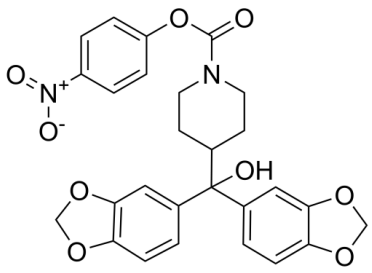
Data Sheet

Product Name:	JZL 184
Cat. No.:	CS-3373
CAS No.:	1101854-58-3
Molecular Formula:	$C_{27}H_{24}N_2O_9$
Molecular Weight:	520.49
Target:	MAGL
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 35 mg/mL



BIOLOGICAL ACTIVITY:

JZL 184 is a potent, selective and irreversible **MAGL** inhibitor that blocks 2-Arachidonoylglycerol (2-AG) hydrolysis in brain membranes (**IC_{50}** of 8 nM). JZL 184 displays >300-fold selectivity for **MAGL** over FAAH[1][2]. IC50 & Target: IC50: 8 nM (2-Arachidonoylglycerol (2-AG) hydrolysis)[1] ***In Vitro:*** JZL 184 displays IC_{50} values of 8 nM and 4 μM for blockade of 2-AG and oleamide (FAAH substrate) hydrolysis in brain membranes, respectively. Comparable inhibitory effects are observed with recombinant MAGL and FAAH when expressed in COS7 cells[1]. ***In Vivo:*** JZL 184 (4-40 mg/kg; intraperitoneal injection; once; C57Bl/6 mice) treatment produces a rapid and sustained blockade of brain 2-AG hydrolase activity in mice, resulting in 8-fold elevations in endogenous 2-AG levels that are maintained for at least 8 h. JZL 184-treated mice shows a remarkable array of CB1-dependent behavioral effects, including analgesia, hypomotility, and hypothermia[1].

JZL 184 prolongs depolarization-induced suppression of excitation (DSE) in Purkinje neurons in cerebellar slices and DSE inhibition (DSI) in CA1 pyramidal neurons in hippocampal slices. JZL 184 produces greater enhancement of DSE/DSI in mouse neurons than that in rat neurons[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] Standard assays were performed by pre-incubating protein samples with JZL184 for 30 min at 37°C prior to the addition of substrate or ABPP probe. Concentration-dependence inhibition curves were obtained from substrate assays and were fit using Prism software to obtain EC50 values with 95% confidence intervals. For measurement of kobs [I]-1 values, brain membrane proteomes (1 mg ml-1, 300 μl total) were incubated with JZL184 (0.01-15 μM, 10-40 min, 37°C). Every 10 min, 50 μl of the reaction was removed and treated with FP-rhodamine (2 μM) for 2 min, quenched with 4X SDS-PAGE loading buffer, and boiled for 5 min at 90°C. The combined reactions were subjected to SDS-PAGE and visualized in-gel using a flatbed fluorescence scanner. The percentage activity remaining was determined by measuring the integrated optical density corresponding to the MAGL or FAAH bands and the results were fit to an exponential curve to determine the pseudo-first order rate constants. Animal administration [1] JZL184 (neat) was dissolved by vortexing, sonicating, and gentle heating directly into 4:1 v/v PEG300:Tween80 (10, 4, 2, or 1 mg ml-1). Male C57Bl/6J mice (6-8 weeks old, 20-26 g) were intraperitoneally (i.p.) administered JZL184 or a 4:1 v/v PEG300:Tween80 vehicle without JZL184 at a volume of 4 ul g-1 weight (40, 16, 8, or 4 mg kg-1 by the dilutions above). After the indicated amount of time, mice were anesthetized with isofluorane and sacrificed by decapitation. Brains were removed, hemisected along the midsagittal plane, and each half was then flash frozen in liquid N2. One half of the brain was prepared as described above for protein analysis and the other half was used for metabolite analysis. The selective inhibition of FAAH by URB597 was achieved in a similar manner as described above, except URB597 was dissolved by sonication into 18:1:1 v/v/v saline:emulphor:ethanol (1 mg ml-1) and administered i.p. at a volume of 10 μl/g weight (10 mg kg-1 final dose). Oral administration was performed exactly as described for i.p.

administration, except that the vehicle was PEG300.

References:

[1]. Long JZ, et al. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat Chem Biol. 2009 Jan;5(1):37-44.

[2]. Pan B, et al. Blockade of 2-arachidonoylglycerol hydrolysis by selective monoacylglycerol lipase inhibitor 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate (JZL184) Enhances retrograde endocannabinoid signaling. J Pharmacol Exp Ther. 2009 Nov;331(2):591-7.

CAIndexNames:

1-Piperidinecarboxylic acid, 4-[bis(1,3-benzodioxol-5-yl)hydroxymethyl]-, 4-nitrophenyl ester

SMILES:

OC(C1=CC=C(OCO2)C2=C1)(C3CCN(C(OC4=CC=C([N+]([O-])=O)C=C4)=O)CC3)C5=CC(OCO6)=C6C=C5

Tel: 610-426-3128 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite F, Monmouth Junction, NJ 08852, USA