ISSUE 26

CAYMAN CURRENTS

Cayman CHEMICAL

FORENSIC CHEMISTRY: CANNABINOID DEGRADANTS

IN THIS ISSUE:

Synthetic Cannabinoids are Recurring Chemical Threats

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Synthetic cannabinoids were originally designed and synthesized as molecular probes to characterize structure-activity relationships and to elucidate the biological basis and pharmacological properties of the chemical constituents in *Cannabis*.[1] These efforts culminated in identification of the chemical structure of the plant's primary psychoactive compound, Δ^9-THC, and its later synthesis.[2,3] Marinol® and Cesamet®, formulations of synthetic cannabinoids based upon the THC structural scaffold, eventually became licensed and marketed for their therapeutic utility, but they were limited in their market acceptability and use due to their central nervous system (CNS) effects, abuse liability, and rigorous scheduling as controlled substances. Hence, considerable interest remained in deriving compounds with increased therapeutic potential and decreased adverse side effects in the CNS.

In the 1980s, Central Pfizer Pharmaceuticals conducted a medicinal chemistry campaign and synthesized an extensive series of potent synthetic cannabinoids, including CP 55,940, a compound that was more than 100-fold more potent than Δ^9-THC in producing cannabinoid (CB) receptor effects in laboratory animals.[4-7] Radiolabeling of this synthetic compound facilitated the demonstration of saturable, high-affinity binding sites (CB_1 and CB_2 receptors) whose localization, activation, and signal transduction could be correlated with the production of cannabimimetic effects.[8-11] However, the clinical development of compounds in this series was terminated due to the continuing presence of cannabimimetic CNS effects. Nevertheless, the series opened a new

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era in cannabinoid research that served to dramatically increase the understanding of the pharmacological effects and structure-activity relationships of synthetic cannabinoids. Pfizer's early efforts in cannabinoid research were followed by others in which the resulting molecular structures of the compounds deviated further from the template of Δ^9-THC. As a result, novel chemical classes of CB receptor agonists with high affinity and efficacy for binding and activation of CB receptors were discovered and were shown to produce pharmacological effects of considerable therapeutic interest.[12-16] Unfortunately, the new agonists also typically possessed cannabimimetic activity that could not be dissociated from the more clinically desirable effects.

While the intoxicating effects and abuse liability of CB receptor agonists were considered to be untoward effects for therapeutic agents, individuals with less noble goals recognized that synthetic cannabinoids based upon non-THC structural scaffolds could be distributed and used recreationally without criminal prosecution and penalty under international scheduling and control laws. Thus, in the early 21st century, compounds originally derived from both Central Pfizer (CP 47,497) and Sterling-Winthrop (WIN 48,098), as well as independent researchers (JWH 018 and AM2201), were detected in herbal designer drug formulations **(Figure 1)**.[17-20] These formulations were often labeled as "incense" and "not for human use," and in many instances, were found to contain more than one synthetic cannabinoid.[21] In response to the rapidly increasing prevalence and use of synthetic cannabinoids, drug and law enforcement agencies across the globe began to control the most commonly occurring versions and to prosecute their manufacturers, distributors, and users. As is often the case with designer drugs, however, new replacement chemical entities would be synthesized as quickly as the older compounds were detected, identified, and banned.

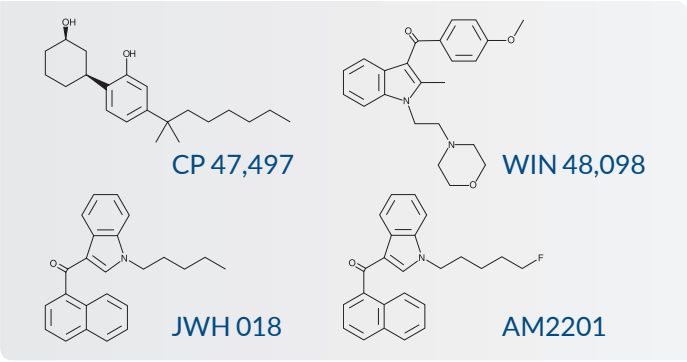

Figure 1. Compounds detected in herbal designer drugs labeled as "incense."

Because of their association with the effects produced by phytocannabinoids in *Cannabis*, synthetic cannabinoids are often mistakenly assumed to be "safer" than other designer drugs. However, the incidence of individuals who have used synthetic cannabinoids and suffered significant adverse effects (including death), called poison control centers, or were admitted into emergency medical care has seen a dramatic increase over time.[22-32] In addition to the adverse effects of the primary chemical contained in these products, the uncontrolled nature of the manufacture, formulation, and use of synthetic cannabinoids may affect identity, purity, strength, or chemical stability of the compounds, resulting in creation of and exposure to other chemical entities. Hence, individuals are often exposed to a variety of chemicals, including chemical degradants and thermolysis products. For example, after JWH 018 and AM2201 were banned by the DEA, similar compounds containing their pentylindole core, but linked *via* a ketone to a tetramethylcyclopropyl ring substituent instead of the prototypical naphthalene ring system, were increasingly encountered in new designer drug formulations. When stored at room temperature for long periods of time, the tetramethylcyclopropyl ring system in UR-144, XLR11, and other tetramethylcyclopropyl ring-containing analogs is prone to ring-opening (*i.e.*, degradation).[33] Studies conducted in RTI International laboratories, performed in collaboration with Cayman Chemical and supported in part by the National Institute of Justice* demonstrated that heating or combusting these compounds speeds up this process and leads to rapid and complete conversion of XLR11 and UR-144 to their ring-open forms **(Figure 2)**. Furthermore, *in vitro* studies revealed that the ring-open degradants possess high affinity and increased efficacy at the CB_1 receptor as well as greater potency over their non-degraded forms in laboratory animal assays selective for cannabimimetics (manuscript in preparation). Exposure to extremely potent synthetic cannabinoid compounds such as these may produce more pronounced dependence and withdrawal, or may be responsible for the continuing incidence of panic attacks, adverse effects, and fatalities that have been reported recently.

"Between January and May 2015, U.S. poison centers in 48 states reported receiving 3,572 calls related to synthetic cannabinoid use, a 229 percent increase from the 1,085 calls received during the same January through May period in 2014. The 2015 figures included a spike of 1,501 calls in April, and 15 reported deaths, a three-fold increase over the five deaths that were reported in 2014."[34]

Despite increasing recognition of the harm associated with the use of synthetic cannabinoid formulations, their abuse continues to occur, particularly in athletes, military personnel, employees who undergo frequent drug testing, and other individuals seeking intoxication while hoping to evade detection.[30,35-38] Yet, while the acute health risks associated with synthetic cannabinoids are scientifically documented and widely disseminated by the press and media, the chronic and long-term toxic effects of these compounds remain relatively unknown and may not become apparent for years or even generations (as occurred with diethylstilbestrol and thalidomide).[35-37] Further collaborative research efforts have demonstrated that some of the newer synthetic cannabinoids found in seized materials, such as NNEI, MN-18, -38, and -39, contain amide-linked naphthylamine substituents that are suspected

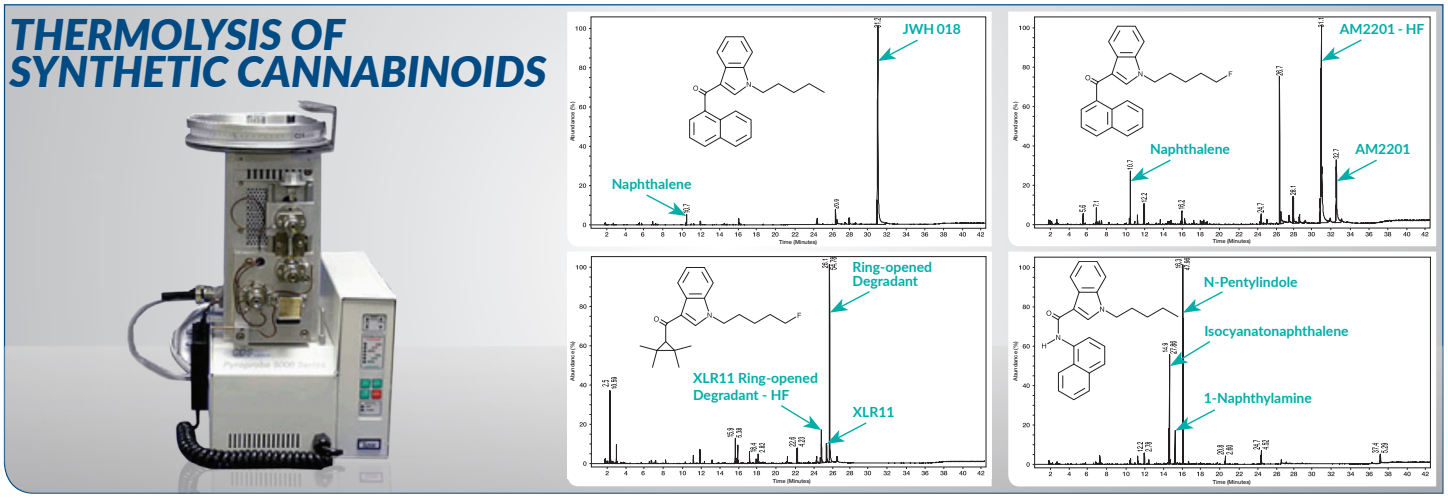

Figure 2. Aerobic thermolysis studies of JWH 018 (top left), AM2201 (top right), XLR11 (bottom left), and NNEI (bottom right) at 800°C. Note the differing degrees of degradation that occur at 800°C due to differences in chemical structure.

or known bladder carcinogens in humans and are liberated as thermolysis products during heating or combustion of herbal products for inhalation. These studies suggest that degradation or heating and thermolysis of the bulk chemicals or herbal products may result in inhalation of a completely different chemical or a mixture of chemicals. Furthermore, the data suggest that the volatility and thermolytic stability of the synthetic cannabinoids identified to date can vary dramatically, even with relatively modest changes in chemical structure, such that they are often difficult to predict with certainty. However, under typical conditions of use involving elevated temperatures, anticipated chemical exposures include lung irritants and known or suspected mutagens and carcinogens (*e.g.*, naphthalene, isocyanatonaphthalene, 8-OH-quinoline, 1-naphthylamine, and 2-naphthylamine) as well as chemicals of unknown health impact.

