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

Contents

1 Introduction 2
2 Tryptamines 3
2.1 Ring Substituents 4
2.2 N-Alkylation 7
2.3 Side Chain Alkylation 8
3 Ergolines 9
3.1 Amide Modifications of Lysergic Acid Derivatives 11

D.E. Nichols (✉)
Division of Chemical Biology and Medicinal Chemistry, University of North Carolina, Chapel Hill, NC 27514, USA
e-mail: drdave@purdue.edu

Curr Topics Behav Neurosci (2017) 36: 1–43
DOI 10.1007/7854_2017_475
Published Online: 26 March 2017

3.2 N(6)-Alkyl Modifications of LSD 16
4 Ergolines as "Research Chemicals" 16
5 Phenethylamines and Related Congeners 16
5.1 Beta-Oxygenated Phenethylamines 18
5.2 Ring Substituents 19
5.3 Methoxy Mimics—Benzofuran and Benzopyran Analogues 22
5.4 Effect of Side Chain Alpha-Alkylation 25
6 Identifying the "Active" Conformation of the Phenethylamines 27
6.1 Effect of an N-Benzyl Group 30
6.2 The Active Conformation of N-Benzylphenethylamines 33
7 Modeling the Receptor–Ligand Interaction 34
8 Conclusion 35
References 36

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

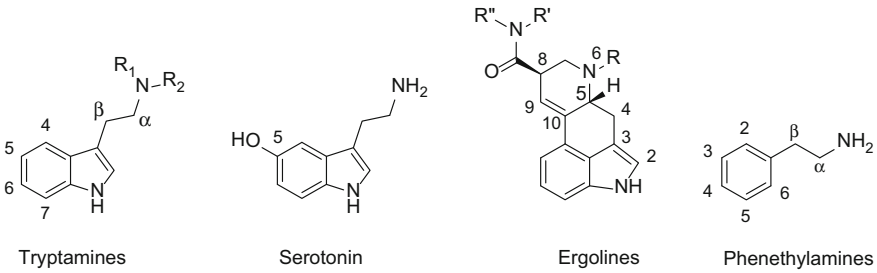


Fig. 1 Comparison of the structure of the neurotransmitter serotonin, with the three basic chemotypes of classic serotonergic hallucinogens

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

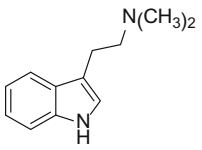
Tryptamines are the chemotypes that most closely resemble the natural neurotransmitter serotonin (5-hydroxytryptamine; 5-HT). Ergolines can essentially be considered to be rigidified tryptamines. Although LSD is the most well-known psychedelic, only a very few structural modifications can be made to 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.

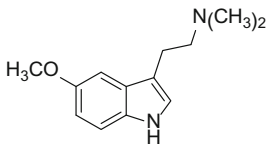
2.1 Ring Substituents

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.

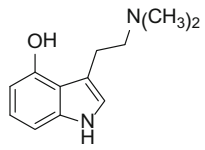
For tryptamines, 5-HT_2 agonist (and psychedelic) activity is generally enhanced by substitution with an oxygen atom at the 4- or 5-position. As an example, *N,N*-dimethyltryptamine (DMT **1**) has a reported K_i of 75 nM in rat brain cortical homogenate (McKenna et al. 1990). Adding a 5-methoxy (**2**)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



1



2

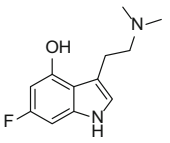


3

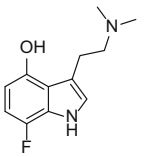
Five decades ago it was reported that 6-fluoro-*N,N*-diethyltryptamine (6-F-DET) lacked activity as a hallucinogen (Kalir and Szara 1963). It was recently found that it did not possess LSD- or DOI-like activity in a drug discrimination paradigm in rats (Blair et al. 2000). The affinity of 6-F-DET at 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.

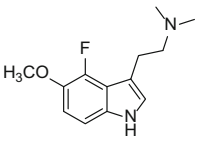
2000). Fluorination of psilocin in the 6- or 7-positions gave compounds with essentially identical affinity at the rat 5-HT_{2A} receptor, and reduced by about one-half compared with psilocin itself. Adding a fluorine to 5-MeO-DMT at either the 4- or 6-position had no significant effect on E_{max}, but 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.



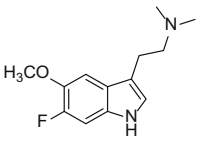
4



5

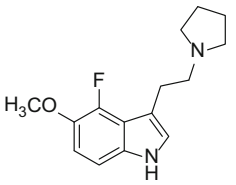


6



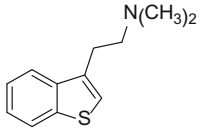
7

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).

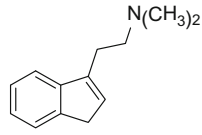


8

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.

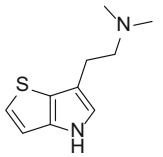


9

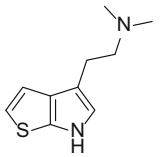


10

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.

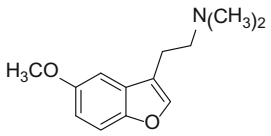


11

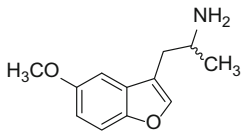


12

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**.



13

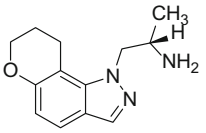


14

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

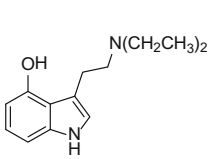
to discriminate the hallucinogen DOM from saline, **15** produced full substitution, with an ED_{50} of 0.05 mg/kg. Similarly, it produced full substitution in monkeys trained to discriminate DOM from saline, with an ED_{50} of 0.04 mg/kg, comparable to the potent 5-$HT_{2A/2C}$ agonist DOI.



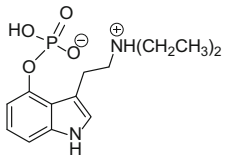
15, AL-38022A

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).



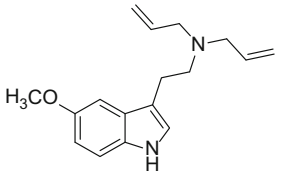
16



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.

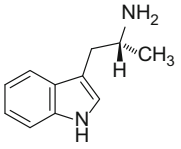


18

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).

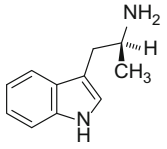
2.3 Side Chain Alkylation

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**

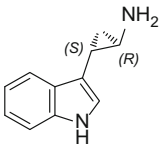


S-(+)-AMT

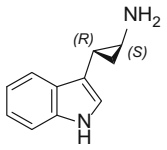
(*S*)-**19**

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**

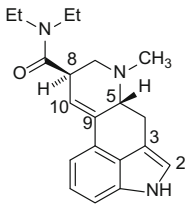
Another variation on side alkylation was provided in a study of *trans*-2-(indol-3-yl)-cyclopropylamines **20** (Vangveravong et al. 1998). Although the (1*R*,2*S*)-(−)- enantiomer of **20** had highest affinity at human 5-HT_{2A} and 5-HT_{2B} sites, the (1*S*,2*R*)-(+)- isomer unexpectedly had higher 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

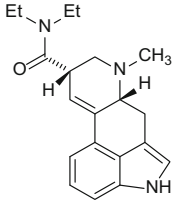
The tetracyclic ergoline molecules are ultimately derived from ergot alkaloids, products of the ergot fungus, of the genus *Claviceps*. From the perspective of psychedelic 5-HT_{2A} agonists, the most important one is lysergic acid diethylamide

(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).

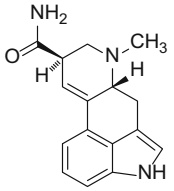
The 9,10-double bond of LSD is apparently crucial for its psychedelic action, and reducing it abolishes hallucinogenic activity (Stoll and Hofmann 1955; Hofmann 1968). Reduced 9,10-dihydro-LSD is still relatively planar, like LSD, so the reason(s) for the loss of activity is unclear (Nakahara et al. 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.

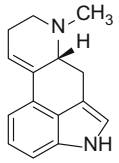
Replacing the *N*(6)-methyl group of LSD with longer alkyl groups results in compounds that in some cases are more potent than LSD in vivo in rodent behavior and which in some cases have potency comparable to, or slightly greater than LSD in humans (Hoffman and Nichols 1985; Shulgin and Shulgin 1997). 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.



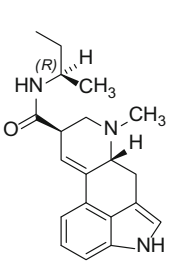
23



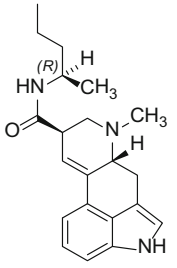
24

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.



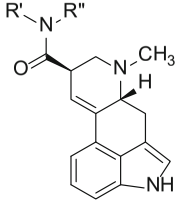
***R*-25**



***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)

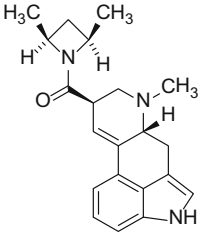
Table 1 (continued)

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

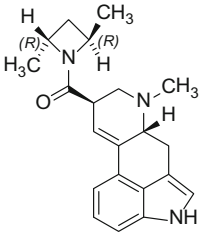
PDSP screening data at human receptors unless otherwise specified; [a]Values with SEM are from Parrish (Parrish 2006) [b][^{125}I]DOI; [c][^{3}H]ketanserin; [d][^{3}H] mesulergine

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.

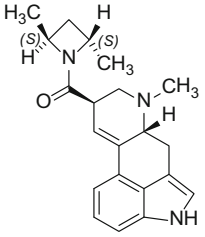
To test the hypothesis that the receptor might have a region that was optimally complementary to the *N,N*-diethylamide, the synthesis and testing of conformationally constrained 2,3-dimethylazetidine amides of lysergic acid was carried out (Nichols et al. 2002). These dimethylazetidines exist in three 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



28



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"

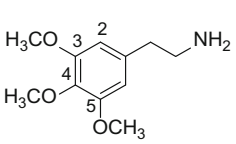
Interestingly, several LSD analogues have recently appeared on the "research chemical" market. Compound **29** has been distributed as "LSZ," and the (*N*) 1-propionyl derivative of LSD, "1P-LSD" also has been reported. 1P-LSD had never been described in the chemical literature and was an unknown compound 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).

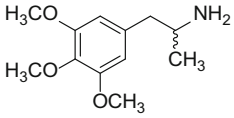
Mescaline **30**, is the prototype for this class. It is a simple 3,4,5-trimethoxyphenethylamine first isolated from the peyote cactus, *Lophophora williamsii*, at the end of the nineteenth century by chemist/pharmacologist Dr. Arthur Heffter (Heffter 1898). It is an orally active hallucinogen in man, 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.



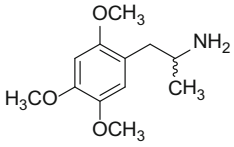
Mescaline

30



TMA

31



TMA-2

32

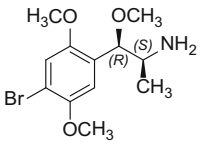
The introduction of the α-methyl into the phenethylamine side chain creates a chiral center, and thus the substituted amphetamine type psychedelics have two optical isomers, or enantiomers. An asymmetric synthesis was developed that allowed the facile preparation of the enantiomers of a large number 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).

