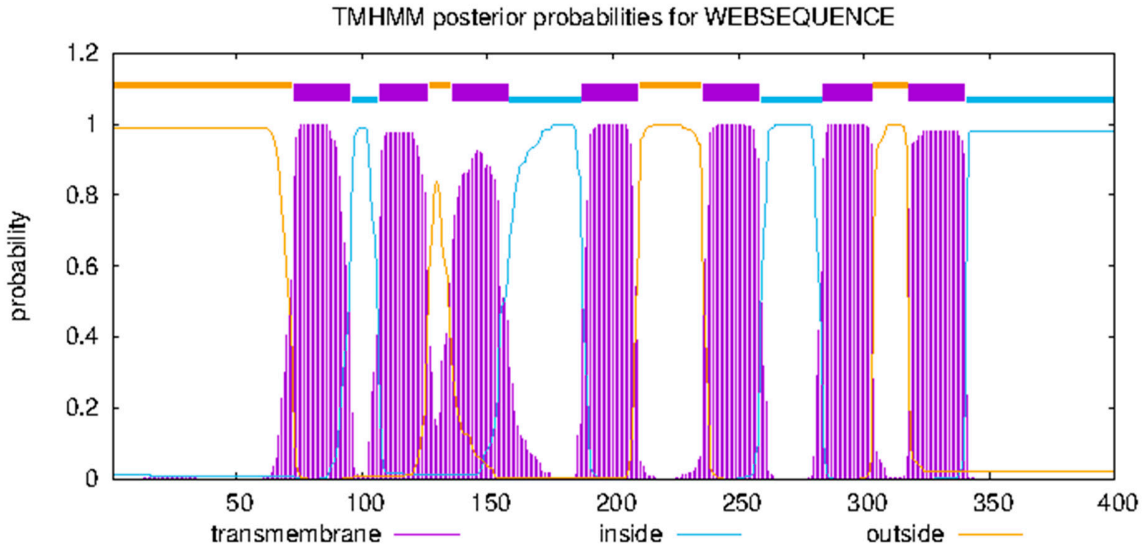


**Figure S2**. Prediction of the transmembrane helices in hMOR using TMHMM 2.0 server [44].

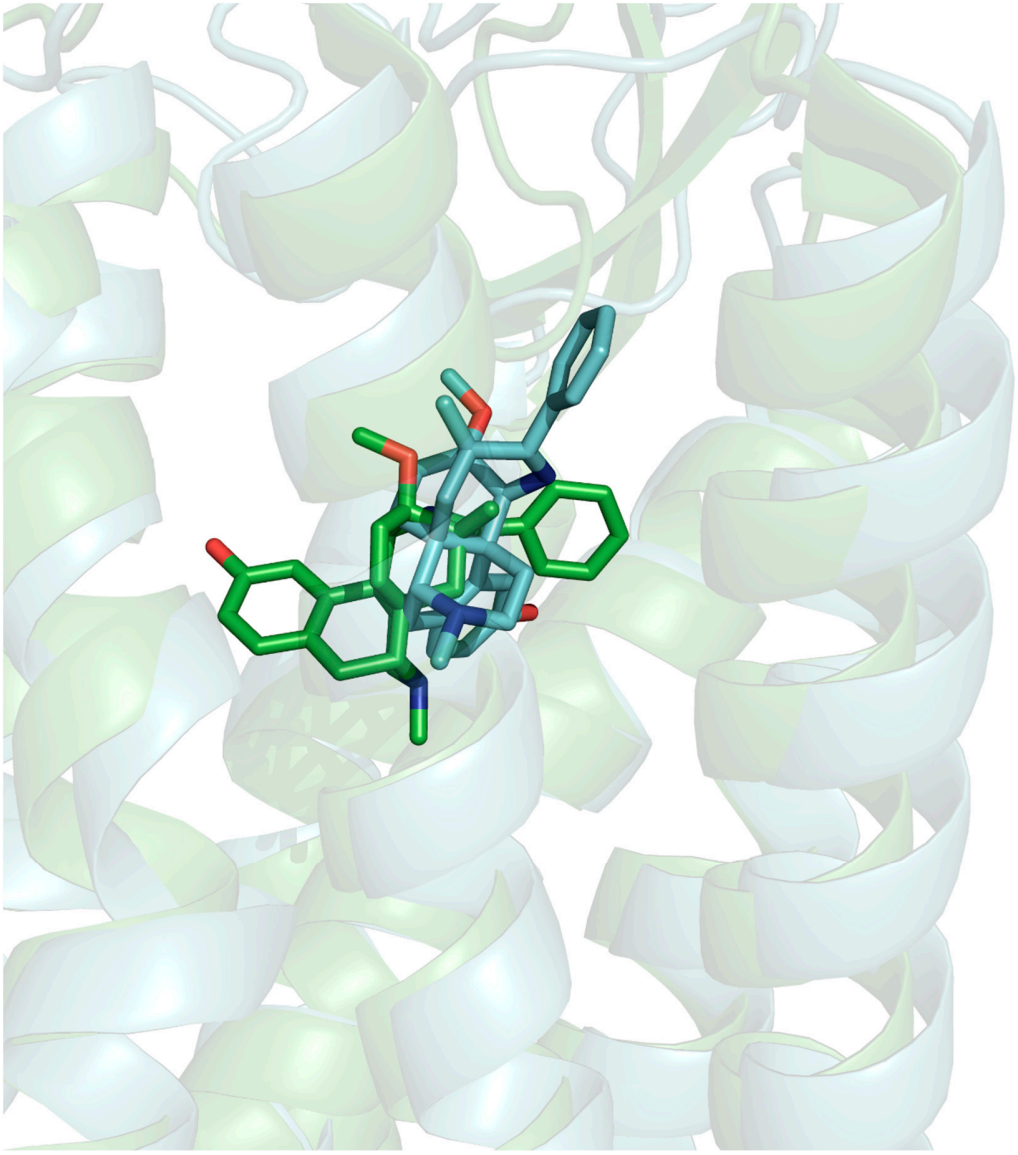

**Figure S3**. Molecular docking of the co-crystallized ligand (green) in mMOR (PDB entry 5C1M_chainA) in the most populated hMOR conformer (cyan) obtained through MD simulations.

**Table S1.** Per-residue free energy for hMOR coupled to naltrexone, NTXOL and HMNTXOL (values kcal/mol).

| Residue | hMOR-NTX | hMOR-NTXOL | hMOR-HMNTXOL |
|---|---|---|---|
| L114 | | -0.131 | |
| A115 | -0.383 | -1.173 | -0.496 |
| L118 | | -0.280 | |
| A119 | -0.771 | -1.128 | -0.812 |
| T120 | | -0.119 | -0.158 |
| T122 | -0.189 | -0.114 | -0.117 |
| L123 | -0.147 | | -0.138 |
| Q126 | -0.300 | | -0.181 |
| N129 | -0.196 | | |
| I148 | -0.184 | | |
