World Health Organization

Critical Review Report:

5F-AMB

Expert Committee on Drug Dependence

Forty-second Meeting

Geneva, 21-25 October 2019

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

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Executive Summary

5F-AMB (CAS: 1801552-03-3), methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl}amino)-3-methylbutanoate, is a synthetic cannabinoid with one chiral center and two enantiomers (S and R). Separation of the enantiomers revealed that the S-enantiomer is the active enantiomer and is the enantiomer found in products on the street. A synthesis method for 5F-AMB has been published. The compound is not readily converted into other controlled substances and has not been previously reviewed by the WHO Expert Committee on Drug Dependence.

The most likely route of administration for 5F-AMB in humans is inhalation via smoking the chemical after it has been sprayed on plant material or vaping it after formulation in liquid. Dosage required for pharmacological effects in humans is unknown. Investigation of the pharmacokinetics of 5F-AMB has been sparse. A single published study focused on delineation of its metabolism in incubated human hepatocytes. Metabolic stability of the compound was low, and metabolism was rapid and extensive. Seventeen metabolites were identified, including 13 of which involved hydrolysis of the ester group, oxidative defluorination, and hydroxylation. While the most abundant metabolite was the ester hydrolyzed metabolite, 5F-AMB carboxylic acid, this metabolite could not be used as a biomarker for 5F-AMB use, as it is also a metabolite of the closely related compound, 5F-AB-PINACA. The authors concluded that the best biomarker might be a phase II glucuronidated metabolite (F2). While distribution of 5F-AMB has not been investigated systematically, a case report describing analysis of tissue samples following autopsy of a person who died from exposure to a product containing AB-CHMINACA, 5F-AMB, and diphenidine noted that quantifiable detection of 5F-AMB occurred only in adipose tissue.

5F-AMB binds to hCB_1 and hCB_2 receptors, with K_i = 8.29 and 7.93 nM, respectively. Its major metabolite (5F-AMB carboxylic acid) also binds to both receptors (K_i = 267 and 197 nM, for CB_1 and CB_2 receptors, respectively), which may serve to prolongs cannabimimetic activity. Functional activity at both receptors was also indicated agonist in [^{35}S]GTPγS binding assays (EC_{50} = 1.3 and 0.272 nM for CB_1 and CB_2 receptors, respectively). In addition, 5F-AMB was a full agonist at both CB_1 and CB_2 receptors expressed in mouse AtT20-FlpIN neuroblastoma cells as measured by agonist-stimulated opening of G protein-gated inwardly rectifying potassium channels (GIRKs), with EC_{50} values of 1.9 and 10 nM, for CB_1 and CB_2 receptors, respectively.

In vivo, limited work has been conducted with 5F-AMB. 5F-AMB induced significant hypothermia, locomotor suppression, and bradycardia in rodents over a dose range of 0.1-3 mg/kg, i.p., with reversal of the hypothermic and locomotor effects upon pre-treatment with a CB_1 antagonist. When infused intracerebroventricularly or injected into the medial prefrontal cortex (mPFC), 5F-AMB impaired acquisition, but not retention, of novel object recognition memory. Consistent with its effects on memory, 5F-AMB shifted the balance of excitatory/inhibitory inputs towards inhibition in L5 neurons of the mPFC in an electrophysiology study. Preclinical evaluation of the toxicology of 5F-AMB has not been undertaken, although one study noted that an i.p. dose of 2.5 mg/kg induced convulsions in 2 of the 5 rats tested with it.

Although its dependence potential has not been evaluated, 5-AMB was tested in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle, where it fully substituted (ED_{50} = 0.19 mg/kg). Full substitution occurred over a period of 60-120 min and was accompanied by response rate suppression. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans. 5F-AMB has not been examined for its abuse potential in self-administration in animals nor has it been evaluated in humans.

5F-AMB is a synthetic cannabinoid that likely shares a profile of centrally mediated effects with other synthetic cannabinoids, including THC-like intoxication. Examination of the in vivo effects of this compound specifically is limited, and formal surveys of adverse reactions in humans consequent to acute administration of 5-AMB specifically are lacking, although at least three deaths have been reported to be associated with its use and its use has been associated with several automobile accidents that resulted in death. Specific information on the nature and magnitude of public health problems associated with 5F-AMB also is not available; however, it is a synthetic cannabinoid, a class of chemicals that have become a global issue with potential for serious public health problems. While the magnitude of these challenges is difficult to determine, issues that have been reported with synthetic cannabinoids include impaired driving, acute psychiatric distress, polysubstance abuse, and increased aggressiveness.