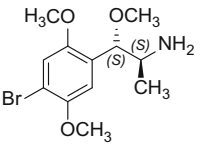
5.1 Beta-Oxygenated Phenethylamines

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.



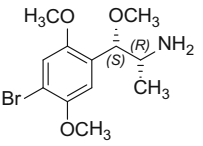
(1*S*,2*R*)
Ki 17.4 nM

33



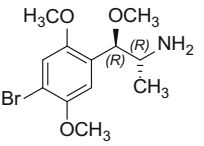
(1*S*,2*S*)
Ki 6 nM

34



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

35



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

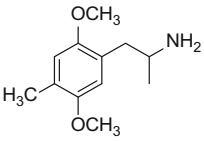
36

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

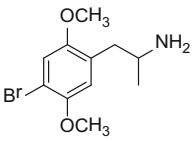
After Shulgin had established that the 2,4,5-substitution pattern was optimal for hallucinogenic activity, extensive work followed to establish the range of substituent types that could be tolerated on the ring. It might be noted, however, that 2,4,5-trimethoxyphenethylamine, an isomer of mescaline, 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.



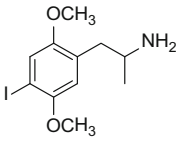
DOM

37



DOB

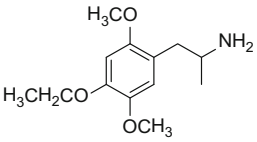
38



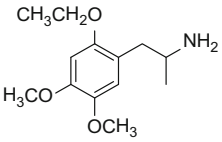
DOI

39

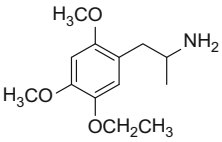
The importance of this substitution pattern is dramatically illustrated by a comparison of the three 2,4,5-substituted isomeric dimethoxy-monoethoxy amphetamines. The 2,5-dimethoxy-4-ethoxy compound (MEM **40**) has good clinical activity, whereas the 2-ethoxy-4,5-dimethoxy **41** 2,4-dimethoxy-5-ethoxy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



MEM **40**

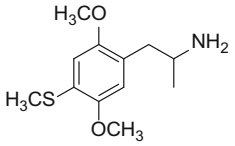


EMM **41**



MME **42**

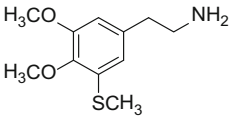
As a similar example, placing a 4-alkylthio substituent at the 4-position gives very active compounds, whereas a methylthio at either the 2- or 5-positions markedly attenuates activity (Jacob et al. 1977). In a rabbit hyperthermia assay, 2,5-dimethoxy-4-methylthio amphetamine **43** had about one-half the potency of DOM (**37**) (Nichols and Shulgin 1976). By contrast, replacing the 2- or 5-methoxy groups with a methylthio afforded much less active compounds (Jacob and Shulgin 1983). Nevertheless, the 5-methylthio analogue had nearly twice the potency of the 2-methylthio compound, indicating some greater receptor tolerance at the 5-position for an atom other than oxygen. Nonetheless, anything other than an oxygen atom at the 2- and 5-positions is very deleterious to activity. The 2- and 5-methoxy groups of DOM (**37**) and its 4-ethyl congener DOET also were individually replaced with methylthio groups. Again, the resulting 2- or 5-thio analogues suffered a dramatic loss of potency (Jacob and Shulgin 1983).



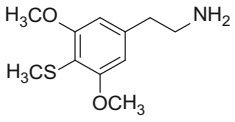
43

Possible explanations for these findings could be that the receptor has hydrogen bond donor residues (e.g., serine or threonine) that interact with the 2- and 5-oxygen atoms (Braden 2007; Braden and Nichols 2007). Sulfur would not provide a good hydrogen bonding partner compared with a methoxy. Another possible explanation could be that the receptor has little tolerance for a group larger than a methoxy in the 2- and 5-positions; the van der Waals radius for oxygen is 1.52 Å, whereas the radius for sulfur is 1.8 Å. Or, both factors could be in play, with the receptor also having less tolerance for steric bulk in the region that interacts with the substituent at the 2-position.

When a parallel approach was applied to mescaline, different results were obtained. In human self-experiments the 3-methylthio compound (**44**) was rated to be about sixfold more potent than mescaline **37** (Jacob and Shulgin 1981). The 4-methylthio compound (**45**) was estimated to be about 12 times more potent than mescaline. Thus, in 3,4,5-trisubstituted compounds, activity increased when either the 3- or the 4-methoxy was replaced with methylthio, suggesting a less critical role for the 3-methoxy in mescaline analogues than the 2-methoxy in 2,4,5-substituted compounds.



44



45

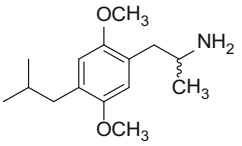
Short straight chain alkyl groups in the 4-position of 2,4,5-trisubstituted compounds have been shown to give very active compounds, including ethyl, propyl, and n-butyl, as well as the halogens Cl, Br (**38**), and I (**39**), and a variety of alkylthio substituents (Shulgin et al. 1971; Aldous et al. 1974; Nichols and Shulgin 1976). Branched alkyl groups such as isopropyl or *tert*-butyl are not tolerated (Shulgin and Shulgin 1991). The 4-trifluoromethyl substituent seems to afford a compound with the highest potency (Nichols et al. 1994).

When **39** (DOI), as well as its phenethylamine counterpart 2C-I, were prepared as their radioactive ^{125}I-labeled 4-Iodo congeners, they proved useful as radioligands to label 5-$HT_{2A/2C}$ receptors (Johnson et al. 1987; Glennon et al. 1988; McKenna et al. 1989; Johnson et al. 1990). Indeed, [^{125}I]DOI (**39**) is now widely used as an agonist radioligand to label the serotonin 5-HT_{2A} receptor. Its theoretical specific activity of 2000 Ci/mmol allows the compound to be used to detect low levels of receptor protein. [^{131}I]-labeled **39** also was briefly examined as a potential imaging agent (Braun et al. 1977), and ^{82}Br and ^{77}Br isotopically labeled versions of DOB **38**, were suggested to be useful as brain-scanning agents (Sargent et al. 1975).

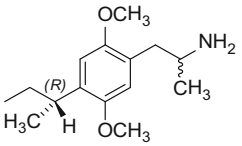
What role does a relatively hydrophobic 4-substituent play? It likely contributes in a number of ways to the overall biological activity of these molecules. First of all, it increases the overall hydrophobicity of the molecule so that it partitions better into the central nervous system (Barfknecht and Nichols 1975). That may be the major factor operating for 3,4,5-substituted mescaline analogues that have more hydrophobic substituents in the 4-position (Nichols and Dyer 1977). There is, however, a limitation to the size and bulkiness that this substituent can possess. For 2,4,5-substituted compounds there appears to be a steric limitation for linear alkyl groups of only about three carbon atoms before activity drops off (Nichols et al. 1977). By contrast, a polar moiety such as OH, NH_2, and COOH at the 4-position gives compounds with very low affinity (K_i > 25,000 nM) (Seggel et al. 1990). The latter study also examined compounds with long lipophilic 4-substituents such as *n*-hexyl and *n*-octyl. These longer alkyl groups gave antagonist molecules with high affinities at [^{3}H]ketanserin-labeled sites, whereas smaller alkyl groups gave agonist molecules.

If the 4-substituent is an alkyl group, branching adjacent to the aromatic ring is not tolerated. For example, 2,5-dimethoxy-4-isobutylamphetamine **46** (DOIB) demonstrated significant activity in a rat drug discrimination task, in animals trained to discriminate LSD from saline. DOIB had only about one-third the activity of DOM in humans, with a dose in the 10 to 15 mg range (Shulgin and Shulgin 1991). By contrast, the 2-butyl homolog was about one-third less potent, but also failed to produce full substitution in the rats. The active oral dose in man is reported to be 25–30 mg (Shulgin and Shulgin 1991). In vitro examination of *R* and *S* stereochemistry in the 2-butyl group by displacement of [^{125}I]DOI from rat frontal cortical homogenate revealed identical affinities (K_i values) of 7.8 nM for both isomers (Oberlender et al. 1995). Drug discrimination tests of the two isomers in LSD-trained rats revealed that the *R* isomer (**47**) was only slightly more potent than the *S* (**48**) (ED_{50} of 3.1 vs. 4.8 μmol, respectively). The conclusion is that there is

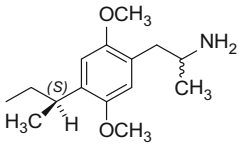
no chiral discrimination by the receptor in the region of the 4-substituent, and that branching in the 4-alkyl group proximal to the aryl ring is detrimental to activity.



46



47



48

Large bulky alkyl groups at the 4-position, such as isopropyl or *tert*-butyl, lead to inactive compounds (Glennon et al. 1981, 1982a; Glennon and Rosecrans 1982; Oberlender et al. 1984). Not surprisingly, therefore, aryl groups attached at the 4-position also gave antagonists, generally with low affinity (Trachsel et al. 2009). Interestingly, however, when a 3-phenylpropyl substituent was introduced at this position, the compound was reported to be a weak partial agonist (Dowd et al. 2000).

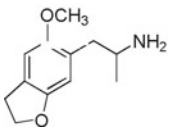
The 2,5-dioxygenation pattern coupled with a hydrophobic 4-substituent that meets certain size and hydrophobicity criteria appears optimal to give the most active compounds. Certain structural modifications to this basic pharmacophore also can lead to antagonists with high affinity at the 5-HT_{2A} receptor (Rangisetty et al. 2001).

Although the 4-substituent can have an overall effect on pharmacokinetics and increasing brain penetration, it must be playing other important roles. The correlation between activity and 4-substituent lipophilicity, as well as limitations on the length and bulk of the substituent would be consistent with the presence of a complementary hydrophobic region within the 5-HT_{2A} receptor orthosteric binding domain. The location of this putative region has not yet been elucidated, but it is evident from simulated docking studies (Chambers and Nichols 2002; Isberg et al. 2011) that it should lie somewhere within the vicinity of transmembrane helices 5 and/or 6. Although mutagenesis studies indicate that indoles (i.e., the indole NH) engage Ser-242 in the human 5-HT_{2A} receptor, this residue is apparently not important for binding of 2,5-dimethoxy-substituted phenethylamines (Braden and Nichols 2007).

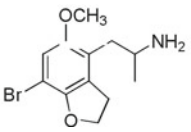
5.3 *Methoxy Mimics—Benzofuran and Benzopyran Analogues*

The need for the 2- and 5-oxygen substituents in the phenethylamine hallucinogens raises the question as to what role they may be playing. The most compelling hypothesis is that they serve as hydrogen bond acceptors in the orthosteric ligand

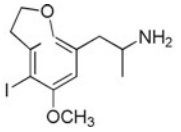
binding site. If true, there should then be a dependence on the oxygen unshared electron pair orientations. "Tethering" the 5-methoxy of DOM (**37**) to the 4-position, leading to compound **49**, reduced activity nearly 20-fold in an in vivo rat drug discrimination assay, compared to DOM. (Nichols et al. 1986) When the 5-methoxy of DOB was tethered to the 6-position, however, compound **50** was as potent as DOM (Nichols et al. 1991). Affinity at the [^{125}I]DOI-labeled 5HT$_{2A}$ receptor in rat prefrontal cortex was consistent with the in vivo findings, where the affinity of **49** was 488 nM and **50** was 3.1 nM. These results were consistent with the hypothesis that the oxygen electrons needed to project in a specific direction for proper receptor interaction.



