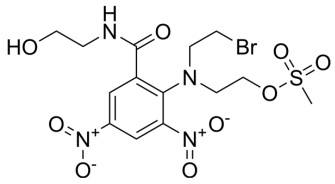
PR-104A

Cat. No.:	HY-14572
CAS No.:	680199-06-8
Molecular Formula:	$C_{14}H_{19}BrN_4O_9S$
Molecular Weight:	499.29
Target:	DNA Alkylator/Crosslinker; Drug Metabolite
Pathway:	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Storage:	-20°C, protect from light, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (500.71 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0028 mL	10.0142 mL	20.0284 mL
	5 mM	0.4006 mL	2.0028 mL	4.0057 mL
	10 mM	0.2003 mL	1.0014 mL	2.0028 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: ≥ 6.25 mg/mL (12.52 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 6.25 mg/mL (12.52 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 6.25 mg/mL (12.52 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PR-104A (SN 27858) is the alcohol metabolite of phosphate proagent PR-104. PR-104A is a hypoxia-selective DNA cross-linking agent/DNA-damaging agent and cytotoxin. Antitumor Activity[1]. PR-104A is metabolized under hypoxia by the 1-electron NADPH:cytochrome P450 oxidoreductase. PR-104A can be used for the research of relapsed/refractory T-lineage acute lymphoblastic leukemia (T-ALL)[2].

In Vitro

PR-104A (1-100 uM) shows antiproliferative potency in a panel of 10 human carcinoma cell lines following 4 hours exposures under aerobic and hypoxic conditions with the lowest IC_{50} (0.51 μM) in H460 non-small cell lung cancer cells and highest (7.3 μM) in PC3 prostate cells[1].

The phosphate ester PR-104 is rapidly converted in vivo to the alcohol PR-104A, a nitrogen mustard prodrug that is metabolised to hydroxylamine (PR-104H) and amine (PR-104M) DNA crosslinking agents by one-electron reductases in hypoxic cells and by aldo-keto reductase 1C3 independently of oxygen[3].

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

Cell Proliferation Assay[1]

Cell Line:	HT29 , HCT116, C33A SiHa A549, H460, H1299 ,PC3,SKOV3, A375 cells
Concentration:	0, 1, 10, 100 uM
Incubation Time:	4 hours under aerobic or hypoxic conditions
Result:	The lowest IC_{50} (0.51 μM) in H460 non-small cell lung cancer cells and highest (7.3 μM) in PC3 prostate cells.

In Vivo

The phosphate ester “pre-prodrug” PR-104 is well tolerated in mice and converted rapidly to the corresponding prodrug PR-104A. H460 xenografts shows significant sensitivity to PR-104 (total dose 3.2 mmol/kg)[1].

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

Animal Model:	Specific pathogen-free homozygous nude (CD1-Foxn1nu) mice with H460 xenografts[1]
Dosage:	Daily (0.23 mmol/kg/dose; qd ×14) or weekly (1.07 mmol/kg/dose; qw ×3)
Administration:	I.p.
Result:	The single-agent activity against H460 tumors refractory to docetaxel, cisplatin, gemcitabine, and cyclophosphamide was particularly striking. Compared a daily (qd ×14) versus weekly (qw ×3) schedule against the chemoresistant H460 xenograft model using the same total dose (3.2 mmol/kg) over 14 days, which was well tolerated using both schedules.

REFERENCES

[1]. Adam V Patterson, et al. Mechanism of action and preclinical antitumor activity of the novel hypoxia-activated DNA cross-linking agent PR-104. Clin Cancer Res. 2007 Jul 1;13(13):3922-32.

[2]. Donya Moradi Manesh, et al. AKR1C3 is a biomarker of sensitivity to PR-104 in preclinical models of T-cell acute lymphoblastic leukemia. Blood. 2015 Sep 3;126(10):1193-202.

[3]. McKeage MJ, et al. A phase I trial of PR-104, a pre-prodrug of the bioreductive prodrug PR-104A, given weekly to solid tumour patients. BMC Cancer. 2011;11:432. Published 2011 Oct 7.

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