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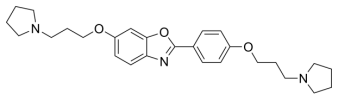
E6446

Cat. No.:	HY-12756
CAS No.:	1219925-73-1
Molecular Formula:	$C_{27}H_{35}N_3O_3$
Molecular Weight:	449.59
Target:	Toll-like Receptor (TLR); Stearoyl-CoA Desaturase (SCD)
Pathway:	Immunology/Inflammation; Metabolic Enzyme/Protease
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 : 8.33 mg/mL (18.53 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2242 mL	11.1212 mL	22.2425 mL
	5 mM	0.4448 mL	2.2242 mL	4.4485 mL
	10 mM	0.2224 mL	1.1121 mL	2.2242 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: ≥ 0.83 mg/mL (1.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

E6446 is a potent and orally acitve TLR7 and TLR9 antagonist, used in the research of deleterious inflammatory responses. E6446 is also a potent SCD1 inhibitor (KD: 4.61 μM), significantly inhibiting adipogenic differentiation and hepatic lipogenesis through SCD1-ATF3 signaling. E6446 also improves liver pathology in high-fat diet (HFD)-fed mice and may be useful in the study of non-alcoholic fatty liver disease (NAFLD)[1][2][3].

IC_{50} & Target	TLR7	TLR9

In Vitro

E6446 is a potent and orally acitve TLR7 and TLR9 inhibitor. E6446 potently suppresses DNA stimulation of HEK:TLR9 cells, with an IC_{50} value of 10 nM, but is significantly less effective at suppressing LPS endotoxin stimulation of HEK:TLR4 cells or R848 stimulation of HEK:TLR7 cells. E6446 potently inhibits IL-6 production induced by CpG2216 but is ineffective against induction by the TLR3 ligand poly inosine-cytosine. The ability of E6446 to inhibit TLR7 is ligand dependent, E6446 is a potent inhibitor of IL-6 induction by RNA but a relatively poor inhibitor of IL-6 induction by the small molecule

	imidazoquinoline ligand R-848. E6446 suppress TLR9-DNA interaction in vitro, with an IC_{50} in the 1 to 10 μM range[1]. E6446 (0.01-0.03 μM) specifically inhibits TLR9 activation with CpG ODN 2006, and blocks TLR7/8 activated by the imidazoquinoline compound R848 at 2-8 μM. E6446 reduces 50% of TLR4 activation at 30 μM, and shows IC_{50}s of 0.01 μM and 0.23 μM in HEK-TLR9 cells stimulated with oligo 2006 and in human PBMCs stimulated with oligo 2216, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	E6446 (20 mg/kg, p.o.) almost cmlpletely inhibits CpG1668-induced IL-6 production, and dose-dependently suppresses the development of ANA (anti-nuclear antibodies) in mice at 20 and 60 mg/kg[1]. E6446 (20, 60 mg/kg, p.o.) dose-dependently inhibits TLR9 signaling in mice. E6446 (60, 120 mg/kg, p.o.) prevents hyperresponsiveness of TLRs and LPS-induced septic shock in rodent malaria, diminishes TLR responsiveness during acute malaria, suppresses activation of both TLR7 and TLR9 [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	E6446 is assayed for the suppression of BALB/c mouse spleen interleukin-6 (IL-6) production in response to stimulation by oligonucleotide CpG1668. E6446 is added to dissociated splenocytes (5×10^5 per well in complete RPMI/10% fetal bovine serum in a 96-well plate) before addition of TLR agonists. Cells are stimulated for 72 hours, and supernatants are removed for ELISA analysis of IL-6. Mouse bone marrow-derived dendritic cells (BMDCs) are generated by culturing BALB/c marrow cells in RPMI containing 100 ng/mL Flt3 ligand for 7 days. Cells (1×10^5) in 50 μL are assayed for IL-6 production after overnight or 24-hour stimulation with various TLR ligands. For studies using human peripheral blood mononuclear cells, Ficoll-separated mononuclear cells are isolated from healthy volunteer donors, washed, and plated with stimulatory oligonucleotide CpG2216 in complete RPMI for 72 hours. Interferon in supernatant is quantified by ELISA[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] MRL/lpr mice are dosed orally five times a week with 20 or 60 mg/kg E6446 or 60 mg/kg hydroxychloroquine beginning at 5 weeks of age. Cytoxan is administered at 50 mg/kg i.p. every 10 days. A serum sample is taken immediately before the beginning of treatment to monitor changes in autoreactive antibodies. Subsequently, serum samples are collected approximately monthly and analyzed for anti-dsDNA by ELISA after 1:500 dilution. Body weights and urine samples are taken at the same interval, and proteinuria is assessed by ChemStrips. Anti-nuclear antibodies (ANA) are assessed using commercially available HEp2 slide kits, with serum diluted to 1:100 in kit buffer. ANA scores are read blinded[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Commun Signal. 2023 Sep 30;21(1):268.

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REFERENCES

[1]. Lamphier M, et al. Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo. Mol Pharmacol. 2014 Mar;85(3):429-40.

[2]. Franklin BS, et al. Therapeutical targeting of nucleic acid-sensing Toll-like receptors prevents experimental cerebral malaria. Proc Natl Acad Sci U S A. 2011 Mar 1;108(9):3689-94.

[3]. Wang W, et al. Identification of novel SCD1 inhibitor alleviates nonalcoholic fatty liver disease: critical role of liver-adipose axis. Cell Commun Signal. 2023 Sep 30;21(1):268.

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

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