



Legal controls on synthetic cannabinoids : an international dilemma

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LGC

Introduction : The 'SPICE' Story

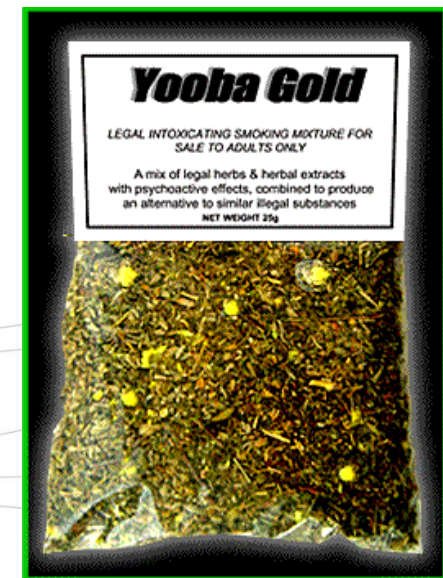


'Herbal High' products



Excellence through measurement

- Long available from 'head shops' and via the internet
- Plant materials, for smoking, eating or drinking
- Some limited activity, but not seen as a significant problem



'Spice' products

- Around 2006, a new range of herbal smoking products appeared on the market
- The 'Spice' range :
 - Spice Diamond
 - Spice Gold
 - Spice Silver, etc
- Distributed by 'Psyche Deli'
 - Then based in London
- Contents declared as a mixture of the usual herbal high materials
- 3 grams in foil sachet, about £20



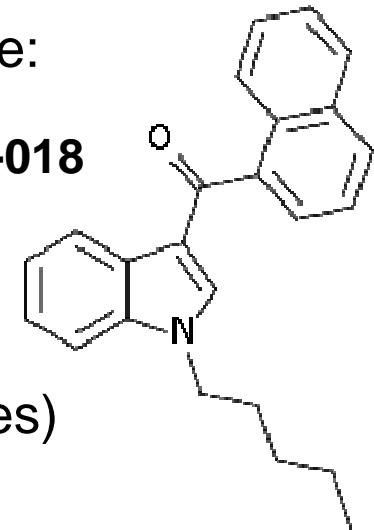
Claimed ingredients of 'Spice'

- Lists of plants, such as:
 - Canavalia Maritima ('Bay Bean')
 - Nymphaea Caerulea ('Blue Lotus')
 - Sactellaria Nana ('Dwarf Skullcap')
 - Pedicularis Densiflora ('Indian Warrior')
 - Leonitis Leonuris ('Lion's Ear')
 - Zornia Latifolia
 - Nelumbo Nuciflora ('Sacred Lotus')
- All herbs with some alleged psychoactive effect
- Typical mixture of 'herbal highs'
- Finely ground, so not possible to identify botanically

The Discovery !

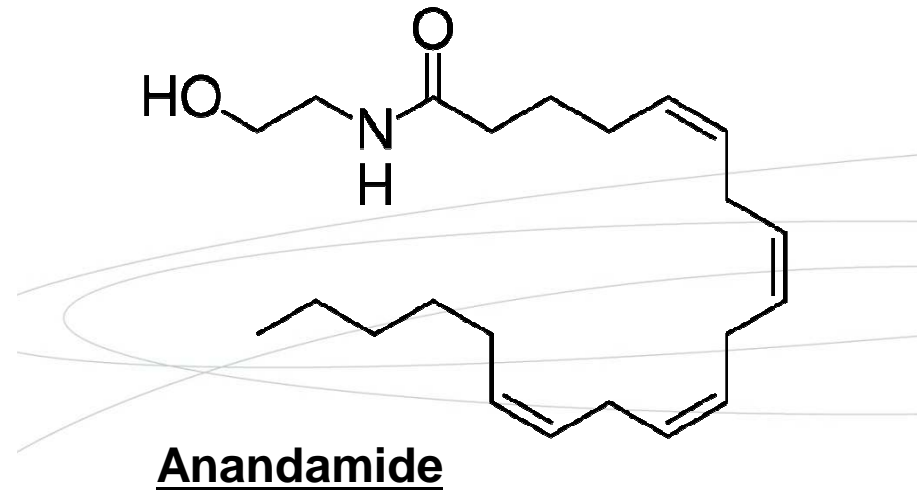
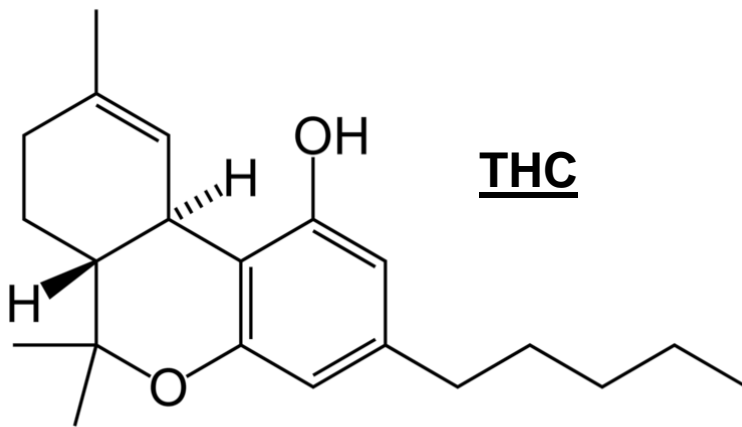
- December 2008
 - German laboratory (THC Pharm)
 - identify a pharmaceutical research chemical in Spice:
 - JWH-018
- January 2009
 - University of Freiberg & BKA
 - Also find JWH-018
 - Plus another compound CP 47,497 (and homologues)
- Synthetic cannabinoid receptor agonists
 - Effects like THC
- The kids were right !
- Spice looked like a ‘herbal high’, but this was just a ‘cover’ for a designer drug product

JWH-018

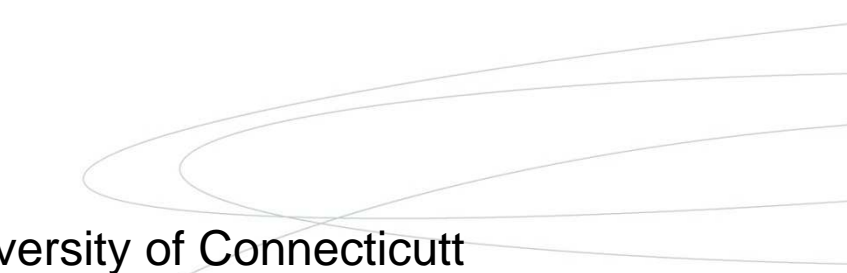


Cannabis receptors

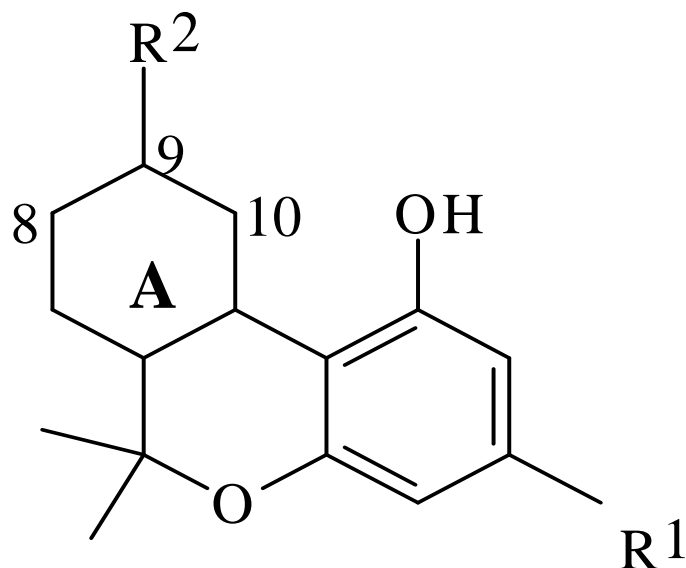
- By the 1980s, medical research had identified how THC (active ingredient of cannabis) works
- Two types of receptors for Tetrahydrocannabinol (THC) :
 - CB1 receptors in the brain and nervous system
 - CB2 receptors around the body in the immune system
- 1992, the endogenous neurotransmitter (Anandamide) discovered



Synthetic Cannabinoids

- Cannabis chemicals have potential for medical uses
 - Pain relief
 - Eating disorders
 - Pharmaceutical industry set to work to find drugs that will work on the Cannabis receptors, including:
 - Structural analogues of THC
 - ‘Nabilone’, HU 210
 - ‘JWH’ range of compounds
 - JW Huffman’s research group, Clemson University
 - The ‘CP’ range of materials
 - Pfizer chemicals
 - The ‘AM’ range of materials
 - Alexandros Makriyannis, University of Connecticut
- 

Structural analogues of THC – Dibenzopyrans



THC

R1 = Pentyl

R2 = Methyl

(A-ring C9-C10 unsaturated)

Nabilone ('Cesamet')

R1 = 1,1-Dimethylheptyl

R2 = Keto

(A-ring saturated)

(Potency = 5 x THC)

HU-210

R1 = 1,1-Dimethylheptyl

R2 = Hydroxymethyl

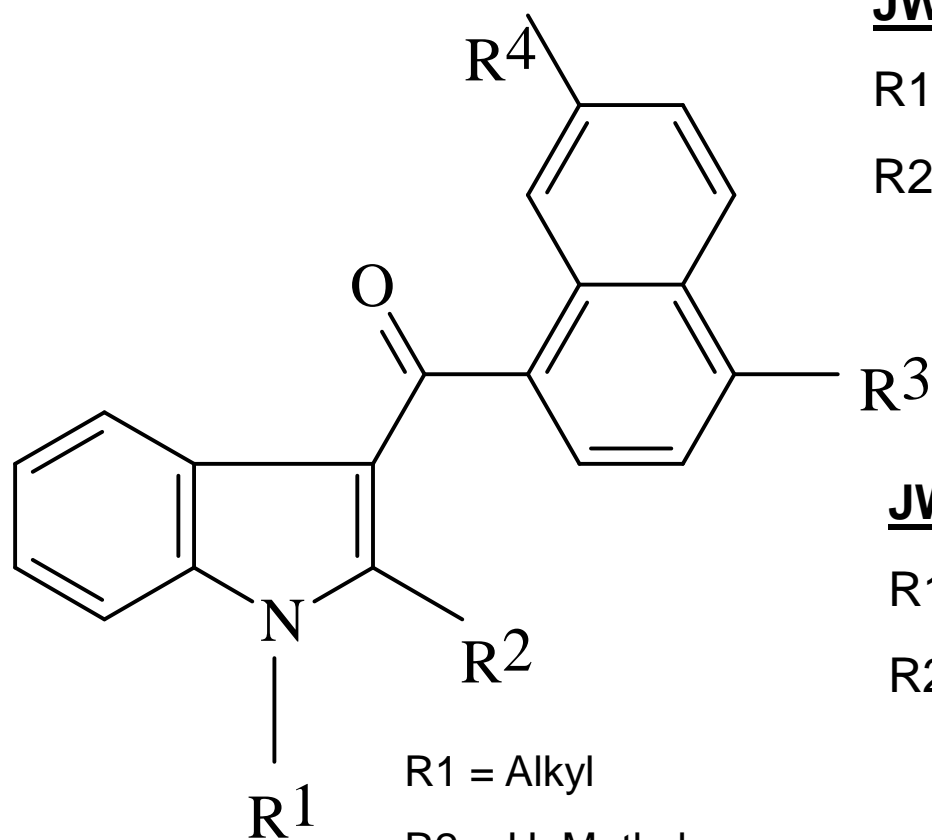
(A-ring C8-C9 unsaturated)

(Potency = 150 x THC)

'JWH' Compounds – (1) Naphthoylindoles



Excellence through measurement



R1 = Alkyl
R2 = H, Methyl
R3 = H, Alkyl, Methoxy or Halogen
R4 = H, Methyl, Ethyl

JWH – 018 (3 x THC)

R1 = Pentyl

R2 = R3 = R4 = H

JWH – 073 (1 x THC)

R1 = Butyl

R2 = R3 = R4 = H

JWH - 200 (3 x THC)

R1 = 2-(4-morpholinyl)ethyl

R2 = R3 = R4 = H

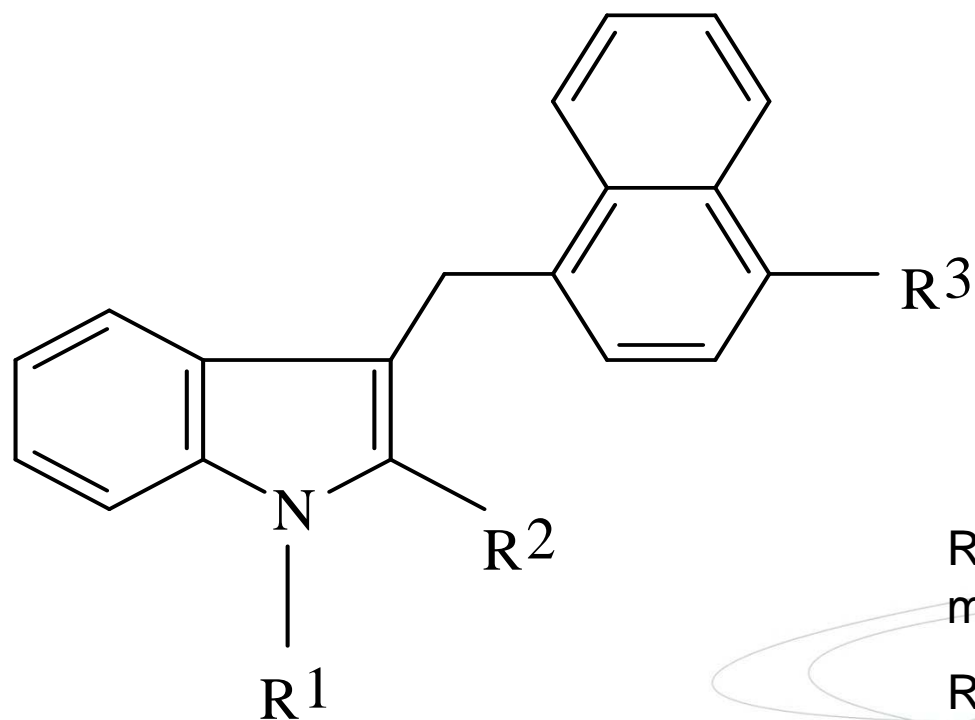
JWH – 398 (4 x THC)

R1 = Pentyl

R2 = R4 = H

R3 = Cl

'JWH' Compounds – (2) Naphthylmethylindoles

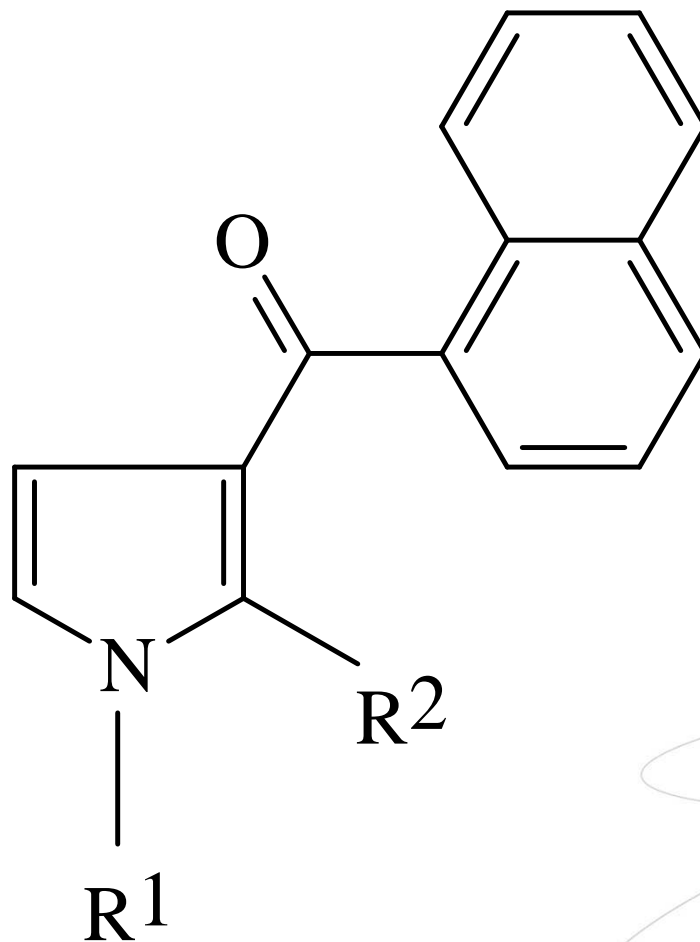


R1 = Pentyl or 2-(4-morpholino) ethyl

R2 = H or Methyl

R3 = H, Methyl or Methoxy

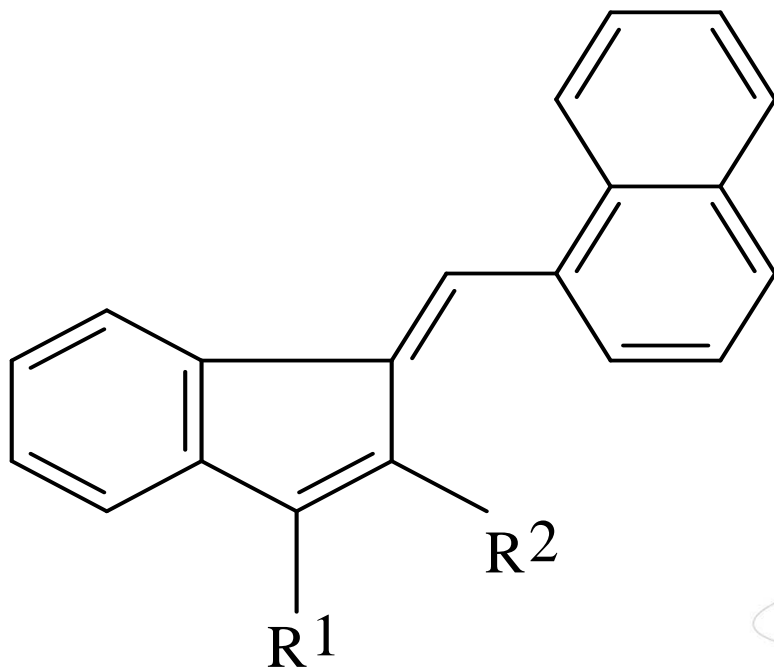
'JWH' Compounds – (3) Naphthoylpyrroles



R1 = alkyl

R2 = phenyl (+ alkyl,
methoxy, halogen, etc)

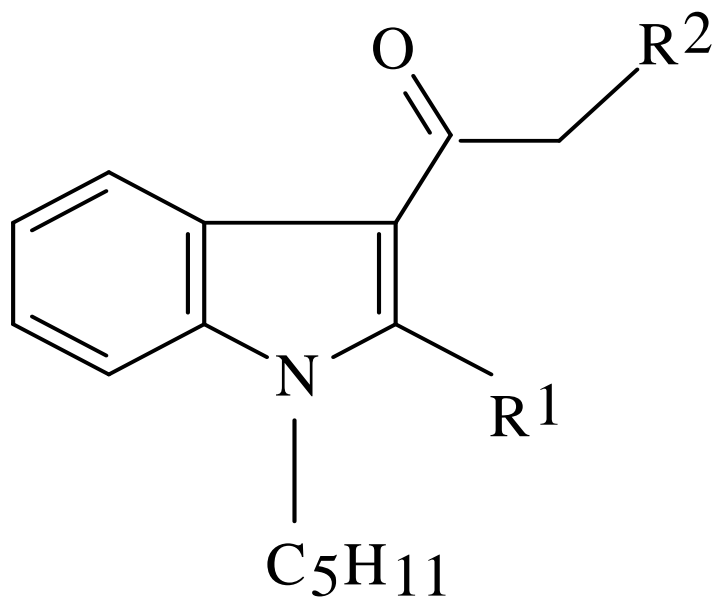
'JWH' Compounds – (4) Naphthylmethyideneindenes



R1 = Pentyl or 2-(4-morpholino) ethyl

R2 = H or Methyl

'JWH' Compounds – (5) Phenylacetylindoles



JWH – 250 (1 x THC)

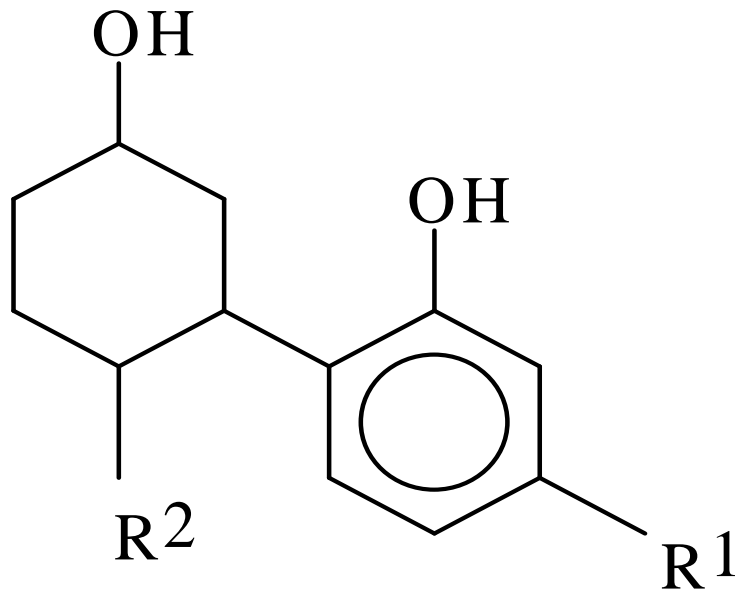
$R_1 = H$

$R_2 = 2\text{-methoxyphenyl}$

$R_1 = H$ or Me

$R_2 = \text{Phenyl (+ methyl, methoxy or halogen)}$

'Pfizer' Compounds – Cyclohexylphenols



CP 47,497 (1 x THC)

R1 = 1,1-dimethylheptyl

R2 = H

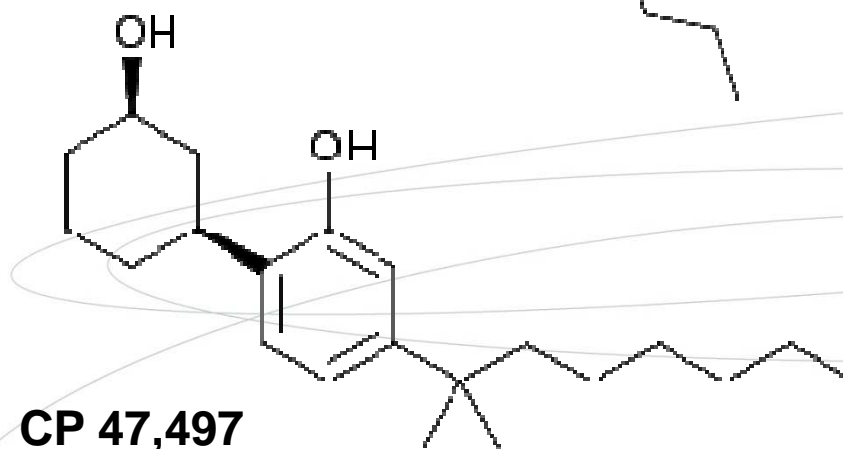
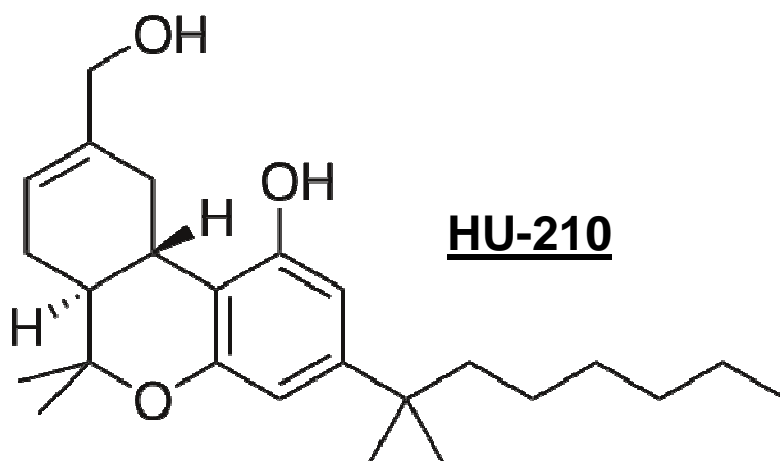
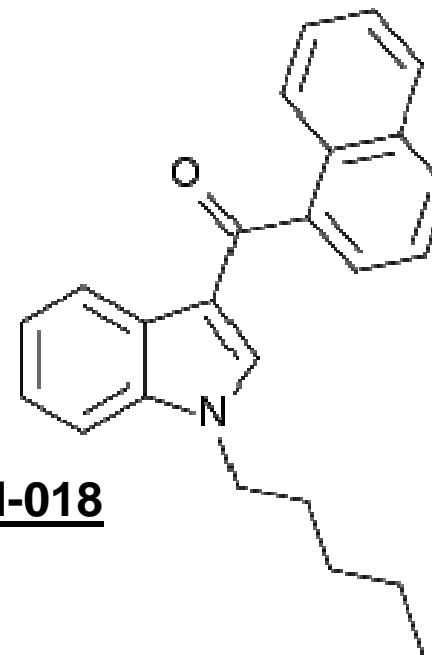
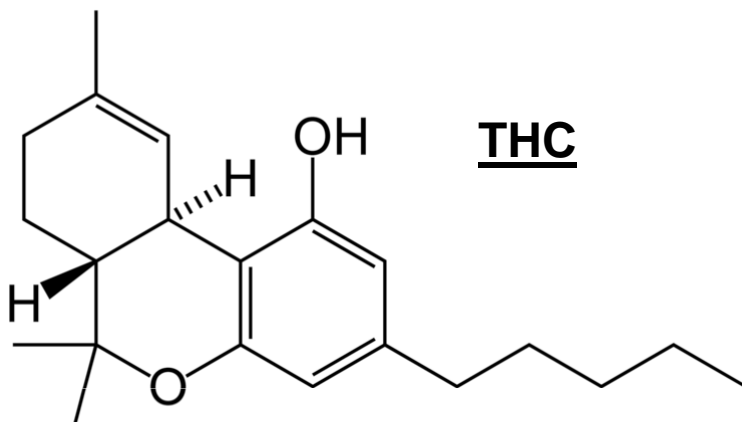
Also homologues:

R1 = 1,1-dimethyloctyl

R1 = 1,1-dimethylhexyl

R1 = 1,1-dimethylnonyl

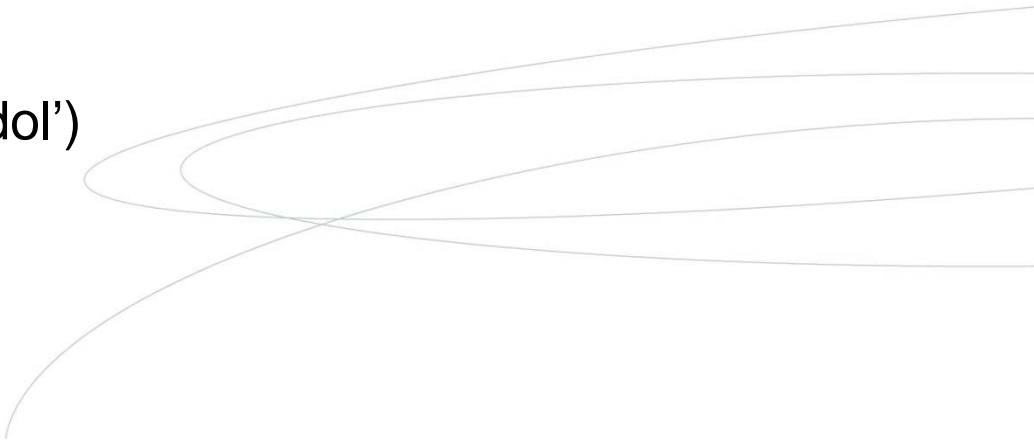
Synthetic cannabinoid receptor agonists: Structures compared with THC



How the chemicals got into 'Spice'

- Believed sourced from China
 - 'No questions asked' chemical synthesis
 - Available in bulk, in return for a credit card payment
- Sprayed or sprinkled, like 'magic dust', over finely ground herbal material
- Range of chemicals being used
 - Several designer cannabinoids identified
 - Can be more than one in each 'Spice' product
 - Small amounts of each
- Variable concentrations found
 - Effects unpredictable
- Pure chemicals also being advertised for sale
 - Delivered direct to your door in unmarked packages

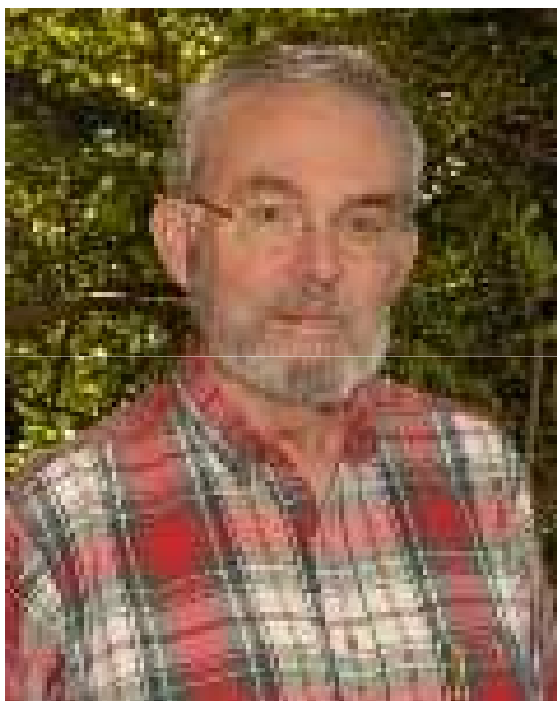
UK Control (December 2009)

- Additions to Misuse of Drugs Act
 - Five generic controls on ‘families’ of materials
 - Naphthoyl indoles (covers JWH-018, -073, -122, -210, etc)
 - Naphthoyl pyrroles (JWH-030, -307, etc)
 - Naphthylmethyl indenenes (JWH-176)
 - Phenylacetylindoles (JWH-201, -250, RCS-8, etc)
 - Hydroxycyclohexylphenols (CP series)
 - Five additional named compounds
 - WIN 55,212-2
 - HU-243
 - CP50,556-1 (‘Levonantrodol’)
 - HU-210
 - Nabilone
- 

Post-2009 developments

- Controls had been drafted to cover materials being marketed (the JWH range, CP materials)
- Soon became apparent that many other structures were equally (or even more) potent
- Suppliers rapidly switched to new materials outside the scope of the 2009 controls
 - Halogenated versions of JWH materials (AM1220, AM 2201, etc)
 - Benzoyl indoles (AM694, RCS-4, etc)
 - Adamantoyl indoles (AB-001, AM 1248, etc)
 - Tetramethylcyclopropyl indoles (UR144, XLR-11)

Academic Researchers



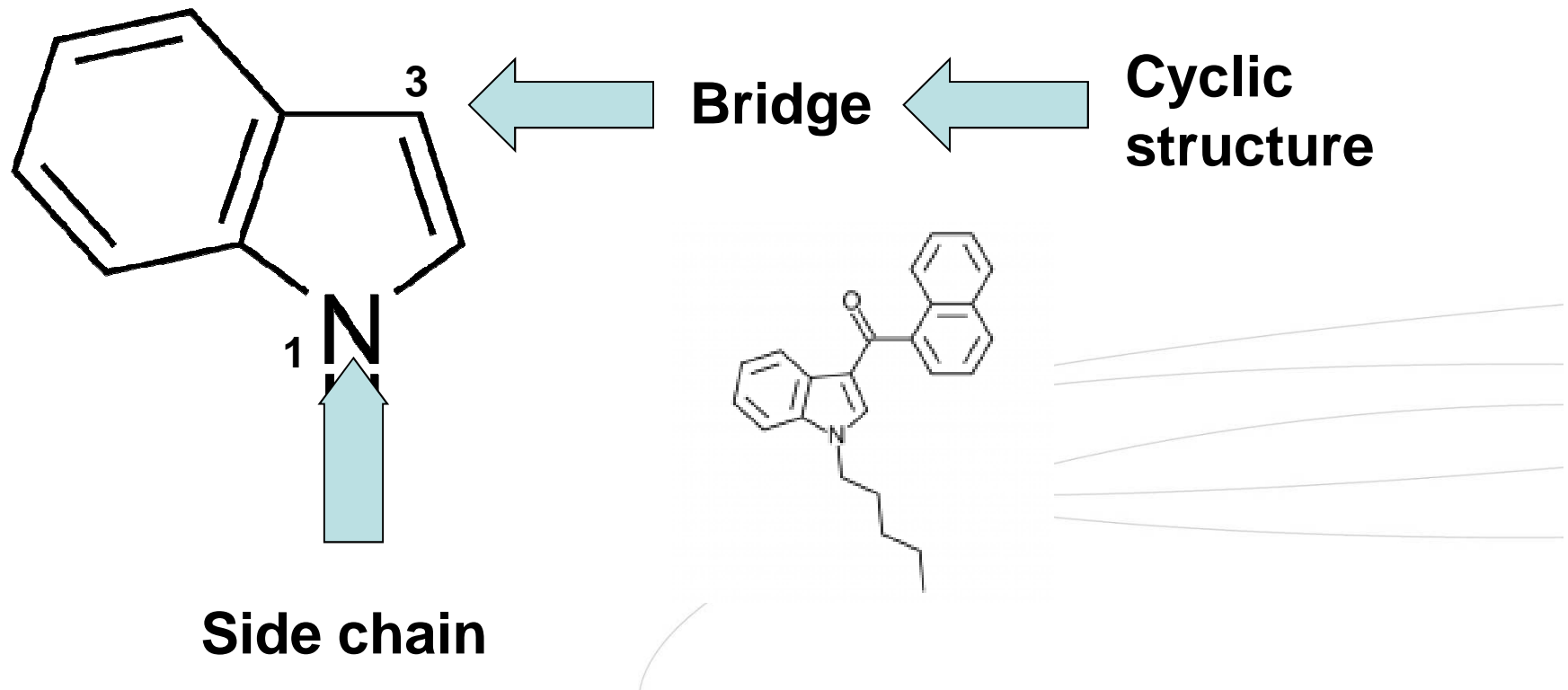
Prof Huffman:
(JWH Cannabinoids)



Prof Makriyannis:
(AM Cannabinoids)

Synthetic cannabinoids : A general structure (‘JWH’, ‘AM’ and ‘A’ series materials)

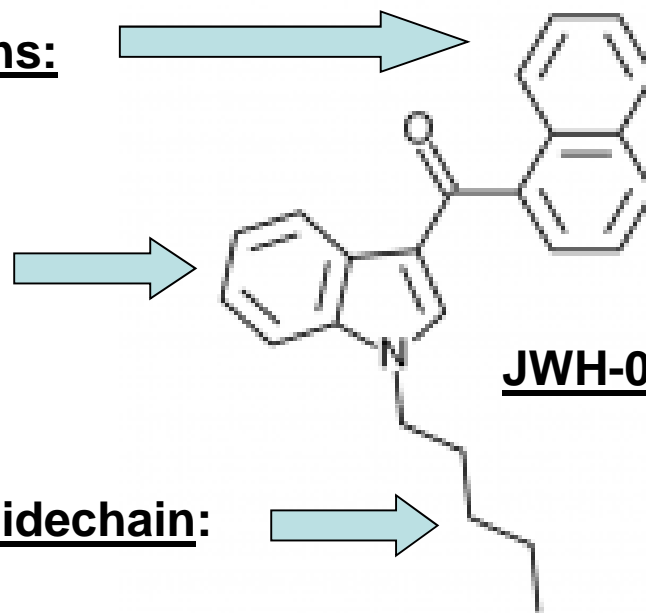
- Indole core structure
- Side chain at Nitrogen atom
- Bridge to a cyclic structure at indole 3-position



Many variants possible:

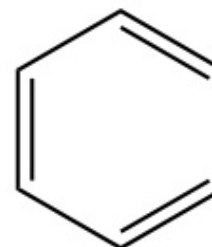
Ring modifications:

- Halogen
- Alkyl (C1 – C3)
- Methoxy
- Nitro, etc,etc

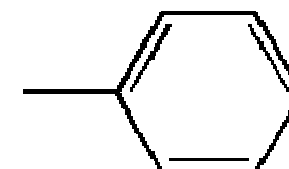


JWH-018

Alternatives for naphthyl:



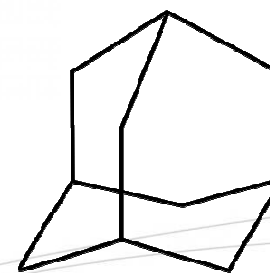
Phenyl



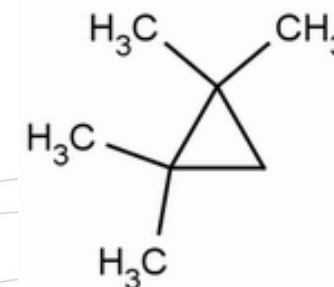
Methylphenyl

Alternatives for sidechain:

- Alkyl (C3 – C6)
- Haloalkyl
- Cycloalkyl
- 2-Morpholino-4-yl-ethyl
- N-Methylpiperidinylmethyl



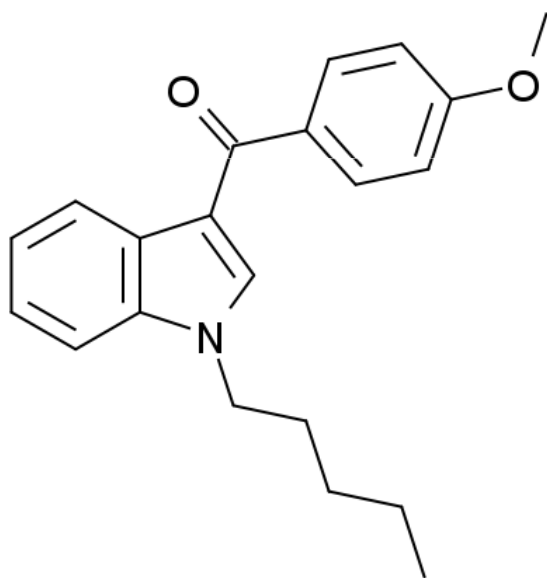
Adamantyl



Tetramethylcyclopropyl

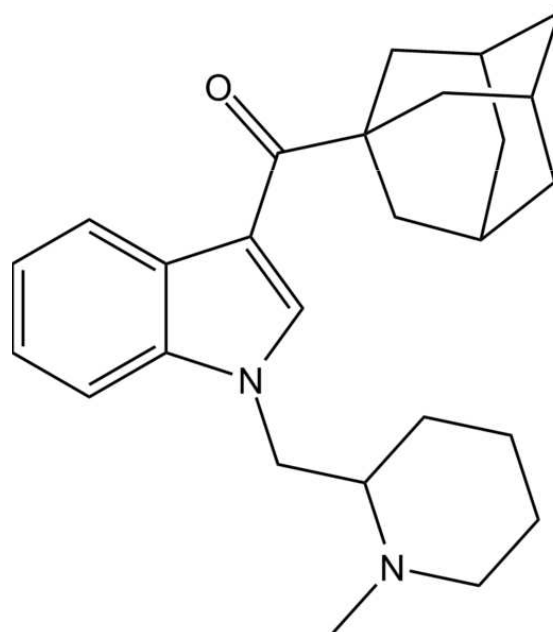
'Second generation' synthetic cannabinoids (2010 - 2012):

RCS-4



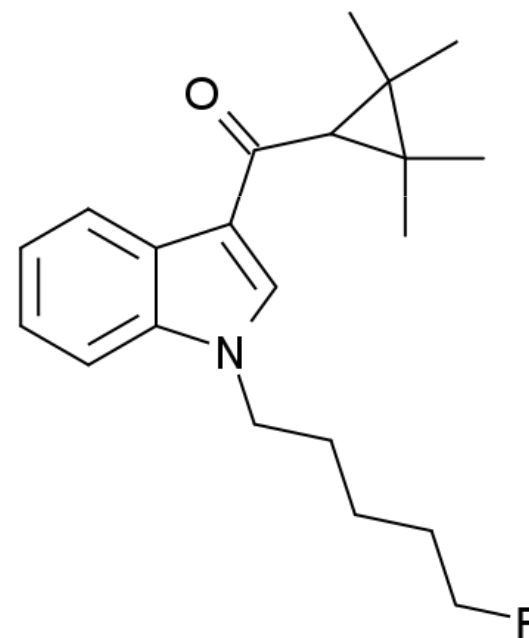
Phenyl ring with methoxy substitution

AM1248



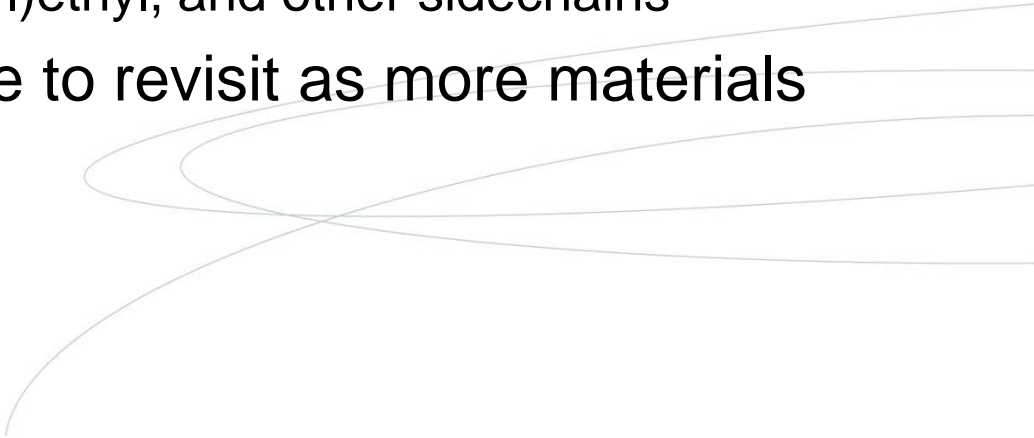
Adamantyl ring and N-methylpiperidinylmethyl sidechain

XLR-11



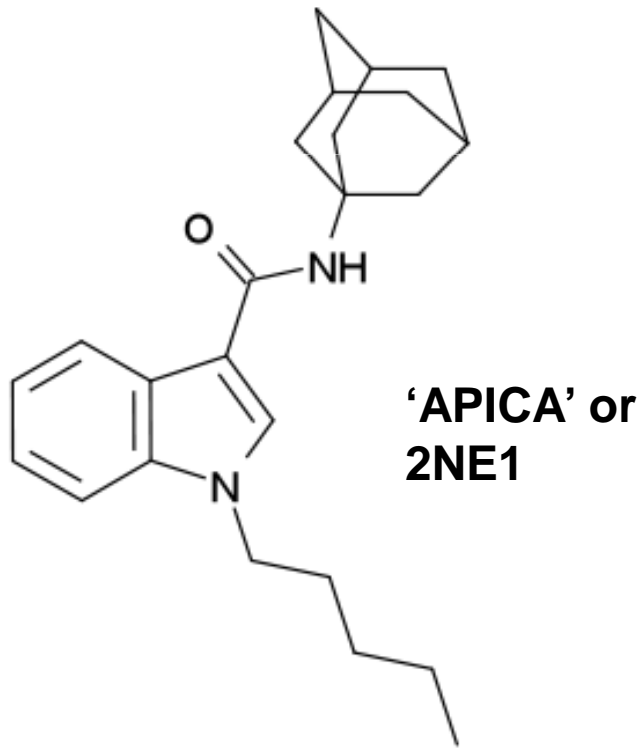
Cyclopropyl ring and haloalkyl sidechain

UK Controls (2) : February 2013

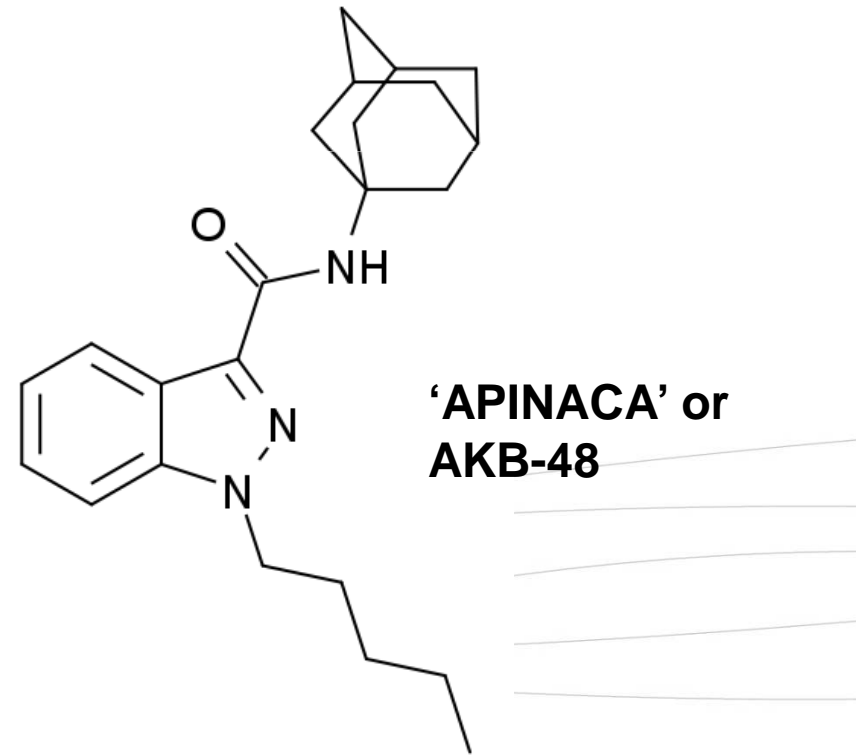
- Further additions to Misuse of Drugs Act
 - Three more 'generic' controls on chemical families
 - Benzoyl indoles
 - Adamantoyl indoles
 - Tetramethyl cyclopropoyl indoles
 - Scope of generics expanded to include broader range of structural modifications
 - Haloalkyl, 2-(4-morpholinyl)ethyl, and other sidechains
 - Accepted that might have to revisit as more materials emerged
- 

'Third generation' synthetic cannabinoids (late 2012)

Carboxamide bridge

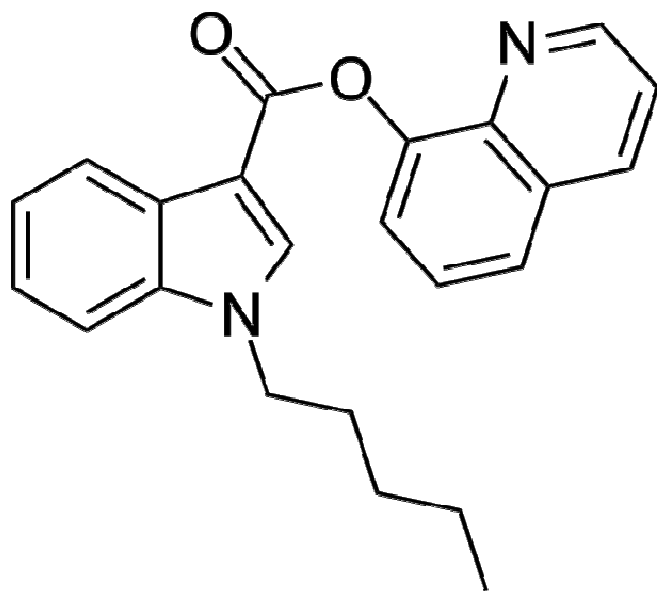


Carboxamide bridge and
indazole ring replaces indole

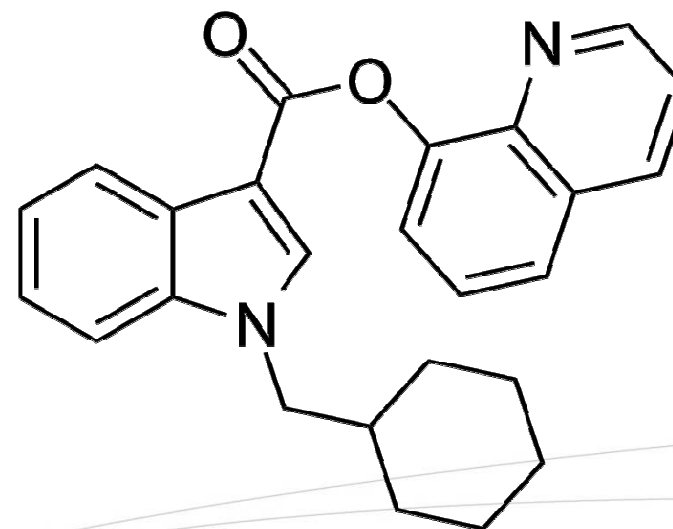


(More) new cannabinoids in 2013

Indole core, ester linkage and quinolinyln ring



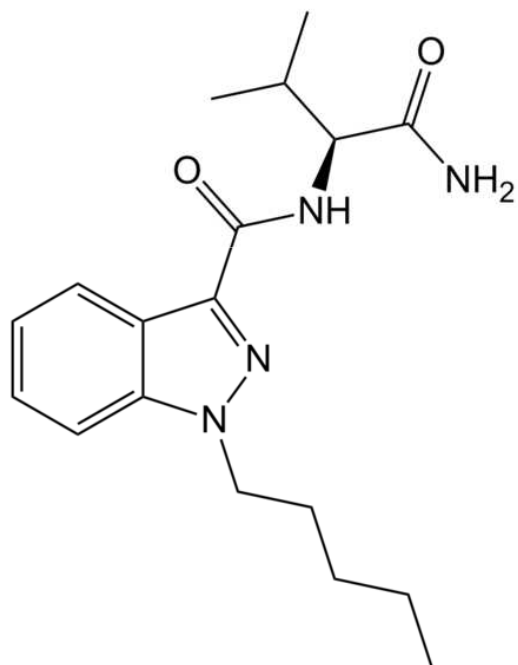
PB-22 or 'QUPIC'



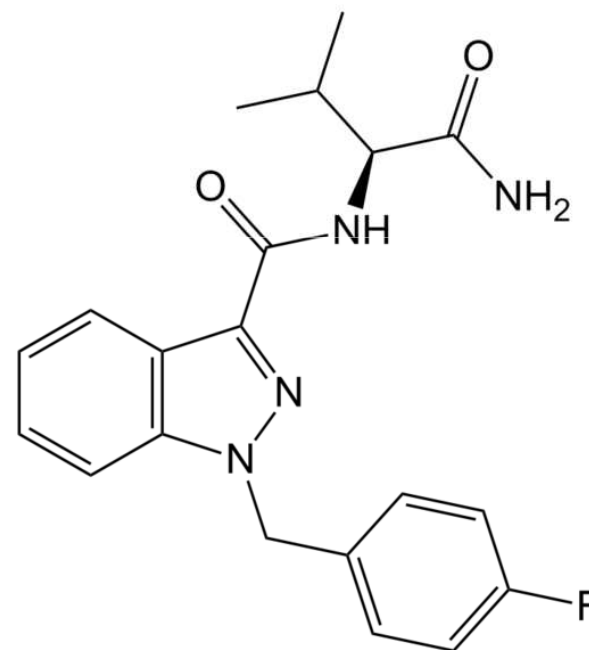
BB-22 or 'QUCHIC'

(Yet more) new cannabinoids seen in 2013

Indazole core, carboxamide linkage

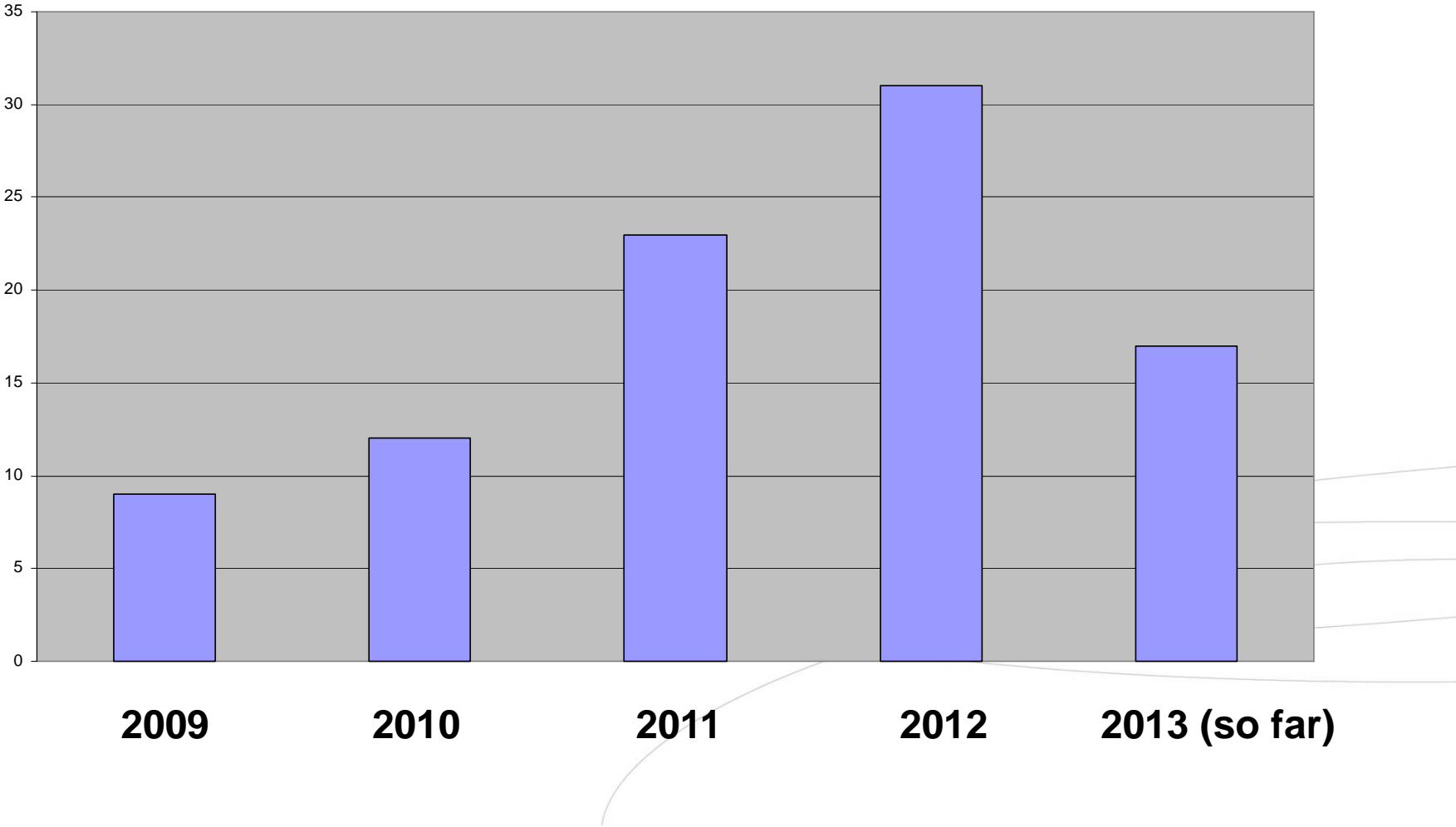


AB-PINACA



AB-FUBINACA

EMCDDA notifications of new synthetic cannabinoids



An international issue

- Products reported from around the world :
 - across Europe,
 - United States
 - Far East
- Used by young people
- Internet distribution
 - Volume of trade unknown
 - Variable results from usage surveys
 - 0.1% to 1% to 10%
- Novel materials untested for any potential harms
 - Persistent reports of young students becoming intoxicated



The new 'Business Model'

- A user's view

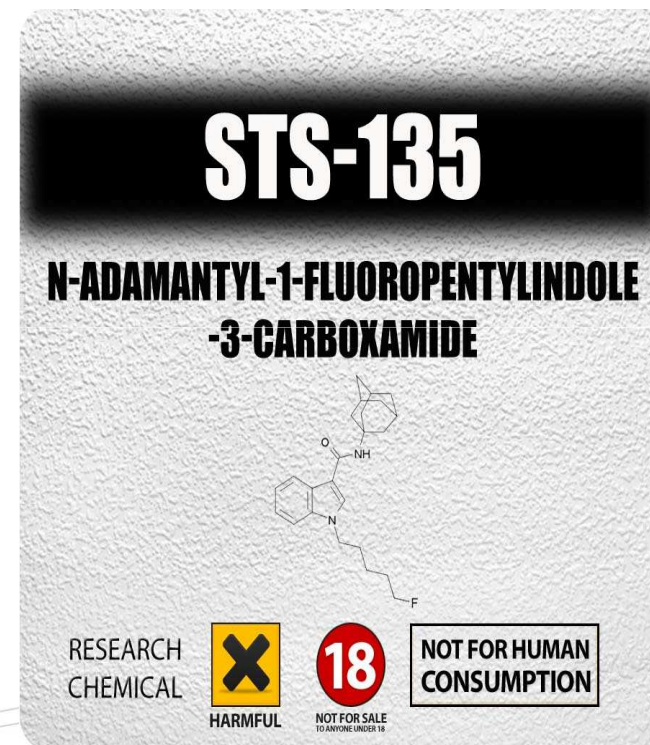
- Products work just like drugs
- Legal
- Commercial product, nicely packaged
- Can order via your computer
 - Delivered to your door
 - No need to interact with street dealers
- 'Undetectable' by standard drug tests
 - Few worries about positive drug/drive tests
 - Employment drug-test problems unlikely
- A modern 'high-tech' business transaction
 - Attractive to smart younger users



