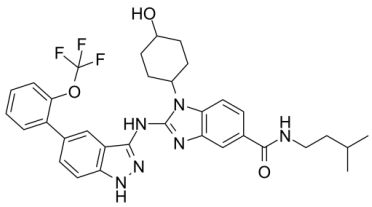
Data Sheet

Product Name:	IRAK inhibitor 4
Cat. No.:	CS-0606
CAS No.:	1012104-68-5
Molecular Formula:	C33H35F3N6O3
Molecular Weight:	620.66
Target:	IRAK
Pathway:	Immunology/Inflammation; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 12.5 mg/mL (20.14 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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.

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.

CAIndexNames:

1H-Benzimidazole-5-carboxamide, 1-(4-hydroxycyclohexyl)-N-(3-methylbutyl)-2-[[5-[2-(trifluoromethoxy)phenyl]-1H-indazol-3-yl]amino]-

SMILES:

OC1CCC(N2C3=C(C=C(C=C3)C(NCCC(C)C)=O)N=C2NC4=NNC5=C4C=C(C=C5)C6=CC=CC=C6OC(F)(F)F)CC1

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