BI-847325

Cat. No.: HY-18955

CAS No.: 1207293-36-4

Molecular Formula: $C_{29}H_{28}N_4O_2$

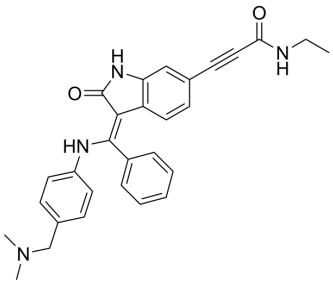
Molecular Weight: 464.56

Target: MEK; Aurora Kinase; Apoptosis

Pathway: MAPK/ERK Pathway; Cell Cycle/DNA Damage; Epigenetics; Apoptosis

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 : 16.67 mg/mL (35.88 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1526 mL	10.7629 mL	21.5257 mL
5 mM	0.4305 mL	2.1526 mL	4.3051 mL
10 mM	0.2153 mL	1.0763 mL	2.1526 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: ≥ 1.67 mg/mL (3.59 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.67 mg/mL (3.59 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BI-847325 is an ATP competitive dual inhibitor of MEK and aurora kinases (AK) with IC_{50} values of 4 and 15 nM for human MEK2 and AK-C, respectively. BI-847325 is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups.

IC_{50} & Target

MEK2	Aurora C
4 nM (IC_{50})	15 nM (IC_{50})

In Vitro

BI 847325 inhibits the activity of X. laevis AK-B with an IC_{50} of 3 nM; the IC_{50} values for human AK-A and AK-C are 25 and 15 nM, respectively. BI 847325 also inhibits human MEK1 and MEK2 with respective IC_{50} values of 25 and 4 nM. BI 847325 at 1,000 nM inhibits 6 enzymes by more than 50% (LCK, MAP3K8, FGFR1, AMPK, CAMK1D and TBK1) and the IC_{50} values are

	below 100 nM only for LCK (5 nM) and MAP3K8 (93 nM). Proliferation is inhibited in A375 and Calu-6 cell lines with GI_{50} values of 7.5 nM and 60 nM, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Daily oral administration of BI 847325 at 10 mg/kg shows efficacy in both BRAF- and KRAS-mutant xenograft models. BI 847325 administered once weekly at 70 mg/kg inhibits both MEK and AK in KRAS-mutant tumors[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Assays are run in the presence of 100 μM ATP using 10 μM of substrate. 30 μL PROTEIN-MIX in 25% DMSO and incubated for 15 min at room temperature. 10 μL PEPTIDE-MIX is added, the mixture is incubated for 60 min at RT and stopped by adding 180 μL 6.4% TCA (final concentration: 5%). Incorporated phosphate is measured in a scintillation counter and IC_{50} values are calculated using a sigmoidal curve analysis program with variable hill slope[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cells are plated in 96-well format and BI 847325 is added 24 hours after cell seeding. At the same time, a “time zero” untreated cell plate is fixed. Compound is serially diluted and assayed over 8 concentrations in triplicates. After 72 h incubation, cells are fixed and stained with fluorescent nuclear dye. Concentration–response curves are analyzed using a four-parameter log-logistic function without upper or lower limitation. GI_{50} are calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Tumor grafted female BomTac:NMRI-Foxn1^{nu} mice are used in the study. BI 847325 is dissolved in 0.5% Natrosol 250 HX with 3% Tween 80 and sonicated until a homogenous suspension is obtained, then 1 M HCl is added and the suspension is vortexed and sonicated again. MEK inhibitors GSK 1120212 and AZD 6244 are suspended in 1% or 0.5% Natrosol, respectively. An administration volume of 10 mL/kg body weight is used and compounds are administered orally with a gavage needle at the indicated dose and schedule. Tumor volumes are measured and mice are inspected daily for clinical signs and body weight is determined daily[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Sini P, et al. Pharmacological Profile of BI 847325, an Orally Bioavailable, ATP-Competitive Inhibitor of MEK and Aurora Kinases. Mol Cancer Ther. 2016 Oct;15(10):2388-2398.

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