The Characterization of 6-(2-Aminopropyl)benzofuran and Differentiation from its 4-, 5-, and 7-Positional Analogues

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ABSTRACT: The isolation, analysis, synthesis, and characterization of 6-(2-aminopropyl)benzofuran (currently and commonly referred to as 6-APB) are briefly discussed. Analytical data (infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance spectroscopy) are presented to differentiate it from the 4-, 5, and 7- positional analogues.

KEYWORDS: 6-(2-aminopropyl)benzofuran, 4-(2-aminopropyl)benzofuran, 5-(2-aminopropyl)benzofuran, 7-(2-aminopropyl) benzofuran, 4-APB, 5-APB, 6-APB, 7-APB, designer drug, synthesis, characterization, forensic chemistry.

This laboratory recently received a request to confirm the identity of a suspected sample of 6-(2-aminopropyl)benzofuran and synthesize a primary standard for its identification in a number of drug exhibits. 6-(2-Aminopropyl)benzofuran (Figure 1, structure **3**) is widely available through Internet vendors, and is currently marketed as "6-APB" or "Benzo fury." Herein, we report the isolation, characterization (nuclear magnetic resonance spectroscopy, mass spectrometry, and infrared spectroscopy), and synthesis of 6-(2-aminopropyl)-benzofuran **3**. Additionally, data is presented for 4-(2-amino-propyl)benzofuran **1**, 5-(2-aminopropyl)benzofuran **2**, and 7-(2-aminopropyl)benzofuran **4** to assist forensic chemists who may encounter these substances in casework.

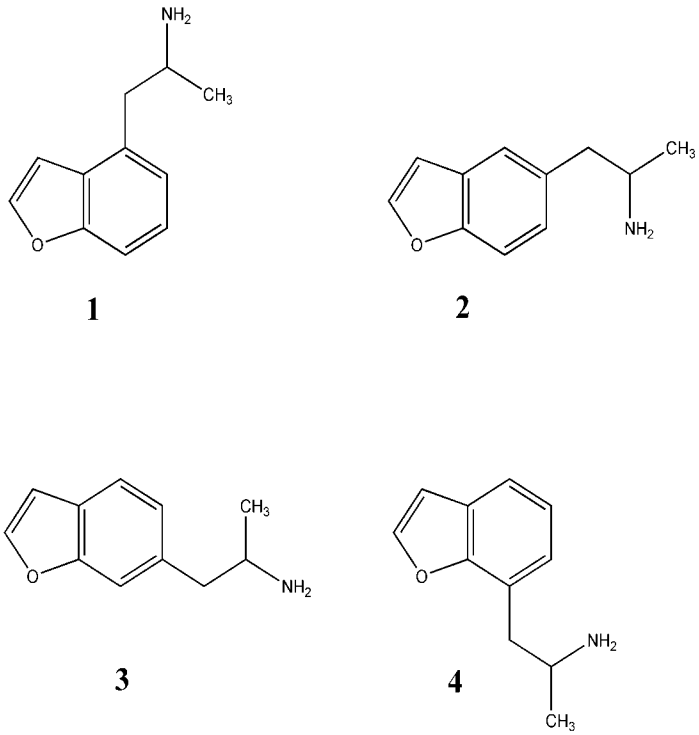

Figure 1 - Structural formulas. **1** = 4-(2-aminopropyl)-benzofuran, **2** = 5-(2-aminopropyl)benzofuran, **3** = 6-(2-amino-propyl)benzofuran, and **4** = 7-(2-aminopropyl)benzofuran.

Experimental

Chemicals, Reagents, and Materials

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). All other chemicals and NMR solvents were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI).

*Synthesis of 6-(2-Aminopropyl)benzofuran **3** and 4-(2-Amino-propyl)benzofuran **1***

In accordance with Journal policy, exact experimental details are not provided, but are outlined in Figure 2. The procedure of Briner *et al*. [1] was utilized. Briefly, bromophenol **5** was refluxed with bromoacetaldehyde **6** and NaH to give the diethyl acetyl **7,** which was heated with polyphosphoric acid to give a mixture of bromobenzofurans **8** and **9**. Compounds **8** and **9** were separated via silica gel column chromatography, catalytically converted to their respective 2-propanones **10** and **11**, and then reductively aminated to **3** (6-APB) and **1** (4-APB). Both **1** and **3** were converted to their HCl ion-pairs.

*Synthesis of 5-(2-Aminopropyl)benzofuran **2** and 7-(2-Amino-propyl)benzofuran **4***

The benzofuran carbaldehydes **12** and **13** were converted to their respective benzonitrostyrenes **14** and **15**, followed by LAH reduction to the amines **2** (5-APB) and **4** (7-APB). Both **2** and **4** were converted to their HCl ion-pairs.

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. 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 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, 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.

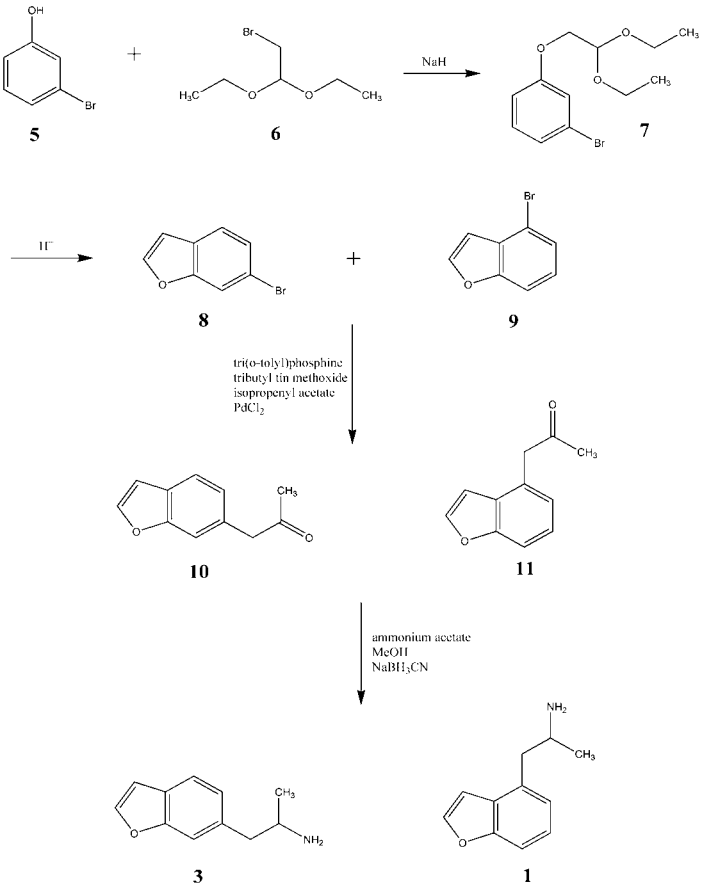

Figure 2 - Synthetic scheme for 4-(2-aminopropyl)benzofuran **1** and 6-(2-aminopropyl)benzofuran **3**.

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.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on an Agilent 400MR NMR with a 400 MHz magnet, a 5 mm Protune indirect detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). The HCl ion-pair of the compound was first dissolved in $CDCl_3$ containing TMS as the 0 ppm reference, and later base extracted using saturated sodium bicarbonate in D_2O. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to collect the following spectra: Proton, carbon (proton decoupled), and gradient versions of the 2 dimensional experiments HSQC, HMBC, and NOESY. Data processing and structure elucidation were performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Results and Discussion

Isolation and Characterization of 6-(2-Aminopropyl)-benzofuran

Approximately 5 grams of illicit material was submitted for characterization/purification. The material was practically insoluble in $CHCl_3$ and had minimal solubility in cold H_2O. A direct FTIR spectrum was non-descriptive. GC/MS analysis of the material as the TMS derivative produced one minor and two major peaks (Figure 4). Peak #1 was identified as the di-TMS derivative of succinic acid and contributed to approximately 65% of the total ion current. Peaks #2 and #3 (representing ca. 2% and 32% of the total ion current, respectively) produced nearly identical spectra having a base peak at *m/z* 116, a trimethylsilyl-loss ion at *m/z* 73, and a cluster of minor ions from *m/z* 244 to *m/z* 248 (the molecular ions could not be determined; spectra not shown). NMR analysis revealed two succinic acid molecules per amine molecule (2:1). A portion of the sample was then dissolved in boiling water, basified with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$ for GC/MS analysis. Two peaks representing 6% (peak #1) and 94% (peak #2) of the total ion current (chromatogram and spectra not shown) produced virtually identical spectra with a base peak at *m/z* 44 and molecular ion at *m/z* 175, consistent with expected ions for **1**-**4**.

For characterization, the major component was isolated from the minor component by dissolving 1.36 grams of illicit material in 16 mL of hot water (80°C), adding 8 mL of saturated aqueous $NaHCO_3$, extracting with Et_2O (2 x 30 mL), drying the organic layer over anhydrous Na_2SO_4, and finally

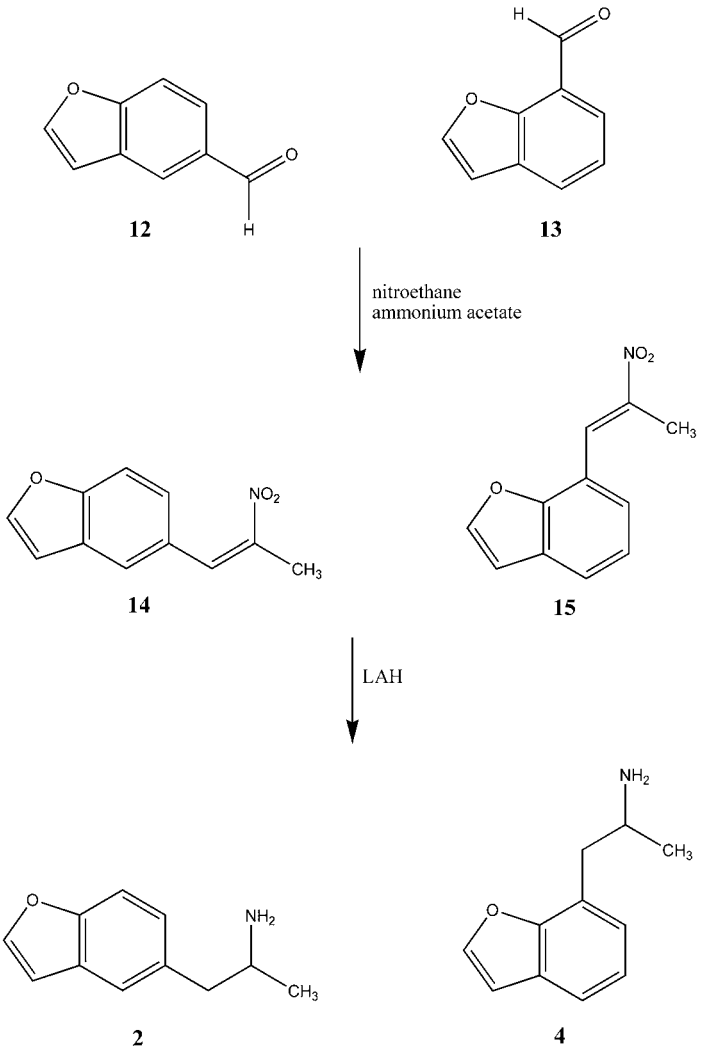

Figure 3 - Synthetic scheme for 5-(2-aminopropyl)benzofuran **2** and 7-(2-aminopropyl)benzofuran **4**.

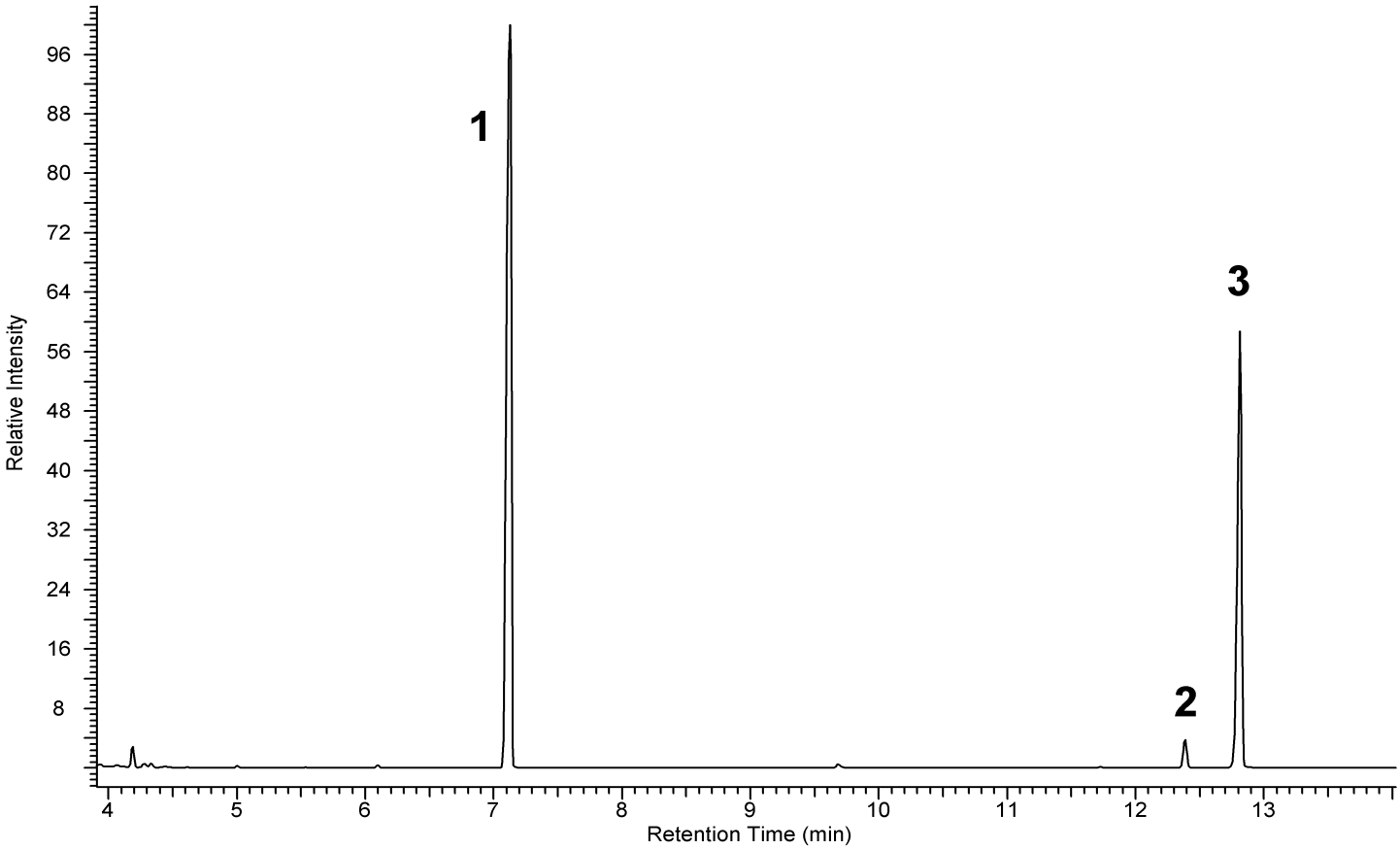

Figure 4 - Reconstructed total ion chromatogram of suspected 6-(2-aminopropyl)benzofuran (as the TMS derivative). Peak identification: 1 = di-TMS derivative of succinic acid, 2= suspected aminopropylbenzofuran-TMS, and 3 = suspected aminopropyl-benzofuran-TMS.

converting to the HCl ion-pair with Et_2O-HCl. The resulting crystalline material was washed with a minimal volume of hot acetone (minor component was soluble in hot acetone) and dried to provide 300 mg of off-white powder that was free of the minor component and 99.5+% chromatographically pure (by GC/MS). This material was examined by NMR. The carbon spectrum showed 11 peaks (8 aromatic and 3 aliphatic) while the proton spectrum showed 14 hydrogens (very broad singlet at 8.5 ppm) has 3 hydrogens (probably $^{+}NH_3$), 5 aromatic hydrogens, and 6 aliphatic hydrogens. The HSQC spectrum aliphatic region revealed one methyl, one methylene, and one methine. The proton splitting patterns and chemical shifts for these aliphatic hydrogens is highly similar to methamphetamine's aliphatic region, indicating Aryl-CH_2-CH(N)-CH_3. The aromatic proton region splitting patterns suggest a 3,4-substituted phenyl, and the HMBC, HSQC, and carbon spectra indicate that the 3,4-substitution group is CH=CH-O. The NOESY spectrum confirms that the orientation of the aliphatic group is at C-6 of the benzofuran ring. ACD/Labs Structure Elucidator software was used to process the NMR data. The compound was identified as 6-(2-aminopropyl)-benzofuran **3**, identical to the synthesized standard.

FTIR, GC/MS, and NMR Characterization/Differentiation of 4-, 5-, 6-, and 7-(2-Aminopropyl)benzofuran

GC retention time data for the respective synthesized compounds (Figure 1) are presented in Table 1. All amines were injected as the free base. The 5- and 6- isomers (compounds **2** and **3**) gave virtually identical retention times and could not be resolved under the conditions utilized. Both **2** and **3** also eluted at approximately the same retention time as MDA in the described system.

The FTIR spectra for compounds **1**-**4** are illustrated in Figures 5-8. All compounds appeared to exhibit polymorphism, depending on how the HCl ion-pair was crystallized. Rapid crystallization gave material with slightly different spectra versus material from slow crystallization; a previously observed phenomenon with MDA HCl as well. Comparison of the four HCl ion-pairs (both rapid and slow crystallization) reveals dissimilar patterns, with the most prominent differences being in the region of 400-1700 cm^{-1}. However, since there appears to be differing polymorphic crystalline forms of each, care must be taken in their identification via FTIR, and additional or supplementary spectroscopic methods should be utilized for identification.

The mass spectra of all four 2-aminopropylbenzofurans were nearly identical and are illustrated in Figures 9 and 10. Each produced a base peak at *m/z* 44 and a moderate molecular ion at *m/z* 175. However, 6-(2-aminopropyl)benzofuran (**3)** produces a much more intense fragment ion at *m/z* 132, relative to *m/z* 131 (*m/z* 132 for **3** has a relative abundance of 16% compared to 6% for **1**, 7% for **2**, and 7% for **4**. Although the relative abundances for the remaining ions are quite similar, **3** can be easily distinguished on the basis of the *m/z* 131/132 ratio (**1** = 2.9:1, **2** = 2.5:1, **3** = 1.3:1, and **4** =2 .4:1). All four

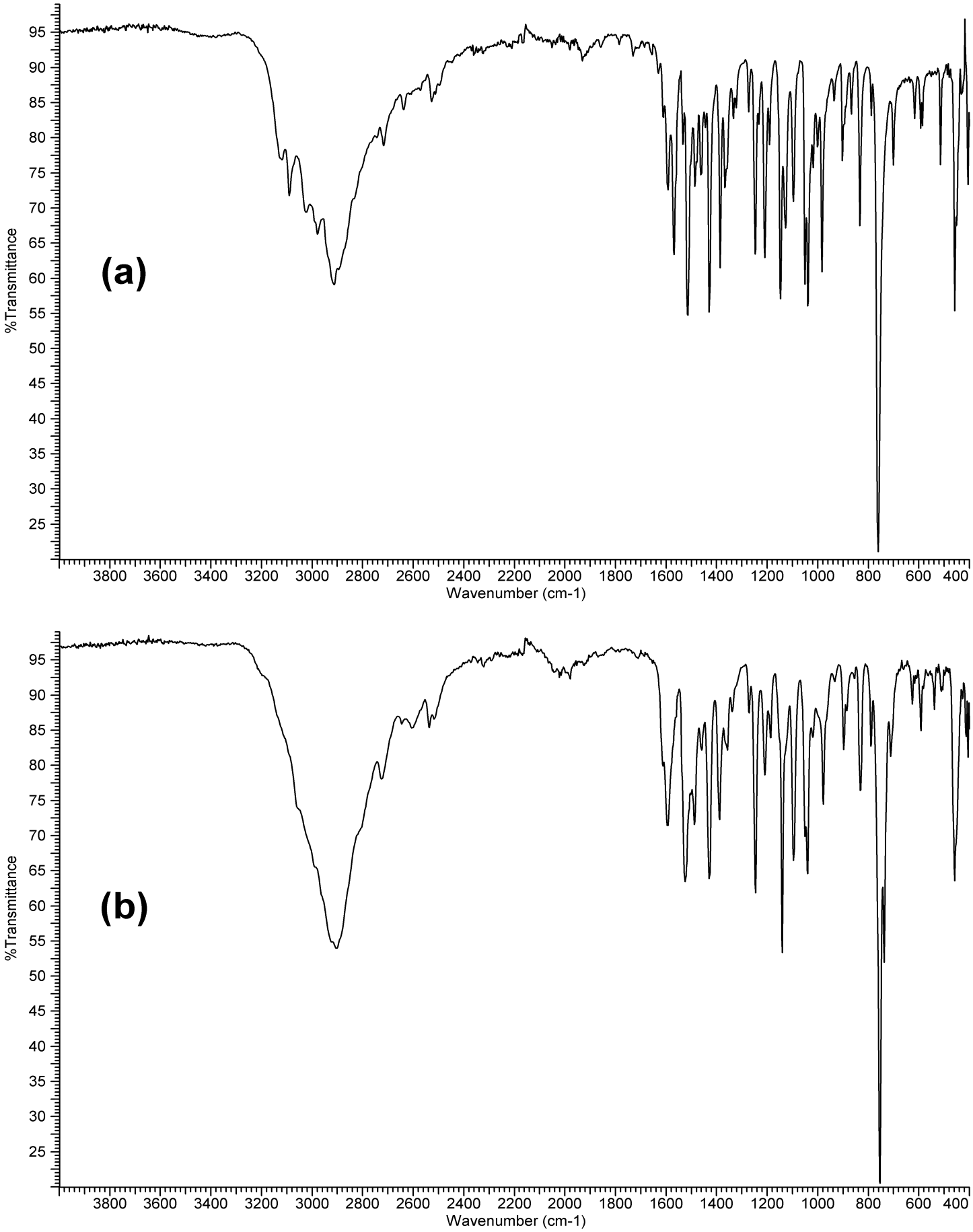

Figure 5 - FTIR of 4-(2-aminopropyl)benzofuran **1.** (a) slow crystallization, (b) rapid crystallization.

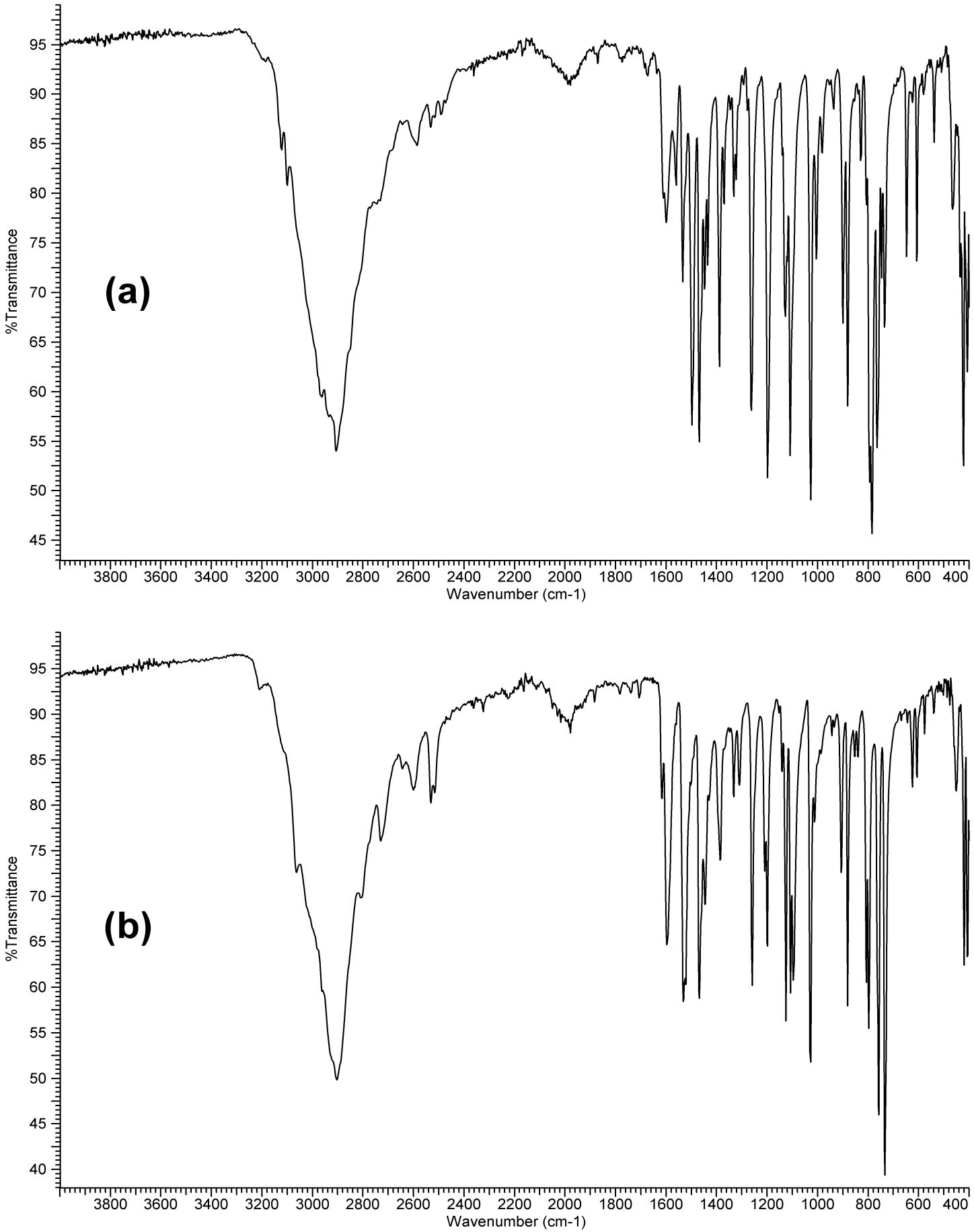

Figure 6 - FTIR of 5-(2-aminopropyl)benzofuran **2.** (a) slow crystallization, (b) rapid crystallization.

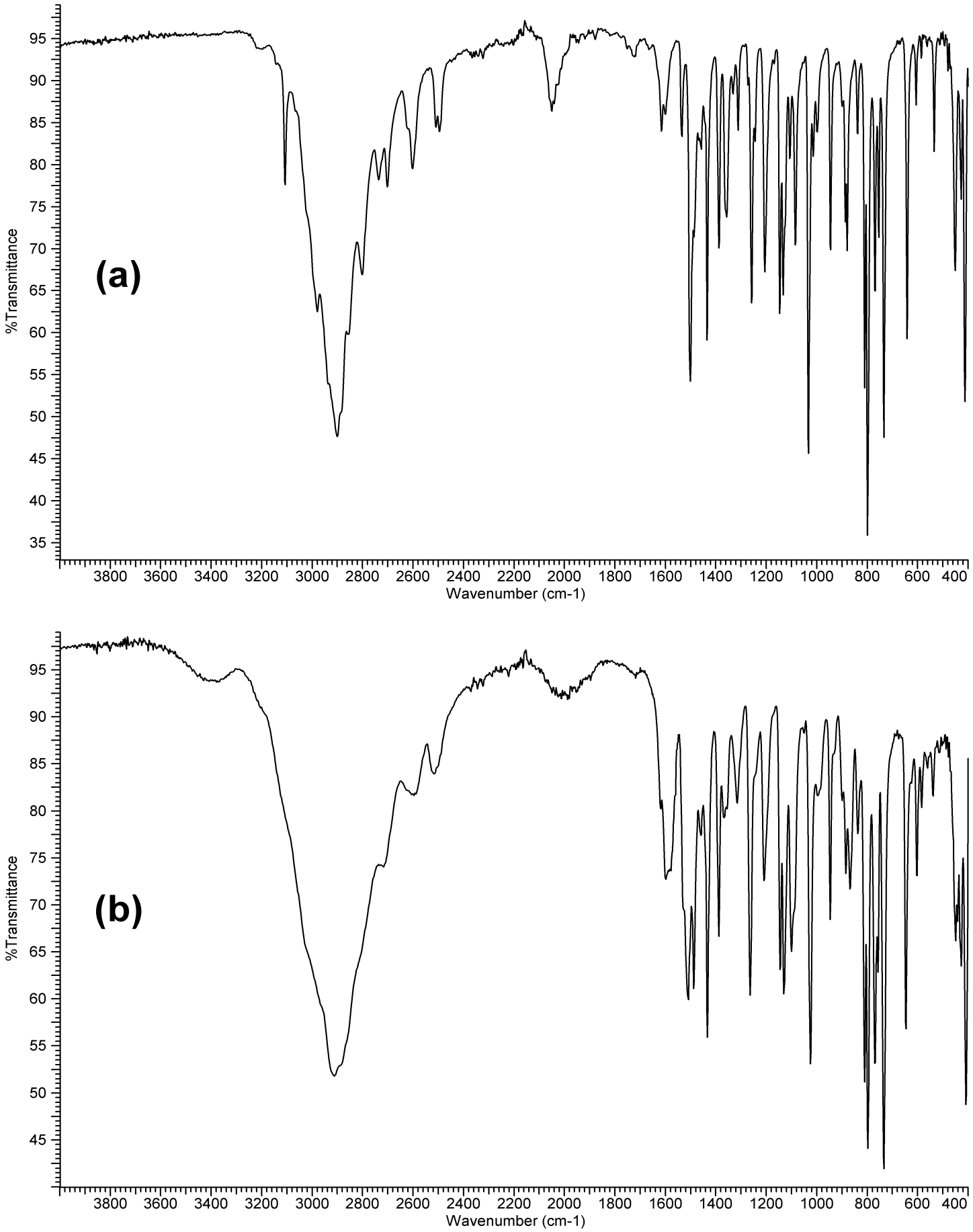

Figure 7 - FTIR of 6-(2-aminopropyl)benzofuran **3.** (a) slow crystallization, (b) rapid crystallization.

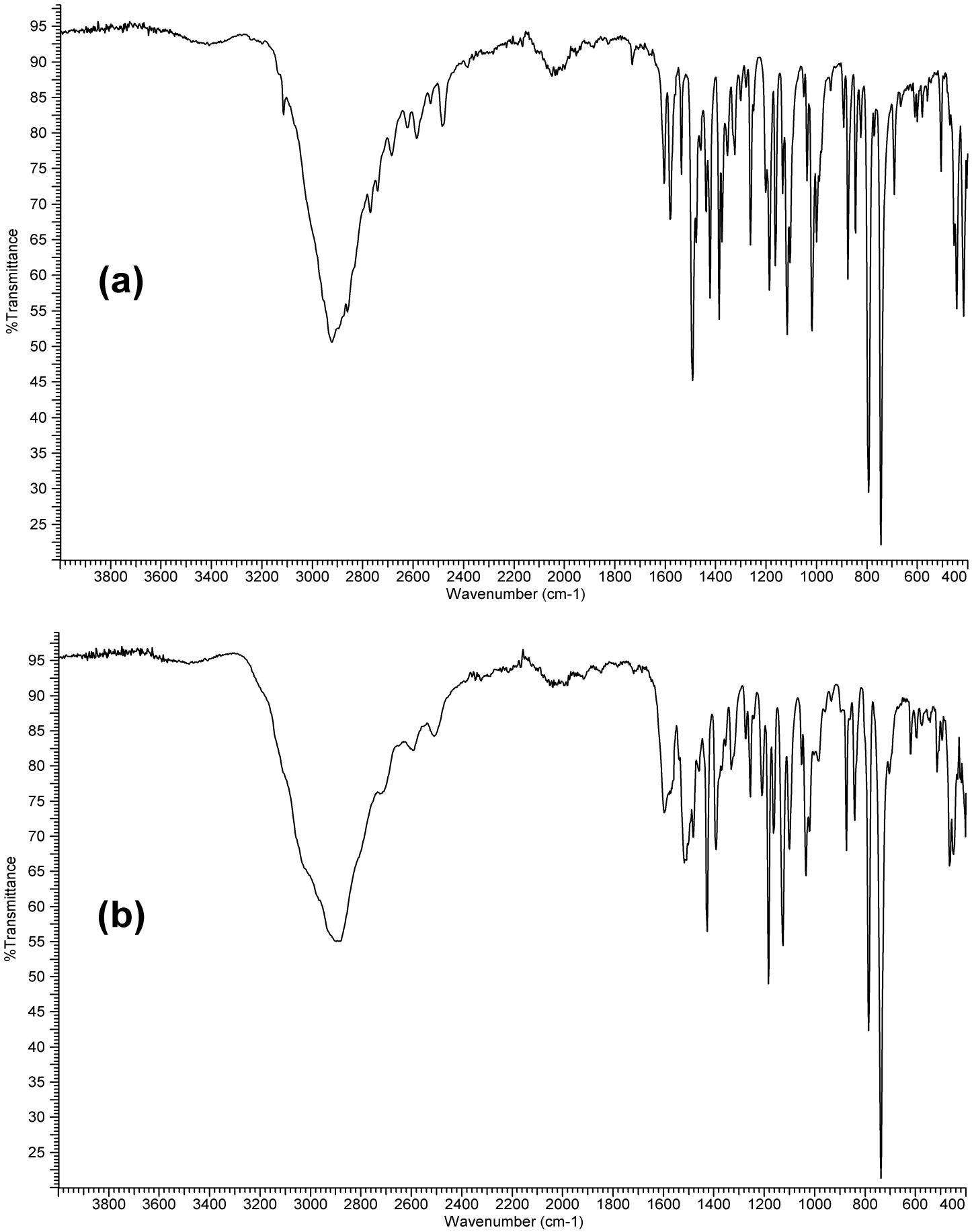

Figure 8 - FTIR of 7-(2-aminopropyl)benzofuran **4.** (a) slow crystallization, (b) rapid crystallization.

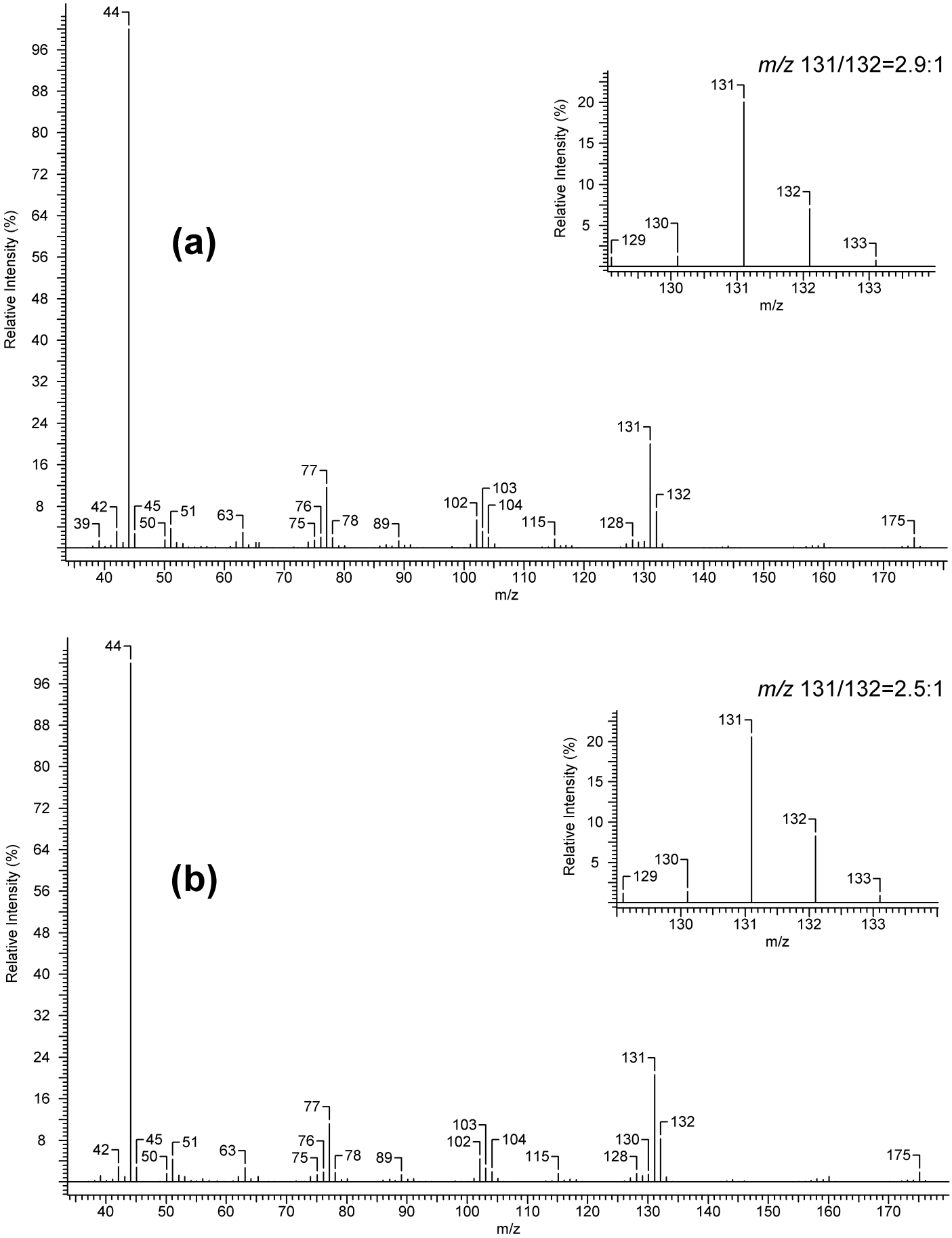

Figure 9 - Mass spectrum of (a) 4-(2-aminopropyl)benzofuran **1** and (b) 5-(2-aminopropyl)benzofuran **2.**

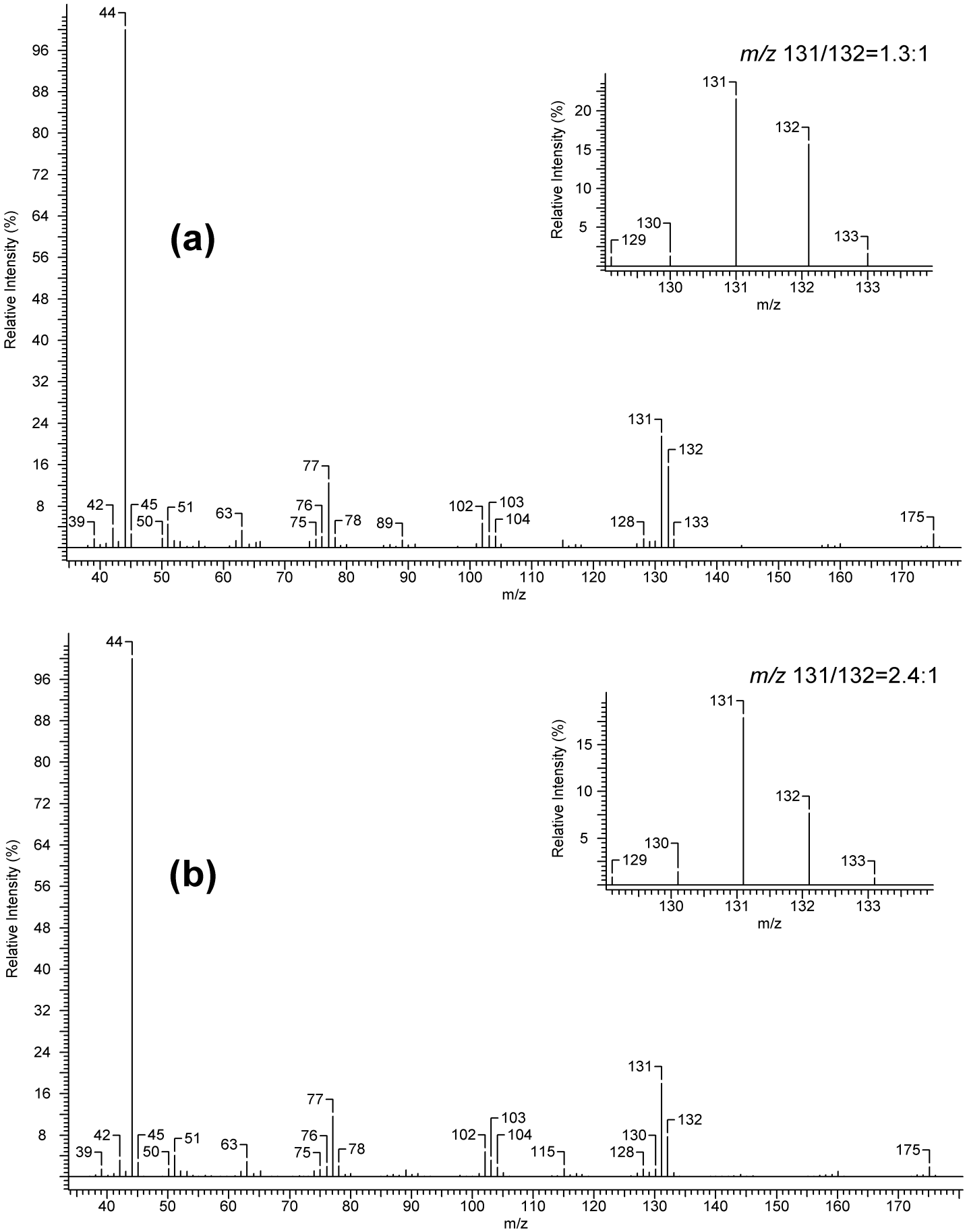

Figure 10 - Mass spectrum of (a) 6-(2-aminopropyl)benzofuran **3** and (b) 7-(2-aminopropyl)benzofuran **4.**

4-APB base				
Position	Carbon (ppm)	Proton (ppm)	^{1}H pattern	J_{HH} (Hz)
2	144.5	7.61	d	2.5
3	105.2	6.82	dd	2.5, 1.0
3a	127.3	-		
4	133.0	-		
5	123.2	7.05	d	7.4
6	124.2	7.23	dd	7.9, 7.4
7	109.5	7.38	d	7.9
7a	154.9	-		
CH_2	44.0	2.77	dd	13.4, 7.9
		2.94	dd	13.4, 5.5
CH	48.0	3.29	dqd	7.9, 6.4 (x3), 5.5
CH_3	23.8	1.15	d	6.4
d = doublet, q = quartet				

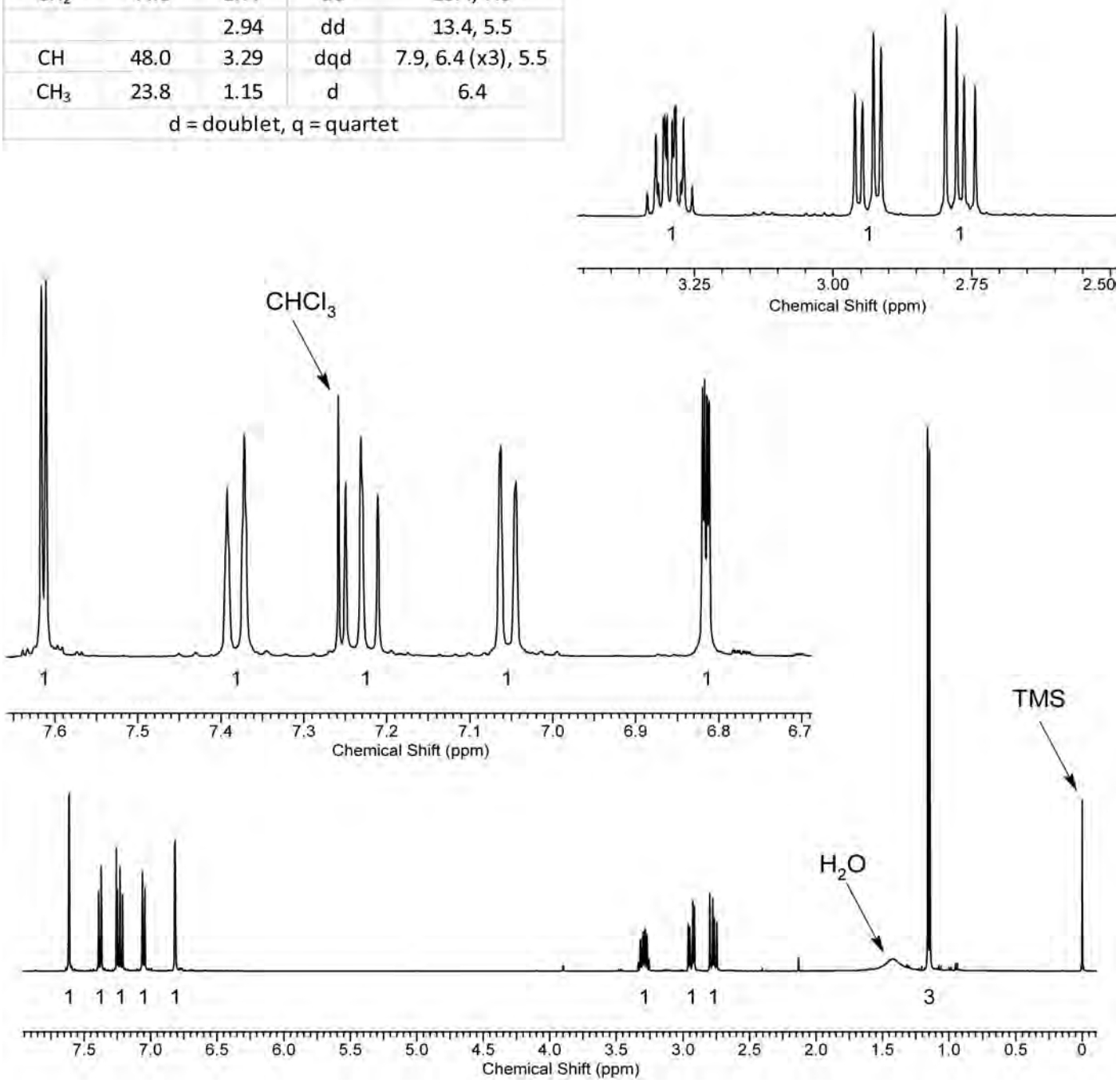

Figure 11 - ^{1}H and ^{13}C NMR data for 4-(2-aminopropyl)benzofuran **1** dissolved in $CDCl_3$.

5-APB base				
Position	Carbon (ppm)	Proton (ppm)	^1H pattern	J_{HH} (Hz)
2	145.1	7.60	d	2.0
3	106.4	6.72	dd	2.0, 1.0
3a	127.6			
4	121.4	7.40	d	1.7
5	134.1			
6	125.5	7.11	dd	8.4, 1.7
7	111.1	7.43	d	8.4
7a	153.8			
CH_2	46.5	2.59	dd	13.3, 7.9
		2.81	dd	13.3, 5.4
CH	48.7	3.19	dqd	7.9, 6.3 (x3), 5.4
CH_3	23.5	1.13	d	6.3
d = doublet, q = quartet				

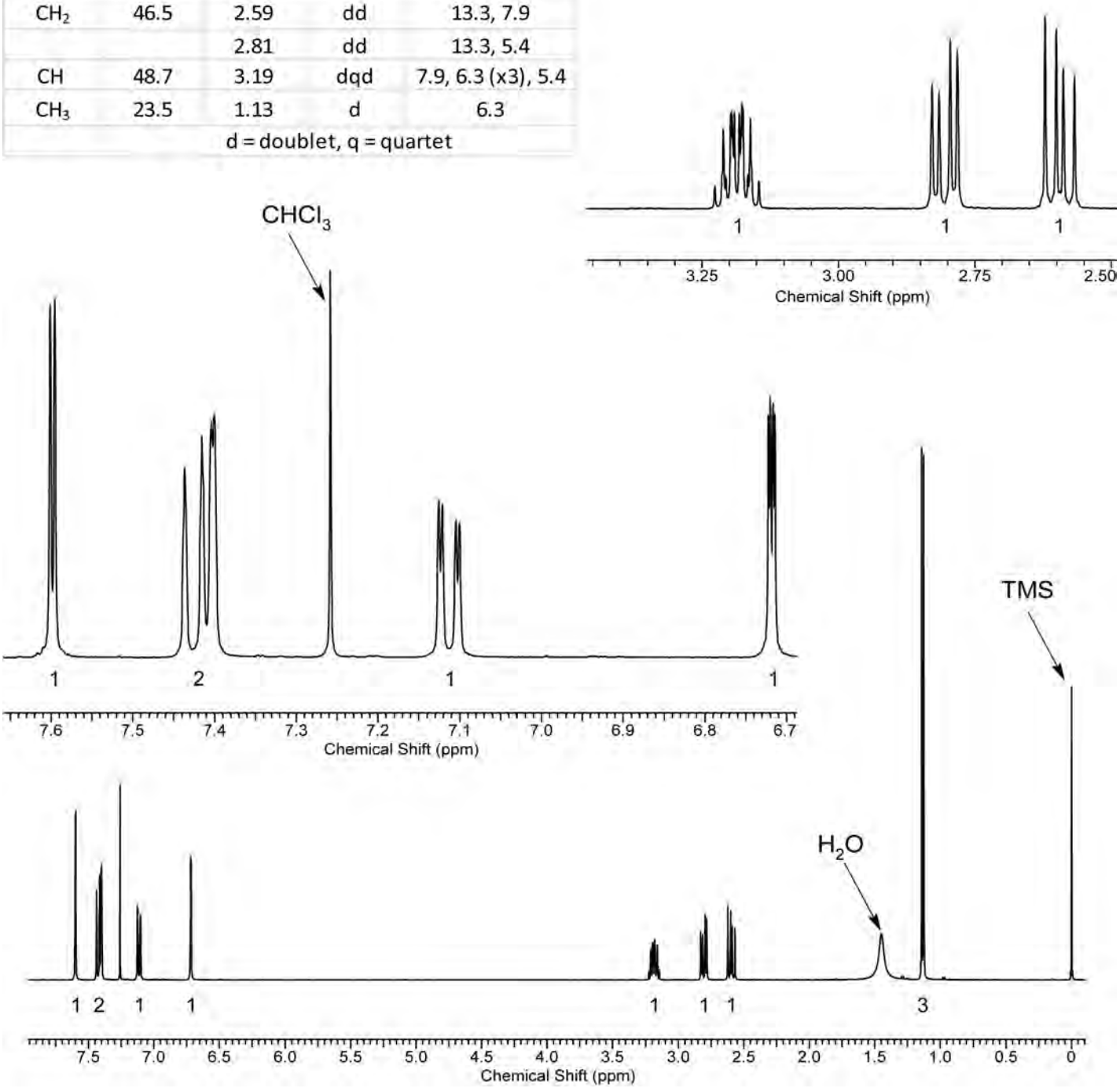

Figure 12 - ^1H and ^{13}C NMR data for 5-(2-aminopropyl)benzofuran **2** dissolved in $CDCl_3$.

Position	6-APB base			
	Carbon (ppm)	Proton (ppm)	^{1}H pattern	J_{HH} (Hz)
2	144.6	7.58	d	2.5
3	106.3	6.73	dd	2.5, 1.0
3a	125.6	-		
4	120.8	7.51	d	7.9
5	124.2	7.08	dd	7.9, 1.5
6	136.3	-		
7	111.8	7.34	bs	
7a	155.3	-		
CH_2	46.7	2.63	dd	13.3, 7.9
		2.83	dd	13.3, 5.4
CH	48.7	3.21	dqd	7.9, 6.4(x3), 5.4
CH_3	23.5	1.14	d	6.4
	bs = broad singlet, d = doublet, q = quartet			

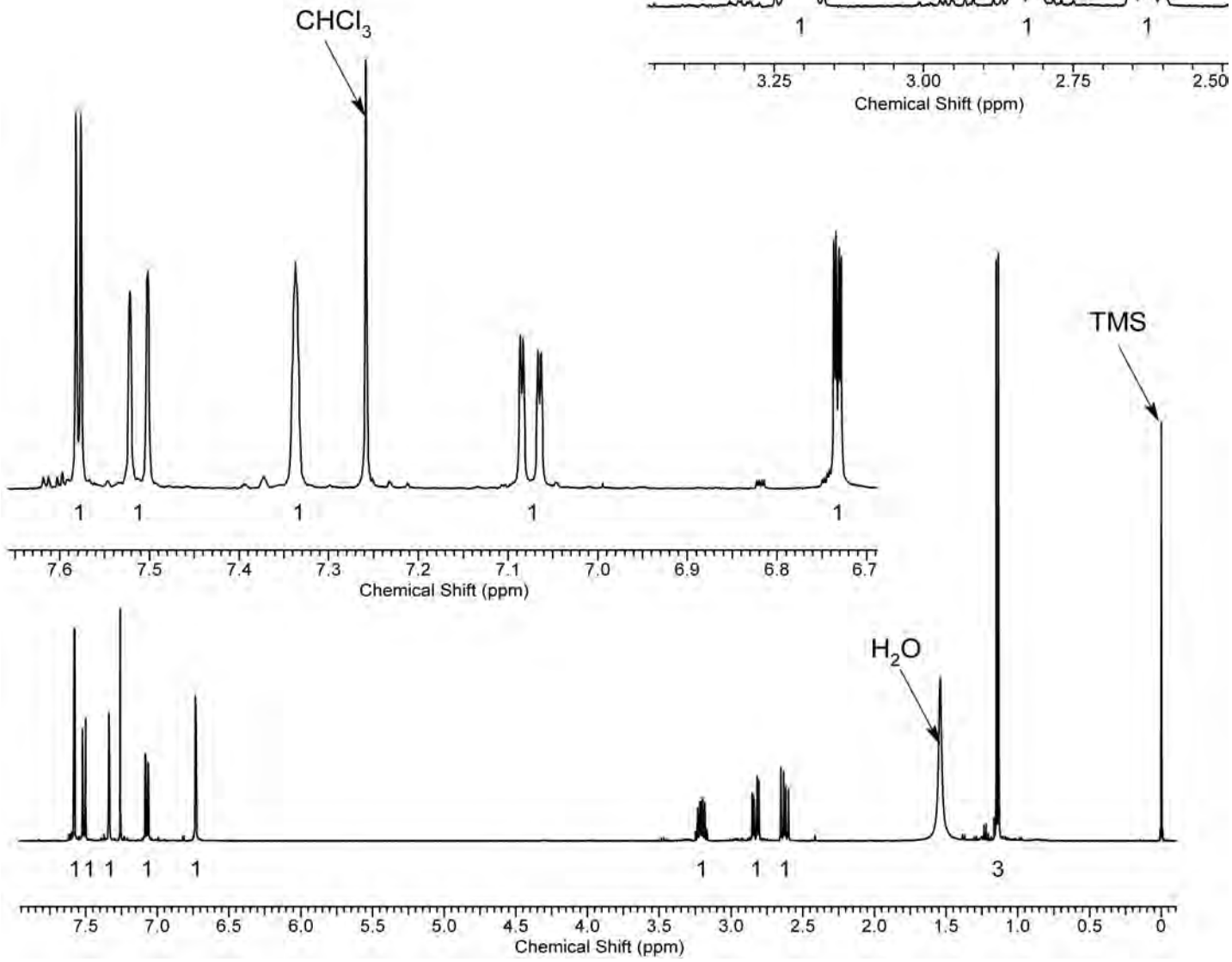

Figure 13 - ^{1}H and ^{13}C NMR data for 6-(2-aminopropyl)benzofuran **3** dissolved in $CDCl_3$.

7-APB base				
Position	Carbon (ppm)	Proton (ppm)	^1H pattern	J_{HH} (Hz)
2	144.7	7.62	d	2.1
3	106.9	6.77	d	2.1
3a	127.3	-		
4	119.4	7.47	d	7.5
5	123.0	7.18	t	7.5
6	125.4	7.11	d	7.5
7	123.6	-		
7a	153.9	-		
CH_2	41.0	2.83	dd	13.5, 8.5
		3.02	dd	13.5, 5.7
CH	47.4	3.38	dtd	8.5, 6.4(x3), 5.7
CH_3	23.8	1.17	d	6.4
d = doublet, q = quartet, t = triplet				

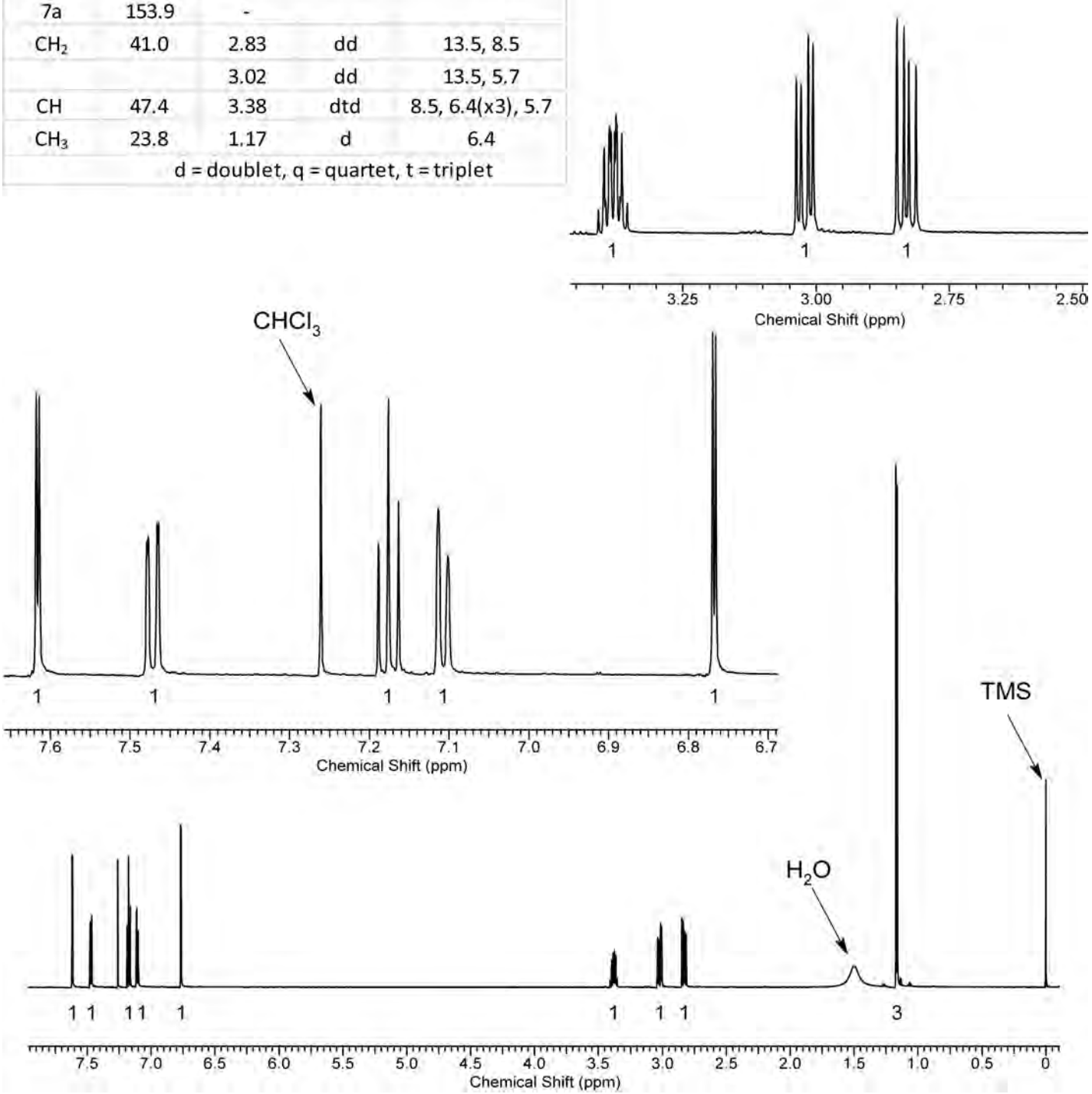

Figure 14 - ^1H and ^{13}C NMR data for 7-(2-aminopropyl)benzofuran **4** dissolved in $CDCl_3$.

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

Compound	R_t (min)
1	9.29
2	9.64
3	9.71
MDA	9.73
4	9.13

[a]Conditions given in the experimental section.

compounds can be distinguished based on a combination of retention times and the *m/z* 131/132 ratio; however, since **2** and **3** elute at essentially the same retention time, care must be taken in differentiating those compounds.

The proton and carbon assignments for **1**-**4** as the free base are presented in Figures 11-14. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton), HMBC (2-4 bond carbon to proton), and NOESY (spatially near protons) spectra. Assignments were further confirmed using ACD Structure Elucidator software. Proton spectra from all four compounds contain small coupling doublets (~2 Hz) at about 6.7 and 7.6 ppm, which are H-3 and H-2, respectively. The other 3 aromatic proton signals fall into one of two patterns; 1) two large coupling doublets and one triplet (or apparent triplet), which results from having a series of 3 bonded methines (compounds **1** and **4**); or 2) one large coupling doublet, one doublet of doublets, and one small coupling doublet due to CH=C-CH=CH series (compounds **2** and **3**). HMBC spectra further distinguish positional isomers **1** from **4** by correlating C-7a (~155 ppm) to the aliphatic protons (only found with **4**) or correlating C-3a (~127 ppm) to the aliphatic protons (only found with **1**). Distinguishing **2** from **3** is done by HMBC correlations from C-3 to H-4 and then examining the proton peak pattern of H-4; small coupling doublet indicates **2** while a large coupling doublet indicates **3**.

Conclusions

The illicit sample was identified as 6-(2-aminopropyl) benzofuran succinate (major component) containing 4-(2-aminopropyl)benzofuran succinate (minor component). The exhibit was also found to be diluted with excess succinic acid.

References

1. Briner K, Burkhart JP, Burkholder TP, Fisher MJ, Gritton WH, Kohlman DT, Liang SX, Miller SC, Mullaney JT, Xu YC, Xu Y. Aminoalkylbenzofurans as serotonin (5-HT (2C)) agonists, US Patent 7,045,545 B1. May 16, 2006.