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ORIGINAL ARTICLE

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

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Abstract Two new cannabimimetic indazole derivatives, *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA, **1**) and *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA, **2**), have been identified as designer drugs in illegal products. These identifications were based on liquid chromatography–mass spectrometry, gas chromatography–mass spectrometry, high-resolution mass spectrometry, and nuclear magnetic resonance spectroscopy. Because there have been neither chemical nor pharmacological data about compound **1** until now, this is the first report of this compound. Compound **2** was reported as a potent cannabinoid CB_1 receptor modulator when synthesized by Pfizer in 2009; but this is the first report of its detection in illegal products.

Keywords *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA · *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) · Synthetic cannabinoid · Indazole derivative · Designer drug · Illegal product

Introduction

Synthetic cannabinoids have become a major class of abused drugs in Japan as well as in European countries [1–3]. Since the first identification of psychotropic synthetic cannabinoids in illegal products in 2009 [4–7], a number of new synthetic cannabinoids have been detected worldwide [3, 8–15]. Our ongoing survey of designer drugs in Japan has revealed that the synthetic cannabinoids detected so far belong to nine groups: cyclohexylphenols [such as cannabicyclohexanol (CCH) and CP-47,497], naphthoylindoles (such as JWH-018 and JWH-073), phenylacetylindoles (such as JWH-250 and JWH-203), benzoylindoles (such as AM-694 and RCS-4), naphthoylnaphthalenes (such as CB-13), pyridinoylindoles (such as 5-fluoropentyl-3-pyridinoylindole), naphthoylpyrroles (such as JWH-307 and JWH-030), cyclopropylindoles [such as UR-144 and XLR11 (synonym: 5FUR-144)], and adamantylindoles (such as APICA, APINACA, and AB-001) [1, 14, 16]. In addition, URB-754 (6-methyl-2-[(4-methylphenyl)amino]-1-benzoxazin-4-one) was detected as a new type of designer drug together with several synthetic cannabinoids in illegal products in March 2012 [16]. A total of 23 synthetic cannabinoids have been regulated as Designated Substances (Shitei-Yakubutsu) under the Pharmaceutical Affairs Law of Japan as of July 2012. Furthermore, among them, 2 synthetic cannabinoids, CCH and JWH-018, have been much more strictly regulated as new narcotic substances in Japan since August 2012. In addition, 10 synthetic cannabinoids [UR-144, XLR11, MAM-2201, JWH398, JWH-182, JWH-007, JWH-122 *N*-(4-pentenyl) analog, AM-2232, AM-679, and RCS-4 *o*-isomer] will be newly listed as designated substances beginning in October 2012. In our previous article [14], we reported the identification of an adamantyl indazole, APINACA, as a synthetic cannabinoid in an illegal product. In this article, we report the identification of 2 novel synthetic cannabinoids, *N*-(1-amino-3-methyl-1-oxobutan-

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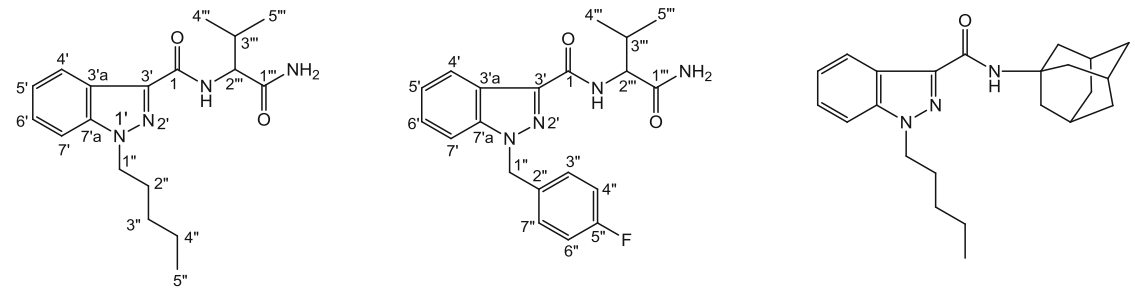

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA, **1**)

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA, **2**)

N-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA)

Fig. 1 Structures of the detected compounds (**1**, **2**) and a related compound (APINACA)

2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA, **1**) and *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA, **2**), as designer drugs in illegal products. Their structures are shown in Fig. 1.

Materials and methods

Samples for analysis

Three products were purchased via the Internet in July 2012 in Japan; one as a chemical and two as herbal products. Each of the herbal products (A and B) contained about 3 g of mixed dried plants. The chemical product (C), which was called "Fragrance Powder," contained about 400 mg of pale yellow powder.

Chemicals and reagents

As solvents for nuclear magnetic resonance (NMR) spectroscopy, deuterated dimethyl sulfoxide (DMSO-d_6, 99.96 %), CD_3OD (99.96 %), and CD_3OH (99.8 %) were purchased from the ISOTEC division of Sigma-Aldrich (St. Louis, MO, USA). All other common chemicals and solvents used were of analytical reagent grade or HPLC grade.

Preparation of sample solution

For qualitative analyses, 10 mg of each herbal product was crushed into powder and extracted with 1 ml of methanol under ultrasonication for 10 min. A 2-mg portion of the chemical product was used for extraction with 1 ml of methanol under ultrasonication for 10 min. After centrifugation (3000 rpm, 5 min) of the extract, the supernatant solution was passed through a centrifugal filter (Ultrafree-MC, 0.45 μm filter unit; Millipore, Bedford, MA, USA) to give sample solution. 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 according to our previous report [14]. The accurate mass spectrum of the target compound was measured using a direct analysis in real time (DART) ion source coupled to a time-of-flight (TOF) mass spectrometer (AccuTOF JMS-100LC; JEOL, Tokyo, Japan) operated in the positive ion mode. The measurement conditions were the same as reported previously [14].

The NMR spectra were obtained on ECA-600 and ECA-800 spectrometers (JEOL). 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 compound **1**

A 30-mg sample of the pale yellow powder (product C) was extracted with 10 ml of chloroform by ultrasonication for 10 min. The extractions were repeated three times, and the supernatant fractions were combined and evaporated to dryness. Finally, compound **1** (15 mg) was obtained as a white solid.

Isolation of compound **2**

A 3-g sample of the herbal product B was extracted with 250 ml of chloroform by ultrasonication for 30 min. The

extractions were repeated three times, and the supernatant fractions were combined and evaporated to dryness. The extract was placed on a preparative thin-layer chromatography (TLC) plate (Silica Gel 60, 20 × 20 cm, 2 mm; Merck, Darmstadt, Germany), and then developed using hexane/ethyl acetate (1:2, v/v) two times. The portion of silica gel containing the target compound was detected by UV 254 nm. It was scraped from the plate and eluted with chloroform to obtain compound **2** (83 mg) as a white solid.

Results and discussion

Identification of unknown peaks 1 and 2

Two unknown peaks **1** and **2** were detected in the GC–MS and LC–MS chromatograms of product A as shown in Figs. 2a–c and 3a. The unknown peak **1** in the LC–MS chromatogram detected at 5.9 min showed an absorbance maximum at 303 nm in the UV spectrum, and major ion peaks at *m/z* 331 ($[M+H]^+$) and *m/z* 329 ($[M-H]^-$) in the positive and negative modes, respectively (Fig. 2d–f). The other unknown peak **2** detected at 5.5 min in the LC–MS chromatogram exhibited an absorbance maximum at 301 nm in the UV spectrum, and major ion peaks at *m/z* 369 ($[M+H]^+$) and *m/z* 367 ($[M-H]^-$) (Fig. 2g–i). In the GC–MS chromatogram, peaks **1** and **2** at 47.82 and 50.09 min showed putative molecular ion signals at *m/z* 330 (Fig. 3b) and *m/z* 368 (Fig. 3c), respectively.

