

Synthetic Drugs of Abuse

DEA Museum Lecture Series

March, 2012

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Science Policy Branch
National Institute on Drug Abuse



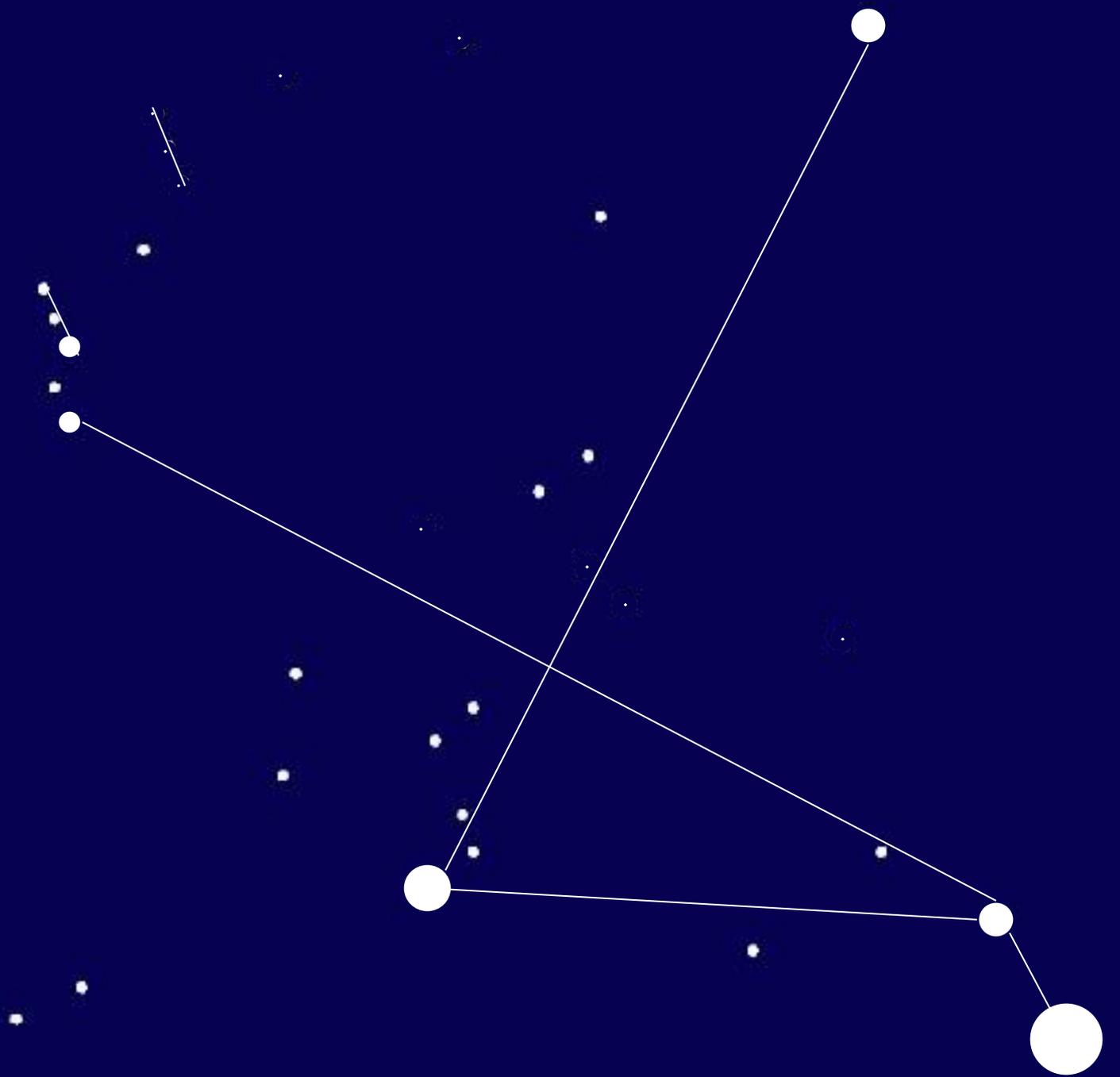
Marijuana ●
GHB ●
PCP ●
Psilocybin ●
Mescaline ●
LSD ●
Heroin ●
Ecstasy ●
Cathinone ●
Amphetamine ●
Methylphenidate ●
Methamphetamine ●
Cocaine ●
Phentanyl ●
Morphine ●
Pentobarbital ●
Buprenorphine ●
Codeine ●
Marinol ●
Ketamine ●
Diazepam ●
Rohypnol ●
Modafinil ●
Zolpidem (Ambien) ●
Absinthe ●
Alcohol ●
Tobacco ●
Salvia ●
Khat ●
Toluene ●
Caffeine ●

DA 5HT GLU GABA MOP KOP CB NR ADR



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- Marijuana
- GHB
- PCP
- Psilocybin
- Mescaline
- LSD
- Heroin
- Ecstasy
- Cathinone
- Amphetamine
- Methylphenidate
- Methamphetamine
- Cocaine
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- Morphine
- Pentobarbital
- Buprenorphine
- Codeine
- Marinol
- Ketamine
- Diazepam
- Rohypnol
- Modafinil
- Zolpidem (Ambien)
- Absinthe
- Alcohol
- Tobacco
- Salvia
- Khat
- Toluene
- Caffeine



Research Chemicals

Phenethylamines

Related to: phenethylamine

2C-x

Related to: mescaline

2C-B 2C-D
2C-I 2C-P
2C-E 2C-T-x
2C-B-FLY

Psychedelic amphetamines (DOx)

Related to: 2C-x, amphetamine

DOB DOM
DOC DON
DOI DOET
Bromo-DragonFLY

β-ketones

Related to: cathinone,
MDMA, amphetamine

Mephedrone Butylone
Methylone Flephedrone
Methedrone MDPV
Naphthylpyrovalerone

Cyclized amphetamines

Related to: MDMA,
amphetamine

2-AI 2-AT
MDAI MDAT
MDMAI MDMAT
MMAI

Ergolines

Related to: LSD, LSA

PRO-LAD
ETH-LAD

Tryptamines

Related to: psilocin, DMT, serotonin

5'-substituted

Related to: psilocin, serotonin

5-MeO-DMT 5-MeO-DALT
5-MeO-MIPT 5-MeO-MET
5-MeO-DIPT 5-MeO-DPT
5-MeO-AMT
5-MeO-AET

4'-substituted

Related to: psilocin

4-AcO-DMT 4-HO-DPT
4-AcO-DET 4-HO-DALT
4-HO-MIPT 4-HO-DIPT
4-MES-DMT

NMT MIPT
DET DALT DIPT
DPT
AMT
AFT

Synthetic Cannabinoids

Functionally related to naturally occurring cannabinoids

Found in a number of branded products, most notably Spice

JWH family

CP-47,497
CP-55,940

JWH-017 JWH-073
JWH-018 JWH-081
JWH-019 JWH-200
JWH-250

WIN-55,212-2

HU-210

CB-25
CB-52

Piperazines

Related to: piperazine

BZP mCPP
MBZP pFPP
DBZP MeOPP
MDBZP TFMPP

Opiates

α-methylfentanyl
3-methylfentanyl
para-fluorofentanyl
MPPP
O-desmethyltramadol
7-acetoxymitragynine

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α-methylfentanyl

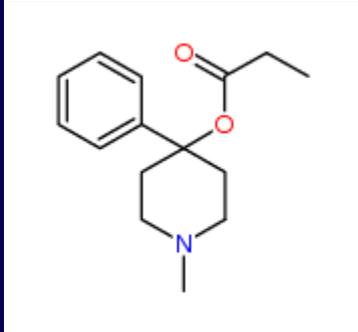
3-methylfentanyl

para-fluorofentanyl

MPPP

O-desmethylnaloxone

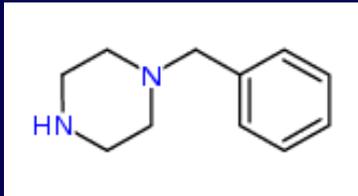
7-acetoxymitragynine



MPPP

1-Methyl-4-phenyl-4-propionoxypiperidine

Opioid analgesic developed in the 1940s by Hoffmann-La Roche. Somewhat less potent than morphine. No longer in clinical use (Schedule I) but illegally manufactured for recreational drug use.



BZP

Benzylpiperazine Early interest stem from its antihelmintic properties, abandoned because of side affects, it was revisited in the '70s as a potential antidepressant medication, but rejected again due to reports of amphetamine-like effects and abuse liability.

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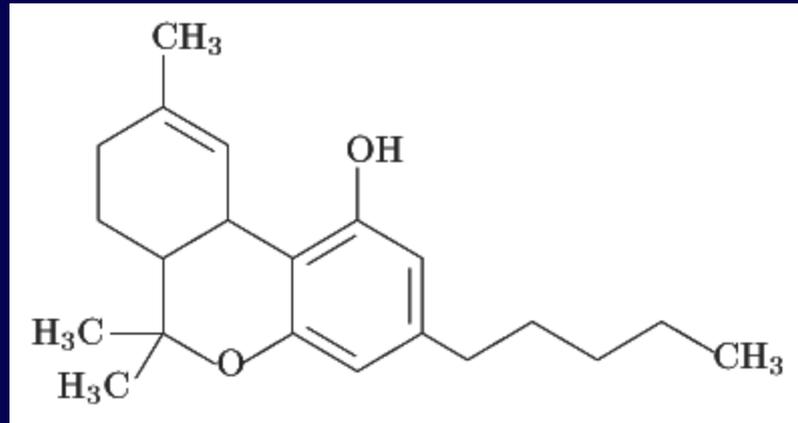
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Structure of THC

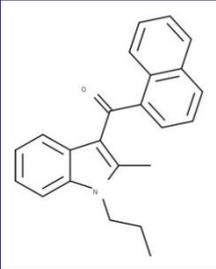


THC is the prototypic cannabinoid and the active ingredient of marijuana

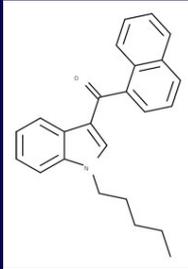
Classes of Cannabinoid Ligands

Naphthoylindole family

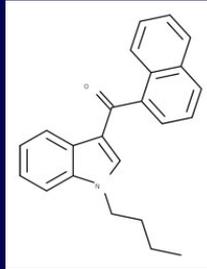
JWH-015



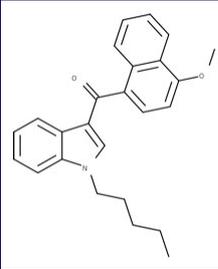
JWH-018



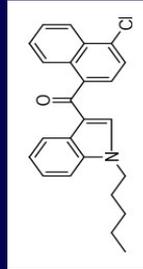
JWH-073



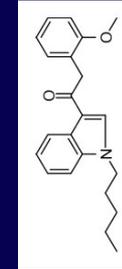
JWH-081



JWH-398

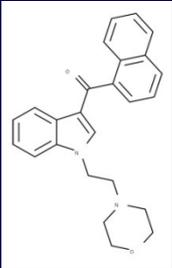


JWH-250

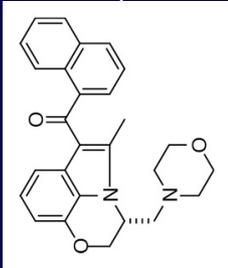


Aminoalkylindole family

JWH-200

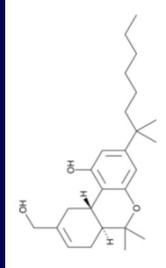


WIN 55,212-2

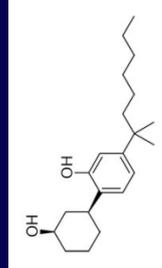


CR agonist family

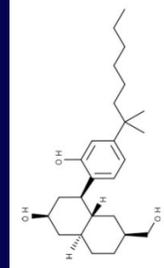
HU-211



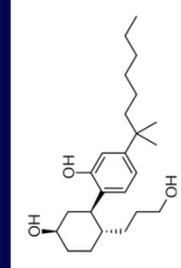
CP 47,497



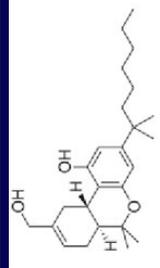
CP 55,244



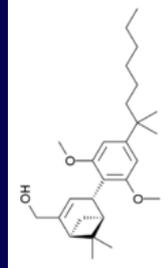
CP 55,940



HU-210

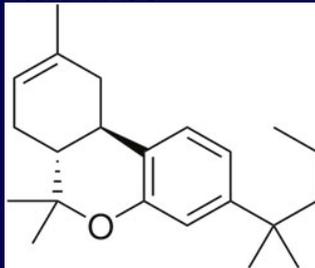


HU-308



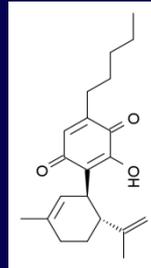
Anti-inflammatory CB2 agpnist

JWH-133

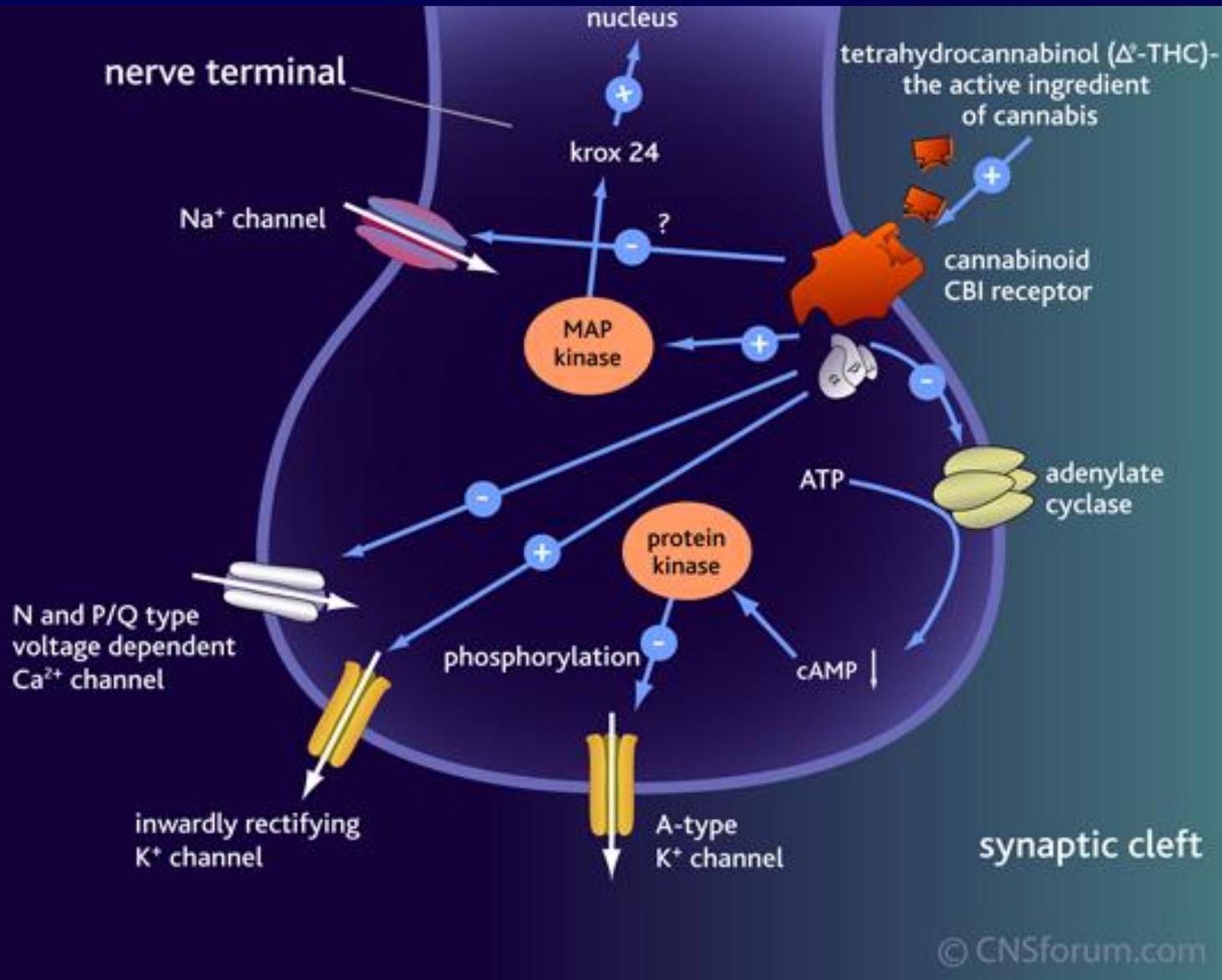


Quinone family

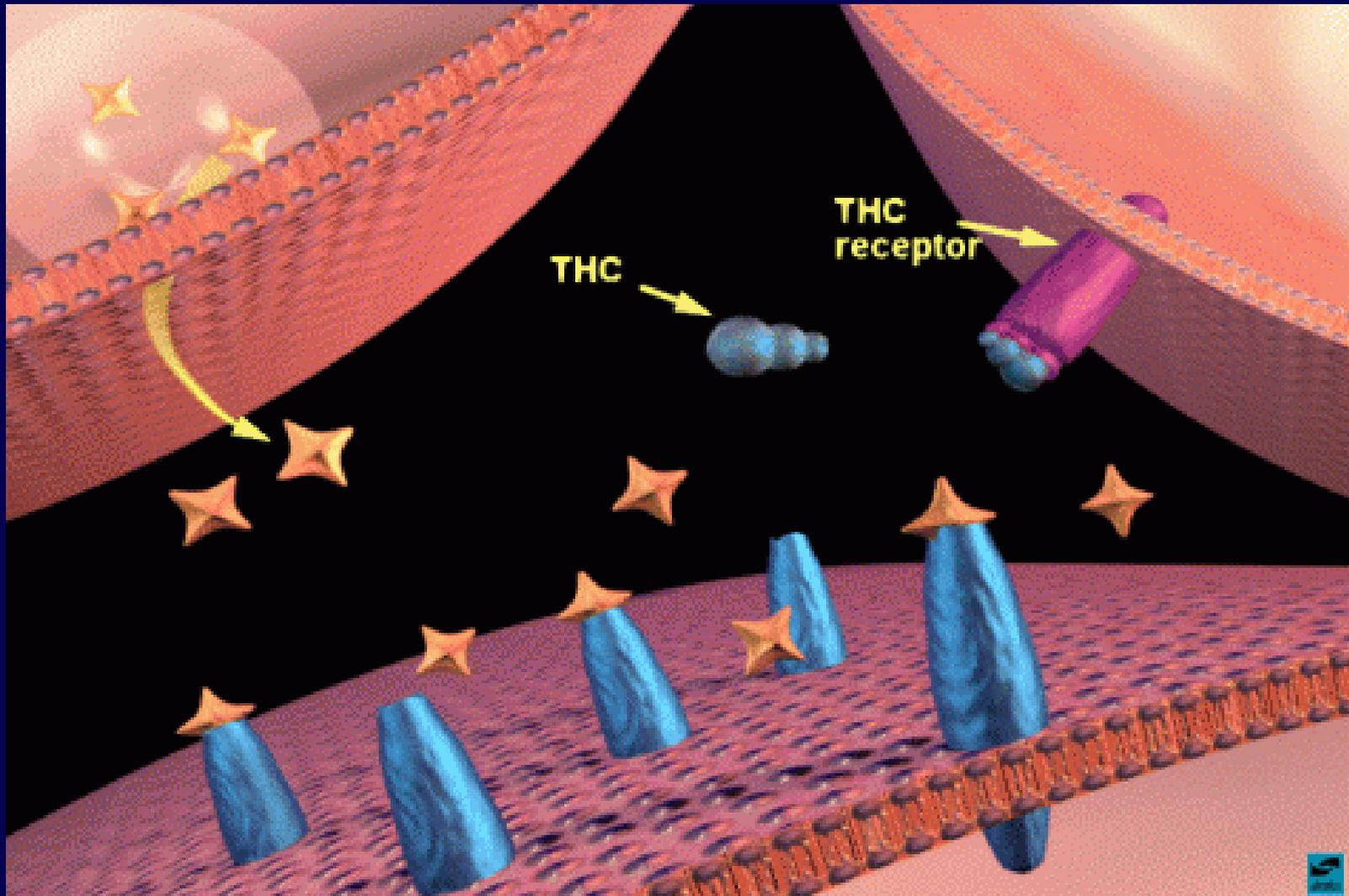
HU-331



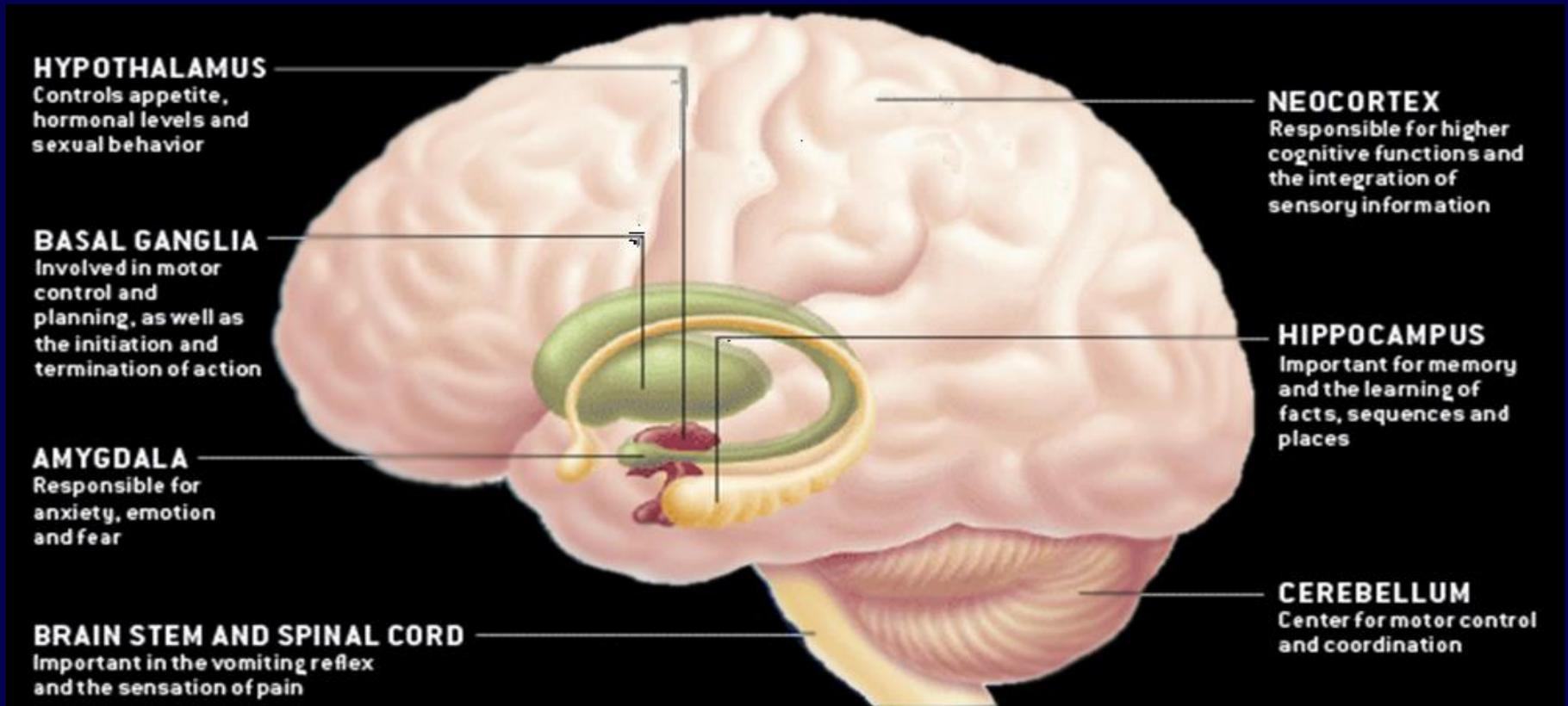
THC acts on receptors located on the presynaptic neuron



**THC binding to THC receptors in the nucleus accumbens:
increased dopamine release**



Where THC Acts in the Human Brain



Contrary to the partial action of THC at the CB1 receptor, synthetic cannabinoids identified so far in Spice products have been shown to act as full agonists with increased potency, which leads to longer durations of action and an increased likelihood of adverse effects.

Synthetic Cannabinoids Popularity and Appeal

- can induce strong cannabis-like psychoactive effects
- readily available on the Internet
- still legal in many countries
- marketed as natural safe substances
- undetectable by conventional drug screening tests

... but we know next to nothing in terms of pharmacology, toxicology, and safety

PSYCHOTIC EFFECTS

- **Anxiety** is often experienced during acute intoxication, resolving within 1-2 h.
- **Paranoia, hallucinations**, alterations in mood and perception in some patients
- **Sudden depression** and extreme anxiety during withdrawal from chronic Spice
- High potency may be due to higher CB affinity and absence of CBD (anxiolytic)

PERIPHERAL EFFECTS

- **GI**: nausea, vomiting, and retching most common after consumption of Spice
- **CV**: elevated heart rate and blood pressure, chest pain, and cardiac ischemia
- Inappropriate laughter, injected conjunctiva, dry mouth, and nystagmus
- **Metabolic**, such as hypokalemia, hyperglycemia, and acidosis
- **Autonomic**, such as fever and pupil dilation

LETHAL EFFECTS

- Reports of coma and suicide attempts after smoking K2
- Two adolescents died of coronary ischemia after ingestion of K2
- One teen reportedly committed suicide due to extreme anxiety
- The non-cannabinoid ingredient *Odesmethyltramadol* is an opioid agonist, which when used in combination with *Kratom* (as in the mixture known as Krypton), may have lethal consequences.

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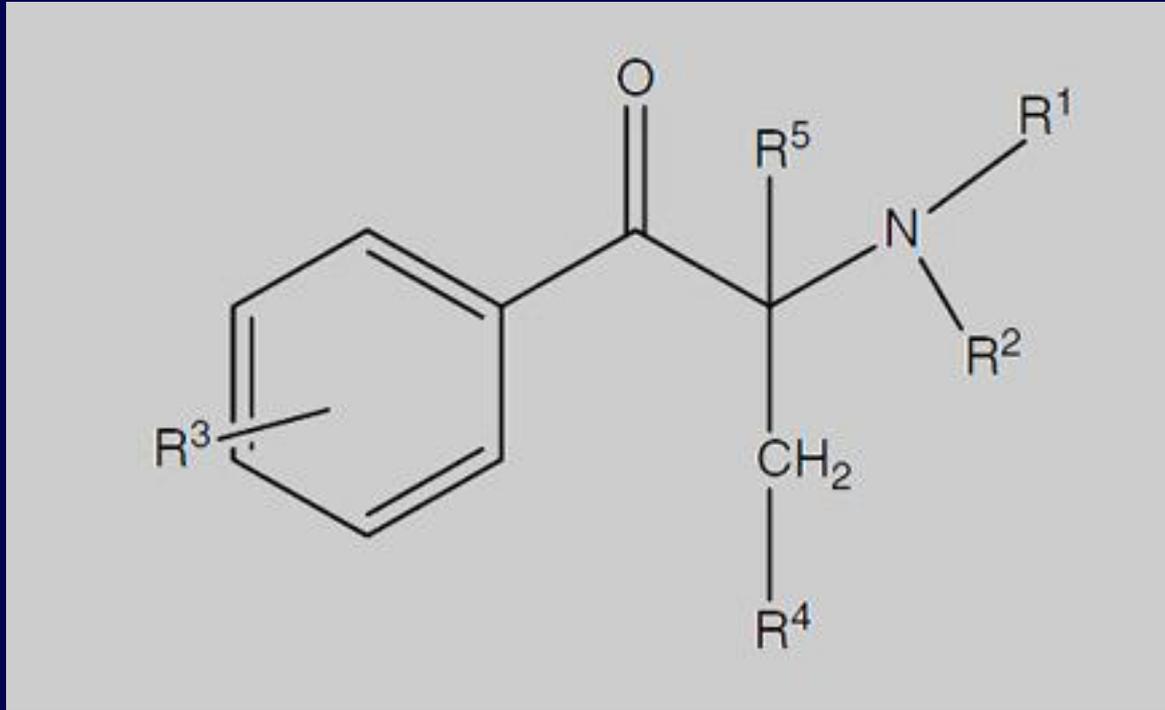
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Bath salts

mephedrone, mephylone, methylenedioxypropylone (MDPV)

Generic Structure of Cathinone Derivatives

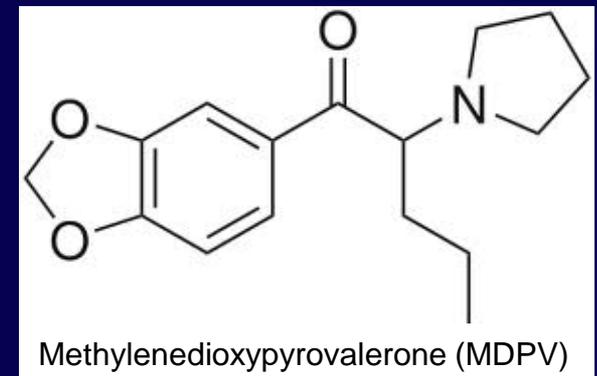
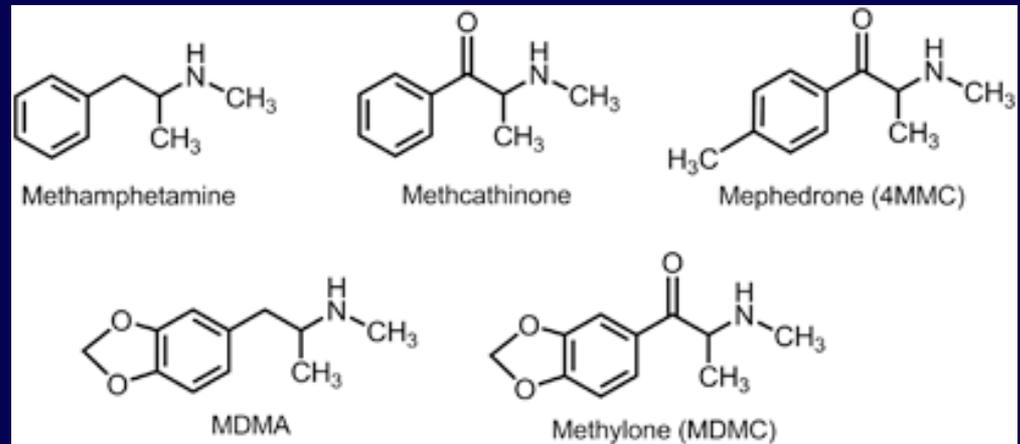
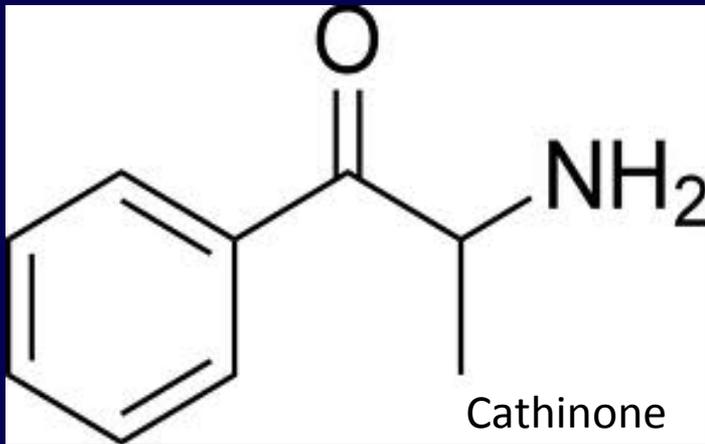


Cathinone is the principal active constituent of khat and responsible for the stimulant effects of this so called “natural amphetamine”

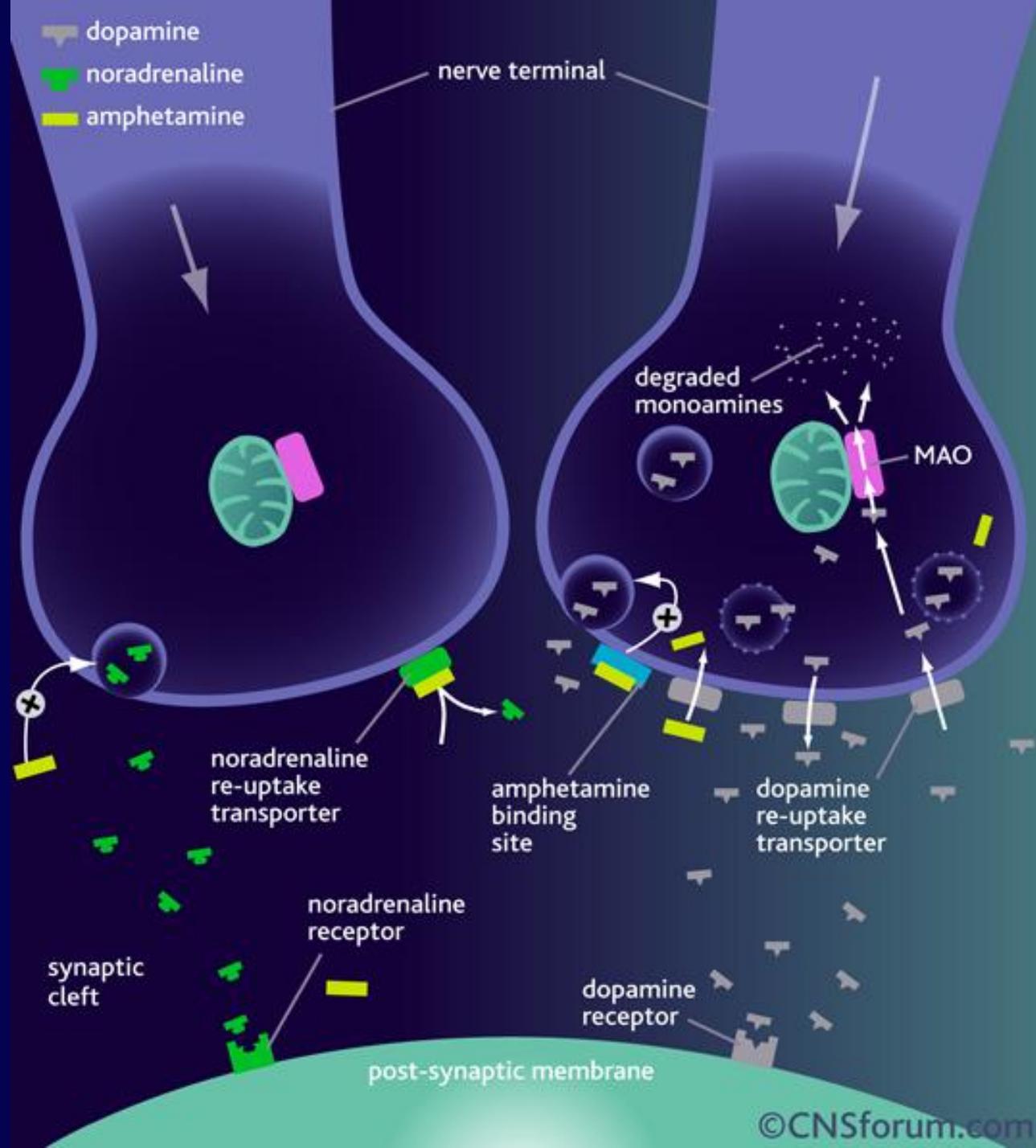
Chemical structure of Cathinone derivatives

| | | | | | | |
|---|---|--------------|--------------------|--------|--------|-------------------|
| Cathinone | H | H | H | H | H | [31] |
| α -phthalimidopropiophenone | NR ² B ³ = phthalimide | | H | H | H | [32] |
| Methcathinone (ephedrone) | Methyl | H | H | H | H | [33] |
| 2-(methylamino)-1-(3-bromophenyl)propan-1-one (3-BMAP) | Methyl | H | 3-Br | H | H | [34] |
| 2-(methylamino)-1-(4-bromophenyl)propan-1-one (4-BMAP) | Methyl | H | 4-Br | H | H | [34] |
| <i>N,N</i> -Dimethylcathinone (metamfepramone) | Methyl | Methyl | H | H | H | [31] |
| <i>N</i> -Ethylcathinone (ethcathinone, EC) | Ethyl | H | H | H | H | [32] |
| 2-methylamino-1-phenylbutan-1-one (buphedrone) | Methyl | H | H | Methyl | H | No published data |
| 4-Methyl- <i>N</i> -ethylcathinone | Ethyl | H | 4-Methyl | H | H | [19] |
| 4-Methylmethcathinone (mephedrone; 4-MMC; M-CAT) | Methyl | H | 4-Methyl | H | H | [35] |
| Diethylpropion (Diethylcathinone; amfepramone) | Ethyl | Ethyl | H | H | H | [31] |
| 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone (Bupropion) | <i>t</i> -Butyl | H | 3-Cl | H | H | [36] |
| 2-(<i>iso</i> -propylamino)-1-phenylpropan-1-one (<i>i</i> -PAP) | Isopropyl | H | H | H | H | [34] |
| 2-(<i>tert</i> -butylamino)-1-phenylpropan-1-one (<i>t</i> -BAP) | <i>t</i> -Butyl | H | H | H | H | [34] |
| 3,4-Methylenedioxyethcathinone (Methylone; bk-MDMA) | Methyl | H | 3,4-Methylenedioxy | H | H | [37] |
| 3,4-Methylenedioxyethcathinone (Ethylone; bk-MDEA) | Ethyl | H | 3,4-Methylenedioxy | H | H | [38] |
| β -keto- <i>N</i> -methyl-3,4-benzodioxolylbutanamine (Butylone; bk-MDBD) Pentylone (bk-MBDP) | Methyl | H | 3,4-Methylenedioxy | Methyl | H | [38] |
| 4-Methoxymethcathinone (Methedrone; bk-PMMA) | Ethyl | H | 3,4-Methylenedioxy | Methyl | H | [39] |
| 4-Fluoromethcathinone (Flephedrone, 4-FMC) | Methyl | H | 4-F | H | H | [18] |
| 3-Fluoromethcathinone (3-FMC) | Methyl | H | 3-F | H | H | [18] |
| 2-Fluoromethcathinone (2-FMC) | Methyl | H | 2-F | H | H | [18] |
| α -Pyrrolidinopropiophenone (α -PPP) | | Pyrrolidinyl | H | H | H | [41] |
| 4-Methyl- α -Pyrrolidinopropiophenone (MPPP) | | Pyrrolidinyl | 4-Methyl | H | H | [42] |
| 4-Methoxy- α -Pyrrolidinopropiophenone (MOPPP) | | Pyrrolidinyl | 4-Methoxy | H | H | [43] |
| 4-Methyl- α -Pyrrolidinohexiophenone (MHPH) | | Pyrrolidinyl | 4-Methyl | Propyl | H | No published data |
| 1-(4-methylphenyl)-2-(1-pyrrolidinyl)pentan-1-one (Pyrovalerone) | | Pyrrolidinyl | 4-Methyl | Ethyl | H | [44] |
| α -Pyrrolidinobutiophenone (α -PBP) | | Pyrrolidinyl | H | Methyl | H | No published data |
| α -Pyrrolidinovalerophenone (α -PVP) | | Pyrrolidinyl | H | Ethyl | H | [45] |
| 4-Methyl- α -Pyrrolidinobutiophenone (MPBP) | | Pyrrolidinyl | 4-Methyl | Methyl | H | [46] |
| 4-Methyl- α -Pyrrolidino- α -methylpropiophenone | | Pyrrolidinyl | 4-Methyl | H | Methyl | [46] |
| 3,4-Methylenedioxy- α -pyrrolidinopropiophenone (MDPPP) | | Pyrrolidinyl | 3,4-Methylenedioxy | H | H | [37] |
| 3,4-Methylenedioxypyrovalerone (MDPV) | | Pyrrolidinyl | 3,4-Methylenedioxy | Ethyl | H | [46] |
| 3,4-Methylenedioxy- α -pyrrolidinobutyrophenone (MDPBP) | | Pyrrolidinyl | 3,4-Methylenedioxy | Methyl | H | [47] |
| 1-naphthalen-2-yl-2-pyrrolidin-1-yl-pentaon-1-one (β -naphyrone) | | Pyrrolidinyl | benzyl | Ethyl | H | [39] |

