

RESEARCH MONOGRAPH . COMPOUND PROFILE

Clomiphene

A racemic mixture of enclomiphene (anti-estrogen) and zuclophiphen (estrogen agonist); the prototype ovulation-inducing agent.

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COMPOUND CLASS	Triphenylethylene SERM (mixed isomers)

ABSTRACT

Clomiphene (2-[4-[(E/Z)-2-chloro-1,2-diphenylvinyl]phenoxy]-N,N-diethylethanamine; CAS 911-45-5; molecular formula C₂₆H₂₈ClNO; molecular weight 405.96) is a triphenylethylene SERM developed at Merrell and approved by the FDA in 1967 under the trade name Clomid. The compound is sold as a racemic mixture of approximately 38 percent zuclophene ((Z)-isomer, an ER agonist) and 62 percent enclophene ((E)-isomer, an ER antagonist). The therapeutic effect in ovulation induction is driven primarily by enclophene-mediated antagonism of hypothalamic ER, releasing the negative feedback on GnRH and consequently increasing pituitary FSH and LH; the resulting follicular development drives ovulation. The zuclophene component is approximately 5-fold longer half-life than enclophene (zuclophene t_{1/2} approximately 30 days, enclophene t_{1/2} approximately 30 hours), causing the agonist component to dominate at later cycles and produce some unwanted estrogen-like effects (cervical mucus changes, antiestrogen rebound). Approved for ovulation induction in anovulatory women. Off-label use in male hypogonadism (induces endogenous testosterone via the same FSH/LH route) is common. Used as the canonical triphenylethylene SERM with HPG-stimulating activity.

1. Compound Identification

Clomiphene is described as triphenylethylene serm (mixed isomers). A racemic mixture of enclomiphene (anti-estrogen) and zuclomiphene (estrogen agonist); the prototype ovulation-inducing agent.

1.1 Class summary

Triphenylethylene SERM (mixed isomers)

1.2 Subtitle

A racemic mixture of enclomiphene (anti-estrogen) and zuclomiphene (estrogen agonist); the prototype ovulation-inducing agent.

2. Abstract

Clomiphene (2-[4-[(E/Z)-2-chloro-1,2-diphenylvinyl]phenoxy]-N,N-diethylethanamine; CAS 911-45-5; molecular formula C₂₆H₂₈ClNO; molecular weight 405.96) is a triphenylethylene SERM developed at Merrell and approved by the FDA in 1967 under the trade name Clomid. The compound is sold as a racemic mixture of approximately 38 percent zuclophene ((Z)-isomer, an ER agonist) and 62 percent enclomiphene ((E)-isomer, an ER antagonist). The therapeutic effect in ovulation induction is driven primarily by enclomiphene-mediated antagonism of hypothalamic ER, releasing the negative feedback on GnRH and consequently increasing pituitary FSH and LH; the resulting follicular development drives ovulation. The zuclophene component is approximately 5-fold longer half-life than enclomiphene (zuclophene t_{1/2} approximately 30 days, enclomiphene t_{1/2} approximately 30 hours), causing the agonist component to dominate at later cycles and produce some unwanted estrogen-like effects (cervical mucus changes, antiestrogen rebound). Approved for ovulation induction in anovulatory women. Off-label use in male hypogonadism (induces endogenous testosterone via the same FSH/LH route) is common. Used as the canonical triphenylethylene SERM with HPG-stimulating activity.

3. Mechanism of Action

Racemic SERM (38 percent agonist zuclophene, 62 percent antagonist enclomiphene). Enclomiphene-mediated hypothalamic ER antagonism increases FSH/LH. Zuclophene's long half-life produces residual agonist activity.

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 50 to 100 mg per oral administration daily for 5 days per cycle (ovulation induction); off-label male hypogonadism 25 to 50 mg/day. 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. Mikkelsen TJ, et al. Single-dose pharmacokinetics of clomiphene citrate in normal volunteers. Fertil Steril 1986.
2. Greenblatt RB, et al. Induction of ovulation with MRL/41. JAMA 1961.
3. Shabsigh A, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med 2005.

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