Roflumilast N-oxide

Cat. No.: HY-100639

CAS No.: 292135-78-5

Molecular Formula: $C_{17}H_{14}Cl_2F_2N_2O_4$

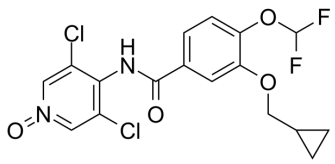
Molecular Weight: 419.21

Target: Phosphodiesterase (PDE)

Pathway: Metabolic Enzyme/Protease

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 : 250 mg/mL (596.36 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3854 mL	11.9272 mL	23.8544 mL
5 mM	0.4771 mL	2.3854 mL	4.7709 mL
10 mM	0.2385 mL	1.1927 mL	2.3854 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.96 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.96 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Roflumilast N-oxide is a PDE type 4 inhibitor.

IC_{50} & Target

PDE type 4[1]

In Vitro

Roflumilast N-oxide at 2 nM partly mitigates the cigarette smoke extract (CSE)-induced epithelial to mesenchymal transition (EMT) in WD-HBEC in vitro. Roflumilast N-oxide (2 nM) reverses the compromised expression of E-cadherin transcripts following CSE by 45%. The expression of collagen type I is abrogated by Roflumilast N-oxide (2 nM). The epithelial cell phenotype appears protected when cells are co-incubated with Roflumilast N-oxide (2 nM). Pre-incubation with Roflumilast N-oxide (2 nM) also partly attenuates the nuclear translocation of β-catenin[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	Single treatment of db/db mice with 10 mg/kg Roflumilast N-oxide enhances plasma glucagon-like peptide-1 (GLP-1) 4-fold. Chronic treatment of db/db mice with Roflumilast N-oxide at 3 mg/kg shows prevention of disease progression. Roflumilast-N-oxide abolishes the increase in blood glucose, reduces the increment in HbA_{1c} by 50% and doubles fasted serum insulin compare with vehicle, concomitants with preservation of pancreatic islet morphology. Furthermore, Roflumilast-N-oxide amplifies forskolin-induced insulin release in primary islets. Roflumilast-N-oxide also shows stronger glucose-lowering effects than its parent compound[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	A549 cells are washed and cultured overnight in serum-free F-12 K medium supplemented with antibiotics, L-glutamine and HEPES. The starved cells are incubated with Neutrophil elastase (NE) for 30 min or vehicle (PBS), washed with PBS and then cultured in serum free F-12 K. After stimulation, cell supernatants are collected at 24 h (for cytokine measurements) and cell pellets are collected after 2 h (for mRNA expression analysis). Alternatively, A549 cells are pre-incubated for 2 h with Roflumilast N-oxide (RNO) (at 0.1 μM, 0.3 μM and 1 μM), vehicle (DMSO 0.01%) prior to the addition of NE. All experiments are performed in serum-free medium in triplicate and are repeated at least three times. At the end of the incubation period, culture supernatants are harvested and stored at -80°C until further analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	At 7 weeks of age, 16 h fasting mice receive a single oral dose of vehicle (4% methocel) or 10 mg/kg Roflumilast-N-oxide, and a glucose bolus of 2 g/kg body weight is co-administered as a physiological initiator for glucagon-like peptide-1 (GLP-1) secretion. Plasma GLP-1 is analyzed 60 min before, and 10 and 60 min after administration of Roflumilast-N-oxide and glucose. The effect of Roflumilast-N-oxide on plasma GLP-1 is also investigated in the absence of the glucose bolus[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Victoni T, et al. Roflumilast n-oxide associated with PGE2 prevents the neutrophil elastase-induced production of chemokines by epithelial cells. Int Immunopharmacol. 2016 Jan;30:1-8.

[2]. Milara J,et al. Simvastatin Increases the Ability of Roflumilast N-oxide to Inhibit Cigarette Smoke-Induced Epithelial to Mesenchymal Transition in Well-differentiated Human Bronchial Epithelial Cells in vitro. COPD. 2015 Jun;12(3):320-31.

[3]. Vollert S, et al. The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-oxide in db/db mice. Diabetologia. 2012 Oct;55(10):2779-2788.

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