

RESEARCH MONOGRAPH . COMPOUND PROFILE

6-MeO-DMT

A 6-position methoxy-substituted N,N-dimethyltryptamine distinguished from its 5-methoxy positional isomer by dramatically reduced serotonin receptor affinity, absence of hallucinogenic activity in animal models, and emerging interest as a non-psychotomimetic tryptamine scaffold for structure-activity dissection and potential psychoplastogenic research.

DOCUMENT	KDC-MN-1594
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Non-hallucinogenic methoxytryptamine with attenuated serotonin receptor agonism at 5-HT2A and 5-HT1A subtypes

ABSTRACT

6-MeO-DMT (6-methoxy-N,N-dimethyltryptamine; CAS 2426-88-2) is a substituted indoleethylamine of the tryptamine structural class, defined by the placement of a methoxy substituent at the 6-position of the indole ring rather than at the 5-position occupied in its well-characterized positional isomer 5-MeO-DMT. The compound was first described in the scientific literature by 1968 and was assessed in structure-activity relationship studies of serotonergic tryptamines during the 1970s and 1980s. Despite acting as an agonist at the serotonin 5-HT_{2A} receptor and as a non-selective agonist at multiple additional serotonin receptor subtypes, 6-MeO-DMT displays markedly reduced receptor affinity relative to both DMT and 5-MeO-DMT: its 5-HT_{2A} binding affinity is 12- to 43-fold lower than that of 5-MeO-DMT and approximately 6-fold lower than that of DMT, while its 5-HT_{1A} affinity is approximately 110-fold lower than that of 5-MeO-DMT. These attenuated binding properties correlate with the absence of the head-twitch response in rodent models, failure to substitute for the classical hallucinogen DOM in drug discrimination paradigms, and overall lack of psychedelic-like behavioral effects in all animal assays conducted to date.

The pharmacological profile of 6-MeO-DMT is of contemporary research interest for two principal reasons. First, the compound exemplifies how a single-atom positional shift of the methoxy group on the indole ring (from position 5 to position 6) produces a qualitative transition from hallucinogenic to non-hallucinogenic pharmacology while preserving the fundamental tryptamine scaffold and serotonin receptor agonist mechanism, providing a

critical negative-control and structure-activity reference point for the investigation of 5-HT_{2A}-mediated psychedelia. Second, the compound belongs to a growing class of non-hallucinogenic serotonin 5-HT_{2A} receptor agonists (alongside tabernanthalog, 6-fluoro-DET, 2-bromo-LSD, lisuride, and others) that retain the capacity to promote neuroplasticity through 5-HT_{2A}-dependent signaling without producing the subjective and behavioral effects associated with classical psychedelics, positioning it as a candidate scaffold for psychoplastogenic drug development.

6-MeO-DMT has not been tested in humans. No human pharmacokinetic, pharmacodynamic, or clinical efficacy data exist. The compound is presumed to undergo oxidative deamination by monoamine oxidase A (MAO-A) consistent with the metabolic fate of structurally related N,N-dimethylated tryptamines, with potential minor O-demethylation pathways contributing to total clearance. The compound is not an explicitly controlled substance in the United States, though it may be considered a Schedule I controlled substance as a positional isomer of 5-MeO-DMT under the Federal Analogue Act. This monograph reviews the chemistry, synthesis, and structural classification of 6-MeO-DMT; the receptor pharmacology and structure-activity relationships within the methoxytryptamine series; the extrapolated pharmacokinetic profile; the preclinical pharmacology evidence base; the absence of clinical data; sourcing and quality verification considerations; reconstitution and handling; stack interactions and combinations; adverse-event and safety signal assessment; and a comparative evaluation of five structurally or mechanistically related tryptamine compounds against 6-MeO-DMT on five assessment standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Systematic name: 6-Methoxy-N,N-dimethyltryptamine.

Common abbreviations: 6-MeO-DMT, 6-OMe-DMT.

Chemical Abstracts Service registry number: 2426-88-2 (free base).

International Union of Pure and Applied Chemistry name: 2-(6-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine.

Structural relationship: 6-MeO-DMT is the 6-methoxy positional isomer of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT; CAS 1019-45-0). It is also a methyl ether derivative of 6-hydroxy-N,N-dimethyltryptamine (6-Hydroxy-DMT; CAS 20088-30-0). The compound shares its N,N-dimethylethylamine side chain with DMT (CAS 61-50-7) and differs from DMT solely by the presence of the 6-methoxy substituent on the indole ring.

1.2 Structural class and chemistry

6-MeO-DMT is a substituted indoleethylamine of the tryptamine structural class. The tryptamine scaffold consists of an indole ring system linked through the 3-position to a two-carbon ethylamine side chain. In 6-MeO-DMT, the nitrogen bears two methyl groups (N,N-dimethyl substitution) and the indole ring carries a methoxy group at the 6-position, one position removed from the canonical 5-position occupied in the biologically more potent 5-MeO-DMT [1, 2].

Molecular formula: C₁₃H₁₈N₂O (free base).

Exact mass: 218.1419 g/mol (free base, monoisotopic).

Molecular weight: 218.30 g/mol (free base).

Physical properties: The free base is expected to present as a white to off-white solid or oil at room temperature, consistent with N,N-dimethylated methoxytryptamines of similar molecular weight. Soluble in methanol, ethanol, dimethyl sulfoxide, and dilute aqueous acid (as the protonated amine); sparingly

soluble in water at physiological pH owing to the lipophilic indole ring and ether substituent. Salt forms (hydrochloride, fumarate, succinate) would be expected to display improved aqueous solubility, though no pharmacopoeial salt form has been registered for this compound.

SMILES: CN(C)CCc1c[nH]c2cc(OC)ccc12.

Stereochemistry: 6-MeO-DMT has no stereocenters and is achiral.

1.3 Synthesis

The synthesis of 6-MeO-DMT follows established indoleethylamine methodology. The most direct route proceeds from 6-methoxyindole (commercially available) through a Speeter-Anthony tryptamine synthesis or a related approach: the indole undergoes Friedel-Crafts acylation or Vilsmeier-Haack formylation at the 3-position, followed by condensation with dimethylamine and reduction to afford the N,N-dimethyltryptamine product [3, 4]. Alternative routes include reductive amination of the corresponding tryptamine aldehyde intermediate, or direct alkylation of the primary tryptamine (6-methoxytryptamine) with formaldehyde and a reducing agent (Eschweiler-Clarke methylation).

A biosynthetic route has also been described. Complete biosynthesis of psychedelic and related tryptamines from tryptophan precursors has been demonstrated in plant expression systems, with the enzymatic steps including tryptophan decarboxylase, N-methyltransferase (indoleethylamine N-methyltransferase), and hydroxylase or methyltransferase enzymes that introduce the methoxy substituent at various ring positions [5]. Whether the 6-position methoxylation occurs through direct enzymatic hydroxylation at C-6 followed by O-methylation, or through an alternative pathway, has not been fully characterized for 6-MeO-DMT specifically.

The compound is available from research chemical suppliers at stated purities of 95 to 99 percent by HPLC. Investigators should confirm identity by nuclear magnetic resonance spectroscopy and mass spectrometry and confirm purity by reversed-phase HPLC on every lot.

2. Abstract

6-MeO-DMT (6-methoxy-N,N-dimethyltryptamine) is a non-hallucinogenic tryptamine that acts as an agonist at the serotonin 5-HT_{2A} receptor and at multiple additional serotonin receptor subtypes, but with substantially reduced affinity and potency relative to its 5-position isomer 5-MeO-DMT and relative to the parent compound DMT [1, 6, 7]. The compound was first described in the scientific literature by 1968 and has been used principally as a structure-activity relationship reference compound for the investigation of positional determinants of hallucinogenic activity within the methoxytryptamine series [8, 9].

The most pharmacologically significant feature of 6-MeO-DMT is its lack of hallucinogenic activity despite retention of serotonin receptor agonism. In rodent behavioral assays, the compound does not produce the head-twitch response (the standard behavioral proxy for 5-HT_{2A}-mediated hallucinogenic activity in mice), does not substitute for the classical hallucinogen DOM (2,5-dimethoxy-4-methylamphetamine) in drug discrimination paradigms, and does not produce other psychedelic-like behavioral signatures [6, 10, 11]. The compound does substitute for the atypical psychedelic 5-MeO-DMT in drug discrimination assays, but with approximately 4-fold lower potency, consistent with its reduced serotonin receptor affinity [6].

The dissociation between serotonin 5-HT_{2A} receptor agonism and hallucinogenic behavioral output has placed 6-MeO-DMT alongside compounds such as 6-fluoro-DET, 2-bromo-LSD (BOL-148), lisuride, 25N-N1-Nap, and tabernanthalog in the category of non-hallucinogenic 5-HT_{2A} agonists [12, 13, 14]. This class is of intense current interest in psychedelic neuroscience because of evidence that 5-HT_{2A} receptor agonism can promote structural neuroplasticity (dendritic arbor growth, spinogenesis, synaptogenesis) independently of the subjective and behavioral hallmarks of classical psychedelia [15, 16]. Whether 6-MeO-DMT itself retains psychoplastogenic (neuroplasticity-promoting) activity has not been directly demonstrated, but its membership in the non-hallucinogenic 5-HT_{2A} agonist class and the precedent set by tabernanthalog and related compounds provide a mechanistic rationale for such investigation.

No human pharmacological, pharmacokinetic, or clinical data exist for 6-MeO-DMT. The compound has not been administered to human subjects in any published study. All characterization is derived from in vitro receptor binding assays, in vitro functional assays, and in vivo rodent behavioral pharmacology.

3. Discovery and Development History

3.1 Early description and structure-activity context

The first documented appearance of 6-MeO-DMT in the scientific literature dates to approximately 1968, within the broader context of tryptamine structure-activity relationship studies that explored the influence of ring substitution position, ring substitution identity (hydroxy, methoxy, halo), and N-alkyl chain length on serotonergic activity and behavioral pharmacology [8]. These studies were motivated by the observation that small structural modifications to the tryptamine scaffold produced dramatic changes in psychotropic potency, exemplified by the high potency of 5-MeO-DMT versus the low potency of 4-MeO-DMT, and by the classical work of Szara and colleagues on the metabolic and pharmacological consequences of 6-hydroxylation of tryptamine derivatives [17].

The Szara et al. (1966) study in *Science* examined the effect of 6-hydroxylation on tryptamine psychotropic potency, reporting that 6-hydroxy-5-methoxy-N,N-dimethyltryptamine displayed reduced psychotropic effects relative to 5-methoxy-N,N-dimethyltryptamine in trained rats [17]. This finding established the principle that substitution at the 6-position of the indole ring diminishes, rather than enhances, the psychotropic activity of serotonergic tryptamines, a principle that 6-MeO-DMT subsequently exemplified.

3.2 Drug discrimination and behavioral pharmacology studies

The lack of hallucinogen-like effects of 6-MeO-DMT was formally characterized by at least 1983, when Glennon and colleagues reported on the drug discrimination properties of tryptamine analogs in rats trained to discriminate the classical hallucinogen DOM from saline [10, 11]. In these paradigms, 6-MeO-DMT failed to substitute for DOM, in contrast to 5-MeO-DMT, DMT, psilocin, and other 5-substituted tryptamines that reliably generalized to the DOM stimulus. The failure to generalize to DOM established that the 6-methoxy substitution pattern does not support the interoceptive stimulus properties characteristic of classical hallucinogens, even though the compound retains measurable affinity at the 5-HT_{2A} receptor.

Subsequent drug discrimination studies confirmed that 6-MeO-DMT does substitute for 5-MeO-DMT in rats trained to discriminate 5-MeO-DMT from saline, but with approximately 4-fold lower potency [6]. This finding indicates that 6-MeO-DMT produces an interoceptive state partially overlapping with that of 5-MeO-DMT (which has a complex stimulus profile involving both 5-HT1A and 5-HT2A components) but distinct from the DOM-type classical hallucinogen stimulus (which is primarily 5-HT2A-mediated).

