

PAPER**CRIMINALISTICS**

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DART-MS as a Preliminary Screening Method for “Herbal Incense”: Chemical Analysis of Synthetic Cannabinoids*

ABSTRACT: Direct analysis in real time mass spectrometry (DART-MS) served as a method for rapid high-throughput screening of six commercially available “Spice” products, detecting various combinations of five synthetic cannabinoids. Direct analysis in real time is an ambient ionization process that, along with high mass accuracy time-of-flight (TOF)-MS to 0.0001 Da, was employed to establish the presence of cannabinoids. Mass spectra were acquired by simply suspending a small portion of sample between the ion source and the mass spectrometer inlet. The ability to test minute amounts of sample is a major advantage when very limited amounts of evidentiary material are available. In addition, reports are widespread regarding the testing backlogs that now exist because of the large influx of designer drugs. This method circumvents time-consuming sample extraction, derivatization, chromatographic, and other sample preparative steps required for analysis by more conventional mass spectrometric methods. Accordingly, the synthetic cannabinoids AM-2201, JWH-122, JWH-203, JWH-210, and RCS-4 were identified in commercially available herbal Spice products, singly and in tandem, at concentrations within the range of 4–141 mg/g of material. Direct analysis in real time mass spectrometry decreases the time necessary to triage analytical evidence, and therefore, it has the potential to contribute to backlog reduction and more timely criminal prosecution.

KEYWORDS: forensic science, direct analysis in real time, mass spectrometry, cannabinoids, designer drugs

The ingestion of “herbal incense” and “Spice” mixtures comprised of plant material laced with synthetic cannabinoids, such as “K2” and “Super Nova”, has become increasingly problematic since their emergence in the United States in late 2008 (1–3). Although labeled as “Not for Human Consumption”, these mixtures are marketed as a legal alternative to marijuana, smoked in a fashion similar to cannabis, and have catchy names such as Happy Hour, Mr. Sticky, and Relaxinol (4–6). The synthetic cannabinoid compounds in these mixtures bind to cannabinoid receptors in the brain with affinities similar to or greatly exceeding that of cannabis (2,5,7–9). Serious medical conditions associated with ingestion of these substances, including anxiety, tachycardia, and myocardial infarction, have led to an increase in calls to poison control centers and emergency room incidences (5,10,11).

Following restriction by Asian and European authorities (1,5, 12–14), the U.S. Drug Enforcement Agency (DEA) as of March 2011, exercised its emergency scheduling authority to control JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol (5,14,15). In response to the growing use of these synthetic cannabinoids, U.S. regulatory agencies have classified numerous chemical compounds as controlled substances under the Synthetic

Drug Abuse Prevention Act of 2012 (16). Although these compounds are now controlled, suppliers have directed their efforts toward synthesis of structurally similar molecules in their attempts to circumvent regulations. These new compounds have slightly modified chemical frameworks and emerged on the market soon after the first generation of substances was banned (1,3,5,6). It appears that the new compounds are chosen based upon their cannabinoid receptor binding affinities as well as their ability to evade detection via routine drug screens (4,17). Importantly, even though much effort is being directed toward designer drug analysis, a number of factors have contributed to large backlogs in testing (18–25). Many crime laboratories do not have the expertise to identify these substances, as their analysis requires new methods and procedures to be developed and validated. The problem is particularly challenging because of the close structural similarities that exist between the hundreds of known cannabinoids. In addition, when detection and identification of the active components is possible, the vagaries associated with prosecuting those who manufacture and distribute cannabinoid analogs further contribute to the backlogs. Thus, synthetic cannabinoid cases are often given lower priority in favor of conventional drug casework such as felony controlled-substance arrests going to trial. Added delays in receiving test results means that police agencies have difficulty with the prosecution of designer drugs casework. If enforcement organizations cannot prove that the seized drugs are illegal in a timely fashion, their ability to charge the individuals involved is jeopardized.

To date, most of the cannabinoid compounds with which herbal incense products are laced belong to the aminoalkylindole family and include AM-2201, JWH-200, JWH-210, and JWH-122. However, cannabinoids from other chemical families including

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naphthylmethylindoles (e.g., JWH-175), naphthoylpyrroles (e.g., JWH-030), and phenylacetylindoles (e.g., JWH-250), among many others, have also been identified in these products (2,6,26). These substances are small molecule drugs with a series of core structural scaffolds, but conventional preliminary tests like immunoassays are not common or necessarily effective in identifying the wide range of analogs. Accordingly, these substances are more commonly tested via GC- and LC-MS, which yield reliable, accurate results, but employ extraction protocols and sample preparation steps that are time- and labor-intensive. The utility of these methods is compromised by the time and effort required to get results, such that they contribute to testing backlogs when high-throughput capabilities are required to keep pace in real time with the growing need to monitor the supply and distribution of designer drugs. Direct analysis in real time mass spectrometry (DART-MS) is an attractive alternative to standard mass spectrometry methods that entails ambient ionization of solid material directly without chromatography or extraction (27–29). DART analysis is instantaneous, and when coupled to a high mass accuracy time-of-flight (TOF)-mass spectrometer has demonstrated utility in analysis of controlled substances (30–34). The technique has proven its utility for analysis of synthetic cannabinoids, particularly in a confirmatory manner when collision-induced dissociation (CID) fragmentation conditions are employed (35,36). Herein, DART-MS served as an efficient, highly accurate, rapid preliminary screening method for synthetic cannabinoids within complex matrices associated with herbal incense products. The technique enabled instantaneous determination of the presence of cannabinoids without the need to perform laborious extractions, sample preparations, or derivatizations. The high mass accuracy allows formula weight determinations to be compared with substances compiled within the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG; www.swgdrug.org) library. The use of DART-MS as a high-throughput preliminary identification tool would enable the large influx of samples tested by crime laboratories to be triaged, reducing sample testing backlogs, providing insight into whether additional testing is even warranted, and providing insight into what other appropriate confirmation tests might be performed to satisfy prosecutorial needs. Direct analysis in real time mass spectrometry employed in this fashion could revolutionize drug analysis screening methodology by serving as a means to manage the rapid production, sale, and abuse of synthetic cannabinoids and other designer drugs.

Shortly after the time of DEA scheduling of five synthetic cannabinoids in 2011, six unregulated Spice products were purchased from vendors in the cities of Albany and Syracuse (NY). The samples were analyzed by DART-MS, and the resulting spectra were compared to those from a library of synthetic cannabinoid standards. Five different cannabinoids were identified singly and in combination, including AM-2201, JWH-210, JWH-122, JWH-203, and RCS-4. To further confirm compound identities, Spice samples were extracted, analyzed by GC-MS, quantitated, and matched against the SWGDRUG library.

Experimental

Materials

Synthetic cannabinoid standards, oleamide, and 13-docosenamide were purchased from Cayman Chemical (Ann Arbor, MI). Herbal "Spice" samples containing synthetic cannabinoids were purchased at multiple retailers in NY, U.S.A., between January and March 2012.

DART Ionization of Synthetic Cannabinoids

Direct analysis in real-time experiments were conducted using a JEOL AccuTOF-DART-MS (JEOL USA, Inc., Peabody, MA), configured with a DART-SVP™ ion source (Ionsense, Saugus, MA). Single leaf segments from the botanical/herbal materials were sampled directly by holding each with tweezers between the DART ion source and the mass spectrometer inlet. Extraction or sample preparation was not required for sampling the synthetic cannabinoids by this method. Standards were solubilized in methanol at a concentration of 1.0 mg/mL, and DART-MS was performed by dipping the closed end of a melting point capillary tube into the solution and positioning it briefly between the ion source and the mass spectrometer inlet.

DART-MS Parameters

A DART-AccuTOF mass spectrometer operating in positive ion mode was employed for all mass measurements. The resolving power of the spectrometer was 6000 (FWHM definition) measured for protonated reserpine. A mass spectrum of polyethylene glycol (average molecular weight 600) was generated with each data set as a reference standard for exact mass measurements. The atmospheric pressure interface was typically operated at the following potentials: orifice 1 = 15 V; orifice 2 = 5 V; ring lens = 3 V. The RF ion guide voltage was generally set to 800 V to allow detection of ions greater than m/z 80. The DART ion source was operated with helium gas at 400°C, and a grid voltage = 530. TSSPro3 software (Shrader Analytical, Detroit, MI) was used for data processing and interpretation. The DART ion source was operated with helium gas (Airgas, Cambridge, MA) at 400°C, with a flow rate of 2 L/min and a grid voltage of 530.

