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ORIGINAL ARTICLE

Chemical analysis of a benzofuran derivative, 2-(2-ethylaminopropyl)benzofuran (2-EAPB), eight synthetic cannabinoids, five cathinone derivatives, and five other designer drugs newly detected in illegal products

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Abstract From November 2013 to May 2014, 19 newly distributed designer drugs were identified in 104 products in our ongoing survey of illegal products in Japan. The identified compounds included 8 synthetic cannabinoids, FUB-PB-22 (**1**), 5-fluoro-NNEI indazole analog (5-fluoro-MN-18, **2**), AM-2201 indazole analog (THJ-2201, **3**), XLR-12 (**4**), 5-fluoro-AB-PINACA (**5**), 5-chloro-AB-PINACA (**6**), AB-CHMINACA (**7**), and 5-fluoro-AMB (**8**); 5 cathinone derivatives, DL-4662 (**9**), α-PHP (**10**), 4-methoxy-α-POP (**11**), 4-methoxy-α-PHPP (**12**), and 4-fluoro-α-PHPP (**13**); and 6 other substances, namely, the benzofuran derivative 2-(2-ethylaminopropyl)benzofuran (2-EAPB, **14**), nitracaine (**15**), diclofensine (**16**), diphenidine (**17**), 1-benzylpiperidine (**18**), and acetylfentanyl (**19**). To our knowledge, this is the first report on the chemical properties of compounds **9**–**11** and **14**. A total of 33 designer drugs, including compounds **1**–**19**, were detected in the 104 illegal products, in 60 different combination patterns. The numbers of detected compounds per product ranged from 1 to 7. In addition, several products contained three different types of compounds, such as synthetic cannabinoids, cathinone derivatives, and phenethylamine derivatives per product. It is apparent that the types of compounds emerging as illegal products are becoming more diverse, as are their combinations.

Keywords 2-(2-Ethylaminopropyl)benzofuran (2-EAPB) · Synthetic cannabinoid · Cathinone derivative · Diclofensine · Diphenidine · Nitracaine

Introduction

Since 2009, the world has seen a dramatic emergence of synthetic cannabinoids, cathinone derivatives, and other new psychoactive substances (NPS) [1–6]. In fact, 384 NPS have been reported to the United Nations Office on Drugs and Crime (UNODC) since 2009, with 97 NPS being reported in 2013 alone [7]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) similarly reported that 81 NPS were identified by the EU Early Warning System in 2013 [8]. As a part of our ongoing survey of designer drugs in the illegal drug market in Japan, we reported the appearance of 26 newly distributed substances in Japan in 2013 [9–11]. The detected compounds were classified into three major types of designer drugs: 10 were synthetic cannabinoids, 8 were cathinone derivatives, and 5 were phenethylamines. In addition, 3 other substances were detected, including the opioid receptor agonist MT-45 and the methylphenidate analog 3,4-dichloromethylphenidate [9–11]. In this study, we describe the identification of 19 newly distributed designer drugs, of which 8 were synthetic cannabinoids (**1**−**8**), 5 were cathinone derivatives (**9**−**13**), and 6 were other substances (**14**−**19**) (Fig. 1). In addition, we investigated the combination patterns of detected designer drugs, including compounds **1**–**19**, in 104 illegal products purchased between November 2013 and May 2014.

Electronic supplementary material The online version of this article (doi:10.1007/s11419-014-0238-5) contains supplementary material, which is available to authorized users.

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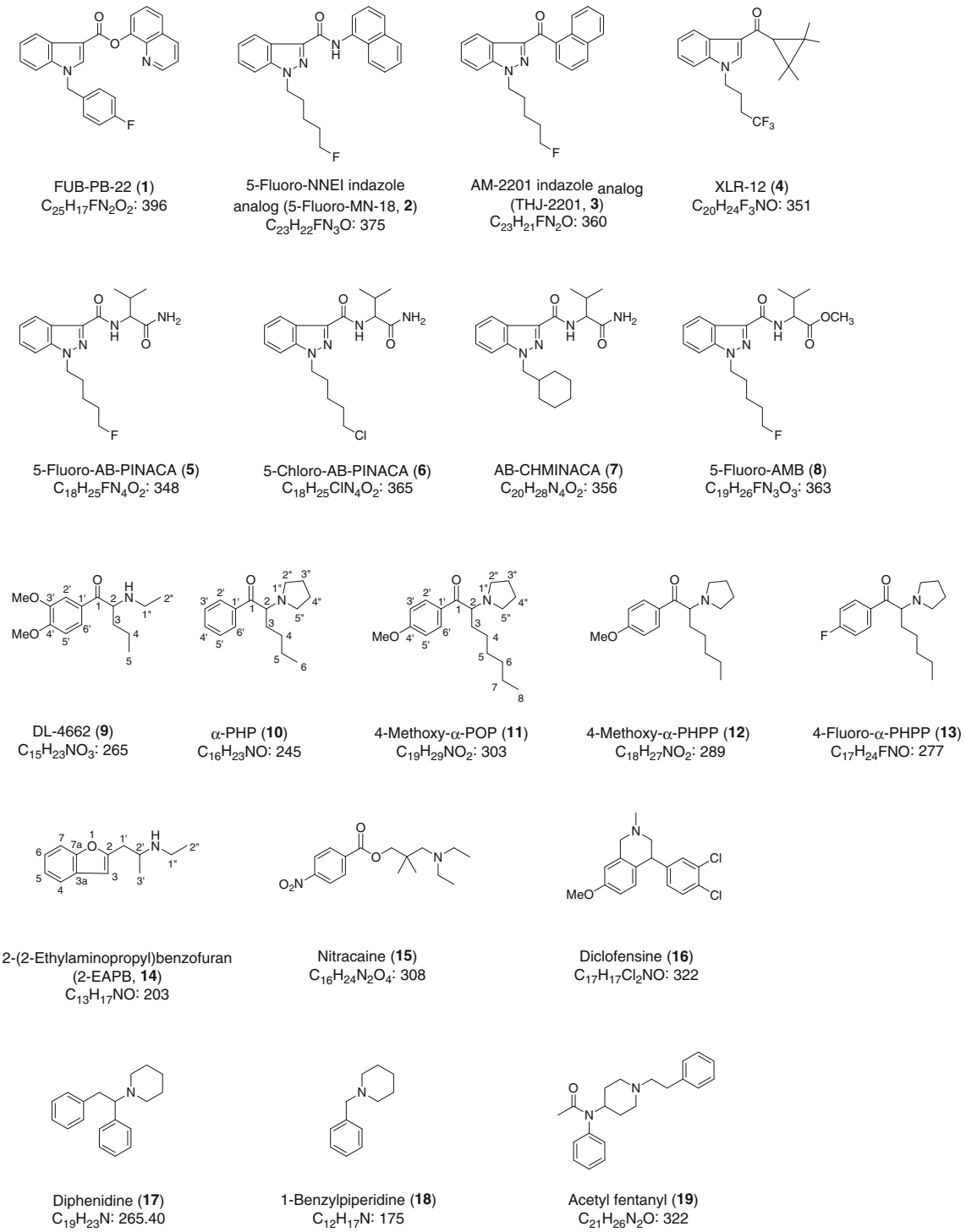

Fig. 1 Structures of the newly detected compounds (**1**–**19**)

Materials and methods

Samples for analyses

The analyzed samples were purchased via the Internet between November 2013 and May 2014 as 104 chemical-type or herbal-type products being sold in Japan. Among them, we show the analytical data of 14 products (A–N) for describing the identification of compounds **1**–**19** in this article. Each of the herbal-type products (A–D) contained about 3 g of mixed dried plants. The 7 powder-type products called ''fragrance powder'' consisted of 400 mg of a

white powder (G, I–L), a mixture of a white solid and a pale brown solid (E), or a mixture of a white solid and a pale purple solid (N). The 3 liquid-type products called ''liquid aroma'' consisted of about 5 ml of brown liquid (F and M) or pale yellow liquid (H). Products M and N were analyzed by nuclear magnetic resonance (NMR) spectroscopy. A 5-ml sample of liquid product M was evaporated to dryness, and then compound **10** (182 mg) was obtained from the dried sample as a brown oil. Compounds **9** and **14** were directly analyzed as white solids from products E and N, respectively, without isolation. Compound **11** from product G was directly analyzed without isolation.

Chemicals and reagents

FUB-PB-22, 5-fluoro-NNEI indazole analog (5-fluoro-MN-18), AM-2201 indazole analog (THJ-2201), XLR-12, 5-fluoro-AB-PINACA, 5-chloro-AB-PINACA, AB-CHMINACA, 5-fluoro-AMB, 4-methoxy-α-PHPP, 4-fluoro-α-PHPP, nitracaine, and acetylfentanyl were purchased from Cayman Chemicals (Ann Arbor, MI, USA). Diclofensine, diphenidine, and 1-benzylpiperidine were purchased from LGC (Teddington, UK), Tocris Bioscience (Bristol, UK), and Wako Pure Chemical Industries (Osaka, Japan), respectively. All other common chemicals and solvents were of analytical reagent grade or HPLC grade. As solvents for NMR analysis, methanol-d_4 (99.96 %), pyridine-d_5 (99.96 %), and dimethyl sulfoxide (DMSO)-d_6 (99.96 %) were purchased from the ISOTEC division of Sigma–Aldrich (St. Louis, MO, USA).

Preparation of sample solutions

For qualitative analyses, 10 mg of each herbal-type product was crushed into powder and extracted with 1 ml of methanol under ultrasonication for 10 min. A 2-mg portion of each powder-type product was extracted with 1 ml of methanol under ultrasonication for 10 min. A 20-μl portion of each liquid-type product was mixed with 1 ml of methanol under ultrasonication for 10 min. After centrifugation (3,000 rpm, 5 min) of each extract, the supernatant solution was passed through a centrifugal filter (Ultrafree-MC, 0.45 μm filter unit; Millipore, Bedford, MA, USA) to serve as the sample solution for the analyses. If necessary, the solution was diluted with methanol to a suitable concentration before the instrumental analyses.

Analytical conditions

Each sample solution was analyzed by ultra-performance liquid chromatography–electrospray ionization mass spectrometry (UPLC–ESI-MS) and by gas chromatography–mass spectrometry (GC–MS) in the electron ionization (EI) mode according to our previous report [12]. Three elution programs were used in the LC–MS analysis. 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). Elution program (1) used for analysis of cannabinoids was as follows: 35 % B (4-min hold) and 65–75 % B (4–16 min), and up to 90 % B (16–17 min, 6-min hold) at a flow rate of 0.3 ml/min. Elution program (2) used for the analysis of cathinone derivatives and other compounds was as follows: 5–20 % B (0–20 min), and up to 80 % B (20–30 min, 5-min hold). Elution program (3) used for the analysis of compounds **5** and **6** was as follows: 45 % B (15-min hold) and up to 90 % B (15–16 min, 2-min hold), and down to 45 % B (18–19 min, 5-min hold). In this study, products A, B, and D were analyzed using program (1), products E–L were analyzed using program (2), and product C was analyzed using program (3). GC–EI-MS was performed on an Agilent 6890N GC with a 5975 mass selective detector (Agilent, Santa Clara, CA, USA) using a capillary column (HP-1MS capillary, 30 m × 0.25 mm i.d., 0.25 μm film thickness; Agilent) with helium gas as a carrier at 0.7 ml/min. The conditions were: electron energy, 70 eV; injector temperature, 220 °C; injection, splitless mode for 1.0 min; mass selective detector temperature, 280 °C; scan range, *m/z* 40–550. Two programs were used in the GC–MS analysis, as follows. The oven temperature program (1), 80 °C (1-min hold) and an increase at a rate of 5 °C/min to 190 °C (15-min hold) followed by an increase at 10 °C/min up to 310 °C (15-min hold), and the oven temperature program (2), 150 °C (1-min hold) and increase at a rate of 20 °C/min to 280 °C (10-min hold) followed by an increase at 5 °C/min up to 310 °C (15-min hold). Program (2) was used for the analysis of product C. Other products were analyzed using program (1).

The obtained GC mass spectra were compared to those of an EI-MS library (Mass Spectra of Designer Drugs 2013; Wiley-VCH, Weinheim, Germany). We also used our in-house EI-MS library of designer drugs obtained by our ongoing survey of illegal products and commercially available reagents for the structural elucidation.

We measured the accurate mass numbers of the target compounds by liquid chromatography–quadrupole time-of-flight mass spectrometry (LC–QTOF-MS) in the ESI mode according to our previous report [6].

NMR spectra were obtained on ECA-800 and 600 spectrometers (JEOL, Tokyo, Japan). Structural assignments were made based on interpretation of ^{1}H NMR, ^{13}C NMR, heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), ^{15}N HMBC, and double quantum filtered correlation spectroscopy (DQF-COSY) spectra.

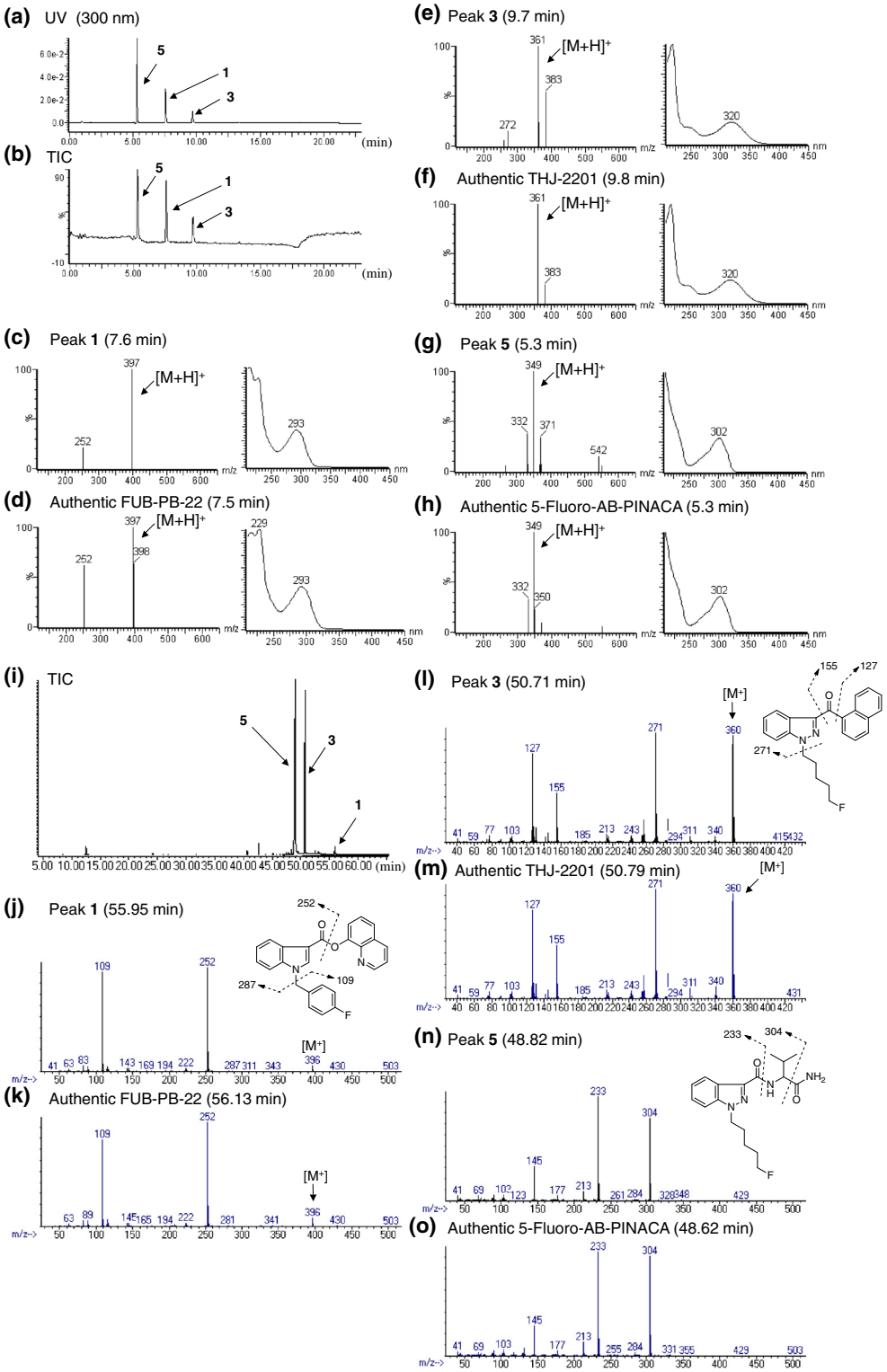

Fig. 2 Liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS) analyses of product A. The LC–ultraviolet photodiode array (LC–UV-PDA) chromatogram (**a**) and total ion chromatogram (TIC) (**b**) are shown. Electrospray ionization (ESI) mass and UV spectra of peaks **1** (**c**), **3** (**e**), **5** (**g**), the authentic FUB-PB-22 (**d**), AM-2201 indazole analog (THJ-2201, **f**), and 5-fluoro-AB-PINACA (**h**) are also presented. Panels (**i**) through (**o**) show TIC (**i**) and electron ionization (EI) mass spectra of peaks **1** (**j**), **3** (**l**), **5** (**n**), the authentic FUB-PB-22 (**k**), AM-2201 indazole analog (THJ-2201, **m**), and 5-fluoro-AB-PINACA (**o**) obtained by GC–MS analysis

Results and discussion

Identification of unknown peaks **1**, **3**, and **5**

LC–MS and GC–MS analyses were performed to identify unknown peaks **1**, **3**, and **5** in product A (Fig. 2a, b, i). Based on the LC–MS and GC–MS data, the three peaks were finally identified as synthetic cannabinoids; namely, FUB-PB-22 (Fig. 2c, j), an AM-2201 indazole analog (THJ-2201) (Fig. 2e, l), and 5-fluoro-AB-PINACA (Fig. 2g, n), by direct comparison of the data to those of the purchased authentic compounds (Fig. 2d, k; Fig. 2f, m; Fig. 2h, o), respectively. Compounds **1**, **3**, and **5** were detected as newly distributed designer drugs in Japan. These compounds are analogs of known cannabimimetic substances, QUPIC (PB-22) [6], AM-2201, and AB-PINACA [4], respectively, the pharmacological effects for which have not been reported. In addition, FUB-PB-22 (**1**) and 5-fluoro-AB-PINACA (**5**) will be controlled as *Shitei-Yakubutsu* (designated substances) in Japan from July 2014.

Identification of unknown peaks **2** and **4**

Two unknown peaks **2** and **4** were detected along with 5-fluoro-AB-PINACA (**5**) in the LC–MS and GC–MS chromatograms for product B (Fig. 3a, b, g). Peaks **2** and **4** were identified as the synthetic cannabinoids 5-fluoro-NNEI indazole analog (5-fluoro-MN-18) (Fig. 3c, h) and XLR-12 (Fig. 3e, j) by direct comparison of the data to those of the purchased authentic compounds (Fig. 3d, i; Fig. 3f, k), respectively. 5-Fluoro-NNEI indazole analog (**2**) is an analog of a known NNEI indazole analog (MN-18), which has already been detected in illegal products [11]. Although there is no pharmacological information about compound **2**, a cyclopropylmethanone-type XLR-12 (**4**), which is an analog of XLR-11, has been reported to show affinity for the cannabinoid CB_1 and CB_2 receptors (K_i = 10 and 0.09 nM, respectively) [13]. In addition, 5-fluoro-NNEI indazole analog (5-fluoro-MN-18, **2**) and XLR-12 (**4**) will be controlled as designated substances in Japan from July 2014.

Identification of unknown peak **6**

An unknown peak **6** was detected along with the 5-fluoro-AB-PINACA (**5**) peak in the LC–MS and GC–MS chromatograms for product C (Fig. 4a–c, f). Based on the GC–MS and LC–MS data, the unknown peak **6** was finally identified as dicarboxamide derivative 5-chloro-AB-PINACA (Fig. 4d, g) by direct comparison of the data to those of the purchased authentic compound (Fig. 4e, h). This is the first report of the detection of 5-chloro-AB-PINACA (**6**) as a newly distributed illegal drug in Japan.

Identification of unknown peaks **7** and **8**

In the LC–MS and GC–MS analyses, unknown peaks **7** and **8** were detected with FUB-PB-22 (**1**) in product D (Fig. 5a, b, g). Peaks **7** and **8** were identified as synthetic cannabinoids AB-CHMINACA (Fig. 5c, h) and 5-fluoro-AMB (Fig. 5e, j), respectively, by direct comparison of the data to those of the purchased authentic compounds (Fig. 5d, i; Fig. 5f, k). The *S*-form of the dicarboxamide derivative AB-CHMINACA (*N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, **7**) has been reported to have a potent affinity for the cannabinoid CB_1 receptor (K_i = 0.5 nM) [14]. Although there is no pharmacological information about 5-fluoro-AMB (methyl 2-[1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido]-3-methylbutanoate, **8**), its analog, methyl 2-[1-(4-cyanobutyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate, has been reported to have a potent affinity for cannabinoid CB_1 receptor (K_i = 0.7 nM) [14].

Identification of the unknown peaks **9** and **12**

We detected two unknown peaks, **9** and **12**, in the LC–MS and GC–MS chromatograms for product E (Fig. 6a, b, f). Peak **12** was identified as the cathinone derivative 4′-methoxy-α-pyrrolidinoheptanophenone (4-methoxy-α-PHPP) (Fig. 6d, h) by direct comparison of the data with those of the purchased authentic compound (Fig. 6e, i). 4-Methoxy-α-PHPP (**12**) is a *para*-methoxy analog of a known α-PHPP [11]. The pharmacological and toxicological properties of **12** are not known. Compound **12** was detected as a newly distributed designer drug in Japan. In the LC–MS analysis, the unknown peak **9** at 14.8 min showed a protonated molecular ion signal at *m/z* 266 ($[M+H]^+$) (Fig. 6c). The accurate mass spectrum obtained by LC–QTOF-MS gave an ion peak at *m/z* 266.1746, suggesting that the protonated molecular formula of compound **9** was $C_{15}H_{24}NO_3$ (calcd. 266.1756).

The ^1H and ^{13}C NMR data (Table 1) and the observed DQF-COSY, HMQC, HMBC, and ^{15}N HMBC correlations shown in Fig. 7a revealed that the structure of compound **9** is 1-(3,4-dimethoxyphenyl)-2-(ethylamino)pentan-1-one (DL-4662), as shown in Fig. 1. The fragment ions at *m/z* 100, 137, and 165 of compound **9** in the GC–MS spectrum (Fig. 6g) further confirmed the structure. Compound **9**, which is a dimethoxy-analog of a known cathinone derivative, α-ethylaminopentiophenone [11], is a novel illegal drug, and its chemical and pharmacological data have not been reported.

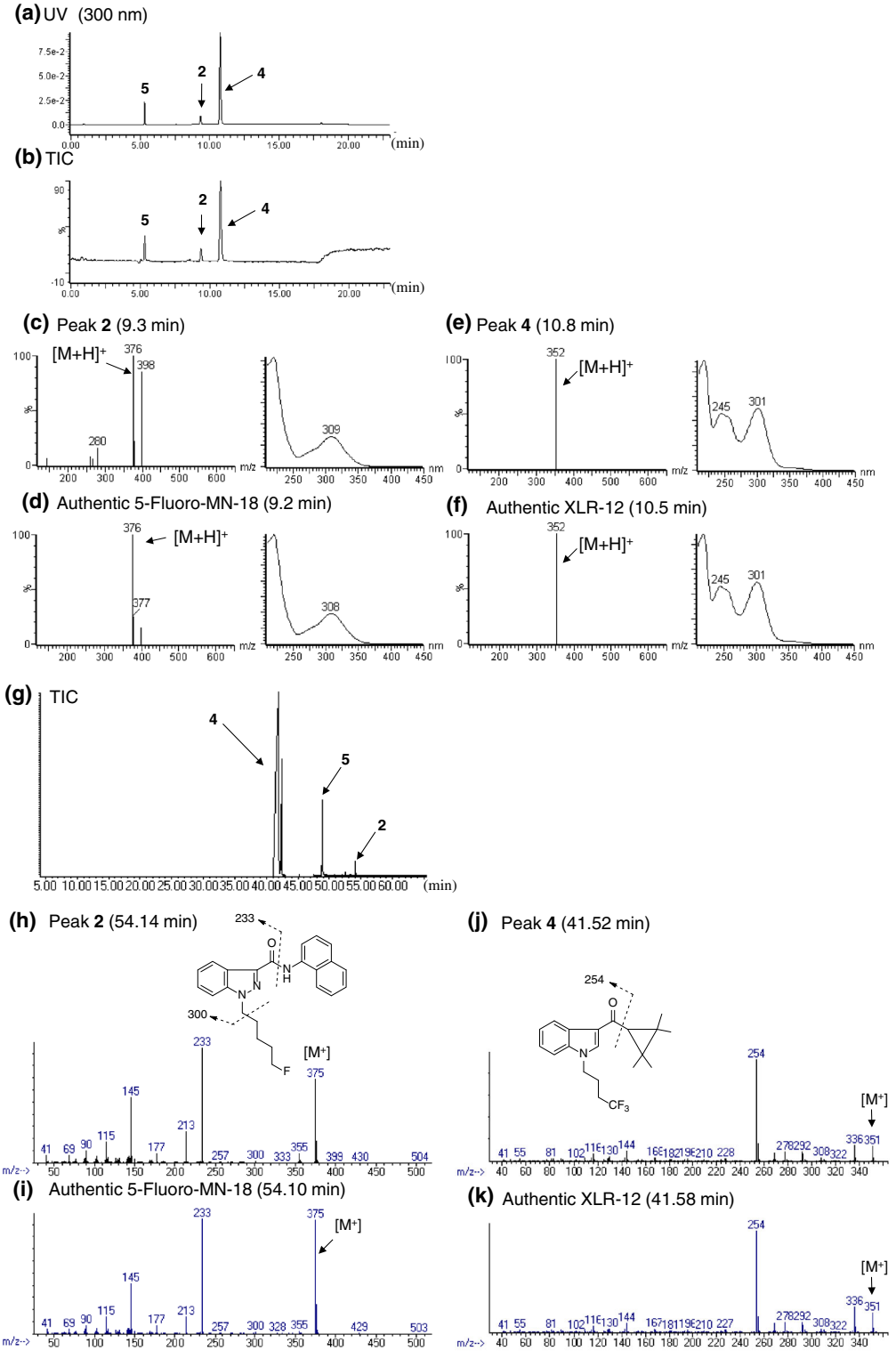

Fig. 3 LC–MS and GC–MS analyses of product B. Panels (**a**) and (**b**) show LC–UV-PDA chromatogram (**a**) and TIC (**b**). ESI mass and UV spectra of peaks **2** (**c**), **4** (**e**), and the authentic 5-fluoro-NNEI indazole analog (**d**) and XLR-12 (**f**) are also shown. Panels (**g**) through (**k**) show TIC (**g**) and EI mass spectra of peaks **2** (**h**), **4** (**j**), and the authentic 5-fluoro-NNEI indazole analog (**i**) and XLR-12 (**k**) obtained by the GC–MS analysis

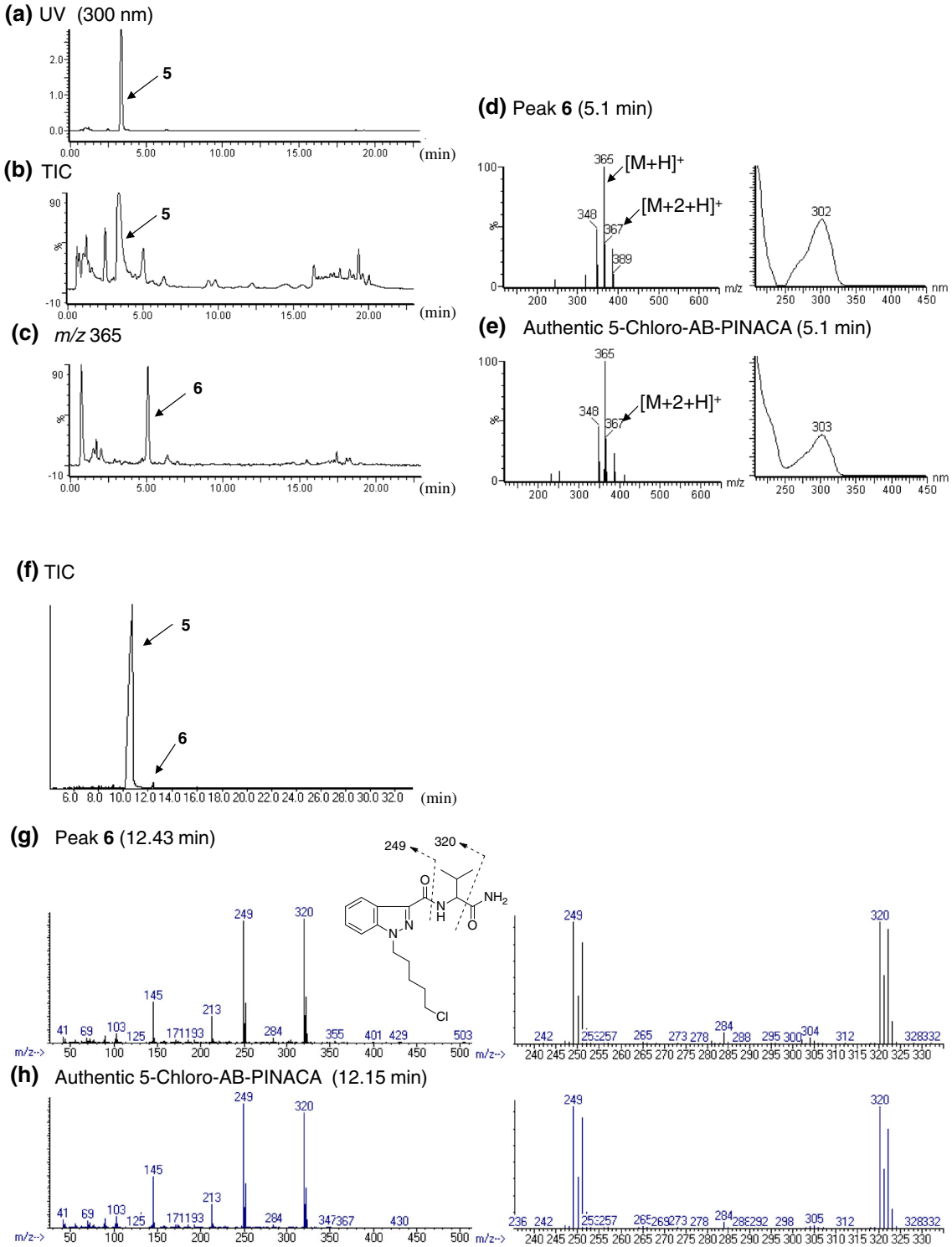

Fig. 4 LC–MS and GC–MS analyses of product C. LC–UV-PDA chromatogram (**a**), TIC (**b**), mass chromatogram at *m/z* 365 (**c**), and ESI mass and UV spectra of peak **6** (**d**) and the authentic 5-chloro-AB-PINACA (**e**) are shown. TIC (**f**) and EI mass spectra of peak **6** (**g**) and the authentic 5-chloro-AB-PINACA (**h**) obtained by GC–MS analysis are also presented

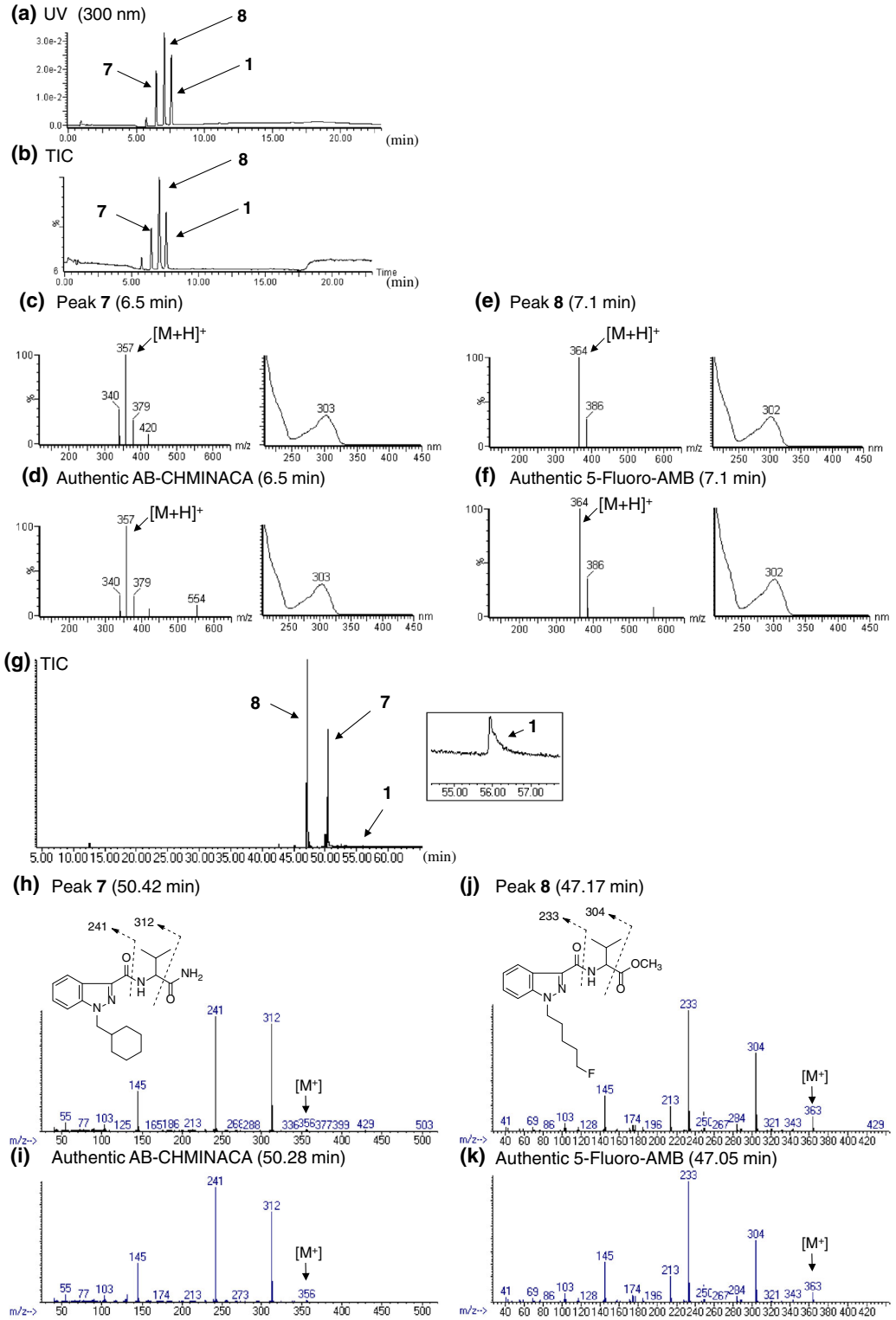

Fig. 5 LC–MS and GC–MS analyses of product D. The LC–UV-PDA chromatogram (**a**) and TIC (**b**) are shown. ESI mass and UV spectra of peaks **7** (**c**), **8** (**e**), and the authentic AB-CHMINACA (**d**) and 5-fluoro-AMB (**f**) are also shown. Panels (**g**) through (**k**) present the TIC (**g**) and EI mass spectra of peaks **7** (**h**), **8** (**j**), and the authentic AB-CHMINACA (**i**) and 5-fluoro-AMB (**k**) obtained by GC–MS analysis