3.3 Contemporary interest as a non-hallucinogenic 5-HT2A agonist

Interest in 6-MeO-DMT has been renewed in the 2020s by the broader scientific focus on non-hallucinogenic psychoplastogens. The demonstration by Olson and colleagues at the University of California, Davis that certain 5-HT2A receptor agonists can promote cortical neuroplasticity without producing hallucinogenic behavioral signatures [15] has driven systematic investigation of the structural determinants that dissociate neuroplasticity from psychedelia. In this framework, 6-MeO-DMT serves as a naturally occurring example (within the tryptamine scaffold) of a compound that preserves the 5-HT2A agonist pharmacophore while lacking the substituent geometry required for hallucinogenic potency.

Duan, Cao, Wang, and Cheng (2024) reviewed 6-MeO-DMT in the context of serotonin 2A receptor agonists as emerging antidepressant candidates, classifying it among the non-hallucinogenic tryptamine analogs of potential therapeutic interest [18]. Cameron and colleagues have identified 6-MeO-DMT within the broader class of non-hallucinogenic 5-HT2A agonists that includes tabernanthalog (TBG), though direct psychoplastogenic testing of 6-MeO-DMT has not been published [14].

3.4 Absence of clinical development

6-MeO-DMT has never entered clinical development. No investigational new drug application, clinical trial registration, or human pharmacokinetic study has been published or registered. The compound exists exclusively as a research tool and structure-activity reference compound in the preclinical pharmacology literature.

4. Mechanism of Action

4.1 Serotonin receptor agonism

6-MeO-DMT acts as an agonist at the serotonin 5-HT_{2A} receptor, the molecular target most closely associated with the psychedelic effects of classical hallucinogens. However, its affinity at this receptor is substantially reduced compared to structurally related hallucinogenic tryptamines. Radioligand binding studies have reported that the affinity of 6-MeO-DMT at the 5-HT_{2A} receptor is 12- to 43-fold lower than that of 5-MeO-DMT and approximately 6-fold lower than that of DMT [1, 6, 7]. For reference, 5-MeO-DMT displays K_i values at the 5-HT_{2A} receptor in the range of approximately 100 to 900 nM depending on species and assay conditions; DMT displays K_i values in the range of approximately 100 to 300 nM. The corresponding values for 6-MeO-DMT are therefore estimated to fall in the low-micromolar range at the 5-HT_{2A} receptor.

At the serotonin 5-HT_{1A} receptor, the reduction in affinity is even more pronounced. The 5-HT_{1A} affinity of 6-MeO-DMT is approximately 110-fold lower than that of 5-MeO-DMT [1, 7]. Given that 5-MeO-DMT displays exceptionally high 5-HT_{1A} affinity (K_i approximately 1.9 to 3 nM), the 6-MeO-DMT 5-HT_{1A} K_i is estimated at approximately 200 to 330 nM [19].

6-MeO-DMT is also a non-selective agonist at additional serotonin receptor subtypes (5-HT_{2B}, 5-HT_{2C}, 5-HT₆, 5-HT₇), consistent with the broad serotonergic agonist profile of simple N,N-dimethylated tryptamines. The affinity at these additional subtypes has not been individually characterized in published literature but is expected to be reduced relative to 5-MeO-DMT and DMT in proportion to the general attenuation imposed by the 6-methoxy substitution pattern [1, 7].

4.2 Structure-activity relationship of methoxy position

The pharmacological distinction between 5-MeO-DMT and 6-MeO-DMT is one of the most instructive examples in tryptamine structure-activity pharmacology. The 5-position of the indole ring is the canonical site for serotonin (5-hydroxytryptamine) itself; 5-substituted tryptamines (5-methoxy, 5-hydroxy, 5-fluoro, 5-bromo) gener-

ally display high affinity at serotonin receptors and, depending on N-alkyl substitution, hallucinogenic activity. Moving the substituent one position to the 6-position dramatically reduces both receptor affinity and hallucinogenic potency [1, 8, 17].

The structural basis for this positional sensitivity is understood in terms of the receptor binding pharmacophore. Molecular modeling and crystallographic studies of the 5-HT_{2A} receptor indicate that the 5-position substituent engages in critical hydrogen bonding and van der Waals contacts with residues in the orthosteric binding pocket (particularly serine 239 and threonine 160 in transmembrane domains 3 and 5, respectively) [20]. Displacement of the substituent to the 6-position places it outside this optimal interaction geometry, reducing binding affinity and functional efficacy while not completely abolishing receptor engagement.

The 7-methoxy positional isomer (7-MeO-DMT) represents a further displacement and shows additional attenuation of serotonergic activity, while the 4-methoxy isomer (4-MeO-DMT; also known as O-methylpsilocin) displays its own distinct pharmacological profile with moderate serotonin receptor affinity [21].

4.3 Absence of head-twitch response and hallucinogenic activity

The head-twitch response (HTR) in mice is the established behavioral proxy for 5-HT_{2A} receptor-mediated hallucinogenic activity and correlates with hallucinogenic potency in humans across multiple structural classes of serotonergic hallucinogens (tryptamines, phenethylamines, ergolines) [22]. 6-MeO-DMT does not produce the HTR in mice at any tested dose, in contrast to DMT, 5-MeO-DMT, psilocin, and other hallucinogenic tryptamines that reliably elicit the HTR [6, 12].

The absence of the HTR can be interpreted as a consequence of insufficient 5-HT_{2A} receptor activation (due to low affinity and low efficacy at the concentrations achieved *in vivo*) or as a consequence of a qualitative difference in downstream signaling (biased agonism). The available data favor the former interpretation: the reduced affinity (12- to 43-fold at 5-HT_{2A}) is sufficient to explain the loss of hallucinogenic activity without invoking biased signaling, although biased agonism has not been formally excluded.

4.4 Drug discrimination pharmacology

Drug discrimination studies provide additional mechanistic resolution. The failure of 6-MeO-DMT to substitute for DOM (a selective 5-HT_{2A} agonist hallucinogen) in trained rats confirms that the compound does not achieve the threshold of 5-HT_{2A} receptor activation required to produce the interoceptive stimulus associated with classical hallucinogens [10, 11]. The partial substitution for 5-MeO-DMT (with approximately 4-fold reduced potency) suggests that at higher doses, 6-MeO-DMT achieves a stimulus state that partially overlaps with the 5-MeO-DMT discriminative stimulus, which is mediated by a combination of 5-HT_{1A} and 5-HT_{2A} receptor activation [6, 23].

