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Identification of five substituted phenethylamine derivatives 5-MAPDB, 5-AEDB, MDMA methylene homolog, 6-Br-MDMA, and 5-APB-NBOMe

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This paper reports analytical properties of five substituted phenethylamine derivatives seized from a clandestine laboratory. These five derivatives include 5-(2-methylaminopropyl)-2,3-dihydrobenzofuran (5-MAPDB, 1), 5-(2-aminoethyl)-2,3-dihydrobenzofuran (5-AEDB, 2), *N*,2-dimethyl-3-(3,4-methylenedioxyphenyl)propan-1-amine (MDMA methylene homolog, 3), 6-bromo-3,4-methylenedioxymethamphetamine (6-Br-MDMA, 4), and 1-(benzofuran-5-yl)-*N*-(2-methoxybenzyl)propan-2-amine (5-APB-NBOMe, 5). These compounds were identified by liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF-MS), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance spectroscopy (NMR). No analytical properties about compounds 1-4 have appeared until now, making this the first report on these compounds. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords: new psychoactive substance; substituted phenethylamine derivatives; 5-AEDB; 5-MAPDB; MDMA methylene homolog; 6-Br-MDMA; 5-APB-NBOMe

Introduction

In recent years, a large number of new psychoactive substances (NPS) have emerged on the drug market.[1,2] By July 2015, 96 countries and territories reported over 540 NPS to United Nations Office on Drugs and Crime (UNODC), far exceeding the 244 substances (10 were newly added to the list of the Convention on Psychotropic Substances of 1971 or the Single Convention on Narcotic Drugs of 1961 on 13 March 2015) currently controlled under the International Drug Conventions.[3] Many different groups of NPS, such as synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, and plant-based substances, etc., have been encountered by law enforcement.[4]

Biogenic monoamine neurotransmitter, for example norepinephrine (NE), dopamine (DA), and serotonin (5-HT), are involved in the regulation of diverse biological functions such as emotion, arousal, and mood. Many phenethylamine derivatives could produce psychoactive effects through modulation of the monoamine neurotransmitter systems, resulting in their abuse as stimulants, psychedelics, or entactogens.[5–8] Ring-substituted phenethylamines have been on the drug market for more than 50 years, but increased interest in these substances originated from the publication of PIHKAL.[9] In addition to substances such as amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA),[10] other ring-substituted derivatives have been continuously detected in the drug market.[11–20]

In June 2015, a clandestine laboratory was dismantled in Hubei Province of China, and about 20 kg of NPS powder samples were seized. About 200 unknown samples were submitted to the national narcotics laboratory of the Ministry of Public Security for analysis. Nineteen species of substituted phenethylamine derivatives were identified, including: 5-(2-methylaminopropyl)-2,3-dihydrobenzofuran (5-MAPDB, **1**), 5-(2-aminoethyl)-2,3-dihydrobenzofuran (5-AEDB, **2**), *N*,2-dimethyl-3-(3,4-methylenedioxyphenyl)propan-1-amine (MDMA methylene homolog, **3**), 6-bromo-3,4-methylenedioxymethamphetamine (6-Br-MDMA, **4**), and 1-(benzofuran-5-yl)-*N*-(2-methoxybenzyl)propan-2-amine (5-APB-NBOMe, **5**). This paper reports on the analytical properties of these five compounds. Their structures are shown in Figure 1. Structure elucidation was carried out by means of liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF-MS), gas chromatography mass spectrometry (GC-MS), and nuclear magnetic resonance spectroscopy (NMR).

Some data about compounds **1-5** are available. The pharmacological information of 5-MAPDB (**1**) has been reported by Rickli *et al.*[7] whereas 5-AEDB (**2**) has been used as chemical reagent for synthesis.[21] Two isomers of MDMA methylene homolog (**3**), called MBDB and HMDMA, have been described in the literatures.[22–25] 6-Br-MDMA (**4**) has been detected in Europe and reported by the

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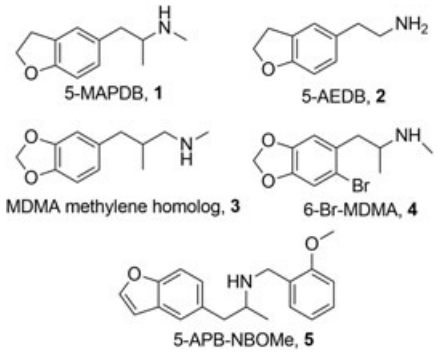


Figure 1. Chemical structures of the five substituted phenethylamine derivatives.

EMCDDA in 2014.[2] But, to our knowledge, analytical data on **1-4** have not been available. The GC-MS, NMR, and IR data of 5-APB-NBOMe (**5**) have been recently reported by Westphal *et al.*, but without high resolution LC-MS data.[26] Our paper added the high resolution LC-MS data and presented the NMR data with a different deuterated solvent to make the analytical properties of **5** more exhaustive.

Materials and methods

Materials

Methanol and formic acid were obtained from Merck Chemicals (Darmstadt, Germany). Acetonitrile was obtained from Fisher Scientific (Aalst, Belgium). All reagents used in the analyses were of high performance liquid chromatography (HPLC) grade. Distilled water was obtained by reverse diffusion in a Millipore system (EMD Millipore, Billerica, MA, USA). For NMR, deuterated methanol (CD_3OD, 99.8 %) was purchased from Cambridge Isotope Laboratories (Tewksbury, MA, USA).

Sample preparation

For GC-MS analysis, 5 mg of sample was added to 5 mL of methanol and sonicated for 10 min followed by filtration. For LC-QTOF-MS analysis, the prepared solution was diluted to 1 μg/mL with 0.1% formic acid (*v/v*) in water. For NMR analysis, about 15 mg of the sample powder was dissolved in 1 mL of deuterated methanol.

Instrumentation

LC-QTOF-MS analysis was carried out using a Waters Acquity UPLC (Waters, Milford, MA, USA) coupled with AB Sciex TripleTOF 5600 detector (AB Sciex, Framingham, MA, USA). Separation was performed at 40 °C with an Acquity UPLC CSH^{TM} C18 column (10 cm × 2.1 mm i.d., 1.7 μm particle diameter; Waters). For gradient elution, the mobile phases 0.1 % formic acid in water (A) and acetonitrile (B) were mixed according to these conditions: 0-1.5 min, 2% B, linear to 90% B at 6.5 min, hold at 90% to 9.4 min, back to 2% B at 9.5 min and equilibration to 12 min. The flow rate was 0.4 mL/min. The QTOF instrument was operated by electrospray ionization (ESI) in positive mode with these parameters: Ion spray voltage, 5.5 kV; turbo spray temperature, 600 °C; nebulizer gas (Gas 1), 50 psi; heater gas (Gas 2), 50 psi; and curtain gas, 30 psi. Nitrogen was used as the nebulizer and auxiliary gas. Typical information dependent acquisition consisted of two steps: the acquisition of a survey full scan spectrum followed by a tandem mass spectrometry (MS/MS) experiment. The full scan experiment was operated in high-resolution mode. The optimized declustering potential and collision energy were set at 80 V and 5 V, respectively. In the second experiment, a sweeping collision energy setting at 25 ± 15 V was applied for collision-induced dissociation (CID) to obtain the fragment ions from the ions in the preceding scan. The full scan and the MS/MS experiment were both operated in the mass range of *m/z* 35-500. Injection volume was 1 μL. Under these conditions the investigated compounds eluted at the following retention times: 2.0 min for 5-AEDB; 2.9 min for 5-MAPDB; 3.1 min for MDMA methylene homolog; 3.3 min for 6-Br-MDMA; and 4 min for 5-APB-NBOMe.

GC-MS analysis was performed using a Shimadzu 2010 gas chromatograph coupled with a QP2010 plus mass selective detector (Shimadzu, Kyoto, Japan). Chromatographic separation was carried out on a DB-5 MS capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness) (J&W Scientific, Agilent Technologies, Palo Alto, CA, USA) and helium at a constant flow rate of 1.0 mL/min was used as the carrier gas. The filtered solutions were injected in split mode (20:1). The initial column temperature (60 °C) was increased to 280 °C at a rate of 20 °C /min, and held at 280 °C for 20 min, then ramped up to 300 °C at a rate of 10 °C /min, and finally held at 300 °C for 20 min. The GC injector and transfer line were maintained at 280 °C and 250 °C, respectively. Ionization energy was set at 70 eV. Acquisition was carried out in a scan mode range of *m/z* 35-500. Injection volume was 1 μL. Under these conditions the retention times for the investigated compounds were 8.0 min for 5-MAPDB; 7.9 min for 5-AEDB; 8.1 min for MDMA methylene homolog; 9.2 min for 6-Br-MDMA; and 11.9 min for 5-APB-NBOMe.

The NMR spectra were obtained on an Avance III 400 spectrometer (Bruker, Bremen, Germany) at 300 K with 400 MHz for ^{1}H and 100 MHz for ^{13}C. Assignments were made via ^{1}H-NMR, ^{13}C-NMR, ^{13}C-distortionless enhancement by polarization transfer (^{13}C-DEPT), $^{1}H/^{1}H$ correlation spectroscopy ($^{1}H/^{1}H$-COSY), $^{1}H/^{13}C$-heteronuclear single-quantum correlation spectroscopy ($^{1}H/^{13}C$-HSQC), and $^{1}H/^{13}C$-hetero nuclear multiple-bond correlation spectroscopy ($^{1}H/^{13}C$-HMBC) spectra. The chemical shifts for ^{1}H and ^{13}C NMR spectra were referenced to the residual solvent peak of CD_3OD at 3.31 ppm for ^{1}H NMR spectra and 49.0 ppm for ^{13}C NMR spectra.

Results and discussion

LC-QTOF-MS and GC-MS analyses of compounds 1-5

Accurate masses and chemical formulae of **1-5** were determined in full scan mode by LC-QTOF-MS (Figure 2, left spectra). The fragmentation of the molecular ion was performed in MS/MS mode, and a collision energy range of 25 ± 15 V was chosen instead of fixed collision energy to obtain more product ions information. In addition, the accurate masses of the product ions obtained (Figure 2, right spectra) provided further structural information. Theoretical and experimental masses, chemical formulae for protonated molecular ions and product ions of **1-5** are summarized in Table 1. Errors between the experimental and theoretical masses were all below 5 ppm. The proposed LC-QTOF-MS fragmentation patterns of these five protonated compounds following ESI ionization are proposed in Figure 3. For GC-MS analysis, mass spectra of compounds **1-5**

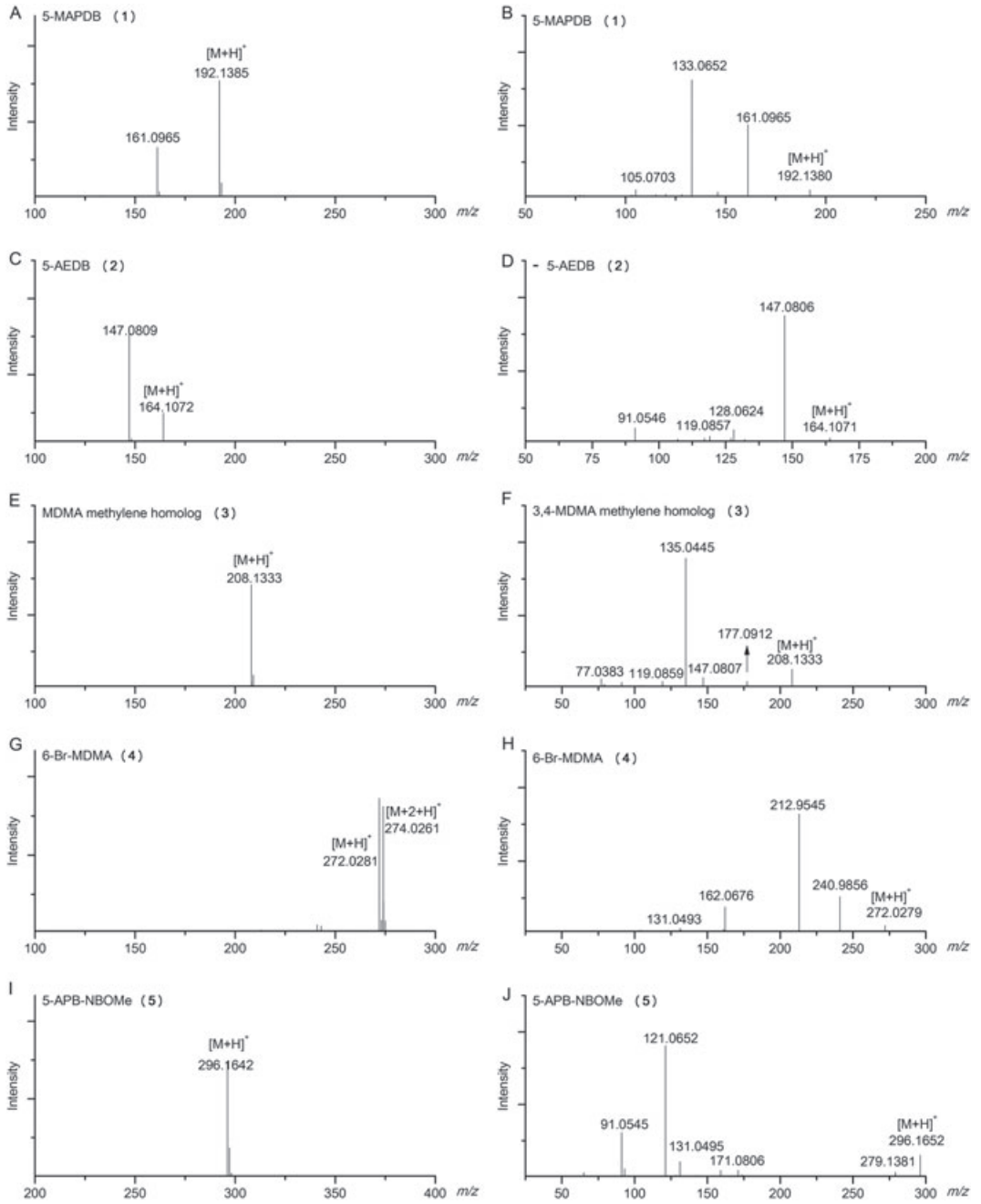


Figure 2. (A-J) Mass spectra of compounds **1-5** obtained by LC-ESI-QTOF-MS in full scan mode (left spectra) and tandem MS/MS mode (right spectra).

under electron ionization and their fragmentation routes are proposed in Figure 4.

Identification of compound 1

The LC-QTOF-MS data of **1** showed the protonated molecule $[M+H]^+$ at *m/z* 192.1385 (Figure 2A and Table 1, fragment A0) and a fragment ion at *m/z* 161.0965 ($C_{11}H_{13}O^+$, A1) formed by the cleavage of the CH_3NH_2 moiety from the molecular ion. The ion observed at *m/z* 133.0652 ($C_9H_9O^+$, A2) was formed by the loss of the C_2H_4 moiety from A1. In turn, the loss of the CO moiety from A2 resulted in the formation of the ion 105.0703 ($C_8H_9^+$, A3).

The EI mass spectrum (Figure 4A) had a base peak at *m/z* 58 which is the immonium ion formed by α-cleavage, which is a characteristic ion for *N*-methyl phenethylamines.[27] The ion at *m/z* 134 ($C_9H_{10}O^{+\cdot}$) was formed by the same α-cleavage. The ion at *m/z* 176 could be formed by the dissociation of the methyl group, whereas ion at *m/z* 161 was generated by the cleavage of C-N bond. The ion at *m/z* 77 is characteristic the phenyl fragment.

Final structure elucidation of **1** was carried out by NMR spectroscopy. The full list of signals and appropriate assignments is presented in Table 2. The NMR spectra showed that **1** had a dihydrobenzofuran moiety bonded to an *N*-methylpropan-2-amine moiety. The key connection of the two moieties was revealed by the proton chemical shifts, peak patterns, carbon

Table 1. Accurate masses of the protonated molecules and product ions and their proposed chemical formulae obtained for compounds **1-5** measured by LC-QTOF-MS

Compound	RT(min)	Fragment	Chemical formula	Theoretical mass	Experimental mass	Error (ppm)
5-MAPDB, **1**	2.9	A0	$C_{12}H_{18}NO^+$	192.1383	192.1385	1.04
		A1	$C_{11}H_{13}O^+$	161.0961	161.0965	2.48
		A2	$C_9H_9O^+$	133.0648	133.0652	3.01
		A3	$C_8H_9^+$	105.0699	105.0703	3.81
5-AEDB, **2**	2.0	B0	$C_{10}H_{14}NO^+$	164.1070	164.1072	1.22
		B1	$C_{10}H_{11}O^+$	147.0804	147.0806	1.36
		B2	$C_{10}H_8^{+\cdot}$	128.0621	128.0624	2.34
		B3	$C_9H_{11}^+$	119.0855	119.0857	1.68
		B4	$C_7H_7^+$	91.0542	91.0546	4.39
MDMA methylene homolog, **3**	3.1	C0	$C_{12}H_{18}NO_2^+$	208.1332	208.1333	0.48
		C1	$C_{11}H_{13}O_2^+$	177.0910	177.0912	1.13
		C2	$C_{10}H_{11}O^+$	147.0804	147.0807	2.04
		C3	$C_8H_7O_2^+$	135.0441	135.0445	2.96
		C4	$C_6H_5^+$	77.0386	77.0383	-3.89
6-Br-MDMA, **4**	3.3	D0	$C_{11}H_{15}BrNO_2^+$	272.0281	272.0281	0
		D1	$C_{10}H_{10}BrO_2^+$	240.9859	240.9856	-1.24
		D2	$C_8H_6BrO_2^+$	212.9546	212.9545	-0.47
		D3	$C_{10}H_{10}O_2^{+\cdot}$	162.0675	162.0676	0.62
		D4	$C_9H_7O^+$	131.0491	131.0493	1.53
5-APB-NBOMe, **5**	4.0	E0	$C_{19}H_{22}NO_2^+$	296.1645	296.1642	-1.01
		E1	$C_{19}H_{19}O_2^+$	279.1380	279.1381	0.36
		E2	$C_{12}H_{11}O^+$	171.0804	171.0806	1.17
		E3	$C_9H_7O^+$	131.0491	131.0495	3.05
		E4	$C_8H_9O^+$	121.0648	121.0652	3.30
		E5	$C_7H_7^+$	91.0542	91.0545	3.29

chemical shifts, and HMBC correlations. The broad singlet proton at 4′ position and the doublet proton at 7′ position indicated that the substitution was at 5′ position. The HMBC correlation between H-1 and H-2 to the C-5′, and between H-4′ and H-6′ to C-1 additionally confirmed the 5′ position substitution.

Identification of compound 2

The LC-QTOF-MS data of **2** showed the protonated molecule $[M+H]^+$ at *m/z* 164.1072 (Figure 2C and Table 1, fragment B0). The difference between the molecular formulae of **2** ($C_{10}H_{13}NO$) and **1** ($C_{12}H_{17}NO$) was represented by C_2H_4. The predominant ion at *m/z* 147.0806 ($C_{10}H_{11}O^+$, B1) can be formed by the cleavage of the NH_3 moiety from B0, indicating that **2** was a primary amine. The radical fragmented ion $C_{10}H_8^{+\cdot}$ at *m/z* 128.0624 (B2) may possibly be formed by the dissociation of the radical OH and H_2 moiety from B1. In turn, the *m/z* 91.0546 species ($C_7H_7^+$, B4) was the tropylium ion.

The EI mass spectrum (Figure 4B) of **2** exhibited similar ions at *m/z* 134, 105, and 77 as **1**, suggesting that **2** had the same methyl-2,3-dihydrobenzofuran moiety like **1**.

The structure of **2** was further elucidated by NMR analysis. The ^{13}C NMR spectrum of **2** was comparable to that of **1** (position 2′ to 7′a) as shown in Table 3, indicating that **2** showed the 2,3-dihydrobenzofuran moiety. The observed one- and two-dimensional spectra showed that the alkyl chain in compound **2** was a 5-substitutted ethylamine.

Identification of compound 3

The LC-QTOF-MS data of **3** showed the protonated molecule $[M+H]^+$ at *m/z* 208.1333 (Figure 2E and Table 1, fragment C0). The ion observed at *m/z* 177.0912 ($C_{11}H_{13}O_2^+$, C1) can be formed by the cleavage of the C-N bond. The predominant ion at *m/z* 135.0445 ($C_8H_7O_2^+$, C3) was a characteristic ion of the methylenedioxybenzyl species, which can be formed by the cleavage of the C_3H_6 moiety from C1. The ion at *m/z* 147.0807 ($C_{10}H_{11}O^+$, C2) was formed by the loss of formaldehyde from C1.

The predominant ion in the EI mass spectrum (Figure 4C) was observed at *m/z* 44 following α-cleavage. The radical ion observed at *m/z* 176 was formed by the cleavage of the C-N bond. The characteristic 3, 4-methylenedioxybenzyl fragment at *m/z* 135 with subsequent loss of formaldehyde gave rise to a suspected tropylium ion at *m/z* 105.

