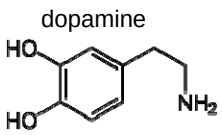
dopamine



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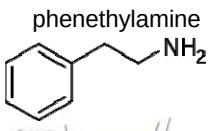
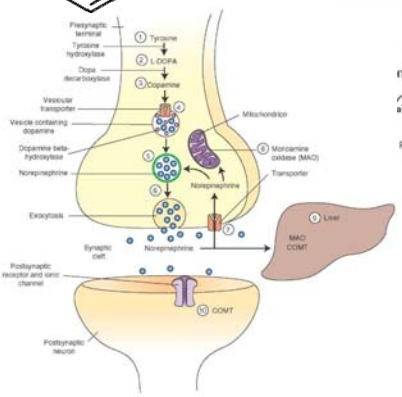
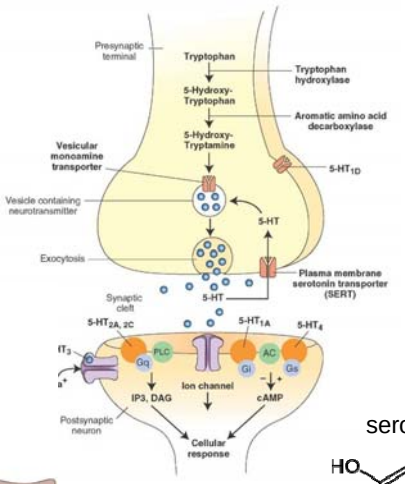
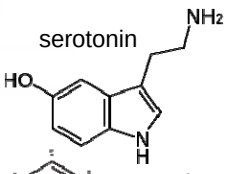


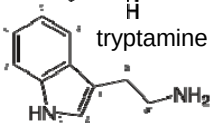




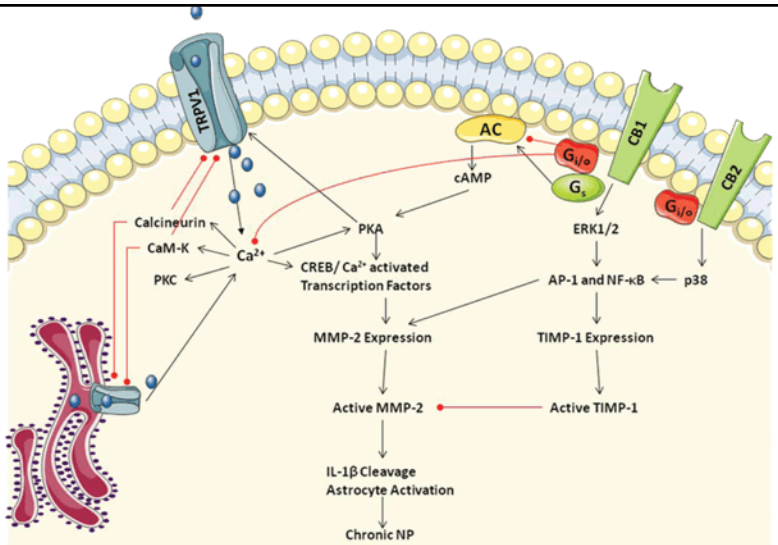
serotonin



tryptamine



http://what-when-how.com/neuroscience/neurotransmitters-the-neuron-part-4/



Pain modulation
Appetite modulation
Anti-inflammatory Response
Immune Response

Annals of Neurosciences, Volume 18, Issue 4 (October), 2011

Drugs: by effect

- Analgesics
  - Pain relievers (at site (aspirin), or at CNS (morphine)
  - opiates
- Depressants
  - Depress CNS (slowed heart beat, reduced anxiety, sleep)
  - Alcohol, benzodiazepines (huge class), barbiturates, inhalants
- Hallucinogens
  - Alter mental perception of time/space/feeling
  - LSD, MDMA (ecstasy), marijuana, cannabis, psilocybin (magic mushrooms), methamphetamine (high doses)
- Narcotics
  - Analgesic and depress CNS
  - Opiates, oxycodone, heroin
- Stimulants
  - Stimulate CNS (promotes alertness, reduces fatigue/sleep)
  - Cocaine, amphetamine, methamphetamine
  - Can be hallucinogenic in high doses

3

Drugs: by use

- Predator drugs
  - Date-rape drugs, drug-facilitated sexual assault (DFSA)
  - Alcohol, ketamine, rohypnol, GHB (gamma hyrdoxybutyrate)
  - Lack of memory often leads to delayed testing
- Club drugs
  - Used to create 'highs' and energy in parties and clubs
  - Ecstasy (MDMA, methylene dioxy methamphetamine), LSD (lysergic acid diethylamide), psilocybin, PCP (phencyclidine)
- Performance-enhancing drugs
  - Mostly humans and horses
  - Anabolic steroids, human growth hormones
- Inhalants
  - Not originally intended for drug use
  - Very nasty side-effects
  - Paint thinners, cleaners, solvents, butane, nail polish etc.

