Découvertes des cannabinoïdes de synthèse
Aspects historiques

Prof Robert WENNIG

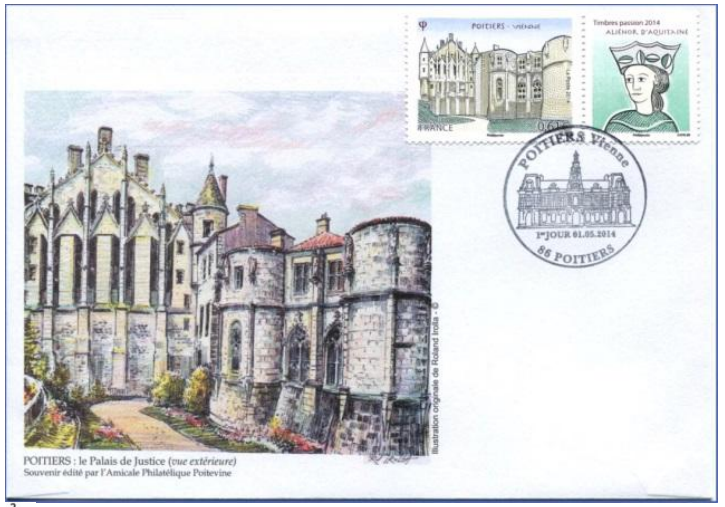
Retired from Work, not Life

Laboratoire **N**ational de **S**anté
Toxicologie

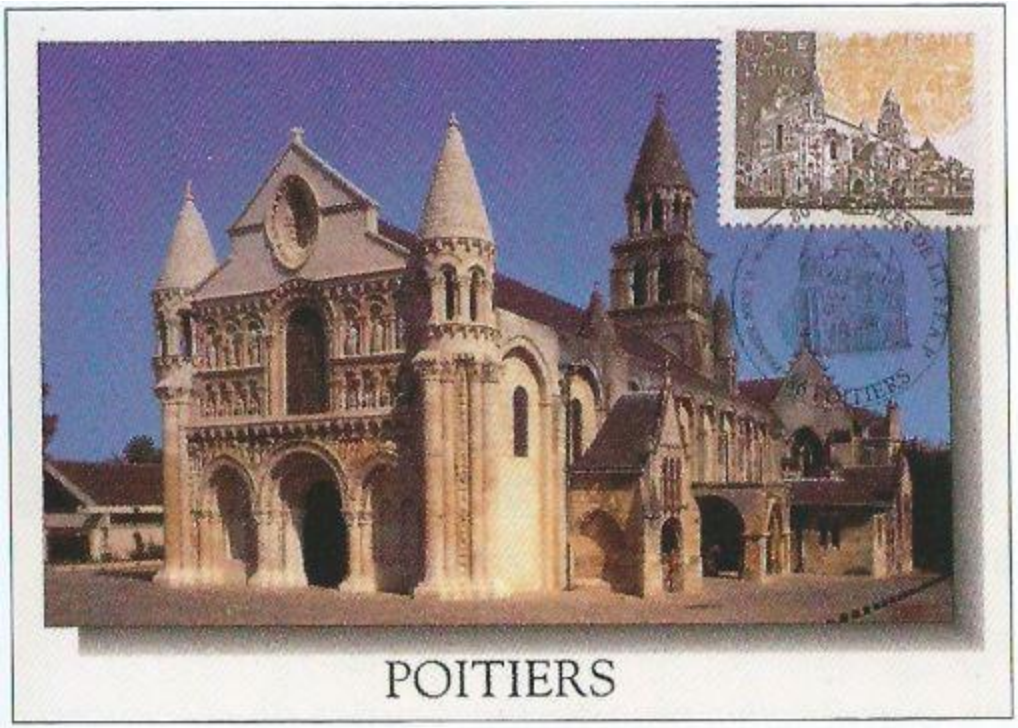
Journée scientifique SFTA & CHU Poitiers

Futuroscope, Septembre 2014

Souvenirs philatéliques de Poitiers



Le Futuroscope en 10 timbres



Chronologie succincte des événements «Spice»

2004 - 2007

Parution en Europe comme alternative légale au cannabis d'herbes suspectes diffusées par la firme *Psyche Deli* de Londres

Selon Financial Times ⇨ Bilan de £65.000 en 2006 à £899.000 en 2007

Notamment discussions sur forums en ligne & comportements anormaux au volant ☞ souvent dépistages biologiques de cannabinoïdes négatifs

2007 Suède

Notification saisies Spice par NFP-REITOX via EWS à l'OEDT

2008 Allemagne

BKA (Pütz) & universités Freiburg i.Br (Auwärter) & Homburg (Krämer)

☞ analyses d'échantillons saisies par autorités

⇨ ni détection de cannabinoïdes naturels, ni alcaloïdes marqueurs des herbes déclarées, mais eucalyptol & tocophérol identifiés

Prévention drogues de Frankfurt demande firme THC-Pharma (Rönitz H, Steup C)

☞ intuition ⇨ Cannabinoïdes synthétiques

CP-47,497-homologue-C8 et JHW-018 dans certains échantillons

THC- Pharma GmbH à Frankfurt/Main = producteur, distributeur de standards & produits phytosanitaires et activités de recherche sur potentiel thérapeutique de cannabinoïdes synthétiques e.a. dronabinol

Catalogue avec 25 cannabinoïdes synthétiques & 31 phytocannabinoïdes

2008 Autriche

AGES PharmMed ⇨notification JWH-018 au OEDT(qq jours plus tard)

Prof Volker Auwärter

Institut de Médecine Légale
de l'Université de Freiburg-im-Breisgau

Coordinateur Projets Européens "Spice" et "Spice II plus"

Expérimentation sur soi-même avec dose 0,3 g de Spice acheté en ligne

⇨ Premiers symptômes après 10 min, max à 30 min - durée 4h à 6h
Tachycardie, xérostomie, légère ébriété, humeur & perception modifiées
fort sentiment subjectif de troubles, non confirmés par tests psychologiques
séquelles perceptibles le lendemain

Auwärter V, Dresen S, Weinmann W, Ferreirós N. «Spice». Toxichem + Krimtech 75:127-129 (2008)

Dresen S, Ferreirós N, Pütz M, Westphal F, Zimmermann R, Auwärter V. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. J Mass Spectrom. 45:1186-1194 (2010)

Michael Pütz

Office fédéral de police judiciaire (en allemand *Bundeskriminalamt*) BKA - KT34 à Wiesbaden, Hessen

Co-Organisateur avec V. Auwärter de la 1ière conférence internationale de „Prévention Spice“ en septembre 2013 à Frankfurt/Main

⇨ ***„Les consommateurs de cannabinoïdes synthétiques sont des cobayes tout à fait insouciants des conséquences sanitaires“***

Coordinateur projet Européen "Spice-Profiling“ EU-ISEC-"Fight against and prevention of crime" de 2015 à 2017 avec V. Auwärter, Police scientifique de Lyon & Douane finlandaise

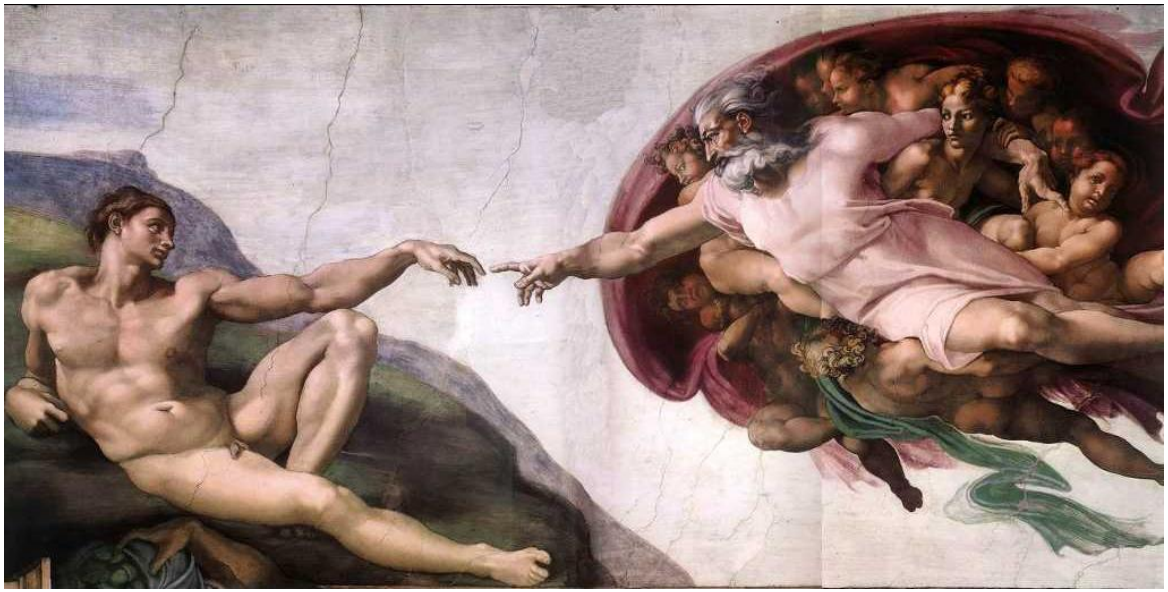
Travaux préliminaires dans mémoire de Master à l’Université Fresenius d’Idstein par S. Münster-Müller présentés à 20th IMSC août 2014 à Genève ☞ détection des impuretés de synthèse & contaminants (Pb) pour comparer les charges (profils)

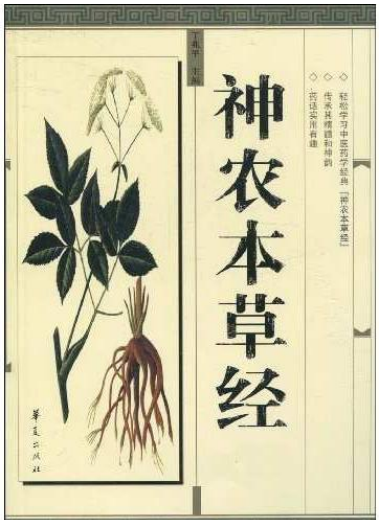
Münster-Müller S. Isolation and structural elucidation of synthetic cannabinoids and related synthesis impurities in „Spice“ Products via MSn and NMR. Université Fresenius, Idstein 2014

Histoire du Cannabis - La création d' Adam

Fresque du plafond Chapelle Sixtine au Vatican

Michelangelo di Lodovico Buonarroti Simoni (1475 - 1564)





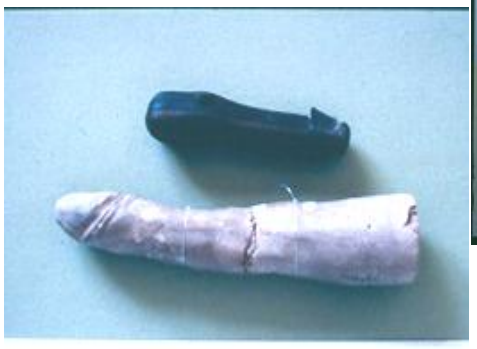
On ne nous a pas tout dit

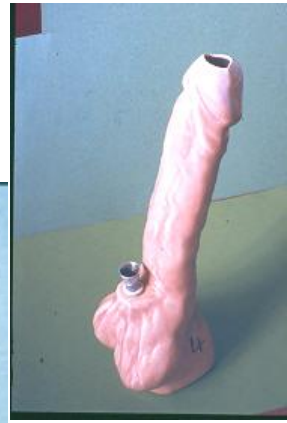
Hachich = arabe Herbe, Herbes

Mentionné en 2800 AEC dans ouvrage Chinois
***Shennong bencao jing* 神農本草經 / 神农本**
sur plantes agricoles & médicinales

Cannabis utilisé par tout le monde et sans limite d'age

Favoris des Baby-Boomers (les 50 à 60 ans)

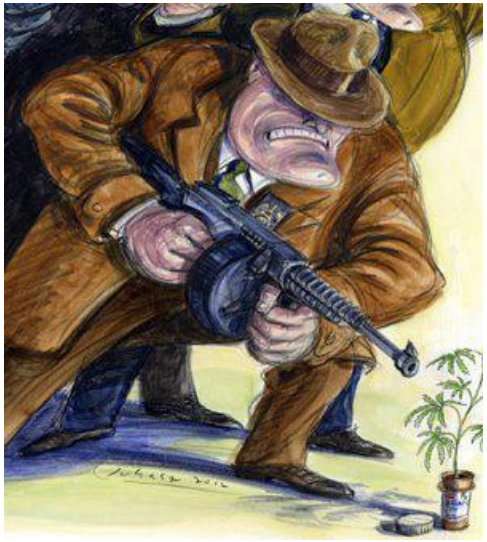




Shillums pour dames

Cannabis thérapeutique vs Légalisation

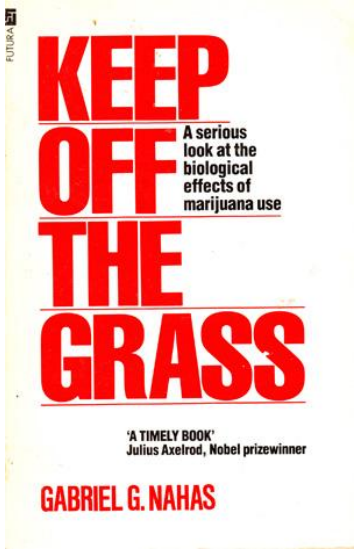
Un des arguments pour légaliser le cannabis
= pour éviter les cannabinoïdes synthétiques

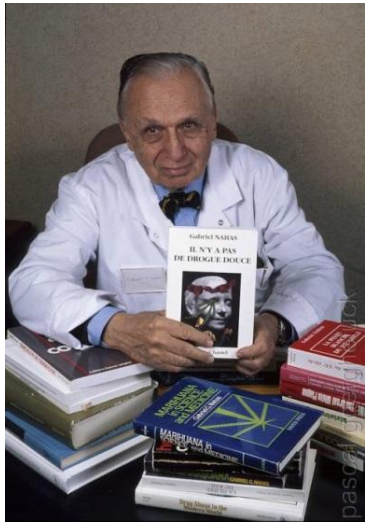


Cannabis thérapeutique vs Légalisation

Gabriel Georges Nahas (1920-2012) de mère française et de père libanais
= médecin connu pour sa plaidoirie contre l'utilisation et la libéralisation du cannabis, professeur à Columbia et New York University

NAHAS G. Haschich, cannabis et marijuana. Le chanvre trompeur. Presses Universitaires de France, 1976





Gabriel G Nahas

Esther Benbassa, sénatrice écolo du Val de Marne

- ⇨ **déposition d'une proposition de loi le 28 Janvier 2014 au Sénat avec l'idée de confier la culture du cannabis,vente et distribution à l'État, plutôt qu'aux réseaux clandestins des trafiquants**

Cannabis thérapeutique vs Légalisation

Utilisation légale ou tolérée dans certains pays

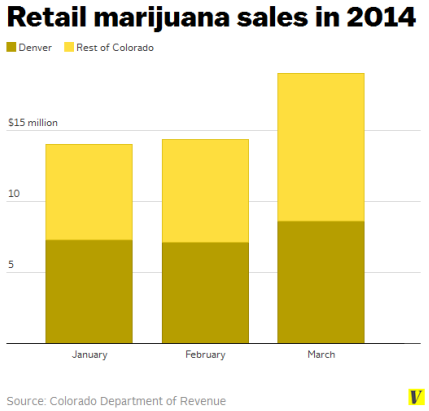
SATIVEX = CBD +THC
contre spasticités sévères en cas de sclérose en plaques

CESAMET= Nabilone
MARINOL = Dronabinol
contre nausées en chimiothérapie

BEDROCAN, BEDROBINOL & BEDIOL
= types de cannabis médicinal au Pays-Bas
contre douleurs neuropathiques

ACOMPLIA ou SR141716 = Rimonabant = agoniste inverse des récepteurs CB_1
= anorexigène, contre l'obésité & sevrage tabagique
EMA⇨ retiré du marché en 2008 ☞ risque de suicide ⇗

Cannabis thérapeutique vs Légalisation



Le 7 juillet 2014 New York = 23e État US autorisant le cannabis médical, prescrit & distribué par des praticiens certifiés, uniquement à des personnes souffrant de cancer, SIDA, sclérose latérale amyotrophique, maladie de Parkinson, sclérose en plaques et épilepsie

Californie = premier État à initier le mouvement en 1996

Herbal Mixtures for Bio-Trip

Herbal Smoking Mixtures aka Herbal Mix for Bio-Smoke, Herbal Blends, Herbal Incense

= exotic Herbs with alleged psychotropic Properties according to Dealers

a.o. London Company *Psyche Deli* up to 2008 Legal Alternative for Cannabis

advertised On-Line as 'exotic Incense Blend releasing a rich Aroma' and 'Not for Human Consumption'

Consumers described either Cannabis-like Effects or no Effects at all

⇨ Addition of synthetic active Ingredient to some Herb Mix?

Abuse Patterns

Inhalation of fumigated Herb Mix or Smoking, rarely as Infusion

Duration of Action < 8 h

Symptoms

Nearly similar to Cannabis (if active): Euphoria, Dizzinesss

Ataxia, Confusion, Somnolence, Anxiety &Tachycardia

However ☞ Case Reports & Surveys

⇨identified serious Side Effects (if high Dose ?) incl. Withdrawal Syndrome Hallucinations, Paranoia, Panic Attacks & Violence, Hypokalaemia, typically not associated with natural Cannabis ⇨ some Users requiring ER Treatment

Herbal Mixtures for Bio-Trip

Herbs could be obtained from Head Shops, Smart Shops, Gas Stations Liquor Stores, Convenient Stores, Smoke Shops (commerces de proximité)

☞But mainly On-Line through Internet

3 g sufficient for approx. 8 joints for 26 to 30 EUR

Different Brand Names

Spice, K2, Yucatan Fire, Herbal Incense, Sence, Smoke, Chill-X , Black Mamba (Turnera diffusa), Manga Xtreme, Fake Weed, Bombay Blue, Skunk, Bliss, Blaze, Moon Rocks, encens, pot-pourri, pot, ….

Herbal Mixtures for Bio-Trip

Toxicological Analysis ⇨ Admixture of synthetic Drugs confirmed

Some Herb Mixes = Carriers only for sprayed highly concentrated Extracts of Endocannabinoid-Receptor Agonists

with considerable intra -&- inter Variability

☞ **Substances developed by Pharmaceutical Companies & Universities, now synthesized in China,Taiwan & Ukraine**

Both scientific and anecdotal Evidence suggest ⇨these Agonists are being widely used, have stronger CB_1 Affinities & up to 800 X more potent than THC

EMCDDA Thematic Paper-Understanding the « Spice » phenomen

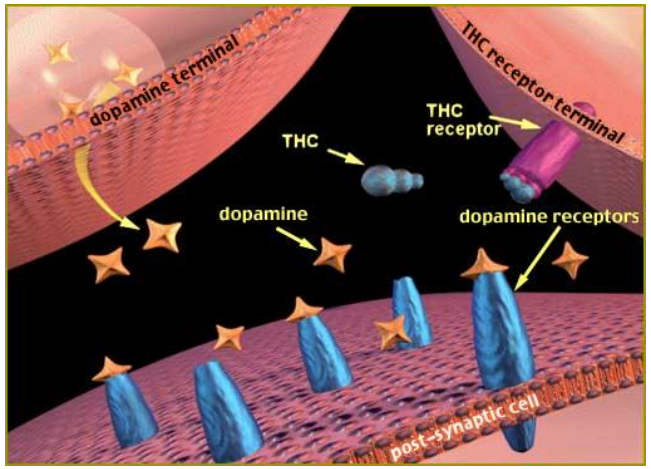
Luxembourg-Office for Official Publications of the European Union, 2009, 37pp

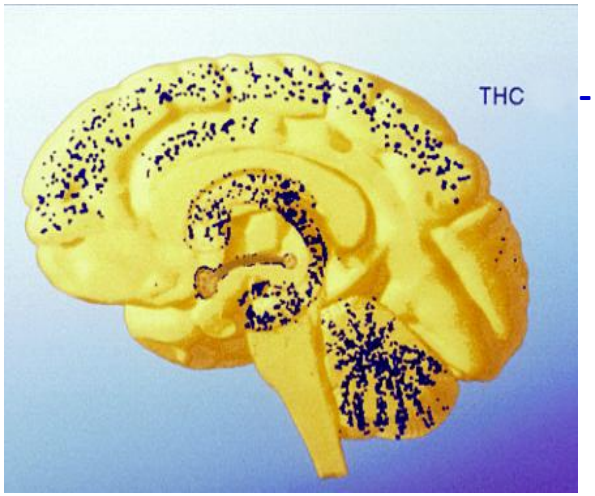
Appendino G, Minassi A, Taglialatela-Scafati O. Recreational drug discovery: natural products as lead structures for the synthesis of smart drugs. Nat Prod Rep 31: 880-904(2014)

Since the Bans ⇨ most Mixes disappeared from Internet & Head Shops

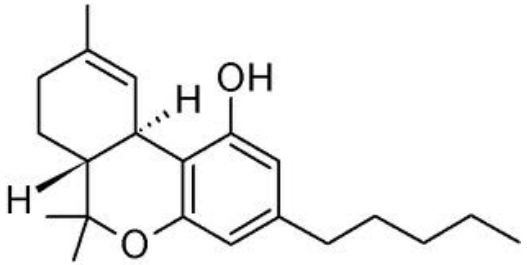
Some are still available as Space or other Brands

Distribution of Endocannabinoid CB_1Receptors in Brain





- CB_1Receptors Distribution in CNS



Mode of Action

THC = partial Agonist of CB_1 and CB_2 = G_i-Protein-coupled Membrane Receptors involved in Nociception

⇨ Inhibition of Adenylcyclase, preventing cAMP-Signalling ⇨ Neuronal Activity ⇘

CB_1 predominately in CNS = related to Mood, Stress, Appetite, and Memory

Other neuronal Systems = also modulated

CB_1 absent in *Medulla oblongata*, involved in vital basic Cardiovascular and Respiratory Functions ⇨ why even in massive THC Overdose no Death occurs

CB_2 = predominately in Immune Cells in peripheral Vascular System & CNS related to Suppression of Immune Cell Function & Pain

Canavalia maritima
Meeresbohne
Baybean
Haricot-bord-de-mer

Nymphaea caerulea
Blaue Lotusblume
Blue Lotus
Lotus bleu

Nelumbo nucifera
Indischer Lotus
Indian Lotus
Lotus sacré
ou Lotus d'Orient

Scuttelaria nana
Helmkraut
Dwarf Scullcap
Scutellaire naine à casque

Leonorus sibiricus
Marihuanilla
Chinese Motherwort
Marijuanilla

Leonotis leonurus
Afrikanisches Löwenohr
Lion's Tail
Queue de lion

Pedicularis densiflora
Indian Warrior
Herbe du Guerrier Indien

Zornia latifolia
Maconha Brava
Fausse marijuana

Spice Ingredients according to Manufacturers

French Herbs Names	Latin Names	Identified Fingerprint psychotropic Molecules
Haricot-bord-de-mer	*Canavalia maritima*	l-Betonicine
Lotus bleu	*Nymphaea caerulea*	Nuciferine, Aporphine
Lotus sacré ou Lotus d'Orient	*Nelumbo nucifera*	Nuciferine, Aporphine
Scutellaire naine à casque	*Scuttelaria nana*	Scutellarine (Flavonoide)
Marijuanilla	*Leonorus sibiricus*	Leonurine Leosiberine (Diterpene)
Queue de lion	*Leonotis leonurus*	Leonurine
Herbe du Guerrier Indien	*Pedicularis densiflora*	Aucubine Betulic Acid (Triterpene)
Fausse marijuana	*Zornia latifolia*	no Ingredient identified

Some of these Plants have been traditionally used as Cannabis Substitutes

Flavouring Additives: Roses, Honey or Vanilla, etc and Vit E =Tocopherols

So far identified Common Herbs

Tussilago farfara **aka Coltsfoot, pas d'âne, chasse-toux, chou de vigne**

= perennial herbaceous of Asteraceae Plant Family

used as "Cough Suppressant" in traditional Medicine

Discovery of mutagenic Pyrrolizidine Alkaloids Senecionine & Senkirkine in Genotoxicity Tests ⇨Liver Health Concerns

Melissa officinalis **aka Lemon Balm, mélisse**

= perennial Herb of Lamiaceae Mint Family

Thymus vulgaris **aka Garden Thyme, thym, serpolet (350 Spp) of aromatic perennial herbaceous Plants of Lamiaceae Family**

Mentha aquatica **aka Mint, menthe (69 Spp)**

perennial Herb of Lamiaceae Family

Other Alleged Cannabis-like Effects from Herbal Products

Hortensia - Hydrangeaceae

Smoked dried Leaves or Flowers

= alleged to have Cannabis-like Effects

No THC detected

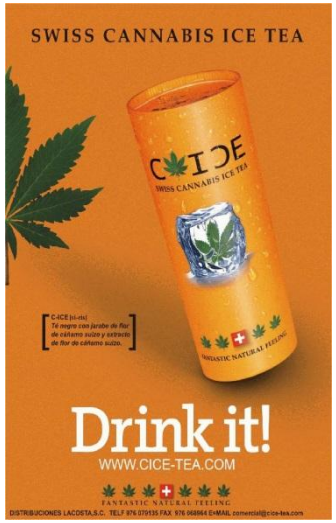
Hydrangenol = iso-Coumarin Derivative

responsible for Contact Dermatitis

Hydrangea paniculata var. grandifolia

Swiss Cannabis Ice Tea

No THC detected

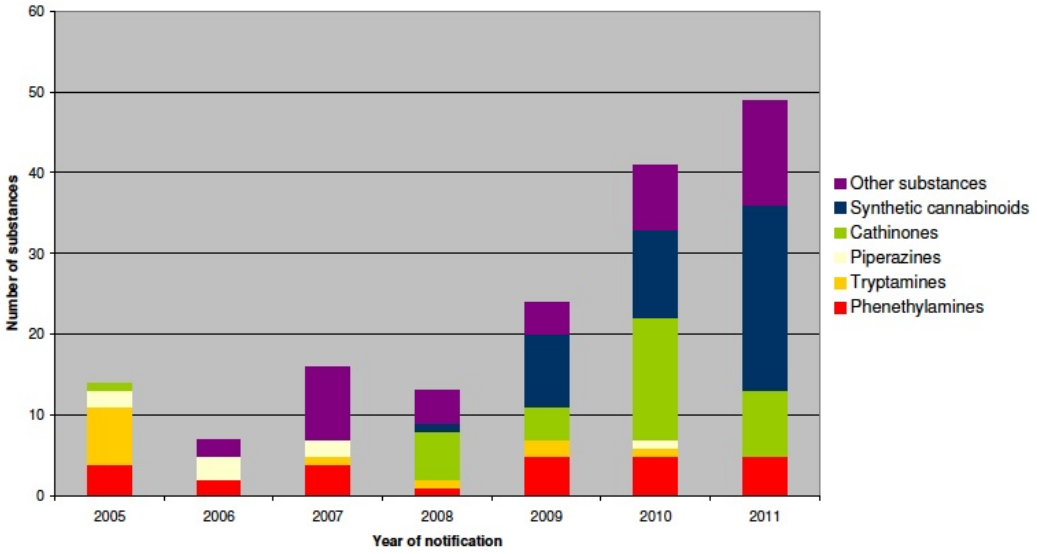


Epidémiologie Cannabis vs Spice

Europe

NPS Notifications par NFP-REITOX via EWS au OEDT, Lisbonne

Graph 1. Number of new psychoactive substances notified in 2005–11, by year



Sondage Royaume Uni en 2009

Selon les lecteurs de Mixmag 1 sur 8 des répondeurs ont consommé du spice ou similaire contre 85 % qui ont consommé du cannabis naturel

Retrospective Study in German State Hessen in 2010

Prevalence of 2.8% exposed to Herbal Mix with Synthetic Cannabinoids, from a representative Number of reanalyzed Blood Samples from Traffic & Criminal Offences Cases

Jaenicke NJ, Pogoda W, Paulke A, Wunder C, Toennes SW. Retrospective analysis of synthetic cannabinoids in serum samples - epidemiology and consumption patterns. Forensic Sci Int. 242: 81-87 (2014)

European Monitoring Centre for Drugs and Drug Addiction **EMCDDA** Observatoire européen des drogues et des toxicomanies

Number of Synthetic Cannabinoids of 14 Chemical Families detected through EWS = increasing Year on Year

JWH-018 first detected in Spice Products in 2008

9 reported in 2009

11 in 2010

23 in 2011

30 in 2012 among 73 NPS

29 in 2013 among 81 NPS

Total of 105 Synthetic Cannabinoids notified to EMCDDA as of January 2014

By 31 March 2014 an additional 5 have been reported

Spice in the US

Spice in USA according to UNODC World Report 2013
In 2012 identified NPS 151 vs 73 in Europe
of which 51 Synthetic Cannabinoids vs 30 in Europe

Feb 2009 RW Talk at Chief Medical Examiner's Office NYU

☞ **Synthetic Cannabinoids = totally unknown**

Borkenstein Drug Course Septembre 2014
Philadelphia, PA
Tuition 1500 USD

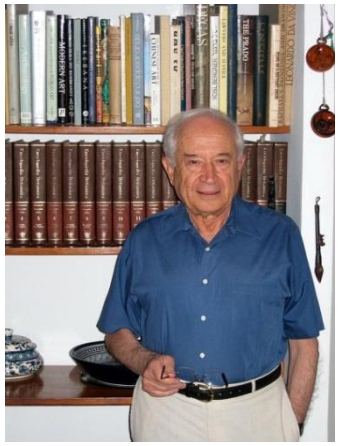
Synthèse d'analogues de cannabinoides

Les pionniers

Israel

Hebrew University of Jerusalem

Raphael Mechoulam (b 1930) = Professor of Organic & Medicinal Chemistry, Pharmacology of Cannabinoids: Isolation, Structure Elucidation, total Synthesis of Δ^9-THC & Congeners, Isolation and Identification of endogenous Cannabinoids Anandamide & 2-Arachidonoylglycerol (2-AG) from the Brain



Gaoni Y, Mechoulam R. Isolation,structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 86: 1646–1647 (1964)

Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 50:83-90 (1995)

Hanus L, Abu-Lafi S, Fride E, Breuer A, Vogel Z, Shalev DE, Kustanovich I, Mechoulam R. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB_1 receptor. Proc Natl Acad Sci U S A. 98:3662-3665 (2001)

Synthèse d'analogues de cannabinoïdes

August Kékulé

Les pionniers

Allemagne

Université rhénane Frédéric-Guillaume de Bonn

Friedhelm Korte (1923-2013)

1964 professeur de chimie organique & biochimie et à partir de 1972 de chimie environnementale à la TH München - Weihenstephan

Korte F, Sieper H.* On the *Chemical Classification of Plants XXIV. Investigation of Hashish constituents by thin layer chromatography. J Chromatogr 13: 90-98 (1964)

Claussen U, Korte F. Herkunft, Wirkung und Synthese der Inhaltsstoffe des Haschisch. Naturwiss 53: 542-546(1965)

Bieniek D, Gau W, Korte F. Hashish-chemistry and problems. Naturwiss. 61:117-121(1974)

Synthèse d'analogues de cannabinoïdes

Les pionniers

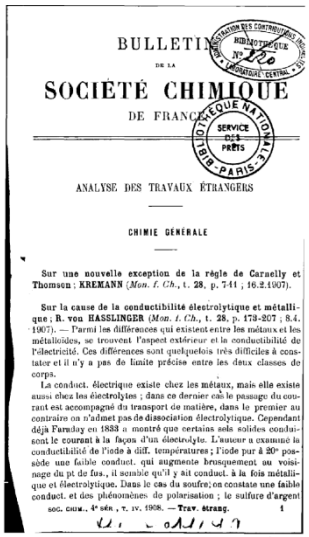
France

Strasbourg - Université Louis Pasteur (ULP)

Thèse de Jean-Bernard Chazan au laboratoire de chimie des substances naturelles ass. au CNRS dirigé par le Pr Guy Ourisson (1926-2006) président de l'ULP (1971à1976) et président de l'Académie des Sciences (2000 à 2001)

Guy Ourisson

Photo © Bernard Braesch, Service de la Communication-ULP



BULLETIN
DE LA
SOCIÉTÉ CHIMIQUE
DE FRANCE

ANALYSE DES TRAVAUX ÉTRANGERS

CHIMIE GÉNÉRALE

Sur une nouvelle exception de la règle de Carnelly et Thomson ; KREMANN (*Mon. f. Ch.*, t. 28, p. 741 ; 16.2.1907).

Sur la cause de la conductibilité électrolytique et métallique ; R. von HASSLINGER (*Mon. f. Ch.*, t. 28, p. 173-207 ; 8.4.1907). — Parmi les différences qui existent entre les métaux et les métalloïdes, se trouvent l'aspect extérieur et la conductibilité de l'électricité. Ces différences sont quelquefois très difficiles à constater et il n'y a pas de limite précise entre les deux classes de corps.

La conduct. électrique existe chez les métaux, mais elle existe aussi chez les électrolytes ; dans ce dernier cas le passage du courant est accompagné du transport de matière, dans le premier au contraire on n'admet pas de dissociation électrolytique. Cependant déjà Faraday en 1833 a montré que certains sels solides conduisent le courant à la façon d'un électrolyte. L'auteur a examiné la conductibilité de l'iode à diff. températures ; l'iode pur à 20° possède une faible conduct. qui augmente brusquement au voisinage du pt de fus., il semble qu'il y ait conduct. à la fois métallique et électrolytique. Dans le cas du soufre, on constate une faible conduct. et des phénomènes de polarisation ; le sulfure d'argent

SOC. CHIM., 4e SÉR., T. IV. 1908. — Trav. étrang. 1

ulp
UNIVERSITÉ LOUIS PASTEUR STRASBOURG

Cazan JB, Ourisson G. Tetrahydrocannabinol Analogues and related compounds. I. Condensation Compounds of Pulegone and Orcinol in Presence of $POCL_3$. Bull Soc Chim Fr 5e sér 35: 1374-1383 (1968)

Chazan JB, Ourisson G. Tetrahydrocannabinol Analogues and related compounds. II. Synthesis in Xanthene Series. Bull Soc Chim Fr 5e sér 35: 1384-1390 (1968)

Synthèse d’analogues de cannabinoïdes

Metz - Université Paul Verlaine

Pr Denise Cagnant (1921- 2005) Travaux sur composés hétérocycliques organo-sulfurés, organo-séléniques & organo-telluriques pour synthétiser des analogues du THC par Gilbert Kirsch & Pierre Seck au laboratoire de chimie organique du Collège Scientifique Universitaire de Metz, devenu Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique

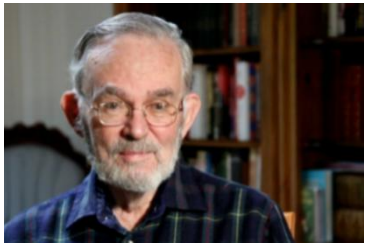
Seck P. Recherches dans la série des Dibenzo-Thiinnes molécules analogues du principe actif du hachisch. **Arch Inst GD Luxembourg. 37: 79-89(1977)**

Pierre Seck

Gilbert Kirsch

JW Huffman (b1932)

John William Huffman, educated at Northwestern & Harvard Universities = Organic Chemistry Emeritus Professor at Clemson University in S. Carolina who funded by NIDA, first synthesized 450 novel Cannabinoids since 1984, focused on making a Drug to target Endocannabinoid Receptors for Research related to Multiple Sclerosis, HIV/AIDS, and Chemotherapy



Synthesis & Pharmacology of Synthetic Cannabinoids

Many synthetic Methods have been published, requiring many Stages, from freely available Precursor Chemicals, sometimes complicated by enantiomeric Separations from Racemic Mixtures

Huffman JW, Lainton JA, Dai D, Jordan RD, Duncan SG Jr. Variation of the alkyl side chain in delta 8-THC. Life Sci. 56:2021-2024 (1995)

Huffman JW, Yu S, Showalter V, Abood ME, Wiley JL, Compton DR, Martin BR, Bramblett RD, Reggio PH. Synthesis and pharmacology of a very potent cannabinoid lacking a phenolic hydroxyl with high affinity for the CB_2 receptor. J Med Chem. 39:3875-3877(1996)

Aung MM, Griffin G, Huffman JW, Wu M, Keel C, Yang B, Showalter VM, Abood ME, Martin BR. Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB_1 and CB_2 receptor binding. Drug Alcohol Depend.60:133-140(2000)

Huffman JW, Zengin G, Wu MJ, Lu J, Hynd G, Bushell K, Thompson AL, Bushell S, Tartal C, Hurst DP, Reggio PH, Selley DE, Cassidy MP, Wiley JL, Martin BR. Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB_1 and CB_2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB_2receptor agonists. Bioorg Med Chem.13:89-112 (2005)

JW Huffman (b1932)

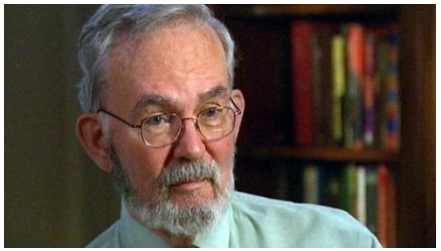


Illustration **How Molecules can take a Life of their own once they leave the Research Lab**

When in 2000s, 2 of his Cannabinoids being sold in Europe as Cannabis Alternatives, he said:

"I figured once it got started in Germany it was going to spread. I'm concerned that it could hurt People"

"I think this was something that was more or less inevitable. It bothers me that People are so stupid as to use this Stuff"

He may have developed these Compounds for Scientific Research, but now he gets blamed for its Abuse

As JWH-018 is more potent and easy to make, he believes it is the more widely used Synthetic Cannabinoid of the JWH Series

SPME-HS-GC-MS **Method** **for rapid & reliable Detection and Structural Identification of many synthetic Cannabinoid potentially be used in Herbal Smoking Mixtures**

Cox AO, Daw RC, Mason MD, Grabenauer M, Pande PG, Davis KH, Wiley JL, Stout PR, Thomas BF, Huffman JW. Use of SPME-HS-GC-MS for the analysis of herbal products containing synthetic cannabinoids. J Anal Toxicol. 36:293-302. (2012)

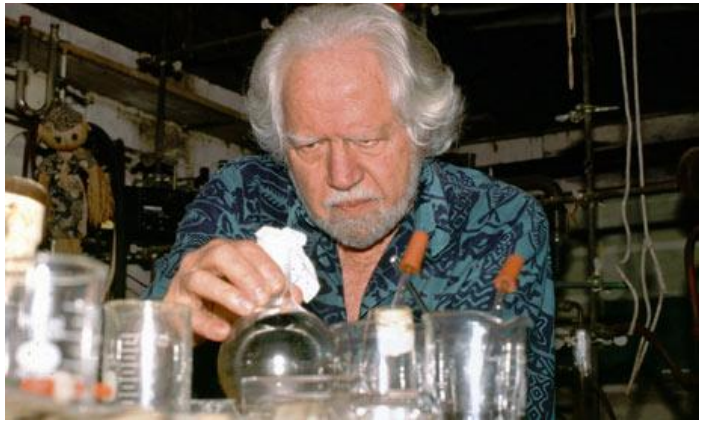
Alexander Sacha Shulgin (1925-2014)

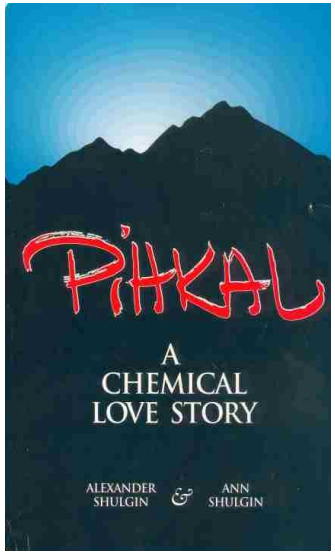
The Dude with a Doctorate

Décédé le 2 juin 2014
Après études de chimie à Harvard,1954 Doctorat en biochimie à l'Université de Berkeley, CA
A partir de 1960, *post-doctoral Research Fellow* en psychiatrie & pharmacologie à l'Université de Californie à San Francisco, directeur de recherches chez BioRad
Puis chimiste chez Dow Chemical Co ad 1965
Comme indépendant, enseignant aux hôpitaux de Berkeley et San Francisco
⇨ Synthèse de mescaline, DOM, MDMA, à partir de 1976 de centaines de psychotropes

Contrairement à Huffman, Shulgin = figure dans communauté psychédélique, dans sa quête de perfection, recherche d'une substance efficace et non toxique, puissante et contrôlable

Avec sa conjointe Ann, conduit des sessions psychédéliques de thérapie avec la MDMA





Familles chimiques des cannabinoïdes synthétiques

Naphthoylindoles (Groupe1)
JWH-007, JWH-015, JWH-018, JWH-019, JWH-073, JWH-081, JWH-098, JWH-116, JWH-122, JWH-149, JWH-182, JWH-193, JWH-198, JWH-200, JWH-210, JWH-398, JWH-424, AM-1220, AM-1221, AM-1235, AM-2201, AM-2232, MAM-2201(=4-Méthyl-AM-2201 ou 5-Fluoro-JWH-122)

Naphthylméthylindoles (Groupe 2)
JWH-175, JWH-184

Naphthoylpyrroles (Groupe 3)
JWH-030, JWH-147, JWH-307

Phénylacétylindoles (Groupe 4)
JWH-167, JWH-203, JWH-250, JWH-251, JWH-320, RCS-8

Benzoylindoles
AM-630, AM-679, AM-694, AM-1241, AM-2233, RCS-4

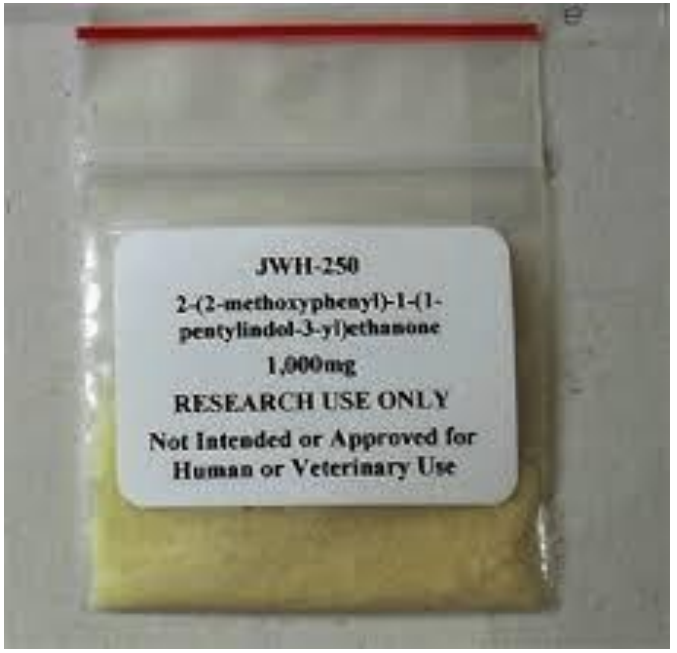
Naphthylméthylindènes
JWH-176

Cyclohexylphénols
CP-47,497et homologues, CP-55,490, HU-308

Adamantoylindoles
AB-001, AM-1248

Cyclopropanoylindoles
UR-144, 5F-UR-144 (ou XLR-11), A-834,735, A-796,260, AB-005

Autres cannabimimétiques
HU-210, HU-211, WIN-55,212-2



Nomenclature des cannabinoïdes synthètiques

Nombreux composés monitorés par le système d'alerte rapide EWS ont des noms de code reliés à leur découverte p.ex les initiales des scientifiques, des institutions ou sociétés qui les ont synthétisés pour le première fois

Composés HU dénommés d'après Hebrew University à Jerusalem

Composés JWH dénommés d'après John W. Huffman (Clemson Univ)

Composés AB & WIN dénommés resp. d'après Abbott ou Sterling-Winthrop

Composés AM dénommés d'après Alexandros Makriyannis (Northeastern Univ)

Composés RCS dénommés d'après un labo en Chine

D'autres composés sont dérivés de leurs longs noms chimiques

p.ex APICA de N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide

APINACA de N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide

Ou dans le but d'une meilleure commercialisation p.ex d'après des groupes Pop

Noms alternatifs pour APINACA = AKB-48 = groupe Japonais de girls de popularité similaire aux Spice Girls Britanniques

ou pour APICA = 2NE1 = groupe Coréen de girls

D'autre part le XLR-11, semble être dénommé d'après un combustible liquide pour fusées développé aux USA

Prototypical JHW-018

WHO Report

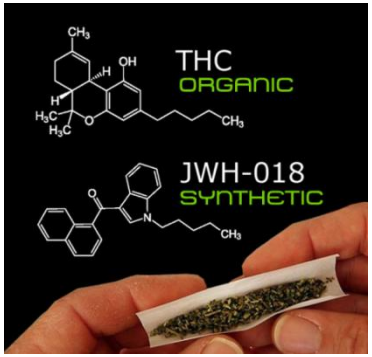
Worldwide JWH-018 most widespread, followed by other Indole Derivatives JWH-073, JWH-250, JWH-081

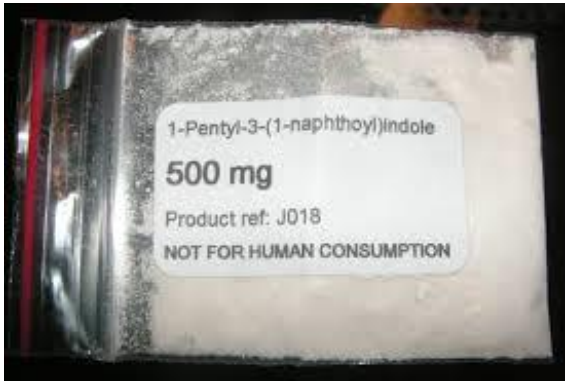
JWH-018 = more potent than THC, with shorter Duration of Action
⇨more frequent Use⇨ Abuse & Dependence Liability ⇗

JWH-018 Critical Review Report WHO Expert Committee on Drug Dependence 36 Meeting item 4.5 Geneva 16-20 June 2014 32 pp

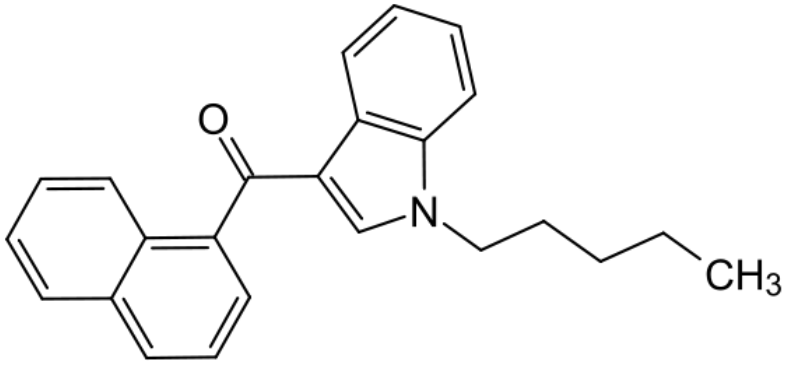
Samples of JWH-018 and JWH-073 from On-Line Sources were of comparable Purity to validated Compounds obtained from Sigma-Aldrich or Cayman Chemical

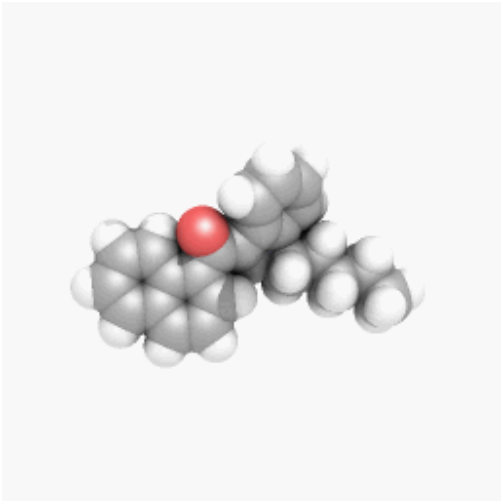
Ginsburg BC, McMahon LR, Sanchez JJ, Javors MA. Purity of synthetic cannabinoids sold online for recreational use. J Anal Toxicol. 36:66-68 (2012)





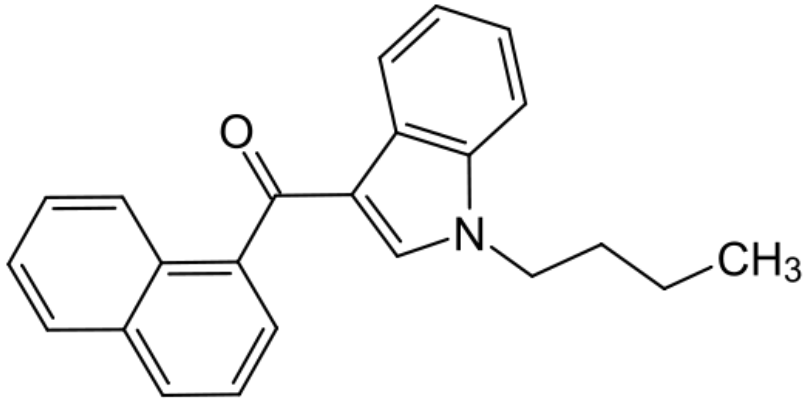
JWH-018 and JWH-073





JWH-018 (1-pentyl-3-(1-naphthoyl)indole) or AM-678
CB_1 Affinity Binding K_i = 9 nM

JWH-073
CB_1 Affinity Binding K_i = 8,9 nM



On 20 April 2009, JWH-073 was found by Auwärter at Freiburg University in a "Fertiliser" called "Forest Humus" together with (C8)-CP 47,497

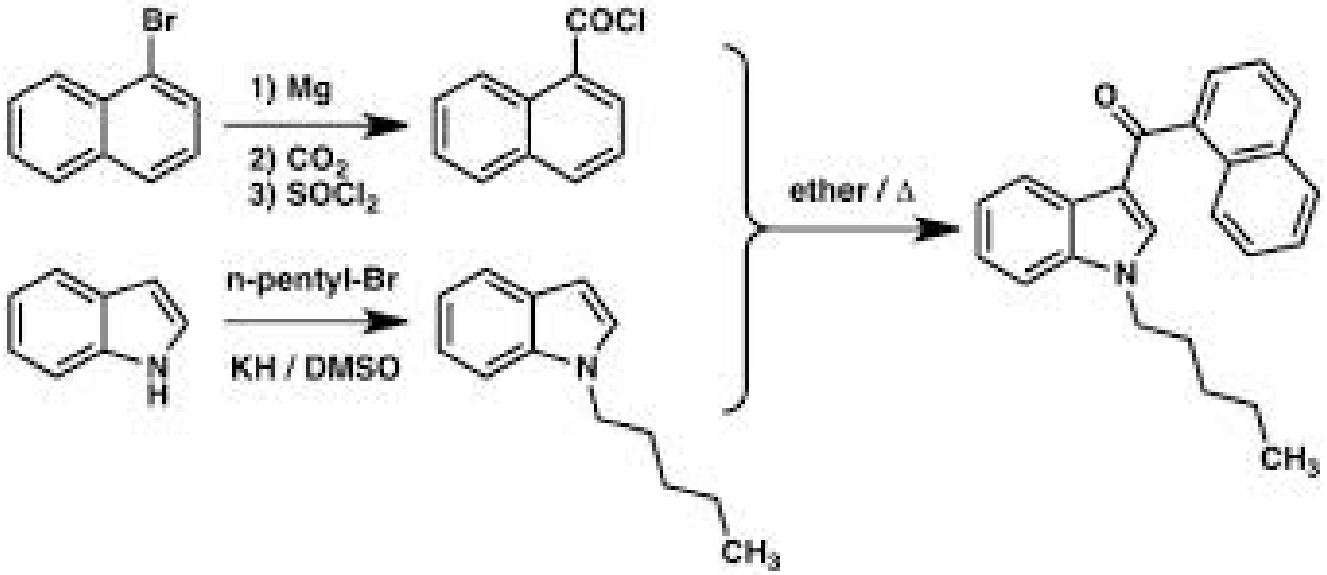
Synthèse du JWH-018

Acylation selon Friedel & Crafts à partir du 1-H- indole N- alcoylé par le 1-bromopentane avec du chlorure de naphtalene-1-carbonyle - obtenu à partir du 1-bromonaphtalène par réaction de Grignard

Huffman JW, Dai D, Martin BR, Compton DR. Design, synthesis, and pharmacology of cannabimimetic indoles. Bioorg Med Chem Lett 4: 563-566 (1994)

Chin CN, Murphy JW, Huffman JW, Kendall DA .The third transmembrane helix of the cannabinoid receptor plays a role in the selectivity of aminoalkylindoles for CB2, peripheral cannabinoid receptor. J Pharmacol Exp Ther 291: 837-844 (1999)

Huffman JW, Mabon R, Wu MJ, Lu J, Hart R, Hurst DP, Reggio PH, Wiley JL, Martin BR. 3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB(1) cannabinoid receptor. Bioorg Med Chem. 11:539-549 (2003)



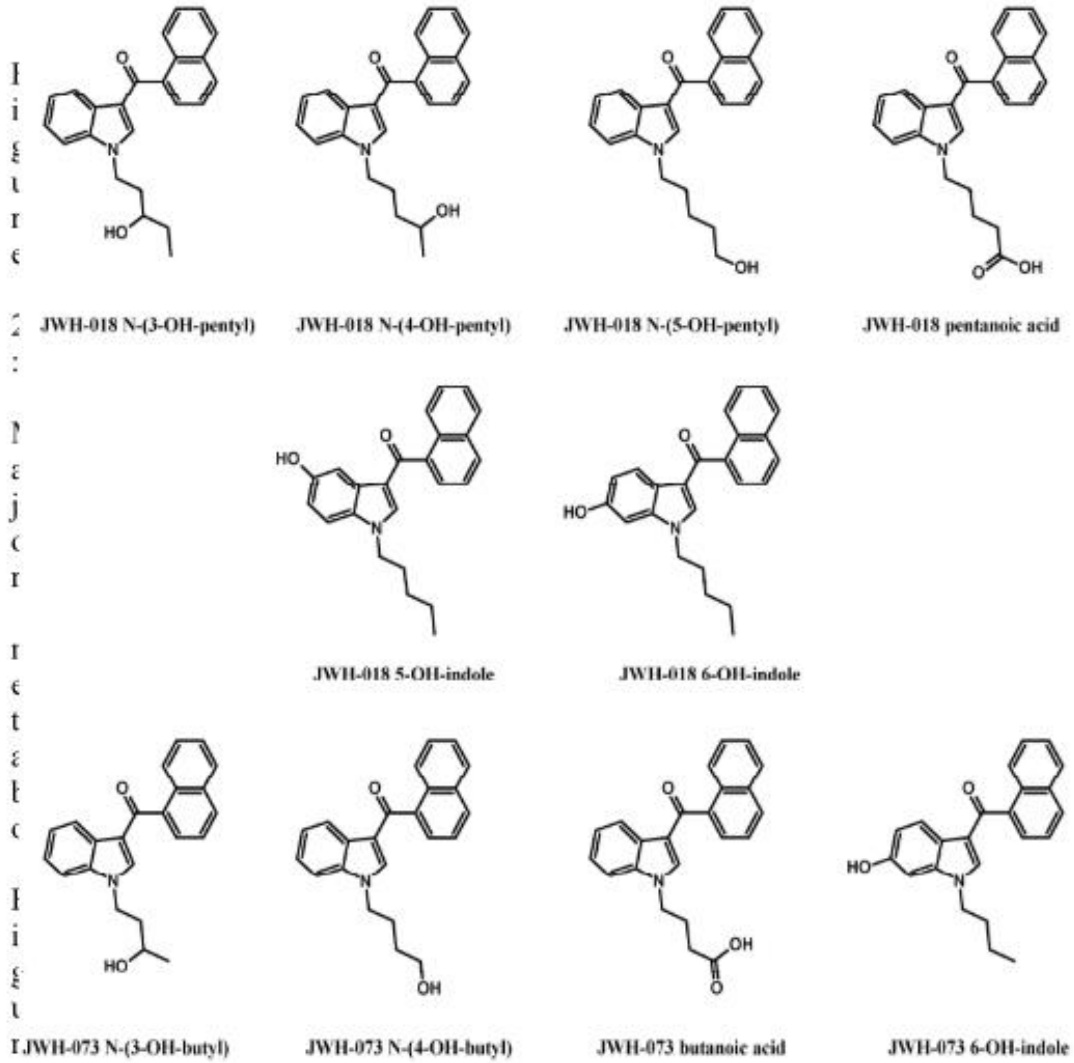
Recette de cuisine détaillé sur Internet
Alkylation pour obtenir JWH-018

Example of alkylation to JWH-018, 1-pentyl-3-(1-naphthoyl)indole, MW 341.4

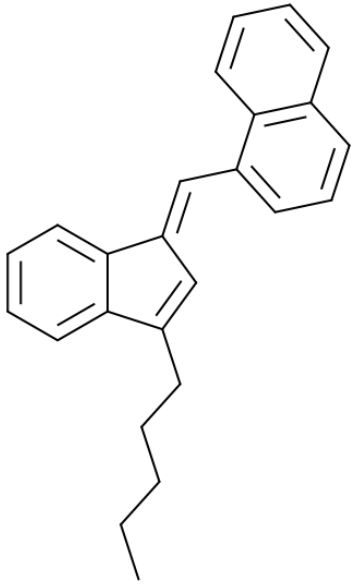
To a 250ml 3 neck RBF fitted with thermometer, condenser and a stir bar there is added 3-(1-naphthoyl)indole (3g, 11mmol) followed by dry DMF 50ml. Potassium hydroxide flakes (1.5g, 27.5mmol 1.5eq.) were added in one portion and the setup purged with butane. The flask was heated to 60-70 degrees C on a water bath for 20 minutes with stirring. A green solution with ppt is obtained. After this time, 1-bromopentane (4.3g, 28.6mmol) was added in one portion via glass syringe. There is an immediate color change to red and the flask is heated at an internal temp of 60-65 C for 3 hours. KBr ppts in the first few minutes after addition of the alkyl halide. It is then cooled to RT and diluted with 150ml H_2O, and extracted with DCM 3x 40ml. The organics are washed with water 3 times then the solvent is evaporated. There is excess bromopentane as noticed by the smell so it is removed under vacuum in a hot water bath. 3g of amber oil was obtained (8.8mmol, 80% yield) The amber oil that remains is the product. It is a pain to get it to crystallize. Only after 1 month in the refrigerator did crystals begin to form. By covering them with a small amount of IPA cleaned them up and caused all of the oil to crystallize. Once you have a seed crystal the oil can be directly crystallized after alkylation, but I have had no luck getting it to crystallize right after without the seed or with ethanol.
The obtained material is completely melted by 61 C, lit Mp is 60-62 C.

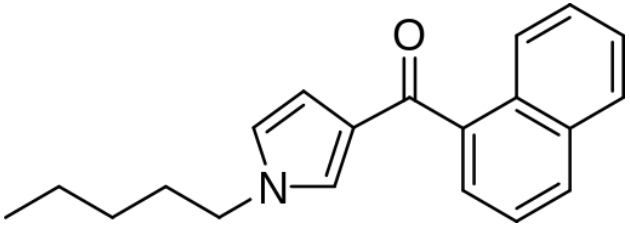
The product is fucking active and is obtained as beige to yellow slightly gummy crystals. It would be best to straight chromotograph the oil but not everyone can do that.

JWH-018 and JWH-073 Metabolites

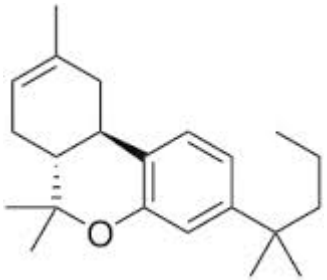


Selection of some Molecular Structures of JHW Synthetic Cannabinoids

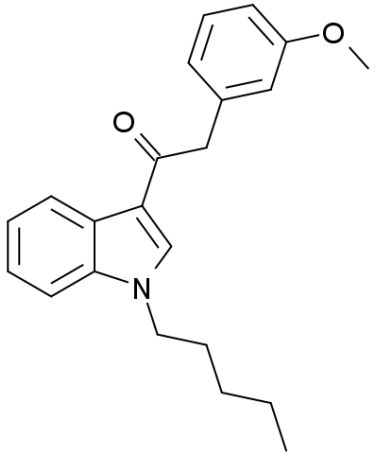




JWH-030
CB_1 Affinity Binding K_i = 87 nM



JWH-133
K_i = 3,4 nM
Selective for CB_2



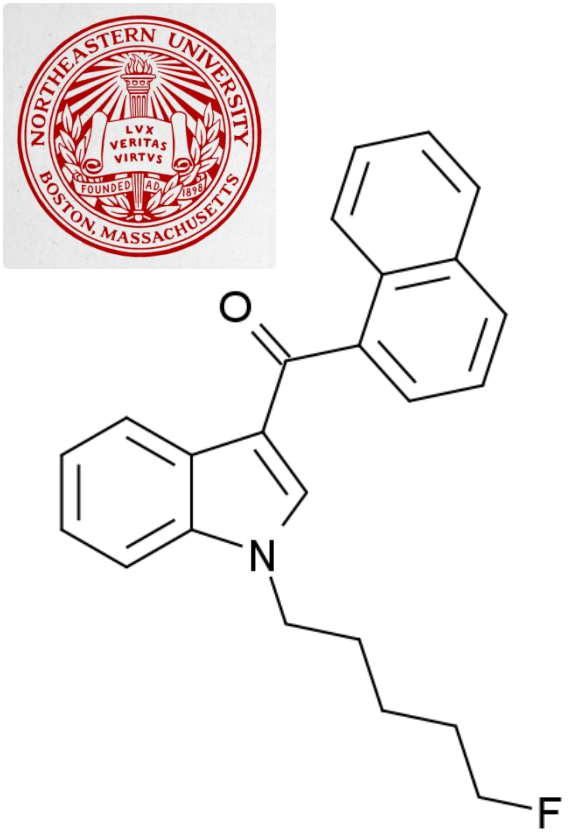
JWH-302
CB_1 Affinity Binding K_i = 17 nM

JWH-176 = Analgesic developed by John W Huffman
CB_1 Affinity Binding K_i = 26 nM

Huffman JW, Padgett LW. Recent Developments in the Medicinal Chemistry of Cannabimimetic Indoles, Pyrroles and Indenes. Curr Med Chem,12: 1395-1411(2005)

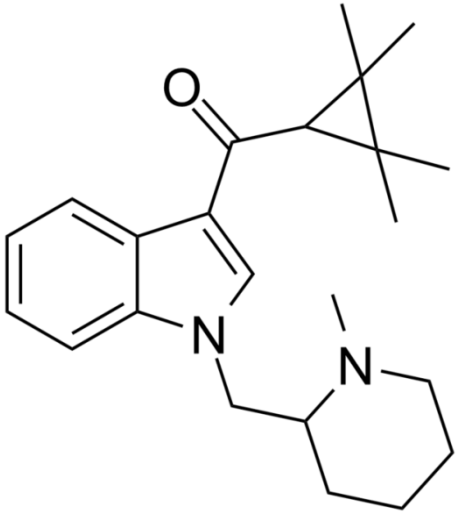
Selection of some Molecular Structures of synthetic Cannabinoids

AM-2201 is 1-(5-fluoropentyl)-3-(1-naphthoyl)indole discovered by Alexandros Makriyannis, at Northeastern University Boston, Massachusetts



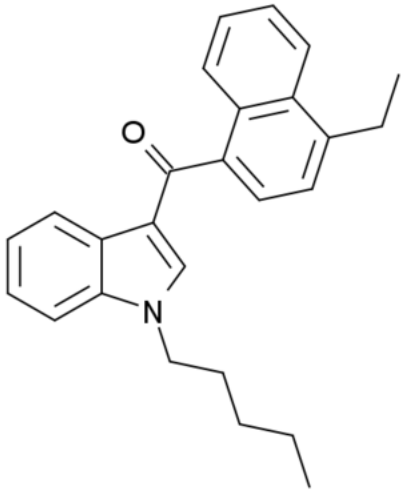
AM-2201
CB_1 Affinity Binding K_i =1nM

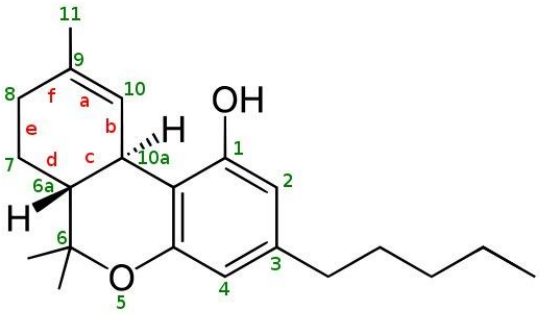
Cyclopropanoylindoles developed by Abbott



AB-005
CB_1 Affinity Binding K_i = 5,5 nM

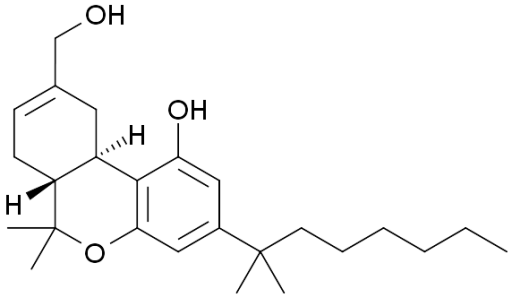
210 vs JWH-210 vs Δ^9-THC





Δ^9-THC
CB$_1$ Affinity Binding K$_i$ =10 to 80 nM

11-OH-Δ^9-THC
CB$_1$ Affinity Binding K$_i$ = 38 nM

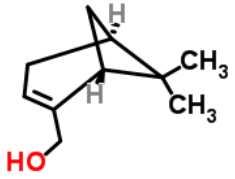


JWH-210 1-Pentyl-3-(4-ethyl-1-naphthoyl)indole
CB$_1$ Affinity Binding K$_i$ = 0,46 nM

Suppliers Names
Nanjing Norris-Pharm Technology Co.,Ltd
Shanghai Worldyang Chemical Co.,Ltd

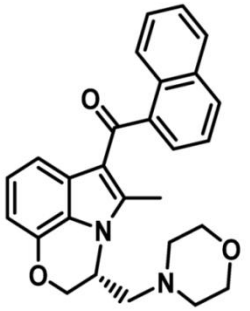
HU-210
CB$_1$ Affinity Binding K$_i$ =0,06 nM

HU-210 is 100 to 800 times more potent than natural THC & with longer Duration of Action
= first synthesized in 1988 from 1R-(-)-Myrtenol at Hebrew University

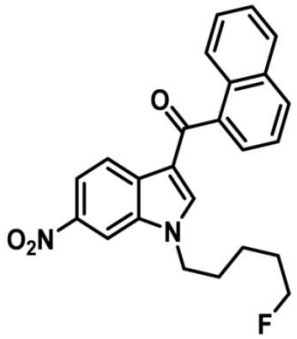


Mechoulam R, Lander N, Breuer A, Zahalka J. Synthesis of the Individual, Pharmacologically Distinct Enantiomers of a Tetrahydrocannabinol Derivative. Tetrahedron: Asymmetry.1: 315-318(1990)

Other Aminoalkylindoles

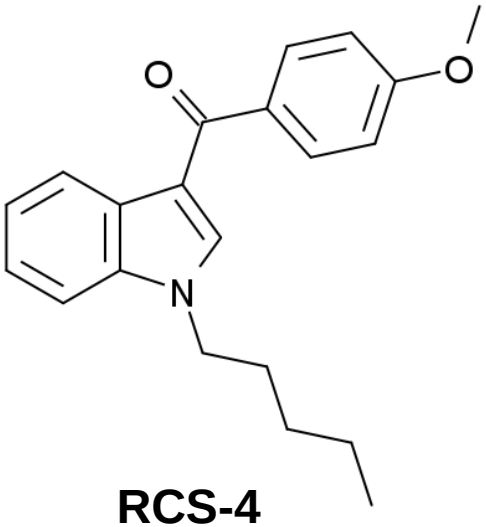


WIN 55,212-2

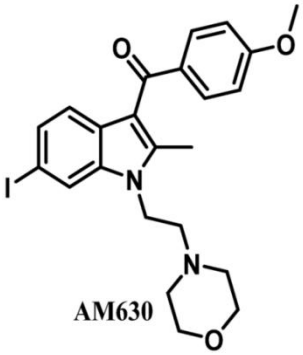


AM1235

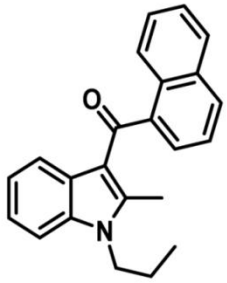
Winthrop ARZNEIMITTEL



RCS-4
K_i = no data



AM630

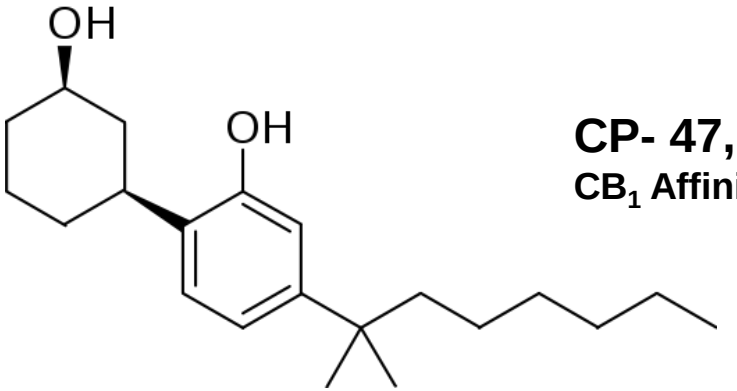


JWH015

Some Aminoalkylindoles = Cannabinoid Receptor Agonists developed by Sterling-Winthrop in the early 1990s as potential Non-Steroidal Anti-Inflammatory Agents

Eissenstat MA, Bell MR, D'Ambra TE, Alexander EJ, Daum SJ, Ackerman JH, Gruett MD, Kumar V, Estep KG, Olefirowicz EM. Aminoalkylindoles: structure-activity relationships of novel cannabinoid mimetics. J Med Chem. 38:3094-3105 (1995)

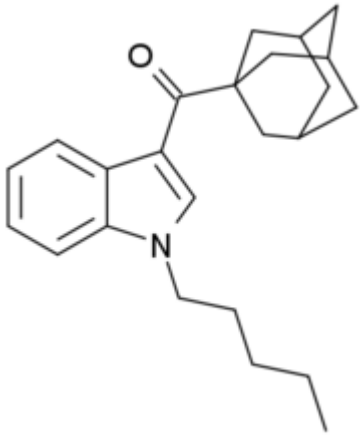
Selection of some Molecular Structures of synthetic Cannabinoids



CP- 47, 497
CB_1 Affinity Binding K_i = 9,54 nM

CP- 47, 497 developed by Pfizer Co (Charles Pfizer)

Weissman A, Milne GM, Melvin LS Jr. Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. J Pharmacol Exp Ther. 223:516-523 (1982)



Adamantane-derived Indoles developed by ABBOTT and School of Chemistry at Sydney University, NSW Australia

Banister SD, Wilkinson SM, Longworth M, Stuart J, Apetz N, English K, Brooker L, Goebel C, Hibbs DE, Glass M, Connor M, McGregor IS, Kassiou M. The synthesis and pharmacological evaluation of adamantane-derived indoles: cannabimimetic drugs of abuse. ACS Chem Neurosci. 4:1081-1092 (2013)

AB-001
K_i = no data

Clinical Cases associated with Synthetic Cannabinoids

Although Descriptions of acute toxic Effects of Synthetic Cannabinoid Preparations are currently limited to Case Reports, some common Findings are emerging

Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K
Withdrawal phenomena and dependence syndrome after the consumption of "spice gold". Dtsch Arztebl Int. 106:464-467 (2009)
Schneir AB, Cullen J, Ly BT."Spice" girls: synthetic cannabinoid intoxication. J Emerg Med. 40:296-299 (2011)

Use of NPS with still unknown pharmacological Effects in Switzerland ⇗ since 1990s ☞ Pleasure turns sometimes in acute medical Emergency
e.g. Side Effects like dystonic Reactions in Spice Consumers

Joye F, Donzé N, Frochaux V, Niquille M, Selz Amaudruz F. Recreational drugs: the complication's pleasure? Rev Med Suisse. 394:1454-1460 (2013)

Case Report

22-y-old Man & his Dog exposed to PB-22 (QUPIC) a 8-Hydroxyquinoline Analog of JWH-018 ⇨ Agitation and generalized tonic-clonic Seizures

Gugelmann H, Gerona R, Li C, Tsutaoka B, Olson KR, Lung D.'Crazy Monkey' Poisons Man and Dog: Human and canine seizures due to PB-22, a novel synthetic cannabinoid.
Clin Toxicol (Phila). 52:635-638 (2014)

Clinical Cases associated with Synthetic Cannabinoids

Cannabinoid Hyperemesis Syndrome

CHS first described in 2004 often unrecognized by Clinicians, characterized by cyclical Nausea & Vomiting, Abdominal Pain, and an unusual Compulsion to take hot Showers

Ukaigwe A, Karmacharya P, Donato A. A Gut Gone to Pot: A Case of Cannabinoid Hyperemesis Syndrome due to K2, a Synthetic Cannabinoid. Case Rep Emerg Med. Epub 2014 Apr 29

Teaching Hospitals in Denver and Aurora

Patients with Symptoms including altered Mental Status, Tachycardia followed by Bradycardia, and Seizures

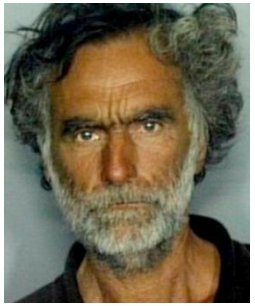
Monte AA, Bronstein, AC, Cao DJ, Heard KJ, Hoppe JA, Hoyte CO, Iwanicki JL, Lavonas EJ. An Outbreak of Exposure to a Novel Synthetic Cannabinoid. N Engl J Med. 370: 389–390 (2014)

Department of Psychiatry, University of Michigan

396 Patients with a total of 150 Patients (38%) reported using Synthetic Cannabinoids with higher Rates of other Substance Use and higher Scores of Psychiatric Diseases, believed it would not result in a positive Drug Test

Bonar EE, Ashrafioun L, Ilgen MA. Synthetic cannabinoid use among patients in residential substance use disorder treatment: Prevalence, motives, and correlates. Drug Alcohol Depend 2014 Jul 17 [Epub ahead of print]

Zombie Apocalypse?



May 2012 in Miami, Florida

Rudy Eugene, ate off almost the Entirity of Homeless Ronald E. Poppo, who survived
At the Time, it was suspected that Eugene may have been High on Bath Salts
Eugene was killed by Police after refusing to stop on a Highway
Miami-Dade County ME's Office Toxicology Laboratory directed by Dr Lee Hearn
⇨ only Cannabis in his System within typical Range of Cannabis Smokers
NMS-Labs ⇨negative Tests for Synthetic Cannabinoids, LSD & Cathinone Derivatives
NBOMe-Drugs were not ruled-out
Zombie Behaviour linked to Cannabis or non-pharmacologically induced Psychosis?

At least 2 similar Incidents occurred since the Florida bizarre Cannibalism Incident
However U.S. CDC denies Existence of "Zombie Apocalypse"

Seized Material

Synthetic Cannabinoids in Europe - Plant Material

Germany

2008 Detection of JWH-018 and CP47,497 detected in Herbal Smoking Mixtures

Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N. Spice' and other herbal blends: harmless incense or cannabinoid designer drugs?J Mass Spectr 44: 832–837(2009)

Kneisel S, Westphal F, Bisel P, Brecht V, Broecker S, Auwärter V. Identification and structural characterization of the synthetic cannabinoid 3-(1-adamantoyl)-1-pentylindole as an additive in 'herbal incense. J Mass Spectrom. 47:195-200 (2012)

Westphal F, Girreser U, Knecht S. Structure elucidation of a new open chain isomer of the cannabimimetic cyclopropoylindole A-796,260. Forensic Sci Int. 234:139-148. (2014)

Belgium

Equipe de Corinne Charlier

Denooz R, Vanheugen JC, Frederich M, de Tullio P, Charlier C. Identification and structural elucidation of four cannabimimetic compounds (RCS-4, AM-2201, JWH-203 and JWH-210) in seized products. J Anal Toxicol. 37:56-63 (2013)

United Kingdom

Hudson S, Ramsey J. The emergence and analysis of synthetic cannabinoids. Drug Test Anal. 3:466-78 (2011)

France

Schlatter J, Chiadmi F, Chariot P. Spice in France: mixed herbs containing synthetic cannabinoids. Ann Biol Clin.70:413-422 (2012)

Japan

Uchiyama N, Kikura-Hanajiri R, Ogata J, Goda Y. Chemical analysis of synthetic cannabinoids as designer drugs in herbal products. Forensic Sci Int.198:31-38(2010)

Uchiyama N, Kawamura M, ikura-Hanajiri R, Goda Y. Identification and quantitation of two cannabimimetic phenylacetylindoles JWH-251 and JWH-250, and four cannabimimetic naphthoylindoles JWH-081, JWH-015, JWH-200, and JWH-073 as designer drugs in illegal products. Forensic Toxicol 29: 25-37 (2011)

USA

2008 1st Material seized by Customs & Border Protection in Dayton, Ohio

United Nations

UNODC Report Synthetic Cannabinoids in Herbal Products 2011

Seized Material

Synthetic Cannabinoids in Europe - Bulk Material Shipments

Multi-kilo Shipments from China or Taiwan as Research Chemicals labeled "NOT FOR HUMAN CONSUMPTION"

Suppliers **Buy-the-mg or Buy-the kg.com in Taiwan**

2012

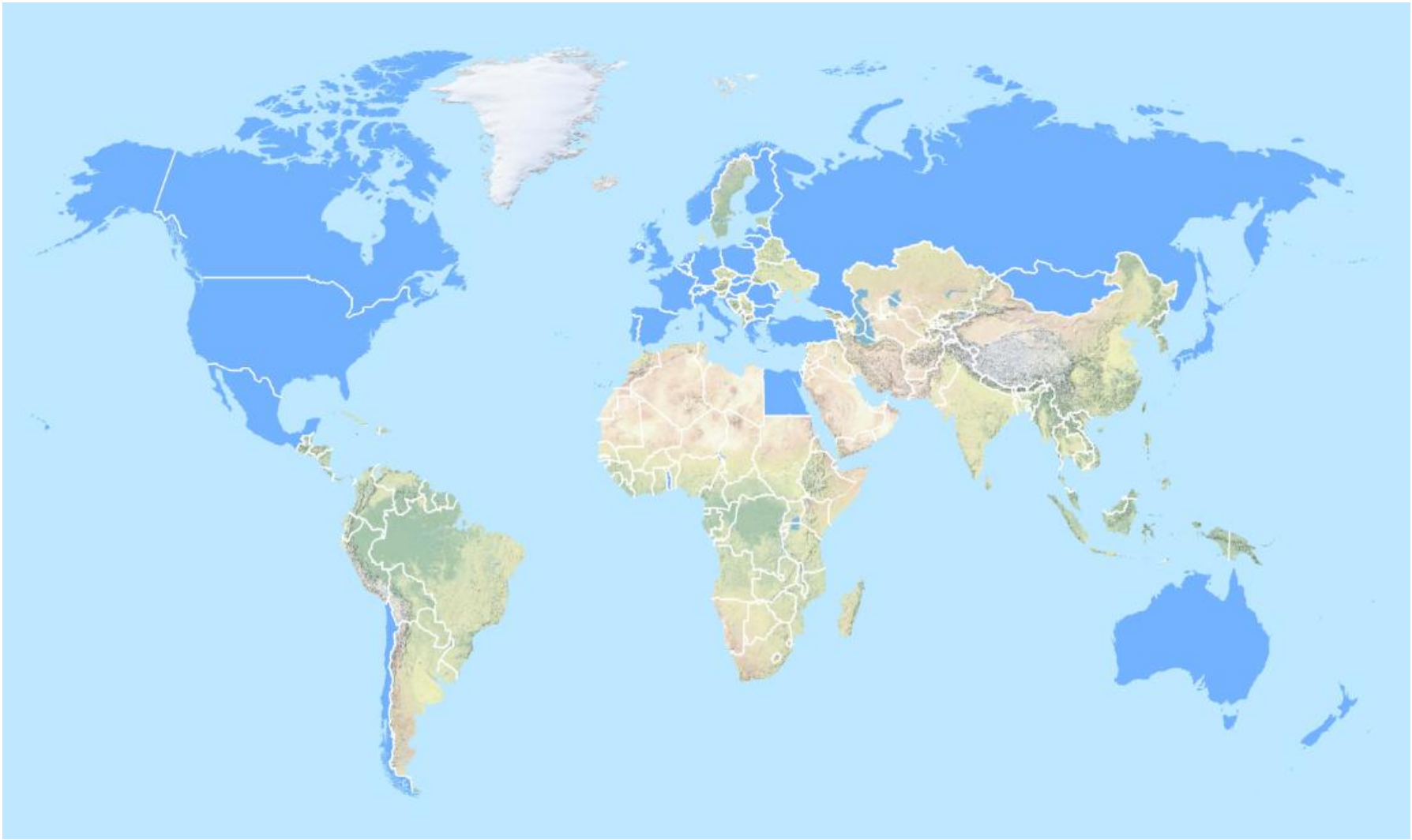
54 kg JWH-018 in Denmark
21 kg JWH-018 in Finland
20 kg AM-2201 in Spain

2013

7 kg AM-6527 in Finland
7 kg XLR-11 and AKBF48-F in France

Perspectives on drugs: Synthetic cannabinoids in Europe. European Monitoring Centre for Drugs and Drug Addiction.(2014)
Manuel UNODC Wien. Méthodes recommandées pour l'identification et l'analyse des agonistes des récepteurs cannabinoïdes contenus dans des substances saisies, 62 pp. New York 2014

Distribution des Saisies



Source: UNODC questionnaire on NPS, 2012

Legal Aspects

Authorities around the World are now controlling Synthetic Cannabinoids by either Naming individual Compounds or using Generic Legislation
Difficulties ⇨ as Synthetic Cannabinoids detected are constantly Changing in Attempts by Manufacturers to evade Legislation
More than 500 different Synthetic Cannabinoids have been created, mostly in Research Laboratories of Universities or Pharmaceutical Industry

King LA. Legal controls on cannabimimetics: an international dilemma? Drug Test Anal. 6:80-87(2014)

☞Anyway Enforcement Authorities = always behind the Market

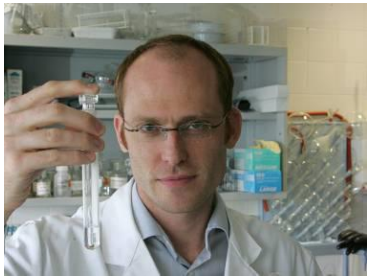
Germany
JWH-018, HU-210, CP 47,497-C8 Homologue scheduled Drugs since January 2009
Luxembourg
Generic Law (loi Wennig) including all Cannabinoid Receptor Agonists April 2009
Switzerland
Many Synthetic Cannabinoids in general Law Septembre 2010
France
JWH-018, CP 47,497 & Homologues, HU-210 made illegal in France on February 24, 2009
USA
DEA⇨several Cannabinoids in April 2009, Novembre 2010, March 2011 on Schedule I of Controlled Substances Act. In July 2012, the Synthetic Drug Abuse Prevention Act banned Synthetic Compounds commonly found under Schedule I

Analysis of Biological Samples

Review Article by Olaf Drummer

Amman J, Drummer OH, **Gerostamoulos D** ***, Beyer J. Detection of synthetic cannabinoids in biological samples. A Review. Bull TIAFT 41:21-27 (2012)***

Equipe de IML avec Haute Ecole des Sports de Cologne



Wintermeyer A, Möller I, Thevis M, Jübner M, Beike J, Rothschild MA, Bender K. In vitro phase I metabolism of the synthetic cannabimimetic JWH-018. Anal Bioanal Chem. 398:2141-2153 (2010)

Möller I, Wintermeyer A, Bender K, Jübner M, Thomas A, Krug O, Schänzer W, Thevis M. Screening for the synthetic cannabinoid JWH-018 and its major metabolites in human doping controls. Drug Test Anal. 3:609-620 (2011)

Detection of Urinary Metabolites of AB-001 by GC-MS

Grigoryev A, Kavanagh P, Melnik A. The detection of the urinary metabolites of 3-[(adamantan-1-yl)carbonyl]-1-pentylindole (AB-001), a novel cannabimimetic, by gas chromatography-mass spectrometry. Drug Test Anal. 4:519-524 (2012)

Automated Screening Procedure for Synthetic Cannabinoids Detection in Serum using a LC-Ion Trap-MS and a Spectra Library-based Approach, including 46 Synthetic Cannabinoids & 8 Isotope labelled Analogues

Huppertz LM, Kneisel S, Auwärter V, Kempf J. A comprehensive library-based, automated screening procedure for 46 synthetic cannabinoids in serum employing liquid chromatography-quadrupole ion trap mass spectrometry with high-temperature electrospray ionization. J Mass Spectrom. 49:117-127 (2014)

Analysis of Biological Samples

Etude NIDA par Marilyn Huestis

2-(4-Methoxyphenyl)-1-(1-pentyl-indol-3-yl)methanone (RCS-4) a potent Cannabinoid Receptor Agonist after 1 h Human Hepatocyte Incubation and TOF high-resolution MS ⇨ Identification of 18 RCS-4 Metabolites, many not yet reported

Gandhi AS, Zhu M, Pang S, Wohlfarth A, Scheidweiler KB, Huestis MA. Metabolite profiling of RCS-4, a novel synthetic cannabinoid designer drug, using human hepatocyte metabolism and TOF-MS. Bioanalysis. 6:1471-1485 (2014)

Etude sur les rats par équipe de Homburg/Sarre

Rats administered a single 20 mg/kg oral Dose of JWH-210 or JWH-122. Autopsy after 1 Month, ⇨ Adipose Tissue JWH-210 and JWH-122 detected in Concentrations of 116 and 9 ng/g by LC-QTrap-MS

Schaefer N, Peters B, Bregel D, Maurer HH, Schmidt PH, Ewald AH. Can JWH-210 and JWH-122 be detected in adipose tissue four weeks after single oral drug administration to rats? Biomed Chromatogr. 28:1043-1047 (2014)

Analysis of Biological Samples

Comparaison IAs vs LC-QTOF-MS ⇨ IAs less suitable for Urine Screening because of rapid illegal Market Changes

Kronstrand R, Brinkhagen L, Birath-Karlsson C, Roman M, Josefsson M. LC-QTOF-MS as a superior strategy to immunoassay for the comprehensive analysis of synthetic cannabinoids in urine. Anal Bioanal Chem.406:3599-3609. (2014)

CP-47,497, CP-47,497-C8 & JWH-250 Quantification in Mice Brains at effective Doses as assessed by classical Tetrad behavioural Paradigm

Samano KL, Poklis JL, Lichtman AH, Poklis A. Development of a High-Performance Liquid Chromatography-Tandem Mass Spectrometry Method for the Identification and Quantification of CP-47,497, CP-47,497-C8 and JWH-250 in Mouse Brain. J Anal Toxicol. 38:307-314 (2014)

ELISA Urinary Screening for common Pentanoic Acid Metabolite UR-144 and fluorinated UR-144 (XLR-11) with no Cross Reactivity with other Synthetic Cannabinoids at Concentrations <1,000 ng/mL

Mohr AL, Ofsa B, Keil AM, Simon JR, McMullin M, Logan BK. Enzyme-Linked Immunosorbent Assay (ELISA) for the Detection of Use of the Synthetic Cannabinoid Agonists UR-144 and XLR-11 in Human Urine. J Anal Toxicol. 2014 Jun 7. [Epub ahead of print]

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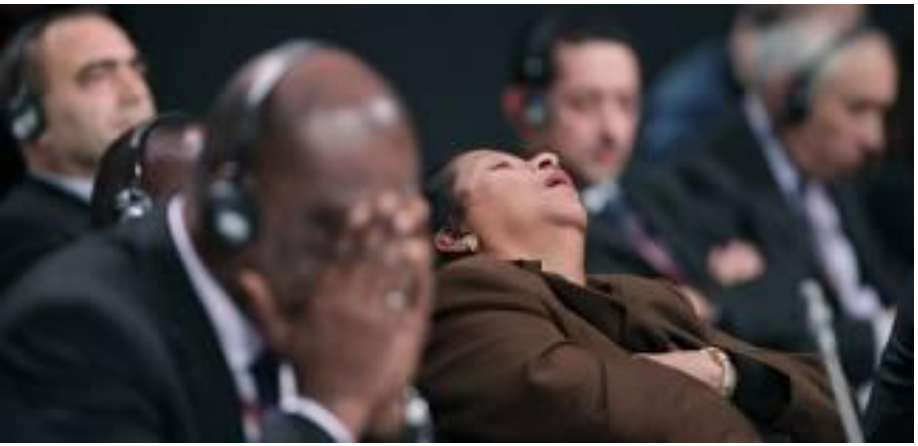
Je vous remercie de votre attention



La Voyante:

Jeune homme

Je vous vois complètement nu sur une table

Une jeune dame séduisante se penche sur vous

Aië! Mon Dieu, je suis choquée

Cette dame s’apprête à vous autopsier