

Chemistry and Biology of Hallucinogens



*Jeffrey Lipshultz
Group Meeting
April 20, 2017*

Chemistry and Biology of Hallucinogens

disclaimer

Don't do illegal or unsafe drugs.

Chemistry and Biology of Hallucinogens

outline

Classes of hallucinogens:

5-HT_{2A} receptor agonists

ergolines (LSD)

tryptamines (psilocybin)

phenethylamines (mescaline)

Serotonin-releasing agents

methylenedioxyphenethylamines (MDxx)

NMDA receptor antagonists

phencyclidine (PCP)

ketamine

dextromethorphan (DM)

κ-Opioid receptor agonists

salvinorin A

CB₁ agonists

cannabinoids (THC)



Chemistry and Biology of Hallucinogens

5-HT_{2A} receptor

Location:

cell membrane of nerve cells, widely distributed in peripheral tissues

Endogenous ligand:

serotonin (5-HT)

Physiological processes:

neuronal excitation, learning, anxiety, attention

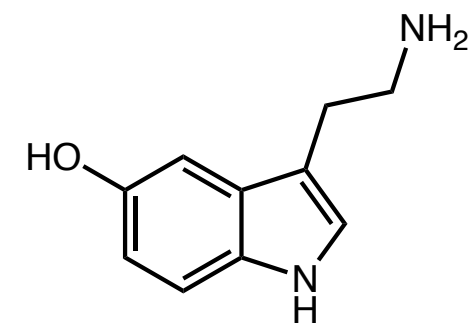
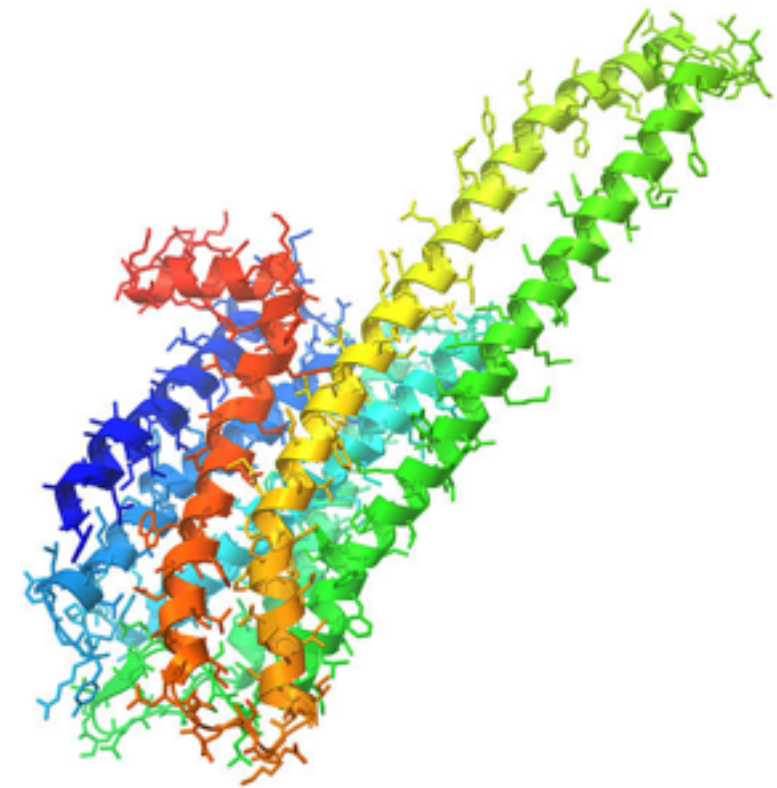
vasoconstriction/dilation, aggregation

inflammation, immune system (vague)

Clinical importance:

may be involved in psychosis, schizophrenia

antagonists/inverse agonists can be used to treat depression, schizophrenia, and hypertension



serotonin (5-HT)

Chemistry and Biology of Hallucinogens

ergot alkaloids

Isolation:

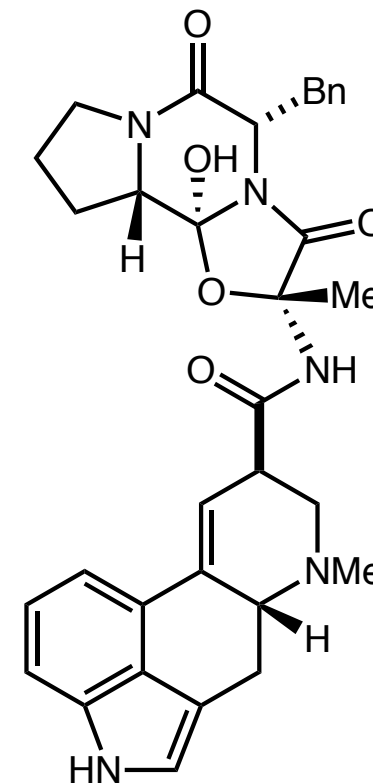
Claviceps purpurea, a fungus effecting barley, rye, and morning glory plants

Effected systems in humans:

neurological, circulatory

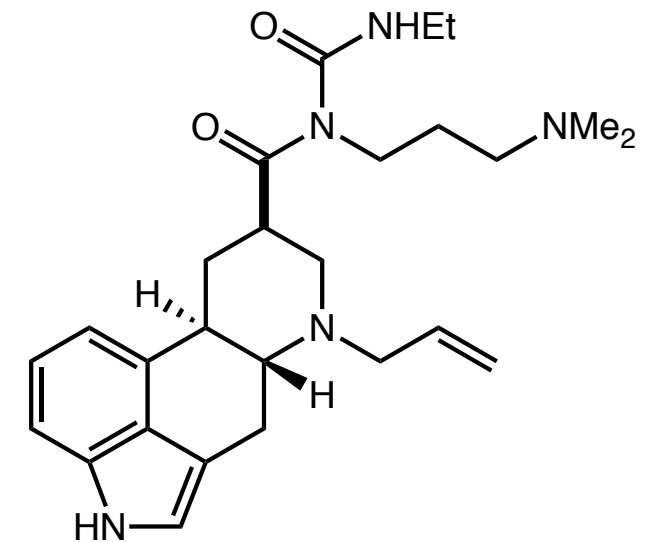
Toxicity:

Ergotism (St. Anthony's fire), none for LSD



ergotamine

migraines



Dostinex (cabergoline)

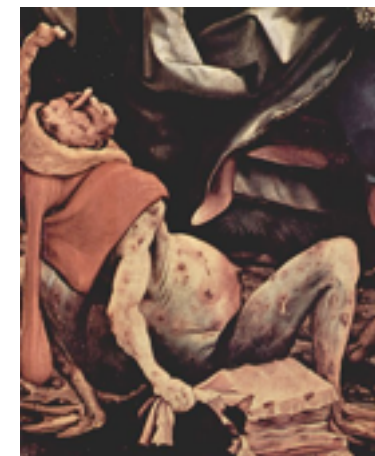
Parkinson's disease



Claviceps purpurea



ergot-contaminated barley



ergotism, aka St. Anthony's Fire



Chemistry and Biology of Hallucinogens

ergot alkaloids

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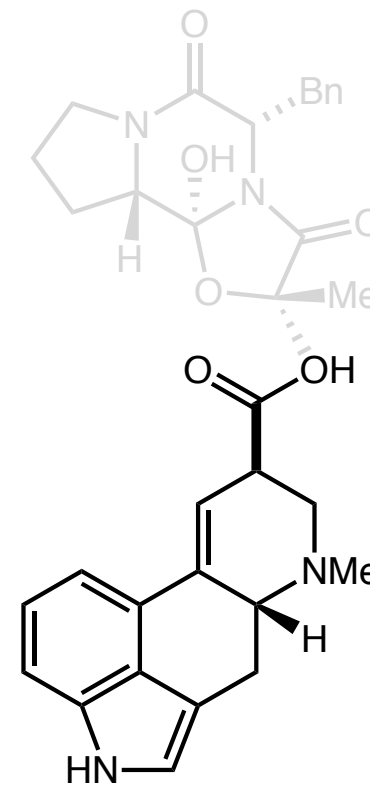
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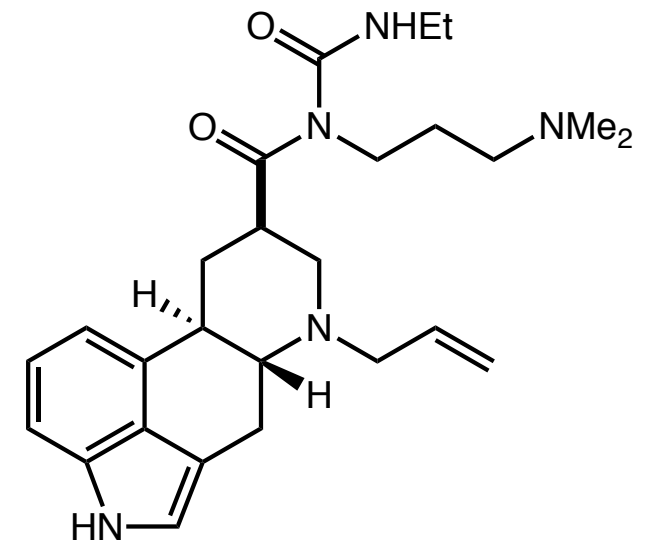
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lysergic acid



Dostinex (cabergoline)

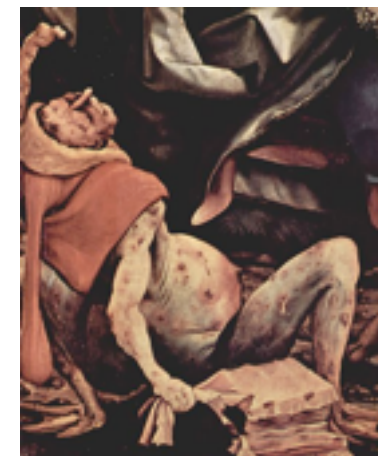
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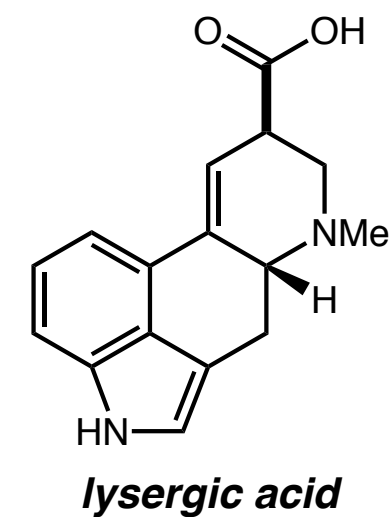
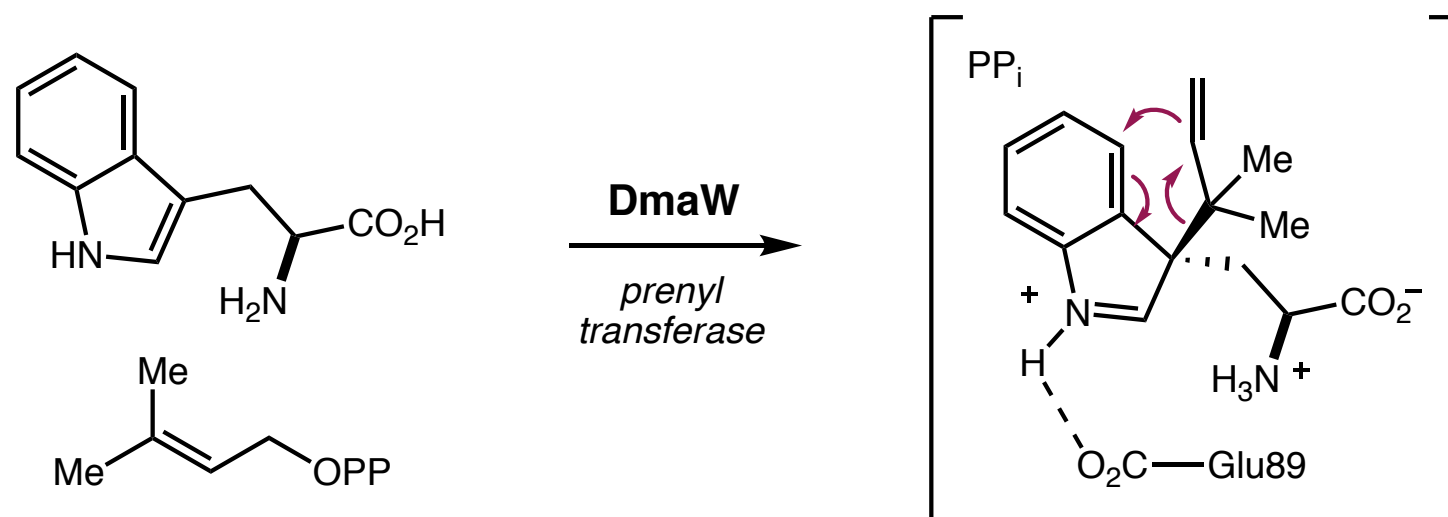


ergotism, aka St. Anthony's Fire



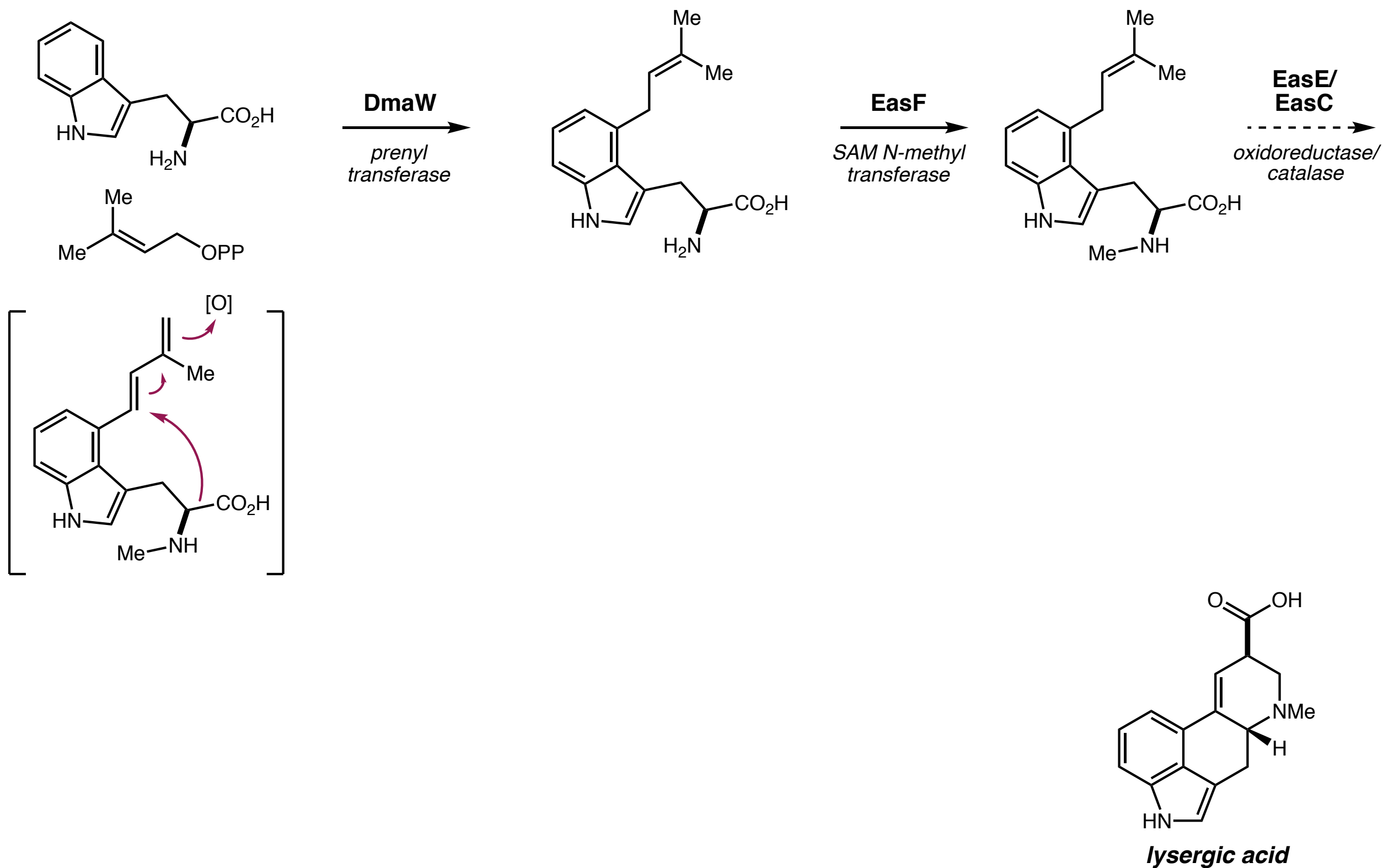
Chemistry and Biology of Hallucinogens

lysergic acid biosynthesis



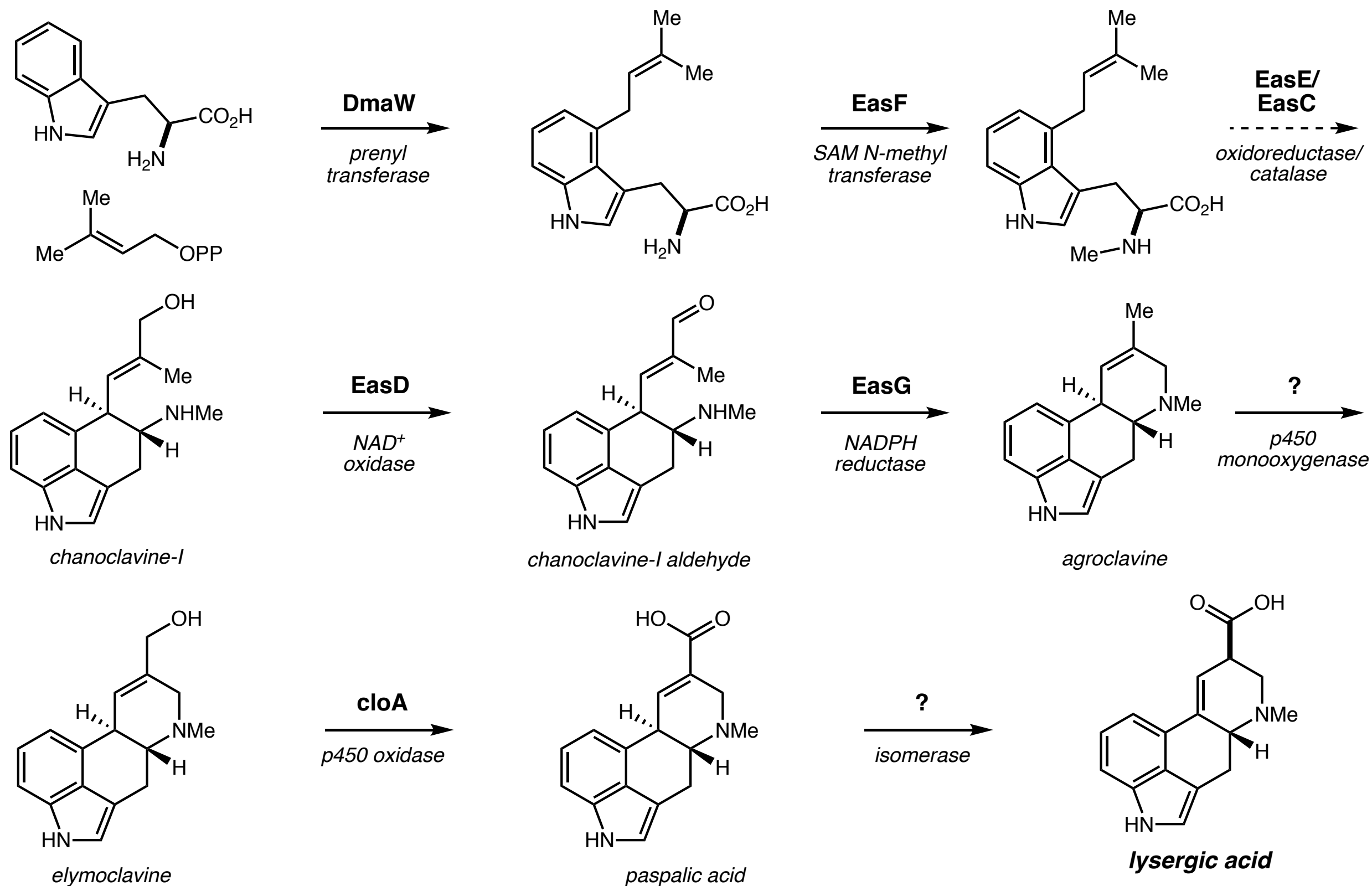
Chemistry and Biology of Hallucinogens

lysergic acid biosynthesis



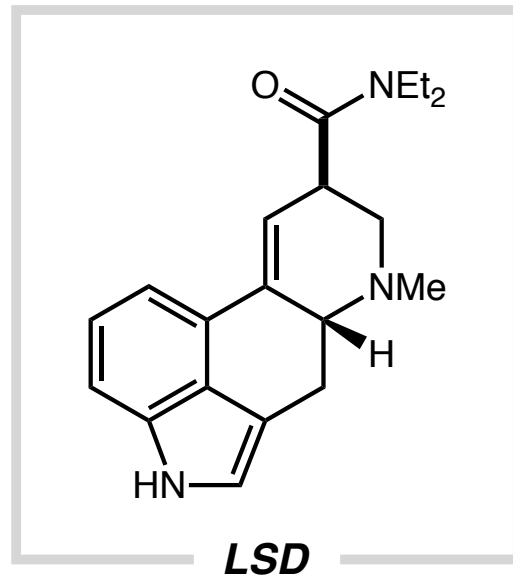
Chemistry and Biology of Hallucinogens

lysergic acid biosynthesis



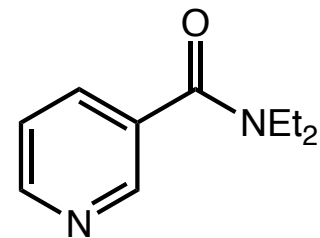
Chemistry and Biology of Hallucinogens

lysergic acid diethylamide

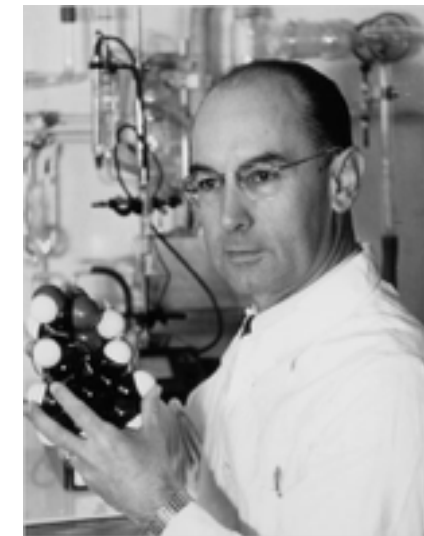


Sandoz Laboratories, Basel, Switzerland

*first synthesized from lysergic acid November
16, 1938, searching for novel analeptics*



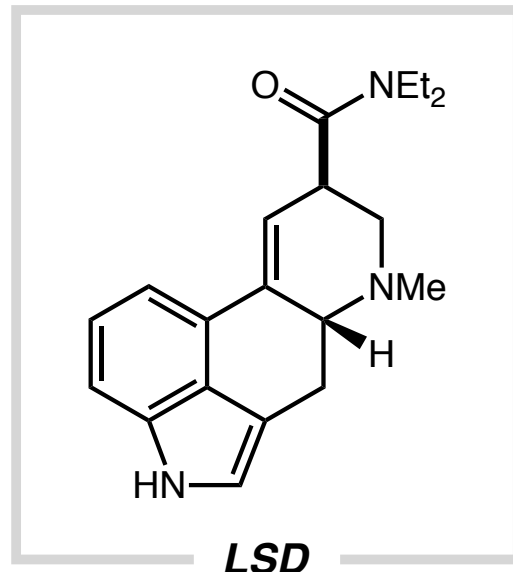
nikethamide



Albert Hoffman

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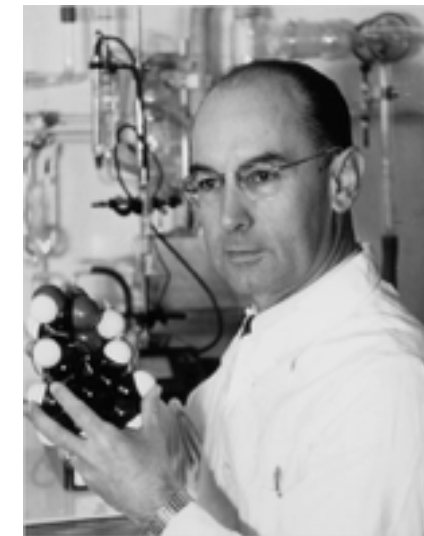
lysergic acid diethylamide



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accidentally ingested April 16, 1943

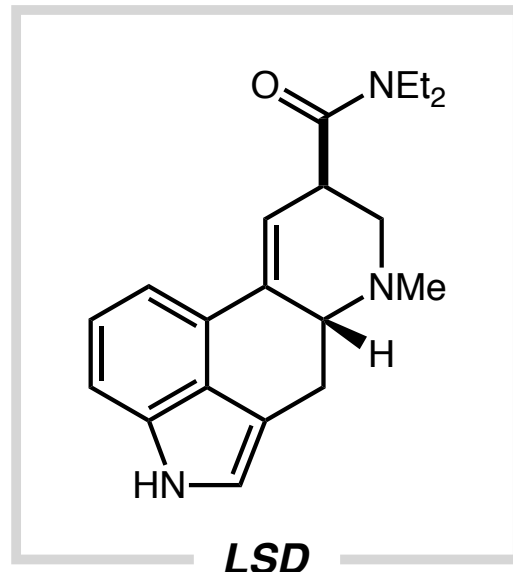


Albert Hoffman

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.

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lysergic acid diethylamide

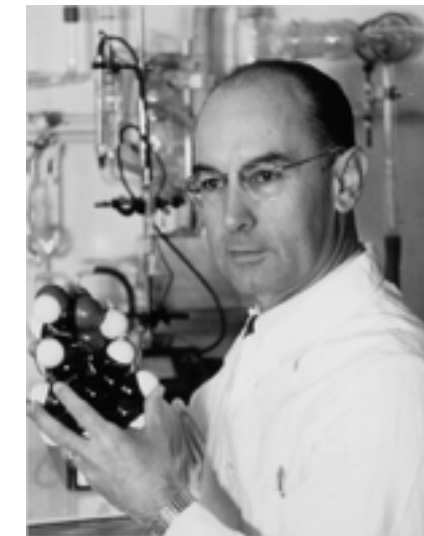


Sandoz Laboratories, Basel, Switzerland

first synthesized from lysergic acid November 16, 1938, searching for novel analeptics

accidentally ingested April 16, 1943

intentionally ingested 250 µg April 19, 1943, known as "Bicycle Day"



Albert Hoffman

April 19, 1943: Preparation of an 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.

