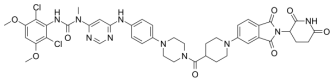
LC-MB12

Cat. No.:	HY-149843
CAS No.:	2828438-38-4
Molecular Formula:	$C_{43}H_{44}Cl_2N_{10}O_8$
Molecular Weight:	899.78
Target:	FGFR; PROTACs
Pathway:	Protein Tyrosine Kinase/RTK; PROTAC
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 : 130 mg/mL (144.48 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.1114 mL	5.5569 mL	11.1138 mL
	5 mM	0.2223 mL	1.1114 mL	2.2228 mL
	10 mM	0.1111 mL	0.5557 mL	1.1114 mL

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

BIOLOGICAL ACTIVITY

Description

LC-MB12 is an orally active PROTAC compound targets FGFR2 degradation with a DC_{50} of 11.8 nM. LC-MB12 contains BGJ398 (a FGFR2 inhibitor), PROTAC linker and CRBN.LC-MB12 inhibits FGFR2 signaling in gastric cancer cells and has anti-tumor activity[1].

IC_{50} & Target

FGFR2
11.8 nM (DC50)

In Vitro

LC-MB12 (0.5-10,000 nM, 3-12 hours) degrades FGFR2 in a time-dependent manner in KATO III, with a DC_{50} of 11.8 nM.
LC-MB12 (100 nM, 6 hours) degrades FGFR2 to 77% in KATO III and 43% in NCI-H1581[1].
LC-MB12 (1-10000 nM, 72 hours) inhibits the growth of KATO III, SNU-16, and NCI-H716 significantly with IC_{50}s of 29.1 nM, 3.7 nM and 3.2 nM, respectively, and induces KATO III G0/G1 phase arrest[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	KATO III, SNU-16, NCI-H716
Concentration:	0.5 nM, 1.5 nM, 4.3 nM, 13 nM, 41 nM, 123 nM, 370 nM, 1111 nM, 3333 nM, 10000 nM
Incubation Time:	72 h
Result:	Inhibited cell growth with IC_{50}s value of 29.1 nM (KATO III); 3.7 nM (SNU-16); 3.2 nM (NCI-H716).

Cell Cycle Analysis[1]

Cell Line:	KATO III
Concentration:	29.1 nM
Incubation Time:	72 h
Result:	Induced G0/G1 cycle arrest.

Immunofluorescence[1]

Cell Line:	KATO III
Concentration:	100 nM
Incubation Time:	3 h, 6 h
Result:	Promoted FGFR2 was relocated from the cell membrane to intracellular vesicles after treated for 3 or 6 h. Induced receptor internalization and re-localization to the perinuclear section after 6 h treatment.

Western Blot Analysis[1]

Cell Line:	KATO III, NCI-H1581
Concentration:	0.5 nM, 1.5 nM, 4.3 nM, 13 nM, 41 nM, 123 nM, 370 nM, 1111 nM, 3333 nM, 10000 nM
Incubation Time:	6 h
Result:	Degraded FGFR2 with a DC_{50} of 11.8 nM and D_{max} of ~80% after 6 h of treatment. Showed time-dependent effect on degradation,with a detectable reduction in FGFR2 levels after 3 h of treatment and ~90% degradation after 12 h. Degraded of FGFR2 in KATO by 77%, and in NCI-H1581 by 43% after 100 nM treatment for 6 h.

In Vivo

LC-MB12 (20 mg/kg/day, p.o., 15 days) inhibits tumor growth to 63.1% in SNU-16 xenograft models of nude mice[1].
LC-MB12 (20 mg/kg, p.o.) shows fast absorption (C_{max}: 2.6 h) and orally bioavailable (F: 13%) in mice[1].
LC-MB12 (20 mg/kg, p.o., 30 days) is well tolerated and has no apparent hepatotoxicity or nephrotoxicity in mice[1].

In Vivo PK Properties of LC-MB12[1]

parameter	$T_{1/2}$	T_{max} (ng•h/mL)	C_{max}	$AUC_{(0-\infty)1/2}$	V_{ss} (h)	CL	F
unit	h	h	ng/mL	h*ng/mL	mL/kg	mL/h/kg	%

iv (3 mg/kg)	0.97	0.083	655.29	421.61	6233.19	7289.12	/
po (20 mg/kg)	1.47	2.67	82.07	387.27	/	/	13.07

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Animal Model:	SNU-16 xenografted in BALB/c-nu mice[1].
Dosage:	20 mg/kg/day
Administration:	oral administration (p.o.) 15 days
Result:	Achieved 63.1% tumor growth inhibition innocuously. Inhibited FGFR phosphorylation and total FGFR2 protein and decreased phosphorylation levels of downstream pPLCγ and ERK1/2.

REFERENCES

[1]. Ma L, et al. Discovery of a Selective and Orally Bioavailable FGFR2 Degrader for Treating Gastric Cancer. J Med Chem. 2023 Jun 8;66(11):7438-7453.

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