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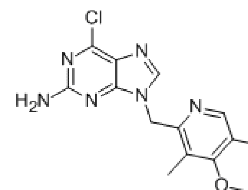
BIIB021 Datasheet

Technical Data

Molecular Weight (MW)	318.76
Formula	$C_{14}H_{15}ClN_6O$
CAS No.	848695-25-0, 848696-06-0 (XHCl), 848696-07-1 (methanesulfonate)
Synonyms	CNF2024

Solubility (25°C)	DMSO 64 mg/mL		
	Water <1 mg/mL		
	Ethanol 2 mg/mL		
Storage	2 years	-20°C	Powder
	2 weeks	4°C	in DMSO
	6 months	-80°C	in DMSO

BIIB021 Chemical Structure



Biological Activity

Description	BIIB021 is a novel inhibitor of **HSP90** with **K_i** and **EC50** of 1.7 nM and 38 nM, respectivley.
Targets	HSP90
IC50	1.7 nM (K_i) and 38 nM (EC50)
In vitro	BIIB021 binds in the ATP-binding pocket of Hsp90, interferes with Hsp90 chaperone function, and results in client protein degradation and tumor growth inhibition. BIIB021 inhibits tumor cell (BT474, MCF-7, N87, HT29, H1650, H1299, H69 and H82) proliferation with IC50 from 0.06-0.31 μM. BIIB021 induces the degradation of Hsp90 client proteins including HER-2, Akt, and Raf-1 and up-regulated expression of the heat shock proteins Hsp70 and Hsp27. [1] BIIB021 inhibits Hodgkin's lymphoma cells (KM-H2, L428, L540, L540cy, L591, L1236 and DEV) with IC50 from 0.24-0.8 μM. BIIB021 shows low activity in lymphocytes from healthy individuals. BIIB021 inhibits the constitutive activity of NF-κB despite defective IκB. BIIB021 induces the expression of ligands for the activating NK cell receptor NKG2D on Hodgkin's lymphoma cells resulting in an increased susceptibility to NK cell–mediated killing. [2] BIIB021 enhanced the in vitro radiosensitivity of HNSCCA cell lines (UM11B and JHU12) with a corresponding reduction in the expression of key radioresponsive proteins, increased apoptotic cells and enhance G2 arrest. [3] BIIB021 is considerably more active than 17-AAG against adrenocortical carcinoma H295R, both in vitro and in vivo. The cytotoxic activity of BIIB021 is not influenced by loss of NQO1 or Bcl-2 overexpression, molecular lesions that do not prevent client loss but are nonetheless associated with reduced cell killing by 17-AAG. BIIB021 is also active in 17-AAG resistant cell lines (NIH-H69, MES SA Dx5, NCI-ADR-RES, Nalm6 and etc.). [4]
In vivo	Oral administration of BIIB021 leads to tumor growth inhibition in many tumor xenograft models including N87, BT474, CWR22, U87, SKOV3 and Panc-1. [1] BIIB021 effectively inhibits growth of L540cy tumor at a dose of 120 mg/kg. [2] BIIB021 significantly enhances antitumor growth effect of radiation in JHU12 xenograft. [3]
Clinical Trials	Phase II study in subjects with gastrointestinal stromal tumors has been completed.
Features	

Protocol (Only for Reference)

Kinase Assay: [1]

Hsp90 Binding Assay	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 $MgCl_2$, 20 mM Na_2MoO_4, 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 contained no BIIB021 or no Hsp90, respectively. The data are fit to a four-parameter curve and IC50 is generated.
HER-2 Degradation Assay	MCF-7 cells (5 × 10^5) in complete DMEM are seeded per well in 24-well plates. The cells are propagated for 24 hours before BIIB021 addition. BIIB021 (1 mM) is prepared in DMSO and serially diluted in complete DMEM. Cells are incubated in the presence of serially diluted BIIB021 for 16 hours. Following incubation, cells are rinsed with PBS and then trypsinized. After stopping the trypsin reaction with fetal bovine serum, the cell suspensions are washed in PBS containing 0.2% bovine serum albumin and 0.2% sodium azide (BA buffer) and then resuspended in 100 μL phycoerythrin-conjugated anti-HER-2 IgG antibody. Untreated cells are resuspended in anti-KLH antibody as background controls. Cells are incubated 15 min at room temperature, washed twice in 200 μL BA buffer, resuspended in 200 μL BA buffer, and transferred to 5 mL round polystyrene tubes. An additional 250 μL BA buffer is then added to each tube. Samples are analyzed using a FACSCalibur flow cytometer equipped with argon-ion laser that emits 15 mW of 488 nm light for excitation of the phycoerythrin fluorochrome.

Cell Assay: [1]

Cell Lines	BT474, MCF-7, N87, HT29, H1650, H1299, H69 and H82 cells
Concentrations	3 nM - 1 μM

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Incubation Time	5 days
Methods	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.

Animal Study:[1]

Animal Models	N87, BT474, CWR22, U87, SKOV3 and Panc-1 tumor models in BALB/c and athymic mice
Formulation	Phospho-lipon/sucrose emulsion [2]
Doses	31, 62.5, and 125 mg/kg
Administration	Orally administered once daily

References

[1] Lundgren K, et al. Mol Cancer Ther, 2009, 8(4), 921-929.
[2] Böll B, et al. Clin Cancer Res, 2009, 15(16), 5108-5116.
[3] Yin X, et al. Int J Cancer, 2010, 126(5), 1216-1225.
[4] Zhang H, et al. Int J Cancer, 2010, 126(5), 1226-1234.

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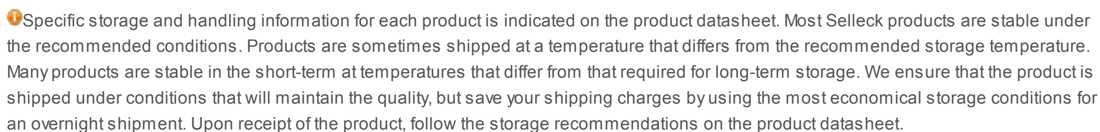
NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE



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