Penetrating the Veil: Hallucinogens

"How long will this last, this delicious feeling of being alive, of having penetrated the veil which hides beauty and the wonders of celestial vistas? It doesn’t matter, as there can be nothing but gratitude for even a glimpse of what exists for those who can become open to it."
- Alexander Schulgin, PiHKAL

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Hallucinogenics: An Overview

Referred to by a variety of names: psychedelic (mind manifesting), psychodysleptic (mind disturbing), onierogen (producing dreams), entheogen (producing religious experience), psychotomimetic (psychosis mimicking), schizotoxin

A hallucinogen is a psychoactive substance that powerfully alters perception, mood, and other cognitive processes.

I have expanded the definition slightly to include Cannabinoids, which don’t induce the same kinds of powerful mood and perception alterations.

Most hallucinogens discussed in this group meeting (but not all) are listed as Schedule 1 drugs under the Controlled Substances Act in the USA. All of the following findings must be made to fall under Schedule 1 (21 USC § 812):

1. The drug or other substance has a high potential for abuse
2. The drug or other substance has no currently accepted medical use in treatment in the United States.
3. There is a lack of accepted safety for use of the drug or other substance under medical supervision.

Those not covered explicitly can fall under the Federal Analog Act (21 USC §813) if it is substantially similar to a Scheduled drug.

Hallucinogens are illegal substances in most locales and safety data is all but non-existant. Additionally, their use in uncontrolled, non-medical settings is extremely dangerous. This presentation is for education purposes only and individuals should consult and follow their applicable laws.

Psilocybe semilanceata

Lophophora williamsii
Penetrating the Veil: Hallucinogens

A History of Hallucinogens: From Natural to Synthetic

Hallucinogens have been used throughout history in religious practices by a number of cultures:

- **Olmec** (12,000 BCE - 400 BCE, South America) priests were buried with Bufo Toads, which are known to produce a number of psychoactive substances on their skin.

- **Native Americans** (3700 BCE - present, North America) have consumed peyote (mescaline) in sacred rituals since as early as 3700 BCE.

- **Vedic** (~2000 BCE, India) consumed Soma as a ritual drink. Although its identity is unknown, it was likely a hallucinogen or stimulant.

- **Ancient Greeks** (~1500 BCE, Greece) consumed the drink *kykeon*, or kykeon, in a ritual to achieve a revelatory state. It is possible that this contamination produced the hallucinations.

- **Aztecs** (1300 AD - 1500 AD, South America) consumed *teonanácatl*, or "god's flesh", which today we know as Psilocybin mushrooms. They also consumed ololiuqui, containing a compound similar to LSD.

- **South American** (1600 AD - present, South America) religious groups consume ayahuasca.

Amanita muscaria, possible source of Soma, contains muscimol, a hallucinogenic GABA_A agonist.

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Ayahuasca is a tea consisting of *Banisteriopsis caapi*, containing Harmine, and a DMT containing plant, such as *Psychotria viridis*.

The first synthetic hallucinogen was Lysergic Acid Diethylamide (LSD), produced accidentally by Albert Hofmann of Sandoz Ltd.

Hofmann was looking for an analeptic compound and prepared LSD in 1938 because of the structural similarity to nikethamide, a known compound.

The compound produced many of the same effects as other ergot alkaloids, as well as a marked excitation in the animals. The compound fell out of interest for a number of years before Hofmann decided to revisit the compound in 1943. From a letter to the Head of the Pharmaceutical Department, professor Arthur Stoll:

"Last Friday, April 16, 1943, I was forced to stop my work in the laboratory in the middle of the afternoon and to go home, as I was seized by a peculiar restlessness associated with a sensation of mild dizziness. On arriving home, I lay down and sank into a kind of drunkenness which was not unpleasant and which was characterized by extreme activity of imagination. As I lay in a dazed condition with my eyes closed (I experienced daylight as disagreeably bright) there surged upon me an uninterrupted stream of fantastic images of extraordinary plasticity and vividness and accompanied by an intense, kaleidoscope-like play of colors. This condition gradually passed off after about two hours."

3 days later, convinced that LSD had caused the effect, he ingested 0.25 mg of LSD (the lowest dose he expected to have an effect):

April 19, 1943: Preparation of a 0.5% aqueous solution of d-lysergic acid diethylamide tartrate

- 4:20 P.M.: 0.5 cc (0.25 mg LSD) ingested orally. The solution is tasteless.
- 4:50 P.M.: no trace of any effect.
- 5:00 P.M.: slight dizziness, unrest, difficulty in concentration, visual disturbances, marked desire to laugh...

At this point Hofmann had a laboratory assistant accompany him home. On his cycling ride home, things took a turn...
A History of Hallucinogens (cont.)

"As far as I remember, the following were the most outstanding symptoms: vertigo, visual disturbances; the faces of those around me appeared as grotesque, colored masks; marked motoric unrest, alternating with paralysis;...clear recognition of my condition, in which state I sometimes observed, in the manner of an independent, neutral observer, that I shouted half insanely or babbled incoherent words."

Subsequent experiments "on volunteer colleagues of the Sandoz Research laboratories" confirmed the effect and showed the effective dose is around 0.03 to 0.05 mg, indicating he had injected around 5-10 times the effective dose.

Hofmann's bike ride celebrated on an LSD blotter

- Sandoz introduced LSD as a drug in 1947
- In the 1950's the CIA began Project MKUltra, where they administered LSD (among other drugs) to investigate whether it could be used to alter someone's loyalty. It was often administered without consent or knowledge
- LSD and other hallucinogens were a significant part of the 1960's counterculture and became nationally known
- Various clinical trials and investigations were undertaken of hallucinogens between 1950 and 1980
- In 1970 the US Congress passed the Controlled Substances Act which banned most hallucinogenic drugs known or used at the time

As a result of US (and other countries) drug laws, studying hallucinogenic substances, especially human trials, is especially challenging

"Hallucinogens have a unique and powerful ability to affect the human psyche. They may alter one's concepts of reality, may change one's views on life and death, and can provoke and challenge one's most cherished beliefs. Therein...lay the roots of much of the fear and hysteria that these substances have fostered in our society."

-David. E. Nichols, Hallucinogens

5-HT<sub>2A</sub> receptor agonists (classical hallucinogens)

**Common Neutrotransmitters**

- serotonin (5-HT)
- Dopamine (DA)

Most hallucinogens increase levels of the neurotransmitter serotonin (5-HT). Classic hallucinogens are believed to act primarily on 5-HT<sub>2A</sub> receptor in the brain.

- 5-HT<sub>2A</sub> receptor

5-HT<sub>2A</sub> is a G-protein coupled receptor and a member of the 5-HT<sub>2</sub> receptor family. It is known to play a physiological role in working memory, regulation of cognitive states, and associative learning.

5-HT<sub>2A</sub> is believed to be involved in neural disorders including psychosis and schizophrenia

Drugs that act as antagonists or inverse agonists to 5-HT<sub>2A</sub> are used in the treatment of hypertension (Ketanserin), depression (Nefazodone) and schizophrenia (Clozapine, Zyprexa).

**Common features of 5-HT<sub>2A</sub> receptor agonists**

- Most 5-HT<sub>2A</sub> receptor agonists are physiologically safe molecules that show no toxicity at active doses. In the millions of people who have used LSD, there is not one case known of death directly attributable to the toxicity of LSD.*

*People have died walking out onto a freeway or attempting to fly. Some of the phenethylamine hallucinogens have caused lethal overdoses, although at doses greatly in excess of active doses

- Classic hallucinogens do not create dependance or addiction. Substances commonly thought of as addictive (cocaine, nicotine, caffeine) affect dopaminergic (DA) transmission and reward systems in the brain. Hallucinogens lack affinity for DA receptors and DA transporters and there is no evidence they product addiction.

Penetrating the Veil: Hallucinogens

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_i^{1}$ 5-HT$_{2A}$ (nM)</th>
<th>Drug discrimination ED50 $^2$ (μM/kg)</th>
<th>Human dose (mg) $^3$</th>
<th>Potency relative to LSD (human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EthLAD</td>
<td>–</td>
<td>0.02</td>
<td>0.04–0.15</td>
<td>140</td>
</tr>
<tr>
<td>AllyLAD</td>
<td>–</td>
<td>0.013</td>
<td>0.08–0.16</td>
<td>110</td>
</tr>
<tr>
<td>LSD</td>
<td>2–4</td>
<td>0.037</td>
<td>0.06–0.20</td>
<td>100</td>
</tr>
<tr>
<td>ProLAD</td>
<td>–</td>
<td>0.037</td>
<td>0.010–0.20</td>
<td>90</td>
</tr>
<tr>
<td>DOB</td>
<td>0.6</td>
<td>1.06</td>
<td>1–3</td>
<td>7</td>
</tr>
<tr>
<td>DOI</td>
<td>0.7</td>
<td>0.28</td>
<td>1.5–3</td>
<td>6</td>
</tr>
<tr>
<td>DOM</td>
<td>19</td>
<td>0.89</td>
<td>3–10</td>
<td>2</td>
</tr>
<tr>
<td>Psilocin</td>
<td>15–25</td>
<td>1.0</td>
<td>10–15</td>
<td>1</td>
</tr>
<tr>
<td>DMCPA</td>
<td>–</td>
<td>0.66</td>
<td>15–20</td>
<td>0.7</td>
</tr>
<tr>
<td>MEM</td>
<td>73</td>
<td>12</td>
<td>20–50</td>
<td>0.4</td>
</tr>
<tr>
<td>MMDA-2</td>
<td>–</td>
<td>7</td>
<td>25–50</td>
<td>0.4</td>
</tr>
<tr>
<td>Mescaline</td>
<td>550</td>
<td>34</td>
<td>200–400</td>
<td>0.04</td>
</tr>
</tbody>
</table>


**Phenethylamines (phenylalkylamines)**

Mescaline is the major psychoactive component of the peyote cactus, which has been used by Native Americans for over 5000 years.

Mescaline is the oldest known hallucinogen, it was isolated in 1897 by Arthur Heffter and the structure was confirmed through synthesis in 1913 by Ernst Spath.

It is a very weak hallucinogen with doses between 200-400 mg (10-20 g of cactus) typical to experience its psychoactive effects.

Shulgin & Shulgin, 1991

**General synthesis of phenalkylamines**

Starting with essential oils

Myristicin

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO}
\]

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

1. H$_2$O$_2$

2. H$_2$SO$_4$

Nitration of styrenes

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{C(NO}_2\text{)$_4$} \quad \text{Py}
\]

SAR data on phenalkylamines

<table>
<thead>
<tr>
<th>R</th>
<th>$\text{MeO}$</th>
<th>$\text{OMe}$</th>
<th>$\text{NH}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative potency</td>
<td>1</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Effective human dose</td>
<td>&gt;300 mg</td>
<td>60-100 mg</td>
<td>20-60 mg</td>
</tr>
</tbody>
</table>

R = OMe (TMPEA)
R = SMe (2C-T)
R = Me (2C-D)
R = Br (2C-B)
R = I (2C-I)
R = Et (2C-E)
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Steven McKerrall

Baran Lab Group Meeting

Phenylalkylamines (cont.)

![ChemMedChem, 2008, 3, 1299-1309](image)

Discerning the binding mode

α-methylation increases potency, although it may not be strictly through binding efficiency

ED$_{50}$ = 1.8 μmol/kg  
$K_i$ = 100 nm

ED$_{50}$ = 5.6 μmol/kg  
$K_i$ = 110 nm

(2C-B (dose 12-24 mg)

(with 100 mg) I had weighed correctly. I had simply picked up the wrong vial. And my death was to be a consequence of a totally stupid mistake. I wanted to walk outside, but there was a swimming pool there and I didn’t dare fall into it...Two hours later, I knew that I would live after all, and the experience became really marvelous. But the moment of facing death is a unique experience.

Rigid phenylalkylamines

The fully aromatic compound is the first alkylamine derivative to show higher potency than LSD (ED$_{50}$ = 40 nmol/kg)

ED$_{50}$ = 1.12 μmol/kg  
$K_i$ = 22 nm

ED$_{50}$ = 61 nmol/kg  
$K_i$ = 18 nm

ED$_{50}$ = 22 nmol/kg  
$K_i$ = 40 pm

K$_i$ for 5-HT$_{2A}$

R = H  
0.73 nM

R = Me  
1907 nM

R = n-Pr  
1295 nM

R = Bn  
0.25 nM

R = BOMe  
0.044 nM

R = BOMe

nearly identical to the non-cyclopropyl compound, indicating a s-trans configuration in the binding mode

ED$_{50}$ = 24 nmol/kg  
$K_i$ = 260 pm

Discerning the binding mode


WIREs Membr Transp Signal, 2012, 1, 559–579
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Tryptamines

\[
\text{Psyilocybin} \rightarrow \text{Psilocin}
\]

The active ingredient of Psyilocybin mushrooms was isolated and characterized by Albert Hofmann in the 1950s.

