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MINIREVIEW

The utility of 2,5-dimethoxy-4-iodoamphetamine for the study of serotonin 2A and 2C receptors

Lindsay P. Cameron [1], Alaina M. Jaster [2], Raul A. Ramos [3], Elijah Z. Ullman [4,*]

[1] Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California
[2] Department of Physiology and Biophysics, Virginia Commonwealth University, Richmond, Virginia
[3] Department of Molecular and Cell Biology, University of California, Berkeley, California
[4] Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, Georgia

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ABSTRACT

2,5-dimethoxy-4-iodoamphetamine (DOI) is a phenethylamine psychedelic with high affinity for 5-HT_2 receptors. In 2022 and 2023, the US Drug Enforcement Administration proposed to place DOI, along with a similar compound, 2,5-dimethoxy-4-chloroamphetamine, in Schedule I of the Controlled Substances Act based on their psychoactivity and alleged abuse potential. Here, we describe the history of DOI, its utility in preclinical neuroscience research, and how it has significantly advanced the study of 5-HT_{2A} and 5-HT_{2C} receptors. Finally, we suggest alternative compounds for studying 5-HT_2 receptors, should obtaining DOI for research become restricted.

Significance Statement: 2,5-Dimethoxy-4-iodoamphetamine, the key pharmacological tool for studying 5-HT_{2A} receptor function and localization, has been used in more 1200 publications across 5 decades. This review covers its utility, research barriers if the Drug Enforcement Administration schedules it, and alternatives for continued investigation of serotonin receptors.

1. Introduction and brief history

The pivotal utility of 2,5-dimethoxy-4-iodoamphetamine (DOI) in serotonin receptor research stems from its single-digit nanomolar affinity for the 5-HT_{2A} and 5-HT_{2C} receptors, coupled with minimal off-target pharmacology.[1] For over 5 decades, this unique pharmacology has made DOI a go-to tool for enabling the precise interrogation of serotonergic signaling pathways. Most notably, DOI is currently unrestricted under the Controlled Substances Act (CSA), preserving its accessibility for foundational basic and translational research.

The parent phenethylamine compound, 3,4,5-trimethoxyphenethylamine (mescaline), was first isolated by Arthur Heffter in 1896. Still, the target of and mechanism of action for psychedelics was not made clear until more than a half century later[2] following the isolation of serotonin in the 1930s and the discovery in the 1950s that the psychedelic, lysergic acid diethylamide (LSD), could antagonize the actions of serotonin.[3–6] In 1963, Alexander T. Shulgin, working at Dow Chemical, was trying to identify new medicines for treating psychiatric disorders and synthesized 2,5-dimethoxy-4-methylamphetamine (DOM).[7,8] By 1969, the structure–function relationship of the phenethylamines was developed sufficiently that the 2,4,5-ring substitution patterns were understood to be the most potent.[9,10]

DOx compounds are substituted amphetamines with methoxy groups at the 2 and 5 positions, a hydrophobic substituent at the 4-position, and a chiral primary amine center (Fig. 1). DOx compounds exist in both (R)-(-)- and (S)-(+)-enantiomers, though almost all scientific literature to date evaluates racemic administration of these compounds. Despite the structural similarity to amphetamine, their psychopharmacological and molecular signaling profile is markedly distinct.

* **Address correspondence to**: Dr Elijah Z. Ullman, Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Rollins Research Center, 1510 Clifton Road, Atlanta, GA 30322-3090. E-mail: eullman@emory.edu

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L.P.C., A.M.J., R.A.R., and E.Z.U. contributed equally to this work

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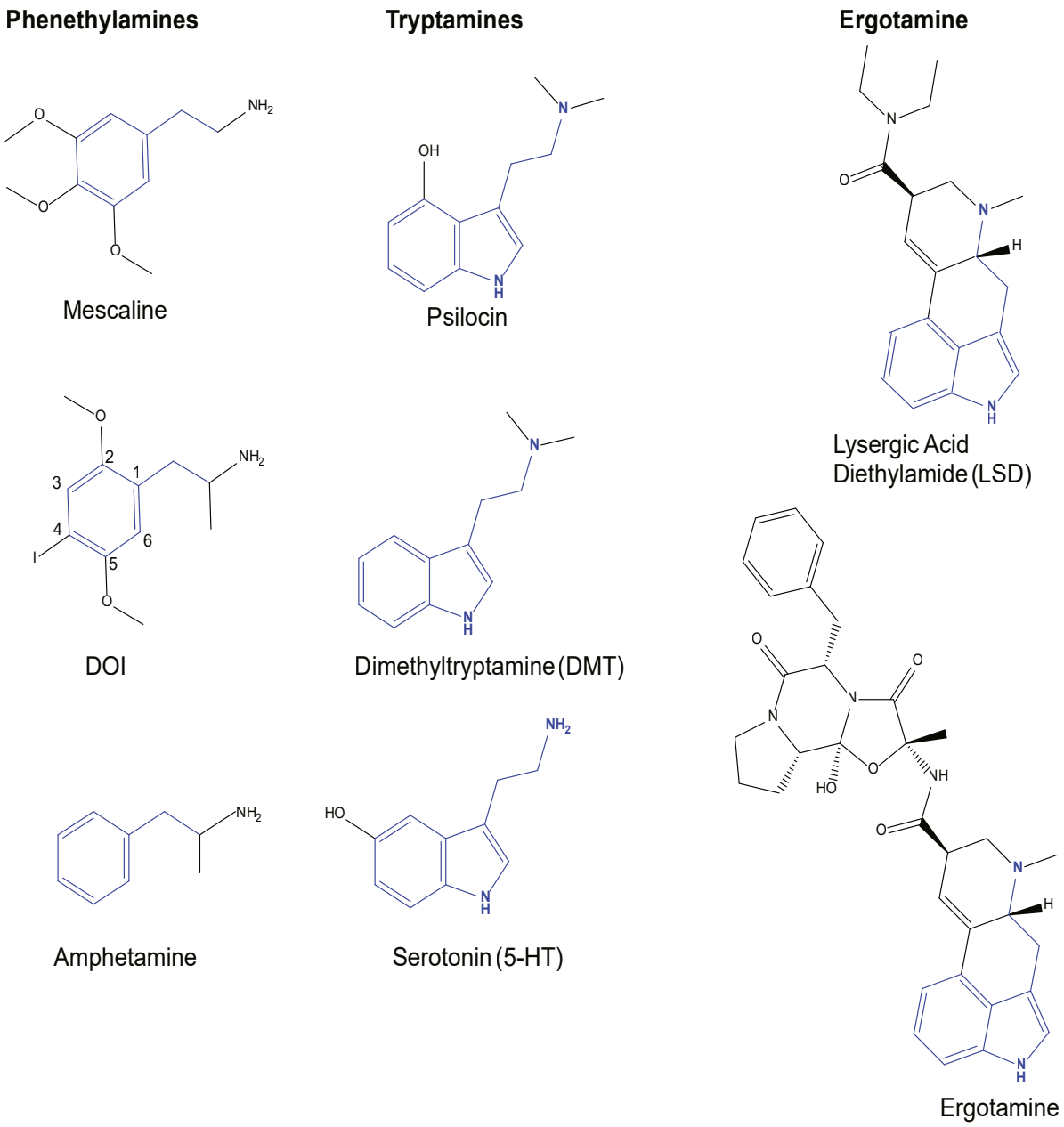

Fig. 1. Molecular scaffolds of psychedelic and psychedelic-like compounds. The indolamine backbone of the serotonin molecule is drawn in blue. The blue scaffold is depicted on all other compounds where possible to demonstrate shared structural features. Atom numbering is shown for mescaline, DOx, DOI, and amphetamine.