4.5 Potential psychoplastic activity

The classification of 6-MeO-DMT among non-hallucinogenic 5-HT_{2A} agonists raises the question of whether it retains the capacity to promote structural neuroplasticity. Psychoplastogens such as tabernanthalog (TBG) have been shown to promote cortical dendritic arbor growth, spinogenesis, and synaptogenesis through a 5-HT_{2A}-dependent, TrkB- and mTOR-dependent signaling cascade, without producing the head-twitch response or other hallmarks of classical psychedelia [14, 15, 16]. Whether 6-MeO-DMT engages this neuroplasticity pathway has not been directly tested. Given its reduced 5-HT_{2A} receptor affinity and efficacy, the magnitude of any psychoplastic effect would be expected to be modest at best, and may require sustained exposure rather than the acute single-dose paradigms used with more potent psychoplastogens. This remains an open experimental question.

5. Pharmacokinetics

5.1 General considerations

No pharmacokinetic data exist for 6-MeO-DMT in any species from dedicated pharmacokinetic studies. The following pharmacokinetic profile is inferred from the well-characterized metabolism and disposition of structurally related N,N-dimethyltryptamines (DMT, 5-MeO-DMT) and from general principles of tryptamine biochemistry.

5.2 Absorption

Based on the physicochemical properties of the compound (molecular weight 218.30, moderate lipophilicity, basic amine pKa approximately 8.5 to 9.5), 6-MeO-DMT is expected to be absorbed from the gastrointestinal tract but to undergo extensive first-pass metabolism by monoamine oxidase A (MAO-A) in the gastrointestinal mucosa and liver, consistent with the oral inactivity of DMT and 5-MeO-DMT when administered without MAO inhibition [24, 25]. Parenteral routes (intravenous, intramuscular, insufflation, inhalation) would be expected to bypass the first-pass MAO-A barrier and achieve systemic exposure.

5.3 Distribution

The compound is expected to distribute into the central nervous system on the basis of its moderate lipophilicity, small molecular weight, and the established CNS penetration of structurally related tryptamines. Volume of distribution is expected to be moderate to large, consistent with DMT and 5-MeO-DMT.

5.4 Metabolism

The primary metabolic pathway for N,N-dimethylated tryptamines is oxidative deamination by monoamine oxidase A (MAO-A), producing the corresponding indoleacetic acid metabolite (6-methoxyindoleacetic acid in the case of 6-MeO-DMT)

[24, 25]. This pathway is rapid and high-capacity, accounting for the short plasma half-lives (minutes) observed with DMT and 5-MeO-DMT after parenteral administration.

A secondary metabolic pathway for methoxytryptamines is O-demethylation by cytochrome P450 enzymes (principally CYP2D6), producing the corresponding hydroxytryptamine metabolite (6-hydroxy-DMT in the case of 6-MeO-DMT) [26, 27]. For 5-MeO-DMT, CYP2D6-mediated O-demethylation produces bufotenine (5-hydroxy-DMT), which is itself pharmacologically active. The corresponding 6-hydroxy-DMT product from 6-MeO-DMT O-demethylation has been described in the literature as a compound with reduced psychotropic activity relative to 5-hydroxy-DMT [17].

N-demethylation by CYP enzymes to produce 6-methoxy-N-methyltryptamine (6-MeO-NMT) is a third potential minor pathway, consistent with the metabolism of DMT.

5.5 Elimination

Renal excretion of the deaminated metabolite (6-methoxyindoleacetic acid) and its conjugates is the expected primary elimination pathway, consistent with the elimination of indoleacetic acid metabolites of DMT and 5-MeO-DMT.

5.6 Predicted pharmacokinetic parameters

By analogy with DMT and 5-MeO-DMT: plasma half-life after parenteral administration is estimated at approximately 5 to 20 minutes; oral bioavailability without MAO inhibition is estimated at less than 5 percent; oral bioavailability with concurrent MAO inhibition is expected to increase substantially.

6. Preclinical Pharmacology

6.1 In vitro receptor binding

The principal in vitro characterization of 6-MeO-DMT is radioligand displacement binding at serotonin receptor subtypes. As summarized in Section 4.1, the compound displays attenuated affinity at the 5-HT_{2A} receptor (12- to 43-fold lower than 5-MeO-DMT; approximately 6-fold lower than DMT) and markedly reduced affinity at the 5-HT_{1A} receptor (approximately 110-fold lower than 5-MeO-DMT) [1, 6, 7]. These affinities have been reported as fold-reductions relative to reference compounds rather than as absolute K_i values in the primary published literature.

6.2 In vivo behavioral pharmacology

The behavioral pharmacology of 6-MeO-DMT has been assessed in three principal paradigms:

Head-twitch response (HTR): 6-MeO-DMT does not produce the HTR in mice at any dose tested, confirming the absence of hallucinogenic-like activity [6, 12].

Drug discrimination (DOM-trained rats): 6-MeO-DMT fails to substitute for DOM in rats trained to discriminate DOM from saline. This result indicates that the compound does not produce the interoceptive stimulus characteristic of classical serotonergic hallucinogens [10, 11].

Drug discrimination (5-MeO-DMT-trained rats): 6-MeO-DMT substitutes for 5-MeO-DMT with approximately 4-fold lower potency. This result indicates partial overlap with the 5-MeO-DMT stimulus, which is mediated by a combination of 5-HT_{1A} and 5-HT_{2A} receptor activation [6].

6.3 Thermoregulatory effects

Serotonergic tryptamines produce characteristic thermoregulatory responses in rodents, including hypothermia (mediated principally by 5-HT_{1A} agonism) and hyperthermia (mediated by 5-HT_{2A} agonism in some dose ranges). No published data

specifically address the thermoregulatory effects of 6-MeO-DMT. Based on its attenuated receptor affinity profile, any thermoregulatory response would be expected to be reduced relative to 5-MeO-DMT and DMT.

6.4 Neuroplasticity and psychoplastogenic potential

No published study has directly assessed the neuroplasticity-promoting effects of 6-MeO-DMT in vitro (dendritic growth assays, spine density measurements) or in vivo. The compound is classified among non-hallucinogenic 5-HT_{2A} agonists by Duan et al. (2024) and by Cameron and colleagues, but the functional demonstration of psychoplastogenic activity has not been reported [14, 18].

6.5 Toxicology

No formal toxicological assessment of 6-MeO-DMT has been published. The compound has not undergone genotoxicity testing, reproductive toxicity testing, or chronic dosing studies in any species.

7. Clinical Evidence Base

No clinical evidence exists for 6-MeO-DMT. The compound has not been administered to human subjects in any published or registered clinical trial. It has not been tested in human volunteers for pharmacokinetic characterization, safety and tolerability, or any therapeutic indication.

The absence of human data is consistent with the compound's status as a structure-activity reference tool rather than a clinical development candidate. Unlike 5-MeO-DMT, which has an extensive ethnobotanical history of human use and a growing clinical evidence base in psychiatric applications, 6-MeO-DMT has no documented history of human consumption or self-experimentation in the published literature.

Any future clinical investigation of 6-MeO-DMT would require *de novo* preclinical safety pharmacology, toxicology, and pharmacokinetic characterization before human exposure could be ethically justified.

8. Sourcing and Quality Verification

6-MeO-DMT is available from several research chemical suppliers including MedChemExpress, Cayman Chemical, and selected specialty tryptamine vendors. Supply is typically in milligram quantities (5 mg to 100 mg) as the free base. Pricing is moderate to high for a research compound of this structural class, reflecting limited demand and small-batch synthesis.

Stated purities from commercial suppliers typically range from 95 to 99 percent by HPLC. Investigators should confirm compound identity and purity on every lot through:

- Reversed-phase high-performance liquid chromatography (HPLC) with UV detection at 220 nm and 280 nm for area-percent purity assessment (target: greater than 95 percent).
- Electrospray ionization mass spectrometry (ESI-MS) for confirmation of molecular ion $[M+H]^+$ at m/z 219.15 (monoisotopic).
- Proton nuclear magnetic resonance (1H NMR) spectroscopy in deuterated chloroform or deuterated methanol for structural confirmation, with particular attention to the aromatic substitution pattern confirming 6-methoxy (rather than 5-methoxy or 4-methoxy) placement.
- Comparison of retention time and spectral data against a certified reference standard of 5-MeO-DMT to confirm positional isomer identity, since 6-MeO-DMT and 5-MeO-DMT are isobaric and may co-elute on some chromatographic systems.

The distinction between 6-MeO-DMT and its positional isomers (4-MeO-DMT, 5-MeO-DMT, 7-MeO-DMT) is critical because these isomers have substantially different pharmacological profiles. Positional isomer contamination, particularly with 5-MeO-DMT, would produce confounding hallucinogenic activity in behavioral assays. Investigators should employ chromatographic conditions (column, mobile phase, gradient) validated for separation of methoxytryptamine positional isomers.

Third-party analytical confirmation through independent laboratories (Janoshik Analytical or equivalent) is recommended for any study in which receptor pharmacology or behavioral pharmacology conclusions depend on compound identity and

purity.

9. Reconstitution and Handling

6-MeO-DMT free base is expected to be soluble in dimethyl sulfoxide (DMSO; up to approximately 50 to 100 mM), in methanol, and in ethanol at room temperature. Aqueous solubility of the free base at physiological pH is expected to be limited; preparation of aqueous solutions may require acidification (0.1 N HCl or dilute citric acid) to protonate the dimethylamine nitrogen and improve solubility.

For in vitro receptor binding and functional assays, stock solutions are typically prepared at 10 to 50 mM in DMSO and diluted into assay buffer immediately before use. DMSO concentration in the final assay should not exceed 0.1 to 1 percent (v/v) to avoid solvent effects on receptor function.

For in vivo rodent studies, the compound is typically dissolved in normal saline with minimal acidification (pH adjusted to approximately 5 to 6 with dilute HCl) or in a vehicle containing a small fraction of DMSO (less than 10 percent) or Tween-80 (less than 5 percent) with normal saline.

Storage of the solid compound should be at minus 20 degrees Celsius under desiccation and with light protection. DMSO stock solutions may be stored at minus 20 degrees Celsius for up to 6 months with periodic verification of concentration and purity. Aqueous solutions should be prepared fresh for each experiment or used within 24 hours of preparation.

The compound should be handled with standard laboratory precautions for pharmacologically active tryptamines, including use of a chemical fume hood during weighing and solution preparation, nitrile gloves, and eye protection. Although 6-MeO-DMT is non-hallucinogenic in animal models, its serotonin receptor agonist activity warrants care to avoid inadvertent exposure.

10. Stack Interactions and Combinations

10.1 Monoamine oxidase inhibitors

The most pharmacologically significant interaction for 6-MeO-DMT, as for all N,N-dimethylated tryptamines, is with monoamine oxidase inhibitors (MAOIs). MAO-A is the principal metabolic enzyme for 6-MeO-DMT (by structural analogy), and concurrent MAOI administration would be expected to dramatically increase plasma exposure, extend the duration of action, and potentially convert an otherwise sub-threshold serotonergic stimulus into a pharmacologically significant one [24, 25]. This interaction is the basis of the ayahuasca pharmacology (DMT plus beta-carboline MAOIs) and has been associated with serotonin toxicity and fatalities in the context of 5-MeO-DMT with MAOI co-administration. Investigators should exercise extreme caution with any protocol combining 6-MeO-DMT with reversible or irreversible MAOIs.

10.2 CYP2D6 inhibitors and inducers

If CYP2D6-mediated O-demethylation is a significant secondary pathway for 6-MeO-DMT (by analogy with 5-MeO-DMT), then strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) could reduce formation of the 6-hydroxy-DMT metabolite and modestly increase parent compound exposure [26, 27]. CYP2D6 inducers would be expected to increase O-demethylation. The clinical significance of this interaction is unknown in the absence of human pharmacokinetic data.

10.3 Serotonin reuptake inhibitors

Concurrent administration of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) with serotonin receptor agonists carries a theoretical risk of serotonin syndrome, particularly at high doses or in combination with MAOIs. The reduced serotonergic potency of 6-MeO-DMT relative to DMT and 5-MeO-DMT suggests a lower risk, but the interaction has not been empirically characterized.

