

RESEARCH MONOGRAPH . COMPOUND PROFILE

Clonidine

An imidazoline alpha-2 adrenergic receptor agonist; an antihypertensive repurposed for ADHD, opioid withdrawal, and Tourette syndrome.

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ABSTRACT

Clonidine (N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine; CAS 4205-90-7; molecular formula C₉H₉Cl₂N₃; molecular weight 230.10) is an imidazoline alpha-2 adrenergic agonist developed at Boehringer Ingelheim in the 1960s and approved by the FDA in 1974 under the trade name Catapres. The compound activates presynaptic alpha-2A adrenergic autoreceptors in the locus coeruleus, reducing central noradrenergic outflow and producing centrally mediated reductions in sympathetic tone, blood pressure, and heart rate. Secondary imidazoline I₁ receptor activity contributes to the antihypertensive effect. Plasma half-life is 12 to 16 hours; renal excretion is the principal clearance pathway. Approved indications include hypertension, ADHD (extended-release Kapvay), opioid withdrawal, and Tourette syndrome; off-label use in insomnia, hot flashes, and PTSD-associated hyperarousal. Rebound hypertension on abrupt discontinuation is a characteristic adverse effect. The compound is widely used in academic neuroscience as the prototype alpha-2 agonist for studies of noradrenergic regulation.

1. Compound Identification

Clonidine is described as central alpha-2 adrenergic agonist. An imidazoline alpha-2 adrenergic receptor agonist; an antihypertensive repurposed for ADHD, opioid withdrawal, and Tourette syndrome.

1.1 Class summary

Central alpha-2 adrenergic agonist

1.2 Subtitle

An imidazoline alpha-2 adrenergic receptor agonist; an antihypertensive repurposed for ADHD, opioid withdrawal, and Tourette syndrome.

2. Abstract

Clonidine (N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine; CAS 4205-90-7; molecular formula C₉H₉Cl₂N₃; molecular weight 230.10) is an imidazoline alpha-2 adrenergic agonist developed at Boehringer Ingelheim in the 1960s and approved by the FDA in 1974 under the trade name Catapres. The compound activates presynaptic alpha-2A adrenergic autoreceptors in the locus coeruleus, reducing central noradrenergic outflow and producing centrally mediated reductions in sympathetic tone, blood pressure, and heart rate. Secondary imidazoline I1 receptor activity contributes to the antihypertensive effect. Plasma half-life is 12 to 16 hours; renal excretion is the principal clearance pathway. Approved indications include hypertension, ADHD (extended-release Kapvay), opioid withdrawal, and Tourette syndrome; off-label use in insomnia, hot flashes, and PTSD-associated hyperarousal. Rebound hypertension on abrupt discontinuation is a characteristic adverse effect. The compound is widely used in academic neuroscience as the prototype alpha-2 agonist for studies of noradrenergic regulation.

3. Mechanism of Action

Central alpha-2A adrenergic agonism; reduces locus coeruleus noradrenergic out-flow. Secondary imidazoline I1 receptor 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 0.1 to 0.6 mg per oral administration daily, in divided doses. Rodent studies 0.01 to 0.5 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. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991.
2. Strange PG. Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. *Pharmacol Rev* 2001.
3. Connor DF, et al. Pharmacological treatment of ADHD: a review of the evidence. *Curr Opin Pediatr* 2008.

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