Supplementary Information

N-Phenethyl Substitution in 14-Methoxy-*N*-methylmorphinan-6-ones Turns Selective μ Opioid Receptor Ligands into Dual μ/δ Opioid Receptor Agonists

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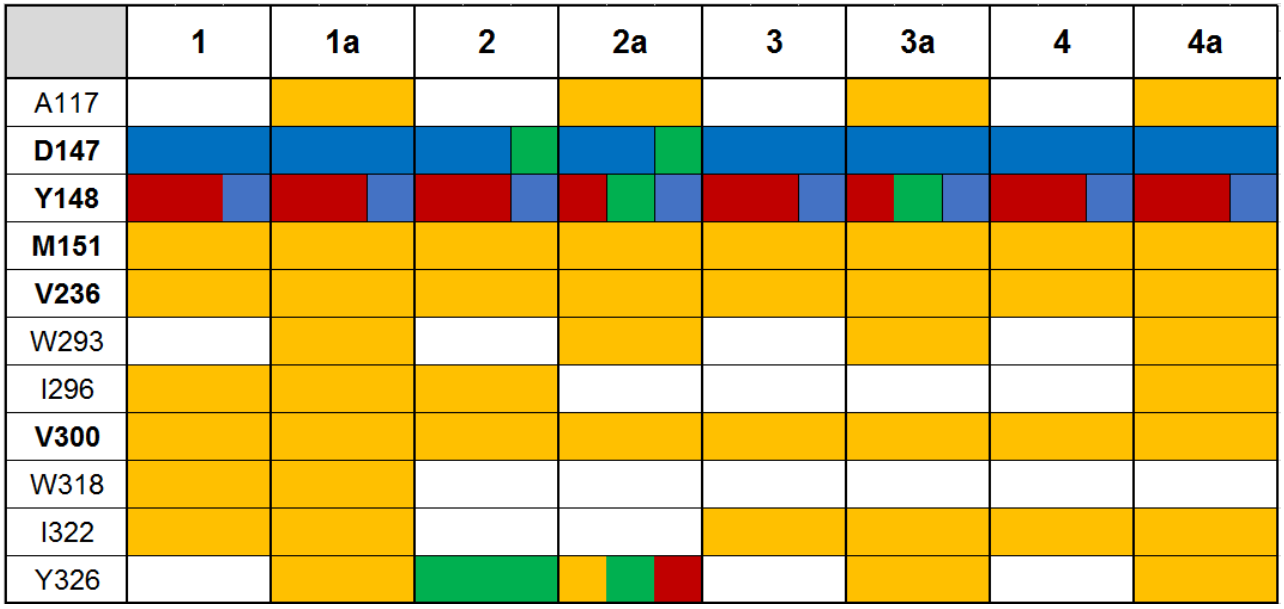

Figure S1. Ligand-μOR interaction patterns derived from molecular docking solutions of *N*-methylmorphinans **1**-**4** and their respective *N*-phenethyl analogues **1a**-**4a**. Yellow fields indicate lipophilic contacts, red fields represent hydrogen bond acceptors, green fields represent hydrogen bond donors and positively charged centers are shown as blue fields. White fields indicate the absence of an interaction with that residue. Residues which show the same type of interaction for all morphinan ligands are marked in bold.

