

RESEARCH MONOGRAPH . COMPOUND PROFILE

AAZ-A-154

A non-hallucinogenic isotryptamine psychoplastogen discovered via engineered 5-HT2A biosensor screening at UC Davis, producing rapid and sustained antidepressant-like effects through serotonin receptor-mediated structural neuroplasticity without psychedelic, dissociative, or psychotomimetic activity.

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ABSTRACT

AAZ-A-154, subsequently designated DLX-001 and assigned the international nonproprietary name zalsupindole, is a substituted isoptryptamine derivative that acts as a low-potency, low-efficacy partial agonist of the serotonin 5-HT_{2A} receptor (EC₅₀ approximately 8,200 nM; E_{max} approximately 17 percent of serotonin maximum) and a moderate-efficacy partial agonist of the 5-HT_{2C} receptor (EC₅₀ approximately 3,300 nM; E_{max} approximately 70 percent), with silent antagonism at the 5-HT_{2B} receptor and selectivity for serotonergic over dopaminergic, adrenergic, and opioid targets. The compound was first synthesized in 2019 in the laboratory of David E. Olson at the University of California, Davis, and was identified from a library screen using psychLight, a genetically encoded fluorescent biosensor constructed from the human 5-HT_{2A} receptor with a circularly permuted green fluorescent protein inserted into the third intracellular loop [1]. PsychLight discriminated hallucinogenic from non-hallucinogenic 5-HT_{2A} ligands on the basis of differential conformational activation signatures, and AAZ-A-154 was selected as a lead compound on the basis of its favorable ligand score, a metric that predicted non-hallucinogenic character despite retention of 5-HT_{2A}-dependent psychoplastogenic activity.

The compound is structurally related to 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) but is an isoptryptamine (the aminoalkyl side chain is attached to the indole nitrogen at position 1 rather than at position 3), a modification that repositions the compound in chemical space outside classical psychedelic

tryptamines. The (R)-enantiomer is the active form; the alpha-methyl substituent on the aminoalkyl chain confers metabolic stability and enantioselective receptor engagement. In rodent models, AAZ-A-154 at doses of 15 to 20 mg/kg intraperitoneally produced rapid-onset (30 minutes) and sustained (7 to 14 days) antidepressant-like behavioral effects in the forced swim test and in the sucrose preference test in VMAT2 heterozygous mice, a genetic model of depressive phenotype [1]. The compound increased dendritic arbor complexity in cultured embryonic rat cortical neurons to a degree comparable to ketamine, and the neuroplastic effect was abolished by the 5-HT₂ receptor antagonist ketanserin, confirming receptor dependence [1]. Critically, AAZ-A-154 failed to produce the head-twitch response in mice at doses up to 100 mg/kg, the standard behavioral proxy for hallucinogenic activity in the 5-HT_{2A} agonist class [1].

A comprehensive preclinical characterization published by Agrawal et al. (2025) in ACS Chemical Neuroscience demonstrated that zalsupindole promoted cortical neuritogenesis in vitro, increased dendritic spine density in the prefrontal cortex in vivo, and enhanced measures of functional plasticity to a degree comparable to or greater than ketamine, psilocybin, and N,N-dimethyltryptamine, despite lacking any of the acute cellular and behavioral characteristics of hallucinogenic or dissociative compounds [2]. Pharmacokinetic studies revealed high brain penetrance, rapid distribution, and rapid clearance. In Phase 1 clinical trials enrolling 106 healthy volunteers, oral zalsupindole was well tolerated across a dose range of 2 to 360 mg, with no reports of psychotomimetic, hallucinogenic, or dissociative effects, and with quantitative electroencephalography demonstrating measurable changes in cortical activity consistent with target engagement [3, 4]. A Phase 1b study in 18 adults with

major depressive disorder reported clinically meaningful reductions in Montgomery-Asberg Depression Rating Scale scores of approximately 12 points (approximately 50 percent improvement) by Day 8, with effects maintained through Day 36, and comparable efficacy between a seven-day once-daily regimen and a two-dose regimen [5]. No serious adverse events were reported across more than 120 individuals studied. Dose-dependent nausea, headache, and dizziness were the principal mild adverse events. In October 2025, the United States Food and Drug Administration cleared the Investigational New Drug application for a Phase 2, multi-site, randomized, double-blind, placebo-controlled trial in major depressive disorder featuring at-home self-administration [5]. This monograph reviews the chemistry, biosensor-guided discovery, receptor pharmacology, neuroplasticity mechanisms, pharmacokinetics, preclinical and clinical evidence, sourcing and handling, stack interactions, adverse-event signal, and a comparative assessment of five psychoplastogen and rapid-acting antidepressant candidates against AAZ-A-154.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Zalsupindole.

Development codes: AAZ-A-154 (Olson laboratory, UC Davis), DLX-001 (Delix Therapeutics), DLX-1. The AAZ-A-154 code is the canonical identifier in the original Dong et al. (2021) Cell publication that introduced the compound [1].

Other systematic names: (R)-5-Methoxy-N,N-dimethyl-alpha-methylisotryptamine; (R)-5-MeO-alpha-methyl-isoDMT; (R)-5-MeO-N,N-dimethyl-isoAMT.

Chemical Abstracts Service registry numbers: 2481740-94-5 (free base); 2930845-89-7 (hydrochloride salt).

PubChem Compound Identifiers: 154694212 (free base); 172652587 (hydrochloride).

ChemSpider ID: 129562407.

International Union of Pure and Applied Chemistry name: (2R)-1-(5-methoxy-1H-indol-1-yl)-N,N-dimethylpropan-2-amine.

1.2 Structural class and chemistry

AAZ-A-154 is a substituted isotryptamine. Classical tryptamines (including N,N-dimethyltryptamine, psilocybin, and 5-MeO-DMT) bear their aminoalkyl side chain at carbon 3 of the indole ring system. In the isotryptamine class, the side chain is attached instead to the indole nitrogen at position 1, producing a fundamentally distinct molecular geometry and pharmacological profile despite retention of the indole pharmacophore. The structural modification repositions the compound outside the classical psychedelic tryptamine series and is a principal determinant of the non-hallucinogenic character [1].

Molecular formula: C₁₄H₂₀N₂O (free base); C₁₄H₂₁ClN₂O (hydrochloride salt).

