URMC-099

Cat. No.: HY-12599

CAS No.: 1229582-33-5

Molecular Formula: $C_{27}H_{27}N_5$

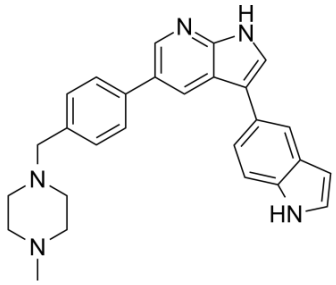
Molecular Weight: 421.54

Target: Mixed Lineage Kinase; Autophagy

Pathway: MAPK/ERK Pathway; Autophagy

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 : ≥ 33 mg/mL (78.28 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3723 mL	11.8613 mL	23.7225 mL
5 mM	0.4745 mL	2.3723 mL	4.7445 mL
10 mM	0.2372 mL	1.1861 mL	2.3723 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.93 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.93 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.93 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

URMC-099 is an orally bioavailable and potent mixed lineage kinase type 3 (MLK3) (IC_{50}=14 nM) inhibitor with with excellent blood-brain barrier penetration properties.

IC_{50} & Target

MLK3	LRRK2	FLT3	FLT1
14 nM (IC_{50})	11 nM (IC_{50})	4 nM (IC_{50})	39 nM (IC_{50})

	ABL1 (T315I) 3 nM (IC_{50})	ABL1 6.8 nM (IC_{50})	SGK 67 nM (IC_{50})	SGK1 201 nM (IC_{50})
	AurA 108 nM (IC_{50})	AurB 123 nM (IC_{50})	AurC 290 nM (IC_{50})	IKKβ 257 nM (IC_{50})
	IKKα 591 nM (IC_{50})	TNFα 460 nM (IC_{50})	ROCK1 1030 nM (IC_{50})	ROCK2 111 nM (IC_{50})
	CDK1 1125 nM (IC_{50})	CDK2 1180 nM (IC_{50})	TRKA 85 nM (IC_{50})	c-MET 177 nM (IC_{50})
	TRKB 217 nM (IC_{50})	IGF1R 307 nM (IC_{50})	LCK 333 nM (IC_{50})	MEKK2 661 nM (IC_{50})
	SYK 731 nM (IC_{50})	AMPK 1512 nM (IC_{50})	JNK1 3280 nM (IC_{50})	SRC 4330 nM (IC_{50})
	ZAP70 5050 nM (IC_{50})	ERK2 6290 nM (IC_{50})	P38α 12050 nM (IC_{50})	CYP3A4 16.2 μM (IC_{50})

In Vitro

The effect of URMC-099 (URMC099) on the in vitro growth of the “brain homing” MDA-MB-231 BR cells expressing eGFP (eGFP8.4) and their parental cell line, MDA-MB-231 is tested. The cells are treated with either 200 nM URMC-099 or vehicle alone. Cells treated with URMC-099 grow at a similar rate to those treated with vehicle. Cell viability is >99% in all cases[2].

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

In Vivo

URMC-099 has moderate terminal elimination half-life ($t_{1/2}$=1.92 h, 2.14 h and 2.72 h for C57 BL/6 mice (10 mg/kg, oral dosing), C57 BL/6 mice (2.5 mg/kg, iv), C57 BL/6 mice (10 mg/kg, iv))[1]. The effect of URMC-099 (URMC099) on tumor formation in vivo is analyzed using a well characterized mouse xenograft model of breast cancer brain metastasis. For these experiments, eGFP8.4 cells are inoculated into the left ventricle of immunodeficient nu/nu mice; animals are then treated with either URMC-099 (10 mg/kg) or vehicle alone, every 12 hours for 20 days. This dose of URMC-099 is chosen because it has been shown to be sufficient to effectively inhibit MLK3 in mice, with good penetration of the blood-brain barrier and potent inhibition of the phosphorylation of Jun N-terminal kinase (JNK) in brain tissue. On day 21 the mice are sacrificed and number of BM is assessed. Fifteen mice are used for each treatment group. BM are detected in 60% of mice, which is consistent with previous studies using this xenograft model by other investigators. URMC-099 treatment significantly ($p<0.05$, two-tailed t-test) increases the total number of brain metastasis (BM) in mice. For micrometastases, the pattern is similar to that observed for total BM. The number of macrometastases is statistically indistinguishable between mice treated with URMC-099 or vehicle[2].

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PROTOCOL

Cell Assay [2]

MDA-MB-231, MCF10A, HS578t and MDA-MB-231 EGFP8.4 cells are seeded in a 24 well plate at an initial density of 5.0×10^4 cells/mL in 0.5 mL of media. The cells are treated with either 200 μM of URMC-099 or vehicle (0.002% DMSO). Cell number in each well is measured by trypsinizing the cells and counting them with a hematocytometer. The viability is tested by trypan blue dye exclusion. Each condition is tested in triplicate[2].

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Animal Administration [2]

Mice[2]

6 to 8 week old female nu/nu mice are injected intraperitoneally with URMC-099 at a dose of 10 mg/kg, or vehicle, twice daily for 20 days. On day 21 mice are sacrificed by CO_2 suffocation. Brains are removed and fixed with 4% formaldehyde in PBS overnight, then transferred to 30% sucrose in PBS. The brains are then quickly frozen by immersing into isopentane

	cooled on dry ice. The frozen brains are sectioned coronally every 30 micrometers. Eight sections starting at bregma 2.0 and separated by 360 μm are mounted on glass slides for tumor evaluation under the microscope. The number of brain metastasis (BM) is counted by examining eGFP signals under a fluorescence microscope at 20× magnification[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Dis. 2020 Jul 24;11(7):574.

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REFERENCES

[1]. Goodfellow VS, et al. Discovery, synthesis, and characterization of an orally bioavailable, brain penetrant inhibitor of mixed lineage kinase 3. J Med Chem. 2013 Oct 24;56(20):8032-48.

[2]. Rhoo KH, et al. Pharmacologic inhibition of MLK3 kinase activity blocks the in vitro migratory capacity of breast cancer cells but has no effect on breast cancer brain metastasis in a mouse xenograft model. PLoS One. 2014 Sep 29;9(9):e108487.

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