Cerdulatinib

Cat. No.: HY-15999

CAS No.: 1198300-79-6

Molecular Formula: $C_{20}H_{27}N_7O_3S$

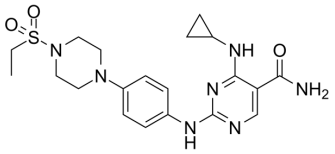
Molecular Weight: 445.54

Target: JAK; Syk

Pathway: Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt

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 : ≥ 30 mg/mL (67.33 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2445 mL	11.2223 mL	22.4447 mL
5 mM	0.4489 mL	2.2445 mL	4.4889 mL
10 mM	0.2244 mL	1.1222 mL	2.2445 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 (5.61 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.61 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cerdulatinib (PRT062070) is a selective Tyk2 inhibitor with an IC_{50} of 0.5 nM. Cerdulatinib (PRT062070) also is a dual JAK and SYK inhibitor with IC_{50}s of 12, 6, 8 and 32 for JAK1, 2, 3 and SYK, respectively.

IC_{50} & Target

Tyk2 0.5 nM (IC_{50})	JAK2 6 nM (IC_{50})	JAK3 8 nM (IC_{50})	JAK1 12 nM (IC_{50})
Syk 32 nM (IC_{50})	MST1 4 nM (IC_{50})	ARK5 4 nM (IC_{50})	MLK1 5 nM (IC_{50})

	FMS 5 nM (IC_{50})	AMPK 6 nM (IC_{50})	TBK1 10 nM (IC_{50})	MARK1 10 nM (IC_{50})
	PAR1B-a 13 nM (IC_{50})	TSSK 14 nM (IC_{50})	MST2 15 nM (IC_{50})	GCK 18 nM (IC_{50})
	JNK3 18 nM (IC_{50})	Rsk2 20 nM (IC_{50})	Rsk4 28 nM (IC_{50})	CHK1 42 nM (IC_{50})
	Flt4 51 nM (IC_{50})	Flt3 90 nM (IC_{50})	Ret 105 nM (IC_{50})	Itk 194 nM (IC_{50})

In Vitro

Cerdulatinib shows inhibitory effect on 60 CLL with IC_{50} ranging from 0.37 to 10.02 μM. Cerdulatinib induces apoptosis in CLL in association with MCL-1 down-regulation and PARP cleavage. Cerdulatinib (2μM) is able to overcome the support of the microenvironment and induces CLL cell death. Cerdulatinib (250-500 nM) blocks proliferation of ibrutinib-sensitive and ibrutinib-resistant primary CLL cells. Cerdulatinib also blocks proliferation of both ibrutinib-sensitive and ibrutinib-resistant primary CLL cells as well as BTKC481S-transfected cell lines, and blocks BCR and JAK-STAT signaling pathways. Furthermore, inhibition of SYK and JAK by cerdulatinib translates to downstream inhibition of AKT and ERK. Cerdulatinib inhibits the activity of NF-kB pathway[1]. PRT062070 reduces the ability of stimulated B cells to upregulate cell-surface expression of the early activation marker CD69 (IC_{50}=0.11 μM). PRT062070 exhibits differential potency against cytokine JAK/STAT signaling pathways. PRT062070 (1 or 3 μM) induces apoptosis in BCR-signaling competent NHL cell lines[2]. Cerdulatinib demonstrates inhibitory activity against both ABC and GCB subtypes of DLBCL cells. Cerdulatinib also induces apoptosis in both GCB and ABC subtypes of DLBCL cell lines via caspase 3 and PARP cleavage. And cerdulatinib blocks cell cycle in both ABC and GCB subtypes of DLBCL via inhibition of RB phosphorylation and down-regulation of cyclin E. Cerdulatinib induces cell cycle arrest and apoptosis under the condition of BCR stimulation in all DLBCL cell lines. Besides, cerdulatinib blocks JAK/STAT and BCR signaling in both ABC and GCB DLBCL cell lines. Cerdulatinib induces cell death in primary human DLBCL samples[3]. Cerdulatinib inhibits BCR-induced signals in a dose-dependent manner and most strongly between 0.3 to 1 μM. and particularly in IGHV-unmutated samples with greater BCR signaling capacity and response to IL4, or samples expressing higher levels of sIgM, $CD49d^+$, or $ZAP70^+$. Cerdulatinib overcomes anti-IgM, IL4/CD40L, or NLC-mediated protection by preventing upregulation of MCL-1 and BCL-X_L; however, BCL-2 expression is unaffected. Furthermore, in samples treated with IL4/CD40L, cerdulatinib synergizes with venetoclax in vitro to induce greater apoptosis than either drug alone[4].

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

In Vivo

PRT062070 (0.5 mg/kg) results in a nonstatistically significant trend toward reduced ankle inflammation, whereas significant reductions in inflammation are achieved with the 1.5, 3, and 5 mg/kg doses. PRT062070 also affects anticollagen antibody formation. PRT062070 (15 mg/kg) suppresses upregulation of splenic B-cell surface CD80/86 and CD69, and inhibits BCR signaling and activation in the spleen after oral dosing in mice[2].

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

PROTOCOL

Cell Assay [1]

TMD8 cells are transfected with constructs of WT BTK or BTKC481S mutants using kit V, Program U-13 on Amaxa Nucleofector. After transfection, the cells are co-cultured with NKTert cells in a 24-well plate for 24 hrs for recovery. Ibrutinib, cerdulatinib and vehicle (DMSO) are then added into the transfected TMD8 cells and cellular viability is determined with Muse™ Count & Viability kit using Muse Cell Analyzer. The cell survival is determined by flow cytometry using the Annexin V/7-AAD Apoptosis Detection Kit I on freshly isolated CLL cells.

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

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- iScience. 2021 Sep 25;24(10):103173.
- Immunohorizons. 2019 May 16;3(5):172-185.
- Patent. US20180263995A1.
- Methods Mol Biol. 2018;1711:351-398.

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REFERENCES

[1]. Guo A, et al. Dual SYK/JAK inhibition overcomes ibrutinib resistance in chronic lymphocytic leukemia: Cerdulatinib, but not ibrutinib, induces apoptosis of tumor cells protected by the microenvironment. Oncotarget. 2017 Feb 21;8(8):12953-12967.

[2]. Coffey G, et al. The novel kinase inhibitor PRT062070 (Cerdulatinib) demonstrates efficacy in models of autoimmunity and B-cell cancer. J Pharmacol Exp Ther. 2014 Dec;351(3):538-48.

[3]. Ma J, et al. Cerdulatinib, a novel dual SYK/JAK kinase inhibitor, has broad anti-tumor activity in both ABC and GCB types of diffuse large B cell lymphoma. Oncotarget. 2015 Dec 22;6(41):43881-96.

[4]. Blunt MD, et al. The Dual Syk/JAK Inhibitor Cerdulatinib Antagonizes B-cell Receptor and Microenvironmental Signaling in Chronic Lymphocytic Leukemia. Clin Cancer Res. 2017 May 1;23(9):2313-2324.

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