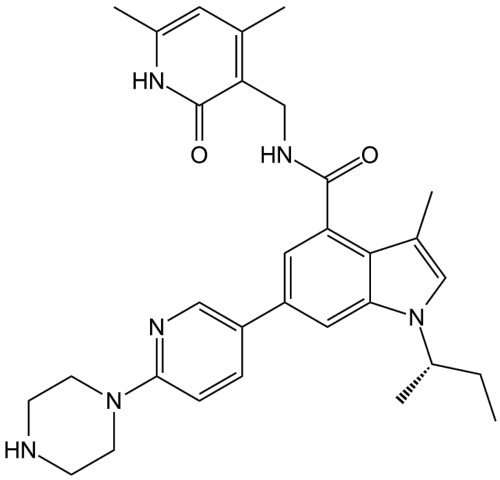
Product Data Sheet

Product Name: GSK126
Cat. No.: GC15783

Chemical Properties

Cas. No.	1346574-57-9		
Chemical Name	1-[(2S)-butan-2-yl]-N-[(4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-3-methyl-6-(6-piperazin-1-ylpyridin-3-yl)indole-4-carboxamide		
SMILES	CCC(C)N1C=C(C2=C(C=C(C=C21)C3=CN=C(C=C3)N4CCNCC4)C(=O)NCC5=C(C=C(NC5=O)C)C)C		
Formula	$C_{31}H_{38}N_6O_2$	M.Wt	526.67
Solubility	≥ 3.29 mg/mL in DMSO, <2.4 mg/mL in EtOH, <2.27 mg/mL in Water	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

Cell experiment [1]:

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Cell lines	human THP-1 cells
Preparation Method	THP-1 cells were cultured in RPMI-1640 medium and treated with PMA for 48h. Subsequently, the cells were treated with GSK126 (5μM) for 36h at 37˚C in a CO_2 incubator. THP-1 macrophages were then washed with PBS and cultured in serum-free RPMI-1640 medium. Following overnight fasting, the macrophages were washed with PBS again and cultured in medium with or without Ox-LDL (100μg/ml) for 48h. After incubation, macrophages were fixed in methanol at room temperature for 30min and stained with Oil Red O for 20min at room temperature and observed under a DP80 fluorescent microscope at x200 magnification. Experiments were repeated in triplicate in each group.
Reaction Conditions	5μM; 36h; 37˚C
Applications	*In vitro*, it was found that pharmacological inhibition of EZH2 by GSK126 markedly reduced lipid transportation and monocyte adhesion during atherogenesis, predominantly through increasing the expression levels of ATP-binding cassette transporter A1 and suppressing vascular cell adhesion molecule 1 in human THP-1 cells.

Animal experiment [1]:

Animal models	Male *ApoE-/-* mice (n=18; age, 6-8 weeks; weight ~20g)

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Preparation Method	Male *ApoE-/-* mice were maintained under a specific pathogen-free environment in microisolator cages. The mice were separated into the control group (chow diet + DMSO/PBS injection), vehicle group (high-fat diet + DMSO/PBS injection) and treatment group (high-fat diet + GSK126 treatment), with six mice in each group. The mice in the control group were fed a chow diet, whereas the mice in the vehicle and treatment groups were fed a high-fat diet (21% fat, 0.15% cholesterol). All animals had free access to foods. In addition, the mice in the treatment group received a daily intraperitoneal injection of GSK126 at a dose of 50mg/kg/day (mouse body weight) for 10 weeks. The mice in the vehicle group were administered a daily intraperitoneal injection of 20% DMSO/PBS (volume, 0.1ml). Animals were sacrificed at 16-18 weeks of age. CO_2 was supplied in a precisely regulated and purified form. Flow meter was used in order to maintain a gradual fill/displacement rate of 10-30% of chamber volume per min. CO_2 flow was maintained for at least 1min after respiratory arrest. Following sacrifice by inhalation of CO2, the animals' heart tissue samples were collected, embedded in the OCT gel without fixation and stored at -80˚C immediately.
Dosage form	50mg/kg/day; 10 weeks; i.p
Applications	*In vivo*, it was found that atherosclerotic plaques in GSK126-treated mice were significantly decreased when comparing with the vehicle-treated animals. These results indicated that the GSK126 has the ability to attenuate the progression of atherosclerosis by reducing macrophage foam cell formation and monocyte adhesion in cell and mouse models.