The most widely known compound in this series is DOM, colloquially known as "serenity, tranquillity and peace." DOM emerged on the streets of San Francisco, California, in June 1967, at an all-day concert at Golden Gate Park, where approximately 5000 individual doses, ranging from 10 to 20 mg, were handed out free of charge primarily by Augustus Owsley Stanley III (aka Owsley).[9,11] This is thought to be the public's first interaction with the drug, and although some had experience with LSD, DOM's duration was reported to be 12–36 hours (2- to 3-fold of LSD) and with reportedly increased physical discomfort.[12] Approximately 60 attendees visited the Haight Ashbury Free Medical Clinic and San Francisco General Hospital.[13] However, most of those who visited the Free Clinic were sent home several hours later after receiving psychological support, and no deaths were reported. Since this incident, DOM and other DOx consumption rates have been virtually nonexistent.[14] See the study by Baggot[11] and Trout and Daley[9] for an extensive history on DOM.

DOM was placed under federal control via the Drug Abuse Control Amendment to the Federal Food, Drug, and Cosmetic Act on April 2, 1968, based on a limited number of studies whose authors were intrigued by its potential therapeutic efficacy in psychotherapy.[9,11,15–18] In 1970, when the CSA was signed into law and replaced Drug Abuse Control Amendment, DOM was placed into Schedule I. This Schedule is reserved for drugs, substances, or chemicals with a high potential for abuse and no medical utility. We have been unable to obtain the analysis that led to its control in 1968 or 1970, or for 2,5-dimethoxy-4-bromoamphetamine (DOB), an analog which was also placed into Schedule I of the CSA in 1973.[19]

In 1973, Coutts and Malicky synthesized the 4-iodo (DOI) and 4-chloro (DOC) analogs of DOM that were not placed under control

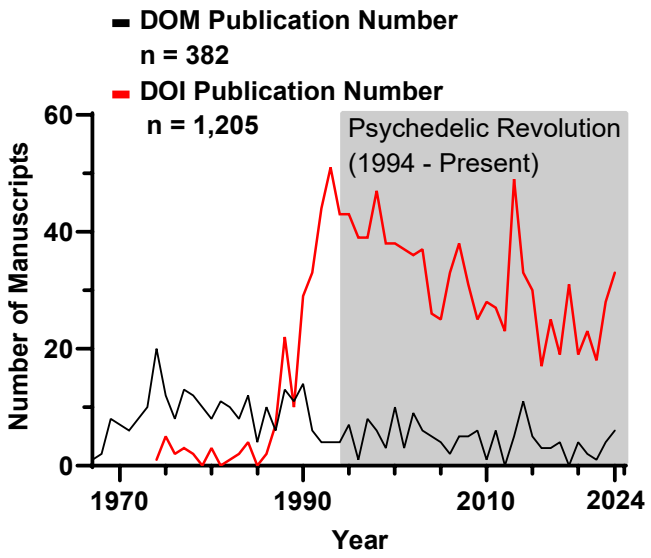

Fig. 2. Publication numbers of DOI and DOM. The total number of papers for DOI and DOM from 1967 to 2024. DOM was first reported in the literature in 1967 and DOI in 1973. The difference in the number of publications for DOM and DOI was statistically significantly different, $P = 2.97E\text{-}08$, paired Student's t test.

by Congress or the newly created Drug Enforcement Administration (DEA).[20] Scientific inquiry using DOI began in the 1970s, shortly after the discovery of 5-HT_1 and 5-HT_2 receptors. DOx compounds, specifically DOI and DOB, were found to have high affinity for the 5-HT_2 receptors and as such were developed into radioligands as a means to label and identify serotonergic receptors in tissue samples.[21] The first DOI radioligands, I^{123}- and I^{131}-DOI, were reported in 1984,[22] but in 1987, the now common I^{125}-DOI radioligand was developed by David Nichols and colleagues.[23] That same year, it was used to identify the localization of 5-HT_{2A} and 5-HT_{2C} receptors in the rat brain.[24,25] This radioligand played a pivotal role in several seminal publications.[26–28] Between 1983 and 1987, there were 15 papers using DOI, and between 1988 and 1992, there were 139 (Fig. 2; Table 1).

Around the same time, Richard Glennon and colleagues studied the interoceptive-like effects of psychedelics using drug discrimination techniques. Many of these foundational studies were done using DOM as the training drug, not DOI, but nonetheless discovered that the discriminative stimulus effects of DOM as a training drug were not dose dependent and could be attenuated or fully reversed by pretreatment with 5-$HT_{2A/2C}$ antagonists. Later studies focused more on DOI, discovering that its interoceptive cue also was attenuated by 5-HT_2 receptor antagonists and it did not substitute in rats trained to discriminate 8-OH-DPAT, a 5-HT_{1A} agonist, further demonstrating selectivity for 5-HT_2 receptors (for a comprehensive review, see the study by Glennon and Dukat[29]).

Since the first peak of DOI publications in the 1980s–1990s, DOI has remained a valuable tool for understanding targets, mechanisms, and disease states related to serotonergic signaling across the central and peripheral nervous systems. Although there was a decline in work following the important discovery of serotonin and its involvement in psychedelic action, as shown in Fig. 2, a large surge of DOI publications took place between 2010 and 2020. This may correspond with some of the clinical findings related to psychedelics such as LSD and psilocybin by high-profile groups[30–35] and the trickling of psychedelics into the mainstream media with mentions of microdosing in *Marie Claire*[36] and the publishing of Michael Pollan's *How to Change Your Mind*.[37] Together, these have increased interest in researching psychedelic outcomes and basic research to understand the mechanisms behind the potential therapeutic action of these serotonergic psychedelics. The continued use of DOI in medical research demonstrates the importance of a selective and accessible compound to encourage rigor, reproducibility, and reliability in science.

In December 2023, the DEA proposed to place DOI and its analog DOC into Schedule I of the CSA,[38] and as of June 2025, the Administrative Law Judge has recommended placement of these substances in Schedule I of the CSA. The present authors provided testimony or otherwise participated in the hearing on the potential Scheduling in November 2024, and argued against scheduling. This review summarizes several representative key findings aided by DOI regarding the 5-HT_{2A} and 5-HT_{2C} receptors, including an overview of the underlying chemistry and behavioral and molecular pharmacology. Finally, we provide a discussion about how the placement of DOI in Schedule I of the CSA will hinder scientific research. Although other compounds may be used as replacements, they would likely be the subject of future scheduling efforts. This iterative suppression impairs the future of 5-HT_{2A} research and discourages efforts aimed at unlocking the therapeutic potential of psychedelics and related serotonergic medications.

Table 1
DOI papers per year: The numbers of manuscripts using DOI per year since its first appearance in the literature by Coutts and Malicky[20]

Year	Publication Number	Year	Publication Number	Year	Publication Number
2025	10	2006	32	1987	7
2024	32	2005	25	1986	2
2023	28	2004	27	1985	0
2022	18	2003	39	1984	4
2021	23	2002	37	1983	2
2020	19	2001	38	1982	1
2019	31	2000	38	1981	0
2018	19	1999	38	1980	2
2017	24	1998	47	1979	0
2016	17	1997	40	1978	2
2015	30	1996	39	1977	0
2014	33	1995	43	1976	1
2013	47	1994	43	1975	0
2012	23	1993	50	1974	4
2011	27	1992	44	1973	1
2010	29	1991	33		
2009	25	1990	30		
2008	31	1989	10		
2007	38	1988	22		

2. Methods

Pubmed and Google Scholar were queried using the Publish or Perish software[39] for the terms "(+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane" OR "2,5-dimethoxy-4-iodoamphetamine" for DOI and 845 and 981 results were identified, respectively, query date April 16, 2025; "(+/−)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane" OR "2,5-dimethoxy-4-methylamphetamine" for DOM and 406 and 990 results were identified, respectively. We then inspected each publication individually for original research articles, removed other forms of experiment dissemination (dissertations, posters, patents, review articles, and book chapters) resulting in 1205 publications for DOI (Table 1) and 382 for DOM (Table 2). The number of publications per year and number of authors per paper were subsequently analyzed. Supplemental Files 1 and 2 are reference manager files (.ris) for all analyzed and identified manuscripts using DOI and DOM, respectively.

Table 2
DOM papers per year: The numbers of papers using DOM since it was first reported in the literature by Snyder et al[16]

Year	Publication Number	Year	Publication Number	Year	Publication Number
2025	3	2008	5	1991	6
2024	6	2007	5	1990	14
2023	4	2006	2	1989	11
2022	1	2005	4	1988	13
2021	2	2004	5	1987	6
2020	4	2003	6	1986	10
2019	0	2002	9	1985	4
2018	4	2001	3	1984	12
2017	3	2000	10	1983	8
2016	3	1999	3	1982	10
2015	5	1998	6	1981	11
2014	11	1997	8	1980	8
2013	5	1996	1	1979	10
2012	0	1995	7	1978	12
2011	6	1994	4	1977	13
2010	2	1993	4	1976	8
2009	6	1992	4	1975	12
1974	20	1973	10	1972	8
1971	7	1970	7	1969	8
1968	2	1967	1		

Multiparameter optimization (MPO) scores were calculated according to standardized methods.[40]

For representative head twitch counts, head twitch response (HTR) assays using magnetic ear tagging were performed as previously reported.[41,42] Following acclimation, DOI (2 mg/kg), LSD (0.32 mg/kg), and psilocybin (1 mg/kg), or vehicle was administered intraperitoneally immediately prior to HTR recording. Data shown are compiled from separate experiments in male C57BL6/J mice (Jackson Laboratories) and are quantified by summing the first 30 minutes of HTR immediately following injection. Drugs were obtained from the following vendors or laboratories: DOI HCl (Sigma-Aldrich), psilocybin (Usona Institute), and LSD freebase (Sigma-Aldrich). Doses were selected based on previously published studies.[43–45]

Animals were housed in cages with up to 4 littermates with a 12-hour light/dark cycle at 23 °C and food and water ad libitum, except during behavioral testing which occurred during the day. Experiments were conducted in accordance with NIH guidelines, and were approved by the Virginia Commonwealth University Animal Care and Use Committee (#AD10001212). All efforts were made to minimize animal suffering and the number of animals used. All behavioral experiments were completed by a female experimenter.

3. Human psychopharmacology

Alexander Shulgin was the only person to publish a description of DOI's behavioral effects in humans, and his consumption is the only confirmed ingestion of DOI.[8] However, online anecdotal reports have described it as producing an energetic high with clear headspace and vivid hallucinations, and occasional stomach discomfort.[46] Characteristic of online self-reports, the purity and doses of these substances are not verifiable. The reported duration of action is 16–30 hours,[38] 2–3 times the duration of LSD, which strongly discourages consumption—in fact, there is a clear lack of availability for DOI in the illicit market and no reported lifetime usage rates.[47,48] According to the National Forensic Library Information Systems, there were no DOI seizures between 2019 and 2022 and only 40 encounters by law enforcement over the last 20 years.[38]

There are no human studies on the metabolism or excretion of DOI. However, urine samples from rats have demonstrated that it is subject to O-demethylation and excretion as sulfate or glucuronide conjugates. However, the relative proportions of these conjugates have not been established.[49]

4. Molecular pharmacology

There are at least 14 distinct subtypes of serotonin receptors, divided into 7 subfamilies, 5-HT_{1-7}.[50] These are G protein-coupled receptors (GPCRs), except for 5-HT_3, a K^+ and Na^+-permeant ion channel. Psychedelic drugs exert their primary effects through the 5-HT_{2A} receptor, a G_q-coupled GPCR expressed most densely in apical dendrites of layer V frontal cortical pyramidal cells,[51] with similar expression patterns across rodents and humans brains, and is the most widely expressed serotonin receptor in the central nervous system.[52,53] Serotonin receptors are involved in a myriad of processes such as cognition, learning and memory, mood, and feeding.[52,54] Peripherally, serotonin receptors on vascular smooth muscle regulates vasoconstriction.[55–58] Furthermore, they mediate immune responses through interactions with T cells, macrophages and monocytes, dendritic cells, B cells, and neutrophils.[52,54] Finally, 5-HT_{2A} receptors on platelets modulate activation and aggregation.[59–62]

Depending on the assay or cell type, DOI is either a full or partial agonist at 5-HT_{2A} receptors. Using a BRET assay in a heterologous cell line where 5-HT_{2A} receptors are overexpressed, Wallach et al,[63] and Jain et al[53] found DOI to be a full agonist for Gq-dissociation and β-arrestin recruitment, with equal efficacy and potency for both. These BRET assays relied on heterologous overexpression of 5-HT_{2A} receptors, β-arrestin, and Gq in HEK293T cells. However, results can vary depending on the cell type or assay readout used, highlighting the need for cautious interpretation. Heterologous expression systems often have a substantially higher concentration of receptors or downstream effectors than in native systems. As such, a compound may appear as a full agonist when overexpressed in heterologous systems like this, whereas it may act as a partial agonist in a native system where the concentration of receptors is more limited. For example, in rat jugular veins, DOI had submaximal efficacy compared to either 5-HT or α-methyl 5-HT in relation to the contractile force elicited by a KCl challenge to the tissue.[64] Likewise, DOI also elicited submaximal efficacy compared to serotonin in firing rate of rat piriform cortex neurons held under voltage clamp relative to 5-HT.[65] It cannot be overlooked that receptor expression levels factor into the determination of full or partial agonism in a given cell.

The effects of G_q signaling are necessary for the cortical activation seen in the prefrontal cortex (PFC), which is thought to be linked to the therapeutic responses of psychedelic compounds.[66] Recent work by the Roth and Herman labs elegantly demonstrated the correlation of Gq signaling with HTRs, and that 5-HT_{2A} Gq signaling is necessary for psychedelic-induced increased neuronal firing, suggesting that Gq pathways also play a role in perceptual disturbances.[53,67] There is conflicting evidence regarding the role of the β-arrestin2 signaling pathway.[53,68,69] Many research groups are attempting to tease apart the signaling pathways contributing to perceptual versus therapeutic effects, although there is not yet a definitive answer. Generally, both agonists (including DOI) and antagonists of the 5HT_{2A} receptor cause internalization within minutes. This is yet another way that DOI has contributed to our understanding of the serotonin system.

