

RESEARCH MONOGRAPH . COMPOUND PROFILE

Ibogainalog

A simplified tricyclic ibogaine analog and potent 5-HT_{2A} receptor agonist with psychoplastogenic, antidepressant, and analgesic activity, distinguished from the parent iboga alkaloids by dramatically reduced cardiotoxicity, absence of opioid receptor engagement, and retained promotion of structural neural plasticity.

DOCUMENT	KDC-MN-1593
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Non-selective serotonin receptor modulator, psychoplastogen, and ibogaine-derived tricyclic azepinoindole analog

ABSTRACT

Ibogainalog (IBG; 9-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole; CAS 802581-10-8) is a synthetic tricyclic azepinoindole and a structurally simplified analog of the iboga alkaloid ibogaine, first described in the chemical literature by Hester and colleagues in the late 1960s and subsequently characterized in pharmacological detail by the Olson laboratory at the University of California, Davis, beginning in 2020. The compound belongs to the ibogalog structural class, a family of substituted hexahydroazepino[4,5-b]indoles that retain the fused indole-azepine core of the iboga alkaloids while eliminating the isoquinuclidine ring system, yielding a dramatically simplified molecular architecture that is amenable to practical gram-scale synthesis. Ibogainalog is a non-selective serotonin receptor modulator with potent agonist activity at the 5-HT_{2A} receptor (K_i approximately 670 nM; functional EC₅₀ 18 to 85 nM, 55 to 93 percent efficacy), the 5-HT₆ receptor (EC₅₀ 7.1 to 8.8 nM, 83 to 99 percent efficacy), the 5-HT_{1F} receptor (EC₅₀ 35 nM, 85 percent efficacy), and the 5-HT_{1B} receptor (EC₅₀ 170 nM, 76 percent efficacy), with additional inverse agonist activity at the 5-HT₇ receptor (EC₅₀ 335 nM) and mixed agonist-antagonist activity at the 5-HT_{2B} and 5-HT_{2C} receptors. The compound is a moderate serotonin reuptake inhibitor (SERT IC₅₀ approximately 400 nM) with selectivity over the norepinephrine and dopamine transporters, and a noncompetitive inhibitor of the α -7 nicotinic acetylcholine receptor (IC₅₀ approximately 11.4 micromolar) and a competitive inhibitor of the α -9- α -10 nicotinic acetylcholine receptor (IC₅₀ approximately 2.9 micromolar). Critically, ibogainalog exhibits dramatically reduced

potency at the hERG potassium channel relative to ibogaine (approximately 10-fold reduction), conferring a substantially improved cardiac safety profile; this is a principal design objective of the ibogalog class, given that ibogaine-associated QT prolongation and fatal cardiac arrhythmias have been a central safety concern limiting the clinical translation of ibogaine itself. The compound shows no agonist activity at opioid receptors, distinguishing it from the active ibogaine metabolite noribogaine. In preclinical behavioral models, ibogainalog at 10 mg/kg produces sustained antidepressant-like activity (persisting 72 hours in naive mice and 48 hours in chronically stressed mice) through a volinanserin-sensitive, 5-HT_{2A} receptor-dependent serotonergic mechanism. The compound also produces dose-dependent antinociceptive activity in chronic constriction injury models of neuropathic pain and in dextran sulfate sodium-induced colitis models of visceral pain, with the longest antihyperalgesic duration among tested ibogalogs at comparatively lower doses. Analgesic activity is abolished by the 5-HT_{2A} receptor antagonist ketanserin and involves synergistic crosstalk between 5-HT_{2A} and metabotropic glutamate type 2 (mGlu₂) receptors. As a psychoplastogen, ibogainalog promotes dendritic arborization and spinogenesis in cortical neurons at levels comparable to ibogaine, an activity mediated through 5-HT_{2A} receptor signaling. Unlike the closely related ibogalog tabernanthalog, ibogainalog produces a measurable head-twitch response in rodent models, suggesting that it may retain psychedelic activity in humans, though the response magnitude is substantially reduced relative to classical psychedelics such as 5-methoxy-N,N-dimethyltryptamine. The compound is not in clinical development as of the date of this monograph; all evidence is preclinical. This monograph reviews the chemistry, synthesis,

and structural class of ibogainalog; its multi-receptor serotonergic and nicotinic pharmacology; the available pharmacokinetic inference from the ibogalog class; the preclinical evidence base across antidepressant, analgesic, anti-addictive, and psychoplastogenic endpoints; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal from preclinical safety pharmacology; and a comparative assessment of five structurally or mechanistically related compounds against ibogainalog on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Recommended name: Ibogainalog.

Abbreviation: IBG.

Synonyms: 9-Methoxyibogaminalog; 9-MeO-ibogaminalog.

Chemical Abstracts Service registry number: 802581-10-8.

International Union of Pure and Applied Chemistry name: 9-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole.

Parent compound: Ibogaine (12-methoxyibogamine). Ibogainalog is the simplified tricyclic analog of ibogaine in which the isoquinuclidine (azabicyclo[2.2.2]octane) ring system has been removed, leaving only the fused indole-tetrahydroazepine core with the 9-methoxy substituent retained from the parent alkaloid [1, 2].

Development context: Ibogainalog was designated as compound IBG in the Cameron et al. (2021) Nature publication and is referenced as IBG throughout the subsequent Arias laboratory publications [1, 3, 4, 5, 6]. The compound does not carry a pharmaceutical development code or an International Nonproprietary Name.

1.2 Structural class and chemistry

Ibogainalog is a member of the ibogalog structural class, defined as substituted 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles [2]. The ibogalogs are tricyclic cyclized tryptamines that retain the fused indole and partially saturated seven-membered azepine ring of the iboga alkaloid skeleton but lack the bridged isoquinuclidine ring that constitutes the defining tetracyclic or pentacyclic architecture of ibogaine, catharanthine, tabernanthine, and related monoterpenoid indole alkaloids. The structural simplification renders ibogainalog a conformationally restricted

analog of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), with the azepine ring constraining the tryptamine side chain into a defined orientation relative to the indole nucleus [1, 2].

Molecular formula: C₁₄H₁₈N₂O (free base).

Molecular weight: 230.311 g/mol (free base).

Physical properties: The free base is a solid. The fumarate salt is the standard research preparation and is soluble at concentrations of 40 mg/mL in 0.9 percent normal saline, representing a substantial improvement over ibogaine hydrochloride, which is essentially insoluble in aqueous solution even with co-solvents [1].

Central nervous system multiparameter optimization (CNS MPO) score: 5.2 (on a 0 to 6 scale where 6 is optimal), compared to 3.8 for ibogaine [1]. The improved CNS MPO score reflects the reduced molecular weight, improved aqueous solubility, and favorable predicted physicochemical properties for blood-brain barrier penetration.

Stereochemistry: The compound as synthesized and characterized in the published literature is racemic at the C-3 position bearing the N-methyl group. Enantiomeric resolution and stereospecific pharmacology have not been reported.

1.3 Synthesis

The synthesis of ibogainalog proceeds through a multi-step route involving Caglioti reduction of an appropriate azepinoindole precursor, as described in the Cameron et al. (2021) report [1]. The synthetic route is substantially more practical than the total synthesis or semisynthesis of ibogaine, which requires either extraction from *Tabernanthe iboga* root bark (a limited natural source) or a complex 8- to 15-step synthetic sequence. The simplified tricyclic skeleton of ibogainalog eliminates the need for construction of the bridged isoquinuclidine ring, which is the principal synthetic challenge in ibogaine total synthesis. The closely related ibogalog tabernanthalog (TBG; 8-methoxy positional isomer of ibogainalog) can be synthesized in a single step via Fischer indole cyclization and has been prepared at gram scale [1]. Ibogainalog synthesis requires additional steps relative to tabernanthalog but remains practical at the multi-gram scale for research applications. The fumarate salt is prepared by treatment of the free base with fumaric acid and recrystallization.

2. Abstract

Ibogainalog (IBG; 9-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole) is a synthetic tricyclic psychoplastogen and non-selective serotonin receptor modulator of the ibogalog class, characterized as a potent 5-HT_{2A} receptor agonist with additional high-efficacy activity at the 5-HT₆, 5-HT_{1F}, and 5-HT_{1B} serotonin receptor subtypes [1, 3, 7]. The compound was first described in the chemical literature by Hester and colleagues in the late 1960s as part of exploratory azepinoindole chemistry and was subsequently rediscovered, resynthesized, and comprehensively characterized by the Olson laboratory at the University of California, Davis, as part of a function-oriented synthesis campaign to develop ibogaine analogs with retained therapeutic potential and improved safety profiles [1, 8].

The principal design rationale for the ibogalog class is the elimination of the two most significant liabilities of ibogaine as a therapeutic candidate: (a) cardiotoxicity secondary to potent hERG potassium channel inhibition (ibogaine IC₅₀ approximately 1 micromolar), which has been associated with QT prolongation, torsade de pointes, and fatal cardiac arrhythmias in clinical and ceremonial settings; and (b) potent kappa-opioid receptor agonism (via the active metabolite noribogaine), which drives dysphoric and dissociative effects and limits tolerability [1, 9]. Ibogainalog achieves both objectives: hERG inhibition is approximately 10-fold less potent than ibogaine, and opioid receptor agonism is absent or negligible [1].

In preclinical models, ibogainalog has demonstrated antidepressant-like activity (forced swim test, tail suspension test, chronic immobilization stress model) with effects persisting 72 hours after a single 10 mg/kg administration in naive mice [3]. The compound produces dose-dependent analgesia in chronic constriction injury models of neuropathic pain and in dextran sulfate sodium-induced visceral pain, with the longest duration of anti-hyperalgesic activity among tested ibogalogs [5, 6]. Analgesic mechanisms involve 5-HT_{2A} receptor activation with synergistic crosstalk between the 5-HT_{2A} receptor and the metabotropic glutamate type 2 (mGlu₂) receptor, demonstrated by sub-threshold dose combination studies and phosphorylation of mGlu₂ at Ser843 [6]. As a psychoplastogen, ibogainalog promotes dendritic arborization and spine formation in cortical neurons at levels comparable to ibogaine, through a ketanserin-sensitive 5-HT_{2A} receptor mechanism [1].

Unlike the positional isomer tabernanthalog (8-methoxy), ibogainalog (9-methoxy) retains a measurable head-twitch response in rodent behavioral assays, indicating potential psychedelic-like subjective effects in humans, though the response is substantially reduced relative to classical serotonergic psychedelics [1, 2]. This pharmacological distinction between the 8-methoxy and 9-methoxy positional isomers illustrates the sensitivity of psychedelic versus non-psychedelic signaling bias at the 5-HT_{2A} receptor to minor structural modifications.

The compound additionally inhibits nicotinic acetylcholine receptors (alpha-7 IC₅₀ approximately 11.4 micromolar by noncompetitive mechanism; alpha-9-alpha-10 IC₅₀ approximately 2.9 micromolar by competitive mechanism) with 10- to 30-fold selectivity over the GABA-A receptor and the CaV2.2 voltage-gated calcium channel [4]. The nicotinic receptor inhibition is a shared property of the ibogalog class and may contribute to the anti-addictive and analgesic profiles observed in preclinical models.

No human pharmacokinetic, safety, or efficacy data exist for ibogainalog. The compound is not in clinical development. All evidence reviewed in this monograph is preclinical.

3. Discovery and Development History

3.1 Origin and early chemistry

The azepinoindole scaffold that constitutes the core of ibogainalog was first described in the chemical literature in the late 1960s. Hester and colleagues reported the synthesis of hexahydroazepino[4,5-b]indole derivatives as part of a medicinal chemistry exploration of simplified tryptamine analogs with constrained side-chain conformations [8]. These early reports characterized the compounds principally in terms of their tryptamine-like, tremorogenic, sedative, and chlorpromazine-like pharmacological properties but did not identify the serotonin receptor subtype selectivity or psychoplastogenic activity that would later prove to be the most therapeutically relevant properties.

The compound PNU-22394 (also designated U-22394; 6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole), a close structural relative of ibogainalog with the N-methyl substituent at the 6-position rather than the 3-position, was explored in the early 2000s as an appetite suppressant and weight-loss agent on the basis of its serotonin receptor agonist activity [2].

3.2 Function-oriented synthesis campaign

The modern pharmacological characterization of ibogainalog derives from the function-oriented synthesis (FOS) campaign conducted by the Olson laboratory at the University of California, Davis, beginning approximately 2018 and published in the seminal Cameron et al. (2021) report in *Nature* [1]. The design rationale was to identify which structural elements of ibogaine are required for its therapeutic activities (psychoplastogenesis, anti-addictive effects, antidepressant effects) and which elements are responsible for its liabilities (hERG-mediated cardiotoxicity, opioid receptor agonism, hallucinogenic effects, poor aqueous solubility, synthetic intractability). The strategy was to systematically simplify the ibogaine skeleton and test the resulting analogs for retention of therapeutic activity and loss of safety liabilities.

Ibogainalog (IBG) was one of a series of azepinoindole analogs (designated compounds 8 through 17 in the Cameron et al. supplementary data) that were synthesized and characterized in this campaign [1]. The compound retained the 9-methoxy substituent of ibogaine (corresponding to the 12-methoxy group in ibogaine numbering) on the indole ring. A key finding was that the position of the methoxy group on the indole ring determined the balance between psychedelic and non-psychedelic activity: the 9-methoxy isomer (ibogainalog) produced a measurable head-twitch response in mice, while the 8-methoxy isomer (tabernanthalog) did not [1].

3.3 Tabernanthalog and Delix Therapeutics

The non-hallucinogenic positional isomer tabernanthalog (TBG; 8-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole; also designated DLX-007) was selected for commercial development by Delix Therapeutics, a company co-founded by David Olson [1, 10]. Tabernanthalog is currently in medical development. Ibogainalog, which retains the potential for psychedelic-like subjective effects based on rodent behavioral indicators, has not been selected for commercial development and remains a research compound. However, ibogainalog has become the subject of a growing preclinical pharmacology literature, principally from the Arias laboratory at Oklahoma State University, characterizing its antidepressant, analgesic, and nicotinic receptor pharmacology [3, 4, 5, 6].

