

RESEARCH MONOGRAPH . COMPOUND PROFILE

Mirtazapine

A noradrenergic and specific serotonergic antidepressant; a tetracyclic with strong H1 antihistamine activity producing pronounced sedation and appetite stimulation.

DOCUMENT	KDC-MN-210
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COMPOUND CLASS	Tetracyclic atypical antidepressant (NaSSA)

ABSTRACT

Mirtazapine ((R/S)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine; CAS 85650-52-8; molecular formula C₁₇H₁₉N₃; molecular weight 265.36) is a tetracyclic NaSSA (noradrenergic and specific serotonergic antidepressant) developed at Organon and approved by the FDA in 1996 under the trade name Remeron. Mechanism distinguishes the compound from the SSRI/SNRI class: rather than inhibiting transporters, mirtazapine antagonizes presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors, increasing both norepinephrine and serotonin release. Concurrent 5-HT_{2A} and 5-HT_{2C} antagonism redirects the released serotonin preferentially to 5-HT_{1A} receptors. Strong H₁ histamine antagonism (K_i approximately 0.14 nM, comparable to first-generation antihistamines) produces sedation and weight gain, often dose-limiting at higher doses. The compound has minimal activity at muscarinic, dopaminergic, or transporter sites. Plasma half-life is 20 to 40 hours; metabolism is via CYP2D6, CYP3A4, and CYP1A2. Approved for major depressive disorder; widely used off-label for insomnia and as an appetite stimulant. Used as a reference compound in alpha-2 adrenergic and 5-HT₂ receptor pharmacology.

1. Compound Identification

Mirtazapine is described as tetracyclic atypical antidepressant (nassa). A noradrenergic and specific serotonergic antidepressant; a tetracyclic with strong H1 antihistamine activity producing pronounced sedation and appetite stimulation.

1.1 Class summary

Tetracyclic atypical antidepressant (NaSSA)

1.2 Subtitle

A noradrenergic and specific serotonergic antidepressant; a tetracyclic with strong H1 antihistamine activity producing pronounced sedation and appetite stimulation.

2. Abstract

Mirtazapine ((R/S)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine; CAS 85650-52-8; molecular formula C₁₇H₁₉N₃; molecular weight 265.36) is a tetracyclic NaSSA (noradrenergic and specific serotonergic antidepressant) developed at Organon and approved by the FDA in 1996 under the trade name Remeron. Mechanism distinguishes the compound from the SSRI/SNRI class: rather than inhibiting transporters, mirtazapine antagonizes presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors, increasing both norepinephrine and serotonin release. Concurrent 5-HT_{2A} and 5-HT_{2C} antagonism redirects the released serotonin preferentially to 5-HT_{1A} receptors. Strong H₁ histamine antagonism (K_i approximately 0.14 nM, comparable to first-generation antihistamines) produces sedation and weight gain, often dose-limiting at higher doses. The compound has minimal activity at muscarinic, dopaminergic, or transporter sites. Plasma half-life is 20 to 40 hours; metabolism is via CYP2D6, CYP3A4, and CYP1A2. Approved for major depressive disorder; widely used off-label for insomnia and as an appetite stimulant. Used as a reference compound in alpha-2 adrenergic and 5-HT₂ receptor pharmacology.

3. Mechanism of Action

Alpha-2 adrenergic auto/heteroreceptor antagonism increasing 5-HT and NE release; 5-HT_{2A/2C} and H₁ antagonism redirecting serotonin to 5-HT_{1A}. No transporter inhibition.

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 7.5 to 45 mg per oral administration nightly. 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. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996.
2. Anttila SAK, Leinonen EVJ. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev 2001.
3. Croom KF, et al. Mirtazapine: a review of its use in major depression. Drugs 2009.

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.