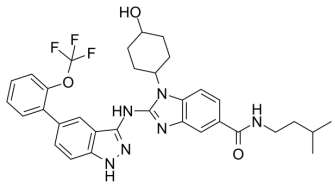
IRAK inhibitor 4

Cat. No.:	HY-13278
CAS No.:	1012104-68-5
Molecular Formula:	$C_{33}H_{35}F_3N_6O_3$
Molecular Weight:	620.66
Target:	IRAK
Pathway:	Immunology/Inflammation
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 : 12.5 mg/mL (20.14 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6112 mL	8.0559 mL	16.1119 mL
	5 mM	0.3222 mL	1.6112 mL	3.2224 mL
	10 mM	0.1611 mL	0.8056 mL	1.6112 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: ≥ 1.25 mg/mL (2.01 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.25 mg/mL (2.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

IRAK inhibitor 4 is an interleukin-1 receptor associated kinase 4(IRAK4) inhibitor.

In Vitro

Lack of IRAK-4 impairs the production of proinflammatory mediators by macrophages and DCs in response to M. bovis and M. tuberculosis. IRAK-4$^{-/-}$ cells stimulated with E. coli LPS display delayed activation kinetics of all signaling proteins analyzed, and exhibit dramatically reduced p65 phosphorylation[1]. IRAK1/4 (20 μM) has an inhibitory effect on LPS mediated IL-6 production. IRAK1/4 inhibitor do not decrease p38 phosphorylation in AMs. Combination of IRAK1/4 and Rip2 inhibitors inhibits TLR2-mediated cytokine production in sarcoidosis PBMCs and AMs[2]. IRAK4 is overexpressed and activated in T-ALL. IRAK4 mRNA level is elevated in T-ALL cells from patients compared with the levels detected in thymic T cells or T cells from peripheral blood[3].

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

In Vivo	IRAK-4$^{-/-}$ mice exhibit a greatly reduced survival rate following aerosol infection compared with IRAK-4$^{+/+}$ or IRAK-4$^{+/-}$ mice. IRAK-4$^{-/-}$ mice show increased bacterial burden in all organs at 15, 30, and 60 d postinfection[1]. MCL1, but not BCL-xL, overrides the therapeutic effects of combinatorial IRAK1/4 inhibitor and ABT-737 therapy in vivo[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	THP-1 cells are grown in RPMI 1640 medium supplemented with 2 mM L-glutamine, 10% heat-inactivated FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin. For monocytic differentiation, cells are seeded in 24-well flat-bottom culture plates at a density of 5×10^5 cells/well and allowed to adhere and differentiate for 48 h at 37°C in the presence of 100 nM PMA. THP-1 cells are incubated with 0.1 or 1 μM IRAK-4 inhibitor (IRAK inhibitor 1) for 45 min and then stimulated with M. bovis BCG Moreau (MOI 5:1) or E. coli LPS (1 μg/mL). Culture supernatants are collected after 24 h of stimulation and assayed for the concentrations of human TNF-α or IL-12/23p40 by ELISA. For Western blot analysis, cells are incubated with IRAK-4 inhibitor, in the same concentrations described above, for 45 min and then stimulated with M. bovis BCG Moreau (MOI 5:1) or E. coli LPS (1 μg/mL) for 30 min. The cells are then processed for Western blot assay, as described below. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	To evaluate IRAK-4 involvement in mycobacterial infection, IRAK-4$^{+/+}$ (wild-type), IRAK-4$^{+/-}$ (heterozygous), and IRAK-4$^{-/-}$ (IRAK-4-knockout) mice are used. Eight-week-old mice are infected i.v. with 1×10^6 CFU of M. bovis strain Moreau. The bacterial loads in the spleens, livers, and lungs are determined at 15, 30, and 60 d postinfection. Briefly, the organs are collected aseptically and homogenized in distilled water that contained 0.05% Tween 80. Serial dilutions of the resulting suspensions are plated on Middlebrook 7H11 agar medium supplemented with 10% oleic acid-albumin-dextrose-catalase, and CFU are counted following a 21-d incubation at 37°C and 5% CO_2. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Eur J Cell Biol. 2019 Jan;98(1):36-50.

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REFERENCES

[1]. Marinho FV, et al. Lack of IL-1 Receptor-Associated Kinase-4 Leads to Defective Th1 Cell Responses and Renders Mice Susceptible to Mycobacterial Infection. J Immunol. 2016 Sep 1;197(5):1852-63.

[2]. Talreja J, et al. Dual Inhibition of Rip2 and IRAK1/4 Regulates IL-1β and IL-6 in Sarcoidosis Alveolar Macrophages and Peripheral Blood Mononuclear Cells. J Immunol. 2016 Aug 15;197(4):1368-78.

[3]. Li Z, et al. Inhibition of IRAK1/4 sensitizes T cell acute lymphoblastic leukemia to chemotherapies. J Clin Invest. 2015 Mar 2;125(3):1081-97.

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