Product Data Sheet

Product Name: TH588 hydrochloride
Cat. No.: GC37777

Chemical Properties

Cas. No.	1640282-30-9		
SMILES	NC1=NC(C2=CC=CC(Cl)=C2Cl)=CC(NC3CC3)=N1.[H]Cl		
Formula	$C_{13}H_{13}Cl_3N_4$	M.Wt	331.63
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	TH588 hydrochloride		

Protocol

Cell experiment [1]:

Cell lines	H460 human lung cancer cells, U2OS osteosarcoma cells, and HeLa cells
Preparation Method	Cells were maintained in Dulbecco's modified eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics at 37°C, 5% CO_2. Cells were treated with TH588 hydrochloride (1-8μM) for 0-48 hours.
Reaction Conditions	1-8μM; 0-48 hours.

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Applications	TH588 hydrochloride rapidly reduced microtubule plus-end mobility, disrupted mitotic spindle assembly and chromosome congression, and prolonged mitosis in a concentration-dependent manner. TH588 hydrochloride activated the USP28-p53 mitotic surveillance pathway, leading to cell cycle arrest in the G1 phase of the subsequent cycle. These effects were independent of its intended target, MTH1 inhibition.

Animal experiment [2]:

Animal models	Female BALB/c-nu nude mice with MCF7, MDA-MB-231, or MDA-MB-453 human breast cancer cell xenografts
Preparation Method	Mice were inoculated subcutaneously with cancer cells. After tumors reached a visible size (~2mm in mean diameter), mice were administered daily subcutaneous injections of TH588 hydrochloride (30mg/kg) or vehicle control for 2-3 weeks.
Dosage form	30mg/kg; s.c.; daily for 2-3 weeks.
Applications	TH588 hydrochloride treatment significantly suppressed tumor growth, causing over 90% regression in MCF7 and MDA-MB-231 tumors and completely eradicating MDA-MB-453 tumors. TH588 hydrochloride also inhibited mouse body weight gain, although no significant hematological or liver function toxicity was observed.

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References:
[1] Gul N, Karlsson J, Tängemo C, et al. The MTH1 inhibitor TH588 is a microtubule-modulating agent that eliminates cancer cells by activating the mitotic surveillance pathway. Sci Rep. 2019 Oct 11;9(1):14667.
[2] Zhang X, Song W, Zhou Y, et al. Expression and function of MutT homolog 1 in distinct subtypes of breast cancer. Oncol Lett. 2017 Apr;13(4):2161-2168.

Background

TH588 hydrochloride is an inhibitor of MTH1 (NUDT1; IC_{50}=5nM)[1-2]. TH588 hydrochloride works by inhibiting MTH1 to prevent cancer cells from clearing oxidized nucleotides, thereby inducing DNA damage and activating the ATM-p53-mediated cell death response and DNA repair. TH588 hydrochloride can be used in research related to lung adenocarcinoma, breast cancer, colon cancer, and melanoma[3-4].

In vitro, TH588 hydrochloride (5-30μM) was used to treat cell lines such as U2OS, HeLa, and RPE-1 for 0 to 4 hours. By inhibiting tubulin polymerization and microtubule dynamics, TH588 hydrochloride significantly suppressed microtubule turnover within the mitotic spindle, leading to chromosome congression defects. TH588 hydrochloride resulted in mitotic arrest, cell death, or cell division with incorrectly aligned chromosomes[5]. TH588 hydrochloride (1–8μM) was applied to H460 human lung cancer cells, U2OS osteosarcoma cells, HeLa, and other cell lines for 0 to 48 hours. TH588 hydrochloride significantly prolonged the duration of mitosis and, by activating the USP28-p53-mediated mitotic surveillance pathway, caused cell cycle arrest in the G1

phase of the subsequent cycle[6].

In vivo, TH588 hydrochloride (50μM) and the photosensitizer Ce6 (20μM) were co-loaded into the nanocarrier T&C@SCLMs. This formulation was administered via tail vein injection (0.2ml; once every 5 days; for a total of 20 days) to nude mice bearing A431 solid tumors. TH588 hydrochloride significantly enhanced the efficacy of photodynamic therapy (PDT), resulting in reduced tumor volume and inducing a higher proportion of tumor cell apoptosis[7]. TH588 hydrochloride (30mg/kg) was administered via daily subcutaneous injection for 2 to 3 weeks to BALB/c-nu nude mice bearing xenografts of MCF7, MDA-MB-231, or MDA-MB-453 human breast cancer cells. TH588 hydrochloride significantly suppressed tumor growth without causing significant hematological or liver function toxicity[8].

References:
[1] Gad H, Koolmeister T, Jemth AS, et al. MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool. Nature. 2014 Apr 10;508(7495):215-21.
[2] Ikejiri F, Honma Y, Kasukabe T, et al. TH588, an MTH1 inhibitor, enhances phenethyl isothiocyanate-induced growth inhibition in pancreatic cancer cells. Oncol Lett. 2018 Mar;15(3):3240-3244.
[3] Wang JY, Jin L, Yan XG, et al. Reactive Oxygen Species Dictate the Apoptotic Response of Melanoma Cells to TH588. J Invest Dermatol. 2016 Nov;136(11):2277-2286.
[4] Pompsch M, Vogel J, Classen F, et al. The presumed MTH1-inhibitor TH588 sensitizes colorectal carcinoma cells to ionizing radiation in hypoxia. BMC Cancer. 2018 Nov 29;18(1):1190.
[5] Rajendraprasad G, Eibes S, Boldú CG, et al. TH588 and Low-Dose Nocodazole Impair Chromosome Congression by Suppressing Microtubule Turnover within the Mitotic Spindle. Cancers (Basel). 2021 Nov 29;13(23):5995.
[6] Gul N, Karlsson J, Tängemo C, et al. The MTH1 inhibitor TH588 is a microtubule-modulating agent that eliminates cancer cells by activating the mitotic surveillance pathway. Sci Rep. 2019 Oct 11;9(1):14667.
[7] Zhao L, Li J, Su Y, et al. MTH1 inhibitor amplifies the lethality of reactive oxygen species to tumor in photodynamic therapy. Sci Adv. 2020 Mar 4;6(10):eaaz0575.
[8] Zhang X, Song W, Zhou Y, et al. Expression and function of MutT homolog 1 in distinct subtypes of breast cancer. Oncol Lett. 2017 Apr;13(4):2161-2168.