

RESEARCH MONOGRAPH . COMPOUND PROFILE

Guanfacine

A selective alpha-2A adrenergic agonist; an antihypertensive repurposed as a non-stimulant ADHD treatment with greater alpha-2A selectivity than clonidine.

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COMPOUND CLASS	Selective alpha-2A adrenergic agonist

ABSTRACT

Guanfacine (N-{[2-(2,6-dichlorophenyl)acetyl]amino}guanidine; CAS 29110-47-2; molecular formula C₉H₉Cl₂N₃O; molecular weight 246.10) is a selective alpha-2A adrenergic agonist developed at Sandoz in the 1970s and approved by the FDA in 1986 under the trade name Tenex (immediate release) and 2009 as Intuniv (extended release for ADHD). Distinct from clonidine by greater alpha-2A subtype selectivity (approximately 25-fold over alpha-2B and alpha-2C); the alpha-2A subtype predominates in the prefrontal cortex where it modulates working memory and executive function, supporting the cognitive enhancement seen in ADHD. The CNS-prefrontal cortex effect is more pronounced than the cardiovascular effect at clinical ADHD doses. Plasma half-life is approximately 17 hours, supporting once-daily dosing in the ER formulation. Renal excretion is the principal clearance pathway. Approved for hypertension and (Intuniv) ADHD in children and adolescents. Used as the canonical alpha-2A selective agonist in prefrontal cortex pharmacology and ADHD research.

1. Compound Identification

Guanfacine is described as selective alpha-2a adrenergic agonist. A selective alpha-2A adrenergic agonist; an antihypertensive repurposed as a non-stimulant ADHD treatment with greater alpha-2A selectivity than clonidine.

1.1 Class summary

Selective alpha-2A adrenergic agonist

1.2 Subtitle

A selective alpha-2A adrenergic agonist; an antihypertensive repurposed as a non-stimulant ADHD treatment with greater alpha-2A selectivity than clonidine.

2. Abstract

Guanfacine (N-[[2-(2,6-dichlorophenyl)acetyl]amino}guanidine; CAS 29110-47-2; molecular formula C₉H₉Cl₂N₃O; molecular weight 246.10) is a selective alpha-2A adrenergic agonist developed at Sandoz in the 1970s and approved by the FDA in 1986 under the trade name Tenex (immediate release) and 2009 as Intuniv (extended release for ADHD). Distinct from clonidine by greater alpha-2A subtype selectivity (approximately 25-fold over alpha-2B and alpha-2C); the alpha-2A subtype predominates in the prefrontal cortex where it modulates working memory and executive function, supporting the cognitive enhancement seen in ADHD. The CNS-prefrontal cortex effect is more pronounced than the cardiovascular effect at clinical ADHD doses. Plasma half-life is approximately 17 hours, supporting once-daily dosing in the ER formulation. Renal excretion is the principal clearance pathway. Approved for hypertension and (Intuniv) ADHD in children and adolescents. Used as the canonical alpha-2A selective agonist in prefrontal cortex pharmacology and ADHD research.

3. Mechanism of Action

Selective alpha-2A adrenergic agonism (~25-fold over 2B/2C). Prefrontal cortex effects on working memory and executive function.

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 1 to 4 mg per oral administration daily (ADHD); 1 to 3 mg twice daily (hypertension). Rodent studies 0.05 to 1 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. Arnsten AF. The use of alpha-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Rev Neurother* 2010.
2. Sallee FR, et al. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2009.
3. Wang M, et al. Alpha-2A adrenoceptor stimulation strengthens working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 2007.

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