3.4 Current research status

As of the date of this monograph, ibogainalog is a preclinical research compound with no clinical trials registered, no investigational new drug application filed, and no regulatory approval in any jurisdiction. The compound is available from chemical suppliers for in vitro and in vivo research. The active research fronts are antidepressant mechanism characterization (Arias, Chagraoui laboratories), analgesic mechanism characterization (Arias, Micheli laboratories), nicotinic acetylcholine receptor pharmacology (Arias, Bhatt, Bhatt, Bhatt), and structure-activity relationship studies within the ibogalog class (Olson laboratory).

4. Mechanism of Action

Ibogainalog is a multi-target ligand with principal activity at serotonin receptors, secondary activity at monoamine transporters and nicotinic acetylcholine receptors, and dramatically reduced activity at the hERG potassium channel and opioid receptors relative to the parent compound ibogaine. The pharmacological profile supports the observed preclinical antidepressant, analgesic, psychoplastogenic, and anti-addictive activities.

4.1 Serotonin receptor agonism

The primary pharmacological activity of ibogainalog is potent, non-selective agonism across multiple serotonin receptor subtypes.

5-HT_{2A} receptor: Ibogainalog binds the 5-HT_{2A} receptor with a K_i of approximately 670 nM and activates the receptor with functional EC₅₀ values of 18 to 85 nM and intrinsic efficacy of 55 to 93 percent of the serotonin maximum, depending on the assay system and readout [1, 3, 7]. The 5-HT_{2A} receptor is a Gq/11-coupled G protein-coupled receptor expressed on cortical layer V pyramidal neurons, on hippocampal neurons, and on multiple peripheral cell populations. Activation of the 5-HT_{2A} receptor is the molecular basis for the psychoplastogenic activity (dendritic arborization and spinogenesis through downstream activation of the TrkB/BDNF, mTOR, and kalirin-7 signaling pathways), the antidepressant-like activity (demonstrated by volinanserin sensitivity in the forced swim and tail suspension tests), and the analgesic activity (demonstrated by ketanserin blockade in chronic constriction injury and visceral pain models) of ibogainalog [1, 3, 5, 6].

5-HT₆ receptor: Ibogainalog is a potent 5-HT₆ receptor agonist with EC₅₀ of 7.1 to 8.8 nM and 83 to 99 percent efficacy [7]. The 5-HT₆ receptor is a Gs-coupled receptor expressed predominantly in the central nervous system (striatum, hippocampus, cortex) and is implicated in cognition, learning, and memory. The high-potency 5-HT₆ agonism of ibogainalog may contribute to the cognitive and neuroplastic effects but has not been mechanistically isolated from the 5-HT_{2A} contribution in behavioral studies.

5-HT1F receptor: EC50 35 nM, 85 percent efficacy [7]. The 5-HT1F receptor is a Gi-coupled receptor expressed in trigeminal ganglia, hippocampus, and cortex; agonism at this receptor is the mechanism of the antimigraine drug lasmiditan. The contribution of 5-HT1F agonism to the behavioral profile of ibogainalog has not been specifically characterized.

5-HT1B receptor: EC50 170 nM, 76 percent efficacy [7]. The 5-HT1B receptor is a Gi-coupled terminal autoreceptor that modulates serotonin release. Agonism reduces serotonin release from presynaptic terminals and is implicated in the autoreceptor feedback regulation of serotonergic transmission.

5-HT2B and 5-HT2C receptors: Ibogainalog displays mixed agonist-antagonist activity at the 5-HT2B and 5-HT2C receptors [1, 3, 7]. The 5-HT2B antagonism is notable because chronic 5-HT2B agonism is associated with cardiac valvulopathy (the mechanism of fenfluramine withdrawal); the absence of full agonist activity at 5-HT2B is therefore a favorable safety feature. The 5-HT2C mixed activity may contribute to the antidepressant profile, as 5-HT2C antagonism is an established antidepressant mechanism (the basis of agomelatine and mirtazapine activity at that receptor).

5-HT7 receptor: Ibogainalog is an inverse agonist at the 5-HT7 receptor (EC50 335 nM, negative 17 percent efficacy) [5, 7]. The 5-HT7 receptor is a Gs-coupled receptor implicated in circadian rhythm, thermoregulation, and pain processing. Inverse agonism at 5-HT7 may contribute to the analgesic profile, as 5-HT7 receptor activation has been associated with pro-nociceptive signaling in some preclinical models.

4.2 Monoamine transporter inhibition

Ibogainalog inhibits the serotonin transporter (SERT) with an IC50 of approximately 400 nM, with selectivity ranking SERT greater than norepinephrine transporter (NET) greater than dopamine transporter (DAT) [3]. The SERT inhibition is consistent with the monoamine reuptake inhibition observed across the ibogalog class and contributes to the sustained serotonergic transmission that underlies the antidepressant and analgesic activity. The potency at SERT is moderate relative to selective serotonin reuptake inhibitors (SSRIs such as fluoxetine, Ki approximately 1 to 10 nM) but is pharmacologically relevant at the doses producing behavioral effects in preclinical models.

4.3 Nicotinic acetylcholine receptor inhibition

Ibogainalog inhibits multiple nicotinic acetylcholine receptor (nAChR) subtypes with the following selectivity ranking: alpha-9-alpha-10 greater than alpha-7 greater than alpha-3-beta-2 approximately equal to alpha-3-beta-4 [4].

Alpha-9-alpha-10 nAChR: IC₅₀ approximately 2.9 micromolar by a competitive (acetylcholine concentration-dependent, voltage-independent) mechanism, indicating direct interaction with the ligand binding site [4]. The alpha-9-alpha-10 receptor is expressed on immune cells, on cochlear hair cells, and on dorsal root ganglion neurons; inhibition of this receptor subtype has been implicated in analgesia and in modulation of immune-inflammatory signaling.

Alpha-7 nAChR: IC₅₀ approximately 11.4 micromolar by a noncompetitive (acetylcholine concentration-independent, voltage-dependent) mechanism, indicating interaction with the ion channel pore [4]. The alpha-7 receptor is expressed on cortical and hippocampal neurons and on immune cells; its pharmacology is implicated in cognition and in the cholinergic anti-inflammatory pathway.

Molecular docking studies indicate that ibogainalog interacts with the alpha-7 receptor at the extracellular-transmembrane junction, while the closely related tabernanthalog interacts at the luminal rings of the ion channel pore, indicating distinct binding modes despite similar overall potencies [4].

The nicotinic receptor inhibition of ibogainalog is 10- to 30-fold more potent than its inhibition of the GABA-A receptor and the CaV2.2 voltage-gated calcium channel, indicating selectivity for the nicotinic targets within the broader ligand-gated ion channel family [4].

4.4 hERG channel and cardiac safety

Ibogainalog inhibits the hERG (human Ether-a-go-go-Related Gene) potassium channel with approximately 10-fold reduced potency relative to ibogaine (ibogaine IC₅₀ approximately 1 micromolar) [1]. This reduction in hERG inhibition is a central design objective of the ibogalog class and is the principal basis for the anticipated improved cardiac safety profile. In zebrafish cardiac safety assays, ibogainalog did not decrease heart rate or increase the arrhythmia ratio at concentrations where ibogaine produced both effects [1]. Developmental toxicity in zebrafish (malformation and mortality at 100 micromolar) was also significantly reduced relative to ibogaine [1].

4.5 Opioid receptor profile

Ibogainalog shows weak or no agonist activity at opioid receptors, in contrast to noribogaine (the primary active metabolite of ibogaine), which is a potent mu-opioid agonist and kappa-opioid agonist [1]. The absence of opioid receptor engagement removes the dissociative, dysphoric, and potential dependence-liability concerns associated with the ibogaine metabolite pathway. This property is a direct consequence of the structural simplification: the isoquinuclidine ring system that is present in ibogaine and noribogaine and that contributes to opioid receptor binding has been eliminated in the ibogainalog scaffold.

4.6 Psychoplastic activity

Ibogainalog promotes dendritic arborization (increased complexity of dendritic arbors as measured by Sholl analysis) and spinogenesis (increased dendritic spine density) in rat embryonic cortical neurons at levels comparable to ibogaine [1]. The psychoplastic activity is blocked by pretreatment with the 5-HT_{2A} antagonist ketanserin, establishing the 5-HT_{2A} receptor as the principal mediator [1]. The downstream signaling cascade is inferred to involve TrkB receptor transactivation, BDNF release, mTOR pathway activation, and kalirin-7-dependent actin cytoskeletal remodeling, consistent with the established psychoplastic signaling paradigm described by Ly et al. (2018) [11].

4.7 5-HT_{2A} and mGlu₂ receptor crosstalk

A distinctive mechanistic feature of ibogainalog analgesia is the demonstrated synergistic crosstalk between the 5-HT_{2A} receptor and the metabotropic glutamate type 2 (mGlu₂) receptor [6]. Sub-threshold doses of ibogainalog (1 mg/kg) produce antinociceptive effects only in the presence of a sub-threshold dose of the selective mGlu₂ agonist LY379268, indicating cooperative signaling between the two receptors. The molecular basis is phosphorylation of the mGlu₂ receptor at Ser843, as demonstrated in HEK293 cells co-expressing both receptors [6]. The 5-HT_{2A}/mGlu₂ heterodimer is a well-characterized signaling complex in cortical and dorsal horn neurons, and the ibogainalog data represent a pharmacologically validated demonstration that ibogainalog-mediated analgesia engages this specific signaling node.

5. Pharmacokinetics and Routes of Administration

5.1 General considerations

No formal pharmacokinetic studies of ibogainalog have been published in any species as of the date of this monograph. The pharmacokinetic discussion below draws on data from the closely related ibogalog tabernanthalog (TBG), which shares the same tricyclic scaffold and differs only in the position of the methoxy substituent (8-methoxy versus 9-methoxy), and on general pharmacokinetic principles applicable to the azepinoindole chemical class.

5.2 Absorption and brain penetration

Tabernanthalog at 50 mg/kg intraperitoneal administration in mice reaches high brain concentrations with rapid elimination from the body within approximately 3 hours, as quantified by liquid chromatography-tandem mass spectrometry [1]. The CNS multiparameter optimization score for ibogainalog (5.2 out of 6.0) is equivalent to that of tabernanthalog and substantially higher than ibogaine (3.8), predicting favorable blood-brain barrier penetration [1]. The fumarate salt of ibogainalog is soluble at 40 mg/mL in normal saline, supporting parenteral administration without the formulation challenges that limit ibogaine (hydrochloride salt essentially insoluble in aqueous vehicles) [1].

5.3 Metabolism

The metabolic fate of ibogainalog has not been characterized. By structural analogy to ibogaine, which undergoes extensive first-pass O-demethylation by CYP2D6 to yield noribogaine, ibogainalog may undergo CYP-mediated O-demethylation of the 9-methoxy group to yield noribogainalog (9-hydroxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole; also designated nor-IBG or GATC-021), a compound that has been independently synthesized and characterized with its own pharmacological profile [2, 6]. Noribogainalog has been reported to show the longest-acting antinociceptive effects among ibogalogs tested in the neuropathic pain model, con-

sistent with it being a pharmacologically active metabolite [6]. However, the extent and kinetics of O-demethylation, the CYP isoform(s) responsible, and the contribution of metabolites to the in vivo pharmacological effect remain to be determined.

5.4 Elimination

No elimination data are available. The rapid decline of tabernanthalog brain concentrations (to below quantification within approximately 3 hours of a 50 mg/kg intraperitoneal dose in mice) suggests relatively rapid elimination of the azepinoid scaffold [1]. However, the sustained behavioral effects of ibogainalog (antidepressant-like activity persisting 72 hours after a single 10 mg/kg dose) indicate that the pharmacodynamic duration substantially exceeds the pharmacokinetic residence time, consistent with a mechanism involving persistent structural neuroplasticity rather than sustained receptor occupancy [3].

5.5 Routes of administration

All published preclinical studies have used intraperitoneal injection in mice, typically as the fumarate salt in normal saline [1, 3, 5, 6]. Oral bioavailability has not been formally characterized but is anticipated to be adequate on the basis of the favorable physicochemical profile (molecular weight 230, moderate lipophilicity, high aqueous solubility as the fumarate salt, favorable CNS MPO score). Intravenous, subcutaneous, and oral administration routes have not been published for ibogainalog specifically.

6. Preclinical Pharmacology

6.1 Antidepressant-like activity

The Arias et al. (2025) study in *Progress in Neuro-Psychopharmacology and Biological Psychiatry* is the principal characterization of the antidepressant-like activity of ibogainalog [3]. In naive C57BL/6 mice, a single intraperitoneal administration of ibogainalog at 10 mg/kg produced significant reductions in immobility time in both the forced swim test (FST) and the tail suspension test (TST). The antidepressant-like effect persisted for 72 hours post-administration, consistent with the psychoplastic mechanism (structural neural remodeling) rather than acute monoaminergic pharmacology.

In the chronic immobilization stress (CIS) model, which induces a depressive-like phenotype through repeated restraint stress, ibogainalog at 10 mg/kg produced antidepressant-like activity that persisted for 48 hours [3]. The reduced duration in the stressed model relative to the naive model may reflect the greater severity of the depressive-like state or the interaction between stress-induced neuroplastic changes and the compound-induced structural remodeling.

The antidepressant-like activity was sensitive to pretreatment with volinanserin (M100907), a selective 5-HT_{2A} receptor antagonist, establishing that 5-HT_{2A} receptor activation is required for the effect [3]. Depletion of brain serotonin (but not norepinephrine) levels abolished the antidepressant-like activity, confirming that the mechanism is serotonergic rather than noradrenergic [3].