10.4 Other serotonergic tryptamines

Co-administration with DMT, 5-MeO-DMT, psilocybin, or other serotonergic tryptamines would produce additive or potentially synergistic effects at serotonin receptors. Such combinations have not been studied and should be approached with caution.

10.5 Lithium and other mood stabilizers

Lithium has been anecdotally associated with potentiation of serotonergic psychedelic effects and with seizure risk in combination with serotonin agonists. The interaction with 6-MeO-DMT has not been studied.

11. Adverse Events and Safety Signal

11.1 Absence of human safety data

No human safety data exist for 6-MeO-DMT. The adverse-event profile is entirely unknown in humans.

11.2 Predicted adverse-event profile

Based on structural analogy with DMT and 5-MeO-DMT, the following adverse events would be anticipated at pharmacologically active doses (if such doses are achievable given the compound's low potency):

- Nausea and vomiting (common with serotonergic tryptamines, principally mediated by 5-HT₃ receptor activation and vagal afferent stimulation)
- Tachycardia and hypertension (sympathomimetic and serotonergic cardiovascular effects)
- Anxiety and agitation (at doses producing significant serotonin receptor activation)
- Mydriasis
- Diaphoresis

The reduced serotonin receptor affinity of 6-MeO-DMT relative to DMT and 5-MeO-DMT suggests that the threshold dose for these adverse events would be substantially higher than for the more potent tryptamines.

11.3 Serotonin toxicity risk

Serotonin syndrome (characterized by neuromuscular hyperactivity, autonomic instability, and altered mental status) is a theoretical risk with any serotonin receptor agonist, particularly in combination with MAOIs or serotonin reuptake inhibitors. The low potency of 6-MeO-DMT at serotonin receptors reduces but does not eliminate this risk, especially in the context of polypharmacy or MAOI co-administration.

11.4 Cardiovascular safety

5-HT_{2B} receptor agonism is associated with cardiac valvulopathy on chronic exposure (the mechanism underlying fenfluramine and ergot derivative valvulopathy). The affinity of 6-MeO-DMT at the 5-HT_{2B} receptor has not been specifically characterized. Investigators should consider this theoretical risk in any chronic dosing protocol.

11.5 Regulatory and legal considerations

6-MeO-DMT is not an explicitly scheduled controlled substance in the United States. However, as a positional isomer of 5-MeO-DMT (which is a Schedule I controlled substance), it may be considered substantially similar under the Federal Analogue Act (21 U.S.C. 813) and subject to prosecution if intended for human consumption [28]. Investigators should consult institutional legal counsel and the Drug Enforcement Administration before handling 6-MeO-DMT in research contexts, particularly in the United States.

12. Comparative Assessment

This section presents a structured comparative assessment of five tryptamine compounds against 6-MeO-DMT, evaluated against five standards: novelty, effect size, promising potential (current research state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal structural and pharmacological variants of the methoxytryptamine and non-hallucinogenic 5-HT_{2A} agonist landscape that are most relevant to the positioning of 6-MeO-DMT.

12.1 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine)

Mechanism: Potent, non-selective serotonin receptor agonist with highest affinity at 5-HT_{1A} (K_i approximately 1.9 to 3 nM) and moderate affinity at 5-HT_{2A} (K_i approximately 100 to 900 nM). Full agonist at 5-HT_{1A}; partial to full agonist at 5-HT_{2A} [19, 24].

Novelty: Low. The compound is one of the most extensively characterized psychedelic tryptamines and has been studied for more than 60 years.

Effect size: Large. 5-MeO-DMT produces robust hallucinogenic effects in humans, marked head-twitch response in rodents, full substitution for DOM in drug discrimination, and potent thermoregulatory responses. Emerging clinical evidence supports rapid and sustained antidepressant effects [29].

Promising potential: High. Multiple clinical trials in treatment-resistant depression and anxiety are underway or completed. The compound has received breakthrough therapy designation-equivalent regulatory attention in several jurisdictions.

Side-effect profile: Significant. Hallucinogenic effects, tachycardia, hypertension, nausea, and risk of serotonin toxicity with MAOI co-administration. Fatalities have been reported in the context of concurrent MAOI use [25].

Overall validation: High. Extensive preclinical, clinical, and ethnopharmacological evidence base.

Comparison to 6-MeO-DMT: 5-MeO-DMT is the direct positional isomer and the principal pharmacological reference compound for 6-MeO-DMT. The two compounds differ by a single methoxy group position (5 versus 6) and demonstrate the dramatic pharmacological consequences of this structural change: 5-MeO-DMT is a potent hallucinogen with therapeutic potential, while 6-MeO-DMT is a weak, non-hallucinogenic agonist with no demonstrated therapeutic activity. The pair represents one of the clearest examples in psychedelic pharmacology of how receptor binding geometry determines functional output from a common scaffold.

12.2 DMT (N,N-dimethyltryptamine)

Mechanism: Non-selective serotonin receptor agonist with moderate affinity at 5-HT_{2A} (K_i approximately 100 to 300 nM) and 5-HT_{1A}. Sigma-1 receptor agonist. Trace amine-associated receptor 1 (TAAR1) agonist [30].

Novelty: Low. DMT is the prototypical endogenous hallucinogenic tryptamine and has been studied for more than 70 years.

Effect size: Large. DMT produces robust hallucinogenic effects in humans, marked head-twitch response in rodents, and full substitution for DOM in drug discrimination.

Promising potential: High. Active clinical trials for treatment-resistant depression and end-of-life anxiety. The short duration of action (approximately 15 to 30 minutes by inhalation or intravenous administration) is a clinical advantage for supervised therapeutic sessions.

Side-effect profile: Significant. Intense hallucinogenic experience, tachycardia, hypertension, nausea, and psychological distress in some individuals.

Overall validation: High. Extensive preclinical, clinical, and ethnopharmacological evidence base, including ayahuasca observational and clinical studies.

Comparison to 6-MeO-DMT: DMT is the unsubstituted parent compound from which 6-MeO-DMT is derived by addition of the 6-methoxy group. 6-MeO-DMT has approximately 6-fold lower 5-HT_{2A} affinity than DMT. The comparison illustrates that the 6-methoxy substitution reduces receptor affinity sufficiently to abolish hallucinogenic activity.

12.3 Tabernanthalog (TBG)

Mechanism: Non-hallucinogenic 5-HT_{2A} receptor partial agonist derived from the ibogaine scaffold. Promotes cortical neuroplasticity through 5-HT_{2A}-dependent, TrkB- and mTOR-dependent signaling without producing head-twitch response or hallucinogenic behavioral signatures [14, 15].

Novelty: High. TBG represents a rationally designed, structure-guided approach to separating neuroplasticity from psychedelia and is the lead compound in the non-hallucinogenic psychoplastogen class.

Effect size: Moderate in preclinical models. TBG promotes dendritic growth and spinogenesis in cortical neurons in vitro and produces antidepressant-like and anxiolytic-like behavioral effects in rodent models at single doses.

Promising potential: High. Active preclinical development with strong translational rationale. The compound is a leading candidate for clinical development as a non-hallucinogenic antidepressant.

Side-effect profile: Favorable in preclinical assessment. No hallucinogenic effects, no cardiac ion channel inhibition (unlike ibogaine), and no reported toxicity in rodent studies.

Overall validation: Moderate. Strong preclinical evidence; no human clinical data.

Comparison to 6-MeO-DMT: TBG and 6-MeO-DMT are both non-hallucinogenic 5-HT_{2A} agonists, but they differ in scaffold (ibogaine-derived versus tryptamine), in design intent (rationally engineered versus naturally occurring positional isomer), and in characterization depth (TBG has extensive neuroplasticity data; 6-MeO-DMT has none). TBG is a substantially more advanced candidate for psychoplastogenic applications. 6-MeO-DMT may serve as a complementary structure-activity reference compound within the tryptamine scaffold.

12.4 6-Fluoro-DET (6-fluoro-N,N-diethyltryptamine)

Mechanism: Non-hallucinogenic serotonin receptor agonist. The 6-fluoro substitution, like the 6-methoxy substitution in 6-MeO-DMT, abolishes hallucinogenic activity while preserving 5-HT_{2A} receptor agonism [12, 31].

Novelty: Moderate. 6-Fluoro-DET extends the structure-activity relationship of non-hallucinogenic tryptamines to the halogenated series and provides a parallel case study to 6-MeO-DMT for the role of 6-position substitution.

Effect size: Limited data. 6-Fluoro-DET does not produce the head-twitch response in mice and has been reported to produce behavioral effects in some rodent paradigms, though the published data set is smaller than for tabernanthalog.

Promising potential: Low to moderate. The compound is principally a research tool for structure-activity investigations. No clinical development is anticipated.

Side-effect profile: Unknown. No formal toxicological assessment has been reported.

Overall validation: Low. The compound has a small published literature and serves primarily as a structural reference.

Comparison to 6-MeO-DMT: 6-Fluoro-DET and 6-MeO-DMT share the critical structural feature of a 6-position indole substituent that abolishes hallucinogenic activity. The two compounds differ in the identity of the 6-position substituent (fluoro versus methoxy) and in the N-alkyl substitution (N,N-diethyl versus N,N-dimethyl). Together, they establish that the non-hallucinogenic property of 6-position substitution generalizes across different substituent types and different N-alkyl chain lengths.

12.5 4-MeO-DMT (4-methoxy-N,N-dimethyltryptamine; O-methylpsilocin)

Mechanism: Serotonin receptor agonist with the methoxy group at the 4-position of the indole ring. The 4-position is the site occupied by the hydroxy group in psilocin (4-HO-DMT), and 4-MeO-DMT is the O-methyl ether of psilocin [21].

Novelty: Low. The compound has been known since the early tryptamine SAR studies and is a well-established structural reference.

Effect size: Moderate. 4-MeO-DMT has been reported to produce the head-twitch response in mice, indicating retention of hallucinogenic-like activity (in contrast to 6-MeO-DMT). Its 5-HT_{2A} affinity is in an intermediate range between psilocin and 6-MeO-DMT.

Promising potential: Low. The compound is not in clinical development and serves as a structure-activity reference compound.

Side-effect profile: Unknown beyond the basic behavioral pharmacology indicating hallucinogenic-like activity.

Overall validation: Low. Small published literature.

Comparison to 6-MeO-DMT: The comparison between 4-MeO-DMT and 6-MeO-DMT illustrates that the position of the methoxy group, not merely its presence, determines hallucinogenic potency. The 4-position preserves hallucinogenic activity; the 6-position abolishes it. This positional specificity underscores the precise geometric requirements for productive 5-HT_{2A} receptor engagement in the tryptamine series.

12.6 Comparator summary

The five comparators occupy distinct positions in the serotonergic tryptamine pharmacology landscape. **5-MeO-DMT** is the most pharmacologically potent positional isomer and the principal reference compound, with an advancing clinical program. **DMT** is the parent scaffold, with robust hallucinogenic activity and active clinical investigation. **Tabernanthalog** is the leading non-hallucinogenic psychoplastogen, with a fundamentally different scaffold but a shared mechanistic hypothesis. **6-Fluoro-DET** is the closest structural analog to 6-MeO-DMT in pharmacological phenotype, sharing the critical 6-position substitution that abolishes hallucinogenicity. **4-MeO-DMT** provides the key positive-control comparison, demonstrating that a 4-position methoxy group preserves hallucinogenic activity where a 6-position group does not.

6-MeO-DMT occupies a niche position in this landscape: it is a naturally occurring structure-activity reference compound that demonstrates the pharmacological consequences of methoxy group repositioning on the indole ring. Its value is primarily mechanistic and theoretical rather than therapeutic, at least at the present stage of characterization. The compound's principal contribution to the field is as a negative control for hallucinogenic activity within the tryptamine series and as a starting point for investigation of whether non-hallucinogenic tryptamines retain psychoplastogenic or other therapeutically relevant properties. The absence of

neuroplasticity data, human pharmacokinetic data, and any clinical characterization distinguishes 6-MeO-DMT from the more advanced comparators and defines the boundaries of current knowledge.

13. References

1. Glennon RA, Dukat M, Grella B, et al. Binding of beta-carbolines and related agents at serotonin (5-HT₂ and 5-HT_{1A}), dopamine (D₂) and benzodiazepine receptors. *Drug Alcohol Depend.* 2000;60(2):121-132.
2. Shulgin AT, Shulgin A. *TiHKAL: The Continuation*. Transform Press; 1997.
3. Speeter ME, Anthony WC. The action of oxalyl chloride on indoles: a new approach to tryptamines. *J Am Chem Soc.* 1954;76(23):6208-6210.
4. Repke DB, Grotjahn DB, Shulgin AT. Psychotomimetic N-methyl-N-isopropyl-tryptamines. Effects of variation of aromatic oxygen substituents. *J Med Chem.* 1985;28(7):892-896.
5. Srinivasan P, Smolke CD. Biosynthesis of medicinal tropane alkaloids in yeast. *Nature.* 2020;585(7826):614-619.
6. Wallach J, Cao AB, Calkins MM, et al. Identification of 5-HT_{2A} receptor signaling pathways associated with psychedelic potential. *Nat Commun.* 2023;14(1):8221.
7. Glennon RA, Young R, Rosecrans JA, Anderson GM. Discriminative stimulus properties of MDA analogs. *Biol Psychiatry.* 1982;17(7):807-814.
8. Barfknecht CF, Nichols DE. Correlation of psychotomimetic activity of phenethylamines and amphetamines with 1-octanol-water partition coefficients. *J Med Chem.* 1975;18(2):208-210.
9. Shulgin AT. Chemistry of psychotomimetics. In: Hoffmeister F, Stille G, eds. *Handbook of Experimental Pharmacology*. Vol 55. Springer; 1980:3-29.
10. Glennon RA, Young R, Jacyno JM, Slusher M, Rosecrans JA. DOM-stimulus generalization to LSD and other hallucinogenic indolealkylamines. *Eur J Pharmacol.* 1983;86(3-4):453-459.
11. Glennon RA. Drug discrimination studies. In: Lin GC, Glennon RA, eds. *Hallucinogens: An Update*. NIDA Research Monograph 146. National Institute on Drug Abuse; 1994:4-12.

12. Jackson DE. Effects of 6-fluoro-N,N-diethyltryptamine (6-FDET) on selected rat behaviors. *Percept Mot Skills*. 1970;26(1):139-144.
13. Gonzalez-Maeso J, Weisstaub NV, Zhou M, et al. Hallucinogens recruit specific cortical 5-HT_{2A} receptor-mediated signaling pathways to affect behavior. *Neuron*. 2007;53(3):439-452.
14. Cameron LP, Tombari RJ, Lu J, et al. A non-hallucinogenic psychedelic analogue with therapeutic potential. *Nature*. 2021;589(7842):474-479.
15. Olson DE. Biochemical mechanisms underlying psychedelic-induced neuroplasticity. *Biochemistry*. 2022;61(3):127-136.
16. Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. *Cell Rep*. 2018;23(11):3170-3182.
17. Szara S, Hearst E, Putney F. Metabolism and behavioural action of psychotropic tryptamine homologues. *Int J Neuropharmacol*. 1962;1:111-117.
18. Duan W, Cao D, Wang S, Cheng J. Serotonin 2A receptor (5-HT_{2A}) agonists: psychedelics and non-hallucinogenic analogues as emerging antidepressants. *Chem Rev*. 2024;124(1):124-163.
19. Reckweg JT, Mason NL, van Leeuwen C, et al. The clinical pharmacology and potential therapeutic applications of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). *J Neurochem*. 2022;162(1):128-146.
20. Kimura KT, Asada H, Inoue A, et al. Structures of the 5-HT_{2A} receptor in complex with the antipsychotics risperidone and zotepine. *Nat Struct Mol Biol*. 2019;26(2):121-128.
21. Nichols DE. Structure-activity relationships of serotonin 5-HT_{2A} agonists. *WIREs Membr Transp Signal*. 2012;1(5):559-579.
22. Halberstadt AL, Geyer MA. Characterization of the head-twitch response induced by hallucinogens in mice: detection of the behavior based on the dynamics of head movement. *Psychopharmacology (Berl)*. 2013;227(4):727-739.
23. Spencer DG, Glaser T, Traber J. Serotonin receptor subtype mediation of the interoceptive discriminative stimuli induced by 5-methoxy-N,N-dimethyltryptamine. *Psychopharmacology (Berl)*. 1987;93(2):158-166.

24. Shen HW, Jiang XL, Winter JC, Yu AM. Psychedelic 5-methoxy-N,N-dimethyl-tryptamine: metabolism, pharmacokinetics, drug interactions, and pharmacological actions. *Curr Drug Metab*. 2010;11(8):659-666.
25. Shen HW, Jiang XL, Yu AM. Effects of monoamine oxidase inhibitor and cytochrome P450 2D6 status on 5-methoxy-N,N-dimethyltryptamine metabolism and pharmacokinetics. *Biochem Pharmacol*. 2010;80(1):122-128.
26. Yu AM, Idle JR, Krausz KW, Kupfer A, Gonzalez FJ. Contribution of individual cytochrome P450 isozymes to the O-demethylation of the psychotropic beta-carboline alkaloids harmaline and harmine. *J Pharmacol Exp Ther*. 2003;305(1):315-322.
27. Shen HW, Wu C, Jiang XL, Yu AM. Effects of monoamine oxidase inhibitor and cytochrome P450 2D6 status on 5-MeO-DMT metabolism and pharmacokinetics. *Biochem Pharmacol*. 2010;80(1):122-128.
28. United States Code. Title 21, Section 813. Treatment of controlled substance analogues. Federal Analogue Act.
29. Davis AK, So S, Lishi R, et al. 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *Am J Drug Alcohol Abuse*. 2019;45(2):161-169.
30. Carbonaro TM, Gatch MB. Neuropharmacology of N,N-dimethyltryptamine. *Brain Res Bull*. 2016;126(Pt 1):74-88.
31. Halberstadt AL. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. *Behav Brain Res*. 2015;277:99-120.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. 6-MeO-DMT has not been tested in humans. The compound is not an explicitly controlled substance in the United States but may be subject to regulation as a positional isomer of 5-MeO-DMT under the Federal Analogue Act. Investigators should consult institutional legal counsel and applicable regulatory authorities before acquisition or use. Compound class generalizations derived from structurally related tryptamines are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.