Faculty of Science & Technology

An assessment of the effects synthetic cannabinoids can have on a person's ability to drive

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Abstract

Cannabis is one of the most commonly used drugs for its euphoric effects but due to its psychotropic effects it has been categorised as a Class B drug. As cannabis became illegal many people turned to what they believed to be a safe legal alternative to cannabis. Because of this reason synthetic cannabinoids emerged into the market. These are man-made chemicals that mimic the effects of cannabis. Although they were classed as 'legal' they were not necessarily safe. As cannabis was one of the most common drugs used found in driving cases this dissertation aimed to look at synthetic cannabinoids and the effect they have on a persons' ability to drive.

To do this a series of monographs will describe the occurrence and usage, blood concentration, metabolism and excretion, toxicity and the use of synthetic cannabinoids in driving under the influence cases. Identifying the relevant specific synthetic cannabinoids in the literature and extracting the related information that is reported created these monographs.

The information collected provides evidence that synthetic cannabinoids cause impairment. Using standardised field sobriety tests, clues were noted by drug recognition experts that indicated impairment for the suspects. Blood concentrations in the related cases were reported to suggest what kind of concentration could produce that level and kind of impairment. Each monograph produced, details the effects that the relevant synthetic cannabinoid has on impairment and the person's ability to drive. Thereby producing further evidence about effects of synthetic cannabinoids in humans that can be used to aid further research and to contribute to law enforcement.

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I would also like to give thanks to my supervisor David Osselton for his continued support and advice throughout the writing of this dissertation.

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List of Abbreviations

5C-MN-24 -	1-(5-chloropentyl)-N-1-naphthalenyl-1H-indole-3-carboxamide
5F-AB-PINACA -	N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
5F-ADB -	N-[[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl]-3-methyl-D-valine, methyl ester
5F-AEB -	ethyl (1-(5-fluoropentyl)-1H-indazole-3-carbonyl)-L-valinate
5F-AMB -	N-[[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl]-L-valine, methyl ester
5F-APINACA -	N-((3s,5s,7s)-adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
5F-JWH-122 -	[1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthalenyl)-methanone
5F-JWH-210 -	(4-ethyl-1-naphthalenyl)[1-(5-fluoropentyl)-1H-indol-3-yl]-methanone
5F-MN-18 -	1-(5-fluoropentyl)-N-1-naphthalenyl-1H-indazole-3-carboxamide
5F-MN-24 -	1-(5-fluoropentyl)-N-(naphthalen-1-yl)-1H-indole-3-carboxamide
5F-PCN -	1-(5-fluoropentyl)-N-(naphthalen-1-yl)-1H-pyrrolo[3,2c]pyridine-3-carboxamide
5F-QUPIC -	1-(5-fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid
5F-SDB-005 -	naphthalen-1-yl 1-(5-fluoropentyl)-1H-indazole-3-carboxylate
5F-SDB-006 -	1-(5-fluoropentyl)-N-(phenylmethyl)-1H-indole-3-carboxamide
5F-UR-144 -	(1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
A-796,260 -	[1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone
A-834,735 -	[1-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone
A-836,339 -	[N(Z)]-N-[3-(2-methoxyethyl)-4,5-dimethyl-2(3H)-thiazolylidene]-2,2,3,3-tetramethyl-cyclopropanecarboxamide

AB-001 -	(1s,3s)-adamantan-1-yl(1-pentyl-1H-indol-3-yl)methanone
AB-005 -	[1-[(1-methyl-2-piperidinyl)methyl]-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone
AB-CHFUPYCA -	(S)-N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide
AB-CHMINACA -	N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide
AB-FUBINACA -	N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide
AB-PINACA -	(S)-N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide
ADB-CHMINACA -	N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide
ADB-FUBINACA -	N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide
ADB-PINACA -	N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-pentyl-1H-indazole-3-carboxamide
ADBICA -	N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indole-3-carboxamide
AM-1220 -	[1-[(1-methyl-2-piperidinyl)methyl]-1H-indol-3-yl]-1-naphthalenyl-methanone
AM-1235 -	[1-(5-fluoropentyl)-6-nitro-1H-indol-3-yl]-1-naphthalenyl-methanone
AM-1241 -	(2-iodo-5-nitrophenyl)-(1-(1-methylpiperidin-2-ylmethyl)-1H-indol-3-yl)methanone
AM-1248 -	[1-[(1-methyl-2-piperidinyl)methyl]-1H-indol-3-yl]tricyclo[3.3.1.13,7]dec-1-yl-methanone
AM-2201 -	[1-(5-fluoropentyl)-1H-indol-3-yl]-1-naphthalenyl-methanone
AM-2232 -	3-(1-naphthalenylcarbonyl)-1H-Indole-1-pentanenitrile
AM-2233 -	(2-iodophenyl)[1-[(1-methyl-2-piperidinyl)methyl]-1H-indol-3-yl]-methanone
AM-630 -	[6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl](4-methoxyphenyl)-methanone

AM-679 -	(2-iodophenyl)(1-pentyl-1H-indol-3-yl)-methanone
AM-694 -	[1-(5-fluoropentyl)-1H-indol-3-yl](2-iodophenyl)-methanone
AMB -	N-[(1-pentyl-1H-indazol-3-yl)carbonyl]-L-valine, methyl ester
APICA -	1-pentyl-N-tricyclo[3.3.1.$1^{3,7}$]dec-1-yl-1H-indole-3-carboxamide
APINACA -	1-pentyl-N-tricyclo[3.3.1.13,7]dec-1-yl-1H-indazole-3-carboxamide
APP-FUBINACA -	N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide
AZ-037 -	(S)-N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-5-(4-fluorophenyl)-1H-pyrazole-3-carboxamide
BIM-018 -	naphthalen-1-yl(1-pentyl-1H-benzo[d]imidazol-2-yl)methanone
CB-13 -	1-naphthalenyl[4-(pentylox)-1-naphthalenyl]-methanone
CB1 -	Cannabinoid Receptor 1
CB1 -	Cannabinoid Receptor 2
CP 47,497 -	*rel*-5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol
CP 55,940 -	5-(1,1-dimethylheptyl)-2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-phenol
DUID -	Driving Under the Influence
EC50 -	Concentration that is effective to 50% of the population
EG-018 -	naphthalen-1-yl(9-pentyl-9H-carbazol-3-yl)methanone
FAB-144 -	(1-(5-fluoropentyl)-1H-indazol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
FDU-PB-22 -	1-[(4-fluorophenyl)methyl]-1H-indole-3-carboxylic acid, 1-naphthalenyl ester
FU-AEB -	ethyl (1-(4-fluorobenzyl)-1H-indazole-3-carbonyl)-L-valinate
FUB-144 -	(1-(4-fluorobenzyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
FUB-AMB -	methyl (1-(4-fluorobenzyl)-1H-indazole-3-carbonyl)-L-valinate
FUB-APINACA -	N-((3s,5s,7s)-adamantan-1-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide

FUB-PB-22 - 1-[(4-fluorophenyl)methyl]-1H-indole-3-carboxylic acid, 8-quinolinyl ester

FUBIMINA - (1-(5-fluoropentyl)-1H-benzo[d]imidazol-2-yl)(naphthalen-1-yl)methanone

HU-210 - 3-(1,1'-dimethylheptyl)-6aR,7,10,10aR-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol

HU-308 - 4-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methanol

JWH-007 - (2-methyl-1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-015 - (2-methyl-1-propyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-018 - (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-019 - (1-hexyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-073 - (1-butyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-081 - (4-methoxy-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone

JWH-098 - (4-methoxy-1-naphthalenyl)(2-methyl-1-pentyl-1H-indol-3-yl)-methanone

JWH-116 - (2-ethyl-1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone

JWH-122 - (4-methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone

JWH-149 - (4-methyl-1-naphthalenyl)(2-methyl-1-pentyl-1H-indol-3-yl)-methanone

JWH-167 - 1-(1-pentyl-1H-indol-3-yl)-2-phenyl-ethanone

JWH-182 - (1-pentyl-1H-indol-3-yl)(4-propyl-1-naphthalenyl)-methanone

JWH-193 - (4-methyl-1-naphthalenyl)[1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]-methanone

JWH-198 - (4-methoxy-1-naphthalenyl)[1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]-methanone

JWH-200 - [1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]-1-naphthalenyl-methanone

JWH-203 - 2-(2-chlorophenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone

JWH-210 - (4-ethyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone

JWH-249 - 2-(2-bromophenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone

JWH-250 - 1-(1-pentyl-1H-indol-3-yl)-2-(2-methoxyphenyl)-ethanone

JWH-251 - 2-(2-methylphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone

JWH-302 - 2-(3-methoxyphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone

JWH-398 - (4-chloronaphthalen-1-yl)(1-pentylindolin-3-yl)-methanone

JWH-424 - (8-bromonaphthalen-1-yl)(1-pentyl-1H-indol-3-yl)methanone

LY-2183240 - 5-([1,1'-biphenyl]-4-ylmethyl)-N,N-dimethyl-1H-tetrazole-1-carboxamide

MDA-19 - (2Z)-2-(1-hexyl-1,2-dihydro-2-oxo-3H-indol-3-ylidene)hydrazide, benzoic acid

MDMB-CHMICA - methyl (S)-2-(1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate

MDMB-CHMINACA - N-[[1-(cyclohexylmethyl)-1H-indazol-3-yl]carbonyl]-3-methyl-L-valine, methyl ester

MDMB-FUBINACA - N-[[1-[(4-fluorophenyl)methyl]-1H-indazol-3-yl]carbonyl]-3-methyl-L-valine, methyl ester

MEPIRAPIM - (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl)methanone, monohydrochloride

MMB-2201 - methyl (1-(5-fluoropentyl)-1H-indole-3-carbonyl)-L-valinate

MN-18 - N-1-naphthalenyl-1-pentyl-1H-indazole-3-carboxamide

MN-24 - N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide

MN-25 - 7-methoxy-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S,4R)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-1H-indole-3-carboxamide

NESS-0327 - 8-chloro-1-(2,4-dichlorophenyl)-1,4,5,6-tetrahydro-N-1-piperidinyl-benzo[6,7]cyclohepta[1,2-c]pyrazole-3-carboxamide

NM-2201 - naphthalen-1-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate

Org-28611 - [1-(cyclohexylmethyl)-7-methoxy-1H-indol-3-yl](3,4-dimethyl-1-piperazinyl)-methanone

Pravadoline - (4-methoxyphenyl)[2-methyl]-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]-methanone

PX-1 - (S)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide

PX-2 - (S)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide

PX-3 - N-[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]-1-(cyclohexylmethyl)-1H-Indazole-3-carboxamide

QUCHIC -	1-(cyclohexylmethyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid
QUPIC -	1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid
RCS-4 -	(4-methoxyphenyl)(1-pentyl-1H-indol-3-yl)methanone
RCS-8 -	1-(1-(2-cyclohexylethyl)-1H-indol-3-yl)-2-(2-methoxyphenyl)ethanone
SDB-005 -	naphthalen-1-yl 1-pentyl-1H-indazole-3-carboxylate
SDB-006 -	1-pentyl-N-(phenylmethyl)-1H-indole-3-carboxamide
STS-135 -	1-(5-fluoropentyl)-N-tricyclo[3.3.1.13,7]dec-1-yl-1H-indole-3-carboxamide
THJ-018 -	1-naphthalenyl(1-pentyl-1H-indazol-3-yl)-methanone
THJ-2201 -	[1-(5-fluoropentyl)-1H-indazol-3-yl]-1-naphthalenyl-methanone
UR-144 -	(1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone

1. Introduction

1.1 Background

This dissertation will cover the topic of synthetic cannabinoids and their use by drivers who were detained for driving under the influence of drugs (DUID). Cannabis, or marijuana, is one of the most common drugs used across the world (Moore et al. 2007). Cannabis is made from the *Cannabis Sativa* and *Cannabis Indica* plants, using the dried leaves and flowers (Bernard Le Foll 2015).

The use of Cannabis originates from the initial addition of the plant into extracts of medicine in China and India as early as the birth of Christ. Cannabis was first used therapeutically in Western medicine around the first half of the 19th century. It was initially prescribed for pain, asthma, coughing and as a sedative. The use of Cannabis for medicinal purposes faded out during the 20th century due to the potency of Cannabis varying and more stable pharmaceutical products being manufactured.

Cannabis became extremely popular as a recreational drug as it affects almost every system in the body. It has an effect on mood by creating a euphoric effect and a feeling of intoxication, as well as decreasing anxiety, alertness, depression and tension. Additionally, it is known to increase sociability, if taken in friendly surroundings. It effects the users perception and can make colours seem more vibrant; music more vivid and can heighten an individual's emotions (Johns 2001).

Although Cannabis causes effects that are perceived as positive for users, there are other effects that could be considered negative. The use of Cannabis impairs cognitive and psychomotor performance. It reduces reaction times, causes defects in the users short-term memory, motor incoordination, difficulty in concentrating and impairment when undertaking tasks in which attention is divided between multiple tasks. Cannabis has been found to be the most prevalent illicit drug that has been identified in drivers involved in either fatal incidents or drivers that have been stopped for impaired driving across the UK, USA, Australia, New Zealand and many European countries (Ashton 2001).

Cannabis produces these effects as the main constituent delta-9-tetrahydrocannabinol (THC) has been shown to have a very high binding affinity with the cannabinoid receptor, CB1, and when consumed it stimulates CB1 receptor in both the brainstem and the gastrointestinal tract (Darmani et al. 2014). Cannabis has also been known to bind to the cannabinoid receptor, CB2.

In todays day and age, the use of Cannabis has significantly changed due to extensive research being undertaken and concluding that the main constituent within Cannabis, (THC), is actively psychotropic and therefore rendering Cannabis as a Class B drug in the UK (Zuardi et al. 2006).

Due to cannabis' illegal status, many people started using synthetic cannabinoids as an alternative; they produce similar effects to that of cannabis. This is because they bind to the same receptors as Cannabis, but due to their dissimilar chemical structure they were legal when they first became available.

The first report regarding of the use of synthetic cannabinoids was in 2004, and then the increased use of them was reported in 2008 (Winstock and Barratt 2013). The more popular they became, the more restrictions were placed on these types of drugs. To get around the restriction of the drug laws and regulations, while selling these products they were classed as incense and packaged "not for human consumption" (Vandrey et al. 2012).

Synthetic cannabinoids are man-made chemical compounds that as stated, bind to cannabinoid receptors in the brain. The chemicals are genetically modified to alter the chemical structure by changing as little as one element to get around the legal restrictions. These chemicals are usually sprayed onto dried plants, to then be smoked, thus creating a perception that they are a very similar substitute to Cannabis (Baker 2015).

Appendix I shows a list of synthetic cannabinoids with their structure, molecular weight and more importantly their potency. This shows how by genetically modifying these substances and changing their structure it has also significantly

changed their potency, and also the ranges of the potency between different synthetic cannabinoids. Thus showing that the more potent the synthetic cannabinoid is, the less of the compound is needed.

Synthetic cannabinoids can be separated into several families related to their structure. The 11 different families are called Benzoylindole, Naphthoylindole, Phenylacetylindole, Indazolecarboxamide, Cyclohexylphenyl, Naphthylmethylindole, Naphthylpyrrole, Naphthylmethylindene Aminoalkylindole, Adamantoylindoles, Tetramethylcyclopropylketone indole, Quinolinyl ester indole and Dibenzopyran (Solimini et al. 2017).

As synthetic cannabinoids were legal, many people perceived them to be a safer version of Cannabis. However, it can be disputed that synthetic cannabinoids are in fact more harmful in relation to their side effects. These include seizures due to the fact that cannabis is an anti-convulsant (Winstock and Barratt 2013). Synthetic cannabinoids have been researched and analysed in order to find the pharmacology of these substances. Psychological effects documented include changes in mood and perception, anxiety, loss of concentration, sedation and paranoia (White 2016). As the popularity of synthetic cannabinoids increased, more research was needed to fully understand the effects they have on the body. Cohen et al. (2017) recognised the following harmful side-effects; recurrent psychosis, tachycardia, seizures and a higher risk of developing dependence from persistent usage.

Synthetic cannabinoids became more renowned to their increase in popularity. As a result, their effects on the body became more apparent but manufacturers would avoid legislation laws by subtly changing the structure of a specific synthetic cannabinoid that had previously been restricted. To avoid manufacturers being able to do this the United Kingdom Home Office (2016) passed the Psychoactive Substances Act. This Act makes it an offence to produce, supply, offer to supply, and import or export psychoactive substances. Therefore it restricts the production of synthetic cannabinoids.

Cannabis is one of the most common drugs found in DUID cases. Synthetic cannabinoids have grown in use due to their similar effects to that of Cannabis. Due to this information, research on the use of synthetic cannabinoids in relation to driving and what effects they produce on a persons ability to drive needs to be explored. To do this a series of monographs will need to be produced to show the pharmacology of a select group of synthetic cannabinoids.

1.2 Aims & Objectives

Aims

The aim of this research is to produce a series of monographs that identify and present the effects the more commonly used synthetic cannabinoids have on a person's ability to drive.

Objectives

The objectives below have been set out in order to achieve the above aim;

- To research synthetic cannabinoids and find any that have been involved in driving under the influence cases.
- To select the most common synthetic cannabinoids in DUID cases to research in depth.
- Find information on these synthetic cannabinoids in relation to their occurrence, metabolism and toxicity.
- Use the information found to produce monographs detailing the use of synthetic cannabinoids in DUID.
- Detail the signs symptoms the drivers exhibit.

1.3 Methodology

This dissertation is a literature-based report and therefore the entire project is a literature review. At the start of the report, it was discussed that the best way to find relevant information on the synthetic cannabinoids was to initially search the library database, and then use further scientific databases, such as Science Direct, Medline and PubMed, to find information and build on the depth from there.

Whilst going through the list of synthetic cannabinoids and reading relevant journals and articles, a list of keywords was produced.

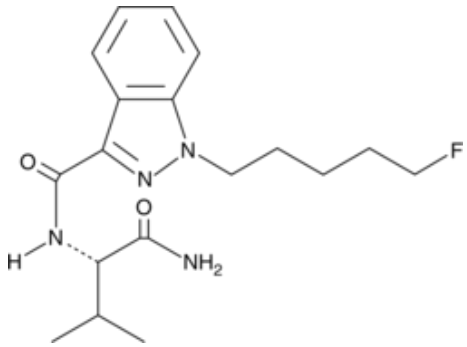
The list of keywords was then used in combination with the list of synthetic cannabinoids when searching in scientific databases and when searching through history of cases. This established a focus for the project and ensured all of the relevant information had been covered and explored in depth before analysis. Also during the search, once a relevant journal or article was identified, the author was used as a search to see if they had published further research on other applicable synthetic cannabinoids. It is highly conceivable for an author to publish articles of related studies to the work they have previously published.

Due to the timescale on the literature searches only the most commonly used synthetic cannabinoids were used to produce monographs on. This action was also appropriate due to the majority of DUID case examples in current literature focusing on these main synthetic cannabinoids. Each of these monographs is referenced in the correct style at the end of the monograph for ease of finding the journal where the information was sourced from for each synthetic cannabinoid.

The monographs are written in a similar style to that of Clarke's analysis of drugs and poisons (Moffat et al. 2011) and Disposition of toxic drugs and chemicals in man (Baselt and Cravey 2011), to make them easily accessible for further research to be undertaken using this work. Also the publications for these books were extremely successful using this format.

2. Monographs

2.1 5F-AB-PINACA



IUPAC Name: N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-(5-fluoropentyl)-1H-indazole-3-carboxamide

Molecular Formula: $C_{18}H_{25}FN_4O_2$

Occurrence and Usage: 5F-AB-PINACA is a carboxamide composed of 1-(5-fluoropentyl)-1*H*-indazole-3-carboxylic acid and a valine amide/methyl ester that was identified in 2014 (Doi et al. 2016). It is a derivative of the synthetic cannabinoid AB-PINACA (Uchiyama et al. 2013).

Blood Concentration: In a reported case from an experts finding there was a blood concentration of 0.4ng/ml of 5F-AB-PINACA detected with several clues to indicate impairment (Peterson and Couper 2015).

Metabolism and Excretion: In a report by Wohlfarth et al. (2015) 18 metabolites were identified through carboxamide hydrolysis, hydroxylation, ketone formation, carboxylation, epoxide formation with subsequent hydrolysis, or reaction combinations. A further 2 metabolites were produced through oxidative defluorination. AB-PINACA pentanoic acid and 5-hydroxypentyl-AB-PINACA we the most concentrated metabolites produced. 5F-AB-PINACA is excreted through urine and the presences of these metabolites through authentic urine samples were documented.

Toxicity: 5F-AB-PINACA has been found to be a potent agonist of the CB1 and CB2 receptors and has effective concentrations of 048nM and 2.6nM respectively (Banister et al. 2015).

DUID Cases: In a documented case a suspect was tested for a suspicion of driving under the influence. There were 6 clues possible for horizontal gaze nystagmus, there was noticeable vertical gaze nystagmus, a lack of convergence, their pupil size was described as normal and eyelid tremors were not detected. They had an average pulse of 84 beats/min, a blood pressure of 120/68mmHg and a body temperature of 98.1°F. During the walk and turn test there was 1 clue that was presented and noted. There was also 1 clue detected during the one-legged stand test. Blood was taken and a concentration of 0.4ng/ml of 5F-AB-PINACA was detected, as well as concentrations of 0.3ng/ml of UR-144 and 4.4ng/ml of AB-CHMINACA. (Peterson and Couper 2015).

References

Banister, S.D., Moir, M., Stuart, J., Kevin, R.C., Wood, K.E., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Glass, M. and Connor, M., 2015. Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS chemical neuroscience*, *6*(9), pp.1546-1559.

Doi, T., Asada, A., Takeda, A., Tagami, T., Katagi, M., Kamata, H. and Sawabe, Y., 2016. Enantioseparation of the carboxamide-type synthetic cannabinoids N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide and methyl [1-(5-fluoropentyl)-1H-indazole-3-carbonyl]-valinate in illicit herbal products. *Journal of Chromatography A*, *1473*, pp.83-89.

Peterson, B.L. and Couper, F.J., 2015. Concentrations of AB-CHMINACA and AB-PINACA and driving behavior in suspected impaired driving cases. *Journal of analytical toxicology*, *39*(8), pp.642-647.

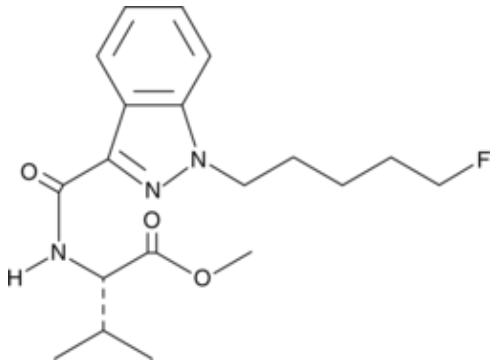
Uchiyama, N., Matsuda, S., Wakana, D., Kikura-Hanajiri, R. and Goda, Y., 2013. New cannabimimetic indazole derivatives, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA) and N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA)

identified as designer drugs in illegal products. *Forensic Toxicology*, *31*(1), pp.93-100.

Wohlfarth, A., Castaneto, M.S., Zhu, M., Pang, S., Scheidweiler, K.B., Kronstrand, R. and Huestis, M.A., 2015. Pentylindole/pentylindazole synthetic cannabinoids and their 5-fluoro analogs produce different primary metabolites: metabolite profiling for AB-PINACA and 5F-AB-PINACA. *The AAPS journal*, *17*(3), pp.660-677.

2.2 5F-AMB

IUPAC Name: N-[[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl]-L-valine, methyl ester



Synonyms: 5F-AMP

Molecular Formula: $C_{19}H_{26}FN_3O_3$

Occurrence and Usage: 5F-AMB is a synthetic cannabinoid that belongs to the indazole-3-carboxamide family. It was first reported as a constituent in herbal incense and potpourri products on the Japanese drug market in 2014. It is a derivative of the synthetic cannabinoid AB-PINACA (Shanks and Behonick 2016). 5F-AMB is a controlled substance in the United States, Germany, Sweden, Singapore, Japan and China (Drug Enforcement Agency 2016).

Blood Concentration: 5F-AMB is a synthetic cannabinoid that was detected in a fatal case, when the cause of death was classed as accidental death due to synthetic cannabinoid toxicity. A concentration of 0.3ng/ml of 5F-AMB was detected through liquid chromatography-tandem mass spectrometry (LC/MS/MS) (Shanks and Behonick 2016).

Metabolism and Excretion: In a report by Andersson et al. (2016) 17 metabolites were detected. These metabolites were produced through oxidative defluorination

and hydroxylation. The most intense metabolites that were produced were 5F-AMB carboxylic acid, 5'-hydroxypentyl AMB carboxylic acid, and carboxypentyl AMB carboxylic acid. It was also found that 5F-AMB had a low metabolic stability and therefore rapidly metabolized.