In summary, identification and detection of the chemicals present in a bulk drug substance or formulation is clearly important for law enforcement efforts. However, as described above, the chemicals present in the substance or formulation may not be the same as those that are actually being inhaled and absorbed into the bloodstream. Understanding the chemical fate of synthetic cannabinoids during use, with emphasis on the actual chemicals of exposure and their metabolic products formed after absorption, is crucial in determining the health effects. Exposure to even minor chemical constituents may have profound implications, as demonstrated by the "frozen addicts" resulting from inadvertent exposure to MPPP, a trace impurity formed from overheating during the synthesis of the designer opiate meperidine.[41] These drug users suffered extensive destruction of dopaminergic neurons in the substantia nigra, producing immediate and irreversible Parkinson's disease symptoms. Determination of the chemical responsible for the Parkinson-like neuronal degradation was understood fully only after careful analytical and pharmacological assessment in multiple laboratory animal species.[41-45] In order to avoid similar painful lessons, research scientists need to continue careful assessment of abused substances, including their chemical exposure profiles and associated pharmacological and toxicological endpoints. Given the increasing number of synthetic cannabinoid variants available and their varying potency and toxicity, this evaluative process is critically necessary for effective prevention and treatment.

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SYNTHETIC CANNABINOIDS

Synthetic cannabinoids are man-made agonists of the central CB_1 and peripheral CB_2 receptors. Originally designed to distinguish the actions of the two receptors, synthetic cannabinoids are commonly abused as adulterants in herbal products. Cayman offers analytical reference standards and Certified Reference Materials (CRMs) dedicated for use in forensic and academic laboratories.

- **More than 650 synthetic cannabinoid standards available**
- **Degradants, metabolites, isomers, and labeled standards available**

UR-144 SERIES

UR-144 — ISO00055

[1199943-44-6] KM-X1

MF: $C_{21}H_{29}NO$ **FW:** 311.5 **Formulation:** A crystalline solid

Summary: A potent synthetic cannabinoid that preferentially binds the peripheral CB_2 receptor (K_i = 1.8 nM) over the central CB_1 receptor (K_i = 150 nM)

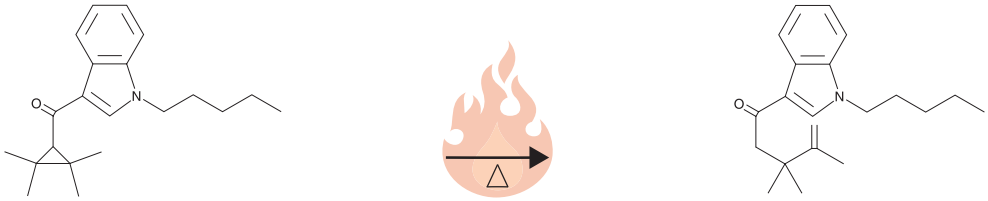
Also Available: UR-144 (CRM) Item No. ISO60055
UR-144-d_5 Item No. 11772

UR-144 Degradant — 11928

[1609273-88-2] KM-X1 Degradant, UR-144 3,3,4-Trimethylpentenoyl isomer

MF: $C_{21}H_{29}NO$ **FW:** 311.5 **Formulation:** A solution in methanol

Summary: Displays a prominent fragment ion that is 15 amu greater than the base peak of UR-144



Item No.	Product Name	Summary
14470	UR-144 N-(2-hydroxypentyl) metabolite	A synthetic cannabinoid that differs from the parent compound, UR-144, by the addition of a hydroxyl group to the alkyl chain
11774	(±)-UR-144 N-(4-hydroxypentyl) metabolite	An expected phase I metabolite of UR-144; should be detectable in either serum or urine
11775	UR-144 N-(5-hydroxypentyl) metabolite	An expected phase I metabolite of UR-144, based on the metabolism of similar cannabimimetics; should be detectable in either serum or urine
11776	UR-144 N-(5-hydroxypentyl) β-D-Glucuronide	An expected major urinary metabolite of UR-144, based on the metabolism of similar cannabimimetics
11773	UR-144 N-pentanoic acid metabolite	An expected phase I metabolite of UR-144; should be detectable in either serum or urine
9001453	UR-144 Degradant N-pentanoic acid metabolite	A potential phase I metabolite of a degradation product observed during GC-MS analysis of samples containing UR-144

XLR11 SERIES

XLR11 — 11565

[1364933-54-9] 5-FUR-144, 5-fluoro UR-144

MF: $C_{21}H_{28}FNO$ **FW:** 329.5 **Formulation:** A neat solid

Summary: An aminoalkylindole compound that binds to CB_1 and CB_2 receptors with K_i values of 24 and 2.1 nM, respectively

