



Advisory Council on the Misuse of Drugs

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Lynne Featherstone MP, Minister for Crime Prevention  
Home Office  
2 Marsham Street  
London  
SW1P 4DF

27 November 2014

Dear Minister,

**RE: ACMD's report on 'Third Generation' synthetic cannabinoids**

I am pleased to enclose the Advisory Council on the Misuse of Drugs' (ACMD) third report on synthetic cannabinoids. Cannabinoids are an increasingly diverse class of chemical compounds which produce psychoactive effects similar to those produced by *Cannabis*.

This report recommends a revised generic description, designed to control a broad-range of 'third generation' synthetic cannabinoids which are currently on the market and not controlled by the Misuse of Drugs Act 1971.

This is based around modifications of a model compound (JWH-018) and is designed to be used in addition to the current generic definitions in the Misuse of Drugs Act 1971.

The enclosed report follows on from two earlier reports by the ACMD on synthetic cannabinoids. The first report in 2009 described the associated physical and social harms and proposed generics legislation to control these substances. The current controls on synthetic cannabinoids came into force following the ACMD's second report in 2012. However, it is now evident that there is now a 'third generation' of these materials which are available on the market and fall outside the scope of these controls.

The increasing availability of these substances in headshops and on the Internet has been confirmed by both the Forensic Early Warning System (FEWS) and Drug Early Warning System (DEWS) networks. Third generation synthetic cannabinoids are being found in herbal smoking products and in materials for use in e-cigarettes.

We attach with this report the scope of the proposed generic definition (Annex 1), the chemical structures of these new materials (Annex 2) and guidance on the interpretation of the proposed definition (Annex 3).

It is increasingly difficult to address the diverse family of synthetic cannabinoids by such controls, which are based on chemical structures. To anticipate future developments, the ACMD therefore favours development of an alternative approach based on the common mechanism of action of these substances as activators of the CB<sub>1</sub> receptor in brain, which can readily be assessed by a simple biochemical test.<sup>1</sup>

We look forward to discussing this report with you in due course.

Yours sincerely,



Professor Les Iversen  
ACMD Chair



Professor Simon Gibbons  
Chair of the ACMD's NPS  
Committee

CC: Rt Hon Theresa May MP, Home Secretary

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<sup>1</sup> <https://www.gov.uk/government/publications/new-psychoactive-substances-review-report-of-the-expert-panel>

# ACMD

Advisory Council on the Misuse of Drugs

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## **‘Third Generation’ Synthetic Cannabinoids**

**November 2014**

## CONTENTS

	Page	
1	Introduction	5
2	Availability	5
3	Synthetic cannabinoids with CB <sub>1</sub> activity	6
4	Developments in the synthetic cannabinoids NPS market after 2012	7
5	Effects	8
6	The UK's current generic controls	8
7	Options for extending control	9
8	Recommendation	9
9	Scope of the proposed generic	10
10	Consultation by the ACMD	10
	Annex 1: Proposed scope	11
	Annex 2: Novel synthetic cannabinoids structures: rendering materials 'legal' by modifications which place them outside existing UK generic controls	15
	Annex 3: Interpretation of the proposed generic definition	20

## 1. Introduction

- 1.1. Synthetic cannabinoid receptor agonists which affect the CB<sub>1</sub> cannabinoid receptors in the brain can produce psychoactive effects similar to those produced by *Cannabis*. Following the identification of such materials in smoking products, the UK enacted two rounds of controls under the Misuse of Drugs Act.
- 1.2. The first, coming into force at the end of 2009, was based around materials then known to be available as novel psychoactive substances (NPS) and included a number of named compounds together with generic controls covering groups of materials related to those known to be in circulation in order to try to avoid simple 'designer' variants being brought to the market (ACMD Report on the Major Cannabinoid Agonists, August 2009).
- 1.3. The second round drafted in 2012 and coming into effect in early 2013, expanded control to include a broader range of 'second generation' materials, which had appeared between 2009 and 2012. However, it was accepted that the controls might have to be revisited if further materials were commercialised as NPS (ACMD Further Consideration of Synthetic Cannabinoids, October 2012).
- 1.4. Since the second round of controls came into effect (February 2013), a 'third generation' of synthetic cannabinoids, outside the scope of the 2012 controls, has indeed entered the NPS market and become widely available, including materials intended for use in electronic cigarettes, so that a further review of controls is required.
- 1.5. This report proposes a revised generic control based around modifications of a 'model' compound (JWH-018). The recommended approach covers the very broad range of new materials now being marketed as cannabinoid NPS, without requiring lengthy additions to the Misuse of Drugs controls.

## 2. Availability

### *FEWS*<sup>2</sup>

- 2.1. The Forensic Early Warning System (FEWS) reported the results obtained after forensic analysis of 345 products seized from head shops from Aberdeen to Plymouth in Spring 2014. 11 different synthetic cannabinoids were seen. Of these 5F-AKB-48 (*N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide; the fluoropentanyl analogue of AKB-48) was seen most often (156 times).

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<sup>2</sup> [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/344551/2014-08-12\\_-\\_FEWS\\_Annual\\_Report\\_Aug\\_2014\\_-\\_Final\\_2\\_.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/344551/2014-08-12_-_FEWS_Annual_Report_Aug_2014_-_Final_2_.pdf)

5F-PB-22 (quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate) was also seen frequently (99 times) either alone or with 5F-AKB-48, AKB-48 (29 times) and PB-22 (4 times). The non-fluorinated analogues of 5F-AKB-48 and 5F-PB-22, were also popular. AB-FUBINACA (21 times) (*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide), AB-PINACA (twice) (*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide) and ADB-PINACA (3 times) (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide) were also seen.

### *DEWS*

- 2.2. The Home Office invoked the Drug Early Warning System (DEWS) on 30<sup>th</sup> July 2014, requesting information in relation to the 3<sup>rd</sup> generation synthetic cannabinoids. This evoked 12 separate responses from a wide variety of specialist areas i.e. police forces, prisons, a treatment centre and PHE (Public Health England). A wide range of synthetic cannabinoids was reported to be available, with a predominance of 5F-AKB-48 and 5F-PB-22.
- 2.3. The new synthetic cannabinoids, and herbal smoking products containing them, are widely advertised on internet webshops and are on sale in headshops. FEWS surveys have confirmed the identity of the active ingredients, which now most commonly include materials such as AKB-48 and PB-22, and their fluorinated forms (5F-AKB-48 and 5F-PB-22), either individually or in mixtures. However, many other uncontrolled synthetic cannabinoids have also been identified.
- 2.4. Recently, liquids suitable for use with 'e-cigarettes' have begun to be advertised, including one claimed to contain a novel synthetic cannabinoid developed so as to be more suitable for this method of ingestion (described as 5F-AKB-48 with the adamantyl group replaced by cumyl).

## **3. Synthetic cannabinoids with CB<sub>1</sub> activity**

- 3.1. Pharmaceutical research has resulted in the publication of a great variety of chemical structures which act on the CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors. To avoid psychoactive effects, the majority of recent medical research has been concentrated on developing materials which preferentially affect the CB<sub>2</sub> receptor in the immune system, or which are CB<sub>1</sub> agonists that do not penetrate the blood-brain barrier so that they affect only the peripheral CB<sub>1</sub> receptors. However, research publications have described many materials which are active at the CB<sub>1</sub> receptor and which are therefore potentially usable as *Cannabis* substitutes.

- 3.2. For example, a 2009 Pfizer patent (WO2009106980) sets out a broad range of indazole derivatives including several pyrazolo(3,4-b)pyridine derivatives with CB<sub>1</sub>-activity.<sup>3</sup>
- 3.3. Over 700 examples are described and the table of CB<sub>1</sub> activities within the patent lists many materials with K<sub>i</sub> < 100, and some with K<sub>i</sub> < 1 (see for example structures #13, 21, 33, 45, 128, 129, 131, 133, 134, 148, 171).
- 3.4. Many of the structural modifications around the core indazole structure shown in the Pfizer patent will be equally applicable to indole-based materials and other core structures such as benzimidazole, so the range of materials potentially suitable for use as synthetic cannabinoid receptor agonists is substantial.

#### 4. Developments in the synthetic cannabinoid NPS market after 2012

- 4.1. Since the second round of UK controls was prepared in 2012, new synthetic cannabinoids which are outside the scope of the UK's controls have appeared on the NPS market. For example, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported the identification of over 20 such compounds during 2013 and another 15 in the first nine months of 2014. In the UK's NPS market, uncontrolled synthetic cannabinoids have now replaced those which had been controlled. The new materials, and smoking products containing them, are widely available via internet webshops and from 'headshops'.
- 4.2. There is a common structure to many of the synthetic cannabinoids. Typical molecules contain four components (*see figure 5*): a core cyclic structure (in one of the original materials identified, JWH-018, this was indole), a 'bridge' (methanone in JWH-018) joining the core to a secondary structure (in JWH-018, naphthyl) with a 'tail' attached to the nitrogen of the core structure (in JWH-018, this was pentyl). This four part structure is demonstrated in an interactive tool available on the EMCDDA website.<sup>4</sup>
- 4.3. The many synthetic cannabinoid materials which have appeared as NPS in the UK since 2012 feature modifications *of the structures* of these component parts, apparently selected or designed so as to place these new materials outside the scope of the UK's generic controls while

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<http://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009106980&recNum=1&maxRec=&office=&prevFilter=&sortOption=&queryString=&tab=PCTDescription>

<sup>4</sup> <http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>

retaining psychoactive activity. Modifications seen include (structures shown in Annex 2):

- i. Replacement of the indole core by an indazole or benzimidazole core (see, for example, AKB-48 and FUBIMINA – *figure 6*)
- ii. Use of a carboxamide or carboxylate bridge (see APICA, SDB-005 – *figure 7*)
- iii. Novel ‘secondary structures’, including quinolinyl rings, 4-methylpiperazinyl rings and more recently, a range of non-cyclic structures (see 5F-PB-22, MEPIRAPIM, ADBICA – *figure 8*)
- iv. Novel ‘tails’ on the ring nitrogen, such as 4-fluorobenzyl (see AB-FUBINACA – *figure 9*)

4.4. Some materials, such as PB-22 (‘QUPIC’) and BB-22 (‘QUCHIC’), include several of these modifications (*figure 10*).

## **5. Effects**

5.1. The reported effects of the new materials are similar to those caused by the now controlled materials and there are suggestions that some of the new substances may be more potent than those which they have replaced. DEWS reports include a number of cases of users being overwhelmed by the effects of smoking materials believed to contain the new cannabinoids, resulting in collapse and hospitalisation.

## **6. The UK’s current generic controls**

6.1. The first two rounds of UK legislation included generic controls designed to cover the materials then known to have been marketed and related materials which had been described in the research literature. By 2013, this included eight generic controls on ‘families’ of synthetic cannabinoids.

6.2. Within the eight generic controls, there are five indole-based generics, covering modifications of naphthoyl indoles, phenylacetyl indoles, benzoyl indoles, adamantoyl indoles and tetramethylcyclopropylcarbonyl indoles. Each of these five indole-based generic controls was therefore based on modifications of a named structure defined by the indole core, the bridge and secondary structure, with the generic modifications covering a list of ‘tails’ on the indole nitrogen together with any substitutions onto the core and secondary structures.



6.3. The three other generics covered derivatives of naphthoylpyrroles, naphthylmethyleneindenes (using a similar approach to the indazole generics) and cyclohexylphenols (using a different wording).

## 7. Options for extending control

7.1. Simply increasing the number of generic controls to cover the broad range of psychoactive cannabinoid structures which are being identified using a similar approach to the existing controls would require an extremely long list of additional paragraphs. It is therefore proposed to adopt a different approach, based on defined modifications of a 'model' compound, 1-pentyl-3-(1-naphthoyl)indole ('JWH-018'). This approach would exclude control on cyclohexylphenols, so the existing generic for these materials would need to be retained.

## 8. Recommendation

8.1. The ACMD recommends the following definition to be used in addition to the existing cannabinoid generic definitions (and would then specifically exclude compounds already within the scope of the existing generic definitions):

"Any compound (not being a compound for the time being specified in subparagraph (c) above) structurally related to 1-pentyl-3-(1-naphthoyl)indole (JWH-018), in that the four sub-structures, that is to say the indole ring, the pentyl substituent, the methanone linking group and the naphthyl ring, are linked together in a similar manner, whether or not any of the sub-structures have been modified, and whether or not substituted in any of the linked sub-structures with one or more univalent substituents and where the modifications of the sub-structures are limited to any the following, that is to say:

- (i) replacement of the indole ring with indane, indene, indazole, pyrrole, pyrazole, imidazole, benzimidazole, or pyrazolo(3,4-b)pyridine;
- (ii) replacement of the pentyl substituent with alkyl, alkenyl, benzyl, cycloalkylmethyl, cycloalkylethyl, (*N*-methylpiperidin-2-yl)methyl, 2-(4-morpholinyl)ethyl, or (tetrahydropyran-4-yl)methyl;
- (iii) replacement of the methanone linking group with an ethanone, carboxamide, carboxylate, methylene bridge or methine group;
- (iv) replacement of the 1-naphthyl ring with 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, cycloalkylethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, or piperazinyl."

## **9. Scope of the proposed generic**

- 9.1. The existing generic definitions are now well established and familiar to those who need to refer to the Misuse of Drugs Act and therefore the preferred option would be to add to the existing legislation rather than replace or modify it.
- 9.2. The scope includes sub-structures which have not yet been encountered in the 3<sup>rd</sup> generation synthetic cannabinoids but which have previously been reported in earlier synthetic cannabinoids or might reasonably be expected to occur in the future. (Structures are shown in Annex 1).
- 9.3. A market for uncontrolled synthetic cannabinoid receptor agonists has developed, so it is possible that further materials, with novel structures outside the proposed controls, may be developed and commercialised for the UK market, so there will remain a requirement to monitor developments in this field.
- 9.4. In anticipation of such developments, the ACMD favours development of an alternative approach of defining the control of novel synthetic cannabinoids by their common mechanism of action as activators of the CB<sub>1</sub> receptor in the brain, which can readily be measured by a simple biochemical test.<sup>5</sup>

## **10. Consultation by the ACMD**

- 10.1. The ACMD consulted with the Department for Business Innovation and Skills (BIS) and the Medicines and Healthcare products Regulatory Agency (MHRA) and found no legitimate medicinal, industrial or commercial use for cannabinoids which would be covered by this proposed generic definition.
- 10.2. Following the Home Office's consultation on scheduling,<sup>6</sup> the ACMD has consulted with industry to check for legitimate uses and active programmes in this area that may potentially be affected by this definition. The ACMD is grateful to the industrial colleagues for their extensive input.
- 10.3. In finalising the proposed generic, the ACMD has also consulted forensic chemists and has taken into account the feedback received.

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<sup>5</sup> <https://www.gov.uk/government/publications/new-psychoactive-substances-review-report-of-the-expert-panel>

<sup>6</sup>

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/329930/LetterSchedule11versen.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/329930/LetterSchedule11versen.pdf)

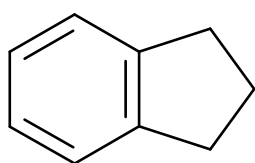
## Annex 1- Proposed Scope

The synthetic cannabinoids related to JWH-018 are generally composed of four sub-structures which can be described as a *core group* attached by a *linking group* to a *secondary structure* and with a *tail* substituent on the core group. These sub-structures may be further substituted with a wide range of univalent substituents including halo, alkyl, cyano etc.

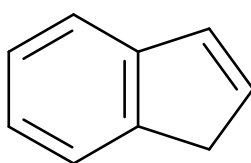
The range of sub-structures that should be included is detailed below.

### Core Structures

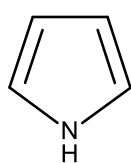
Figure 1- Core structures



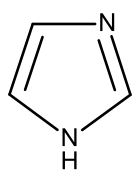
Indane



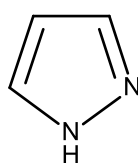
Indene



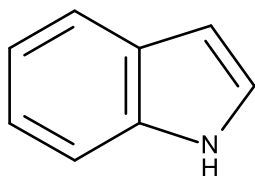
Pyrrole



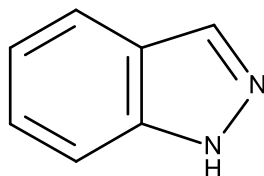
Imidazole



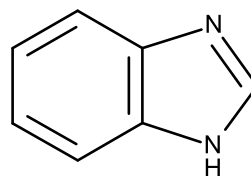
Pyrazole



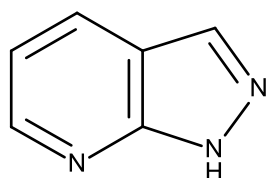
Indole



Indazole



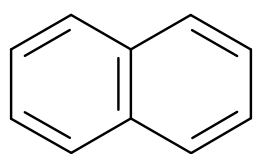
Benzimidazole



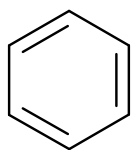
Pyrazolo(3,4-b)pyridine

## Secondary Structures

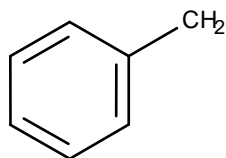
Figure 2- Secondary structures



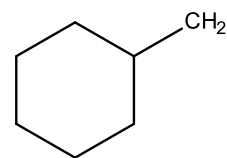
Naphthyl



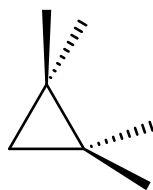
Phenyl



Benzyl

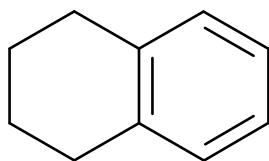


Cycloalkylmethyl

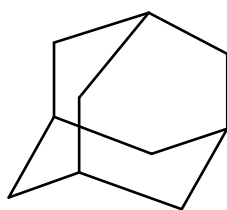


Cycloalkyl (e.g. tetramethylcyclopropyl)

