A new pyrazole-carboxamide type synthetic cannabinoid AB-CHFUPYCA [*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide] identified in illegal products

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Abstract A new pyrazole-carboxamide type synthetic cannabinoid, AB-CHFUPYCA (**1**), was detected in illegal herbal products by our ongoing survey in Japan. The structure of **1** was identified by gas chromatography–mass spectrometry (GC–MS), liquid chromatography–mass spectrometry (LC–MS), liquid chromatography–high-resolution-mass spectrometry (LC–HR-MS) and nuclear magnetic resonance (NMR) analyses. Compound **1** showed a molecular weight of 400, and accurate mass measurement using LC–HR-MS revealed its molecular formula to be $C_{22}H_{29}N_4O_2F$. The MS and NMR spectrometric data revealed that the structure of **1** was *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide. Compound **1**, which is a new type of synthetic cannabinoid, has a 3-(4-fluorophenyl)-1*H*-pyrazole group in place of a 1*H*-indazole group of AB-CHMINACA. To our knowledge, data on the chemistry and pharmacology of compound **1** have never been reported, and we therefore named compound **1** "AB-CHFUPYCA."

derivative · Synthetic cannabinoid · New psychoactive substance · Illegal product · Drug of abuse

Introduction

Synthetic cannabinoids have become a major group of new psychoactive substances (NPSs) both in Japan and worldwide. Since the first appearance of synthetic cannabinoids at the end of 2008, various types have continued to emerge on the illegal drug market [1, 2], as follows: cyclohexylphenols (e.g., cannabicyclohexanol) [3], indoles (e.g., JWH-018) [4], indazoles (e.g., APINACA) [5], benzimidazoles (e.g., FUBIMINA) [6], quinolinyl carboxylates (e.g., QUPIC: PB-22) [7] and carboxamide derivatives (e.g., AB-PINACA) [8], among others. Many types of synthetic cannabinoids are regulated in some countries in attempts to prevent the spread of their abuse. In Japan, a total of 858 synthetic cannabinoids were regulated as narcotics or designated substances as of April 2015. These synthetic cannabinoids contain 8 narcotics and 850 designated substances, including 759 substances that became controlled after the introduction of the generic scheduling for designating naphthoylindole-type synthetic cannabinoids [1].

Despite the various regulatory control measures, the appearance of new synthetic cannabinoids continues. In European countries, more than 30 new synthetic cannabinoids were reported as NPSs for the first time in 2014, monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [9]. Additionally, 2*H*-indazole isomers of synthetic cannabinoids were detected in illegal products purchased during the first half of the year in 2014 in Japan [10]. There is little pharmacological information about most of the detected synthetic

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cannabinoids. Several fatal cases resulting from carbox-amide derivatives of synthetic cannabinoids such as 5-flu-oro-AMB, AB-CHMINACA, 5-fluoro-ADB and MAB-CHMINACA were reported in 2015 in Japan [11–13]. It is thus of concern that further serious harm may be caused by synthetic cannabinoids, especially the carboxamide derivatives.
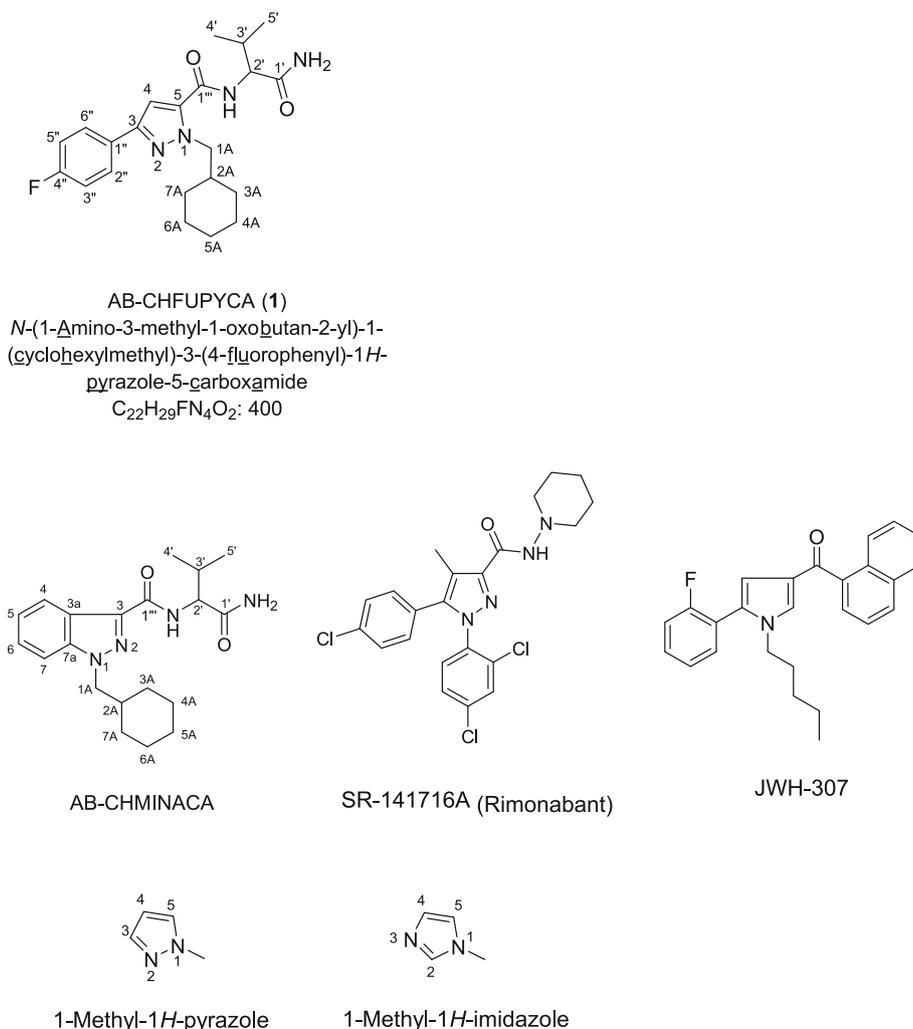
In this study, we describe the identification of a new pyrazole-carboxamide-type synthetic cannabinoid (**1**) in illegal products obtained in February 2015 (Fig. 1).

Materials and methods

Sample for analyses

The analyzed sample was obtained via the Internet in February 2015 as an herbal-type product being sold in Japan. The herbal-type product A contained approximately 3 g of mixed dried plants.

Chemicals and reagents

All common chemicals and solvents were of analytical reagent or high-performance liquid chromatography (HPLC) grade. As a solvent for the nuclear magnetic res-onance (NMR) analysis, chloroform-d_3 (99.96 %) was purchased from the ISOTEC division of Sigma-Aldrich (St. Louis, MO, USA).

Preparation of sample solutions

For the qualitative analyses, 10 mg of each herbal-type product was crushed into powder and extracted with 1 ml of methanol under ultrasonication for 10 min. After cen-trifugation (3000 rpm, 5 min) of each extract, the super-natant 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.

Fig. 1 Structures of the newly detected compound (**1**) and related compounds

AB-CHFUPYCA (**1**)
N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide
$C_{22}H_{29}FN_4O_2$: 400

AB-CHMINACA

SR-141716A (Rimonabant)

JWH-307

1-Methyl-1*H*-pyrazole

1-Methyl-1*H*-imidazole

Analytical conditions

A 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 [14]. The UPLC–ESI-MS analysis was performed on an ACQUITY UPLC system with a mass detector and a photodiode array (PDA) detector (Waters, Milford, MA, USA). The LC–MS analysis was carried out with a binary mobile phase consisting of solvent A (0.1 % formic acid in water) and solvent B (0.1 % formic acid in acetonitrile). The elution program was as follows: 5 % B to 20 % B (0–20 min) and up to 80 % B (20–30 min, 10-min hold) at a flow rate of 0.3 ml/min. GC–EI-MS was performed on an Agilent 6890 N GC system with a 5975 mass selective detector (Agilent Technologies, Santa Clara, CA, USA) using a capillary column (HP-1MS capillary, 30 m × 0.25 mm i.d., 0.25-μm film thickness; Agilent Technologies) with helium gas as a carrier at 0.7 ml/min. The conditions were: electron energy, 70 eV; injector temperature, 220 °C; injection, splitless mode for 1.0 min; oven temperature program, 80 °C (1-min hold) and an increase at a rate of 5 °C/min to 190 °C (15-min hold) followed by an increase at 10 °C/min up to 310 °C (15-min hold); transfer line temperature, 280 °C; scan range, m/z 40–550.

