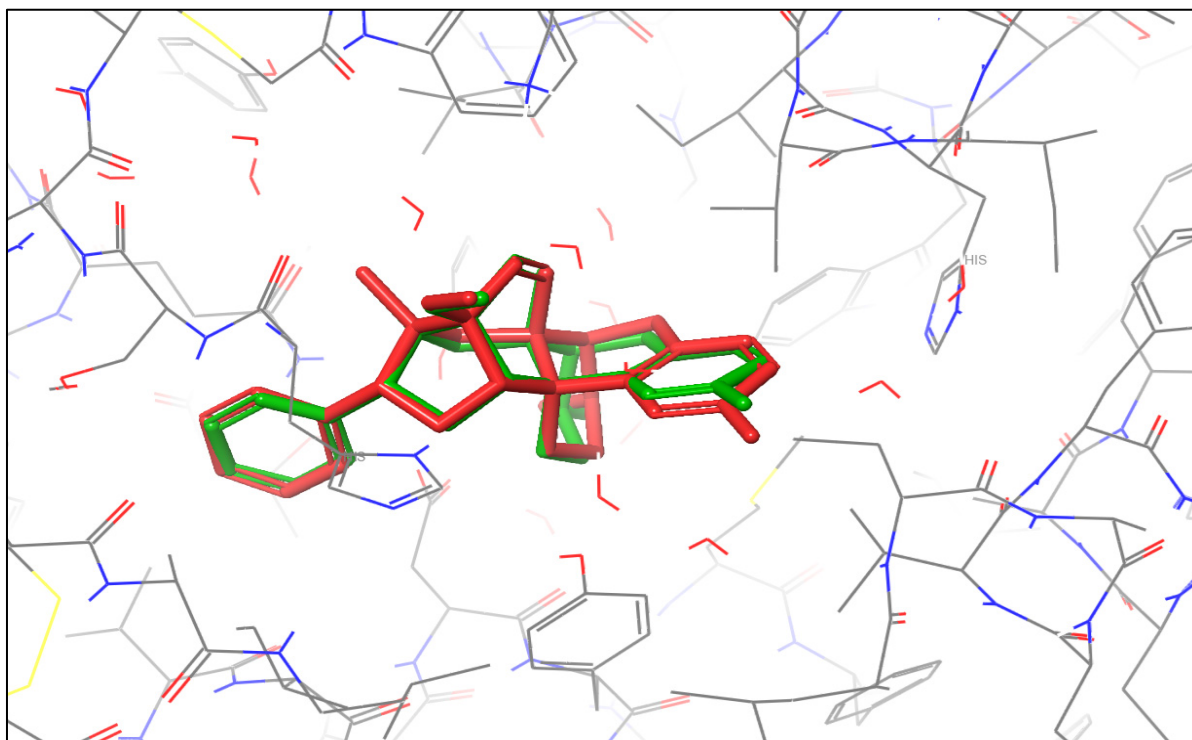


Supplementary

A)



B)