Note: the tetramethyl groups would be covered by the phrase “*substituted in any of the linked sub-structures*”



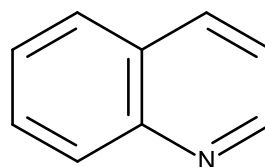
1,2,3,4-Tetrahydronaphthyl



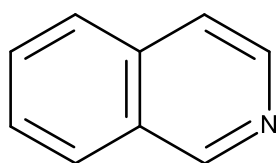
Adamantyl



Bicyclo[2.2.1]heptanyl



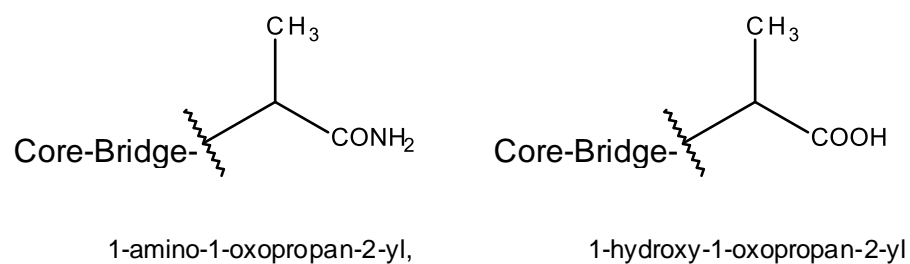
Quinolinylnyl



Isoquinolinyl

Recently encountered non-cyclic replacements for secondary structures:

**Figure 3- Non-cyclic replacements for secondary structures**



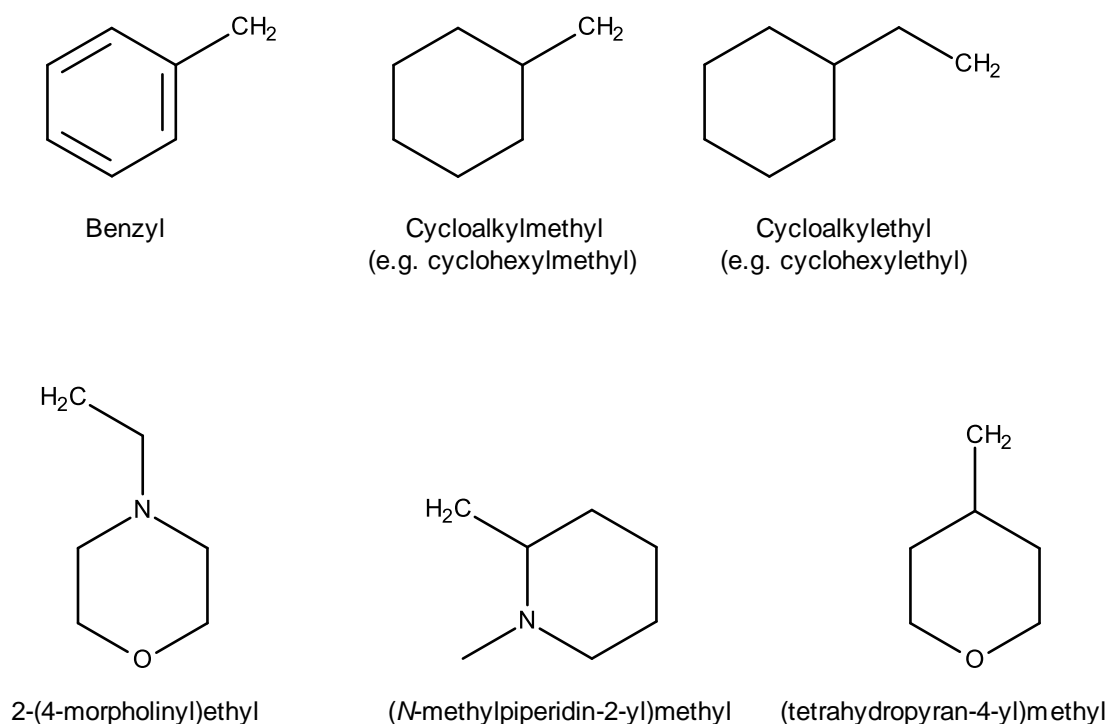
Compounds with this secondary structure include ADBICA, AB-FUBINACA and MMB-CHMINACA and would be included by virtue of the phrase “...whether or not substituted in any of the linked sub-structures with one or more univalent substituents...”.

### Tails

Alkyl – an acyclic saturated hydrocarbon radical (including straight and branched chain alkyl groups)

Alkenyl – a univalent acyclic hydrocarbon radical with one or more carbon-carbon double bonds.

**Figure 4- Tails**



## Linking Groups

Methanone (-CO-)    Ethanone (-COCH<sub>2</sub>-)

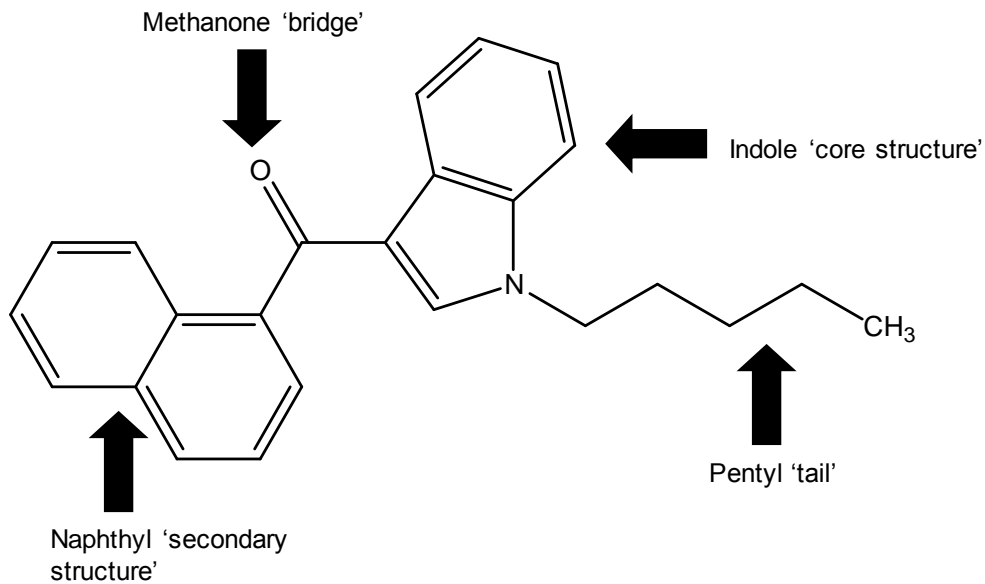
Carboxamide (-CONH-)    Carboxylate (-COO-)

Methylene bridge (-CH<sub>2</sub>-)

Methine (=CH-)

**Annex 2- Novel synthetic cannabinoid structures: rendering materials 'legal' by modifications which place them outside existing UK generic controls**