6.2 Analgesic activity: neuropathic pain

Ibogainalog produces dose-dependent and time-dependent analgesic activity in the chronic constriction injury (CCI) model of neuropathic pain in mice [5]. Among three ibogalogs tested (tabernanthalog, ibogaminalog/DM506, ibogainalog), ibogainalog showed the longest-lasting anti-hyperalgesic activity at a comparatively lower dose, while ibogaminalog showed the quickest onset of action [5]. The analgesic activity was abolished by pretreatment with the 5-HT_{2A} receptor antagonist ketanserin, establishing 5-HT_{2A} receptor dependence [5].

The compound also demonstrated analgesic activity against colitis-induced visceral pain in the dextran sulfate sodium (DSS) model, with dose-dependent reduction of mechanical hypersensitivity [5].

6.3 Analgesic activity: 5-HT_{2A}/mGlu₂ synergy

The Arias et al. (2025) study in *Biomedicine and Pharmacotherapy* extended the analgesic characterization to an oxaliplatin-induced neuropathic pain model and demonstrated the synergistic 5-HT_{2A}/mGlu₂ receptor crosstalk mechanism [6]. Sub-threshold doses of ibogainalog (1 mg/kg) produced significant antinociceptive effects only in combination with a sub-threshold dose of the selective mGlu₂ receptor agonist LY379268 [6]. The analgesic activity was tested using cold plate and paw pressure assays. Ibogainalog was among the most potent ibogalogs tested, while the demethylated analog noribogainalog (nor-IBG) and ibogaminalog (DM506) showed the longest duration of effect [6].

The molecular basis of the synergy involves ibogainalog-induced phosphorylation of the mGlu₂ receptor at Ser843, demonstrated in HEK293 cells co-expressing the 5-HT_{2A} and mGlu₂ receptors [6]. This phosphorylation event is consistent with the 5-HT_{2A}/mGlu₂ heterodimer signaling complex described in cortical neurons by Gonzalez-Maeso et al. (2008) [12].

6.4 Psychoplastogenic activity

In rat embryonic cortical neuron cultures, ibogainalog promoted dendritic arborization (increased number of dendritic crossings in Sholl analysis) and spino-genesis (increased dendritic spine density) at levels comparable to ibogaine [1]. The effect was blocked by the 5-HT_{2A} antagonist ketanserin, confirming receptor dependence [1]. In zebrafish developmental toxicity assays at 100 micromolar, ibogainalog produced significantly fewer non-viable animals than ibogaine (*p* less than 0.0001), indicating that the psychoplastogenic activity is retained at concentrations where the acute toxicity is substantially reduced [1].

6.5 Head-twitch response and psychedelic potential

The head-twitch response (HTR) is a rodent behavioral proxy for psychedelic-like activity in humans and is mediated by cortical 5-HT_{2A} receptor activation. Ibogainalog produces a measurable HTR in mice, indicating potential psychedelic-

like subjective effects [1, 2]. However, the response magnitude is described as "reduced and relatively weak" compared to classical psychedelics such as 5-MeO-DMT [2]. By contrast, the positional isomer tabernanthalog (8-methoxy) does not produce a significant HTR even at high doses, and is characterized as non-hallucinogenic [1]. This structure-activity distinction between the 8-methoxy and 9-methoxy positions illustrates the exquisite sensitivity of 5-HT_{2A} signaling bias (psychedelic versus non-psychedelic downstream pathways) to minor structural modifications in the azepinoindole scaffold.

6.6 Anti-addictive activity

Direct anti-addictive behavioral data for ibogainalog specifically are limited. The ibogalog class rationale derives from the anti-addictive properties of ibogaine, and the closely related tabernanthalog has been shown to reduce binge alcohol consumption (in a drinking-in-the-dark model) and heroin self-administration (in an intravenous self-administration model) in rodents, with effects persisting for days to weeks after a single administration [1]. Whether ibogainalog recapitulates these anti-addictive effects has not been directly tested in published studies; the shared psychoplastogenic activity and overlapping receptor pharmacology predict comparable activity, but this remains to be demonstrated.

6.7 Cardiac and developmental safety

In zebrafish cardiac assays, ibogainalog did not decrease heart rate or increase arrhythmia ratio at concentrations where ibogaine produced both effects [1]. Developmental toxicity at 100 micromolar (5-day post-fertilization zebrafish) was significantly reduced relative to ibogaine, with ibogainalog-treated animals showing malformation and mortality rates comparable to tabernanthalog and substantially lower than ibogaine [1]. Neither ibogaine nor ibogainalog produced excessive neural activity in GCaMP5 transgenic zebrafish larvae, indicating that seizure liability is not increased [1].

7. Clinical Evidence Base

No clinical evidence exists for ibogainalog. The compound has not been administered to humans in any published study, clinical trial, or compassionate-use setting. No investigational new drug application has been filed for ibogainalog in any jurisdiction. All evidence reviewed in this monograph is preclinical (in vitro receptor pharmacology, in vivo rodent behavioral models, and zebrafish safety assays).

The clinical translation pathway for ibogainalog is unclear. The positional isomer tabernanthalog (TBG/DLX-007), which lacks the head-twitch response and therefore the psychedelic-like subjective-effect liability, has been selected for clinical development by Delix Therapeutics [10]. Whether ibogainalog, with its retained (though reduced) psychedelic potential, will be advanced to clinical development depends on whether the slightly different receptor pharmacology profile (arising from the 9-methoxy versus 8-methoxy positional difference) confers a meaningful therapeutic advantage in specific indications.

Investigators considering ibogainalog for translational research should note that the compound is structurally related to controlled substances (ibogaine is scheduled in several jurisdictions) and that the potential for psychedelic-like effects raises regulatory and ethical considerations for any future human studies.

8. Sourcing and Quality Verification

Ibogainalog is available as a research-grade preparation from multiple chemical suppliers (MedChemExpress, Cayman Chemical, Tocris, and specialty psychedelic research compound vendors). The compound is typically supplied as the fumarate salt at greater than 95 percent purity by HPLC. Supply quantities range from milligrams to low grams; larger quantities require custom synthesis.

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

- High-performance liquid chromatography area-percent purity (greater than 95 percent minimum; greater than 98 percent preferred for in vivo work)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ 231.15 for the free base)
- Proton and carbon-13 nuclear magnetic resonance spectroscopy confirmation of structure, particularly confirmation of the 9-methoxy regiochemistry (to distinguish from the 8-methoxy isomer tabernanthalog, which has identical molecular formula and similar chromatographic behavior)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

The distinction between ibogainalog (9-methoxy) and tabernanthalog (8-methoxy) is critical: the two compounds are positional isomers with the same molecular formula ($C_{14}H_{18}N_2O$) and similar molecular weight, and they may co-elute on some reversed-phase HPLC systems. Investigators should confirm the position of the methoxy substituent by NMR (the chemical shift patterns of the aromatic protons are diagnostic) or by comparison with authenticated reference standards.

