Structure-Activity Relationships of the Classic Hallucinogens and Their Analogs

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The path that leads to the appearance of a new psychotropic drug in the practice of medicine usually consists of four stages: discovery of activity, the development of animal behavioral models that can be correlated to this activity, the study of mechanisms of action and nature of toxicity, and the demonstration of effectiveness and benefit. The final studies of effectiveness for drugs intended for human use must be done in human subjects. This is the essence of the Phases 1 through 4 studies found in the Food and Drug Administration (FDA) regulations associated with the investigatory new drug (IND) application. With many drug families, the results of the animal model studies (steps 2 and 3) can allow prediction of new drug structures (step 1). However, with research in the hallucinogenic drugs (where the desired pharmacological activity can be demonstrated only in humans), the confirmation of activity must occur of necessity in humans. Therefore, it is of potential value for future research in this area to bring together in a single review the known human potencies of the classic hallucinogens and their analogs.

Two words in the title of this chapter must be defined: hallucinogen and classic. A hallucinogen is a drug that changes a person's state of awareness by modifying sensory inputs, loosening cognitive and creative restraints, and providing access to material normally hidden in memory or material of an unconscious nature. The changes thus gained are not masked by amnesia, although they will last only a finite period of time, and they are demonstrable only in humans. A generation ago these drugs were inaccurately called psychotomimetics, things that imitate psychosis. Today the term "hallucinogen" is allowed as a euphemism, although that term is also inaccurate because hallucinations are not part of the usual syndrome. In another generation, the synonym psychedelics may become acceptable in the medical and scientific literature.

Several chemical families that include drugs which have been clinically associated with the term "hallucinogen" have been excluded by design from this review, These substances have been the topics of other

conferences or monographs sponsored. by the National Institute on Drug Abuse (NIDA). Among these exclusions are marijuana, tetrahydrocannabinol (THC), ketamine, and related parasympatholytics such as the *Datura* alkaloids and the JB compounds, opiates, and agents related to 3,4-methylenedioxymethamphetamine (MDMA).

The term "classic" depends on the views of the person who defines it. A compound achieves a classic status when it has served as the focus of a considerable amount of research attention, With compounds such as mescaline, lysergic acid diethylamide (LSD), 2,5-dimethylthiophenethylamine (DOM), dimethyltryptamine (DMT), and psilocybin, the status as classic hallucinogens might be due to the extensive animal and clinical research that has appeared in the literature. But with other compounds such as thiomescaline, 2,5-dimethoxy-4-methylphenethylamine (2C-D), 2,5-dimethoxy-4-methylthiophenethylamine (2C-T), and 3,4,5-trimethoxyamphetamine (TMA), the bulk of the published literature has been focused at a structural and chemical level. The analogs of these nine prototypic classic hallucinogens are reviewed here, and nine tables list structurally related variants that have been explored in humans.

The oldest classic hallucinogen known to Western science is mescaline, the major alkaloid of the dumpling cactus peyote. Mescaline was isolated from the peyote cactus, the pharmacology was defined in 1896, and the structure of mescaline verified by synthesis in 1919. It is used as the potency standard against which all other phenethylamine bases have been compared. Table 1 shows the relative potency of mescaline along with the several alkyl homologs that have been studied with the oxygen atoms maintained in the vicinal 3,4,5-orientation.

A generalization is that there is an increase in potency with increasing the length of the alkyl group on the 4-position oxygen atom but not with such changes with the meta-oriented groups. The naming of these synthetic compounds has exploited the coincidence that mescaline carries the methoxy group at the 4-position and both words begin with the same syllable. The names "escaline," "proscaline," and "buscaline" follow easily as the groups become ethoxy, propoxy, and butoxy. The names for the diethoxy homologs (here and in table 2) incorporate the nomenclature prefix from being symmetrical (sym) or asymmetrical (asym) and having two (bis) ethoxy groups (bescaline).

