

Product Data Sheet

Product Name: URMC-099

Cat. No.: GC15004

Chemical Properties

Cas. No. 1229582-33-5

Chemical Name 3-(1H-indol-5-yl)-5-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]-1H-pyrrolo[2,3-b]pyridine

SMILES CN1CCN(CC1)CC2=CC=C(C=C2)C3=CN=C4C(=C3)C(=CN4)C5=CC6=C(C=C5)NC=C6

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

M.Wt 421.54

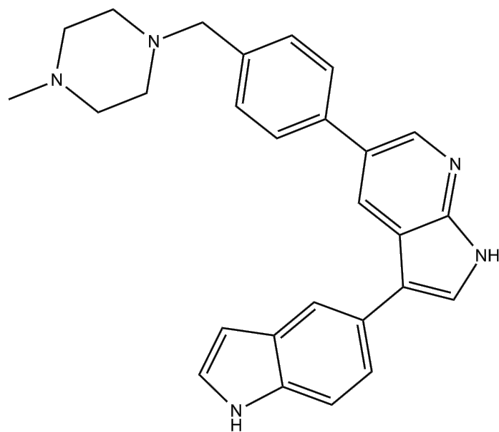
Solubility ≥ 21.1 mg/mL in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

Cell lines Microglia

Caution: Product has not been fully validated for medical applications. For research use only.

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Microglia were plated at a density of 2×10^5 onto 24-well plates for RNA/protein extraction or onto 24-well plates with glass coverslips for confocal microscopy. 2×10^4 cells were placed in each 96-well plate for immunofluorescence studies.

Preparation Method One day before A β exposure and URM-099 treatment, media was replaced without MCSF. Microglia were pre-incubated for 30 min with URM-099 (100 nM). After pre-incubation with URM-099, microglia were incubated with media containing the monomeric A β 42.

Reaction Conditions 100 nM; 30 min

Applications URM-099 administered at 100 nM did not affect microglial viability as measured by the MTT assay. Phagocytosis of A β 42 was facilitated by URM-099 with up-regulation of scavenger receptors.

Animal experiment [2]:

Animal models Four-month-old APP/PS1 mice

Four-month-old APP/PS1 mice were administered intraperitoneal URM-099 injections at 10 mg/kg daily for 3 weeks. Brain tissues were examined by biochemical, molecular and immunohistochemical tests.

Preparation Method

Dosage form 10 mg/kg; i.p.

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Applications

URMC-099 inhibited mitogen-activated protein kinase 3/4-mediated activation and attenuated β -amyloidosis. Microglial nitric oxide synthase-2 and arginase-1 were co-localized with lysosomal-associated membrane protein 1 (Lamp1) and A β . Importantly, URMC-099 restored synaptic integrity and hippocampal neurogenesis in APP/PS1 mice.

References:

Dong W, et al. The mixed-lineage kinase 3 inhibitor URMC-099 facilitates microglial amyloid- β degradation. *J Neuroinflammation*. 2016 Jul 11;13(1):184.

Kiyota T, et al. URMC-099 facilitates amyloid- β clearance in a murine model of Alzheimer's disease. *J Neuroinflammation*. 2018 May 5;15(1):137.

Background

URMC-099, as a 7-azaindole-based MLK3 inhibitor with IC₅₀ of 14 nM, could specifically affect specific A β species engaged in disease pathobiology^[1].

In vitro, the average half maximal inhibitory concentrations (IC₅₀) of URMC-099 in seven GBM cell lines was 4.57 μ M. *In vitro*, treatment with ≥ 5 μ M URMC-099 for 48 h in 7 GBM cell lines reduced cell viability^[2]. *In vitro* experiment it shown that treatment with 100 or 300 nM URMC-099 in neuronal cell prevented neuronal death and maintained healthy neurites up to 48 h after NGF withdrawal in a dose-dependent manner^[3]. *In vitro*, URMC-099 treatment (100 nM) reduced inflammatory cytokine production by HIV-1 Tat-exposed microglia and prevented destruction and phagocytosis of cultured neuronal axons by these cells^[4].

In vivo, URMC-099 treatment in C57BL/6 mice (10 mg/kg, i.v.) reduced inflammatory cytokine production, protected neuronal architecture, and altered the morphologic and ultrastructural response of microglia to HIV-1 Tat exposure^[4]. *In vivo* efficacy test it shown that 10 mg/kg URMC-099 (i.p.) prophylaxis prevents the induction of VCAM-1 in the SLM of 6-month-old CVN-AD (APPSwDI/mNos2^{-/-} AD) mice following surgery^[5]. *In vivo*, prophylactic URMC-099 (10 mg/kg, i.p.) treatment in mice is sufficient to prevent surgery-induced microgliosis and cognitive impairment

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without affecting fracture healing^[6].

References:

- [1] Goodfellow VS, Loweth CJ, Ravula SB, Wiemann T, Nguyen T, Xu Y, Todd DE, Sheppard D, Pollack S, Polesskaya O, Marker DF, Dewhurst S, Gelbard HA. 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] Zhao HF, et al. Synergism between the phosphatidylinositol 3-kinase p110 β isoform inhibitor AZD6482 and the mixed lineage kinase 3 inhibitor URM-099 on the blockade of glioblastoma cell motility and focal adhesion formation. *Cancer Cell Int.* 2021 Jan 6;21(1):24.
- [3] Bellizzi MJ, et al. The Mixed-Lineage Kinase Inhibitor URM-099 Protects Hippocampal Synapses in Experimental Autoimmune Encephalomyelitis. *eNeuro.* 2018 Dec 3;5(6):ENEURO.0245-18.2018.
- [4] Marker DF, et al. The new small-molecule mixed-lineage kinase 3 inhibitor URM-099 is neuroprotective and anti-inflammatory in models of human immunodeficiency virus-associated neurocognitive disorders. *J Neurosci.* 2013 Jun 12;33(24):9998-10010.
- [5] Miller-Rhodes P, et al. URM-099 prophylaxis prevents hippocampal vascular vulnerability and synaptic damage in an orthopedic model of delirium superimposed on dementia. *FASEB J.* 2022 Jun;36(6):e22343.
- [6] Miller-Rhodes P, et al. The broad spectrum mixed-lineage kinase 3 inhibitor URM-099 prevents acute microgliosis and cognitive decline in a mouse model of perioperative neurocognitive disorders. *J Neuroinflammation.* 2019 Oct 28;16(1):193.

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