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Identification of Eight Synthetic Cannabinoids, Including 5F-AKB48 in Seized Herbal Products Using DART-TOF-MS and LC-QTOF-MS as Nontargeted Screening Methods*

Katherine N. Moore, M.S.¹, Demetra Garvi, Pharm.D.², Brian F. Thomas, Ph.D.¹, and Megan Grabenauer, Ph.D.¹

¹RTI International, Research Triangle Park, NC 27709.

²Richland County Sheriff's Department, Columbia, SC 29223.

Abstract

Synthetic cannabinoids are sprayed onto plant material and smoked for their marijuana-like effects. Clandestine manufacturers modify synthetic cannabinoid structures by creating closely related analogs. Forensic laboratories are tasked with detection of these analog compounds, but targeted analytical methods are often thwarted by the structural modifications. Here, direct analysis in real time coupled to accurate mass time-of-flight mass spectrometry (DART-TOF-MS) in combination with liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) are presented as a screening and nontargeted confirmation method, respectively. Methanol extracts of herbal material were run using both methods. Spectral data from four different herbal products were evaluated by comparing fragmentation pattern, accurate mass and retention time to available reference standards. JWH-018, JWH-019, AM2201, JWH-122, 5F-AKB48, AKB48-N-(4-pentenyl) analog, UR144, and XLR11 were identified in the products. Results demonstrate that DART-TOF-MS affords a useful approach for rapid screening of herbal products for the presence and identification of synthetic cannabinoids.

Keywords

forensic science; synthetic cannabinoids; nontargeted analysis; mass spectrometry; direct analysis in real time; herbal products

Herbal products are sold over the Internet and in local head-shops to individuals who smoke them for their marijuana-like effects (1–3). These packages list natural herbs and state “not for human consumption” but have been confirmed to contain synthetic cannabinoids (1,4–6). Herbal products may contain multiple synthetic cannabinoids and may vary in composition and concentration between packages (7,8). The United States Drug Enforcement

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Additional information and reprint requests: Megan Grabenauer, Ph.D., RTI International, 3040 E. Cornwallis Road, Research Triangle Park, NC 27709, mgrabenauer@rti.org.

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Administration (DEA) started to temporarily ban selected synthetic cannabinoids in March 2011 (9) followed by permanently placing a number of emerging compounds into Schedule I of the Controlled Substances Act under the Synthetic Drug Abuse and Prevention Act (SDAPA) of 2012 (10). As clandestine manufacturers continue to modify synthetic cannabinoid structures to avoid judicial consequences, there has been a continuing trend in the appearance of novel drugs within the illicit drug market (3).

Forensic laboratories must continue to develop and modify analytical methods to identify the growing number of synthetic cannabinoids. ElSohly et al. and Seely et al. reviewed the literature for various analytical methods used in the identification and quantification of synthetic cannabinoids in herbal products as well as metabolites in various biological matrices (3,11). Newly emerging drugs have been identified and characterized in herbal products by gas chromatography–mass spectrometry (GC-MS), ultra-performance liquid chromatography–mass spectrometry (UPLC-MS), and direct analysis in real time coupled to accurate mass time-of-flight mass spectrometry (DART-TOF-MS) (12). Emerging compounds have also been detected using nontargeted acquisition methods as these allow retrospective data mining for unknown compounds and an alternative to targeted analyses that cannot detect unknown compounds within a sample (13,14). DART-TOF-MS has been validated in forensic laboratories for screening of controlled substances (15) and could also be used to screen for synthetic cannabinoids in herbal products without extensive extraction methods (16–20).

The purpose of this study was to demonstrate the utility of DART-TOF-MS as a screening technique and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) as a subsequent nontargeted confirmation method for the detection and identification of synthetic cannabinoids in confiscated herbal products. In addition, we investigated the homogeneity of synthetic cannabinoid formulations across several packages of a single brand and type of herbal product.

