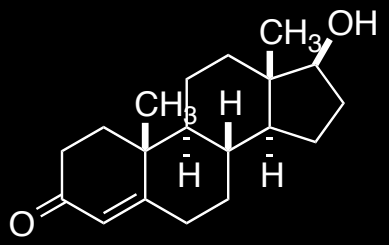
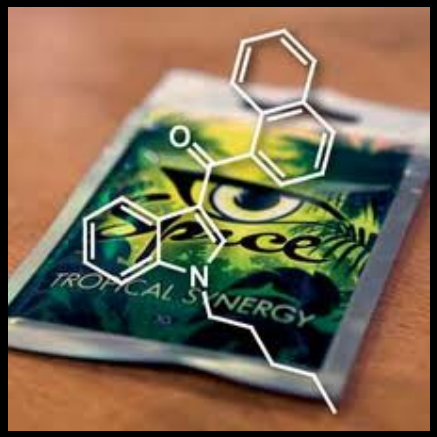
Designer Drugs: From Performance Enhancers to Legal Highs



Testosterone



Eric E. Buck
Frontiers of Chemistry
June 30, 2012

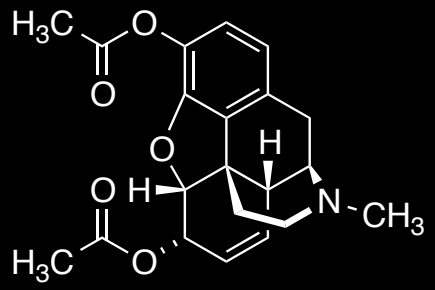
Outline

- Doping in Major League Baseball
- Anabolic Steroids
- An Overview of Cannabinoids
- A Frontier of Legal Highs

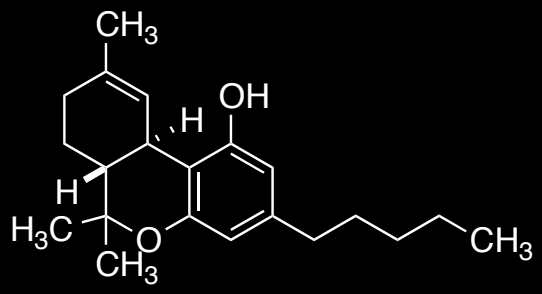
5 Classifications of Controlled Substances

Schedule I Controlled Substances

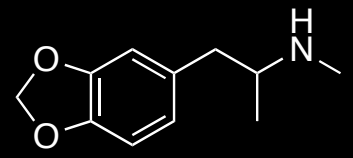
Substances in this schedule have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for use of the drug or other substance under medical supervision.



Heroin



THC

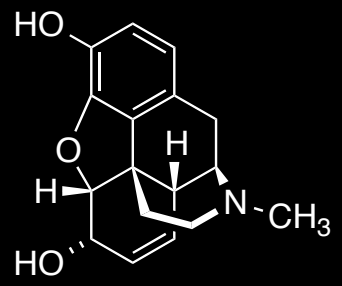


MDMA
Ecstasy

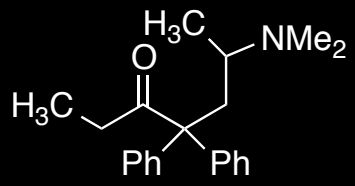
5 Classifications of Controlled Substances

Schedule II Controlled Substances

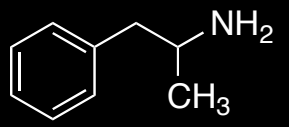
Substances in this schedule have a high potential for abuse which may lead to severe psychological or physical dependence. There is currently accepted medical us with severe restrictions.



morphine



methadone



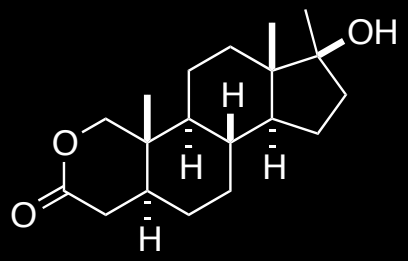
amphetamine

Adderall, Dexedrine,
Dextrostat, Desoxyn

5 Classifications of Controlled Substances

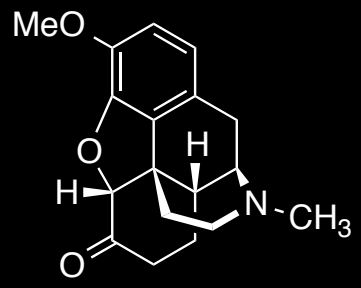
Schedule III Controlled Substances

Substances in this schedule have a potential for abuse less than substances in schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence. Includes anabolic steroids.

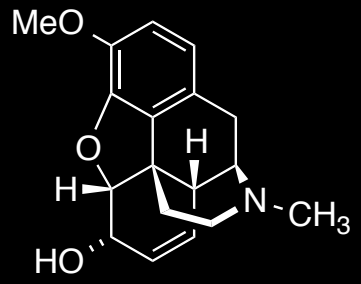


oxandrolone

Ketamine



hydrocodone

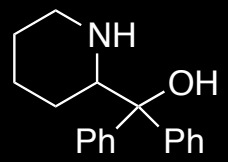


Codeine

5 Classifications of Controlled Substances

Schedule IV Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances in schedule III.



Pipradrol

Schedule V Controlled Substances

Substances in this schedule have a low potential for abuse relative to substances listed in schedule IV and consist primarily of preparations containing limited quantities of certain narcotics. These are generally used for antitussive, antidiarrheal, and analgesic purposes.

Other Notable Laws

The Designer Drug Enforcement Act of 1986: "a substance that has a chemical structure substantially similar to that of a controlled substance in schedule I or II or that was specifically designed to produce an effect similar to that of a controlled substance in schedule I or II

Anti-Drug Abuse Act of 1988: This law amended the Food, Drug and Cosmetic Act and created criminal penalties for persons who ""distribute or possess anabolic steroids with the intent to distribute for any use in humans other than the treatment of disease based on the order of a physician." Anti-Drug Abuse Act of 1988, Pub. L. No. 100-690, Section 4181.

In the Controlled Substances Act of 1990, anabolic steroids are defined to be any drug or hormonal substance chemically and pharmacologically related to testosterone (other than estrogens, progestins, and corticosteroids) that promote muscle growth. They were also added to schedule III of controlled substances.

Anabolic Steroid Control Act of 2004: Added prohormones to the list.

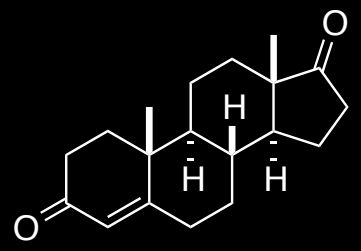
Baseball and the Steroid Era

• Baseball strike from 1994-1995. Lasted 232 days. 1994 post-season cancelled.

• In 1998 Mark McGwire is discovered with a jar of androstenedione in his locker. He is in a homerun race with Sammy Sosa to break the 1961 homerun record of 61 home runs. There are no penalties or testing in place for anabolic steroids, steroid precursors, or performance enhancing drugs.

• April 2001 MLB implements minor league testing.

• February 2003 Steve Bechler (23 yrs old) dies from heat exhaustion while on the mound. The OTC supplement Ephedra was determined to be the cause. (Ripped Fuel)



androstenedione

Ephedrine

Psuedoephedrine

http://www.baseballssteroidera.com/

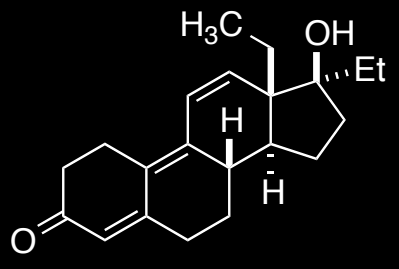
Baseball and the Steroid Era

• In March 2003, MLB begins drug testing during spring training.

• In October of 2003 the FDA bans THG. MLB also places a ban on the substance.

• In November 2005 MLB changes the penalties to 50 game ban for first offense, 100 games for second offense, and lifetime ban for third offense. Testing now includes amphetamines.

• In 2008 MLB players agree to new drug testing policies. Added to the list of prohibited substances now include insulin-like growth factor, gonadotropins, aromatase inhibitors, selective estrogen receptor modulators and antiestrogens, including Clomid (inhibits estrogen receptors. Used by anabolic steroid users to restore natural prouction of testosterone.)



Tetrahydrogestrinone

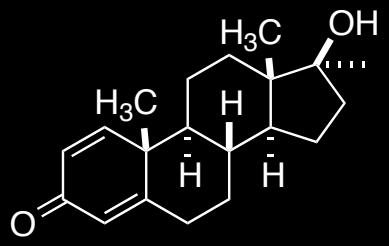
http://www.baseballssteroidera.com/

Designer Steroids, BALCO, and Patrick Arnold

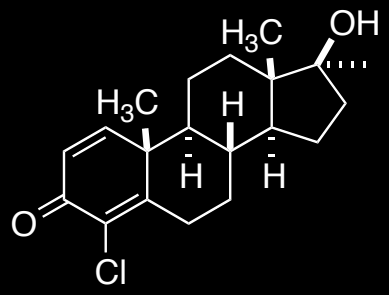
• Dr. John B. Ziegler learned the use of testosterone from the Russian team doctor in the 1954 world weightlifting championships. He begins experimental use of Dianabol with USA weightlifters.

• Despite the fact that a 4 week course of Dianabol increased body weight by 5% and maximum weight lifted by 18%, the American College of Sports Medicine officially acknowledged that anabolic steroids did little for athletic performance (1977).

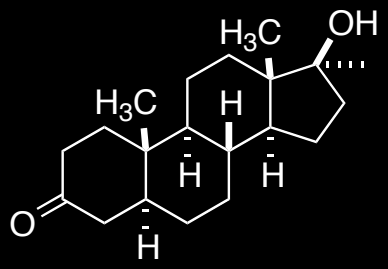
• From the late 1960's to 1990 the German Democratic Republic government encouraged the use of steroids in their international athletes.



Dianabol



Oral-Turinabol



Mestanolone

Bowers, L. D. *Steroids.* **2009**, 285-287.
Franke, W. W.; Berendonk, B. *Clinical. Chem.* 1997, 43, 1262-1279.

Anabolic Steroids

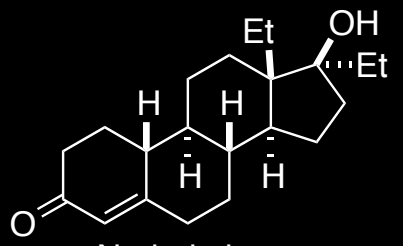
• As the ability of anti-doping agencies to detect steroids in athletes increased in the early 1980's, users of steroids would cycle between several different acyl esters of testosterone.

• The first "designer Steroid" was considered to be norbolethone. It was developed in 1966 for weight gain but never made it to market. Patrick Arnold, a chemist at Bay Area Laboratory Co-operative (BALCO), was responsible for being it to market. It was first detected in the urine of an athlete in 2002.

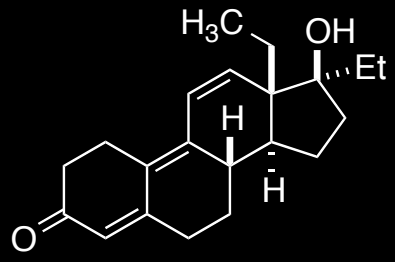
• The BALCO laboratories next introduced tetrahydrogestrinone (THG). Nicked named "the clear" it was undetectable at the time. Only by receiving a used syringe that contained THG was the Doping agency able to develop a test for THG.

Bowers, L. D. *Steroids*. **2009**, 285-287.
Catlin, D. H.; Sekera, M. K.; Ahrens, B. D.; Starcevic, B.; Chang, Y. Hatton, C. K. *Rapid. Commun. Mass Spectrum.* 2004, 18, 1245-1249.
Sekera, M. K.; Ahrens, B. D.; Chang, Y. Starcevic, B.; Georgakopoulos, C.; Catlin, D. H. *Rapid. Commun. Mass Spectrum.* 2005, 19, 781-784.

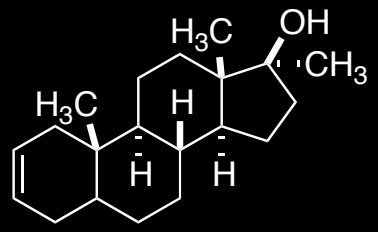
Anabolic Steroids



Norbolethone



Tetrahydrogestrinone



Madrol

- In 2005 Madrol, another "designer steroid," was discovered by the anti doping agency.

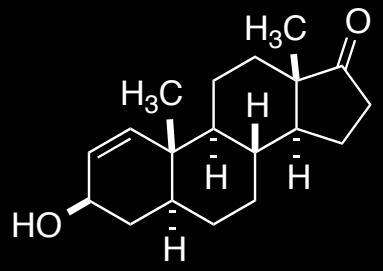
- On January 4 2010 Madrol became a controlled substance in the USA.

- Typically new dietary supplements continuously reach the market that contain steroid compounds that have never been tested in humans. These dietary supplements do not need FDA approval and many are obtained easily from the internet.

Bowers, L. D. *Steroids.* **2009**, 285-287.
Catlin, D. H.; Sekera, M. K.; Ahrens, B. D.; Starcevic, B.; Chang, Y. Hatton, C. K. *Rapid. Commun. Mass Spectrum.* 2004, 18, 1245-1249.
Sekera, M. K.; Ahrens, B. D.; Chang, Y. Starcevic, B.; Georgakopoulos, C.; Catlin, D. H. *Rapid. Commun. Mass Spectrum*. 2005, 19, 781-784.

Anabolic Steroids

- In a paper published in 2011 the dietary supplement 1-Androsterone was found to contain 3β-hydroxy-5α-androst-1-en-17-one.

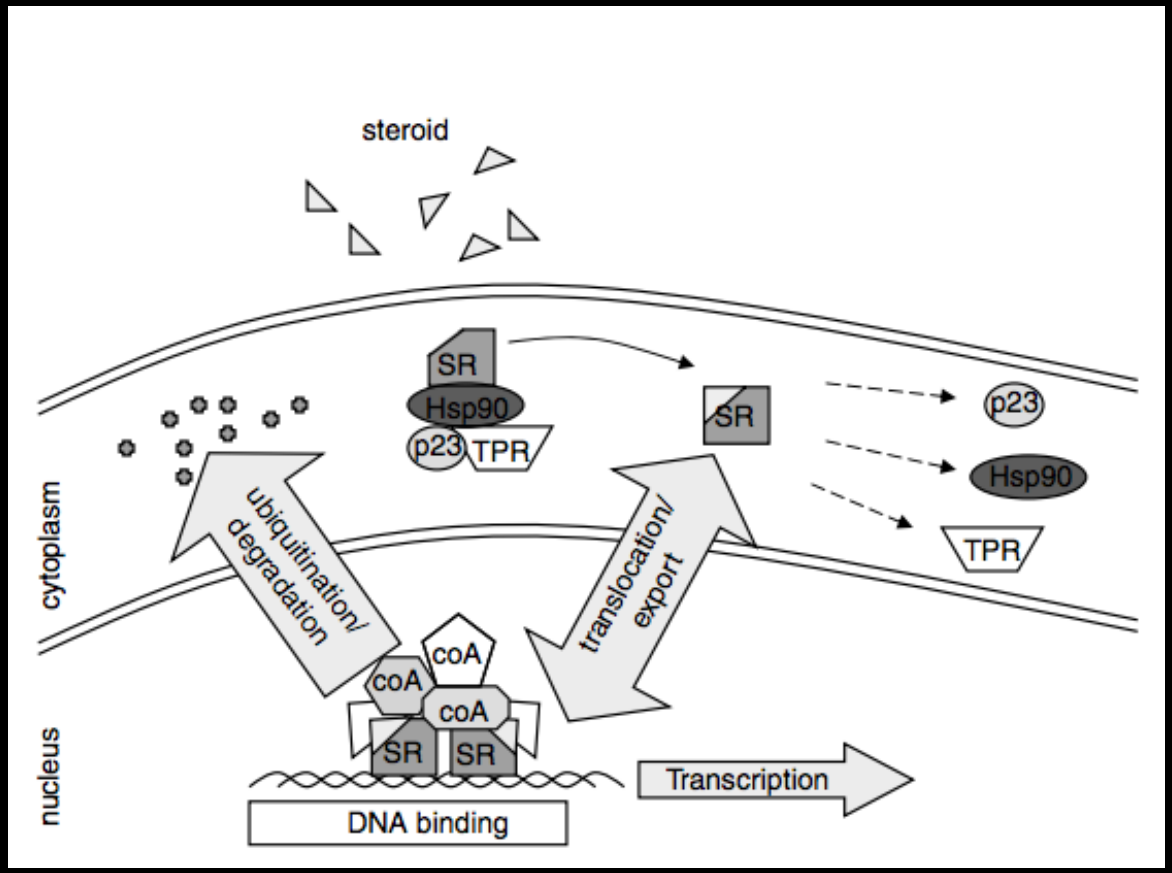


3β-hydroxy-5α-androst-1-en-17-one

- GC-MS analysis of the urine of a volunteer provided evidence that the above steroid was a prohormone, which is covered as a banned substance by the WADA list of banned substances.

Parr, M. K.; Opfermann, G.; Geyer, H.; Westphal, F.; Sönnichsen, F. D.; Zapp, J.; Kwiatkowska, D.; Schänzer, W. *Steriods.* **2011**, 540-547.

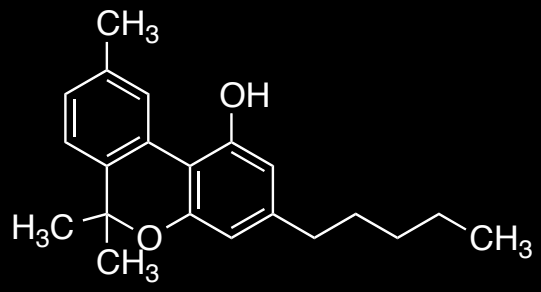
MOA of Anabolic Steroids



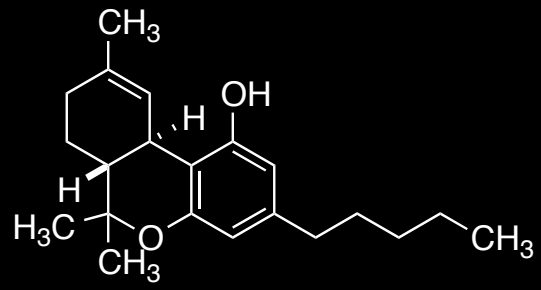
Kicman, A. T. *Brit. J. Pharmacol*. **2008**, 154, 502-521

History of THC and structure isolation

- The structure of Cannabinol is fully elucidated and synthesized in 1940.[1]
- THC was isolated, synthesized, and shown to be the main psychoactive constituent of marijuana in 1967.[2]



Cannabinol



Δ^9-tetrahydrocannabinol (THC)

[1] Jacob, A.; Todd, A. R. *J. Chem. Soc.* **1940**, 649-653. Adams, R.; Baker, B. R.; Wearn, R. B. *J. Am. Chem. Soc.* **1940**, 62, 2204-2207.

[2] Mechoulam, R.; Gaoni, Y. *Tetrahedron Lett.* 1967, 8(12), 1109-1111. Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc*. 1967, 89, 4552-4554.

Isolation of CB1 and CB2

- In 1988 a specific binding site of THC was determined in the brain.[1]

- The First THC-specific receptor was cloned in 1990 and identified as a G-protein-coupled receptor, named CB_1.[2]

- A few years later in 1993 a second cannabinoid receptor was identified, CB_2.[3]

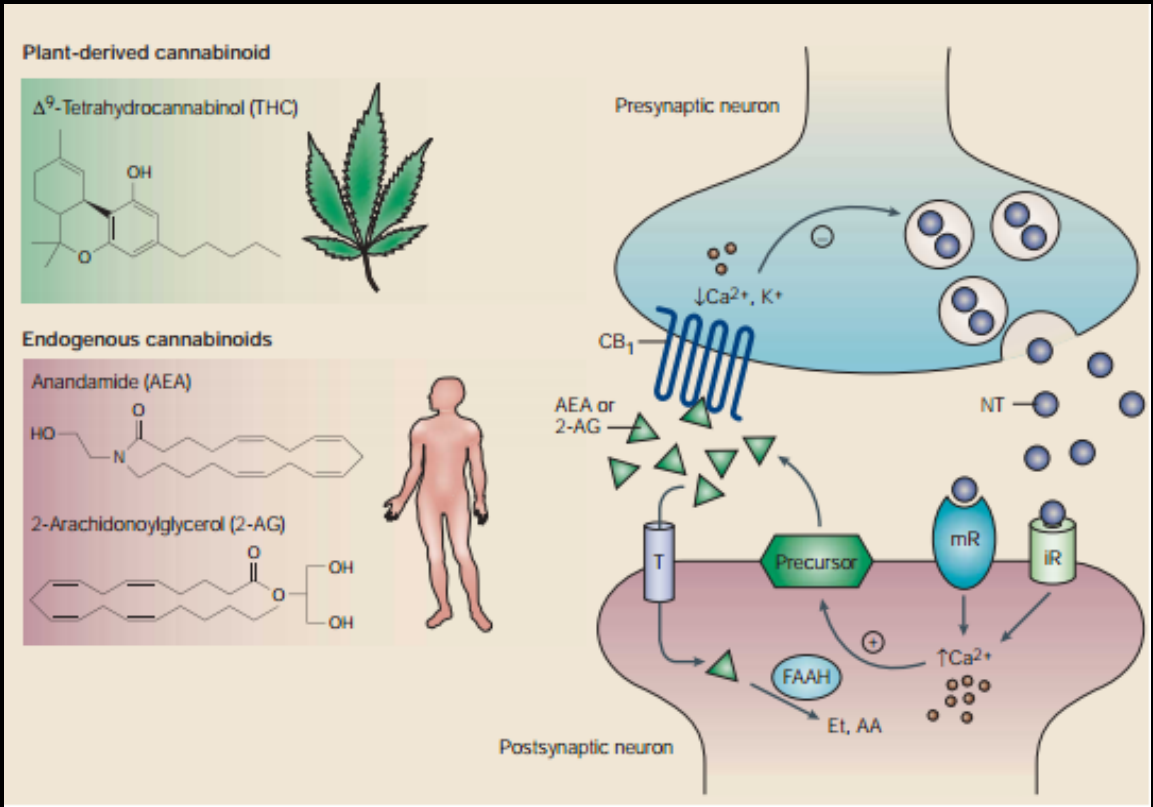
- The CB_1 receptor is found abundantly in the brain and is attributed to the psychoactive effects of THC.

- The CB_2 receptor is found mostly in immune cells.

- Recently, this split of the CB receptors has become more complex with the liver being a low source of CB_1 and CB_2 being expressed in low amounts in the brain.

[1] Devane W. A; Dysarz 3rd, F. A.; Johnson, M. R. *Mol. Pharm*. **1988**, 34, 605-613
[2] Matsuda, L, A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature*. **1990**, 346, 561-564
[3] Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature*, **1993**, 365, 61-65

The Discovery of endocannabinoids

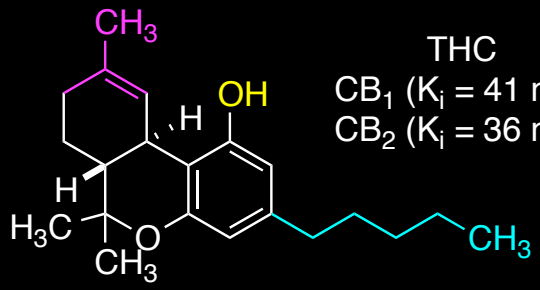


- The first endocannabinoid, anandamide, was identified in 1992.
- Later in 1995 the second endocannabinoid was identified.

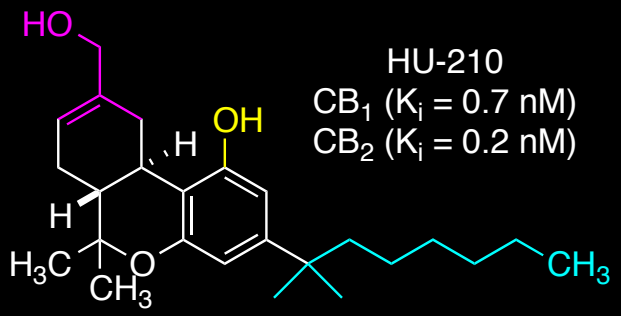
Guzmán, M. *Nature Rev*. **2003**, 3, 745-755

Classification of Ligands that Bind to CB_1 and CB_2: The agonists

- Classical Cannabinoids:



THC
CB_1 (K_i = 41 nM)
CB_2 (K_i = 36 nM)



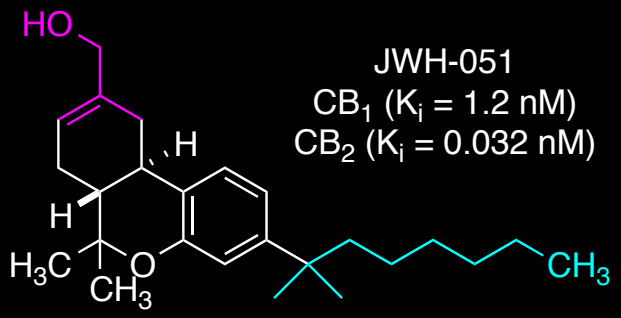
HU-210
CB_1 (K_i = 0.7 nM)
CB_2 (K_i = 0.2 nM)

- Initial experiments on bonding affinity gave rise to 3 important areas for binding affinity: 1) The phenol substituent, 2) the non-polar alkyl side-chain, and 3) the C-9 position on the cyclohexane ring.

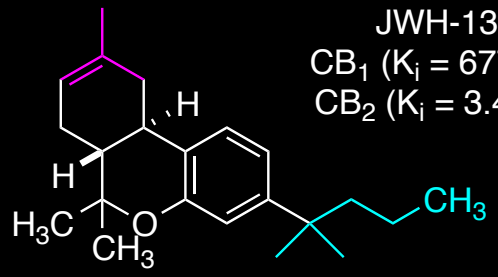
Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol Rev.* **2002**, 54, 161-202

Classification of Ligands that Bind to CB_1 and CB_2: The agonists

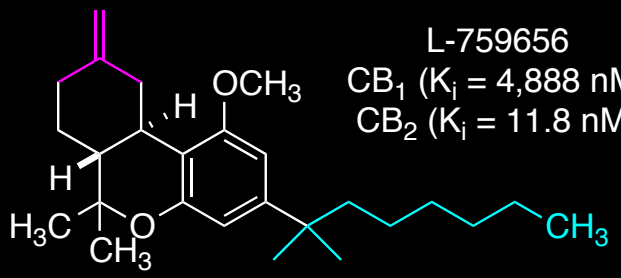
- Classical Cannabinoids: CB_2 selectivity



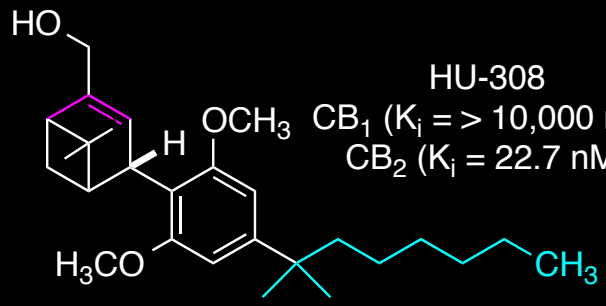
JWH-051
CB_1 (K_i = 1.2 nM)
CB_2 (K_i = 0.032 nM)



JWH-133
CB_1 (K_i = 677 nM)
CB_2 (K_i = 3.4 nM)



L-759656
CB_1 (K_i = 4,888 nM)
CB_2 (K_i = 11.8 nM)