Extraction of Herbal Mixtures

The commercially available herbal incense samples were subjected to Soxhlet extraction with methanol. The products and the weights of each plant material sample that were subjected to extraction were as follows: Happy Hour Cherry Bomb (0.5552 g); California Kronik-Blueberry (2.3882 g); Dead Man Walking (2.1286 g); Mr. Sticky Extreme (0.7205 g); Relaxinol (0.5004 g); and Mr. Nice Guy-Strawberry (0.5011 g). Soxhlet extractions were performed in 150 mL methanol in cycles of 15 turns each. Subsequently, a 10 mL sample of each solution was evaporated to dryness and then reconstituted in 200 μ L of methanol for GC-MS analysis.

GC-MS Parameters

An HP 6890 Series gas chromatograph equipped with an HP-5 30 \times 0.25 mm \times 0.25 μ L analytical column and helium as a carrier gas (1.0 mL/min; constant flow mode) was employed. The temperature was held at 130°C for 2 min, ramped at 12°C/min to 330°C, and then held for 7 min. The GC was coupled to an HP 5972A selective mass detector in electron ionization (EI) mode at 70 eV. The transfer line was set at 285°C. The acquisition range was m/z 30–600.

Quantitation

Two separate calibration curves were developed for the synthetic cannabinoids AM-2201 and JWH-210 in methanol, using lidocaine as an internal standard. Chromatogram (GC-MS) peak

area ratios were plotted, based on the relative peak intensities of the active component to the internal standard across a range of concentrations, to determine linear correlation. From these graphs, the amount of each cannabinoid, in mg/g sample, was determined.

Results and Discussion

Three of the herbal Spice products containing synthetic cannabinoids are shown in Fig. 1, including the products “Mr. Nice Guy-Strawberry”, “Relaxinol”, and “Mr. Sticky”. Table 1 shows the entire list of herbal products tested and the synthetic cannabinoids detected in each. Also listed are the calculated and observed masses, which illustrate the high mass accuracy of the TOF-MS. The herbal products were contained in eye-catching packaging and labeled with various statements including: “not for human consumption”, “100% legal blend”, and “not FDA approved”. Also outlined on the packaging were a series of synthetic cannabinoid and cathinone substances that were listed as *not* present as ingredients. The packaged amount of herbal material ranged from 1 to 5 g and varied in odor and the appearance of the dried leaves/botanical material. Plant material from each package was tested via DART-MS to determine the presence of synthetic cannabinoids. Because of the sample heterogeneity,

multiple tests were performed on different leaves from each of the herbal Spice products. In each case, three to five samples were analyzed, including samples of differing morphology (e.g., leaves and stems), and in each case, all tested positive and proved identical to the various synthetic cannabinoid standards (data not shown).

The structures of the five synthetic cannabinoids are shown in Fig. 2. Figure 3a–f shows the mass spectra obtained from DART-MS analysis of the Spice products (the details of which are described in Table 1). The cannabinoid spectra were dominated by protonated ion peaks (i.e., $[M + H]^+$). The high mass accuracy of the technique allowed a candidate formula weight of each substance to be determined. In five of the six samples tested, multiple cannabinoids were identified. Additionally, in every sample tested, the herbal matrix contributed minimal spectral complexity and did not interfere with peaks associated with the synthetic cannabinoids. Standards of the synthetic cannabinoids were also run for comparison and confirmation (Fig. 4a–e; Table 2). However, many synthetic cannabinoids are known to have multiple structural isomers, and so in some cases, only a tentative identification or group classification was possible. For example, analysis of the “Mr. Nice Guy-Strawberry” gave two major parent ion peaks at m/z 360.1745 and 356.1997. The first of these is related to an unprotonated formula weight of $C_{24}H_{22}FNO$, which is associated with AM-2201 or a structural analog. The second parent ion peak at m/z 356.1997 was determined to correspond to an unprotonated formula weight of $C_{25}H_{25}NO$. However, definitive identification of which isomer this compound might represent was more problematic as multiple synthetic cannabinoids are known to have this formula weight, including JWH-122, JWH-007, and JWH-180. While the US has a Federal Analog Act as a section of its Controlled Substances Act which allows a chemical similar to a controlled substance to also be considered as scheduled, oftentimes exact identification of the specific analog is still desirable.

Accordingly, each of the herbal materials was subjected to a Soxhlet extraction with methanol for GC-MS comparison to a SWGDRUG library containing synthetic cannabinoids. Aliquots of the extract were concentrated via solvent evaporation and analyzed by GC-MS (GC-MS data are available upon request). Matches were made against the library resulting in the identifications listed in Table 1. Interestingly, within the chromatograms of the cannabinoid extracts, traces of multiple other substances were detected in both DART-MS and GC-MS spectra. Specifically, two other chemical substances of concern were observed, namely oleamide and 13-docosenamide, both of which were found in Relaxinol, Mr. Sticky Extreme, and Mr. Nice Guy-Strawberry.



FIG. 1—The packaging of three of the herbal Spice products testing positive for the presence of synthetic cannabinoids. Each product contained nonhomogenous plant material doped with active compounds.

TABLE 1—Synthetic cannabinoids identified by direct analysis in real time mass spectrometry in herbal “Spice” products. Measured masses ($[M+H]^+$), and calculated masses are listed.

| “Spice” Product Analyzed | AM-2201 | JWH-122 | JWH-203 | JWH-210 | RCS-4 | Calculated | Difference |
|-----------------------------|----------|----------|----------|----------|----------|------------|------------|
| Happy Hour Cherry Bomb | 360.1757 | | | | | 360.1764 | 0.0007 |
| California Kronik-Blueberry | 360.1765 | | | | | 360.1764 | 0.0001 |
| Mr. Sticky Extreme | | | 340.1466 | 370.2167 | | 370.2170 | 0.0003 |
| | | | | | 322.1778 | 340.1468 | 0.0002 |
| | | | | | | 322.1807 | 0.0029 |
| Relaxinol | 360.1780 | | | | | 360.1764 | 0.0016 |
| | | | | 370.2179 | | 370.2170 | 0.0009 |
| Mr. Nice Guy-Strawberry | 360.1745 | | | | | 360.1764 | 0.0019 |
| | | 356.1997 | | | | 356.2014 | 0.0017 |
| Dead Man Walking | 360.1746 | | | | | 360.1764 | 0.0018 |
| | | | | 370.2150 | | 370.2170 | 0.0020 |