The structure of **3** was further elucidated by NMR analysis. Proton spectrum for **3** indicated the typical 1, 3, 4-trisubstituted benzene peak pattern, an O-CH_2-O group, and a CH_2-CH (CH_3)-CH_2-NH-CH_3 group. Finally, on the basis of mass spectra and NMR data (Table 4) as shown above, the structure of **3** was determined as *N*,2-dimethyl-3-(3,4-methylenedioxyphenyl)propan-1-amine, which is a MDMA methylene homolog.

Identification of compound 4

The LC-QTOF-MS spectrum of **4** showed the protonated molecule $[M+H]^+$ at *m/z* 272.0281 (Table 1, fragment D0), which included

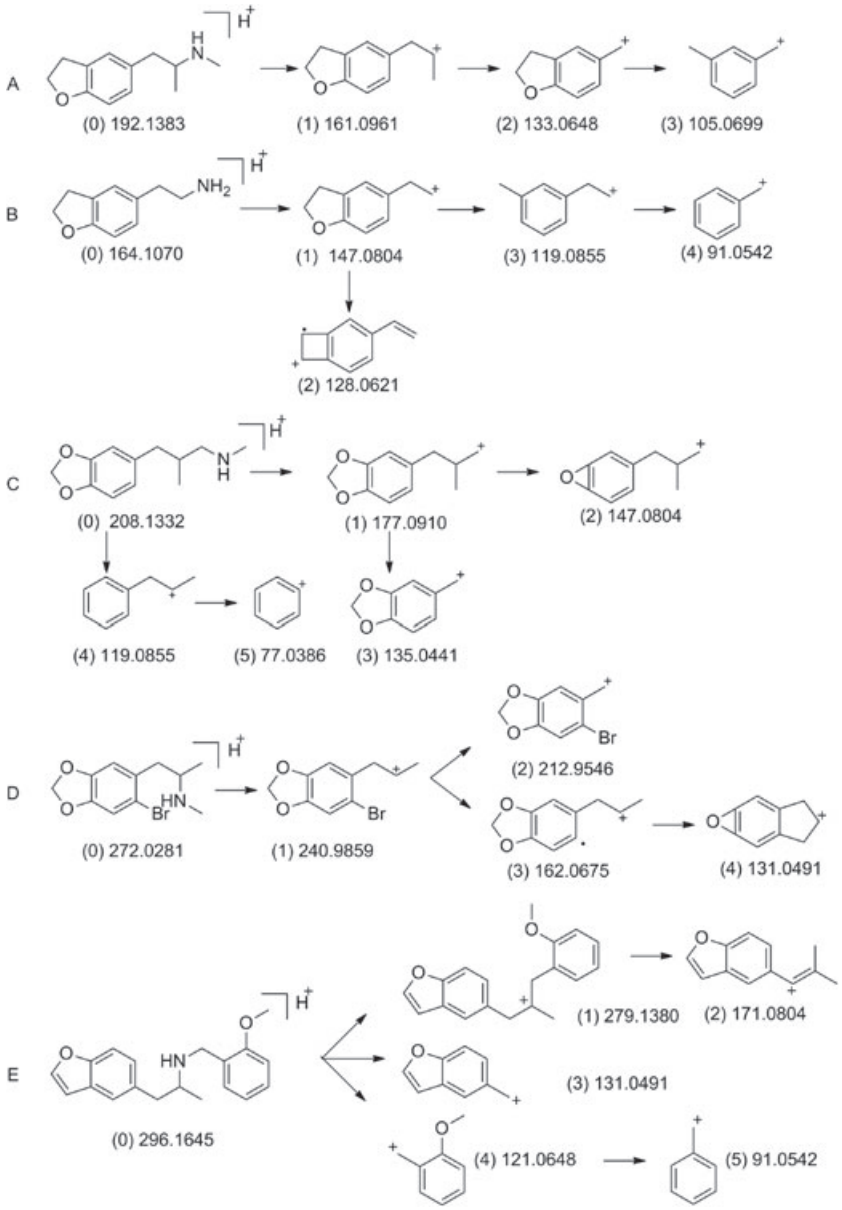


Figure 3. (A-E) Proposed fragmentation routes of protonated compounds **1-5** by LC-ESI-QTOF-MS.

the presence of the bromine isotopic pattern consistent with mono bromine substitution (Figure 2G). The ion recorded at *m/z* 240.9856 ($C_{10}H_{10}BrO_2^+$, D1) was formed by cleavage of the C-N bond and loss of CH_3NH_2 moiety from $C_{11}H_{15}BrNO_2^+$ (D0). The dissociation of C_2H_4 and bromine radical from D1 resulted in the formation of the ions at *m/z* 212.9545 ($C_8H_6BrO_2^+$, D2) and 162.0676 ($C_{10}H_{10}O_2^{+\cdot}$, D3), respectively. Further dissociation of D3 resulted in the loss of the CH_3O radical and the formation of ion 131.0493 ($C_9H_7O^+$, D4).

The predominant ion observed at *m/z* 58 ($C_3H_8N^+$) in the EI mass spectrum (Figure 4D) was a result of α-cleavage of the amine side chain (Figure 4D). The higher mass ranges were relatively weak and the molecular ion was not detected in the spectrum. Nitrogen-driven α-cleavage is the predominate fragmentation process of this class of compounds.[6] NMR spectra were obtained for structural confirmation, especially pertaining to the position of the bromine atom on the aromatic ring. The NMR spectra suggested the presence of two aromatic protons [δ_H 6.91 ppm and 7.07 ppm] as shown in Table 5. These two aromatic protons with their singlet appearance and the HMBC spectra confirmed the *para* arrangement of the protons on the aromatic ring, i.e., in the 2′ and 5′ positions, therefore the bromine atom was determine to be in the 6′ position.

