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**PAPER**

**CRIMINALISTICS**

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# Identification of Synthetic Cannabinoids in Herbal Incense Blends in the United States

**ABSTRACT:** Synthetic cannabinoid agonists are chemically diverse with multiple analogs gaining popularity as drugs of abuse. We report on the use of thin layer chromatography, gas chromatography mass spectrometry, high-performance liquid chromatography, and liquid chromatography time of flight mass spectrometry for the identification and quantitation of these pharmacologically active chemicals in street drug dosage forms. Using these approaches, we have identified the synthetic cannabinoids JWH-018, JWH-019, JWH-073, JWH-081, JWH-200, JWH-210, JWH-250, CP47,497 (C=8) (cannabicyclohexanol), RCS-4, RCS-8, AM-2201, and AM-694 in various commercially available products. Other noncannabinoid drugs including mitragynine have also been detected. Typical concentrations of drug in the materials are in the range 5–20 mg/g, or 0.5–2% by weight for each compound, although many products contained more than one drug.

**KEYWORDS:** forensic science, synthetic cannabinoids, K2, spice, liquid chromatography time of flight mass spectrometry, LCMSMS, drug identification, JWH

An increasingly popular trend in the recreational drug community is the smoking of mixtures of herbal or incense products laced with one or more synthetic cannabinoid agonists, drugs with cannabinoid-like properties. The early history of the development of the drugs in this market is discussed in detail elsewhere (1). Synthetic cannabinoid agonists were synthesized in the 1990s in academic research centers and in the pharmaceutical industry as candidate investigational drugs and have in common an affinity for the cannabinoid $CB_1$ and/or $CB_2$ receptors. They are diverse in structure, although homologs of each distinct chemical type have been synthesized. Examples are shown in Fig. 1. One of these compounds HU-210 was scheduled by the U.S. Drug Enforcement Agency (DEA) in 2009 as a schedule I drug, having no recognized medical use (2,3). In November 2010, the DEA proposed adding JWH-018, JWH-073, JWH-200, CP-47,497 (C=7), and cannabicyclohexanol to schedule I, and this scheduling went into effect in March 2011 (4). Cannabicyclohexanol is the (C=8) homolog of CP47,497. Additionally, some states and municipal jurisdictions have moved to schedule the chemical compounds on a local level because of community concerns about their abuse, and the absence of any Federal control. This has created a patchwork of laws not completely addressed by the DEA's most recent action as local jurisdictions have scheduled some compounds not included in the DEA's current list. Links to state-by-state scheduling are updated regularly on the Wikipedia page on JWH-018 and others (http://en.wikipedia.org/wiki/JWH-018, accessed June 21, 2012). Shortly after the first states (Missouri and Kansas) took action to outlaw JWH-018 and JWH-073, the two most common constituents of these herbal products, new products appeared in the online "incense" marketplace including K3, K4, K20, and many others, discussed later. Although they are arguably analogs, these products were marketed as legal in those states that had banned those two chemicals. As we describe in this article, these new products have been shown to contain a variety of synthetic cannabinoids with similar receptor binding and presumably similar pharmacological effect.

Synthetic cannabinoid products for sale on the Internet go by a wide variety of names. Early in their availability, the most common blended material in the United States was called "K2" and was marketed as incense. The material was typically sold in a 2.5 × 2.5 inch metallic Mylar bag with a zip lock closure. The contents of the bag were typically 1–3 g of a mixture of dried and crushed plant material (flowers, stems, leaves) often with a perfumed, aromatic odor. In appearance and smell, they are similar to finely ground potpourri, mixed herbs. The material is sold as incense for burning, and drug-user websites indicate that the material should be smoked, in either cigarettes, joints, or pipes of the type used for marijuana smoking. Many of the materials are however labeled "not for human consumption." As popularity has increased, the products have become widely available from more diverse suppliers, in both online and physical stores, and a greater number of related product names appeared, for example, K2 Pink, K2 Strawberry, K2 Blueberry, K2 Sex, K2 Sex on the Mountain, K2 Blonde, K2 Ultra, K2 Citron, K2 Blue, and many others. A recent review of websites selling these products revealed product names including Space, Spike, Mr. Nice Guy Blend (MNGB), Banana Cream Nuke, p.e.p. pourri, Pep spice, Voo Doo Remix, C4, and K1, K3, K4 and K20, and more, discussed later.

This report describes the response of thin layer chromatography (TLC), gas chromatography mass spectrometry (GCMS), high-performance liquid chromatography (HPLC), and liquid chromatography time of flight mass spectrometry (LCTOF) assays in use in our laboratory in the analysis of constituent chemicals in a variety of "legal high" or "incense" and related products on the illicit drug market.

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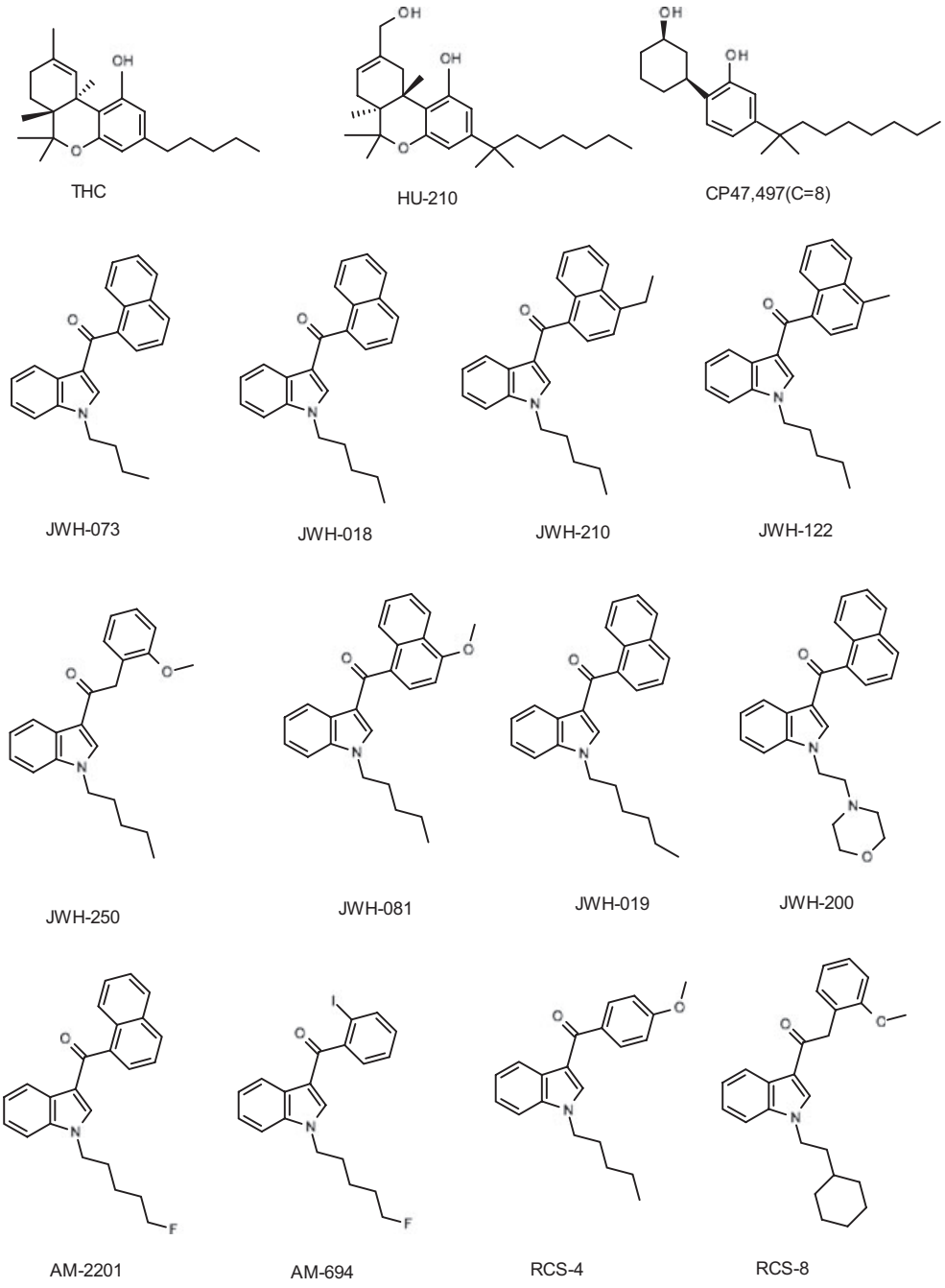


FIG. 1—*Structures of selected synthetic cannabinoid compounds identified in commercial incense products.*

## Methods

Several different blends of incense products were either purchased online from a variety of vendors or were submitted as evidence exhibits by investigators for law enforcement or private investigation agencies. Samples were screened using TLC and GCMS drug identification techniques as described below. Selected samples were additionally analyzed by HPLC and/or accurate mass LCTOF.

Authenticated reference standards of synthetic cannabinoids were obtained as follows: CP 47,497 (C = 7), JWH-018, JWH-133, WIN 55,212-3 (Tocris Bioscience, Ellisville, MO); CP 47,497 (C=8), CP 55,940, HU-210, HU-211, JWH-015, JWH-019, JWH-073, JWH-081, JWH-200, JWH-250, JWH-251, JWH-398, RCS-4, RCS-8, JWH-210, AM-2201 (Cayman Chemical, Ann Arbor, MI); JWH-018, WIN 55,212-2 (Sigma Aldrich, St. Louis, MO). The CP47,497 (C=8) homolog is also known as cannabicyclohexanol, and RCS-4 is referred to in some online forums as BTM-4.

### *Homogenization*

Initial assessments of purchased products were made on aliquots of botanical materials taken directly from the packages without any pretreatment. It became clear, however, during these assessments that there was a significant lack of homogeneity within individual packages. Subsequently, prior to quantitative assessments of drug content by HPLC, the contents of each packet were homogenized as follows: Approximately 500 mg of botanical material was placed on a 5 inch by 5 inch square piece of medium grade (grit#100) sandpaper and then rubbed between a second piece of 5 inch by

5 inch sandpaper until a fine powder was obtained. This process was repeated until the entire contents of the package were homogenized and then combined. Cuttings from each piece of sandpaper were removed prior to grinding and analyzed as a negative control. A second negative control consisting of dried *Damiana* leaves and flowers (Shamansgarden.com, Chicago IL) was prepared in the same manner to confirm that the sandpaper was free of any potential interference. This homogenization procedure is recommended for further work, or if quantitative analysis is to be performed.

### *Extractions*

As part of routine systematic analysis, methanolic extracts were prepared using 1 mL of methanol added to a glass test tube (12 × 75 mm) containing preweighed botanical material (*c.* 100 mg). Samples were thoroughly vortex-mixed.

Also as part of our routine systematic analysis, an acid/base extraction procedure was performed as follows: Approximately 100 mg of botanical material was weighed and transferred into a glass test tube. If extracts were being prepared for GCMS, 100 μL of internal standard (0.5 mg/mL methanolic solution of *N*-Propylamphetamine and 10,11-Dihydrodibenz (b,f)(1,4) oxazepin-11-one) was added to the material. De-ionized water (1 mL) was added to the tube, along with three drops of 10% HCl. One milliliter of extraction solvent (95% methylene chloride: 5% isopropyl alcohol) was added and thoroughly vortex-mixed. The bottom organic layer (containing acidic drugs) was transferred to a separate test tube and retained. Next, two drops of concentrated $NH_4OH$ and 1 mL of extraction solvent (95% methylene chloride: 5% isopropyl alcohol) were added to the tube and thoroughly vortex-mixed. The bottom organic layer (containing basic drugs) was removed and combined with the acidic fraction. The tube was thoroughly vortex-mixed, and the combined extract aliquoted for application to the TLC plate, or transferred to an automatic liquid sampler (ALS) vial, capped, and sealed for GCMS analysis.

### *Thin Layer Chromatography*

Methanolic extracts and combined acid/base extracts of samples were analyzed using two different solvent systems and nine different visualization techniques (Table 1). Fifty microliters of extract was applied to the TLC plate. Reference standards (1 mg/mL) of the target analytes was prepared in methanol and applied in a similar manner.

TLC was performed using premade Whatman Partisil® LK6DF TLC plates, Silica Gel 60 Å, layer thickness, 250 μm (Whatman, Piscataway, NJ). Results from suspected drug containing materials were compared to methanolic reference standards and acid/base extracts of those reference standards.

### *Gas Chromatography Mass Spectrometry*

The combined acid/base extract prepared as described above was analyzed directly, and following conversion to trimethylsilyl (TMS) derivatives. For derivatization, the combined acid/base extract was dried completely under a gentle stream of nitrogen at room temperature. Fifty microliters Selectra-Sil® BSTFA w/1% TMCS (United Chemical Technologies, Bristol, PA) was added to the tube, the tube capped, and then heated at 70°C for 30 min. After cooling, the reaction mixture was transferred to an ALS vial containing a 200-μL insert, capped, and sealed.

Underivatized sample extracts were analyzed by GCMS using an Agilent 6890 GC/5973 MSD with ALS (Agilent, Santa Clara, CA). Chromatography was performed on a J&W DB-1 Capillary Column, 12 m × 200 × 0.33 μm (Agilent). Injection volume was 1 μL, and injection mode was splitless with constant pressure. Gas chromatographic analysis used a temperature program starting at 50°C with a 30°/min ramp to a final temperature of 340°C with a final time of 2.00 min. Inlet temperature was 265°C. Transfer line temperature was 300°C. Helium was used as the carrier gas.

Derivatized samples were analyzed by GCMS using an Agilent 6890 GC/5973 MSD with ALS. Chromatography was performed on a J&W DB-1 Capillary Column, 12 m × 200 × 0.33 μm. Injection volume was 1 μL, and injection mode was splitless with constant flow. Analysis used a temperature program starting at 80°C with a 25°/min ramp to a final temperature of 340°C with final time 2.00 min. Inlet temperature was 265°C. Transfer line temperature was 300°C. Helium was used as the carrier gas.

A mass spectral database of both derivatized and underivatized products was created by analysis of the available reference materials. Mass spectra were compared to reference literature and/or established databases, when available (http://forendex.southernforensic.org/, accessed June 21, 2012), and molecular weight and formula were confirmed by LCTOF. The relative retention times (to two internal standards) of the compounds of interest were also generated and compared to those of known standards.

For quantitative analysis, approximately 0.05 g of botanical material was weighed accurately and diluted in 1 mL of MeOH. The methanolic extract was then diluted appropriately with MeOH to bring the expected concentration into the calibration range. Drug concentrations in the extracts were estimated using a four-point calibration curve. Two controls were run with each batch.

TABLE 1—*Thin layer chromatography (TLC) systems evaluated for responses from synthetic cannabinoids.*

| System | Solvent | Visualization |
|---|---|---|
| 1 | 9:1 Toluene:Diethylamine | 1. UV (254 nm)<br>2. 1.5 g Dianiside Tetrazotized in a 50:50 MeOH:DI water mixture |
| 2 | 18.5:18:3:1 Ethyl Acetate: Methylene Chloride:Methanol: Concentrated $NH_4OH$ | 1. UV (254 nm)<br>2. UV (366 nm)<br>3. 50 mg fluorescamine in 1000 mL acetone. Spray then view at 366 nm UV.<br>4. 0.5 g ninhydrin in 500 mL acetone. Spray then heat.<br>5. 10% sulfuric acid. Spray then view at 366 nm UV.<br>6. 5 g chlorplatanic acid hexahydrate and 35 g potassium iodide dissolved in 1650 mL of DI water then add 49.5 mL concentrated HCl.<br>7. 50% nitric acid. Spray then heat.<br>8. 20 g mercuric oxide dissolved in 900 mL DI water then add 80 mL concentrated $H_2SO_4$.<br>9. 10 g 4-dimethylaminobenzaldehyde dissolved in 900 mL reagent alcohol then add 100 mL concentrated HCl. Spray then heat. |

*High-Performance Liquid Chromatography*

Methanolic extracts were prepared as described above. For HPLC analysis, the extracts were diluted appropriately using a 50:50 Acetonitrile/Water mixture with 0.1% TFA to bring the expected concentration into the 10 μg/mL range.

Samples were analyzed by HPLC using an Agilent 1100 series HPLC with UV/Vis Diode-Array Detection (DAD). HPLC analysis was performed on a 4.6 × 100 mm, 5 μm Hypersil Keystone Aquasil C18 column (Thermo Fisher Scientific, Bellefonte, PA). Injection volume was 10 μL. The column was maintained at a temperature of 40°C with a 1.0 mL/min flow rate. An isocratic mobile phase of 70:30 ACN/water with 0.1% TFA was used. The DAD was set to monitor wavelength 316 nm.

Known reference standards were run in conjunction with samples to establish the retention time for the most frequently encountered analytes. UV spectral patterns of the known standards were compared to the unknown samples.