A recent paper from the Olson lab suggests that most of the 5-HT_{2A} receptors may be expressed intracellularly.[70–72] That could explain why compounds such as psychedelics—which are lipophilic and readily pass the blood-brain barrier—are able to easily

bind and activate these intracellular pools. In contrast, endogenous compounds such as serotonin are not able to pass through the membrane back into the cell. The resultant effect is that psychedelics, even as partial agonists, activate greater numbers of serotonin receptors than the endogenous ligand. Alternatively, there could be something different or unique about intracellular signaling pathways. Whether this effect contributes to psychedelics' therapeutic effects, perceptual effects, or both remains to be delineated.[73] Although a limited number of psychedelics were tested in this study, it is an interesting and plausible mechanism by which psychedelics may be posed to work. Additional studies with DOI and DOC within this framework are needed. Finally, quantification of internal receptor pools is needed in native tissue to understand this putative signaling mechanism. Researchers in this field should be cautious of the fact that many serums used in cell media contain serotonin and cause internalization of receptor pools. Using native, intact tissue and/or cultures that mimic 5-HT_{2A} receptor surface expression should be employed.

In addition to the effects on GPCRs, DOI has a substantial indirect effect on ion channels. These effects are thought to be downstream of 5-HT_{2A} receptor activation, as inhibition of 5-HT_{2A} receptors blocks the changes to ion channels.[74] That suggests activation of the ion channels through a mediator such as protein kinase C.[75,76] This yields 5-HT_{2A} receptor agonists to increase synaptic release, while simultaneously decreasing the intrinsic excitability of neurons in layer V PFC cells via a 5-HT_{2A}-independent suppression of M-current (resulting in decreased firing rate).[77,78] Further studies are needed to fully delineate the cellular mechanisms underlying the effects of these compounds. This is now an active area of research for many electrophysiologists. To our knowledge, there are no computational models or crystal structures of DOx compounds with the 5-HT_{2A} receptor.

Engagement of DOI and other psychedelic compounds with the cortical 5-HT_{2A} receptor elicits cfos activation in animals,[79] which appears to be dependent on Gq signaling.[66] Interestingly, psychedelics, but not non-psychedelic analogs, initiate increased expression of transcription factors *egr-1*, *egr-2*, and *period-1*.[79–81] This may be due to non-psychedelic analogs not surpassing a Gq threshold enough to elicit immediate early gene expression or HTR,[63] or due to differences in polypharmacology between ligands. Downstream differences in transcription factor activation may allow future insight into optimizing therapeutic properties.

Although DOx compounds may exist as either R-enantiomers, S-enantiomers, or a racemic mixture, most literature to date studies racemate mixtures. Early studies indicate that the R-enantiomer had slightly higher affinity (~2-fold) than the racemate or S-enantiomers for 5-HT_{2A} receptors in rat cortical neurons and human recombinant receptors.[28,82,83] Behavioral reports suggest that R-DOI is also mildly more potent in animal assays and human reports.[8,84–86] Delineating the therapeutic and perceptual effects of one enantiomer versus the other is an open question.

5. Behavioral pharmacology

Following the discoveries described above and the labeling of 5-HT receptors, researchers turned their interest toward understanding which receptors are responsible for which physiological responses and pharmacological actions in various brain regions. The majority of data related to the pharmacodynamics and behaviors following DOI administration are from rodent models due to the lack of engagement with this substance in human populations.[48]

DOI, along with other psychedelics, has played an important role in advancing our understanding of neuropsychiatric and cognitive disorders such as schizophrenia, depression, anxiety, and substance use disorders (SUDs).[1,87] This area of investigation bloomed into a full-fledged field following the earlier studies that characterized and established the role of serotonin receptors in DOI pharmacology. Although behavioral studies in animal models do not capture the whole human condition, the use of DOI in these assays has shed light on characteristics of these nonneurotypical mental states. Several behavioral paradigms have emerged in this context, including the mouse HTR, locomotor behavior, elevated plus maze (EPM), forced swim test (FST), and fear conditioning paradigms, to name a few (for a more comprehensive list, see the study by Hanks and González-Maeso[88]).

Seminal behavioral studies using drug discrimination assays were some of the first to assess the role of the 5-HT_{2A} and 5-HT_{2C} receptors in behaviors related to psychedelics.[85,89,90] Since those studies, several others have assessed the discriminative stimulus effects of DOI as a training drug, at a variety of doses and schedules of reinforcement. These studies have used several psychedelics as test drugs, including LSD, *N,N*-dimethyltryptamine, and other DOx compounds, and have had high reproducibility.[29] In contemporary studies, drug discrimination is used to assess novel psychoactive substances' acute pharmacological effects in animal models. Importantly, this paradigm investigates the similarities between 2 drug experiences, not abuse potential.

5.1. Mouse HTR

Of these, HTR is the most widely employed to understand psychedelic drug action in rodent models. Importantly, the number of head twitches elicited in this paradigm is highly correlated with hallucinogenic potency in humans.[45] This response is an unconditioned behavior that can be characterized as a rapid side-to-side rotational head movement that occurs in mice and rats after administration of a serotonergic psychedelic.[91] Different species display different responses to psychedelic compounds. Researchers report “wet dog shakes” in rats, head bobs in rabbits, nictitating membrane response in cats, and pigs exhibit a scratching response.[92–97] Interestingly, dogs do not seem to have a characteristic reflex-like response that has been noted. Since the first description of HTR induced by 5-HTP and LSD in the 1950s, several reports have consistently demonstrated that this behavior increases in frequency following administration of serotonergic psychedelics (for a comprehensive review, see the study by Canal and Morgan[93]). DOI, DOM, and DOB all elicit an HTR when administered to rodents.[79]

The use of DOI in this assay, along with other compounds, including various antagonists, shed light on the 5-HT_2 specific mechanism related to this behavior.[79,98–101] Although false positives have been reported related to the specificity of 5-HT_{2A} receptor activation in HTR,[102,103] it is commonly accepted that 5-HT_{2A} receptor activation, specifically in the frontal cortex,[79,80] is responsible for the induction of increased HTR following psychedelic administration. Interestingly, DOI has been integral in delineating the modulatory effects of 5-HT_{2C} receptors in the dose-response and temporal effects of the HTR.[104,105] DOI has been reported to produce the most robust HTR across doses when compared with other classical psychedelics.[45] See Fig. 3 for a visual representation of pooled HTR data. Given the robust and reproducible behavioral outcomes with DOI in this assay, it has been used to develop various automated head twitch systems that have been key for the development of novel rapid-acting antidepressants.[41,42,106,107]

5.2. Locomotion

Locomotor assays have remained a staple for decades for understanding the acute physiological effects of drugs. In early

