Ataluren

Cat. No.: HY-14832

CAS No.: 775304-57-9

Molecular Formula: $C_{15}H_9FN_2O_3$

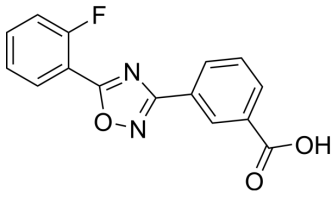
Molecular Weight: 284.24

Target: CFTR; Autophagy

Pathway: Membrane Transporter/Ion Channel; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 52 mg/mL (182.94 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent, Mass	1 mg	5 mg	10 mg
1 mM	3.5182 mL	17.5908 mL	35.1815 mL
5 mM	0.7036 mL	3.5182 mL	7.0363 mL
10 mM	0.3518 mL	1.7591 mL	3.5182 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (8.80 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (7.32 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ataluren (PTC124) is an orally available CFTR-G542X nonsense allele inhibitor.

IC_{50} & Target

CFTR[1]

In Vitro

This premature “stop” signal (a class I mutation) prevents the cell from producing a full-length CFTR protein[1]. Ataluren (PTC124)-a new chemical entity that selectively induces ribosomal readthrough of premature but not normal termination codons[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	Ataluren (PTC124) activity, optimized using nonsense-containing reporters, promotes dystrophin production in primary muscle cells from humans and mdx mice expressing dystrophin nonsense alleles, and rescues striated muscle function in mdx mice within 2-8 weeks of drug exposure. Ataluren (PTC124) is well tolerated in animals at plasma exposures substantially in excess of those required for nonsense suppression[2]. To induce nonsense suppression and increase PPT1 enzyme activity, the read-through drug Ataluren (PTC124) is given via intraperitoneal (i.p.) injection to male $Cln1^{R151X}$ mice at 2 months of age. These treatments are performed four times daily for 2 consecutive days in a proof-of-principle study. Used at 10 mg/kg, Ataluren (PTC124) increased PPT1 enzyme activity (P=0.0001 by unpaired t-test) and protein level (P=0.0014 by unpaired t-test) in the liver, but did not increase PPT1 enzyme activity or protein level in the cortex. This tissue-specific effect is likely due to the inability of Ataluren (PTC124) to breach the blood brain barrier (BBB), which decreased the bioavailability of Ataluren (PTC124) within the brain, and prevented Ataluren (PTC124) from reaching an efficacious concentration within the therapeutic window[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Duplicate samples of HEK293 cells harbouring LUC-190 (UGA) are incubated in the presence of 5 μM Ataluren (PTC124) (treated) or 1% DMSO (untreated) for 20 h. The cells are collected, washed twice in phosphate buffered saline (PBS), resuspended in sample buffer (Bio-Rad) and shipped on dry ice to Kendrick Laboratories for two-dimensional electrophoretic analysis Isoelectric focusing (pH 3.5-10) is carried out in glass tubes for 20,000 V-hours. One μg of a tropomyosin internal standard is added to each sample. Second dimension SDS slab gel electrophoresis is carried out for approximately 6 h at 25 mA per gel. After electrophoresis, gels are transferred to PVDF paper. Computerized analysis of spot mobility used Phoretix software[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Mice[3] Male mice are randomly assigned to either a treatment group or vehicle control group. Six to eight mice per group are treated with 10 or 100 mg/kg Ataluren (PTC124) dissolved in PBS containing DMSO (2% for 10 mg/kg and 20% for 100 mg/kg) and (2-hydroxypropyl)-β-cyclodextrin (22%) via intraperitoneal (i.p.) injections four times daily for 2 consecutive days. Six to eight control mice are treated with the vehicle of the drug: PBS containing DMSO (2% or 20%) and (2-hydroxypropyl)-β-cyclodextrin (22%). Immediately following the last injection on the second day, tissues are collected and stored at −80°C for further use. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Mol Ther Nucleic Acids. 2023 Jun 26.
- Int J Mol Sci. 2021, 22(1), 344.
- Biomedicines. 2023 Apr 28, 11(5), 1310.
- Biomedicines. 2022, 10(11), 2948
- Hum Mol Genet. 2020 Mar 13;29(4):624-634.

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REFERENCES

[1]. Pettit RS, et al. CFTR Modulators for the Treatment of Cystic Fibrosis. P T. 2014 Jul;39(7):500-11.

[2]. Welch EM, et al. PTC124 targets genetic disorders caused by nonsense mutations. Nature, 2007, 447(7140), 87-91.

[3]. Miller JN, et al. The novel Cln1(R151X) mouse model of infantile neuronal ceroid lipofuscinosis (INCL) for testing nonsense suppression therapy. Hum Mol Genet. 2015 Jan 1;24(1):185-96.

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