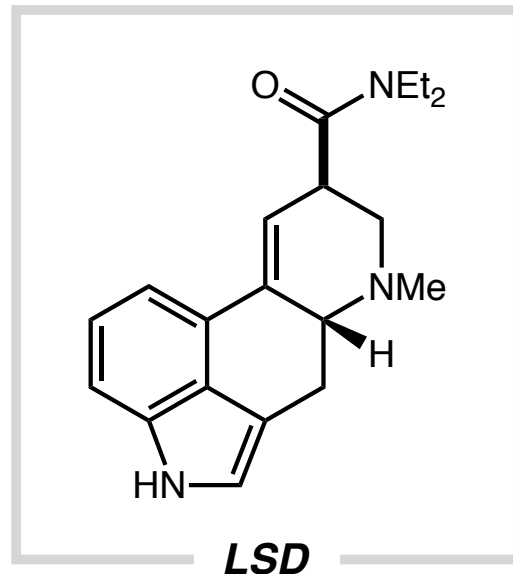
5:00 P.M.: slight dizziness, unrest, difficulty in concentration, visual disturbances, marked desire to laugh...

At this point the laboratory notes are discontinued: The last words were written only with great difficulty. I asked my laboratory assistant to accompany me home as I believed that I should have a repetition of the disturbance of the previous Friday. While we were cycling home, however, it became clear that the symptoms were much stronger than the first time. I had great difficulty in speaking coherently, my field of vision swayed before me, and objects appeared distorted like images in curved mirrors. I had the impression of being unable to move from the spot, although my assistant told me afterwards that we had cycled at a good pace.... Once I was at home the physician was called.



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lysergic acid diethylamide

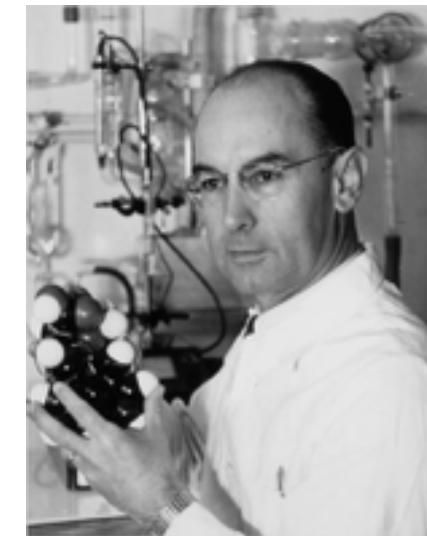


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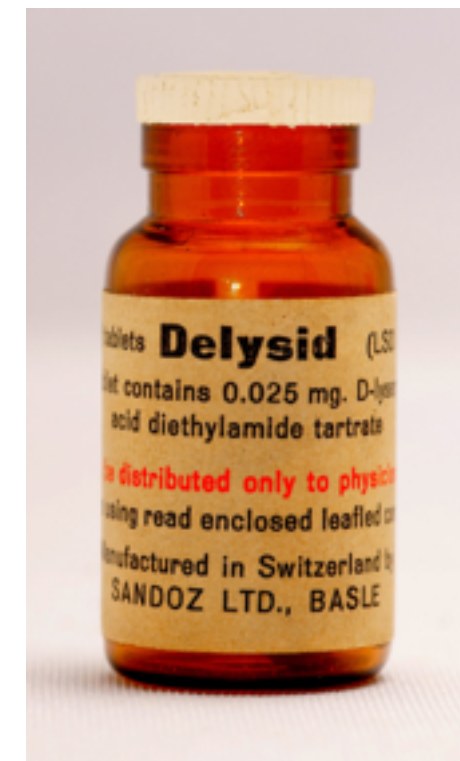
Albert Hoffman

commercialized as Delysid in 1947, for psychiatric use (induce model psychoses, mental relaxation, etc)

25 µg sugar-coated tablet or 100 µg in 1mL ampule

1950s: CIA conducted Project MKULTRA to see if LSD could be a “truth serum”

patents expired in 1963, and counterculture use began around this time, leading to ban in 1968 in the United States



Delysid

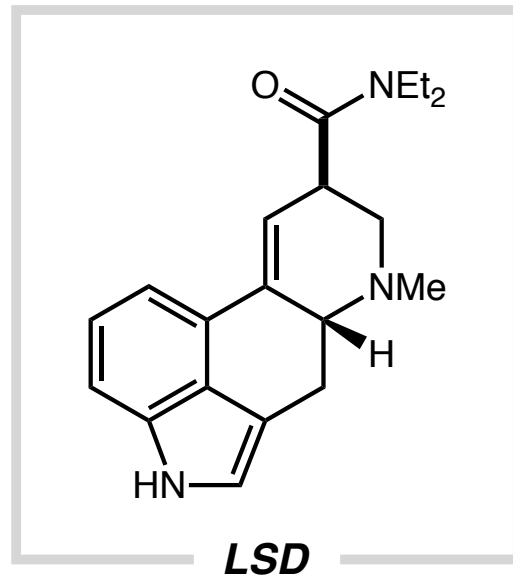
Stoll, A.; Hoffman, A. U.S. Patent 2438259, assigned to Sandoz Ltd. <https://www.erowid.org/archive/rhodium/chemistry/lspdpatent.html>.

Hoffman, A. LSD – My Problem Child. <http://www.psychedellic-library.org/child4.htm>.

Hoffman, A. The Discovery of LSD and Subsequent Investigations on Naturally Occurring Hallucinogens. In *Discoveries in Biological Psychiatry*. Ayd, Jr., F. J.; Blackwell, B.; J. B. Lippincott: Philadelphia, 1970.

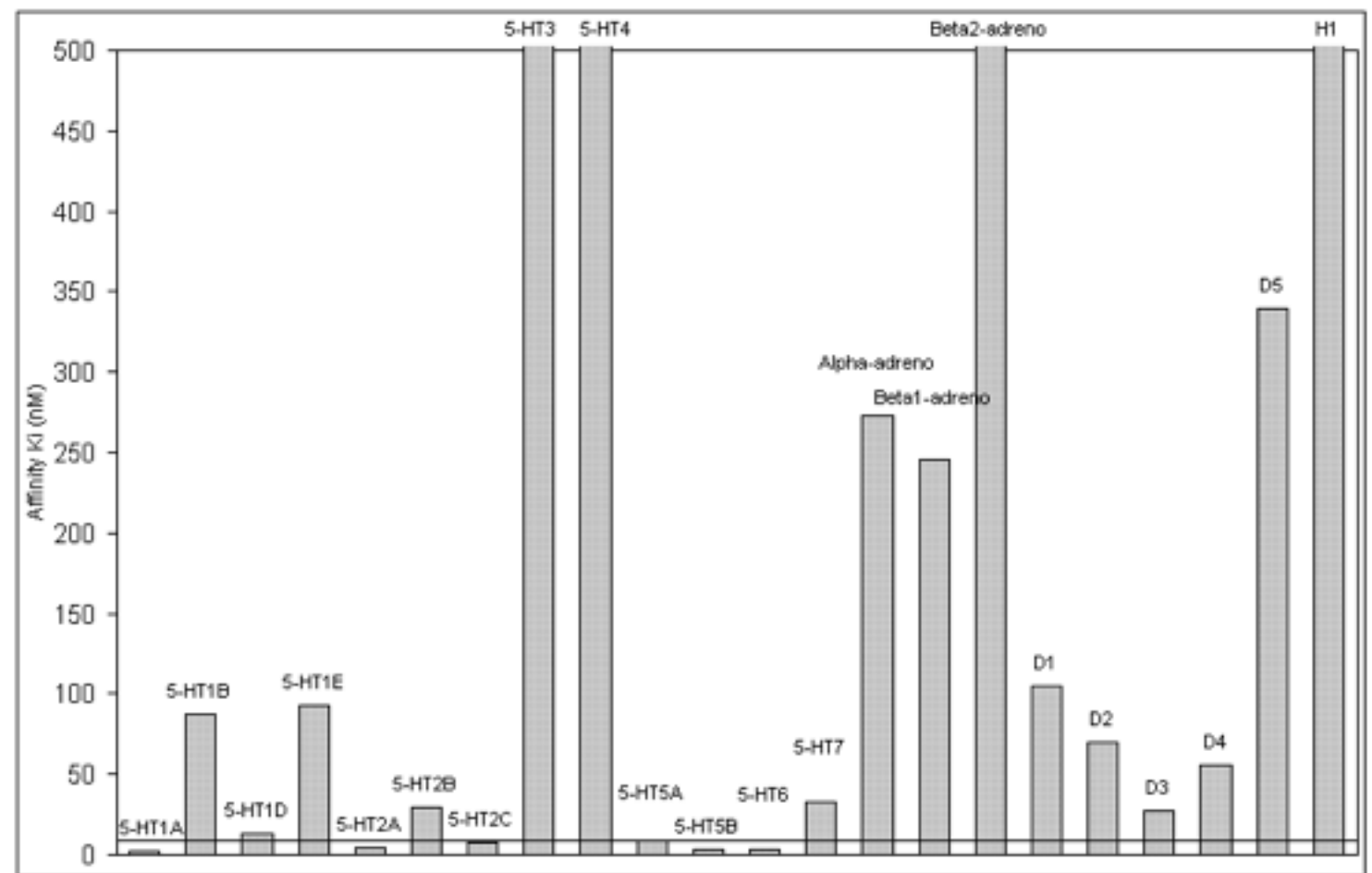
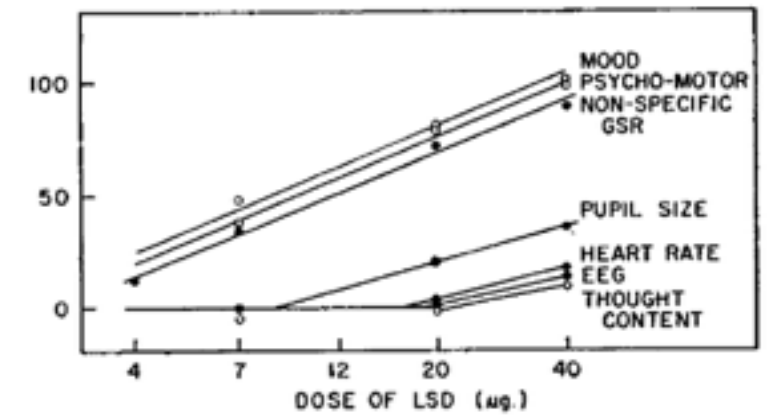
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lysergic acid diethylamide



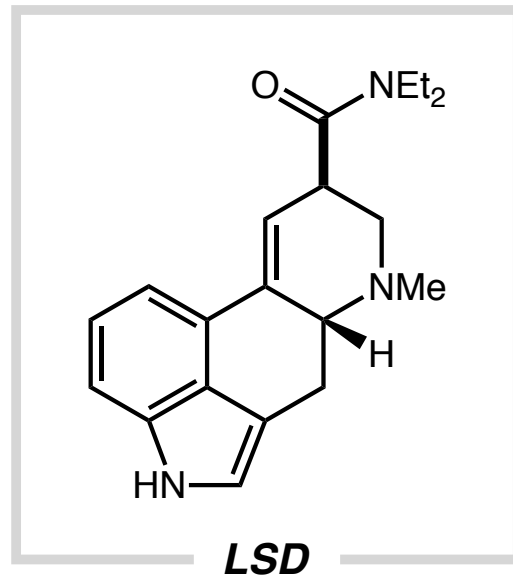
dosing studies indicated that 20 µg was the threshold for physical response

at typical brain concentrations (10-20 nM), LSD should activate numerous 5-HT receptors



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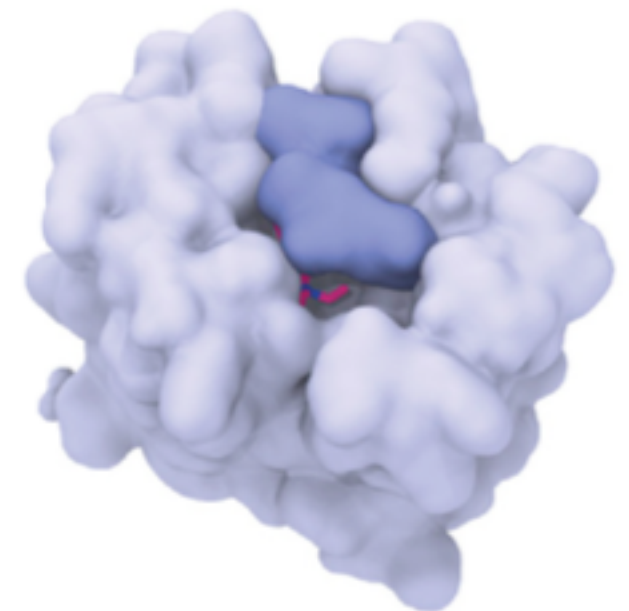
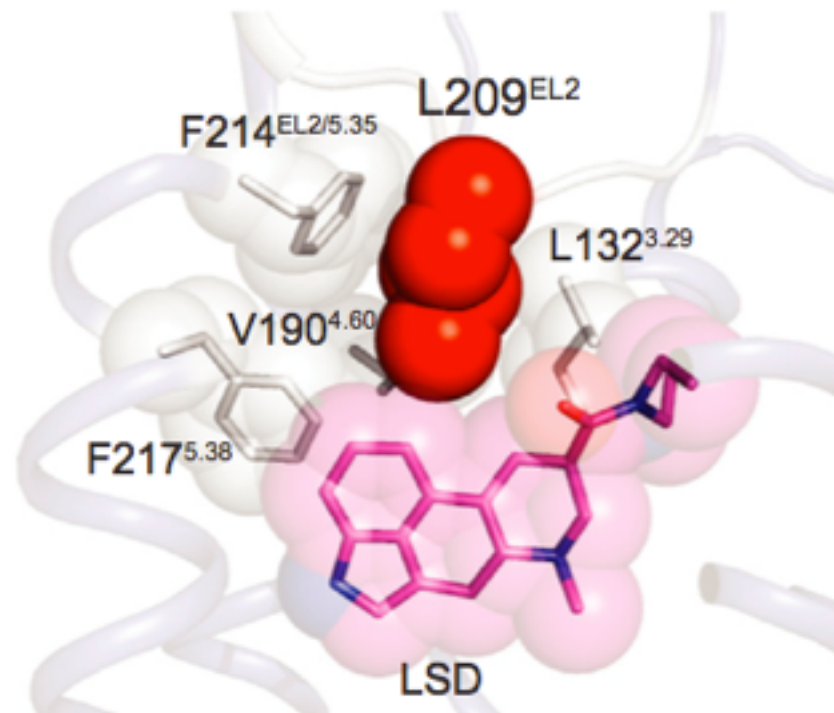
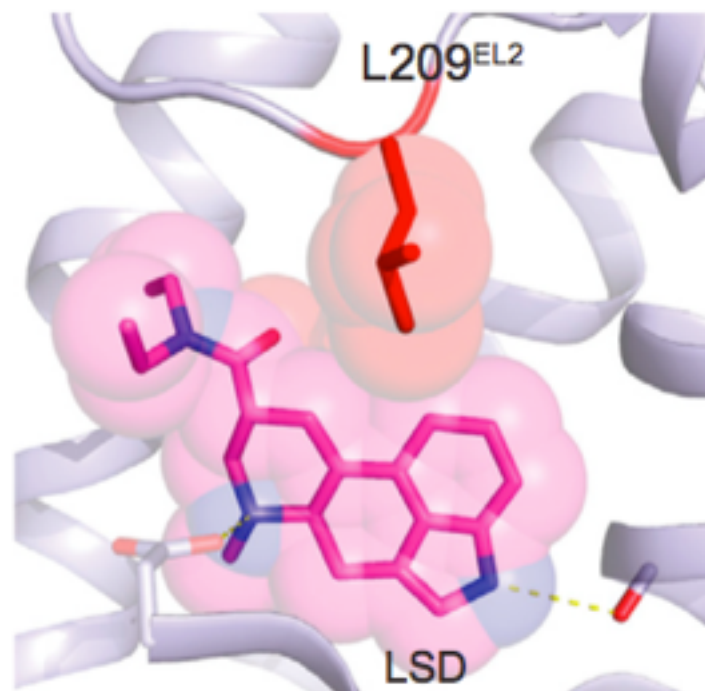
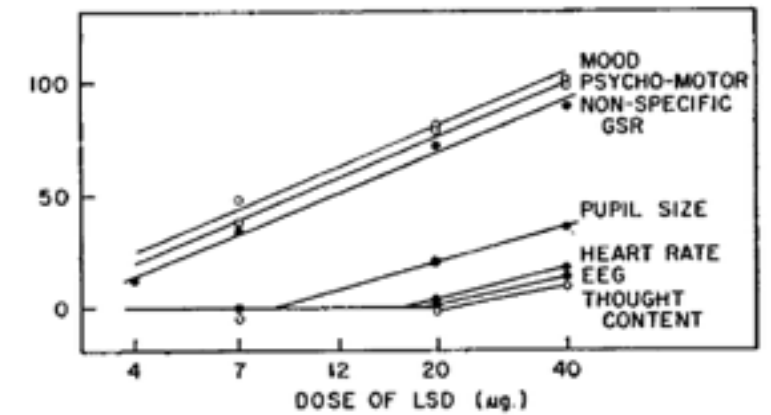
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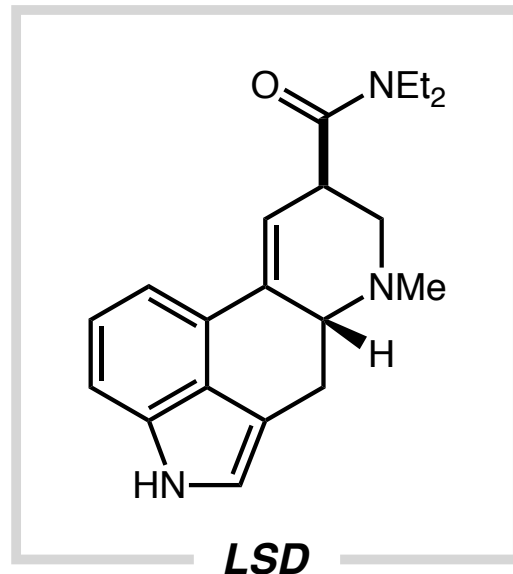
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lysergic acid diethylamide



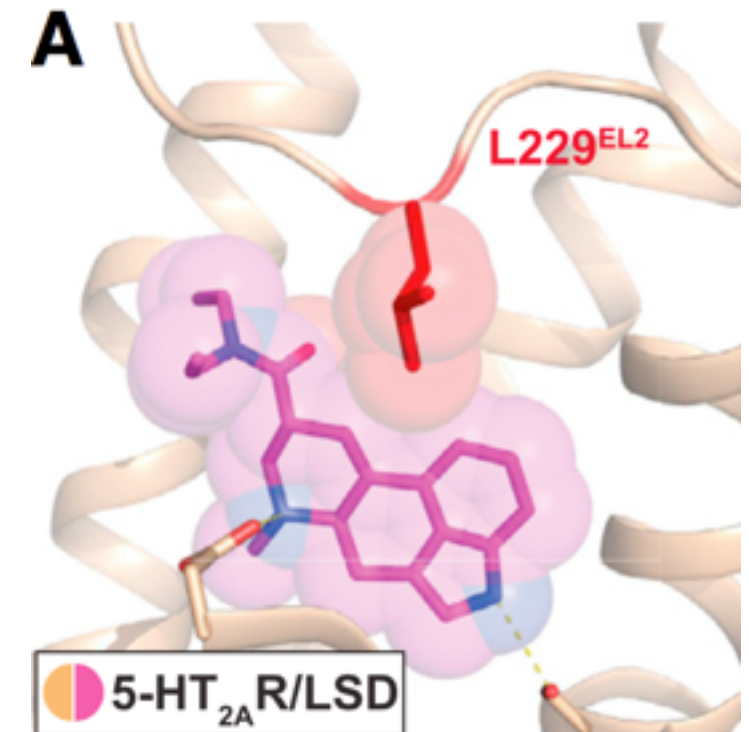
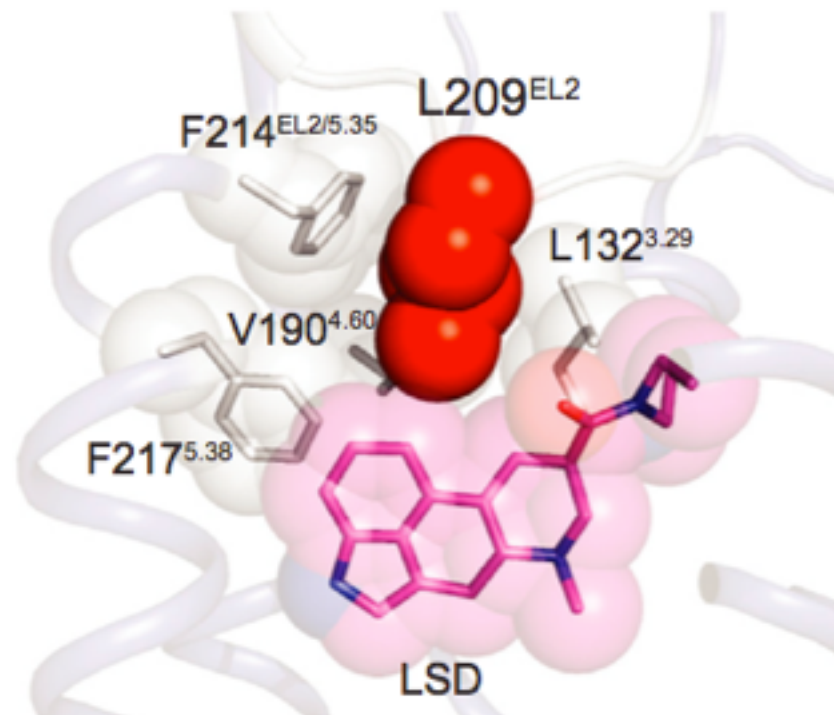
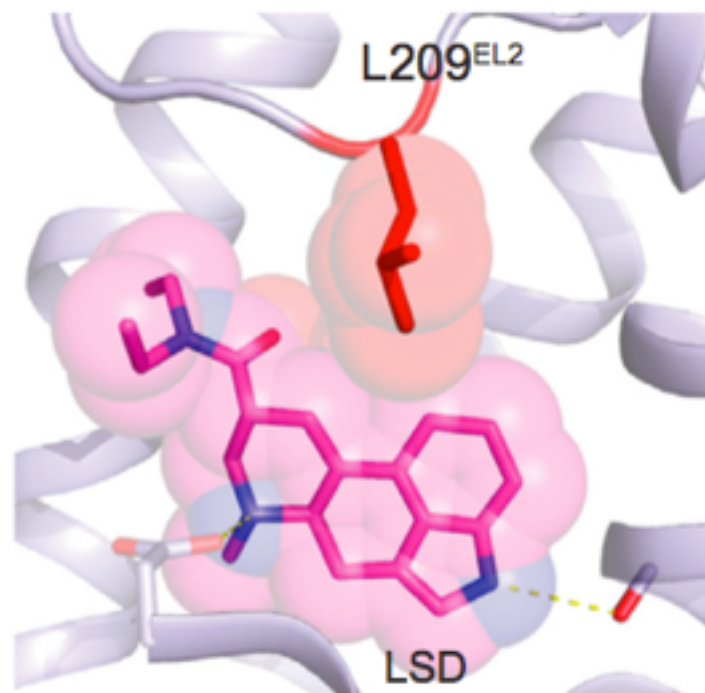
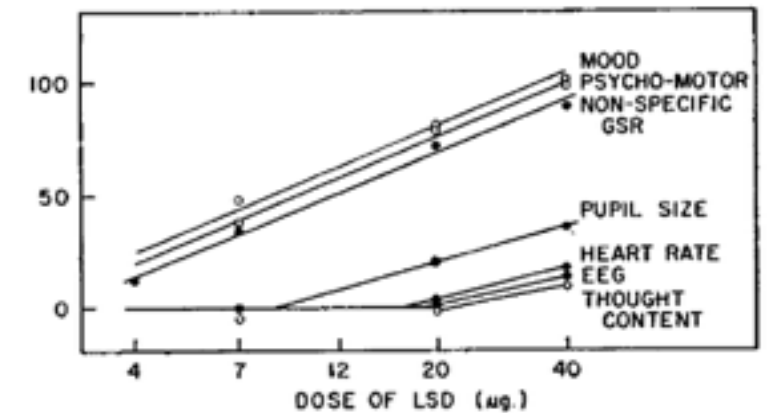
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simulations show L229 serves same role for 5-HT_{2A}

exceptionally slow dissociation $t_{1/2} > 220$ minutes at body temperature (37 °C) in 5-HT_{2A} in [³H] studies

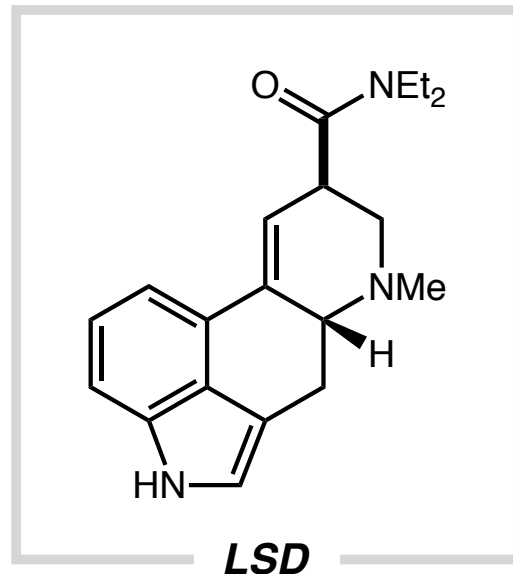


Wacker, D.; Dror, R. O.; Roth, B. L. *et al. Cell* **2017**, 168, 377.

Greiner, T.; Burch, N. R.; Edelberg, R. A.M.A. *Archives Neuropsych.* **1958**, 79, 208.

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lysergic acid diethylamide



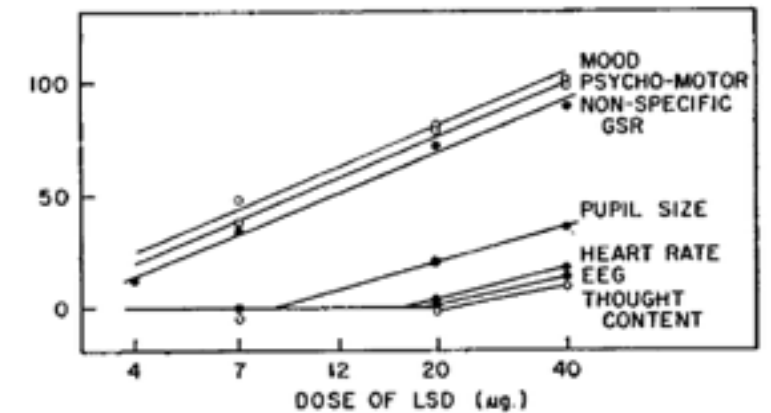
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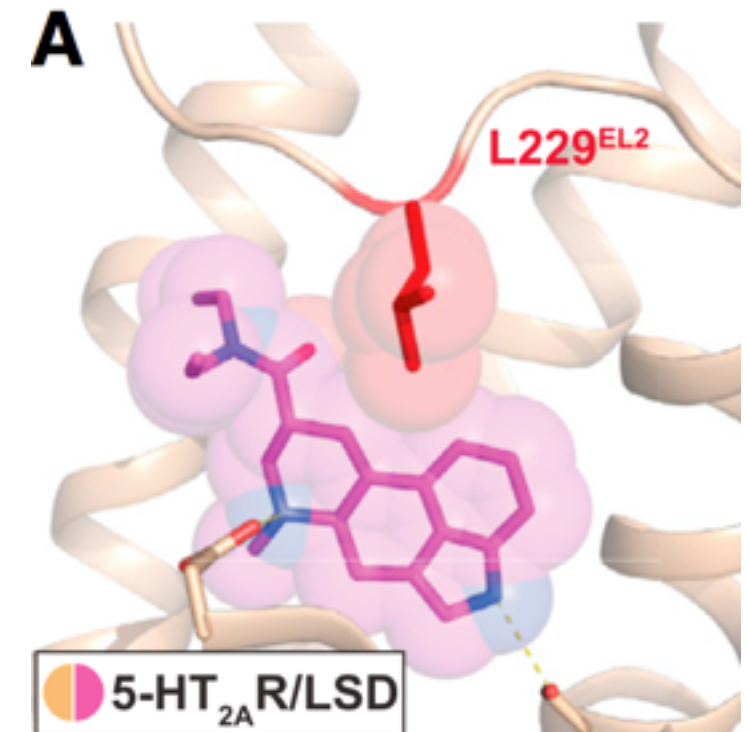
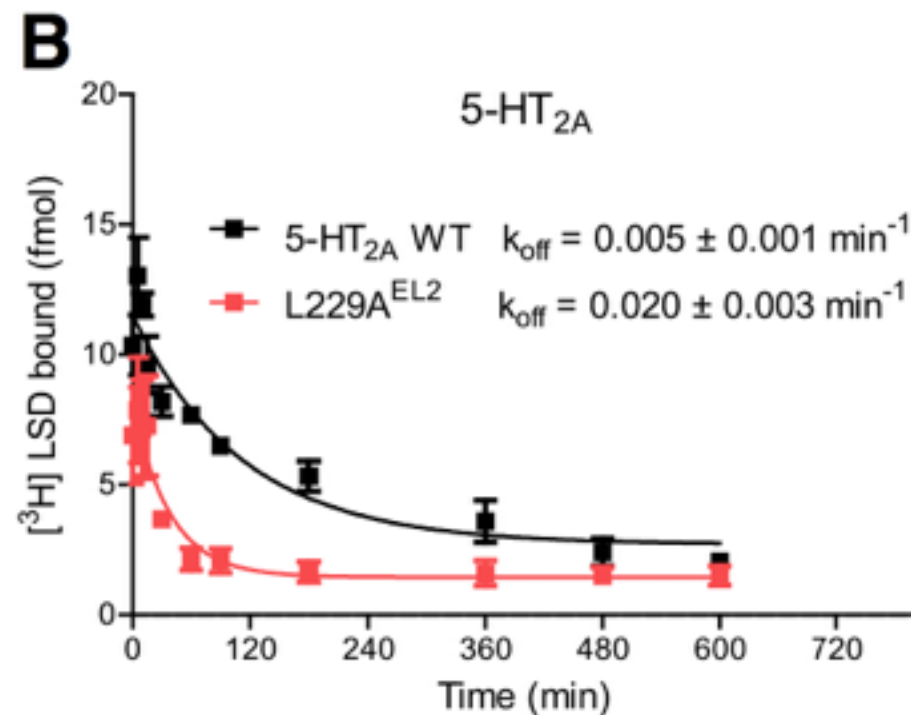
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Receptor	Residence Time, min ($k_{\text{off}} \pm \text{SEM}$) min^{-1}
5-HT _{2A} R wild-type	221 (0.005 \pm 0.001)
5-HT _{2A} R L229A ^{EL2}	50 (0.020 \pm 0.003)
5-HT _{2B} R wild-type	46 (0.022 \pm 0.004)
5-HT _{2B} R L209A ^{EL2}	4 (0.236 \pm 0.033)

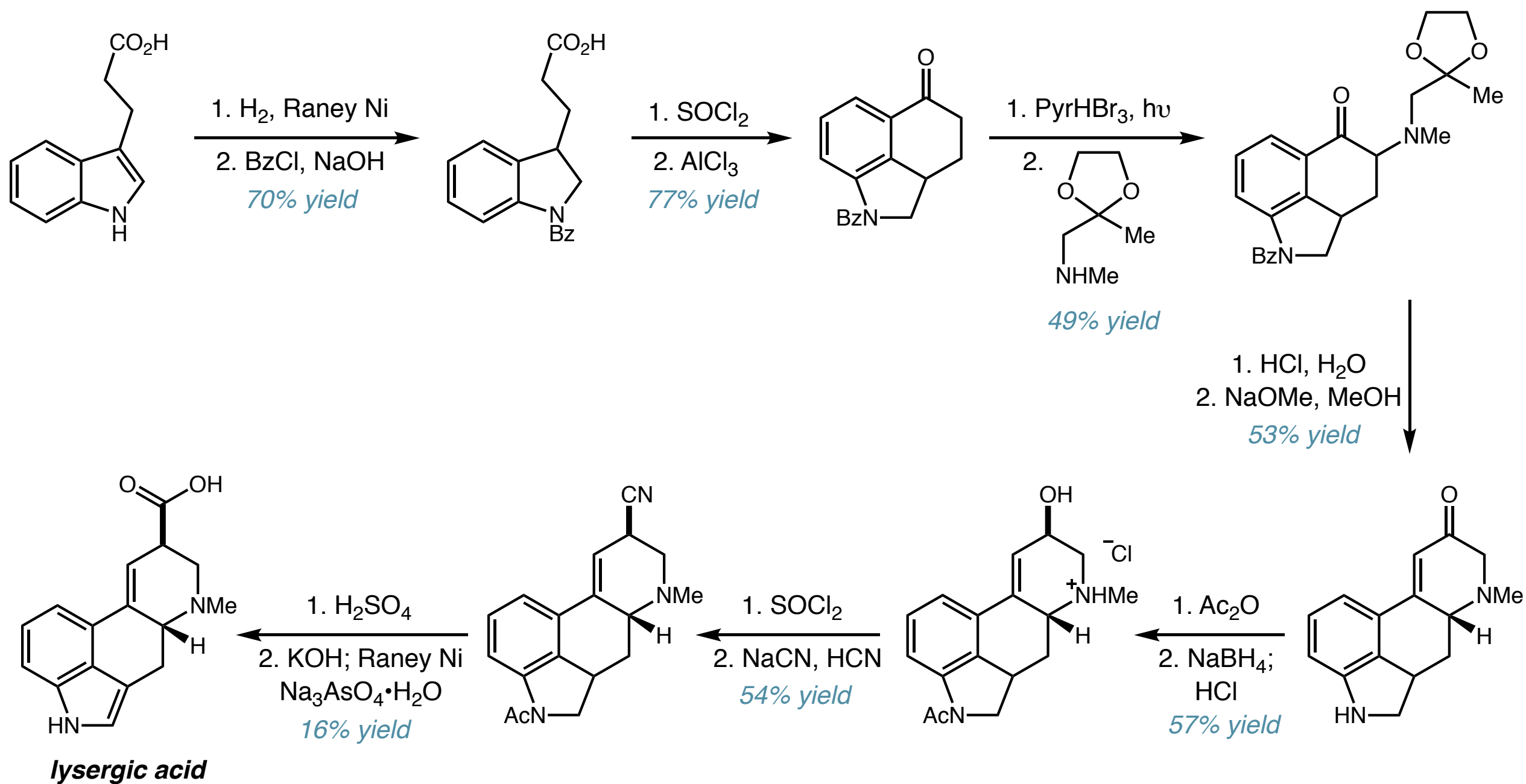


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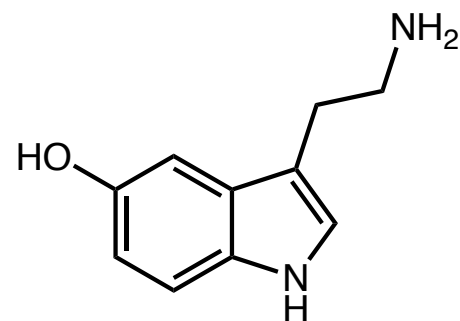
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Woodward's total synthesis of lysergic acid

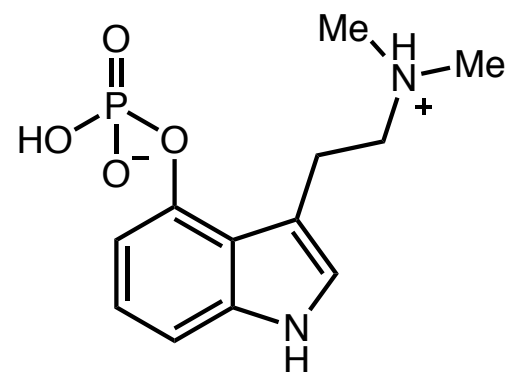
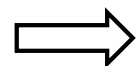


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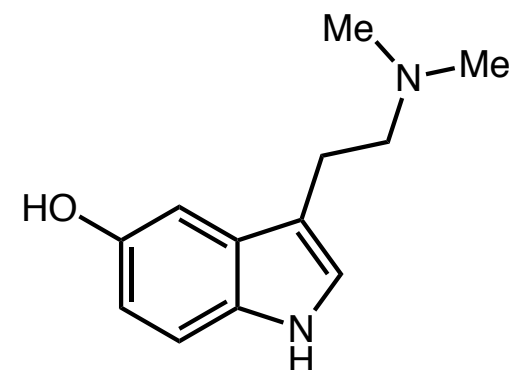
tryptamines



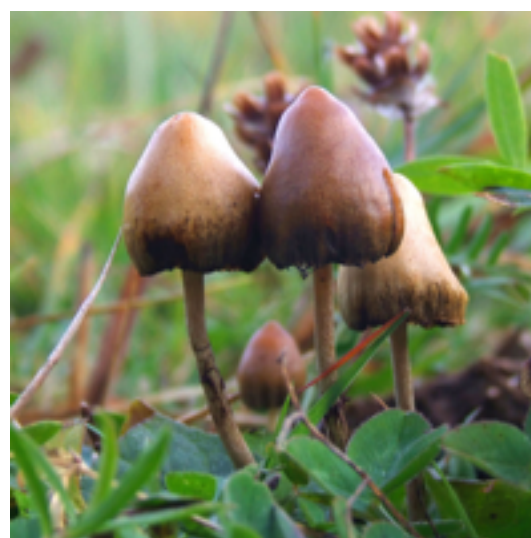
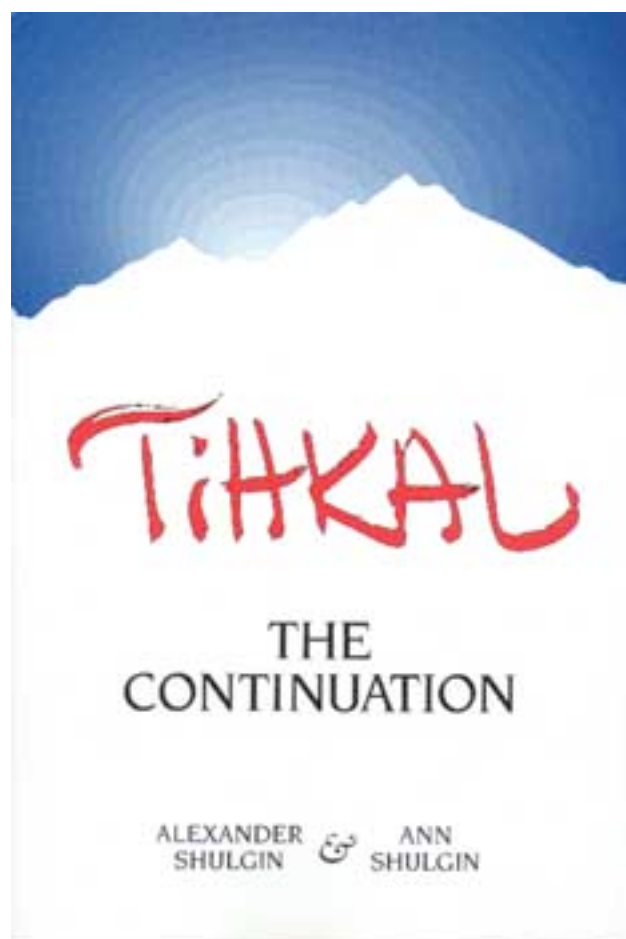
serotonin (5-HT)



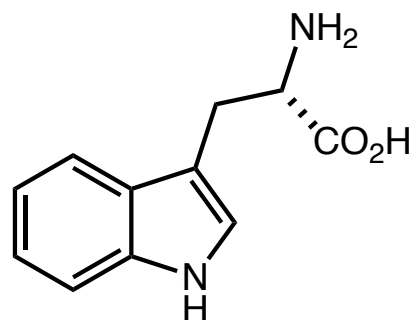
psilocybin



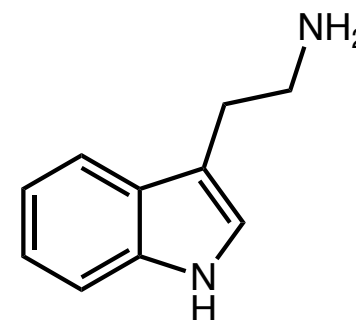
bufotenin



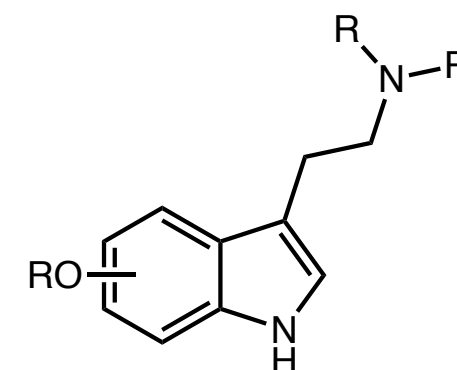
many naturally-occurring tryptamines, with common biosynthetic pathways:



tryptophan



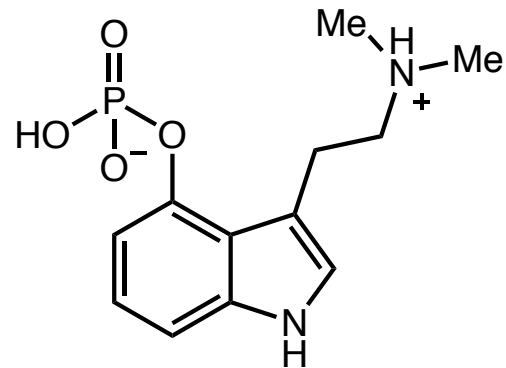
tryptamine



hallucinogen

Chemistry and Biology of Hallucinogens

psilocybin



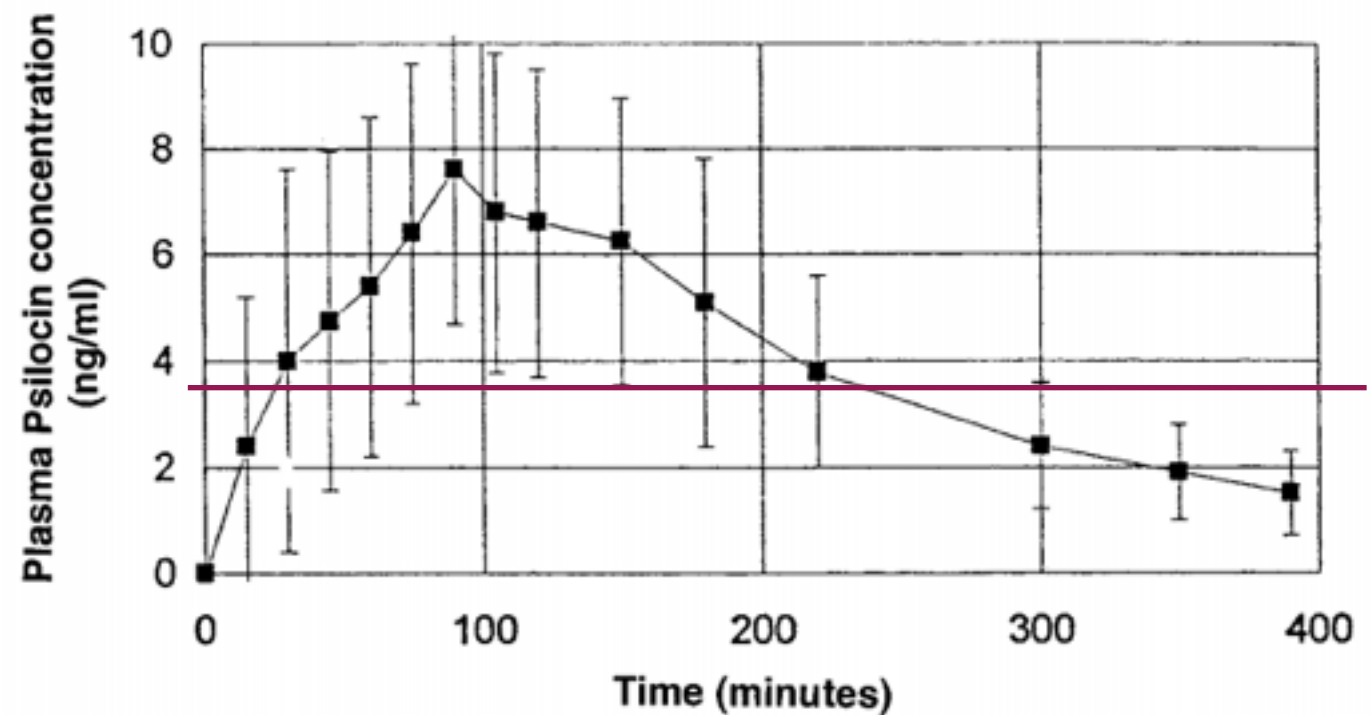
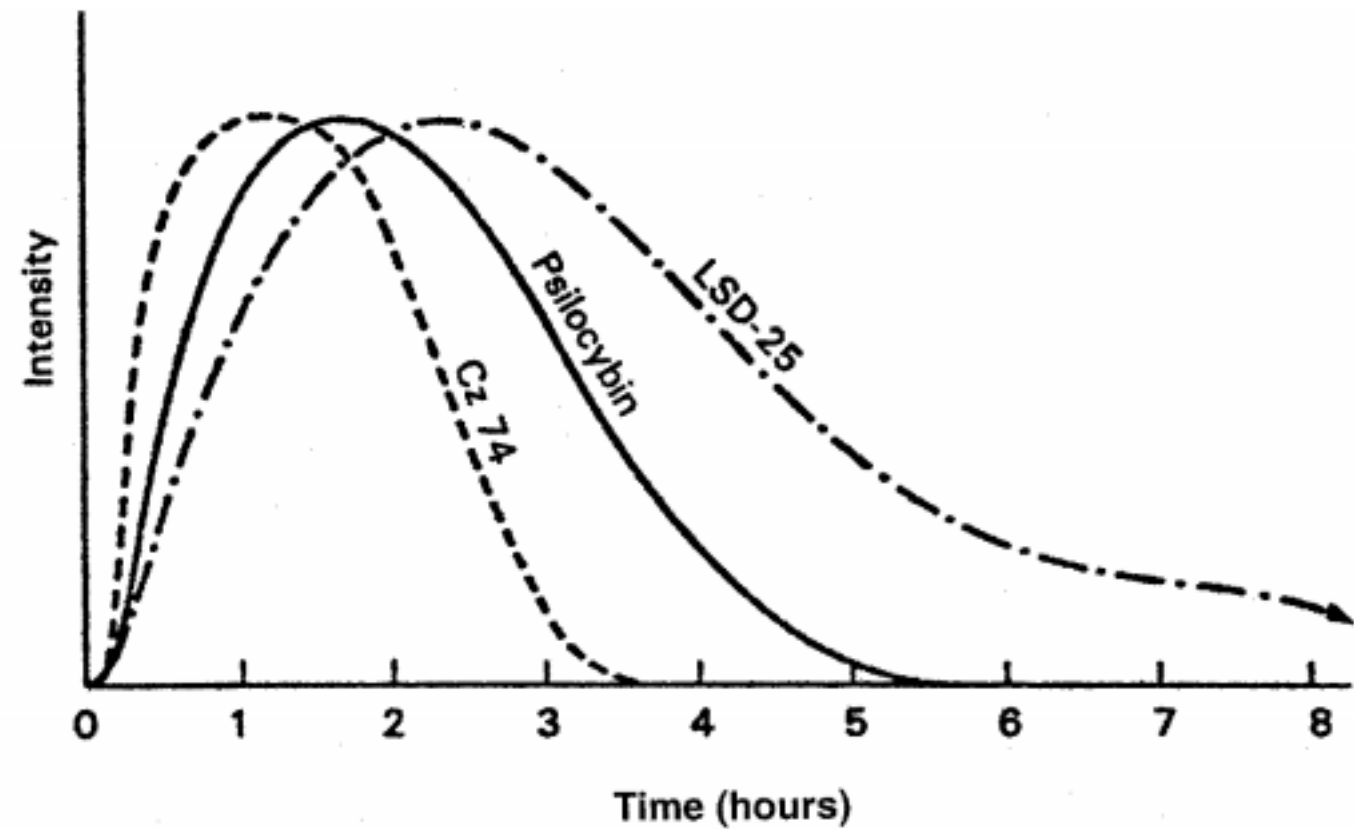
psilocybin

isolated by Hoffman from *Psilocybe mexicana* (1957)

synthesized by Hoffman (1958)

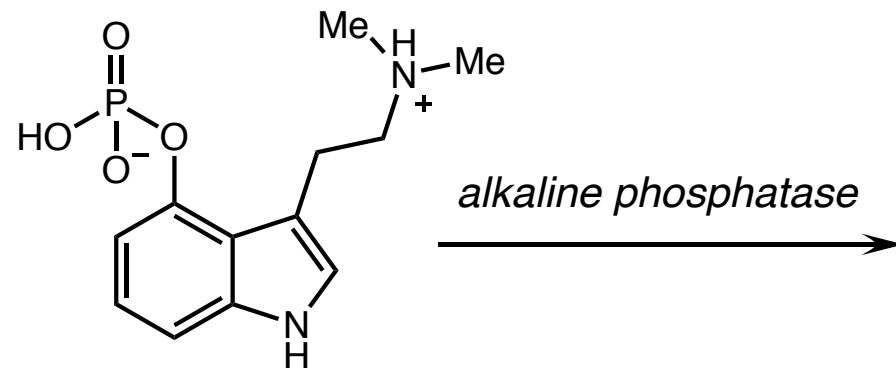
commercialized by Sandoz (Indocybin)

4-10 mg dose, ~ 50-300 mg/kg



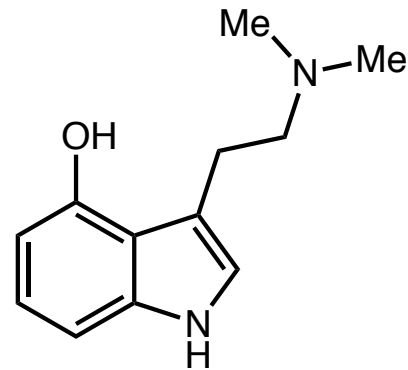
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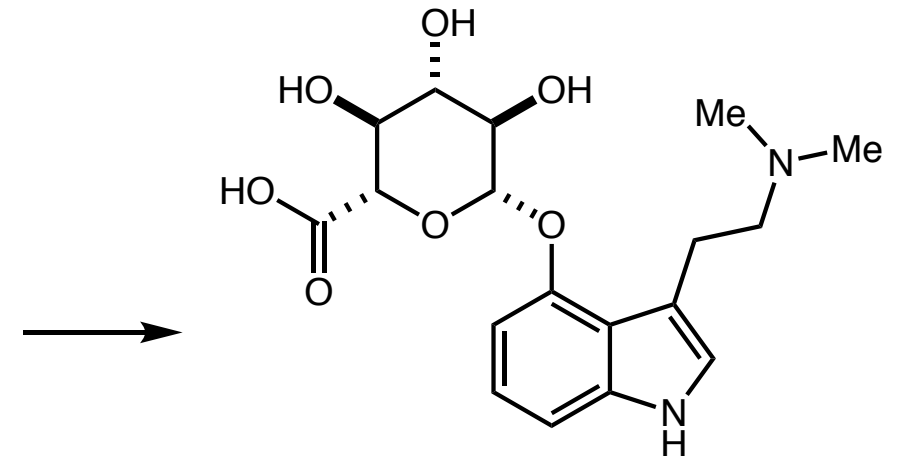


psilocybin

alkaline phosphatase



psilocin
pharmacologically active



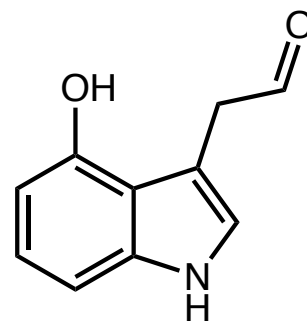
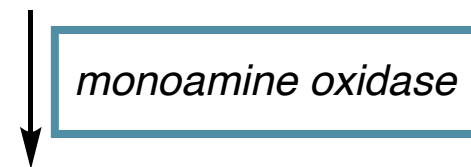
psilocin O-glucoronide
excreted in urine

isolated by Hoffman from Psilocybe mexicana (1957)

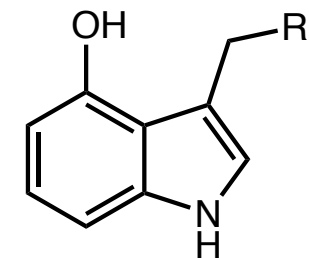
synthesized by Hoffman (1958)

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4-10 mg dose, ~ 50-300 mg/kg



