Characterization of Three Methcathinone Analogs: 4-Methylmethcathinone, Methylone, and bk-MBDB

Chad R. Maheux * **and Catherine R. Copeland**
Science and Engineering Directorate
Canada Border Services Agency
Ottawa, Ontario, K2E 6T7, Canada
[email: chad.maheux -at- cbsa-asfc.gc.ca and cathy.copeland -at- cbsa-asfc.gc.ca]

Michael M. Pollard†
Department of Chemistry
York University
Toronto, Ontario, M3J 1P3, Canada

ABSTRACT: Complete spectroscopic characterization (FTIR, FT-Raman, ^{1}H NMR, ^{13}C NMR, GC/MS, and EI-HRMS) is presented for the hydrochloride salts of 3,4-methylenedioxymethcathinone (methylone), 1-(1,3-benzodioxol-5-yl)-2-(methylamino) butan-1-one (bk-MBDB), and 4-methylmethcathinone (mephedrone). These three methcathinone analogs were synthesized in our laboratory as reference materials for comparison with submitted exhibits. Additionally, the identification of bk-MBDB is reported in tablets which are available over the internet.

KEYWORDS: Methcathinone, methylone, 4-methylmethcathinone, bk-MBDB, forensic chemistry

Most new designer drugs are prepared to circumvent existing legislation, to create new drugs with desirable pharmacological properties, and/or to avoid detection through normal testing protocols. Since 2006, analogs of methcathinone **1** and structurally similar β-ketophenethylamine derivatives have been intercepted in cross-border shipments by the Canada Border Services Agency (CBSA) with increasing frequency. Since many of these designer drugs are regulated in Canada under the *Controlled Drugs and Substances Act*, it is important to confirm the identity of these chemicals for regulatory and intelligence purposes.

The identification of new designer drugs presents certain challenges. Certified reference materials and published peer-reviewed analytical data are often unavailable when new substances are encountered. Reference standards for some analogs of methcathinone are not presently available, hindering the detection and identification of these materials.

Methcathinone (also known as ephedrone) is the β-keto analog of methamphetamine and the *N*-methyl derivative of cathinone, a central nervous stimulant found in leaves of the "khat" bush (*Catha edulis*) [1]. Methamphetamine and methcathinone syntheses are well documented in the literature

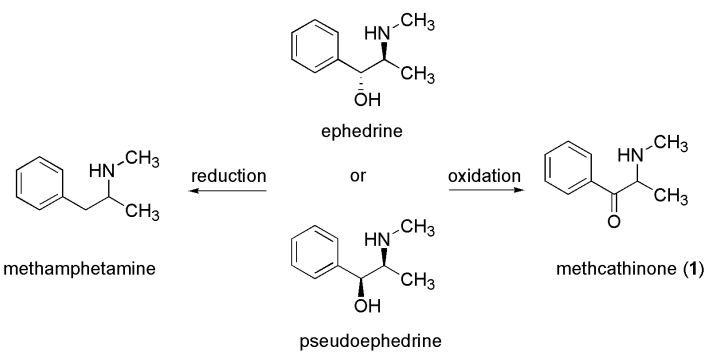


Figure 1 - Ephedrine (or pseudoephedrine) undergoes reduction to give methamphetamine and oxidation to afford methcathinone.

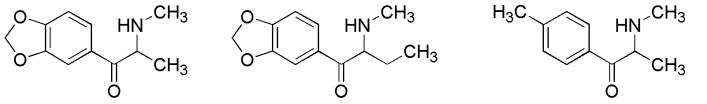


Figure 2 - Structures of methcathinone analogs prepared in this study.

and these substances can be readily prepared by reduction [2,3] and oxidation [4] of ephedrine (and pseudoephedrine), respectively (Figure 1). The names methamphetamine and methcathinone are used for these compounds regardless of their enantiopurity, which may vary depending on the methods used in their synthesis [5].

Analogs of methcathinone that possess the methylenedioxy ring substituent on the phenyl ring resemble 3,4-methylene-dioxymethamphetamine (MDMA, "Ecstasy"). Methylone (**2a**, Figure 2) is the benzylic ketone analog of MDMA. This analog was patented in 1996 as an antidepressant [6] and some analytical data was published shortly thereafter [7]. It is the main ingredient of the designer drug "Explosion," found and reported in 2005 in the Netherlands [8]. bk-MBDB, or 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one, (**2b**, Figure 2) is the β-keto analog of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB), a psychoactive agent with similar pharmacology to MDMA [9]. bk-MBDB is commonly referred to as "butylone" on the internet. Recently, our laboratory analyzed two different sets of tablets that were confirmed to contain **2b** by FTIR and GC/MS. The tablets in the first set were biconvex, slightly off-white in color, with an image of a dove imprinted on one side (Figure 3A). Tablets in another set, which were also found to contain fenfluramine hydrocholoride (an anorectic), were round, flat, and yellow with an image of a sun imprinted on one side (Figure 3B).

†Dr. Michael Pollard recently passed away unexpectedly at the age of 36. He will be remembered as an inspiring teacher, colleague, and friend.

Figure 3 - Tablets identified to contain A) bk-MBDB and B) bk-MBDB with fenfluramine.

In a separate case in 2008, our laboratory identified a white powder as the hydrochloride salt of 4-methylmethcathinone (**2c**, Figure 2). Some websites have referred to this designer drug as "mephedrone." At that time, this analog had not been reported in the scientific literature and therefore required structural elucidation and synthesis of a reference compound to unequivocally determine its identity. Our data supports and supplements the work that was recently published on this analog [10].

To provide spectroscopic data for the hydrochloride salts of **2a** and **2b**, and to confirm the structure of **2c**, we synthesized the hydrochloride salts of these racemic methcathinone analogs and provide complete spectroscopic (FTIR, FT-Raman, ^{1}H NMR, ^{13}C NMR) and spectrometric characterization (GC/MS, EI-HRMS).

Experimental Procedures

Chemicals, Reagents and Methods

All solvents and reagents were purchased from Sigma-Aldrich, used without purification and were analytical grade. Derivatization grade *N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide (MSTFA) was used to prepare the trimethylsilyl derivatives for GC/MS analysis. Trimethylsilyl derivatives were prepared by adding 5 mg of sample to 1 mL of 50% (v/v) MSTFA in chloroform and then heating to 70˚C for 1 h.

Sample solutions for analysis by nuclear magnetic resonance (NMR) spectroscopy were prepared with 99.9% D anhydrous DMSO-d_6 in 1 mL ampoules.

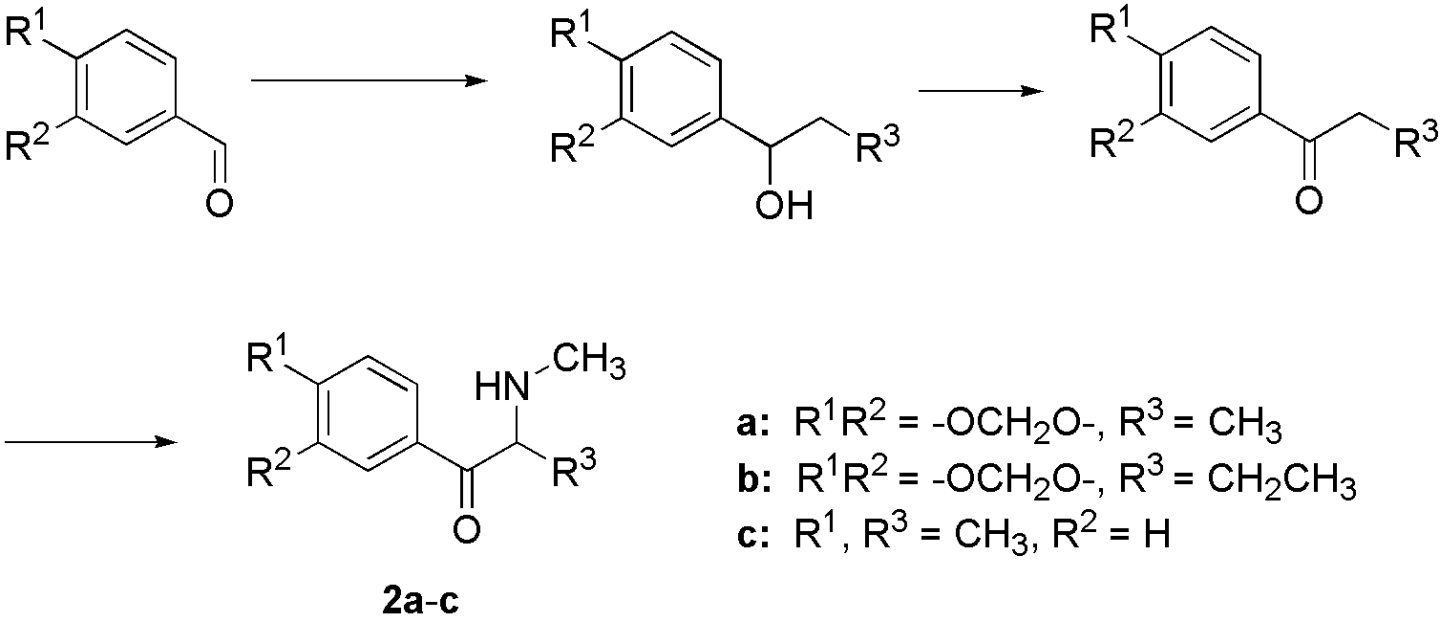
Instrumentation

ATR-FTIR spectra were recorded on a Nicolet Avatar 370 FTIR, with single reflection diamond ATR accessory. Range: 4000 cm^{-1} - 650 cm^{-1}, 16 scans and 4 cm^{-1} resolution. Raman spectroscopy was performed using a Nicolet 6700 FTIR with NXR FT-Raman module on samples in an NMR tube with laser wattage at 1.0 W and an InGaAs detector. Range: 4000 cm^{-1} - 100 cm^{-1} Raman shift, 128 scans, 1064 nm Nd-YAG excitation laser.

