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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

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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)

N. Uchiyama · S. Matsuda · M. Kawamura · R. Kikura-Hanajiri · Y. Goda (✉)
National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
e-mail: goda@nihs.go.jp

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new psychotropic substances has emerged around the world over the past few years, and many of the existing drugs have been replaced by other new drugs in a short period of time.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.

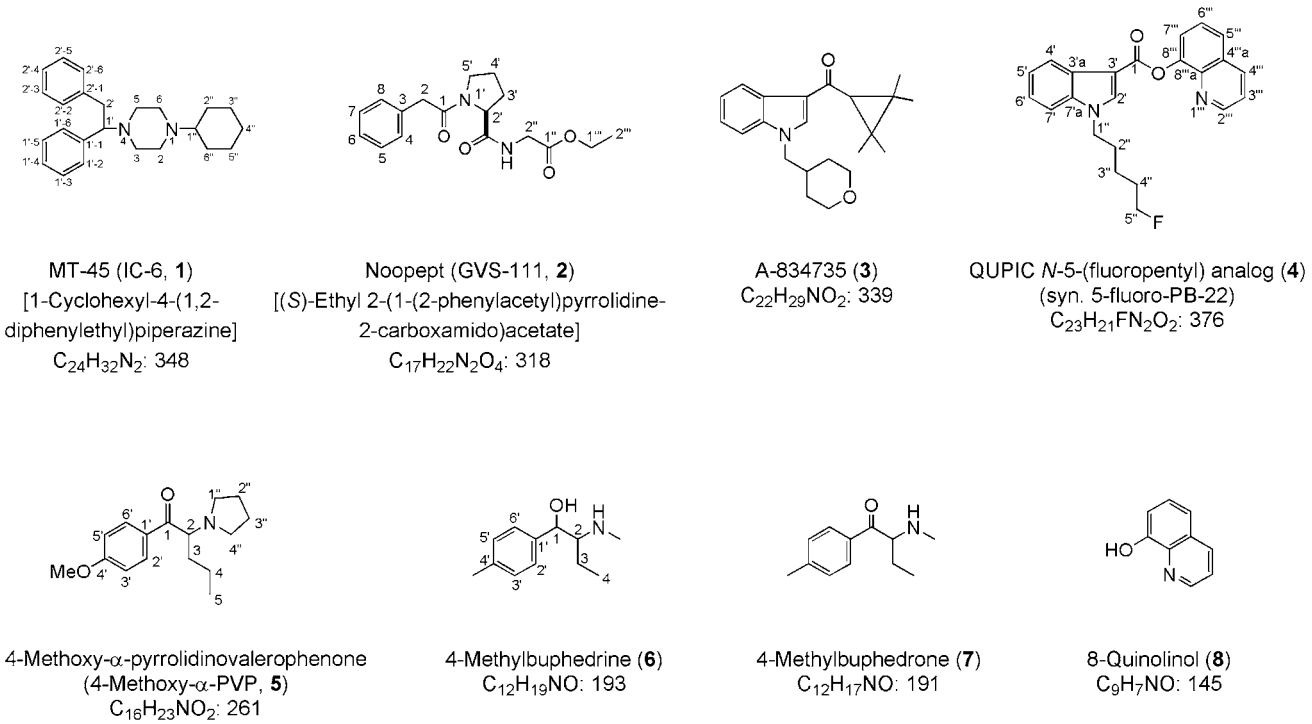

Fig. 1 Structures of newly detected compounds (**1**–**6**) and detected but known compounds (**7** and **8**)

