

RESEARCH MONOGRAPH . COMPOUND PROFILE

Brexpiprazole

A second-generation D2 partial agonist refined from aripiprazole; lower D2 intrinsic activity producing reduced akathisia.

DOCUMENT	KDC-MN-237
ISSUED	2026-05-09
REVISION	1.0
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COMPOUND CLASS	D2 partial agonist atypical antipsychotic

ABSTRACT

Brexpiprazole (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one; CAS 913611-97-9; molecular formula C₂₅H₂₇N₃O₂S; molecular weight 433.57) is a D₂ partial agonist developed at Otsuka as a successor to aripiprazole and approved by the FDA in 2015 under the trade name Rexulti. The structural change from aripiprazole replaces the 2,3-dichlorophenyl with a benzothiophen-4-yl, modulating receptor binding kinetics. D₂ affinity (K_i approximately 0.30 nM) is comparable to aripiprazole, but intrinsic activity is lower (approximately 14 percent versus 30 percent), producing reduced akathisia and less D₂ receptor activation in low-dopaminergic-tone regions. 5-HT_{1A} partial agonism (K_i approximately 0.12 nM) and 5-HT_{2A} antagonism are retained. Plasma half-life is 91 hours; metabolism is via CYP3A4 and CYP2D6. Approved for schizophrenia, MDD adjunctive, and (2023) Alzheimer-associated agitation. Used as the reference second-generation D₂ partial agonist with reduced intrinsic activity.

1. Compound Identification

Brexiprazole is described as d2 partial agonist atypical antipsychotic. A second-generation D2 partial agonist refined from aripiprazole; lower D2 intrinsic activity producing reduced akathisia.

1.1 Class summary

D2 partial agonist atypical antipsychotic

1.2 Subtitle

A second-generation D2 partial agonist refined from aripiprazole; lower D2 intrinsic activity producing reduced akathisia.

2. Abstract

Brexiprazole (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one; CAS 913611-97-9; molecular formula C₂₅H₂₇N₃O₂S; molecular weight 433.57) is a D₂ partial agonist developed at Otsuka as a successor to aripiprazole and approved by the FDA in 2015 under the trade name Rexulti. The structural change from aripiprazole replaces the 2,3-dichlorophenyl with a benzothiophen-4-yl, modulating receptor binding kinetics. D₂ affinity (K_i approximately 0.30 nM) is comparable to aripiprazole, but intrinsic activity is lower (approximately 14 percent versus 30 percent), producing reduced akathisia and less D₂ receptor activation in low-dopaminergic-tone regions. 5-HT_{1A} partial agonism (K_i approximately 0.12 nM) and 5-HT_{2A} antagonism are retained. Plasma half-life is 91 hours; metabolism is via CYP3A4 and CYP2D6. Approved for schizophrenia, MDD adjunctive, and (2023) Alzheimer-associated agitation. Used as the reference second-generation D₂ partial agonist with reduced intrinsic activity.

3. Mechanism of Action

D2 partial agonist (lower intrinsic activity ~14 percent versus aripiprazole's ~30 percent). 5-HT1A partial agonist, 5-HT2A antagonist. Reduced akathisia.

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. Rodent studies 0.1 to 3 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. Maeda K, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther 2014.
2. Citrome L. Brexpiprazole for schizophrenia and as adjunct for major depressive disorder. Int J Clin Pract 2015.
3. Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. Ther Adv Psychopharmacol 2017.

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.