The Characterization of 5- and 6-(2-Aminopropyl)-2,3-dihydrobenzofuran

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ABSTRACT: The synthesis, analysis, and characterization of 5- and 6-(2-aminopropyl)-2,3-dihydrobenzofuran are discussed. Analytical data (mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy) are presented with direct comparisons of the analytical data to correctly differentiate these isomers in suspected drug exhibits.

KEYWORDS: 5-(2-aminopropyl)-2,3-dihydrobenzofuran, 6-(2-aminopropyl)-2,3-dihydrobenzofuran, benzofury, designer drug, synthesis, characterization, forensic chemistry.

6-(2-Aminopropyl)-2,3-dihydrobenzofuran, commonly referred to as "Benzofury" or "6-APB," has become a popular "*research chemical*" for sale over the internet. A positional isomer, 5-(2-aminopropyl)-2,3-dihydrobenzofuran (5-APB) became available only a few weeks after 6-APB was first sold. Although not currently scheduled under the U.S. Controlled Substances Act, both may be considered to be analogs of 3,4-methylenedioxyamphetamine (MDA) [1], since an oxygen atom within the methylenedioxy moiety of MDA has been replaced with a methylene (CH_2) group (Figure 1). Analytical data is presented to assist forensic chemists who may encounter these substances in casework.

Experimental

Chemicals, Reagents, and Materials

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). All NMR solvents and other chemicals were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI). 3,4-Methylenedioxy-amphetamine (MDA) was obtained from the authentic reference collection maintained by the Drug Enforcement Administration's Special Testing and Research Laboratory.

Synthesis

In accordance with Journal policy, exact experimental details are not provided. The procedures of Monte *et al*. [2] were followed (Figures 2 and 3) for the preparation of 5-APB, 6-APB, and their intermediates.

Infrared Spectroscopy (FTIR)

Infrared spectra were obtained on a Thermo-Nicolet Nexus 670 FTIR equipped with a single bounce attenuated total reflectance (ATR) accessory. Instrument parameters were: resolution = 4 cm^{-1}; gain = 8; optical velocity = 0.4747; aperture = 150; and scans/sample = 16.

Gas Chromatography/Mass Spectrometry (GC/MS)

Mass spectra were obtained on an Agilent Model 5975C quadrupole mass-selective detector (MSD) that was interfaced with an Agilent Model 7890A gas chromatograph (GC). The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 34-600 amu, and at a scan rate of 2.59 scans/s. The GC was fitted with a 30 m x 0.25 mm ID fused-silica capillary column coated with 0.25 μm 100% dimethylpolysiloxane, DB-1 (J & W Scientific,

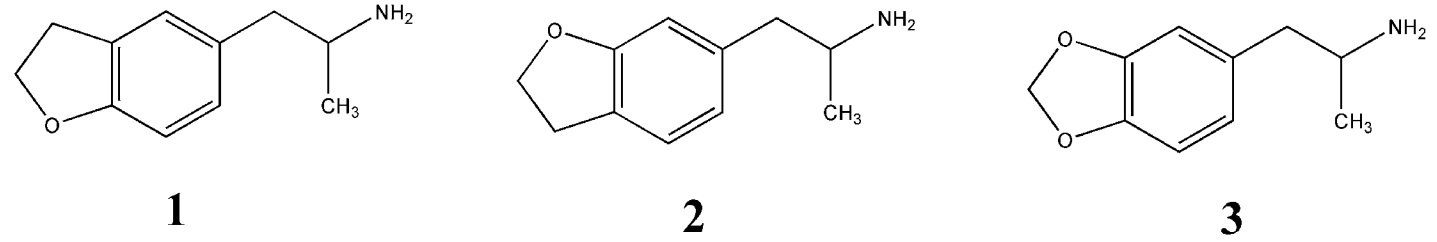


Figure 1 - Structural formulas of **(1)** 5-APB, **(2)** 6-APB, and **(3)** MDA.

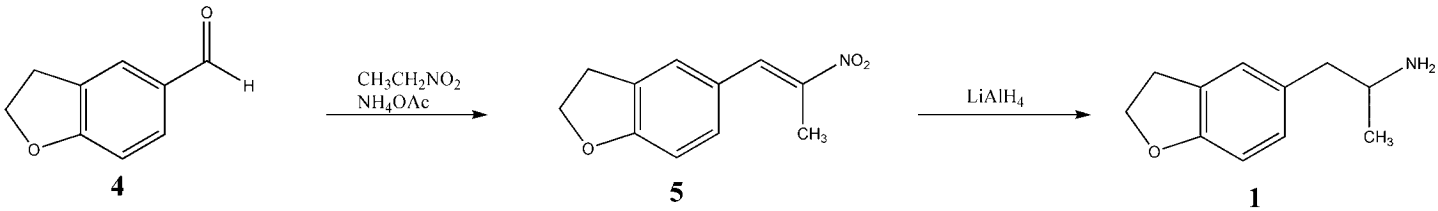


Figure 2 - Synthetic route for 5-(2-aminopropyl)-2,3-dihydrobenzofuran **1**.