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

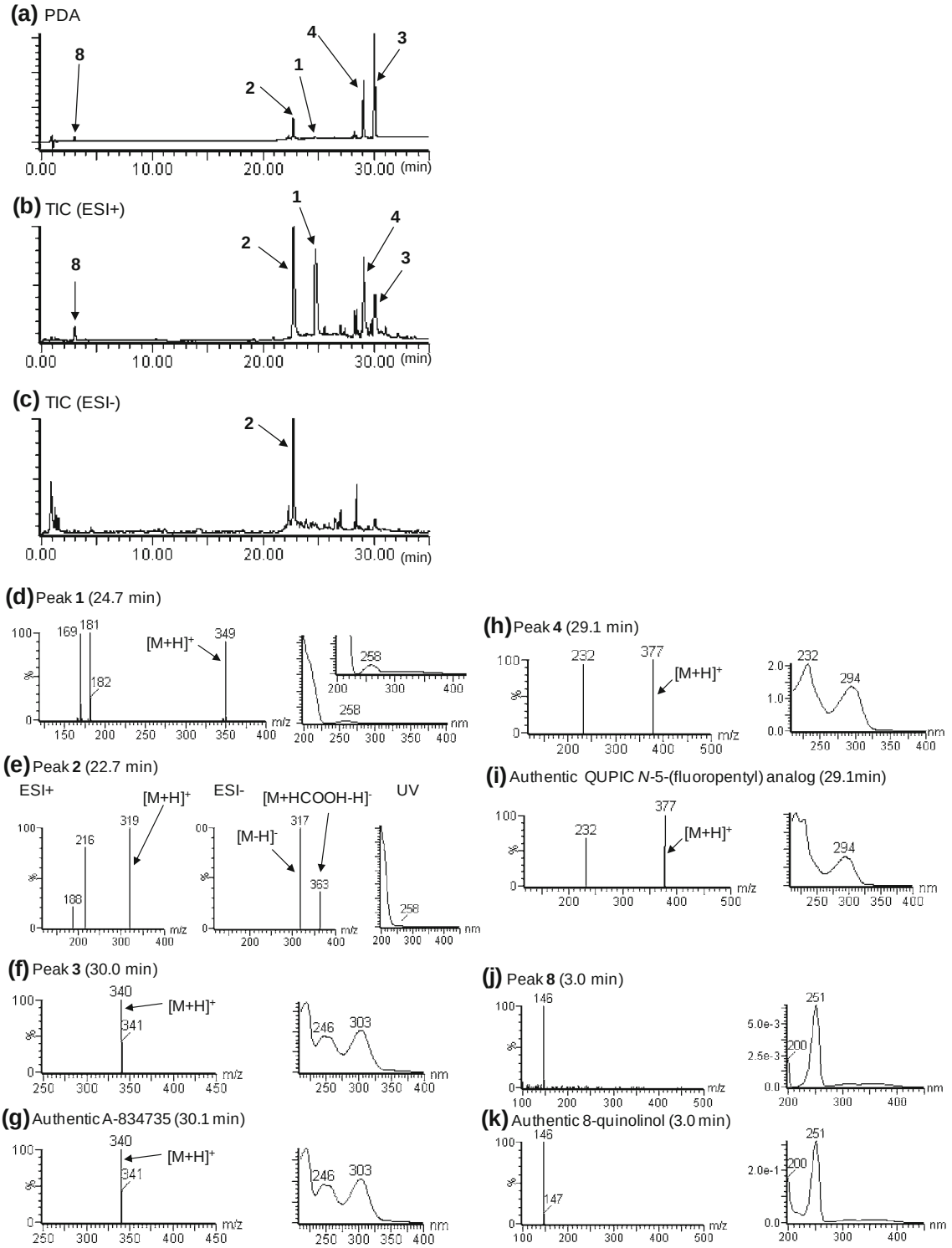

Fig. 2 Liquid chromatography−mass spectrometry (LC−MS) analysis of product A. Liquid chromatography−ultraviolet photodiode array (LC−UV−PDA) chromatogram (**a**), total ion chromatograms (TICs) in positive (**b**) and negative (**c**) modes using elution program 2. Ultraviolet (UV) and electrospray ionization (ESI) mass spectra of peaks **1** (**d**), **2** (**e**), **3** (**f**), **4** (**h**), **8** (**j**), authentic A-834735 (**g**), authentic QUPIC *N*-(5-fluoropentyl) analog (**i**), and authentic 8-quinolinol (**k**) obtained by LC−MS are also shown

(Waters, Milford, MA, USA) with a photodiode array (PDA) detector (Waters). The measurement conditions were the same as reported previously [9].

For the isolation of each compound, preparative gel permeation liquid chromatography (GPLC) was performed on a JAI (Japan Analytical Industry, Tokyo, Japan) LC-