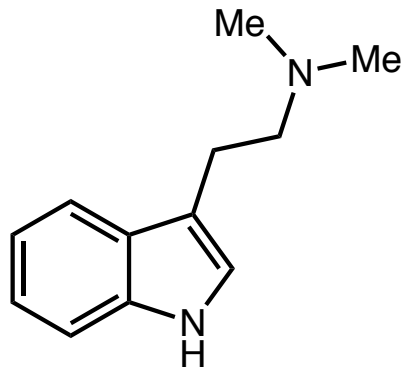
4-hydroxyindole-3-acetaldehyde



R = CH₂OH, 4-hydroxytryptophol
R = CO₂H, 4-hydroxyindole-3-acetic acid

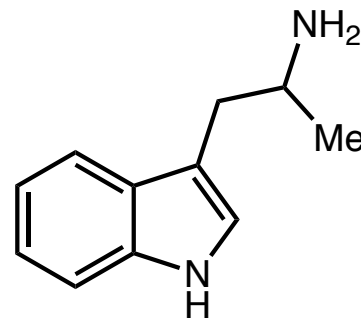
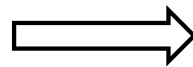
Chemistry and Biology of Hallucinogens

tryptamine pharmacokinetics



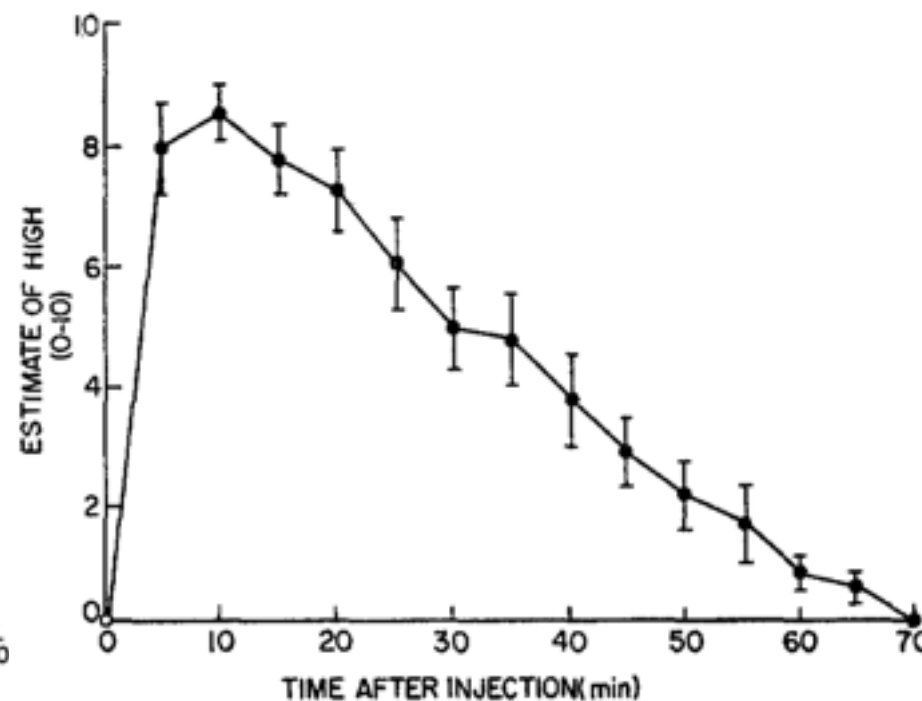
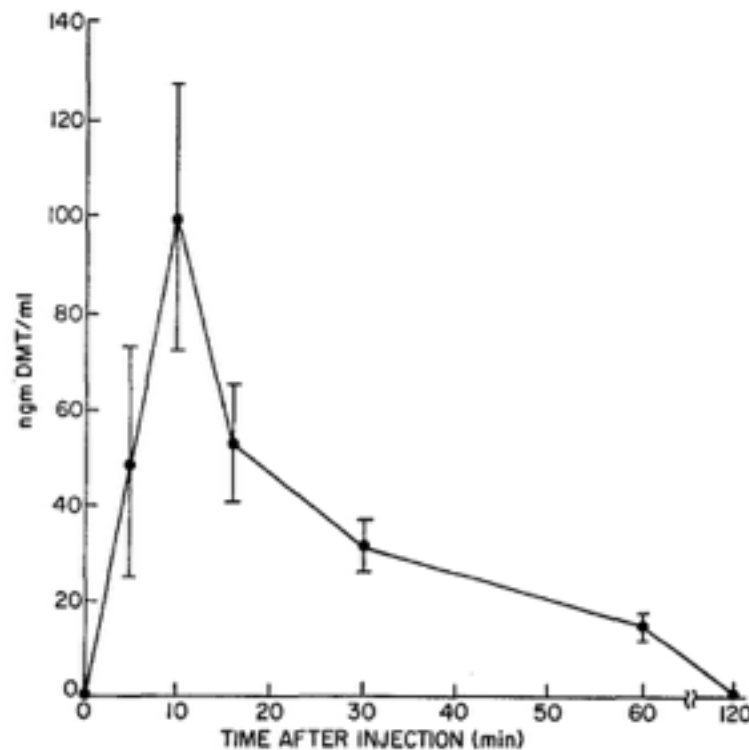
N,N-dimethyltryptamine (DMT)

*inactive orally
effects clear very quickly
“businessman’s trip”*



***α*-methyltryptamine (AMT)**

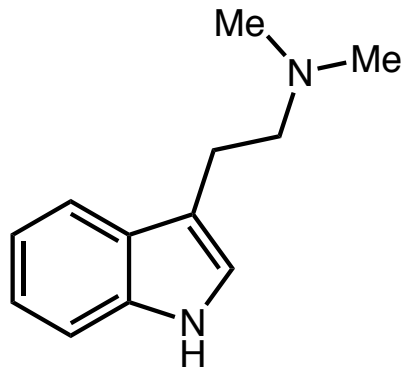
*effects last up to 12 hours
α-Me slows MAO activity*



MAO-A is a flavin oxidase, which was targeted for depression, is currently targeted for Parkinson’s disease

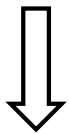
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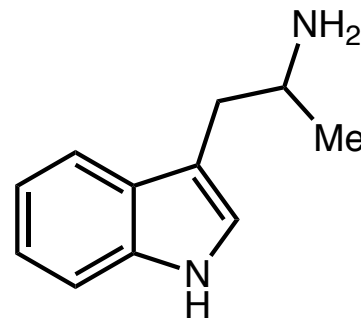
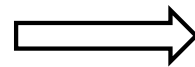
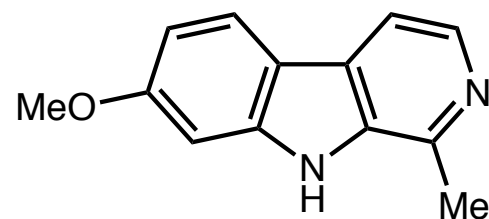


N,N-dimethyltryptamine (DMT)

*inactive orally
effects clear very quickly
“businessman’s trip”*



*combine with **harmine**
(selective MAO-A inhibitor)*



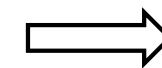
***α*-methyltryptamine (AMT)**

*effects last up to 12 hours
α-Me slows MAO activity*

*Ayahuasca (Amazonian spiritual medicine)
combine *Psychotria viridis* (DMT) and
Banisteriopsis caapi (harmine)*



~ 160 mg harmine, 30 mg DMT



*Ott found activity threshold to be
120 mg harmine, 20-30 mg DMT*

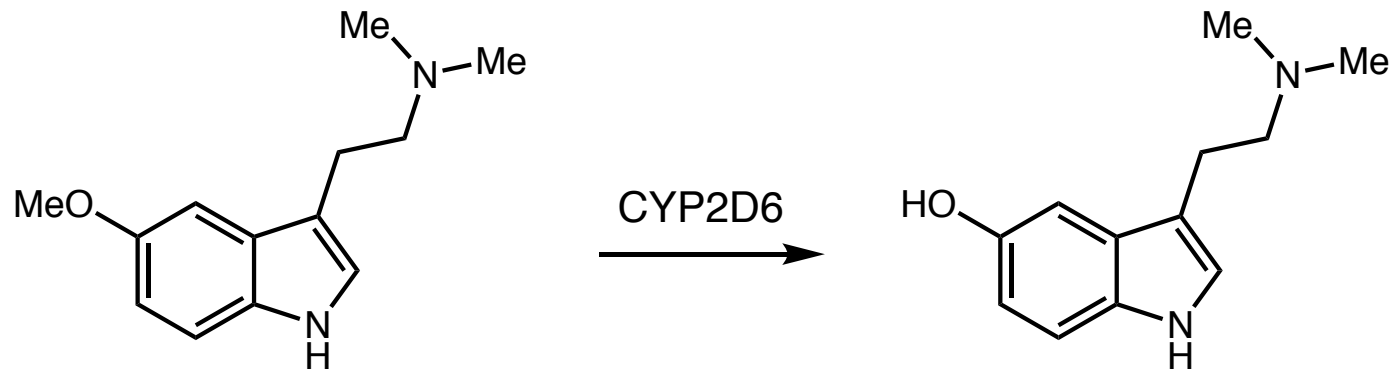
Ott, J. J. *Psychoactive Drugs* **1999**, 31, 171.

Wilcox, J. J. *Psychoactive Drugs* **2012**, 44, 274.

Kaplan, J.; Mandel, L. R.; Stillman, R.; Walker, R. W.; VandenHeuvel, W. J. A.; Gillin, J. C.; Wyatt, R. J. *Psychopharmacologia* **1974**, 38, 239.

Chemistry and Biology of Hallucinogens

tryptamine pharmacokinetics

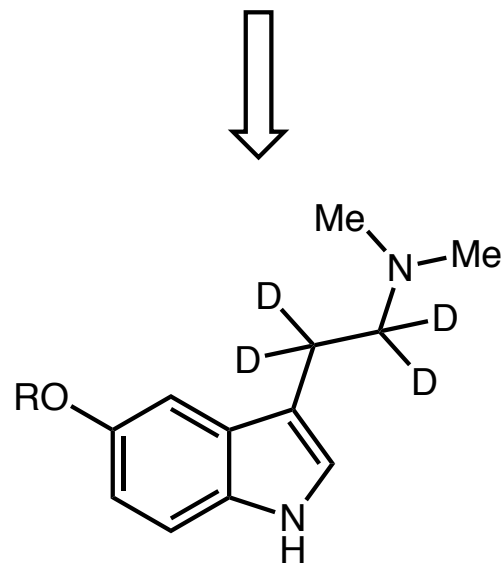


5-OMe-dimethyltryptamine

bufotenine

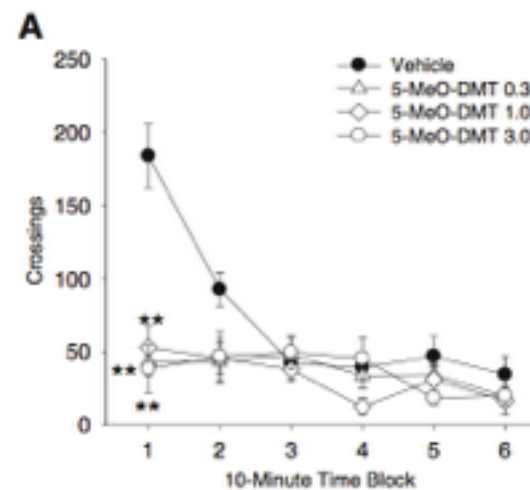


both found in numerous sources, including the skin of the Colorado River Toad

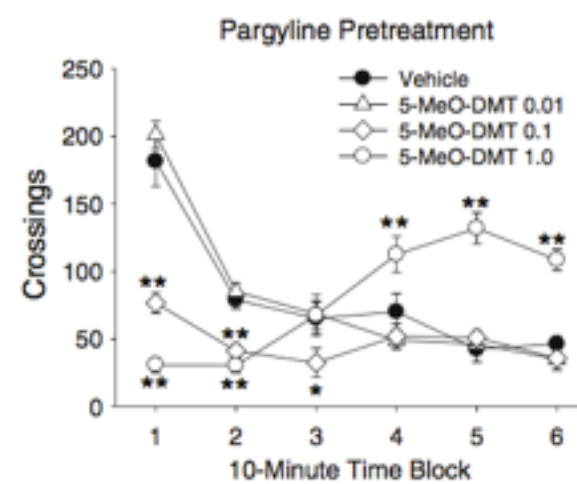


5-OMe-DMT-d₄

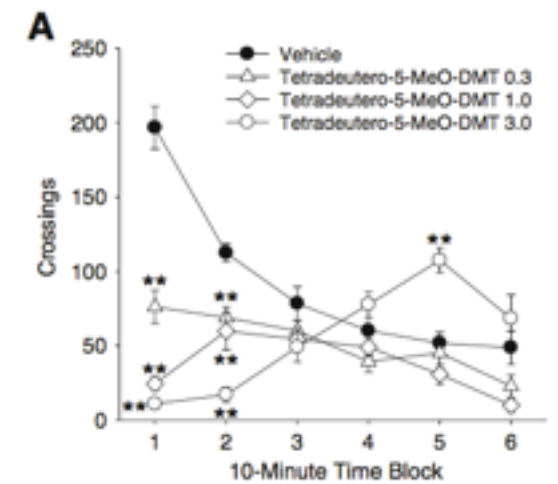
dose with 5-OMe-DMT



pre-treat with MAOI



dose with 5-OMe-DMT-d₄



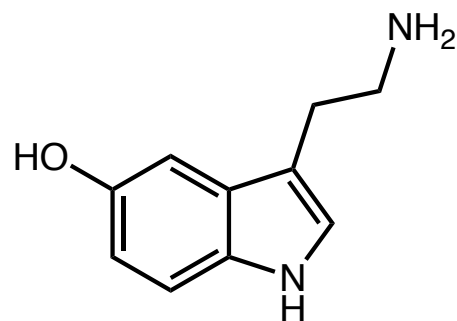
Halberstadt, A. L.; Nichols, D. E.; Geyer, M. A. *Psychopharma.* **2012**, 221, 709.

Shen, H.-W.; Wu, C.; Jiang, X.-L.; Yu, A.-M. *Biochem. Pharma.* **2010**, 80, 122.

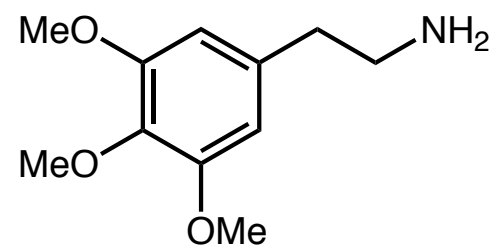
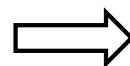
Ott, J. J. *Psychoactive Drugs* **2011**, 33, 273.

Chemistry and Biology of Hallucinogens

phenethylamines



serotonin (5-HT)

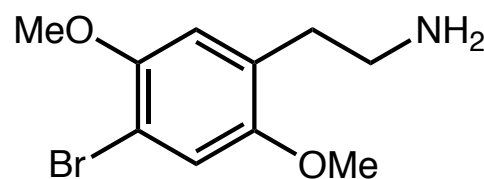


mescaline

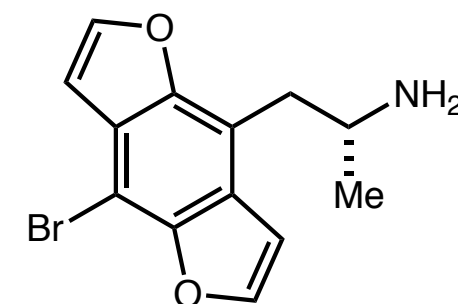


peyote (Lophophora williamsii)

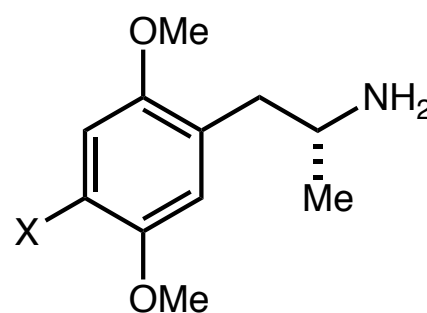
*very few (only one?) naturally occurring hallucinogenic phenethylamines
(they're mostly stimulants, not hallucinogens)*



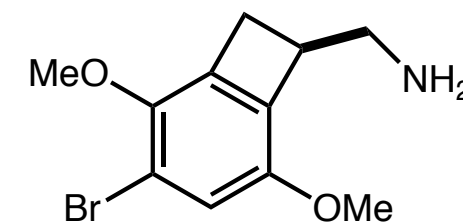
2C-B



Bromo-DragonFLY



$X = Br, DOB$
 $X = I, DOI$

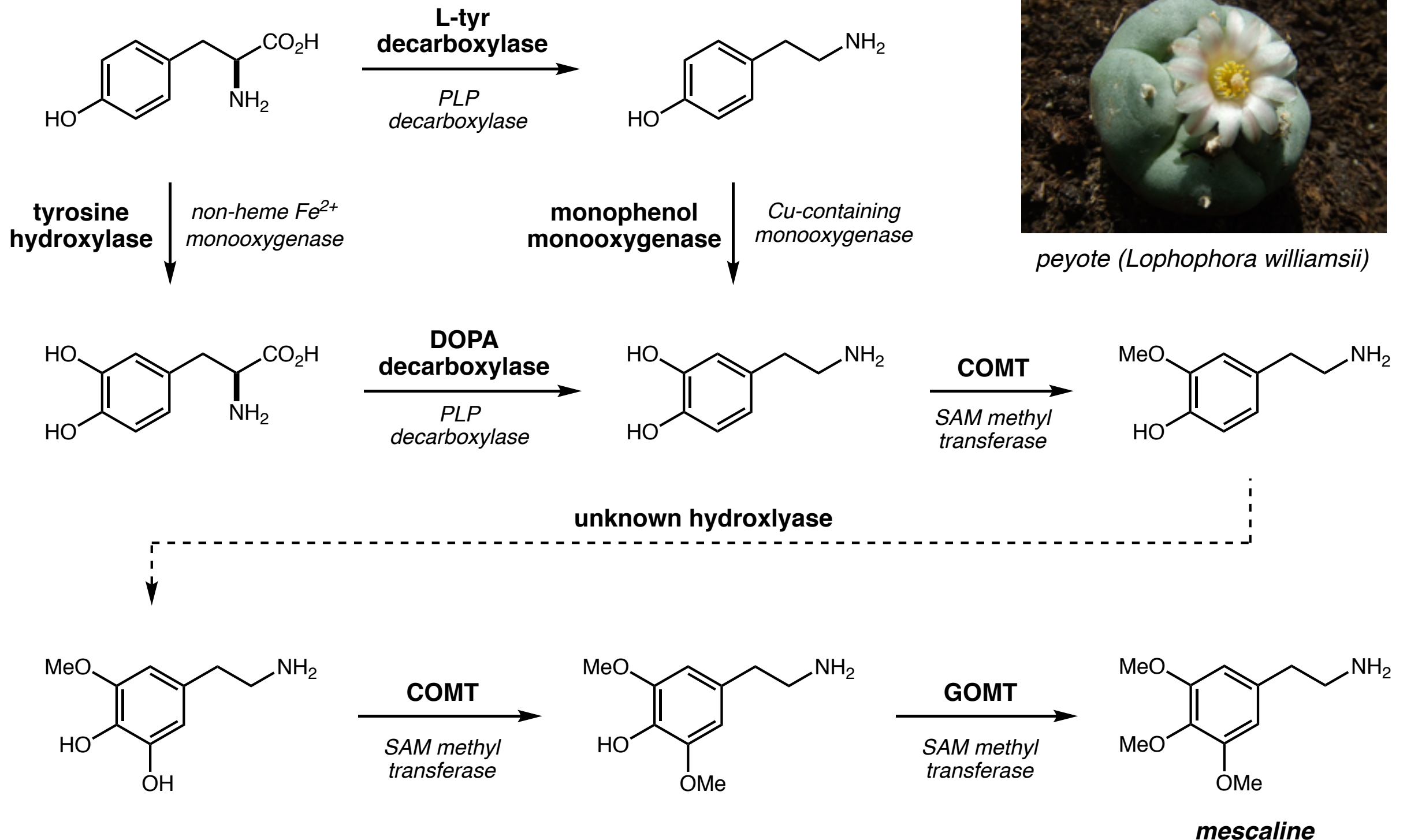


TCB-2



Chemistry and Biology of Hallucinogens

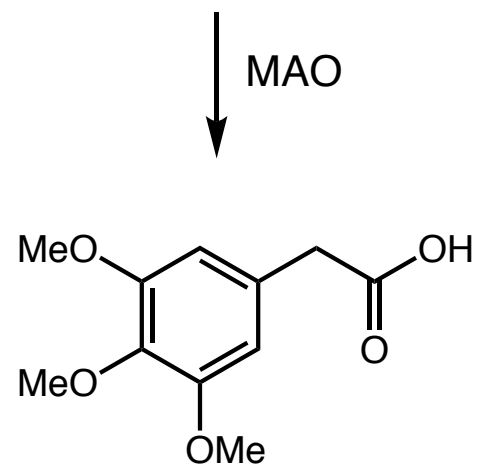
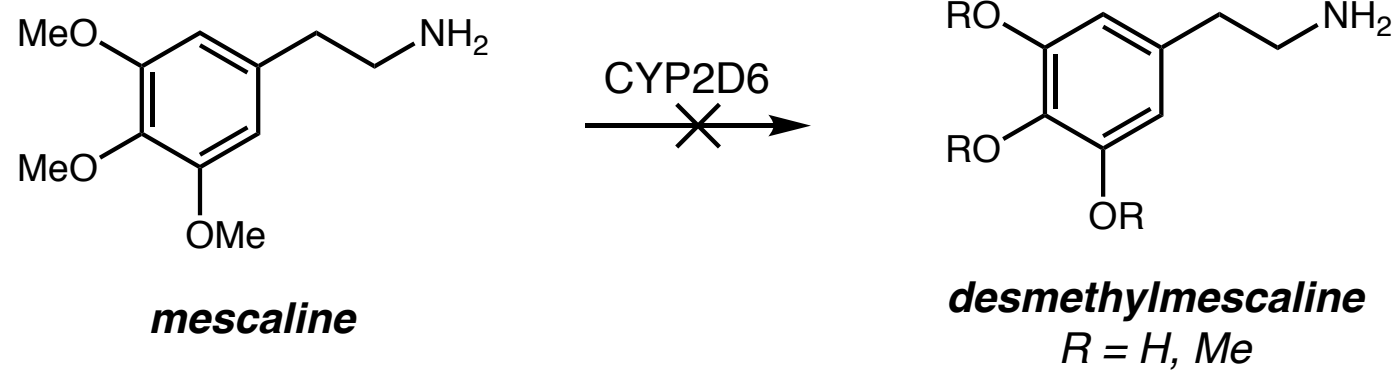
mescaline biosynthesis



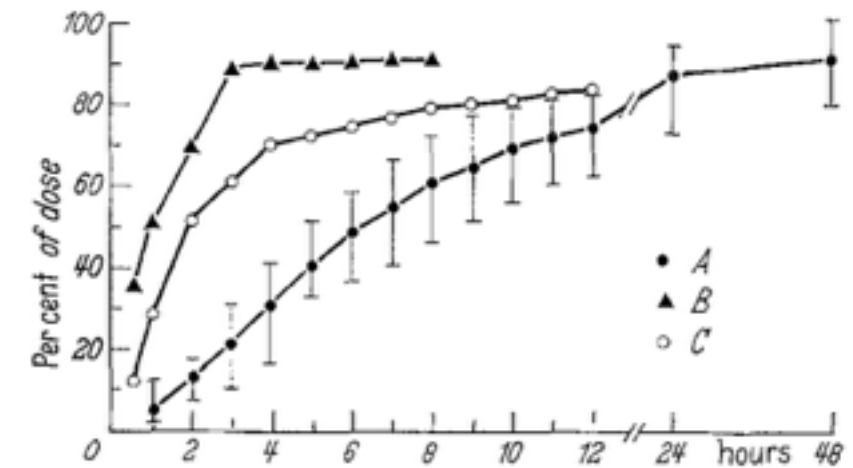
peyote (*Lophophora williamsii*)

Chemistry and Biology of Hallucinogens

mescaline pharmacokinetics



[¹⁴C]mescaline in humans



$t_{1/2} \sim 6$ hours

significantly less potent than LSD, psilocin

Drug	K_i^1 5-HT _{2A} (nM)	Human dose (mg) ³	Potency relative to LSD (human)
EthLAD	—	0.04–0.15	140
AllyLAD	—	0.08–0.16	110
LSD	2–4	0.06–0.20	100
ProLAD	—	0.10–0.20	90
DOB	0.6	1–3	7
DOI	0.7	1.5–3	6
DOM	19	3–10	2
Psilocin	15–25	10–15	1
DMCPA	—	15–20	0.7
MEM	73	20–50	0.4
MMDA-2	—	25–50	0.4
Mescaline	550	200–400	0.04

Nichols, D. E. *Pharmacol. Ther.* **2004**, 101, 131.

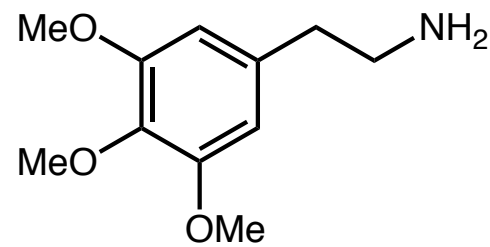
Hermle, L. *et al. Biol. Psych.* **1992**, 32, 976.

Charalampous, K. D.; Walker, K. E.; Kinross-Wright, J. *Psychopharmacologia* **1966**, 9, 48.

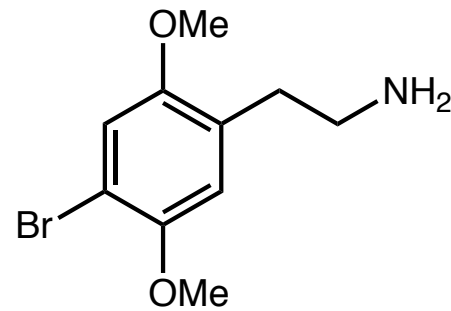
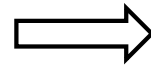
Wu, D.; Otton, S. V.; Inaba, T.; Kalow, W.; Sellers, E. M. *Biochem. Pharma.* **1997**, 53, 1605.