The HPLC analyses revealed that products C and B mainly contained compounds **1** and **2**, respectively. Therefore, these compounds were isolated from the corresponding products. After isolation, the accurate mass spectra were measured by DART–TOF–MS in the positive mode. The observed ion peaks at *m/z* 331.2151 and 369.1704 suggested that the protonated molecular formulas of compounds **1** and **2** were $C_{18}H_{27}N_4O_2$ (calcd. 331.2134) and $C_{20}H_{22}FN_4O_2$ (calcd. 369.1727), respectively.

The structure of compound **1** was elucidated by NMR analysis (Table 1; Fig. 4). The ^{1}H and ^{13}C NMR spectra of compound **1** suggested 26 protons and 18 carbons as shown in Table 1. The NMR spectra of this compound suggested the presence of two amide carbonyl groups [δ_C 161.3, δ_H 7.68 (1-N<u>H</u>) and δ_C 172.7, δ_H 7.66 and 7.23 (1‴-N<u>H</u>$_2$)]. The fragment ions at *m/z* 215 and 286 of peak **1** by GC–MS analysis (Fig. 3b) and the observed DQF-COSY, HMQC, HMBC, and 1D-ROE spectra of compound **1** suggested the presence of 1-pentyl-1*H*-indazole and *N*-(3-methyl-1-butanamide-2-yl)carboxyamide moieties, as shown in Fig. 4a and Table 1. The key connections of the two moieties were revealed by the HMBC correlations (Fig. 4a). Namely, the HMBC correlations from the amide proton (1-CON<u>H</u>) to the carbon atom at the 3′-positon of the indazole suggested that the carboxyamide carbon (C-1, δ_C 161.3) in the *N*-(3-methyl-1-butanamide-2-yl)carboxyamide moiety was attached to the carbon at the 3′-position (δ_C 136.3) of the 1-pentyl-1*H*-indazole moiety (Fig. 4a). In addition, the ^{15}N HMBC spectrum was measured and the

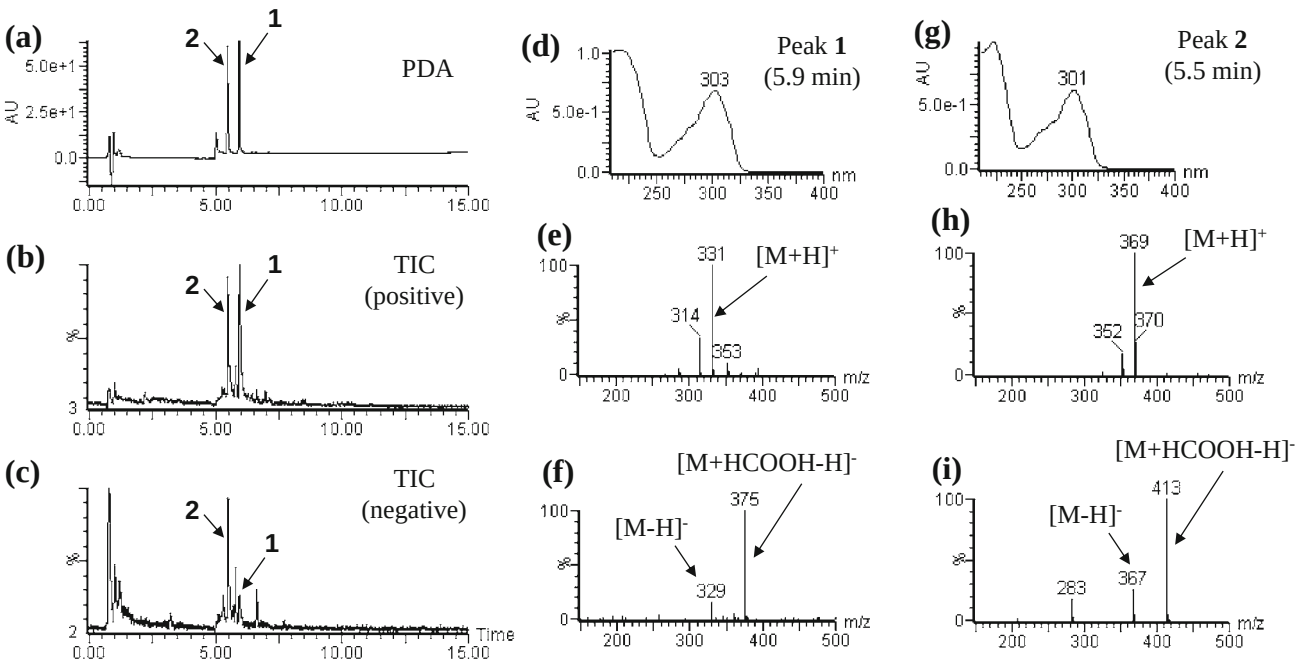

Fig. 2 HPLC-UV (**a**) and total ion chromatograms (**b**, **c**) for the extract of the product A. UV and ESI mass spectra of peaks **1** (**d**–**f**) and **2** (**g**–**i**) in both positive and negative modes are shown

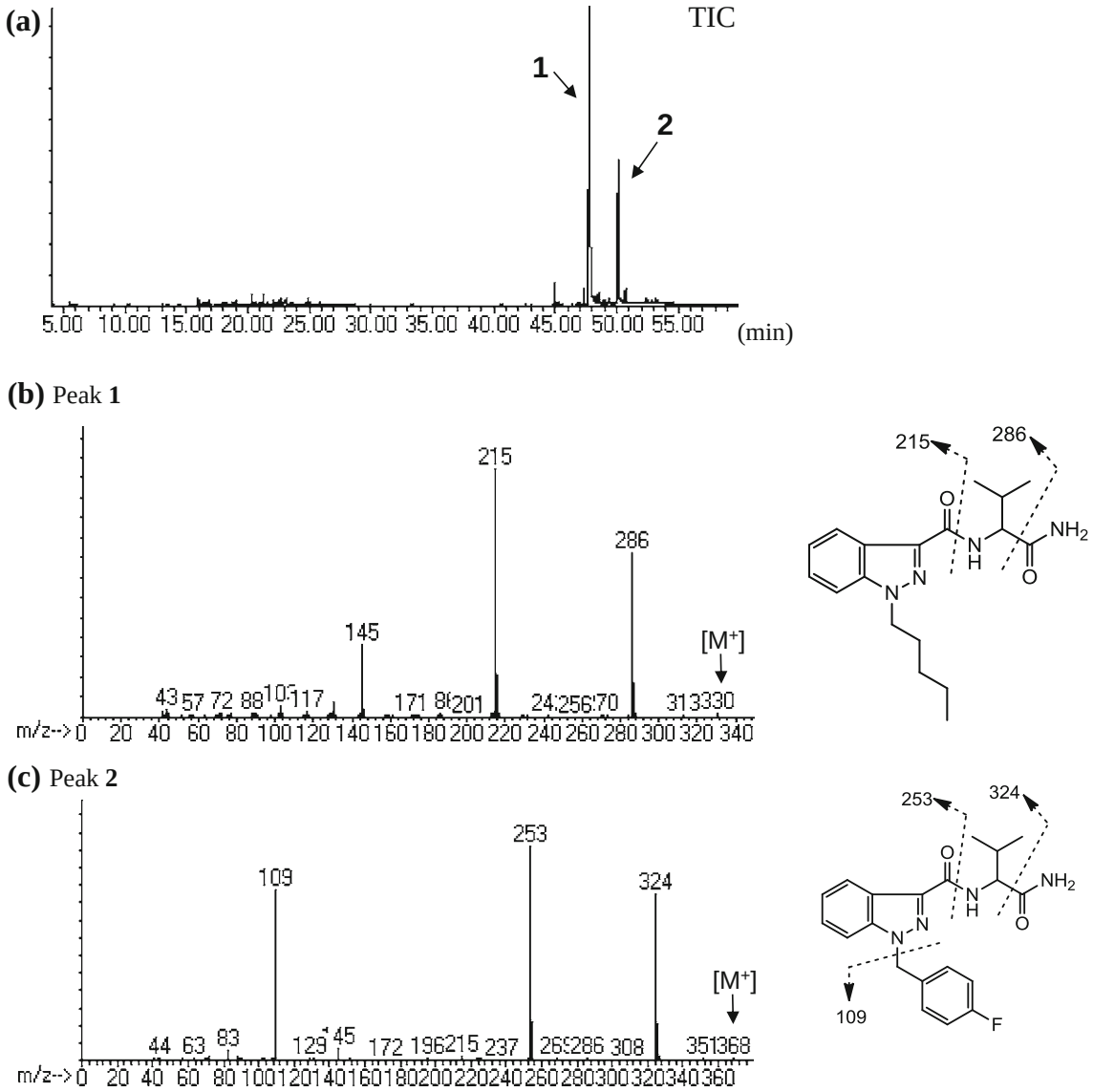

Fig. 3 GC–MS analysis of the extract of product A. The total ion chromatogram (TIC) (**a**) and EI mass spectra of the peaks detected at 47.82 min (**b**, compound **1**) and 50.09 min (**c**, compound **2**) are shown

observed correlations as shown in Fig. 4b strongly support the existence of 1-pentyl-1*H*-indazole and butanamide moieties.

On the basis of mass spectral and NMR data as shown above, the structure of compound **1** was finally determined as *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide and we named it AB-PINACA (Fig. 1). This is the first report in which compound **1** has been detected in an illegal product.

Compound **1** is a novel cannabimimetic substance and its chemical and pharmacological data have not been reported. However, an analog of compound **1**, in which the CN group was substituted for the terminal methyl of the pentyl moiety (position 5″ in Fig. 4), was synthesized as a cannabinoid CB_1 receptor modulator (*S*-form: K_i = 78.4 nM) [17]. Therefore, it is assumed that compound **1** may have a similar cannabimimetic activity.

The ^{1}H and ^{13}C NMR spectra of compound **2** suggested 21 protons and 20 carbons as shown in Table 2. The chemical shifts of compound **2**, with the exception of the pentyl moiety, were very similar to those of compound **1**, as shown in Tables 1 and 2. The observed DQF-COSY, HMQC, HMBC, ^{15}N HMBC, and 1D-ROE correlations of compound **2** strongly suggested the presence of the *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1*H*-indazole-3-carboxamide moiety (IUPAC: *N*-(3-methyl-1-butanamide-2-yl)-1*H*-indazole-3-carboxamide moiety) (Fig. 5a, b; Table 2). Furthermore, the ^{1}H NMR, ^{13}C NMR, and 2D-NMR

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

No.	Compound **1** in DMSO-d_6[a]		
	^{13}C	^{1}H	HMBC[b]
1	161.3	–	–
3′	136.3	–	–
3′a	121.9	–	–
4′	121.7	8.15, 1H, d-like, $J = 7.9$ Hz	3′, 3′a, 5′, 6′, 7′a
5′	122.5	7.27, 1H, ddd, $J = 7.9$, 6.9, 1.0 Hz	3′a, 6′, 7′
6′	126.6	7.45, 1H, ddd, $J = 7.9$, 6.9, 1.0 Hz	4′, 7′a
7′	110.5	7.77, 1H, d, $J = 8.6$ Hz	3′a, 5′
7′a	140.6	–	–
1″	48.7	4.49, 2H, t, $J = 7.2$ Hz	7′a, 2″, 3″
2″	29.1	1.85, 2H, q, $J = 7.2$ Hz	1″, 3″, 4″
3″	28.3	1.23, 2H, m	1″, 2″, 4″, 5″
4″	21.7	1.29, 2H, m	3″, 5″
5″	13.9	0.82, 3H, t, $J = 7.2$ Hz	3″, 4″
1‴	172.7	–	–
2‴	56.7	4.40, 1H, dd, $J = 8.9$, 6.2 Hz	1, 1‴, 3‴, 4‴, 5‴
3‴	31.3	2.08, 1H, m	1‴, 2‴, 4‴, 5‴
4‴	19.4	0.93, 3H, d, $J = 6.9$ Hz	2‴, 3‴, 5‴
5‴	18.0	0.89, 3H, d, $J = 6.5$ Hz	2‴, 3‴, 4‴
1-CONH	–	7.68, 1H, d, $J = 8.6$ Hz	1, 3′, 1‴, 2‴, 3‴
1‴-CONH$_{2a}$	–	7.66, 1H, brs	1‴
1‴-CONH$_{2b}$	–	7.23, 1H, brs	1‴, 2‴

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

[b] $J = 8$ or 4 Hz; the proton signal correlated with the indicated carbons

spectra of the remaining $C_7H_6F_1$ unit suggested the existence of a *p*-fluorobenzyl moiety (position-1″ to 7″), as shown in Fig. 5a and Table 2. The connection of the remaining unit to the indazole group was revealed by the HMBC correlations between the benzyl methylene proton (H-1″) and the indazole carbon (C-7′a).

Unfortunately, the HMBC correlation from the carboxamide proton (1-CONH) to the indazole carbon (C-3′) was not observed for compound **2** (Fig. 5a). Therefore, the deuterium isotope effect of the NH amide proton on the ^{13}C chemical shift was measured to determine the connection between the 1-(4-fluorobenzyl)-1*H*-indazole moiety and the carboxamide (1-CONH) moiety. The ^{13}C NMR spectrum of compound **2**, measured in CD_3OH, was compared to that recorded in CD_3OD. The isotope shift values for the ^{13}C NMR signals of this compound are shown in Fig. 6. The first, second, and third largest deuterium shifts (0.15, 0.14, and 0.05 ppm) were observed at the C-2‴ and C-1‴

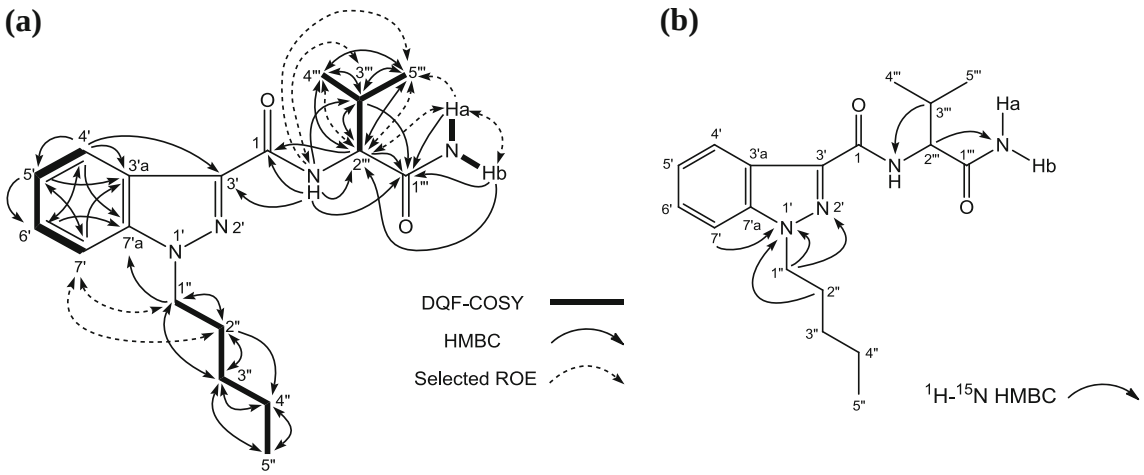

Fig. 4 DQF-COSY, selected HMBC, and selected ROE correlations (**a**) and ^{1}H–^{15}N HMBC correlations (**b**) for compound **1**

Table 2 NMR data for compound **2**

No.	Compound **2** in DMSO-d_6[a]		
	^{13}C	^{1}H	HMBC[b]
1	161.2	–	–
3′	137.1	–	–
3′a	122.3	–	–
4′	121.8	8.17, 1H, d-like, $J = 8.3$ Hz	3′, 3′a, 6′, 7′a
5′	122.8	7.28, 1H, t, $J = 7.2$ Hz	3′a, 6′, 7′
6′	127.0	7.45, 1H, ddd, $J = 8.3, 6.9, 0.7$ Hz	4′, 5′, 7′, 7′a
7′	110.6	7.78, 1H, d, $J = 8.6$ Hz	3′a, 5′
7′a	140.6	–	–
1″	51.6	5.77, 2H, s	7′a, 2″, 3″/7″
2″	133.0, $J = 2.9$ Hz	–	–
3″/7″	129.5, $J = 8.7$ Hz	7.32, 1H, dd, $J = 8.5, 2.1$ Hz, overlapped	1″, 4″/6″, 5″
		7.31, 1H, dd, $J = 8.5, 2.1$ Hz, overlapped	1″, 4″/6″, 5″
4″/6″	115.5, $J = 21.7$ Hz	7.16, 1H, d-like, $J = 7.9$ Hz, overlapped	2″, 5″
		7.15, 1H, d-like, $J = 7.9$ Hz, overlapped	2″, 5″
5″	161.6, d, $J = 242.8$ Hz	–	–
1‴	172.6	–	–
2‴	56.9	4.40, 1H, dd, $J = 8.9, 6.5$ Hz	1, 1‴, 3‴, 4‴, 5‴
3‴	31.2	2.09, 1H, m	1‴, 2‴, 4‴, 5‴
4‴	19.4	0.93, 3H, d, $J = 6.9$ Hz	2‴, 3‴, 5‴
5‴	18.1	0.89, 3H, d, $J = 6.5$ Hz	2‴, 3‴, 4‴
1-CONH	–	7.75, 1H, d, $J = 8.9$ Hz	1, 1‴, 2‴
1‴-CONH$_{2a}$	–	7.66, 1H, brs	1‴
1‴-CONH$_{2b}$	–	7.23, 1H, brs	1‴, 2‴

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

[b] $J = 8$ Hz; the proton signal correlated with the indicated carbons

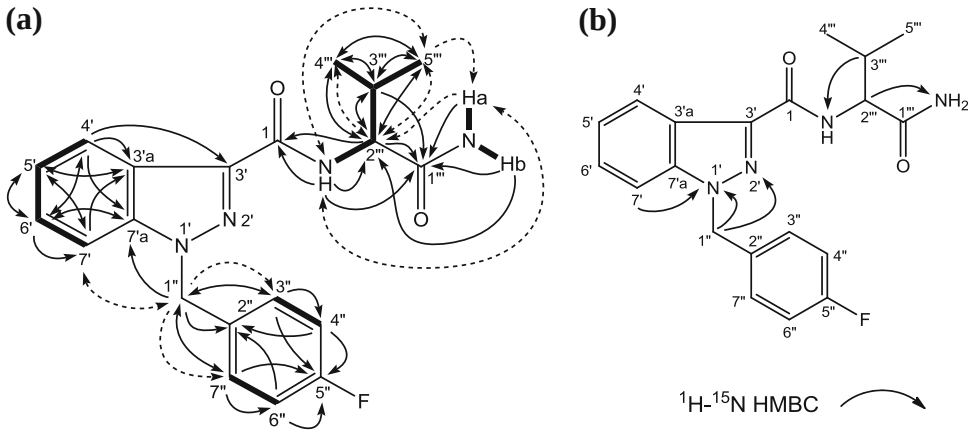

Fig. 5 DQF-COSY, selected HMBC, and selected ROE correlations (**a**) and ^{1}H–^{15}N HMBC correlations (**b**) for compound **2**

position of the 3-methyl-1-butanamide moiety and the C-1 position of the carboxamide moiety, respectively. The fourth largest shift of 0.03 ppm was attributed to the three-bond deuterium isotope effects of the NH amide proton on the indazole carbon (C-3′). These results strongly suggested that the 1-(4-fluorobenzyl)-1*H*-indazole moiety was connected at the 3′-position of the indazole to the carboxyamide (1-CONH). In addition, the major fragment ions at *m*/*z* 109, 253, and 324 by GC–MS analyses supported the presumed structure of compound **2** (Fig. 3c). Therefore, compound **2** was identified as *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (Fig. 1).

The *S*-form of compound **2** has been reported as a cannabimimetic substance having potent affinity for the cannabinoid CB_1 receptor ($K_i = 0.9$ nM) by Pfizer [18]. Its affinity was 10-fold greater than that of the CB_1 receptor agonist JWH-018 ($K_i = 9.0$ nM) [19]. Considering its general properties, this compound was renamed AB-FUBINACA (**2**) with the agreement of Pfizer. This is

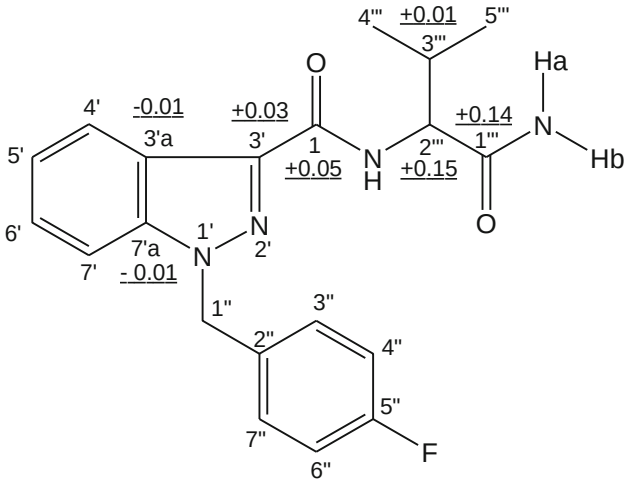

Fig. 6 Deuterium-induced isotope shifts of NH protons for the ^{13}C NMR signals of compound **2** in CD_3OD

the first case in which compound **2** has been detected in an illegal product.

Both compounds detected (compounds **1** and **2**) have a 1*H*-indazole-3-carboxamide moiety. Many indazole-carboxamide derivatives have been synthesized and reported to have binding affinity for the cannabinoid CB_1 receptor by Pfizer [17, 18]. Therefore, there is the worrisome possibility that analogs of compounds **1** and **2** will appear as new designer drugs on the illegal market.

Conclusions

In this study, two new cannabimimetic indazole derivatives, *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (AB-PINACA, **1**) and *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA **2**), have been identified as designer drugs in illegal products. Compound **1** is an absolutely novel compound, which has not been reported to date. Compound **2** has previously been reported to have a potent binding affinity for cannabinoid CB_1 receptor [18]. There is a recent trend that various synthetic cannabinoids are appearing on the illegal drug market shortly after their appearance in academic journals or patents. In fact, compound **2** (AB-FUBINACA) was first reported by Pfizer in a patent only in September 2009 [18], and then we have found it in an illegal herbal product in 2012 as shown in this study. Therefore, we have to continuously monitor newly distributed designer drugs to prevent drug abuse and serious health risks.

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