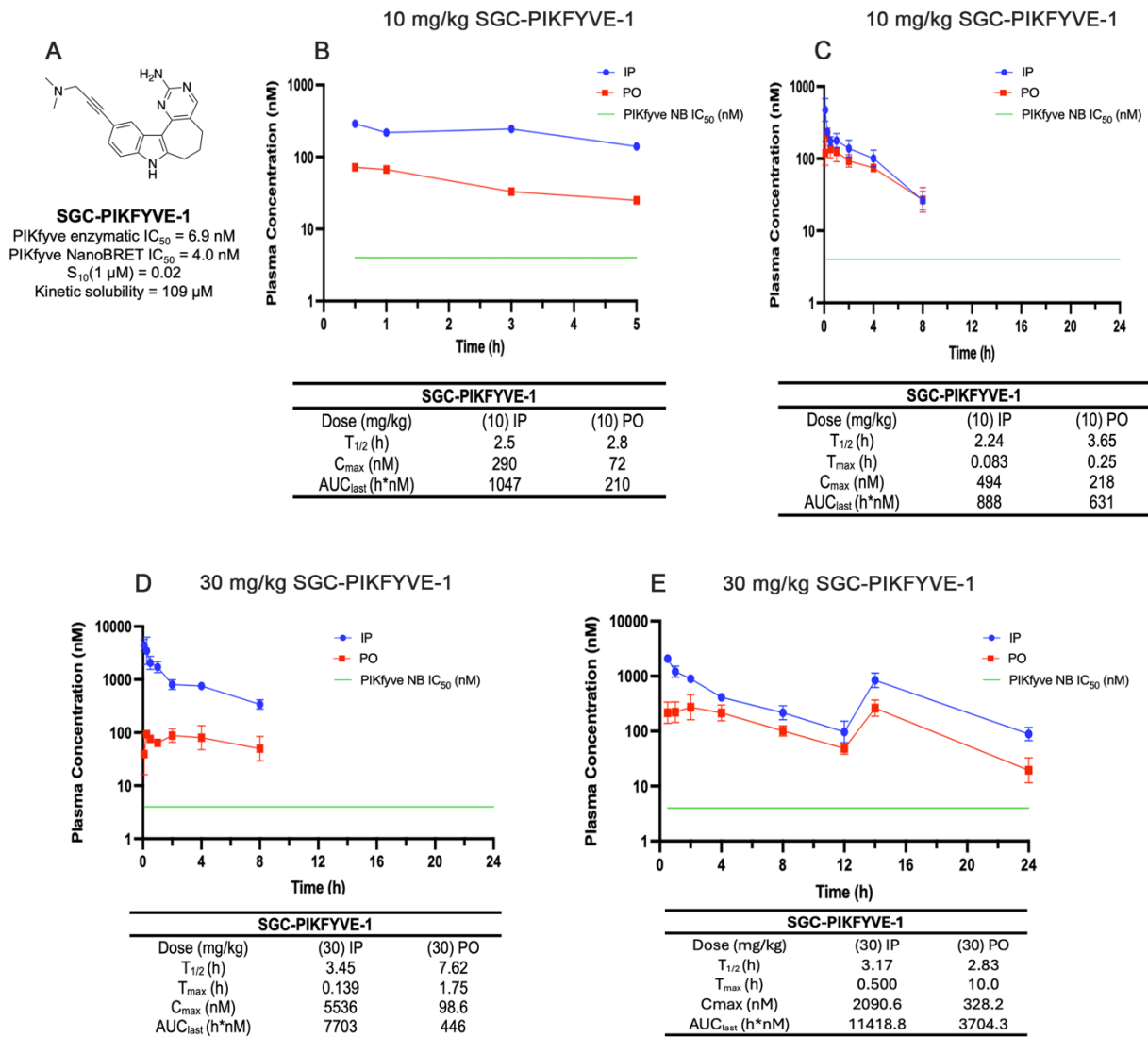


Table S1. All data for brain/ plasma measurements

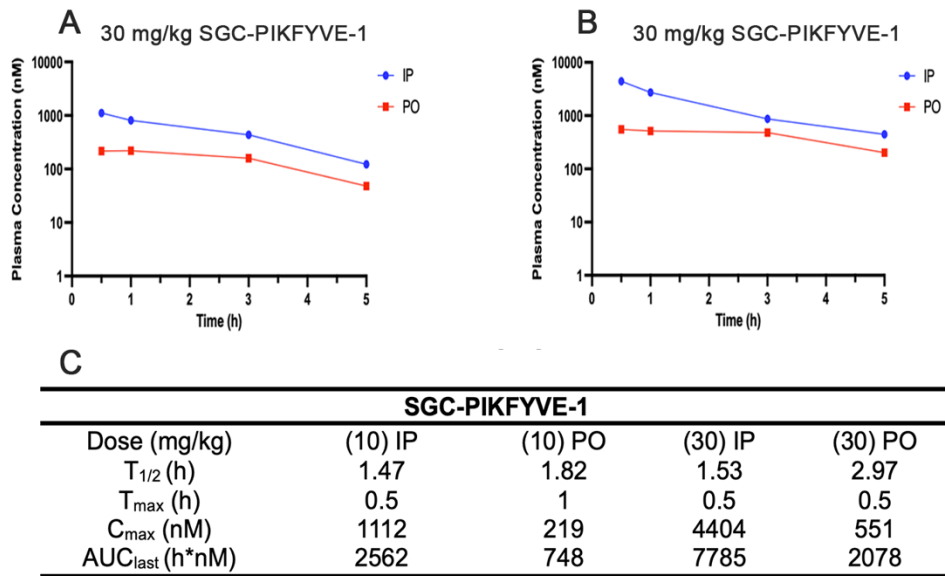
Ratio of SGC-PIKFYVE-1 between Brain and Plasma following IP Administration								
IP Dose 30 mg/kg								
Route	Time (h)	Animal ID	Brain (ng/g)	Plasma (ng/mL)	Ratio (Brain/Plasma)	Mean	SD	CV
IP	1	1	416	622	0.669	0.660	0.019	2.95
		2	516	809	0.638			
		3	444	659	0.674			

