

RESEARCH MONOGRAPH . COMPOUND PROFILE

Fluoxetine

The first widely prescribed SSRI; a long-acting serotonergic antidepressant and a foundational reference compound for serotonin pharmacology.

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COMPOUND CLASS	Selective serotonin reuptake inhibitor

ABSTRACT

Fluoxetine ((R/S)-N-methyl-3-phenyl-3-[(alpha,alpha,alpha-trifluoro-p-tolyl)oxy]propylamine; CAS 54910-89-3; molecular formula C₁₇H₁₈F₃NO; molecular weight 309.33) is a phenoxyphenylpropylamine SSRI synthesized at Eli Lilly in 1972 and approved by the FDA in 1987 as the first commercial SSRI under the trade name Prozac. The compound exhibits high affinity for the serotonin transporter (SERT, K_i approximately 1 nM) with comparatively weak activity at the norepinephrine transporter (K_i approximately 240 nM) and the dopamine transporter. Notable for an extraordinarily long elimination half-life (1 to 3 days for the parent compound, 7 to 15 days for the active norfluoxetine metabolite) which renders steady-state achievement slow but mitigates discontinuation syndrome. Pharmacologically distinguished from later SSRIs by 5-HT_{2C} antagonism that contributes to noradrenergic and dopaminergic disinhibition in the prefrontal cortex, partially explaining the activating subjective profile. Hepatic metabolism is via CYP2D6 (primary) and CYP3A4 (secondary); the compound is itself a potent CYP2D6 inhibitor, producing clinically significant interactions with TCAs, antipsychotics, and beta-blockers. Used widely as a reference SSRI in serotonergic mechanism studies, animal models of depression, and as a positive control in receptor binding and reuptake assays.

1. Compound Identification

Fluoxetine is described as selective serotonin reuptake inhibitor. The first widely prescribed SSRI; a long-acting serotonergic antidepressant and a foundational reference compound for serotonin pharmacology.

1.1 Class summary

Selective serotonin reuptake inhibitor

1.2 Subtitle

The first widely prescribed SSRI; a long-acting serotonergic antidepressant and a foundational reference compound for serotonin pharmacology.

2. Abstract

Fluoxetine ((R/S)-N-methyl-3-phenyl-3-[(alpha,alpha,alpha-trifluoro-p-tolyl)oxy]propylamine; CAS 54910-89-3; molecular formula C₁₇H₁₈F₃NO; molecular weight 309.33) is a phenoxyphenylpropylamine SSRI synthesized at Eli Lilly in 1972 and approved by the FDA in 1987 as the first commercial SSRI under the trade name Prozac. The compound exhibits high affinity for the serotonin transporter (SERT, K_i approximately 1 nM) with comparatively weak activity at the norepinephrine transporter (K_i approximately 240 nM) and the dopamine transporter. Notable for an extraordinarily long elimination half-life (1 to 3 days for the parent compound, 7 to 15 days for the active norfluoxetine metabolite) which renders steady-state achievement slow but mitigates discontinuation syndrome. Pharmacologically distinguished from later SSRIs by 5-HT_{2C} antagonism that contributes to noradrenergic and dopaminergic disinhibition in the prefrontal cortex, partially explaining the activating subjective profile. Hepatic metabolism is via CYP2D6 (primary) and CYP3A4 (secondary); the compound is itself a potent CYP2D6 inhibitor, producing clinically significant interactions with TCAs, antipsychotics, and beta-blockers. Used widely as a reference SSRI in serotonergic mechanism studies, animal models of depression, and as a positive control in receptor binding and reuptake assays.

3. Mechanism of Action

High-affinity SERT inhibition; secondary 5-HT_{2C} antagonism; weak NRI activity. Active metabolite norfluoxetine drives steady-state effect. Potent CYP2D6 inhibitor.

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 20 to 80 mg per oral administration daily. Rodent studies typically 5 to 20 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. Wong DT, et al. A selective inhibitor of serotonin uptake: Lilly 110140. Life Sci 1974.
2. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther 2000.
3. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. J Affect Disord 1998.
4. Wernicke JF. The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.