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Identification and Structural Elucidation of a New Synthetic Cannabinoid, MDMB-5′Br-PINACA, in Seized Herbal Materials

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ABSTRACT

Synthetic cannabinoids (SCs) remain the most frequently detected class of new psychoactive substances (NPS) worldwide. Despite a recent decline in the overall number of newly reported NPS, SCs continue to emerge with remarkable structural diversity. Here, we report the discovery and structural elucidation of MDMB-5′Br-PINACA, a previously unreported SC identified in three seized herbal materials. The compound was isolated by semipreparative liquid chromatography and subsequently characterized using an integrated analytical approach combining gas chromatography–mass spectrometry (GC-MS), liquid chromatography–high-resolution mass spectrometry (LC-HRMS), and nuclear magnetic resonance (NMR) spectroscopy. In addition to MDMB-5′Br-PINACA, other SCs were detected in the analyzed materials, such as 5F-ADB and MDMB-4en-PINACA, also including the synthetic precursor MDMB-INACA. Other NPS classes were also observed, including designer benzodiazepines (*N*-desalkylgidazepam and bromazolam), and synthetic opioids (metonitazene). Recent years have also seen the emergence of brominated SCs as a strategy to evade legislative control, with several 5-bromo analogs detected across different regions. This analytical workflow enabled the unambiguous identification of MDMB-5′Br-PINACA and provided a detailed chemical profile of the seized samples, highlighting the continued evolution and complexity of NPS mixtures in herbal formulations. The findings emphasize the importance of continuous monitoring and early detection of emerging substances, which are essential not only for forensic and toxicological investigations but also for public health surveillance and the development of evidence-based drug control and harm-reduction policies.

1 | Introduction

In recent years, the rise of new psychoactive substances (NPS) has posed major challenges to forensic laboratories worldwide. These compounds are designed to mimic controlled drugs while evading legislation through subtle chemical modifications. Among these, synthetic cannabinoids (SCs) constitute the most diverse class and are widely seized worldwide 1. Initially found in herbal mixtures, SCs have also been identified in other materials, such as infused paper 2. They are structurally diverse and act as agonists of cannabinoid receptors (CB_1 and CB_2), with greater potency than Δ^9-tetrahydrocannabinol (Δ^9-THC) 3. Their rapid emergence

is largely driven by legislative controls, which push clandestine laboratories to create new analogs 4. To tackle this complexity, laboratories have employed integrated strategies combining liquid chromatography–high-resolution mass spectrometry (LC-HRMS), gas chromatography–mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy to fully characterize these substances, in line with international recommendations such as those of the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) 5. Moreover, semipreparative liquid chromatography coupled with advanced spectroscopic methods is particularly valuable for isolating compounds from complex matrices, such as herbal materials, enabling their extraction and purification 6. Here, we report the first identification of MDMB-5′Br-PINACA (Figure 1), a previously unreported brominated SC detected in three herbal materials seized in Brazil. This compound illustrates ongoing structural innovation to evade detection and control, underscoring the need for robust, multimodal analytical workflows in forensic toxicology investigations.

2 | Materials and Methods

2.1 | Materials

HPLC and LC-MS-grade methanol, acetonitrile, water, ethanol, *n*-hexane, and ethyl acetate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Formic acid was obtained from Scharlab (Sentmenat, Barcelona, Spain). MDMB-INACA and metonitazene reference materials were provided by the Brazilian Federal Police through the INSPEQT Project (grant 16/2020). MDMB-INACA, MDMB-4en-PINACA, *N*-desalkylgidazepam, and bromazolam were purchased from Cayman Chemical (Ann Arbor, MI, USA), and 5F-ADB was obtained from Cerilliant (Round Rock, TX, USA). The three herbal materials analyzed were seized between May and July 2024 in the city of Jundiaí, Sao Paulo, by the Sao Paulo State Police in Campinas-SP and delivered to the Laboratory of Analytical Toxicology through the INSPEQT Project.

