

ACMD

Advisory Council on the Misuse of Drugs

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Rt. Hon. Theresa May MP
Home Office
2 Marsham Street
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18th October 2012

Dear Home Secretary,

Further consideration of the synthetic cannabinoids

In July 2009 the Advisory Council on the Misuse of Drugs (ACMD) provided advice on harmful synthetic compounds (synthetic cannabinoid receptor agonists). These compounds had been identified in samples of smoking mixes such as 'Spice' and have a pharmacology similar to that of cannabis¹. At the time, these previously unreported compounds were outside the control of the Misuse of Drugs Act (1971). It was concluded that these novel substances contained compounds with the potential for harm, similar to the harms of cannabis. Therefore, the ACMD recommended the compounds considered in that review should be made Class B and placed in Schedule I of the Misuse of Drugs Regulations (2001) under a generic definition.

Given the wide range of compounds reported in the literature, the ACMD proposed five generic definitions for the synthetic cannabinoid agonists and five substances listed by name. The purpose of the generic definitions was to control similar compounds that would have associated harms that could be introduced at a later date. The cannabinoids targeted for control under these generic definitions were CB₁ receptor agonists, identified by their ability to bind to this receptor. The CB₁ receptor in the brain mediates the psychoactive effects of the principle active compounds in cannabis (Tetrahydrocannabinol (THC) and Cannabinol (CBN)).

The ACMD's previous advice made clear that generic control for these compounds would likely require updating as those intent on producing such compounds find ways to circumvent the legislation.

¹ <http://www.homeoffice.gov.uk/acmd1/acmd-report-agonists?view=Binary>

At present, an ever increasing number of compounds are being promoted by internet retailers as legal versions of, or alternatives to, controlled drugs. Websites vary greatly in their quality, from reliable sources to 'rip-off' sites, but certain themes in their offerings are apparent. For those drug groups which are controlled in the UK by generic legislation, such as the synthetic cannabinoids, gaps in the generic controls are being exploited which permit 'designer' versions (specifically formulated to have certain effects and avoid legislation) to be offered.

As with all 'legal highs' the ACMD would caution the correlation of 'brand name' to constituent compounds – these are rarely consistent and compounds may be different to those advertised on the packet or at point of sale. This is an important point when considering the reporting of brands for sale without supporting analysis.

Test purchasing from UK forensic and intelligence units, including reports from Guernsey and the Isle of Man, indicates that there are a number of synthetic cannabinoids outside of existing legislation that are available for purchase through the internet. Many of the mixtures available under different brand names contain the same compounds, for example AM2201 has been identified in 'Black Mamba', 'Annihilation', 'Tai High Hawaiian Haze' and 'Bombay Blue Extreme'.

The compounds are generally available as ingredients of smoking products, but are also available from websites as pure compounds which purchasers can combine with herbal materials to produce their own smoking mixtures.

Prevalence of the synthetic cannabinoids

Synthetic cannabinoids are an issue of concern internationally. The ACMD understands that an estimated total of 2,977 reports of synthetic cannabinoids were submitted to State and local forensic laboratories in the United States from 1 January to 31 December 2010. This is a considerable increase from the estimated 15 synthetic cannabinoid reports identified during 2009 (in part this may be due to increased detection, and therefore not prevalence). However, the active compounds at the time of seizure cannot anyway be readily identified.

Data from the Home Office Forensic Early Warning System (FEWS) in July 2012 included results from a test purchasing exercise showing the presence of uncontrolled synthetic cannabinoids, such as AM2201, RCS-4 and UR-144, in substances on sale via the internet. In addition, the FEWS has identified AM-2201 in samples recovered from attendees at music festivals during the summer months of 2012. Seizures received up to July 2012 from Jersey have indicated a number of compounds found in a variety of named brands.

