ISRIB (trans-isomer)

Cat. No.: HY-12495

CAS No.: 1597403-47-8

Molecular Formula: $C_{22}H_{24}Cl_2N_2O_4$

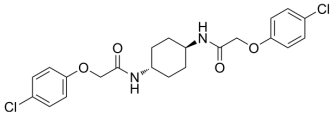
Molecular Weight: 451.34

Target: PERK; Autophagy; Apoptosis

Pathway: Cell Cycle/DNA Damage; Autophagy; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 4.55 mg/mL (10.08 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2156 mL	11.0781 mL	22.1562 mL
5 mM	0.4431 mL	2.2156 mL	4.4312 mL
10 mM	0.2216 mL	1.1078 mL	2.2156 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 0.83 mg/mL (1.84 mM); Suspended solution; Need ultrasonic and warming and heat to 60°C

BIOLOGICAL ACTIVITY

Description

ISRIB (trans-isomer) is a potent inhibitor of PERK with an IC_{50} of 5 nM. ISRIB potently reverses the effects of eIF2α phosphorylation (IC_{50}=5 nM).

IC_{50} & Target

PERK
5 nM (IC_{50})

In Vitro

Trans-ISRIB is 100-fold more potent (IC_{50}=5 nM) than cis-ISRIB (IC_{50}= 600 nM), indicating that the compound's interaction with its cellular target is stereospecific. ISRIB reduces the viability of cells subjected to PERK-activation by chronic endoplasmic reticulum stress[1]. ISRIB substantially reverses the translational effects elicited by phosphorylation of eIF2α and induces no major changes in translation or mRNA levels in unstressed cells. eIF2α phosphorylation-induced stress granule (SG) formation is blocked by ISRIB[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	ISRIB increases long-term memory in rodents. ISRIB-treated mice display significant enhancement in spatial and fear-associated learning. ISRIB displays a half-life in plasma of 8 hr and readily crossed the blood-brain barrier, quickly equilibrating with the central nervous system[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	U2OS cells are plated on 96-well plates and left to recover overnight. Cells are treated with either with 2 μg/ml tunicamycin or 100 nM thapsigargin in the presence or absence of 100 nM ISRIB or with ISRIB alone for the indicated and the level of eIF2 α phosphorylation is determined[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Intra-peritoneal (ip) route of administration is performed on 6-7 wk old female CD-1 mice. Animals receives a single, 5 mg/kg dose in groups of three mice/compound/route of administration. ISRIB is dissolved in DMSO then diluted 1:1 in Super-Refined PEG 400. Blood (80 μL) is collected from the saphenous vein at intervals post-dosing (20 min, 1 hr, 3 hr, 8 hr, 24 hr) in EDTA containing collection tubes and plasma is prepared for analysis. Compounds are detected by time-of-flight mass spectroscopy[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2022 Sep 1;185(18):3356-3374.e22.
- Nat Commun. 2022 Nov 10;13(1):6796.
- Adv Sci (Weinh). 2023 May 11;e2205949.
- Biomaterials. 2021, 120757.
- Pharmacol Res. 2022 Aug;182:106285.

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REFERENCES

[1]. Sidrauski C, et al. Pharmacological brake-release of mRNA translation enhances cognitive memory. Elife. 2013 May 28;2:e00498.

[2]. Sidrauski C, et al. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stressgranule assembly. Elife. 2015 Feb 26;4. doi: 10.7554/eLife.05033.

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