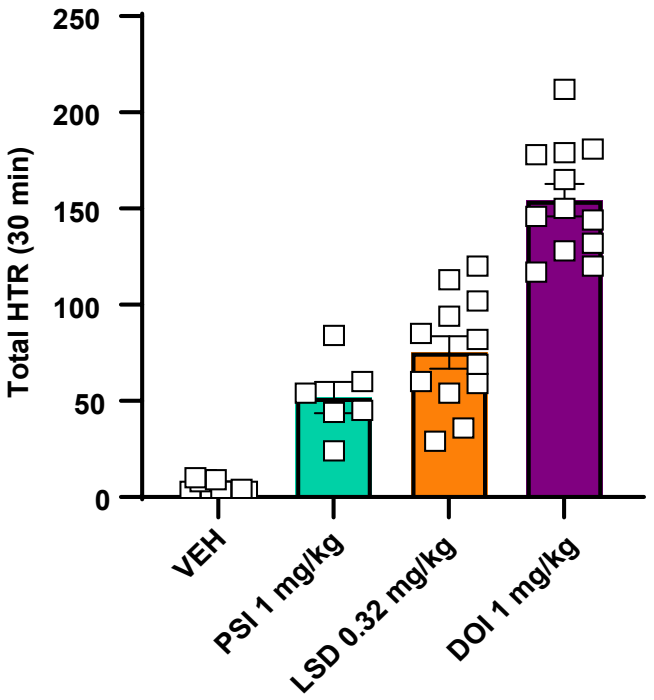

Fig. 3. Visual representation of peak 30-minute psychedelic-induced HTR. Pooled data from experiments utilizing the automated HTR system in male adult C57BL6/J mice ($n = 6–12$ per compound) used for visual representation. DOI (1 mg/kg) elicited 100–200 HTR responses compared with 50–100 HTR movements for psilocybin (1 mg/kg), among other compounds, within the peak 30-minute period following intraperitoneal administration. Unpublished data from Jaster and González-Maseo.[87]

studies with LSD and DOI, Geyer et al[108] found psychedelics decreased locomotor activity and increased avoidance behavior in nonstressed rats.[109] They discovered that acute treatment with DOI (0.25 mg/kg), like LSD, produced reductions in locomotor activity and exploratory behavior, classifying it as acutely anxiogenic. The effects of DOI were fully attenuated by all doses of the antagonist, volinanserin, whereas those of LSD were only partially reversed. Interestingly, more modern studies using DOI across doses in healthy animals have reported mixed results related to locomotor and exploratory behavior. In contrast to earlier studies, recent data have indeed shown that acute DOI across doses is able to promote increased locomotion and exploratory behavior,[110–114] but the postacute effects of DOI, which are thought to be indicative of the robust therapeutic potential of psychedelics, have had mixed results.[115]

5.3. Effects on anxiety

Other behaviors commonly seen in the psychedelic literature are behaviors related to anxiety, such as anxiety-inducing assays such as the light-dark paradigm, EPM, and marble burying tasks. These assays exploit natural tendencies of mice to avoid certain situations that are deemed risky (going into the lighted side of a box, or into the open arms of a maze). By measuring the aversion, or lack thereof, researchers are helped to understand how administration of a drug can produce anxiolytic-like effects.

Many recent studies have indicated that psychedelics can increase exploratory behavior in open-field tests, light-dark paradigm, and the EPM,[112,113] although these conclusions are confounded by acute drug effects. To this end, DOI has been shown to decrease anxiety-like behaviors shortly after injection, as measured by the EPM and marble burying tasks.[113] These effects last for several hours after treatment. However, 24 hours after treatment, the effects may reverse to be anxiogenic. More research is necessary to delineate the acute versus postacute effects of DOI, and other psychedelics, on these behaviors.

5.4. Behavioral despair

Similarly, models of antidepressant-like effects also have provided mixed results with acute and postacute effects. These types of assays include the FST. The FST has predictive validity for determining antidepressant efficacy in humans,[116] by directly measuring motivated behavior of animals. This test was the gold standard when developing antidepressants such as selective serotonin-reuptake inhibitors but has led to mixed results with psychedelic compounds. Indeed, early studies of acute DOI in the FST have demonstrated no changes of immobility time in mice or locomotor activity across a large dose range (up to 4 mg/kg, i.p.), and interestingly demonstrated that antagonism, not agonism, produced and potentiated the antidepressant-like response in the FST.[117] More recent studies have employed the FST either in combination with chronic stress models or have measured the effects of DOI postacutely, suggesting these variations better mimic the human experience in the rodent model. When these models are employed, the recent literature suggests that DOI (at 1–2 mg/kg i.p.) does produce a decrease in immobility time long after the acute effects have gone.[115,118,119] Following these studies with DOI, through experiments using genetically modified mice lacking the 5-HT_{2A} receptor, it has been accepted that these antidepressant-like effects are mediated by 5-HT_{2A} receptors. Current research with these models and various psychedelics, including DOI, is still ongoing.

5.5. Fear extinction paradigms

Fear conditioning paradigms are built on a framework of classical conditioning that can also be applied to human subjects research.[120] Many of the fear conditioning assays within the psychedelic space have used DOI to understand whether a serotonergic agonist can produce decreases in behaviors associated with “traumatic events” such as a footshock in rodents. For example, de la Fuente et al[115] found that when given before or after fear acquisition, DOI was able to produce decreased freezing time in measures of fear extinction in a 5-HT_{2A} receptor-dependent manner. Others have demonstrated similar findings, even with slight paradigm adaptations.[111]

5.6. Cognitive flexibility

Cognitive flexibility is the ability to adapt behavior to changes in one’s environment, the physiological correlate of “changing one’s mind.” To date, there have been a few studies investigating DOI for its effects on cognitive flexibility. Many neuropsychiatric disorders are characterized by perseveration, and drug molecules able to enhance cognitive flexibility are strongly sought after. A single dose of racemic DOI (2 mg/kg) appears to enhance cognitive flexibility on a reversal learning task in mice for several days following injection by accelerating strategy changes.[121] Similar changes have been observed with other psychedelics, such as psilocybin, being able to enhance cognitive flexibility.[122] Prefrontal cortical activity has been linked to cognitive flexibility,[123–125] so it is not unexpected that pharmacological agents targeting the PFC generate this potential.

5.7. Substance use disorder

There has been increasing interest in using 5-HT_{2A} receptor agonists to treat SUDs, which targets PFC-subcortical circuitry. DOI has been used to demonstrate utility in critical assays of SUD, and employed as a tool to probe relevant neural circuits. When substances (eg, cocaine, heroin, or methamphetamine) are used chronically, the communications across and within brain regions are altered, impacting decision making, impulse control, and motivation[126] Self-administration protocols are the gold standard for measuring abuse potential of addictive compounds. Research with DOx compounds in both rodent[127–131] and nonhuman primate models[132,133] of substance use has demonstrated that they do not produce self-administration on their own (therefore considered to be nonaddictive), but actually are able to reduce behaviors associated with increased consumption or demand for alcohol, opioids, and psychomotor stimulants. In particular, acute DOI administration is sufficient to block alcohol place preference and reduces ethanol consumption.[127,128] DOI's utility for curbing SUD has extended beyond just alcohol use disorder. A behavioral economic analysis revealed that DOI reduced fentanyl motivation and consumption in both continuous and intermittent access paradigms.[129] In a model of comorbid heroin and alcohol use, the Peters group demonstrated that DOI is able to reduce heroin seeking and consumption.[134]

Intracranial self-stimulation models stimulate brain regions associated with rewarding processes, and animals will repeatedly self-stimulate for a rewarding experience. After treatment with DOI, animals reduce responding for stimulation.[135,136] In a study by Jaster et al,[137] it was found that DOI effects were completely blocked by a selective 5-HT_{2A} receptor antagonist, whereas other psychedelics with more promiscuous receptor profiles were not, suggesting a possible mechanism to target novel pharmacotherapies for addiction. Furthermore, Jaster et al[137] discovered unique epigenetic ensembles related to structural plasticity in the nucleus accumbens that may be involved in the adaptive versus maladaptive behavioral outcomes seen in rodents following administration of psychedelics and opioids.

