Product Data Sheet

Product Name: MRT68921
Cat. No.: GC14086

Chemical Properties

Cas. No.	1190379-70-4		
SMILES	O=C(C1CCC1)NCCCNC2=NC(NC3=CC4=C(CN(C)CC4)C=C3)=NC=C2C5CC5.[xHCl]		
Formula	$C_{25}H_{34}N_6O \cdot xHCl$	M.Wt	434.58
Solubility	≥ 2.2mg/mL in DMSO with ultrasonic and warming	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	MRT68921		

Protocol

Cell experiment [1]:

Cell lines	HeLa cells
Preparation Method	HeLa cells were cultured in DMEM medium supplemented with 10% fetal bovine serum (FBS), 2mM GlutaMAX, and 1% penicillin-streptomycin at 37℃ in the presence of 5% CO_2. Cells were seeded at 1×10^3 cells/well in a 96-well flat-bottomed plate for 24h, treated with varying concentrations of MRT68921 (0, 1, 5, 10, 20, 50, and 100μM) and incubated for an additional 24h, then analyzed the cell viability.
Reaction Conditions	0, 1, 5, 10, 20, 50, and 100μM; 24h

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Applications	MRT68921 treatment significantly reduced the cell viability of HeLa cells in a dose-dependent manner.

Animal experiment [2]:

Animal models	BALB/c mice
Preparation Method	BALB/c mice (5-week-old) were at constant room temperature with a 12h light/12h dark cycle and fed a standard rodent diet and water. 4T1 cells were harvested and injected intravenously (2×10^5 cells in 100μl of PBS) into BALB/c mice. The treatment started on the third day after injection. All mice were randomly and blindly divided into different groups. The mice were intravenously injected with DMSO or MRT68921 (20mg/kg) every day until the seventh treatment. The Kaplan-Meier method was used to measure overall survival. Lung tissues were excised, fixed, and stained by H&E for the counting of metastatic nodes.
Dosage form	20mg/kg/day for 7 days; i.v.
Applications	MRT68921 treatment inhibited the metastasis of cancer cells in the 4T1 murine breast cancer model, decreased metastatic nodules in the lungs, and improved the survival rate of the mice.

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References:
[1] Ji X, Zhang X, Li Z. ULK1 inhibitor induces spindle microtubule disorganization and inhibits phosphorylation of Ser10 of histone H3[J]. FEBS open bio, 2020, 10(11): 2452-2463.
[2] Chen Y, Xie X, Wang C, et al. Dual targeting of NUAK1 and ULK1 using the multitargeted inhibitor MRT68921 exerts potent antitumor activities[J]. Cell death & disease, 2020, 11(8): 712.

Background

MRT68921 is a potent dual inhibitor of ULK1 and ULK2 with IC_{50} values of 2.9nM and 1.1nM, respectively [1]. MRT68921 can induce the lipidation of LC3-II, the formation of GFP/LC3 aggregates, leading to an increase in the phosphorylation level of AMPKα (T712) and promoting cellular apoptosis [2]. MRT68921 has been widely used to inhibit the growth of cancer cells and to develop new combined therapies for the elimination of tumor cells[3].

In vitro, MRT68921 treatment for 20 hours significantly inhibited the viability of THP-1

cells and HL60, with the IC_{50} values being 3.6μM and 2.6μM, respectively[4]. Treatment with 10μM MRT68921 for 12 hours can induce spindle microtubule disarray and abnormal mitosis in HeLa cells[5]. Treatment with 2μM MRT68921 for 24 hours inhibited autophagy in serum-starved $p53^{-/-}$ mouse embryonic stem cells (mESCs) and increased caspase activity[6].

In vivo, MRT68921 treatment via intravenous injection at a dose of 20mg/kg/day for 7 consecutive days significantly inhibited the metastasis of cancer cells in the 4T1 murine breast cancer model, reduced tumor burden, and improved the survival rate of the mice[7]. Intraperitoneal injection of MRT68921 twice a week at a dose of 20mg/kg, in combination with SAR405 (20mg/kg; i.p.) and paclitaxel (5mg/kg; i.p.) for 21 days, significantly inhibited tumor growth in the MDA-MB231 xenograft mouse model [8].

References:
[1] Petherick K J, Conway O J L, Mpamhanga C, et al. Pharmacological inhibition of ULK1 kinase blocks mammalian target of rapamycin (mTOR)-dependent autophagy[J]. Journal of Biological Chemistry, 2015, 290(18): 11376-11383.
[2] Jang J, Jeung H, Seol S Y, et al. Inhibition of Unc-51-like Kinase 1 (ULK1) with novel small molecular inhibitor MRT68921 preferentially induces apoptosis and autophagy in FLT3-ITD-mutated acute myeloid leukemia[J]. Blood, 2018, 132: 3499.
[3] Xu Z, Bao J, Jin X, et al. The effects of cinobufagin on hepatocellular carcinoma cells enhanced by MRT68921, an autophagy inhibitor[J]. The American Journal of Chinese Medicine, 2023, 51(06): 1595-1611.
[4] Yang W, Li Y, Liu S, et al. Inhibition of ULK1 promotes the death of leukemia cell in an autophagy irrelevant manner and exerts the antileukemia effect[J]. Clinical and Translational Medicine, 2021, 11(1): e282.
[5] Ji X, Zhang X, Li Z. ULK1 inhibitor induces spindle microtubule disorganization and inhibits phosphorylation of Ser10 of histone H3[J]. FEBS open bio, 2020, 10(11): 2452-2463.
[6] Vorobev M L, Alhasan B A, Suvorova I I. The upregulation of Ulk1-dependent autophagy does not require the p53 activity in mouse embryonic stem cells[J]. Biochemical and biophysical research communications, 2021, 552: 78-83.
[7] Chen Y, Xie X, Wang C, et al. Dual targeting of NUAK1 and ULK1 using the multitargeted inhibitor MRT68921 exerts potent antitumor activities[J]. Cell death &

disease, 2020, 11(8): 712.
[8] Abd El-Aziz Y S, du Toit-Thompson T, McKay M J, et al. Novel combinatorial autophagy inhibition therapy for triple negative breast cancers[J]. European Journal of Pharmacology, 2024, 973: 176568.

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