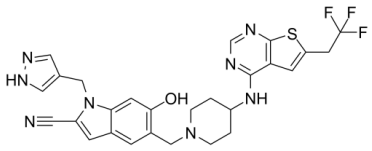
Data Sheet

Product Name:	MI-538
Cat. No.:	CS-6431
CAS No.:	1857417-10-7
Molecular Formula:	C27H25F3N8OS
Molecular Weight:	566.60
Target:	Epigenetic Reader Domain
Pathway:	Epigenetics
Solubility:	DMSO : 100 mg/mL (176.49 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

MI-538 is an inhibitor of the interaction between **menin** and **MLL** fusion proteins with an **IC_{50}** of 21 nM. IC50 & Target: IC50 : 21 nM (menin and MLL interaction); Kd: 6.5 nM (menin)[1] **In Vitro:** MI-538 inhibits the proliferation of MLL leukemia cells with a GI_{50} of 83 nM. MI-538 shows no effect (up to 6 μM) on growth of the control cell lines HL-60 and HM-2, which do not harbor MLL translocations, demonstrating good selectivity toward MLL fusion protein transformed cells. MI-538 binds to menin with low nanomolar affinity (K_d =6.5 nM). Its potent cellular activity originates from the improved binding affinity to menin and possibly increased cell membrane permeability. Treatment with MI-538 results in strong down regulation of expression of Hoxa9 and Meis1 genes. About 100 nM 27 was sufficient to reduce by ~50% Hoxa9 expression in MLL-AF9 cells, and even more pronounced effect was seen on Meis1 expression [1]. **In Vivo:** Treatment with MI-538 results in a pronounced, about 80%, reduction in the MV4;11 tumor volume, without causing substantial signs of toxicity reflected by less than 10% reduction of the body weight. MI-538 demonstrates markedly improved exposure (area under the curve, AUC, values), Cmax (maximum compound concentration) in the blood plasma, and the lowest value of clearance. The half-life of MI-538 is about 1.6 h. MI-538 has also high oral bioavailability (~50%)[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]MOLM-13, MV4;11, HL-60 human leukemia cells as well as MLL-AF9 and HM-2 murine bone marrow cells are treated with MI-538 or 0.25% DMSO for 7 days. Media are changed at day 4 with viable cell number restored to the original concentration, and MI-538 are resupplied. An amount of 100 μL of cell suspension is transferred to 96-well plates for each sample in quadruplicates. Cell viability is measured using the MTT assay. Plates are read for absorbance at 570 nm[1]. **Animal Administration:** MI-538 is dissolved in the vehicle containing 25% (v/v) DMSO, 25% (v/v) PEG-400, and 50% (v/v) PBS.[1]Mice: Mice xenograft are randomly grouped with each group containing eight mice. Vehicle or MI-538 (45 mg/kg) are administrated once daily at designated doses using ip injections for 2 weeks. Body weight and tumor sizes are monitored three times a week[1].

References:

[1]. Borkin D, et al. Property Focused Structure-Based Optimization of Small Molecule Inhibitors of the Protein-Protein Interaction between Menin and Mixed Lineage Leukemia (MLL). J Med Chem. 2016 Feb 11;59(3):892-913.

CAIndexNames:

1H-Indole-2-carbonitrile, 6-hydroxy-1-(1H-pyrazol-4-ylmethyl)-5-[[4-[[6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]amino]-1-piperidinyl]methyl]-

SMILES:

FC(F)(F)CC(S1)=CC2=C1N=CN=C2NC3CCN(CC4=C(O)C=C(N(CC5=CNN=C5)C(C#N)=C6)C6=C4)CC3

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

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