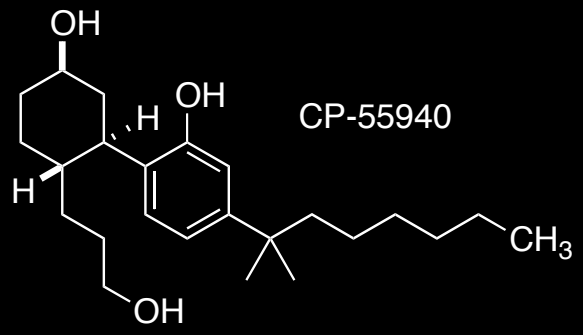


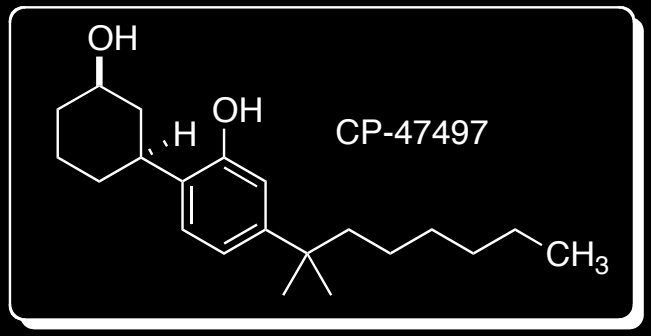
HU-308
CB_1 (K_i = > 10,000 nM)
CB_2 (K_i = 22.7 nM)

Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol Rev.* **2002**, 54, 161-202

Classification of Ligands that Bind to CB_1 and CB_2: The agonists

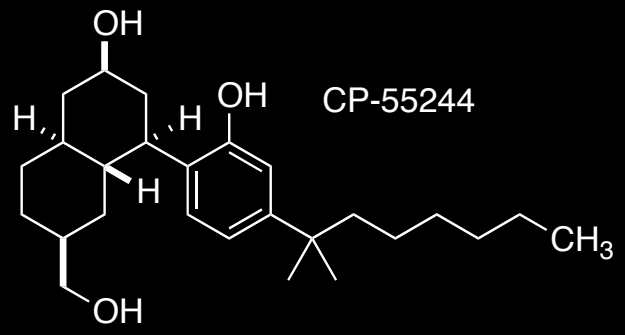
- Nonclassical Cannabinoids





- Developed by Pfizer while studying the analgesic activity of classical cannabinoids.

- CP-55940 is 10 to 50 times more potent than THC.



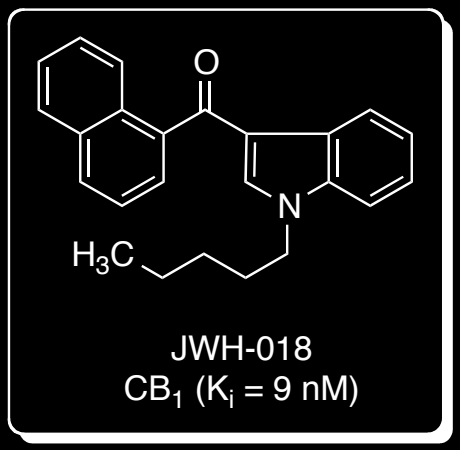
- CP-55244 displays a higher affinity for CB_1 than CP-55940 but CB_2 affinity remains untested.

Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol Rev.* **2002**, 54, 161-202

Classification of Ligands that Bind to CB_1 and CB_2: The Agonists

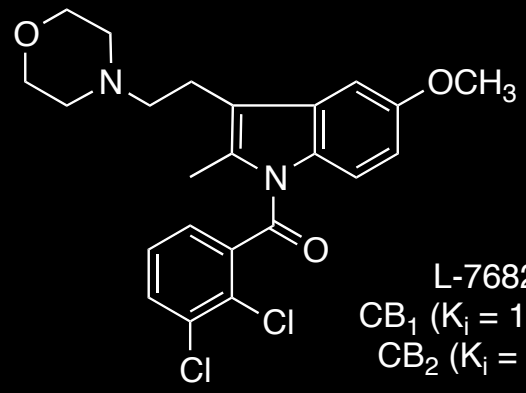
- Aminoalkylindoles

R-(+)-WIN-55,212
CB_1 (K_i = 1.89 nM)
CB_2 (K_i = 0.28 nM)



JWH-018
CB_1 (K_i = 9 nM)

- WIN-55212 was the first Agonist to display notable difference in binding affinity between CB_1 and CB_2

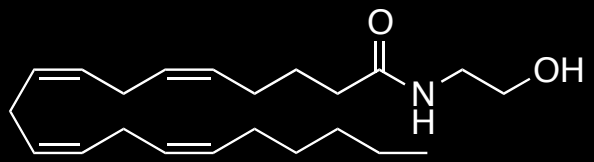


L-768242
CB_1 (K_i = 1917 nM)
CB_2 (K_i = 12 nM)

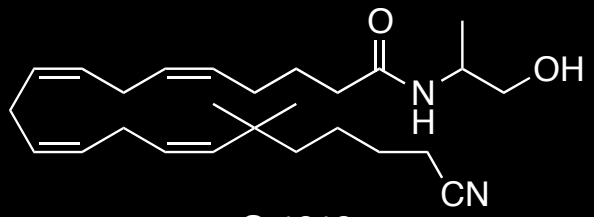
Poso, A.; Huffman J. W. *Brit. J. PHarmacol*. **2008**, 153, 335-346-S18
Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol Rev.* **2002**, 54, 161-202

Classification of Ligands that Bind to CB_1 and CB_2: The agonists

- Eicosanoids

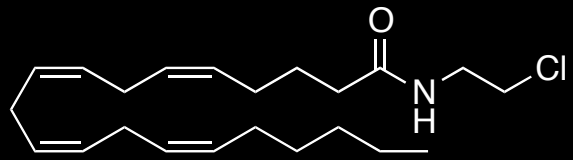


anandamide
CB_1 (K_i = 89 nM)
CB_2 (K_i = 371 nM)



O-1812
CB_1 (K_i = 3.4 nM)
CB_2 (K_i = 3870 nM)

- These compounds function as both neuromodulators and immunomodulators and served as retrograde synaptic messengers.

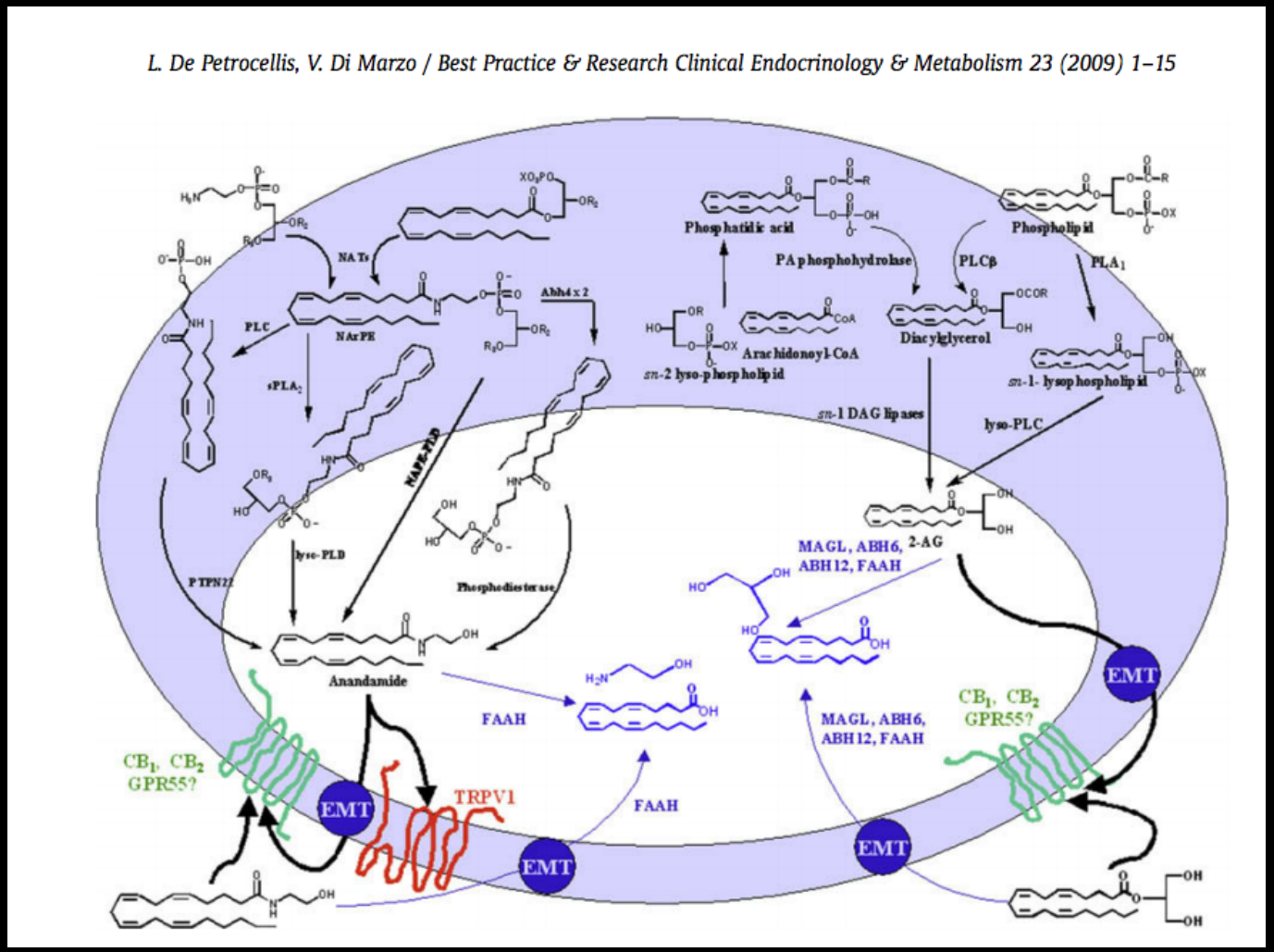


ACEA
CB_1 (K_i = 1.4 nM)
CB_2 (K_i > 2,000 nM)

- Serve in an autoprotective role in some disease states. These compounds are released in response to skeletal muscle spasm and inflammatory pain.