TABLE 1. *Mescaline analogs*

Name	Code	Potency (mg)	Potency x mescaline
(4-Modified)			
Mescaline (4-methoxy)	M	200-400	1
Escaline (4-ethoxy)	E	40-60	6
Proscaline [4-(n)-propoxy]	P	30-60	7
Isoproscaline (4-isopropoxy)	IP	40-80	5
Buscaline [4-(n)-butoxy]	B	>150	<1
Cyclopropylmethyl-	CPM	60-80	5
Allyloxy-	AL	20-35	10
Methallyloxy-	MAL	40-65	6
Propynyloxy-	PROPYNYL	>80	<2
4-Desoxymescaline (4-methyl)	DESOXY	40-120	4
Phenescaline (4-phenethyloxy)	PE	>150	<1
(Other modified; substituent and location defined)			
Metaescaline (3,4-dimethoxy-5-ethoxy)	ME	200-350	1
Metaproscalme (3,4-dimethoxy-5-propoxy)	MP	>240	1
Asymbescaline (3,4-diethoxy-5-methoxy)	ASB	200-280	1
Symbescaline (3,5-diethoxy-4-methoxy)	SB	>240	<1
Trescaline (3,4,5-triethoxy)	TRIS	>240	<1
(Chain relocation)			
Isomescaline (2,3,4-trimethoxy)	IM	>400	<1
(Deuterium substitution)			
4-Trideuteromescaline	4-D	200-400	1
ß-Dideuteromescaline	ß-D	200-400	1

A comment is appropriate for the use of the symbols ">" and "<" in these tables. When a dosage weight is given as >250 milligrams (mg), the implicit statement is that no activity had been found at 250 mg. It is not known whether the compound is active at any dose, but, if it is, it will be at a dose greater than 250 mg. Thus, the potency relative to mescaline shown as < 1 means that if activity is found, it will be less than that of mescaline. There is no implication that the compound is or is not active.

There have been reports of mescaline analogs with a methoxy group removed. The analog 3,4-dimethoxyphenethylamine (DMPEA) has achieved some notoriety with the report of the observation of a pink spot in the thin-layer chromatographic analysis of the extracts of the urine of schizophrenic patients. The association of the spot with the diagnosis of schizophrenia has remained controversial, but the chemical identity has been shown to be DMPEA. Efforts to evoke some central nervous system (CNS) disturbance with this compound (orally, to > 1.5 grams (g); intravenously [IV], to > 10 mg) have produced no effects. Because of its close structural resemblance to the neurotransmitter dopamine (DA) (3,4-dihydroxyphenethylamine), this result has been disappointing. The 4-ethoxy homolog, 3-methoxy-4-ethoxyphenethylamine (2,3,4-trimethoxyphenethylamine) (MEPEA) has been assayed to 300 mg but has little if any activity.

An additional compound is isomescaline (2,3,4-trimethoxyphenethylamine). There is a fascinating report in the literature concerning its activity. It has been stated to be inactive in normal subjects but to promote a distinct intoxication in schizophrenic patients. If this effect were confirmed, it might play an interesting role as a marker or a biochemical probe of schizophrenia.

The two last compounds in table 1 are the only known deuterium analogs that have been explored in humans, and neither can be distinguished from mescaline. Other uniquely deuterated isotopomers that may be of interest are 3,5-(bis-trideuteromethoxy)-4-methoxyphenethylamine (3,5-D); 2,6-dideuteromescaline (2,6-D), and α,α-dideuteromescaline (α-D). The last compound, being deuterated at the most probable primary site for metabolic attack, might be of a different potency due to the kinetics of a-proton removal, and a study of the (R)-α-monodeuteroisotopomers [(R)α-D] and (S)-α-monodeuteroisotopomers [(S)α-D] might be informative. None of these latter compounds has as yet been studied.

The substitution of a sulfur atom for the 4-oxygen atom of mescaline yields the remarkably potent analog thiomescaline. Although this compound has not been widely studied in clinical trials, it has been the starting point of extensive synthetic studies that have further emphasized the importance of the 4-position of the aromatic ring of the phenethylamines (see table 2).

Homologation at the 4-position again increases or maintains potency until the chain reaches a length of three carbon atoms (4-thioproscaline), and then activity begins to disappear. None of the unsaturated (allylthio, methallylthio) or related electron-rich alkylthio counterparts (cyclopropylmethylthio) has been studied for comparison to the relatively potent oxygen counterparts (table 1). They should be reasonably simple to synthesize and might be exceptionally potent.

One additional degree of structural variation is introduced with the sulfur atom replacement for the oxygen. It may occupy either of two positions, para or meta, to the ethylamine side chain. The meta-sulfur positional isomers still emphasize the importance of the nature of the alkyl substituent on the para-heteroatom. The three possible thioanalogs of isomescaline were without activity.

The two remaining prototypes for structure-activity analysis are close relatives to well-known amphetamine counterparts. The well-studied drug DOM has a 2-carbon homolog, 4-methyl-2,5-dimethoxyphenethylamine (2C-D). The bromo counterpart 2,5-dimethoxy-4-bromoamphetamine (DOB) has a 2-carbon homolog, 2,5-dimethoxy-4-bromophenethylamine (2C-B). Both phenethylamines have engendered large families of analogs, and both amphetamines are presented in table 6.

The simplest 4-alkyl-substituted hallucinogenic compound is 2C-D. This base has been widely explored in the United States as a prototype for the exploration of new compound. In Germany 2C-D has been used as a psychotherapeutic agent in its own right, at larger dosages, usually under the code name of LE-25. The base without this para-alkyl group is 2,5-dimethoxyphenethylamine (2C-H), but if this group is homologated to an ethyl, the extraordinarily powerful and effective compound 2,5-dimethoxy-4-ethylphenethylamine (2C-E) is found. Potency continues to increase with further chain lengthening, but the positive nature of the observed psychopharmacological effects is lessened.

TABLE 2. *Thiomescaline analogs*

Name	Code	Potency (mg)	Potency x mescaline
(Sulfur para)			
4-Thiomescaline (3-Me-4-MeS-5-MeO)	4-TM	20-40	10
4-Thioescaline (3-MeO-4-EtS-5-MeO)	4-TE	20-30	10
4-Thioproscaline [3-MeO-4-(n)-PrS-5-MeO]	4-TP	20-25	10
4-Thiobuscaline [3-MeO-4-(n)BuS-5-MeO]	4-TB	60-120	4
4-Thioasymbescaline (3-EtO-4-EtS-5-MeO)	4-TASB	60-100	4
4-Thiosymbescaline (3-EtO-4-MeS-5-EtO)	4-TSB	>240	<1
4-Thiotrescaline (3-EtO-4-EtS-5-EtO)	4-T-Tris	>200	<1
(Sulfur meta)			
3-Thiomescaline (3-MeS-4-MeO-5-MeO)	3-TM	60-100	4
3-Thioescaline (3-MeS-4-MeO-5-MeO)	3-TE	60-80	5
3-Thiometaescaline (3-EtS-4-MeO-S-MeO)	3-TME	60-100	4
5-Thiometaescaline (3-EtO-4-MeO-5-MeS)	5-MTE	>200	<1
3-Thiosymbescaline (3-EtS-4-MeO-5-EtO)	3-TSB	>200	<1
3-Thioasymbescaline (3-EtS-4-EtO-5-MeO)	3-TASB	~160	<1
5-Thioasymbescalien (3-EtO-4-EtO-5-MeS)	5-TASB	~160	<1
3-Thiotrescaline (3-EtS-4-EtO-5-EtO)	3-T-Tris	>160	<1
(Chain relocation)			
2-Thioisomescaline (2-MeS-3-MeO-4-MeO)	2-TIM	>240	<1
3-Thioisomescaline (2-MeO-3-MeS-4-MeO)	3-TIM	>240	<1
4-Thioisomescaline (2-MeO-3-MeO-4-MeS)	4-TIM	>240	<1

TABLE 3. *2C-D analogs*

Name	Code	Potency (mg)	Potency x mescaline
(4-Alkyl groups)			
4-Proteo-2,5-DMPEA	2C-H	?	
4-Methyl-2,5DMPEA	2C-D(LE-25)[a]	20-60	8
4-Ethyl-2,5-DMPEA	2C-E	10-15	24
4-(n)-Propyl-2,5-DMPEA	2C-P	6-10	40
(3,4-Dialkyl groups)			
Dimethyl-2,5-DMPEA	2C-G	20-35	10
Trimethylene-2,5-DMPEA	2C-G-3	16-25	14
Tetramethylene-2,5-DMPEA	2C-G-4	?	
Norbornyl-2,5-DMPEA	2C-G-5	10-16	24
Naphthyl[b]	2C-G-N	20-40	10
(Other groups)			
1-Fluoro-2,5-DMPEA	2C-F	>250	<1
4-Chloro-2,5-DMPEA	2C-C	20-40	10
4-Bromo-2,5-DMPEA	2C-B	12-24	16
4-Iodo-2,5-DMPEA	2C-I	14-22	16
4-Nitro-2,5-DMPEA	2C-N	100-150	2
4-Isopropoxy-2,5-DMPEA	2C-O-4	>60	?
4-Methylthio-2,5-DMPEA	2C-T[c]	60-100	4
4-Methylseleno-2,5-DMPEA	2C-SE	ca. 100	ca. 3