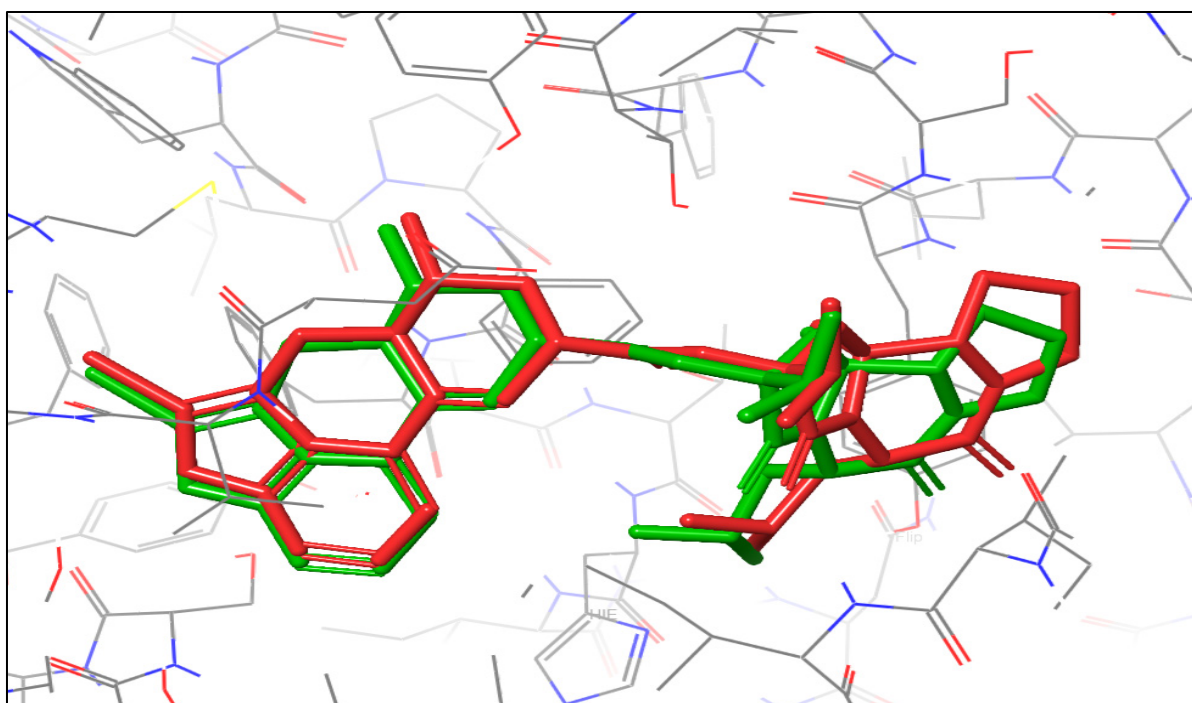


Figure S1. Validation of the molecular docking setup by redocking of the co-crystallized ligands. (A) Superposition of the crystallographic and redocked poses of BU72 in the μ -opioid receptor (MOR, PDB ID: 5C1M). (B) Superposition of the

crystallographic and redocked poses of bromocriptine in the dopamine D2 receptor (D2R, PDB ID: 7JVR). Crystallographic ligand poses are shown in green and redocked poses in red. The corresponding heavy-atom RMSD values were 0.410 Å for BU72 and 0.915 Å for bromocriptine.

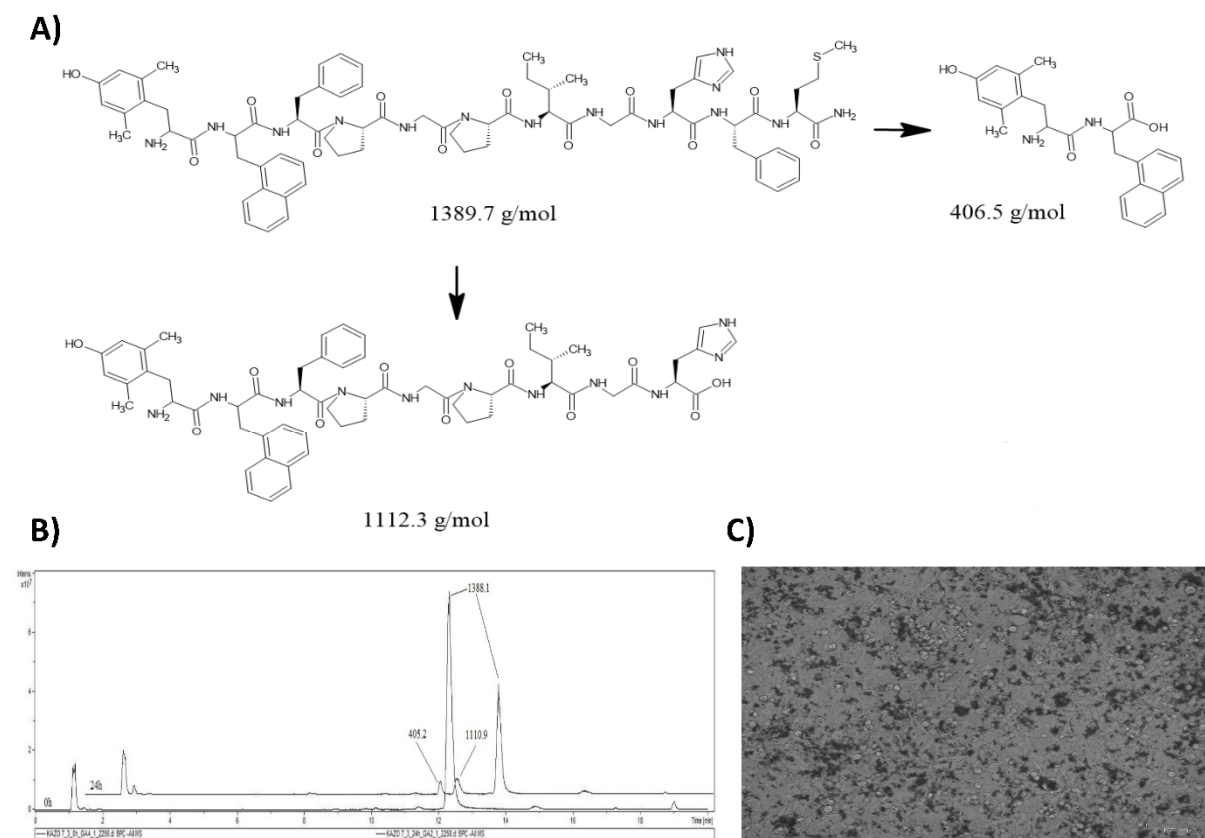


Figure S2. A) Representative structures of putative KAZO_7.3 degradation products detected in the culture medium used for the MTT assay, based on the observed molecular masses. **B)** LC-MS chromatograms of KAZO_7.3-containing culture medium collected immediately after preparation (0 h) and after 24 h of incubation under cell culture conditions. Major detected ions are indicated by their m/z values. Compounds were identified as Dmt-Nal(2')-FPGPIGH [m/z observed = 1110.9]; and Dmt-Nal(2') [m/z observed = 405.2] with KAZO_7.3 [m/z observed = 1388.1]. **C)** Representative image of an MTT assay plate showing HCT116 cells treated with KAZO_7.3 at a concentration of 300 $\mu\text{g/mL}$.

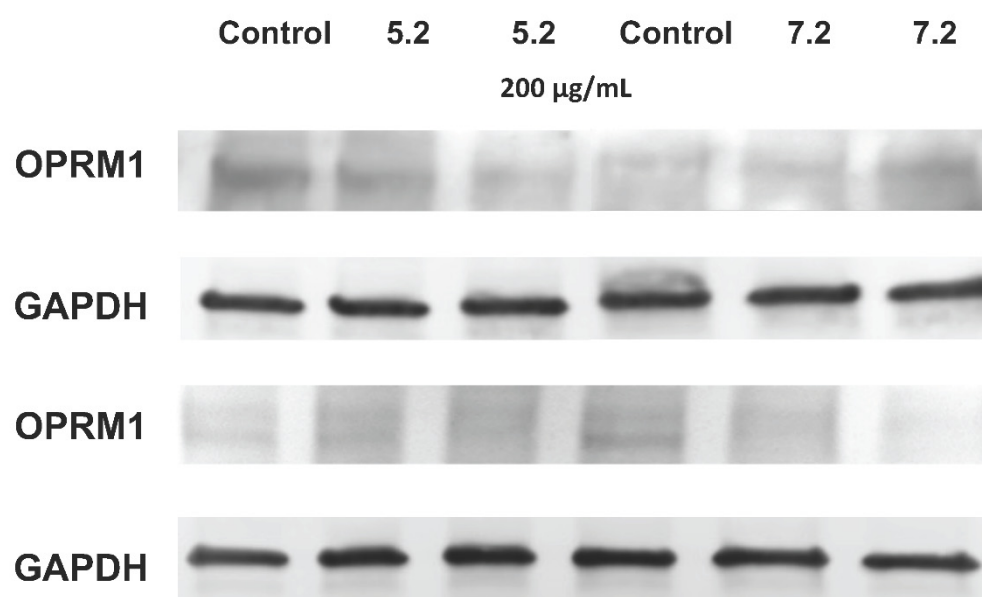


Figure S3. Western blot analysis of OPRM1 (MOR) protein in HCT116 cancer cells following treatment with KAZO_5.2 and KAZO_7.2 (200 µg/mL).

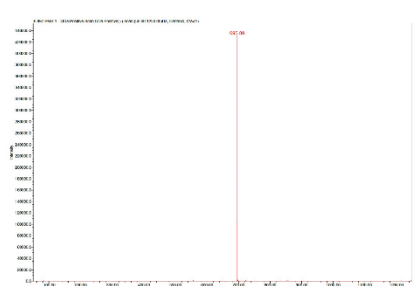


Figure S4. HPLC (left panel) and LC-MS (right panel) chromatograms for synthesized casomorphin-based hybrid peptides: A) KAZO_5.1; B) KAZO_5.2; C) KAZO_5.3; D) KAZO_7.1; E) KAZO_7.2; F) KAZO_7.3