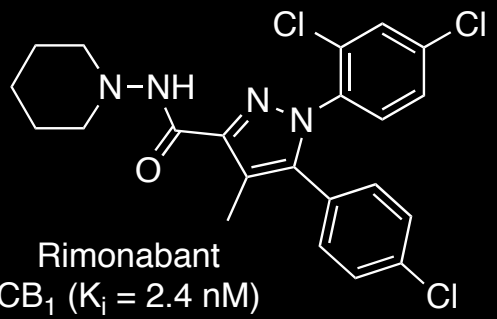
Pertwee, P. G. *Int. J. Obesity*. **2006**, 30, S13-S18

Endocrinology and Metabolism



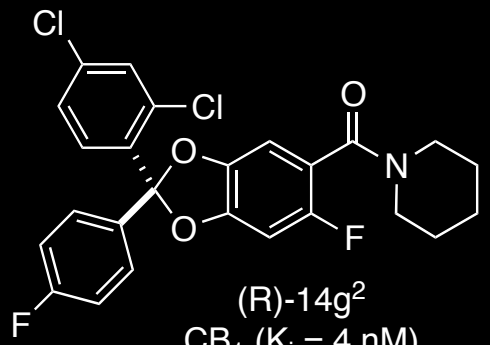
Petrocellis, L.. Marzo, V. *Best. Pract. Res. Cl. En*. **2009**, 23, 1-15

CB_1 Antagonists: Obesity

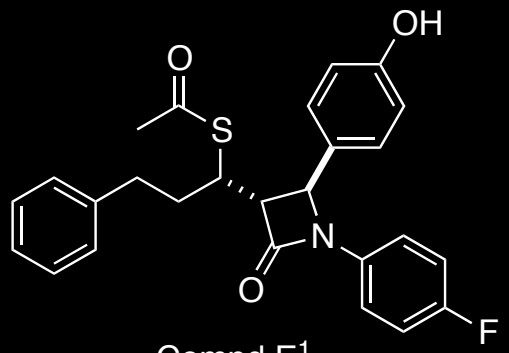


Rimonabant
CB_1 (K_i = 2.4 nM)
CB_2 (K_i = 560 nM)

• Rimonabant was the first developed CB_1 antagonist. It was approved for use in Europe in 2006 but was suspended in 2009 due to side-effects. Reports of severe depression and suicidal thoughts. More severe than reported in clinical studies.



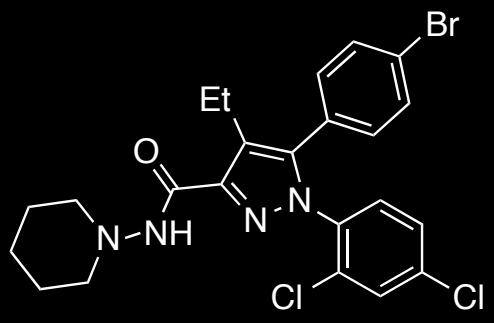
(R)-14g[2]
CB_1 (K_i = 4 nM)



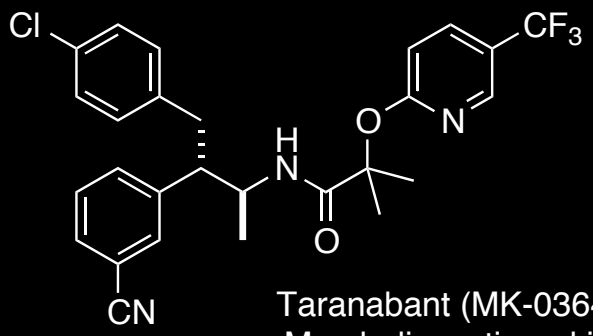
Compd E[1]
CB_1 (K_i = 52.8 nM)
CB_2 (K_i = 282.0 nM)

[1]Wang, H.; *et al*. *J. Med. Chem*. **2008**, 51, 2439-2446
[2] Alig, L.; *et al*. *J. Med. Chem*. **2008**, 51, 2115-2127

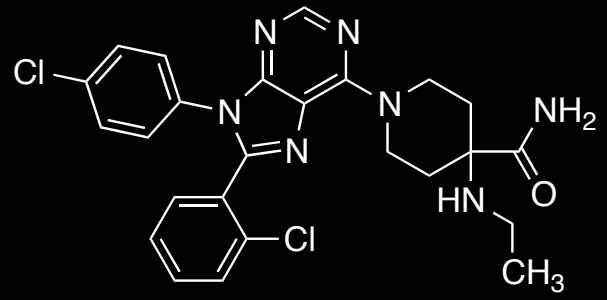
CB_1 Antagonists: Obesity



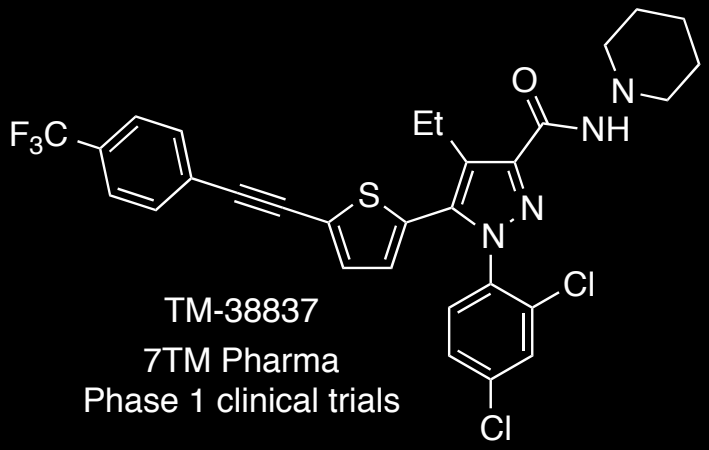
Surinabant
Sanofi-Aventis
discontinued in
2008



Taranabant (MK-0364)
Merck discontinued in
phase III trials (2008)



Otenanbant (CP-945,598)
Pfizer: Discontinued

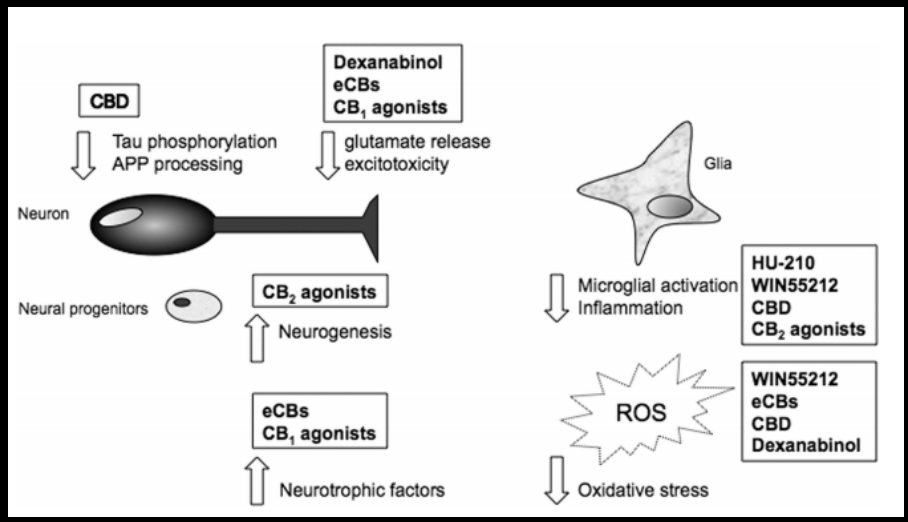


TM-38837
7TM Pharma
Phase 1 clinical trials

Current Targets for Therapeutics

- CB_2 agonists for the treatment of pain have shown promise in pre-clinical studies. Only 1 compound has completed phase 1.

- Using Cannabinoids for treating neurodegeneration



- Endocannabinoid pathology
  - Inhibition of FAAH
  - Inhibition of MAGL
  - Inhibition of DAGL - Orlistat®

- Non-CNS CB_1 antagonists for obesity

Gowran, A.; Noonan, J. *CNS Neurosci. Ther*. **2011**, 17, 637-644
Petrosino, S.; Ligresti, A.; Marzo, V. D. *Curr. Opin. Chem. Bio*. **2009**, 13, 309-320

The Legal High Issue

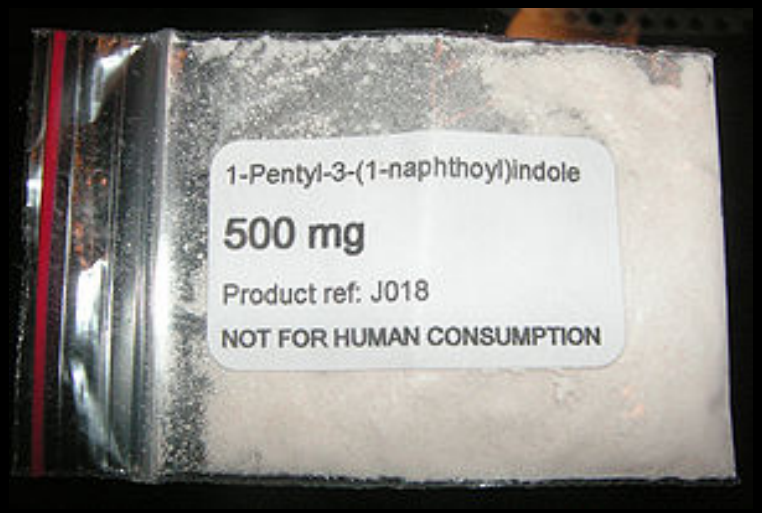
- First seen in Europe in 2004
- First reports in the USA was 2008
- Sold has plant food or incense at local head or glass shops.
- Can be bought and sold over the internet
- Carried the label of not for human consumption.
- Sold under several names (K2, Spice, Serenity Now, Tribal Warrior, Colorado chronic, and…

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

The Legal High Issue

- These mixtures contain a random assortment of herbs with the active ingredient sprayed on the plant material.

- In 2008 Huffman received an email from a blogger in Germany that the major substituent of K2 spice was JWH-018.

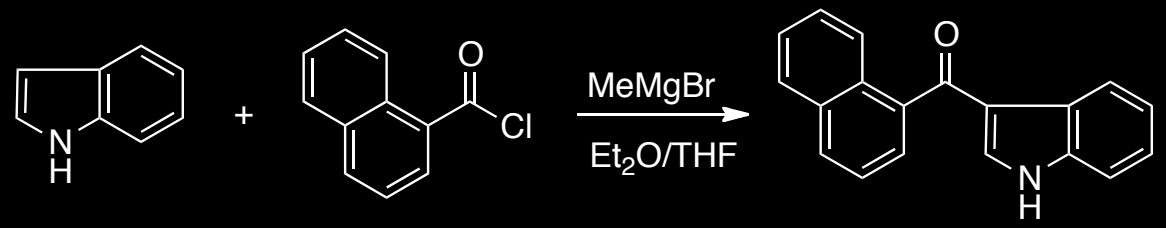


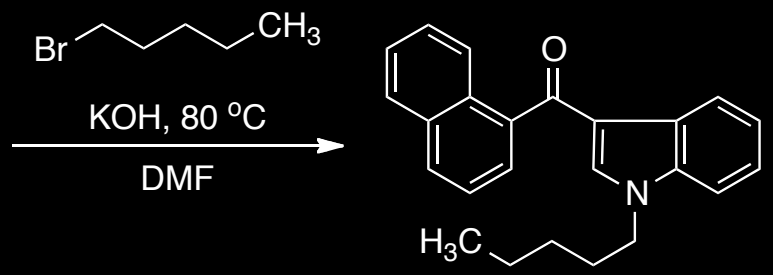
- "We made the stuff in 1995" "I had a undergraduate student working under the supervision of a very capable postdoc, and this was just one of the things we made." – John W. Huffman

- "We reported it as an amber-colored gum and these people are getting it as a solid. I suspect that they purify it by some sort of automated chromatography, and we used a classic column." – John W. Huffman

Chemical & Engineering News. **2010**, 88(26), 43

The Legal High Issue

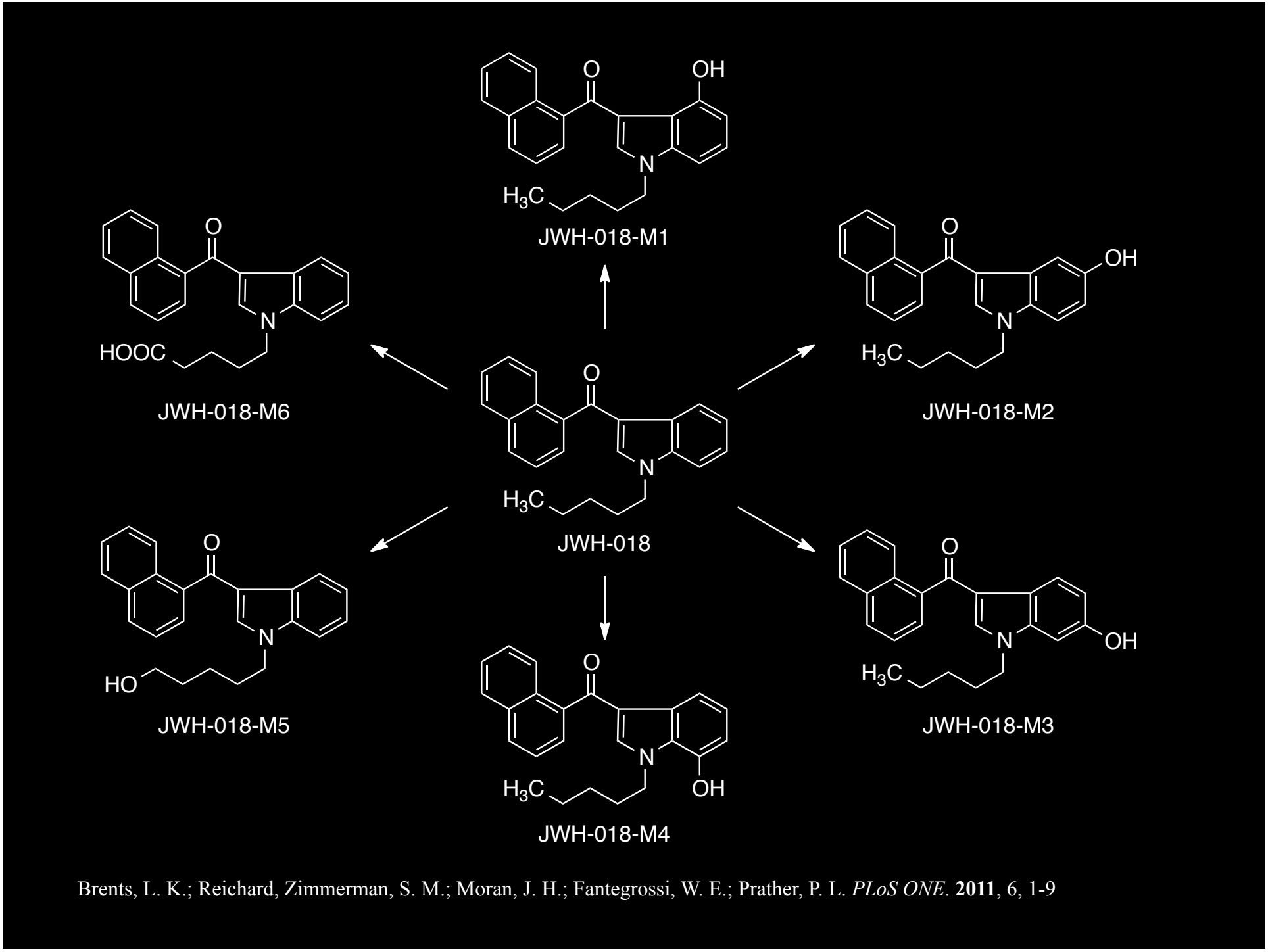




JWH-018

- Very easy to make
- More potent CB_1 and CB_2 agonist than THC
- Unknown side-effects

Huffman, H. W.; *et al. Bio. Med. Org*. **2005**, 13, 89-112



Brents, L. K.; Reichard, Zimmerman, S. M.; Moran, J. H.; Fantegrossi, W. E.; Prather, P. L. *PLoS ONE*. **2011**, 6, 1-9

The Legal High Issue

- Smoking or oral consumption of THC generally produces mild side such as appetite stimulation and orthostatic hypotension.

- K2 products produce similar desired effects as THC, however the frequency and severity of side-effects is much greater.

- The side-effects include hypertension, agitation, hallucinations, psychoses, seizures, and panic attacks.

- Most Pharmacological and toxic profiles of different cannabinoid compounds are unknown.

- Only 1 major psychoactive metabolite of THC is known.

- Five JWH-018 metabolites bind CB_1 receptors with affinities greater to or equal to THC.

Brents, L. K.; Reichard, Zimmerman, S. M.; Moran, J. H.; Fantegrossi, W. E.; Prather, P. L. *PLoS ONE*. **2011**, 6, 1-9

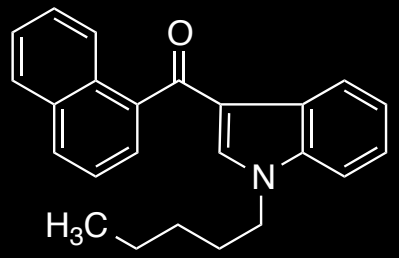
The Legal High Issue

- Initially different countries/states imposed there own restrictions on the brand name K2 and spice.

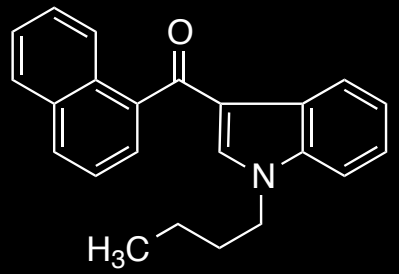
- The USA classified JWH-018 and 4 other compounds as Schedule 1 controlled substances for 1 year on November 2010.

- As of March 2011 they have been officially banned.

- There is recent evidence of an un-reported compound found in a herbal mixture seized in Germany.

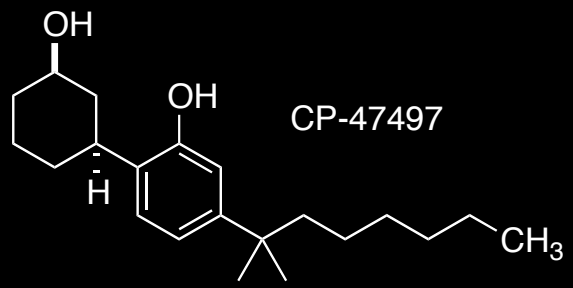


JWH-018

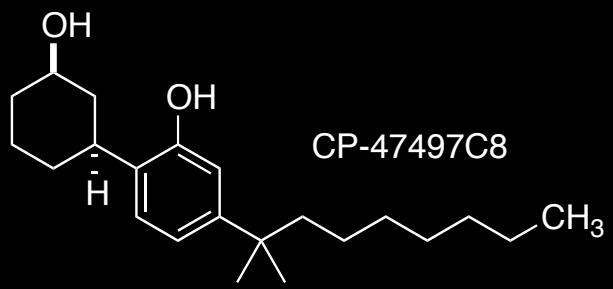


JWH-073

JWH-200



CP-47497



CP-47497C8

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38

Bath Salts: Synthetic Cathinones

252 comments

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Report: Miami police shoot naked man chewing on victim's face

By Jim Gold, msnbc.com

A Miami police officer fatally shot a naked man chewing the face of another man Saturday afternoon on a downtown causeway off-ramp, officials said.

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The Miami Herald reported that the naked man chewed off half the face of his victim, who is struggling for his life.

The violence started at 2 p.m. on the MacArthur Causeway off-ramp, just south of the Herald's offices, the newspaper said.

Witnesses said that a woman saw two men fighting and flagged down a police officer, who came upon the naked man mauling the other man, the Herald reported.

The officer, who was not identified, ordered the naked man to back away, but when the man continued the assault, the officer shot him, the Herald said. Witnesses told the Herald the wounded attacker continued to eat his victim, so the officer continued firing.

Witnesses said they heard at least a half-dozen shots, the Herald said.

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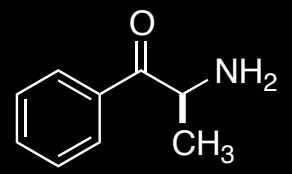
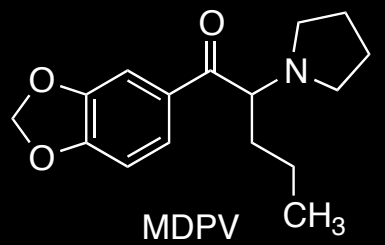
LivingTo113.com

Bath Salts: Synthetic Cathinones

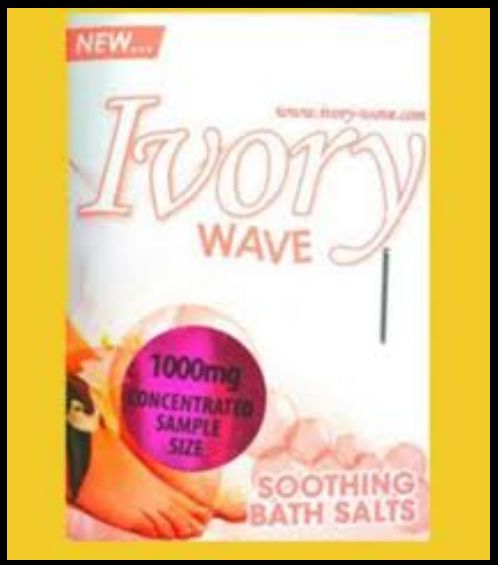


Cathinone

Mephedrone



MDPV



Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38

Bath Salts: Synthetic Cathinones

- In 2009 a decrease in the purity of cocaine seized in the UK attributed to an increase in the number of drug raids.

- Also around this time the change in the composition of MDMA (ecstasy) tablets in the Netherlands changed to include less than half of MDMA.

- In 2010 the American Association of Poison Control Centers reports 300 calls related to bath salts. There were 2370 calls by May of 2011.

- MDPV was reclassified as a Class B controlled drug in April 2010 in the UK. Soon after the constituents of "Ivory wave" were changed to circumvent the law (Naphyrone).

- On September 7, 2011 the DEA used emergency scheduling to make possession or sale of mephedrone, MDPV, and methylone illegal.

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38
Prosser, J. M.; Nelson, L. S. *J. Med. Toxicol.* **2012**, 8, 33-42.
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

Bath Salts: Synthetic Cathinones

- Similarly to synthetic marijuana, bath salts can be purchased from head shops, gas stations, or over the internet.

- There is almost no information on the pharmacokinetics and pharmacodynamics of synthetic cathinones.

- Symptoms tend to vary due to the unknown purity and/or compounds present in these bath salts. They vary widely per "package."

- There is mounting evidence in support that MDPV and mephedrone use carries a greater risk of psychosis. Several recent reports describe severely aggressive and psychotic behavior by patients who have snorted bath salts.

- MDPV and other synthetic cathinones are not detected by currently used methods.

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38
Prosser, J. M.; Nelson, L. S. *J. Med. Toxicol.* **2012**, 8, 33-42.
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

Effects and MOA of Cathinones

- Synthetic cathinone users describe feeling euphoric, heightened alertness, increased energy, talkativeness, and increased sexual arousal.

- There have been cases of paresthesias and mood changes for days to weeks after use.

- Symptoms of synthetic cathinone toxicity include hypertension, tachycardia, hyperthermia, dehydration.

- Commonly reported adverse effects include chest pain, tremors, insomnia, and paranoia.

- Synthetic cathinones strongly inhibit the reuptake of dopamine, serotonin, and norepinephrine.

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38
Prosser, J. M.; Nelson, L. S. *J. Med. Toxicol.* **2012**, 8, 33-42.
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

Bath Salts: Synthetic Cathinones

post-gazette.com
Pittsburgh Post-Gazette

Congress OKs ban on 'bath salt' drugs

June 27, 2012 12:00 am

By Tracie Mauriello / Post-Gazette Washington Bureau

WASHINGTON -- A stroke of President Barack Obama's pen is all it will take now to send bath salts down the drain.

These bath salts are not the kind found in tubs, but instead hallucinogenic drugs that are said to cause bizarre and violent behavior in users. The drug is sold under such innocuous names as "Ivory Wave," "Vanilla Sky" and "Purple Haze."

State laws already ban the drug in Pennsylvania and several other states, but congressional action Tuesday would make it illegal nationwide and impose penalties of as much as 30 years in prison. The maximum penalty under Pennsylvania law is five years in prison and $15,000 in fines.

Following an earlier House vote, the U.S. Senate on Tuesday permanently banned the chemical ingredients used to make bath salts and similar synthetic drugs.

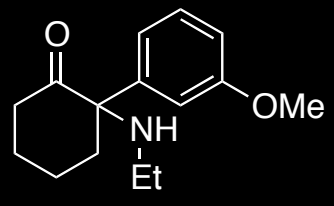
"These drugs are labeled and disguised as legitimate products to circumvent the law. They're easily purchased online, at gas stations, in shopping malls and in other novelty stores," Sen. Chuck Grassley, R-Iowa, said during a floor speech Monday. "A number of people across the country have acted violently while under the influence of these drugs."

Post Gazette, 2012. Congress Oks ban on 'bath salt' drugs. Mauriello, T. From *http://www.post-gazette.com/stories/news/us/congress-oks-ban-on-bath-salt-drugs-642084/?print=1*

Bath Salts: Synthetic Cathinones

Ketamine and Methoxetamine

Ketamine



methoxetamine

- Ketamine requires a veterinary license to obtain.
- Used as a veterinary anesthesia drug. Also used as a pain reliever and to reduce convulsions.
- "MXE" is not illegal in any country currently and was first seen in 2010.
- Initial reports describe "MXE" to behave similar to Ketamine with longer lasting dissociative effects supposedly without the long term urinary tract problems.
- The change from chloro to methoxy seems to give MXE lower levels of analgesic and anesthetic properties.

Corazza, O.; *et al*. *Hum. Psychopharmacol. Clin. Exp.* **2012**, 27, 145-149
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

Effects and MOA of Ketamine and Methoxetamine

- There are no scientific evidence for the MOA of methoxetamine. However, it is assumed that it is an antagonist of N-methyl-D-aspartate (NMDA) receptor and inhibition of dopamine reuptake.

- Methoxetamine users describe euphoria, perceptional distortions, and hallucinations. It can induce a state of dissociative anesthesia (out of body experience).

- Unwanted side-reactions include severe nausea, vomiting, diarrhea, paranoia, and anxiety.

- Unlike Ketamine hypertension, laryngospasm, and pulmonary edema have not been reported for methoxetamine.

Corazza, O.; *et al*. *Hum. Psychopharmacol. Clin. Exp.* **2012**, 27, 145-149
Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

Ketamine and Methoxetamine

Vice: You did what?

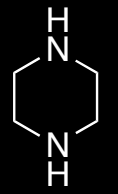
M.: I taught neurobiology as part of my postgraduate degree. But then I transitioned from academia into the sort of independent research I'm doing now.