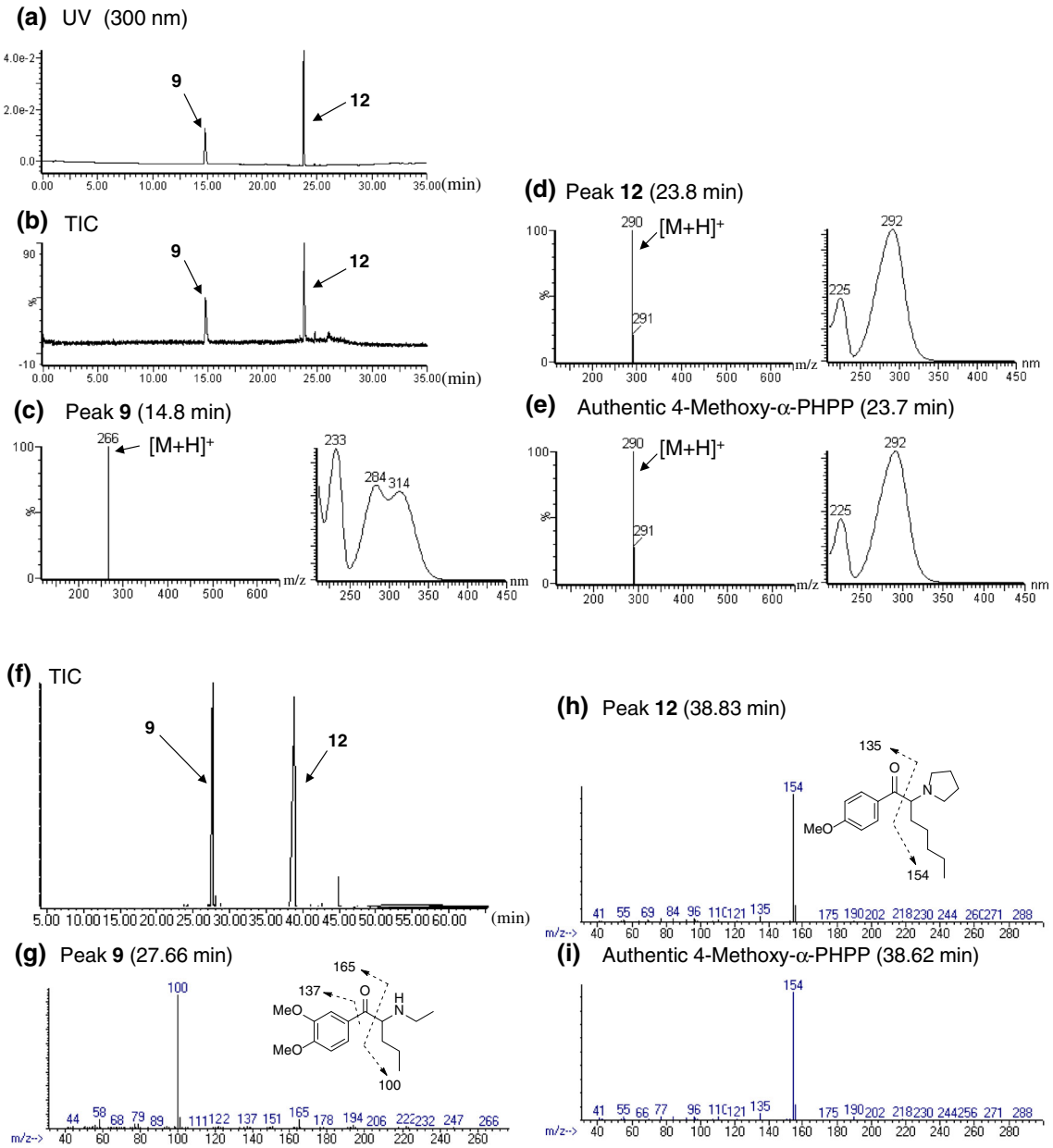

Fig. 6 LC–MS and GC–MS analyses of product E. The LC–UV-PDA chromatogram (**a**) and TIC (**b**) are shown, along with the ESI mass and UV spectra of peaks **9** (**c**), **12** (**d**), and the authentic 4-methoxy-α-PHPP (**e**). Panels (**f**) through (**i**) show TIC (**f**) and EI mass spectra of peaks **9** (**g**), **12** (**h**), and the authentic 4-methoxy-α-PHPP (**i**) obtained by GC–MS analysis

Identification of the unknown peaks **10** and **13**

Unknown peaks **10** and **13** were detected along with a peak for known compound 25B-NBOMe [10] in the LC–MS and GC–MS chromatograms for product F (Fig. 8a, b, f). Based on the GC–MS and LC–MS data, peak **13** was finally identified as the cathinone derivative 4′- fluoro-α-pyrrolidinoheptanophenone (4-fluoro-α-PHPP) (Fig. 8d, h) by direct comparison of the data to those of the purchased authentic compound (Fig. 8e, i). In the LC–MS analysis, unknown peak **10** at 19.0 min showed a protonated molecular ion signal at *m/z* 246 ($[M+H]^+$) (Fig. 8c). The accurate mass spectrum obtained by LC–QTOF-MS gave an ion peak at *m/z* 246.1840, suggesting that the protonated molecular formula of compound **10** was $C_{16}H_{24}NO$ (calcd. 246.1858).

The ^{1}H and ^{13}C NMR spectra of compound **10** were very similar to those of a known cathinone derivative, α-POP, except for the additional C_2H_4 of the *n*-alkyl moiety (positions 5 and 6) of α-POP, as shown in Tables 2 and 3 [11]. The observed ^{1}H and ^{13}C NMR data (Tables 2, 3) and DQF-COSY, HMQC, HMBC, and ^{15}N HMBC correlations

(data not shown) revealed that the structure of compound **10** corresponded to α-pyrrolidinohexylphenone (α-PHP), as shown in Fig. 1. The fragment ions at *m/z* 77, 105, and 140 of compound **10** in the GC–MS spectrum (Fig. 8g) further confirmed the structure. Compound **10** is a desmethyl analog of MPHP, which is controlled as a designated substance in Japan, and its chemical and pharmacological data have not been reported.

Identification of unknown peak **11**

Unknown peak **11** was detected in the GC–MS and LC–MS chromatograms for product G (Fig. 9a, b, d). The proposed fragmentation and the presumed structure of peak **11** obtained by GC–MS analysis are shown in Fig. 9e. The LC–MS data revealed that peak **11** gave a protonated ion signal at *m/z* 304 ($[M+H]^+$) (Fig. 9c). The accurate mass spectrum obtained by LC–QTOF-MS gave an ion peak at *m/z* 304.2269, suggesting that the protonated molecular formula of compound **11** was $C_{19}H_{30}NO_2$ (calcd. 304.2269).

The ^{13}C NMR spectrum of compound **11** was similar to that of α-POP except for the C-1′ and C-3′ to C-5′ carbons of a phenyl group and the 4′-methoxy carbon (Table 2) [11]. The observed ^1H and ^{13}C NMR data (Tables 2, 3) and DQF-COSY, HMQC, HMBC, and ^{15}N HMBC correlations (data not shown) suggested that the structure of compound **11** is 4′-methoxy-α-pyrrolidinooctanophenone (4-methoxy-α-POP), as shown in Fig. 1. The fragment ions at *m/z* 135 and 168 of compound **11** in the GC–MS spectrum corroborated the structure (Fig. 9e). Compound **11** was detected as a newly distributed designer drug, and its chemical and pharmacological data have not been reported.

Table 1 Nuclear magnetic resonance (NMR) data of DL-4662 (**9**)

No	^{13}C	^1H
1	195.1	–
2	62.5	5.12, 1H, t, $J = 5.5$ Hz
3	34.4	1.94, 2H, m
4	18.8	1.35, 1H, m, overlapped
		1.26, 1H, m
5	14.2	0.90, 3H, t, $J = 7.3$ Hz
1′	128.2	–
2′	111.8	7.57, 1H, d, $J = 1.8$ Hz
3′	151.1	–
4′	156.7	–
5′	112.0	7.12, 1H, d, $J = 8.3$ Hz
6′	125.4	7.74, 1H, dd, $J = 8.3$, 2.3 Hz
1″	43.3	3.08 and 3.00, each 1H, m
2″	11.8	1.34, 3H, t, $J = 7.3$ Hz, overlapped
3′-OMe	56.5	3.90, 3H, s
4′-OMe	56.7	3.94, 3H, s

Spectra recorded in methanol-d_4 at 800 MHz (^1H) and 200 MHz (^{13}C); data in δ ppm; *OMe* methoxy

Identification of unknown peak **14**

We detected unknown peak **14** in the LC–MS and GC–MS chromatograms for product H (Fig. 10a, b, d). In LC–MS analysis, unknown peak **14** at 15.5 min showed a protonated molecular ion signal at *m/z* 204 ($[M+H]^+$) (Fig. 10c). The accurate mass spectrum obtained by LC–QTOF-MS gave an ion peak at *m/z* 204.1377, suggesting that the protonated molecular formula of compound **14** was $C_{13}H_{18}NO$ (calcd. 204.1388).

