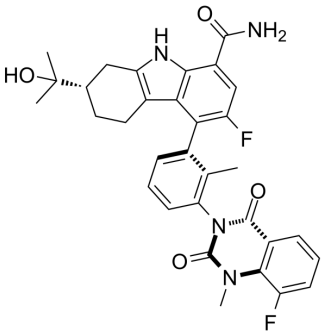
BMS-986142



Cat. No.:	HY-101856
CAS No.:	1643368-58-4
Molecular Formula:	$C_{32}H_{30}F_2N_4O_4$
Molecular Weight:	572.6
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 : 125 mg/mL (218.30 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7464 mL	8.7321 mL	17.4642 mL
	5 mM	0.3493 mL	1.7464 mL	3.4928 mL
	10 mM	0.1746 mL	0.8732 mL	1.7464 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 (3.63 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (3.63 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.63 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS-986142 is a potent and highly selective reversible inhibitor of Bruton's tyrosine kinase (BTK) with an IC_{50} of 0.5 nM.

IC_{50} & Target

IC50: 0.5 nM (BTK), 10 nM (TEC), 15 nM (ITK), 23 nM (BLK), 28 nM (TXK), 32 nM (BMX), 71 nM (LCK), 1100 nM (SRC) [1].

In Vitro

BMS-986142 potently inhibits human recombinant BTK with an IC_{50} of 0.5 nM in enzymatic assays. Against a panel of 384 kinases, BMS-986142 is highly selective, with only five other kinases (Tec, ITK, BLK, Txk, BMX) inhibited with <100-fold selectivity for BTK. Four of these kinases are Tec family kinases, of which BTK is a member, and only Tec (IC_{50}=10 nM) is

	inhibited with <30-fold selectivity compared with BTK. BMS-986142 does not inhibit CD40L-induced expression of CD86 or CD69 on peripheral blood B cells (IC_{50}>10,000 nM for both). When Ramos B cells are treated with anti-IgM to activate BCR, BMS-986142 inhibits BTK-dependent calcium flux with an IC_{50} of 9 nM[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	BMS-986142 at 4, 10, and 30 mg/kg results in dose-dependent reductions of 26%, 43%, and 79% in clinically evident disease, respectively, at the end of the study. Interestingly, 4 mg/kg BMS-986142 provides an additive benefit in clinical scores (54% inhibition) when co-administered with MTX versus 19% inhibition with MTX alone. Co-administration of BMS-986142 at 4 mg/kg with MTX result in a 53% reduction in inflammation and bone resorption compared with 24% and 10%, respectively, with either drug alone. Furthermore, serum anti-collagen II IgG titers are significantly inhibited with 10 and 30 mg/kg BMS-986142. BMS-986142 also produces dose-dependent reductions in clinical scores when administration is delayed until the collagen booster on day 21. BMS-986142 doses of 2, 4, and 25 mg/kg in this therapeutic dosing regimen result in clinical score reductions of 17%, 37%, and 67%, respectively, at the end of the study[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2]	Mice[2] Male DBA/1 mice are injected subcutaneously at the base of the tail with bovine type II collagen (200 μg) admixed. The mice are boosted 21 days later in the same manner. For preventative administration, PO QD dosing is immediately started with BMS-986142 in EtOH: TPGS: PEG300 (5:5:90); for therapeutic administration, start of dosing is delayed until the booster immunization on day 21. For BMS-986142 plus MTX preventative studies, mice receive vehicle; BMS-986142 at 4, 10, or 30 mg/kg; BMS-986142 at 4 mg/kg plus MTX 0.25 mg/kg; or MTX at 0.25 mg/kg daily. For BMS-986142 plus etanercept therapeutic studies, mice receive vehicle daily; BMS-986142 at 2, 4, or 25 mg/kg daily ; BMS-986142 at 2 or 4 mg/kg daily plus etanercept at 15 mg/kg IP twice weekly (BIW); or etanercept at 15 mg/kg IP BIW. For BMS-986142 plus murine cytotoxic T lymphocyte-associated protein 4 immunoglobulin (CTLA-4-Ig) preventative studies, mice receive vehicle daily; BMS-986142 at 10 or 30 mg/kg daily; murine CTLA-4-Ig at 0.05 or 0.2 mg/kg IP BIW; or BMS-986142 at 10 mg/kg daily plus murine CTLA-4-Ig at 0.05 or 0.2 mg/kg IP BIW. Dosing proceed from day 0 through study completion (36 days)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Watterson SH, et al. Discovery of 6-Fluoro-5-(R)-(3-(S)-(8-fluoro-1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)-2-methylphenyl)-2-(S)-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (BMS-986142): A Reversible Inhibitor of Bruton'

[2]. Kathleen M. Gillooly, et al. Bruton'styrosine kinase inhibitor BMS-986142 in experimental models of rheumatoid arthritis enhances efficacy of agents representing clinical standard-of-care. PLoS One. 2017; 12(7): e0181782.

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