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Lumacaftor

Cat. No.: HY-13262

CAS No.: 936727-05-8

Molecular Formula: $C_{24}H_{18}F_2N_2O_5$

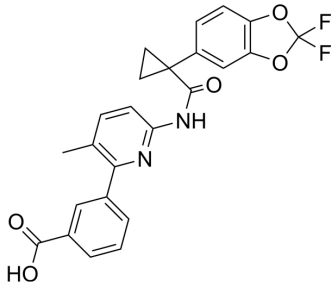
Molecular Weight: 452.41

Target: CFTR; Autophagy

Pathway: Membrane Transporter/Ion Channel; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (55.26 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2104 mL	11.0519 mL	22.1038 mL
	5 mM	0.4421 mL	2.2104 mL	4.4208 mL
	10 mM	0.2210 mL	1.1052 mL	2.2104 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 (6.63 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (6.63 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Lumacaftor (VX-809; VRT 826809) is a CFTR modulator that corrects the folding and trafficking of CFTR protein.

IC_{50} & Target

EC50: 0.1 μM (CFTR)[1]

In Vitro

In fischer rat thyroid (FRT) cells, Lumacaftor improves F508del-CFTR maturation by 7.1±0.3 fold (n=3) compared with vehicle-treated cells (EC_{50}, 0.1±0.1 μM; n=3) and enhances F508del-CFTR-mediated chloride transport by approximately fivefold (EC_{50}, 0.5±0.1 μM; n=3). At Lumacaftor concentrations greater than 10 μM, the response is reduced, resulting in a bell-shaped dose-response relationship with an IC_{50} of approximately 100 μM. Lumacaftor is orally bioavailable in rats and achieved in vivo plasma levels significantly above concentrations required for in vitro efficacy[1]. Lumacaftor produces a concentration-dependent increase in the HRP luminescence signal after incubation with cells at 37°C or 27°C in both cell

	lines, with a similar EC_{50} value of approximately 0.3 μM. In F508-HRP CFBE41o$^-$ cells at 37°C, Lumacaftor increases the signal maximally to approximately 250 luminescence arbitrary units (a.u.) over the DMSO control baseline of approximately 60 a.u., representing an approximately 4-fold signal increase. Similarly, with the R1070W-HRP CFBE41o$^-$ cells, Lumacaftor increases the signal maximally to approximately 220 a.u. over the DMSO control baseline of approximately 85 a.u., representing an approximately 2.5-fold signal increase. Therefore, both cell lines produced robust signals with a good dynamic range for high-throughput screening[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Oral dosing of 1 mg/kg Lumacaftor in male Sprague-Dawley rats results in a C_{max} of 2.4±1.3 μM with a $t_{1/2}$ of 7.7±0.4 h (mean±SD; n=3), indicating that that Lumacaftor is orally bioavailable and able to reach plasma levels that significantly exceeded EC_{50}s for F508del-CFTR correction[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Screening is carried out using a Beckman Coulter Biomek FX platform. In one set of assays, R1070W-F508-CFTR-HRP (R1070W-HRP)-expressing CFBE41o$^-$ cells are incubated with 100 μL medium containing 25 μM test compounds and 0.5 μg/mL Doxycycline for 24 hours at 37°C. In a second set of assays, F508-CFTR-HRP (F508-HRP)-expressing CFBE41o$^-$ cells are incubated with 100 μL medium containing 25 μM test compounds, 2 μM Lumacaftor, and 0.5 μg/mL doxycycline for 24 hours at 37°C. All compound plates contain negative controls (DMSO) and positive controls (2 μM Lumacaftor). In both assays, the cells are washed four times with PBS, and HRP activity is assayed by the addition of 50 μL/well of HRP substrate. After shaking for 5 minutes, chemiluminescence is measured using a Tecan Infinite M1000 plate reader equipped with an automated stacker (integration time, 100 milliseconds)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	.A549 cells expressing F508-CFTR YFP are grown at 37°C/5% CO_2 for 18-24 hours after plating. The cells are then incubated with 100 μL of medium containing test compounds for 18-24 hours. At the time of the assay, cells are washed with PBS and then incubated for 10 minutes with PBS containing forskolin (20 μM) and genistein (50 μM). Each well is assayed individually for I^- influx by recording fluorescence continuously (200 milliseconds per point) for 2 seconds (baseline) and then for 12 seconds after rapid addition of 165 μL PBS in which 137 mM Cl^- is replaced by I^-. The initial I^- influx rate is computed by fitting the final 11.5 seconds of the data to an exponential for extrapolation of initial slope, which is normalized for background-subtracted initial fluorescence. All compound plates contain negative controls (DMSO vehicle) and positive controls (5 μM Lumacaftor). Fluorescence is measured using a Tecan Infinite M1000 plate reader equipped with a dual syringe pump (excitation/emission 500/535 nm)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats[1] Male rats (n=3 per dose group) are orally administered Lumacaftor in a vehicle consisting of 0.5% Tween80/0.5% methylcellulose/water at a dose volume of 5 mL/kg. The concentration of Lumacaftor in plasma samples is determined with a liquid chromatography/tandem MS method. Pharmacokinetic parameters are calculated byusing WinNonlin Professional Edition software. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2022 Jan 6;185(1):158-168.e11.
- Stem Cell Reports. 2020 Nov 10;15(5):1127-1139.
- Cells. 2022, 11(3), 319.

- Int J Mol Sci. 2022, 23(17), 9612.
- Sci Rep. 2020 Oct 2;10(1):16383.

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REFERENCES

[1]. Van Goor F, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. Proc Natl Acad Sci U S A. 2011 Nov 15;108(46):18843-8.

[2]. Phuan PW, et al. Synergy-based small-molecule screen using a human lung epithelial cell line yields ΔF508-CFTR correctors that augment VX-809 maximal efficacy. Mol Pharmacol. 2014 Jul;86(1):42-51.

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