The structure of compound **14** was elucidated by NMR analysis (Fig. 7b; Table 4). The ^1H and ^{13}C NMR spectra of compound **14** suggested the existence of 17 protons and 13 carbons (Table 4). Interpretation of DQF-COSY, HMQC, and HMBC spectra of compound **14** revealed the presence of a 2-propylbenzofuran moiety (positions 2 to 7a and position 1′ to 3′, Fig. 7b). The remaining C_2H_6N unit was presumed to be an *N*-ethylamine group. In addition,

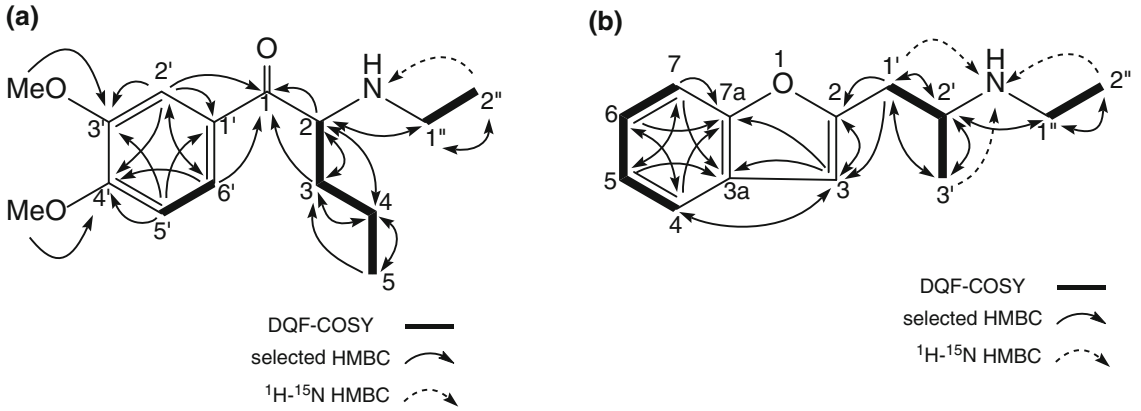

Fig. 7 Double quantum filtered correlation spectroscopy (DQF-COSY), selected heteronuclear multiple-bond correlation (HMBC), and ^1H–^{15}N HMBC correlations for compound **9** (DL-4662, **a**), and for compound **14** (2-EAPB, **b**)

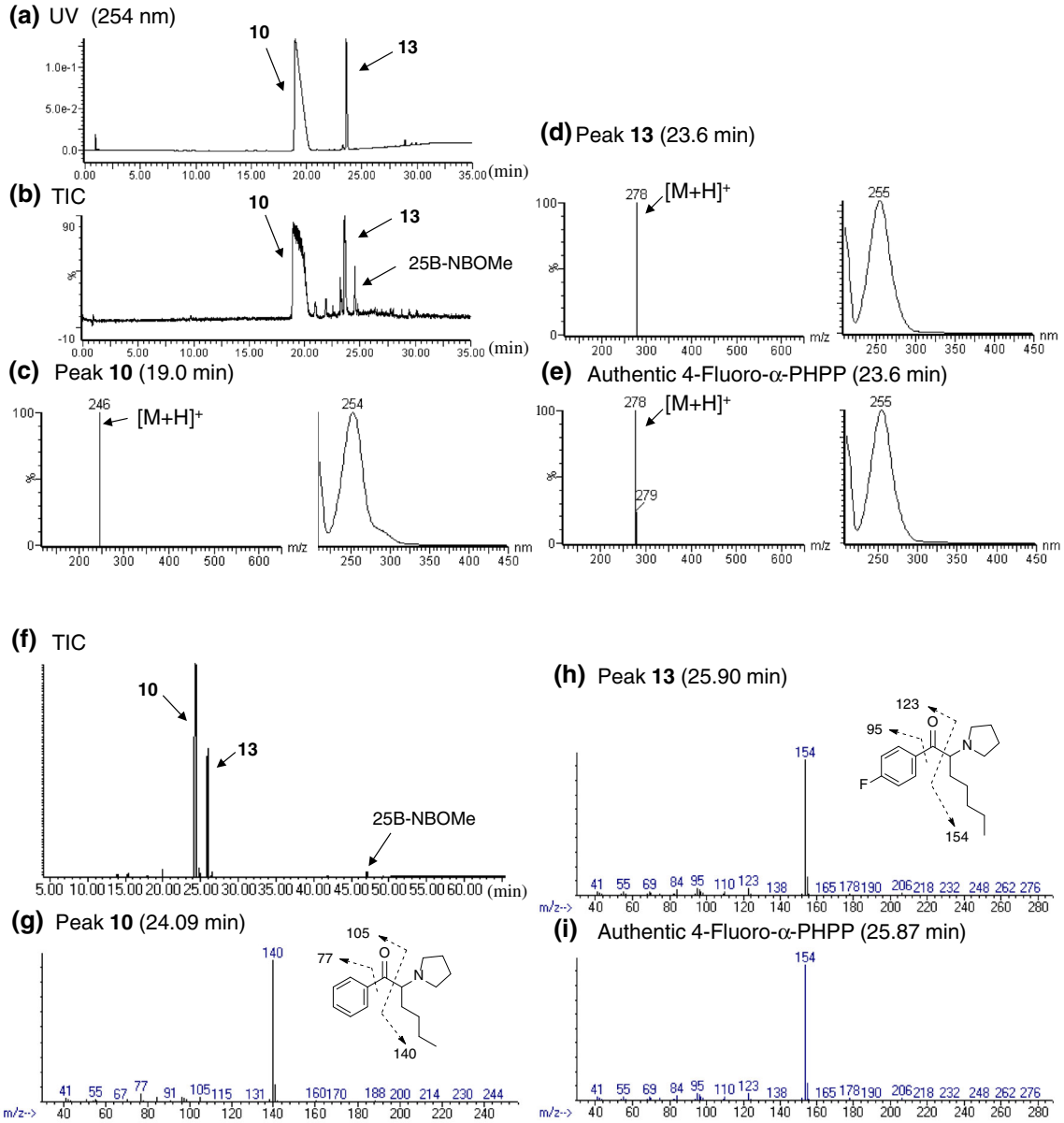

Fig. 8 LC–MS and GC–MS analyses of product F. The LC–UV-PDA chromatogram (**a**) and TIC (**b**) are shown, along with ESI mass and UV spectra of peaks **10** (**c**), **13** (**d**), and the authentic 4-fluoro-α-PHPP (**e**). Panels (**f**) through (**i**) show TIC (**f**) and EI mass spectra of peaks **10** (**g**), **13** (**h**), and the authentic 4-fluoro-α-PHPP (**i**) obtained by GC–MS analysis

^{15}N HMBC correlations between NH and each of H-1′, H-3′, and H-2″, and an HMBC correlation between a methine (position 2′) and a methylene (position 1″) were observed (Fig. 7b). These results revealed that a 2-propylbenzofuran moiety was connected at position 2′ to the *N*-ethylamine group at nitrogen (Fig. 7b). Therefore, the structure of compound **14** was clarified as a benzofuran derivative, 2-(2-ethylaminopropyl)benzofuran (2-EAPB), as shown in Fig. 1. Compound **14** was detected as a newly distributed designer drug, and its pharmacological data have not been reported. However, the benzofuran derivatives 5-APB [5-(2-aminopropyl)benzofuran] and 6-APB [6-(2-aminopropyl)benzofuran] have been reported as potent triple monoamine reuptake inhibitors for dopamine, norepinephrine, and serotonin in vitro [15]. In addition, it has been reported that the 2-ethylaminopropyl regioisomer of **14**, 5-EAPB [5-(2-ethylaminopropyl)benzofuran], is offered for sale as an alternative to other benzofurans in the UK [16].

Identification of the unknown peaks **15**–**19**

GC–MS and LC–MS analyses were performed to identify the five unknown peaks **15**, **16**, **17**, and **18** and **19** in

Table 2 ^{13}C NMR data of compounds **10** and **11** and α-POP

No.	α-PHP (**10**)	α-POP [a]	4-MeO-α-POP (**11**)
1	198.0	198.7	196.7
2	66.8	66.8	66.9
3	30.2	30.1	30.7
4	27.9	26.2	26.0
5	22.8	29.5	29.5
6	13.7	31.6	31.6
7	–	22.7	22.7
8	–	14.1	14.1
1′	136.5	137.0	130.0
2′/6′	129.4	129.2	131.9
3′/5′	129.5	129.3	114.7
4′	134.7	134.2	164.8
2″/5″	52.0	51.3	51.7
3″/4″	24.0	24.0	23.9
4′-OMe	–	–	55.7

Spectra recorded at 200 MHz in pyridine-d_5

4-MeO-α-POP 4-methoxy-α-POP

[a] Data from Uchiyama et al. [11]

Table 3 ^{1}H NMR data of compounds **10** and **11** and α-POP

No.	α-PHP (**10**)	α-POP [a]	4-MeO-α-POP (**11**)
1	–	–	–
2	5.59, 1H, brs	5.03, 1H, brs	5.42, 1H, brs
3	2.18, 2H, m	2.11, 2H, m	2.17, 2H, m
4	1.42, 1H, m	1.37, 2H, m	1.38, 2H, m
	1.31, 1H, m	–	–
5	1.11, 2H, m	1.12, 2H, m, overlapped	1.12, 2H, m, overlapped
6	0.65, 3H, t, $J = 7.3$ Hz	1.02, 2H, m, overlapped	1.02, 2H, m, overlapped
7	–	1.08, 2H, m, overlapped	1.07, 2H, m, overlapped
8	–	0.72, 3H, t, $J = 7.6$ Hz	0.70, 3H, t, $J = 7.3$ Hz
1′	–	–	–
2′/6′	8.35, 2H, dd, $J = 8.2$, 0.8 Hz	8.33, 2H, dd, $J = 8.6$, 1.4 Hz	8.44, 2H, d, $J = 8.7$ Hz
3′/5′	7.51, 2H, t, $J = 7.8$ Hz	7.50, 2H, t, $J = 8.6$ Hz	7.09, 2H, t, $J = 8.7$ Hz
4′	7.59, 1H, t, $J = 7.3$ Hz	7.58, 1H, tt, $J = 8.6$, 1.4 Hz	–
2″/5″	3.53, 3.39, each 2H, brs	3.28, 3.10, each 2H, brs	3.44, 3.30, each 2H, brs
3″/4″	1.95, 1.89, each 2H, m	1.80, 4H, m	1.88, 1.84, each 2H, m
4′-OMe	–	–	3.71, 3H, s

