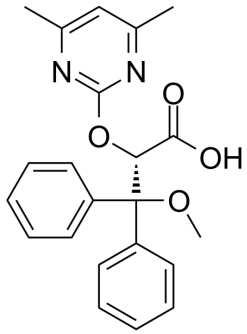
Ambrisentan



Cat. No.:	HY-13209
CAS No.:	177036-94-1
Molecular Formula:	$C_{22}H_{22}N_2O_4$
Molecular Weight:	378.42
Target:	Endothelin Receptor
Pathway:	GPCR/G Protein
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 (264.26 mM; Need ultrasonic)
Ethanol : 7.14 mg/mL (18.87 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6426 mL	13.2128 mL	26.4257 mL
	5 mM	0.5285 mL	2.6426 mL	5.2851 mL
	10 mM	0.2643 mL	1.3213 mL	2.6426 mL

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

In Vivo

1. Add each solvent one by one: 0.5% CMC-Na/saline water
   Solubility: 12.5 mg/mL (33.03 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.61 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.61 mM); Clear solution
4. Add each solvent one by one: 10% EtOH >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.71 mg/mL (1.88 mM); Clear solution
5. Add each solvent one by one: 10% EtOH >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.71 mg/mL (1.88 mM); Clear solution
6. Add each solvent one by one: 10% EtOH >> 90% corn oil
   Solubility: ≥ 0.71 mg/mL (1.88 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Ambrisentan is a selective ET type A receptor (ETAR) antagonist.
IC_{50} & Target	ETA receptor[1]
In Vitro	Ambrisentan is an endothelin type A receptor antagonist[1]. Ambrisentan induces Nrf2 activation. Endothelial permeability increased in BMEC monolayers at 24 h of hypoxia exposure and compared to vehicle control, Ambrisentan attenuates hypoxia-induced BMEC leak. These results are reversed when prior to treatment BMEC are transfected with siRNA against Nrf2[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the Ambrisentan group, hepatic hydroxyproline content is significantly lower than in the control group (18.0 μg/g±6.1 μg/g vs 33.9 μg/g±13.5 μg/g liver, respectively, P=0.014). Hepatic fibrosis estimated by Sirius red staining and areas positive for α-smooth muscle actin, indicative of activated hepatic stellate cells, are also significantly lower in the Ambrisentan group (0.46%±0.18% vs 1.11%±0.28%, respectively, P=0.0003; and 0.12%±0.08% vs 0.25%±0.11%, respectively, P=0.047). Moreover, hepatic RNA expression levels of procollagen-1 and tissue inhibitor of metalloproteinase-1 (TIMP-1) are significantly lower by 60% and 45%, respectively, in the Ambrisentan group. Inflammation, steatosis, and endothelin-related mRNA expression in the liver are not significantly different between the groups. Ambrisentan attenuates the progression of hepatic fibrosis by inhibiting hepatic stellate cell activation and reducing procollagen-1 and TIMP-1 gene expression. Ambrisentan did not affect inflammation or steatosis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Unless otherwise stated, for each BMEC experiment cells are randomly divided into 4 groups: (1) normoxia vehicle control (Nx-CTRL); (2) normoxia-treated; (3) hypoxia (24 h) control (Hx-CTRL) and (4) hypoxia (24 h) treated. As previously described, Nrf2 activators are added 24 h prior to any hypoxic exposures. Cell treatments are; Protandim (100 μg/mL), methazolamide (125 μg/mL, nifedipine (7 μg/mL) or Ambrisentan (40 μg/mL). In addition, some cells are treated with Nrf2 siRNA. In these experiments, siRNA is added 24 h prior to drug treatments. The rationale for 24 h hypoxia exposure for BMEC is to ensure that cells remained transfected with siRNA for the pre-treatment of drugs (24 h in normoxia) and during the 24 h hypoxia exposure. Data is collected from at least three separate cell culture preparations on three separate days (n=9)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] A total of 13 male FLS-ob/ob mice (age, 8 wk; body weight, 42.88 g±1.74 g) are used. At the age of 12 wk, male FLS-ob/ob mice are randomly assigned to the Ambrisentan (n=8) or control (n= 5) group. Intragastric gavage administration is carried out in conscious animals with an appropriately sized gastric tube. Ambrisentan (2.5 mg/kg per day) is orally administered every afternoon for 4 wk as a bolus through a gastric tube. Water is administered to the control group. At week 4, animals are fasted for 4 h and tail vein blood is drawn and subjected to blood glucose determination. Animals are killed by pentobarbital anesthesia injection after 4 wk and blood is collected from the right ventricle. Plasma samples are frozen and stored at -80°C Liver and visceral fat are then weighed, snap-frozen in liquid nitrogen, and stored at -80°C. Additional liver specimens are fixed in 10% buffered formalin and embedded in paraffin for histological analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Mol Cell Cardiol. 2022 Jul 7;171:16-29.
- Patent. US20220317132A1.

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REFERENCES

[1]. Okamoto T, et al. Antifibrotic effects of Ambrisentan, an endothelin-A receptor antagonist, in a non-alcoholic steatohepatitis mouse model. World J Hepatol. 2016 Aug 8;8(22):933-41.

[2]. Lisk C, et al. Nrf2 activation: a potential strategy for the prevention of acute mountain sickness. Free Radic Biol Med. 2013 Oct;63:264-73.

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