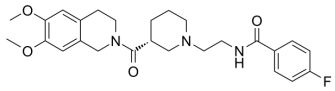
YM758

Cat. No.:	HY-U00309
CAS No.:	312752-85-5
Molecular Formula:	$C_{26}H_{32}FN_3O_4$
Molecular Weight:	469.55
Target:	Others
Pathway:	Others
Storage:	Powder -20°C 3 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (212.97 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1297 mL	10.6485 mL	21.2970 mL
	5 mM	0.4259 mL	2.1297 mL	4.2594 mL
	10 mM	0.2130 mL	1.0648 mL	2.1297 mL

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

BIOLOGICAL ACTIVITY

Description

YM758 is a “funny” I_f current channel (I_f channel) inhibitor.

IC_{50} & Target

I_f channel[1]

In Vitro

The inhibitory effect of YM758 on [^{3}H]MPP uptake via human/rat organic cation transporters (hOCT1/rOct1) is investigated. YM758 inhibits rOct1- and hOCT1-mediated [^{3}H]MPP uptake in a concentration-dependent manner with IC_{50} values of 23.8 and 40.5 μM, respectively. The IC_{50} value of YM758 for [^{14}C]Metformin uptake via rOct1 may be estimated below 10 μM in the same way, whereas that is much smaller than that for [^{3}H]MPP uptake. In addition, the inhibitory effect of YM758 on [^{3}H]E_2 17βG uptake via OATP1B1 and OATP1B3 is investigated. YM758 inhibits OATP1B1-mediated [^{3}H]$E_2$17βG uptake in a concentration-dependent manner with a IC_{50} value of 13.0 μM. YM758 has no inhibitory effect on OATP1B3-mediated [^{3}H]E_2 17βG uptake[1].

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

In Vivo

After a single intravenous administration of 0.03, 0.1, and 0.3 mg/kg to tachycardia-induced beagles, YM758 plasma concentrations rapidly decrease with $t_{1/2}$ values of 1.62, 4.93, and 1.63 h, respectively. At the corresponding doses, the CL_{tot} values amount to 1.71, 1.69, and 1.48 L/h/kg, and Vd_{ss} values are 3.19, 5.78, and 2.94 L/kg, respectively. Because the plasma

concentration 24 h after administration is quantified only in the 0.1 mg/kg dosing group, the larger values of $t_{1/2}$ and Vd_{ss} are obtained compared with those in other dosing groups. The PK profile of YM758 in tachycardia-induced dogs appears to be linear within the dose range of 0.03 to 0.3 mg/kg. The CL_{tot} of YM758 in the blood basis ($CL_{b,dog}$) is estimated to be 1.47 to 1.69 L/h/kg[2]. The radioactivity in the rat eyeballs after dosing ^{14}C-YM758 is extracted with a mixture of 2 mol/L hydrochloric acid and Methanol (5:95, v/v); the radioactivity recovery is 97.1% at 4 h and 67.1% at 24 h. The HPLC recovery of radioactivity from the extracted samples is 90.6 and 100.6% at 4 and 24 h, respectively. In the eyeball at 4 h after administration, YM758 (the unchanged drug) is the main compound detected (66.7%), and the metabolites YM-252124 (14.5%), YM-394111 (2.4%), and YM-234903 (1.8%) are also observed[3].

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PROTOCOL

Kinase Assay [1]

