Current Topics in Behavioral Neurosciences 36

Adam L. Halberstadt
Franz X. Vollenweider
David E. Nichols *Editors*

Behavioral Neurobiology of Psychedelic Drugs

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Preface

To fathom Hell or soar angelic,

Just take a pinch of psychedelic.

—Humphry Osmond, in a letter written to Aldous Huxley, March 30, 1956

Scientific interest in psychedelic drugs has increased exponentially over the past decade. Just in the last few years, small controlled clinical trials examining the potential therapeutic utility of psilocybin-assisted therapy in patients suffering from anxiety, depression, and substance abuse have reported extremely positive outcomes (Grob et al. 2011; Bogenschutz et al. 2015; Carhart-Harris et al. 2016a; Griffiths et al. 2017; Johnson et al. 2017; Ross et al. 2016). Several human research studies with LSD have also been reported (Gasser et al. 2014, 2015; Carhart-Harris et al. 2016b; Liechti et al. 2017; Kraehenmann et al. 2017). Hence, we believe it is now an appropriate time for Springer to publish a volume about research with psychedelic drugs as part of their prestigious *Current Topics in Behavioral Neurosciences* (CTBN) series. Our objective for the volume has been to summarize the current state-of-the-art of psychedelics research. As editors, we faced the seemingly impossible task of distilling the entire breadth and depth of this rapidly expanding field into a single volume. It proved difficult to narrow the scope down to a reasonable level. We selected topics that span a wide range of areas, including pharmacological interactions occurring at the molecular level, changes in signaling pathways, effects on individual neurons and neural networks, and reaching all the way up to the level of the whole brain and the mind. We believe the 14 peer-reviewed chapters that were selected for inclusion provide up-to-date information about the pharmacology, neurobiological effects, subjective experience, and therapeutic effects of psychedelic drugs.

The editors of this volume represent three generations of scientists working in the field of psychedelics research. One of us (DEN) entered the field in 1969, at a time when research with LSD, psilocybin, and indeed all psychedelics had become very controversial. Strict legal controls were placed on research projects, most funding sources had dried up, and work with these substances acquired a stigma.

When Dave founded the Heffter Research Institute in 1993 to help promote legitimate scientific research with psychedelics, the possibility that psilocybin would ever again be widely studied in human clinical trials seemed remote, at best. Around that time, however, there were several promising developments. For example, in the early 1990s, Dr. Rick Strassman received permission from the FDA to conduct a research study with intravenous DMT, demonstrating that it was again possible to administer psychedelic drugs to humans. The results of those DMT studies were published in 1994 (Strassman and Qualls 1994; Strassman et al. 1994).

The second editor of this volume (FXV) was one of the first scientists to receive funding from the Heffter Institute. At the time, Franz was a very promising young psychiatrist who was motivated to conduct basic research with psychedelics in humans. With support from Heffter, Franz was able to create a Heffter Research Center in his hospital at the University of Zürich in 1999, enabling him to use state-of-the-art neurophysiological and imaging techniques to investigate the actions and effects of psychedelics. His groundbreaking work continues to demonstrate the high value that psychedelics possess as tools to understand brain function and consciousness (Geyer and Vollenweider 2008; Vollenweider and Kometer 2010).

The third editor (ALH) is a member of the new generation of psychedelics researchers who entered the field after the turn of the century, just as this topic was moving toward the scientific mainstream. Adam completed his postdoctoral training in the translational behavioral neuroscience group headed by Dr. Mark Geyer at UCSD, another founding member of Heffter, and is now running his own laboratory with independent research funding from NIDA.

We are greatly indebted to the corresponding authors and their coauthors for all of their hard work; this volume could not have been completed without their help and expertise. The staff at Springer deserves special recognition for their patience, as well as for guiding us through the publication process. We also owe a debt of gratitude to Mark Geyer, Bart Ellenbroek, Charles Marsden, and Thomas Barnes for their willingness to include this volume in the CTBN series.

Finally, we should provide a comment about our use of the term *psychedelic* in the title of this volume. Despite the recent rapid advancement of this field of research, the terminology used to classify LSD, mescaline, psilocybin, and related substances still remains controversial. Many names have been proposed for these substances over the years, including *delusinogenics, entheogens, hallucinogens, illusinogenics, misperceptionogens, mysticomimetics, oneirogens, phanerothymes, phantasticants, psychedelics, psychodysleptics, psycholytics, psychotaraxics, psychoticants, psychotomimetics, psychotoxins, and schizogens*. Unfortunately, most of these terms are overly specific for one aspect of the drug experience or are nonneutral terms reflecting their perceived utility. The term *psychotomimetic*, which was introduced by Gerard (1956), is a pejorative that emphasizes the ability of these substances to induce a psychosis-like state. However, the effects of these drugs approximate only some of the symptoms of schizophrenia. Similarly, *entheogen*, proposed by several prominent ethnobotanists in 1979 (Ruck et al. 1979), is a narrow term with religious connotations that focuses on the mystical or religious effects that can be produced by this drug class. *Hallucinogen* has perhaps been most

widely used in the scientific literature and is the legal designation used to classify these substances in many countries. Unfortunately, it also is a misnomer because these compounds rarely evoke true hallucinations and do not normally impair reality testing. Furthermore, a wide range of psychoactive substances, including cannabinoids, dissociative anesthetics, anticholinergics, and entactogens such as MDMA, can produce "hallucinogenic" effects. Hence, LSD-like drugs are often referred to as *classical hallucinogens* or *serotonergic hallucinogens* in order to distinguish them from other drug classes.

The psychiatrist Humphrey Osmond first proposed the term *psychedelic* at a meeting of the New York Academy of Sciences in 1957 (Osmond 1957). Osmond coined this term (which means "mind manifesting") to highlight the ability of these substances to facilitate exploration of the mind by exposing latent mental states. The word psychedelic was constructed to avoid the negative connotation associated with words such as psychotomimetic, which had been adopted by many medical professionals. This classification did not take hold among many researchers, likely because it carried a stigma due to its association with the counterculture in the 1960s and 1970s. It effectively disappeared from the *scientific literature* for many decades, although it has probably remained the most widely used name in popular culture for more than half a century. These issues, however, have faded with time, and the recent resumption of research with these substances has been accompanied by a reintroduction of the word psychedelic into the scientific vocabulary. During the past two years, papers specifically about "psychedelics" have appeared in several respected scientific journals, for example, *Lancet Psychiatry, Neuropsychopharmacology, Pharmacological Reviews, and Journal of Psychopharmacology* (Carhart-Harris et al. 2016a; Griffiths et al. 2017; Ross et al. 2016; Carhart-Harris and Goodwin 2017; Nichols 2016). Recently, when many prominent investigators gathered together to discuss the therapeutic effects of psilocybin at a conference organized by the Usona Institute, there was much reflection about the need for a professional society devoted to research with these substances. The attendees agreed to form a society, and the unanimous decision was made to name it the International Society for Research on Psychedelics. Hence, there is now a consensus among researchers in the field that these substances should be referred to as psychedelic drugs, and this volume has been titled accordingly.

La Jolla, CA, USA — Adam L. Halberstadt
Chapel Hill, NC, USA — David E. Nichols
Zurich, Switzerland — Franz X. Vollenweider

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Contents

Chemistry and Structure–Activity Relationships of Psychedelics

David E. Nichols

Abstract This chapter will summarize structure–activity relationships (SAR) that are known for the classic serotonergic hallucinogens (aka psychedelics), focusing on the three chemical types: tryptamines, ergolines, and phenethylamines. In the brain, the serotonin 5-HT_{2A} receptor plays a key role in regulation of cortical function and cognition, and also appears to be the principal target for hallucinogenic/psychedelic drugs such as LSD. It is one of the most extensively studied of the 14 known types of serotonin receptors. Important structural features will be identified for activity and, where possible, those that the psychedelics have in common will be discussed. Because activation of the 5-HT_{2A} receptor is the principal mechanism of action for psychedelics, compounds with 5-HT_{2A} agonist activity generally are quickly discarded by the pharmaceutical industry. Thus, most of the research on psychedelics can be related to activation of 5-HT_{2A} receptors. Therefore, much of the discussion will include not only clinical or anecdotal studies, but also will consider data from animal models as well as a certain amount of molecular pharmacology where it is known.

Keywords Hallucinogen · Psychedelic · Structure–activity relationships · Serotonin 5-HT_{2A} receptor · Tryptamines · Phenethylamines · Ergolines · LSD

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1 Introduction

Psychedelics (hallucinogens) have remained of high interest for many decades due to their ability to produce unique and dramatic alterations in consciousness. Before they had been pharmacologically classified as 5-HT_{2A} receptor agonists or partial agonists, psychedelic drugs like mescaline, psilocybin, and LSD, were recognized for their powerful effects on the human psyche. They produce such profound effects on perception that it is natural to ask how they work in the brain. What are their biological targets? Where are these targets located in the brain? Are those brain areas recognized to play key roles in perception and cognition? Further, as recent clinical research studies have begun attempts to unravel the basis for human consciousness, it has become apparent that psychedelics offer unique and powerful tools to help to elucidate the basis of consciousness. The age-old questions of who we are and why we are here seem inevitably to arise when people talk about their experiences with psychedelic drugs. Yet, this fascinating class of mind-altering substances has not received significant research attention for more than 50 years, and it is only within the past decade or so that they have been the subject of renewed research interest. A comprehensive review on psychedelics has recently appeared (Nichols 2016).

As modern molecular pharmacology techniques have developed, our understanding has expanded of the roles played by the 5-HT_{2A} receptor in normal brain function, so that studies of 5-HT_{2A} receptor agonist structure–activity relationships (SAR) today take on greater significance, both from a theoretical and practical perspective.

There are three main chemical types of classic hallucinogens: the tryptamines, ergolines related to LSD, which can be considered to be rigidified tryptamines, and phenethylamines. These templates are illustrated in Fig. 1.

Serotonin receptor affinity and functional potency data are not available for many of the known psychedelics. Except for very limited human studies half a century ago, much of the research on hallucinogens involved animal behavioral studies or experiments with a variety of smooth muscle assays (e.g., rat fundus, rat

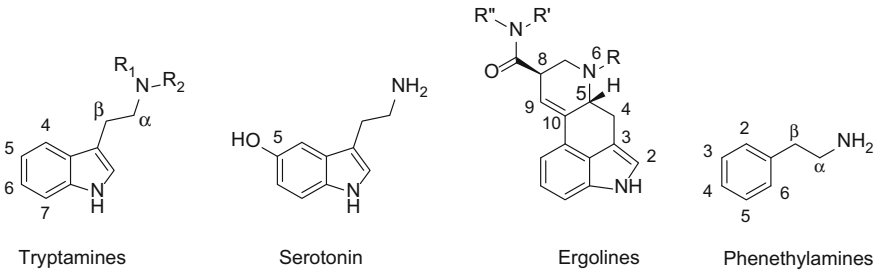


Fig. 1 Comparison of the structure of the neurotransmitter serotonin, with the three basic chemotypes of classic serotonergic hallucinogens

uterus, sheep umbilical artery strips). By contrast, the molecular pharmacology may be known for more recently developed compounds, but these usually lack formal clinical studies, so their human effects can often only be inferred. Fortunately, these substances have been shown to be serotonin 5-HT_{2A} agonists or partial agonists, so there is a sound basis for clinical inferences. Nonetheless, in many cases it is necessary to rely on animal behavioral or smooth muscle data in order to provide a more complete understanding of the SAR of psychedelics. Therefore, reports from early studies that are relevant to a consideration of SAR will largely focus on animal behavior, or in some cases, human hallucinogenic activity. Discussion of more recently developed molecules will include more of the molecular pharmacology, when and where it is known.

There are other types of molecules that are sometimes called hallucinogens, and in some cases they might more properly be called psychotomimetics, but this chapter will address only what are called classic hallucinogens; molecules that activate serotonin 5-HT_{2A} receptors. This chapter will not devote any discussion to 3,4-methylenedioxymethamphetamine (MDMA), salvinorin A (a kappa opioid receptor agonist), ketamine analogues (NMDA receptor antagonists), cannabinoids, or synthetic cannabimimetics. Certainly these latter molecules have become quite popular as recreational drugs, often marketed as "research chemicals," but they differ in their mechanism of action and complete monographs could be devoted to each of them.

2 Tryptamines

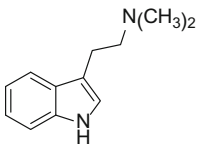
Tryptamines are the chemotypes that most closely resemble the natural neurotransmitter serotonin (5-hydroxytryptamine; 5-HT). Ergolines can essentially be considered to be rigidified tryptamines. Although LSD is the most well-known psychedelic, only a very few structural modifications can be made to its structure, and nearly all of those attenuate its activity by about an order of magnitude. In addition, there is a paucity of structure–activity data for ergolines, principally due to

the synthetic difficulty inherent in their chemistry. Surprisingly few molecular modifications can be carried out on the tryptamines that allow retention of activity. A number of simple tryptamines, largely *N,N*-substituent variations, have been administered to humans (Shulgin and Shulgin 1997), but their receptor pharmacology remains largely unknown.

2.1 Ring Substituents

The 5-hydroxy group of serotonin (see Fig. 1) stands out as perhaps a key structural feature of this molecule. Serotonin also is a primary amine, and as we shall see psychedelic tryptamine derivatives are generally tertiary amines. High agonist activity at the 5-HT_{2A} receptor, as well as at other serotonin receptor subtypes is also seen in its *O*-methylated derivative, 5-methoxytryptamine. The affinities of 5-HT and 5-methoxytryptamine at the rat 5-HT_{2A} receptor are identical (Gupta et al. 1990; Johnson et al. 1990). Neither serotonin nor 5-methoxytryptamine has activity in vivo if administered orally, presumably as a result of a high first pass effect due side chain deamination by monoamine oxidase A in the liver.

For tryptamines, 5-HT_2 agonist (and psychedelic) activity is generally enhanced by substitution with an oxygen atom at the 4- or 5-position. As an example, *N,N*-dimethyltryptamine (DMT **1**) has a reported K_i of 75 nM in rat brain cortical homogenate (McKenna et al. 1990). Adding a 5-methoxy (**2**) increased the affinity to 14 nM, and the 4-OH compound (psilocin **3**) had a reported affinity of 6 nM.



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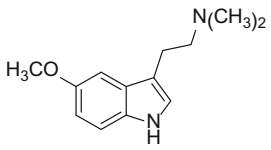

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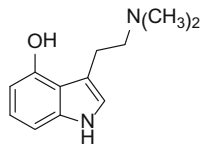

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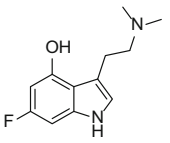
Five decades ago it was reported that 6-fluoro-*N,N*-diethyltryptamine (6-F-DET) lacked activity as a hallucinogen (Kalir and Szara 1963). It was recently found that it did not possess LSD- or DOI-like activity in a drug discrimination paradigm in rats (Blair et al. 2000). The affinity of 6-F-DET at the rat 5-HT_{2A} receptor was found to be essentially identical to DET, but its 40 μM EC_{50} in a phosphoinositide (PI) turnover assay was markedly reduced from that of DET (5.4 μM). Further, at a concentration of 100 μM 6-F-DET had an E_{max} of only 63%. The loss of functional efficacy and potency seems the most likely explanation for its absence of significant DET-like activity in man.

The effect of ring fluorination has been studied for four other tryptamines, with comparisons made between 6- and 7-F-psilocin and 4- and 6-fluoro-5-methoxy-DMT, **4**, **5**, **6**, and **7**, respectively, with their nonfluorinated counterparts (Blair et al.

2000). Fluorination of psilocin in the 6- or 7-positions gave compounds with essentially identical affinity at the rat 5-HT_{2A} receptor, and reduced by about one-half compared with psilocin itself. Adding a fluorine to 5-MeO-DMT at either the 4- or 6-position had no significant effect on E_{max}, but the EC_{50} values for the fluorinated compounds were increased to 7.9 and 18.1 μM for the 6-fluoro and 4-fluoro congeners, **6** and **7**, respectively, compared to 2.4 μM for 5-MeO-DMT. Fluorination had almost no effect on affinity at the rat 5-HT_{2C} receptor, but had marked effects on 5-HT_{1A} receptor affinity.



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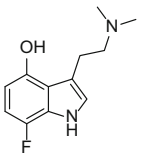

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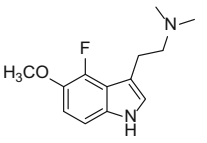

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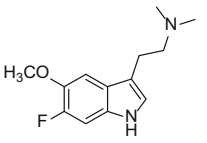

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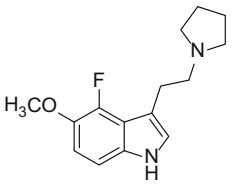
The 4-fluoro compound (**6**) had 0.23 nM affinity at the human 5-HT_{1A} receptor, nearly ten-fold greater than 5-MeO-DMT itself (1.7 nM). This substitution pattern was then exploited to create a 5-HT_{1A} ligand by replacing the *N,N*-dimethyl substituents with a pyrrolidyl moiety to afford molecule **8**, with 0.12 nM affinity at the human 5-HT_{1A} receptor and in vivo potency in the drug discrimination assay in rats comparable to the 5-HT_{1A} agonist 8-OH-DPAT (Laban et al. 2001).



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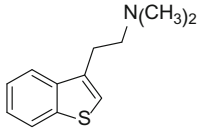
Much earlier work with benzo[*b*]thiophenes **9** and 3-indenalkylamines **10** had shown that when the compounds lacked ring substituents, their agonist activity in the rat fundus assay was about comparable to that of tryptamines (Winter et al. 1967). That is, the indole NH was not essential to activate the 5-HT_2 receptor in the rat fundus. The rat fundus receptor was subsequently classified as a 5-HT_{2B} receptor subtype (Baxter et al. 1994), and no recent studies have reported affinity or potency at the 5-HT_{2A} receptor.



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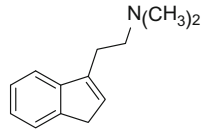

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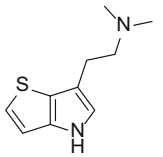
Replacing the phenyl ring of DMT with a bioisosteric thiophene was anticipated to lead to molecules that might possess DMT-like activity. The synthesis and biological activity of the thieno[3,2-*b*]-and thieno[2,3-*b*]pyrrole analogues of DMT (**11** and **12**, respectively) were reported by Blair et al. (1999). Both isosteres had lower affinity at the 5-HT_{2A} receptor than DMT, with **12** having greatest affinity (106 nM vs. 65 nM for DMT). Both isomers had somewhat higher affinities than DMT at the 5-HT_{1A} receptor and had higher affinities than DMT at the rat 5-HT_{2C}. DMT substituted in a drug discrimination study in rats trained to discriminate LSD from saline, but neither of the thienopyrrole isosteres substituted. Similarly, neither of the isosteres substituted in rats trained to discriminate DOI from saline.



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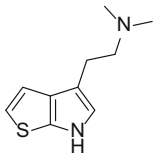
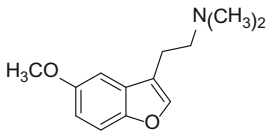


12

In rats trained to discriminate either LSD or DOI, isomer **11** gave the greatest degree of partial substitution, leading to speculation that a hydrogen bond donor in the receptor might be able to engage the sulfur atom in the thienyl ring when it was present in the edge of the molecule that normally carries the oxygen atom of serotonin. Both thiophene isosteres substituted in rats trained to discriminate the 5-HT_{1A} agonist LY293284 from saline, with **11** being about twice the potency of **12**.



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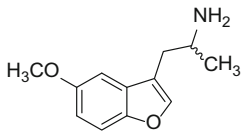
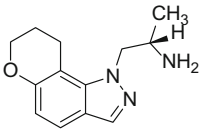


14

Replacing the indole nitrogen of the tryptamines with an oxygen atom affords a benzo[*b*]furan, another potential bioisostere of tryptamines. Compounds **13** and **14** both had about one-sixth the affinity of their indole congeners, using displacement of [^{125}I]DOI from rat frontal cortical homogenate (Tomaszewski et al. 1992). McKenna et al. (1990) reported a similar finding, assessing ability of *N*-methyl-*N*-isopropyltryptamine to displace [^{125}I]-*R*-DOI from rat cortical homogenate, compared with its benzo[*b*]furan isostere. The tryptamine IC_{50} of 38 nM was about 13-fold lower than the benzofuran, which had an IC_{50} of 500 nM.