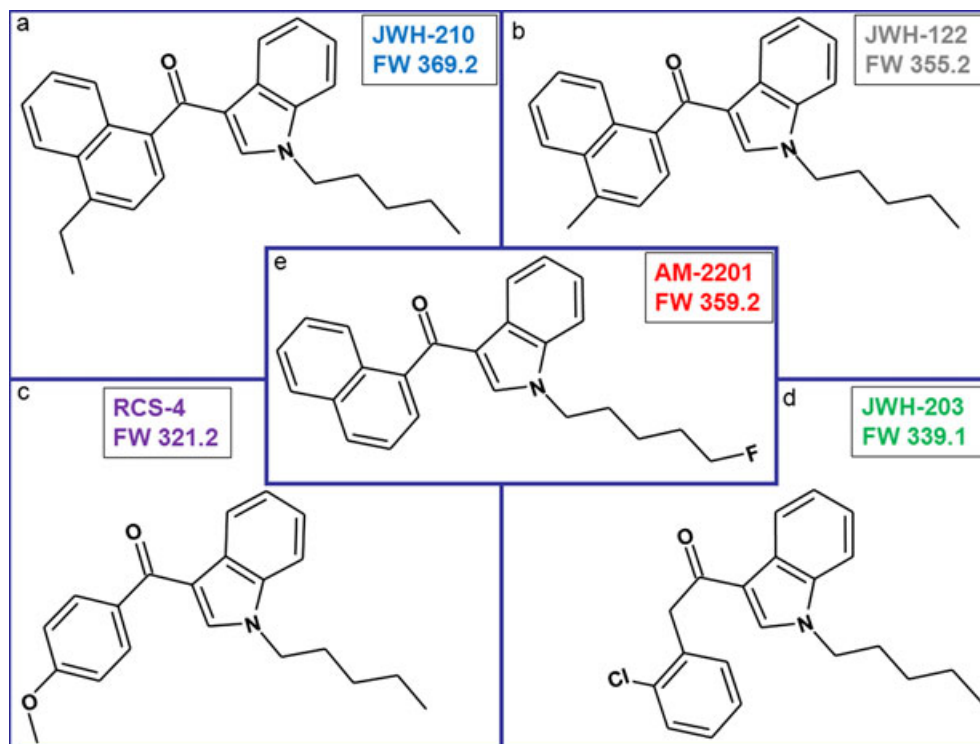


FIG. 2—Structures of the five synthetic cannabinoids identified in the herbal Spice products. Panel a: JWH-210; Panel b: JWH-122; Panel c: RCS-4; Panel d: JWH-203; Panel e: AM-2201.

TABLE 2—The high mass accuracy direct analysis in real time mass spectrometry data of synthetic cannabinoid standards. Measured masses ($[M+H]^+$), and calculated masses are listed.

| Standard | AM-2201 | JWH-122 | JWH-203 | JWH-210 | RCS-4 | Calculated | Difference |
|----------|----------|----------|----------|----------|----------|------------|------------|
| AM-2201 | 360.1769 | — | — | — | — | 360.1764 | 0.0005 |
| JWH-122 | — | 356.2012 | — | — | — | 356.2014 | 0.0002 |
| JWH-203 | — | — | 342.1473 | — | — | 340.1468 | 0.0005 |
| JWH-210 | — | — | — | 370.2157 | — | 370.2170 | 0.0013 |
| RCS-4 | — | — | — | — | 322.1787 | 322.1807 | 0.0020 |

Oleamide is an endogenous cannabinoid agonist and has been previously identified as a component of herbal Spice products (5,12). The 13-docosamide is a structural analog of oleamide and to the best of our knowledge has not yet been reported as a dopant in synthetic cannabinoid products. However, both substances are common components of plastics and polymers and are known to leach out of packaging materials. Therefore, the origin of these compounds cannot be confirmed.

Contributing to the negative health effects associated with ingestion of combinations of synthetic cannabinoids is the wide range of binding affinities associated with the different agonists. However, this problem is further compounded because the concentrations of agonists vary significantly from product to product (13). We observed in quantitation studies of AM-2201 that these compounds ranged in amounts from 26 mg/g in Happy Hour Cherry Bomb to 142 mg/g in Relaxinol (GC-MS quantitation data are available upon request). However, the concentration of JWH-210 ranged from 4 mg/g in California Kronic to 38 mg/g in Relaxinol. The variability between Spice products of active component concentrations (*c.* 5.5-fold in the case of AM-2201 and *c.* 10-fold in the case of JWH-210) is illustrative of this problem. The concentrations observed are on par with what has been reported in other quantitation studies (3,12,13,37). As performed herein, qualitative studies with DART-MS required

identification of individual components of mixtures through the high mass accuracy associated with the m/z ratios. In principle, the diversity of sample dopants and the observed significant differences in their concentrations could complicate DART-MS analyses due to ion suppression effects. However, in our analyses, we did not encounter evidence of ion suppression. In every case, the cannabinoids were the dominant species in the spectra and the plant background contributed minimally. Furthermore, in the California Kronic sample, both AM-2201 and JWH-210 were readily detected, even though AM-2201 was present at a concentration *c.* 14× greater than JWH-210. As such, DART-MS appears to be an ideal technique for high-throughput screening of synthetic cannabinoids.

Direct analysis in real time mass spectrometry was employed as a rapid preliminary screening tool, in an attempt to provide tentative and/or presumptive information that can be the basis for more directed confirmatory analyses. The SWGDRUG defines mass spectrometric methods as a Category A analytical technique on par with nuclear magnetic resonance and infrared analyses. However, the soft ionization of DART-MS alone does not provide fragmentation of the analytes, but as high-resolution TOF-MS was employed here for rapid identification of synthetic cannabinoids, precise molecular weight analysis could, in theory, supplant the need for the conventional

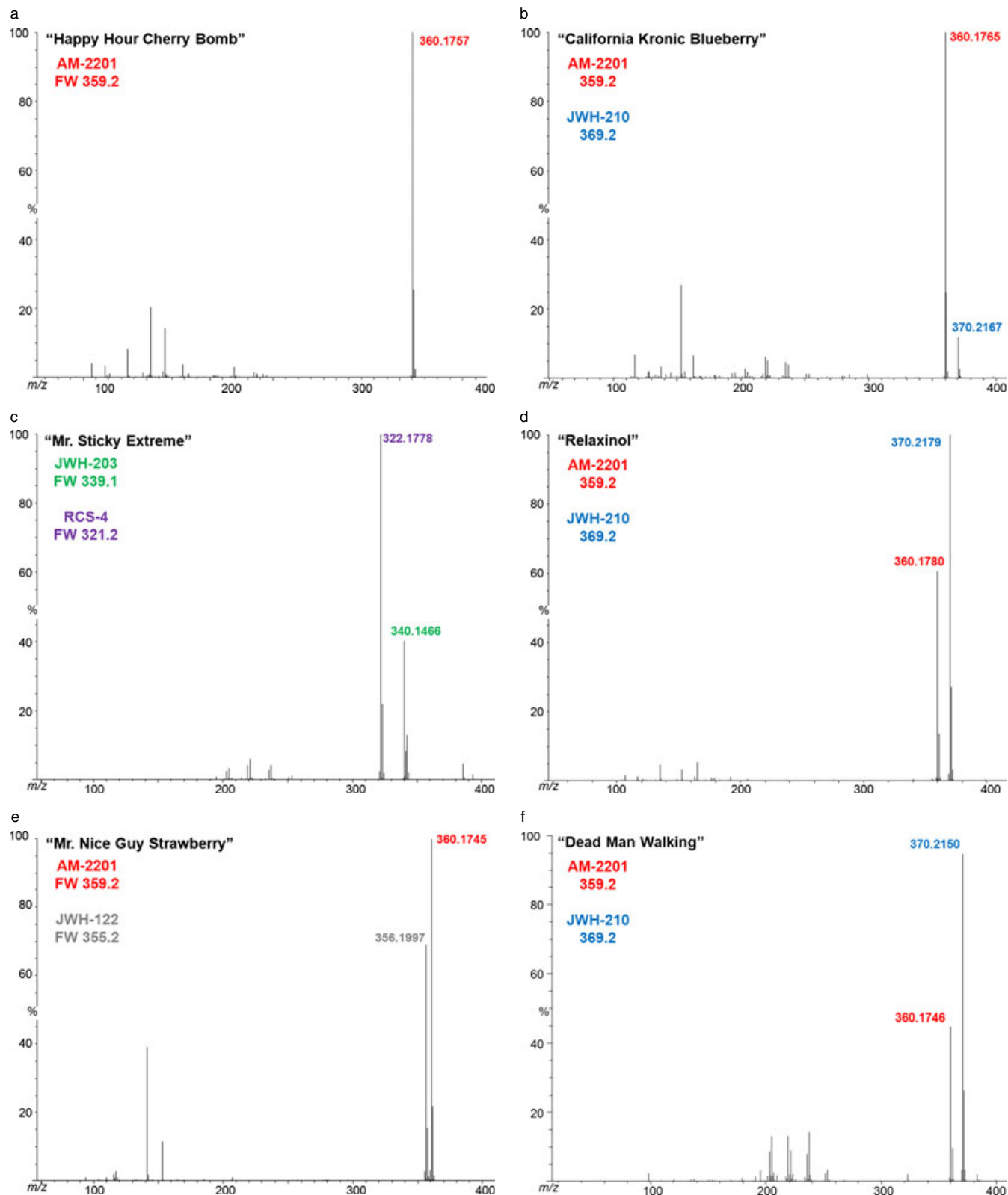


FIG. 3—Direct analysis in real time mass spectra of six different herbal Spice products containing various combinations of five synthetic cannabinoids. Their names and identified compound monoisotopic formula weights are listed within each spectrum. Measured masses of each $[M+H]^+$ ion peak are color-coded to match the names of the cannabinoids and are summarized in Table 1.

hyphenated techniques which employ chromatography. Indeed, DART-MS (CID) experiments have demonstrated utility in inducing molecular fragmentation analogous to that observed

in tandem mass spectrometry (30,31,38) and our group has applied DART-MS CID to the analysis of these synthetic cannabinoids to also provide more detailed structural information