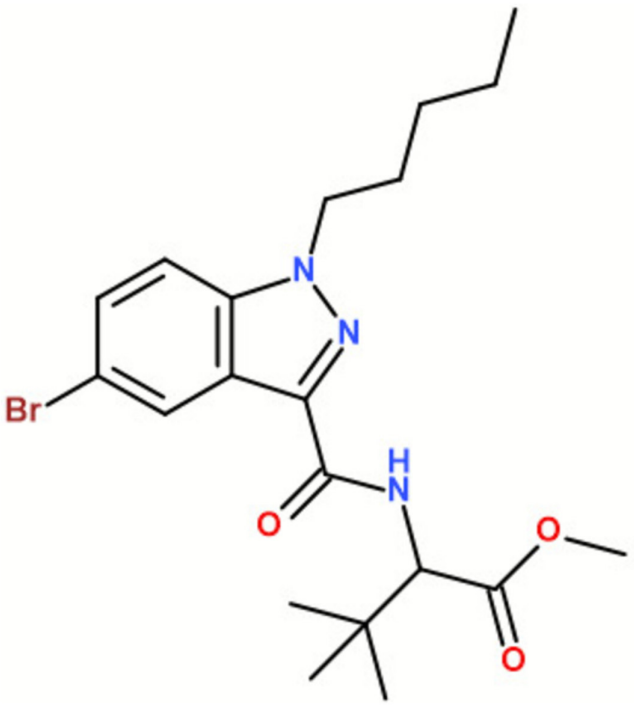


FIGURE 1 | Molecular structure of MDMB-5′Br-PINACA.

2.2 | Sample Preparation and Purification

For extraction, approximately 50 mg of herbal material (material 3) was weighed into 1.5 mL polypropylene tubes and treated with 1 mL of HPLC-grade methanol. Other solvents (acetonitrile, ethanol, ethyl acetate, and *n*-hexane) were tested using the same procedure. Samples were agitated for 10 min at 2000 rpm in a multitube vortex (BenchMixer XL, Benchmark, NJ, USA) and then centrifuged at 14,000×*g* for 10 min at 20°C. Supernatants were transferred to vials for GC-MS and semipreparative LC with photodiode-array (PDA) detection. For LC-HRMS analysis, samples were diluted (1:999, *v/v*) in the corresponding solvents.

Semipreparative LC-PDA was performed on a Nexera LC-40 XR system with a PDA detector (Shimadzu, Kyoto, Japan) using a Shim-pack GIST C8 column (4.6×250 mm, 5 μm) at 40°C. The mobile phases consisted of water (MPA) and acetonitrile (MPB) containing 0.1% (*v/v*) formic acid at a flow rate of 1.0 mL/min. The gradient started at 40% MPB (0.5 min), increased to 100% MPB (9.5 min), was held until 15 min, returned to initial conditions at 15.1 min, and equilibrated until 18 min. The injection volume was 30 μL, with PDA detection from 200 to 600 nm. Peaks corresponding to the target analyte were collected across multiple injections until sufficient material was obtained for characterization. Fractions were dried under a nitrogen stream and weighed, yielding 0.8 mg of powder. For NMR analysis, 0.6 mg was diluted in 600 μL deuterated methanol (CD_3OD), whereas for GC-MS and LC-HRMS, 0.2 mg was diluted in 200 μL of the respective solvents.

2.3 | GC-MS Analysis

Seized materials and the purified fraction containing MDMB-5′Br-PINACA were analyzed by GC coupled to a triple-quadrupole mass spectrometer (TQ8040NX, Shimadzu, Kyoto, Japan) with an AOC-5000 autosampler. Separation was achieved on a DB-5MS UI capillary column (30 m×0.25 mm i.d., 0.25 μm film). The oven temperature program was as follows: 80°C for 1.5 min, ramp at 25°C/min to 310°C, hold at 310°C for 8 min (total run time 18.7 min). The injection port, ion source, and transfer line temperatures were set to 280°C, 230°C, and 290°C, respectively. Ultrapure helium was used as the carrier gas at 1.0 mL/min, and samples were injected in split mode (1:10). The mass spectrometer was operated in full-scan mode over *m/z* 40–550. Acquired spectra were compared against the SWGDRUG Mass Spectral Library, Version 3.14 (January 22, 2025), and compound identities were further confirmed by comparison of retention times with certified reference materials.

