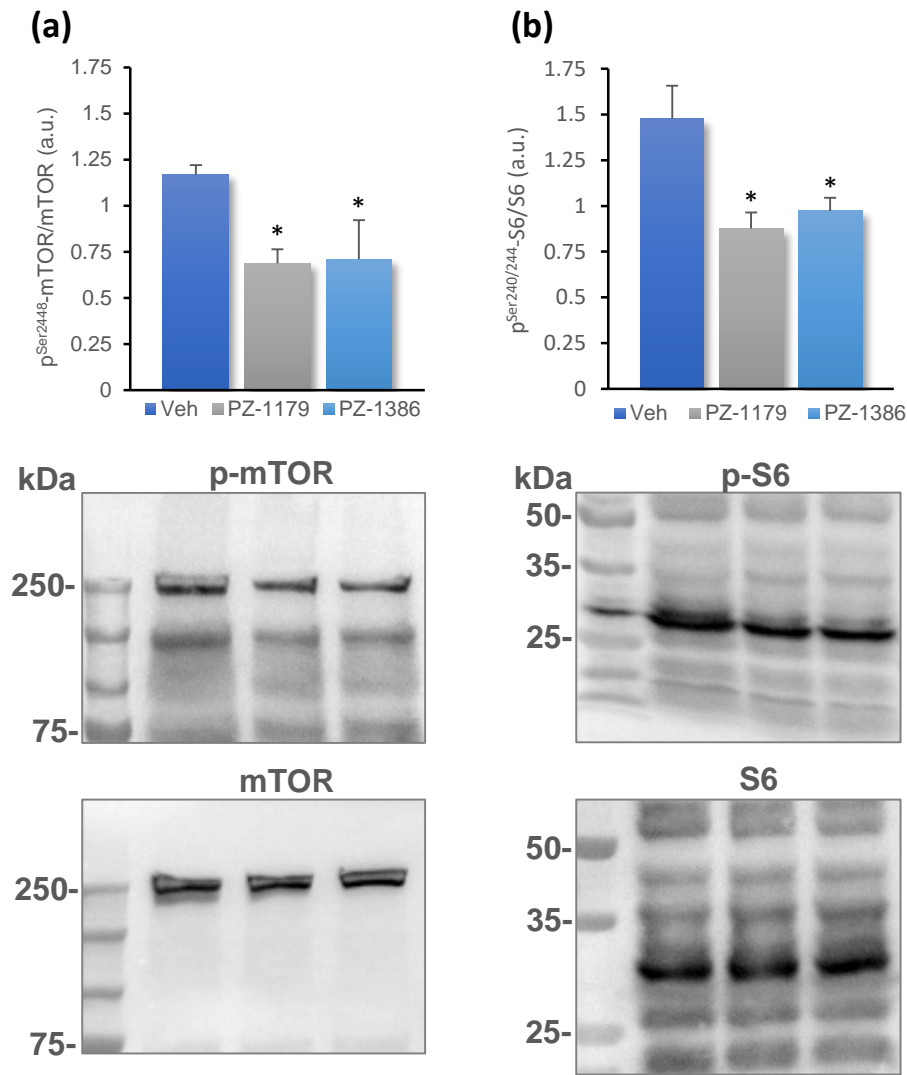
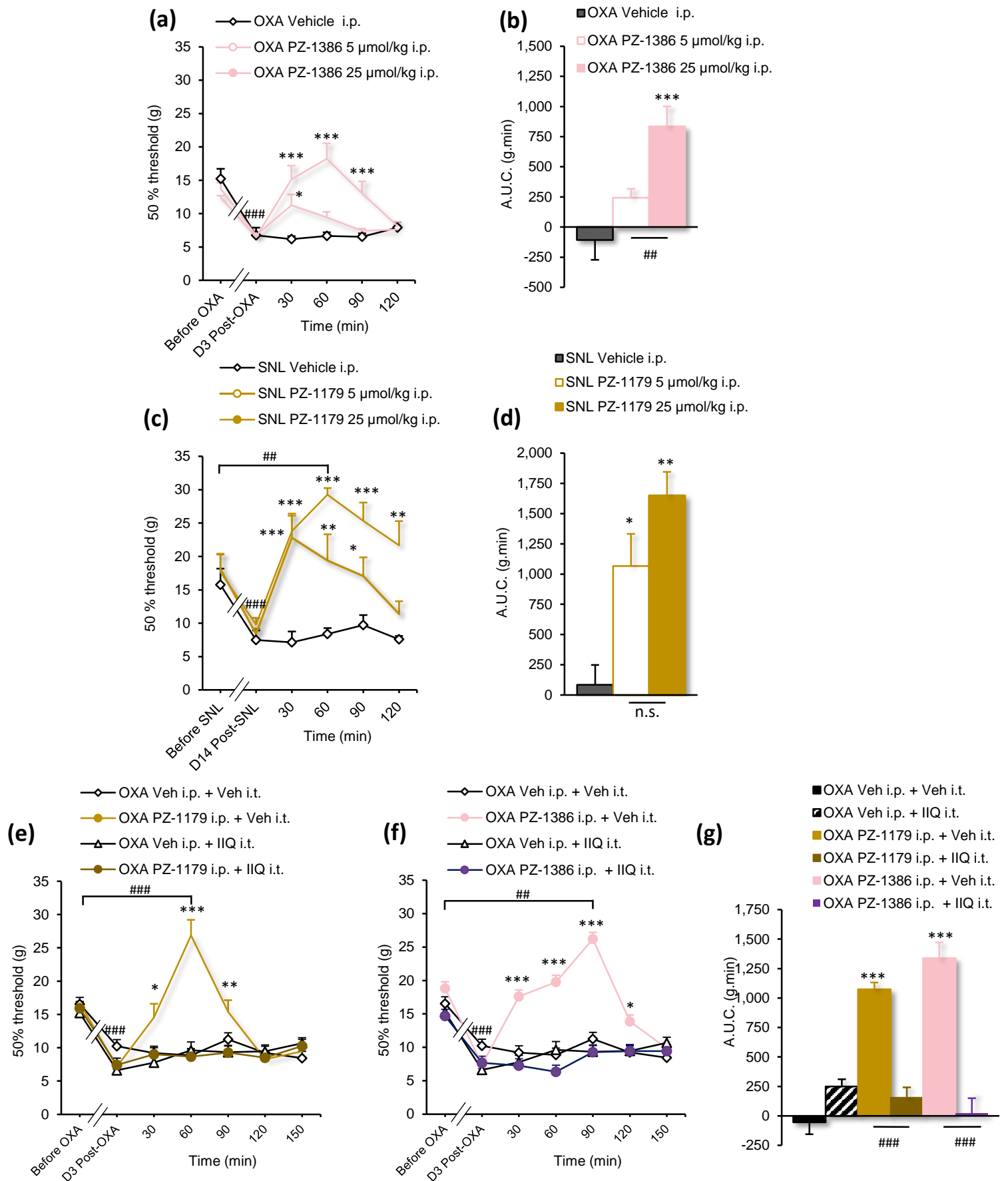