4

Controlled substances

Table 2. Schedules of Controlled Substances

Schedule	Classification Criteria	Examples
C-I	Substances have a high potential for abuse, have no currently accepted medical use in treatment in the U.S., and have a lack of accepted safety for use under medical supervision	Ecstasy (MDMA), heroin, LSD, marijuana, methaqualone, peyote
C-II	Substances have a high potential for abuse, which may lead to severe psychological or physical dependence, and have a currently accepted medical use (with severe restrictions)	Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, codeine, cocaine, amphetamine, methamphetamine, methylphenidate
C-III	Have less potential for abuse than substances in C-I or C-II, and abuse may lead to moderate or low physical dependence or high psychological dependence	Hydrocodone/acetaminophen (Vicodin), Tylenol with Codeine, buprenorphine, benzphetamine, phendimetrazine, ketamine, anabolic steroids (Depo-Testosterone)
C-IV	Have a low potential for abuse relative to substances in C-III	Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, triazolam
C-V	Have a low potential for abuse relative to substances listed in C-IV and consist primarily of preparations containing limited quantities of certain narcotics	Robitussin AC, Phenergan with Codeine, ezogabine

LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine. Source: References 4, 5.

US Phamracist, Drug Rescheduling and Controlled Substances, Gerald Gianutsos, PhD, JD
Associate Professor of Pharmacology
University of Connecticut School of Pharmacy

5

Abused drugs in the USA

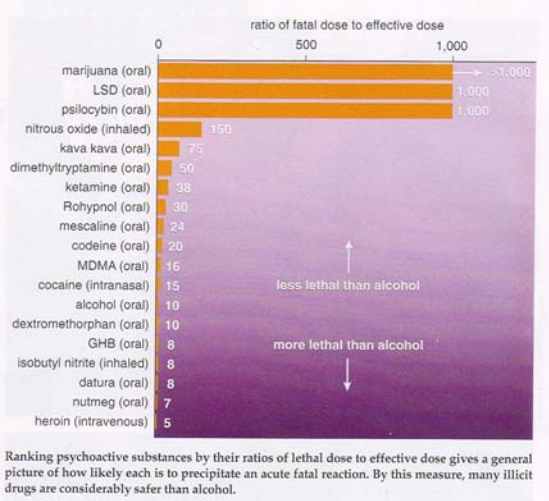
Drug	% users	# users
Caffeine	?	?
Alcohol	53%	110M users
Tobacco	26.00%	55M users
Prescription drugs	0.80%	1.6M users
Inhalents	1%	1.6M users
Marijuana	5%	10M users
Cocaine	0.80%	1.6 M users
Narcotics and analgesics	0.60%	1.2M users
Hallucinogens	0.40%	0.8M users
Depressants	0.30%	0.5M users
Stimulants	0.10%	0.2M users

6

Mc Cord,, B.. Chemistry 487 Lecture Notes, Spring 2004.

Barlag, R.E. Chemistry 487 Lecture Notes, Spring 2005.

Toxicity v. effective doses of drugs



Ranking psychoactive substances by their ratios of lethal dose to effective dose gives a general picture of how likely each is to precipitate an acute fatal reaction. By this measure, many illicit drugs are considerably safer than alcohol.

7

Gable, R.S. The Toxicity of Recreational Drugs. *American Scientist* **2006,** 94, *206-208*

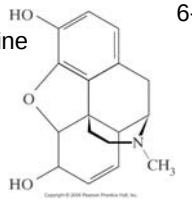
Cutting agents

- Substances used to dilute illegal drugs
  - Similar to excipients (used to dilute OTC drugs, legally)
  - Maximize profits
- Chosen based on physical and chemical properties
  - texture, color, taste, smell etc.
  - cocoa powder (brown), or quinine (bitter) for heroin
  - Procaine, lidocaine, tetracaine etc. for cocaine
    - all local anesthetics
- Diluents (thinners) have no pharmacological influence
- Adulterants do have pharmacological properties (e.g. caffeine)
- Warning*
  - In Forensic Toxicology, the term "adulterant" refers to a substance that will give a false negative in a urine or blood screen
- Contaminants
  - Unintentional diluents of the active drug
  - E.g. Na_2CO_3 in 'crack' cocaine, codiene as a by-product in heroin synthesis

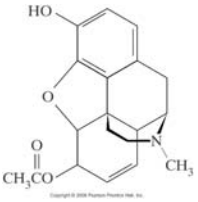
8

Opiate alkaloids

morphine

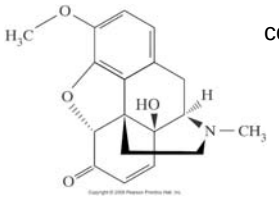


6-O-monoacetyl morphine
6-MAM

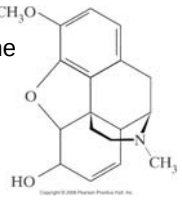


heroin

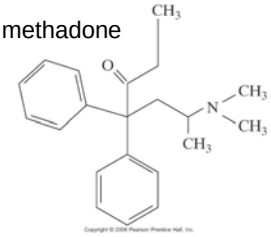
oxycodone



codeine



methadone



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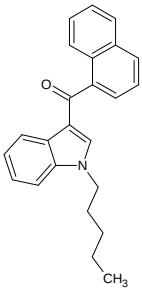
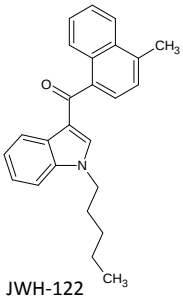
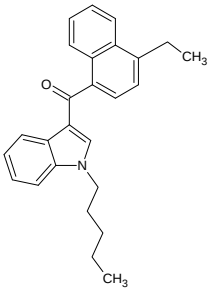


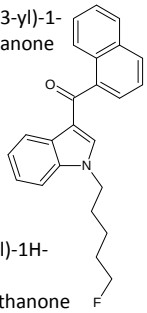
JWH-018
(1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone



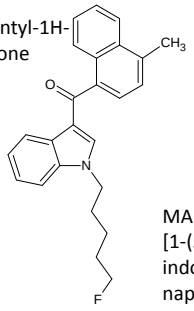
JWH-122
(4-methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone



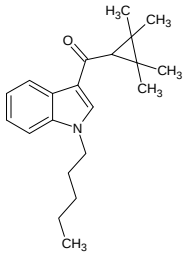
JWH-210
(4-ethyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone



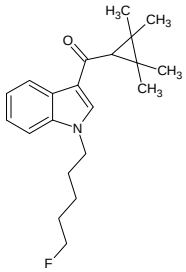
AM2201
[1-(5-fluoropentyl)-1H-indol-3-yl]-1-naphthalenyl-methanone



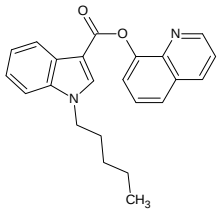
MAM2201
[1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthalenyl)-methanone



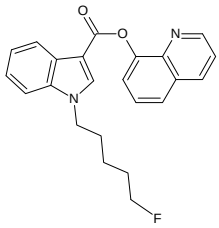
UR-144
[1-Pentylindo 1-3-yl]-(2,2, 3,3-tetramethylcyclopropyl) methanone



5F-UR-144
[1-(5-fluoropentyl)indol-3-yl]-(2,2,3,3-tetra-methylcyclopropyl)methanone



PB-22
1H-indole-3-carboxylic acid, 1-pentyl-, 8-quinolinyl ester



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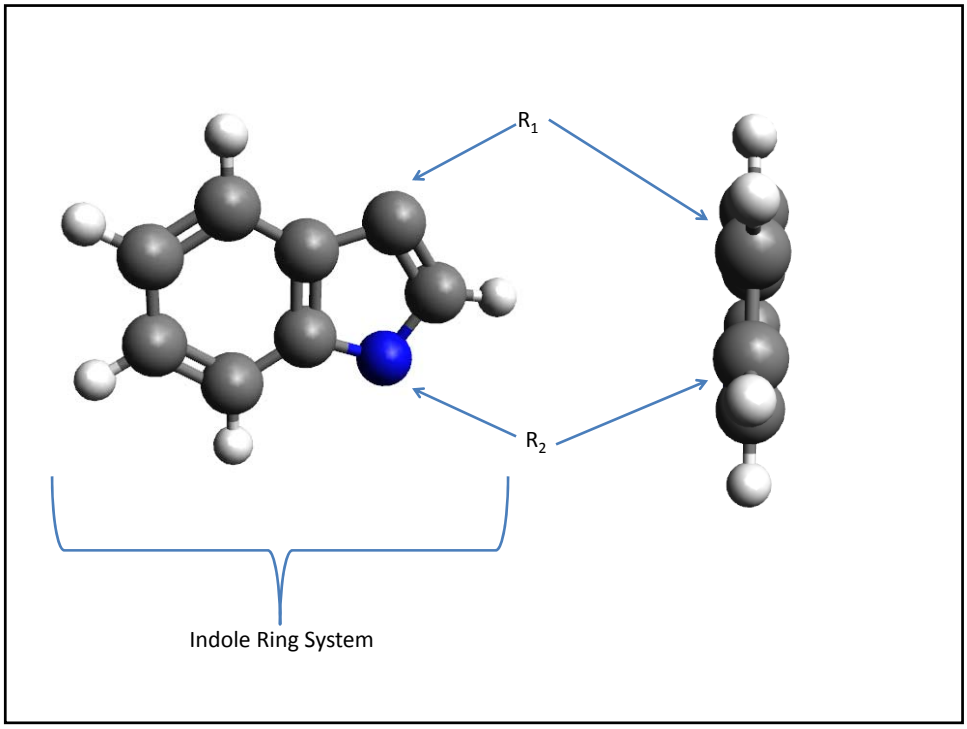
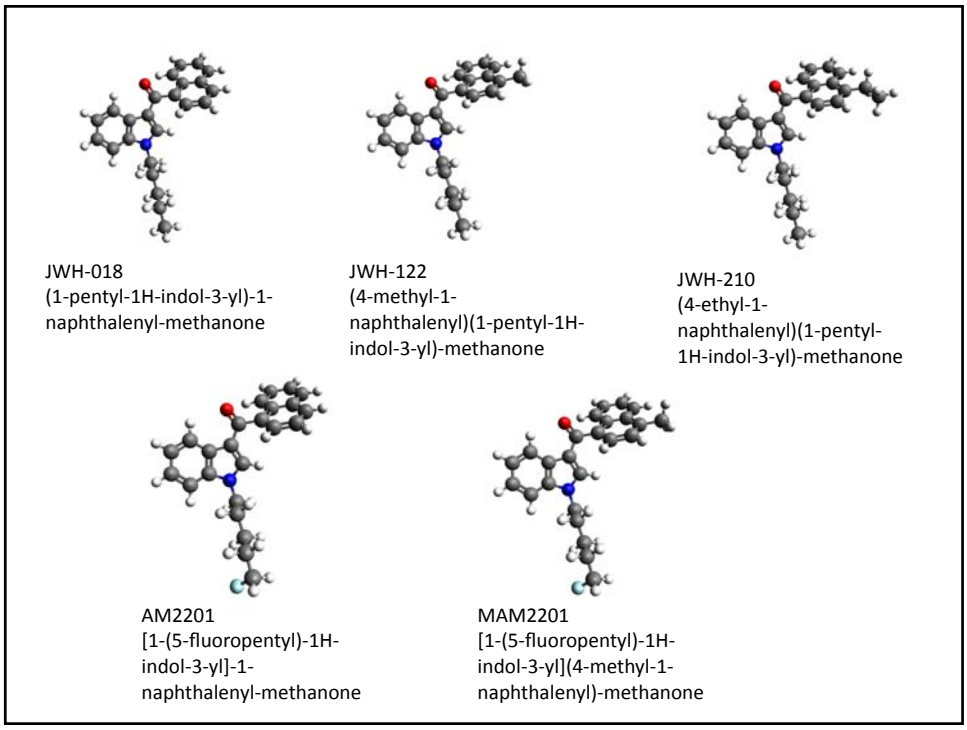
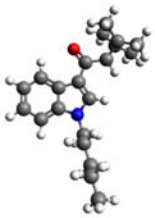
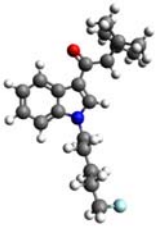
1-(5-fluoropentyl)-1*H*-indole-3-acid 8-quinolinyl ester


R1
R2
Indole Ring System


JWH-018
(1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone
JWH-122
(4-methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone
JWH-210
(4-ethyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone
AM2201
[1-(5-fluoropentyl)-1H-indol-3-yl]-1-naphthalenyl-methanone
MAM2201
[1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthalenyl)-methanone



UR-144
[1-Pentylindo 1-3-yl]-(2,2, 3,3-tetramethylcyclopropyl) methanone

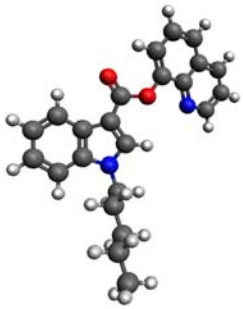


5F-UR-144
[1-(5-fluoropentyl)indol-3-yl]-(2,2,3,3-tetra-methylcyclopropyl)methanone

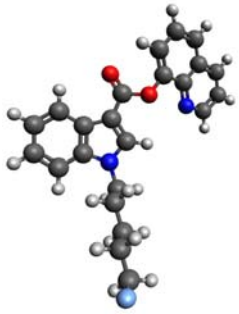
Analogue Drug Law

A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I. [21 USC 813]

(32)(A) Except as provided in subparagraph (C), the term "controlled substance analogue" means a substance--(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II; [21 USC 802]

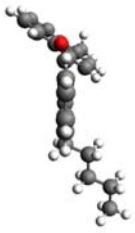


PB-22
1H-indole-3-carboxylic acid, 1-pentyl-, 8-quinolinyl ester

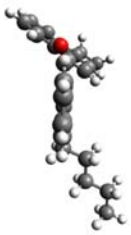


5F-PB22
1-(5-fluoropentyl)-1*H*-indole-3-acid 8-quinolinyl ester

JWH-018



JWH-122



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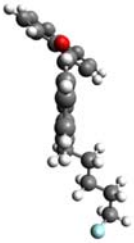
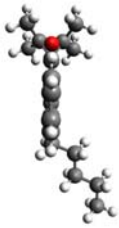
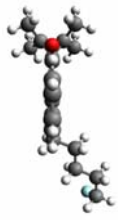