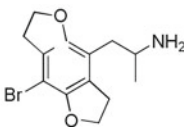
49



50

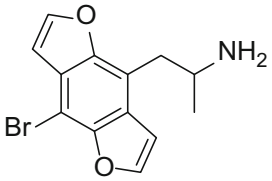


51



52

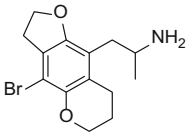
Tethering the 2-methoxy into the 3-position to afford compound **51** also led to a potent compound (Monte et al. 1996). Tethering both the 2- and 5-methoxy functions into dihydrofuran rings increased potency even further, as typified by compound **52**, which had an affinity of 0.48 nM at the cloned human 5-HT$_{2A}$ receptor (Monte et al. 1996; Chambers et al. 2001). Although it might be expected that aromatization of the dihydrofuran rings would reduce the hydrogen bonding donor capacity of the furan oxygen atoms, in fact compound **53** was even more potent than its tetrahydrofuranyl congeners, and represents one of the most potent known phenethylamines (Parker et al. 1998). Although the hydrogen bonding potential may be reduced for the oxygen atoms, the large hydrophobic surfaces of the fully aromatic furan rings may be complementary to the relatively hydrophobic interior of the receptor orthosteric binding site.



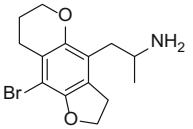
53

These studies naturally led the question: what is the optimal size of the oxygen-containing heterocyclic rings? To address this question, hybrid benzofuran/benzopyran molecules were designed and tested (Schultz et al. 2008). Replacing the 2-methoxy with a dihydrofuran and the 5-methoxy with a dihydropyran gave compound **54**, which had only slightly higher 5-HT$_{2A}$ affinity than

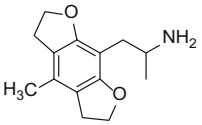
did isomer **55** (3.6 nM vs. 5.3 nM, respectively). Compound **54** also was fourfold more potent than **55** in stimulating functional PI turnover. Parallel results were observed in vivo, in rats trained to discriminate LSD from saline, where **54** was three times more potent than **55**. Mutagenesis studies had shown that the 5-methoxy of the phenethylamines likely served as a hydrogen bond acceptor from Ser-239 near the top of transmembrane helix 5 of the receptor (Braden and Nichols 2007). Using that information to guide virtual docking of phenethylamines into a homology model of the 5-HT_{2A} receptor (Chambers and Nichols 2002) directs the 2-methoxy downward toward an intracellular region inside the binding site. Thus, there may well be less space, and hence less steric tolerance for modifications to the 2-methoxy. It should be mentioned that incorporating both oxygen atoms into six-membered dihydropyran rings, to provide hexahydrobenzodipyrans, gave a compound that was about ten-fold less active in a rat drug discrimination task, in rats trained to discriminate LSD from saline. Similarly, the affinity of the dipyrano compound at the rat 5-HT_{2A} receptor was 3.87 nM, whereas the affinity of the difurano homolog was 0.48 nM, approximately paralleling the rat discrimination data (Whiteside et al. 2002).



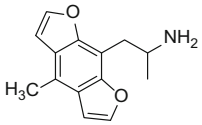
54



55

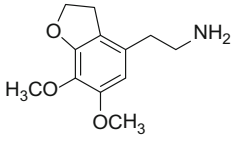


56

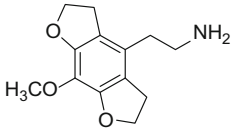


57

Application of a similar approach to 2,6-dimethoxy-4-methylamphetamine likewise resulted in significant potency enhancement in bisdihydrofuran **56**, with a further increase in the fully aromatic **57** (Chambers et al. 2002). For example, the affinity of 2,6-dimethoxy-4-methylamphetamine at the cloned rat 5-HT_{2A} receptor was 49 nM, whereas the affinities of **56** and **57** were 6.3 and 1.8 nM, respectively.



58

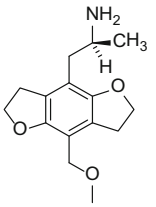


59

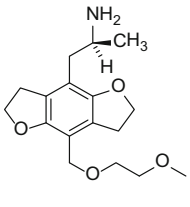
When this strategy was applied to 3,4,5-substituted mescaline analogues, however, activity of the tethered compounds was reduced. Although affinity at the 5-HT_{2A} receptor increased compared to mescaline, the monocyclic furano compound **58** lost both efficacy and mescaline-like potency in a rat behavioral model, and difuranyl compound **59** was even less active (Monte et al. 1997). These divergent results suggest that the binding pose of 2,4,5-substituted compounds differs from that of 3,4,5-substituted compounds. Mutagenesis studies support that

conclusion, as mutations of polar residues in the orthosteric binding site of the human 5-HT_{2A} receptor have different effects, depending on whether the ligand being examined is a 2,4,5- or a 3,4,5-substituted molecule (McCorvy 2012).

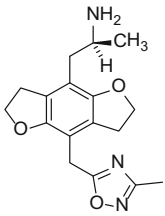
It also has been found that 5-HT_{2A} agonists can reduce intraocular pressure (May et al. 2003b). That finding led to identification of novel 5-HT_{2A} agonists that might be useful to treat glaucoma, but which lacked the hallucinogenic effects that are characteristic of most 5-HT_{2A} agonists. A number of benzodifurans were developed with 4-alkoxymethyl and oxadiazole methyl substituents with high 5-HT_{2A} agonist activity. The purpose of these hydrophilic substituents was to retain 5-HT_{2A} agonist activity, while minimizing penetration into the CNS. Compounds **60**, **61**, and **62** were reported as promising candidates (Feng et al. 2007).



60



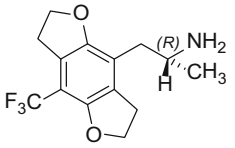
61



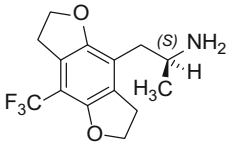
62

5.4 *Effect of Side Chain Alpha-Alkylation*

Racemic amphetamines have approximately the same affinity at the human 5-HT_{2A} receptor as their nonmethylated phenethylamine congeners (Johnson et al. 1987; Glennon et al. 1992; Nash et al. 1994; Parrish et al. 2005). At the rat 5-HT_{2A} receptor Parrish et al. (2005) reported that EC_{50}s for stimulating phosphoinositide hydrolysis were virtually identical for phenethylamines and amphetamines, although efficacy for PI hydrolysis was higher for racemic amphetamines. Substituted amphetamine enantiomers, however, have significantly greater affinity, potency, and efficacy in their *R*-(−) enantiomer than in the *S*-(+) antipode. For the enantiomers of DOB (**38**) and DOI (**39**), the difference in EC_{50} was about fourfold higher for the *R* isomer than for the *S*. When the 4-substituent was a CF_3, however, and the two methoxy groups were constrained into dihydrofuran rings (*R*- or *S*-**63**), the difference in *affinity* for the enantiomers was more than 40-fold, but the difference in EC_{50} was less than twofold. In the PI turnover assay *R* enantiomers were about 50% more potent than the *S* enantiomers.



***R*-63**

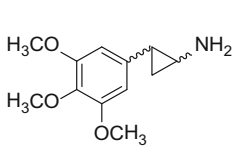


***S*-63**

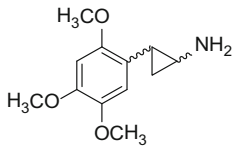
Based on molecular modeling studies, Parrish et al. (2005) speculated that only in *R* enantiomers could the alpha-methyl group interact with Phe-340$^{(6.52)}$ in the receptor through van der Waals interactions, possibly explaining the basis for the higher potency and efficacy of the (*R*) enantiomers. It should be mentioned that the SAR of ring-substitution patterns described for substituted amphetamine hallucinogens parallel those for their non-α-methylated phenethylamine congeners. In general, the phenethylamines are less potent and have a shorter duration of action than the alpha-methylated amphetamines with the same ring substitutions. The phenethylamines seem to be considered more pharmacologically benign in vivo than their amphetamine counterparts, and thus are more popular on the illicit drug market than the substituted amphetamines.

For use as a radioligand, a racemic alpha-methyl compound had no advantage over the simpler achiral phenethylamine. That is, [^{125}I]2C-I gave results comparable to [^{125}I]DOI when used as a radioligand to label 5-HT$_{2A/2C}$ receptors (Johnson et al. 1990).

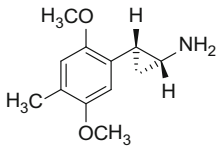
Incorporating the alpha methyl into a cyclopropane ring gives substituted 2-phenylcyclopropylamines with high in vitro and in vivo potency. The cis and trans cyclopropane analogues of mescaline were first reported by Cooper and Walters, who found that trans compound **64** produced an effect in rodents qualitatively resembling mescaline, but with a potency slightly greater than mescaline (Walters and Cooper 1968; Cooper and Walters 1972).



64



65



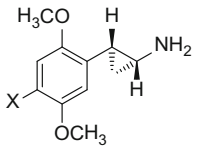
(1*R*,2*S*)-(-)-**66**

Subsequently Aldous et al. (1974) explored cyclopropane analogues of several substituted amphetamines. Using an assay that measured hyperthermia in rabbits, as well as assessing changes in cat EEG, *trans*-2,4,5-trimethoxy compound **65** and *trans*-2,5-dimethoxy-4-methyl compound **66** (DMCPA) had hallucinogen-like activity, with about 20 and 35%, respectively, of the activity of DOM (**37**).

In a later study of the 1*R*,2*S* and 1*S*,2*R* enantiomers of **66**, in three different behavioral responses, DMCPA had activity nearly comparable to DOM (**37**) (Nichols et al. 1978). The (1*R*,2*S*)-(−)-isomer **66** was most potent, with the (1*S*,2*R*)-(+)-antipode being almost inert. Both racemic and the (−) isomer of **66** produced a robust response in the rabbit hyperthermia assay, with the (+) isomer not being different from saline (Nichols et al. 1979). When [^{125}I]2C-I was used to label the

5-$HT_{2A/2C}$ receptor in rat cortical homogenate, affinities of the (1*R*,2*S*)-(−) and (1*S*,2*R*)-(+) enantiomers were about ten-fold different, 2.2 and 21.6 nM, respectively. The K_i of (*R*)-DOI was virtually identical (2.6 nM) to (−)-DMCPA (Johnson et al. 1990). Adding methyl groups to the cyclopropane ring abolished activity (Jacob and Nichols 1982).

The cyclopropyl analogues of DOB (**38**) and DOI (**39**) also have been prepared and receptor affinities and functional potencies measured (Pigott et al. 2012). The two analogues were resolved into their enantiomers and compared with the enantiomers of DOI (**39**). Affinities of the racemic compounds **67** and **68** at the 5-HT_{2A} receptor were five–sixfold higher than those of the open chain analogues **38** and **39**. Assay measuring calcium release at the cloned human 5-HT_{2A} receptor revealed an EC_{50} and E_{max} for (−)-**39** of 3.3 nM and 87%, whereas (−)-**67** had values of 2 nM and 89%, respectively. The bromo compound was somewhat less active, with (−)-**68** having an EC_{50} of 6.3 nM and an E_{max} of 76%.

