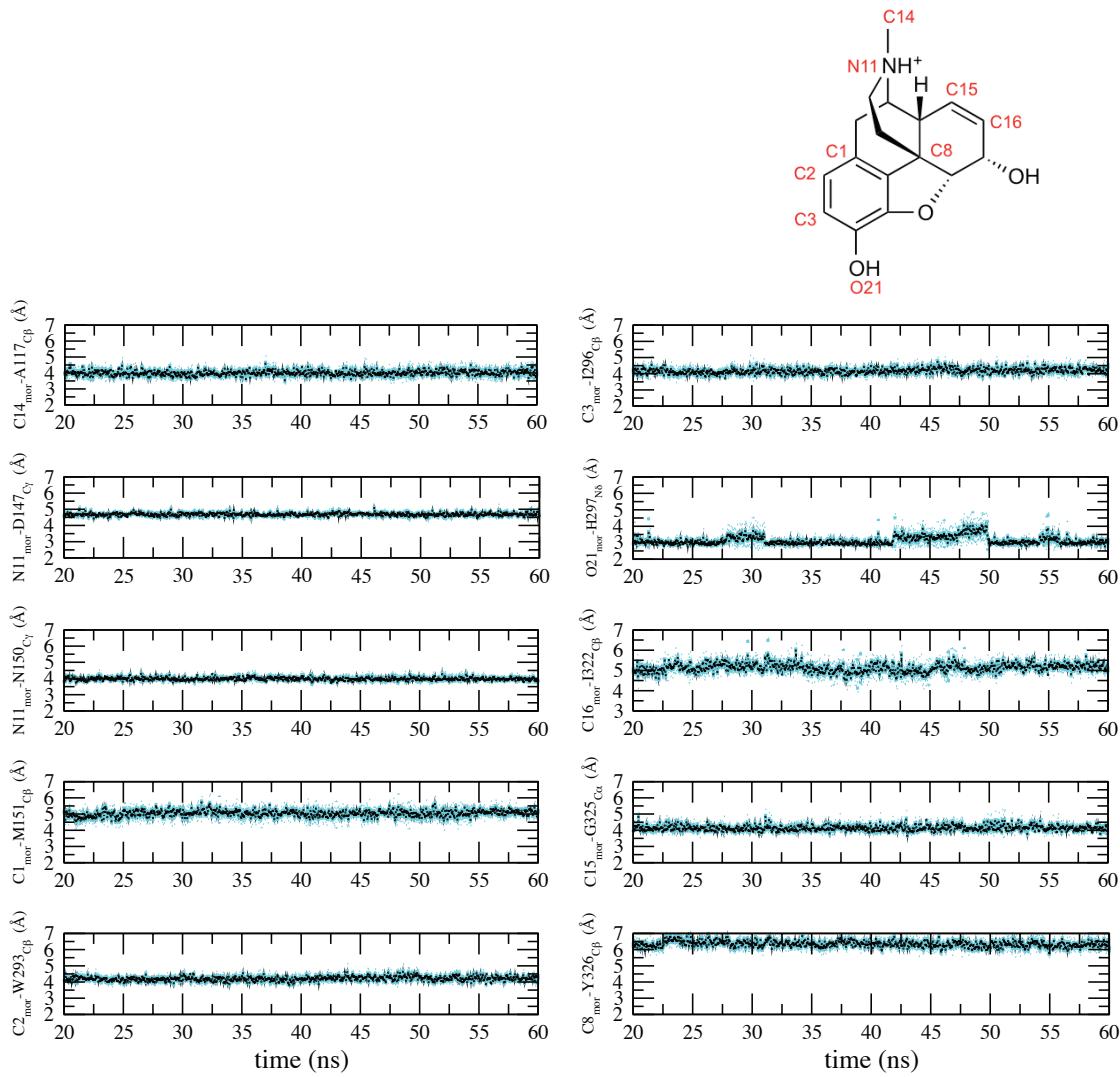
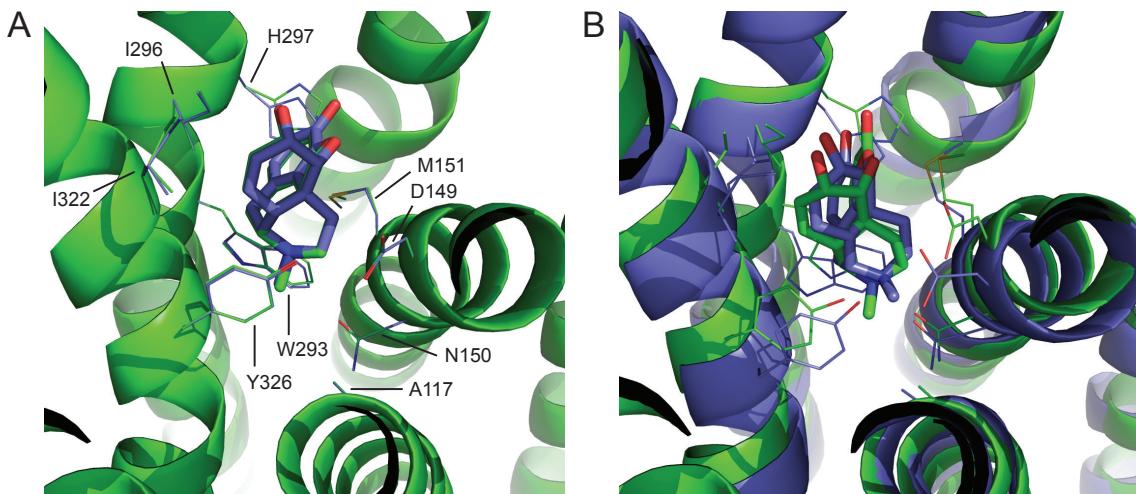


