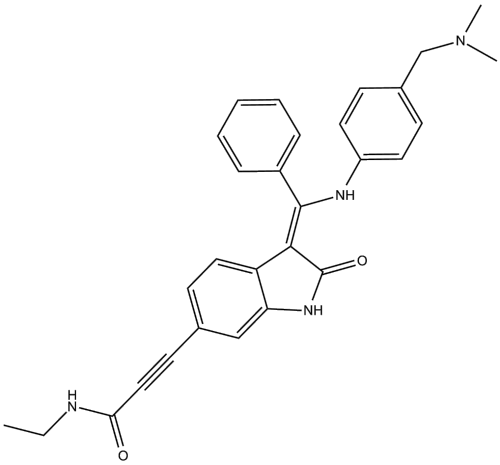
Product Data Sheet

Product Name: BI-847325
Cat. No.: GC17828

Chemical Properties

Cas. No.	1207293-36-4		
Chemical Name	(Z)-3-(3-(((4-((dimethylamino)methyl)phenyl)amino)(phenyl)methylene)-2-oxoindolin-6-yl)-N-ethylpropiolamide		
SMILES	CCNC(C#CC1=CC=C2C(NC(/C2=C(NC3=CC=C(CN(C)C)C=C3)/C4=CC=CC=C4)=O)=C1)=O		
Formula	$C_{29}H_{28}N_4O_2$	M.Wt	464.56
Solubility	DMF: 16 mg/ml,DMF:PBS(pH 7.2) (1:6): 0.14 mg/ml,DMSO: 5 mg/ml,Ethanol: 0.3 mg/ml	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

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Kinase experiment: 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 IC50 values are calculated using a sigmoidal curve analysis program with variable hill slope[1].

Cell experiment: 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. GI50 are calculated[1].

Animal experiment: Mice: Tumor grafted female BomTac:NMRI-Foxn1nu 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.

Background

Product Data Sheet

BI 847325 is a dual inhibitor of Ras-mitogen-activated protein kinase kinases (MEK) and Aurora kinases [1,2]. BI 847325 inhibits MEK1 and MEK2 with IC50 values of 25 and 4 nM, respectively. For inhibiting the activity of Aurora A, B and C, IC50 values are 3, 25 and 15 nM, respectively [1].

The RAS-dependent MAP kinase signaling pathway is important in the regulation of cell survival and proliferation. It is hard to design direct inhibitors of RAS proteins. MEK is a downstream kinase of MAP kinase [1]. MEK is a ERK kinase [3].

In cells treated with BI 847325, based on levels of phospho-histone H3 (pHH3) and phospho-ERK (pERK), EC50 values were determined. To KRAS-and-PI3Kα-mutant NCI-H460 cells, the EC50 value was 44 nM. To BRAF-mutant A375 cells, the EC50 value was 37 nM. In a panel of 240 cell lines from diverse tissues with diverse genetic background, BI 847325 produced a potent inhibition of cell proliferation with a gm GI50 value of 28 nM. In a subset of cell lines, BI 847325 induced cell death. These in vitro potency correlated with mutations in BRAF or RAS, significantly [1].

In nude mouse xenograft models of cutaneous melanoma (A375, mutant BRAF) and NSCLC (Calu-6, mutant KRAS), BI 847325 at a daily oral dose of 10 mg/kg produced complete inhibition of tumor growth. In animals with A375 tumors, treatment with BI 847325 significantly reduced levels of both pHH3 and pERK in the tumors compared to controls [1].

References:
[1]. Sini P, Gürtler U, Zahn SK, et al. Pharmacological characterization of BI 847325, a dual inhibitor of MEK and Aurora kinases. Cancer Research, 2012, 72(8 Supplement): 1919-1919.
[2]. Hideshima T, Chauhan D, Richardson P, et al. NF-κB as a therapeutic target in multiple myeloma. Journal of Biological Chemistry, 2002, 277(19): 16639-16647.
[3]. Rommel C, Clarke BA, Zimmermann S, et al. Differentiation stage-specific inhibition of the Raf-MEK-ERK pathway by Akt. Science, 1999, 286(5445): 1738-1741..

Caution: Product has not been fully validated for medical applications. For research use only.
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