Halofuginone hydrochloride

Cat. No.: HY-N1584B

CAS No.: 1217623-74-9

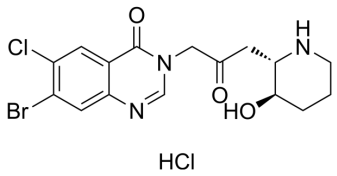
Molecular Formula: $C_{16}H_{18}BrCl_2N_3O_3$

Molecular Weight: 451.14

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

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

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

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

IC_{50} & Target

Ki: 18.3±0.5 nM (prolyl-tRNA synthetase)[2]

In Vitro

Halofuginone hydrobromid competitively inhibits prolyl-tRNA synthetase by occupying both the prolineand tRNA-binding pockets of prolyl-tRNA synthetase[1].

The IC_{50}s of Halofuginone hydrobromid (1, 10, 100, 1000, 10000 nM; 48 hours) are 114.6 and 58.9 nM in KYSE70 and A549 cells, respectively[1].

The IC_{50}s of Halofuginone hydrobromid (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 hydrobromid 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) hydrobromid inhibits receptor-operated Ca^{2+} entry (ROCE) in HEK cells transfected with calcium-sensing receptor gene and attenuated store-operated (SOCE) Ca^{2+} entry in PASMC[5].

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

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, 10000 nM
Incubation Time:	24 h
Result:	The IC_{50}s for NRF2 protein were 22.3 and 37.2 nM in KYSE70 and A549 cells, respectively.

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 h
Result:	The IC_{50}s were 114.6 and 58.9 nM in KYSE70 and A549 cells, respectively.

In Vivo

Halofuginone hydrobromid (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 hydrobromid (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 hydrobromid (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 hydrobromid administration of Halofuginone (0.3mg/kg, for 2 weeks) partially reverses the established pulmonary hypertension in mice[5].

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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.

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.

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

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