A variation on ring-substitution patterns was the discovery of indazole ligands with potent 5-HT_{2A} agonist activity (May et al. 2003a, 2006). For example, AL-38022A **15** was developed as a highly potent 5-HT_{2A} agonist that had efficacy in reducing intraocular pressure in glaucoma. Compound **15** was a full agonist at all three 5-HT_2 family receptors, with EC_{50} values between 0.5 and 2.2 nM for several functional responses (May et al. 2009). In a drug discrimination assay in rats trained

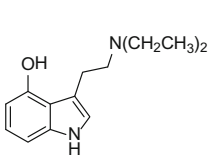
to discriminate the hallucinogen DOM from saline, **15** produced full substitution, with an ED_{50} of 0.05 mg/kg. Similarly, it produced full substitution in monkeys trained to discriminate DOM from saline, with an ED_{50} of 0.04 mg/kg, comparable to the potent 5-$HT_{2A/2C}$ agonist DOI.



15, AL-38022A

2.2 *N*-Alkylation

Another area for structural modification is the side chain amino group, where *N*-alkylation provides a variety of secondary or tertiary amines. Extensive data have been published for hallucinogenic effects of a number of *N*-substituted tryptamines in humans (Shulgin and Shulgin 1997), but only scant data are available for their receptor affinities or potencies. One of the earliest modifications of the tryptamines to be studied for psychoactive effects was the *N,N*-diethyl analogue of psilocin (CZ-74, **16**). Both CZ-74 and its *O*-phosphoryl derivative CEY 19 (**17**) were studied in humans. Qualitatively, these compounds were very similar to psilocin and psilocybin, respectively, but had somewhat reduced durations of action (Leuner and Baer 1965).



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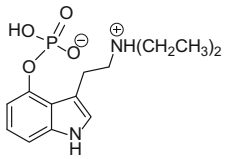
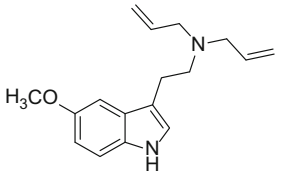


17

A systematic study of the effect of *N*-alkylation on tryptamine receptor affinities was reported by McKenna et al. (1990). *N*-alkylated tryptamines were examined with no ring substituents, a 5-methoxy, or 4-hydroxy group. Highest affinities (4–30 nM) for displacement of [^{125}I]DOI from rat cortical homogenate were observed with *N,N*-dimethyl, *N,N*-diethyl, *N*-methyl-*N*-isopropyl, and *N,N*-diisopropyl substituents. An affinity of 39 nM was reported for 4-OH-*N,N*-di(*sec*-butyl) tryptamine, but the affinity of 4-OH-*N,N*-diisobutyltryptamine was only 260 nM. Tethering the dialkyl groups into a heterocyclic ring gave mixed results; *N*-pyrrolidyl had an affinity similar to *N,N*-dimethyltryptamine (110 vs. 75 nM, respectively), but the affinity for the *N*-piperidyl was much lower, at 760 nM. The *N,N*-disubstituted compound 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT **18**) has recently appeared as a new "legal high" on the illicit market (Corkery et al. 2012;

Strano Rossi et al. 2014). Results from broad-based receptor screening led Cozzi and Daley (2016) to conclude that multiple serotonin receptors, as well as several nonserotonergic sites are important for the psychoactive effects of **18** and other *N, N*-diallyltryptamines.

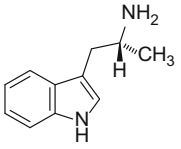


18

Although *N,N*-dimethyltryptamine and its 5-methoxy congener are not orally active, larger *N*-alkyl groups can confer oral activity on the molecules. It was demonstrated *N*-methyl-*N*-isopropyl- and *N,N*-diisopropyltryptamine, as well as the 5-methoxy analogue were both orally active in man, with durations of action of several hours (Shulgin and Carter 1980; Repke et al. 1985).

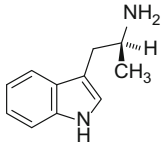
2.3 Side Chain Alkylation

Alpha-methylation of tryptamine side chains generally renders them orally active, presumably by blocking deamination by liver MAO. For example, 5-methoxytryptamine is inactive in man when given orally, but α-methyl-5-methoxytryptamine is a very potent orally active hallucinogen (Kantor et al. 1980). In mice, racemic α-methyltryptamine (AMT) increased motor activity by a mechanism that apparently involved both dopamine and serotonin (Rusterholz et al. 1979). In man, racemic α-methyltryptamine has been reported to be hallucinogenic (Murphree et al. 1961; Szara 1961; Shulgin and Shulgin 1997). Introduction of the alpha-methyl group also creates a chiral center in the molecule, and tryptamine enantiomers, not surprisingly, have differing biological activities. Affinity of (±)-α-methyltryptamine at the human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors was reported to be 164, 58, and 30 nM, respectively (Vangveravong et al. 1998). The affinities of *R*- and *S*-α-methyltryptamine, *R*-**19** and *S*-**19**, were reported as 130 and 46 nM, respectively, for [^{125}I]DOI displacement in rat cortical homogenate (McKenna et al. 1990).



R-(-)-AMT

(*R*)-**19**

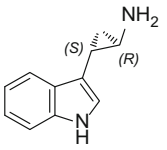


S-(+)-AMT

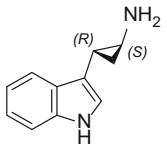
(*S*)-**19**

The enantiomer with the *S*-(+)-configuration has highest 5-HT_{2A} in vitro agonist activity, at least for molecules with a 5-OH or 5-OCH_3 substituent (Nichols et al. 1988). This in vitro observation is mirrored by human hallucinogenic activity, where 2.4 mg of (*S*)-(+)-5-methoxy-α-methyltryptamine is an effective hallucinogenic dosage in humans, whereas 3.0 mg of the *R* isomer produced no significant effect (Shulgin and Shulgin 1991). The *S*-(+)-enantiomer had 5-HT_{2A} affinity comparable to the non-alkylated 5-methoxytryptamine, whereas the *R*-(−) isomer was less potent. The affinities of (*R*)- and (*S*)-5-MeO-AMT at the agonist-labeled rat 5-HT_{2A} receptor were reported as 47 and 2 nM, respectively (Johnson et al. 1990). By contrast, the *R* enantiomer had higher affinity than the *S* isomer at the rat 5-HT_{1B} receptor (Nichols et al. 1988).

