

Product Data Sheet

Product Name: Cucurbitacin I

Cat. No.: GC13347

Chemical Properties

Cas. No. 2222-07-3

Chemical Name (10 α)-2,16 α ,20,25-tetrahydroxy-9 β -methyl-19-norlanosta-1,5,23E-triene-3,11,22-trione

SMILES CC1(C2=CCC3C4(CC(C(C4(CC(=O)C3(C2C=C(C1=O)O)C)C)C(C)(C(=O)C=CC(C)(C)O)O)C)C

Formula C₃₀H₄₂O₇

M.Wt 514.65

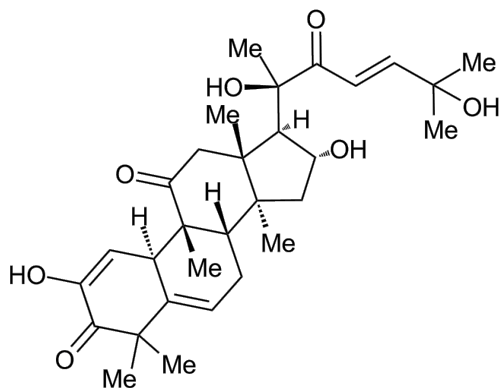
Solubility 5mg/mL in DMSO, 10mg/mL in Ethanol

Storage Store at 2-8°C, protect from light

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

Kinase experiment [1]:

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Preparation Method A549, MDA-MB-468, and v-Src-transformed NIH 3T3 cells were harvested and then lysed for 30min on ice in JAK kinase or Src kinase lysis buffer. Immunoprecipitation was performed using 50ng of JAK1 or JAK2 antibody or 2µg of v-Src antibody. Kinase reactions were performed at 30°C for 15min. Samples were pretreated with DMSO control, Cucurbitacin I (10µM), and control compounds [AG490 (100µM) and PD180970 (2µM)] before addition of 20µCi/sample [γ -³²P] ATP. Auto-phosphorylation results were visualized by autoradiography.

Reaction Conditions 10µM; 15min

Applications PD180970 inhibited Src but not JAK1 or JAK2 activities, AG490 inhibited JAK1 and JAK2 but not Src kinase activities, all three kinase activities were not affected by Cucurbitacin I directly in vitro.

Cell experiment [1]:

Cell lines A549, MDA-MB-468, MDA-MB-231, Panc-1, v-Src-transformed NIH3T3 cells

Preparation Method These human cancer cell lines, along with the positive control cell line (v-Src-transformed NIH3T3 cells), were treated with either vehicle or Cucurbitacin I (10µM) for 4h, and the cell lysates were processed for Western blotting with anti phosphotyrosine STAT3 antibody

Reaction Conditions 10µm; 4h

Applications Cucurbitacin I suppresses the phosphotyrosine levels of STAT3 without affecting its protein levels.

Animal experiment [1]:

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Animal models Eight-week-old female nude mice subcutaneously injected with A549, MDA-MB-468, Calu-1 and NIH3T3 cells transformed with v-Src and H-Ras

Preparation Method After tumors reached about 150mm³, animals were randomized and dosed i.p. with 0.2ml vehicle of drug once daily. Control animals received DMSO vehicle, whereas treated animals were injected with Cucurbitacin I. The tumor volumes were determined by measuring the length (*l*) and the width (*w*) and calculating the volume ($V = lw^2/2$).

Dosage form 1mg/kg/d; i.p.

Applications A549 and Calu-1 tumors from animals treated with vehicle grew to about 500mm³ 26 days after tumor implantation. MDA-MB-468 tumors treated with vehicle control grew to about 300mm³ 60 days after tumor implantation. Cucurbitacin I inhibited A549 and MDA-MB-468 tumor growth by 76% and 86%, respectively. In contrast, Cucurbitacin I had little effect on the growth of Calu-1 cells in nude mice.

References:

[1]. Blaskovich MA, Sun J, Cantor A, Turkson J, Jove R, Sebt SM. Discovery of JSI-124 (cucurbitacin I), a selective Janus kinase/signal transducer and activator of transcription 3 signaling pathway inhibitor with potent antitumor activity against human and murine cancer cells in mice. *Cancer Res.* 2003;63(6):1270-1279.

Background

Cucurbitacin I is a selective Janus Kinase (JAK)/STAT3 signaling pathway inhibitor with an IC₅₀ value of 500nM in A549 [1]. A variety of cancers exhibit an aberrant activation of STAT3, which plays a pivotal role in malignant transformation and tumor cell survival. Cucurbitacin I can inhibit STAT3 expression, therefore it has a potent anticancer effect in a number of cancer cell lines and in vivo tumor models [2].

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In vitro, 10 μ M Cucurbitacin I suppressed the levels of phosphotyrosine STAT3 in v-Src-transformed NIH3T3 cells and human cancer cells potently [1]. 100nM Cucurbitacin I treatment reduced COLO205 colon cancer cell proliferation, migration and invasion [2]. 100nM Cucurbitacin I sensitized the colon cancer cell line COLO205 to 5-FU treatment and decreased MMP-9 expression and phosphorylated STAT3 protein levels [2]. Treatment with 100nM Cucurbitacin I inhibited the growth of U251 and T98G cells with an IC₅₀ value of 170nM and 245nM, respectively [3]. 200nM Cucurbitacin I for 48h triggered autophagy and activated the autophagy-related gene *Beclin 1* in GBM Cells [3]. 1 μ M Cucurbitacin I can prevent hypertrophic responses in PE-stimulated cardiomyocytes [4]. Cucurbitacin I significantly inhibited the cell viability and proliferation and prevented the tube formation of MDA-MB-468 in a dose-dependent manner from 0.2 μ mol/L to 1 μ mol/L [5].

In vivo, Cucurbitacin I (1mg/kg/d) potently inhibited the growth in nude mice of A549 tumors, v-Src-transformed NIH3T3 tumors, and the human breast carcinoma MDA-MB-468 and significantly increased survival of immunologically competent mice bearing murine melanoma with constitutively activated STAT3 [1]. Intraperitoneal administration of Cucurbitacin I (1mg/kg/d) for 18 days resulted in massive apoptotic cell death, and markedly inhibited tumor volume and tumor weight in mice with xenografted glioma cells [4].

References:

- [1] Blaskovich MA, Sun J, Cantor A, Turkson J, Jove R, Sefti SM. Discovery of JSI-124 (cucurbitacin I), a selective Janus kinase/signal transducer and activator of transcription 3 signaling pathway inhibitor with potent antitumor activity against human and murine cancer cells in mice. *Cancer Res.* 2003;63(6):1270-1279.
- [2] Song J, Liu H, Li Z, Yang C, Wang C. Cucurbitacin I inhibits cell migration and invasion and enhances chemosensitivity in colon cancer. *Oncol Rep.* 2015;33(4):1867-1871.
- [3] Yuan G, Yan SF, Xue H, Zhang P, Sun JT, Li G. Cucurbitacin I induces protective autophagy in glioblastoma in vitro and in vivo. *J Biol Chem.* 2014;289(15):10607-10619.
- [4] Jeong MH, Kim SJ, Kang H, et al. Cucurbitacin I Attenuates Cardiomyocyte Hypertrophy via Inhibition of Connective Tissue Growth Factor (CCN2) and TGF- β /Smads Signalings. *PLoS One.* 2015;10(8): e0136236.
- [5] Qi J, Xia G, Huang CR, Wang JX, Zhang J. JSI-124 (Cucurbitacin I) inhibits tumor angiogenesis of

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human breast cancer through reduction of STAT3 phosphorylation. *Am J Chin Med.* 2015;43(2):337-347.

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