MK-4256

Cat. No.: HY-13466

CAS No.: 1104599-69-0

Molecular Formula: $C_{27}H_{23}FN_8O$

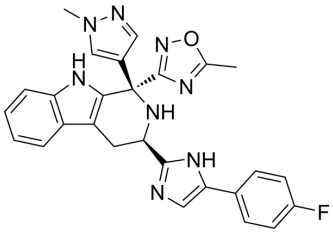
Molecular Weight: 494.52

Target: Somatostatin Receptor

Pathway: GPCR/G Protein; Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (202.22 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0222 mL	10.1108 mL	20.2216 mL
5 mM	0.4044 mL	2.0222 mL	4.0443 mL
10 mM	0.2022 mL	1.0111 mL	2.0222 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: ≥ 3 mg/mL (6.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (6.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MK-4256 is a potent and selective SSTR3 antagonist with IC_{50}s of 0.66 nM and 0.36 nM in human and mouse receptor binding assays, respectively.

IC_{50} & Target

IC50: 0.66 nM (human SSTR3), 0.36 nM (mouse SSTR3)[1]

In Vitro

MK-4256 has excellent selectivity against other SSTR subtypes based on in vitro assays. In human receptor binding assays, MK-4256 has IC_{50}s >2 μM for SSTR1 and SSTR2. Although the binding IC_{50} values on SSTR4 and SSTR5 are below 1 μM, there is still >500-fold selectivity. MK-4256 is tested in functional antagonist assays against SSTR4 and SSTR5. The IC_{50} values are greater than 5 μM (at least 5000-fold selectivity)[1]. MK-4256 inhibits radiolabeled MK-499 binding of the hERG channel with

	an IC_{50}=1.74 μM. In a functional patch clamp assay, MK-4256 exhibits 50% blockade of hERG at 3.4 μM concentration[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	MK-4256 reduces glucose excursion in a dose-dependent fashion with maximal efficacy achieves at doses as low as 0.03 mg/kg po. MK-4256 demonstrates exceptional SSTR3-mediated glucose-lowering efficacy in the mouse oGTT model with minimal hypoglycemia risk. MK-4256 achieves complete ablation of glucose excursion (109%) at 1 mg/kg po. MK-4256 reduces the glucose excursion from 0.003 to 10 mg/kg in a dose-dependent manner. The plasma C_{max} of MK-4256 is determined from parallel mouse PK studies. At 0.01, 0.1, and 1 mg/kg oral dose, MK-4256 achieves C_{max} of 7, 88, and 493 nM, respectivley[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] To demonstrate that the observed glucose lowering by MK-4256 is SSTR3-dependent, the effect of a maximally efficacious dosage of MK-4256 on blood glucose excursion during an oGTT was investigated in SSTR3 KO mice. Administration of MK-4256 (1 mg/kg) and compound A (1 mg/kg; des-F-sitagliptin, a DPP-4 inhibitor included as a positive control) to age-matched C57BL/6N male WT mice significantly inhibits blood glucose excursion by 112 and 91%, respectively. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Physiol. 2020 Jul;229(3):e13464.
- Islets. 2023 Dec 31;15(1):2252855.

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REFERENCES

[1]. He S, et al. The Discovery of MK-4256, a Potent SSTR3 Antagonist as a Potential Treatment of Type 2 Diabetes. ACS Med Chem Lett. 2012 May 7;3(6):484-9.

[2]. He S, et al. Investigation of Cardiovascular Effects of Tetrahydro-β-carboline sstr3 antagonists. ACS Med Chem Lett. 2014 Apr 21;5(7):748-53.

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