This work has inspired a growing field of researchers to investigate how serotonin and other 5-HT_2 agonists, such as psychedelics, are used for treating SUD.[138–140] In this way, DOI has provided critical data for the addiction field. Limiting access to this crucial tool will inevitably hinder research progress. This is of utmost importance given the world's current substance use epidemic.

6. Potential therapeutic mechanisms of psychedelics

DOI has proven to be an invaluable tool in assessing the role of the 5-HT_{2A} receptor in the mechanism of action and therapeutic potential of a plethora of novel drugs. A remarkable phenomenon of psychedelic pharmacology is the ability for compounds, like DOI, to induce long-lasting structural and functional changes to neurophysiology long after the drug has been metabolized and eliminated from the animal. In the past year, multiple studies have been published combining behavioral pharmacology techniques with molecular and genetic mechanisms, utilizing DOI as the test drug.[77,113,141] DOI's ability selectivity to activate 5-HT_2 receptors serves a great purpose to identify molecular targets in specific brain regions or behaviors related to psychiatric pathology.[112,142] Importantly, DOI has contributed to foundational knowledge about serotonin-mediated neuroplasticity.[138,143,144]

6.1. Plasticity as a possible mechanism

The 5-HT_{2A} receptor is an excitatory receptor and the most widely expressed 5-HT receptor in the body.[145] In the brain, it is most densely expressed in layer V pyramidal cells in the anterior cortex, making it a prime target for activating the PFC system. Disorders such as depression, anxiety, post-traumatic stress disorder, and addiction all present with atrophied neurons in the PFC, including a reduction in dendritic length, spine density and synapses, as well as a functional decrease in activity.[146,147] The atrophy of neurons in the PFC can be so substantial it can lead to a reduction in the overall gray matter volume.[148] That is mirrored in clinical populations wherein patients have deficits in motivated activity, reward processing, or fear responses.[146,149]

That 5-HT_{2A} receptor agonists, such as DOI, reverse this atrophy and increase spine density in PFC after treatment, which has been demonstrated both in vitro and in vivo.[115,138,143] Drugs that are able to restore structure and function of cells in the PFC like this, along with rapid-acting antidepressant action, are referred to as psychoplastogens. This increase in growth is sufficient to increase gray matter volume in the cortex,[121] which demonstrates potential to restore the structure of the cortex after chronic stress atrophy. In fact, DOI was the first psychedelic to demonstrate growth of spines in cortical neurons,[143] demonstrating both the role of the 5-HT_{2A} receptor in neuroplasticity and DOI's invaluable use as a tool for neurobiology. DOI treatment of animals enhances long-term plasticity in layer II/III cortical pyramidal neurons.[115] The Gq-mediated cellular activation of cells in the PFC has been demonstrated after DOI administration.[66] Not surprisingly, this growth is blocked by pretreatment with the 5-$HT_{2A/C}$ antagonist, ketanserin. That suggests that engagement with the 5-HT_{2A} and/or 5-HT_{2C} receptor is integral to the therapeutic action of these compounds. The increase in structural growth and functional activity is thought to underlie the long-lasting changes in behavioral effects of psychedelic compounds like DOI.

7. Inflammation and pain research

The utility of DOI extends beyond the brain. Given its selectivity for 5-HT_2 receptors and the expression of these receptors in both the central and peripheral nervous system, DOI is a unique tool for understanding serotonergic modulation of pain, inflammation, and respiration.[150,151] For example, DOI was found to have highly potent anti-inflammatory properties through serotonergic receptors located in pulmonary tissue and the spinal cord. For a more extensive discussion on psychedelics as anti-inflammatories, see the review by Flanagan and Nichols.[152] Research with DOI in inflammatory responses related to respiration has been reported since the 1990s, when it was demonstrated through experiments with selective compounds, including DOI, that serotonin modulates respiratory rhythms in rodents, partially through 5-HT_2 spinal receptors and partially through 5-HT_1 receptors in the medulla.[153] Recent breakthrough findings with DOI have demonstrated this approach to be relevant for inflammatory diseases such as asthma and pulmonary fibrosis, discovering that DOI (1 mg/kg, inhaled) is able to reduce pulmonary inflammation, decrease mucous production, and help lungs return to a more normal physiological state.[150]

DOI has also played an important role in advancing our understanding of nociception in injured and inflamed tissues. In both humans and rodents, the skin is innervated by the axons of sensory neurons that reside in the dorsal root ganglia of the spine. Upon tissue injury, serotonin is released and can act on these axons to modulate their function. Many studies have characterized the expression of the 5-HT_{2A} receptor in these sensory neurons,[154–161] one having done so using [I^{125}]-DOI.[157] These studies found that the 5-HT_{2A} receptor is expressed in neurons important for thermal and mechanical nociception. Thus, DOI is poised to be an

important pharmacological tool for dissecting the role of the 5-HT_{2A} receptor in injury and inflammation.

At the cellular and circuit level, it has been demonstrated that DOI alone can depolarize dorsal root ganglia sensory neurons, as well as enhance the number of action potentials evoked in the spinal cord in response to the application of mechanical punctate and noxious heat stimuli.[162,163] DOI's excitatory action on these primary sensory neurons was then used to map their second order targets in the spinal cord.[164] It was additionally found that DOI enhanced the monosynaptic sensory reflex circuit between the dorsal sensory root and the ventral motor root.[165] In addition to DOI's direct actions, it is able to modulate the function of ion channels and circuits important for nociception. Work by Ohta et al found that DOI potentiates the function of the transient receptor potential V1 ion channel, and Kjørsvik Bertelsen et al demonstrated that DOI potentiates the release of substance P in the spinal cord.[166,167] Taken together, these findings suggest a pronociceptive role of the 5-HT_{2A} receptor in the periphery. Behaviorally, this conclusion has been supported by a series of studies using DOI. Two earlier reports found that DOI alone induces nocifensive behaviors (licking, biting, scratching, and paw favoring) when administered to healthy animals.[168,169] Moreover, it was observed that when administered in conjunction with proinflammatory mediators, DOI potentiated their effects.[169] DOI is also capable of enhancing the nociceptive response induced by local formalin injections in the paw.[170]

However, 2 studies have found that DOI can have antinociceptive effects.[171,172] A recent article by Koseli et al[172] compared DOI and psilocybin in mouse models of chronic neuropathic and inflammatory pain. They found both compounds were able dose dependently to produce antinociceptive and anti-inflammatory effects in these models via a 5-HT_{2A} mechanism, but with different time courses, highlighting the importance of comparison across substances that activate similar receptor types. In fact, compounds like DOI with phenethylamine backbones elicit maximal anti-inflammatory responses (Emax equivalent to the 5-HT-elicited Emax) compared with other psychedelic classes.[173,174] Although there is an abundance of literature suggesting that agonists of the 5-HT_{2A} receptor, like DOI, augment pain sensitivity in some models,[170,175] recent work using molecular and genetic techniques has demonstrated that the effects can vary greatly depending on route of administration, cell type, and area of receptor expression (for an extensive review on 5-HT receptors and pain, see the articles by Courteix et al and Heijmans et al).[171,176–178] Indeed, it is known that following injury, there are transcriptional changes that alter the expression pattern of the 5-HT_{2A} receptor in the spinal cord and dorsal root ganglia.[159,178,179] Collectively, these findings emphasize the importance of ongoing research, which would be compromised by scheduling compounds such as DOI.

