

Product Name: APETx2
Cat. No.: GC17168

Cas. No. 713544-47-9

SMILES CCC(C(/N=C(O)/C/N=C(O)/C(/N=C(O)/C(/N=C(O)/C(/N=C(O)/C/N=C(O)\C1CSSCC(N= C(O)C(N=C(O)CN=C(O)C(N=C(O)C(N=C(O)CN=C(O)C(N=C(O)C(N=C(O)C(N=C(O)C 2CCCN23)C(O)C)CC(O)=O)CCNC(N)=N)CC4=CC=C(O)C=C4)C(O)C)CO)/C(O)=N/C (/C(O)=N/C(/C(O)=N/C(/C(O)=N/C(/C(O)=N/C(/C(O)=N/C(/C(O)=N/C(/C(O)=N/C

Formula	C ₁₉₆ H ₂₈₀ N ₅₄ O ₆₁ S ₆	M.Wt	4561.06
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Solubility	Soluble to 5 mg/ml in Water	Storage	Store at -20°C
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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.
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Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.
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The image displays a highly complex, large macrocyclic molecule. It features a long, continuous chain of amide bonds (peptide backbone) that forms a large ring. The chain is decorated with numerous side chains, including aromatic groups (like phenyl and indolyl), aliphatic groups (like isopropyl and butyl), and various functional groups such as hydroxyl groups, amide groups, and a terminal amine group. The molecule is shown in a 2D chemical representation, with atoms labeled with their respective symbols (C, H, N, O, S) and bonds indicating the connectivity. The overall structure is highly branched and complex, typical of a large natural product or a synthetic macrocycle.

Cell experiment [1]:

Cell lines	Articular chondrocytes
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Preparation Method Articular chondrocytes were cultured in DMEM supplemented with 10% fetal bovine serum (FBS) at 37°C, 5% CO₂. Cells were pretreated with ASIC3-specific blocker APETx2 (3μM) for 1 hour, and exposure to pH 6.0 solution for 3 hours.

Reaction Conditions 3μM; 1-hour pretreatment.

Applications Pretreatment with APETx2, in combination with the ASIC1a-specific blocker PcTx1, significantly attenuated acidosis (pH=6.0)-induced chondrocyte cytotoxicity and apoptosis. This protective effect was characterized by increased cell viability, reduced LDH release, decreased intracellular Ca²⁺ concentration ([Ca²⁺]_i) elevation, reduced apoptotic rate, and inhibition of the p38 and ERK1/2 MAPK signaling pathways. Additionally, the combination treatment (PcTx1 and APETx2) reversed the acid-induced decrease in type II collagen levels.

Animal experiment [2]:

Animal models Male Sprague-Dawley rats (with MIA-induced osteoarthritis model)

Preparation Method A single dose of monosodium iodoacetate (MIA, 3mg dissolved in 50μl saline) was injected into the left knee joint to induce osteoarthritis. Rats were treated with intra-articular injections of the selective ASIC3 blocker APETx2 (2.5μg/kg) daily, either during the early phase (Days 1-7 after MIA) or the late phase (Days 7-13 after MIA). Pain-related behaviors (weight distribution asymmetry and mechanical hyperalgesia) were assessed at specified time points, and histological evaluation of knee joints was performed at Day 14.

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Dosage form 2.5µg/kg; intra-articular injection; Daily continuous injection.

Applications Continuous administration of APETx2 inhibited the upregulation of ASIC3 in knee joint afferent neurons. APETx2 significantly reduced mechanical hyperalgesia (secondary hyperalgesia) in both early- and late-phase treatment groups. APETx2 also significantly inhibited weight distribution asymmetry in the early-phase group at Day 3. Furthermore, early administration of APETx2 (Days 1-7) prevented cartilage damage and reduced the severity of osteoarthritis, as evidenced by improved histological scores (modified Mankin score).