GC/MS data was collected using an Agilent 6890N GC with a 7683B series autosampler, 1 µL injection, split 150:1 - 4 mm single gooseneck liner (deactivated, no glass wool), DB5MS column (30 m × 0.25 mm × 0.25 µm) with constant flow (1 mL/min of helium) coupled to an Agilent 5973 Mass Selective Detector. EI operating parameters were: inlet temperature 280˚C, interface temperature 280˚C, MS source 230˚C, MS Quad 150˚C, 70 eV ionization energy. The GC oven temperature program started at an initial temperature of 100˚C with a ramp of 10˚C/min to 300˚C. The final temperature was held for 25 min (total run time 45 min).

High-resolution mass spectra (HRMS) were recorded using electron-impact ionization at the University of Ottawa Mass Spectrometry Centre on a Kratos Concept double focusing mass spectrometer with 70 eV ionization energy. All measurements are within 3 millimass units (mmu).

^{1}H and ^{13}C NMR spectra were recorded in 5 mm NMR tubes on a Bruker AVANCE III 400 MHz spectrometer on solutions in DMSO-d_6. Chemical shifts are given in parts per million (ppm) (± 0.01 ppm) relative to the residual undeuterated solvent absorptions (2.50 ppm for DMSO-d_6 in ^{1}H NMR spectroscopy; and 39.5 ppm for DMSO-d_6 in ^{13}C NMR spectroscopy). Coupling constants (*J*) are expressed in Hertz (Hz). The following abbreviations are used to designate NMR absorption patterns: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; AA'MM', multiplet characteristic of the *para*-substituted benzene ring.



Scheme 1 - Synthetic pathway used for the preparation of methcathinone analogs **2a-c.**

Synthetic Procedures

The following synthetic pathway was used to prepare analogs **2a-c** (Scheme 1). Experimental details on these syntheses are not provided, in accordance with the *Journal* policy.

Results and Discussion:

Infrared spectroscopy and Raman spectroscopy

The IR (Figure 4) and Raman spectra (Figure 5) collected from samples of **2a-c** synthesized in our laboratory were consistent with the ATR-FTIR and FT-Raman spectra previously recorded for exhibits submitted from intercepted shipments. While IR spectroscopy has traditionally served as an important method for screening and identifying unknowns, we also present Raman spectroscopic data because it has emerged as a powerful technique in the forensic laboratory. Raman spectroscopy is a non-destructive technique which, like IR, provides a "fingerprint" spectrum of chemical compounds. In many cases, bands which are weak or completely inactive in IR tend to be strong in Raman and vice versa. Therefore, these techniques are complementary and, together, provide a more complete characterization of the molecule.

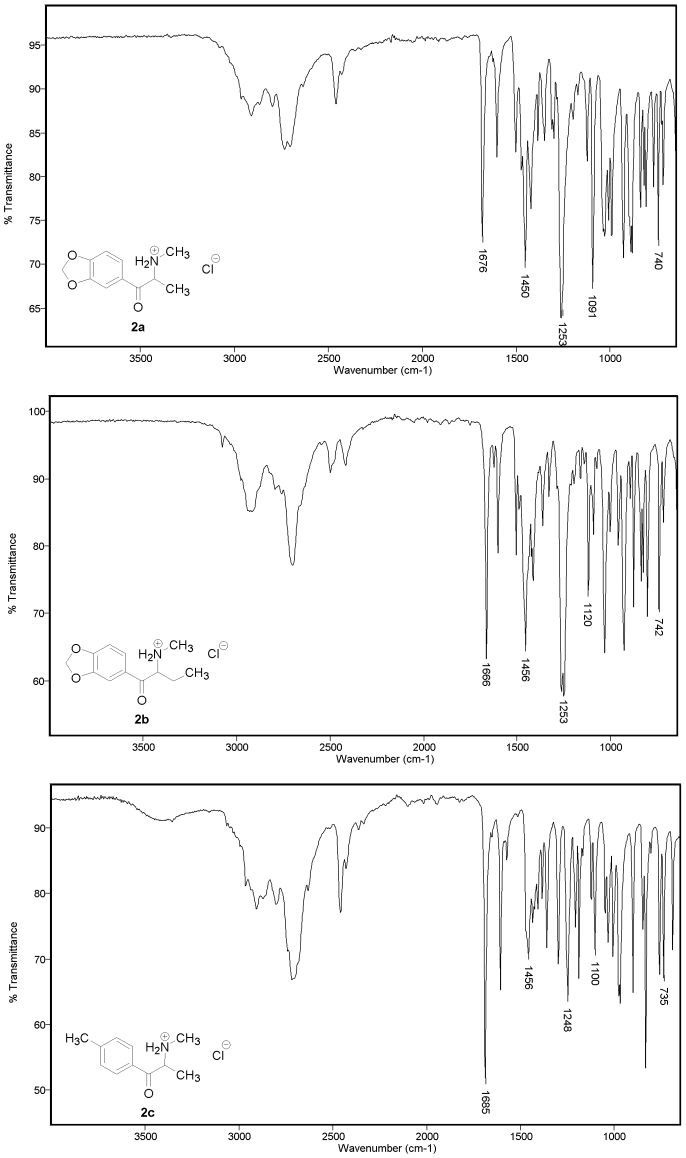


Figure 4 - ATR-FTIR spectra of methcathinone analogs **2a-c** hydrochloride**.**

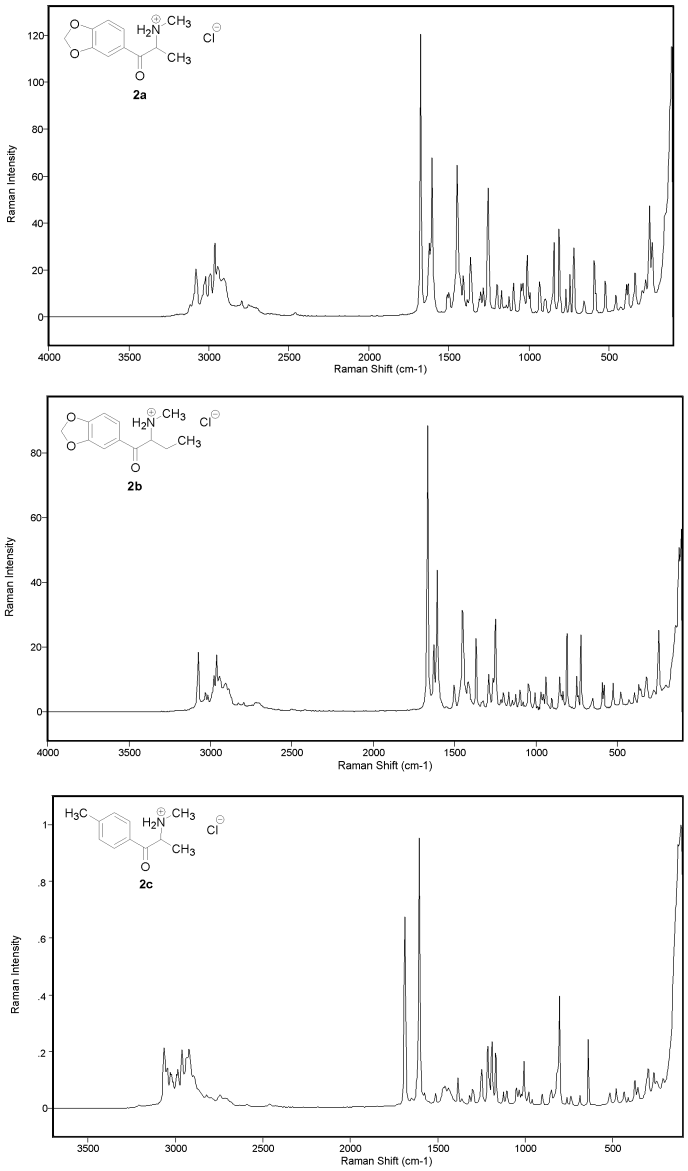


Figure 5 - FT-Raman spectra of methcathinone analogs **2a-c** hydrochloride.

Gas chromatography - mass spectrometry and high resolution mass spectrometry

As shown in Figure 6, the molecular ions for analogs **2a-c** were either weak or absent. As a result, each analog **2a-c** was treated with MSTFA to give the thermally stable trimethylsilyl derivative for GC/MS analysis. The GC/MS data for the trimethylsilyl derivatives of **2a**, **2b** and **2c** showed a similar fragmentation pattern and gave molecular ions of *m/z* 279, 293, and 249 respectively (Figure 7). The base peak for silylated **2a** and **2c**, each at *m/z* 130, corresponds to the formation of an iminium ion ($C_6H_{16}NSi^+$) and is also characteristic of methcathinone. Silylated **2b** gave a base peak of *m/z* 144 ($C_7H_{18}NSi^+$) which is consistent with the extension in the alkyl chain length. The α-cleavage (M-15) fragments were found at *m/z* 264, 278, and 234 at low intensities for **2a**, **2b** and **2c** derivatives respectively. The ions at *m/z* 149 and *m/z* 121 for

Table 1 - EI-HRMS data for analogs **2a-c**.

	2a	**2b**	**2c**
Calculated mass (m/z)	207.0895	221.1052	176.1075
Measured mass (m/z)	207.0882	221.1038	176.1071
Molecular ion	$C_{11}H_{13}NO_3$ $[M]^+$	$C_{12}H_{15}NO_3$ $[M]^+$	$C11H_{14}NO$ $[M\text{-}H]^+$

Figure 6 - GC/MS data for analogs 2a (top), 2b (middle), and 2c (bottom).

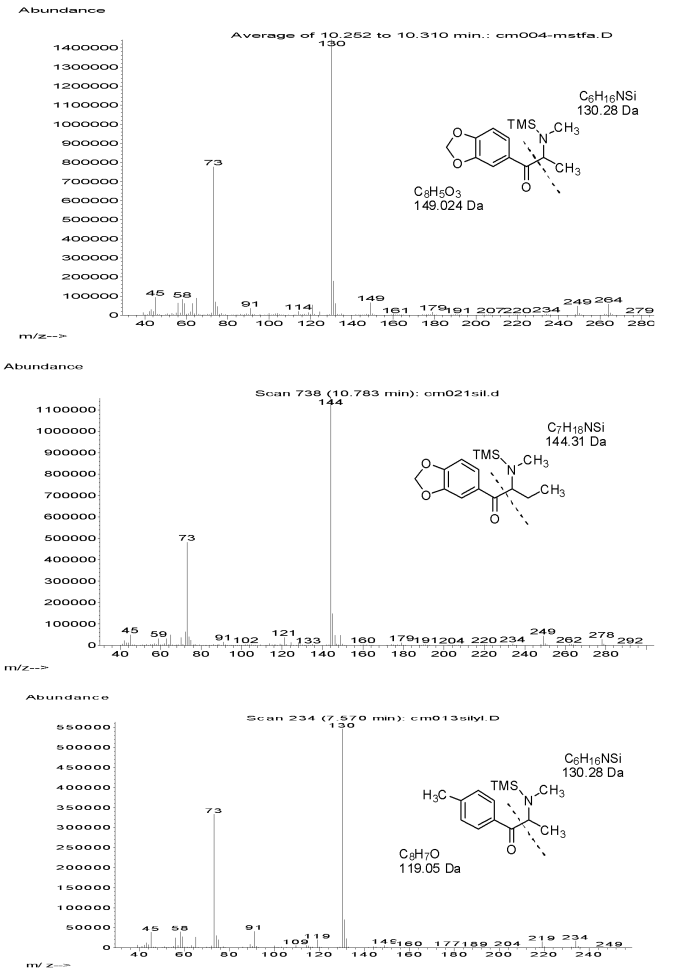


Figure 7 - GC/MS data for trimethylsilylated derivatives 2a (top), 2b (middle), and 2c (bottom).

2a and **2b** are consistent with the methylenedioxybenzoyl cation and methylenedioxyphenyl cation (formed by subsequent loss of CO) reported for the designer drug 3,4-methylenedioxy-pyrovalerone (MDPV) [11]. The mass spectra of all TMS-functionalized derivatives of **2a-c** all show an ion at *m/z* 73 that corresponds to the $(CH_3)_3Si^+$ fragment.

Table 1 presents data from electron-impact ionization high resolution mass spectrometry (EI-HRMS) for compounds **2a-c**. The HRMS data for each analog agrees with molecular formula and is accurate within a 3 millimass unit error.

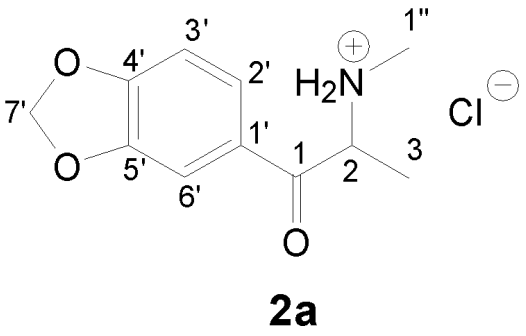
Nuclear Magnetic Resonance (NMR)

The ^1H and ^{13}C NMR spectra in DMSO-d_6 are presented for the hydrochloride salts of **2a-c** in Figures 8-10. Data from correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) experiments was used to assign aromatic protons for each analog and to distinguish methyl groups for **2c**. By preparing the amine hydrochloride salt, the N-H protons in each analog are diastereotopic and hence chemically inequivalent. As a result, these protons are observed as two broad singlets.

Conclusion

We have synthesized and characterized the hydrochloride salts of 3,4-methylenedioxymethcathinone (methylone), 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one (bk-MBDB), and 4-methylmethcathinone (mephedrone). The spectroscopic data collected on samples of these racemic analogs synthesized in our laboratory is consistent with the corresponding data from samples intercepted previously by the Canada Border Services Agency.

	^{13}C (ppm)	^{1}H (ppm)	Multiplicity	*J* (Hz)	Structure Assignment
1	194.3	-	-	-	
2	57.9	5.08	q	7.1	
3	15.7	1.43	d	7.1	
1’	127.4	-	-	-	
2’	125.8	7.69	dd	1.4, 8.2	
3’	108.5	7.13	d	8.2	
4’	152.7	-	-	-	
5’	148.2	-	-	-	
6’	107.9	7.53	d	1.4	
7’	102.4	6.19	s	-	
1”	30.6	2.55	s	-	