References:

[1] Wei, Xianjing et al. “Pharmacological inhibition of EZH2 by GSK126 decreases atherosclerosis by modulating foam cell formation and monocyte adhesion in apolipoprotein E-deficient mice.” *Experimental and therapeutic medicine*vol. 22,2 (2021): 841. doi:10.3892/etm.2021.10273

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Background

GSK126 (GSK2816126A, GSK2816126) is a highly selective EZH2 methyltransferase inhibitor with IC_{50} 12.6-17.4nM *in vitro* (MM cells), and IC_{50} 9.9nM *in vivo* (Male *ApoE-/-* mice) [1,2]. Published researches show that targeting EZH2 by GSK126 is beneficial to reduces atherosclerotic plaque, and suppresses carcinogenesis, cell migration, and angiogenesis[3].

In vitro, GSK126 (5μM; 36h; 37˚C) pharmacologically inhibits EZH2, reduces lipid transportation and monocyte adhesion during atherogenesis by increasing the expression levels of ATP-binding cassette transporter A1 and suppressing vascular cell adhesion molecule 1 in human THP-1 cells[2]. GSK126 (5, 10μM; 48h) suppress colorectal cancer by regulating macrophage polarization in the tumor microenvironment in a MC38 and RAW264.7 cells based 3D culture model[4]. GSK126 (1nM-10μM; 7 days) suppress HTLV-1-infected $CD4^+$ T cell proliferation and hyperimmune response in HTLV-1-associated myelopathy[5].

In vivo, GSK126-treated(50mg/kg/day; 10 weeks; i.p) mice showed significantly decreased atherosclerotic plaques[2]. GSK126 (100mg/kg; 1 month; i.p) inhibits the growth of colorectal cancer cells/xenografts in BALB/c nu/nu model[6]. GSK126(1nM-100μM; 3 times a week; i.p) enhances antigen presentation, antitumor immunity, and circumvents anti-PD-1 resistance in head and neck cancer C57BL/6 mice model[7].

References:
[1] Zeng, Delong et al. “Blocking EZH2 methylation transferase activity by GSK126 decreases stem cell-like myeloma cells.” *Oncotarget* vol. 8,2 (2017): 3396-3411. doi:10.18632/oncotarget.13773
[2] Wei, Xianjing et al. “Pharmacological inhibition of EZH2 by GSK126 decreases atherosclerosis by modulating foam cell formation and monocyte adhesion in apolipoprotein E-deficient mice.” *Experimental and therapeutic medicine*vol. 22,2 (2021): 841. doi:10.3892/etm.2021.10273
[3] Chen, Ya-Tian et al. “The novel EZH2 inhibitor, GSK126, suppresses cell migration and angiogenesis via down-regulating VEGF-A.” *Cancer chemotherapy and pharmacology* vol. 77,4 (2016): 757-65. doi:10.1007/s00280-016-2990-1
[4] Li, Chen et al. “EZH2 Inhibitors Suppress Colorectal Cancer by Regulating Macrophage Polarization in the Tumor Microenvironment.” *Frontiers in immunology* vol. 13 857808. 1 Apr. 2022, doi:10.3389/fimmu.2022.857808

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[5] Koseki, Akihito et al. “EZH1/2 dual inhibitors suppress HTLV-1-infected cell proliferation and hyperimmune response in HTLV-1-associated myelopathy.” *Frontiers in microbiology* vol. 14 1175762. 12 Jun. 2023, doi:10.3389/fmicb.2023.1175762
[6] Yang, Liu et al. “PRMT5 functionally associates with EZH2 to promote colorectal cancer progression through epigenetically repressing CDKN2B expression.” *Theranostics* vol. 11,8 3742-3759. 27 Jan. 2021, doi:10.7150/thno.53023
[7]Zhou, Liye et al. “Targeting EZH2 Enhances Antigen Presentation, Antitumor Immunity, and Circumvents Anti-PD-1 Resistance in Head and Neck Cancer.” *Clinical cancer research : an official journal of the American Association for Cancer Research* vol. 26,1 (2020): 290-300. doi:10.1158/1078-0432.CCR-19-1351