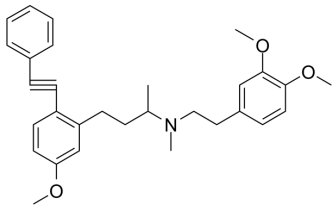
McN5691

Cat. No.:	HY-U00218
CAS No.:	99254-95-2
Molecular Formula:	$C_{30}H_{35}NO_3$
Molecular Weight:	457.6
Target:	Calcium Channel
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	McN5691 is a voltage-sensitive calcium channel blocker.
IC_{50} & Target	Calcium Channel[1]
In Vitro	McN5691 (1 and 10 μM) prevents 60 mM KCl-induced contraction and calcium uptake and causes concentration-dependent relaxation (EC_{50}=190 μM) of 30 mM KCl-contracted aortic rings. At or below 10 μM, McN5691 (McN-5691) has no effects on basal tone or calcium uptake (45Ca) in isolated rings of rabbit thoracic aorta. McN5691 causes complete high affinity inhibition (K_d=39.5 nM) of specific diltiazem binding to the benzothiazepine receptor on the voltage-sensitive calcium channel in skeletal muscle microsomal membranes. In contrast to diltiazem, McN5691 inhibits specific dihydropyridine receptor binding, but the effect is biphasic with high (K_d=4.7 nM) and low (K_d=919.8 nM) affinity components. McN5691 inhibits norepinephrine (NE)-induced contraction (10 μM) and calcium uptake (1 and 10 μM) and causes concentration-dependent relaxation (EC_{50}=159 μM) of 1 μM NE-contracted rings of rabbit thoracic aorta[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The excretion and metabolism of a 2-ethynylbenzenealkanamine analog, antihypertensive McN5691 (RWJ-26240), in beagle dogs is investigated. A total of 96.8% and 2.8% of the radioactive dose are excreted in feces and urine, respectively, during the 7 days after oral administration of ^{14}C-McN5691. Of the radioactive dose, 96.8% and 2.8% is recovered in feces and urine, respectively, in the 7 days after oral administration of ^{14}C-McN5691. More than 87% of the dose is excreted in feces during the 48 hours. McN5691 is extensively metabolized in dogs. Unchanged McN5691 is found in less than 0.1% and 19% of the dose in the 0-24 hour urine and 0-48 hour fecal extract, respectively, and 36% of the sample in the 4 hour plasma[2]. In the McN5691 (McN-5691) study, vascular resistances tend to be higher in spontaneously hypertensive rat (SHR) than in Wistar-Kyoto (WKY) but the differences are statistically significant only in the cerebellum and the midbrain[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2][3]	Dogs[2] ^{14}C- McN5691 is administered by gavage to male and female beagle dogs (3 of each sex, weight 10.2-12.8 kg) as a single 6 mg/kg (as free base in corn oil) dose. Plasma samples are obtained for 24 hours after dosing. Urine and fecal samples are collected over a 7-day period. Each collected sample is assayed for total radioactivity and analyzed by TLC and HPLC. Rats[3]

Studies are conducted in male SHR and control normotensive Wistar-Kyoto (WKY) rats. All animals are housed in constant temperature and environment facilities and given standard lab chow and water ad libitum. Four separate studies are conducted using conscious, age-matched animals:(a) SHR receiving McN5691 as a hydrochloride salt (McN5691) (n=8, body weight=361±7 g); (b) SHR receiving vehicle (VH) (n= 8, bodyweight=381±5g); (c) WKY receiving McN5691(n=9, body weight=355±7 g); and (d) WKY receiving VH (n=6, body weight=342±7g). McN5691 or VH alone is administered i.v. (right jugular vein) as a 15 min continuous infusion for each dose. Each animal receives three doses of McN5691 (0.3, 1.0 and 3.0 mg/kg) in a cumulative fashion or VH infused at an equal rate (0.0408 mL/min).

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

REFERENCES

[1]. Flaim SF, et al. Structurally novel antihypertensive compound, McN-5691, is a calcium channel blocker in vascular smooth muscle. J Pharmacol Exp Ther. 1991 Jan;256(1):279-88.

[2]. Wu WN, et al. Excretion and metabolism of the antihypertensive agent, RWJ-26240 (McN-5691) in dogs. Drug Metab Dispos. 1998 Feb;26(2):115-25.

[3]. Flaim SF, et al. Effects of the novel calcium channel blocker, McN-5691, on cardiocirculatory dynamics and cardiac output distribution in conscious spontaneously hypertensive rat. J Cardiovasc Pharmacol. 1988 Apr;11(4):489-500.

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