Product Data Sheet

Product Name: GSK2606414
Cat. No.: GC17450

Chemical Properties

Cas. No.	1337531-36-8		
Chemical Name	1-[5-(4-amino-7-methylpyrrolo[2,3-d]pyrimidin-5-yl)-2,3-dihydroindol-1-yl]-2-[3-(trifluoromethyl)phenyl]ethanone		
SMILES	CN1C=C(C2=C1N=CN=C2N)C3=CC4=C(C=C3)N(CC4)C(=O)CC5=CC(=CC=C5)C(F)(F)F		
Formula	$C_{24}H_{20}F_3N_5O$	M.Wt	451.44
Solubility	≥ 22.57 mg/mL in DMSO, ≥ 12.03 mg/mL in EtOH with ultrasonic and warming	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.		

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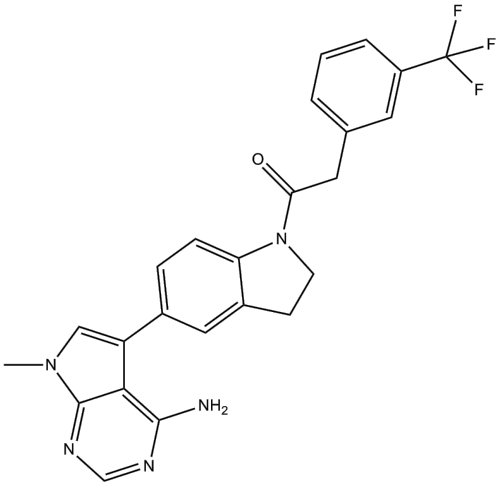
Structure



Protocol

Cell experiment [1]:

Cell lines	ARPE-19 cells
Preparation Method	ARPE-19 cells were seeded into a 96-well plate at a density of 2×10^{3} cells/well and incubated with 0.01-50μM GSK2606414 for 24, 48 or 72h at 37°C.
Reaction Conditions	0.01-50μM; 24, 48 or 72h

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Applications	GSK2606414 inhibits cell viability in a dose- and time-dependent manner.

Animal experiment [2]:

Animal models	Male wild-type C57BL/6 mice
Preparation Method	Mice were injected with 6-OHDA and treated with GSK2606414 (100mg/kg/day) orally for 21 days, then euthanized, and the brains were quickly removed and the striatum was dissected.
Dosage form	100 mg/kg/day; p.o.
Applications	GSK2606414 protected nigral-dopaminergic neurons against a PD-inducing neurotoxin, improving motor performance.

References:

[1]Jiang X, Wei Y, Zhang T, et al. Effects of GSK2606414 on cell proliferation and endoplasmic reticulum stress-associated gene expression in retinal pigment epithelial cells[J]. Molecular Medicine Reports, 2017, 15(5): 3105-3110.

[2]Mercado G, Castillo V, Soto P, et al. Targeting PERK signaling with the small molecule GSK2606414 prevents neurodegeneration in a model of Parkinson's disease[J]. Neurobiology of disease, 2018, 112: 136-148.

Background

GSK2606414 is an orally active, selective protein kinase R-like endoplasmic reticulum kinase (PERK) inhibitor with an IC_{50} value of 0.4 nM [1]. GSK2606414 is a potent inhibitor of KIT (K_d=664±294 nM), a type III receptor tyrosine kinase (RTK)[2]. GSK2606414 also inhibits RIPK1, a kinase involved in

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TNFα-mediated cell death[3]. GSK2606414 has anticancer activity and is also a potential inhibitor of ABCG2 protein, also known as breast cancer resistance protein (BCRP)[4].

In vitro, GSK2606414 (0.01-50μM) treatment of human retinal pigment epithelial cell line (ARPE-19 cells) for 24-72h inhibited cell viability in a dose- and time-dependent manner, but did not induce apoptosis, inhibited thapsigargin (TG)-induced eIF2α phosphorylation, and downregulated the expression levels of co-binding protein homologous protein (CHOP) and vascular endothelial growth factor (VEGF)[5]. GSK2606414 (0.5 and 1μM) treatment of Neuro2a cells for 24h significantly reduced high glucose (HG)-induced ROS production, attenuated HG-induced mitochondrial dysfunction and neuronal apoptosis, and reduced the expression of GRP78 protein in the endoplasmic reticulum[6].

In vivo, oral administration of GSK2606414 (100mg/kg/day) to Parkinson's disease (PD) model mice for 21 days protected substantia nigra dopaminergic neurons from neurotoxins, increased the survival rate of dopaminergic neurons in the substantia nigra pars compacta (SNpc), and improved the motor performance of PD mice, but induced pancreatic toxicity[7].

References:
[1] Axten J M, Medina J R, Feng Y, et al. Discovery of 7-methyl-5-(1-{[3-(trifluoromethyl) phenyl] acetyl}-2, 3-dihydro-1 H-indol-5-yl)-7 H-pyrrolo [2, 3-d] pyrimidin-4-amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK)[J]. Journal of medicinal chemistry, 2012, 55(16): 7193-7207.
[2] Mahameed M, Wilhelm T, Darawshi O, et al. The unfolded protein response modulators GSK2606414 and KIRA6 are potent KIT inhibitors[J]. Cell death & disease, 2019, 10(4): 300.
[3] Ouyang Y. The Involvement of Receptor Interacting Protein Kinase 1 (RIPK1) in the Pathogenesis of Acute Pancreatitis[M]. The University of Liverpool (United Kingdom), 2017.
[4] Yu Z Z, Xu B Q, Wang Y Y, et al. GSK2606414 sensitizes ABCG2-overexpressing multidrug-resistant colorectal cancer cells to chemotherapeutic drugs[J]. Biomedicines, 2023, 11(11): 3103.
[5] Jiang X, Wei Y, Zhang T, et al. Effects of GSK2606414 on cell proliferation and endoplasmic reticulum stressassociated gene expression in retinal pigment epithelial cells[J]. Molecular Medicine Reports, 2017, 15(5): 3105-3110.
[6] Gundu C, Arruri V K, Sherkhane B, et al. GSK2606414 attenuates PERK/p-eIF2α/ATF4/CHOP axis and augments mitochondrial function to mitigate high glucose induced neurotoxicity in N2A cells[J]. Current research in pharmacology and drug discovery, 2022, 3: 100087.

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[7] Mercado G, Castillo V, Soto P, et al. Targeting PERK signaling with the small molecule GSK2606414 prevents neurodegeneration in a model of Parkinson's disease[J]. Neurobiology of disease, 2018, 112: 136-148.

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