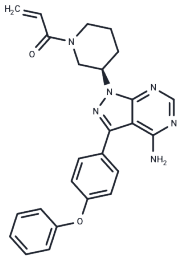
Data Sheet (Cat.No.T1835)

TargetMol

Ibrutinib

Chemical Properties



CAS No. : 936563-96-1

Formula: C25H24N6O2

Molecular Weight: 440.5

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	Ibrutinib (PCI-32765) is an irreversible inhibitor of BTK (IC50: 0.5 nM) that selectively blocks B cell activation.
Targets(IC50)	BTK,Ligands for Target Protein for PROTAC,Src,Tyrosine Kinases
In vitro	In DOHH2, a cell line in which the BCR pathway can be activated by stimulation with anti-IgG, Ibrutinib (PCI-32765) inhibits autophosphorylation of Btk (IC50: 11 nM), phosphorylation of Btk's physiological substrate PLCγ (IC50: 29 nM), and phosphorylation of a further downstream kinase, ERK (IC50: 13 nM). Continuous exposure to 10 nM PCI-32765 for 18 h completely prevented up-regulation of the B-cell activation marker CD69. A 1-h pulse exposure to 10 nM PCI-32765 resulted in a similar level of CD69 inhibition in B cells [1]. PCI-32765 inhibited BCR-activated primary B cell proliferation (IC50: 8 nM). Following FcγR stimulation, PCI-32765 inhibited TNFα, IL-1β and IL-6 production in primary monocytes (IC50s: 2.6/0.5/3.9 nM). Following FcεRI stimulation of cultured human mast cells, PCI-32765 inhibited release of histamine, PGD (2), TNF-α, IL-8, and MCP-1 [2]. Treatment of CD40 or BCR activated CLL cells with PCI-32765 results in inhibition of BTK tyrosine phosphorylation and also effectively abrogates downstream survival pathways activated by this kinase including ERK1/2, PI3K, and NF-κB. In addition, PCI-32765 inhibits activation-induced proliferation of CLL cells in vitro and effectively blocks survival signals provided externally to CLL cells from the microenvironment [3].
In vivo	PCI-32765 (3.125, 12.5, or 50 mg/kg per day) markedly inhibited clinical arthritis scores. Partial and nearly complete elimination of clinical signs of the disease occurred after 9 to 11 d of treatment at dosages of 3.125 and 12.5 mg/kg per day, respectively. An oral single dose of PCI-32765 at 3.125 mg/kg per day resulted in partial Btk occupancy in splenocytes, and the maximally efficacious dose (12.5 mg/kg per day) was sufficient to fully occupy Btk for 12 h [1]. PCI-32765 dose-dependently and potently reversed arthritic inflammation in a therapeutic CIA model (ED50: 2.6 mg/kg/day). PCI-32765 also prevented clinical arthritis in CAIA models. In both models, infiltration of monocytes and macrophages into the synovium was completely inhibited [2].
Kinase Assay	In vitro kinase IC50s were measured using 33P filtration binding assay after 1 h incubation of kinase, 33P-ATP, inhibitor, and substrate [0.2 mg/mL poly(EY)(4:1]. Assays were performed at Reaction Biology [1].

Cell Research	CD20+ B and CD3+ T cells were purified by negative selection (RosetteSep, >90% purity) from buffy coat PBMCs and viably frozen in 10% DMSO. Cells were thawed at 37 °C and maintained in growth media (RPMI media containing 10% FCS). B cells were stimulated with goat anti-human IgM F(ab')2 (10 μg/mL) and T cells were stimulated with anti-CD3/CD28 coated beads at a 1:1 bead/cell ratio. Cells were stained with PE-CD69 and analyzed by flow cytometry, gating on viable lymphocytes. PCI-32765 at concentrations lower than 10 μM did not decrease B- or T-cell viability during the course of the experiment, although PCI-32765 did block the modest survival benefit of anti-IgM stimulation in B cells. For washout experiments, cells were rinsed three times in 10 volumes of growth media, a protocol that was confirmed to completely wash away inhibition of BCR signaling by PCI-29732, a reversible Btk inhibitor [1].
Animal Research	ale DBA/1 mice were immunized with type II collagen plus Freund adjuvant and boosted 21 d later. On a rolling basis, as significant swelling appeared in at least one paw, mice were enrolled and randomized. PCI-32765 or dexamethasone (0.2 mg/kg) was administered orally once per day for 11 d. Arthritis scores (0–5) were assigned to the mice based on the degree and extent of paw swelling. Mouse anti-type II collagen antibody and total IgG levels were measured by ELISA. Female MRL/MpJ-Faslpr mice received PCI-32765 by oral gavage once per day from week 8 through week 20. Proteinuria was monitored weekly. At week 20, serum was collected and analyzed for BUN and mouse anti-dsDNA antibody levels. Kidney histology was scored according to established criteria (26). No drug-induced weight loss was observed at any of the dose levels tested. These studies were carried out at Boulder Biopath according to approved animal care protocols. Results are presented as the mean ± SEM. Statistical significance between groups were evaluated with repeated measures one-way ANOVA or one-way ANOVA using GraphPad Prism with Tukey or Bonferroni multicomparison posttest [1].

Solubility Information

Solubility	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 8.2 mg/mL (18.62 mM),Suspension. Ethanol: < 1 mg/mL (insoluble or slightly soluble), DMSO: 45 mg/mL (102.16 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.2701 mL	11.3507 mL	22.7015 mL
5 mM	0.454 mL	2.2701 mL	4.5403 mL
10 mM	0.227 mL	1.1351 mL	2.2701 mL
50 mM	0.0454 mL	0.227 mL	0.454 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Reference

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.
Guo W, Liang D, Wang P, et al. HIF-PH Encoded by EGLN1 Is a Potential Therapeutic Target for Chronic Lymphocytic Leukemia. Pharmaceuticals. 2022, 15(6): 734
Huang F, Liang J, Lin Y, et al.Repurposing of Ibrutinib and Quizartinib as potent inhibitors of necroptosis. Communications Biology.2023, 6(1): 972.
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.
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.
Zhang Z, Zhou H, Gu W, et al.CGI1746 targets σ1R to modulate ferroptosis through mitochondria-associated membranes.Nature Chemical Biology.2024: 1-11.