5F-AMB was first identified in samples originating from Japan in 2014. The magnitude of illicit manufacture and trafficking is unknown; however, similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific compounds. Synthesis of the compound occurs predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped. Direct marketing and purchase over the internet also are common.

Currently, 5F-AMB is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. It is controlled as a schedule I substance in the United States and is also under national control in Germany, Sweden, Singapore, Japan, and China.

1. Substance identification

A. *International Nonproprietary Name (INN)*

N/A

B. *Chemical Abstract Service (CAS) Registry Number*

1801552-03-3

C. *Other Chemical Names*

5-Fluoro-AMB
5F-AMP
5-Fluoro-AMP
5F-MMB-PINACA
5F-AMB-PINACA

D. *Trade Names*

N/A

E. *Street Names*

5F-AMB has been identified in products labelled Kali Berry 2, Herbal Incense: The Super Lemon,[1] Apollo,[2] Rainbow Special and Luminated Aroma.[3] It was also identified in Japan in a product labelled Soutou.[4] Other street names are probable, but unknown.

F. *Physical Appearance*

(For example: color, taste and smell)
Crystalline solid[5]

G. *WHO Review History*

5F-AMB has not been previously reviewed by the WHO.

2. Chemistry

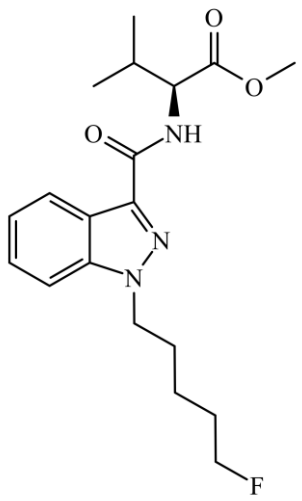
A. *Chemical Name*

IUPAC Name: Methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl}amino)-3-methylbutanoate

CA Index Name: N/A

B. Chemical Structure

Figure 1: Chemical structure of 5F-AMB



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

Molecular Weight: 363.4 g/mol

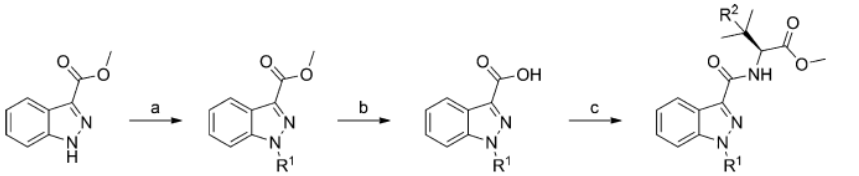
C. Stereoisomers

5F-AMB has one chiral center, with two enantiomers (*S* and *R*). Separation of the enantiomers has been achieved successfully.[6] The *S*-enantiomer is the active enantiomer and was detected in all tested herbal samples that were used to validate the separation method, while the *R*-enantiomer was absent from all samples. Further, the Pfizer patent for this series of compounds lists only the *S*-enantiomers.[7]

D. Methods and Ease of Illicit Manufacturing

A synthesis method has been published (5F-AMB is compound **12** in Scheme 2 presented below). Figure is copied directly from Banister et al.[8]

Scheme 2. Synthesis of Indazole SCs 12, 13, 16, 17, 20, 21, 24, and 25[a]



35

36: $R^1 = (CH_2)_5F$
37: R^1 = 4-F-Bn
38: $R^1 = CH_2Cy$
39: $R^1 = (CH_2)_4CH_3$

40: $R^1 = (CH_2)_5F$
41: R^1 = 4-F-Bn
42: $R^1 = CH_2Cy$
43: $R^1 = (CH_2)_4CH_3$

12: $R^1 = (CH_2)_5F$; $R^2 = H$
13: $R^1 = (CH_2)_5F$; $R^2 = CH_3$
16: R^1 = 4-F-Bn; $R^2 = H$
17: R^1 = 4-F-Bn; $R^2 = CH_3$
20: $R^1 = CH_2Cy$; $R^2 = H$
21: $R^1 = CH_2Cy$; $R^2 = CH_3$
24: $R^1 = (CH_2)_4CH_3$; $R^2 = H$
25: $R^1 = (CH_2)_4CH_3$; $R^2 = CH_3$

[a]Reagents and conditions: (a) *t*-BuOK, BrR^1, THF, 0 °C–rt, 48 h; 65–84%; (b) 1 M aq. NaOH, MeOH, reflux, 24 h, 76–91%; (c) methyl L-valinate or methyl L-*tert*-leucinate, EDC·HCl, HOBt, DIPEA, DMSO, rt, 24 h, 60–77%.

