产品名称：GSK1324726A
产品别名： I-BET726

生物活性：

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 IC50 value (gIC50; inhibitor concentration resulting in 50% growth inhibition) equal to 75 nM[1].
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].
Solvent&Solubility	***In Vitro:*** **DMSO： ≥ 46 mg/mL (105.77 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / 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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.75 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

	2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.75 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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].
Animal Administration	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.
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.