

Product Data Sheet

Product Name: DDD85646

Cat. No.: GC43386

Chemical Properties

Cas. No. 1215010-55-1

Chemical Name 2,6-dichloro-4-[2-(1-piperazinyl)-4-pyridinyl]-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-benzene sulfonamide

SMILES ClC1=CC(C2=CC=NC(N3CCNCC3)=C2)=CC(Cl)=C1S(=O)(=O)NC4=C(C)N(C)N=C4C

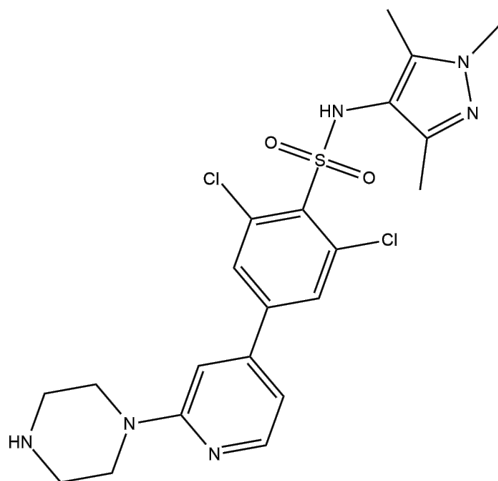
Formula $C_{21}H_{24}Cl_2N_6O_2S$ M.Wt 495.4

Solubility 25mg/ml in DMSO & DMF Storage Store 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]:

Cell lines THP-1 cells (human acute monocytic leukemia cell line)

Caution: Product has not been fully validated for medical applications. For research use only.

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Preparation Method	THP-1 cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 2mM L-glutamine, and 1% penicillin-streptomycin at 37°C, 5% CO ₂ . Cells were treated with the ferroptosis inducer Erastin (10μM) and/or DDD85646 (10μM) for 36 hours.
Reaction Conditions	10μM; 36h
Applications	Co-treatment with DDD85646 and Erastin significantly increased susceptibility to ferroptosis in THP-1 cells, characterized by elevated lipid peroxidation (increased MDA and 4-HNE levels), glutathione (GSH) depletion, and mitochondrial shrinkage observed via electron microscopy.

Animal experiment [2]:

Animal models	Female NMRI mice infected with <i>Trypanosoma brucei brucei</i> S427
Preparation Method	Mice were infected intraperitoneally with trypomastigotes. For the model (<i>T. b. brucei</i> S427), infected mice were treated orally (by gavage) with DDD85646 at a dose of 12.5mg/kg or 50mg/kg twice daily for 4 days.
Dosage form	12.5-50mg/kg; p.o.; twice daily for 4 days.
Applications	DDD85646 demonstrated potent efficacy in the mouse model, achieving complete cure at 12.5mg/kg for 4 days against <i>T. b. brucei</i> S427 and at 50mg/kg for 4 days against <i>T. b. rhodesiense</i> STIB900.

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References:

- [1] Tan X, He Y, Yu P, et al. The dual role of FSP1 in programmed cell death: resisting ferroptosis in the cell membrane and promoting necroptosis in the nucleus of THP-1 cells. *Mol Med*. 2024 Jul 15;30(1):102.
- [2] Brand S, Norcross NR, Thompson S, et al. Lead optimization of a pyrazole sulfonamide series of *Trypanosoma brucei* N-myristoyltransferase inhibitors: identification and evaluation of CNS penetrant compounds as potential treatments for stage 2 human African trypanosomiasis. *J Med Chem*. 2014 Dec 11;57(23):9855-69.

Background

DDD85646 is a potent inhibitor of *Trypanosoma brucei* N-myristoyltransferase (NMT), exhibiting half-maximal inhibitory concentration (IC₅₀) values of 2nM against *T. brucei* NMT (TbNMT) and 4nM against human NMT (hNMT)^[1]. DDD85646 effectively inhibits the proliferation of trypanosomes^[2], and also demonstrates antiviral activity by suppressing viral replication^[3-4].

In vitro, co-treatment of acute monocytic leukemia THP-1 cells with DDD85646 (10μM) and the ferroptosis inducer Erastin (10μM) for 36 hours enhanced susceptibility to ferroptosis—characterized by lipid peroxidation, glutathione depletion, and mitochondrial shrinkage—via inhibition of FSP1 localization to the cell membrane^[5]. Pretreatment of A549, HEK293T, HAP1, and Vero E6 cells with DDD85646 (0.1–10μM) for 1–5 hours, followed by infection with *lymphocytic choriomeningitis virus* (LCMV; MOI=0.05–1) for 24–72 hours, significantly suppressed viral protein expression, reduced viral titers, and decreased the number of infected cells^[6].

In vivo, oral administration of DDD85646 (12.5–50mg/kg) twice daily for 4 days to mice infected with *Trypanosoma brucei* strains S427 or STIB900 resulted in significant clearance of parasites from peripheral blood^[7]. Subcutaneous injection of DDD85646 (20–60mg/kg) once daily or every other day for 7–16 days in mice bearing DOHH2 or BL2 lymphoma xenografts led to significant suppression of tumor growth and induction of complete tumor regression^[8].

References:

- [1] Spinks D, Smith V, Thompson S, et al. Development of Small-Molecule *Trypanosoma brucei* N-Myristoyltransferase Inhibitors: Discovery and Optimisation of a Novel Binding Mode.

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ChemMedChem. 2015 Nov;10(11):1821-36.

[2] Begolo D, Erben E, Clayton C. Drug target identification using a trypanosome overexpression library. Antimicrob Agents Chemother. 2014 Oct;58(10):6260-4.

[3] Carnec X, Borges-Cardoso V, Reynard S, et al. Targeting n-myristoyltransferases promotes a pan-Mammarenavirus inhibition through the degradation of the Z matrix protein. PLoS Pathog. 2024 Dec 3;20(12):e1012715.

[4] Xiao P, Meng L, Cui X, et al. VP0 Myristoylation Is Essential for Senecavirus A Replication. Pathogens. 2024 Jul 21;13(7):601.

[5] Tan X, He Y, Yu P, et al. The dual role of FSP1 in programmed cell death: resisting ferroptosis in the cell membrane and promoting necroptosis in the nucleus of THP-1 cells. Mol Med. 2024 Jul 15;30(1):102.

[6] Witwit H, Betancourt CA, Cubitt B, et al. Cellular N-Myristoyl Transferases Are Required for Mammarenavirus Multiplication. Viruses. 2024 Aug 26;16(9):1362.

[7] Brand S, Norcross NR, Thompson S, et al. Lead optimization of a pyrazole sulfonamide series of Trypanosoma brucei N-myristoyltransferase inhibitors: identification and evaluation of CNS penetrant compounds as potential treatments for stage 2 human African trypanosomiasis. J Med Chem. 2014 Dec 11;57(23):9855-69.

[8] Beauchamp E, Yap MC, Iyer A, et al. Targeting N-myristoylation for therapy of B-cell lymphomas. Nat Commun. 2020 Oct 22;11(1):5348.

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