**Table S1.** Detailed statistics for figures S1 and S2.

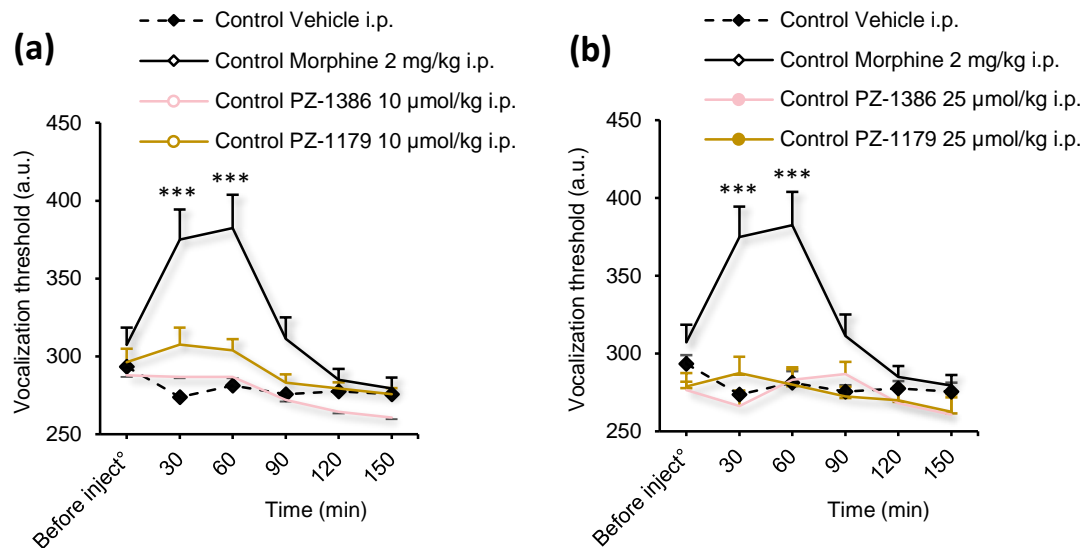
Figure	Analysis	Statistics (DFn, DFs)	P value
Figure S1a	1-way ANOVA	$F(2, 6) = 4.226$	P=0.0715
Figure S1b	1-way ANOVA	$F(2, 9) = 6.788$	P=0.0159
Figure S2a	2-way RM ANOVA	$F(14, 203) = 7.586$	P<0.0001
Figure S2b	1-way ANOVA	$F(2, 27) = 13.93$	P<0.0001
Figure S2c	2-way RM ANOVA	$F(10, 80) = 5.018$	P<0.0001
Figure S2d	1-way ANOVA	$F(2, 17) = 8.8555$	P=0.0023
Figure S2e, f	2-way RM ANOVA	$F(25, 190) = 6.067$	P<0.0001
Figure S2g	1-way ANOVA	$F(5, 38) = 33.40$	P<0.0001
Figure S3a, b	2-way ANOVA	$F(25, 200) = 5.257$	P<0.0001



