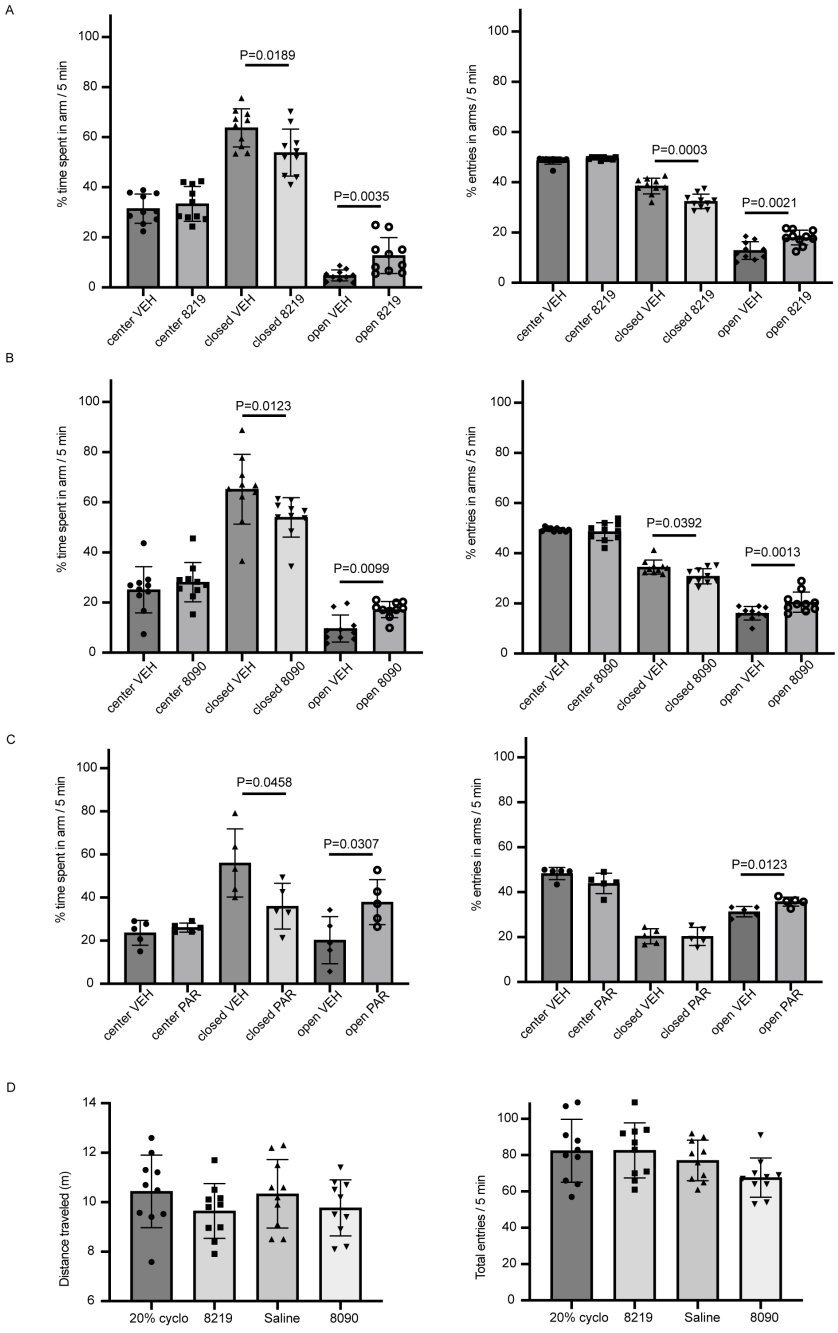
Data S1

Experiments related to anxiolytic effects, pharmacokinetic analysis, locomotor activities; and anxiety like behavior in learned helplessness for compounds ‘8090 and ’8219, related to Figure 5,6 and 7.

