

Product Data Sheet

Product Name: ML216
Cat. No.: GC12786

Chemical Properties

Cas. No. 1430213-30-1

Chemical Name 1-(4-fluoro-3-(trifluoromethyl)phenyl)-3-(5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl)urea

SMILES FC(C(C(F)(F)F)=C1)=CC=C1NC(NC2=NN=C(C3=CC=NC=C3)S2)=O

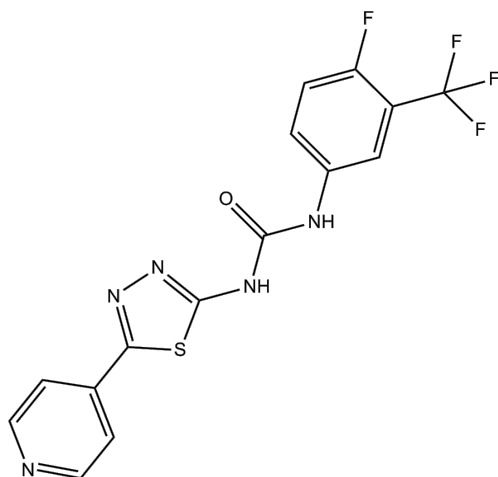
Formula $C_{15}H_9F_4N_5OS$ M.Wt 383.32

Solubility 25mg/ml in DMSO with gentle warming Storage Desiccate 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]:

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Cell lines	Bloom syndrome protein (BLM)-complemented PSNF5 and BLM-deficient PSNG13 human fibroblasts
Preparation Method	PSNF5 and PSNG13 human fibroblasts were cultured with different ML216 concentrations, and cell proliferation was quantified at each time point. In a separate arm, cells were labeled with bromodeoxyuridine, exposed to ML216, and prepared as metaphase chromosome spreads for microscopic quantification of sister chromatid exchange frequency.
Reaction Conditions	12.5μM and 50μM; 24h, 48h, and 72h
Applications	ML216 concentration- and time-dependently reduced proliferation in BLM-complemented PSNF5 cells, exerted minimal effects on BLM-deficient PSNG13 cells, and increased sister chromatid exchange frequency in PSNF5 cells.
Animal experiment [2]:	
Animal models	PC3 prostate cancer xenograft model in male BALB/c nude mice
Preparation Method	PC3 cells were implanted subcutaneously into male BALB/c nude mice to establish xenografts. Mice were randomized to ML216, olaparib, the combination, or vehicle control. Tumor volume was measured every 4 days, and tumor weight and Ki-67 expression were assessed at the study endpoint.
Dosage form	15mg/kg; intraperitoneal injection three times weekly for 3 weeks
Applications	ML216 combined with olaparib reduced PC3 xenograft tumor volume, tumor weight, and Ki-67 expression and inhibited tumor growth more strongly than either monotherapy.

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References: [1] Nguyen GH, Dexheimer TS, Rosenthal AS, Chu WK, Singh DK, Mosedale G, et al. A small molecule inhibitor of the BLM helicase modulates chromosome stability in human cells. Chem Biol. 2013;20(1):55-62. doi:10.1016/j.chembiol.2012.10.016.[2] Huang M, Chen L, Guo Y, Ruan Y, Xu H. PARP1 negatively regulates transcription of BLM through its interaction with HSP90AB1 in prostate cancer. J Transl Med. 2023;21(1):445. doi:10.1186/s12967-023-04288-z.

Background

ML216 is a potent, selective, and cell-permeable inhibitor of Bloom syndrome protein (BLM) helicase with IC₅₀ values of 2.98μM for full-length BLM and 0.97μM for BLM636-1298^[1]. ML216 competitively interferes with BLM binding to deoxyribonucleic acid (DNA), inhibits BLM-dependent DNA unwinding and single-stranded DNA (ssDNA)-dependent adenosine triphosphatase (ATPase) activity, and perturbs homologous recombination (HR) repair and chromosome stability^[1,2]. ML216 is used in research on DNA-damage repair, replication stress, chromosome stability, cellular senescence, tumor-cell sensitization to DNA-damaging agents, and xenograft responses^[1,3,4,5,6,7].

