

RESEARCH MONOGRAPH . COMPOUND PROFILE

Letrozole

A potent non-steroidal aromatase inhibitor; superior to anastrozole at suppressing plasma estradiol and used in postmenopausal breast cancer and ovulation induction.

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AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Non-steroidal aromatase inhibitor (third generation)

ABSTRACT

Letrozole (4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis(benzonitrile); CAS 112809-51-5; molecular formula C₁₇H₁₁N₅; molecular weight 285.31) is a non-steroidal third-generation aromatase inhibitor developed at Novartis and approved by the FDA in 1997 under the trade name Femara. The compound is a more potent aromatase inhibitor than anastrozole, reducing plasma estradiol by approximately 88 to 99 percent at a 2.5 mg daily dose in postmenopausal women. The greater potency translates to slightly superior progression-free survival in head-to-head trials versus anastrozole in metastatic breast cancer, with similar tolerability. Plasma half-life is approximately 42 hours; metabolism is hepatic via CYP2A6 and CYP3A4. Approved indications include adjuvant and metastatic ER-positive postmenopausal breast cancer; off-label use in PCOS-related anovulatory infertility (often more effective than clomiphene per the PPCOS II trial) and as estrogen control in androgen-using populations. Used as the most potent reference aromatase inhibitor.

1. Compound Identification

Letrozole is described as non-steroidal aromatase inhibitor (third generation). A potent non-steroidal aromatase inhibitor; superior to anastrozole at suppressing plasma estradiol and used in postmenopausal breast cancer and ovulation induction.

1.1 Class summary

Non-steroidal aromatase inhibitor (third generation)

1.2 Subtitle

A potent non-steroidal aromatase inhibitor; superior to anastrozole at suppressing plasma estradiol and used in postmenopausal breast cancer and ovulation induction.

2. Abstract

Letrozole (4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis(benzonitrile); CAS 112809-51-5; molecular formula C₁₇H₁₁N₅; molecular weight 285.31) is a non-steroidal third-generation aromatase inhibitor developed at Novartis and approved by the FDA in 1997 under the trade name Femara. The compound is a more potent aromatase inhibitor than anastrozole, reducing plasma estradiol by approximately 88 to 99 percent at a 2.5 mg daily dose in postmenopausal women. The greater potency translates to slightly superior progression-free survival in head-to-head trials versus anastrozole in metastatic breast cancer, with similar tolerability. Plasma half-life is approximately 42 hours; metabolism is hepatic via CYP2A6 and CYP3A4. Approved indications include adjuvant and metastatic ER-positive postmenopausal breast cancer; off-label use in PCOS-related anovulatory infertility (often more effective than clomiphene per the PPCOS II trial) and as estrogen control in androgen-using populations. Used as the most potent reference aromatase inhibitor.

3. Mechanism of Action

Reversible competitive aromatase (CYP19) inhibition with greater potency than anastrozole. Plasma estradiol suppression 88 to 99 percent.

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 2.5 mg per oral administration daily. Ovulation induction 2.5 to 7.5 mg daily for 5 days. Off-label estrogen control 0.25 to 0.5 mg every other 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. Bhatnagar AS. The discovery and mechanism of action of letrozole. Breast Cancer Res Treat 2007.
2. Mouridsen H, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women. J Clin Oncol 2003.
3. Legro RS, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome (PPCOS II). N Engl J Med 2014.

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.