产品名称：GSK 525762A
产品别名：Molibresib

生物活性：

Description	Molibresib (GSK 525762A; I-BET 762) is a **BET bromodomain** inhibitor with **IC_{50}** of 32.5-42.5 nM.
IC_{50} & Target	IC50: 32.5-42.5 nM (BET)[1]
In Vitro	Molibresib (I-BET 762) shows the highest affinity interaction with BET. Molibresib binds to the tandem bromodomains of BET with high affinity (dissociation constant Kd of 50.5-61.3 nM). Molibresib displaces, with high efficacy (half-maximum inhibitory concentration IC50 of 32.5-42.5 nM), a tetra-acetylated H4 peptide that had been pre-bound to tandem bromodomains of BET[1]. Molibresib has high affinity for BD1/BD2 domain of BRD2/3/4 proteins. Molibresib treatment leads to a reduction in the recruitment of all three proteins to chromatin[2]. Molibresib inhibits OPM-2 cell proliferation with IC50 of 60.15 nM[3].
In Vivo	The antimyeloma activity of Molibresib (I-BET 762) is tested dosed orally in an in vivo systemic xenograft model generated by injecting OPM-2 cells into NOD-SCID mice. Daily oral doses of Molibresib up to 10 mg/kg and 30 mg/kg given every other day are well tolerated with no clear impact on body weight compared with vehicle control. The plasma hLC concentration is significantly reduced in mice treated with Molibresib[3].
Solvent&Solubility	***In Vitro:*** **DMSO : 33.33 mg/mL** (**78.63 mM**; Need ultrasonic) **H_2O : < 0.1 mg/mL** (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3590 mL	11.7952 mL	23.5905 mL
	5 mM	0.4718 mL	2.3590 mL	4.7181 mL
	10 mM	0.2359 mL	1.1795 mL	2.3590 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 (5.90 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.90 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。

[1]. Nicodeme E, et al. Suppression of inflammation by a synthetic histone mimic. Nature. 2010 Dec 23;468(7327):1119-23.

References	[2]. Asangani IA, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature. 2014 Jun 12;510(7504):278-82. [3]. Chaidos A, et al. Potent antimyeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood. 2014 Jan 30;123(5):697-705.

实验参考：

Cell Assay	VCaP, LNCaP, 22RV1, DU145 and PC3 prostate cancer cell lines are seeded in 96-well plates at 2000-10,000 cells/well (optimum density for growth) in a total volume of 100μL media containing 10% FBS. Serially diluted compounds in 100μL media are added to the cells 12hr later. Following 96 hr. incubation, cell viability is assessed by Cell-Titer GLO. The values are normalized and IC50 is calculated using GraphPad Prism software. For long-term colony formation assay, 10,000-50,000 cells/well are seeded in six-well plates and treated with either 100 nM or 500 nM of JQ1 or DMSO. After 12 days cells are fixed with methanol, stained with crystal violet and photographed. For colorimetric assays, the stained wells are treated with 500μL 10% acetic acid and the absorbance is measured at 560nm using a spectrophotometer[2].
Animal Administration	Mice[3] The antimyeloma efficacy of orally administered Molibresib is tested in a systemic xenograft myeloma model. For this purpose, sublethally irradiated (200 cGy) NOD/SCID mice age 9 to 11 weeks are given 10^7 OPM-2 myeloma cells via tail vein injection. On day 15 following inoculation, animals are started on oral treatment with Molibresib at escalating doses or vehicle (1% methylcellulose and 0.2% sodium lauryl sulfate), which is continued up to day 83. Specifically, 1 group of mice are treated with vehicle and 4 groups with different dosing schedules of Molibresib: 3 mg/kg per day; 10 mg/kg per day; 30 mg/kg on alternate days; and 30 to 20 mg/kg per day (ie, 30 mg/kg per day for 14 days, followed by 2 weeks [days 15 to 31] off treatment [drug is withheld due to a decline in body weight until animals has regained weight], follow by 20 mg/kg per day until termination of the experiment [days 43 to 82]). Blood samples (~70 μL) are removed at 0.5 hours after oral administration of Molibresib on day 15 (treatment initiation); days 27, 45, and 82 (3, 10, and 20 to 30 mg/kg once per day groups only); and day 83 (30 mg/kg once every other day group only). The blood is centrifuged to obtain 20 μL plasma and stored at -20°C prior to analysis for Molibresib by using a specific liquid chromatography/mass spectrometry/mass spectrometry assay.
References	[1]. Nicodeme E, et al. Suppression of inflammation by a synthetic histone mimic. Nature. 2010 Dec 23;468(7327):1119-23. [2]. Asangani IA, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature. 2014 Jun 12;510(7504):278-82. [3]. Chaidos A, et al. Potent antimyeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood. 2014 Jan 30;123(5):697-705.