Materials and Methods

Materials

All solvents were high-performance liquid chromatography (HPLC) grade, purchased from Fisher Scientific (Fair Lawn, NJ), EMD Chemical (Gibbstown, NJ), and Sigma-Aldrich (St. Louis, MO). JWH-018, AM2201, JWH-122, UR144, XLR11, and 5F-AKB48 reference standards were obtained from Cayman Chemical (Ann Arbor, MI). JWH-019 reference standard was synthesized in the laboratory of Dr. John W. Huffman and provided by Dr. Jenny L. Wiley. Herbal products were obtained from the Richland County Sheriff's Department (Columbia, SC). These products were seized between December 2011 and August 2013 and were scheduled for destruction. Custody was turned over to RTI International, and products were stored in accordance with established protocols.

Sample Preparation

Approximately 10–25 µg of herbal material was extracted with methanol at 70 µL/mg of plant material as previously described (13). Samples were sonicated for 10 min followed by

centrifugation at 4000 rpm for 10 min. Supernatants were filtered using 0.22- μ M spin filters (Agilent Technologies, Cedar Creek, TX) and centrifuged for 5 min at 10,000 relative centrifugal force (rcf). Extracts were diluted 10-fold with 50:50 methanol:water (v:v) prior to LC-QTOF-MS analysis.

DART-TOF-MS Parameters

A direct analysis in real time (DART) source (IonSense, Saugus, MA) was coupled to a JEOL accurate mass time-of-flight (AccuTOF) mass spectrometer (JEOL USA Inc, Peabody, MA). The DART-TOF-MS instrument was operated under the following conditions: orifice 1 temperature at 80°C, orifice 1 voltages were 20, 30, 60, and 90 V using function switching mode in which the voltage was switched every 0.25 sec, orifice 2 and ring lens at 5 V, helium gas flow at 2.5 L/min at 275°C, needle voltage at 4000 V, and grid electrode at 250 V. A dilute methanolic solution of polyethylene glycol with an average mass of 1000 (PEG 1000, Sigma-Aldrich, St. Louis, MO) was run within each data file as an internal calibration. The closed end of a capillary melting point tube (Kimble Chase, Vineland, NJ) was dipped into methanolic standards or undiluted methanolic herbal product extracts and placed into the DART-TOF-MS sample gap. The exact mass of the protonated molecule for each compound was expected to fall within ± 5 mDa of its calculated exact mass. The system was controlled by Mass Center software (JEOL USA Inc, Peabody, MA). TSSPro 3.0 software (Shrader Analytical, Detroit, MI) was used to create averaged and background-subtracted spectra.

LC-QTOF-MS Parameters

Samples were analyzed on a Waters Synapt G2 HDMS QTOF-MS coupled to a Waters ACQUITY UPLC system (Waters, Milford, MA). Data were acquired using the following conditions: 0.5 sec scan time, positive mode electrospray ionization, capillary voltage of 2.99 kV, source temperature of 150°C, desolvation temperature of 500°C, desolvation gas at 100 L/h, sampling cone at 35 V, and extraction cone at 4.3 V. Sodium formate was used to externally calibrate the instrument. Leucine enkephalin was used as a lock mass to correct for mass shifts during acquisition. Data were acquired using MS and MS^E acquisition methods. Samples were injected (2 μ L) onto a BEH C18 column (1.7 μ m 2.1 $\times$ 50 mm) connected to a Vanguard BEH C18 precolumn and held at 30°C. A gradient elution was used consisting of water with 0.1% formic acid (mobile phase A) and acetonitrile with 0.1% formic acid (mobile phase B) with a flow rate of 500 μ L/min. The gradient was held at 10% B for 1.5 min and increased to 25% B linearly over 15.5 min, increased to 65% B over 3 min, increased to 95% B for 1.1 min, and then held at 10% B for 2.9 min for column reequilibration. During the first 30 sec, the liquid chromatography eluate was diverted to waste and mass spectrometry data were not acquired. Data analysis was performed using Waters MassLynx software.

