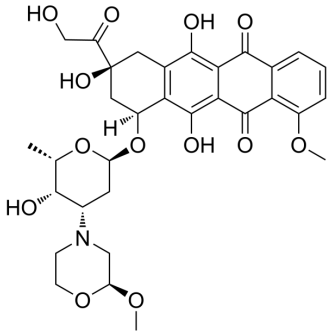
Nemorubicin

Cat. No.:	HY-15794
CAS No.:	108852-90-0
Molecular Formula:	$C_{32}H_{37}NO_{13}$
Molecular Weight:	643.64
Target:	G-quadruplex
Pathway:	Cell Cycle/DNA Damage
Storage:	4°C, protect from light * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 65 mg/mL (100.99 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.5537 mL	7.7683 mL	15.5366 mL
	5 mM	0.3107 mL	1.5537 mL	3.1073 mL
	10 mM	0.1554 mL	0.7768 mL	1.5537 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: ≥ 3.25 mg/mL (5.05 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Nemorubicin (Methoxymorpholinyl doxorubicin) is a Doxorubicin derivative with potent antitumor activity. Nemorubicin is highly cytotoxic to a variety of tumor cell lines presenting a multidrug-resistant phenotype. Nemorubicin not only intercalate into the duplex DNA, but also result in significant ligands for G-quadruplex DNA segments, stabilizing their structure. Nemorubicin requirs an intact nucleotide excision repair (NER) system to exert its activity[1][2][3][4].

In Vitro

Nemorubicin has antitumor activity, with IC_{70}s of 578 nM, 468 nM, 193 nM, 191 nM, 68 nM, and 131 ± 9 nM for HT-29, A2780, DU145, EM-2, Jurkat and CEM cell lines, respectively[1].

Nemorubicin is CYP3A-activated anticancer prodrug, which can produce a more cytotoxic metabolite, PNU-159682[1][2].

Nemorubicin acts through nucleotide excision repair (NER) system to exert its activity. Nemorubicin (0-0.3 μM) is more active in the L1210/DDP cells with intact NER than in the XPG-deficient L1210/0 cells. Cells resistant to nemorubicin show increased sensitivity to UV damage[3].

Nemorubicin is cytotoxic to 9L/3A4 cells, with an IC_{50} of 0.2 nM, 120-fold lower than that of P450-deficient 9L cells (IC_{50}, 23.9 nM). Nemorubicin also potently inhibits Adeno-3A4 infected U251 cells with IC_{50} of 1.4 nM. P450 reductase overexpression enhances cytotoxicity of Nemorubicin[4].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Nemorubicin is converted to PNU-159682 by human liver cytochrome P450 (CYP) 3A4 in rat, mouse, and dog liver microsomes[2]. Nemorubicin (60 μg/kg) induces sifnificant tumor growth delay in scid mice bearing 9L/3A4 tumors, but shows no obvious effect on the tumor growth delay of 9L tumors in mice by i.v. or intratumoral injection (i.t.). Nemorubicin (40 μg/kg, i.p.) exhibits no antitumor activity and no host toxicity in mice bearing 9L/3A4 tumors[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [4]	9L and CHO cells are plated in triplicate wells of a 96-well plate at 3000 cells per well 24 hr prior to drug treatment. Cells are treated with various concentrations of Nemorubicin or IFA for 4d. Cells are then stained with crystal violet (A595) and relative cell survival is calculated. IC_{50} values are determined from a semi-logarithmic graph of the data points using Prism 4 [4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [4]	9L and 9L/3A4 cells are grown as solid tumors in male ICR/Fox Chase SCID mice. Cells cultured in DMEM medium to 75% confluence are trypsinized and washed in PBS and then adjusted to 2×10^7 cells/mL of FBS-free DMEM. Four-week-old SCID mice (18-20 g) are implanted with either 9L or 9L/3A4 tumor cells by injection of 4×10^6 cells/0.2 mL of cell suspension, s.c. on each hind flank. Tumor sizes (length and width) are measured twice a week using Vernier calipers beginning 7d after tumor implantation. When the average tumor size reach 300 to 400 mm^3, Nemorubicin dissolved in PBS is administered by tail vein injection (i.v.) or by direct intratumoral (i.t.) injection (three injections spaced 7 d apart, each at 60 μg Nemorubicin per kg body weight). Intratumoral injections are performed using a syringe pump set a 1 μL/s with a 30-gauge needle. Each i.t. treatment dose is divided into three injections per tumor, with the injected volume set at 50 μL per tumor per 25 g mouse. Thus, for a 30 g mouse, a total of 120 μL of 15 μg/mL of Nemorubicin solution is administered: 20 μL per site × 3 sites per tumor × 2 tumors/mouse. Drug-free controls are injected i.t. with the same vol of PBS. In some experiments, Nemorubicin is administered by i.p. injection at 40 or 60 μg/kg body weight. Tumor sizes and body weights are measured twice/wk for the duration of the study. Tumor volumes are calculated using the formula: $V = \pi/6\ (L \times W)^{3/2}$. Percent tumor regression is calculated as $100 \times (V_1\text{-}V_2)/V_1$, where V_1 is the tumor vol on the day of drug treatment and V_2 is the vol on the day when the largest the decrease in tumor size is seen following drug treatment. Tumor doubling time is calculated as the time required for tumors to double in vol after drug treatment[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Quintieri L, et al. Formation and antitumor activity of PNU-159682, a major metabolite of nemorubicin in human liver microsomes. Clin Cancer Res. 2005 Feb 15;11(4):1608-17.

[2]. Quintieri L, et al. In vitro hepatic conversion of the anticancer agent nemorubicin to its active metabolite PNU-159682 in mice, rats and dogs: a comparison with human liver microsomes. Biochem Pharmacol. 2008 Sep 15;76(6):784-95.

[3]. Sabatino MA, et al. Down-regulation of the nucleotide excision repair gene XPG as a new mechanism of drug resistance in human and murine cancer cells. Mol Cancer. 2010 Sep 24;9:259.

[4]. Lu H, et al. Potentiation of methoxymorpholinyl doxorubicin antitumor activity by P450 3A4 gene transfer. Cancer Gene Ther. 2009 May;16(5):393-404.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA