Product Data Sheet

Product Name: GMX1778 (CHS828)
Cat. No.: GC14815

Chemical Properties

Cas. No.	200484-11-3		
Chemical Name	(Z)-2-(6-(4-chlorophenoxy)hexyl)-1-cyano-3-(pyridin-4(1H)-ylidene)guanidine		
SMILES	ClC1=CC=C(OCCCCCC/N=C(\N=C2C=CNC=C/2)NC#N)C=C1		
Formula	$C_{19}H_{22}ClN_5O$	M.Wt	371.86
Solubility	≥ 18.3mg/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.		

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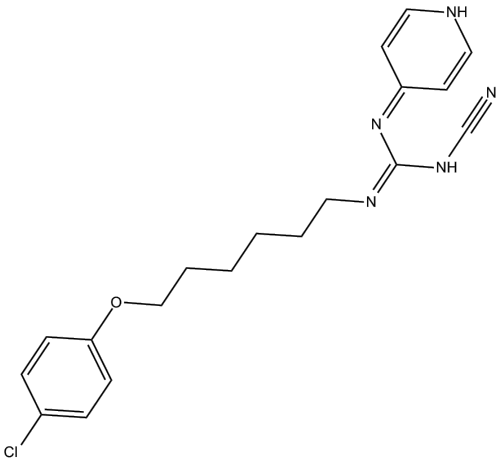
Structure



Protocol

Cell experiment [1]:

Cell lines	U251 and MDA-MB-231BR cells

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Preparation Method	Human glioblastoma cell line (U251) were grown in RPMI 1640 media containing 2mM L-glutamine and 5% fetal bovine serum. MDA-MB-231 BR cells were grown in high glucose DMEM with 10% fetal bovine serum. Cultures were maintained at 37°C in an atmosphere of 5% CO_2 and 95% room air. GMX1778 was reconstituted in DMSO (10mM) and stored at -80°C. Cells were seeded in 60mm^2 plates and allowed to attach for 24h prior to 48h of exposure to GMX1778 (5nM). Superoxide levels were measured using the oxidation of the fluorescent dye, dihydroethidine (DHE). Apoptosis was measured using a Guava EasyCyte Plus.
Reaction Conditions	5nM; 48h
Applications	GMX1778 significantly increased intracellular reactive oxygen species (ROS) levels and led to apoptosis in NAPRT1-negative cancer cells such as U251 and MDA-MB-231BR.

Animal experiment [2]:

Animal models	female BALB/c nude mice

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Preparation Method	The xenograft model with human small intestinal NET cell line GOT1 in nude mice was constructed by transplanted subcutaneously small pieces (about 1mm) of excised tumor to female BALB/c nude mice. GMX1778 was formulated as a 20mg/ml suspension in 2% carboxymethyl cellulose in 0.9% saline. Animals were divided into 4 groups; controls (vehicle only, n=6), 177Lu-DOTATATE (7.5MBq, n=10), GMX1778 (100mg/kg/week; 3 week; n=5), 177Lu-DOTATATE (7.5MBq) + GMX1778 (n=5). 177Lu-DOTATATE was injected in a tail vein and GMX1778 was given by oral gavage. In the combined therapy groups GMX1778 was given one hour after 177Lu-DOTATATE. Animals were followed up to 17 weeks and were killed when tumor weight exceeded 10% of body weight, or body weight was reduced by more than 10%. Animal weights and tumor sizes (longest diameter and the two perpendicular diameters measured by calipers) were monitored regularly. The relative tumor volume at a given time point was defined as the tumor volume divided by the volume at day 0.
Dosage form	100mg/kg/week; 3 weeks; oral gavage
Applications	GMX1778 significantly enhanced the antitumor effect of 177Lu-DOTATATE treatment, prolonged the median time to tumor progression and reduced tumor volume in a neuroendocrine tumor (NET) xenograft model.

References:

[1] Cerna D, Li H, Flaherty S, Takebe N, Coleman CN, Yoo SS. Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) activity by small molecule GMX1778 regulates reactive oxygen species (ROS)-mediated cytotoxicity in a p53- and nicotinic acid phosphoribosyltransferase1 (NAPRT1)-dependent manner. *J Biol Chem*. 2012;287(26):22408-22417.
[2] Elf AK, Bernhardt P, Hofving T, et al. NAMPT Inhibitor GMX1778 Enhances the Efficacy of 177Lu-DOTATATE Treatment of Neuroendocrine Tumors. *J Nucl Med*. 2017;58(2):288-292.

Background

GMX1778 (CHS828) is a specific inhibitor of nicotinamide phosphoribosyltransferase (NAMPT) [1].

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NAD^+ (Nicotinamide Adenine Dinucleotide) is a key coenzyme found in all living cells, playing an important role in cellular energy metabolism and redox reactions[2]. GMX1778 blocks the biosynthesis of NAD+ and decreases intracellular NAD+ levels by inhibiting the activity of NAMPT, which in turn causes ATP depletion and ultimately induces apoptosis-like programmed cell death[3]. GMX1778 is commonly used in cancer-related research[4].

In vitro, GMX1778 (30nM-1μM; 24h) significantly depleted intracellular NAD+ levels and induced cytotoxicity in HT1080 cells[5]. GMX1778 (5nM; 48h) significantly increased intracellular reactive oxygen species (ROS) levels and led to apoptosis in NAPRT1-negative cancer cells such as U251 and MDA-MB-231BR[6].

In vivo, GMX1778 (100mg/kg/week; 3 weeks; oral gavage) significantly enhanced the antitumor effect of 177Lu-DOTATATE treatment, prolonged the median time to tumor progression and reduced tumor volume in a neuroendocrine tumor (NET) xenograft mice model[7].

References:

[1] Watson M, Roulston A, Bélec L, et al. The small molecule GMX1778 is a potent inhibitor of NAD+ biosynthesis: strategy for enhanced therapy in nicotinic acid phosphoribosyltransferase 1-deficient tumors. *Mol Cell Biol*. 2009;29(21):5872-5888.

[2] Zapata-Perez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD^+ homeostasis in human health and disease. *EMBO Mol Med*. 2021;13(7):e13943.

[3] Olesen UH, Christensen MK, Björkling F, et al. Anticancer agent CHS-828 inhibits cellular synthesis of NAD. *Biochem Biophys Res Commun*. 2008;367(4):799-804.

[4] Ekelund S, Nygren P, Larsson R. Guanidino-containing drugs in cancer chemotherapy: biochemical and clinical pharmacology. *Biochem Pharmacol*. 2001;61(10):1183-1193.

[5] Guo J, Lam LT, Longenecker KL, et al. Identification of novel resistance mechanisms to NAMPT inhibition via the de novo NAD^+ biosynthesis pathway and NAMPT mutation. *Biochem Biophys Res Commun*. 2017;491(3):681-686.

[6] Cerna D, Li H, Flaherty S, Takebe N, Coleman CN, Yoo SS. Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) activity by small molecule GMX1778 regulates reactive oxygen species (ROS)-mediated cytotoxicity in a p53- and nicotinic acid phosphoribosyltransferase1 (NAPRT1)-dependent manner. *J Biol Chem*. 2012;287(26):22408-22417.

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[7] Elf AK, Bernhardt P, Hofving T, et al. NAMPT Inhibitor GMX1778 Enhances the Efficacy of 177Lu-DOTATATE Treatment of Neuroendocrine Tumors. *J Nucl Med*. 2017;58(2):288-292.

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