Siremadlin

Cat. No.: HY-18658

CAS No.: 1448867-41-1

Molecular Formula: $C_{26}H_{24}Cl_2N_6O_4$

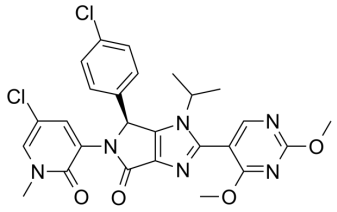
Molecular Weight: 555.41

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

Pathway: Apoptosis; Metabolic Enzyme/Protease

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 : ≥ 56.75 mg/mL (102.18 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8005 mL	9.0024 mL	18.0047 mL
5 mM	0.3601 mL	1.8005 mL	3.6009 mL
10 mM	0.1800 mL	0.9002 mL	1.8005 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 (4.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.50 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (4.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Siremadlin (NVP-HDM201) is a potent, orally bioavailable and highly specific p53-MDM2 interaction inhibitor.

In Vitro

Siremadlin (NVP-HDM201) disrupts both human and murine TP53- MDM2 interactions, with nanomolar cellular IC_{50} values, blocking TP53 degradation[1].

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

In Vivo	Siremadlin (NVP-HDM201) is an imidazolopyrrolidinone analogue, showing a very advantageous in vivo profile. NVP-HDM201 has recently entered Phase 1 clinical trials in cancer patients[2]. Constitutive PB mutagenesis in $Arf^{-/-}$ mice provides a collection of spontaneous tumors with characterized insertional genetic landscapes. Tumors are allografted in large cohorts of mice to assess the pharmacologic effects of Siremadlin (NVP-HDM201). Sixteen out of 21 allograft models are sensitive to Siremadlin (NVP-HDM201) but ultimately relapse under treatment. A comparison of tumors with acquired resistance to Siremadlin (NVP-HDM201) and untreated tumors identified 87 genes that are differentially and significantly targeted by the PB transposon[1]. Siremadlin (NVP-HDM201) administered either daily at a low dose or once at a high dose revealed a differentiated engagement of the p53 molecular response. In contrast to the daily low dose treatment regimen, the single high dose Siremadlin (NVP-HDM201) regimen results in a rapid and dramatic induction of p53-dependent PUMA expression and apoptosis. This is consistent with the finding that a single high dose Siremadlin (NVP-HDM201) treatment, administered orally or intravenously, results in a robust and sustained tumor regression. Overall, both daily and once every 3 weeks dosing regimen shows comparable long term efficacy in preclinical studies. The ongoing clinical trial is currently designed to compare both dosing regimens with regard to efficacy and tolerability[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Oncogenesis. 2022 Jul 2;11(1):37.
- Int J Mol Sci. 2022, 23(19), 11939.
- Cancers (Basel). 2022 Oct 19;14(20):5127.
- SSRN. 2023 Oct 9.

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REFERENCES

[1]. Chapeau EA, et al. Resistance mechanisms to TP53-MDM2 inhibition identified by in vivo piggyBac transposon mutagenesis screen in an Arf-/- mouse model. Proc Natl Acad Sci U S A. 2017 Mar 21;114(12):3151-3156.

[2]. Furet P, et al. Discovery of a novel class of highly potent inhibitors of the p53-MDM2 interaction by structure-based design starting from a conformational argument. Bioorg Med Chem Lett. 2016 Oct 1;26(19):4837-41.

[3]. Stéphane F, et al. Abstract 1224: Insights into the mechanism of action of NVP-HDM201, a differentiated and versatile Next-Generation small-molecule inhibitor of Mdm2, under evaluation in phase I clinical trials. Insights into the mechanism of action of N

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