

RESEARCH MONOGRAPH . COMPOUND PROFILE

KML29

A second-generation covalent MAGL inhibitor with improved selectivity over FAAH.

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COMPOUND CLASS	Selective MAGL inhibitor (second-generation)

ABSTRACT

KML29 (CAS 1366507-82-3; molecular formula C₂₇H₂₄F₄N₂O₄; molecular weight 516.49) is a second-generation covalent MAGL inhibitor developed by Cravatt and colleagues. The compound has improved selectivity for MAGL over FAAH (greater than 4000-fold) compared to JZL184 (300-fold), reducing the off-target FAAH inhibition that complicated interpretation of some JZL184 studies. Mechanism is the same as JZL184: irreversible carbamoylation of MAGL's active-site serine. Used in academic research where clean MAGL inhibition without FAAH crossover is required. No human clinical development.

1. Compound Identification

KML29 is described as selective magl inhibitor (second-generation). A second-generation covalent MAGL inhibitor with improved selectivity over FAAH.

1.1 Class summary

Selective MAGL inhibitor (second-generation)

1.2 Subtitle

A second-generation covalent MAGL inhibitor with improved selectivity over FAAH.

2. Abstract

KML29 (CAS 1366507-82-3; molecular formula C₂₇H₂₄F₄N₂O₄; molecular weight 516.49) is a second-generation covalent MAGL inhibitor developed by Cravatt and colleagues. The compound has improved selectivity for MAGL over FAAH (greater than 4000-fold) compared to JZL184 (300-fold), reducing the off-target FAAH inhibition that complicated interpretation of some JZL184 studies. Mechanism is the same as JZL184: irreversible carbamoylation of MAGL's active-site serine. Used in academic research where clean MAGL inhibition without FAAH crossover is required. No human clinical development.

3. Mechanism of Action

Covalent MAGL inhibitor; approximately 4000-fold MAGL/FAAH selectivity. Cleaner research tool than JZL184 for selective 2-AG elevation.

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 5 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. Chang JW, et al. Highly selective inhibitors of monoacylglycerol lipase bearing a reactive group that is bioisosteric with endocannabinoid substrates. Chem Biol 2012.
2. Niphakis MJ, et al. Evaluation of NHS carbamates as a potent and selective class of endocannabinoid hydrolase inhibitors. ACS Chem Neurosci 2013.
3. Mulvihill MM, Nomura DK. Therapeutic potential of monoacylglycerol lipase inhibitors. Life Sci 2013.

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