Drug concentrations were established using a four-point calibration curve for each drug of interest. Selected samples were first ground into a fine powder using the sand paper method described above, individually weighed, and then analyzed in triplicate, including a fourth replicate that was spiked with the drug(s) of interest to evaluate recovery. For quantitative analysis, approximately 30 mg of the ground botanical material was weighed and diluted in 1 mL of MeOH. The methanolic extract was then diluted appropriately with 50:50 ACN/water with 0.1% TFA to bring the expected concentration into the calibration range.

*Liquid Chromatography Time of Flight Mass Spectrometry*

Analysis for the detection of synthetic cannabinoids in botanical material was performed by accurate mass LCTOF. Two milliliters of methanol was added to a glass test tube contain preweighed botanical material (*c.* 100 mg). The sample was sonicated for 5 min. Fifty microliters of the methanolic extract was transferred to a glass test tube containing 10 mL of methanol and vortex-mixed. Fifty microliters of the above solution was transferred to an HPLC injection vial containing 1 mL of aqueous mobile phase. The vial was vortex-mixed, and 5 μL of reconstituted sample was injected into the

TABLE 2—*Thin layer chromatography (TLC) characteristics of available synthetic cannabinoid standards on system I and II.*

| TLC System 1 | Retention Factor | UV 254 nm Absorbance | Fast Blue B |
|---|---|---|---|
| AM-2201 | 0.75 | Yes | – |
| CP 47,497 (C=7) | 0.31 | Yes | Red with yellow edges |
| CP 47,497 (C=8) | 0.31 | Yes | Red with yellow edges |
| CP 55,940 | 0.14 | Yes | Red with yellow edges |
| HU-210 | 0.34 | Yes | Red |
| HU-211 | 0.34 | Yes | Red |
| JWH-015 | 0.73 | Yes | – |
| JWH-018 | 0.76 | Yes | – |
| JWH-019 | 0.76 | Yes | – |
| JWH-073 | 0.75 | Yes | – |
| JWH-081 | 0.71 | Yes | – |
| JWH-133 | 0.85 | Yes | – |
| JWH-200 | 0.60 | Yes | – |
| JWH-210 | 0.75 | Yes | – |
| JWH-250 | 0.74 | Yes | – |
| JWH-251 | 0.71 | Yes | – |
| JWH-398 | 0.71 | Yes | – |
| RCS-4 | 0.67 | Yes | – |
| RCS-8 | 0.70 | Yes | – |
| WIN 55,212-2 | 0.58 | Yes | – |
| WIN 55,212-3 | 0.58 | Yes | – |

| TLC System 2 | Retention Factor | UV 254 nm (Absorbance) | UV 366 nm (Fluorescence) | Fluorescamine (366 nm) | Ninhydrin (Heat) | 10% $H_2SO_4$ (366 nm) | Iodoplatinate | 50% $HNO_3$ (Heat) | Mercuric Sulfate | D-MAB (Heat) |
|---|---|---|---|---|---|---|---|---|---|---|
| AM-2201 | 0.82 | Yes | White | Yellow | – | Yellow | Green/yellow | Yellow | – | – |
| CP 47,497 (C=7) | 0.77 | Yes | – | – | – | – | White/pink | – | – | – |
| CP 47,497 (C=8) | 0.77 | Yes | – | – | – | – | White/pink | – | – | – |
| CP 55,940 | 0.52 | Yes | – | – | – | – | White/pink | – | – | – |
| HU-210 | 0.78 | Yes | – | – | – | – | White/pink | Yellow | Yellow | – |
| HU-211 | 0.78 | Yes | – | – | – | – | White/pink | Yellow | Yellow | – |
| JWH-015 | 0.91 | Yes | – | – | – | – | Green/yellow | Brown | – | – |
| JWH-018 | 0.91 | Yes | Yellow | – | – | Yellow | Green/yellow | Yellow | – | – |
| JWH-019 | 0.91 | Yes | Yellow | – | – | Yellow | Green/yellow | Yellow | – | – |
| JWH-073 | 0.91 | Yes | Yellow | – | – | Yellow | Green/yellow | Yellow | – | – |
| JWH-081 | 0.88 | Yes | Yellow | – | – | – | Green/yellow | – | – | – |
| JWH-133 | 0.94 | Yes | – | – | – | – | Green/yellow | – | – | – |
| JWH-200 | 0.85 | Yes | Yellow | – | – | Yellow | Purple | Orange | – | – |
| JWH-210 | 0.85 | Yes | – | – | – | – | Green/yellow | – | – | – |
| JWH-250 | 0.91 | Yes | – | – | – | – | Green/yellow | – | – | – |
| JWH-251 | 0.88 | Yes | – | – | – | – | Green/yellow | – | – | – |
| JWH-398 | 0.88 | Yes | Yellow | – | – | – | Green/yellow | – | – | – |
| RCS-4 | 0.87 | Yes | White | White | – | White | Yellow with purple edges | Orange | – | – |
| RCS-8 | 0.88 | Yes | – | – | – | – | Green/yellow | – | – | – |
| WIN 55,212-2 | 0.86 | Yes | Yellow | – | – | Yellow | Purple | Orange/brown | – | – |
| WIN 55,212-3 | 0.86 | Yes | Yellow | – | – | Yellow | Purple | Orange/brown | – | – |

LCTOF system. Analysis is performed on an Agilent 6230 TOF with an Agilent 1200 UPLC with binary pump, using a Zorbax Eclipse Plus C18, 100 × 3 mm, 1.8 micron HPLC column (Agilent, Palo Alto, CA). The mobile phase consisted of the binary mobile phase A: 0.05% formic acid/5 mM ammonium formate in water, with mobile phase B: 0.05% formic acid in methanol, at a flow rate of 0.7 mL/min. The gradient program had a total run time of 10 min. Scan range was from 50 to 1700 m/z at 2 GHz HiGain. The instrument was calibrated daily before sample analysis. Mass resolution and accuracy were measured each day of analysis. A database was compiled with authentic known standards of synthetic cannabinoids that were also used to identify the retention time and confirm the accurate mass of the target analyte.

## Results

### *Thin Layer Chromatography*

The response and retention factor ($R_f$) of the synthetic cannabinoid standards for both TLC solvent systems and their respective visualizations are shown in Table 2. No differences between the methanolic extracts and the acid/base extracts of the reference standards were observed. Each reference standard evaluated could be visualized by one or both of the solvent systems. CP 47,497 (C=7 and C=8), CP 55,940, HU-210, and HU-211 gave the characteristic red band, similar to that seen with tetrahydrocannabinol (THC), in system 1 with the Fast Blue B visualization spray. While all of the JWH, AM, RCS, and WIN compounds had observable absorbance bands under UV (254 nm), none were visualized upon spraying.

Utilization of TLC system 2 in combination with several different visualization techniques could serve as an identification method for each standard evaluated. The white/pink bands observed for CP 47,497 (C=7 and C=8), CP 55,940, HU-210, and HU-211 and the green/yellow bands observed for JWH-015, JWH-018, JWH-019, JWH-073, JWH-081, JWH-133, JWH-210, JWH-250, JWH-251, JWH-398, and RCS-8 with the iodoplatinate visualization spray were obscured by over-spraying and, thus, could be missed by the untrained eye. Low concentrations of these compounds may also be difficult to visualize by TLC. The purple bands of JWH-200 and WIN 55,212-(2 and 3) were quite clear even at low concentrations.

TABLE 3—*Popular name, chemical name, and chemical and analytical data for synthetic cannabinoid standards.*

| Reference Standard | Formal Name | Molecular Formula | Molecular Mass (g/mol) | Major GCMS Ions | LOD (μg/g) |
|---|---|---|---|---|---|
| AM-694 | 1-[(5-fluoropentyl)-1H-indol-3-yl]-(2-iodophenyl)methanone | $C_{20}H_{19}FINO$ | 435.04954 | 435, 232, 220, 360, 204, 144, 308, 415 | – |
| AM-2201 | 1-(5-fluoropentyl)-3-(1-naphthoyl)indole | $C_{24}H_{22}FNO$ | 359.16854 | 359, 342, 284, 232, 127, 270, 144, 155 | – |
| CP 47,497 (C=7) | 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol | $C_{21}H_{34}O_2$ | 318.25588 | 318, 215, 233, 300, 246, 161, 147, 187 | 9 |
| CP 47,497 (C=8) (Cannabicyclohexanol) | 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol | $C_{22}H_{36}O_2$ | 332.27153 | 332, 215, 233, 214, 161, 260, 147, 187 | 19 |
| CP 55,940 | 5-(1,1-dimethylheptyl)-2-[(1,2,5)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-phenol | $C_{24}H_{40}O_3$ | 376.29775 | 376, 273, 147, 121, 187, 304, 358, 213 | 47 |
| HU-210 | (6aR,10aR)-3-(1,1'-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol | $C_{25}H_{38}O_3$ | 386.29775 | 386, 302, 287, 316, 330, 344, 269, 241 | 20 |
| HU-211 | 3-(1,1-dimethylheptyl)-6aS,7,10,10aS-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol | $C_{25}H_{38}O_3$ | 386.29775 | 386, 302, 287, 316, 330, 344, 269, 241 | 20 |
| JWH-015 | (2-methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone | $C_{23}H_{21}NO$ | 327.16231 | 327, 310, 270, 200, 127, 155, 298, 284 | 19 |
| JWH-018 | (1-pentyl-1H-indol-3yl)-1-naphthalenylmethanone | $C_{24}H_{23}NO$ | 341.17796 | 341, 284, 324, 214, 270, 127, 241, 144 | 20 |
| JWH-019 | (1-hexyl-1H-indol-3-yl)-1-naphthalenylmethanone | $C_{25}H_{25}NO$ | 355.19361 | 355, 284, 338, 228, 127, 270, 155, 144 | 19 |
| JWH-073 | (1-butyl-1H-indol-3-yl)-1-naphthalenylmethanone | $C_{23}H_{21}NO$ | 327.16231 | 327, 284, 310, 200, 270, 127, 241, 254 | 18 |
| JWH-081 | 4-methoxynaphthalen-1-yl-(1-pentylindol-3-yl)methanone | $C_{25}H_{25}NO_2$ | 371.18853 | 371, 354, 314, 214, 185, 300, 197, 144 | 15 |
| JWH-133 | (6aR,10aR)-3-(1,1-dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran | $C_{22}H_{32}O$ | 312.24532 | 312, 269, 270, 229, 201, 185, 159, 297 | 20 |
| JWH-200 | [1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]-1-naphthalenylmethanone | $C_{25}H_{24}N_2O_2$ | 384.18378 | 384, 100, 127, 155 | 47 |
| JWH-210 | 4-ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone | $C_{26}H_{27}NO$ | 369.20926 | 369, 352, 312, 214, 340, 144, 254, 195 | – |
| JWH-250 | 2-(2-methoxyphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone | $C_{22}H_{25}NO_2$ | 335.18853 | 335, 214, 144, 116 | 19 |
| JWH-251 | 2-(2-methylphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone | $C_{22}H_{25}NO$ | 319.19361 | 214, 144, 319, 215 | 15 |
| JWH-398 | 1-pentyl-3-(4-chloro-1-naphthoyl)indole | $C_{24}H_{22}ClNO$ | 375.13899 | 375, 214, 318, 358, 304, 144, 189, 161 | 15 |
| RCS-4 | (4-methoxyphenyl)(1-pentyl-1H-indol-3-yl)methanone | $C_{21}H_{23}NO_2$ | 321.17288 | 321, 264, 135, 214, 144, 186, 222 | – |
| RCS-8 | 1-(1-(2-cyclohexylethyl)-1H-indol-3-yl)-2-(2-methoxyphenyl)ethanone | $C_{25}H_{29}NO_2$ | 375.21983 | 375, 254, 144, 255 | – |
| WIN 55,212-2 | (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo(1,2,3-de)-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone | $C_{27}H_{26}N_2O_3$ | 426.19434 | 426, 100, 326, 127, 155 | 118 |
| WIN 55,212-3 | [(3*S*)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone | $C_{27}H_{26}N_2O_3$ | 426.19434 | 426, 100, 326, 127, 155 | 115 |

LOD, limit of detection.

RCS-4 was easily identified and separated from the other standards by its unique yellow band with purple edges. As many of the standards give the same responses ($R_f$ and color) with multiple visualization techniques, differentiation based on TLC was not always possible and complementary analytical techniques are necessary.

### *Gas Chromatography Mass Spectrometry*

All available reference standards tested were identifiable by GCMS. Each gave a unique mass spectrum and retention time with the exception of the HU-210/HU-211 and the WIN 55,212-2/3 stereoisomeric pairs, which were indistinguishable. A limit of detection was determined for each authenticated reference standard (Table 3).

Figure 2 shows the total ion chromatogram for a standard mix of all of the reference standards evaluated, including THC. The mass spectra of the standards are reproduced in Fig. 3.

HU-210/211 and CP 47,497 (C=7 and C=8) contain two active hydrogen sites, and CP 55,940 contains three active hydrogen sites that allow for derivatization using BSTFA. Using 100% BSTFA, the derivatized standards resulted predominately in a single product. Figure 4 shows the mass spectra of the main product for each analyte that underwent derivatization, forming TMS derivatives. The JWH series and WIN 55,212 compounds did not derivatize using BSTFA. Lower limits of detection were possible when the compounds were derivatized owing to enhanced chromatographic behavior. As this procedure concentrates the extracted sample by a factor of 20, detection limits using the derivatization procedure were improved, even for compounds that did not derivatize.

### *High-Performance Liquid Chromatography*

Figure 5 shows the HPLC chromatogram of the analytes that could be detected and quantitated by HPLC with UV/Vis DAD. For quantitative analysis, the calibration range was 2–20 μg/mL, and linear regression analysis yielded R squared values >0.9999 for each analyte. Controls were prepared independently from a secondary source and analyzed, at a minimum, in the beginning and end of each quantitative batch. All controls quantitated within 10% of the target concentration. HPLC was the preferred method for quantitative analysis over GCMS. CP 47,497 (C=7 and C=8), CP 55,940, HU-210/211, and JWH-133 were not detected using the established HPLC system parameters, but could be quantified by GCMS. Quantitative measurement of the synthetic cannabinoid content of the various materials is shown in Table 4.

### *Liquid Chromatography Time of Flight Mass Spectrometry*

LCTOF was used as a useful adjunct to the other techniques, to assist in identifying compounds for which standards were not preliminarily available. LCTOF has inherent advantages over traditional mass spectral analyzers in that it has the increased resolving power to accurately measure exact masses (accurate to within 5 ppm) as compared to low-mass-resolution analyzers, which are accurate to parts-per-thousand at best. The second advantage is that data can be collected as full-scan data with no loss in sensitivity. Finally, as LCTOF data are accurate to ppm levels, it can provide the molecular formulae for unknown compounds based on their accurate mass and distinguish between compounds having the same nominal molecular weight but different molecular formulae. The established accurate mass and associated molecular formulae are listed in Table 3.

### *Identification of Synthetic Cannabinoids and Other Drugs in Commercial Products*

A total of 82 botanical incenses, capsules, powders, and liquid products were analyzed using the techniques described above, and the analytical characteristics of the synthetic cannabinoid standards are listed in Table 4. Commercial incense materials were either purchased over the Internet or submitted in the course of investigations by law enforcement, investigative, or public safety agencies. For forensic purposes, positive results were reported only if the analyte was identified and confirmed by two independent analytical techniques (e.g., TLC and GCMS or HPLC and GCMS; http://www.swgdrug.org/, accessed June 21, 2012). The compounds identified in the materials were JWH-018,

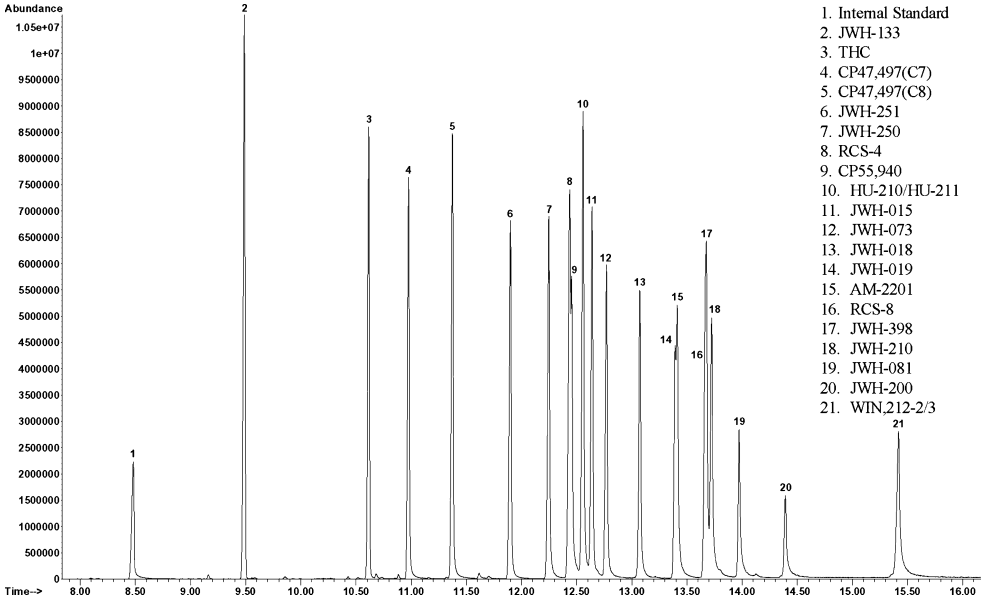


FIG. 2—*GCMS total ion chromatogram of the synthetic cannabinoids included in the scope of testing.*

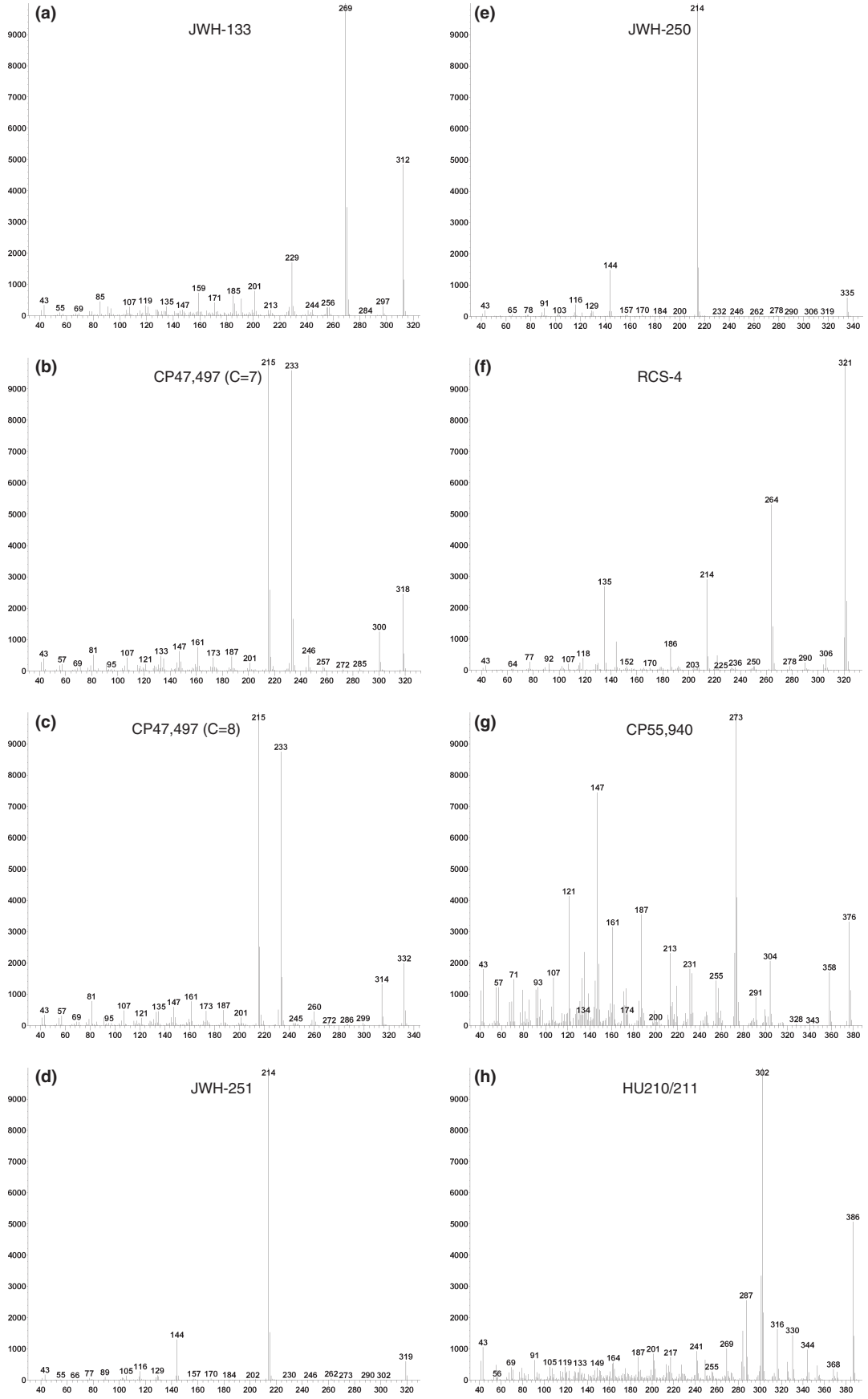


FIG. 3—*Mass spectra of synthetic cannabinoid compounds included in the scope of analysis. (a) JWH-133, (b) CP47,497 (C=7), (c) CP47,497 (C=8), (d) JWH-251, (e) JWH-250, (f) RCS-4, (g) CP55,940, (h) HU210/211, (i) JWH-015, (j) JWH-073, (k) JWH-018, (l) JWH-019, (m) AM-2201, (n) RCS-8, (o) JWH-398, (p) JWH-210, (q) JWH-081, (r) JWH-200, and (s) WIN 55,212-2/3.*

