

Product Data Sheet

Product Name: MK 0893

Cat. No.: GC14793

Chemical Properties

Cas. No. 870823-12-4

Chemical Name 3-[[4-[(1S)-1-[3-(3,5-dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)pyrazol-1-yl]ethyl]benzoyl]amino]propanoic acid

SMILES CC(C1=CC=C(C=C1)C(=O)NCCC(=O)O)N2C(=CC(=N2)C3=CC(=CC(=C3)Cl)Cl)C4=C(C5=C(C=C4)C=C(C=C5)OC

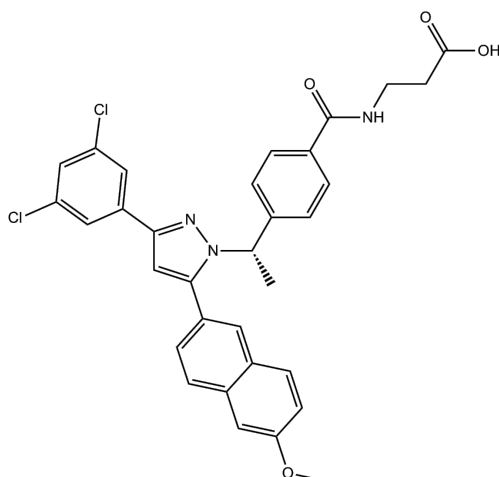
Formula $C_{32}H_{27}Cl_2N_3O_4$ M.Wt 588.48

Solubility ≥ 24.05 mg/mL in DMSO, ≥ 4.8 mg/mL in EtOH with ultrasonic and warming 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

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

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Cell experiment [1]:

Cell lines	Human primary hepatocytes
Preparation method	4,000 cells per well were preincubated with MK-0893, GRA1, and GRA2 (0-1000nM) for 30 min and restimulated with glucagon (5nM) for 30 min at room temperature.
Reaction Conditions	0-1000nM; 1 h
Applications	In the presence of glucagon, MK-0893, GRA1, and GRA2 all inhibit cAMP production with IC ₅₀ of 563, 448, and 292 nM, respectively.

Animal experiment [2]:

Animal models	hGCGR ob/ob mice
Preparation method	hGCGR ob/ob mice at 1 h post MK 0893 (3, 10mg/kg) administration via po, glucagon dissolved in PBS was injected at 15µg/kg ip followed by glucose measurements using a glucometer via tail bleeding.
Dosage form	3, 10mg/kg; p.o.

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Applications MK 0893 at 10 and 3 mg/kg oral doses lowered blood glucose level by 39%, 32% respectively.

References:

[1] Guan H P, Yang X, Lu K, et al. Glucagon receptor antagonism induces increased cholesterol absorption [S][J]. Journal of lipid research, 2015, 56(11): 2183-2195.

[2] Xiong Y, Guo J, Candelore M R, et al. Discovery of a Novel Glucagon Receptor Antagonist N-[(4-{(1S)-1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1 H-pyrazol-1-yl] ethyl} phenyl) carbonyl]-β-alanine (MK-0893) for the Treatment of Type II Diabetes[J]. Journal of medicinal chemistry, 2012, 55(13): 6137-6148.

Background

MK 0893 is a potent and selective glucagon receptor (GCGR) antagonist with an IC₅₀ value of 6.6 nM^[1]. The mechanism of action of MK 0893 is to prevent GCGR activation by limiting the movement of transmembrane helix 6 (TM6) protein required for G protein signaling^[2]. MK-0893 treats patients with type 2 diabetes and effectively reduces postprandial blood sugar, but it will cause an increase in liver transaminases and is not suitable for clinical development^[3].

In vitro, MK 0893 (0-1000nM) treated human primary liver cells for 1 hour, inhibited the effect of glucagon and prevented it from inducing the production of cAMP, with an IC₅₀ value of 563nM^[4]. MK 0893 (0-400nM) treated INS-1 832/13 cells and inhibited the effects of glucagon and also inhibited the effects of glucagon-like peptide-1 (GLP-1)^[5].

In vivo, oral administration of MK 0893 (3, 10 mg/kg) to hGCGR ob/ob mice reduced blood glucose levels by 32% and 39% at single doses of 3 and 10 mg/kg, respectively^[1]. MK 0893 (3, 10 mg/kg) administered orally to WT and hGCGR mice did not significantly affect plasma cholesterol or plant sterol levels in WT mice, however, at a dose of 10 mg/kg, it significantly increased campesterol levels. In hGCGR mice, MK 0893 exhibited a dose-dependent increase in plasma sitosterol levels^[4].

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- [1] Xiong Y, Guo J, Candelore M R, et al. Discovery of a Novel Glucagon Receptor Antagonist N-[(4-[(1S)-1-[3-(3, 5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1 H-pyrazol-1-yl] ethyl] phenyl) carbonyl]-β-alanine (MK-0893) for the Treatment of Type II Diabetes[J]. Journal of medicinal chemistry, 2012, 55(13): 6137-6148.
- [2] Crunkhorn S. Glucagon receptor antagonist binding site identified[J]. Nature Reviews Drug Discovery, 2016, 15(6): 384-384.
- [3] Christensen M, Bagger J I, Vilsboll T, et al. The alpha-cell as target for type 2 diabetes therapy[J]. The review of diabetic studies: RDS, 2011, 8(3): 369.
- [4] Guan H P, Yang X, Lu K, et al. Glucagon receptor antagonism induces increased cholesterol absorption [S][J]. Journal of lipid research, 2015, 56(11): 2183-2195.
- [5] Chepurny O G, Matsoukas M T, Liapakis G, et al. Nonconventional glucagon and GLP-1 receptor agonist and antagonist interplay at the GLP-1 receptor revealed in high-throughput FRET assays for cAMP[J]. Journal of Biological Chemistry, 2019, 294(10): 3514-3531.

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