Results

Four brands of herbal products, Aztec Potpourri, K2 Pink, Sexy Exotic Herbal Potpourri, and Mad Hatter Cloud 9, were screened using DART-TOF-MS and further analyzed using LC-QTOF-MS for confirmation of the DART-TOF-MS results. Using these combined

techniques, JWH-018, JWH-019, AM2201, JWH-122, 5F-AKB48, AKB48-N-(4-pentenyl) analog, UR144, and XLR11 were identified in the herbal products. Compound structures, along with their calculated exact masses, are provided in Fig. 1.

DART-TOF-MS and LC-QTOF-MS

Figure 2 shows the DART-TOF-MS mass spectra at 90 V of Aztec Potpourri (A) and K2 Pink (B). The protonated ($[M+H]^+$) molecule at m/z 360.1774 and characteristic fragment ions at m/z 232.1126 and m/z 155.0479 are indicative of AM2201 or a related isomer. Aztec Potpourri also contains a compound with an $[M+H]^+$ at m/z 356.2022 and fragment ions at m/z 214.1253 and m/z 169.0621. These fragment ions are consistent with a pentyl indole moiety with an attached carbonyl group and a methylated naphthoyl group, respectively, suggesting that the synthetic cannabinoid is likely JWH-122 or a related isomer. The m/z 360.1774 has a relative intensity of 81.7% compared to 4.30% m/z 356.2022 which suggests that the sample contains a much higher concentration of the AM2201-related compound than the JWH-122-related compound. K2 Pink contains a compound with the same (within five mDA) $[M+H]^+$ m/z 356.2037 as the Aztec Potpourri sample but with different diagnostic fragment ions at m/z 155.0485 and m/z 228.1371. These fragment ions reveal an additional methyl group on the alky indole side of the molecule and the presence of an unmodified naphthoyl group which could be JWH-019 or an isomer.

Figure 3A shows the 90 V mass spectrum of Sexy Exotic Herbal Potpourri with a protonated molecule of m/z 312.2316. The fragment ion at m/z 214.1199 is indicative of a pentyl indole moiety with an attached carbonyl group while m/z 125.0970 and m/z 97.1064 are characteristic of a tetramethylcyclopropyl (TMCP) moiety with and without an attached carbonyl group, respectively. Both the $[M+H]^+$ and fragment ion accurate masses indicate that this product contains UR144 or a related isomer. The 90 V mass spectrum of Mad Hatter Cloud 9 appeared to contain only fragment ions; therefore, the 60 V mass spectrum for this product was obtained and is shown in Fig. 3B. The spectrum contains an $[M+H]^+$ of m/z 384.2440 and fragment ion base peak at m/z 135.1213 which reveals an adamantyl moiety and the protonated molecule of 5F-AKB48 or related compound. No other fragment ions related to 5F-AKB48 were observed. It has been reported that the main fragment ion for other adamantyl-type compounds is the adamantyl moiety (21,22). Upon further evaluation of the Mad Hatter Cloud 9 mass spectrum, several suspected $[M+H]^+$ peaks with the same exact masses of common synthetic cannabinoids, UR144 (m/z 312.2341) and XLR11 (m/z 330.2260), were observed. A typical pentyl indole carbonyl fragment ion at m/z 214.1262 and a TMCP fragment ion at m/z 97.0988 are inconsistent with the structure of the suspected 5F-AKB48 compound. These results further indicate that additional synthetic cannabinoids may be present. Also observed is a peak at m/z 364.2376 indicating a loss of HF from m/z 384.2440, which corresponds to an AKB48-N-(4-pentenyl) analog. Using DART-TOF-MS alone, it is unclear whether this compound is a fragmentation product of 5F-AKB48 or is an additional synthetic cannabinoid contained in the herbal product.

After DART-TOF-MS screening, the samples were analyzed using LC-QTOF-MS to confirm the identities of the suspected compounds. Table 1 lists the synthetic cannabinoids confirmed in each herbal product using LC-QTOF-MS analysis. Identifications were

confirmed based on exact mass, retention time, and fragmentation pattern match to reference standards for all compounds with the exception of the AKB48-N-(4-pentenyl) analog as no reference standard was available for this compound. AKB48-N-(4-pentenyl) analog was tentatively identified by the presence of a peak at an m/z corresponding to the exact mass of a protonated AKB48-N-(4-pentenyl) analog molecule and interpretation of the fragmentation pattern. As the AKB48-N-(4-pentenyl) analog detected in the Mad Hatter Cloud 9 product has a different retention time than 5F-AKB48, it was determined that this analog is a unique cannabinoid present, and not simply a fragmentation product of 5F-AKB48.

Table 2 summarizes the calculated protonated molecule exact masses, retention times, and observed fragment ions for each synthetic cannabinoid identified. The LC-QTOF-MS high-energy mass spectra of synthetic cannabinoids confirmed in the herbal products are shown in Figs 4 and 5. The sodium adducts ($[M+Na]^+$) for these compounds are also observed in the LC-QTOF-MS data which provides further accurate mass identification. As these are high-energy spectra, most of the protonated parent ions have been fragmented, while the sodium adducts remain intact. In addition to the compounds detected with the DART-TOF-MS screening technique, JWH-018 was identified in K2 Pink using the nontargeted LC-QTOF-MS method. Figure 5 does not include a spectrum for XLR11 identified in Mad Hatter Cloud 9 due to its low intensity. To provide the expected fragment ions, the high-energy mass spectrum of the XLR11 reference standard is shown in Fig. 5. The XLR11 reference standard retention time matched the sample retention time and the parent compound accurate mass.

To assess sample homogeneity within the Mad Hatter Cloud 9 product packages, five 10–25 mg aliquots from each of three separate packages ($n = 15$) were analyzed using the LC-QTOF-MS method. The absolute peak areas of 5F-AKB48 and AKB48-N-(4-pentenyl) analog were consistent within and between packages, while the peak areas of UR144 and XLR11 were more varied. The same four synthetic cannabinoids were identified in each of the 15 aliquots. Additionally, one sample from each of the 25 packages was tested to determine whether each package contained the same compounds. In all packages, 5F-AKB48 was the primary compound detected, accounting for approximately 95% of the total integrated peak area for all four compounds. XLR11 was the least abundant cannabinoid detected in each sample, accounting for approximately 0.4% of the total peak area. Table 3 shows the average peak areas and coefficient of variance (%CV) for each component identified in the 25 Mad Hatter Cloud 9 samples and from the five aliquots within three packages.

Discussion

Within the last decade, synthetic cannabinoids have entered the realm of designer drugs that are manufactured clandestinely, formulated haphazardly, distributed with no toxicological testing, and marketed to appeal especially to uninformed youth. These herbal products are formulated to produce intoxication while avoiding detection by forensic or law enforcement agencies, and can contain multiple synthetic cannabinoids which may vary in composition and concentration between packages (7,8). As public awareness and concern increased, the

DEA enacted temporary bans on selected synthetic cannabinoids in March 2011 (9), leading to permanent placement of a number of emerging compounds into Schedule I of the Controlled Substances Act under the SDAPA of 2012 (10). Clandestine manufacturers quickly responded by modifying synthetic cannabinoid structures to avoid targeted detection methods and judicial consequences, giving rise to an ever-changing shift toward the appearance of novel substances in the illicit drug market (3).

In the current study, LC-QTOF-MS was used to assess homogeneity between different packages of the Mad Hatter Cloud 9 product, as well as homogeneity within a single package. The same four compounds were seen at similar relative concentrations in each 10–25 mg sample of plant material. There was a high level of homogeneity both within each of the three packages tested, and between all 25 packages. This indicates product uniformity that is not unexpected as the products were from a single seizure and are likely from the same manufacturing lot.

As DART is an ambient ionization technique, samples can be introduced as a solid material (17,18) or as a liquid from a solvent extraction of the plant material (19). Nonuniformity of synthetic cannabinoid distribution within herbal products can present a challenge when a small sample, such as a single leaf, is analyzed. Lesiak et al. used DART-TOF-MS to identify the synthetic cannabinoids present on single leaves of herbal products and found that each leaf was positive for the same synthetic cannabinoids (16). We did not find that to be the case for our samples. In this study, direct analysis of the solid plant material (leaves stems and flowers) from the confiscated products produced inconsistent results by DART-TOF-MS, despite the relatively good homogeneity demonstrated by extraction and analysis of 10–25 mg samples by LC-QTOF. Therefore, dipping a glass capillary into a simple methanolic extraction was chosen as the preferred sample introduction technique for DART-TOF-MS. Marino et al. reported on the use of DART-TOF-MS and proton nuclear magnetic resonance (NMR) spectroscopy for identification of synthetic cannabinoids in herbal products as an alternative or complementary method to traditional chromatography-based methods. They observed nonuniformity of synthetic cannabinoids identified on a single leaf from the same product and determined that several measurements using different leaves should be conducted (23).

An ideal rapid screening method for herbal products would sample plant material directly to minimize sample preparation. However, even with the addition of a simple solvent extraction step, the time for sample preparation and analysis using DART-TOF-MS is considerably faster than other chromatography-based screening methods. DART-TOF-MS analysis provides accurate mass determination as well as characteristic fragment ions from collision-induced dissociation (15,17), making it a reliable screening technique.

To address the continually evolving need for detection and identification of synthetic cannabinoid-containing herbal formulations, a rapid and reliable screening and confirmation method for the identification of synthetic cannabinoids in herbal products is required. Results from the current studies demonstrate that DART-TOF-MS affords a useful approach for rapid screening of herbal products in the identification of synthetic cannabinoids. Although DART-TOF-MS lacks chromatographic compound separation, it can provide

evidence for structure modifications or typical fragments indicative of specific synthetic cannabinoid structural classes and substituents by generating accurate mass data and characteristic fragment ions. This conclusion is supported by differentiation of JWH-019 and JWH-122 through the presence of characteristic fragment ions, even though they both have the same exact mass. The reliability of these screening and confirmation techniques was further strengthened by the observation that m/z values for all protonated molecules were within 5 mDa of their calculated values for both DART-TOF-MS and LC-QTOF-MS analyses. DART-TOF-MS and LC-QTOF-MS methods show similar fragmentation patterns for synthetic cannabinoids detected in herbal products and reference standards. Both methods identified multiple synthetic cannabinoids in each of the confiscated herbal products, except for Sexy Exotic Herbal Potpourri, which contained only one. Furthermore, using a nontargeted LC-QTOF-MS during confirmatory analysis permits retrospective data mining for other compounds that may have been previously undetected in the herbal products. Use of a nontargeted method confirmed the presence of JWH-018 in the K2 Pink product, an unexpected finding based on DART-TOF-MS analysis further indicating that DART-TOF-MS is a complementary screening method to LC-QTOF-MS. These techniques were successfully able to identify eight synthetic cannabinoids in four different herbal products confiscated by law enforcement.

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FIG. 1—.

Chemical structures and monoisotopic exact masses of synthetic cannabinoids detected in the herbal products tested.

FIG. 2—
DART-TOF mass spectrum at 90 V for Aztec Potpourri (A) containing JWH-122 and AM2201 and mass spectrum at 90 V for K2 Pink (B) containing JWH-019.

FIG. 3—

DART-TOF mass spectrum at 90 V for Sexy Exotic Herbal Potpourri containing UR144 and mass spectrum at 60 V for Mad Hatter Cloud 9 containing 5F-AKB48, AKB48-N-(4-pentenyl) analog, UR144, and XLR11.

FIG. 4—

LC-QTOF high-energy mass spectra of synthetic cannabinoids in herbal products. AM2201 in Aztec Potpourri (A), JWH-122 in Aztec Potpourri (B), JWH-019 in K2 Pink (C), JWH-018 in K2 Pink (D), UR144 in Sexy Exotic Herbal Blend (E).

FIG. 5—

LC-QTOF high-energy mass spectra of synthetic cannabinoids identified in Mad Hatter Cloud 9. 5F-AKB48 (A), AKB48-N-(4-pentenyl) analog (B), UR144 (C), and XLR11 reference standard (D).

TABLE 1—

Synthetic cannabinoids confirmed in herbal products by LC-QTOF.

Type	Description	JWH-018	JWH-019	AM2201	JWH-122	5F-AKB48	AKB48-N-(4-pentenyl)*	UR144	XLR11
Aztec	Potpourri			X	X				
K2	Pink		X						
Sexy	Exotic Herbal Potpourri	X						X	
Mad Hatter	Cloud 9					X	X	X	X

* Not confirmed with reference standard.

TABLE 2—

Protonated molecule accurate mass, retention time and fragment ions of synthetic cannabinoids by LC-QTOF and DART-TOF.

Compound	Calculated [M+H] ⁺	Retention Time	Fragment Ions Observed in Standards on QTOF	Fragment Ions Observed in Samples on QTOF	Fragment Ions Observed in Standards on DART-TOF (90 V)
JWH-018	342.1852	15.21	127.0542, 144.0443, 155.0490, 214.1229, 342.1851, 364.1672	127.0549, 155.0501, 214.1252, 342.1857, 364.1722	103.0559, 144.0427, 145.0621, 155.0497, 214.1186, 284.1015, 324.1741, 342.1880
JWH-019	356.2009	16.70	127.0546, 144.0451, 155.0492, 228.1381, 356.2011, 378.1833	127.0553, 144.0456, 155.0497, 228.1391, 356.2007, 378.1832	103.0583, 127.0578, 144.0493, 145.0683, 155.0528, 167.0502, 200.1439, 228.1380, 284.1055, 338.1884, 356.2033
AM2201	360.1758	12.57	127.0548, 144.0448, 155.0494, 232.1133, 360.1756, 382.1577	127.0554, 144.0455, 155.0498, 232.1138, 360.1760, 382.1587	103.0519, 144.0498, 155.0471, 232.1120, 284.1104, 342.1685, 360.1761
JWH-122	356.2009	16.38	141.0703, 144.0447, 169.0645, 214.1228, 356.2006, 278.1830	141.0708, 144.0454, 169.0650, 214.1234, 325.2160, 356.2013, 378.1841	67.0574, 91.0560, 101.0608, 111.0462, 129.0552, 141.0695, 169.0616, 214.1187, 299.0566, 356.1947
5F-AKB48	384.2445	15.52	79.0544, 93.0702, 107.0855, 135.1176, 364.239, 384.2452, 406.2272	79.0544, 93.0702, 107.0858, 135.1177, 268.0764, 364.2385, 384.2448, 406.2270	N/A
AKB48N-(4-pentenyl)	364.2383	17.14	N/A	79.0549, 93.0702, 107.0866, 135.1179, 364.2383, 386.2213	N/A
URI44	312.2322	16.84	97.1010, 125.0963, 144.0446, 214.1229, 264.174, 279.1978, 294.2211, 312.2319, 334.2147	97.1013, 125.0966, 144.0450, 214.1230, 264.1750, 279.1987, 294.2220, 312.2322, 334.2139	97.1000, 125.0962, 144.0442, 214.1221, 279.1963, 294.2210, 312.2340
XLR11	330.2227	14.18	91.1010, 125.0962, 144.0447, 232.1139, 282.1653, 297.1890, 312.2124, 330.2228, 352.2045	N/A	97.0999, 125.0962, 144.0442, 232.1125, 274.1623, 297.1870, 312.2130, 330.2233

TABLE 3—

Average areas (%CV) for synthetic cannabinoids identified in 25 Mad Hatter samples and the five aliquots each from three packages.

	5F-AKB48	AKB48N- (4-pentenyl) analog	UR144	XLR11
Twenty five samples	122,691 (18)	2547 (21)	3899 (58)	502 (103)
Five aliquots from package 1	110,228 (12)	2375 (13)	730 (26)	122 (20)
Five aliquots from package 2	120,159 (11)	2421.20 (15)	2719 (26)	400 (92)
Five aliquots from package 3	111,708 (13)	2121.60 (21)	5576 (18)	371 (77)