**Figure 5: JWH-018 as a model compound**



**Figure 6: Different core structures**

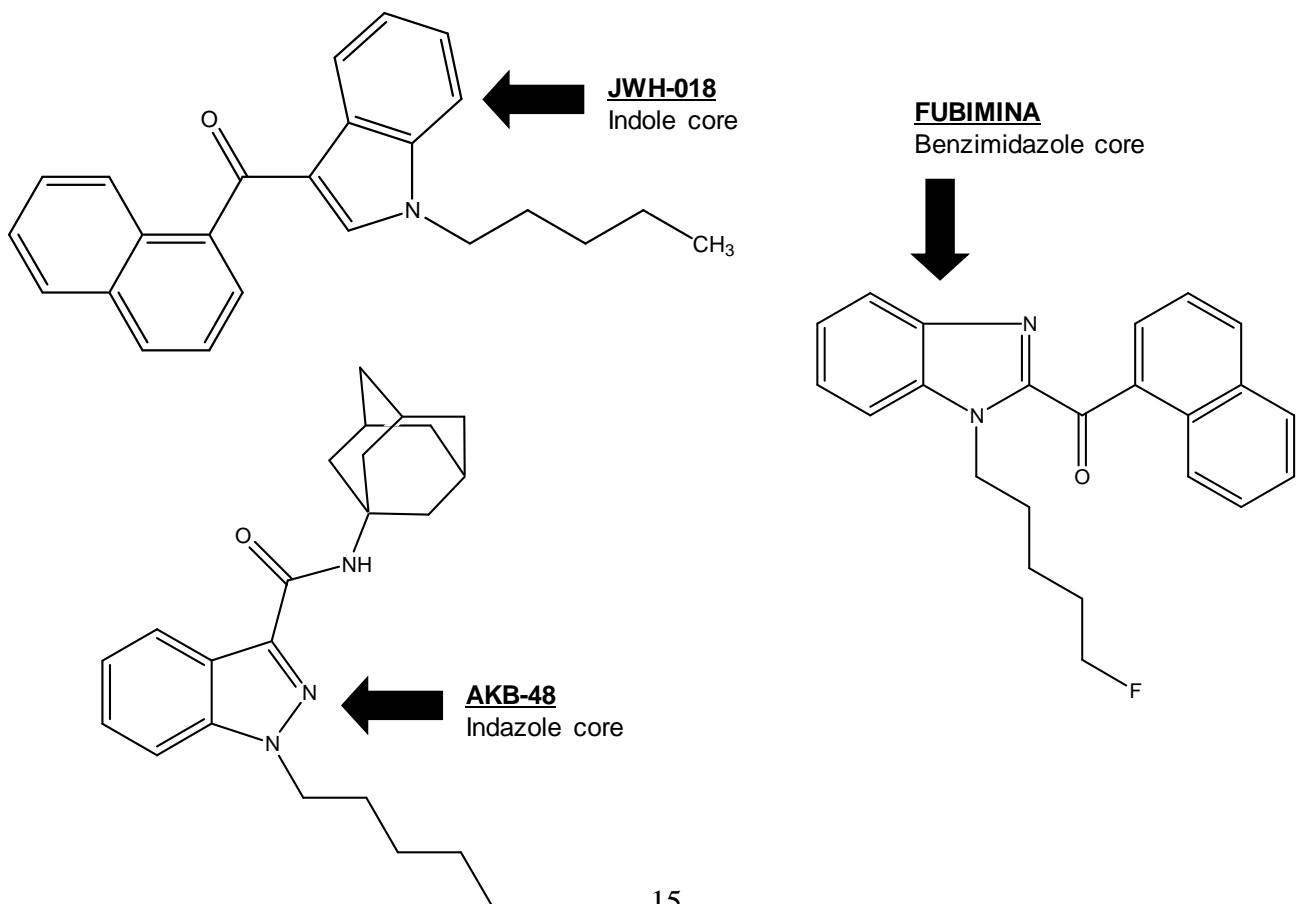
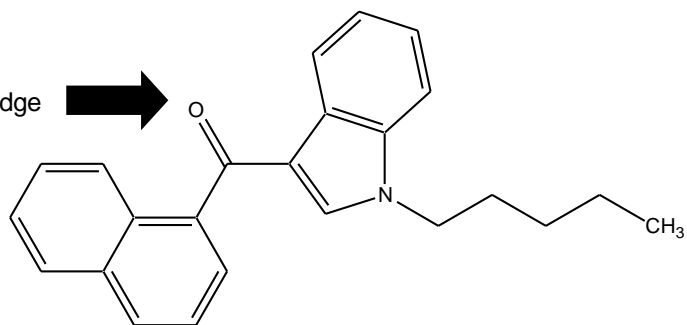
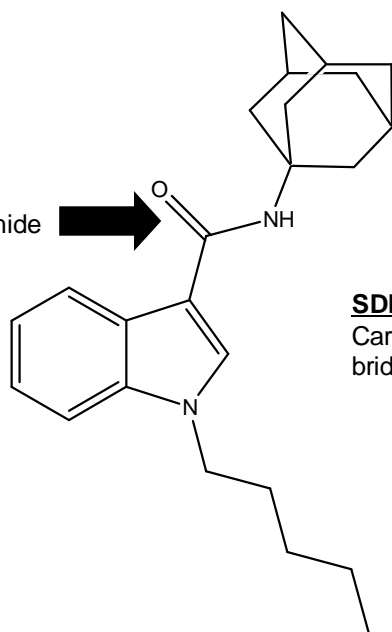


Figure 7: Different bridge structures

**JWH-018**  
Methanone bridge



**APICA**  
Carboxamide bridge



**SDB-005**  
Carboxylate bridge

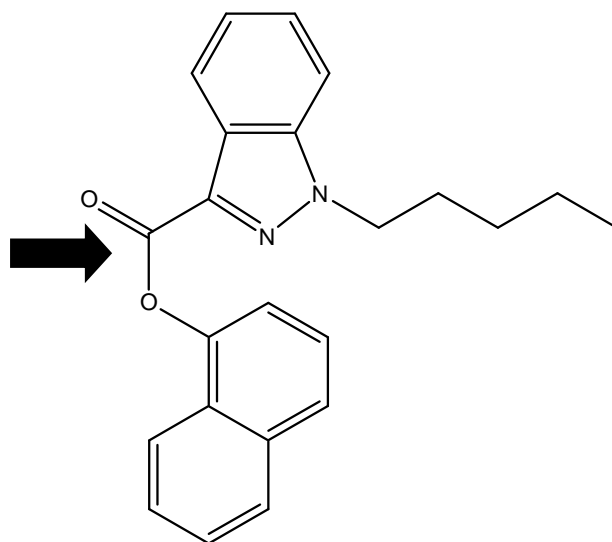




Figure 8: Novel secondary structures

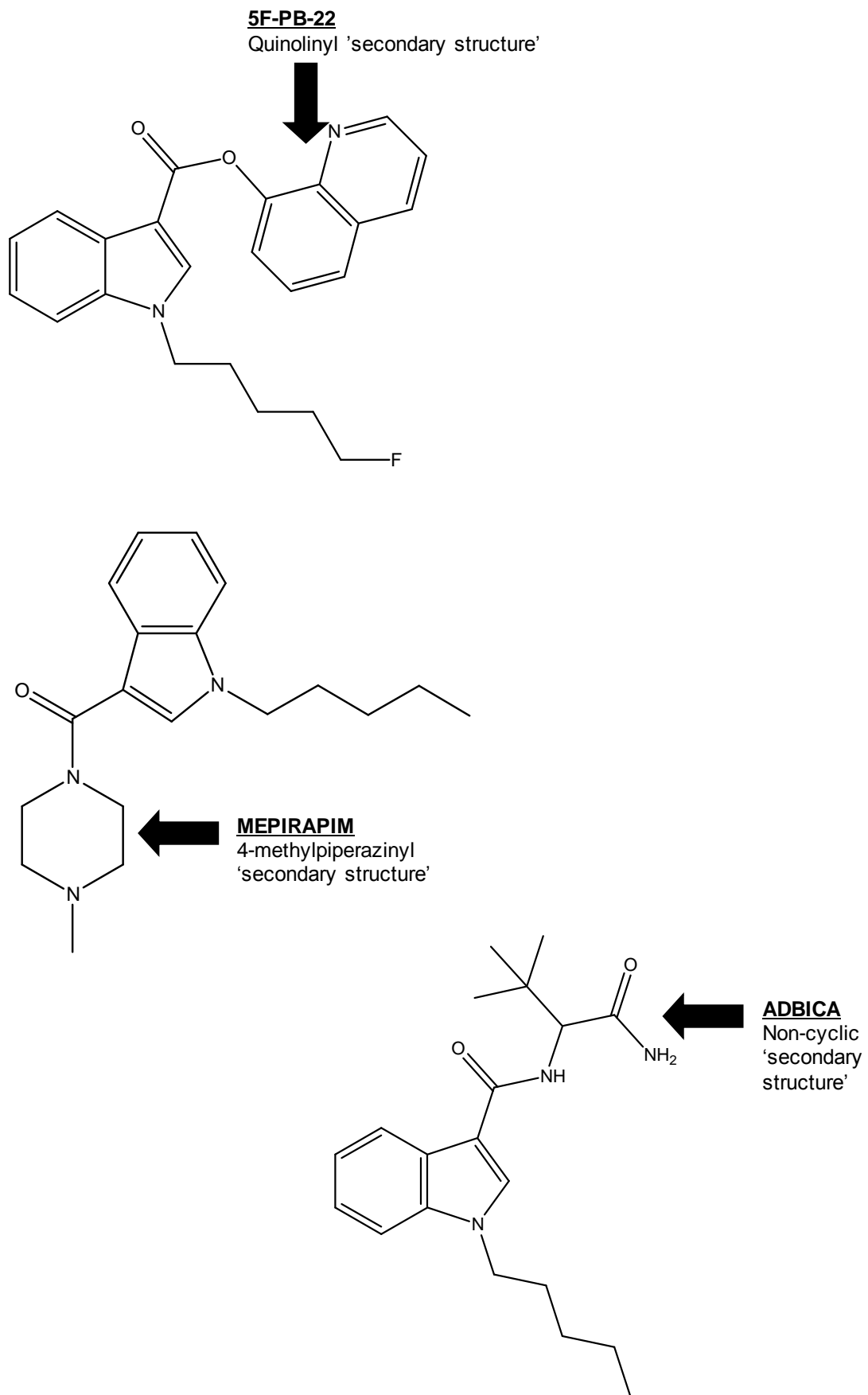


Figure 9: Combining several novel components

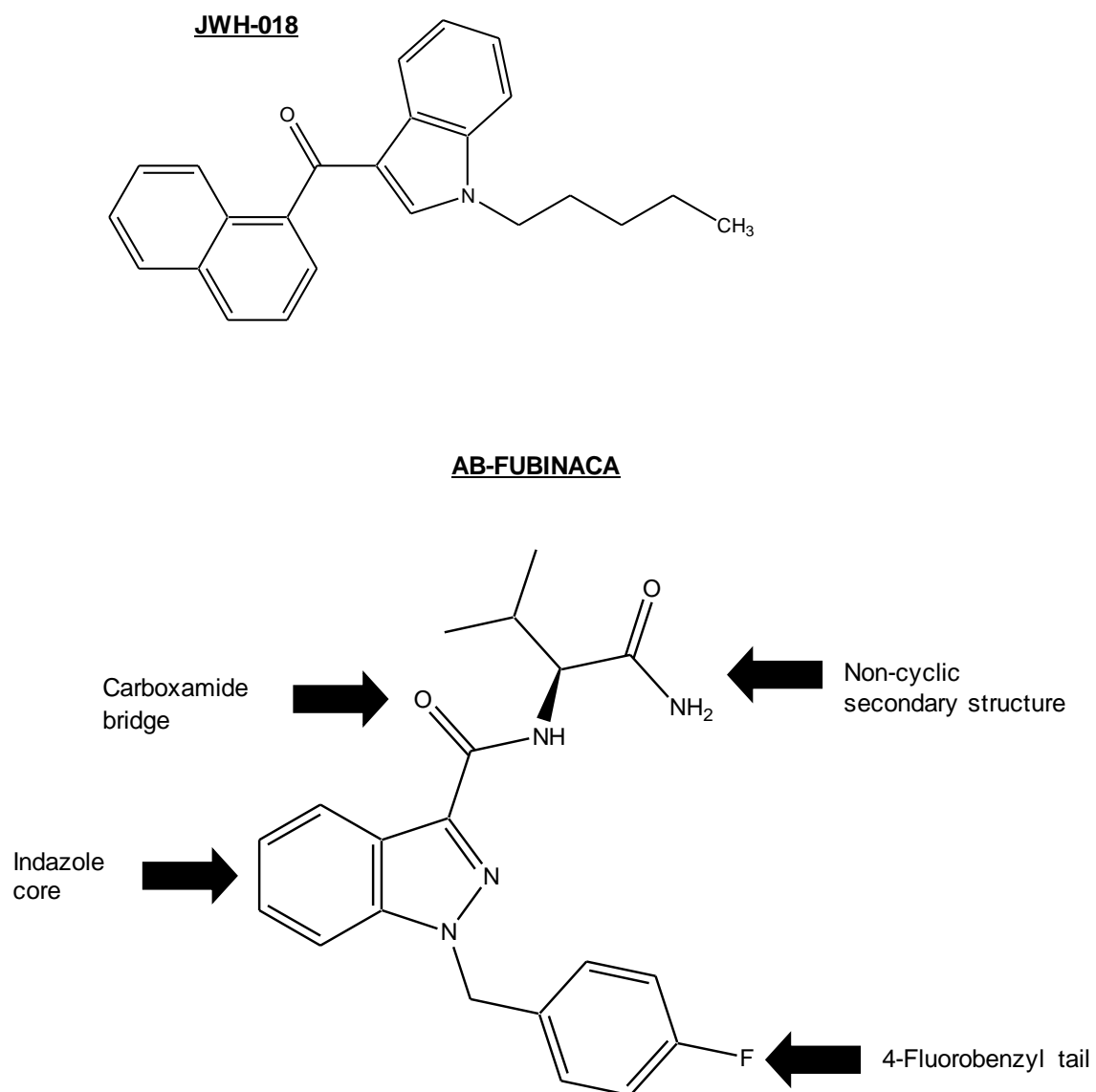
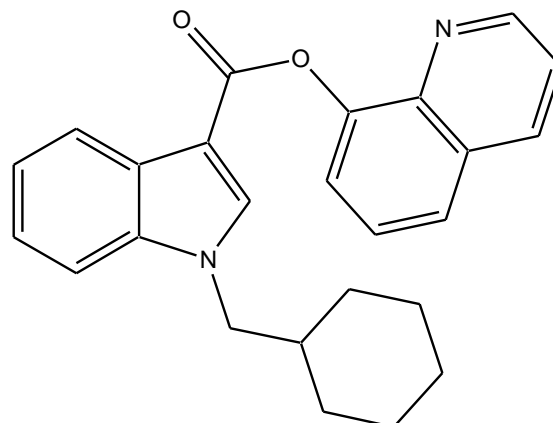
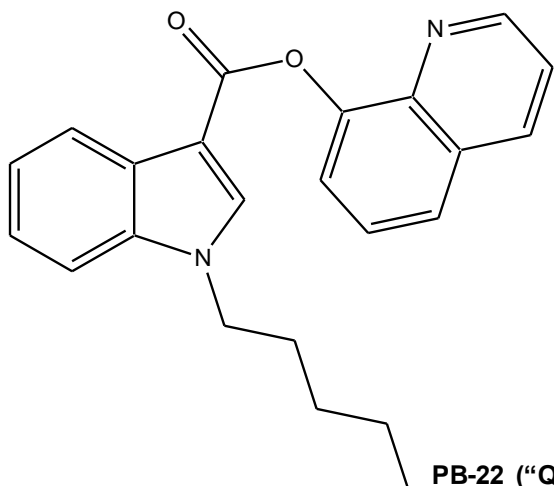
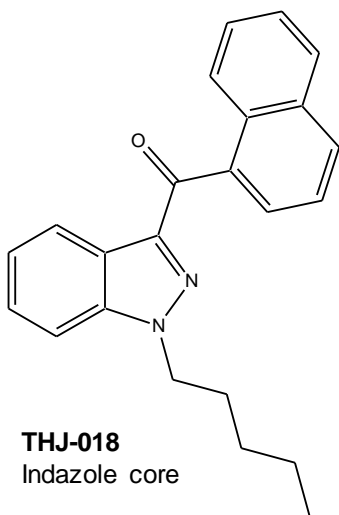


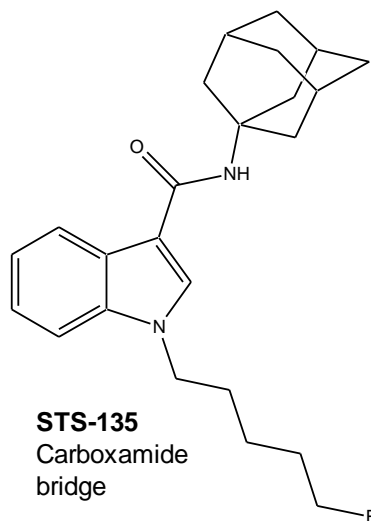
Figure 10: Some other currently available materials



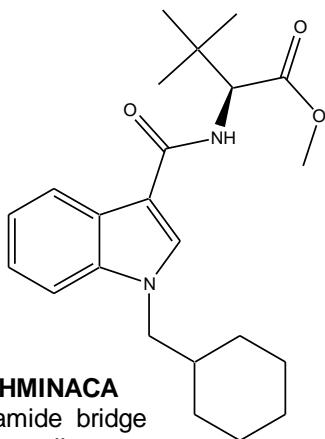
**PB-22 ("QUPIC") and BB-22 ("QUCHIC")**  
Indole carboxylates with a quinoline  
'secondary structure'



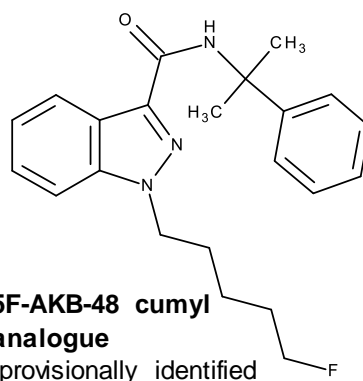
**THJ-018**  
Indazole core



**STS-135**  
Carboxamide  
bridge



**MMB-CHMINACA**  
Carboxamide bridge  
and non-cyclic  
'secondary structure'



**5F-AKB-48 cumyl  
analogue**  
(provisionally identified  
as an ingredient of C-  
Liquid)

### Annex 3- Interpretation of the proposed generic definition

The ACMD have consulted widely on the interpretation of the proposed generic definition and as far as possible, the feedback from this consultation has been taken into consideration to produce a workable generic definition. However, one of the main issues arising from the feedback was the need for guidance on the interpretation of the proposed generic definition. Whilst interpretation of the legislation is the responsibility of the courts after hearing evidence from experts, it is intended that the generic definition should be interpreted to include the examples included in the ACMD report and likely future iterations of these compounds. The following discussion may also help to clarify interpretation, particularly for the purposes of Home Office licensing enquiries.

#### 1) Interpreting “any of”

The term “any of” is often used in generic definitions within the Misuse of Drugs Act 1971 and is intended to mean “one or more”.

*“whether or not any of the sub-structures have been modified”* means that the sub-structures can all be the same as those in the model compound JWH-018, or one or more of the four sub-structures can be modified.