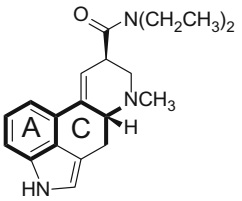


67, X= I
68, X= Br,

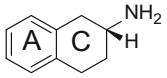
Expansion of a cyclopropane to a cyclobutane ring led to a 50–75-fold loss of in vivo activity (Nichols et al. 1984a). Coupled with a variety of studies that have examined conformationally constrained analogues of phenethylamine type hallucinogens, it is reasonable to speculate that the orthosteric binding site within the receptor is sterically restricted around the side chain.

6 Identifying the "Active" Conformation of the Phenethylamines

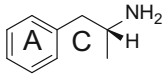
To understand how phenethylamines and tryptamines may dock in the same receptor site, it can sometimes be useful to identify the active binding conformation through the use of rigid analogues. That is, if a flexible ligand can be conformationally constrained through the use of carefully selected tethers, and if the constrained molecule has high biological activity, it is usually inferred that the constrained conformation is a good representation of how the more flexible ligand binds to the receptor.



LSD



(*R*)-2-aminotetralin

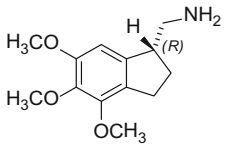


(*R*)-amphetamine

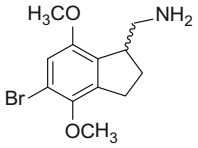
A substantial amount of work was carried out in the late 1940s and 1950s to identify the structural element within ergoline molecules (e.g., ergotamine) responsible for their oxytocic and adrenergic activities. The challenges faced by total chemical synthesis of substituted ergoline structures prompted evaluation of much simpler and more synthetically tractable molecules. For example, several early groups focused efforts on structures such as substituted aminotetralins, which they envisioned as representing the A and C rings of the ergolines. When later workers began to study the substituted phenethylamines and amphetamines, and particularly after the more active enantiomer of the amphetamines was shown to have stereochemistry similar to the 5*R* stereochemistry of LSD, this idea was further reinforced. Nonetheless, such a simple analogy is probably not justified, as many studies of rigid analogues of phenethylamines have subsequently shown. The substituted A-ring of the phenethylamines simply mimics, in some unknown way, the indole nucleus of LSD or serotonin. Today we understand that receptors are flexible and dynamic. There is no reason that the structural elements within the orthosteric binding site of the 5-HT_{2A} receptor that engage LSD or the tryptamines must necessarily be the same ones that engage the substituted phenethylamines. Even so, study of rigid analogues of phenethylamines may afford insight into how ligands as structurally different as LSD, tryptamines, and phenethylamines can activate the same receptor.

For phenethylamines (and tryptamines) the side chain has two major rotatable bonds, giving two degrees of conformational freedom: the aryl-Cβ bond, and the Cβ-Cα bond. The trans phenylcyclopropylamines discussed earlier (i.e., **65–68**) lock the Cβ-Cα bond into an approximately trans orientation. Their high activity clearly indicates that the side chain of phenethylamines must exist in a trans extended conformation. Earlier studies had found that 2-aminotetralin and 2-aminoindan derivatives lacked activity, therefore indicating that the side chain probably could not reside in the plane of the aryl ring (Coutts and Malicky 1974; Nichols et al. 1974; Monte et al. 1998). When mescaline was virtually docked into a homology model of an in silico "activated" model of the 5-HT_{2A} receptor (Chambers and Nichols 2001), it was observed that tethering the side chain β carbon back into the aryl ring would afford an aminomethylindan that would closely mimic the docked conformation of mescaline. Interestingly, the modeling also predicted that the active absolute configuration of that molecule would be *R,* because the *S* enantiomer did not provide an acceptable docked pose. Synthesis and

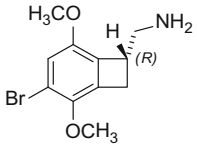
subsequent testing of the two enantiomers demonstrated that the *R* enantiomer **69** had 70 nM affinity at the cloned human 5-HT_{2A} receptor. By contrast, the affinity of the *S* enantiomer was only 1120 nM (McLean et al. 2006a). In a functional assay for activation of IP_3 accumulation, the *R* enantiomer had an EC_{50} of 3200 nM, whereas the EC_{50} for the *S* enantiomer was >50,000 nM. The efficacy of the *R* enantiomer was essentially identical to that of mescaline.



69



70



(*R*)-71

When this strategy was applied to a potentially more potent template, a 2,5-dimethoxy-4-bromo substituted ring to afford molecule **70**, its affinity at the human 5-HT_{2A} receptor was slightly greater than that of **69**, but was much lower than the unconstrained phenethylamine. This somewhat surprising finding may indicate that the binding conformation of 3,4,5-substituted compounds differs somewhat from that of 2,4,5-substituted compounds.

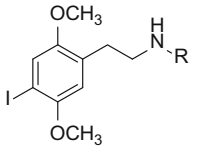
When, however, the five-membered ring was contracted to a four-membered benzocyclobutene, the highly potent **71** (TCB-2) was obtained (McLean et al. 2006b). Virtual docking of the enantiomers of **71** into a homology model of the receptor also revealed that only the *R* enantiomer gave an acceptable pose. After resolution and pharmacological evaluation, *R* benzocyclobutene **71** indeed was found to have a K_i of 0.26 nM, whereas the K_i of the *S*-isomer was only 42 nM. In a functional test for IP_3 accumulation, the EC_{50} for the *R* enantiomer was 18 nM, with an E_{max} of 97%. The EC_{50} for the *S* enantiomer was only 460 nM. The contrast between the biological activities of **70** and **71** is not readily explained. The dihedral angle for the aryl-Cβ bond in aminomethylindanes is approximately 100°, whereas for the aminomethylbenzocyclobutene the angle is about 117°. The steric footprint of the five-membered ring is somewhat greater than for the four-membered ring, which could also be a contributing factor. The basis for the difference between the effect of rigidification of mescaline and 2,5-dimethoxy-4-bromophenethylamine is worth further study.

In the two-lever drug discrimination assay in rats trained to discriminate LSD or DOI from saline *R*-**71** had potency comparable to each training drug. LSD had an ED_{50} of 38 nmol/kg in LSD-trained rats, whereas *R*-**71** was slightly more potent than LSD, with an ED_{50} of 24 nmol/kg! No substitution occurred with the *S* enantiomer of **71** at doses up to 250 nmol/kg. These results support the hypothesis that the phenethylamine side chain of hallucinogens binds to the receptor in a conformation displaced out of the aryl ring plane.

6.1 *Effect of an N-Benzyl Group*

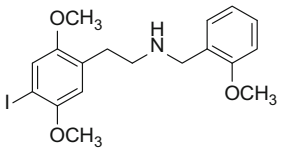
Although the most active tryptamine hallucinogens are *N,N*-dialkylated, the phenethylamines generally cannot tolerate even a single *N*-substitution. Even small groups such as methyl or ethyl (see Table 2) abolish their hallucinogenic activity. It was quite remarkable, therefore, when Heim and coworkers reported that *N*-benzyl groups afforded compounds with remarkable affinity and potency (Heim et al. 1999; Elz et al. 2002; Heim 2003). An oxygen atom at the ortho position of the *N*-benzyl group enhanced activity further (Braden et al. 2006). When an alpha-methyl was introduced into the side chain, affinity dropped about 20-fold. Thus, a side chain alpha-methyl enhances potency of ring-substituted phenethylamines, but is deleterious when an *N*-benzyl is added to the amino group. Compound **72** (25I-NBOMe) is the most studied of these *N*-benzylated analogues. The high potency of this compound, as well as the 4-chloro and 4-bromo analogues has made them very attractive for sale as "research chemicals," often being distributed on blotter papers and deceptively labeled as being LSD. Surprisingly, the NBOMe-type compounds are not orally active, but are typically administered so that they are absorbed through buccal tissues. Sadly, several deaths have occurred as a result of use of NBOMe-type compounds (Poklis et al. 2014; Walterscheid et al. 2014; Nikolaou et al. 2015). In the past, lethality has not been associated with ingestion of hallucinogens, so it is not clear whether death has resulted from toxic amounts of pure drug, or whether there is some inherent toxicity not seen with other hallucinogens. The iodo compound **72**, as well as its 4-bromo and 4-chloro analogues have recently been placed into Schedule 1 of the controlled substances act.

Table 2 Effects of phenethylamine *N*-substituents on affinity at several serotonin receptor subtypes (Braden et al. 2006)



R	h5-HT_{2A} K_i (nM)	r5-HT_{2A} K_i (nM)	h5-HT_{2C} K_i (nM)	r5-HT_{2C} K_i (nM)	h5-HT_{1A} K_i (nM)
H	0.73 ± 0.06	0.65 ± 0.07	1.82 ± 0.20	1.22 ± 0.03	123 ± 24
CH_3	1907 ± 254	1286 ± 64	nd	206 ± 34	247 ± 23
n-Pr	1295 ± 151	734 ± 30	nd	656 ± 127	879 ± 64
Benzyl	0.25 ± 0.05	0.31 ± 0.03	1.08 ± 0.24	1.15 ± 0.90	2205 ± 106
BOMe[a]	0.044 ± 0.006	0.09 ± 0.010	0.43 ± 0.08	0.13 ± 0.02	1696 ± 311

Values are mean ± SEM. *nd* not determined
[a]*N*-(ortho-methoxybenzyl)



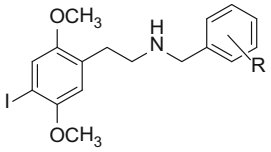
72

The exceptionally high 5-HT_{2A} affinity of **72** made it useful as a radioligand for receptor binding studies (Nichols et al. 2008), and its 4-bromo analogue has found application as a ^{11}C-labeled PET ligand for in vivo imaging studies of the 5-HT_{2A} receptor (Ettrup et al. 2010, 2011). It appears that an aryl group with a hydrogen bond *acceptor*, such as an ether, gives highest activity (see Table 3). Additional modifications of the *N*-benzyl moiety are given in Tables 3 and 4.

Ettrup et al. (2011) examined a series of eight *N*-benzyl substituted phenethylamines for potential as PET imaging agents. The most favorable profile (*i.e.,* largest target-to-background binding ratio) was obtained with the 4-bromo-*N*-(2-methoxybenzyl) compound (25B-NBOMe), which was designated [^{11}C] Cimbi-36. This compound was described as "the most promising candidate for investigation of 5-HT_{2A} receptor binding in the living human brain with PET."

An extensive structure–activity analysis of 48 *N*-benzylphenethylamines by Hansen et al. (2014) identified a highly selective 5-HT_{2A} agonist in the *N*-benzyl series, compound **73** (25CN-NBOH), with the 4-cyano substituent on the ring, and

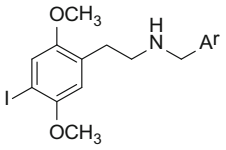
Table 3 Effect of benzyl group substitution on affinity of *N*-benzylphenethylamines (Braden 2007)



R	h5-HT_{2A} K_i (nM)	r5-HT_{2A} K_i (nM)	h5-HT_{2C} K_i (nM)	r5-HT_{2C} K_i (nM)
2-OCH_3	0.044 ± 0.006	0.09 ± 0.01	0.43 ± 0.08	0.13 ± 0.02
2-OH	0.061 ± 0.012	0.12 ± 0.02	0.13 ± 0.01	0.21 ± 0.02
2-CN	nd	276 ± 65	23.2 ± 4.1	nd
2-$CONH_2$	1.18 ± 0.22	0.84 ± 0.1	nd	0.73 ± 0.09
2-CH_2OH	0.79 ± 0.05	0.44 ± 0.03	nd	0.43 ± 0.01
2-CF_3	1.31 ± 0.15	nd	nd	nd
4-CF_3	205 ± 44	nd	nd	nd
2-F	0.26 ± 0.05	0.28 ± 0.04	2.36 ± 0.41	0.85 ± 0.11
4-F	37.3 ± 6.0	nd	nd	nd
2,3-OCH_2O	0.049 ± 0.008	0.193 ± 0.022	1.7 ± 0.23	0.41 ± 0.07
3,4-OCH_2O	0.69 ± 0.05	nd	nd	nd
2-OH-4,5-OCH_2O	0.82 ± 0.17	nd	nd	nd

Values are mean ± SEM. *nd* not determined

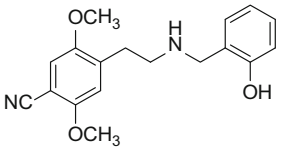
Table 4 Effect of other *N*-aryl groups on phenethylamine affinity (Braden 2007)



Ar	h5-HT_{2A} K_i (nM)	r5-HT_{2A} K_i (nM)	r5-HT_{2C} K_i (nM)
2-furyl	nd	0.78 ± 0.12	0.99 ± 0.1
2-thienyl	1.02 ± 0.09	0.45 ± 0.09	0.59 ± 0.06
2-pyridyl	nd	3.45 ± 0.7	5.81 ± 1.14
3-indolyl	nd	2.67 ± 0.49	11.8 ± 1.7
1-naphthyl	nd	1.07 ± 0.11	14.0 ± 1.5
2-naphthyl	4.83 ± 0.55	3.74 ± 0.52	176 ± 30
2,3-dihydrobenzofuran-7-yl	0.026 ± 0.006	nd	nd

Values are mean ± SEM. *nd* not determined

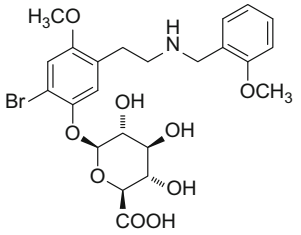
the *N*-2-hydroxybenzyl moiety. It had affinity at the human 5-HT_{2A} receptor of 1.3 nM and at the rat 5-HT_{2C} receptor of 132 nM. In functional measures of ability to stimulate inositol phosphate production, **73** had an EC_{50} at the 5-HT_{2A} receptor of 2.1 nM, and at the 5-HT_{2C} receptor of 190 nM. In the mouse head twitch response, an animal behavioral model that has a general correlation with human hallucinogenic activity, **73** elicited the head twitch, but was less potent than DOI (Fantegrossi et al. 2015). In mice trained to discriminate DOI from saline in a two-lever drug discrimination task, **73** engendered 55% generalization to the DOI training dose. These effects were blocked by the selective 5-HT_{2A} antagonist M100907, indicating that the behavioral action of **73** was mediated by 5-HT_{2A} receptor activation.



73

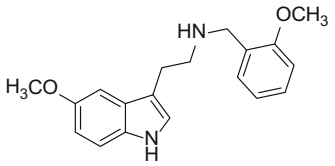
The absence of oral activity for the *N*-benzylphenethylamines led Leth-Petersen et al. (2014) to examine the metabolism of a series of NBOMe compounds in human liver microsomes. What they observed was high intrinsic clearance, indicative of high first pass metabolism of the compounds if given orally. In a subsequent study from the same laboratory (Leth-Petersen et al. 2016), an in vivo experiment in pigs confirmed the predicted high first pass metabolism, with the principle phase II metabolism being rapid O-demethylation of the 5-methoxy on the core phenethylamine ring. This hydroxyl metabolite was then rapidly conjugated to provide the 5-*O*-glucuronide **74**. Both metabolic steps (demethylation and

glucuronidation) were very fast, with the authors reporting that only minute levels of the intermediate phenolic demethylation product were present at any time point, with the glucuronide being eliminated much slower from the plasma. The authors propose that the glucuronide metabolite may be toxic, and responsible for the adverse effects of NBOMe compounds in humans. Another possibility is that some individuals may lack the P450 isozyme necessary for the rapid *O*-demethylation and that the persistence of the very potent parent compound may lead to toxicity.



74

An *N*-benzyl moiety also enhances 5-HT_{2A} activity in the tryptamine series, for example compounds such as **75**. A series of 15 analogues of **75** had affinities at the human 5-HT_{2A} receptor ranging from 0.6 to 11 nM (Nichols et al. 2015). Broad receptor screening showed that they had highest affinities for the 5-HT_2 family of receptors, but demonstrated no selectivity for 5-HT_{2A} versus 5-HT_{2C} receptors. In functional assays measuring Ca^{+2} mobilization the compounds generally had an E_{max} between 70 and 90%. Only some of the compounds were active in the mouse head twitch assay, however, but for those that were active, linear regression analysis revealed a significant correlation between the pED_{50} for the head twitch and the pEC_{50} for functional potency in the rat 5-HT_{2A} receptor.

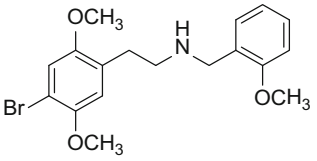


75

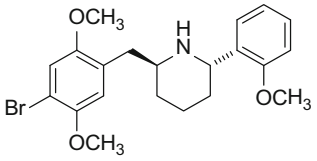
6.2 *The Active Conformation of N-Benzylphenethylamines*

In an attempt to identify the active binding conformation of the *N*-benzylphenethylamines, a series of nine of conformationally constrained analogues of **76** was prepared (Juncosa et al. 2013). The most potent of these analogues was *S,S* enantiomer **77**. This compound, as the racemate, had an EC_{50} of 74 nM and an E_{max} of 73% for PI hydrolysis through activation of the human 5-HT_{2A} receptor. In drug

discrimination experiments in rats trained to discriminate LSD from saline, **77** had an ED_{50} of 0.41 μmol/kg. Furthermore, (*S,S*)-(−)-**77** had 124-fold selectivity for the 5-HT_{2A} receptor versus the 5-HT_{2C} receptor, using antagonist radioligands to measure affinity.

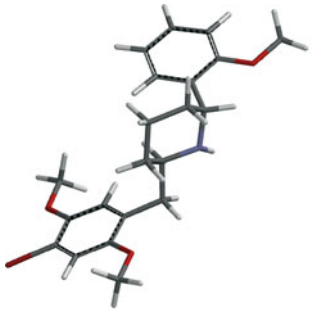


76

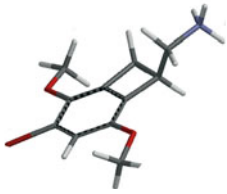


(*S,S*)-77

The absolute configuration of (*S,S*)-**77** was determined by X-ray crystallography of the molecule with an *N*-acyl chiral auxiliary. If one uses the stereochemistry of (*R*)-**71** discussed earlier, to define the side chain orientation as anti and in a plane approximately perpendicular to the aromatic ring plane, then given its relatively constrained structure, an active binding orientation for (*S,S*)-**77** might be envisioned as shown below.



(*S,S*)-77



(*R*)-71

7 Modeling the Receptor–Ligand Interaction

The serotonin 5-HT_{2A} receptor is a member of the family A G protein-coupled receptors. It is known that it is comprised of seven membrane-spanning helical segments, and a short helical segment at the C-terminus that lies parallel to the inner leaflet of the membrane. The next step in the evolution of our understanding of SAR for hallucinogens will be the solution of a crystal structure for the 5-HT_{2A} receptor, and of particular importance would be a phenethylamine type ligand.

There have been tremendous strides in receptor protein crystallography over the past 15 years, with nearly two dozen unique structures being characterized

(Costanzi and Wang 2014; Yin et al. 2014). Most recently, the structures of the serotonin 5-HT_{1B} and 5-HT_{2B} receptors with ergotamine bound have been solved (Wacker et al. 2013; Wang et al. 2013). Yet, as of the date of this writing in mid-2016, the structure of the 5-HT_{2A} receptor still has not been solved. One may speculate that the binding of LSD to the 5-HT_{2A} receptor will closely resemble the ergotamine pose in the 5-HT_{2B} receptor crystal structure, but unfortunately there is nothing in that structure that indicates how phenethylamines might bind. If the 5-HT_{2A} receptor could be crystallized with a phenethylamine hallucinogen molecule bound inside, the underlying basis for much of what we know about the SAR of psychedelics should become apparent. In particular, we might finally understand how a phenethylamine can be complementary to a receptor that has evolved to accommodate an indole.

Homology models have so far been the best approach to understanding how hallucinogens bind to their receptors. The earliest in silico-activated homology model of the human 5-HT_{2A} receptor was proposed by Chambers and Nichols (2002) and was developed by in silico activation of the crystal structure of bovine rhodopsin. Virtual docking with various 5-HT_{2A} agonist ligands allowed the formulation of a number of hypotheses about the ligand binding site, which were subsequently validated by site-directed mutagenesis and ligand testing (Braden et al. 2006; Braden and Nichols 2007). Those studies allowed the design of new agonist ligands, including the prediction of their active enantiomers (McLean et al. 2006a, b). Isberg et al. (2011) have recently developed an in silico-activated model of the 5-HT_{2A} receptor from the published structure of the β_2-adrenergic receptor. Nonetheless, these homology models have failed to explain the basis for the binding poses for different ring-substitution patterns in the phenethylamines. In particular, studies have demonstrated that mutations of polar residues in helices 3, 5, and 6 have different consequences for 2,5-dimethoxy versus 3,5-dimethoxy-substituted compounds (McCorvy 2012). Further, homology models have failed to indicate why the 4-position substituent in the 2,4,5-substituted compounds is so important. These, and other aspects of hallucinogen SAR, will likely become apparent when the crystal structure of the 5-HT_{2A} receptor is ultimately solved.

8 Conclusion

The SAR of psychedelics, which are serotonin 5-HT_{2A} receptor agonists or partial agonists, are now well developed for the three major chemotypes of ligands. There were early attempts to identify structural similarities between phenethylamines and tryptamines that might account for the ability of phenethylamines to engage the 5-HT_{2A} receptor, but those were unsuccessful. Despite our current level of understanding, intriguing questions still remain. It is still a mystery why LSD is such a potent hallucinogen when it appears to have rather unremarkable in vitro pharmacological properties. Slight variations in amide substituents of lysergic acid

amides have profound effects on the psychopharmacology of lysergamides, and an explanation for this phenomenon is not yet evident.

A complicating factor in the psychopharmacology of hallucinogens is the fact that receptors can couple to multiple effectors, and that different agonists can produce different intracellular biochemical signals. Thus, specific agonists with particular substitution patterns may be able selectively to activate a subset of effectors, a phenomenon now known as functional selectivity (Urban et al. 2007). It seems likely that functional selectivity can at least partially explain some of the differences reported for the human psychopharmacology of hallucinogens. To date there has been no attempt to correlate specific signaling pathways with any aspect of human psychopharmacology of hallucinogens. In addition, Ray (2010) has pointed out that psychedelics often have numerous off-target receptors that could have physiological relevance. A complete and comprehensive study of a particular molecule that involved looking not only at the affinity for each potentially significant brain receptor, but also their functional potency at the most likely signaling pathways would be a herculean task, yet might ultimately be necessary to understand fully the molecular pharmacology of psychedelics.

Clearly, the field of research on psychedelics still offers tremendous challenges. It is a sad fact that there is no significant government funding for this work, despite many emerging clinical studies now demonstrating potential medical utility for these fascinating molecules.

References

Aldous FA, Barrass BC, Brewster K, Buxton DA, Green DM, Pinder RM, Rich P, Skeels M, Tutt KJ (1974) Structure-activity relationships in psychotomimetic phenylalkylamines. J Med Chem 17:1100–1111

Bach NJ, Hall DA, Kornfeld EC (1974) Descarboxylysergic acid (9,10-didehydro-6-methylergoline). J Med Chem 17:312–314

Barfknecht CF, Nichols DE (1975) Correlation of psychotomimetic activity of phenethylamines and amphetamines with 1-octanol-water partition coefficients. J Med Chem 18:208–210

Baxter GS, Murphy OE, Blackburn TP (1994) Further characterization of 5-hydroxytryptamine receptors (putative 5-HT2B) in rat stomach fundus longitudinal muscle. Br J Pharmacol 112:323–331

Bennett JP Jr, Snyder SH (1976) Serotonin and lysergic acid diethylamide binding in rat brain membranes: relationship to postsynaptic serotonin receptors. Mol Pharmacol 12:373–389

Blaazer AR, Smid P, Kruse CG (2008) Structure-activity relationships of phenylalkylamines as agonist ligands for 5-HT(2A) receptors. ChemMedChem 3:1299–1309

Blair JB, Marona-Lewicka D, Kanthasamy A, Lucaites VL, Nelson DL, Nichols DE (1999) Thieno[3,2-b]- and thieno[2,3-b]pyrrole bioisosteric analogues of the hallucinogen and serotonin agonist N, N-dimethyltryptamine. J Med Chem 42:1106–1111

Blair JB, Kurrasch-Orbaugh D, Marona-Lewicka D, Cumbay MG, Watts VJ, Barker EL, Nichols DE (2000) Effect of ring fluorination on the pharmacology of hallucinogenic tryptamines. J Med Chem 43:4701–4710

Braden MR (2007) Towards a biophysical understanding of hallucinogen action. PhD Dissertation

Braden MR, Nichols DE (2007) Assessment of the roles of serines 5.43(239) and 5.46(242) for binding and potency of agonist ligands at the human serotonin 5-HT2A receptor. Mol Pharmacol 72:1200–1209

Braden MR, Parrish JC, Naylor JC, Nichols DE (2006) Molecular interaction of serotonin 5-HT2A receptor residues Phe339(6.51) and Phe340(6.52) with superpotent N-benzyl phenethylamine agonists. Mol Pharmacol 70:1956–1964

Brandt SD, Kavanagh PV, Westphal F, Stratford A, Elliott SP, Hoang K, Wallach J, Halberstadt AL (2016) Return of the lysergamides. Part I: Analytical and behavioural characterization of 1-propionyl-d-lysergic acid diethylamide (1P-LSD). Drug Test Anal 8:891–902

Brandt SD, Kavanagh PV, Westphal F, Elliott SP, Wallach J, Colestock T, Burrow TE, Chapman SJ, Stratford A, Nichols DE, Halberstadt AL (2017) Return of the lysergamides. Part II: Analytical and behavioural characterization of N6 -allyl-6-norlysergic acid diethylamide (AL-LAD) and (2′S,4′S)-lysergic acid 2,4-dimethylazetidide (LSZ). Drug Test Anal 9:38–50

Braun U, Shulgin AT, Braun G, Sargent T III (1977) Synthesis and body distribution of several iodine-131 labeled centrally acting drugs. J Med Chem 20:1543–1546

Brimblecombe RW, Pinder RM (1975) Hallucinogenic agents. Wright-Scientechnica, Bristol

Chambers JJ, Nichols DE (2001) A model of the human 5-HT_{2A} receptor based on constrained homology. Great Lakes/Central Regional American Chemical Society Meeting

Chambers JJ, Nichols DE (2002) A homology-based model of the human 5-HT2A receptor derived from an in silico activated G-protein coupled receptor. J Comput Aided Mol Des 16:511–520

Chambers JJ, Kurrasch-Orbaugh DM, Parker MA, Nichols DE (2001) Enantiospecific synthesis and pharmacological evaluation of a series of super-potent, conformationally restricted 5-HT (2A/2C) receptor agonists. J Med Chem 44:1003–1010

Chambers JJ, Kurrasch-Orbaugh DM, Nichols DE (2002) Translocation of the 5-alkoxy substituent of 2,5-dialkoxyarylalkylamines to the 6-position: effects on 5-HT(2A/2C) receptor affinity. Bioorg Med Chem Lett 12:1997–1999

Cheng HC, Long JP, Nichols DE, Barfknecht CF (1974) Effects of psychotomimetics on vascular strips: studies of methoxylated amphetamines and optical isomers of 2,5-dimethoxy-4-methylamphetamine and 2,5-dimethoxy-4-bromoamphetamine. J Pharmacol Exp Ther 188:114–123

Cooper PD, Walters GC (1972) Stereochemical requirements of the mescaline receptor. Nature 238:96–98

Corkery JM, Durkin E, Elliott S, Schifano F, Ghodse AH (2012) The recreational tryptamine 5-MeO-DALT (N, N-diallyl-5-methoxytryptamine): a brief review. Prog Neuropsychopharmacol Biol Psychiatry 39:259–262

Costanzi S, Wang K (2014) The GPCR crystallography boom: providing an invaluable source of structural information and expanding the scope of homology modeling. Adv Exp Med Biol 796:3–13

Coutts RT, Malicky JL (1974) The synthesis of Analogus of the Hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). II. Some ring-methoxylated 1-amino-and 2-aminoindanes. Can J Chem 52:381–389

Cozzi NV, Daley PF (2016) Receptor binding profiles and quantitative structure-affinity relationships of some 5-substituted-N, N-diallyltryptamines. Bioorg Med Chem Lett 26:959–964

Daldrup T, Heller C, Matthiesen U, Honus S, Bresges A, Haarhoff K (1986) Etryptamine, a new designer drug with a fatal effect. Z Rechtsmed 97:61–68

Dowd CS, Herrick-Davis K, Egan C, Dupre A, Smith C, Teitler M, Glennon RA (2000) 1-[4-(3-Phenylalkyl)phenyl]-2-aminopropanes as 5-HT(2A) partial agonists. J Med Chem 43:3074–3084

Elz S, Klass T, Heim R, Wamke U, Pertz HH (2002) Development of highly potent partial agonists and chiral antagonists as tools for the study of 5-HT2A-receptor mediated functions. Nauynn-Schmiedeberg's Arch Pharmacol 365(Suppl 1):R29

Ettrup A, Palner M, Gillings N, Santini MA, Hansen M, Kornum BR, Rasmussen LK, Nagren K, Madsen J, Begtrup M, Knudsen GM (2010) Radiosynthesis and evaluation of 11C-CIMBI-5 as a 5-HT2A receptor agonist radioligand for PET. J Nucl Med 51:1763–1770

Ettrup A, Hansen M, Santini MA, Paine J, Gillings N, Palner M, Lehel S, Herth MM, Madsen J, Kristensen J, Begtrup M, Knudsen GM (2011) Radiosynthesis and in vivo evaluation of a series of substituted 11C-phenethylamines as 5-HT (2A) agonist PET tracers. Eur J Nucl Med Mol Imaging 38:681–693

Fantegrossi WE, Gray BW, Bailey JM, Smith DA, Hansen M, Kristensen JL (2015) Hallucinogen-like effects of 2-([2-(4-cyano-2,5-dimethoxyphenyl) ethylamino]methyl)phenol (25CN-NBOH), a novel N-benzylphenethylamine with 100-fold selectivity for 5-HT(2)A receptors, in mice. Psychopharmacology 232:1039–1047

Feng Z, Mohapatra S, Klimko PG, Hellberg MR, May JA, Kelly C, Williams G, McLaughlin MA, Sharif NA (2007) Novel benzodifuran analogs as potent 5-HT2A receptor agonists with ocular hypotensive activity. Bioorg Med Chem Lett 17:2998–3002

Ginzel KH, Mayer-Gross W (1956) Prevention ofpsychological effects of d-lysergic acid diethylamide (LSD 25) by its 2-brom derivative (BOL 148). Nature 178:210

Glennon RA, Rosecrans JA (1982) Indolealkylamine and phenalkylamine hallucinogens: a brief overview. Neurosci Biobehav Rev 6:489–497

Glennon RA, Doot DL, Young R (1981) DOM and related 2,5-dimethoxy-4-alkylphenylisopropylamines: behavioral and serotonin receptor properties. Pharmacol Biochem Behav 14:287–292

Glennon RA, Young R, Rosecrans JA (1982a) A comparison of the behavioral effects of DOM homologs. Pharmacol Biochem Behav 16:557–559

Glennon RA, Young R, Rosecrans JA (1982b) Discriminative stimulus properties of DOM and several molecular modifications. Pharmacol Biochem Behav 16:553–556

Glennon RA, Seggel MR, Soine WH, Herrick-Davis K, Lyon RA, Titeler M (1988) [125I]-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane: an iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT2 serotonin receptors. J Med Chem 31:5–7

Glennon RA, Teitler M, Sanders-Bush E (1992) Hallucinogens and serotonergic mechanisms. NIDA Res Monogr 119:131–135

Glennon RA, Bondarev ML, Khorana N, Young R, May JA, Hellberg MR, McLaughlin MA, Sharif NA (2004) Beta-oxygenated analogues of the 5-HT2A serotonin receptor agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane. J Med Chem 47:6034–6041

Gorodetzky CW, Isbell H (1964) A comparison of 2,3-dihydro-lysergic acid diethylamide with LSD-25. Psychopharmacologia 6:229–233

Gupta SK, Diez E, Heasley LE, Osawa S, Johnson GL (1990) A G protein mutant that inhibits thrombin and purinergic receptor activation of phospholipase A2. Science 249:662–666

Hansen M, Phonekeo K, Paine JS, Leth-Petersen S, Begtrup M, Brauner-Osborne H, Kristensen JL (2014) Synthesis and structure-activity relationships of N-benzyl phenethylamines as 5-HT2A/2C agonists. ACS Chem Neurosci 5:243–249

Hartig PR, Kadan MJ, Evans MJ, Krohn AM (1983) 125I-LSD: a high sensitivity ligand for serotonin receptors. Eur J Pharmacol 89:321–322

Heffter A (1898) Ueber pellote. Beitrag zur chemischen und pharmakologischen kenntnis der cacteen. Naunyn Schmiedebergs Arch Exp Path Pharmacol 40:385–429

Heim R (2003) Synthese und Pharmakologie potenter 5-HT2A-Rezeptoragonisten mit *N*-2-Methoxybenzyl-Partialstruktur Entwicklung eines neen Struktur-Wirkungskonzepts. vol. Dr. rer. nat. Freien Universität Berlin, Berlin

Heim R, Pertz HH, Elz S (1999) Preparation and in vitro pharmacology of novel secondary amine-type 5-HT2A receptor agonists: from submillimolar to subnanomolar activity. Arch Pharm Pharm Med Chem 332:34

Hey P (1947) The synthesis of a new homolog of mescaline. Quart J Pharm Pharmacol 20:129–134

Hoffman AJ, Nichols DE (1985) Synthesis and LSD-like discriminative stimulus properties in a series of N(6)-alkyl norlysergic acid N, N-diethylamide derivatives. J Med Chem 28:1252–1255

