产品名称：**GSK2656157**
产品别名：**GSK2656157**

生物活性：

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)	MEKK3
0.9 nM (IC_{50})	460 nM (IC_{50})	905 nM (IC_{50})	905 nM (IC_{50})	954 nM (IC_{50})
Aurora B	KHS	LCK	MLK2	MEKK3
1259 nM (IC_{50})	1764 nM (IC_{50})	2344 nM (IC_{50})	2796 nM (IC_{50})	2847 nM (IC_{50})
ALK5	MLCK2	EIF2AK4(GCN2)	c-MER	PI3Kγ
3020 nM (IC_{50})	3039 nM (IC_{50})	3162 nM (IC_{50})	3431 nM (IC_{50})	3802 nM (IC_{50})
WNK3	LRRK2	ROCK1	MSK1	NEK1
5951 nM (IC_{50})	6918 nM (IC_{50})	7244 nM (IC_{50})	8985 nM (IC_{50})	9807 nM (IC_{50})
AXL	JAK2			
9808 nM (IC_{50})	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 IC50 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].
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].

Solvent&Solubility

In Vitro:

DMSO : ≥ 41 mg/mL (98.45 mM)

* "≥" means soluble, but saturation unknown.

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

*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→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution 此方案可获得 ≥ 0.5 mg/mL (1.20 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 5.0 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% (20% SBE-β-CD in saline) Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution 此方案可获得 ≥ 0.5 mg/mL (1.20 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 5.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 0.5 mg/mL (1.20 mM); Clear solution 此方案可获得 ≥ 0.5 mg/mL (1.20 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 5.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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. [1]
Animal Administration	Exponentially growing HPAC (5×10^6 cells/mouse), Capan-2 (10×10^6 cells/mouse), or NCI-H929 (1×^{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)]. [1]
Kinase Assay	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. [1]
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.