5F-ADB

Critical Review Report

Agenda Item 4.2

Expert Committee on Drug Dependence

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Contents

Acknowledgements

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Summary

5F-ADB is a synthetic cannabinoid receptor agonist (SCRA) with an aminoalkylindazole structure used as an active ingredient of products sold as cannabis substitutes. 5F-ADB has no known therapeutic or medical use. In different regions it is being used and abused for non-medical purposes. Furthermore, some countries have put 5F-ADB under national control.

When smoked, 5F-ADB produces cannabimimetic effects like Δ9-tetrahydrocannabinol (THC). Doses needed to produce these effects are lower than for THC Many of the risks linked to cannabis use are also present in the case of 5F-ADB, among them complications in patients suffering from cardiovascular diseases and triggering of acute psychosis.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

1715016-75-3 (racemate)
1838134-16-9 (R-enantiomer)

C. Other Chemical Names

5F-MDMB-PINACA
N-[[1-(5-fluoropentyl)-1H-indazole-3-yl]carbonyl]-3-methyl-D-valine, methylester
MDMB(N)-2201

D. Trade Names

None

E. Street Names

Spice, K2, legal weed, synthetic cannabis, herbal incense are common terms for SCRAs containing products.

5F-ADB has been detected in the following brands: Jamaican Gold Extreme [1], Heart Shot Red [2], Heart Shot Black [3], Cherry Bomb formula 6A and Volume 2 formula 6A [4], GM sapphire, AP 31, and AL 37. [5]

Mixtures sold under specific brand names do not always contain the same substance or mixture of substances over time.

F. Physical Appearance

White crystalline solid (in pure form).

G. WHO Review History

5F-ADB has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 5F-ADB is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

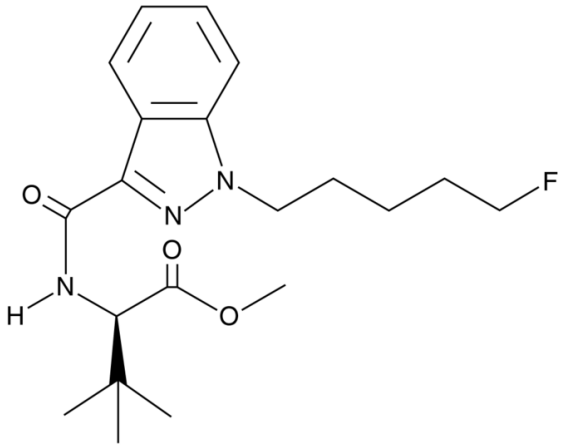
2. Chemistry

A. Chemical Name

IUPAC Name: methyl-S-2-[1-(5-fluoropentyl)-1H-indazole-3-carboxamido]-3,3-dimethylbutanoate
CA Index Name: n/a

B. Chemical Structure

Free base:



Molecular Formula: $C_{20}H_{28}FN_3O_3$
Molecular Weight: 377.46 g/mol

C. Stereoisomers

5F-ADB contains a chiral center at the C-2 carbon of the oxobutan-2-yl sidechain, so that two enantiomers exist: R-5F-ADB and S-5F-ADB.

Based on the literature regarding other indazole containing SCRAs it can be expected that 5F-ADB also has a positional isomer, in which the 5-fluoropentyl tail is attached to the nitrogen at position 2 of the indazole.

D. Methods and Ease of Illicit Manufacturing

The synthesis of 5F-ADB has been described in detail by Banister et al. [6]
The synthesis started with methyl-1H-indazole-3-carboxylate. This compound was regioselectively alkylated with the suitable bromoalkane (bromo-5-fluoropentane) to give the 1-(5-fluoropentyl)-1H-indazole-3-carboxylate methyl ester. Saponification of the ester afforded the corresponding acid, which was coupled to methyl tert-L-leucinate to furnish 5F-ADB.

E. Chemical Properties

Melting point: not available.

