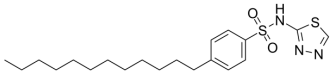
PHT-427

Cat. No.:	HY-12063
CAS No.:	1191951-57-1
Molecular Formula:	$C_{20}H_{31}N_3O_2S_2$
Molecular Weight:	409.61
Target:	Akt; Apoptosis
Pathway:	PI3K/Akt/mTOR; Apoptosis
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 : 25 mg/mL (61.03 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4413 mL	12.2067 mL	24.4135 mL
	5 mM	0.4883 mL	2.4413 mL	4.8827 mL
	10 mM	0.2441 mL	1.2207 mL	2.4413 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: ≥ 2.5 mg/mL (6.10 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.10 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PHT-247 is an inhibitor of the pleckstrin homology (PH) domain of Akt, and it is also an inhibitor of PDPK1 with K_is of 2.7 μM and 5.2 μM and for Akt and PDPK1, respectively.

IC_{50} & Target

PDPK1
5.2 μM (Ki)

In Vitro

The effects of PHT-427 on cell signaling are investigated by RPPA using a panel of 86 antibodies to phospho- and non-phosphorylated signaling protein related to PtdIns-3-K/PDPK1/Akt signaling in PC-3 prostate cells where PtdIns-3-K/PDPK1/Akt signaling is activated because of homozygous PTEN mutation. After 16 hours, a reduction is observed in phospho-Ser^{241}-PDPK1 phospho-Thr^{308}-Akt by both 10 μM PH-427 and 0.1 μM Wortmannin. Finally, phospho-Ser^{657}-protein

	kinase C (PKC) and total SGK1 are decreased by treatment with both PHT-427 and Wortmannin. These results suggest that at 10 μM PHT-427 inhibits both Akt and PDKP1. The BxPC-3 and MiaPaCa-2 pancreatic cancer cell lines are probed by Western blotting following up to 24 hr exposure to 10 μM PHT-427, which is below the IC_{50} for cell growth inhibition of around 30 μM, to determine the effects of PHT-427 on of the PtdIns-3-K/PDPK1/Akt signaling pathway components[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Mice with BxPC-3 pancreatic, MCF-7 breast or A-549 NSCL cancer xenografts are administered PHT-427, or its analogs with a C-4, C-6 or C-8 alkyl chain by oral gavage twice a day for 10 days. The results show that PHT-427 has the greatest antitumor activity with the C-8 chain analog having less activity, and analogs with a C-4 or C-6 chain very little activity. All further antitumor studies are conducted using compound PHT-427. Plasma levels of PHT-427 following oral administration to mice of a dose of 200 mg/kg show rapid absorption, without a lag phase, C_{max} is 8.2 μg/mL 1 hr following dosing, and the elimination half-life is 1.4 hr with a terminal PHT-427 concentration of 0.1 μg/mL 10 hr after dosing. The plasma concentration of PH-427 is above the level which gave inhibition of Akt and PDPK1 signaling in cells of 10 μM (4 μg/mL) for at least 3 hr[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Panc-1 cells stably transfected with green fluorescent protein (GFP) tagged Akt or PDKP1 PH domains are serum starved in phenol red free growth medium on glass-bottom 96-well imaging plates for 16 hours. They are then treated with PHT-427 at 1, 5, and 10 μM or PI-103 for 4 hr, and stimulated with 50 ng/mL IGF-1 for 10 min. Images are taken before and after IGF-1 treatment using an IN Cell Analyzer 1000 instrument with a Nikon Plan Fluor ELWD 20X/0.45 objective loaded and using a 300msec exposure time[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female C57Bl/6 mice are administered PHT-427 as a single oral dose of 200 mg/kg. The mice are killed at different times (3 mice at each time point), blood collected into heparinized tubes and plasma prepared and stored frozen at -80°C. For assay 0.2 mL plasma is mixed with 0.2 mL of 0.1 M sodium phosphate buffer, pH 4.0, and extracted for 1 hr by inversion with 1 ml ethyl acetate. After centrifugation 0.8 mL of the organic layer is removed, evaporated under N_2 and redissolved in 0.2 mL ethanol and 10 μL injected onto a Waters Quattro Ultima tandem mass spectrometer using a Phenomenex Luna 3.0 μm, 2.0×50 mm C8 analytical column with detection and quantification by multiple reaction monitoring with the mass spectrometer operating in electrospray positive ionization mode. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Funct Foods. 55 (2019) 296-304.

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REFERENCES

[1]. Meuillet EJ, et al. Molecular pharmacology and antitumor activity of PHT-427, a novel Akt/phosphatidylinositide-dependent protein kinase 1 pleckstrin homology domain inhibitor. Mol Cancer Ther. 2010 Mar;9(3):706-17.

Caution: Product has not been fully validated for medical applications. For research use only.

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