

RESEARCH MONOGRAPH . COMPOUND PROFILE

Olanzapine

A thienobenzodiazepine atypical antipsychotic structurally and mechanistically related to clozapine, without the agranulocytosis risk.

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ABSTRACT

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine; CAS 132539-06-1; molecular formula C₁₇H₂₀N₄S; molecular weight 312.43) is a thienobenzodiazepine atypical antipsychotic developed at Eli Lilly and approved by the FDA in 1996 under the trade name Zyprexa. The receptor profile is closely related to clozapine: D₂ (K_i approximately 11 nM, higher affinity than clozapine), 5-HT_{2A} (K_i approximately 4 nM), H₁ (K_i approximately 0.087 nM, among the most potent in clinical use), α-1, muscarinic, 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇. The structural difference from clozapine eliminates the agranulocytosis liability while preserving the broad-spectrum atypical pharmacology. Plasma half-life is 21 to 54 hours; metabolism is via CYP1A2 and direct glucuronidation. The compound carries the highest metabolic risk profile of any commonly used antipsychotic: dyslipidemia, weight gain (mean 4 to 12 kg over 12 weeks), and incident type 2 diabetes are well-documented, attributed to combined H₁ and 5-HT_{2C} antagonism. Approved for schizophrenia, bipolar I disorder, and treatment-resistant depression in combination with fluoxetine (Symbyax). Used as a reference broad-spectrum atypical antipsychotic.

1. Compound Identification

Olanzapine is described as atypical antipsychotic. A thienobenzodiazepine atypical antipsychotic structurally and mechanistically related to clozapine, without the agranulocytosis risk.

1.1 Class summary

Atypical antipsychotic

1.2 Subtitle

A thienobenzodiazepine atypical antipsychotic structurally and mechanistically related to clozapine, without the agranulocytosis risk.

2. Abstract

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine; CAS 132539-06-1; molecular formula C₁₇H₂₀N₄S; molecular weight 312.43) is a thienobenzodiazepine atypical antipsychotic developed at Eli Lilly and approved by the FDA in 1996 under the trade name Zyprexa. The receptor profile is closely related to clozapine: D₂ (K_i approximately 11 nM, higher affinity than clozapine), 5-HT_{2A} (K_i approximately 4 nM), H₁ (K_i approximately 0.087 nM, among the most potent in clinical use), α-1, muscarinic, 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇. The structural difference from clozapine eliminates the agranulocytosis liability while preserving the broad-spectrum atypical pharmacology. Plasma half-life is 21 to 54 hours; metabolism is via CYP1A2 and direct glucuronidation. The compound carries the highest metabolic risk profile of any commonly used antipsychotic: dyslipidemia, weight gain (mean 4 to 12 kg over 12 weeks), and incident type 2 diabetes are well-documented, attributed to combined H₁ and 5-HT_{2C} antagonism. Approved for schizophrenia, bipolar I disorder, and treatment-resistant depression in combination with fluoxetine (Symbyax). Used as a reference broad-spectrum atypical antipsychotic.

3. Mechanism of Action

Broad multireceptor antagonist (D2, 5-HT_{2A}, H₁, α-1, muscarinic, 5-HT_{2C/3/6/7}). Highest metabolic risk profile in the antipsychotic class.

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 5 to 20 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. Bymaster FP, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996.
2. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects. CNS Drugs 2005.
3. Tollefson GD, et al. Olanzapine versus haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997.

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