[a]Higher levels have been used in psychotherapeutic research.
[b]1,4-Dimethoxy-2-(2-aminoethyl)naphthalene
[c]Extensively studied via homologation, see separate table.

As discussed with the 3-carbon amphetamine analogs below, it had been observed that the addition of a second alkyl group at the ring 3-position led to compounds that were of reduced potency but still maintained hallucinogenic activity (table 6). The 2-carbon counterparts are shown in table 3. They form an unusual group with unique properties. Of all the

phenethylamine/amphetamine pairs explored so far, the phenethylamine is of a lower potency than the amphetamine homolog, and the potency of each increases yet further with the increasing of the molecular weight of the 4-alkyl group. However, with these 3,4-dialkyl analogs, as the two alkyl groups become increasingly large and complex, not only do the phenethylamines become more potent than the amphetamine homologs, but the absolute potency also tends to increase with increased mass and bulk of these alkyl groups. The most potent compound yet found in this structural family is the illustrated norbornyl material 3,6-dimethoxy-4-(2-aminoethyl)-benzobornane (2C-G-5), with a total of 5 aliphatic carbons arranged between the 3- and 4-positions.

Many directions can be pursued here, both synthetically and pharmacologically. So far, all the compounds that have been prepared-those that have been evaluated psychopharmacologically and those whose evaluation has not yet been completed-are symmetrically substituted about the 3,4-axis. The use of a Diels-Alder reaction with benzoquinone as the dieneophyle ensures an almost unlimited degree of variation in the 3,4-dialkyl-2,5-dimethoxyphenethylamines. With the increase in mass suggesting greater potency, there may be some remarkable compounds here. Two further avenues of promising exploration are obvious. An asymmetric substitution is possible in which the 3- and 4-position groups are different from one another. Also, one must investigate the optical isomers of the racemates produced (as with 2C-G-5).

Two additional centrally active structural variations of the prototype 2C-D have been observed and explored to a small degree. The p-oxygenated analogs are known as the ß-methoxy-ß-arylethylamine (BOX) series, and the materials with ethoxy groups in place of either of the methoxy groups are called the tweetios. Neither family is entered in table 3, but both are logical extensions of it.

The BOX compounds are ß-oxy analogs of phenethylamines, masked as the methyl ether. The X then is the initial or identifier of the 2C analog that has been oxygenated. This manipulation introduces an oxygen heteroatom at a position identical to that found in the neurotransmitters norepinephrine (NE) and epinephrine. But it also introduces a new chiral center, and in the corresponding amphetamine derivatives a threo-erythro system of diastereoisomers that resembles that of ephedrine and pseudoephedrine would be produced. The ß-methoxy analogs of 2C-ß, ß,2,5-trimethoxy-4-bromophenethylamine (BOB), and 2C-D (ß,2,5-trimethoxy-4-methylphenethylamine [BOD]) are a little more potent than

their oxygen-free counterparts but not as interesting subjectively. There has been no research done on the pure enantiomers.

The two tweetio analogs (2-ethoxy and 5-ethoxy) of both 2C-D and 2C-B have been explored and have dramatically reduced activity. The 5-tweetio (5-ethoxy) compounds are of twofold lessened potency, and the 2-tweetio (2-ethoxy) materials are down by another factor of five. The bis-etios (2,5-diethoxy homologs of 2C-D and 2C-B) are not known to be active at all.

Near the bottom of table 3 is a sulfur compound, 2C-T. Although only modest in activity, its homologs show a wide and varied psychopharmacology and constitute yet another family of hallucinogenics. These 2C-T analogs are listed and compared in table 4.

The optimum alkyl substitution is two to three carbons, with 2C-T-2, 2C-T-4, and 2C-T-7 (the S-ethyl, S-isopropyl, and S-propyl) being both potent and LSD-like. The placement of a methoxy on the S-ethyl group of 2C-T-2 yields the active methoxyethylthio derivative 2C-T-13, and the replacement of this methoxy group with a fluorine gives the potent ß-fluoroethylthio-2,5-dimethoxyphenethylamine (2C-T-21). This structure is interesting because it is the first hallucinogenic drug with six separate elements in its formula (C, H, N, O, S, and F) and is potentially valuable as a vehicle for ^{18}F studies of brain kinetics with positron emission tomography (PET). In this case the fluorine atom is intrinsic to the expressed central activity.

There are two classic amphetamine hallucinogens that have provided the starting point for extensive structure-activity investigations. The first, based on the well-known 3-carbon homolog of mescaline 3,4,5-trimethoxyamphetamine (TMA), is shown in table 5. Here all compounds are characterized by the presence of an oxygen atom on the 4-position of the benzene ring, where the l-position is always defined as the point of attachment of the aminoalkyl side chain. All six possible positional isomers of TMA have been prepared and compared. Two isomers that stand out from the others are the 2,4,5- and the 2,4,6-isomers, TMA-2 and TMA-6. Both are active in the 20 to 50 mg range orally. The first of these has been broadly modified, with the most productive area of change being the nature of the alkoxy group in the 4-position to give 2,5-dimethoxy-4-ethoxyamphetamine (MEM) or the cycling of it into the 5-membered dioxole ring to give 2-methoxy-4,5-methylenedioxyamphetamine (MMDA-2). This latter methylenedioxy base also has been

TABLE 4. *2C-T analogs*

Name	Code	Potency (mg)	Potency x mescaline
(4-Alkylthio-2,5-DMPEA)			
Methyl-	2C-T	60-100	4
Ethyl-	2C-T-2	12-25	16
Propyl-	2C-T-7	10-30	15
Isopropyl-	2C-T-4	8-20	20
Sec-butyl-	2C-T-17	60-100	4
Tert-butyl-	2C-T-9	60-100	4
Cyclopropyl-	2C-T-15	>30	?
Cyclopropylmethyl-	2C-T-8	30-50	8
(4-Heteroalkylthio-2,5-DMPEA)			
2-Methoxyethyl-	2C-T-24	25-40	10
2-Fluoroethyl-	2C-T-21	8-12	30

subjected to positional isomerization. Dropping of the methoxyl group from MMDA-2 (or MMDA) provides one of the few known phenethylamine hallucinogens with only two ring substituents. This base, 3,4-methylenedioxyamphetamine (MDA), is also remarkable because the N-methyl homolog 3,4 (MDMA) has biological activity, although the nature of its action places it outside of this review. No other phenethylamine hallucinogen retains central activity on N-methylation. The mono-substituted analog 4-methoxyamphetamine (4-MA) is an active compound, but it is largely a cardiovascular stimulant.

A similar group of compounds is known that has the 4-alkoxy group replaced with something without an oxygen atom. These are gathered in table 6. Among the more potent of these are the halogen-containing analogs. DOM, DOB, and especially 1(2,5-dimethoxy-4-[^{125}I] iodo-phenyl)-2-aminopropane (DOI), have recently received much research attention as ligands in the study of serotonin receptors.

Two families related to DOM are mentioned here but are not included in table 6. A few 4-alkylthio analogs called the Aleph compounds are

