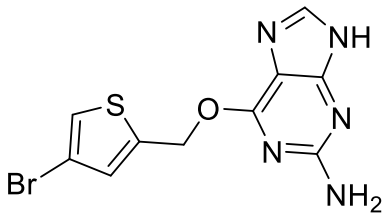
Product data sheet

MedKoo Cat#: 201750 Name: Lomeguatrib CAS#: 192441-08-0 Chemical Formula: $C_{10}H_8BrN_5OS$ Exact Mass: 324.96329 Molecular Weight: 326.17	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Lomeguatrib, also known as PaTrin-2, is a potent Inhibitor of O6-Alkylguanine-DNA-Alkyltransferase. Lomeguatrib is also a nontoxic low-molecular weight pseudosubstrate that has the ability to inactivate MGMT. Lomeguatrib can be used with temozolomide (TMZ) for GBM treatment.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	51.21	156.99

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.07 mL	15.33 mL	30.66 mL
5 mM	0.61 mL	3.07 mL	6.13 mL
10 mM	0.31 mL	1.53 mL	3.07 mL
50 mM	0.06 mL	0.31 mL	0.61 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Clemons M, Kelly J, Watson AJ, Howell A, McElhinney RS, McMurry TB, Margison GP. 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. doi: 10.1038/sj.bjc.6602833. PMID: 16278661; PMCID: PMC2361498.
2. Wu X, Luo Q, Zhao P, Chang W, Wang Y, Shu T, Ding F, Li B, Liu Z. MGMT-activated DUB3 stabilizes MCL1 and drives chemoresistance in ovarian cancer. Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966. doi: 10.1073/pnas.1814742116. Epub 2019 Feb 4. PMID: 30718431; PMCID: PMC6386650.

In vivo study

1. Clemons M, Kelly J, Watson AJ, Howell A, McElhinney RS, McMurry TB, Margison GP. 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. doi: 10.1038/sj.bjc.6602833. PMID: 16278661; PMCID: PMC2361498.

7. Bioactivity
Biological target:

Lomeguatrib is a O6-methylguanine-DNA methyltransferase (MGMT) inhibitor, with IC50s of 9 nM in cell-free assay and ~6 nM in MCF-7 cells.

Product data sheet

In vitro activity

To determine whether targeting DUB3 could be an alternative choice for indirectly mitigating MCL1 activity, several SMIs were screened and expression level of DUB3 was detected. Both the results from qRT-PCR screening and further immunoblotting validation revealed that PaTrin-2 was the most effective SMI in repressing DUB3 expression (SI Appendix, Fig. S6 A and B). PaTrin-2 treatment reduced the mRNA and protein levels of DUB3 in a dose-dependent manner, whereas only the protein expression level of MCL1 was decreased in response to treatment (Fig. 4A and SI Appendix, Fig. S6 C and D). PaTrin-2 is a potent and minimally toxic MGMT inhibitor that acts as a pseudosubstrate of MGMT. To verify that the PaTrin-2-induced suppression of DUB3 was mediated by the inhibition of MGMT, MGMT was knocked down in OVCAR3 and OVCA433 cells and found that the MGMT depletion significantly reduced the protein levels of both DUB3 and MCL1, but only the mRNA expression of DUB3 (Fig. 4B and SI Appendix, Fig. S6 E and F). The ubiquitin assay showed that MCL1 ubiquitination was increased after the PaTrin-2 treatment (SI Appendix, Fig. S6G), further confirming that PaTrin-2 promotes the ubiquitination and degradation of MCL1 by suppressing DUB3 transcription. To investigate the potential therapeutic effect of PaTrin-2 on chemoresistance in ovarian cancer, administered PaTrin-2 was administered to OVCAR3 and OVCA433 cells expressing high levels of MGMT-DUB3-MCL1 and A2780 and ES-2 cells expressing low levels of MGMT-DUB3-MCL1. The PaTrin-2 treatment significantly inhibited proliferation of ovarian cancer cells expressing high levels of MGMT-DUB3-MCL1.

Reference: Proc Natl Acad Sci U S A. 2019 Feb 19; 116(8): 2961–2966. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6386650/

In vivo activity

It was considered worthwhile to examine the extent to which PaTrin-2 could inactivate MGMT and increase sensitivity to temozolomide in a human breast tumour model as a prerequisite for any potential clinical trial in breast cancer. The results show that PaTrin-2 is also a potent inactivator of MGMT in MCF-7 cells both in culture and in xenografts in vivo. Tumour MGMT depletion by PaTrin-2 was as extensive as was reported with O6-BeG in other tumour types (see Dolan and Pegg, 1997). It also showed that MGMT was inactivated in all host tissues with complete inactivation in kidney and extensive inactivation in other tissues. This collateral depletion again raises the concern about the potentiation of toxicity in healthy tissues following PaTrin-2/alkylating agent combinations. The MGMT inactivation by PaTrin-2 in MCF-7 cells resulted in marked sensitisation to temozolomide growth inhibition. Following implantation into immune deficient mice, PaTrin-2 alone had, as anticipated, no effect on tumour growth rates. However, PaTrin-2 overcame the resistance to temozolomide producing highly significant tumour growth delays, but without increasing toxicity as judged by animal weights. Thus, the therapeutic index of temozolomide is increased by PaTrin-2 in this animal model. Given the results of the xenograft studies with melanoma, and now breast cancer, it seems reasonable to speculate that the greatest benefit from PaTrin-2-mediated inactivation of MGMT might be seen in tumours with the highest levels of MGMT expression and inherent resistance to temozolomide.

Reference: Br J Cancer. 2005 Nov 14; 93(10): 1152–1156. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2361498/