8. DOI versus DOC as a research tool

DOC has not been widely used by scientists as a tool to study 5-HT_2 receptors. Research articles using DOC are only around 1% (around 10 publications) as abundant as those which use DOI. In 2020, the United Nations Commission on Narcotic Drugs voted to add DOC to Schedule I of the 1971 Convention on Psychotropic Substances, thus requiring the DEA to initiate scheduling protocols to place it in the CSA. DOI was not added to the UN Convention on Psychotropic Substances. Although DOC was included in the current DEA case, the scientific community has seldom used DOC as a tool, the way that DOI has been heavily used. A recent article assessing recreational use of both compounds found that DOC was used in higher frequency but still extremely infrequent to other compounds outside of this drug class.[48]

9. The effects of Schedule I status on research

If DOC and DOI are placed in Schedule I of the CSA following the recent recommendation of the Administrative Law Judge, researchers will be subject to several new restrictions.[180] These include a review of the application for a Schedule I license by the Food and Drug Administration (FDA), a requirement not in place for research with Schedule II–V drugs, physical modification to the laboratory for a floor-mounted safe, and additional review by the DEA and FDA if the researcher wishes to amend their protocol. For example, if a researcher uses their drug supply of a Schedule I substance and wishes to purchase more, the FDA and DEA must approve additional purchase quantities. This amendment review may take several months until it is accepted, and at many institutions research related to that substance or protocol must be paused until the amendment is approved. Similarly, if a researcher wishes to conduct an experiment different than what was listed in their Schedule I application, they must also submit a protocol revision subject to FDA and DEA review.[181] The processes and barriers of CSA licensure in the context of psychedelic research have been outlined by Barnett et al.[182] and Johnson et al.[183]

We sought to understand whether the Schedule I status of a substance has any implications for collaborative research, using DOI and DOM publications. We tracked the number of authors per publication for all identified publications using either compound. The median number of authors on publications for both compounds was 3, where DOI had 234 publications and DOM had 108. DOI publications are associated with more collaborative higher author count papers, however. For example, of the manuscripts using DOI, 35% had 5–10 authors, versus 21% of manuscripts using DOM (Fig. 4; Table 3). One interpretation of this could be that collaborations using a nonscheduled compound may be easier than its Schedule I counterpart. However, the caveat that a radiolabeled version of DOI is available and that DOI is more selective for 5HT_{2A} than DOM should not be ignored. Likewise, Fig. 2 displays the number of publications utilizing DOM before and after the passage of the CSA. Although DOM was placed in Schedule I, there are more than 3-fold publications using the unscheduled DOI than scheduled DOM.

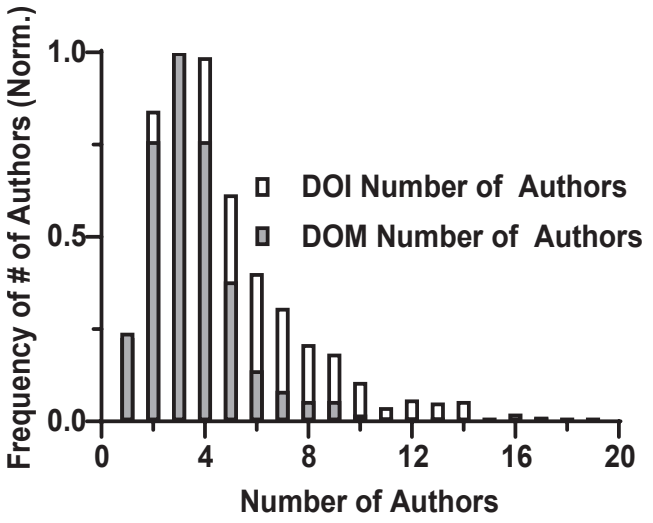

Fig. 4. Normalized frequency of the number of authors per paper. The maximum number of authors per paper peaked at 3 authors with 234 and 108 papers, respectively, for DOI and DOM. There were a total of 1205 and 382 papers for DOI and DOM, respectively. The skewness for DOI and DOM was 1.61 and 1.45, and kurtosis was 1.38 and 0.777 for DOI and DOM, respectively.

Table 3
Number of authors per publication using DOI or DOM: The number of authors for manuscripts using either DOI or DOM

Number of Authors	Publication Number (DOI)	Publication % (DOI)	Publication Number (DOM)	Publication % (DOM)
1	53	4.4	26	6.8
2	197	16.3	82	22
3	234	19	108	28
4	231	19	82	22
5	144	12	41	11
6	94	7.8	15	3.9
7	72	6.0	9	2.4
8	49	4.1	6	1.6
9	43	3.6	6	1.6
10	25	2.1	2	0.5
11	9	0.7	1	0.3
12	14	1.2	1	0.3
13	12	1.0	1	0.3
14	13	1.1	–	–
15	2	0.2	–	–
16	5	0.4	–	–
17	3	0.2	1	0.3
18	1	0.1	–	–
19	2	0.2	–	–
21	1	0.1	1	0.3
22	2	0.2	–	–
29	1	0.1	–	–
38	1	0.1	–	–

10. Future directions

It has previously been argued that the placement of DOI in the CSA will be harmful to research,[184] so many have prompted the question: What are the alternative compounds if DOI is placed in Schedule I of the CSA? A likely path for many scientists will be to use another nonscheduled drug with high selectivity for the 5-HT_{2A} and 5-HT_{2C} receptors[185–204] (see Table 4), although all are substantially less well characterized than DOI.

One such compound could be the conformationally restricted analog of 2-CB (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (colloquially called TCB-2).[185,205] However, TCB-2 is poorly characterized, and animal dosing regimens, metabolites, pharmacokinetics, and off-target pharmacology may be unknown, leading to further uncertainty in experimentation. DOI is an *invaluable* tool because decades of experiments give confidence as to which doses cause stereotypical behavior or in vitro effects. TCB-2, for example, has several-fold greater affinity for the 5-HT_{2A} receptor than DOI (TCB-2: 0.26 nM and DOI: 0.1–32 nM),[185–190] but has only been used in less than 10 publications. Recent work has used it to describe the role of 5-HT_{2A} receptors in synaptic maturation in the maturing prefrontal cortex,[206] but studies understanding its full range of behavioral and molecular effects are limited. TCB-2 could be considered a Schedule I drug under the Federal Analogs Act provisions of the CSA as it is a structurally constrained analog of 2C-B. Analog Act Provisions however do not prevent researchers from studying a compound unless it is explicitly added to the CSA. As of this publication, there are no restrictions for research with TCB-2.

