

RESEARCH MONOGRAPH . COMPOUND PROFILE

Ariadne

A non-hallucinogenic serotonin 5-HT_{2A} receptor agonist of the substituted phenylalkylamine class, distinguished from hallucinogenic congeners DOM and DOI by a single alpha-ethyl extension that attenuates signaling efficacy while preserving therapeutic activity across psychiatric, neurological, and movement disorder indications.

DOCUMENT	KDC-MN-1572
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Non-hallucinogenic 5-HT _{2A} receptor agonist of the substituted phenylalkylamine (phenylisobutylamine) class

ABSTRACT

Ariadne (4C-D; BL-3912; dimoxamine), the alpha-ethyl homolog of the hallucinogenic amphetamine DOM, is a potent and selective agonist of the serotonin 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors that is distinguished by a striking dissociation between receptor activation and hallucinogenic effect in humans. First synthesized by Alexander Shulgin in 1968 and advanced through Phase II clinical trials at Bristol-Myers Laboratories in the early 1970s under the development code BL-3912A (the pharmacologically preferred R-enantiomer), the compound produced rapid remission of psychotic symptoms in schizophrenia and bipolar patients at 50 to 100 mg per day, nearly complete reversal of motor deficits in Parkinson's disease patients at 100 mg per day, and improved cognitive alertness in geriatric subjects at 50 mg per day, all without hallucinogenic effects at doses up to and beyond 300 mg. Development was halted for strategic economic reasons rather than for safety or efficacy concerns, and the actual clinical data from the Bristol-Myers trials were never publicly disclosed.

The molecular pharmacology of Ariadne was formally characterized by the Cunningham, Sames, and McCorvy laboratories at Columbia University in a 2022 publication in ACS Chemical Neuroscience. The R-enantiomer binds the human 5-HT_{2A} receptor with a K_i of 53 nM (radioligand displacement against [¹²⁵I]-DOI), activates Gq-coupled signaling with an EC₅₀ of 149 nM and an E_{max} of 83 percent relative to serotonin, and produces calcium flux with an EC₅₀ of 30 nM and an E_{max} of 96 percent. The compound shows no substantial bias between Gq/11 and beta-arrestin2 signaling pathways. Instead, the non-

hallucinogenic profile is attributed to a consistent 4- to 6-fold reduction in potency and a 10 to 20 percent reduction in maximal efficacy across all measured signaling channels relative to the hallucinogenic reference compound DOM. This "signaling efficacy hypothesis" proposes that the lower overall transduction amplitude, rather than pathway-selective biased agonism, accounts for the preservation of therapeutic effects in the absence of hallucination.

Selectivity profiling across a 44-target safety panel identified only the 5-HT_{2A} and 5-HT_{2B} receptors as targets displaced above 50 percent at 10 micromolar concentration. The compound has no measurable activity at dopamine, norepinephrine, or serotonin transporters (IC₅₀ values exceeding 50 micromolar), no activity at dopamine D₁ or D₂ receptors, and weak submicromolar activity at 5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptors. In mice, subcutaneous administration at 10 mg/kg produces peak plasma concentrations of approximately 467 ng/mL at 15 minutes, a brain-to-plasma ratio of 10.23 at 1 hour, and a plasma elimination half-life of approximately 2.1 hours, confirming high central nervous system penetration.

Preclinical studies in auxilin-knockout mice (a genetic model of Parkinson's disease) demonstrated that a single 10 mg/kg dose of (R)-Ariadne restored balance beam performance to wildtype levels and eliminated hind limb clasping scores, mirroring the effects of levodopa despite the compound's lack of dopaminergic receptor or transporter activity. In the novelty-suppressed feeding test, a sustained anxiolytic-like effect was observed 7 days after a single administration, consistent with the neuroplasticity-dependent mechanisms proposed for 5-HT_{2A} agonist therapeutic effects. A 2024 patent application by Columbia University

(WO2024073601A2) claims therapeutic applications across movement disorders, neuropsychiatric conditions, cognitive impairment, substance use disorders, and catatonia. This monograph reviews the chemistry, stereochemistry, and synthesis of Ariadne; the receptor pharmacology and signaling mechanism in molecular detail; available pharmacokinetic data; the historical clinical evidence from Bristol-Myers and the contemporary preclinical pharmacology from the Sames laboratory; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications; adverse-event and safety signal; and a structured comparative assessment of five non-hallucinogenic 5-HT_{2A} receptor agonists against Ariadne on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed nonproprietary name: Dimoxamine (tentative; never formally adopted as an International Nonproprietary Name).

Common name: Ariadne. The name was given by Alexander Shulgin, referencing the figure from Greek mythology. The compound is catalogued under this name in Shulgin's published phenylalkylamine index and has been adopted in the contemporary pharmacological literature [1, 2].

Systematic synonyms: 4C-D; 4C-DOM; alpha-ethyl-DOM; alpha-ethyl-2C-D; alpha-Et-DOM.

Development codes: BL-3912 (racemic mixture, Bristol-Myers Laboratories); BL-3912A (R-enantiomer, Bristol-Myers Laboratories). The BL-3912A designation identifies the pharmacologically active enantiomer used in the 1970s clinical program [1, 3].

Chemical Abstracts Service registry numbers: 52842-58-7 (racemic free base); 52842-59-8 (R-enantiomer free base). The hydrochloride salt is catalogued under CAS 52663-86-2.

International Union of Pure and Applied Chemistry name: 1-(2,5-dimethoxy-4-methylphenyl)butan-2-amine.

PubChem compound identifier: 169886.

ChemSpider identifier: 148565.

1.2 Structural class and chemistry

Ariadne is a substituted phenylalkylamine of the phenylisobutylamine subclass. The structural class is defined by a 2,5-dimethoxy-4-substituted phenyl ring bearing a two-carbon side chain terminating in a primary amine, with the alpha-carbon

carrying an ethyl substituent. This places Ariadne in the 4C family of phenylalkylamines, where "4C" denotes the four-carbon chain between the ring and the amine nitrogen [1, 2].

The compound is the alpha-ethyl homolog of the hallucinogenic amphetamine DOM (2,5-dimethoxy-4-methylamphetamine, in which the alpha-carbon bears a methyl group) and the alpha-ethyl homolog of the non-amphetamine phenethylamine 2C-D (2,5-dimethoxy-4-methylphenethylamine, in which the alpha-carbon is unsubstituted). The single methylene group extension from alpha-methyl (DOM) to alpha-ethyl (Ariadne) is the structural basis for the dramatic pharmacological difference between the potent hallucinogen and the non-hallucinogenic therapeutic agent [3].

Molecular formula: C₁₃H₂₁NO₂ (free base).

Exact mass: 223.1572 g/mol (free base, monoisotopic).

Molecular weight: 223.316 g/mol (free base).

Physical properties: The free base is an oil at room temperature. The hydrochloride salt is a white to off-white crystalline solid, soluble in water and in polar organic solvents (methanol, ethanol, dimethyl sulfoxide). Melting point data for the hydrochloride salt have not been reported in the peer-reviewed literature.

Stereochemistry: Ariadne contains one stereocenter at the alpha-carbon (C-2 of the butylamine chain). The R-enantiomer ((R)-Ariadne, BL-3912A) is the pharmacologically preferred form, exhibiting approximately 2- to 4-fold higher binding affinity and functional potency at the 5-HT_{2A} receptor compared to the S-enantiomer [3]. The racemic mixture (BL-3912) was used in Shulgin's original human self-experiments; the R-enantiomer was selected by Bristol-Myers for clinical development. Investigators acquiring research-grade Ariadne should confirm enantiomeric composition by chiral high-performance liquid chromatography or by supercritical fluid chromatography, as the pharmacological distinction between enantiomers is substantial.

1.3 Synthesis

The published synthesis of Ariadne proceeds through a nitrostyrene intermediate. The standard route begins with 2,5-dimethoxy-4-methylbenzaldehyde, which is condensed with nitropropane (rather than nitroethane, as used for DOM) under ba-

sic conditions (ammonium acetate catalysis in glacial acetic acid) to yield the corresponding beta-nitro-alpha-ethylstyrene [1, 2]. Reduction of the nitrostyrene to the primary amine is accomplished by lithium aluminum hydride in anhydrous tetrahydrofuran. The product is purified by vacuum distillation or by conversion to the hydrochloride salt and recrystallization from ethanol or isopropanol.

Alternative synthetic routes described in the Columbia University patent application (WO2024073601A2) include sodium borohydride reduction of the nitrostyrene followed by functional group manipulation, and the preparation of fluorinated analogs using diethylaminosulfur trifluoride [4]. Chiral resolution of the racemic product into R and S enantiomers is accomplished by supercritical fluid chromatography on chiral stationary phases or by diastereomeric salt formation with chiral acids.

Industrial-scale synthesis has not been reported; the compound has been prepared only at laboratory scale (milligram to gram quantities). Typical yields for the nitrostyrene condensation are 60 to 80 percent; lithium aluminum hydride reduction yields are 50 to 70 percent. The overall two-step yield is approximately 30 to 55 percent from the aldehyde starting material.

2. Abstract

Ariadne (4C-D; BL-3912A; dimoxamine) is a potent, selective, non-hallucinogenic agonist of the serotonin 5-HT_{2A} receptor and a member of the substituted phenylalkylamine structural class. The compound was first synthesized by Alexander Shulgin in 1968, characterized in human self-experiments as producing "the alert of a psychedelic, with none of the rest of the package" at 25 to 32 mg oral doses [1, 2], and advanced through Phase II clinical trials at Bristol-Myers Laboratories between approximately 1972 and 1975 under the development code BL-3912A (R-enantiomer) [3, 4].

The Bristol-Myers clinical program reported rapid remission of psychotic symptoms in schizophrenia and bipolar patients at 50 to 100 mg per day, nearly complete reversal of motor symptoms in Parkinson's disease patients at 100 mg per day, relaxation in catatonic patients, and improved cognitive alertness and sociability in geriatric subjects at 50 mg per day [3, 4, 5]. At all studied doses, including a reported maximum of 300 mg in a National Institute on Drug Abuse study, no hallucinogenic effects were observed [1, 3]. Development was discontinued for strategic economic reasons, and the actual clinical datasets were never publicly disclosed.

The molecular pharmacology of Ariadne remained incompletely characterized until the Cunningham, Sames, and McCorvy (2022) report in ACS Chemical Neuroscience, which provided comprehensive receptor binding, functional signaling, selectivity, and in vivo behavioral data [3]. The R-enantiomer binds the 5-HT_{2A} receptor with a K_i of 53 nM, activates G_q-coupled signaling with an EC₅₀ of 149 nM and 83 percent maximal efficacy relative to serotonin, and produces calcium mobilization with an EC₅₀ of 30 nM and 96 percent maximal efficacy. The compound demonstrates selectivity for 5-HT_{2A} over 5-HT_{2B} (K_i exceeding 10,000 nM) and shows no measurable activity at dopamine, norepinephrine, or serotonin transporters. In a 44-target safety panel, only the 5-HT_{2A} and 5-HT_{2B} receptors were identified as significant interaction targets at 10 micromolar concentration [3].

The non-hallucinogenic profile is explained not by biased agonism (preferential activation of one intracellular pathway over another) but by a consistent reduction in both potency (4- to 6-fold) and maximal efficacy (10 to 20 percent) across all measured signaling pathways relative to the hallucinogenic congener DOM [3]. This

"signaling efficacy hypothesis" positions Ariadne as the prototype of a mechanistically distinct drug class: 5-HT_{2A} agonists that retain therapeutic neuroplasticity-promoting and behavioral effects while falling below the signaling threshold required for hallucinogenesis.

Preclinical pharmacology in the auxilin-knockout mouse model of Parkinson's disease demonstrated that (R)-Ariadne at 10 mg/kg restored motor function to wild-type levels and eliminated pathological hind limb claspings, effects comparable to levodopa despite the compound's absence of dopaminergic pharmacology [3]. In the novelty-suppressed feeding paradigm, a sustained anxiolytic-like effect persisted 7 days after a single dose, consistent with 5-HT_{2A}-mediated neuroplastic remodeling [3].

Pharmacokinetic characterization in mice (10 mg/kg subcutaneous) confirmed high brain penetration (brain-to-plasma ratio of 10.23 at 1 hour), rapid absorption (C_{max} of 467 ng/mL at 15 minutes), and a plasma elimination half-life of approximately 2.1 hours [4]. Human pharmacokinetic data from the Bristol-Myers program have not been disclosed.

A 2024 patent application by Columbia University (WO2024073601A2) claims therapeutic applications of Ariadne and structural analogs across Parkinson's disease, dystonia, essential tremor, schizophrenia, depression, anxiety, bipolar disorder, obsessive-compulsive disorder, substance use disorders, catatonia, and cognitive enhancement [4]. The compound is not currently in active clinical development by any sponsor identified in public registries.

3. Discovery and Development History

3.1 Origin

Ariadne was first synthesized by Alexander Shulgin in 1968 at his private laboratory in Lafayette, California, as part of a systematic exploration of the structure-activity relationships within the 2,5-dimethoxy-4-substituted phenylalkylamine series [1, 2]. The compound was designed as the alpha-ethyl homolog of DOM, extending the alpha-carbon substituent from methyl to ethyl to probe the effect of this modification on psychoactive properties. Shulgin's original self-experiments at 32 mg of the racemic mixture and 25 mg of the R-enantiomer revealed a psychoactive but non-hallucinogenic profile, which he described as "the alert of a psychedelic, with none of the rest of the package" [2]. The absence of visual distortion, perceptual alteration, or cognitive disruption at active doses was a notable departure from the structurally related DOM, which produces intense hallucinations at 3 to 10 mg.

3.2 Bristol-Myers clinical development

The unusual non-hallucinogenic profile attracted the attention of Bristol-Myers Laboratories (later Bristol-Myers Squibb), which initiated a formal clinical development program between approximately 1972 and 1975 under the development codes BL-3912 (racemic) and BL-3912A (R-enantiomer) [3, 4, 5]. The tentative brand name "dimoxamine" was assigned but never formalized as an International Nonproprietary Name.

Phase I and Phase II clinical trials were conducted across multiple psychiatric and neurological indications. Published summaries (none of which include the underlying clinical datasets) report the following observations [3, 4, 5]:

At 50 to 100 mg per day orally, (R)-Ariadne produced rapid remission of psychotic symptoms in patients with schizophrenia and bipolar disorder. The time course of response was notably rapid relative to conventional antipsychotics, though the quantitative response data have not been disclosed.

At 100 mg per day, nearly complete remission of motor symptoms was reported in patients with Parkinson's disease. The effect was described as comparable to levodopa, a striking observation given that the compound has no measurable activity at dopamine receptors or transporters.

Catatonic patients showed relaxation; anxious patients showed increased sociability. Geriatric subjects at 50 mg per day showed improved alertness, mobility, sociability, and learning capacity.

At all studied doses, including a reported maximum of approximately 270 to 300 mg administered to healthy subjects in a National Institute on Drug Abuse Addiction Research Center study, no hallucinogenic effects or perceptual disturbances were observed [1, 3]. Euphoric effects were noted at high doses in the NIDA study, but no hallucinations.

3.3 Discontinuation

Bristol-Myers discontinued development of BL-3912A for strategic economic reasons rather than for safety or efficacy concerns [3, 4]. The contemporary regulatory and commercial environment for serotonergic psychoactive agents in the 1970s was unfavorable, and the compound class carried association with hallucinogenic drugs of abuse despite the demonstrated absence of hallucinogenic activity. The actual clinical datasets from the Bristol-Myers trials were never published and remain proprietary [4].

3.4 Contemporary research

The compound remained essentially dormant in the research literature for approximately four decades, appearing only in Shulgin's published compilations [1, 2] and in isolated online self-experimentation reports.

The resurgence of interest in non-hallucinogenic psychedelics as potential therapeutic agents for depression, anxiety, substance use disorders, and neurological conditions prompted the laboratory of Dalibor Sames at Columbia University to undertake a comprehensive pharmacological characterization of Ariadne. The Cunningham, Sames, and McCorvy (2022) report in ACS Chemical Neuroscience provided the first detailed molecular pharmacology, selectivity profiling, in vivo behavioral characterization, and Parkinson's disease model efficacy data for the compound [3].

In September 2023, Columbia University filed international patent application WO2024073601A2, claiming therapeutic applications of Ariadne and structural analogs (including fluorinated, trifluoromethyl, iodo, methoxymethyl, and cyclopropyl variants at the 4-position) across a broad range of neurological and psychiatric indications [4]. The patent was published in April 2024. As of the most recent monograph revision, no clinical trial registrations for Ariadne have been identified in ClinicalTrials.gov or other public registries.

4. Mechanism of Action

Ariadne is a serotonin receptor agonist whose primary molecular target is the 5-HT_{2A} receptor, with secondary activity at the 5-HT_{2C} and 5-HT_{2B} subtypes and weak activity at several 5-HT₁ family members. The compound is pharmacologically distinguished from structurally related hallucinogenic phenylalkylamines by a consistent reduction in both potency and maximal signaling efficacy across all measured intracellular transduction pathways [3].

4.1 5-HT_{2A} receptor agonism

The 5-HT_{2A} receptor is a G protein-coupled receptor (GPCR) of the class A (rhodopsin-like) family, coupled primarily through Gq/11 to phospholipase C-beta, inositol trisphosphate generation, intracellular calcium mobilization, and protein kinase C activation. The receptor is expressed at high density in layer V pyramidal neurons of the prefrontal cortex, in the claustrum, in multiple thalamic nuclei, and at lower density throughout the limbic system, basal ganglia, and brainstem [6, 7]. It is the primary molecular target for both hallucinogenic and non-hallucinogenic serotonergic agonists and is the site of action for classical psychedelics (psilocybin, LSD, mescaline, DOM, DOI) as well as for the emerging class of non-hallucinogenic psychoplastogens.

(R)-Ariadne binds the human 5-HT_{2A} receptor with a K_i of 53 nM, determined by radioligand displacement of [125I]-DOI [3]. The racemic mixture binds with a K_i of 120 nM, and the S-enantiomer binds with a K_i of 220 nM. These affinities are within one order of magnitude of the hallucinogenic congener DOM and substantially higher than the endogenous agonist serotonin.

Functional characterization in the Gq dissociation bioluminescence resonance energy transfer (BRET) assay at the 5-HT_{2A} receptor yielded an EC₅₀ of 149 nM and an E_{max} of 83 percent relative to serotonin for (R)-Ariadne [3]. In the calcium flux functional assay, (R)-Ariadne showed an EC₅₀ of 30 nM and an E_{max} of 96 percent relative to serotonin, while (S)-Ariadne showed an EC₅₀ of 132 nM and an E_{max} of 63 percent [3].

Beta-arrestin2 recruitment at the 5-HT2A receptor was measured at approximately 4.5-fold lower potency than DOM, with an Emax of 83 percent compared to 103 percent for DOM [3].

4.2 The signaling efficacy hypothesis

The central pharmacological finding of the Cunningham et al. (2022) study is the absence of substantial pathway bias between Gq/11 and beta-arrestin2 signaling [3]. Earlier hypotheses proposed that non-hallucinogenic 5-HT2A agonists might be G protein-biased (preferentially activating Gq signaling over beta-arrestin2 recruitment), but the Ariadne data do not support this model. Instead, the compound shows a consistent, parallel reduction in both potency (4- to 6-fold) and maximal efficacy (10 to 20 percent) across Gq dissociation, G11 dissociation, calcium flux, and beta-arrestin2 recruitment, relative to DOM [3].

The authors propose a "signaling efficacy hypothesis": the non-hallucinogenic profile arises from an overall reduction in the amplitude of 5-HT2A receptor signal transduction, such that downstream effectors responsible for hallucinogenesis (likely including cortical glutamate release, immediate early gene activation, and network-level disruption of default mode network processing) are not sufficiently engaged, while effectors responsible for therapeutic neuroplasticity (including brain-derived neurotrophic factor expression, TrkB signaling, mTOR-dependent spine growth, and AMPA receptor potentiation) remain above threshold [3, 6, 8].

4.3 Structural basis of reduced efficacy

Molecular docking analysis using the crystal structure of the 5-HT2A receptor in the active state (PDB ID: 6WHA) reveals that the alpha-ethyl substituent of Ariadne produces steric clash with hydrophobic residues W336 (position 6.48, the "toggle switch" tryptophan) and F339 (position 6.51) in the orthosteric binding pocket [3]. The minimal interatomic distances (3.15 angstroms to W336 and 2.77 angstroms to F339 in the extended conformation) indicate that the alpha-ethyl group impedes the full conformational transition of the receptor from the inactive to the maximally activated state. The alpha-methyl group of DOM fits within this pocket without steric penalty, permitting full receptor activation. Higher homologs (alpha-propyl, as in 5C-D) produce even greater steric clash and correspondingly greater reductions in efficacy, to the point where the head-twitch response (the mouse behavioral correlate of hallucinogenesis) becomes indistinguishable from vehicle [3].

4.4 Selectivity profile

The selectivity of Ariadne was characterized across a 44-target Eurofins SafetyScreen panel and a comprehensive serotonin receptor (5-HTome) functional screen [3].

At 10 micromolar concentration, only two molecular targets exceeded the 50 percent displacement threshold: the 5-HT2A receptor and the 5-HT2B receptor. All other targets (including dopamine D1 through D5, adrenergic alpha-1 and alpha-2, histamine H1 through H3, muscarinic M1 through M5, opioid mu/delta/kappa, ion channels, and transporters) showed less than 50 percent displacement.

In the 5-HTome functional screen, (R)-Ariadne showed weak submicromolar agonist activity at 5-HT1A (EC50 approximately 300 to 600 nM), 5-HT1D, 5-HT1E, and 5-HT1F receptors [3]. Activity at 5-HT1B was weaker (EC50 approximately 4 micromolar). Activity at 5-HT5, 5-HT6, and 5-HT7 receptors was absent or negligible (EC50 exceeding 10 micromolar).

Monoamine transporter inhibition was essentially absent: serotonin transporter (SERT) IC50 exceeded 50 micromolar; dopamine transporter (DAT) and norepinephrine transporter (NET) showed no relevant activity [3].

4.5 Downstream therapeutic mechanisms

The therapeutic effects of 5-HT2A agonism, both hallucinogenic and non-hallucinogenic, are increasingly attributed to the promotion of cortical neuroplasticity [6, 8, 9]. Activation of the 5-HT2A receptor in cortical pyramidal neurons triggers a cascade of intracellular events including phospholipase C-dependent calcium release, activation of calcium/calmodulin-dependent protein kinase II, ERK1/2 mitogen-activated protein kinase signaling, increased expression of brain-derived neurotrophic factor, activation of TrkB receptor tyrosine kinase signaling, mTOR-dependent dendritic spine formation, and potentiation of AMPA receptor-mediated glutamatergic transmission [6, 8].

Recent work on the structurally unrelated non-hallucinogenic psychoplastogen tabernanthalog has demonstrated that cortical spinogenesis induced by 5-HT2A agonism is required for sustained antidepressant-like behavioral effects, but that this spinogenesis can occur without the immediate early gene activation and glutamate burst that characterize hallucinogenic 5-HT2A agonists [9]. This dissociation provides a mechanistic framework for the Ariadne pharmacological profile: reduced

signaling efficacy is sufficient to engage the neuroplasticity program while remaining below the threshold for the network-level cortical disruption that produces hallucinations.

The anti-parkinsonian activity observed in both the Bristol-Myers clinical program and the auxilin-knockout mouse model is less well understood mechanistically, since Ariadne does not engage dopamine receptors or transporters. One proposed mechanism involves 5-HT_{2A} agonist-mediated increases in dopamine release in the nucleus accumbens and striatum, which have been documented for serotonergic agonists independently of direct dopaminergic pharmacology [3, 5]. A second proposed mechanism involves 5-HT_{2A}-mediated neuroplasticity in corticostriatal circuits that bypasses the nigrostriatal dopaminergic deficit.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and distribution (mouse data)

Pharmacokinetic characterization has been reported only in mice [4]. Following subcutaneous administration of (R)-Ariadne at 10 mg/kg:

Peak plasma concentration (C_{max}): 466.69 ng/mL, reached at 0.25 hours (15 minutes) post-administration.

Brain-to-plasma ratio: peaked at 10.23 at 1 hour post-administration, indicating rapid and extensive central nervous system penetration. Brain tissue retained the compound longer than plasma, suggesting tissue sequestration or slow efflux from the central compartment.

Plasma elimination half-life: approximately 2.11 hours.

The high brain-to-plasma ratio is consistent with the compound's physicochemical properties (moderate molecular weight of 223 g/mol, lipophilic dimethoxyphenyl ring, basic amine amenable to ion trapping in the acidic intracellular environment of neuronal tissue) and supports the observed central pharmacological effects at the doses studied.

5.2 Human pharmacokinetic data

Human pharmacokinetic data from the Bristol-Myers clinical program (BL-3912A) have not been publicly disclosed [4]. Self-experimentation reports from Shulgin and from online sources (Erowid) describe an onset of psychoactive effects within 30 to 60 minutes of oral administration, peak effects at 1 to 2 hours, and a total duration of action of approximately 2 to 5 hours at doses of 25 to 125 mg [1, 2]. These subjective pharmacodynamic timelines are broadly consistent with the mouse pharmacokinetic profile scaled for species differences in metabolic rate and are suggestive of rapid oral absorption and moderate duration.

5.3 Metabolism

The metabolic pathway of Ariadne has not been formally characterized in published literature. By structural analogy to other 2,5-dimethoxy-4-substituted phenylalkylamines (DOM, DOI, DOB, mescaline), the principal expected metabolic transformations are hepatic O-demethylation of the 2- and 5-methoxy groups (likely mediated by cytochrome P450 enzymes, including CYP2D6 and CYP3A4), oxidative deamination of the primary amine, and conjugation (glucuronidation or sulfation) of the resulting phenolic metabolites [10, 11].

A notable drug interaction observation supports the involvement of cytochrome P450 enzymes in Ariadne metabolism: Hamilton Morris reported that co-administration of (R)-Ariadne (25 mg) with fluoxetine (10 mg, a potent CYP2D6 inhibitor and serotonin reuptake inhibitor) produced an unexpectedly potent and prolonged psychedelic effect lasting over 24 hours, suggesting that CYP2D6 inhibition substantially increases Ariadne exposure and may shift the compound above the hallucinogenic signaling efficacy threshold [1].

5.4 Routes of administration

All documented human administration of Ariadne has been by the oral route. The Bristol-Myers clinical program used oral dosing at 50 to 100 mg per day [3, 4, 5]. Shulgin's self-experiments used oral administration of the free base or hydrochloride salt [2].

Preclinical studies in mice used subcutaneous injection, with formulation in 0.85 percent saline acidified with 2 molar equivalents of glacial acetic acid, administered at 10 mL/kg body weight [3, 4].

Intravenous, intramuscular, and intranasal routes have not been characterized.

5.5 Special populations

No data are available on the pharmacokinetics of Ariadne in pediatric, geriatric, hepatically impaired, or renally impaired populations. The Bristol-Myers clinical program included geriatric subjects, but pharmacokinetic parameters were not reported.

6. Clinical Evidence Base

6.1 Bristol-Myers Phase I and Phase II trials (1972 to 1975)

The clinical evidence base for Ariadne is derived almost entirely from the Bristol-Myers clinical program conducted with (R)-Ariadne (BL-3912A) in the early 1970s [3, 4, 5]. The actual clinical datasets have never been published, and the evidence is available only through secondary descriptions in the Cunningham et al. (2022) ACS Chemical Neuroscience report, the Columbia University patent application (WO2024073601A2), and historical references in the Shulgin literature.

Schizophrenia and bipolar disorder. At oral doses of 50 to 100 mg per day, BL-3912A reportedly produced rapid remission of psychotic symptoms in patients with schizophrenia and bipolar disorder. The rapidity of onset was noted as exceptional relative to conventional antipsychotic agents of the era (chlorpromazine, haloperidol). The compound did not produce extrapyramidal symptoms or the sedation characteristic of first-generation antipsychotics [3, 4, 5].

Parkinson's disease. At 100 mg per day orally, nearly complete remission of motor symptoms was reported in patients with Parkinson's disease. The effect was described as comparable to levodopa. This observation is particularly striking because the compound has no measurable activity at dopamine receptors or transporters, suggesting a serotonergic mechanism for motor symptom relief [3, 4].

Catatonia. Catatonic patients showed relaxation and increased spontaneous activity [3, 5].

Geriatric cognition. Elderly subjects at 50 mg per day showed improved alertness, mobility, sociability, and learning capacity [3, 4, 5].

Absence of hallucinogenic effects. At all clinical doses studied (up to and beyond 100 mg per day), including in patients with active psychosis who would be expected to be vulnerable to perceptual disturbances, no hallucinogenic effects were reported [3, 4].

6.2 NIDA Addiction Research Center study

An unpublished study conducted at the National Institute on Drug Abuse Addiction Research Center administered (R)-Ariadne at doses up to approximately 270 mg to healthy human subjects [1, 3]. No hallucinogenic effects or perceptual alterations were observed. Euphoric effects were noted at higher doses. The study data have not been published in the peer-reviewed literature.

6.3 Shulgin self-experimentation

Alexander Shulgin conducted self-experiments with racemic Ariadne at 32 mg and with (R)-Ariadne at 25 mg, administered orally [1, 2]. He reported a mild threshold psychoactive effect without any hallucinogenic, visual, or perceptual disturbance. Duration of effect was approximately 2 to 5 hours. Shulgin described the compound as producing feelings of mental alertness and well-being.

6.4 Online self-experimentation reports

Limited online self-experimentation reports (Erowid, PsychonautWiki) describe oral doses of 50 to 125 mg producing empathogenic and stimulant-like effects (described as similar to MDMA) without hallucinations [1]. The reliability and controlled conditions of these reports are limited.

6.5 Limitations of the evidence base

The clinical evidence for Ariadne is profoundly limited by the non-disclosure of the Bristol-Myers trial data. No randomized controlled trial data are available in the public domain. No dose-response curves, no formal efficacy analyses, no standardized outcome measures, and no adverse-event tabulations from the clinical program have been published. The secondary descriptions of clinical findings are impressive but unverifiable. Investigators should weight the evidence accordingly: the compound has produced provocative signals across multiple high-value indications, but the evidentiary standard falls far short of registration-quality clinical data.

7. Reported Research Dose Ranges

7.1 Human doses

Self-experimentation (Shulgin): 25 to 32 mg orally (R-enantiomer and racemic, respectively), producing threshold psychoactive effects [1, 2].

Bristol-Myers clinical program (BL-3912A): 50 to 100 mg per day orally across psychiatric and neurological indications [3, 4, 5].

NIDA study: Up to approximately 270 to 300 mg orally in healthy subjects, producing euphoria without hallucinations [1, 3].

Online reports: 50 to 125 mg orally, producing empathogenic and stimulant effects [1].

7.2 Preclinical doses (mouse)

Behavioral pharmacology (Cunningham et al. 2022): 10 mg/kg subcutaneous (standard behavioral dose); 30 mg/kg subcutaneous (high dose, producing marked sedation in open field test) [3].

Head-twitch response assessment: 1 to 30 mg/kg subcutaneous, with peak attenuated head-twitch response at 10 mg/kg [3].

Parkinson's disease model (auxilin-knockout mice): 10 mg/kg intraperitoneal, single dose [3].

7.3 Patent-claimed dose ranges

The Columbia University patent application claims effective human doses of 10 to 500 mg, with a typical range of 100 to 300 mg, and weight-based dosing of 0.1 to 20 mg/kg [4].

8. Sourcing and Quality Verification

Ariadne is not commercially available as a pharmaceutical-grade preparation. The compound has never been registered as a medicine in any jurisdiction and is not available through pharmaceutical distribution channels.

Research-grade Ariadne hydrochloride has limited commercial availability. The compound may be sourced from specialized custom synthesis providers and from select research chemical suppliers. Availability is substantially more limited than for well-characterized research compounds such as DOM, DOI, or mescaline, reflecting the compound's historical obscurity and the absence of a registered pharmaceutical form.

The Columbia University patent application (WO2024073601A2) describes preparation of the compound for research use, and investigators affiliated with the Sames laboratory may have access to characterized material [4].

Investigators acquiring research-grade Ariadne should confirm compound identity and purity through:

- High-performance liquid chromatography area-percent purity, targeting greater than 98 percent
- Mass spectrometry confirmation of molecular weight (224.165 for the protonated free base $[M+H]^+$)
- Chiral high-performance liquid chromatography or supercritical fluid chromatography for enantiomeric composition, with specification of R-enriched versus racemic material, given the approximately 4-fold potency difference between enantiomers
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography, particularly for tetrahydrofuran (from the lithium aluminum hydride reduction step) and other synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. Given the limited market for Ariadne and the consequent higher risk of misidentified or impure material, on-receipt analytical confirmation is strongly recommended for any investigation.