Contents

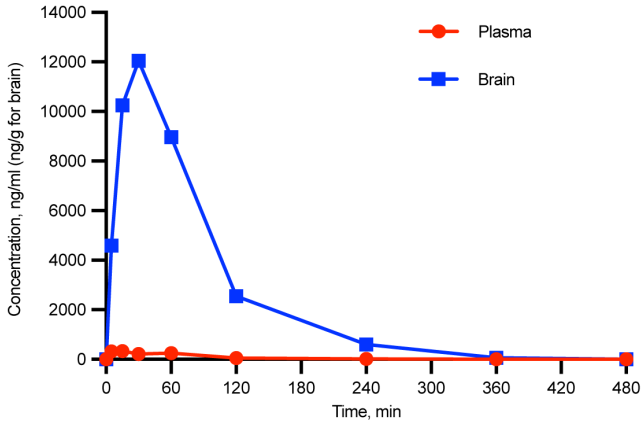
Figure S1. Anxiolytic effects of compounds 8219 and 8090 in the Elevated plus maze assay.



(A-B) Effect of chronic administration of ‘8219 (A; 10 mg/kg for 10 days; N=10) and ‘8090 (B; 10 mg/kg for 10 days; N=10) on the time spent (left) and the number of entries (right) into each arm (center, closed and open) of the elevated plus maze. **(C)** Effect of a single administration of paroxetine (PAR; 10 mg/kg; N=5) on the time spent (left) and the number of entries (right) into each arm (center, closed and open) of the elevated plus maze. **(D)** Effect of compounds ‘8219 (N=10) and ‘8090 (N=10) on the traveled distance (left) and the total number of entries (right) into all arms of the elevated plus maze. Data are presented as mean ± SEM. Significance levels were determined using an unpaired Student’s t-test and comparing the effect of compounds 8219 and 8090 to their own vehicle (20% cyclodextrin and saline respectively).

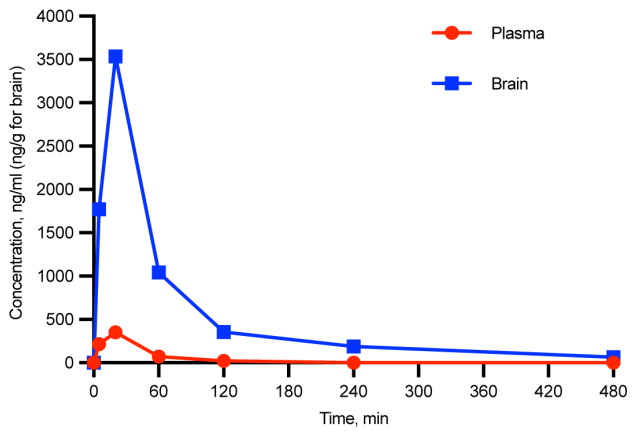
Figure S2. Pharmacokinetic analysis of ‘8090 and ‘8219.

A



Pharmacokinetic parameters	Brain	Plasma
$T_{1/2}$	44.3 min	47.2 min
C_{max}	12000 ng/g	332 ng/ml
AUC	1150000 ng*min/g	29000 ng*min/ml

