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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

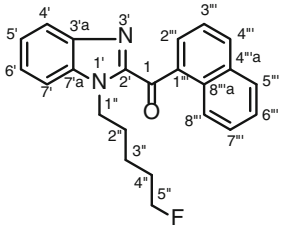
Recently, several countries have adapted their main drug control legislation to control new psychotropic substances such as synthetic cannabinoids and cathinone derivatives by introducing some degree of flexibility to the individual listing system; they have tried to legislate inclusive drug control 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.

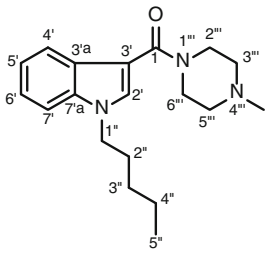
Materials and methods

Samples for analysis

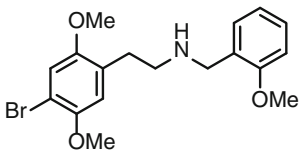
The analyzed samples were purchased in Japan between April and September 2013 from the Internet as chemical-type or herbal-type products A–D. Herbal-type product A contained approximately 3 g of mixed dried plants. The powder-type product B called "fragrance powder" was in the form of a white powder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



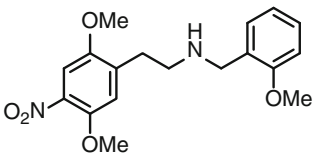
AM-2201 benzimidazole analog
(1-(5-Fluoropentyl)-1*H*-benzo[*d*]imidazol-2-yl)(naphthalen-1-yl)methanone
(FUBIMINA, **1**)
$C_{23}H_{21}FN_2O$: 360



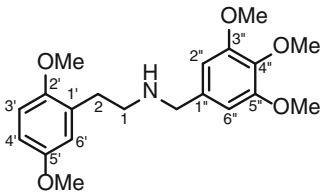
(4-Methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
(MEPIRAPIM, **2**)
$C_{19}H_{27}N_3O$: 313



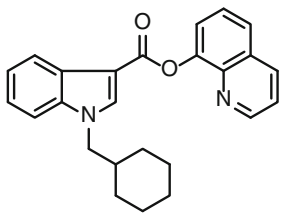
25B-NBOMe (**3**)
$C_{18}H_{22}BrNO_3$: 380



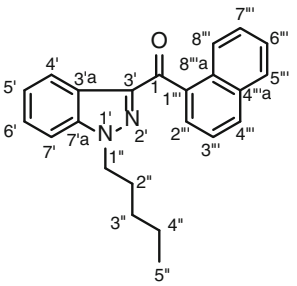
2C-N-NBOMe (**4**)
$C_{18}H_{22}N_2O_5$: 346



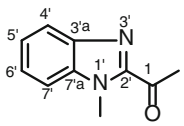
25H-NBOMe 3,4,5-trimethoxybenzyl analog (**5**)
2-(2,5-Dimethoxyphenyl)-*N*-(3,4,5-trimethoxybenzyl)ethanamine
$C_{20}H_{27}NO_5$: 361



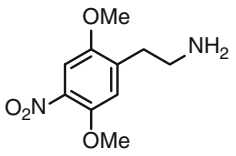
QUCHIC (BB-22)
$C_{25}H_{24}N_2O_2$: 384



