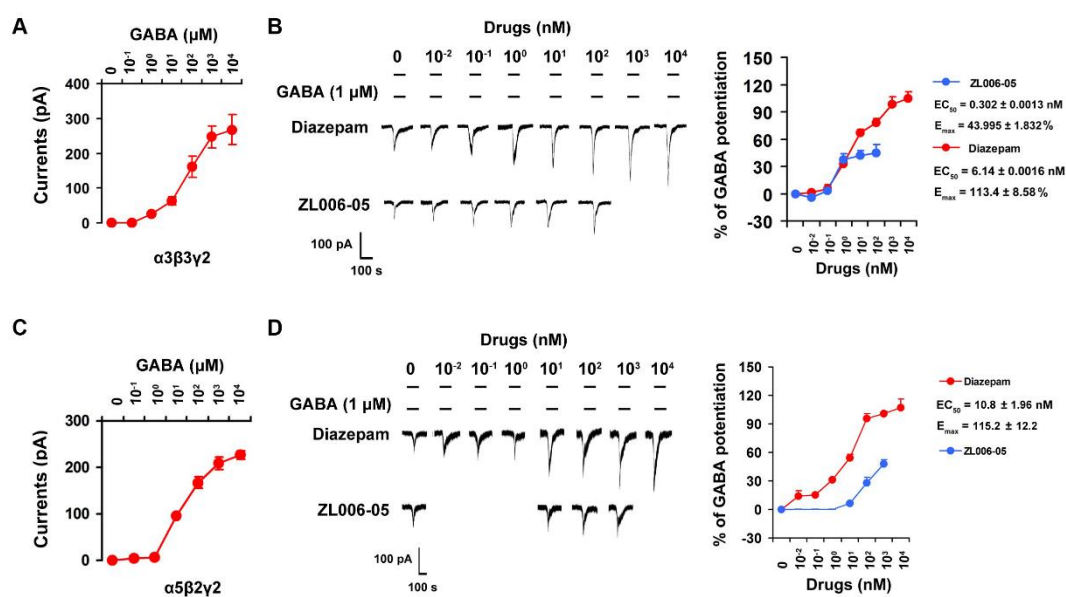
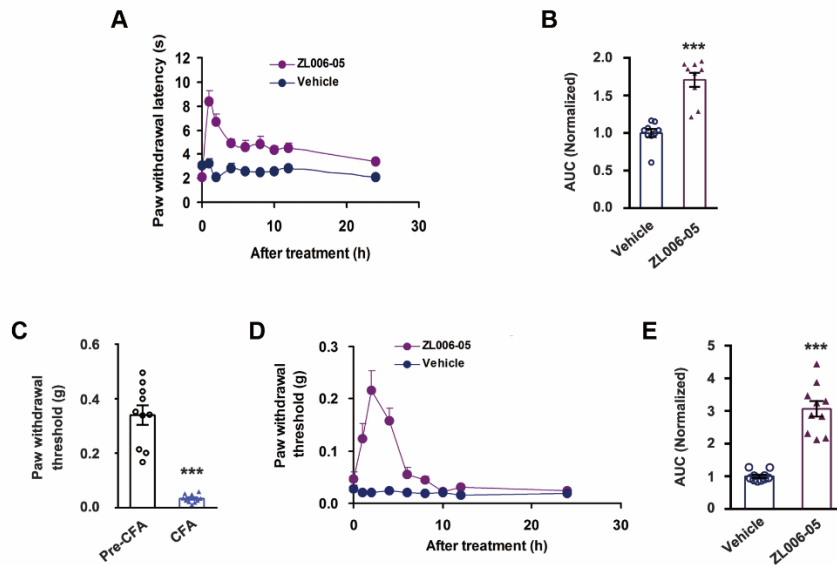


