Izorlisib

Cat. No.: HY-15466

CAS No.: 1007207-67-1

Molecular Formula: $C_{15}H_{19}N_7O_3S$

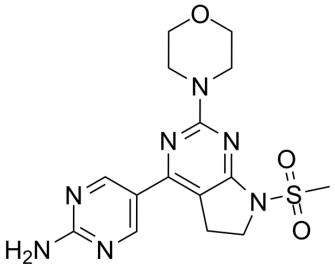
Molecular Weight: 377.42

Target: PI3K

Pathway: PI3K/Akt/mTOR

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

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

Preparing Stock Solutions	Mass / Solvent / 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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.46 mg/mL (1.22 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

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

IC_{50} & Target

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

In Vitro	Izorlisib (CH5132799) is a selective class I PI3K inhibitor with potent antitumor activity against tumors harboring the PIK3CA mutations. Izorlisib selectively inhibits class I PI3Ks and PI3Kα mutants in in vitro kinase assays. Izorlisib inhibits class I PI3Ks, particularly PI3Kα, with an IC_{50} of 14 nM. IC_{50} 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 IC_{50} 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), Izorlisib is shown to interact with ATP-binding sites of the enzyme, suggesting an ATP competitive mode of inhibition. No significant inhibitory activities of Izorlisib are observed against a representative panel of 26 protein kinases, including RTKs, nonreceptor tyrosine kinases, and serine/threonine kinases. These data indicate that Izorlisib is a selective class I PI3K inhibitor, especially against PI3Kα and its mutants. Izorlisib shows superior antiproliferative activity across the 4 tumor types, with 75% (45/60) of lines having an IC_{50} below 1 μM and 38% (23/60) of lines having an IC_{50} below 0.3 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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 Izorlisib 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. Izorlisib 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. Izorlisib 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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 IC_{50} values are calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Sci Rep. 2022 Apr 12;12(1):6090.
- Molecules. 2020 Apr 23;25(8):1980.

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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.

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