

Product Data Sheet

Product Name: CSN5i-3

Cat. No.: GC34340

Chemical Properties

Cas. No. 2375740-98-8

SMILES O=C(C1=CC(C(F)F)=NN1C(C)C)NC2=CC(C3=CC=CC=C3)=C([C@@H]4N5C(CCC[C@@H]4O)=CN=C5)C=C2

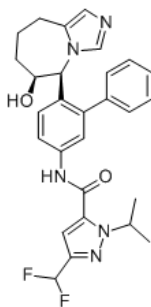
Formula $C_{28}H_{29}F_2N_5O_2$ M.Wt 505.56

Solubility DMSO: ≥ 100 mg/mL (197.80 mM) Storage Store at -20°C , protect from light, stored under nitrogen

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 BT474, SKBR3 cells

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

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BT474 and SKBR3 cells were seeded in a 6-well plate. After exposure to 2μM CSN5i-3 for 24h, cells were stained with Annexin V-FITC and analyzed by FACSCalibur to assess the apoptotic cell percentages.

Reaction
Conditions 2μM; 24h

Applications Jab1 inhibitor CSN5i-3 can significantly induce apoptosis in BT474 and SKBR3 cells.

Animal experiment [2]:

Animal models BALB/c nude mice

MDA-MB-231 cells were subcutaneously injected into the right flanks of 4- to 5-week-old female BALB/c nude mice. When tumors reached 1000mm³, they were excised, diced into 2mm×2mm×2mm pieces, and implanted into the right flanks of BALB/c nude mice. Tumors were allowed to grow to 100mm³ before random assignment into four groups (n=5): vehicle, CSN5i-3 (10mg/kg), Talazoparib (0.33mg/kg), or a combination of CSN5i-3 and Talazoparib. Tumor size was measured every 3 days. On day 19, mice were euthanized, and tumors were harvested. Tumors were either formalin-fixed or paraffin-embedded for histological analysis.

Dosage form 10mg/kg; 18 days; s.c.

Applications Combined treatment with CSN5i-3 and Talazoparib significantly enhanced antitumor efficacy.

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References:

- [1] Xiao H, Claret F X, Shen Q. The novel Jab1 inhibitor CSN5i-3 suppresses cell proliferation and induces apoptosis in human breast cancer cells[J]. Neoplasma, 2019, 66(3).
- [2] Peng X, Wang Y, Yu Z, et al. Jab1 regulates HRR mRNA stability to modulate PARP inhibitor sensitivity in triple-negative breast cancer[J]. Molecular Cancer, 2025, 24(1): 217.

Background

CSN5i-3 is a novel, potent, highly selective, and orally bioavailable small molecule inhibitor that targets the CSN5/Jab1 (COPS5) protein—a key protein hydrolytic subunit of the COP9 signaling complex. CSN5i-3 exhibits extremely high inhibitory activity against this target, with an IC₅₀ value of 5.8nM^[1, 2]. The core function of CSN5 is to cleave the NEDD8 modification from the Cullin-RING E3 ubiquitin ligase. CSN5i-3 can potently inhibit this de-Neddase activity of CSN5, thereby interfering with the normal function of the CRL ubiquitin ligase^[3].

In vitro, treatment of human breast cancer BT474 and SKBR3 cells with CSN5i-3 (2μM) for 24h significantly induced apoptosis and G1 phase cell cycle arrest, and increased the levels of the apoptosis marker cleaved PARP and the cell cycle-related protein p27^[4]. Treatment of human umbilical vein endothelial cells (HUVECs) with CSN5i-3 (1, 4μM) for 5h induced a significant weakening of endothelial barrier function, induced the expression of RhoGTPase RhoB in endothelial cells, and formed actin stress fibers^[5].

In vivo, subcutaneous injection of CSN5i-3 (10mg/kg) into MDA-MB-231 cell xenograft mice for 18 days inhibited tumor growth in mice, and combined treatment with Talazoparib significantly enhanced the antitumor efficacy^[6].

References:

- [1] Schlierf A, Altmann E, Quancard J, et al. Targeted inhibition of the COP9 signalosome for treatment of cancer[J]. Nature communications, 2016, 7(1): 13166.
- [2] Yin L, Xue Y, Shang Q, et al. Pharmaceutical inhibition of neddylation as promising treatments for various cancers[J]. Current Topics in Medicinal Chemistry, 2019, 19(12): 1059-1069.
- [3] Wu J T, Chan Y R, Chien C T. Protection of cullin–RING E3 ligases by CSN–UBP12[J]. Trends in cell biology, 2006, 16(7): 362-369.

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- [4] Xiao H, Claret F X, Shen Q. The novel Jab1 inhibitor CSN5i-3 suppresses cell proliferation and induces apoptosis in human breast cancer cells[J]. Neoplasma, 2019, 66(3).
- [5] Majolée J, Pronk M C A, Jim K K, et al. CSN5 inhibition triggers inflammatory signaling and Rho/ROCK-dependent loss of endothelial integrity[J]. Scientific reports, 2019, 9(1): 8131.
- [6] Peng X, Wang Y, Yu Z, et al. Jab1 regulates HRR mRNA stability to modulate PARP inhibitor sensitivity in triple-negative breast cancer[J]. Molecular Cancer, 2025, 24(1): 217.

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