9. Reconstitution and Handling

Ariadne hydrochloride is soluble in water at room temperature. The free base is an oil and is not directly suitable for aqueous formulation without salt formation or co-solvent use.

For in vivo research applications, the compound is formulated in 0.85 percent normal saline with the addition of 2 molar equivalents of glacial acetic acid to ensure complete dissolution of the free base form, as described in the Cunningham et al. (2022) protocol [3, 4]. Sonication and gentle heating may be applied to achieve complete dissolution. The resulting solution is administered subcutaneously at a volume of 10 mL/kg body weight.

For in vitro research applications, stock solutions may be prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM and stored at minus 20 degrees Celsius. Aqueous dilutions from DMSO stock should maintain final DMSO concentrations below 0.1 percent to avoid solvent-related cellular effects.

Storage of the solid material (free base or hydrochloride salt) should be at minus 20 degrees Celsius in a desiccated, light-protected container. The compound is a primary amine and is susceptible to oxidative degradation on prolonged exposure to air and light, particularly in the free base form.

Aqueous solutions should be prepared fresh for each experiment or stored at 2 to 8 degrees Celsius for no longer than 7 days. The stability of Ariadne in aqueous solution has not been formally characterized; investigators should confirm potency retention by analytical methods when using stored solutions.

Aliquoting of stock solutions for single-use is recommended to avoid repeated freeze-thaw cycles.

10. Stack Interaction Considerations

Ariadne interacts with several drug classes through its serotonergic pharmacology and its likely cytochrome P450-mediated metabolism. Investigators conducting research with Ariadne, particularly in combination protocols, should consider the following interaction categories:

CYP2D6 inhibitors. The Hamilton Morris observation that co-administration of (R)-Ariadne (25 mg) with fluoxetine (10 mg) produced a potently psychedelic effect lasting over 24 hours suggests that CYP2D6 inhibition substantially increases Ariadne exposure [1]. Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine, terbinafine) should be considered as major interaction risks. Concurrent use may shift the compound above the signaling efficacy threshold for hallucinogenesis and may substantially prolong duration of action.

Serotonin reuptake inhibitors (SSRIs and SNRIs). Beyond the metabolic interaction, SSRIs produce additive serotonergic pharmacology. The combination of a 5-HT_{2A} agonist with a serotonin reuptake inhibitor increases synaptic serotonin concentration and may potentiate both therapeutic and adverse serotonergic effects. Serotonin syndrome risk should be monitored in any combination protocol, particularly at the higher dose ranges.

Monoamine oxidase inhibitors (MAOIs). MAO-A inhibition reduces oxidative deamination of phenylalkylamine substrates, substantially increasing exposure and duration of action. The combination of Ariadne with irreversible or potent reversible MAOIs is expected to produce dangerous potentiation and is contraindicated in clinical and research applications.

Other 5-HT_{2A} agonists. Concurrent administration of Ariadne with other 5-HT_{2A} agonists (psilocybin, LSD, DOM, DOI, mescaline, DMT, or non-hallucinogenic analogs such as tabernanthalog or lisuride) produces additive receptor activation and may exceed the signaling threshold for hallucinogenesis even with individually sub-hallucinogenic doses.

5-HT_{2A} antagonists. Concurrent administration with 5-HT_{2A} antagonists (ketanserin, risperidone, olanzapine, quetiapine, MDL100907) would be expected to block the pharmacological effects of Ariadne. The Cunningham et al. (2022) study

confirmed that pretreatment with MDL100907 at 0.01 and 0.032 mg/kg completely abolished the (R)-Ariadne-induced head-twitch response in mice [3].

Dopaminergic agents. Although Ariadne does not directly engage dopaminergic targets, the anti-parkinsonian activity suggests indirect dopaminergic modulation. Concurrent levodopa or dopamine agonist therapy may produce additive motor effects. The interaction has not been characterized.

QT-prolonging agents. The cardiac safety of Ariadne has not been formally characterized. The 5-HT_{2B} agonist activity (Gq EC₅₀ 739 nM for (R)-Ariadne) raises a theoretical concern for cardiac valvulopathy with chronic high-dose exposure, based on the precedent of fenfluramine and other 5-HT_{2B} agonists [12]. Combination with other QT-prolonging or valvulopathy-associated agents should be approached with caution.

11. Adverse Events and Safety

11.1 Reported adverse events

The adverse-event profile of Ariadne is poorly characterized due to the non-disclosure of Bristol-Myers clinical trial data. Available information is derived from secondary descriptions, self-experimentation reports, and preclinical studies.

Sedation. In the mouse open field test, (R)-Ariadne at 10 mg/kg produced minor sedation (reduced locomotor activity), and at 30 mg/kg produced marked sedation [3]. Sedation at higher doses is consistent with the pharmacology of 5-HT_{2A} agonism and is expected to be dose-dependent.

Anxiogenic effects (acute). In the mouse elevated plus maze, (R)-Ariadne produced decreased entries and time in open arms acutely, consistent with an anxiogenic-like effect in the immediate post-administration period [3]. This acute anxiogenic effect transitioned to a sustained anxiolytic-like effect by 7 days post-administration (reduced latency to feed in the novelty-suppressed feeding test), suggesting a biphasic anxiety profile consistent with 5-HT_{2A} agonist neuroplasticity mechanisms [3].

Euphoria. The NIDA Addiction Research Center study reported euphoric effects at high doses (up to 270 mg), which raises a theoretical abuse liability concern [1, 3].

No hallucinogenic effects. Across all documented human exposures (clinical trials, NIDA study, self-experimentation), no hallucinogenic, perceptual, or visual disturbance effects have been reported at doses up to 300 mg [1, 3].

11.2 Theoretical safety concerns

5-HT_{2B} agonism and cardiac valvulopathy. Ariadne activates the 5-HT_{2B} receptor with a G_q EC₅₀ of 739 nM and an E_{max} of 64 percent relative to serotonin for the R-enantiomer [3]. The 5-HT_{2B} receptor on cardiac valve interstitial cells mediates mitogenic signaling that, with chronic activation, produces fibrotic valvulopathy. This mechanism was responsible for the withdrawal of fenfluramine and pergolide. The clinical relevance for Ariadne depends on the dose, duration, and frequency of ad-

ministration; short-course or intermittent dosing (as in the Bristol-Myers 50 to 100 mg/day protocols) would be expected to carry substantially lower risk than chronic daily dosing. Nevertheless, the 5-HT_{2B} signal warrants echocardiographic monitoring in any chronic dosing protocol [12].

