

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

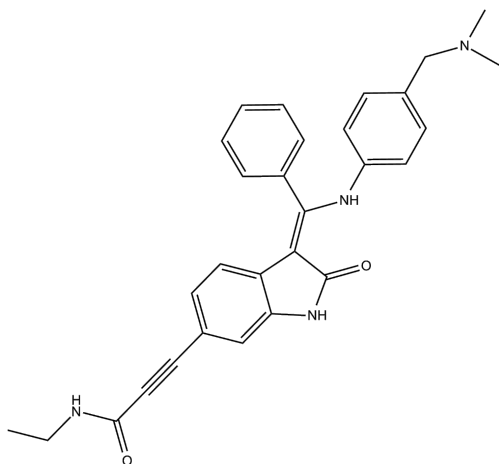
Formula $C_{29}H_{28}N_4O_2$ M.Wt 464.56

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

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

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Kinase experiment:	Assays are run in the presence of 100 μ M ATP using 10 μ M of substrate. 30 μ L PROTEIN-MIX in 25% DMSO and incubated for 15 min at room temperature. 10 μ L PEPTIDE-MIX is added, the mixture is incubated for 60 min at RT and stopped by adding 180 μ L 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

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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-PI3K α -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- κ B 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..

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