References:

- [1] Zhou RP, Ni WL, Dai BB, et al. ASIC2a overexpression enhances the protective effect of PcTx1 and APETx2 against acidosis-induced articular chondrocyte apoptosis and cytotoxicity. *Gene*. 2018 Feb 5;642:230-240.
- [2] Izumi M, Ikeuchi M, Ji Q, et al. Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis. *J Biomed Sci*. 2012 Aug 21;19(1):77.

Background

APETx2 is a peptide toxin derived from *Anthopleura elegantissima* and serves as a selective, reversible inhibitor of the acid-sensing ion channel 3 (ASIC3)^[1-2]. By inhibiting the activity of the ASIC3 channel, APETx2 blocks acid-induced pain signaling. APETx2 can be used in research related to inflammatory pain, post-infectious irritable bowel syndrome, and gastric mucosal injury^[3-4].

In vitro, rat articular chondrocytes were pretreated with APETx2 (3µM) and PcTx1 (100ng/ml) for 1 hour, followed by incubation under acidic conditions (pH=6.0) for 3 hours. APETx2 significantly alleviated acidosis-induced cytotoxicity and apoptosis, exerting a chondroprotective effect by reducing intracellular Ca²⁺ levels and inhibiting the phosphorylation of the p38/ERK1/2 MAPK signaling pathway^[5]. Under magnesium-free medium conditions (used to induce epileptiform discharge), primary hippocampal neurons were incubated with APETx2 (63nM) for 1 hour. APETx2

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significantly increased the frequency of burst discharges induced by the magnesium-free medium^[6].

In vivo, APETx2 (20pmol per mouse) was injected into the Zusanli acupoint (ST36) of a fibromyalgia mouse model. By antagonizing ASIC3, APETx2 significantly reduced mechanical hyperalgesia on day 14 post-induction and decreased the overexpression of pain-related channel proteins ASIC3, Nav1.7, and Nav1.8 in the dorsal root ganglia, spinal cord, and thalamus^[7]. In a rat model of osteoarthritis, daily continuous intra-articular injections of APETx2 (2.5µg/kg) for 7 days, APETx2 significantly inhibited weight-bearing asymmetry and secondary mechanical hyperalgesia in the knee joint. APETx2 also effectively prevented articular cartilage damage by reducing chondrocyte loss and matrix destruction^[8].

References:

- [1] Yuan L, Xiao H, Li H, et al. APETx2 regulates intestinal motility and visceral sensitivity in post-infectious irritable bowel syndrome mice through 5-HT signalling pathway. J Pharm Pharmacol. 2023 Apr 17;75(5):712-717.
- [2] Li J, Wei Y, Wang Y, et al. Metabolomics study of APETx2 post-conditioning on myocardial ischemia-reperfusion injury. Front Pharmacol. 2024 Dec 6;15:1470142.
- [3] Diochot S, Baron A, Rash LD, et al. A new sea anemone peptide, APETx2, inhibits ASIC3, a major acid-sensitive channel in sensory neurons. EMBO J. 2004 Apr 7;23(7):1516-25.
- [4] Chagot B, Escoubas P, Diochot S, et al. Solution structure of APETx2, a specific peptide inhibitor of ASIC3 proton-gated channels. Protein Sci. 2005 Aug;14(8):2003-10.
- [5] Zhou RP, Ni WL, Dai BB, et al. ASIC2a overexpression enhances the protective effect of PcTx1 and APETx2 against acidosis-induced articular chondrocyte apoptosis and cytotoxicity. Gene. 2018 Feb 5;642:230-240.
- [6] Cao Q, Xiao ZM, Wang X, et al. Inhibition of Acid Sensing Ion Channel 3 Aggravates Seizures by Regulating NMDAR Function. Neurochem Res. 2018 Jun;43(6):1227-1241.
- [7] Yen LT, Hsieh CL, Hsu HC, et al. Preventing the induction of acid saline-induced fibromyalgia pain in mice by electroacupuncture or APETx2 injection. Acupunct Med. 2020 Jun;38(3):188-193.
- [8] Izumi M, Ikeuchi M, Ji Q, et al. Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis. J Biomed Sci. 2012 Aug 21;19(1):77.

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