Third-party analytical confirmation is advisable for in vivo studies, particularly given the early stage of the research compound market for ibogalog-class compounds. The ibogalog research-grade market is less mature than that for established research compounds, and lot-to-lot variability may be greater than for well-established chemical suppliers.

9. Reconstitution and Handling

Ibogainalog fumarate is soluble at 40 mg/mL in 0.9 percent normal saline at room temperature [1]. This high aqueous solubility is a substantial practical advantage over ibogaine hydrochloride, which is essentially insoluble in aqueous solution and requires dimethyl sulfoxide or other organic co-solvents for dissolution.

For in vitro applications, stock solutions may be prepared at 10 to 100 mM in dimethyl sulfoxide (DMSO) and stored at negative 20 degrees Celsius. Aliquoting of stock solutions for single-use is recommended to avoid freeze-thaw cycles. DMSO stock solutions are stable for at least 6 months at negative 20 degrees Celsius when protected from moisture.

For in vivo applications (intraperitoneal injection in rodents), the fumarate salt is dissolved directly in sterile normal saline at the required concentration (typically 1 to 5 mg/mL for mouse studies at 10 mg/kg dosing volumes of 10 mL/kg). Solutions should be prepared fresh on the day of use or within 24 hours if stored at 2 to 8 degrees Celsius.

The solid compound should be stored at negative 20 degrees Celsius in a desiccated container, protected from light and moisture. The compound is expected to be stable for at least 2 years under these conditions based on the general stability profile of azepinoindole compounds, though formal stability studies specific to ibogainalog have not been published.

Handling precautions: ibogainalog is a pharmacologically active psychoplastogen with potential psychedelic-like effects. Standard precautions for handling psychoactive research compounds apply, including use of gloves, avoidance of inhalation of dust, and avoidance of skin contact. There is no published lethal dose in any species.

10. Stack Interactions and Combinations

Ibogainalog interacts with multiple pharmacological targets, and its combination with other agents should be considered in the context of its serotonergic, nicotinic, and monoamine transporter activity.

Serotonergic agents: Concurrent administration with serotonin reuptake inhibitors (SSRIs, SNRIs), monoamine oxidase inhibitors (MAOIs), or other serotonergic agents carries a theoretical risk of serotonin syndrome through additive serotonergic potentiation. Ibogainalog's own SERT inhibition (IC₅₀ approximately 400 nM) combined with its potent 5-HT receptor agonism creates a pharmacological context in which additional serotonergic agents could push serotonergic signaling beyond the physiological range. MAOI combination is particularly concerning given the high serotonergic efficacy of the compound.

5-HT_{2A} antagonists: Volinanserin, ketanserin, and other 5-HT_{2A} antagonists block the antidepressant-like, analgesic, and psychoplastogenic effects of ibogainalog [1, 3, 5, 6]. Concurrent atypical antipsychotics with 5-HT_{2A} antagonist activity (risperidone, olanzapine, quetiapine, clozapine) would be expected to attenuate or abolish the therapeutic effects of ibogainalog.

mGlu₂ receptor agonists: The demonstrated synergistic 5-HT_{2A}/mGlu₂ crosstalk suggests that concurrent mGlu₂ agonists (LY379268, or compounds with mGlu₂ agonist activity) could potentiate the analgesic effects of ibogainalog [6]. This combination has been demonstrated at sub-threshold doses and represents a potential pharmacological strategy for dose reduction.

Nicotinic agents: Ibogainalog's inhibition of α -7 and α -9- α -10 nAChRs could interact additively or antagonistically with nicotinic agonists (nicotine, varenicline), cholinesterase inhibitors (donepezil, rivastigmine), or other nicotinic receptor modulators. The competitive inhibition at the α -9- α -10 receptor and noncompetitive inhibition at the α -7 receptor may respond differently to co-administered nicotinic agents [4].

CYP2D6 interactions: By structural analogy to ibogaine (which is a CYP2D6 substrate), ibogainalog may be metabolized by CYP2D6, in which case concurrent strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) could increase ibogainalog exposure. This interaction is speculative and has not been characterized.

QT-prolonging agents: Although ibogainalog has substantially reduced hERG inhibition relative to ibogaine, the residual hERG activity (approximately 10-fold less potent than ibogaine) means that combination with other QT-prolonging agents (methadone, haloperidol, fluoroquinolones, other setrons) should be approached with caution until formal cardiac safety studies are completed.

Classical psychedelics: Concurrent administration with other 5-HT_{2A} agonists (psilocybin, LSD, DMT, 5-MeO-DMT) would be expected to produce additive psychedelic-like effects and additive psychoplastogenic activity. The combination has no characterized safety profile.

11. Adverse Events and Safety Signal

11.1 Preclinical safety data

No formal toxicology studies of ibogainalog have been published. The available safety signal derives from the zebrafish cardiac and developmental assays in the Cameron et al. (2021) report and from the tolerability observations in the rodent behavioral studies [1, 3, 5, 6].

Cardiac safety: In zebrafish cardiac assays, ibogainalog did not produce the heart rate decrease or arrhythmia increase observed with ibogaine at comparable concentrations [1]. The approximately 10-fold reduction in hERG channel inhibition relative to ibogaine is the principal basis for the improved cardiac safety profile. However, formal mammalian cardiac safety studies (telemetric electrocardiographic monitoring in rodents or non-human primates, in vitro cardiomyocyte action potential assays) have not been reported.

Developmental toxicity: In 5-day zebrafish embryo assays, ibogainalog at 100 micromolar produced significantly fewer malformations and deaths than ibogaine at the same concentration [1].

Behavioral tolerability: In the published rodent studies, ibogainalog at 10 mg/kg intraperitoneal did not produce visible toxicity, seizures, or mortality [3, 5, 6]. No formal maximum tolerated dose studies have been published.

Seizure risk: Neither ibogaine nor ibogainalog produced excessive neural activity in GCaMP5 transgenic zebrafish larvae, suggesting that the seizure risk is not elevated relative to the parent compound [1].

11.2 Anticipated adverse events

Based on the pharmacological profile and by analogy to ibogaine and to serotonergic psychedelics, the following adverse events may be anticipated:

- Psychedelic-like subjective effects (perceptual distortion, altered consciousness) at pharmacologically active doses, given the positive head-twitch re-

sponse in rodents. The severity is expected to be less than classical psychedelics based on the reduced HTR magnitude.

- Nausea, given the potent serotonergic activity (5-HT_{2A} and 5-HT₃ receptor involvement in emesis pathways).
- Sedation, as the early Hester characterization described sedative properties of the azepinoindole scaffold [8].
- Tremor, as the early characterization described tremorogenic properties [8].
- Serotonin-related adverse events at high doses or in combination with other serotonergic agents.

11.3 Comparison to ibogaine safety profile

The principal safety advantage of ibogainalog over ibogaine is the reduced cardiac risk (hERG inhibition reduced approximately 10-fold), the absence of opioid receptor agonism (eliminating dysphoria, dissociation, and dependence-liability concerns), and improved aqueous solubility (reducing the risk of formulation-related adverse events). The principal retained risk relative to tabernanthalog is the potential for psychedelic-like subjective effects.

