

Product Data Sheet

Product Name: KU-0060648

Cat. No.: GC14346

Chemical Properties

Cas. No. 881375-00-4

Chemical Name 2-(4-ethylpiperazin-1-yl)-N-[4-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-1-yl]acetamide

SMILES CCN1CCN(CC1)CC(=O)NC2=C3C4=CC=CC=C4SC3=C(C=C2)C5=CC=CC6=C5OC(=CC6=O)N7CCOCC7

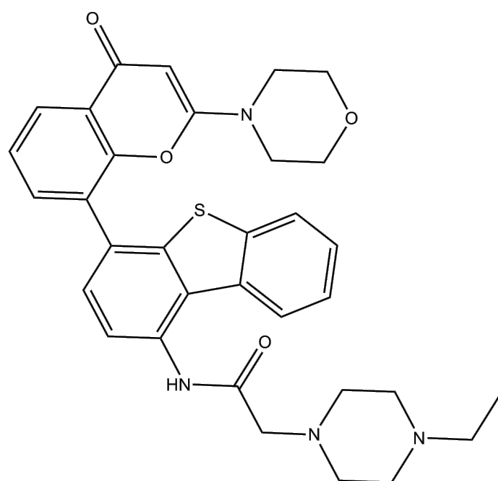
Formula $C_{33}H_{34}N_4O_4S$ M.Wt 582.71

Solubility DMF: 1 mg/ml, DMSO: 1 mg/ml Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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

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Cell lines	Human breast cancer cells (MCF7, T47D and MDA-MB-231) and colon cancer cells (LoVo and SW620)
Preparation method	The solubility of this compound in DMSO is limited. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	1 µM; 5 days
Applications	Five-day exposure to 1 µM KU-0060648 resulted in more than 50% inhibition of cell growth in all cancer cell lines. KU-0060648 showed the greatest effect on growth inhibition of LoVo and MCF7 cells, the total cell growth of which over 5 days was only 10% and 4% of that of the control group, respectively.
Animal experiment [1]:	
Animal models	Mice bearing MCF7 xenografts
Dosage form	10 mg/kg; i.p.; b.i.d.
Applications	In mice bearing MCF7 xenografts, KU-0060648 alone resulted in a median growth delay of 30 days with negligible toxicity, and the combination of KU-0060648 and Etoposide Phosphate caused a median growth delay of 55 days with acceptable toxicity.

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Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Munck JM, Batey MA, Zhao Y, Jenkins H, Richardson CJ, Cano C, Tavecchio M, Barbeau J, Bardos J, Cornell L, Griffin RJ, Menear K, Slade A, Thommes P, Martin NM, Newell DR, Smith GC, Curtin NJ. Chemosensitization of cancer cells by KU-0060648, a dual inhibitor of DNA-PK and PI-3K. Mol Cancer Ther. 2012;11(8):1789-98.

Background

IC50: KU-0060648 inhibited cellular DNA-PK autophosphorylation with IC50 values of 0.17 $\mu\text{mol/L}$ (SW620 cells) and 0.019 $\mu\text{mol/L}$ (MCF7 cells), and PI-3K-mediated AKT phosphorylation with IC50 values of 0.039 $\mu\text{mol/L}$ (MCF7 cells) and more than 10 $\mu\text{mol/L}$ (SW620 cells).

DNA double-strand breaks (DSB) are the most cytotoxic lesions induced by topoisomerase II poisons. Nonhomologous end joining (NHEJ) is a major pathway for DSB repair and requires DNA-dependent protein kinase (DNA-PK) activity. DNA-PK catalytic subunit (DNA-PKcs), which promotes cell survival and proliferation and is upregulated in many cancers, is structurally similar to PI-3K. KU-0060648 is a dual inhibitor of DNA-PK and PI-3K in vitro.

In vitro: KU-0060648 was investigated in a panel of human breast and colon cancer cells. Five-day exposure to 1 μM KU-0060648 was found to inhibit cell proliferation by more than 95% in MCF7 cells but only by 55% in SW620 cells. KU-0060648 increased the etoposide and doxorubicin cytotoxicity across the DNA-PKcs-proficient cell panel rather than in DNA-PKcs-deficient cells, therefore confirming the enhanced cytotoxicity was due to the inhibition of DNA-PK [1].

In vivo: In mice bearing SW620 and MCF7 xenografts, KU-0060648 concentrations that were sufficient for in vitro growth inhibition and chemosensitization were maintained within the tumor at nontoxic doses for at least 4 hours. KU-0060648 alone delayed the MCF7 xenografts growth and increased etoposide-induced tumor growth delay in both in MCF7 and SW620 xenografts by up to 4.5 folds, without causing etoposide toxicity to unacceptable levels [1].

Clinical trial: KU-0060648 is still in pre-clinical development stage and no clinical trial is ongoing currently.

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