Vismodegib (GDC-0449) Datasheet

**Biological Activity**

### Description
GDC-0449 (Vismodegib, HhAntag691) is a potent, novel and specific hedgehog inhibitor with IC50 of 3 nM.

### Targets
Hedgehog

### IC50
3 nM

### In vitro

GDC-0449 targets the Hedgehog signaling pathway, blocking the activities of the Hedgehog-ligand cell surface receptors PTCH and/or SMO and suppressing Hedgehog signaling. GDC-0449 prevents multiple ATP-binding cassette (ABC) transporters. GDC-0449 also blocks ABCG2, Pgp, and MRP1-imporant ABC transporters associated with MDR. GDC-0449 is a potent inhibitor of ABC transporters, ABCG2/BCRP and ABCB1/Pgp, and is a mild inhibitor of ABCB1/MDR1. In ABCG2-overexpressing HEK293 cells, GDC-0449 increases retention of the fluorescent ABCG2 substrate BODIPY-prazosin and resensitizes these cells to mitoxantrone. In Madin-Darby canine kidney II cells engineered to overexpress Pgp or MRP1, GDC-0449 increases the retention of calcineum-AM and resensitizes them to colchicine. GDC-0449 also resensitizes human non-small cell lung carcinoma cells NCI-H460 (par and NCI-H460/MDR), which overexpress ABCG2 in response to mitoxantrone, to mitoxantrone, and to topotecan or SN-38. The IC50 values of GDC-0449 for prevention of ABCG2 and Pgp are about 1.4 μM and 3.0 μM respectively. [2] GDC-0449 alters intracellular Ca²⁺ homeostasis and inhibits cell growth in cisplatin-resistant lung cancer cells. [3]

### In vivo

GDC-0449 has been used to treat medulloblastoma in animal models. [2] GDC-0449 prevents the growth of primary pancreatic xenografts without non-specifically inhibiting pancreatic cell proliferation. Oral dosing of GDC-0449 causes tumor regressions in the Ptch(+/-) allograft model of multiple ATP-binding cassette (ABC) transporters. GDC-0449 also blocks ABCG2, Pgp, and MRP1-imporant ABC transporters associated with MDR. GDC-0449 is a potent inhibitor of ABC transporters, ABCG2/BCRP and ABCB1/Pgp, and is a mild inhibitor of ABCB1/MDR1. In ABCG2-overexpressing HEK293 cells, GDC-0449 increases retention of the fluorescent ABCG2 substrate BODIPY-prazosin and resensitizes these cells to mitoxantrone. In Madin-Darby canine kidney II cells engineered to overexpress Pgp or MRP1, GDC-0449 increases the retention of calcineum-AM and resensitizes them to colchicine. GDC-0449 also resensitizes human non-small cell lung carcinoma cells NCI-H460 (par and NCI-H460/MDR), which overexpress ABCG2 in response to mitoxantrone, to mitoxantrone, and to topotecan or SN-38. The IC50 values of GDC-0449 for prevention of ABCG2 and Pgp are about 1.4 μM and 3.0 μM respectively. [2] GDC-0449 alters intracellular Ca²⁺ homeostasis and inhibits cell growth in cisplatin-resistant lung cancer cells. [3]

### Clinical Trials
GDC-0449 has entered into a phase II clinical trials in the treatment of basal cell carcinoma.

### Features

**Protocol (Only for Reference)**

**Cell Assay:** [2]

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>MDCKII cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentrations</strong></td>
<td>20 μM</td>
</tr>
<tr>
<td><strong>Incubation Time</strong></td>
<td>2 hours</td>
</tr>
</tbody>
</table>

**Methods**

MDCKII cells are seeded into 24-well plates at a density of 3 x 10⁵ cells per well and are allowed to attach. Medium is then changed to that containing different drugs (50 μM VP, 50 μM indomethacin, or 20 μM GDC-0449 in DMSO or DMSO alone as control, and nonfluorescent calcein-AM is added to a final concentration of 1 μM and incubated at 37 °C for 2 hours. Cells are then washed twice with Ca²⁺-, Mg²⁺-containing Hank’s balanced salt solution buffer and lysed by shaking in 0.01% Triton X-100 in PBS buffer for 1 hour at room temperature or overnight at 4 °C. The lysate is then transferred into 96-well plates, and the fluorescence signal caused by the cell-derived calcein was quantified spectrophotometrically with a SpectraMax M5 Multi-Detection Reader using an excitation wavelength of 495 nm and an emission wavelength of 515 nm. All manipulations are performed in the dark. All readings are expressed as mean ± SEM normalized to the control.

**Animal Study:** [4]

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Ptch(+/-) allograft model, D5123 and 1040830</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
<td>In 0.5% methyl-cellulose, 0.2% tween-80</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>~ 100 mg/kg</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Orally</td>
</tr>
</tbody>
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**Website:**

www.selleckchem.com/datasheet/GDC-0449-Datasheet.html
References


Customer Reviews

Data from [J Neurooncol, 2011, 105(3), 475-483]
Vismodegib (GDC-0449) purchased from Selleck
Mouse medulloblastoma primary cells (U51669)
showed inhibition of Gli1 by GDC-0499 in dose
dependent manner. *P<0.01.

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

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