

RESEARCH MONOGRAPH . COMPOUND PROFILE

Aripiprazole

A piperazinyl-quinolinone partial agonist at D2 and 5-HT1A receptors; the prototype third-generation antipsychotic.

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AUTHOR	Kodi ac bio l abs Research
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ABSTRACT

Aripiprazole (7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1H)-one; CAS 129722-12-9; molecular formula C₂₃H₂₇Cl₂N₃O₂; molecular weight 448.39) is a piperazinyl-quinolinone D₂ partial agonist developed at Otsuka and approved by the FDA in 2002 under the trade name Abilify. Distinct from earlier antipsychotics by partial agonism: D₂ affinity is high (K_i approximately 0.34 nM) but intrinsic activity is approximately 30 percent, producing antagonism in regions of high dopaminergic tone (mesolimbic, treating psychosis) and agonism in regions of low tone (mesocortical, mitigating negative symptoms; nigrostriatal, reducing extrapyramidal effects). Additional 5-HT_{1A} partial agonism (K_i approximately 1.7 nM, intrinsic activity approximately 70 percent) and 5-HT_{2A} antagonism complete the profile. The metabolic risk is intermediate (lower than olanzapine or clozapine). Plasma half-life is 75 hours; metabolism is via CYP3A4 and CYP2D6. Approved for schizophrenia, bipolar I disorder, MDD adjunctive, autism-associated irritability, and Tourette syndrome. Long-acting injectable formulations (Abilify Maintena, Aristada) provide monthly administration. Used as the reference D₂ partial agonist in mechanism studies.

1. Compound Identification

Aripiprazole is described as d2/d3 partial agonist atypical antipsychotic. A piperazinyl-quinolinone partial agonist at D2 and 5-HT1A receptors; the prototype third-generation antipsychotic.

1.1 Class summary

D2/D3 partial agonist atypical antipsychotic

1.2 Subtitle

A piperazinyl-quinolinone partial agonist at D2 and 5-HT1A receptors; the prototype third-generation antipsychotic.

2. Abstract

Aripiprazole (7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1H)-one; CAS 129722-12-9; molecular formula C₂₃H₂₇Cl₂N₃O₂; molecular weight 448.39) is a piperazinyl-quinolinone D2 partial agonist developed at Otsuka and approved by the FDA in 2002 under the trade name Abilify. Distinct from earlier antipsychotics by partial agonism: D2 affinity is high (K_i approximately 0.34 nM) but intrinsic activity is approximately 30 percent, producing antagonism in regions of high dopaminergic tone (mesolimbic, treating psychosis) and agonism in regions of low tone (mesocortical, mitigating negative symptoms; nigrostriatal, reducing extrapyramidal effects). Additional 5-HT_{1A} partial agonism (K_i approximately 1.7 nM, intrinsic activity approximately 70 percent) and 5-HT_{2A} antagonism complete the profile. The metabolic risk is intermediate (lower than olanzapine or clozapine). Plasma half-life is 75 hours; metabolism is via CYP3A4 and CYP2D6. Approved for schizophrenia, bipolar I disorder, MDD adjunctive, autism-associated irritability, and Tourette syndrome. Long-acting injectable formulations (Abilify Maintena, Aristada) provide monthly administration. Used as the reference D2 partial agonist in mechanism studies.

3. Mechanism of Action

D2 partial agonist (intrinsic activity approximately 30 percent), 5-HT1A partial agonist, 5-HT2A antagonist. Region-dependent dopaminergic effect.

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 2 to 30 mg per oral administration daily. Long-acting injectable 300 to 400 mg monthly. Rodent studies 0.3 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. Burris KD, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002.
2. Tamminga CA. Partial dopamine agonists in the treatment of psychosis. J Neural Transm 2002.
3. Pae CU, et al. Aripiprazole augmentation for major depressive disorder. CNS Drugs 2011.

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