E. Chemical Properties

Melting point No data

Boiling point No data

Solubility Soluble in ethanol, DMSO, and dimethyl formamide (~ 25 mg/ml)[5]

F. Identification and Analysis

UV-Visible spectrum: λmax at 209 and 301 nm[5]
Various methods have been used to identify and/or analyze 5F-AMB. These methods have included gas chromatography-mass spectrometry (GC-MS),[3, 5] liquid chromatography–high-resolution mass spectrometry (LC-HR-MS),[6] nuclear magnetic resonance spectroscopy,[6] time-of-flight high-resolution mass spectrometry,[9] LC-MS/MS,[2, 10] ^{1}H and ^{13}C nuclear magnetic resonance (NMR),[11] high-resolution tandem mass-spectrometry (HR-MS/MS),[11] and Raman spectroscopy.[11]

3. Ease of Convertibility Into Controlled Substances

Ease of its convertibility into a controlled, but non-cannabinoid substance, is unlikely.

4. General Pharmacology

A. Routes of administration and dosage

The primary route of administration for 5F-AMB is presumed to be the same as for other synthetic cannabinoids: inhalation via smoking or vaping. Inhalation of smoke from chemical sprayed on herbal material is the most common route of administration for synthetic cannabinoids.[12] Dosage required for pharmacological effects in humans is unknown. A preliminary study in mice suggests that 5F-AMB has in vivo pharmacological activity up 60 min after exposure to smoke from a product containing the compound.[4]

B. Pharmacokinetics

Investigation of the pharmacokinetics of 5F-AMB has been sparse. A single published study focused on delineation of its metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes.[9] This study examined metabolism of 5F-AMB in incubated human hepatocytes. Metabolic stability of the compound was low, and metabolism was rapid and extensive. Seventeen metabolites were identified, including 13 of which involved hydrolysis of the ester group, oxidative defluorination, and hydroxylation. While the most abundant metabolite was the ester hydrolyzed metabolite, 5F-AMB carboxylic acid, this metabolite could not be used as a biomarker for 5F-AMB use, as it is also a metabolite of the closely related compound, 5F-AB-PINACA. The authors concluded that the best biomarker might be a phase II glucuronidated metabolite (F2).[9]
While distribution of 5F-AMB has not been investigated systematically, a case report describing analysis of tissue samples following autopsy of a person who died from

exposure to a product containing AB-CHMINACA, 5F-AMB, and diphenidine noted that quantifiable detection of 5F-AMB occurred only in adipose tissue.[1]

C. Pharmacodynamics

Similar to other synthetic cannabinoids that have appeared on the market, 5F-AMB binds to hCB_1 and hCB_2 receptors with nanomolar affinity (K_i = 8.29 and 7.93 nM, respectively), as does its major metabolite (5F-AMB carboxylic acid; K_i = 267 and 197 nM, for CB_1 and CB_2 receptors, respectively).[13] Further, 5F-AMB activates both cannabinoid receptors as a full agonist in [^{35}S]GTPγS binding assays (EC_{50} = 1.3 and 0.272 nM for CB_1 and CB_2 receptors, respectively).[13] While its major metabolite 5F-AMB carboxylic acid also activates both receptors, it does so at reduced potency (EC_{50} = 66.9 and 89.9 nM for CB_1 and CB_2 receptors, respectively). Yet, the efficacy of 5F-AMB carboxylic acid for CB_1 receptors in this assay is still high (E_{max} = 95.6),[13] suggesting that the metabolite might extend duration of cannabimimetic effects produced by use of a product containing 5F-AMB. In addition, 5F-AMB activated both CB_1 and CB_2 receptors expressed in mouse AtT20-FlpIN neuroblastoma cells in a fluorometric imaging plate reader (FLIPR) assay. At both receptors, 5F-AMB exhibited full agonism and potency was substantially greater than THC as measured by agonist-stimulated opening of G protein-gated inwardly rectifying potassium channels (GIRKs), with EC_{50} values of 1.9 and 10 nM, for CB_1 and CB_2 receptors, respectively.[8]