AM2201

AM2201



UR-144



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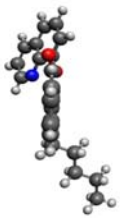
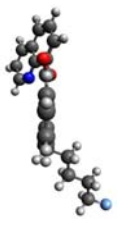
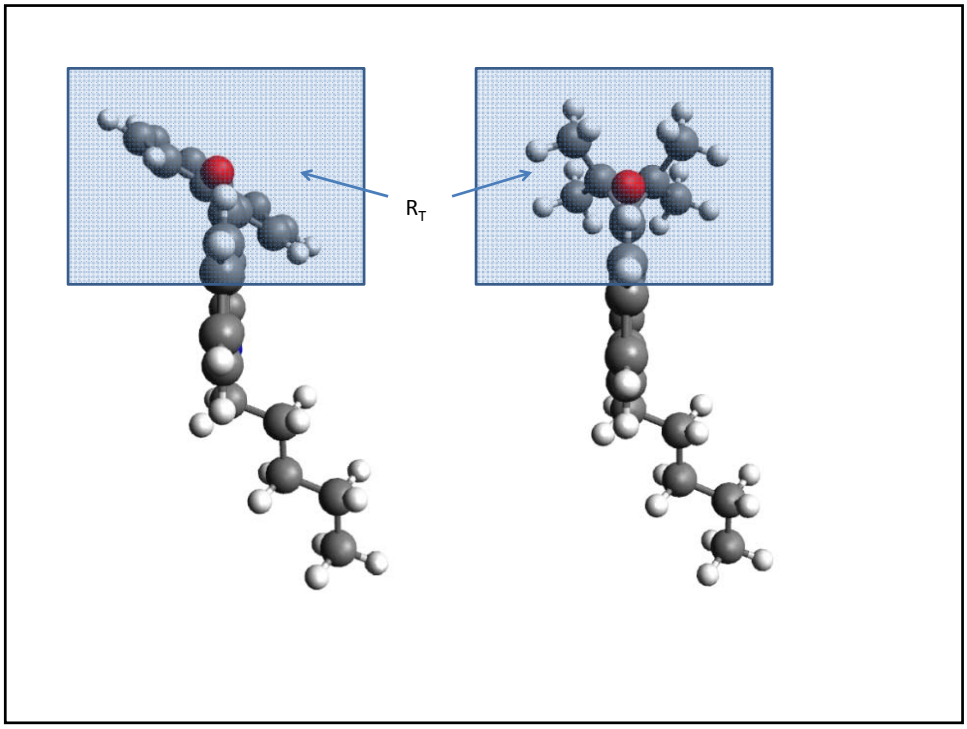
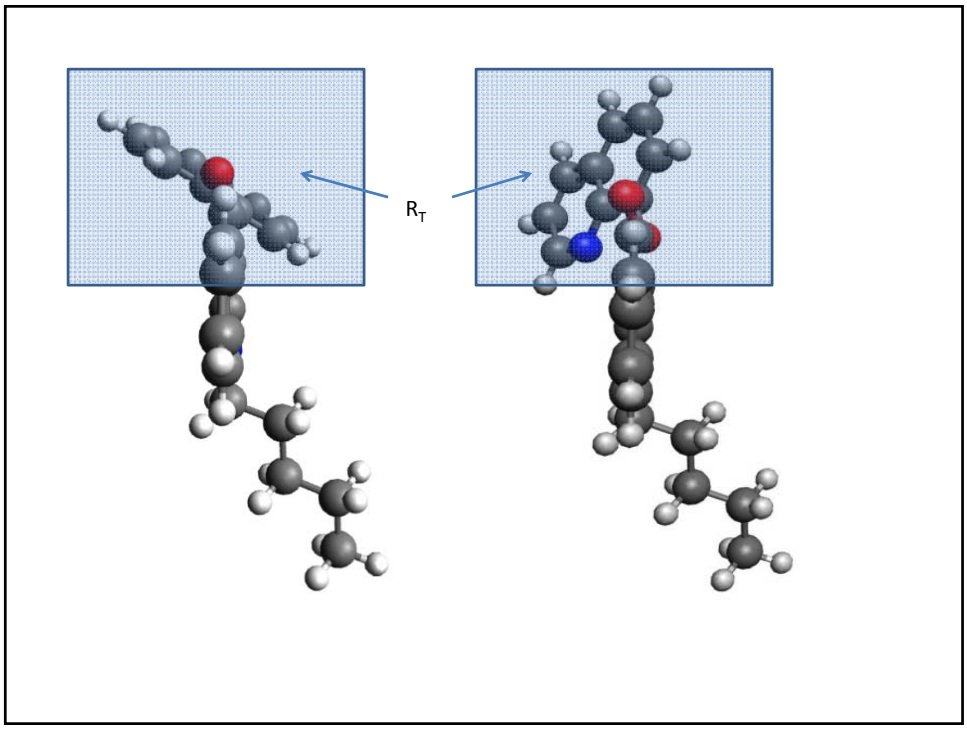


PB-22



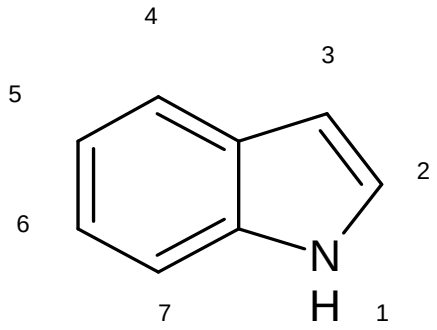
5F-PB-22


R_T

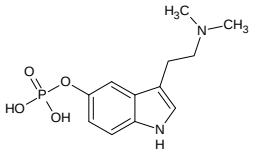

R_T

	Affinity CB1 nM	Affinity CB2 nM
JWH-018	9.00	2.94
JWH-122	0.69	1.20
JWH-210	0.46	0.69
MAM2201	1.00	2.60
AM2201	1.00	2.60
UR-144	150	1.80
XLR-11	?	?

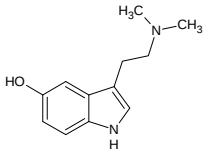
According to Drug Data Sheet from Cayman Chemical



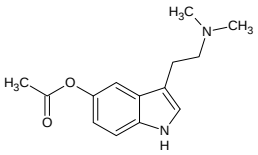
Indole Ring Structure with Points of Substitutions 1-7.



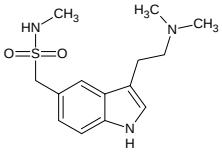
Psilocybin
4-phosphoryloxy-*N,N*-dimethyltryptamine



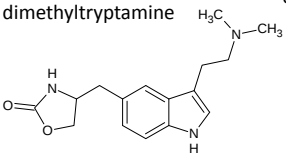
Bufotenin
5-hydroxy-*N,N*-dimethyltryptamine



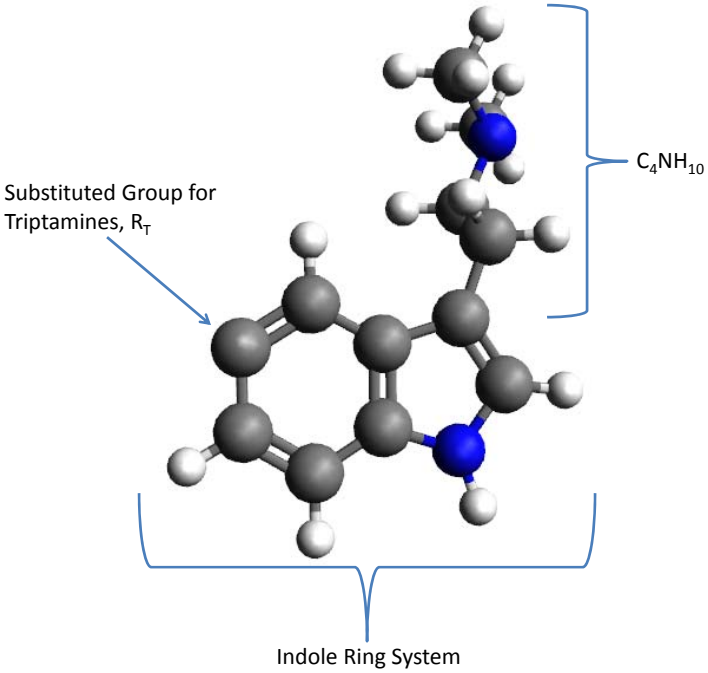
O-Acetylpsilocin
4-acetoxy-*N,N*-dimethyltryptamine

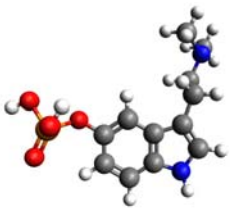


Sumatriptan
5-(methylaminosulfonylmethylene)-*N,N*-dimethyltryptamine

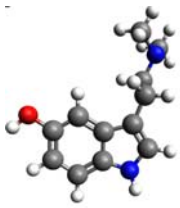


Zolmitriptan
5-(4-(*S*)-1,3-oxazolidin-2-one)-*N,N*-dimethyltryptamine

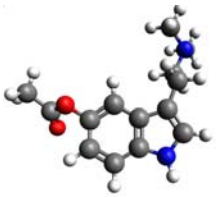




Psilocybin
4-phosphoryloxy-*N,N*-dimethyltryptamine

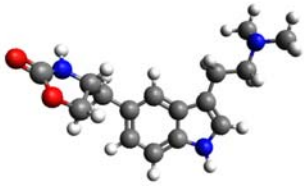


Bufotenin
5-hydroxy-*N,N*-dimethyltryptamine

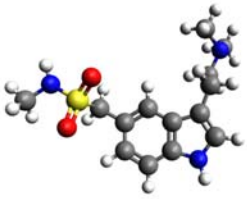


O-Acetylpsilocin
4-acetoxy-*N,N*-dimethyltryptamine

Psilocybin, Bufotenin, O-Acetylpsilocin, Zolmitriptan, a

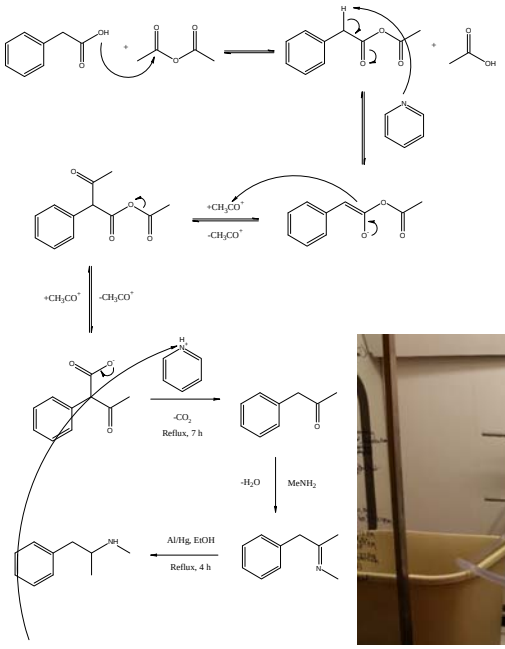


Zolmitriptan
5-(4-(*S*)-1,3-oxazolidin-2-one)-*N,N*-dimethyltryptamine

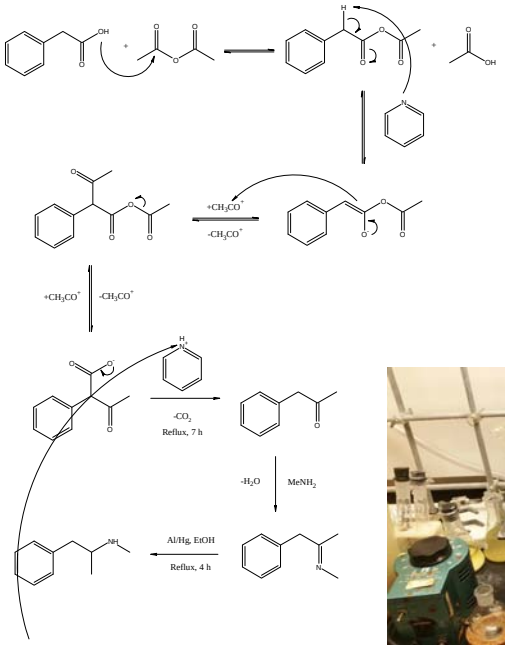


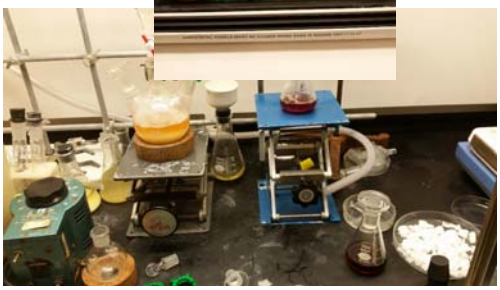
Sumatriptan
5-(methylaminosulfonylmethylene)-*N,N*-dimethyltryptamine