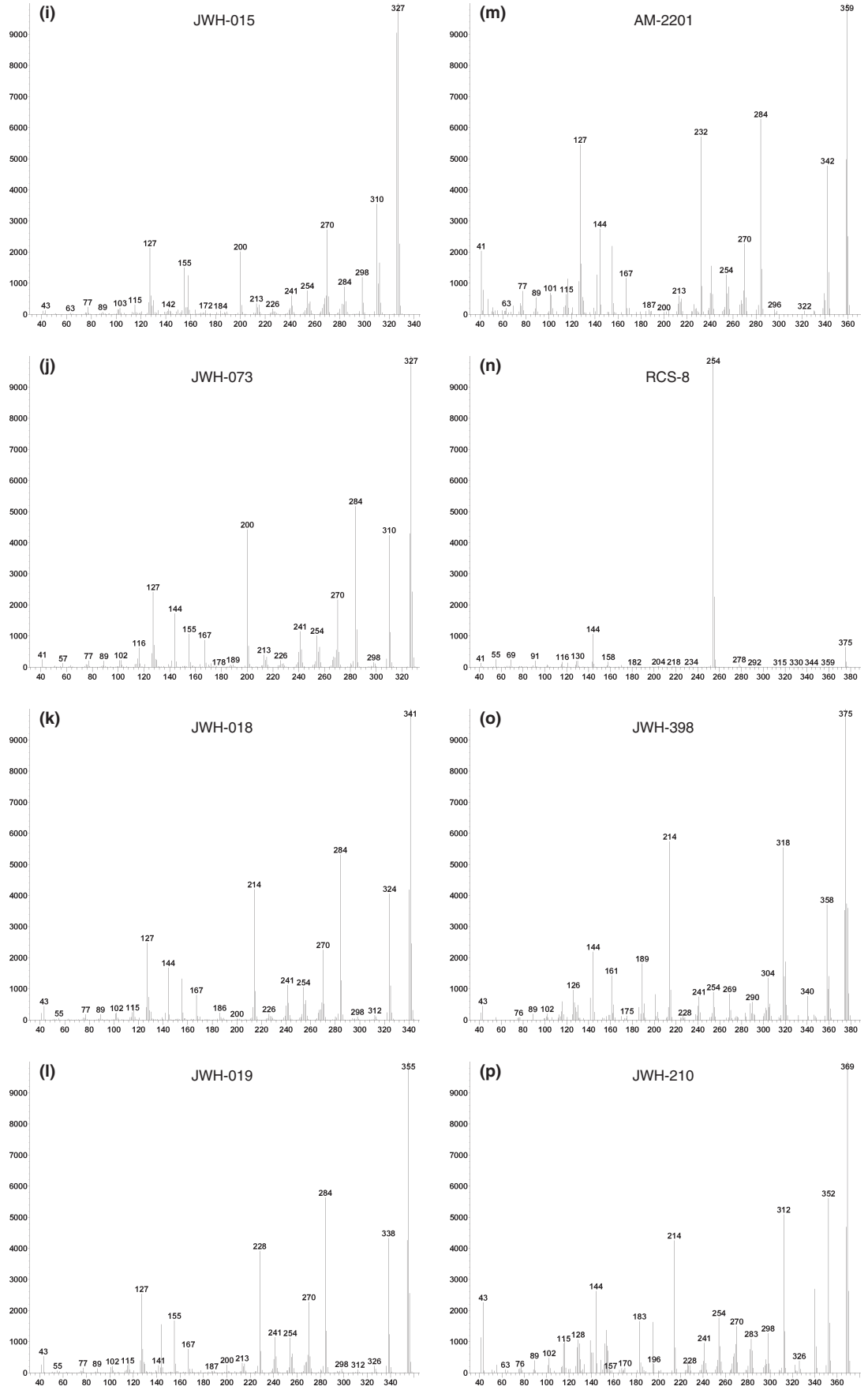


FIG. 3—*Continued.*

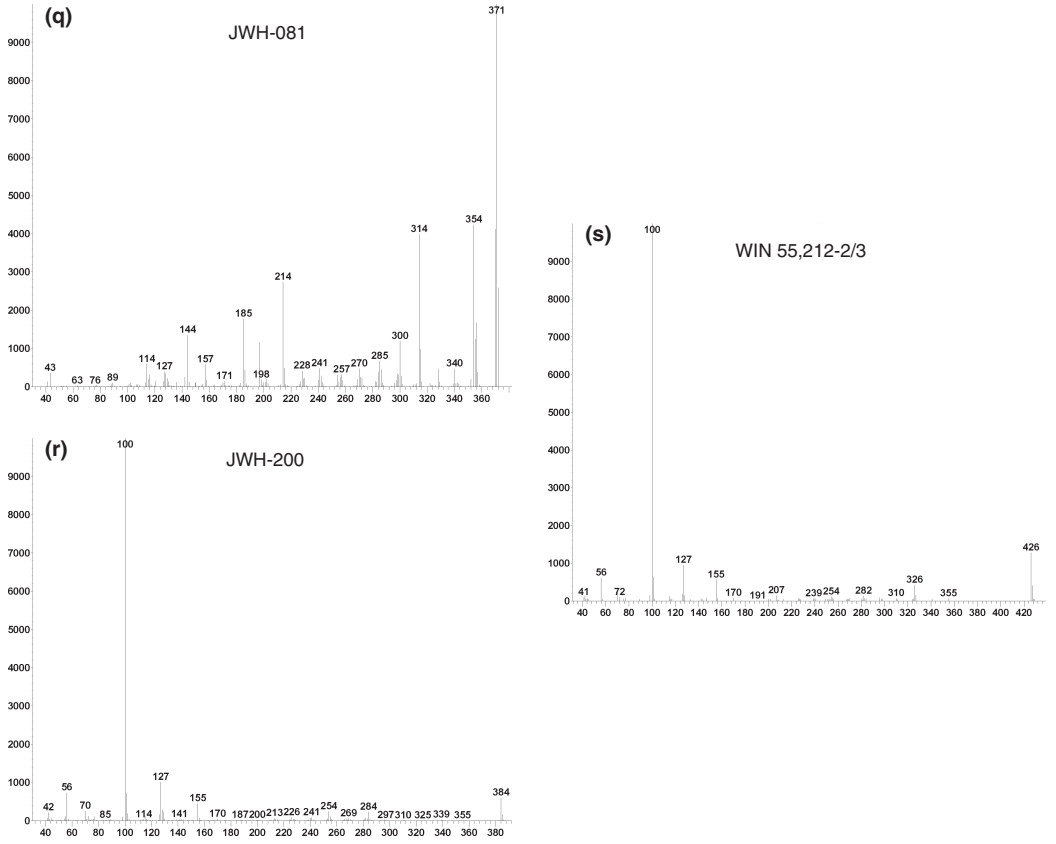


FIG. 3—*Continued.*

JWH-019, JWH-073, JWH-081, JWH-200, JWH-210, JWH-250, CP47,497 (C=8) (cannabicyclohexanol), RCS-4, RCS-8, AM-2201, and AM-694. When identifications were made by accurate mass LCTOF only, the data are included in Table 4 as indicated, but were not reported forensically. Initial quantitative estimates were made of the active constituents using GCMS, while the final determinations on the ground materials were made by HPLC.

Quantitation was not attempted on residues of <500 mg in the packet and in some cases where the investigating agency requested identification only. In Table 4, "Positive" without a number indicates that the agency did not request quantitation or insufficient volume was available for quantitation.

Some products purchased were advertised as being "legal everywhere" or legal in specific states that have controlled JWH-018 and JWH-073. While most of these products contained only JWH-250, at least three did contain trace levels of JWH-018. Other analytes identified included JWH-200, JWH-019, RCS-4, AM-2201, AM-694, and mitragynine (a psychoactive noncannabinoid). There was no indication on the package or labeling that mitragynine was included.

As discussed, the products lacked homogeneity, and significant variability existed between aliquots taken from the same packages. In some instances, aliquots taken from the same package were negative, while others were positive for active drug. Materials with the same name acquired from different vendors in some cases contained different drugs, for example, K2 Pink purchased from an Internet vendor on July 8, 2010, contained only JWH-018, while K2 Pink purchased from a different vendor on July 21, 2010, contained both JWH-018 and JWH-073.

Based on preliminary triplicate measurements of unhomogenized material, 53% of the samples quantitated by GCMS had a CV of <10%, 33% had a CV of between 11 and 20%, and 14% had a CV of over 20%, leading to the conclusion that the material lacked homogeneity. Consequently, homogenization is highly recommended when attempting to estimate drug concentration, but also for qualitative purposes as some aliquots taken from the same packet contained no detectable drug.

HPLC was used for the final quantification of the drug content of the materials. Prior to analysis, the samples were homogenized using the sandpaper technique described above, to produce a fine powder. This led to greatly improved reproducibility, with 76% of the replicate measurements having CV's of <10% and 96% having CV's of <20%. Qualitative and quantitative results from analysis of selected products are listed in Table 4. Quantitative results reported are from the analysis of homogenized botanical material using HPLC, except where noted. Concentrations were typically in the range 5–20 mg/g, or 1–2% by weight.

## Discussion

Identification of active cannabinoid agonists in these so-called legal highs or herbal products represents a major challenge to forensic chemists and toxicologists, as demonstrated by the rapidly changing list of drugs present in the products, and the dynamic scheduling of new compounds that occurs in response. When this project was begun, the principal drugs detected in the materials were the same as those reported earlier in Europe. Auwärter et al. (5), had described the chemical identity of the active components of material sold as "Spice" in Germany in 2008. They identified

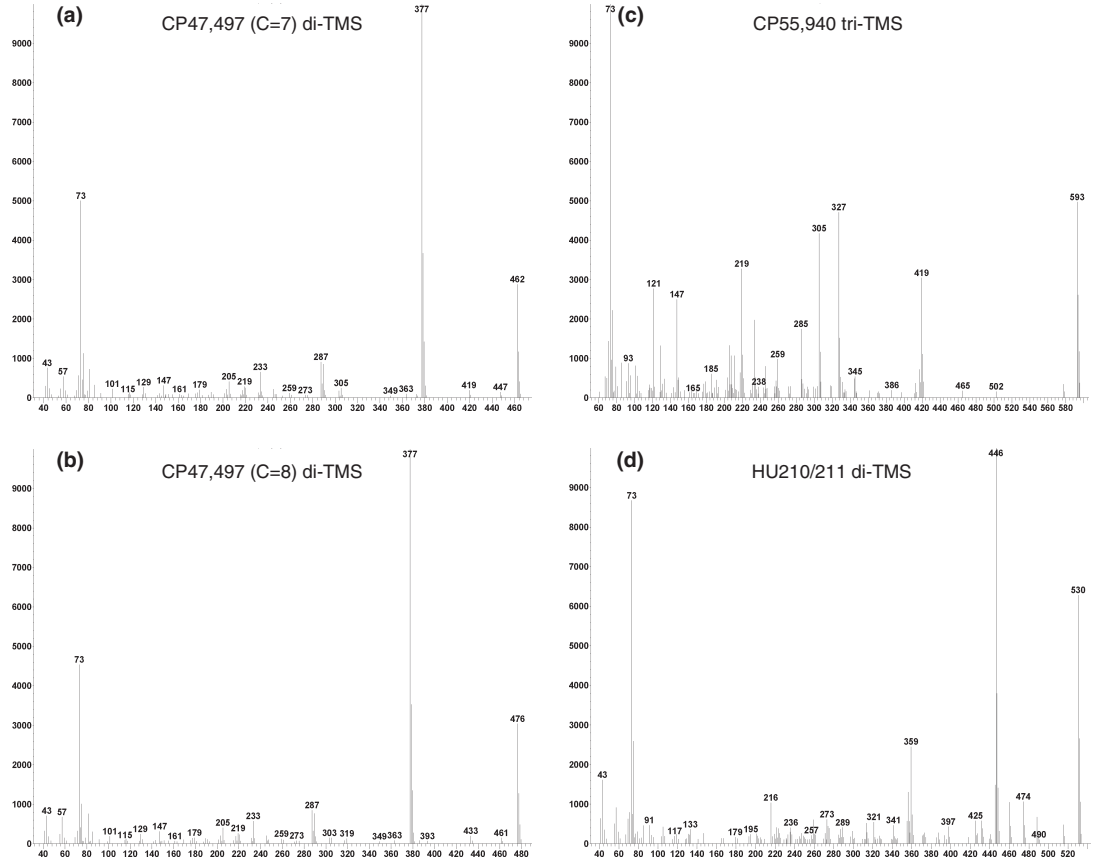


FIG. 4—*TMS mass spectra of synthetic cannabinoid compounds included in the scope of analysis that undergo trimethylsilylation. (a) CP47,497 (C=7) di-TMS, (b) CP47,497 (C=8) di-TMS, (c) CP55,940 tri-TMS, and (d) HU210/211 di-TMS.*

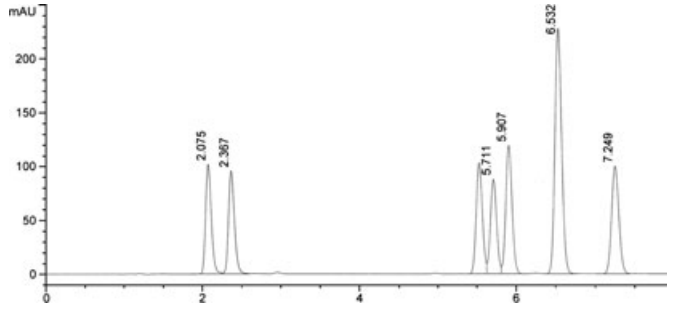


FIG. 5—*High-performance liquid chromatogram of selected synthetic cannabinoid standards.*

JWH-018 and CP47,497 (C=7 and C=8 homologs) in these materials using TLC, GCMS, liquid chromatography tandem mass spectrometry (LCMSMS), nuclear magnetic resonance (NMR), and LCTOF. Lindigkeit et al. (6) in 2009 first reported identification of JWH-073 in commercial smokeable materials. These two compounds have remained the most frequently detected in these herbal blends until recently as reflected in our findings in Table 4. Later in 2010, Uchiyama et al. (7) reported on the contents of materials contained in similar products on sale in Japan, confirming JWH-018, JWH-073, and CP47,497 (C=8) (now also called cannabicyclohexanol) to be the active components in 46 different products. Hudson et al. (8) reported on the analysis of synthetic cannabinoids in ''Spice''-related products in the United Kingdom, using high mass accuracy LCTOF; however, this technique on its own fails to distinguish between molecular or optical isomers, so for example JWH-007, JWH-019, JWH-047, and JWH-122 cannot be distinguished, all having the same molecular formula ($C_{25}H_{25}NO$) and weight 356.2009 amu. Further identifying information from LCMSMS suggested the presence of the new compounds, JWH-398, JWH-007 or JWH-019, JWH-049 or JWH-182 or JWH-213, and JWH-081. Most recently Dresen et al. (9) reported on the analysis of the drug content of 140 different incense products and additionally reported the presence of JWH-250, in these products. Other noncannabinoid drugs were also reported including myrsiticin, hamin/harmaline, cannabidiol, and O-desmethyltramadol.

In the materials we analyzed, various other components were also identified including, alpha and beta amyrin, vanillin, eucalyptol, marrubiin, alpha-tocopherol, and limonene. The general trend from mainstream JWH compounds (JWH-018, and JWH-073) to more obscure compounds (JWH-019, JWH-250, JWH-200, and JWH-210), and the first reported appearance of RCS-4, RCS-8, AM-2201, and AM-694, suggests a very dynamic illicit drug synthesizing industry, with the ability to rapidly change products based on changes in the legal environment. Many potential modifications to these structures are possible, and the relative change in receptor binding, potency, and toxicity is not being established before the drugs are released to the recreational market.

The names of products sold appeared to be unrelated to their contents, and the labeling was misleading. Some materials advertised as legal in specific states did contain compounds specifically scheduled in these states.

A series of K2 products were found to contain no identifiable synthetic cannabinoids, but did contain mitragynine, a natural

TABLE 4—*Identification of synthetic cannabinoids and other drugs in commercial herbal incense products.*

| Product | Purchased/ Received from: | Date of Purchase/ Submission | Matrix | JWH-018 (mg/g) | JWH-073 (mg/g) | JWH-250 (mg/g) | Other |
|---|---|---|---|---|---|---|---|
| K2 Blonde | Missouri | 3/1/10 | Botanical | 12* | 13* | –[†] | JWH-200[‡] |
| K2 Standard | Missouri | 3/10/10 | Botanical | 9* | 9* | – | – |
| K2 Citron | Missouri | 3/30/10 | Botanical | 10* | 10* | – | – |
| K2 (unknown variety) | Missouri | 3/30/10 | Botanical | Positive[‡] | Positive[‡] | – | CP 47,497 (C=8) (6 mg/g)* |
| K2 Summit | Missouri | 6/17/10 | Botanical | 11* | 9* | – | – |
| Space | Pennsylvania | 3/20/10 | Botanical | 10 | Positive[‡] | – | JWH-200[‡] |
| K2 Blue | Internet Vendor | 7/8/10 | Ground Botanical | 20 | – | – | – |
| K2 Pink | Internet Vendor | 7/8/10 | Ground Botanical | Positive | – | – | – |
| K2 Latte | Internet Vendor | 7/8/10 | Ground Botanical | 11 | Positive | 7.5 | – |
| K2 Mint | Internet Vendor | 7/8/10 | Ground Botanical | 22 | 0.04 | – | – |
| K2 Silver | Internet Vendor | 7/8/10 | Ground Botanical | 5.9 | – | 14 | – |
| K2 Peach | Internet Vendor | 7/21/10 | Ground Botanical | 4.7 | – | – | – |
| Spike Gold | Internet Vendor | 7/8/10 | Ground Botanical | 25 | 10 | – | – |
| Spike Maxx | Internet Vendor | 7/8/10 | Ground Botanical | 21 | – | 18 | – |
| Spike Diamond | Internet Vendor | 7/8/10 | Ground Botanical | 49 | 0.03 | – | – |
| Spike Silver | Internet Vendor | 7/8/10 | Ground Botanical | 10 | 21 | – | – |
| K2 Strawberry | Internet Vendor | 7/21/10 | Ground Botanical | 3.7 | – | – | – |
| K2 Pineapple Express | Internet Vendor | 7/21/10 | Ground Botanical | 5.4 | – | – | – |
| K2 Blueberry | Internet Vendor | 7/21/10 | Ground Botanical | 5.5 | – | – | – |
| K2 Pink | Internet Vendor | 7/21/10 | Ground Botanical | 13 | 15 | – | – |
| K2 Blonde | Internet Vendor | 7/21/10 | Ground Botanical | 15 | 16 | – | – |
| K2 Summit | Internet Vendor | 7/21/10 | Ground Botanical | 18 | 19 | – | – |
| K2 Citron | Internet Vendor | 7/21/10 | Ground Botanical | 10 | 12 | – | – |
| K2 Ultra | Internet Vendor | 7/21/10 | Ground Botanical | Positive | Positive | – | – |
| K2 Blue | North Carolina | 7/20/10 | Ground Botanical | Positive | – | – | – |
| MNGB Tropical Thunder | Pennsylvania | 8/6/10 | Botanical | Positive | – | – | – |
| MNGB Pinata Colada | Pennsylvania | 8/6/10 | Botanical | Positive | – | – | – |
| MNGB Almond/Vanilla | Pennsylvania | 8/6/10 | Botanical | Positive | – | – | – |
| MNGB Peppermint | Pennsylvania | 8/6/10 | Botanical | Positive | – | – | – |
| MNGB Spear Mint | Pennsylvania | 8/6/10 | Botanical | Positive | – | – | – |
| p.e.p. pourri Twisted Vanilla | Internet Vendor | 8/19/10 | Ground Botanical | 10 | 7.7 | – | – |
| p.e.p. pourri Original Spearmint | Internet Vendor | 8/19/10 | Ground Botanical | 17 | – | – | – |
| p.e.p. pourri Love Strawberry | Internet Vendor | 8/19/10 | Ground Botanical | 20 | 0.18 | – | – |
| p.e.p. pourri X Blueberry | Internet Vendor | 8/19/10 | Ground Botanical | 21 | – | – | – |
| K2 Summit | Pennsylvania | 9/21/10 | Botanical | Positive | – | – | – |
| Voo Doo Remix (orange pack) | Pennsylvania | 9/21/10 | Botanical Residue | Positive | Positive[‡] | – | – |
| Voo Doo Remix (black pack) | Pennsylvania | 9/21/10 | Botanical Residue | Positive[‡] | – | - | – |
| Banana Cream Nuke | California | 9/21/10 | Botanical Residue | Positive | Positive | – | – |
| K4 Silver | Internet Vendor | 9/22/10 | Ground Botanical | – | – | 62 | – |
| K4 Gold | Internet Vendor | 9/22/10 | Ground Botanical | – | – | 65 | – |
| K3 Heaven Improved | Internet Vendor | 9/22/10 | Ground Botanical | 16 | – | – | – |
| K3 Heaven Legal | Internet Vendor | 9/22/10 | Ground Botanical | 0.21 | – | 14 | – |
| K3 Sun Improved | Internet Vendor | 9/22/10 | Ground Botanical | 17 | 2.4 | – | – |
| K3 Sun Legal | Internet Vendor | 9/22/10 | Ground Botanical | Positive | – | 14 | – |
| K3 Kryptonite | Internet Vendor | 9/22/10 | Ground Botanical | 20 | – | – | – |
| K3 XXX | Internet Vendor | 9/22/10 | Ground Botanical | 6.0 | 3.5 | 3.3 | – |
| K3 Cosmic Blend | Internet Vendor | 9/22/10 | Ground Botanical | 15 | – | – | – |
| K3 Original | Internet Vendor | 9/22/10 | Ground Botanical | 10 | – | – | – |
| C4 | Internet Vendor | 9/29/10 | Ground Botanical | Positive[‡] | | 23 | – |
| K1 Gravity | Internet Vendor | 9/29/10 | Ground Botanical | Positive[‡] | Positive[‡] | – | – |
| K1 Orbit | Internet Vendor | 9/29/10 | Ground Botanical | 2.1 | 0.12 | – | – |
| K2 Pina Colada | Internet Vendor | 9/29/10 | Ground Botanical | 1.4 | 0.19 | – | – |
| K3 Kryptonite | Internet Vendor | 9/29/10 | Ground Botanical | 17 | Positive[‡] | Positive[‡] | – |
| K3 XXX | Internet Vendor | 9/29/10 | Ground Botanical | Positive[‡] | – | 10 | – |
| K3 Cosmic Blend | Internet Vendor | 9/29/10 | Ground Botanical | 15 | Positive[‡] | Positive[‡] | – |
| K3 Original | Internet Vendor | 9/29/10 | Ground Botanical | 15 | Positive[‡] | – | – |
| Rasta Citrus Spice | Washington, DC | 9/14/10 | Ground Botanical | 16 | 16 | – | – |
| Kind Spice | Washington, DC | 9/14/10 | Ground Botanical | 33 | 13 | – | – |
| Time Warp | Washington, DC | 9/14/10 | Ground Botanical | 18 | 26 | – | – |
| Rasta Citrus Spice | Internet Vendor | 9/17/10 | Ground Botanical | 15 | 16 | – | – |
| Pink Tiger | Internet Vendor | 9/17/10 | Ground Botanical | 23 | 25 | – | – |
| Humboldt Gold | Internet Vendor | 9/17/10 | Ground Botanical | 18 | 20 | – | – |
| K2 Orisha Regular | Internet Vendor | 9/20/10 | Powder | – | – | – | Mitragynine |
| K2 Orisha Max | Internet Vendor | 9/20/10 | Powder | – | – | – | Mitragynine |
| K2 Orisha Super | Internet Vendor | 9/20/10 | Powder | – | – | – | Mitragynine |
| K2 Amazonian Shelter | Internet Vendor | 9/20/10 | Liquid | – | – | – | Mitragynine |
| K2 Solid Sex on the Mountain | Internet Vendor | 10/11/10 | Solid (rock-like) | – | – | – | Mitragynine |
| Midnight Chill | Louisiana | 10/25/10 | Botanical | Positive | – | – | – |
| Unknown Cigarette | Louisiana | 10/25/10 | Botanical | Positive | Positive | – | – |