Spectra recorded at 800 MHz in pyridine-d_5; data in δ ppm

[a] Data from Uchiyama et al. [11]

products I (Supplementary material, Fig. S1a, b, e), J (Fig. S2a–d, g), K (Fig. S3a–d, i), and L (Fig. S4a, b, e), respectively. Based on the GC–MS and LC–MS data, the five peaks were finally identified as nitracaine (Fig. S1c, f), diclofensine (Fig. S2e, h), diphenidine (Fig. S3e, j), 1-benzylpiperidine (Fig. S3g, l), and acetylfentanyl (Fig. S4c, f), respectively, by direct comparison of the data with those of the purchased authentic compounds (Fig. S1d, g; Fig. S2f, i; Fig. S3f, k; Fig. S3h, m; Fig. S4d, g). Researchers in Ireland reported that nitracaine (**15**), which is the nitro analog of the local anesthetic dimethocaine, emerged in December 2013 as a new psychoactive substance on an Internet website selling "research chemicals" [17]. Diclofensine (**16**) has been reported as an inhibitor of monoamine uptake [18], while diphenidine (**17**) has been reported as an *N*-methyl-D-aspartate (NMDA) channel blocker [19]. The opioid receptor agonist acetylfentanyl (**19**) will be controlled as a designated substance in Japan from July 2014.

Combination patterns of detected compounds in illegal products

As described in our previous reports [3, 20], our survey of illegal products distributed in Japan revealed that the average number of synthetic compounds detected per illegal product was 2.6 in 2010–2012. In some cases, synthetic compounds of different types, such as synthetic cannabinoids and cathinone derivatives, were present in the same product [3]. In this study, 34 compounds, including compounds **1**–**19**, were detected in the products, and the detected compounds were categorized into three types: synthetic cannabinoids (10 compounds), cathinone derivatives (13 compounds), and other classes of designer drugs (10 compounds) (Table 5). Table 6 provides a list of the different combination patterns of detected compounds in 104 illegal products purchased between November 2013 and May 2014. Sixty combination patterns were detected, with the number of compounds per product ranging from one to seven: one detected compound (10 patterns), two (23 patterns), three (14 patterns), four (4 patterns), five (6 patterns), six (2 patterns), and seven (1 pattern), as shown in Table 6.

The combination patterns were classified broadly into seven groups (A–G) based on the types of compounds, as shown in Table 6. Group A consisted of a mixture of only synthetic cannabinoid(s) with 17 patterns, group B was a mixture of only cathinone derivative(s) with 11 patterns, group C was a mixture of other compound(s) with 4 patterns, group D was a mixture of synthetic cannabinoid(s) and cathinone derivative(s) with 21 patterns, group E was a mixture of a synthetic cannabinoid and another compound with 1 pattern, group F was a mixture of cathinone

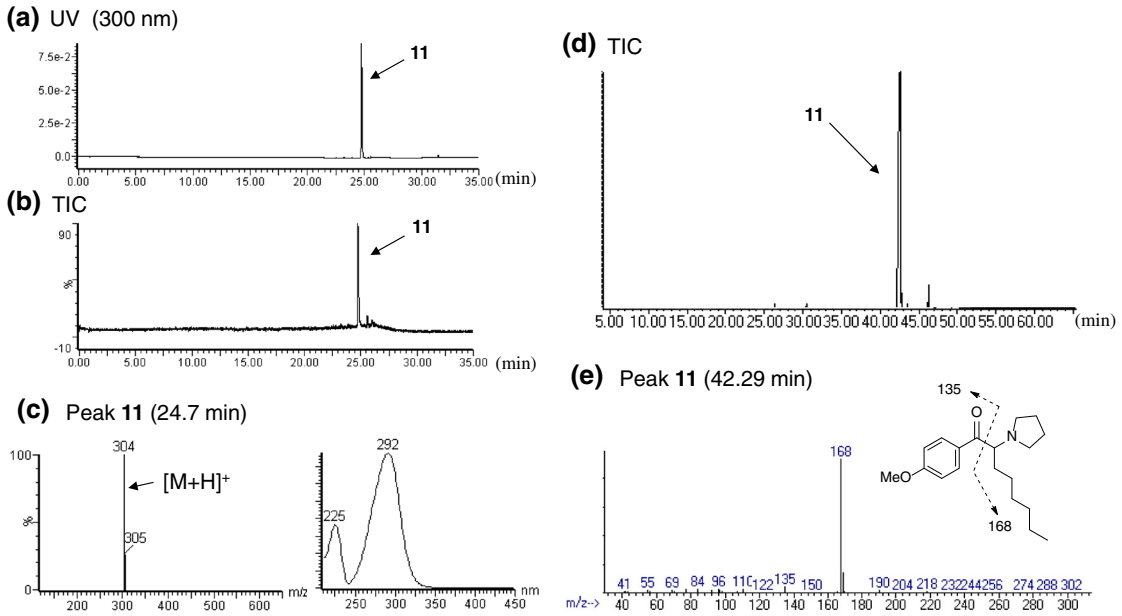

Fig. 9 LC–MS and GC–MS analyses of product G. The LC–UV-PDA chromatogram (**a**), TIC (**b**), and ESI mass and UV spectra of peak **11** (**c**) are shown. TIC (**d**) and EI mass spectra of peak **11** (**e**) obtained by GC–MS analysis are also presented

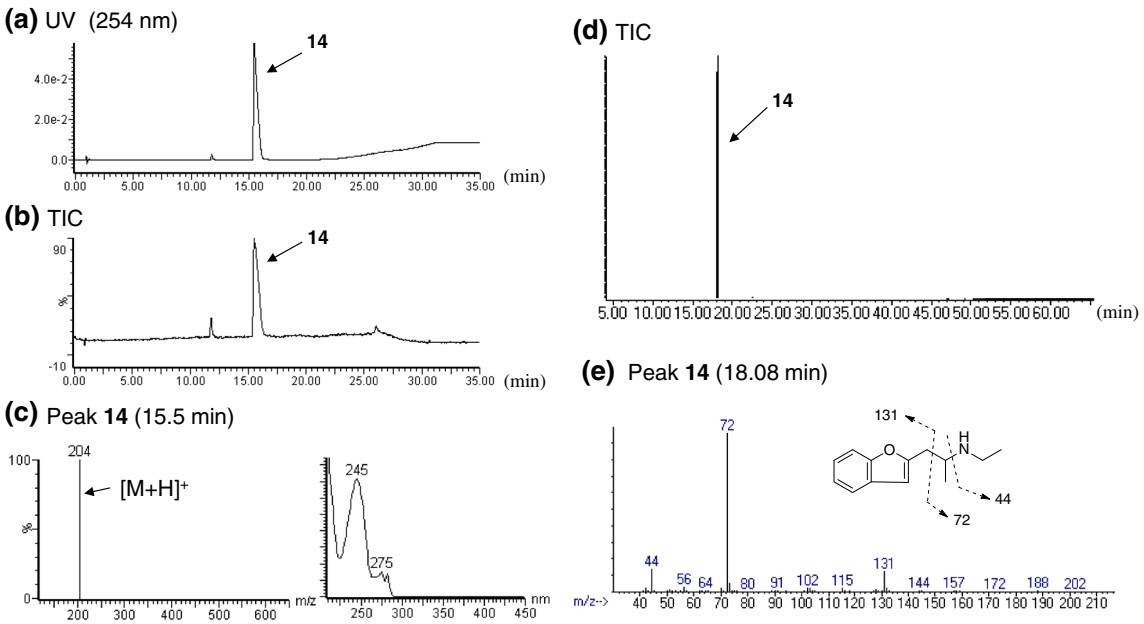

Fig. 10 LC–MS and GC–MS analyses of product H. The LC–UV-PDA chromatogram (**a**), TIC (**b**), and ESI mass and UV spectra of peak **14** (**c**) are presented. Also shown are the TIC (**d**) and EI mass spectra of peak **14** (**e**) obtained by GC–MS analysis

derivative(s) and another compound with 2 patterns, and group G was a mixture of synthetic cannabinoid(s), cathinone derivative(s), and other compound(s) with 4 patterns.

