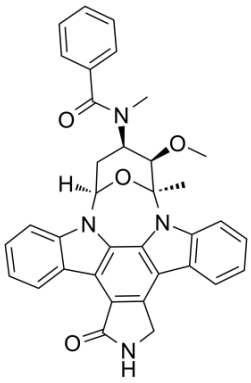
Midostaurin

Cat. No.:	HY-10230
CAS No.:	120685-11-2
Molecular Formula:	$C_{35}H_{30}N_4O_4$
Molecular Weight:	570.64
Target:	PKC
Pathway:	Epigenetics; TGF-beta/Smad
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 : ≥ 50 mg/mL (**87.62 mM**)
H_2O : < 0.1 mg/mL (insoluble)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7524 mL	8.7621 mL	17.5242 mL
5 mM	0.3505 mL	1.7524 mL	3.5048 mL
10 mM	0.1752 mL	0.8762 mL	1.7524 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 (3.65 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.08 mg/mL (3.65 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Midostaurin (PKC412; CGP 41251) is a multi-targeted protein kinase inhibitor which inhibits **PKCα/β/γ**, **Syk**, **Flk-1**, **Akt**, **PKA**, **c-Kit**, **c-Fgr**, **c-Src**, **FLT3**, **PDFRβ** and **VEGFR1/2** with **IC_{50}**s ranging from 22-500 nM[1][2].

IC_{50} & Target

cPKC-α 22 nM (IC_{50})	cPKC-γ 24 nM (IC_{50})	cPKC-β1 30 nM (IC_{50})	cPKC-β2 31 nM (IC_{50})
nPKC-δ	nPKC-η	nPKC-ε	aPKC-ζ

	33 nM (IC_{50})	160 nM (IC_{50})	1250 nM (IC_{50})	465000 nM (IC_{50})
	PPK 38 nM (IC_{50})	KDR 86 nM (IC_{50})	c-Syk 95 nM (IC_{50})	cdk1/cycB 570 nM (IC_{50})
	Protein kinase A 570 nM (IC_{50})	c-Fgr 790 nM (IC_{50})	c-Src 800 nM (IC_{50})	Flt-1 912 nM (IC_{50})
	EGF-R 1100 nM (IC_{50})	Myosin-light chain kinase 1900 nM (IC_{50})	Flk-1 3900 nM (IC_{50})	c-Lyn 4300 nM (IC_{50})
	P70S6 kinase 5000 nM (IC_{50})	CSK 8000 nM (IC_{50})		

In Vitro

Midostaurin (PKC412) shows a broad antiproliferative activity against various tumor and normal cell lines in vitro, and is able to reverse the Pgp-mediated multidrug resistance of tumor cells in vitro. Exposure of cells to Midostaurin (PKC412) results in a dose-dependent increase in the G2/M phase of the cell cycle concomitant with increased polyploidy, apoptosis and enhanced sensitivity to ionizing radiation[1]. Midostaurin (PKC412) induces substantial inhibition of KIT-, Lyn-, and STAT5 activity, but does not suppress Btk in HMC-1 cells and primary neoplastic mast cells[3]. Midostaurin (PKC412) inhibits EN fusion tyrosine kinase in hematopoietic Ba/F3 cells. Midostaurin (PKC412) significantly inhibits EN phosphorylation in M0-91 and IMS-M2 cells in a dose-dependent manner[4].

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

In Vivo

Midostaurin (PKC412) strongly inhibits retinal neovascularization as well as laser-induced choroidal neovascularization in murine models[1]. Midostaurin (PKC412) (25 mg/kg, i.p.) protects mouse livers of the K18 Arg90Cys-overexpressing transgenic mice from Fas-induced apoptosis[5].

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PROTOCOL

Cell Assay [3]

Proliferation is determined by trypan blue dye exclusion test. Cells in suspension are seeded in six-well plates at a density of 1×10^5 cells/mL in the presence of different concentrations of PKC412 for 3 days. In control wells, DMSO instead of Midostaurin (PKC412) is added. After the treatment, 10 µL of the cell suspension is mixed with 10 µL of 0.4% trypan blue, and alive cells are counted manually using a hemacytometer. Results are calculated as the percentage of the values measured when cells are grown in the absence of the reagent. All experiments are performed in triplicate[3].

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Animal Administration [4]

K8-deficient, K18-deficient, and human K18 R90C-overexpressing mice with age of 6-8 weeks are used in the assay. Age and sex matched mice are treated with Midostaurin (25 mg/kg), daily for 4 d or with an equal volume of DMSO as vehicle (both administered intraperitoneally). On day 5 post-treatment, apoptosis is induced by intraperitoneal injection of Fas ligand (Fas-L) (0.15 µg/g body weight). Mice are fasted overnight before Fas Ab injection, and 18 mice are used per DMSO or Midostaurin (PKC412) group for the Fas-treated mice while 6 mice are used per DMSO or Midostaurin (PKC412) group for the control non-Fas-treated mice. Mice are sacrificed by CO_2 inhalation 6 h after Fas Ab injection. Blood is collected by intracardiac puncture, and livers are harvested for hematoxylin and eosin (HE) staining (after fixation in 10% formalin) or frozen in optimum cutting temperature compound for immunofluorescence staining[4].

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

CUSTOMER VALIDATION

- **Cell**. 2018 Sep 20;175(1):171-185.e25.
- **Sci Transl Med**. 2018 Jul 18;10(450). pii: eaaq1093.
- **Cancer Lett**. 2020 Mar 31;473:130-138.
- **Haematologica**. 2018 Nov;103(11):1862-1872.
- **Cancers (Basel)**. 2020 Jun 14;12(6):E1574.

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REFERENCES

[1]. Fabbro D, et al. PKC412--a protein kinase inhibitor with a broad therapeutic potential. Anticancer Drug Des. 2000 Feb;15(1):17-28.

[2]. Gleixner KV, et al. Synergistic growth-inhibitory effects of Midostaurin (PKC412) on neoplastic mast cells carrying KIT D816V. Haematologica. 2013 Sep;98(9):1450-7.

[3]. Chi HT, et al. ETV6-NTRK3 as a therapeutic target of small molecule inhibitor PKC412. Biochem Biophys Res Commun. 2012 Dec 7;429(1-2):87-92.

[4]. Kwan R, et al. PKC412 normalizes mutation-related keratin filament disruption and hepatic injury in mice by promoting keratin-myosin binding. Hepatology. 2015 Dec;62(6):1858-69.

[5]. Fabbro D, et al. Inhibitors of protein kinases: CGP 41251, a protein kinase inhibitor with potential as an anticancer agent. Pharmacol Ther. 1999 May-Jun;82(2-3):293-301.

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