Chemistry and Biology of Hallucinogens

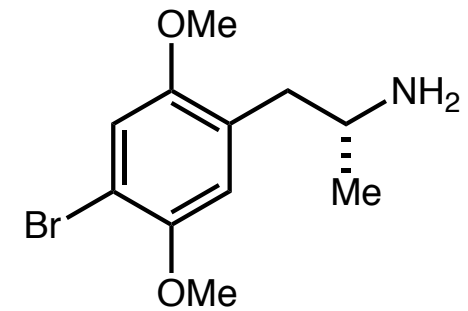
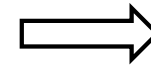
synthetic phenethylamines



mescaline
200-400 mg



2C-B
5-25 mg



DOB
0.2-2 mg



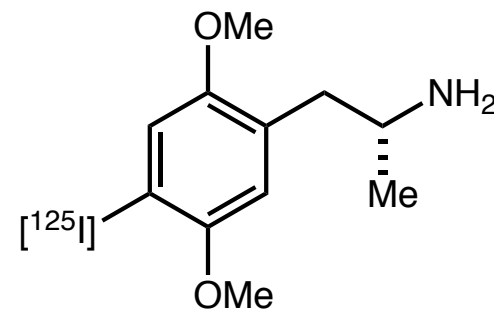
LSD



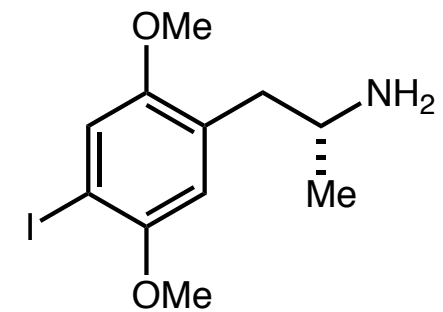
R-DOI



S-DOI



[¹²⁵I]DOI

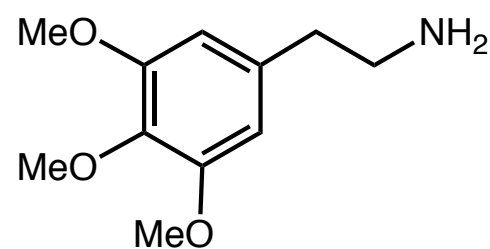


DOI
0.5-3 mg

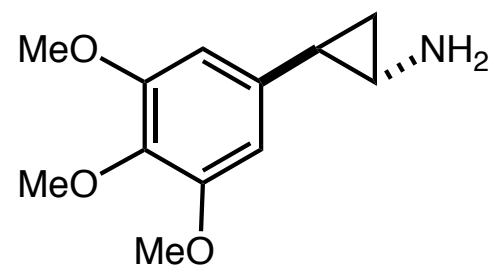
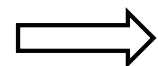
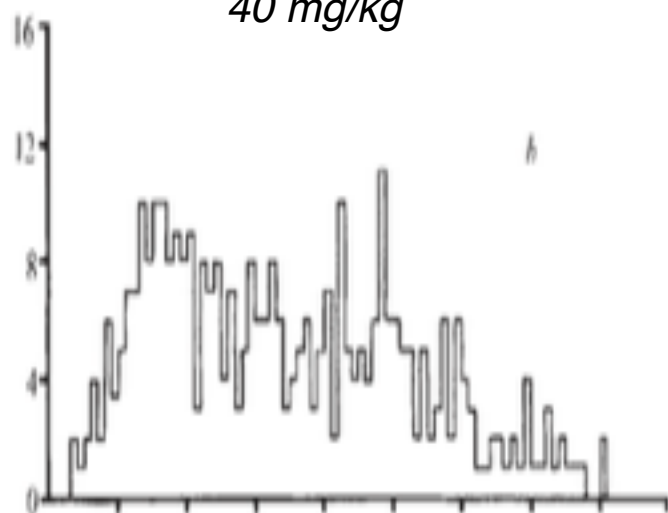
highly selective 5-HT₂ ligand
 $K_i = 0.7-20 \text{ nM (5-HT}_2\text{)}$
 $K_i > 1000 \text{ nM (5-HT}_1, 5\text{-HT}_5\text{)}$

Chemistry and Biology of Hallucinogens

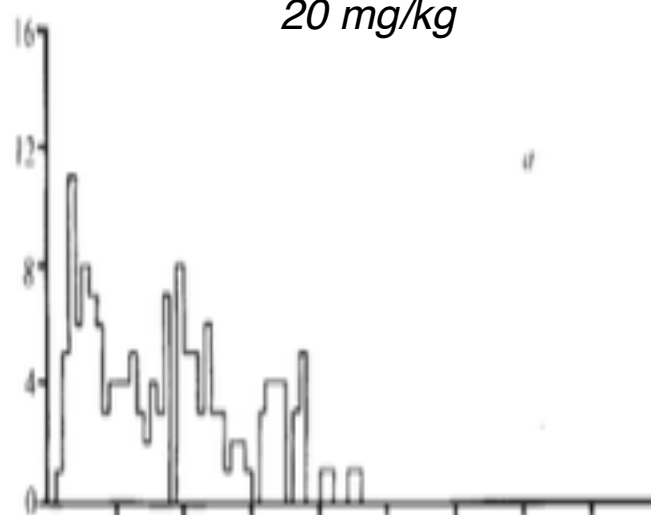
constrained mescaline analogues



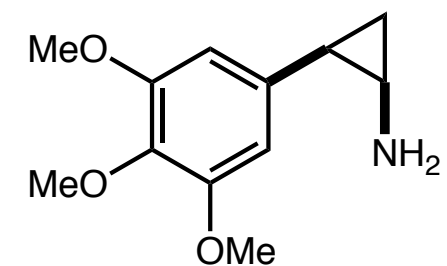
mescaline
40 mg/kg



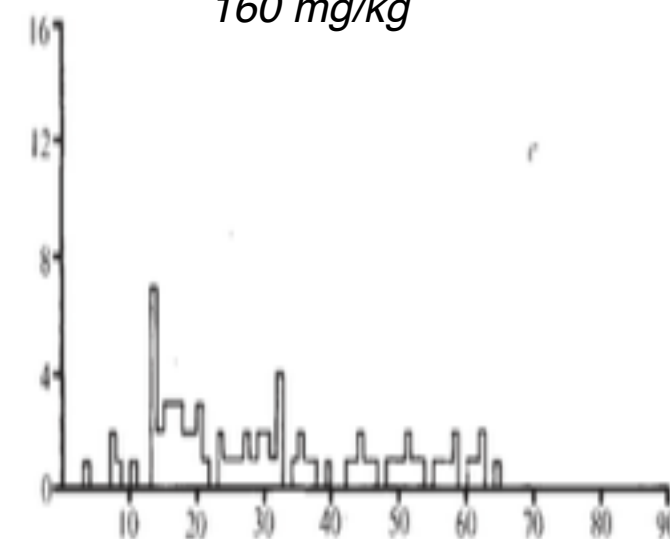
transoid mescaline
20 mg/kg



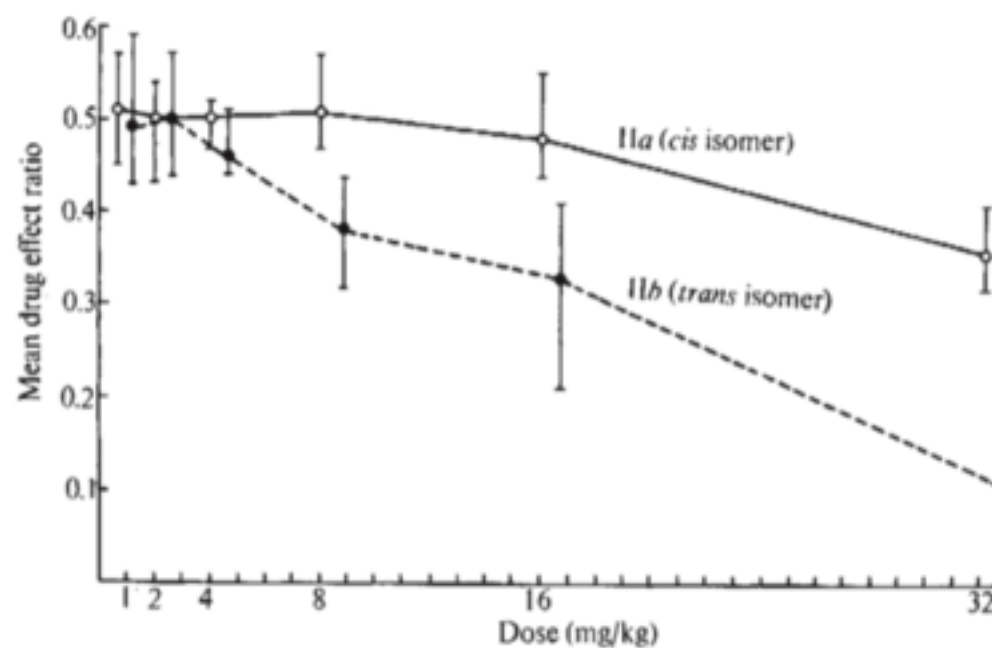
vs.



cisoid mescaline
160 mg/kg

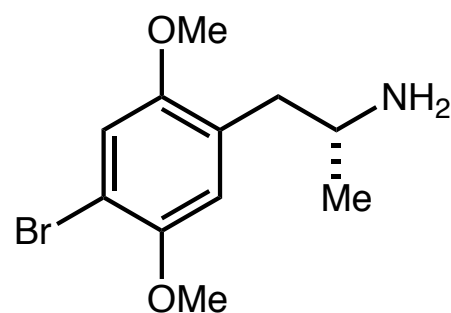


could constraining the alkylamino chain
lead to increased potency?



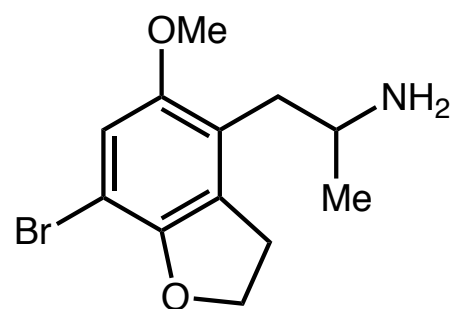
Chemistry and Biology of Hallucinogens

synthetic phenethylamines

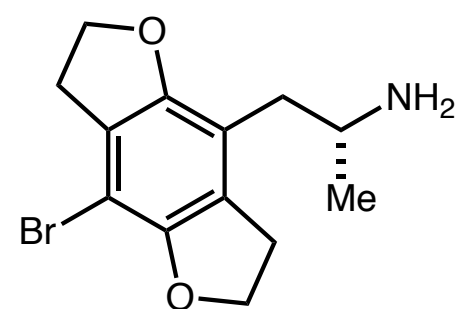


DOB

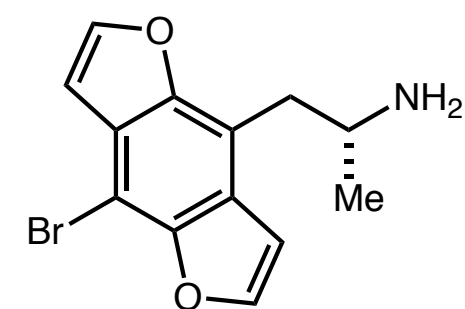
$K_i = 2.6 \text{ nM}$ for 5-HT₂
 $ED_{50} = 250 \text{ nmol/kg}$



$K_i = 3.1 \text{ nM}$ for 5-HT₂
 $ED_{50} = 570 \text{ nmol/kg}$

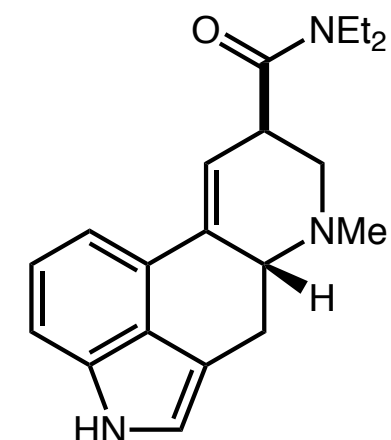
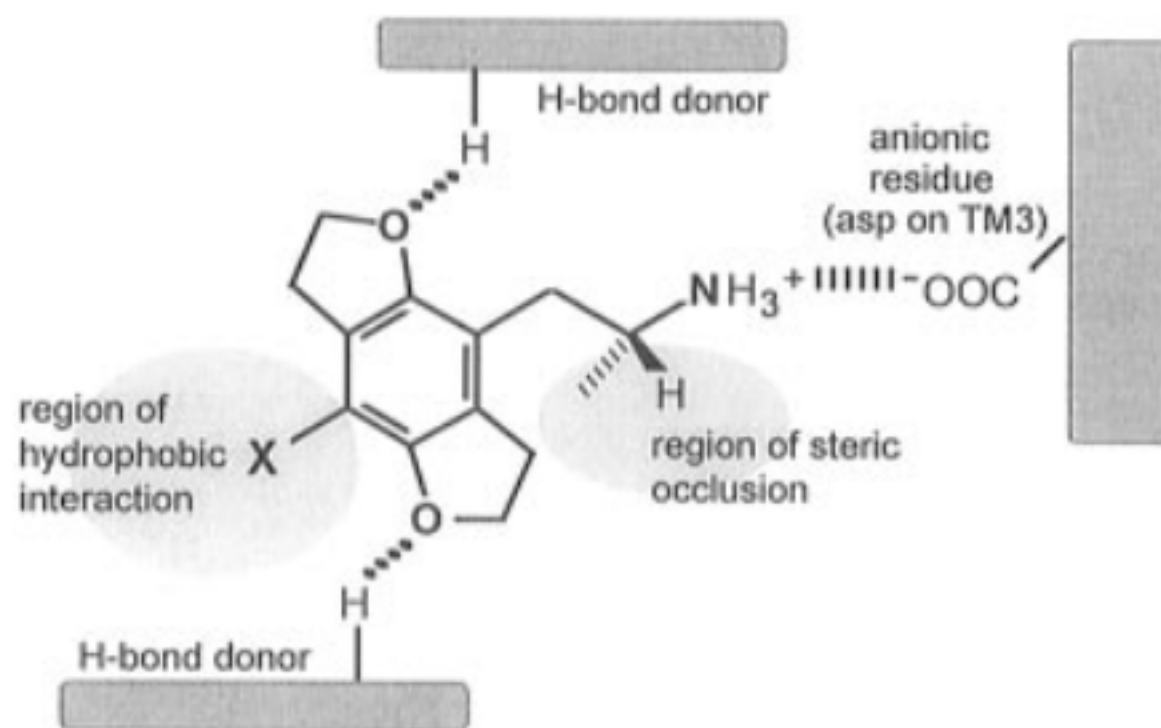


$K_i = 1.2 \text{ nM}$ for 5-HT_{2A}
 $ED_{50} = 61 \text{ nmol/kg}$



Bromo-DragonFLY

$K_i = 0.31 \text{ nM}$ for 5-HT_{2A}
 $ED_{50} = 22 \text{ nmol/kg}$



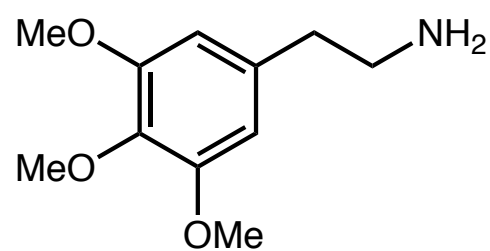
LSD

$ED_{50} = 40 \text{ nmol/kg}$

Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, 44, 1003.
 Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, 44, 1003.
 Parker, M. A.; Marona-Lewicka, D.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1998**, 41, 5148.
 Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1996**, 2953.
 Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Johnson, M. P.; Huang, X. *J. Med. Chem.* **1991**, 34, 276.

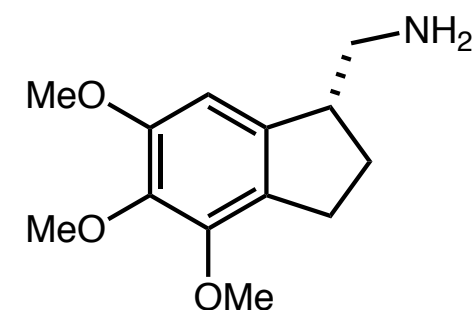
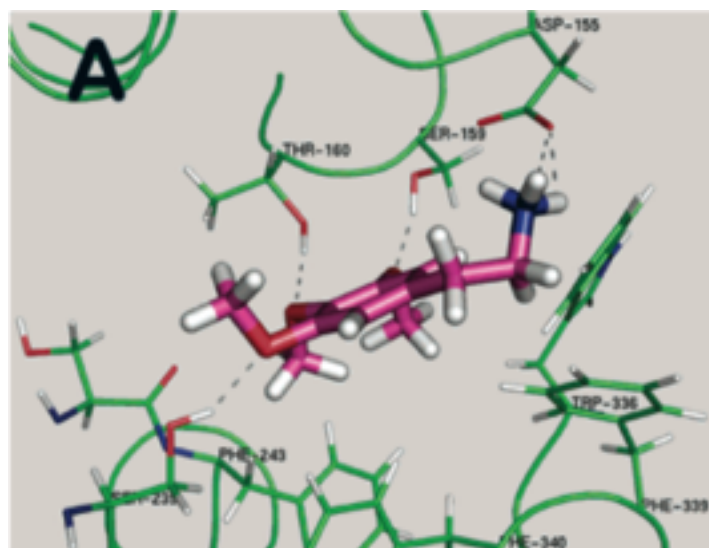
Chemistry and Biology of Hallucinogens

synthetic phenethylamines



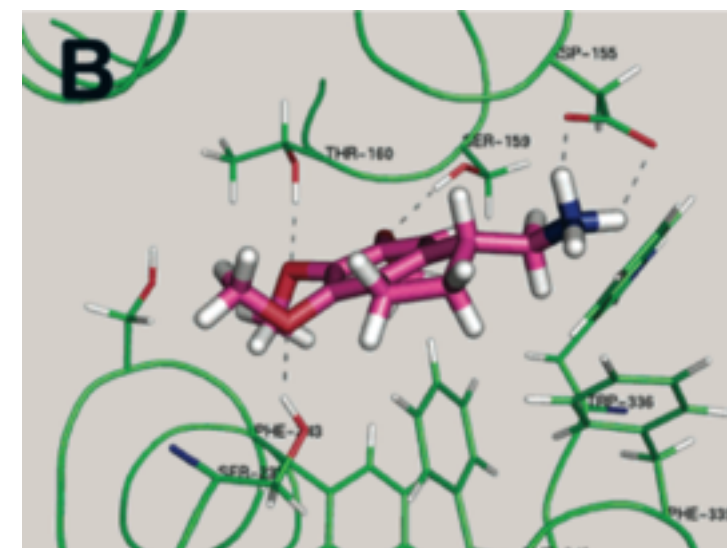
mescaline

$K_i = 360 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 113000 \text{ nM}$



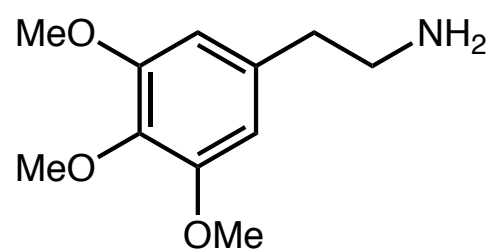
Jimscaline

$K_i = 69 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 3200 \text{ nM}$



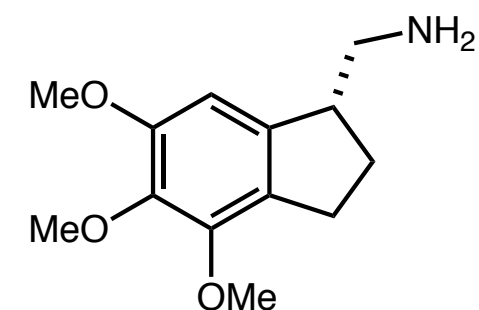
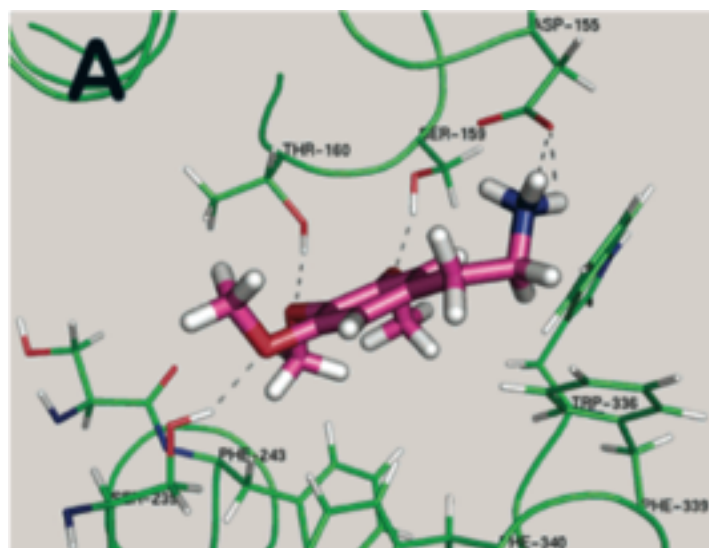
Chemistry and Biology of Hallucinogens

synthetic phenethylamines



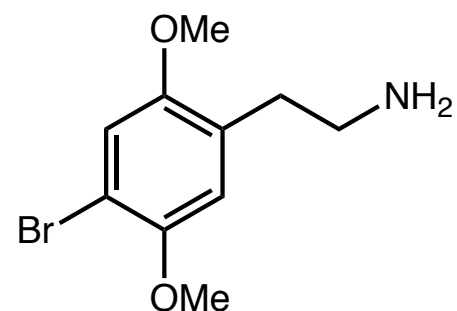
mescaline

$K_i = 360 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 113000 \text{ nM}$



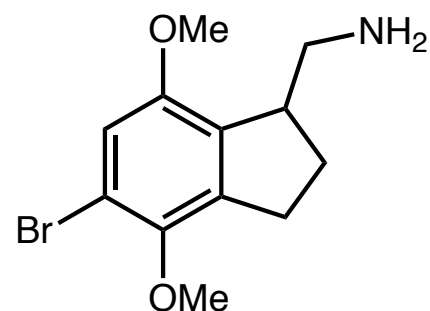
Jimscaline

$K_i = 69 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 3200 \text{ nM}$



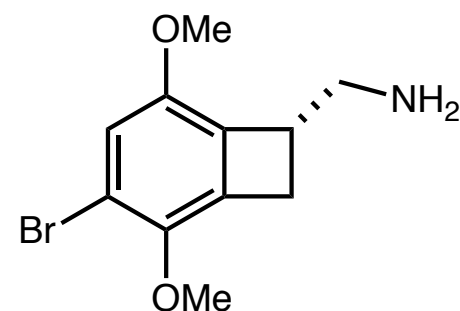
2C-B

$K_i = 0.88 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 27 \text{ nM}$



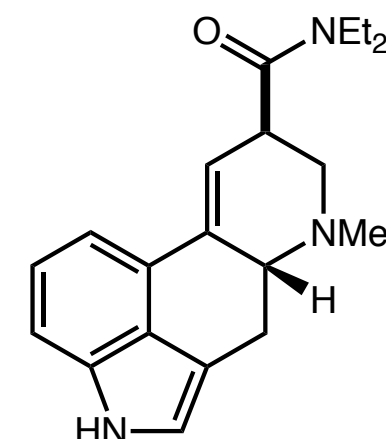
2CB-Ind

$K_i = 47 \text{ nM}$ for 5-HT_{2A}



TCB-2

$K_i = 0.26 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 18 \text{ nM}$

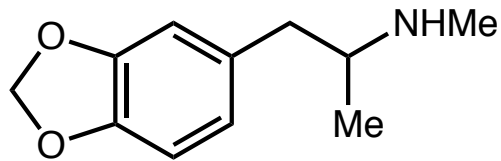


LSD

$K_i = 3.5 \text{ nM}$ for 5-HT_{2A}
 $EC_{50} = 9.8 \text{ nM}$

Chemistry and Biology of Hallucinogens

serotonin-releasing agents



**3,4-methylenedioxymethamphetamine
(MDMA, ecstasy)**

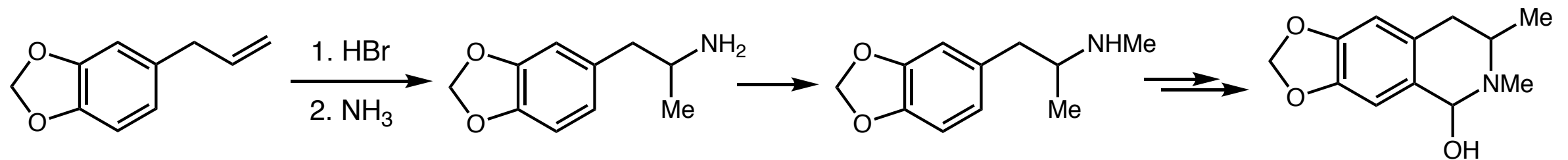
dubbed empathogen (generating a state of empathy)

- Metzner and Nichols, 1983-84

renamed as entactogen (touching within)