Extension of the α-methyl to α-ethyl afforded a compound named etryptamine (Monase), which was marketed until 1962 as an antidepressant. It appeared in Germany in 1986 as a "designer drug" that was associated with one death (Daldrup et al. 1986). It was found to have "neurotoxic" properties similar to MDMA in rats (Huang et al. 1991) and has been described as having MDMA-like psychopharmacology in humans (Krebs and Geyer 1993; Schechter 1998). Both isomers substituted with nearly equal potency in rats trained to discriminate MDMA from saline (Hong et al. 2001). In the same report, the (+)-enantiomer substituted in rats trained to discriminate the hallucinogenic phenethylamine DOM from saline, whereas the (−)-isomer substituted in rats trained to discriminate (+)-amphetamine. No data have been published on its affinity at 5-HT_2 family receptors.



(1*R*,2*S*)-(-)-**20**



(1*S*,2*R*)-(+)-**20**

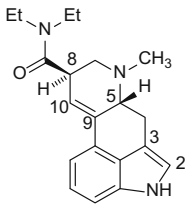
Another variation on side alkylation was provided in a study of *trans*-2-(indol-3-yl)-cyclopropylamines **20** (Vangveravong et al. 1998). Although the (1*R*,2*S*)-(−)- enantiomer of **20** had highest affinity at human 5-HT_{2A} and 5-HT_{2B} sites, the (1*S*,2*R*)-(+)- isomer unexpectedly had higher affinity at the 5-HT_{2C} human receptor. Ring substituents 4-OMe, 5-OMe, and 5-F generally increased affinity over unsubstituted **20**. The difficulty of synthesis and chemical instability of these indolecyclopropylamine compounds precluded preparation of the enantiomeric ring-substituted compounds.

3 Ergolines

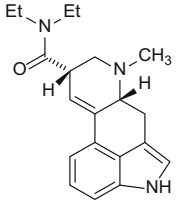
The tetracyclic ergoline molecules are ultimately derived from ergot alkaloids, products of the ergot fungus, of the genus *Claviceps*. From the perspective of psychedelic 5-HT_{2A} agonists, the most important one is lysergic acid diethylamide

(LSD **21**), also known as LSD-25. Although LSD is the most potent psychedelic agent in humans, its affinity and potency at the human 5-HT_{2A} receptor is rather unremarkable compared with much simpler molecules such as DOI. Numerous clinical studies of LSD and several of its amide-modified congeners were carried out in the 1950s and 1960s have been reviewed in detail earlier (Brimblecombe and Pinder 1975; Siva Sankar 1975; Shulgin 1982; Nichols 1986). Little new information has been published in the years since, with a few exceptions to be discussed below.

It is only ergolines with the 5*R*,8*R* stereochemistry, as illustrated earlier in Fig. 1 that have biological activity. That isomer is dextrorotatory, so LSD is referred to as (+)-LSD or *d*-LSD. Receptor binding studies by Bennett and Snyder in 1976 first demonstrated that LSD had nanomolar affinity for [^{3}H]LSD-labeled binding sites in rat cortex (Bennett and Snyder 1976). By contrast, its 5*S*,8*S* enantiomer, (−)-LSD, had 2500-fold lower affinity. The 8-position epimerizes readily, particularly at acidic pH, to provide the 5*R*,8*S* epimer (+)-isolysergic acid diethylamide **22**, which has about 30-fold lower receptor affinity and is inactive as a psychedelic.



(5*R*,8*R*)-(+)-LSD **21**



(5*R*,8*S*)-(+)-isoLSD **22**

Because of its structural complexity and tedious approaches to its total synthesis, only a few structural modifications of LSD have been reported. Those principally involved changes to the amide function, reduction of the 2,3- or 9,10-double bonds, a few substitutions on the indole nitrogen, oxidation or halogenation at the 2-position, and replacing the methyl group on the basic nitrogen atom with a small series of other alkyl groups. Unfortunately, only a few of them have been assessed in human psychopharmacology, most being much less active than LSD itself. Although some have been partially characterized for affinity at a few receptors, none of them have been the focus of comprehensive studies using modern molecular pharmacology methods.

If a halogen is introduced at the 2-position of LSD, for example in 2-bromo-LSD (BOL-148) or 2-iodo-LSD, the resulting molecules lack hallucinogenic activity and are antagonists at the 5-HT_{2A} receptor. No work with BOL-148 has been reported since the early 1970s, but it was shown that it could block the effects of LSD in humans.(Ginzel and Mayer-Gross 1956) The radiolabeled 2-iodo congener, [^{125}I] 2-iodo-LSD, has been employed as a radioligand for 5-HT_2 family receptors (Hartig et al. 1983; Nakada et al. 1984; McKenna et al. 1989; Watts et al. 1994). More recently, BOL has shown efficacy in aborting and/or preventing cluster headaches (Karst et al. 2010).

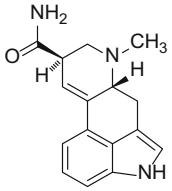
The 9,10-double bond of LSD is apparently crucial for its psychedelic action, and reducing it abolishes hallucinogenic activity (Stoll and Hofmann 1955; Hofmann 1968). Reduced 9,10-dihydro-LSD is still relatively planar, like LSD, so the reason(s) for the loss of activity is unclear (Nakahara et al. 1977). Although 9,10-dihydro-LSD lacks psychedelic effects in humans, there has so far not been a comparison of its receptor activities with those of LSD that might explain its inactivity.

Reducing the 2,3-bond of the indole nucleus results in a compound with about one-eighth the activity of LSD (Gorodetzky and Isbell 1964). It was reported to have a delayed onset of action relative to LSD, and it was speculated that "a metabolic change to a more active substance" might be the explanation. It might be noted that 2,3-dihydroindoles can be fairly readily oxidized to indoles, so such an oxidative transformation might take place in the body, perhaps by action of a mixed function oxidase in the liver.

Replacing the *N*(6)-methyl group of LSD with longer alkyl groups results in compounds that in some cases are more potent than LSD in vivo in rodent behavior and which in some cases have potency comparable to, or slightly greater than LSD in humans (Hoffman and Nichols 1985; Shulgin and Shulgin 1997). Assessment of receptor affinities for some of these analogues has failed to identify any correlation between hallucinogenic potency and nature of the *N*(6) alkyl group.

3.1 Amide Modifications of Lysergic Acid Derivatives

The simplest ergoline with human psychoactive properties is lysergic acid amide (**23**, ergine), reported by Hofmann and Tscherter to be the active component in *Rivea corymbosa* seeds used by the Aztecs in various magical potions and ointments (Hofmann 1971). If the C(8) amide substituent is removed completely to provide the 8-descarboxy **24**, the compound is reported to produce a mouse behavioral profile "remarkably similar to that shown by LSD" (Bach et al. 1974). Unfortunately, no other assays were carried out, nor were human studies carried out that would elucidate whether the presence of an amide substituent is an absolute requirement for activity. That is an important question because even slight modifications to the diethylamide moiety of LSD result in dramatic losses of in vivo activity.