In vivo, limited work has been conducted with 5F-AMB. As discussed in greater detail in section 8A of this report, 5F-AMB substitutes for THC in drug discrimination in rats.[14] It also induces significant hypothermia and bradycardia in rats over a dose range of 0.1-3 mg/kg, i.p., with reversal of the hypothermic effect after rimonabant (CB_1 antagonist), but not SR144528 (CB_2 antagonist), administration.[8] Pre-treatment with a CB_1 antagonist (AM251) also attenuated locomotor suppression produced by 0.3 mg/kg, i.p., 5F-AMB in male C57BL/6J mice, suggesting that this effect was CB1 receptor mediated.[15] When infused intracerebroventricularly (i.c.v.), 5F-AMB elicited an anxiolytic response in an open field test and impaired acquisition, but not retention, of novel object recognition memory.[15] The latter effect, but not the former, was also observed when 5F-AMB was injected into the medial prefrontal cortex (mPFC). In a related study, electrophysiology was used to demonstrate that 5F-AMB shifted the balance of excitatory/inhibitory inputs towards inhibition in L5 neurons of the mPFC,[16] an effect that is consistent with the effects of the compound on memory acquisition.

5. Toxicology

While preclinical evaluation of the acute and chronic toxicology of 5F-AMB has not been conducted, one study noted that convulsions were produced by a 2.5 mg/kg (i.p.) dose of the compound in 2 of 5 rats.[14]

6. Adverse Reactions in Humans

Case reports of 5F-AMB effects in humans are few. Three deaths have been reported with analytical verification of 5F-AMB in the consumed product and/or in tissue or serum samples from the decedent; however, other psychotropic substances (including other

synthetic cannabinoids) were detected in two of these cases,[1, 10] with an additional medical complication (diabetic ketoacidosis in insulin-dependent diabetic) listed as the cause of death for one of the two deaths.[10] In the third death, 5F-AMB was the only substance detected in an apparently healthy 34-year-old male.[2] In the single available report of analytically confirmed intoxication with 5F-AMB alone, clinical symptoms were consistent with previous reports with other synthetic cannabinoids and included bloodshot eyes, cognitive impairment, slowed movement and verbal slur, anxiety, and incoordination.[3]

Formal surveys of adverse reactions in humans consequent to acute administration of 5F-AMB do not exist; however, the chemical and pharmacological data that are available from the single case report with 5F-AMB and from studies with other cannabinoids suggest that it would produce adverse reactions that are similar to those reported for other synthetic cannabinoids.[17] In humans, the acute psychological effects of synthetic cannabinoids may resemble those reported during acute intoxication with cannabis, ranging from a relaxed and unfocused euphoria to feelings of distress (e.g., confusion, anxiety, and fear). Time perception may be distorted, and in susceptible individuals, hallucinations, paranoia, and more serious psychiatric disorder may occur. Physical effects may include bloodshot eyes (as is characteristic of THC), tachycardia, somnolence, mydriasis, nausea, vomiting, seizures, and impaired motor performance. Because synthetic cannabinoids are usually more potent (and also may be more efficacious) than phytocannabinoids, their effects occur at lower doses, and overdose may be more common, as suggested by increased reports of deaths and serious adverse reactions compared to cannabis.[18-22] Since users usually are unaware of which synthetic cannabinoid is contained in a product, they may administer a chemical with greater potency than the chemical contained in previous products. Further, the chemical may not be evenly distributed throughout the plant material, creating "hot spots" containing higher concentrations of synthetic cannabinoid. For these reasons, dose (in THC equivalents) often exceeds intended dose. Contaminants (e.g., pesticides, heavy metals, rodent feces) may also be present and may contribute to adverse reactions.

Reports on the pharmacological effects of 5F-AMB in humans after chronic use are not available.

7. Dependence Potential

A. Animal Studies

5F-AMB has not been assessed for dependence potential in animals.

B. Human Studies

5F-AMB has not been assessed for dependence potential in humans.

8. Abuse Potential

A. Animal Studies

The abuse potential of 5F-AMB has been assessed in drug discrimination in one study. Results showed that 5F-AMB fully substituted in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle (ED_{50} = 0.19 mg/kg).[14] Unlike for THC, substitution by 5F-AMB was accompanied by significant response rate suppression at the dose (1 mg/kg) that produced maximal substitution. Full substitution occurred over a period of 60-120 min after intraperitoneal injection and was rimonabant reversible, suggesting CB_1 receptor mediation. Suppressed responding accompanied substitution in most rats at 5-15 min after injection. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans.[23]

B. Human Studies

5F-AMB has not been assessed for abuse potential in humans.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

N/A

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing Authorizations (as a Medicinal Product)

