Palovarotene

Cat. No.: HY-14799

CAS No.: 410528-02-8

Molecular Formula: $C_{27}H_{30}N_2O_2$

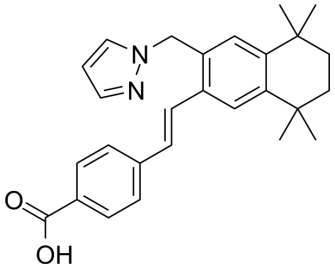
Molecular Weight: 414.54

Target: RAR/RXR; Autophagy

Pathway: Metabolic Enzyme/Protease; Vitamin D Related/Nuclear Receptor; 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 : 25 mg/mL (60.31 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4123 mL	12.0616 mL	24.1231 mL
	5 mM	0.4825 mL	2.4123 mL	4.8246 mL
	10 mM	0.2412 mL	1.2062 mL	2.4123 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.03 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.02 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Palovarotene is a nuclear retinoic acid receptor γ (RAR-γ) agonist.

IC_{50} & Target

RAR-γ[1]

In Vivo

Palovarotene suppresses post-traumatic chondrogenesis and osteogenesis and mitigated trauma-induced ectopic bone formation. Palovarotene inhibits subcutaneous and intramuscular heterotopic ossification (HO) in mice. Palovarotene is given orally for 14 days at 1 mg/kg/day starting on post-operative day (POD) 1 or POD-5, and HO amount, wound dehiscence and related processes are monitored for up to 84 days post injury. Compared to vehicle-control animals, Palovarotene significantly decreases HO by 50 to 60% regardless of when the treatment started and if infection is present[1]. Starting from day 1 of injury, half of the $Acvr1^{cR206H/+}$ mice are treated with Palovarotene by daily gavage for 14 days and the other half

received vehicle as control. Analysis by mCT and 3D image reconstruction at day 14 shows that large HO tissue masses have formed in the targeted leg of Acvr1$^{cR206H/+}$ mutant mice receiving vehicle, but HO formation is greatly diminished in Palovarotene-treated companions by more than 80% based on bone volume/total volume quantification[2].

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

PROTOCOL

Animal Administration [1][2]

Rats[1]

A total of 110 young adult pathogen-free male Sprague Dawley rats (Rattus norvegicus; 400-600 g) are used. Rats receive via oral gavage (100 μL) either Palovarotene (1.0 mg/kg) or vehicle as control (5% DMSO in corn oil) prepared every other day for 14 days, starting at postoperative day 1 (POD-1) or POD-5. Rats are euthanized at indicated time points post-injury for ex vivo end point analysis by micro-computed CT (μCT), histology and RT-PCR gene transcript expression.

Mice[2]

One-month-old Acvr1$^{cR206H/+}$ mice are provided doxycycline chow for 3 days to induce mutant gene expression globally. Mouse quadriceps muscles are injured by injection with 50 mL of 10mM cardiotoxin. Beginning on the day of injury, Palovarotene or vehicle (1:4 DMSO in corn oil) is administered daily for 14 days by oral gavage (100 mg/mouse from days 1 to 3 and 15mg/mouse from days 4 to 14) using a 20-gauge gavage needle. Palovarotene solution in DMSO is stored at -20°C under argon and diluted (1:4) with corn oil for administration.

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

CUSTOMER VALIDATION

- Cell Res. 2022 Jun;32(6):513-529.
- Elife. 2018 Sep 18;7:e40814.
- Patent. US20200345695A1.
- Patent. 20200330415A1.
- Patent. US20190134002Al

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REFERENCES

[1]. Pavey GJ, et al. Targeted stimulation of retinoic acid receptor-γ mitigates the formation of heterotopic ossification in an established blast-related traumatic injury model. Bone. 2016 Sep;90:159-67.

[2]. Chakkalakal SA, et al. Palovarotene Inhibits Heterotopic Ossification and Maintains Limb Mobility and Growth in Mice With the Human ACVR1(R206H) Fibrodysplasia Ossificans Progressiva (FOP) Mutation. J Bone Miner Res. 2016 Sep;31(9):1666-75.

[3]. Lees-Shepard JB, et al. Palovarotene reduces heterotopic ossification in juvenile FOP mice but exhibits pronounced skeletal toxicity. Elife. 2018 Sep 18;7. pii: e40814.

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