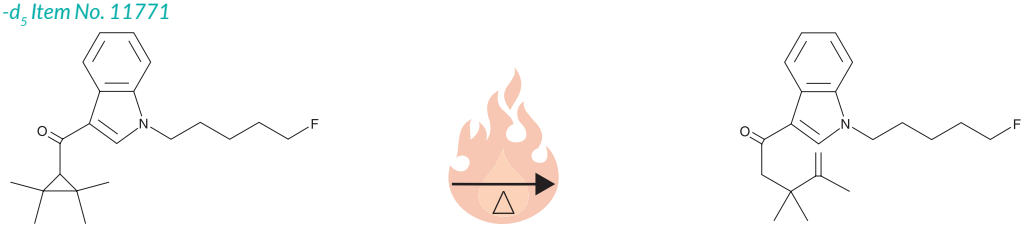
Also Available: XLR11-d_5 Item No. 11771

XLR11 Degradant — 14055

[1616469-09-0] 5-FUR-144 Degradant, TCMP-2201 thermal isomer

MF: $C_{21}H_{28}FNO$ **FW:** 329.5 **Formulation:** A solution in methanol

Summary: Displays a prominent fragment ion that is 15 amu greater than the base peak of XLR11



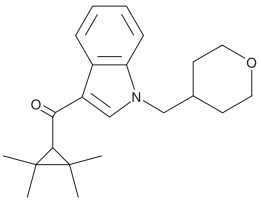
Item No.	Product Name	Summary
14354	XLR11 6-hydroxyindole metabolite	An expected minor monohydroxylated urinary metabolite of XLR11
17727	XLR11 N-(4-hydroxypentyl) metabolite (CRM)	An expected phase I metabolite of XLR11

SYNTHETIC CANNABINOIDS

A-834735 & A-796260 SERIES

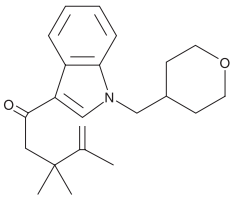
A-834735 — 11163

[895155-57-4]
MF: $C_{22}H_{29}NO_2$ **FW:** 339.5 **Formulation:** A crystalline solid
Summary: An indole-derived cannabinoid that acts as a full agonist at both the CB_1 and CB_2 receptors (K_is = 4.6 and 0.31 nM, respectively; EC_{50}s = 12 and 0.21 nM, respectively)



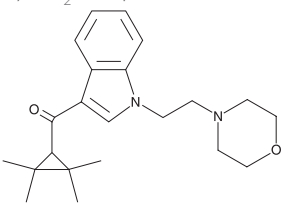
A-834735 Degradant — 14165

MF: $C_{22}H_{29}NO_2$ **FW:** 339.5 **Formulation:** A solution in methanol
Summary: Displays a prominent fragment ion that is 15 amu greater than the base peak of A-834735



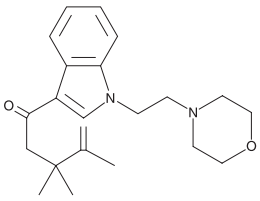
A-796260 — 11606

[895155-26-7] LTI-258
MF: $C_{22}H_{30}N_2O_2$ **FW:** 354.5 **Formulation:** A crystalline solid
Summary: A synthetic cannabinoid that shows high selectivity for the CB_2 receptor (K_i = 0.77 nM) over the CB_1 receptor (K_i = 2,100 nM); shows efficacy *in vivo* in models of pain and is selectively blocked by CB_2 receptor-selective antagonists



A-796260 Degradant — 17515

[1616469-10-3] LTI-258 Degradant
MF: $C_{22}H_{30}N_2O_2$ **FW:** 354.5 **Formulation:** A solution in methanol
Summary: Displays a prominent fragment ion that is 15 amu greater than the base peak of A-796260



SYNTHETIC CANNABINOIDS

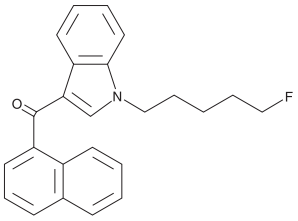
AM2201 SERIES

AM2201 — 10707

[335161-24-5]

MF: $C_{24}H_{22}FNO$ **FW:** 359.4 **Formulation:** A neat solid
Summary: A potent synthetic cannabinoid with K_i values of 1.0 and 2.6 nM for the CB_1 and CB_2 receptors, respectively

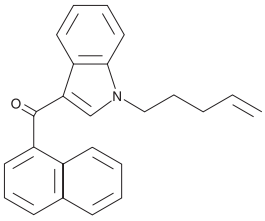
Also Available: AM2201-d_5 Item No. 10706



JWH 022 — 9001056

[209414-16-4] AM2201 N-(4-pentenyl) analog

MF: $C_{24}H_{21}NO$ **FW:** 339.4 **Formulation:** A solution in methanol
Summary: A cannabimimetic indole that is structurally related to JWH 018, a mildly selective agonist of the peripheral CB_2 receptor



