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ORIGINAL ARTICLE

Identification of new synthetic cannabinoid analogue APINAC (adamantan-1-yl 1-pentyl-1H-indazole-3-carboxylate) with other synthetic cannabinoid MDMB(N)-Bz-F in illegal products

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Abstract Two synthetic cannabinoid analogues were detected using high-performance liquid chromatography (HPLC)–diode array detector, and gas chromatography–time-of-flight-mass spectrometry during the inspection of illegal products in an airmail package. The analogues were separated by semi-preparative HPLC, and their structures were determined by performing liquid chromatography–high-resolution-mass spectrometry, infrared analysis, and nuclear magnetic resonance spectroscopy. Compound **1** was MDMB(N)-Bz-F, which has been reported previously. Compound **2** was elucidated as adamantan-1-yl 1-pentyl-1*H*-indazole-3-carboxylate (APINAC), in which the amide group of APINACA was replaced with an ester group. Because there has been no chemical or pharmacological data about this compound until now, this is the first report of its detection in illegal products.

J. H. Lee and H. N. Park contributed equally.

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Keywords Methyl 2-[1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate · 1-(4-Fluorobenzyl)-*N*-(1-methoxycarbonyl-2,2-dimethylpropyl)-1*H*-indazole-3-carboxamide [MDMB(N)-Bz-F] · Adamantan-1-yl 1-pentyl-1*H*-indazole-3-carboxylate (APINAC) · Synthetic cannabinoids · Illegal product · APINACA analogues

Introduction

The recent rise in the abuse of new synthetic cannabinoids has become a worldwide issue. Synthetic cannabinoids act on cannabinoid CB_1 (central type) and/or CB_2 (peripheral type) receptors to produce psychoactive effects [1–5]. Synthetic cannabinoids have been classified into several groups based on their structural motif by the National Forensic Services: naphthylindoles, phenylacetylinoles, benzoylindoles, cyclopropylindoles, aminocarbonylindazoles, adamantylindoles, adamantylindazoles, quinolinylindoles, CP-47,497 homologs, and cyclopropylthiazoles [6–9]. Although the use of cannabinoids for restrictive medicinal purposes is permitted, their recreational use is illegal in most countries. Several adverse effects due to abuse of cannabinoids include hallucination, psychosis, hypertension, tachycardia, agitation, vomiting, seizures, and convulsions [10–13].

Illegal herbal products and dietary supplements containing synthetic cannabinoids are available for purchase via the Internet and through international postal services [14–17]. Since unapproved synthetic cannabinoids have not been assessed pharmacologically and toxicologically, the products that contain these ingredients could pose a significant risk to public health [18, 19]. In spite of great efforts and the cooperation of authorities in most countries to protect public health from the toxic effects of synthetic cannabinoids, new synthetic cannabinoids have been

detected in a variety type of products [20–24]. Since first synthetic cannabinoids was identified at the end of 2008, more than 130 synthetic cannabinoids have been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [25].

We identified two synthetic cannabinoids in illegal products in an airmail package. These compounds were isolated and structurally elucidated by means of high-performance liquid chromatography (HPLC), gas chromatography–time-of-flight-mass spectrometry (GC–TOF-MS), liquid chromatography–high-resolution-mass spectrometry (LC–HR-MS), infrared (IR) analysis, and nuclear magnetic resonance (NMR) spectroscopy. Compound **1** in herbal-type products was MDMB(N)-Bz-F with an indazole-3-carboxamide group that has been reported recently [26]. Compound **2** in a powder-type product was determined as adamantan-1-yl 1-pentyl-1*H*-indazole-3-carboxylate (APINAC), an analogue of APINACA that is a type of adamantylindazole synthetic cannabinoid. The APINACA was modified to APINAC by replacement of an amide group with an ester group. In this article, we described two synthetic cannabinoids in illegal products in detail. The structures of the compounds are shown in Fig. 1.

Materials and methods

Chemicals and reagents

Methanol and acetonitrile were obtained from Merck KGaA (Darmastadt, Germany); sodium 1-hexanesulfonate and formic acid from Sigma-Aldrich (St. Louis, MO, USA); deuterated chloroform and methyl alcohol (99.9 %, isotopic) from Alfa Aesar (Ward Hill, MA, USA); deuterated dimethyl sulfoxide (99.8 %) from AMAR chemicals (Dottingen, Switzerland). Deionized water (18.2 MΩ cm) was generated using a Milli-Q water system (Millipore, Billerica, MA, USA). All solvents and reagents were of HPLC grade.

Sample preparation

About 1 mg of powder-type or 0.2 g of herbal product was dissolved in 10 mL methanol, respectively. The mixture was sonicated for 10 min and filtered through a polytetraflouroethylene filter (0.2 μm). The resulting residue was diluted appropriately with methanol for instrumental analyses.