Dimethyltryptamine

Harmine

In the absence of either the DMT or the Harmine containing plant, the tea has no unusual effects. Why?

DMT is the psychoactive ingredient, but it is not orally bioavailable, as it is rapidly degraded by monoamine oxidase enzymes. Harmine is a monoamine oxidase inhibitor (MAOI), and so it makes the DMT orally bioavailable.

Structure-Activity Relationship

\[
\text{R}^1 \quad \text{R}^2 \quad \text{Name} \quad \text{Reaction} \quad \text{Dose}
\]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Name</th>
<th>Reaction</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>5-MeO-T</td>
<td>not a psychedelic</td>
<td>?</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>5-MeO-NMT</td>
<td>unknown activity</td>
<td>?</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>5-MeO-DMT</td>
<td>positive, psychedelic, out-of-body</td>
<td>6-20 mg</td>
</tr>
<tr>
<td>Me</td>
<td>i-Pr</td>
<td>5-MeO-MIPT</td>
<td>mixed, complex</td>
<td>4-6 mg</td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>5-MeO-DET</td>
<td>negative, vertigo, erotic</td>
<td>2-3 mg</td>
</tr>
<tr>
<td>pyr</td>
<td>pyr</td>
<td>5-MeO-pyr-T</td>
<td>very negative, amnesia</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
<td>5-MeO-DPT</td>
<td>neutral, balance, good and bad</td>
<td>6-10 mg</td>
</tr>
<tr>
<td>i-Pr</td>
<td>i-Pr</td>
<td>5-MeO-DIPT</td>
<td>positive, LSD-like psychedelic</td>
<td>8-12 mg</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-Bu</td>
<td>5-MeO-DBT</td>
<td>unknown activity</td>
<td>?</td>
</tr>
</tbody>
</table>

Schulgin & Schulgin, *TiHKAL*

Tryptamine Synthesis

\[
\begin{align*}
\text{R}_2 \text{NH} & \xrightarrow{(\text{COCl})_2} \text{R}_2\text{NH}(\text{COCl})_2 \\
\text{R}_2\text{NH}(\text{COCl})_2 & \xrightarrow{\text{LiAlH}_4} \text{R}_2\text{NH}\text{CO}\text{NR}_2 \\
\text{R}_2\text{NH}\text{CO}\text{NR}_2 & \xrightarrow{\text{LiAlH}_4} \text{R}_2\text{NH}\text{NR}_2
\end{align*}
\]

*JACS, 1954, 76, 6208-6210*

"(25 mg, smoked)...The entire universe imploded through my consciousness. It's as if the mind is capable of experiencing a very large number of objects, situations, and feelings, but normally perceives the only one at a time. I felt that my mind was perceiving them all at once. This was simply the most intense experience possible."
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**Tryptamines (cont.)**

**Structure-Activity Relationship (cont.)**

Tryptamines are extremely sensitive to substitution on the indole ring and nearly any substitution besides those shown previously results in diminished activity.

Switching the indole for another heterocycle (benzofuran, benzothiophene, etc.) produces compounds with modest, but diminished activity.

![Tryptamine Structure](Image)

- ED<sub>50</sub> = 0.04 mg/kg
- K<sub>i</sub> = 46 nM
- Effective dose = 2.4 mg

**Lysergic Acid Diethylamide (Ergolines)**

- Synthesized from Lysergic acid in 1938, activity discovered in 1943.
- At the time of its discovery it was the most potent (by effective dose) drug molecule ever known.
- Investigated for a number of treatments (alcoholism, psychotherapy).
- No toxicity related deaths from LSD have ever been reported. Biggest risk is inducing psychosis (~8 in 10,000). "Flashbacks" are also reported, but there is no good data or even consensus about the exact clinical symptoms.

![LSD Structure](Image)

LSD is a physically fragile molecule, and is sensitive to base and light. Base epimerizes the molecule to isolysergic acid (inactive) and light promotes addition of water across the olefin.

"Taking LSD was a profound experience, one of the most important things in my life. LSD shows you that there's another side of the coin, and you can't remember it when it wears off, but you know it. It reinforced my sense of what was important - creating great things instead of making money, putting things back into the stream of history and of human consciousness as much as I could."

- Steve Jobs

- Consumption of ergot contaminated wheat leads to ergotism (St. Anthony's Fire), which is characterized by hallucinations, irrational behavior, convulsions, and even death.
- Ergotism has been proposed as a explanation for the behavior that preceeded the salem witch trials.
- Ergot alkaloids are used in the prevention of postnatal bleeding.
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Lysergic Acid Diethylamide (cont.)

Woodward (1954): The Total Synthesis of Lysergic Acid

Julia (1969): Une Nouvelle Synthese de L’acide Lysergique

Oppolzer (1981): Total Synthesis of (±)-Lysergic Acid by an Intramolecular Imino-Diels-Alder Reaction

"The difficulty was surmounted by treating the hydrochloride of 73 with excess sodium cyanide in anhydrous liquid hydrogen cyanide, under which conditions the desired nitrile 74 was formed in good yield."

JACS, 1954, 76, 5256-5257
JACS, 1956, 78, 3087-3114

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Lysergic Acid Diethylamide (cont.)

Ninomiya (1982): A New Synthesis of Lysergic Acid

\[
\begin{align*}
\text{H} & \stackrel{\text{NMe}}{\text{C}} \text{O} \text{Me} \\
\text{H} & \text{NMe} \text{NMe} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{align*}
\]

\[
\text{h} \nu \text{NaBH}_4 \\
10:1 \text{PhH/MeOH} \\
81\% \ 7:1 \text{ d.r.}
\]

\[\text{Heterocycles, 1982, 19, 2279-2282}\]


Rebek (1983): A New Synthesis of Lysergic Acid

\[
\begin{align*}
\text{NHBz} & \text{Br} \text{CO}_2\text{Et} \\
\text{Zn} & \rightarrow \\
\text{NHBz} & \text{H} \\
\end{align*}
\]

\[
\text{1) Mel} \\
\text{2) HBr}
\]

\[\text{Tet. Lett., 1983, 24, 859-860}\]

Vollhardt (1994): A Cobalt-Catalyzed Entry into the Ergot Alkaloids: Total Syntheses of Lysergene and LSD

\[
\begin{align*}
\text{H} & \text{C} \text{N} \\
\text{NMe} & \text{NMe} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{align*}
\]

\[
\text{CpCo(CO)}_2 \\
\rightarrow \\
17\%
\]

\[\text{Synlett, 1994, 7, 487-489}\]

Ohno (2008): Total Synthesis of Lysergic Acid, Lysergol, and Isolysergol by Palladium-Catalyzed Domino Cyclization of Amino Alenes Bearing a Bromoindolyl Group

\[
\begin{align*}
\text{Br} & \text{CHO} \\
\rightarrow \\
\text{NiCl}_2, \text{CrCl}_2 \\
90\%
\end{align*}
\]


\[\text{Org. Lett., 2008, 10, 5239-5242}\]

Padwa (1995): An Approach to Lysergic Acid

\[
\begin{align*}
\text{MeN} & \text{NMe} \\
\text{O} & \text{MeO} \\
\text{O} & \text{O} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{align*}
\]

\[
\text{Rh}_2(\text{pfb})_4 \\
93\%
\]

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Lysergic Acid Diethylamide (cont.)

Any change in the amide substitution results in at least an order of magnitude decrease in potency

LSD's extreme in vitro potency does not correlate well with it's 5-HT2A binding, indicating an additional mechanism may be responsible for it's unusual potency

Serotonin Releasers

3,4-methylenedioxymethamphetamine (MDMA, ecstasy)

MDMA stimulates serotonin release through membrane transport systems responsible for reuptake and storage.

While not capable of typically producing hallucinations, it causes derealization, depersonalization, and other alterations of consciousness.

Unlike classical hallucinogens MDMA has some significant toxicity issues and overdoses can result in death

Overdose results in serotonin syndrome, which can cause increases in heart rate, blood pressure, and body temperature, which can result in shock and death

4-methylthioamphetamine (4-MTA)

Introduced by David Nichol's lab in the 1990s.

A highly selective serotonin releasing agent. It additionally inhibits the enzymes that break down serotonin

In the early 2000's it appeared as a street drug, resulting in 6 deaths associated with overdose.

"I was stunned that I had published information that ultimately led to human death."

"What if a substance that seems innocuous is marketed and becomes wildly popular on the dance scene, but then millions of users develop an unusual type of kidney damage that proves irreversible and difficult to treat, or even life-threatening or fatal? That would be a disaster of immense proportions. This question, which was never part of my research focus, now haunts me."

-David E. Nichols

Nature, 2011, 469, 7

Mesembrine

There is mixed data about whether mesembrine produces hallucinogenic effects.

It is the major alkaloid found in Sceletium tortuosum (Kanna), which has mood altering, empathogenic effects.

Believed to be an selective serotonin reuptake inhibitor (SSRI)

J. Ethnopharmacology, 2011, 137, 1124-1129
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**Rigby (2000): Total Synthesis of Mesembrine**

\[
\text{PhH, reflux} \quad 66\%
\]

**You (2011): Total Synthesis of Mesembrine**

\[
\text{5 mol\% A} \quad 91\% \text{ yield} \quad 97\% \text{ e.e.}
\]

**Dissociative (NMDA receptor antagonists)**

**Phenylcyclidine (PCP)**

PCP is an antagonist for the NMDA receptor.

It produces an anesthetic effect and at high doses produces dissociative hallucinations.

General features include sensory deprivation, dissociation (feeling of separation from reality), and a trance-like state.

PCP use produces a host of psychological effects such as paranoia, depersonalization and aggressive behavior.

**Misc. Hallucinogens**

**Salvinorin A**

Salvinorin A is the principle psychoactive component of *Salvia divinorum*.

It has a unique mechanism as a \(\kappa\)-opioid receptor agonist.

It is the only non-alkaloid hallucinogen known and the most potent natural hallucinogen (~200 \(\mu\)g dose).
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Salvia divinorum

It was used by Mazatec shamans in religious experiences.

It has attracted significant attention as it is the first opioid receptor agonists that is not an alkaloid and has been investigated for the treatment of opioid addiction.

Salvia is a potent and quick-acting hallucinogen, with typical durations of 15-30 minutes.

It produces a dissociative effects with uncontrollable laughter, sensations of motion, merging with or becoming objects, and overlapping realities.


**Total Synthesis of Salvinorin A**

Evans (2007): Asymmetric Synthesis of Salvinorin A, A Potent κ Opioid Receptor Agonist

Ibogaine

Psychoactive ingredient in *Tabernanthe iboga*, or just Iboga

Ibogaine has complex pharmacology, interacting with 5-HT<sub>2A</sub>, NMDA, and κ-opioid receptors.

It has significant stimulant effects as well, “the hallucinogenic dose appears to be several times higher than the stimulant dose, the user must endure intense and unpleasant central stimulation in order to experience the hallucinogenic effects”

-Schulgin & Schulgin, *TiHKAL*

It is known for it's extreme duration, with the most intense effects lasting for 24 hours or more, and after effects such as difficulty sleeping for an additional day or two.

**Total Synthesis of Ibogaine (Ibogamine)**

Zeigler (1966): Total Synthesis of Iboga Alkaloids

Penetrating the Veil: Hallucinogens

**Total Synthesis of Ibogaine (Ibogamine)**

Trost (1978): A Total Synthesis of Racemic and Optically Active Ibogamine. Utilization and Mechanism of a New Silver Ion Assisted Palladium Catalyzed Cyclization

![Chemical Structure]

**Synthesis of Cannabinoids**

Mechoulam, *JACS*, 1967, 89, 4552

**Cannabinoids**

Tetrahydrocannabinol (THC)

Cannabinoids activate the cannabinoid receptors CB₁ and CB₂. CB₁ is a GPCR responsible for the psychoactive effects of cannabis.

Not hallucinogenic but causes relaxation, euphoria, munchies

4th most popular recreational drug in the world (most popular broadly illegal)

100 million (1/3) Americans have tried cannabis and 25 (1/12) million have used it in the last year.

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The philosopher in each of us yearns for greater understanding of who we are and why we are here. Irrational fear of inquiries into the nature of consciousness and conscious experience must be put aside, and hallucinogens should be recognized for what they are: tools that will ultimately help us to understand ourselves. The answers lie in further research for somewhere in the complexity of the brain exists the source of answers to all questions about ourselves. In the coming years, we may look forward to substantial progress in understanding how hallucinogens affect brain function, how those changes alter perception and cognition, and ultimately whether these ancient healing substances have medical value and wisdom to impart to our modern age.

-David Nichols