

RESEARCH MONOGRAPH . COMPOUND PROFILE

Clozapine

The prototype atypical antipsychotic; the gold standard for treatment-resistant schizophrenia, limited by agranulocytosis risk requiring weekly blood monitoring.

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ABSTRACT

Clozapine (8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine; CAS 5786-21-0; molecular formula C₁₈H₁₉ClN₄; molecular weight 326.82) is a dibenzodiazepine atypical antipsychotic developed at Wander/Sandoz and approved by the FDA in 1989 under the trade name Clozaril. The compound is the prototype atypical antipsychotic, introducing the receptor profile that defines the class: weak D₂ antagonism (K_i approximately 130 nM) combined with potent 5-HT_{2A} antagonism (K_i approximately 16 nM), producing antipsychotic efficacy without the extrapyramidal symptoms typical of high-affinity D₂ antagonists. Off-target activity is broad: H₁, α₁, muscarinic M₁-M₅ (K_i approximately 7 nM at M₁), 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇ antagonism, contributing to sedation, weight gain, sialorrhea (paradoxical from M₄ partial agonism), and orthostatic hypotension. The defining clinical feature is efficacy in treatment-resistant schizophrenia, where clozapine consistently outperforms other antipsychotics; the limitation is approximately 1 percent agranulocytosis incidence, requiring weekly CBC monitoring through the first 6 months and biweekly thereafter. Plasma half-life is 12 hours; metabolism is via CYP1A2 (primary), CYP3A4, CYP2D6. Used as the canonical atypical antipsychotic in mechanism studies and as the gold standard for treatment-resistant schizophrenia.

1. Compound Identification

Clozapine is described as atypical antipsychotic / d4-d2 multireceptor antagonist. The prototype atypical antipsychotic; the gold standard for treatment-resistant schizophrenia, limited by agranulocytosis risk requiring weekly blood monitoring.

1.1 Class summary

Atypical antipsychotic / D4-D2 multireceptor antagonist

1.2 Subtitle

The prototype atypical antipsychotic; the gold standard for treatment-resistant schizophrenia, limited by agranulocytosis risk requiring weekly blood monitoring.

2. Abstract

Clozapine (8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine; CAS 5786-21-0; molecular formula C₁₈H₁₉ClN₄; molecular weight 326.82) is a dibenzodiazepine atypical antipsychotic developed at Wander/Sandoz and approved by the FDA in 1989 under the trade name Clozaril. The compound is the prototype atypical antipsychotic, introducing the receptor profile that defines the class: weak D₂ antagonism (K_i approximately 130 nM) combined with potent 5-HT_{2A} antagonism (K_i approximately 16 nM), producing antipsychotic efficacy without the extrapyramidal symptoms typical of high-affinity D₂ antagonists. Off-target activity is broad: H₁, α-1, muscarinic M₁-M₅ (K_i approximately 7 nM at M₁), 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇ antagonism, contributing to sedation, weight gain, sialorrhea (paradoxical from M₄ partial agonism), and orthostatic hypotension. The defining clinical feature is efficacy in treatment-resistant schizophrenia, where clozapine consistently outperforms other antipsychotics; the limitation is approximately 1 percent agranulocytosis incidence, requiring weekly CBC monitoring through the first 6 months and biweekly thereafter. Plasma half-life is 12 hours; metabolism is via CYP1A2 (primary), CYP3A4, CYP2D6. Used as the canonical atypical antipsychotic in mechanism studies and as the gold standard for treatment-resistant schizophrenia.

3. Mechanism of Action

Weak D2 antagonism, potent 5-HT_{2A} antagonism, broad off-target activity (H₁, α -1, muscarinic, 5-HT_{2C/3/6/7}). Defines the atypical antipsychotic profile.

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 100 to 900 mg per oral administration daily, slowly titrated. Rodent studies 1 to 30 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. Kane J, et al. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 1988.
2. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999.
3. Lieberman JA. Maximizing clozapine therapy: managing side effects. J Clin Psychiatry 1998.

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