

RESEARCH MONOGRAPH . COMPOUND PROFILE

Paroxetine

A piperidine SSRI with the highest SERT affinity in the class and clinically significant muscarinic antagonism.

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ABSTRACT

Paroxetine ((3S,4R)-3-[(2H-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine; CAS 61869-08-7; molecular formula C₁₉H₂₀FNO₃; molecular weight 329.36) is a phenylpiperidine SSRI developed at Ferrosan and licensed to SmithKline Beecham (now GSK), approved by the FDA in 1992 under the trade name Paxil. SERT affinity is the highest of any SSRI (K_i approximately 0.13 nM); off-target activity at muscarinic acetylcholine receptors (K_i approximately 100 nM) produces sedation and dry mouth at clinical doses, and weak NET inhibition contributes to noradrenergic effects at higher doses. Plasma half-life is approximately 21 hours with significant interpatient variability driven by CYP2D6 polymorphism (paroxetine is both a substrate and a potent inhibitor of CYP2D6, producing nonlinear pharmacokinetics at high doses). The compound exhibits the most pronounced discontinuation syndrome of the SSRI class, attributed to the relatively short half-life and muscarinic rebound on cessation. Used as a high-affinity SERT reference compound in receptor binding assays and as a comparator in OCD and anxiety disorder research.

1. Compound Identification

Paroxetine is described as selective serotonin reuptake inhibitor. A piperidine SSRI with the highest SERT affinity in the class and clinically significant muscarinic antagonism.

1.1 Class summary

Selective serotonin reuptake inhibitor

1.2 Subtitle

A piperidine SSRI with the highest SERT affinity in the class and clinically significant muscarinic antagonism.

2. Abstract

Paroxetine ((3S,4R)-3-[(2H-1,3-benzodioxol-5-yl)oxy)methyl]-4-(4-fluorophenyl)piperidine; CAS 61869-08-7; molecular formula C₁₉H₂₀FNO₃; molecular weight 329.36) is a phenylpiperidine SSRI developed at Ferrosan and licensed to SmithKline Beecham (now GSK), approved by the FDA in 1992 under the trade name Paxil. SERT affinity is the highest of any SSRI (K_i approximately 0.13 nM); off-target activity at muscarinic acetylcholine receptors (K_i approximately 100 nM) produces sedation and dry mouth at clinical doses, and weak NET inhibition contributes to noradrenergic effects at higher doses. Plasma half-life is approximately 21 hours with significant interpatient variability driven by CYP2D6 polymorphism (paroxetine is both a substrate and a potent inhibitor of CYP2D6, producing nonlinear pharmacokinetics at high doses). The compound exhibits the most pronounced discontinuation syndrome of the SSRI class, attributed to the relatively short half-life and muscarinic rebound on cessation. Used as a high-affinity SERT reference compound in receptor binding assays and as a comparator in OCD and anxiety disorder research.

3. Mechanism of Action

Highest-affinity SERT inhibition in the SSRI class; muscarinic M1-M3 antagonism contributes to anticholinergic profile. Potent CYP2D6 inhibitor with nonlinear PK at high doses.

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 10 to 60 mg per oral administration daily. Rodent studies 1 to 10 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. Bourin M, et al. Paroxetine: a review. CNS Drug Rev 2001.
2. Kaye CM, et al. A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatr Scand Suppl 1989.
3. Tatsumi M, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997.

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