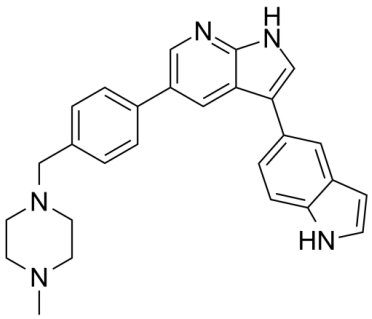
Data Sheet

Product Name:	URMC-099
Cat. No.:	CS-4182
CAS No.:	1229582-33-5
Molecular Formula:	C27H27N5
Molecular Weight:	421.54
Target:	Autophagy; Mixed Lineage Kinase
Pathway:	Autophagy; MAPK/ERK Pathway
Solubility:	H2O : < 0.1 mg/mL (insoluble); DMSO : ≥ 33 mg/mL (78.28 mM)



BIOLOGICAL ACTIVITY:

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. **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **Animal Administration:** URMC-099 (URMC099) is dissolved in 5% DMSO/45% saline/50% PEG400 to 2 mg/mL[2].[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].

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.

CAIndexNames:

1H-Pyrrolo[2,3-b]pyridine, 3-(1H-indol-5-yl)-5-[4-[(4-methyl-1-piperazinyl)methyl]phenyl]-

SMILES:

CN(CC1)CCN1CC(C=C2)=CC=C2C3=CN=C4C(C(C5=CC=C(NC=C6)C6=C5)=CN4)=C3

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA