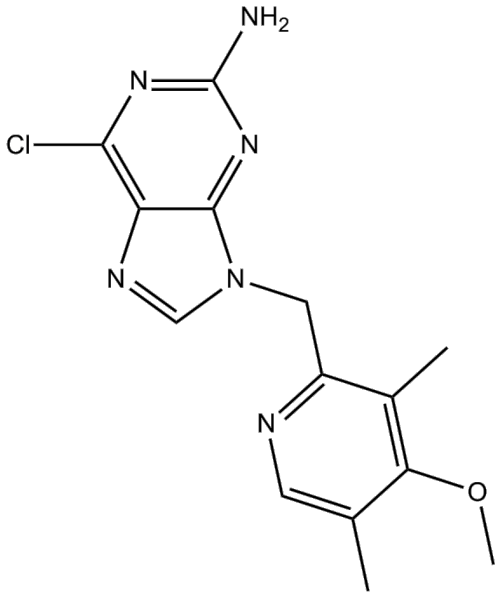
Product Data Sheet

Product Name: BIIB021
Cat. No.: GC12218

Chemical Properties

Cas. No.	848695-25-0		
Chemical Name	6-chloro-9-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]purin-2-amine		
SMILES	CC1=CN=C(C(=C1OC)C)CN2C=NC3=C2N=C(N=C3Cl)N		
Formula	$C_{14}H_{15}ClN_6O$	M.Wt	318.8
Solubility	≥ 14.95 mg/mL in DMSO	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

Product Data Sheet

Kinase experiment: For fluorescence polarization competition measurements, the FITC-geldanamycin probe (20 nM) is reduced with 2 mM TCEP at room temperature for 3 hours, after which the solution is aliquoted and stored at -80°C until used. Recombinant human Hsp90α (0.8 nM) and reduced FITC-geldanamycin (2 nM) are incubated in a 96-well microplate at room temperature for 3 hours in the presence of assay buffer containing 20 mM HEPES (pH 7.4), 50 mM KCl, 5 mM MgCl2, 20 mM Na2MoO4, 2 mM DTT, 0.1 mg/mL BGG, and 0.1% (v/v) CHAPS. Following this preincubation, BIIB021 in 100% DMSO is then added to final concentrations of 0.2 nM to 10 μM (final volume 100 μL, 2% DMSO). The reaction is incubated for 16 hours at room temperature and fluorescence is then measured in an Analyst plate reader, excitation=485 nm, emission=535 nm. High and low controls contain no BIIB021 or no Hsp90, respectively. The data are fit to a four-parameter curve and IC50 is generated.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Cell experiment: A modified tetrazolium salt assay is used to measure the IC50. Tumor cells are added to 96-well plates and propagated for 24 hours before BIIB021 addition. BIIB021 is added to the plated cells. DMSO (0.03-0.003%) is included as a vehicle control. After incubation phenazine methosulfate (stock concentration 1 mg/mL) and 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (stock concentration 2 mg/mL) are mixed at a ratio of 1:20 and added to each well of a 96-well plate. Reduction of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt gives rise to a soluble formazan product that is secreted into the culture medium. After 4 hours incubation, the formazan product is quantitated spectrophotometrically at a wavelength of 490 nm. Data are acquired using SOFTmaxPRO software, and 100% viability is defined as the A490 of DMSO-treated cells stained with 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (the mean A490 of cells treated with DMSO at a range of 0.03-0.003%). Percent viability of each sample is calculated from the A490 values as follows: % viability=(A490 nm sample/A490 nm DMSO-treated cells × 100). The IC50 is defined as the concentration that gives rise to 50% inhibition of cell viability.

Caution: Product has not been fully validated for medical applications. For research use only.
Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Animal experiment: BALB/c and athymic mice are obtained from Harlan Sprague-Dawley at age 6 to 8 weeks. The mice are maintained in sterilized cages in a ventilated caging system with a 12 h light/12 h dark photoperiod at temperature of 21°C to 23°C and a relative humidity of 50±5%. Irradiated pelleted food and autoclaved deionized water are provided ad libitum. Animals are identified by the use of individually numbered ear tags. N87 tumor fragments (appr 2 mm3) are implanted s.c. in the right flank of the animal. BIIB021 is administered to animals bearing N87 stomach carcinoma tumors at doses of 31, 62.5, and 125 mg/kg, once daily, from Monday to Friday, for 5 weeks. Tumor dimensions are measured using calipers and tumor volumes are calculated using the equation for an ellipsoid sphere (l×w2)/2=mm3, where l and w refer to the larger and smaller dimensions collected at each measurement, respectively. Tumor volumes are measured and animals are weighed and monitored for toxicity at least twice weekly. P values are calculated using the two-tailed Student's t test to assess the difference in tumor volumes between control and treated groups. $P<0.05$ is considered significant.

References:

[1]. Lundgren, Karen., et al. BIIB021, an orally available, fully synthetic small-molecule inhibitor of the heat shock protein Hsp90. Molecular Cancer Therapeutics (2009), 8(4), 921-929.
[2]. B ll B, et al. Heat shock protein 90 inhibitor BIIB021 (CNF2024) depletes NF-kappaB and sensitizes Hodgkin's lymphoma cells for natural killer cell-mediated cytotoxicity. Clin Cancer Res. 2009 Aug 15;15(16):5108-16.
[3]. Yin X, et al. BIIB021, a novel Hsp90 inhibitor, sensitizes head and neck squamous cell carcinoma to radiotherapy. Int J Cancer. 2010 Mar 1;126(5):1216-25
[4]. Zhang H, et al. BIIB021, a synthetic Hsp90 inhibitor, has broad application against tumors with acquired multidrug resistance. Int J Cancer. 2010 Mar 1;126(5):1226-34

Background

BIIB021 is a selective inhibitor of Hsp90 with Ki and EC50 values of 1.7 nM and 38 nM, respectively.

Product Data Sheet

[1]
HSP90 (heat shock protein 90) is widely expressed as a molecular chaperone. It plays a major role in the folding and stabilization of cellular proteins. HSP90 protects client proteins from degradation and maintains them in an active conformation. Many clients of HSP90 are transcription factors or protein kinases such as: Bcr-Abl, tyrosine kinases, EGFR family members, IGF1-R, c-Met, steroid hormone receptors, p53, Mdm2 and telomerase. In a variety of cancers, overexpressed hsp90 has been found. Hsp90 also play an important role in maintaining the transformed phenotype of cancer cells so. Hsp 90 is one attractive target for cancer therapy.[2]
BIIB021 competitive binds in the ATP-binding pocket and inhibits Hsp90 chaperone function, and lead to client protein degradation, cell death and tumor growth inhibition. BIIB021 leads to degradation of HER-2 which is an Hsp90 client protein. BIIB021 can also the growth of a variety of cancer cell lines in cell proliferation assays. In MCF-7 cells, BIIB021 leaded to HER-2 degradation with the EC50 value of was38 ± 10 nmol/L. BIIB021 inhibit the cell proliferation with IC50 values of 0.06 μ mol/L in N87 cells, 0.31μ mol/L in MCF-7 cells and 0.14 μ mol/L in BT474 cells. In MCF-7 cells, BIIB021 significantly reduced the phosphorylation levels of HER-2 at a concentration of 50 nM.[1] BIIB021 selectively inhibited Hodgkin's lymphoma cell viability at nanomolar concentrations but not in lymphocytes from healthy individuals. BIIB021 can increase the susceptibility to NK cell mediated killing by inducing the expression of ligands for the activating NK cell receptor NKG2D on Hodgkin's lymphoma cells.[3] BIIB021 reduced the expression of key radioresponsive proteins, then enhanced the radiosensitivity of HNSCCA cell lines in vitro, increased apoptosis cells and induced G2 arrest.[2]
BIIB021 showed significant activity at doses of 31,62.5, and 125 mg/kg in human in nude mice bearing N87 stomach carcinoma tumors.[1] HSP90 significantly inhibited tumor growth in a xenograft model of Hodgkin's lymphoma.[1]

References:

1.Lundgren K, Zhang H, Brekken J, Huser N, Powell RE, Timple N, Busch DJ, Neely L, Sensintaffar JL, Yang YC et al: BIIB021, an orally available, fully synthetic small-molecule inhibitor of the heat shock protein Hsp90. Mol Cancer Ther 2009, 8(4):921-929.
2.Yin X, Zhang H, Lundgren K, Wilson L, Burrows F, Shores CG: BIIB021, a novel Hsp90 inhibitor, sensitizes head and neck squamous cell carcinoma to radiotherapy. Int J Cancer 2010, 126(5):1216-1225.
3.Boll B, Eltaib F, Reiners KS, von Tresckow B, Tawadros S, Simhadri VR, Burrows FJ, Lundgren K, Hansen HP, Engert A et al: Heat shock protein 90 inhibitor BIIB021 (CNF2024) depletes NF-kappaB

and sensitizes Hodgkin's lymphoma cells for natural killer cell-mediated cytotoxicity. Clin Cancer Res 2009, 15(16):5108-5116.