

Product Data Sheet

Product Name: GSK2656157

Cat. No.: GC11068

Chemical Properties

Cas. No. 1337532-29-2

Chemical Name 1-(5-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-4-fluoroindolin-1-yl)-2-(6-methylpyridin-2-yl)ethanone

SMILES NC1=NC=NC2=C1C(C3=CC=C4C(CCN4C(CC5=NC(C)=CC=C5)=O)=C3F)=CN2C

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

M.Wt 416.45

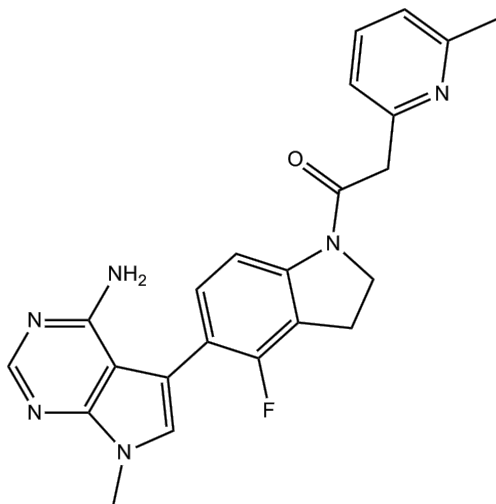
Solubility $\geq 20.8225\text{mg/mL}$ in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Kinase experiment [1,2]:

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Inhibitory potency of GSK2656157 is measured using recombinant GST-PERK (536-1116 amino acids) with 6-His-full-length human eIF2 α as a substrate. To evaluate kinase selectivity, the compound is profiled against a set of 27 kinases internally at GSK, in addition to a broader panel of 300 kinases. (1) Reactions are performed in black 384-well polystyrene low volume plates in a final volume of 10 μ L. The reaction volume contains, in final concentrations, 10mM HEPES, 5mM MgCl₂, 5 μ M ATP, 1mM DTT, 2mM CHAPS, 40nM biotinylated 6-His-eIF2 α , and 0.4nM GST-PERK.

Preparation Method

(2) Compounds under analysis are dissolved in DMSO to 1.0mM and serially diluted 1-3 with DMSO through 11 dilutions.

(3) GST-PERK solution is added to assay plates containing compounds and preincubated for 30min at room temperature. The reaction is initiated by the addition of ATP and eIF2 α substrate solution. After 1h of incubation, the quench solution is added. The plates are covered for 2h at room temperature prior to determination of signal.

Reaction Conditions

1h and additional 2h

Applications

GSK2656157 is a potent and selective PERK inhibitor with an IC₅₀ of 0.9nM. It shows significant activity in a broad kinase panel, inhibiting 44 kinases by >50% and 15 by >80% at 10 μ M.

Cell experiment [1]:

Cell lines

BxPC3 (human pancreatic adenocarcinoma) cells

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Preparation Method BxPC3 cells were treated with various concentrations of GSK2656157 (0, 0.004, 0.012, 0.037, 0.11, 0.33, 1.0, 3.0 μ M) for 1h, followed by addition of 5 μ g/mL tunicamycin or 1 μ M thapsigargin for an additional 6h to induce endoplasmic reticulum-stress.

Reaction Conditions 0, 0.004, 0.012, 0.037, 0.11, 0.33, 1.0, and 3.0 μ M; 1h and additional 6h

Applications GSK2656157 effectively inhibits tunicamycin- or thapsigargin-induced PERK activation and decreases in the downstream substrates, phospho-eIF2 α , ATF4, and CHOP with an IC₅₀ in the range of 10-30nM.

Animal experiment [1]:

Animal models Naive female CD-1 mice

Preparation Method Naive female CD-1 mice were given a single 1.5, 5, 15, 50, 150mg/kg oral dose of GSK2656157. Animals were euthanized after 4h, and blood and pancreas were collected.

Dosage form 1.5, 5, 15, 50, 150mg/kg; p.o.

Applications A single oral dose of GSK2656157 (1.5-150mg/kg) produced dose-dependent inhibition of phospho-PERK Thr980 with more than 80% inhibition at 50 and 150mg/kg.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

References:

- [1] ATKINS C, LIU Q, MINTHORN E, et al. Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity[J]. Cancer Research, 2013, 73(6): 1993-2002.
- [2] AXTEN J M, MEDINA J R, FENG Y, et al. Discovery of 7-methyl-5-(1-([3-(trifluoromethyl)phenyl]acetyl)-2,3-dihydro-1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R-like endoplasmic reticulum kinase (PERK)[J]. Journal of Medicinal Chemistry, 2012, 55(16): 7193-7207.

Background

GSK2656157 is a potent, selective, and cell-permeable ATP-competitive inhibitor of PERK (protein kinase R (PKR)-like endoplasmic reticulum kinase) with an IC_{50} value of 0.9nM^[1]. PERK is a key mediator of the unfolded protein response (UPR) and plays a central role in endoplasmic reticulum stress signaling^[2]. GSK2656157 is commonly used in studies investigating antitumor activity, pancreatic tissue homeostasis, endoplasmic reticulum stress, and related areas^[3,4].

In vitro, pretreatment of BxPC3 cells with GSK2656157 (10-30nM) for 1h followed by co-treatment with tunicamycin (5μg/mL) or thapsigargin (1μM) for 6h effectively inhibited PERK activation induced by these agents and decreased the production of downstream substrates, including phospho-eIF2α, ATF4, and CHOP. Pretreatment with GSK2656157 (1μM) for 1h prior to tunicamycin (5μg/mL) exposure for 1h blocked the impact on de novo protein synthesis upon UPR induction^[2]. Additionally, pre-incubation of J774.1 cells with GSK2656157 (2.5, 5, 10μM) for 0.5h followed by stimulation with 1000ng/mL lipopolysaccharide (LPS) for 24h resulted in a dose-dependent inhibition of Caspase-1 activity and reduced LPS-induced IL-1β production^[5].

In vivo, oral administration of GSK2656157 (50mg/kg/day) to CD-1 mice resulted in complete inhibition of phospho-PERK Thr980 in the pancreas within 8h^[2]. In mice bearing various human tumor xenografts (BxPC3, NCI-H929, HPAC, and Capan2), oral treatment with GSK2656157 (50 or 150mg/kg; twice daily) induced dose-dependent inhibition of tumor growth in all four models. At the dose of 150mg/kg twice daily, tumor growth inhibition rates reached 54-114%^[2].

References:

- [1] AXTEN J M, MEDINA J R, FENG Y, et al. Discovery of 7-methyl-5-(1-([3-

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

(trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R-like endoplasmic reticulum kinase (PERK)[J]. Journal of Medicinal Chemistry, 2012, 55(16): 7193-7207.

[2] ATKINS C, LIU Q, MINTHORN E, et al. Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity[J]. Cancer Research, 2013, 73(6): 1993-2002.

[3] ZHANG W, FENG D, LI Y, et al. PERK EIF2AK3 control of pancreatic β cell differentiation and proliferation is required for postnatal glucose homeostasis[J]. Cell Metabolism, 2006, 4(6): 491-497.

[4] GUPTA S, MCGRATH B, CAVENER D R. PERK regulates the proliferation and development of insulin-secreting beta-cell tumors in the endocrine pancreas of mice[J]. PLoS One, 2009, 4(11): e8008.

[5] FARZANEH Z, KALANTAR K, IRAJI A, et al. Inhibition of LPS-induced inflammatory responses by Satureja hortensis extracts in J774.1 macrophages[J]. Journal of Immunoassay and Immunochemistry, 2018, 39(3): 274-291.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA