

RESEARCH MONOGRAPH . COMPOUND PROFILE

# JZL184

*A covalent inhibitor of monoacylglycerol lipase (MAGL); the canonical research probe for elevating endogenous 2-AG.*

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## ABSTRACT

JZL184 (CAS 1101854-58-3; molecular formula C<sub>27</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>; molecular weight 510.49) is a covalent piperidinyl-carbamate inhibitor of monoacylglycerol lipase (MAGL) developed by Cravatt and colleagues at Scripps. The compound carbamoylates the active-site serine of MAGL, producing irreversible enzyme inactivation. Selective for MAGL over FAAH (approximately 300-fold) and other serine hydrolases. Pharmacological consequence: elevation of endogenous 2-AG (the principal full-agonist endocannabinoid) without direct CB receptor agonism. Behavioral effects are more THC-like than FAAH inhibition (anxiolysis, analgesia, hypothermia, catalepsy at high dose), reflecting the higher tonic CB1 occupancy from elevated 2-AG. Used as the canonical MAGL inhibitor in academic neuroscience for studies of 2-AG signaling and CB1-mediated synaptic plasticity. No human clinical development.

# 1. Compound Identification

JZL184 is described as selective magl inhibitor (research). A covalent inhibitor of monoacylglycerol lipase (MAGL); the canonical research probe for elevating endogenous 2-AG.

## 1.1 Class summary

Selective MAGL inhibitor (research)

## 1.2 Subtitle

A covalent inhibitor of monoacylglycerol lipase (MAGL); the canonical research probe for elevating endogenous 2-AG.

## 2. Abstract

JZL184 (CAS 1101854-58-3; molecular formula C<sub>27</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>; molecular weight 510.49) is a covalent piperidinyl-carbamate inhibitor of monoacylglycerol lipase (MAGL) developed by Cravatt and colleagues at Scripps. The compound carbamoylates the active-site serine of MAGL, producing irreversible enzyme inactivation. Selective for MAGL over FAAH (approximately 300-fold) and other serine hydrolases. Pharmacological consequence: elevation of endogenous 2-AG (the principal full-agonist endocannabinoid) without direct CB receptor agonism. Behavioral effects are more THC-like than FAAH inhibition (anxiolysis, analgesia, hypothermia, catalepsy at high dose), reflecting the higher tonic CB1 occupancy from elevated 2-AG. Used as the canonical MAGL inhibitor in academic neuroscience for studies of 2-AG signaling and CB1-mediated synaptic plasticity. No human clinical development.

### 3. Mechanism of Action

Covalent carbamate MAGL inhibitor; irreversible inactivation. Approximately 300-fold selective for MAGL over FAAH. Elevates endogenous 2-AG.

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

Rodent research 4 to 40 mg/kg intraperitoneal.

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. Long JZ, et al. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat Chem Biol 2009.
2. Long JZ, et al. Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo. Proc Natl Acad Sci 2009.
3. Mulvihill MM, Nomura DK. Therapeutic potential of monoacylglycerol lipase inhibitors. Life Sci 2013.

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