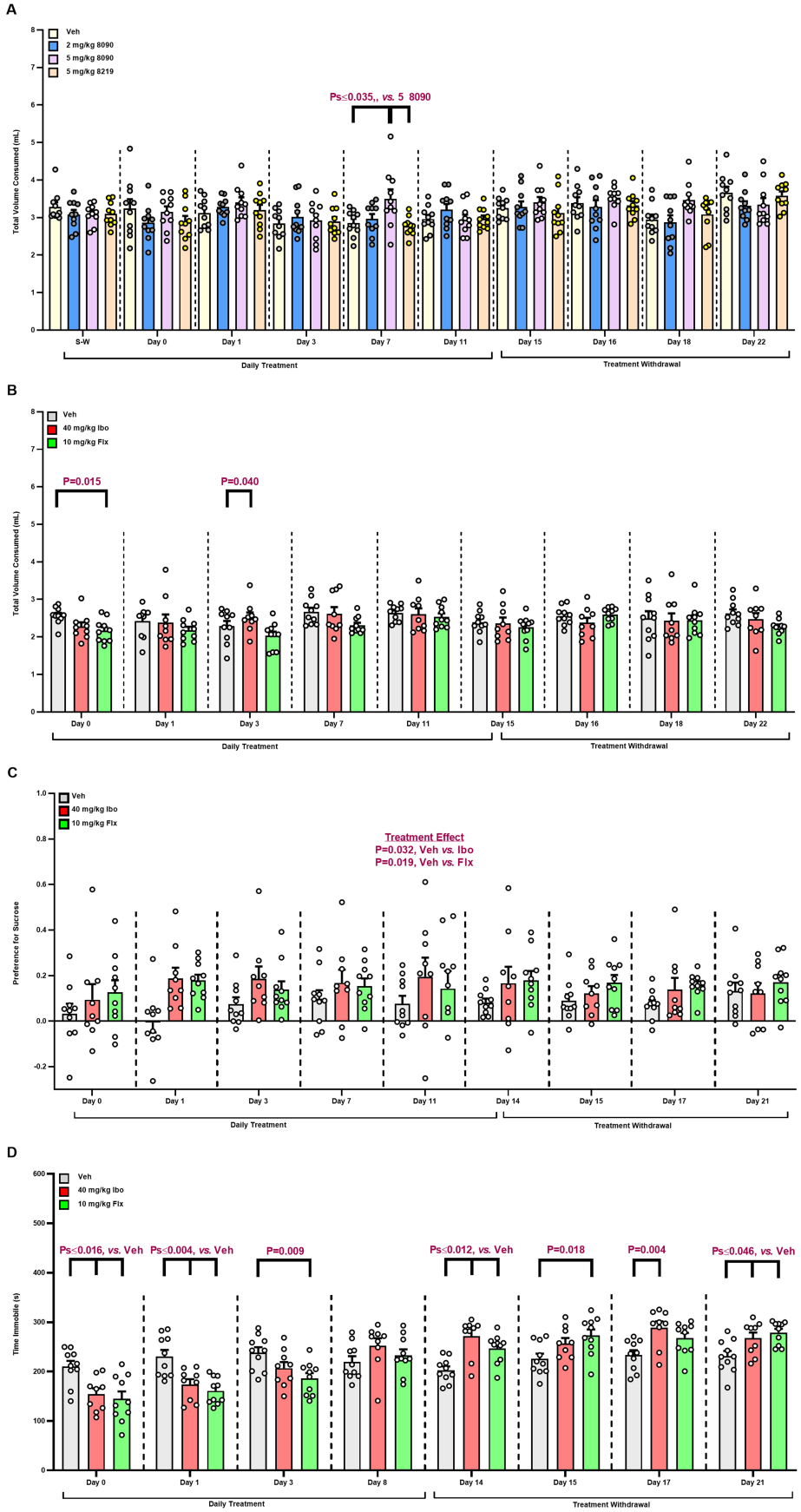
B



Pharmacokinetic parameters	Brain	Plasma
$T_{1/2}$	147 min	25.9 min
C_{max}	3530 ng/g	352 ng/ml
AUC	241000 ng*min/g	16900 ng*min/ml

