AEE788 (NVP-AEE788) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>440.58</th>
</tr>
</thead>
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<tr>
<td>Formula</td>
<td>C_{21}H_{32}N_{4}S</td>
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<tr>
<td>CAS No.</td>
<td>497839-62-0</td>
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<td>Synonyms</td>
<td>N/A</td>
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</tbody>
</table>

Solubility (25°C)

- DMSO 88 mg/mL
- Water <1 mg/mL
- Ethanol 11 mg/mL
- 2 years -20°C Powder
- 2 weeks 4°C in DMSO
- 6 months -80°C in DMSO

Biological Activity

**Description**
AEE788 is a potent dual inhibitor of EGFR and ErbB2 with IC50 of 2 nM and 6 nM, respectively.

**Targets**
- EGFR
- erbB2

**IC50**
- 2 nM
- 6 nM[1]

**In vitro**
AEE788 also inhibits KDR, c-abl, c-Src, and Fli-1 with IC50 of 50-80 nM. AEE788 is not sensitive to ErbB-4, PDGF receptor-β, Fli-3, Fli-4, RET, and c-kit and has no inhibitory to Ins-R, IGF-1R, PKC-α, and PDK1. AEE788 potently inhibits EGFR phosphorylation in A31 tumors with IC50 of 11 nM. AEE788 also inhibits the phosphorylation of KDR in CHO cells and erbB2 in BT-474 cells, without any effects on PDGF-induced phosphorylation in A31. AEE788 inhibits the proliferation of NCI-H560, MDA-MB-231, and BT-474 and SK-BR-3 cells with IC50 of 78, 56, and 381 nM, respectively. Outside, AEE788 has the additional property of inhibiting cellular proliferation driven by EGFR mutant including 32D/EGFR and 32D/EGFR-N1. AEE788 further also inhibits both EGF- and VEGF-driven HUVEC proliferation with IC50 of 43 and 155 nM, respectively. AEE788 inhibits the phosphorylation of EGFR, VEGFR2, Akt, and MAPK in human cutaneous SCC cell lines (Colo16, HaCaT, SRB1, and SRB12 cells), which leads to growth inhibition and induction of apoptosis. AEE788 inhibits the phosphorylation of ErbB and Akt in HT29 cells at 0.2 to 1.0 μM. AEE788 inhibits cell proliferation and prevents EGF- and neuregulin-induced HER1, HER2, and HER3 activation in medulloblastoma cell lines. AEE788 shows growth-suppressive activities in chemosensitive and chemoresistant medulloblastoma cells.[4]

**In vivo**
AEE788 produces a dose-dependent inhibition of tumor growth in NCI-H569 and DU145 xenograft models, with only minor body weight changes. AEE788 induces tumor regression by 57% at 50 mg/kg in the NeuT/TBR2 GeMy model. AEE788 potently inhibits EGFR-induced EGFR phosphorylation in A31 tumors and erbB2 phosphorylation in GeMy tumors. AEE788 dose-dependently inhibited angiogenesis induced by VEGF and does not inhibit BfG-induced angiogenesis. AEE788 suppresses the growth of tumor volume by 54% in Colo16 xenografts at 50 mg/kg, which due to the growth inhibition of phosphorylation of EGFR, VEGFR, Akt, and MAPK. AEE788 (50 mg/kg) also inhibits growth of tumors in the cecum and peritoneum (>50%) and reduces the incidence of lymph node metastasis to 70% in HT29 cells implanted in the cecum of nude mice, without loss of body weight and gross evidence of neovascularization. AEE788 significantly lowers the expression levels of pEGFR and pVEGFR in HT29 cecal tumors and does not alter those of EGF, VEGF, ER, or VEGF. Combined with CPT-11, AEE788 has significantly smaller tumors and complete inhibition of lymph node metastasis. AEE788 inhibits the growth of Daco, DacoPl, and DacoHER2 xenografts by 51%, 45%, and 72%, respectively. AEE788 could promote LBH589-mediated generation of reactive oxygen species in K562 tumor cells, which in turn increase apoptosis.[5]

**Clinical Trials**
A Phase III study in adult patients with recurrent or relapsing glioblastoma multiforme has been completed.

**Features**

Protocol (Only for Reference)

**Kinase Assay**[1]
The in vitro kinase assays are performed in 96-well plates (30 μL) at ambient temperature for 15–45 min using the recombinant glutathione S-transferase-fused kinase domains (4–100 ng, depending on specific activity). [γ^{32}P]ATP is used as phosphate donor and polyGluTyr-(4:1) peptide as acceptor. With the exception of protein kinase Cα, cyclin-dependent kinase 1 (cdkB) and protein kinase A are protamine sulfate (250 μg/mL), histone H1 (100 μg/mL), and the heptapeptide Leu-Arg-Arg-Ala-Ser-Leu-Gly (known as Kemptide Bachem) respectively and are used as peptide substrates. Assays are optimized for each kinase using the following ATP concentrations: 1.0 μM (c-Ki, c-Met, c-Fms, c-Raf-1, and RET), 2.0 μM (EGFR, erbB2, erbB3, and ErbB4), 5.0 μM (c-abl), 8.0 μM (Fli-1, Fli-3, Fli-4, Fik, KDR, FGFR-1, and Tek), 10.0 μM (PDGF receptor-β, protein kinase Cα, and cyclin-dependent kinase 1), and 20.0 μM (c-src and protein kinase A). The reaction is terminated by the addition of 20 μL 125 mM EDTA. Thirty μL c-abl, c-Src, insulin-like growth factor-1R, RET-MET2A, and RET-MET2B (or 40 μL (all other kinases) of the reaction mixture is transferred onto Immobilon-polyvinylidene difluoride membrane, presoaked with 0.5% H3PO4 and mounted on a vacuum manifold. Vacuum is then applied and each well rinsed with 200 μL 0.5% H3PO4. Membranes are removed and washed four times with 1.0% H3PO4 and once with ethanol. Dried membranes are counted after mounting in a Packard TopCount 96-well frame with the addition of 20 μL Microscint and counted at 15 and 11 s intervals.

**Protein Kinase Assays**

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Websites:
- www.selleckchem.com
- www.selleckchem.com/datasheet/AEE788-DataSheet.html
Cell Assay:[1]

**Cell Lines**
T24, BT-474, SK-BR-3, and NCI-H596 cells

**Concentrations**
~10 μM

**Incubation Time**
4 or 6 days

**Methods**
Methylene Blue Cell Proliferation Assay. Cells are seeded at 1.5 × 10^3 cells/well into 96-well microtiter plates and incubated overnight at 37 °C, 5% v/v CO₂ and 80% relative humidity. AEE788 dilutions are added on day 1, with the highest concentration being 10 μM. After incubation of the cell plates for an additional 4 (T24) or 6 (BT-474, SK-BR-3, and NCI-H596) days, cells are fixed with 3.3% v/v glutaraldehyde, washed with water, and stained with 0.05% w/v methylene blue. After washing, the dye is eluted with 3% HCl and the absorbance measured at 665 nm with a SpectraMax 340 spectrophotometer. IC50 values are determined by mathematical curve-fitting and are defined as the drug concentration leading to 50% inhibition of net cell mass increase compared with untreated control cultures.

Animal Study:[1]

**Animal Models**
NCI-H596, DU145, A431, B16 and oncogenic NeuT-transfected HC11 cells in female BALB/c nu/nu (nude) mice

**Formulation**
N-methylpyrrolidone and PEG300 1:9 (v:v)

**Doses**
50 mg/kg

**Administration**
Dosed orally

References

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

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