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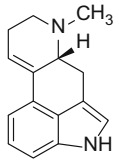
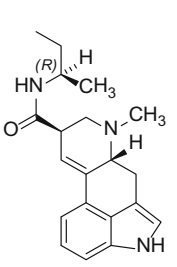


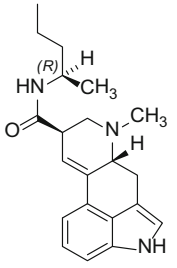
24

With respect to lysergic acid amides, it should be pointed out that the high in vivo potency of LSD seems to depend on the presence of the *N,N*-diethylamide moiety. It has been known for about five decades that any change to the amide moiety, however slight, leads to about an order of magnitude loss in potency. This decreased activity cannot be related simply to hydrophobicity, because compounds such as the *N*-methyl-*N*-propyl, or *N*-methyl-*N*-isopropyl, which are isomers of LSD, are much less potent than LSD itself. It also seems doubtful that it could be related to metabolic stability of the diethyl moiety. Rather, recent work, to be described later, suggests that the 5-HT_{2A} receptor might have a stereochemically defined and sterically constrained region that specifically accommodates the diethylamide moiety.

Evidence that the amide binding region in the receptor might be well defined was provided with the discovery that lysergamides of (*R*)- and (*S*)-2-aminobutane differed in their pharmacological properties (Oberlender et al. 1992). The *R*-configuration in the alkyl of amide **25** was nearly equipotent to LSD in drug discrimination in rats trained to discriminate LSD from saline. By contrast, the lysergamide with the *S*-alkylamide had only one-fourth the potency of LSD in the same assay. Using displacement of [^{125}I]DOI in rat frontal cortical homogenate, the lysergamides with the *R*- and *S*-2-aminobutane amide had affinities of 2.6 and 7.8 nM, respectively, which correlated with their in vivo potencies.



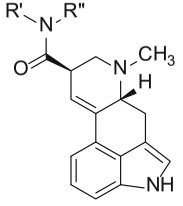
***R*-25**



***R*-26**

This approach was extended to study of a series of chiral 2-aminoalkane amides of lysergic acid, with the alkyl group extended from butyl to heptyl (Monte et al. 1995). Using [^{3}H]ketanserin displacement from rat frontal cortex homogenate to measure 5-HT_{2A} receptor affinity, the lysergamide with the *R*-configuration in the secondary alkyl amide group had higher affinity in every case than the one with the *S* configuration. As the chain length increased affinity decreased, with the *R*-2-heptylamide having a K_i of only 80 nM. The pentyl isomers of **26** were the only compounds tested in functional assays, where each isomer proved to be a full agonist in the PI hydrolysis assay, but the *S*-isomer was less potent (see Table 1). Surprisingly, however, extending the length of the 2-alkyl group of the amide *increased* 5-HT_{1A} receptor affinity, with the *R*-2-hexyl substituted amide having a K_i of 0.32 nM! Clearly, the 5-HT_{1A} receptor has greater tolerance for bulk attached to the amide.

Table 1 5-HT_{2A} 5-HT_{2C}, and 5-HT_{1A} receptor affinity and functional effects for selected lysergamides



R′	R″	5-HT^{a}_{2A} K_i (nM) (DOI)[b]	5-HT_{2A} K_i (nM) (Ket)[c]	pEC_{50} (G_q)	pEC_{50} (arrestin)	5-HT^{a}_{2C} K_i (nM) (Mes)[d]	5-HT_{2C} K_i (nM) (DOI)[b]	5-HT_{1A} K_i (nM)
Ethyl	Ethyl (LSD)	2.1 ± 0.03	13	6.93	6.69	30	7.8	1.1 ± 0.3
H	*R*-2-Butyl (**25**)	2.6 ± 0.4	18	6.67	7.07	19	15	2.8
H	*S*-2-Butyl	7.8 ± 0.2	21	6.69	6.67	36	8.6	5.9
H	*R*-2-Pentyl (**26**)	4.5 ± 0.5	10	6.28	5.63	18	5.5	1.4
H	*S*-2-Pentyl	34 ± 2	29	6.26	5.44	52	25	7.4
H	*R*-2-Hexyl	16 ± 2	16	5.58	6.03	16	2	1.1
H	*S*-2-Hexyl	55 ± 7	21	5.75	5.29	35	9.7	5.1
H	*R*-2-Heptyl	80 ± 9	13	5.34	7.13	23	5.1	1.4
H	S-2-Heptyl	360 ± 20	35	5.41	5.83	47	17	4.2
H	3-Pentyl	8 ± 0.2	17	6.48	6.02	36	9.6	5.8
H	Isopropyl	1.4	15	7.19	6.94	31	6.4	5.1
H	*tert*-Butyl	33	468	<5	5.65	60	23	163
H	*R*-α-Methylbenzyl	2.3	19	5.86	7.48	16	12	2.8
H	*S*-α-Methylbenzyl	5.5	55	5.58	5.19	82	25	14
Methyl	*R*-2-Butyl	3.2	4.9	6.24	7.02	37	6	8.6
Methyl	*S*-2-Butyl	4.7	6.5	6.06	6.06	81	34	15

(continued)

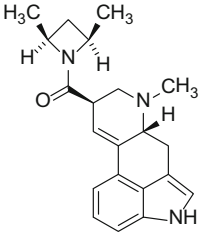
Table 1 (continued)

R′	R″	5-HT$^{a}_{2A}$ K_i (nM) (DOI)[b]	5-HT$_{2A}$ K_i (nM) (Ket)[c]	pEC$_{50}$ (G_q)	pEC$_{50}$ (arrestin)	5-HT$^{a}_{2C}$ K_i (nM) (Mes)[d]	5-HT$_{2C}$ K_i (nM) (DOI)[b]	5-HT$_{1A}$ K_i (nM)
Ethyl	*R*-2-Butyl	2.8	3.3	6.99	6.49	25	7.6	6.9
Ethyl	*S*-2-Butyl	5.2	4.3	6.83	6.56	42	7.9	12
Methyl	Isopropyl	3.2 ± 0.1	6.6	6.71	6.84	53	15	8.5
Ethyl	Isopropyl	10	6.9	6.14	6.71	25	6.2	10
Isopropyl	Isopropyl	9.1	9	5.73	5.94	47	12	35
Allyl	Allyl	8.9	2.85	6.10	6.12	27	11	17
Ethyl	*n*-Propyl	7	4.2	6.20	6.00	48	7.6	11
Ethyl	2,2,2-Trifluoroethyl	1.6 ± 0.03	4.8	5.79	6.46	1.8 ± 0.2	10	21
Ethyl	2-Methoxyethyl	7.1 ± 0.4	9	6.25	5.94	7.8 ± 0.5	7.6	20
cis-2,3-Dimethylazetidide (**27**)		7.9 ± 0.85	10	6.27	6.99	23 ± 2.9	4.4	7.5
R,R-trans-2,3-Dimethylazetidide (**28**)		21 ± 4	10	6.42	6.21	130 ± 11	58	13
S,S-trans-2,3-Dimethylazetidide (**29**)		8.3 ± 1.7	6.2	6.60	7.06	6.5 ± 0.15	2	4.6
cis-2,5-Dimethylpyrrolidide		27 ± 1	6.4	6.11	6.59	11.2 ± 0.5	15	9.4
cis-2,6-Dimethylpiperidide		7.9	5.3	5.81	6.75	31	3.5	5.9
Pyrrolidide		12.2 ± 0.2	57	7.20	6.83	6.1 ± 0.5	29	6.6
Piperidide		2.6 ± 0.1	21	6.66	7.25	2.3 ± 0.1	14	4
Morpholide		16.2 ± 1.8	62	7.14	6.23	51 ± 2.0	16	8.8

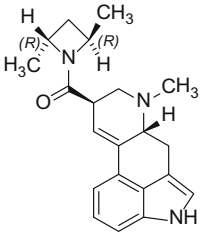
PDSP screening data at human receptors unless otherwise specified; [a]Values with SEM are from Parrish (Parrish 2006) [b][^{125}I]DOI; [c][^{3}H]ketanserin; [d][^{3}H] mesulergine

Tests in rats trained to discriminate LSD from saline showed that full substitution occurred with the *R*-2-pentyl lysergamide **26**, but not with the *S*-pentyl, hexyl, or heptyl compounds. In vitro affinities observed at the rat 5-HT_{2A} receptor parallel these in vivo results.

To test the hypothesis that the receptor might have a region that was optimally complementary to the *N,N*-diethylamide, the synthesis and testing of conformationally constrained 2,3-dimethylazetidine amides of lysergic acid was carried out (Nichols et al. 2002). These dimethylazetidines exist in three isomeric forms: the 2,3-*cis* meso isomer **27**, the *R,R-trans* **28,** and the *S,S-trans* **29** isomers. The amide of each of these was prepared from lysergic acid and tested. In the drug discrimination assay in rats trained to discriminate the effects of LSD, *S,S-trans* azetidide **24** had potency most similar to LSD. As shown in Table 1, the *S,S* congener **29** had an affinity and potency profile most comparable to LSD. *R,R* isomer **28** had two–threefold lower affinity at the 5-HT_{2A} receptor and 50–60-fold lower affinity at the 5-HT_{2C} receptor. Cis compound **27** differed from the *S,S*-isomer in that it had about fourfold lower affinity at the 5-HT_{2C} receptor. Although the *S,S*-isomer had about one-half the potency of LSD in activating phosphoinositide hydrolysis through the 5-HT_{2A} receptor, the *R,R* isomer and cis compound were 8–12-fold less potent.



27



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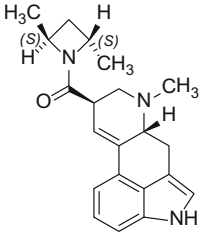


29

Virtual docking of LSD, **28**, and **29** into an in silico agonist-activated model of the 5-HT_{2A} receptor revealed that the diethyl groups of LSD nestle into a region that is bounded by a number of residues near the extracellular face of the receptor (Juncosa 2011). Further, extracellular loop 2 (EL2) was observed to interact with the diethylamide moiety. In particular, Leu-229 in EL2 was found to be critical for this interaction (McCorvy 2012). The conformation of EL2 was very similar after docking either LSD or *S,S*-isomer **29**, whereas EL2 was significantly displaced (ca. 4 Å at Leu-229) by docking of *R,R*-**28**. After docking of LSD, followed by molecular dynamics and minimization, the conformations adopted by the ethyl groups were observed to mirror the configurations in *S,S*-**29**. Curiously, the receptor appears to have evolved to be complementary to the diethyl moiety of LSD in a specific conformation.

3.2 *N(6)-Alkyl Modifications of LSD*

One other structural modification that has led to potent psychedelics is replacement of the *N*(6)-methyl of LSD with a variety of other alkyl groups (Hoffman and Nichols 1985). In a rat drug discrimination assay, in animals trained to discriminate LSD from saline, the *N*(6)-allyl derivative had about twice the potency of LSD itself. The *N*(6)-ethyl was about 1.6-fold more potent than LSD, with the *N*(6)-*n*-propyl being essentially comparable in potency to LSD. The *N*(6)-isopropyl had about 40% of the potency of LSD, with the *N*(6)-*n*-butyl having approximately 10% of the potency of LSD. Neither norLSD (*N*(6)=H), or *N*(6)-2-phenethyl-norLSD gave full substitution in the rats. Anecdotal human experiments then confirmed that the *N*(6)-allyl (AL-LAD) and *N*(6)-ethyl (ETH-LAD) congeners were psychoactive in man at doses that were not all that different from LSD itself, but the two compounds had psychopharmacology that was different from that of LSD (Shulgin and Shulgin 1997). The same source reported that the *N*(6)-n-propyl was much less active, with an oral dose in the range of 100–200 μg. The *N*(6)-propynyl (pargy-LAD) had some activity at 160 μg, and the *N*(6)-*n*-butyl was reported to do "something" at 500 μg. The *N*(6)-2-phenethyl congener was inactive up to 500 μg. These human reports, although anecdotal, do generally parallel the results obtained in the drug discrimination tests.

4 Ergolines as "Research Chemicals"

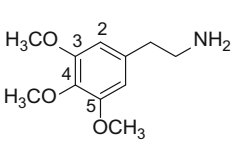
Interestingly, several LSD analogues have recently appeared on the "research chemical" market. Compound **29** has been distributed as "LSZ," and the (*N*) 1-propionyl derivative of LSD, "1P-LSD" also has been reported. 1P-LSD had never been described in the chemical literature and was an unknown compound prior to its appearance as a new psychoactive substance (NPS). It was hypothesized to be a prodrug of LSD, and when incubated with human serum at 37 °C LSD was detected by LC–MS analysis after a variety of exposure times (Brandt et al. 2016). *N*(6)-ethyl-norLSD (ETH-LAD) also has appeared on the research chemical market, as has *N*(6)-allyl-norLSD (AL-LAD) (Brandt et al. 2017).

5 Phenethylamines and Related Congeners

The phenethylamines are the most extensively explored class of psychedelics largely due to the relatively facile synthesis of phenethylamines. To complement this discussion, the reader is encouraged to read an earlier review on this topic (Nichols 1981), and also a recent review on phenethylamine 5-HT_{2A} agonists (Blaazer et al. 2008).

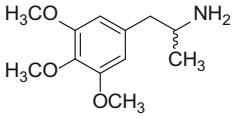
Mescaline **30**, is the prototype for this class. It is a simple 3,4,5-trimethoxyphenethylamine first isolated from the peyote cactus, *Lophophora williamsii*, at the end of the nineteenth century by chemist/pharmacologist Dr. Arthur Heffter (Heffter 1898). It is an orally active hallucinogen in man, but has very low potency, a typical dose of the sulfate salt being in the range 250–400 mg. The earliest modification to the structure of mescaline was the introduction of an α-methyl into the side chain, giving compound **31**, known as TMA (Hey 1947; Peretz et al. 1955) This compound was the first example of a very large class generically referred to as "substituted amphetamine" hallucinogens. From 1964 to 1969, Dr. Alexander Shulgin carried out an early series of experiments, moving the methoxy ring substituents to different positions. These experiments established that the most potent hallucinogenic amphetamines had the 2,4,5-ring-substitution pattern (Shulgin et al. 1969). Moving the 3-methoxy of TMA to the 2-position afforded TMA-2 **32**.

Additional studies were summarized by Shulgin in 1978 (Shulgin 1978), with a much more comprehensive treatise published on this subject in 1991 (Shulgin and Shulgin 1991). Although no receptor or animal data were reported by the Shulgins in this latter compendium, it does list human dosages and qualitative psychopharmacological effects for a large number of substituted phenethylamines. Studies of many of these compounds in other laboratories have shown that active compounds in man generally have high affinity and are agonists or partial agonists at the 5-HT_{2A} receptor. Much of those data will be cited in the following discussion.



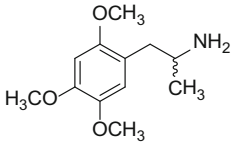
Mescaline

30



TMA

31



TMA-2

32

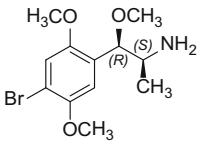
The introduction of the α-methyl into the phenethylamine side chain creates a chiral center, and thus the substituted amphetamine type psychedelics have two optical isomers, or enantiomers. An asymmetric synthesis was developed that allowed the facile preparation of the enantiomers of a large number of ring-substituted amphetamines (Nichols et al. 1973). Aldous et al. (1974) later reported a method for chemical resolution of the enantiomers by recrystallization of *N*-benzyloxycarbonyl-L-phenalanine-*p*-nitrophenyl esters. These developments preceded the era of modern molecular biology, and affinity and potency of enantiomers at receptors could not be reported at that time. Some of the assays used then

were highly correlated with in vivo hallucinogenic activity in humans, and today we know the effects in those assays are mediated by activation of serotonin 5-HT_{2A} receptors. Thus, one can probably infer that much of the early structure–activity data for hallucinogenic agents reflects agonist activity at that receptor.

R-(−) enantiomers of substituted hallucinogenic amphetamines are most potent in humans, and also are more potent than their *S*-(+) antipodes in activating the human 5-HT_{2A} receptor. This stereochemistry is reversed from that of unsubstituted amphetamine, where the (*S*)-(+)-enantiomer is the more potent psychostimulant. In dog peripheral vasculature, however, the *S*-(+)-isomers of hallucinogenic amphetamines are more potent in producing smooth muscle contraction (Cheng et al. 1974).

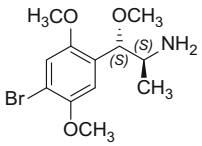
5.1 Beta-Oxygenated Phenethylamines

The effect of beta-oxygenation on the 5-HT_{2A} agonist properties of DOB has been studied by Glennon et al. (2004). All four possible stereoisomers of beta-oxygenated amphetamines were studied. As shown below, 1*R*,2*R* stereoisomer **36** had the highest affinity at the 5-HT_{2A} receptor.



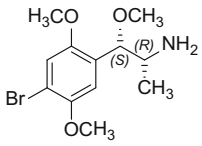
(1*S*,2*R*)
Ki 17.4 nM

33



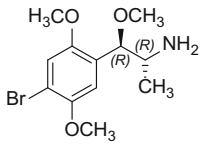
(1*S*,2*S*)
Ki 6 nM

34



(1*R*,2*S*)
Ki 0.8 nM

35



(1*R*,2*R*)
Ki 0.3 nM

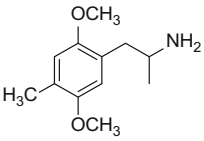
36

Compounds with the *R* stereochemistry at the alpha-carbon have highest affinity in the beta-unsubstituted amphetamines, so it is perhaps not surprising that the highest affinity compounds have the *R* stereochemistry at that position. In a cell-based Ca^{2+} mobilization assay, the 1*R*,2*R* stereoisomer **36** had an E_{max} of 93%, whereas the other isomers were partial agonists, with efficacies varying from 31 to 54%. The analogous beta-hydroxy compounds were both less potent and less efficacious, although the 1*R*,2*R* beta-hydroxy analogue fully substituted in a drug discrimination task in rats trained to discriminate DOM from saline. These data are consistent with an earlier report of analogous beta-oxygenated compounds producing hallucinogen-like effects in man (Lemaire et al. 1985).

5.2 Ring Substituents

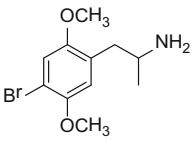
After Shulgin had established that the 2,4,5-substitution pattern was optimal for hallucinogenic activity, extensive work followed to establish the range of substituent types that could be tolerated on the ring. It might be noted, however, that 2,4,5-trimethoxyphenethylamine, an isomer of mescaline, lacks mescaline-like effects in man (Shulgin 1978). Although that particular substitution requires an α-methyl in the side chain to be active, we shall see that replacing the 4-methoxy with other groups does afford active compounds, including many that lack the α-methyl group. As a general rule, 2,5-dimethoxy substituents provide optimal hallucinogenic activity, as well as receptor affinity and efficacy. An early drug discrimination study in rats suggests that the 2-methoxy, but not the 5-methoxy, may be replaced by an OH group (Glennon et al. 1982b).

A relatively hydrophobic substituent at the 4-position in 2,4,5- or 3,4,5-substituted molecules affords the most potent compounds. The earliest example of this effect was seen in the potency of the 4-methyl compound, DOM (**37**, STP), which was about ten times more potent than the methoxy congener TMA-2 **32**. The 4-bromo and 4-iodo compounds, **38** and **39**, respectively, had even higher potency.



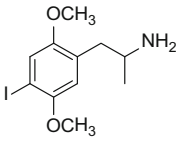
DOM

37



DOB

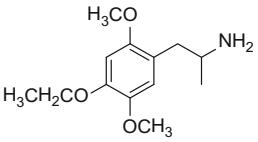
38



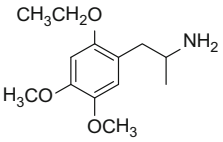
DOI

39

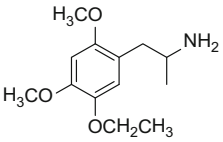
The importance of this substitution pattern is dramatically illustrated by a comparison of the three 2,4,5-substituted isomeric dimethoxy-monoethoxy amphetamines. The 2,5-dimethoxy-4-ethoxy compound (MEM **40**) has good clinical activity, whereas the 2-ethoxy-4,5-dimethoxy **41** 2,4-dimethoxy-5-ethoxy **42** and congeners did not (Shulgin 1968; Nichols et al. 1984b).



MEM **40**



EMM **41**



MME **42**