Serotonin syndrome. As a 5-HT_{2A} agonist, Ariadne has the potential to contribute to serotonin syndrome when combined with other serotonergic agents, particularly serotonin reuptake inhibitors, MAOIs, or other 5-HT_{2A} agonists.

CYP2D6 pharmacogenomic variability. If CYP2D6 is confirmed as a principal metabolic enzyme for Ariadne (supported by the fluoxetine interaction observation), CYP2D6 poor metabolizers may experience substantially elevated exposure, prolonged duration, and potentially qualitatively different pharmacological effects (as demonstrated by the fluoxetine co-administration producing hallucinogenic effects at a dose that is otherwise non-hallucinogenic) [1].

Abuse liability. The euphoric effects at high doses and the structural relationship to controlled substances (DOM, DOI, mescaline) raise theoretical abuse liability concerns. The compound is not currently scheduled under United States federal law but may be considered a positional isomer of DOET (a Schedule I substance) under the Federal Analogue Act [1].

11.3 Preclinical safety

No formal preclinical toxicology (acute LD₅₀, subchronic toxicity, genotoxicity, reproductive toxicity, carcinogenicity) has been published for Ariadne. The Bristol-Myers clinical program presumably included preclinical safety studies, but these data have not been disclosed.

No documented human overdoses of Ariadne have been reported in the published literature or in poison control databases [1]. By structural analogy to DOM, potential overdose effects would include hyperthermia, serotonergic hyperactivation, tachycardia, and agitation, manageable with benzodiazepines, active cooling, and supportive care.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five non-hallucinogenic 5-HT_{2A} receptor agonists against Ariadne, evaluated against 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 non-hallucinogenic 5-HT_{2A} agonists or psychoplastogens with substantive research literature and therapeutic relevance to the same indication space.

12.1 Tabernanthalog (TBG)

Mechanism: Non-hallucinogenic analog of ibogaine, functioning as a partial agonist at the 5-HT_{2A} receptor with psychoplastogenic (neuroplasticity-promoting) activity. TBG promotes cortical spinogenesis through 5-HT_{2A} activation of TrkB, mTOR, and AMPA receptor signaling without producing the immediate early gene activation or glutamate burst characteristic of hallucinogenic 5-HT_{2A} agonists [9, 13].

Development trajectory: Developed at the Olson laboratory at UC Davis. Preclinical studies have demonstrated antidepressant-like effects in multiple rodent models, anxiolytic effects, and anti-addictive effects (reduced ethanol and heroin self-administration) [13]. The compound has been advanced to preclinical development by Delix Therapeutics.

Novelty: High. The ibogaine-derived scaffold is chemically distinct from the phenylalkylamine class. The demonstration that neuroplasticity can be dissociated from hallucination at the level of immediate early gene activation is a mechanistic advance.

Effect size: Moderate in preclinical antidepressant and anti-addiction models. Sustained behavioral effects after single dosing. No human clinical data.

Promising potential: Moderate to high. Active preclinical development with commercial backing. No clinical trial registrations as of the most recent monograph revision.

Side-effect profile: Preclinical only. No major safety concerns identified in published rodent studies. The ibogaine scaffold raises theoretical concerns about hERG channel inhibition and cardiac arrhythmia, though TBG was designed to eliminate this liability.

Overall validation: Moderate. Strong preclinical data, novel mechanism, commercial development interest, but no human data.

Comparison to Ariadne: TBG and Ariadne share the non-hallucinogenic 5-HT_{2A} partial agonist profile but differ in chemical class (ibogaine analog versus phenylalkylamine), mechanism of non-hallucinogenesis (dissociation at the immediate early gene level for TBG versus signaling efficacy reduction for Ariadne), and clinical evidence (none for TBG versus Phase II historical data for Ariadne). Ariadne has the operational advantage of documented human safety and efficacy across multiple indications; TBG has the mechanistic advantage of a more detailed understanding of the dissociation between neuroplasticity and hallucinogenesis at the molecular level.

12.2 Lisuride

Mechanism: Ergoline derivative functioning as a 5-HT_{2A} partial agonist with G protein-biased agonism (preferential G_q activation over beta-arrestin2 recruitment). Also active at dopamine D₂ receptors as an agonist, distinguishing it from Ariadne's dopamine-independent profile [14].

Development trajectory: Lisuride is an approved medicine in several European jurisdictions for Parkinson's disease and hyperprolactinemia. Its 5-HT_{2A} agonist properties were characterized more recently. A 2023 study demonstrated antidepressant-like effects in mice [14]. The compound is not currently in development specifically as a non-hallucinogenic psychoplastogen.

Novelty: Low to moderate. The compound is a well-characterized ergoline with decades of clinical use. The non-hallucinogenic 5-HT_{2A} agonist characterization is relatively recent.

Effect size: Moderate in the mouse chronic despair model for antidepressant activity. Established efficacy in Parkinson's disease through dopaminergic mechanisms. No clinical data specifically for psychoplastogenic applications.

Promising potential: Moderate. Registered medicine with established safety profile. Potential for repositioning as a non-hallucinogenic psychoplastogen, but no active development program for this application.

Side-effect profile: Well characterized from decades of clinical use. Nausea, orthostatic hypotension, and psychiatric adverse events (including hallucinations at higher doses, notably) are the principal concerns. The hallucination risk at higher doses complicates the positioning as a non-hallucinogenic agent.

Overall validation: Moderate. Extensive clinical safety data from Parkinson's disease use. Limited data for psychoplastogenic applications.

Comparison to Ariadne: Lisuride has the advantage of regulatory approval and extensive human safety data. However, it is a multi-target agent (5-HT_{2A} plus D₂ plus other receptors), making it difficult to isolate 5-HT_{2A}-mediated therapeutic effects. Ariadne's cleaner selectivity profile (no dopaminergic activity, no ergoline-associated risks) and its well-defined signaling efficacy mechanism provide advantages for mechanistic research and for therapeutic development targeting 5-HT_{2A}-specific neuroplasticity.

12.3 2-Bromo-LSD (BOL-148)

Mechanism: Non-hallucinogenic ergoline functioning as a 5-HT_{2A} agonist with reduced efficacy relative to LSD. The compound binds the 5-HT_{2A} receptor with high affinity but produces substantially lower signaling amplitude than LSD [15].

Development trajectory: 2-Bromo-LSD has been studied principally for the treatment of cluster headache, an indication shared with LSD and psilocybin. Clinical reports have demonstrated efficacy against cluster headache attacks. The compound was studied in the 1950s and 1960s as a non-hallucinogenic LSD derivative and has experienced renewed interest in the context of psychedelic medicine [15].

Novelty: Low. The compound was synthesized in the 1950s and its non-hallucinogenic properties were characterized decades ago.

