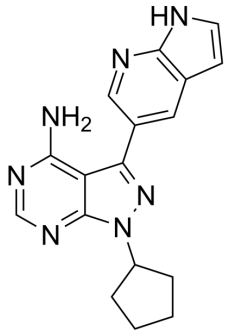
PP121

Cat. No.:	HY-10372
CAS No.:	1092788-83-4
Molecular Formula:	$C_{17}H_{17}N_7$
Molecular Weight:	319.36
Target:	mTOR; PDGFR; VEGFR; Src; Apoptosis
Pathway:	PI3K/Akt/mTOR; Protein Tyrosine Kinase/RTK; 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 : 20 mg/mL (62.63 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1313 mL	15.6563 mL	31.3126 mL
	5 mM	0.6263 mL	3.1313 mL	6.2625 mL
	10 mM	0.3131 mL	1.5656 mL	3.1313 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 mg/mL (6.26 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (6.26 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2 mg/mL (6.26 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PP121 is a multi-targeted kinase inhibitor with IC_{50}s of 10, 60, 12, 14, 2 nM for mTOR, DNK-PK, VEGFR2, Src, PDGFR, respectively.

IC_{50} & Target

mTOR 10 nM (IC_{50})	PDGFR 2 nM (IC_{50})	VEGFR2 12 nM (IC_{50})	Src 14 nM (IC_{50})
DNK-PK 60 nM (IC_{50})			

In Vitro	PP121 blocks the PI3K pathway by direct inhibition of PI3K/mTOR in two glioblastoma cell lines, U87 and LN229. PP121 potently inhibits the proliferation of a diverse panel of tumor cell lines containing mutations in the PI3-K pathway components PIK3CA, PTEN, or RAS. PP121 induces a G_0G_1 arrest in most tumor cells. PP121 directly inhibits Src in cells and reverses its biochemical and morphological effects. PP121 potently inhibits the Ret kinase domain in vitro (IC_{50}<1 nM). PP121 potently blocks VEGF stimulated activation of the PI3-K and MAPK pathways. PP121 inhibits VEGFR2 autophosphorylation at low nanomolar concentrations, confirming that this molecule directly targets VEGFR2 in cells. PP121 inhibits Bcr-Abl induced tyrosine phosphorylation in K562 cells as well as BaF3 cells that express Bcr-Abl[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Oral administration of PP121 remarkably inhibits Eca-109 xenograft growth. Mice body weights are not significantly affected by PP121 or the vehicle treatment. PP121 oral administration dramatically inhibits activations of Akt-mTOR and NFkB in xenograft tumors. p-Akt Ser 473 and p-IKKa/b are both inhibited by PP121 administration[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Purified kinase domains are incubated with inhibitors (PP121) at 2- or 4-fold dilutions over a concentration range of 50-0.001 μM or with vehicle (0.1% DMSO) in the presence of 10 μM ATP, 2.5 μCi of γ- ^{32}P-ATP and substrate. Reactions are terminated by spotting onto nitrocellulose or phosphocellulose membranes, depending on the substrate; this membrane is then washed 5-6 times to remove unbound radioactivity and dried. Transferred radioactivity is quantitated by phosphorimaging and IC_{50} values are calculated by fitting the data to a sigmoidal doseresponse using Prism software[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay	Cells grown in 96-well plates are treated with PP121 at 4-fold dilutions (10 μM - 0.040 μM) or vehicle (0.1% DMSO). After 72 h cells are exposed to Resazurin sodium salt (22 μM) and fluorescence is quantified. IC_{50} values are calculated. For proliferation assays involving single cell counting, non-adherent cells are plated at low density (3–5% confluence) and treated with drug (2.5 μM) or vehicle (0.1% DMSO). Cells are diluted into trypan blue daily and viable cells counted using a hemocytometer[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: Eca-109 cells are injected into the axillary regions of nude mice (5×10^6 cells/mouse). When the tumor volumes reach around 200 mm^3, the mice are randomly separated to three groups: Untreated control, PP121 (30 mg/kg) and vehicle (10% 1-methyl-2-pyrrolidinone and 90% PEG 300) group. Tumor volumes and the mice body weights are measured every 10 d[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Molecules. 2020 Apr 23;25(8):1980.

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REFERENCES

[1]. Apsel B, et al. Targeted polypharmacology: discovery of dual inhibitors of tyrosine and phosphoinositide kinases. Nat Chem Biol, 2008, 4(11), 691-699.

[2]. Peng Y, et al. The anti-esophageal cancer cell activity by a novel tyrosine/phosphoinositide kinase inhibitor PP121. Biochem Biophys Res Commun. 2015 Sep 11;465(1):137-44.

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

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