BEZ235 (NVP-BEZ235) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>Solubility (25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>469.55</td>
<td>DMSO 1 mg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formula</th>
<th>Water &lt;1 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂₀H₂₇N₂O₃</td>
<td>Ethanol &lt;1 mg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAS No.</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>915019-65-7, 1028385-32-1 (4-methylbenzenesulfonate)</td>
<td>2 years -20°C Powder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synonyms</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>N/A</td>
<td>4 weeks 4°C in DMso</td>
</tr>
</tbody>
</table>

|                   | 6 months -80°C in DMso |

Biological Activity

Description

BEZ235 (NVP-BEZ235) is a dual ATP-competitive PI3K and mTOR inhibitor of p110α, p110β, p110δ, and p110γ with IC50 of 4 nM, 5 nM, 7 nM, and 75 nM, respectively.

Targets

p110α: p110β: p110δ: p110γ:

IC50

4 nM: 5 nM: 7 nM: 75 nM

In vitro

BEZ235 significantly reduces the phosphorylation levels of the mTOR activated kinase p70S6K. BEZ235 results in a reduction of S235/S236P-RPS6 levels with IC50 of 6.5 nM. The activity of BEZ235 against mTOR is determined using a biochemical mTOR K-LISA assay with IC50 of 20.7 nM. BEZ235 shows slightly lower activity against its β paralogue with IC50 of 75 nM. The PI3K/Akt/mTOR pathway is often constitutively activated in human tumor cells. BEZ235 blocks PI3K and mTOR kinase activity by binding to the ATP-binding cleft of these enzymes. Both PTEN-null cell lines PC3M and U87MG show a dose-dependent reduction in cell proliferation when treated with increasing concentrations of BEZ235 with an average GI50 of 10 to 12 nM. [1] BEZ235 is an mTORC1/2 catalytic inhibitor. [2]

In vivo

BEZ235 induces regression of the tumors (69%) without statistically significant effect on body weight gain. Altogether, these preliminary in vivo efficacy results show that BEZ235 causes disease stasis when administered orally as a single agent and can enhance the efficacy of other anticancer agents when used in combination studies. [1]

Clinical Trials

 Features

Protocol (Only for Reference)

Kinase Assay: [1]

In vitro Protein

P110α, β, and δ proteins are composed of the iSH2 domain of p85 NH2-terminally fused to the full-length protein p110 protein, with the exception of α that also does not contain the last 20 amino acids. PI3Kγ is produced as full-length protein deleted for its first 144 amino acids. All constructs are fused to a COOH-terminal His tag for convenient purification and then cloned into the pBlue-Back4.5 (for α, β, and δ isoforms) or pVL1393 (for γ isoform) plasmids. The different vectors are then cotransfected with BaculoGold WT genomic DNA using methods recommended by the vendor for production of the respective recombinant baculoviruses and proteins. BEZ235 are tested for their activity against PI3K using a Kinase-Glo assay. The kinase reaction is done in 384-well black substrate (l-α-phosphatidylinositol; Avanti Polar Lipids; prepared in 3% octyl-glucoside) and the PI3K proteins (10, 25, 10, and 150 nM of p110α, p110β, p110δ, and p110γ, respectively) are then added to it. The reaction is started by the addition of 5 µL of 1 µM ATP prepared in the reaction buffer and is incubated for either 60 min (for p110α, p110β, p110δ, and p110γ, respectively) or 20 min (for p110γ). It is terminated by the addition of 10 µL Kinase-Glo buffer. The plates are then read in a Synergy 2 reader for luminescence detection.

Cell Assay: [2]

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>Concentrations</th>
<th>Incubation Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT116, DLD-1 and SW480 cells</td>
<td>0-1 µM</td>
<td>48 hours</td>
</tr>
</tbody>
</table>

Methods

The human CRC cell lines, HCT116 (PIK3CA mutant; kinase domain at H1047R), DLD-1 (PIK3CA mutant; helical domain at E545K), and SW480 (PIK3CA wild-type) and isogenic DLD-1 PIK3CA mutant as well as wild-type cells are maintained in DMEM with 10% FBS and 1 x Penicillin/Streptomycin. Cells are plated at different initial densities (HCT116: 3 x 10³ cells/well, DLD-1: 5.5 x 10³ cells/well, SW480: 4.5 x 10³ cells/well, DLD-1 PIK3CA mutant: 7 x 10³ cells/well, and DLD-1 PIK3CA wild-type: 9 x 10³ cells/well) to account for differential growth kinetics. After 16 hours, cells are incubated with increasing concentrations of BEZ235, and the drug-containing growth medium is changed every 24 hours. Cell viability is assessed 16 hours after the initial plating and 48 hours after initiation of drug treatment using the colorimetric MTS assay CellTiter 96® AQueous One Solution Cell Proliferation Assay, as per the manufacturer’s instructions. Cell viability after drug treatment is normalized to that of untreated cells also grown for 48 hours. For western blot analysis, cells are plated with zero or maximum inhibitory dose (500 nM) BEZ235 for 2, 6, 24, or 48 hours.

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www.selleckchem.com/datasheet/BEZ235-DataSheet.html
Animal Study\[1\]

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Female Harlan athymic nude mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>NMP/polyethylene glycol 300 (10/90, v/v)</td>
</tr>
<tr>
<td>Doses</td>
<td>45 mg/kg</td>
</tr>
<tr>
<td>Administration</td>
<td>p.o.</td>
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</tbody>
</table>

References

Customer Reviews

Data from [Breast Cancer Research, 2011, September, 13:R52]
BEZ235 (NVP-BEZ235) purchased from Selleck
Three-dimensional responses of MCF7/IGF-1R cells to TAM (1 μM), E2 and IGF-1. Compared to parental MCF7 cells (a), MCF7/IGF-1R cells (b) in three-dimensional (3D) culture formed bigger acini in response to IGF-1 stimulation and displayed significant TAM resistance when treated with TAM (1 μM) + E2 + IGF-1, which was removable by kinase inhibitors BMS-536924, U0126 and BEZ235 (c). Cells (10,000/well) were seeded in 96-well plates. Acini were formed on 100% Matrigel and cultured for 14 days in starving medium containing 2% Matrigel and 5% charcoal/dextran-stripped fetal bovine serum with the treatments as indicated. Concentrations used: TAM (1 μM), E2 (1 nM) and IGF-1 (100 ng/mL). Confocal image original magnification, x 20. Red, rhodamine phalloidin (actin). Blue, Hoechst blue stain. Results are representative of two individual experiments.

BEZ235 (NVP-BEZ235) purchased from Selleck
ZSTK474 and GDC-0941 selectively inhibit class I PI3K over mTOR. (A) Inhibition profiles of the selected five PI3K inhibitors for mTOR. Data shown are mean ± SD (n = 3), representative of 2 or 3 independent experiments. (B) IC50 values of the PI3K inhibitors for mTOR. (C) Selectivity of each PI3K inhibitor for PI3Ka over mTOR. The selectivity index is expressed as the ratio of the IC50 value for mTOR over that for PI3Ka. The IC50 values of ZSTK474, NVP-BEZ235 and LY294002 for PI3Ka are 0.016, 0.007 and 0.6 nM, respectively, as reported previously by us.

PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.

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www.selleckchem.com/datasheet/BEZ235-DataSheet.html