Hofmann A (1968) Psychotomimetic agents. In: Burger A (ed) Drugs affecting the central nervous system. Edward Arnold, London, p 169

Hofmann A (1971) Teonanacatl and Ololuiqui, two ancient magic drugs of Mexico. Bull Narcotics XXIII:3–14

Hong SS, Young R, Glennon RA (2001) Discriminative stimulus properties of alpha-ethyltryptamine optical isomers. Pharmacol Biochem Behav 70:311–316

Huang XM, Johnson MP, Nichols DE (1991) Reduction in brain serotonin markers by alpha-ethyltryptamine (Monase). Eur J Pharmacol 200:187–190

Isberg V, Balle T, Sander T, Jorgensen FS, Gloriam DE (2011) G Protein- and agonist-bound serotonin 5-HT(2A) receptor model activated by steered molecular dynamics simulations. J Chem Inf Model 51:315–325

Jacob JN, Nichols DE (1982) Isomeric cyclopropyl ring-methylated homologues of trans-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine, an hallucinogen analogue. J Med Chem 25:526–530

Jacob P III, Shulgin AT (1981) Sulfur analogues of psychotomimetic agents. Monothio analogues of mescaline and isomescaline. J Med Chem 24:1348–1353

Jacob P III, Shulgin AT (1983) Sulfur analogues of psychotomimetic agents. 2. Analogues of (2,5-dimethoxy-4-methylphenyl)-and (2,5-dimethoxy-4-ethylphenyl)isopropylamine. J Med Chem 26:746–752

Jacob P III, Anderson G III, Meshul CK, Shulgin AT, Castagnoli N Jr (1977) Monomethylthio analogues of 1-(2,4,5-trimethoxyphenyl)-2-aminopropane. J Med Chem 20:1235–1239

Johnson MP, Hoffman AJ, Nichols DE, Mathis CA (1987) Binding to the serotonin 5-HT2 receptor by the enantiomers of 125I-DOI. Neuropharmacology 26:1803–1806

Johnson MP, Mathis CA, Shulgin AT, Hoffman AJ, Nichols DE (1990) [125I]-2-(2,5-dimethoxy-4-iodophenyl)aminoethane ([125I]-2C-I) as a label for the 5-HT2 receptor in rat frontal cortex. Pharmacol Biochem Behav 35:211–217

Juncosa JI (2011) Organic synthesis combined with molecular modeling: a powerful approach to map the functional topography of dopamine and serotonin receptors. PhD, Purdue University

Juncosa JI Jr, Hansen M, Bonner LA, Cueva JP, Maglathlin R, McCorvy JD, Marona-Lewicka D, Lill MA, Nichols DE (2013) Extensive rigid analogue design maps the binding conformation of potent N-benzylphenethylamine 5-HT2A serotonin receptor agonist ligands. ACS Chem Neurosci 4:96–109

Kalir A, Szara S (1963) Synthesis and pharmacological activity of fluorinated tryptamine derivatives. J Med Chem 6:716–719

Kantor RE, Dudlettes SD, Shulgin AT (1980) 5-methoxy-alpha-methyltryptamine (alphs, o-dimethylserotonin), a hallucinogenic homolog of serotonin. Biol Psychiatry 15:349–352

Karst M, Halpern JH, Bernateck M, Passie T (2010) The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: an open, non-randomized case series. Cephalalgia 30:1140–1144

Krebs KM, Geyer MA (1993) Behavioral characterization of alpha-ethyltryptamine, a tryptamine derivative with MDMA-like properties in rats. Psychopharmacology 113:284–287

Laban U, Kurrasch-Orbaugh D, Marona-Lewicka D, Nichols DE (2001) A novel fluorinated tryptamine with highly potent serotonin 5-HT1A receptor agonist properties. Bioorg Med Chem Lett 11:793–795

Lemaire D, Jacob P III, Shulgin AT (1985) Ring-substituted beta-methoxyphenethylamines: a new class of psychotomimetic agents active in man. J Pharm Pharmacol 37:575–577

Leth-Petersen S, Bundgaard C, Hansen M, Carnerup MA, Kehler J, Kristensen JL (2014) Correlating the metabolic stability of psychedelic 5-HT(2)A agonists with anecdotal reports of human oral bioavailability. Neurochem Res 39:2018–2023

Leth-Petersen S, Gabel-Jensen C, Gillings N, Lehel S, Hansen HD, Knudsen GM, Kristensen JL (2016) metabolic fate of hallucinogenic NBOMes. Chem Res Toxicol 29:96–100

Leuner H, Baer G (1965) Two new short-acting hallucinogens of the psilocybin group. Neuropsychopharmacol 4:471–474

May JA, Chen HH, Rusinko A, Lynch VM, Sharif NA, McLaughlin MA (2003a) A novel and selective 5-HT2 receptor agonist with ocular hypotensive activity: (S)-(+)-1-(2-aminopropyl)-8,9-dihydropyrano[3,2-e]indole. J Med Chem 46:4188–4195

May JA, McLaughlin MA, Sharif NA, Hellberg MR, Dean TR (2003b) Evaluation of the ocular hypotensive response of serotonin 5-HT1A and 5-HT2 receptor ligands in conscious ocular hypertensive cynomolgus monkeys. J Pharmacol Exp Ther 306:301–309

May JA, Dantanarayana AP, Zinke PW, McLaughlin MA, Sharif NA (2006) 1-((S)-2-aminopropyl)-1H-indazol-6-ol: a potent peripherally acting 5-HT2 receptor agonist with ocular hypotensive activity. J Med Chem 49:318–328

May JA, Sharif NA, Chen HH, Liao JC, Kelly CR, Glennon RA, Young R, Li JX, Rice KC, France CP (2009) Pharmacological properties and discriminative stimulus effects of a novel and selective 5-HT2 receptor agonist AL-38022A [(S)-2-(8,9-dihydro-7H-pyrano[2,3-g]indazol-1-yl)-1-methylethylamine]. Pharmacol Biochem Behav 91:307–314

McCorvy JD (2012) Mapping the binding site of the 5-HT2A receptor using mutagenesis and ligand libraries: insights into the molecular actions of psychedelics. In: Chemistry Medicinal, Pharmacology Molecular (eds) vol. Purdue, PhD West Lafayette, IN

McKenna DJ, Nazarali AJ, Hoffman AJ, Nichols DE, Mathis CA, Saavedra JM (1989) Common receptors for hallucinogens in rat brain: a comparative autoradiographic study using [125I]LSD and [125I]DOI, a new psychotomimetic radioligand. Brain Res 476:45–56

McKenna DJ, Repke DB, Lo L, Peroutka SJ (1990) Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. Neuropharmacology 29:193–198

McLean TH, Chambers JJ, Parrish JC, Braden MR, Marona-Lewicka D, Kurrasch-Orbaugh D, Nichols DE (2006a) C-(4,5,6-trimethoxyindan-1-yl)methanamine: a mescaline analogue designed using a homology model of the 5-HT2A receptor. J Med Chem 49:4269–4274

McLean TH, Parrish JC, Braden MR, Marona-Lewicka D, Gallardo-Godoy A, Nichols DE (2006b) 1-Aminomethylbenzocycloalkanes: conformationally restricted hallucinogenic phenethylamine analogues as functionally selective 5-HT2A receptor agonists. J Med Chem 49:5794–5803

Monte AP, Marona-Lewicka D, Kanthasamy A, Sanders-Bush E, Nichols DE (1995) Stereoselective LSD-like activity in a series of d-lysergic acid amides of (R)- and (S)-2-aminoalkanes. J Med Chem 38:958–966

Monte AP, Marona-Lewicka D, Parker MA, Wainscott DB, Nelson DL, Nichols DE (1996) Dihydrobenzofuran analogues of hallucinogens. 3. Models of 4-substituted (2,5-dimethoxyphenyl)alkylamine derivatives with rigidified methoxy groups. J Med Chem 39:2953–2961

Monte AP, Waldman SR, Marona-Lewicka D, Wainscott DB, Nelson DL, Sanders-Bush E, Nichols DE (1997) Dihydrobenzofuran analogues of hallucinogens. 4. Mescaline derivatives. J Med Chem 40:2997–3008

Monte AP, Marona-Lewicka D, Lewis MM, Mailman RB, Wainscott DB, Nelson DL, Nichols DE (1998) Substituted naphthofurans as hallucinogenic phenethylamine-ergoline hybrid molecules with unexpected muscarinic antagonist activity. J Med Chem 41:2134–2145

Murphree HB, Dippy RH, Jenney EH, Pfeiffer CC (1961) Effects in normal man of alpha-methyltryptamine and alpha-ethyltryptamine. Clin Pharmacol Ther 2:722–726

Nakada MT, Wieczorek CM, Rainbow TC (1984) Localization and characterization by quantitative autoradiography of [125I]LSD binding sites in rat brain. Neurosci Lett 49:13–18

Nakahara Y, Niwaguchi T, Ishii H (1977) Studies on lysergic acid diethylamide and related compounds. V. Syntheses of dihydrolysergic acid diethylamides and related compounds. Chem Pharm Bull (Tokyo) 25:1756–1763

Nash JF, Roth BL, Brodkin JD, Nichols DE, Gudelsky GA (1994) Effect of the R(-) and S(+) isomers of MDA and MDMA on phosphatidyl inositol turnover in cultured cells expressing 5-HT2A or 5-HT2C receptors. Neurosci Lett 177:111–115