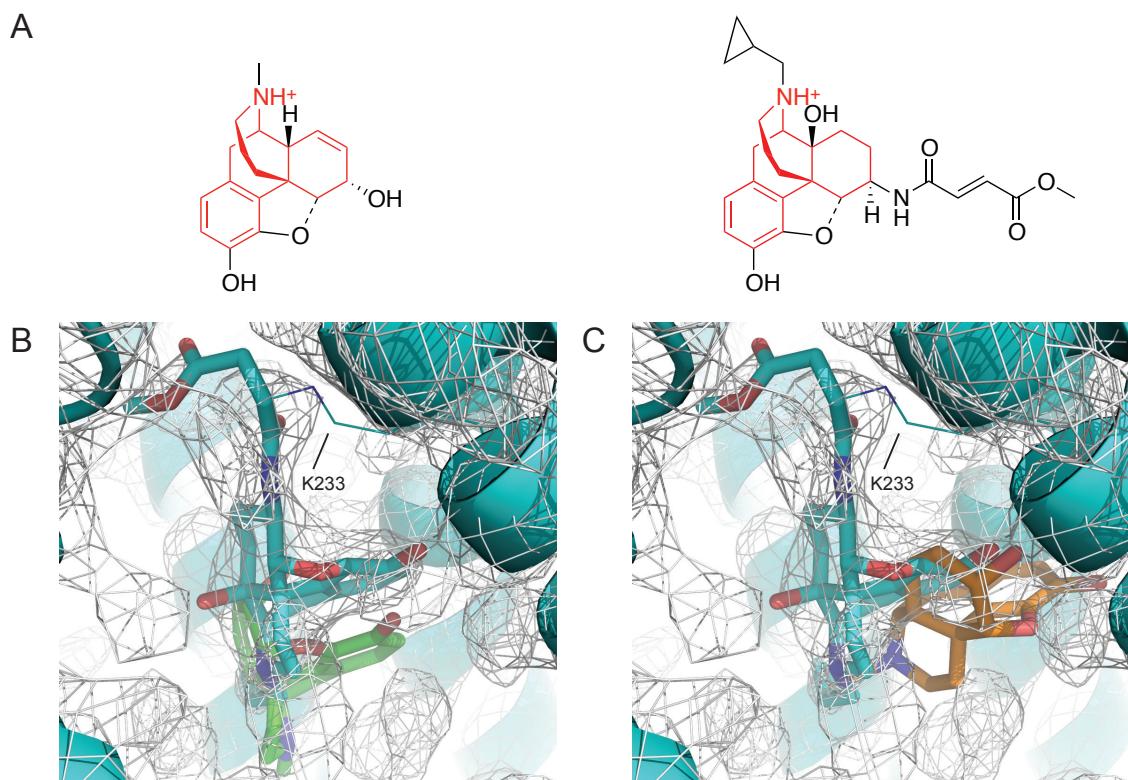
**Fig. S1. Inter-atomic distances between morphine and 7TM-mOR.** Average (in black) and standard deviation (cyan) of distances between atoms of morphine (in red at the top) and amino acids in 7TM-mOR binding site are reported. Specifically, from top to bottom in the left column: morphine-C14-A117-C $\beta$ , morphine-N11-D147-C $\gamma$ , morphine-N150-C $\gamma$ , morphine-M151-C $\beta$ , and morphine-C2-W293-C $\beta$ . From top to bottom in the right column: morphine-C3-I296-C $\beta$ , morphine-O21-H297-N $\delta$ , morphine-C16-I322-C $\beta$ , morphine-C15-G325-C $\alpha$ , and morphine-C8-Y326-C $\beta$ . Analyses are performed on the last 40 ns of simulations of three independent simulations.



**Fig. S2. Inter-atomic distances between morphine and 6TM-mOR.** Average (in black) and standard deviation (cyan) of distances between atoms of morphine (in red at the top) and amino acids in 6TM-mOR binding site are reported. Specifically, from top to bottom in the left column: morphine-C14-A117-C $\beta$ , morphine-N11-D147-C $\gamma$ , morphine-N150-C $\gamma$ , morphine-M151-C $\beta$ , and morphine-C2-W293-C $\beta$ . From top to bottom in the right column: morphine-C3-I296-C $\beta$ , morphine-O21-H297-N $\delta$ , morphine-C16-I322-C $\beta$ , morphine-C15-G235-C $\alpha$ , and morphine-C8-Y326-C $\beta$ . Analyses are performed on the last 40 ns of simulations of three independent simulations.

