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Medicinal Chemistry and Structure–Activity Relationships

I. INTRODUCTION

Amphetamine remains the chemist's "Cinderella" molecule. No other compound has displayed such a plethora of pharmacological, biochemical, and physiological effects, . . . nor have many other molecules served as so versatile a starting base for the synthetic elaboration of a host of novel therapeutic agents.

(Biel and Bopp, 1978)

This description of amphetamine remains as true today as it was in 1978. As a simple molecule of only nine carbon atoms with one chiral center, amphetamine is dwarfed by the structural complexity of most other classes of drugs. Nevertheless, the pharmacophoric template, an aromatic ring separated by two carbon atoms from a basic nitrogen, is a motif that occurs repeatedly in many classes of biologically active molecules. Perhaps a remarkable characteristic of amphetamine is that relatively minor structural changes can alter the pharmacology of the molecule

completely. Thus, for example, simple changes in the aromatic substitution pattern lead to compounds that may have potent actions on presynaptic neuronal amine carriers and stores of dopamine, norepinephrine, or serotonin. Other substitution patterns give potent agonist actions at postsynaptic serotonin receptor subtypes. Central actions of substituted amphetamines in humans range from sedation to stimulation to hallucinogenic effects.

The reader should be aware, however, that in this chapter no attempt is being made to provide an encyclopedic compendium of all possible substituted amphetamine derivatives, with a companion commentary on their particular pharmacologies. Such an endeavor would occupy at least one large volume itself, and would not be a manageable chapter in this book. Further, such compendia fail to "distill" the essence of structure–activity relationships, leaving the reader full of facts but lacking a coherent framework within which to understand how molecular structure influences biological activity. Therefore, after reading this chapter and examining the structure of a substituted amphetamine, the author hopes that the reader will be able to predict with reasonable certainty the type of pharmacology that molecule would likely possess. The author has attempted to provide a representative and reasonably comprehensive set of examples, with sufficient discussion to categorize these compounds in the context of structure–activity relationships.

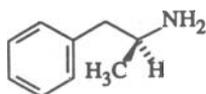
In general, one may recognize that substituted amphetamines interact with receptors and biological targets that have evolved to accommodate the monoamine neurotransmitters norepinephrine, epinephrine, dopamine, and serotonin. Since all these chemical molecules ultimately are derived from the aromatic amino acids tyrosine or tryptophan which, after further biosynthetic elaboration, lead to molecules containing an aromatic system spaced two carbons away from a basic amine, this action of substituted amphetamines is not surprising.

One can gain an appreciation for the pharmacology of substituted amphetamines by understanding the normal physiology of the neurotransmitter systems and receptors for the monoamine transmitters. With a knowledge of how a particular amphetamine derivative affects those processes, the pharmacology of that molecule can be understood. For example, the pressor effects of amphetamine can be largely understood from the knowledge that amphetamine causes the release of norepinephrine from peripheral sympathetic neurons, leading to increased vascular tone.

II. DERIVATIVES THAT RELEASE NEURONAL CATECHOLAMINES

Amphetamine (1) is an acronym for *alpha-methylphenethylamine*, also known as 1-phenyl-2-aminopropane or phenylisopropylamine. The homolog lacking the α -methyl group, 2-phenethylamine, lacks central effects after systemic administration because of its rapid degradation by monoamine oxidase (MAO). However, the simple addition of a methyl group to the α carbon yields amphetamine, which is a rather poor substrate for MAO and

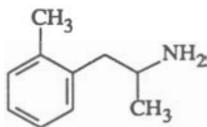
thus survives in the body and penetrates the central nervous system (CNS) to exert its effects. The presence of the methyl group also introduces chirality into the side chain; the isomer with the *S*-(+) configuration, as shown, is now well known to be more potent. A 4- to 10-fold stereoselectivity typically is observed for the enantiomers, depending on the assay used.



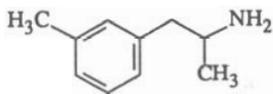
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Amphetamine itself might be called the prototype psychostimulant. The more prominent actions of this molecule include CNS stimulation, production of euphoria, increased motor activity, and appetite suppression. These effects all are believed to be the result of the release of central stores of the endogenous catecholamines dopamine and norepinephrine. The focus of most recent studies of amphetamine has been on its dopaminergic effects; the role of norepinephrine is less well understood.

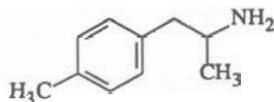
Perhaps also unique about amphetamine is the surprisingly small number of structural modifications that can be made to the structure to lead to compounds that retain psychostimulant activity. For example, Higgs and Glennon (1990) compared the three isomeric ring methyl-substituted amphetamines 2, 3, and 4 in the two-lever drug discrimination paradigm using rats trained to discriminate 1 mg/kg (+)-amphetamine sulfate from saline. Whereas the ED_{50} for substitution with amphetamine itself was 0.42 mg/kg, only the *ortho*-methyl compound gave full substitution with an ED_{50} of 4.1 mg/kg, approximately one order of magnitude less potent than amphetamine itself. The *meta* and *para* substituted compounds 3 and 4 produced disruption only at higher doses.



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Indeed, simple monosubstitution of amphetamine at the *para* position with a halogen such as chlorine or iodine gives compounds that seem to possess, as their predominant pharmacology, the ability to release neuronal serotonin rather than dopamine (Johnson *et al.*, 1990a; Fuller, 1992), although this activity does not preclude many of these compounds from hav-

ing significant effects on catecholamine systems. Indeed, *p*-chloroamphetamine, *p*-methoxyamphetamine, 3,4-methylenedioxyamphetamine, and 3,4-methylenedioxymethamphetamine all have the ability to induce the release of neuronal catecholamines. Although all these compounds possess significant potency in this respect, they are discussed in the section on serotonin-releasing compounds since this activity appears to be a more prominent feature of their mechanisms of action.

Apparently, then, no group or moiety can be placed on the aromatic ring and allow retention of the simple catecholamine-releasing activity of amphetamine. Structures substituted at the 4 or 3,4 positions that do retain an amphetamine-like psychostimulant component of action typically also seem to possess significant potency as serotonin-releasing agents, complicating interpretation of their pharmacology. However, a number of side-chain modifications of amphetamine have been studied; several have psychostimulant properties similar to those of amphetamine, although most are generally less potent.

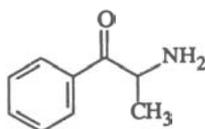
A. N Substitution

The types of substituents that can be added to the amino group of amphetamine are relatively restricted. *N*-Methyl substitution of amphetamine gives methamphetamine, which has nearly twice the *in vivo* potency of amphetamine. However, the *N*-ethyl and *N*-*n*-propyl derivatives have about half the activity of amphetamine (Van der Schoot *et al.*, 1961). In drug discrimination tests in rats, both *N*-ethyl and *N*-hydroxy amphetamine gave complete substitution in (+)-amphetamine-trained rats (Glennon *et al.*, 1988). The *N,N*-dimethyl compound has only about one-fifth the potency of amphetamine. Note that tertiary amine congeners may be *N*-dealkylated *in vivo* to generate secondary amines, which are inherently more potent. Except for these few modifications, catecholamine-releasing activity seems to be lost. This result might be anticipated since the monoamine transport systems have evolved to accommodate either a primary or an *N*-methyl-substituted amine.

B. Analogs Oxidized at the Benzylic Carbon

Analogs oxidized at the benzylic position also retain activity. For example, cathinone (5) has stimulant effects similar to those of amphetamine. Using the drug discrimination paradigm in rats trained to discriminate amphetamine from saline, racemic cathinone was essentially equipotent to (+)-amphetamine (Glennon, 1986). Schechter *et al.* (1984) trained rats to discriminate 0.6 mg/kg racemic cathinone from saline. In these rats, (+)-amphetamine gave full substitution with a dose-response curve parallel to that of cathinone, the training drug. The ED₅₀ values for racemic cathinone

and (+)-amphetamine were identical. Glennon *et al.* (1984a) established that, in (+)-amphetamine-trained rats, *S*-(-)-cathinone has about twice the potency of the racemic mixture. In cathinone-trained rats, *S*-(-)-cathinone is equipotent to the racemate, whereas the *R*-(+) enantiomer is only about one-third as potent. Thus, the more potent enantiomers of both amphetamine and cathinone possess the *S* configuration at the α side-chain carbon. *N,N*-Diethyl substitution on the nitrogen gives diethylpropion, a related compound with similar but quantitatively lower (about half) activity.

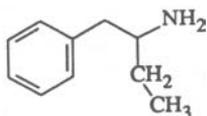


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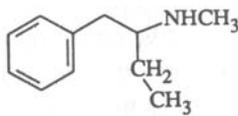
Reduction of the benzylic ketone of cathinone and incorporation of the oxygen and nitrogen into a morpholine ring gives compounds such as phenmetrazine and phendimetrazine. Although these molecules are also potent CNS stimulants, strictly speaking they are not amphetamines. Such structures will not be addressed in this discussion. A general overview of psychostimulants and anorectics related to amphetamine can be consulted for a comprehensive discussion (e.g., see Biel and Bopp, 1978).

C. Modification of the Side Chain: Rigid Analogs

Extension of the side-chain α -methyl to an ethyl group dramatically attenuates amphetamine-like activity. For example, the (+)- α -ethyl homolog 6 does not produce full substitution in rats trained to discriminate saline from 1 mg/kg (+)-amphetamine sulfate. Using the same paradigm, the racemic α -ethyl homolog of *N*-methylamphetamine (7) produced full substitution but had only about one-tenth the potency of amphetamine itself.



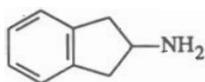
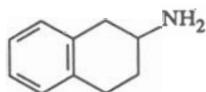
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Interesting effects occur when the side chain of amphetamine is incorporated into carbocyclic rings. For example, 2-aminoindan (8) can be viewed as an amphetamine analog in which the α -methyl has been "attached" to the aromatic ring. Using the drug discrimination paradigm in rats trained to

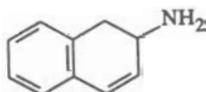
discriminate 1.0 mg/kg (+)-amphetamine sulfate, **8** fully substituted with an ED_{50} of 2.1 mg/kg whereas, for comparison, (+)-amphetamine sulfate had an ED_{50} of 0.42 mg/kg (Glennon *et al.*, 1984a). Using a different training schedule but the same training drug and dose, a more recent report failed to observe substitution with **8** (Oberlender and Nichols, 1991). In this latter report, **8** gave a maximum of 75% amphetamine-appropriate responding at nearly three times the training drug dose.

**8****9**

Expansion of the carbocyclic ring leads to 2-aminotetralin (**9**). Glennon *et al.* (1984a) also report complete substitution with this analog in (+)-amphetamine sulfate-trained animals. An ED_{50} of 1.2 mg/kg places the tetralin at about one-third the potency of (+)-amphetamine. Similarly, Oberlender and Nichols (1991) observed complete substitution for this compound with an ED_{50} of 11.9 $\mu\text{mol/kg}$, whereas the ED_{50} for (+)-amphetamine sulfate was 1.57 $\mu\text{mol/kg}$ (0.29 mg/kg). Thus, **9** had about one-eighth the potency of amphetamine in this study.

Although the two groups did not report consistent results for 2-aminoindan (**8**), both studies were in agreement that 2-aminotetralin (**9**) was more potent than 2-aminoindan (**8**) as an amphetamine-like agent. Further expansion of the carbocyclic ring to seven carbon atoms resulted in a compound that no longer gave (+)-amphetamine-appropriate responding (Glennon *et al.*, 1984a).

Curiously, introduction of a double bond at the 3,4 position of 2-aminotetralin (**9**) gave compound **10** which, in the drug discrimination paradigm, completely substituted in (+)-amphetamine-trained rats, with very little behavioral disruption. The *S*-(-)-isomer of **10** had nearly half the activity of (+)-amphetamine, whereas the *R*-(+)-enantiomer failed to possess amphetamine-like properties. These results are in agreement with those of an earlier study of the effects of the enantiomers of **10** on spontaneous locomotor activity in mice (Hathaway *et al.*, 1982).

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D. Mechanism of Action

Although the mechanism by which amphetamine causes catecholamine release is not well understood, several reports (Sulzer *et al.*, 1992, 1993) have suggested that amphetamine and other weak bases reduce intracellular pH gradients of synaptic vesicles. Once the buffering capacity of the vesicle has been exceeded, the decreased proton gradient reduces the driving force for transmitter uptake. Deprotonated catecholamine then may diffuse from the vesicle, following its concentration gradient. This elevated cytosolic monoamine then may be released from the cell by reversal of the uptake carrier.

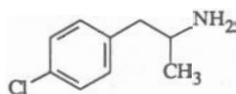
E. Summary of Structure-Activity Relationships

One may conclude that the amphetamine molecule tolerates very little structural variation without great attenuation, or even complete loss, of amphetamine-like effects. If one assumes, as most research results suggest, that the effects of amphetamine are produced by a drug-induced efflux of presynaptic neuronal catecholamines (principally dopamine), one can infer that the structural requirements for this process are very rigid. The optimal compound may be amphetamine itself, lacking any aromatic ring substituents.

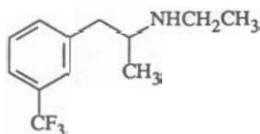
III. AMPHETAMINE DERIVATIVES THAT RELEASE NEURONAL SEROTONIN

The class of substituted amphetamines that release serotonin had relatively few members until recently. Even now, this group comprises a relatively small number of compounds. Although amphetamine itself can cause release of neuronal serotonin, this action is fairly weak (e.g., see Steele *et al.*, 1987). However, the introduction of a single substituent in the *para* position can increase this effect dramatically. The most well-known example is *p*-chloroamphetamine (PCA; 11). Although PCA itself seems not to have received clinical study, its *N*-methyl derivative was evaluated briefly as an antidepressant agent (Verster and Van Praag, 1970). PCA potently releases serotonin from neuron terminals, but in relatively small doses also leads to profound and long-lasting depletion of central serotonin (Fuller and Snoddy, 1974; Harvey *et al.*, 1975; for an overview see Fuller, 1992). This depletion is accompanied by loss of serotonin (5-HT) neuronal markers such as tryptophan hydroxylase, a decrease in the B_{\max} for the serotonin uptake site (Battaglia *et al.*, 1987; Huang *et al.*, 1992), and a loss of serotonin immunoreactivity (Mamounas and Molliver, 1988; O'Hearn *et al.*, 1988). Therefore, PCA generally is considered a serotonergic neurotoxin. Although this

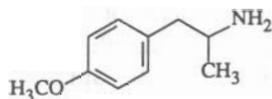
neurotoxic action has been the subject of intense scrutiny for nearly two decades, the mechanism still remains elusive. This topic is discussed at greater length in other chapters of this volume.



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Another compound that interacts potently with serotonin neurons and shares certain toxicological similarities with PCA is fenfluramine (12; *N*-ethyl-*meta*-trifluoromethylamphetamine). Marketed many years ago as an appetite suppressant under the trade name Pondimin, this drug is no longer available in the United States but is prescribed widely in Europe as the *dextro* isomer dexfenfluramine. Fenfluramine also has been studied for efficacy in infantile autism (Du Verglas *et al.*, 1988). Fenfluramine appears to cause the same types of neuronal serotonin deficits produced by PCA (e.g., see Johnson and Nichols, 1990, and references therein). However, some researchers argue that fenfluramine is not neurotoxic and only depletes serotonin levels acutely (e.g., see Kalia, 1991).

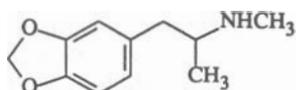
A third compound with potent effects on serotonin neurons is *p*-methoxyamphetamine (PMA; 13). Although for legal purposes PMA has been classified as a "hallucinogenic" amphetamine, the only description of the clinical effects of PMA suggests that it bears little resemblance to a hallucinogenic amphetamine, but may act more like a stimulant (Shulgin and Shulgin, 1991). Further, in the chronic spinal dog, Martin *et al.* (1978) were able to distinguish PMA from hallucinogenic amphetamines as more "amphetamine-like." Although PMA has been known for a long time to have significant indirect adrenergic and peripheral cardiovascular effects (e.g., see Cheng *et al.*, 1974a,b; Nichols *et al.*, 1975, and references therein), Tseng *et al.* (1976, 1978) and Loh and Tseng (1978) first provided evidence for the potent serotonin-releasing action of PMA. Nichols *et al.* (1982) later compared the ability of the PMA enantiomers to induce the release of [³H]5-HT from prelabeled rat brain synaptosomes; the isomers had similar potency. Nevertheless, although researchers generally recognize the "hallucinogenic" and adrenergic effects of PMA, researchers seem to have had less awareness of its potent indirect serotonergic actions.

Until recently, these three compounds—PCA, fenfluramine, and PMA—were the only well-known examples in this class of drug. With the exceptions of the use of PCA as an experimental serotonergic neurotoxin and of

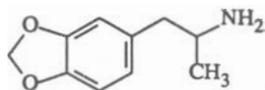
numerous studies focused on the pharmacological effects of fenfluramine, serotonin-releasing agents seemed to generate little scientific interest until the mid-1980s.

However, in 1984, 3,4-methylenedioxyamphetamine (14; MDMA, "Ecstasy") began to gain popularity as a new recreational drug, used primarily among college students and young professionals. Beginning in 1985 and for the subsequent 4–5 years, the popular literature contained numerous articles about "Ecstasy" (for a review, see Peroutka, 1990). The drug is still generating controversy, primarily in the context of its use in connection with raves—all-night dance parties with elaborate sound and light systems.

Since MDMA was the catalyst that focused attention on serotonin-releasing agents and returned attention to the issue of serotonin neuron toxicity, a portion of the discussion in this section is appropriately devoted to this compound. However, information also must be presented on 3,4-methylenedioxyamphetamine (MDA; 15). Not only does MDA serve as the chemical progenitor to MDMA, but certain features of the pharmacology of MDA also are retained in MDMA. A good review of the earlier literature on the effects of MDA was presented by Thiessen and Cook (1973). The clinical effects of MDA first described by Alles (1959) seemed to suggest that MDA had mild hallucinogenic actions. Clearly, racemic MDA does have effects similar to those of other hallucinogenic amphetamine derivatives (Shulgin, 1978). However, in contrast to the effects of virtually all other hallucinogenic phenethylamine derivatives, MDA was reported to produce in its users a need to be with and talk to other people (Jackson and Reed, 1970). In addition, this unusual effect was associated with a feeling of enhanced emotional closeness that earned MDA a reputation as the "love drug" (Weil, 1976). Studies in chronic spinal dogs by Martin and his colleagues (1978) reported MDA to have an action that was both "amphetamine-like" and "LSD-like," whereas other substituted amphetamines simply gave an LSD-like effect. However, additional clarification of the mechanism of action of MDA required studies of its enantiomers.



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Marquardt *et al.* (1978) were the first to report studies with the optical isomers of MDA. Behavioral scoring in mice showed that the LSD-like effects of racemic MDA were completely attributable to the *R*-(-) isomer of MDA, where the *S*-(+)-enantiomer possessed an amphetamine-like profile. In cats, the *S* enantiomer also produced a marked pressor response. Pretreatment with reserpine to deplete endogenous norepinephrine stores, or with

the α -adrenergic antagonist phenoxybenzamine, blocked the pressor response to MDA, suggesting its action to be one of releasing endogenous neuronal norepinephrine. Indeed, the potent adrenergic effect of MDA has been described earlier (Fujimori and Himwich, 1969; Nichols *et al.*, 1975), but Marquardt *et al.* (1978) first showed that the *S* isomer of MDA was primarily responsible for these effects.

Nichols *et al.* (1982) subsequently demonstrated that MDA was also a potent releaser of serotonin from synaptosomes prelabeled with [^3H]5-HT. Weak stereoselectivity for the *S* isomer was observed in these experiments. MDA then also was shown to release [^3H]5-HT from prelabeled slices of rat hippocampus (Johnson *et al.*, 1986); no selectivity was observed for its enantiomers. MDA was a moderately potent inhibitor of [^3H]5-HT uptake into rat brain hippocampal synaptosomes, with IC_{50} values for the *S*-(+) and the *R*-(-) enantiomers that indicated an approximately 3-fold stereoselectivity (Steele *et al.*, 1987). This study also showed that MDA was a potent inhibitor of [^3H]norepinephrine uptake into rat hypothalamic synaptosomes and had modest inhibitory effects against [^3H]dopamine uptake into rat striatal synaptosomes. Johnson *et al.* (1986) also showed that MDA induced the release of [^3H]dopamine from rat caudate slices; the *S* enantiomer had approximately twice the potency of the *R* antipode.

Animal studies, particularly using the two-lever drug discrimination paradigm, have shown clearly that substitution of MDA in animals trained to discriminate saline from LSD or the hallucinogenic amphetamine 2,5-dimethoxy-4-methylamphetamine (DOM) is the result of the effects of the *R* enantiomer (Glennon *et al.*, 1982b; Nichols *et al.*, 1986a; Oberlender and Nichols, 1988). The rabbit hyperthermia model also shows that the *R* enantiomer of MDA is a more potent hallucinogen (Anderson *et al.*, 1978).

Thus, although racemic MDA has behavioral effects characteristic of both hallucinogens and psychostimulants, the preceding discussion demonstrates that this activity can be attributed to "hallucinogenic" actions of the *R* enantiomer and indirect adrenergic and serotonin-releasing actions of the *S* enantiomer. Additional experiments using the drug discrimination paradigm support this hypothesis (Shannon, 1980; Glennon *et al.*, 1981, 1982; Glennon and Young, 1984a,b; Nichols *et al.*, 1986a; Nichols and Oberlender, 1990a,b). Whereas the studies of Glennon and his colleagues suggested that *S*-MDA had an amphetamine-like action, the lack of symmetrical substitution and generalization of serotonergic training cues to the *S* isomer in other studies (Nichols and Oberlender, 1990a,b) suggest that the primary discriminative cue of *S*-(+)-MDA is serotonergic in nature. Studies by Shannon (1980) also indicated that racemic MDA was not amphetamine-like.

With this background information for MDA, we can proceed to a discussion of the *N*-methyl derivative of MDA, MDMA [*N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane; 3,4-methylenedioxyamphetamine]. Although MDMA first was synthesized in 1912 (Shulgin, 1990), this compound did not become widely popular as a recreational drug until the

mid- to late 1980s. Although the United States Army carried out toxicological tests on MDMA in the early 1950s, these results remained classified until 1969. The first public report of the effect of MDMA in humans was in 1978 (Shulgin and Nichols, 1978). Use of MDMA by a number of psychiatrists as an adjunct to psychotherapy apparently began at about this time; use gradually escalated into the population at large over the next decade. As for MDA, the popularity of MDMA could be attributed to its ability to induce a sense of emotional "closeness" with other individuals, while lacking the sensory disrupting effects characteristic of hallucinogens (Peroutka *et al.*, 1988). Thus, whereas MDA had been referred to as the "love drug," MDMA became known as the "hug drug."

Although amphetamine itself could be classified as a psychostimulant and other substituted amphetamines could be classified as hallucinogens, a pharmacological classification for MDA or MDMA was less certain. Indeed, these drugs have been proposed to belong to a new pharmacological category with unique psychoactive effects. The name "entactogen" has been suggested for this drug class (Nichols, 1986). Further, because of the unique psychopharmacology of these compounds—particularly their powerful actions on affect, empathy, and emotion—the neuronal substrates of their mechanisms of action were of great interest.

As discussed elsewhere in this volume, both MDA and MDMA induce the selective loss of brain serotonin axons in a manner that appears similar to the toxic actions of PCA and fenfluramine. Thus, additional interest was raised in the mechanisms of action of MDA and MDMA from the perspective of the mechanisms underlying this neurotoxic effect. On the other hand, despite apparent similarities in the pharmacology of these agents, no evidence suggests that the human psychopharmacology of PCA or fenfluramine in any way resembles that of MDA or MDMA.

What is the predominant pharmacology of MDMA? The *in vitro* pharmacologies of MDMA and MDA are very similar, with the exception of the hallucinogen-like effects seen with MDA. Researchers generally believe that the animal behavioral effects of molecules known to be hallucinogenic in humans, such as LSD and DOM, are mediated primarily by an interaction with postsynaptic serotonin 5-HT₂ or 5-HT_{1C} receptors. Further, the *R* enantiomer of hallucinogenic amphetamines is the more potent hallucinogen (for a review, see Nichols *et al.*, 1991b). As might be anticipated, therefore, the *R* enantiomer of MDMA also has higher affinity than the *S* isomer for the 5-HT₂ receptor (Lyon *et al.*, 1986). However, the *S* isomer is more potent *in vivo*. Further, the discriminative cue of MDMA is not blocked by the 5-HT₂ antagonist ketanserin (Nichols and Oberlender, 1990a,b), nor is the disruption of operant responding in mice caused by either enantiomer of MDMA blocked by the 5-HT₂ antagonist pirenperone (Rosecrans and Glennon, 1987). Also, *N*-methylation of hallucinogenic amphetamines is known to decrease hallucinogenic activity by about one order of magnitude (Shulgin, 1978). Thus, in drug discrimination studies, *R*-(-)-

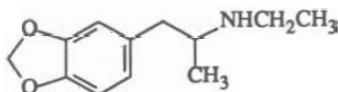
MDA substitutes for hallucinogenic training drugs (Glennon *et al.*, 1981b, 1982; Nichols *et al.*, 1986a) whereas *R*-(-)-MDMA does not (Glennon *et al.*, 1982b; Nichols *et al.*, 1986).

Thus, the *R* enantiomer of MDA has hallucinogen-like pharmacology, presumably by acting directly at postsynaptic 5-HT₂ receptors, and the *S* enantiomer induces the release of endogenous stores of serotonin and catecholamines. *N*-Methylation of MDA to yield MDMA seems to abolish the activity of the *R* enantiomer but has little effect on the activity of the *S* enantiomer. Therefore, although racemic MDA has a complex pharmacological action resulting from the combined effects of both isomers, racemic MDMA has a pharmacology derived predominantly from its *S* enantiomer. All studies carried out to date with the enantiomers of MDA and MDMA seem consistent with this concept.

A. Effects of *N* Substitution

Clearly the preceding discussion shows that the addition of an *N*-methyl group to MDA to yield MDMA has little effect on the ability of the compound to release endogenous neuronal stores of serotonin. PCA and *N*-methyl PCA also have similar neurochemical effects (Fuller, 1992). Although *N*-methyl PCA is metabolized rapidly to PCA in rats (Fuller and Baker, 1977) and MDA is a metabolic *N*-demethylation product of MDMA in rats, numerous *in vitro* studies, some already discussed, have established clearly that the *N*-methyl group does not have a significant deleterious effect on the ability of substituted amphetamines to induce the release of endogenous neuronal monoamines.

However, the range of substituent modification that is tolerated on the nitrogen atom seems fairly limited, although comprehensive pharmacology has not been carried out on many other *N*-alkylated derivatives. The most well studied other *N*-substituted compound in this family is *N*-ethyl MDA (16; MDE, MDEA). MDE appears to have subjective effects in humans that are somewhat similar to those produced by MDMA (Hermle *et al.*, 1993). In addition, the animal behavioral effects (Boja and Schechter, 1987) and the *in vitro* actions of MDE on the uptake and release of serotonin, dopamine, and norepinephrine appear similar to those of MDMA (Johnson *et al.*, 1986; Boja and Schechter, 1991; McKenna *et al.*, 1991a; Paulus and Geyer, 1992). However, the dopaminergic effects of MDE are weaker than those of MDMA (Schmidt, 1987; McKenna *et al.*, 1991a; Nash and Nichols, 1991).



In a study of the analgesic and psychopharmacological effects of a series of *N*-alkylated MDA derivatives, Braun *et al.* (1980) reported that only the *N*-methyl, *N*-ethyl, and *N*-hydroxy compounds were active. However, evidence suggests that the *N*-hydroxy compound may be reduced metabolically to MDA, a process known to occur with the *N*-hydroxy derivative of PCA (Fuller *et al.*, 1974). MDE also produces long-term serotonin deficits similar to those induced by MDMA, but MDE is somewhat less potent in this regard (Ricaurte *et al.*, 1987; Schmidt, 1987; Stone *et al.*, 1987).

Some mention should be made of fenfluramine, which has an *N*-ethyl group. Both fenfluramine and norfenfluramine are potent serotonin-releasing agents and inhibitors of serotonin uptake (e.g., see Boja and Schecter, 1988; McKenna *et al.*, 1991a; Berger *et al.*, 1992). Similar to PCA and MDMA, both fenfluramine and norfenfluramine induce persistent deficits in rat brain serotonin markers after a single high dose (e.g., Johnson and Nichols, 1990, and references therein). Racemic fenfluramine and norfenfluramine are nearly equipotent to PCA, (+)-MDA, and (+)-MDMA in inhibition of serotonin uptake into rat brain synaptosomes (McKenna *et al.*, 1991a). However, these compounds are somewhat less potent than the other drugs in inhibiting synaptosomal dopamine uptake.

Only one other *N* substituent is known to produce a compound in this class with pharmacology similar to that of the parent: *N*-cyclopropyl-*p*-chloroamphetamine. However, Fuller *et al.* (1987) have shown that this activity can be attributed to rapid metabolic *N*-dealkylation, leading to PCA itself.

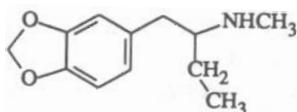
N,N Dialkylation appears to lead to compounds that lack *in vivo* activity. For example, *N,N*-dimethyl MDA lacked effects in humans (Shulgin and Shulgin, 1991). However, no *in vitro* pharmacology studies have been carried out on this compound to ascertain whether or not it retains effects on serotonin neurons.

B. Side-Chain Modifications

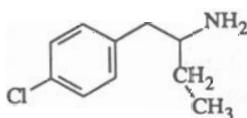
The two-carbon side chain appears optimal for serotonin release, as might be anticipated since it inherently represents a key feature of the arylethylamine pharmacophoric motif. In a series of PCA analogs, changing the length of the side chain gave compounds that were inactive or much less active than PCA (Fuller *et al.*, 1972). Addition of a second α -methyl to the side chain of MDA or MDMA gave compounds that were clinically inactive (Shulgin and Shulgin, 1991) and also lacked significant potency in inducing the release of [3 H]labeled serotonin from prelabeled rat brain synaptosomes (Nichols *et al.*, 1982).

The α -methyl substituent, however, can be extended to an α -ethyl group in serotonin-releasing agents. This modification was demonstrated first with the α -ethyl homolog of MDMA (MBDB; 17, e.g., Nichols, 1986; Nichols *et al.*, 1986a; Oberlender and Nichols, 1988). *In vitro* studies of monoamine

uptake and release from rat brain synaptosomes and brain slices show a similar pharmacological profile for MDMA and MBDB (Johnson *et al.*, 1986; Steele *et al.*, 1987). However, whereas the actions of MDMA and MBDB at serotonin neurons are of comparable potency, MBDB is considerably weaker at dopamine neurons (Johnson *et al.*, 1986; Steele *et al.*, 1987; Nash and Nichols, 1991). This result is consistent with the structure-activity relationships of catecholamine-releasing amphetamine analogs discussed earlier, in which an α -ethyl group dramatically attenuates the ability of the compounds to interact with the dopamine carrier. Although MBDB does induce long-term serotonin deficits after repeated dosing, the magnitude of the effect is less than with MDMA (Johnson and Nichols, 1989) and does not occur after a single dose (Nash and Nichols, 1991). Although complete pharmacological characterization of compounds with an α -alkyl group longer than ethyl has not been carried out, none of those compounds with longer α -alkyl groups tested clinically possessed activity (Shulgin and Shulgin, 1991).



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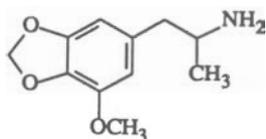
Another compound in this series is the α -ethyl homolog of PCA reported by Johnson *et al.* (1990a). This compound, 1-(4-chlorophenyl)-2-amino-butane (18, CAB), was compared with PCA in drug discrimination assays in animals trained to discriminate MDMA or (+)-MBDB from saline. Using microdialysis, CAB also was compared with PCA in its ability to induce *in vivo* dopamine release and to increase dihydroxy phenylacetic acid (DOPAC) concentrations in striatum. CAB and PCA also were compared for their ability to inhibit the uptake of [3 H]5-HT and [3 H]dopamine in rat whole brain synaptosomes. Finally, the relative potencies of CAB and PCA to induce persistent deficits in serotonin markers were examined. In this study, CAB was only 2-fold less potent at inhibiting serotonin uptake but 5-fold less potent at inhibiting dopamine uptake. In drug discrimination assays, CAB had about one-third the potency of PCA. A single 10 mg/kg dose of PCA caused a very large increase in extracellular dopamine (2000% of basal!), whereas twice the molar dose of CAB led only to an approximate doubling of extracellular dopamine. These studies indicate that the α -ethyl analog 18 retains the ability to affect serotonergic transmission, as noted from the drug discrimination and monoamine uptake studies, but has a marked loss of dopaminergic action. Further, whereas 10 mg/kg PCA led to

approximately 80% reductions in brain serotonin markers at sacrifice 1 wk after drug treatment, twice the molar dose of CAB (22 mg/kg) gave only 30–50% reductions.

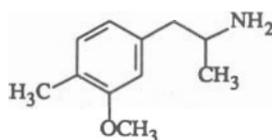
Thus, two clear examples—MBDB and CAB—illustrate how the extension of the α -methyl of the amphetamine derivative to an α -ethyl gives compounds that largely retain their ability to induce release of neuronal serotonin stores. The marked attenuation of the ability of these compounds to release dopamine, however, compared with the analogous amphetamine parent, indicates that this structural modification strategy is effective in increasing the selectivity of serotonin-releasing amphetamines when dopaminergic effects complicate the pharmacology.

C. Aromatic Ring Substituents

Although our knowledge is limited in the area of structure-activity relationships of aromatic ring substituents, amphetamines with a single substituent at the 3 position (or at least the *meta*-trifluoromethyl group, as in fenfluramine), at the 4 position (PCA or PMA), or at the 3,4 positions (MDMA or MBDB) provide potent serotonin-releasing agents. 3,4-Methylenedioxy-5-methoxyamphetamine (MMDA; 19) also is a moderately potent inhibitor of serotonin uptake (McKenna *et al.*, 1991).



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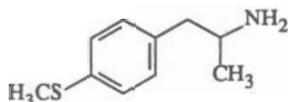
However, when the amphetamine contains an *ortho*-methoxy substituent, the compound appears to lose its ability to interact with monoamine carriers (Steele *et al.*, 1987; Johnson *et al.*, 1991b; McKenna *et al.*, 1991a). For example, 3-methoxy-4-methylamphetamine (20) is a potent indirect-acting serotonin-releasing agent (Johnson *et al.*, 1991a,b). However, when an *ortho*-methoxy group is added to the molecule to give 2,5-dimethoxy-4-methylamphetamine (the potent hallucinogenic amphetamine DOM, discussed subsequently), all effects on serotonin, dopamine, and norepinephrine transporters are lost (Steele *et al.*, 1987; Johnson *et al.*, 1991b; McKenna *et al.*, 1991a). In addition, 2-methoxy-4,5-methylenedioxyamphetamine, an *ortho*-methoxy derivative of MDA, and a 2,5-dimethoxyamphetamine in which the 3,4 positions are bridged to a cyclopentane ring (a benzobicycloheptane derivative; see 37) both lack affinity for the serotonin and dopamine uptake carriers (McKenna *et al.*, 1991a). Thus, although an *ortho*-methoxy group gives optimal activity in hallucinogenic amphet-

amines, as discussed later in this chapter, it prevents the amphetamines from interacting with the monoamine uptake carriers.

1. Other 4-Substituted Derivatives

In addition to PCA, the other halogens also give compounds that are potent serotonin-releasing agents. Early studies compared the *p*-fluoro, *p*-chloro, *p*-bromo, and *p*-iodoamphetamines (Fuller *et al.*, 1975, 1980). The member of the series that appeared most similar to PCA was *p*-iodoamphetamine (Fuller *et al.*, 1980). A more recent study also compared PCA with *p*-iodoamphetamine (Nichols *et al.*, 1991a). In this report, *p*-iodoamphetamine was somewhat more potent than PCA in inhibiting the uptake of [³H]5-HT into rat brain synaptosomes, but had only about one-fourth the potency of PCA in producing substitution in MDMA-trained rats in the drug discrimination assay. Although a single dose of *p*-iodoamphetamine was able to induce long-term serotonin deficits in rats, PCA was much more potent in this regard.

