Product Data Sheet

Product Name: MRTX-1719
Cat. No.: GC63558

Chemical Properties

Cas. No.	2630904-45-7		
Formula	$C_{23}H_{18}ClFN_6O_2$	M.Wt	464.88
Solubility		Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	MRTX-1719		

Protocol

Cell experiment [1]:

Cell lines	Isogenic MTAP-del and WT HCT116 (colorectal cancer)

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Preparation Method	MTAP-del and WT HCT116 cells were seeded into 96-well, clear round-bottom plates 250 cells per well and cultured for 24h. MRTX-1719 was serially diluted (1:3) in DMSO. A 10× dosing plate was prepared from the DMSO serial dilutions using an intermediate dilution (1:100) into complete growth media. Cells were dosed with 10µL of the 10× intermediate drug dilutions added to the 96-well cell plates. After drug treatment for 5 days, cells were rinsed with PBS, trypsinized, and split 1:20 into a new 96-well plate containing fresh media and 1× drug with a final volume of 100µL per well. After 5 additional days of treatment, cell plates were equilibrated to room temperature, 30µL of luminescent reagent was added to each well, and incubated at room temperature for 30 minutes on a microtiter plate shaker and day-10 luminescence readings were collected using a microplate reader. Percent inhibition values were calculated by dividing relative luminescence unit (RLU) values from each treated well by the average RLU values in the vehicle-treated wells and multiplying by 100.
Reaction Conditions	0-10µM, serially diluted 1:4; 10 days
Applications	MRTX-1719 significantly reduced cell viability in MTAP-deleted cells in a time- and dose-dependent manner.

Animal experiment [1]:

Animal models	Hsd:Athymic Nude-Foxn1nu mice

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Preparation Method	6- to 8-week-old female Hsd:Athymic Nude-Foxn1nu mice were injected subcutaneously with tumor cells in 100μL of PBS and Matrigel matrix in the right hind flank of each mouse with 5e6 cells (LU99) or 1e6 cells (HCT116 parental and HCT116 MTAP del) 50:50 cells:Matrigel. When tumors reached the desired average study start tumor volume (LU99: 179mm^3 or 116mm^3; HCT116 MTAP WT:140mm^3; HCT116 MTAP del: 185mm^3), mice were randomized into treatment groups. MRTX-1719 was formulated in 0.5% methylcellulose (4,000cps) + 0.2% Tween-80 in water once per week and stored at room temperature protected from light. Mice were orally administered vehicle, MRTX-1719 at indicated doses and schedules. Mice were monitored daily, with tumor volumes and bodyweights measured 2 or 3 times per week.
Dosage form	50 or 100mg/kg/day for 22 days; orally administration.
Applications	In isogenic HCT116 xenograft models, MRTX-1719 selectively inhibited tumor growth and SDMA modification in MTAP-del tumors, with minimal effect on WT tumors at the same doses.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

References:
[1] Engstrom, Lars D., et al. "MRTX1719 is an MTA-cooperative PRMT5 inhibitor that exhibits synthetic lethality in preclinical models and patients with MTAP-deleted cancer." Cancer discovery 13.11 (2023): 2412-2431.

Background

MRTX-1719 is a potent, selective inhibitor of the PRMT5, with an average IC_{50} 20.4nM without MTA and 3.6nM with MTA present. PRMT5 (protein arginine methyltransferase 5) is an enzyme that catalyzes symmetric demethylation of arginine residues on target proteins, regulating essential cellular functions such as RNA splicing, transcription, and translation. MTAP (methylthioadenosine phosphorylase) loss was commonly found in cancer, which can lead to MTA accumulation. Elevated MTA (5'-deoxy-5'-methylthioadenosine) acts as a competitive inhibitor of PRMT5, partially inhibiting its activity. In cancer, PRMT5 is particularly important because its activity becomes a synthetic lethal vulnerability in tumors with MTAP deletion, making it a promising therapeutic target[1]. MRTX-1719 selectively binds to the PRMT5-MTA complex, retaining

Product Data Sheet

PRMT5 in a catalytically inactive state, further inhibiting its methyltransferase activity and exploiting the synthetic lethal vulnerability of MTAP-deleted tumors. MRTX-1719 is a potent, orally bioavailable small-molecule inhibitor with K_D of 0.14pM for the MTA/PRMT5 complex and 9.4pM for SAM-bound PRMT5, high selectivity for the PRMT5-MTA complex, long dissociation half-life (~14 days), and demonstrates strong selectivity and antitumor activity in MTAP-deleted cancer models[2].

In vitro, treatment of isogenic MTAP-del and WT HCT116 cells with MRTX-1719 (0-10μM) for 4 days significantly inhibited PRMT5-dependent SDMA levels with IC_{50} values of 8nM for MTA-del cells and 653nM for WT cells. Treatment of isogenic MTAP-del and WT HCT116 cells with MRTX-1719(0-10μM) for 10 days significantly reduced cell viability with IC_{50} values of 12nM for MTA-del cells and 890nM for WT cells. Overall selectivity of MRTX-1719 reach to 82-fold in SDMA assay and 74 -fold in viability assay. Treatment of isogenic MTAP-del and WT PK-1 cells with MRTX-1719 (0-10μM) for 10 days significantly reduced cell viability with IC_{50} values of 7.1nM for MTA-del cells and 818nM for WT cells[3].

In human tumor xenograft animal models, oral administration of MRTX-1719 (50 or 100mg/kg/day) for 22 days remarkably reduce the growth of colorectal cancer cells in mice bearing HCT116 cell xenografts showed specificity to MTAP-del tumor xenografts. In patient-derived xenograft (PDX) animal models, oral administration of MRTX-1719 (100mg/kg/day) for 60 days significantly reduce the growth of colorectal cancer cells in mice with 99% TGI (Tumor Growth Inhibition value) at 50 days[3]. Oral administration of MRTX-1719 (30mg/kg/day) for 7 days can efficiently decreased SDMA levels in mice and inhibit PRMT5 function in MTAP-loss tumors. Combination therapy of MRTX-1719 and anti-PD-1 antibody significantly reduced tumor volume and enhancing tumor sensitivity to immune attacks [4].

References:
[1] Mavrakis, Konstantinos J., et al. "Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5." Science 351.6278 (2016): 1208-1213.
[2] Smith, Christopher R., et al. "Fragment-based discovery of MRTX1719, a synthetic lethal inhibitor of the PRMT5• MTA complex for the treatment of MTAP-deleted cancers." Journal of Medicinal Chemistry 65.3 (2022): 1749-1766.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

[3] Engstrom, Lars D., et al. "MRTX1719 is an MTA-cooperative PRMT5 inhibitor that exhibits synthetic lethality in preclinical models and patients with MTAP-deleted cancer." Cancer discovery 13.11 (2023): 2412-2431.
[4] Chen, Si, et al. "MTA-cooperative PRMT5 inhibitors enhance T cell-mediated antitumor activity in MTAP-loss tumors." Journal for immunotherapy of cancer 12.9 (2024): e009600.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA