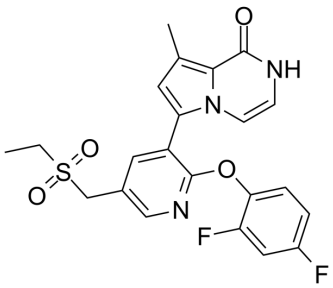
BET bromodomain inhibitor 1

Cat. No.:	HY-131061
CAS No.:	2411226-02-1
Molecular Formula:	$C_{22}H_{19}F_2N_3O_4S$
Molecular Weight:	459.47
Target:	Epigenetic Reader Domain
Pathway:	Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 62.5 mg/mL (136.03 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1764 mL	10.8821 mL	21.7642 mL
	5 mM	0.4353 mL	2.1764 mL	4.3528 mL
	10 mM	0.2176 mL	1.0882 mL	2.1764 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.44 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.53 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.53 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BET bromodomain inhibitor 1 is an orally active, selective bromodomain and extra-terminal (BET) bromodomain inhibitor with an IC_{50} of 2.6 nM for BRD4. BET bromodomain inhibitor 1 binds to BRD2(2), BRD3(2), BRD4(1), BRD4(2), and BRDT(2) with high affinities (K_d values of 1.3 nM, 1.0 nM, 3.0 nM, 1.6 nM, 2.1 nM, respectively). bromodomain inhibitor 1 has anti-cancer activity[1].

IC_{50} & Target				
	BRD4	BRD2(2)	BRD3(2)	BRD4(1)
	2.6 nM (IC_{50})	1.3 nM (Kd)	1.0 nM (Kd)	3.0 nM (Kd)

	BRD4(2) 1.6 nM (Kd)	BRDT(2) 2.1 nM (Kd)

In Vitro

BET bromodomain inhibitor 1 (compound 38; 31.25-125 nM; 24 hours) leads to more pronounced G1-phase cell cycle arrest [1].

BET bromodomain inhibitor 1 (31.25-500 nM; 6 or 24 hours) is highly effective in inducing dose-dependent inhibition on c-Myc expression and upregulation of p21 levels[1].

BET bromodomain inhibitor 1 (31.25-125 nM; 6 hours) robustly reduces the expressions of c-Myc, BCL-2, and CDK6[1].

BET bromodomain inhibitor 1 does not inhibit five cytochrome P450 enzymes (IC_{50}>20 μM)[1].

BET bromodomain inhibitor 1 demonstrates an excellent selectivity for the BET bromodomain family over other bromodomains, with an -1500-fold selectivity for BRD4(1) over EP300 (IC_{50}=3857 nM)[1].

BET bromodomain inhibitor 1 strongly inhibited the growth of acute myeloid leukemia cell line MV4-11, acute leukemia cell lines Kasumi-1 and RS-4-11, and multiple myeloma cancer cell line MM1.S cells with IC_{50} values of 2.4, 4.8, 17.6 and 15.1 nM, respectively[1].

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

Cell Cycle Analysis[1]

Cell Line:	MV-4-11 cells
Concentration:	31.25, 62.5, 125 nM
Incubation Time:	24 hours
Result:	Led to more pronounced G1-phase cell cycle arrest.

Western Blot Analysis[1]

Cell Line:	MV-4-11 cells
Concentration:	31.25, 62.5, 125, 250, 500 nM
Incubation Time:	6 or 24 hours
Result:	Induced dose-dependent inhibition on c-Myc expression and upregulation of p21 levels.

RT-PCR[1]

Cell Line:	MV-4-11 cells
Concentration:	31.25, 62.5, 125 nM
Incubation Time:	6 hours
Result:	Robustly reduced the expressions of c-Myc, BCL-2, and CDK6.

In Vivo

BET bromodomain inhibitor 1 (compound 38; 6.25, 12.5 mg/kg; PO; daily ; for 28 days) exhibits stronger antitumor activities and completely inhibits the growth of tumor with a tumor growth inhibition (TGI) of 99.7% at 12.5 mg/kg[1].

BET bromodomain inhibitor 1 (1 mg/kg; IV) has a $T_{1/2}$ of 1.3 and 0.9 hours, a CL of 21.5 and 15.3 mL/min•kg, and a V_{ss} of 1464 and 782 mL/kg for rats and mouse, respectively[1].

BET bromodomain inhibitor 1 (3 mg/kg; PO) has a $T_{1/2}$ of 3.6 hours, a C_{max} of 159 ng/mL and an AUC of 884 ng•h/mL for rats [1].

BET bromodomain inhibitor 1 (1.3 mg/kg; PO) has a $T_{1/2}$ of 1.3 hours, a C_{max} of 399 ng/mL and an AUC of 1710 ng•h/mL for mouse[1].

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

Animal Model:	An MV4-11 mouse xenograft model[1]
Dosage:	6.25, 12.5 mg/kg
Administration:	PO; daily ; for 28 days
Result:	Exhibited stronger antitumor activities and completely inhibited the growth of tumor with a tumor growth inhibition (TGI) of 99.7% at 12.5 mg/kg.

Animal Model:	Male SD rats[1]
Dosage:	1 mg/kg (Pharmacokinetic Analysis)
Administration:	IV
Result:	Had a $T_{1/2}$ of 1.3 hours, a CL of 21.5 mL/min•kg, and a V_{ss} of 1464 mL/kg.

REFERENCES

[1]. Zizhou Li, et al. Discovery of 8-Methyl-pyrrolo[1,2- a]pyrazin-1(2 H)-one Derivatives as Highly Potent and Selective Bromodomain and Extra-Terminal (BET) Bromodomain Inhibitors. J Med Chem. 2020 Apr 23;63(8):3956-3975.

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