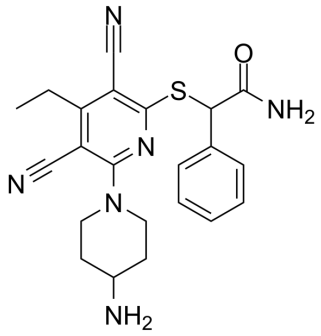
GSK-3685032

Cat. No.:	HY-139664
CAS No.:	2170137-61-6
Molecular Formula:	$C_{22}H_{24}N_6OS$
Molecular Weight:	420.53
Target:	DNA Methyltransferase
Pathway:	Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (59.45 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3780 mL	11.8898 mL	23.7795 mL
5 mM	0.4756 mL	2.3780 mL	4.7559 mL
10 mM	0.2378 mL	1.1890 mL	2.3780 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.94 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.94 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.94 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK-3685032 is a non-time-dependent, noncovalently, first-in-class reversible DNMT1-selective inhibitor, with an IC_{50} of 0.036 μM. GSK-3685032 induces robust loss of DNA methylation, transcriptional activation, and cancer cell growth inhibition [1].

IC_{50} & Target

DNMT1[1]

In Vitro

GSK-3685032 (6 days) has cell growth inhibition of majority cancer cell lines, with a median growth IC_{50} value of 0.64 μM[1].

GSK-3685032 (0.1-1000 nM, 1-6 days) exhibits growth inhibition after 3 days, with decreasing growth IC_{50} throughout a 6 d time course[1].
GSK3685032 (10-10000 nM, day 4) dose-dependently increases the immune-related gene transcription[1].
GSK3685032 (3.2-10,000 nM, 2 days) inhibits DNMT1 protein expression[1].
GSK3685032 induces DNA hypomethylation and gene activation[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	15 leukemia, 29 lymphoma and 7 multiple myeloma cell lines, e.g., EOL-1, Ki-JK, MM.IR cells.
Concentration:	0.01-100 μM
Incubation Time:	6 days
Result:	Showed cell growth inhibition of majority cancer cell lines, with a median growth IC_{50} value of 0.64 μM.

Cell Proliferation Assay[1]

Cell Line:	MV4-11 cells
Concentration:	0.1-1000 nM
Incubation Time:	1-6 days
Result:	Exhibited growth inhibition after 3 days, with decreasing growth IC_{50} throughout a 6 d time course.

RT-PCR[1]

Cell Line:	MV4-11 cells
Concentration:	10-10000 nM
Incubation Time:	4 days
Result:	Dose-dependent increased of CXCL11, IFI27, HLA-DQA1 and MAGEA4 following treatment of MV4-11 cells.

Western Blot Analysis[1]

Cell Line:	GDM-1 cells
Concentration:	3.2-10,000 nM
Incubation Time:	2 days
Result:	Inhibited DNMT1 protein expression

In Vivo

GSK-3685032 (1-45 mg/kg; subcutaneous twice daily for 28 days) inhibits tumor growth in the subcutaneous MV4-11 or SKM-1 xenograft models[1].

Summary of mouse pharmacokinetic parameters for GSK-3685032[1]

Dose,Route	C_{max}	$AUC_{0\text{-}8hr}$	DNAUC	Clearance	$Volume_{dss}$	$T_{1/2}$

	(ng/mL)	(h*ng/mL)	(h*kg*ng/mL/mg)	(mL/min/kg)	(L/kg)	(h)
2 mg/kg,IV	5103	2418	1209	13	1.3	1.8
2 mg/kg,SC	252	921	461	NA	NA	2.8
2 mg/kg,SC	5473	15400	513	NA	NA	ND

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	MV4-11 xenograft models (female CD1-Foxn1 mice, 12 weeks of age) or SKM-1 xenograft models (NOD. CB17-Prkdc1NCrCrl mice, 8-11 weeks of age)[1]
Dosage:	1, 5, 15, 30, 45 mg/kg (10% captisol adjusted to pH 4.5-5 with 1 M acetic acid, stored for up to 1 week at 4 °C)
Administration:	Subcutaneous injection, twice daily for 4 weeks
Result:	Revealed statistically significant dose-dependent tumor growth inhibition with clear regression at ≥30 mg/kg.

CUSTOMER VALIDATION

- J Cell Biol. 2024 Apr 1;223(4):e202307026.
- NPJ Breast Cancer. 2023 Aug 11;9(1):66.
- bioRxiv. 2023 May 9.

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REFERENCES

[1]. Pappalardi MB, et al. Discovery of a first-in-class reversible DNMT1-selective inhibitor with improved tolerability and efficacy in acute myeloid leukemia. Nat Cancer. 2021;2(10):1002-1017.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA