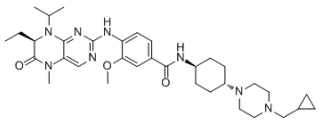
Data Sheet

Product Name:	Volasertib
Cat. No.:	HY-12137
CAS No.:	755038-65-4
Molecular Formula:	$C_{34}H_{50}N_8O_3$
Molecular Weight:	618.81
Target:	Polo-like Kinase (PLK)
Pathway:	Cell Cycle/DNA Damage
Solubility:	10 mM in DMSO



BIOLOGICAL ACTIVITY:

Volasertib is a highly potent **PLK1** inhibitor with an **IC50** of 0.87 nM, as well as the two closely related kinases **Plk2** and **Plk3** with **IC50** va lues of 5 and 56 nM, respectively.

IC50 & Target: IC50: 0.87 nM (PLK1), 5 nM (PLK2), 56 nM (PLK3)[3]

In Vitro: Volasertib is potent against HeLa and Caski cells with IC_{50} 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, EC_{50}=23 nM) and lung (NCI-H460, EC_{50}=21 nM), melanoma (BRO, EC_{50}=11 nM), and hematopoietic cancers (GRANTA-519, EC_{50}=15 nM; HL-60, EC_{50}=32 nM; THP-1, EC_{50} =36 nM and Raji, EC_{50}=37 nM) with EC_{50} 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.) potentiates the activity of cisplatin to 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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [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 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. **Cell Assay:** Volasertib is dissolved in DMSO.[1]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:** Volasertib is formulated in hydrochloric acid (0.1 N), diluted with 0.9% NaCl for i.v. treatment; Volasertib is resuspended in 0.5% Natrosol 250 hydroxyethyl-cellulose for oral treatment.[3]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).

References:

[1]. Xie FF, et al. Volasertib suppresses tumor growth and potentiates the activity of cisplatin 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 and Synergy with Vincristine 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

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