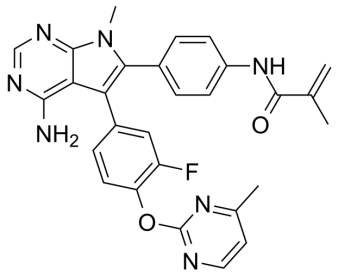
Lirafugratinib

Cat. No.:	HY-147250
CAS No.:	2549174-42-5
Molecular Formula:	$C_{28}H_{24}FN_7O_2$
Molecular Weight:	509.53
Target:	FGFR
Pathway:	Protein Tyrosine Kinase/RTK
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 : 62.5 mg/mL (122.66 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9626 mL	9.8130 mL	19.6259 mL
	5 mM	0.3925 mL	1.9626 mL	3.9252 mL
	10 mM	0.1963 mL	0.9813 mL	1.9626 mL

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

BIOLOGICAL ACTIVITY

Description

Lirafugratinib (RLY-4008) is an orally active, irreversible and highly selective FGFR2 inhibitor with an IC_{50} of 3 nM. Lirafugratinib covalently binds to Cys491. Lirafugratinib targets FGFR2 primary alterations and resistance mutations and induces tumor regression while sparing other FGFRs[1].

IC_{50} & Target

FGFR2
3 nM (IC_{50})

In Vitro

Lirafugratinib (RLY-4008) has >250-fold selectivity over FGFR1, and >80- and >5,000-fold selectivity over FGFR3 and FGFR4, respectively. The reversible binding of Lirafugratinib promotes a rigid and extended P-loop in FGFR1 that disfavors covalent bond formation while minimally affecting the conformation of the P-loop in FGFR2, enabling efficient covalent bond formation and leading to FGFR2 selectivity[1].

Lirafugratinib (24h) induces dose-dependent cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP)-early markers of apoptosis[1].

Lirafugratinib (2h) demonstrates a dose-dependent reduction of phosphorylation of FGFR2 signaling pathway nodes, including FRS2, AKT, and ERK[1].

RLY-4008 inhibits cellular proliferation with IC_{50}<14 nM in FGFR2-dependent cell lines including KATO III, SNU-16 and NCI-H716, ICC13-7, and MFE-296, FGFR2N549K and AN3CA, FGFR2K310R; N549K and JHUEM-2, FGFR2C383R[1].

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

Apoptosis Analysis[1]

Cell Line:	FGFR2-amplified gastric cancer cell line SNU-16
Concentration:	IC50 (6 nM), IC90
Incubation Time:	24 h
Result:	Induced dose-dependent cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP)-early markers of apoptosis.

Apoptosis Analysis[1]

Cell Line:	FGFR2-amplified gastric cancer cell line SNU-16
Concentration:	IC50 (6 nM), IC90
Incubation Time:	2 h
Result:	Demonstrated a dose-dependent reduction of phosphorylation of FGFR2 signaling pathway nodes, including FRS2, AKT, and ERK.

In Vivo

Lirafugratinib (RLY-4008; 1-30 mg/kg; orally, twice daily; 15-30 days) demonstrates antitumor activity in FGFR2-altered cancer xenograft models[1].

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

Animal Model:	Female BALB/c nude mice with SNU-16 and AN3CA xenografts; female NOD SCID mice with CC13-7 and ICC13-7-$FGFR2^{V564F}$ xenografts[1]
Dosage:	1, 3, 10, 30 mg/kg
Administration:	Orally; twice daily; for 15-30 days
Result:	Exhibited dose-dependent antitumor activity and induced tumor regression in all models.

REFERENCES

[1]. Vivek Subbiah, et al. RLY-4008, the First Highly Selective FGFR2 Inhibitor with Activity across FGFR2 Alterations and Resistance Mutations. Cancer Discov. 2023 Sep 6;13(9):2012-2031.

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