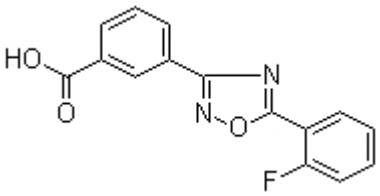
Product Introduction

Ataluren (PTC124)

PTC124 (Ataluren) selectively induces ribosomal read-through of premature but not normal termination codons, with **EC50** of 0.1 μM, may provide treatment for genetic disorders caused by **nonsense mutations** (e.g. CF caused by CFTR nonsense mutation). Phase 3.

Technical Data:

Molecular Weight (MW):	284.24	
Formula:	$C_{15}H_9FN_2O_3$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 57 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	775304-57-9	

Biological Activity

Compared with Gentamicin which is only active at much higher concentrations, PTC124 is a more potent nonsense-suppressing agent and exhibits 4- to 15-fold stimulation of read-through relative to controls. PTC124 (0.01-3 μM) promotes dose-dependent read-through of all three nonsense codons in HEK293 cells harboring LUC-190 nonsense alleles with the highest read-through at UGA, followed by UAG and then UAA, but it does not suppress multiple proximal nonsense codons. Like Gentamicin, PTC124 is most active when a pyrimidine (in particular cytosine, C) follows the nonsense codon. Consistent with the stable cell

line reporter assay, PTC124 (17 μM) promotes significant production of dystrophin in primary muscle cells from Duchenne muscular dystrophy (DMD) patients or MDXMDX mice expressing dystrophin nonsense alleles. PTC124 selectively promotes ribosomal read-through of premature termination but not normal termination codons, even at concentrations substantially greater than the values achieving maximal activity. [1]

Due to functional recovery of dystrophin production, oral, intraperitoneal or combined dosing of PTC124 for 2-8 weeks partially rescues functional strength deficit in dystrophic muscles of MDX mice, and results in partial protection against contraction-induced injury in the extensor digitorum longus (EDL) muscles, as well as significant reductions in serum creatine kinase values. [1] In Cftr-/- mice expressing a human CFTR-G542X transgene, subcutaneous or oral administration of PTC124 (~60 mg/kg) suppresses the G542X nonsense mutation in a dose-dependent manner, leading to a significant restoration of human (h)CFTR protein expression and function without any effect on nonsense-mediated mRNA decay (NMD) or other aspects of mRNA stability. PTC124 treatment (60 mg/kg) restores 29% of the normal intestinal transepithelial cAMP-stimulated shortcircuit currents observed in Cftr+/+ mice, displaying a significant advantage compared with Gentamicin. [2]

Demonstrates oral bioavailability, and an appropriate safety toxicology profile.

References

[1] Welch EM, et al. Nature, 2007, 447(7140), 87-91.

[2] Du M, et al. Proc Natl Acad Sci U S A, 2008, 105(6), 2064-2069.