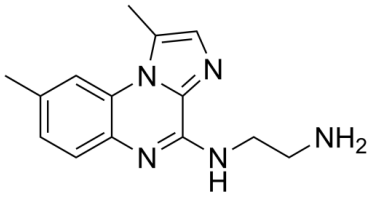
Data Sheet

Product Name:	BMS-345541
Cat. No.:	CS-1238
CAS No.:	445430-58-0
Molecular Formula:	$C_{14}H_{17}N_5$
Molecular Weight:	255.32
Target:	IKK
Pathway:	NF-κB
Solubility:	DMSO : 10 mg/mL (39.17 mM; Need ultrasonic); H2O : 10 mg/mL (39.17 mM; ultrasonic and warming and heat to 60°C)



BIOLOGICAL ACTIVITY:

BMS-345541 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. IC50 & Target: IC50: 0.3 μM (IKK-2), 4 μM (IKK-1)[1] ***In Vitro:*** BMS-345541 selectively inhibits the stimulated phosphorylation of IκBα in cells (IC_{50}=4 μM). Consistent with the role of IKK/NF-κB in the regulation of cytokine transcription, BMS-345541 inhibits lipopolysaccharide-stimulated tumor necrosis factor α, interleukin-1β, interleukin-8, and interleukin-6 in THP-1 cells with IC_{50} values in the 1 to 5 μM range[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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

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 mM Tris-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[1].

Cell Assay: BMS-345541 is dissolved in DMSO to produce a 50 mM stock solution and then diluted before use[2].[2]**SK-MEL-5 cells** are treated with **BMS-345541** at different concentrations (**0, 1.0, 10, and 100 μM**) 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[2].

Animal Administration: BMS-345541 is formulated as a 2 mg/mL solution in 3% Tween 80, water[1].[1]Mice[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.

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.

CAIndexNames:

1,2-Ethanediamine, N1-(1,8-dimethylimidazo[1,2-a]quinoxalin-4-yl)-

SMILES:

CC1=CN=C2C(NCCN)=NC3=CC=C(C)C=C3N21

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