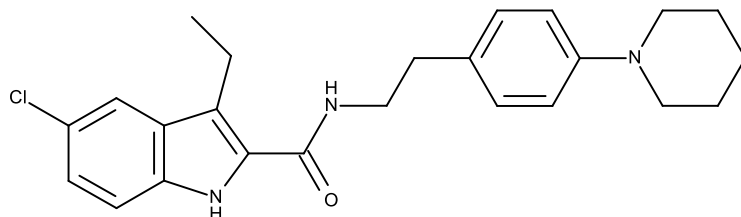
*“whether or not substituted in any of the linked sub-structures”* means that none or one or more of the four sub-structures, whether or not they have been modified, can have one or more substituents on them.

*“where the modifications of the sub-structures are limited to any of the following”* means one or more of the sub-paragraphs can be applied when modifying the sub-structures.

#### 2) Interpreting “substituted in any of the linked sub-structures with one or more univalent substituents”

This phrase extends the scope of substitution used in the 2013 Modification Order (SI 2013/239), which was limited to substitution in the core ring structure and substitution in a ring on the secondary structure, to substitution in any of the four sub-structures.

The inclusion of the phrase “*linked sub-structures*” means that sub-structures cannot be linked together via any of the substituents on the sub-structures. For example, the compound Org 27569, an allosteric modulator of the cannabinoid CB<sub>1</sub> receptor, would not be within scope because the phenylethyl secondary structure is not listed in sub-paragraph (iv) as an allowed replacement for the 1-naphthyl ring and although the phenyl group is an allowed secondary structure, the ethyl substituent is being used to link the phenyl sub-structure to the carboxamide linking group, which is not allowed (see figure 11). Substituents can only be attached to the linked sub-structures so substituents cannot therefore be used to link the sub-structures together.



**Figure 11: Org 27569**

The term “*substituted*” and the related terms “*substituent*” and “*substitution*” are often used in generic definitions within the Misuse of Drugs Act 1971. In the field of chemistry, the term substitution, as in a substitution reaction, literally means substituting one group with another group. However, in the Misuse of Drugs Act 1971, the position of substitution in a chemical structure is usually specified and implies substitution of a hydrogen atom with another atom or group of atoms. However, there are some instances in which the position is not specified but it is still implied that a hydrogen atom is being substituted rather than some other group being substituted.

For example, in the Misuse of Drugs Act 1971, sub-paragraph (ii) of the generic definition for pethidine compounds states:

*“by substitution in the piperidine ring with alkyl or alkenyl groups or with a propano bridge, whether or not further substituted”*. This sub-paragraph is only intended to apply to substitution of the hydrogen atoms on the ring carbon atoms. The piperidine ring already has substituents at the 1 and 4 positions but substitution of these substituents is not intended. In fact, replacement of these substituents is specifically dealt with in sub-paragraphs (i) and (iv).

Likewise, in the Misuse of Drugs Act 1971, sub-paragraph (ii) of the generic definition for fentanyl compounds states:

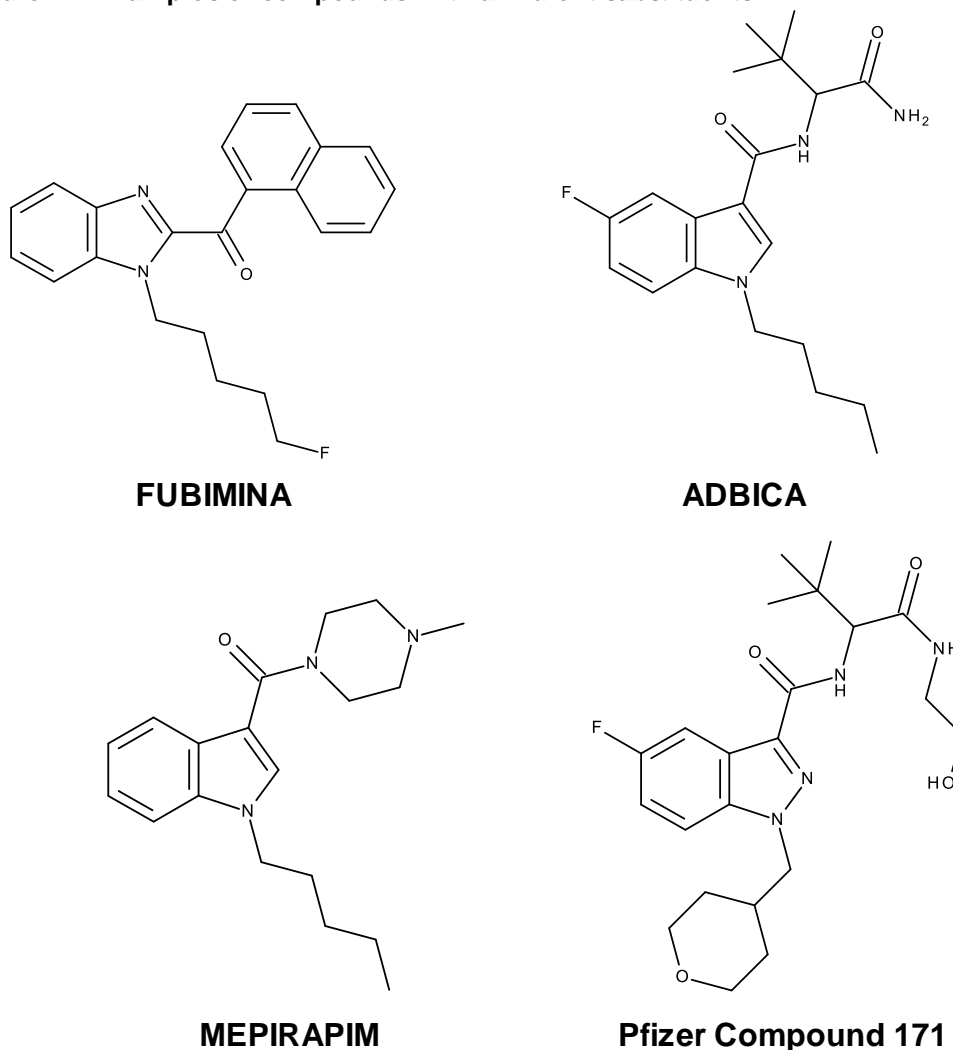
*“by substitution in the phenylethyl group with alkyl, alkenyl, alkoxy, hydroxy, halogeno, haloalkyl, amino or nitro groups”*. This sub-paragraph is only intended to apply to substitution of the hydrogen atoms on the phenyl ring or on the ethyl group. It is not intended to apply to substitution of the phenyl group. In fact, replacement of the phenyl group is specifically dealt with in sub-paragraph (i).

When interpreting the phrase “*substituted in any of the linked sub-structures*” it is therefore implied that this relates to replacement of a hydrogen atom with another atom or group of atoms.

*“Univalent substituents”* are substituents attached to the sub-structures by a single covalent bond. Examples of univalent substituents include but are not limited to, alkyl, alkoxy, thioalkyl, phenyl, benzyl, cyano, halide, and hydroxy.

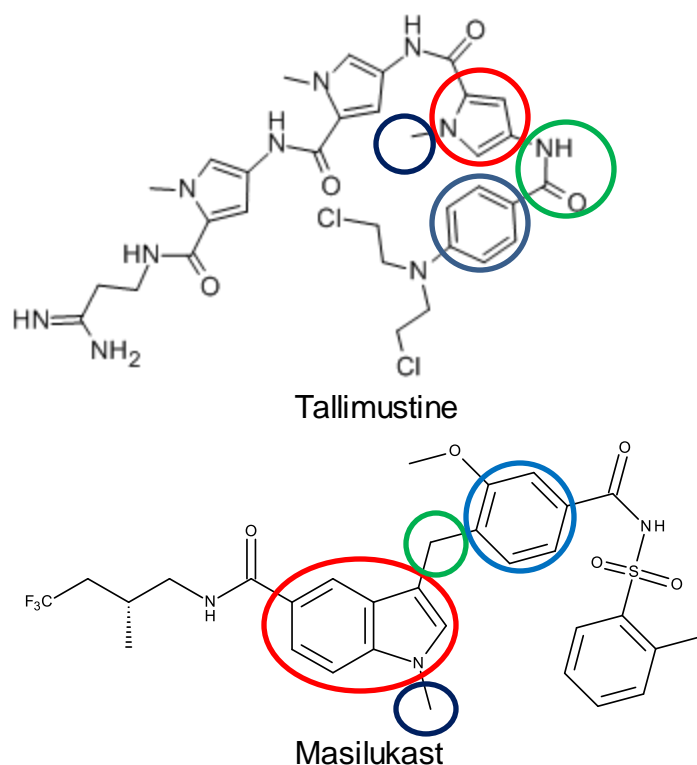
Examples of compounds with “*univalent substituents*” include the 5-fluoropentyl compounds such as FUBIMINA, compounds substituted with alkyl groups on the 3-carbon atom of 1-amino-1-oxopropan-2-yl secondary structure as in ADBICA, compounds substituted on the nitrogen atom in the 1-amino-1-oxopropan-2-yl secondary structure with a 2-hydroxyethyl group as in compound 171 of the Pfizer patent (WO2009106980), and compounds substituted on the piperazinyl secondary structure with an alkyl group as in MEPIRAPIM (*figure 12*).

**Figure 12: Examples of compounds with univalent substituents**



Apart from being univalent, there is no restriction on the type of substituents or extent of substitution. Consequently, some compounds of pharmaceutical interest such as tallimustine and masilukast fall within the scope of the proposed generic definition (*figure 13*). However, the substituents on these two compounds are on the core ring structure and the ring of the secondary structure and therefore their inclusion within the scope does not relate to the extended scope of substitution in the proposed generic definition.

Figure 13: Substituents on tallimustine and masilukast



Red –core ring structure

Dark blue – Tail sub-structure

Green – linking group

Light blue – Secondary Structure

All the other groups are substituents on the sub-structures.

### 3) Interpreting “*linked together in a similar manner*”

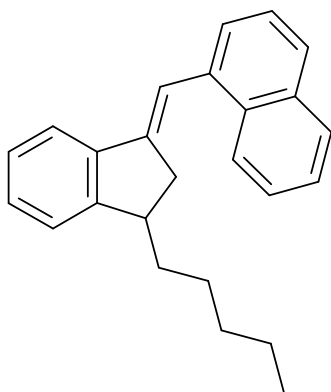
**Does the interpretation depend on comparison of the methods of synthesis?**

The generic definition defines compounds “*structurally related*” to 1-pentyl-3-(1-naphthoyl)indole (JWH-018), which implies that the methods of synthesis used to produce these compounds are not relevant when considering whether the “*sub-structures are linked together in a similar manner.*”

**Can sub-structures be linked together with different types of chemical bonds?**

Whilst the methods of synthesis are not relevant, the term “*structurally related*” does imply that the types of chemical bonds linking the sub-structures are important. The sub-structures of JWH-018 are all linked together by covalent bonds and therefore links formed by other types of chemical bonds would not be within the scope of the term “*linked together in a similar manner*”. The chemical definition of a covalent bond includes both single and double bonds, so the structure below (*figure 14, Structure A*) in which the core

indane sub-structure is linked to a naphthyl ring by means of a methine linking group, would be within the scope of the generic definition.

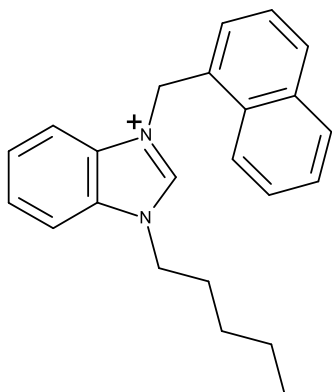


**Structure A**

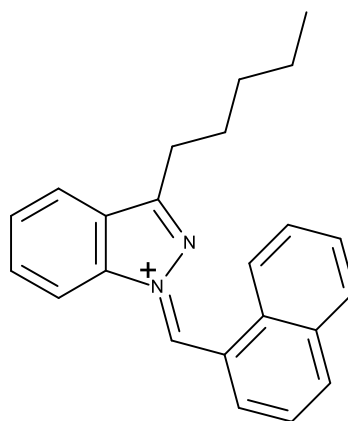
**Figure 14: Example of a structure which would be within scope of the generic definition**

Coordinate (dative covalent) bonds can be formed by attaching tail or linking sub-structures to an unsaturated nitrogen atom (e.g. a nitrogen atom without any hydrogen atoms attached) in a core ring structure. Such bonds lead to formation of quaternary compounds with a positively charged nitrogen atom, such as those in structures B and C below (*figure 15*). Sub-structures linked together by coordinate (dative covalent) bonds are not “*linked together in a similar manner*” to the sub-structures in JWH-018 and therefore quaternary compounds such as those represented by structures B and C would not be within the scope of the generic definition.

**Figure 15: Examples of structures which would not be within scope of the generic definition**



**Structure B**



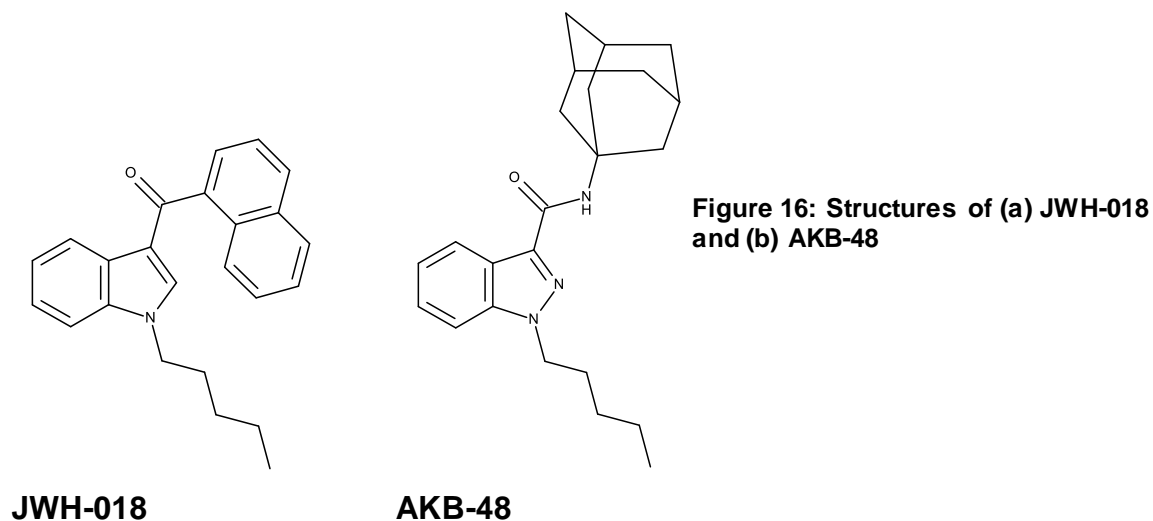
**Structure C**

### Examples of what “*linked together in a similar manner*” means

In 1-pentyl-3-(1-naphthoyl)indole (JWH-018) the pentyl tail and methanone linking group are both attached to the same ring, the 5-membered ring of the indole core, and are attached to non-adjacent positions on this ring. The pentyl tail is attached to the nitrogen atom of the indole ring.

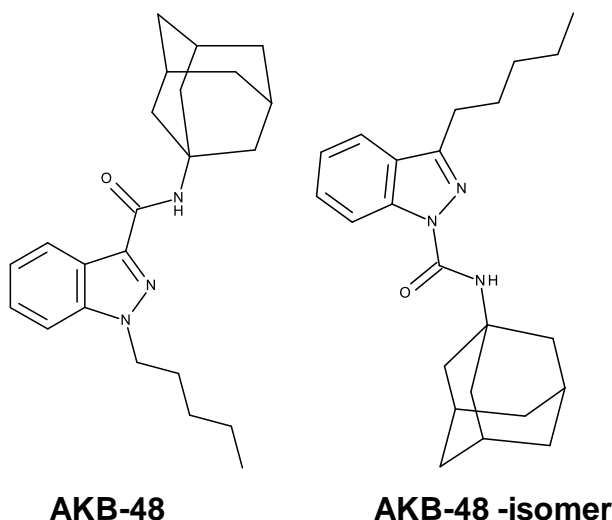


In the compound AKB-48 the indole ring has been replaced by an indazole core ring, the pentyl tail is also attached to a nitrogen atom and the linking carboxamide group is also attached to the same ring as the pentyl tail and is not adjacent to the pentyl tail. In this case the sub-structures could be regarded as linked together in the same way and therefore are clearly “*linked together in a similar manner*” as those in JWH-018, and therefore AKB-48 is within the scope of the generic definition (*figure 16*).



**Can the positions of the tails and linking structures on the ring be reversed?**

Indane and indene cores are included in the generic definition but these rings do not contain a nitrogen atom, so it is not a necessary requirement for the tail sub-structure to be attached to a nitrogen atom in order to fulfil the requirement that the sub-structures are “*linked together in a similar manner*”. The positions of the tail and linking group in AKB-48 could therefore be swapped and the sub-structures would still be “*linked together in a similar manner*”. The AKB-48 isomer shown below is therefore interpreted as being within the scope of the generic definition (*figure 17*).



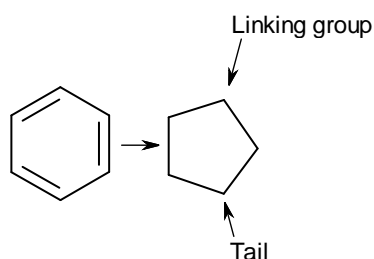
**Figure 17: Structures of (a) AKB-48 and (b) AKB-48 -isomer**

**Does the tail group have to be attached to a position on the 5-membered ring adjacent to a 6-membered ring?**

This raises the question of the importance of the six membered ring. The proposed generic definition and those of the earlier generic definitions, include 5-membered monocyclic rings, such as pyrrole and imidazole, as core ring structures so the presence of a 6-membered ring is not a necessary requirement. Therefore the tail group does not have to be adjacent to a 6-membered ring.