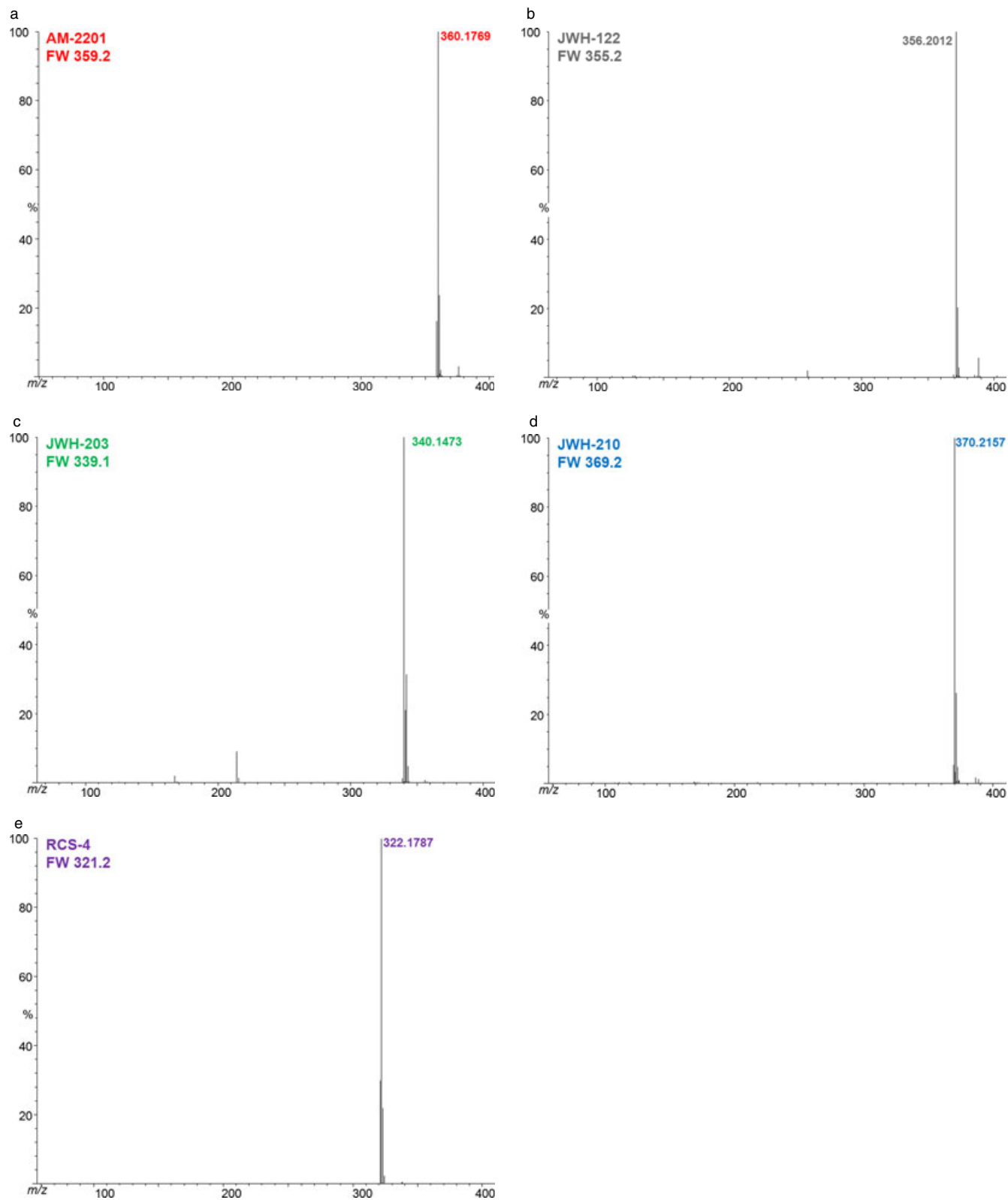


FIG. 4—Direct analysis in real time mass spectra of five synthetic cannabinoid standards. Their names and their monoisotopic formula weights are listed within each spectrum. Measured masses of the $[M+H]^+$ ion peak of each of the cannabinoid standards are summarized in Table 2.

and/or confirmatory analyses (36). Regardless, it is demonstrated here that DART-AccuTOF analyses can serve as an efficient preliminary screening technique by providing a chemi-

cal formula based on high mass accuracy measurements, drastically narrowing the range of active ingredients potentially present.

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