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QUANTITATIVE ANALYSIS OF FLUORINATED SYNTHETIC CANNABINOIDS USING ^{19}F NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY AND GAS CHROMATOGRAPHY-MASS SPECTROMETRY

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Abstract

The objective of this study was to quantify the concentration of fluorinated synthetic cannabinoids in an authentic unknown sample using ^{19}fluorine nuclear magnetic resonance spectroscopy (^{19}F NMR) and gas chromatography-mass spectrometry (GC-MS). The two synthetic cannabinoids targeted in this study were XLR-11 and AM-2201, which are 5-fluoro-pentyl derivative synthetic cannabinoids. An adjudicated casework sample of "Mind Wave Blueberry" was identified to contain only AM-2201 and was quantified based on standard calibration curves developed from analytical reference standards. The results of this study indicate a 7.2% difference between the ^{19}F NMR and GC-MS quantification results, which highlights the agreement between these two analytical techniques. Given that XLR-11 and AM-2201 are indistinguishable with ^{19}F NMR, GC-MS was used for the qualitative screening of the unknown street sample prior to quantitative analysis.

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Introduction

Synthetic cannabinoids were first identified in 2008, being sold under the name "spice" through the internet and headshops[1]. The plant material, which was being sold as incense, contained man-made substances designed to mimic the physiological effects of Δ9-tetrahydrocannabinol (Δ9-THC), which is the main psychoactive ingredient of marijuana[2,3]. The man-made substances, known as synthetic cannabinoids, are dissolved in a solvent and sprayed onto plant material, dried, then smoked to receive the psychotropic effects[4]. Synthetic cannabinoids bind to the CB1 and CB2 receptors, which are part of the complex endocannabinoid system (3,4). However, unlike Δ9-THC which is only a partial agonist of the CB1 and CB2 receptors, synthetic cannabinoids are typically full agonists of the CB1 and CB2 receptors, which leads to increased potency relative to Δ9-THC[5,6].

The availability and consumption of synthetic cannabinoids increased steadily in both the United States and Europe in the early 2010s. In 2012, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) released a special issue focused on understanding the "spice" phenomenon[7], and the United States passed the Synthetic Drug Abuse Prevention Act that placed 26 types of synthetic cannabinoids and synthetic cathinones into Schedule I of the Controlled Substances Act[8]. Schedule I controlled substances are chemical substances that have no currently accepted medicinal use and have a high potential for abuse. By 2014, the National Forensic Laboratory Information System (NFLIS) identified more than 37,000 synthetic cannabinoid reports, which accounted for nearly 2% of all drugs reported. Two synthetic cannabinoids in particular, XLR-11 and AM-2201 (Figure 1), combined for more than 30% of all synthetic cannabinoid-related reports[9].

XLR-11 is a potent CB2 agonist and the 5-fluoro derivative of the UR-144 synthetic cannabinoid that was developed by Abbott Laboratories[10]. The first reported presence of XLR-11 was in Japan, in 2012, where XLR-11 was identified in herbal incense products[11]. XLR-11 is different than most other synthetic cannabinoids due to the presence of the 2,2,3,3-tetramethylcyclopropyl ring substituent. In comparison, AM-2201 is the 5-fluoro derivative of JWH-018, which was first synthesized in John W. Huffman's laboratory at Clemson[12]. AM-2201 is named after Alexandros Makriyannis from Northeastern University who is responsible for the synthesis of the AM series of synthetic cannabinoids. By 2013, there were already reports of AM-2201 usage in Europe[13] and the United States, with at least one death confirmed due to AM-2201 exposure[14].

Synthetic cannabinoids pose a significant analytical challenge for forensic laboratories because as each new synthetic cannabinoid becomes regulated, new analogs emerge on the drug market through slight modifications to the core synthetic cannabinoid structure[3,4]. One common modification that was likely borrowed from scientific literature in the medicinal chemistry field is the replacement of a hydrogen atom with a fluorine atom, which is present in many indole-based synthetic cannabinoids[15]. This constant influx of novel synthetic cannabinoids has created a growing need for the development of analytical techniques for the qualitative and quantitative analysis of synthetic cannabinoids outside of traditional gas chromatography-mass spectrometry (GC-MS). Techniques investigated included Raman spectroscopy both with

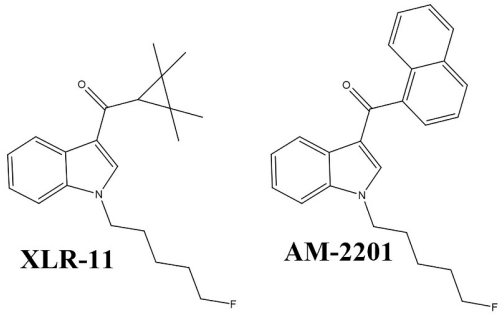

Figure 1. Structures of XLR-11 and AM-2201.

benchtop instruments[16] and portable instruments[17], GC-infrared spectroscopy (GC-IR)[18-20], ambient ionization mass spectrometry, such as direct analysis in real time mass spectrometry (DART-MS)[21-23], and nuclear magnetic resonance (NMR) spectroscopy[24-29]. Although NMR is not readily available in most forensic laboratories [30], the advent of miniaturized benchtop NMR spectrometers is particularly promising for forensic applications in terms of the cost and laboratory space requirements[31,32]. While not used in this study, benchtop NMR spectrometers may provide another avenue for the detection and differentiation of synthetic cannabinoids given their demonstrated success for the identification of falsified medicines[33], differentiation of fentanyl analogs[34], discrimination of stimulants[35], quantification of synthetic cannabinoids[36] and the identification of classical seized drugs[37].

The goal of this study was to quantitatively analyze an authentic unknown adjudicated casework sample using ^{19}F NMR and GC-MS. At the time of this study, XLR-11 and AM-2201 were the fluorinated synthetic cannabinoids chosen given their 5-fluoro pentyl side chain and prevalence in casework samples submitted to the Cumberland County Forensic Laboratory. A benefit of ^{19}F NMR analysis relative to traditional ^{1}H and ^{13}C NMR analysis is that street samples, which are of unknown quality, purity, and plant material origin, could lead to complex ^{1}H and ^{13}C NMR spectra and potentially require purification prior to analysis. Likewise, the use of ^{19}F specific NMR provides an analytical advantage over non-chromatography techniques for the analysis of mixtures due to the rarity of fluorinated adulterants or diluents[38]. Quantitation was determined by GC-MS followed by ^{19}F NMR. Quantitative analysis involved the development of standard curves from analytical reference standards and the quantification of an unknown street sample provided through adjudicated casework.

Experimental Methods

Chemicals and Reagents

The XLR-11 and AM-2201 analytical reference standards were purchased through Cayman Chemical (Ann Arbor, MI, USA). The hexafluorobenzene (HFB) internal standard was purchased through Acros (Fair Lawn, NJ, USA) and the deuterated acetone solvent (acetone-d_6) was purchased through Sigma Aldrich (St. Louis, MO, USA). The unknown street sample, which was provided by the Cumberland County Forensic Laboratory, was labeled as "Mind Wave Blueberry." Hexafluorobenzene and acetone-d_6 are both respiratory and skin irritants and were handled using gloves within a chemical fume hood. The reference standards were classified as respiratory irritants and could be absorbed through the skin and were likewise handled with gloves within a chemical fume hood. Given the unknown composition of the authentic street sample, it was also handled using gloves within a chemical fume hood.

Instrumentation

A JEOL (Peabody, MA, USA) ECX 400 MHz NMR was operated with a broadband probe set to detect ^{19}F with the following experimental parameters: relaxation delay of 5 seconds, x-angle of 45 degrees, x-acquisition duration of 34.8 seconds, x-offset of -190 ppm, x-sweep of 80 ppm, 1,048,576 x-points, 16 scans, and a receiver gain of 26. Deuterated acetone (acetone-d_6) was selected as the sample solvent due to cannabinoid solubility and GC elution relative to the HFB internal standard. The HFB internal standard was selected as an internal reference due to its stability, ^{19}F peak location (-165 ppm), and fluorine content for integration. All samples were run in triplicate with the cannabinoid peaks being manually integrated relative to the HFB internal standard. JEOL Delta NMR software v4.3.6 was used for experimental parameters and processing.

An Agilent Technologies (Santa Clara, CA, USA) 6890 GC-5973 MS with a 7683 autosampler was used for the GC-MS analysis. The GC-MS analysis used ultra-high purity helium as the carrier gas at a flow rate of 1.5 mL/min. The autosampler injected 1 µL of sample with a split ratio of 10:1. The GC capillary column was an Agilent Technologies VF-5MS column (30 m x 250 µm x 0.25 µm). The inlet temperature was set to 250 °C with an initial oven temperature of 50 °C. After an initial 1 min hold period, the oven was ramped to 100 °C at a rate of 15 °C/min and then held for 1 min before a second temperature ramp to 280 °C at a rate of 25 °C/min, which was held for 12 mins. The mass spectrometer was scanned from *m/z* 40-550 after a 1 min solvent delay. The source and quadrupole temperatures were set to 230 °C and 150 °C, respectively. All data analysis for the Agilent Technologies GC-MS was performed using ChemStation version G170EA.02.02.1431.

Quantification

The quantitative analysis with ^{19}F NMR and GC-MS was performed through the generation of standard curves that were collected in triplicate at five non-zero calibrators at the following concentrations: $1.5x10^{-3}$ M, $3.0x10^{-3}$ M, $6.0x10^{-3}$ M, $9.0x10^{-3}$ M, and $1.5x10^{-2}$ M. Concentrations are reported in molarity (M) due to the increased concentration required for NMR analysis relative to GC-MS. Each sample was prepared with the synthetic cannabinoid of interest and the HFB internal standard in a deuterated acetone solvent (acetone-d_6) in a total volume of 0.5 mL. The HFB concentration was kept constant across all samples at $1.0x10^{-3}$ M. The XLR-11 and AM-2201 analytical reference standards were used to create standard calibration curves from which an unknown could be quantified. The standard curves were generated by plotting the concentration versus the peak area ratio of the synthetic cannabinoid of interest relative to the HFB internal standard.

Unknown Sample Preparation

The unknown street sample used for quantification was labeled as "Mind Wave Blueberry" and was analyzed in triplicate for the quantitative and qualitative analyses. The extraction procedure involved the addition of 2 mL of the acetone-d_6 solvent to approximately 100 mg of plant material. The solution was vortexed for 10 seconds and allowed to sit for 5 minutes before the solvent was removed with a cotton filled Pasteur pipette and transferred to a 4 mL glass vial. For analysis, 175 µL of stock HFB and 325 µL of extract solution were combined for a final HFB concentration of $1.0x10^{-3}$ M, which was held constant across all samples.

Results and Discussion

Quantitative Analysis

Initial study development envisioned extracting street samples containing synthetic cannabinoids with deuterated acetone followed by the addition of HFB as an internal standard and then

quantitation by ^{19}F NMR using standard curves. Since XLR-11 and AM-2201 are fluorine containing cannabinoids,^{19}F NMR was solely utilized in an effort to analyze samples directly after extraction given that purification would likely be necessary to separate potential impurities from contaminants in the plant material prior to ^{1}H and ^{13}C NMR interpretation. A comparison to GC-MS standard curve quantitation was necessary to provide proof of concept while also providing an opportunity to compare quantitation techniques at concentrations necessary for NMR analysis.

Quantitation by ^{19}F utilized a relaxation delay of 5 seconds followed by an acquisition time of 34.8 seconds was used to make sure that all fluorines in both the cannabinoids and the HFB internal standard had completely relaxed before taking the next scan. Analysis of the XLR-11 and AM-2201 fluorine containing synthetic cannabinoids was performed by measuring the integrated peak area relative to that of the hexafluorobenzene (HFB) internal standard. A calibration curve comprised of five non-zero calibrators was created from which an unknown sample could be quantified. Figure 2 provides a comparison of the ^{19}F NMR spectra collected for XLR-11 (Figure 2a) and AM-2201 (Figure 2b) at a concentration of $6.0x10^{-3}$ M. The integration results, which are a function of the number of fluorine atoms present in the molecule and the concentration of the sample, highlight the six fluorine atoms present in the HFB internal standard observed at -165 ppm (6.00) relative to the single fluorine atom in XLR-11 (1.03) and AM-2201 (1.04) observed at -221 ppm. It is important to note that with ^{19}F NMR, XLR-11 and AM-2201 are indistinguishable. Therefore, GC-MS was used for the qualitative analysis of the unknown adjudicated casework sample prior to ^{19}F NMR quantitative analysis. The GC-MS analysis indicated the presence of only AM-2201 in the unknown adjudicated casework sample.

