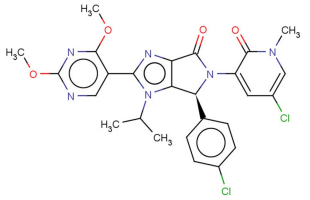
Data Sheet (Cat.No.T5555)

TargetMol
A DRUG SCREENING EXPERT

Siremadlin

Chemical Properties



CAS No.:	1448867-41-1
Formula:	C26H24Cl2N6O4
Molecular Weight:	555.41
Appearance:	N/A
Storage:	0-4℃ for short term (days to weeks), or -20℃ for long term (months).

Biological Description

Description	Siremadlin is a potent, orally bioavailable and highly specific p53-MDM2 interaction inhibitor.
In vitro	Siremadlin inhibits both human and murine TP53- MDM2 interactions, with nanomolar cellular IC50 values, blocking TP53 degradation[1]
In vivo	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[1]. Siremadlin has recently entered Phase 1 clinical trials in cancer patients[2]. 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].

Solubility Information

Solubility	DMSO: 56.75 mg/mL (102.18 mM) (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.800 mL	9.002 mL	18.005 mL
5 mM	0.360 mL	1.800 mL	3.601 mL
10 mM	0.180 mL	0.900 mL	1.800 mL
50 mM	0.036 mL	0.180 mL	0.360 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. The storage conditions and period of the stock solution: - 80 ℃ for 6 months; - 20 ℃ for 1 month. Please use it as soon as possible.

Reference

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 NVP-HDM201, a differentiated and versatile Next-Generation small-molecule inhibitor of Mdm2, under evaluation in phase I clinical trials. [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl):Abstract nr 1224.

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