| Y150 | | | -0.805 |
| N152 | -0.206 | -0.533 | |
| M153 | -1.780 | -1.551 | -3.050 |
| F154 | | -0.152 | -0.134 |
| T155 | | -0.240 | |
| S156 | | -0.417 | |
| I157 | | -1.016 | -0.229 |
| T159 | | -0.142 | |
| L160 | | -0.462 | |
| V238 | | | -0.730 |
| A242 | | -0.247 | -0.129 |
| V290 | | -0.158 | |
| C294 | -0.351 | -0.210 | |

| | | | |
|---|---|---|---|
| W295 | -1.572 | -1.176 | -0.757 |
| I298 | -1.184 | -0.731 | -1.725 |
| H299 | -0.218 | | -0.556 |
| V302 | | | -0.345 |
| C323 | | | -0.374 |
| I324 | -1.216 | -0.271 | -1.382 |
| A325 | -0.168 | | |
| L326 | -0.297 | -0.143 | -0.218 |
| G327 | -1.547 | -0.319 | -0.445 |
| Y328 | -2.774 | -0.991 | -1.522 |
| T329 | -0.219 | -0.167 | |
| N330 | -0.876 | -1.566 | -0.160 |
| S331 | -0.316 | -0.650 | -0.439 |
| L333 | | -0.156 | |
| N334 | | -1.942 | -0.228 |