Table S2. Data corresponding with the mean plasma and brain concentrations of SGC-PIKFYVE-1

Ratio of SGC-PIKFYVE-1 between brain and plasma				
IP Dose 30 mg/kg				
Mean brain Concentration (ng/g)	Mean plasma Concentration (ng/ml)	Mean brain/plasma ratio	SD	CV
459	697	0.660	0.019	2.95



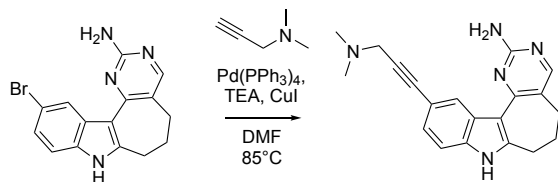
Supplementary Fig. 1. SGC-PIKFYVE-1 pharmacokinetic data in CD-1 mice. (A) Structure of SGC-PIKFYVE-1. (B) Snapshot pharmacokinetic data when SGC-PIKFYVE-1 was dosed at 10 mg/kg IP or PO over a 5-hour time course. (C) Snapshot pharmacokinetic data when SGC-PIKFYVE-1 was dosed at 10 mg/kg IP or PO over a 24-hour time course. (D) Snapshot pharmacokinetic data when SGC-PIKFYVE-1 was dosed at 30 mg/kg IP or PO over a 5-hour time course. (E) Data associated with the optimized dose of SGC-PIKFYVE-1 in CD-1 mice at 30 mg/kg BID.



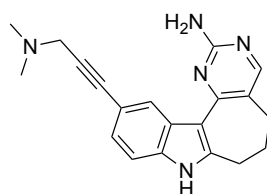
Supplementary Fig. 2. SGC-PIKFYVE-1 pharmacokinetic data in Balb/C mice. (A) Snapshot pharmacokinetic data when SGC-PIKFYVE-1 was dosed at 10 mg/kg IP or PO over a 5-hour time course. (B) Snapshot pharmacokinetic data when SGC-PIKFYVE-1 was dosed at 30 mg/kg IP or PO over a 5-hour time course. (C) Data generated when SGC-PIKFYVE-1 was dosed at 10 mg/kg or 30 mg/kg IP or PO.

Data S1. Synthetic procedure to prepare SGC-PIKFYVE, related to Fig. 1, 2, and 3.

Scheme S1. Route to prepare SGC-PIKFYVE-1, related to Figure 1



TEA: triethylamine; DMF: *N,N*-dimethylformamide



SGC-PIKFYVE-1

11-(3-(dimethylamino)prop-1-yn-1-yl)-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indol-2-amine (SGC-PIKFYVE-1): A mixture of 11-bromo-5,6,7,8-tetrahydropyrimido[4',5':3,4]cyclohepta[1,2-b]indol-2-amine (100 mg, 0.304 mmol), *N,N*-dimethylprop-2-yn-1-amine (101 mg, 1.22 mmol), and triethylamine (61.5 mg, 608 μmol) in *N,N*-dimethylformamide (2 mL) was degassed, followed by addition of Pd(PPh₃)₄ (35.1 mg, 30.4 μmol) and copper(I) iodide (5.79 mg, 30.4 μmol). The reaction mixture was heated to 85 °C and stirred overnight. After stirring overnight, the mixture was cooled to room temperature, diluted with ethyl acetate, and passed through a thin pad of celite. The filtrate was concentrated *in vacuo* and the crude residue was purified by preparative HPLC using a Phenomenex Luna 5u Phenyl-Hexyl 100Å column (75 x 30 mm, 5 μm) with a 90%/10% gradient of water/methanol as the mobile phase (flow rate = 70 mL/min) monitored at a wavelength of 254 nm to yield SGC-PIKFYVE-1 (21.6 mg, 21% yield) as a light yellow solid. The analytical data for SGC-PIKFYVE-1 matches that previously reported (Drewry et al., 2022): ¹H NMR (400 MHz, methanol-*d*₄) δ 8.97 (s, 1H), 7.84 (s, 1H), 7.43 – 7.37 (m, 2H), 4.32 (s, 2H), 3.35 (t, *J* = 6.5 Hz, 2H), 3.05 (s, 6H), 2.85 – 2.82 (m, 2H), 2.16 – 2.10 (m, 2H). Purity (LC–MS): 100%.