The obtained GC mass spectra were compared to those of an EI-MS library (Mass Spectra of Designer Drugs 2014; Wiley-VCH, Weinheim, Germany). We also used our in-house EI-MS library of designer drugs obtained by our ongoing survey of illegal products and commercially available reagents for the structural elucidation.

We measured the accurate mass numbers of the target compounds by liquid chromatography–quadrupole-time-of-flight-mass spectrometry (LC–QTOF-MS) in the ESI mode according to our previous report [7].

The nuclear magnetic resonance (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, HH correlation spectroscopy (HH-COSY) and nuclear Overhauser effect (NOE) spectra.

Isolation of compound 1

A 1.0-g sample of mixed dried plants (product A) was extracted with 100 ml of chloroform by ultrasonication for 10 min. Additionally, the extraction was repeated twice without sonication, and the supernatant fractions were combined and concentrated. 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/ethyl acetate (3:1, 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 isopropyl ether/acetone/isopropanol (10:1:1, v/v). The extract was then recrystallized in acetone and washed with methanol, which gave compound 1 (7 mg) as a white needle.

Results and discussion

Identification of an unknown peak 1

An unknown peak 1 was detected in the LC–MS and GC–MS for product A (Fig. 2a, b, d). By LC–MS analysis, peak 1 showed the protonated molecular ion at m/z 401 ([M+H]$^+$) (Fig. 2c). In the GC–MS analysis, peak 1 showed a molecular ion at m/z 400 (Fig. 2e). The fragment ions of peak 1 (m/z 95, 257, 285 and 356) were different from those of known synthetic cannabinoids such as indole or indazole derivatives (i.e., JWH-018 or AB-CHMI-NACA) [4, 10]. The accurate mass spectrum obtained by LC–QTOF-MS gave an ion peak at m/z 401.2344, suggesting that the protonated molecular formula of compound 1 was $C_{22}H_{30}N_4O_2F$ (calcd. 401.2353).

The observed ^{1}H and ^{13}C NMR spectra (Table 1), HH-COSY, HMQC, HMBC and ^{15}N HMBC correlations for compound 1 indicated the presence of three moieties, cyclohexylmethyl group (A), N-(1-amino-3-methyl-1-oxobutan-2-yl)-carboxamide group (B) and 4-fluorophenyl group (C), as shown in Table 1 and Fig. 3a, b. Groups A and B are the same parts as in AB-CHMINACA, but group C is not (Figs. 1, 3a, b; Table 1). Additionally, it was presumed that the remaining $C_3H_1N_2$ unit was a pyrazole group or an imidazole group based on the one-dimensional (1D)- and 2D-NMR spectra (Figs. 1, 3a, b; Tables 1, 2).

First, we compared the ^{15}N NMR and ^{13}C NMR data of compound 1 with those of the known 1-methyl-1H-pyrazole and 1-methyl-1H-imidazole (Fig. 1; Tables 1, 2) [15, 16]. The chemical shifts of the corresponding nitrogens and carbons of compound 1 [N-1 (δ_N −167.8), N-2 (δ_N −71.1) and C-4 (δ_C 103.3)] were different from those of the 1H-imidazole moiety in 1-methyl-1H-imidazole [N-1 (δ_N −218.5), N-2 (δ_N −118.1) and C-4 (δ_C 130.2)], respectively. However, their chemical shifts of 1 were similar to those of 1-methyl-1H-pyrazole [N-1 (δ_N −178.4), N-2 (δ_N −71.6) and C-4 (δ_C 105.3)] (Tables 1, 2). These results strongly suggest that compound 1 has a pyrazole group.

(a) PDA

(b) TIC

(c) Compound 1 (29.0 min)

(d) TIC

(e) Compound 1 (51.06 min)
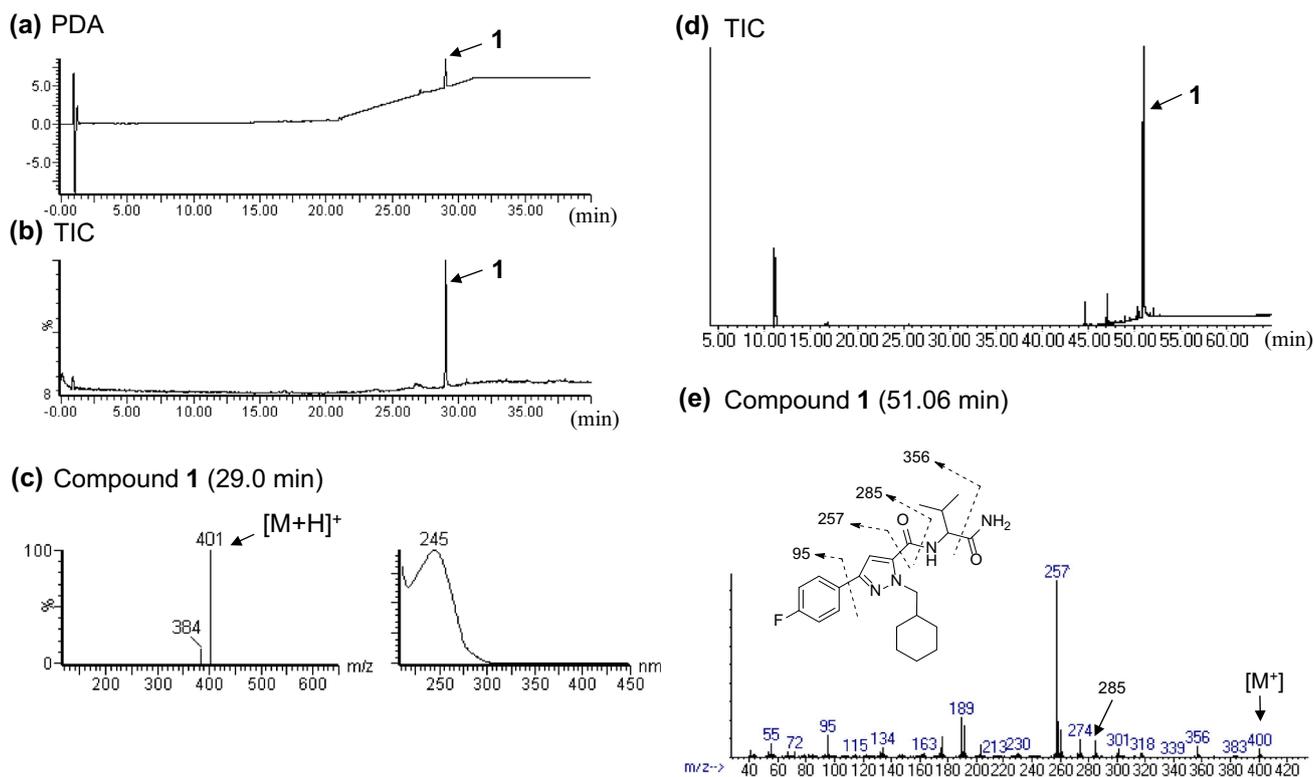
Fig. 2 Liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry (GC–MS) analyses of product A. The liquid chromatography–ultraviolet-photodiode array (LC–UV-PDA) chromatogram (a), total ion chromatogram (TIC) (b), and electrospray ionization mass and ultraviolet spectra of peak 1 (c) are shown. TIC (d) and electron ionization mass spectra (e) of peak 1 obtained by GC–MS are also shown

In addition, we observed the HMBC correlations from H-4 to C-3, C-5 and the amide carbon (C-1‴), from H-1A to C-5, and from H-2″ and H-6″ to C-3 (Fig. 3a). The [15N] HMBC correlations from H-4 to N-1 and N-2, and from H-1A to N-2, were also observed (Fig. 3b). These results revealed that the pyrazole group was connected at position 1 to the cyclohexylmethyl group at position 1A, at position 3 to the 4-fluorophenyl group at position 1″, and at position 5 to the N-(1-amino-3-methyl-1-oxobutan-2-yl)-carboxamide group at position 1‴ (Fig. 3a, b).

