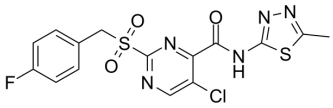
PK11007

Cat. No.:	HY-128784
CAS No.:	874146-69-7
Molecular Formula:	$C_{15}H_{11}ClFN_5O_3S_2$
Molecular Weight:	427.86
Target:	MDM-2/p53; Reactive Oxygen Species
Pathway:	Apoptosis; Immunology/Inflammation; Metabolic Enzyme/Protease; NF-κB
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (584.30 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3372 mL	11.6861 mL	23.3721 mL
	5 mM	0.4674 mL	2.3372 mL	4.6744 mL
	10 mM	0.2337 mL	1.1686 mL	2.3372 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: ≥ 2.08 mg/mL (4.86 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.86 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PK11007 is a mild thiol alkylator with anticancer activity. PK11007 stabilizes p53 via selective alkylation of two surface-exposed cysteines without compromising its DNA binding activity. PK11007 induces mutant p53 cancer cell death by increasing reactive oxygen species (ROS) levels[1][2].

In Vitro

PK11007 (0-120 μM; 24 hours; four p53 wild-type cell lines and fours p53 mutant cell lines) treatment results in a large viability reduction in mutant p53 cell lines MKN1 (V143A), HUH-7 (Y220C), NUGC-3 (Y220C), and SW480 (R273H/P309S) at concentrations ranging from 15 to 30 μM. PK11007 induces mainly caspase-independent cell death[1].
PK11007 (0-60 μM; 3 hours or 6 hours; NUGC-4, NUGC-3, MKN1, HUH-6, and HUH-7 cancer cells) treatment up-regulates protein levels of the p53 target genes p21, MDM2, and PUMA in a mostly concentration-dependent manner in NUGC-3 (p53-Y220C), HUH-7 (p53-Y220C) and MKN1 (p53-V143A) cells, suggesting partial restoration of transcriptional activity to

destabilized p53 mutants. PK11007 also increases p53 activity in HUH-6 and NUGC-4 cells, as indicated by the increase of MDM2, PUMA, and p21 protein levels[1].

PK11007 (15-20 μM; 4.5 hours or 6 hours; MKN1, HUH-7, NUGC-3, HUH-6 cells) treatment increases transcription of p53 target genes in three mutant p53 cell lines after 6-h treatment. PUMA and p21 mRNA levels are up-regulated by a factor of 2 upon treatment of NUGC-3, MKN, and HUH-7 cells, as well as NOXA for the latter two. MDM2 levels are halved in MKN1 and NUGC-3 cells[1].

PK11007 viability reduction is potentiated by glutathione depletion. To test whether PK11007 also increases ROS levels, NUGC-3, NUGC-4, HUH-6, HUH-7, and MKN1 cells with PK11007 are incubated for 2 h. There are elevated ROS levels in all cell lines after 2 h. In the mutant p53 cells MKN1, HUH-7, and NUGC-3, however, the ROS increase is higher at 60 μM PK11007 than in NUGC-4 and HUH-6 cells, suggesting that the higher PK11007 sensitivity of the mutant p53 cell lines is mediated by a stronger ROS induction. Basal and PK11007-induced ROS levels in MKN1 cells are at least twofold higher than in other cell lines[1].

PK11007 inhibits cell proliferation, induces apoptosis and alters genes involved in cell death are all consistent with the ability of PK11007 to reactivate mutant p53[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	p53 wild-type cell lines (WI-38, HUH-6, NUGC-4, SJSA-1) and p53 mutant cell lines (HUH-7, NUGC-3, SW480, MKN1)
Concentration:	0 μM, 20 μM, 40 μM, 60 μM, 80 μM, 100 μM and 120 μM
Incubation Time:	24 hours
Result:	There was a large viability reduction in mutant p53 cell lines MKN1 (V143A), HUH-7 (Y220C), NUGC-3 (Y220C), and SW480 (R273H/P309S) and in p53 WT cell line SJSA-1 at concentrations ranging from 15 to 30 μM. The p53 WT cancer cell lines HUH-6, NUGC-4 and WI-38 were less sensitive with reduced cell viability only at high concentrations of compound (60 and 120 μM).

Western Blot Analysis[1]

Cell Line:	NUGC-4, NUGC-3, MKN1, HUH-6, and HUH-7 cancer cells
Concentration:	0 μM, 15 μM, 30 μM, 60 μM
Incubation Time:	3 hours or 6 hours
Result:	Up-regulated protein levels of the p53 target genes p21, MDM2, and PUMA in a mostly concentration-dependent manner in NUGC-3 (p53-Y220C), HUH-7 (p53-Y220C) and MKN1 (p53-V143A) cells. Also increased p53 activity in HUH-6 and NUGC-4 cells, as indicated by the increase of MDM2, PUMA, and p21 protein levels.

RT-PCR[1]

Cell Line:	MKN1, HUH-7, NUGC-3, HUH-6 cells
Concentration:	15 μM, 20 μM
Incubation Time:	4.5 hours or 6 hours
Result:	Increased transcription of p53 target genes in three mutant p53 cell lines after 6-h treatment. PUMA and p21 mRNA levels were up-regulated by a factor of 2 upon treatment of NUGC-3, MKN, and HUH-7 cells, as well as NOXA for the latter two. MDM2 levels were halved in MKN1 and NUGC-3 cells.

REFERENCES

[1]. Bauer MR, et al. 2-Sulfonylpyrimidines: Mild alkylating agents with anticancer activity toward p53-compromised cells. Proc Natl Acad Sci U S A. 2016 Sep 6;113(36):E5271-80.

[2]. Synnott NC, et al. Mutant p53 as a therapeutic target for the treatment of triple-negative breast cancer: Preclinical investigation with the anti-p53 drug, PK11007. Cancer Lett. 2018 Feb 1;414:99-106

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