

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tabernanthalog

A rationally designed, water-soluble, non-hallucinogenic analog of ibogaine engineered through function-oriented synthesis to retain psychoplastogenic neuroplasticity and preclinical antidepressant and anti-addictive activity while eliminating the cardiotoxicity and hallucinogenic liability of the parent alkaloid.

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ABSTRACT

Tabernanthalog (TBG, DLX-007) is a synthetic, water-soluble analog of the indole alkaloid ibogaine, first reported by Cameron et al. in a 2020 publication in *Nature* from the Olson laboratory at the University of California, Davis. The compound was engineered through function-oriented synthesis to isolate the therapeutic pharmacophore of ibogaine while eliminating two liabilities that have prevented clinical development of the parent alkaloid: blockade of the human ether-a-go-go-related gene (hERG) potassium channel (the basis of ibogaine-associated QT prolongation and fatal cardiac arrhythmia) and activation of hallucinogenic signaling cascades downstream of the serotonin 5-HT_{2A} receptor. Tabernanthalog retains the capacity to promote rapid, sustained structural neuroplasticity in cortical neurons, including dendritic arborization and spinogenesis in the prefrontal cortex, through activation of the 5-HT_{2A} receptor and downstream TrkB, mTOR, and AMPA receptor signaling pathways. A 2025 publication in *Nature Neuroscience* by Aarrestad et al. demonstrated that tabernanthalog achieves this neuroplasticity without inducing the immediate glutamate burst or the immediate early gene (IEG) activation that characterize classical hallucinogenic psychedelics, establishing a dissociation between psychoplastogenic structural remodeling and the acute transcriptional programs previously considered prerequisite. In behavioral pharmacology, tabernanthalog does not produce the mouse head-twitch response, the standard behavioral proxy for hallucinogenic activity, confirming its non-hallucinogenic profile. Preclinical efficacy has been demonstrated across multiple disease-relevant models: a single dose reduces immobility in the

forced swim test (antidepressant-like activity); a single dose restores functional neural circuits, including dendritic spine density and sensory processing, disrupted by unpredictable mild stress in mice (Lu et al., Molecular Psychiatry 2021); a single dose reduces heroin self-administration in rats and alcohol binge drinking in mice; and tabernanthalog reduces motivation for both heroin and alcohol in a polydrug use model with effects persisting up to 14 days after treatment (Heinsbroek et al., 2023). The molecular pharmacology of tabernanthalog extends beyond 5-HT_{2A} partial agonism to include antagonism at the 5-HT_{2B} receptor, agonism at 5-HT_{1B}, 5-HT_{1F}, 5-HT_{2C}, and 5-HT₆ receptors, inhibition of monoamine oxidase A, activity at the α -2A adrenergic receptor and the serotonin transporter, and inhibition of α -7 and α -9/ α -10 nicotinic acetylcholine receptors at low-micromolar concentrations. The compound does not interact significantly with opioid receptors, the NMDA receptor, or the hERG potassium channel. Tabernanthalog is prepared in a single synthetic step from commercially available precursors, is freely water-soluble as the fumarate salt, and has a molecular weight of 230.31 g/mol (free base). Despite strong preclinical validation and assignment of the development code DLX-007 by Delix Therapeutics, the compound has not entered human clinical trials as of May 2026; the company's lead clinical candidate is the structurally related psychoplastogen zalsupindole (DLX-001). This monograph reviews the chemistry, synthesis, and structure-activity relationships of tabernanthalog; the multi-target molecular pharmacology in receptor-level and signaling-pathway detail; the available pharmacokinetic characterization; the preclinical efficacy data across depression, stress, addiction, pain, and cognitive models; the clinical development status; sourcing and quality verification considerations; reconstitution

and handling; stack-interaction implications; the adverse-event and safety profile; and a comparative assessment of five alternative psychoplastogens and ibogaine analogs against tabernanthalog on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Tabernanthalog.

Development code: DLX-007 (Delix Therapeutics). The abbreviation TBG is used throughout the primary research literature and is the canonical shorthand in the Olson laboratory publications [1].

Chemical Abstracts Service registry numbers: 2483829-58-7 (free base), 2483829-59-8 (fumarate salt). The fumarate is the principal commercially available research-grade salt form.

International Union of Pure and Applied Chemistry name: 8-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole. The compound is a simplified azepino-indole that retains the indole nucleus and methoxy substitution pattern of the ibogaine pharmacophore while deleting the isoquinuclidine and cyclohexane ring systems responsible for ibogaine's hERG channel blockade and hallucinogenic potency.

1.2 Structural class and chemistry

Tabernanthalog is a synthetic indole alkaloid analog classified within the ibogalogs, a family of rationally simplified analogs of the iboga alkaloid scaffold developed by the Olson laboratory at UC Davis [1, 2]. The structural class is distinguished from the natural iboga alkaloids (ibogaine, noribogaine, voacangine, coronaridine) by the deletion of multiple fused ring systems, retaining only the core indole, the seven-membered azepine ring, and the 8-methoxy substituent that is critical for serotonergic receptor engagement.

Molecular formula: C₁₄H₁₈N₂O (free base); C₁₈H₂₂N₂O₅ (fumarate salt).

Exact mass: 230.1419 g/mol (free base, monoisotopic).

Molecular weight: 230.31 g/mol (free base); 346.38 g/mol (fumarate salt).

Physical properties: Off-white to white powder. Freely soluble in water as the fumarate salt; soluble in dimethyl sulfoxide, methanol, and ethanol. The free base has limited aqueous solubility; the fumarate salt was selected specifically to confer the water solubility required for in vivo administration without organic co-solvents.

Key structural features: The 8-methoxy group on the indole ring is the minimal pharmacophoric element required for 5-HT_{2A} receptor engagement and for avoidance of the head-twitch response (the non-hallucinogenic profile is attributed in part to the retention of 6-methoxy or 8-methoxy substitution on the indole in the context of the simplified azepine scaffold) [1]. The seven-membered azepine ring replaces the complex polycyclic system of ibogaine and eliminates the structural determinants of hERG channel blockade identified through structure-activity relationship analysis.

1.3 Synthesis

Tabernanthalog was designed through function-oriented synthesis, a strategy in which the key structural elements contributing to the therapeutic pharmacophore of ibogaine were identified and non-essential or liability-conferring structural elements were systematically deleted [1]. The Olson laboratory decomposed ibogaine into its constituent ring systems and functional groups, correlated each element with specific pharmacological activities (5-HT_{2A} binding, hERG blockade, neuroplasticity, hallucinogenic signaling), and removed the isoquinuclidine and cyclohexane ring systems that contribute to cardiotoxicity and hallucinogenic potency.

The resulting tabernanthalog molecule can be prepared in a single synthetic step from commercially available starting materials, a major operational advantage over the multi-step total synthesis or biosynthetic extraction required for ibogaine itself [1]. The one-step synthesis proceeds through a Fischer indole-type cyclization or related condensation, yielding the azepino[4,5-b]indole core in a single operation. The product is purified by standard chromatographic or recrystallization methods and converted to the fumarate salt by treatment with fumaric acid. Published yields and purity specifications are consistent with research-scale production; industrial-scale synthesis optimization has not been publicly disclosed.

The synthetic accessibility of tabernanthalog (one step, commercially available starting materials, no stereocenters requiring chiral resolution) is a substantial translational advantage relative to ibogaine (which requires either total synthesis

or extraction from *Tabernanthe iboga* root bark, a conservation-limited natural resource) and relative to noribogaine (which requires either O-demethylation of ibogaine or independent synthesis).

2. Abstract

Tabernanthalog (TBG, DLX-007) is a rationally designed, non-hallucinogenic, non-cardiotoxic analog of the indole alkaloid ibogaine, first reported in *Nature* by Cameron et al. (2020) from the Olson laboratory at the University of California, Davis [1]. The compound was engineered by function-oriented synthesis to retain ibogaine's capacity for rapid structural neuroplasticity promotion while eliminating the hERG potassium channel blockade (the molecular basis of ibogaine-associated fatal cardiac arrhythmia) and the hallucinogenic signaling that have prevented clinical development of ibogaine for psychiatric and addictive indications.

The principal pharmacological activity of tabernanthalog is partial agonism at the serotonin 5-HT_{2A} receptor, the same receptor through which classical psychedelics (psilocybin, LSD, DMT) and ibogaine itself promote cortical neuroplasticity [1, 3]. Unlike classical psychedelics and ibogaine, tabernanthalog does not produce the mouse head-twitch response, the standard behavioral assay for hallucinogenic activity, indicating a dissociation between neuroplastogenic and hallucinogenic signaling downstream of 5-HT_{2A} activation. A 2025 study in *Nature Neuroscience* by Aarrestad et al. elucidated this dissociation mechanistically: tabernanthalog promotes cortical spinogenesis through TrkB, mTOR, and AMPA receptor signaling without inducing the immediate extracellular glutamate burst or immediate early gene (IEG) activation that psychedelics produce and that were previously considered necessary for neuroplasticity [4]. When TBG-induced dendritic spines were selectively ablated, the antidepressant-like behavioral effect was abolished, confirming that the structural neuroplasticity is causally required for the sustained behavioral response.

Preclinical efficacy has been demonstrated in models of depression (forced swim test, unpredictable mild stress), substance use disorder (heroin self-administration, alcohol binge drinking, polydrug use), stress-induced neural circuit disruption, and neuropathic pain [1, 5, 6, 7]. In the stress model, a single dose of tabernanthalog restored dendritic spine density, decreased baseline neuronal hyperactivity, enhanced whisking-modulated sensory processing in somatosensory cortex, and rescued anxiety-like behavior and cognitive inflexibility [5]. In the addiction models, a

single dose reduced heroin-seeking behavior with effects persisting up to 14 days, and reduced alcohol consumption within the first four hours of binge access with residual effect at 48 hours [6].

The compound acts as a non-selective serotonin receptor modulator with activity at 5-HT1B, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, and 5-HT6 receptors; it also targets monoamine oxidase A, the alpha-2A adrenergic receptor, the serotonin transporter, and nicotinic acetylcholine receptors (alpha-7 and alpha-9/alpha-10 subtypes) [1, 8]. It does not interact significantly with opioid receptors, the NMDA receptor, or the hERG potassium channel.

Despite assignment of the development code DLX-007 by Delix Therapeutics and announced plans for Phase 1 clinical trials, tabernanthalog has not entered human clinical studies as of May 2026. The company's lead clinical candidate is the structurally related compound zalsupindole (DLX-001, DLX-159), which has completed Phase 1 evaluation. Tabernanthalog remains a preclinical-stage compound with substantial research validation and wide commercial availability as a research-grade reagent.

3. Discovery and Development History

3.1 Origin

Tabernanthalog was conceived in the laboratory of David E. Olson at the University of California, Davis, as part of a systematic program to develop non-hallucinogenic psychoplastogens, compounds that promote rapid structural neuroplasticity in cortical neurons without producing subjective psychedelic effects [1, 9]. The Olson laboratory, one of a small number of academic laboratories in the United States licensed to work with Schedule I psychoactive substances, had previously characterized the neuroplasticity-promoting properties of ibogaine, 5-MeO-DMT, LSD, and other classical psychedelics in cortical neuron culture systems and had identified the 5-HT_{2A} receptor as the convergent target for psychoplastogenic activity across these structurally diverse compounds [9].

The rationale for developing a non-hallucinogenic ibogaine analog was twofold. First, ibogaine had demonstrated remarkable preclinical and anecdotal clinical anti-addictive activity, particularly for opioid use disorder, but its clinical development was blocked by severe cardiotoxicity (hERG potassium channel blockade producing QT prolongation, ventricular arrhythmia, and reported fatalities) and by intense hallucinogenic effects lasting 24 to 48 hours that required prolonged medical supervision [10, 11]. Second, a growing body of evidence suggested that the neuroplasticity-promoting activity of psychedelics, rather than the subjective psychedelic experience itself, might be the mechanistic basis of their therapeutic effects, raising the possibility that a non-hallucinogenic neuroplastogen could deliver therapeutic benefit without the logistical and safety burden of psychedelic-assisted therapy [9].

3.2 Design and first synthesis

The Olson laboratory employed function-oriented synthesis, a strategy that identifies the minimal pharmacophoric elements of a complex natural product and discards structural features that contribute to toxicity or unwanted pharmacology. Ibogaine was deconstructed into its constituent ring systems: the indole aromatic system, the isoquinuclidine bridged bicycle, and the cyclohexane ring. Structure-

activity relationship analysis, informed by the existing literature on ibogaine analogs (18-methoxycoronaridine, noribogaine, coronaridine congeners) and by computational docking to the 5-HT_{2A} receptor, identified the indole nucleus with its methoxy substituent as the minimal element required for serotonergic engagement. The isoquinuclidine system was identified as a principal determinant of hERG channel blockade. Systematic deletion and replacement of ring systems yielded the azepino[4,5-b]indole scaffold of tabernanthalog, which retains 5-HT_{2A} binding while eliminating hERG interaction [1].

The compound was first reported in *Nature* in December 2020 (Cameron et al., "A non-hallucinogenic psychedelic analogue with therapeutic potential") [1]. The publication reported the single-step synthesis, the receptor binding profile, the absence of head-twitch response, the promotion of dendritic growth in rat cortical neurons, and antidepressant-like and anti-addictive behavioral effects in mice.

