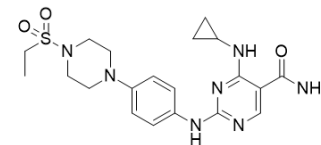


Cerdulatinib

Cat. No.:	HY-15999		
CAS No.:	1198300-79-6		
Molecular Formula:	C ₂₀ H ₂₇ N ₇ O ₃ S		
Molecular Weight:	445.54		
Target:	JAK; Syk		
Pathway:	Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt; Protein Tyrosine Kinase/RTK		
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 : ≥ 30 mg/mL (67.33 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		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

- 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
- 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 IC₅₀ of 0.5 nM. Cerdulatinib (PRT062070) also is a dual JAK and SYK inhibitor with IC₅₀s of 12, 6, 8 and 32 for JAK1, 2, 3 and SYK, respectively.

IC₅₀ & 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 IC₅₀ ranging from 0.37 to 10.02 μM. Cerdulatinib induces apoptosis in CLL in association with MCL-1 down-regulation and PARP cleavage. Cerdulatinib (2 μM) 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-κB pathway^[1]. PRT062070 reduces the ability of stimulated B cells to upregulate cell-surface expression of the early activation marker CD69 (IC₅₀=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].

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].

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

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- **Science**. 2017 Dec 1;358(6367). pii: eaan4368.
 - **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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Caution: Product has not been fully validated for medical applications. For research use only.

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