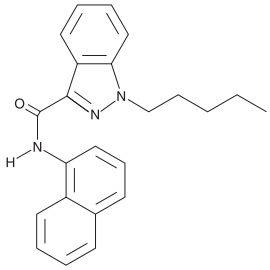
Item No.	Product Name	Summary
11196	AM2201 5-hydroxyindole metabolite	An expected phase I metabolite of AM2201, detectable in serum or as a glucuronidated derivative in urine
11192	AM2201 6-hydroxyindole metabolite	An expected metabolite of AM2201 generated during phase I metabolism, detectable in blood and urine
11193	AM2201 7-hydroxyindole metabolite	An expected minor monohydroxylated urinary metabolite of AM2201
10203	AM2201 N-(4-hydroxypentyl) metabolite	An expected urinary metabolite of AM2201

MN-18 & NNEI SERIES

MN-18 — 14817

[1391484-80-2]

MF: $C_{23}H_{23}N_3O$ **FW:** 357.5 **Formulation:** A crystalline solid
Summary: A synthetic cannabinoid modeled after AKB48, with the adamantyl group replaced by a naphthalenyl group

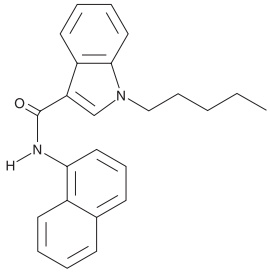


NNEI — 15001

[1338925-11-3] MN-24

MF: $C_{24}H_{24}N_2O$ **FW:** 356.5 **Formulation:** A crystalline solid
Summary: An analog of JWH 018 that differs by having an amide linker inserted between the naphthalene and ketone groups

Also Available: NNEI 2'-indazole isomer Item No. 17520
NNEI 2'-naphthyl isomer Item No. 14738



ask Cayman

QUESTIONS FROM THE FIELD

Q: What is the difference between a CRM and an RM?

A: Use the reference chart below to guide which analytical standard formulation is right for you.

	Certified Reference Materials	Reference Materials
Quantitative Solutions	⬢	
Sealed Ampule Packaging	⬢	
Produced in Cayman's ISO Guide 34:2009 and ISO/IEC 17025:2005 Accredited Lab	⬢	⬢
Enhanced Certificate of Analysis	⬢	⬢
Recommended for ISO/IEC 17025:2005 Testing Labs	⬢	⬢
Multiple and/or Custom Sizes		⬢
Qualitative Solids		⬢
Recommended for General Research		⬢
Standard Certificate of Analysis		
Qualitative Solutions		

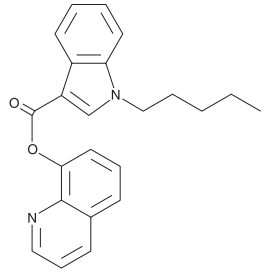
PB-22 SERIES

PB-22 — ISO00122

[1400742-17-7] QUPIC

MF: $C_{23}H_{22}N_2O_2$ **FW:** 358.4 **Formulation:** A neat solid
Summary: An analog of JWH 018 with 8-hydroxyquinoline replacing the naphthalene group of JWH 018

Also Available: PB-22 (CRM) Item No. ISO60122
PB-22-d_9 Item No. 14298

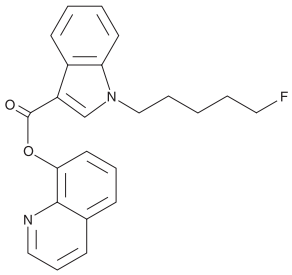


5-fluoro PB-22 — 14095

[1400742-41-7] 5-fluoro QUPIC

MF: $C_{23}H_{21}FN_2O_2$ **FW:** 376.4 **Formulation:** A neat solid
Summary: A derivative of the JWH 018 analog PB-22, having a fluorine atom at the terminal carbon of the pentyl chain

Also Available: 5-fluoro PB-22 (CRM) Item No. ISO60123



Item No.	Product Name	Summary
14385	PB-22 3-carboxyindole metabolite	An expected metabolite of PB-22 that would be detectable in serum and urine
14386	PB-22 N-(4-hydroxypentyl) metabolite	An expected metabolite of PB-22
14387	PB-22 N-(5-hydroxypentyl) metabolite	An expected metabolite of PB-22
14563	PB-22 N-(4-hydroxypentyl)-3-carboxyindole metabolite	A potential metabolite of PB-22
14564	PB-22 N-(5-hydroxypentyl)-3-carboxyindole metabolite	A potential metabolite of PB-22
14389	PB-22 N-pentanoic acid metabolite	A potential metabolite of PB-22
14565	PB-22 N-pentanoic acid-3-carboxyindole metabolite	A potential metabolite of PB-22
14381	5-fluoro PB-22 3-carboxyindole metabolite	A metabolite of 5-fluoro PB-22 in which the 8-hydroxyquinoline group characteristic of PB-22 analogs has been removed

SYNTHETIC CANNABINOIDS

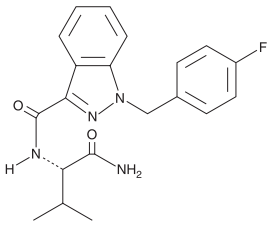
AB-FUBINACA SERIES

AB-FUBINACA 14039

[1185282-01-2]

MF: $C_{20}H_{21}FN_4O_2$ **FW:** 368.4 **Formulation:** A neat solid
Summary: An indazole-based synthetic cannabinoid with potent affinity for the CB_1 receptor (K_i = 0.9 nM)

