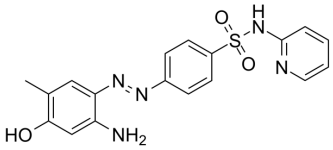
MS436

Cat. No.:	HY-13959
CAS No.:	1395084-25-9
Molecular Formula:	$C_{18}H_{17}N_5O_3S$
Molecular Weight:	383.42
Target:	Epigenetic Reader Domain
Pathway:	Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25.5 mg/mL (66.51 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6081 mL	13.0405 mL	26.0811 mL
	5 mM	0.5216 mL	2.6081 mL	5.2162 mL
	10 mM	0.2608 mL	1.3041 mL	2.6081 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (2.61 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (2.61 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MS436 is a new class of bromodomain inhibitor, exhibits potent affinity of an estimated K_i=30-50 nM for the BRD4 BrD1 and a 10-fold selectivity over the BrD2.

IC_{50} & Target

Ki: 30-50 nM (BRD4 bromodomain)[1]

In Vitro

MS436, through a set of water-mediated interactions, exhibits low nanomolar affinity (estimated K_i of 30-50 nM) with preference for the first bromodomain over the second. MS436 effectively inhibits BRD4 activity in NF-κB-directed production of NO and pro-inflammatory cytokine interleukin-6 in murine macrophages. MS436 represents a new class of bromodomain inhibitors and will facilitate further investigation of the biological functions of the two bromodomains of BRD4 in gene expression. MS436 exhibits potent affinity of an estimated K_i=30-50 nM for the BRD4 BrD1 and a 10-fold selectivity over the

BrD2, which is achieved through a unique set of water-mediated intermolecular interactions[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

Binding affinity of the newly synthesized diazobenzene compounds (e.g., MS436) for various bromodoamins is assessed in a fluorescence anisotropy competition assay using a fluorescein isothiocyanate (FITC)-labeled MS417 as an assay probe. Competition experiments are performed with a BrD protein (0.25-1 μM) and the fluorescent probe (80 nM), and increasing concentration of unlabeled competing ligand in a PBS buffer (pH 7.4) in total volume of 80 μL Measurements are obtained after a 1 hour incubation of the fluorescent ligand and the protein at 25°C with Safire 2 microplate reader. In a competition-binding assay, fluorescent ligand concentration is ≤2K_d, and protein concentration is set at which 50-80% of fluorescent ligand is bound. Dissociation constant of a competing ligand is calculated with the correction to Cheng-Prussoff equation introduced by Nicolovska-Coleska and colleagues. Assuming one-site competitive binding model, the equation used to calculate K_i's from IC_{50} values[1].

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Cell Assay [1]

Murine macrophage RAW264.7 cells are plated at a density of 1×10^4 cells per well in a 96-well plate and incubated at 37°C for 18 h. The cells are then treated with the diazobenzene bromodomain inhibitors (e.g., MS436) up to 100 μM for 24 hours. At the end of the 24 hr incubation, 10 μL of the MTT solution (4 mg/mL) is added to each well and incubated at 37°C for 4 h. The supernatants are then removed and the cells are solubilized in 100 μL of 100% DMSO. The diazobenzene compounds are first dissolved in DMSO then diluted with culture medium to concentrations that ranged from 0.28 to 50000 nM. The final concentration of DMSO is adjusted to 0.05% (v/v). The extent of the reduction is measured by the absorbance at 570/630 nm using EnVison 2104 Multilabel Reader[1].

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CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.

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REFERENCES

[1]. Zhang G, et al. Structure-Guided Design of Potent Diazobenzene Inhibitors for the BET Bromodomains. J Med Chem. 2013 Nov 27;56(22):9251-64.

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