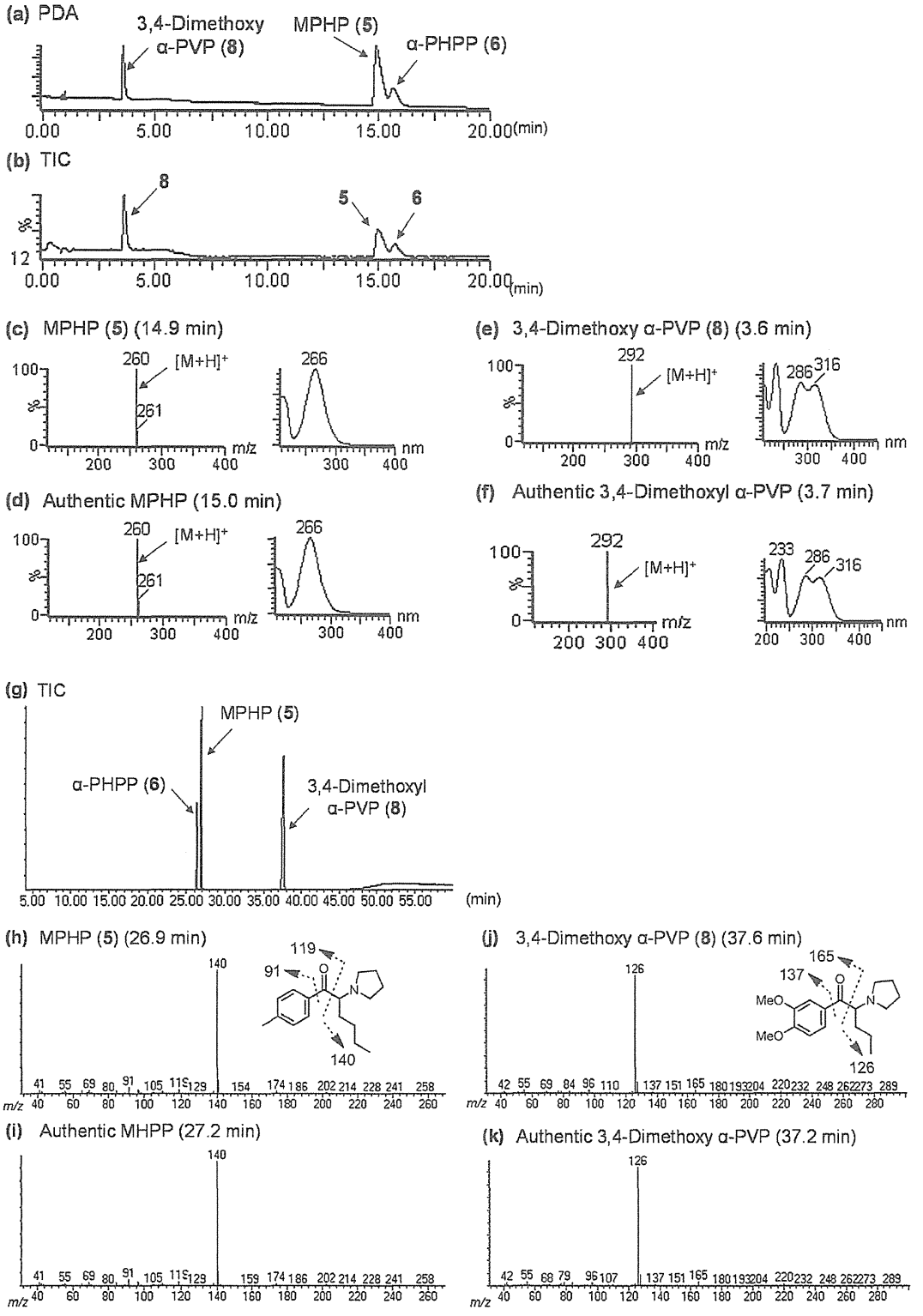


**Fig. 6.** LC–MS and GC–MS analyses of product D. LC–UV–PDA chromatogram (a) and TIC (b). ESI mass and UV spectra of peaks **5** (c), **8** (e) and authentic MPHP and 3,4-dimethoxyl-α-PVP (d and f), respectively. TIC (**g**) and EI mass spectra of peaks **5** (h), **8** (j) and authentic MPHP and 3,4-dimethoxyl-α-PVP (i and k), respectively, obtained by the GC–MS analysis.

very weak monoamine uptake inhibitor [16], Compound **5** was detected as a newly distributed designer drug in Japan, and compound **8** was detected as a newly distributed designer drug.

### 3.5. Identification of unknown peak 7

Unknown peak **7** was detected in the LC–MS and GC–MS chromatograms for product E (Fig. 7a, b and d). In the LC–MS

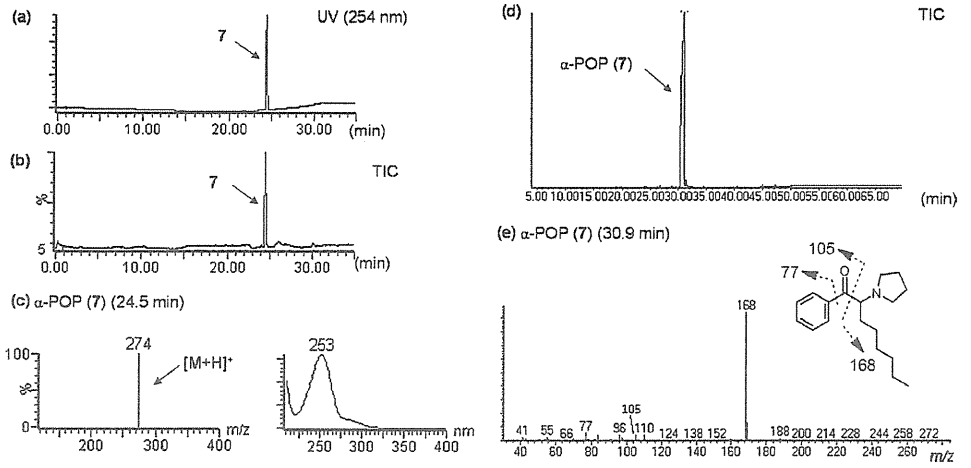


**Fig. 7.** LC–MS and GC–MS analyses of product E. LC–UV–PDA chromatogram (a), TIC (b) and ESI mass and UV spectra of peak **7** (c). TIC (d) and EI mass spectrum of peak **7** (e) obtained by the GC–MS analysis.

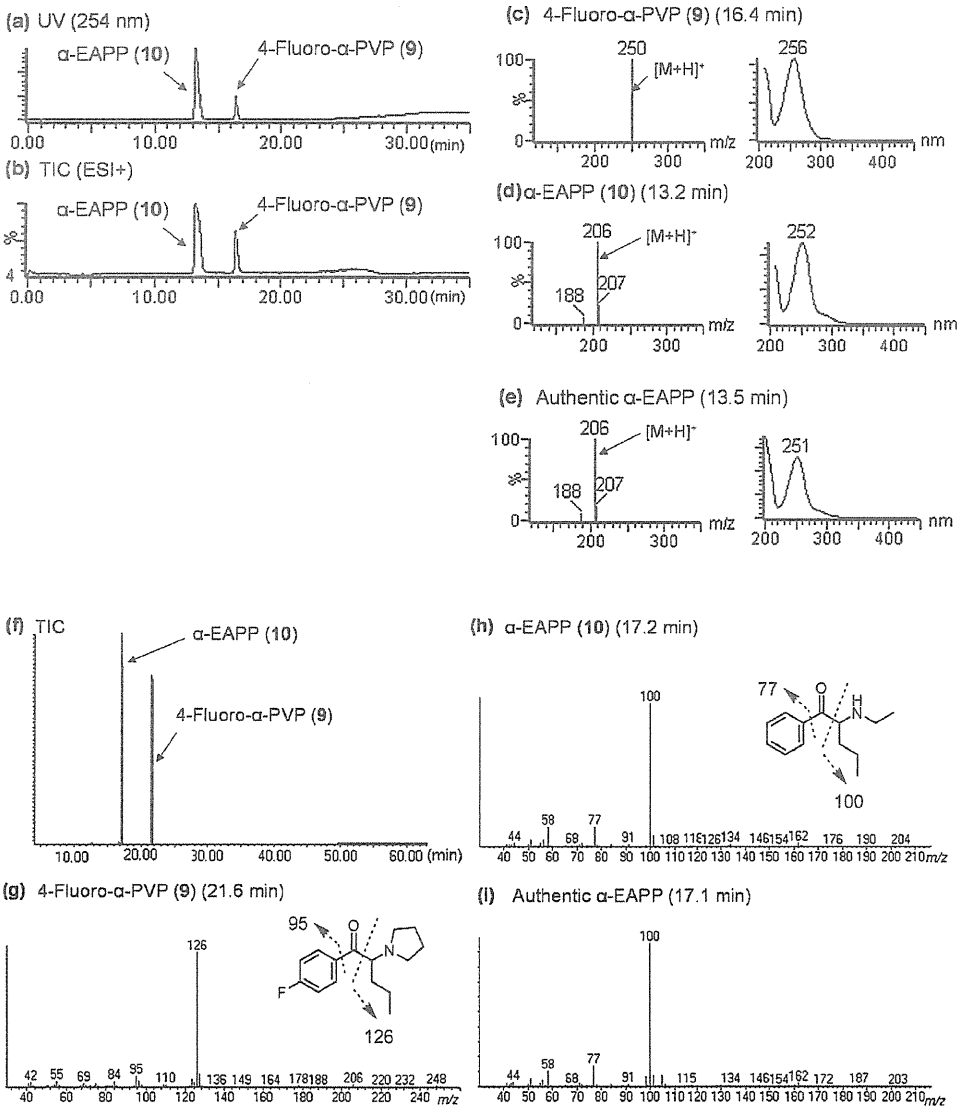


**Fig. 8.** LC–MS and GC–MS analyses of product F. LC–UV–PDA chromatogram (a) and TIC (b). ESI mass and UV spectra of peaks **9** (c), **10** (d) and authentic α-EAHP (e), respectively. TIC (f) and EI mass spectra of peaks **9** (g), **10** (h) and authentic α-EAHP (i), respectively, obtained by the GC–MS analysis.

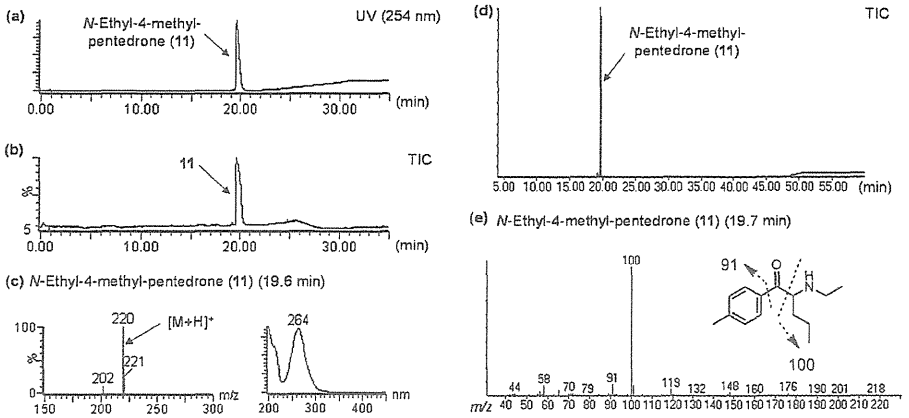


**Fig. 9.** LC–MS and GC–MS analyses of product G. LC–UV–PDA chromatogram (a), TIC (b) and ESI mass and UV spectra of peak **11** (c). TIC (d) and EI mass spectrum of peak **11** (e) obtained by the GC–MS analysis.

analysis, the unknown peak **7** at 24.5 min showed a protonated molecular ion signal at *m/z* 274 ($[M+H]^+$) (Fig. 7c). The accurate mass spectrum obtained by LC–Q-TOF–MS gave an ion peak at *m/z* 274.2168, suggesting that the protonated molecular formulae of compound **7** was $C_{18}H_{28}NO$ (calcd. 274.2171). The $^{13}C$ NMR spectrum of compound **7** was very similar to that of α-PHPP (**6**), except for the additional $CH_2$ of an *n*-alkyl moiety (position-8) of compound **7** as shown in Tables 2 and 3.

