产品名称：Volasertib(BI 6727)
产品别名：伏拉塞替 ；Volasertib

生物活性：

Description

Volasertib is a highly potent Polo-like kinase 1 (PLK1) inhibitor with an IC_{50} of 0.87 nM, as well as the two closely related kinases PLK2 and PLK3 with IC_{50}s of 5 and 56 nM, respectively.

IC_{50} & Target

PLK1	PLK2	PLK3
0.87 nM (IC_{50})	5 nM (IC_{50})	56 nM (IC_{50})

In Vitro

Volasertib is potent against HeLa and Caski cells with IC50 values of 0.02 μM and 2.02 μM, respectively. Volasertib (0.03 μM) induces cell cycle arrest at G2/M Phase in cervical cancer cells. Volasertib (0.003-0.03 μM) induces apoptosis in HeLa cells, and Volasertib (0.3-3 μM) results in Caski cell apoptosis. Volasertib (1, 3 μM or 0.01,0.03 μM) augments the fluorescent intensity of DHE in Caski and HeLa cells in a dose-dependent manner[1]. Volasertib shows inhibitory activities against the proliferation of all 40 cell lines tested, with a mean half-maximal growth inhibitory concentration of 313 nM (range: 4-5000 nM)[2]. Volasertib inhibits proliferation of multiple cell lines derived from various cancer tissues, including carcinomas of the colon (HCT 116, EC50=23 nM) and lung (NCI-H460, EC50=21 nM), melanoma (BRO, EC50=11 nM), and hematopoietic cancers (GRANTA-519, EC50=15 nM; HL-60, EC50=32 nM; THP-1, EC50=36 nM and Raji, EC50=37 nM) with EC50 values of 11 to 37 nM. Volasertib (100 nM) causes G2-M arrest and induces apoptosis in NCI-H460 cells[3].

In Vivo

Volasertib (15 mg/kg, i.p.) inhibit xenograft tumor growth of cervical cancer cells in nude mice[1]. Volasertib (70 mg/kg, p.o. once a week or 10 mg/kg, p.o. daily) significantly delays tumor growth in a non-small cell lung carcinoma xenograft model. In addition, Volasertib (15 mg/kg, i.v.) markedly suppresses tumor growth and is well tolerated[3].

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (**80.80 mM**; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.6160 mL	8.0800 mL	16.1600 mL
5 mM	0.3232 mL	1.6160 mL	3.2320 mL
10 mM	0.1616 mL	0.8080 mL	1.6160 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 (4.04 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (4.04 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: 2.08 mg/mL (3.36 mM); Suspended solution; Need ultrasonic 此方案可获得 2.08 mg/mL (3.36 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 20.8 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 (4.04 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.04 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]. Xie FF, et al. Volasertib suppresses tumor growth in cervical cancer. Am J Cancer Res. 2015 Nov 15;5(12):3548-59. [2]. Abbou S, et al. Polo-like Kinase Inhibitor Volasertib Exhibits Antitumor Activity in Pediatric Malignancies. Anticancer Res. 2016 Feb;36(2):599-609. [3]. Rudolph D, et al. BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity.Clin Cancer Res. 2009 May 1;15(9):3094-102. Epub

实验参考：

Cell Assay	Cells are firstly seeded into a 96-well plate at a density of 5000 cells per well, and incubated with drugs in three parallel wells for 72 hr. Then MTT is added to each well at a final concentration of 0.5 mg/mL. After incubation for 4 hr, formazan crystals are dissolved in 100 μL of DMSO, and absorbance at 570 nm is measured by plate reader. The concentrations required to inhibit growth by 50% (IC_{50}) are calculated from survival curves[1]
Animal Administration	Female BomTac: NMRI-Foxn1nu mice are grafted s.c. with 2×10^6 HCT 116 human colon carcinoma cells (ATCC CCL-247), 1×10^6 NCI-H460 non-small cell lung cancer cells (ATCC HTB-177), or CXB1 human colon carcinoma tumor pieces derived from patient material by serial transplantation in nude mice. When tumors have reached a volume of appr 50 to 100 mm^3, animals are randomized into treatment and control groups of 10 mice each. Volasertib is formulated in hydrochloric acid (0.1 N), diluted with 0.9% NaCl, and injected i.v. into the tail vein at the indicated dose and schedule. For oral treatment, Volasertib is resuspended in 0.5% Natrosol 250 hydroxyethyl-cellulose and given intragastrally via gavage needle. An administration volume of 10 mL per kilogram of body weight is used for both administration routes. Tumor volumes are determined thrice a week using a caliper. The results are converted to tumor volume (mm^3) by the formula length×$width^2$×π/6. The weight of the mice is determined as an indicator of tolerability on the same days. Median tumor volumes on the last day of the experiment are used to calculate treated versus control values (= tumor volumetreated mice ×100/tumor volumecontrol mice). [3]
	Enzyme activity assays for Plk1, Plk2, and Plk3 are done in the presence of serially diluted inhibitor using 20 ng of recombinant kinase and 10 μg casein from bovine milk as substrate. Kinase reactions are done in a final volume of 60 μL for 45 min at 30°C [15 mM $MgCl_2$, 25 mM MOPS (pH 7.0), 1 mM

Kinase Assay	DTT, 1% DMSO, 7.5 μM ATP, 0.3 μCi γ-^{32}P-ATP]. Reactions are terminated by the addition of 125 μL of ice-cold 5% TCA. After transferring the precipitates to MultiScreen mixed ester cellulose filter plates, plates are washed with 1% TCA and quantified radiometrically. Dose-response curves are used for calculating IC_{50} values. To establish a kinase selectivity profile, additional kinase assays are done by contract research organizations or reagents are purchased from commercial sources and assays are done according to the supplier's instructions. Appropriate positive and negative controls are included in the assay design. [3]
References	[1]. Xie FF, et al. Volasertib suppresses tumor growth in cervical cancer. Am J Cancer Res. 2015 Nov 15;5(12):3548-59. [2]. Abbou S, et al. Polo-like Kinase Inhibitor Volasertib Exhibits Antitumor Activity in Pediatric Malignancies. Anticancer Res. 2016 Feb;36(2):599-609. [3]. Rudolph D, et al. BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity.Clin Cancer Res. 2009 May 1;15(9):3094-102. Epub