Alrizomadlin

Cat. No.: HY-101518

CAS No.: 1818393-16-6

Molecular Formula: $C_{34}H_{38}Cl_2FN_3O_4$

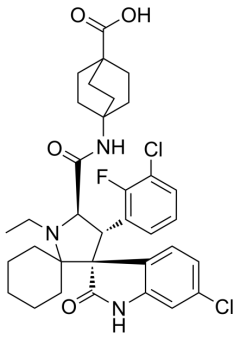
Molecular Weight: 642.59

Target: MDM-2/p53; Apoptosis; E1/E2/E3 Enzyme

Pathway: Apoptosis; Metabolic Enzyme/Protease

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 : 100 mg/mL (155.62 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.5562 mL	7.7810 mL	15.5620 mL
5 mM	0.3112 mL	1.5562 mL	3.1124 mL
10 mM	0.1556 mL	0.7781 mL	1.5562 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: ≥ 5 mg/mL (7.78 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 5 mg/mL (7.78 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.89 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Alrizomadlin (APG-115) is an orally active MDM2 protein inhibitor binding to MDM2 protein with IC_{50} and K_i values of 3.8 nM and 1 nM, respectively[1]. Alrizomadlin blocks the interaction of MDM2 and p53 and induces cell-cycle arrest and apoptosis in a p53-dependent manner[2][3].

IC_{50} & Target

IC50: 3.8 nm (APG-115)[1]

In Vitro

Alrizomadlin (0.001-100 μM; 72 hours) inhibits cell proliferation in concentration-dependent manner, with IC_{50}s of 18.9 ± 15.6

nM and 103.5 ± 18.3 nM respectively in AGS and MKN45 cells[3].
Alrizomadlin (0.02 μM, 0.2 μM; 48 hours) enhances the anti-proliferative effect of radiotherapy at different radiation dose[3].
Alrizomadlin (0.02 μM, 0.2 μM; 48 hours) affects progression by inducing cells arrested at G0/G1 phase in AGS and MKN45 cell with wild p53[3].
Alrizomadlin (0.02 μM, 0.2 μM; 24 hours) activates p53 to enhance radiosensitivity in AGS and MKN45 cells; stable knockout of p53 abrogates expression of MDM2, p53, p21, PUMA, BAX, Cleaved-caspase3, γH2AX[3].
Alrizomadlin (0.3 μM, 1 μM, 3 μM, 10 μM; 24 hours) leads to a concentration-dependent cell cycle arrest in G2/M phases and a decreasing in S-phase in p53 wide-type cell lines (TPC-1, KTC-1)[4].

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

Cell Proliferation Assay[3]

Cell Line:	AGS and MKN45 cells
Concentration:	0.0001 μM, 0.001 μM, 0.01 μM, 0.1 μM, 1 μM, 10 μM, 100 μM
Incubation Time:	72 hours
Result:	Inhibited cell proliferation in a concentration-dependent manner.

RT-PCR[3]

Cell Line:	AGS and MKN45 cells
Concentration:	0.02 μM, 0.2 μM
Incubation Time:	48 hours
Result:	Elevated MDM2, p21, PUMA and BAX mRNA expression.

Cell Cycle Analysis[3]

Cell Line:	AGS and MKN45 cells
Concentration:	0.02 μM, 0.2 μM
Incubation Time:	48 hours
Result:	Arrested cells at G0/G1 phase.

Apoptosis Analysis[4]

Cell Line:	DePTC p53 wide-type cell line: TPC-1 cells, KTC-1 cells
Concentration:	0.3μM, 1μM, 3μM, 10 μM
Incubation Time:	24 hours
Result:	Reduced cell population in S-phase, whereas accumulation of cells at G2/M phases.

Western Blot Analysis[3]

Cell Line:	AGS and MKN45 cells
Concentration:	0.2 μM
Incubation Time:	72 hours
Result:	Enhanced expressions of MDM2 and p53, stable knockout of p53 abrogated them.

In Vivo	Alrizomadlin (Delivered orally; 100 mg/kg; once daily; 10 days) enhances radiation antitumor effect in gastric adenocarcinoma in vivo[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Four-week-old male BALB/c athymic nude mice with MKN45 cells[3]
Dosage:	100 mg/kg
Administration:	Deliverer orally; once daily; 10 days
Result:	Decreased xenograft tumor growth.

REFERENCES

[1]. Angelo Aguilar, et al. 4-((3′R,4′S,5′R)-6″-Chloro-4′-(3-chloro-2-fluorophenyl)-1′-ethyl-2″-oxodispiro[cyclohexane-1,2′-pyrrolidine-3′,3″-indoline]-5′-carboxamido)bicyclo[2.2.2]octane-1-carboxylic Acid (AA-115/APG-115): A Potent and Orally Active Murine Double Minute 2 (MDM2) Inhibitor in Clinical Development. J Med Chem. 2017 Apr 13; 60(7): 2819–2839.

[2]. A W Tolcher et al, A phase Ib/II study of APG-115 in combination with MK-3475 in patients with unresectable or metastatic melanomas or advanced solid tumors, Ann Oncol. 2019 Feb 1; 30(Supplement_1). pii: mdz027.

[3]. Hanjie Yi ea al, A novel small molecule inhibitor of MDM2-p53 (APG-115) enhances radiosensitivity of gastric adenocarcinoma, J Exp Clin Cancer Res. 2018 May 2;37(1):97.

[4]. Chen H, et al. Restoration of p53 using the novel MDM2-p53 antagonist APG115 suppresses dedifferentiated papillary thyroid cancer cells. Oncotarget. 2017 Jun 27;8(26):43008-43022.

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