The standard curves generated for XLR-11 (Figure 3a) and AM-2201 (Figure 3b) with ^{19}F NMR are shown in Figure 3. The standard curves were generated using five non-zero calibrators ranging from $1.5x10^{-3}$ M to $1.5x10^{-2}$ M. Each standard was analyzed in triplicate with the error bars corresponding to the standard deviation of the replicate measurements. The corresponding coefficient of determination (R^2) for the least squares regression analysis was ≥ 0.999 for both XLR-11 (Figure 3a) and AM-2201 (Figure 3b) indicating excellent agreement between the data and the regression line. The unknown street sample provided by the Cumberland County Forensic Laboratory only contained AM-2201 (as determined by GC-MS). Figure 3b demonstrates the quantification of AM-2201 from the unknown street sample. The unknown street sample was analyzed in triplicate and the linear equation of the standard curve (y = 167.09x + 0.0013) was used to convert the ra-

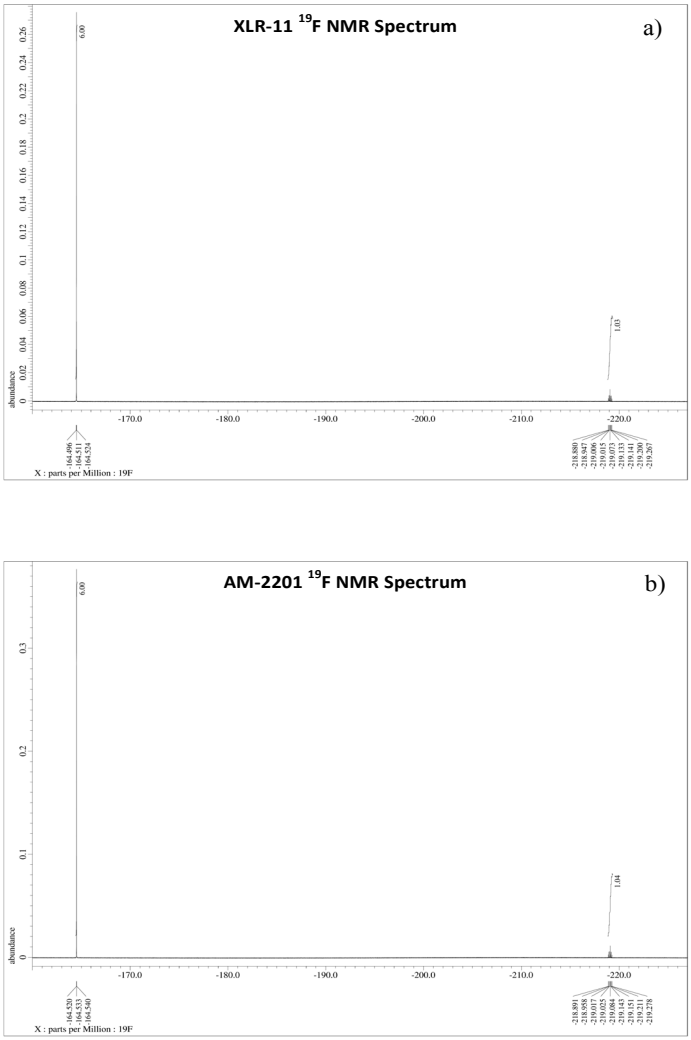

Figure 2. ^{19}F NMR spectra for XLR-11 (a) and AM-2201 (b).

