Onvansertib

Cat. No.: HY-15828

CAS No.: 1034616-18-6

Molecular Formula: $C_{24}H_{27}F_3N_8O_3$

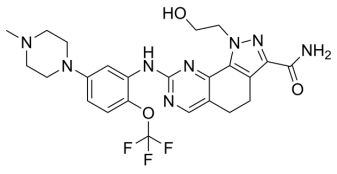
Molecular Weight: 532.52

Target: Polo-like Kinase (PLK); Apoptosis

Pathway: Cell Cycle/DNA Damage; Apoptosis

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 21 mg/mL (39.44 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8779 mL	9.3893 mL	18.7786 mL
	5 mM	0.3756 mL	1.8779 mL	3.7557 mL
	10 mM	0.1878 mL	0.9389 mL	1.8779 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 0.5% MC >> 0.5% Tween-80
   Solubility: 10 mg/mL (18.78 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2 mg/mL (3.76 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (3.76 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2 mg/mL (3.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

NMS-1286937 is a potent, selective and orally available PLK1 inhibitor, with an IC_{50} of 2 nM.

IC_{50} & Target				
	PLK1	FLT3	MELK	CK2
	2 nM (IC_{50})	510 nM (IC_{50})	744 nM (IC_{50})	826 nM (IC_{50})

In Vitro	NMS-1286937 is a potent, selective and orally available PLK1 inhibitor, with IC_{50} of 2 nM. NMS-1286937 also shows inhibitory activities against FLT3, MELK, and CK2, with IC_{50}s of 510, 744, and 826 nM, respectively[1]. NMS-P937 possesses a pure ATP competitive mechanism with a reversible dissociation and no time dependency. NMS-P937 (10 μM) is selective with a marginal activity of 48% and 40% inhibition on PLK2 and PLK3, respectively. NMS-P937 shows antiproliferative activity against a panel of 137 cell lines, with IC_{50} values of below 100 nM for 60 of 137 cell lines and higher than 1 μM for only 9 of 137 cell lines[2]. NMS-P937 shows cytotoxic activity against AmL-NS8 cells with IC_{50} of 36 nM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	NMS-1286937 (45 mg/kg, i.v.) shows a good tumor growth inhibition with acceptable and reversible body weight loss in CD1 nu/nu mice xenografted with human HCT116 colon adenocarcinoma cells. NMS-1286937 (60 mg/kg, p.o.) also inhibits the growth of tumor on HCT116 xenograft model[1]. NMS-P937 (45 mg/kg, i.v.or 60 mg/kg, p.o) inhibits tumor growth to a comparable degree (TGI, 83% and 79% intravenously and orally, respectively) in HCT116-bearing mice. The combination of NMS-P937 (120 mg/kg given for 4 cycles of 2 consecutive days with 10-day rest) and cytarabine (75 mg/kg for 4 cycles of 5 consecutive days with 7-day rest) in the disseminated leukemia model AmL-PS is well tolerated and clearly showed increased mice survival[2]. NMS-P937 (60 mg/kg bid os per day over 2 days with a 5 day rest) shows good efficacy compared to standard therapies, with a significant increase in median survival time (MST) in the established disease setting[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The inhibitory activity of putative kinase inhibitors and the potency of selected compounds are determined using a trans-phosphorylation assay. Specific peptide or protein substrates are trans-phosphorylated by their specific serine-threonine or tyrosine kinase, in the presence of ATP traced with ^{33}P-γ-ATP, at optimized buffer and cofactors conditions. At the end of the phosphorylation reaction, more than 98% unlabeled ATP and radioactive ATP is captured by adding an excess of the ion exchange dowex resin; the resin then settles down to the bottom of the reaction plate by gravity. Supernatant, containing the phosphorylated substrate, is subsequently withdrawn and transferred into a counting plate, followed by evaluation by b-counting. Inhibitory potency evaluation for all the tested kinases is performed at 25°C using a 60 min end-point assay where the concentrations of ATP and substrates are kept equal to 2 × αK_m and saturated (>5 × αK_m), respectively. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Cells are seeded into 96- or 384-well plates at densities ranging from 10,000 to 30,000/cm^2 for adherent and 100,000/mL for nonadherent cells in appropriate medium supplemented with 10% fetal calf serum. After 24 hours, cells are treated in duplicate with serial dilutions of NMS-P937, and 72 hours later, the viable cell number is assessed by the CellTiter-Glo Assay. IC_{50} values are calculated with a sigmoidal fitting algorithm. Experiments are carried out independently at least twice. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	For carcinoma xenograft studies, 5- to 6-week-old female Hsd, athymic nu/nu mice (average weight, 20-22 g), are used. HCT116, HT29, Colo205 colorectal, and A2780 ovarian human carcinoma cell lines are inoculated subcutaneously. Mice bearing a palpable tumor (100-200 mm^3) are treated with vehicle or NMS-P937 following doses and schedules starting from the day after randomization. Tumor dimensions are measured regularly with Vernier calipers, and tumor growth inhibition (TGI) is calculated. Toxicity is evaluated on the basis of body weight reduction. For leukemia studies, 5- to 6-week-old female severe combined immunodeficient mice (SCID; average weight, 20-22 g) are used. The AmL cell line HL-60 (5×10^6 cells) is injected subcutaneously and treatments initiated when tumor size reaches 200 to 250 mm^3. Tumor dimensions and TGI are assessed. For disseminated models, 5×10^6 AmL primary cells (AmL-PS) are injected intravenously and treatments start after 2 days. Mice are monitored daily for clinical signs of disease, and the median survival time is determined for each group. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cell Death Dis. 2023 Oct 23;14(10):695.
- Comput Struct Biotechnol J. 2019 Feb 8;17:352-361.
- Cancers (Basel). 2022 Mar 19;14(6):1575.
- Eur J Pharmacol. 2023 Aug 23;176004.

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REFERENCES

[1]. Beria I, et al. NMS-P937, a 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor. Bioorg Med Chem Lett. 2011 May 15;21(10):2969-74.

[2]. Valsasina B, et al. NMS-P937, an orally available, specific small-molecule polo-like kinase 1 inhibitor with antitumor activity in solid and hematologic malignancies. Mol Cancer Ther. 2012 Apr;11(4):1006-16.

[3]. Casolaro A, et al. The Polo-Like Kinase 1 (PLK1) inhibitor NMS-P937 is effective in a new model of disseminated primary CD56+ acute monoblastic leukaemia. PLoS One. 2013;8(3):e58424.

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