

**Supplemental information: The CB<sub>1</sub> Receptor Positive Allosteric Modulator, ZCZ011, Attenuates Naloxone-Precipitated Diarrhea and Weight Loss in Oxycodone-Dependent Mice**

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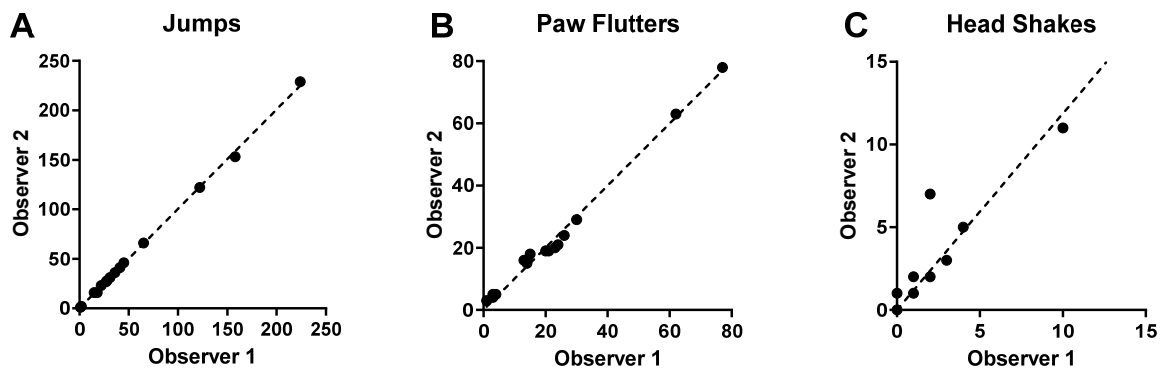
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**Supp. Fig. 1.** Determining inter-rater reliability for jumps, paw flutters, and head shakes between two independent observers blinded with respect to treatment. These data were from a pilot experiment including sixteen oxycodone-dependent mice undergoing withdrawal. Withdrawal signs include jumps (A), paw flutters (B), and head shakes (C). Pearson correlations were used to determine the correlation between each observer and the dotted line represents the line of best fit.

## Synthesis of ZCZ011

**6-Methyl-3-(2-nitro-1-(thiophen-2-yl)ethyl)-2-phenyl-1H-indole (ZCZ011).** D-camphorsulfonic acid (24 mg, 0.1 mmol) was added to a suspension of 6-methyl-2-phenyl-1H-indole (100 mg, 0.48 mmol) and *trans*-2-(2-nitrovinyl)thiophene (75 mg, 0.48 mmol) in 2.5 mL of the mixture of MeOH and H<sub>2</sub>O (1:4). The resulting mixture was stirred at 100°C under argon atmosphere for 3 hours and cooled to room temperature. The Reaction mixture was partitioned between ethyl acetate and water. The organic extract was separated and washed with saturated sodium bicarbonate aqueous solution, water, and brine. The resultant organic layer was separated and dried over sodium sulfate. Filtration and concentration provided solid crude product, which was purified by Combi-flash chromatography (EtOAc/Hexane = 0-20%) to yield the desired product ZCZ011 (142 mg, 81.6%) as a pale yellow solid. mp. 139-140°C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 8.04 (s, 1H), 7.39-7.49 (m, 6H), 7.19 (s, 2H), 6.94-6.97 (m, 3H), 5.47 (t, *J* = 7.7 Hz, 1H), 5.18 (1H, dd, *J* = 7.4, 12.5 Hz, 1H), 5.06 (dd, *J* = 8.2, 12.5 Hz, 1H), 2.46 (s, 3H). APCI-MS *m/z*: 363.1 (M+H)<sup>+</sup>.