Also Available: AB-FUBINACA (CRM) Item No. ISO60211
AB-FUBINACA-d_4 Item No. 15292



Item No.	Product Name	Summary
15529	AB-FUBINACA metabolite 2A	An expected carboxy metabolite of AB-FUBINACA, based on the major metabolites produced from similar synthetic cannabinoids in humans
17947	AB-FUBINACA metabolite 2B	An expected carboxy metabolite of AB-FUBINACA, based on the major metabolites produced from similar synthetic cannabinoids in humans

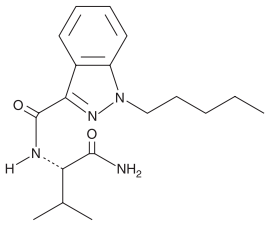
AB-PINACA SERIES

AB-PINACA 14038

[1445752-09-9]

MF: $C_{18}H_{26}N_4O_2$ **FW:** 330.4 **Formulation:** A neat solid
Summary: A synthetic cannabinoid that has been identified as a designer drug in illegal herbal products

Also Available: AB-PINACA (CRM) Item No. ISO60210
AB-PINACA-d_9 Item No. 15057



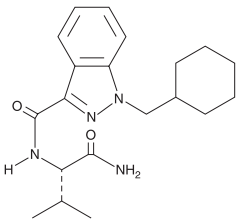
Item No.	Product Name	Summary
15049	AB-PINACA N-(4-hydroxypentyl) metabolite	An expected metabolite of AB-PINACA that would be detectable both in serum and in urine
15050	AB-PINACA N-(5-hydroxypentyl) metabolite	An expected metabolite of AB-PINACA that would be detectable both in serum and in urine
15051	AB-PINACA pentanoic acid metabolite	An expected compound produced by phase I metabolism of AB-PINACA *in vivo*, based on the metabolism of comparable alkylindole cannabinoids

AB-CHMINACA SERIES

AB-CHMINACA 15434

[1185887-21-1]

MF: $C_{20}H_{28}N_4O_2$ **FW:** 356.5 **Formulation:** A crystalline solid
Summary: A synthetic cannabinoid structurally related to AB-FUBINACA in which a cyclohexyl group is substituted for the 4-fluorophenyl group

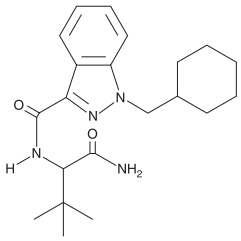


MAB-CHMINACA

MAB-CHMINACA 16616

[1863065-92-2] ADB-CHMINACA

MF: $C_{21}H_{30}N_4O_2$ **FW:** 370.5 **Formulation:** A neat solid
Summary: A synthetic cannabinoid structurally related to AB-CHMINACA in which the isobutyl moiety is substituted with a *tert*-butyl group

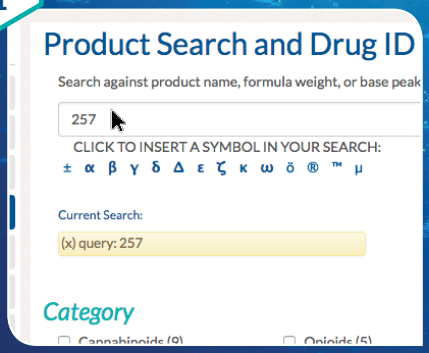


Item No.	Product Name	Summary
16387	AB-CHMINACA metabolite M1A	A monohydroxylated metabolite of AB-CHMINACA
16388	AB-CHMINACA metabolite M1B	A potential metabolite produced during metabolism of AB-CHMINACA *in vivo*
16389	AB-CHMINACA metabolite M2	A carboxylic acid metabolite of AB-CHMINACA
16391	AB-CHMINACA metabolite M3A	An expected metabolite produced during metabolism of AB-CHMINACA in the liver
16394	AB-CHMINACA metabolite M5A	A potential metabolite produced during metabolism of AB-CHMINACA in the liver
16453	AB-CHMINACA metabolite M6	A potential metabolite of AB-CHMINACA in which the isopropyl group has been oxidized
17084	AB-CHMINACA metabolite M7	A potential metabolite produced during metabolism of AB-CHMINACA *in vivo*

GC-MS DRUG IDENTIFICATION TOOL

SEARCH UNKNOWNS AGAINST BASE PEAK OR 2ND BASE ION:

STEP 1

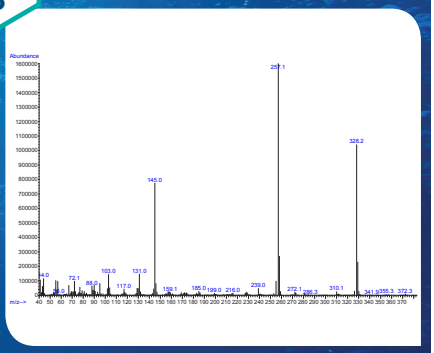


SEARCH BY FW, BASE PEAK, OR 2ND BASE ION

STEP 2

SELECT PRODUCT

STEP 3



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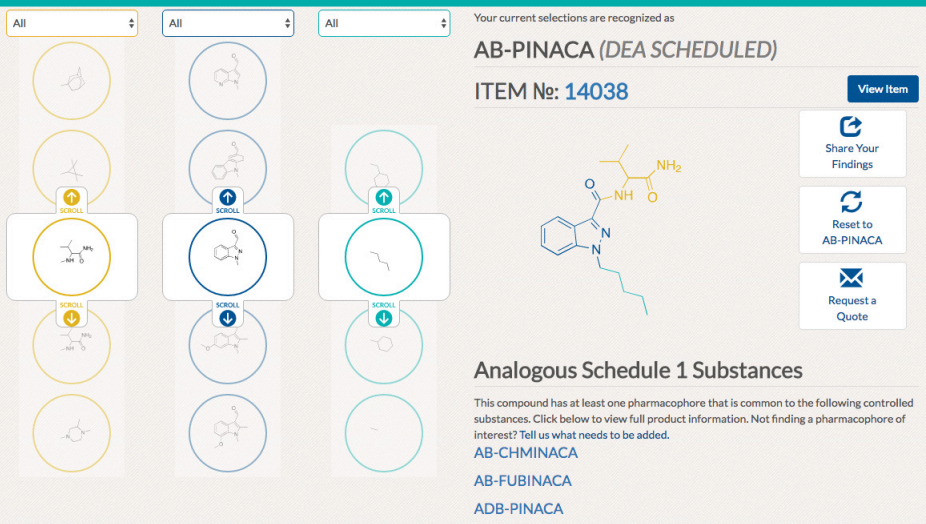

A new tool to explore structural similarities to known Schedule I synthetic cannabinoids by assembling head, core, and tail pharmacophores

www.caymanchem.com/syncanflipbook

Review of *Cannabis* Dosage Formulations

by Brian F. Thomas, Ph.D.
Principal Scientist, Analytical Chemistry and Pharmaceutics, RTI International

Cannabinoid pharmaceutical preparations are available in the United States and are regulated by the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA). However, patients and recreational users can also obtain cannabinoid-containing medications and recreational products in herbal form or in *Cannabis*-derived dosage formulations through dispensaries and statewide programs. Medicinal *Cannabis* or *Cannabis*-derived products available in these dispensaries have not been approved for use by the FDA and are still considered Schedule I controlled substances by the DEA. Due to a lack of registration, documentation, inspection, and approval of these products by the FDA, there is public concern about their quality, reliability, and safety. Indeed, these products have been distributed without safety packaging, tamper resistance, or clear unit doses and have been inadvertently consumed by both children and adults who have become intoxicated or suffered adverse effects.[1,2]

Individuals who visit dispensaries typically have access to several varieties of *Cannabis* that are distinguished through the use of popular names or a plethora of *Cannabis*-derived dosage formulations. It is often difficult to distinguish whether their relatively informal nomenclature and labeling are accurate or reflect any significant differences in chemical composition. If best practices are followed, the quality and reproducibility of the *Cannabis* plant material has been optimized through control of the seeds or rooted clones used and the growth conditions employed. For example, when grown indoors, systematic control of soil conditions, water, nutrients, temperature, and lighting conditions is possible and advantageous for maximizing yields and consistency in the content of chemical constituents. Specific methods used for harvesting, drying, manicuring, processing, and storing the inflorescence may vary but should be documented and adhered to as this can also have a significant impact on the chemical constituents. Even under ideal conditions, the cannabinoid acids undergo slow degradation to their decarboxylated forms and the terpenes and flavonoids can also isomerize, degrade, or suffer loss through evaporation.[3,4] While the product label cannot contain all of the relevant analytical information that is required to reflect that appropriate selection, processing, manufacturing, analytical characterization, and quality control of *Cannabis*-based dosage formulations has occurred, this information should be documented and retained in the form of a batch production record and certificate of analysis.

Proper analytical characterization and labeling is particularly important for the final *Cannabis*-derived products because many of the chemical constituents within the *Cannabis* plant may interact and contribute to their pharmacological activity and therapeutic potential. It has even been proposed that the development and therapeutic application of *Cannabis*-based medicines containing multiple cannabinoids, in defined ratios, and other non-cannabinoid fractions can provide better clinical utility than the single synthetic cannabinoid pharmaceuticals currently available.[5] In this case, all clinically relevant constituents, and any excipients that have been added to the formulation or plant, should be analytically characterized, quantitated, and clearly identified and described on the label. Furthermore, since *Cannabis* is a natural product that can harbor a variety of pests and microbes, including harmful bacteria and fungi, careful analytical monitoring and quality control to preclude these potentially harmful contaminants from medicinal products is also a necessity. Unfortunately, even when chemical contents are provided on the label, the accuracy of the label has been questioned, and the nomenclature that is used to describe the chemical constituents can be unclear or lacking in sufficient detail.[6] For example, the phytocannabinoids in edible products may be referred to as "activated cannabinoids" to indicate that the biosynthetically-derived carboxylic acid forms of the phytocannabinoids in the product have undergone decarboxylation during manufacture. It is also often the case that a single dispensary distributes such a wide variety of products that it presents a considerable challenge for analytical characterization and proper quality control.

