

Identification of two new-type synthetic cannabinoids, *N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide (APICA) and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA), and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products

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Abstract Two new-type synthetic cannabinoids, *N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide (APICA, **1**) and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA, **2**), have been identified as designer drugs in illegal products being sold in Japan. The identification was based on liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), high-resolution MS and nuclear magnetic resonance (NMR) analyses. Both mass and NMR spectrometric data revealed that **1** was 1-pentyl-*N*-tricyclo[3.3.1.1^{3,7}]dec-1-yl-1*H*-indole-3-carboxamide, and **2** was 1-pentyl-*N*-tricyclo[3.3.3.1^{3,7}]dec-1-yl)-1*H*-indazole-3-carboxamide. Although many of the synthetic cannabinoids detected in illegal products, such as JWH-018, have a 3-carbonyl indole moiety, compounds **1** and **2** are a new type of synthetic cannabinoid having an amide and an adamantyl group, and **2** also has an indazole group in place of an indole group. There has been no synthetic, chemical, or biological information about **1** or **2** until now, making this the first report of these cannabimimetic compounds (**1** and **2**) as designer drugs. In addition, five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, are also described herein as newly distributed designer drugs in Japan.

Keywords *N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide · *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide · AM-1220 · AM-2233 · AM-1241 · AM-1248

Introduction

Many herbal products with brand names such as “Spice” and “Herbal Incense” began to appear in the illegal drug market in 2006 [1]. Following the identification of synthetic cannabinoids as the psychoactive ingredients of these products by our group and a group in Germany in 2009 [2–4], these illegal herbal products, adulterated with synthetic cannabinoids, have received broad global attention due to their cannabimimetic effects. Since then, more than 20 synthetic cannabinoids have been detected as psychoactive ingredients in herbal products or chemical powders around the world [1–21].

The cannabinoids detected so far belong to six different groups: cyclohexylphenol [such as cannabicyclohexanol (CCH) and CP-47497], classical cannabinoids (such as HU-210), naphthoylindoles (such as JWH-018 and JWH-073), phenylacetylindoles (such as JWH-250 and JWH-203), benzoylindoles (such as AM-694 and RCS-4), and naphthoynaphthalenes (such as CB-13) [9, 15]. In addition, most of these agents have been shown to have binding affinity for cannabinoid CB₁ (central type) and/or CB₂ (peripheral type) receptors [22].

A number of countries began to control these compounds in 2009, in consideration of their potential health problems [1, 15, 16]. In Japan, 16 synthetic cannabinoids (CCH, CP-47,497, JWH-018, JWH-073, JWH-250, JWH-

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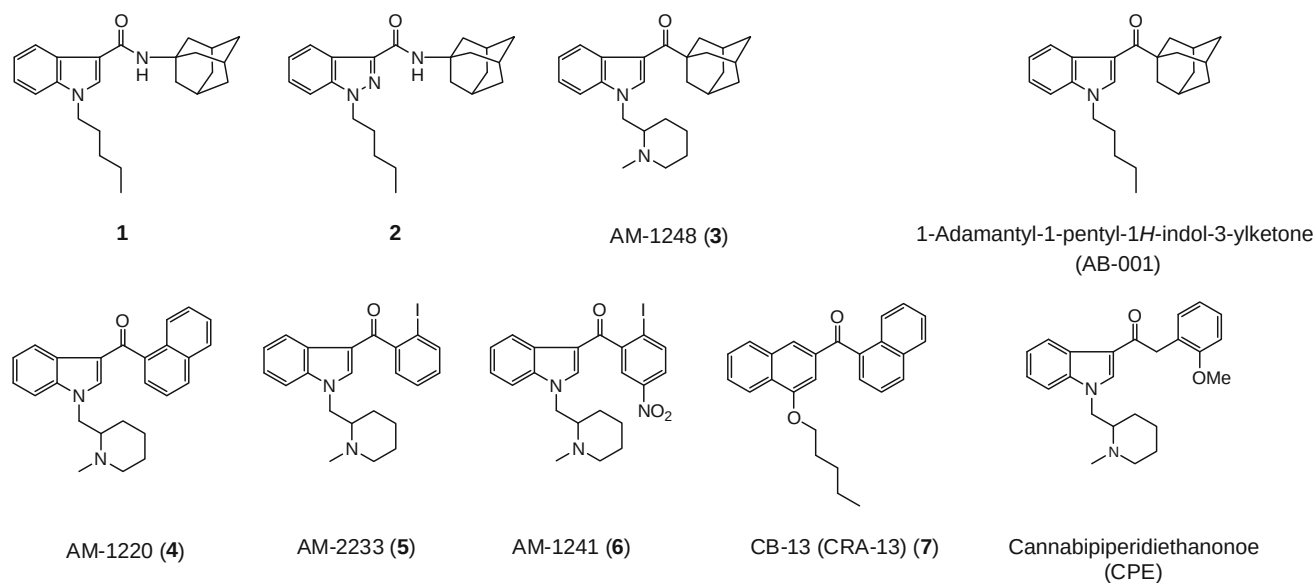


Fig. 1 Structures of the detected (1–7) and related synthetic cannabinoids

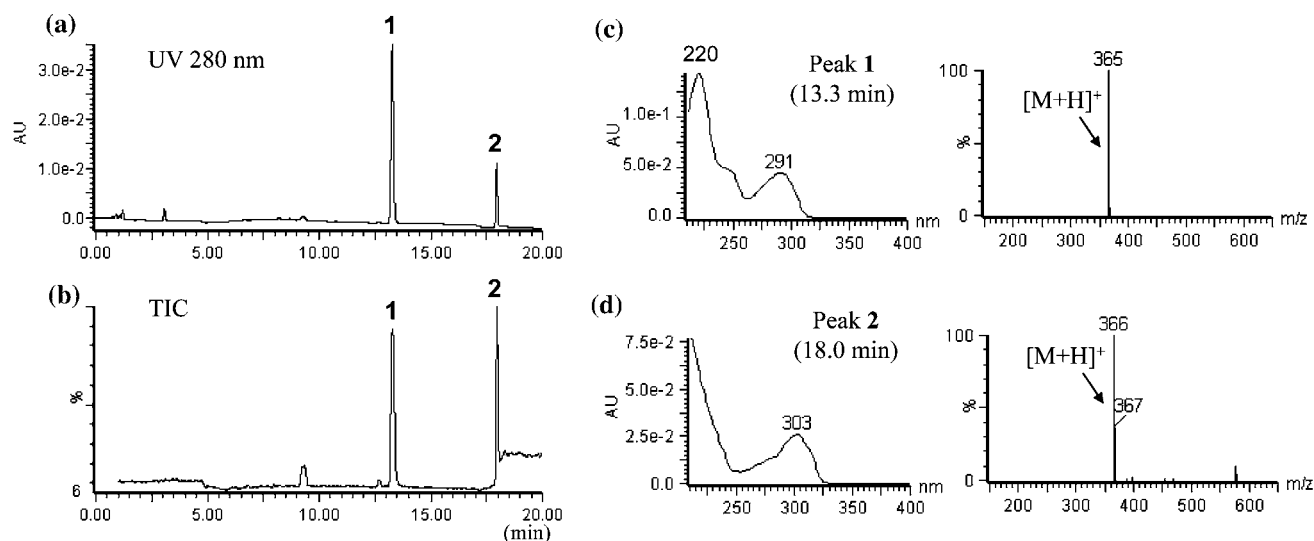


Fig. 2 HPLC UV and total ion chromatograms (a, b, respectively) of the extract of product A and UV and ESI mass spectra of peaks 1 and 2 (c, d, respectively)

015, JWH-122, JWH-081, JWH-200, JWH-251, JWH-019, JWH-203, JWH-210, AM-2201, AM-694, and RCS-4) were controlled as designated substances (Shitei-Yakubutsu) under the Pharmaceutical Affairs Law as of October 2011. However, in response to such control measures, new analogs of the controlled substances subsequently appeared as other ingredients in these herbal and chemical products.

As described in our earlier reports [2, 3, 6, 8–10], we have been conducting an ongoing survey of designer drugs in illegal markets in Japan, and we have found two synthetic cannabinoids of a new type, *N*-(1-adamantyl)-1-pentyl-1*H*-indole-3-carboxamide (APICA, **1**) and *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA, **2**), which cannot be classified into the previous six

cannabinoid groups (Fig. 1). In this study, we describe our identification of these two new compounds (**1** and **2**) in a chemical product along with the detection of five newly distributed synthetic cannabinoids, AM-1248 (**3**), AM-1220 (**4**), AM-2233 (**5**), AM-1241 (**6**), and CB-13 (CRA-13, **7**) in herbal products (Fig. 1).

Materials and methods

Samples for analysis

The analyzed samples were purchased via the Internet from August to December 2011 as chemical or herbal products

being sold in Japan. The chemical product (A), which was called “Fragrance Powder,” consisted of about 400 mg of a pale brown powder. Each of the herbal products (B–D) contained about 3 g of mixed dried plants.

Chemicals and reagents

Authentic AM-1248 (**3**), AM-1220 (**4**), AM-2233 (**5**), and CB-13 (**7**) were purchased from Cayman Chemical Company (Ann Arbor, MI, USA). AM-1241 (**6**) was obtained from Sigma-Aldrich (St. Louis, MO, USA). All other common chemicals and solvents were of analytical reagent grade or HPLC grade. As solvents for nuclear magnetic resonance (NMR) analysis, pyridine-*d*₅ (99.96 %), benzene-*d*₆ (99.96 %), CD₃OD (99.96 %), and CD₃OH (99.8 %) were purchased from the ISOTEC division of Sigma-Aldrich.

Preparation of sample solution

For qualitative analyses, 2 mg of the chemical product was used for extraction with 1 ml of methanol under ultrasonication for 10 min. For the herbal products, 10 mg of each product was crushed into powder and extracted with 1 ml of methanol under ultrasonication for 10 min. After centrifugation (5 min, 3000 rpm) of the extract, the supernatant solution was passed through a centrifugal filter (Ultrafree-MC, 0.45 µm filter unit; Millipore, Bedford, MA, USA) to afford sample solution. If necessary, the solution was diluted with methanol to a suitable concentration before instrumental analyses.

Analytical conditions

Ultra-performance liquid chromatography-electrospray ionization-mass spectrometry (UPLC-ESI-MS) was

Table 1 NMR data of compounds **1** and **2**

Position	APICA (1) in pyridine- <i>d</i> ₅ ^a			APINACA (2) in benzene- <i>d</i> ₆ ^{a,b}		
	¹³ C	¹ H	HMBC ^c	¹³ C	¹ H	HMBC ^c
1	165.2	–	–	161.8	–	–
2'	130.7	8.14, 1H, s	1, 3', 3'a, 7'a, 1'',	–	–	–
3'	112.6	–	–	139.3	–	–
3'a	127.8	–	–	123.8	–	–
4'	122.4	8.86, 1H, m	3', 3'a, 5', 6', 7'a	124.2	8.97, 1H, dd-like, <i>J</i> = 7.9, 1.0 Hz	3', 3'a, 5', 6', 7'a
5'	121.3	7.36, 1H, td, <i>J</i> = 6.9, 1.4 Hz, overlapped	3'a, 7'	122.5	7.07, 1H, td, <i>J</i> = 7.9, 1.0 Hz, overlapped	3'a, 6', 7'
6'	122.6	7.34, 1H, td, <i>J</i> = 6.9, 1.4 Hz, overlapped	4', 7', 7'a	126.6	7.10, 1H, td, <i>J</i> = 7.9, 1.0 Hz, overlapped	4', 5', 7'a
7'	110.5	7.48, 1H, dd-like, <i>J</i> = 6.9, 1.4 Hz	3'a, 5', 6'	109.1	6.95, 1H, dd, <i>J</i> = 7.9, 1.0 Hz	3'a, 5'
7'a	137.1	–	–	141.3	–	–
1''	46.5	3.92, 2H, t, <i>J</i> = 7.2 Hz	2', 7'a, 2'', 3''	49.1	3.87, 2H, t, <i>J</i> = 7.2 Hz	7'a, 2'', 3''
2''	29.9	1.53, 2H, quintet, <i>J</i> = 7.6 Hz	1'', 3'', 4''	29.6	1.60, 2H, m, overlapped	1'', 3'', 4''
3''	29.0	0.99, 2H, m	2'', 4'', 5''	29.0	0.98, 2H, m	1'', 2'', 4'', 5''
4''	22.4	1.05, 2H, m	2'', 3'', 5''	22.4	1.06, 2H, m	2'', 3'', 5''
5''	13.9	0.66, 3H, t, <i>J</i> = 7.2 Hz	3'', 4''	13.9	0.71, 3H, t, <i>J</i> = 7.2 Hz	3'', 4''
1'''	52.0	–	–	51.7	–	–
2'''/8'''/9'''	42.3	2.36, 6H, brs	1''', 3'''/5'''/7''', 4'''/6'''/10'''	42.1	2.21, 6H, brs	1''', 3'''/5'''/7''', 4'''/6'''/10'''
3'''/5'''/7'''	30.0	1.99, 3H, brs	1'''	29.9	1.92, 3H, brs	1''', 4'''/6'''/10'''
4'''/6'''/10'''	36.8	1.65, 3H, brd, <i>J</i> = 11.3 Hz	3'''/5'''/7'''	36.7	1.59, 3H, brd, <i>J</i> = 12.4 Hz, overlapped	3'''/5'''/7''', 2'''/8'''/9'''
		1.57, 3H, brd, <i>J</i> = 11.3 Hz	3'''/5'''/7''', 2'''/8'''/9'''		1.51, 3H, brd, <i>J</i> = 12.4 Hz	3'''/5'''/7''', 2'''/8'''/9'''
NH	–	7.20, 1H, brs	1, 1'', 2'''/8'''/9'''	–	6.92, 1H, brs	1, 1'', 2'''/8'''/9'''

^a Recorded at 600 MHz (¹H) and 150 MHz (¹³C), respectively; data in δ ppm (*J* in Hz)

^b Recorded at 30 °C

^c *J* = 8 or 4 Hz; the proton signal correlated with the indicated carbons

performed on an ACQUITY UPLC system with a mass detector and a photodiode array (PDA) detector (Waters, Milford, MA, USA) [6, 8]. The sample solutions were separated with an ACQUITY UPLC HSS T3 column

(100 mm × 2.1 mm i.d., particle size 1.8 μm; Waters) protected by a Van Guard column (5 mm × 2.1 mm i.d., 1.8 μm; Waters) at 40 °C. Each analysis was carried out with a binary mobile phase consisting of solvent A (0.1 % formic acid in

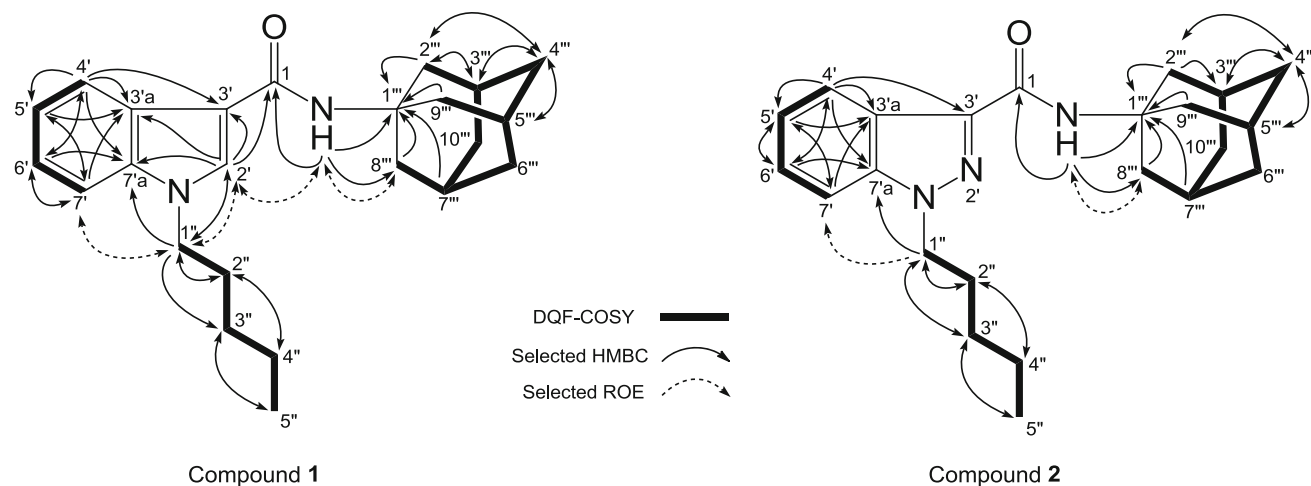


Fig. 3 DQF-COSY, selected HMBC, and selected ROE correlations of **1** and **2**

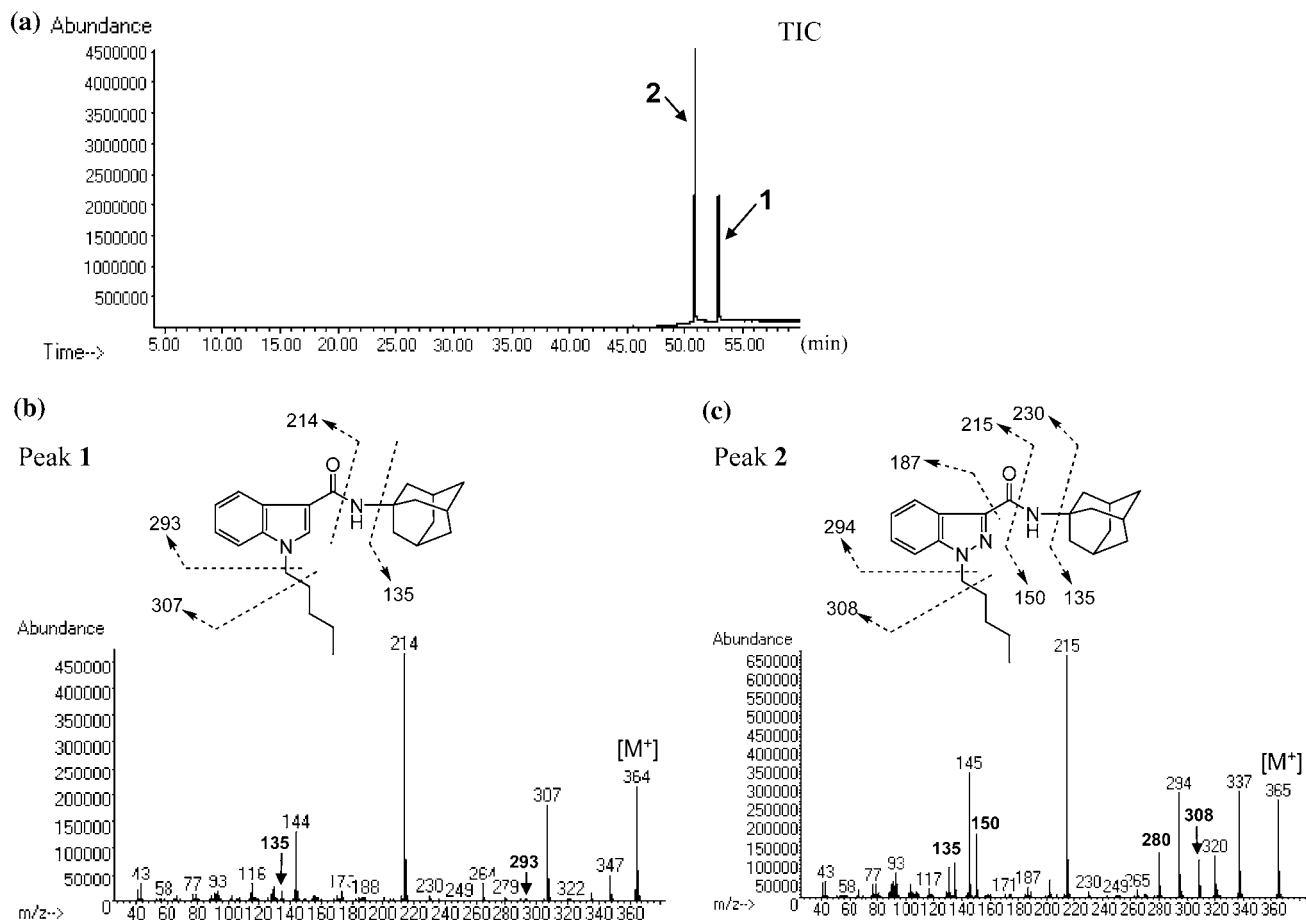


Fig. 4 GC-MS analysis of product A. Total ion chromatogram (a); EI mass spectra of the detected peaks at 52.85 min (b, **1**) and 50.82 min (c, **2**)

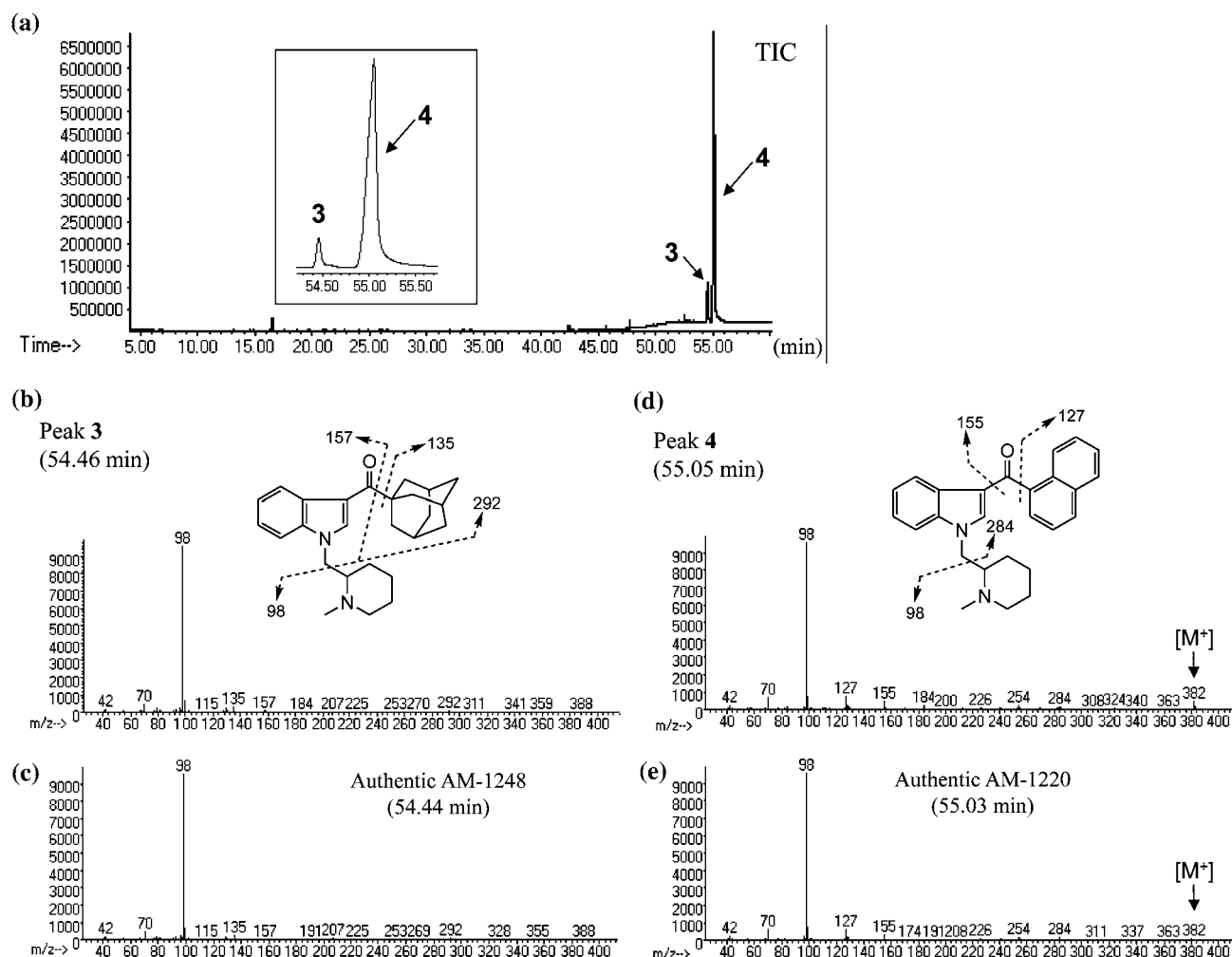


Fig. 7 GC-MS analysis of product B. Total ion chromatogram (a); EI mass spectra of the detected peaks **3** (54.46 min) and **4** (55.05 min) and authentic AM-1248 and AM-1220 (b, d and c, e, respectively)

helium gas flow rate, 2.0 l/min; gas heater temperature, 250 °C; discharge electrode needle voltage, 3200 V; and voltages of electrodes 1 and 2, 100 and 250 V, respectively. Internal mass number calibration was achieved using PEG600, and diphenhydramine (C₁₇H₂₁NO) and verapamil (C₂₇H₃₈N₂O₄) were used as internal standards for each accurate mass analysis. The product itself or an extract was directly exposed to the vicinity of the DART ion source.

The NMR spectra were obtained on ECA-600 spectrometers (JEOL). Assignments were made via ¹H-NMR, ¹³C-NMR, heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), double quantum filtered correlation spectroscopy (DQF-COSY), and rotating frame nuclear Overhauser effect (ROE) spectra.

Isolation of compounds **1** and **2**

A 400-mg sample of a pale brown powder was extracted with 20 ml of methanol by ultrasonication for 10 min. The

extractions were repeated three times, and the supernatant fractions were combined and evaporated to dryness. The extract was placed on a preparative silica-gel thin-layer chromatography (TLC) plate (Silica Gel 60, 20 × 20 cm, 2 mm; Merck, Darmstadt, Germany), which was then developed using hexane/ethyl acetate (3:1). A portion of the silica gel in the TLC plate that contained the target compound, as detected by UV 254 nm and DART-TOF-MS, was scraped from the plate to get fractions 1 and 2. Each fraction was eluted with chloroform to obtain compound **1** (55 mg) as a white solid, and compound **2** (26 mg) as a yellow oil, respectively.

Results and discussion

Identification of unknown peaks **1** and **2**

By UPLC-MS analysis of the chemical product A, two peaks **1** and **2**, both having UV280 absorption, were mainly

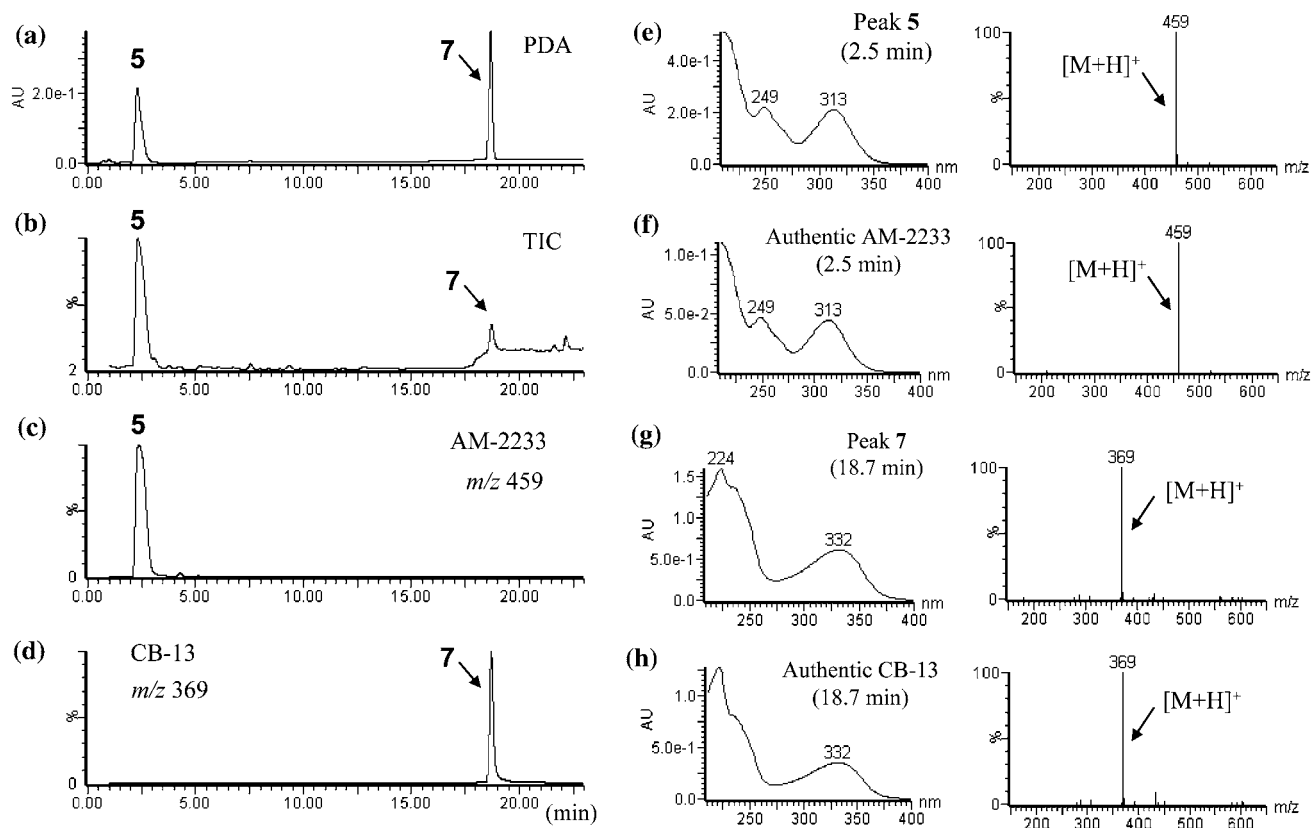


Fig. 8 HPLC UV and total ion chromatograms (a, b, respectively) and mass chromatograms of m/z 459 and m/z 369 (c, d, respectively) of product C and UV and ESI mass spectra of peaks 5 and 7 and authentic AM-2233 and CB-13 (e, g and f, h, respectively)

observed in the total ion chromatogram (TIC) (Fig. 2a, b). Their quasi-molecular ion $[M+H]^+$ signals were m/z 365 and 366, respectively (Fig. 2c, d).

After isolation of compounds 1 and 2, their accurate mass spectra were measured by DART-TOF-MS (positive mode). The observed ion peaks at 365.2590 and 366.2553 suggested that the quasi-molecular formulae of 1 and 2 were $C_{24}H_{33}N_2O$ (calcd. 365.2593) and $C_{23}H_{32}N_3O$ (calcd. 366.2545), respectively.

Next, we elucidated the chemical structure of compound 1 by NMR analyses (Table 1; Fig. 3). The 1H - and ^{13}C -NMR spectra of 1 suggested 32 protons and 24 carbons as shown in Table 1. These NMR data were very similar to those of 1-adamantyl-1-pentyl-1*H*-indol-3-yl ketone (AB-001; molecular formula: $C_{24}H_{31}NO$) (Fig. 1) [19] except for the quarternary carbon signal at δ_c 165.2 (C-1), which was high-field shifted from δ_c 202.0 and for the additional broad proton signal at δ_H 7.20 (1H, brs). The difference in molecular formula between AB-011 and compound 1 was NH, and HMQC analysis of the broad proton signal suggested that the hydrogen atom connected to a heteroatom. These data strongly suggested that compound 1 possessed an amide group instead of the keto group of AB-011. Therefore, the structure was deduced to be *N*-(1-

adamantyl)-1-pentyl-1*H*-indole-3-carboxamide (IUPAC name: 1-pentyl-*N*-tricyclo[3.3.3.1^{3,7}]dec-1-yl)-1*H*-indole-3-carboxamide) and named APICA. The fragment ions by GC-MS analysis of peak 1, as shown in Fig. 4b, and the observed DQF-COSY, HMBC, and ROE correlations in Fig. 3 further confirmed the structure.

The difference between the molecular formula of compound 2 and that of compound 1 is the additional nitrogen atom in the place of the absent CH. The comparison of 1H -NMR and ^{13}C -NMR data between compounds 2 and 1 revealed the loss of the methine unit at the 2'-position of the indole group of compound 1 in the structure of compound 2. Furthermore, the major fragment ions at m/z 215, 294, and 308 of peak 2 instead of those at m/z 214, 293, and 307 of peak 1 (Fig. 4b, c) by GC-MS analyses strongly suggested the replacement of the methine unit with a nitrogen atom. Therefore, the structure of compound 2 was elucidated as *N*-(1-adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide.

The clear difference of the UV spectrum of peak 2 compared with that of peak 1 (Fig. 2c, d), also supports the structural change from an indole to an indazole moiety. To confirm the structure, DQF-COSY, HMBC, and ROE NMR analyses were carried out and the observed

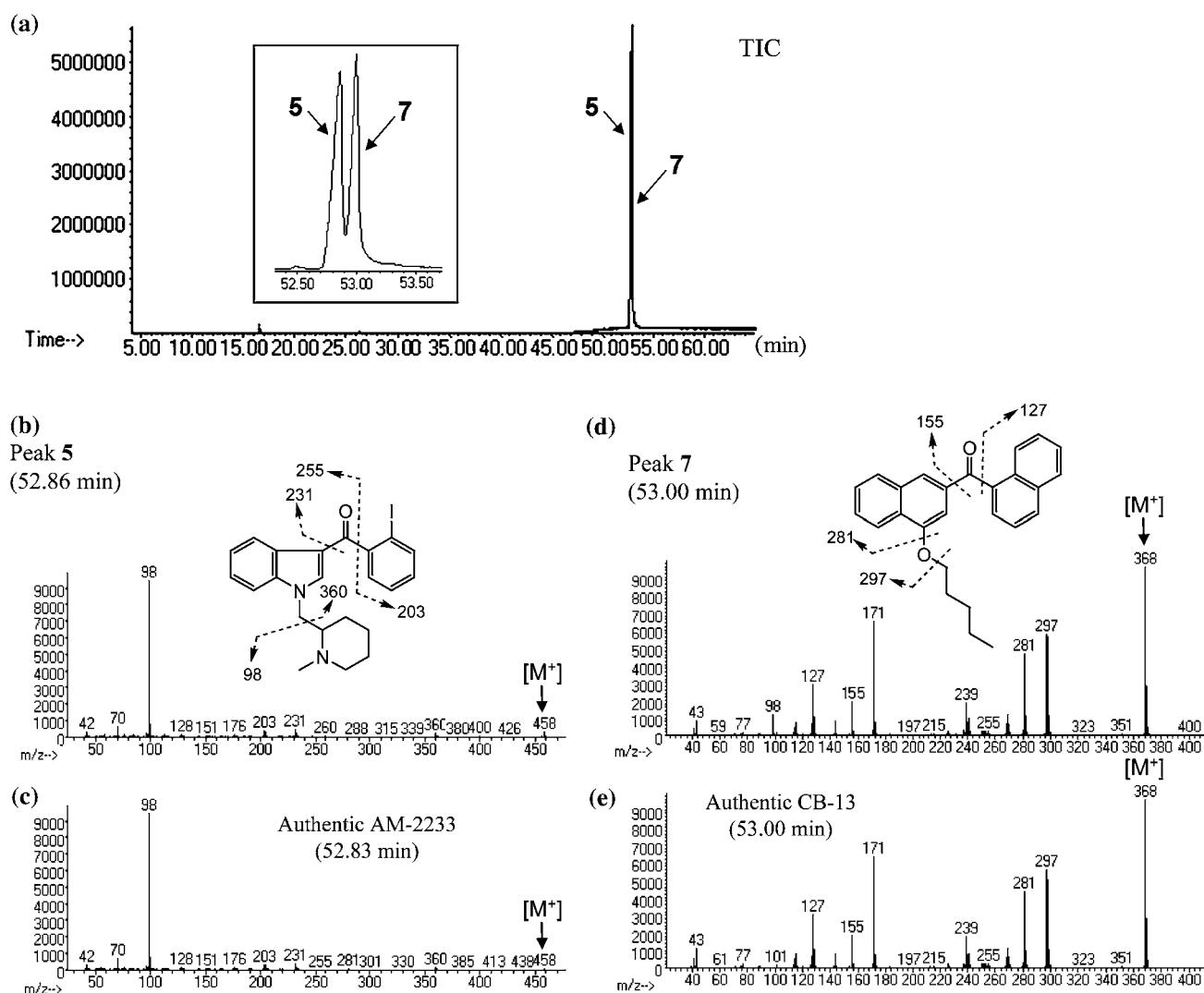


Fig. 9 GC-MS analysis of product C. Total ion chromatogram (a); EI mass spectra of the detected peaks 5 (52.86 min) and 7 (53.00 min) and authentic AM-2233 and CB-13 (b, d and c, e, respectively)

correlations shown in Table 1 and Fig. 3 are well consistent with it.

Finally, the deuterium isotope effect of the NH amide proton on the ¹³C chemical shift was measured to definitively determine the connection between the 1-pentyl-1H-indazole moiety and the 1-adamantyl-carboxamide moiety. The ¹³C-NMR spectrum of **2**, recorded in CD₃OH, was compared with that recorded in CD₃OD. The isotope shift values for the ¹³C-NMR signals of **2** are shown in Fig. 5. The largest and second largest deuterium shifts (0.11 and 0.07 ppm) were observed at the C-1''' position of the adamantyl moiety and the C-1 position of the carbonyl moiety, respectively. The third largest shift of 0.02 ppm, which was attributed to the three-bond deuterium isotope effects of the NH proton on each carbon, was observed in the ¹³C-NMR signal at C-3' of the indazole group or C-2'''/8'''/9''' of the adamantyl group. These results strongly

suggested that the 1-pentyl-1H-indazole moiety was connected at the 3'-position of the indazole to the carboxy-amide. Therefore, compound **2** was definitively identified as *N*-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (IUPAC name: 1-pentyl-*N*-tricyclo[3.3.3.1^{3,7}]dec-1-yl)-1H-indazole-3-carboxamide) and named APINACA.

Compounds **1** and **2** are novel cannabimimetic substances and their chemical or pharmacological information has not been reported, although the analogs of compound **2** in which the Cl-, I-, or CN-group was substituted for the terminal methyl of the pentyl moiety (position 5'' in Fig. 3) were synthesized as cannabimimetic ligands [23].

Identification of unknown peaks 3–7

Unknown peaks **3** and **4** were detected in the LC-MS and GC-MS chromatograms of product B, as shown in Figs. 6

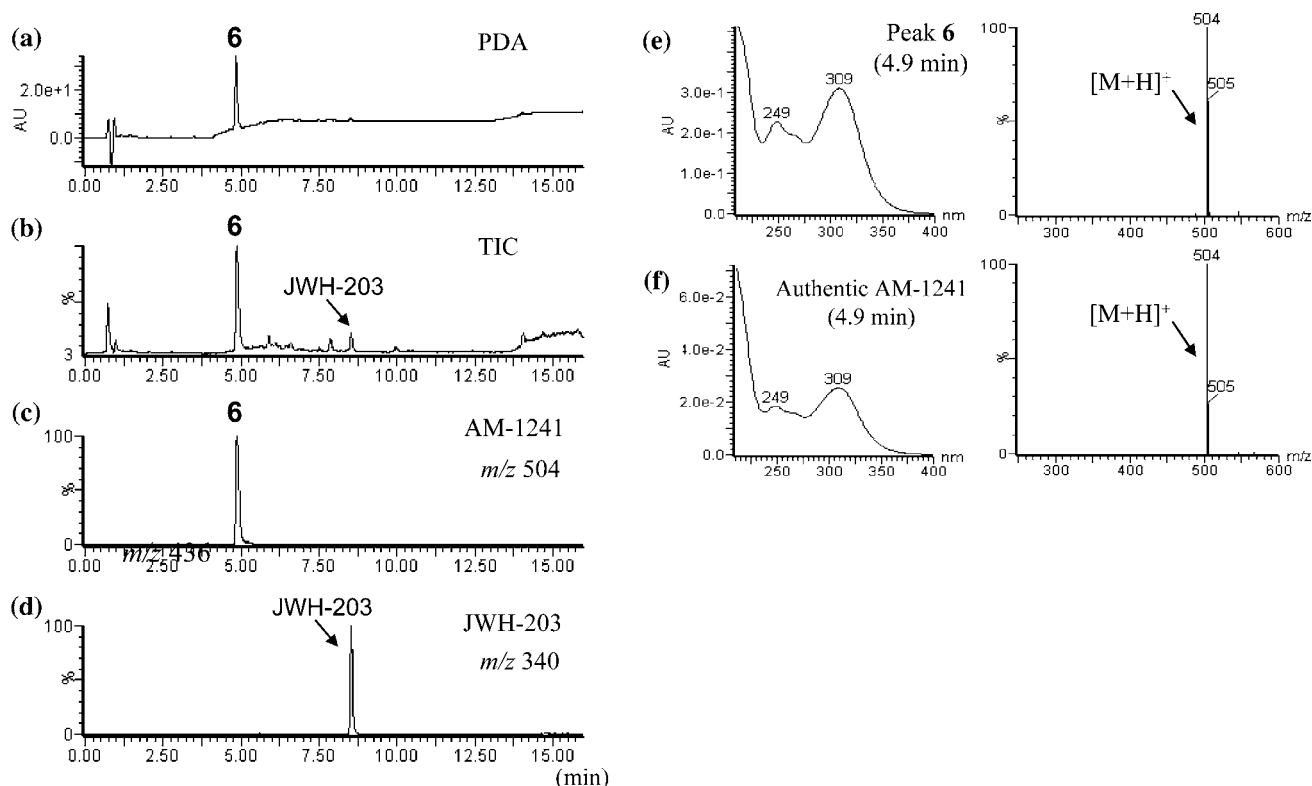


Fig. 10 HPLC UV and total ion chromatograms (a, b, respectively) and mass chromatograms of m/z 504 and m/z 340 (c, d, respectively) of product D and UV and ESI mass spectra of peak 6 and authentic AM-1241 (e, f, respectively)

and 7. The LC-MS chromatograms demonstrated that peak 3 at 5.2 min (Fig. 6d, e) and peak 4 at 3.7 min (Fig. 6c, g) showed protonated ion signals ($[M+H]^+$) at m/z 391 and 383, respectively. In the GC-MS chromatogram of peaks 3 and 4 (Fig. 7), the most obvious common feature was the presence of the fragment at m/z 98, which indicated that these compounds (3 and 4) may contain an *N*-methyl-piperidine-2-yl-methyl group as seen in cannabipiperidethanone (CPE), as shown in Fig. 1. CPE was previously reported by us as a cannabimimetic compound used in designer drugs and shown to have binding affinity to cannabinoid CB₁/CB₂ receptors [10]. The proposed fragment patterns and the presumed structures of 3 (AM-1248) and 4 (AM-1220) are also shown in Fig. 7b, d. The LC-MS and GC-MS spectra of the purchased authentic AM-1248 and AM-1220, the molecular weights of which were 390 and 382, are shown (Figs. 6f, h, 7c, e); compounds 3 and 4 were found to be identical to AM-1248 and AM-1220, respectively. It is worth noting in this context that AM-1220 (4) has been detected in herbal products present on the German market [20].

As shown in Figs. 8 and 9, unknown peaks 5 and 7 were detected in LC-MS and GC-MS chromatograms of product C. The LC-MS chromatograms showed that peaks 5 and 7 exhibited protonated ion signals ($[M+H]^+$) at m/z 459 and 369, respectively (Fig. 8e, g). The proposed fragment

