

Product Data Sheet

Product Name: MLN-4760

Cat. No.: GC31354

Chemical Properties

Cas. No. 305335-31-3

SMILES O=C(O)[C@H](CC1=CN=CN1CC2=CC(Cl)=CC(Cl)=C2)N[C@H](C(O)=O)CC(C)C

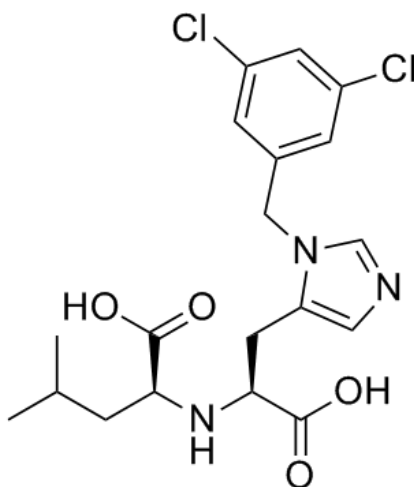
Formula $C_{19}H_{23}Cl_2N_3O_4$ M.Wt 428.31

Solubility DMSO: 200 mg/mL (466.95 mM) 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

Cell experiment [1]:

Cell lines Human Umbilical Vein Endothelial Cells (HUVECs)

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

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HUVECs were cultured in Ham's F-12K complete medium at 37°C in a Preparation Method humidified atmosphere of 5% CO₂. HUVECs were treated with the selective ACE2 inhibitor MLN-4760 at a concentration of 100nM for 24 hours.

Reaction
Conditions 100nM; 24h

Applications MLN-4760 significantly downregulation of ACE2 and Mas protein expression in high glucose (HG)-treated HUVECs. MLN-4760 also upregulation of proinflammatory cytokines and oxidative stress.

Animal experiment [2]:

Animal models Spontaneously Hypertensive Rats (SHR)

Preparation Method Rats were administered the specific ACE2 inhibitor MLN-4760 (1mg/kg/day) via subcutaneously implanted Alzet® mini-osmotic pumps (model 2002, pumping rate 0.5µL/hour) for 14 days.

Dosage form 1mg/kg/day; s.c.; Continuous infusion for 14 days.

Applications MLN-4760 administration led to a significant increase in body weight gain and visceral fat mass, elevated plasma Angiotensin II (Ang II) levels, and increased plasma hydrogen sulfide (H₂S) concentration. MLN-4760 also induced deterioration of erythrocyte morphology and osmotic resistance.

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- [1] Wang Y, Fu W, Xue Y, et al. Ginsenoside Rc Ameliorates Endothelial Insulin Resistance via Upregulation of Angiotensin-Converting Enzyme 2. *Front Pharmacol.* 2021 Feb 23;12:620524.
- [2] Cacanyiova S, Cebova M, Simko F, et al. The effect of zofenopril on the cardiovascular system of spontaneously hypertensive rats treated with the ACE2 inhibitor MLN-4760. *Biol Res.* 2023 Oct 25;56(1):55.

Background

MLN-4760 is a selective inhibitor of human angiotensin-converting enzyme 2 (ACE2; $IC_{50}=0.44nM$). MLN-4760 binds with high affinity to the zinc ion in the active site of ACE2, mimicking the transition state during peptide hydrolysis, thereby blocking the conversion of angiotensin II to angiotensin(1-7)^[1-2]. MLN-4760 is primarily used in studies related to kidney diseases, cardiovascular diseases, and inflammatory bowel disease^[3-4].

In vitro, treatment of high glucose (HG)-cultured human umbilical vein endothelial cells (HUVECs) with MLN-4760 (100nM) for 24 hours, MLN-4760 significantly inhibited the expression of ACE2 and Ang-(1-7) in HUVECs. MLN-4760 also downregulated the activity of the insulin signaling pathway (IRS-1/PI3K/Akt/eNOS) and exacerbated oxidative stress and inflammatory responses^[5]. Pretreatment of high glucose (30mM)-cultured human renal tubular epithelial cells (HK2) with MLN-4760 (5 μ M) for 24 hours, followed by intervention with Dapagliflozin (10 μ M) for 24 hours, MLN-4760 significantly reversed the Dapagliflozin-induced upregulation of ACE2 expression and inhibition of epithelial-mesenchymal transition (EMT), while restoring the expression level of the pro-fibrotic factor TGF- β 1^[6].

In vivo, administration of MLN-4760 (1mg/kg/day) via subcutaneous implantation of a mini-osmotic pump for 14 days in spontaneously hypertensive rats, MLN-4760 significantly increased the body weight gain rate and the visceral fat-to-body weight ratio, while elevating the concentration of hydrogen sulfide (H₂S) in both plasma and cardiac tissues^[7]. MLN-4760 (1mg/kg/day) administered via subcutaneous implantation of a mini-osmotic pump for 14 days in spontaneously hypertensive rats, MLN-4760 significantly reduced the osmotic resistance of red blood cells and induced morphological abnormalities in erythrocytes^[8].

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- [1] Kluknavsky M, Micurova A, Cebova M, et al. MLN-4760 Induces Oxidative Stress without Blood Pressure and Behavioural Alterations in SHRs: Roles of Nfe2l2 Gene, Nitric Oxide and Hydrogen Sulfide. *Antioxidants* (Basel). 2022 Dec 1;11(12):2385.
- [2] Joshi S, Balasubramanian N, Vasam G, et al. Angiotensin converting enzyme versus angiotensin converting enzyme-2 selectivity of MLN-4760 and DX600 in human and murine bone marrow-derived cells. *Eur J Pharmacol*. 2016 Mar 5;774:25-33.
- [3] Jasenovec T, Radosinska D, Kollarova M, et al. Effects of Taxifolin in Spontaneously Hypertensive Rats with a Focus on Erythrocyte Quality. *Life* (Basel). 2022 Dec 7;12(12):2045.
- [4] Berenyiova A, Bernatova I, Zemancikova A, et al. Vascular Effects of Low-Dose ACE2 Inhibitor MLN-4760-Benefit or Detriment in Essential Hypertension? *Biomedicines*. 2021 Dec 24;10(1):38.
- [5] Wang Y, Fu W, Xue Y, et al. Ginsenoside Rc Ameliorates Endothelial Insulin Resistance via Upregulation of Angiotensin-Converting Enzyme 2. *Front Pharmacol*. 2021 Feb 23;12:620524.
- [6] Wang S, Zhang X, Chong N, et al. Dapagliflozin ameliorates high glucose-induced epithelial-mesenchymal transition via up-regulating ACE2 mediated by EZH2 in diabetic nephropathy. *J Endocrinol Invest*. 2025 Oct;48(10):2499-2509.
- [7] Cacanyiova S, Cebova M, Simko F, et al. The effect of zofenopril on the cardiovascular system of spontaneously hypertensive rats treated with the ACE2 inhibitor MLN-4760. *Biol Res*. 2023 Oct 25;56(1):55.
- [8] Jasenovec T, Radosinska D, Kollarova M, et al. Angiotensin System Modulations in Spontaneously Hypertensive Rats and Consequences on Erythrocyte Properties; Action of MLN-4760 and Zofenopril. *Biomedicines*. 2021 Dec 14;9(12):1902.

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