

Product Data Sheet

Product Name: MK-8245

Cat. No.: GC11681

Chemical Properties

Cas. No. 1030612-90-8

Chemical Name 2-[5-[3-[4-(2-bromo-5-fluorophenoxy)piperidin-1-yl]-1,2-oxazol-5-yl]tetrazol-2-yl]acetic acid

SMILES C1CN(CCC1OC2=C(C=CC(=C2)F)Br)C3=NOC(=C3)C4=NN(N=N4)CC(=O)O

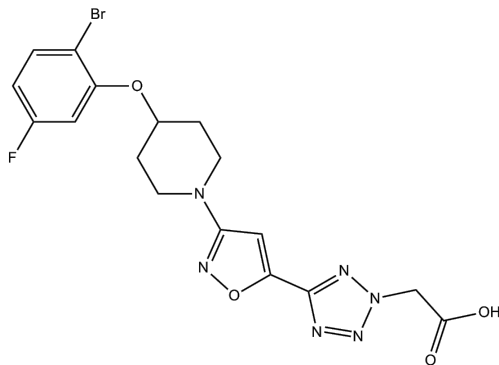
Formula $C_{17}H_{16}BrFN_6O_4$ M.Wt 467.25

Solubility ≥ 23.35 mg/mL in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Kinase experiment [1]:

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

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SCD1 enzyme activity assay

The potency of MK-8245 against the stearyl-CoA desaturase was determined by measuring the conversion of radiolabeled stearyl-CoA to oleoyl-CoA using rat liver microsome or human SCD1 (hSCD-1). Liver microsome was prepared from male Wistar or Sprague Dawley rats on a high carbohydrate diet for 3 days. The livers were homogenized (1:10 w/v) in a buffer containing 250 mM sucrose, 1 mM EDTA, 5 mM DTT and 50 mM Tris-HCl (pH 7.5). After a 100,000 × g centrifugation for 60 mins, the liver microsome pellet was suspended in a buffer containing 100 mM sodium phosphate, 20% glycerol, 2 mM DTT and stored at -78 °C. The human SCD1 desaturase system was reconstituted using human SCD1 from a baculovirus/Sf9 expression system, cytochrome B5 and cytochrome B5 reductase. Typically, different concentrations of MK-8245 in 2 µL DMSO was incubated for 15 mins at room temperature with 180 µL of the SCD enzyme in a buffer containing 100 mM Tris-HCl (pH 7.5), ATP (5 mM), Coenzyme-A (0.1 mM), Triton X-100 (0.5 mM) and NADH (2 mM). The reaction was initiated by the addition of 20 µL of [3H]-stearyl-CoA (final concentration = 2 µM, radioactivity concentration = 1 µCi/mL). After 10 mins, the reaction mixture (80 µL) was mixed with a calcium chloride/charcoal aqueous suspension (100 µL charcoal (10% w/v) plus 25 µL CaCl₂ (2N)). After centrifugation to precipitate the radioactive fatty acid species, tritiated water released from 9,10-[3H]-stearyl-CoA by the SCD enzyme was quantified on a scintillation counter.

Cell experiment [1]:

Cell lines Rat hepatocytes

Preparation method

The solubility of this compound in DMSO is > 10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20 °C for several months.

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Reaction Conditions < 200 nM

Applications In the rat hepatocyte assay which contains functional and active OATPs, MK-8245 significantly inhibited SCD with an IC₅₀ value of 68 nM.

Animal experiment [1]:

Animal models eDIO mice

Dosage form 3, 10 or 30 mg/kg; p.o.

Applications MK-8245, a liver-targeted small molecule SCD inhibitor, improved whole body insulin sensitivity.

Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Oballa RM, Belair L, Black WC, Bleasby K, Chan CC, Desroches C, Du X, Gordon R, Guay J, Guiral S, Hafey MJ, Hamelin E, Huang Z, Kennedy B, Lachance N, Landry F, Li CS, Mancini J, Normandin D, Pocai A, Powell DA, Ramtohul YK, Skorey K, Sørensen D, Sturkenboom W, Styhler A, Waddleton DM, Wang H, Wong S, Xu L, Zhang L. Development of a liver-targeted stearyl-CoA desaturase (SCD) inhibitor (MK-8245) to establish a therapeutic window for the treatment of diabetes and dyslipidemia. J Med Chem. 2011 Jul 28;54(14):5082-96.

Background

MK-8245 is a potent and liver-selective inhibitor of stearyl-CoA desaturase (SCD) with IC₅₀ value of

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1nM [1].

SCD1 represents a therapeutic target for the treatment of type II diabetes, dyslipidemia, obesity, and metabolic diseases. As an inhibitor of SCD1, MK-8245 shows potency in both the rat enzyme and hepatocyte assay. There are no significant differences in potencies between the rat, mouse, and human SCD1. MK-8245 is developed as a liver-targeting SCD inhibitor. It demonstrates a liver-targeted tissue distribution profile resulting from a substrate recognition by organic anionic transporter proteins (OATPs) [1, 2].

MK-8245 is effective at lowering glucose level. It can improve glucose clearance dose-dependently with ED50 value of 7mg/kg. In the chronic eDIO mouse study, MK-8245 shows prevention of body weight gain with the maximally efficacious dose of 20 mg/kg bid based on body weight and liver triglyceride reduction [1].

Reference:

[1] Oballa RM, Belair L, Black WC, Bleasby K, Chan CC, Desroches C, Du X, Gordon R, Guay J, Guiral S, Hafey MJ, Hamelin E, Huang Z, Kennedy B, Lachance N, Landry F, Li CS, Mancini J, Normandin D, Poci A, Powell DA, Ramtohul YK, Skorey K, Srensen D, Sturkenboom W, Styhler A, Waddleton DM, Wang H, Wong S, Xu L, Zhang L. Development of a liver-targeted stearyl-CoA desaturase (SCD) inhibitor (MK-8245) to establish a therapeutic window for the treatment of diabetes and dyslipidemia. J Med Chem. 2011 Jul 28;54(14):5082-96.

[2] Lachance N, Guiral S, Huang Z, Leclerc JP, Li CS, Oballa RM, Ramtohul YK, Wang H, Wu J, Zhang L. Discovery of potent and liver-selective stearyl-CoA desaturase (SCD) inhibitors in an acyclic linker series. Bioorg Med Chem Lett. 2012 Jan 1;22(1):623-7.

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