CX-5461 dihydrochloride

Cat. No.: HY-13323A

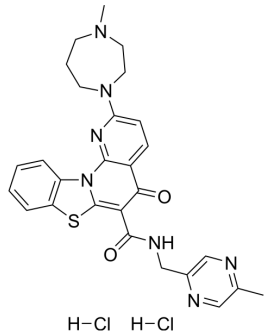
Molecular Formula: $C_{27}H_{29}Cl_2N_7O_2S$

Molecular Weight: 586.54

Target: DNA/RNA Synthesis

Pathway: Cell Cycle/DNA Damage

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 2 years; -20°C, 1 year (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

H_2O : 5 mg/mL (8.52 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7049 mL	8.5246 mL	17.0491 mL
	5 mM	0.3410 mL	1.7049 mL	3.4098 mL
	10 mM	---	---	---

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
Solubility: 6.25 mg/mL (10.66 mM); Clear solution; Need ultrasonic and warming and heat to 60°C

BIOLOGICAL ACTIVITY

Description

CX-5461 dihydrochloride is a potent and orally bioavailable inhibitor of Pol I-mediated rRNA synthesis, with IC_{50}s of 142 nM in HCT-116, 113 nM in A375, and 54 nM in MIA PaCa-2 cells, and shows little or no effect on Pol II (IC_{50} ≥25 μM).

IC_{50} & Target

IC50: 54 nM (rRNA synthesis, MIA PaCa-2 cells), 113 nM (rRNA synthesis, A375 cells), 142 nM (rRNA synthesis, HCT-116 cells)[1]

In Vitro

CX-5461 is a potent and orally bioavailable inhibitor of Pol I-mediated rRNA synthesis, with IC_{50}s of 142 nM in HCT-116, 113 nM in A375, and 54 nM in MIA PaCa-2 cells, and shows little or no effect on Pol II (IC_{50}, ≥25 μM). CX-5461 has modest inhibition on DNA replication and protein translation. CX-5461 also exhibits broad antiproliferative activity against a panel of human cancer cell lines, with a mean EC_{50} of 147 nM, but has minimal effect on viability of nontransformed human cells, with EC_{50} values of appr 5000 nM. EC_{50}s of CX-5461 for HCT-116, A375, and MIA PaCa-2 cell lines are 167, 58, and 74 nM, respectively. CX-5461 induces autophagy and senescence in solid tumor cancer cells, rather than apoptosis, through a p53-independent process[1]. Eμ-Myc lymphoma cells from tumor-bearing mice are exquisitely sensitive to CX-5461 with an IC_{50} of 27.3 nM ± 8.1 nM for Pol I transcription after 1 hr and IC_{50} of 5.4 nM ± 2.1 nM for cell death after 16 hr. CX-5461 activates p53 via the nucleolar stress response in Eμ-MycLymphoma Cells[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CX-5461 displays antitumor activity against human solid tumors in murine xenograft models. CX-5461 (50 mg/kg, p.o.) shows significant MIA PaCa-2 growth inhibition with TGI equal to 69% on day 31 and 79% TGI on A375 on day 32[1]. CX-5461 (50 mg/kg, p.o.) inhibits the Eμ-Myc tumor cells with 84% repression in Pol I transcription at 1 hr posttreatment in C57BL/6 mice. CX-5461 also induces a rapid reduction in tumor burden in the lymph nodes and a concomitant reduction of spleen size to within the normal range[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are plated on 96-well plates and treated the next day with dose response of CX-5461 for 96 hours. Cell viability is determined using Alamar Blue and CyQUANT assays[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Animal experiments are performed with 5- to 6-week-old female athymic (NCr nu/nu fisol) mice of Balb/c. Mice are inoculated with athymic (NCr nu/nu fisol) mice in 100 μL of cell suspension subcutaneously in the right flank. Tumor measurements are performed by caliper analysis, and tumor volume is calculated using the formula $(l \times w^2)/2$, where w=width and l=length in mm of the tumor. established tumors (appr 110-120 mm^3) are randomized into vehicle (50 mM NaH_2PO_4, pH 4.5), NSC 613327, or CX-5461 treatment groups. Tumor growth inhibition (TGI) is determined on the last day of study according to the formula: TGI (%)=[100 − $(Vf^D - Vi^D)$/ $(Vf^V - Vi^V)$ × 100], where Vi^V is the initial mean tumor volume in vehicle-treated group, Vf^V is the final mean tumor volume in vehicle-treated group, Vi^D is the initial mean tumor volume in drug-treated group, and Vf^D is the final mean tumor volume in drug-treated group. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Cell Biol. 2022 Jul;24(7):1154-1164.
- Nat Commun. 2022 Jun 28;13(1):3706.
- Nat Commun. 2017 Sep 25;8(1):693.
- J Extracell Vesicles. 2023 Oct;12(10):e12361.
- Nucleic Acids Res. 2022 May 6;50(8):4574-4600.

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REFERENCES

[1]. Drygin D et al. Targeting RNA polymerase I with an oral small molecule CX-5461 inhibits ribosomal RNA synthesis and solid tumor growth. Cancer Res. 2011 Feb 15;71(4):1418-30.

[2]. Bywater MJ, et al. Inhibition of RNA Polymerase I as a Therapeutic Strategy to Promote Cancer-Specific Activation of p53.

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

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