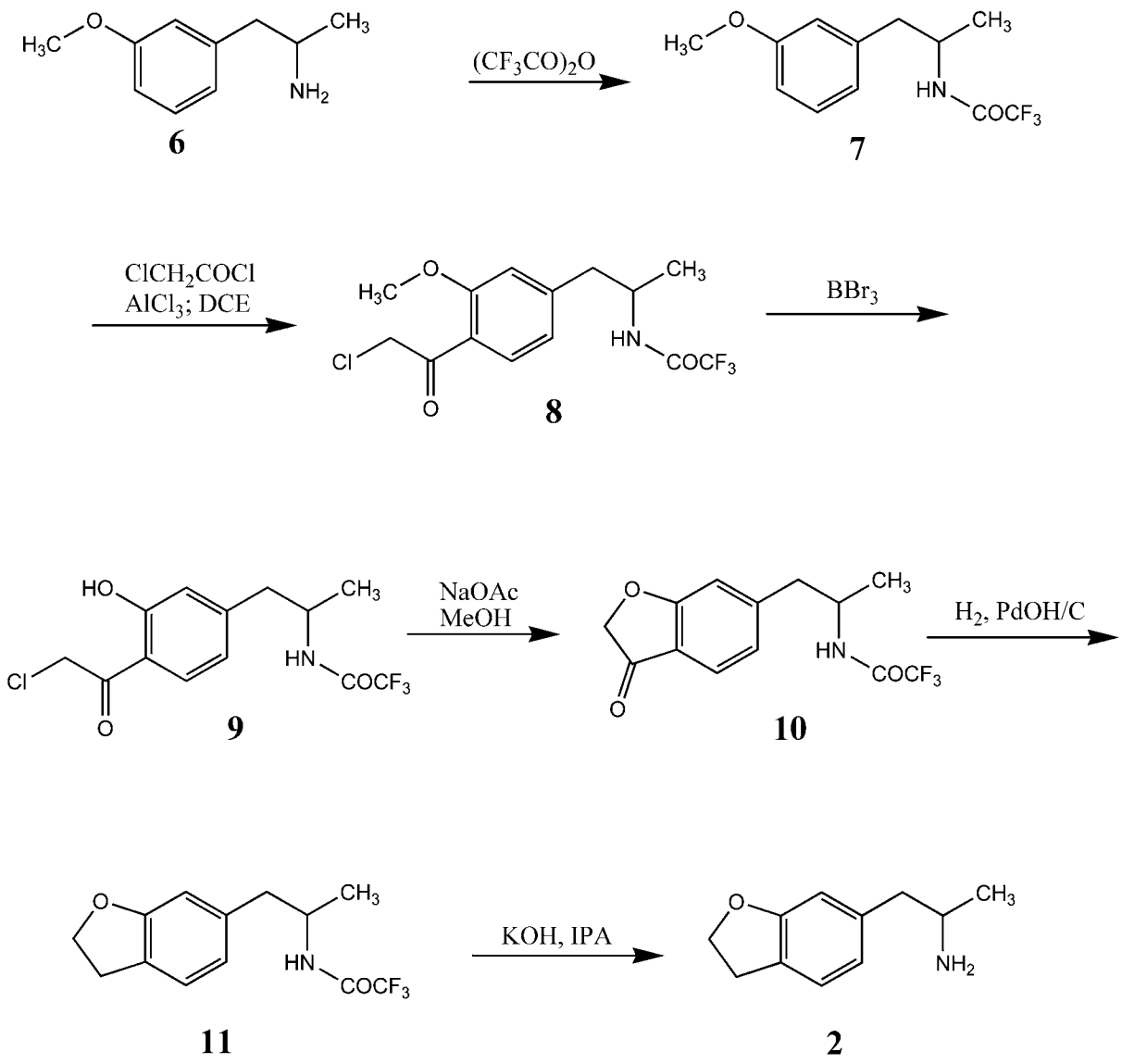


Figure 3 - Synthetic route for 6-(2-aminopropyl)-2,3-dihydrobenzofuran **2**.

Rancho Cordova, CA). The oven temperature was programmed as follows: Initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1) at 280°C. The MSD source was operated at 230°C.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on a Agilent VNMRS 600 MHz NMR using a 5 mm Protune broad band detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). The HCl salt of the compounds were dissolved in deuterochloroform ($CDCl_3$) containing 0.03% v/v tetramethylsilane (TMS) as the 0 ppm reference compound (methanol-d_4 added dropwise to solubilize, if necessary). The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to collect the following spectra: Proton, carbon (proton decoupled), NOESY1D, and gradient versions of 2 dimensional experiments COSY, HSQC, and HMBC. Data processing and structure elucidation was performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Table 1 - Gas chromatographic retention times (R_t) for the (2-aminopropyl)-2,3-dihydrobenzofurans and related compounds[a].

Compound	R_t (min)
1	11.13
2	11.11
3	9.73
4	8.75
5	17.82
6	7.86
7	10.48
8	18.35
9	18.62
10	16.19
11	13.63

[a]Conditions given in the experimental section.

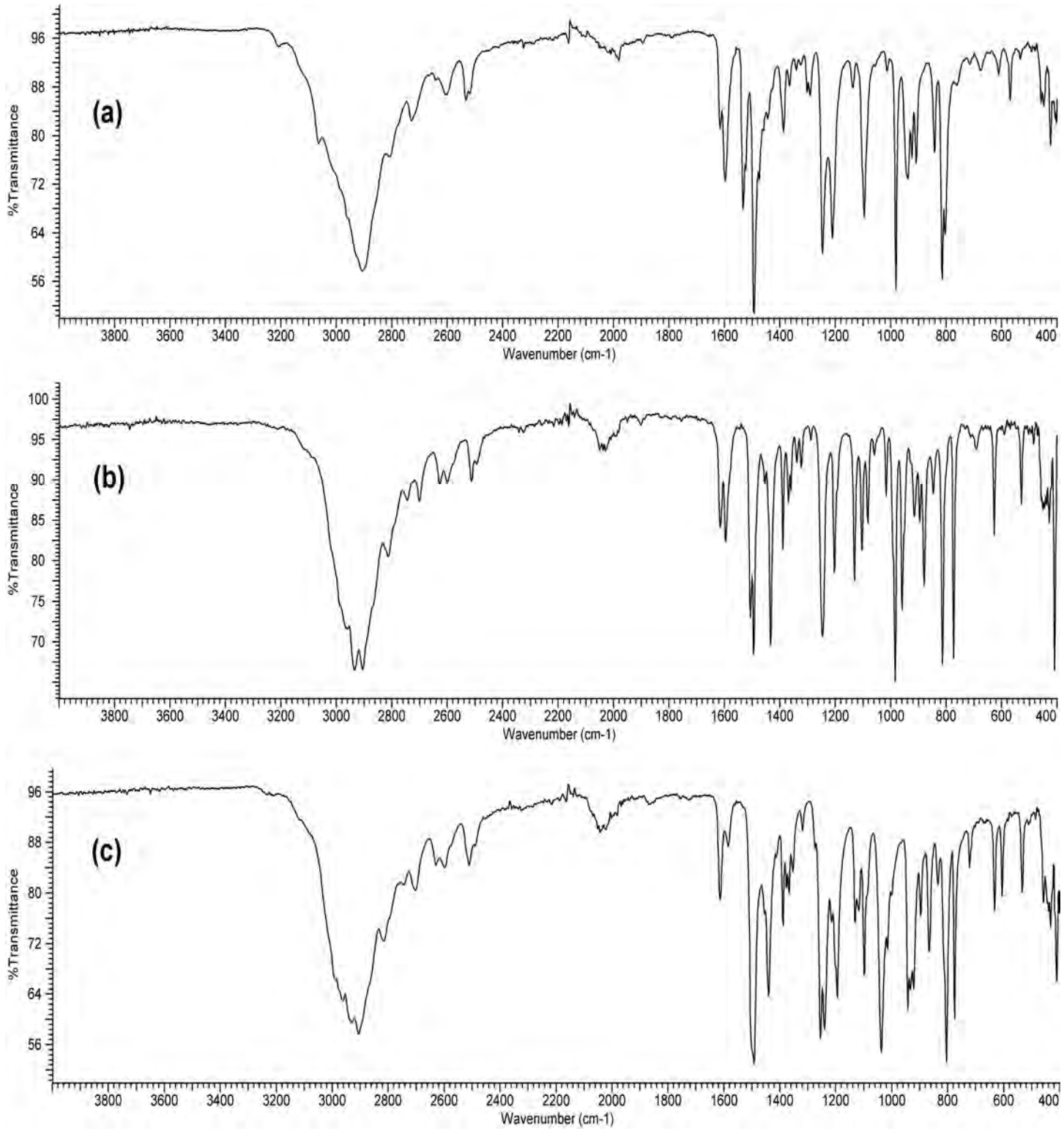


Figure 4 - Infrared spectrum (FTIR) of (**a**) 5-(2-aminopropyl)-2,3-dihydrobenzofuran HCl **1**, (**b**) 6-(2-aminopropyl)-2,3-dihydrobenzofuran HCl **2**, and (**c**) 3,4-methylenedioxyamphetamine HCl **3**.

Results and Discussion

GC retention time data for the respective compounds (Figures 1-3) are presented in Table 1. All amines were injected as the free base. 5-APB and 6-APB gave virtually identical retention times and could not be resolved under the conditions utilized. Both compounds eluted approximately 1.4 minutes later than MDA in the described system.

The FTIR spectra for 5-APB HCl and 6-APB HCl are illustrated in Figure 4, along with MDA HCl. Comparison of the hydrochloride ion pairs reveals similar absorption patterns with the most prominent differences being in the region of 500-1750 cm^{-1}. When compared to MDA HCl (Figure 4), significant differences in this region can differentiate the compounds. However, since the spectra are somewhat similar,

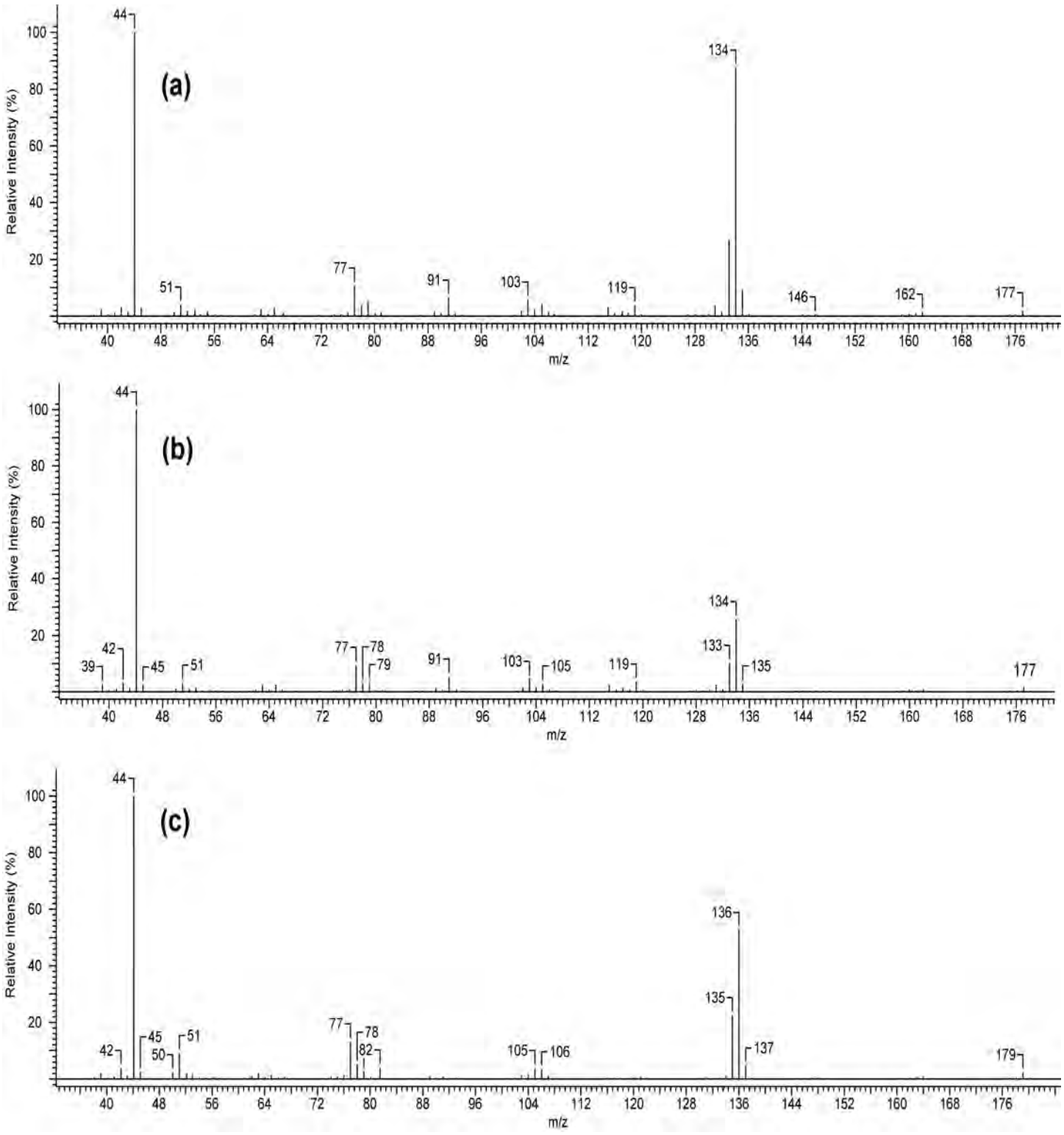


Figure 5 - Electron ionization mass spectra of **(a)** 5-(2-aminopropyl)-2,3-dihydrobenzofuran **1**, **(b)** 6-(2-aminopropyl)-2,3-dihydrobenzofuran **2**, and **(c)** 3,4-methylenedioxyamphetamine **3**.

and because 3,4-MDA is known to have differing polymorphic crystalline forms (each of which has a slightly different IR spectrum), and 5-APB and 6-APB may exhibit similar behavior, additional or supplementary spectroscopic methods should be utilized for identification.

Mass spectra for 5-APB, 6-APB, and their respective intermediates are presented in Figures 5-9. Spectra produced from 5-APB and 6-APB gave a base peak at *m/z* 44 and a moderate molecular ion at *m/z* 177 (Figure 5), with logical 2-Dalton differences from MDA (Figure 5). However, 5-APB produces a much more intense ion at *m/z* 134, relative to 6-APB (*m/z* 134 is approx. 3.5 times greater for 5-APB). Although the relative abundances for the remaining ions are quite similar, the two compounds are easily distinguished on this basis.

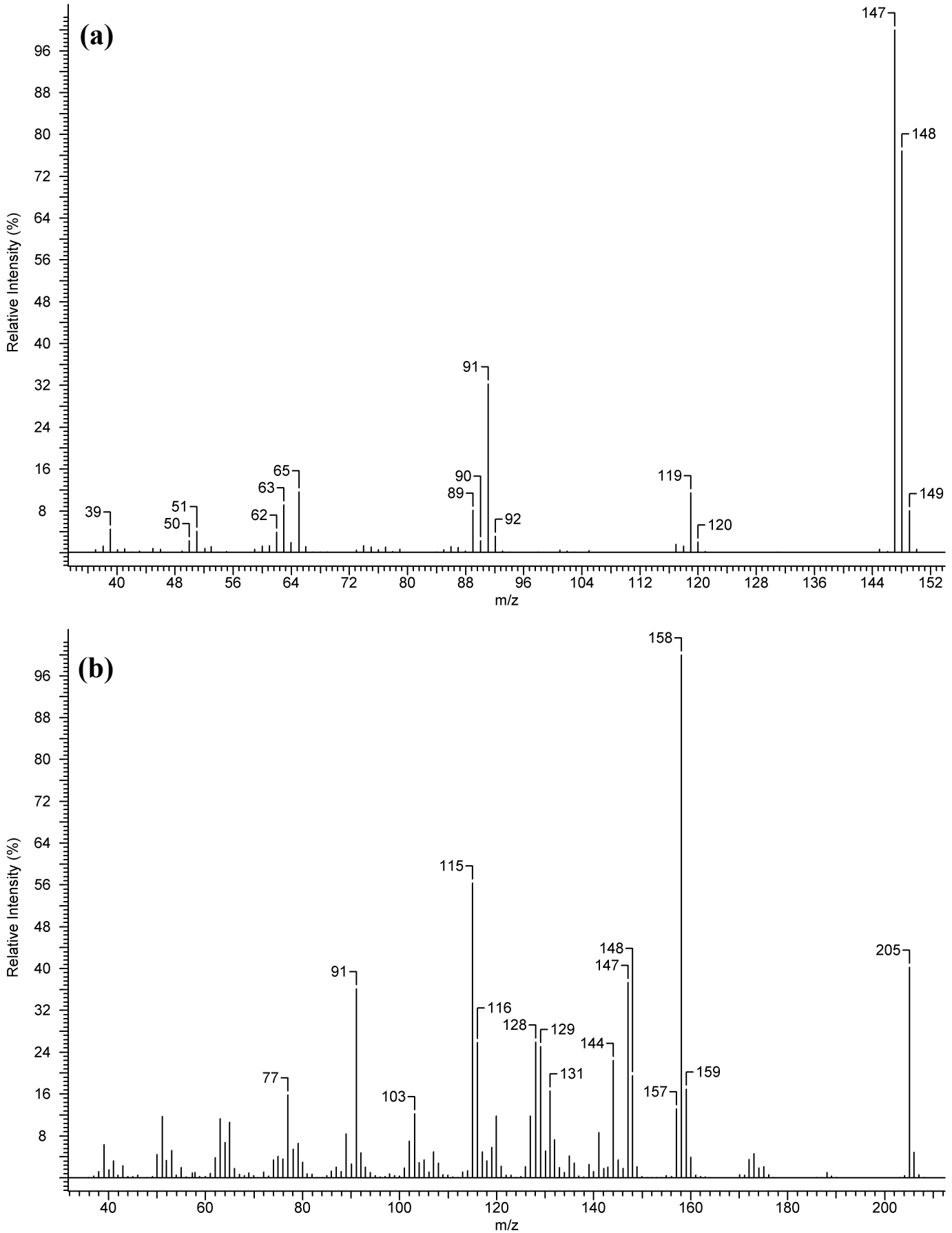


Figure 6 - Electron ionization mass spectra of **(a)** 2,3-dihydrobenzofuran-5-carboxaldehyde **4** and **(b)** 5-[1-(2-nitro-1-propenyl)]-2,3-dihydrobenzofuran **5**.

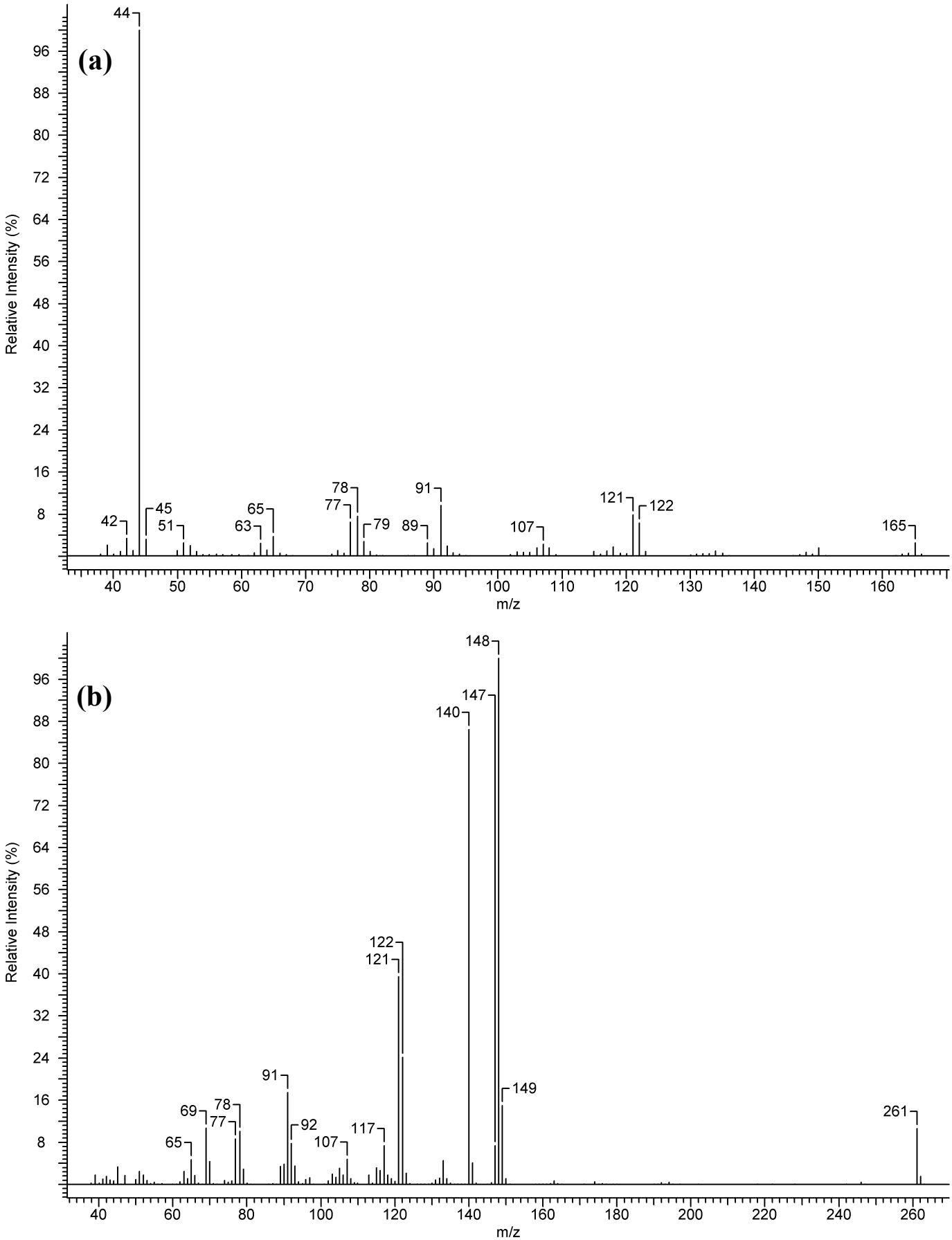


Figure 7 - Electron ionization mass spectra of **(a)** 3-methoxyamphetamine **6** and **(b)** N-(trifluoroacetyl)-1-(3-methoxyphenyl)-2-aminopropane **7**.

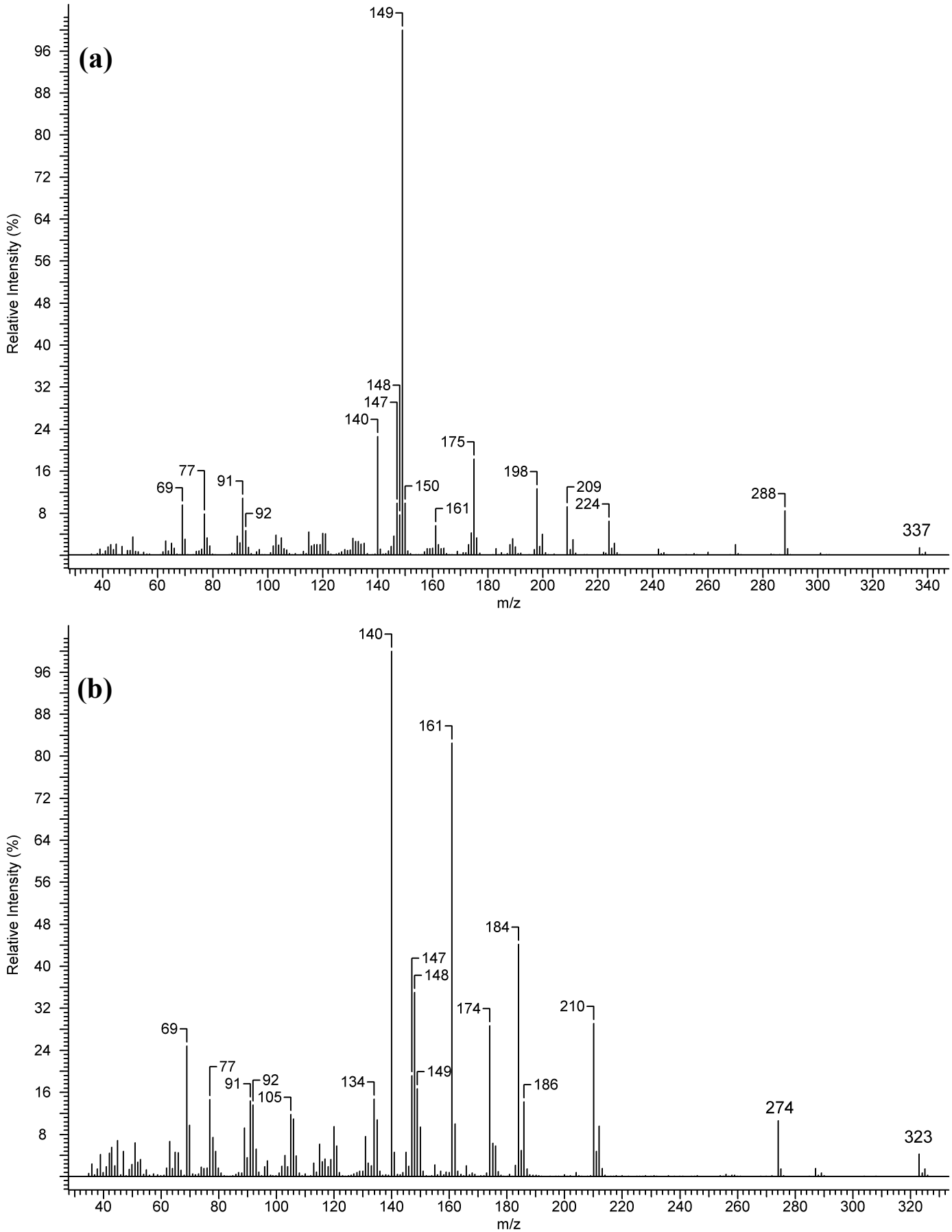


Figure 8 - Electron ionization mass spectra of **(a)** N-(trifluoroacetyl)-1-[3-methoxy-4-(chloroacetyl)phenyl]-2-aminopropane **8** and **(b)** N-(trifluoroacetyl)-1-[3-hydroxy-4-(chloroacetyl)phenyl]-2-aminopropane **9**.

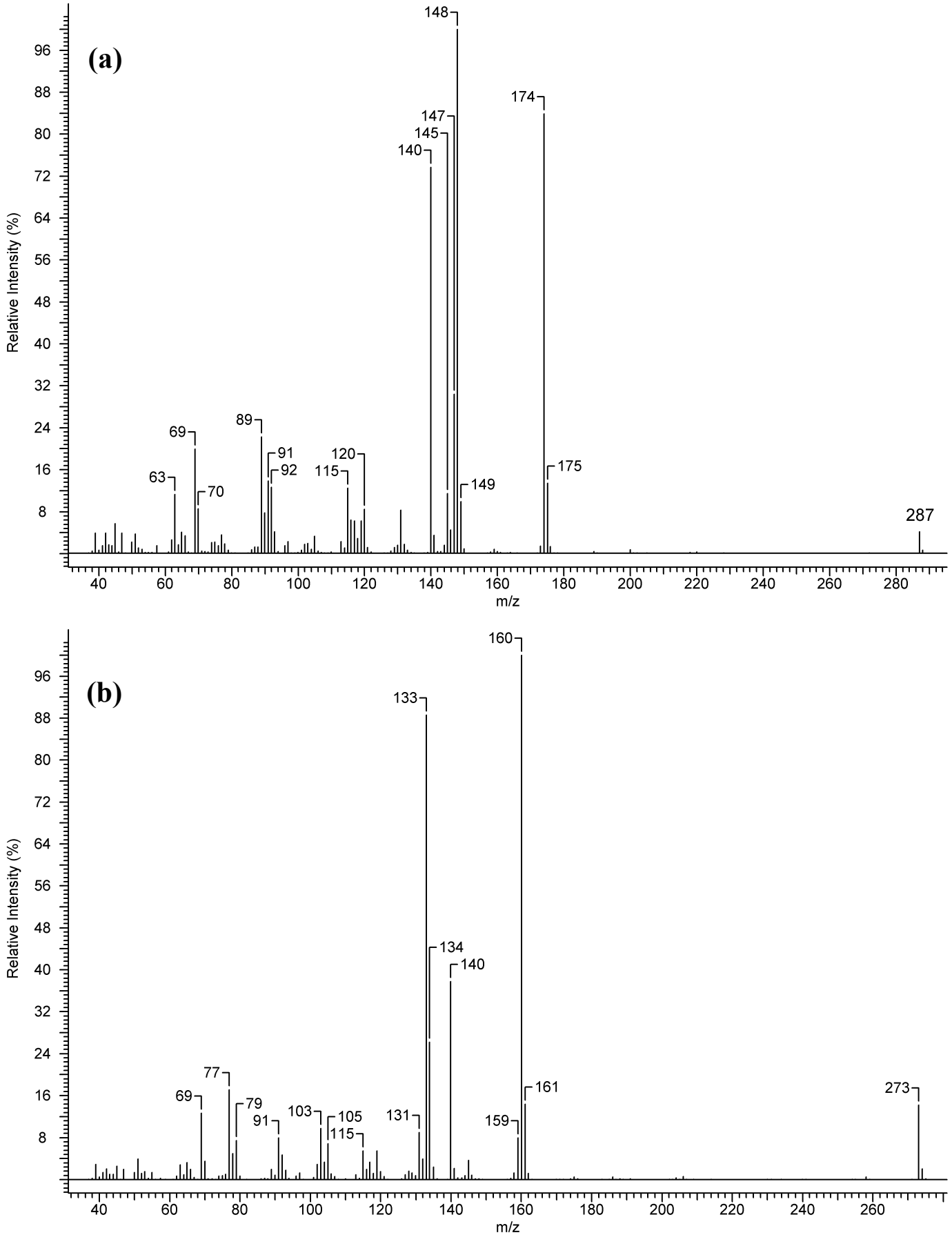
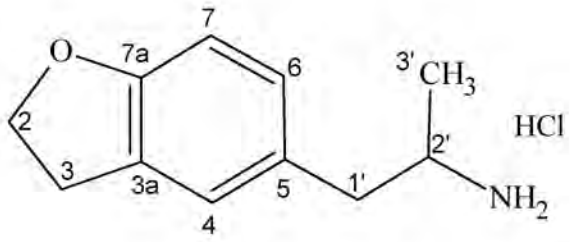


Figure 9 - Electron ionization mass spectra of **(a)** 6-[2-[N-(trifluoroacetyl)amino]propyl]-2,3-dihydrobenzofuran-3-one **10** and **(b)** 6-[2-[N-(trifluoroacetyl)amino]propyl]-2,3-dihydrobenzofuran **11**.

	Carbon	Proton
2	71.3	4.55 (t, 8.5 Hz)
3	29.7	3.19 (t, 8.5 Hz)
3a	127.8	-
4	125.9	7.06 (bs)
5	127.4	-
6	129.0	6.95 (bd, 8.2 Hz)
7	109.5	6.72 (d, 8.2 Hz)
7a	159.4	-
1'	40.6	2.79 (dd, 13.7, 8.5 Hz), 3.13 (dd, 13.7, 5.9 Hz)
2'	50.1	3.49 (m)
3'	18.2	1.39 (t, 6.5 Hz)
NH3+	-	8.40 (vbs, 3H)

Structure



$CDCl_3$ only

b = broad, d = doublet, m = multiplet, s = singlet, t = triplet, vbs = very broad singlet

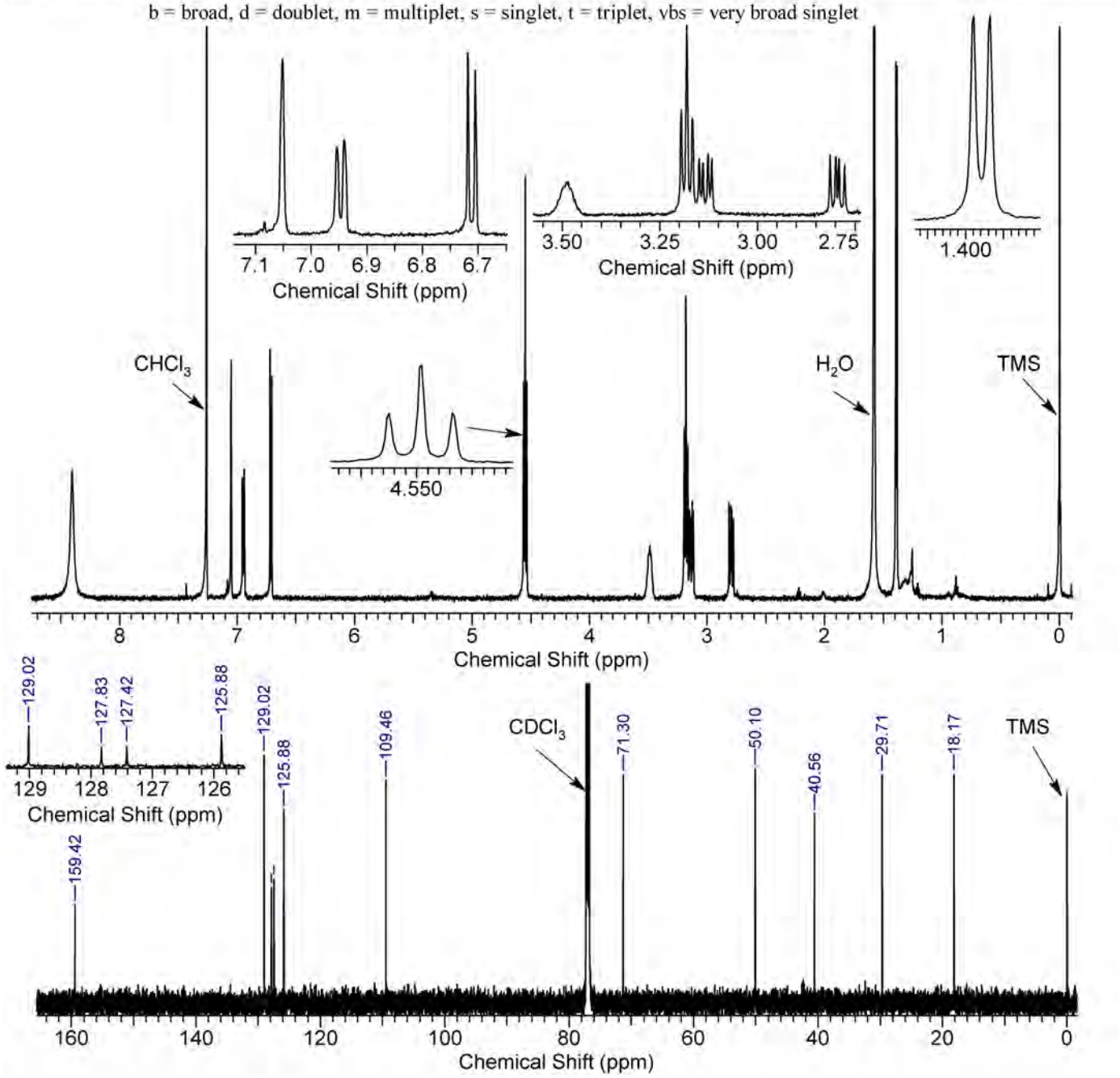
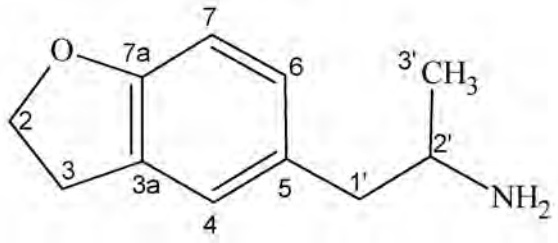


Figure 10 - ^{1}H and ^{13}C NMR data for 5-(2-aminopropyl)-2,3-dihydrobenzofuran HCl **1**.

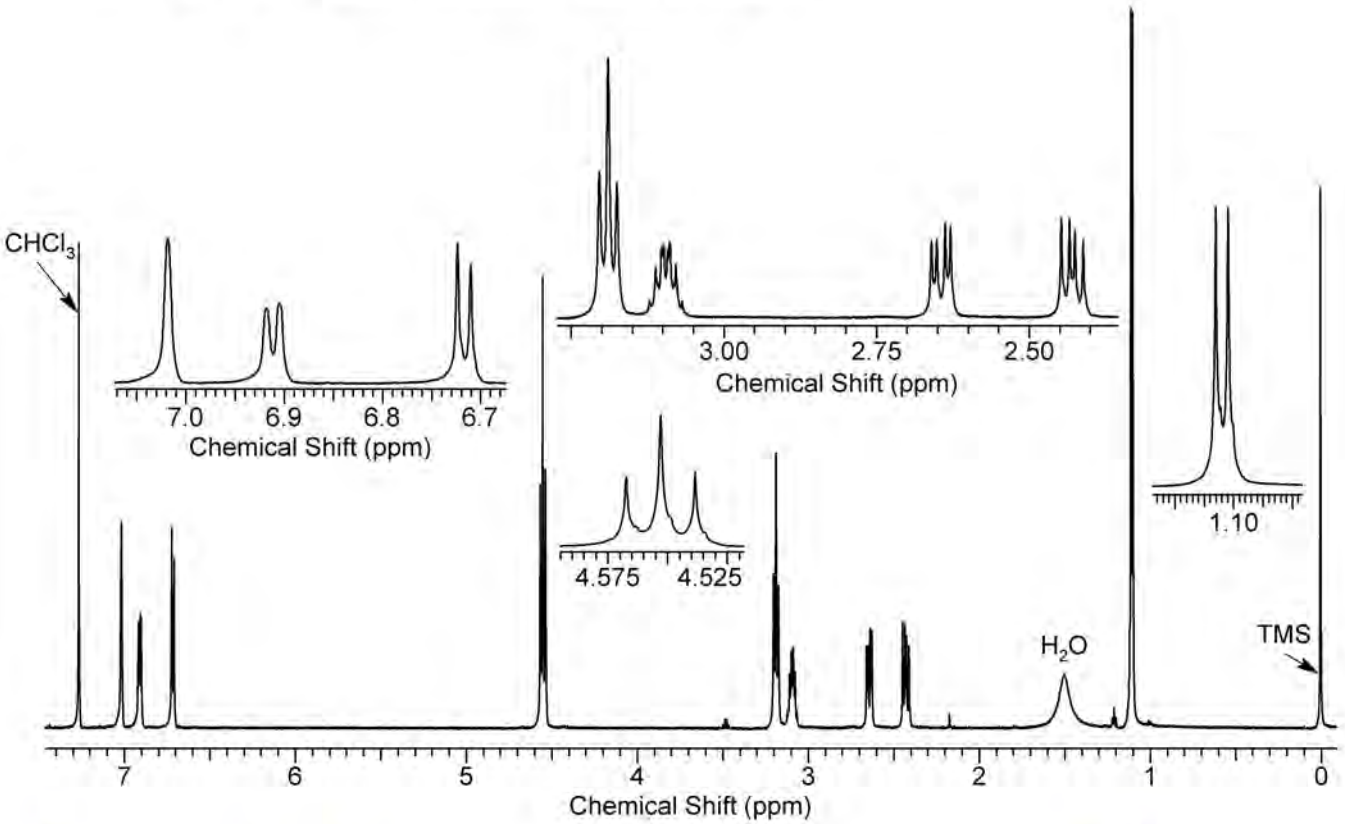
	Carbon	Proton
2	71.1	4.55 (t, 8.7 Hz)
3	29.8	3.19 (t, 8.7 Hz)
3a	127.1	-
4	125.7	7.02 (bs)
5	131.6	-
6	128.6	6.91 (bd, 8.1 Hz)
7	109.0	6.72 (d, 8.1 Hz)
7a	158.6	-
1'	46.0	2.43 (dd, 13.4, 8.1 Hz), 2.64 (dd, 13.5, 5.3 Hz)
2'	48.6	3.10 (dqd, 8.1, 6.3, 5.3 Hz)
3'	23.5	1.11 (d, 6.3 Hz)

Structure



Saturated $NaHCO_3$ D_2O - $CDCl_3$ Base Extraction

b = broad, d = doublet, q = quartet, s = singlet, t = triplet



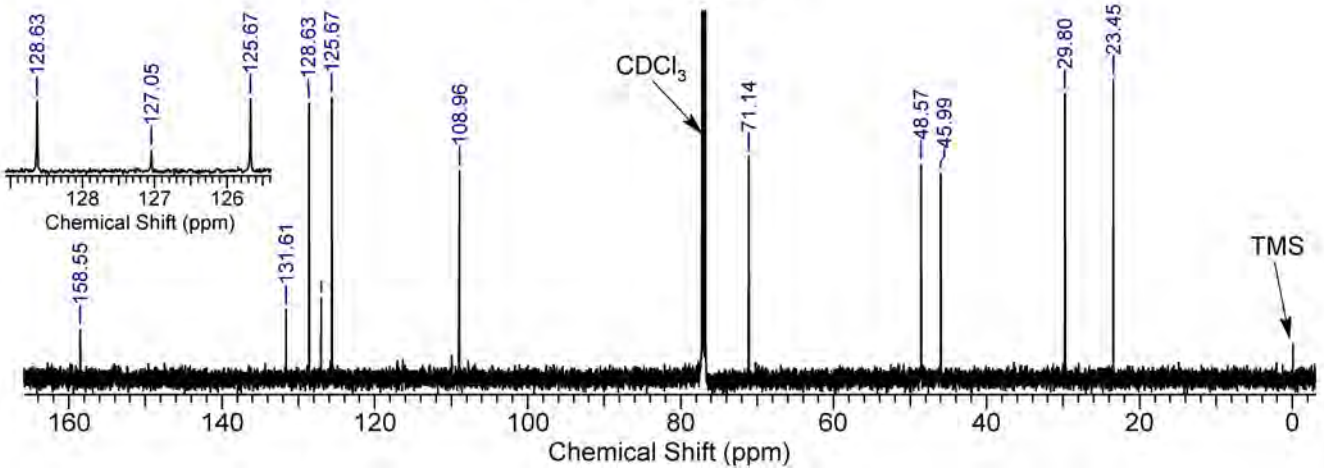
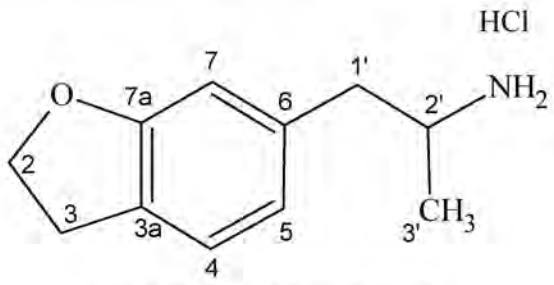


Figure 11 - ^{1}H and ^{13}C NMR data for 5-(2-aminopropyl)-2,3-dihydrobenzofuran base **1**.

	Carbon	Proton
2	71.7	4.58 t(8.6 Hz)
3	29.6	3.20 t(8.6 Hz)
3a	126.4	-
4	125.4	7.16 d(7.8 Hz)
5	121.6	6.71 d(7.8 Hz)
6	136.1	-
7	110.2	6.63 s
7a	160.8	-
1'	40.9	2.72 dd(13.6, 8.5 Hz), 3.01 dd(13.6, 6.0 Hz)
2'	49.4	3.44 dqd(8.5, 6.4, 6.0 Hz)
3'	17.9	1.29 d(6.4 Hz)

Structure



1 mL $CDCl_3$ w/ 20 drops CD_3OD

d = doublet, q = quartet, s = singlet, t = triplet

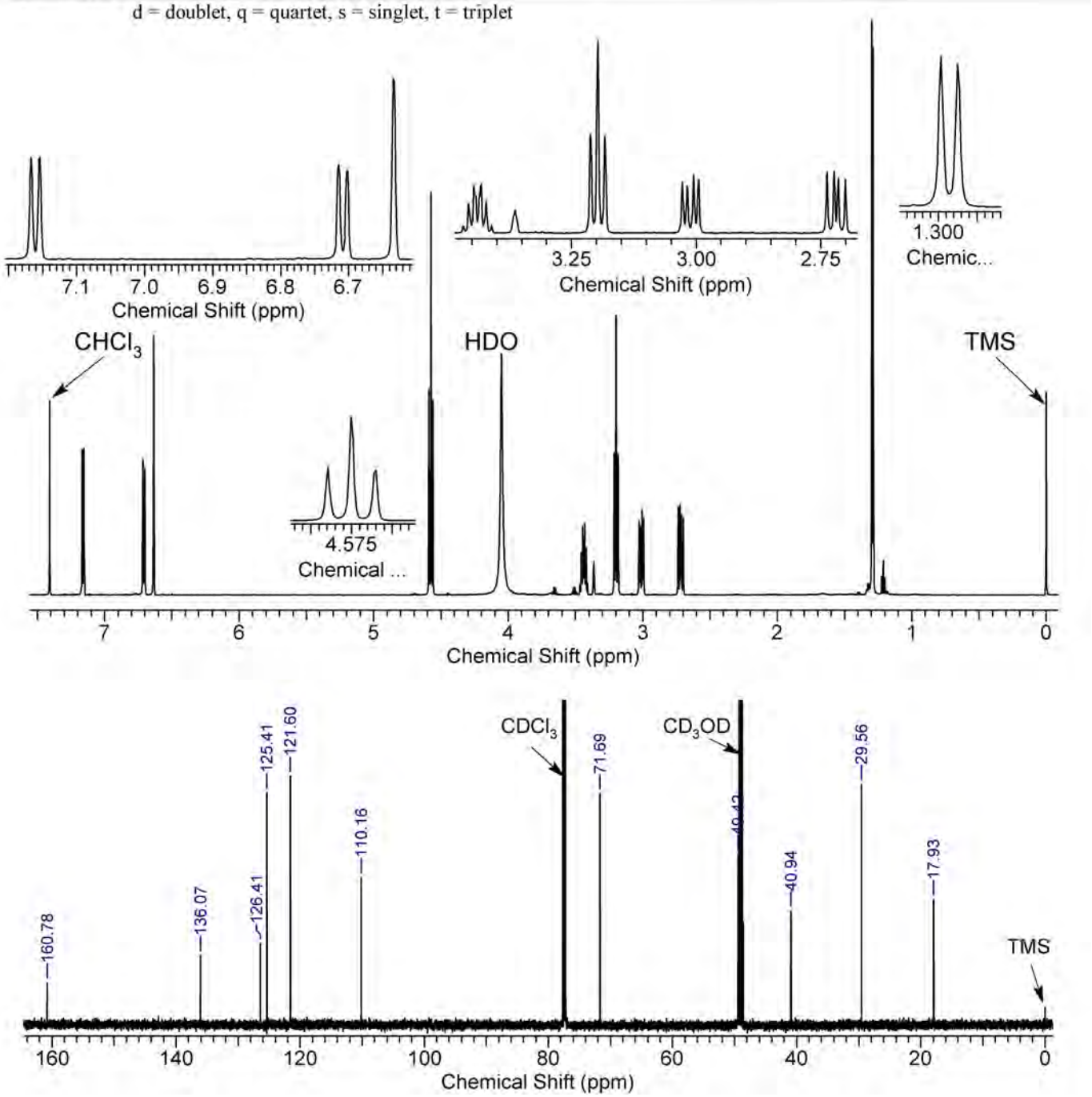
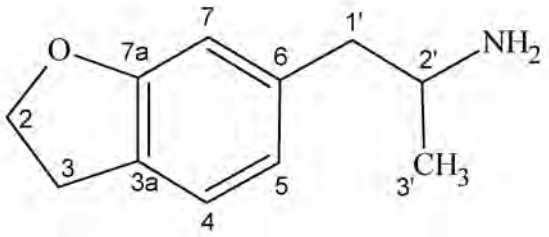


Figure 12- ^{1}H and ^{13}C NMR data for 6-(2-aminopropyl)-2,3-dihydrobenzofuran HCl **2**.

	Carbon	Proton
2	71.3	4.56 t(8.8 Hz)
3	29.5	3.18 t(8.8 Hz)
3a	124.8	-
4	124.6	7.10 d(7.4 Hz)
5	121.4	6.66 d(7.4 Hz)
6	140.0	-
7	110.1	6.63 s
7a	160.4	-
1'	46.7	2.45 dd(13.2, 8.1 Hz), 2.66 dd(13.2, 5.0 Hz)
2'	48.5	3.13 dqd(8.1, 6.4, 5.0 Hz)
3'	23.6	1.11 d(6.4 Hz)

Structure



Saturated $NaHCO_3$ D_2O - $CDCl_3$ Base Extraction

d = doublet, q = quartet, s = singlet, t = triplet

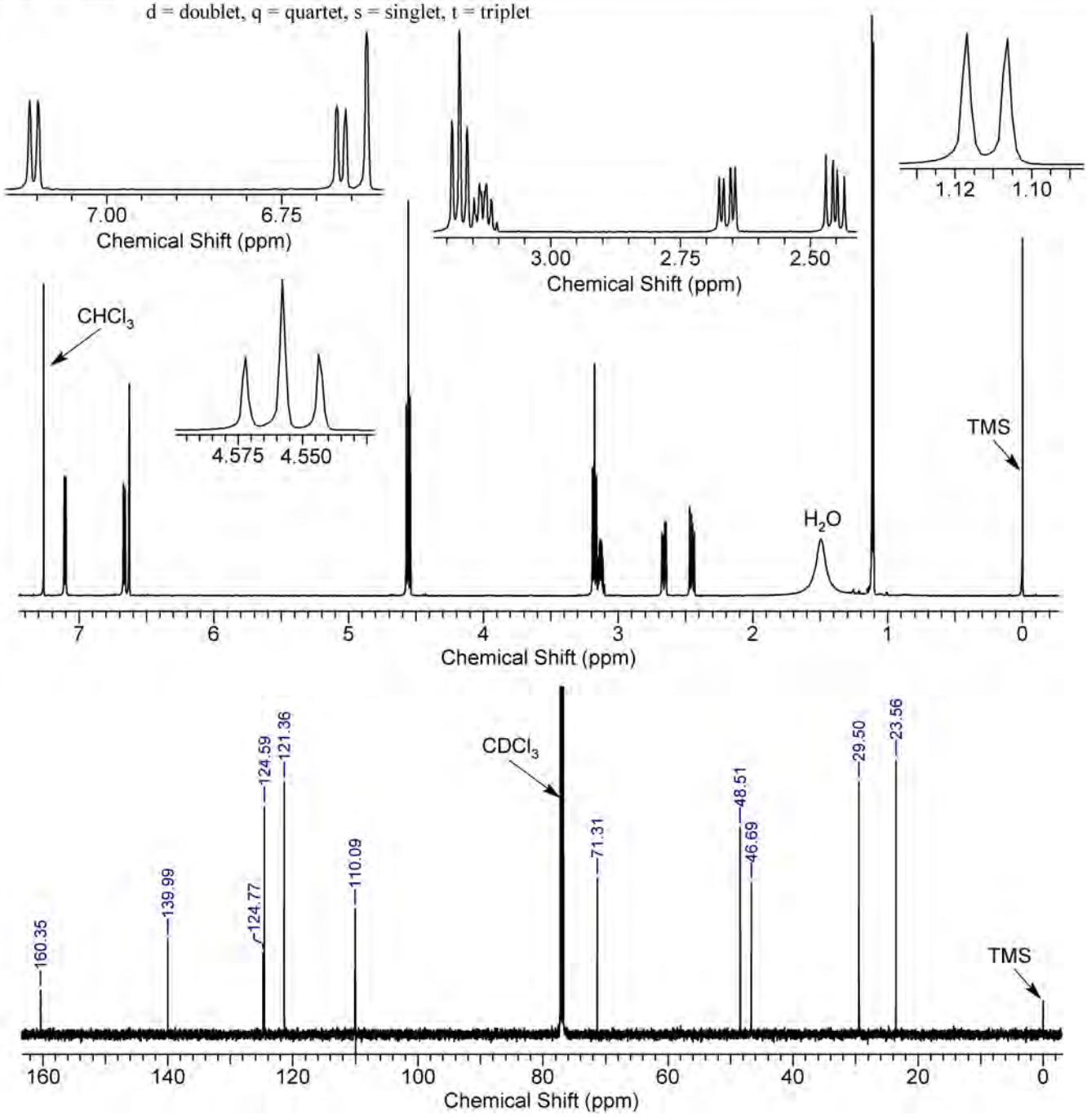


Figure 13 - ^{1}H and ^{13}C NMR data for 6-(2-aminopropyl)-2,3-dihydrobenzofuran base **1**.

However, since both compounds elute at the same retention time, care must be taken in differentiating the spectra. Mass spectra for intermediates 4-11 are illustrated in Figures 6-9.

The proton and carbon assignments for 5-APB and 6-APB (base and HCl) are presented in Figures 10-13. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton correlations), HMBC (2-4 bond carbon to proton correlations correlations), COSY (2-3 bond proton-proton correlations), and NOESY1D (spatial proximity between protons) spectra. Assignments were further confirmed by the ACD software.

Proton spectra for both compounds indicated the typical 1,3,4-trisubstituted benzene peak pattern (broad singlet, broad doublet, sharp doublet above 6.5 ppm), a CH_2-CH_2-O group (two triplets, 3.2 ppm and 4.5 ppm), and a CH_2-$CH(NH_2)$-CH_3 group (non-equivalent methylene protons that were doublet of doublets, a methine multiplet, and methyl doublet; all between 2.4 and 3.2 ppm). The molecular formula, $C_{11}H_{15}NO$, indicates 5 degrees of unsaturation and/or rings which are accounted for in the benzofuran ring system. This ring system is supported by HMBC correlations from the OCH_2CH_2 protons to benzene carbons, benzene protons to OCH_2CH_2 carbons, and the benzene carbon chemical shift near 160 ppm indicating it is bonded to oxygen. The NOESY1D of 6-APB base showed that H-3 (3.17 ppm) was spatially near H-4 (7.10 ppm), a narrow doublet which must be adjacent to a proton (H-5), requiring substitution of the propyl group on C-6. In addition, the predicted carbon spectra of both 5-APB and 6-APB have C-4 at approximately 125 ppm and C-7 at approximately 110 ppm, due to the strong effect of the oxygen on C-7. In the case of 5-APB base, the carbon at 109.0 ppm (C-7) has a proton doublet (8.1 Hz coupling) at 6.72 ppm; C-6 must be protonated. In the case of 6-APB, the carbon at 110.1 ppm has a proton singlet at 6.63 ppm; C-6 must be a quaternary carbon.

Conclusions

Analytical data is presented to assist forensic laboratories that encounter 5-APB or 6-APB in casework. Any combination of two of the three presented spectral techniques can provide unequivocal characterization.

References

1. Code of Federal Regulations. 21 U.S.C. § 802(32)(A).
2. Monte AP, Marona-Lewicka D, Cozzi NV, Nichols DE. Synthesis and pharmacological examination of benzofuran, indan, and tetralin analogues of 3,4-(methylenedioxy) amphetamine. Journal of Medicinal Chemistry 1993;36:3700-6.