Two seizures from Scotland (Strathclyde police), marketed as 'Annihilation' and analysed in June, have been found to contain un-controlled cannabinoids (AM-2201, MAM-2201 and UR144). In addition to these compounds, one sample contained the controlled analog of JWH -122.

Information has been collated through the Home Office Drugs Early Warning System (July 2012) from National Treatment Agency local teams. Several nil responses were received from local areas; however, there were also a significant number of reports from partnership teams of anecdotal user reports, test purchases and forensic

testing. In summary, the information made available indicates a trend towards increased availability and use of synthetic cannabinoids that are currently outside legal control in the UK.

It should be noted that detection of novel synthetic cannabinoids is potentially an issue, as police dogs are not trained to detect the substances and there is no routine urine test currently available for employment drug testing and testing of arrestees and prisoners.

Chemistry and pharmacology

When the UK's generic controls on synthetic cannabinoids were developed in 2009, they were based on the published research of JW Huffman's research team (the team developed many of the JWH compounds) of a number of other compounds which were known at the time. A number of modifications of Huffman's basic structures have since appeared and fall outside the UK controls. These are based on other published research, such as the work of Alexandros Makriyannis at North Eastern University who developed the 'AM' range of compounds. The USA "Synthetic Drug Control Act 2012" defines synthetic cannabinoids (known in the USA as cannabimimetic agents) as "any substance that is a cannabinoid receptor type CB₁ agonist as demonstrated by binding studies and functional pharmacological tests".

Modifications of chemical structure noted since the 2009 report include:

- Substitution with halogen atoms on the side chain attached to the indole nitrogen atom (for example AM 694, AM 2201). It appears that such modifications can enhance potency. The onset of psychoactive effects of AM2201 are cited as occurring rapidly and may last for up to 3 hours (ReDNET, 2012).
- Modification of the indole nitrogen substitution into a methylpiperidin-2-yl structure (AM 1220, AM 2233).
- Use of a benzoylindole core structure (AM-694, RCS-4). This structure was not included in the 2009 generic controls.
- Replacement of the benzoyl/naphthoyl structure by an adamantoyl group (AB-001, AM-1248).
- Replacement of the benzoyl/naphthoyl structure by a tetramethylcyclopropylcarbonyl group (UR-144, AB-034).

Other variants are appearing, however, current knowledge indicates that many of these compounds do not seem to be particularly psychoactive and/or are primarily CB₂ agonists, rather than CB₁, and so are not an issue that presently needs to be addressed.

Examples of synthetic cannabinoids incorporating the above modifications, together with CB₁ binding data (where available), seizure data and availability are listed in Annex B.

In structures containing naphthoyl and adamantoyl groups, positional isomers may also be exploited and, as identification of a particular positional isomer could impose an unnecessary burden on forensic providers, we propose broadening the definitions of controlled compounds of these types to include all possible structures.

Physical Harms

There is limited data available on the patterns of acute harm associated with the use of synthetic cannabinoid receptor agonists. AM2201 has psychoactive effects and anecdotal user reports suggest that it can produce severe adverse effects: increased heart rate, panic attacks and convulsions (RedNet, 2012). Recently, there has been a report of an individual who smoked 'black mamba' and presented to an Emergency Department with convulsions. Analysis of biological samples confirmed that the convulsions were due to AM2201 (McQuade, 2012). A police report from a central England force details three separate incidents in early 2012 that resulted in the hospitalisation of five young people who had taken 'Black Mamba'. However, there was no toxicological screening of blood/urine samples to be able to determine which synthetic cannabinoid receptor agonists were responsible and/or to exclude the use of other drugs. The ACMD notes that the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published a briefing paper that identifies potential harms (EMCDDA, 2011).

With regard to the product branded 'Annihilation' (see above for analytical chemistry) Strathclyde Police issued a public health warning following 13 people whom were taken to hospital between July and October this year. The ACMD are not aware of any deaths linked to the substance branded as 'Annihilation'.

Tomiyama and Funada (2011) reported that the synthetic cannabinoids CP-55,940, CP-47,497 and CP-47,497-C8 were cytotoxic to NG 108-15 cells in tissue culture, and the effects were prevented by the CB₁ antagonist AM251, but not by the CB₂ antagonist AM630. If this has any relevance to human users, it needs to be established.

In the USA synthetic cannabinoids are reported to have resulted in nationwide emergency department visits for severe agitation, sympathomimetic toxicity, and death (Rosenbaum *et al*, 2012). Texas Poison Centres recorded 464 cases of cannabinoid-related toxicity in 2010, the most common features being tachycardia, agitation, drowsiness, vomiting, hallucinations and nausea (Forrester *et al*, 2011).

There is very limited data available on chronic toxicity and dependence associated with the use of synthetic cannabinoid receptor agonists. However there have been isolated reports of acute withdrawal associated with cessation of long-term use of these products suggesting their use may be associated with dependence (Zimmermann, 2009). There have also been reports of psychosis and other psychiatric presentations associated with their use (Every-Palmer, 2010, Every-Palmer, 2010, Benford, 2011, Tung, 2012), however, it is too early to be able to determine the role of synthetic cannabinoid receptor agonists in the symptoms reported in these presentations.

The National Poisons Information Service (NPIS) is a network of specialist poisons information units commissioned by the Health Protection Agency. The purpose of the NPIS is to assist the NHS in poisons management of patients. During the period 1st January to 30th June 2012 there were 532 accesses (web site) to Toxbase² under

² The primary clinical toxicology database of the NPIS

the term 'synthetic cannabinoids'. Of these, 356 were related to synthetic cannabinoid agonists not currently controlled in the UK and 334 were to the page on 'Black Mamba'. The data show that enquiries about synthetic cannabinoids have increased over time.

Social Harms

Evidence concerning the social harms of the synthetic cannabinoids is scarce and there is little in the scientific literature because of their relatively recent appearance.

The Crime Survey for England and Wales – Drug Misuse Declared 2011/12 highlights that 0.1% of 16 to 59 year olds reported using 'Spice' and other cannabinoids in the last year. For 2010/11, the figure was 0.2%. It is reasonable to expect that the societal harms would be comparable to those of cannabis.

FRANK

The FRANK website provides information about synthetic cannabinoids. It provides details of appearance, use, effects and the legal situation. The information suggests it is very likely that synthetic cannabinoids will produce harmful effects similar to those associated with THC and CBN (the active ingredients of cannabis) because of the way the chemicals in synthetic cannabinoids work. The information also cautions that many synthetic cannabinoids are new substances and so they may have further unknown effects.

Recommendations

Recommendation 1

The ACMD recommends that the substances detailed in Annex A, herein termed synthetic cannabinoids, have potential harms commensurate with those of cannabis and should, therefore, be classified and controlled under the Misuse of Drugs Act (1971) as Class B (2001) under an extended generic definition³.

Recommendation 1 above represents an extension to the ACMD's 2009 advice on the synthetic cannabinoids.

Recommendation 2

The ACMD has conducted a non-exhaustive search of the potential uses of synthetic cannabinoids and therefore recommends that those compounds covered by the proposed generic definition (listed in Annex A) are placed in Schedule 1 of the Misuse of Drugs Regulations (2001) on the grounds they have no recognised medicinal use.

Recommendation 3

The ACMD has carefully considered the available legislative vehicles available in making this recommendation for full control under the Misuse of Drugs Act 1971. In making this recommendation it is important that there is on-going *active monitoring* of the prevalence and harms of the synthetic cannabinoids listed. The ACMD will

³ Annex A also includes a small correction to the chemical nomenclature in one of the generic definitions currently provided for in the legislation.

look to conduct this through relevant channels and will provide you with further advice should there be substantive developments.

Recommendation 4

Public health messaging, through FRANK, should be kept up to date based on the most recent information available.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Les Iversen". The signature is written in a cursive style with a large initial 'L'.