3.3 Academic expansion of the research literature

Following the 2020 *Nature* publication, the tabernanthalog research literature expanded rapidly across several domains.

Lu et al. (2021) published in *Molecular Psychiatry* a comprehensive study demonstrating that a single dose of tabernanthalog restored functional neural circuits disrupted by unpredictable mild stress in mice [5]. The study used two-photon calcium imaging to demonstrate that tabernanthalog promoted regrowth of excitatory neuron dendritic spines lost during stress exposure, decreased pathological baseline neuronal hyperactivity, and enhanced sensory-evoked cortical responses. Behavioral assays confirmed rescue of anxiety-like behavior and cognitive inflexibility.

Heinsbroek et al. (2023) reported in *Psychedelic Medicine* that tabernanthalog reduced motivation for both heroin and alcohol in a polydrug use model in rats, with effects persisting for up to 14 days after a single treatment [6]. This study extended the anti-addictive profile from single-substance models to the clinically relevant polydrug context.

Bhatt et al. (2024) characterized the off-target pharmacology of tabernanthalog at nicotinic acetylcholine receptors, demonstrating inhibition of α -7 (IC₅₀ approximately 10 micromolar) and α -9/ α -10 (IC₅₀ approximately 1.1 micro-

molar) subtypes through distinct mechanisms (noncompetitive and competitive, respectively), with 10- to 30-fold lower potency at GABAA receptors and CaV2.2 voltage-gated calcium channels [8].

Aarrestad et al. (2025) published in *Nature Neuroscience* the mechanistic dissociation between tabernanthalog-induced neuroplasticity and immediate early gene activation [4]. This study demonstrated that tabernanthalog promotes cortical spinogenesis through the canonical 5-HT_{2A}, TrkB, mTOR, and AMPA receptor pathway but, unlike psychedelics, does not induce an immediate glutamate burst or IEG expression. Selective ablation of TBG-induced dendritic spines abolished the antidepressant-like behavioral effect, establishing a causal link between structural neuroplasticity and sustained behavioral response.

A 2026 review in the *International Journal of Molecular Sciences* by Pereira et al. evaluated tabernanthalog as a scaffold for "silent neuroplasticity" and broad-spectrum therapy, synthesizing the literature on its genomic and transcriptomic effects [12].

3.4 Commercial development

Delix Therapeutics, a biotechnology company co-founded by David Olson and focused on psychoplastogen-based therapeutics, assigned tabernanthalog the development code DLX-007 and included it in its preclinical pipeline alongside the lead candidate DLX-001 (zalsupindole, later DLX-159) [13]. Delix announced plans for Phase 1 clinical trials of tabernanthalog in the first half of 2023; however, this timeline did not materialize, and the company prioritized advancement of DLX-001, which completed Phase 1 evaluation with positive safety and tolerability data. As of May 2026, tabernanthalog has not entered human clinical trials. No recent development updates have been publicly disclosed for the DLX-007 program specifically. The compound remains available from multiple commercial research chemical suppliers and continues to generate academic research publications at an increasing rate.

4. Mechanism of Action

Tabernanthalog is a multi-target serotonergic modulator and psychoplastogen. Its principal molecular activities, characterized in heterologous expression systems, primary neuronal cultures, and behavioral pharmacology, are partial agonism at the serotonin 5-HT_{2A} receptor; antagonism at the serotonin 5-HT_{2B} receptor; agonism at multiple additional serotonin receptor subtypes; inhibition of nicotinic acetylcholine receptors; and promotion of rapid structural neuroplasticity in cortical pyramidal neurons through TrkB/mTOR/AMPA receptor signaling.

4.1 Serotonin 5-HT_{2A} receptor partial agonism

The 5-HT_{2A} receptor is a G-protein-coupled receptor of the class A rhodopsin-like family, coupled primarily to G_q/11 and to beta-arrestin signaling pathways. It is expressed at high density on layer V pyramidal neurons of the prefrontal cortex, on hippocampal pyramidal cells, on claustrum neurons, and on thalamocortical projection neurons. It is the convergent molecular target for classical hallucinogenic psychedelics (LSD, psilocin, DMT, mescaline) and for the neuroplasticity-promoting effects of these compounds [9].

Tabernanthalog binds the 5-HT_{2A} receptor as a partial agonist, activating the receptor with lower intrinsic efficacy than full agonists such as serotonin or the classical psychedelics [1, 14]. The partial agonism is sufficient to engage the intracellular signaling cascade responsible for structural neuroplasticity (phospholipase C activation, inositol trisphosphate generation, intracellular calcium mobilization, TrkB transactivation, mTOR complex 1 activation, AMPA receptor trafficking to the postsynaptic density) but insufficient to drive the full hallucinogenic signaling cascade. The molecular basis of this dissociation has been characterized in the Aarrestad et al. (2025) study: tabernanthalog activates the 5-HT_{2A}/TrkB/mTOR/AMPA pathway without producing the immediate extracellular glutamate burst or the cortical IEG expression (c-Fos, Arc, Egr1) that accompany psychedelic 5-HT_{2A} activation [4]. The implication is that the hallucinogenic experience and the neuroplastogenic mechanism are separable at the level of 5-HT_{2A} re-

ceptor signaling, and that tabernanthalog exploits this separation through its specific pattern of receptor engagement (biased agonism or functionally selective partial agonism).

The behavioral confirmation of non-hallucinogenic 5-HT_{2A} engagement is the absence of the mouse head-twitch response, a 5-HT_{2A}-dependent stereotyped behavior that is the standard preclinical proxy for hallucinogenic activity [1]. Tabernanthalog does not produce the head-twitch response at any tested dose, in contrast to ibogaine, psilocin, and LSD, which produce dose-dependent head-twitch responses.

4.2 Serotonin 5-HT_{2B} receptor antagonism

Tabernanthalog acts as an antagonist at the serotonin 5-HT_{2B} receptor [1]. The 5-HT_{2B} receptor is expressed on cardiac valvular interstitial cells, on gastrointestinal smooth muscle, and on pulmonary endothelial cells. Chronic agonism at this receptor is the molecular mechanism of cardiac valvulopathy associated with fenfluramine, ergotamine, and pergolide. Antagonism at 5-HT_{2B} is therefore a favorable safety feature, particularly for a compound intended for chronic or repeated dosing, and distinguishes tabernanthalog from classical psychedelics (which have variable 5-HT_{2B} activity) and from ibogaine (which has partial agonist activity at 5-HT_{2B}).

4.3 Additional serotonin receptor activity

Tabernanthalog acts as an agonist at serotonin 5-HT_{1B}, 5-HT_{1F}, 5-HT_{2C}, and 5-HT₆ receptor subtypes [1]. The 5-HT_{1B} agonism is relevant to the antidepressant profile (5-HT_{1B} agonists modulate serotonergic autoreceptor function and have demonstrated antidepressant activity in preclinical models). The 5-HT_{2C} agonism may contribute to anxiolytic activity and to appetite modulation. The 5-HT₆ agonism may contribute to cognitive effects, as the 5-HT₆ receptor is expressed at high density in the striatum, hippocampus, and cortex and has been implicated in learning and memory. The functional significance of each of these secondary serotonergic activities to the overall behavioral profile of tabernanthalog has not been fully dissected through selective pharmacological antagonism studies.

4.4 Monoamine oxidase A inhibition and monoamine transporter activity

Tabernanthalog inhibits monoamine oxidase A (MAO-A) and interacts with the serotonin transporter (SERT) and the alpha-2A adrenergic receptor [1]. MAO-A inhibition elevates synaptic concentrations of serotonin, norepinephrine, and dopamine and is a well-established antidepressant mechanism. SERT interaction (whether inhibition or modulation) further supports serotonergic enhancement. The alpha-2A adrenergic activity may contribute to noradrenergic effects. The relative contribution of these monoaminergic mechanisms to the overall pharmacological profile, particularly in comparison to the 5-HT2A-driven neuroplasticity mechanism, has not been fully characterized.

4.5 Nicotinic acetylcholine receptor inhibition

Bhatt et al. (2024) characterized the pharmacology of tabernanthalog at nicotinic acetylcholine receptor subtypes expressed in *Xenopus* oocytes [8]. Tabernanthalog inhibited nicotinic receptors with the following selectivity profile: alpha-9/alpha-10 (IC₅₀ 1.1 plus or minus 0.1 micromolar) greater than alpha-7 (IC₅₀ 10.2 plus or minus 0.3 micromolar) greater than alpha-3/beta-2 (IC₅₀ 27.6 plus or minus 2.0 micromolar) approximately equal to alpha-3/beta-4 (IC₅₀ 31.4 plus or minus 1.8 micromolar). The mechanism of inhibition differed by subtype: alpha-7 inhibition was acetylcholine-concentration-independent and voltage-dependent, consistent with open-channel block or a noncompetitive mechanism; alpha-9/alpha-10 inhibition was acetylcholine-concentration-dependent and voltage-independent, consistent with competitive antagonism [8]. GABA_A receptor and CaV2.2 voltage-gated calcium channel inhibition occurred at 10- to 30-fold lower potency than nicotinic receptor inhibition. These off-target nicotinic and ion-channel activities occur at concentrations above those expected to be achieved at standard preclinical dosing for 5-HT2A-mediated neuroplasticity but may contribute to the compound's pharmacological profile at higher exposures.

4.6 Absence of ibogaine-associated liabilities

In contrast to the parent alkaloid ibogaine and its active metabolite noribogaine, tabernanthalog shows negligible interaction with the hERG (KCNH2) potassium channel, eliminating the molecular basis of ibogaine-associated QT prolongation and ventricular arrhythmia [1]. Tabernanthalog also shows negligible binding to

opioid receptors (mu, kappa, delta) and to the NMDA receptor, both of which are engaged by ibogaine and noribogaine and contribute to the complex and incompletely characterized pharmacology of the natural alkaloid [1]. The elimination of these interactions simplifies the pharmacological profile and reduces the risk of respiratory depression (opioid), dissociative effects (NMDA), and cardiac arrhythmia (hERG).

4.7 Neuroplasticity signaling pathway

The downstream signaling cascade through which tabernanthalog promotes structural neuroplasticity has been characterized in cortical neuron culture systems and in vivo. Activation of 5-HT_{2A} leads to Gq/11-mediated phospholipase C activation, intracellular calcium mobilization, and transactivation of the receptor tyrosine kinase TrkB (the high-affinity receptor for brain-derived neurotrophic factor). TrkB activation engages the PI3K/Akt/mTOR complex 1 (mTORC1) signaling axis, which promotes local protein synthesis at the dendritic spine. Concurrently, AMPA glutamate receptors are trafficked to the postsynaptic density, strengthening excitatory synaptic transmission [4, 9]. The net structural consequence is increased dendritic branching, increased dendritic spine density, and increased spine head diameter in layer V pyramidal neurons of the prefrontal cortex, effects that persist for at least 12 days after a single dose in rodent models and that reverse the dendritic atrophy produced by chronic stress [4, 5].

The critical mechanistic distinction from classical psychedelics is that tabernanthalog achieves this structural remodeling without producing an immediate extracellular glutamate burst in the cortex (as measured by microdialysis or by glutamate-sensing fluorescent indicators) and without activating the immediate early gene program (c-Fos, Arc, Egr1) in cortical neurons [4]. This dissociation suggests that the glutamate burst and IEG activation that accompany psychedelic experiences are correlates of the subjective hallucinogenic state rather than requirements for structural neuroplasticity per se.

5. Pharmacokinetics and Routes of Administration

5.1 General considerations

Detailed human pharmacokinetic data for tabernanthalog are not available, as the compound has not entered clinical trials. The available pharmacokinetic characterization is derived from rodent studies (mouse and rat) conducted at the Olson laboratory and by collaborating groups. The summary below reflects preclinical pharmacokinetic parameters.

5.2 Absorption and administration

Tabernanthalog has been administered to rodents by intraperitoneal injection and by oral gavage. The compound is water-soluble as the fumarate salt and does not require organic co-solvents for parenteral or oral administration, a practical advantage over ibogaine (which has limited water solubility) [1]. Intraperitoneal administration at doses of 10 to 50 mg/kg in mice has been the standard route in the majority of published behavioral studies. Oral bioavailability has been characterized in rodents but detailed values (fraction absorbed, first-pass extraction) have not been published in the primary literature. The behavioral efficacy observed after oral gavage in the Lu et al. (2021) stress model study confirms that oral bioavailability is sufficient for pharmacological activity at tested doses [5].

5.3 Distribution

Tabernanthalog crosses the blood-brain barrier in rodents, as confirmed by the central nervous system pharmacological effects observed after systemic administration (dendritic spine changes in prefrontal cortex, cortical neuron calcium activity modulation, behavioral effects consistent with central 5-HT_{2A} engagement) [1, 4, 5]. Specific brain-to-plasma ratios, volume of distribution, and plasma protein binding values have not been published.

5.4 Metabolism

The metabolic pathways of tabernanthalog in rodents have not been comprehensively published. Given the indole-containing structure and the methoxy substituent, plausible metabolic transformations include O-demethylation (analogous to the CYP2D6-mediated O-demethylation of ibogaine to noribogaine), ring hydroxylation, and N-dealkylation. The presence or absence of active metabolites has not been established.

5.5 Elimination

Plasma elimination half-life and clearance values in rodents have not been published in detail. The behavioral pharmacology literature indicates that the effects of a single dose persist for at least 24 hours (forced swim test and sucrose preference endpoints), for at least 7 to 14 days (heroin self-administration and relapse endpoints), and that structural neuroplasticity (dendritic spine density increases) persists for at least 12 days [4, 5, 6]. These durations substantially exceed the expected plasma residence time of the compound and are consistent with a mechanism in which the transient pharmacological signal triggers sustained structural remodeling that outlasts the presence of the drug.

5.6 Routes of administration

The two routes used in published preclinical work are intraperitoneal injection (the most common) and oral gavage. Subcutaneous and intravenous routes have not been reported in the published literature. For in vitro neuroplasticity assays, the compound is applied in aqueous solution at concentrations of 1 to 100 micromolar [1, 4].

6. Preclinical Pharmacology

6.1 Neuroplasticity

The foundational preclinical observation for tabernanthalog is the promotion of structural neuroplasticity in cortical neurons. In rat embryonic cortical neuron cultures, tabernanthalog at 10 micromolar increased dendritic branch number and total dendritic length comparably to ibogaine, LSD, and DMT [1]. In vivo, tabernanthalog at 10 to 30 mg/kg intraperitoneal in mice increased dendritic spine density in layer V pyramidal neurons of the prefrontal cortex, with effects persisting for up to 12 days [4, 5]. The dendritic spines formed after tabernanthalog treatment are morphologically mature (mushroom-type) and are incorporated into functional synaptic circuits, as demonstrated by enhanced whisking-modulated sensory processing in somatosensory cortex after tabernanthalog treatment in stressed mice [5].

6.2 Antidepressant-like activity

Tabernanthalog reduced immobility time in the mouse forced swim test after a single dose, an effect that is the standard preclinical proxy for antidepressant-like activity [1]. In the unpredictable mild stress model (Lu et al., 2021), a single dose of tabernanthalog rescued sucrose preference deficits (a measure of anhedonia), reduced anxiety-like behavior in the elevated plus maze, and restored cognitive flexibility in reversal learning tasks [5]. The antidepressant-like behavioral effect was abolished when the TBG-induced dendritic spines were selectively ablated using an optogenetic shrinkage approach, establishing that structural neuroplasticity is causally required for the sustained behavioral response [4].

6.3 Anti-addictive activity

Cameron et al. (2020) reported that tabernanthalog reduced alcohol consumption in the drinking-in-the-dark binge drinking model in mice and reduced heroin self-administration in a rat self-administration paradigm [1]. A single dose reduced

heroin-seeking behavior with effects persisting for multiple days. In cue-induced relapse experiments, tabernanthalog treatment reduced relapses for a period lasting up to 14 days after a single administration.

Heinsbroek et al. (2023) extended the anti-addictive profile to a polydrug use model in which rats self-administered both heroin and alcohol [6]. Tabernanthalog significantly reduced break points (a measure of motivation for drug seeking) for both heroin and alcohol on progressive ratio schedules. The polydrug finding is clinically relevant because substance use disorders frequently involve multiple substances, and a treatment effective across substances would have greater translational utility than a substance-specific intervention.

6.4 Stress reversal and neural circuit restoration

Lu et al. (2021) published in *Molecular Psychiatry* the most comprehensive preclinical characterization of tabernanthalog's effects on stress-disrupted neural circuits [5]. Mice were exposed to an unpredictable mild stress protocol that produced anxiety-like behavior, cognitive inflexibility, anhedonia, dendritic spine loss in somatosensory and prefrontal cortex, increased baseline neuronal activity (hyperexcitability), and impaired sensory-evoked cortical responses. A single dose of tabernanthalog (administered after the stress protocol was complete) produced the following effects: regrowth of excitatory neuron dendritic spines lost during stress; decreased pathological baseline neuronal hyperactivity; enhanced whisking-modulated sensory processing; rescue of anxiety-like behavior; and rescue of cognitive inflexibility. Two-photon longitudinal imaging confirmed that the dendritic spine regrowth was sustained and that the new spines were incorporated into functional circuits.

6.5 Pain models

Tabernanthalog has demonstrated efficacy in preclinical models of neuropathic and visceral pain, extending the therapeutic scope beyond depression and addiction [12]. The analgesic activity is plausibly related to the serotonergic modulation of descending pain pathways and to the neuroplasticity-mediated restoration of cortical pain-processing circuits.

6.6 Cognitive impairment

Preliminary evidence suggests efficacy in the rescue of cognitive deficits associated with cancer-related cognitive impairment in rodent models [12]. This application is mechanistically consistent with the neuroplasticity-promoting profile and the established role of dendritic spine density in cognitive function.

6.7 Absence of hallucinogenic-like behavior

At all doses tested (up to 50 mg/kg intraperitoneal in mice), tabernanthalog did not produce the head-twitch response [1]. The compound also did not produce conditioned place preference or conditioned place aversion at the doses tested for anti-addictive efficacy, suggesting low abuse liability and no rewarding or aversive subjective properties.

7. Clinical Evidence Base

7.1 Current status

As of May 2026, tabernanthalog has not entered human clinical trials. Delix Therapeutics assigned the development code DLX-007 and announced plans for Phase 1 clinical evaluation in the first half of 2023, but this timeline was not met [13]. The company's publicly disclosed clinical focus has been on the related psychoplastogen zalsupindole (DLX-001, subsequently DLX-159), which completed Phase 1 evaluation with positive safety and tolerability data in healthy volunteers.

7.2 Clinical translation considerations

The preclinical evidence base for tabernanthalog supports potential clinical development in major depressive disorder, treatment-resistant depression, post-traumatic stress disorder, opioid use disorder, alcohol use disorder, and polydrug substance use disorder. The mechanistic basis (5-HT_{2A}-driven cortical neuroplasticity) is shared with the classical psychedelics that have demonstrated efficacy in clinical trials (psilocybin for treatment-resistant depression and major depressive disorder, MDMA-assisted therapy for post-traumatic stress disorder), but tabernanthalog's non-hallucinogenic profile would eliminate the requirement for prolonged supervised sessions that currently limit the scalability of psychedelic-assisted therapy.

7.3 Regulatory pathway

Tabernanthalog is not a scheduled substance in the United States as of May 2026. The compound is structurally distinct from ibogaine (which is Schedule I in the United States) and from the classical psychedelics. The regulatory pathway for clinical development would follow standard investigational new drug (IND) application procedures, with the requirement for comprehensive preclinical toxicology, pharmacokinetics, and safety pharmacology data prior to first-in-human dosing.

8. Sourcing and Quality Verification

Research-grade tabernanthalog is supplied by multiple chemical and pharmaceutical research suppliers. The principal commercial sources include Sigma-Aldrich (catalog number SML3134, as the fumarate salt, greater than or equal to 98 percent purity by HPLC), Tocris Bioscience, Cayman Chemical, MedChemExpress, TargetMol, Biosynth, DC Chemicals, and several additional suppliers [15]. The compound is available in milligram to gram quantities, primarily as the fumarate salt. Pricing is moderate for a research-grade small molecule, typically in the range of \$100 to \$500 per 50 mg of pharmaceutical-grade research material.

Pharmaceutical-grade tabernanthalog is not commercially available, as the compound has not been formulated for clinical use.

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

- High-performance liquid chromatography area-percent purity (target: greater than or equal to 98 percent)
- Mass spectrometry confirmation of molecular weight (231.15 for the protonated free base $[M+H]^+$)
- Proton and carbon-13 nuclear magnetic resonance spectroscopy confirmation of structure
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical confirmation (Janoshik Analytical or equivalent) is recommended for investigations where dose-response precision is important. The tabernanthalog research chemical market is established and growing; lot-to-lot variability may be observed across suppliers, and on-receipt analytical confirmation is appropriate.

9. Reconstitution and Handling

Tabernanthalog fumarate is freely soluble in water at room temperature. For in vivo research applications, the compound is reconstituted in sterile normal saline or phosphate-buffered saline at concentrations of 1 to 10 mg/mL without the requirement for organic co-solvents [1]. For in vitro applications, stock solutions of 10 to 100 mM may be prepared in dimethyl sulfoxide (DMSO) for subsequent dilution into aqueous media; the final DMSO concentration in the assay should be maintained below 0.1 percent to avoid vehicle effects.

Storage of the solid compound should be at minus 20 degrees Celsius in a desiccated container protected from light. Aqueous stock solutions should be prepared fresh for each experiment or aliquoted for single-use storage at minus 20 degrees Celsius. The stability of aqueous solutions under various conditions (temperature, pH, light exposure) has not been comprehensively published; investigators should treat the compound as moderately sensitive and minimize storage of reconstituted solutions.

Lyophilized or powdered material should be equilibrated to room temperature in a desiccator before opening the vial to minimize condensation-related degradation. Aliquoting into single-use quantities is recommended to avoid repeated freeze-thaw cycles of stock solutions.

The compound is not classified as hazardous under standard chemical safety frameworks; however, standard laboratory personal protective equipment (gloves, lab coat, eye protection) should be used during handling. The compound is biologically active at low concentrations and should be handled with appropriate precautions against dermal absorption and inhalation.

10. Stack Interactions and Combinations

Tabernanthalog has a multi-target pharmacological profile, and interactions with other compounds should be considered in research contexts involving combination dosing or in animals receiving concurrent pharmacological treatments.

Serotonergic agents: Concurrent administration with serotonin reuptake inhibitors (SSRIs, SNRIs), monoamine oxidase inhibitors, or other serotonergic compounds (triptans, tramadol, lithium) should be approached with caution owing to the potential for additive serotonergic stimulation. The MAO-A inhibitory activity of tabernanthalog raises theoretical serotonin syndrome risk in combination with other serotonergic agents, although this has not been characterized in published studies.

Other 5-HT_{2A} agonists: Concurrent administration with classical psychedelics (psilocybin, LSD, DMT), other psychoplastogens (zalsupindole, 5-MeO-DMT), or 5-HT_{2A} agonist research compounds produces additive or competitive effects at the 5-HT_{2A} receptor. The combination has research utility for mechanistic dissection but is unlikely to be therapeutically productive and may produce unpredictable behavioral phenotypes.

5-HT_{2A} antagonists: The 5-HT_{2A} antagonists ketanserin and volinanserin block the neuroplastogenic and behavioral effects of tabernanthalog, confirming the 5-HT_{2A} dependence of the mechanism [1, 4]. Concurrent administration of 5-HT_{2A} antagonists (including atypical antipsychotics with 5-HT_{2A} inverse agonist activity, such as risperidone, olanzapine, clozapine, quetiapine) would be expected to attenuate or abolish the neuroplastogenic effects of tabernanthalog.

Nicotinic agents: Given the inhibition of alpha-7 and alpha-9/alpha-10 nicotinic receptors at low-micromolar concentrations [8], concurrent administration with nicotinic agonists (varenicline, nicotine) or with alpha-7 nicotinic positive allosteric modulators may produce pharmacological interactions. The clinical significance is uncertain at therapeutic doses of tabernanthalog.

mTOR inhibitors: Rapamycin and other mTORC1 inhibitors block the neuroplastic effects of tabernanthalog (and of all characterized psychoplastogens), abolishing dendritic spine formation and the associated behavioral effects [4, 9]. Concurrent treatment with mTOR inhibitors (rapamycin, everolimus, temsirolimus) in oncology or transplant contexts would be expected to abolish the therapeutic mechanism of tabernanthalog.

TrkB signaling modulators: The TrkB receptor kinase is a required node in the tabernanthalog neuroplasticity pathway. Concurrent treatment with TrkB inhibitors would attenuate the neuroplastic effect; concurrent treatment with TrkB agonists (7,8-dihydroxyflavone, LM22A-4) or with BDNF-enhancing compounds may produce additive or synergistic neuroplastic effects.

QT-prolonging agents: Tabernanthalog itself does not block the hERG potassium channel and is not expected to prolong the QT interval [1]. The compound therefore does not carry the same QT-prolongation interaction risk as ibogaine. However, in the absence of clinical cardiac safety data, caution is appropriate with concurrent QT-prolonging agents until human safety pharmacology is established.

11. Adverse Events and Safety

11.1 Preclinical safety profile

The preclinical safety profile of tabernanthalog is favorable relative to ibogaine. The principal safety advantages are the absence of hERG potassium channel blockade (eliminating the cardiac arrhythmia risk), the absence of hallucinogenic activity (eliminating the requirement for prolonged supervision and the risk of psychological adverse events), and the absence of significant opioid and NMDA receptor interaction (eliminating respiratory depression and dissociative risks) [1].

11.2 Cardiac safety

Tabernanthalog was rationally designed to eliminate the hERG channel interaction that produces ibogaine-associated QT prolongation and fatal cardiac arrhythmia [1]. In the Cameron et al. (2020) characterization, tabernanthalog did not block hERG channels at concentrations that produce full 5-HT_{2A} receptor engagement. This is the most significant safety differentiation from the parent alkaloid ibogaine, which has been associated with at least 30 reported fatalities in clinical and non-clinical settings, with QT prolongation and ventricular arrhythmia as the principal mechanism [10, 11].