2.4 | LC-HRMS Analysis

Analyses of the seized materials and of the MDMB-5′Br-PINACA fraction were performed on a Nexera HPLC system coupled to an LC-MS 9030 quadrupole time-of-flight (QToF) mass spectrometer (Shimadzu, Kyoto, Japan) equipped with an ESI source operating in positive mode. Separation employed a Kinetex C18 column (3.0×50 mm, 2.6 μm) at 40°C, with water

(MPA) and acetonitrile (MPB) containing 0.1% (*v*/*v*) formic acid at 0.3 mL/min. The gradient started at 5% MPB (1 min), increased to 100% MPB (8 min), was held to 11.3 min, returned at 11.5 min, and equilibrated until 13.5 min. Data-independent acquisition (DIA) was used together with a full-scan event, both over *m/z* 100–600, with a collision energy of 30 ± 25 eV. DIA events used a mass-window width of *m/z* 20.

2.5 | NMR Analysis

The resuspended fraction was transferred to a 5-mm NMR tube and analyzed on a Bruker Avance NEO 600 MHz spectrometer (Bruker BioSpin, Karlsruhe, Germany) equipped with a CryoProbe Prodigy TCI. Data were acquired at 25°C using the following experiments: proton (^{1}H) (128 scans), carbon-13 (^{13}C) (27,648 scans), double-quantum filtered correlated spectroscopy (DQF-COSY) (16 scans, 256 points in F1), selective total correlation spectroscopy (SelTOCSY) (128 scans), ^{1}H-^{13}C heteronuclear single-quantum coherence (^{1}H-^{13}C-HSQC) (32 scans, 128 points in F1), and ^{1}H-^{13}C heteronuclear multiple-bond correlation (^{1}H-^{13}C HMBC) (32 scans, 4096 points in F1). All experiments used standard pulse programs from the TopSpin library.

3 | Results and Discussion

Initial GC-MS screening (Figures S1 and S2) revealed multiple NPS in the three herbal materials. Table 1 summarized the materials and substances detected in each material by GC-MS and LC-HRMS. In addition, a prominent unknown compound eluting at 13.2 min was observed. Its spectrum partially matched those of brominated SCs—76% ADB-5′Br-PINACA, 63% MDMB-5′Br-4en-PINACA, and 60% ADB-5′Br-4en-PINACA—but all materials displayed a molecular ion at *m/z* 437, suggesting a related yet distinct compound (Figure S3).

In the GC-MS spectrum, the base peak at *m/z* 293 ($C_{13}H_{14}N_2OBr^+$) indicated a loss of the *tert*-leucinate methyl ester ($C_7H_{15}NO_2$, 145.11 Da). Subsequent loss of the pentyl chain (C_5H_{12}) generated *m/z* 223 ($C_8H_4N_2OBr^+$). Loss of the methyl ester moiety ($C_2H_4O_2$, 60.02 Da) from the MDMB-5′Br-PINACA head group was attributed to the ion at *m/z* 378 ($C_{18}H_{25}N_3OBr^+$). The ion at *m/z* 381, consistent with a loss of a *tert*-butyl radical ($C_4H_9\cdot$, 57.07 Da), may have resulted from α-cleavage adjacent to the quaternary carbon of the *tert*-butyl group ($C_{16}H_{20}BrN_3O_3^+$). Bromine-specific isotopic patterns were observed in all major fragments, supporting the presence of a brominated SC (Figure 2a).

TABLE 1 | Summary of seized herbal materials and identified substances by GC-MS and LC-HRMS.

	Material 1	Material 2	Material 3
Seized material			
Material type	Herbal material	Herbal material	Herbal material
ID	ID-17	ID-21	ID-88
Received mass (g)	~20	~20	~20
Date of seizure	July 2024	May 2024	June 2024
Substances identified by GC-MS	ADB-INACA	ADB-INACA	ADB-INACA
	5F-ADB	5F-ADB	5F-ADB
	MDMB-4en-PINACA	MDMB-4en-PINACA	MDMB-4en-PINACA
	N-desalkylgidazepam	*N*-desalkylgidazepam	*N*-desalkylgidazepam
	—	—	Bromazolam
	—	—	Metonitazene
Substances identified by LC-HRMS	MDMB-INACA	MDMB-INACA	MDMB-INACA
	5F-ADB	5F-ADB	5F-ADB
	MDMB-4en-PINACA	MDMB-4en-PINACA	MDMB-4en-PINACA
	N-desalkylgidazepam	*N*-desalkylgidazepam	*N*-desalkylgidazepam
	—	—	Bromazolam
	—	—	Metonitazene