Molecular weight: 232.33 g/mol (free base); 268.79 g/mol (hydrochloride salt).

Structural features: The compound incorporates a 5-methoxyindole core (shared with the psychedelic tryptamine 5-MeO-DMT), an N,N-dimethylaminoalkyl side chain attached at the indole nitrogen, and an alpha-methyl substituent on the propylamine chain that confers chirality and metabolic resistance to monoamine oxidase degradation.

Stereochemistry: AAZ-A-154 contains one stereocenter at the alpha-carbon of the aminoalkyl chain and is supplied as the single (R)-enantiomer. The (R)-configuration is the pharmacologically active form and the material advanced into clinical development. Investigators acquiring research-grade material should confirm enantiomeric purity by chiral high-performance liquid chromatography.

Physical properties: The free base is a solid at room temperature. The hydrochloride and fumarate salts have been used in preclinical and clinical formulations respectively. The compound is orally bioavailable in animal and human studies.

1.3 Synthesis

The published synthesis of AAZ-A-154 proceeds by nucleophilic aromatic substitution of 5-methoxyindole with (R)-1-chloro-N,N-dimethylpropan-2-amine, yielding the isotryptamine scaffold in a single coupling step [1]. The reaction exploits the nucleophilicity of the indole nitrogen under basic conditions to effect N-alkylation rather than C3-alkylation, producing the isotryptamine regiochemistry. Purification is by column chromatography or recrystallization. Salt forms (fumarate, hydrochloride, mesylate) have been prepared for formulation purposes. The synthesis is short (one to two steps from commercial starting materials), the key reagents are commercially available, and the procedure is amenable to scale-up. Enantiomeric integrity is preserved from the chiral starting amine; the compound is generally obtained in high enantiomeric excess (greater than 98 percent) from enantiopure commercial (R)-1-chloro-N,N-dimethylpropan-2-amine.

2. Abstract

AAZ-A-154 (zalsupindole, DLX-001) is a non-hallucinogenic psychoplastogen of the isoptryptamine class, identified through psychLight biosensor-guided screening and advanced into clinical development by Delix Therapeutics for major depressive disorder and other central nervous system conditions [1, 2]. The compound is defined pharmacologically by three properties that distinguish it from classical psychedelic tryptamines: low-efficacy partial agonism at the 5-HT_{2A} receptor (E_{max} approximately 17 percent), sufficient to activate neuroplasticity signaling cascades but insufficient to produce the sustained, high-efficacy receptor activation associated with hallucinogenic effects; absence of 5-HT_{2B} agonism, a favorable feature for cardiovascular safety; and preservation of rapid and sustained structural neuroplasticity in cortical neurons comparable in magnitude to ketamine, psilocybin, and DMT [1, 2].

The pharmacological concept underlying AAZ-A-154 is the separation of psychoplastogenic activity from hallucinogenic activity within the 5-HT_{2A} receptor agonist class. Classical psychedelic tryptamines (psilocin, DMT, 5-MeO-DMT) produce both neuroplasticity and hallucinations through 5-HT_{2A} receptor activation. The Olson laboratory demonstrated with the psychLight biosensor that these two functional outputs could be dissociated on the basis of ligand-specific conformational signatures at the receptor, and that AAZ-A-154 activated the receptor in a conformation associated with neuroplasticity but not with the downstream signaling cascades (including immediate early gene activation and cortical glutamate release) associated with hallucinogenic effects [1, 6].

Preclinical pharmacology in rodent models demonstrated antidepressant-like efficacy comparable to ketamine in the forced swim test and in the sucrose preference test, with a single administration producing behavioral effects that persisted for 7 to 14 days [1, 2]. In vivo neuroplasticity studies in rats demonstrated increased dendritic spine density in prefrontal cortex comparable to or greater than ketamine and psilocybin [2]. Pharmacokinetic characterization revealed high brain penetrance, rapid central nervous system distribution, and rapid clearance [2].

Clinical development has advanced through Phase 1a (106 healthy volunteers, oral doses 2 to 360 mg, no psychotomimetic effects) and Phase 1b (18 adults with major depressive disorder, approximately 50 percent improvement in MADRS scores by Day 8, sustained through Day 36) [3, 4, 5]. No serious adverse events have been reported across more than 120 individuals. The FDA cleared a Phase 2 trial design featuring at-home self-administration in October 2025, a regulatory milestone enabled by the non-hallucinogenic profile [5].

3. Discovery and Development History

3.1 Origin and biosensor-guided discovery

AAZ-A-154 was first synthesized in 2019 in the laboratory of Professor David E. Olson at the University of California, Davis, as part of a systematic exploration of isoptryptamine chemical space guided by the psychLight biosensor [1]. PsychLight is a genetically encoded fluorescent indicator constructed by inserting circularly permuted green fluorescent protein (cpGFP) into the third intracellular loop (ICL3) of the human 5-HT_{2A} receptor. Ligand binding induces conformational changes in the receptor that are transduced to the cpGFP domain, producing fluorescence changes that report on the specific binding mode of the ligand. The biosensor was calibrated against a panel of known hallucinogenic (LSD, psilocin, DMT, 5-MeO-DMT, DOI) and non-hallucinogenic (lisuride, ketanserin) 5-HT_{2A} ligands, and a "ligand score" metric was derived from the fluorescence signature that discriminated the two classes with high accuracy [1].

AAZ-A-154 was identified from a library screen as a compound with a psychLight ligand score consistent with non-hallucinogenic character. The compound had never been previously described in the scientific literature and occupied a region of chemical space outside classical psychedelic tryptamines owing to its isoptryptamine connectivity [1].

3.2 Preclinical characterization

The initial preclinical characterization was published by Dong et al. in *Cell* in May 2021 and included receptor pharmacology (selectivity for 5-HT₂ receptors over other GPCR families), head-twitch response testing (absent up to 100 mg/kg), neuroplasticity assays (dendritic arbor complexity comparable to ketamine), and behavioral pharmacology (rapid-onset and sustained antidepressant-like effects in the forced swim test and sucrose preference test) [1].