**Figure S1.** Inverse agonists reduce 5-HT<sub>6</sub> receptors constitutive activity at mTOR signaling. PZ-1179 and PZ-1386 reduces agonist-independent 5-HT<sub>6</sub> receptor-operated mTOR (a) and S6 (b) phosphorylation (at Ser<sup>2448</sup> and Ser<sup>240/244</sup>, respectively) in HEK-293 cells. HEK-293 cells expressing 5-HT<sub>6</sub> receptors were incubated with either vehicle (Veh), PZ-1179, or PZ-1386 (1  $\mu$ M each) for 1h. \* $P$ <0.05 *vs.* vehicle, 1-way ANOVA.



**Figure S2.** Effect of 5-HT<sub>6</sub> receptor inverse agonists on tactile hypersensitivity (von Frey hair test) in OXA and SNL rats. Intraperitoneal administration of PZ-1386 in OXA rats (**a**, **b**), PZ-1179 in SNL (**c**, **d**) and OXA (**e**) rats (5 and/or 25  $\mu\text{mol/kg}$  each) but not vehicle (water for injections) suppresses mechanical hypersensitivity ( $n = 5-11/\text{group}$ ). 50% thresholds are expressed as grams (g). ### $P < 0.001$  vs. values measured before OXA or SNL; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs. values measured before the drug/vehicle (water) injection (D3 Post-OXA or D14 Post-SNL), 2-way ANOVA; (**e**, **f**) Intrathecal administration of IIQ (2 nmol/rat) but not vehicle (water for injections, 10  $\mu\text{l}$ /rat) suppressed the effect of (**e**) PZ-1179 (25  $\mu\text{mol/kg}$ , i.p.) and (**f**) PZ-1386 (25  $\mu\text{mol/kg}$ , i.p.) on paw withdrawal threshold induced by von Frey hair application ( $n = 5-8/\text{group}$ ). ### $P < 0.001$  vs. values measured before OXA; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs. values measured before drug/vehicle injection (D3 Post-OXA), 2-way ANOVA; (**b**, **d**, **g**) Area under the (A.U.C.) between 0-120 min of 50 % threshold variations in OXA and SNL rats calculated by the trapezoidal rule and expressed as g . min.. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , vs. OXA or SNL Vehicle group; # $P < 0.05$  ### $P < 0.001$  vs. values measured in corresponding group, 1-way ANOVA.



**Figure S3.** Effect of 5-HT<sub>6</sub> receptor inverse agonists on mechanical nociception in healthy control rats. Intraperitoneal administration of vehicle (water for injections), PZ-1386 or PZ-1179 at the dose of 10 µmol/kg (**a**) or 25 µmol/kg (**b**) fails to induce antinociception to paw pressure (n = 6-8/ group). Vocalization thresholds are expressed as arbitrary units (a.u.). \*\*\**P* < 0.001 *vs.* values measured before the drug/vehicle injection, 2-way ANOVA.