Finally, compound 1 was identified as N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1H-pyrazole-5-carboxamide and named "AB-CHFUPYCA." The fragment ions at m/z 95, 257, 285 and 356 of peak 1 in the GC–MS spectrum further confirmed the structure of compound 1 (Fig. 2e). Compound 1 is a new substance; its chemical and pharmaceutical data have not been reported previously.

Although it is not yet clear whether compound 1 has any pharmacological effects, it is possible that compound 1 has cannabimimetic activity, in light of its structure. Compound 1 was not a previously detected type of synthetic cannabinoid, such as indazole and indole derivatives (i.e., JWH-018, AB-CHMINACA and ADBICA [4, 7, 10]), but rather is a pyrazole derivative. A pyrazole derivative SR141716A (Rimonabant) is a selective cannabinoid (CB₁) receptor antagonist (Ki = 1.98 nM), and it acts as an inverse agonist (IC50 = 48 nM) (Fig. 1) [17, 18]. SR141716A was developed as an appetite suppressant and anti-obesity drug. However, it has been withdrawn from the market because of concerns over its serious side effects, including suicidality and depression [19]. The other pyrazole derivatives, AM251 and AM281, which are analogs of SR141716A, are also selective CB₁ receptor antagonists [Ki (nM) values = 7.5 and 12, respectively] [20, 21]. On the other hand, a pyrrole derivative of synthetic cannabinoid JWH-307, which was detected in illegal products [22], is known to have affinity for CB₁ and CB₂ receptors [Ki (nM) values = 7.7 and 7.1, respectively] [23]. Some detected types of synthetic cannabinoids were reported to have affinities for CB₁ and/or CB₂ receptors [23]. Nevertheless, the effects of compound 1 are unclear, and it is therefore necessary to elucidate the pharmacological functions of compound 1.

Table 1 Nuclear magnetic resonance (NMR) spectroscopy data for compound **1** and related compounds

No.	Compound **1**[a]		No.	1-Methyl-1H-pyrazole[b,c]	1-Methyl-1H-imidazole[c,d]	AB-CHMINACA[e]
	^{13}C	^1H		^{13}C	^{13}C	^{13}C
1	–	–	1	–	–	–
2	–	–	2	–	138.7	–
3	148.8	–	3	139.0	–	136.4
3a	–	–	3a	–	–	121.8
4	103.3	6.78, 1H, s	4	105.3	130.2	121.6
5	136.4	–	5	129.6	121.0	122.4
6	–	–	6	–	–	126.6
7	–	–	7	–	–	110.6
7a	–	–	7a	–	–	141.2
1′	172.7	–	1′	–	–	172.6
2′	57.9	4.44, 1H, dd, $J = 8.2$, 6.9 Hz,	2′	–	–	56.7
3′	31.4	2.19, 1H, m	3′	–	–	31.2
4′	19.1	1.02, 3H, d, $J = 7.6$ Hz, overlapped	4′	–	–	19.3
5′	18.2	1.04, 3H, d, $J = 7.6$ Hz, overlapped	5′	–	–	17.9
1″	128.9	–		–	–	–
2″/6″	127.3	7.73 and 7.72, each 1H, d, $J = 8.9$ Hz, overlapped		–	–	–
3″/5″	115.6	7.07 and 7.06, each 1H, d, $J = 8.9$ Hz, overlapped		–	–	–
4″	162.7	–		–	–	–
1A	57.2	4.39, 4.39, each 1H, d, $J = 6.9$ Hz, overlapped	1A	–	–	54.5
2A	39.1	1.91, 1H, m	2A	–	–	38.3
3A	30.4	0.99, 1H, m, overlapped 1.56, 1H, brd, $J = 12.4$ Hz	3A	–	–	30.0
4A	25.7	1.67, 1H, brd, $J = 10.3$ Hz 1.15, 1H, m, overlapped	4A	–	–	25.0
5A	26.3	1.61, 1H, brd, $J = 10.3$ Hz, overlapped 1.13, 1H, m, overlapped	5A	–	–	25.7
6A	25.7	1.15, 1H, m, overlapped 1.67, 1H, brd, $J = 10.3$ Hz	6A	–	–	25.1
7A	30.4	1.56, 1H, brd, $J = 12.4$ Hz 0.99, 1H, m, overlapped	7A	–	–	29.9
1‴-CONH	159.9	6.75, 1H, d, $J = 8.3$ Hz	1‴-CONH	–	–	161.3
1′-NH$_2$	–	5.85 and 5.60, each 1H, brs	1′-NH$_2$	–	–	–