The criteria defined for LC-HRMS analysis followed a precursor ion mass error <5 ppm, isotopic pattern match >80%, MS/MS spectral similarity score >80% to reference spectra in the HighResNPS library (version updated October 2023), and percentage of retention time variation <2%. The substances identified by LC-HRMS were listed in Table 1. Interestingly, the two analytical techniques employed for initial drug screening were fully congruent in the identification of all substances, corroborating the reliability of the analytical findings presented herein. The unknown compound eluted at 9.42 min with *m/z* 438.1391, closely matching the calculated value for $C_{20}H_{29}BrN_3O_3^+$ (438.1387, Δ = −1.14 ppm). Adducts $[M+Na]^+$ (460.1207, Δ = −1.09 ppm) and $[M+K]^+$ (476.0942, Δ = −1.89 ppm) were also observed. The isotopic fingerprint indicated the presence of a single bromine atom, corroborating a brominated SC analog. High-resolution mass spectra revealed a fragmentation pattern similar to ADB-5′Br-PINACA, even though the precursor ion was 14.9975 Da higher, consistent with the replacement of the terminal amide group (–$CONH_2$) by a methyl ester (–$COOCH_3$). The ion at *m/z* 406.1122 ($C_{19}H_{25}N_3O_2Br^+$; Δ = −1.97 ppm) corresponded to the neutral loss of methanol (CH_3OH, 32.0262 Da) from the methyl ester moiety. The fragment at *m/z* 378.1177 ($C_{18}H_{25}N_3OBr^+$; Δ = −1.06 ppm) may be attributed to the loss of the entire methyl ester moiety ($C_2H_4O_2$, 60.0211 Da). The fragment at *m/z* 293.0287 ($C_{13}H_{14}N_2OBr^+$; Δ = −0.68 ppm) was attributed to the loss of the *tert*-leucinate methyl ester side chain ($C_7H_{15}NO_2$, 145.1102 Da). Finally, the ion at *m/z* 222.9502 ($C_8H_4N_2OBr^+$; Δ = −2.24 ppm) was attributed to the loss of both the *tert*-leucinate methyl ester side chain and the five-carbon tail of the indazole ring ($C_{12}H_{27}NO_2$, 217.2042 Da) (Figure 2b). Figures S4 and S5 in the Supporting Information (SI) demonstrated similar findings for materials 1 and 2, respectively.

A semiquantitative comparison of the brominated compound among the three seized herbal materials was carried out by integrating their extracted-ion chromatogram (EIC) areas for

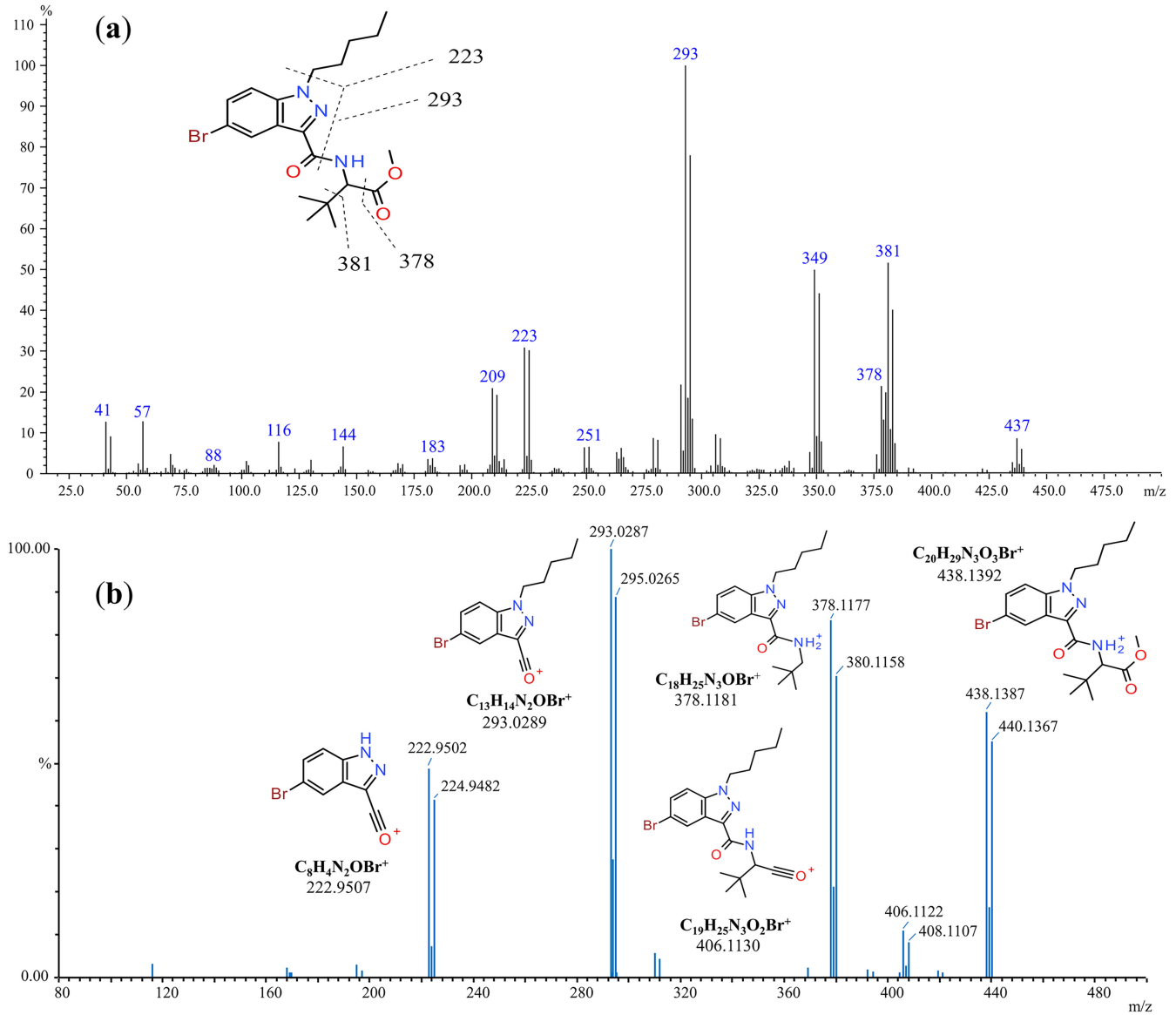


FIGURE 2 | MDMB-5′Br-PINACA mass spectra and proposed fragments using (a) gas chromatography–mass spectrometry (GC-MS; EI, 70 eV) and (b) liquid chromatography–high-resolution mass spectrometry (LC-HRMS; ESI^+).

MDMB-5′Br-PINACA within a 5-ppm mass accuracy window. The brominated compound was equivalently found to be more abundant in materials 1 and 3, both presenting around 30 times more of the new SC than material 2.

Figure 3 displayed the EICs for the NPS detected in seized material 3 (Figure 3a) and for the purified fraction (Figure 3b). EICs for materials 1 and 2 were presented in Figure S6. Additionally, ESI-MS/MS spectra obtained by LC-HRMS analysis for all identified substances were shown in Figure S7. To confirm the structure of MDMB-5′Br-PINACA, a semipreparative LC method was developed to isolate the compound from the seized herbal materials. The isolated fraction was analyzed by LC-PDA (Figure S8), GC-MS (Figure S9), LC-HRMS, and NMR, all confirming its identity.

To further confirm the structure, the sample was analyzed by NMR spectroscopy using ^{1}H, SelTOCSY, ^{13}C, DQF-COSY, ^{1}H-^{13}C HMBC, and ^{1}H-^{13}C HSQC experiments. The complete assignments are listed in Table 2, and all spectra and correlation maps are provided in the SI (Figures S10–S15). Proton H-4 was readily assigned based on two small long-range couplings (4 J = 1.9 Hz and 5 J = 0.7 Hz). Subsequently, H-6 and H-7 were assigned, each showing a large *ortho* coupling together with the expected small *meta* and *para* couplings. Protons H-11 and H-19 were assigned to singlets at 4.60 and 4.71 ppm, respectively. The amide carbonyl resonated at 163.7 ppm and showed an HMBC correlation exclusively with H-8. The ester carbonyl appeared at 173.0 ppm and demonstrated HMBC correlations to H-11 and H-19. These assignments corroborated the presence of the pentyl chain and the *tert*-leucinate methyl ester residue and their connectivity, as supported by the 2D NMR correlation maps. The presence of the ester carbonyl and the characteristic methoxy signal indicated that the compound is a methyl ester. Taken together, the data indicate that the unknown compound is the methyl ester analog of ADB-5′Br-PINACA, in which the tert-leucine–derived primary amide is replaced by a methyl ester at the 3-position side chain.

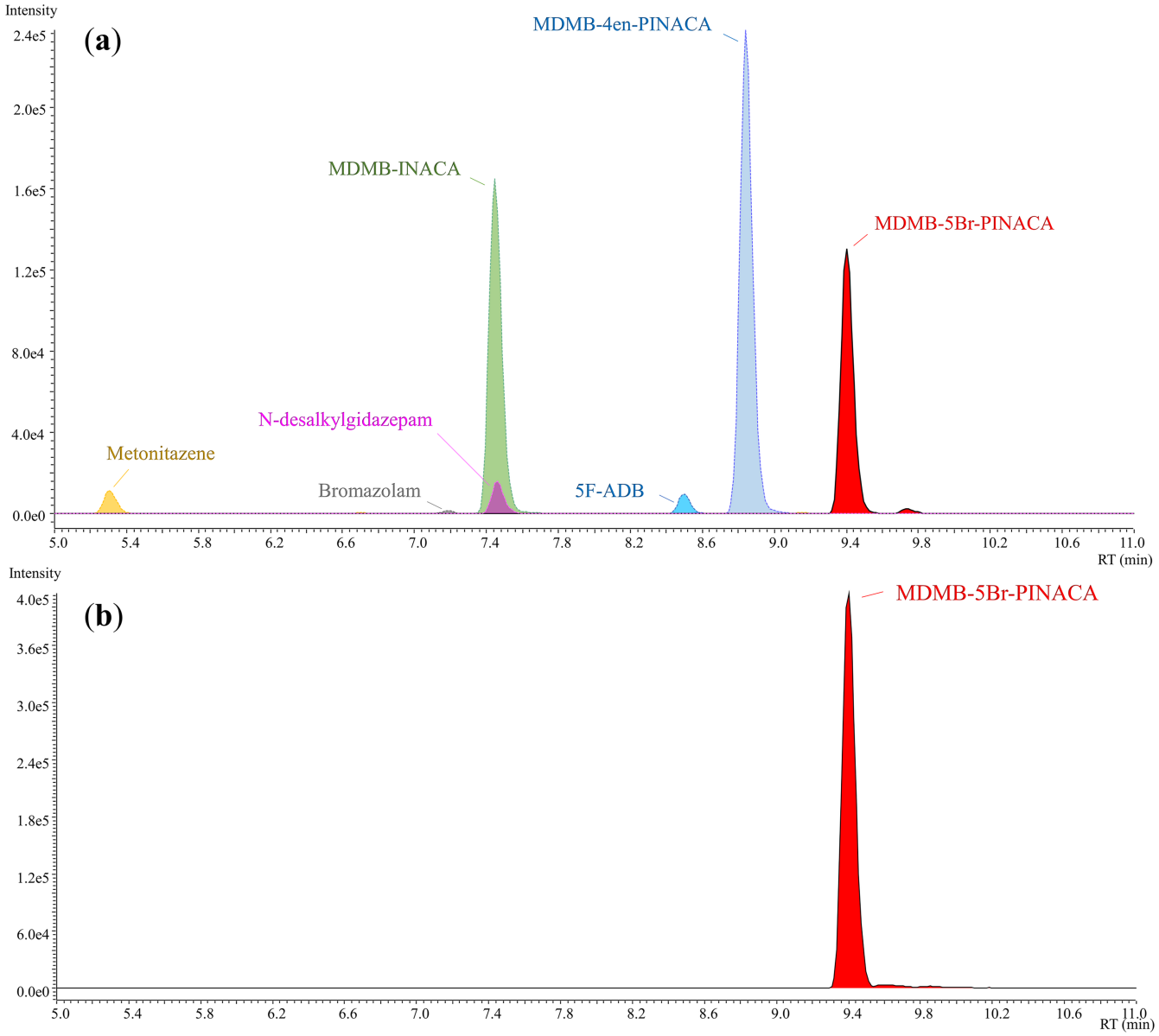
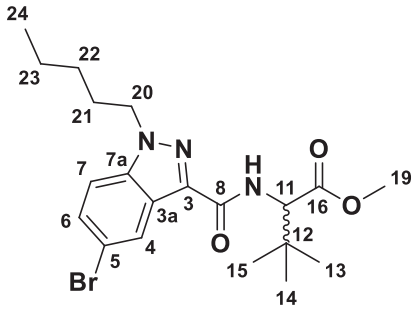


FIGURE 3 | Extracted-ion chromatograms (EICs) of LC-HRMS analyses of (a) seized material 3, showing peaks of all identified substances and (b) the purified fraction of the same material containing only MDMB-5′Br-PINACA.

TABLE 2 | NMR spectral data and structural interpretation of MDMB-5′Br-PINACA.



Label	^{13}C shift (ppm)	^{1}H shift (ppm)	^{1}H multiplicity (coupling constants in Hz)****	^{1}H-COSY correlations	^{1}H-^{13}C-HMBC
3	*	—	—	—	—
3a	*	—	—	—	—
4	125.4	8.37	dd (1.9, 0.7)	2, 3	1, 2, 4
5	117.3	—	—	—	—
6	131.2	7.57	dd (9.0, 1.8)	2, 6	4, 6
7	113.1	7.63	dd (9.0, 0.7)	3, 6	1, 6
7a	141.2	—	—	—	—
8	163.7	—	—	—	—
11	61.2	4.60	s	—	10, 14, 15, 16, 17, 18
12	35.8	—	—	—	—
13–15	27.0	1.09	s	—	13, 14, 15, 16, 17
16	173.0	—	—	—	—
19	52.5	3.78	s	—	18
20	50.6	4.52	t (7.1)	23	4, 23, 24
21***	30.5	1.98	m	22, 24	22, 24, 25
22***	29.9	1.32	m	23, 25	**
23***	23.2	1.39	m	24, 26	**
24***	14.3	0.91	m	25	25, 24

*Correlation to carbons 3 and 3a was not observed in the HMBC spectra recorded; therefore, the chemical shifts for these atoms were not attributed.
**Due to impurities overlapping H-22 and H-23, they were not used for HMBC assignments.
***Chemical shifts were extracted from a selective-TOCSY experiment (SI Figure S13).
****Singlet (s), double-doublet (dd), triplet (t), and multiplet (m).

To exclude the possibility that MDMB-5′Br-PINACA resulted from methanolic esterification of an amide precursor (ADB-5′Br-PINACA), additional extractions were performed using acetonitrile, ethanol, ethyl acetate, and *n*-hexane 7. All extracts were analyzed by GC-MS and revealed only MDMB-5′Br-PINACA. Altogether, these data supported that the detected compound is not an artifact of methanol-induced esterification of ADB-5′Br-PINACA (Figures S16 and S17).

Recent years have seen the emergence of brominated core analogs as a notable strategy to circumvent legislative control. These 5-bromo compounds include not only tail-containing analogs such as ADB-5′Br-PINACA and MDMB-5′Br-4en-PINACA but also tail-less precursors, including ADB-5′Br-INACA and MDMB-5′Br-INACA, which have been detected in Europe and in the United States. Many brominated analogs retain substantial CB_1 receptor activity in vitro, with several exhibiting potencies comparable to earlier SCRAs. Metabolically, the bromine substituent is typically preserved on the core, yielding metabolites with intact brominated scaffolds. The strategy of core bromination of already potent SCRAs not only produces highly active new compounds but also opens a wide array of possible future analogs, highlighting the continuous evolution and diversification of these substances 8.

4 | Conclusion

The synthetic cannabinoid MDMB-5′Br-PINACA was identified in seized herbal materials through comprehensive analytical characterization for the first time. Structural elucidation combined GC-MS, LC-HRMS, and NMR. MDMB-5′Br-PINACA was

characterized as a methyl ester analog of ADB-5′Br-PINACA, featuring a pentyl side chain and a *tert*-leucinate–derived ester moiety. This compound represents a new entry in the growing class of indazole-3-carboxylate cannabinoids, underscoring the need for continued surveillance of emerging NPS.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **FIGURE S1:** GC-MS total ion chromatograms (TIC) of seized herbal materials (a) 1, (b) 2, and (c) 3, extracted with LC-MS-grade methanol. **FIGURE S2:** GC-MS spectra at 70 eV of the compounds identified in the seized materials: (a) MDMB-4en-PINACA, (b) *N*-desalkylgidazepam, (c) 5F-ADB, (d) MDMB-INACA, (e) bromazolam, and (f) metonitazene. **FIGURE S3:** GC-MS spectra at 70 eV of the unknown compound peak at 13.2 min in seized herbal materials (a) 1, (b) 2, and (c) 3, extracted with LC-MS-grade methanol. **FIGURE S4:** LC-HRMS analysis showing the (a) extracted-ion chromatogram, (b) full-scan, and (c) fragmentation mass spectrum of the unknown peak at 9.42 min in seized material 1. **FIGURE S5:** LC-HRMS analysis showing the (a) extracted-ion chromatogram, (b) full-scan, and (c) fragmentation mass spectrum of the unknown peak at 9.42 min in seized material 2. **FIGURE S6:** LC-HRMS extracted-ion chromatogram demonstrating all detected substances in (a) seized material 1 and (b) seized material 2. **FIGURE S7:** ESI-MS/MS spectra of LC-HRMS analysis of the compounds identified in the seized materials: (a) MDMB-INACA, (b) 5F-ADB, (c) MDMB-4en-PINACA, (d) N-desalkylgidazepam, (e) bromazolam, and (f) metonitazene. **FIGURE S8:** LC-PDA analysis at 306 nm of (a) seized herbal material 3 and (b) the purified peak containing MDMB-5′Br-PINACA. **FIGURE S9:** GC-MS analysis of the purified peak containing MDMB-5′Br-PINACA showing the (a) GC-MS total ion chromatogram and (b) GC-MS mass spectrum at 70 eV. **FIGURE S10:** dta70012-sup-0010-Supplementary_FigureS10.tif. ^{1}H spectrum (600 MHz) of purified MDMB-5′Br-PINACA in CD_3OD. **FIGURE S11:** dta70012-sup-0011-Supplementary_FigureS11.tif. ^{13}C spectrum (151 MHz) of purified MDMB-5′Br-PINACA in CD_3OD. **FIGURE S12:** DQF-COSY correlation map (600 MHz) of purified MDMB-5′Br-PINACA in CD_3OD. (a) Full correlation map −1 to 10 ppm; (b) expansion of the aromatic region of the correlation map; (c) expansion of the aliphatic region of the correlation map. **FIGURE S13:** SelTOCSY spectrum (600 MHz) of purified MDMB-5′Br-PINACA in CD_3OD. The selective pulse was applied at the peak at 4.52 ppm with a TOCSY spinlock duration of 80 ms. **FIGURE S14:** dta70012-sup-0014-Supplementary_FigureS14.tif. ^{1}H-^{13}C-HSQC correlation map (600 MHz) of purified MDMB-5′Br-PINACA in CD_3OD (phase edition: CH and CH_3 red/CH_2 blue). (a) Full correlation map 0 to 8.5 ppm; (b) expansion of the aromatic region of the correlation map; (c) expansion of the 3.5- to 5-ppm region of the correlation map; (d) expansion of the aliphatic region of the correlation map. **FIGURE S15:** dta70012-sup-0015-Supplementary_FigureS15.tif. ^{1}H-^{13}C-HMBC correlation map (600 MHz) of purified MDMB-5′Br-PINACA in CD_3OD. (a) Full correlation map −1 to 10 ppm; (b) expansion of the aromatic region of the correlation map; (c) expansion of the 3.5- to 5-ppm region of the correlation map; (d) expansion of the aliphatic region of the correlation map. **FIGURE S16:** GC-MS total ion chromatogram of seized material 3 extracted by (a) LC-MS grade acetonitrile, (b) ethyl acetate, (c) *n*-hexane, and (d) ethanol. **FIGURE S17:** GC-MS spectra at 70 eV of seized material 3 extracted by (a) LC-MS grade acetonitrile, (b) ethyl acetate, (c) *n*-hexane, and (d) ethanol, corresponding to the chromatographic peak at 13.2 min identified as MDMB-5′Br-PINACA. **Data S1:** Supplementary Information.