N/A

12. Industrial Use

N/A

13. Non-Medical Use, Abuse and Dependence

The prevalence of non-medical use of 5F-AMB has not been determined specifically, primarily because the chemicals contained in packages of synthetic cannabinoids are not labeled. Hence, users may not even know which synthetic cannabinoids they are using. Prevalence estimates for specific synthetic cannabinoids rely upon analysis of seized materials and bodily fluids of persons who appear in hospital or morgue following administration, both of which undoubtedly underestimate actual use. In a report covering the period from January 2016 to December 2017, synthetic cannabinoids represented the largest group of substances monitored by the European Union (EU) Early Warning System.[12] Non-medical use and abuse of synthetic cannabinoids has also been reported outside of the EU, including in the United States, Australia, New Zealand, and Asia.[24-28]

In a report that covered identifications from 2015-2018 (provided by the UNODC to the ECDD Secretariat), 5F-AMB was detected in 3 regions and 33 countries. Numbers of detections decreased over the time period, with 23 detections in 2015 and 3 detections in 2018. A similar pattern was observed in the U.S. DEA Emerging Threat reports. While 79 identifications of 5F-AMB occurred in 2016, 6 and 11 identifications were reported in 2017 and 2018, respectively. The mid-year 2019 report did not list any identifications for 5F-AMB.

The prevalence of chronic use and dependence of synthetic cannabinoids has not been reported.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Although specific information on the nature and magnitude of public health problems associated with 5F-AMB is not available, misuse and abuse of synthetic cannabinoids is a global issue with potential for serious public health problems.[22, 28, 29] The magnitude of these challenges is difficult to determine; however, newer compounds (i.e., "second and third generation" synthetic cannabinoids) may have increased potential for harm.[30] Issues that have been reported include impaired driving,[31, 32] acute psychiatric distress,[33, 34] and polysubstance abuse with several synthetic cannabinoids and/or synthetic cannabinoids and other substances (e.g., alcohol).[35, 36] Increased aggressiveness has also been reported with some of the newer compounds,[37] but a definitive causal link is lacking. This increase could conceivably could be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons and the homeless,[17, 38, 39] the former of whom might already be prone to be more aggressive. From 2012-2014, 5F-AMB was identified as a causal factor in 21 motor vehicle accidents in Japan, some of which involved deaths of individuals other than the driver.[31] Notably, drivers frequently reported anterograde amnesia for events occurring while they were intoxicated. In addition, severe drug-induced muscle rigidity that prevented braking or steering may have contributed to some accidents.[31]

15. Licit Production, Consumption and International Trade

N/A

16. Illicit Manufacture and Traffic and Related Information

5F-AMB was first identified in samples sold on the internet to users in Japan in 2014.[40] The magnitude of illicit manufacture and trafficking is unknown; however, similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific

compounds. Detection of 5F-AMB has been reported in Europe, Asia, and the United States.[40, 41]

Synthesis of 5F-AMB (and many other synthetic cannabinoids) is believed to occur predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.[12] This hypothesis is supported by the observation that shipments confiscated by law enforcement organizations frequently originate from China. Direct marketing and purchase over the internet also are common.

More recent email correspondence (August 13, 2019) from the International Narcotic Control Board Secretariat, United Nations Office on Drugs and Crime (UNODC), to the ECDD Secretariat stated that survey of the IONICS platform revealed 28 contact incidents with 5F-AMB to date. The United Kingdom reported 12 incidents (9 in 2016, 2 in 2017 and 1 in 2018); 8 incidents were reported from Latvia in 2014; 6 incidents were reported from the United States (5 in 2015 and 1 in 2018); and 2 incidents were reported from Greece (1 incident in 2014 and 1 incident in 2015). Of these 28 incidents, origin of the substance was traced from Asia: Hong Kong SAR of China (n=7), China (n=5), and the Republic of Korea (South Korea; n=1). The origin was unknown in the 15 other incidents.

See Annex 1 for additional information on illicit manufacture and traffic in WHO Member States.

17. Current International Controls and Their Impact

5F-AMB is not currently under international control.

18. Current and Past National Controls

In the United States, 5F-AMB is a Schedule I controlled substance.

5F-AMB is an Anlage II controlled substance in Germany as of May 2015.

Sweden's public health agency suggested classifying 5F-AMB as hazardous substance on November 10, 2014.

5F-AMB is controlled by the Fifth Schedule of the Misuse of Drugs Act (MDA) in Singapore as of May 2015.

5F-AMB was also scheduled in Japan on July 25, 2014.

As of October 2015, 5F-AMB is a controlled substance in China.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances