Supplementary information for

Opioid receptor signaling, analgesic and side effects induced by a computationally designed pH-dependent agonist

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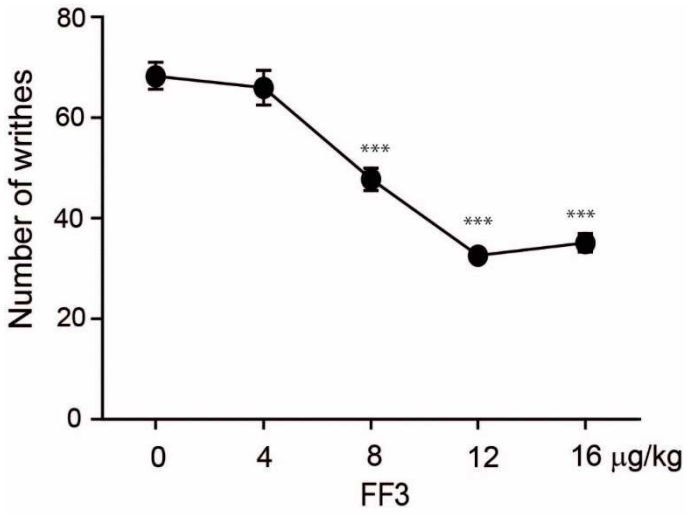
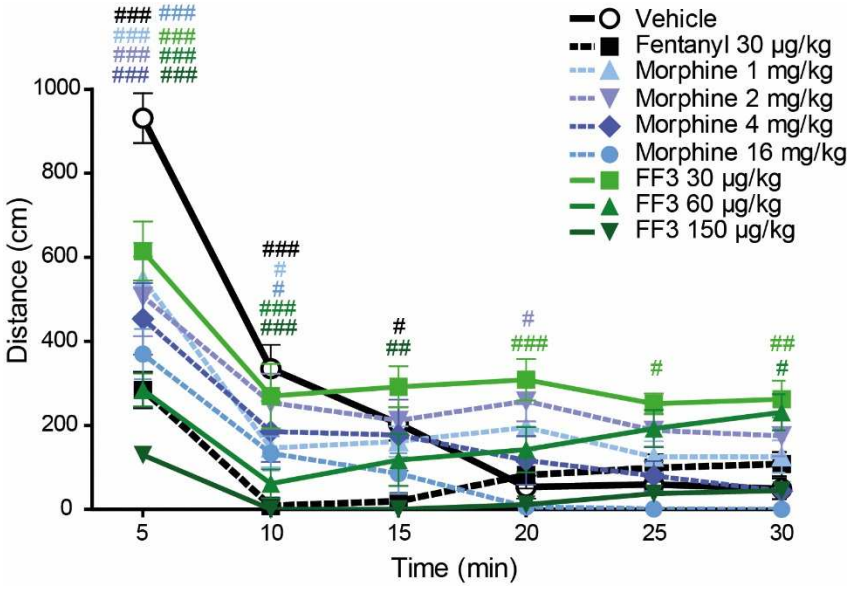
Supplementary Materials:



Supplementary Fig. S1. *Systemic FF3 dose-dependently reduces abdominal writhing.* Effects after intravenous injection of FF3 on number of writhes during 5-35 min after intraperitoneal 1 % acetic acid injection (*** $P < 0.001$ vs. "0", one-way ANOVA and Bonferroni's multiple comparison test, n = 9 rats per group, means ± SEM).



Supplementary Fig. S2. *Systemic FF3 induces sedation at high doses.* Effects of subcutaneous fentanyl, morphine, and FF3 on locomotor activity presented as the distance (in cm) travelled during 30 min after drug injection (# $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ vs. vehicle, two-way RM-ANOVA and Bonferroni's multiple comparison test; vehicle, fentanyl and FF3, n=12, morphine, n=10, means ± SEM).

Supplementary text

FF3, morphine, and fentanyl induced significantly decreased locomotor activity at 5 min after injection compared to vehicle. This effect was not seen for morphine (2 mg/kg) or FF3 (30 and 60 µg/kg) at later time points. At time points 20, 25, and 30 min FF3 (30 µg/kg) and at 30 min (60 µg/kg), locomotor activity was significantly increased compared to vehicle.