Pimavanserin

Cat. No.: HY-14557

CAS No.: 706779-91-1

Molecular Formula: $C_{25}H_{34}FN_3O_2$

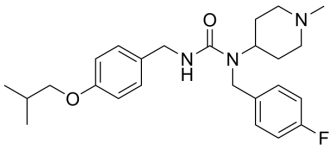
Molecular Weight: 427.55

Target: 5-HT Receptor

Pathway: GPCR/G Protein; Neuronal Signaling

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 : 50 mg/mL (116.95 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3389 mL	11.6945 mL	23.3891 mL
	5 mM	0.4678 mL	2.3389 mL	4.6778 mL
	10 mM	0.2339 mL	1.1695 mL	2.3389 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.85 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pimavanserin is a selective inverse agonist of the 5-HT2A receptor with pIC_{50} and pK_d of 8.73 and 9.3, respectively.

IC_{50} & Target

$5\text{-}HT_{2A}$ Receptor
8.7 (pIC_{50})

In Vitro

Pimavanserin (ACP-103) competitively antagonizes the binding of [^{3}H]ketanserin to heterologously expressed human $5\text{-}HT_{2A}$ receptors with a mean pK_i of 9.3 in membranes and 9.70 in whole cells. Pimavanserin demonstrates lesser affinity (mean pK_i

	of 8.80 in membranes and 8.00 in whole cells, as determined by radioligand binding) and potency as an inverse agonist (mean pIC_{50} 7.1 in R-SAT) at human 5-HT_{2C} receptors, and lacked affinity and functional activity at 5-HT_{2B} receptors, dopamine D_2 receptors, and other human monoaminergic receptors[1]. Pimavanserin (ACP-103) is highly selective for 5-HT_{2A} receptors, lacking affinity for other receptors in a broad profile screen including 65 different molecular targets; the only other receptor for which Pimavanserin demonstrates affinity is 5-HT_{2C}, and Pimavanserin is approximately 30-fold selective for 5-HT_{2A} receptors over 5-HT_{2C} receptors depending on the assay[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Pimavanserin (ACP-103) is a potent, efficacious, orally active 5-HT_{2A} receptor inverse agonist with a behavioral pharmacological profile consistent with utility as an antipsychotic agent. Pimavanserin attenuates head-twitch behavior (3 mg/kg p.o.), and prepulse inhibition deficits (1-10 mg/kg s.c.) induced by the 5-HT_{2A} receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride in rats and reduces the hyperactivity induced in mice by the N-methyl-D-aspartate receptor noncompetitive antagonist 5H-dibenzo[a,d]cyclohepten-5,10-imine (dizocilpine maleate; MK-801) (0.1 and 0.3 mg/kg s.c.; 3 mg/kg p.o.), consistent with a 5-HT_{2A} receptor mechanism of action in vivo and antipsychotic-like efficacy. Pimavanserin demonstrates >42.6% oral bioavailability in rats[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	For the membrane binding, NIH-3T3 cells are grown to 70% confluence in 15 cm^2 dishes and transfected with 10 μg of receptor plasmid DNA using Polyfect transfection reagent. Two days after transfection, cells expressing the desired serotonin receptor are homogenized in 20 mM HEPES/10 mM EDTA and spun down at 11,000g at 4°C for 30 min. The supernatant is discarded, and the pellet is resuspended in 20 mM HEPES/1 mM EDTA and spun down at the same setting. The pellet is then resuspended in 20 mM HEPES/0.5 mM EDTA, and membranes are used for binding assays. Bradford analysis is used to determine total membrane protein. K_d and B_{max} values are derived from 12-point concentration experiments using 1 nM [^{3}H]ketanserin for the 5-HT_{2A} receptor and 3 nM [^{3}H]mesulergine for the 5-HT_{2B} and 5-HT_{2C} receptors. Membranes are incubated at room temperature for 3 h with various concentrations of test ligand in the presence of a fixed concentration of radioligand. The suspension is filtered as explained below for whole-cell binding, washed with ice-cold buffer, and dried, and radioactivity is determined using TopCount[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	For the whole-cell binding, 6 million human embryonic kidney 293T cells are plated in 10-cm dishes and transfected with 5 μg of plasmid DNA using Polyfect. Two days after transfection, cells are harvested with 10 mM EDTA, washed, and resuspended in binding buffer (1× DMEM with 0.1% bovine serum albumin). Then, 60,000 cells transfected with the 5-HT_{2A} receptor or 20,000 cells transfected with the 5-HT_{2C}-INI receptor are incubated at 37°C for 3 h in the presence of 5 nM radioligand ([^{3}H]ketanserin for 5-HT_{2A} receptors and [^{3}H]mesulergine for 5-HT_{2C}-INI receptors) and varying concentrations of ligands (total volume 100 μL in a 96-well plate). Cells are filtered onto a 96-well GF/B filter plate and washed with 300 mL of wash buffer (25 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.25 M NaCl) using a Filtermate 196 harvester. The filter plates are dried under a heat lamp before addition of 50 μL of scintillation fluid to each well. Plates are counted on a TopCount. Separately, the hydrochloride salt form of Pimavanserin (10 μM) is evaluated at MDS Pharma Services for activity in a broad screen of radioligand binding assays at 65 different receptors[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Non-Swiss albino mice are used for locomotor activity experiments. For determination of spontaneous activity, Pimavanserin is administered alone (s.c. 60 min before session start or p.o. 60 min before session start). For hyperactivity experiments, mice are treated with 0.3 mg/kg MK-801 (i.p.) 15 min presession (the peak dose for producing hyperactivity in an inverted-U dose-effect curve as determined in pilot experiments) in combination with vehicle or Pimavanserin. Motor activity data are collected during a 15-min session in a lit room. Mice had no prior exposure to the motor cages. Immediately before placing the mice in the locomotor chambers, effects on myorelaxation/ataxia are determined by placing each of the mouse's forepaws in contact with a horizontal wire while holding the mouse by the base of the tail. Mice are required to bring at least one hindpaw in contact with the wire within 10 s to be scored as a “pass” and failure to do so is considered

ataxic. Each dose or dose combination is tested in a separate group of mice (n=8).

Rats[1]

For DOI head-twitch experiments in rats, vehicle or a dose of Pimavanserin is administered orally 120 min before DOI administration. DOI HCl (2.5 mg/kg i.p.) is administered immediately before observations. After injection of DOI, each rat is placed into an empty cage and observed. Latency to the first head twitch and the number of head twitches occurring over 5 min are recorded. Each rat is used only once with eight to 16 rats per dose group.

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

CUSTOMER VALIDATION

- Nat Commun. 2023 Dec 15;14(1):8221.
- Proc Natl Acad Sci U S A. 2020 Oct 20;117(42):26438-26447.
- J Med Chem. 2023 Jun 28.
- ACS Chem Neurosci. 2019 Nov 20;10(11):4476-4491.
- Int J Neuropsychopharmacol. 2021 Jul 6;pyab040.

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REFERENCES

[1]. Vanover KE, et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. J Pharmacol Exp Ther. 2006 May;317(2):910-8.

[2]. Vanover KE, et al. A 5-HT2A receptor inverse agonist, ACP-103, reduces tremor in a rat model and levodopa-induced dyskinesias in a monkey model. Pharmacol Biochem Behav. 2008 Oct;90(4):540-4.

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