In vitro, ML216 (12.5μM and 50μM; 24h, 48h, and 72h) concentration- and time-dependently reduced the proliferation of BLM-complemented PSNF5 fibroblasts while exerting minimal effects on BLM-deficient PSNG13 fibroblasts^[1]. ML216 (50μM; 36h) increased sister chromatid exchange (SCE) frequency in PSNF5 cells without significantly changing SCE frequency in PSNG13 cells^[2]. ML216 (10μM) combined with cisplatin (CDDP; 1μM; 48h) reduced PC3 prostate cancer cell proliferation, increased phosphorylated histone H2AX (γH2AX) foci and cleaved caspase-3, activated checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2), and increased apoptosis^[3]. ML216 (10μM; 24h) with 8Gy irradiation reduced RAD51 recombinase (RAD51) foci, increased phosphorylated DNA-dependent protein kinase catalytic subunit (pDNA-PKcs), and delayed DNA double-strand break (DSB) repair in H460, H1299, and A549 non-small cell lung cancer (NSCLC) cells^[4]. ML216 (0.78125μM, 1.5625μM, 3.125μM, 6.25μM, 12.5μM, and 25μM) combined with melphalan (0.78125μM, 1.5625μM, 3.125μM, 6.25μM, 12.5μM, 25μM, and 50μM; 4 days) reduced proliferation and increased apoptosis and DNA damage in XG19, XG2, and XG1 multiple myeloma cells^[5]. ML216 (50μM) combined with etoposide (100μM; 24h) strengthened deleted in breast cancer 1 (DBC1)-BLM interaction, preserved cellular BLM, and reduced p21 induction in HEK293T cells^[6]. ML216 (5μM) combined with olaparib (40μM; 48h) reduced PC3 cell viability, proliferation, clonogenic

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growth, migration, and invasion^[7].

In vivo, ML216 (1mg/kg; intraperitoneal injection twice weekly for 5 weeks) reduced pulmonary senescence and fibrosis and improved pulmonary function in 22-month-old mice^[6]. ML216 (15mg/kg) combined with olaparib (30mg/kg; intraperitoneal injection three times weekly for 3 weeks) reduced tumor volume, tumor weight, and Ki-67 expression in male BALB/c nude mice bearing PC3 xenografts^[7].

References:

- [1] Nguyen GH, Dexheimer TS, Rosenthal AS, Chu WK, Singh DK, Mosedale G, et al. A small molecule inhibitor of the BLM helicase modulates chromosome stability in human cells. *Chem Biol.* 2013;20(1):55-62. doi:10.1016/j.chembiol.2012.10.016.
- [2] Rosenthal AS, Dexheimer TS, Gileadi O, Nguyen GH, Chu WK, Hickson ID, et al. Synthesis and SAR studies of 5-(pyridin-4-yl)-1,3,4-thiadiazol-2-amine derivatives as potent inhibitors of Bloom helicase. *Bioorg Med Chem Lett.* 2013;23(20):5660-5666. doi:10.1016/j.bmcl.2013.08.025.
- [3] Ma XY, Zhao JF, Ruan Y, Zhang WM, Xu HQ. ML216-induced BLM helicase inhibition sensitizes PCa cells to the DNA-crosslinking agent cisplatin. *Molecules.* 2022;27(24):8790. doi:10.3390/molecules27248790.
- [4] Kong Y, Xu C, Sun X, Sun H, Zhao X, He N, et al. BLM helicase inhibition synergizes with PARP inhibition to improve the radiosensitivity of olaparib-resistant non-small cell lung cancer cells by inhibiting homologous recombination repair. *Cancer Biol Med.* 2022;19(8):1150-1171. doi:10.20892/j.issn.2095-3941.2021.0178.
- [5] Ovejero S, Viziteu E, Dutrieux L, Devin J, Lin YL, Alaterre E, et al. The BLM helicase is a new therapeutic target in multiple myeloma involved in replication stress survival and drug resistance. *Front Immunol.* 2022;13:983181. doi:10.3389/fimmu.2022.983181.
- [6] Cui F, Han X, Zhang X, Wang S, Liang N, Tan Q, et al. ML216 prevents DNA damage-induced senescence by modulating DBC1-BLM interaction. *Cells.* 2023;12(1):145. doi:10.3390/cells12010145.
- [7] Huang M, Chen L, Guo Y, Ruan Y, Xu H. PARP1 negatively regulates transcription of BLM through its interaction with HSP90AB1 in prostate cancer. *J Transl Med.* 2023;21(1):445. doi:10.1186/s12967-023-04288-z.

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