11.3 Behavioral safety

Tabernanthalog does not produce the head-twitch response (the preclinical proxy for hallucinogenic activity) at any tested dose [1]. It does not produce conditioned place preference or conditioned place aversion, suggesting low abuse liability. Gross behavioral observation in rodents at pharmacologically active doses has not revealed sedation, ataxia, or seizure activity in published reports.

11.4 Nicotinic and ion channel off-targets

The nicotinic acetylcholine receptor inhibition (alpha-7 IC₅₀ approximately 10 micromolar, alpha-9/alpha-10 IC₅₀ approximately 1.1 micromolar) and the lower-potency GABAA and CaV2.2 inhibition represent off-target activities that could pro-

duce adverse effects at supratherapeutic exposures [8]. The alpha-7 inhibition at 10 micromolar is within an order of magnitude of the concentrations used in in vitro neuroplasticity assays (10 micromolar), raising the possibility that alpha-7 nicotinic blockade contributes to the in vitro phenotype and may contribute to in vivo effects at higher doses.

11.5 5-HT2B safety consideration

The 5-HT2B antagonist activity of tabernanthalog is a favorable safety feature [1]. Chronic agonism at the 5-HT2B receptor is the molecular mechanism of drug-induced cardiac valvulopathy (as observed with fenfluramine, pergolide, and cabergoline at high cumulative exposures). The antagonist profile at 5-HT2B suggests that chronic tabernanthalog administration would not carry this risk. This is a differentiating advantage over ibogaine (which has mixed 5-HT2B activity) and over some psychedelic analogs with uncharacterized 5-HT2B pharmacology.

11.6 Limitations of the safety database

The safety profile of tabernanthalog is based entirely on preclinical studies in rodents and on in vitro receptor and channel assays. No human safety data exist. Comprehensive preclinical toxicology studies (14-day and 28-day repeat-dose toxicology, genotoxicity, reproductive toxicology, safety pharmacology including cardiovascular, respiratory, and central nervous system assessment) have not been published, although they may have been conducted by Delix Therapeutics as part of the IND-enabling program. The compound should be treated as an investigational research chemical with an incompletely characterized safety profile. Investigators should exercise standard precautions for biologically active research compounds.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds against tabernanthalog, evaluated on five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal compounds in the psychoplastogen, ibogaine analog, and non-hallucinogenic serotonergic neuroplasticity space with substantive published pharmacology.

12.1 Ibogaine

Mechanism: Multi-target indole alkaloid with complex pharmacology including 5-HT_{2A} agonism, NMDA receptor antagonism, kappa and mu opioid receptor activity, sigma receptor binding, nicotinic acetylcholine receptor inhibition, and hERG potassium channel blockade [10, 11]. The natural alkaloid from which tabernanthalog was derived.

Development trajectory: Ibogaine has been used in non-clinical settings for opioid detoxification for decades. It is classified as Schedule I in the United States. Several clinical trials have been conducted or are ongoing in jurisdictions where ibogaine is legal (Brazil, Mexico, New Zealand). A recent observational study (Noller et al., 2018) in New Zealand reported reduced opioid withdrawal symptoms and reduced opioid use at follow-up [16]. However, the compound has not been approved by any major regulatory authority, and clinical development is constrained by the cardiac safety concerns.

Novelty: Low. Ibogaine is the prototype compound; tabernanthalog and all ibogalogs derive from it.

Effect size: Substantial in anecdotal and observational reports for opioid use disorder; the effect size in controlled trials is less well characterized owing to the difficulty of conducting blinded trials with a strongly hallucinogenic compound.

Promising potential: Moderate. Legal and regulatory barriers, cardiac safety concerns, and the intense hallucinogenic experience limit scalability. Clinical development is proceeding slowly in permissive jurisdictions.

Side-effect profile: Poor. hERG blockade produces QT prolongation with reported fatalities. Intense hallucinogenic experience lasting 24 to 48 hours. Nausea, ataxia, and tremor are common. NMDA antagonism produces dissociative effects. Opioid activity contributes to complex pharmacokinetic-pharmacodynamic interactions.

Overall validation: Moderate. Decades of observational and anecdotal evidence; limited controlled clinical data; significant safety concerns.

Comparison to tabernanthalog: Tabernanthalog was specifically engineered to retain ibogaine's neuroplastic and anti-addictive properties while eliminating the hERG blockade, hallucinogenic activity, and opioid/NMDA receptor interactions. The trade-off is the loss of ibogaine's complex multi-target pharmacology, which may contribute to its unique efficacy profile for opioid withdrawal, and the loss of ibogaine's direct opioid receptor activity, which may be relevant to the acute anti-withdrawal effect. Tabernanthalog's advantage is a dramatically improved safety profile and a simplified pharmacology amenable to standard drug development.

12.2 Noribogaine (12-hydroxyibogamine)

Mechanism: Active metabolite of ibogaine, formed by CYP2D6-mediated O-demethylation. Pharmacology substantially overlaps with ibogaine: NMDA antagonism, opioid receptor binding (higher affinity at mu and kappa receptors than ibogaine), serotonin transporter inhibition, and hERG channel blockade [17]. Plasma half-life substantially longer than ibogaine (approximately 24 to 49 hours versus 4 to 7 hours for ibogaine).

Development trajectory: DemeRx (now atai Life Sciences subsidiary) advanced noribogaine through Phase 1 clinical trials for opioid use disorder. Phase 1 data demonstrated dose-related QTc prolongation, prompting careful dose optimization. The compound has been explored as a potentially safer alternative to ibogaine on the basis of a somewhat different receptor binding profile, but the hERG blockade remains a concern.

Novelty: Low. Active metabolite of a known compound.

Effect size: Moderate in preclinical opioid withdrawal and self-administration models.

Promising potential: Low to moderate. The QTc prolongation observed in Phase 1 constrains the therapeutic window.

Side-effect profile: Moderate to poor. QTc prolongation comparable to or less severe than ibogaine, but still present. No hallucinogenic effects at moderate doses (an advantage over ibogaine).

Overall validation: Low to moderate. Phase 1 human data available; QTc liability constrains development.

Comparison to tabernanthalog: Noribogaine retains the hERG liability that tabernanthalog was designed to eliminate. Noribogaine has human clinical data that tabernanthalog lacks. Noribogaine's opioid receptor activity may provide anti-withdrawal effects that tabernanthalog does not; tabernanthalog's mechanism operates through neuroplasticity rather than direct opioid modulation.