Professor Les Iversen

Cc:

Minister of State for Crime Prevention
Parliamentary Under Secretary of State for Health

Annex A.

Extended generic definition of the synthetic cannabinoid receptor based agonists.

Proposed changes to the current generic definitions:

Any compound structurally derived from 3-(1-naphthoyl) indole, 3-(2-naphthoyl) indole, 1H-indol-3-yl-(1-naphthyl)methane or 1H-indol-3-yl-(2-naphthyl)methane by substitution at the nitrogen atom of the indole ring by alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent and whether or not substituted in the naphthyl ring to any extent.

Any compound structurally derived from 3-(1-naphthoyl)pyrrole or 3-(2-naphthoyl)pyrrole by substitution at the nitrogen atom of the pyrrole ring by alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the pyrrole ring to any extent and whether or not substituted in the naphthyl ring to any extent.

Any compound structurally derived from 1-(1-naphthylmethylene)indene or 1-(2-naphthylmethylene)indene by substitution at the 3-position of the indene ring by alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indene ring to any extent and whether or not substituted in the naphthyl ring to any extent.

Any compound structurally derived from 3-phenylacetylindole by substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent.

Proposed additional generic definitions (to that above):

Any compound structurally derived from 3-benzoylindole by substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent.

Any compound structurally derived from 3-(1-adamantoyl) indole or 3-(2-adamantoyl)indole by substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent and whether or not substituted in the adamantyl ring to any extent.

Any compound structurally derived from 3-(2,2,3,3-tetramethylcyclopropylcarbonyl)indole by substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent.

No changes proposed for this generic definition:

Any compound structurally derived from 2-(3-hydroxycyclohexyl)phenol by substitution at the 5-position of the phenolic ring by alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the cyclohexyl ring to any extent.

Stereoisomers, esters, ethers and salts

Schedule 2, Part 2 also includes any stereoisomers, ester or ether, salts, preparations and other products.

Annex B

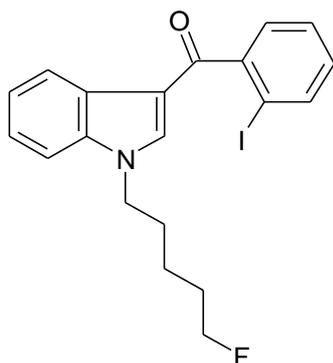
Examples of Synthetic Cannabinoid Receptor Agonists not controlled by the Misuse of Drugs Act but which have been encountered in seizures or collected samples, or are available on websites, and which will be captured by the proposed revisions to the generic definition.

Since the introduction in the UK of generic legislation in 2009 to control the synthetic cannabinoid receptor agonists, a number of new substances have appeared on the market that fall outside the scope of this legislation. Compounds with a low affinity for the CB₁ receptor ($K_i > 100\text{nM}$) would not normally be attractive to users as they would be more than 10x less potent than THC. However, a number of new substances with low affinity for the CB₁ receptor have been encountered in commercial products and are therefore included in the examples below:

Compounds with haloalkyl sidechains

AM-694

1-(5-Fluoropentyl)-3-(2-iodobenzoyl)indole



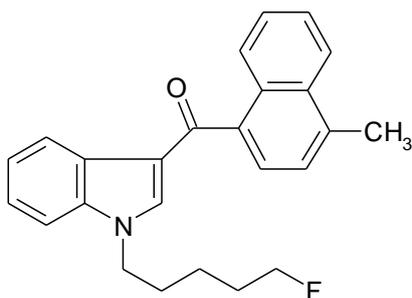
Binding affinity: K_i (CB₁) = 0.08nM; K_i (CB₂) = 1.44nM

Comments:

1. EMCDDA Early Warning System Report 2010 - Collected samples of "Shamrock" herbal mixture from Head Shop in Dublin
2. Makriyannis A, Deng H (2001) Cannabimimetic indole derivatives. *WO Patent 2001/028557 A1, assignee University of Connecticut.*
3. Makriyannis A, Deng H (2001) Cannabimimetic indole derivatives. *US Patent 2005/0119234 A1, assignee University of Connecticut.*

MAM-2201

1-(5-fluoropentyl)-3-(4-methyl-naphthoyl)indole
(4-methyl homologue of AM-2201)



Binding affinity: no data, but structure is related to JWH-122 [K_i (CB_1) = 0.69 nM] and AM-2201 [K_i (CB_1) = 1.0 nM]:

Comments:

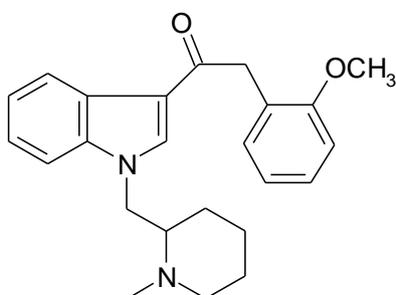
1. EMCDDA Early Warning System Report 2011 - large seizure in the Netherlands
2. EMCDDA Early Warning System Report 2011 – collected sample of herbal product “XoXo” in Germany. Also contained AM-2201 and reported to be available from www.goldkraut.com
3. EMCDDA Early Warning System Report 2012 - two seizures in Finland mixed with AM-2201

Compounds with (N-methylpiperidin-2-yl)methyl sidechains

Cannabipiperidiethanone

1-(N-methylpiperidin-2-yl)methyl-3-(2-methoxyphenylacetyl)indole

1-(N-methylpiperidin-2-yl)methyl derivative of JWH-250



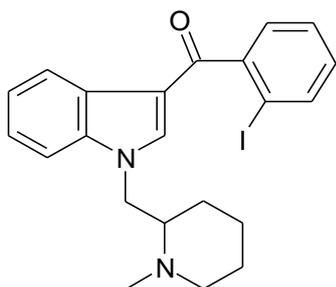
Binding affinity: K_i (CB_1) = 591nM; K_i (CB_2) = 968nM

Comments:

1. EMCDDA Early Warning System Report in 2011: substance was found in 20 different samples of herbal mixtures from Polish ‘smart shops’ October 2010. The samples also contained JWH-122 and procaine.
2. Identified in a herbal product in Japan together with JWH-122 and JWH-081 Uchiyama N, Kikura-Hanajiri R, Goda Y (2011) Identification of a Novel Cannabimimetic Phenylacetylindole, Cannabipiperidiethanone, as a designed Drug in a Herbal Product and its affinity for cannabinoid CB_1 and CB_2 receptors. *Chem. Pharm. Bull.* 59 (9), 1203-1205.

AM-2233

1-[(N-methylpiperidin-2-yl)methyl]-3-(2-iodobenzoyl)indole



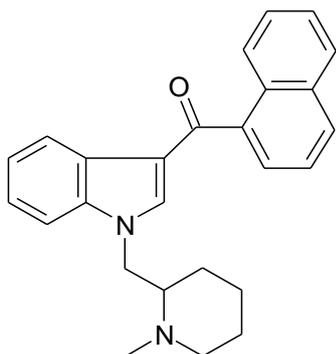
Binding affinity: K_i (CB₁) = 3.4 nM; K_i (CB₂) = 7.6 nM [1]

Comments:

1. EMCDDA Early Warning System Report 2011 – seizure in Finland.
2. Hongfeng Deng (2000) Design and synthesis of selective cannabinoid receptor ligands: Aminoalkylindole and other heterocyclic analogs. *PhD Dissertation, University of Connecticut.*