Toxicity: There is not much pharmacological information in the literature about 5F-AMB and its toxicity. However the 4-cyanobutyl analogue of 5F-AMB has been reported to be a potent agonist for the CB1 receptor with a concentration of 0.7nM (Banister et al. 2016).

DUID Cases: Although there isn't much information on any cases involving driving under the influence there is information on its effects. There are various effects that can occur, these include seizures, tachycardia, acute kidney injury and death (Shanks and Behonick 2016). These symptoms suggest how driving under the influence of 5F-AMB could cause incidents due to impairment.

References

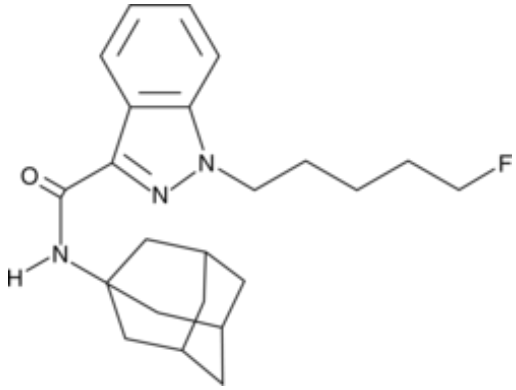
Andersson, M., Diao, X., Wohlfarth, A., Scheidweiler, K.B. and Huestis, M.A., 2016. Metabolic profiling of new synthetic cannabinoids AMB and 5F- AMB by human hepatocyte and liver microsome incubations and high- resolution mass spectrometry. *Rapid Communications in Mass Spectrometry*, *30*(8), pp.1067-1078.

Banister, S.D., Longworth, M., Kevin, R., Sachdev, S., Santiago, M., Stuart, J., Mack, J.B., Glass, M., McGregor, I.S., Connor, M. and Kassiou, M., 2016. Pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and their analogues. *ACS Chemical Neuroscience*, *7*(9), pp.1241-1254.

Drug Enforcement Administration, Department of Justice, 2016. Schedules of Controlled Substances: Temporary Placement of Six Synthetic Cannabinoids (5F-ADB, 5F-AMB, 5F-APINACA, ADB-FUBINACA, MDMB-CHMICA and MDMB-FUBINACA) Into Schedule I. Notice of Intent. *Federal register*, *81*(245), p.93595.

Shanks, K.G. and Behonick, G.S., 2016. Death after use of the synthetic cannabinoid 5F-AMB. *Forensic science international*, *262*, pp.e21-e24.

2.3 5F-APINACA



IUPAC Name: N-((3s,5s,7s)-adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide

Synonyms: 5F-AKB48

Molecular Formula: $C_{23}H_{30}FN_3O$

Occurrence and Usage: 5F-APINACA is an indazole based synthetic cannabinoid that is also known as 5F-AKB-48. It was identified in South Korea in 2013 as a derivative of the synthetic cannabinoid APINACA (Chung et al. 2014). 5F-APINACA is a controlled substance in the United States, Germany and China as well as being a banned substance in the Czech Republic (Drug Enforcement Agency 2016).

Blood Concentration: A report by Karinen et al. (2015) shows blood concentrations in a driving under the influence cases when 5F-APINACA has been detected. The blood concentration ranges from 0.9µg/L to 6.5µg/L.

Metabolism and Excretion: Holm et al. (2015) wrote a paper that described the metabolism of 5F-APINACA. 16 metabolites were detected in human urine. The main metabolites that were produced were monohydroxylated, dihydroxylated and trihydroxylated either just on the adamantyl group or can also be combined with hydroxylation on the N-fluoropentylindazole moiety. More common metabolites can be produced through the oxidative loss of fluorine also in combination with mono and dihydroxylation on the adamantyl ring.

Toxicity: 5F-APINACA when it was first discovered was expected to be a potent agonist of the CB1 and CB2 receptors. However it has been reported that 5F-

APINACA is a full agonist of CB1 and CB2 receptors with binding affinities of 1.94nM and 0.266nM, respectively (Hess et al. 2016).

DUID Cases: In a report by Karinen et al. (2015) there were four driving under the influence cases with 5F-APINACA detected. In the four cases that were reported the blood concentrations were 0.9µg/L, 6.5µg/L, 2.2µg/L and 5.3µg/L. However the report doesn't show any roadside tests that indicate impairment, although there would likely have been signs of impairment for blood to be taken and tested.

References

Chung, H., Choi, H., Heo, S., Kim, E. and Lee, J., 2014. Synthetic cannabinoids abused in South Korea: drug identifications by the National Forensic Service from 2009 to June 2013. *Forensic toxicology*, *32*(1), pp.82-88.

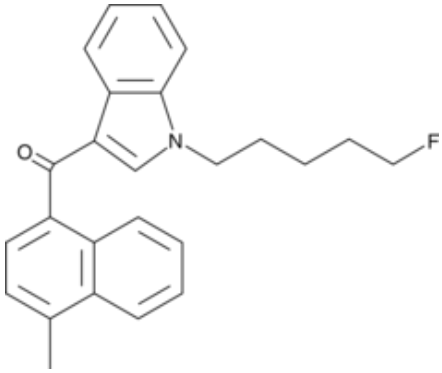
Drug Enforcement Administration, Department of Justice, 2016. Schedules of Controlled Substances: Temporary Placement of Six Synthetic Cannabinoids (5F-ADB, 5F-AMB, 5F-APINACA, ADB-FUBINACA, MDMB-CHMICA and MDMB-FUBINACA) Into Schedule I. Notice of Intent. *Federal register*, *81*(245), p.93595.

Hess, C., Schoeder, C.T., Pillaiyar, T., Madea, B. and Müller, C.E., 2016. Pharmacological evaluation of synthetic cannabinoids identified as constituents of spice. *Forensic toxicology*, *34*(2), pp.329-343.

Holm, N.B., Pedersen, A.J., Dalsgaard, P.W. and Linnet, K., 2015. Metabolites of 5F- AKB- 48, a synthetic cannabinoid receptor agonist, identified in human urine and liver microsomal preparations using liquid chromatography high- resolution mass spectrometry. *Drug testing and analysis*, *7*(3), pp.199-206.

Karinen, R., Tuv, S.S., Øiestad, E.L. and Vindenes, V., 2015. Concentrations of APINACA, 5F-APINACA, UR-144 and its degradant product in blood samples from six impaired drivers compared to previous reported concentrations of other synthetic cannabinoids. *Forensic science international*, *246*, pp.98-103.

2.4 5F-JWH-122



IUPAC Name: [1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthalenyl)-methanone

Synonyms: MAM-2201

Molecular Formula: $C_{25}H_{24}FNO$

Occurrence and Usage: 5F-JWH-122, also known as MAM-2201, was first identified as an ingredient in synthetic cannabis in The Netherlands and Germany due to experiments being undertaken in June 2011 (Simolka et al. 2012). Structurally it is a combination of two fellow synthetic cannabinoids AM-2201 and JWH-122. Although it has not being formally identified in Italy, 5F-JWH-122 became a controlled substance in May 2011; this is likely due to the reports made by other countries at the time (Lonati et al 2014).

Blood Concentration: A report by Kim et al. (2015) describes a case in which 21 samples of hair were taken when 5F-JWH-122 was seized. The report shows how the concentration varied between 0.2pg/mg and 276.0pg/ml; additionally a concentration of 49µg/L was detected in a study by Derungs et al. (2013).

Metabolism and Excretion: Jang et al. (2014) presented a study that showed the metabolic pathways for 5F-JWH-122. Their results show that 5F-JWH-122 readily underwent oxidative dehalogenation to produce JWH-122 *N*-5-OH and MAM-2201 *N*-COOH. Another metabolite that was found in the study was MAM-2201 *N*-4-OH, this is a characteristic metabolite of 5F-JWH-122.

Toxicity: A case review in Switzerland stated a 31-year-old male smoked 300mg of 5F-JWH-122 and within a few minutes' symptoms such as agitation, aggression, anxiety, confusion, panic, vomiting, dilated pupils, tachycardia, elevated blood pressure and hyperglycaemia were present. A urine drug screen took place

around 3 hours after inhalation and 49µg/L of 5F-JWH-122 was detected (Derungs et al. 2013).

Another study in Germany stated a 17-year-old male smoked and unknown amount and suffered symptoms such as, somnolence, tachycardia, mydriasis, unequal pupil sizes and retrograde amnesia shortly after smoking. Less than 12 hours after inhalation a concentration of 0.2µg/L of 5F-JWH-122 was detected (Hermanns-Clausen et al.2013).

A report by Saito et al. (2013) describes a case in which a 59-year-old Japanese man was found deceased in his house with 3 sachets of herbal blends on a table, these were later discovered to be 5F-JWH-122. During the forensic autopsy there were concentrations of 5F-JWH-122 in the blood, liver, kidney, brain and adipose tissue, the concentrations that were found were 12.4ng/ml, 18.1ng/ml, 11.2ng/ml, 4.3ng/ml and 1.535ng/ml respectively. It was concluded that the cause of death was acute intoxication from 5F-JWH-122.

DUID Cases: A case was reported when a 22-year-old male overran a red traffic light and later tried to escape arrest by running on foot. On his arrest police noted that the male had a retarded movement sequence, apathetic, nervous, inert, and delayed reaction of pupils to light. It was later found that the male had a blood concentration of 0.1ng/ml of 5F-JWH-122, this was also in combination with AM-2201, JWH-018, JWH-122, JWH-210, JWH-307 and UR-144 with concentrations of 0.1ng/ml, 1.9ng/ml, 28ng/ml, 2.5ng/ml, 0.1ng/ml and 0.1ng/ml respectively. (Musshoff et al. 2014).

References

Derungs, A., Schwaninger, A.E., Mansella, G., Bingisser, R., Kraemer, T. and Liechti, M.E., 2013. Symptoms, toxicities, and analytical results for a patient after smoking herbs containing the novel synthetic cannabinoid MAM-2201. *Forensic toxicology*, *31*(1), pp.164-171.

Hermanns- Clausen, M., Kneisel, S., Hutter, M., Szabo, B. and Auwärter, V., 2013. Acute intoxication by synthetic cannabinoids–four case reports. *Drug testing and analysis*, *5*(9-10), pp.790-794.

Jang, M., Shin, I., Yang, W., Chang, H., Yoo, H.H., Lee, J. and Kim, E., 2014. Determination of major metabolites of MAM-2201 and JWH-122 in in vitro and in vivo studies to distinguish their intake. *Forensic science international*, *244*, pp.85-91.

Kim, J., Park, Y., Park, M., Kim, E., Yang, W., Baeck, S., Lee, S. and Han, S., 2015. Simultaneous determination of five naphthoylindole-based synthetic cannabinoids and metabolites and their deposition in human and rat hair. *Journal of pharmaceutical and biomedical analysis*, *102*, pp.162-175.

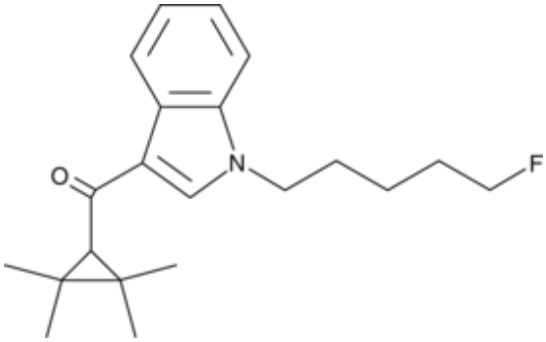
Lonati, D., Buscaglia, E., Papa, P., Valli, A., Coccini, T., Giampreti, A., Petrolini, V.M., Vecchio, S., Serpelloni, G. and Locatelli, C.A., 2014. MAM-2201 (analytically confirmed) intoxication after “Synthacaine” consumption. *Annals of emergency medicine*, *64*(6), pp.629-632.

Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V., 2014. Driving under the influence of synthetic cannabinoids (“Spice”): a case series. *International journal of legal medicine*, *128*(1), pp.59-64.

Saito, T., Namera, A., Miura, N., Ohta, S., Miyazaki, S., Osawa, M. and Inokuchi, S., 2013. A fatal case of MAM-2201 poisoning. *Forensic Toxicology*, *31*(2), pp.333-337.

Simolka, K., Lindigkeit, R., Schiebel, H.M., Papke, U., Ernst, L. and Beuerle, T., 2012. Analysis of synthetic cannabinoids in “spice-like” herbal highs: snapshot of the German market in summer 2011. *Analytical and bioanalytical chemistry*, *404*(1), pp.157-171.

2.5 5F-UR-144



IUPAC Name: (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone

Synonyms: XLR-11

Molecular Formula: $C_{11}H_{28}FNO$

Occurrence and Usage: 5F-UR-144 is a synthetic cannabinoid most commonly known a XLR-11; it is a derivative of another synthetic cannabinoid UR-144. It was first reported when it was detected in herbal incense products in Japan in 2012. In 2013 the Drug Enforcement Agency placed 5F-UR-144 into Schedule I of the Controlled Substance Act (Shanks et al. 2015).

Blood Concentration: In the first documented case for driving under the influence of 5F-UR-144 a blood concentration of 1.34ng/ml was quantified (Lemos 2014).

Metabolism and Excretion: Park et al. (2015) used a quantitative analytical method to analyse the metabolites of XLR-11 and the parent drug itself in hair by liquid chromatography (LC). 14 hair samples were taken for analysis and the results showed that XLR-11 UR-144, UR-144 *N*-5-hydroxypentyl metabolite and UR-144 *N*-pentanoic acid metabolite, XLR-11 *N*-4-hydroxypentyl metabolite were detected across all the samples. As XLR-11 was the parent drug its concentrations found were much higher than that of the other metabolites. The metabolite UR-144 *N*-4- hydroxypentyl was not detected in all of the samples that were taken.

Toxicity: 5F-UR-144 is found to be a potent agonist for the CB1 and CB2 receptors with effective concentrations of 98nM and 83nM respectively (Banister et al. 2015). Reports of the use of this drug have been linked to acute kidney injury in some users (Thornton et al. 2013).

DUID Cases: Louis et al. (2014) produced a report in which the presence of XLR-11 was found in driving under the influence cases. A 27-year-old male was stopped for driving with an inconsistent speed and colliding with a barrier multiple times. In a summary of physical observations it was found that his eyes were bloodshot and pupils were dilated, horizontal gaze nystagmus was not noticed. His speech appeared to be slurred. The presence of body and eyelid tremors were not present, however blood was taken 1 hour and 50 minutes after the initial contact and the blood analysis found XLR-11.

In another case another 27-year-old male was apprehended after travelling between lanes and hitting the curb frequently before going off the road. A summary of his physical observations were noted and it was stated that the male had poor coordination, his eyes were bloodshot, pupils were dilated and there was a lack of convergence, however there was no noticeable horizontal gaze nystagmus but body and eyelid tremors were present. During the walk and turn test, one-legged stand test and finger to nose test there were 4, 1 and 2 clues respectively that were noticed. The male admitted to smoking 72 hours prior, his blood was attained 2 hours and 45 minutes after contact and blood analysis detected the presence of XLR-11.

A 30-year-old male was attained after failing to stop at a stop sign. He was found to have bloodshot eyes and constricted pupils as well as providing 6 clues towards horizontal gaze nystagmus. During the walk and turn test there were 4 clues and during the one-legged stand test there were 2 clues present. The male admitted smoking 2 hours prior to driving and XLR-11 was present in the blood that was obtained 4 hours and 45 minutes after initial contact.

Police were notified about a 17-year-old male who was driving with severe lane travel, nearly making contact with another vehicle and nearly driving into a ditch. The police noticed that the male's eyes were bloodshot, watery and his pupils were dilated. During the roadside tests no noticeable clues were present however the male admitted to smoking whilst driving and the presence of XLR-11 was found in the male's blood that was taken approximately 1 hour and 30 minutes after initial contact.

A 22-year-old male was found unconscious in his vehicle near a busy intersection, it was reported that he also nearly hit other vehicles and pedestrians. He was found to have poor coordination as well as slurred speech. His eyes were bloodshot, watery and his pupils were dilated as well as producing 4 clues towards horizontal gaze nystagmus. 3 clues were present for both the walk and turn test and the one-legged stand test. The male denied using in the past day but XLR-11 was detected in the blood that was taken 1 hour and 30 minutes after contact.

A 19-year-old male was contacted due to traffic violations. It was noted that the male's eyes were bloodshot, watery and that his eyelids were droopy, also it was noted that he had a lack of convergence as well as producing 6 clues for horizontal gaze nystagmus. He was said to have poor coordination and that his speech was slurred. Body tremors were noticed, however eyelid tremors were not. There was 1 clue on both the walk and turn test and the one-legged stand, but there were 5 clues present on the finger to nose test. The male's internal clock signified that he thought 30 seconds had passed when in fact 44 seconds had. He admitted to smoking 4 hours prior and blood was taken 2 hours and 45 minutes after contact. The blood showed the presence of XLR-11.

Another case showed a 22-year-old male who was stopped by members of the public and the fire department as he was driving on the curb. Police noted that the male had bloodshot eyes and droopy eyelids and also had slow coordination. 6 clues were present for horizontal gaze nystagmus. During the walk and turn test, one-legged stand test and finger to nose test there were 2, 1 and 5 clues respectively that were noticed. The male admitted to smoking 1 hour prior to driving and XLR-11 was present in the blood that was taken 90 minutes from the initial contact.

The final case involving XLR-11 shows a 23-year-old male who was stopped by police after he was driving for 20 miles in the wrong direction of traffic. It was noted that the male had bloodshot eyes, a lack of convergence, eyelid tremors but no horizontal gaze nystagmus. There were 2 clues present on both the walk and turn test and one-legged stand test and 3 clues on the finger to nose test. The male

admitted to smoking twice in the previous day and also 1 hour prior to driving. Blood was taken 1 hour and 45 minutes after contact and it showed the presence of XLR-11.

References

Banister, S.D., Stuart, J., Kevin, R.C., Edington, A., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Hibbs, D.E., Glass, M. and Connor, M., 2015. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS chemical neuroscience*, *6*(8), pp.1445-1458.

Lemos, N.P., 2014. Driving Under the Influence of Synthetic Cannabinoid Receptor Agonist XLR- 11. *Journal of forensic sciences*, *59*(6), pp.1679-1683.

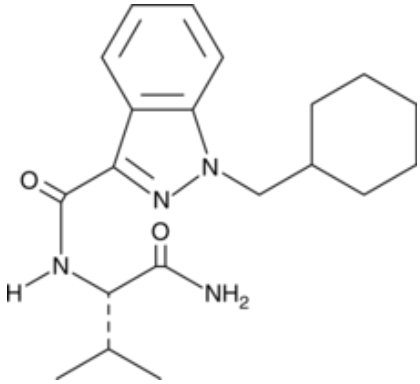
Louis, A., Peterson, B.L. and Couper, F.J., 2014. XLR-11 and UR-144 in Washington state and state of Alaska driving cases. *J Anal Toxicol*, *38*(8), pp.563-568.

Park, M., Yeon, S., Lee, J. and In, S., 2015. Determination of XLR-11 and its metabolites in hair by liquid chromatography–tandem mass spectrometry. *Journal of pharmaceutical and biomedical analysis*, *114*, pp.184-189.

Shanks, K.G., Winston, D., Heidingsfelder, J. and Behonick, G., 2015. Case reports of synthetic cannabinoid XLR-11 associated fatalities. *Forensic science international*, *252*, pp.e6-e9.

Thornton, S.L., Wood, C., Friesen, M.W. and Gerona, R.R., 2013. Synthetic cannabinoid use associated with acute kidney injury. *Clinical Toxicology*, *51*(3), pp.189-190.

2.6 AB-CHMINACA



IUPAC Name: N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide

Molecular Formula: $C_{20}H_{28}N_4O_2$

Occurrence and Usage: AB-CHMINACA is a member of the AB-INACA family; it has an indazole-carboxamide backbone with an amino-methyl-oxobutanyl group. It was first reported in 2013 in Japan; it was placed as a Schedule 1 drug in 2015 (Sim et al 2017).

Blood Concentration: Peterson and Couper (2015) produced an article that reviews 33 cases in which AB-CHMINACA was found in drivers; in these cases there was a blood concentration range of 0.6 ng/ml to 10 ng/ml.

Metabolism and Excretion: Erratico et al. (2015) produced a report in which a study of the metabolism of AB-CHMINACA was monitored. 26 metabolites of AB-CHMINACA were produced, using the cytochrome P450 enzyme 14 metabolites were produced, 7 of which were mono-hydroxylated, six of which were di-hydroxylated metabolites and one metabolite resulted from the *N*-dealkylation of AB-CHMINACA. Amidase enzymes were used to produce further metabolites such as, 2 carboxylated metabolites and 5 glucoronidated metabolites.

Toxicity: AB-CHMINACA has been found to be a potent agonist against the CB1 and CB2 receptors with values of 0.78nM and 0.45nM respectively (Wiley et al. 2015).

DUID Cases: In a report by Peterson and Couper (2015) there were 7 cases that report an experts finding involving the use of AB-CHMINACA in driving cases. One case reports that there were 6 clues for horizontal gaze nystagmus as well as suffering from vertical gaze nystagmus, a lack of convergence and dilated pupils.

The suspect was reported to have an average pulse of 70 beats/min, blood pressure of 110/68mmHg and a body temperature of 98.8°F. Both the walk and turn and the one-legged stand tests showed 4 clues to suggest impairment. It was reported that they had a blood concentration of 2.3ng/ml.

Another case shows the suspect suffering from vertical gaze nystagmus, a lack of convergence and dilated pupils. There were also 6 clues towards horizontal gaze nystagmus. The suspect had an average pulse of 98 beats/min, blood pressure of 110/60mmHg and a body temperature of 98.1°F. Both the walk and turn test and one-legged stand test produced 1 clue towards impairment. They had a blood concentration of 2.4ng/ml of AB-CHMINACA.

There is a case where a suspect did not suffer from vertical gaze nystagmus or a lack of convergence. They also showed no clues towards horizontal gaze nystagmus and their pupils were normal. They had an average pulse of 95 beats/min, blood pressure of 108/70mmHg and a body temperature of 98.4°F. However, they showed 7 clues and 3 clues towards the walk and turn test and one-legged stand test respectively. A blood concentration of 3.5ng/ml was detected.

In a similar case a suspect also showed no vertical gaze nystagmus, lack of convergence and no clues towards horizontal gaze nystagmus and also had normal pupils. They had an average pulse of 63 beats/min, blood pressure of 110/58mmHg and body temperature of 97°F. The suspect showed 1 clue during the walk and turn test and 2 clues during the one-legged stand test. They had a blood concentration of 4.5ng/ml.

Another case showed a suspect who also showed no vertical gaze nystagmus, lack of convergence or clues towards horizontal gaze nystagmus, however, the suspect had dilated pupils. They had an average pulse of 83 beats/min, blood pressure of 132/86mmHg and a body temperature of 98°F. There were no clues towards impairments during both the walk and turn test and the one-legged stand test. However they had a blood concentration of 6.3ng/ml.

In another case no clues were present for horizontal gaze nystagmus, vertical gaze nystagmus and a lack of convergence were present, their pupils were classed as normal. They had an average pulse of 71 beats/min, blood pressure of 115/50mmHg and body temperature of 99.2°F. During the walk and turn test and the one-legged stand test there were 4 and 3 clues respectively, indicating impairment. Blood was taken and a concentration of 7.3ng/ml was recorded.

Another case shows a suspect that showed no clues towards horizontal gaze nystagmus or a lack of convergence, however vertical gaze nystagmus was present and their pupils were dilated. They had an average pulse of 102 beats/min, blood pressure of 124/80mmHg and a body temperature of 99.3°F. There were 4 clues present during the walk and turn test but no clues were present during the one-legged stand test. They had a blood concentration of 9.5ng/ml.

References

Erratico, C., Negreira, N., Norouzizadeh, H., Covaci, A., Neels, H., Maudens, K. and Nuijs, A.L., 2015. In vitro and in vivo human metabolism of the synthetic cannabinoid AB- CHMINACA. *Drug testing and analysis*, *7*(10), pp.866-876.

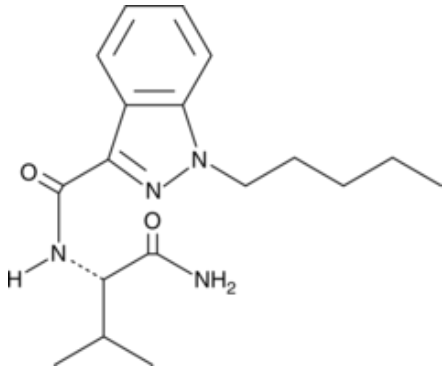
Peterson, B.L. and Couper, F.J., 2015. Concentrations of AB-CHMINACA and AB-PINACA and driving behavior in suspected impaired driving cases. *Journal of analytical toxicology*, *39*(8), pp.642-647.

Sim, J., Cho, H.S., Lee, J., In, S. and Kim, E., 2017. Determination of AB-CHMINACA and its metabolites in human hair and their deposition in hair of abusers. *Journal of Pharmaceutical and Biomedical Analysis*.

Wiley, J.L., Marusich, J.A., Lefever, T.W., Antonazzo, K.R., Wallgren, M.T., Cortes, R.A., Patel, P.R., Grabenauer, M., Moore, K.N. and Thomas, B.F., 2015. AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency of Novel Synthetic Cannabinoids in Producing Δ9-Tetrahydrocannabinol–Like Effects in

Mice. *Journal of Pharmacology and Experimental Therapeutics*, *354*(3), pp.328-339.

2.7 AB-PINACA



IUPAC Name: (S)-N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide

Molecular Formula: $C_{18}H_{26}N_4O_2$

Occurrence and Usage: AB-PINACA is a compound first identified in synthetic cannabis in Japan in 2012 (Uchiyama et al. 2013). It has been listed as a controlled substance in Germany since November 2014, it has been illegal in Singapore since May 2015, designated a controlled substance in China as of October 2015 and categorised as a controlled substance in USA (Drug Enforcement Agency 2015).

Blood Concentration: In an article by Peterson and Couper (2015) in which they review 25 cases in which AB-PINACA was found in DUID; the blood concentrations that they report range from 0.6ng/ml to 41.3ng/ml.

Metabolism and Excretion: Wohlfarth et al. (2015) produced a study on the metabolism of AB-PINACA in which 23 metabolites were produced through methods such as carboxamide hydrolysis, hydroxylation, ketone formation and carboxylation. They report that the most intense metabolites that were produced were AB-PINACA carboxylic acid, carbonyl AB-PINACA, hydroxypentyl AB-PINACA, carbonyl AB-PINACA carboxylic acid, and a hydroxypentyl AB-PINACA carboxylic acid isomer.

Toxicity: AB-PINACA has been found to be a potent agonist against the CB1 and CB2 receptors with effective concentrations of 1.2nM and 2.5nM respectively (Banister et al. 2015).

DUID Cases: Peterson and Couper (2015) review 9 cases in which the use of AB-PINACA was found in suspects of DUID cases. One case reports that a suspect showed 4 clues towards horizontal gaze nystagmus as well as a lack of convergence, however vertical gaze nystagmus was not present. The suspect's pupils were constricted in dark conditions. They had an average pulse of 79 beats/min, blood pressure of 80/50mmHg and a body temperature of 96.3°F. There were 6 clues present during the walk and turn test and 2 clues present during the one-legged stand test. There was a blood concentration of 4.6ng/ml.

Another case indicated 6 clues for horizontal gaze nystagmus, and both vertical gaze nystagmus and a lack of convergence were present. Their pupils were dilated when in direct light. They had an average pulse of 96 beats/min, blood pressure of 82/50mmHg and a body temperature of 97.6°F. During the walk and turn test and the one-legged stand test there was 6 clues and 4 clues present respectively. They had a blood concentration of 5.7ng/ml.

A suspect indicated 5 clues towards horizontal gaze nystagmus, but vertical gaze nystagmus and a lack of convergence were not present. They had an average pulse of 86 beats/min, blood pressure of 122/78mmHg and a body temperature of 98.3°F. The walk and turn test indicated only 1 clue towards impairment and the one-legged stand test indicated 2 clues. They were found to have a blood concentration of 8.3ng/ml.

Another case showed 4 clues towards horizontal gaze nystagmus as well as vertical gaze nystagmus, however a lack of convergence was not present and their pupils were dilated. Their average pulse was 75 beats/min, blood pressure was 108/60mmHg and a body temperature of 99.1°F. There was only 1 clue during the walk and turn test and no clues were present during the one-legged stand test. A blood concentration of 9.1ng/ml was found.

Another case when a blood concentration of 9.1ng/ml was recorded showed 6 clues towards horizontal gaze nystagmus and a lack of convergence was present. However vertical gaze nystagmus was not present and their pupils were classed as normal. They had an average pulse of 57 beats/min, blood pressure of 102/56mmHg and a body temperature of 97°F. 3 clues were present during the walk and turn test and 2 clues were present during the one-legged stand test.

There were 3 cases in which a blood concentration of more than 10ng/ml was present. None of the 3 cases indicated any clues for horizontal gaze nystagmus or vertical gaze nystagmus and 2 of the 3 cases showed a lack of convergence. 2 cases showed that their pupils were normal and the other case showed dilated pupils. The average pulse in the 3 cases ranged from 57 beats/min to 87 beats/min, the blood pressures ranged from 102/68mmHg to 140/70mmHg and the body temperatures ranged from 96.7°F and 97.9°F. The clues in the walk and turn test ranged from 2 clues to 5 clues and in the one-legged stand test they ranged from 2 clues to 3 clues.

Another case showed no clues towards horizontal gaze nystagmus or vertical gaze nystagmus. A lack of convergence was present and the pupils were classed as normal. The suspect had an average pulse of 67 beats/min, blood pressure of 118/84mmHg and a body temperature of 98.1°F. During the walk and turn test there were 2 clues indicating impairment and during the one-legged stand test there was 1 clue indicating impairment. Blood was taken and it was found that they had a concentration of 41.3ng/ml.

References

Banister, S.D., Moir, M., Stuart, J., Kevin, R.C., Wood, K.E., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Glass, M. and Connor, M., 2015. Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS chemical neuroscience*, *6*(9), pp.1546-1559.

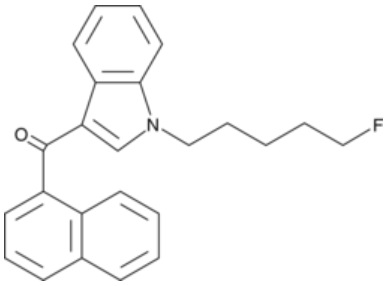
Drug Enforcement Administration, Department of Justice, 2015. Schedules of controlled substances: temporary placement of three synthetic cannabinoids into schedule I. Final order. *Federal register*, *80*(20), p.5042.

Uchiyama, N., Matsuda, S., Wakana, D., Kikura-Hanajiri, R. and Goda, Y., 2013. New cannabimimetic indazole derivatives, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA) and N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA) identified as designer drugs in illegal products. *Forensic Toxicology*, *31*(1), pp.93-100.

Wohlfarth, A., Castaneto, M.S., Zhu, M., Pang, S., Scheidweiler, K.B., Kronstrand, R. and Huestis, M.A., 2015. Pentylindole/pentylindazole synthetic cannabinoids and their 5-fluoro analogs produce different primary metabolites: metabolite profiling for AB-PINACA and 5F-AB-PINACA. *The AAPS journal*, *17*(3), pp.660-677.

2.8 AM-2201

IUPAC Name: [1-(5-fluoropentyl)-1H-indol-3-yl]-1-naphthalenyl-methanone



Synonyms: 5F-JWH-018

Molecular Formula: $C_{24}H_{22}FNO$

Occurrence and Usage: AM-2201 is an aminoalkylindole synthetic cannabinoid that was first synthesized in 2000 (Carlier et al. 2016). AM-2201 is similar to another synthetic cannabinoid, JWH-018; the difference is that AM-2201 has a fluorine atom on the pentyl chain (Jang et al. 2014).

Blood Concentration: Tuv et al. (2014) produced a study in which AM-2201 was found in the blood in DUID cases. They report that from the five cases the ranges

of blood concentrations was from 0.07µg/l to 1.33µg/l. Yeakel and Logan (2013) also produced a report on the study of blood concentrations and found that in six cases the blood concentrations ranged from 0.43ng/ml to 4.0ng/ml.

Metabolism and Excretion: Sobolevsky et al. (2012) produced a report in which they documented the *in vitro* metabolism of AM-2201. They reported that 7 metabolites were produced as well as the parent compound itself. These compounds were *N*-(5-hydroxypentyl)-dihydrodiol-JWH-018, dihydroxy-AM-2201, dihydrodiol-AM-2201, hydroxy-AM-2201, despentyl-AM-2201, *N*-(5-hydroxypentyl)-JWH-018 and JWH-018-N-pentanoic acid.

Toxicity: AM-2201 has been found to be a full agonist of the CB1 and CB2 receptors with effective concentrations of 38nM and 58nM respectively (Banister et al. 2015).

DUID Cases: Yeakel and Logan (2013) documented 6 cases in which the use of AM-2201 was present in the blood of drivers. One case states that a 31-year-old did not suffer from horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. They had an average pulse of 93 beats/min and a blood pressure of 140/90mmHg. During the walk and turn test it was noted that they were swaying, during the one-legged stand test they swayed and raised their arms during the test and during the Romberg test they suffered from eye tremors. Their internal clock thought 30 seconds had passed when in fact it had only been 23 seconds. Blood was taken and it was found that they had a concentration of 1.4ng/ml; this was also in combination with JWH-081, JWH-122 and JWH-210 with concentrations of 0.12ng/ml, 2.5ng/ml and 0.10ng/ml respectively.

Another case shows a 27-year-old who also did not suffer from horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. They had an average pulse of 112 beats/min and a blood pressure of 175/95mmHg. During the Romberg test they suffered from eye tremors and their internal clock thought 30 seconds had passed when only 22 seconds had. In their blood was a

concentration of AM-2201 of 0.43ng/ml, a concentration of 0.1ng/ml of JWH-018 and possible traces of JWH-122 and JWH-210.

A 21-year-old who was suspected of driving under the influence underwent roadside tests. During the walk and turn test the suspect suffered from leg and body tremors, during the one-legged stand they swayed and also had leg and body tremors and during the Romberg test they also swayed and had leg, body and eye tremors. It was found that in their blood was AM-2201 and JWH-250; with concentrations of 3.1ng/ml and 0.38ng/ml respectively.

Another case shows an 18-year-old who underwent roadside tests to detect any impairment. During the walk and turn test the suspect raised their arms and had leg tremors, during the one-legged stand test they swayed, raised their arms and put their foot down and during the Romberg test they also swayed and had leg tremors. They had a concentration of 3.6ng/ml of AM-2201 in their blood.

A 19-year-old was involved in a road accident and during both the walk and turn test and the one-legged stand test they suffered from leg tremors. Their blood was taken and a concentration of 4.0ng/ml of AM-2201 was found and also traces of JWH-210 were also present.

In another report by Musshoff et al. (2014) they document a case in which an 18-year-old male arrived at a local meeting point for young people. Police arrived and noted that the male was unable to follow instructions, had a retarded sequence of movements, was lazy, cumbersome, confused and disoriented, suffered from slurred and babbling speech, inappropriate freezing, reduced breathing and enlarged pupils. He was taken to hospital where he became dizzy and nearly lost consciousness. A blood sample was taken and it was found that there was a concentration of 4.6ng/ml of AM-2201 and also 0.17ng/ml of JWH-018.

References

Banister, S.D., Stuart, J., Kevin, R.C., Edington, A., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Hibbs, D.E., Glass, M. and Connor, M., 2015.

Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS chemical neuroscience*, *6*(8), pp.1445-1458.

Carlier, J., Scheidweiler, K.B., Wohlfarth, A., Salmeron, B.D., Baumann, M.H. and Huestis, M.A., 2016. Quantification of [1-(5-fluoropentyl)-1H-indol-3-yl](naphthalene-1-yl) methanone (AM-2201) and 13 metabolites in human and rat plasma by liquid chromatography-tandem mass spectrometry. *Journal of Chromatography A*, *1451*, pp.97-106.

Jang, M., Yang, W., Shin, I., Choi, H., Chang, H. and Kim, E., 2014. Determination of AM-2201 metabolites in urine and comparison with JWH-018 abuse. *International journal of legal medicine*, *128*(2), pp.285-294.

Makriyannis, A. and Deng, H., University of Connecticut, 2005. *Cannabimimetic indole derivatives*. U.S. Patent 6,900,236.

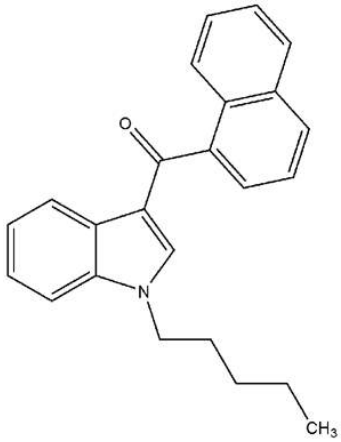
Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V., 2014. Driving under the influence of synthetic cannabinoids ("Spice"): a case series. *International journal of legal medicine*, *128*(1), pp.59-64.

Sobolevsky, T., Prasolov, I. and Rodchenkov, G., 2012. Detection of urinary metabolites of AM- 2201 and UR- 144, two novel synthetic cannabinoids. *Drug testing and analysis*, *4*(10), pp.745-753.

Tuv, S.S., Krabseth, H., Karinen, R., Olsen, K.M., Øiestad, E.L. and Vindenes, V., 2014. Prevalence of synthetic cannabinoids in blood samples from Norwegian drivers suspected of impaired driving during a seven weeks period. *Accident Analysis & Prevention*, *62*, pp.26-31.

Yeakel, J.K. and Logan, B.K., 2013. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of analytical toxicology*, *37*(8), pp.547-551.

2.9 JWH-018



IUPAC Name: (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone

Synonyms: AM678

Molecular Formula: $C_{24}H_{23}NO$

Occurrence and Usage: JWH-018 is one of a series of synthetic cannabinoids, which belongs to the naphthoylindole class of compounds (Couceiro et al. 2016). It began appearing in 2008 and due to its abusive consumption; plans for the control of the drug began in 2009 and was finally deemed a controlled substance in 2011 (Jang et al. 2013). The effects it produces are very similar to that of THC (Moffat et al. 2011).

Blood Concentration: In eight reported cases the concentration of JWH-018 that was present in the blood varied from 0.1 ng/ml and 9.9 ng/ml each with varying degrees of symptoms (Yeakel and Logan 2013).

Metabolism and Excretion: Reports analysing the metabolism of JWH-018 show that the hydroxylated *N*-dealkylated species is the main metabolite, the original drug and the *N*-dealkylated metabolite were also detected but in smaller amounts (Möller et al. 2011). Other reports show that the parent compound was not detected in urine, whereas the minor metabolites were present in the free fraction and main metabolites were completely glucuroconjugated (Sobolevsky et al. 2010).

Toxicity: The desired effects of JWH-018 are generally similar to that of marijuana, however marijuana rarely causes the adverse effects that JWH-018 produces. These adverse effects are hypertension, agitation, hallucinations, psychoses, seizures and panic attacks (Brents et al. 2011).

DUID Cases: Police were called to a meeting point for young people under a bridge, where an 18-year-old male arrived in his car in an intoxicated state. The police noted that the male was unable to follow instructions, had a retarded sequence of movements, lazy, cumbersome, confused and disorientated, slurred and babbling speech, inappropriate freezing, reduced breathing and enlarged pupils. The male later became dizzy and nearly lost consciousness once he arrived at hospital. A sample of blood was taken and it was found that he had a concentration of 0.17ng/ml of JWH-018 in his blood; this was in combination with a concentration of 4.6ng/ml of AM-2201.

In another case a 21-year-old male was examined in a road traffic check. The police recorded that the male had delayed reactions, retarded movement sequences, nervous, lazy and also was a known drug user. Later the physician noted that the male had constricted pupils, his pupils had no reaction to light, and he had a dizzy mind and was in a depressive mood. A sample of blood was taken and it was found that the male had a concentration of 0.52 ng/ml of JWH-018 in his blood; this was in combination with JWH-122 and JWH-210 with blood concentration of 0.26ng/ml and 0.66ng/ml respectively.

Another case reported a 22-year-old male was arrested for overrunning several red lights and later running away on foot. During his arrest the police officer noted the male had retarded movement sequences, apathetic, nervous, inert, and his pupils had a delayed reaction to light. A sample of blood was taken for analysis and the results show that the male had a concentration of 1.9ng/ml of JWH-018 in his blood, this was in combination with several other synthetic cannabinoids such as AM-2201, JWH-122, JWH-210, JWH-307, MAM-2201 and UR-144 with blood concentrations of 0.1ng/ml, 28ng/ml, 2.5ng/ml, 0.1ng/ml, 0.1ng/ml and 0.1ng/ml respectively. (Musshoff et al. 2014).

Other reports show evaluations for roadside tests for suspected impaired driving. One reports states that the driver fidgeted, raised their arms, swayed and performed an improper turn during the walk and turn test. Also during the one-legged stand test they fidgeted, flexed their foot and raised their arms. Blood was

collected and the sample showed that the driver had a concentration of 1.1 ng/ml of JWH-018.

An 18-year-old who was suspected of having driving impairment was roadside tested and during the walk and turn test they raised their arms and performed an improper turn, during the one-legged stand they raised their arms and during the Romberg test there was noticeable eye flutters. It was found that they had a concentration of 0.24 ng/ml of JWH-018 in their blood.

Two cases were reported with possible traces of JWH-018 in their blood after having roadside tests for impaired driving. The 25-year-old that underwent the roadside tests exhibited swaying, raised their arms and displayed hand tremors during the one-legged stand. During the Romberg test their hands were trembling and had rapid eyelid tremors. The 18-year-old had leg tremors and could not keep their balance during the walk and turn test, exhibited incorrect counting, swaying and leg tremors during the one-legged stand and had eye tremors during the Romberg test (Yeakel and Logan 2013).

References

Brents, L.K., Reichard, E.E., Zimmerman, S.M., Moran, J.H., Fantegrossi, W.E. and Prather, P.L., 2011. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. *PloS one*, *6*(7), p.e21917.

Couceiro, J., Bandarra, S., Sultan, H., Bell, S., Constantino, S. and Quintas, A., 2016. Toxicological impact of JWH-018 and its phase I metabolite N-(3-hydroxypentyl) on human cell lines. *Forensic science international*, *264*, pp.100-105.

Jang, M., Yang, W., Choi, H., Chang, H., Lee, S., Kim, E. and Chung, H., 2013. Monitoring of urinary metabolites of JWH-018 and JWH-073 in legal cases. *Forensic science international*, *231*(1), pp.13-19.

Moffat, A.C., Osselton, M.D., Widdop, B. and Watts, J., 2011. *Clarke's analysis of drugs and poisons*. Pharmaceutical Press,.

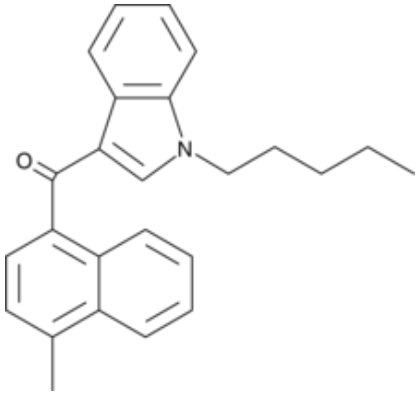
Möller, I., Wintermeyer, A., Bender, K., Jübner, M., Thomas, A., Krug, O., Schänzer, W. and Thevis, M., 2011. Screening for the synthetic cannabinoid JWH- 018 and its major metabolites in human doping controls. *Drug testing and analysis*, *3*(9), pp.609-620.

Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V., 2014. Driving under the influence of synthetic cannabinoids ("Spice"): a case series. *International journal of legal medicine*, *128*(1), pp.59-64.

Sobolevsky, T., Prasolov, I. and Rodchenkov, G., 2010. Detection of JWH-018 metabolites in smoking mixture post-administration urine. *Forensic science international*, *200*(1), pp.141-147.

Yeakel, J.K. and Logan, B.K., 2013. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of analytical toxicology*, *37*(8), pp.547-551.

2.10 JWH-122



IUPAC Name: (4-methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone

Synonyms: 4-Ethyl-JWH-018

Molecular Formula: $C_{25}H_{25}NO$

Occurrence and Usage: JWH-122 is a synthetic cannabinoid that is a member of the napthoylindole class of compounds. It is structurally related to other synthetic cannabinoids such as JWH-018 and JWH-073 (Ernst et al. 2011).

Blood Concentration: In similar studies by Musshoff et al. (2014) and Yeakel and Logan (2013) who both study the blood concentrations of drivers suspected of driving under the influence; they find that the range of concentrations of JWH-122 range from 0.26ng/ml to 28ng/ml.

Metabolism and Excretion: In a study by ElSohly et al. (2014) the metabolites of JWH-122 are expressed. 5 metabolites are shown, 3 of which are monohydroxylated; one is at the N-alkyl chain, another is at the naphthalene moiety and the other is at the indole moiety. Another metabolite is dehydrogenated at the N-alkyl chain. The final metabolite is hydroxylated at the N-alkyl chain.

Toxicity: JWH-122 has been found to have an affinity of 0.69nM at CB1 and 1.2nM at CB2 receptors (Huffman et al. 2005).

DUID Cases: There are three cases that are reported by Yeakel and Logan (2013) that involve JWH-122. The first of which reports a 31-year-old who during the walk and turn test swayed, during the one-legged stand test also swayed and raised their arms and during the Romberg test had eye tremors. There were no signs of horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. There were several synthetic cannabinoids found in their blood, such as JWH-122, AM-2201, JWH-081 and JWH-210 with concentrations of 2.5ng/ml, 1.4ng/ml, 0.12ng/ml and 0.1ng/ml respectively.

The two other cases showed trace signs of JWH-122 with varying signs of impairment. One of which was in combination with a concentrations of 0.1ng/ml and 0.43ng/ml of JWH-018 and AM-2201 respectively. This case shows a 27-year-old who did not show signs of horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. During the Romberg test they suffered from eye tremors.

The other case is also in combination with other synthetic cannabinoids, 2.8ng/ml of AM-2201 and traces of JWH-081. The case involves a 21-year-old who suffered from horizontal gaze nystagmus at 45° and vertical gaze nystagmus, however did not suffer a lack of convergence. They underwent the walk and turn test and

nearly fell during the turn. They believed 30 seconds had passed when in fact 36 seconds had passed.

Musshoff et al. (2014) produced five cases in which the use of JWH-122 was detected. One of which mentions a 20-year-old male who was checked during a general road traffic control. The police noted that the male had a vestibular disorder, suffered from a disturbance of fine motor skills, and had enlarged pupils and a blunt mood. Blood was taken and a concentration of 7.6ng/ml of JWH-122 was found. This was in combination with JWH-019, JWH-210 and AM-2201 with concentrations of 1.7ng/ml, 4.4ng/ml and 0.31ng/ml respectively.

Another case shows a 29-year-old male who had a history of drug abuse was also checked during a general road traffic control. The police noted that the male was very dismissive towards them. A physician noted that the male had enlarged pupils, a delayed reaction of pupils to light, a dizzy mind and retarded behaviour. In his blood there were concentrations of JWH-122 and JWH-210 with values of 1.0ng/ml and 6.2ng/ml respectively.

A 21-year-old male was stopped at another general road traffic check. The police documented that the male suffered from delayed reactions, a retarded sequence of movements, was nervous, lazy and a known drug user. The physician noted that the male had constricted pupils and they had no reaction to light, also suffered from a dizzy mind and depressive mood. Concentrations of 0.26ng/ml, 0.52ng/ml and 0.66ng/ml were found of JWH-122, JWH-018 and JWH-210 respectively.

Police stopped two 14-year-old girls who were cycling in wavy lines. They admitted to smoking a cigarette offered to them by a third person. When the police stopped the girls one started to talk in a confused manner and then became unconscious for a while. Both of the girls blood was taken and it was found that one of the girls had concentrations of 0.33ng/ml and 4.0ng/ml of JWH-122 and JWH-210 respectively.

A 22-year-old motorcyclist was eventually stopped after escaping a general road traffic control by overtaking several traffic lights and then running on foot. The

police noted that during his arrest the male seemed nervous, inert, and apathetic, had a retarded sequence of movement and a delayed reaction of pupils to light. In his blood was 28ng/ml of JWH-122, 2.5ng/ml of JWH-210, 1.9ng/ml of JWH-018 and traces of AM-2201, JWH-307, MAM-2201 and UR-144.

References

ElSohly, M.A., Gul, W., Wanas, A.S. and Radwan, M.M., 2014. Synthetic cannabinoids: analysis and metabolites. *Life sciences*, *97*(1), pp.78-90.

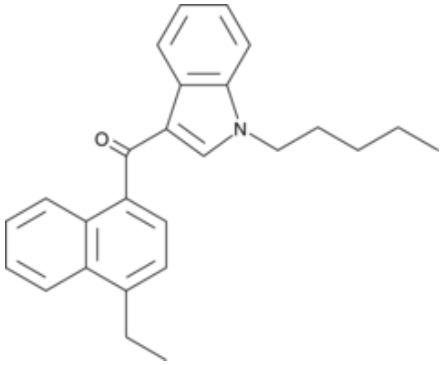
Ernst, L., Schiebel, H.M., Theuring, C., Lindigkeit, R. and Beuerle, T., 2011. Identification and characterization of JWH-122 used as new ingredient in “Spice-like” herbal incenses. *Forensic Science International*, *208*(1), pp.e31-e35.

Huffman, J.W., Zengin, G., Wu, M.J., Lu, J., Hynd, G., Bushell, K., Thompson, A.L., Bushell, S., Tartal, C., Hurst, D.P. and Reggio, P.H., 2005. 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 2 receptor agonists. *Bioorganic & medicinal chemistry*, *13*(1), pp.89-112.

Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V., 2014. Driving under the influence of synthetic cannabinoids (“Spice”): a case series. *International journal of legal medicine*, *128*(1), pp.59-64.

