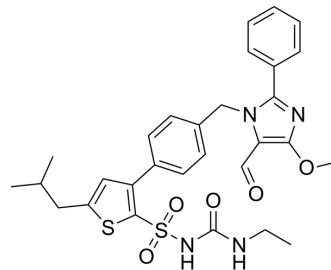


AVE 0991

Cat. No.:	HY-15778		
CAS No.:	304462-19-9		
Molecular Formula:	C ₂₉ H ₃₂ N ₄ O ₅ S ₂		
Molecular Weight:	580.72		
Target:	Angiotensin 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 : 41.67 mg/mL (71.76 mM; Need ultrasonic)

Concentration	Mass		
	1 mg	5 mg	10 mg
1 mM	1.7220 mL	8.6100 mL	17.2200 mL
5 mM	0.3444 mL	1.7220 mL	3.4440 mL
10 mM	0.1722 mL	0.8610 mL	1.7220 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.5 mg/mL (4.31 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: 2.5 mg/mL (4.31 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (4.31 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AVE 0991 is a nonpeptide and orally active angiotensin-(1-7) receptor agonist with an IC₅₀ of 21 nM^[1].

IC₅₀ & Target

IC₅₀: 21±35 nM (Ang-(1-7) receptor)^[1]

In Vitro

AVE 0991 is a nonpeptide compound that evokes effects similar to Ang-(1-7) on the endothelium. AVE 0991 and unlabeled Ang-(1-7) compete for high-affinity binding of [¹²⁵I]-Ang-(1-7) to bovine aortic endothelial cell membranes with IC₅₀s of 21±35 and 220±280 nM, respectively. Peak concentrations of NO and O₂⁻ release by AVE 0991 sodium salt and Ang-(1-7) (both

10 μM) are not significantly different (NO: 295 ± 20 and 270 ± 25 nM; O_2^- : 18 ± 2 and 20 ± 4 nM). However, the released amount of bioactive NO is ≈ 5 times higher for AVE 0991 in comparison to Ang-(1-7)^[1].

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

In Vivo

AVE 0991 (0.58 nmol/g) produces a significant decrease of water diuresis in WT mice compared with vehicle-treated animals (0.06 ± 0.03 mL versus 0.27 ± 0.05 ; $n=9$ for each group; $P < 0.01$). The antidiuretic effect of AVE 0991 (AVE) is associated with an increase in urine osmolality (1669 ± 231.0 mOsm/KgH₂O versus 681.1 ± 165.8 mOsm/KgH₂O in vehicle-treated mice; $P < 0.01$). The genetic deletion of Mas abolishes the antidiuretic effect of AVE 0991 during water loading (0.37 ± 0.10 mL [$n=9$] versus 0.27 ± 0.03 mL [$n=11$] in AVE 0991-treated mice). As observed with C57BL/6 mice, administration of AVE 0991 (0.58 nmol/g) in water-loaded Swiss mice also produces a significant decrease of the urinary volume compared with vehicle-treated animals (0.13 ± 0.05 mL [$n=16$] versus 0.51 ± 0.04 mL [$n=40$]; $P < 0.01$)^[2]. One week of treatment with AVE-0991 produces a significant decrease in perfusion pressure (56.55 ± 0.86 vs. 68.73 ± 0.69 mmHg in vehicle-treated rats) and an increase in systolic tension (11.40 ± 0.05 vs. 9.84 ± 0.15 g in vehicle-treated rats), rate of tension rise (+dT/dt; 184.30 ± 0.50 vs. 155.20 ± 1.97 g/s in vehicle-treated rats), rate of tension fall (?dT/dt; 179.60 ± 1.39 vs. 150.80 ± 2.42 g/s in vehicle-treated rats). A slight increase in heart rate (HR) is also observed (220.40 ± 0.71 vs. 214.20 ± 0.74 beats/min in vehicle-treated rats)^[3].