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 %

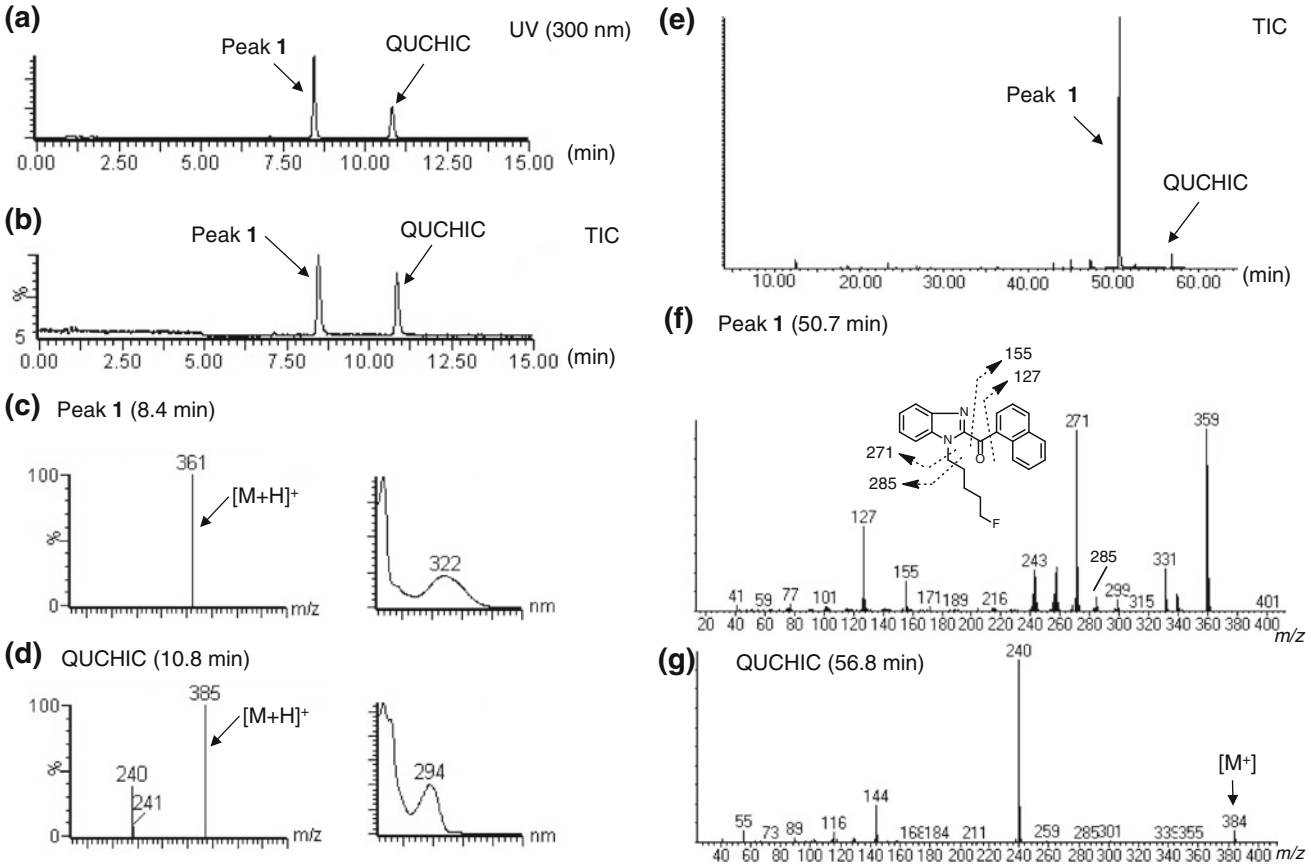


Fig. 2 Liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS) analyses of product A. Liquid chromatography–ultraviolet photodiode array (LC–UV–PDA) chromatogram (**a**) and the total ion chromatogram (TIC) (**b**). Electrospray ionization (ESI) mass and UV spectra (**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 [δ_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** [δ_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 [δ_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

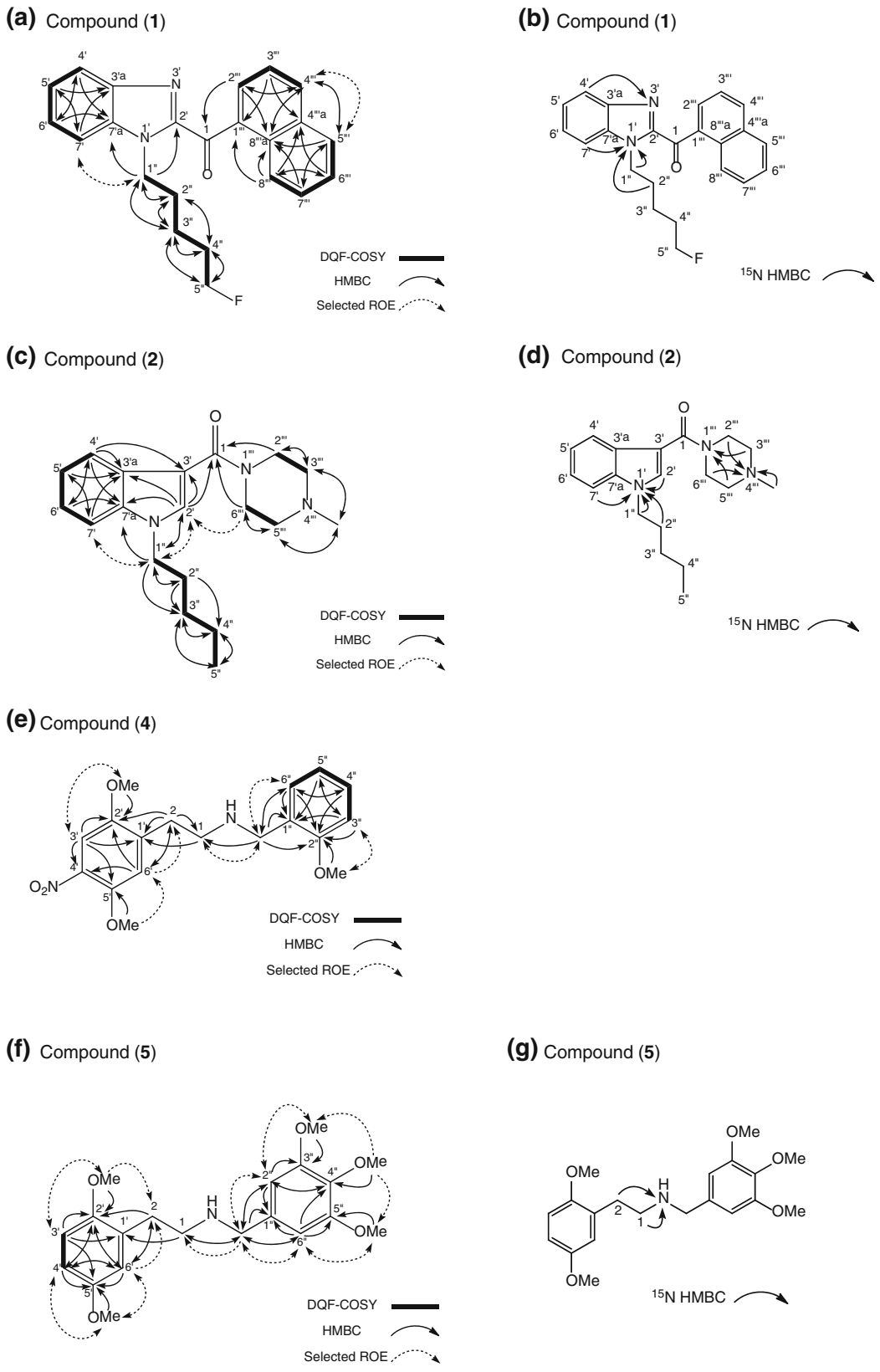


Fig. 3 Double quantum filtered correlation spectroscopy (DQF–COSY), selected heteronuclear multiple-bond correlation (HMBC), and selected rotating-frame nuclear Overhauser effect (ROE) correlations for compounds **1** (**a**), **2** (**c**), **4** (**e**), and **5** (**f**), and ^{15}N HMBC correlations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

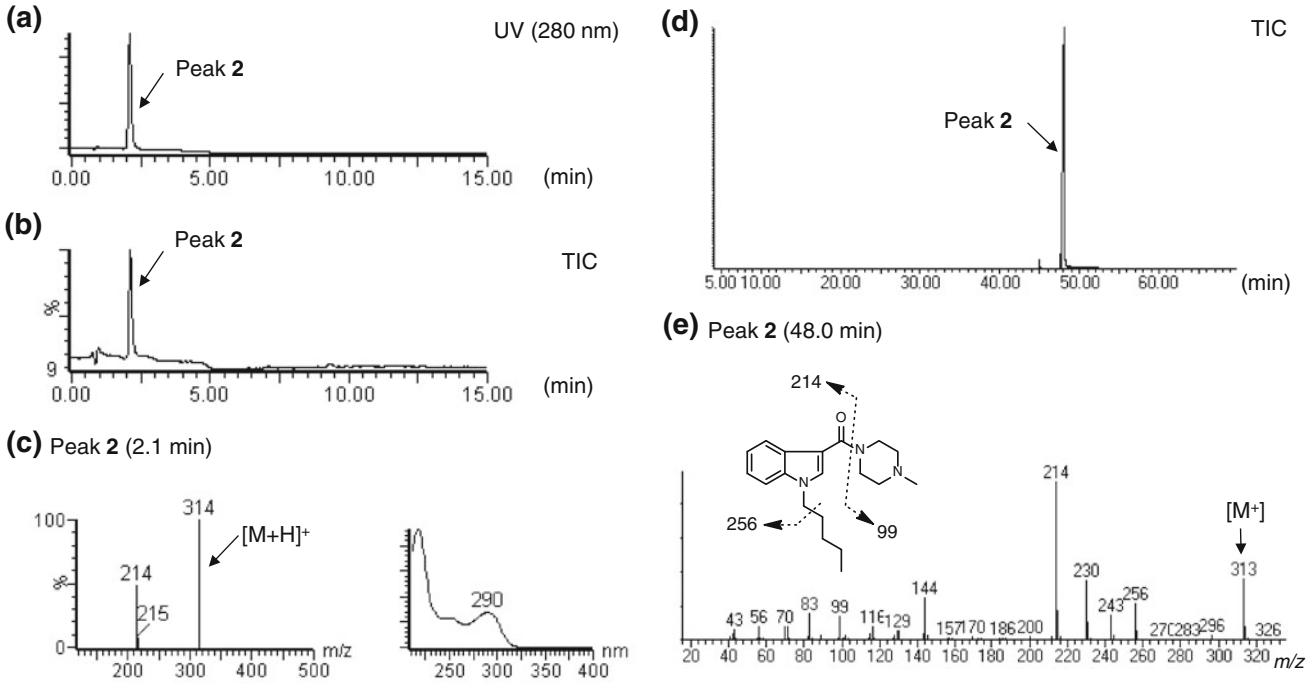


Fig. 4 LC–MS and GC–MS analyses of product B. LC–UV–PDA chromatogram (**a**) and TIC (**b**). ESI mass and UV spectra (**c**) of peak **2** obtained by LC–MS. TIC (**d**) and EI mass spectrum (**e**) of peak **2** obtained by GC–MS

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** [δ_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] [δ_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** (λ_{max} 244, 276, 371 nm), which was different from that of 25B-NBOMe (**3**) (λ_{max} 296 nm) (Fig. 5 c, d) and similar to that of 2C-N (λ_{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

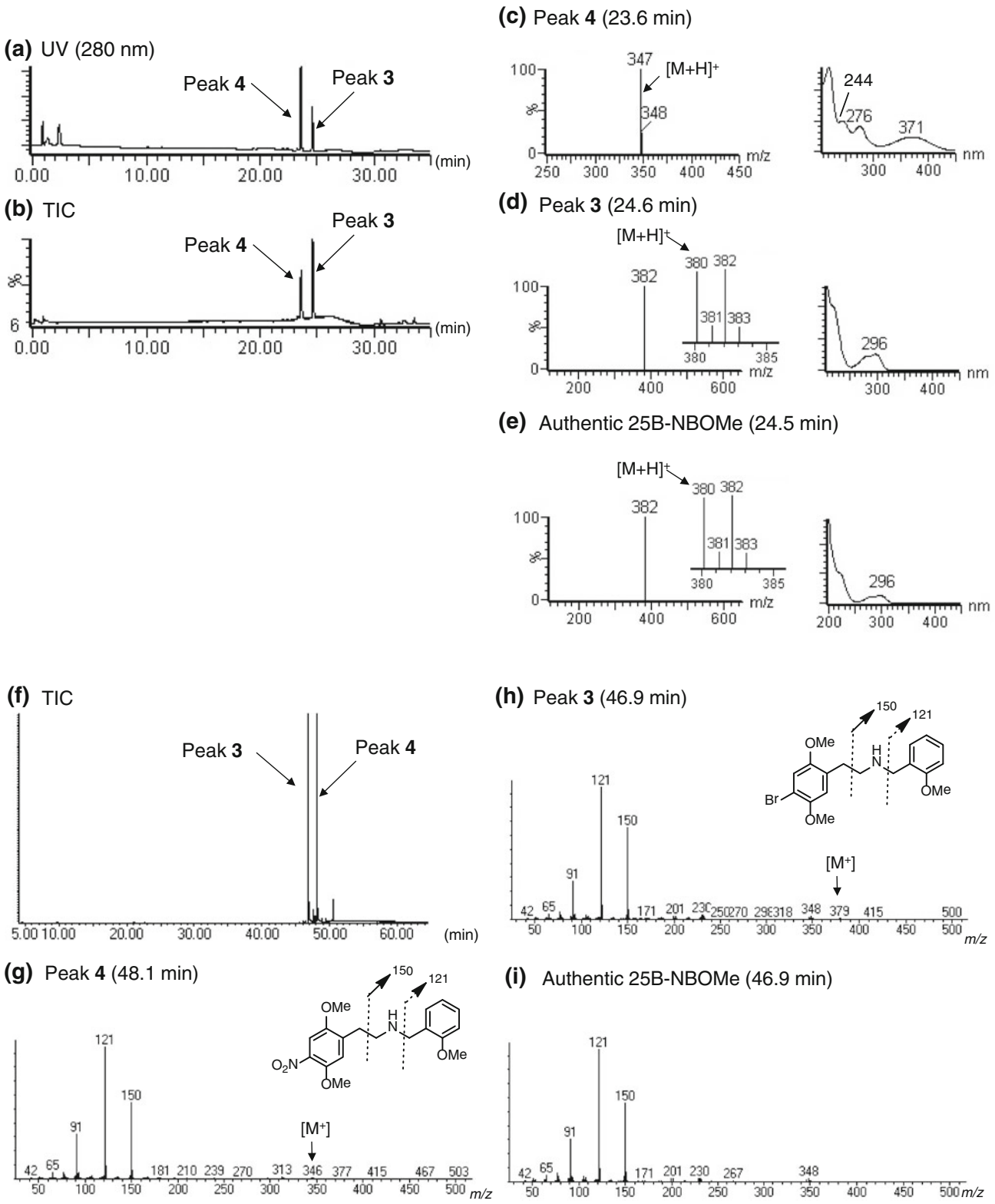


Fig. 5 LC–MS and GC–MS analyses of product C. LC–UV–PDA chromatogram (**a**), TIC (**b**), and ESI mass and UV spectra of peaks **4** (**c**), **3** (**d**), and authentic 25B-NBOMe (**e**) obtained by LC–MS. TIC (**f**) and EI mass spectra of peaks **4** (**g**), **3** (**h**), and authentic 25B-NBOMe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

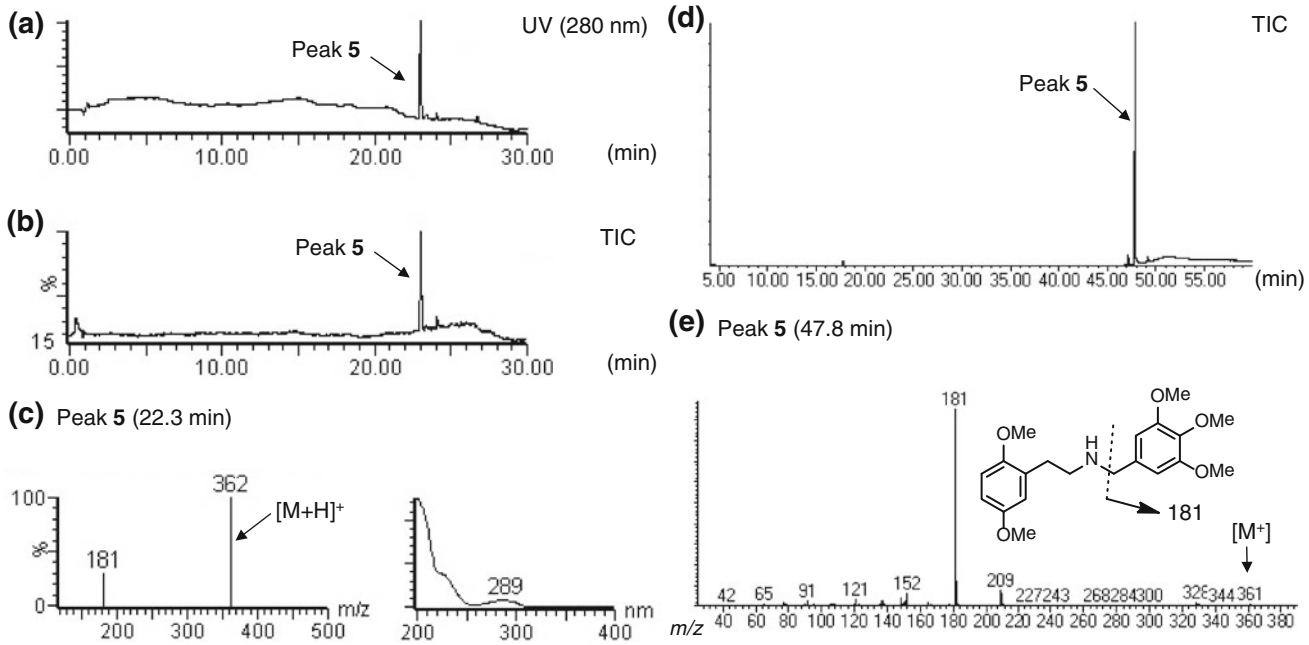


Fig. 6 LC–MS and GC–MS analyses of product D. LC–UV–PDA chromatogram (**a**) and TIC (**b**), and ESI mass and UV spectra (**c**) of peak **5** obtained by LC–MS. TIC (**d**) and EI mass spectrum (**e**) of peak **5** obtained by GC–MS

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 [δ_c and δ_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.

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

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