## Supplementary Material



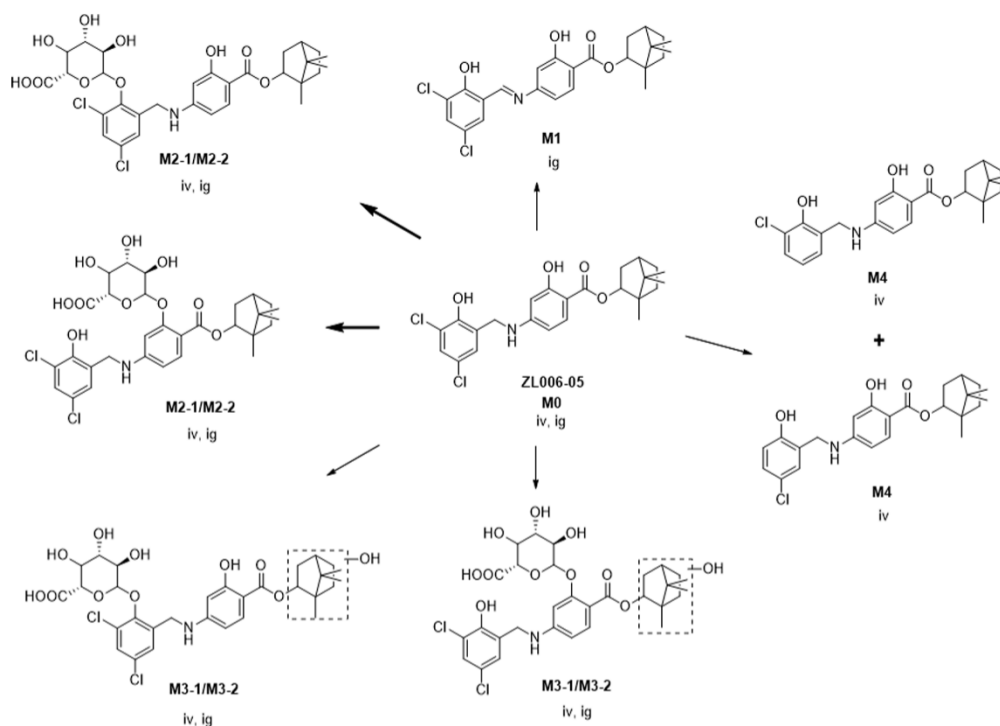
**Supplementary Figure 1. Effects of Diazepam and ZL006-05 on  $\alpha 3$ - and  $\alpha 5$ -containing GABAARs.**

(A) Dose/response plots of GABA-evoked currents in the HEK293 cells transiently expressing  $\alpha 3\beta 3\gamma 2$  GABA<sub>A</sub>Rs. (B) Representative recordings of GABA-evoked currents in the HEK293 cells transiently expressing  $\alpha 3\beta 3\gamma 2$  GABA<sub>A</sub>Rs (left) and Dose/response plots (right) of potentiation of GABA-evoked currents by diazepam or ZL006-05 ( $n = 8$ ). (C) Dose/response plots of GABA-evoked currents in the HEK293 cells transiently expressing  $\alpha 5\beta 3\gamma 2$  GABA<sub>A</sub>Rs. (D) Representative recordings of GABA-evoked currents in the HEK293 cells transiently expressing  $\alpha 5\beta 3\gamma 2$  GABA<sub>A</sub>Rs (left) and dose/response plots (right) of potentiation of GABA-evoked currents by diazepam or ZL006-05 ( $n = 8$ ).  $E_{max}$  and  $EC_{50}$  were not estimated because of the solubility limit of ZL006-05. All data are shown as mean  $\pm$  SEM.



**Supplementary Figure 2. Effect of ZL006-05 on SNL-induced thermal hyperalgesia and CFA-induced inflammatory pain in mice.**

(A) Time course of SNL-induced thermal hyperalgesia after treating with ZL006-05 (60 mg/kg, i.g.) in mice. Paw withdrawal latency response to thermal stimulation was detected at 0, 1, 2, 4, 6, 8, 10, 12 and 24 h after drug administration. (B) Areas under the curve of paw withdrawal latency 0-24 h after treatment calculated from (A) ( $F(1,16) = 43.07$ ,  $***p < 0.001$ , two-tailed  $t$ -test,  $n = 9$ ). (C) Paw withdrawal threshold response to mechanical stimulation before and 24 h after CFA injection in mice ( $F(1,18) = 72.12$ ,  $***p < 0.001$ , two-tailed  $t$ -test,  $n = 10$ ). (D) Time course of ZL006-05 on CFA-induced inflammatory pain. (E) Areas under the curve of paw withdrawal latency 0-24 h after treatment calculated from (D) ( $F(1,18) = 71.73$ ,  $***p < 0.001$ , two-tailed  $t$ -test,  $n = 10$ ). ZL006-05 (60 mg/kg, i.g.) was given 24 h after CFA injection and paw withdrawal threshold response to mechanical stimulation was detected at 0, 1, 2, 4, 6, 8, 10, 12 and 24 h after drug administration. All data are shown as mean  $\pm$  SEM.



**Supplementary Figure 3. Proposed metabolic pathways of ZL006-05 in rats.**

Three metabolites except parent drug were found in plasma after intravenous injection of ZL006-05, including M2-2 (glucuronide conjugation), M3-2 (Mono-oxidation & glucuronide conjugation) and M4 (dechlorination reduction); five metabolites except parent drug were found in plasma after oral administration of ZL006-05, including M1 (Oxidation by de-H<sub>2</sub>), M2-1 and M2-2 (glucuronide conjugation), M3-1 and M3-2 (Mono-oxidation & glucuronide conjugation). Based on the chromatogram of UPLC-UV, the main metabolite was parent drug (M0) in plasma after iv dosing, the main metabolite were parent drug (M0) and glucuronide conjugation (M2-2) in plasma after oral dosing, the proposed metabolic pathways of ZL006-05 in blood were summarized.

i.v.: intravenous injection; i.g.: oral administration.