The new 'Business Model'

- A supplier's view

- Selling legal products,
 - Law enforcement agencies can't act
- "Not intended for human use"
 - Medicines agencies can't act
- Marketing via the internet
 - International sales
 - Direct to customer (no 'middle men')
- Can operate 'below the radar'
 - Non-traditional import routes
 - Materials hard to detect
- Can base operations 'offshore'
 - Select a relaxed jurisdiction as business base
 - Production outsourced to China or India
- No conflict with established drug supply networks



A new era of 'Designer Drugs'

- Many pharmaceutical research materials have been described in the literature
 - Relatively easy to synthesise
 - Some have remarkable potency
- 'Legal High' producers have access to chemical expertise
 - Wealth of information now available via the internet
 - Actively seeking potential new materials
- Principles understood
 - New variants being designed
- Dozens of branded 'herbal' products appearing



Current position

- There is now a complete business infrastructure for NPS:
 - Research and design
 - Synthesis
 - Packaging
 - Internet marketing
 - Direct distribution
- This is an international phenomenon
 - Europe is at centre
- Spread of new materials is rapid
 - Internet driven
- Traditional legal responses are too slow and fragmented
- When materials are controlled, new variants rapidly appear



NPS and International Drug Controls



- International system operated via the United Nations
 - Two main Conventions, covering Narcotics and Psychotropics
 - Nations ratify Conventions and then control the UN-listed materials using their national legislation
 - Gives consistency between nations
- Evidence-based system to assess drugs for control
 - Slow and can only process limited number of materials
- Most NPS therefore currently outside the UN system
 - Nations have to make their own decisions/arrangements
- EC system similar (2 years to review and advise)
 - Recent proposal to reduce to 10 months and to introduce immediate 12 month 'temporary bans'

NPS have highlighted problems in drug control systems

NPS and National Drug Controls

Without international system, nations acting individually:

- Standard approach – control individually named materials
- Increasing use of emergency controls/temporary bans
- US – analogue controls
 - Similar in chemistry and effect to a Schedule I or II material ?
 - Flexible, but can be debatable
- UK – generic controls
 - Define core structure and modifications
 - Clear, but can be ‘designed around’
- Ireland – close down the retailers
 - Internet trade can continue
- New Zealand – the great experiment

The US approach

- Analogues
 - ‘Substantially similar’, chemically and pharmacologically, to a controlled material within Schedules I and II
 - Still need a controlled material as a basis for comparison
- 2011, Emergency scheduling of five ‘1st generation’ cannabinoids under US Controlled Substances Act
- 2012, Synthetic Drug Abuse Prevention Act
 - ‘Cannabimetic agents’ controlled
 - Any CB1 agonists within 5 listed families of synth cannabinoids
- April 2013, Emergency scheduling of 3 more materials
 - UR-144, XLR-11 and AKB-48
 - Analogue control wasn’t seen as sufficient

The UK Approach

- Generic Controls
- Temporary Class Drug Orders wef November '11
 - December 2009: 1st generation synthetic cannabinoids controlled
 - February 2013: 2nd generation materials controlled
- UK synthetic cannabinoid market now dominated by (legal) 3rd generation materials
 - Indazoles, carboxamides, quinolins, etc, etc
 - Little or no scientific data available to assess
- Issues for the ACMD
 - Do we create more generics ?
 - If we do, what will appear next ?
 - Could we have to play 'whack-a-mole' for ever ?
 - Should we consider US-style analogue controls ?

The Irish Approach

- Concerns about proliferation of ‘head shops’ selling NPS
 - Geographically widespread
 - Evidence of organised crime involvement
- Criminal Justice (Psychoactive Substances) Act 2010
 - Bans supply or advertising of any ‘psychoactive substance’
 - Anything which stimulates or depresses the CNS
 - Excludes pharmaceuticals, alcohol and tobacco
- Number and scope of head shops now much reduced
- Internet purchasing from other jurisdictions still possible

The New Zealand Experience(Experiment?)



- New Zealand had early exposure to NPS issues
 - Piperazines 1999
- 2005 Tried a 'Restricted Substances' classification
 - 'Class D'
 - Legal snafu developed, as materials can't be 'a bit hazardous'
- 2011 Temporary Class Drug approach
 - 12 month ban (renewable) while research conducted
 - 1st batch August 2011 (16 '1st generation' cannabinoids)
 - Further batches in 2011, 2012 and 2013
 - 35 cannabinoids in system by July 2013 (+ DMAA and RTI 126)
- 2013 Interesting alternative approach being applied

Psychoactive Substances Act 2013

- Radically different approach
- System operated by New Zealand's Health Ministry
- NPS products can be sold if tested and proved 'safe'
 - Suppliers have to pay for testing (? \$250k/product ?)
 - Controversial (involves some animal testing)
- Restrictions on how and to whom licensed products sold:
 - Only licensed outlets
 - Not with food/drink ('dairies' or supermarkets) or at petrol stations
 - Not to under-18s
- Any Temporary Class-listed materials remain banned
- Over 100 applications for licenses to retail

'Licensed' products

- 'Grandfather' clause for materials on sale for >3 months
 - \$10k per product for license
 - Limited period and then have to be tested
- Around 60 such products given 'Interim Product Approval'
 - Almost all appear to be smoking materials
 - From 'Anarchy' to 'Ziggy'
 - 5 rejected (not clear why)
- Suppliers had to declare active ingredients and dosage
 - Information listed on NZ Ministry of Health website
 - Useful snapshot of what's currently being used in NZ

Declared ingredients of products with NZ Interim Approvals

- 9 = PB22
- 10 = PB22F
- 2 = PB22 + PB22F
- 10 = AB-FUBINACA
- 6 = 'Cl-2201' (? Chlorine analogue of AM 2201?)
- 3 = 'SGT-24' (? a.k.a. 'MN-25', an indazole carboxamide with fenchyl ring and morpholinoethyl chain ?)
- 1 = AB005 (sim to UR-144, with methylpiperidinyl chain)
- 1 = CP55244 (! as potent as HU-210 !)
- 15 = Ingredients unclear

Most active ingredients are '3rd generation' cannabinoids

Issues with NZ approach....

- Inconsistencies
 - BB22 remains banned (Temporary Class), but PB22 permitted
 - UR-144 banned, but AB005 permitted
- How safe is 'safe'
 - 'Fast track' assessment, compared with process for pharmaceutical approvals
 - Who is liable if problems identified later ?
- How will rest of world react if/when product approved?

WATCH THIS SPACE.....



Summary

- New psychoactive substances (NPS), including synthetic cannabinoids, are testing traditional drug control systems to their limits
- There seems to be an endless stream of novel materials
 - EMCDDA : 73 NPS in 2012; >50 in 2013 so far
- Development of new products to replace banned materials is faster than the legal response time
 - Gather data (including toxicology), assess risk, legislate
- UN and EC trying to catch up
- Innovative national approaches are being developed
- How to frame controls without provoking marketing of more, and potentially more dangerous, substances ?

Some big questions :

- What will appear next ?
 - Yet more new (and legal) cannabinoids possible
- Can legal controls ever end the trade ?
 - Or will the trade just continue via the internet ?
 - An underground ‘virtual’ market place
- Can legal controls be enforced ?
 - Supply : how to police internet trading ? (TOR/‘Silk Road’ + ‘Bitcoins’)
 - Possession/supply : can drugs labs identify the many possible substances ? (UK FEWS initiative)
- Detecting use ?
 - What are the metabolites ?
 - Can toxicology labs routinely identify them? (role of LC-MS-MS)
- How do forensic and toxicology labs keep up ?
 - Need for national and international systems for information sharing, including analytical data and access to reference materials



Excellence through measurement



Excellence through measurement