-Nichols, 1986

first synthesized in 1912 by Merck KGaA



safrole

*safrylamine
(MDA)*

*safrylmethylamine
(MDMA)*

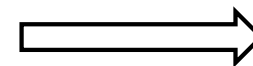
3-methylhydrastinine

*first studied in animals in the 1950s at University
of Michigan, commissioned by the US Army*

synthesized by Shulgin in 1965 at Dow, not tested

confirmed to be in use in Chicago in 1970

*Shulgin and Nichols publish first report of MDMA's
effect on humans in 1978*

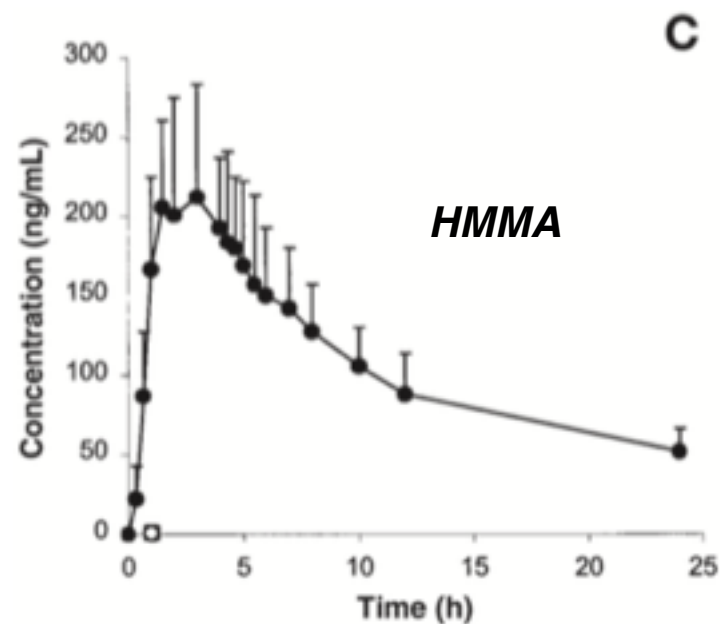
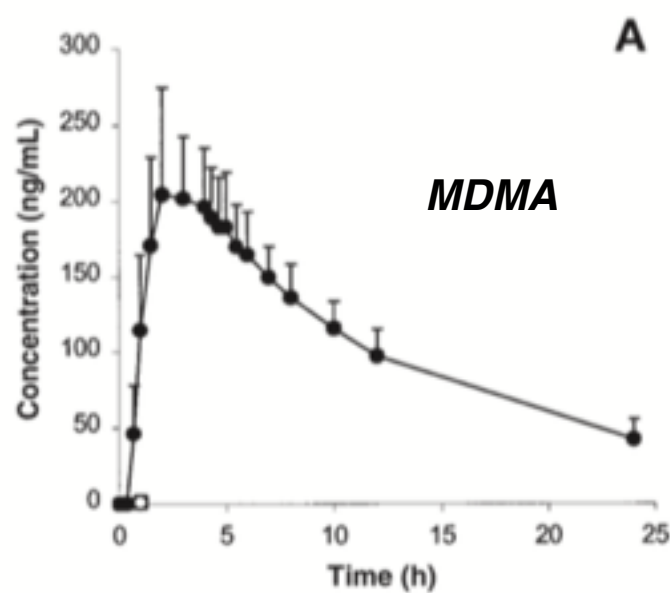
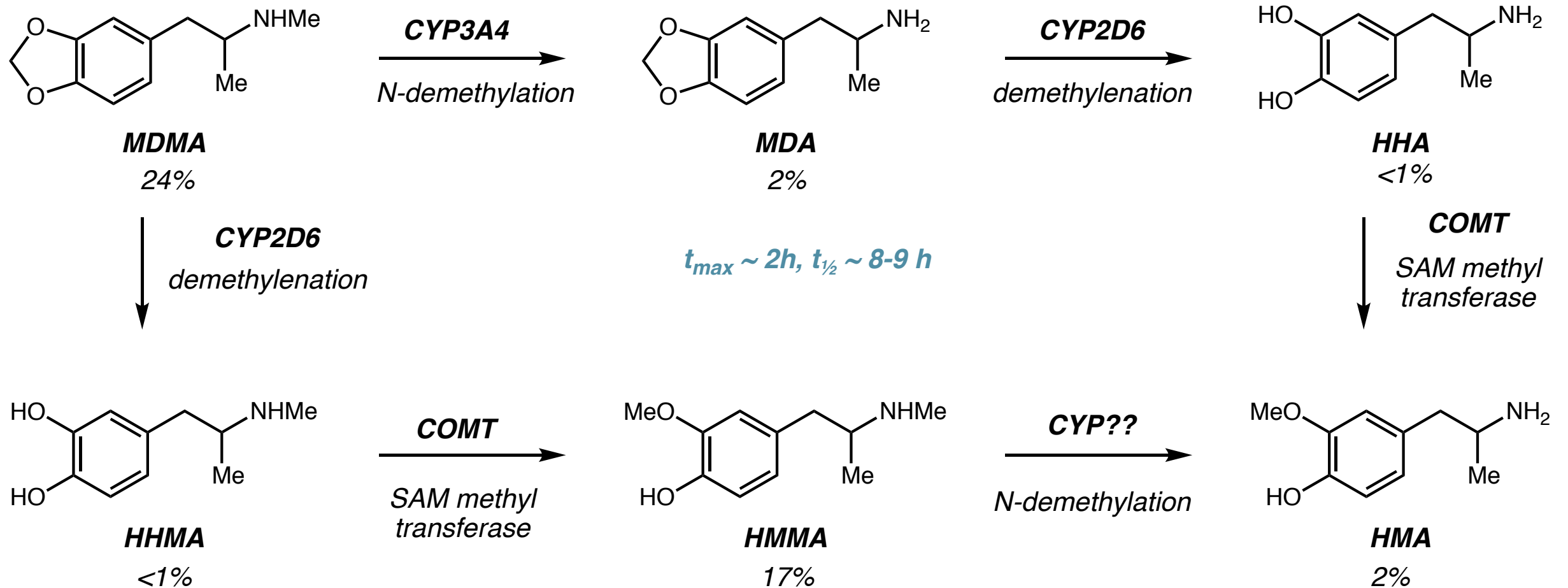


*increased serotonin release,
combined with reuptake inhibition*

*acute toxicity at high doses due to
serotonin syndrome – increased heart
rate, blood pressure, body
temperature, tremors, hallucinations*

Chemistry and Biology of Hallucinogens

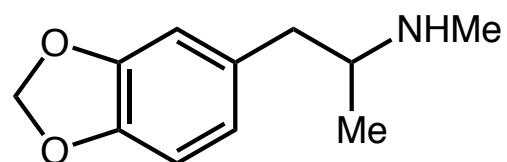
MDMA metabolism and pharmacokinetics



de la Torre, R. et al. *Annal. NY Acad. Sci.* **2000**, 914, 225.
 de la Torre, R. et al. *Br. J. Clin. Pharmacol.* **1999**, 49, 104.
 de la Torre, R. et al. *J. Anal. Toxicol.* **2002**, 26, 157.

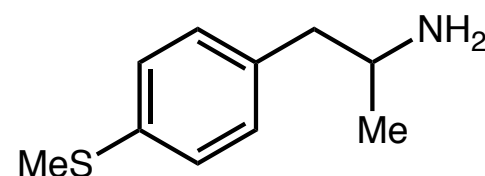
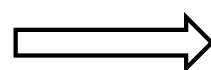
Chemistry and Biology of Hallucinogens

4-MTA



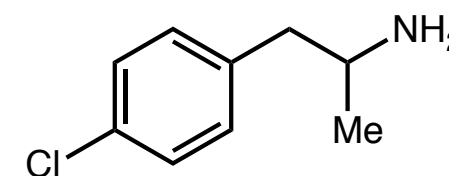
MDMA

$ED_{50} = 2.79 \mu\text{mol/kg}$



**4-methylthioamphetamine
(MTA)**

$ED_{50} = 0.95 \mu\text{mol/kg}$



**p-chloroamphetamine
(PCA)**

$ED_{50} = 0.84 \mu\text{mol/kg}$

IC₅₀ (nM) to inhibit uptake

[³H]serotonin	74	182
[³H]dopamine	3073	424
[³H]norepinephrine	2375	207

MTA's serotonin-selective uptake inhibition should make it a more effective tool compound than PCA

illicit production and distribution lead to several deaths in Europe in the early 2000's

"I was particularly disturbed to see my name in the article, and that I had been 'especially valuable' to their cause [of preparing designer drugs]... Without my knowledge, MTA was synthesized by others and made into tablets call, appropriately enough, 'flatliners'. Some people who took them died... It not only caused the release of serotonin from neurons, but also prevented the breakdown of this neurotransmitter... I had published information that had ultimately lead to human death... I strive to find positive things, and when my research is used for negative ends it upsets me... This question, which was never part of my research focus, now haunts me."

Chemistry and Biology of Hallucinogens

NMDA receptor

Location:

ion channel protein in nerve cells

Endogenous ligands:

glutamate and glycine

Physiological processes:

synaptic plasticity (learning, memory)

Ca²⁺, Na⁺ into cell, K⁺ out of cell

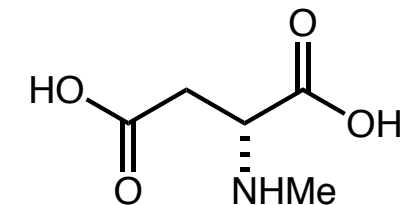
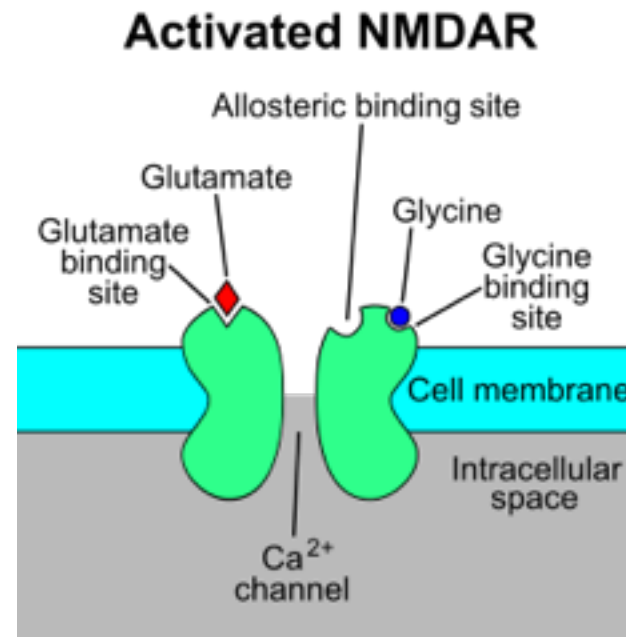
Clinical importance:

age-related memory loss

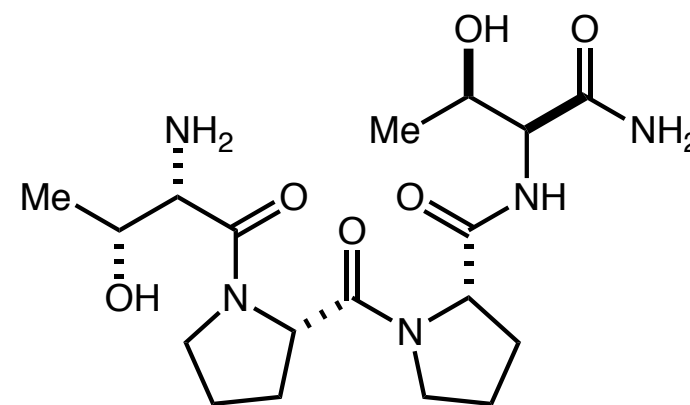
potentially Alzheimer's disease

alcohol withdrawal

partial agonism of glycine site allosteric site has led to breakthrough antidepressants, namely Rapastinel (Allergan)



N-methyl-D-aspartate is a specific agonist, mimicking glutamate



Rapastinel

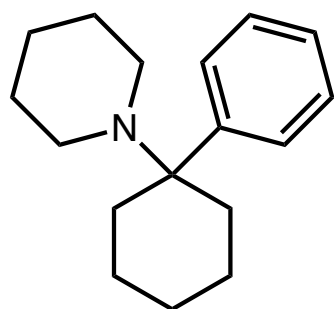
Moskal, J. R. *et al. Neuropharmacol.* **2005**, 49, 1077.

Mishina, M. *et al. Nature* **1992**, 358, 36.

MacDermott, A. B.; Mayer, M. L.; Wetbrook, G. L.; Smith, S. J.; Barker, J. L. *Nature* **1986**, 321, 519.

Chemistry and Biology of Hallucinogens

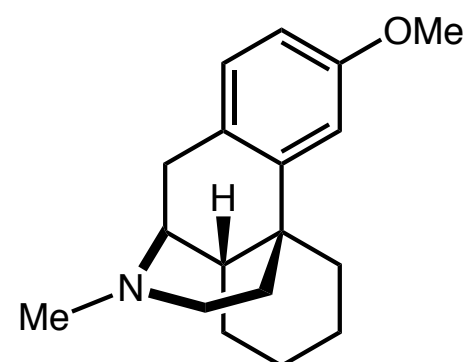
NMDAR antagonists (dissociatives)



**phencyclidine
(PCP)**

first synthesized by Parke-Davis in 1956

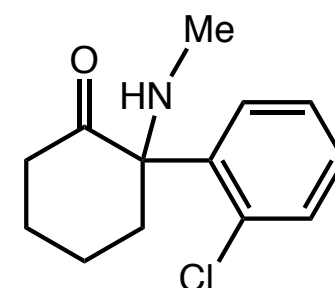
*FDA approved anaesthetic in 1957, marketed as Sernyl
pulled in 1965 due to adverse
behavioral effects*



**dextromethorphan
(DXM, DM)**

first synthesized by Hoffman-La Roche in 1947

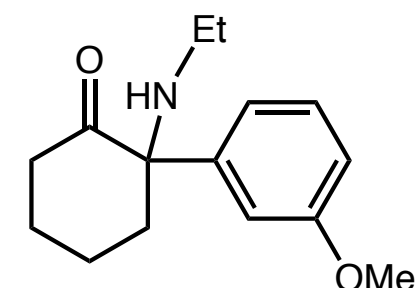
*FDA approved OTC
antitussive, as Romilar*



ketamine

first synthesized by Parke-Davis in 1962

FDA approved anaesthetic in 1969, marketed as Ketalar



**methoxetamine
(MXE)**

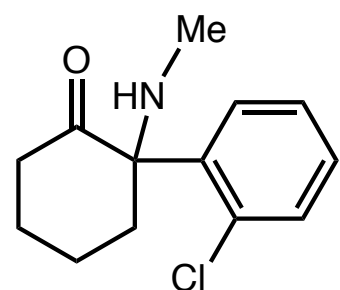
*first synthesized in 2010 by
www.bluelight.ru users*

“designer” drug

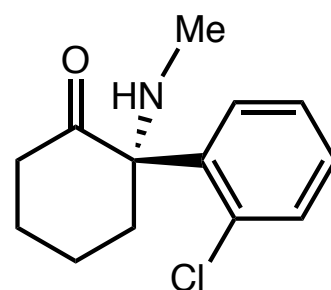


Chemistry and Biology of Hallucinogens

ketamine pharmacology

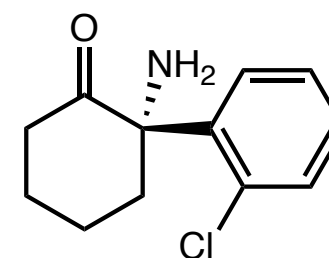
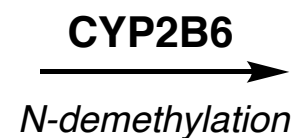


ketamine



(S)-ketamine

~ 4x more active than (R)
0.5–1 mg/kg for
general anaesthesia



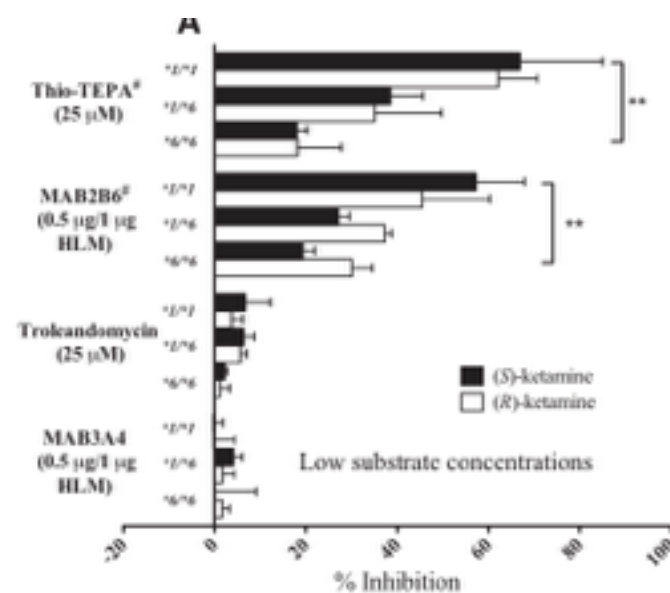
norketamine

detectable in plasma
2-3 min after IV

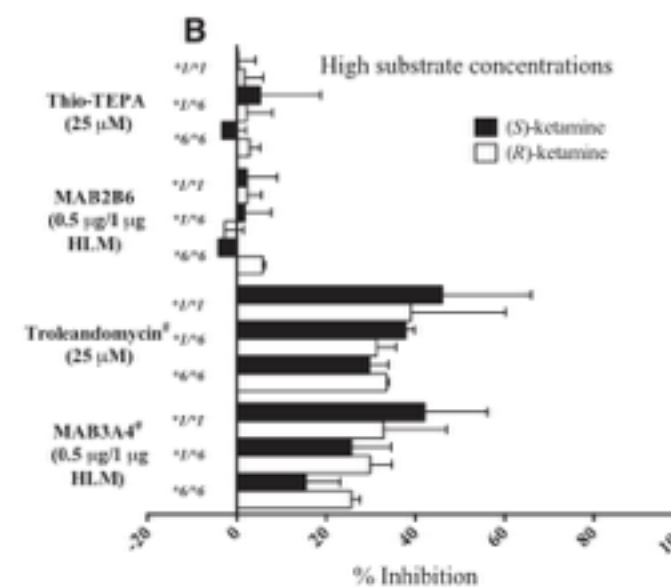
**CYP2B6
inhibitors**

**CYP3A4
inhibitors**

20-80 μM [ketamine]

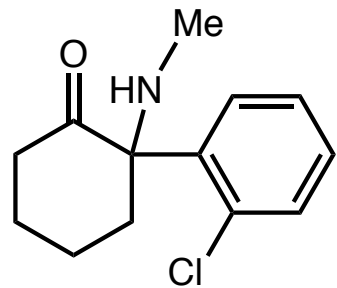


300-850 μM [ketamine]

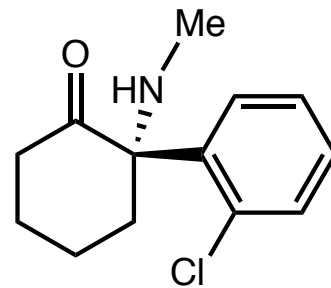


Chemistry and Biology of Hallucinogens

ketamine pharmacology

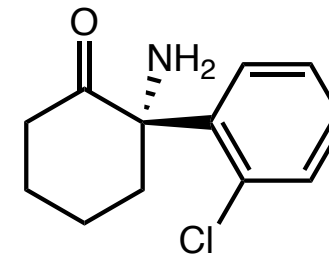
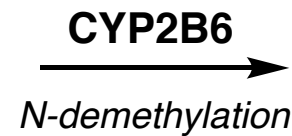


ketamine



(S)-ketamine

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0.5–1 mg/kg for
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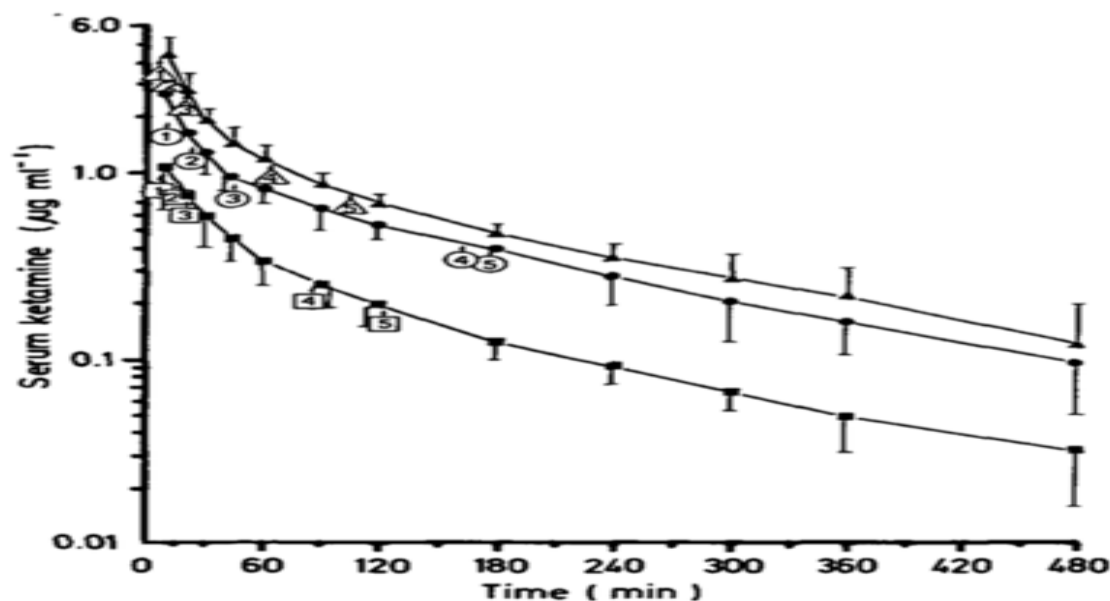


norketamine

detectable in plasma
2-3 min after IV

(S)-ketamine clearance > (R)-ketamine clearance
21.3 mL/kg min 17.4 mL/kg min

(R)-ketamine inhibits (S)-ketamine clearance

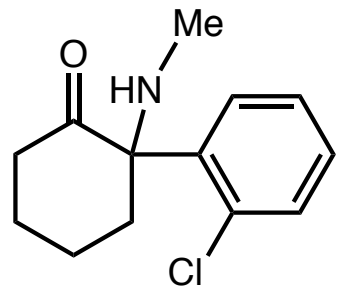


	S(+)- Ketamine	S(+)-Ketamine in racemate
k_{12} (min ⁻¹)	0.10 ± 0.02	0.087 ± 0.012
k_{21} (min ⁻¹)	0.056 ± 0.010	0.066 ± 0.012
k_{13} (min ⁻¹)	0.044 ± 0.004	0.051 ± 0.006
k_{31} (min ⁻¹)	0.0078 ± 0.0017	0.0073 ± 0.0010
CL (ml · kg ⁻¹ · min ⁻¹)	$26.3 \pm 3.5^{*†‡}$	$18.5 \pm 0.7§$

White, P. F.; Schuttler, J.; Shafer, A.; Stanski, D. R.; Horai, Y.; Trevor, A. J. *Br. J. Anaesth.* **1985**, 57, 197.
Ihmsen, H.; Geisslinger, G.; Schuttler, J. *Clin. Pharmacol. Ther.* **2001**, 70, 431.
Mion, G.; Villeveille, T. *CNS Neurosci. Ther.* **2013**, 19, 370.

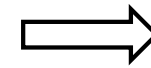
Chemistry and Biology of Hallucinogens

ketamine psychadelic effects



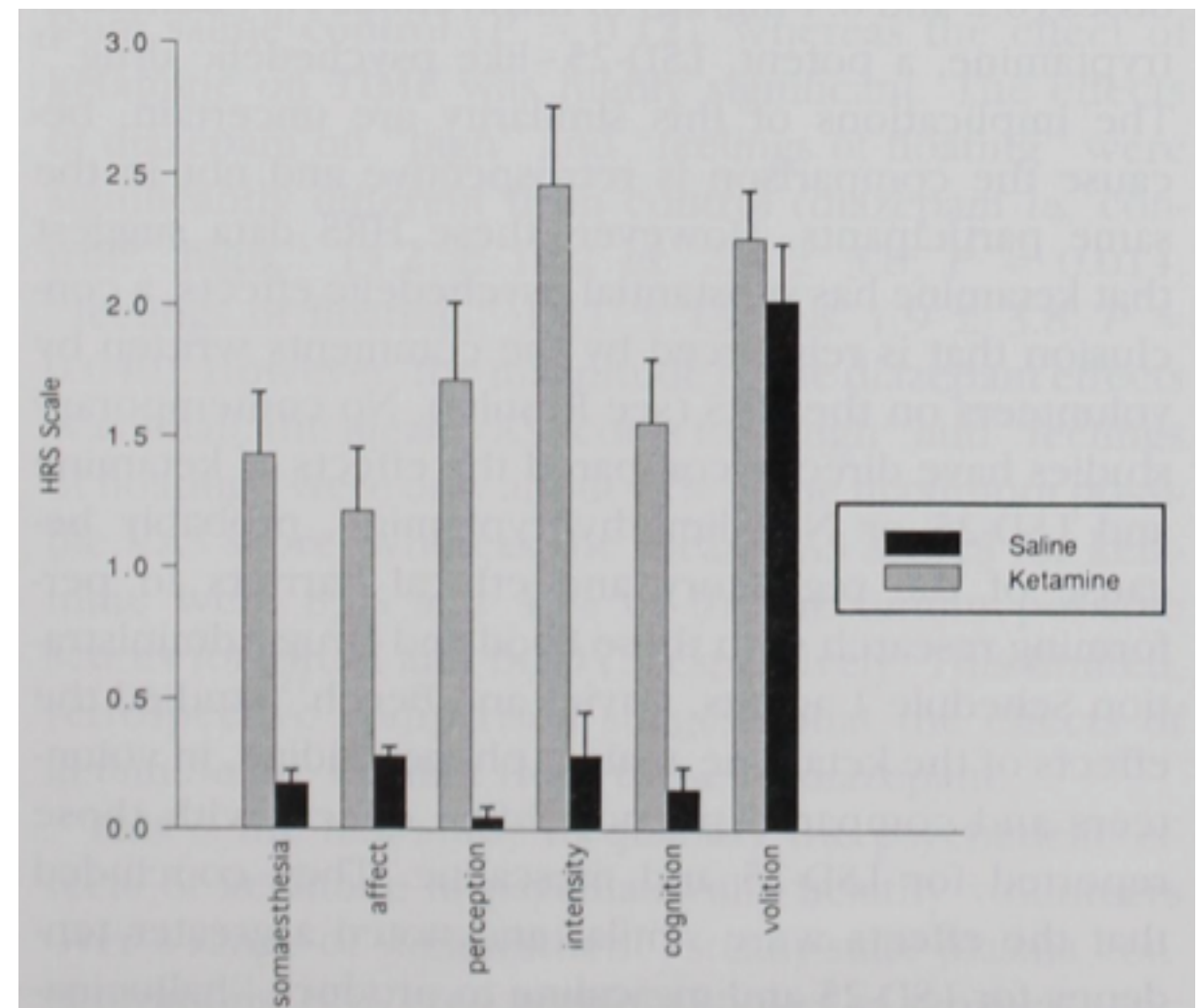
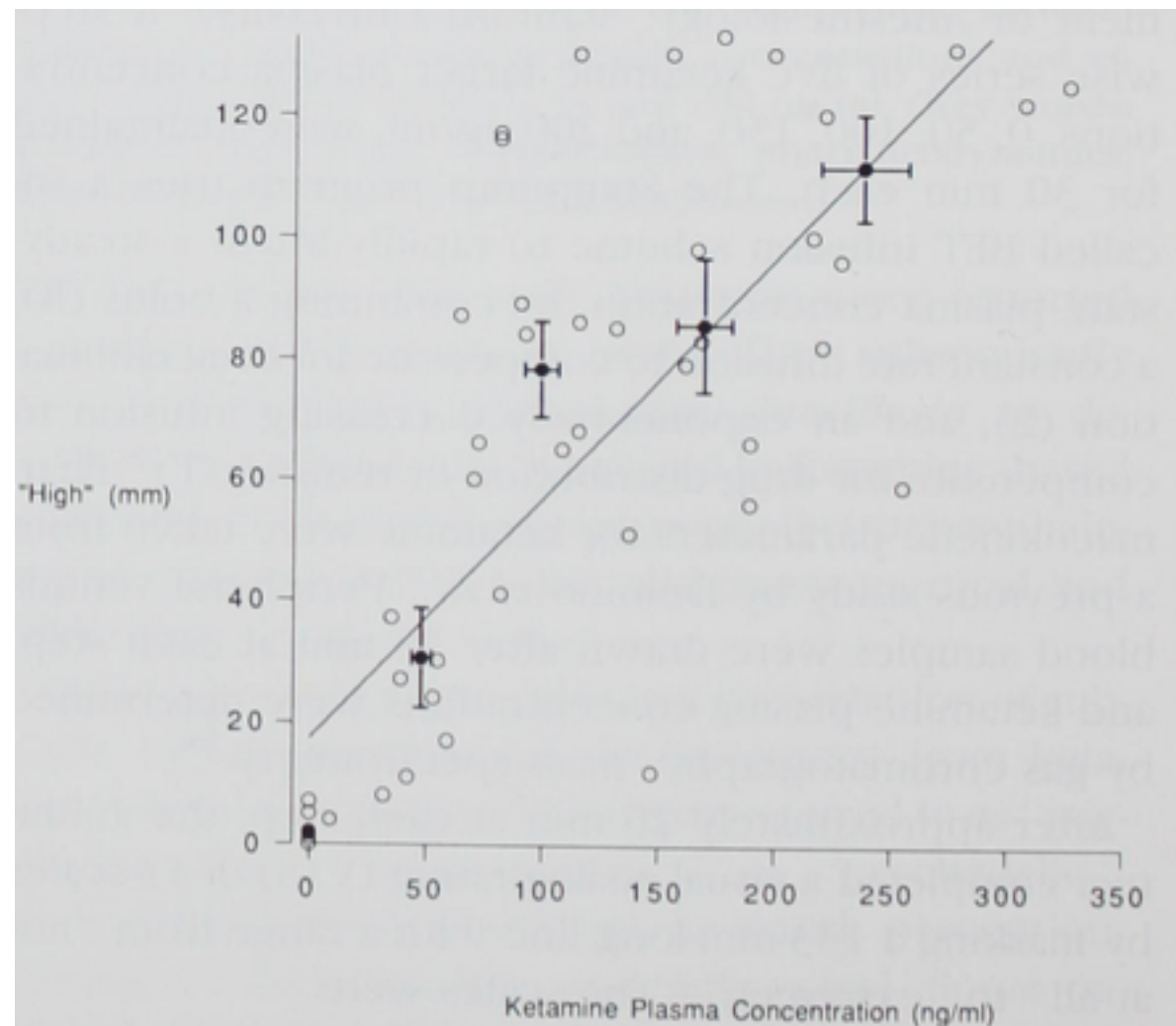
ketamine

administered plasma level:
50 – 200 ng/mL



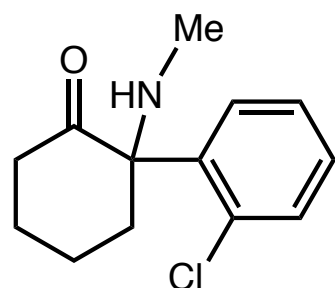
general anesthesia plasma level:
600 – 1100 ng/mL

analgesic plasma level:
100 – 200 ng/mL



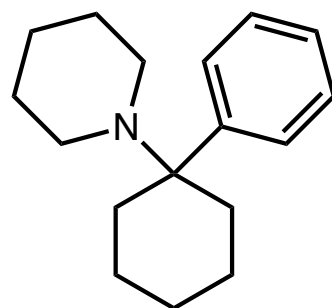
Chemistry and Biology of Hallucinogens

development of methoxetamine

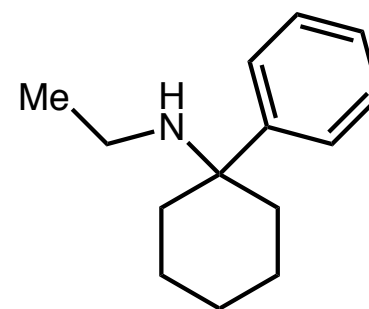


ketamine

10–250 mg
<30 min onset
<3 h duration

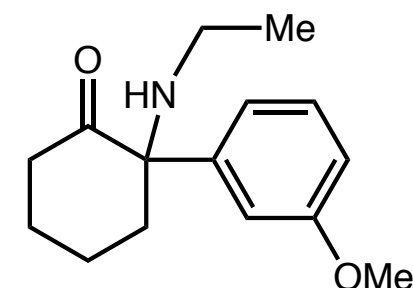


PCP



PCE

“more active than PCP”