Effect size: Moderate for cluster headache (based on case series and open-label data). No controlled trial data for psychiatric or neurological indications.

Promising potential: Low to moderate. Limited commercial development interest. The ergoline class carries manufacturing and regulatory complexity.

Side-effect profile: Limited formal safety data. By structural analogy to LSD, potential concerns include ergotism-related vasoconstriction and 5-HT_{2B}-mediated cardiac effects with chronic use.

Overall validation: Low. Case series and historical data only. No controlled trials.

Comparison to Ariadne: 2-Bromo-LSD shares the non-hallucinogenic 5-HT_{2A} agonist profile with Ariadne but differs in chemical class (ergoline versus phenylalkylamine), therapeutic focus (cluster headache versus psychiatric and neurological indications), and depth of pharmacological characterization (limited for 2-Bromo-LSD versus comprehensive for Ariadne following the Cunningham et al. 2022 study). Ariadne has substantially more clinical evidence across indications.

12.4 AAZ-A-154 (R-70; DLX-001; 5-MeO-alpha-Me-isoDMT)

Mechanism: Tryptamine derivative functioning as a selective 5-HT₂ receptor agonist. Classified as a non-hallucinogenic psychoplastogen with reported neuroplasticity-promoting activity [16].

Development trajectory: Developed by Delix Therapeutics. The compound has been characterized in preclinical studies and has shown neuroplasticity-promoting effects without hallucinogenic behavioral signatures in rodents. Detailed receptor binding and functional signaling data have been reported in limited form.

Novelty: Moderate. The tryptamine scaffold is chemically distinct from the phenylalkylamine and ergoline classes but is within a well-explored chemical space.

Effect size: Preclinical data suggest neuroplasticity-promoting effects comparable to psilocybin without hallucinogenic behavioral markers. Quantitative effect sizes are not widely published.

Promising potential: Moderate. Active commercial development by Delix Therapeutics, which has raised substantial venture capital for the non-hallucinogenic psychoplastogen approach.

Side-effect profile: Preclinical only. No major safety signals reported.

Overall validation: Low to moderate. Early-stage preclinical development with commercial backing.

Comparison to Ariadne: AAZ-A-154 and Ariadne are both non-hallucinogenic 5-HT2A agonists from different chemical classes (tryptamine versus phenylalkylamine). Ariadne has the substantial advantage of historical clinical data across multiple indications; AAZ-A-154 has the advantage of active commercial development and a contemporary drug development program designed with modern regulatory standards. The selectivity profiles and mechanism of non-hallucinogenesis may differ.

12.5 DOM (2,5-dimethoxy-4-methylamphetamine)

Mechanism: Hallucinogenic 5-HT2A full agonist of the amphetamine class. DOM is the alpha-methyl analog of 2C-D and the direct structural comparator for Ariadne (which is the alpha-ethyl analog). DOM produces potent hallucinations in humans at 3 to 10 mg through full activation of the 5-HT2A receptor signaling cascade [3, 17].

Development trajectory: DOM is a Schedule I controlled substance in the United States and has not been developed as a therapeutic agent. It serves as the primary hallucinogenic reference compound for the 2,5-dimethoxy-4-substituted phenylalkylamine series.

Novelty: Not applicable (reference compound, not a therapeutic candidate).

Effect size: Potent hallucinogenic activity at low milligram doses. Robust head-twitch response in mice. Neuroplasticity-promoting effects comparable to other hallucinogenic 5-HT2A agonists but inseparable from the hallucinogenic experience.

Promising potential: None as a therapeutic candidate (Schedule I, potent hallucinogen).

Side-effect profile: Hallucinations (defining feature), anxiety, panic, tachycardia, hypertension, hyperthermia, and rare reports of prolonged psychosis. The adverse-event profile is dominated by the hallucinogenic effects.

Overall validation: High as a pharmacological reference compound. Zero as a therapeutic candidate.

Comparison to Ariadne: DOM is the direct structural comparator and the mechanistic reference for understanding Ariadne's non-hallucinogenic profile. The single methylene group extension from alpha-methyl (DOM) to alpha-ethyl (Ariadne) is the molecular basis for the 4- to 6-fold reduction in signaling potency and the 10 to 20 percent reduction in maximal efficacy that separates the hallucinogenic from the non-hallucinogenic phenotype [3]. The DOM comparison defines Ariadne's therapeutic space: Ariadne preserves the 5-HT_{2A} receptor engagement and the downstream neuroplasticity, anti-parkinsonian, and psychiatric therapeutic effects while falling below the signaling threshold for hallucinogenesis.

12.6 Comparator summary

The five comparators occupy distinct positions in the non-hallucinogenic 5-HT_{2A} agonist landscape. **Tabernanthalog** represents the most mechanistically novel approach, with dissociation of neuroplasticity from hallucinogenesis at the immediate early gene level, but lacks human data. **Lisuride** is the most clinically validated (registered medicine for Parkinson's disease) but is multi-target and produces hallucinations at higher doses. **2-Bromo-LSD** has historical precedent but limited pharmacological characterization and a narrow therapeutic focus on cluster headache. **AAZ-A-154** is the most commercially advanced non-hallucinogenic psychoplastogen program but is in early preclinical development. **DOM** is the hallucinogenic reference that defines the signaling threshold above which hallucinations occur.

Ariadne occupies a unique position: it is the only compound in this comparator panel with documented Phase II clinical efficacy data across multiple high-value indications (schizophrenia, Parkinson's disease, catatonia, cognitive impairment), the only compound with a fully characterized signaling efficacy mechanism (Cunningham et al. 2022), the only compound with both historical clinical evidence and contemporary preclinical validation (auxilin-knockout Parkinson's model), and the compound with the cleanest selectivity profile (no dopaminergic, adrenergic, or transporter activity). Its principal weakness is the non-disclosure of the Bristol-

Myers clinical datasets, which reduces the evidentiary weight of the clinical claims. Its principal strength is the convergence of historical clinical observations, contemporary molecular pharmacology, preclinical disease model efficacy, and a coherent mechanistic explanation for the non-hallucinogenic therapeutic profile.

The practical question for the research-clinical positioning of Ariadne is whether the signaling efficacy hypothesis is sufficient to support a therapeutic window in which 5-HT_{2A}-mediated neuroplasticity and behavioral effects are preserved while hallucinogenesis is reliably avoided, and whether this window is robust to inter-individual variation in pharmacokinetics (particularly CYP2D6 polymorphism). The fluoxetine interaction observation suggests that the window may be narrow and pharmacokinetically sensitive. Investigators considering Ariadne for research should manage this variable with appropriate metabolic phenotyping and drug-interaction screening.

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authority and institutional review board before any research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.