A comprehensive follow-up characterization was published by Agrawal et al. in *ACS Chemical Neuroscience* in October 2025, which demonstrated that zalsupindole promoted cortical neuritogenesis in vitro, increased dendritic spine density in vivo in the prefrontal cortex, and enhanced functional plasticity measures to a de-

gree comparable to or greater than ketamine, psilocybin, and DMT [2]. This study also established the pharmacokinetic profile (high brain penetrance, rapid distribution, rapid clearance) and confirmed the absence of hallmark hallucinogenic markers including glutamate surge and head-twitch response.

3.3 Licensing and clinical development

AAZ-A-154 was licensed by Delix Therapeutics, a biotechnology company co-founded by David E. Olson, and was redesignated DLX-001 and subsequently assigned the international nonproprietary name zalsupindole. Delix Therapeutics advanced the compound through IND-enabling studies and into a Phase 1 clinical trial program beginning in 2023 [3, 4].

The Phase 1 program comprised three parts enrolling a total of 106 healthy volunteers across single-ascending-dose, multiple-ascending-dose, and food-effect cohorts, with oral doses ranging from 2 to 360 mg [3, 4]. The compound was well tolerated across the entire dose range, with no reports of psychotomimetic, hallucinogenic, or dissociative effects, establishing the human translation of the preclinical non-hallucinogenic profile.

A Phase 1b study in 18 adults with major depressive disorder was completed in 2025, demonstrating preliminary antidepressant efficacy [5]. In October 2025, Delix Therapeutics announced positive Phase 1b efficacy data and FDA clearance of a Phase 2 trial design featuring at-home self-administration, a regulatory pathway made possible by the compound's non-hallucinogenic, non-dissociative profile [5].

3.4 Current development status

As of the most recent monograph revision, zalsupindole is in preparation for Phase 2 clinical trials for major depressive disorder. The Phase 2 trial is designed as a multi-site, randomized, double-blind, placebo-controlled study with three arms (placebo, once-daily dosing, twice-weekly dosing) and includes an adaptive interim analysis [5]. The compound is not approved by any regulatory authority for any indication. It is available as a research-grade preparation from multiple chemical suppliers. Delix Therapeutics is also advancing a second compound, tabernanthalog (DLX-007), a non-hallucinogenic ibogaine analog psychoplastogen, for substance use disorders, though tabernanthalog has not yet entered clinical trials as of early 2026 [7].

4. Mechanism of Action

AAZ-A-154 is a multi-target serotonergic ligand whose principal pharmacological activities are partial agonism at the 5-HT_{2A} receptor, partial agonism at the 5-HT_{2C} receptor, and silent antagonism at the 5-HT_{2B} receptor. The downstream consequence of the 5-HT_{2A} activity is the promotion of structural and functional neuroplasticity in cortical and hippocampal neurons through signaling cascades involving TrkB, mTOR, and AMPA receptor pathways.

4.1 5-HT_{2A} receptor partial agonism

The 5-HT_{2A} receptor is a G-protein-coupled receptor (Gq/11-coupled) expressed at high density on cortical pyramidal neurons (particularly in layer V of the prefrontal cortex), on hippocampal neurons, and on multiple peripheral cell populations. It is the principal molecular target mediating the hallucinogenic effects of classical psychedelic tryptamines and phenethylamines, and it is the primary receptor through which psychoplastogenic compounds promote structural neuroplasticity [1, 6].

AAZ-A-154 binds the 5-HT_{2A} receptor and functions as a low-potency, low-efficacy partial agonist with an EC₅₀ of approximately 8,200 nM and a maximal efficacy (E_{max}) of approximately 17 percent of the serotonin maximum in calcium flux and beta-arrestin recruitment assays [1, 2]. This places the compound at the low end of the efficacy spectrum for 5-HT_{2A} agonists; by comparison, the classical psychedelics psilocin and DMT achieve E_{max} values of 80 to 100 percent in the same assays.

The low efficacy is the principal molecular basis for the non-hallucinogenic profile. The Olson laboratory's working model, supported by the psychLight biosensor data and by subsequent studies of tabernanthalog and related compounds, is that hallucinogenic activity requires sustained, high-efficacy activation of the 5-HT_{2A} receptor that produces a cascade of downstream effects including cortical glutamate release, immediate early gene (IEG) activation (c-Fos, Arc, Egr1), and 5-HT_{2A} receptor internalization [1, 6]. AAZ-A-154 activates the receptor with sufficient efficacy to engage the TrkB/mTOR/AMPA neuroplasticity signaling cascade but with insufficient efficacy to trigger the glutamate release, IEG activation, and behavioral correlates (head-twitch response) of the hallucinogenic pathway [1, 2, 6].

Schild regression analysis in the psychLight system classified AAZ-A-154 as a competitive antagonist at the biosensor level, consistent with its low intrinsic activity producing predominantly competitive occupancy rather than robust receptor activation under the assay conditions [1]. This is not contradictory to partial agonism at the receptor; the psychLight biosensor reports a specific conformational change that correlates with hallucinogenic signaling, and antagonism at the biosensor reflects the absence of that specific conformation rather than a lack of receptor activation per se.

4.2 5-HT_{2C} receptor partial agonism

AAZ-A-154 acts as a moderate-efficacy partial agonist at the 5-HT_{2C} receptor with an EC₅₀ of approximately 3,300 nM and an E_{max} of approximately 70 percent of the serotonin maximum [1]. The 5-HT_{2C} receptor is expressed in the prefrontal cortex, hippocampus, amygdala, choroid plexus, and basal ganglia and is implicated in the regulation of mood, anxiety, appetite, and reward processing. Partial agonism at the 5-HT_{2C} receptor may contribute to the antidepressant-like behavioral profile of AAZ-A-154 through modulation of mesolimbic dopamine release and through anxiolytic activity.

4.3 5-HT_{2B} receptor antagonism

AAZ-A-154 functions as a silent antagonist at the 5-HT_{2B} receptor with an IC₅₀ of approximately 27,600 nM [1]. The 5-HT_{2B} receptor is expressed on cardiac valvular interstitial cells, and chronic 5-HT_{2B} receptor agonism is the established molecular mechanism of drug-induced valvular heart disease (as observed with fenfluramine, ergotamine, and pergolide). The absence of 5-HT_{2B} agonism is a favorable cardiovascular safety feature that distinguishes AAZ-A-154 from certain classical psychedelic tryptamines that produce measurable 5-HT_{2B} activation.

4.4 Receptor selectivity

AAZ-A-154 demonstrates selectivity for 5-HT₂ receptors over 5-HT_{1A} receptors, dopamine D₁ and D₂ receptors, adrenergic α -1 and α -2 receptors, and kappa-opioid receptors when tested against a panel of GPCR-based sensors [1]. The selectivity profile reduces the risk of off-target pharmacological effects and positions the compound as a relatively clean serotonergic ligand within the broader tryptamine class.

4.5 Neuroplasticity signaling cascade

The principal therapeutic mechanism of AAZ-A-154 is the promotion of structural and functional neuroplasticity through 5-HT_{2A} receptor-dependent signaling. The downstream signaling cascade, characterized for both psychedelic and non-hallucinogenic psychoplastogens, involves activation of the TrkB (tropomyosin receptor kinase B) receptor by brain-derived neurotrophic factor (BDNF) release, downstream mTORC1 (mechanistic target of rapamycin complex 1) signaling, and enhancement of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor-mediated glutamatergic transmission [6, 8].

The structural consequences of this signaling include increased dendritic spine density in prefrontal cortex pyramidal neurons, increased dendritic arbor complexity, and enhanced synaptogenesis [1, 2, 6]. These structural changes are measurable within hours of compound administration and persist for days to weeks, corresponding to the time course of the behavioral antidepressant-like effects. The structural plasticity is the proposed molecular substrate for the rapid and sustained antidepressant activity, paralleling the neuroplasticity hypothesis of ketamine's antidepressant mechanism.

Importantly, AAZ-A-154 promotes this neuroplasticity cascade without producing the proximate cortical glutamate surge and immediate early gene activation that accompany hallucinogenic 5-HT_{2A} agonists [2, 6]. This dissociation supports the model that neuroplasticity and hallucination are separable downstream consequences of 5-HT_{2A} receptor activation, mediated by distinct conformational states and signaling pathways.

4.6 Composite pharmacology

The composite pharmacology of AAZ-A-154 (low-efficacy 5-HT_{2A} partial agonism, moderate-efficacy 5-HT_{2C} partial agonism, 5-HT_{2B} silent antagonism) produces a pharmacological profile that retains the neuroplasticity-promoting activity of the psychedelic tryptamines while eliminating the hallucinogenic, dissociative, and cardiovascular liabilities. The profile is mechanistically distinct from the glutamatergic mechanism of ketamine and esketamine (NMDA receptor antagonism) and from the high-efficacy 5-HT_{2A} agonism of psilocybin and DMT, and represents a third pharmacological strategy for rapid-acting antidepressant neuroplasticity.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

AAZ-A-154 is orally bioavailable in both rodent and human studies. In the Phase 1 clinical trial, oral administration across a dose range of 2 to 360 mg produced linear pharmacokinetic absorption profiles consistent with dose-proportional exposure [3, 4]. Formal bioavailability parameters from the Phase 1 trial have been disclosed at conference presentations but have not yet appeared in full peer-reviewed publication as of the monograph revision date.

5.2 Distribution

Preclinical pharmacokinetic studies in rats demonstrated high brain penetrance with rapid central nervous system distribution [2]. The compound distributes rapidly to brain tissue, consistent with its moderate molecular weight (232.33 g/mol), moderate lipophilicity conferred by the 5-methoxyindole system, and the absence of strong efflux transporter liability. Brain-to-plasma ratios and volume of distribution data from the Agrawal et al. (2025) preclinical characterization indicate favorable central nervous system exposure supporting the observed neuroplasticity and behavioral effects [2].

In the Phase 1 clinical trial, quantitative electroencephalography (qEEG) demonstrated measurable changes in cortical electrical activity consistent with central nervous system target engagement at pharmacologically relevant oral doses [3, 4]. The qEEG changes provide indirect human evidence of brain penetration and receptor occupancy.

5.3 Metabolism

The alpha-methyl substituent on the aminoalkyl chain confers resistance to monoamine oxidase (MAO) degradation, a principal metabolic vulnerability of classical tryptamines such as DMT that limits their oral bioavailability without MAO inhibitor co-administration [1]. This structural feature is a key contributor to the oral

bioavailability of AAZ-A-154 and differentiates it from DMT and 5-MeO-DMT pharmacokinetically. Detailed hepatic cytochrome P450 isoform profiling has not been publicly disclosed in peer-reviewed form as of the monograph revision date.

5.4 Elimination

Preclinical data indicate rapid clearance from both plasma and brain [2]. The rapid clearance is consistent with the short duration of acute pharmacodynamic effects (absence of prolonged psychoactive episodes) while the sustained structural neuroplasticity and behavioral effects persist for days to weeks beyond the pharmacokinetic residence of the compound, reflecting the durability of the downstream structural changes in dendritic spine density and synaptic connectivity.

5.5 Routes of administration

Oral: The principal route for both preclinical research (mouse and rat) and clinical development. Oral dosing in the Phase 1 trial ranged from 2 to 360 mg [3, 4]. The compound has been formulated as capsules for clinical administration.

Intraperitoneal: The standard route for rodent behavioral pharmacology. Published doses range from 15 to 20 mg/kg for antidepressant-like behavioral effects and up to 100 mg/kg for head-twitch response assessment [1].

Other routes: Subcutaneous, intravenous, and other parenteral routes have not been reported in the published literature. The oral route is the development route for clinical translation.

5.6 Special populations

No special population pharmacokinetic data (renal impairment, hepatic impairment, pediatric, geriatric) have been publicly disclosed. The Phase 1 trial enrolled healthy adult volunteers; the Phase 1b trial enrolled adults with major depressive disorder [3, 4, 5].

6. Preclinical Pharmacology

6.1 In vitro neuroplasticity

In cultured embryonic day 18 (E18) rat cortical neurons, AAZ-A-154 increased dendritic arbor complexity as measured by Sholl analysis, producing a maximal number of crossings (Nmax) comparable to ketamine [1]. The effect was abolished by co-incubation with 1 micromolar ketanserin (a selective 5-HT_{2A/2C} receptor antagonist), confirming that the neuroplastogenic activity is mediated through 5-HT₂ receptors rather than through an off-target mechanism [1].

The Agrawal et al. (2025) study extended the in vitro characterization to neurogenesis assays, demonstrating that zalsupindole promoted cortical neurite outgrowth to a degree comparable to or greater than ketamine, psilocybin, and DMT [2].

6.2 In vivo neuroplasticity

In vivo neuroplasticity studies in rats demonstrated that a single administration of zalsupindole increased dendritic spine density in the prefrontal cortex to a degree comparable to or greater than ketamine, psilocybin, and DMT [2]. Measures of functional plasticity, including markers of synaptic potentiation, were similarly enhanced. These structural and functional plasticity effects support the proposed mechanism of action and provide a preclinical basis for the sustained antidepressant-like behavioral effects.

6.3 Head-twitch response

The head-twitch response (HTR) in mice is the standard preclinical behavioral proxy for hallucinogenic activity of 5-HT_{2A} agonists. AAZ-A-154 failed to produce any head-twitches at doses up to 100 mg/kg intraperitoneally in C57BL/6J mice [1]. By comparison, the hallucinogenic tryptamines 5-fluoro-DMT and 5-chloro-DMT, which were identified in the same psychLight screen as having positive (hallucinogenic-type) ligand scores, produced robust head-twitch responses across all tested

doses [1]. The absence of HTR at the highest tested dose (100 mg/kg, approximately 5-fold the antidepressant-effective dose) provides a substantial margin between the therapeutic dose range and any potential hallucinogenic threshold.

6.4 Locomotor effects

At the antidepressant-effective dose range (15 to 20 mg/kg), AAZ-A-154 did not produce hyperlocomotion, a behavioral marker of stimulant-like or dissociative activity [1]. At 100 mg/kg, a decrease in locomotion was observed, consistent with sedative or motor-suppressant effects at high suprapharmacological doses [1].

6.5 Forced swim test

In the forced swim test (FST) in C57BL/6J mice (male and female, $n = 12$), a single intraperitoneal administration of AAZ-A-154 at 20 mg/kg produced a significant reduction in immobility time in the final 4 minutes of a 6-minute session [1]. The antidepressant-like effect was rapid in onset (measurable at 30 minutes post-administration) and sustained (still present at 1 week post-administration). The magnitude and time course of effect were comparable to ketamine at 3 mg/kg, the clinical reference standard for rapid-acting antidepressant mechanisms [1].

6.6 Sucrose preference test

In the sucrose preference test in VMAT2 heterozygous mice (a genetic model of depressive phenotype characterized by baseline anhedonia and reduced sucrose preference), a single intraperitoneal administration of AAZ-A-154 at 15 mg/kg restored sucrose preference to a level indistinguishable from wild-type controls [1]. The effect was present immediately following administration and persisted for at least 12 days. The compound did not alter sucrose preference in wild-type (non-depressed) mice, ruling out nonspecific changes in palatability or fluid consumption [1]. The 12-day sustained effect in a genetic depression model with a single administration is a particularly notable finding, as it exceeds the duration of behavioral effects typically observed with single-dose ketamine in similar paradigms.

6.7 Comparison to ketamine, psilocybin, and DMT

The Agrawal et al. (2025) study provided a systematic head-to-head comparison of zalsupindole against ketamine, psilocybin, and DMT across neuroplasticity, behavioral, and pharmacokinetic endpoints [2]. Zalsupindole produced comparable or superior effects on cortical spine density and functional plasticity measures, comparable antidepressant-like behavioral effects, and a favorable pharmacokinetic profile (rapid brain penetration, rapid clearance) while lacking all hallmark markers of hallucinogenic and dissociative activity (head-twitch response, glutamate surge, immediate early gene activation). This comprehensive comparison established zalsupindole as a psychoplastogen with therapeutic-class efficacy and a differentiated safety profile.

7. Clinical Evidence Base

7.1 Phase 1a: healthy volunteers

The Phase 1 clinical trial enrolled 106 healthy adult volunteers in a three-part design comprising single-ascending-dose, multiple-ascending-dose, and food-effect cohorts [3, 4]. Oral doses ranged from 2 to 360 mg. Primary objectives were safety, tolerability, and pharmacokinetics; secondary objectives included pharmacodynamic biomarkers.

The compound was well tolerated across the entire dose range. No serious adverse events were reported. All adverse events were mild and self-resolving. No psychotomimetic, hallucinogenic, or dissociative effects were observed at any dose, confirming the human translation of the preclinical non-hallucinogenic profile [3, 4].

Pharmacokinetic assessments demonstrated linear absorption and central nervous system penetration. Quantitative electroencephalography (qEEG) demonstrated measurable changes in cortical electrical activity consistent with target engagement, providing a pharmacodynamic biomarker of central 5-HT_{2A} pathway modulation without accompanying subjective psychoactive effects [3, 4].

7.2 Phase 1b: major depressive disorder

A Phase 1b study enrolled 18 adults with major depressive disorder in two dosing cohorts [5]:

Cohort A: Once-daily oral administration for 7 consecutive days.

Cohort B: Two oral doses administered during the first week only.

Follow-up continued for 36 days (4 weeks after the final dose). Primary endpoints were translational biomarkers of neuroplasticity measured by qEEG and polysomnography. Secondary endpoints included safety, tolerability, pharmacokinetics, and preliminary antidepressant efficacy measured by the Montgomery-Asberg Depression Rating Scale (MADRS).

Efficacy results: Clinically meaningful reductions in MADRS scores of approximately 12 points (approximately 50 percent improvement from baseline) were observed by Day 8 [5]. The improvements were maintained through Day 36, demonstrating durability of the antidepressant effect beyond the pharmacokinetic residence of the compound. Both dosing regimens (seven daily doses and two doses) produced similar antidepressant outcomes, suggesting that even minimal dosing may be sufficient to trigger sustained neuroplastic changes [5].

Biomarker results: qEEG and polysomnography demonstrated "robust results" consistent with neuroplasticity promotion. Detailed biomarker data have been deferred to conference presentations and subsequent publications [5].

Safety results: No serious adverse events were reported. All adverse events were mild and self-resolving without intervention. No hallucinatory, dissociative, or psychotomimetic effects were observed [5].

7.3 Phase 2: planned trial

In October 2025, the FDA cleared the Investigational New Drug application for a Phase 2 trial of zalsupindole in major depressive disorder [5]. The trial is designed as a multi-site, randomized, double-blind, placebo-controlled study with three arms: placebo, once-daily dosing, and twice-weekly dosing. The trial design includes an adaptive interim analysis and, notably, allows at-home self-administration of the investigational compound, a regulatory concession enabled by the established non-hallucinogenic and non-dissociative safety profile [5]. This is a significant differentiator from psilocybin, MDMA, and esketamine clinical programs, all of which require in-clinic administration with professional supervision.

7.4 Current clinical status

As of the monograph revision date, zalsupindole is in the Phase 2 preparatory stage. No Phase 2 data have been reported. The compound is not approved by any regulatory authority for any indication. The clinical evidence base consists of Phase 1a safety and pharmacokinetic data in 106 healthy volunteers and Phase 1b preliminary efficacy data in 18 adults with major depressive disorder.

8. Sourcing and Quality Verification

Research-grade AAZ-A-154 is supplied by multiple chemical and pharmaceutical research suppliers including MedChemExpress, TargetMol, Invivochem, MedKoo Biosciences, Probechem Biochemicals, and Cayman Chemical. Supply is in milligram to gram quantities as the free base, hydrochloride salt, or mesylate salt. Typical reported purity is greater than 98 percent by HPLC.

Pharmaceutical-grade material (clinical-grade zalsupindole) is manufactured under GMP conditions by or for Delix Therapeutics and is not commercially available for research use.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (233.16 for the protonated free base $[M+H]^+$, or 269.13 for the hydrochloride)
- Chiral HPLC confirmation of enantiomeric purity (greater than 98 percent enantiomeric excess of the (R)-form)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structure and regiochemistry (isotryptamine vs. tryptamine connectivity)
- Karl Fischer or loss-on-drying analysis for residual water content

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The isotryptamine regiochemistry is a critical quality attribute; NMR confirmation that the aminoalkyl chain is attached at the indole nitrogen (N1) rather than at carbon 3 is essential, as the tryptamine regioisomer would have fundamentally different pharmacological properties.

9. Reconstitution and Handling

AAZ-A-154 free base and salt forms are soluble in dimethyl sulfoxide (DMSO) for in vitro applications. The hydrochloride and mesylate salts have improved aqueous solubility for in vivo formulation. Stock solutions for in vitro assays are typically prepared at 10 to 100 mM in DMSO and diluted into aqueous assay buffer at final DMSO concentrations below 0.1 percent.

For in vivo rodent studies, the compound has been administered intraperitoneally in saline or in saline with a small fraction of DMSO or Tween-80 as cosolvent [1]. Oral gavage formulations for rodent studies and capsule formulations for clinical trials have been developed by Delix Therapeutics.

Storage of the solid is at -20 degrees Celsius under desiccation and protection from light. DMSO stock solutions are stable at -20 degrees Celsius for at least 3 months. Aqueous solutions should be prepared fresh for each experiment. The compound should be handled with standard laboratory precautions for pharmacologically active serotonergic agents, including use of gloves and avoidance of inhalation of powder.

10. Stack Interaction Considerations

AAZ-A-154 interacts with several drug and compound classes through its serotonergic pharmacology and through potential pharmacokinetic interactions. Investigators conducting research with AAZ-A-154, particularly in combination with other compounds, should consider the following:

Serotonergic agents: Concurrent use with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, triptans, or other serotonergic compounds increases the theoretical risk of serotonin syndrome. The low efficacy of AAZ-A-154 at 5-HT_{2A} may mitigate this risk relative to high-efficacy psychedelic agonists, but the interaction has not been formally characterized.

MAO inhibitors: Although the alpha-methyl substituent confers resistance to MAO degradation, concurrent MAOI use may alter the pharmacokinetics of AAZ-A-154 metabolites and may increase serotonergic tone through other pathways. The combination has not been studied.

Other 5-HT_{2A} ligands: Concurrent use with classical psychedelics (psilocybin, LSD, DMT) would produce competitive interactions at the 5-HT_{2A} receptor. AAZ-A-154, as a low-efficacy partial agonist, would be expected to attenuate the effects of high-efficacy agonists at the same receptor through partial agonist ceiling effects. Concurrent use with 5-HT_{2A} antagonists (ketanserin, risperidone, olanzapine) would be expected to block the neuroplastic effects of AAZ-A-154.

Ketamine and esketamine: The combination of AAZ-A-154 with NMDA receptor antagonists has not been studied. The two classes promote neuroplasticity through convergent but non-identical signaling pathways (5-HT_{2A}/TrkB/mTOR for AAZ-A-154; NMDA/AMPA/mTOR for ketamine). Additive or synergistic neuroplasticity effects are plausible but uncharacterized.

Antipsychotics: First-generation and second-generation antipsychotics with 5-HT_{2A} antagonist activity (clozapine, olanzapine, risperidone, quetiapine) would be expected to antagonize the neuroplastic effects of AAZ-A-154. This interaction is relevant for schizophrenia research populations and for MDD patients on antipsychotic augmentation.

CYP450 interactions: Formal CYP450 interaction profiling has not been publicly disclosed. Investigators should consider potential interactions with strong CYP inhibitors and inducers pending disclosure of the metabolic pathway.

11. Adverse Events and Safety

11.1 Preclinical safety

In preclinical studies, AAZ-A-154 was well tolerated at antidepressant-effective doses (15 to 20 mg/kg intraperitoneal in mice) without observable adverse effects [1, 2]. At the highest tested dose (100 mg/kg), decreased locomotion was the principal observed effect [1]. No seizures, convulsions, or other signs of central nervous system toxicity were reported at any dose.

The absence of 5-HT_{2B} receptor agonism is a favorable preclinical safety feature, as chronic 5-HT_{2B} agonism is the established mechanism of drug-induced valvular heart disease [1].

11.2 Clinical adverse events

Across more than 120 individuals studied in Phase 1a and Phase 1b trials, no serious adverse events have been reported [3, 4, 5]. All reported adverse events were mild and self-resolving without intervention. The principal adverse events are:

- Nausea (dose-dependent, mild, self-resolving)
- Headache (mild)
- Dizziness (mild)

No hallucinatory, dissociative, psychotomimetic, or sedative effects were observed at any dose from 2 to 360 mg oral in healthy volunteers or in the MDD cohort [3, 4, 5].

11.3 Hallucinogenic safety margin

The absence of head-twitch response in mice at doses up to 100 mg/kg (approximately 5-fold the antidepressant-effective dose) and the absence of psychotomimetic effects in humans at doses up to 360 mg establish a substantial safety margin between the therapeutic dose range and any potential hallucinogenic or psychotomimetic threshold [1, 3, 4]. This margin is the basis for the FDA's clearance of at-home self-administration in the Phase 2 trial design [5].

11.4 Cardiovascular safety

The silent antagonism at the 5-HT_{2B} receptor (IC₅₀ approximately 27,600 nM) is a favorable cardiovascular safety feature [1]. No cardiovascular adverse events, QT prolongation signals, or valvulopathy concerns have been reported in preclinical or clinical studies to date.

11.5 Abuse liability

Formal abuse liability studies have not been publicly reported. The absence of subjective psychoactive effects (no euphoria, no hallucinations, no dissociation) at therapeutic and supratherapeutic doses suggests low abuse potential relative to classical psychedelics and ketamine. The regulatory clearance for at-home administration is consistent with a low-abuse-liability assessment by the FDA [5].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five psychoplastogen and rapid-acting antidepressant candidates against AAZ-A-154, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected as the principal compounds with substantive clinical or advanced preclinical pharmacology programs in rapid-acting antidepressant or psychoplastogen applications.

12.1 Psilocybin

Mechanism: Prodrug of psilocin, a high-efficacy agonist at the 5-HT_{2A} receptor (E_{max} approximately 80 to 100 percent). Produces both neuroplasticity and hallucinogenic effects through the same receptor target.

Development trajectory: Psilocybin has been studied extensively in clinical trials for treatment-resistant depression and major depressive disorder. Multiple Phase 2 trials have reported response rates of 50 to 70 percent and remission rates of approximately 30 to 58 percent [9]. Compass Pathways and Usona Institute have advanced psilocybin into Phase 3 clinical trials. Regulatory review is ongoing in multiple jurisdictions.

Novelty: Moderate. Psilocybin is a naturally occurring compound with a 60-year research history. The clinical revival is novel; the molecular entity is not.

Effect size: Large. Clinical trials have reported MADRS reductions of 15 to 25 points in treatment-resistant and moderate-to-severe MDD populations, with rapid onset (within days) and sustained effects (weeks to months) [9].

Promising potential: High. Multiple Phase 3 trials are active or completed. Regulatory approval is plausible in the near term for treatment-resistant depression.

Side-effect profile: The principal limitation is the hallucinogenic effect, which requires in-clinic administration with trained therapist supervision (typically 6 to 8 hours per session), Risk Evaluation and Mitigation Strategy (REMS) programs, and specialized clinical infrastructure. Acute adverse events include anxiety, nausea, headache, and transient cardiovascular effects. Rare adverse events include prolonged psychological distress, psychotic episodes, and suicidal ideation in vulnerable populations.

Overall validation: High. The most clinically advanced psychoplastogen with the largest evidence base.

Comparison to AAZ-A-154: Psilocybin has a substantially larger clinical evidence base and higher effect sizes in depression. AAZ-A-154 has the advantage of non-hallucinogenic administration enabling at-home dosing, absence of the need for supervised clinical sessions, and potentially broader patient accessibility. The two compounds share the 5-HT_{2A}-mediated neuroplasticity mechanism but differ fundamentally in receptor efficacy and the consequent hallucinogenic profile. The clinical question is whether AAZ-A-154's lower receptor efficacy translates to lower antidepressant efficacy or whether the neuroplasticity promotion (comparable in preclinical models) is sufficient for clinical benefit.

12.2 Esketamine (Spravato)

Mechanism: NMDA receptor antagonist (S-enantiomer of ketamine). Promotes neuroplasticity through glutamatergic AMPA receptor potentiation and BDNF/TrkB/mTOR signaling. The mechanism is fundamentally distinct from the serotonergic pathway of AAZ-A-154.

Development trajectory: Esketamine nasal spray (Spravato, Janssen/Johnson and Johnson) was approved by the FDA in March 2019 for treatment-resistant depression and in August 2020 for major depressive disorder with suicidal ideation. It is the only approved rapid-acting antidepressant in the United States.

Novelty: Low. Ketamine has been used as an anesthetic for over 50 years; the antidepressant repurposing is novel, the molecule is not.

Effect size: Moderate. MADRS reductions of approximately 4 to 8 points greater than placebo have been reported in registration trials, smaller than the effect sizes observed in psilocybin trials but clinically meaningful [10].

Promising potential: Established. The compound is approved and commercially available. Ongoing research extends to post-traumatic stress disorder and other indications.

Side-effect profile: The principal limitation is the dissociative effect, which requires in-clinic administration with 2-hour post-dose monitoring under the REMS program. Adverse events include dissociation, dizziness, nausea, sedation, and transient blood pressure elevation. Abuse liability is a regulatory concern (Schedule III controlled substance).

Overall validation: High. The approved reference standard for rapid-acting antidepressant neuroplasticity.

Comparison to AAZ-A-154: Esketamine has the advantage of regulatory approval and established clinical utility. AAZ-A-154 has the advantage of non-dissociative administration enabling at-home dosing, absence of the need for in-clinic monitoring, and a mechanistically distinct serotonergic pathway. The sustained antidepressant effect of AAZ-A-154 at 36 days post-treatment in the Phase 1b study [5] compares favorably with esketamine's requirement for ongoing twice-weekly to weekly maintenance dosing.

12.3 Tabernanthalog (TBG, DLX-007)

Mechanism: Non-hallucinogenic ibogaine analog. Acts as a partial agonist at 5-HT_{2A} receptors and promotes neuroplasticity through TrkB/mTOR/AMPA signaling without producing hallucinogenic effects, glutamate surge, or immediate early gene activation [6, 7].

Development trajectory: Developed by the Olson laboratory at UC Davis and licensed by Delix Therapeutics. GLP IND-enabling studies have been completed for substance use disorder indications [7]. As of early 2026, tabernanthalog has not yet entered clinical trials, representing a delay from earlier projections of Phase 1 initiation in 2023 [7].