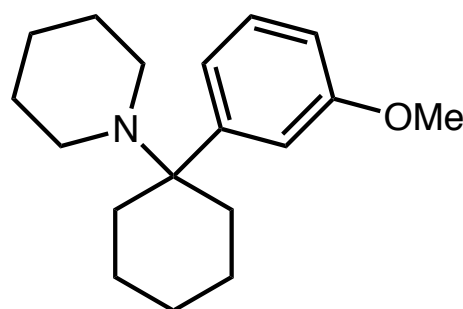


methoxetamine

10–100 mg
30–90 min onset
5–7 h duration

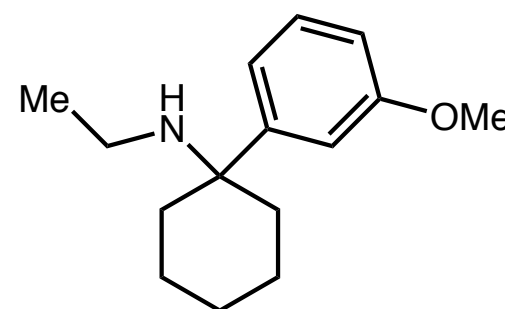
“3-MeO-PCP and 3-MeO-PCE are simply incredible drugs. They have a true capacity for healing... At 15 mg, I felt 3-MeO-PCP was possibly the most amazing drug I had ever consumed, and 3-MeO-PCE seemed to have the full capacity to be the next LSD.”

- M



3-OMe-PCP

“extremely similar to PCP
in potency and quality”



3-OMe-PCE

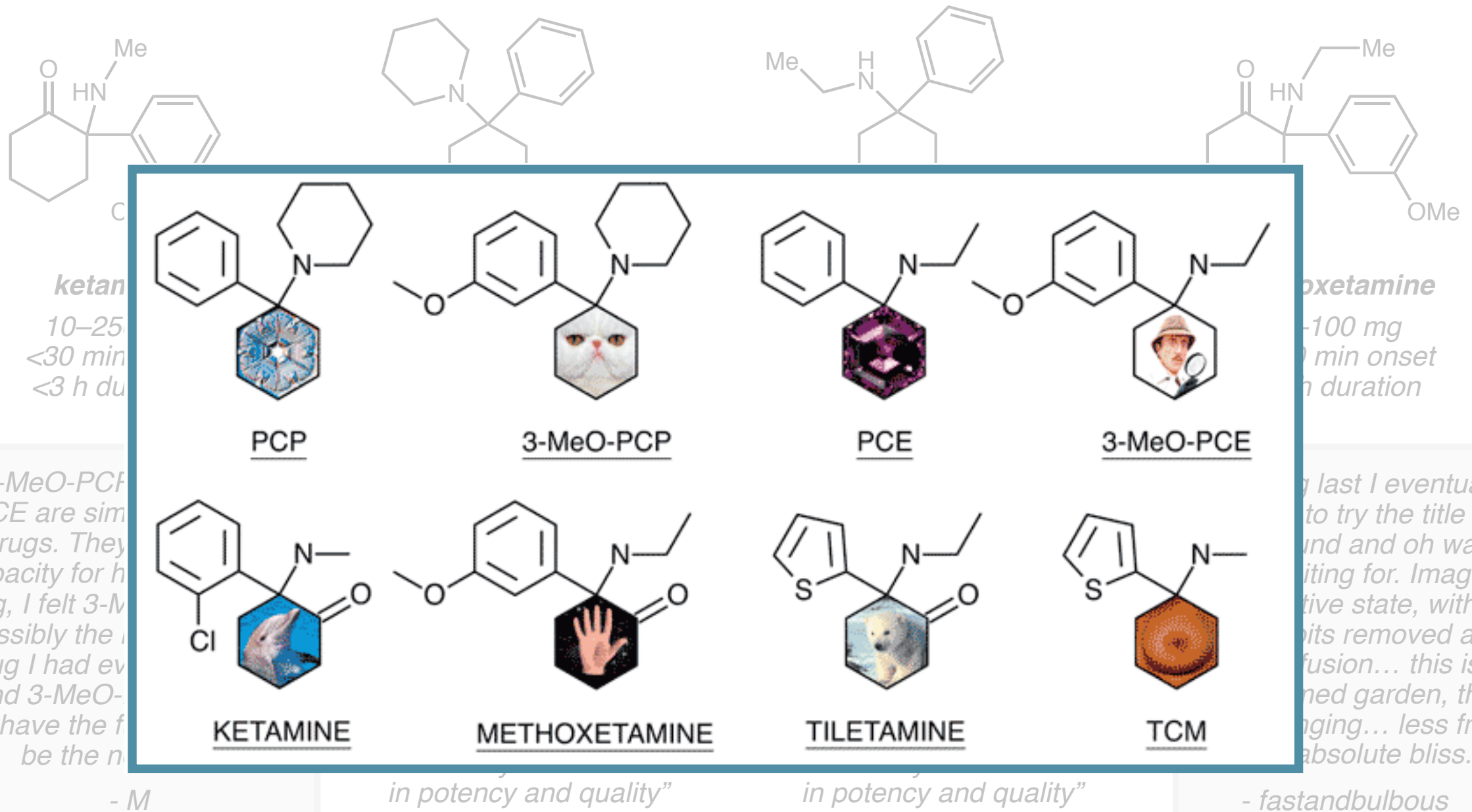
“extremely similar to PCP
in potency and quality”

“At long last I eventually got to try the title compound and oh was it worth waiting for. Imagine a dissociative state, with the scary bits removed and less confusion... this is the perfumed garden, the sirens singing... less freaky and absolute bliss.”

- fastandbulbous

Chemistry and Biology of Hallucinogens

development of methoxetamine



Chemistry and Biology of Hallucinogens

κ -Opioid Receptor

Location:

cell membrane of nerve cells, in
brain and spinal cord

Endogenous ligand:

dynorphins

Physiological processes:

pain

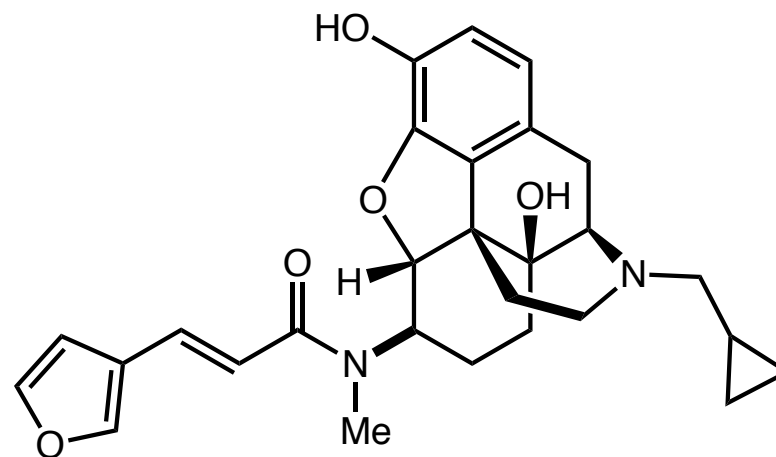
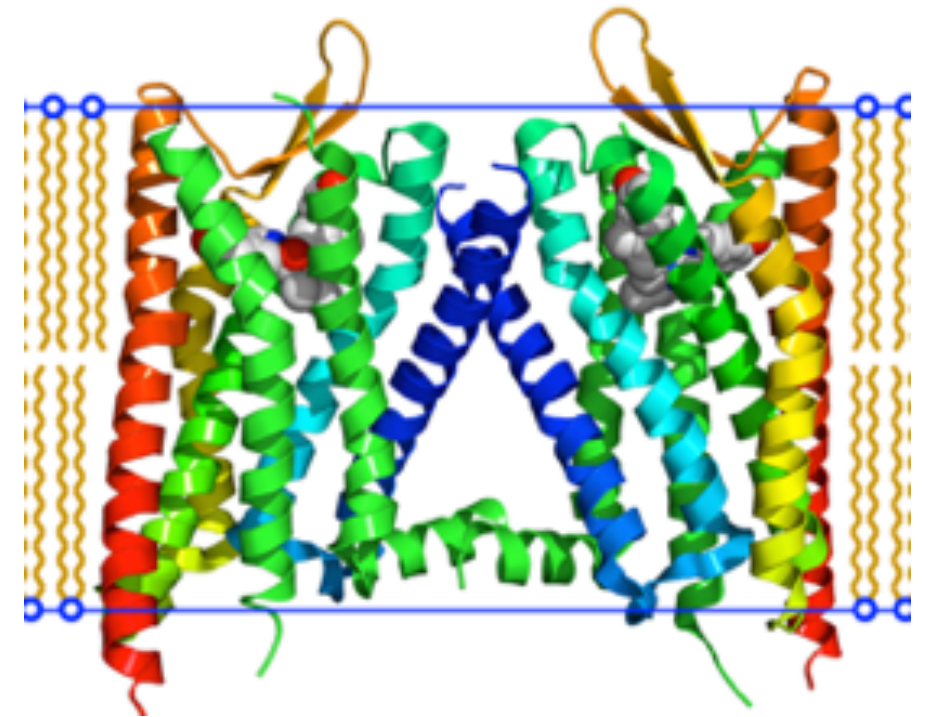
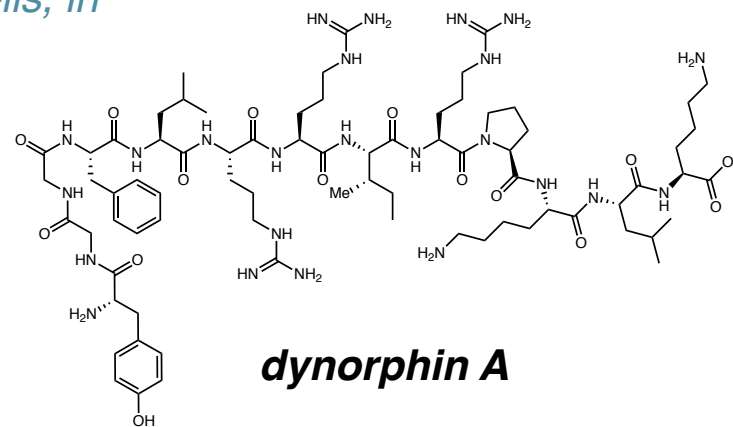
consciousness

addiction

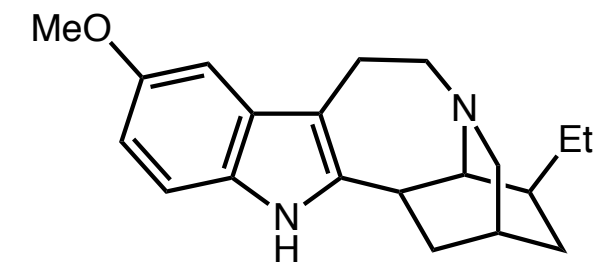
Clinical importance:

targeted for analgesic effects

potentially a natural addiction
control mechanism



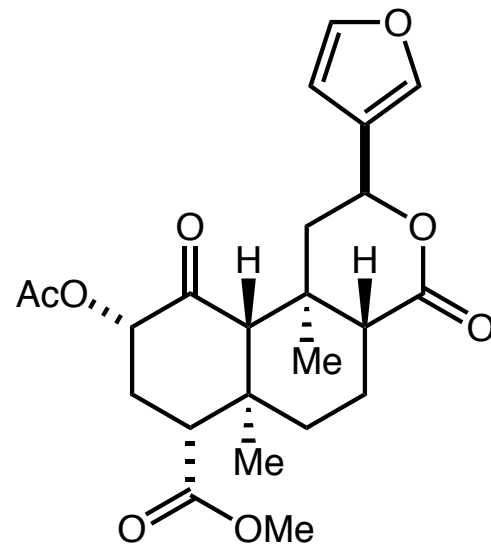
nalfurafine
antipruritic (anti-itch)



ibogaine
anti-addiction and hallucinogen

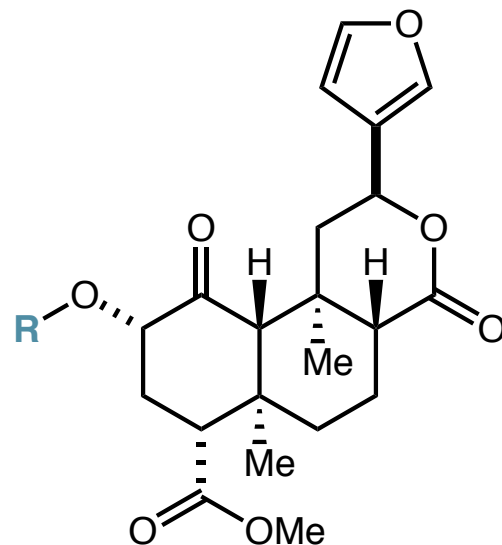
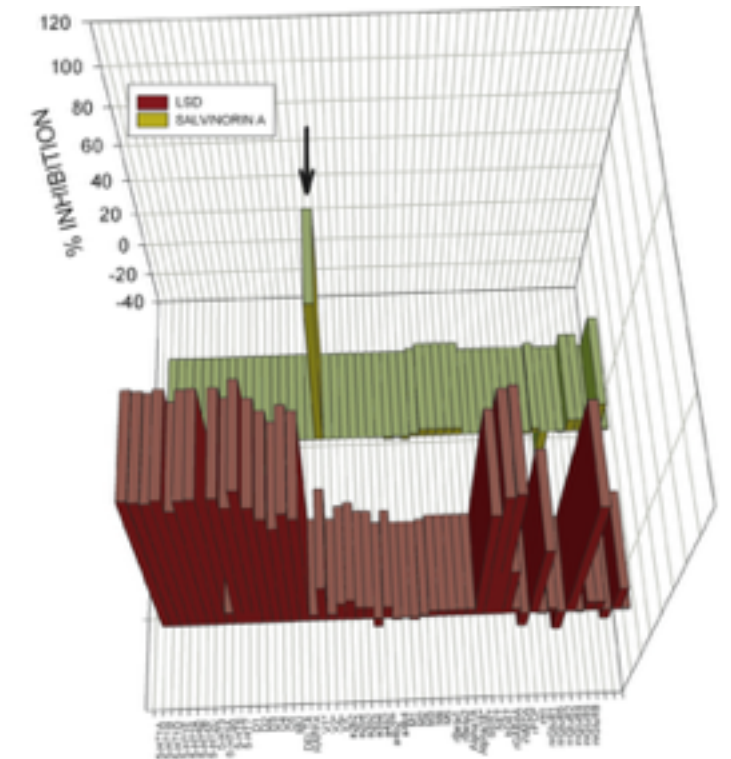
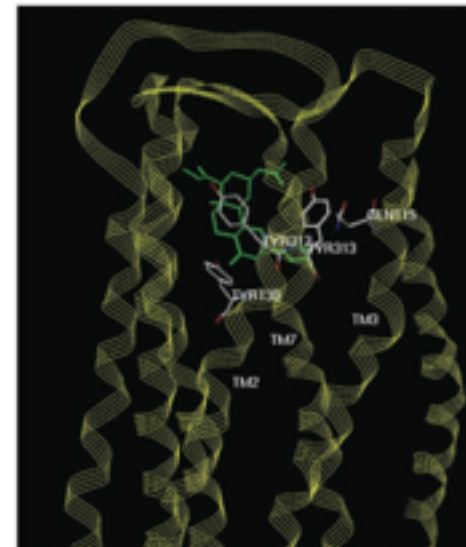
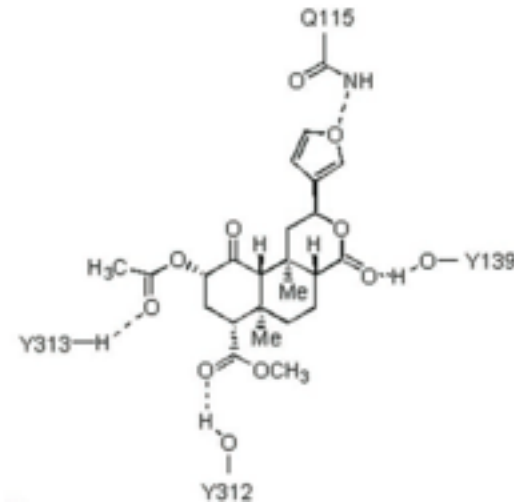
Chemistry and Biology of Hallucinogens

salvinorin A



salvinorin A

isolated from *Salvia divinorum* in 1982



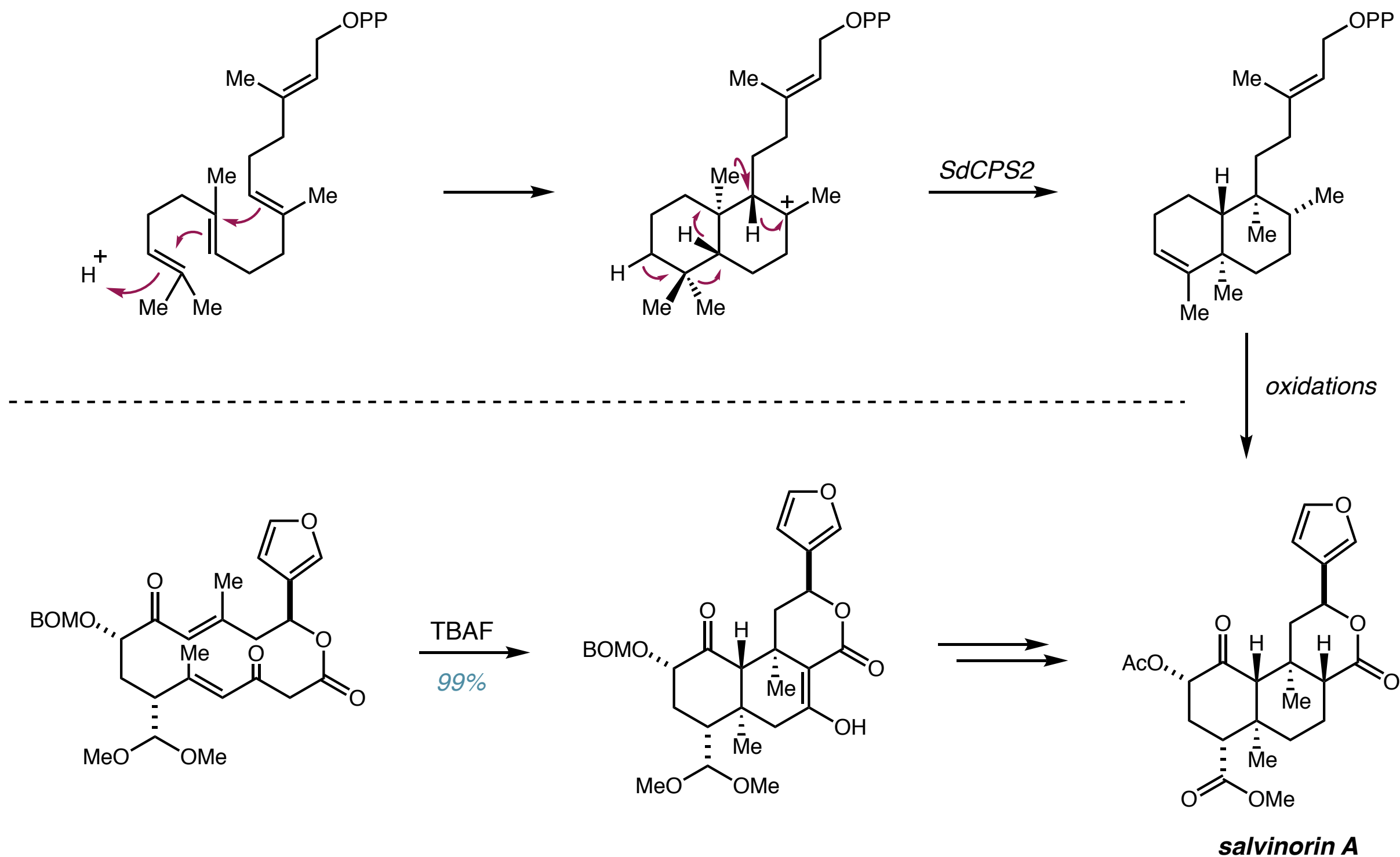
	$K_i \pm \text{S.E.M. (nM)}$	$\text{EC}_{50} \text{ in nM}$ ($\text{pEC}_{50} \pm \text{S.E.M.}$)
Salvinorin A	18.74 ± 3.38	$0.63 (-0.2 \pm 0.07)$
Propionate	32.63 ± 15.7	$4.7 (0.7 \pm 0.3)$
Heptanoate	3199 ± 961.2	$40 (1.6 \pm 0.4)$
Privalate	$>10,000$	NA
<i>p</i> -Bromobenzoate	$>10,000$	NA
2,2,2-Triethylcarbonate	$>10,000$	NA
Ethylcarbonate	$>10,000$	NA
Piperonylate	$>10,000$	NA
1-Napthoate	$>10,000$	NA
Cyclopropanecarboxylate	$>10,000$	NA
Salvinorin B	$>10,000$	NA

dose (smoked): 200–500 μg
duration: < 1 hour
 $K_i = 2.4 \text{ nM}$, $\text{EC}_{50} = 1.8 \text{ nM}$
for κ -opioid receptor

Prisinzano, T. E.; Rothman, R. B. *Chem. Rev.* **2008**, 108, 1732.
Cohen, B. *et al. Bioorg. Med. Chem.* **2005**, 13, 5635.
Prisinzano, T. E. *Life Sci.* **2005**, 78, 527.
MacLean, K. A. *et al. Psychopharmacol.* **2013**, 226, 381.
Roth, B. L. *et al. J. Pharmacol. Exp. Ther.* **2004**, 308, 1197.
Roth, B. L. *et al. Proc. Nat. Acad. Sci.* **2002**, 99, 11934.

Chemistry and Biology of Hallucinogens

biosynthesis and total synthesis of salvinorin A



Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, 129, 8968.

Zerbe, P. *Plant Journal* **2017**, 89, 885.

Kutrzeba, L.; Dayan, F. E.; Howell, J.; Feng, J.; Giner, J.-L.; Zjakiony, J. K. *Phytochem.* **2007**, 68, 1872.

