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ISOLATION OF THE COMPOUND MDMA FOR APPLICATION AS A REFERENCE MATERIAL

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Abstract: In toxicological analyses, there is a significant need to utilize reference materials for the proper identification and quantification of suspicious samples, as well as for the identification of users of illicit drugs. In this regard, this study aimed to develop a methodology to isolate and purify the compound MDMA from seized "ecstasy" tablets by CP-ES (Civil Police of Espírito Santo) and subsequently characterize it using classical techniques such as high-resolution mass spectrometry by direct infusion, nuclear magnetic resonance, and finally, for purity evaluation, liquid chromatography technique. Based on the obtained results, a good yield in the isolation process, exceeding 90%, was achieved, with a calculated purity above 80%, affirming the proposed methodology as an attractive and accessible alternative for the isolation of the MDMA compound and its subsequent application in forensic analysis as a reference material.

Keywords: MDMA, isolation, chromatography, forensic sciences.

1 INTRODUCTION

3,4-Methylenedioxymethamphetamine, commonly referred to as MDMA, is a synthetic amphetamine stimulant that initially emerged as a prominent constituent of "ecstasy," a widely consumed recreational drug (BERNSCHNEIDER-REIF, ÖXLER and FREUDENMANN, 2006).

Chemically, MDMA belongs to the class of hallucinogenic amphetamines or phenethylamines, and its structure resembles that of methamphetamine, a compound with stimulant properties, differing only by the presence of a methylenedioxy (-O-CH_2-O-) group attached to the aromatic ring. Due to the presence of a chiral carbon, this molecule displays optical isomerism, presenting the S(+)-MDMA and R(-)-MDMA forms. Moreover, despite being produced as a racemic mixture, studies indicate that both forms are pharmacologically active and

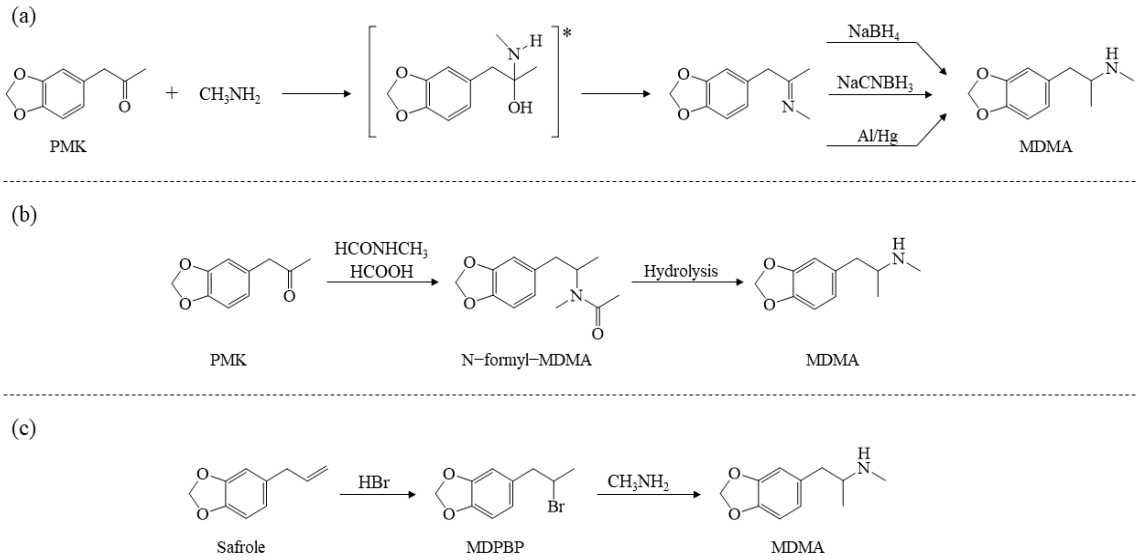
elicit distinct effects. The R-form (levorotatory) exhibits hallucinogenic action similar to mescaline, while the S-form (dextrorotatory) produces stimulant effects analogous to amphetamine (SHULGIN, 1986).

MDMA exists in two primary forms: as a free base and as salts, ie hydrochloride (MDMA.HCl) and phosphate (MDMA.H_3PO_4), and can be found in the form of powder, crystals, liquid, or tablet. When marketed in the form of tablets, exhibiting diverse shapes, colors, figures, and logos, adulterants such as paracetamol, ketamine, caffeine, and phenacetin may be included, alongside other constituents like carbohydrates in the form of glucose, starch, and lactose (COLE and SUMNALL, 2003).