Another selective serotonin-releasing agent is *p*-methylthioamphetamine (MTA; 21; Huang *et al.*, 1992). In drug discrimination assays in rats trained to discriminate either racemic MDMA or (+)-MBDB from saline, MTA was equipotent to PCA. MTA was twice as potent as PCA in inhibiting synaptosomal serotonin uptake but, whereas PCA was not selective for inhibition of serotonin over norepinephrine uptake and had only about 2-fold selectivity for serotonin over dopamine, MTA had 40-fold and 30-fold selectivity, respectively, for uptake inhibition of serotonin over dopamine and norepinephrine. In experiments with superfused rat frontal cortex slices prelabeled with [³H]5-HT, MTA was equipotent to PCA in inducing tritium overflow. Further, a single large dose of MTA in rats had no effect on serotonin markers in rat brain on sacrifice 1 wk after treatment, whereas half the molar dose of PCA produced over 90% depletion. Thus, MTA appears to be potent, selective, and nontoxic to neurons that release serotonin.



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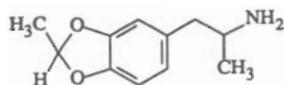
Earlier, we noted that PMA is also a potent serotonin-releasing agent. Although some uncertainty exists regarding its exact pharmacological classification, PMA appears to possess complex components of action, including not only an ability to induce the release of neuronal serotonin but also hallucinogen-like effects by an agonist action at 5-HT₂ receptors as well as a

potent tyramine-like releasing action on catecholamine stores. By analogy to MDA, one might anticipate that *N* methylation of PMA would attenuate the hallucinogen-like actions of PMA while allowing the molecule to retain its serotonin-releasing action. Consistent with this idea, Glennon and Higgs (1992) showed that the *N*-methyl derivative of PMA (PMMA) fully substituted in rats trained to discriminate MDMA hydrochloride (1.5 mg/kg) from saline. Based on ED₅₀ values, PMMA had approximately three times the potency of MDMA, the training drug. Thus, as for MDA, the *N* methylation of PMA allows the molecule to retain its serotonin-releasing action. The structurally related 3,4-dimethoxyamphetamine failed to substitute in these animals, suggesting the lack of MDMA-like behavioral effects. Although these investigators characterized the MDMA cue in these experiments as "an additional non-amphetamine-like effect," little doubt exists that the cue is mediated by endogenous serotonin release.

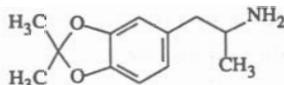
The similarities between MDMA and PMMA are also evident in the finding that PMMA can induce persistent serotonin deficits in rat brain (Steele *et al.*, 1992). However, both PMA and PMMA require doses in rats that are four times higher than those of MDMA to induce serotonin deficits that were comparable to those induced by MDMA. Despite these apparent similarities between PMMA and MDMA, the human psychopharmacology seems to differ (Shulgin and Shulgin, 1991). Shulgin and Shulgin reported that an acute 100-mg dose of PMMA hydrochloride failed to produce MDMA-like psychopharmacology in humans.

2. Other 3,4-Substituted Derivatives

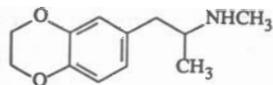
The most extensively studied 3,4-disubstituted compounds are those with a 3,4-methylenedioxy function (more correctly called a 1,3-dioxole ring): MDA, MDMA, MDE, and MBDB. The dioxole ring has been modified in several ways. First, one or two methyl groups have been added to the central methylene atom to afford ethylidenedioxyamphetamine (EDA; 22) and isopropylidenedioxyamphetamine (IDA; 23). EDA and IDA were tested for their ability to substitute in rats trained to discriminate saline from MDMA, and were compared with MDA. Compound 22 had half the potency of MDA, whereas 23 was only one-fifth as potent (Nichols *et al.*, 1989). In the same report, these compounds also were compared for their ability to induce the release of [³H]5-HT or [³H]dopamine from superfused slices of rat hippocampus or caudate, respectively. MDA and EDA were nearly equipotent in inducing the release of serotonin, whereas IDA only had about one-tenth the potency. The drug-induced efflux of dopamine from caudate slices was most pronounced with MDA; EDA was somewhat less potent and IDA again was about one-tenth as potent as MDA. Thus, the progressive methylation of the methylenedioxy function of MDA decreases potency with each additional methyl group added. The monoamine uptake carriers evidently do not tolerate the addition of steric bulk to the dioxole ring.



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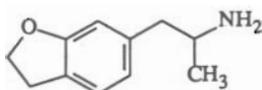


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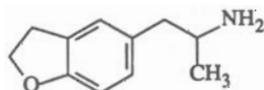
The oxygen atom at the 4 position of a dioxole ring, in a compound that also possesses an *ortho*-methoxy group, has been replaced with a sulfur atom. This compound has slightly greater potency than its oxygen isostere MDMA-2 in inducing the release of [^3H]5-HT from rat brain synaptosomes (McKenna *et al.*, 1991a). Although the presence of the *ortho*-methoxy group confounds interpretation of the results, one might infer that the 4-thio isostere of MDA or MDMA retains effects on serotonin neurons.

Expansion of the dioxole ring of MDMA by an additional methylene gives ethylenedioxyamphetamine (EDMA; 24). This compound retains serotonin- and dopamine-releasing potency comparable to that of racemic fenfluramine (McKenna *et al.*, 1991a). Nevertheless, the one report of clinical experiments with this compound revealed it to be inactive at a dose that was more than twice the active dose for MDA (Shulgin and Shulgin, 1991).

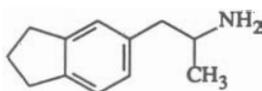
Very recently, the oxygen atoms in the dioxole ring of MDA were replaced individually with methylene units to give compounds 25, 26, and 27. In addition, the ring-expanded compound 28 was prepared for comparison.



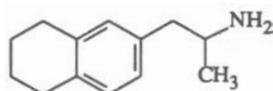
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Studies of inhibition of uptake of [^3H]5-HT into rat whole brain synaptosomes revealed that the presence of the oxygen atoms in 25 and 26 was not critical for inhibiting serotonin uptake. Indeed, the carbocyclic analog 27 proved to be the most active in this series, although all the compounds were

relatively potent, with only 3- to 4-fold variation in activity (Monte *et al.*, 1993). These compounds were much less potent in inhibiting catecholamine uptake; 25 and 27 were nearly equipotent and about 3-fold more active than 26 or 28.

Finally, a compound mentioned earlier, 3-methoxy-4-methylamphetamine (MMA; 20), has shown the highest selectivity for serotonin over catecholamines for inducing the release and inhibiting the uptake of monoamines (Johnson *et al.*, 1991a,b). The ratios of the IC_{50} s for inhibition of serotonin versus dopamine and norepinephrine were 120 and 33, respectively. This particular amphetamine appears to be the most serotonin selective of all the substituted amphetamines studied to date. Based on the earlier discussion, one could anticipate that extension of the α -methyl group in this structure would lead to a compound with even greater serotonin selectivity.

D. Mechanism of Action

As for the catecholamine-releasing agents, the exact mechanism by which these drugs induce the release of neuronal serotonin is unclear. These compounds are not simply uptake inhibitors; studies of many of these compounds in superfused preparations have shown that they actively cause the release of endogenous neuronal serotonin. The mechanism may be similar to that proposed for the amphetamine-type catecholamine-releasing agents. Berger *et al.* (1992) provided evidence that MDMA, PCA, and fenfluramine all release serotonin by a common mechanism. Rudnick and Wall (1992a,b) showed that both PCA and MDMA release serotonin by an action that must involve the serotonin transporter protein. The results of their studies suggest that direct interactions with the amine transporter, for example, in serotonin–MDMA exchange, may be at least partially responsible for serotonin efflux from vesicles. Also, passive diffusion into synaptic vesicles may increase the pH, leading to efflux of uncharged serotonin from the storage vesicle. This serotonin, in turn, may be transported out of the neuron by a reverse action of the uptake pump across the plasma membrane.

E. Summary of Structure–Activity Relationships

One can draw some general conclusions regarding structure–activity relationships for serotonin-releasing agents. First, monosubstitution at the 4 position leads to compounds that have a significant serotonergic component of action. The halogens or a methoxy group at this position also have appreciable adrenergic properties, attributable to a neuronal catecholamine-releasing action. Second, a 3-trifluoromethyl substituent, as in fenfluramine and norfenfluramine, gives a relatively selective serotonin-releasing agent. A 3,4-disubstitution pattern also leads to compounds with selective serotonergic effects. If this substitution takes the form of a dioxole ring, as in

MDA or MDMA, the compounds also have appreciable catecholaminergic effects. However, other substituents may give a very selective serotonin effect. Note that the addition of an *ortho*-methoxy group to any of these structures appears to decrease markedly their ability to release neuronal serotonin.

Generally, primarily amines are most potent, but their effects are attenuated only slightly by an *N*-methyl or *N*-ethyl substituent. However, the latter substituent dramatically reduces the ability of the compound to interact with catecholamine carriers and improves serotonin selectivity of the compound (e.g., MDE). All compounds studied to date that have potent releasing actions on both serotonin and catecholamine neurons, when given in high or repeated doses, lead to long-term serotonin deficits and apparent degeneration of brain serotonin terminals and axons.

Finally, extension of the α -methyl to an α -ethyl group allows retention of serotonin effects and improves serotonin selectivity by attenuating effects of the compound on catecholaminergic neurons. Based on the limited data currently available, α -alkyl groups longer than ethyl are inactive.

However, all these conclusions should be considered subject to further refinement. In actuality, the number of substituted amphetamines that have been tested for a selective serotonin-releasing action is very small. Consequently, the database used to derive these structure–activity relationship conclusions is incomplete. With further effort in this field, undoubtedly other substitution patterns and structural modifications will be uncovered that will lead to further refinement of these structure–activity relationship features.

IV. HALLUCINOGENIC AMPHETAMINE DERIVATIVES

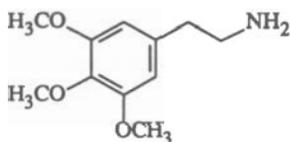
The hallucinogens are a fascinating class of molecules. These drugs have been called psychotomimetic, hallucinogenic, or psychedelic at various times by various groups of people. For many years, the term “psychotomimetic,” which implies that these drugs produce a psychosis-like effect, was used most frequently in the scientific literature as the descriptor for these compounds. Gradually, “psychotomimetic” has been replaced by the more neutral term “hallucinogen.” Although it has a less negative connotation, this descriptor nevertheless implies that these drugs produce hallucinations, which is not strictly correct. Although some compounds, generally at high dosages, may produce hallucinations in some individuals, this action of this drug class is not reliable and reproducible. The term “psychedelic” has been used widely in the lay press but was never favored in the scientific literature because of the positive connotation of “mind manifesting,” meaning that these drugs bring out desirable qualities of the mind.

However, Jaffe (1990) argued for the use of “psychedelic” as the appropriate designation for this drug class. He noted that “the feature that distin-

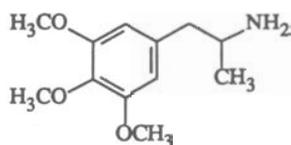
guishes the psychedelic agents from other classes of drugs is their capacity reliably to induce states of altered perception, thought, and feeling that are not experienced otherwise except in dreams or at times of religious exaltation." This definition illustrates nicely the profound effects these drugs may exert on the human psyche. The chemical types that are included in this definition are substituted phenethylamines and tryptamines, of which the potent compound (+)-lysergic acid diethylamine (LSD) can be considered representative of the latter.

As the most structurally simple class of molecules possessing hallucinogenic effects, a large number of substituted amphetamines now has been studied. Of particular note are the extensive studies by Shulgin and collaborators, the results of which have been compiled into a book (Shulgin and Shulgin, 1991). Most of the human data discussed in this section (and in this chapter) are from this reference.

The starting compound for this series was mescaline (29). Addition of an α -methyl group led to the "substituted amphetamine" 3,4,5-trimethoxyamphetamine (TMA; 30; Peretz *et al.*, 1955) and began the journey that ultimately led to the synthesis and pharmacological evaluation of nearly 200 potentially hallucinogenic substituted amphetamines. Medicinal chemists readily envision several parts of the molecule that are modified easily to develop structure-activity relationships for the series, including (1) the basic nitrogen atom, (2) aromatic ring substituents, and (3) the side chain. The following discussion focuses on structural modifications of these three portions of the molecule, in that order.



29



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A. N Substitution

In contrast to the catecholamine- or serotonin-releasing amphetamines discussed earlier in this chapter in which an *N*-methyl group or, in some cases, an *N*-ethyl group may be tolerated, *N* alkylation of hallucinogenic amphetamines dramatically attenuates or abolishes hallucinogenic activity (Shulgin, 1981; Shulgin and Shulgin, 1991). Not only does receptor affinity decrease (Shannon *et al.*, 1984), but *in vivo* activity also is diminished. Whereas an *N*-methyl group seems to reduce activity by about one order of magnitude, substituting the nitrogen with *N,N*-dialkyl groups, even as small as methyls, completely abolishes hallucinogenic activity (Shulgin, 1978). *N*

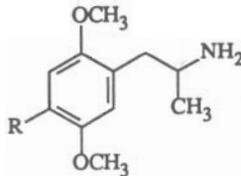
Substitution with a single alkyl larger than a methyl also seems to abolish hallucinogenic activity. Incorporation of the basic nitrogen into a heterocyclic ring leads to inactive compounds as well (Wolters *et al.*, 1974).

B. Aromatic Ring Substitution

1. 2,4,5- and 3,4,5-Substituent Orientation

Although the 3,4,5-trimethoxy pattern of mescaline was the example of aromatic ring substitution, this configuration also seems to afford the lowest potency of all the substitutions studied to date. However, moving the 3-methoxy group to the 2 position and/or replacing the 4-methoxy group with a more hydrophobic group leads to highly active compounds, that is, compounds with a 2,4,5-substituent orientation in which the 2 and 5 substituents are methoxy groups possess the highest potency. Some represen-

TABLE I Representative 4-Substituted Hallucinogenic Amphetamines Based on 2,5-Dimethoxyamphetamine



R	Trivial name	Approximate dose (mg) ^a
H	2,5-DMA	80–160
OCH ₃	TMA-2	20–40
OCH ₂ CH ₃	MEM	20–50
SCH ₃	<i>p</i> -DOT	5–10
NO ₂	DON	3–4.5
CH ₃	DOM	3–10
CH ₂ CH ₃	DOEt	2–6
CH ₂ CH ₂ CH ₃	DOPr	2.5–5
Br	DOB	1–3
I	DOI	1.5–3
CF ₃	DOTFM	— ^b

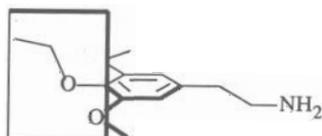
^aHuman data are for the hydrochloride salts, and are from Shulgin and Shulgin (1991).

^bAlthough DOTFM has not been tested in humans, it has somewhat higher affinity for the rat brain 5-HT₂ receptor labeled with [¹²⁵I]-DOI than does DOI itself (D. E. Nichols, unpublished data).

Although resistance to metabolism might contribute to *in vivo* potency, the *para* substituent also seems to be the major determinant of *in vitro* serotonin 5-HT₂ receptor affinity in this series. Based on recently proposed three-dimensional models of serotonin receptor geometries (e.g., see Trumpp-Kallmeyer *et al.*, 1992) the *para* substituent seems most likely to interact with specific amino acid residues or perhaps to lie in a hydrophobic pocket or groove in the binding site of the receptor.

In the 2,5-dimethoxy-4-*n*-alkyl homolog series, optimum activity seems to reside in the *n*-propyl group. The *n*-butyl substituent retains activity, but the *n*-pentyl is much less active. The human data generally parallel the ability of the compounds to elicit a contraction in isolated sheep umbilical artery strips (Shulgin and Dyer, 1975). However, the descriptions of the clinical effects of the *n*-propyl, *n*-butyl, and *n*-pentyl homologs suggest that they differ significantly from the lower alkyl homologs in the nature of their human psychopharmacology (Shulgin and Shulgin, 1991). Glennon and co-workers (Seggel *et al.*, 1990) provided evidence that, as the alkyl group is lengthened in this series from methyl to *n*-octyl, the action of the compounds may change from agonist to antagonist. In this same study, radioligand binding data for the ketanserin-labeled serotonin 5-HT₂ site were presented for several analogs possessing polar 4 substituents such as OH, NH₂, and carboxylic acid esters. The receptor affinities for these compounds were reduced markedly relative to those of compounds with hydrophobic 4 substituents, indicating again the apparent nonpolar nature of the complementary portion of the binding site in the receptor.

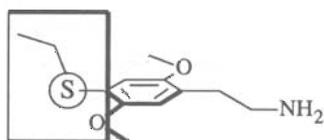
Some evidence suggests that the 4 substituent may adopt a conformation that is out of the aromatic ring plane. For example, in 3,4,5-substituted compounds, the buttressing of the adjacent methoxy groups is known to force the 4-methoxy group into a conformation that lies in a plane nearly perpendicular to the aromatic ring plane (Ernst and Cagle, 1973). Further, homologous compounds with a 4-ethoxy or even a 4-isopropoxy substituent are quite potent (Braun *et al.*, 1978). These more bulky substituents clearly will be forced out of the aromatic ring plane (see Fig. 1 in Nichols and Glennon, 1984). This conformation is depicted here:



In contrast, in the 2,5-dimethoxy-substituted series, a 4-alkoxy group larger than methoxy does *not* increase potency. Indeed, 2,5-dimethoxy-4-ethoxyamphetamine has somewhat lower potency in humans than does the 4-methoxy congener TMA-2 (Shulgin and Shulgin, 1991) and has about half the affinity of TMA-2 at the ketanserin-labeled serotonin 5-HT₂ recep-

tor (Seggel *et al.*, 1990). The different effect on potency of a large 4-alkoxy substituent in the 3,4,5 compared with the 2,4,5 series could be explained as a consequence of the need for the 4 substituent to lie in a plane perpendicular to the aromatic ring plane, as just illustrated. On the other hand, in the 2,4,5 series, the 4-alkoxy group will tend to lie in a conformation that maximizes the overlap of the oxygen unshared electron pairs with the π system of the aromatic ring (Anderson *et al.*, 1979; Makriyannis and Knittel, 1979; Knittel and Makriyannis, 1981). This overlap will force the alkyl attached to this oxygen to lie in the aromatic ring plane, which must be postulated to be an unfavorable conformation.