Chemistry and Biology of Hallucinogens

CB₁ receptor

Location:

*nerve cell membrane receptors,
primarily in brain and spinal cord*

Endogenous ligands:

arachidonic acid derivatives

Physiological processes:

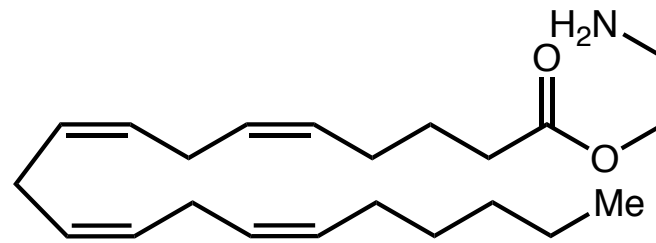
pain, mood, memory

appetite

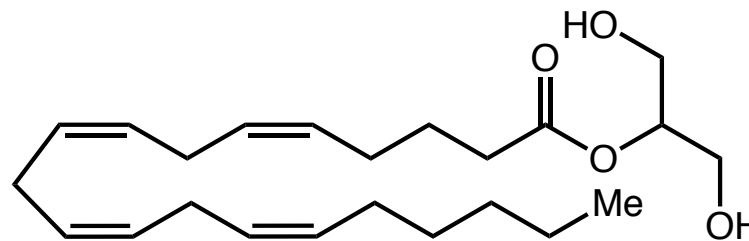
Clinical importance:

substance abuse

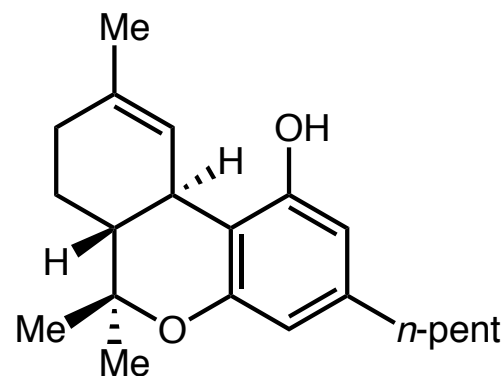
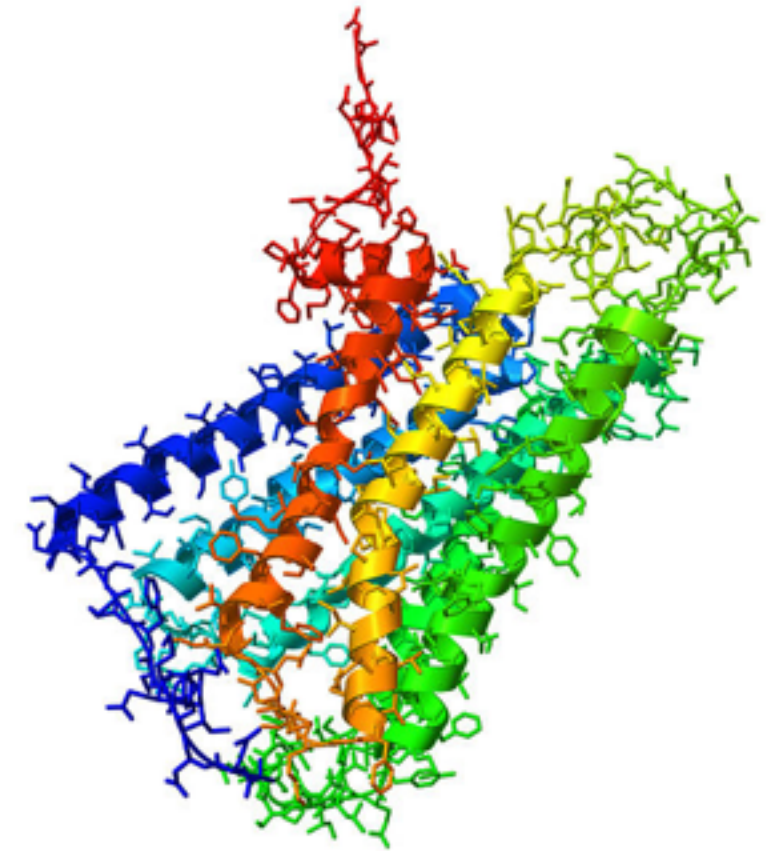
obesity



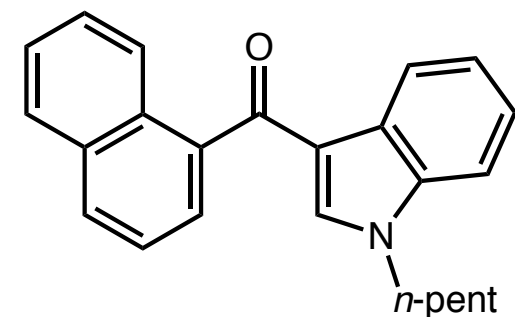
**O-arachidonylethanolamine
(virodhamine)**
antagonist



2-arachidonoylglycerol (2-AG)
agonist



Δ^9 -tetrahydrocannabinol (THC)



JWH-018

Chemistry and Biology of Hallucinogens

CB_1 receptor

Location:

*nerve cell membrane receptors,
primarily in brain and spinal cord*

Endogenous ligands:

arachidonic acid derivatives

Physiological processes:

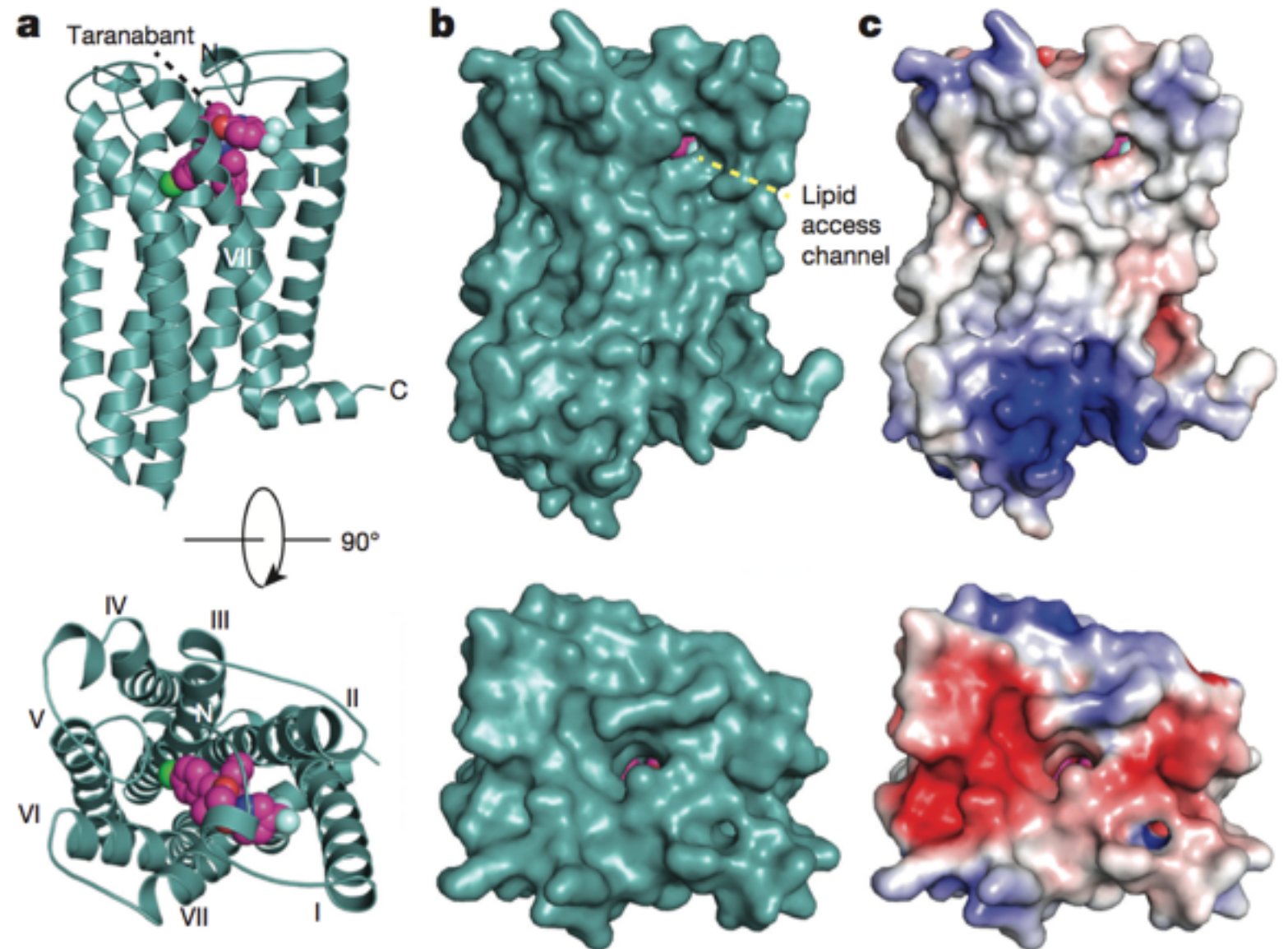
pain, mood, memory

appetite

Clinical importance:

substance abuse

obesity



Chemistry and Biology of Hallucinogens

CB₁ receptor

Location:

*nerve cell membrane receptors,
primarily in brain and spinal cord*

Endogenous ligands:

arachidonic acid derivatives

Physiological processes:

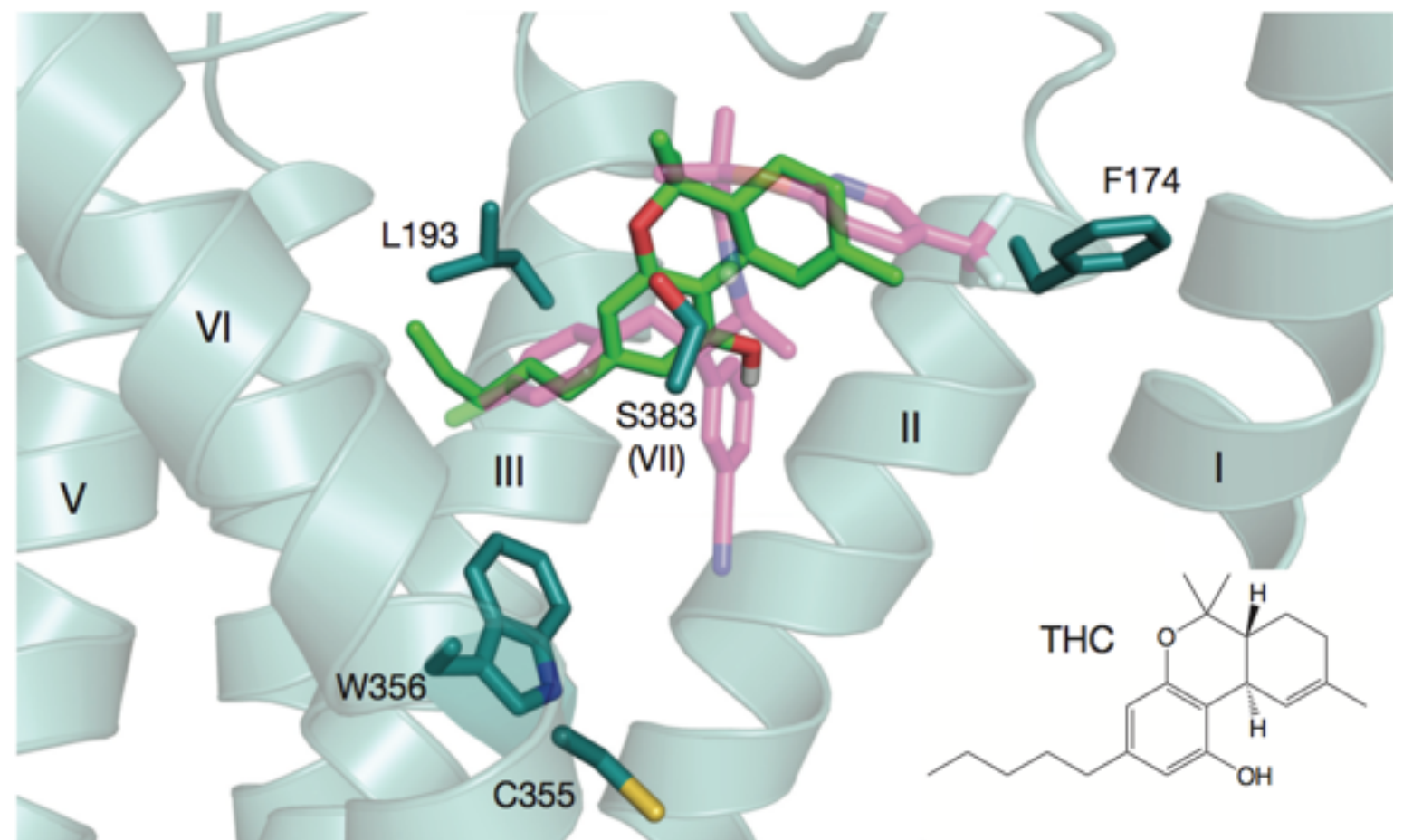
pain, mood, memory

appetite

Clinical importance:

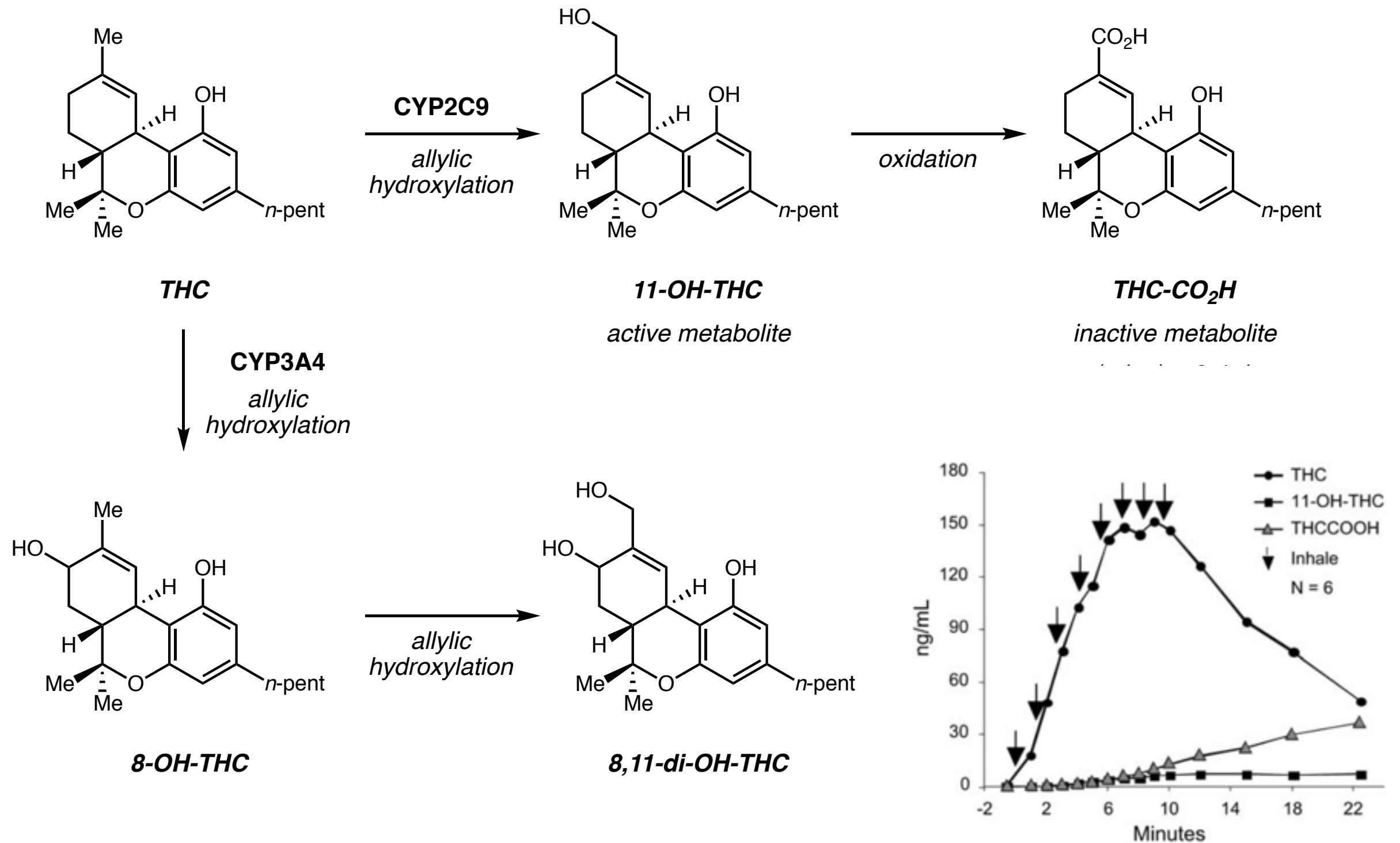
substance abuse

obesity



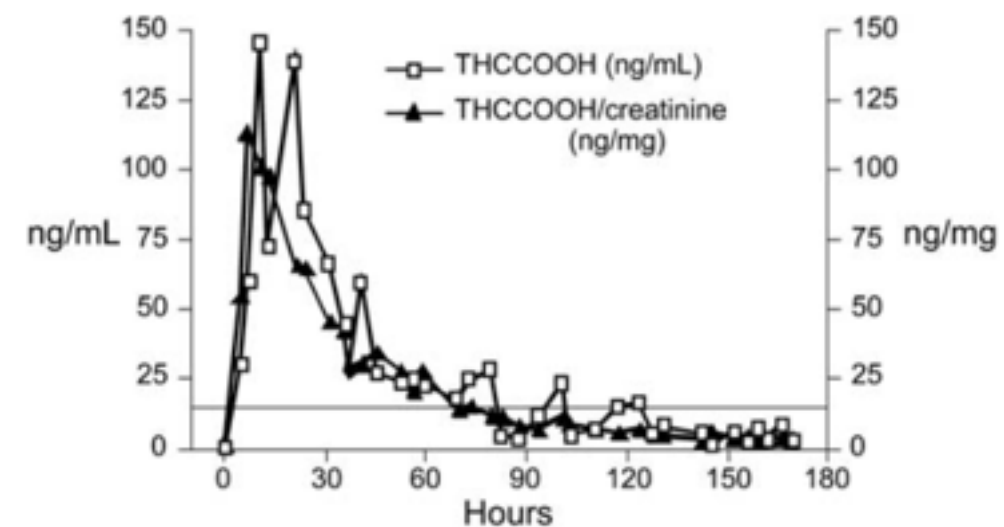
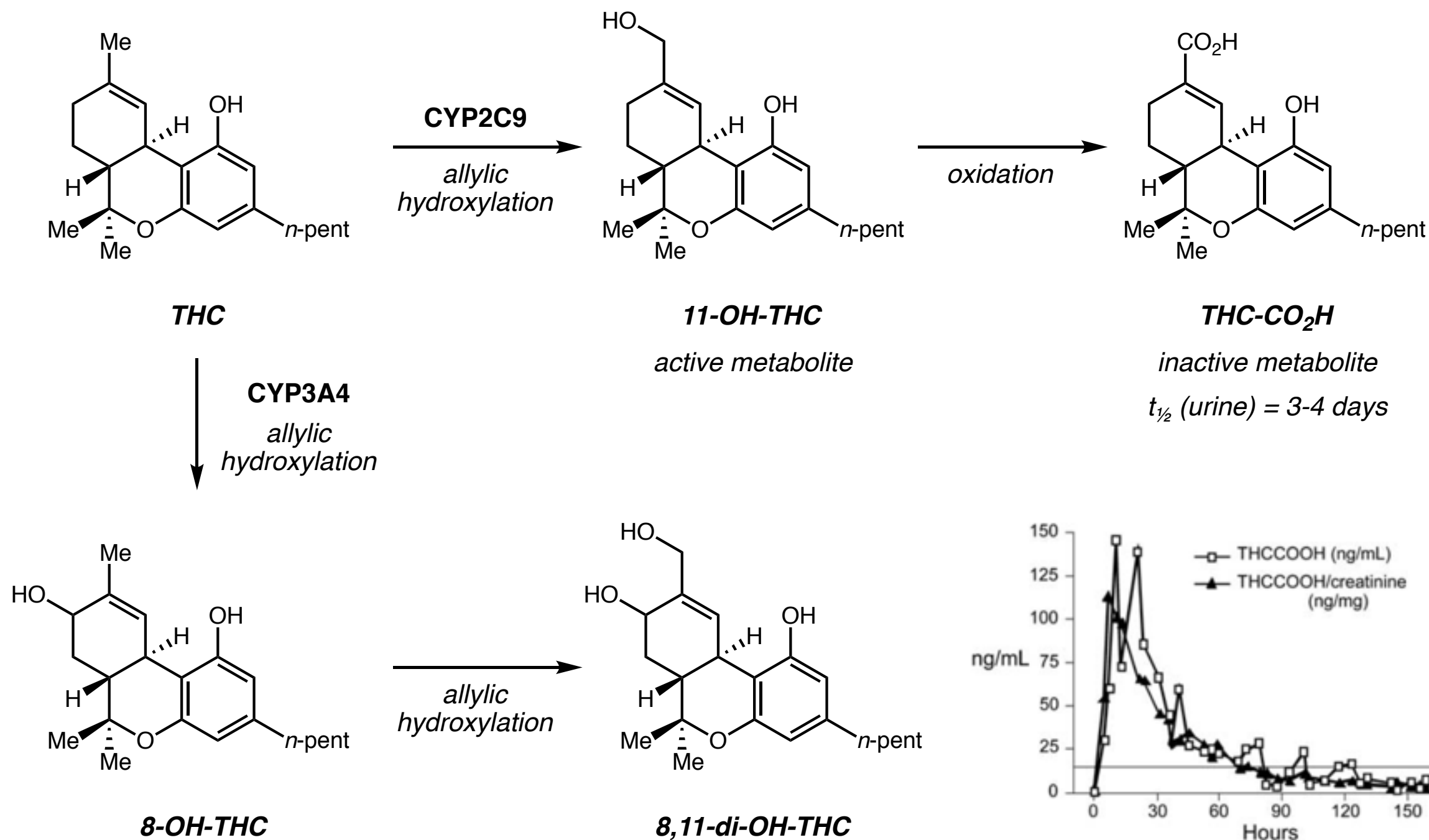
Chemistry and Biology of Hallucinogens

tetrahydrocannabinol metabolism



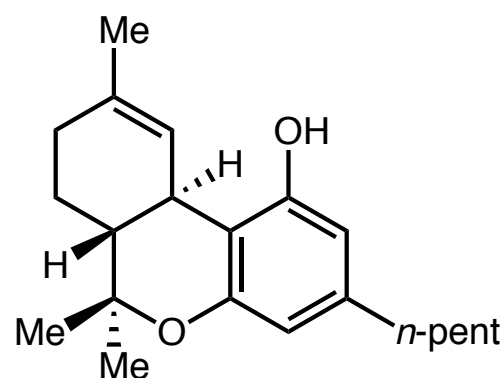
Chemistry and Biology of Hallucinogens

tetrahydrocannabinol metabolism



Chemistry and Biology of Hallucinogens

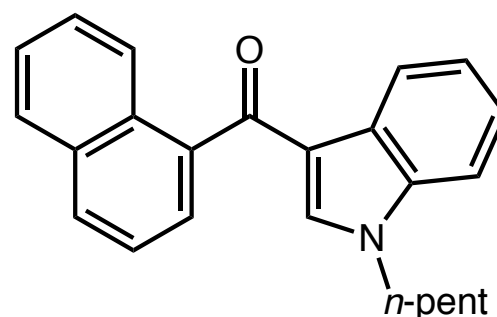
synthetic cannabinoids



THC

$K_i (CB_1) = 41 \text{ nM}$

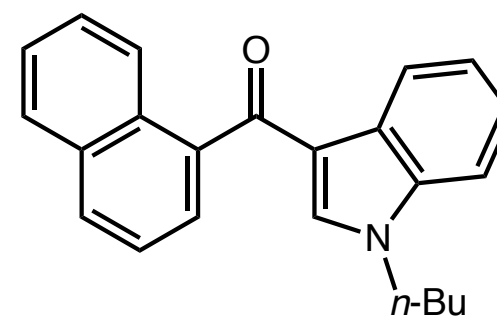
$K_i (CB_2) = 36 \text{ nM}$



JWH-018

$K_i (CB_1) = 9 \text{ nM}$

$K_i (CB_2) = 2.9 \text{ nM}$



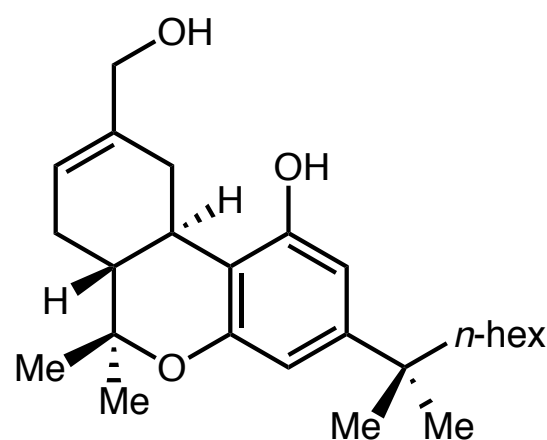
JWH-073

$K_i (CB_1) = 8.9 \text{ nM}$

$K_i (CB_2) = 38 \text{ nM}$



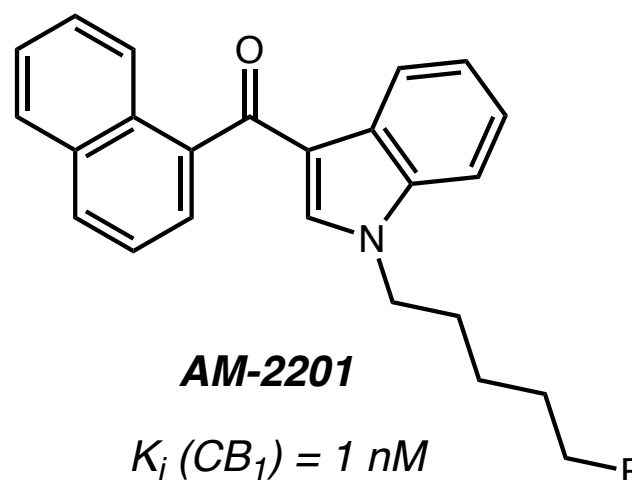
Prof. John Huffman
Clemson



HU-210

$K_i (CB_1) = 234 \text{ pM}$

$K_i (CB_2) = 36 \text{ nM}$



AM-2201

$K_i (CB_1) = 1 \text{ nM}$

$K_i (CB_2) = 2.6 \text{ nM}$



Chemistry and Biology of Hallucinogens

"Taking LSD was a profound experience, one of the most important things in my life. LSD shows you that there's another side to 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

"I was completely astonished by the beauty of nature. Our eyes see just a small fraction of the light in the world. It is a trick to make a colored world, which does not exist outside of human beings."

– Albert Hofmann

*Picture yourself in a boat on a river
With tangerine trees and marmalade skies
Somebody calls you, you answer quite slowly
A girl with kaleidoscope eyes*

*Cellophane flowers of yellow and green
Towering over your head
Look for the girl with the sun in her eyes
And she's gone*

Lucy in the sky with diamonds
– The Beatles

"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."

"Our entire universe is contained in the mind and the spirit. We may choose not to find access to it, we may even deny its existence, but it is indeed there inside us..."

– Alexander Shulgin

"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

"LSD is a psychedelic drug which occasionally causes psychotic behavior in people who have NOT taken it."

– Timothy Leary

Chemistry and Biology of Hallucinogens

“Taking LSD was a profound experience, one of the most important things in my life. LSD shows you that there’s another side to 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 it into the stream of history and making consciousness as much as much as possible.”
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...is contained in the mind and does not to find access to it, its existence, but it is indeed inside us...”
– **Aldous Huxley**

...the unique and powerful ability to alter the psyche. They may alter one's perception of reality and may change one's views on life and death. They can provoke and challenge one's beliefs. Therein...lay the seeds of fear and hysteria that these substances have fostered in our society.”
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