Forensic Science International 227 (2013) 21–32

Contents lists available at SciVerse ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

URB-754: A new class of designer drug and 12 synthetic cannabinoids detected in illegal products☆

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ARTICLE INFO

Article history:
Received 27 July 2012
Received in revised form 23 August 2012
Accepted 27 August 2012
Available online 9 October 2012

Keywords:
URB-754
(*N*,5-dimethyl-*N*-(1-oxo-1-(*p*-tolyl) butan-2-yl)-2-(*N*′-(*p*-tolyl)ureido)benzamide)
5-Fluoropentyl-3-pyridinoylindole
(4-Ethylnaphtyl)-AM-2201 (EAM-2201)
Synthetic cannabinoids
4-Methylbuphedrone

ABSTRACT

URB-754 (6-methyl-2-[(4-methylphenyl)amino]-1-benzoxazin-4-one) was identified as a new type of designer drug in illegal products. Though many of the synthetic cannabinoids detected in illegal products are known to have affinities for cannabinoid CB_1/CB_2 receptors, URB-754 was reported to inhibit an endocannabinoid deactivating enzyme. Furthermore, an unknown compound (*N*,5-dimethyl-*N*-(1-oxo-1-(*p*-tolyl)butan-2-yl)-2-(*N*′-(*p*-tolyl)ureido)benzamide), which is deduced to be the product of a reaction between URB-754 and a cathinone derivative 4-methylbuphedrone (4-Me-MABP), was identified along with URB-754 and 4-Me-MABP in the same product. It is of interest that the product of a reaction between two different types of designer drugs, namely, a cannabinoid-related designer drug and a cathinone-type designer drug, was found in one illegal product. In addition, 12 cannabimimetic compounds, 5-fluoropentyl-3-pyridinoylindole, JWH-307, JWH-030, UR-144, 5FUR-144 (synonym: XLR11), (4-methylnaphtyl)-JWH-022 [synonym: *N*-(5-fluoropentyl)-JWH-122], AM-2232, (4-methylnaphtyl)-AM-2201 (MAM-2201), *N*-(4-pentenyl)-JWH-122, JWH-213, (4-ethylnaphtyl)-AM-2201 (EAM-2201) and AB-001, were also detected herein as newly distributed designer drugs in Japan. Furthermore, a tryptamine derivative, 4-hydroxy-diethyltryptamine (4-OH-DET), was detected together with a synthetic cannabinoid, APINACA, in the same product.

1. Introduction

Since the appearance of synthetic cannabinoids as psychotropic drugs in illegal products in 2009 [1–3], there has been a continuous stream of new synthetic cannabinoids detected in illegal products [4]. Our ongoing survey of designer drugs in the illegal market in Japan has shown that synthetic cannabinoids are becoming a major abused drug family in Japan as well as in European countries [4–6]. In Japan, 23 synthetic cannabinoids [cannabicyclohexanol (CCH), CP-47, 497, JWH-015, JWH-018, JWH-019, JWH-022, JWH-073, JWH-081, JWH-122, JWH-200, JWH-203, JWH-210, JWH-250, JWH-251, RCS-4, AM-694, AM-1220, AM-2201, AM-2233, APICA, APINACA, CB-13 and cannabipiperidiethanone] were controlled as designated substances (Shitei-Yakubutsu) under the Pharmaceutical Affairs Law as of July 2012. Furthermore, among them, two synthetic cannabinoids, CCH and JWH-018, have been strictly regulated as new narcotic substances in Japan since August 2012.

As a consequence of our continuous survey of designer drugs in Japanese illegal markets, we found a completely new type of designer drug, URB-754 (**I**), which cannot be classified into synthetic cannabinoids (Fig. 1). Additionally, a reaction product (**II**) of URB-754 (**I**) was also found in the same illegal product. In this study, were report the identification of these new compounds (**I** and **II**) along with 12 newly distributed synthetic cannabinoids, which belong to five different groups: the pyridinoylindole (5-fluoropentyl-3-pyridinoylindole, **III**), naphthoylpyrrole[JWH-307 (**IV**) and JWH-030 (**V**)], cyclopropylindole[UR-144 (**VI**) and 5FUR-144 (synonym: XLR11, **VII**)], naphthoyindole[(4-methylnaphtyl)-JWH-022 (synonym: *N*-(4-pentenyl)-JWH-122, **XIII**), AM-2232 (**IX**), (4-methylnaphtyl)-AM-2201 (MAM-2201, **X**), *N*-(5-hydroxypentyl)-JWH-122 (**XI**), JWH-213 (**XII**) and (4-ethylnaphtyl)-AM-2201 (EAM-2201, **XIII**)] and adamantylindole (AB-001,**XIV**) groups, as shown in Fig. 1. Furthermore, we describe the identification of a cathinone derivative, 4-methylbuphedrone (4-Me-MABP, **XV**) or a tryptamine derivative, 4-hydroxy-diethyltryptamine (4-OH-DET, **XVI**), along with several synthetic cannabinoids in one product.

2. Materials and methods

2.1. Samples for analysis

The analyzed samples were purchased *via* the Internet from October 2011 to April 2012 as herbal-type products being sold in

☆ This paper is part of the special issue entitled "The 50th Annual Meeting of the International Association of Forensic Toxicologists (TIAFT)", June 3–8, 2012, Hamamatsu, Japan. Guest edited by Adjunct Professor Einosuke Tanaka and Associate Professor Masaru Terada.

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http://dx.doi.org/10.1016/j.forsciint.2012.08.047

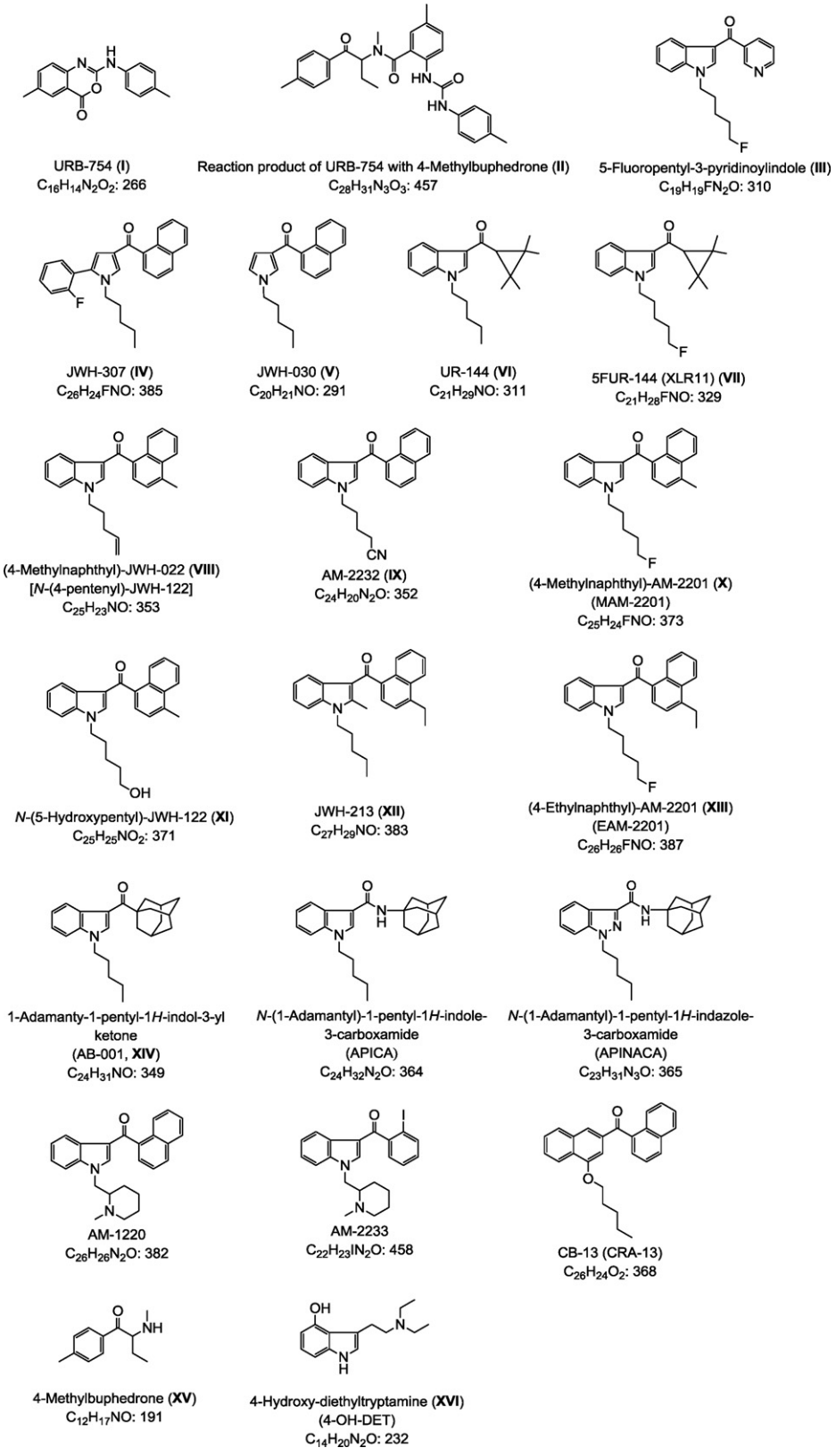

Fig. 1. Structures of the newly detected compounds (**I**–**XVI**) and related synthetic cannabinoids.

Japan. Each of the herbal-type products (A–I) contained about 3 g of mixed dried plants.

2.2. Chemicals and reagents

Authentic URB-754 (**I**), JWH-307 (**IV**), JWH-030 (**V**), UR-144 (**VI**), 5FUR-144 (**VII**), (4-methylnaphtyl)-JWH-022 (**VIII**), AM-2232 (**IX**), (4-methylnaphtyl)-AM-2201 (MAM-2201, **X**), *N*-(5-hydroxypentyl)-JWH-122 (**XI**), AB-001 (**XIV**), JWH-018, AM-1220, AM-2233 and CB-13were purchased from Cayman Chemical Company (Ann Arbor, MI, USA). JWH-213 (**XII**) was isolated from an herbal-type product and identified by nuclear magnetic resonance (NMR) and high-resolution mass spectrometer (MS) analyses [7]. 4-Methylbuphedrone (4-Me-MABP, **XV**) was originally purchased as a white powder and identified by spectroscopic analyses (data not shown). Authentic 4-hydroxy-diethyltryptamine (4-OH-DET, **XVI**) was purchased from Aurora Fine Chemicals, Ltd. (Graz, Austria). As authentic APICA and APINACA, compounds previously isolated from an herbal product [8] were used. All other common chemicals and solvents were of analytical reagent grade or HPLC grade. As solvents for NMR analysis, $CDCl_3$ (99.96%) and DMSO-d_6 were purchased from the ISOTEC division of Sigma–Aldrich (St. Louis, MO, USA).

2.3. Preparation of sample solution

For qualitative analyses, 10 mg of each herbal 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 (Ultra free-MC, 0.45 μm filter unit; Millipore, Bedford, MA, USA) to afford the sample solution. If necessary, the solution was diluted with methanol to a suitable concentration before instrumental analyses.

2.4. Analytical conditions

The ultra-performance liquid chromatography–electro spray ionization–mass spectrometer (UPLC–ESI–MS) analysis was performed on an ACQUITY UPLC system with a mass detector and a photodiode array (PDA) detector (Waters, Milford, MA, USA) [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 water) and solvent B (0.1% formic acid in acetonitrile). The elution program (1) used for analysis of cannabinoids was as follows: 35% B (4-min hold) and 65% B to 75% B (4–16 min), and up to 90% B (16–17 min, 5 min hold) at a flow rate of 0.3 ml/min. The elution program (2) used for the analysis of cathinones and other compounds was as follows: 5% B–20% B (0–20 min), and up to 80% B (20–30 min, 5 min hold). The injection volume was 1 μl and the wavelength of the PDA detector for screening was set from 210 to 450 nm. The MS conditions for the LC-ESI-MS were: ionization, positive and negative; desolvation gas, nitrogen at a flow rate of 650 l/h at 350 °C; capillary and cone voltages, 3000 V and 30 V, respectively; mass spectral range, *m/z* 150–650.

The sample solutions were also analyzed by using a gas chromatograph–mass spectrometer (GC–MS) in electron ionization (EI) mode according to our previous report [8]. GC-EI-MS was performed on an Agilent 6890N GC with a 5975 mass selective detector (Agilent Technologies, Santa Clara, CA) using a capillary column (HP-1MS capillary, 30 m × 0.25 mm i.d., 0.25 μm film thickness; Agilent Technologies) with helium gas as a carrier at 0.7 ml/min. The conditions were: electron energy, 70 eV; injector temperature, 200 °C; injection, splitless mode for 1.0 min; oven temperature program, 80 °C (1.2 min hold) and increase at a rate of 5 °C/min to 190 °C (15 min hold) followed by increase at 10 °C/min up to 310 °C (10 min hold); mass selective detector temperature, 280 °C; scan range, *m/z* 40–650. The obtained mass spectra were compared to an EI–MS library [Mass Spectra of Designer Drugs 2011 (WILEY-VCH, Germany)]. In addition, our in-house EI–MS library of designer drugs obtained by our successive survey of illegal products and commercially available reagents were also used for structural elucidation.

The accurate mass spectrum of the target compound was measured using a direct analysis in real time (DART) ion source coupled to a time-of-flight (TOF) mass spectrometer (Accu TOF JMS-100LC; JEOL, Tokyo, Japan) operated in positive ion mode. The measurement conditions were: ion guide peak voltage, 500 V; reflectron voltage, 950 V; orifice 1 voltage, 15 V; orifice 2 voltage, 5 V; ring lens voltage, 5 V; orifice 1 temperature, 80 °C; mass range, *m/z*100–1000. The conditions of the DART ion source were: 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 ($C_{17}H_{21}NO$) and verapamil ($C_{27}H_{38}N_2O_4$) 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, ^{13}C NMR, heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), double quantum filtered correlation spectroscopy (DQF-COSY), and rotating framenuclear Overhauser effect (ROE) spectra.

2.5. Isolation of compound **II**

A 3 g sample of mixed dried plants (product A) was extracted with 250 ml of $CHCl_3$ by ultrasonication for 30 min. The extractions were repeated three times, and the supernatant fractions were combined and evaporated to dryness, to afford a brown oil. The extract was placed on a preparative silica-gel thin-layer chromatography (TLC) plate (Silica Gel 60, 20 cm× 20 cm, 2 mm; Merck, Darmstadt, Germany), which was then developed using hexane/ethyl acetate (3:1). A portion of the silica gel containing the target compound in the TLC plate was detected by UV 254 nm. Then, it was scraped from the plate and eluted with $CHCl_3$ to get fraction 1. The fraction 1 was further purified by repeated preparative TLC with hexane/ethyl acetate (3:1) and then hexane/ethyl acetate (2:1). Finally, compound **II** (5 mg) was obtained as a brown oil.

2.6. Isolation of compound **III**

A 3 g sample of mixed dried plants (product B) was extracted with 250 ml of $CHCl_3$ by ultrasonication for 30 min. The extractions were repeated three times, and the supernatant fractions were combined and evaporated to dryness, to afford a brown oil. The extract was placed on a preparative TLC plate (Silica Gel 60, 20 cm × 20 cm, 2 mm; Merck), which was then developed using $CHCl_3$/acetone (4:1). A portion of the silica gel containing the target compound was detected by UV 254 nm. Then it was scraped from the plate and eluted with $CHCl_3$ to obtain compound **III** (42 mg) as a brown oil.

2.7. Isolation of compound **XIII**

A 3 g sample of mixed dried plants (product H) was extracted with 250 ml of $CHCl_3$ by ultrasonication for 30 min. The extractions were repeated three times, and the supernatant fractions were

combined and evaporated to dryness, to afford a brown oil. The extract was placed on a preparative TLC plate (Silica Gel 60, 20 cm × 20 cm, 2 mm; Merck), which was then developed using hexane/ethyl acetate (4:1). A portion of the silica gel containing the target compound was detected by UV 254 nm. Then it was scraped from the plate and eluted with $CHCl_3$ to obtain compound **XIII** (43 mg) as a brown oil.

2.8. Binding assay for cannabinoid CB_1 and CB_2 receptors

The binding affinities of APICA, APINACA and AB-001 (**XIV**) for the CB_1/CB_2 receptors were determined by the competition of agonist [^{3}H]-CP-55,940 (PerkinElmer Inc., MA, USA) binding to human recombinant cannabinoid CB_1/CB_2 receptors. To determine the IC_{50} values of the tested compounds, eight different concentrations of each compound in the range of 3 nM to 10 μM were investigated. (*R*)-(+)-WIN-55,212-2 and JWH-018, which are cannabinoid receptor agonists, were used as positive controls.

3. Results and discussion

3.1. Identification of unknown peaks *I*, *II*, *VIII-X* and *XV*

Six unknown peaks, **I**, **II**, **VIII-X** and **XV,** were detected in the GC–MS and LC–MS chromatograms of product A, as shown in Figs. 2 and 3. The unknown peak **I** in the GC–MS chromatogram at 45.65 min showed a molecular ion signal at *m*/*z* 266 (Fig. 2b). The LC–MS analysis determined that the peak **I** at 7.3 min showed a protonated molecular ion $[M+H]^+$signal at *m*/*z* 267 and absorbance maxima at 246, 282 and 350 nm of the UV spectrum, respectively (Fig. 3c). The proposed fragment patterns and presumed structure **I** of (URB-754) are also shown in Fig. 2b. The GC–MS and LC–MS spectra of the purchased authentic URB-754, the molecular weight of which was 266, are shown in Figs. 2d and 3e; compound **I** was found to be identical to URB-754. This is the first report to detect URB-754 (**I**) as an ingredient in illegal products. Though most of the detected compounds in herbal-type products hinting at cannabis-like effects are synthetic cannabinoids [5,6], URB-754 (**I**) is a completely new type of designer drug. URB-754 was synthesized by Papadopoulos et al. in 1982 [9] and Garin et al. in 1983 [10] from different schemes, and it was reported to be a potent inhibitor of an endocannabinoid-deactivating enzyme—namely, monoacylglycerol lipase (MGL) [11]. However, data from other labs indicated that it does not inhibit human recombinant, rat or mouse brain MGL up to 100 μM [12]. Therefore, the biological activity of URB-754 has remained unexplained.

An unknown peak **XV** was presumed to be a cathinone derivative, 4-methylbuphedrone, based on the fragment patterns of the GC–MS analysis (Fig. 2c) and LC–MS analysis (Fig. 3d). The peak (**XV**) was finally found to be identical to4-methylbuphedrone by direct comparison of the data to those of the authentic 4-methylbuphedrone (Figs. 2e and 3f).

The unknown peaks **VIII, IX** and **X** were presumed to be (4-methylnaphtyl)-JWH-022, AM-2232 and MAM-2201, respectively, from the proposed fragment patterns in the GC–MS analysis, as shown in Fig. 2(g)–(i). The LC–MS chromatograms showed that peaks **VIII, IX** and **X** exhibited protonated ion signals ($[M+H]^+$) at *m*/*z* 354, 353 and 374, respectively (Fig. 3(h)–(j)). These peaks (**VIII, IX** and **X**) were finally found to be identical to the cannabimimetic compounds (4-methylnaphtyl)-JWH-022, AM-2232 and MAM-2201, respectively, by direct comparison of the data to those of the purchased authentic compounds (data not shown). 4-Methylbuphedrone (**XV**), AM-2232 (**IX**) and MAM-2201 (**X**) were detected in the Netherlands and/or Germany [4,13].

Table 1
NMR Data of reaction product (**II**).

No.	Reaction product (**II**) in DMSO-d_6[a]	
	^{13}C	^{1}H
1	127.6	–
2	133.2	–
3	123.9	7.53, 1H, d, *J* = 8.3 Hz
4	130.1	7.15, 1H, d, *J* = 8.3 Hz
5	131.9	–
6	126.5	6.73, 1H, s
5-Me	20.2	2.21, 3H, s
1-CO-NMe	169.2	–
1-CO-NMe	33.1	2.61, 3H, s
1′	198.1	–
2′	58.8	5.82, 1H, dd, *J* = 8.9, 5.8 Hz
3′	20.2	1.96, 1.80, each 1H, m
4′	10.4	0.96, 3H, dd, *J* = 7.6, 7.2 Hz
1″	132.9	–
2″	128.1	7.87, 1H, d, *J* = 7.9 Hz
3″	129.3	7.29, 1H, d, *J* = 7.9 Hz
4″	143.8	–
5″	129.3	7.29, 1H, d, *J* = 7.9 Hz
6″	128.1	7.87, 1H, d, *J* = 7.9 Hz
4″-Me	21.0	2.17, 3H, s
1‴	137.4	–
2‴	117.9	7.29, 1H, d, *J* = 8.3 Hz
3‴	129.1	7.05, 1H, d, *J* = 8.3 Hz
4‴	130.4	–
5‴	129.1	7.05, 1H, d, *J* = 8.3 Hz
6‴	117.9	7.29, 1H, d, *J* = 8.3 Hz
4‴-Me	20.3	2.22, 3H, s
NH-CO-NH	152.6	–
2-NH-CO	–	8.08, 1H, s
1‴-NH-CO	–	9.17, 1H, s

[a] Recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C), respectively data in δ ppm (*J* in Hz).

One of the remaining unknown peaks in the TIC of GC–MS analyses was the peak **II** detected at 46.93 min (Fig. 2a and f). The corresponding peak in the LC–MS chromatogram detected at 8.4 min showed an absorbance maximum at 255 nm in the UV spectrum and major ion peaks at *m*/*z* 458 ($[M+H]^+$) and *m*/*z* 456 ($[M-H]^-$), respectively (Fig. 3g). After isolation of compound **II**, the accurate mass spectrum of **II** was measured by DART-TOF-MS (positive mode). The observed ion peak at 458.2453 suggested that the protonated molecular formula of **II** was $C_{28}H_{32}N_3O_3$ (calcd.458.2444).

The structure of compound **II** was elucidated by NMR analysis (Table 1 and Fig. 4). The ^{1}H and ^{13}C NMR spectra of **II** suggested 31 protons and 28 carbons, as shown in Table 1. The analyses of the DQF-COSY, HMQC and HMBC spectraof **II** revealed the presence of an *N*-methyl-*p*-tolyl-1-oxobutan-2-imino group, as shown in Fig. 4 and Table 1. Therefore, compound **II** was presumed to have the 4-methylbuphedrone moiety. Additionally, NMR spectra of the remaining unit suggested the presence of an amide carbonyl group (δ_C 169.2) and an ureido group [δ_C 152.6, δ_H 8.08 (2-NH) and δ_H 9.17 (1‴-NH)], 1,2-substituted-4-methylphenyl moiety (positions-1–6) and 4-methylphenyl moiety (positions-1‴–6‴). The HMBC correlations between the *N*-methyl protons at δ_H 2.61 and the amide (1-CONMe) and the C-2′carbons, and between the aromatic proton (H-6) and the amide carbon (1-CONMe) suggested that the 4-methylbuphedrone moiety was attached to the 1,2-substituted-4-methylphenyl moiety in the amide linkage at position-1 (Fig. 4). The connections of the remaining units were revealed by the HMBC and ROE correlations (Fig. 4). The ureido proton of 2-NH correlated to three aromatic carbons (C-1, C-2 and C-3), and an ureido carbon. The other ureido proton (1‴-NH) correlated to three aromatic carbons (C-1‴, C-2‴ and C-6‴), and an ureido carbon. Furthermore, the irradiation of the ureido proton of 2-NH resulted in ROE correlations on the other ureido proton (1‴-NH) and an aromatic proton (H-3). The other

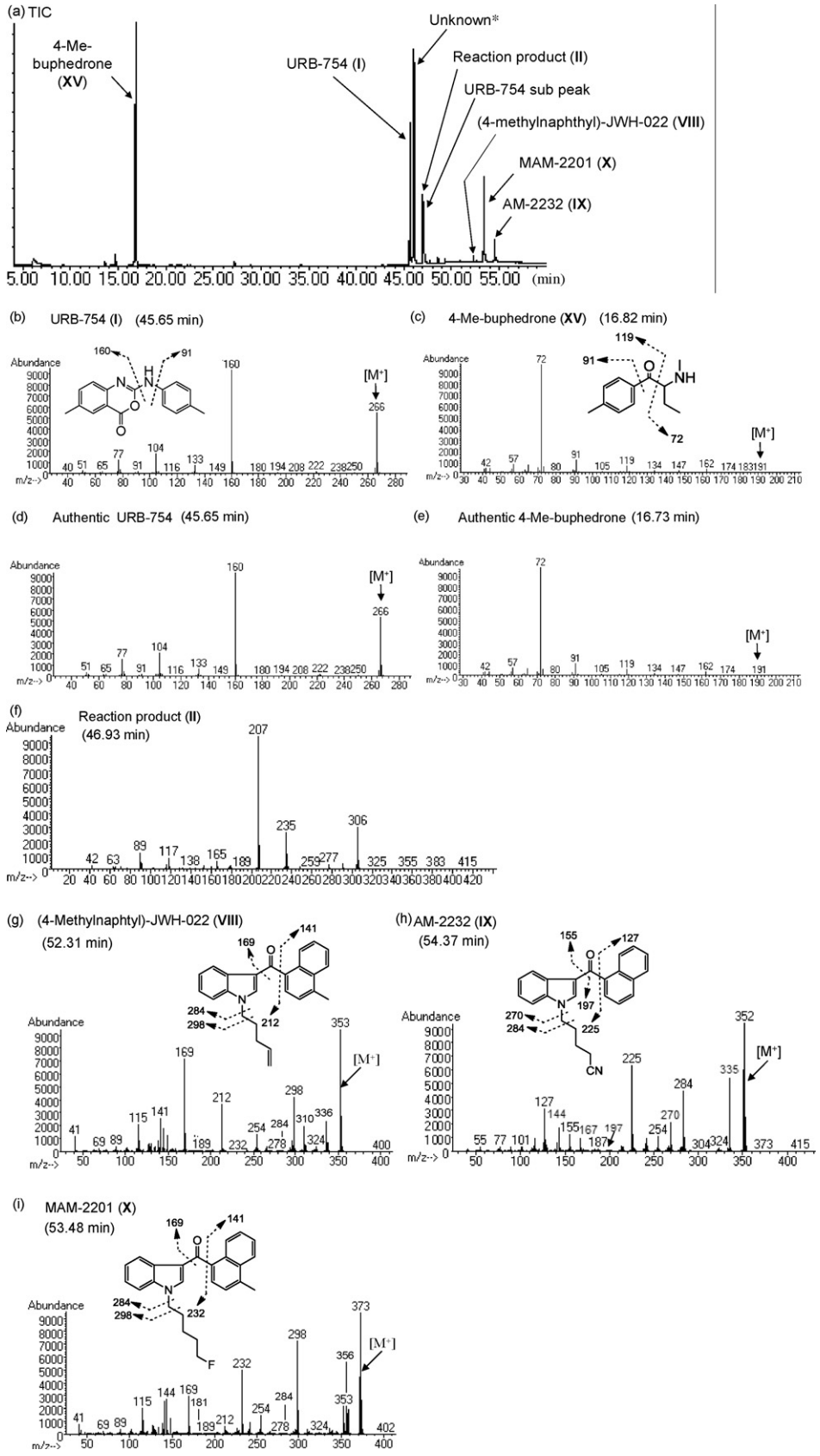

Fig. 2. GC–MS analysis of product A. Total ion chromatogram (a), EI mass spectra of the detected peaks **I** (b), **XV** (c), **II** (f), **VIII**–**X** (g–i), and authentic URB-754 and 4-Me-buphedrone (d and e, respectively). *The chromatographic peak having fragment ion peaks at *m/z* 291 and 306 might be derived from a degradative product of compound **II**, but we could not confirm its correct structure.

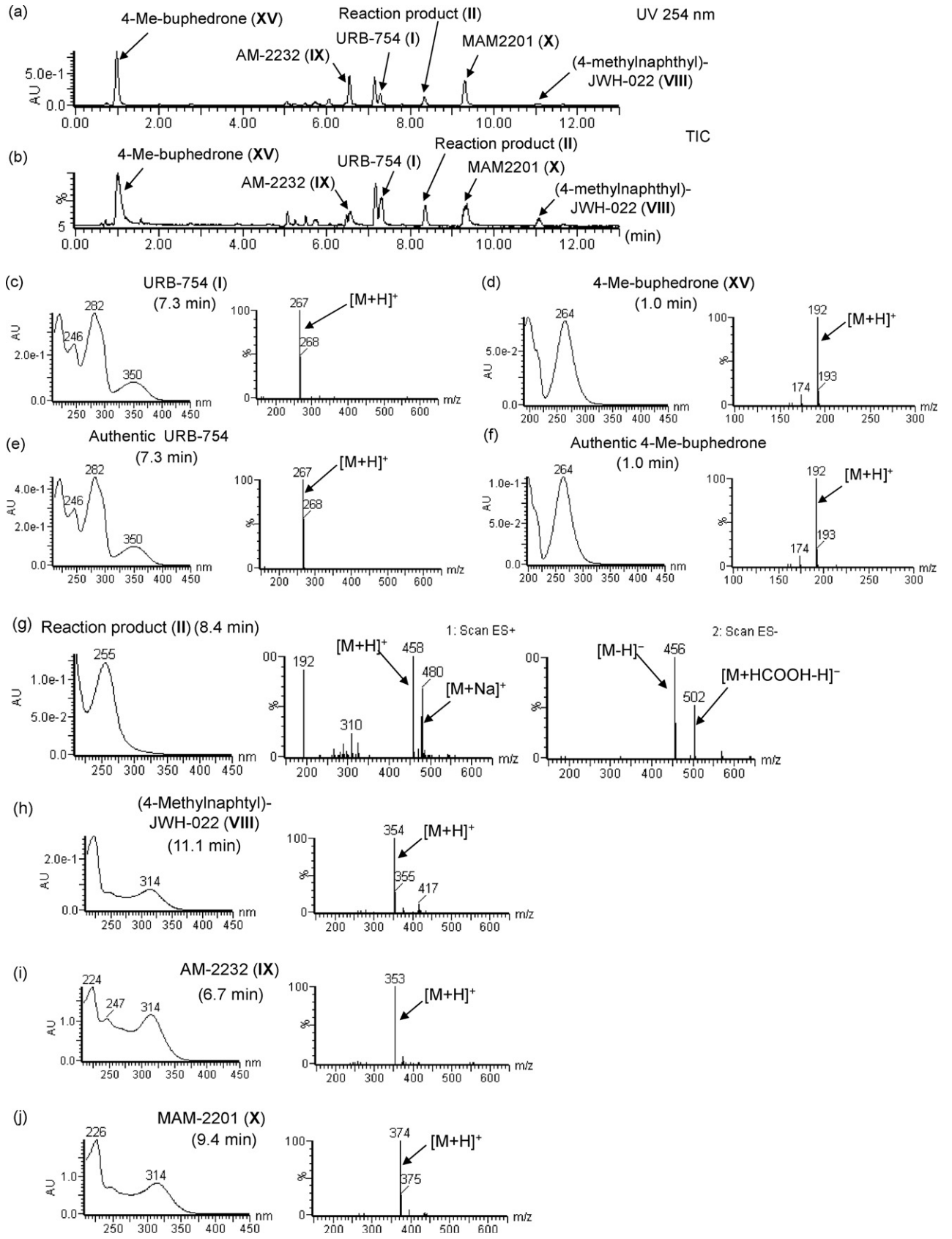

Fig. 3. LC–UV and total ion chromatogram (a, b, respectively) of product A. UV and ESI mass spectra of peaks **I** (c), **XV** (d), **II** (g), **VIII–X** (h–j), and authentic URB-754 and 4-Me-buphedrone (e and f, respectively).

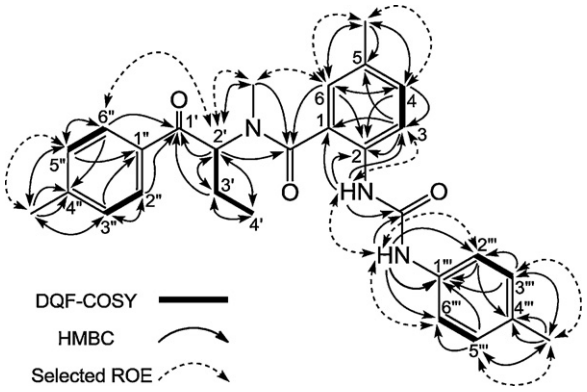

Fig. 4. DQF-COSY, HMBC selected and ROE correlations of reaction product (**II**).

ureido proton (1‴-NH) also showed ROE correlations to the ureido proton (2-NH) and two aromatic protons (H-2‴ and H-6‴), as shown in Fig. 4. On the basis of mass and NMR spectral data, the structure of compound **II** was finally deduced as *N*,5-dimethyl-*N*-(1-oxo-1-(*p*-tolyl)butan-2-yl)-2-(3-(*p*-tolyl)ureido)benzamide.

This structure suggested that compound **II** would be the product of a reaction between URB-754 (**I**) and 4-methylbuphedrone (**XV**). In order to verify this hypothesis, we mixed these two authentic compounds in MeOH or acetone solution. MeOH was the same solvent as used for the extraction of illegal products in our analysis. Acetone has been reported to be used as one of the solvents for dissolving synthetic cannabinoids before spraying them on the plant material contained in herbal products [14]. Then, the mixture was analyzed by GC–MS and LC–MS. In the MeOH solution, compound **II** was detected in the mixture (Fig. 5a,b,d–g) and identified by direct comparison of its spectral data with those of the isolated compound **II** (Fig. 5c and h). In the acetone solution, compound **II** was also detected in the mixture (data not shown). Therefore, it was revealed that compound **II** was a product of the reaction between URB-754 and 4-methylbuphedrone. It is interesting that are action product obtained from two different types of designer drugs (the cathinone derivative 4-methylbuphedrone and URB-754) was found in an illegal product. We think it is important to pay attention for the possible presence of such a reaction product when URB-754 is detected with a cathinone derivative in illegal products, because of the reactive character of both compounds.

3.2. Identification of an unknown peak *III*

An unknown peak **III** was detected together with AM-2233 in the GC–MS and LC–MS chromatograms of product B (Fig. 6a, c and d). In the GC–MS chromatogram, the peak **III** at 48.64 min showed a putative molecular ion signal at *m/z* 310 (Fig. 6b). The LC–MS chromatogram demonstrated that peak **III** at 5.4 min showed a protonated ion signal ($[M+H]^+$) at *m/z* 311 and absorbance maxima at 262 and 322 nm in the UV spectrum (Fig. 6e). After the isolation of compound **III**, the accurate mass spectrum of **III** was measured by DART-TOF-MS (positive mode). The observed ion peak at 311.1544 suggested that the protonated molecular formula of **III** was $C_{19}H_{20}FN_2O$ (calcd. 311.1560).

Then, the structure of compound **III** was elucidated by NMR analyses (Table 2, Fig. 7). The ^1H and ^{13}C NMR spectra of **III**

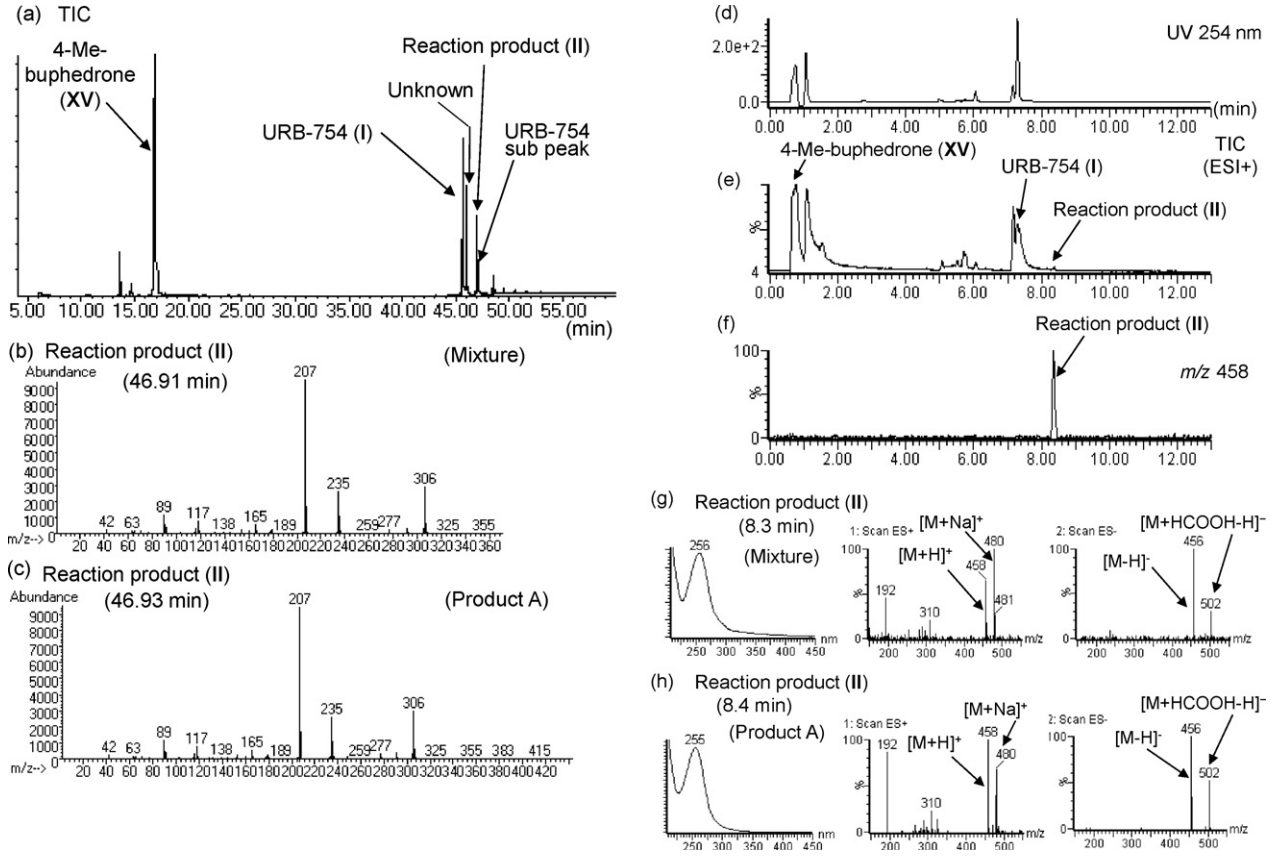

Fig. 5. GC–MS chromatogram of the mixture of 4-Me-buphedrone and URB-754 in MeOH solution. Total ion chromatogram (a), and EI mass spectra of the sdetected peaks **II** in the mixture (b), and in the product A (c), LC-UV (d), and mass chromatograms of the mixture. TIC (e) and mass chromatograms of *m/z* 458 (f) in the mixture. UV and MS spectra of peak **II** in the mixture (g) and in the products A (h).

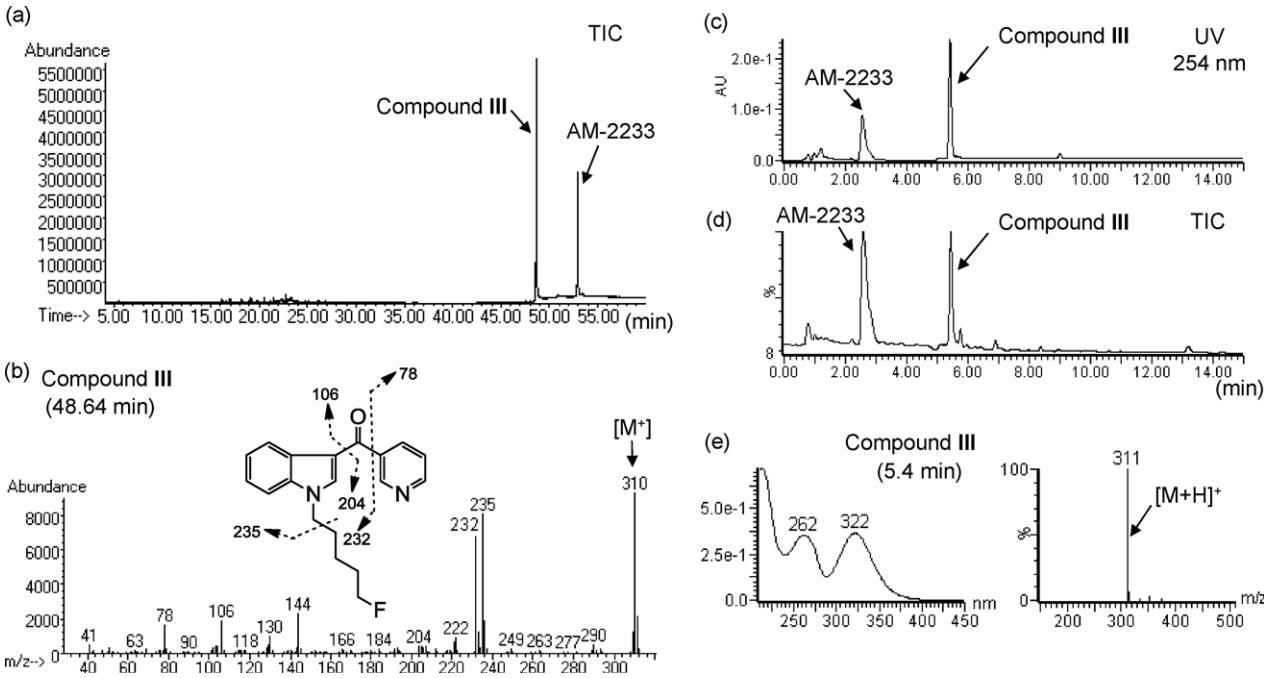

Fig. 6. GC–MS chromatogram of product B. Total ion chromatogram (a) and EI mass spectra of the detected peaks **III** (b), LC–UV (c) and TIC (d) of product B. UV and MS spectra of peak **III** (e).

suggested 19 protons and 19 carbons, as shown in Table 2. The two-dimensional NMR of **III** suggested the presence of an *N*-(5-fluoropentyl)-3-carbonylindole moiety (Fig. 7). The fragment at *m/z* 232 and 204 of **III** in the GC-EI-MS spectra also indicated the presence of that moiety (Fig. 6b). ^{1}H, ^{13}C NMR and 2D-NMR spectra of the remaining $C_5H_4N_1$ unit suggested the existence of a 3-substituted pyridine moiety (position-1‴–6‴), as shown in Fig. 7. The connection of the remaining unit to the carbonyl group was revealed by the HMBC correlations from the aromatic protons (H-2‴ and H-4‴) to the carbonyl carbon (C-1). Additionally, the major fragment ions at *m/z* 78, 106 and 235 by GC–MS analyses suggested the presence of the 3-substituted pyridine moiety (Fig. 6b). Therefore, the structure of compound **III** was determined as 5-fluoropentyl-3-pyridinoylindole (IUPAC: 1-(5-fluoropentyl)-1*H*-indol-3-yl)(pyridin-3-yl) methanone). Compound **III** has been detected in a powder product named "NG-3" in Japan [15].

Table 2
NMR data of 5-fluoropentyl-3-pyridinoylindole (**III**).

No.	Compound **III** in $CDCl_3$ [a]	
	^{13}C	^{1}H
1	187.6	–
2′	136.9	7.56, 1H, s
3′	115.5	–
3′a	127.1	–
4′	122.8	8.41, 1H, m
5′	123.2	7.36, 1H, m, overlapped
6′	124.1	7.35, 1H, m, overlapped
7′	110.0	7.40, 1H, m
7′a	136.9	–
1″	47.2	4.19, 2H, t, *J* = 7.2 Hz
2″	29.5	1.93, 2H, quintet, *J* = 7.6 Hz
3″	22.9, d, *J* = 5.8 Hz[b]	1.46, 2H, m
4″	29.8, d, *J* = 18.8 Hz[b]	1.73, 1.68, each 1H, m
5″	83.6, d, *J* = 164.8 Hz[b]	4.45, 4.37, each 1H, t, *J* = 5.8 Hz
2‴	148.5	9.03, 1H, brd, *J* = 1.7 Hz
3‴	136.7	–
4‴	137.2	8.19, 1H, dt, *J* = 7.9, 1.7 Hz
5‴	124.0	7.51, 1H, dd-like, *J* = 7.9, 4.8 Hz
6″	150.8	8.78, 1H, dd, *J* = 4.8, 1.7 Hz

[a] Recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C), respectively; data in δ ppm (*J* in Hz).
[b] Observed as double signals by coupling with fluorine.

3.3. Identification of the unknown peaks *IV-VII* and *XI-XIII*

In GC–MS analyses of the illegal product C, the unknown peaks **IV** and **V**, which were detected along with AM-2233 and CB-13, were presumed to be the naphthoylpyrrole derivatives JWH-307 (**IV**) and JWH-030 (**V**), respectively (Supplementary Fig. S1a, b and d). The LC–MS chromatograms showed that peaks **IV** and **V** exhibited protonated ion signals ($[M+H]^+$) at *m/z* 386 and 292, respectively (Supplementary Fig. S2a–e and g). These peaks **IV** and **V** were finally found to be identical to the cannabimimetic compounds JWH-307 (**IV**) and JWH-030 (**V**), respectively, by direct comparison of the data to those of the purchased authentic compounds (Supplementary Fig. S1c and e, S2f and h).

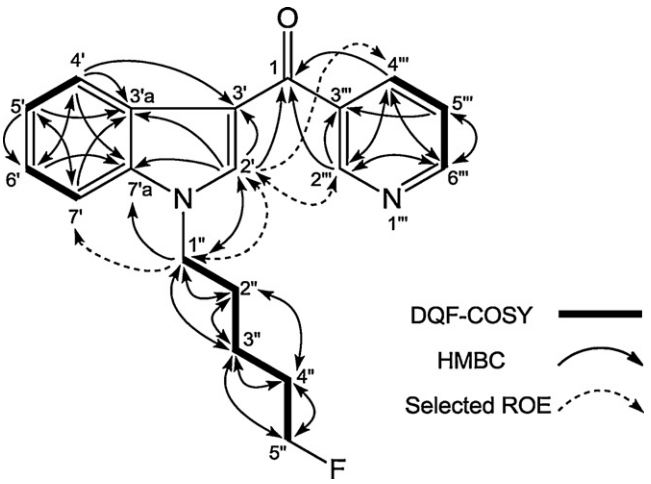

Fig. 7. DQF-COSY, HMBC selected and ROE correlations of Compound **III**.

