

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pimavanserin

*The first FDA-approved drug for
Parkinson disease psychosis; a selective 5-
HT2A inverse agonist with no dopamine
receptor activity.*

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RESEARCH USE ONLY

ABSTRACT

Pimavanserin (1-[(4-fluorophenyl)methyl]-1-[(1-methyl-4-piperidiny)methyl]-3-{4-[(2-methylpropoxy)]phenyl}urea; CAS 706779-91-1; molecular formula C₂₅H₃₄FN₃O₂; molecular weight 427.56) is a selective 5-HT_{2A} inverse agonist developed at ACADIA and approved by the FDA in 2016 under the trade name Nuplazid. Distinct among antipsychotics by absence of dopamine receptor activity: D₂ affinity is greater than 1000 nM, with no clinically relevant binding. Selectivity is for 5-HT_{2A} (K_i approximately 0.087 nM) over 5-HT_{2C} (K_i approximately 0.4 nM, approximately 5-fold selective). The compound is a high-efficacy inverse agonist (not merely an antagonist), reducing constitutive 5-HT_{2A} signaling below baseline. The dopaminergically clean profile is uniquely suited to Parkinson disease psychosis, where conventional antipsychotics' D₂ antagonism worsens motor symptoms; pimavanserin treats hallucinations and delusions without aggravating bradykinesia or rigidity. Plasma half-life is 57 hours for parent compound, 200 hours for active metabolite. Metabolism is via CYP3A4 and CYP3A5. The compound carries an FDA black-box warning for increased mortality in elderly dementia patients (a class warning for all antipsychotics). Used as the reference selective 5-HT_{2A} inverse agonist.

1. Compound Identification

Pimavanserin is described as selective 5-HT_{2A} inverse agonist. The first FDA-approved drug for Parkinson disease psychosis; a selective 5-HT_{2A} inverse agonist with no dopamine receptor activity.

1.1 Class summary

Selective 5-HT_{2A} inverse agonist

1.2 Subtitle

The first FDA-approved drug for Parkinson disease psychosis; a selective 5-HT_{2A} inverse agonist with no dopamine receptor activity.

2. Abstract

Pimavanserin (1-[(4-fluorophenyl)methyl]-1-[(1-methyl-4-piperidinyl)methyl]-3-{4-[(2-methylpropoxy)]phenyl}urea; CAS 706779-91-1; molecular formula C₂₅H₃₄FN₃O₂; molecular weight 427.56) is a selective 5-HT_{2A} inverse agonist developed at ACADIA and approved by the FDA in 2016 under the trade name Nuplazid. Distinct among antipsychotics by absence of dopamine receptor activity: D₂ affinity is greater than 1000 nM, with no clinically relevant binding. Selectivity is for 5-HT_{2A} (K_i approximately 0.087 nM) over 5-HT_{2C} (K_i approximately 0.4 nM, approximately 5-fold selective). The compound is a high-efficacy inverse agonist (not merely an antagonist), reducing constitutive 5-HT_{2A} signaling below baseline. The dopaminergically clean profile is uniquely suited to Parkinson disease psychosis, where conventional antipsychotics' D₂ antagonism worsens motor symptoms; pimavanserin treats hallucinations and delusions without aggravating bradykinesia or rigidity. Plasma half-life is 57 hours for parent compound, 200 hours for active metabolite. Metabolism is via CYP3A4 and CYP3A5. The compound carries an FDA black-box warning for increased mortality in elderly dementia patients (a class warning for all antipsychotics). Used as the reference selective 5-HT_{2A} inverse agonist.

3. Mechanism of Action

Selective 5-HT_{2A} inverse agonist (no dopamine receptor activity). Approximately 5-fold selectivity over 5-HT_{2C}. High-efficacy inverse agonism rather than simple antagonism.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Clinical 17 to 34 mg per oral administration daily. Rodent studies 0.1 to 3 mg/kg/day.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. 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 as a novel 5-hydroxytryptamine(2A) receptor inverse agonist. J Pharmacol Exp Ther 2006.
2. Cummings J, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014.
3. Stahl SM. Mechanism of action of pimavanserin in Parkinson's disease psychosis. CNS Spectr 2016.

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