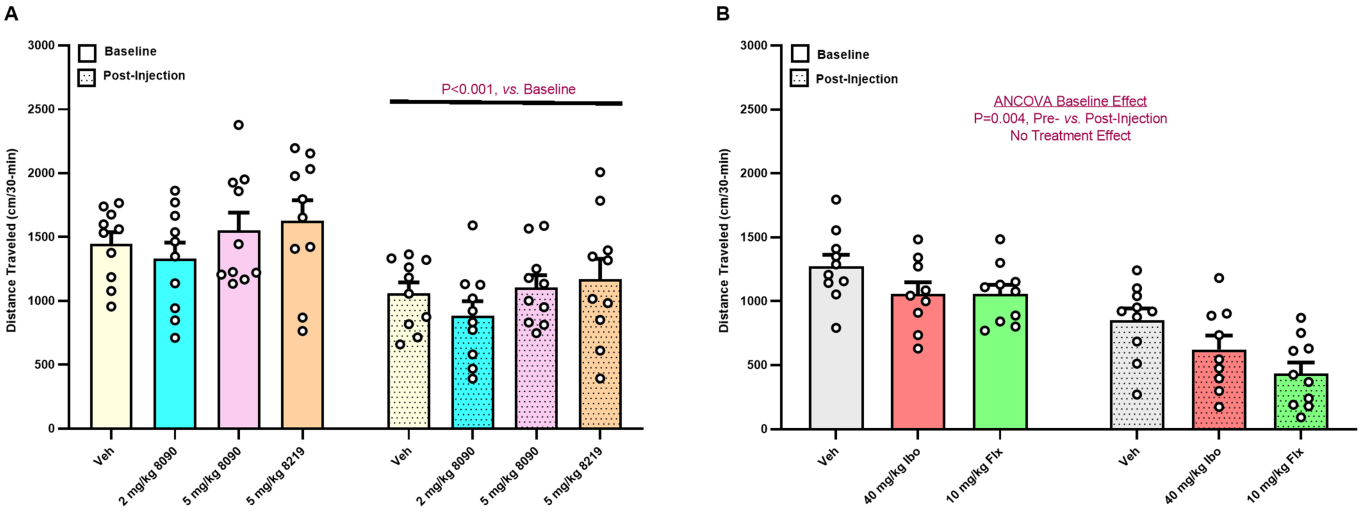
(A) Concentration-time curve for ‘8090 in mice following IP dosing at 10 mg/kg.
(B) Concentration-time curve for ‘8219 in mice following IP dosing at 10 mg/kg.

Figure S3. Total fluid consumed in response to the vehicle, ‘8090, or ‘8219, or the vehicle, ibogaine, or fluoxetine, related the sucrose preference test in Figure 6 and sucrose preference and tail suspension results in response to the vehicle, ibogaine, or fluoxetine.



