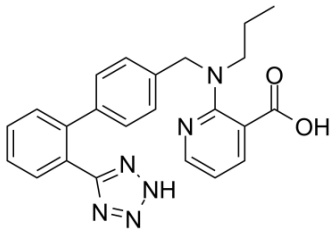
A81988

Cat. No.:	HY-U00188
CAS No.:	141887-34-5
Molecular Formula:	$C_{23}H_{22}N_6O_2$
Molecular Weight:	414.46
Target:	Angiotensin Receptor
Pathway:	GPCR/G Protein
Storage:	Please store the product under the recommended conditions in the COA.



BIOLOGICAL ACTIVITY

Description	A81988 is a potent, competitive, non-peptidic antagonist of **angiotensin AT_1** receptors.
IC_{50} & Target	Angiotensin AT_1 receptor[1]
In Vitro	A81988 (A-81988) is labeled with tritium to high specific activity (16 Ci/mmol) and radioligand binding assays performed in rat liver membranes. [^{3}H]A81988 binds with high affinity (K_D=0.57 nM) and the K_D determined from kinetics assays is similar. Non-specific binding (defined with 1 μM angiotensin-II) is very low (< 6% at the K_D). The binding of [^{3}H]A81988 is competitive and exhibits appropriate pharmacological specificity for compounds acting at angiotensin AT_1 receptors[1].
In Vivo	To verify this hypothesis, $B_2^{-/-}$ or wild-type mice ($B_2^{+/+}$) are administered a nonpeptide antagonist of Ang II type 1 (AT_1) receptors (A81988) from conception through 180 days of age. Untreated $B_2^{+/+}$ and $B_2^{-/-}$ served as controls. Blood pressure (BP) and heart rate are monitored with the use of tail-cuff plethysmography at regular intervals. Ventricular weights, diameters, wall thickness, chamber volume, and myocardial fibrosis are measured at 40 and 180 days. No differences are observed in BP, heart rate, and cardiac weight and dimensions between treated and untreated $B_2^{+/+}$. The BP of AT_1 antagonist-treated $B_2^{-/-}$ is reduced until 70 days; then, it increases to the levels found in untreated $B_2^{-/-}$. AT_1 receptor blockade results in a reduction in left ventricular mass, chamber volume, and wall thickness and abrogated myocardial fibrosis in $B_2^{-/-}$[2]. A81988 (A-81988) decreases the BP of $Bk2r^{-/-}$ either in normosodic conditions or after sodium deprivation, whereas in $Bk2r^{+/+}$ it produces a modest decrease under hyposodic conditions only[3].

PROTOCOL

Animal Administration [2][3]	Mice[2] $B_2^{-/-}$ mice and wild-type J129Sv controls ($B_2^{+/+}$) are used. Pregnant mice are administered the nonpeptidic antagonist of Ang II AT_1 receptors, A81988 (1.7 mg/kg BW per day in drinking water) or vehicle. At the dose indicated above, A81988 (A-81988) is able to antagonize the vasopressor effect of 10 pmol intravenous Ang II by 75% in mice. At 2 days after birth, the gender of the pups is determined, and each litter is culled to 5 male pups. Mice whose mother is treated during pregnancy continued to receive the antagonist until 180 days of age (treated $B_2^{+/+}$ and $B_2^{-/-}$, n=25 each group). Untreated controls of each strain (n=25 per group) are provided regular tap water. The

animals are housed at a constant room temperature (24±1°C) and humidity (60±3%).

Rats[3]

Animals are randomly assigned to a normal (0.12 mmol/g chow, n=8 each group), a low (0.02 mmol/g chow, n=8 each group), or a high (0.84 mmol/g chow, n=8 each group) sodium diet. After 15 days, they received the antagonist A81988 (A-81988) for 10 days at the dose of 170 μg/100 g body wt per day orally. In the rat, the antagonist potency of A81988 on the vasopressor response to intravenous angiotensin II is greater than that of losartan by a factor of at least 10. A81988 has no affinity for adrenergic, cholinergic, endothelin, or PAF receptors, and it is >1000-fold more selective for AT1- versus AT_2-receptors. In preliminary experiments, A81988 is able to antagonize the vasopressor effect of 10 pmol intravenous angiotensin II by 75%. Tail-cuff BP is measured twice under basal conditions, every 5 days during A81988 administration, and then after discontinuation of the compound.

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

REFERENCES

[1]. Hancock AA, et al. [3H]A-81988, a potent, selective, competitive antagonist radioligand for angiotensin AT1 receptors. Eur J Pharmacol. 1994 Mar 15;267(1):49-54.

[2]. Madeddu P, et al. Angiotensin II type 1 receptor blockade prevents cardiac remodeling in bradykinin B(2) receptor knockout mice. Hypertension. 2000 Jan;35(1 Pt 2):391-6.

[3]. Madeddu P, et al. Circulation. 1997 Nov 18;96(10):3570-8.

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