Rucaparib hydrochloride

Cat. No.: HY-10617B

CAS No.: 773059-19-1

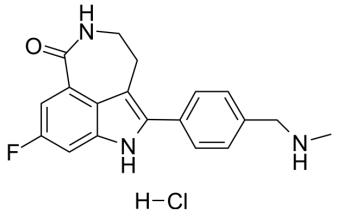
Molecular Formula: $C_{19}H_{19}ClFN_3O$

Molecular Weight: 359.83

Target: PARP

Pathway: Cell Cycle/DNA Damage; Epigenetics

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Rucaparib (AG014699) hydrochloride is an orally active, potent inhibitor of PARP proteins (PARP-1, PARP-2 and PARP-3) with a K_i of 1.4 nM for PARP1. Rucaparib hydrochloride is a modest hexose-6-phosphate dehydrogenase (H6PD) inhibitor. Rucaparib hydrochloride has the potential for castration-resistant prostate cancer (CRPC) research[1][2][3][4].

IC_{50} & Target	PARP-1	PARP-2	PARP-3
	1.4 nM (Ki)		

In Vitro

Rucaparib (AG014699) hydrochloride is a possible N-demethylation metabolite of AG14644[1].

Rucaparib (0.1, 1, 10, 100 μM; 24 hours) hydrochloride is cytotoxic and has the LC_{50} being 5 μM in Capan-1 (BRCA2 mutant) cells and only 100 nM in MX-1 (BRCA1 mutant) cells[2].

The radio-sensitization by Rucaparib hydrochloride is due to downstream inhibition of activation of NF-κB, and is independent of SSB repair inhibition. Rucaparib hydrochloride can target NF-κB activated by DNA damage and overcome toxicity observed with classical NF-κB inhibitors without compromising other vital inflammatory functions[5].

Rucaparib hydrochloride inhibits PARP-1 activity by 97.1% at a concentration of 1 μM in permeabilised D283Med cells[6].

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

In Vivo

Rucaparib (AG014699) hydrochloride and AG14584 significantly increase Temozolomide toxicity. Rucaparib (1 mg/kg) hydrochloride significantly increases Temozolomide-induced body weight loss. Rucaparib (0.1 mg/kg) hydrochloride results in a 50% increase in the temozolomide-induced tumor growth delay[1].

Rucaparib (10 mg/kg for i.p. or 50, 150 mg/kg for p.o.; daily for 5 days per week for 6 weeks) hydrochloride significantly inhibits the growth of the tumor, and there is one complete tumor regression and two persistent partial regressions[2].

Rucaparib (150 mg/kg; p.o.; once per week for 6 weeks or three times per week for 6 weeks) hydrochloride has greatest antitumor effect with three complete regressions[2].

Rucaparib (1 mg/kg; i.p.; daily for 5d) hydrochloride enhances the antitumor activity of temozolomide and indicates complete and sustained tumor regression in NB1691 and SHSY5Y xenografts[6].

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

Animal Model:	Female athymic nude mice, implanted SW620 colorectal tumor cells (1×10^7 cells per animal) s.c.[1]
Dosage:	0.1 mg/kg in combination with Temozolomide (p.o., 200 mg/kg), 0.05, 0.15, and 0.5 mg/kg in combination with Temozolomide (p.o., 68 mg/kg) or 10 mg/kg

Administration:	IP, single dose for 0.1 mg/kg and 10 mg/kg, five daily doses for 0-0.5 mg/kg
Result:	Significantly increased Temozolomide toxicity, showed outstanding chemosensitization potency and caused enhancement of Temozolomide-induced tumor growth delay.

Animal Model:	CD-1 nude mice bearing established Capan-1 xenografts[2]
Dosage:	10 mg/kg or 50, 100 and 150 mg/kg
Administration:	IP for 10 mg/kg; PO for 50, 100 and 150 mg/kg, single dose (Pharmacokinetics)
Result:	Parent drug was detectable in the plasma only at 30 min after 10 mg/kg i.p and up to 4 h for 50–150 mg/kg p.o.. Was still detectable in most mice receiving oral rucaparib at 3 days. Does not easily cross the plasma membrane.

Animal Model:	CD-1 nude mice bearing established Capan-1 xenografts[2]
Dosage:	10 mg/kg i.p. daily for 5 days per week for 6 weeks, 50 or 150 mg/kg p.o. daily × five weekly × six, 150 mg/kg p.o. once per week for 6 weeks or three times per week for 6 weeks, or 150 mg/kg p.o. daily for five days every 3 weeks
Administration:	IP or PO
Result:	10 mg/kg i.p. significantly inhibited the growth of the tumor, daily oral administration at 150 mg/kg had an equivalent effect on tumor growth to 10 mg/kg i.p.. The schedule with the greatest antitumor effect was oral administration of 150 mg/kg on a once weekly schedule with three complete regressions.

Animal Model:	CD-1 nude mice, NB1691 and SHSY5Y xenografts[6]
Dosage:	1 mg/kg
Administration:	IP, daily for 5 d in combination with Temozolomide (orally daily ×5 at a dose of 68 mg/kg)
Result:	Enhanced the antitumor activity of Temozolomide and indicated complete and sustained tumor regression.

CUSTOMER VALIDATION

- Sci Transl Med. 2021 May 26;13(595):eabe8226.
- Sci Adv. 2022 Feb 18;8(7):eabl9794.
- Theranostics. 2020 Jul 25;10(21):9477-9494.
- Clin Cancer Res. 2017 Feb 15;23(4):1001-1011.
- Genes Dis. 2023 Apr 12.

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REFERENCES

[1]. Thomas HD, et al. Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial. Mol Cancer Ther, 2007, 6(3), 945-956.

[2]. J Murray, et al. Tumour cell retention of rucaparib, sustained PARP inhibition and efficacy of weekly as well as daily schedules. Br J Cancer. 2014 Apr 15;110(8):1977-84.

[3]. Matt Shirley, et al. Rucaparib: A Review in Ovarian Cancer. Target Oncol. 2019 Apr;14(2):237-246.

[4]. Jianneng Li, et al. Hexose-6-phosphate dehydrogenase blockade reverses prostate cancer drug resistance in xenograft models by glucocorticoid inactivation. Sci Transl Med. 2021 May 26;13(595):eabe8226.

[5]. Hunter JE, et al. NF-κB mediates radio-sensitization by the PARP-1 inhibitor, AG-014699. Oncogene, 2012, 31(2), 251-264.

[6]. Daniel RA, et al. Inhibition of poly(ADP-ribose) polymerase-1 enhances temozolomide and topotecan activity against childhood neuroblastoma. Clin Cancer Res, 2009, 15(4), 1241-1249.

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