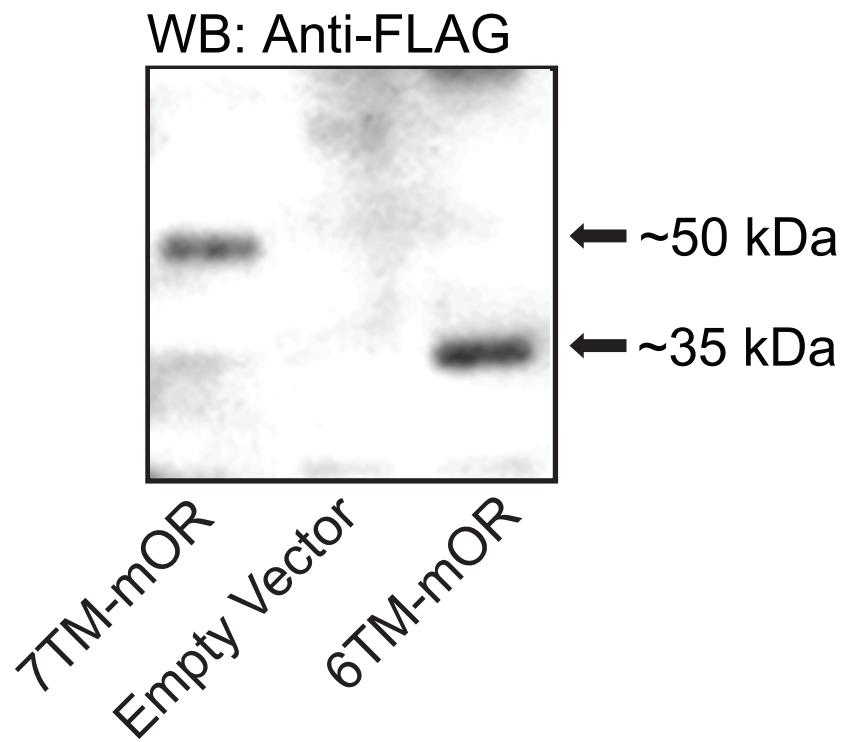


**Fig. S3. Similarity of morphine bound conformations in 7TM- and 6TM-mOR.** **A)** Superimposition of morphine binding mode in 7TM- (green) and 6TM-mOR (blue) as obtained with MedusaDock ( $t = 0$  ns). The energy of binding, estimated using MedusaScore, is equal to -40.3 kcal/mol and -39.5 kcal/mol for 7TM-mOR and 6TM-mOR, respectively. The RMSD of superimposed conformations is  $\sim 0.3$  Å. **B)** Superimposition of the lowest energy bound conformations of morphine in 7TM- (green) and 6TM-mOR (blue) obtained from three independent MD simulations. No clustering analysis has been performed for the selection of bound conformations because of the persistence of morphine coordinates within the crystallographic resolution of the receptor along the entire MD simulation (*i.e.*, 2.8 Å, Fig. 1A). The energy of binding of the final conformations ( $t = 60$  ns), estimated using MedusaScore, is equal to -42.9 kcal/mol and -46.5 kcal/mol for 7TM-mOR and 6TM-mOR, respectively. The RMSD of superimposed conformations is  $\sim 1.3$  Å. Residue labels are reported only in the left figure.



**Fig. S4. Morphinan core orientation of morphine and  $\beta$ -FNA in complex with 7TM-mOR.**

**A)** Chemical structures of morphine (left) and  $\beta$ -FNA (right), in which the morphinan core is highlighted in red. **B)** Superimposition of MedusaDock docking solution of morphine (green) to the crystallographic conformation of  $\beta$ -FNA covalently bound to K233 in 7TM-mOR binding site. **C)** Superimposition of previously published docking solution of morphine [7] (orange) to the crystallographic conformation of  $\beta$ -FNA covalently bound to K233 in 7TM-mOR binding site. In (B) and (C) mOR electron density map as available from the Electron Density Server (ref. [53] in the main text) is reported as white mesh.



**Fig. S5. Western blot analysis of HEK293 cell total lysates using antibodies against FLAG tag.** Cells were transiently transfected with FLAG-tagged 7TM-, 6TM-mOR, or empty vector. 48h after cells were lysed with RIPA lysis buffer (ThermoFisher Scientific); protein concentrations were determined with the BCA protein assay kit (ThermoFisher Scientific) and 20 µg lysates were loaded per lane for a SDS-PAGE gel separation. WB: probing antibody.

**Table S1. Root mean square distances among docking solutions.**

Morphinan core RMSD (Å)	MedusaDock	Previous Docking*	$\beta$ -FNA
MedusaDock	0	5.7	3.8
Previous Docking	5.7	0	4.7
$\beta$ -FNA	3.8	4.7	0

Values are computed over the morphinan core's heavy atoms of the MedusaDock solution, the previously published docking solutions for morphine,\* and the crystallographic conformation of  $\beta$ -FNA covalently bound to 7TM-mOR. \*Ref. [7] in the main text.