Transporter-expressing or vector-transfected HEK293 cells are grown in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin (v/v) and 100 μg/mL Zeocin at 37°C in an atmosphere of 5% CO_2 and 95% humidity. The cells are subcultured in a medium containing 0.05% trypsin-EDTA solution. Cells are then seeded in poly-D-lysine-coated 12-well plates at a density of 1.2×10^5 cells/well. For the transport study, the cell culture medium is replaced with culture medium supplemented with 5 mM sodium-butyrate for 24 h before the transport assay to induce the expression level of hOCT1, rOct1, OATP1B1, and OATP1B3. The transport study is performed. Uptake is initiated by adding Krebs-Henseleit buffer containing radiolabeled substrates (0.6 nM [^{3}H]MPP, 10 μM[^{14}C]Metformin, 20 nM [^{3}H]$E_2$17βG, or 10 μM [^{14}C]YM758) after the cells have been washed twice and preincubated with Krebs-Henseleit buffer at 37°C for 15 min. In the concentration-dependent uptake and/or inhibition studies, the cells are incubated further in the presence of YM758 (1-1000 μM). The Krebs-Henseleit buffer consists of 2.0 mg/mL D-glucose, 0.141 mg/mL Magnesium sulfate, 0.16 mg/mL Potassium phosphate monobasic, 0.35 mg/mL Potassium chloride, 6.9 mg/mL Sodium chloride, 0.373 mg/mL Calcium chloride dihydrate, 1.5 mg/mL HEPES, and 2.1 mg/mL Sodium bicarbonate. The pH of this solution is adjusted to 7.4 with Sodium hydroxide. The uptake is terminated at the designated time by adding ice-cold Krebs-Henseleit buffer after removing the incubation buffer. The cells then are washed twice with 1 mL of ice-cold Krebs-Henseleit buffer, solubilized in 0.5 mL of 1.0 M Sodium hydroxide, and kept overnight at 4°C. Aliquots (0.5 mL) are transferred to scintillation vials after adding 0.25 mL of 2.0 M hydrochloric acid. The radioactivity associated with the cells and incubation buffer is measured in a liquid scintillation counter after adding 5 mL of scintillation fluid to the scintillation vials. The remaining cell lysate is used to determine the protein concentration by the method of Lowry, with bovine serum albumin as the standard[1].

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Animal Administration [2][3]

Beagle[2]

Four male beagles (11.0-15.0 kg) are used for the intravenous administration study. Heart rate (HR) (beats/min) is determined by doubling the number of the QRS complexes on the ECG recorded for 30 s. First, HR is measured at rest and just after initiation of tachycardia induced by intravenous Isoproterenol (0.1 μg/kg) administration, and then YM758, which is dissolved in saline, is intravenously administered at doses of 0.03, 0.1, and 0.3 mg/kg. At 0.1, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after the YM758 administration, HR is measured just after intravenous isoproterenol (0.1 μg/kg) to induce tachycardia, following the measurement of resting HR at each designated point. This is followed by a minimum 1-week washout period between each study period. Blood samples (approximately 3.0 mL) are withdrawn from the vein using a heparin-treated syringe, and the electrocardiogram (ECG) is recorded at the times designated (0.1, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after administration). Plasma is obtained by centrifugation of the blood samples at 1870g for 15 min at 4°C and then stored at -20°C until determination of the YM758 concentrations[2].

Rats[3]

Male Long-Evans rats (7 weeks) and Sprague-Dawley rats (9 weeks) are used. 3 mg/2.57 MBq/10 mL/kg is given to rats orally by gavage using a syringe with a gastric tube.The nonalbino rats are sacrificed by ether overdose 4 and 24 h after a single oral administration of 3 mg/kg ^{14}C-YM758. The fur is then rapidly clipped off, and the nasal cavity and anus are filled with 4% carboxymethylcellulose-Na. The carcass is frozen in a dry ice-acetone mixture, and the forelimbs, hind limbs, and tail are surgically removed[3].

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REFERENCES

[1]. Umehara K, et al. Hepatic uptake and excretion of (-)-N-{2-[(R)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidino]ethyl}-4-fluorobenzamide (YM758), a novel i_f channel inhibitor, in rats and humans. Drug Metab Dispos. 2008 Jun;36(6):1030-8.

[2]. Umehara K, et al. Relationship between exposure of (-)-N-{2-[(R)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidino]ethyl}-4-fluorobenzamide (YM758), a "funny" i_f current channel inhibitor, and heart rate reduction in tachycardia-induced beagle dogs. Drug Metab Dispos. 2009 Jul;37(7):1427-33.

[3]. Umehara K, et al. Investigation of long-term retention of unchanged (-)-N-{2-[(R)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidino]ethyl}-4-fluorobenzamide, a novel "funny" I_f current channel inhibitor, and its metabolites in the eyeball and thoracic aorta of rats. Drug Metab Dispos. 2009 Nov;37(11):2137-44.

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