If a 2,5-dimethoxy compound is substituted with a sulfur atom in the *para* position, large and bulky alkyls can be attached to the sulfur to give compounds that possess considerable potency. For example, hydrochloride salts of the 4-ethylthio and 4-*n*-propylthio compounds are active in humans in the 4–8 mg range, whereas the 4-isopropylthio compound is only slightly less active in a dose range of 7–12 mg (Shulgin and Shulgin, 1991). Qualitatively, the effects, particularly of the 4-*n*-propylthio compound, seem to deviate from classical psychedelic action, tending to produce a state of emotional detachment and anhedonia. Nevertheless, if these compounds are assumed to bind to the same receptor population as their oxygen isosteres, receptor complementarity still can be rationalized by hypothesizing that the alkyl substituent is directed into an out-of-plane conformation. Because sulfur is a larger atom than oxygen, its orbital structure differs from that of oxygen; when the unshared electrons of sulfur overlap with the aromatic π cloud, the alkyl group is not forced to lie in the ring plane. Sulfur is also considerably more lipophilic than oxygen. Thus, in 4-alkylthio compounds, a hydrophobic substituent may be envisioned where the alkyl group projects above the aromatic ring, as shown here:



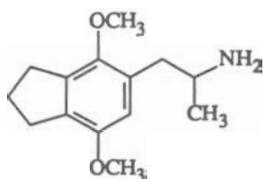
Biological activity is low in compounds in which the oxygen atom of either the 2- or the 5-methoxy group has been replaced with a sulfur, illustrating the difficulty in developing bioisosteres of the 2,5-dimethoxy-substituted aromatic nucleus. However, if relative importance were assigned to the two methoxy groups, the 2-methoxy group would appear to be more critical for optimal activity (Jacob *et al.*, 1977). For example, referring to Table I, when the 2-methoxy group of DOEt is replaced with a methylthio group, *in vivo* activity is reduced by more than one order of magnitude (Jacob and Shulgin, 1983; Shulgin and Shulgin, 1991). However, the replacement of the 5-methoxy oxygen with a sulfur reduces activity only 4-

6-fold. Similarly, when the 2-methoxy group of DOM is replaced with a methylthio group, activity drops by a factor of 10–20, whereas similar replacement of the 5-methoxy only reduces activity 5- to 10-fold (Jacob *et al.*, 1977; Shulgin and Shulgin, 1991).

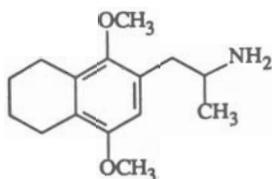
2. Other Substituent Orientations

Although the majority of compounds and the most extensive pharmacological studies have been carried out on molecules with 2,4,5 or 3,4,5 substitution patterns, several other orientations have been examined and some afford psychoactive compounds. In disubstituted compounds, the hydrochlorides of 2,4- and 2,5-dimethoxyamphetamine are reported to be psychoactive in humans at oral doses of 60 and 50 mg, respectively (Shulgin, 1978). However, the published descriptions of the effects of these substances leave some doubt about their exact potencies and whether they truly may be categorized as hallucinogenic amphetamines (Shulgin and Shulgin, 1991). The biological activity of 3,4-dimethoxyamphetamine, which would perhaps bear greatest similarity to the catecholamines, is controversial. No clear evidence exists that it is psychoactive in humans, but this compound appears to be active in the range of a few hundred milligrams (Shulgin, 1978).

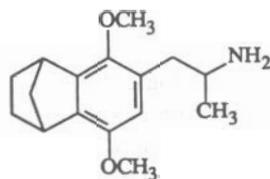
Perhaps some of the more interesting, but certainly less well studied, derivatives are the bicyclic derivatives such as 35, 36, and 37. These compounds all appear to be quite potent in humans, with oral dosages of the hydrochlorides in the 12–32 mg range, but the action is very long, typically exceeding 12 hr. The benzonorbornane derivative 37 has a good deal of steric bulk in the *para* region and, based on the known structure–activity relationships, might have been predicted to be inactive. However, no pharmacological studies exist to indicate whether the mechanism of action is similar to that of other 2,5-dimethoxy-substituted amphetamines. This compound does not, however, have any effect on uptake or release of serotonin or dopamine from rat brain synaptosomes (McKenna *et al.*, 1991a).



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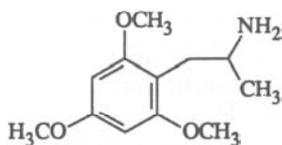
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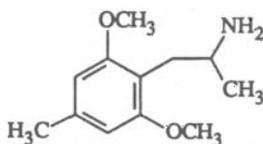
37

The 2,4,6 trisubstitution pattern has received very little attention, but appears quite interesting. The 2,4,6-trimethoxyamphetamine 38 appears to be active in humans in the 30–40 mg range, not too far removed from the

potency of 2,4,5-trimethoxyamphetamine (Shulgin and Shulgin, 1991). Further, 2,6-dimethoxy-4-methylamphetamine (39), a positional isomer of DOM, has been reported to be active in humans in the 15–25 mg range (Shulgin and Shulgin, 1991). Based on the known structure-activity relationships in the 2,4,5-substituted series, one might anticipate that more hydrophobic 4 substituents in this series would lead to quite active compounds. However, no additional members of the series have been reported, nor have any animal or biochemical pharmacological studies been carried out to indicate whether the mechanism of action of the 2,4,6-substituted series is similar to that of compounds with the other substituent orientations.



38



39

Finally, 2,3,4,5-tetramethoxyamphetamine was reported earlier to be active in humans (Shulgin, 1978). However, the more recent description of its effects leaves some doubt about this conclusion (Shulgin and Shulgin, 1991).

C. Side Chain Modifications

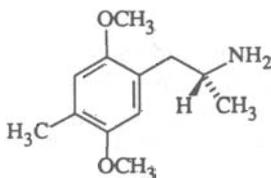
The topic of this volume is “amphetamines.” Strictly speaking, amphetamine is α -methyl-substituted 2-phenethylamine. However, much has been learned about structure-activity relationships of “amphetamine” from examination of side-chain-substituted hallucinogenic phenethylamine derivatives. The simplest modification is to remove the α -methyl group completely, since mescaline lacks an α -methyl group and is active. On the other hand, 2,4,5-trimethoxyphenethylamine is completely inactive whereas its α -methylated analog 2,4,5 trimethoxyamphetamine (TMA-2; Table I) is quite potent (Shulgin, 1978). Many of the non- α -methylated analogs of hallucinogenic amphetamines retain potency within about one order of magnitude of their amphetamine congeners (e.g., Shulgin and Carter, 1975). Although a decrease of this magnitude may seem dramatic from the perspective of structure-activity relationships, these compounds still remain active in humans with relatively small acute oral dosages. For example, 2,5-dimethoxy-4-bromophenethylamine (2C-B) and 2,5-dimethoxy-4-iodophenethylamine (2C-I) possess only about one-tenth the potency of their amphetamine counterparts DOB and DOI, respectively. Nevertheless, DOB and

DOI are two of the most potent hallucinogenic amphetamines known. Therefore, oral human dosages of 2C-B and 2C-I are in the 5–20 mg range.

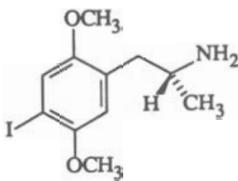
The presence or absence of an α -methyl group has a much less dramatic effect if the 4- substituent is an alkylthio group. Although an approximately 10-fold difference in potency is seen if the substituent is a methylthio group, if the alkyl portion is larger—for example, ethyl, *n*-propyl, or isopropyl—the difference in potency is at most 2- to 3-fold (Shulgin and Shulgin, 1991).

α -Methylation also seems to have less of an effect on potency in 3,4,5-substituted compounds, with perhaps a 2-fold increase of activity from mescaline to its amphetamine counterpart. Fewer examples are available in this substitution series, but the α -methyl congener of escaline (3,5-dimethoxy-4-ethoxyphenethylamine) is virtually equipotent to escaline (Shulgin and Shulgin, 1991). Although Clare (1990) was not able to demonstrate a statistically significant correlation between potency and the presence or absence of an α -methyl group in the two substitution patterns, only limited data are available. To find a differential effect on metabolism that could affect *in vivo* potency would not be surprising, that is, one might speculate that 3,4,5-substituted phenethylamines are generally less susceptible to side-chain deamination than are 2,4,5-substituted phenethylamines. Thus, an α -methyl group would have more of an effect on *in vivo* potency in the latter series. As discussed later, an α -methyl group does not enhance receptor affinity, so any increase in potency as a consequence of adding this structural element would appear to be related to pharmacokinetic effects. To date, however, no one has tested this hypothesis.

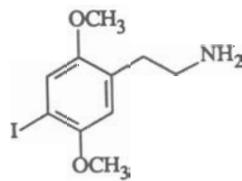
The *R* and *S* side-chain enantiomers of a large number of substituted hallucinogenic amphetamines have been studied. Early on Shulgin (1973) discovered that the clinical effects of racemic DOM were reproduced by its *R*-(-)-enantiomer (40), which was more potent than the *S*-(+) antipode. The development of an asymmetric synthesis for these compounds (Nichols *et al.*, 1973) was followed by several studies that clearly showed that, in all cases, hallucinogen-like activity both *in vivo* and *in vitro* was higher for the *R* enantiomers (Benington *et al.*, 1973; Dyer *et al.*, 1973; Cheng *et al.*, 1974b; Snyder *et al.*, 1974; Anderson *et al.*, 1978; Glennon *et al.*, 1982a,b; Johnson *et al.*, 1987). However, this difference is not stereospecific. Rather, the difference in the activity of the enantiomers is stereoselective, typically being 3- to 6-fold in most assays, whether *in vivo* or *in vitro*.



Receptor binding studies have shown that the α -methyl group does not enhance affinity for the serotonin 5-HT₂ receptor and actually may reduce affinity for the 5-HT_{1A} receptor. Indeed, the basis for the stereoselectivity of the *R* over the *S* enantiomer of hallucinogenic amphetamines now can be understood based on receptor binding studies. Studies of the rat cortical 5-HT₂ receptor, labeled with the agonist ligand 2,5-dimethoxy-4-[¹²⁵I]iodophenethylamine (2C-[¹²⁵I]I), have shown that the *R* isomer of DOI (41) has the same affinity as the non- α -methylated compound 2C-I (42). On the other hand, the affinity of the *S* enantiomer of DOI is reduced, that is, in the more active *R* enantiomer the α -methyl group has no effect on receptor affinity whereas in the less active *S* enantiomer the group has a deleterious effect. As discussed earlier, the higher *in vivo* activity of hallucinogenic amphetamines relative to their nonmethylated phenethylamine homologs is explained most easily if the α -methyl group provides protection from side-chain deamination. Note that the increased hydrophobicity contributed by an α -methyl group also will increase CNS penetration for compounds with hydrophobicities below the optimum. Using human data, Barfknecht *et al.* (1975) calculated this optimum octanol–water log *P* to be 3.1.

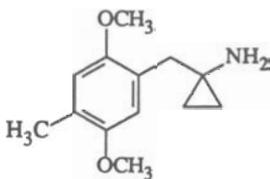


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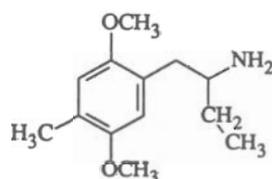


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Addition of a second α -methyl group to the side chain to give α,α -dimethyl compounds abolishes activity (Barfknecht *et al.*, 1978). “Linking” these two methyl groups to form a cyclopropyl ring, as in 43, restores activity. An explanation for these differences in activity may lie in the inability of the α,α -dimethyl compound to adopt an antiperiplanar conformation, as a consequence of nonbonded steric interactions between the side chain and the aromatic ring, whereas conformational mobility is restored in the less bulky cyclopropyl compound (Weintraub *et al.*, 1980).



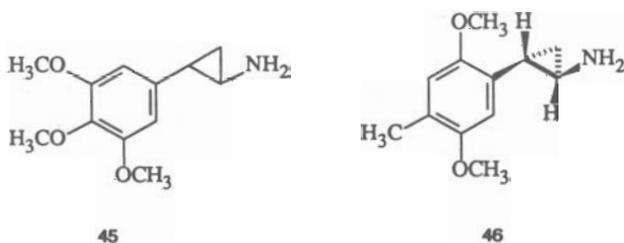
43



44

Extensions of the α -methyl group to longer alkyls abolishes activity completely. For example, the α -ethyl analogs of mescaline (Shulgin, 1963; Shulgin and Shulgin, 1991) and DCM (44; Standridge *et al.*, 1976) are completely inert. Solution NMR and molecular mechanics studies have failed to provide any explanation for this loss of activity based on conformational preferences. A steric effect at the receptor seems most likely to be the reason. In fact, Johnson *et al.* (1990b) showed that the α -ethyl homolog of DOM (44) had only about 1/100th the affinity of DOM for the agonist-labeled 5-HT₂ receptor in rat cortex.

However, the α -methyl group of the amphetamines can be incorporated into a cyclopropane ring with retention of activity. Cooper and Walters (1972) first compared the *cis* and *trans* cyclopropylamine analogs of mescaline for behavioral activity in rats. Only the *trans* compound (45) was active. Aldous *et al.* (1974) subsequently examined several *trans* cyclopropylamine analogs of hallucinogenic amphetamines. This group reported that these congeners had activity and potency similar to those of their amphetamine counterparts. The cyclopropylamine analog of DOM, DMCPA (46), first reported by this group subsequently was resolved into its enantiomers, which were tested by Nichols *et al.* (1979). The 1*R*,2*S*(-) enantiomer (46, as shown) proved to be most active. This result is, perhaps, not surprising since the stereochemistry at the α carbon of the cyclopropyl ring is identical to that of the *R* isomer of the amphetamines. Further, although the difference in affinity for the 5-HT₂ receptor between the *R* and *S* enantiomers of the amphetamines was small, Johnson *et al.* (1990b) reported that the enantiomers of DMCPA have a \sim 30-fold difference in affinity.



Steric effects operative in the amphetamines still apply to these more rigid congeners. Addition of a methyl group to the cyclopropane ring at C3 abolishes activity (Jacob and Nichols, 1982), as does expansion of the cyclopropane ring to a cyclobutane (Nichols *et al.*, 1984). Both these systems could be envisioned as conformationally constrained α -ethyl analogs. Rigid analogs in which the α -methyl group is incorporated into a carbocyclic 5- or 6-membered ring also lack hallucinogen-like activity in animal models (Nichols *et al.*, 1974), although the tetralin analog is a potent agonist in dog vascular smooth muscle (Cheng *et al.*, 1974c). The steric demands of the receptor(s) involved seem to be very stringent.

β -Methoxy-substituted phenethylamines also have been examined briefly. Lemaire *et al.* (1985) noted that a series of four β -methoxy phenethylamines, substituted with 3,4,5-trimethoxy, 3,4-methylenedioxy, 2,5-dimethoxy-4-methyl, and 2,5-dimethoxy-4-bromo substituents, were slightly more potent than the homologs lacking the β -methoxy group but were less active than the corresponding amphetamines.

D. Mechanism of Action

Although the intent of this discussion is not to delve into the mechanism of action for hallucinogenic agents, note that hallucinogenic amphetamine derivatives seem to have pharmacological properties similar to those of the other structural types of hallucinogens, including tryptamines such as psilocin or ergolines such as LSD. Thus, the following discussion of the structure–activity relationships of hallucinogenic amphetamines generally assumes that the mechanisms of action being discussed are the same. However, the reader should be aware that the measurement of biological activity, at least *in vivo* or in clinical studies, is not entirely precise.

The previous sections of this chapter have focused on amphetamine derivatives that act at monoamine uptake carriers, leading to “indirect” pharmacological effects as a consequence of the release of endogenous neuronal monoamines. In contrast, the hallucinogenic amphetamines apparently have a direct postsynaptic agonist action (e.g., see Nichols *et al.*, 1991b, for a review). Further, the receptor that seems to be most important is the serotonin 5-HT₂ subtype. All hallucinogenic agents have high affinity for the agonist state of this receptor (Glennon *et al.*, 1984a; Titeler *et al.*, 1988). However, all hallucinogenic agents also have high affinity for the 5-HT_{1C} receptor subtype. The possibility that this site is also important for the actions of hallucinogens cannot be ruled out (Burris *et al.*, 1991; Sanders-Bush and Breeding, 1991). In addition, although the hallucinogenic amphetamines have relatively selective affinity for these two serotonin receptor subtypes, the tryptamines and LSD also have high affinity for the serotonin 5-HT_{1A} receptor (McKenna *et al.*, 1991b). Thus, the hallucinogenic amphetamines may have a fairly simple pharmacological mechanism, whereas other structural types may owe some of their effects to actions at various other receptors. Despite this relatively recent knowledge concerning the receptors that may be important for the mechanism of action of these chemicals, we really are very far away from any satisfactory explanation of how effects at receptors produce changes in consciousness.

E. Summary of Structure–Activity Relationships

Hallucinogenic activity generally is found in phenethylamines with a primary amino group, containing 3,5- or 2,5-dimethoxy substituents and a hydrophobic group at the 4 position. Although the 4 substituent has not

been studied as extensively in the 3,4,5 orientation, a wide variety of groups has been examined in 2,4,5-trisubstituted compounds. In general, the most active compounds contain, at the 4 position, an unbranched alkyl no longer than three carbons, a halogen larger than fluorine, or an alkylthio group. Some indication exists that 2,6-dimethoxy-4-substituted compounds also may possess high potency.

When an α -methyl group is present, these molecules commonly are called "hallucinogenic amphetamines" and usually are 2–10 times more potent than the nonmethylated phenethylamine. The stereochemistry at the α carbon of the more active enantiomer has the *R* absolute configuration, and the compounds are levorotatory. The α -methyl group can be incorporated into a cyclopropane ring, but no other structural modification is known that leads to compounds that clearly retain hallucinogenic activity. Although certain other derivatives appear to have psychoactive properties (e.g., a side-chain β -methoxy group), whether their mechanism of action can be considered to be the same as that of the "classical" hallucinogens remains unknown.

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