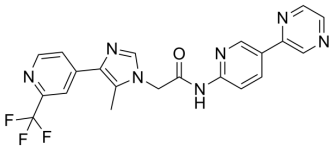
Zamaporvint

Cat. No.:	HY-153855
CAS No.:	1900754-56-4
Molecular Formula:	$C_{21}H_{16}F_3N_7O$
Molecular Weight:	439.39
Target:	Wnt; Acyltransferase; Porcupine
Pathway:	Stem Cell/Wnt; Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (284.49 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2759 mL	11.3794 mL	22.7588 mL
	5 mM	0.4552 mL	2.2759 mL	4.5518 mL
	10 mM	0.2276 mL	1.1379 mL	2.2759 mL

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

BIOLOGICAL ACTIVITY

Description

Zamaporvint (RXC004) is an orally active and selective inhibitor of Wnt. Zamaporvint targete membrane-bound o-acyltransferase Porcupine and inhibited Wnt ligand palmitoylation, secretion, and pathway activation. Zamaporvint displays a favorable pharmacokinetic profile and shows potent antiproliferative effects in Wnt ligand-dependent colorectal and pancreatic cell lines. Zamaporvint possesses multiple antitumor mechanisms and can be used in cancer research[1].

In Vitro

Zamaporvint (300 nM, 48 h) treatment of L- wnt3a cells reduce the ability of conditioned medium to activate the β-catenin-responsive luciferase reporter gene in a concentration-dependent manner, with an IC_{50} of 64 pM, and the addition of recombinant Wnt3a restore the luciferase activity, suggesting no effect on downstream Wnt signaling[1].

The effect of Zamaporvint (100 nM, 24 hr) on proliferation reflects a concentration-dependent downregulation of c-Myc mRNA. Reduced the proportion of cells in S phase and strongly suppressed the expression of the mitotic marker phospho-histone-H3 in cells with abnormal upstream components of the Wnt pathway, indicative of cell cycle arrest, and was found to have reduced immunosuppression at the same dose as after administration Sexual support[1] .

Zamaporvint (20 μM, 18 h) in plasma across species ranged from 2.5% to 7.5%, microsomal CL_{int} values ranged from 3.9 to 31.6 μL/min?mg, with mouse having the lowest and dog the highest predicted clearances, rodents and humans display low clearance[1].

Zamaporvint (10 μM, 2 h) has good intrinsic permeability, showing some evidence of efflux in MDR1-MDCKII cells but not in Caco-2 cells[1].

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

Western Blot Analysis[1]

Cell Line:	L-Wnt5a
Concentration:	300 nM
Incubation Time:	48 h
Result:	Activated the β-catenin-responsive luciferase reporter gene in a concentration-dependent manner, with an IC_{50} of 64 pmol/L.

Apoptosis Analysis[1]

Cell Line:	L-Wnt5a
Concentration:	100 nM
Incubation Time:	24 h
Result:	Downregulated c-Myc mRNA and reduce the proportion of cells in S-phase, and strongly inhibited expression of the mitosis marker phospho-histone-H3 in cells with upstream aberrations in Wnt pathway components.

In Vivo

Zamaporvint (1.5 mg/kg or 5 mg/kg orally twice daily, or 5 mg/kg Zamaporvint orally once daily, for 28 days) reduces in tumor growth, and inhibition of Wnt-responsive gene expression including cMyc, was observed in the Wnt ligand–dependent SNU-1411, AsPC1, and HPAFII models, and no effected tumor growth in the Wnt ligand–independent HCT116 xenograft mode[1].

Zamaporvint (1.5 mg/kg, 5 mg/kg, once daily) reduces Ki67-positive cells in the total tumor area, and its effect is more pronounced in differentiated tumor areas, and by inhibiting immune evasion in the B16F10 "cold" tumor model Antitumor effect [1].

Zamaporvint (1.5 or 5 mg/kg once daily) stimulates host tumor immunity, reduces resident myeloid-derived suppressor cells within B16F10 tumors and synergizing with anti-programmed cell death protein-1 (PD-1, HY-P73361) to increase CD8+/regulatory T cell ratios within CT26 tumors[1].

Pharmacokinetic Parameters of Zamaporvint in Mice. [1]

species	Dose (i.v./p.o., mg/kg)	C_{max} (p.o., μM)	$C_{24\,h}$ (p.o., μM)	AUC_{inf} (p.o., μM.h)	Cl (mL/min/kg)	V_{ss} (L/kg)	F (p.o., %)	$T_{1/2}$ (hr)
mouse	2/5	7.6	0.002	33.9	2.9	0.40	48	1.8
rat	2/5	3.6	0.009	10.5	5.8	0.64	31	2.5
dog	2/5	10.4	0.012	8.6	8.9	0.39	137	0.8

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

Animal Model:	SCID-Beige mice were dosed at Translational Drug Discovery with vehicle[1]
Dosage:	1.5 mg/kg or 5 mg/kg; 5 mg/kg

Administration:	1.5 mg/kg or 5 mg/kg orally twice daily, or 5 mg/kg RXC004 orally once daily, for 28 days
Result:	Reduced in tumor growth, and inhibition of Wnt-responsive gene expression including cMyc, was observed in the Wnt ligand–dependent SNU-1411, AsPC1, and HPAFII models. No effected tumor growth in the Wnt ligand–independent HCT116 xenograft mode.

Animal Model:	HPAF-II (5 × 106 cells; athymic nude mice), AsPC1 (3 × 106 cells; athymic nude mice), and SNU-1411 (1×107 cells; NOD-SCID mice) were implanted bilaterally, subcutaneously, whereas HCT116 (3 × 106 cells; athymic nude mice) were implanted in a single flank[1]
Dosage:	Dosing was either 1.5 mg/kg twice daily RXC004 for 7–13 days then once daily for the remainder of study (up to 29 days), or 28 days 1.5 mg/kg twice daily RXC004 for HCT116
Administration:	p.o.
Result:	Demonstrated to inhibit tumor growth and Wnt-responsive gene expression

Animal Model:	B16F10/C57BL/6 syngeneic model was performed at Axis Bioservices. Mouse B16F10 cells (2 × 105) were subcutaneously implanted in flanks of the immunocompetent male C57BL/6 mice[1]
Dosage:	5 mg/kg once daily
Administration:	p.o.
Result:	Inhibited tumor growth and improved model survival.

Animal Model:	CT26/BALB/c syngeneic model was performed at ProQuinase GmbH. Mouse CT26 cells (5 × 105) were subcutaneously implanted in the flanks of the immunocompetent female BALB/c mice[1]
Dosage:	1.5 or 5 mg/kg (once daily).
Administration:	p.o.
Result:	Increased CD8+/regulatory T cell ratio.

REFERENCES

[1]. Phillips C, The Wnt Pathway Inhibitor RXC004 Blocks Tumor Growth and Reverses Immune Evasion in Wnt Ligand-dependent Cancer Models. Cancer Res Commun. 2022 Sep 2;2(9):914-928.

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