2a

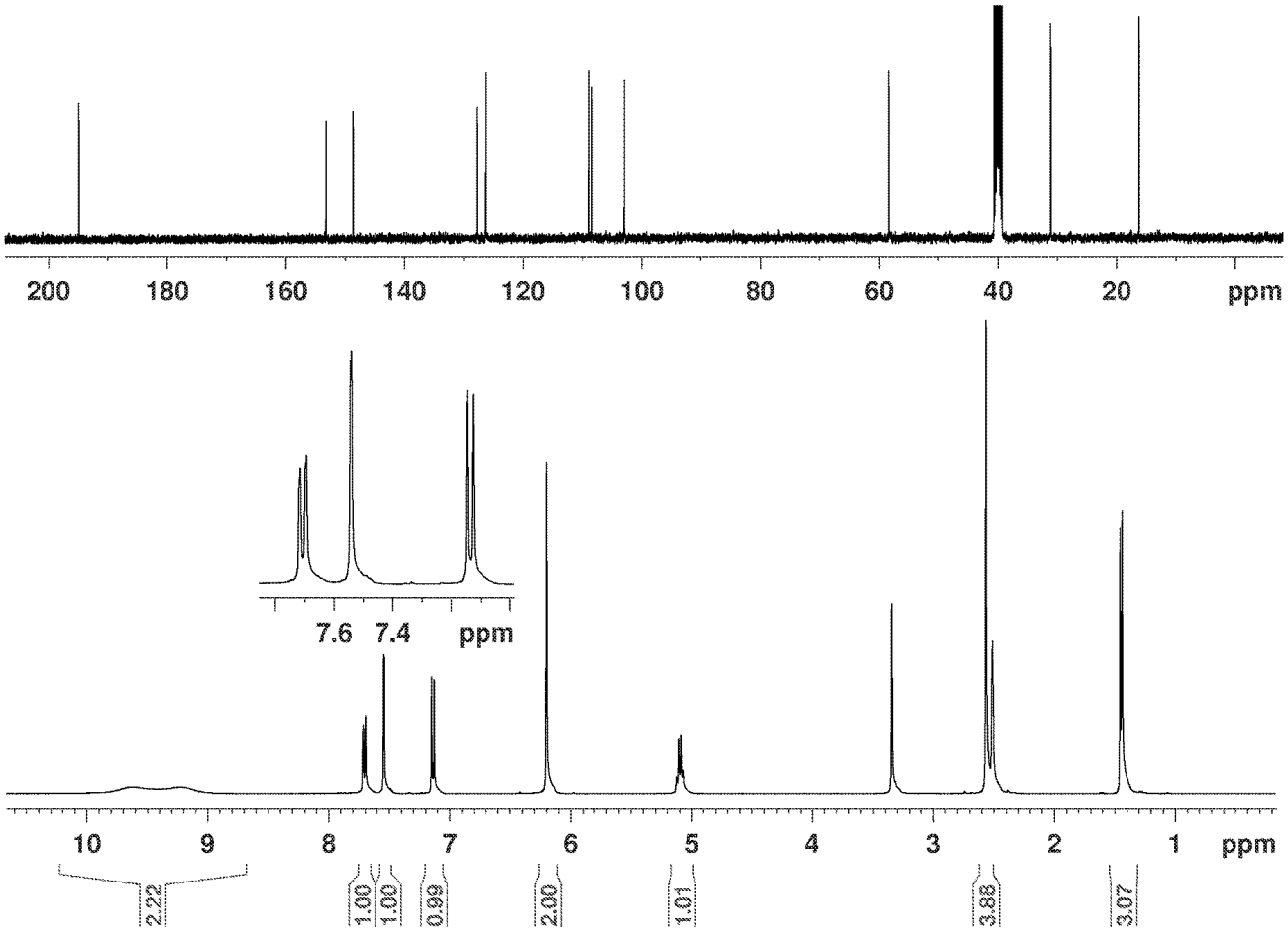
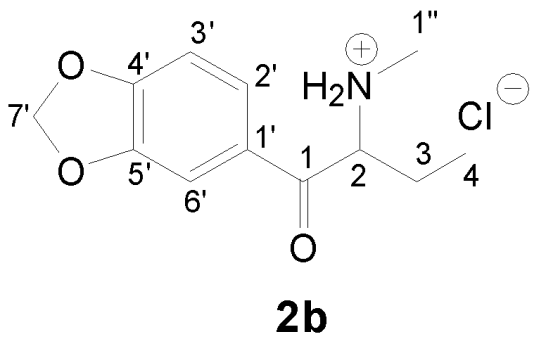


Figure 8 - ^{1}H and ^{13}C NMR data for **2a** hydrochloride in DMSO-d_6.

	^{13}C (ppm)	^{1}H (ppm)	Multiplicity	*J* (Hz)	Structure Assignment
1	193.8	-	-	-	
2	62.4	5.15	t	5.0	
3	22.9	1.79-2.10	m		
4	8.2	0.77	t	7.6	
1’	128.4	-	-	-	
2’	125.8	7.72	dd	1.7, 8.2	
3’	108.5	7.12	d	8.2	
4’	152.8	-	-	-	
5’	148.2	-	-	-	
6’	107.8	7.55	d	1.7	
7’	102.5	6.19	s	-	
1”	31.2	2.52	s	-	



2b

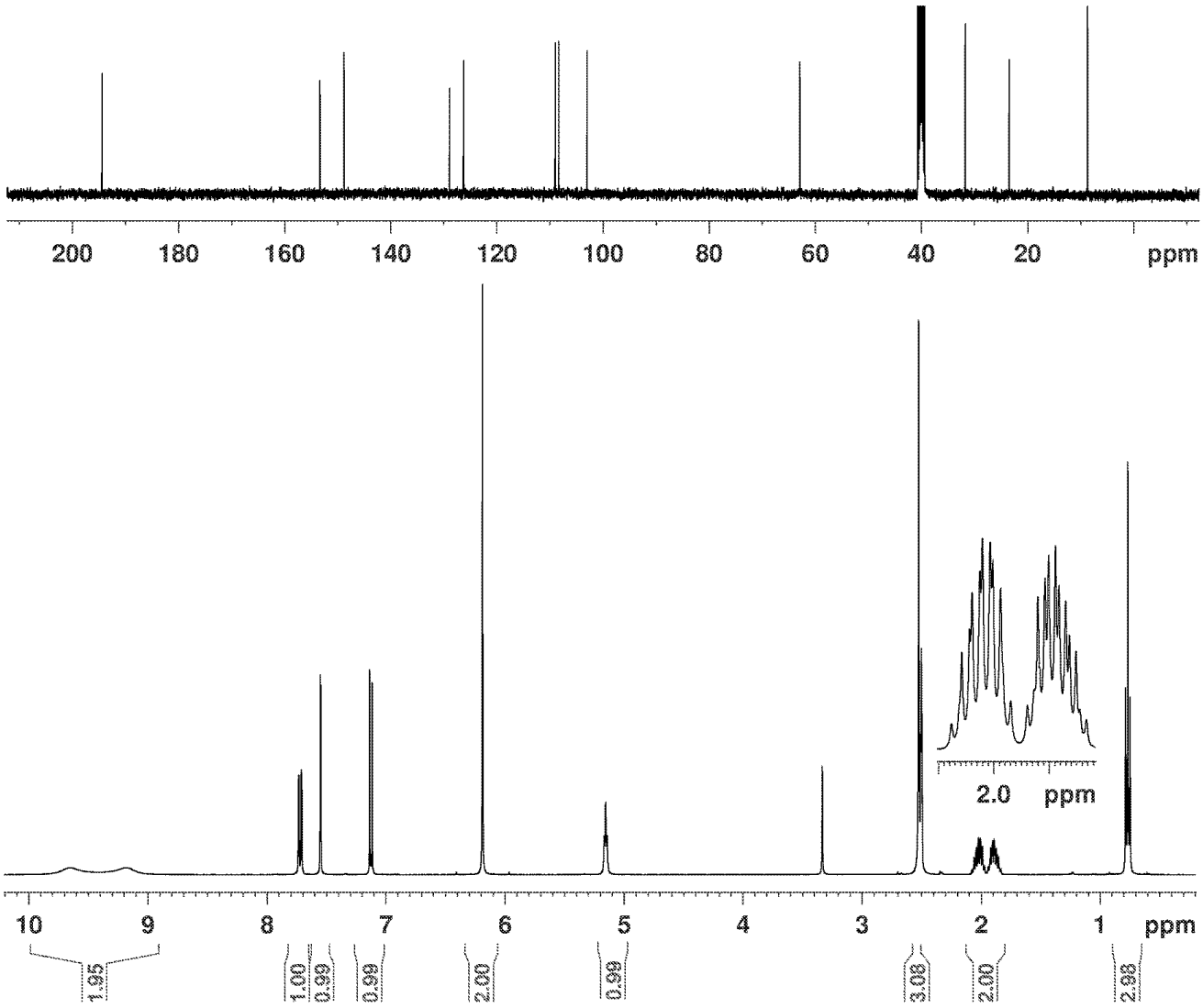
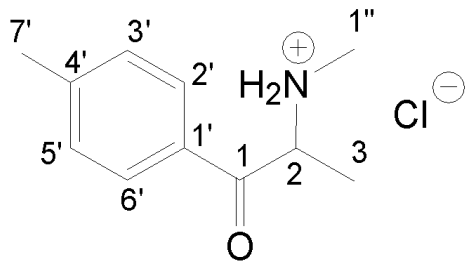


Figure 9 - ^{1}H and ^{13}C NMR data for **2b** hydrochloride in DMSO-d_6.

	^{13}C (ppm)	^{1}H (ppm)	Multiplicity	J (Hz)	Structure Assignment
1	195.8	-	-	-	
2	58.0	5.13	q	7.2	
3	15.5	1.44	d	7.2	
1’	130.4	-	-	-	
2’	128.9	7.94	AA’MM’	8.1*	
3’	129.7	7.41	AA’MM’	8.1*	
4’	145.4	-	-	-	
5’	129.7	7.41	AA’MM’	8.1*	
6’	128.9	7.94	AA’MM’	8.1*	
7’	21.2	2.41	s	-	
1”	30.6	2.58	s	-	