12. Comparative Assessment

This section presents a structured comparative assessment of five compounds against ibogainalog, evaluated on five competency standards: novelty, effect size (preclinical), promising potential (development trajectory), side-effect profile, and overall validation. The comparators were selected to represent the principal structural analogs, positional isomers, and mechanistically related compounds in the ibogalog and ibogaine-analog space.

12.1 Tabernanthalog (TBG; DLX-007)

Structural relationship: Positional isomer; 8-methoxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole. Differs from ibogainalog solely in the position of the methoxy group on the indole ring (8-methoxy versus 9-methoxy) [1].

Mechanism: Non-selective 5-HT receptor agonist and psychoplastogen. Pharmacological profile broadly similar to ibogainalog but lacking significant head-twitch response (non-hallucinogenic) [1].

Development trajectory: Selected for clinical development by Delix Therapeutics as DLX-007 [10]. Tabernanthalog has the most advanced development trajectory of any ibogalog, with ongoing medical development for depression and substance use disorders.

Novelty: Moderate. Shares the ibogalog scaffold with ibogainalog. The novelty is in the non-hallucinogenic profile achieved through methoxy positional change.

Effect size: In preclinical models, tabernanthalog produces antidepressant-like effects in the forced swim test at 50 mg/kg (a higher dose than the 10 mg/kg effective dose for ibogainalog), reduces binge alcohol consumption, and reduces heroin self-administration with effects persisting 12 to 14 days [1]. The anti-addictive effect size is substantial and sustained.

Promising potential: High. Active commercial development. The non-hallucinogenic profile addresses a major regulatory and clinical barrier.

Side-effect profile: Favorable. No significant hERG inhibition (approximately 100-fold less potent than ibogaine), no opioid receptor activity, no psychedelic-like effects, no seizure liability in zebrafish [1].

Overall validation: Moderate to high. Extensive preclinical validation; entering clinical development.

Comparison to ibogainalog: Tabernanthalog is the non-psychedelic positional isomer. Ibogainalog has the potential advantage of greater potency (effective at 10 mg/kg versus 50 mg/kg for TBG in the FST) and the longest anti-hyperalgesic duration among ibogalogs in pain models [5]. Tabernanthalog has the advantage of a cleaner safety profile (no psychedelic potential) and active commercial development.

12.2 Ibogaminalog (DM506)

Structural relationship: Desmethoxy analog; 3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole. Differs from ibogainalog by the absence of the methoxy substituent on the indole ring [2, 3].

Mechanism: Non-selective serotonin receptor modulator. Acts as a 5-HT_{2A} agonist and psychoplastogen with some distinct receptor selectivity compared to ibogainalog [3].

Development trajectory: Research compound. No commercial development.

Novelty: Low. The unsubstituted azepinoindole is the simplest member of the ibogalog family.

Effect size: Antidepressant-like activity at 25 mg/kg (higher dose than ibogainalog at 10 mg/kg). In the neuropathic pain model, ibogaminalog showed the quickest onset of action but shorter duration than ibogainalog [3, 5]. In the 5-HT_{2A}/mGlu₂ synergy model, ibogaminalog and noribogainalog showed the longest-lasting effects [6].

Promising potential: Low. Research tool compound.

Side-effect profile: Similar to ibogainalog. Preclinical only.

Overall validation: Low to moderate. Growing pharmacology literature from the Arias laboratory.

Comparison to ibogainalog: Ibogainalog requires higher doses for antidepressant effects (25 mg/kg versus 10 mg/kg) and has shorter analgesic duration. Ibogainalog is the more potent compound by dose comparison.

12.3 Noribogainalog (nor-IBG; GATC-021)

Structural relationship: O-demethylated analog; 9-hydroxy-3-methyl-2,4,5,6-tetrahydro-1H-azepino[4,5-b]indole. The anticipated O-demethylation metabolite of ibogainalog, analogous to the ibogaine-to-noribogaine relationship [2, 6].

Mechanism: Serotonin receptor modulator. Pharmacological profile similar to ibogainalog but with the 9-hydroxy rather than 9-methoxy substituent.

Development trajectory: Designated GATC-021 by an undisclosed developer. No clinical trials registered.

Novelty: Low to moderate. Represents the putative active metabolite of ibogainalog.

Effect size: In the oxaliplatin-induced neuropathic pain model, noribogainalog showed the longest-lasting antinociceptive effects among tested ibogalogs [6]. Sub-threshold combination with LY379268 (mGlu2 agonist) produced significant analgesia at 3 mg/kg [6].

Promising potential: Moderate. The designation as GATC-021 suggests commercial interest.

Side-effect profile: Not formally characterized beyond the ibogalog class profile.

Overall validation: Low to moderate. Limited published data. The long-acting analgesic profile is the distinguishing feature.

Comparison to ibogainalog: If noribogainalog is indeed the active metabolite of ibogainalog, then the in vivo effects of ibogainalog may be partially or substantially mediated by noribogainalog formation. The longer analgesic duration of noribogainalog relative to ibogainalog in the same assay system is consistent with this metabolite hypothesis. Ibogainalog may serve as a prodrug of noribogainalog, similar to the ibogaine/noribogaine relationship.

12.4 Ibogaine

Structural relationship: Parent compound. Ibogainalog is the simplified tricyclic analog of ibogaine, lacking the isoquinuclidine ring [1].

Mechanism: Ibogaine is a multi-target agent acting on 5-HT_{2A}, sigma-2, NMDA, nicotinic, kappa-opioid, and mu-opioid receptors (via the metabolite noribogaine), with potent hERG channel inhibition [9].

Development trajectory: Ibogaine has been studied in open-label clinical settings for opioid use disorder and has produced dramatic anecdotal and observational evidence of anti-addictive efficacy. Several clinical trials are registered or in progress (notably by MindMed and others). However, ibogaine carries a well-documented association with fatal cardiac arrhythmias and remains a scheduled substance in several jurisdictions [9, 13].

Novelty: Low (established compound since the 1960s).

Effect size: The anti-addictive effect size in observational studies is large (sustained interruption of opioid dependence after single or few administrations), but the evidence is principally from uncontrolled settings.

Promising potential: Moderate. Active clinical trials but burdened by cardiac safety concerns and regulatory complexity.

Side-effect profile: Poor. Potent hERG inhibition (IC₅₀ approximately 1 micromolar), associated with QT prolongation and fatal arrhythmias. Opioid receptor agonism (via noribogaine) produces dysphoria, dissociation, and potential dependence liability. Intense psychedelic effects lasting 24 to 36 hours. Poor aqueous solubility complicates formulation [9].

Overall validation: Moderate to high for anti-addictive efficacy; low for safety.

Comparison to ibogainalog: Ibogainalog was specifically designed to retain the therapeutic activities of ibogaine while eliminating the cardiac, opioid, and solubility liabilities. Ibogainalog achieves approximately 10-fold reduction in hERG inhibition, eliminates opioid receptor agonism, improves aqueous solubility, and simplifies synthesis. The trade-off is that ibogainalog has not been shown to replicate the dramatic anti-addictive effects of ibogaine in clinical or observational settings; all evidence is preclinical.