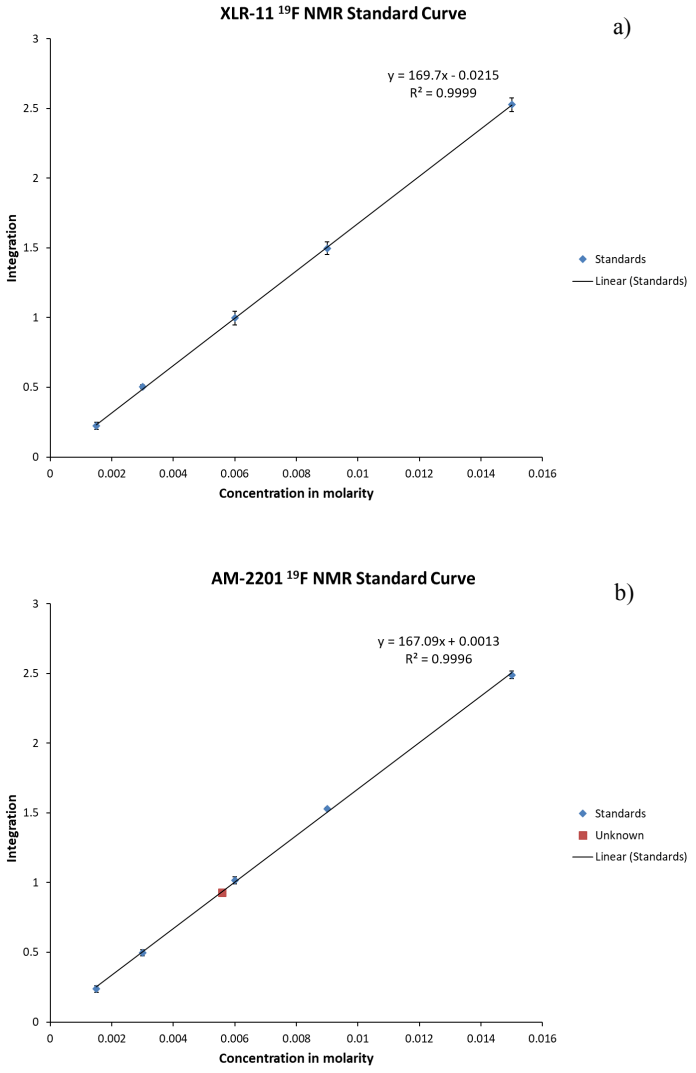

Figure 3. ^{19}F NMR standard curves for XLR-11 (a) and AM-2201 (b). The AM-2201 standard curve includes the unknown sample quantified with ^{19}F NMR.

tio between the peak area of AM-2201 to the peak area of the HFB internal standard to concentration in molarity (M) of AM-2201 in the unknown street sample. The 95% confidence interval unknown concentration was determined to be $5.56x10^{-3} \pm 0.0004$ M, which fell well within the standard curve generated for AM-2201.

Figure 4 provides a comparison between the total ion chromatogram (TIC) collected for XLR-11 (Figure 4a) and AM-2201 (Figure 4b) at a concentration of $6.0x10^{-3}$ M. The first two peaks observed in Figure 4a at 1.256 minutes and 1.326 minutes correspond with a split peak from the acetone-d_6 solvent. The peak observed at 1.571 minutes is the HFB internal standard and the peak observed at 14.289 minutes corresponds with XLR-11. Similarly, the peaks observed at 1.262 minutes and 1.332 minutes in Figure 4b correspond with a split peak from the acetone-d_6 solvent. The HFB internal standard elutes at 1.576 minutes and the AM-2201 peak is observed at 23.259 minutes. Unlike the analysis with ^{19}F NMR, XLR-11 and AM-2201 are easily differentiated with GC-MS in terms of both their retention time and EI mass spectra. Again, the peak area ratio between the analyte of interest and the HFB internal standard was used for the creation of the GC-MS standard curves across five non-zero calibrators ranging from $1.5x10^{-3}$ M to $1.5x10^{-2}$ M.

The standard curves generated for XLR-11 (Figure 5a) and AM-2201 (Figure 5b) with GC-MS are shown in Figure 5. All analytical reference standards were analyzed in triplicate across five concentrations and the equation of the line from the AM-2201 standard curve was used to quantify AM-2201 in the unknown street sample. Again, the coefficient of determination (R^2) for the least squares regression analysis was ≥ 0.999 for both XLR-11 (Figure 5a) and AM-2201 (Figure 5b) indicating excellent agreement between the data and the regression line. The linear equation for the standard curve (y = 1217.4x - 0.6777) was used to convert the ratio between the peak area of AM-2201 to the peak area of the HFB internal standard to concentration in molarity (M). Based on the GC-MS data, the 95% confidence interval concentration of AM-2201 in the unknown street sample was $5.99x10^{-3} \pm 0.0005$ M, which fell well within the standard curve generated for AM-2201.

The results of this study indicate a 7.2% difference between the ^{19}F NMR and GC-MS quantitation results for the unknown street sample, which highlights agreement between these two techniques. Given that both the ^{19}F NMR and GC-MS quantitation results had similar precision, the sensitivity of the two analytical methods was compared based on the slopes of the corresponding calibration curves. For both XLR-11 and AM-2201, the GC-MS

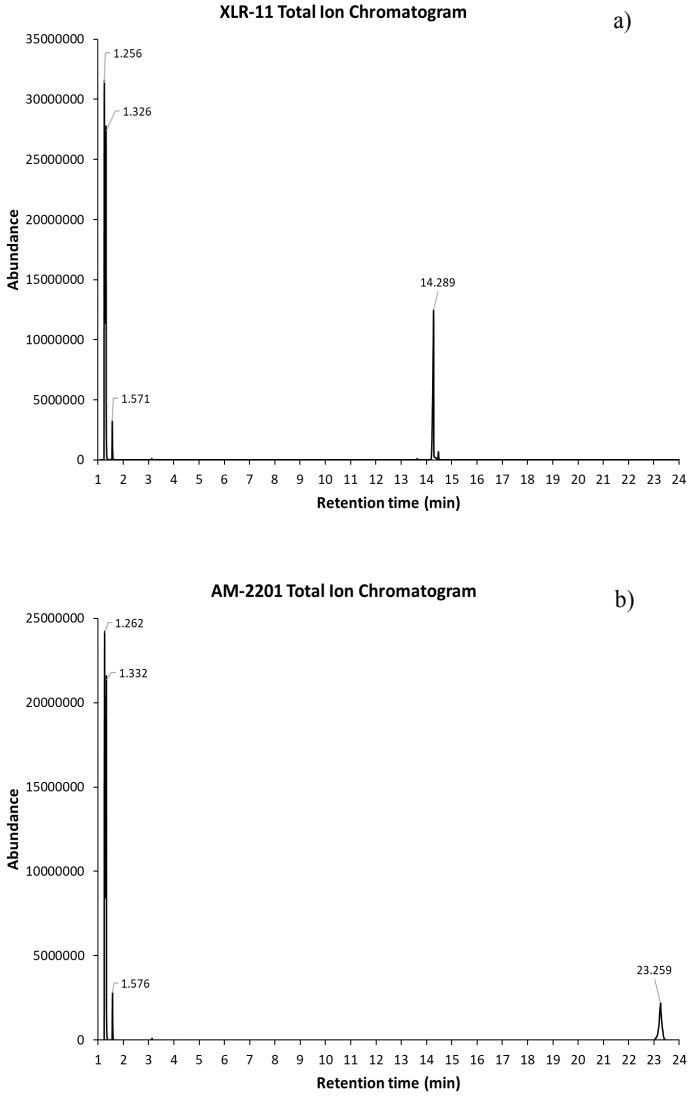

Figure 4. Total ion chromatograms for XLR-11 (a) and AM-2201 (b).

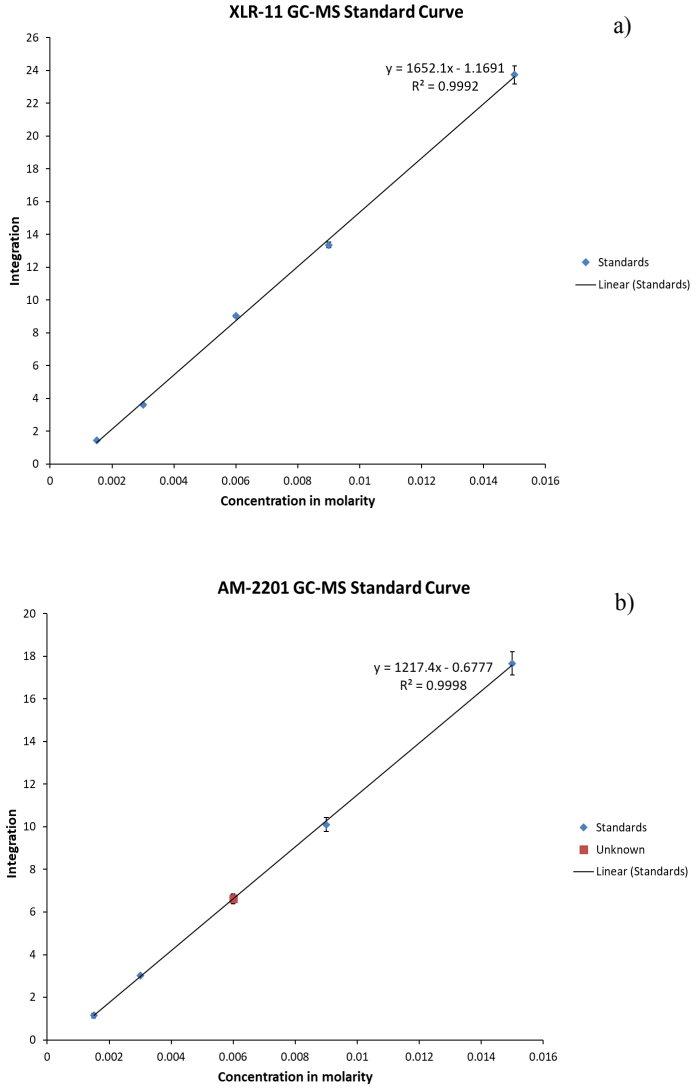

Figure 5. GC-MS standard curves for XLR-11 (a) and AM-2201 (b). The AM-2201 standard curve includes the unknown sample quantified with GC-MS.

slope of the calibration curve (Figure 5) was on the order of a magnitude greater than the ^{19}F NMR calibration curve (Figure 3) with precision for both methods within the same order of magnitude, indicating superior sensitivity for GC-MS relative to ^{19}F NMR.

Qualitative Analysis

Due to the identical shift observed for the 5-fluoro atom of the pentyl side chain (-221 ppm) for both XLR-11 and AM-2201 (Figure 2a and Figure 2b), ^{19}F NMR cannot be used to differentiate between these fluorinated synthetic cannabinoids. However, XLR-11 and AM-2201 can be easily differentiated with GC-MS by retention time (Figure 4) and EI mass spectra (Figure 6). Under the specific method parameters from this study, XLR-11 eluted around 14.2 minutes, whereas AM-2201 eluted around 23.2 minutes. XLR-11 produced a split peak in the TIC, likely due to thermal degradation in the injection port, which has been described previously in the literature[39,40]. In comparison, AM-2201 produced a very broad peak in the TIC, likely due to band broadening from the increased amount of time spent on the analytical column relative to XLR-11. The resulting EI mass spectra of XLR-11 and AM-2201 are easily distinguishable due to the presence of molecular ions and distinctly different fragmentation patterns. The XLR-11 mass spectrum (Figure 6a) shows the presence of the molecular ion at *m/z* 329, the dominant base peak at *m/z* 232, and relatively low abundance fragment ions at *m/z* 314, *m/z* 144, *m/z* 130, and *m/z* 116. These observations are consistent with previously reported EI mass spectra for XLR-11 (39, 40). In comparison, the AM-2201 mass spectrum (Figure 6b) shows the presence of the molecular ion at *m/z* 359, the base peak at *m/z* 127, and a distribution of varying abundance ions at *m/z* 342, *m/z* 284, *m/z* 270, *m/z* 232, *m/z* 155, *m/z* 144, and *m/z* 116. Again, these observations are consistent with previously reported EI mass spectra of AM-2201[19].

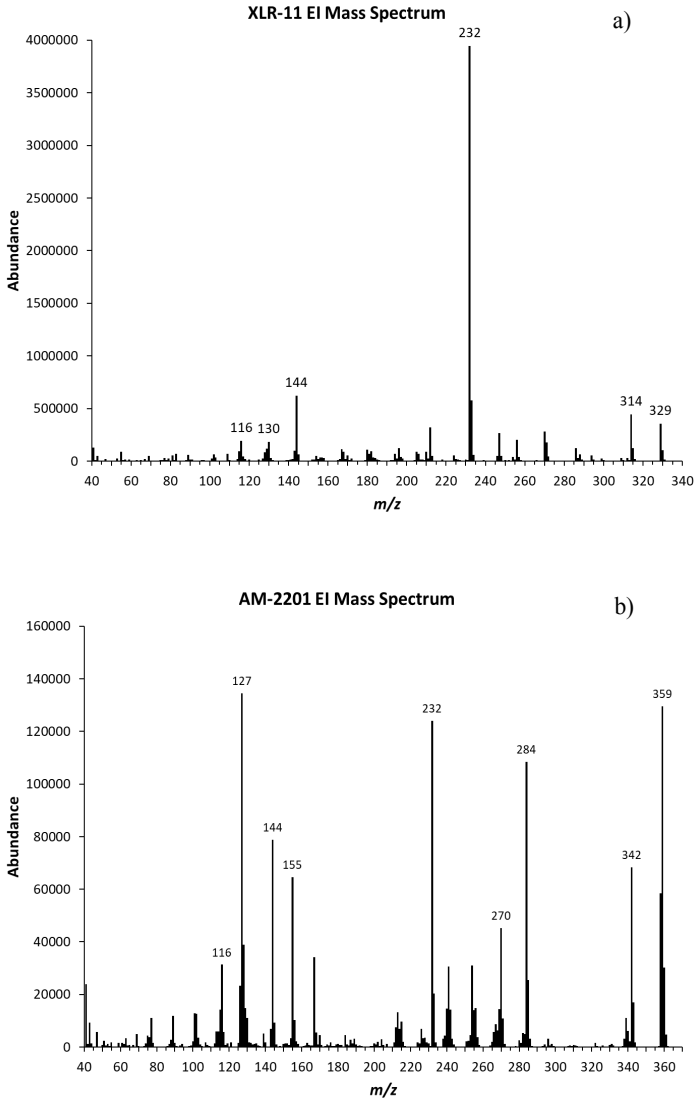

Figure 6. Electron ionization (EI) mass spectra of XLR-11 (a) and AM-2201 (b).

Conclusions

This study demonstrated the successful quantification of AM-2201 from an adjudicated casework sample using a standard curve generated across five non-zero calibrators and analyzed in triplicate with both ^{19}F NMR and GC-MS. Unfortunately, the adjudicated casework sample only contained AM-2201, so the quantification of XLR-11 from an unknown sample was not demonstrated. However, the quantitative results achieved with ^{19}F NMR and GC-MS from a single unknown sample resulted in a percent difference of only 7.2%, which further provides support for the similarity of quantitative analyses between NMR and chromatographic-based techniques such as GC-MS and GC-FID[41,42]. Despite having a limited data set, the agreement between the ^{19}F NMR and GC-MS quantification provides additional evidence for the capabilities of NMR relative to the traditional GC-MS approach for the analysis of synthetic cannabinoids, particularly at the increased concentrations typically available with seized drug synthetic cannabinoid evidence.

The application of ^{19}F NMR in the quantitative analysis of fluorinated synthetic cannabinoids, such as XLR-11 and AM-2201, was explored relative to traditional GC-MS analysis. Initially, we thought the benefit of ^{19}F NMR analysis relative to traditional ^{1}H and ^{13}C NMR analysis would reduce concerns with sample purity and interferences from the plant material given the rarity of fluorinated adulterants in botanical material. However, traditional ^{1}H and ^{13}C NMR approaches have shown the capability to differentiate synthetic cannabinoids, although with increased spectral interpretation requirements[24-29]. Whereas ^{19}F NMR was able to produce similar quantitative results, GC-MS was required for qualitative identification because of the indistinguishable ^{19}F NMR spectra for XLR-11 and AM-2201; due to the fluorine peaks appearing at the same location, -221 ppm, relative to HFB. Another consideration in the determination of which analytical technique may be most appropriate is the discernable difference in sensitivity. Previous literature has demonstrated that accurate NMR measurements can be made in the 10^{-3} M concentration range, whereas accurate full scan GC-MS measurements can be made as low as 10^{-6} M[43]. This means that GC-MS instrumentation can be up to three orders of magnitude more sensitive than NMR instrumentation. As such, GC-MS is still the preferred analytical method for quantitation. However, with the expanding use of NMR, particularly technological advances in benchtop NMR, this work helps demonstrate the capabilities of ^{19}F NMR for the quantification of fluorinated synthetic cannabinoids.

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