Boiling point: not available
Solubility: 5F-ADB is soluble in organic solvents such as ethanol, dimethyl sulfoxide and dimethyl formamide. The solubility of 5F-ADB in these solvents is approximately 25 mg/ml. 5F-ADB is sparingly soluble in aqueous buffers. [7]

F. Identification and Analysis

Quantification of 5F-ADB in products can be carried out according to the general procedure described by United Nations Office on Drugs and Crime (UNODC). [8]

The analytical profile of 5F-ADB has been described in various papers. Utilized methods include gas chromatography–mass spectrometry (GC-MS)[1, 4, 9, 10] , liquid chromatography–tandem mass spectrometry (LC-MS/MS) [10], Fourier-transform infrared spectroscopy (FTIR)[6, 9] and nuclear magnetic resonance spectroscopy (NMR)[6, 10] .

Detection of 5F-ADB in biological matrices was described in postmortem blood [3] and tissue.[5] In urine samples, the main metabolites are the analytical targets. [3, 4, 11]

3. Ease of Convertibility Into Controlled Substances

5F-ADB is not readily converted into other internationally controlled substances.

4. General Pharmacology

5F-ADB is a synthetic cannabinoid receptor agonist (SCRA). It has an indazole core, which is a common structural feature in a number of the SCRAs monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the UNODC.

A. Routes of administration and dosage

5F-ADB is mainly offered on the Internet either in the form of 'herbal mixtures', where the chemical has been sprayed on plant material, as a powder, or in a liquid to be used in e-cigarette devices. Based on user reports and on the dosage forms offered, the primary route of administration is inhalation either by smoking the 'herbal mixture' as a joint or utilizing a vaporizer, or vaping through an e-cigarette.

The effects of 5F-ADB are felt on doses as small as 50 micrograms on cigarettes or buds.[12] Users reported strong cannabimimetic effects after smoking the drug.

B. Pharmacokinetics

Kusano et al. [3] present a case of an acute and fatal intoxication with 5F-ADB and diphenidine. Using LC/Q-TOFMS they could detect 3 metabolites of 5F-ADB in postmortem urine. First ester hydrolysis (M1) takes place, followed by oxidative defluorination (M2) and further oxidation to the carboxylic acid (M3). Although oxidative defluorination as a first step could not be excluded, no such substance could be detected in this case.

C. Pharmacodynamics

Banister et al. [6] synthesized a number of indole and indazole SCRAs featuring either a l-valinate or l-tert-leucinate pendant group and an alkylgroup attached to the indole or indazole core. All synthesized SCRAs were tested in in a fluorometric imaging plate reader assay for CB1 and CB2 activity. For the CB1 receptor 5F-ADB has an EC_{50} of 0.59 nM compared to 171 nM for THC. The EC_{50} for the CB2 receptor is 7.5 nM for 5F-ADB. So, 5F-ADB is more selective for the CB1 than for the CB2 receptor (12,7x). And 5F-ADB has shown to be more potent than THC in this assay (almost 290x).

A number of the symptoms caused by acute inhalation of SCRAs, such as agitation, seizure, muscle rigidity, high body temperature and tachycardia, resemble those of the serotonin syndrome, which is caused by excessive serotonin release. Therefore Asaoka et al. [13] investigated the effect of 5F-ADB on midbrain dopaminergic and serotonergic neurons. Using ex vivo electrophysiological techniques they looked at changes in the spontaneous firing activity of dopaminergic and serotonergic neurons.

In a concentration of 1 μM 5F-ADB significantly increased the spontaneous firing rate of dopaminergic neurons. When the CB1 antagonist AM251 was present 5F-ADB failed to affect the dopaminergic neurons. The same concentration of 5F-ADB did not affect the activity of serotonergic neurons.

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of 5F-ADB.

6. Adverse Reactions in Humans

The acute effects of THC (and consequently cannabis) include: relaxation, euphoria, lethargy, depersonalisation, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, conjunctival injection ("red eyes"), tachycardia, and nausea and vomiting. Similar effects to cannabis have been reported for SCRAs such as 5F-ADB. Compared to cannabis, severe and fatal poisoning appears to be more common with SCRAs. [14] Poisoning may include rapid loss of consciousness/coma, cardiovascular effects (such as hypertension, tachycardia, bradycardia, chest pain, myocardial infarction, and stroke), seizures and convulsions, vomiting/hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour. Sudden death has also been reported.

Acute intoxications

A series of 5 non-fatal intoxications in Spain in which 5F-ADB was involved has been reported by Barceló et al. [4] Patients were 4 males and 1 female aged 14 till 21 years. All had clinical manifestations common for use of SCRAs. Using UHPLC–MS/MS phase I metabolites of 5F-ADB have been detected in urine samples of all patients. In the urine of the 14 year old girl also phase I metabolites of MMB-2201 were detected.

All patients were discharged without any complication.

Deaths

In several publications from Japan referral is made to about ten people that have died from smoking a SCRA later identified as 5F-ADB. Unfortunately, no data has been published regarding these cases.

Hasegawa et al. [5] presented an autopsy case in which 5F-ADB was involved. The deceased was a 34 year old male who was found dead in his room. The direct cause of the death was asphyxia due to aspiration of stomach contents. The levels of 5F-ADB in solid tissues were 1.17–7.95 ng/g. With the highest levels found in adipose tissue and heart muscle.

Kusano et al. [3] presented a fatal intoxication involving 5F-ADB and diphenidine.
The victim was a 53 year old male and found at home. Postmortem blood concentrations are 0.19±0.04 ng/mL for 5F-ADB and 12±2.6 ng/mL for diphenidine.

Urine levels of SCRAs in unchanged forms are usually much lower than their blood and tissue levels. Therefore Minakata et al. [11] developed a new sensitive LC-MSMS method for the identification and quantitation of parent forms of six SCRAs in urine samples of human cadavers. Using this method, they could detect urine levels of MAB-CHMINACA and 5F-ADB of 229 and 19 pg/mL, respectively in one victim.

7. Dependence Potential

A. Animal Studies

No data available.

B. Human Studies

No data available.

8. Abuse Potential

A. Animal Studies

No data available.

B. Human Studies

No data available.

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

5F-ADB has not been used in therapy.

10. Listing on the WHO Model List of Essential Medicines

5F-ADB is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

5F-ADB has never been marketed as a medicinal product.

12. Industrial Use

5F-ADB has no industrial use

13. Non-Medical Use, Abuse and Dependence

Similar to other SCRAs, 5F-ADB is sold and used as a 'legal' substitute for cannabis.[15] The most common way of using it is by smoking a joint or vaping through an e-cigarette. Because these products rarely state the ingredients, most users will be unaware that they are using 5F-ADB.

People who use 5F-ADB may include recreational users, high-risk drug users, and groups who experiment with the substance (such as psychonauts). Furthermore, individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) may use 5F-ADB because routine drug tests/screens will be unable to detect SCRAs.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

In Japan in the period from 2012 to 2014, 214 cases of motor vehicle collisions were attributed to the use of illegal drugs. 30 In 93 out of 96 investigated cases, one or more SCRAs were found. The following observations were made on the appearance of the drivers just after the collision:

- impaired consciousness 73 cases;
- excited states such as agitation, shouting, confusion, and continuous stereotyped behaviors 16 cases.

In 24 cases blood samples and in 17 cases urine samples were available.

- 5F-ADB was involved in 23 cases and detected in urine in 2 cases.
- All cases involving 5F-ADB were recorded in the second half of 2014.

While there are limited data for 5F-ADB, the social risks might share similarities with other SCRAs.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

Not applicable.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

5F-ADB is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Placed under temporary control in USA. [16]

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

No data.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of 5F-ADB

Please refer to separate Annex 1 document published on ECDD website