2c

* $J_{apparent}$

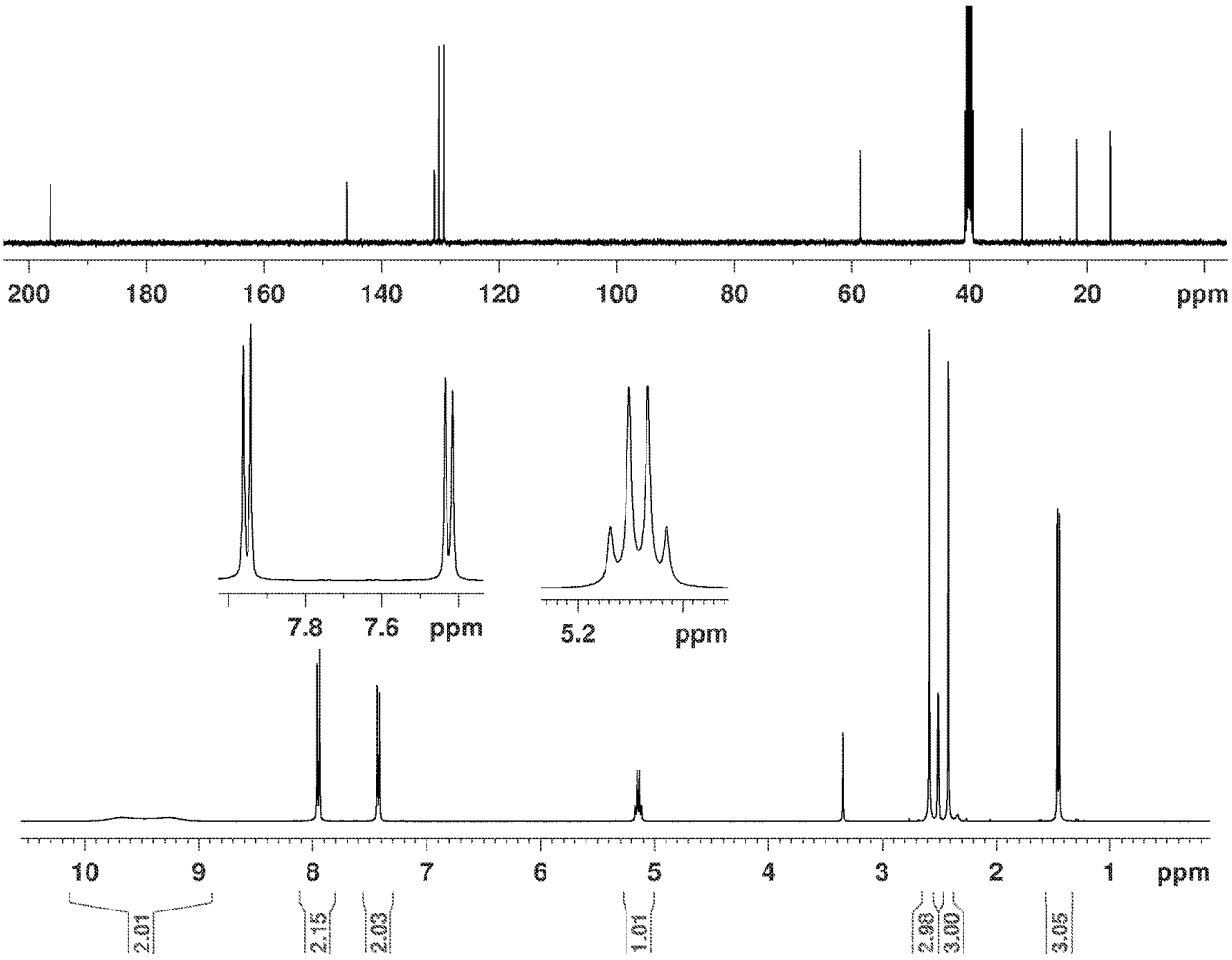


Figure 10 - ^{1}H and ^{13}C NMR data for **2c** hydrochloride in DMSO-d_6.

Acknowledgements

The authors would like to thank the National Anti-Drug Strategy for funding of this project, Pat Latour for performing GC/MS experiments, Mario Larouche for running NMR spectroscopy experiments, and Dr. Clem Kazakoff for HRMS analysis.

References

1. Cozzi NV, Sievert MK, Shulgin AT, Jacob P, III, Ruoho AE. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. Eur J Pharmacol 1999;381(1):63-9.
2. Zvilichovsky G, Gbara-Haj-Yahia I. Birch reduction of (-)-ephedrine. Formation of a new, versatile intermediate for organic synthesis. J Org Chem 2004;69(16):5490-3.
3. Skinner HF. Methamphetamine Synthesis Via Hydriodic Acid Red Phosphorus Reduction of Ephedrine. Forensic Sci Int 1990;48(2):123-34.
4. Deruiter J, Hayes L, Valaer A, Clark CR, Noggle FT. Methcathinone and Designer Analogs - Synthesis, Stereochemical Analysis, and Analytical Properties. J Chromatogr Sci 1994;32:552-64.
5. Mendelson J, Uemura N, Harris D, Nath RP, Fernandez E, Jacob P, Everhart ET, Jones RT. Human pharmacology of the methamphetamine stereoisomers. Clin Pharmacol Ther 2006;80:403-20.
6. Jacob P, III, Shulgin AT. Preparation of novel *N*-substituted-2-amino-3',4'-methylenedioxypropiophenones as anti-depressant and anti-Parkinsonism agents. PCT Int Appl 1996;96-US9603; 95-467406:19.
7. Dal Cason TA. The characterization of some 3,4-methylenedioxycathinone (MDCATH) homologs. Forensic Sci Int 1997;87(1):9-53.
8. Bossong MG, Van Dijk JP, Niesink RJ. Methylone and mCPP, two new drugs of abuse? Addict Biol 2005;10 (4):321-3.
9. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J Psychoactive Drugs 1986;18(4):305-13.
10. Camilleri A, Johnston MR, Brennan M, Davis S, Caldicott DGE. Chemical analysis of four capsules containing the controlled substance analogues 4-methylmethcathinone, 2-fluoromethamphetamine, α-phthalimidopropiophenone and *N*-ethylcathinone. Forensic Sci Int 2010; 197(1-3):59-66.
11. Westphal F, Junge T, Rosner P, Sonnichsen F, Schuster F. Mass and NMR spectroscopic characterization of 3,4-methylenedioxypyrovalerone: a designer drug with α-pyrrolidinophenone structure. Forensic Sci Int 2009;190(1-3):1-8.