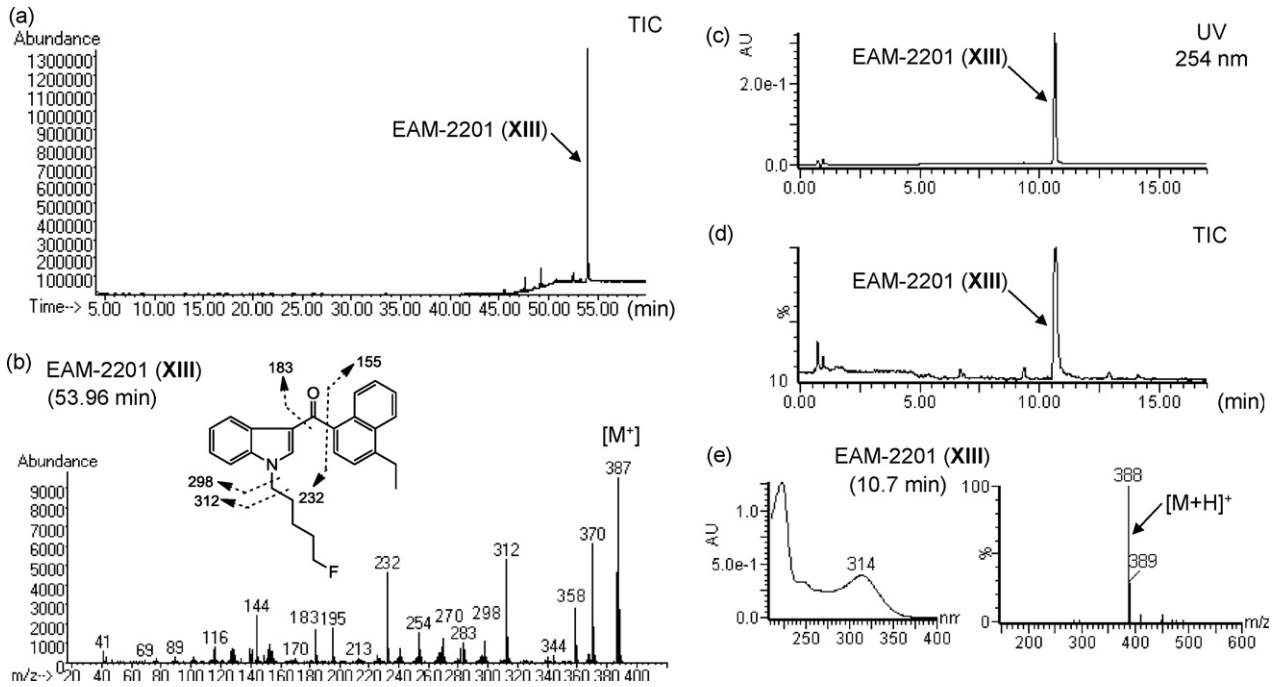

Fig. 8. GC–MS chromatogram of product H. Total ion chromatogram (a) and EI mass spectra of the detected peaks **XIII** (b), LC-UV (c) and TIC (d) of product H. UV and MS spectra of peak **XIII** (e).

Similar GC–MS and LC–MS analyses were performed to determine the unknown peaks **VI**, **VII**, **XI**, **XII** and **XIV** in products D (Supplementary Figs. S3 and S4), E (Supplementary Figs. S5 and S6), F (Supplementary Fig. S7) and G (Supplementary Figs. S8 and S9), respectively. Based on the LC–MS and GC–MS data, these peaks (**VI**, **VII**, **XI**, **XII** and **XIV**) were finally identified as UR-144 (Supplementary Fig. S3b and S4e), 5FUR-144 (XLR11, (Supplementary Fig. S5b and S6e), *N*-(5-hydroxypentyl)-JWH-122 (Supplementary Fig. S7b and f), JWH-213 and AB-001 (Supplementary Fig. S8b and d, S9f and h) by the direct comparison of the data to those of the purchased or isolated authentic compounds, respectively (Supplementary Figs. S3c, S4f, S5c, S6f, S7c and g, S8c and e, S9g and i).

JWH-307 (**IV**), AM-2232 (**IX**), MAM-2201 (**X**), AB-001 (**XIV**), and 4-methylbuphedrone (**XV**) have been detected in European countries [4,13,16,17].

3.4. Identification of an unknown peak *XIII*

An unknown peak **XIII** was detected in the GC–MS and LC–MS chromatograms of product H (Fig. 8a–e). By the GC–MS analysis, the proposed fragment patterns and presumed structure of peak **XIII** are shown in Fig. 8b. The LC–MS chromatogram revealed that the peak **XIII** showed a protonated ion signal ($[M+H]^+$) at *m/z* 388 and an absorbance maximum at 314 nm in the UV spectrum (Fig. 8e). After isolation of **XIII**, in the accurate mass spectrum obtained by DART-TOF-MS, the observed ion peak at *m/z* 388.2077 suggested that the protonated molecular formula of **XIII** was $C_{26}H_{27}FNO$ (calcd. 388.2075).

The ^{13}C NMR spectrum of **XIII** was very similar to that of AM-2201 (**X**) except for the ethyl moiety of **XIII**. In addition, the chemical shifts of 4-ethylnaphthyl moiety of **XIII** were almost completely the same of the moiety of JWH-210 (Table 3, Fig. 9). The observed DQF-COSY, HMBC and 1D-ROE correlations in Fig. 10 suggested that the structure of **XIII** was a mixed structure of these known synthetic cannabinoids, AM-2201 and JWH-210, and compound **XIII** was identified as (4-ethylnaphthalen-1-yl)(1-(5-fluoropentyl)-1*H*-indol-3-yl) methanone. Although the chemical and biological information of compound **XIII** have not yet been reported, **XIII** is sold as a chemical product by the name of (4-ethylnaphthyl)-AM-2201 (EAM-2201) on the Internet.

3.5. Identification of an unknown peak *XVI*

An unknown peak **XVI** was detected along with the known peak of APINACA (Fig. 1) [8], which is controlled as a designated substance (Shitei-Yakubutsu) in Japan, in the GC–MS and LC–MS chromatograms of product I (Supplementary Figs. S10a, b, d–h. The proposed fragment pattern and presumed structure of **XVI** from the GC–MS analysis are shown in Supplementary Fig. S10b. Based on the LC–MS and GC–MS analyses, this peak (**XVI**) was finally found to be identical to 4-hydroxy-diethyltryptamine (4-OH-DET) by direct comparison of the data to those of the purchased authentic compound (Supplementary Fig. S10c and i).

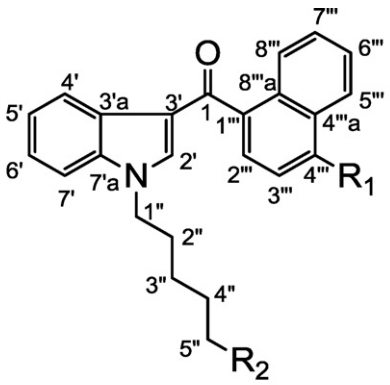

Fig. 9. Structures of EAM-2201 (**XIII**), JWH-210 and AM-2201.

Table 3
NMR Data for EAM-2201 (**XIII**) and related compounds (JWH-210 and AM-2201) in $CDCl_3$.

No.	JWH-210[a]	AM-2201[a]	EAM-2201 (compound **XIII**)[a]		
	^{13}C	^{13}C	^{13}C	^{1}H	HMBC[b]
1	192.3	192.0	192.3	–	–
2′	137.9	137.8	137.8	7.35, 1H, s, overlapped	1, 3′, 3′a, 7′a, 1″
3′	117.6	117.7	117.8	–	–
3′a	127.0	127.0	127.0	–	–
4′	122.9	123.0	123.0	8.49, 1H, m	3′, 3′a, 6′, 7′a
5′	122.8	122.9	122.8	7.34, 1H, m, overlapped	3′a, 4′, 7′
6′	123.5	123.7	123.6	7.34, 1H, m, overlapped	4′[d], 7′, 7′a[d]
7′	109.9	109.9	109.8	7.36, 1H, m, overlapped	3′a, 5′
7′a	137.0	137.0	136.9	–	–
1″	47.1	47.0	47.0	4.08, 1H, t, J = 7.2 Hz	2′, 7′a, 2″, 3″
2″	29.5	29.5	29.5	1.85, 1H, q, J = 7.2 Hz	1″, 3″, 4″
3″	28.9	22.8, d, J = 4.3 Hz[c]	22.8 d, J = 5.8 Hz[c]	1.39, 2H, m, overlapped	1″, 2″, 4″, 5″
4″	22.2	29.8, d, J = 18.7 Hz [c]	29.8 d, J = 18.8 Hz [c]	1.67 and 1.63, each 1H, m	3″, 5″
5″	13.9	83.5, d, J = 163.7 Hz [c]	83.6 d, J = 166.2 Hz [c]	4.41 and 4.33, each 1H, *t*, J = 5.8 Hz	3″, 4″
1‴	137.5	139.0	137.4	–	–
2‴	125.9	125.8	125.9	7.58, 1H, d, J = 6.9 Hz	1, 4‴, 8‴a
3‴	123.5	124.6	123.5	7.37, 1H, m, overlapped	1‴, 4‴a, E-1
4‴	142.5	130.0	142.6	–	–
4‴a	132.0	133.7	132.0	–	–
5‴	123.8	128.2	123.8	8.12, 1H, d, J = 8.6 Hz	4‴, 4‴a, 7‴, 8‴a
6‴	126.1	126.3	126.1	7.53, 1H, t-like, J = 8.3 Hz	4‴a, 8‴
7‴	126.2	126.8	126.2	7.45, 1H, t-like, J = 8.3 Hz	5‴, 6‴[d], 8‴a
8‴	126.8	126.0	126.7	8.23, 1H, d, J = 8.6 Hz	1‴, 4‴a, 6‴, 8‴a
8‴a	131.1	130.8	131.1	–	–
E-1	26.2	–	26.2	3.17, 2H, q, J = 7.6 Hz	3‴ 4‴, 4‴a, E-2
E-2	14.9	–	14.9	1.42, 3H, t, J = 7.6 Hz	4‴, E-1

[a] Recorded in $CDCl_3$ at 600 MHz (^{1}H) and 150 MHz (^{13}C), respectively; data in δ ppm (J in Hz).
[b] J = 8 or 4 Hz; the proton signal correlated with the indicated carbons.
[c] Observed as double signals by coupling with fluorine.
[d] Recorded in CD_3OD.

