

Product Data Sheet

Product Name: PTC124(Ataluren)

Cat. No.: GC12346

Chemical Properties

Cas. No. 775304-57-9

Chemical Name 3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid

SMILES C1=CC=C(C(=C1)C2=NC(=NO2)C3=CC(=CC=C3)C(=O)O)F

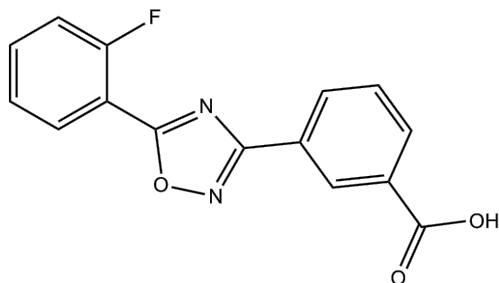
Formula $C_{15}H_9FN_2O_3$ M.Wt 284.24

Solubility $\geq 10.6\text{mg/mL}$ 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.

Structure



Protocol

Cell experiment: [1]

Cell lines HEK293 cells

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

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Preparation method The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reaction Conditions 3 µM, 16 hours

Applications Cultured HEK293 cells harbouring UAA, UAG or UGA LUC-190 nonsense alleles were treated with increasing concentrations of PTC124 for 16 h, and assayed for luciferase activity. PTC124 promoted dose-dependent readthrough of all three nonsense codons. Levels of suppression correlated inversely with established termination efficiencies, with the highest readthrough at UGA, followed by UAG and then UAA. The minimal concentration of PTC124 showing discernable readthrough was 0.01–0.1 µM, whereas the concentration promoting maximal activity was approximately 3 µM.

Animal experiment: [2]

Animal models Cftr^{-/-} hCFTR-G542X Mice

Dosage form Subcutaneous injection, 60, 30, or 15 mg/kg body weight for 14–21 days

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Applications

After the treatment, the mice were killed and intestinal tissues were harvested for immunofluorescence staining to determine whether hCFTR protein could be detected. No hCFTR protein was detected in intestinal tissues from untreated mice with hCFTR-specific antiserum. However, strong hCFTR staining was observed at the apical surface of epithelial cells in submucosal glands from mice treated with 60 mg/kg PTC124. Much weaker staining was detected in submucosal glands from mice treated with 30 mg/kg PTC124, whereas no signal could be detected in mice treated with 15 mg/kg PTC124. These results indicate that PTC124 can suppress the G542X mutation and partially restore hCFTR protein expression in Cftr^{-/-} hCFTR-G542X mice.

Other notes

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1] Welch E M, Barton E R, Zhuo J, et al. PTC124 targets genetic disorders caused by nonsense mutations. *Nature*, 2007, 447(7140): 87-91.

[2] Du M, Liu X, Welch E M, et al. PTC124 is an orally bioavailable compound that promotes suppression of the human CFTR-G542X nonsense allele in a CF mouse model. *Proceedings of the National Academy of Sciences*, 2008, 105(6): 2064-2069.

Background

PTC124 is a selective inhibitor of nonsense mutations with IC₅₀ value of 0.1μM [1].

Nonsense mutation is a point mutation in a sequence of DNA which promotes premature translational termination. Different from missense mutation, nonsense mutation means a single nucleotide is changed and results in the substitution of a different amino acid. It has been reported that some genetic disorders (thalassemia, DMD, CF, Hurler syndrome) are correlated with nonsense mutation [1, 2].

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PTC124 is a potent nonsense mutations inhibitor. When tested with human or mdx mice primary muscle cells expressing dystrophin nonsense alleles, 2-8 weeks treatment of PTC124 enhanced the production of dystrophin [1]. In iPSC-derived RPE cells with nonsense mutation c.519C>T (p.R120X), PTC124 treatment restored endogenous, full-length RP2 protein with near 20% [3]. When tested with COS7 cells carrying the nonsense mutation pDsRed-EGFPmtag-Y445X, EGFP transcript level was increased after treated by PTC124 in a dose-dependent manner [2].

In mdx mice model, oral administration of PTC124 for 2-8 weeks rescued striated muscle function [1]. In a model of Cftr^{-/-} mice expressing a human CFTR-G542X transgene, s.c. injection or oral administration of PTC124 restored a considerable amount of human (h) CFTR protein and function via suppressing G542X nonsense mutation [4].

References:

- [1]. Welch, E.M., et al., *PTC124 targets genetic disorders caused by nonsense mutations. Nature*, 2007. 447(7140): p. 87-91.
- [2]. Shen, Q., P. Guo, and B. Chai, *pDsRed-EGFPmtag-, an effective dual fluorescent reporter system for cell-based screens of premature termination codon. Cytotechnology*, 2014.
- [3]. Schwarz, N., et al., *Translational read-through of the RP2 Arg120stop mutation in patient iPSC-derived retinal pigment epithelium cells. Hum Mol Genet*, 2015. 24(4): p. 972-86.
- [4]. Du, M., et al., *PTC124 is an orally bioavailable compound that promotes suppression of the human CFTR-G542X nonsense allele in a CF mouse model. Proc Natl Acad Sci U S A*, 2008. 105(6): p. 2064-9.

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