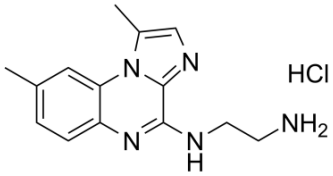
BMS-345541 hydrochloride

Cat. No.:	HY-10518
CAS No.:	547757-23-3
Molecular Formula:	$C_{14}H_{18}ClN_5$
Molecular Weight:	291.78
Target:	IKK
Pathway:	NF-κB

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (68.54 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.4272 mL	17.1362 mL	34.2724 mL
	5 mM	0.6854 mL	3.4272 mL	6.8545 mL
	10 mM	0.3427 mL	1.7136 mL	3.4272 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 mg/mL (6.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (6.85 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2 mg/mL (6.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS-345541 hydrochloride is a selective inhibitor of the catalytic subunits of IKK (IKK-2 IC_{50}=0.3 μM, IKK-1 IC_{50}=4 μM). BMS-345541 binds at an allosteric site of IKK.

IC_{50} & Target

IKK-2	IKK-1
0.3 μM (IC_{50})	4 μM (IC_{50})

In Vitro

BMS-345541 inhibits IKK-2 and IKK-1 in dose-dependent manner. BMS-345541 fails to inhibit a panel of both

	serine/threonine and tyrosine kinases at concentrations as high as 100 μM. MS-345541 at concentrations as high as 100 μM fails to block both the anisomycin-stimulated phosphorylation of c-Jun and LPS-stimulated activation of MAPKAP K2 in THP-1 cells, as well as the EGF-stimulated phosphorylation of STAT3 in H292 cells[1]. BMS-345541 treatment results in a concentration-dependent inhibition of melanoma cell proliferation in SK-MEL-5, A375, and Hs 294T cells. BMS-345541 (0, 100 μM) shows apoptotic features as revealed by TUNEL staining and nuclear condensation[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	BMS-345541 (10 mg/kg, p.o.) results in prolonged serum drug levels, with concentrations sustained at or above 1 μM for many hours in mice. BMS-345541 dose-dependently inhibits the production of TNFα measured in the serum of animals challenged with an intraperitoneal administration of LPS[1]. BMS-345541 (0, 10, 25, and 75 mg/kg, p.o.) effectively inhibits SK-MEL-5 tumor growth in a dose-dependent manner in the mice. Tumor-bearing mice treated with 75 mg/kg of BMS-345541 show effective inhibition of growth of SK-MEL-5, A375, and Hs 294T tumors by 86±2.8%, 69±11% and 67±3.4%, respectively[2]. BMS-345541 (30 and 100 mg/kg, p.o.) is effective in blocking both clinical and histological endpoints of inflammation and injury in mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Assays measuring the enzyme-catalyzed phosphorylation of GST-IκBα are performed by adding enzyme (IKK-2, IKK-1, or IKK-ε, typically to a final concentration of 0.5 μg/mL) at 30°C to solutions of 100 μg/mL GST-IκBα and 5 μM [^{33}P]ATP in 40 mMTris·HCl, pH 7.5, containing 4 mM $MgCl_2$, 34 mM sodium phosphate, 3 mM NaCl, 0.6 mM potassium phosphate, 1 mM KCl, 1 mM dithiothreitol, 3% (w/v) glycerol, and 250 μg/mL bovine serum albumin. The specific activity of [^{33}P]ATP used in the assay is 100 Ci/mmol. After 5 min, the kinase reactions are stopped by the addition of 2× LaemmLi sample buffer and heat-treated at 90°C for 1 min. The samples are then loaded on to NuPAGE 10% BisTris gels. After completion of SDS-PAGE, gels are dried on a slab gel dryer. The bands are then detected using a 445Si PhosphorImager, and the radioactivity is quantified using ImageQuant software. Under these conditions, the degree of phosphorylation of GST-IκBα is linear with time and concentration of enzyme. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Briefly, SK-MEL-5 cells are treated with BMS-345541 at different concentrations or for different time periods. The cells are collected by trypsinization, fixed in 70% ethanol for 2 hours on ice and stained with PI solution (PBS containing 2 μg/mL PI, 0.1% Triton X-100, and 125 units/mL RNase A) at 37°C for 30 minutes. Cell fluorescence is measured by flow cytometry with 488 nm excitation and 620 nm emission filters and resulting data are analyzed using the software program MultiCycle. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	BMS-345541 is administered either by intravenous tail vein injection or by peroral gavage to groups of three 18-22-g female BALB/c mice. BMS-345541 is formulated as a 2 mg/mL solution in 3% Tween 80, water. Mice receive either a 2 mg/kg (1 mL/kg) intravenous bolus or a 10 mg/kg (5 mL/kg) peroral gavage. Whole blood samples are taken from individual mice by orbital bleed and cardiac puncture at 0, 0.05, 0.25, 0.5, 1.0, 3.0, 6.0, and 8.0 h after dosing. Whole blood is centrifuged at $20\times10^3\times g$ for 5 min. Serum is stored at −20°C until analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2015 Mar 9;27(3):409-25.
- Cell Res. 2019 Mar;29(3):193-205.
- Sci Transl Med. 2021 Jan 27;13(578):eaba7308.
- Cell Syst. 2018 Apr 25;6(4):424-443.e7.

- J Dent Res. 2019 Jul;98(8):896-903.

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REFERENCES

[1]. Burke JR, et al. BMS-345541 is a highly selective inhibitor of I kappa B kinase that binds at an allosteric site of the enzyme and blocks NF-kappa B-dependent transcription in mice. J Biol Chem, 2003, 278(3), 1450-1456.

[2]. Yang J, et al. BMS-345541 targets inhibitor of kappaB kinase and induces apoptosis in melanoma: involvement of nuclear factor kappaB and mitochondria pathways. Clin Cancer Res, 2006, 12(3 Pt 1), 950-960.

[3]. MacMaster JF, et al. An inhibitor of IkappaB kinase, BMS-345541, blocks endothelial cell adhesion molecule expression and reduces the severity of dextran sulfate sodium-induced colitis in mice. Inflamm Res, 2003, 52(12), 508-511.

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