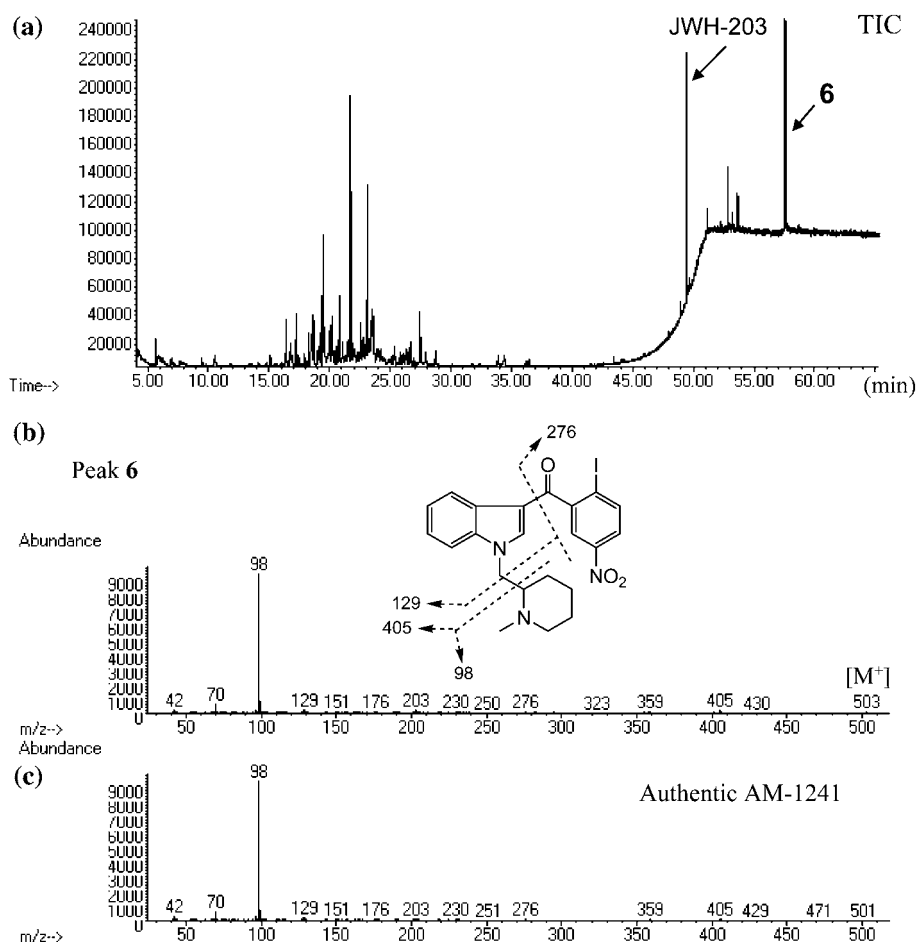
patterns and the presumed structures of 5 (AM-2233) and 7 (CB-13) from the GC-MS analysis are also shown in Fig. 9b, d. LC-MS and GC-MS analyses of the purchased authentic AM-2233 and CB-13, the molecular weights of which were 458 and 368, were performed (Figs. 8f, h, 9c, e), and compounds 5 and 7 were identified as AM-2233 and CB-13, respectively. CB-13 (7) has also been detected in herbal products present in European countries [20].

Similar analyses were used to determine the unknown peak 6 with the known peak of JWH-203, which is controlled as a designated substance (Shitei-Yakubutsu), in the chromatograms of product D (Figs. 10, 11). First, it was deduced that peak 6 was nitro-AM2233 (5) based on the LC-MS and GC-MS data (Figs. 10e, 11b), and this peak was finally attributed to AM-1241 by direct comparison of the data to those of the purchased authentic AM-1241 (Figs. 10f, 11c). Although AM-1241 is known as a selective CB₂ receptor agonist [24], this is the first report to detect AM-1241 as an ingredient in illegal products.

Features of synthetic cannabinoids detected in illegal products

The pharmacological activities of the two novel compounds 1 and 2 have not been reported. However, analogs of 2 in which a Cl-, I-, or CN-group is substituted for the

Fig. 11 GC-MS analysis of product D. Total ion chromatogram (a); EI mass spectra of the detected peak 6 (57.57 min) and authentic AM-1241 (b, c, respectively)



terminal methyl of the pentyl moiety (position 5'' in Fig. 3) have been reported to exhibit potent affinity for cannabinoid CB₁/CB₂ receptors; their K_i (nM) values for CB₁/CB₂ are 1.7/1.3, 0.6/0.2, and 2.3/0.3, respectively [23]. Therefore, it is assumed that compounds **1** and **2** may have similar cannabimimetic activities. On the other hand, compounds **3–7** have been reported as synthetic cannabinoids possessing affinity for cannabinoid CB₁ and/or CB₂ receptors. Makriyannis and Deng [25] described the high affinity of AM-1248 (**3**) for CB₁/CB₂ receptors [K_i (nM) = 11.9/4.8]. AM-1220 (**4**) and AM-2233 (**5**) were first synthesized as candidates for radioactive ligands for imaging the neuronal cannabinoid receptor, and their binding activities to the CB₁ receptor were reported [K_i (nM) values = 0.8 and 2.8 nM, respectively] [26, 27]. AM-2233 (**5**) was also reported to have the effect of drug discrimination for rats together with JWH-018 [28]. CB-13 (CRA-13, **7**) was reported as a dual agonist for CB₁/CB₂ receptors with cannabimimetic pharmaceutical effects [29]. On the other hand, AM-1241 (**6**) acts as a selective agonist for CB₂ receptor [24].

The detected compounds (**1–6**) have bulky structures such as an adamantyl group and *N*-methyl-piperidine-2-methyl group, although CB-13 (**7**) does not (Fig. 1).

Adamantyl-based compounds are used clinically for the treatment of neurological conditions. It has been reported that the steric bulk of the adamantyl group can: (1) restrict or modulate intramolecular reactivity; and (2) impede the access of hydrolytic enzymes, thereby increasing drug stability and plasma half-life [30]. AM-411, in which an adamantyl group is appended to the C-3 position of Δ⁸-tetrahydrocannabinol (Δ⁸-THC), was reported to have sevenfold higher selectivity for CB₁ receptor than its des-adamantyl analog, Δ⁸-THC, and its *in vivo* cannabimimetic activity was shown to have greater potency than that of Δ⁹-tetrahydrocannabinol [30]. The *N*-methyl-piperidine-2-methyl group also may be an important moiety for controlling the lipophilicity of the aminoalkylindole ligands such as AM-1220 and AM-2233 in binding to CB₁/CB₂ receptors [26, 27]. Therefore, there is a worrisome possibility that the related analogs of compounds **1–6** will appear as new designer drugs in illegal products.

Conclusions

In the present study, we have identified two novel cannabimimetic compounds (**1** and **2**) having an amide and an

adamantyl group in illegal products being sold in Japan. Compound **2** also has an indazole group in place of an indole group. In addition, five newly distributed cannabimimetic cannabinoids, AM-1248 (**3**), AM-1220 (**4**), AM-2233 (**5**), AM-1241 (**6**), and CB-13 (CRA-13, **7**) were found in illegal products. The five compounds (**3–7**) have previously been shown to have binding affinity for cannabinoid CB₁ and/or CB₂ receptors and limited cannabimimetic effects, albeit only in animal models [24–29]. However, there are no pharmacological data on compounds **1** and **2**. Because of the limited pharmacological and toxicological information for most of these cannabimimetic compounds, it is difficult to predict the health risks associated with their use. Therefore, continuous monitoring of illegal products, rapid identification of unknown ingredients, and sharing of the information globally will be needed to prevent their abuse worldwide.

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