Meth Synthesis

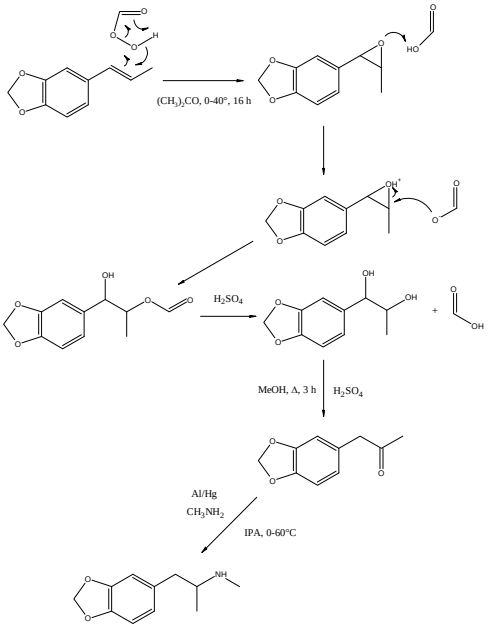


Meth Synthesis

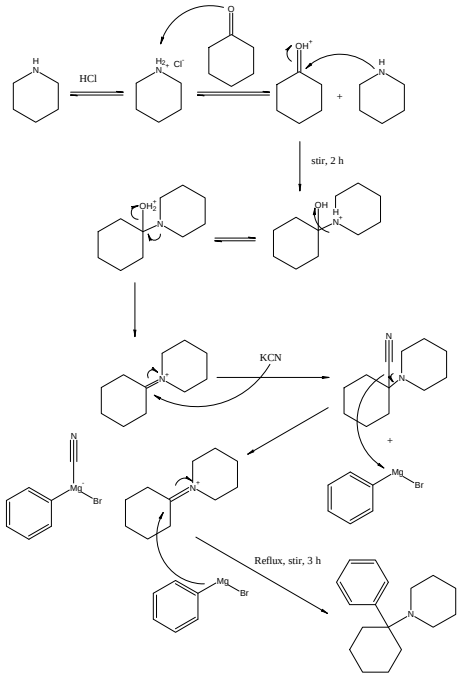


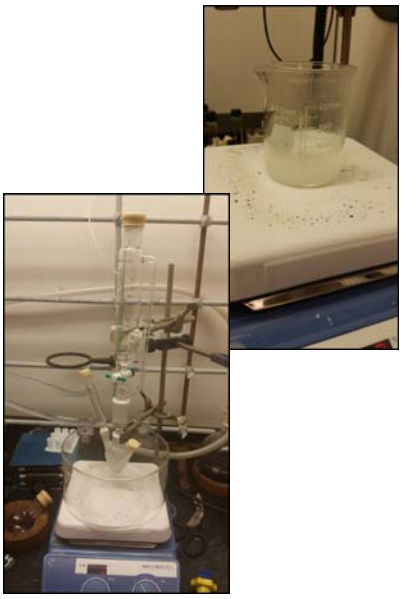


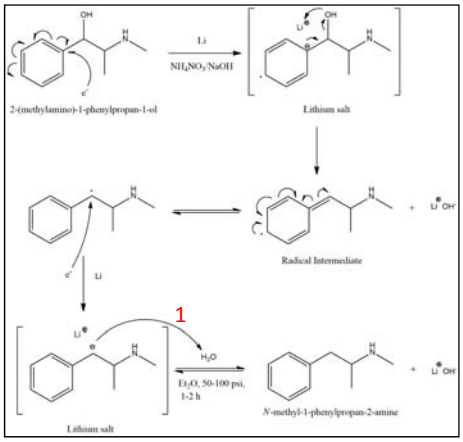
MDMA Synthesis

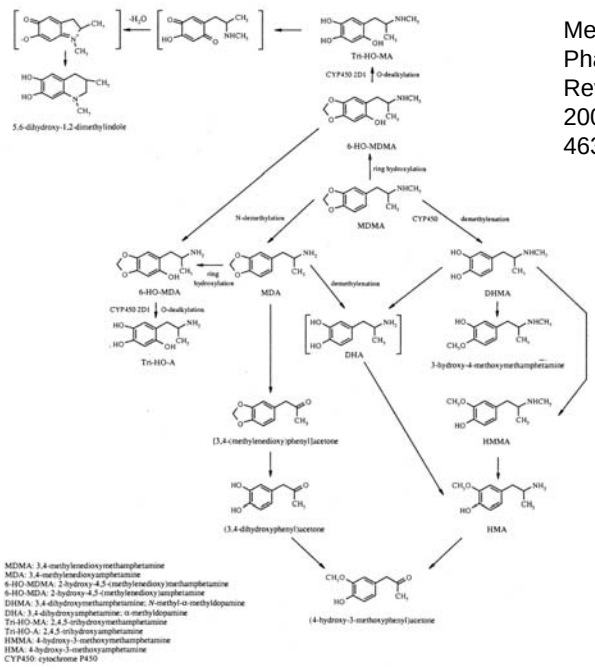


PCP Synthesis







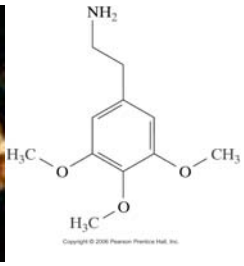


Metabolism of MDMA Pharmacological Reviews September 2003 vol. 55 no. 3 463-508

Ergot and tryptamine alkaloids and hallucinogens

- LSD derived from ergot alkaloids
  - Ergot is a fungus found mostly on grains
  - Difficult synthesis = fewer, but more specialized labs
- Mescaline
  - From cactus plants (peyote)
  - Legal for native americans

www.aldeaeducativa.com



www.mescaline.com/exp/

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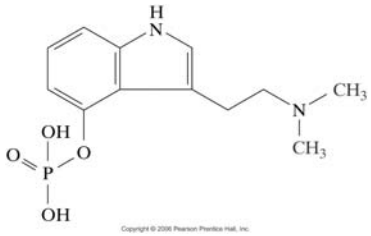
Ergot and tryptamine alkaloids and hallucinogens