Yeakel, J.K. and Logan, B.K., 2013. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of analytical toxicology*, *37*(8), pp.547-551.

2.11 JWH-210



IUPAC Name: (4-ethyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone

Synonyms: 4-Methyl-JWH-018

Molecular Formula: $C_{26}H_{27}NO$

Occurrence and Usage: JWH-210 is a member of the naphthoylindole family, classified by the aminoalkylindole group (Cha et al. 2015). It is classed as one of the most potent 4-substituted naphthoyl derivatives in the naphthoylindole family (Huffman et al. 2005).

Blood Concentration: There are two similar reports by Musshoff et al. (2014) and Yeakel and Logan (2013) who both report cases of the use of JWH-210 in DUID. The blood concentrations that were taken from the suspects range from 0.66ng/ml to 6.2ng/ml.

Metabolism and Excretion: ElSohly et al. (2014) describe the metabolism of JWH-210, in which three metabolites were produced. One of which monohydroxylated JWH-210 at the *N*-alkyl chain, another also monohydroxylated JWH-210 but at the indole moiety and the final metabolite is monohydroxylated at the naphthalene moiety.

Toxicity: JWH-210 is found to be a potent cannabinoid agonist both the CB1 and CB2 receptors with K values of 0.46nM and 0.69nM respectively (Huffman et al. 2005)

DUID Cases: There are five cases reported by Musshoff et al. (2014) that record the use of JWH-122 in drivers. The first of which reports a case where two 14-year-old girls were handed and smoked a cigarette by a third person. They began cycling home and police were called due to them both cycling in wavy lines. The

police noted that one of the girls was talking in a confused manor and later became unconscious for a short period of time. The physician that took samples of blood noted that one of the girls had an instable appearance, slurred and babbling speech, dizzy conscious mind and a blunt mood. From the blood taken it was shown that one of the girls had a concentration of 4.0ng/ml of JWH-210, this was also in combination with another synthetic cannabinoid, JWH-122 with a concentration of 0.33ng/ml. The other girl also had JWH-210 in her blood with a concentration of 0.80ng/ml.

Another case reports a 20-year-old male, who was stopped during a general road traffic control. Police noted that the male suffered from a vestibular disorder, had a disturbance of fine motor skills, enlarged pupils and a blunt mood. The physician who took his blood noted that the male had obviously enlarged pupils and a delayed reaction of pupils to light. Four different synthetic cannabinoids were found in his blood they were JWH-210, JWH-019, JWH-122 and AM-2201. They had respective concentrations of 4.4ng/ml, 1.7ng/ml, 7.6ng/ml and 0.31ng/ml.

A 29-year-old male who was a known drug user was stopped and checked at a general road traffic control. He was reported to be very dismissive towards the police. Found in his vehicle were herbal products with the title “BooM” and “OMG”. The physician noted that the male had enlarged pupils, a delayed reaction of pupils to light, dizzy mind and retarded behaviour. In the blood that was taken there were concentrations of 6.2ng/ml of JWH-210 and 1.0ng/ml of JWH-122.

At another general road traffic control a 21-year-old male was examined and the police documented that the male had delayed reactions, retarded sequence of movements, nervous, lazy and was also a known drug user. The physician noted 81 minutes after initial contact that the male had constricted pupils, no reaction of the pupils to light, dizzy mind and a depressive mood. In the males blood there was a concentration of 0.66ng/ml of JWH-210, 0.52ng/ml of JWH-018 and 0.26ng/ml of JWH-122.

The final case reported by Musshoff et al. (2014) talks about a 22-year-old male who was about to be stopped at a general road traffic control, but escaped the

check by overtaking other vehicles and going through red lights and later trying to escape on foot. Once caught the police noted that the male had a retarded sequence of movements, apathetic, nervous, inert, and had a delayed reaction of pupils to light. After 1 hour and 35 minutes the physician noted that the male suffered no abnormalities. In the males blood was a concentration of 2.5ng/ml of JWH-210, 28ng/ml of JWH-122, 1.9ng/ml of JWH-018 and traces of AM-2201, JWH-307, MAM-2201and UR-144.

In a case reported by Yeakel and Logan (2013) a 31-year-old was apprehended for suspected impaired driving. The drug recognition expert noted that the suspect did not suffer from horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. The suspect had an average pulse of 93 beats/min and a blood pressure of 140/90mmHg. During the standardised field sobriety tests the suspect swayed during the walk and turn test, swayed and raised their arms during the one-legged stand and suffered eye tremors during the Romberg test. The suspect's internal clock believed 30 seconds had passed when in fact only 23 seconds had. In their blood were concentrations of 0.10ng/ml of JWH-210, 1.4ng/ml of AM-2201, 0.12ng/ml of JWH-081 and 2.5ng/ml of JWH-122.

References

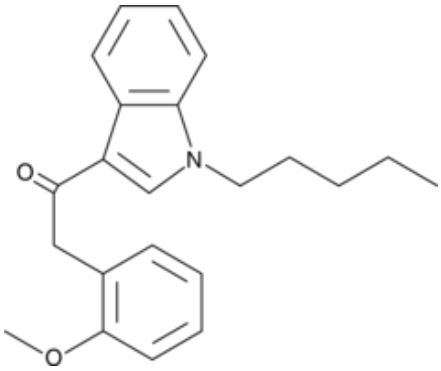
Cha, H.J., Seong, Y.H., Song, M.J., Jeong, H.S., Shin, J., Yun, J., Han, K., Kim, Y.H., Kang, H. and Kim, H.S., 2015. Neurotoxicity of synthetic cannabinoids JWH-081 and JWH-210. *Biomolecules & therapeutics*, *23*(6), p.597.

ElSohly, M.A., Gul, W., Wanas, A.S. and Radwan, M.M., 2014. Synthetic cannabinoids: analysis and metabolites. *Life sciences*, *97*(1), pp.78-90.

Huffman, J.W., Zengin, G., Wu, M.J., Lu, J., Hynd, G., Bushell, K., Thompson, A.L., Bushell, S., Tartal, C., Hurst, D.P. and Reggio, P.H., 2005. 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 2 receptor agonists. *Bioorganic & medicinal chemistry*, *13*(1), pp.89-112.

Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V., 2014. Driving under the influence of synthetic cannabinoids ("Spice"): a case series. *International journal of legal medicine*, *128*(1), pp.59-64.
Yeakel, J.K. and Logan, B.K., 2013. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of analytical toxicology*, *37*(8), pp.547-551.

2.12 JWH-250



IUPAC Name: 1-(1-pentyl-1H-indol-3-yl)-2-(2-methoxyphenyl)-ethanone

Molecular Formula: $C_{22}H_{25}NO_2$

Occurrence and Usage: JWH-250 is a synthetic cannabinoid that is a member of the phenylacetylindole family (Solimini et al. 2017). It differs to the naphthylindole family of JWH compounds due to it not having a naphthalene ring and instead having a 2-methoxy-phenyacetyl group (Huffman et al. 2005). JWH-250 was found to be prevalent in Spice mixtures in Germany around 2010-2011 (Harris et al. 2014).

Blood Concentration: Yeakel and Logan (2013) produced a report in which the synthetic cannabinoid JWH-250 was found in DUID cases. The blood concentrations that were found in the drivers range from 0.38ng/ml to 2.7ng/ml.

Metabolism and Excretion: Grigoryev et al. (2011) produced a report in which the metabolism of JWH-250 is expressed through gas chromatography-mass spectrometry (GC-MS). 22 metabolites were produced through urine, these metabolites can be categorised structurally into six groups. There were five metabolites that were products of monohydroxylation, six that were products of dihydroxylation, two that were products of trihydroxylation and dehydration of the N-alkyl chain, five that were products of trihydroxylation, one that was a product of

N-dealkylation and three that were products of N-dealkylation with monohydroxylation.

Toxicity: JWH-250 is known to be an agonist against both the CB1 and CB2 receptors with affinities of 11nM and 33nM respectively (Huffman et al. 2005).

DUID Cases: There were two reported cases of DUID of JWH-250 that were examined by Yeakel and Logan (2013), the first of which evaluates a 22-year-old who was examined by a drug recognition expert and they found that the suspect suffered from horizontal gaze nystagmus, but not vertical gaze nystagmus. It was also reported that they had pinpoint pupils and that the test for a lack of convergence was not recorded. The suspects average pulse; blood pressure and internal clock were not recorded. In the one-legged stand test it was recorded that the suspect completed it without any clues towards impairment. In the blood sample that was taken there was a concentration of 2.7ng/ml of JWH-250 and this was in combination with JWH-018 with a concentration of 9.9ng/ml.

In the other case that was reported it assesses a 21-year-old who was involved in a car accident. The drug recognition expert reported that they didn't suffer from horizontal gaze nystagmus, vertical gaze nystagmus or a lack of convergence. They had an average pulse of 84 beats/min and a blood pressure of 126/72mmHg. During the walk and turn test the suspect suffered from leg and body tremors, during the one-legged stand they swayed, raised their arms and also put their foot down and during the Romberg test they swayed and suffered leg, body and eyelid tremors. In the blood that was taken there was a concentration of 0.38ng/ml of JWH-250, this was in combination with AM-2201 with a concentration of 3.1ng/ml.

References

Grigoryev, A., Melnik, A., Savchuk, S., Simonov, A. and Rozhanets, V., 2011. Gas and liquid chromatography–mass spectrometry studies on the metabolism of the synthetic phenylacetylindole cannabimimetic JWH-250, the psychoactive component of smoking mixtures. *Journal of chromatography B*, *879*(25), pp.2519-2526.

Harris, D.N., Hokanson, S., Miller, V. and Jackson, G.P., 2014. Fragmentation differences in the EI spectra of three synthetic cannabinoid positional isomers: JWH-250, JWH-302, and JWH-201. *International Journal of Mass Spectrometry*, *368*, pp.23-29.

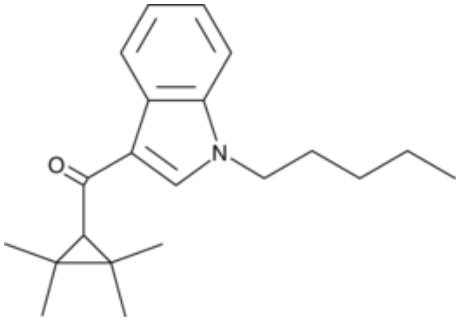
Huffman, J.W., Szklennik, P.V., Almond, A., Bushell, K., Selley, D.E., He, H., Cassidy, M.P., Wiley, J.L. and Martin, B.R., 2005. 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. *Bioorganic & Medicinal Chemistry Letters*, *15*(18), pp.4110-4113.

Solimini, R., Busardò, F.P., Rotolo, M.C., Ricci, S., Mastrobattista, L., Mortali, C., Graziano, S., Pellegrini, M., di Luca, N.M. and Palmi, I., 2017. Hepatotoxicity associated to synthetic cannabinoids use. *Eur Rev Med Pharmacol Sci*, *21*(1 Suppl), pp.1-6.

Yeakel, J.K. and Logan, B.K., 2013. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of analytical toxicology*, *37*(8), pp.547-551.

2.13 UR-144

IUPAC Name: (1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone



Synonyms: TMCP-018, KM-X1, MN-001, YX-17

Molecular Formula: $C_{21}H_{29}NO$

Occurrence and Usage: UR-144 is a synthetic cannabinoid that is a member of the tetramethylcyclopropylketone indole family (Solimini et al. 2017). UR-144 is a drug that was first synthesized in Abbott Laboratories (Pace et al. 2006). It was found in herbal products in Korea 2012 and since then has rapidly spread across

Europe, Japan and the USA. UR-144 is most commonly smoked to achieve marijuana like effects, however it can also be taken orally or vaporised and then inhaled (Adamowicz et al. 2017).

Blood Concentration: In a report that was written by Karinen et al. (2015) they examine cases in which the use of UR-144 was found in the blood of drivers. In the cases that were examined the blood concentrations range from 0.22µg/L to 0.47µg/L.

Metabolism and Excretion: Sobolevsky et al. (2012) produced a report in which the *in vitro* metabolism of UR-144 was documented. During their study they found that five metabolites were produced as well as the parent compound itself. These compounds were despentylhydroxy-UR-144, dihydroxy-UR-144, despentyl-UR-144, dehydrated dihydroxy-UR-144 and hydroxyl-UR-144.

Toxicity: Frost et al. (2009) found that UR-144 had a high affinity for both the CB1 and CB2 receptor with values of 1.8nM and 150nM respectively. Banister et al. (2015) found that UR-144 had an effective concentration of 421nM for CB1 and 72nM for CB2.

DUID Cases: Louis et al (2014) produced a report in which they examine cases when UR-144 was present in the blood of drivers. The first of which states a 22-year-old male who was reported to the police for erratic driving. The police noted that the male had slurred speech and a lack of coordination whilst trying to exit the car and find the paperwork he was asked for. They also noted the male had bloodshot watery eyes, dilated pupils and droopy eyelids. During the standardised field sobriety tests it was recorded that the male did not suffer from horizontal gaze nystagmus. The presence of body and eyelid tremors was noted. During the walk and turn test there were 5 clues present and during the one-legged stand there were 3 clues present. In the males possession was a pipe and Spice, he had admitted to smoking 2 hours prior to being stopped. Blood was taken 1 hour and 10 minutes after initial contact and UR-144 was present.

Another 22-year-old male was stopped due to severe lane travel and for driving on the hard shoulder. The police noted that the male had slow, slurred and repetitive speech and also had problems standing. It was also found that the male was in fact driving in the opposite direction to his destination. The drug recognition expert noted that the male had bloodshot eyes, droopy eyelids, dilated pupils and a lack of convergence. The male underwent both the walk and turn test and the one-legged stand test and it was found that there were 2 clues and 1 clue respectively for the tests. The male was found to have Spice and a pipe. The male admitted to smoking 1 hour and 30 minutes prior to driving. His blood was taken 1 hour and 50 minutes after initial contact and UR-144 was found to be present.

Another case reports a 25-year-old male who was observed by police stopping on the highway, potentially causing a hazard to other drivers and then accelerating away. The male was later involved in a collision with a barrier. When contact was made the male was exhibiting seizure like behaviour and was taken to hospital. The passenger in the male's car admitted that they smoked 15 minutes before the accident. At the hospital, horizontal gaze nystagmus was present and the male was noticeably shaking while being seated. He had bloodshot and watery eyes and his speech was slurred. The male stated that at one point he had blacked out. Blood was taken 1 hour after contact and UR-144 was found.

A 42-year-old male was reported to the police for erratic driving and then the police observed severe lane travel. When the police made contact they noted the male had bloodshot watery eyes, droopy eyelids, horizontal gaze nystagmus and a lack of convergence. There were 2 clues present during the walk and turn test and 1 clue present during the one-legged stand test. The male thought 30 seconds had passed when in fact only 11 seconds had passed. The male admitted to smoking 10 hours prior to being stopped. The male had blood taken 1 hour after contact and UR-144 was found.

Another case reports a 29-year-old man who was stopped due to erratic driving. It was noted that the male had slurred speech, bloodshot eyes and droopy eyelids. Horizontal gaze nystagmus and a lack of convergence were not present. During the walk and turn test there were 3 clues present and there were also 2 clues

present during the one-legged stand test. Spice was found in a container in the vehicle, however the male denied using it. His blood was taken 4 hours and 55 minutes after initial contact and UR-144 was present.

A 25-year-old male was stopped after crossing a fog line. The police noted that the male had trouble finding the button to lower the window, also noted horizontal gaze nystagmus, bloodshot watery eyes, a lack of convergence and slurred speech. During the walk and turn test the male exhibited 3 clues and during the one-legged stand test the male exhibited 2 clues. In the male's vehicle Spice was clearly visible and the male admitted to consumption. 1 hour and 35 minutes after initial contact the male's blood was taken and after analysis UR-144 was detected.

References

Adamowicz, P., Gieroń, J., Gil, D., Lechowicz, W., Skulska, A. and Tokarczyk, B., 2017. The effects of synthetic cannabinoid UR-144 on the human body—A review of 39 cases. *Forensic Science International*, *273*, pp.e18-e21.

Banister, S.D., Stuart, J., Kevin, R.C., Edington, A., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Hibbs, D.E., Glass, M. and Connor, M., 2015. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS chemical neuroscience*, *6*(8), pp.1445-1458.

Frost, J.M., Dart, M.J., Tietje, K.R., Garrison, T.R., Grayson, G.K., Daza, A.V., El-Kouhen, O.F., Yao, B.B., Hsieh, G.C., Pai, M. and Zhu, C.Z., 2009. Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB2 cannabinoid receptor activity. *Journal of medicinal chemistry*, *53*(1), pp.295-315.

Karinen, R., Tuv, S.S., Øiestad, E.L. and Vindenes, V., 2015. Concentrations of APINACA, 5F-APINACA, UR-144 and its degradant product in blood samples from six impaired drivers compared to previous reported concentrations of other synthetic cannabinoids. *Forensic science international*, *246*, pp.98-103.

Louis, A., Peterson, B.L. and Couper, F.J., 2014. XLR-11 and UR-144 in Washington state and state of Alaska driving cases. *J Anal Toxicol*, *38*(8), pp.563-568.

Pace, J.M., Tietje, K., Dart, M.J. and Meyer, M.D., 2006. 3-Cycloalkylcarbonyl indoles as cannabinoid receptor ligands. *Published in*, pp.06-29.

Sobolevsky, T., Prasolov, I. and Rodchenkov, G., 2012. Detection of urinary metabolites of AM- 2201 and UR- 144, two novel synthetic cannabinoids. *Drug testing and analysis*, *4*(10), pp.745-753.

Solimini, R., Busardò, F.P., Rotolo, M.C., Ricci, S., Mastrobattista, L., Mortali, C., Graziano, S., Pellegrini, M., di Luca, N.M. and Palmi, I., 2017. Hepatotoxicity associated to synthetic cannabinoids use. *Eur Rev Med Pharmacol Sci*, *21*(1 Suppl), pp.1-6.

3. Discussion & Conclusion

3.1 Discussion

The monographs that have been produced each describe the general aspects of the synthetic cannabinoid that is being discussed. The monographs detail the occurrence and usage, blood concentrations, metabolism and excretion, toxicity and DUID cases that all specifically relate to the individual synthetic cannabinoids.

The synthetic cannabinoids that have been discussed each record their results for roadside impairment by using standardised field sobriety tests. These tests give an indication as to what impairment the user is suffering from. General signs and symptoms are also recorded in the person's appearance and manner to produce a description. When possible blood concentrations of the related synthetic cannabinoid were produced in order to relate concentration to the effects recorded in the monograph.

In the blood samples taken from suspects with impaired driving, combinations of synthetic cannabinoids were also found. This indicates that while users believe what they are taking is a pure substance; there is no way of telling this without significant testing. Therefore, users are taking these synthetic cannabinoids believing that they know and can understand what kind of effects they will produce, however this is not the case. A certain blood concentration of one synthetic cannabinoid might not be enough to produce the impairment that a user could experience but with it being in combination with other synthetic cannabinoids could offer an explanation to why a user might demonstrate certain signs of impairment.

The synthetic cannabinoids that are presented also specify how potent they are to the relevant cannabinoid receptors. Thus, providing evidence as to the dangers and unknown aspects of synthetic cannabinoids. Although this dissertation has only touched the subject of synthetic cannabinoids in the recreational use of drivers it shows how similar the impairment is between several different synthetic cannabinoids that are not in the same family. Although some of the synthetic

cannabinoids documented here only describe effects and impairment, there are some synthetic cannabinoids that discussed produce undesirable effects and make them extremely dangerous to use such as 5F-AMB that has been discussed in relation to death.

3.2 Conclusion

This dissertation collates and presents the findings of common synthetic cannabinoids and their effects on a person's ability to drive. This research has produced a series of monographs with detailed descriptions and examinations on each. The research has shown that synthetic cannabinoids are used in driving and that the use of them is on the increase. This is supported by the dates of the publications used as literature and research analysed is relatively recent.

Synthetic cannabinoids were somewhat unknown until they became present in the public eye due to its advertisement as 'legal' and as they produce similar effects to that of cannabis. Due to synthetic cannabinoids becoming more popular and the harmful side-effects recognised, more research is being undertaken on them. This emphasises how unknown some synthetic cannabinoids are as the research on them is limited in certain aspects of their pharmacology.

However there is sufficient research available in the literature to implicate certain synthetic cannabinoids and how they affect impairment during driving. It is important to establish the association between signs of impairment in driving and recreational use of synthetic cannabinoids, as it provides the general public with evidence detailing the side-effects that they could expect if taking one of these synthetic cannabinoids. Additionally, it helps with further cases involving synthetic cannabinoids and ultimately can be used in future publications when these synthetic cannabinoids are being researched.

This research demonstrates the anonymities of synthetic cannabinoids as although they are commonly perceived as safe they are not and still further research is needed to fully understand the effects they produce. Appendix I demonstrates that much more research is needed regarding synthetic cannabinoids and their concentrations towards the cannabinoid receptors.

Also further research is needed regarding the metabolism and excretion of synthetic cannabinoids as during the project, there is very little information in the literature regarding this. This would benefit researchers and practitioners as it would provide a better understanding of synthetic cannabinoids and how they exhibit their effects. Also, when metabolism of the synthetic cannabinoids has been published it will provide evidence for law enforcement, as when blood is taken from a suspect they will be able to look for the specific metabolites and distinguish what parent compound this could have come from.

The research highlights how synthetic cannabinoids have been detected in users whilst driving. It has described how each synthetic cannabinoid is metabolised and listed what their metabolites are. It has reported the signs and symptoms that often occurred when certain synthetic cannabinoids were used. It has shown these signs and symptoms by noting clues of impairment in standardised field sobriety tests.

4. References

Ashton, C.H., 2001. Pharmacology and effects of cannabis: a brief review. *The British Journal of Psychiatry*, *178*(2), pp.101-106.

Aung, M.M., Griffin, G., Huffman, J.W., Wu, M.J., Keel, C., Yang, B., Showalter, V.M., Abood, M.E. and Martin, B.R., 2000. Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB 1 and CB 2 receptor binding. *Drug and alcohol dependence*, *60*(2), pp.133-140.

Baker, S., 2015. An Examination of the Reasons that Prisoners use Spice (Synthetic Cannabinoids). *University of Cambridge*.

Banister, S.D., Longworth, M., Kevin, R., Sachdev, S., Santiago, M., Stuart, J., Mack, J.B., Glass, M., McGregor, I.S., Connor, M. and Kassiou, M., 2016. Pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and their analogues. *ACS Chemical Neuroscience*, *7*(9), pp.1241-1254.

Banister, S.D., Moir, M., Stuart, J., Kevin, R.C., Wood, K.E., Longworth, M., Wilkinson, S.M., Beinat, C., Buchanan, A.S., Glass, M. and Connor, M., 2015a. Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS chemical neuroscience*, *6*(9), pp.1546-1559.

Banister, S.D., Stuart, J., Conroy, T., Longworth, M., Manohar, M., Beinat, C., Wilkinson, S.M., Kevin, R.C., Hibbs, D.E., Glass, M. and Connor, M., 2015b. Structure–activity relationships of synthetic cannabinoid designer drug RCS-4 and its regioisomers and C4 homologues. *Forensic Toxicology*, *33*(2), pp.355-366.

Banister, S.D., Stuart, J., Kevin, R.C., Edington, A., Longworth, M., Wilkinson,

S.M., Beinat, C., Buchanan, A.S., Hibbs, D.E., Glass, M. and Connor, M., 2015c. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS chemical neuroscience*, *6*(8), pp.1445-1458.

Banister, S.D., Wilkinson, S.M., Longworth, M., Stuart, J., Apetz, N., English, K., Brooker, L., Goebel, C., Hibbs, D.E., Glass, M. and Connor, M., 2013. The synthesis and pharmacological evaluation of adamantane-derived indoles: cannabimimetic drugs of abuse. *ACS chemical neuroscience*, *4*(7), pp.1081-1092.

Baselt, R.C. and Cravey, R.H., 2011. *Disposition of toxic drugs and chemicals in man* (Vol. 8). Seal Beach: Biomedical publications.

Bernard Le Foll, M.D., 2015. Is Cannabis Addictive?. *Foreword by Rita Notarandrea 1 Foreword by Joy Johnson 3 Introduction 5 Joanna Henderson 1 What Are the Brain and Behavioural Effects of Cannabis Use in Youth? 16*, p.48.

Brents, L.K., Gallus-Zawada, A., Radominska-Pandya, A., Vasiljevik, T., Prisinzano, T.E., Fantegrossi, W.E., Moran, J.H. and Prather, P.L., 2012. Monohydroxylated metabolites of the K2 synthetic cannabinoid JWH-073 retain intermediate to high cannabinoid 1 receptor (CB1R) affinity and exhibit neutral antagonist to partial agonist activity. *Biochemical pharmacology*, *83*(7), pp.952-961.

Buchler, I.P., Hayes, M.J., Hegde, S.G., Hockerman, S.L., Jones, D.E., Kortum, S.W., Rico, J.G., TenBrink, R.E. and Wu, K.K., Pfizer Inc., 2009. *Indazole derivatives*. U.S. Patent Application 12/918,914.