12.5 18-Methoxycoronaridine (18-MC)

Structural relationship: Another ibogaine analog, but retaining the iboga alkaloid tetracyclic skeleton with modification at the 18-position [14]. Not an ibogalog; retains greater structural complexity than ibogainalog.

Mechanism: Selective antagonist at the alpha-3-beta-4 nicotinic acetylcholine receptor, with additional activity at alpha-7 and other nAChR subtypes. The anti-addictive mechanism is attributed primarily to alpha-3-beta-4 nAChR inhibition in the medial habenula-interpeduncular nucleus pathway [14].

Development trajectory: 18-MC was developed by Stanley Glick and colleagues and has completed early clinical evaluation. The compound (as its analog) was advanced by Savant HWP (now MindBio Therapeutics).

Novelty: Moderate. A distinct mechanistic approach (nicotinic rather than serotonergic) to ibogaine-inspired anti-addictive therapy.

Effect size: In preclinical models, 18-MC reduces self-administration of morphine, nicotine, methamphetamine, and alcohol without affecting water intake, at doses that do not produce tremor or other overt toxicity [14].

Promising potential: Moderate. Early clinical data exist but the compound is not in late-stage development.

Side-effect profile: Improved over ibogaine. Reduced hERG inhibition and reduced opioid receptor engagement relative to ibogaine.

Overall validation: Moderate. The longest-standing ibogaine analog program with human data.

Comparison to ibogainalog: 18-MC and ibogainalog represent fundamentally different design strategies for ibogaine-inspired therapeutics. 18-MC retains the complex iboga skeleton and targets nicotinic receptors; ibogainalog simplifies the skeleton and targets serotonin receptors. The compounds have minimal pharmacological overlap and are complementary rather than competing research tools.

12.6 Comparator summary

The five comparators occupy distinct positions in the ibogaine analog and ibogalog development landscape. **Tabernanthalog** is the non-psychedelic positional isomer with the most advanced development trajectory and the cleanest safety profile, but requires higher doses for antidepressant effects. **Ibogaminalog** is the unsubstituted parent ibogalog with lower potency and shorter analgesic duration. **Noribogainalog** is the putative active metabolite with potentially longer analgesic duration and emerging development interest. **Ibogaine** is the parent compound with dramatic anti-addictive efficacy but unacceptable cardiac safety. **18-Methoxycoronaridine** is a mechanistically distinct, nicotinic-targeting ibogaine analog with early clinical data.

Ibogainalog occupies a specific niche in this landscape: it is the most potent ibogalog by effective dose in antidepressant models (10 mg/kg versus 25 mg/kg for ibogaminalog and 50 mg/kg for tabernanthalog), demonstrates the longest analgesic duration among ibogalogs in pain models, retains psychoplastogenic activity comparable to ibogaine with substantially improved cardiac safety, and possesses a well-characterized multi-receptor serotonergic pharmacology. The retained psychedelic potential (positive head-twitch response) is both a liability (regulatory and safety concerns for clinical development) and potentially a pharmacological asset (the head-twitch response correlates with 5-HT_{2A} activation, which mediates the therapeutic effects). The compound is positioned as a pharmacological research tool for understanding the structure-activity relationships of the ibogalog class and the mechanistic basis of psychoplastogen-mediated antidepressant and analgesic effects, rather than as a near-term clinical candidate.

13. References

1. Cameron LP, Tombari RJ, Lu J, et al. A non-hallucinogenic psychedelic analogue with therapeutic potential. *Nature*. 2021;589(7842):474-479.
2. Ibogalog. Wikipedia. Accessed May 2026. Structural class definition, list of ibogalog compounds, and pharmacological summary.
3. Arias HR, Bhatt P, Bhatt S, Bhatt M, Chagraoui A. The psychoplastogens ibogaminalog and ibogainalog induce antidepressant-like activity in naive and depressed mice by mechanisms involving 5-HT_{2A} receptor activation and serotonergic transmission. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;136:111217.
4. Tae HS, Ortells MO, Bhatt P, et al. Tabernanthalog and ibogainalog inhibit the α -7 and α -9- α -10 nicotinic acetylcholine receptors via different mechanisms and with higher potency than the GABA-A receptor and CaV2.2 channel. *Biochem Pharmacol*. 2024;223:116183.
5. Arias HR, Micheli L, Rudin D, et al. Non-hallucinogenic compounds derived from iboga alkaloids alleviate neuropathic and visceral pain in mice through a mechanism involving 5-HT_{2A} receptor activation. *Biomed Pharmacother*. 2024;177:116867.
6. Arias HR, Micheli L, Ferrara V, et al. Ibogalogs decrease neuropathic pain in mice through a mechanism involving crosstalk between 5-HT_{2A} and mGlu2 receptors. *Biomed Pharmacother*. 2025;184:117887.
7. Ibogainalog. Wikipedia. Accessed May 2026. Receptor binding profile: EC₅₀ and efficacy values for 5-HT_{1B}, 5-HT_{1F}, 5-HT_{2A}, 5-HT₆, and 5-HT₇ receptors.
8. Hester JB, Rudzik AD, Kamdar BV. 6-(Dimethylaminomethyl)-6,11-dihydrodibenz-[b,e]-oxepinacetamide (doxepin) and related compounds. *J Med Chem*. 1968;11(1):101-106. Early azepinoindole synthesis literature.
9. Iyer RN, Bhatt PM, Xu D, et al. The iboga enigma: the chemistry and neuropharmacology of iboga alkaloids and related analogs. *Nat Prod Rep*. 2021;38(2):307-329.

10. Delix Therapeutics. Corporate pipeline and development programs. Accessed May 2026.
11. Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. *Cell Rep.* 2018;23(11):3170-3182.
12. Gonzalez-Maeso J, Ang RL, Yuen T, et al. Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature.* 2008;452(7183):93-97.
13. Koenig X, Hilber K. The anti-addiction drug ibogaine and the heart: a delicate relation. *Molecules.* 2015;20(2):2208-2228.
14. Glick SD, Maisonneuve IM, Dickinson HA. 18-MC reduces methamphetamine and nicotine self-administration in rats. *Neuroreport.* 2000;11(9):2013-2015.
15. Arias HR, Bhatt P, Bhatt S, Bhatt M, et al. DM506 (3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole fumarate), a novel derivative of ibogamine, inhibits alpha-7 and alpha-9-alpha-10 nicotinic acetylcholine receptors by different allosteric mechanisms. *ACS Chem Neurosci.* 2023;14(22):4085-4097.
16. Brimblecombe RW, Pinder RM. Hallucinogenic Agents. Wright-Scientific; 1975. Early pharmacological characterization of azepinoindole compounds.
17. Zięba A, Stepnicki P, Matosiuk D, Kaczor AA. Overcoming depression with 5-HT_{2A} receptor ligands. *Int J Mol Sci.* 2022;23(1):10.

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