上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：IPI549
产品别名：IPI549

生物活性：

Description	IPI549 is a potent and selective PI3Kγ inhibitor with an IC_{50} of 16 nM.		
IC_{50} & Target	PI3Kα	PI3Kα	PI3Kγ
	3.2 μM (IC_{50})	3.2 μM (IC_{50})	16 nM (IC_{50})
In Vitro	IPI-549 inhibits PI3Kγ with IC_{50} of 16 nM, with >100-fold selectivity over other lipid and protein kinases (PI3Kα IC_{50}=3.2 μM, PI3Kβ IC_{50}=3.5 μM, PI3Kδ IC_{50}>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 K_d of 290 pM and >58-fold weaker affinity for other Class I PI3K isoforms (PI3Kα K_d=17 nM, PI3Kβ K_d=82 nM, PI3Kδ K_d=23 M). In PI3K-α, -β, -γ, and -δ dependent cellular phospho-AKT assays, IPI549 demonstrates excellent PI3K-γ potency (IC_{50}=1.2 nM) and selectivity against other Class I PI3K isoforms (>146-fold). Cellular IC_{50}s 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 $t_{1/2}$ 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].		

In Vitro:

DMSO : 15 mg/mL (28.38 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8919 mL	9.4597 mL	18.9193 mL
	5 mM	0.3784 mL	1.8919 mL	3.7839 mL
	10 mM	0.1892 mL	0.9460 mL	1.8919 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现

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邮箱：shyysw@sina.com

Solvent&Solubility	用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (4.73 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.73 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.73 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.73 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Animal Administration	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 mm^3. 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.