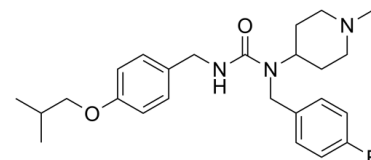


Data Sheet

Product Name:	Pimavanserin
Cat. No.:	CS-3378
CAS No.:	706779-91-1
Molecular Formula:	C ₂₅ H ₃₄ N ₃ O ₂
Molecular Weight:	427.55
Target:	5-HT Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : 50 mg/mL (116.95 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Pimavanserin is a selective inverse agonist of the **5-HT_{2A}** receptor with **pIC₅₀** and **pK_d** of 8.73 and 9.3, respectively. IC₅₀ & Target: pIC₅₀: 8.7 (5-HT_{2A})^[1] **In Vitro:** Pimavanserin (ACP-103) competitively antagonizes the binding of [³H]ketanserin to heterologously expressed human 5-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 pIC₅₀ 7.1 in R-SAT) at human 5-HT_{2C} receptors, and lacked affinity and functional activity at 5-HT_{2B} receptors, dopamine D₂ 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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: ^[1]For the membrane binding, NIH-3T3 cells are grown to 70% confluence in 15 cm² 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 [³H]ketanserin for the 5-HT_{2A} receptor and 3 nM [³H]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]. **Cell Assay:** Pimavanserin (ACP-103) is dissolved in DMSO and stored, and then diluted with appropriate media before use^[1].^[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 ([³H]ketanserin for 5-HT_{2A} receptors and [³H]mesulergine for 5-HT_{2C} receptors).

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 CaCl₂, 5 mM MgCl₂, 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]. **Animal Administration:** Pimavanserin (ACP-103) is dissolved in 0.9% saline (Mice and Rats)^[1].^[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 pre-session (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.

References:

- [1]. Vanover KE, et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropoxy)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-HT_{2A} 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.

CAIndexNames:

Urea, N-[(4-fluorophenyl)methyl]-N-(1-methyl-4-piperidinyl)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-

SMILES:

CC(C)COC1=CC=C(CNC(N(CC2=CC=C(F)C=C2)C3CCN(C)CC3)=O)C=C1

Caution: Product has not been fully validated for medical applications. For research use only.

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