Rilzabrutinib

Cat. No.: HY-112166

CAS No.: 1575596-29-0

Molecular Formula: $C_{36}H_{40}FN_9O_3$

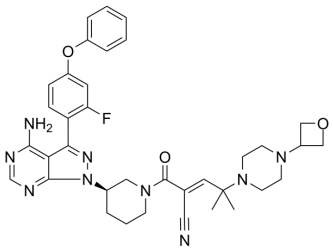
Molecular Weight: 665.76

Target: Btk

Pathway: Protein Tyrosine Kinase/RTK

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 : ≥ 130 mg/mL (195.27 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.5020 mL	7.5102 mL	15.0204 mL
5 mM	0.3004 mL	1.5020 mL	3.0041 mL
10 mM	0.1502 mL	0.7510 mL	1.5020 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: ≥ 2.08 mg/mL (3.12 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.12 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.12 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Rilzabrutinib (PRN1008) is a reversible covalent, selective and oral active inhibitor of Bruton's Tyrosine Kinase (BTK), with an IC_{50} of 1.3 nM.

IC_{50} & Target

BTK 1.3 nM (IC_{50})	BMX 1.0 nM (IC_{50})	ITK 440 nM (IC_{50})	TEC 0.8 nM (IC_{50})
RLK	BLK	EGFR	ERBB2

	1.2 nM (IC_{50})	6.3 nM (IC_{50})	520 nM (IC_{50})	3900 nM (IC_{50})
	ERBB4 11.3 nM (IC_{50})			
In Vitro	Rilzabrutinib is a reversible covalent inhibitor of Bruton's Tyrosine Kinase (BTK), with an IC_{50} of 1.3±0.5 nM. Rilzabrutinib is also found to be highly selectively when tested in a panel of 251 other kinases. Cysteine targeting of BTK by Rilzabrutinib results in a slow off-rate demonstrated by retention of 79±2% of binding to BTK in PBMC 18 hours after washing away the compound in vitro. The covalent cysteine binding is completely reversible after denaturation of the target. Anti-IgM induces human B cell proliferation (10% serum) and B cell CD69 expression are inhibited by Rilzabrutinib with IC_{50} of 5±2.4 nM and 123±38 nM, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.			
In Vivo	In vivo Rilzabrutinib demonstrates enduring pharmacodynamic effects after the compound has cleared from circulation, consistent with extended target residence time. Rilzabrutinib also reverses and completely suppresses collagen-induced arthritis in rats in a dose dependent manner which allows correlation of target occupancy and disease modification[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.			

REFERENCES

[1]. Smith PF, et al. A phase I trial of PRN1008, a novel reversible covalent inhibitor of Bruton's tyrosine kinase, in healthy volunteers. Br J Clin Pharmacol. 2017 Nov;83(11):2367-2376.

[2]. Hill RJ, Bradshaw JM, Bisconte A, Tam D, Owens TD, Brameld KA, Smith PF, Funk JO, Goldstein DM, Nunn PA. Preclinical Characterization of PRN1008, a Novel Reversible Covalent Inhibitor of BTK that Shows Efficacy in a RAT Model of Collagen-Induced Arthritis

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