*Continued.*

TABLE 4—*Continued.*

| Product | Purchased/ Received from: | Date of Purchase/ Submission | Matrix | JWH-018 (mg/g) | JWH-073 (mg/g) | JWH-250 (mg/g) | Other |
|---|---|---|---|---|---|---|---|
| Freedom | Missouri | 11/8/10 | Botanical | – | – | – | RCS-4 |
| K2 Sex | Internet Vendor | 11/9/10 | Botanical | Positive | Positive | Positive | – |
| K2 Orisha White Magic Super | Internet Vendor | 11/10/10 | Powder | – | – | – | Mitragynine |
| K2 Orisha Black Magic Max | Internet Vendor | 11/10/10 | Powder | – | – | – | Mitragynine |
| K2 Thai Dream | Internet Vendor | 11/10/10 | Capsule | – | – | – | Mitragynine |
| K4 Bubble Bubble | Tennessee | 11/12/10 | Botanical | Positive | – | – | JWH-210<br>AM-2201 |
| MTN-787 | Internet Vendor | 11/24/10 | Powder | Positive | – | – | JWH-210<br>RCS-4<br>AM-694 |
| K2 Kryptonite | Missouri | 11/26/10 | Botanical | Positive | – | – | |
| Legal Eagle Apple Pie | Internet Vendor | 11/30/10 | Botanical | Positive | Positive | Positive | JWH-019<br>JWH-081<br>RCS-8 |
| K4 Purple Haze | Internet Vendor | 11/30/10 | Botanical | Positive | – | Positive | JWH-019<br>JWH-081<br>RCS-8 |
| K420 Summit Remix | Internet Vendor | 11/30/10 | Botanical | – | – | Positive | JWH-081 |
| 8-Ball | Internet Vendor | 11/30/10 | Botanical | – | – | Positive | JWH-081 |
| C4 | Internet Vendor | 11/30/10 | Botanical | – | – | Positive | – |

*Quantitative analysis by GCMS on unhomogenized botanical material.
†Indicates not detected.
‡Identification by LCTOF only.

product present in Kratom (Mitragyna speciosa), a medicinal plant from Southeast Asia (10). Mitragynine has been shown to have both adrenergic and opioid-like activity and has resulted in significant adverse effects (11). It is not currently regulated in the United States.

We cannot exclude the possibility that some of the more potent cannabinoid agonists such as HU-210 may be present in these products below our limits of detection. Extracts prepared to measure other synthetic cannabinoid compounds such as JWH-018 and JWH-073 at their typical concentrations may be too dilute to detect the presence of pharmacologically significant high-potency drugs. Preparation of more concentrated extracts, or routine use of derivatization, may be warranted, especially in cases where no active drug is initially found.

The concentration of the active compounds in the incense products we analyzed was highly variable, as the manufacturing method is not well controlled. Anecdotally, the preparation process consists of spraying an acetone solution of the chemicals onto plant material with manual mixing in a mixing bowl. The mean data were consistent with published preparation methods posted on the various Internet websites that serve as forums for drug users. The recipes usually call for the addition of 1 g of active ingredient to 50 g of leaf material for a final concentration of 20 mg per gram of substrate. Homogenization of the material by grinding with sandpaper was found to be an effective approach for homogenizing the contents of individual packages and was shown to be free from interference. Good forensic practice would include the use of appropriate sandpaper controls in any forensic determinations.

## Conclusions

Traditional analytical techniques for drug chemistry casework have been validated for identification of the diverse synthetic cannabinoids compounds contained in many commercially available incense and designer drug products including botanicals, powders, liquids, and capsules. Given the variety of different formulations, general drug screening mass spectral databases should be regularly updated to include these chemicals. Some materials analyzed contained no identifiable drug, and the possibility of high-potency and low-dose novel compounds, as well as counterfeit drug-free material, must be considered in these samples when encountered in forensic casework. The lack of homogeneity in the packaged material makes it important to homogenize plant or botanical material before aliquoting for analysis. The sandpaper technique we used proved to be highly effective. Newly available analytical techniques such as high mass accuracy LCTOF have proven to be very useful for identifying novel compounds for which analytical characteristics have not been previously reported, and which may not be included in mass spectral databases. In most products, there were either one or two major components, and in many cases evidence of trace amounts of other drugs, possibly resulting either from the manufacturing process of the synthetic cannabinoid itself or from the contamination from previous batches during the commercial preparation of the herbal product.

Finally, it appears that even before the November 2010 DEA scheduling of five synthetic cannabinoids, that more recently purchased products were more likely to contain previously unreported synthetic cannabinoids. These compounds are not included in any of Federal or local statutory scheduled substances lists. This drug market is extremely dynamic with new compounds being substituted for existing ones as legislation attempts to restrict their distribution and use. As there is no governance of this ad hoc drug discovery process, the naming conventions for newly synthesized compounds is likely to be confusing and inconsistent.

*Acknowledgments*

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