

RESEARCH MONOGRAPH . COMPOUND PROFILE

Donepezil

A piperidine-class selective reversible acetylcholinesterase inhibitor, FDA-approved as Aricept for Alzheimer disease, with the largest clinical evidence base of the AChE inhibitor class.

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ABSTRACT

Donepezil (Aricept; (R/S)-2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one hydrochloride; CAS 120014-06-4; molecular formula C₂₄H₂₉NO₃; molecular weight 379.49) is a piperidine-class selective reversible acetylcholinesterase inhibitor developed by Eisai and approved by the FDA in 1996 for mild, moderate, and severe Alzheimer disease. The compound has the highest AChE selectivity (over 1000-fold versus butyrylcholinesterase) of the marketed AChE inhibitors and a long plasma half-life (70 hours) that supports once-daily dosing. Mechanism is selective AChE inhibition without significant secondary activities at nicotinic receptors or other targets. The clinical evidence base in Alzheimer disease is extensive; multiple Phase 3 trials demonstrate small but consistent improvements in cognitive endpoint measures (ADAS-cog, MMSE) and global functional status. The compound is also approved for vascular dementia and Parkinson disease dementia in some jurisdictions. Pharmacokinetics: oral bioavailability essentially complete; metabolism is hepatic via CYP2D6 and CYP3A4 with minor active metabolites. Approved doses are 5 to 23 mg per day; the 23 mg formulation was approved in 2010 for severe Alzheimer disease. Schedule status: prescription-only but not federally scheduled.

1. Compound Identification

Donepezil is described as selective acetylcholinesterase inhibitor. A piperidine-class selective reversible acetylcholinesterase inhibitor, FDA-approved as Aricept for Alzheimer disease, with the largest clinical evidence base of the AChE inhibitor class.

1.1 Class summary

Selective acetylcholinesterase inhibitor

1.2 Subtitle

A piperidine-class selective reversible acetylcholinesterase inhibitor, FDA-approved as Aricept for Alzheimer disease, with the largest clinical evidence base of the AChE inhibitor class.

2. Abstract

Donepezil (Aricept; (R/S)-2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one hydrochloride; CAS 120014-06-4; molecular formula C₂₄H₂₉NO₃; molecular weight 379.49) is a piperidine-class selective reversible acetylcholinesterase inhibitor developed by Eisai and approved by the FDA in 1996 for mild, moderate, and severe Alzheimer disease. The compound has the highest AChE selectivity (over 1000-fold versus butyrylcholinesterase) of the marketed AChE inhibitors and a long plasma half-life (70 hours) that supports once-daily dosing. Mechanism is selective AChE inhibition without significant secondary activities at nicotinic receptors or other targets. The clinical evidence base in Alzheimer disease is extensive; multiple Phase 3 trials demonstrate small but consistent improvements in cognitive endpoint measures (ADAS-cog, MMSE) and global functional status. The compound is also approved for vascular dementia and Parkinson disease dementia in some jurisdictions. Pharmacokinetics: oral bioavailability essentially complete; metabolism is hepatic via CYP2D6 and CYP3A4 with minor active metabolites. Approved doses are 5 to 23 mg per day; the 23 mg formulation was approved in 2010 for severe Alzheimer disease. Schedule status: prescription-only but not federally scheduled.

3. Mechanism of Action

Selective reversible AChE inhibitor with >1000-fold selectivity over BChE. No significant nAChR or NMDA 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

5 to 23 mg once daily (clinical use).

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. Sugimoto H, et al. Donepezil hydrochloride: a review of its use in Alzheimer's disease. Drugs Aging 2003.
2. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2018.

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