

Product Data Sheet

Product Name: TAK-243 (MLN7243)

Cat. No.: GC32737

Chemical Properties

Cas. No. 1450833-55-2

SMILES O=S(OC[C@@H]1[C@@H](O)[C@@H](O)[C@H](NC2=CC=NC3=CC(C4=CC=CC(SC(F)(F)F)=C4)=NN23)C1)(N)=O

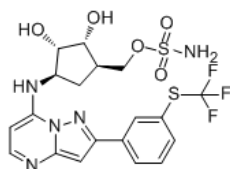
Formula $C_{19}H_{20}F_3N_5O_5S_2$ M.Wt 519.52

Solubility DMSO : 50 mg/mL (96.24 mM); Water : 1 mg/mL (1.92 mM) 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]:

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Cell lines DU145、Li-7、MOLT4 cells (SLFN11 wild-type (WT) and SLFN11 knockout (KO))

Cells were plated in 96-well white plates. After 24-hours incubation, TAK-243 (0-Preparation Method 1000nM) was added and incubated for 72h. Cell viability was measured using EnVision™ with ATPlite solution.

Reaction
Conditions 0-1000nM; 72h

Applications TAK-243 inhibited cell viability in a concentration-dependent manner, and SLFN11-KO cells were significantly more sensitive to TAK-243 than their WT counterparts.

Animal experiment [2]:

Animal models NSG mice

Preparation Method A total of 4×10^6 H295R cells were suspended in 100μL of Matrigel and inoculated subcutaneously into the right flank of NSG female mice. One week later, mice were divided into three groups (vehicle, TAK-243 10mg/kg, TAK-243 20mg/kg intraperitoneally twice weekly; n=5 per group). Xenograft diameters and mouse weights were measured weekly, and on day 29 all mice were euthanized, and xenografts were harvested.

Dosage form 10, 20mg/kg; 29 days; i.p.

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Applications TAK-243 treatment significantly inhibits tumor growth, reduces ubiquitinated proteins, and induces apoptosis in H295R xenografts.

References:

[1] Murai Y, Jo U, Murai J, et al. SLFN11 inactivation induces proteotoxic stress and sensitizes cancer cells to ubiquitin activating enzyme inhibitor TAK-243[J]. Cancer research, 2021, 81(11): 3067-3078.

[2] Arakawa Y, Jo U, Kumar S, et al. Activity of the ubiquitin-activating enzyme inhibitor TAK-243 in adrenocortical carcinoma cell lines, patient-derived organoids, and murine xenografts[J]. Cancer Research Communications, 2024, 4(3): 834-848.

Background

TAK-243 (MLN7243) is a selective inhibitor of ubiquitin activating enzyme (UBA1) with an IC₅₀ value of 1 nM^[1]. TAK-243 can block ubiquitin binding, disrupt monoubiquitin signaling and global protein ubiquitination, and is currently used as an anticancer drug in clinical trials^[2]. TAK-243 can induce endoplasmic reticulum stress (ERS) response, eliminate NF-κB pathway activation, and promote cell apoptosis^[3].

In vitro, TAK-243 (0-1000 nM) treatment of SLFN11 wild-type (WT) and SLFN11 knockout (KO) prostate cancer DU145, hepatocellular carcinoma Li-7 and leukemia MOLT4 cells for 72h inhibited cell viability in a concentration-dependent manner. SLFN11-KO cells were significantly more sensitive to TAK-243 than their WT counterparts^[4]. TAK-243 (0-100 nM) was used to treat multiple myeloma cell lines (MM1.S and MOLP-8 TP53 wild-type cells) for 24h, with an IC₅₀ value of approximately 25 nM, which significantly increased the levels of intracellular cleaved caspase-3, -8, and -9 and reduced the content of ubiquitin-protein conjugates^[5].

In vivo, TAK-243 (10, 20 mg/kg) was used to treat H295R cell xenograft mice by intraperitoneal injection for 29 days, which significantly inhibited tumor growth, reduced the expression level of ubiquitinated proteins in tumor tissues, and induced tumor cell apoptosis^[6]. TAK-243 (20 mg/kg) was used to treat acute myeloid leukemia (AML) cell xenograft mice by subcutaneous injection for 3

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weeks, which reduced the AML tumor burden and the levels of monoubiquitinated and polyubiquitinated proteins in tumor tissues^[7].

References:

- [1] Hyer M L, Milhollen M A, Ciavarrri J, et al. A small-molecule inhibitor of the ubiquitin activating enzyme for cancer treatment[J]. Nature medicine, 2018, 24(2): 186-193.
- [2] Best S, Hashiguchi T, Kittai A, et al. Targeting ubiquitin-activating enzyme induces ER stress-mediated apoptosis in B-cell lymphoma cells[J]. Blood advances, 2019, 3(1): 51-62.
- [3] Wang G, Fan F, Sun C, et al. Looking into endoplasmic reticulum stress: the key to drug-resistance of multiple myeloma?[J]. Cancers, 2022, 14(21): 5340.
- [4] Murai Y, Jo U, Murai J, et al. SLFN11 inactivation induces proteotoxic stress and sensitizes cancer cells to ubiquitin activating enzyme inhibitor TAK-243[J]. Cancer research, 2021, 81(11): 3067-3078.
- [5] Zhuang J, Lee H, Kuitse I, et al. The anti-tumor effect of the ubiquitin-activating enzyme (UAE) inhibitor TAK-243 on pre-clinical models of multiple myeloma[J]. 2016.
- [6] Arakawa Y, Jo U, Kumar S, et al. Activity of the ubiquitin-activating enzyme inhibitor TAK-243 in adrenocortical carcinoma cell lines, patient-derived organoids, and murine xenografts[J]. Cancer Research Communications, 2024, 4(3): 834-848.
- [7] Barghout S H, Patel P, Wang X, et al. TAK-243 is a selective UBA1 inhibitor that displays preclinical activity in acute myeloid leukemia (AML)[J]. Blood, 2017, 130: 814.

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