The synthesis of MDMA in clandestine laboratories involves the reductive amination of PMK (piperonyl methyl ketone), which is commercially accessible. This method is widely employed due to the availability of various reducing agents. Sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaCNBH_3$), and aluminum amalgam (Al/Hg) are among the most utilized agents in this process. The Leuckart method can also be used in the synthesis of MDMA, which results in an amide intermediate product instead of an imine, as observed in reductive amination (ŚWIST, WILAMOWSKI and PARCZEWSKI, 2005).

Several precursors for MDMA are subject to controlled commercialization, such as safrole, isosafrole, 3,4-methylenedioxyphenyl-2-propanone (MDP2P), and piperonal. However, certain alternative precursors like catechol, vanillin, piperine, and eugenol are freely traded, thereby facilitating clandestine production. Among them, safrole is commonly cited in the literature as a precursor for MDMA due to its phenylmethylene-dioxy group, employing the safrole bromination method. This precursor undergoes an initial bromination, resulting in the formation of the intermediate 3,4-methylenedioxyphenyl-2-bromopropane (MDPBP), which subsequently undergoes a nucleophilic substitution reaction with methylamine. **Figure 1** illustrates the synthetic pathways of MDMA (GIMENO, 2005; ŚWIST, WILAMOWSKI and PARCZEWSKI, 2005).

Figure 1: Scheme of MDMA syntheses (a) reductive amination method, (b) Leuckart method, and (c) bromination method.



Due to its effects on mood control, appetite, sleep, thermoregulation, and the autonomic nervous system, MDMA can cause various bodily changes in users. The main physical changes include euphoria, sensory changes, increased sensitivity, increased communicative skills, and loss of time perception. Although it temporarily induces a sense of well-being, MDMA use can lead to symptoms of intoxication such as tachycardia, hypertension, hepatotoxicity, hyperthermia, and, in extreme cases, death (WOLFF, 1995; STOJANOVSKA et al., 2013).

In suspected MDMA samples, to achieve their proper identification, colorimetric tests can be conducted for amphetamines, methamphetamines, and their derivatives, such as the Marquis Test (CUMBA et al., 2016), the Simon Test (KHAJEAMIRI, 2016), and the Gallic Acid Test (UNDCP, 1994).

In addition to traditional colorimetric techniques, there are other classical techniques employed for the determination of MDMA in suspected samples, such as thin-layer chromatography (TLC), gas chromatography (GC), and liquid chromatography (LC). These techniques are extensively utilized as toxicological screening methods (MAURER et al., 2000; POPE, 2021).

Especially in quantitative analyses, the MDMA standard is utilized for constructing analytical calibration curves (KAHL et al., 2021; FARO et al., 2022; MADIA et al., 2023), however, it possesses a high commercial value. In this regard, taking into consideration the substantial quantity of samples confiscated yearly by law enforcement agencies and subsequently incinerated, a proposition to isolate the MDMA compound for subsequent application as a reference material emerges as an appealing and promising alternative for the forensic field.

2 THEORETICAL REFERENCE

Among the analytical techniques employed for the identification and quantification of MDMA in suspicious materials and biological samples, LC coupled with mass spectrometry (MS) is noteworthy. This technique is widely utilized in forensic studies (FIORENTIN et al., 2019; ABD-ELSALAM et al., 2019; NG et al., 2019; MACHADO et al., 2020; POYATOS et al., 2019). As seen in the study by Concheiro et al. (2006), a method for the determination of MDMA and other associated compounds in suspect samples was developed. The proposed method had a total execution time of 8 minutes and demonstrated a limit of detection (LOD) of 0.2 ng/mL and a limit of quantification (LOQ) of 1 ng/mL for MDMA.

Cheze et al. (2007) proposed a rapid and sensitive method for the determination of MDMA and other associated compounds in hair, blood, and urine samples. The developed method exhibited a LOQ of 0.1 ng/mL for all analytes in blood and urine, whereas, for hair, the LOQ was lower than 5 pg/mg specifically for MDMA. Additionally, the detection of the MDMA compound in urine was assessed for approximately eight days.