**Can the tail and the linking group be adjacent on a 5-membered ring fused to a 6-membered ring?**

There are only two possible arrangements for two substituents in a 5-membered homocyclic ring, either adjacent or non-adjacent (in which the two substituents are separated by one ring atom).



**Figure 18: (i) Non-adjacent positions**

In the non-adjacent case, a 6-membered ring can only be fused to the 5-membered ring at one location and therefore the tail group will always be adjacent to the 6-membered ring. Such an arrangement definitely has the sub-structures linked together in the same manner as those in the model compound JWH-018.

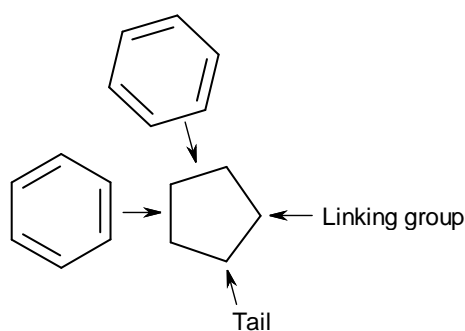
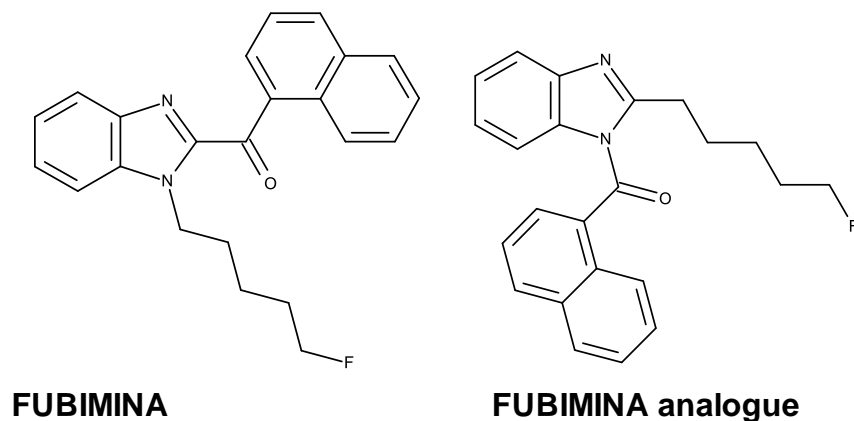


Figure 19 (ii) Adjacent positions

If the tail group and linking group are adjacent to each other in a 5-membered ring, then the groups are not linked together in exactly the same way as in the model compound JWH-018. However, since two adjacent groups is the only other arrangement possible, the sub-structures must be regarded as “*linked together in a similar manner*”.

In this arrangement, a 6-membered ring can be fused to the 5-membered ring at two possible locations. As the presence of a 6-membered core ring is not a necessary requirement of the generic (e.g. pyrrole, imidazole), either of these positional arrangements would be within scope and therefore the tail group on the 5-membered ring need not be adjacent to the 6-membered ring to fulfil the requirement of being “*linked together in a similar manner*”. In the compound FUBIMINA the tail group (i.e. the 5-fluoropentyl substituent) and the methanone linking group are attached to adjacent positions on the 5-membered ring of a benzimidazole ring. Based on the above arguments we can conclude that the sub-structures in this compound are “*linked together in a similar manner*” to those in the model compound JWH-018 and therefore FUBIMINA is within the scope of the generic definition.

As with AKB-48, if the positions of the tail group and linking groups are swapped, the resulting structure can also be interpreted as being within the scope of the generic definition.



FUBIMINA

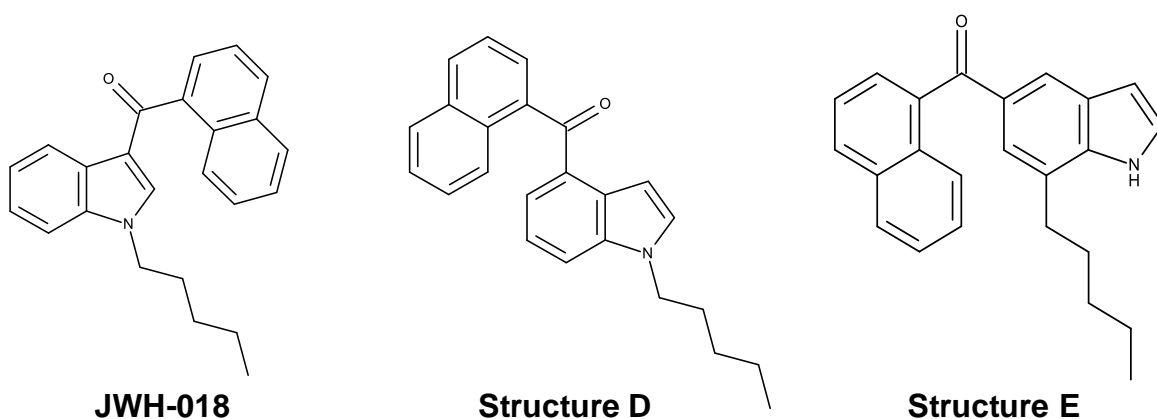
FUBIMINA analogue

Figure 20: Structures of (a) FUBIMINA and (b) FUBIMINA analogue

## Can the tail and/or the linking group be attached to the 6-membered ring?

As the 6-membered ring is not a necessary requirement (see above) then the tail group and the linking group must both be attached to the same ring (the 5-membered ring) in order for the sub-structures to be “*linked together in a similar manner*”. The structures D and E below, which are structural isomers (but not stereoisomers) of JWH-018, would therefore not be within the scope of the generic definition.

Figure 21: Structures D and E would not be in the scope of the generic definition



## At what position of the secondary structure can the linking group be attached?

The model compound JWH-018 contains a naphthyl group attached at its 1-position to a methanone linking group. The legislation in 2013 specifically included both the 1-naphthyl and 2-naphthyl isomers and therefore in sub-paragraph (iv) of the proposed generic definition it was necessary to include replacing the 1-naphthyl sub-structure with a 2-naphthyl sub-structure. However, no attachment positions are specified for the other possible secondary structures that can be attached to the linking group. All possible attachment points are therefore included within the scope of the generic definition e.g. adamantyl includes attachment at the 1- or 2-position of the adamantyl secondary structure (i.e. adamant-1-yl and adamant-2-yl).

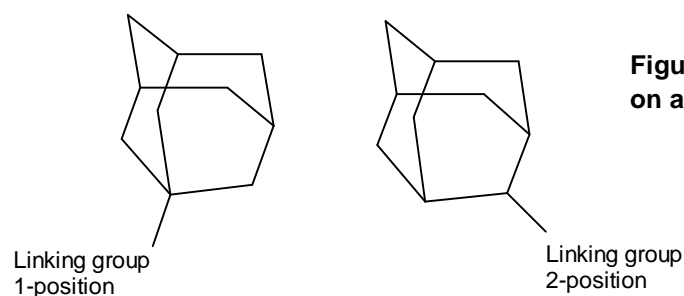
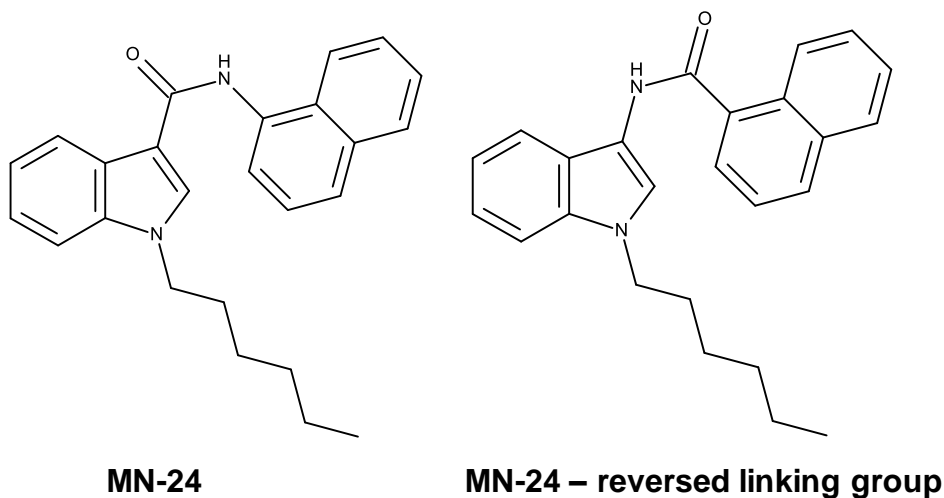


Figure 22: Linking groups at different positions on a secondary structure

## Can asymmetric linking groups be reversed?

Methanone and the methylene bridge linking groups are symmetrical, but the other linking groups are asymmetric and so can link the core ring to the secondary structure in two different ways. An example of a reversed carboxamide linking group is shown below (*figure 23*).

**Figure 23: Example of a reversed carboxamide linking group**



So far, each of the asymmetric linking groups has only been encountered in one orientation. However, if only one orientation was specified, future iterations of the synthetic cannabinoids are likely to include reversing the orientation of the linking group. The generic definition does not specify which orientation is required and therefore both orientations would be within the scope of the generic definition.