[a] Recorded in CDCl$_3$ at 800 MHz (^1H) and 200 MHz (^{13}C), respectively; data in δ ppm (J in Hz)
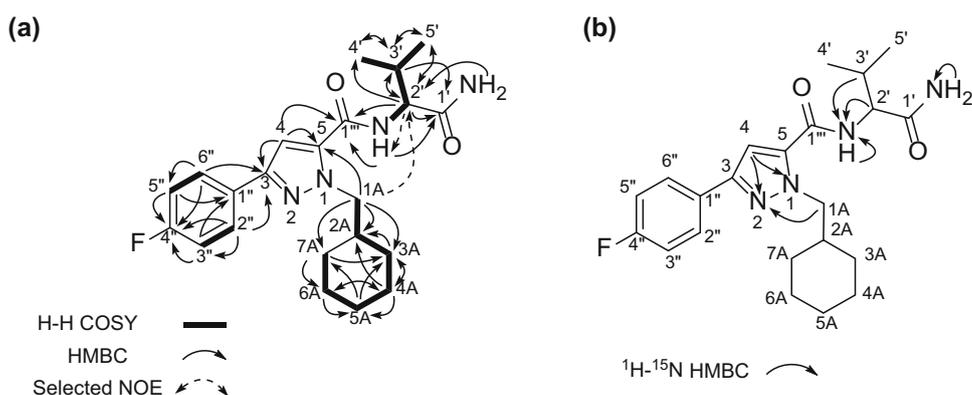
[b] Ref. [15]

[c] Recorded in CDCl$_3$

[d] Ref. [16]

[e] Recorded in dimethyl sulfoxide (DMSO)-d_6 at 800 MHz (^1H) and 200 MHz (^{13}C), respectively; Ref. [10]

Fig. 3 Results of HH-correlation spectroscopy (HH-COSY), heteronuclear multiple-bond correlation (HMBC), selected nuclear Overhauser effect (NOE) correlations (a) and ^{1}H-^{15}N HMBC correlations (b) of compound **1** in CDCl$_3$

Table 2 ^{15}N NMR spectroscopy data of detected compound **1** and the related compounds

Type	1*H*-Pyrazole		1*H*-Imidazole	1*H*-Indazole
Position No.	Compound **1**[a,b]	1-Methyl-1*H*-pyrazole[c,d]	1-Methyl-1*H*-imidazole[d,e]	AB-CHMINACA[b,f]
N-1	−167.8	−178.4	−218.5	−191.4
N-2	−71.1	−71.6	–	−62.8
N-3	–	–	−118.1	–
1‴-CONH	−265.8	–	–	−273.3
1′-CONH$_2$	−281.0	–	–	−273.3

[a] Recorded in CDCl$_3$

[b] ^{15}N NMR chemical shifts, which were observed in the ^{1}H-^{15}N HMBC spectrum, are referenced to the signal of CH$_3$NO$_2$ (δ_N 0.0 ppm)

[c] Ref. [16]

[d] Recorded in DMSO-d_6

[e] Ref. [15]

[f] Recorded in DMSO-d_6; Ref [10]

Conclusions

This report describes the identification of a new synthetic cannabinoid, AB-CHFUPYCA [*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide, **1**], in illegal products. Compound **1** is a novel pyrazole-carboxamide derivative, and its pharmacological effects are unknown. The continuous provision of timely and objective information about NPSs and current trends is important to prevent the abuse of NPSs.

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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