GSK1324726A

Cat. No.: HY-13960

CAS No.: 1300031-52-0

Molecular Formula: $C_{25}H_{23}ClN_2O_3$

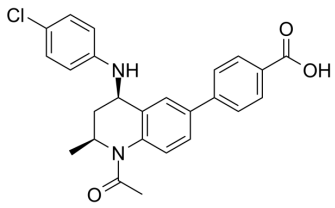
Molecular Weight: 434.91

Target: Epigenetic Reader Domain; Apoptosis

Pathway: Epigenetics; Apoptosis

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 : ≥ 46 mg/mL (105.77 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2993 mL	11.4966 mL	22.9933 mL
	5 mM	0.4599 mL	2.2993 mL	4.5987 mL
	10 mM	0.2299 mL	1.1497 mL	2.2993 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 (5.75 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK1324726A is a novel, potent, and selective inhibitor of BET proteins with high affinity to BRD2 (IC_{50}=41 nM), BRD3 (IC_{50}=31 nM), and BRD4 (IC_{50}=22 nM).

IC_{50} & Target

IC50: 22 nM (BRD4), 31 nM (BRD3), 41 nM (BRD2)[1]

In Vitro

A panel of neuroblastoma cell lines are treated with GSK1324726A (I-BET726), and observed potent growth inhibition and cytotoxicity in most cell lines irrespective of MYCN copy number or expression level. All neuroblastoma cell lines tested exhibit potent growth inhibition, with a median growth IC_{50} value (gIC_{50}; inhibitor concentration resulting in 50% growth inhibition) equal to 75 nM[1].

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

In Vivo

GSK1324726A (I-BET726) inhibits neuroblastoma tumor growth. In the SK-N-AS model, mice in the vehicle group are euthanized on day 14 due to large tumor size. While there is no significant difference in tumor growth between the vehicle and GSK1324726A (5 mg/kg) group, 58% tumor growth inhibition (TGI) is observed in the GSK1324726A (15 mg/kg) group on day 14 of the study (n=9; p=0.006). Mice in the GSK1324726A (15 mg/kg) group are treated for an additional 7 days before tumor volume reaches a level comparable to that observed in the vehicle group, at which point the study is terminated. Tumors in the CHP-212 model grow much more slowly. After 42 days, tumors in vehicle-treated mice are only half the size those in the SK-N-AS model at the end of the study (Day 14). In the CHP-212 model, treatment with 5 mg/kg GSK1324726A results in TGI equal to 50% (n=8; p=0.1816), and mice in the 15 mg/kg group exhibits a TGI of 82% at the end of the study (n=5; p=0.0488)[1].

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PROTOCOL

Cell Assay [1]

Cell line growth-death assays are performed with a few modifications. Briefly, cells are seeded into 384-well or 96-well plates at a density optimized for 6 days of growth. The following day, T_0 measurements are taken using CellTiter-Glo, CellTiter-Fluor, or CyQuant Direct. Plates are read on an Envision, Safire 2, or SpectraMax Gemini EM plate reader. Remaining plates are treated with DMSO or a titration of GSK1324726A. Cells are incubated for 6 days and developed. Results are plotted as a percentage of the T_0 value, normalized to 100%, versus concentration of compound. A 4-parameter equation is used to generate concentration response curves. Growth IC_{50} (gIC_{50}) values are calculated at the mid-point of the growth window (between DMSO and T_0 values). Y_{min}-T_0 values are calculated by subtracting the T_0 value (100%) from the Y_{min} value on the curve, and are a measure of net population cell growth or death[1].

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Animal Administration [1][2]

Mice[1]

CHP-212 (1×10^7) or SK-N-AS (5×10^6) cells in 100% matrigel are implanted subcutaneously into the right flank of approximately 9 week old female nude (Crl:CD-1-Foxn1 nu) mice. Tumors are measured with calipers and randomized using stratified sampling according to tumor size into treatment groups of 10 mice. GSK1324726A in vehicle or vehicle alone is administered orally by individual body weight at 10mls/kg. Mice are weighed and tumors are measured with calipers twice weekly, and mice are observed daily for any adverse treatment affects. Mice are euthanized using CO_2 inhalation according to AVMA guidelines after two consecutive tumor measurements greater than 2500mm^3, or if body weight loss greater than 20% is observed. For mouse pharmacodynamic studies, mice are euthanized as described above. Tumors are harvested from euthanized mice and placed in RNAlater for RNA isolation. Blood is collected after euthanasia via cardiac puncture.

Rats[2]

Male CD rats (253-283 g) are surgically prepared with implanted cannulae in the femoral vein (for GSK1324726A administration) and jugular vein (for blood sampling). Each rat receives Duphacillin (100 mg/kg s.c.) and Carprofen (7.5 mg/kg s.c.) as a pre-operative antibiotic and analgesic respectively. Each rat is allowed to recover for at least 2 days prior to dosing. Rats have free access to food and water throughout. Rat PK studies are conducted as a crossover design over 2 dosing occasions, with 3 days between dose administrations. Serial blood samples are taken (via indwelling jugular cannula) up to 26 h post dose administration on both dosing occasions. On study day 1, n=3 male rats each receives a 1 h intravenous infusion of GSK1324726A formulated in DMSO and 10% (w/v) KleptoseTM in saline (2%:98%) at a concentration of 0.2 mg/mL and the dose is filtered using a ca. 0.2 µm syringe filter unit. GSK1324726A is administered as a 1 h i.v. infusion at 5 mL/kg/h to achieve a target dose of 1 mg/kg. On study day 2, the same three rats each receives an oral administration of GSK1324726A suspended in 3% Pharmacoat 603/0.2% Sodium Lauryl Sulphate (w/v) aq. at a concentration of 0.6 mg/mL administered by gavage at 5 mL/kg to achieve a target dose of 3 mg/kg. At the end of the study the rats are euthanised by administration of sodium pentobarbital through the jugular vein cannula.

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CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.
- J Med Chem. 2018 Jan 25;61(2):504-513.
- Bioorg Med Chem. 2018 Jan 1;26(1):25-36.
- Patent. US20190255066A1.
- Patent. US20180263995A1.

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REFERENCES

[1]. Wyce A, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PLoS One. 2013 Aug 23;8(8):e72967.

[2]. Gosmini R, et al. The discovery of I-BET726 (GSK1324726A), a potent tetrahydroquinoline ApoA1 up-regulator and selective BET bromodomain inhibitor. J Med Chem. 2014 Oct 9;57(19):8111-31.

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