Novelty: High. The compound represents a structurally simplified, water-soluble, non-hallucinogenic analog of ibogaine with a distinct mechanism from the isoptryptamine class of AAZ-A-154.

Effect size: Preclinical only. Demonstrated increases in dendritic spine density, cortical spinogenesis, and antidepressant-like behavioral effects in rodent models [6].

Promising potential: Moderate. The compound is pre-clinical; the development timeline has extended. The target indication (substance use disorders) is distinct from the MDD focus of AAZ-A-154.

Side-effect profile: Preclinical only. Favorable safety in rodent studies. No human safety data. The ibogaine class historically carries cardiovascular concerns (QT prolongation, cardiac arrhythmia with ibogaine itself); tabernanthalog was designed to eliminate these liabilities.

Overall validation: Low. The compound has produced extensive preclinical data but no human clinical data.

Comparison to AAZ-A-154: Both compounds are non-hallucinogenic psychoplastogens from the Olson laboratory, but they differ in structural class (isotryptamine vs. ibogalog), target indication (MDD vs. substance use disorders), and development stage (AAZ-A-154 is in Phase 2 preparation; tabernanthalog is pre-clinical). AAZ-A-154 has the advantage of clinical data and a more advanced regulatory pathway.

12.4 Arketamine (PCN-101, HR-200)

Mechanism: NMDA receptor antagonist (R-enantiomer of ketamine). Proposed to have superior neuroplasticity-promoting activity and lower dissociative effects compared to esketamine (S-enantiomer) based on preclinical data.

Development trajectory: Multiple companies (Perception Neuroscience, Jiangsu Hengrui) have advanced arketamine into clinical trials for treatment-resistant depression. Phase 2 trials have been completed in China and are ongoing internationally.

Novelty: Low. The compound is the R-enantiomer of a 50-year-old anesthetic.

Effect size: Phase 2 data from Chinese trials have reported significant MADRS reductions, though full peer-reviewed results and cross-study comparisons are pending.

Promising potential: Moderate. The compound is in Phase 2 with an active development program, but regulatory and commercial positioning relative to approved esketamine remains uncertain.

Side-effect profile: Expected to produce lower dissociative effects than esketamine based on receptor pharmacology. Clinical data suggest a more tolerable profile, though formal comparative studies are limited.

Overall validation: Low to moderate. Phase 2 data exist but registration-quality evidence is pending.

Comparison to AAZ-A-154: Arketamine and AAZ-A-154 share the conceptual positioning of "next-generation rapid antidepressants with reduced psychoactive side effects." They differ fundamentally in mechanism (glutamatergic vs. serotonergic) and in the degree of psychoactive effect reduction (arketamine still produces some dissociative effects; AAZ-A-154 appears to produce none). AAZ-A-154 has the advantage of at-home administration feasibility.

12.5 GL-0120 (Gilgamesh Pharmaceuticals)

Mechanism: 5-HT_{2A} receptor agonist designed as a short-acting, non-hallucinogenic or minimally hallucinogenic psychoplastogen. The compound is structurally distinct from AAZ-A-154 and approaches the non-hallucinogenic psychoplastogen concept from a pharmacokinetic (rapid clearance limiting psychedelic duration) rather than pharmacodynamic (low receptor efficacy) perspective.

Development trajectory: Gilgamesh Pharmaceuticals has advanced GL-0120 into Phase 1 clinical trials. The compound is intended for depression and anxiety indications.

Novelty: High. The rapid-clearance pharmacokinetic strategy for managing psychedelic side effects is mechanistically distinct from the low-efficacy strategy of AAZ-A-154.

Effect size: Preclinical and early Phase 1 only. Insufficient data for effect-size comparison.

Promising potential: Moderate. Early clinical development with active program.

Side-effect profile: The rapid-clearance strategy may still produce brief psychedelic effects; the compound may not be fully non-hallucinogenic. Clinical data are limited.

Overall validation: Low. Early-stage development.

Comparison to AAZ-A-154: Both compounds address the same therapeutic hypothesis (psychoplastogen-mediated rapid antidepressant without hallucinogenic burden) but through different strategies. AAZ-A-154 achieves the non-hallucinogenic profile through low receptor efficacy (pharmacodynamic strategy); GL-0120 approaches it through rapid pharmacokinetic clearance. The AAZ-A-154 approach may be more robust, as the absence of hallucinogenic effects appears to be intrinsic to the pharmacology rather than dependent on kinetic timing. AAZ-A-154 has the advantage of more advanced clinical data and FDA Phase 2 clearance.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the rapid-acting antidepressant and psychoplastogen landscape. **Psilocybin** represents the most clinically advanced psychoplastogen with the largest effect sizes but carries the operational burden of hallucinogenic supervision requirements. **Esketamine** is the approved reference standard but requires in-clinic monitoring and ongoing maintenance dosing. **Tabernanthalog** is the most closely related compound to AAZ-A-154 (same laboratory, same company) but is substantially earlier in development and targets a different indication. **Arketamine** represents a glutamatergic approach to reduced-side-effect rapid antidepressant treatment. **GL-0120** represents an alternative serotonergic strategy based on pharmacokinetics rather than pharmacodynamics.

AAZ-A-154 occupies a distinctive position in this landscape as the most clinically advanced non-hallucinogenic psychoplastogen. Its combination of 5-HT_{2A}-mediated neuroplasticity, complete absence of psychedelic and dissociative effects across a wide dose range, at-home administration feasibility, and preliminary evidence of rapid and sustained antidepressant efficacy with only one or two doses addresses multiple limitations of the existing rapid-acting antidepressant approaches. The principal uncertainty is whether the low receptor efficacy that enables the non-hallucinogenic profile will translate to clinically adequate antidepressant ef-

fect sizes in adequately powered Phase 2 and Phase 3 trials; the Phase 1b signal (approximately 12-point MADRS reduction, approximately 50 percent improvement) is encouraging but is derived from 18 patients without placebo control [5].

Investigators considering AAZ-A-154 for neuroplasticity or antidepressant research should position it as a tool compound for studying 5-HT_{2A}-mediated neuroplasticity in the absence of hallucinogenic confounds, and as a clinical candidate with a differentiated safety and operational profile relative to the hallucinogenic and dissociative reference compounds.

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