Cohen, K., Kapitány-Fövény, M., Mama, Y., Arieli, M., Rosca, P., Demetrovics, Z. and Weinstein, A., 2017. The effects of synthetic cannabinoids on executive function. *Psychopharmacology*, *234*(7), pp.1121-1134.

Darmani, N.A., Chebolu, S., Zhong, W., Trinh, C., McClanahan, B. and Brar, R.S., 2014. Additive antiemetic efficacy of low-doses of the cannabinoid CB 1/2 receptor

agonist Δ 9-THC with ultralow-doses of the vanilloid TRPV1 receptor agonist resiniferatoxin in the least shrew (Cryptotis parva). *European journal of pharmacology*, *722*, pp.147-155.

De Luca, M.A., Castelli, M.P., Loi, B., Porcu, A., Martorelli, M., Miliano, C., Kellett, K., Davidson, C., Stair, J.L., Schifano, F. and Di Chiara, G., 2016. Native CB1 receptor affinity, intrinsic activity and accumbens shell dopamine stimulant properties of third generation SPICE/K2 cannabinoids: BB-22, 5F-PB-22, 5F-AKB-48 and STS-135. *Neuropharmacology*, *105*, pp.630-638.

Deng, H., 2000. Design and synthesis of selective cannabinoid receptor ligands: Aminoalkylindole and other heterocyclic analogs.

Frost, J.M., Dart, M.J., Tietje, K.R., Garrison, T.R., Grayson, G.K., Daza, A.V., El-Kouhen, O.F., Yao, B.B., Hsieh, G.C., Pai, M. and Zhu, C.Z., 2009. Indol-3-ylcycloalkyl ketones: effects of N1 substituted indole side chain variations on CB2 cannabinoid receptor activity. *Journal of medicinal chemistry*, *53*(1), pp.295-315.

Hess, C., Schoeder, C.T., Pillaiyar, T., Madea, B. and Müller, C.E., 2016. Pharmacological evaluation of synthetic cannabinoids identified as constituents of spice. *Forensic toxicology*, *34*(2), pp.329-343.

Huffman, J.W., 2009. Cannabimimetic indoles, pyrroles, and indenes: structure–activity relationships and receptor interactions. In *The cannabinoid receptors* (pp. 49-94). Humana Press.

Huffman, J.W., Mabon, R., Wu, M.J., Lu, J., Hart, R., Hurst, D.P., Reggio, P.H., Wiley, J.L. and Martin, B.R., 2003. 3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB 1 cannabinoid receptor. *Bioorganic & medicinal chemistry*, *11*(4), pp.539-549.

Huffman, J.W., Szklennik, P.V., Almond, A., Bushell, K., Selley, D.E., He, H., Cassidy, M.P., Wiley, J.L. and Martin, B.R., 2005a. 1-Pentyl-3-

phenylacetylindoles, a new class of cannabimimetic indoles. *Bioorganic & Medicinal Chemistry Letters*, *15*(18), pp.4110-4113.

Huffman, J.W., Zengin, G., Wu, M.J., Lu, J., Hynd, G., Bushell, K., Thompson, A.L., Bushell, S., Tartal, C., Hurst, D.P. and Reggio, P.H., 2005b. 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 2 receptor agonists. *Bioorganic & medicinal chemistry*, *13*(1), pp.89-112.

Ibrahim, M.M., Deng, H., Zvonok, A., Cockayne, D.A., Kwan, J., Mata, H.P., Vanderah, T.W., Lai, J., Porreca, F., Makriyannis, A. and Malan, T.P., 2003. Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. *Proceedings of the National Academy of Sciences*, *100*(18), pp.10529-10533.

Johns, A., 2001. Psychiatric effects of cannabis. *The British Journal of Psychiatry*, *178*(2), pp.116-122.

Kapur, A., Zhao, P., Sharir, H., Bai, Y., Caron, M.G., Barak, L.S. and Abood, M.E., 2009. Atypical responsiveness of the orphan receptor GPR55 to cannabinoid ligands. *Journal of Biological Chemistry*, *284*(43), pp.29817-29827.

Langer, N., Lindigkeit, R., Schiebel, H.M., Papke, U., Ernst, L. and Beuerle, T., 2016. Identification and quantification of synthetic cannabinoids in “spice-like” herbal mixtures: update of the German situation for the spring of 2015. *Forensic Toxicology*, *34*(1), pp.94-107.

Makriyannis, A. and Deng, H., University of Connecticut, 2005. *Cannabimimetic indole derivatives*. U.S. Patent 6,900,236.

McGaraughty, S., Chu, K.L., Dart, M.J., Yao, B.B. and Meyer, M.D., 2009. A CB 2 receptor agonist, A-836339, modulates wide dynamic range neuronal activity in neuropathic rats: contributions of spinal and peripheral CB 2 receptors.

Neuroscience, *158*(4), pp.1652-1661.

Moffat, A.C., Osselton, M.D., Widdop, B. and Watts, J., 2011. *Clarke's analysis of drugs and poisons*. Pharmaceutical Press,.

Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M. and Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *The Lancet*, *370*(9584), pp.319-328.

Poso, A. and Huffman, J.W., 2008. Targeting the cannabinoid CB2 receptor: modelling and structural determinants of CB2 selective ligands. *British journal of pharmacology*, *153*(2), pp.335-346.

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Ross, R.A., Brockie, H.C., Stevenson, L.A., Murphy, V.L., Templeton, F., Makriyannis, A. and Pertwee, R.G., 1999. Agonist- inverse agonist characterization at CB1 and CB2 cannabinoid receptors of L759633, L759656 and AM630. *British journal of pharmacology*, *126*(3), pp.665-672.

Ruiu, S., Pinna, G.A., Marchese, G., Mussinu, J.M., Saba, P., Tambaro, S., Casti, P., Vargiu, R. and Pani, L., 2003. Synthesis and characterization of NESS 0327: a novel putative antagonist of the CB1 cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics*, *306*(1), pp.363-370.

Shim, J.Y., Welsh, W.J. and Howlett, A.C., 2003. Homology model of the CB1 cannabinoid receptor: sites critical for nonclassical cannabinoid agonist interaction. *Peptide Science*, *71*(2), pp.169-189.

Solimini, R., Busardò, F.P., Rotolo, M.C., Ricci, S., Mastrobattista, L., Mortali, C., Graziano, S., Pellegrini, M., di Luca, N.M. and Palmi, I., 2017. Hepatotoxicity associated to synthetic cannabinoids use. *Eur Rev Med Pharmacol Sci*, *21*(1 Suppl), pp.1-6.

Uchiyama, N., Kawamura, M., Kikura-Hanajiri, R. and Goda, Y., 2013. URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products. *Forensic science international*, *227*(1), pp.21-32.

Uchiyama, Nahoko, Maiko Kawamura, Ruri Kikura-Hanajiri, and Yukihiro Goda. "Identification of two new-type synthetic cannabinoids, N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide (APICA) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA), and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products." *Forensic Toxicology* 30, no. 2 (2012): 114-125.

Vandrey, R., Dunn, K.E., Fry, J.A. and Girling, E.R., 2012. A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug and alcohol dependence*, *120*(1), pp.238-241.

White, C.M., 2016. The Pharmacologic and Clinical Effects of Illicit Synthetic Cannabinoids. *The Journal of Clinical Pharmacology*.

Wiley, J.L., Marusich, J.A., Lefever, T.W., Antonazzo, K.R., Wallgren, M.T., Cortes, R.A., Patel, P.R., Grabenauer, M., Moore, K.N. and Thomas, B.F., 2015. AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency of Novel Synthetic Cannabinoids in Producing Δ9-Tetrahydrocannabinol–Like Effects in Mice. *Journal of Pharmacology and Experimental Therapeutics*, *354*(3), pp.328-339.

Winstock, A.R. and Barratt, M.J., 2013. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug and alcohol dependence*, *131*(1), pp.106-111.

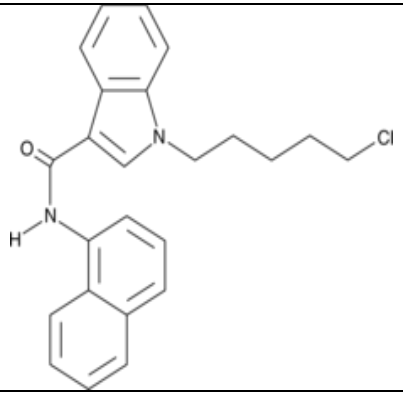
Wohlfarth, A., Castaneto, M.S., Zhu, M., Pang, S., Scheidweiler, K.B., Kronstrand, R. and Huestis, M.A., 2015. Pentylindole/pentylindazole synthetic cannabinoids and their 5-fluoro analogs produce different primary metabolites: metabolite profiling for AB-PINACA and 5F-AB-PINACA. *The AAPS journal*, *17*(3), pp.660-677.

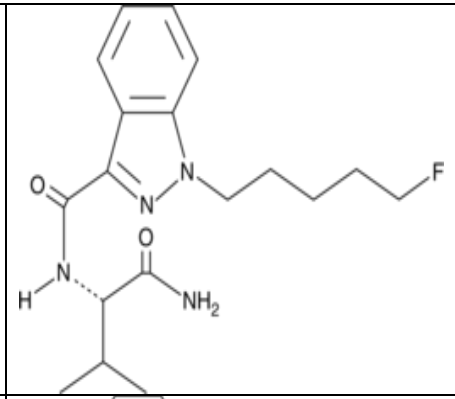
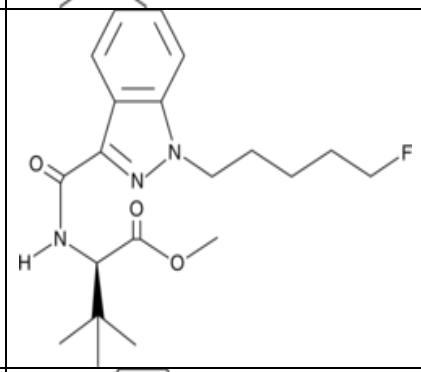
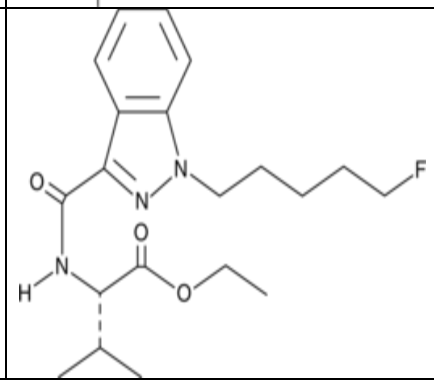
Zuardi, A.W., Crippa, J.A.S., Hallak, J.E.C., Moreira, F.A. and Guimaraes, F.S., 2006. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Brazilian Journal of Medical and Biological Research*, *39*(4), pp.421-42

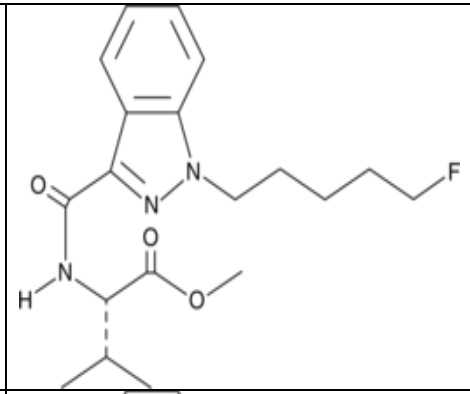
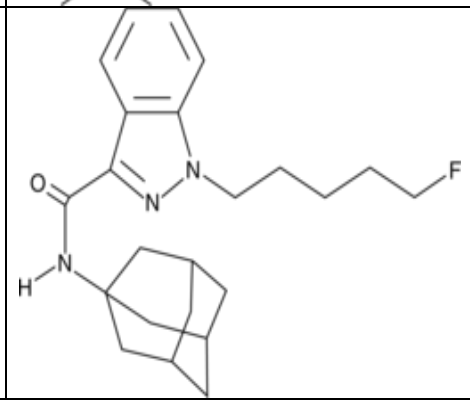
5. Appendices

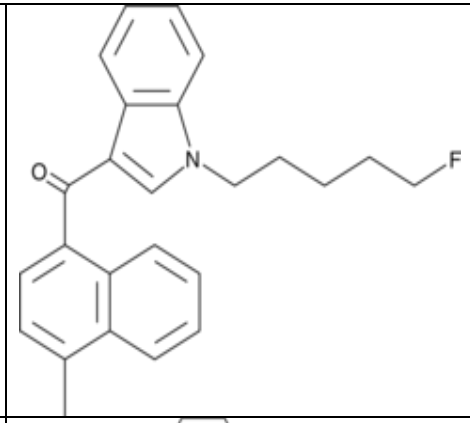
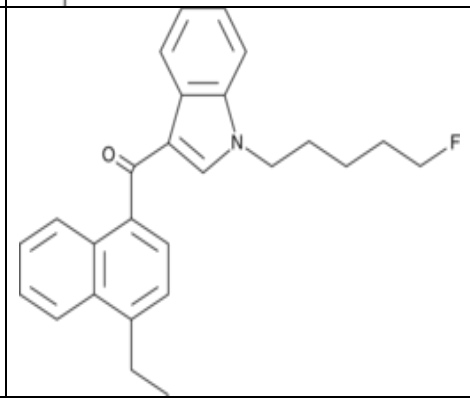
Appendix I

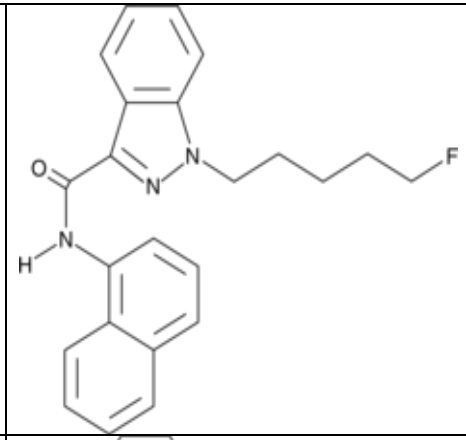
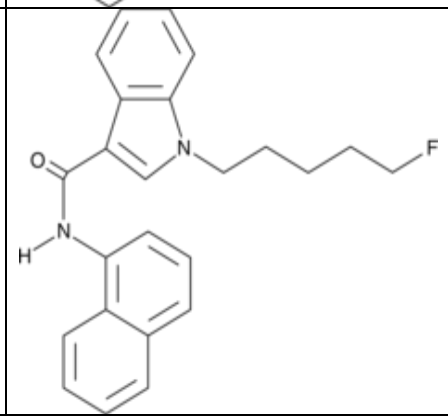
Table 1 – Potency of Known Synthetic Cannabinoids

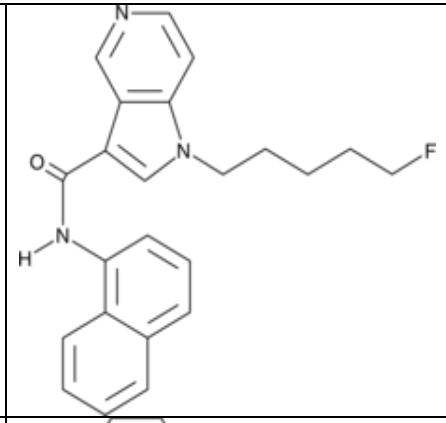
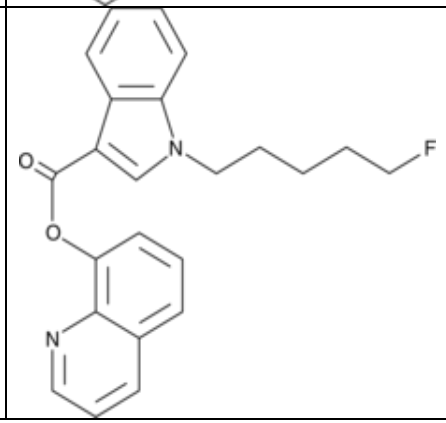
Synthetic Cannabinoids	Chemical Structure	Molecular Weight (g/mol)	CB1 Receptor (EC_{50} Value) (nM)	CB2 Receptor (EC_{50} Value) (nM)	CB1 Receptor (Affinity) (nM)	CB2 Receptor (Affinity) (nM)	Reference
5C-MN-24		390.9	-	-	-	-	-

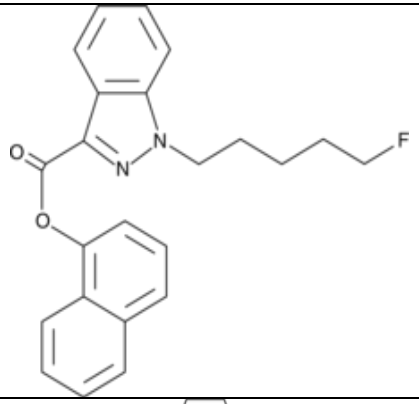
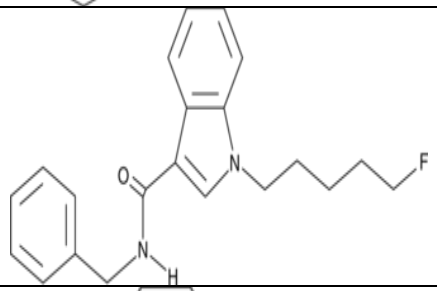
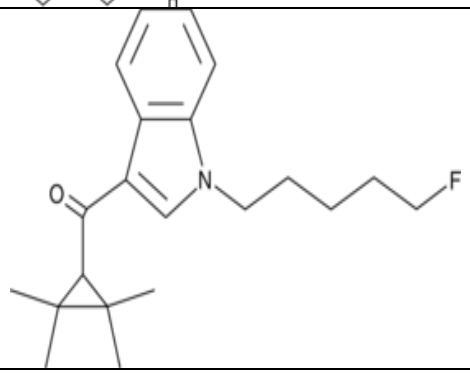
5F-AB-PINACA		348.4	0.48	2.6	-	-	(Banister et al. 2015a)
5F-ADB		377.5	-	-	-	-	-
5F-AEB		377.5	-	-	-	-	-

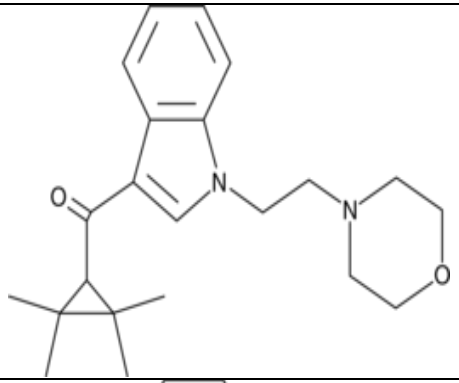
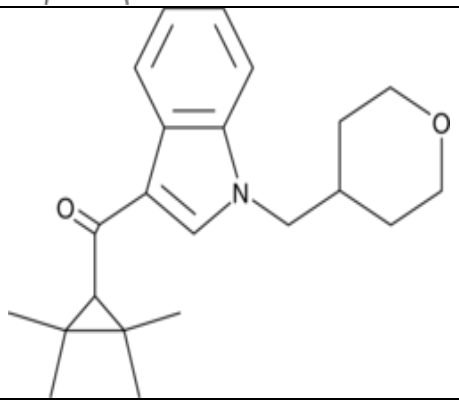
5F-AMB		363.4	-	-	0.7 -	-	(Banister et al. 2015)
5F-APINACA		383.5	-	-	1.94	0.266	(Wohlfarth et al. 2015)

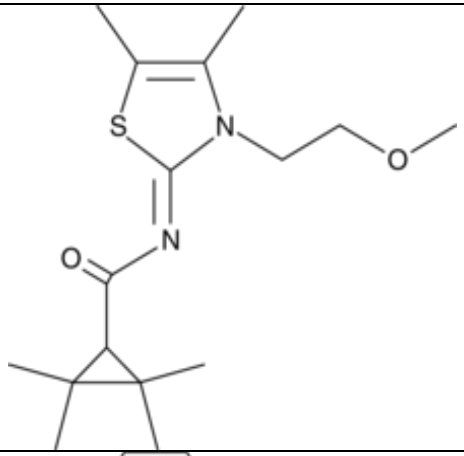
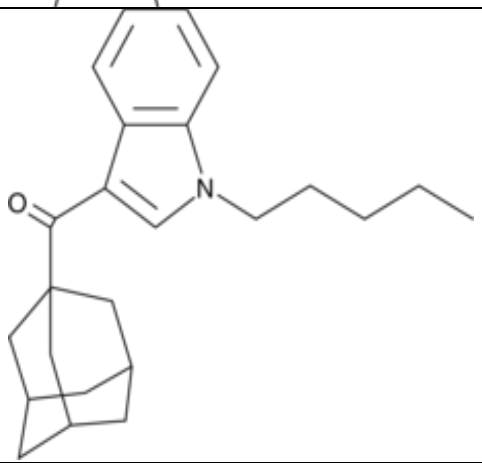
5F-JWH-122		373.5	-	-	-	-	-
5F-JWH-210		387.5	-	-	0.38	0.37	(Hess et al. 2016)

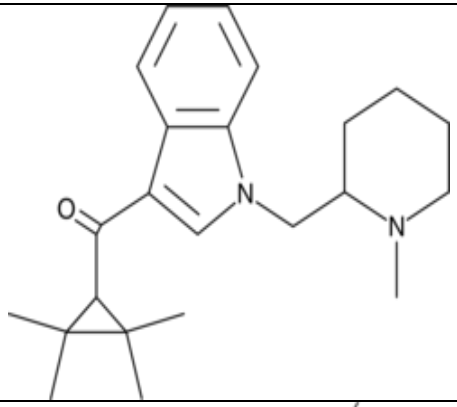
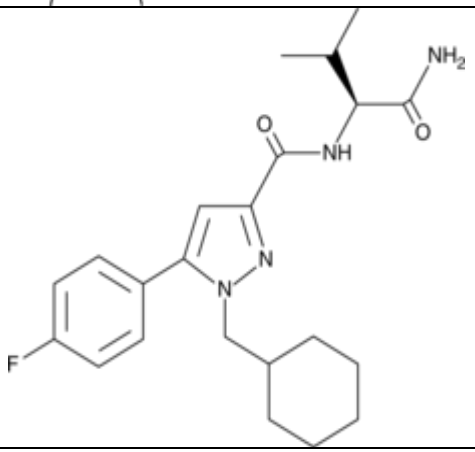
5F-MN-18		375.5	-	-	-	-	-
5F-MN-24		374.5	-	-	-	-	-

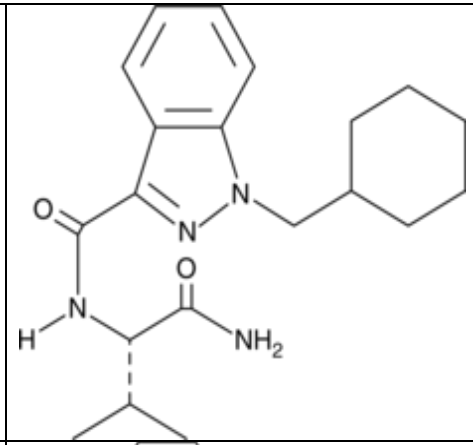
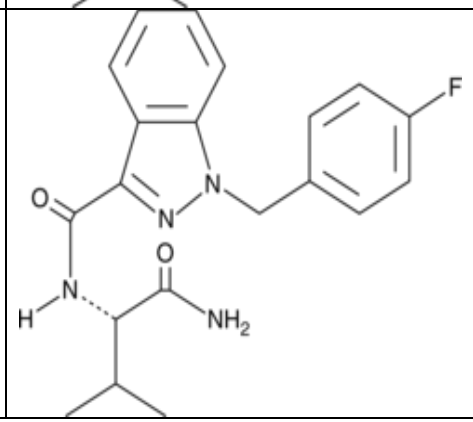
5F-PCN		375.4	-	-	-	-	-
5F-QUPIC		376.4	1.7	-	0.468	0.633	(De Luca et al. 2016; Hess et al. 2016)

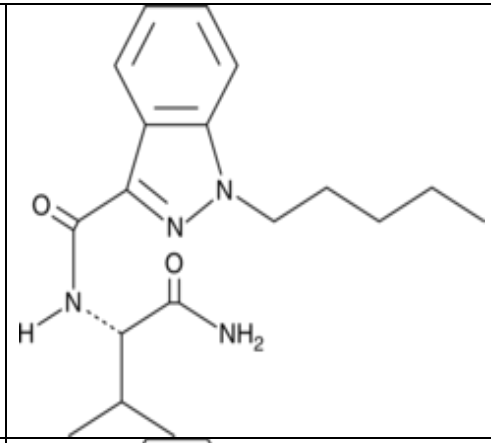
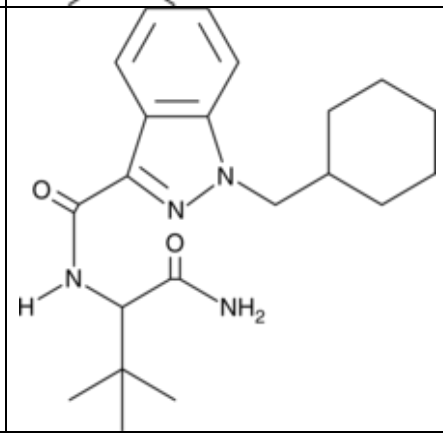
5F-SDB-005		376.4	-	-	-	-	-
5F-SDB-006		338.4	50	123	-	-	(Banister et al. 2015c)
5F-UR-144		329.5	98	83	-	-	(Banister et al. 2015c)

