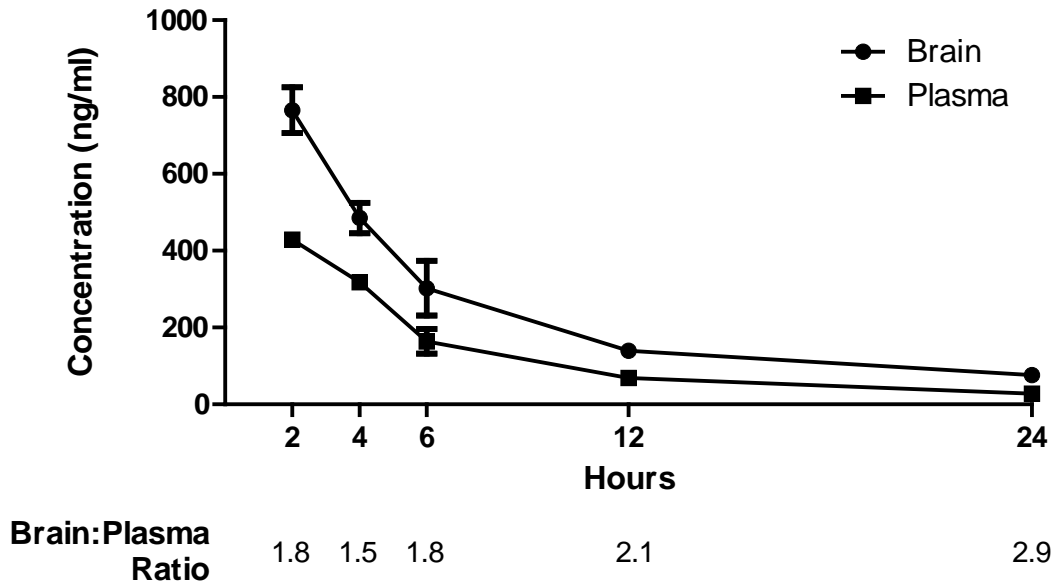


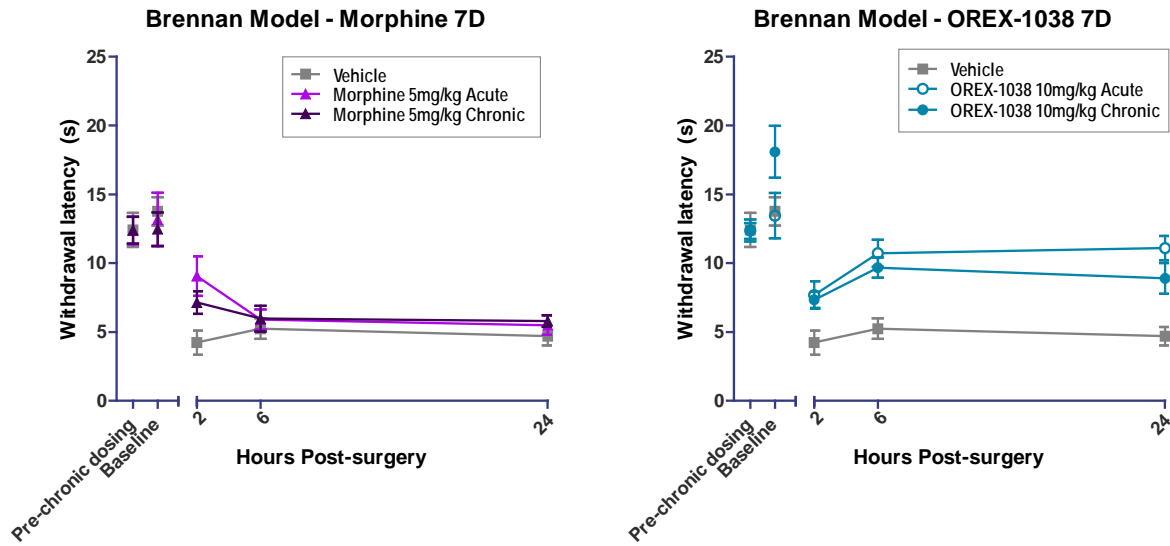
Supplemental Figures

Supplemental Figure 1



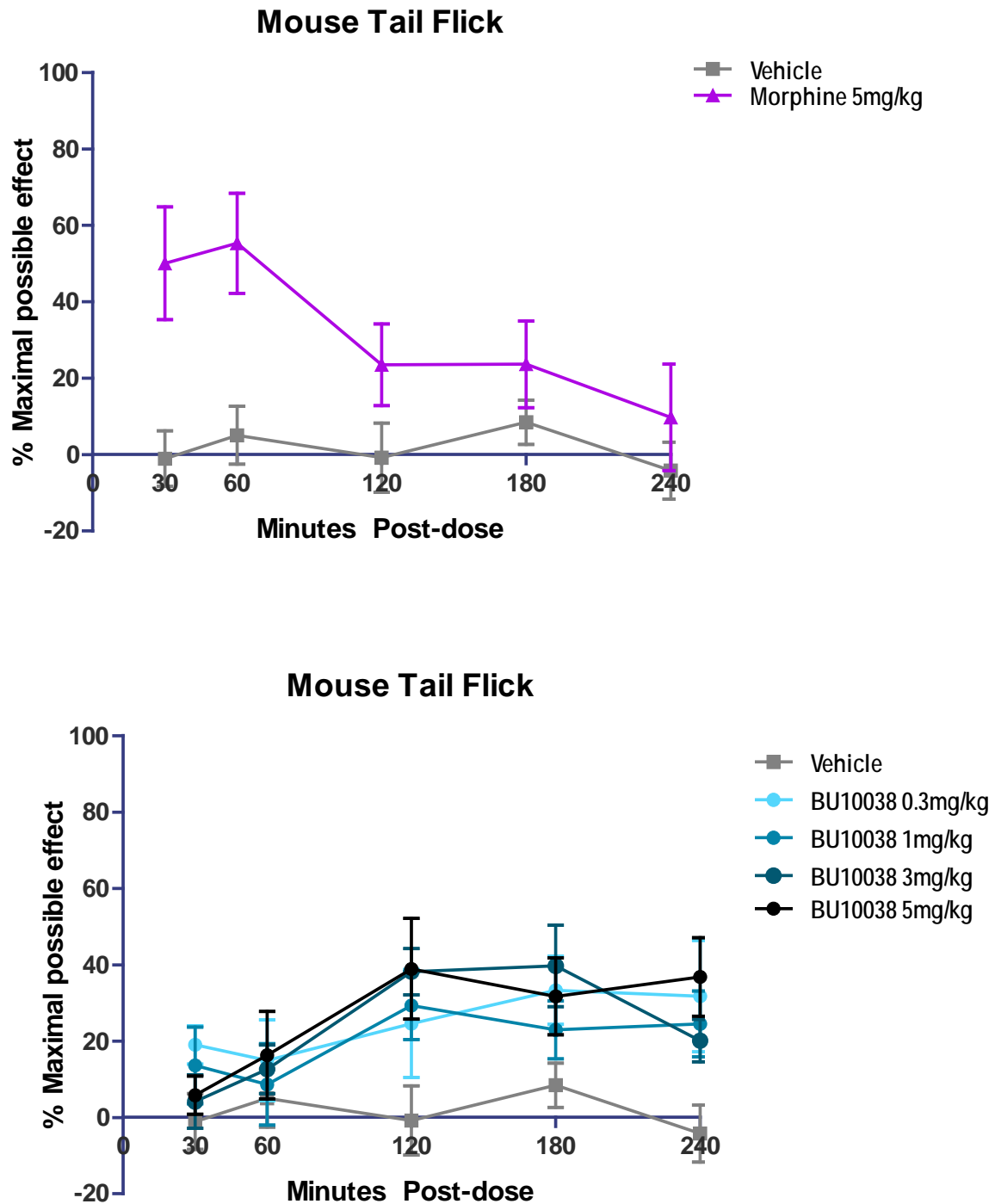
The brain-to-plasma ratio of OREX-1038 was evaluated following subcutaneous administration at 20 mg/kg in male Sprague-Dawley rats. Following dosing, blood and brain tissues were collected up to 24 hours post dose. Plasma and brain homogenate concentrations for OREX-1038 were determined by LC-MS/MS and brain-to-plasma ratios were then calculated.

Supplemental Figure 2



Morphine (5 mg/kg s.c.) and OREX-1038 (10 mg/kg s.c.) were administered once a day for 7 consecutive days and antinociceptive activity compared to that obtained following a single acute dose.

Supplemental Figure 3



Effects of morphine (5 mg/kg; top panel) and OREX-1038 (0.3-5.0 mg/kg, bottom panel) on under a tail flick procedure in mice.