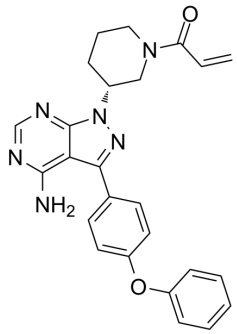
Ibrutinib

Cat. No.:	HY-10997
CAS No.:	936563-96-1
Molecular Formula:	$C_{25}H_{24}N_6O_2$
Molecular Weight:	440.5
Target:	Btk; Ligand for Target Protein for PROTAC
Pathway:	Protein Tyrosine Kinase/RTK; PROTAC
Storage:	4°C, protect from light * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (227.01 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2701 mL	11.3507 mL	22.7015 mL
5 mM	0.4540 mL	2.2701 mL	4.5403 mL
10 mM	0.2270 mL	1.1351 mL	2.2701 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (6.24 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.68 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.68 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.68 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ibrutinib (PCI-32765) is a selective, irreversible Btk inhibitor with an IC_{50} of 0.5 nM[1].

IC_{50} & Target

IC50: 0.5 nM (Btk)

In Vitro

Ibrutinib (PCI-32765) selectively inhibits B-cell signaling and activation. It inhibits autophosphorylation of Btk (IC_{50}=11 nM), phosphorylation of Btk's physiological substrate PLCγ (IC_{50}=29 nM), and phosphorylation of a further downstream kinase, ERK (IC_{50}=13 nM)[1].

	Ibrutinib (PCI-32765) inhibits BCR-activated primary B cell proliferation (IC_{50}=8 nM). Following FcγR stimulation, Ibrutinib (PCI-32765) inhibits TNFα, IL-1β and IL-6 production in primary monocytes (IC_{50}=2.6, 0.5, 3.9 nM, respectively)[3]. Ibrutinib binds C481 (Cysteine481) of BTK with an ideal IC_{50} of 0.5 nM. Ibrutinib cannot form a covalent bond with the hydroxyl group of serine, C481S mutation increases the IC_{50} against BTK-C481S phosphorylation from 2.2 nM to 1 μM[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ibrutinib (PCI-32765) (3.125-50 mg/kg, p.o.) reduces the level of circulating autoantibodies and completely suppresses disease in mice with collagen-induced arthritis. Ibrutinib (PCI-32765) inhibits autoantibody production and the development of kidney disease in the MRL-Fas(lpr) lupus model. Ibrutinib (PCI-32765) (3.125-50 mg/kg, p.o.) reduces renal disease and autoantibody production in MRL-Fas(lpr) mice[1]. Ibrutinib (PCI-32765) (0.1 μM) inhibits activation-induced proliferation of CLL cells, induces selective cytotoxicity in B cells compared with T cells, but alters activation induced T-cell cytokine production[2]. Ibrutinib (PCI-32765) dose-dependently and potently reverses arthritic inflammation in a therapeutic CIA model with an ED_{50} of 2.6 mg/kg/day. Ibrutinib (PCI-32765) also prevents clinical arthritis in CAIA models[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	Primary human B cells are isolated from peripheral blood mononuclear cell using human Miltenyl human B cell Isolation Kit II. In 0.2 mL RPMI plus 10% FBS, 100,000 B cells are treated with Ibrutinib (PCI-32765) (0.3 nM-10 μM) in triplicate wells or vehicle control in 0.1% DMSO final concentration for 30 minutes at 37°C, 5% CO_2, then cells are stimulated with 10 μg/mL anti-IgM $F(ab')_2$, 5 μg/mL anti-CD3/CD28 as a negative control or 0.5 μg/mL PMA (Phorbal 12-myristate 13-acetate) as a positive control. B cells are stimulated for 72 hours at 37°C, 5% CO_2. Proliferation is measured with Cell Titer Glo reagent and measured on a luminometer. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Male DBA1/1OlaHsd mice are injected on days 0 and 21 with Freunds' Complete Adjuvant containing bovine type II collagen. On days 21 to 35, mice are randomized into treatment groups when the average clinical score of each animal is 1.5 (in a scale of 5). Ibrutinib (PCI-32765) treatment (1.56-12.5 mg/kg, p.o.) is initiated following enrollment and continues for 18 days. Clinical scores are given to each mouse daily for each paw. Clinical score assessment is made using the following criteria: 0=normal; 1=one hind paw or fore paw joint affected or minimal diffuse erythema and swelling; 2=two hind or fore paw joints affected or mild diffuse erythema and swelling; 3=three hind or fore paw joints affected or moderate diffuse erythema and swelling; 4=marked diffuse erythema and swelling or four digit joints affected; 5=severe diffuse erythema and severe swelling of entire paw, unable to flex digits. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2020 Apr 13;37(4):551-568.e14.
- Blood. 2021 Jun 16;blood.2021011405.
- Blood. 2016 Jun 23;127(25):3237-52.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Signal Transduct Target Ther. 2020 Sep 14;5(1):200.

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REFERENCES

[1]. Honigberg LA, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A. 2010 Jul 20;107(29):13075-80.

[2]. Herman SE, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011 Jun 9;117(23):6287-96.

[3]. Chang BY, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis Res Ther. 2011 Jul 13;13(4):R115.

[4]. Sun Y, et al. PROTAC-induced BTK degradation as a novel therapy for mutated BTK C481S induced ibrutinib-resistant B-cell malignancies. Cell Res. 2018 Jul;28(7):779-781.

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