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Gas chromatography-flame ionization detector analysis of AMB-Fubinaca from criminal evidences in Vietnam

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ABSTRACT

Synthetic cannabinoids are currently the largest group of new psychoactive substances. Among them, one of the most recent compounds in Vietnam is AMB-Fubinaca. No quantitative method has been officially implied for AMB-Fubinaca in criminal evidences, thus, making the police investigations burdensome. This study, for the 1st time, aimed to develop and validate the gas chromatography with flame ionization detector (GC-FID) method to determine and quantify AMB-Fubinaca in criminal evidences found in the South of Vietnam from 2016 to 2018. Chromatography separation was achieved on diphenyl dimethyl polysiloxane GC column (30 m × 0.32 mm × 0.25 μm) with a total run time of 10 min. The method was validated in terms of specificity, linearity, precision, accuracy, and sensitivity. The method satisfied all validation requirements. The limit of detection and limit of quantitation for AMB-Fubinaca was 1.5 μg/mL and 4.5 μg/mL, respectively. Tested with 30 criminal samples collected in Vietnam from 2016 to 2018, the validated method proved its cost-effectiveness, simplicity, and usefulness for the rapid determinations of AMB-Fubinaca, as compared to the GC-MS method. In conclusion, the GC-FID could be a potential analytical method for the rapid and inexpensive determination of AMB-Fubinaca in criminal evidences.

Keywords: AMB-fubinaca, criminal evidences, gas chromatography, synthetic cannabinoids, Vietnam

INTRODUCTION

Recently, the utilization of synthetic cannabinoids, both legal and illegal, has increased significantly worldwide.[1] This group of cannabinoid receptor agonists (i.e., CB1 receptor) is pharmacologically similar to the natural cannabinoids in cannabis plants such as Δ^9-tetrahydrocannabinol and cannabidiol.[2] Synthetic cannabinoids, commonly sold under the names of K2 and Spice,[3] are designed to avoid legal restrictions on natural cannabis due to their structural differences. Their psychoactive action is related to the strong binding affinity to the CB1 receptor; sometimes even surpass the natural compound potency. Thus, they have remained one of the most consumed psychoactive compounds among teenagers. Terribly, the uncontrollably use of these compounds has not only affected the users themselves (i.e., seizures, anxiety attacks, elevated heart rates, and death), but also been linked to countless violent behavior and criminal acts. Moreover, thousands of synthetic cannabinoids have been identified, divided into various families of WIN-xxx, JWH-xxx, CP-xxx, UR-xxx, and PB-xx, thus, making the management and criminal control processes become problematic. Therefore, urgent works are necessary to prevent this issue, especially in the developing countries, where laws regarding synthetic cannabinoid are ambiguous.

AMB-Fubinaca (methyl (2S)-2-{[1-[(4-fluorophenyl) methyl]indazole-3-carbonyl]amino}-3-methylbutanoate) is a new yet increasingly used indazole-based synthetic cannabinoid. AMB-Fubinaca was originally developed by Pfizer® in 2009, but was banned before any clinical trial registration.[4] It was the most common synthetic cannabinoid in drug seizures related patients, with >50% of the total criminal evidences, in the USA in 2017 and 2018.[5] Designed under the trade names of Carat Gold, Train Wreck 2, Barely Legal, iBlaze, Cloud 10, Kush, and Zombie, AMB-Fubinaca and its related derivatives have been increasingly uncovered

in numerous criminal evidences in Europe, the USA, and New Zealand, leading to dozens of mortal cases.[2,6-9] As a result, AMB-Fubinaca has been listed in the psychoactive substance list in many countries, including the Southeast Asia ones.[10] Nevertheless, in Vietnam, this compound was recently added into the official list by the end of 2018, with no specific guideline on the detection and quantitation of AMB-Fubinaca in criminal evidences. Consequently, the police investigation has encountered various limitations since then. Therefore, it is crucial to develop and validate the method for the determination of AMB-Fubinaca in samples related to drug-abuse criminal acts.

The previous reports have developed gas/liquid chromatography (GC/LC) methods to determine AMB-Fubinaca.[9,11-13] However, these methods mostly utilized the mass spectrometry (MS) as a detector (i.e., LC-MS and GC-MS). Although possessing acceptable separation and detection parameters, these methods require advance instruments, high expertise, lengthy analytical procedure development, and expensive running cost. Thus, they might not be suitable for quick and inexpensive detections in developing countries such as Vietnam, especially in the rural areas, where the most of the drug-abuse criminal evidences were found. To this end, we proposed a simpler method using the flame ionization detector (FID), which is commercially coupled with the GC machines.

This study aimed to develop and validate a novel gas chromatography with FID (GC-FID) method for the quantitation of AMB-Fubinaca in criminal evidences in the South of Vietnam from 2016 to 2018. The sample extraction process was optimized and the AMB-Fubinaca structure was elucidated using UV-visible spectroscopy, infrared spectroscopy, differential scanning calorimetry (DSC), MS, and nuclear magnetic resonance (NMR) techniques. Then, the GC-FID method was developed based on the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline. Finally, 30 criminal evidences were quantified using the novel method, in comparison with the well-known GC-MS method.

MATERIALS AND METHODS

Materials

Standardized AMB-Fubinaca (purity: 98.34%) and the internal standard, procaine (purity: 99.70%, batch QT125040518), were purchased from Institute of Drug Quality Control-Ho Chi Minh City, Vietnam. All solvents and other chemical reagents were of analytical grades or higher.

Sample Collection and Extraction

Thirty criminal evidences were collected from various drug-abuse criminal acts in the South of Vietnam during the period of 2016–2018. The samples were dried at 50°C, ground, labeled A1-A10, B1-B10, and C1-C10 for the year 2016, 2017, and 2018, respectively; and stored at 4°C for further investigations.

To extract the AMB-Fubinaca from criminal evidences, ultrasound-assisted extraction method was utilized. Briefly, 100 mg of the samples were mixed with the extraction solvent for 5 min, followed by sonication for a fixed amount of time. Finally, the extracts were filtered to remove the undissolved solids. To optimize the extraction conditions, several parameters were varied accordingly, including the extraction solvent (methanol, ethyl acetate, acetonitrile, and dichloromethane), the solvent volume (5, 10, and 20 mL), extraction temperature (40, 50, and 60°C), extraction time (10, 15, and 20 min), and extraction replication (1, 2, and 3 times). The AMB-Fubinaca peak area of each condition was analyzed and compared using the validated GC-MS method previously developed by Ivanov *et al*.[13]

AMB-Fubinaca Determination

To confirm that the extracted compound was AMB-Fubinaca, the extract solvent was evaporated using a rotavapor, followed by recrystallization in methanol. The obtained compound was tested its purity by thin layer chromatography; and its structure was determined by UV-visible spectrophotometry (Cintra 10e, solvent: Methanol, scanning mode), DSC (DSC Q200 V24.9), Fourier-transform infrared spectroscopy (FT-IR) (Perkin Elmer Spectrum RX1 FT-IR, KBr method, range: 4000–400 cm^{-1}), MS (MS mode from GC-MS equipment), and NMR (Avance 500, Bruker, solvent: DMSO, internal standard: Tetramethylsilane).

GC-FID Sample Preparation

The standard AMB-Fubinaca stock solution (1000 μg/mL) was prepared by dissolving 20 mg standardized AMB-Fubinaca in a 20-mL volumetric flask by methanol. Similarly, 40 mg of standardized procaine was dissolved in methanol to generate the internal standard procaine stock solution (2000 μg/mL). To prepare the standard samples, 3 mL of AMB-Fubinaca stock solution and 1 mL of procaine stock solution were thoroughly mixed in a 10-mL volumetric flask. Methanol was used to fill up the volume. The mixture was then filtered through a 0.45-μm membrane to yield the standard samples containing 300 μg/mL AMB-Fubinaca and 200 μg/mL procaine.

For the test samples, extracts with optimal condition from the "sample collection and extraction" section were mixed with the internal standard procaine, and filtered through a 0.45-μm membrane.

GC-FID Method Development and Validation

The GC-FID method was developed using the chromatography equipment (SCION, model GC-456) by determination of the suitable chromatographic conditions, including the carrier gas speed and temperature program. The requirement was that the AMB-Fubinaca peak resolution factor (Rs) of > 1.5 and asymmetry factor (As) in the range of 0.8–1.5. The method validation was conducted followed the ICH guideline, including system suitability, linearity, accuracy, precision, limit of detection (LOD), and limit of quantitation (LOQ).

Determination of AMB-Fubinaca in Criminal Evidences

Utilizing the newly developed GC-FID method, 30 samples, collected and extracted following Section 2.2 and Section 2.4 were determined their respective AMB-Fubinaca content. For the sake of comparison, these samples were also analyzed

by GC-MS method, previously reported by Ivanov *et al.*[13] Each sample was measured in triplicate and the results were presented in mean content percentages. Statistical differences between GC-FID and GC-MS method were noted.

Statistical Analysis

Differences between samples and groups were compared by Student's t-test and one-way ANOVA followed by Tukey's *post hoc* test, respectively. The results were considered to be statistically significant at $P < 0.05$.

RESULTS AND DISCUSSION

Extraction Optimization

To optimize the AMB-Fubinaca extraction conditions, several parameters were varied. In terms of extraction solvent, expectedly, due to its high solubility in methanol (100 µg/mL), methanol was the best solvent compared to ethyl acetate, acetonitrile, and dichloromethane. The AMB-Fubinaca amount extracted using methanol was 3 times higher than that of the least suitable one, dichloromethane. For the solvent volume, 10 mL was adequate for extracting 100 mg of samples, as a volume of 5 mL yielded low extracted amount and a volume of 20 mL had no significant difference compared to that of 10 mL. In addition, temperature plays a crucial role in the extraction process, as higher temperature could increase the AMB-Fubinaca solubility, yet might accelerate its degradation. Our results showed that 50°C was a suitable temperature, as higher ones reduce the extracted amount. Finally, the extraction time of 15 min, with two replications, yielded the highest AMB-Fubinaca amount, as longer extraction time and extra replications showed no significant difference. Overall, the optimal condition for AMB-Fubinaca extraction was to use 10 mL of methanol per 100 mg sample, sonicate at 50°C for 15 min, collect the extract, and repeat the process one more time with the remaining crude.

AMB-Fubinaca Determination

To re-confirm the isolated compound was AMB-Fubinaca, we further purified it using the recrystallization method, followed by structural elucidation by DSC and spectroscopic techniques such as UV-visible, FT-IR, MS, and NMR. All data, specifically the FT-IR and NMR peaks, were in agreement with the previous studies,[14-16] indicating that the extracted compound was AMB-Fubinaca [Table 1].

GC-FID Condition Development

To optimize the GC-FID condition for the AMB-Fubinaca quantitation, we varied numerous factors including the internal standard, the injector and detector temperatures, the carrier gas type and flow rate, and the heating programs. Our preliminary studies showed that the optimal condition was using nitrogen gas as a carrier at a flow rate of 3 mL/min, procaine as an internal standard, with a split ratio of 1:5 and an injection volume of 1 µL, utilizing the Rtx-5 column (30 m × 0.32 mm × 0.25 µm) with an injector temperature at 300°C and detector temperature at 280°C. The temperature program was 200°C for 2 min initially, followed by 290°C for 5 min with an increment of 30°C/min. The total runtime was 10 min for each sample. A standard chromatogram is demonstrated in Figure 1.

GC-FID Method Validation

Linearity and system suitability

Utilizing the optimal GC-FID condition, AMB-Fubinaca possessed a linearity with a regression equation of $y = 0.0059x–0.0062$ and $R^2 = 0.9994$, in the range of 4.5–900 µg/mL, with LOD and LOQ of 1.5 µg/mL and 4.5 µg/mL, respectively. Table 2 shows the analytical data from six replicate injections of both the standard samples and the test samples using the GC-FID optimal condition. The relative standard deviations (RSD) of all parameters were < 5%, the As was in the range of 0.8–1.5, the Rs was > 1.5, and the theoretical plates (N) was > 2000. Thus, these results indicated that this condition satisfied the system suitability test.

Specificity

Figure 2 shows the gas chromatograms of the carrier gas, the sample solvent, the standard and test samples, and the standard added test sample. The results clearly demonstrated

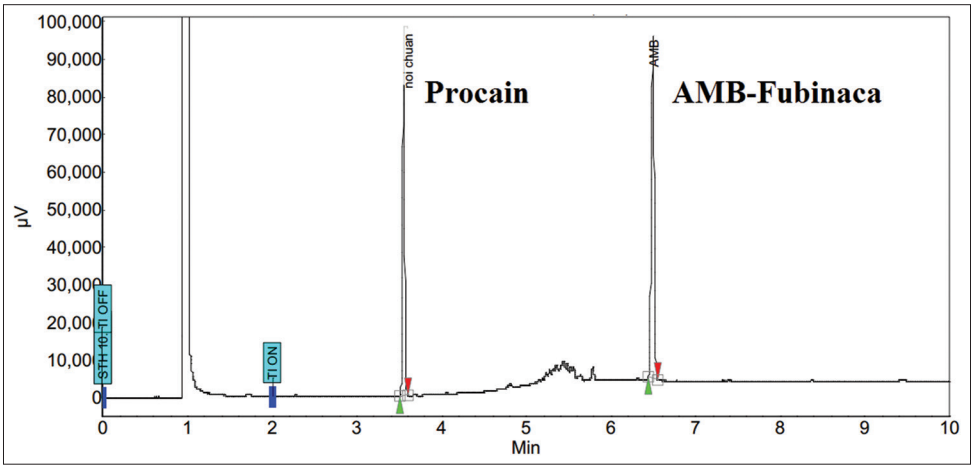


Figure 1: Standard chromatogram of AMB-Fubinaca using optimal GC-FID condition. Procain: the internal standard procaine

Table 1: Structural properties of AMB-Fubinaca, in comparison with data from the literature

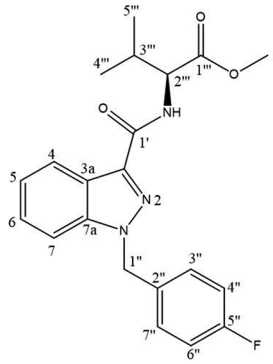
Physical properties: White crystal, odorless, soluble in DMSO, methanol, acetonitrile, and acetone, less soluble in water and chloroform.

Melting point: 121.8°C (DSC data)

Molecular weight: 383.423 g/mol (MS data)

UV-Visible spectroscopy

- Our data: 2 peaks, λ_{max} at 209 nm and 299 nm
- Literature:[16] 2 peaks, λ_{max} at 208 nm and 299 nm



FT-IR spectroscopy		
Wavenumber (cm^{-1})		**Functional group**
Our data	**Literature[14]**	
3422 (w)	3415 (w)	N – H amine
1740 (s)	1740 (s)	C = O ester
1674 (s)	1667 (s)	C = O amide
1534 (s)	1527 (s)	C = C aromatic
1218 (s)	1261 (s)	C – N
1181 (s)	1172 (s)	C – F
781 (m)	750 (m)	C – H aromatic

NMR spectroscopy				
Chemical shift (ppm, H number, peak cluster, J-coupling constant)				**Position (C, H)**
Our data		**Literature[15]**		
^{13}C (125 MHz)	**^{1}H (500 MHz)**	**^{13}C (150 MHz)**	**^{1}H (600 MHz)**	
162.6	-	161.2	-	1’
136.9	-	137.1	-	3
122.4	-	122.3	-	3a
121.7	8.15, ^{1}H, J = 8 Hz	121.8	8.17, ^{1}H, J = 8.3 Hz	4
122.7	7.29, ^{1}H, t, J = 7 Hz	122.8	7.28, ^{1}H, t, J = 7.2 Hz	5
127.0	7.45, ^{1}H, m	127.0	7.45, ^{1}H, J = 8.3, 6.9, 0.7 Hz	6
110.5	7.78, ^{1}H, J = 8.5 Hz	110.6	7.78, ^{1}H, J = 8.6 Hz	7
140.5	-	140.6	-	7a
51.8	5.78, 2H, s	51.6	5.77, 2H, s	1”
132.9	-	133.0	-	2”
129.4	7.32–7.35, 2H, m	129.5	7.32, ^{1}H, dd, J = 8.5, 2.1 Hz 7.31, ^{1}H, dd, J = 8.5, 2.1 Hz	3”/7”
115.5	7.14–7.18, 2H, m	115.5	7.16, ^{1}H, J = 7.9 Hz 7.15, ^{1}H, J = 7.9 Hz	4”/6”
161.2	-	161.6	-	5”
171.9	-	172.6	-	1”’

(Contd...)

Table 1: *(Continued)*

57.3	4.45, ^{1}H, dd, J = 7.1 Hz	56.9	4.40, ^{1}H, dd, J = 8.9, 6.5 Hz	2'''
29.9	2.26, ^{1}H, m	31.2	2.09, ^{1}H, m	3'''
19.0	0.97, 3H, d, J = 6.5 Hz	19.4	0.93, 3H, d, J = 6.9 Hz	4'''
18.6	0.95, 3H, d, J = 6.5 Hz	18.1	0.89, 3H, d, J = 6.5 Hz	5'''
51.6	0.945–0.977, 3H, m	-	-	OCH3
-	7.78, ^{1}H, J = 8.5 Hz	-	7.75, ^{1}H, J = 8.9 Hz	CONH

Table 2: System suitability parameters of the AMB-Fubinaca GC-FID method

Parameter	t_R (min)	S (mAU)	N	k'	Rs	As
Standard sample						
AMB-Fub						
Average	6.47	4002.5	161067.79	6.27	54.27	0.91
RSD%	0.10	0.75	1.09	0.10	1.07	0.01
Procaine						
Average	3.54	2248.6	105654.48	2.98		1.04
RSD%	0.12	1.37	1.85	1.28		1.56
Peak area ratio						
Average		1.78				
RSD%		0.8				
Test sample						
AMB-Fub						
Average	6.55	4557	157494	6.25	53.73	0.90
RSD%	0.06	0.78	1.67	0.20	0.67	0.45
Procaine						
Average	3.59	2005	104011	2.81		0.99
RSD%	0.11	2.18	2.72	1.05		1.48
Peak area ratio						
Average		2.27				
RSD%		0.95				

AMB-Fub: AMB-Fubinaca, t_R: Retention time, S: Peak area, N: Theoretical plates, k': Capacity factor, Rs: Resolution factor, As: Asymmetry factor

Table 3: Accuracy and precision (repeatability and intermediate precision) test data of the AMB-Fubinaca GC-FID method

Repeatability (n = 6)			
Average		0.48%	
RSD%		1.63%	
Inter-day precision (n = 18)			
Average		0.48%	
RSD%		0.79%	
Accuracy (n = 6)			
Added amount (%)	80.00%	100.00%	120.00%
Recovery (%)	98.85%	101.29%	100.63%
RSD%	1.04%	0.78%	0.81%

that the method possessed specificity for AMB-Fubinaca, as all peaks were completely separated, with no interference from both the carrier gas and the sample solvent. Moreover, similar retention time was observed in the test sample, standard sample, and standard added test sample, with corresponding peak areas in the latter.

Accuracy and precision

Table 3 shows the repeatability and inter-day precision, as well as the recovery rates of three batches of standard added test samples (80%, 100%, and 120%) following the ICH precision and accuracy test protocols, respectively. The recovery percentages were in the range of 98–102%, and all tests showed RSD% of <2%. Therefore, the method possessed accuracy and intermediate precision.

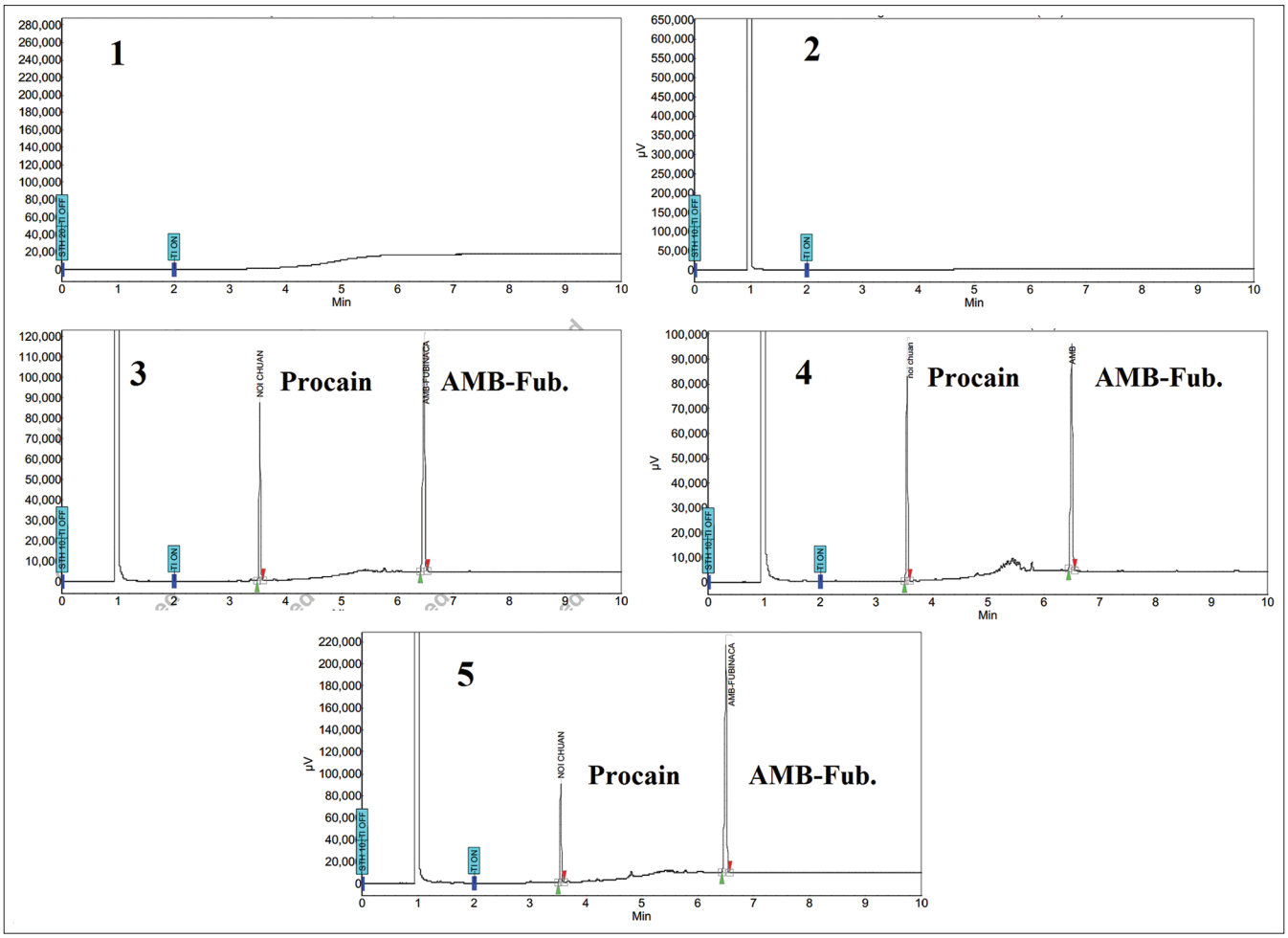


Figure 2: Gas chromatograms of (1) carrier gas (nitrogen); (2) sample solvent (methanol); (3) standard sample; (4) test sample; and (5) standard added test sample. AMB-Fub.: AMB-Fubinaca; Procain: The internal standard procaine

Table 4: AMB-Fubinaca content (% w/w) in 30 samples, collected in the South of Vietnam from 2016 to 2018, using the novel developed GC-FID method, in comparison with the available GC-MS method. No significant difference between GC-FID and GC-MS methods was noted

Year 2016			Year 2017			Year 2018		
Sample	**GC-FID (%)**	**GC-MS (%)**	**Sample**	**GC-FID (%)**	**GC-MS (%)**	**Sample**	**GC-FID (%)**	**GC-MS (%)**
A1	3.91	3.94	B1	4.32	4.23	C1	4.21	4.16
A2	2.67	2.71	B2	1.34	1.31	C2	6.00	5.97
A3	4.27	4.23	B3	4.74	4.64	C3	1.18	1.13
A4	2.93	3.03	B4	4.43	4.31	C4	0.62	0.70
A5	–	–	B5	5.37	5.34	C5	0.81	0.79
A6	–	–	B6	0.30	0.34	C6	2.92	2.95
A7	–	–	B7	2.75	2.69	C7	0.62	0.64
A8	2.45	2.36	B8	3.26	3.37	C8	0.62	0.63
A9	3.04	3.11	B9	–	–	C9	–	–
A10	–	–	B10	5.52	5.46	C10	3.92	4.01

–: Undetectable

Determination of AMB-Fubinaca in Criminal Evidences

The newly developed and validated GC-FID method was utilized for analyzing 30 samples collected from various drug-abuse criminal acts in the South of Vietnam during the period of 2016–2018. For the sake of comparison, a previously reported GC-MS method[13] was additionally used to determine the AMB-Fubinaca amount in the same samples. Interestingly, no significant difference was observed between the two

methods [Table 4], indicating the GC-FID method can be an alternative method in addition to the official GC-MS method, especially in access-limited laboratories in the developing countries.

CONCLUSION

This study was successful in the development and validation of a novel GC-FID method for the synthetic cannabinoid AMB-Fubinaca determination. A simple extraction and concentration process was additionally elaborated for samples obtained from drug-abuse criminal acts. This method demonstrated wide quantitation range from 4.5 to 900 μg/mL, with low LOD at 1.5 μg/mL. Moreover, in comparison to the GC-MS method, GC-FID showed no significant difference in terms of AMB-Fubinaca quantitative analysis. Therefore, this method could be utilized as an alternative method in addition to the official GC-MS method, especially in access-limited laboratories. Finally, as official method for determining AMB-Fubinaca in criminal evidences is lacking in Vietnam, this work might accelerate the process of crime detection and prevention.

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None.

CONFLICT OF INTERESTS

None.

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