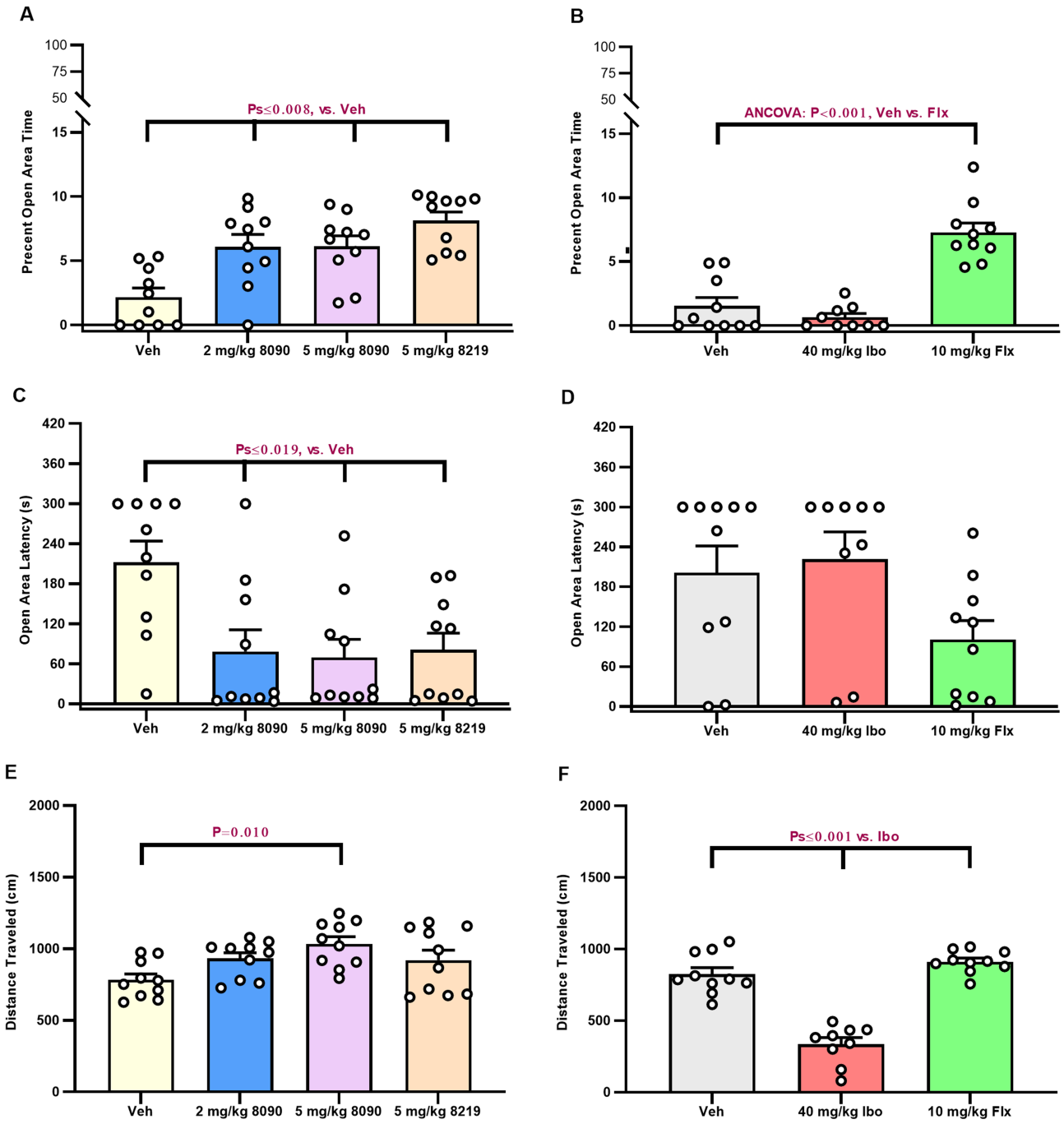
(A) Total volume consumed by learned helpless (LH) C57BL/6J mice treated chronically with the vehicle (Veh), ‘8090, or ‘8219. Mice were administered the Veh, 2 or 5 mg/kg ‘8090, or 5 mg/kg ‘8219 and tested over days for sucrose preference. N=10 mice mice/treatment. **(B)** The total volume consumed by LH C57BL/6J mice. Mice received the Veh, 40 mg/kg ibogaine (Ibo), or 10 mg/kg fluoxetine (Flx) and were tested over days for sucrose preference. N=9-10 mice/treatment. The primary statistics are found in Table S6. **(C)** Sucrose preference in learned helpless mice. **(D)** Tail suspension in LH mice. N=9-10 mice/treatment. The primary statistics reside in Table S6.

Figure S4. Locomotor activities in the open field in response to the vehicle, '8090, or '8219, or the vehicle, ibogaine, or fluoxetine.



(A) Locomotion in learned helpless (LH) C57BL/6J mice treated chronically with the vehicle (Veh), 2 or 5 mg/kg '8090, or 5 mg/kg '8219. Mice were tested on day 12. N=10 mice mice/treatment. **(B)** Locomotor activities in LH C57BL/6J mice that received the Veh, 40 mg/kg ibogaine (Ibo), or 10 mg/kg fluoxetine (Flx) and were tested on day 12. N=9-10 mice/treatment. The primary statistics are located in Table S6.

Figure S5. Anxiety-like behaviors in learned helplessness C57BL/6J mice given the vehicle, 8090, or ‘8219, or the vehicle, ibogaine, or fluoxetine.



Mice were treated chronically with the vehicle (Veh), 2 or 5 mg/kg ‘8090, or 5 mg/kg ‘8219; or with the Veh, 40 mg/kg ibogaine (Ibo), and 10 mg/kg fluoxetine (Flx). Thirty min after injection, mice were tested for 5 min in the elevated zero maze. **(A-B)** Percent time in the open areas. **(C-D)** Latency to enter the open areas. **(E-F)** Locomotor activities. N=10 mice/treatment for panels A, C, and E; or N=9-10 for panels B, D, and F. The primary statistics are in Table S6.