Nichols DE (1981) Structure-activity relationships of phenethylamine hallucinogens. J Pharm Sci 70:839–849
Nichols DE (1986) Hallucinogens. In: Verderame M (ed) Handbook of CNS agents and local anesthetics. CRC Press, Inc, Boca Raton, pp 303–325
Nichols DE (2016) Psychedelics. Pharmacol Rev 68:264–355
Nichols DE, Dyer DC (1977) Lipophilicity and serotonin agonist activity in a series of 4-substituted mescaline analogues. J Med Chem 20:299–301
Nichols DE, Shulgin AT (1976) Sulfur analogs of psychotomimetic amines. J Pharm Sci 65:1554–1556
Nichols DE, Barfknecht CF, Rusterholz DB, Benington F, Morin RD (1973) Asymmetric synthesis of psychotomimetic phenylisopropylamines. J Med Chem 16:480–483
Nichols DE, Barfknecht CF, Long JP, Standridge RT, Howell HG, Partyka RA, Dyer DC (1974) Potential psychotomimetics. 2. Rigid analogs of 2,5-dimethoxy-4- methylphenylisopropylamine (DOM, STP). J Med Chem 17:161–166
Nichols DE, Shulgin AT, Dyer DC (1977) Directional lipophilic character in a series of psychotomimetic phenethylamine derivatives. Life Sci 21:569–575
Nichols DE, Pfister WR, Yim GK (1978) LSD and phenethylamine hallucinogens: new structural analogy and implications for receptor geometry. Life Sci 22:2165–2170
Nichols DE, Woodard R, Hathaway BA, Lowy MT, Yom KW (1979) Resolution and absolute configuration of trans-2-(2,5-dimethoxy-4- methylphenyl)cyclopropylamine, a potent hallucinogen analogue. J Med Chem 22:458–460
Nichols DE, Jadhav KP, Oberlender RA, Zabik JE, Bossart JF, Hamada A, Miller DD (1984a) Synthesis and evaluation of substituted 2-phenylcyclobutylamines as analogues of hallucinogenic phenethylamines: lack of LSD-like biological activity. J Med Chem 27:1108–1111
Nichols DE, Schooler D, Yeung MC, Oberlender RA, Zabik JE (1984b) Unreliability of the rat stomach fundus as a predictor of hallucinogenic activity in substituted phenethylamines. Life Sci 35:1343–1348
Nichols DE, Hoffman AJ, Oberlender RA, Riggs RM (1986) Synthesis and evaluation of 2,3-dihydrobenzofuran analogues of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane: drug discrimination studies in rats. J Med Chem 29:302–304
Nichols DE, Lloyd DH, Johnson MP, Hoffman AJ (1988) Synthesis and serotonin receptor affinities of a series of enantiomers of alpha-methyltryptamines: evidence for the binding conformation of tryptamines at serotonin 5-HT1B receptors. J Med Chem 31:1406–1412
Nichols DE, Snyder SE, Oberlender R, Johnson MP, Huang XM (1991) 2,3-Dihydrobenzofuran analogues of hallucinogenic phenethylamines. J Med Chem 34:276–281
Nichols DE, Frescas S, Marona-Lewicka D, Huang X, Roth BL, Gudelsky GA, Nash JF (1994) 1-(2,5-Dimethoxy-4-(trifluoromethyl)phenyl)-2-aminopropane: a potent serotonin 5-HT2A/2C agonist. J Med Chem 37:4346–4351
Nichols DE, Frescas S, Marona-Lewicka D, Kurrasch-Orbaugh DM (2002) Lysergamides of isomeric 2,4-dimethylazetidines map the binding orientation of the diethylamide moiety in the potent hallucinogenic agent N, N-diethyllysergamide (LSD). J Med Chem 45:4344–4349
Nichols DE, Frescas SP, Chemel BR, Rehder KS, Zhong D, Lewin AH (2008) High specific activity tritium-labeled N-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (INBMeO): a high-affinity 5-HT2A receptor-selective agonist radioligand. Bioorg Med Chem 16:6116–6123
Nichols DE, Sassano MF, Halberstadt AL, Klein LM, Brandt SD, Elliott SP, Fiedler WJ (2015) N-Benzyl-5-methoxytryptamines as potent serotonin 5-HT2 receptor family agonists and comparison with a series of phenethylamine analogues. ACS Chem Neurosci 6:1165–1175
Nikolaou P, Papoutsis I, Stefanidou M, Spiliopoulou C, Athanaselis S (2015) 2C-I-NBOMe, an "N-bomb" that kills with "Smiles". Toxicological and legislative aspects. Drug Chem Toxicol 38:113–119
Oberlender RA, Kothari PJ, Nichols DE, Zabik JE (1984) Substituent branching in phenethylamine-type hallucinogens: a comparison of 1-[2,5-dimethoxy-4-(2-butyl)phenyl]-

2-aminopropane and 1- [2,5-dimethoxy-4-(2-methylpropyl)phenyl]-2-aminopropane. J Med Chem 27:788–792

Oberlender R, Pfaff RC, Johnson MP, Huang XM, Nichols DE (1992) Stereoselective LSD-like activity in d-lysergic acid amides of (R)- and (S)-2-aminobutane. J Med Chem 35:203–211

Oberlender R, Ramachandran PV, Johnson MP, Huang X, Nichols DE (1995) Effect of a chiral 4-alkyl substituent in hallucinogenic amphetamines. J Med Chem 38:3593–3601

Parker MA, Marona-Lewicka D, Lucaites VL, Nelson DL, Nichols DE (1998) A novel (benzodifuranyl)aminoalkane with extremely potent activity at the 5-HT2A receptor. J Med Chem 41:5148–5149

Parrish JC (2006) Toward a molecular understanding of hallucinogen action. PhD, Purdue University

Parrish JC, Braden MR, Gundy E, Nichols DE (2005) Differential phospholipase C activation by phenylalkylamine serotonin 5-HT 2A receptor agonists. J Neurochem 95:1575–1584

Peretz DI, Smythies JR, Gibson WC (1955) A new hallucinogen: 3,4,5-trimethoxyphenyl-beta-aminopropane (with notes on a stroboscopic phenomenon). J Mental Sci 101:317–329

Pigott A, Frescas S, McCorvy JD, Huang XP, Roth BL, Nichols DE (2012) trans-2-(2,5-Dimethoxy-4-iodophenyl)cyclopropylamine and trans-2-(2,5-dimethoxy-4-bromophenyl)cyclopropylamine as potent agonists for the 5-HT(2) receptor family. Beilstein J Org Chem 8:1705–1709

Poklis JL, Devers KG, Arbefeville EF, Pearson JM, Houston E, Poklis A (2014) Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl] ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a traumatic death. Forensic Sci Int 234:e14–e20

Rangisetty JB, Dukat M, Dowd CS, Herrick-Davis K, Dupre A, Gadepalli S, Teitler M, Kelley CR, Sharif NA, Glennon RA (2001) 1-[2-methoxy-5-(3-phenylpropyl)]-2-aminopropane unexpectedly shows 5-HT(2A) serotonin receptor affinity and antagonist character. J Med Chem 44:3283–3291

Ray TS (2010) Psychedelics and the human receptorome. PLoS ONE 5:e9019

Repke DB, Grotjahn DB, Shulgin AT (1985) Psychotomimetic N-methyl-N-isopropyltryptamines. Effects of variation of aromatic oxygen substituents. J Med Chem 28:892–896

Rusterholz DB, Long JP, Nichols DE (1979) Effect of alpha-methyltryptamine on spontaneous activity in mice. Pharmacol Biochem Behav 10:223–227

Sargent T III, Kalbhen DA, Shulgin AT, Stauffer H, Kusubov N (1975) A potential new brain-scanning agent: 4-77Br-2,5-dimethoxyphenylisoproplamine (4-Br-DPIA). J Nucl Med 16:243–245

Schechter MD (1998) MDMA-like stimulus effects of hallucinogens in male Fawn-Hooded rats. Pharmacol Biochem Behav 59:265–270

Schultz DM, Prescher JA, Kidd S, Marona-Lewicka D, Nichols DE, Monte A (2008) 'Hybrid' benzofuran-benzopyran congeners as rigid analogs of hallucinogenic phenethylamines. Bioorg Med Chem 16:6242–6251

Seggel MR, Yousif MY, Lyon RA, Titeler M, Roth BL, Suba EA, Glennon RA (1990) A structure-affinity study of the binding of 4-substituted analogues of 1-(2,5-dimethoxyphenyl)-2-aminopropane at 5-HT2 serotonin receptors. J Med Chem 33:1032–1036

Shulgin AT (1968) The ethyl homologs of 2,4,5-trimethoxyphenylisopropylamine. J Med Chem 11:186–187

Shulgin AT (1978) Psychotomimetic Drugs: Structure-activity relationships. In: Iversen LL et al (eds) Handbook of psychopharmacology, vol 11. Plenum Press, New York, pp 243–333

Shulgin AT (1982) Chemistry of Psychotomimetics. In: Hoffmeister F, Stille G (eds) Handbook of experimental pharmacology, vol 55/III. Springer, New York, pp 3–29

Shulgin AT, Carter MF (1980) N, N-Diisopropyltryptamine (DIPT) and 5-methoxy-N, N-diisopropyltryptamine (5-MeO-DIPT). Two orally active tryptamine analogs with CNS activity. Commun Psychopharmacol 4:363–369

Shulgin A, Shulgin A (1991) PIHKAL A chemical love story. Berkeley, CA 94701: Transform Press

Shulgin AT, Shulgin A (1997) TIHKAL. The continuation. Transform Press, Berkeley
Shulgin AT, Sargent T, Naranjo C (1969) Structure–activity relationships of one-ring psychotomimetics. Nature 221:537–541
Shulgin AT, Sargent T, Naranjo C (1971) 4-Bromo-2,5-dimethoxyphenylisopropylamine, a new centrally active amphetamine analog. Pharmacology 5:103–107
Siva Sankar DV (1975) LSD: a total study. PJD Publications, Westbury
Stoll A, Hofmann A (1955) Amide der sterreoisomeren lysergsauren und dihydro-lysergsauren. Helv Chim Acta 38:421–433
Strano Rossi S, Odoardi S, Gregori A, Peluso G, Ripani L, Ortar G, Serpelloni G, Romolo FS (2014) An analytical approach to the forensic identification of different classes of new psychoactive substances (NPSs) in seized materials. Rapid Commun Mass Spectrom 28:1904–1916
Szara S (1961) 6-Hydroxylation: an important metabolic route for alpha-methyltryptamine. Experientia 17:76–77
Tomaszewski Z, Johnson MP, Huang X, Nichols DE (1992) Benzofuran bioisosteres of hallucinogenic tryptamines. J Med Chem 35:2061–2064
Trachsel D, Nichols DE, Kidd S, Hadorn M, Baumberger F (2009) 4-aryl-substituted 2,5-dimethoxyphenethylamines: synthesis and serotonin 5-HT(2A) receptor affinities. Chem Biodivers 6:692–704
Urban JD, Clarke WP, von Zastrow M, Nichols DE, Kobilka B, Weinstein H, Javitch JA, Roth BL, Christopoulos A, Sexton PM, Miller KJ, Spedding M, Mailman RB (2007) Functional selectivity and classical concepts of quantitative pharmacology. J Pharmacol Exp Ther 320:1–13
Vangveravong S, Kanthasamy A, Lucaites VL, Nelson DL, Nichols DE (1998) Synthesis and serotonin receptor affinities of a series of trans-2-(indol-3-yl)cyclopropylamine derivatives. J Med Chem 41:4995–5001
Wacker D, Wang C, Katritch V, Han GW, Huang XP, Vardy E, McCorvy JD, Jiang Y, Chu M, Siu FY, Liu W, Xu HE, Cherezov V, Roth BL, Stevens RC (2013) Structural features for functional selectivity at serotonin receptors. Science 340:615–619
Walters GC, Cooper PD (1968) Alicyclic analogue of mescaline. Nature 218:298–300
Walterscheid JP, Phillips GT, Lopez AE, Gonsoulin ML, Chen HH, Sanchez LA (2014) Pathological findings in 2 cases of fatal 25I-NBOMe toxicity. Am J Forensic Med Pathol 35:20–25
Wang C, Jiang Y, Ma J, Wu H, Wacker D, Katritch V, Han GW, Liu W, Huang XP, Vardy E, McCorvy JD, Gao X, Zhou XE, Melcher K, Zhang C, Bai F, Yang H, Yang L, Jiang H, Roth BL, Cherezov V, Stevens RC, Xu HE (2013) Structural basis for molecular recognition at serotonin receptors. Science 340:610–614
Watts SW, Gackenheimer SL, Gehlert DR, Cohen ML (1994) Autoradiographic comparison of [125I]LSD-labeled 5-HT2A receptor distribution in rat and guinea pig brain. Neurochem Int 24:565–574
Whiteside MS, Kurrasch-Orbaugh D, Marona-Lewicka D, Nichols DE, Monte A (2002) Substituted hexahydrobenzodipyrans as 5-HT2A/2C receptor probes. Bioorg Med Chem 10:3301–3306
Winter JC, Gessner PK, Godse DD (1967) Synthesis of some 3-indenealkylamines. Comparison of the biological activity of 3-indenealkylamines and 3-benzo[b]thiophenealkylamines with their tryptamine isosteres. J Med Chem 10:856–858
Yin X, Xu H, Hanson M, Liu W (2014) GPCR crystallization using lipidic cubic phase technique. Curr Pharm Biotechnol 15:971–979