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Direct analysis in real time mass spectrometry with collision-induced dissociation for structural analysis of synthetic cannabinoids

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RATIONALE: The emergence of numerous cannabinoid designer drugs has been tied to large spikes in emergency room visits and overdoses. Identifying these substances is difficult for the following reasons: (1) the compounds are novel, closely structurally related, and do not usually test positive in drug screens; (2) novel analogs rapidly appear on the market; (3) no standard protocols exist for their identification; and (4) customized and extensive sample preparation/extraction and analysis procedures are required to demonstrate their presence.

METHODS: Direct analysis in real time mass spectrometry (DART-MS) employing collision-induced dissociation (CID) provided confirmatory structural information that was useful in characterizing the various cannabinoid analogs, including those contained in mixtures. CID analysis illustrated that, although closely related compounds fragment in a similar fashion, their structural differences still resulted in multiple diagnostic peaks that provided additional confidence towards structural identification.

RESULTS: DART-MS spectra were acquired under CID conditions to rapidly differentiate among five synthetic cannabinoids contained within 'herbal' products purchased locally in New York State (USA). The spectra exhibited $[M+H]^+$ ions and product ions unique to each cannabinoid that corresponded to major structural features. Five different cannabinoid analogs, alone and as mixtures of at least two cannabinoids, were identified in six herbal products and differentiated by their CID product ion patterns.

CONCLUSIONS: Illicit synthetic cannabinoid products continue to be readily available despite national and international restrictions. These products contain a wide range of active components, and, in many cases, multiple active ingredients. DART-MS allows rapid analyses of these synthetic cannabinoids based on the exact masses of their $[M+H]^+$ ions and product ion peaks generated using CID. Copyright © 2012 John Wiley & Sons, Ltd.

The past decade has seen the emergence of numerous illicit designer drugs, leading to new challenges for crime laboratories. Synthetic cannabinoids are one such class of drugs, which, despite their structural dissimilarities, bind the same brain receptors as the active ingredient of marijuana, tetrahydrocannabinol (THC).^[1–5] These cannabinoids are documented as having varying receptor binding strength, and in some cases exhibit much higher cannabinoid receptor affinity than THC. Repeatedly, new structural analogs of these drugs, having different names, packaging, and active ingredients, have been sold to circumvent legal restrictions and scheduling. Despite existing regulations, large increases in annual

emergency room cases have been documented related to the use of these substances.^[1,6–10] The diversity of structural analogs along with the varied nature of current restrictions internationally, at the national level, and between jurisdictions, results in a lack of consensus as to which compounds are illegal and what the most appropriate testing methods to detect them are.

Identification procedures for these designer drugs are often incomplete or less effective. The absence of library mass spectra for many designer drugs hinders their identification and detection. Challenges for detecting and identifying these substances are the lengthy extraction or sample preparation steps associated with their analyses, the variability of active ingredients, and the relatively large numbers of structural analogs. As such, the details of how to best determine their presence have not been systematically established. Liquid chromatography/mass spectrometry (LC/MS) and gas chromatography/mass spectrometry (GC)/MS protocols used

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to detect compounds often require time-consuming sample pre-processing, including extraction, derivatization, and chromatographic separation.

To keep pace with the rapid profusion and abuse of these products, and to inform the development of appropriate policies that permit prosecution of those who synthesize, sell and use them, more rapid, reliable methods to detect their presence are needed. Direct analysis in real time mass spectrometry (DART-MS) is a technique that utilizes an atmospheric pressure ion source that produces a heated stream of metastable helium species directed at sample surfaces to vaporize and ionize liquids or desorb and ionize semi-volatile molecules from solid surfaces in open air under ambient conditions.^[11,12] Semi-volatile substances, like the cannabinoids mixed with the plant material, desorb from the leaf surface and are ionized. The metastable helium atoms initiate a cascade of ion-molecule reactions in ambient air to provide protonated water clusters as a chemical ionization reagent to produce $[M+H]^+$ ions from the cannabinoid drugs.^[11,12] DART-MS provides the ability to sample material directly, without the need for extractions, sample preparation, or chromatographic separations. These beneficial qualities have allowed DART-MS to be applied towards an extremely wide range of analytes, including controlled substances,^[13–19] pesticides,^[20] fragrances,^[21] pepper spray,^[22] and residues associated with sexual assault,^[13,23] among many others.^[24,25]

DART-MS is a means to not only simplify but also revolutionize sample analysis for the detection of designer drugs. Although the presence of a $[M+H]^+$ ion and the high mass resolution associated with time-of-flight (TOF)-MS may be enough to identify an unknown substance, additional structural information could provide support to the identification and/or an additional level of confidence. DART-MS provides a higher degree of certainty as to the identity of a compound's structure with in-source collision-induced dissociation (CID). Specifically, DART-MS CID induces fragmentation of the $[M+H]^+$ precursor ion into product ions when the electrode voltage at the inlet orifice to the mass spectrometer is increased.^[15,16,26–28] Steiner and Larson utilized in-source CID to distinguish between isomeric pairs of drugs based on different product ions,^[15] demonstrating the utility of fragmentation patterns for distinguishing between closely related structures. Similarly, our group reports the use of in-source CID to produce product ions corresponding to portions of synthetic cannabinoid molecules desorbed from dried leaves. In this work, five different cannabinoid analogs which could be differentiated from one another based on their CID product ion fragmentation patterns, were observed in six herbal 'Spice' products purchased locally in New York State (USA).

EXPERIMENTAL

DART ionization of designer drugs

Positive ion mass spectra were acquired using a DART-SVP100TM ion source (Ionsense, Saugus, MA, USA) interfaced to an AccuTOF mass spectrometer (JEOL USA, Inc., Peabody, MA, USA). Leaves/botanical materials were sampled directly. Plant samples were grasped with tweezers and

inserted into the heated helium stream between the DART ion source and the mass spectrometer. Standards were dissolved in methanol (~1 mg/mL), and sampled by two different methods: (a) dipping a melting point tube into the solution and positioning the liquid droplet on the sample coated tube between the ion source and the detector, and (b) dipping the closed end of capillary Dipit-tubesTM (Ionsense) into the solution as previously described.^[29] The Dipit system is equipped with a 12-position rack that is used to hold the sampling capillary tubes. The rack is perpendicular to the ionizing gas stream and allows reproducible, automated, and optimal positioning of samples. Four Dipit-tubes dipped into each standard solution were positioned ~1.8 cm apart in the rack and transported through the helium stream laterally at a speed of 1.5 mm/s while acquiring spectra.

DART-MS parameters

An AccuTOF time-of-flight (TOF) mass spectrometer operated in positive ion mode was employed for mass measurements. The spectrometer resolving power was 6000 (FWHM definition) as measured for protonated reserpine. A mass spectrum of poly(ethylene glycol) (Sigma, St. Louis, MO, USA) with average molecular weight 600 was obtained with each data acquisition as a reference standard for exact mass measurements. The atmospheric pressure interface was typically operated at the following potentials: orifice 1 varied from 15 to 120 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 (Airgas, Cambridge, MA, USA) at 400 °C, a flow rate of 2 L min⁻¹, and a grid voltage of 530 V. The mass range was m/z 80–600. TSSPro3 software (Shrader Analytical, Detroit, MI, USA) together with Mass Spec Tools programs (ChemSW Inc., Fairfield, CA, USA) were used for data processing.

Synthetic cannabinoid standards

All synthetic cannabinoid standards were purchased from Cayman Chemical (Ann Arbor, MI, USA). Herbal 'Spice' samples doped with cannabinoids were purchased at various stores in New York State, USA, between January and March, 2012.

RESULTS

Mass spectra acquired for the six 'Spice' products, typified by the example shown in Fig. 1, displayed ions representative of five (5) different cannabinoids. In five of the products, two synthetic cannabinoids were detected (Table 1). Since the cannabinoids were on botanical material and not in their pure form, we sought to determine the extent to which CID product ions could inform tentative identification of individual cannabinoids within each mixture. Thus, the spectra of relevant cannabinoid standards as a function of orifice 1 voltage were acquired in order to find the optimal conditions for fragmentation of the $[M+H]^+$ ion. As a representative example, Fig. 2 shows the mass spectra acquired for cannabinoid standard JWH-210 at four orifice 1 voltages. Fragmentation increased as the voltage was increased. Based on these

results, an orifice 1 voltage of 90 V was chosen since it provided fragmentation helpful in identification of specific structural features, while maintaining the presence of the $[M+H]^+$ ion from which the product ions were derived. We refer to any spectra demonstrating product ions (orifice 1 voltage ≥ 60 V), as 'CID spectra'. Whereas the non-CID spectra typically appear as a plot of the $[M+H]^+$ ion of each of the species in the sample vs. its relative abundance (Fig. 2(a)), the CID spectra show multiple peaks derived from the breakdown of the $[M+H]^+$ ions of the parent molecules (Figs. 2(b)–2(d)). As the voltage was increased, product ions formed from each precursor ion were observed. At voltages above 60 V, the product ions were more abundant than the $[M+H]^+$ precursor ions in the CID spectra (Figs. 2(c) and 2(d)). Figure 3 shows the DART-MS CID spectra of the five synthetic cannabinoid standards. In each spectrum, the precursor $[M+H]^+$ ion and an additional four to six product ions were observed. The mass spectra in Fig. 4 obtained for the herbal products displayed precursor and product ions consistent with the five synthetic cannabinoid standards. Table 2 lists the exact masses and relative abundances obtained for the standards and the herbal products. Chemical constituents

of the botanical matrix contribute minimally to the spectra, with minor abundances. In all cases, the cannabinoids are responsible for the dominant peaks in the spectra. While $[M+H]^+$ ions with different m/z values were observed for the five standards under non-CID conditions, the CID spectra displayed several product ions for each compound and provided confirmatory evidence of the presence of each compound.

DISCUSSION

In general, a concern with DART-MS is that analysis of complex mixtures could be problematic in terms of identification of individual components because there is no chromatographic interface to the mass analyzer. Often, drugs and/or other analytes are not found in their pure form, but rather are found in the presence of a diluent or as mixtures, such that both the drug(s) of interest and any adulterant, diluting substance, or background matrix could also be observed, thereby complicating the spectra. In such situations, DART-MS analysis could produce spectra containing ions from numerous desorbed components. However, because all the components of a mixture introduced to the DART-MS TOF mass analyzer are detected simultaneously, the technique relies on high-resolution mass accuracy to identify individual components rather than separation by retention time. The CID spectra showed several ions related to each synthetic cannabinoid, providing an increased level of confidence as opposed to determining the $[M+H]^+$ ion alone. If detection by DART-MS CID results in a mass interference that distorts the ion abundance observed for the $[M+H]^+$ precursor ion or a particular product ion, other resolved diagnostic ions from the molecule could indicate the presence of the illicit compound. Importantly, comparison between our standards and the samples analyzed showed that the background matrix contributed minimally to the spectra and the only significant peaks observed were those originating from cannabinoids. The minimal contribution to the spectra from the background material drastically simplified analysis, and stems from the lack of volatile organic compounds associated with dried botanicals as compared to fresh plant material.



Figure 1. One of the herbal 'Spice' products testing positive for the presence of synthetic cannabinoids, in this case for AM-2201. Each product contained non-homogeneous plant material.

Table 1. Synthetic cannabinoid compounds identified in six 'Spice' products*

'Spice' product name	Synthetic cannabinoids				
	AM-2201	JWH-122	JWH-203	JWH-210	RCS-4
Happy Hour Cherry Bomb	X				
California Kronik-Blueberry	X			X	
Mr. Sticky Extreme			X		X
Relaxinol	X			X	
Mr. Nice Guy-Strawberry	X	X			
Dead Man Walking	X			X	

*Cannabinoid compound structures are shown in Fig. 3.

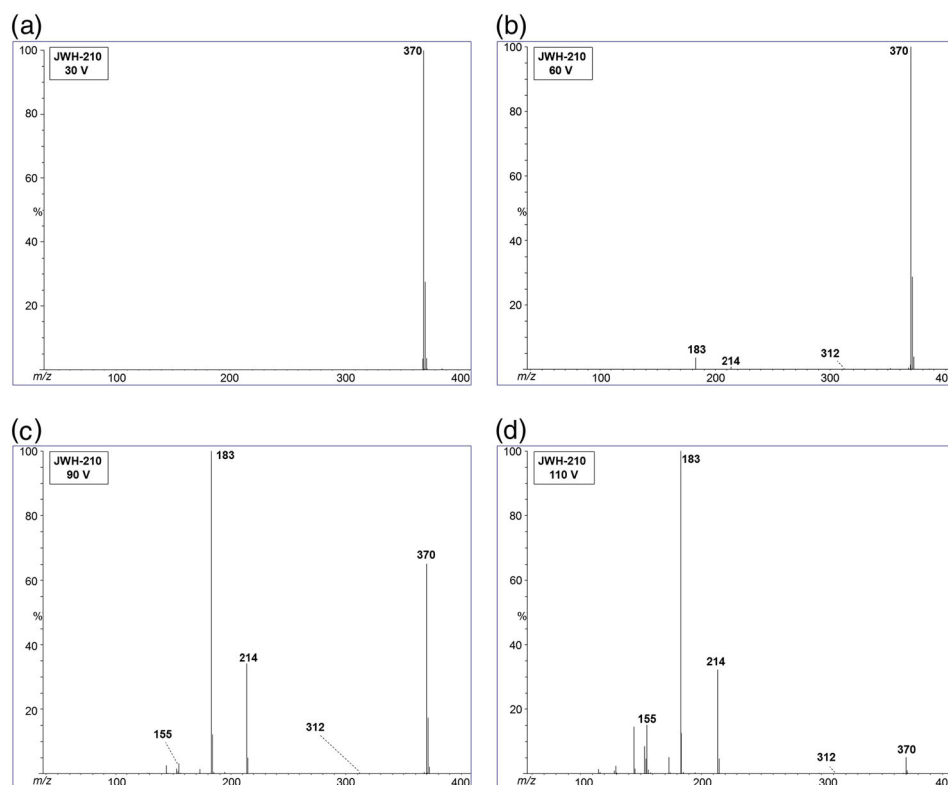


Figure 2. DART-MS analysis of the synthetic cannabinoid JWH-210 under collision-induced dissociation (CID) conditions at orifice 1 voltages of 30 V, 60 V, 90 V, and 110 V. In each case, the $[M+H]^+$ peak was at m/z 370. The number of product ions increased with increasing voltage, demonstrating that the extent of fragmentation can be manipulated to characterize unknowns structurally.

As an extension of our previous work,^[14] we have found that DART-MS permitted the detection of synthetic cannabinoids in various botanical matrices by yielding readily identifiable peaks characteristic of the active components. However, by fragmenting the cannabinoids under CID conditions, identification was improved significantly for the following reasons: first, the $[M+H]^+$ precursor ions were still present in the mass spectra; second, common core structural features were identified for sub-classification of closely related compounds, such as those containing indole and/or naphthyl functionalities; and, third, fragmentation also allowed the identification of structural features unique to each substance so that unambiguous differentiation of each species could be accomplished. Ultimately, precursor and product ions were observed based on both common structural features and structural differences between the compounds, and detection of multiple ions characteristic of each drug provided greater confidence that the drugs had been detected. This concept is based on the idea that closely related compounds are likely to fragment in a similar fashion, but their inherent structural differences will result in unique product ions that vary enough between the singular cannabinoids and can serve as a means to better identify each substance.

The CID spectra are predictable and permit identification of core structural features as well as unique chemical functionalities, thus facilitating identification and differentiation of each substance. The important CID

product ions were mirrored in both the standards and the herbal samples. Unique fragmentation patterns were present in all five synthetic cannabinoids, based on cleavage at either side of the carbonyl group and within the *N*-alkyl chain (Fig. 3, Table 2). Specifically, the *N*-pentylindoyl fragment was identified in all five compounds with charge retention on the *N*-pentylindoyl group. For JWH-122, JWH-203, JWH-210, and RCS-4, which contain an *N*-alkyl group, a common product ion at m/z 214 was observed based on this fragmentation pattern. A detection strategy based on the observation of a diagnostic peak at m/z 214 for JWH-*N*-alkyl indoyl derivatives would not recognize AM-2201, because of its fluorinated *N*-alkyl chain. Thus, although AM-2201 exhibits a similar fragmentation pattern, the presence of fluorine results in the observation of a peak at m/z 232 instead of m/z 214. This example demonstrates how these derivatives are used to evade, or at the very least, complicate detection by regulators. For the three cannabinoids with the naphthyl group (AM-2201, JWH-122, JWH-210), product ions derived from cleavage on either side of the carbonyl group were observed. This fragmentation pattern results in peaks at m/z 155 and 127 in AM-2201 for the naphthoyl and naphthyl groups, respectively (Fig. 3, Table 2). Whereas the AM-2201 molecule has an unsubstituted naphthyl moiety, the naphthyl rings in JWH-122 and JWH-210 are substituted with methyl and ethyl, respectively. Thus, the JWH-122 fragmentation, which is similar to that of AM-2201, results in peaks at m/z 141 and 169 for the methyl naphthyl and methyl naphthoyl fragments,

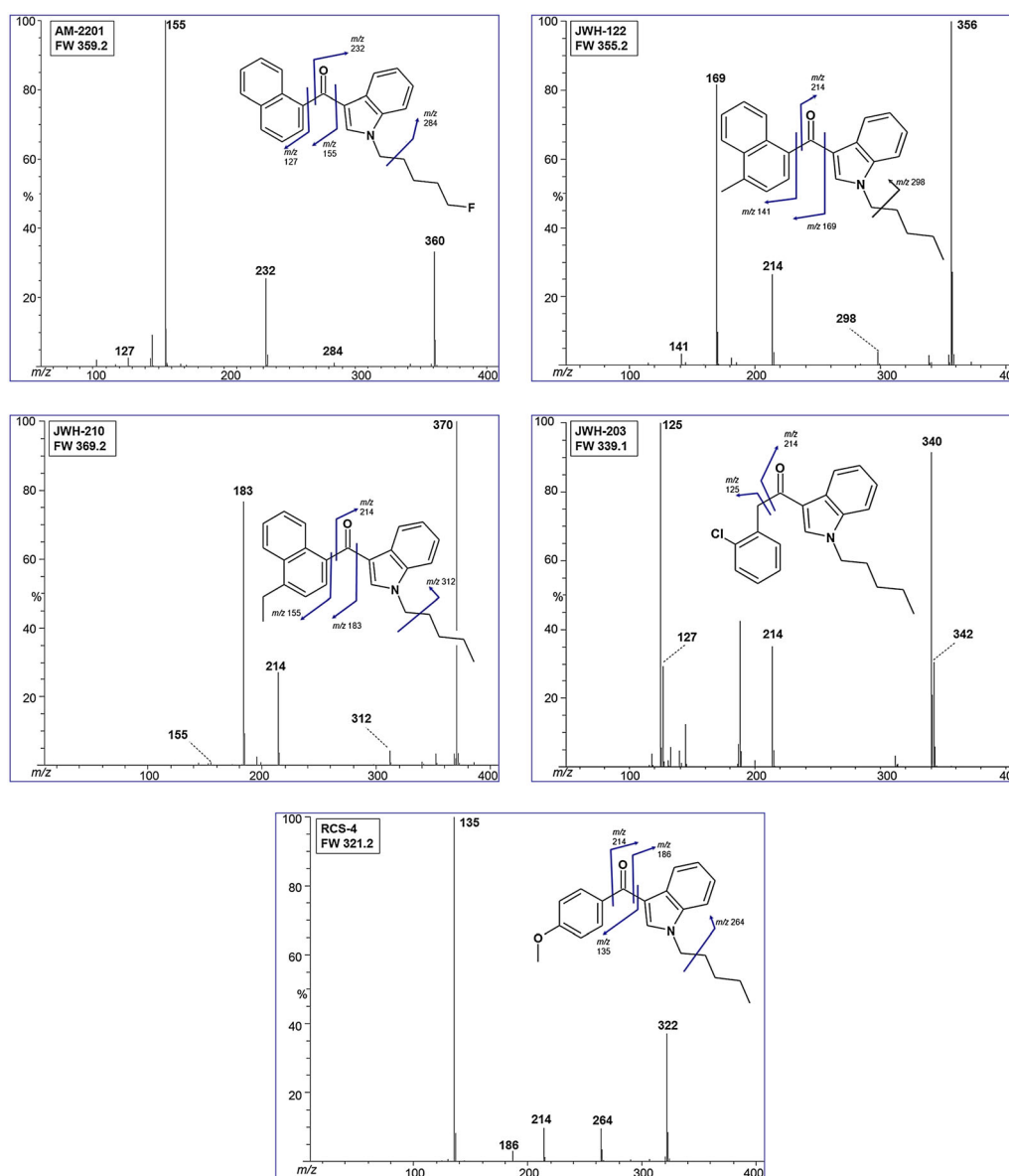


Figure 3. DART-MS spectra of five synthetic cannabinoid standards with an orifice 1 voltage of 90 V to provide CID. In each case, the orifice 1 voltage was set at 90 V. The name and formula weights are listed in the upper left corner and measured masses appear in Table 2. The $[M+H]^+$ ion peak is labeled along with the key peaks that aid in structural characterization of the cannabinoids. The structures and cleavage sites of the product ions are shown.

respectively. Analogously, JWH-210 exhibits peaks at m/z 155 and 183 for ethyl naphthyl and ethyl naphthoyl, respectively. However, while these trends are important for structural characterization, some important differences were observed between the cannabinoids. The spectrum of RCS-4 has a peak indicative of charge site retention on the methoxyphenyl functionality, resulting in a peak at m/z 135 (methoxyphenyl). Four of the five cannabinoids showed a peak of weak intensity from fragmentation of the alkyl chain, resulting in a loss of 58 Da (76 Da for AM-2201) from the $[M+H]^+$ ion. Interestingly, this alkyl fragmentation does not appear to occur in the JWH-203 cannabinoid under our conditions, a difference presumably influenced by the electron-withdrawing nature of chlorine. Nevertheless, the JWH-203 cannabinoid

provided a readily interpretable mass spectrum, with the characteristic A+2 isotope peak associated with the presence of chlorine in both the $[M+H]^+$ ion and the m/z 125 product ion (from loss of *N*-pentylindoyl).

Further optimization of the instrumental parameters to yield mass spectra containing $[M+H]^+$ ions and product ions for enhanced structural characterization will be of benefit for applications in forensics drug analysis. We continue to study the identification and characterization of designer drugs by DART-MS, and to establish how this technique can be used in crime labs to quickly detect their presence. DART-MS can serve as a means to simplify sample analysis by eliminating significant sample preparation and the concomitant loss/consumption of sample that inevitably accompanies extraction of analytes.

