

Product Data Sheet

Product Name: Linsitinib
Cat. No.: GC15749

Chemical Properties

Cas. No. 867160-71-2

Chemical Name 3-[8-amino-1-(2-phenylquinolin-7-yl)imidazo[1,5-a]pyrazin-3-yl]-1-methylcyclobutan-1-ol

SMILES CC1(CC(C1)C2=NC(=C3N2C=CN=C3N)C4=CC5=C(C=C4)C=CC(=N5)C6=CC=CC=C6)O

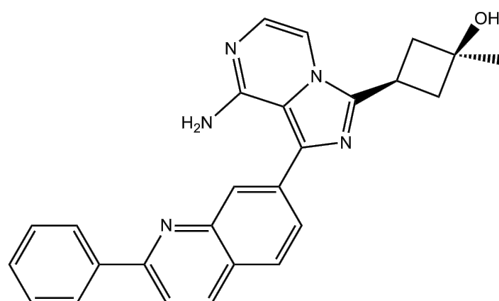
Formula $C_{26}H_{23}N_5O$ M.Wt 421.51

Solubility ≥ 21.1 mg/mL in DMSO 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]:

Cell lines TE-7 cells

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TE-7 cells were cultured in RPMI1640 medium supplemented with 10% fetal bovine serum, 100units/ml penicillin, and 100µg/ml streptomycin. Cells were cultured in a 5% CO₂ incubator at 37°C. TE-7 cells were seeded in 96-well Preparation Method plates and cultured for 24 hours. After 48 hours of treatment with various concentrations of Linsitinib (1, 2, 4, 6, 8, 10µM), 20µl MTT (5mg/ml) was added to each well and incubated for 4 hours at 37°C. Formazan was dissolved in 150µl DMSO, and the optical density at 570nm was then measured.

Reaction
Conditions 1, 2, 4, 6, 8, 10µM; 48h

Applications Linsitinib treatment reduced the proliferation of TE-7 cells in a concentration-dependent manner.

Animal experiment [2]:

Animal models Male C57BL/6J mice

10 to 12-week-old male C57BL/6J mice had ad libitum access to food and water and were housed under standard housing conditions with a 12-h light/12-h dark cycle, humidity of 30 to 70%, and temperature of 20°C-23°C. Two days before surgery and on the morning of surgery, Linsitinib (20mg/kg/day) was injected intraperitoneally every morning. Mice were anesthetized with 3% isoflurane in 2L Preparation Method O₂ and kept at 37°C with an electrical heating pad. Following a 2-cm abdominal incision, the vascular pedicles of the right and left kidneys were identified under a microscope. First, the right renal artery, vein, and ureter were ligated and cauterized. The left pedicle was clamped for mice with vascular micro-clamps. The wound was closed, and the mouse tissues were collected for analysis on the second day after renal IR injury.

Dosage form 20mg/kg/day for 3 days; i.p.

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Applications Linsitinib treatment significantly reduced IR injury in mice, inhibited histological tubulointerstitial damage, and tubular necrosis.

References:

- [1] Kang J, Guo Z, Zhang H, et al. Dual inhibition of EGFR and IGF-1R signaling leads to enhanced antitumor efficacy against esophageal squamous cancer[J]. International Journal of Molecular Sciences, 2022, 23(18): 10382.
- [2] Lyon A, Agius T, Macarthur M R, et al. Dietary or pharmacological inhibition of insulin-like growth factor-1 protects from renal ischemia-reperfusion injury in mice[J]. iScience, 2024, 27(12).

Background

Linsitinib is a potent, selective, and orally bioavailable dual IGF-1R/IR kinase inhibitor, with the IC₅₀ values of 0.035μM, and 0.075μM, respectively [1]. Linsitinib inhibits the autophosphorylation after binding of the cognate ligands to the IGF-1R and IR, and therefore blocks the IGF-I and IGF-II induced activation of downstream pathways, such as AKT and ERK signaling[2]. Linsitinib has been widely used in different cancer cell models and xenograft tumor models to inhibit tumor growth[3].

