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产品名称：Cerdulatinib
产品别名：PRT062070; PRT2070

生物活性：

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.					
IC_{50} & Target	Tyk2	JAK2	JAK3	JAK1	Syk	MST1
	0.5 nM (IC_{50})	6 nM (IC_{50})	8 nM (IC_{50})	12 nM (IC_{50})	32 nM (IC_{50})	4 nM (IC_{50})
	ARK5	MLK1	FMS	AMPK	TBK1	MARK1
	4 nM (IC_{50})	5 nM (IC_{50})	5 nM (IC_{50})	6 nM (IC_{50})	10 nM (IC_{50})	10 nM (IC_{50})
	PAR1B-a	TSSK	MST2	GCK	JNK3	Rsk2
	13 nM (IC_{50})	14 nM (IC_{50})	15 nM (IC_{50})	18 nM (IC_{50})	18 nM (IC_{50})	20 nM (IC_{50})
	Rsk4	CHK1	Flt4	Flt3	Ret	Itk
	28 nM (IC_{50})	42 nM (IC_{50})	51 nM (IC_{50})	90 nM (IC_{50})	105 nM (IC_{50})	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 (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 (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					

<table>
<tr><td></td><td>of splenic B-cell surface CD80/86 and CD69, and inhibits BCR signaling and activation in the spleen after oral dosing in mice[2].</td></tr>
<tr><td>Solvent&Solubility</td><td>
In Vitro:
DMSO : ≥ 30 mg/mL (67.33 mM)
* "≥" means soluble, but saturation unknown.
<table>
<tr><td rowspan="4">Preparing Stock Solutions</td><td>Solvent / Mass / Concentration</td><td>1 mg</td><td>5 mg</td><td>10 mg</td></tr>
<tr><td>1 mM</td><td>2.2445 mL</td><td>11.2223 mL</td><td>22.4447 mL</td></tr>
<tr><td>5 mM</td><td>0.4489 mL</td><td>2.2445 mL</td><td>4.4889 mL</td></tr>
<tr><td>10 mM</td><td>0.2244 mL</td><td>1.1222 mL</td><td>2.2445 mL</td></tr>
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*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。
储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。
In Vivo:
请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：
——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶
1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline
Solubility: ≥ 2.5 mg/mL (5.61 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (5.61 mM，饱和度未知) 的澄清溶液。
以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

2.请依序添加每种溶剂： 10% DMSO →90% corn oil
Solubility: ≥ 2.5 mg/mL (5.61 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (5.61 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。
以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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<tr><td>References</td><td>
[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
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	1;23(9):2313-2324.
实验参考：	
Cell Assay	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.
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.