- Psilocybin/psilicin
  - From mushrooms

www.drug-information-resource.com/



www.potseeds.co.uk

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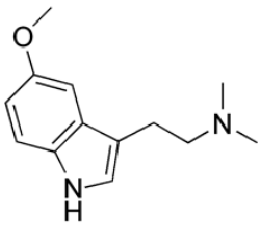
Ergot and tryptamine alkaloids and hallucinogens

- 5-MeO-DMT & bufotoxins
  - 5-methoxy-dimethyltryptamine
  - from *Bufo alvarius (*colarado river) toads
  - excreted in venum
  - semi synthetic versions enhance methylation
  - usually smoked, not licked!



www.eitangrunwald.com

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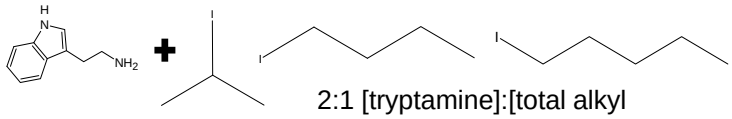
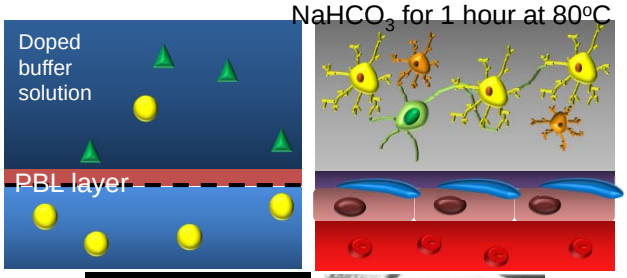
Three Step Method for Comparing Analogs to Scheduled Substances

Synthesize



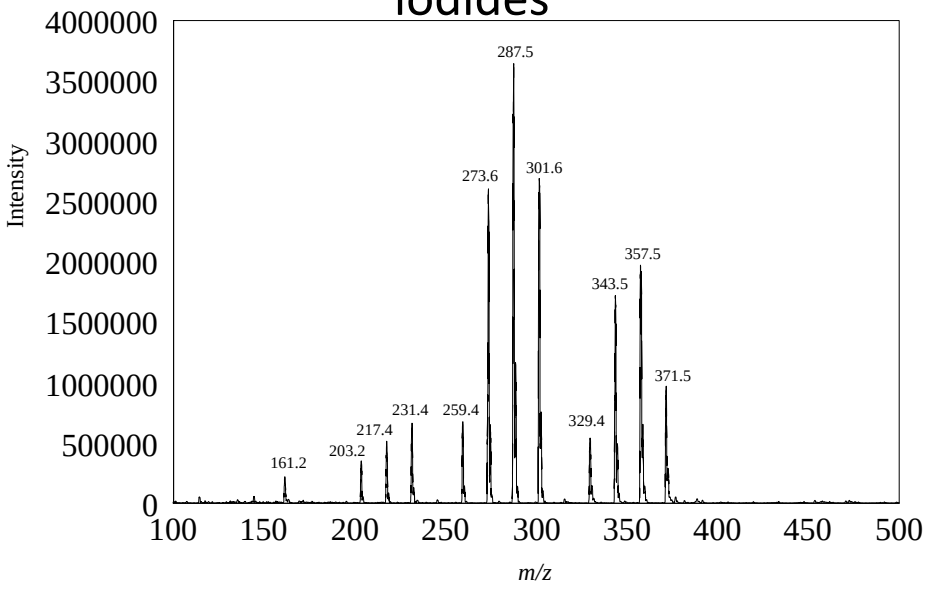
2:1 [tryptamine]:[total alkyl iodide] in water with SDS and $NaHCO_3$ for 1 hour at 80°C

Gauge BBB Permeability

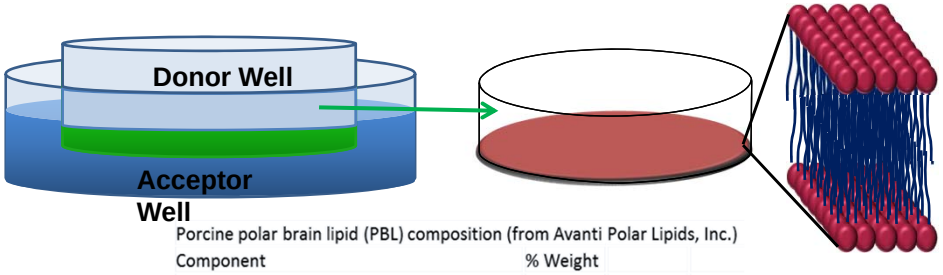


Measure Receptor Activity

ESI-MS of Synthesis using 3 alkyl iodides



Parallel Artificial Membrane Permeability Assay (PAMPA)



Porcine polar brain lipid (PBL) composition (from Avanti Polar Lipids, Inc.)

Component	% Weight
Phosphatidylethanolamine	33.1
Phosphatidylserine	18.5
Phosphatidylcholine	12.6
Phosphatidic acid	0.8
Phosphatidylinositol	4.1
Other[a]	30.9

[a]Other = cerobrosides, sulfatides, pigments

L. Di et al. European Journal of Medicinal Chemistry. 38 (2003) 223-232.