产品名称：(S)-(+)-Tert-butyl 2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]

产品别名：(+)-JQ-1

生物活性：	
Description	(+)-JQ-1 (JQ-1) is a potent, specific, and reversible BET bromodomain inhibitor, with IC50s of 77 and 33 nM for the first and second bromodomain (BRD4(1/2))[1]. (+)-JQ-1 also activates autophagy[2].
IC_{50} & Target	IC50: 77/33 nM (BRD4(1/2))[1]
In Vitro	(+)-JQ-1 represents a potent, highly specific and Kac competitive inhibitor for the BET family of bromodomains. (+)-JQ-1 (100 nM, 48 h) prompts squamous differentiation exhibited by cell spindling, flattening and increased expression of keratin. (+)-JQ-1 (250 nM) induces rapid expression of keratin in treated NMC 797 cells compared to (-)-JQ1 (250 nM) and vehicle controls, as determined by quantitative immunohistochemistry.(+)-JQ-1 (250 nM) elicits a time-dependent induction of strong (3+) keratin staining of treated NMC 797 cells, compared to (-)-JQ1 (250 nM)[1]. De-repression of autophagy genes is observed almost immediately after (+)-JQ-1 addition[2]. (+)-JQ-1 is a potent thienodiazepine inhibitor (Kd=90 nM) of the BET family coactivator protein BRD4, which is implicated in the pathogenesis of cancer via transcriptional control of the MYC oncogene. Dose-ranging studies of (+)-JQ-1 demonstrates potent inhibition of H4Kac4 binding with a IC50 value of 10 nM for murine BRDT(1) and 11 nM for human BRDT(1)[3].
In Vivo	Matched cohorts of mice with established tumors are randomized to treatment with (+)-JQ1 (50 mg/kg) or vehicle, administered by daily intraperitoneal injection. Prior to randomization, and after four days of therapy, mice are evaluated by FDG-PET imaging. A marked reduction in FDG uptake is observed with (+)-JQ1 treatment. Tumor-volume measurements confirm a reduction in tumor growth with JQ1 treatment. Pharmacokinetic studies of (+)-JQ1 are performed in CD1 mice following intravenous and oral administration. Mean plasma concentration-time profiles of (+)-JQ1 after intravenous dosing (5 mg/kg). The pharmacokinetic parameters for intravenous (+)-JQ1 demonstrate excellent drug exposure (AUC=2090 hr*ng/mL) and an approximately one hour half-life (T1/2). Mean plasma concentration-time profiles of (+)-JQ1 after oral dosing (10 mg/kg). The pharmacokinetic parameters for oral (+)-JQ1 demonstrate excellent oral bioavailability (F=49%), peak plasma concentration (Cmax=1180 ng/mL) and drug exposure (AUC=2090 hr*ng/mL)[1].

In Vitro:

DMSO : ≥ 45 mg/mL (98.47 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1882 mL	10.9412 mL	21.8823 mL
5 mM	0.4376 mL	2.1882 mL	4.3765 mL
10 mM	0.2188 mL	1.0941 mL	2.1882 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。

Solvent&Solubility	***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 (5.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.47 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% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (5.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.47 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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.47 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]. Filippakopoulos P, et al. Selective inhibition of BET bromodomains. Nature. 2010 Dec 23;468(7327):1067-73. [2]. Sakamaki JI, et al. Bromodomain Protein BRD4 Is a Transcriptional Repressor of Autophagy and LysosomalFunction. Mol Cell. 2017 May 18;66(4):517-532.e9. [3]. Matzuk MM, et al. Small-molecule inhibition of BRDT for male contraception. Cell. 2012 Aug 17;150(4):673-84.

实验参考：

Cell Assay	NUT midline carcinoma patient cell lines (797 and 11060) are plated in T-25 flasks and grown in DMEM (797) or RPMI (11060) containing 10 % fetal bovine serum. Cells are treated with either 250 nM (+)-JQ1, 250 nM (-)-JQ1 or the equivalent volume of DMSO (0.025%). At the desired time point, 2×106 cells are spun at 500× g for 5 minutes at 4°C and washed with PBS. Pellets are resuspended in 1 mL of cold PBS and added dropwise while gently vortexing to 9 mL 70 % ethanol in a 15 mL polypropylene centrifuge tube. Fixed cells are then frozen at -20°C overnight. The next day, cells are centrifuged at 500× g for 10 minutes at 4°C and washed with 3 mL of cold PBS. Cells are resuspended in 500 μL of propidium iodide staining solution (0.2 mg/mL RNAse A, 0.02 mg/mL propidium iodide, 0.1 % Triton-X in PBS) and incubated for 20 minutes at 37°C. Samples are then transferred to ice and analyzed on a BD FACS Canto II. Histograms are generated and cell cycle analysis is performed using FlowJo flow cytometry analysis software[1].
	Mice[1] Matched cohorts of mice with established tumors are randomized to treatment with (+)-JQ1 (50

Animal Administration	mg/kg) or vehicle, administered by daily intraperitoneal injection. Male CD1 mice (24-29 g) are treated with a single dose of (+)-JQ1 at 5 mg/kg for intravenous tail vein injection studies and 10 mg/kg for oral gavage studies. Rats[3] Adult male Sprague-Dawley rats are treated with vehicle or (+)-JQ1 (10 mg/kg). Treatment is administered IP at 1/100 body mass. Rats are checked twice-daily for mortality and weighed on days 1, 3, 7, 14, and 21. The treatment regimen utilized 4 days of 50 mg/kg JQ1 administered daily which is decreased to 10 mg/kg twice daily for the remainder of the study due to the appearance of adverse effects in a subset of animals. For all animals completing 3 weeks of treatment, testis mass, sperm motility, and sperm counts are determined as described for mouse studies. In brief, testes are fixed in Bouin's and prepared for histology. The other half is minced in warm M16 buffer and used for sperm counts and motility studies.
References	[1]. Filippakopoulos P, et al. Selective inhibition of BET bromodomains. Nature. 2010 Dec 23;468(7327):1067-73. [2]. Sakamaki JI, et al. Bromodomain Protein BRD4 Is a Transcriptional Repressor of Autophagy and LysosomalFunction. Mol Cell. 2017 May 18;66(4):517-532.e9. [3]. Matzuk MM, et al. Small-molecule inhibition of BRDT for male contraception. Cell. 2012 Aug 17;150(4):673-84.