Vice: Yes, it would seem methoxetamine has already been welcomed with open arms.

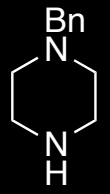
M.: ….Eventually I found someone who was interested and made a small batch, and when I tested it… I was blown away. It doubtless has great potential as an antidepressant. A vendor took interest and synthesized a batch for public distribution, and it took off. …. but I was surprised by the willingness of Chinese laboratories to synthesize it. A few years ago Chinese labs would not produce arylcyclohexylamines under any circumstances. In China, those suspected of trafficking large quantities of ketamine are executed.

Viceland. 2011. Interview with a ketamine chemist. Viceland, from http://www.vice.com/read/interview-with-ketamine-chemist-704-v18n2

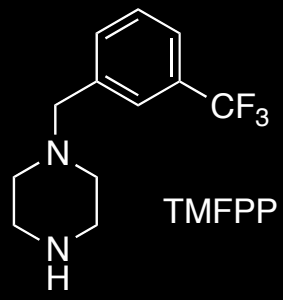
Piperazine Derivatives



Piperazine



1-Benzylpiperazine (BZP)

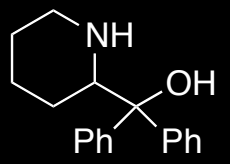


TMFPP

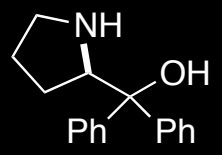
- Piperazine was developed as an antihelminthic that displayed amphetamine-like properties.
- Piperazine derivatives are marketed as "legal ecstasy"
- BZP was given Schedule I status in 2004 however the popularity of piperazine derivatives has increased in recent years.
- Although packaging remains consistent the contents change dramatically and most "party pills" contain a mixture of 2-4 piperazine derivatives.

Rosenbaum, C. D.; Carreiro, S. P. *J. Med. Toxicol.* **2012**, 8, 15-32

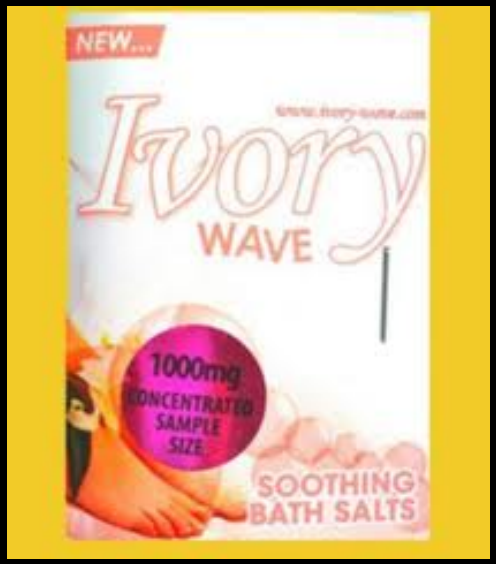
Pipradrol derivatives



Pipradrol



Diphenylprolinol



- Pipradrol was developed in the 1940s for the treatment of obesity, depression, ADHD, and narcolepsy.
- There currently are no pharmacokinetic or pharmacodynamic data on diphenylprolinol in animals or humans.
- Clinical cases have shown toxicity to resemble amphetamine toxicity. Including server agitation, hallucinations, and aggression.
- Symptoms were still present in Scottish patients 7 days after consumption of ivory wave.
- Desoxypipradrol was scheduled to be banned in the UK in March 2012 but has since been pushed back.

Coppola, M.; Mondola, R. *Toxicol. Lett.* **2012**, 212, 57-60

MOA of Piperazine and Pipradrol derivatives

- BZP was considered as an anti-depressant. In low doses cause stimulant effects and at high doses causes hallucinogenic effects.

- BZP is agonist and inhibits serotonin reuptake. Also inhibits serotonin transportation.

- TMFPP acts on the serotonin transporter to release serotonin from neurons. Similarly to ecstasy and other amphetamines.

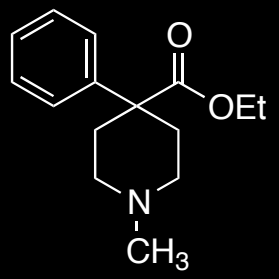
- Pipradrol inhibits the reuptake of and stimulates the release of dopamine and norepinepherine. The synthetic derivatives are assumed to have similar MOA but no experimental data exists.

- Pipradrol derivatives have an stimulant effect similar to amphetamines.

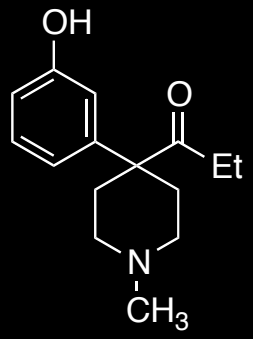
- Symptoms of pipradrol toxcity are similar to amphetamine toxicity and include severe agitation, hallucinations, paranoid ideation, insomina, and aggression.

Coppola, M.; Mondola, R. *Toxicol. Lett.* **2012**, 212, 57-60

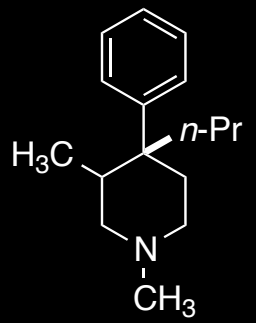
Piperidine Opioids: old trouble back again?



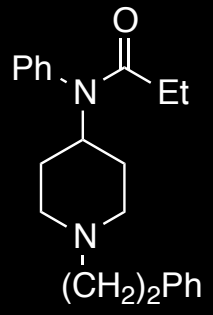
Meperidine



ketobemidone

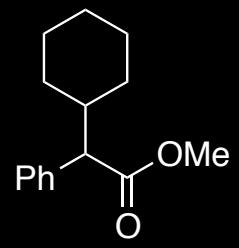


picenadol



fentanyl

- This class of opioid compounds have gone through extensive SAR studies.
- Thousands of these compounds have been published and evaluated in pain models. Several have been tested in animals and a few in humans.
- Some of these compounds are used clinically for ADHD and narcolepsy.
- The fentanyl class are the most potent.

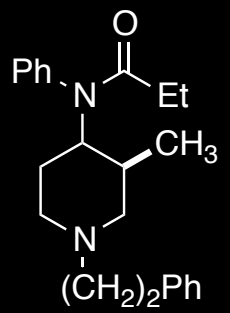


methylphenidate

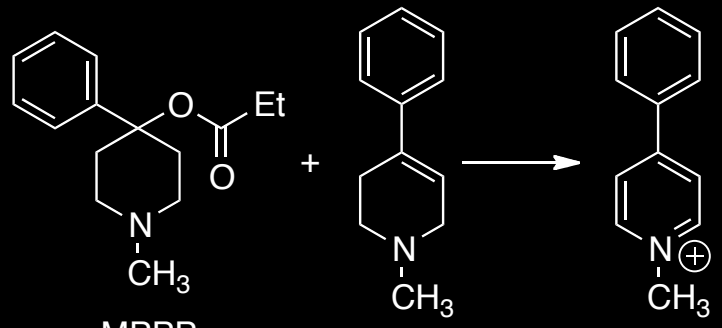
Concerta
Ritalin
metadate CD
Focalin (cis-isomer)

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38

Piperidine Opioids: old trouble back again?



China White



MPPP MPTP MPP

- MPPP was a "designer drug" in the 80's and 90's. There were several cases of people developing an irreversible Parkinsonian-like syndromes due to the impurity, MPTP.

- Currently designer opioids are not a major issue due to the relative ease and cheap cost of other opiates.

Carroll, F. I.; Lewin, A. H.; Mascarella, S. W.; Seltzman, H. H.; Reddy, P. A. *Ann. N.Y. Acad. Sci.* **2012**, 1248, 18-38

Piperidine Opioids: old trouble back again?

Afghans defy warnings as poppy season opens

April 23, 2012 by AFP

US soldiers walk through a poppy field during a joint mission with the Afghan Army in the Maiwand district in Kandahar province, southern Afghanistan.—Reuters Photo

KANDAHAR: It is the start of Afghanistan's poppy season and at Kandahar bus station thousands of men and boys, some as young as 10, are gathered to seek work harvesting the opium crop.

Landowner Abdul Rahman travelled from his village in neighbouring Helmand province looking for workers to help him in the short harvest season. He has 10 recruits already and is looking for another 10.

"I own 50 hectares of land in my village in Khaneshin district and have cultivated them all with poppy," he said.

Two-thirds of the income from his fields will go to local Taliban militants in the form of protection money, but he says he will still be left with $10,000-$15,000 depending on the price of opium on local and foreign markets.

"Where else can I make this amount of money?" he says.

http://dawn.com/2012/04/23/afghans-defy-warnings-as-poppy-season-opens-fm/

Summary

• Currently the world's response to these designer drugs are reactionary. From new synthetic steroids constantly being introduced as supplements to unknown mixtures of bath salts. The world waits until problems arise before acting.

• The harm comes from not knowing the strength, identity, or the adverse effects of most of these compounds. Not to mention the ease of buying them over the internet generates a false sense of safety.

• These clandestine chemist have evolved from copying the published literature to rationally designing their own compounds.

"we made this as a research compound and published it and did what we were supposed to do. You can't stop people from being idiots."

"Using these things is like playing Russian roulette because we don't have toxicity data, we don't know the metabolites, and we don't know the pharmacokinetics." – John W Huffman.

Chemical & Engineering News. **2010**, 88(26), 43