GSK2656157

Cat. No.: HY-13820

CAS No.: 1337532-29-2

Molecular Formula: $C_{23}H_{21}FN_6O$

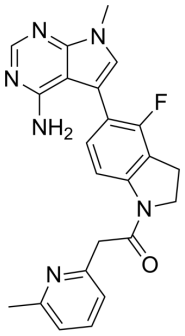
Molecular Weight: 416.45

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	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

1M HCl : 100 mg/mL (240.12 mM; ultrasonic and adjust pH to 1 with HCl)

DMSO : 8.33 mg/mL (20.00 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4012 mL	12.0062 mL	24.0125 mL
5 mM	0.4802 mL	2.4012 mL	4.8025 mL
10 mM	0.2401 mL	1.2006 mL	2.4012 mL

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

In Vivo

1. Add each solvent one by one: 0.5% HPMC >> 0.2%Tween80
   Solubility: 4.17 mg/mL (10.01 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK2656157 is a selective and ATP-competitive inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) with an IC_{50} of 0.9 nM.

IC_{50} & Target				
	EIF2AK3 (PERK)	EIF2AK1 (HRI)	BRK	EIF2AK2 (PKR)

	0.9 nM (IC_{50})	460 nM (IC_{50})	905 nM (IC_{50})	905 nM (IC_{50})
	MEKK3 954 nM (IC_{50})	Aurora B 1259 nM (IC_{50})	KHS 1764 nM (IC_{50})	LCK 2344 nM (IC_{50})
	MLK2 2796 nM (IC_{50})	MEKK3 2847 nM (IC_{50})	ALK5 3020 nM (IC_{50})	MLCK2 3039 nM (IC_{50})
	EIF2AK4(GCN2) 3162 nM (IC_{50})	c-MER 3431 nM (IC_{50})	PI3Kγ 3802 nM (IC_{50})	WNK3 5951 nM (IC_{50})
	LRRK2 6918 nM (IC_{50})	ROCK1 7244 nM (IC_{50})	MSK1 8985 nM (IC_{50})	NEK1 9807 nM (IC_{50})
	AXL 9808 nM (IC_{50})	JAK2 24547 nM (IC_{50})		

In Vitro

GSK2656157 results in inhibition of PERK activation as well as decreases in the downstream substrates, phospho-eIF2α, ATF4, and CHOP with an IC_{50}?in the range of 10-30 nM in the BxPC3 pancreatic tumor cell line. Cells that are exposed to 1 μM GSK2656157 before UPR induction are able to block this effect on de novo protein synthesis[1].
GSK2656157 causes the activation of another eIF2α kinase to compensate for the loss of PERK activity in HT1080 cells. GSK2656157 inhibits the growth of the HT1080 cells[2].
GSK2656157 inhibits LPS-induced IL-1β production, LPS-induced Caspase 1 activation and LPS-induced eIF-2α phosphorylation, but does not inhibit LPS-induced TNF-α production[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

GSK2656157 (1.5-150 mg/kg, p.o.) results in dose-dependent inhibition of phospho-PERK Thr980, with more than 80% inhibition at 50 and 150 mg/kg. GSK2656157 (50-150 mg/kg, p.o.) results in dose-dependent inhibition of tumor growth in human tumor xenograft models[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

BxPC3 (human pancreatic adenocarcinoma) or LL/2 (murine lung carcinoma) cells are treated with DMSO or various concentrations of GSK2656157 for 1 hour, followed by addition of 5 μg/mL tunicamycin or 1 μM thapsigargin for an additional 6 hours to induce endoplasmic reticulum-stress. Cells are lysed in cold radioimmunoprecipitation assay (RIPA) buffer [150 mM NaCl, 50 mM Tris-Cl pH 7.5, 0.25% sodium deoxycholate, 1% NP-40, protease inhibitors, and 100 mM sodium orthovanadate]. Clarified lysates are resolved by SDS-PAGE and transferred to nitrocellulose membrane using NuPAGE system. Blots are incubated with antibodies to total PERK, p-eIF-2α Ser51, total eIF-2α, ATF4, and CHOP. IRDye700DX-labeled goat anti-mouse immunoglobulin G (IgG), IRDye800-CW donkey anti-goat IgG, and IRDye800-CW goat anti-rabbit IgG are used as secondary antibodies. Proteins are detected on the Odyssey Infrared Imager.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

BxPC3 cells are treated with DMSO or 1 μM GSK2656157 for 1 hour before adding 5 μg/mL tunicamycin for an additional hour. Cells are metabolically labeled with 125 μCi ^{35}S-methionine for the subsequent 1 hour. Cells are lysed in cold RIPA buffer and lysates are resolved by SDS-PAGE, followed by exposure to a phosphorimager screen. Control cells are also pretreated with 100 μM cyclohexamide for 1 hour followed by metabolic labeling. Radioisotope incorporation is quantitated using ImageQuant 5.2 software.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration [1]

Exponentially growing HPAC (5×10^6 cells/mouse), Capan-2 (10×10^6 cells/mouse), or NCI-H929 ($1\times^6$ cells/mouse) cells are implanted subcutaneously into the right flank of 8- to 12-week-old female SCID mice. Similarly, 10×10^6 BxPC3 cells per

mouse are implanted in female nude mice. When the tumors reached approximately 200 mm3 in size, the animals are weighed, and block randomized according to tumor size into treatment groups of 8 mice each. Mice are dosed orally with the formulating vehicle or GSK2656157. Mice are weighed and tumors measured by calipers twice weekly. Tumor volumes are calculated. The percentage of tumor growth inhibition is calculated on each day of tumor measurement using the formula: 100× [1 − (average growth of the compound-treated tumors/average growth of vehicle-treated control tumors)].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Discov. 2021 Oct 26;7(1):98.
- Cell Metab. 2022 Mar 8;S1550-4131(22)00054-7.
- Nat Commun. 2022 Oct 16;13(1):6108.
- Mol Cell. 2023 Aug 30;S1097-2765(23)00643-3.
- Sci Adv. 2021 Jun 16;7(25):eabf8577.

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REFERENCES

[1]. Atkins C, et al. Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res. 2013 Mar 15;73(6):1993-2002.

[2]. Krishnamoorthy J, et al. Evidence for eIF2α phosphorylation-independent effects of GSK2656157, a novel catalytic inhibitor of PERK with clinical implications. Cell Cycle. 2014 Mar 1;13(5):801-6.

[3]. Ando T, et al. GSK2656157, a PERK inhibitor, reduced LPS-induced IL-1β production through inhibiting Caspase 1 activation in macrophage-like J774.1 cells. Immunopharmacol Immunotoxicol. 2016 Aug;38(4):298-302.

[4]. Zhao Q, et al. Thioredoxin-interacting protein links endoplasmic reticulum stress to inflammatory brain injury and apoptosis after subarachnoid haemorrhage. J Neuroinflammation. 2017 May 11;14(1):104.

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