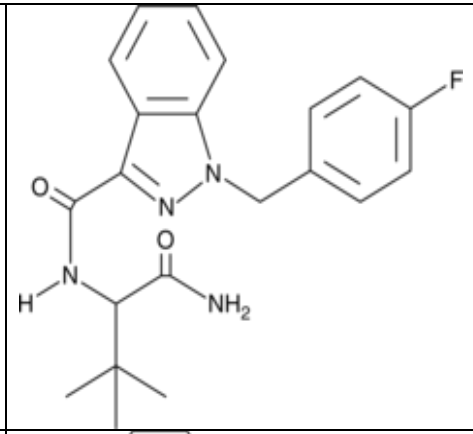
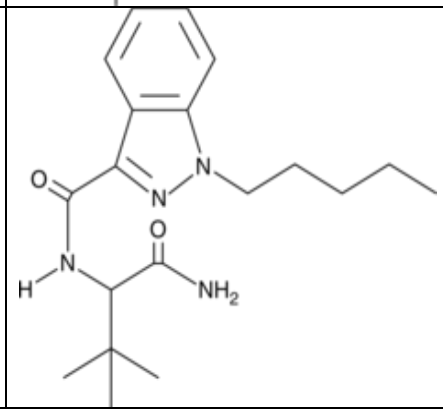
A-796,260		354.5	-	-	4.6	945	(Frost et al. 2009)
A-834,735		339.5	-	-	12	0.21	(Poso and Huffman 2008)

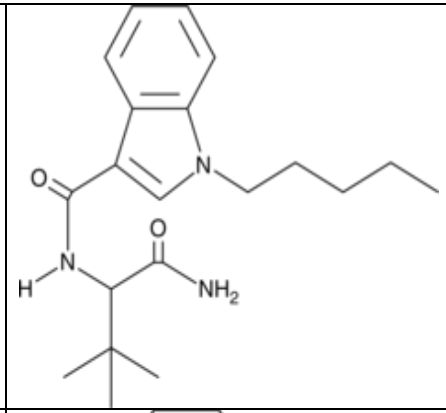
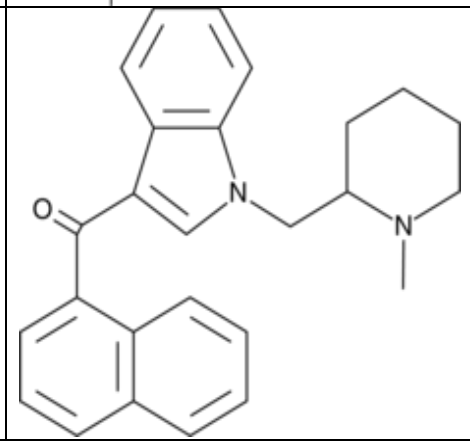
A-836,339		310.5	-	-	270	0.64	(McGaraughty et al. 2009)
AB-001		349.5	35	48	-	-	(Banister et al. 2013)

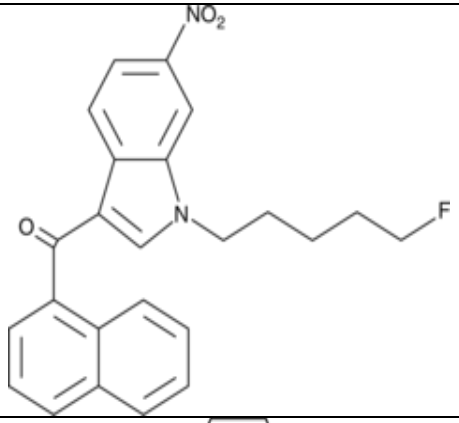
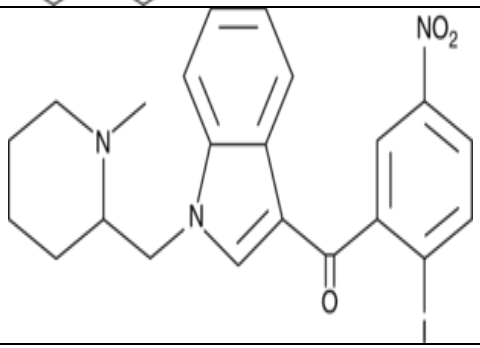
AB-005		352.5	-	-	5.5	0.48	(Frost et al. 2009)
AB-CHFUPYCA		400.5	-	-	-	-	-

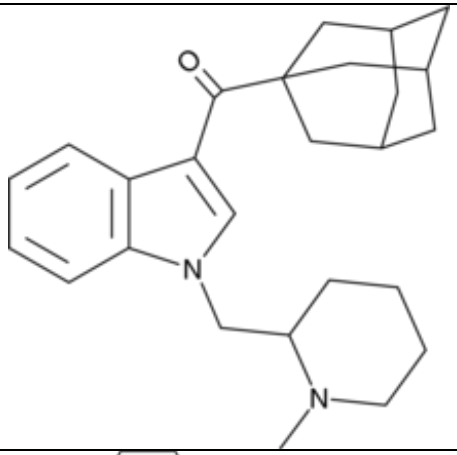
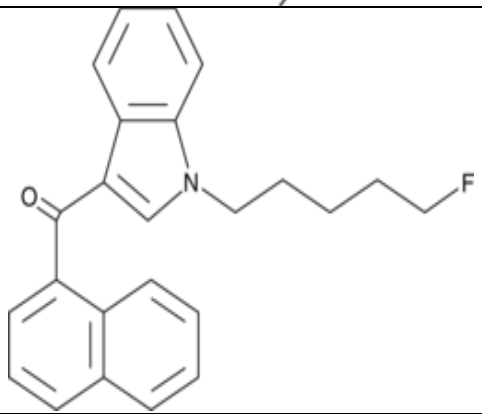
AB-CHMINACA		356.5	-	-	0.78	0.45	(Wiley et al. 2015)
AB-FUBINACA		368.4	1.8	3.2	0.9	23.3	(Banister et al. 2015a)

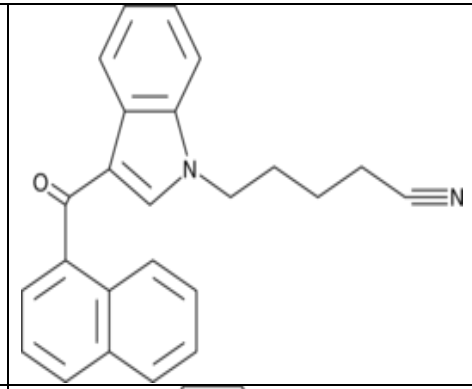
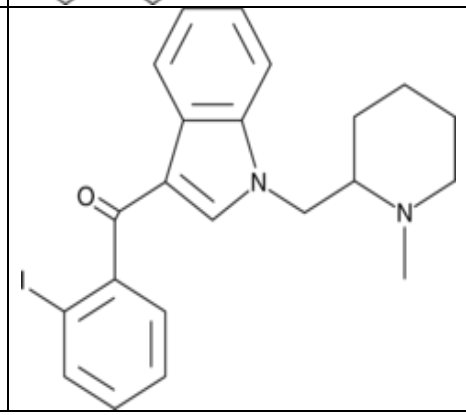
AB-PINACA		330.4	1.2	2.5	2.87	0.88	(Banister et al. 2015a; Wiley et al. 2015)
ADB-CHMINACA		370.5	-	-	-	-	-

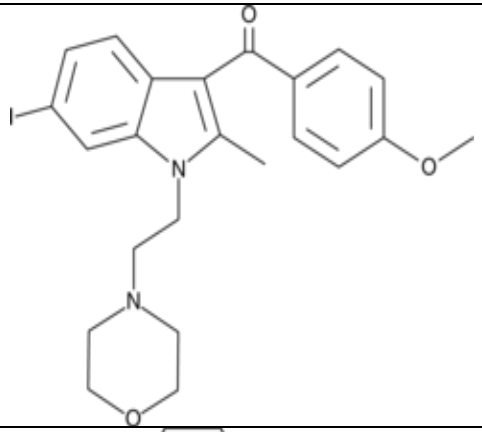
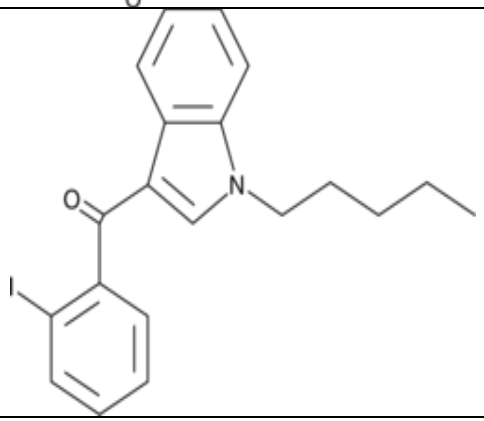
ADB-FUBINACA		382.4	1.2	3.5	-	-	(Banister et al. 2015a)
ADB-PINACA		344.5	0.52	0.88	-	-	(Banister we al. 2015a)

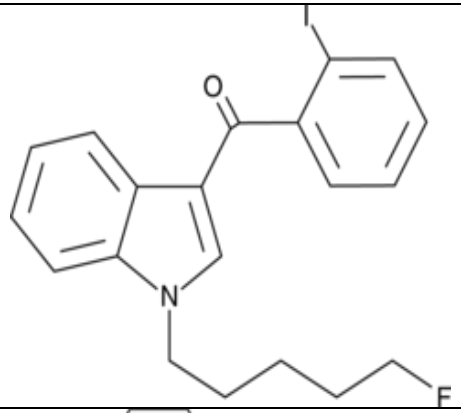
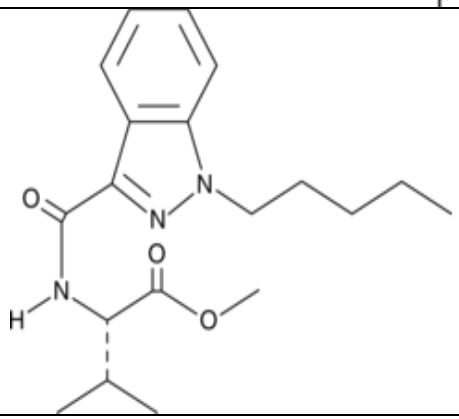
ADBICA		343.5	0.69	1.8	-	-	(Banister et al. 2015a)
AM-1220		382.5	-	-	-	-	-

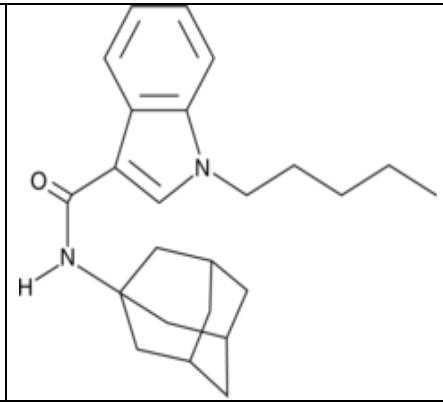
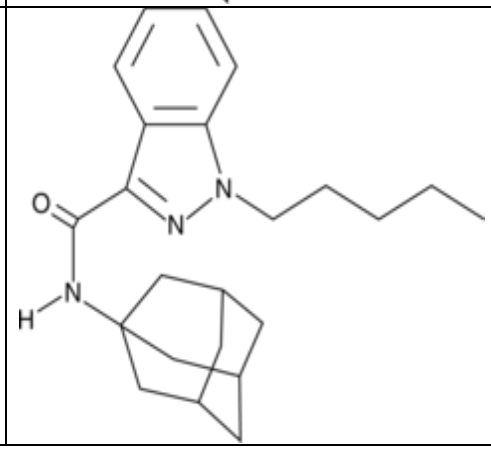
AM-1235		404.4	-	-	1.5	20.4	(Makriyannis and Deng 2005)
AM-1241		503.3	-	-	-	3.4	(Ibrahim et al. 2003)

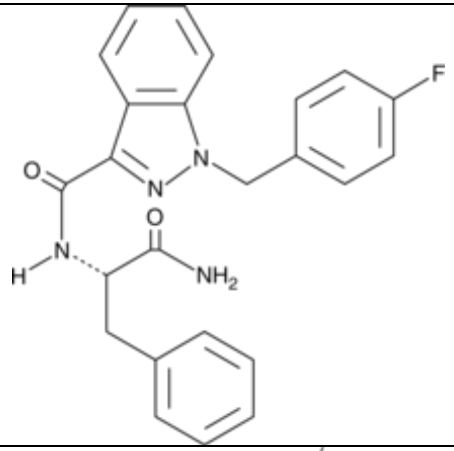
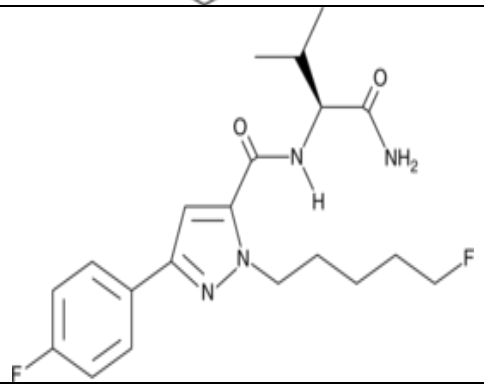
AM-1248		390.6	-	-	100	332	(Makriyannis and Deng 2005)
AM-2201		359.4	38	58	1.0	2.6	(Makriyannis and Deng 2005; Banister et al. 2015c)

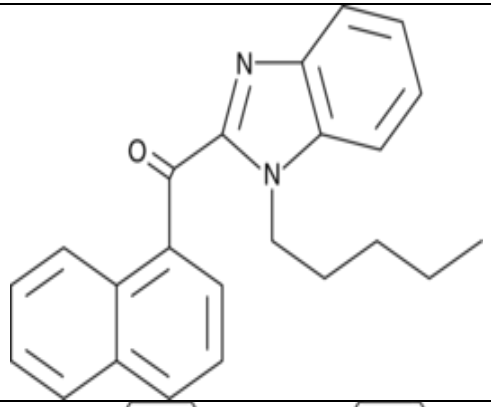
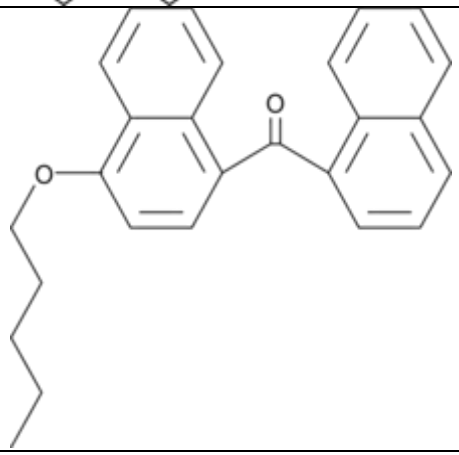
AM-2232		352.4	-	-	0.28	1.48	(Makriyannis and Deng 2005)
AM-2233		458.3	-	-	1.8	2.2	(Deng 2000)

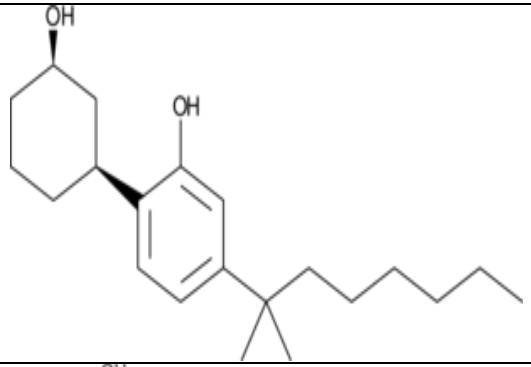
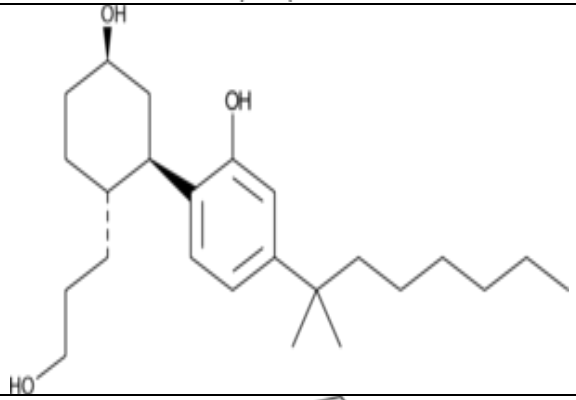
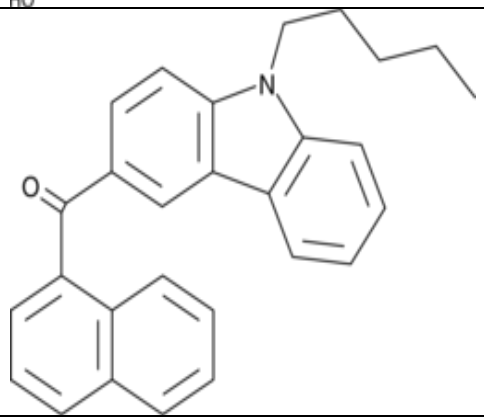
AM-630		504.4	-	-	-	31.2	(Ross et al. 1999)
AM-679		417.3	-	-	13.5	49.5	(Makriyannis and Deng 2005)

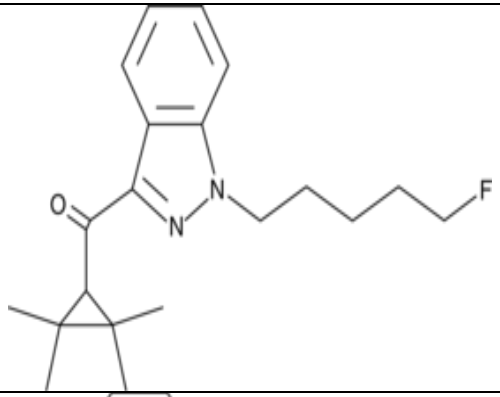
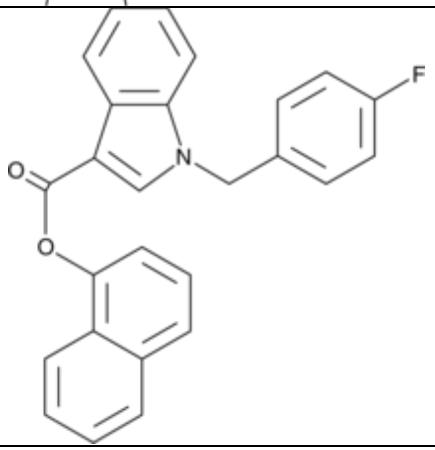
AM-694		435.3	-	-	0.08	1.44	(Makriyannis and Deng 2005)
AMB		345.4	-	-	-	-	-

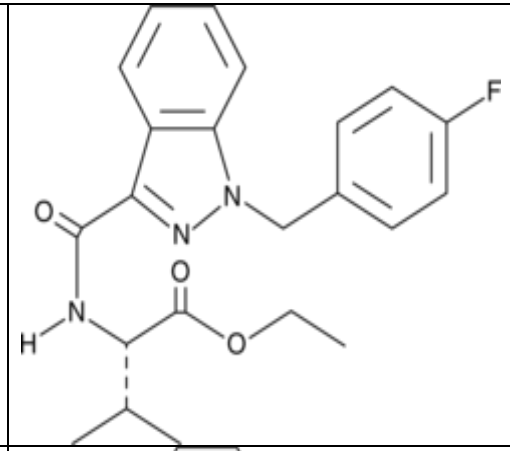
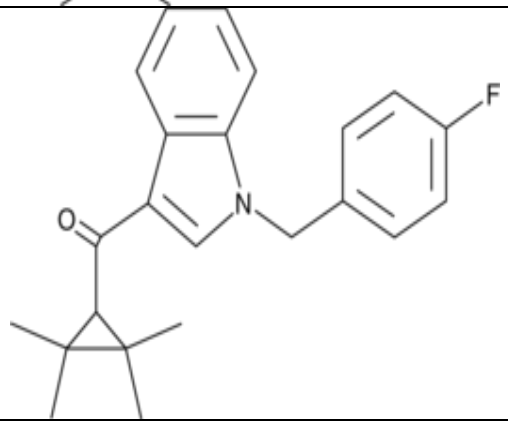
APICA		364.5	34	29	175	176	(Banister et al. 2013; Uchiyama et al. 2013)
APINACA		365.5	585	-	304.5	-	(Uchiyama et al. 2012)

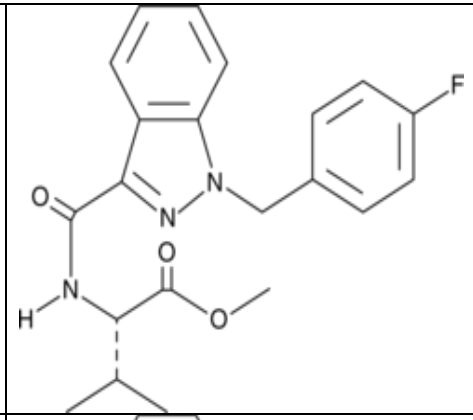
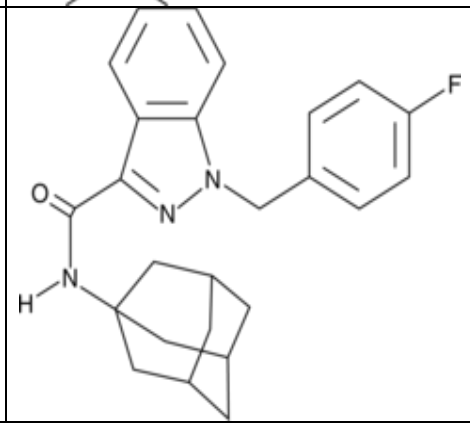
APP-FUBINACA		416.5	-	-	708	-	(Buchler et al. 2009)
AZ-037		392.4	-	-	-	-	-

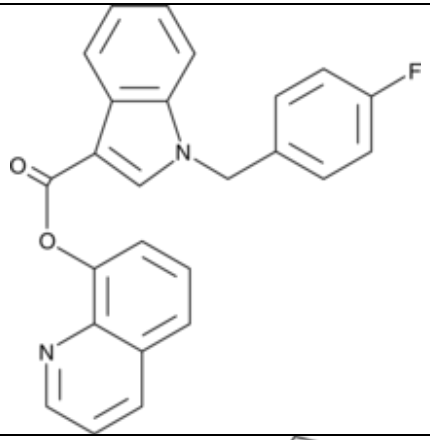
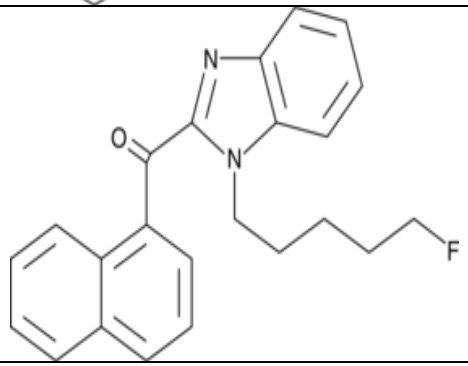
BIM-018		342.4	-	-	-	-	-
CB-13		368.5	-	-	-	-	-

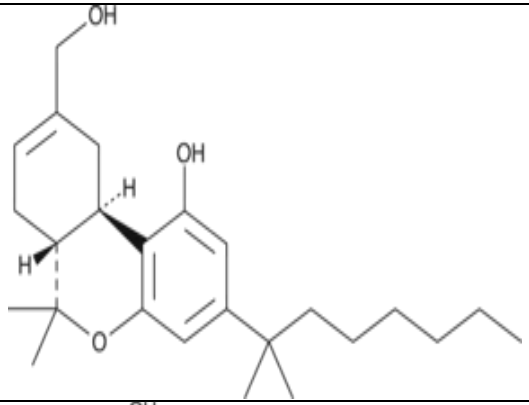
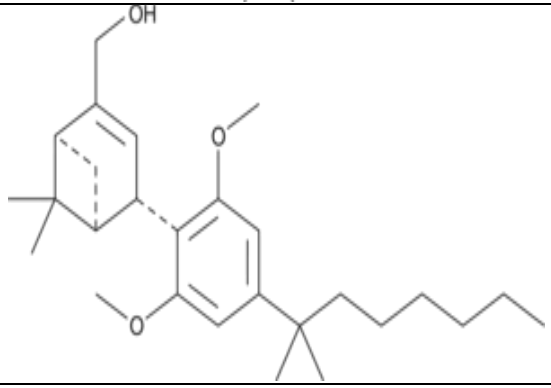
CP 47,497		318.5	-	-	2.1	-	(Shim et al. 2003)
CP 55,940		376.6	-	-	0.58	0.68	(Kapur et al. 2009)
EG-018		391.5	-	-	-	-	-

