Dovitinib

Cat. No.: HY-50905

CAS No.: 405169-16-6

Molecular Formula: $C_{21}H_{21}FN_6O$

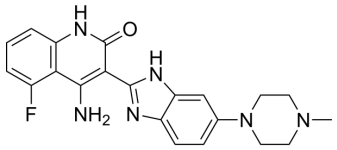
Molecular Weight: 392.43

Target: c-Kit; FLT3; FGFR; VEGFR; PDGFR; c-Fms

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (63.71 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5482 mL	12.7411 mL	25.4823 mL
	5 mM	0.5096 mL	2.5482 mL	5.0965 mL
	10 mM	0.2548 mL	1.2741 mL	2.5482 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 (6.37 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.37 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.37 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Dovitinib (CHIR-258) is an orally active, potent multi-targeted tyrosine kinase (RTK) inhibitor with IC_{50}s of 1, 2, 36, 8/9, 10/13/8, 27/210 nM for FLT3, c-Kit, CSF-1R, FGFR1/FGFR3, VEGFR1/VEGFR2/VEGFR3 and PDGFRα/PDGFRβ, respectively. Dovitinib has potent antitumor activity[1][2].

IC_{50} & Target

FLT3 1 nM (IC_{50})	c-Kit 2 nM (IC_{50})	FGFR1 8 nM (IC_{50})	FGFR3 9 nM (IC_{50})
VEGFR3	VEGFR1	VEGFR2	PDGFRβ

	8 nM (IC_{50})	10 nM (IC_{50})	13 nM (IC_{50})	27 nM (IC_{50})
	PDGFRα 210 nM (IC_{50})	CSF-1R 36 nM (IC_{50})		

In Vitro

Dovitinib (CHIR-258) shows more than 10-fold inhibition InsR (IC50=2 μM), EGFR1 (IC50=2 μM), c-Met (IC50>3 μM), EphrinA2 (EphA2; IC50=4 μM), Tie2 (IC50=4 μM), IGFR1 (IC50>10 μM), and HER2 (IC50>10 μM)[1].

Dovitinib (12.5-400 nM; 48 hours) potently inhibits the FGF-stimulated growth of WT and F384L-FGFR3-expressing B9 cells with IC50 values of 25 nM[1].

Dovitinib (100, 500 nM; 96 hours) inhibits FGF-mediated ERK1/2 phosphorylation and induces apoptosis of FGFR3-expressing human myeloma cell lines[1].

Dovitinib (72 hours) inhibits cell proliferation of KMS11 (FGFR3-Y373C), OPM2 (FGFR3-K650E), and KMS18 (FGFR3-G384D) cells with IC50 of values of 90 nM (KMS11 and OPM2) and 550 nM, respectively[1].

Dovitinib (100 nM) augments Dexamethasone (0.5 μM) cytotoxicity in KMS11 cells[1].

Dovitinib significantly reduces the basal phosphorylation levels of FGFR-1, FGFR substrate 2α (FRS2-α) and ERK1/2 but not Akt in both SK-HEP1 and 21-0208 cells[2].

Dovitinib enhances the BMP-2-induced alkaline phosphatase (ALP) induction, which is a representative marker of osteoblast differentiation. Dovitinib also stimulates the translocation of phosphorylated Smad1/5/8 into the nucleus and phosphorylation of mitogen-activated protein kinases, including ERK1/2 and p38[3].

Dovitinib strongly inhibits both the interaction of TNIK with ATP (K_i, 13 nM) and the activation of Wnt signaling effectors such as β-catenin and TCF4. Dovitinib also induces caspase-dependent apoptosis in IM-9 cells without significant cytotoxicity in PBMCs[4].

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

Cell Viability Assay[1]

Cell Line:	WT and F384L-FGFR3-expressing B9 cells
Concentration:	12.5, 25, 50, 100, 200, 300, 400 nM
Incubation Time:	48 hours
Result:	Potently inhibited the FGF-stimulated growth of the cells.

Apoptosis Analysis[1]

Cell Line:	KMS11, OPM2, and KMS18 cells
Concentration:	100 nM or 500 nM
Incubation Time:	96 hours
Result:	Induced apoptosis of FGFR3-expressing human myeloma cell lines.

In Vivo

Dovitinib (CHIR-258; 10-60 mg/kg/day; gavage; for 21 days) has a significant antitumor effect[1].

Dovitinib (50 and 75 mg/kg) results in 97% and 98% tumor growth inhibition, respectively, and the maximal efficacy is at 50 mg/kg[2].

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

Animal Model:	6- to 8-week-old female BNX mice with KMS11 cells[1]
Dosage:	10, 30, 60 mg/kg
Administration:	Gavage; daily for 21 days
Result:	Had a significant antitumor effect in all 3 dose groups with 48%, 78.5%, and 94% growth

	inhibition in the 10 mg/kg, 30 mg/kg, and 60 mg/kg treatment.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Theranostics. 2018 Jul 30;8(15):4262-4278.
- NPJ Precis Oncol. 2021 Jul 16;5(1):66.
- Front Cell Dev Biol. 2020 May 7;8:287.
- J Biol Chem. 2023 Apr;299(4):104595

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REFERENCES

[1]. Trudel S, et al. CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma. Blood. 2005, 105(7), 2941-2948.

[2]. Huynh H, et al. Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma. J Hepatol. 2012, 56(3), 595-601.

[3]. Lee Y, et al. A Receptor Tyrosine Kinase Inhibitor, Dovitinib (TKI-258), Enhances BMP-2-Induced Osteoblast Differentiation In Vitro. Mol Cells. 2016 May 31;39(5):389-94

[4]. Chon HJ, et al. Traf2- and Nck-interacting kinase (TNIK) is involved in the anti-cancer mechanism of dovitinib in human multiple myeloma IM-9 cells. Amino Acids. 2016 Jul;48(7):1591-9.

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