Nutlin-3a

Cat. No.: HY-10029

CAS No.: 675576-98-4

Molecular Formula: $C_{30}H_{30}Cl_2N_4O_4$

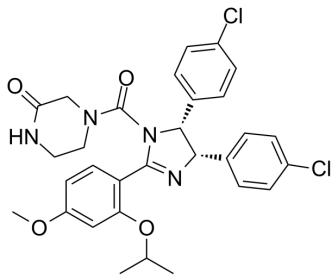
Molecular Weight: 581.49

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

Pathway: Apoptosis; Autophagy; Metabolic Enzyme/Protease

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (171.97 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7197 mL	8.5986 mL	17.1972 mL
	5 mM	0.3439 mL	1.7197 mL	3.4394 mL
	10 mM	0.1720 mL	0.8599 mL	1.7197 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 8 mg/mL (13.76 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.30 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.30 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.30 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Nutlin-3a (Rebemadlin), an active enantiomer of Nutlin-3, is a potent murine double minute (MDM2) inhibitor (IC_{50}=90 nM). Nutlin-3a inhibits MDM2-p53 interactions and stabilizes the p53 protein, and induces cell autophagy and apoptosis. Nutlin-3a has the potential for the study of TP53 wild-type ovarian carcinomas[1][2].

IC_{50} & Target

MDM2-p53[1]

In Vitro	Nutlin-3a is a therapeutic which inhibits MDM2, activates wild-type p53, and induces apoptosis-as a therapeutic compound for TP53 wild-type ovarian carcinomas. Three cell lines (HOC-7, OVCA429 and A2780) with wild-type TP53 are highly sensitive to Nutlin-3a (IC_{50}=4 to 6 μM). SKOV3 cells have an IC_{50} of 38 μM to Nutlin-3a. The two remaining ovarian clear cell lines (TOV21G and OVAS), both with TP53 wild-type, are relatively more sensitive to growth inhibition with Nutlin-3a (IC_{50}=14 and 25 μm respectively) than the TP53 mutant cell lines[1]. Nutlin-3a is the active enantiomer of Nutlin-3. Nutlin-3a is a highly selective MDM2 antagonist and p53 inducer. Seven days of incubation with 10 μM Nutlin-3a leads to >90% inhibition of NIH/3T3 cells'growth but does not affect the proliferation of MEF in which both targets of the drug are eliminated. Nutlin-3a effectively arrestes cell-cycle progression in all cell lines, depleting the S-phase compartment to 0.2-2% and increasing the G_1- and G_2/M-phase compartments, indicating G_1 and G_2 arrest. The p53 targets p21 and MDM2 are elevated significantly 3 h after Nutlin-3a addition and reach maximal levels at 8 h. Nutlin-3a induces apoptosis in ≈60% of SJSA-1 and MHM cells after 40 h, which increase further after 60 h (85% and 65%, respectively)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Nutlin-3a is efficacious in all models with average tumor growth inhibition ≥98%. Nutlin-3a suppresses xenograft growth in a dose-dependent fashion with the highest dose (200 mg/kg) showing a substantial tumor shrinkage (eight partial and one full regressions). The established SJSA-1 and MHM osteosarcoma xenografts with Nutlin-3a causes extensive tumor regression[2] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	All 15 cell lines are plated at a density of 1×10^3 cells per well in 96-well plates. After 24h, media is exchanged and cells are treated with incremental concentrations of Nutlin 3a (1 μM, 5 μM, 10 μM, 25 μM, 50 μM, and 70 μM). After 72 h of incubation, WST-1 is added to each well, and a microplate reader is used at an absorbance of 450 nm to measure the number of remaining viable cells. Experiments are repeated with smaller titrations of Nutlin 3a as needed to determine the exact IC_{50} of cell lines. The IC_{50} is defined. Cell lines are again plated in a manner identical to above and treated with Nutlin 3a at their respective IC_{50}, and WST-1 is added with cell viability measurement at 24, 48, and 72h[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Nude mice bearing s.c. tumor xenografts (10 mice per group in the SJSA-1, LnCaP, and 22Rv1 study and 15 mice per group in the MHM study) are dosed orally twice daily with Nutlin 3a (50-200 mg/kg) or vehicle (1% Klucel, 0.1% Tween 80) for 2 weeks (22Rv1 and LnCap) or 3 weeks (SJSA-1 and MHM). Tumor volume is measured with a caliper and calculated. For Western blot analysis, nude mice with established SJSA-1 tumors (200-400 mm^3, three animals per group are treated with three doses of Nutlin 3a at 150 mg/kg (at 0, 8, and 24 h), and tumors are harvested 3 h after the last dose. Tumor samples are flash-frozen and processed[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Immunol. 2023 May;24(5):780-791.
- Nat Commun. 2022 Aug 4;13(1):4534.
- Cell Death Differ. 2022 Nov 12.
- Cell Death Differ. 2022 Apr 28.
- Dev Cell. 2022 Feb 23;S1534-5807(22)00079-X.

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REFERENCES

[1]. Crane EK, et al. Nutlin-3a: A Potential Therapeutic Opportunity for TP53 Wild-Type Ovarian Carcinomas. PLoS One. 2015 Aug 6;10(8):e0135101.

[2]. Tovar C, et al. Small-molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: implications for therapy. Proc Natl Acad Sci U S A. 2006 Feb 7;103(6):1888-93.

[3]. M Ulrich, et al. Murine tumor models for the in vivo evaluation of natural compounds and their derivatives as new cancer therapeutics. München. 2016.

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