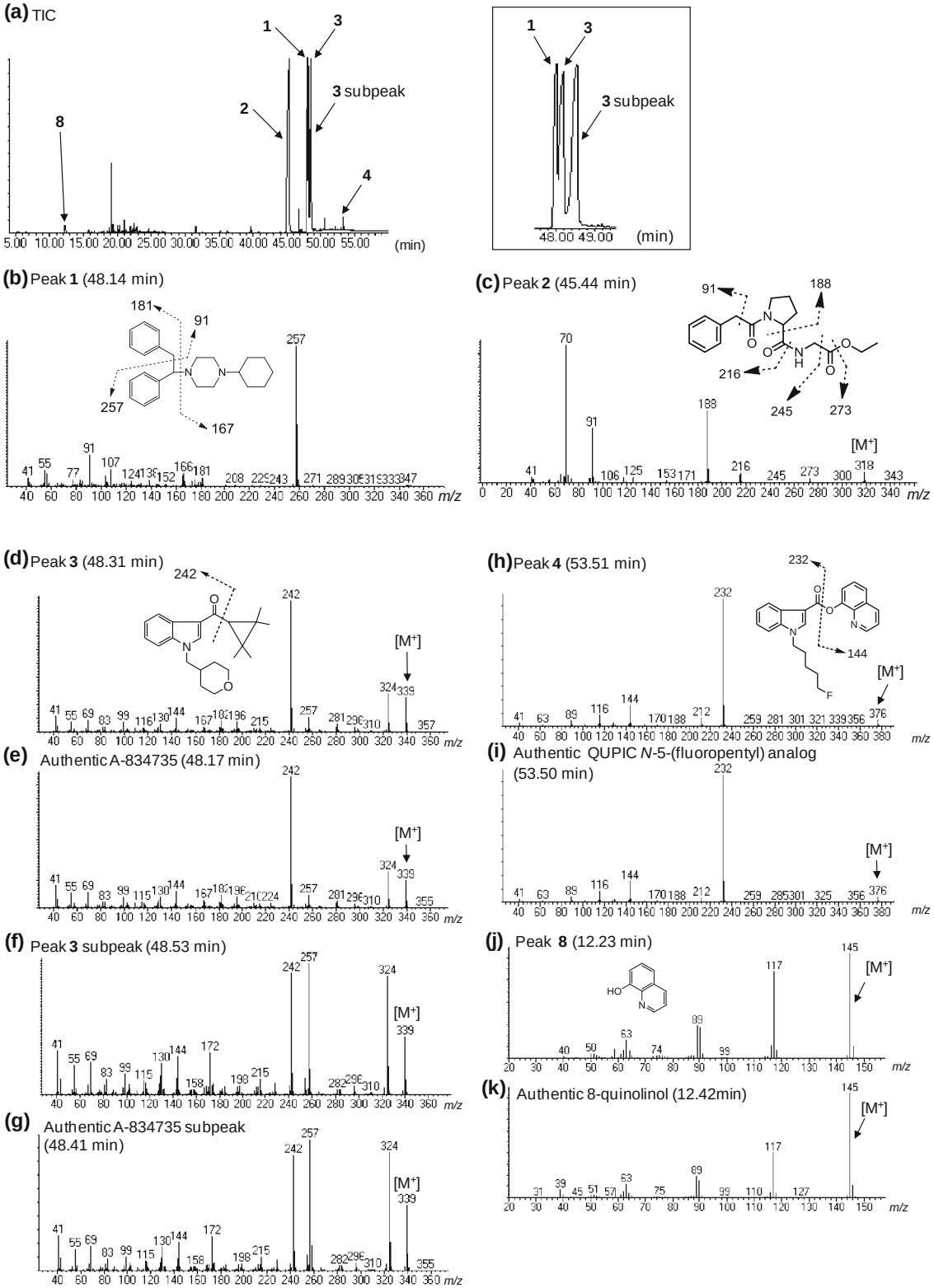

Fig. 3 Gas chromatography−mass spectrometry (GC−MS) analysis of product A. TIC (**a**) and electron ionization (EI) mass spectra of peaks **1** (**b**), **2** (**c**), **3** (**d**, **f**), **4** (**h**), **8** (**j**), authentic A-834735 (**e**), authentic A-834735 subpeak (**g**), authentic QUPIC *N*-(5-fluoropentyl) analog (**i**), and authentic 8-quinolinol (**k**)

9201 instrument with JAIGEL GS-310 columns (JAI) and 0.5 % triethylamine (TEA) in methanol as eluent. Optical rotations were obtained with a digital polarimeter (DIP-370, JASCO, Tokyo, Japan).

The 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), double quantum filtered correlation spectroscopy (DQF-COSY), and rotating-frame nuclear Overhauser effect (ROE) spectra.

Isolation of compounds **1** and **5**

A white solid precipitate in a 5-ml sample of colorless liquid (product D) was filtered, and compound **1** was obtained as a white solid (6 mg). A 5-ml sample of liquid product B was evaporated to dryness, and then the extract was dissolved in 0.5 % TEA in methanol and purified by recycle GPLC (eluent: 0.5 % TEA in methanol) to give compound **5** (88 mg) as a pale yellow oil.

Isolation of compound **6**

A 5-ml sample of liquid product C was 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 thick; Merck, Darmstadt, Germany), which was then developed using hexane/acetone/TEA (10:30:1, v/v). A portion of the silica gel containing a target compound in the TLC plate was detected under ultraviolet (UV) light (254 nm). It was then scraped from the plate and eluted with chloroform to obtain fraction 1, which was further purified by repeated preparative TLC with hexane/acetone/TEA (10:30:1, v/v). Finally, compound **6** (1 mg) was obtained as a white solid.

Results and discussion

Identification of unknown peaks **1**–**4**

Four unknown peaks (**1**–**4**) were detected along with a known 8-quinolinol (**8**) in the LC–MS and GC–MS chromatograms for product A, as shown in Figs. 2a–c and 3a. In the LC–MS analysis, the unknown peak **1** at 24.7 min showed a protonated molecular ion $[M + H]^+$ signal at *m/z* 349 (Fig. 2d). The other unknown peak **2** at 22.7 min showed major ion peaks at *m/z* 319 ($[M + H]^+$) and *m/z* 317 ($[M - H]^-$) in the positive and negative modes, respectively (Fig. 2e). The UV spectra of both compounds showed the same absorbance maximum at 258 nm (Fig. 2d, e).

The LC–MS and GC–MS analyses revealed that products D and E mainly contained compounds **1** and **2**, respectively. Therefore, compound **1** was isolated from product D and compound **2** was directly analyzed without isolation from product E. The accurate mass spectra of compounds **1** and **2** were measured by LC–TOF–MS in the positive mode. The ion peaks observed at *m/z* 349.2643 and 319.1653 suggested that the protonated molecular formulae of compounds **1** and **2** were $C_{24}H_{33}N_2$ (calcd. 349.2644) and $C_{17}H_{23}N_2O_4$ (calcd. 319.1658), respectively.

The structure of compound **1** was elucidated by NMR analysis (Table 1; Fig. 4a). The ^{1}H and ^{13}C NMR spectra of compound **1** suggested the existence of 32 protons and 24 carbons, as shown in Table 1. The observed DQF-COSY, HMQC, HMBC, and one-dimensional (1D) ROE spectra of compound **1** suggested the presence of a 1,2-diphenylethyl moiety, a piperazine group, and a cyclohexane group as shown in Fig. 4a and Table 1. The connections of the three moieties were revealed by the HMBC

Table 1 Nuclear magnetic resonance (NMR) data for compound **1**

No.	Compound **1** in $CDCl_3$[a]	
	^{13}C	^{1}H
2	44.5	4.14, 1H, tdd, J = 12.7, 9.6, 3.0 Hz
		3.38, 1H, brd, J = 12.7 Hz
3	47.2	3.95, 1H, tdd, J = 12.7, 9.6, 3.0 Hz
		3.22, 1H, brd, J = 12.7 Hz
5	48.1	4.22, 1H, m, overlapped
		4.04, 1H, brd, J = 12.7 Hz
6	44.5	4.49, 1H, tdd, J = 12.7, 9.6, 3.0 Hz
		3.55, 1H, brd, J = 12.7 Hz
1′	74.4	4.20, 1H, m
2′	37.4	3.77, 1H, dd, J = 13.4, 4.5 Hz
		3.51, 1H, dd, J = 13.4, 10.7 Hz
1′-1	131.3	–
1′-2/1′-6	129.4	7.50, 2H, brs
1′-3/1′-5	129.8	7.36, 2H, m, overlapped
1′-4	130.5	7.36, 1H, m, overlapped
2′-1	134.5	–
2′-2/2′-6	129.1	6.92, 2H, dd, J = 7.6, 2.4 Hz
2′-3/2′-5	128.8	7.13, 2H, m, overlapped
2′-4	127.4	7.14, 1H, m, overlapped
1″	64.5	3.11, 1H, tq, J = 12.4, 3.4 Hz
2″/6″	26.7	2.26, 2H, brd, J = 12.4 Hz
		1.52, 2H, m
3″/5″	24.8	1.94, 2H, brd, J = 12.4 Hz
		1.29, 2H, brq, J = 12.4 Hz
4″	24.7	1.70, 1H, brd, J = 12.4 Hz
		1.14, 1H, qt, J = 12.4, 3.4 Hz

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

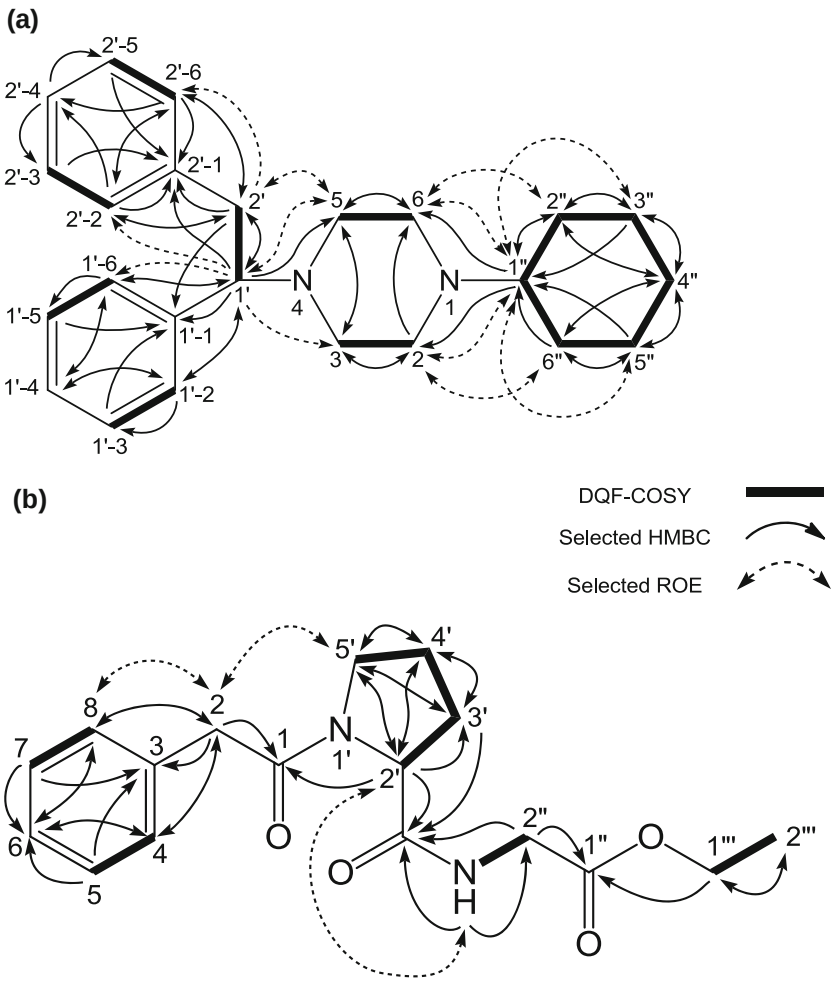

Fig. 4 Double quantum filtered correlation spectroscopy (DQF-COSY), selected heteronuclear multiple-bond correlation (HMBC), and selected rotating-frame nuclear Overhauser effect (ROE) correlations of compound **1** (**a**) and compound **2** (**b**)

correlations between the piperazine protons (H-3 and H-5) and the 1,2-diphenylethyl carbon (C-1′), and between the other piperazine protons (H-2 and H-6) and the cyclohexyl carbon (C-1″) (Fig. 4a). In addition, the major fragment ions at *m*/*z* 181, 167, 91, and 257 of peak **1** in the GC−MS spectra suggested the presence of 1,2-diphenylethyl and 1-cyclohexylpiperazine moieties (Fig. 3b). Therefore, the structure of **1** was determined as 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45, synonym: IC-6), as shown in Fig. 1. MT-45 (**1**) has been reported to have affinities for the μ and κ opioid receptors and a potent analgesic activity similar to that of morphine [11, 12]. Natsuka et al. [12] have also reported that the analgesic activity of (*S*)-(+)-MT-45 in mice was 1.6- and 26.4-fold more potent than those of the racemate and (*R*)-(−)-MT-45, respectively. No optical rotation of compound **1**, which was isolated from product D, was observed (*c* 0.5, methanol), revealing that compound **1** exists as racemic MT-45. This is the first case in which MT-45 has been detected as a designer drug in illegal products.

The ^{1}H and ^{13}C NMR spectra of compound **2** suggested the existence of 22 protons and 17 carbons (Table 2). The 1D NMR spectra of compound **2** suggested the presence of two carbonyl amide carbons [δ_c 171.5 (C-1), δ_c 171.4 (2′-CONH)] and a carbonyl ester carbon [δ_c 169.6 (C-1″)] as shown in Table 2. The 2D NMR spectra of compound **2** indicated the presence of three moieties; namely, a phenylacetyl group, a prolylglycine group, and an ethoxy group (Fig. 4b). In addition, the connections of the three moieties were revealed by two HMBC correlations between the prolyl proton (H-2′) and the carbonyl amide carbon (C-1), and between the ethyl proton (H-1‴) and the carbonyl ester carbon (C-1″) as shown in Fig. 4b. In addition, the 1D ROE correlations (Fig. 4b) and the major fragment ions at *m*/*z* 91, 188, 216, 245, and 273 of peak **2** in GC−MS spectra (Fig. 3c) supported the existence of the three moieties and their connections. Therefore, the structure of compound **2** was determined as ethyl 2-[1-(2-phenylacetyl)pyrrolidine-2-carboxamido]acetate (synonym IUPAC: *N*-phenylacetyl-prolylglycine ethyl ester) and called Noopept (synonym: GVS-111), as shown in Fig. 1. Noopept (**2**) was reported by a Russian group as a synthetic *N*-phenylacetyl dipeptide and having nootropic (cognitive enhancer) activity [13]. Compound **2** showed optical

Table 2 NMR data for compound **2**

No.	Compound **2** in $CDCl_3$[a]	
	^{13}C	^{1}H
1	171.5	–
2	41.9	3.70, 2H, s
3	134.2	–
4/8	129.0	7.26, 2H, d, $J = 6.9$ Hz, overlapped
5/7	128.7	7.31, 1H, t, $J = 7.6$ Hz, overlapped
		7.30, 1H, t, $J = 7.6$ Hz, overlapped
6	127.0	7.24, 1H, t, $J = 6.8$ Hz, overlapped
1′	–	–
2′	59.7	4.65, 1H, d, $J = 7.2$ Hz
3′	27.2	2.40, 1H, m
		1.83, 1H, m
4′	25.0	2.07, 1H, m
		1.94, 1H, m
5′	47.7	3.56, 1H, td, $J = 9.9$, 2.8 Hz
		3.45, 1H, td, $J = 9.6$, 7.2 Hz
1″	169.6	–
2″	41.4	3.95, 2H, dd, $J = 12.7$, 5.8 Hz
1‴	61.3	4.16, 2H, qd, $J = 7.2$, 2.4 Hz
2‴	14.1	1.24, 3H, t, $J = 7.2$ Hz
CONH	171.4	–
CONH	–	7.44, 1H, brs

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

activity $\{[\alpha]_D^{25}$ −115.0° (*c* 0.4, chloroform)} and a value similar to that of authentic Noopept $\{[\alpha]_D^{25}$ −120.0° (*c* 0.4, chloroform)} [13]. Thus, compound **2** was identified as the *S*-(−)-form, the same form as that of authentic Noopept (*N*-phenylacetyl-L-prolylglycine ethyl ester) [13]. Although Noopept is sold as a dietary supplement on the Internet, this is the first detection of Noopept from illegal products.

The remaining unknown peaks **3** and **4** were identified as two synthetic cannabinoids, A-834735 (Figs. 2f, 3d, f) and QUPIC *N*-5-(fluoropentyl) analog (Figs. 2h, 3h), by direct comparison of the data with those of the purchased authentic compounds, respectively (Figs. 2g, i, 3e, g, i). In addition, 8-quinolinol (**8**) was detected as the synthetic component of compound **4** in the same manner in which compound **8** was detected with a known cannabimimetic quinolynyl carboxylate QUPIC (PB-22) in illegal products (Figs. 2j, k, 3j, k) [9]. A-834735 (**3**) was reported to act as an agonist at both cannabinoid CB_1 and CB_2 receptors (K_i values for CB_1 and CB_2 of 4.6 and 0.31 nM, respectively) [14]. Compounds **3** and **4** were detected as newly distributed designer drugs in Japan.

Identification of unknown peaks **5** and **6**

Unknown peak **5** was detected together with known cathinone derivative 4-methylbuphedrone (**7**) (Fig. 1) in the GC−MS and LC−MS chromatograms of product B

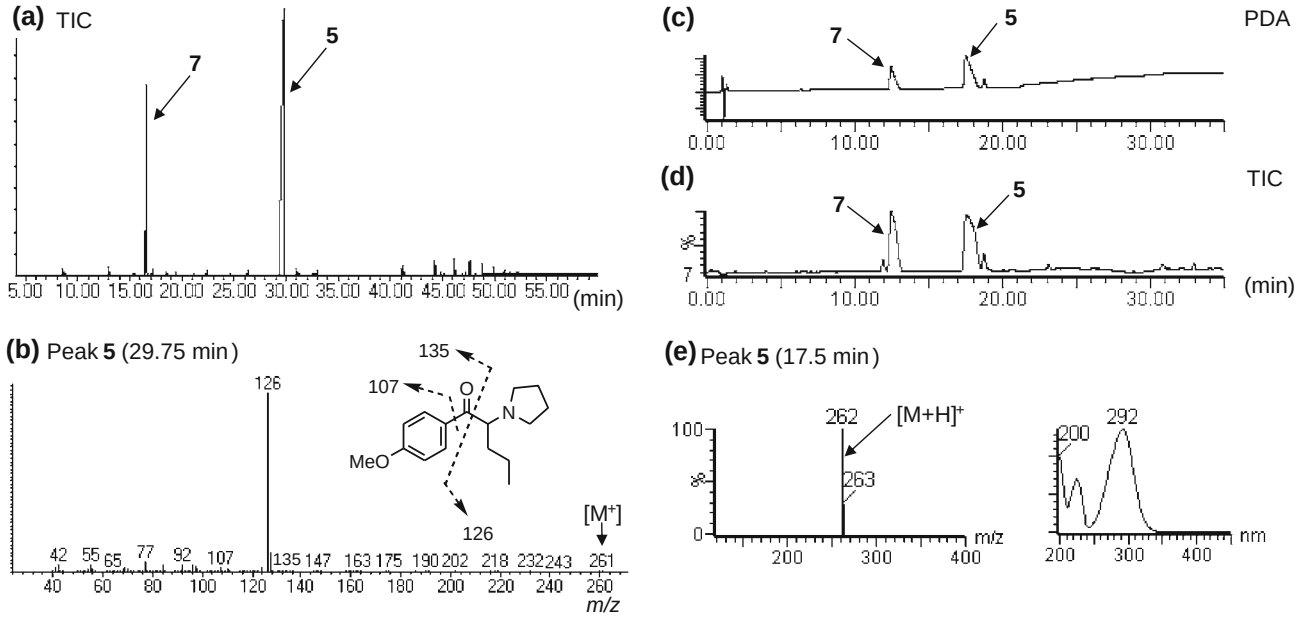

Fig. 5 GC−MS and LC−MS analyses of product B. TIC (**a**) and EI mass spectra of peak **5** (**b**) obtained by GC−MS analysis. LC−UV−PDA chromatogram (**c**) and TIC (**d**) using elution program 2 obtained by LC−MS. UV and ESI mass spectra of peak **5** (**e**)

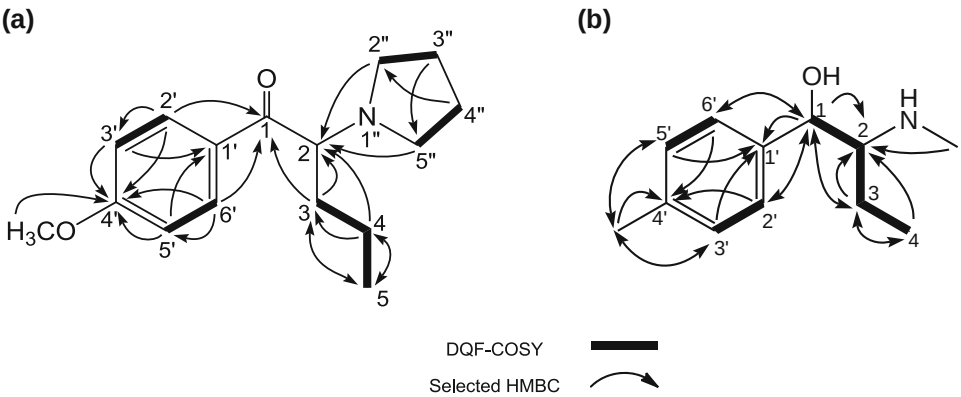

Fig. 6 DQF-COSY and selected HMBC correlations of compound **5** (**a**) and compound **6** (**b**)

Table 3 NMR data for compound **5**

No.	Compound **5** in pyridine-d_5[a]	
	^{13}C	^{1}H
1	197.2	–
2	66.7	4.88, 1H, brs
3	32.6	2.05, 2H, m
4	19.8	1.36, 2H, m
5	14.2	0.77, 3H, t, $J = 7.4$ Hz
1′	129.9	–
2′/6′	131.7	8.35, 2H, d, $J = 8.7$ Hz
3′/5′	114.6	7.06, 2H, d, $J = 8.7$ Hz
4′	164.6	–
2″/5″	51.3	3.23, 2H, brs
		3.03, 2H, brs
3″/4″	23.9	1.77, 4H, m
4′-MeO	55.6	3.72, 3H, s

[a] Recorded at 800 MHz (^{1}H) and 200 MHz (^{13}C), respectively; data in δ ppm

(Fig. 5a, c, d). The proposed fragment pattern and the presumed structure of peak **5** obtained by GC−MS analysis are shown in Fig. 5b. The LC−MS data revealed that peak **5** showed an absorbance maximum at 292 nm in the UV spectrum, and a protonated ion signal at *m/z* 262 ($[M + H]^+$) as shown in Fig. 5e. After the isolation of compound **5**, the accurate mass spectrum obtained by LC−QTOF−MS gave an ion peak at *m/z* 262.1795, suggesting that the protonated molecular formula of compound **5** was $C_{16}H_{24}NO_2$ (calcd. 262.1807). The observed DQF-COSY and HMBC spectra of compound **5** suggested the presence of 2-(pyrrolidin-1-yl)pentan-1-one and a methoxyphenyl moiety as shown in Fig. 6a and Table 3. The fragment ions at *m/z* 107, 126, and 135 of compound **5** in the GC−MS spectrum supported the presence of these moieties (Fig. 5b). The connection of the two moieties was revealed by HMBC correlations from the phenyl protons (H-2′/H-6′) to the carbonyl carbon (C-1), as shown in Fig. 6a. Therefore, the structure of compound **5** was identified as 4-methoxy-α-pyrrolidinovalerophenone (4-methoxy-α-PVP, Fig. 1). No optical rotation was observed for the isolated compound **5** (*c* 0.3, methanol), revealing that compound **5** was present as a racemate. In addition, compound **7**, which was isolated with compound **5** from the same product B (data not shown), also showed no optical rotation (*c* 0.5, methanol). Hence, compound **7** also exists as a racemate.

In the GC−MS and LC−MS chromatograms of product C, unknown peak **6** was detected along with the peak of 4-methylbuphedrone (**7**) (Fig. 7a, d, e). The fragment pattern of compound **6** was very similar to that of 4-methylbuphedrone (**7**) by GC−MS analysis (Fig. 7b, c). However, the LC−MS data revealed that peak **6** showed a protonated ion signal at *m/z* 194 ($[M + H]^+$) (Fig. 7f) and the UV spectra of peaks **6** and **7** showed quite different patterns (Fig. 7f, g). After the isolation of compound **6**, the accurate mass spectrum obtained by LC−QTOF−MS showed an ion peak at *m/z* 194.1540, suggesting that the protonated molecular formula of compound **6** was $C_{12}H_{20}NO$ (calcd. 194.1545). The ^{13}C NMR spectra of compound **6** suggested the presence of a tertiary hydroxyl carbon (δ_C 71.6) instead of the carbonyl group (δ_C 196.0, data not shown) in 4-methylbuphedrone (**7**). In addition, on the basis of the observed NMR spectra as shown in Fig. 6b and Table 4, the structure of compound **6** was deduced as 4-methylbuphedrine (Fig. 1), which is a reduced form of 4-methylbuphedrone (**7**). The relative configuration of compound **6** was presumed on the basis of data for buphedrine [2-(*N*-methylamino)-1-phenyl-1-butanol], which is a reduced form of buphedrone, published by Fraser et al. [15]; they reported that the anti-form of buphedrine has a smaller *J* value (δ_H 4.83, d, $J = 4.0$ Hz) for the H-1 position (C*H*OH) than that of the syn-form (δ_H 4.30, d, $J = 7.8$ Hz); these *J* values are consistent with expectations based on Karplus relationships [15]. Hence, the relative configuration of compound **6** with a *J* value of 3.8 Hz (δ_H 4.82, d, H-1), as shown in Table 4, was assigned as the anti-form (1*R**, 2*R**).

Although compounds **5** and **6** are analogs of the known cathinone derivatives α-PVP and 4-methylbuphedrone,

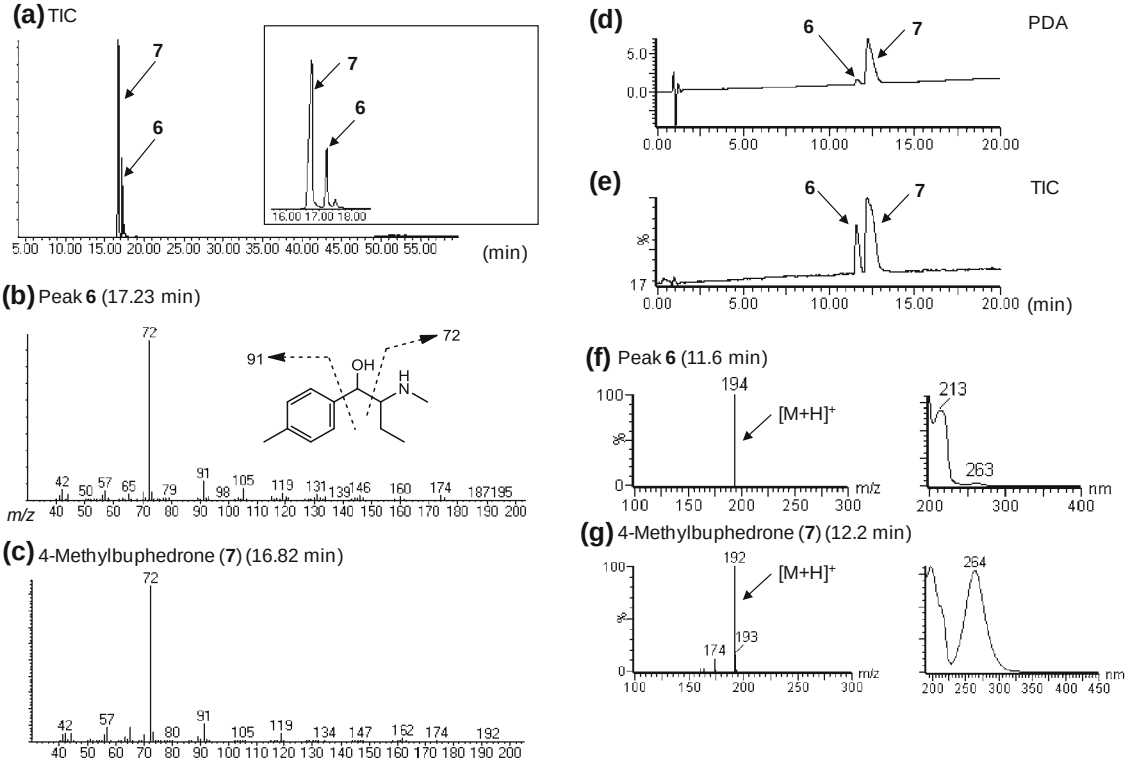

Fig. 7 GC−MS and LC−MS analyses of product C. TIC (**a**) and EI mass spectra of peaks **6** (**b**) and **7** (**c**) obtained by GC−MS. LC−UV−PDA chromatogram (**d**) and TIC (**e**) using elution program 2 obtained by LC−MS. UV and ESI mass spectra of peaks **6** (**f**) and **7** (**g**)

Table 4 NMR data for compound **6**

No.	Compound **6** in $CDCl_3$[a]	
	^{13}C	^{1}H
1	71.6	4.82, 1H, d, $J = 3.8$ Hz
2	66.9	2.54, 1H, m
3	20.9	1.30 and 1.20, each 1H, m
4	10.9	0.82, 3H, t, $J = 7.6$ Hz
1′	138.2	–
2′/6′	126.0	7.20, 2H, d, $J = 7.9$ Hz
3′/5′	128.8	7.12, 2H, d, $J = 7.9$ Hz
4′	136.6	–
N-Me	34.4	2.51, 3H, s
4′-Me	21.1	2.32, 3H, s

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

respectively, no pharmacological information for compounds **5** and **6** is available.

Conclusions

We detected two new-type designer drugs, piperazine derivative MT-45 (I-C6, **1**) and synthetic peptide Noopept (GVS-111, **2**), along with synthetic cannabinoids A-834735 (**3**) and QUPIC *N*-(5-fluoropentyl) analog (synonym: 5-fluoro-PB-22, **4**) in illegal products distributed in Japan. We also detected cathinone derivative 4-methoxy-α-PVP (**5**) and phenethylamine derivative 4-methylbuphedrine (**6**) in the products. Considering the results of this study, it is obvious that new types of designer drugs emerge rapidly, and their combinations in illegal products can be expected to become more and more diverse. The provision of timely and objective information on new designer drugs and the current trends are thus essential to prevent abuse of these drugs.

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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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