TABLE 5. *TMA analogs*

Name	Code	Potency (mg)	Potency x mescaline
(Alkoxyamphetamine)			
4-Methoxy	4-MA	50-80	5
2,4-Dimethoxy	2,4-DMA	>60	?
2,5-Dimethoxy	2,5-DMA	80-160	2.5
3,4-Dimethoxy	3,4-DMA	in the 100s	<1
3,4,5-Trimethoxy	TMA	100-250	1.7
2,4,5-Trimethoxy	TMA-2	20-40	10
2,5-Dimethoxy-4-Ethoxy	MEM	20-50	10
2,5-Dimethoxy-4-Propoxy	MPM	>30	?
2,3,4-Trimethoxy	TMA-3	>100	?
2,3,5-Trimethoxy	TMA-4	>80	?
2,3,6-Trimethoxy	TMA-5	ca. 30	ca. 10
2,4,6-Trimethoxy	TMA-6	25-50	8
2,3,4,5-Tetramethoxy	TA	>50	?
(Methylenedioxyamphetamine)			
3,4-Methylenedioxy	MDA[a]	80-160	2.5
3-Methoxy-4,5-Methylenedioxy	MMDA	100-250	1.7
2-Methoxy-4,5-Methylenedioxy	MMDA-2	25-50	8
2-Methoxy-3,4-Methylenedioxy	MMDA-3a	20-80	6
4-Methoxy-2,3-Methylenedioxy	MMDA-3b	>80	?

[a]The N-methyl homolog of MDA (MDMA) is not appropriate to this review of hallucinogens.

known, These correspond exactly to the 2C-T bases listed in table 4. Aleph, Aleph 2, Aleph 4, and Aleph 7 are the 4-methylthio-, 4-ethylthio-, 4-isopropylthio-, and 4-propylthio-2,5-dimethoxyamphetamine isomers, respectively. They are consistently more potent than their 2-carbon phenethylamine counterparts.

TABLE 6. *DOM analogs*

Name	Code	Potency (mg)	Potency x mescaline
(4-Alkyl-2,5dimethoxyamphetamine)			
Methyl	DOM (STP)	3-10	50
Ethyl	DOET	2.0-6.0	80
Propyl	DOPR	2.5-5.0	80
Butyl	DOBU	>3	?
Iso-Butyl	DOIB	>10	?
Set-Butyl	DOSB	>25	?
Tert-Butyl	DOTB	>10	?
(4-Substituted-2,5dimethoxyamphetamine)			
Chloro	DOC	1.5-3.0	150
Bromo	DOB	1.0-3.0	150
Iodo	DOI	1.5-3.0	150
Nitro	DON	3.0-4.5	80
2-Fluoroethyl	DOEF	2.0-3.5	100
(3,4-Disubstituted-2,5-dimethoxyamphetamine)			
Dimethyl	G	20-32	10
Trimethylene	G-3	12-18	20
Norbornyl	G-5	14-20	18

The second group has a 2,4,6-substitution pattern. The majority of the compounds listed in the last few tables has carried the 3,4,5- or the 2,4,5-substitution pattern. The similarity of potency between TMA-2 and TMA-6 (the latter with the 2,4,6 substitution pattern, see table 5) has opened up a new family of hallucinogenic amphetamines, one of the authors' current areas of research. With this group also, the 4-position appears to dictate the potency and nature of response. It seems that each of the 2,4,5-substituted materials may have an active 2,4,6-counterpart. The isomer that corresponds to DOM (2,6-dimethoxy-4-methylamphetamine [pseudo-DOM]) is active at 15 to 25 mg orally. Synthetic procedures are now in hand to prepare the pseudo analogs of the 2C-T family with various alkylthio groups at the 4-position.

The first six tables have been devoted to the phenethylamine hallucinogens; the remaining three list the second "kingdom" of pharmacologically related compounds, the tryptamine hallucinogens. Table 7 lists the known active tryptamines other than the psilocybe group. The N,N-dialkyltryptamines are the oldest and most thoroughly studied. Those with low molecular weight groups, DMT and N,N-diethyltryptamine [DET], are presumably inactivated through metabolic deamination and hence must be administered parenterally or with some amine oxidase inhibitor. The presence of groups with increased bulk, such as isopropyl groups, on the nitrogen atom allows these compounds to be active orally.

The indole ring can carry a single oxygen substituent in the aromatic ring, and activity can be retained. The 4-substituted indoles are discussed below. The 5-hydroxylation of DMT (the substitution position of the neurotransmitter serotonin, 5-hydroxytryptamine [5-HT]) yields bufotenine, which is probably not a hallucinogen. Converting this to its methyl ether yields a group of N,N-dialkyl tryptamines whose parenteral/oral availabilities closely parallel the DMT counterparts, except that there is generally an appreciable increase in potency. The masking of the two vulnerable locales of serotonin, the O-methylation to allow entry into the CNS and the α-methylation to avert enzymatic deamination, provide α,, O-dimethylserotonin. This is an orally active hallucinogen of uniquely high potency. Any other substitution on the indole ring (6-, 7-, or multisubstitution) gives inactive compounds. Almost nothing is known about the oral versus parenteral requirements, potency, or nature of action of tryptamines (5-proteo and 5-methoxy) with mixed alkyl groups on the basic nitrogen atom. This is the second area of the authors' current research.

TABLE 7. *DMT analogs*

Name		Code	Potency (mg)	Potency x DMT
(N,N-dialkyltryptamine)				
H		Tryptamine	>100	<1
Dimethyl		DMT	60-100 (4-30 IV)	1
Diethyl		DET	60-150	1
Dipropyl		DPT	20-100 (100s po)	1
Methylisopropyl		MIPT	10-25	4
Diisopropyl		DIPT	40-100	2
Diallyl			80	1
(Ar-substituted — alkyltryptamine)				
H	α-Methyl	IT-290	20-40	3
4-Me	α-Methyl		>60	<1
4-OH	N,N-Dimethyl	(psilocin, see separate table)		
S-OH	N,N-Dimethyl	(bufotenine, not CNS active?)		
5-OCH_3	N,N-Dimethyl	5-MeO-DMT	6-10	10
5-OCH_3	N,N-Disopropyl	5-MeO-DIPT	8-12	7
5-OCH_3	N-Methyl-n-isopropyl	5-MeO-MIPT	4-6	15
5-OCH_3	a-Methyl	α,,O-DMS	3-5	20
5,6-OCH_3	N-Methyl-n-isopropyl	5,6-OMe-MIPT	>60	<1
5,6-OCH_2O	N-Methyl-n-isopropyl		>60	<1
6-OH	N,N-Dimethyl	6-OH-DMT	>80	<1
6-F	N,N-Diethyl	6-F-DET	>80	<1
6-OCH_3	N-Methyl-N-Isopropyl	6-MeO-DIPT	>50	<1
7-OCH_3	N-Methyl-N-Isopropyl	7-MeO-DIPT	>70	<1

IV = intravenous

TABLE 8. *Psilocybin analogs*

Name	Code	Potency (mg)	Potency x mescaline
(4-Oxy,N,N-dialkyltryptamine)			
Dimethyl (phosphate ester)	CY-39 (PSOP)	10-15	6
Dimethyl (free OH)	CX-59 (PSOH)	7-10	8
Methylpropyl (free OH)	4-OH-MPT	10-15	6
Methylisopropyl (methyl ether)	4-MeO-MIPT	20-30	3
Diethyl (phosphate ester)	CEY-19	20-30	3
Diethyl (free OH)	CZ-74	15-20	4
Diisopropyl (free OH)	4-OH-DIPT	15-20	4

An additional family of compounds should be mentioned here, the ß-carbolines. Their use has been well documented in the ethno-pharmacological literature as enzyme inhibitors that allow the tryptamines normally only active parenterally to be orally active, presumably by inhibiting first-pass metabolism in the liver. Also, they can be generated by the cyclization of 6-methoxytryptamine with a 2-carbon unit such as acetaldehyde. In nature, they usually are found in one of three degrees of hydrogenation: harmine, harmaline, and tetrahydroharmine. The isomers more closely related to serotonin are similarly formed, synthetically, from 5-methoxytryptamine. Only harmaline, one of the principal components of Ayahuasca, has a reputation for being intrinsically an active hallucinogen. The aromatic analog, harmine, has little if any psychotropic activity. No reports have been published concerning the three cyclization products of 5-methoxytryptamine.

The family of tryptamines with an oxygen function at the 4-position is based on the active alkaloids of the mushroom genus *Psilocybe* (table 8). The phosphate ester alkaloid is psilocybin, and the free phenolic counterpart is the less stable compound psilocin. The dephosphorylation of psilocybin to psilocin appears to occur in the body, as both are molecularly equipotent. The N,N-diethyl homologs have been synthesized and explored in connection with psychotherapy. They appear to be a little less potent than the methyl counterparts. Another study has looked at other groupings on the nitrogen atom, and all materials

investigated are potent and orally active. Both the monomethylated and nonmethylated homologs, baeocystin and norbaeocystin, occur as congeners of psilocin in some species of the mushrooms. They have not been assayed in humans.

The last and by far most potent family of the tryptamine hallucinogens is found in the ergolines related to LSD. These are listed in table 9. Classically, the diethylamide has been considered the most potent of all and the prototype for comparison. The earliest work done in this area usually gave human potencies as an explicit fraction of the potency of LSD itself, and some of these values have been derived from a single dosage administration. The microgram (μg) ranges offered have been obtained by back calculations from these fractions. The N-1 acetyl derivative is equipotent, probably due to an easy loss of the acetyl group by hydrolysis in the body. All variations studied on the amide nitrogen have led to compounds of diminished activity.

However, variations of the N-6 substitution have maintained the potency of LSD and in some cases enhanced it. No studies have been made of the more potent N-6 homologs with amide nitrogen substituents other than the diethyl group found in LSD.

CONCLUSION

This chapter presents a brief picture of the present state of knowledge of the analogs of the classic hallucinogens. Relating these to the logical neurotransmitters, no structural theme is apparent that would allow a working theory of their mode of action. Many attractive research directions are obvious from the omissions in these tables. Two have been mentioned as being in progress. If the 2,4,6-substitution pattern proves to provide consistently active compounds, hypotheses suggesting some involvement of a hydroquinone intermediate explaining the activity of the 2,4,5-substituted compounds will have to be reconsidered. Analysis of the geometry surrounding the basic nitrogen in the DMT homologs might accurately define the geometry requirements of the active site involving that location. These studies are also in progress.

Other provocative questions remain. Might the remarkable activity of the N-methyl N-isopropyl substitution patterns of the tryptamines apply to the phenethylamines? Why are the active phenethylamines so active

TABLE 9. *LSD analogs*

Name	Code	Potency (mg)	Potency x DMT
(Amide variations)			
Diethyl	LSD-25	50-200	1
(1-AC, 2-H)	ALD-52	100-200	1
(1-Me, 2-H)	MLD-41	200-300	0.3[a]
(1-H, 2-Br)	BOL-148	>1,000	<0.1
(l-Me, 2-Br)	MBL-61	>10,000	<0.01
Ethyl	LAE-32	500-1,400	0.1[a]
(1-AC, 2-H)	ALA-10	1,200	0.1
(l-Me, 2-H)	MLA-74	2,000	0.05[a]
Methyl		ca. 500	ca. 0.2[a]
Dimethyl	DAM-57	500-1,200	0.1
Methylpropyl	LMP	>100	<1
1-Hydroxy-2-Propyl	Ergonovine	10,000	0.01[a]
1-Hydroxy-2-Butyl	Methylergonovine	2,000	0.05[a]
(l-Me, 2-H)	UML-491 (Sansert)	4,000-8,000	0.02
-$(CH_2)_5$-(pyrrolidinyl)	LPD-824	800	0.1[a]
(l-Me, 2-H)	MPD-75	>1,600	<0.05
-$CH_2CH_2OCH_2CH_2$-(morpholinyl)	LSM-775	300-600	0.3
(N-6 variations)			
H	Nor-LSD	>500	<0.3
Methyl	LSD	50-200	1
Ethyl	EHLAD	40-80	2
Propyl	PROLAD	80-175	
Allyl	ALLYLAD	50-150	1
Butyl	BULAD	>400	<0.3
Phenethyl	PHENETHYLAD	>350	<0.3

"Relative potency is based on intensity of described effects, In some cases only a single dosage level was employed.

whereas common wisdom would predict that they should be deaminated and thus inactive? Also, with these compounds and their amphetamine homologs, why is it only the 4-position that allows such extensive structural manipulation without much attenuation in activity? In the tryptamine world, might there not be a host of active compounds to be found pursuing the amphetamine-like structure of α,O-DMS, and perhaps further homologs with one or two alkyl groups on the basic nitrogen?

The answers to these and other related questions might provide valuable information to help explain the remarkable activity of this class of psychotropic agents.

NOTE

Some of the data presented here have not been published previously. A comprehensive bibliography documenting the known data reviewed in this article would contain hundreds of citations. For leading reviews that provide these references, the following should be consulted.

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