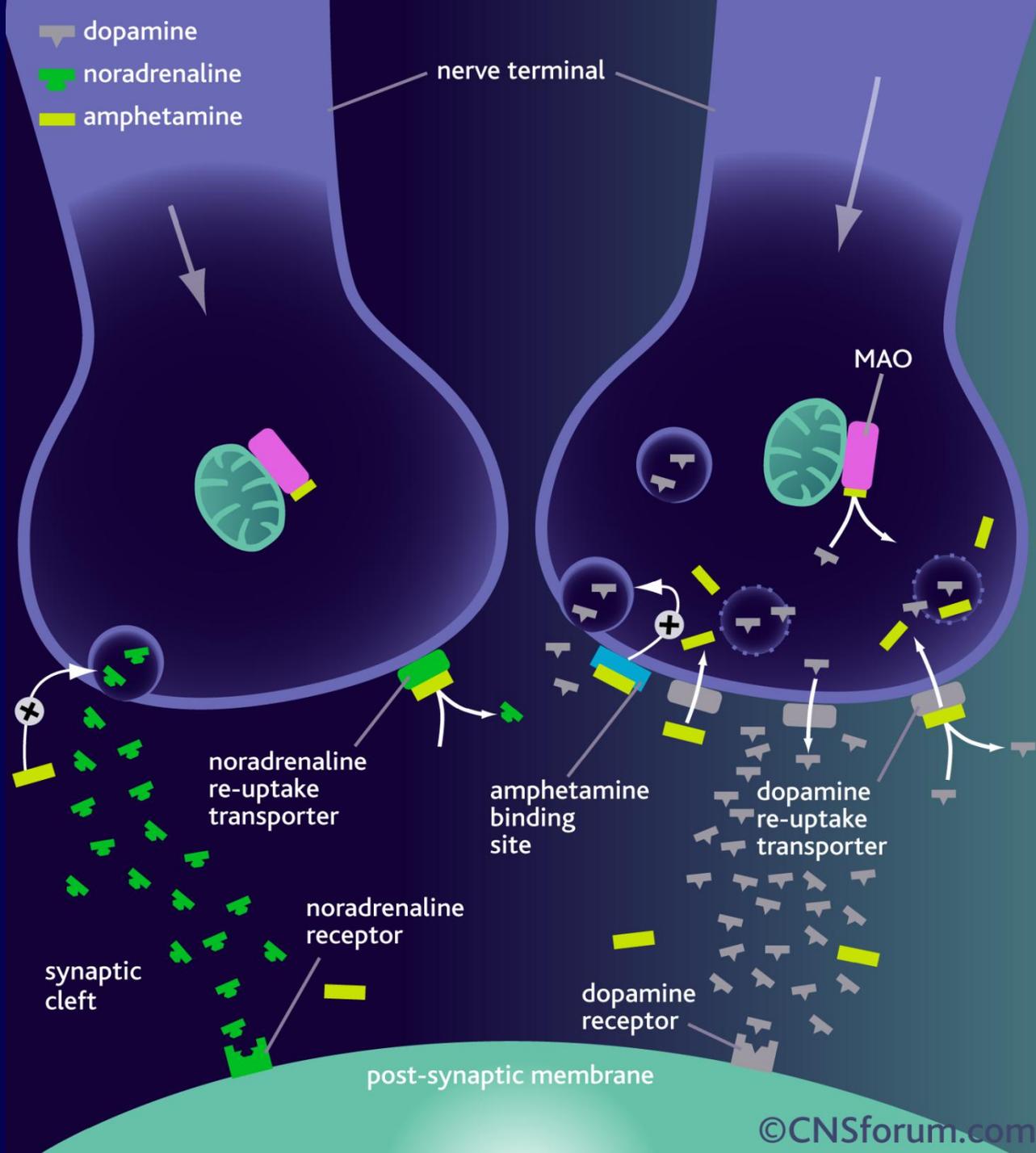
Chemical structures of designer methcathinone analogs and related compounds



At low doses
amphetamine acts on
catecholaminergic
synapses to inhibit the
reuptake of NE or DA

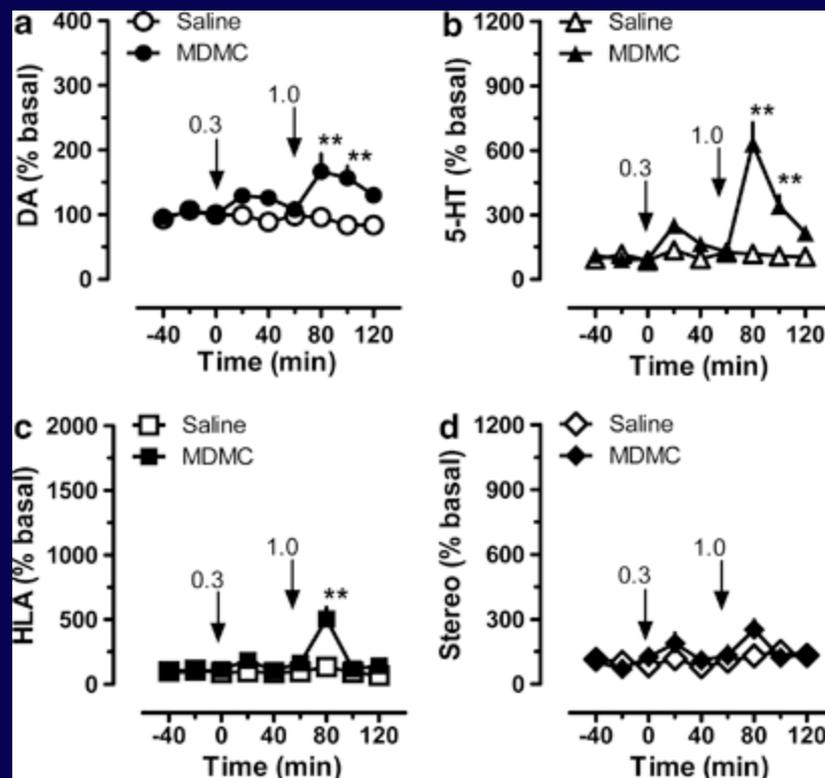
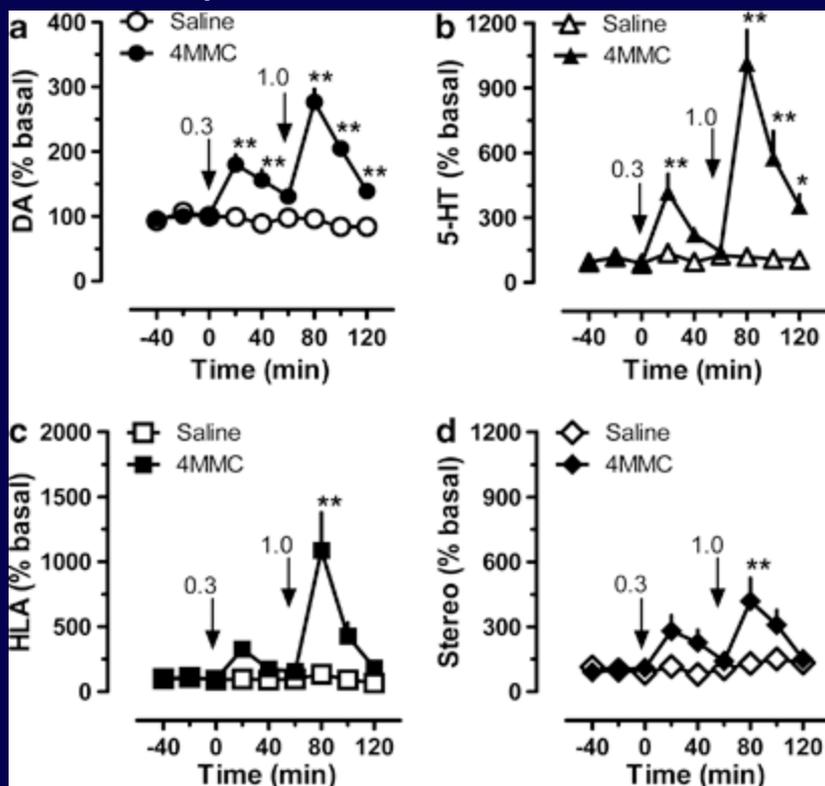


At high doses it can also trigger direct release of internal vesicles that are filled with these neurotransmitters.



Mephedrone and Methytlone

Potent substrates for monoamine transporters in rat brain, with a capacity to trigger dopamine and serotonin release that more closely resembles MDMA than methamphetamine



However, even though they induce hyperthermia, they do not deplete brain tissue 5-HT

3,4-Methylenedioxypropylamphetamine (MDPV) toxicology

Case report.

25-year-old man who injected bath salts and developed:

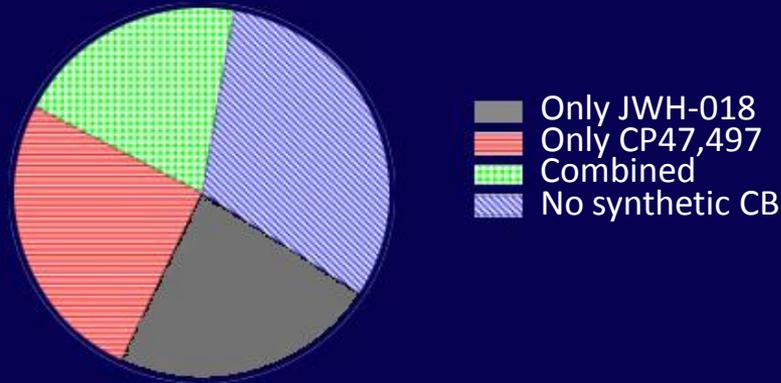
- severe agitation
- hyperthermia
- tachycardia

In spite of aggressive dialysis he progressed to multi-organ system failure due to rhabdomyolysis, cardiac injury, hepatic injury, and renal failure.

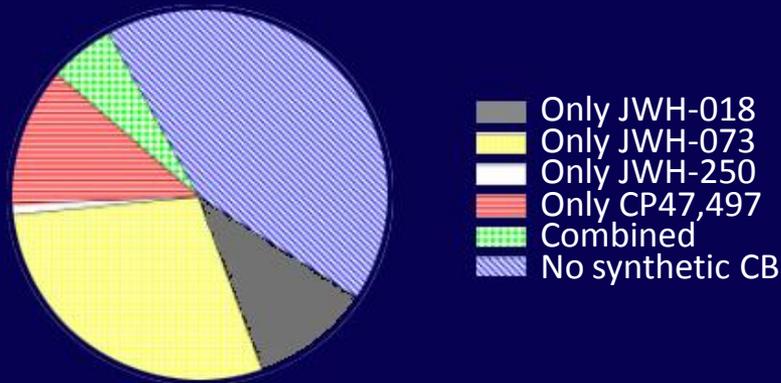
He ultimately recovered after a prolonged hospital course.

A comprehensive toxicologic test revealed MDPV as the only chemical substance

On January 22nd 2009 Germany instituted legal control of Spice of synthetic cannabinoids



Distribution of synthetic cannabinoids in 'Spice' products before



Distribution of synthetic cannabinoids in 'Spice' products after