Lomeguatrib

Cat. No.: HY-13668

CAS No.: 192441-08-0

Molecular Formula: $C_{10}H_8BrN_5OS$

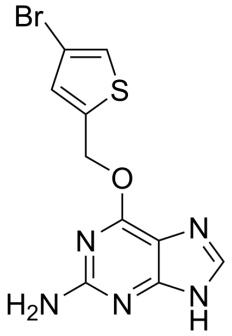
Molecular Weight: 326.17

Target: DNA Methyltransferase

Pathway: Epigenetics

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 56 mg/mL (171.69 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.0659 mL	15.3294 mL	30.6589 mL
5 mM	0.6132 mL	3.0659 mL	6.1318 mL
10 mM	0.3066 mL	1.5329 mL	3.0659 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 (6.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (6.38 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (6.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Lomeguatrib is a O^6-methylguanine-DNA methyltransferase (MGMT) inhibitor, with IC_{50}s of 9 nM in cell-free assay and ~6 nM in MCF-7 cells.

IC_{50} & Target

MGMT 6 nM (IC_{50}, in MCF-7 cells)	MGMT 9 nM (IC_{50})

In Vitro	Lomeguatrib (Compound 10) is a O^6-methylguanine methyltransferase (MGMT) inhibitor, with an IC_{50} of 9 nM in cell-free assay[1] and -6 nM in MCF-7 cells. Lomeguatrib (10 μM) substantially increases the growth inhibitory effects of temozolomide in MCF-7 cells (D_{60}=10 μM with Lomeguatrib vs 400 μM without)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Lomeguatrib (20 mg/kg i.p.) completely inactivates MGMT within 2 h, but shows no significant effect on tumor growth in MCF-7 xenografts[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Briefly, 200 μg of extracted cellular protein from HeLaS3 cells in 200 μL of 70 mM HEPES buffer (with 1 mM dithiothreitol (DTT), 5 mM EDTA, pH 7.8) is incubated at 37°C with a defined concentration of Lomeguatrib (added as a DMSO solution). After 30 min an excess of [^{3}H]-methylated DNA (120 000 cpm) is added, and the incubation is continued for an additional 90 min. The reaction is stopped by the addition of 400 μL TCA (13%), and the DNA is hydrolyzed by heating the reaction mixture for 30 min at 98°C. The precipitated protein is washed three times with 400-μL portions of 5% TCA, solubilized in 0.1 N NaOH, and analyzed by liquid scintillation counting using the cocktail Rotiszint eco plus and a TRI-CARB. Enzyme activity is expressed as fmol of [^{3}H]methyl transferred to TCA-insoluble protein material per mg of total cellular protein. Percent inhibition is calculated relative to untreated control samples. Each assay is repeated three times, and IC_{50} values are determined graphically from plots of percent inhibition vs inhibitor concentration[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	To determine toxicity, the MTT growth inhibition assay is employed. Cells (1000 per well) are plated into a 96-well plate and following a 24 h attachment period, Lomeguatrib is added to the cells. After 2 h incubation with Lomeguatrib (10 μM) at 37°C, 5% CO_2, increasing doses of temozolomide or vehicle are added and the cells are incubated for a further 4-5 days. At the end of the exposure period, 150 μg MTT is added to each well and plates are incubated for 3 h at 37°C, 5% CO_2. The media are removed and the formazan crystals formed in the viable cells are solubilised in 200 μL DMSO. The absorbances at 540 and 690 nm are determined using a ELISA plate reader and growth inhibition calculated as a percentage of the A540-A690 of untreated wells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] To assess the ability of Lomeguatrib to sensitise human breast tumour xenografts to the tumour growth inhibitory effects of temozolomide, groups of at least six nude mice are treated as follows: the vehicle control group are given corn oil then 20% DMSO in PBS; the temozolomide only group are given corn oil then temozolomide (100 mg/kg/day); the Lomeguatrib only group are given Lomeguatrib (20 mg/kg/day) then DMSO in PBS, and the Lomeguatrib plus temozolomide group are given Lomeguatrib (20 mg/kg/day) then temozolomide (100 mg/kg/day). Drugs or vehicles are administered i.p. once daily for 5 days with a separation of 1 h. Up to 10 and at least six animals are assigned to each group, and mean tumour volume is standardised across the groups at the start of the experiment: thus the control, Lomeguatrib, temozolomide and Lomeguatrib plus temozolomide groups had mean tumour volumes of 29.8±7.6 (range 19.0-38.7), 33.2±14.7 (range 16.5-58.7), 35.1±10.9 (range 20.9-52.4) and 30.3±10.0 (range 20.7-44.5) mm^3, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.
- Oncogene. 2021 Apr;40(15):2711-2724.
- CNS Neurosci Ther. 2021 Jan 18.

- Molecules. 2022, 27(19), 6219.
- Preprints. 2021, 2021060097.

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REFERENCES

[1]. Reinhard J, et al. Monosaccharide-linked inhibitors of O(6)-methylguanine-DNA methyltransferase (MGMT): synthesis, molecular modeling, and structure-activity relationships. J Med Chem. 2001 Nov 22;44(24):4050-61.

[2]. Clemons M, et al. O6-(4-bromothenyl)guanine reverses temozolomide resistance in human breast tumour MCF-7 cells and xenografts. Br J Cancer. 2005 Nov 14;93(10):1152-6.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

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