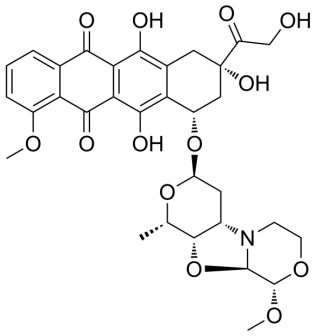
PNU-159682

Cat. No.:	HY-16700
CAS No.:	202350-68-3
Molecular Formula:	$C_{32}H_{35}NO_{13}$
Molecular Weight:	641.62
Target:	ADC Cytotoxin; Topoisomerase
Pathway:	Antibody-drug Conjugate/ADC Related; Cell Cycle/DNA Damage
Storage:	4°C, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (155.86 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Concentration / Solvent / Mass	1 mg	5 mg	10 mg
	1 mM	1.5586 mL	7.7928 mL	15.5855 mL
	5 mM	0.3117 mL	1.5586 mL	3.1171 mL
	10 mM	0.1559 mL	0.7793 mL	1.5586 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 (3.90 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (3.90 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PNU-159682, a metabolite of the anthracycline Nemorubicin, is a highly potent DNA topoisomerase II inhibitor with excellent cytotoxicity. PNU-159682 acts as a more potent and tolerated ADC cytotoxin than Doxorubicin for ADC synthesis. PNU-159682 can be used in EDV-nanocell technology to overcome agent resistance.

IC_{50} & Target		
	Daunorubicins/Doxorubicins	Topoisomerase I

In Vitro

PNU-159682 (0-500 nM; exposed to the compounds for 1 hour and then cultured in compound-free medium for 72 hours) has cytotoxic effects on human tumor cell lines in a sulforhodamine B assay. The IC_{70} values are 0.577 nM, 0.39 nM, 0.128 nM, and 0.081 nM, 0.086 nM and 0.075 nM for HT-29, A2780, DU145, EM-2, Jurkat and CEM cells, respectively[1]. It against human

tumor cell lines with IC_{70} in the ranging 68 nM-578 nM and 181 nM-1717 nM towards MMDX and doxorubicin, respectively[1].
?PNU-159682 is more potent than MMAE on NHL cell lines. In a cell viability assay, PNU-159682 is against BJAB.Luc, Granta-519, SuDHL4.Luc, and WSU-DLCL2 with IC_{50} values of 0.10 nM, 0.020 nM, 0.055 nM, and 0.1 nM, respectively. While MMAE is against BJAB.Luc, Granta-519, SuDHL4.Luc, and WSU-DLCL2 with IC_{50} values of 0.54 nM, 0.25 nM, 1.19 nM and 0.25 nM, respectively[2].
PNU-159682 is thousands of times more cytotoxic than doxorubicin and can be used to develop a new class of ADCs. PNU159682?to?anti-CD22?antibody (anti-CD22-NMS249) exhibits strong anti-tumor effects in vitro. Anti-CD22-NMS249 (PNU159682?to?anti-CD22?antibody) is active in in vitro viability assays of NHL cell lines and is 2 to 20 fold more potent than pinatuzumab vedotin, the ADC anti-CD22-NMS249 is against BJAB.Luc, Granta-519, SuDHL4.Luc, and WSU-DLCL2 with IC_{50} values of 0.058 nM, 0.030 nM, 0.0221 nM, and 0.01 nM, respectively[3].
PNU-159682 (100 μM) weakly inhibits topoisomerase II unknotting activity. PNU-159682 shows cytotoxic effect on CAIX-expressing SKRC-52 cells with IC_{50} of 25 nM[4].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[2]

Cell Line:	HT-29, A2780, DU145, EM-2, Jurkat and CEM cells
Concentration:	0-500 nM
Incubation Time:	Exposed to the PNU-159682 for 1 hour and then cultured in compound-free medium for 72 hours
Result:	Was 2,360- to 790-fold and 6,420- to 2,100-fold more potent than MMDX and doxorubicin, respectively. Exhibited IC_{70} values of PNU-159682 are in the subnanomolar range (0.07-0.58 nM) and noticeably lower than that recorded for both MMDX and doxorubicin.

In Vivo

PNU-159682 (single-dose; i.v.15 μg/kg) is a maximum tolerated dose in murine L1210 leukemia model. PNU-159682 shows an improved antitumor activity in vivo. The antitumor effect of PNU-159682 (increase in life span=29%) is comparable to that afforded by 90 μg/kg MMDX (increase in life=36%)[1].
PNU-159682 (i.v. 4 μg/kg; q7dx3; 40 days) has a therapeutic response in MX-1 human mammary carcinoma mice. What's more, from day 39, four out of seven mice receiving PNU-159682 exhibits complete tumor regression[1].
PNU-159682 is more cytotoxic than doxorubicin and can be used to develop a new class of ADCs. PNU159682?to?anti-CD22?antibody (anti-CD22-NMS249) exhibits strong anti-tumor effects in vivo. ADC dose (anti-CD22-NMS249; 50 μg/m2 conjugated PNU-159682) is well tolerated in mice and results in less than 10% weight loss[2].
In the BJAB.Luc model the efficacy of antiCD22-NMS249 (single dose; 2 mg/kg) is similar to anti-CD22-vc-MMAE. At 2 mg/kg dosage, antiCD22-NMS249 gives complete remission of the tumors (NMS249: 110-134%TGI vs. vc-MMAE: 114-143%TGI). Additionally, a single dose of antiCD22-NMS249 at 2 mg/kg results in tumor stasis for three weeks[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Four- to six-week-old female CD-1 athymic nude mice with MX-1 tumor fragments[1]
Dosage:	4 μg/kg
Administration:	Intravenous injection; q7dx3; 40 days
Result:	Exhibited anti-cancer effects in MX-1 human mammary carcinoma xenografts to PNU-159682.

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]. Cazzamalli S, et al. Acetazolamide Serves as Selective Delivery Vehicle for Dipeptide-Linked Drugs to Renal Cell Carcinoma. Mol Cancer Ther. 2016 Dec;15(12):2926-2935.

[3]. Pengxuan Zhao, et al. Recent advances of antibody drug conjugates for clinical applications. Acta Pharm Sin B. 2020 Sep;10(9):1589-1600.

[4]. Joanne Lundy, Interim data: Phase I/IIa study of EGFR-targeted EDV nanocells carrying cytotoxic drug PNU-159682 (E-EDV-D682) with immunomodulatory adjuvant EDVs carrying α-galactosyl ceramide (EDV-GC) in patients with recurrent, metastatic pancreatic cancer. GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Caution: Product has not been fully validated for medical applications. For research use only.

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