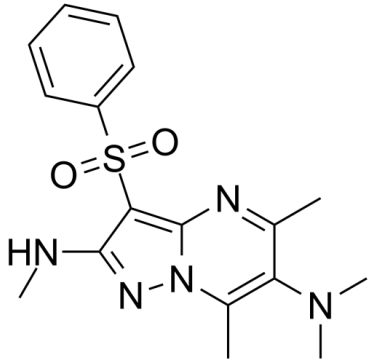
Data Sheet

Product Name:	AVN-492
Cat. No.:	CS-7581
CAS No.:	1220646-23-0
Molecular Formula:	C17H21N5O2S
Molecular Weight:	359.45
Target:	5-HT Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : ≥ 100 mg/mL (278.20 mM)



BIOLOGICAL ACTIVITY:

AVN-492 is a very specific and highly-selective antagonist with picomolar affinity to **5-HT6R** (K_i=91 pM). IC50 & Target: Ki: 91 pM (5-HT6R)[1] **In Vitro:** The affinity of AVN-492 to bind to 5-HT6R (K_i=91 pM) is more than three orders of magnitude higher than that to bind to the only other target, 5-HT2BR, (K_i=170 nM). Thus, AVN-492 displays great 5-HT6R selectivity against all other serotonin receptor subtypes, and is extremely specific against any other receptors such as adrenergic, GABAergic, dopaminergic, histaminergic, etc[1]. **In Vivo:** In rats, the plasma, brain, and CSF concentrations of the PO administered AVN-492 are dose-dependent. The drug concentration curves for the plasma and brain are of hyperbolic shape and at all doses the brain-plasma ratio is near 11%. The drug concentration in CSF, however, is nearly linearly dependent on the dose, reaching 50% of the plasma level at 10mg/kg. In mice, the plasma and brain concentrations of AVN-492, given IV at a dose of 2 mg/kg, decreased with time but at both time points, 15 min and 60 min, the brain/plasma ratio (mean±SEM) is nearly the same, at 13.2±0.7% and 9.0±1.5%, respectively. This indicates that the steady-state concentration gradient of AVN-492 is established by at least 15 min after the drug administration[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]AVN-492 is dissolved into 100% DMSO to a concentration of 10mM. This DMSO solution is then diluted 50-fold with either anMQ water or a buffer with corresponding pH[1].

The Caco-2 permeability assay is performed using the MultiScreen 96-well plates. In short, the Caco-2 cells (ATCC, Cat. No HTB-37) are seeded into each well with a porous membrane bottom. The cells are grown for 20-23 days at 37°C in CO_2 thermostat until total confluence. The growth medium is changed every 2-3 days. The physical integrity of the cell monolayer established on the well porous membrane is tested using a “leak test” with Lucifer Yellow CH. Permeability ofAVN-492 (200μM) is determined in both directions, the apical-to-basal and basal-to-apical. Permeabilities of comparison compounds Ranitidine (lowpermeability) and Propranolol (high permeability) are measured in apical-to-basal direction only. The Pgp-dependent permeability of Rhodamine 123 (30 μM) is determined with or without the Pgp inhibitor Verapamil (100 μM). To assess participation of the Pgp pump in a possible efflux of AVN-492, the apical-to-basal and basalto-apical permeabilities are also registered in the presence of Verapamil. Concentrations of AVN-322 in donor and acceptor chambers are determined using LC/MS/MS API2000. The apparent permeability is calculated[1].

Animal Administration: [1]Mice and Rat[1]

For pharmacokinetic, behavior, and toxicity studies, male Wistar rats (220-242 g), male CD1 mice (24-30 g), male SHK mice (20-25 g), and male Balb/C mice (15-20 g) are used. The pharmacokinetic profiling of AVN-492 is performed on male CD-1 mice and male Wistar rats. Each dose-route group of rodents consist of 3 animals. AVN-492 is administered either intravenously (IV) or orally (PO). At different time points after the drug administration, the animals are quickly euthanized by placing them into CO_2 chamber. Blood samples are drawn through a cardiopuncture. In separate experiments, AVN-492 is orally administered to male Wistar rats at doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg (3 independent groups, 3 animals per group). The animals are anesthetized 60 min later with 5% halothane, positioned in a stereotaxic frame, and samples of cerebrospinal fluid (CSF) are taken through 23G needle from the cisterna

magna. CSF samples are checked for the absence of blood contamination. After the CSF samples are taken, the blood samples are drawn through a cardiopuncture and the brains are removed, washed immediately with ice-cold saline, and homogenized in a 1:4 brain tissue/water mixture. AVN-492 is extracted from all the samples with acetonitrile and concentrations are determined using LC/MS/MS API2000.

References:

[1]. Ivachtchenko AV, et al. AVN-492, A Novel Highly Selective 5-HT6R Antagonist: Preclinical Evaluation. J Alzheimers Dis. 2017;58(4):1043-1063.

CAIndexNames:

Pyrazolo[1,5-a]pyrimidine-2,6-diamine, N2,N6,N6,5,7-pentamethyl-3-(phenylsulfonyl)-

SMILES:

O=S(C1=CC=CC=C1)(C2=C3N(C(C)=C(N(C)C)C(C)=N3)N=C2NC)=O

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