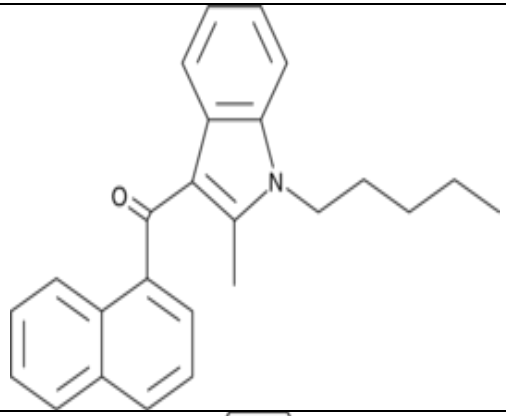
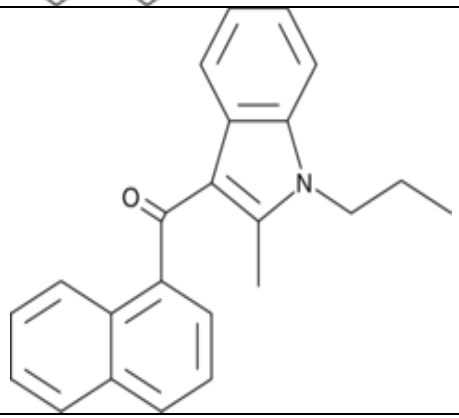
FAB-144		330.4	-	-	-	-	-
FDU-PB-22		395.4	-	-	1.19	2.43	(Hess et al. 2016)

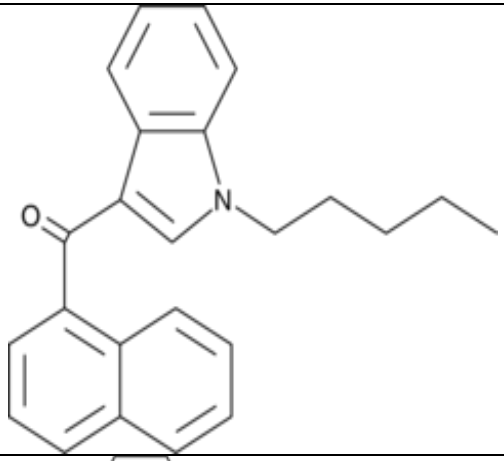
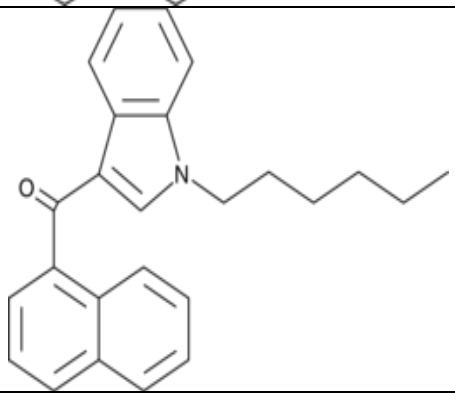
FU-AEB		397.5	-	-	-	-	-
FUB-144		349.5	-	-	-	-	-

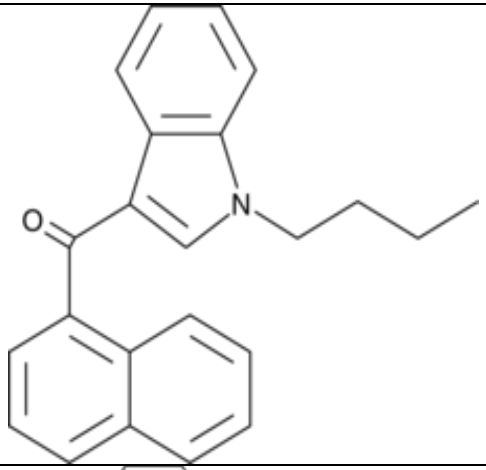
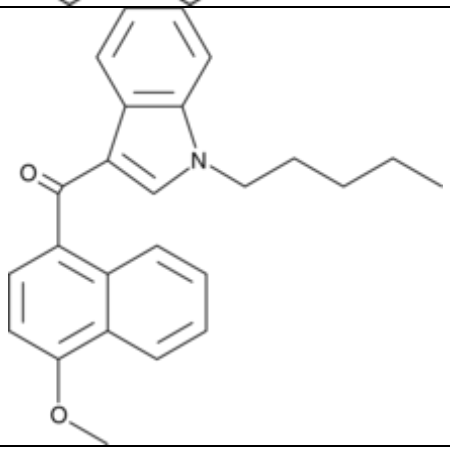
FUB-AMB		383.4	-	-	-	-	-
FUB-APINACA		403.5	-	-	1.06	0.174	(Hess et al. 2016)

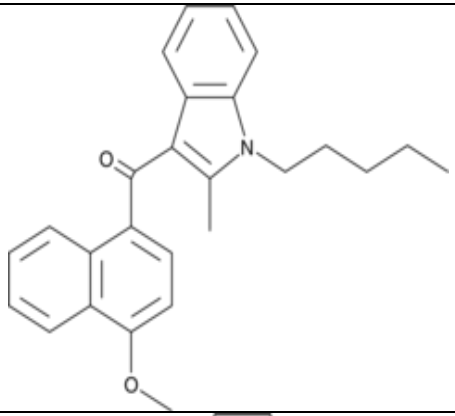
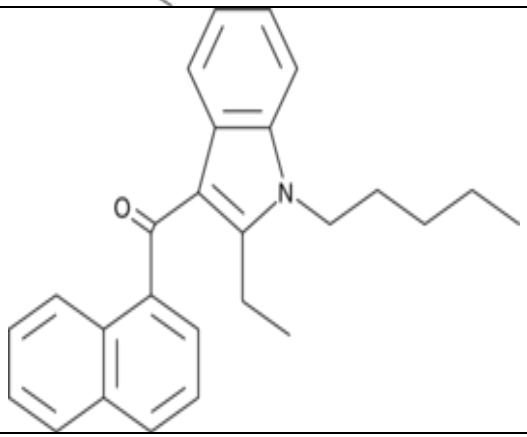
FUB-PB-22		396.4	-	-	0.386	0.478	(Hess et al. 2016)
FUBIMINA		360.4	-	-	296.1	23.45	(Wiley et al. 2015)

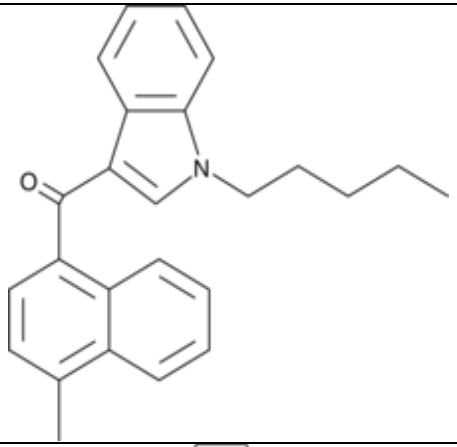
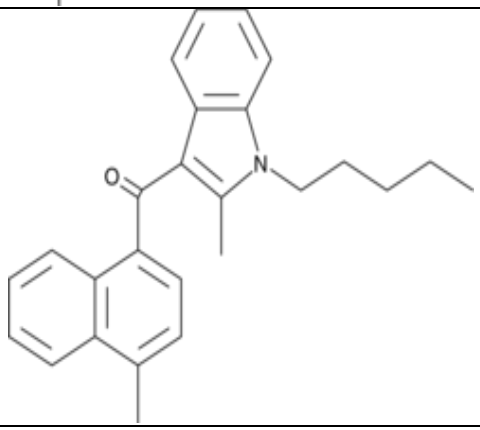
HU-210		386.6	-	-	-	-	-
HU-308		414.6	-	-	-	-	-

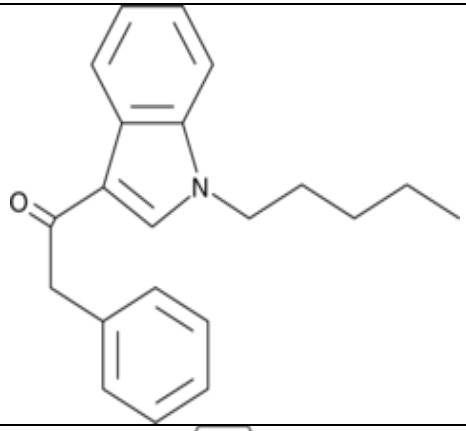
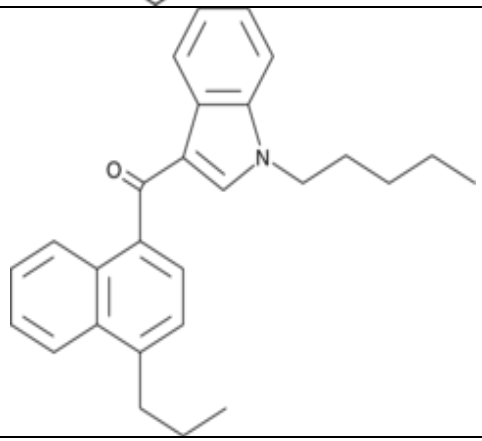
JWH-007		355.5	-	-	9.5	2.94	(Aung et al. 2000)
JWH-015		327.4	-	-	383	13.8	(Aung et al. 2000)

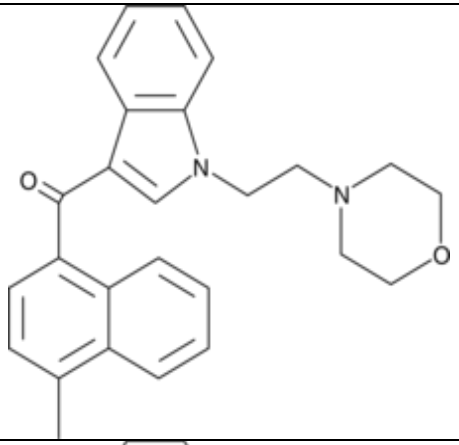
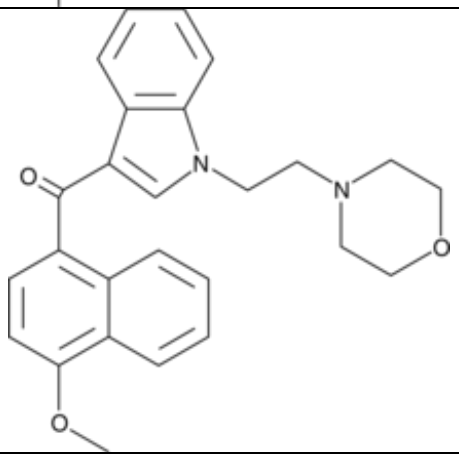
JWH-018		341.5	102	133	9.00 ± 5.00	2.94 ± 2.65	(Aung et al. 2000; Banister et al. 2015c)
JWH-019		355.5	-	-	-	-	-

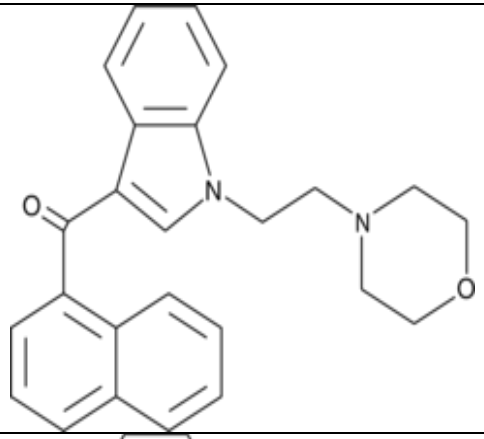
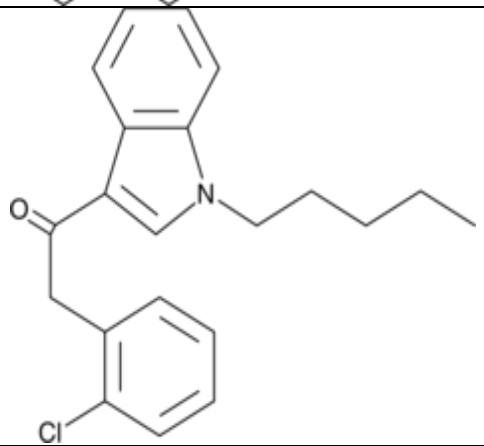
JWH-073		327.4	-	-	12.9 ± 3.4	-	(Brents et al. 2012)
JWH-081		371.5	-	-	1.2 ± 0.03	12.4 ± 2.2	(Huffman et al. 2005b)

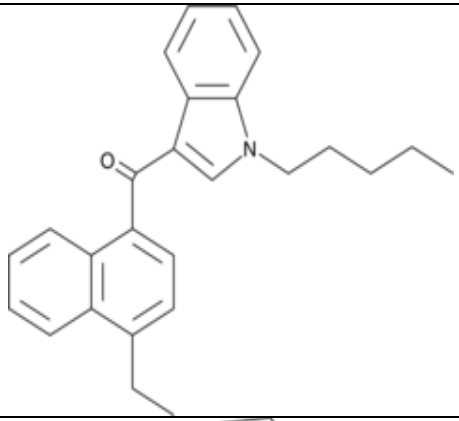
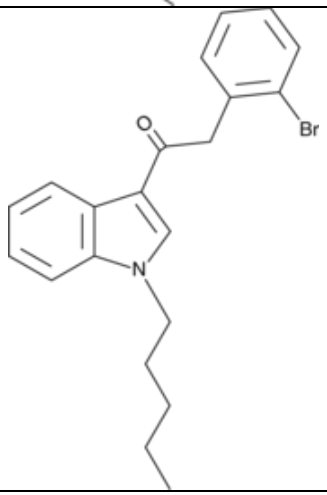
JWH-098		385.5	-	-	4.5 ± 0.1	1.9 ± 0.3	(Huffman et al. 2005b)
JWH-116		369.5	-	-	52 ± 5	-	(Huffman et al. 2003)

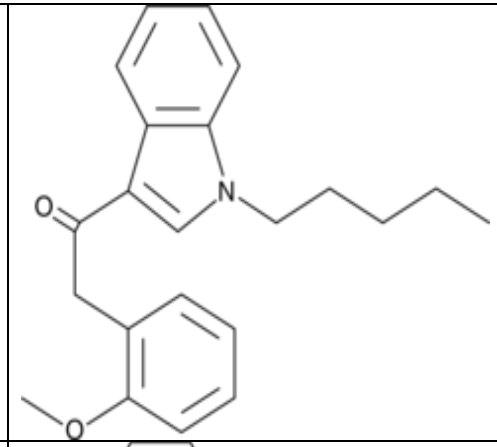
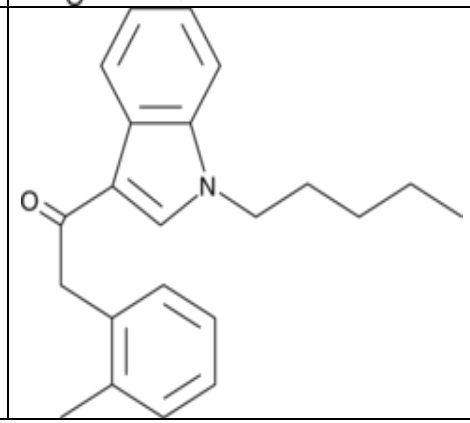
JWH-122		355.5	-	-	0.69 ± 0.5	1.2 ± 1.2	(Huffman et al. 2005b)
JWH-149		369.5	-	-	5.0 ± 2.1	0.73 ± 0.03	(Huffman et al. 2005b)

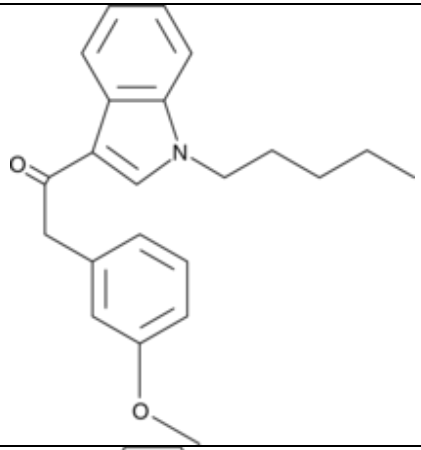
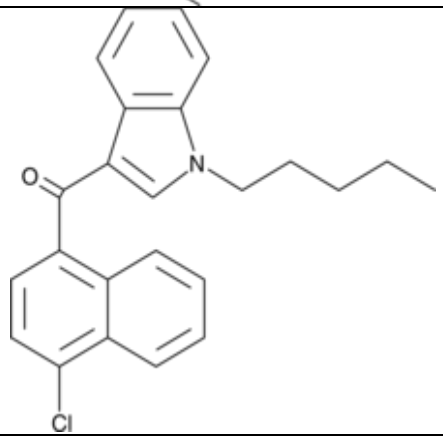
JWH-167		305.4	-	-	90 ± 17	159 ± 14	(Huffman et al. 2005a)
JWH-182		383.5	-	-	0.65 ± 0.03	1.1 ± 0.1	(Huffman et al. 2005b)

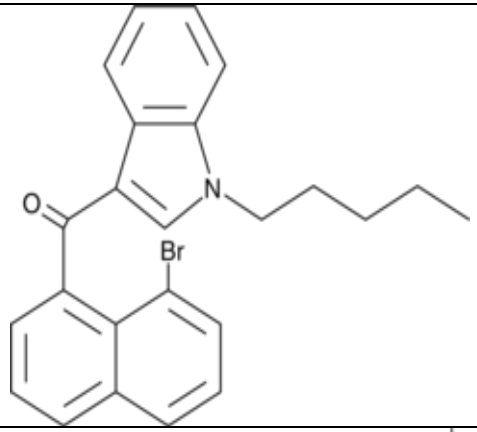
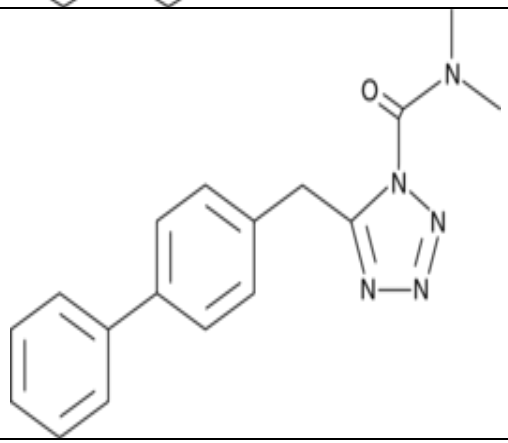
JWH-193		398.5	-	-	-	-	-
JWH-198		414.5	-	-	-	-	-

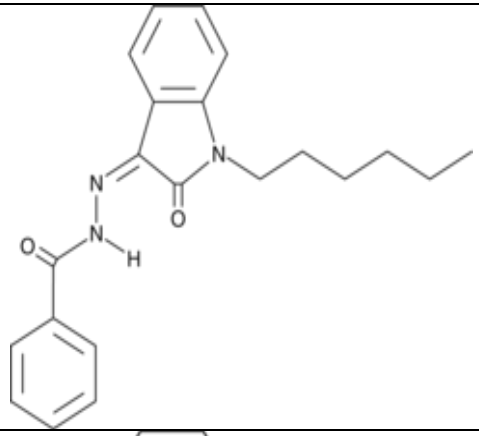
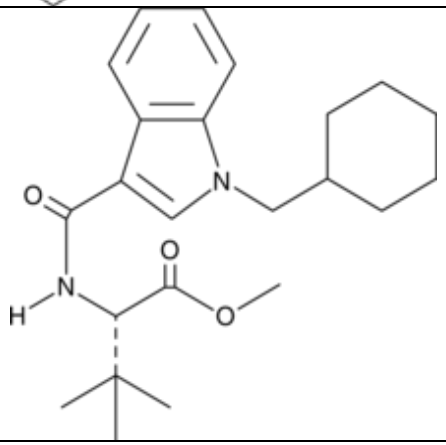
JWH-200		384.5	-	-	-	-	-
JWH-203		339.9	-	-	8.0 ± 0.9	7.0 ± 1.3	(Huffman et al. 2005a)

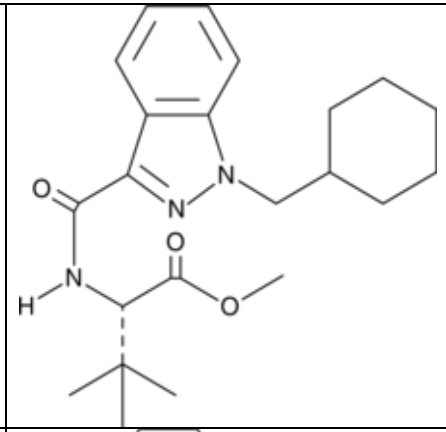
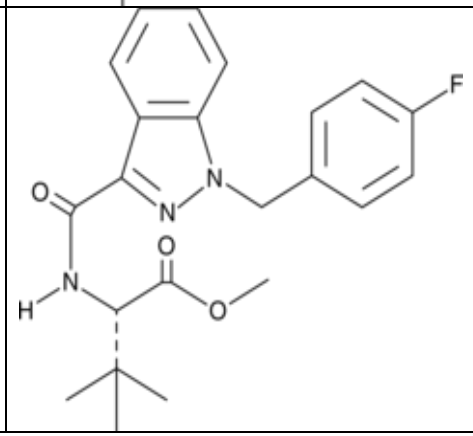
JWH-210		369.5	-	-	0.46 ± 0.03	0.69 ± 0.01	(Huffman et al. 2005b)
JWH-249		384.3	-	-	8.4 ± 1.8	20 ± 2	(Huffman et al. 2005a)

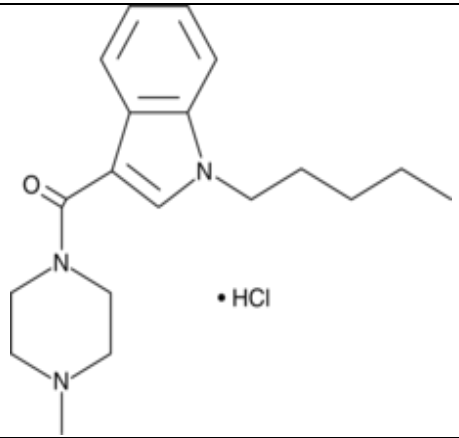
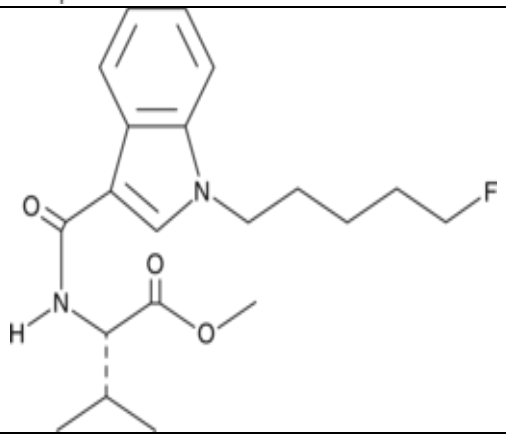
JWH-250		335.2	-	-	11 ± 2	33 ± 2	(Huffman et al. 2005a)
JWH-251		319.4	-	-	29 ± 3	146 ± 36	(Huffman et al. 2005a)

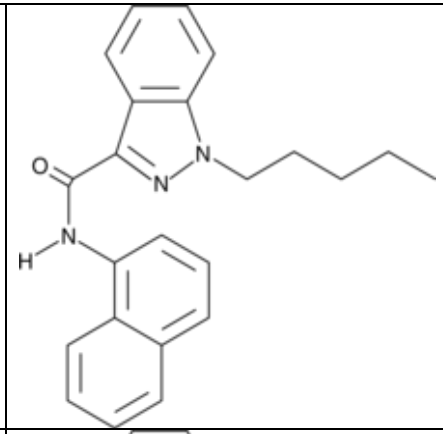
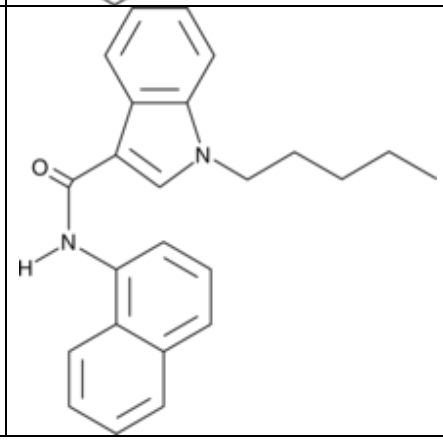
JWH-302		335.4	-	-	17 ± 2	89 ± 15	(Huffman et al. 2005a)
JWH-398		375.9	-	-	-	-	(Huffman 2009)

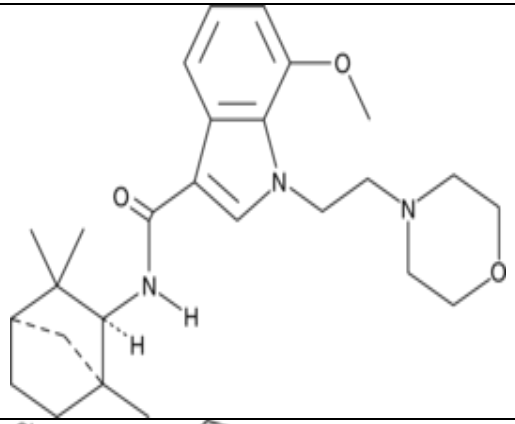
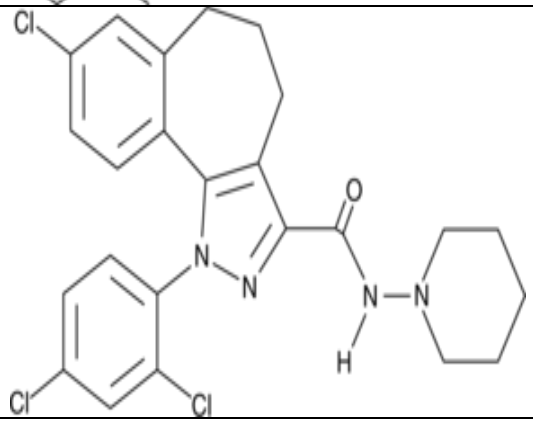
JWH-424		420.3	-	-	-	-	-
LY-2183240		307.4	-	-	-	-	-

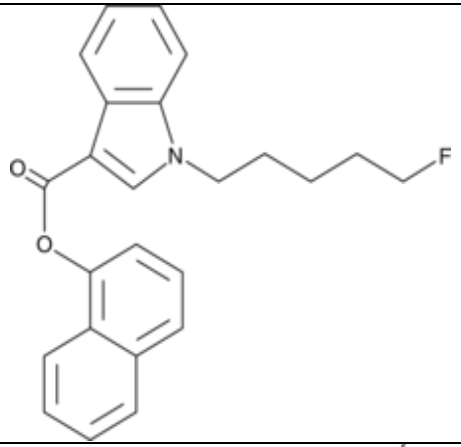
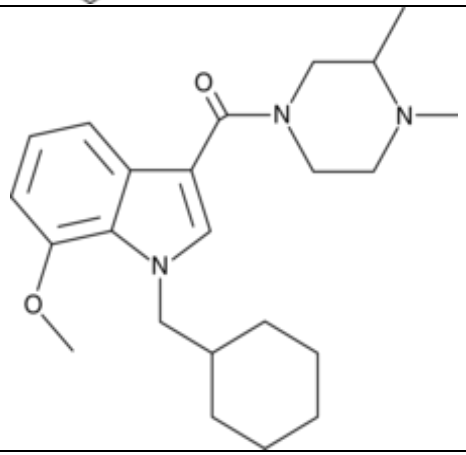
MDA-19		349.4	-	-	-	-	-
MDMB-CHMICA		384.5	0.14	-	-	-	(Langer et al. 2016)

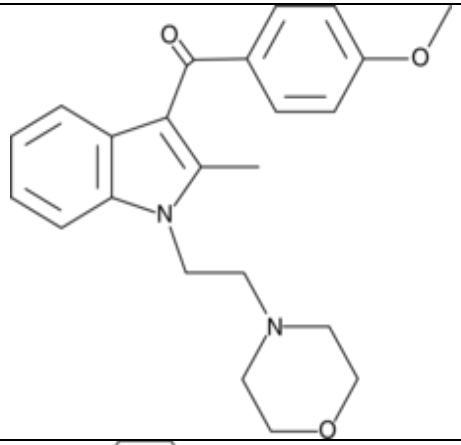
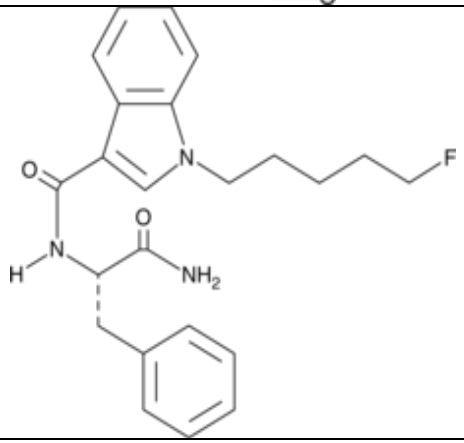
MDMB-CHMINACA		385.5	-	-	-	-	-
MDMB-FUBINACA		397.4	2.42	-	0.14	-	(Banister et al. 2016)

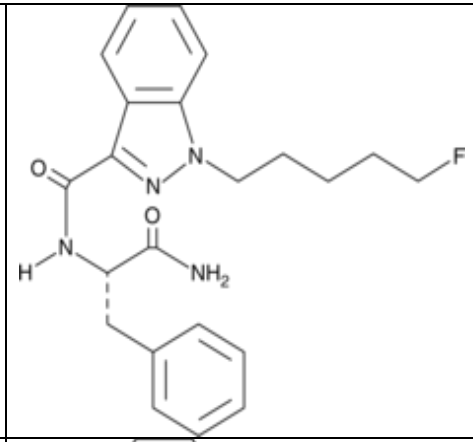
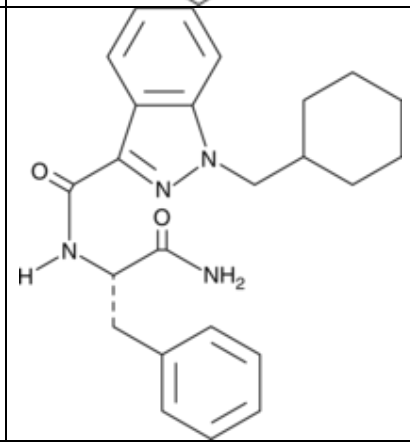
MEPIRAPIM		349.9	-	-	-	-	-
MMB-2201		362.5	-	-	-	-	-

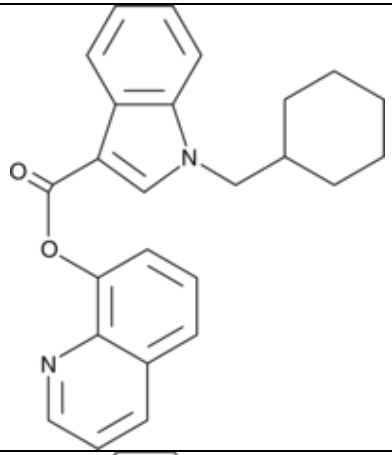
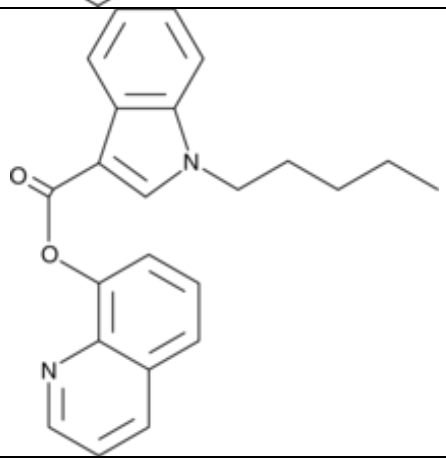
MN-18		357.5	-	-	-	-	-
MN-24		356.5	-	-	-	-	-

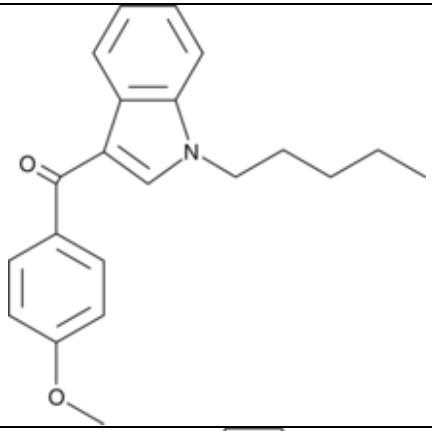
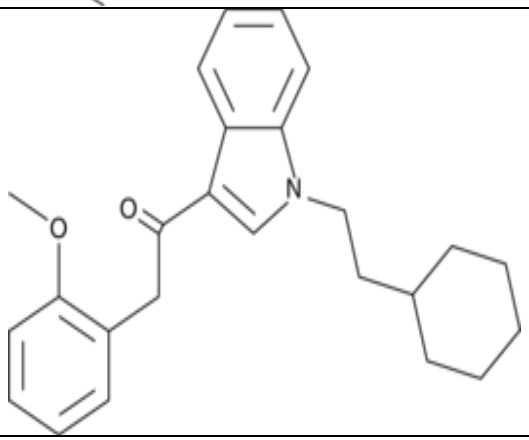
MN-25		439.6	-	-	-	-	-
NESS-0327		489.8	-	-	0.00035	-	(Ruiu et al. 2003)

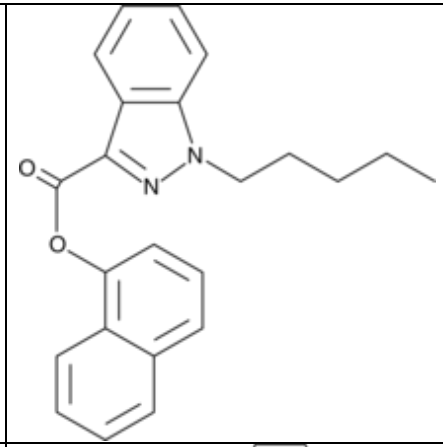
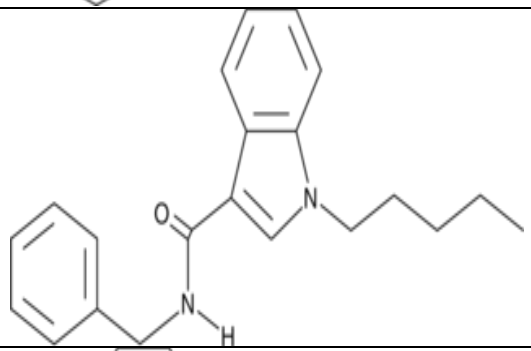
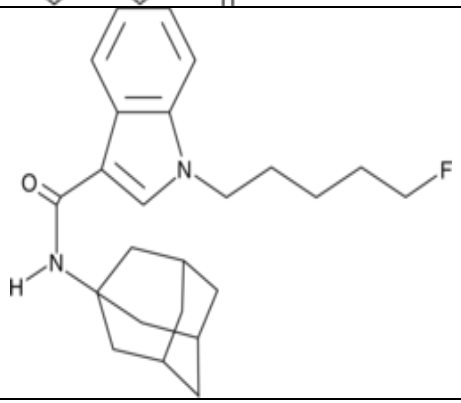
NM-2201		375.4	-	-	0.332	0.732	(Hess et al. 2016)
Org-28611		383.5	-	-	-	-	-

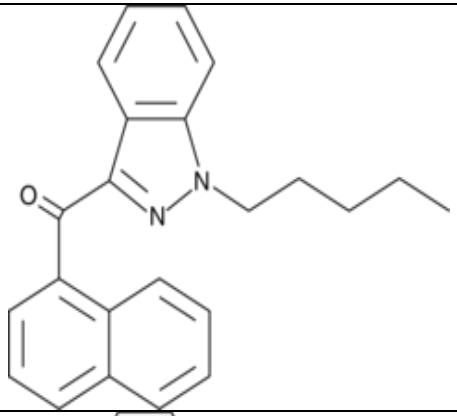
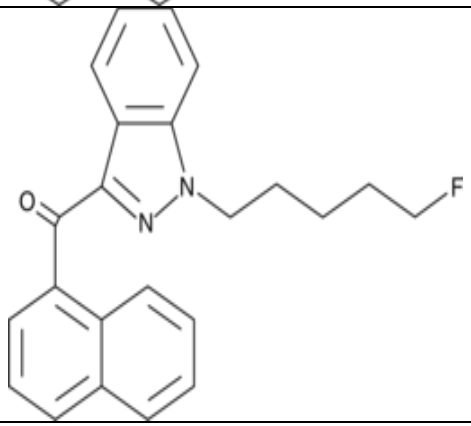
Pravadoline		378.5	-	-	-	-	-
PX-1		395.5	-	-	-	-	-

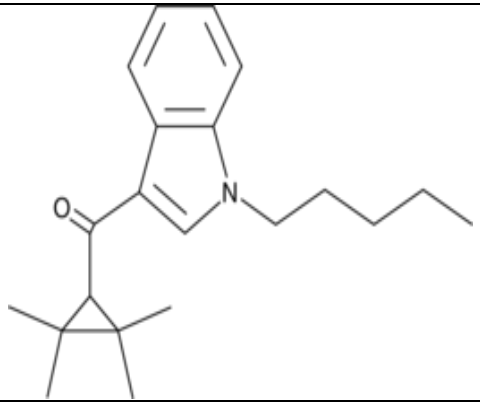
PX-2		396.5	-	-	-	-	-
PX-3		404.5	-	-	-	-	-

QUCHIC		384.5	-	-	0.217	0.338	(Hess et al. 2016)
QUPIC		358.4	5.1	37	-	-	(Banister et al. 2015c)

RCS-4		321.4	146	46	-	-	(Banister et al. 2015b)
RCS-8		375.5	-	-	-	-	-

SDB-005		358.4	-	-	21	140	(Banister et al. 2013)
SDB-006		320.4	19	134	-	-	(Banister et al. 2015c)
STS-135		382.5	51	13	-	-	(Banister et al. 2015c)

THJ-018		342.4	-	-	5.84	4.57	(Hess et al. 2016)
THJ-2201		360.4	-	-	1.34	1.32	(Hess et al. 2016)

UR-144		311.5	421	72	1.8	150	(Banister et al. 2015c; Frost et al. 2009)

Appendix II

Evaluative Supplement

Conducting this research project has been a learning experience and has highlighted a variety of factors that will aid in proceeding forward in the future when conducting further research. At the start of the literature review, it was challenging to find sufficient journals and articles that produced sufficient evidence. For example, some information on some synthetic cannabinoids was on the correct compound but there was not much significance in relating them to either driving under the influence cases, metabolism, excretion or background information. Additionally, it was a struggle to find journals when searching for synthetic cannabinoids due to using the abbreviated name of the synthetic cannabinoid. Once using the IUPAC name, more results of significance and relevance emerged when searching through scientific databases. This is something that I have learnt which I will be able to use and take forward in further studies. Also, even once using search engines with the IUPAC name for the synthetic cannabinoids, it would still come up with too much information to search through to find the information necessary for this dissertation. To narrow down the information, lists of keywords were used in order to use with the name of the synthetic cannabinoid. This produced less results when conducting the literature search but the results that were produced were more relevant to the dissertation I was writing.

This however, proved to also be a limitation as whilst literature searching there was very little information out there for many of the synthetic cannabinoids. This limited the dissertation, as I wasn't able to discuss more synthetic cannabinoids due to the information that would be needed to produce a monograph on the synthetic cannabinoid not being there. Therefore I was only able to produce monographs on more common synthetic cannabinoids as they had more information available in scientific databases. I was also only able to write about these synthetic cannabinoids due to having limited time with which being able to find information and write up the dissertation. This would be something that I would try to improve if I were to produce a similar piece of research, as I wouldn't be under such strict time limits to produce the assessment.

I also feel that a strength that I have learnt during this dissertation has been being able to enhance my scientific writing by reading through scientific journal using articles, to see how they are written and use similar structures. This will also help me to produce better-structured and more scientific reports in further studies.

I believe that the monographs that I have produced are of a high quality in their structure due to having a similar structure to other reports or articles that were very successful in being published. I also believe that by using a recognised structure from published work I have read I have produced relevant information found from literature searches to write the monographs.

In my opinion future work that would need to be produced would firstly need to be undertaken more synthetic cannabinoids. I found that it was hard to produce monographs on more synthetic cannabinoids, as there was very little information on many synthetic cannabinoids. The information that I would have needed to produce a monograph was not found in literature searches and therefore I recommend further research being undertaken on the metabolism, excretion, toxicity, usage and occurrence.

Once this information is studied and reported in journals it will be able to enhance work, such as this, on synthetic cannabinoids and will be able to encourage further research to take place to decipher full details on synthetic cannabinoids. This information will help for further cases involving these synthetic cannabinoids as when the metabolism of them is studied, when taking blood from suspect of impairment the metabolites can also be looked for and therefore be able to distinguish what the parent drug compound is.

If I were to repeat this topic now I would be able to use the skills I have learnt from this current dissertation to perform superior literature searches to that would provide me with sufficient information to produce monographs on.

Also I would aim to research more information when only one synthetic cannabinoid was found in the blood in driving under the influence cases. I would

make the effort to do this, as then I would be able to predict signs and symptoms for a certain synthetic cannabinoid. As in the research I have undertaken it is difficult to detain what synthetic cannabinoids have produced what effect in impairment cases when multiple synthetic cannabinoids have been found in the blood.

Overall I believe that this dissertation has provided me with researching skills and a further knowledge into the use and pharmacology of synthetic cannabinoids. I believe that if I were to undertake further education or complete more research in either this field or other scientific fields I would be well adapted to complete these in a sufficient scientific manner.

Appendix III

Learning Contract

BU Bournemouth University **LEARNING CONTRACT: INDEPENDENT RESEARCH PROJECT**

Student Name:	**Ellis George**
Degree Programme:	Forensic Science
Proposed Project Title:	How Synthetic Cannbinoids affect a persons ability to drive?
Supervisor:	David Osselton

Research Proposal Attached ☒ **YES** ☐ **NO** **and includes:**

☐ **YES**	☒ **NO**	**Risk Assessment for fieldwork and evidence of COSSH assessment for all laboratory procedures (online risk assessment completed)**
☐ **YES**	☒ **NO**	**Completed booking forms for all field equipment**
☐ **YES**	☒ **NO**	**Letters of permission where appropriate providing evidence of access to such things as field sites and/or museum archives**
☒ **YES**	☐ **NO**	**Completed Ethics Checklist**

Copies of all relevant forms may be found on myBU - SciTech tab - Projects - Project Forms

INTERIM INTERVIEW – Progress evaluation

The nature of this review should be clearly defined and agreed. Please complete the box below with the agreed details including the agreed submission date which is normally the first week of November in Level 6/H. Submission is via a formal tutorial with the supervisor.

Assessment Due: 3/12/16

FINAL ASSESSMENT – RESEARCH PAPER/REPORT

This assessment is normally governed by the guidance provided in the Independent Research Project Guide. Any variance in terms of format and word limit should be agreed and specified in the box below. Submission date cannot however be changed unless evidence of mitigating circumstances are provided in accordance with the standard BU Guidelines.

PTO

As the student undertaking the above project I agree to:

- E-mail my supervisor on a fortnightly basis with a progress report
- Meet with my supervisor at least once a month to discuss progress and I understand that it is my responsibility to organise these meetings
- Comply with the terms of this learning contract and the guidance set out in the Guide to Independent Research Projects
- I understand that this is an *independent* project and that I am solely responsible for its completion
- I agree to comply with all laboratory and fieldwork protocols established by the Faculty.

As the supervisor of this project I agree to:

- Meet with the student undertaking this project on at least a monthly basis and to respond to the progress e-mails as appropriate
- To meet formally with the student during the first week in November to undertake the interim interview
- To provide guidance and support to the student undertaking this project bearing in mind that it is an *independent* research project. This is inclusive of commenting on drafts of the final report in a timely fashion.

Both of the undersigned parties agree to be bound by this learning contract:	
Student Signature:	E. George
PRINT NAME:	ELLIS GEORGE
Date:	01/11/16

Supervisor Signature:	
PRINT NAME:	M DAVID OSSELTON
Date:	1/11/2016

When completed, this form should be handed in to SciTech Admin (C114) and a copy retained by the student to be included in an appendix to the final IRP document.

Appendix IV

Ethics Checklist

Bournemouth University

Initial Research Ethics

Note: ***All researchers*** must complete this brief checklist to identify any ethical issues associated with their research. Before completing, please refer to the BU *Research Ethics Code of Practice* which can be found www.bournemouth.ac.uk/researchethics. School Research Ethics Representatives (or Supervisors in the case of students) can advise on appropriate professional judgement in this review. A list of Representatives can be found at the aforementioned webpage.

Sections 1-5 must be completed by the researcher and Section 6 by School Ethics

1 RESEARCHER DETAILS						
Name	**Ellis George**					
Email	**i7661343@bournemouth.ac.uk**					
Status	☒ **Undergraduate**		☐ **Postgraduate**		☐ **Staff**	
School	☒ **BS**	☐ **AS**	☐ **DEC**	☐ **HSC**	☐ **MS**	☐ **ST**
Degree Framework & Programme	**Forensic Science**					
2 PROJECT DETAILS						
Project Title	How Synthetic Cannbinoids affect a persons ability to drive?					
Project Summary *Sufficient detail is needed; include methodology, sample, outcomes etc*	**To research synthetic cannabinoids, create monographs for each substance that I research. Find out how each of the substances affect a persons ability to drive.**					
Proposed Start & End Dates	**September 2016 – May 2017**					
Project Supervisor	**David Osselton**					
Framework Project Co-ordinator						

3 ETHICS REVIEW CHECKLIST – PART A			
I	Is approval from an external Research Ethics Committee (e.g. Local Research Ethics Committee (REC), NHS REC) required/sought?	☐ **Yes**	☒ **No**
II	Is the research solely literature-based?	☒ **Yes**	☐ **No**
III	Does the research involve the use of any dangerous substances, including radioactive materials?	☐ **Yes**	☒ **No**
IV	Does the research involve the use of any potentially dangerous equipment?	☐ **Yes**	☒ **No**
V	Could conflicts of interest arise between the source of funding and the potential outcomes of the research? (see section 8 of BU Research Ethics Code of Practice).	☐ **Yes**	☒ **No**
VI	Is it likely that the research will put any of the following at risk: Living creatures?	☐ **Yes**	☒ **No**
		☐ **Yes**	☒ **No**
	Stakeholders?	☐ **Yes**	☒ **No**

Research Ethics Checklist (Graduate School & CRE) December 2010

	Researchers?	☐ Yes	☒ No
	Participants?	☐ Yes	☒ No
	The environment?	☐ Yes	☒ No
	The economy?		
VII	Does the research involve experimentation on any of the following: Animals?	☐ Yes	☒ No
	Animal tissues?	☐ Yes	☒ No
	Human tissues (including blood, fluid, skin, cell lines)?	☐ Yes	☒ No
	Genetically modified organisms?	☐ Yes	☒ No
VIII	Will the research involve prolonged or repetitive testing, or the collection of audio, photographic or video materials?	☐ Yes	☒ No
IX	Could the research induce psychological stress or anxiety, cause harm or have negative consequences for the participants or researcher (beyond the risks encountered in normal life)?	☐ Yes	☒ No
X	Will the study involve discussion of sensitive topics (e.g. sexual activity, drug use, criminal activity)?	☐ Yes	☒ No
XI	Will financial inducements be offered (other than reasonable expenses/ compensation for time)?	☐ Yes	☒ No
XII	Will it be necessary for the participants to take part in the study without their knowledge / consent at the time?	☐ Yes	☒ No
XII	Are there problems with the participant's right to remain anonymous?	☐ Yes	☒ No
XIV	Does the research *specifically* involve participants who may be vulnerable?	☐ Yes	☒ No
XV	Might the research involve participants who may lack the capacity to decide or to give informed consent to their involvement?	☐ Yes	☒ No

4 ETHICS REVIEW CHECKLIST – PART B

Please give a summary of the ethical issues and any action that will be taken to address these.

Ethical Issue:	**Action:**

5 RESEARCHER STATEMENT

I believe the information I have given is correct. I have read and understood the BU Research Ethics Code of Practice, discussed relevant insurance issues, performed a health & safety evaluation/ risk assessment and discussed any issues/ concerns with a School Ethics Representative/ Supervisor. I understand that if any substantial changes are made to the research (including methodology, sample etc), then I must notify my School Research Ethics Representative/ Supervisor and may need to submit a revised Initial Research Ethics Checklist. By submitting this form electronically I am confirming the information is accurate to my best knowledge.

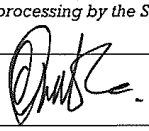
Signed	E. Geeteh	**Date**	**01/11/16**

6 AFFIRMATION BY SCHOOL RESEARCH ETHICS REPRESENTATIVE/ SUPERVISOR

Satisfied with the accuracy of the research project ethical statement, I believe that the appropriate action is:

The research project proceeds in its present form	**X Yes**	☐ **No**
The research project proposal needs further assessment under the School Ethics procedure*	☐ **Yes**	**X No**
The research project needs to be returned to the applicant for modification prior to further action*	☐ **Yes**	**X No**

** The School is reminded that it is their responsibility to ensure that no project proceeds without appropriate assessment of ethical issues. In extreme cases, this can require processing by the School or University's Research Ethics Committee or by relevant external bodies.*

Reviewer Signature		**Date**	**1/11/2016**
Additional Comments			

Appendix V

Interim Meeting

Independent Research Project Interim Interview : Agreed Comments Form

Student Name: Ellis George	Programme: Forensic Science
Date: 3/12/16	IRP Title: How Synthetic Cannabinoids affect a persons ability to drive?
Supervisor Name: David Osselton	

David and I had several meetings and discussions over the course of the year covering several topics.
We agreed the format of the dissertation; we agreed that my literature searching was going well and that I was going through the correct steps to find articles and journals that would give me sufficient information to include in my dissertation.
We also discussed the idea of including a potency table to give details on where further research needs to take place and to find what information is available on these synthetic cannabinoids..

Two copies of this form are needed – student to retain one copy the other is to be handed in to the student admin office C114.

Student Signature: E. George	Supervisor Signature: