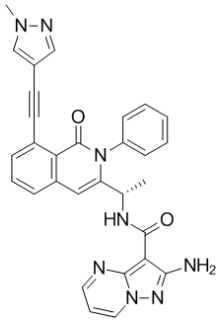
Data Sheet

Product Name:	IPI549
Cat. No.:	HY-100716
CAS No.:	1693758-51-8
Molecular Formula:	C30H24N8O2
Molecular Weight:	528.56
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO: 15 mg/mL



BIOLOGICAL ACTIVITY:

IPI549 is a potent and selective PI3Kγ Inhibitor with an IC50 of 16 nM.
IC50 & Target: IC50: 16 nM (PI3Kγ), 3.2 μM (PI3Kα), 3.5 μM (PI3Kβ), >8.4 μM (PI3Kδ)^[1]
In Vitro: IPI–549 inhibits PI3Kγ with IC50 of 16 nM, with >100–fold selectivity over other lipid and protein kinases (PI3Kα IC50=3.2 μM, PI3Kβ IC50=3.5 μM, PI3Kδ IC50>8.4 μM). IPI549 is evaluated for activity across all Class I PI3K isoforms. The binding affinity of IPI549 for PI3K–γ is determined by measuring the individual rates constants and for PI3K–α, β and δ using equilibrium fluorescent titration. IPI549 is found to be a remarkably tight binder to PI3Kγ with a Kd of 290 pM and >58–fold weaker affinity for other Class I PI3K isoforms (PI3Kα Kd=17 nM, PI3Kβ Kd=82 nM, PI3Kδ Kd=23 M). In PI3K–α, –β, –γ, and –δ dependent cellular phospho–AKT assays, IPI549 demonstrates excellent PI3K–γ potency (IC50=1.2 nM) and selectivity against other Class I PI3K isoforms (>146–fold). Cellular IC50s for Class I PI3Kα (250 nM), PI3Kβ (240 nM), PI3Kγ (1.2 nM), PI3Kδ (180 nM) are determined in SKOV–3, 786–O, RAW 264.7, and RAJI cells, respectively, by monitoring inhibition of pAKT S473 by ELISA. Furthermore, IPI549 dose dependently inhibits PI3Kγ dependent bone marrow–derived macrophage (BMDM) migration. IPI549 is also found to be selective against a panel of 80 GPCRs, ion channels, and transporters at 10 μM^[1].
In Vivo: IPI–549 demonstrates favorable pharmacokinetic properties and robust inhibition of PI3K–γ mediated neutrophil migration. In vivo (mice, rats, dog, and monkeys), IPI–549 has excellent oral bioavailability, low clearance, and distributed into tissues with a mean volume of distribution of 1.2 L/kg. Overall, IPI–549 has a favorable pharmacokinetic profile to allow potent and selective inhibition of PI3K–γ in vivo. The t1/2 of IPI–549 for mouse, rat, dog and monkey is 3.2, 4.4, 6.7 and 4.3 h, respectively. IPI–549 significantly reduces neutrophil migration in a dose dependent manner in this model when administered orally at all of the tested doses^[1].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: IPI–549 is dissolved at 5% 1–Methyl–2–pyrrolidinone.^[2]C57BL/6J and Balb/c mice (6 to 8 weeks old) are used in this study. On day 0 of the experiments, tumor cells are injected intradermally (i.d.) in the right flank. IPI–549 is administered by oral gavage once a day at 15 mg/kg. Treatment is initiated on day 7 ending on day 21 post tumor implant. Control groups receive vehicle (5% NMP, 95% PEG). Tumors are measured every second or third day with a caliper, and the volume (length×width×height) is calculated. Animals are euthanized for signs of distress or when the total tumor volume reaches 2500 mm³. Finally, Tumors are isolated, and frozen until needed^[2].

References:

[1]. Evans CA, et al. Discovery of a Selective Phosphoinositide–3–Kinase (PI3K)–γ Inhibitor (IPI–549) as an Immuno–Oncology Clinical Candidate. ACS Med Chem Lett. 2016 Jul 22;7(9):862–7.
 [2]. De Henau O, et al. Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. Nature. 2016 Nov 17;539(7629):443–447.

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