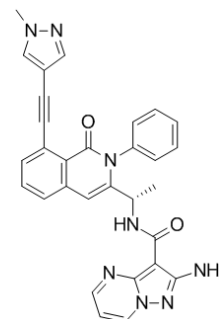


Data Sheet

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 PI3K γ Inhibitor with an IC₅₀ of 16 nM.

IC₅₀ & Target: IC₅₀: 16 nM (PI3K γ), 3.2 μ M (PI3K α), 3.5 μ M (PI3K β), >8.4 μ M (PI3K δ)^[1]

In Vitro: IPI-549 inhibits PI3K γ with IC₅₀ of 16 nM, with >100-fold selectivity over other lipid and protein kinases (PI3K α IC₅₀=3.2 μ M, PI3K β IC₅₀=3.5 μ M, PI3K δ IC₅₀>8.4 μ M). 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 PI3K γ with a K_d of 290 pM and >58-fold weaker affinity for other Class I PI3K isoforms (PI3K α K_d=17 nM, PI3K β K_d=82 nM, PI3K δ K_d=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 PI3K α (250 nM), PI3K β (240 nM), PI3K γ (1.2 nM), PI3K δ (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 PI3K γ 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 μ M^[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 t_{1/2} 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 PI3K γ in myeloid cells. Nature. 2016 Nov 17;539(7629):443-447.

Caution: Product has not been fully validated for medical applications. For research use only.

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