Molibresib

Cat. No.: HY-13032

CAS No.: 1260907-17-2

Molecular Formula: $C_{22}H_{22}ClN_5O_2$

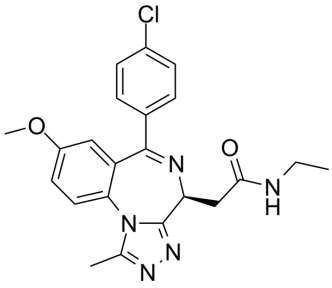
Molecular Weight: 423.9

Target: Epigenetic Reader Domain

Pathway: Epigenetics

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 200 mg/mL (471.81 mM; Need ultrasonic)

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

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 (5.90 mM); Clear solution
2. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (5.90 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.90 mM); Clear solution
4. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: ≥ 0.5 mg/mL (1.18 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Molibresib (I-BET762; GSK525762) 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 K_d of 50.5-61.3 nM). Molibresib displaces, with high efficacy (half-maximum inhibitory concentration IC_{50} 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 IC_{50} of 60.15 nM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	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 IC_{50} 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 500 µL 10% acetic acid and the absorbance is measured at 560nm using a spectrophotometer[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2021 Apr 15;184(8):2167-2182.e22.
- Nat Med. 2017 Sep;23(9):1055-1062.
- Sci Adv. 2021 Feb 19;7(8):eabe4038.
- J Exp Med. 2017 Aug 7;214(8):2349-2368.
- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.

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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.

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