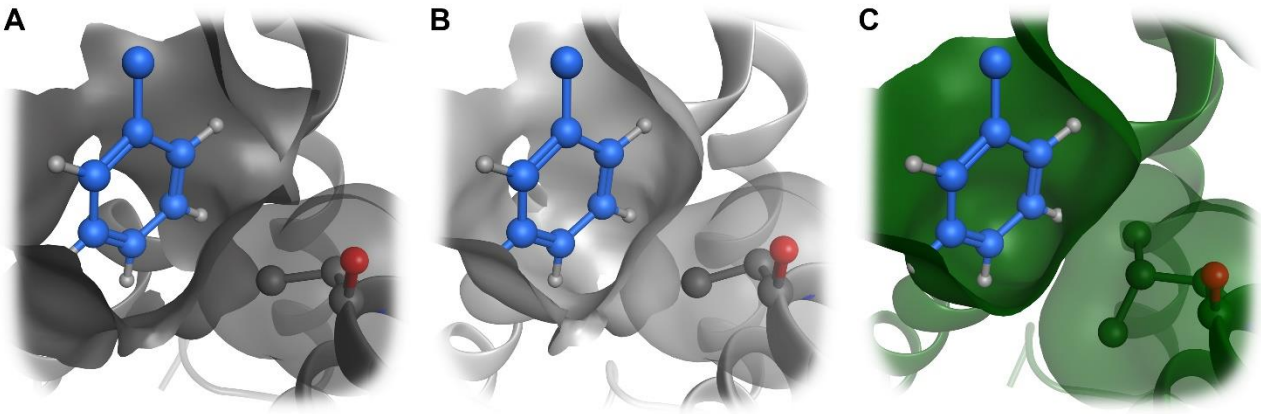

Figure S2. The phenyl ring system (blue) is embedded in a lipophilic subpocket. While the μOR (A) and the δOR (B) have an alanine residue at position 2.53, the κOR has a valine at this position. This reduces the size of the lipophilic subpocket in the κOR and represent a steric hindrance to optimally host a phenyl ring.