AM-1220

1-[(N-methylpiperidin-2-yl)methyl]-3-(1-naphthoyl)indole



Binding affinity: K_i (CB₁) = 3.88 nM; K_i (CB₂) = 73.4 nM

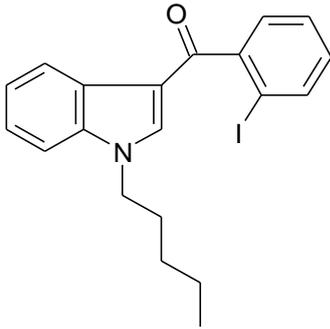
Comments:

1. EMCDDA Early Warning System Report 2011 – collected sample of herbal mixture (“Soulman”). Also contained AM-1220 azepane isomer.
2. Makriyannis A, et al. (2008) Cannabimimetic Indole Derivatives, *US Patent 2008/0090871*

Benzoylindoles

AM-679

1-pentyl-3-(2-iodobenzoyl)indole



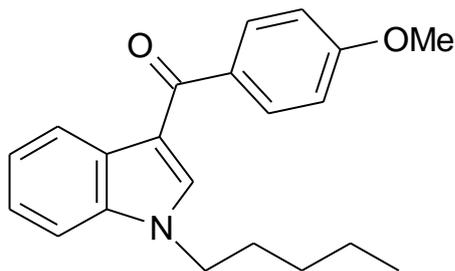
Binding affinity: K_i (CB_1) = 13.5nM; K_i (CB_2) = 49.5nM

Comments:

1. Was available from www.legalchem.co.uk (this website no longer exists), was also available from other sites for example <http://www.thrivechem.com/am-679-40595-p.asp>
2. Makriyannis A, Deng H (2001) Cannabimimetic indole derivatives. *WO Patent 2001/028557 A1, assignee University of Connecticut.*
3. Makriyannis A, Deng H (2001) Cannabimimetic indole derivatives. *US Patent 2005/0119234 A1, assignee University of Connecticut.*

RCS-4 and the C4 homologue

1-pentyl-3-(4-methoxybenzoyl)indole



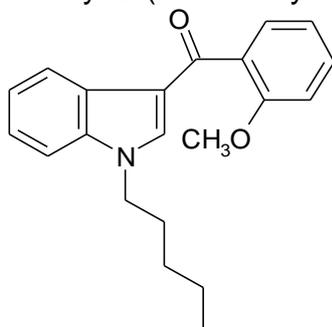
Binding affinity: no data

Comments:

1. EMCDDA Early Warning System 2010 – seizure in Hungary

RCS-4 2-isomer

1-Pentyl-3-(2-methoxybenzoyl)indole



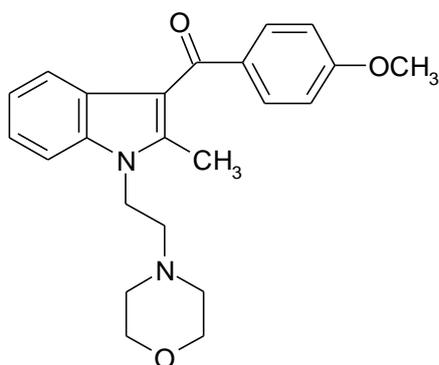
Binding affinity: no data

Comments:

1. EMCDDA Early Warning System Report 2011 – seizure in Sweden
2. Available from <http://legalhighzone.com/rcs-4.html>

WIN 48,098 (Pravadoline)

1-(2-Morpholin-4-ylethyl)-2-methyl-3-(4-methoxybenzoyl)indole



Binding affinity: K_i (CB₁) = 3155 nM [2]

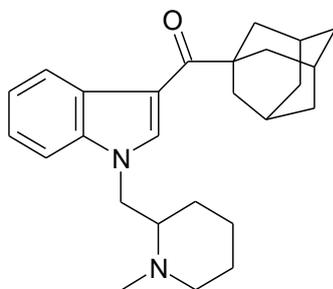
Comments:

1. EMCDDA Early Warning System Report 2010 - seizures of products labelled "GIT ROMAN" and "TAWNIOL" in Poland from 'smart shops'. Other active ingredients included AM-694, JWH-081 and JWH-250
2. EMCDDA Early Warning System Report 2011 – seizure of product labelled "Love" in Germany. Also contained AM-694

Adamantoylindoles

AM-1248

3-(1-Adamantoyl)-1-(N-methylpiperidin-2-ylmethyl)indole



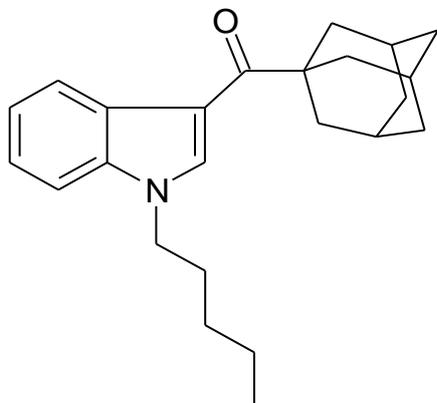
Binding affinity: K_i (CB₁) = 100 nM; K_i (CB₂) = 332 nM

Comments:

1. At least 2 vendors are reported to be selling this in the United States. Available from <http://legalhighzone.com/am-1248.html> (lasted checked 28/5/2012)
2. Notification was received from the EMCDDA 26th Sept 2012 reporting AM-1248 as an ingredient of 'Annihilation' (the smoking mixture which has recently been reported to be causing problems amongst school children in the North of England.)
http://www.thisislancashire.co.uk/news/9947927. Legal_high_puts_Darwen_boy_in_hospital/
<http://www.sunderlandecho.com/news/health/legal-high-taken-off-shelves-after-substance-landed-teenager-in-hospital-1-4890988>

AB-001

1-Pentyl-3-(1-adamantoyl)indole
JW-018 adamantyl analogue



Binding affinity: no data

Comments:

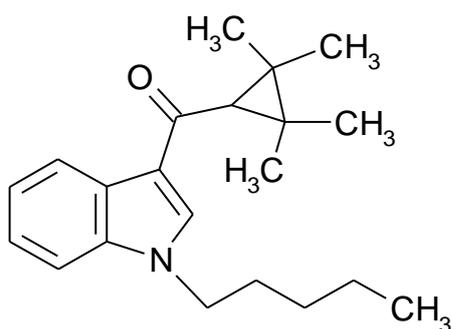
1. EMCDDA Early Warning System Report 2011 - collected samples of "Nuclear Reactor", "Toxic Waste" and "Radio Active" herbal mixtures in Germany.
NOTE: the structure shown in the EMCDDA report is actually the 2-adamantoyl isomer

3-(2,2,3,3-Tetramethylcyclopropylcarbonyl)indoles

These are primarily CB₂ agonists, but some have significant affinity for the CB₁ receptor.

UR-144.

1-Pentyl-3-(2,2,3,3-tetramethylcyclopropylcarbonyl)indole



K_i(CB₁) = 150nM

Frost, J.M. et al., (2010). *Journal of Medicinal Chemistry*, 53, 295-315. Available from: <https://www.buyresearchchemicals.co.uk/cannabinoids/ur-144.html>

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- Tung CK, Chiang TP, Lam M (2012) Acute mental disturbance caused by synthetic cannabinoid: a potential emerging substance of abuse in Hong Kong. *East Asian Archives Psychiatry*. 22(1):31-3
- UNOCD (2011) Synthetic Cannabinoids in herbal products (January 2011) http://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf
- U.S. Senate Bill S.3178 passed – May 24, 2012, Synthetic Drug Abuse Prevention Act of 2012

U.S. Department of Justice, Drug Enforcement Administration, (Special Report),
Synthetic Cannabinoids and Synthetic Cathinones Reported in NFLIS, 2009 - 2010

Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K
(2009) Withdrawal phenomena and dependence syndrome after the consumption of
"spice gold". Deutsches Aerzteblatt International 106(27):464