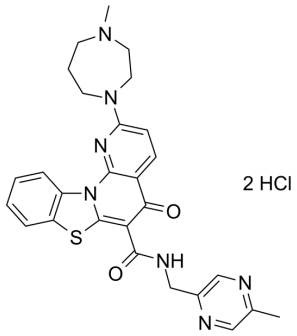
CX-5461 dihydrochloride

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, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

H_2O : ≥ 25 mg/mL (42.62 mM)

* "≥" means soluble, but saturation unknown.

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	0.1705 mL	0.8525 mL	1.7049 mL

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

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 Commun. 2017 Sep 25;8(1):693.
- Clin Cancer Res. 2017 Nov 1;23(21):6529-6540.
- Cancer Res. 2022 Jan 12;canres.1707.2021.
- EMBO Mol Med. 2021 Mar 5;13(3):e12834.
- Acta Biomater. 2018 Oct 1;79:317-330.

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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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