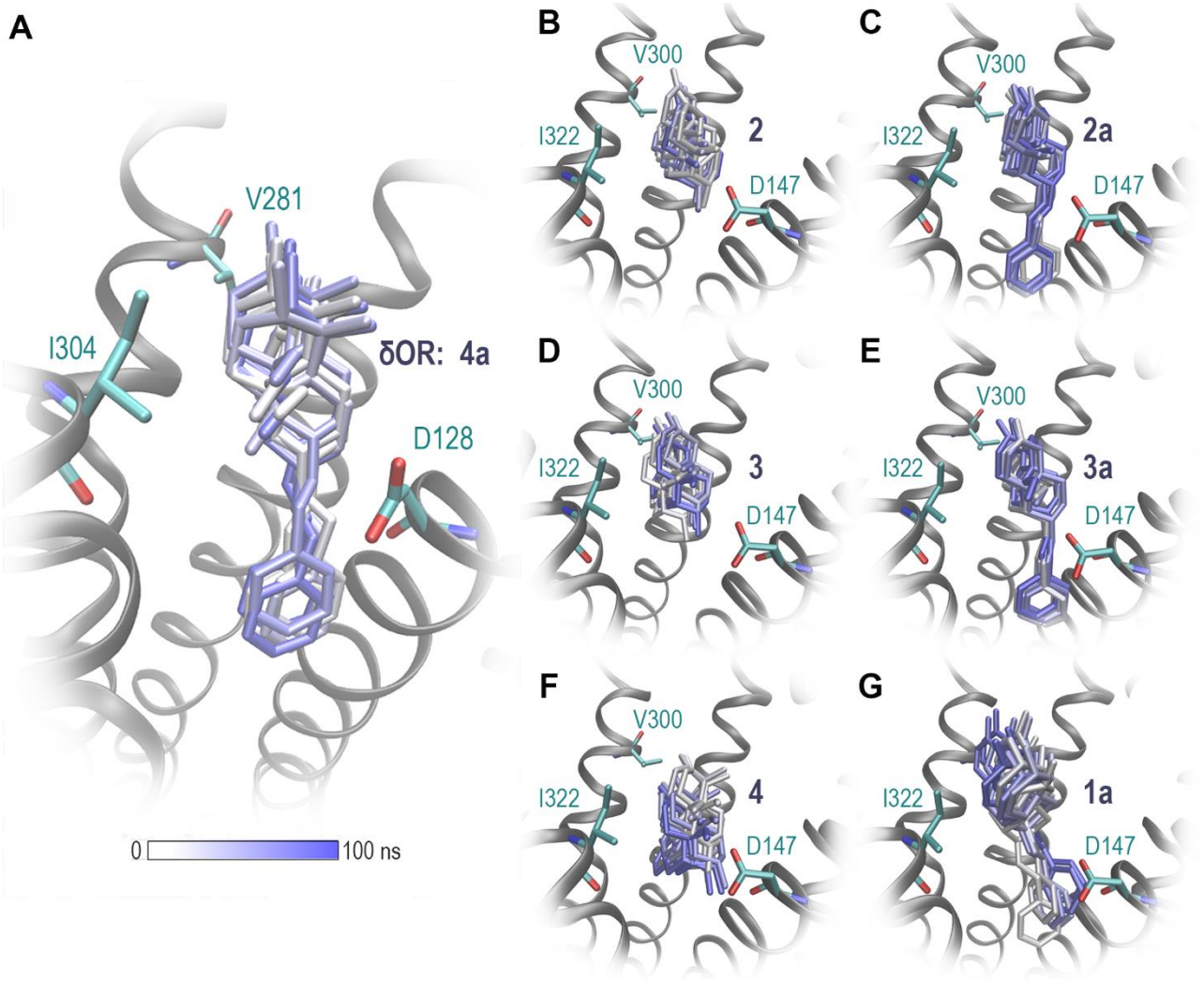

Figure S3. All-atoms MD simulations support the docking results. The binding mode of **4a** in the structural δOR model (A) is comparable to the μOR (see Figure 4 in the main text). The results are in accordance with the δOR crystal structure (PDB ID: 6PT3) The binding location and the major ligand orientation in the binding pocket for compounds **1a**, **2**, **2a**, **3**, **3a**, and **4** in complex with the μOR (PDB ID: 5C1M) are visualized in panels B-G. All key interactions reported from the docking experiments remain firm over 100 ns of MD simulations for all investigated compounds.

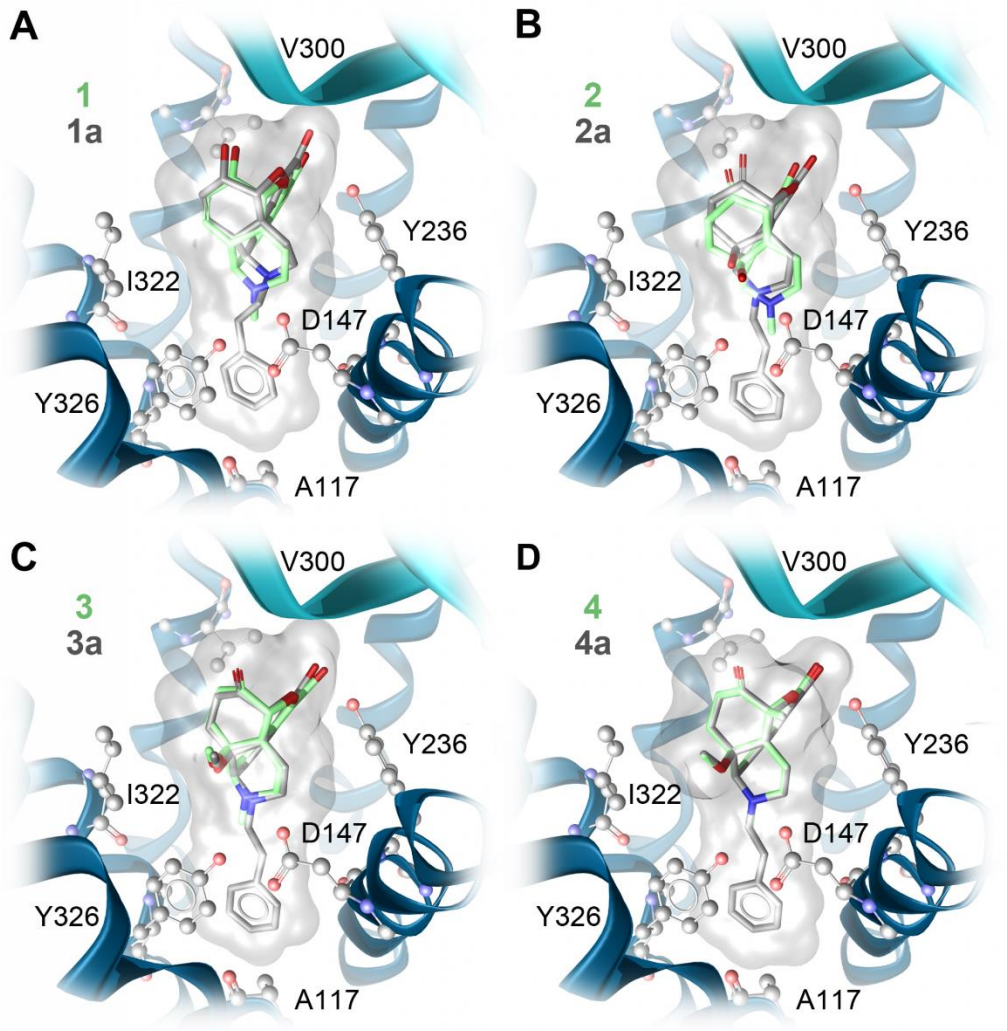

Figure S4. Docking of *N*-methylmorphinans **1**-**4** (green) and their respective *N*-phenethyl analogues **1a**-**4a** (gray) to the active structure of μOR (PDB ID: 5C1M). (A) Overlay of morphine (**1**) and **1a**. (B) Overlay of oxymorphone (**2**) and **2a**. (C) Overlay of 14-OMO (**3**) and **3a**. (D) Overlay of 14-MM (**4**) and **4a**.

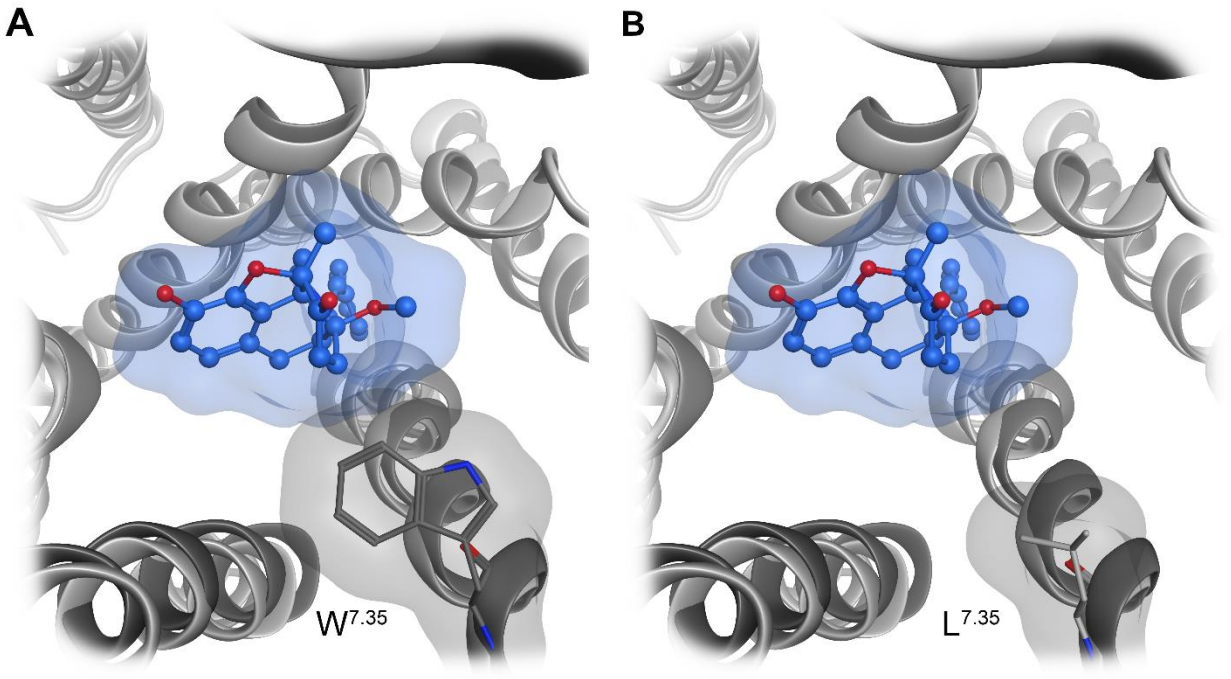

Figure S5. A comparison of the μOR and the δOR indicates a major difference at the beginning of helix seven at position 7.35. Whereas the tryptophan of the μOR (A) can form lipophilic contacts with the morphinan ring system of **4a** (blue), the leucine residue of the δOR cannot directly contribute to ligand binding (B).