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PROTOCOL

Cell Assay ^[1]

Monkey kidney (COS) cells and Chinese hamster ovary (CHO) cells are stably transfected with rat Mas cDNA driven by a cytomegalovirus promoter and selected by neomycin. ¹²⁵I-Ang-(1-7) (0.5×10^{-9} mol/L) is incubated in 24-well plates for 60 minutes at 4°C in 0.3 mL of serum-free medium (DMEM) supplemented with 0.2% BSA, 0.005% bacitracin, 0.1 mol/L PMSF, and 0.5 mol/L orthophenanthroline with Mas-transfected COS cells in the presence or absence of AVE 0991 (AVE, 10^{-10} to 10^{-5} mol/L). After 2 washes with ice-cold serum-free DMEM, cells are disrupted with 0.1% Triton X-100. Bound radioactivity is measured in a gamma counter. Binding of rhodamine-Ang-(1-7) in Mas-transfected CHO cells is performed under similar conditions using 2×10^{-9} mol/L rhodamine-labeled-Ang-(1-7) in the presence or absence of AVE (10^{-6} mol/L), CV11974 (10^{-6} mol/L), or PD123319 (10^{-6} mol/L). NSB is determined in the presence of 10^{-6} mol/L Ang-(1-7)^[1].

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Animal Administration ^{[2][3]}

Mice^[2]

Swiss male mice, Mas-KO (Mas^{-/-}) male mice on the pure genetic background C57BL/6, and WT C57BL/6 control mice (Mas^{+/+}) are used. Water diuresis is induced by intraperitoneal water injection (0.05 mL/g of body weight [BW]) in conscious mice. Drugs are administered in the same injection with water load at prefixed volumes (0.01 mL/g BW). In the first set of experiments, WT mice (C57BL/6, control group) or Mas-KO mice are treated with: (1) 0.58 nmol/g AVE 0991 ($n=9$, control; $n=11$, Mas-KO mice); or (2) vehicle for AVE 0991 (10 μM KOH, 0.01 mL/g; $n=9$, control; $n=9$, Mas-KO). In the second set, Swiss mice are treated with: (1) vehicle ($n=36$); (2) 0.58 nmol/g AVE 0991 ($n=16$); (3) 46 pmol/g Ang-(1-7) antagonist A-779 ($n=4$); (4) 2 nmol/g DuP-753 or CGP 48933 ($n=5$); (5) 2 nmol/g AT₂ receptor antagonists PD123319 or PD123177 ($n=9$); (6) AVE 0991 combined with A-779; (7) AVE 0991 combined with DuP-753 or CGP 48933 ($n=4$ for each); (8) or AVE 0991 combined with PD123319 ($n=5$) or PD123177 ($n=4$). The urinary volume is measured for 60 minutes after water loading, and urine samples are obtained to determine the osmolality. The dose of AVE 0991 is based in preliminary experiments performed in Swiss mice.

Rats^[3]

Male Wistar rats weighting 250-300 g are used. Rats are treated either with AVE-0991 (1 mg/kg, $n=9$) or vehicle (0.9% NaCl, $n=11$) administered orally by gavage.

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CUSTOMER VALIDATION

- J Hepatol. 2022 Nov 9;S0168-8278(22)03285-8.

- Blood. 2015 Jan 22;125(4):710-9.
- Redox Biol. 2019 Jan;20:75-86.
- Diabetes. 2017 Aug;66(8):2201-2212.
- Aging (Albany NY). 2018 Apr 17;10(4):645-657.

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REFERENCES

- [1]. Wiemer G, et al. AVE 0991, a nonpeptide mimic of the effects of angiotensin-(1-7) on the endothelium. Hypertension. 2002 Dec;40(6):847-52.
- [2]. Pinheiro SV, et al. Nonpeptide AVE 0991 is an angiotensin-(1-7) receptor Mas agonist in the mouse kidney. Hypertension. 2004 Oct;44(4):490-6.
- [3]. Ferreira AJ, et al. The nonpeptide angiotensin-(1-7) receptor Mas agonist AVE-0991 attenuates heart failure induced by myocardial infarction. Am J Physiol Heart Circ Physiol. 2007 Feb;292(2):H1113-9.
- [4]. Mo J, et al. AVE 0991 attenuates oxidative stress and neuronal apoptosis via Mas/PKA/CREB/UCP-2 pathway after subarachnoid hemorrhage in rats. Redox Biol. 2018 Sep 28;20:75-86.
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