In order to ensure therapeutic utility and safety, the analytical methods used for the characterization of medicinal or recreational *Cannabis* products should ideally follow good manufacturing practices and use analytical reference standards and internal standardization to control for the recovery and quantitation of active ingredients. The analytical methods must be accurate, reproducible, stability indicating, and suitable for their intended use. The quantitative information on active ingredients should be provided in a clear and concise form on a properly reviewed and approved product label. Finally, the packaging should be appropriately secured and include a product insert with more detailed information regarding the ingredients, excipients, and the product's pharmacology.

References

1. Berger, E. Legal marijuana and pediatric exposure pot edibles implicated in spike in child emergency department visits. *Ann. Emerg. Med.* **64(4)**, A19-21 (2014).
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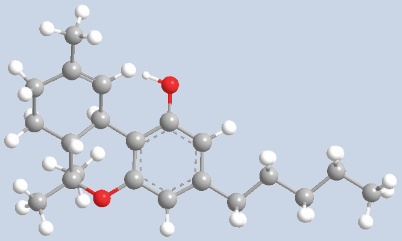
PHYTOCANNABINOIDS

A large number of structurally and physiologically distinct compounds are unique to plants of the genus *Cannabis*, known collectively as phytocannabinoids. Some, like Δ^9-tetrahydrocannabinol (Δ^9-THC), activate CB receptors. Others antagonize the same receptors or act through completely different signaling pathways.

- **More than 30 phytocannabinoid standards available**
- **Labeled standards available**



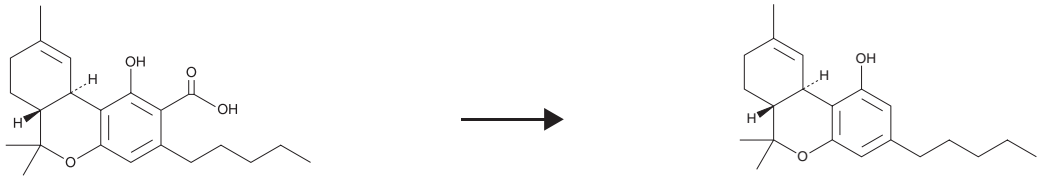
THCA-A (CRM) ISO60175

[23978-85-0] Δ^9-Tetrahydrocannabinolic Acid, Δ^9-THC Carboxylic Acid
MF: $C_{22}H_{30}O_4$ **FW:** 358.5 **Formulation:** A 1 mg/ml solution in acetonitrile
Summary: A precursor of Δ^9-THC in *Cannabis* spp.; lacks psychoactive activity *in vivo*, but can be decarboxylated to form Δ^9-THC; an inhibitor of TrpM8 (IC_{50} = 150 nM) and diacylglycerol lipase α (IC_{50} = 27.3 µM)

Δ^9-THC (CRM) ISO60157

[1972-08-3] Dronabinol, NSC 134454, Δ^9-Tetrahydrocannabinol
MF: $C_{21}H_{30}O_2$ **FW:** 314.5 **Formulation:** A 1 mg/ml solution in methanol
Summary: A natural psychoactive compound found in plants of the genus *Cannabis*; binds with high affinity to both the central CB_1 receptor (K_i = 41 nM) and the peripheral CB_2 receptor (K_i = 36 nM)

Also Available: Δ^9-THC-d_9 Item No. 16206



Item No.	Product Name	Summary
ISO60163	(±)-Cannabichromene (CRM)	A non-psychoactive cannabinoid that modulates nociception by acting as a TRPV1 (EC_{50} = 24.2 µM) and TRPA1 (EC_{50} = 90 nM) agonist and inhibiting proteins that facilitate anandamide inactivation (IC_{50} = 12.3 µM); does not activate CB receptors
ISO60156	Cannabidiol (CRM)	An active phytocannabinoid that is considered to be non-psychoactive; acts as a CB_2 receptor inverse agonist, GPR55 antagonist, and a 5-HT_{1A} receptor agonist; also allosterically modulates µ- and δ-opioid receptors, agonizes PPARγ receptors, and stimulates intracellular calcium release
ISO60183	Cannabinol (CRM)	A natural endocannabinoid and analog of the psychoactive cannabinoid Δ^9-THC; weakly selective for the peripheral CB_2 receptor over the central CB_1 receptor (K_is = 126 and 211 nM, respectively)
ISO60158	Δ^8-THC (CRM)	An analog of the natural psychoactive compound Δ^9-THC; binds both the central CB_1 receptor (K_i = 28.5 nM) and the peripheral CB_2 receptor (K_i = 25 nM)

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Dr. Brian Thomas is a Principal Scientist in RTI International's Discovery Sciences Division. His research interests include cannabinoid pharmacology, substance abuse disorders, and the application of analytical chemistry and pharmacological testing to facilitate the discovery and development of novel therapeutic agents. Since 1992, he has served as Principal Investigator on two research contracts funded through the National Institute on Drug Abuse (NIDA). He has also held two R01 grants through NIDA and served on contracts and grants funded by the NIH, the Food and Drug Administration, and the Drug Enforcement Administration.

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