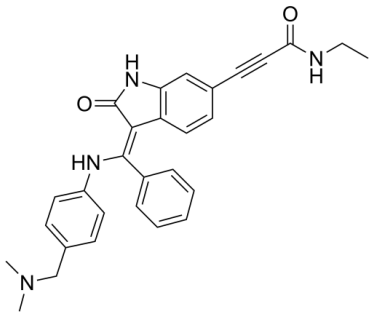
Data Sheet

Product Name:	BI-847325
Cat. No.:	CS-6291
CAS No.:	1207293-36-4
Molecular Formula:	$C_{29}H_{28}N_4O_2$
Molecular Weight:	464.56
Target:	Apoptosis; Aurora Kinase; MEK
Pathway:	Apoptosis; Cell Cycle/DNA Damage; Epigenetics; MAPK/ERK Pathway
Solubility:	DMSO : 16.67 mg/mL (35.88 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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, itcontains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups. IC50 & Target: IC50: 25 nM (hAK-A), 15 nM (hAK-C), 25 nM (MEK1), 4 nM (MEK2)[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **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]. **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].

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.

CAIndexNames:

2-Propynamide, 3-[3-[[[4-[(dimethylamino)methyl]phenyl]amino]phenylmethylene]-2,3-dihydro-2-oxo-1H-indol-6-yl]-N-ethyl-

SMILES:

O=C(NCC)C#CC1=CC(NC/2=O)=C(C=C1)C2=C(NC3=CC=C(CN(C)C)C=C3)/C4=CC=CC=C4

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