In vitro, Linsitinib treatment for 48h inhibited the proliferation of KYSE150 cells, KYSE450 cells, KYSE510 cells, and TE-7 cells with IC₅₀ values of 22.42μM, 8.524μM, 15.83μM, and 5.669μM, respectively[4]. A 2-hour pretreatment with 20μM Linsitinib inhibited IGF-1-induced phosphorylation of IGF-1Rβ at Tyr1135, phosphorylation of Akt at Ser473, and phosphorylation of ERK in orbital fibroblasts (OFs), and reduced hyaluronic acid secretion[5]. Treatment of IGF-1R-expressing NCI-H295R cells with 31.6125μg/ml Linsitinib for 24h inhibited proliferation and induced apoptosis, accompanied by a significant increase in caspase-3/7 activity[6].

In vivo, Linsitinib treatment via oral administration at a dose of 60mg/kg/day for 10 days resulted in inhibition of tumor growth in NCI-H292 xenograft mice[7]. Intragastric administration of Linsitinib (50mg/kg/day) for 3 consecutive days significantly reduced seizure severity, prolonged seizure latency, and reduced electroencephalogram (EEG) power density in the lithium-pilocarpine rat model[8]. Intraperitoneal injection of Linsitinib (20mg/kg/day) 3 days before ischemia-reperfusion (IR) injury improved the survival of mice after renal IR injury and reduced tubulointerstitial damage and

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tubular necrosis^[9].

References:

- [1] Mulvihill M J, Cooke A, Rosenfeld-Franklin M, et al. Discovery of OSI-906: a selective and orally efficacious dual inhibitor of the IGF-1 receptor and insulin receptor[J]. Future medicinal chemistry, 2009, 1(6): 1153-1171.
- [2] Wang Y J, Zhang Y K, Kathawala R J, et al. Repositioning of tyrosine kinase inhibitors as antagonists of ATP-binding cassette transporters in anticancer drug resistance[J]. Cancers, 2014, 6(4): 1925-1952.
- [3] Ji Q S, Mulvihill M, Rosenfeld-Franklin M, et al. Preclinical characterization of OSI-906: a novel IGF-1R kinase inhibitor in clinical trials[J]. Molecular Cancer Therapeutics, 2007, 6(11_Supplement): C192-C192.
- [4] Kang J, Guo Z, Zhang H, et al. Dual inhibition of EGFR and IGF-1R signaling leads to enhanced antitumor efficacy against esophageal squamous cancer[J]. International Journal of Molecular Sciences, 2022, 23(18): 10382.
- [5] Lee J Y, Lee S B, Yang S W, et al. Linsitinib inhibits IGF-1-induced cell proliferation and hyaluronic acid secretion by suppressing PI3K/Akt and ERK pathway in orbital fibroblasts from patients with thyroid-associated ophthalmopathy[J]. Plos one, 2024, 19(12): e0311093.
- [6] Luffy M, Ganz A L, Wagner S, et al. Linsitinib inhibits proliferation and induces apoptosis of both IGF-1R and TSH-R expressing cells[J]. Frontiers in Immunology, 2024, 15: 1488220.
- [7] McKinley E T, Bugaj J E, Zhao P, et al. 18FDG-PET predicts pharmacodynamic response to OSI-906, a dual IGF-1R/IR inhibitor, in preclinical mouse models of lung cancer[J]. Clinical Cancer Research, 2011, 17(10): 3332-3340.
- [8] Jiang G, Wang S, Chen M, et al. Linsitinib (OSI-906) modulates brain energy metabolism and seizure activity in the lithium-pilocarpine rat model[J]. Acta Epileptologica, 2021, 3(1): 19.
- [9] Lyon A, Agius T, Macarthur M R, et al. Dietary or pharmacological inhibition of insulin-like growth factor-1 protects from renal ischemia-reperfusion injury in mice[J]. iScience, 2024, 27(12).

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