Halofuginone

Cat. No.: HY-N1584

CAS No.: 55837-20-2

Molecular Formula: $C_{16}H_{17}BrClN_3O_3$

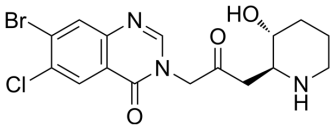
Molecular Weight: 414.68

Target: DNA/RNA Synthesis; TGF-beta/Smad; Parasite; Sodium Channel; Calcium Channel

Pathway: Cell Cycle/DNA Damage; Stem Cell/Wnt; TGF-beta/Smad; Anti-infection; Membrane Transporter/Ion Channel; Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (48.23 mM; ultrasonic and adjust pH to 5 with HCl)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4115 mL	12.0575 mL	24.1150 mL
5 mM	0.4823 mL	2.4115 mL	4.8230 mL
10 mM	0.2411 mL	1.2057 mL	2.4115 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 mg/mL (4.82 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (4.82 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.67 mg/mL (1.62 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Halofuginone (RU-19110), a Febrifugine derivative, is a competitive prolyl-tRNA synthetase inhibitor with a K_i of 18.3 nM[1][2]. Halofuginone is a specific inhibitor of type-I collagen synthesis and attenuates osteoarthritis (OA) by inhibition of TGF-β activity[3][4]. Halofuginone is also a potent pulmonary vasodilator by activating Kv channels and blocking voltage-gated, receptor-operated and store-operated Ca^{2+} channels. Halofuginone has anti-malaria, anti-inflammatory, anti-cancer, anti-fibrosis effects[5].

IC_{50} & Target	Plasmodium

In Vitro

Halofuginone competitively inhibits prolyl-tRNA synthetase by occupying both the prolineand tRNA-binding pockets of prolyl-tRNA synthetase[1].
The IC_{50}s of Halofuginone (1, 10, 100, 1000, 10000 nM; 48 hours) are 114.6 and 58.9 nM in KYSE70 and A549 cells, respectively.

The IC_{50}s of Halofuginone (1, 10, 100, 1000 nM; 24 hours) for NRF2 protein are 22.3 and 37.2 nM in KYSE70 and A549 cells, respectively. The IC_{50} of Halofuginone for global protein synthesis is 22.6 and 45.7 nM in KYSE70 and A549 cells, respectively [1].
Halofuginone increases voltage-gated K^+ (Kv) currents in pulmonary artery smooth muscle cells (PASMC) and K^+ currents through KCNA5 channels in HEK cells transfected with KCNA5 gene. Halofuginone (0.03-1μM) inhibits receptor-operated Ca^{2+} entry (ROCE) in HEK cells transfected with calcium-sensing receptor gene and attenuates store-operated Ca^{2+} entry (SOCE) in PASMC[5].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	KYSE70 cells from human oesophageal cancer harbouring a mutation in the NRF2 gene and A549 cells harbouring theKEAP1 gene mutation
Concentration:	1, 10, 100, 1000, 10000 nM
Incubation Time:	48 hours
Result:	The IC_{50}s were 114.6 and 58.9 nM in KYSE70 and A549 cells, respectively.

Western Blot Analysis[1]

Cell Line:	KYSE70 cells from human oesophageal cancer harbouring a mutation in the NRF2 gene and A549 cells harbouring theKEAP1 gene mutation.
Concentration:	1, 10, 100, 1000 nM
Incubation Time:	24 hours
Result:	The IC_{50}s for NRF2 protein were 22.3 and 37.2 nM in KYSE70 and A549 cells, respectively.

In Vivo

Halofuginone (0.2, 0.5, 1 or 2.5 mg/kg; injected intraperitoneally every other day for 1 month) attenuates progression of OA in anterior cruciate ligament transection (ACLT) mice. Lower concentration (0.2 or 0.5 mg/kg) has minimal effects on subchondral bone and higher concentration (2.5 mg/kg) induces proteoglycan loss in articular cartilage[3].
Halofuginone (0.25 mg/kg; intraperitoneally injected; every day; 16 days) decreases NRF2 protein levels in tumors. While the tumor volumes do not change substantially between treatments with the vehicle, Halofuginone (0.25 mg/kg, intraperitoneally injected, every day) or cisplatin alone. Combined treatment with Halofuginone and Cisplatin significantly suppresses the tumor volume compared to treatment with Halofuginone or cisplatin alone[1].
Intraperitoneal administration of Halofuginone? (0.3mg/kg, for 2 weeks) partially reverses the established pulmonary hypertension in mice[5].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	3-month-old male C57BL/6J (WT) mice[3]
Dosage:	0.2, 0.5, 1 or 2.5 mg/kg
Administration:	Injected intraperitoneally every other day for 1 month
Result:	Attenuated progression of OA in ACLT mice.

Animal Model:	Male nude mice (BALB/C nu/nu mice) (6-8-week)[1]
Dosage:	0.25 mg/kg
Administration:	Intraperitoneally injected; every day; 16 days
Result:	The combined treatment with Cisplatin significantly suppressed the tumor volume. NRF2 protein levels in tumors were indeed decreased.

CUSTOMER VALIDATION

- Cell Metab. 2023 Nov 11:S1550-4131(23)00385-6.
- Br J Pharmacol. 2021 Mar 10.
- iScience. 2023 Mar.
- ACS Infect Dis. 2023 Mar 15.
- Hum Gene Ther. 2021 Aug 18.

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REFERENCES

[1]. Tsuchida K, et al. Halofuginone enhances the chemo-sensitivity of cancer cells by suppressing NRF2 accumulation. Free Radic Biol Med. 2017 Feb;103:236-247.

[2]. Keller TL, et al. Halofuginone and other Febrifugine derivatives inhibit prolyl-tRNA synthetase. Nat Chem Biol. 2012 Feb 12;8(3):311-7.

[3]. Cui Z, et al. Halofuginone attenuates osteoarthritis by inhibition of TGF-β activity and H-type vessel formation in subchondral bone. Ann Rheum Dis. 2016 Sep;75(9):1714-21.

[4]. Tracy L McGaha, et al. Halofuginone, an inhibitor of type-I collagen synthesis and skin sclerosis, blocks transforming-growth-factor-beta-mediated Smad3 activation in fibroblasts. J Invest Dermatol. 2002 Mar;118(3):461-70.

[5]. Pritesh P Jain, et al. Halofuginone, a Promising Drug for Treatment of Pulmonary Hypertension. Br J Pharmacol. 2021 Mar 10.

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