Nakanishi et al. (2012) developed a method using LC-MS for the simultaneous determination of enantiomers of MDMA and its metabolites in urine, employing chiral derivatization. The analytes in urine were directly derivatized with Marfey's reagent, N α- (5-fluoro-2,4-dinitrophenyl)-D-leucinamide, without the requirement of extraction. The diastereomers generated were determined by LC-MS/MS, which achieved satisfactory chromatographic separation for the enantiomers of MDMA and its metabolites. By employing multiple reaction monitoring mode, the LOD for these analytes ranged from 0.01 to 0.03 μg/mL. It is worth highlighting that, as stated by the authors, this study represents the first report of a straightforward

analytical procedure based on LC-MS/MS with direct chiral derivatization in an aqueous medium. This innovative approach enables the simultaneous determination of the drug and its metabolites' enantiomers.

Spectroscopic techniques have also been investigated and utilized for the determination and quantification of MDMA, as evidenced by the study conducted by Deconinck et al. (2018). This research reported the application of infrared spectroscopy for this specific purpose. The authors compared spectra in the near and mid-infrared regions, employing chemometric methods such as Partial Least Squares Discriminant Analysis (PLS-DA) and PLS. They demonstrated promising results in situ analyses.

Hussain et al. (2020) reported the utilization of the nuclear magnetic resonance (NMR) technique for the quantification of MDMA in tablets. The signals from aromatic hydrogen atoms and hydrogen atoms present in the methoxy carbon were employed as references for quantification. The results were compared to those obtained by GC-MS, demonstrating their equivalence. The use of NMR proved to be alternative and advantageous due to its ability to not require pre-treatment of the analysis and its capability to recover the analytes from the sample.

In this sense, the use of MDMA as a reference material becomes essential in the context of forensic analysis, both for the unequivocal confirmation of the MDMA molecule and for its quantification in biological materials. Therefore, the present work aimed to develop a methodology to isolate and purify the MDMA compound from “ecstasy” pills seized by the CP-ES.

3 MATERIALS AND METHODS

3.1 Samples and reagents

A mixture was prepared using different seizures of "ecstasy" tablets provided by CP-ES, under a technical cooperation agreement with the Civil Police of Espírito Santo, process nº. 23068.022157/2020-69, originating from the four macroregions into which the state of Espírito Santo is divided (Central, Metropolitan, North, and South). The tablets were previously characterized by the present research group (DOS SANTOS et al., 2020), by the Fourier transform ion cyclotron resonance mass spectrometry technique (FT-ICR MS) and electrospray ionization source (ESI) in positive mode, and by gas chromatography.

For the present study, the samples were solubilized at a concentration of 1 mg/mL in HPLC-grade methanol from NEON (Suzano, São Paulo, BR). Then, 10 µL of this solution was used in 1 mL of methanol for subsequent analysis by direct infusion into the mass spectrometer (section 3.3).

3.1.1 Isolation of MDMA

0.5060 g of "ecstasy" tablets were weighed and crushed. 2 mL of dichloromethane, acquired from Sigma-Aldrich (San Luis, Missouri, USA), were added, and the system was agitated for 30 minutes. Then, it was filtered. The filtrate was left at room temperature to evaporate, resulting in 0.09 g of extract. The extract was dissolved in 3 mL of HPLC-grade methanol from NEON (Suzano, São Paulo, BR).

3.2 HPLC-DAD

To optimize the separation parameters using High-Performance Liquid Chromatography (HPLC), an Agilent Technologies instrument (Santa Clara, California, USA), model 1260 with a DAD detector, was utilized. The analytical column employed was a Waters SunFire C18 (Milford, Massachusetts, USA) with a particle size of 3.8 µm, an internal diameter of 4.6 mm, and a length of 150 mm. The mobile phases consisted of solvent A, which was composed of water with 0.1% formic acid, and solvent B, which was acetonitrile. An isocratic elution mode was employed, with a ratio of 20:80

for solvent A and solvent B, respectively. The flow rate was maintained at 1.0 mL/min, and the total run time was set to 6 minutes. The detection wavelength was set at 234 nm, and the injection volume was 5 µL.

For the effective separation of MDMA, a Preparative Agilent Technologies equipment (Santa Clara, California, USA) model 1260 Infinity with DAD detector was used, along with a preparative ZORBAX SB-C18 Prep HT Technologies (Santa Clara, California, USA) column. The particle size of the column was 7 µm, with an inner diameter of 21.2 mm and a length of 250 mm; solvent A - water (0.1% formic acid) and solvent B - acetonitrile were used for elution in an isocratic mode (Solvent A: 20%, Solvent B: 80%). The flow rate was set at 4.0 mL/min, and the total run time was 6 minutes. The detection wavelength was set at 234 nm, and each injection had a volume of 100 µL. In total, 10 injections were performed. After the sample injection in the preparative equipment, an approximate yield of 26 mg of material was obtained.

The purity of the compound was calculated by **equation (1-4)** proposed by Yang et al. (2017).

$$P\% = (1-x_i).(1-x_{vi}-x_{sa}).100\% \quad \textbf{(equation 1)}$$

$$Xi = \frac{Axi}{A\,tot} \,.100\% \quad \textbf{(equation 2)}$$

Where x_i represents the amount of organic impurities; A_{xi} represents the peak area of the chromatogram of organic impurities, and A_{tot} represents the sum of the areas of all compounds.

$$Xvi = \frac{m_0 - m_1}{m_0} \,.100\% \quad \textbf{(equation 3)}$$

X_{vi} represents the quantity of volatile compounds, m_0 represents the initial mass of the sample, and m_1 is the mass of the sample in constant weight after drying.

$$Xsa = \frac{m_3}{m_2} \,.100\% \quad \textbf{(equation 4)}$$

X_{sa} is the quantity of ashes, m_2 initial mass, and m_3 is the ashes mass.

3.3 ESI-FT-ICR MS

The initial analysis of the starting substance was performed using the ESI-FT-ICR MS technique at a magnetic field strength of 9.4 T. The analysis was conducted using a Bruker Daltonics instrument located in Bremen, Germany. All mass spectra were externally calibrated previously by using an arginine solution, VETEC (Duque de Caxias, Rio de Janeiro, BR), 0.05 mg/ml.

Furthermore, parameters were optimized to obtain improved results with lower errors (ppm) and improved signal-to-noise ratios. The ESI(+) MS analyses were conducted using a mass range of 150-1500 Da, an accumulation of 16 scans, and an acquisition domain of 4 M.

Fragmentation experiments, using ESI(+) MS/MS, were also performed on the prominent signals obtained in the ESI(+) MS spectra. These experiments involved an accumulation of 16 scans and an acquisition domain of 512 k.

3.4 NMR

In the NMR analyses, a Varian 400 MHz spectrometer (model VNMRS 400) was employed, operating at a magnetic field strength of 9.4 Tesla. The detection probe utilized was a 5 mm BroadBand 1H/19F/X direct detection probe. All spectra were processed using the MestReNova® software and calibrated using the signal at 4.87 ppm (methanol-d4) for MDMA.

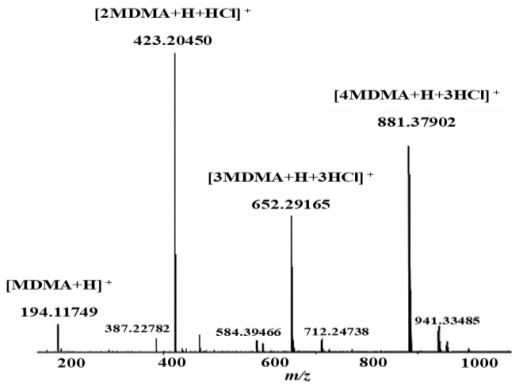
4 RESULTS AND DISCUSSION

In the process of isolating the MDMA compound present in ecstasy tablets, a yield of 17% (w/w) of crude extract was obtained from the measured mass of tablets. Using this extract, a mass of 26 mg was obtained through high-performance

liquid chromatography (HPLC) isolation, corresponding to 91% (w/w) of the mass present in the injected volume. The spectral profile (**Figure 2**) obtained from the ESI(+)FT-ICR MS analysis displays the primary observed signals that signify the existence of the MDMA molecule, M = $C_{11}H_{15}NO_2$ (M_w = 193 Da), which are additionally documented in **Table 1**.

