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Mutant IDH1/NAMPT-IN-1

Cat. No.: HY-158319

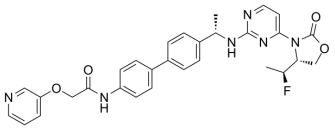
Molecular Formula: $C_{30}H_{29}FN_6O_4$

Molecular Weight: 556.59

Target: Apoptosis; Isocitrate Dehydrogenase (IDH); NAMPT

Pathway: Apoptosis; Metabolic Enzyme/Protease

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



BIOLOGICAL ACTIVITY

Description

Mutant IDH1/NAMPT-IN-1 (Compound 23h) is a dual inhibitor of mutant isocitrate dehydrogenase 1 (mutant IDH1) (IC_{50} =14.93 nM) and nicotinamide phosphoribosyltransferase (NAMPT) (IC_{50}=12.56 nM). Mutant IDH1/NAMPT-IN-1 can induce apoptosis. Mutant IDH1/NAMPT-IN-1 crosses the blood-brain barrier effectively[1].

IC_{50} & Target

IDH1
14.93 nM (IC_{50})

In Vitro

Mutant IDH1/NAMPT-IN-1 (0.5-2 μM; 48 h) is able to dose-dependently reduce 2-HG levels in U87 MG-IDH1^{R132H} cells[1].
Mutant IDH1/NAMPT-IN-1 shows antiproliferative activity against U87 MG IC_{50}=1.26 μM (24 h), 0.77 μM (48 h), 0.42 μM (72 h).
Antiproliferative activity against U87 MG-IDH1^{R132H} IC_{50}=0.89 μM (24 h), 0.47 μM (48 h), 0.32 μM (72 h)[1].
Mutant IDH1/NAMPT-IN-1 (0.5 μM; 6 h) improves the thermal stability of NAMPT and IDH1R132H in U87 MG-IDH1^{R132H} cells[1].
Mutant IDH1/NAMPT-IN-1 (0.1-2 μM; 48 h) dose-dependently induces apoptosis in U87 MG-IDH1^{R132H} cells[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Apoptosis Analysis[1]

Cell Line:	U87 MG-IDH1^{R132H}
Concentration:	0.1 μM, 0.5 μM, 1 μM, 2 μM
Incubation Time:	48 h
Result:	The apoptosis rate at the concentration of 2 μM was significantly higher than that of the combined group of AG-120 (HY-18767) and FK866 (HY-50876).

Western Blot Analysis[1]

Cell Line:	U87 MG-IDH1^{R132H}
Concentration:	0.5 μM
Incubation Time:	6 h
Result:	Reduced the expression levels of IDH1R132H, downstream protein TET2, and NAMPT, as well as the upstream protein NAPRT. Decreased the expression of H3K4me3 and H3K27me3.

In Vivo

Mutant IDH1/NAMPT-IN-1 (i.v.; 10-40 mg/kg; twice daily for 35 days) inhibits tumor growth in a dose-dependent manner in BALB/c nude mice[1].
Mutant IDH1/NAMPT-IN-1 (i.v.;400 mg/kg; single dose) is safe to administer in ICR mice[1].

Pharmacokinetic Analysis in SD rats[1]

Route	Dose (mg/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	Cl ((L/h)/kg)	F (%)
i.v.	1	1.16 ± 0.08	4065.66 ± 565.86	0.033	1933.17 ± 131.71	1944.08 ± 132.42	0.26 ± 0.02	/
p.o.	10	2.06 ± 0.29	866.57 ± 225.07	0.75	919.04 ± 40.19	921.26 ± 40.82	/	4.75%

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

Animal Model:	BALB/c nude mice[1]
Dosage:	10, 20, and 40 mg/kg
Administration:	i.v.; twice daily for 35 days
Result:	Median survival times were 25.5, 30.5, and 34 days for the low, middle, and high dose groups, respectively. 40 mg/kg group significantly prolonged survival time in mice and showed superior efficacy compared to FK866 (HY-50876) and IDH305 (HY-104036). Alleviated weight loss in mice.

REFERENCES

[1]. Wen F, et al. Discovery of Novel Dual Inhibitors Targeting Mutant IDH1 and NAMPT for the Treatment of Glioma with IDH1Mutation. J Med Chem. 2024 Apr 23.

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