12.3 Zalsupindole (DLX-001, DLX-159)

Mechanism: Non-hallucinogenic psychoplastogen developed by Delix Therapeutics. Mechanism involves 5-HT_{2A} receptor engagement and promotion of structural neuroplasticity, similar to tabernanthalog. Detailed receptor binding profile has not been fully published [13].

Development trajectory: Lead clinical candidate for Delix Therapeutics. Completed Phase 1 clinical evaluation in healthy volunteers with positive safety and tolerability data. The company has announced plans for Phase 2 development. Zalsupindole is the most clinically advanced non-hallucinogenic psychoplastogen in development as of May 2026.

Novelty: High. Novel chemical entity in a novel therapeutic class.

Effect size: Preclinical effect sizes comparable to tabernanthalog in published models; clinical effect size not yet established.

Promising potential: High. Most advanced compound in the psychoplastogen class, with Phase 1 complete and Phase 2 planned.

Side-effect profile: Phase 1 data reported positive safety and tolerability. Detailed adverse-event profile not publicly available.

Overall validation: Moderate to high. Phase 1 human safety data available; pre-clinical efficacy data published.

Comparison to tabernanthalog: Zalsupindole and tabernanthalog are from the same research program (Olson laboratory, Delix Therapeutics) and share the psychoplastogen mechanism. Zalsupindole has been prioritized for clinical development and has human safety data; tabernanthalog has the larger published preclinical research literature. The two compounds are complementary within the Delix pipeline.

12.4 18-Methoxycoronaridine (18-MC)

Mechanism: Semi-synthetic iboga alkaloid analog that selectively targets the α -3/ β -4 nicotinic acetylcholine receptor with reduced hERG channel affinity compared to ibogaine [18]. Unlike tabernanthalog, 18-MC's primary mechanism is nicotinic rather than serotonergic.

Development trajectory: MindMed (formerly Savant HWP) advanced 18-MC through preclinical and early clinical development for substance use disorders. The compound has demonstrated anti-addictive efficacy in multiple preclinical models (morphine, nicotine, methamphetamine, alcohol self-administration). Phase 1/2 clinical trials have been initiated for opioid use disorder.

Novelty: Moderate. A structurally modified iboga alkaloid with a differentiated mechanism (nicotinic rather than serotonergic).

Effect size: Moderate in preclinical addiction models; clinical effect size not yet established.

Promising potential: Moderate. Clinical development is proceeding but has not produced Phase 2 efficacy data.

Side-effect profile: Moderate. Reduced cardiac risk relative to ibogaine; the compound is non-hallucinogenic. Detailed clinical adverse-event data not publicly available.

Overall validation: Low to moderate. Early clinical development; preclinical evidence base moderate.

Comparison to tabernanthalog: 18-MC and tabernanthalog represent different mechanistic approaches to non-toxic ibogaine analog development. 18-MC targets nicotinic receptors; tabernanthalog targets serotonergic receptors and neuroplasticity. 18-MC has entered clinical trials; tabernanthalog has not. The compounds address overlapping indications (substance use disorders) but through different molecular mechanisms.

12.5 Psilocybin

Mechanism: Classical hallucinogenic psychedelic; prodrug of psilocin, a non-selective 5-HT_{2A/2C} agonist. Promotes cortical neuroplasticity through the same 5-HT_{2A}/TrkB/mTOR pathway as tabernanthalog, but with full agonism producing hallucinogenic signaling, glutamate burst, and IEG activation [9].

Development trajectory: The most clinically advanced psychedelic compound. COMPASS Pathways received FDA Breakthrough Therapy Designation for psilocybin therapy in treatment-resistant depression. Usona Institute has conducted Phase 2 trials for major depressive disorder. Multiple Phase 3 trials are ongoing or completed.

Novelty: Low as a compound (ancient natural product); high as a clinical paradigm (psychedelic-assisted therapy).

Effect size: Large. Phase 2 trials in treatment-resistant depression and major depressive disorder have reported effect sizes of Cohen's *d* approximately 1.0 to 1.5 on depression rating scales, among the largest reported for any psychiatric intervention.

Promising potential: High. Multiple Phase 3 programs; FDA Breakthrough Therapy Designation; broad regulatory and academic interest.

Side-effect profile: Moderate. The hallucinogenic experience is the principal safety and scalability concern. Physical adverse events are mild (headache, nausea, transient anxiety). The requirement for prolonged supervised sessions (6 to 8 hours per administration) limits scalability and increases treatment cost.

Overall validation: High. The most extensively validated psychoplastogenic compound, with large-scale clinical trial data.

Comparison to tabernanthalog: Psilocybin and tabernanthalog share the 5-HT2A/TrkB/mTOR neuroplasticity mechanism but differ fundamentally in the hallucinogenic liability. Psilocybin has vastly more clinical validation, including Phase 3 trial data and Breakthrough Therapy Designation. Tabernanthalog's potential advantage is the elimination of the hallucinogenic experience, which would enable scalable administration without supervised sessions. The unresolved scientific question is whether the hallucinogenic experience itself contributes to the therapeutic effect beyond the structural neuroplasticity; the Aarrestad et al. (2025) data suggest that neuroplasticity is causally sufficient for antidepressant-like effects in rodents, but the human translation of this finding is unknown.

12.6 Comparator summary

The five comparators occupy distinct positions in the psychoplastogen and ibogaine-analog landscape. **Ibogaine** is the prototype with the strongest anecdotal anti-addictive evidence but the most severe safety liabilities. **Noribogaine** represents an incremental improvement over ibogaine with reduced but persistent cardiac risk. **Zalsupindole** is the closest mechanistic comparator to tabernanthalog and the most clinically advanced non-hallucinogenic psychoplastogen. **18-Methoxycoronaridine** offers a nicotinic-mechanism alternative to the serotonergic approach. **Psilocybin** is the most clinically validated psychoplastogenic compound but requires hallucinogenic-assisted therapy infrastructure.

Tabernanthalog occupies a position of strong preclinical validation with a uniquely well-characterized mechanism of non-hallucinogenic neuroplasticity. Its principal advantage over ibogaine and noribogaine is the elimination of cardiac and hallucinogenic risk. Its principal advantage over psilocybin is the non-hallucinogenic profile that could enable scalable, unsupervised administration. Its principal disadvantage relative to all comparators except zalsupindole is the complete absence of human clinical data. The compound's future positioning depends on whether Delix Therapeutics or another sponsor advances tabernanthalog (or a derivative) into clinical trials, and on whether the non-hallucinogenic neuroplasticity mechanism demonstrated in rodents translates to human therapeutic efficacy comparable to the hallucinogenic psychedelics.

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cific data are sparse; investigators should weight the evidence accordingly. Investigators should obtain analytical confirmation of identity and purity on every lot and should exercise standard precautions for biologically active research compounds.