The detection of the MDMA molecule in the protonated form, $[MDMA+H]^+$, with *m/z* 194.11749; $[C_{11}H_{16}NO_2+H]^+$, mass error of 0.34 ppm, and, together with this signal, the presence of *m/z* 423.20450 was verified; $[C_{22}H_{30}N_2O_4+H+HCl]^+$, which corresponds to a protonated MDMA dimer next to a hydrochloric acid molecule, $[2MDMA+H+HCl]^+$, with mass error on the ppm scale, as well as *m/z* 652.29168. The detection of *m/z* 881.37902 was observed, corresponding to $[C_{33}H_{48}N_3O_6+H+2HCl]^+$, which represents a trimer of protonated MDMA combined with two molecules of hydrochloric acid, $[3MDMA+H+2HCl]^+$. The mass error for this compound is -0.32 ppm; $[C_{44}H_{60}N_4O_6+H+3HCl]^+$, corresponding to a tetramer of protonated MDMA combined with three hydrochloric acid molecules, $[4MDMA+H+3HCl]^+$, was detected with a mass error of -0.68 ppm. These signals were also observed for MDMA in the study conducted by Romão et al. (2011) on samples of "ecstasy" tablets, which were analyzed using the easy ambient sonic-spray ionization mass spectrometry (EASI-MS) technique.

Figure 2: (a) ESI(+) MS spectrum of MDMA.

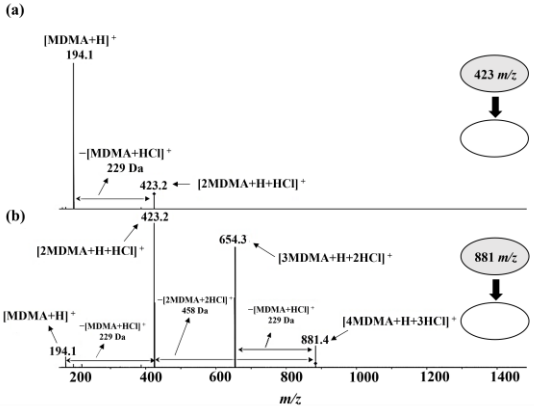


Based on the primary signals observed in ESI(+) MS, as listed in **Table 1**, experiments of ESI(+) MS/MS were conducted (**Figure 3a-b**).

In **Figure 3a**, the fragmentation of the *m/z* 423.2 signal, $[2MDMA+H+HCl]^+$, was observed at a collision energy of -6.5 V. Its primary transition revealed the detection of *m/z* 194.1, corresponding to the $[MDMA+H]^+$ ion. This ion is generated through a mass loss of 229 Da, which signifies the dissociation of one MDMA molecule and one molecule of hydrochloric acid.

In **Figure 3b**, the fragmentation of the *m/z* 881.4 signal, $[4MDMA+H+3HCl]^+$, was observed with a collision energy of -6.0 V, resulting in the formation of the ion $[3MDMA+H+2HCl]^+$ with *m/z* 654.3. This ion is generated through the loss of a mass of 229 Da, which corresponds to the dissociation of one molecule of MDMA and one molecule of hydrochloric acid, [MDMA+HCl]. Furthermore, another transition from *m/z* 881.4 to *m/z* 423.2 is observed, corresponding to the formation of the ion $[2MDMA+H+HCl]^+$. This ion is generated through the loss of a mass of 458 Da, representing the dissociation of two molecules of MDMA and two molecules of hydrochloric acid, [2MDMA+2HCl].

Figure 3: ESI(+) MS/MS spectrum (collision energy) (a) *m/z* 423.2 (-6.5 V) and (b) *m/z* 881.4 (-6.0 V).



Sequentially, the structure of MDMA was elucidated based on the ^{1}H NMR spectra, depicted in **Figure 4**, the ^{13}C NMR spectra, depicted in **Figure 5**, and the DEPT spectra, depicted in **Figure 6**. The respective values were listed in **Table 2**, where characteristic chemical shifts of the molecule could be observed. To identify the hydrogens of the MDMA molecule in the ^{1}H NMR spectrum, each signal's chemical shift, multiplicity, integral value, and coupling constants were evaluated (ALMEIDA et al. 2018).

Figure 4. ^{1}H NMR spectrum of MDMA.

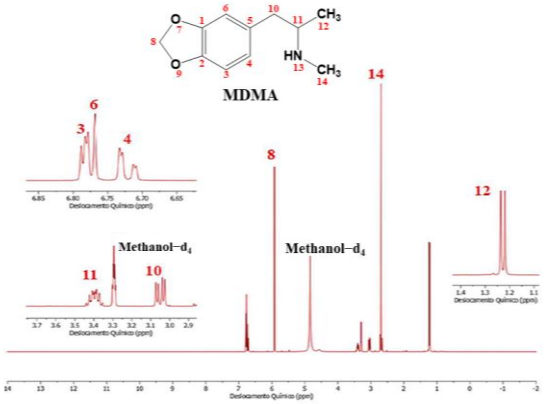


Figure 5. ^{13}C NMR spectrum of MDMA.

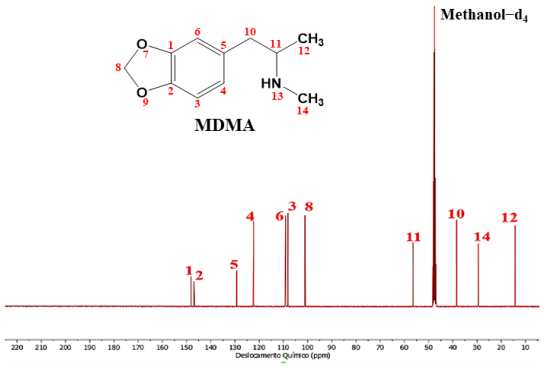
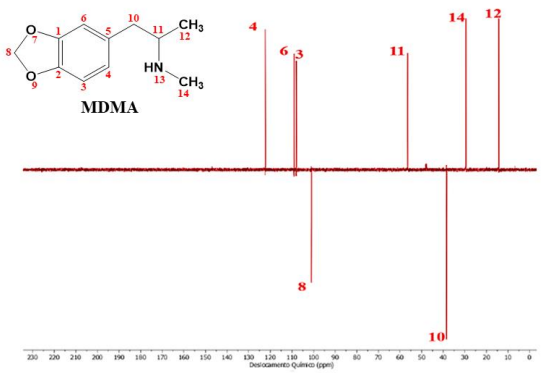
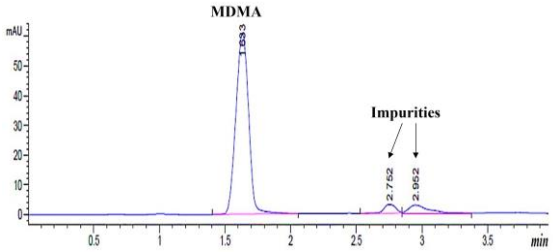


Figure 6. DEPT spectrum of ^{13}C NMR of MDMA.



Finally, the purity of MDMA was determined by HPLC-DAD, using the calculation (**equation 1-4**) proposed by Yang et al. (2017). From the obtained chromatogram, depicted in **Figure 7**, it was determined that the purity was 89.49%.

Figure 7: Chromatogram obtained from MDMA for the calculation of relative purity through HPLC.



In this study, based on the purity obtained for MDMA, its application in qualitative analysis is suggested, in which the objective is the correct identification of the compound, as in routine forensic analyses.

5 CONCLUSIONS

In this study, the compound MDMA was isolated, obtained, and characterized from seized "ecstasy" tablets, with an isolation yield of 91% (w/w) and a purity of 89.49%. The methodology employed for the purification and isolation of the molecule proved to be promising in obtaining psychoactive substances present in illegally marketed tablets for recreational purposes. These molecules become potential reference materials for forensic purposes.

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Table 1. Chemical profile of the ESI (+) MS spectrum obtained for MDMA.

Compound	Molecular Formula	Measured *m/z*	Theorical *m/z*	Error (ppm)	Resolution
$[MDMA+H]^+$	$[C_{11}H_{16}NO_2+H]^+$	194.11749	194.11756	0.34	709.326
$[2MDMA+H+HCl]^+$	$[C_{22}H_{30}N_2O_4+H+HCl]^+$	423.20450	423.20451	0.00	376.855
$[3MDMA+H+2HCl]^+$	$[C_{33}H_{48}N_3O_6+H+2HCl]^+$	652.29165	652.29147	-0.32	239.248
$[4MDMA+H+3HCl]^+$	$[C_{44}H_{60}N_4O_6+H+3HCl]^+$	881.37902	881.37842	-0.68	180.816

Table 2. NMR data found for MDMA in methanol-d_4.

Position	δ_H (ppm) Mult. J (Hz)	δ_C (ppm)	DEPT
1	-	147.93	C
2	-	146.11	C
3	6.79 m	108.33	CH
4	6.72 dd (7.9; 1.7)	122.92	CH
5	-	129.32	C
6	6.77 s	109.00	CH
8	5.92 s (1.1)	100.11	CH_2
10	3.05 dd (13.6; 5.3)	38.57	CH_2
11	3.40 dtt (11.8; 9.6; 6.0)	56.74	CH
12	1.23 d (6.6)	14.38	CH_3
14	2.70 s	29.79	CH_3

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