



Critical Review Report: CUMYL-4CN-BINACA

**Expert Committee on Drug Dependence
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Executive Summary

Substance identification: CUMYL-4CN-BINACA (CAS: 1631074-54-8) is a synthetic cannabinoid that was first documented in international patent WO 2014/167530-A1 issued to Matthew Bowden and James Williamson on October 16, 2014.

WHO Review History: The WHO has not previously reviewed CUMYL-4CN-BINACA.

Chemistry: CUMYL-4CN-BINACA is 1-(4-cyanobutyl)-N-(1-methyl-1-phenylethyl)-1H-indazole-3-carboxamide. It does not have any stereoisomers.

Ease of convertibility into controlled substances: CUMYL-4CN-BINACA is not readily converted into other controlled substances.

Similarity to known substances / Effects on the central nervous system: CUMYL-4CN-BINACA 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.

General pharmacology: The most likely route of administration for CUMYL-4CN-BINACA 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. Little is known about its absorption, distribution, elimination or time course. Pharmacokinetic investigation has focused on metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Based upon results of experiments in human liver cells and analysis of urine and blood samples from verified users, CUMYL-4CN-BINACA undergoes extensive biotransformation catalyzed by cytochrome P450 enzymes prior to elimination of metabolites in the urine. A primary metabolic pathway for CUMYL-4CN-BINACA is hypothesized to be decyanation via hydroxylation at the carbon adjacent to the cyano group, a reaction that releases free cyanide. Subsequently, further oxidation or reduction produces the major metabolites, CUMYL-BINACA butanoic acid (most abundant metabolite in urine) and 4-hydroxyl-CUMYL-BINACA, respectively. A third major metabolite, 4-cyano-4-hydroxybutyl-CUMYL BINACA, was also identified in vitro and in vivo in human liver cells and urine, respectively. Biotransformation resulting from other chemical reactions produced only minor metabolites.

Scientific data on the specific pharmacodynamics of CUMYL-4CN-BINACA are sparse. CUMYL-4CN-BINACA is a full agonist at both CB₁ and CB₂ receptors, with 6.3-fold lower potency at CB₂ receptors. At CB₁ receptors, its binding affinity is in between that of Δ^9 -tetrahydrocannabinol (THC) and the prototypic aminoalkylindole cannabinoid WIN55,212-2. CUMYL-4CN-BINACA has not been assessed for activity at non-cannabinoid receptors. Published data on the in vivo pharmacology of CUMYL-4CN-BINACA are not available. Unpublished data have shown that it produced hypothermia in male ICR mice that peaked between 30 and 120 minutes.

41st ECDD (2018): CUMYL-4CN-BINACA

Toxicology: Preclinical evaluation of the acute or chronic toxicological effects of CUMYL-4CN-BINACA has not been conducted.

Adverse reactions in humans: Formal surveys of adverse reactions in humans consequent to acute administration of CUMYL-4CN-BINACA specifically are lacking. In 2016, 5 confirmed cases of acute intoxication with CUMYL-4CN-BINACA were reported. In the same year, CUMYL-4CN-BINACA was listed as a cause or contributor to 11 deaths.

Dependence potential: The dependence potential of CUMYL-4CN-BINACA has not been evaluated in humans or in animals.

Abuse potential: The abuse potential of CUMYL-4CN-BINACA has not been evaluated in humans. Unpublished preclinical data show dose-dependent substitution of aerosolized CUMYL-4CN-BINACA for delta⁹-tetrahydrocannabinol (THC) in female mice trained to discriminate 5.6 mg/kg THC (i.p.) from vehicle.

Therapeutic applications / usefulness: None

Listing on WHO Model List of Essential Medicines: Not listed as an essential medicine.

Marketing authorizations: None

Industrial use: None

Non-medical use: The prevalence of non-medical use of CUMYL-4CN-BINACA specifically has not been determined; however, synthetic cannabinoids (as a class) is the largest group of substances monitored by the European Union Early Warning System. Non-medical use has also been reported outside of the European Union, including in the United States, Australia, New Zealand, and Asia.

Nature and magnitude of public health problems: Specific information on the nature and magnitude of public health problems associated with CUMYL-4CN-BINACA 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, and increased aggressiveness.

Licit production, consumption, and international trade: None

Illicit manufacture and traffic: CUMYL-4CN-BINACA has been detected in 11 Member States of the European Union and in the U.S. Underreporting is likely due to lack of routine screening for the compound. Synthesis of the compound occurs predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped. In 2016, CUMYL-4CN-BINACA was among the top five synthetic cannabinoids seized in powder form.

Current international controls and their impact: CUMYL-4CN-BINACA has not been subject to international control under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

Current and past national controls: Regulatory authorities in the European Union and the United States issued statements of intent to subject CUMYL-4CN-BINACA to control measures in May 2018. In the U.S., CUMYL-4CN-BINACA will be classified as a Schedule I controlled substance. In Canada, CUMYL-4CN-BINACA is classified as a Schedule II controlled substance.

1. Substance identification

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

1631074-54-8

C. Other Chemical Names

SGT-78; 4-CN-CUMYL-BINACA; CUMYL-CB-PINACA; CUMYL-CYBINACA; 4-CYANO
CUMYL-BUTINACA

D. Trade Names

N/A.

E. Street Names

Specific street names for CUMYL-4CN-BINACA are not available. However, there are dozens of street names for synthetic cannabinoids (which may contain one or more unidentified synthetic cannabinoids). These names include K2, K2XXX, barely legal, iBlaze, spice, cloud 10, herbal incense, fake weed, kush, and zombie, among others.

F. Physical Appearance

crystalline solid (in pure form)^{1,2}
off-white powder (in seized samples)³

G. WHO Review History

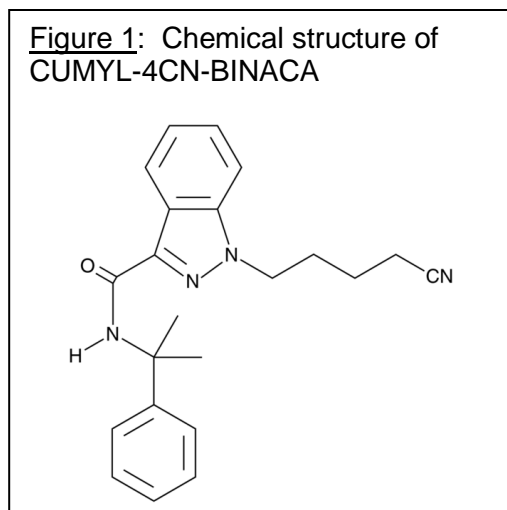
WHO has not previously reviewed CUMYL-4CN-BINACA.

2. Chemistry

A. Chemical Name

IUPAC Name: 1-(4-cyanobutyl)-N-(1-methyl-1-phenylethyl)-1H-indazole-3-
carboxamide

CA Index Name: n/a

B. Chemical Structure**Molecular Formula:** C₂₂H₂₄N₄O**Molecular Weight:** 360.452 g/mol**C. Stereoisomers**

CUMYL-4CN-BINACA does not have stereoisomers but has one positional isomer with the same chemical structure. The formal name for this isomer is 2-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-2H-indazole-3-carboxamide, but it is also known as 4-cyano CUMYL-BUTINACA isomer 2 (<https://www.caymanchem.com/product/20748>). In this isomer, the CN-butyl group is attached at the 2-position of the indazole instead of at the 4-position, as in CUMYL-4CN-BINACA.

D. Methods and Ease of Illicit Manufacturing

Specific synthesis methods for CUMYL-4CN-BINACA were not provided in the original patent filed for the compound (identified as SGT-78).⁴ Based upon risk assessment conducted on behalf of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), one general method of synthesis is initiated through conversion of the key precursor, 1-(4-cyanobutyl)-1H-indazole-3-carboxylic acid, to an acid chloride followed by reaction with 2-phenylpropan-2-amine (cumylamine). Alternatively, the key precursor can be coupled with cumylamine directly. The key precursor, 1-(4-cyanobutyl)-1H-indazole-3-carboxylic acid, may be synthesized from several chemicals (e.g., methyl 1H-indazole-3-carboxylate or 1H-indazole-3-carboxylic acid) using standard techniques that have been used previously for cannabinoids with similar indazole structures.⁵

Manufacture in illicit laboratories is straightforward and dependent primarily upon availability of suitable precursors. Impurities in the precursors could result in impurities in the resulting product and possible resultant toxicity. To date, illicit manufacture has not been prominent in the European Union or in the United States, but rather, is believed to occur primarily in China.⁶

E. Chemical Properties

Melting point: 89.9 °C⁷

Boiling point: No data.

Solubility: Soluble in CH₂CL₂ and MeOH (limits not specified); low solubility in H₂O.³

F. Identification and Analysis

UV-Visible spectrum: λ_{max} at 209 and 302 nm.²

Various methods have been used to identify and/or analyze CUMYL-4CN-BINACA. These methods have included gas chromatography–mass spectrometry (GC-MS), high performance liquid chromatography time-of-flight (HPLC-TOF), Fourier transform infrared spectroscopy attenuated total reflectance (FTIRATR), gas chromatography–mass spectrometry–infrared (GC-MS-IR) condensed phase, ion chromatography (IC), nuclear magnetic resonance spectroscopy (NMR).^{3,4,8}

3. Ease of Convertibility Into Controlled Substances

Ease of convertibility of CUMYL-4CN-BINACA into a controlled, but non-cannabinoid substance, is low. However, conversion of CUMYL-4CN-BINACA into another psychoactive synthetic cannabinoid with a core indazole structure is possible, especially given the large number of possible substituents that could be substituted for the 4CN group with retention of nM affinity for the CB₁ receptor.⁸

4. General Pharmacology

A. Routes of administration and dosage

Route of administration for CUMYL-4CN-BINACA has not been determined; however, it is presumed to be inhalation via smoking or vaping, as inhalation of smoke from chemical sprayed on herbal material is the most common route of administration for synthetic cannabinoids.¹ Seizures in which the chemical has been identified have been comprised of plant material, liquid, or powder.^{6,9} Dosage required for pharmacological effects in humans is unknown.

B. Pharmacokinetics

Investigation of the pharmacokinetics of CUMYL-4CN-BINACA has focused on delineation of its metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Based upon results of experiments in human liver cells and analysis of urine and blood samples from verified users, CUMYL-4CN-BINACA undergoes extensive biotransformation catalyzed by cytochrome P450 enzymes prior to elimination of metabolites in the urine.¹⁰⁻¹² Indeed, detectability of the parent compound in the urine is low.^{11,12} A primary metabolic pathway for CUMYL-4CN-BINACA is

hypothesized to be decyanation via hydroxylation at the carbon adjacent to the cyano group, a reaction that releases free cyanide.¹⁰ Subsequently, further oxidation or reduction produces the major metabolites, CUMYL-BINACA butanoic acid (most abundant metabolite in urine) and 4-hydroxyl-CUMYL-BINACA, respectively.^{10, 11} A third major metabolite, 4-cyano-4-hydroxybutyl-CUMYL BINACA, was also identified in vitro and in vivo in human liver cells and urine, respectively.¹⁰ Additional minor metabolites were produced from hydroxylation, dihydroxylation, glucuronidation, N-dealkylation, and dihydrodiol formation.¹⁰⁻¹² Specific information on other pharmacokinetic parameters (absorption, distribution, elimination, and time course) for CUMYL-4CN-BINACA was not available in the literature.

C. Pharmacodynamics

Scientific data on the specific pharmacodynamics of CUMYL-4CN-BINACA are sparse, available primarily from the United States Drug Enforcement Agency and contained in the annex of a risk assessment report from the European Monitoring Centre for Drugs and Drug Addiction.⁶ Based on these reports, CUMYL-4CN-BINACA is a CB₁ receptor agonist, with a binding affinity in between that of delta⁹-tetrahydrocannabinol (THC) and the prototypic aminoalkylindole cannabinoid WIN55,212-2 in hCB₁ receptors expressed in human embryonic kidney (HEK) cells. Functionally, it is a full agonist comparable in efficacy with CP55,940, but 5 times more potent, at activating the CB₁ receptor, as shown by inhibition of forskolin-stimulated production of cyclic adenosine monophosphate (cAMP). CUMYL-4CN-BINACA also acts as a full agonist of CB₂ receptors with 6.3-fold lower potency than at CB₁ receptors, as demonstrated by changes in membrane potential mediated by G protein-gated inwardly rectifying potassium channels (GIRKs). CUMYL-4CN-BINACA has not been assessed for activity at non-cannabinoid receptors.

Published data on the in vivo effects of CUMYL-4CN-BINACA are not available. Unpublished data have shown that 1 mg/kg (intraperitoneal, i.p.) CUMYL-4CN-BINACA produced hypothermia in male ICR mice (J.L. Wiley, RTI International, Research Triangle Park, NC). A minor decrease (-2.6 °C) in rectal temperature was observed 15 min after i.p. injection, with further decreases occurring between 30 and 120 min for a maximum of -7.9 °C. Although temperature started to increase after 120 min, complete recovery to pre-injection baseline temperature had still not occurred by 300 min after injection.

5. Toxicology

Preclinical evaluation of the acute or chronic toxicological effects of CUMYL-4CN-BINACA has not been conducted.

6. Adverse Reactions in Humans

Although there have not been any formal surveys of adverse reactions in humans consequent to acute administration of CUMYL-4CN-BINACA, the chemical and pharmacological data that are available suggest that it would produce adverse reactions that are similar to those reported for other synthetic cannabinoids.⁶ 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, 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 with this class of cannabinoids as compared to cannabis.¹³⁻¹⁷ 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.

In 2016, 5 confirmed cases of acute intoxication with CUMYL-4CN-BINACA were reported, with 4 in Hungary and 1 in Sweden.⁶ Deaths in which CUMYL-4CN-BINACA was listed as a cause or contributor to death numbered 11 in 2016, all of which were in the same two European Union Member States, with 3 in Hungary and 8 in Sweden.⁶

Reports on the pharmacological effects of CUMYL-4CN-BINACA in humans after chronic use are not available.

7. Dependence Potential

A. *Animal Studies*

No available data.

B. *Human Studies*

No available data.

8. Abuse Potential

A. *Animal Studies*

Published animal studies on the abuse potential of CUMYL-4CN-BINACA are not available; however, unpublished drug discrimination data from the lab of Dr. Jenny Wiley at RTI International (Research Triangle Park, NC USA) show that aerosolized CUMYL-4CN-BINACA substituted for THC in female C57/Bl6 mice (n=7) trained to discriminate 5.6 mg/kg THC (i.p.) from vehicle in a two nose poke drug discrimination procedure. Mice were exposed to CUMYL-4CN-BINACA via inhalation for 10 3-s exposures over 2 min in a commercially available system in which aerosolization is accomplished through use of modified electronic cigarette technology (LJARI, La Jolla, CA USA). Subsequently, they were placed into the operant drug discrimination chambers. Substitution was concentration-dependent, with 0.24 mg/ml producing 3% responding on the THC-

associated aperture and steady increases to a maximum of 81% THC-aperture responding at a concentration of 4.8 mg/ml (highest concentration tested). Response rates were similar across all concentrations and did not differ substantially from baseline rates following vehicle administration. While inability to calculate dosage and potency is a limitation of the system, these results demonstrate that CUMYL-4CN-BINACA produces THC-like discriminative stimulus effects at a dose that does not impair responding.

B. Human Studies

No available data.

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

No known medical use or therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines

N/A

11. Marketing Authorizations (as a Medicinal Product)

None

12. Industrial Use

None

13. Non-Medical Use, Abuse and Dependence

The prevalence of non-medical use of CUMYL-4CN-BINACA 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.¹⁷ 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.¹⁸⁻²²

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 CUMYL-4CN-BINACA is not available, misuse and abuse of synthetic cannabinoids is a global issue with potential for serious public health problems.^{17, 22, 23} The magnitude of these challenges is difficult to determine; however, newer compounds (i.e., “second generation” synthetic cannabinoids) may have increased

potential for harm.²⁴ Issues that have been reported include impaired driving^{25, 26} and acute psychiatric distress.^{27, 28} Increased aggressiveness has also been reported with some of the newer compounds,¹ but a definitive causal link is lacking. This increase could conceivably be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons and the homeless,^{6, 29, 30} the former of whom might already be prone to be more aggressive.

15. Licit Production, Consumption and International Trade

N/A

16. Illicit Manufacture and Traffic and Related Information

The first known seizure of CUMYL-4CN-BINACA occurred in October 2015 in Estonia, but it was brought to the attention of the EMCDDA by Hungary in 2016. Since then, CUMYL-4CN-BINACA has been detected in 11 Member States of the European Union (Estonia, Finland, France, Germany, Hungary, Lithuania, Romania, Slovenia, Spain, Sweden, and the United Kingdom) and Turkey;⁶ however, underreporting is likely due to lack of routine screening for the compound.

Synthesis of CUMYL-4CN-BINACA (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.^{6, 17} 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. There may also be trade within the European Union, as indicated by seizures of packages of synthetic cannabinoids including those containing CUMYL-4CN-BINACA. In 2016, CUMYL-4CN-BINACA was among the top five synthetic cannabinoids seized in powder form.¹⁷

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

17. Current International Controls and Their Impact

CUMYL-4CN-BINACA is not subject to international controls under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and Past National Controls

European Union: EU Early Warning System reports¹ and subsequent risk assessment⁶ resulted in the decision to subject CUMYL-4CN-BINACA to control measures on May 14, 2018.

United States: On May 30, 2018, the U.S. Drug Enforcement Agency issued a statement of its intent for temporary placement of CUMYL-4CN-BINACA under Schedule I control.³¹

Canada: CUMYL-4CN-BINACA is classified as a Schedule II controlled substance under Canada's Controlled Drugs and Substances Act which was originally passed in 1996.

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

None

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