Identification of compound 5

The LC-QTOF-MS data of **5** showed the protonated molecule at *m/z* 296.1642 (Table 1, fragment E0) ($C_{19}H_{22}NO_2^+$). The predominant ion at *m/z* 121.0652 ($C_8H_9O^+$, E4) was formed by the cleavage of the C-N bond and corresponded to the methoxylated tropylium ion. The ion at *m/z* 91.0545 ($C_7H_7^+$, E5) was formed by the loss of formaldehyde form E4. The ion at *m/z* 131.0495 ($C_9H_7O^+$, E3) could be a benzofuran-5-ylmethylium formed by the dissociation of the C-C

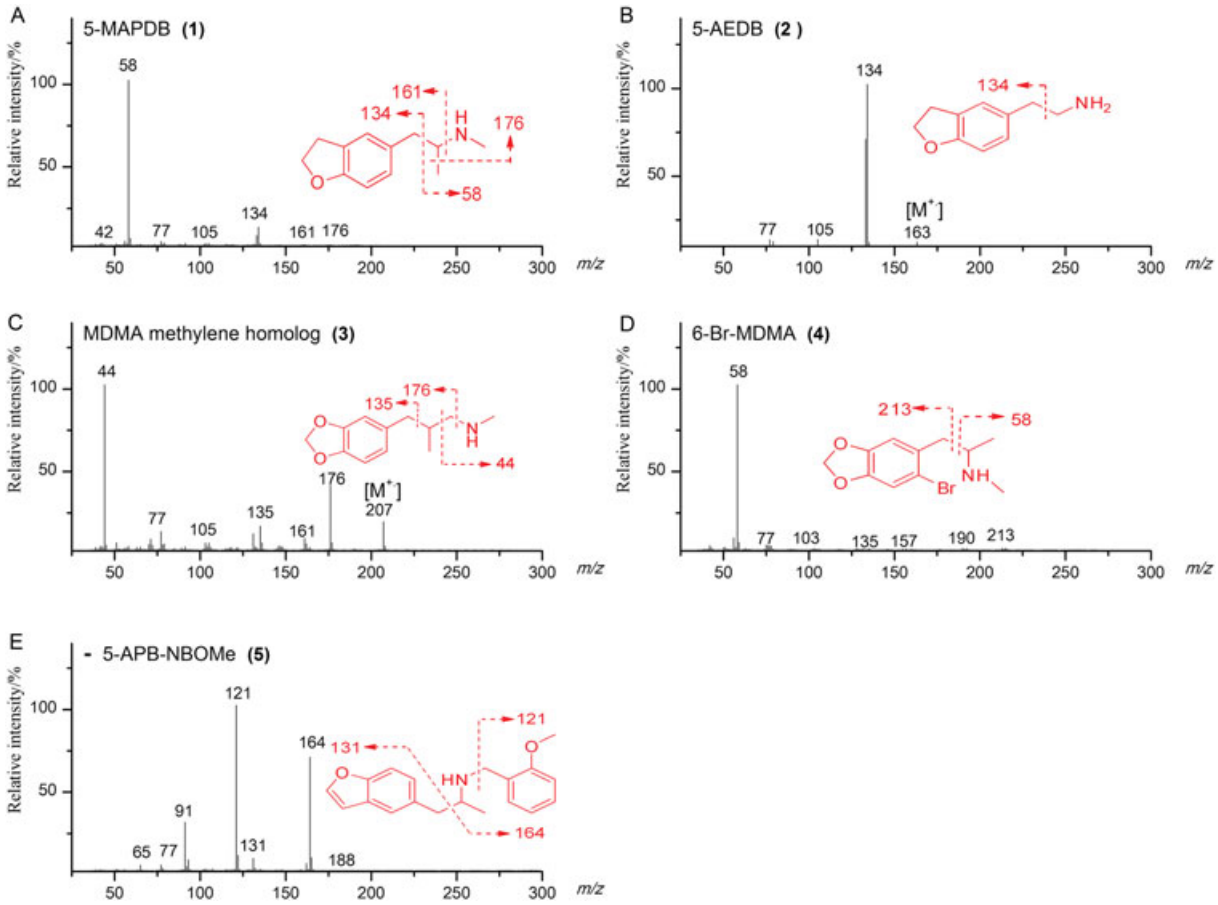
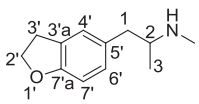


Figure 4. (A-E) Mass spectra of compounds **1-5** obtained by GC-EI-MS together with their probable fragmentation modes.

Table 2. ^{1}H and ^{13}C NMR chemical shifts and diagnostic correlations in two-dimensional spectra of 5-MAPDB (**1**)

Position



	^{13}C (δ/ppm)	^{1}H (δ/ppm, protons, multiplicity[a], coupling constants) $^{1}H/^{13}C$-HSQC correlation	$^{1}H/^{1}H$-COSY correlation	$^{1}H/^{13}C$-HMBC correlation[b]
1	39.7	3.06, 1H, dd, J = 13.6, 5.6 Hz and 2.70, 1H, dd, J = 13.6, 9.2 Hz, overlapped	2	2, 3, 4′, 5′, 6′
2	58.1	3.40, 1H, m	1, 3	1, 3, 5′, N-CH_3
3	15.7	1.24, 3H, d, J = 6.8 Hz	2	1, 2
2′	72.4	4.53, 2H, t, J = 8.7 Hz	3′	3′, 3′a, 7′a
3′	30.5	3.19, 2H, t, J = 8.7 Hz	2′, 4′	2′, 3′a, 4′,7′a
3′a	129.4	-	-	-
4′	127.0	7.13, 1H, brs	3′, 6′	1, 3′, 6′, 7′a
5′	128.7	-	-	-
6′	130.0	6.98, 1H, dd, J = 8.3, 1.4 Hz	4′, 7′	1, 4′, 7′a
7′	110.3	6.70, 1H, d, J= 8.3 Hz	6′	3′a, 5′, 7′a
7′a	160.9	-	-	-
N-CH_3	30.9	2.71, 3H, s, overlapped	-	2

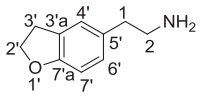
Recorded in CD_3OD at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively.

[a]br = broad, d = doublet, m = multiplet, s = singlet, t = triplet.

[b]HMBC: heteronuclear multiple-bond correlation spectroscopy. The proton signal correlated with the indicated carbons.

Table 3. ^{1}H and ^{13}C NMR chemical shifts and diagnostic correlations in two-dimensional spectra of 5-AEDB (**2**)

Position



	^{13}C (δ/ppm)	^{1}H (δ/ppm, protons, multiplicity[a], coupling constants) $^{1}H/^{13}C$-HSQC correlation	$^{1}H/^{1}H$-COSY correlation	$^{1}H/^{13}C$-HMBC Correlation[b]
1	34.0	2.89, 2H, m	2	2, 4′, 5′, 6′
2	42.4	3.12, 2H, m	1	1, 5′
2′	72.3	4.52, 2H, t, J = 8.7 Hz	3′	3′, 3′a, 7′a
3′	30.5	3.18, 2H, t, J = 8.7 Hz	2′, 4′	2′, 3′a, 4′, 7′, 7′a
3′a	129.30	-	-	-
4′	126.4	7.13, 1H, brs	3′, 6′	1, 3′, 6′, 7′a
5′	129.6	-	-	-
6′	129.33	6.99, 1H, m	4′, 7′	1, 4′, 7′a
7′	110.3	6.69, 1H, d, J = 8.0 Hz	6′	3′a, 5′, 7′a
7′a	160.7	-	-	-

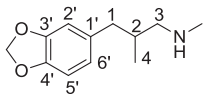
Recorded in CD_3OD at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively.

[a]br = broad, d = doublet, m = multiplet, s = singlet, t = triplet.

[b]HMBC: heteronuclear multiple-bond correlation spectroscopy. The proton signal correlated with the indicated carbons.

Table 4. ^{1}H and ^{13}C NMR chemical shifts and diagnostic correlations in two-dimensional spectra of MDMA methylene homolog (**3**)

Position



	^{13}C (δ/ppm)	^{1}H (δ/ppm, protons, multiplicity[a], coupling constants) $^{1}H/^{13}C$-HSQC correlation	$^{1}H/^{1}H$-COSY correlation	$^{1}H/^{13}C$-HMBC correlation[b]
1	41.4	2.69, 1H, dd, J = 13.6, 6.0 Hz, overlapped and 2.37, 1H, dd, J = 13.6, 8.8 Hz	2	2, 3, 4, 1′, 2′, 6′
2	34.2	2.13, 1H, m	1, 3, 4	1, 3, 4, 1′
3	56.2	2.86, 1H, dd, J = 12.2, 5.8 Hz and 2.75, 1H, dd, J = 12.2, 8.2 Hz, overlapped	2	1, 2, 4, N-CH_3
4	17.4	0.96, 3H, d, J = 6.8 Hz	2	1, 2, 3
1′	134.4	-	-	-
2′	110.4	6.73, 1H, d, J = 1.5 Hz, overlapped	6′	1, 4′, 6′
3′	149.2	-	-	-
4′	147.5	-	-	-
5′	109.0	6.73, 1H, d, J = 7.7 Hz, overlapped	6′	1′, 3′
6′	123.2	6.66, 1H, dd, J = 7.7, 1.5 Hz	2′, 5′	1, 2′, 4′
O-CH_2	102.2	5.89, 2H, s	-	3′, 4′
N-CH_3	34.4	2.64, 3H, s	-	3

Recorded in CD_3OD at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively.

[a]br = broad, d = doublet, m = multiplet, s = singlet, t = triplet.

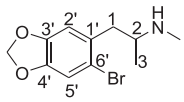
[b]HMBC: heteronuclear multiple-bond correlation spectroscopy. The proton signal correlated with the indicated carbons.

bond between α- and β-carbon atoms. The ion at *m/z* 297.1381 ($C_{19}H_{19}O_2^+$, E1) might have been formed by cleavage of the NH_3 moiety from E0, which is consistent with what was proposed by Sekula *et al.*[19] Moreover, the dissociation of E1 resulted in the formation of the ion at *m/z* 171.0806 ($C_{12}H_{11}O^+$, E2).

The predominant ion at *m/z* 121 in the EI mass spectrum (Figure 4E) can be formed by the cleavage of the C-N bond leading to the formation of a methoxy-benzyl cation. The ions observed at *m/z* 164 and 131 were formed by the cleavage of C-C bond the between α- and β-carbon atoms. Such cleavage is a characteristic feature of the EI mass spectra of phenylethylamines.

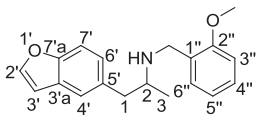
The structure of **5** was further elucidated by NMR analysis. The observed 1D and 2D NMR spectra suggested the presence of 5-(2-aminopropyl)benzofuran (5-APB) and (2-methoxy)benzyl (NBOMe) moieties as shown in Table 6. The key connections of the two moieties were revealed by the HMBC correlations. Namely, HMBC correlation from the proton at position 2 and the benzyl CH_2 carbon suggested that the amine nitrogen was attached to the CH_2 moiety of the benzyl group.

Table 5. ^{1}H and ^{13}C NMR chemical shifts and diagnostic correlations in two-dimensional spectra of 6-Br-MDMA (**4**)

Position				
	^{13}C (δ/ppm)	^{1}H (δ/ppm, protons, multiplicity[a], coupling constants) $^{1}H/^{13}C$-HSQC correlation	$^{1}H/^{1}H$-COSY correlation	$^{1}H/^{13}C$-HMBC correlation[b]
1	39.7	3.22, 1H, dd, J = 13.6, 5.2 Hz, overlapped and 2.89, 1H, dd, J = 13.6, 9.6 Hz	2	2, 3, 1′, 2′, 3′, 6′
2	56.6	3.51, 1H, m	1, 3	1, 3, 1′, N-CH_3
3	15.7	1.27, 3H, d, J = 6.4 Hz	2	1, 2
1′	129.4	-	-	-
2′	112.1	6.91, 1H, s	-	1, 4′, 6′
3′	149.4	-	-	-
4′	149.5	-	-	-
5′	113.8	7.07, 1H, s	-	1, 1′, 3′, 4′, 6′
6′	115.9	-	-	-
O-CH_2	103.6	6.01, 2H, s	-	3′, 4′
N-CH_3	31.0	2.76, 3H, s	-	2

Recorded in CD_3OD at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively.
[a]br = broad, d = doublet, m = multiplet, s = singlet, t = triplet.
[b]HMBC: heteronuclear multiple-bond correlation spectroscopy. The proton signal correlated with the indicated carbons.

Table 6. ^{1}H and ^{13}C NMR chemical shifts and diagnostic correlations in two-dimensional spectra of 5-APB-NBOMe (**5**)

Position				
	^{13}C (δ/ppm)	^{1}H (δ/ppm, protons, multiplicity[a], coupling constants) $^{1}H/^{13}C$-HSQC correlation	$^{1}H/^{1}H$-COSY correlation	$^{1}H/^{13}C$-HMBC correlation[b]
1	40.1	3.29, 1H, dd, J = 13.6, 5.6 Hz, overlapped and 2.95, 1H, dd, J = 13.6, 9.2 Hz	2	2, 3, 4′, 5′, 6′
2	57.3	3.54, 1H, m	1, 3	1, 3, 5′, N-CH_2
3	16.1	1.35, 3H, d, J = 6.4 Hz	2	1, 2
2′	147.3	7.78, 1H, d, J = 2.3 Hz	3′	3′, 3′a, 7′a
3′	107.5	6.84, 1H, dd, J = 2.3, 1.0 Hz	2′, 7′	2′, 3′a, 7′a
3′a	129.6	-	-	-
4′	122.9	7.52, 1H, brd, J = 1.2 Hz, overlapped	6′	1, 3′, 6′, 7′a
5′	131.7	-	-	-
6′	126.5	7.18, 1H, dd, J = 8.4, 2.0 Hz	4′, 7′	1, 4′, 7′a
7′	112.6	7.50, 1H, d-like, J = 8.4 Hz, overlapped	3′, 6′	3′a, 5′, 7′a
7′a	155.7	-	-	-
1″	120.4	-	-	-
2″	159.3	-	-	-
3″	112.1	7.06, 1H, d, J = 8.0 Hz, overlapped	4″, 5″, O-CH_3	1″, 2″, 5″
4″	132.65	7.45, 1H, m, overlapped	3″, 5″, 6″	2″, 6″
5″	122.1	7.03, 1H, td, J = 7.6, 0.8 Hz, overlapped	3″, 4″, 6″	1″, 3″, 4″, 6″
6″	132.73	7.43, 1H, m, overlapped	4″, 5″	2″, 4″, N-CH_2
N-CH_2	45.8	4.30, 2H, m	-	2, 1″, 2″, 6″
O-CH_3	56.1	3.77, 3H, s	3″	2″, 3″

Recorded in CD_3OD at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively.
[a]br = broad, d = doublet, m = multiplet, s = singlet, t = triplet.
[b]HMBC: heteronuclear multiple-bond correlation spectroscopy. The proton signal correlated with the indicated carbons.

Conclusion

In this study, five substituted phenethylamine derivatives of 5-MAPDB (**1**), 5-AEDB (**2**), MDMA methylene homolog (**3**) 6-Br-MDMA (**4**), and 5-APB-NBOMe (**5**) were identified in illegal products seized in a clandestine laboratory. The applied procedure for structure elucidation was based on LC-QTOF-MS, GC-MS, and NMR. Analytical data is presented to assist forensic laboratories that encounter these newly emerging compounds in casework.

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