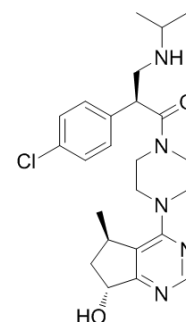


Ipatasertib

Cat. No.:	HY-15186		
CAS No.:	1001264-89-6		
Molecular Formula:	C ₂₄ H ₃₂ ClN ₅ O ₂		
Molecular Weight:	458		
Target:	Akt		
Pathway:	PI3K/Akt/mTOR		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 28 mg/mL (61.14 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Mass Concentration	1 mg	5 mg	10 mg
	1 mM	2.1834 mL	10.9170 mL	21.8341 mL
5 mM	0.4367 mL	2.1834 mL	4.3668 mL	
10 mM	0.2183 mL	1.0917 mL	2.1834 mL	

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

In Vivo

- Add each solvent one by one: **10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline**
Solubility: ≥ 2.08 mg/mL (4.54 mM); Clear solution
- Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
Solubility: ≥ 2.08 mg/mL (4.54 mM); Clear solution
- Add each solvent one by one: **10% DMSO >> 90% corn oil**
Solubility: ≥ 2.08 mg/mL (4.54 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ipatasertib (GDC-0068) is a highly selective and ATP-competitive **pan-Akt** inhibitor with IC₅₀s of 5, 18 and 8 nM for **Akt1**, **Akt2** and **Akt3**, respectively.

IC₅₀ & Target

Akt1 5 nM (IC ₅₀)	Akt3 8 nM (IC ₅₀)	Akt2 18 nM (IC ₅₀)	PKA 3100 nM (IC ₅₀)
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In Vitro	Ipatasertib (GDC-0068) shows more than 600 and more than 100-fold selectivity for Akt1 in IC ₅₀ against the closely related kinases PKA and p70S6K, respectively. When tested at 1 μM in a panel of 230 protein kinases, which includes 36 human AGC family members, GDC-0068 inhibits only 3 other kinases by more than 70% at 1 μM concentration (PRKG1α, PRKG1β, and p70S6K). IC ₅₀ s measured for these 3 kinases are 98, 69, and 860 nM, respectively. Thus, with the exception of PKG1 (relative to which Ipatasertib (GDC-0068) is >10-fold more selective for Akt1), Ipatasertib (GDC-0068) displays a more than 100-fold selectivity for Akt1 over the next most potently inhibited non-Akt kinase, p70S6K, in the screening kinase panel. The relationship between pharmacokinetics (PK) and pharmacodynamics (PD) of Ipatasertib (GDC-0068) is investigated in 3 xenograft models that showed dose-dependent response to drug treatment: MCF7-neo/HER2, TOV-21G.x1, and LNCaP. The mean cell viability IC ₅₀ of GDC-0068 in these 3 cell lines is 2.56, 0.44, and 0.11 μM, respectively ^[2] .
In Vivo	Ipatasertib (GDC-0068) is typically efficacious in xenograft models in which Akt is activated because of genetic alterations including PTEN loss, PIK3CA mutations/amplifications, or HER2 overexpression. In these models, tumor growth delay, stasis, or regression is achieved at or below 100 mg/kg daily oral dose, which is the maximum dose tested in immunocompromised mice that is well tolerated. When tested in vivo, daily dosing of Ipatasertib (GDC-0068) in combination with RP-56976 induces tumor regression and stasis in the PC-3 and MCF7-neo/HER2 xenograft models, at doses where each single agent is ineffective or only causes modest tumor growth delay. Similarly, increased TGI is observed in the OVCAR3 ovarian cancer xenograft model when Ipatasertib (GDC-0068) is combined with NSC 241240. The combination of Ipatasertib (GDC-0068) with RP-56976 or NSC 241240 is tolerated with less than 5% body weight loss when compared with treatment with each chemotherapeutic agent alone ^[2] .

PROTOCOL

Cell Assay ^[2]

The 384-well plates are seeded with 2,000 cells per well in a volume of 54 μL per well followed by incubation at 37°C under 5% CO₂ overnight (~16 hours). Compounds (e.g., Ipatasertib (GDC-0068)) are diluted in DMSO to generate the desired stock concentrations then added in a volume of 6 μL per well. All treatments are tested in quadruplicates. After 4 days incubation, relative numbers of viable cells are estimated using CellTiter-Glo and total luminescence is measured on a Wallac Multilabel Reader. The concentration of drug resulting in IC₅₀ is calculated from a 4-parameter curve analysis (XLfit) and is determined from a minimum of 3 experiments. For cell lines that failed to achieve an IC₅₀, the highest concentration tested (10 μM) is listed^[2].

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

Animal Administration ^[2]

Mice^[2]

In vivo efficacy is evaluated in multiple tumor cell line- and patient-derived xenograft models. Cells or tumor fragments are implanted subcutaneously into the flank of immunocompromised mice. Female or male nude (nu/nu) or severe combined immunodeficient mice (SCID)/beige mice are used. The LuCaP35V patient-derived primary tumors are obtained; male mice are castrated before implantation of tumor fragments. After implantation of tumor cells or fragments into mice, tumors are monitored until they reached mean tumor volumes of 180 to 350 mm³ and distributed into groups of 8 to 10 animals/group. Ipatasertib (GDC-0068) is formulated in 0.5% methylcellulose/0.2% Tween-80 (MCT) and administered daily (QD), via oral (per os; PO) gavage. RP-56976 is formulated in 3% EtOH/97% saline and dosed intravenously (IV) every week (QW) at 2.5 or 7.5 mg/kg. NSC 241240 is formulated in saline and dosed intraperitoneally (IP) weekly at 50 mg/kg.

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

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.

- **Mol Cell.** 2020 Aug 20;S1097-2765(20)30519-0.
- **Mol Cell.** 2019 Jan 3;73(1);22-35.e6.
- **EMBO Rep.** 2020 Feb.
- **Haematologica.** 2019 Jul 9.

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REFERENCES

[1]. Blake JF, et al. Discovery and preclinical pharmacology of a selective ATP-competitive Akt inhibitor (GDC-0068) for the treatment of human tumors. *J Med Chem.* 2012 Sep 27;55(18):8110-27.

[2]. Lin J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. *Clin Cancer Res.* 2013 Apr 1;19(7):1760-72.

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

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