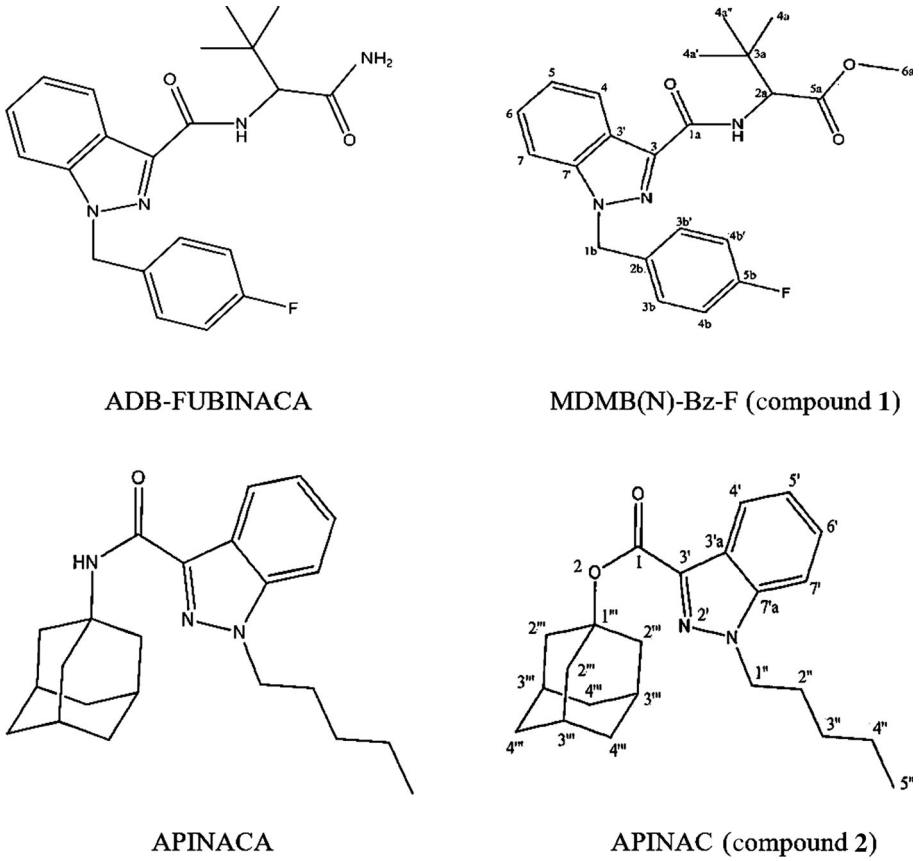

Fig. 1 Chemical structures of ADB-FUBINACA, APINACA, compound **1** and compound **2**

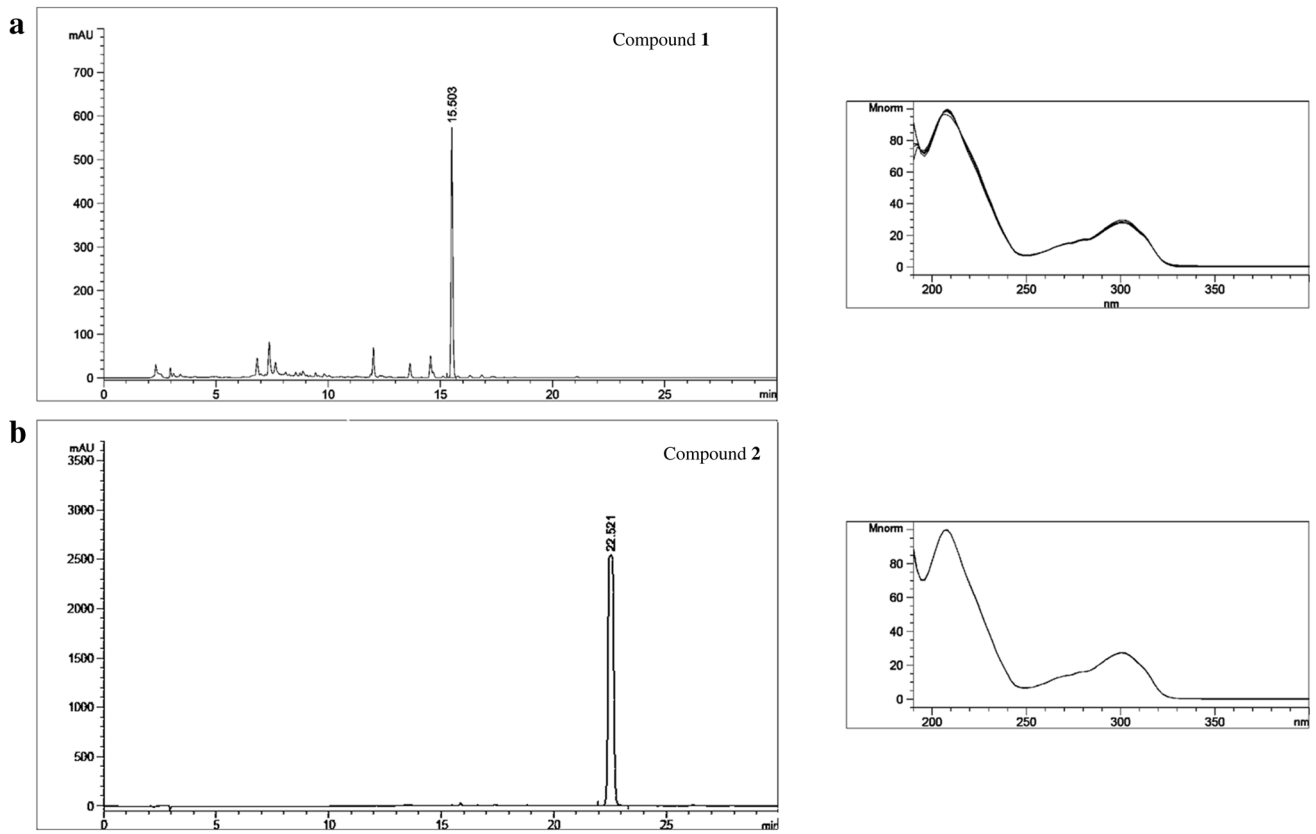

Fig. 2 **a** High-performance liquid chromatography chromatograms at 210 nm and ultraviolet spectra (190–400 nm) for compound **1** and **b** compound **2**

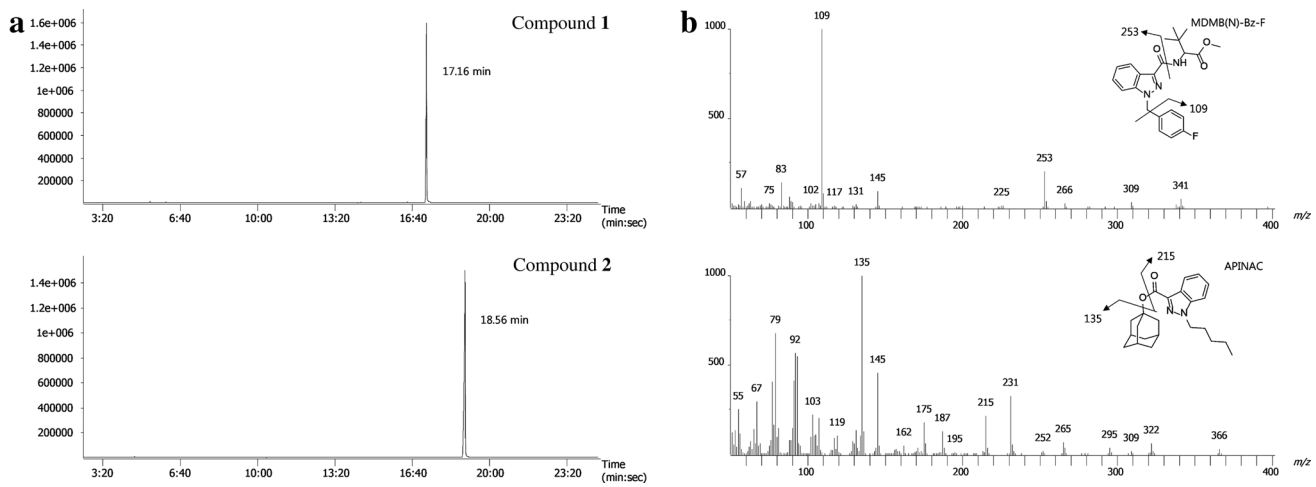

Fig. 3 **a** Gas chromatography–time-of-flight- mass spectrometry chromatograms of compounds **1** and **2** in the sample solution, and **b** mass spectra of the compounds

Analytical conditions

High-performance liquid chromatography–diode array detector (DAD) analysis was performed using an Agilent 1200 series HPLC system (Agilent Technologies, Santa Clara, CA, USA) with a DAD. A ZORBAX Eclipse XDB-C_{18} (250 mm × 4.6 mm i.d., particle size 5 μm) column (Agilent Technologies) was used with the column chamber set at 40 °C. The injection volume was 10 μL, and the flow rate was 1.0 mL/min. Gradient elution was applied using 0.5 mM aqueous sodium 1-hexanesulfonate containing 0.1 % phosphoric acid at pH 2.3 (A) and 95 % acetonitrile

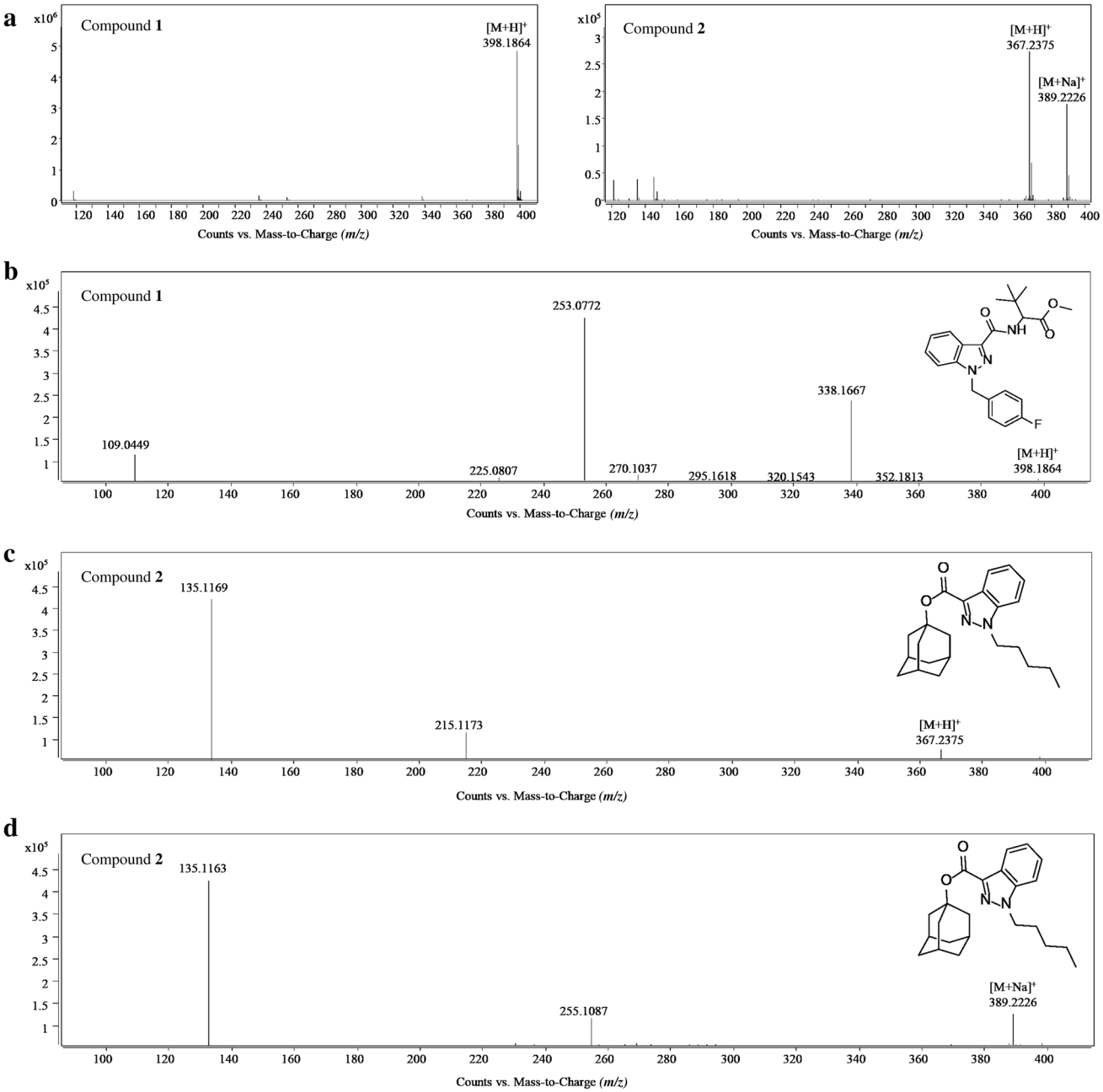

Fig. 4 **a** Liquid chromatography–quadrupole time-of-flight-mass spectrometry (LC–QTOF-MS) spectra in the single-stage mode for compounds **1** and **2** with parent ions and LC–QTOF-MS/MS spectra of **b** protonated compound **1** with a parent ion at *m/z* 398.1864, of **c** protonated compound **2** with a parent ion at *m/z* 367.2375, and of **d** sodium adducted compound **2** with a parent ion at *m/z* 389.2226

(B), and was programmed as follows: 0–2 min (A: 80 %, B: 20 %), 2–10 min (A: 80–20 %, B: 20–80 %), 10–15 min (A: 20–0 %, B: 80–100 %), 15–28 min (A: 0 %, B: 100 %), 28–28.1 min (A: 0–80 %, B: 100–20 %), 28.1–30 min (A: 80 %, B: 20). The ultraviolet (UV) spectra were recorded from 210 to 400 nm, while the chromatograms were acquired at 210 nm.

GC–TOF-MS analysis was carried out using an Agilent 7890A system (Agilent Technologies) with a LECO Pegasus HT TOF-MS (LECO Corp., St. Joseph, MI, USA). The column was Agilent HP 5MS (30 m × 0.25 mm i.d., 0. 25 μm; Agilent Technologies) and the extracts were injected in split mode (10:1). Helium at a constant flow rate of 1.0 mL/min was used as the carrier gas and the injection volume was 1 μL. The initial column temperature (100 °C) was increased to 200 °C at a rate 15 °C/min, ramped up to 300 °C at 10 °C/min, and held at 300 °C for 8 min. The GC injector was set at 250 °C and the transfer line was

Table 1 LC–HR-MS (LC–QTOF-MS) data for compounds **1** and **2**

Compound	Chemical formula	Calculated mass	Experimental mass	Error (ppm)
Compound **1**	$C_{22}H_{25}FN_3O_3^+$	398.1874	398.1864	−2.5
	$C_{20}H_{21}FN_3O^+$	338.1663	338.1667	1.2
	$C_{15}H_{10}FN_2O^+$	253.0772	253.0772	0
	$C_7H_6F^+$	109.0448	109.0449	0.9
Compound **2**	$C_{23}H_{30}N_2O_2^+$	367.2380	367.2375	−1.4
	$C_{13}H_{15}N_2O^+$	215.1179	215.1167	−2.8
	$C_{10}H_{15}^+$	135.1168	135.1169	0.7

maintained at 280 °C. The mass conditions were as follows: ionization mode, electron ionization; electron energy 70 eV; source temperature, 230 °C; scan range, 50–500 amu; selected ion monitoring dwell time, 100 ms.

The LC–HR-MS experiments were conducted on an Agilent 1200 series HPLC system connected to an Agilent 6530 Accurate-Mass Quadrupole (QTOF-MS) spectrometer equipped with an electrospray ionization Jet Stream Technology source (Agilent Technologies). The chromatographic separation was performed on an X-Bridge C_{18} column (150 mm × 2.1 mm i.d, particle size 3.5 µm) at 35 °C. The mobile phase was composed of 0.1 % formic acid in both distilled water (A) and acetonitrile (B). The elution profile was as follows: 0–3 min (A: 80 %, B: 20 %), 3–13 min (A: 80–40 %, B: 20–60 %), 13–16 min (A: 40 %, B: 60 %), 16–18 min (A: 40–0 %, B: 60–100 %), 18–21 min (A: 0 %, B: 100 %), 21–22 min (A: 0–80 %, B: 100–20 %), 22–25 min (A: 80 %, B: 20 %). The injected sample volume was 3 µL, and the flow rate was 0.3 mL/min. The MS conditions were as follows: positive ion mode; gas temperature, 350 °C; drying gas flow, 8 L/min; nebulizer pressure, 35 psig; sheath gas temperature, 350 °C; sheath gas flow, 11 mL/min; capillary voltage, 3.5 kV; nozzle voltage, 1.0 kV; fragment voltage, 0.12 kV. After acquiring a full scan MS spectrum, tandem mass spectrometry (MS/MS) experiment was performed.

An Agilent 1200 series semi-preparative HPLC system with a DAD was used for isolation of analogues. A ZORBAX Eclipse XDB C_{18} (250 mm × 9.4. mm i.d, particle size 5 µm) column was used, and the column chamber was maintained at 40 °C. The flow rate was 3.0 mL/min, and the injection volume was 100 µL, with detection at 210 nm. Gradient elution was applied using distilled water (A) and methanol (B). The mixed isocratic and gradient elution profile was as follows: 0–2 min (A: 80 %, B: 20 %), 2–20 min (A: 70–0 %, B: 30–100 %), 20–23 min (A: 0 %, B: 100 %), 23–25 min (A: 0–80 %, B: 100–20 %), 25–28 min (A: 80 %, B: 20 %). The fractions were collected and concentrated in vacuo.

The analogues isolated from powder- and herbal-type samples were dissolved in $CDCl_3$ and $(CD_3)_2CO$, respectively. All NMR experiments [^{1}H, ^{13}C, distortionless enhancement by polarization transfer (DEPT), heteronuclear single quantum coherence (HSQC), ^{1}H-^{1}H correlation spectroscopy (COSY), heteronuclear multiple bond correlation (HMBC), and nuclear Overhauser effect spectroscopy (NOESY)] were performed using a Bruker Avance II 600 MHz FT-NMR spectrometer (Bruker, Ettlingen, Germany). IR spectra were recorded over the spectral range 4000–400 cm^{-1} using a Perkin Elmer Frontier Fourier transform (FT)-IR spectrometer (Perkin Elmer, Waltham, MA, USA).

Results and discussion

Identification of compound 1

The UV spectrum of compound **1** at 15.5 min was maximally absorbed at 210 and 302 nm (Fig. 2). For GC–TOF-MS, this compound at 17.1 min produced ions at *m/z* 109 and 253 (Fig. 3). We predicted that compound **1** was ADB-FUBINACA analogue in comparison to the previous report [27]. The accurate mass spectrum of compound **1** was measured by LC–QTOF-MS (Fig. 4). The ion peak was detected at *m/z* 398.1864 and suggested as the protonated molecular formula of $C_{22}H_{25}FN_3O_3^+$ (calcd. 398.1874) (Table 1). The product ions appeared at *m/z* 109.0449 ($C_7H_6F^+$), 253.0772 ($C_{15}H_{10}FN_2O^+$), and 338.1667 ($C_{20}H_{21}FN_3O^+$) indicated the presence of indazole-3-carboxamide moiety and fluorotropylium ion like ADB-FUBINACA.

By NMR analyses in CD_3OD, we confirmed that compound **1** is MDMB-Bz-F reported as an ADB-FUBINCA analogue [26]. Most of ^{1}H- and ^{13}C spectral data were similar to those of ADB-FUBINACA (Fig. 5). For example, the ^{1}H NMR spectra were identified the presence of *t*-butyl group (δ_H 1.08), benzylic proton (δ_H 5.71) and eight protons of the aryl group. The two

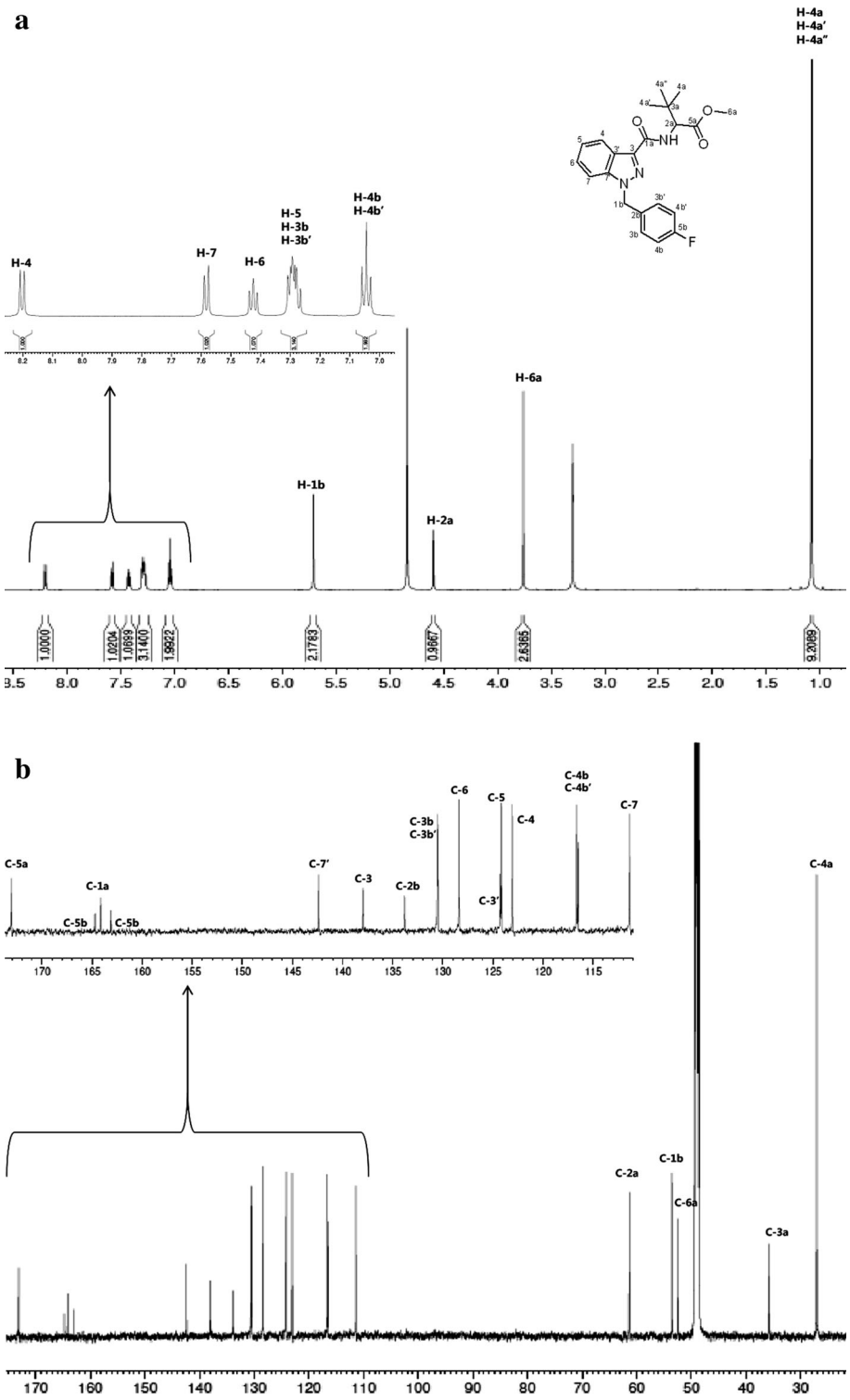

Fig. 5 **a** ^{1}H nuclear magnetic resonance (NMR) and **b** ^{13}C NMR (600 MHz, CD_3OD) spectra of the compound **1**

carbonyl groups were proved by the peaks at δ_C 173.1 and 164.1 while the doublet peak at δ_C 163.9, (d, $J_{C-F} = 243$ Hz) was assigned as a peak for C-5b due to coupling between aryl carbon and fluoride. The oxygenated methyl group was indicated by the peaks at δ_H 3.76 and δ_C 52.4, which suggested that amide group of ADB-FUBINACA was substituted by methyl ester. When compound **1** was dissolved in DMSO-d_6, its NMR spectral data were in good agreement with the reported data (Table 2) [26].

Table 2 Comparison of the nuclear magnetic resonance (NMR) data of compound **1** with those reported previously

Position no.	MDMB(N)-Bz-F[a] (reported) ^{1}H (400 MHz, DMSO-d_6)	Compound **1** ^{1}H (600 MHz, DMSO-d_6)	MDMB(N)-Bz-F[a] (reported) ^{13}C (100 MHz, DMSO-d_6)	Compound **1** ^{13}C (150 MHz, DMSO-d_6)
3	–	–	136.6	137.1
3′	–	–	122.2	123.4
4	8.14 (*d*, 1H, $J = 8.0$ Hz)	8.13 (*d*, 1H, $J = 8.4$ Hz)	121.6	122.1
5	7.26–7.33 (m, 1H)	7.29–7.31 (t, 1H)	122.8	122.7
6	7.45–7.47 (m, 1H)	7.4–7.48 (t, 1H)	127.1	127.6
7	7.79 (*d*, 1H, $J = 8.0$ Hz)	7.80 (*d*, 1H, $J = 9.0$ Hz)	110.6	111.2
7′	–	–	140.6	141.1
1a	–	–	161.4	161.9
2a	4.51 (*d*, 1H, $J = 9.2$ Hz)	4.50 (*d*, 1H, $J = 9.0$ Hz)	59.5	60.0
3a	–	–	34.2	34.7
4a	1.02 (s, 3H) overlapping	1.02 (s, 3H) overlapping	26.4	26.9
4a′	1.02 (s, 3H) overlapping	1.02 (s, 3H) overlapping	26.4	26.9
4a″	1.02 (s, 3H) overlapping	1.02 (s, 3H) overlapping	26.4	26.9
5a	–	–	171.3	171.8
6a	3.70 (s, 3H)	3.70 (s, 3H)	51.8	52.2
NH	7.69 (*d*, 1H, $J = 8.0$ Hz)	7.71 (*d*, 1H, $J = 9.6$ Hz)	–	–
1b	5.78 (s, 2H)	5.79 (m, 2H)	51.7	52.3
2b	–	–	132.8 (*d*, $^{4}J_{C-F} = 3.0$ Hz)	133.4
3b, 3b′	7.34–7.38 (m, 2H)	7.33–7.36 (m, 2H)	129.5 (*d*, $^{3}J_{C-F} = 8.4$ Hz)	130.0 (*d*, $^{3}J_{C-F} = 9.0$ Hz)
4b, 4b′	7.14–7.18 (m, 2H)	7.15–7.18 (m, 2H)	115.5 (*d*, $^{2}J_{C-F} = 21.6$ Hz)	116.0 (*d*, $^{2}J_{C-F} = 22.5$ Hz)
5b	–	–	161.6 (*d*, $^{1}J_{C-F} = 244.9$ Hz)	162.1 (*d*, $^{1}J_{C-F} = 241.5$ Hz)

DMSO dimethyl sulfoxide

[a] Shevyrin et al. [26]

Identification of compound 2

Compound **2** was detected on the HPLC at 22.5 min and GC–TOF-MS at 18.5 min, as depicted in Figs. 2 and 3. Not only the UV spectrum had two absorption maxima at 210 and 303 nm but also its GC–TOF-MS spectra showed distinguishable two peaks at *m/z* 135 and 215, which were quite similar to those reported for APINACA [8]. To identify the quasi-molecular ion(s) of the compound, LC–QTOF-MS experiments were carried out under several sets of conditions (Fig. 4). Ions at *m/z* 367.2375 and 389.2226 were identified as quasi-molecular ions corresponding to the molecular formula $C_{23}H_{30}N_2O_2^+$ (calcd. 367.2380) and $C_{23}H_{30}N_2NaO_2^+$ (calcd. 389.2199), respectively. Further fragmentation of the quasi-molecular ions by LC–QTOF-MS/MS produced product ions at *m/z* 135.1169 and 215.1167 that were also detected in the MS^2 spectra of APINACA [9]. Given that the compound **2** is an APINACA analogue, it possessed both an adamantine group and an indazole moiety, as shown in Fig. 6. The ions at *m/z* 135.1169 corresponded to an adamantine cation and the ion at *m/z* 215.1167 was predicted as an indazole carbonium ion. The ion at *m/z* 255.1087 was considered a sodium salt of an indazolecarboxylic acid. The mass spectral data were consistent with an ester analogue of APINACA. To complete the structural determination of the compound, we conducted NMR and IR analyses. As summarized in Table 3, 30 proton and 17 carbon signals were recorded in the NMR spectra in $CDCl_3$. The ^{1}H and ^{13}C NMR spectral data of the compound strongly resembled those of APINACA [24]. The chemical shift values of all the proton and carbon signals, except for two, were slightly different from those of APINACA when the spectra of both compounds were compared. However, the NH signal (δ_H 6.81, APINACA) was not observed, and one carbon signal (C-1‴, δ_C 52.2, APINACA) was shifted downfield largely (δ_C 81.8) in the ^{1}H and ^{13}C NMR spectra of the compound (Fig. 7). These observations further confirmed that the amide group of APINACA was replaced with an ester group. Interpretation of ^{1}H-^{1}H COSY, HSQC, DEPT, and HMBC spectra also indicated that the compound was structurally identical to APINACA except for an "NH" group (supplementary material figure). The existence of an ester group in the compound was further confirmed by the strong IR absorption band at 1718 cm^{-1} (Fig. 8). Based on all the above data and careful analysis, the structure of the

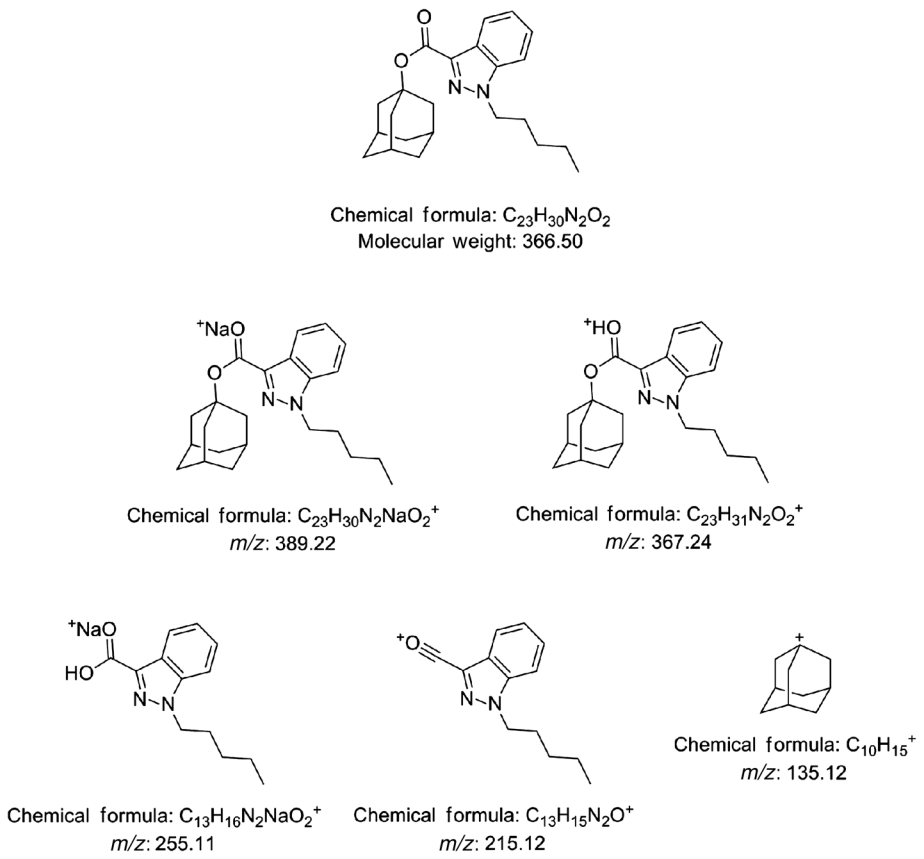

Fig. 6 Proposed fragmentation process for the quasi-molecular ions $[M + H]^+$ at *m/z* 367.24, and $[M+Na]^+$ at *m/z* 389.22 of compound **2**

Table 3 NMR data for compound **2**

Position no.	Unknown compound					
	$^1H(\delta_H)$	$^{13}C(\delta_H)$	DEPT	HSQC	^1H-^1H COSY	HMBC
1	–	161.7	C	–	–	–
3′	–	136.2	C	–	–	–
3′a	–	123.4	C	–	–	–
4′	8.15 (*d*, $J = 8.2$ Hz, 1H)	122.6	CH	C-4′	H-5′	C-3′, C-6′, C-7′a
5′	7.26 (t, $J = 7.2$ Hz, 1H)	122.6	CH	C-5′	H-4′, H-6′	C-3′a, C-6′, C-7′
6′	7.40 (td, $J = 8.4$, 1.0 Hz, 1H)	126.4	CH	C-6′	H-5′, H-7′	C-4′, C-7′a
7′	7.44 (*d*, $J = 8.4$ Hz, 1H)	109.5	CH	C-7′	H-6′	C-3′a, C-5′
7′a	–	140.6	C	–	–	–
1″	4.44 (t, $J = 7.4$ Hz, 2H)	49.8	CH_2	C-1″	H-2″	C-2″, C-3″, C-7′a
2″	1.99–1.94 (m, 2H)	29.5	CH_2	C-2″	H-1″, H-3″	C-1″, C-3″, C-4″
3″	1.39–1.28 (m, 2H)	28.9	CH_2	C-3″	H-2″	C-4″
4″	1.39–1.28 (m, 2H)	22.3	CH_2	C-4''	H-5″	C-3″, C-5″
5″	0.88 (t, $J = 7.0$ Hz, 3H)	13.9	CH_3	C-5″	H-4″	C-3″, C-4″
1‴	–	81.8	C	–	–	–
2‴	2.39 (brs, 6H)	41.7	CH_2	C-2‴	H-3‴	C-1‴, C-3‴, C-4‴
3‴	2.25 (brs, 3H)	31.0	CH	C-3‴	H-2‴, H-4‴	C-1‴, C-2‴, C-4‴
4‴	1.78 (brd, $J = 12.0$ Hz, 3H)	36.3	CH_2	C-4‴	H-3‴	C-2‴, C-3‴
	1.72 (brd, $J = 12.0$ Hz, 3H)					

DEPT distortionless enhancement by polarization transfer, *HSQC* heteronuclear single quantum correlation, *COSY* correlation spectroscopy, *HMBC* heteronuclear multiple bond correlation

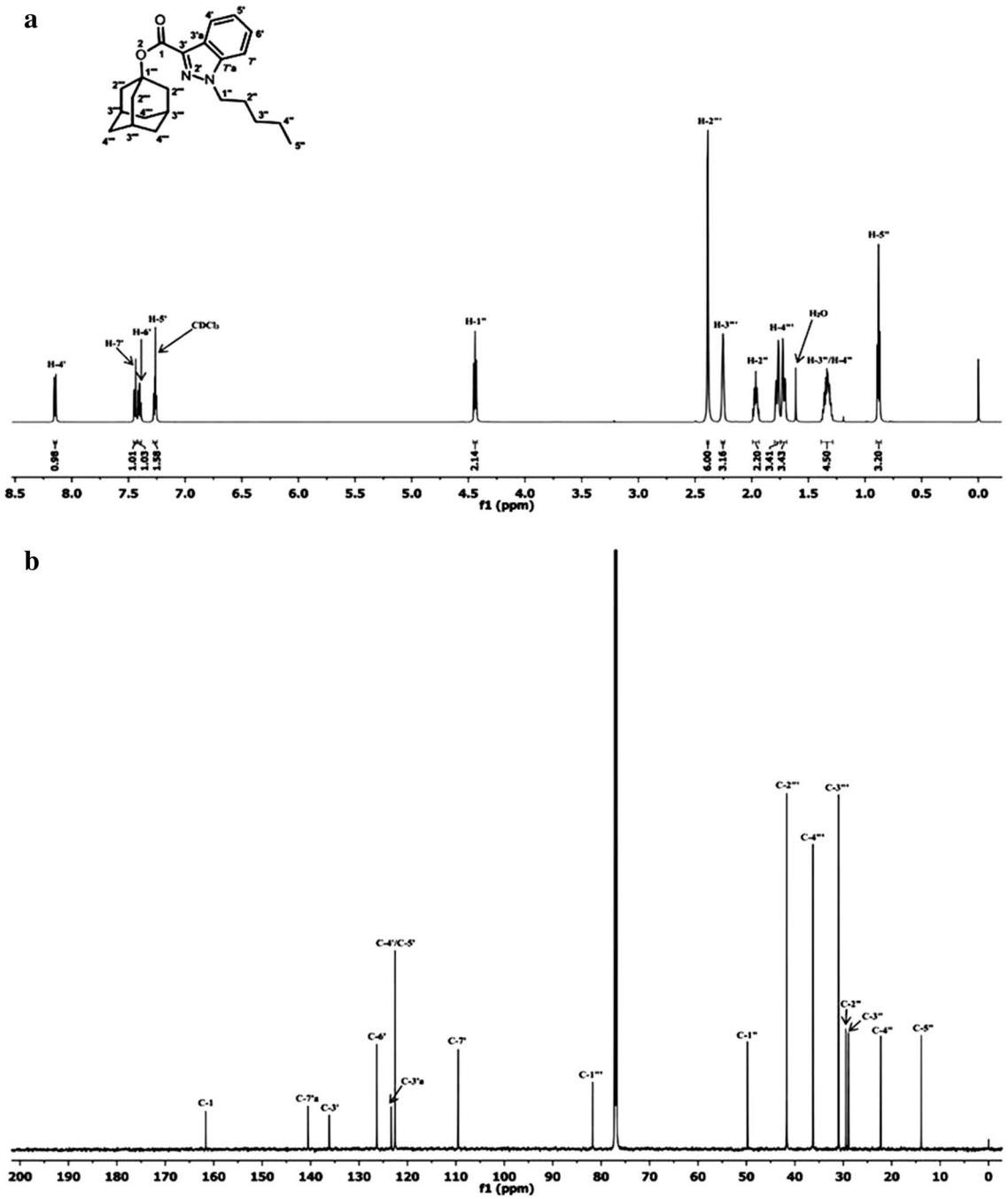

Fig. 7 **a** ^{1}H NMR (600 MHz, $CDCl_3$) and **b** ^{13}C NMR (150 MHz, $CDCl_3$) spectra of the compound **2**

compound **2** was elucidated as "adamantan-1-yl 1-pentyl-1*H*-indazole-3-carboxylate (APINAC)".

Conclusions

A new synthetic cannabinoid was detected by HPLC–DAD and GC–TOF-MS in illegal products, which was seized during the custom inspection of an airmail parcel. Compound **1** was confirmed as MDMB(N)-Bz-F and compound **2** was determined as an analogue of APINACA by combination of LC–HR-MS, IR, and NMR analyses. The amide group of APINACA was modified to an ester group in this analogue, which was thus named APINAC. Synthetic cannabinoids are abused worldwide, and new ones continue to be generated by modification of existing compounds to avoid being detected by authorities' inspection. Since unsupervised and addictive use of

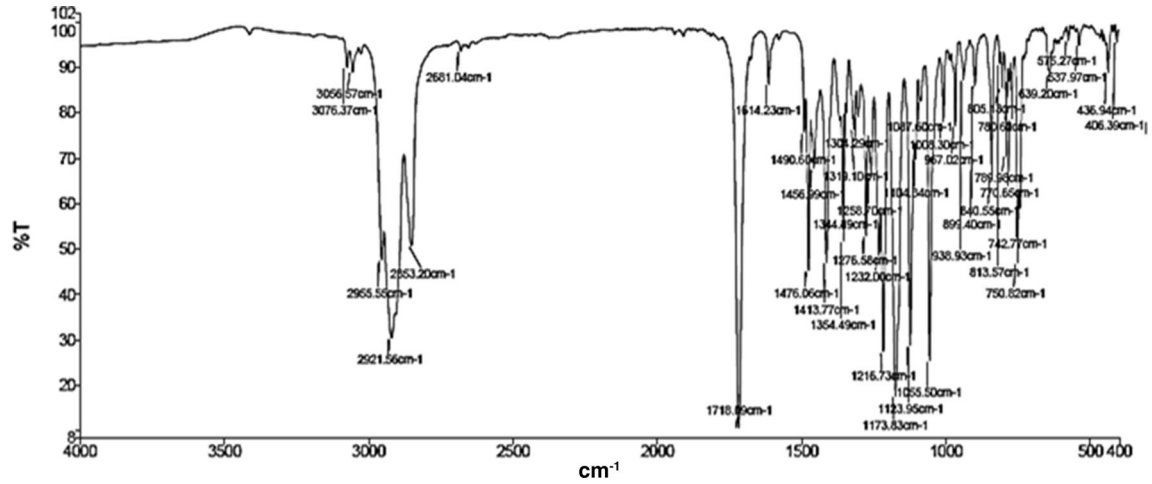

Fig. 8 Infrared spectrum of compound **2**

synthetic cannabinoids may cause social and health problems, this new analogue should be included on the list for the inspection of illegal products.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no 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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