BIIB021

Cat. No.: HY-10212
CAS No.: 848695-25-0
Molecular Formula: C₁₄H₁₅ClN₆O
Molecular Weight: 318.76
Target: HSP; Autophagy
Pathway: Cell Cycle/DNA Damage; Metabolic Enzyme/Protease; Autophagy
Storage: Powder
-20°C 3 years
4°C 2 years
In solvent
-80°C 6 months
-20°C 1 month

SOLVENT & SOLUBILITY

In Vitro
DMSO: ≥ 45 mg/mL (141.17 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>3.1372 mL</td>
<td>15.6858 mL</td>
<td>31.3716 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.6274 mL</td>
<td>3.1372 mL</td>
<td>6.2743 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.3137 mL</td>
<td>1.5686 mL</td>
<td>3.1372 mL</td>
</tr>
</tbody>
</table>

Please refer to the solubility information to select the appropriate solvent.

In Vivo
1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (7.84 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.84 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
BIIB021 (CNF2024) is an orally active, fully synthetic inhibitor of HSP90 with a \( K_i \) and an \( EC_{50} \) of 1.7 nM and 38 nM, respectively\(^1\).

IC\(_{50}\) & Target

<table>
<thead>
<tr>
<th>HSP90</th>
<th>HSP90</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7 nM (Ki)</td>
<td>38 nM (EC(_{50}))</td>
</tr>
</tbody>
</table>

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 IC\(_{50}\) from 0.06-0.31 \( \mu \)M. BIIB021 induces the degradation of Hsp90 client proteins including HER-2, Akt, and
Oral administration of BIIB021 leads to tumor growth inhibition in many tumor xenograft models including N87, BT474, CWR22, U87, SKOV3 and Panc-1 cells. The cytotoxic activity of BIIB021 is considerably more active than 17-AAG against adrenocortical carcinoma H295R. 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).

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**PROTOCOL**

**Kinase Assay** [1]

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.

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**Cell Assay** [1]

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.

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**Animal Administration** [1]

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. Tumor growth is calculated using the equation for an ellipsoid sphere ((l×w²)/2)=mm³.
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.

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CUSTOMER VALIDATION


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REFERENCES


[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

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

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