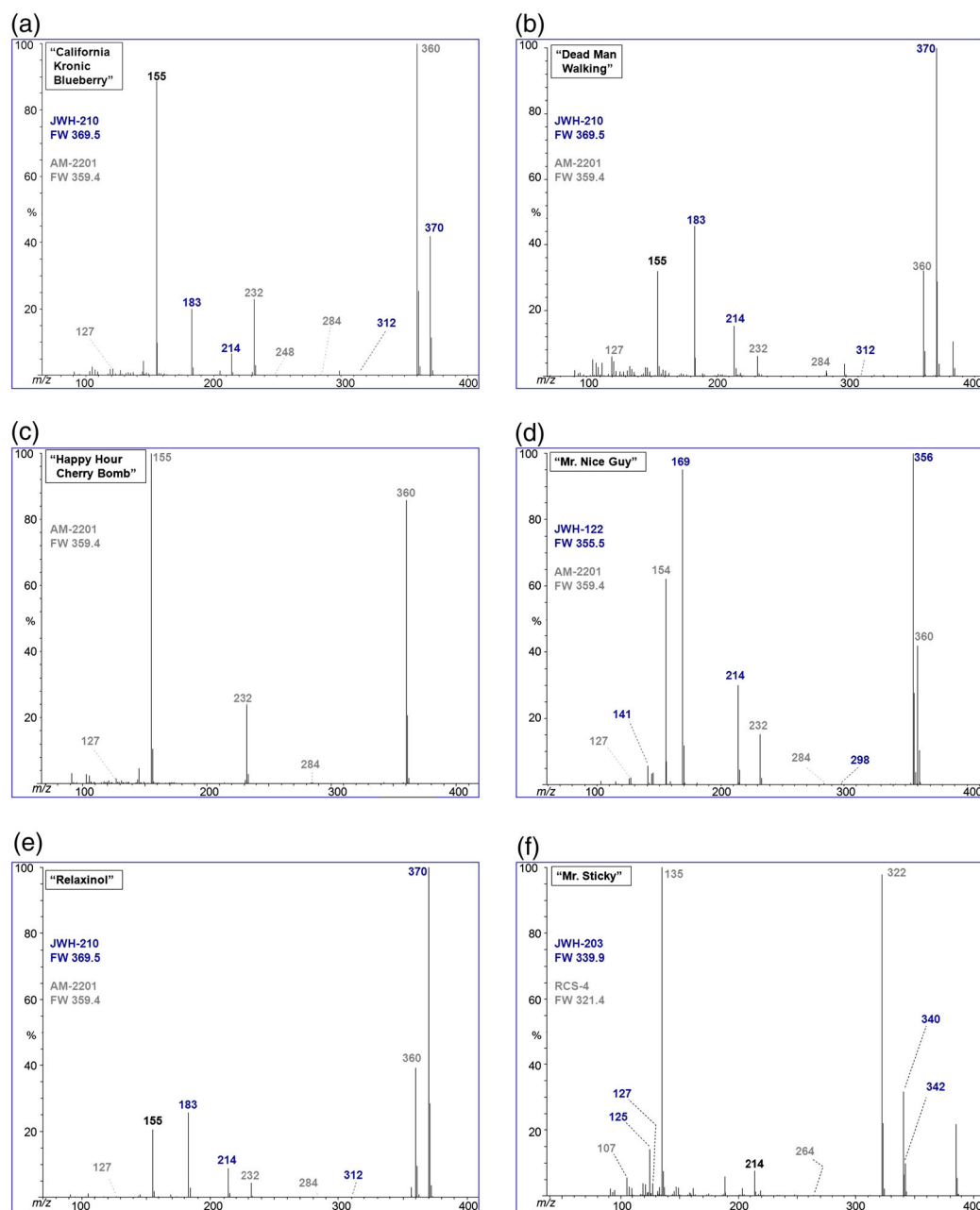


Figure 4. DART-MS spectra of the five synthetic cannabinoids tentatively identified in six different herbal products (with an orifice 1 voltage of 90 V to provide CID). The name of the herbal product, the synthetic cannabinoids, and their formula weights are listed on the left side of each spectrum. Masses of each peak are listed and color-coded to match the name of the cannabinoid in the legend. In cases where a product ion peak results from contributions from two cannabinoids, the mass is indicated in black font (i.e. m/z 155). The same $[M+H]^+$ ions and the key product ions identified in Fig. 3 were observed in the spectra from the six products. In five of the six herbal products tested, multiple synthetic cannabinoids were detected.

CONCLUSIONS

DART-MS provided direct, rapid, and efficient analyses of highly complex mixtures, detecting and differentiating five synthetic cannabinoids in six commercially available 'Spice' products. The speed and simplicity of DART-MS analyses demonstrate that the technique is an attractive and viable alternative to GC/MS and LC/MS analyses; sample preparation was eliminated and only a trace amount

of the 'Spice' was required to acquire mass spectra, which is a particular advantage when limited evidentiary material is available. To maximize the potential of this method, in-source collision-induced dissociation was used to identify both the parent compound and key product ion peaks, which enabled identification of characteristic core structural features. The product ions provided additional confidence of the compounds present in the herbal mixtures. This concept complements past work demonstrating that cannabinoids and other drugs can be

Table 2. The data generated from the spectra in Fig. 3, highlighting the major $[M+H]^+$ and product ion peaks and their relative abundances

Sample	Formula	m/z	Meas.	Abund.
AM-2201	$C_{24}H_{22}FNO$	$[M+H]^+$	360.1768	91.5
			284	6.6
			232	37.8
			155	100.0
			127	1.2
JWH-122	$C_{25}H_{25}NO$	$[M+H]^+$	356.2024	100.0
			298	4.3
			214	39.0
			169	94.0
			141	4.4
JWH-203	$C_{21}H_{22}ClNO$	A + 2	342.1405	28.1
		$[M+H]^+$	340.1456	77.8
			214	39.2
			127	33.6
			125	100.0
JWH-210	$C_{26}H_{27}NO$	$[M+H]^+$	370.2185	100.0
			312	2.1
			214	25.2
			183	68.9
			155	2.0
RCS-4	$C_{21}H_{23}NO_2$	$[M+H]^+$	322.1810	72.9
			264	8.7
			214	18.8
			186	3.0
			135	100.0

rapidly and conveniently detected through screening with DART-MS.^[14] The speed and efficiency of DART-MS can improve forensic analyses by reducing the amount of time required to gather evidence and rendering sample extraction and other preparative steps such as chromatographic separation unnecessary. This, in turn, reduces the time required to prepare analytical evidence, which could lead to more timely prosecution of court cases. Both the rapid screening and the direct sampling ability will contribute a substantial time-saving component to crime labs that normally perform extractions or other preparations associated with analysis of complex matrices, in particular those associated with marijuana, fungi, and other substances of biological origin.

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