产品名称：CH5132799
产品别名：CH5132799

生物活性：

Description

CH5132799 is a selective class I PI3K inhibitor. CH5132799 inhibits class I PI3Ks, particularly PI3Kα, with an IC_{50} of 14 nM.

IC_{50} & Target

PI3Kα	PI3Kα-H1047R	PI3Kα-E545K	PI3Kα-E542K	PI3Kγ	PI3Kβ
14 nM (IC_{50})	5.6 nM (IC_{50})	6.7 nM (IC_{50})	6.7 nM (IC_{50})	36 nM (IC_{50})	120 nM (IC_{50})
PI3Kδ	PI3KC2β	mTOR			
500 nM (IC_{50})	5.3 μM (IC_{50})	1.6 μM (IC_{50})			

In Vitro

CH5132799 is a selective class I PI3K inhibitor with potent antitumor activity against tumors harboring the PIK3CA mutations. CH5132799 selectively inhibits class I PI3Ks and PI3Kα mutants in in vitro kinase assays. CH5132799 inhibits class I PI3Ks, particularly PI3Kα, with an IC50 of 14 nM. IC50 values against class II PI3Ks (C2α and C2β), a class III PI3K (Vps34), and a class IV PI3K (mTOR) are more than 100-fold higher than that against PI3Kα. Interestingly, slightly lower IC50 values are observed against PI3Kα with oncogenic mutations E542K, E545K, and H1047R than against wild-type (WT) PI3Kα. In an analysis of cocrystal structure with PI3Kγ (PBD ID: 3APC), CH5132799 is shown to interact with ATP-binding sites of the enzyme, suggesting an ATP competitive mode of inhibition. No significant inhibitory activities of CH5132799 are observed against a representative panel of 26 protein kinases, including RTKs, nonreceptor tyrosine kinases, and serine/threonine kinases. These data indicate that CH5132799 is a selective class I PI3K inhibitor, especially against PI3Kα and its mutants. CH5132799 shows superior antiproliferative activity across the 4 tumor types, with 75% (45/60) of lines having an IC50 below 1 μM and 38% (23/60) of lines having an IC50 below 0.3 μM[1].

In Vivo

Mice bearing BT-474 tumors (n=14) are orally administered 50 mg/kg of Everolimus on a daily basis for 31 days and then randomized. After randomization, the mice are orally administered 50 mg/kg of Everolimus (n=4) and 12.5 mg/kg (n=5), and 25 mg/kg (n=5) of CH5132799 on a daily basis for 7 days. C, the vehicle-, Everolimus, and CH5132799-treated (25 mg/kg) tumors are resected at 4 hours after terminal administration in B, lysed, and analyzed by Western blotting. CH5132799 administration leads to a remarkable regression in a dose-dependent manner of the tumors regrown after the long-term Everolimus treatment. The tumors are resected at the end of treatment and analyzed by Western blotting with respect to PI3K pathway inhibition. CH5132799 suppresses various effectors in the PI3K pathway, including Akt, FoxO1, S6K, S6, and 4E-BP1, whereas Everolimus inhibits only phosphorylation of S6K and S6, both downstream effectors of mTORC1[1].

Solvent&Solubility

In Vitro:

DMSO : 4.55 mg/mL (12.06 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6496 mL	13.2478 mL	26.4957 mL
	5 mM	0.5299 mL	2.6496 mL	5.2991 mL
	10 mM	0.2650 mL	1.3248 mL	2.6496 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→ 90% corn oil Solubility: ≥ 0.46 mg/mL (1.22 mM); Clear solution 此方案可获得 ≥ 0.46 mg/mL (1.22 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 4.6 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Tanaka H, et al. The selective class I PI3K inhibitor CH5132799 targets human cancers harboring oncogenic PIK3CA mutations. Clin Cancer Res, 2011, 17(10), 3272-3281. [2]. Ohwada J, et al. Discovery and biological activity of a novel class I PI3K inhibitor, CH5132799. Bioorg Med Chem Leff, 2011, 21(6), 1767-1772.

实验参考：

Cell Assay	The cell lines are added to the wells of 96-well plates containing 0.076 to 10,000 nM CH5132799 and incubated at 37°C. After 4 days of incubation, Cell Counting Kit-8 solution is added and, after incubation for several more hours, absorbance at 450 nm is measured with Microplate-Reader iMark. The antiproliferative activity is calculated. The IC50 values are calculated[1].
Animal Administration	Mice[1]. Female BALB-nu/nu mice (CAnN.Cg-Foxn1/CrlCrlj nu/nu) are used. A total of 4×10^6 to 1.2×10^7 cells are suspended in 100 to 200 μL serum-free culture medium and injected subcutaneously into the right flank of the mice. Tumor size is measured by using a gauge twice per week, and tumor volume (TV) is calculated. Once the tumors reach a volume of approximately 200 to 300 mm^3, animals are randomized into groups (n=4 or 5 in each group) and treatment is initiated. CH5132799 and Everolimus are orally administered once a day and Trastuzumab is intravenously injected once a week.
References	[1]. Tanaka H, et al. The selective class I PI3K inhibitor CH5132799 targets human cancers harboring oncogenic PIK3CA mutations. Clin Cancer Res, 2011, 17(10), 3272-3281. [2]. Ohwada J, et al. Discovery and biological activity of a novel class I PI3K inhibitor, CH5132799. Bioorg Med Chem Leff, 2011, 21(6), 1767-1772.