The observed $^1H$ and $^{13}C$ NMR (Tables 2 and 3), DQF-COSY, HMBC and 1D-ROE correlations (data not shown) revealed that the structure of compound **7** is α-Pyrrolidino-octanophenone (α-POP) as shown in Fig. 1. The fragment ions at *m/z* 77, 105 and 168 of compound **7** in the GC–MS spectrum (Fig. 7e) further confirmed the structure. Compound **7** is a novel substance, and its chemical and pharmaceutical data have not been reported.

### 3.6. Identification of unknown peaks 9 and 10

In the GC–MS and LC–MS analyses, we detected two unknown peaks, **9** and **10**, in product F (Fig. 8a, b and f). Based on the GC–MS and LC–MS data, peak **10** was finally identified as α-ethylamino-pentiophenone (α-EAPP) (Figs. 1 and 8d and h), by direct comparison of the data to those of the purchased authentic compound (Fig. 8e and i). Peak **9** at 16.4 min showed a protonated molecular ion signal at *m/z* 250 ($[M+H]^+$) in the LC–MS spectrum (Fig. 8c). The accurate mass spectrum obtained by LC–Q-TOF–MS gave an ion peak at *m/z* 250.1604, suggesting that the protonated molecular formulae of compound **9** was $C_{15}H_{21}FNO$ (calcd. 250.1607).

The proposed fragment patterns and presumed structure of compound **9** revealed by the GC–MS analysis are shown in Fig. 8g. The $^{13}C$ NMR spectrum of compound **9** was very similar to that of α-PVP, except for the phenyl moiety (position-1′ to 6′) of α-PVP as indicated in Table 2. Additionally, four doublet signals by coupling with fluorine (position-1′ to 6′) were observed in the $^{13}C$ NMR spectrum (Table 2). The observed $^1H$ and $^{13}C$ NMR (Tables 2 and 3), DQF-COSY, HMBC and 1D-ROE correlations (data not shown) suggested that the structure of compound **9** is 4-fluoro-α-Pyrrolidinovalerophenone (4-fluoro-α-PVP) as shown in Fig. 1. Moreover, the fragment ions at *m/z* 95 and 126 of compound **9** in GC–MS spectrum (Fig. 8g) further confirmed the structure. Compounds **9** and **10**, which were reported as a monoamine uptake inhibitor [16] and a stimulant substance [17], respectively were also detected as newly distributed designer drugs.

### 3.7. Identification of unknown peak 11

An unknown peak **11** was detected in the GC–MS and LC–MS chromatograms for product G (Fig. 9a, b and d). The proposed fragment pattern and the presumed structure of peak **11** obtained by the GC–MS analysis are shown in Fig. 9e. The LC–MS data revealed that peak **11** gave a protonated ion signal at *m/z* 220 ($[M+H]^+$) (Fig. 9c). The accurate mass spectrum obtained by LC–Q-TOF–MS gave an ion peak at *m/z* 220.1680, suggesting that the protonated molecular formula of compound **11** was $C_{14}H_{22}NO$ (calcd. 220.1701). The $^{13}C$ NMR spectrum of compound **11** was

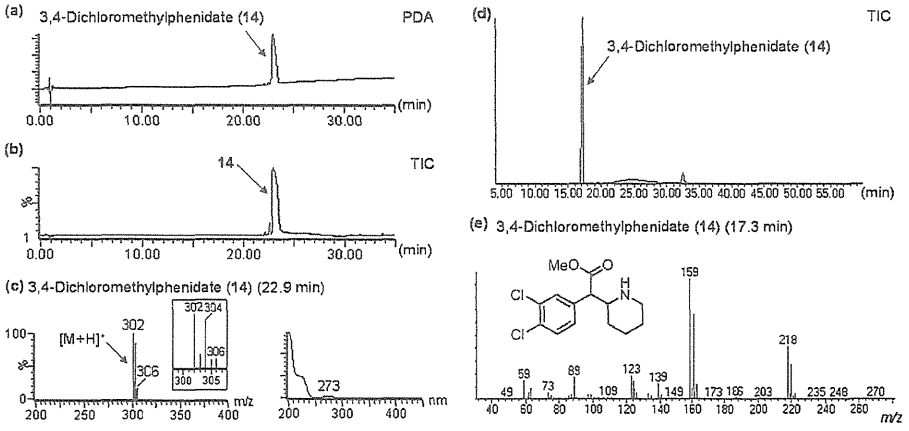


**Fig. 10.** LC–MS and GC–MS analyses of product H. LC–UV–PDA chromatogram (a), TIC (b) and ESI mass and UV spectra of peak **14** (c). TIC (d) and EI mass spectrum of peak **11** (e) obtained by the GC–MS analysis.

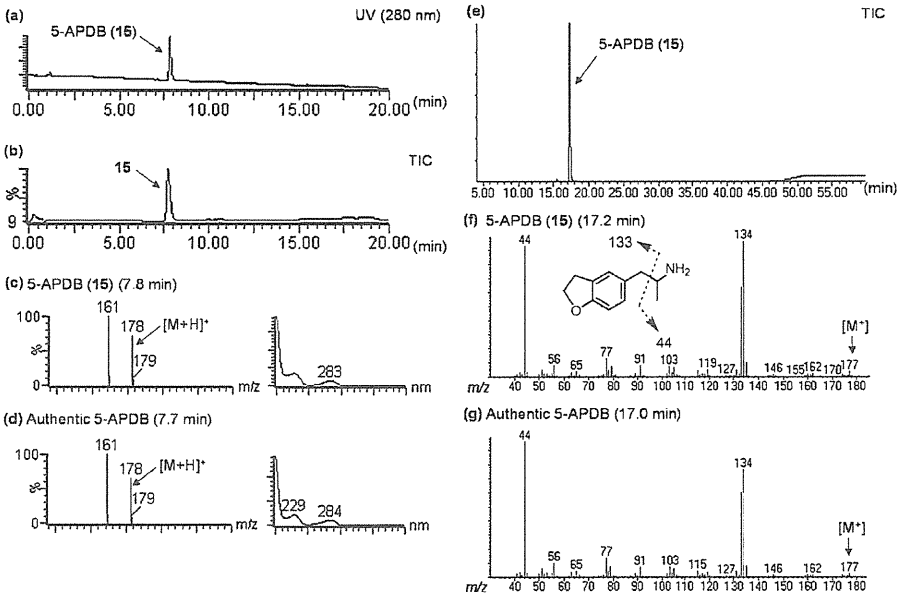


**Fig. 11.** LC–MS and GC–MS analyses of product I. LC–UV–PDA chromatogram (a) and TIC (b). ESI mass and UV spectra of peaks **15** (c) and authentic 5-APDB (d), respectively. TIC (e) and EI mass spectra of peaks **15** (f) and authentic 5-APDB (g), respectively, obtained by the GC–MS analysis.

similar to that of compound **10** except for the C-4′ carbon of a phenyl group (Table 2). The observed $^{1}H$ and $^{13}C$ NMR (Tables 2 and 3), DQF-COSY, HMBC and 1D-ROE correlations (data not shown) suggested that the structure of compound **11** is *N*-ethyl-4-methylpentedrone [synonym: 4-methyl-α-ethylaminopentiophenone, IUPAC: 2-(ethylamino)-1-(*p*-tolyl)pentan-1-one] as shown in Fig. 1. The fragment ions at *m/z* 91 and 100 of compound **11** in the GC–MS spectrum established the structure (Fig. 9e). Compound **11**, which was reported as a stimulant substance [17], was detected as a newly distributed designer drug.

### 3.8. Identification of unknown peaks 14

We detected an unknown peak **14** in the LC–MS and GC–MS chromatograms for product H (Fig. 10a, b, d and e). In the LC–MS analysis, the unknown peak **14** at 22.9 min showed a protonated molecular ion signal at *m/z* 302 [M+H$^+$] and isotopic ion signals at *m/z* 304 [M+2+H$^+$] and 306 [M+4+H$^+$] due to the presence of two chlorine atoms (Fig. 10c). The accurate mass spectrum obtained by LC–Q-TOF–MS gave an ion peak at *m/z* 302.0719, suggesting that the protonated molecular formula of compound **14** was $C_{14}H_{18}Cl_2NO_2$ (calcd. 302.0715).

The structure of compound **14** was elucidated by NMR analysis (Fig. 4d, Table 4). The $^{1}H$ and $^{13}C$ NMR spectra of compound **14** suggested the existence of 17 protons and 14 carbons (Table 4). The 1D NMR spectra of compound **14** suggested the presence of a methyl acetylate moiety [$\delta_C$ 170.5 (C-1), 53.0 (O<u>C</u>H$_3$), $\delta_H$ 3.67 (OC<u>H</u>$_3$),] as shown in Table 4. The 2D NMR spectra of compound **14** indicated the presence of three moieties, which are a dichlorophenyl group, a piperidine group and methyl acetylate moieties (Fig. 4d). Additionally, the connections of the three moieties were revealed by HMBC correlations between a methine proton (H-2) and the phenyl carbons (C-2′, 6′), the piperidine carbons (C-2″, 3″) and the carbonyl ester carbon (C-1), as shown in Fig. 4d. Therefore, the structure of compound **14** was determined as 3,4-dichloromethylphenidate [IUPAC: methyl 2-(3,4-dichlorophenyl)-2-(piperidin-2-yl)acetate] as provided in Fig. 1. 3,4-Dichloromethylphenidate (**14**) was reported as an analog of methylphenidate, which is a stimulant medicine treatment for narcolepsy and attention deficit hyperactivity disorder (ADHD) (Ritalin®), with 32-fold and 57-fold more potent dopamine reuptake inhibitory activity than methylphenidate and cocaine, respectively [18]. In addition, 3,4-dichloromethylphenidate (**14**) showed an eightfold more potent cocaine-like discriminative effect compared to methylphenidate [18]. Compound **14** was detected as a newly distributed designer drug.

### 3.9. Identification of unknown peaks 15

An unknown peak **15** was detected in the LC–MS and GC–MS chromatograms for product I (Fig. 11a, b and e). Peak **15** was identified as 5-APDB (Fig. 11c and f) by direct comparison of the data with those of the purchased authentic compounds (Fig. 11d and g). 5-APDB, which was reported to have a monoamine

**Table 4**
NMR Data of 3,4-Dichloromethylphenidate (**14**).[a]

| No. | $^{13}C$ | $^{1}H$ |
|---|---|---|
| 1 | 170.5 | – |
| 2 | 52.0 | 4.16, 1H, d, *J* = 8.6 Hz |
| 1′ | 134.7 | – |
| 2′ | 130.9 | 7.61, 1H, brs |
| 3′ | 131.6 | – |
| 4′ | 131.2 | – |
| 5′ | 131.1 | 7.68, 1H, d, *J* = 8.3 Hz |
| 6′ | 129.3 | 7.30, 1H, d, *J* = 8.3 Hz |
| 1″ | – | N<u>H</u> 8.90, 1H, brs |
| 2″ | 56.4 | 3.83, 1H, brs |
| 3″ | 25.7 | 1.41, 1H, m, overlapped<br>1.26, 1H, q, *J* = 12.7 Hz |
| 4″ | 21.2 | 1.67, 1H, t, *J* = 12.7 Hz, overlapped<br>1.41, 1H, m, overlapped |
| 5″ | 21.6 | 1.67, 1H, t, *J* = 12.7 Hz, overlapped<br>1.54, 1H, q, *J* = 12.7 Hz |
| 6″ | 44.6 | 3.26, 1H, brd, *J* = 12.7 Hz<br>2.93, 1H, t, *J* = 12.7 Hz |
| 1-OMe | 53.0 | 3.67, 3H, s |

[a] Recorded in DMSO-$d_6$ at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$), respectively; data in $\delta$ ppm (*J* in Hz).

reuptake inhibitory effect [19], has been detected in European countries [11] but is newly detected in Japan.

## 4. Conclusions

In this study, we detected 15 newly distributed designer drugs including four synthetic cannabinoids: NNEI (**1**), 5-fluoro-NNEI (**2**), 5-chloro-NNEI (**3**) and NNEI indazole analog (**4**), and seven cathinone derivatives: MPHP (**5**), α-PHPP (**6**), α-POP (**7**), 3,4-dimethoxy-α-PVP (**8**), 4-fluoro-α-PVP (**9**), α-ethylaminopentiophenone (**10**) and *N*-ethyl-4-methylpentedrone (**11**). We also detected two endocannabinoid uptake inhibitors LY-2183240 (**12**) and LY-2183240 2′-isomer (**13**), a methylphenidate analog 3,4-dichloromethylphenidate (**14**), and an MDA analog 5-APDB (**15**) in illegal products. Among them, no chemical and pharmaceutical data for compounds **3**, **4**, **6** and **7** have been appeared until now, and thus this is the first report of these compounds. Compounds **8**–**14** were detected as newly distributed designer drugs and compounds **1**, **2**, **5** and **15** were newly detected as designer drugs in Japan.

The types of designer drugs and their combinations in illegal products seem to be diversifying, and the health risks that may be associated with their use are more serious than ever. The continuous monitoring and rapid identification of newly distributed designer drugs are important for preventing their abuse.

## Conflict of interest

There are no financial or other relations that could lead to a conflict of interest.

## References


[1] EMCDDA/Europol, 2005/387/JHA, EMCDDA-Europol 2012 Annual Report on the implementation of Council Decision, http://www.emcdda.europa.eu/publications/implementation-reports/2012 (accessed May 13).

[2] UNODC. The challenge of new psychoactive substances. A Report from the Global SMART Programme, http://www.unodc.org/documents/scientific/NPS_2013_SMART.pdf (access September 13).

[3] R. Kikura-Hanajiri, N. Uchiyama, M. Kawamura, Y. Goda, Changes in the prevalence of synthetic cannabinoids and cathinone derivatives in Japan, Forensic Toxicol. 31 (2013) 44–53.

[4] R. Kikura-Hanajiri, N. Uchiyama, M. Kawamura, J. Ogata, Y. Goda, Prevalence of new designer drugs and their legal status in Japan, Yakugaku Zasshi 133 (2013) 31–40.

[5] N. Uchiyama, S. Matsuda, K. Kawamura, R. Kikura-Hanajiri, Y. Goda, Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative α-PVT and an opioid receptor agonist AH-7921 identified in illegal products, Forensic Toxicol. 31 (2013) 223–240.

[6] N. Uchiyama, S. Matsuda, D. Wakana, R. Kikura-Hanajiri, Y. Goda, New cannabimimetic indazole derivatives, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA) and N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA), identified as designer drugs, Forensic Toxicol. 31 (2013) 93–100.

[7] N. Uchiyama, S. Matsuda, M. Kawamura, R. Kikura-Hanajiri, Y. Goda, Identification of two new-type designer drugs, a piperazine derivative MT-45 (I-C6) and a synthetic peptide Noopept (GVS-111), with a synthetic cannabinoid A-834735, a cathinone derivative 4-methoxy-α-PVP and a phenethylamine derivative 4-methylbuphedrine from illegal products, Forensic Toxicol., 32 (2014) 9-18.

[8] R. Kikura-Hanajiri, N. Uchiyama, M. Kawamura, Y. Goda, Changes in the prevalence of new psychoactive substances before and after the introduction of the generic scheduling of synthetic cannabinoids in Japan, Drug Test. Anal., online available, http://dx.doi.org/10.1002/dta.1584.

[9] N. Uchiyama, Kawamura, R. Kikura-Hanajiri, Y. Goda, URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products, Forensic Sci. Int. 227 (2013) 21–32.

[10] A.R. Blaazer, J.H. Lange, M.A. van der Neut, A. Mulder, F.S. den Boon, J.R. Werkman, C.G. Kruse, W.J. Wadman, Novel indole and azaindole pyrrolopyridine cannabinoid (CB) receptor agonists: design, synthesis, structure-activity relationships, physicochemical proper, Eur. J. Med. Chem. 46 (2011) 5086–5098.

[11] V. Shevyrin, V. Melkozerov, A. Nevero, O. Eltsov, Y. Morzherin, Y. Shafran, Analytical characterization of some synthetic cannabinoids, derivatives of indole-3-carboxylic acid, Forensic Sci. Int. 232 (2013) 1–10.

[12] S.A. Moore, G.G. Nomikos, A.K. Dickason-Chesterfield, D.A. Schober, J.M. Schaus, B.P. Ying, Y.C. Xu, L. Phebus, R.M. Simmons, D. Li, S. Iyengar, C.C. Felder, Identification of a high-affinity binding site involved in the transport of endocannabinoids, Proc. Natl. Acad. Sci. U.S.A. 102 (2005) 17852–17857.

[13] G. Ortar, M.G. Cascio, A.S. Moriello, M. Camalli, L. Morera, M. Nalli, V. Di Marzo, Carbamoyl tetrazoles as inhibitors of endocannabinoid inactivation: a critical revisitation, Eur. J. Med. Chem. 43 (2008) 62–72.

[14] F. Westphal, I. Junge, P. Rösner, G. Hrtschi, B. Klein, U. Girreser, Mass spectral and NMR spectral data of two new designer drugs with an α-aminophenone structure: 4?-methyl-α-pyrrolidinohexanophenone and 4?-methyl-α-pyrrolidinobutyrophenone, Forensic Sci. Int. 169 (2007) 32–42.

[15] C. Sauer, K. Hofmann, U. Schimmel, F.T. Peters, Acute poisoning involving the pyrrolidinophenone-type designer drug 4?-methyl-alpha-pyrrolidinohexanophenone (MPHP), Forensic Sci. Int. 208 (2011) e20–e25.

[16] P.C. Meltzer, D. Butler, J.R. Deschamps, B.K. Madras, 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors, J. Med. Chem. 49 (2006) 1420–1432.

[17] α-Aminoketone derivatives, Patent, GB 1069797 19670524 (1967).

[18] M.M. Schweri, H.M. Deutsch, A.I. Massey, S.G. Holtzman, Biochemical and behavioral characterization of novel methylphenidate analogs, J. Pharmacol. Exp. Ther. 301 (2002) 527–535.

[19] A.P. Monte, D. Marona-Lewicka, N.V. Cozzi, D.E. Nichols, Synthesis and pharmacological examination of benzofuran, indan, and tetralin analogues of 3,4-methylenedioxyamphetamine, J. Med. Chem. 36 (1993) 3700–3706.

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ORIGINAL ARTICLE

# Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products

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**Abstract** Two new types of synthetic cannabinoids, an AM-2201 benzimidazole analog (FUBIMINA, **1**) and (4-methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM, **2**), and three newly emerged phenethylamine derivatives, 25B-NBOMe (**3**), 2C-N-NBOMe (**4**), and a 25H-NBOMe 3,4,5-trimethoxybenzyl analog (**5**), were detected in illegal products distributed in Japan. The identification was based on liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS), high-resolution MS, and nuclear magnetic resonance analyses. Different from the representative synthetic cannabinoids, such as JWH-018, which have a naphthoylindole moiety, compounds **1** and **2** were completely new types of synthetic cannabinoids; compound **1** had a benzimidazole group in place of an indole group, and compound **2** had a 4-methylpiperazine group in place of the naphthyl group. Compounds **3** and **4** were *N*-*o*-methoxybenzyl derivatives of 2,5-dimethoxyphenethylamines (25-NBOMe series), which had been previously detected in European countries, but have newly emerged in Japan. Compound **5** had an *N*-trimethoxybenzyl group in place of an *N*-*o*-methoxybenzyl group. Data on the chemistry and pharmacology of compounds **1**, **2**, and **5** have never been reported to our knowledge.

**Keywords** AM-2201 benzimidazole analog (FUBIMINA) · (4-Methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM) · 25H-NBOMe 3,4,5-trimethoxybenzyl analog · 25B-NBOMe · 2C-N-NBOMe · Synthetic cannabinoid

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## Introduction

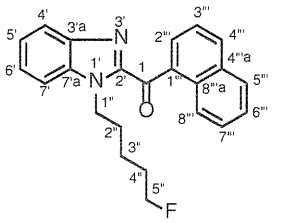
Recently, several countries have adapted their main drug control legislation to control new psychotropic substances such as synthetic cannabinoids and cathinone derivatives by introducing some degree of flexibility to the individual listing system; they have tried to legislate inclusive drug control laws according to basic structures of psychotropic drugs [1]. Other countries have issued specific new psychotropic substances legislation to control these substances considering the danger they pose to health [1–3]. In Japan, new psychotropic substances have been controlled as designated substances (Shitei-Yakubutsu) under the Pharmaceutical Affairs Law and as narcotics under the Narcotics and Psychotropics Control Law on a case-by-case basis. We have been conducting an ongoing survey of designer drugs in the illegal drug market in Japan [4–9], and have recently reported the identification of 2 synthetic cannabinoids 5-fluoro-QUPIC (5-fluoro-PB-22) and A-834735, a cathinone derivative 4-methoxy-α-PVP, an opioid receptor agonist MT-45 (I-C6), and a synthetic peptide Noopept (GVS-111) online in June 2013 [8]. More recently, we have detected 15 newly distributed designer drugs among illegal products that include 4 synthetic cannabinoids *N*-1-naphthalenyl-1-pentyl-1*H*-indole-3-carboxamide (NNEI), 5-fluoro-NNEI, 5-chloro-NNEI, and an NNEI indazole analog [IUPAC: *N*-(naphthalen-1-yl)-1-pentyl-1*H*-indazole-3-carboxamide], and 7 cathinone derivatives 4′-methyl-α-pyrrolidinohexanophenone (MPHP), α-pyrrolidinoheptanophenone

(α-PHPP, synonym: PV8), α-pyrrolidinooctanophenone (α-POP, synonym: PV9), 3,4-dimethoxy-α-pyrrolidinopentiophenone (3,4-dimethoxy-α-PVP), 4-fluoro-α-PVP, α-ethylaminopentiophenone, and *N*-ethyl-4-methylpentedrone, 2 endocannabinoid uptake inhibitors LY-2183240 and an LY-2183240 2′-isomer, a methylphenidate analog 3,4-dichloromethylphenidate, and a 3,4-methylenedioxyamphetamine (MDA) analog 5-APDB (synonym: 3-desoxy-MDA) in illegal products during the latter part of 2013 (Uchiyama et al., submitted for publication). In the present study, we describe the identification of 5 newly distributed designer drugs (**1**–**5**, Fig. 1) in illegal products as the newest article submitted in 2013.

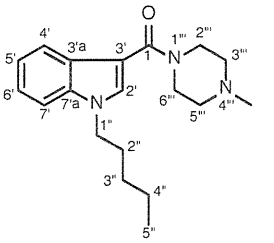
## Materials and methods

### Samples for analysis

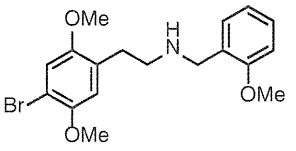
The analyzed samples were purchased in Japan between April and September 2013 from the Internet as chemical-type or herbal-type products A–D. Herbal-type product A contained approximately 3 g of mixed dried plants. The powder-type product B called "fragrance powder" was in the form of a white powder (~400 mg). Liquid-type products called "liquid aroma" were supplied as 5-ml volumes of yellow liquid (C) and pale blue liquid (D).



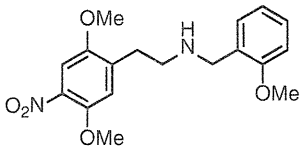
AM-2201 benzimidazole analog
(1-(5-Fluoropentyl)-1*H*-benzo[*d*]imidazol-2-yl)(naphthalen-1-yl)methanone
(FUBIMINA, **1**)
$C_{23}H_{21}FN_2O$: 360



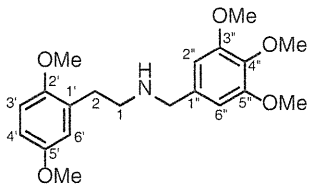
(4-Methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
(MEPIRAPIM, **2**)
$C_{19}H_{27}N_3O$: 313



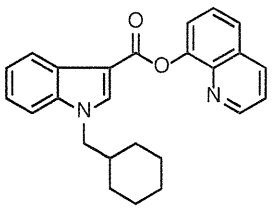
25B-NBOMe (**3**)
$C_{18}H_{22}BrNO_3$: 380



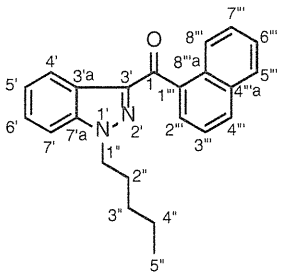
2C-N-NBOMe (**4**)
$C_{18}H_{22}N_2O_5$: 346



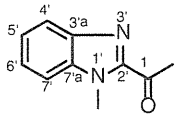
25H-NBOMe 3,4,5-trimethoxybenzyl analog (**5**)
2-(2,5-Dimethoxyphenyl)-*N*-(3,4,5-trimethoxybenzyl)ethanamine
$C_{20}H_{27}NO_5$: 361



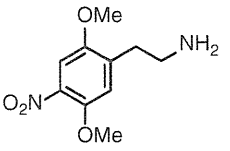
QUCHIC (BB-22)
$C_{25}H_{24}N_2O_2$: 384



JWH-018 indazole analog
$C_{23}H_{22}N_2O$: 342



2-Acetyl-1-methyl-1*H*-benzimidazole



2C-N

**Fig. 1** Structures of the newly detected (**1**–**5**) as well as the known detected and related compounds

## Chemicals and reagents

25B-NBOMe, QUCHIC (BB-22), and the JWH-018 indazole analog were purchased from Cayman Chemicals (Ann Arbor, MI, USA). Compounds **1**, **4**, and **5** were isolated from herbal or chemical products as described below. Compound **2** was directly analyzed without the isolation of product B. All other common chemicals and solvents were of analytical reagent grade or HPLC grade. As solvents for the nuclear magnetic resonance (NMR) analysis, $CDCl_3$ (99.96 %), pyridine-$d_5$ (99.96 %), and benzene-$d_6$ (99.96 %) were purchased from the ISOTEC division of Sigma-Aldrich (St. Louis, MO, USA).

## Preparation of sample solutions

For qualitative analyses (not for NMR analysis), 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 the powder-type product was extracted with 1 ml of methanol under ultrasonication for 10 min. A 20-μl portion of the liquid-type product was mixed with 1 ml of methanol under ultrasonication for 10 min. After centrifugation (5 min, 3,000 rpm) 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 [10]. Two elution programs were used in the LC–MS analysis. Program (1) was used for the synthetic cannabinoids, and program (2) was used for the other compounds including cathinone derivatives [10]. In this study, products A and B were analyzed using program (1), and products C and D were analyzed using program (2). In the GC–MS analysis, the oven temperature program was: 80 °C (1-min hold) with 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 (20-min hold). The obtained GC mass spectra were compared with those from an EI–MS library [Mass Spectra of Designer Drugs 2012 (Wiley, Weinheim, Germany)]. We also used our in-house EI–MS library of designer drugs generated from our continuous survey of illegal products and commercially available reagents for structural elucidation.

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

For isolation of compounds **4** and **5**, we used preparative gel permeation liquid chromatography (GPLC) on a JAI (Japan Analytical Industry, Tokyo, Japan) LC-9201 instrument with JAIGEL 1H columns (JAI) using 0.5 % triethylamine (TEA) in chloroform as eluent.

NMR spectra were obtained on ECA-800 and 600 spectrometers (JEOL, Tokyo, Japan). Assignments were made via $^{1}H$ NMR, $^{13}C$ NMR, heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), $^{15}N$ HMBC, double quantum filtered correlation spectroscopy (DQF–COSY), and rotating-frame nuclear Overhauser effect (ROE) spectra.

## Isolation of compound 1

A 3-g sample of mixed dried plants (product A) was extracted with 250 ml of chloroform by ultrasonication for 30 min. The extraction was repeated three times, and the combined supernatant fractions were 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, v/v). The location of the silica gel containing a target compound in the TLC plate was detected under ultraviolet (UV) light at 254 nm. It was then scraped from the plate and eluted with chloroform to obtain fraction 1. It was then loaded onto an ODS column (Bond Elut Mega Be-C18, 60 ml, 10 g; Agilent, Santa Clara, CA, USA), which was then eluted with a stepwise gradient of methanol/water (60:20–100:0) to obtain compound **1** (204 mg) as a yellow solid.

## Isolation of compound 4

A 5-ml sample of liquid product C was evaporated to dryness, and the residue was then dissolved in 0.5 % TEA in chloroform and purified by recycle GPLC (eluent: 0.5 % TEA in chloroform) as described above to give compound **4** (2 mg) as a yellow oil.

## Isolation of compound 5

A 5-ml sample of liquid product D was evaporated to dryness, and the residue was then dissolved in 0.5 % TEA in chloroform and purified by recycle GPLC (eluent: 0.5 %

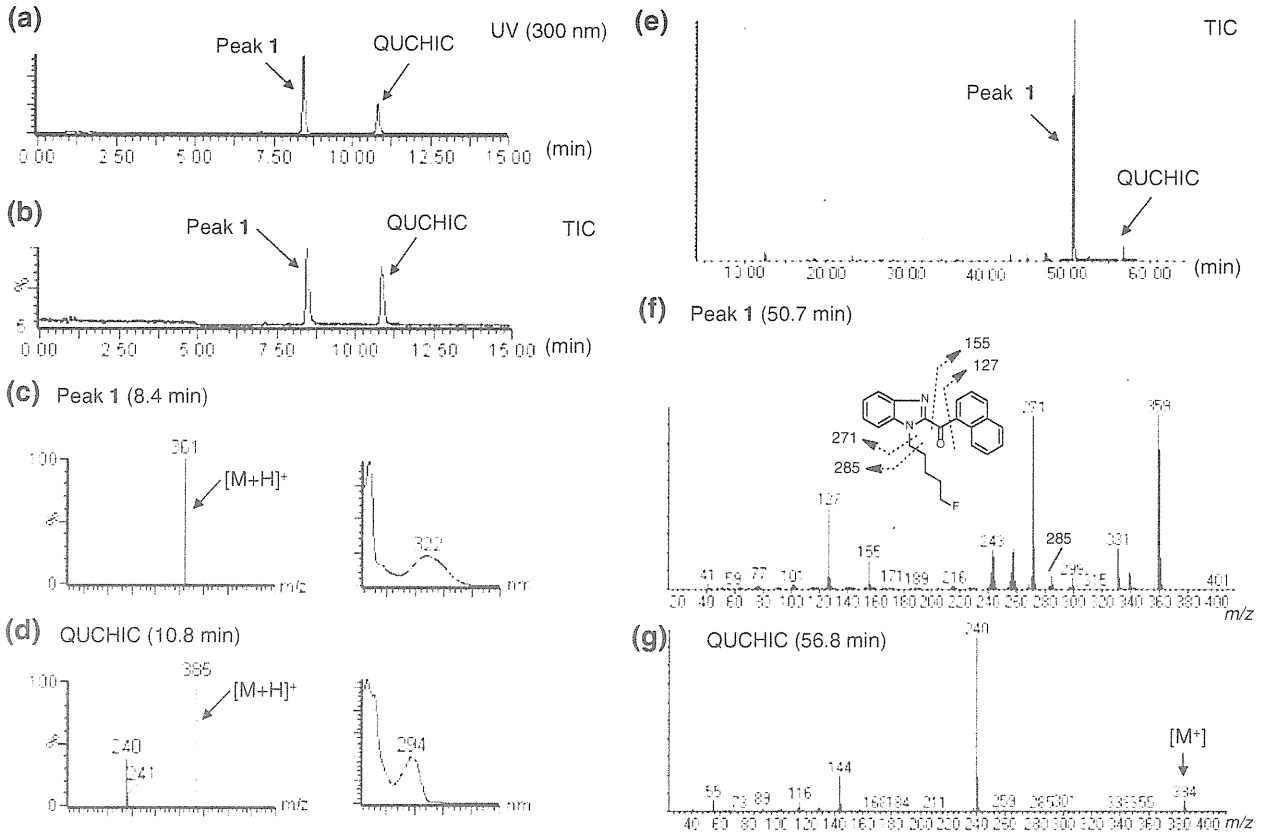



**Fig. 2** Liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS) analyses of product A. Liquid chromatography–ultraviolet photodiode array (LC–UV–PDA) chromatogram (**a**) and the total ion chromatogram (TIC) (**b**). Electrospray ionization (ESI) mass and UV spectra (**c**) of peaks **1** and QUCHIC (**d**) obtained by LC–MS. TIC (**e**) and electron ionization (EI) mass spectra of peak **1**(**f**) and QUCHIC (**g**) obtained by GC–MS

TEA in chloroform) to obtain compound **5** (15 mg) as a yellow oil.

## Results and discussion

### Identification of unknown peak 1

Unknown peak **1** was detected in the LC–MS and GC–MS chromatograms of product A (Fig. 2a–c, e, f) together with QUCHIC (BB-22, Figs. 1, 2d, g) [6]. In the LC–MS analysis, the unknown peak **1** at 8.4 min showed a protonated molecular ion $[M + H]^+$ signal at *m/z* 361 (Fig. 2c). The accurate mass spectrum obtained by LC–QTOF–MS gave an ion peak at *m/z* 361.1705, suggesting that the protonated molecular formula of compound **1** was $C_{23}H_{22}FN_2O$ (calcd. 361.1716).

The structure of compound **1** was elucidated by NMR analysis (Fig. 3a, b; Table 1). The $^1H$ and $^{13}C$ NMR spectra of compound **1** suggested the existence of 21 protons and 23 carbons (Table 1). The one-dimensional (1D) NMR spectra of compound **1** suggested the presence of a carbonyl moiety [$\delta_c$ 188.9 (C-1)], as shown in Table 1. The 2D NMR spectra of compound **1** indicated the presence of two moieties, a naphthoyl group (positions 1 and 1″ to 8‴a) and a 5-fluoropentyl group (Fig. 3a). Because the NMR spectra showed an AA′BB′ type phenyl group (positions 4′ to 7′, Table 1; Fig. 3a), we hypothesized that the remaining $C_7H_4N_2$ unit was a benzimidazole group or an indazole group. We therefore compared the $^{13}C$ NMR data of compound **1** with those of the known 2-acetyl-1-methyl-1*H*-benzimidazole (Fig. 1). The chemical shifts of the corresponding carbons of compound **1** (C-1, C-2′, and C-3′a to C-7′a) were similar to those of 2-acetyl-1-methyl-1*H*-benzimidazole, as shown in Table 1 [11]. On the other hand, because cannabimimetic indazole analogs such as APINACA and ADB-FUBICACA were previously detected in illegal products [6, 12], we compared the $^{13}C$ NMR data of compound **1** with that of the JWH-018 indazole analog (Fig. 1) as shown in Table 1. The chemical shifts of the corresponding carbons of compound **1** [$\delta_c$ 147.3 (C-2′), 141.8 (C-3′a), and 136.1 (C-7′a)] were different from those

**Table 1** NMR data for compound **1** and known related compounds

| No. | Compound **1**[a,b] | | 2-Acetyl-1-methyl-1*H*-benzimidazole[c] | JWH-018 indazole analog[a] |
|---|---|---|---|---|
| | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{13}C$ |
| 1 | 188.9 | – | 193.1 | 191.6 |
| 2′ | 147.3 | – | 146.5 | – |
| 3′ | – | – | – | 142.6 |
| 3′a | 141.8 | – | 141.5 | 124.3 |
| 4′ | 122.3 | 7.87, 1H, d, $J$ = 8.3 Hz | 121.2 | 123.1 |
| 5′ | 123.8 | 7.35, 1H, ddd, $J$ = 8.3, 7.2, 1.0 Hz | 124.2 | 123.7 |
| 6′ | 125.9 | 7.46, 1H, ddd, $J$ = 8.3, 7.2, 1.0 Hz | 126.3 | 126.9 |
| 7′ | 110.6 | 7.51, 1H, m, overlapped | 111.3 | 109.5 |
| 7′a | 136.1 | – | 137.3 | 140.6 |
| 1″ | 45.4 | 4.70, 2H, t, $J$ = 7.6 Hz | 31.8 (NMe) | 49.8 |
| 2″ | 30.1 | 2.05, 2H, q, $J$ = 7.9 Hz | 27.1 (COMe) | 29.4 |
| 3″ | 22.8, d, $J$ = 4.3 Hz[b] | 1.59, 2H, m | – | 28.8 |
| 4″ | 30.0, d, $J$ = 20.2 Hz[b] | 1.80 and 1.76, each 1H, m, overlapped | – | 22.2 |
| 5″ | 83.7, d, $J$ = 164.7 Hz[b] | 4.48 and 4.41, each 1H, t, $J$ = 5.8 Hz | – | 13.9 |
| 1‴ | 134.0 | – | – | 136.3 |
| 2‴ | 131.9 | 8.03, 1H, dd, $J$ = 7.2, 1.0 Hz | – | 129.3 |
| 3‴ | 124.3 | 7.56, 1H, m, overlapped | – | 124.3 |
| 4‴ | 133.3 | 8.05, 1H, d, $J$ = 8.3 Hz | – | 131.4 |
| 4‴a | 134.4 | – | – | 133.8 |
| 5‴ | 128.6 | 7.91, 1H, d, $J$ = 7.9 Hz | – | 128.3 |
| 6‴ | 126.5 | 7.53, 1H, m, overlapped | – | 126.1 |
| 7‴ | 127.9 | 7.57, 1H, m, overlapped | – | 127.1 |
| 8‴ | 125.3 | 8.46, 1H, d, $J$ = 8.3 Hz | – | 125.8 |
| 8‴a | 131.2 | – | – | 131.1 |

[a] Recorded in $CDCl_3$ at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$), respectively; data in δ ppm

[b] Observed as double signals by coupling with fluorine

[c] Ref [11], recorded in $CD_3OD$

of JWH-018 indazole analog [$\delta_c$ 142.6 (C-3′), 124.3 (C-3′a), and 140.6 (C-7′a)] (Table 1). These results strongly suggest that compound **1** has a benzimidazole group connected with a carbonyl group.

In addition, $^{15}N$ HMBC correlations from H-4′ to N-3′ and from H-7′, H-1″, and H-2″ to N-1′ were observed (Fig. 3b), and HMBC correlations between a methylene proton (H-1″) and two carbons of the remaining unit (C-2′ and C-7′a) were observed (Fig. 3a). These results revealed that the benzimidazole group was connected at position 1′ to the 5-fluoropentyl group at position 1″, and that the 1-(5-fluoropentyl)-1*H*-benzimidazole moiety was connected at position 2′ to the naphthoyl group at position 1 (Fig. 3a). Finally, compound **1** was identified as an AM-2201 benzimidazole analog [IUPAC: (1-(5-fluoropentyl)-1*H*-benzo[*d*]imidazol-2-yl)(naphthalen-1-yl)methanone] and named FUBIMINA as shown in Fig. 1. The fragment ions at *m/z* 127, 155, 271, and 285 of compound **1** in the GC–MS spectrum further confirmed the structure (Fig. 2f). Compound **1** was detected as a new substance, and its chemical and pharmacological data have not been reported previously.

## Identification of unknown peak 2

In the LC–MS and GC–MS analyses, unknown peak **2** was detected in product B (Fig. 4a, b, d). In the LC–MS analysis, unknown peak **2** at 2.1 min showed a protonated molecular ion $[M + H]^+$ signal at *m/z* 314 (Fig. 4c). The accurate mass spectrum of compound **2** was measured by LC–TOF–MS in the positive mode. The ion peak observed at *m/z* 314.2226 suggested that the protonated molecular formula of compound **2** was $C_{19}H_{28}N_3O$ (calcd. 314.2232).

The structure of compound **2** was elucidated by NMR analysis (Table 2; Fig. 3c, d). The $^{1}H$ and $^{13}C$ NMR spectra of compound **2** suggested the existence of 27 protons and 19 carbons as shown in Table 2. The analyses by DQF–COSY, HMQC, HMBC, and 1D ROE spectra for compound **2** revealed the presence of an *N*-(1-pentyl)-1*H*-indole-3-carbonyl moiety (Fig. 3c). In addition, it was presumed that the remaining $C_5H_{11}N_2$ unit was a 4-methylpiperazine moiety based on the $^{15}N$ HMBC correlations from H-3‴/H-5‴ to N-1‴, and from H-2‴/H-6‴ and 4‴-$CH_3$ protons to N-4‴, and DQF–COSY and HMBC correlations (Fig. 3c, d). The HMBC correlations between the

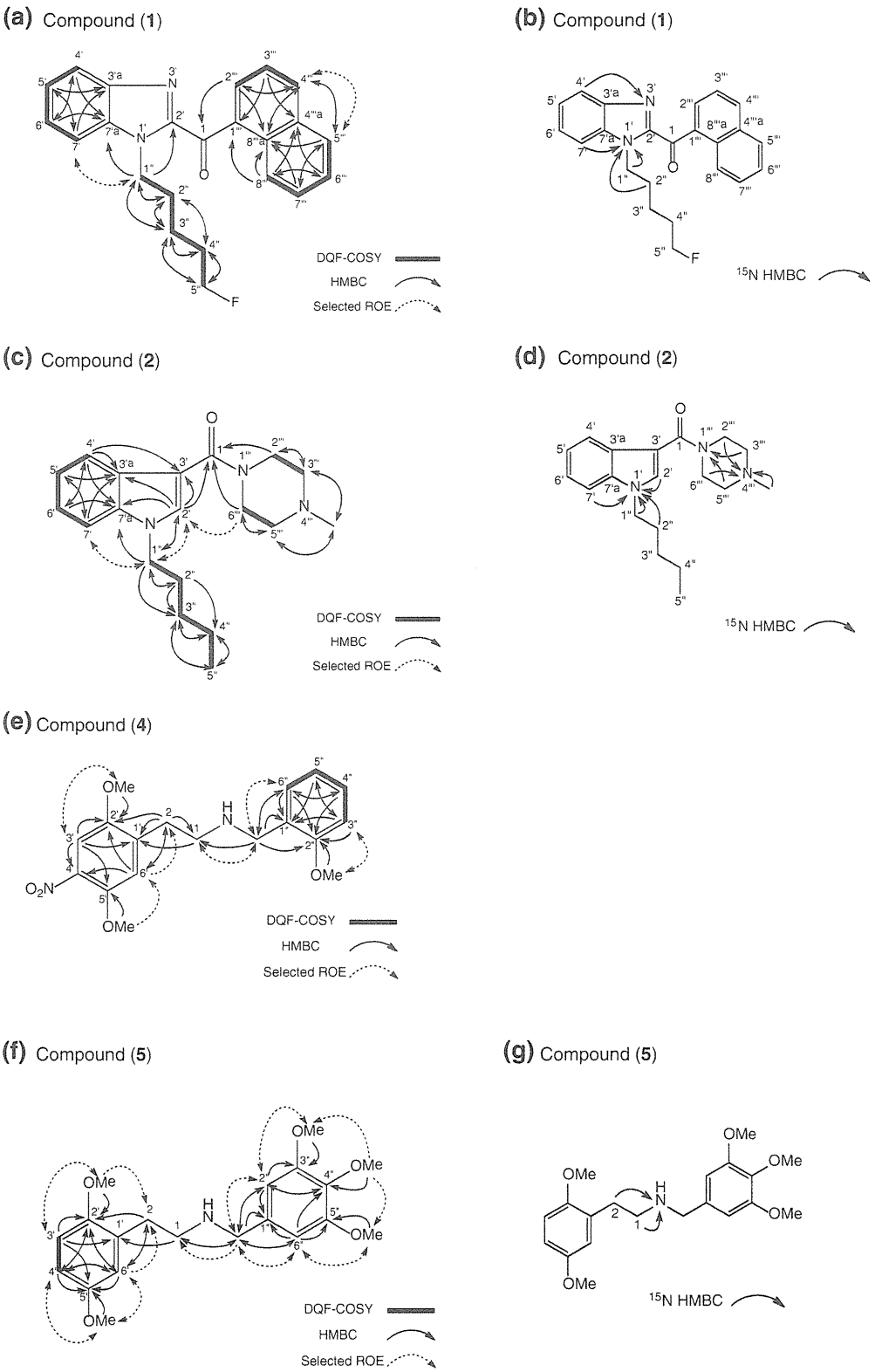



**Fig. 3** Double quantum filtered correlation spectroscopy (DQF–COSY), selected heteronuclear multiple-bond correlation (HMBC), and selected rotating-frame nuclear Overhauser effect (ROE) correlations for compounds **1** (**a**), **2** (**c**), **4** (**e**), and **5** (**f**), and $^{15}N$ HMBC correlations for compounds **1** (**b**), **2** (**d**), and **5** (**g**)

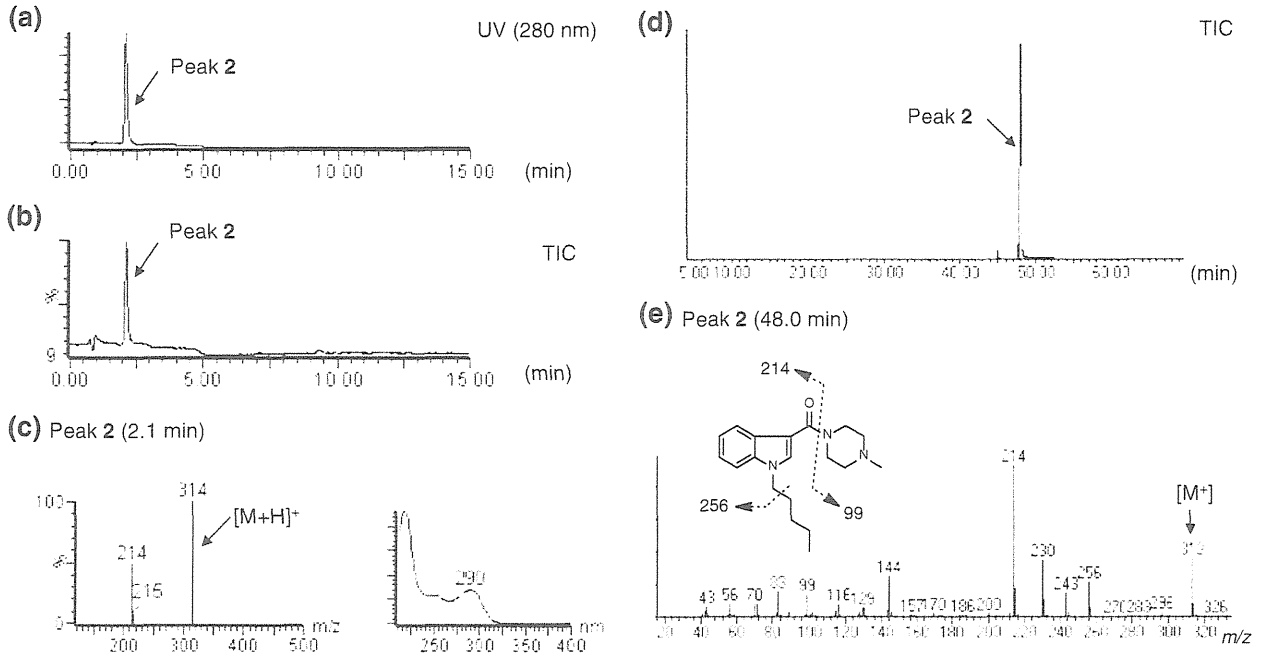



**Fig. 4** LC–MS and GC–MS analyses of product B. LC–UV–PDA chromatogram (**a**) and TIC (**b**). ESI mass and UV spectra (**c**) of peak **2** obtained by LC–MS. TIC (**d**) and EI mass spectrum (**e**) of peak **2** obtained by GC–MS

piperazine protons (H-2‴ and H-6‴) and the carbonyl carbon (C-1) revealed that the *N*-(1-pentyl)-1*H*-indole-3-carbonyl moiety is connected at the 1-position of the carbonyl carbon to the N-1‴ position of 4-methylpiperazine (Fig. 3c). In addition, the fragment ions at *m/z* 99, 214, and 256 of peak **2** obtained by the GC–MS analysis (Fig. 4e) supported the presumed structure of compound **2**. Therefore, compound **2** was identified as (4-methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone and named MEPIRAPIM (Fig. 1). Compound **2** is also a new substance, and its chemical and pharmacological data have not been reported previously. However, the *N*-cyclohexylmethyl-substituted (position 1″ to 5″ in Fig. 1) indole analog of compound **2** has been reported as a cannabinoid $CB_1$ receptor agonist [13]. We therefore presume that compound **2** has a similar activity.

## Identification of unknown peaks 3 and 4

In the GC–MS and LC–MS analyses, we detected unknown peaks **3** and **4** in product C (Fig. 5a, b, f). Based on the GC–MS and LC–MS data, peak **3** was finally identified as 25B-NBOMe by direct comparison of the data (Figs. 1, 5d, h) to those of the purchased authentic compound (Fig. 5e, i). Peak **4** at 23.6 min (Fig. 5a) showed a protonated molecular ion $[M + H]^+$ signal at *m/z* 347 in the LC–MS spectrum (Fig. 5c). The accurate mass spectrum obtained

**Table 2** NMR data for compound **2**

| No. | $^{13}C$ | $^{1}H$ |
|---|---|---|
| 1 | 167.0 | – |
| 2′ | 132.0 | 7.53, 1H, brs |
| 3′ | 108.4 | – |
| 3′a | 125.6 | – |
| 4′ | 120.4 | 7.63, 1H, d, $J$ = 7.9 Hz |
| 5′ | 121.6 | 7.22, 1H, td, $J$ = 7.9, 1.0 Hz |
| 6′ | 122.8 | 7.27, 1H, td, $J$ = 7.2, 1.0 Hz |
| 7′ | 110.3 | 7.37, 1H, d, $J$ = 8.3 Hz |
| 7′a | 136.0 | – |
| 1″ | 46.9 | 4.11, 2H, t, $J$ = 7.2 Hz |
| 2″ | 29.6 | 1.85, 2H, q, $J$ = 7.6 Hz |
| 3″ | 29.0 | 1.30, 2H, m, overlapped |
| 4″ | 22.2 | 1.35, 2H, m, overlapped |
| 5″ | 13.9 | 0.88, 3H, t, $J$ = 7.2 Hz |
| 1‴ | – | – |
| 2‴/6‴ | 42.2 | 4.50, 2H, brd, $J$ = 14.1 Hz |
| | | 3.97, 2H, brt, $J$ = 13.1 Hz |
| 3‴/5‴ | 53.6 | 3.42, 2H, m |
| | | 2.82, 2H, m, overlapped |
| 4‴ | – | – |
| 4‴-Me | 43.6 | 2.79, 3H, s, overlapped |

Recorded in $CDCl_3$ at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$), respectively; data in δ ppm

**Table 3** NMR data for compounds **4** and **5**, and 2C-N

| No. | 2C-N[a] | Compound **4**[b] | | Compound **5**[b] | | |
|---|---|---|---|---|---|---|
| | $^{13}C$ | $^{13}C$ | $^{1}H$ | No. | $^{13}C$ | $^{1}H$ |
| 1 | 38.2 | 47.9 | 2.82, 2H, brs | 1 | 49.6 | 2.95, 2H, s, overlapped |
| 2 | 28.0 | 30.7 | 2.82, 2H, brs | 2 | 31.6 | 2.95, 2H, s, overlapped |
| 1′ | 132.4 | 135.5 | – | 1′ | 130.2 | – |
| 2′ | 150.4 | 150.8 | – | 2′ | 152.3 | – |
| 3′ | 107.3 | 107.4 | 7.06, 1H, s | 3′ | 111.4 | 6.51, 1H, d, $J$ = 8.9 Hz |
| 4′ | 137.8 | 138.4 | – | 4′ | 111.6 | 6.65, 1H, dd, $J$ = 8.9, 3.1 Hz |
| 5′ | 146.1 | 147.4 | – | 5′ | 154.2 | – |
| 6′ | 116.8 | 116.7 | 6.61, 1H, brs | 6′ | 117.2 | 6.91, 1H, d, $J$ = 3.1 Hz |
| 1″ | – | 126.6 | – | 1″ | 136.5 | – |
| 2″ | – | 157.9 | – | 2″/6″ | 105.8 | 6.59, 2H, s |
| 3″ | – | 110.4 | 6.46, 1H, d, $J$ = 7.9 Hz | 3″/5″ | 154.1 | – |
| 4″ | – | 129.1 | 7.03, 1H, t, $J$ = 7.9 Hz | 4″ | 138.3 | – |
| 5″ | – | 120.6 | 6.82, 1H, t, $J$ = 7.6 Hz | 5″ | – | – |
| 6″ | – | 130.4 | 7.30, 1H, d, $J$ = 6.9 Hz | 6″ | – | – |
| *N*-$CH_2$ | – | 48.3 | 3.87, 2H, s | *N*-$CH_2$ | 54.2 | 3.64, 2H, s |
| 2′-OMe | 57.0 | 55.2 | 2.99, 3H, s | 2′-OMe | 55.4 | 3.34, 3H, s |
| 5′-OMe | 56.3 | 56.5 | 3.23, 3H, s | 5′-OMe | 55.1 | 3.37, 3H, s |
| 2″-OMe | – | 54.8 | 3.27, 3H, s | 2″-OMe | – | – |
| – | – | – | – | 3″/5″-OMe | 55.8 | 3.44, 6H, s |
| – | – | – | – | 4″-OMe | 60.5 | 3.85, 3H, s |

[a] Ref [14], recorded in DMSO-$d_6$ at 150 MHz ($^{13}C$)

[b] Recorded in benzene-$d_6$ at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$), respectively; data in δ ppm

by LC–QTOF–MS gave an ion peak at *m/z* 347.1591, suggesting that the protonated molecular formula of compound **4** was $C_{18}H_{23}N_2O_5$ (calcd. 347.1607).

The observed fragment ions at *m/z* 121 and 150 of peak **4** (Fig. 5g) were similar to those of 25B-NBOMe (**3**) obtained by GC–MS analysis (Fig. 5i). It was therefore presumed that compound **4** had a 2-methoxybenzyl group.

The structure of compound **4** was elucidated by NMR analysis (Fig. 3e; Table 3). The $^{1}H$ and $^{13}C$ NMR spectra of compound **4** indicated the existence of 22 protons and 18 carbons (Table 3). The 2D NMR spectra of compound **4** suggested the presence of two moieties, a 2,5-dimethoxy-4-substituted phenyl moiety and a 2-methoxybenzyl group (Fig. 3e) like those of 25B-NBOMe (**3**). In addition, the HMBC correlations from methylene protons (N-C$\underline{H_2}$) to an ethylene carbon (C-1) and from the ethylene protons (H-1) to a phenyl carbon (C-1′) suggested that the 2-methoxybenzyl group was attached to the 2,5-dimethoxy-4-substituted phenyl moiety through the ethanamine group (Fig. 3e). The remaining $NO_2$ unit was presumed to be a nitro group. The chemical shifts of the 2,5-dimethoxy-4-nitrophenyl moiety of compound **4** [$\delta_c$ 135.5 (C-1′), 150.8 (C-2′), 107.4 (C-3′), 138.4 (C-4′), 147.4 (C-5′), and 116.7 (C-6′)] were similar to those of a known 2C-N [2-(2,5-dimethoxy-4-nitrophenyl)ethanamine] [$\delta_c$ (DMSO-$d_6$) 132.4 (C-1′), 150.4 (C-2′), 107.3 (C-3′), 137.8 (C-4′), 146.1 (C-5′), and 116.8 (C-6′), 14] (Table 3; Fig. 1). In addition, the UV spectrum of compound **4** ($\lambda_{max}$ 244, 276, 371 nm), which was different from that of 25B-NBOMe (**3**) ($\lambda_{max}$ 296 nm) (Fig. 5 c, d) and similar to that of 2C-N ($\lambda_{max}$ 245, 279, 375 nm, data not shown), supported the existence of a $NO_2$ group. On the basis of the above spectroscopic analyses, the structure of compound **4** was determined as 2C-N-NBOMe [IUPAC: 2-(2,5-dimethoxy-4-nitrophenyl)-*N*-(2-methoxybenzyl)ethanamine], as provided in Fig. 1. Compounds **3** and **4**, called the 25-NBOMe series, were derived from the hallucinogenic phenethylamine 2C-series (2,5-dimethoxyphenethylamine) by substitution on the *N*-(*o*-methoxy)benzyl (NBOMe) group such as 25I-NBOMe and 25C-NBOMe (synonym: 2C-C-NBOMe) [3, 15]. Compounds **3** and **4** have been detected as newly distributed designer drugs in European countries [3], but they have not previously been detected in Japan. Compound **3** has been reported to have an affinity for the serotonin 5-$HT_{2A}$ receptor, which is similar to the action of 25I-NBOMe [16]. Compound **4**, for which no pharmacological information is available, is a derivative of hallucinogenic 2C-N (2,5-dimethoxy-4-nitrophenethylamine) [17]. Therefore, it

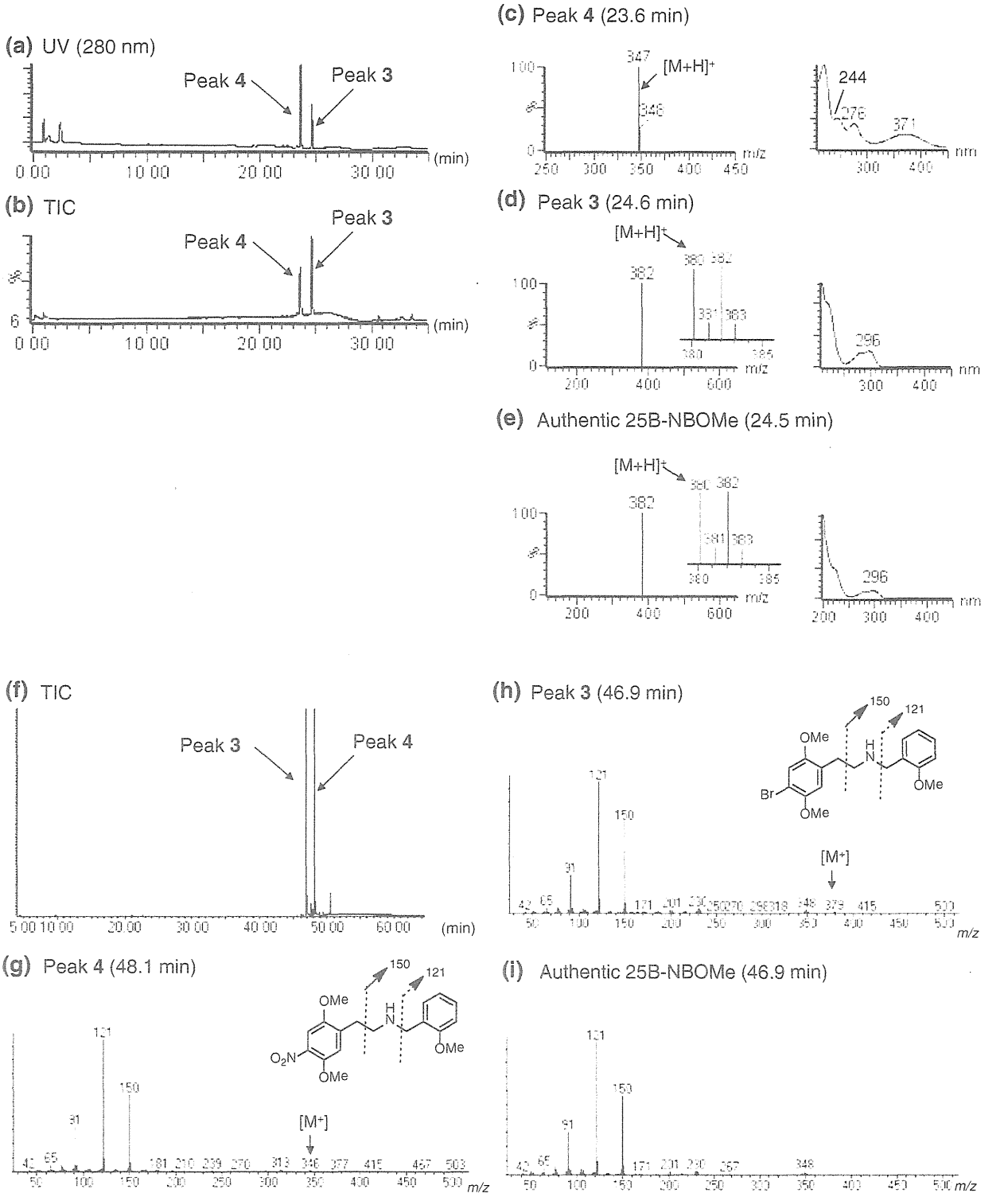



**Fig. 5** LC–MS and GC–MS analyses of product C. LC–UV–PDA chromatogram (**a**), TIC (**b**), and ESI mass and UV spectra of peaks 4 (**c**), 3 (**d**), and authentic 25B-NBOMe (**e**) obtained by LC–MS. TIC (**f**) and EI mass spectra of peaks 4 (**g**), 3 (**h**), and authentic 25B-NBOMe (**i**) obtained by GC–MS

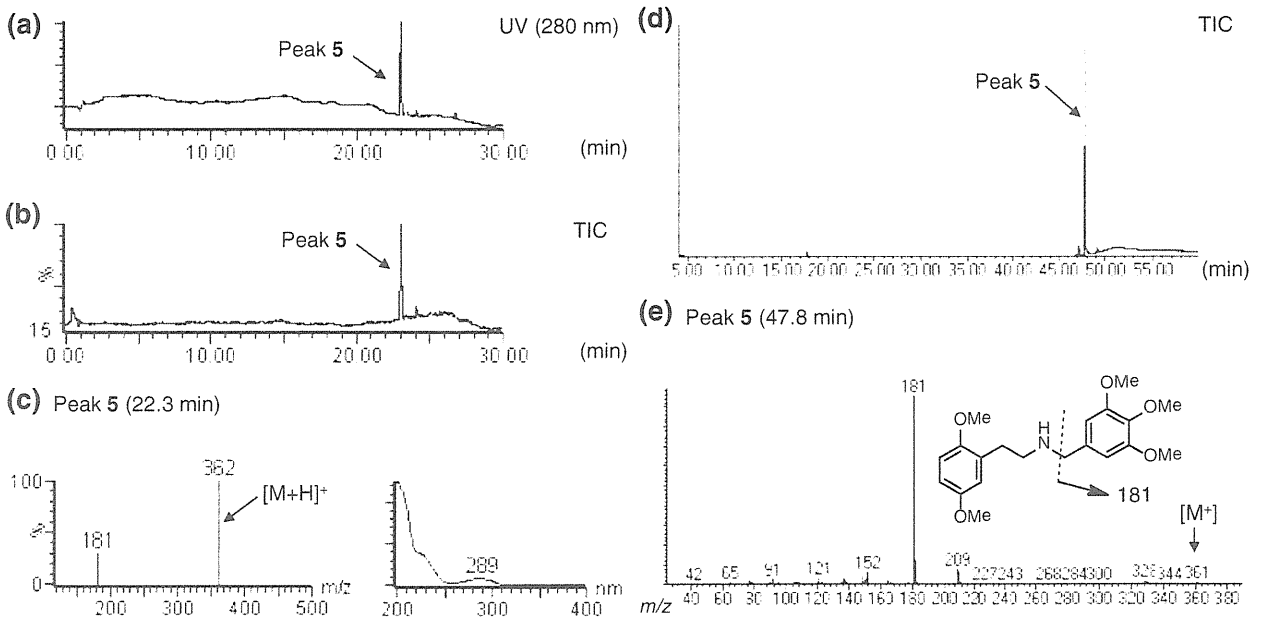



**Fig. 6** LC–MS and GC–MS analyses of product D. LC–UV–PDA chromatogram (**a**) and TIC (**b**), and ESI mass and UV spectra (**c**) of peak **5** obtained by LC–MS. TIC (**d**) and EI mass spectrum (**e**) of peak **5** obtained by GC–MS

is considered that compound **4** likely has activity similar to that of 2C-N.

Identification of unknown peak **5**

Unknown peak **5** was detected in the LC–MS and GC–MS chromatograms for product D (Fig. 6a, b, d). In the LC–MS analysis, unknown peak **5** at 22.3 min showed a protonated molecular ion $[M + H]^+$ signal at *m/z* 362 (Fig. 6c). The accurate mass spectrum obtained by LC–QTOF–MS gave an ion peak at *m/z* 362.1948, suggesting that the protonated molecular formula of compound **5** was $C_{20}H_{28}NO_5$ (calcd. 362.1967).

The $^1H$ and $^{13}C$ NMR spectra of compound **5** suggested the existence of 27 protons and 20 carbons (Table 3). The 1D NMR spectra of compound **5** suggested the presence of five methoxy groups [$\delta_c$ and $\delta_H$: 55.4 and 3.34 (2′-OMe), 55.1 and 3.37 (5′-OMe), 55.8 and 3.44 (3″/5″-OMe), 60.5 and 3.85 (4″-OMe)] as shown in Table 3. The 2D NMR spectra of compound **5** indicated the presence of two moieties. One was a 2,5-dimethoxyphenethyl group, similar to 25B-NBOMe (**3**), and the other was a 3,4,5-trimethyoxybenzyl group (Fig. 3f). The connections of the two moieties were suggested by the HMBC correlation between ethylene protons (H-1) and the benzyl carbons (N-$\underline{C}H_2$), and the $^{15}N$ HMBC correlation between ethylene protons (H-1 and H-2) and the $\underline{N}H$ atom (Fig. 3f, g). Therefore, the structure of compound **5** was identified as a 25H-NBOMe 3,4,5-trimethoxybenzyl analog [IUPAC: 2-(2,5-dimethoxyphenyl)-*N*-(3,4,5-trimethoxybenzyl)ethanamine] as shown in Fig. 1. Compound **5**, which consists of a 2,5-dimethoxyphenethyl group and a methyoxy benzyl group, is similar to the "25-NBOMe series," but it has a trimethoxybenzyl group in place of a 2-methoxybenzyl group. Compound **5** was detected as a novel substance, and its chemical and pharmaceutical data have not been reported previously.

## Conclusions

In this study, we disclosed five newly distributed designer drugs, including two new types of synthetic cannabinoids, an AM-2201 benzimidazole analog (FUBIMINA, **1**) and (4-methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM, **2**), and three newly emerged phenethylamine derivatives, 25B-NBOMe (**3**), 2C-N-NBOMe (**4**), and a 25H-NBOMe 3,4,5-trimethoxybenzyl analog (**5**), in illegal products. Among them, no chemical and pharmacological data for compounds **1**, **2**, and **5** have appeared until now. Compounds **3** and **4** were newly detected as designer drugs in Japan. The distribution of new miscellaneous "other" substances such as 5-APDB (3-deoxy-MDA), α-pyrrolidinopentiothiophenone (α-PVT), and MT-45 has obviously been increasing since 2012, as described in previous reports [3, 6, 8]. Considering the present situation, we believe it necessary to continue our monitoring and identification of newly distributed psychotropic

substances so as to prevent their abuse and to minimize their risks to human health.

**Acknowledgments** Part of this work was supported by a Health and Labor Sciences Research Grant from the Ministry of Health, Labour, and Welfare, Japan.

**Conflict of interest** There are no financial or other relations that could lead to a conflict of interest.

## References

1. UNODC (2013) Global SMART update 2013—vol 10, September 2013. http://www.unodc.org/documents/scientific/Global_SMART_Update_10_web.pdf. Accessed Sept 2013
2. UNODC (2013) The challenge of new psychoactive substances. A report from the global SMART programme, March 2013. http://www.unodc.org/documents/scientific/NPS_2013_SMART.pdf. Accessed Sept 2013
3. EMCDDA (2013) EMCDDA/Europol, 2005/387/JHA, EMCDDA-Europol 2012 annual report on the implementation of council decision, Lisbon, May 2013. http://www.emcdda.europa.eu/publications/implementation-reports/2012. Accessed May 2013
4. Kikura-Hanajiri R, Uchiyama N, Kawamura M, Goda Y (2013) Changes in the prevalence of synthetic cannabinoids and cathinone derivatives in Japan until early 2012. Forensic Toxicol 31:44–53
5. Kikura-Hanajiri R, Uchiyama N, Kawamura M, Ogata J, Goda Y (2013) Prevalence of new designer drugs and their legal status in Japan. Yakugaku Zasshi 133:31–40 (in Japanese with English abstract)
6. Uchiyama N, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y (2013) Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative α-PVT and an opioid receptor agonist AH-7921 identified in illegal products. Forensic Toxicol 31:223–240
7. Uchiyama N, Matsuda S, Wakana D, Kikura-Hanajiri R, Goda Y (2013) New cannabimimetic indazole derivatives, *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA) and *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) identified as designer drugs in illegal products. Forensic Toxicol 31:93–100
8. Uchiyama N, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y (2013) Identification of two new-type designer drugs, a piperazine derivative MT-45 (I-C6) and a synthetic peptide Noopept (GVS-111), with a synthetic cannabinoid A-834735, a cathinone derivative 4-methoxy-α-PVP and a phenethylamine derivative 4-methylbuphedrine from illegal products. Forensic Toxicol. doi:10.1007/s11419-013-0194-5
9. Kikura-Hanajiri R, Uchiyama N, Kawamura M, Goda Y (2013) Changes in the prevalence of new psychoactive substances before and after the introduction of the generic scheduling of synthetic cannabinoids in Japan. Drug Test Anal. doi:10.1002/dta.1584
10. Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2013) URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products. Forensic Sci Int 227:21–32
11. Lopyrev VA, Larina LI, Vakul'skaya TI, Shibanova EF, Titova IA, Voronkov MG, Liepins E (1982) Investigation of benzimidazoles. III. Transmission of the substituent effects in 2-substituted 1-methylbenzimidazoles studied by carbon-13 nuclear magnetic resonance. Org Magn Reson 20:212–216
12. Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2012) 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. Forensic Toxicol 30:114–125
13. Moir EM, Yoshiizumi K, Cairns J, Cowley P, Ferguson M, Jeremiah F, Kiyoi T, Morphy R, Tierney J, Wishart G, York M, Baker J, Cottney JE, Houghton AK, McPhail P, Osprey A, Walker G, Adam JM (2010) Design, synthesis, and structure–activity relationships of indole-3-carboxamides as novel water soluble cannabinoid CB1 receptor agonists. Med Chem Commun 1:54–60
14. Zuba D, Sekuła K, Buczek A (2012) Identification and characterization of 2,5-dimethoxy-4-nitro-β-phenethylamine (2C-N)—a new member of 2C-series of designer drug. Forensic Sci Int 222:298–305
15. Zuba D, Sekuła K, Buczek A (2013) 25C-NBOMe—new potent hallucinogenic substance identified on the drug market. Forensic Sci Int 227:7–14
16. Silva ME, Heim R, Strasser A, Elz S, Dove S (2011) Theoretical studies on the interaction of partial agonists with the 5-$HT_{2A}$ receptor. J Comput Aided Mol Des 25:51–66
17. Acuña-Castillo C, Villalobos C, Moya PR, Sáez P, Cassels BK, Huidobro-Toro JP (2002) Differences in potency and efficacy of a series of phenylisopropylamine/phenylethylamine pairs at 5-HT(2A) and 5-HT(2C) receptors. Br J Pharmacol 136:510–519

Forensic Toxicol (2014) 32:116–117
DOI 10.1007/s11419-013-0219-0

ERRATUM

# Erratum to: Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl)-(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products

**Nahoko Uchiyama · Yoshihiko Shimokawa · Satoru Matsuda · Maiko Kawamura · Ruri Kikura-Hanajiri · Yukihiro Goda**

Published online: 11 December 2013


**Erratum to: Forensic Toxicol**
**DOI 10.1007/s11419-013-0217-2**

There were some mistakes in Fig. 3a and Table 1 ($^{13}$C NMR chemical shifts of compound **1**), please find the correct figure and table below.

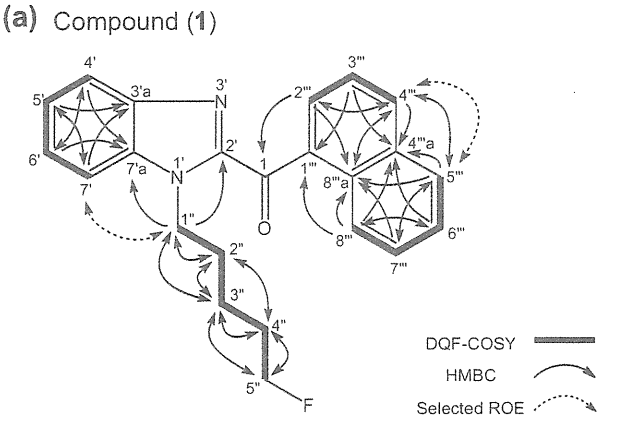



**Fig. 3** Double quantum filtered correlation spectroscopy (DQF-COSY), selected heteronuclear multiple-bond correlation (HMBC), and selected rotating frame nuclear Overhauser effect (ROE) correlations for compounds **1** (**a**), **2** (**c**), **4** (**e**) and **5** (**f**), and $^{15}$N HMBC correlations for compounds **1** (**b**), **2** (**d**), and **5** (**g**)

The online version of the original article can be found under doi:10.1007/s11419-013-0217-2.

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**Table 1** NMR data for compound **1** and known related compounds

| No. | Compound **1**[a,b] | | 2-Acetyl-1-methyl-1*H*-benzimidazole[c] | JWH-018 indazole analog[a] |
|---|---|---|---|---|
| | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{13}C$ |
| 1 | 188.9 | – | 193.1 | 191.6 |
| 2′ | 147.3 | – | 146.5 | – |
| 3′ | – | – | – | 142.6 |
| 3′a | 141.8 | – | 141.5 | 124.3 |
| 4′ | 122.3 | 7.87, 1H, d, $J$ = 8.3 Hz | 121.2 | 123.1 |
| 5′ | 123.8 | 7.35, 1H, ddd, $J$ = 8.3, 7.2, 1.0 Hz | 124.2 | 123.7 |
| 6′ | 125.9 | 7.46, 1H, ddd, $J$ = 8.3, 7.2, 1.0 Hz | 126.3 | 126.9 |
| 7′ | 110.6 | 7.51, 1H, m, overlapped | 111.3 | 109.5 |
| 7′a | 136.1 | – | 137.3 | 140.6 |
| 1″ | 45.4 | 4.70, 2H, t, $J$ = 7.6 Hz | 31.8 (NMe) | 49.8 |
| 2″ | 30.1 | 2.05, 2H, q, $J$ = 7.9 Hz | 27.1 (COMe) | 29.4 |
| 3″ | 22.8, d, $J$ = 4.3 Hz[c] | 1.59, 2H, m | – | 28.8 |
| 4″ | 30.0, d, $J$ = 20.2 Hz[c] | 1.80 and 1.76, each 1H, m, overlapped | – | 22.2 |
| 5″ | 83.7, d, $J$ = 164.7 Hz[c] | 4.48 and 4.41, each 1H, t, $J$ = 5.8 Hz | – | 13.9 |
| 1‴ | 134.4 | – | – | 136.3 |
| 2‴ | 131.9 | 8.03, 1H, dd, $J$ = 7.2, 1.0 Hz | – | 129.3 |
| 3‴ | 124.3 | 7.56, 1H, m, overlapped | – | 124.3 |
| 4‴ | 133.3 | 8.05, 1H, d, $J$ = 8.3 Hz | – | 131.4 |
| 4‴a | 134.0 | – | – | 133.8 |
| 5‴ | 128.6 | 7.91, 1H, d, $J$ = 7.9 Hz | – | 128.3 |
| 6‴ | 126.5 | 7.53, 1H, m, overlapped | – | 126.1 |
| 7‴ | 127.9 | 7.57, 1H, m, overlapped | – | 127.1 |
| 8‴ | 125.3 | 8.46, 1H, d, $J$ = 8.3 Hz | – | 125.8 |
| 8‴a | 131.2 | – | – | 131.1 |

[a] Recorded in $CDCl_3$ at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$), respectively; data in δ ppm ($J$ in Hz)

[b] Observed as double signals by coupling with fluorine

[c] Ref [11], recorded in $CD_3OD$

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DOI 10.1007/s11419-013-0194-5

ORIGINAL ARTICLE

# Identification of two new-type designer drugs, piperazine derivative MT-45 (I-C6) and synthetic peptide Noopept (GVS-111), with synthetic cannabinoid A-834735, cathinone derivative 4-methoxy-α-PVP, and phenethylamine derivative 4-methylbuphedrine from illegal products

**Nahoko Uchiyama · Satoru Matsuda · Maiko Kawamura · Ruri Kikura-Hanajiri · Yukihiro Goda**

Received: 23 May 2013 / Accepted: 3 June 2013 / Published online: 23 June 2013


**Abstract** We identified two new-type designer drugs, piperazine derivative MT-45 [1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, synonym: I-C6, **1**] and synthetic peptide Noopept [ethyl 2-(1-(2-phenylacetyl)pyrrolidine-2-carboxamido)acetate, synonym: GVS-111, **2**], in chemical and herbal products. MT-45 (**1**) was previously reported as an opiate-like analgesic substance, and Noopept (**2**) was reported to have nootropic (cognitive enhancer) activity. We also detected two synthetic cannabinoids, A-834735 (**3**) and QUPIC *N*-(5-fluoropentyl) analog (synonym: 5-fluoro-PB-22, **4**), in the illegal products. A-834735 (**3**) was previously reported to act as an agonist at both cannabinoid $CB_1$ and $CB_2$ receptors. In addition, cathinone derivative 4-methoxy-α-pyrrolidinovalerophenone (4-methoxy-α-PVP, **5**) and phenethylamine derivative 4-methylbuphedrine (**6**) were newly detected with known cathinone derivative 4-methylbuphedrone (**7**) in the products.

**Keywords** MT-45 [1-cyclohexyl-4-(1,2-diphenylethyl) piperazine, synonym: I-C6] · Noopept [ethyl 2-(1-(2-phenylacetyl)pyrrolidine-2-carboxamido)acetate, synonym: GVS-111] · A-834735 · 4-Methoxy-α-PVP · 4-Methylbuphedrine · QUPIC *N*-(5-fluoropentyl) analog (synonym: 5-fluoro-PB-22)

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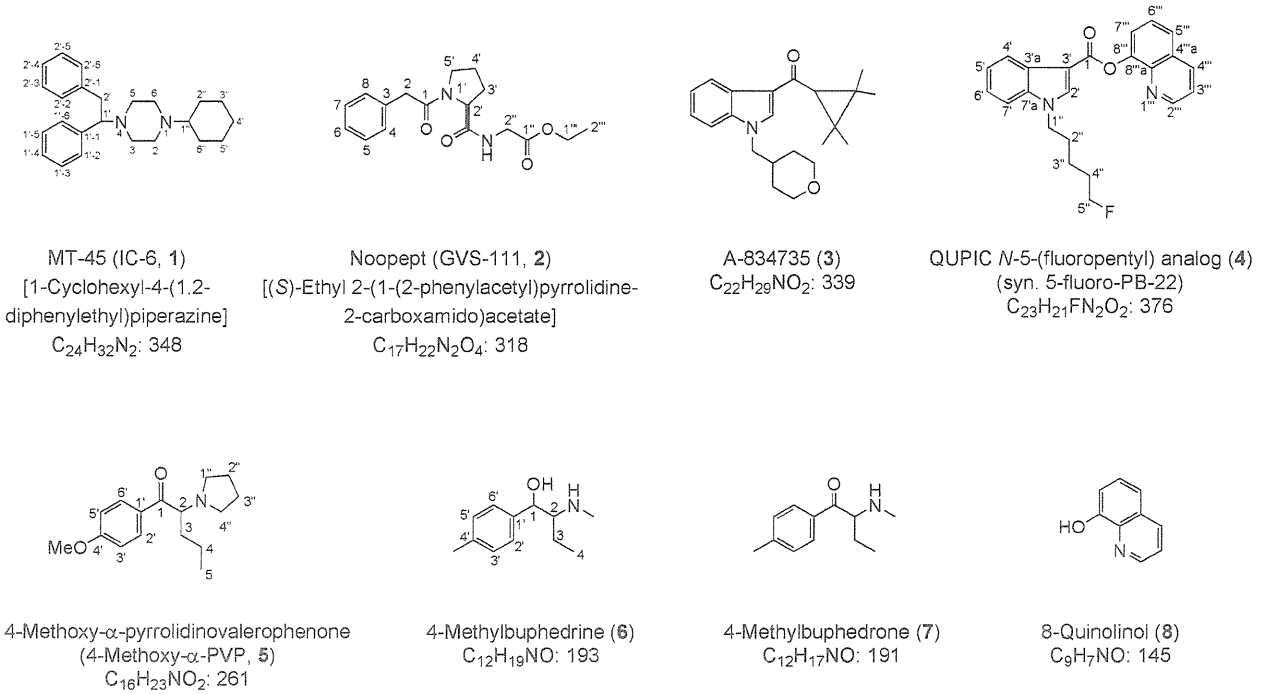
## Introduction

A wide variety of new psychotropic substances has emerged around the world over the past few years, and many of the existing drugs have been replaced by other new drugs in a short period of time. Among the new psychotropics, synthetic cannabinoids and cathinone derivatives have become major classes of abused drugs not only in Japan but worldwide [1–8]. We have been conducting an ongoing survey of designer drugs in the illegal drug market in Japan [1, 5, 7, 9, 10], and have reported the identification of newly distributed designer drugs among illegal products purchased mostly in 2012 that include the following synthetic cannabinoids: QUPIC (PB-22), QUCHIC (BB-22), ADBICA, ADB-FUBINACA, AB-PINACA, AB-FUBINACA, APICA *N*-(5-fluoropentyl) analog, APINACA *N*-(5-fluoropentyl) analog, UR-144 *N*-(5-chloropentyl) analog, JWH-122 *N*-(5-chloropentyl) analog, AM-2201 4-methoxynaphthyl analog, and AB-001 *N*-(5-fluoropentyl) analog; thiophene derivative α-PVT and opioid receptor agonist AH-7921 have also been reported [9, 10]. In the present study, we describe the identification of novel designer drugs (**1**–**6**, Fig. 1) in illegal products purchased in 2013.

## Materials and methods

### Samples for analyses

Five analyzed samples (products A–E) were purchased via the Internet from January to March 2013 as chemical-type or herbal-type products being sold in Japan. The herbal-type product (A) contained about 3 g of mixed dried plants.



MT-45 (IC-6, **1**)
[1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine]
$C_{24}H_{32}N_2$: 348

Noopept (GVS-111, **2**)
[(*S*)-Ethyl 2-(1-(2-phenylacetyl)pyrrolidine-2-carboxamido)acetate]
$C_{17}H_{22}N_2O_4$: 318

A-834735 (**3**)
$C_{22}H_{29}NO_2$: 339

QUPIC *N*-5-(fluoropentyl) analog (**4**)
(syn. 5-fluoro-PB-22)
$C_{23}H_{21}FN_2O_2$: 376

4-Methoxy-α-pyrrolidinovalerophenone
(4-Methoxy-α-PVP, **5**)
$C_{16}H_{23}NO_2$: 261

4-Methylbuphedrine (**6**)
$C_{12}H_{19}NO$: 193

4-Methylbuphedrone (**7**)
$C_{12}H_{17}NO$: 191

8-Quinolinol (**8**)
$C_9H_7NO$: 145

**Fig. 1** Structures of newly detected compounds (**1**–**6**) and detected but known compounds (**7** and **8**)

The liquid-type products called "liquid aroma" were each about 5 ml of a pale green liquid (B) and colorless liquids (C and D). The powder-type product (E) called "fragrance powder" was about 400 mg of white powder.

## Chemicals and reagents

Authentic A-834735 (**3**), QUPIC *N*-(5-fluoropentyl) analog (synonym: 5-fluoro-PB-22, **4**), and 4-methylbuphedrone (**7**) were purchased from Cayman Chemical (Ann Arbor, MI, USA). 8-Quinolinol (**8**) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Other compounds (**1**, **2**, **5**, and **6**) were isolated from herbal or chemical products. All other common chemicals and solvents were of analytical reagent grade or HPLC grade. As solvents for nuclear magnetic resonance (NMR) analysis, $CDCl_3$ (99.96 %) and pyridine-$d_5$ (99.96 %) were purchased from the ISOTEC division of Sigma-Aldrich (St. Louis, MO, USA).

## Preparation of sample solution

For qualitative analyses, 10 mg of each herbal-type product (crushed into powder) and a 1-mg portion of the powder-type product were extracted with 1 ml of methanol under ultrasonication for 10 min. A 20-μl portion of the liquid-type product was mixed with 1 ml of methanol under ultrasonication for 10 min. After centrifugation (5 min, 3,000 rpm) 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 analyses. If necessary, the solution was diluted with methanol to a suitable concentration before instrumental analyses.

## Analytical conditions

Each sample solution was analyzed by ultra-performance liquid chromatography–electrospray ionization–mass spectrometry (UPLC–ESI–MS) and gas chromatography–mass spectrometry (GC–MS) in the electron ionization (EI) mode as described in our previous report [7]. Two elution programs were used in the LC–MS analysis. Programs 1 and 2 were used for synthetic cannabinoids and for the other compounds including cathinone derivatives, respectively [7]. In this study, we showed the LC–MS data analyzed by the program 2. The obtained GC–MS data were compared to those of an EI–MS library (Mass Spectra of Designer Drugs 2012; Wiley-VCH, Weinheim, Germany). In addition, our in-house EI–MS library of designer drugs obtained by our continuous survey of illegal products and commercially available reagents was also used to assist in structural elucidation.

The accurate mass numbers of the target compounds were measured by a liquid chromatography–quadrupole time-of-flight mass spectrometry (LC–QTOF–MS) system consisting of an Acquity UPLC and Xevo QTOF-MS