4-OH-DET was synthesized as analog of psilocin (4-hydroxydimethyltryptamine: 4-OH-DMT) in 1977 [18] and reported to have 3-fold more potent hallucinogenic activity than mescaline (3,4,5-trimethoxyphenethylamine) [19]. As described in Section 3.1, the recent trend seems to be to mix different types of designer drugs such as cathinones or tryptamines with synthetic cannabinoids in illegal products.

4. Cannabimimetic activity of the detected compounds

4.1. Reported binding activities of the detected compounds to cannabinoid CB_1 and CB_2 receptors

Several newly detected compounds have been reported to have cannabimimetic activity. The binding activities of JWH-307 (**IV**), JWH-030 (**V**), UR-144 (**VI**), AM-2232 (**IX**) and JWH-213 (**XII**) to the cannabinoid CB_1 receptor have been reported [Ki (nM) values = 7.7, 87, 150, 0.28, and1.5 respectively] [20–24]. Furthermore, (4-methylnaphtyl)-JWH-022 (**VIII**) and *N*-(5-hydroxypentyl)-JWH-122 (**XI**) are analogs of JWH-022 or JWH-122, which have been reported to exhibit affinity for CB receptors [25,26]. MAM-2201 (**X**) and EAM-2201 (**XIII**) are analogs of AM-2201, which is also known to have affinity for CB receptors [20]. Therefore, it is assumed that the analogs of the previously detected synthetic cannabinoids [5FUR-144 (**VII**), (4-methylnaphtyl)-JWH-022 (**VIII**), MAM-2201 (**X**), *N*-(5-hydroxypentyl)-JWH-122 (**XI**), EAM-2201(**XIII**) and 5-fluoropentyl-3-pyridinoylindole (**III**)] may have similar cannabimimetic activities.

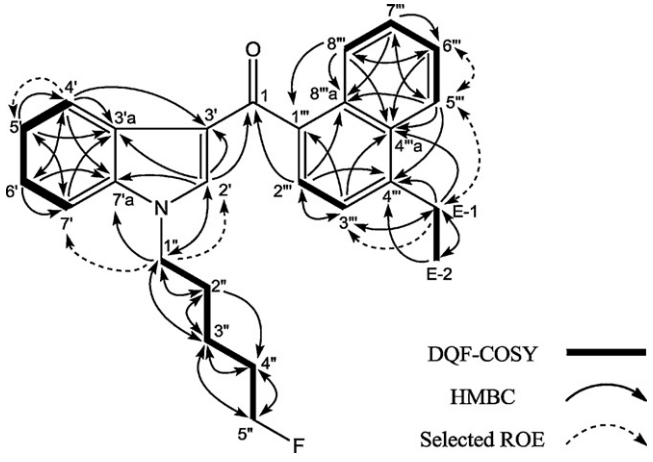

Fig. 10. DQF-COSY, HMBC selected and ROE correlations of EAM-2201 (**XIII**).

*4.2. Binding activities of APICA, APINACA and AB-001 (**XIV**) to cannabinoid CB_1 and CB_2 receptors*

In our present and previous studies [27], we have been conducting an examination of the affinities of the abused synthetic cannabinoids for cannabinoid CB_1 and CB_2 receptors. No pharmacological information about the three adamantyl-type cannabinoids APICA, APINACA and AB-001 (**XIV**) has yet been reported. However, analogs of APINACA have been reported to exhibit potent affinity for cannabinoid CB_1 and CB_2 receptors [28]. Therefore, we thought that APICA, APINACA and AB-001 (**XIV**) might have some cannabinoid receptor-binding activity. Therefore, we determined the binding affinity of APICA, APINACA and AB-001 (**XIV**) for cannabinoid CB_1 and CB_2 receptors by competition with agonist [^{3}H]-CP-55, 940 binding as shown in Table 4. The results showed that APICA, APINACA and AB-001 (**XIV**) had affinity for the CB_1 and CB_2 receptors. The affinity of APICA for the CB_1 receptors (IC_{50} = 175 nM) was similar to the affinity of JWH-018 for the CB_1 receptor (IC_{50} = 169 nM), and the affinity for the CB_2 receptor was 3.4-fold higher for APICA than for JWH-018. The affinities of

Table 4
Effect of synthetic cannabinoids on [^{3}H]-CP-55,940 binding to human cannabinoid receptors.

Compound	IC_{50} (nM)		
	CB_1	CB_2	Ratio CB_1/CB_2
APICA	175	176	0.99
APINACA	824	430	1.92
AB-001	927	899	1.03
JWH-018[a,b]	169	593	0.28
(*R*)-(+)-WIN-55,212–2[a]	32.0	9.51	3.36

[a] Positive control, cannabinoid receptor agonist.
[b] Narcotic substance in Japan since August 2012.

APINACA and AB-001 (**XIV**) for the CB_1 receptor were 4.9- and 5.5-fold lower than that of JWH-018, respectively. The affinities of APICA, APINACA and AB-001 (**XIV**) for the CB_1receptor were 5.5-, 25.8- and 29.0-fold lower than that of (*R*)-(+)-WIN-55, 212–2, as shown in Table 4. JWH-018, which has been controlled as a narcotic substance in Japan, was reported to affect drug discrimination for rats and to change the electroencephalogram (EEG) power spectra and suppress the locomotor activity of rats more significantly and for a longer duration time than did Δ^9-tetrahydrocannabinol (Δ^9-THC) [29,30]. Therefore, there is a possibility that these compounds, especially APICA, may have cannabimimetic activity similar to that of JWH-018. We will continue to examine the affinities of newly detected compounds for cannabinoid $CB_1$and CB_2 receptors.

5. Conclusions

In this study, a new type of designer drug, URB-754 (**I**), along with its reaction product (**II**) and 12 newly distributed synthetic cannabinoids (**III**–**XIV**) were identified from illegal products being sold in Japan. The 12 synthetic cannabinoids belong to five different groups: the pyridinoylindole (**III**), naphthoylpyrrole (**IV** and **V**), cyclopropylindole (**VI** and **VII**), naphthoylindole (**VIII**–**XIII**) and anadamantlyindole (**XIV**) groups. Furthermore, a cathinone derivative, 4-methylbuphedrone (**XV**) or a tryptamine derivative, 4-OH-DET (**XVI**), was detected together with synthetic cannabinoids in the same product. In addition, the binding affinities of adamantlyindoles (APICA, APINACA and AB-001 (**XIV**)) for cannabinoid CB_1/CB_2 receptors were revealed. Although the binding affinities of some of the detected synthetic cannabinoids (**IV**–**VI**, **IX** and **XII**) have been reported previously, there is little information about most of the newly detected compounds. Furthermore, the recent trend seems to be to mix different types of designer drugs such as cathinones (stimulants) or tryptamines (hallucinogens) with synthetic cannabinoids in illegal products. Therefore, there is the potential for serious health risks associated with their use. Hence, constant monitoring and rapid identification of newly distributed designer drugs will be necessary to prevent drug abuse.

Acknowledgments

The authors thank Dr. Satoru Matsuda for his unflagging work in isolating the compounds. A portion of this work was supported by a Health and Labor Sciences Research Grant from the Ministry of Health, Labour, and Welfare, Japan.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.forsciint.2012.08.047.

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