Another nonscheduled 5-HT_{2A} receptor selective alternative is 25CN-NBOH. This compound is one of the most selective 5HT_{2A} agonists, with a Ki of 2.2 nM and greater than 100-fold selectivity for 5-HT_{2A} over 5-HT_{2B}.[207] The central nervous system MPO score for 25CN-NBOH is 4.6. This compound has been characterized in the HTR in mice across a wide range of doses (0.5–10 mg/kg, i.p. or 1.5 mg/kg, s.c.),[208] with the ED_{50} response reported to be 0.51 mg/kg.[209] Furthermore, the effects on locomotor behavior were characterized at only a single dose (1.5 mg/kg, i.p.) and found to increase locomotor behavior across 30 and 90 minute time points.[208] These behavioral effects are all reported to be blocked with 5-HT_2 antagonists, suggesting a selective mechanism of action similar to DOI.

LPH-5 is another compound with high selectivity for 5-HT_{2A} over other receptors. It functions as a potent partial agonist at 5-HT_{2A} with a Ki of 1.3 nM, while exhibiting antagonist properties at 5-HT_{2C}, with a Ki of 13 nM.[191] This is a unique compound able to activate 5-HT_{2A} selectively, but with less of an effect at the 5-HT_{2C} receptor. This compound's MPO score is 3.9, suggesting a good blood-brain barrier permeability. In rats, LPH-5 evoked robust head twitching across a large range of doses (1.5, 3.0, 6.0, and 12.0 mg/kg), but with a variable time course. No changes in locomotor behavior were reported in an open field test, but some changes in activity were reported in the FST.[210]

11. Conclusions

In June 2025, a DEA Administrative Law Judge recommended placing both DOI and DOC in Schedule I.[38] Until the rule is finalized in the Federal Register, researchers can work uninterrupted. Soon,

Table 4
Affinity of several psychedelics for relevant receptors and targets

	Ki (nM)						
Receptor	R(-)DOI	DOM	LSD	25I-NBOMe	25CN-NBOH	LPH-5	TCB-2
$5HT_{1A}$	2220–3840[189,a,192,b]	7270– >10,000[193,195]	4.92[187,e]	1800[195]	–	–	–
$5HT_{1B}$	1260[192,c]	2060[192,c]	151[196,d]	–	–	–	–
$5HT_{2A}$	0.1–32[186–190]	2.06–306[194,197]	0.48–5.2[194,195,197]	0.6[195]	2.2[198]	1.3[191,199]	0.26[185]
$5HT_{2B}$	7.07–53.7[82,186,188,190,200]	400[28,a]	0.97–8.9[82,201,202]	130[195]	58[198]	13[191,199]	–
$5HT_{2C}$	2.4–18.6[186,190,192,200,d]	25.7[192,194,d]	1.09–46[82,194,195,201,203]	4.6[195]	49.8[198]	13[191,199]	–
D1	9687[204]	>10,000[204]	177–310[194,195,204]	6700[195]	–	–	–
D2	>10,000[204]	>10,000[204]	25–110[194,195,204]	900[195]	–	–	–
D3	>10,000[204]	>10,000[204]	27–96[194,204]	2100[195]	–	–	–
D4	>10,000[204]	>10,000[204]	158–330[194,204]	–	–	–	–
D5	>10,000[204]	>10,000[204]	344[204]	–	–	–	–
DAT	>10,000[204]	>10,000[204]	>10,000[194]	5400[195]	–	–	–
NET	>10,000[204]	>10,000[204]	5600– >10,000[194,195]	1300[195]	–	–	–
SERT	685[204]	>10,000[204]	>10,000[194]	1000[195]	–	–	–

Ki values are from cloned human receptors in recombinant cell lines unless indicated otherwise.
– indicates not available.
[a]Rat cortex.
[b]Rat hippocampus.
[c]Rat striatum.
[d]Pig cortex.
[e]Human cortex.

laboratories will need to engage with their local field offices, which have complete discretion over how cases are handled. Some offices might insist on Reverse Distribution Programs to send all drugs back to the DEA, whereas others may allow researchers to complete experiments while they apply for a DEA Schedule I license.[38,182,211,212] Regardless, any researcher working with DOI or DOC will have to apply for a DEA Schedule I license and likely purchase new compounds following an approval process that often takes more than 1 year.[38] The time it takes may vary by institution, as some require extra registrations within the universities, state, or local offices.

DOI is more selective for 5-HT_{2A} than any other agonist frequently used in serotonin research. Psychedelic medicine recently has garnered much attention in the media and industry, with millions of dollars pouring into the industry to develop novel therapeutics for psychiatric disorders. Current antidepressants are ineffective in 30% of the population, leaving millions across the country without proper neurological support. Depression and suicide rates have soared in recent years, particularly after the COVID pandemic, leaving millions across the country without access to mental health treatment. Psychedelics may be the key to helping resolve this mental health epidemic, but developing better therapeutics depends on understanding these compounds' mechanism of action. The 5-HT_{2A} receptor is the major target of all psychedelic compounds and plays an integral role in the perceptual effects of these compounds. Without understanding the role of the 5-HT_{2A} receptor, our understanding of psychedelic medicine is severely impeded and drug discovery efforts will be hampered. DOI's selectivity makes it an indispensable tool for studying novel therapeutic mechanisms and the role of the 5-HT_{2A} receptor. Given the vast array of research areas discussed herein and the critical role that DOI has played in catalyzing research into the 5-HT_{2A} receptor, including it in the CSA will place substantial burdens on both pharmacologists and neuroscientists, and substantially slow progress in the field. Even more importantly, restricting access to DOI, a crucial neuroscience tool with a proven history and utility, will delay progress toward understanding and developing new treatments for patients suffering with a variety of psychiatric illnesses.

Abbreviations

CSA, Controlled Substances Act; DEA, Drug Enforcement Administration; DOB, 2,5-dimethoxy-4-bromoamphetamine; DOC, 2,5-dimethoxy-4-chloroamphetamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; EPM, elevated plus maze; FDA, Food and Drug Administration; FST, forced swim test; GPCR, G protein-coupled receptor; HTR, head twitch response; LSD, lysergic acid diethylamide; MPO, multiparameter optimization; PFC, prefrontal cortex; SUD, substance use disorder.

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Conflict of interest

The authors have no relevant conflicts of interest.

Data availability

The authors declare that all supporting data are contained within the paper or as supplemental documents. We have included reference manager files for all manuscripts using DOI (Supplemental File 1) or DOM (Supplemental File 2) that we could identify, and were used to make the tables and histograms as a reference for the field. If any publications were omitted from the list, it was unintentional, as it was believed to be the most complete at the time of submission.

CRediT authorship contribution statement

Lindsay P. Cameron: Conceptualization, Writing - Original Draft, Review & Editing, Visualization; **Alaina M. Jaster:** Conceptualization, Writing – Original Draft, Review & Editing, Formal Analysis, Resources, Visualization; **Raul A. Ramos:** Conceptualization, Writing – Original Draft, Review & Editing, Visualization; **Elijah Z. Ullman:** Conceptualization, Writing – Original Draft, Review & Editing, Formal Analysis, Visualization.

Supplemental material

This article has supplemental material available at molpharm.aspetjournals.org.

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