As in the case of group G-(1), the product contained three different types of compounds with different pharmacological effects: the synthetic cannabinoid 5-fluoro-NNEI

Table 4 NMR data of 2-EAPB (**14**)

No.	^{13}C	^{1}H
1	–	–
	153.9	–
3	106.8	6.72, 1H, s
3a	129.8	–
4	121.9	7.55, 1H, d, $J = 7.6$ Hz
5	124.1	7.21, 1H, t, $J = 7.6$ Hz
6	125.3	7.27, 1H, t, $J = 7.6$ Hz
7	111.9	7.45, 1H, d, $J = 7.6$ Hz
7a	156.5	–
1′	33.0	3.27, 1H, dd, $J = 15.0$, 5.0 Hz
		3.11, 1H, m, overlapped
2′	53.4	3.68, 1H, m
3′	16.7	1.35, 3H, t, $J = 6.9$ Hz, overlapped
1″	41.7	3.16, 3.14, each 1H, m, overlapped
2″	11.8	1.33, 3H, t, $J = 7.2$ Hz, overlapped
NH	–	8.87, 1H, brs [a]

Spectra recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C) in methanol-d_4; data in δ ppm

[a] Recorded in dimethyl sulfoxide-d_6

Table 5 List of detected compounds

Types of compounds	Detected compounds
10 Synthetic cannabinoids	FUB-PB-22 (**1**)
	5-Fluoro-NNEI indazole analog (5-fluoro-MN-18) (**2**)
	AM2201indazole analog (THJ-2201) (**3**)
	XLR-12 (**4**)
	5-Fluoro-AB-PINACA (**5**)
	5-Chloro-AB-PINACA (**6**)
	AB-CHMINACA (**7**)
	5-Fluoro-AMB (**8**)
	NNEI indazole analog (MN-18)
	QUPIC N-(5-fluoropentyl) analog (5-fluoro-PB-22)
13 Cathinone derivatives	DL-4662 (**9**)
	α-PHP (**10**)
	4-Methoxy-α-POP (**11**)
	4-Methoxy-α-PHPP (**12**)
	4-Fluoro-α-PHPP (**13**)
	α-POP
	3,4-Dimethoxy-α-PVP
	4-Ethylmethcathinone
	4-Methoxy-α-PVP
	4-Methylbuphedrone
	4-Methyl-α-ethylaminopentiophenone
	N-Ethylbuphedrone (NEB)
	Pentedrone
10 Other compounds	2-EAPB (**14**)
	Nitracaine (**15**)
	Diclofensine (**16**)
	Diphenidine (**17**)
	1-Benzylpiperidine (**18**)
	Acetyl fentanyl (**19**)
	α-PVT
	25I-NBOMe
	25B-NBOMe
	25N-NBOMe

indazole analog (**2**), the cathinone derivative α-POP, and the NMDA channel blocker diclofensine (**16**). On the other hand, in the case of group G-(2), the product contained the synthetic cannabinoid FUB-PB-22 (**1**), the two cathinone derivatives 4-methyl-α-ethylaminopentiophenone and 3,4-dimethoxy-α-PVP, and the phenethylamine derivative 25I-NBOMe, which is a 5-HT_{2A} receptor agonist with hallucinogenic effects. Considering the results, it is apparent that the types of emerging compounds are becoming more diverse, as are their combinations in illegal products.

Conclusions

Nineteen newly distributed designer drugs, including eight synthetic cannabinoids (**1**–**8**), five cathinone derivatives (**9**–**13**), and six other substances—2-EAPB (**14**), nitracaine (**15**), diclofensine (**16**), diphenidine (**17**), 1-benzylpiperidine (**18**), and acetylfentanyl (**19**)—were identified in illegal products that are available in Japan. Most of the detected compounds (**1**–**14** and **19**) appeared as alternatives to controlled substances such as narcotics and designated substances in Japan. It is apparent that the types of designer drugs and their combinations in illegal products seem to be increasing in diversity. Thus, serious side effects from these combinations are possible, although it is hard to predict them. The emergence of designer drugs that are neither synthetic cannabinoids nor cathinone derivatives also seems to be increasing. Therefore, continuous

Table 6 List of 60 combination patterns of 34 detected compounds in 104 illegal products purchased between November 2013 and May 2014

Nubmer of compound(s) (Number of patterns)	Number of product(s)	Groups of combinations	Detected compound(s)						
1 (10 patterns)	2	A	**5-Fluoro-AB-PINACA**						
	7	A	**FUB-PB-22**						
	3	B	*α-PHP*						
	3	B	*DL-4662*						
	2	B	*4-Fluoro-α-PHPP*						
	2	B	*4-Methoxy-α-PHPP*						
	1	B	*4-Methoxy-α-POP*						
	1	C	Nitracaine						
	4	C	2-EAPB						
	1	C	Acetyl fentanyl						
2 (23 patterns)	7	A	**FUB-PB-22**	**NNEI indazole analog**					
	2	A	**FUB-PB-22**	**AM2201indazole analog (THJ-2201)**					
	4	A	**FUB-PB-22**	**5-Fluoro-AB-PINACA**					
	5	A	**FUB-PB-22**	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**					
	3	A	**FUB-PB-22**	**QUPIC N-(5-fluoropentyl) analog**					
	3	A	**NNEI indazole analog**	**5-Fluoro-AB-PINACA**					
	1	A	**NNEI indazole analog**	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**					
	2	A	**QUPIC N-(5-fluoropentyl) analog**	**5-Fluoro-AB-PINACA**					
	1	A	**5-Chloro-AB-PINACA**	**5-Fluoro-AB-PINACA**					
	6	D	**FUB-PB-22**	*DL-4662*					
	2	D	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*					
	1	D	**FUB-PB-22**	*4-Methylbuphedrone*					
	1	D	**XLR-12**	*α-PHP*					
	1	D	**XLR-12**	*4-Methoxy-α-PHPP*					
	3	E	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**	2-EAPB					
	1	B	*α-PHP*	*DL-4662*					
	1	B	*α-POP*	*4-Methoxy-α-PHPP*					
	1	B	*α-POP*	*4-Fluoro α-PHPP*					
	1	B	*DL-4662*	*4-Fluoro-α-PHPP*					
	1	B	*DL-4662*	*4-Methoxy-α-PHPP*					
	1	B	*4-Fluoro-α-PHPP*	*4-Methoxy-α-PHPP*					
	1	F	*α-PHP*	25N-NBOMe					
	1	C	Diphenidine	1-Benzylpiperidine					
3 (14 patterns)	1	A	**AB-CHMINACA**	**FUB-PB-22**	**5-Fluoro-AMB**				
	1	A	**AB-CHMINACA**	**NNEI indazole analog**	**5-Fluoro-AMB**				
	2	A	**FUB-PB-22**	**NNEI indazole analog**	**5-Fluoro-AB-PINACA**				
	1	A	**FUB-PB-22**	**NNEI indazole analog**	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**				
	1	A	**FUB-PB-22**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AB-PINACA**				
	1	A	**XLR-12**	**5-Fluoro-AB-PINACA**	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**				
	1	D	**FUB-PB-22**	**NNEI indazole analog**	*4-Methyl-α-ethylaminopentiophenone*				
	1	D	**FUB-PB-22**	**NNEI indazole analog**	*4-Methoxy-α-PHPP*				
	1	D	**5-Fluoro-AMB**	*α-PHP*	*DL-4662*				
	1	D	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*	*3,4-Dimethoxy-α-PVP*				
	1	D	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*	*4-Methoxy-α-PVP*				
	1	D	**XLR-12**	*4-Fluoro-α-PHPP*	*4-Methoxy-α-PHPP*				
	1	G-(1)	**5-Fluoro-NNEI indazole analog (5-Fluoro-MN-18)**	*α-POP*	Diclofensine				
	1	F	*α-PHP*	*4-Fluoro-α-PHPP*	25B-NBOMe				
4 (4 patterns)	1	D	**FUB-PB-22**	**NNEI indazole analog**	*3,4-Dimethoxy-α-PVP*	*4-Methoxy-α-PVP*			
	1	D	**FUB-PB-22**	*Pentedrone*	*4-Methyl-α-ethylaminopentiophenone*	*3,4-Dimethoxy-α-PVP*			
	1	G-(2)	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*	*3,4-Dimethoxy-α-PVP*	25I-NBOMe			
	1	G	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*	*3,4-Dimethoxy-α-PVP*	α-PVT			
5 (6 patterns)	1	D	**AB-CHMINACA**	**NNEI indazole analog**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AMB**	*α-PHP*		
	1	D	**AB-CHMINACA**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AMB**	*α-PHP*	*DL-4662*		
	1	D	**FUB-PB-22**	**NNEI indazole analog**	*Pentedrone*	*4-Methylbuphedrone*	*4-Methyl-α-ethylaminopentiophenone*		
	1	D	**FUB-PB-22**	*N-Ethylbuphedrone (NEB)*	*4-Methyl-α-ethylaminopentiophenone*	*3,4-Dimethoxy-α-PVP*	*4-Ethylmethcathinone*		
	1	D	**FUB-PB-22**	*4-Methyl-α-ethylaminopentiophenone*	*Pentedrone*	*4-Methoxy-α-PVP*	*4-Methylbuphedrone*		
	1	G	**FUB-PB-22**	*3,4-Dimethoxy-α-PVP*	*4-Ethylmethcathinone*	*4-Methoxy-α-PVP*	α-PVT		
6 (2 patterns)	1	D	**AB-CHMINACA**	**FUB-PB-22**	**NNEI indazole analog**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AMB**	*DL-4662*	
	1	D	**AB-CHMINACA**	**FUB-PB-22**	**NNEI indazole analog**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AMB**	*α-PHP*	
7 (1 pattern)	1	D	**AB-CHMINACA**	**FUB-PB-22**	**NNEI indazole analog**	**AM2201indazole analog (THJ-2201)**	**5-Fluoro-AB-PINACA**	**5-Fluoro-AMB**	*DL-4662*
(60 patterns)	Total 104								

Synthetic cannabinoids (Bold), *cathinone derivatives (Italic)* and other compounds (Roman)

monitoring and rapid identification of newly distributed designer drugs, combined with global information sharing, will be needed to supress illegal drug abuse.

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