Midostaurin

Cat. No.: HY-10230

CAS No.: 120685-11-2

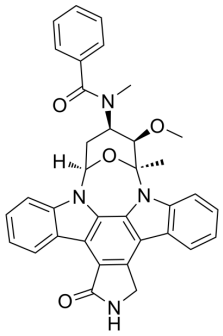
Molecular Formula: $C_{35}H_{30}N_4O_4$

Molecular Weight: 570.64

Target: PKC; Apoptosis; VEGFR; c-Kit; NO Synthase

Pathway: Epigenetics; TGF-beta/Smad; Apoptosis; Protein Tyrosine Kinase/RTK; Immunology/Inflammation

Storage: -20°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (87.62 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / 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: ≥ 2.5 mg/mL (4.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Midostaurin (PKC412; CGP 41251) is an orally active, reversible multi-targeted protein kinase inhibitor. Midostaurin 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]. Midostaurin also upregulates endothelial nitric oxide synthase (eNOS) gene expression. Midostaurin shows powerful anticancer effects[3].

IC_{50} & Target

cPKC-α 22 nM (IC_{50})	eNOS	cPKC-γ 24 nM (IC_{50})	cPKC-β1 30 nM (IC_{50})
cPKC-β2 31 nM (IC_{50})	nPKC-δ 33 nM (IC_{50})	nPKC-η 160 nM (IC_{50})	nPKC-ε 1250 nM (IC_{50})

	aPKC-ζ 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].

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

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].

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

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.

- Blood. 2022 Aug 18;blood.2021015246.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2023 Oct 10;14(1):6332.
- Biomaterials. 16 September 2022.

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REFERENCES

[1]. Huige Li, et al. Midostaurin upregulates eNOS gene expression and preserves eNOS function in the microcirculation of the mouse. Nitric Oxide. 2005 Jun;12(4):231-6.

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

[3]. 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.

[4]. 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.

[5]. 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.

[6]. 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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