Analytical Methods

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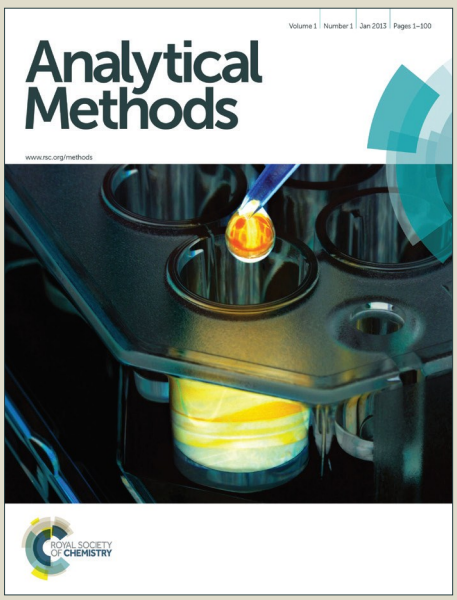

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ARTICLE

Qualitative Analysis of Designer Drugs by Paper Spray Ionisation Mass Spectrometry (PSI-MS)

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The application of the ambient ionization mass spectrometry such as the paper spray ionisation (PSI) is a fast, powerful, and simple method to analyze designer drugs directly on the surface of blotters. PS-MS does not require nebulizing gas and heating temperature and as well as not complex protocols for sample preparation. Herein, it was possible to identify and elucidate the chemical structure of designer drugs using tandem mass spectrometry experiments from triangular blotter. Substances such as lysergic acid diethylamide (LSD), and five new designer drugs (2,5-Dimethoxy-4-chloroamphetamine (DOC), 2,5-Dimethoxy-4-bromoamphetamine (DOB), 25C-NBOMe, 25B-NBOMe, and 25I-NBOMe) were characterized by PS-MS. The PSI(+)-MS and PSI(+)-MS/MS data confirmed the assignments of the designer drugs and fragmentation mechanisms have been proposed. From losses of 17 Da (NH_3), which is typical of primary amines, the CID results suggest the presence of isomers in the chemical composition of the NBOMe class. Additionally, the data were compared to ultra-high-resolution mass spectra (positive-ion electrospray ionization coupled with Fourier transform ion cyclotron mass spectrometry, ESI(+)FT-ICR MS).

Introduction

Recently, a series of new compounds known as designer drugs, such as ecstasy derivatives, methamphetamine, and cannabinoids, are being synthesized and sold as psychoactive substances.[1] Designer drugs are synthesized and designed in a way similar to psychoactive substances proscribed and criminalized by legislation. Small changes in the chemical structure of the substance have the advantage of taking the substance out of the category of a controlled substance, thus, enabling it to be marketed legally instead of being banned. It is estimated that more than 100 new psychoactive substances or designer drugs have been introduced.[2] These new substances are now being widely sold over the Internet, in varying degrees of purity and concentration. The continuous introduction of new varieties is a significant problem faced by police around the world.[3] Although legislation has been continuously updated on several occasions due to the constant input of new variants of proscribed substances, the control of access to these new drugs is still a great challenge.[4,5]

Among the largest and most important classes of designer drugs are phenethylamine derivatives.[6] Several of these derivatives, such as 2,5-Dimethoxy-4-cloroamphetamine (DOC), and 2,5-Diemethoxy-4-bromoamphetamine (DOB), have become popular with young users and are of growing concern from a public safety perspective.[7] However, recently, many highly potent hallucinogenic phenethylamine derivatives have been synthesized and introduced on the market. These derivatives are commonly referred to as "NBOMe"; they are (2-methoxy) benzyl derivatives of the 2,5-dimethoxyphenethylamines with various substituents at C-4, e.g., 25C-NBOMe, 25B-NBOMe, and 25I-NBOMe.[6]

Many variants of designer drugs constitute a major challenge for analytical identification.[7] Few methods have been developed to detect these new psychoactive substances. In general, methods based on gas chromatography–mass spectrometry (both EI and CI conditions), [8] as well as liquid chromatography–mass spectrometry,[9] are used most. However, these methods require chromatographic separation and a laborious process of sample preparation, making it difficult to rapidly identify designer drugs. The development of new, cheap, and reliable methods to identify these new classes of drugs is necessary.

Paper spray ionization (PSI), introduced in 2010 by Wang et al.,[10] is a new ambient mass spectrometry technique for qualitative and quantitative analysis of complex mixtures. PSI-MS involves directly loading the sample onto a triangular paper, which is moistened with a solvent and placed in front of a mass spectrometer inlet. The spray of the charged microdroplets is formed by the application of usually 3-5 kV on the opposite side of the paper tip, and desolvation occurs without any sheath gas. [11] The PSI-MS mechanism of ion formation in the gaseous phase is similar to ESI process.

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PSI-MS has been explored in various applications, mainly to analyze directly samples, such as illicit substances in raw urine,[11] pharmaceuticals in whole blood,[12] biological tissue,[13] contaminants in foodstuffs,[14] Sudan dyes in chili pepper[15], and chemical fingerprint analysis for quality assessment.[16] Furthermore, other elements, such as wick microporous polymers,[17] wooden toothpicks,[18] plant leaves (leaf spray), or other vegetable materials were also employed as both sample and substrate.[19]

Cooks et al. [20] had demonstrated the quantification of other designer drugs, such as synthetic cannabinoids (JWH-018, JWH-081, AM-2201, RCS-4, and XLR-11), using a miniature mass spectrometer and ambient ionization methods (PSI and extraction spray ionization). In general, a limit of detecting 2 ng was estimated for the detection of trace powders on a bench surface, and limits of quantitation of 10 ng mL^{-1} were obtained for the analysis of blood and urine samples. Also, 14 commonly abused drugs were identified in spiked oral fluid (ng mL^{-1} levels) analyzed directly from medical swabs using touch spray mass spectrometry (TS-MS), exemplifying a rapid test for drug detection.[21]

As new designer drugs are sold in the form of blotter, in this manuscript we report the application of PSI-MS for the direct blotter analysis. Blotter is used as both the sample and ionization source to analyze qualitatively the following substances: LSD, DOC, DOB, 25C-NBOMe, 25B-NBOMe, and 25I-NBOMe. **Figure 1** shows the chemical structures and formulas for six designer drugs investigated by PSI-MS and ESI(+)-FT-ICR MS.

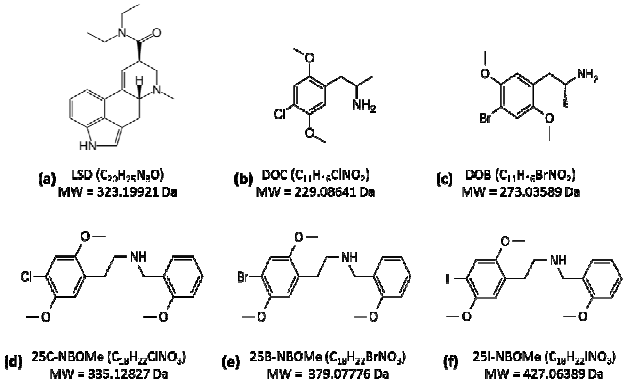

Figure 1. Designer drugs analyzed by PSI-MS: **(a)** LSD, **(b)** DOC, **(c)** DOB, **(d)** 25C-NBOMe, **(e)** 25B-NBOMe, and **(f)** 25I-NBOMe.

Experimental

Materials

Six blotter samples containing different designer drugs were supplied by the Brazilian Federal Police (LSD, DOC, 25C-NBOMe, 25B-NBOMe, and 25I-NBOMe). Methanol (HPLC grade, Vetec Fine Chemicals LTDA, Duque de Caxias, RJ, Brazil) was used to moisten the blotter for the ionization process. Formic acid (Sigma–Aldrich Chemicals, St. Louis, MO, US) was used for the ESI(+)-FT-ICR MS measurements. All reagents were used as received.

Blotter paper spray ionization

For the PSI methodology using blotter as substrate, each one of the blotters was cut into a triangle (12 mm height and 7 mm of base) and held by a metal alligator clip at a distance of 5-7 mm from the mass spectrometry inlet. Five microliters of methanol were spotted onto the blotter without further treatment, and a high voltage (3 kV) supplied by the mass spectrometer was applied to the paper to generate the PSI(+) mass spectra.

PSI-MS experiments were performed using a Thermo LTQ mass spectrometer (Thermo Fisher Scientific, United States). The following settings were used: spray voltage = 3 kV, capillary temperature = 275 °C, tube lens voltage = 100 V, and capillary voltage = 50 V. The full scan mass spectra were acquired in the positive ion mode over the range of *m/z* 100–1,000. Tandem mass spectrometry (PSI(+)-MS/MS) was performed using collision-induced dissociation with a collision energy of 15%–30% (manufacturer's unit).

ESI(+)-FT-ICR MS

For each blotter containing a designer drug (LSD, DOC, 25C-NBOMe; 25B-NBOMe; or 25I-NBOMe), 1 g of the paper was submitted to extraction with 1 mL of acetonitrile/water (1:1) during 5 min under shaking. Briefly, the samples were acidified with 0.1% m/v of HCOOH 95 %. The resulting solution was directly infused at a flow rate of 5 µl min^{-1} into the ESI source. The mass spectrometer (model 9.4 T Solarix, Bruker Daltonics, Bremen, Germany) [22] was set to operate over a mass range of *m/z* 200-1300. The ESI (+) source conditions were as follows: nebulizer gas pressure 3 bar, a capillary voltage 4.2 kV, and a transfer capillary temperature 250°C. The ion accumulation time in the hexapole was of 10^{-2} s, followed by transport to the analyzer cell (ICR) through the multipole ion guide system (another hexapole). Each spectrum was acquired by accumulating 64 scans of the time-domain transient signals in 4 mega-point, time-domain data sets. The front and back trapping voltages in the ICR cell were + 0.80 V and - 0.85 V, respectively. All mass spectra were externally calibrated using a NaTFA solution (*m/z* from 200-1200) after they were internally recalibrated using a set of the most abundant homologous, alkylated compounds for each sample. A resolving power, $m/\Delta m_{50\%} \cong$ 500 000 to 1 300 000, in which $\Delta m_{50\%}$ is the full peak width at half-maximum peak height, of *m/z* 400 and a mass accuracy of < 1 ppm provided the unambiguous molecular formula assignments for singly charged molecular ions. Mass accuracy is determined from mass error, defined as error = $((m/_{measured} - m/_{theoretical})/m/_{theoretical}) \times 10^6$ and the aromaticity level of each molecule is deduced directly from its DBE (double bond equivalent) value as follows:

$$DBE = c - h/2 + n/2 + 1 \quad \textbf{(Equation 1)},$$

where c, h, and n are the numbers of carbon, hydrogen, and nitrogen atoms, respectively, in the molecular formula. The mass spectra were acquired and processed using data analysis software.

ESI (+)-FT-ICR MS/MS

The tandem mass spectrometry (MS^2) experiments were performed on a quadrupole analyser coupled with the FT-ICR mass spectrometer, Q-FT-ICR MS. The ESI(-)-MS/MS spectra were acquired using the following: **i)** infusion flow rate of 5 µL min^{-1}; **ii)** capillary voltage of 3.0 kV; **iii)** nebulizing temperature of 250 °C; **iv)** argon as the collision gas; **v)** ion accumulation time of 1 s; **vi)** isolation window of 1.0 (*m/z* units); **vii)** and 25%–45% of the collision energy. The spectra were acquired by accumulating 32 time-domain transient scans and processed using data analysis software. [23]

Results and discussion

PSI (+)-MS

A blotter triangle of the designer drugs moistened with methanol produces spray droplets when a voltage (3 kV) is applied (**Figure 2**). The spray forms at the tip of the paper and is, presumably, due to field-assisted evaporation, while the transport of the solvent is the result of capillary action through the micro-channels in the blotter paper substrate. This gentle new method of ionization can be applied to a wide range of designer drugs and can be easily used as a method of choice to identify these types of drugs in forensic laboratories around the world, without the need of sample preparation. With the development of portable mass spectrometers, this method promises to be used in the field during police operations.

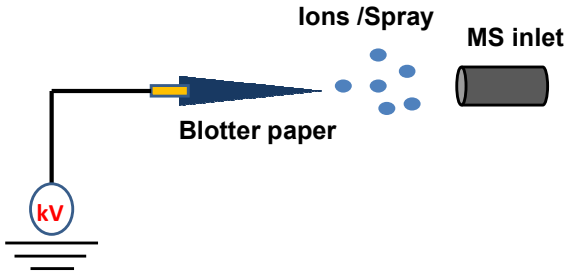

Figure 2. Picture of the experimental schematic of the blotter PS method developed.

The process of moistening the sample with a spray solvent was necessary due to the low water content of the blotter paper. A distance of 5mm between the blotter and the MS inlet was chosen because a shorter distance could lead to an electrical discharge while a longer one would result in a decrease in ion intensity. Positive ion mode, PSI(+), was successfully employed, and a stable spray with an average duration of 2 minutes was achieved. This time could also be increased by adding more solvent to the sample.

Figure 3 shows the PSI(+) mass spectra in which the active 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, DOB, DOC, and LSD ingredients are identified as protonated molecules, $[M+H]^+$, at *m/z* 380, 336, 428, 274, 230, and 324, respectively. Additionally, the experimental isotopologue patterns of all designer drugs, except LSD, are characteristic of the presence of chlorine and bromine atoms in their chemical structure.[24] For 25C-NBOMe and DOC drugs, the relative intensity of the ions at *m/z* 338 and 232 is one-third of that at *m/z* 336 and 230, respectively; whereas for the 25B-NBOMe and DOB drugs, the relative intensity of the ions at *m/z* 382 and 276 is one-to-one of that at *m/z* 380 and 274, respectively (see the insert in **Figure 3**). Dimers for active DOB and DOC ingredients are also identified as $[2M+H]^+$ ions at *m/z* 549 and 459, respectively. In general, PSI(+)-MS can access the chemical composition of synthetic drugs in a simple, gentle, robust, and rapid manner.

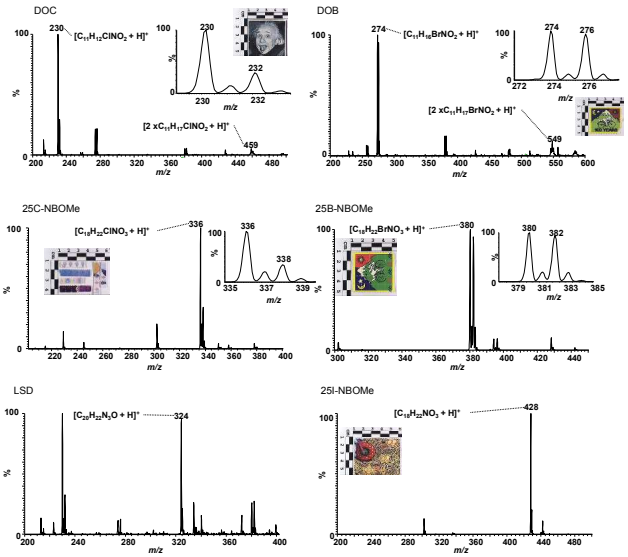

Figure 3. Positive ion blotter paper spray mass spectra of 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, DOB, DOC, and LSD.

Figure 4 shows the PSI(+)MS/MS of $[M + H]^+$ ions for DOC, DOB, 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, and LSD. The observed fragment ions are listed in **Table 1**. When $[M + H]^+$ ions of DOC and DOB collide, a unique product originating from the ammonia loss (17 Da) is observed. The loss of 17 Da(NH_3) is typical of primary amines. [25] This is better visualized from the fragmentation mechanism (mechanism I), proposed in **Figure 1S**. Similar to DOB and DOC, the fragmentation of the 25C, 25B, and 25I-NBOMe molecules also occurs predominantly on the nitrogen atom. The ions recorded at *m/z* 199, 243, and 291 for 25C, 25B, and 25I, respectively, were formed by the cleavage of the C-N bond as illustrated by mechanism II (**Figure 1S**). The cation, *m/z* 121, is also formed by the cleavage of the C-N bond (mechanism III – **Figure 1S**), and it corresponds to the most abundant ion in the CID spectrum of 25C and 25B-NBOMe, **Figure 4.** The ions detected at *m/z* 214, 258, and 308 for 25C, 25B, and 25I, respectively, are produced by a [1-3] H shift rearrangement, which is very common in the fragmentation of an even electron ions of amines (mechanism IV, **Figure 1S**).[26] For the 25C and 25B-NBOMe, further fragmentation can be follow by loss of HCl from *m/z* 214 and by the loss of a Br radical from *m/z* 258. Another fragmentation pathway is the loss of HX (X = Cl, Br) directly from the precursor ion of 25C and 25B, yielding the ion of *m/z* 300 that subsequently loses a methoxy radical, leading to the ion of the *m/z* 269. For the 25I-NBOMe, the loss of the $I^{\bullet}$ radical was observed, yielding the ion of *m/z* 301. As previously reported in the literature, [27,28],the fragmentation of LSD processes according to the even-electron rule $[M+H]^+$ mainly takes place through the neutral losses of diethylamine ($[MH-C_4H_{11}N]^+$) and dimethylformamide ($[MH-C_4H_{11}NCO]^+$) to yield species with *m/z* 251 and 223, respectively, **Figure 4** and **Table 1**. Abundant ions at *m/z* 281 are produced through the cleavage of two bonds in the pyrimidine ring, producing a radical loss of C_2H_5N. Also, less abundant ions are due to radical losses: $[MH-CH_3]^{+\cdot}$ and $[MH-NH_2CH_3]^{+\cdot}$ At *m/z* 309 and 293, respectively. The other less abundant ions are due to loss: $[MH-CH_3NCH_2 - C_4H_{11}N]^+$ at *m/z* 208, $[MH - C_4H_{11}NCOCH_2CH]^+$ at *m/z* 197 and $[MH-C_4H_{11}NCO - NH_2R]^+$.

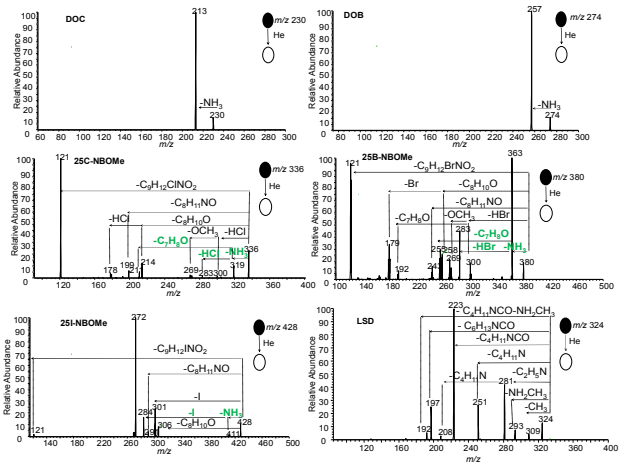

Figure 4. PS(+)-MS/MS of the $[M+H]^+$ ions for DOC, DOB, 25C-NBOMe, 25B-NBOME, and 25I-NBOMe molecules.

Table 1. Molecular formula, measured *m/z* values and fragment ions (MS^2) from PS(+) MS/MS mass spectra data for six designer drugs seized as blotter paper.

Sample	*Formula [M+H]⁺*	*m/z measured*	*Fragment ions - MS²*
DOC	$[C_{11}H_{16}ClNO_2 + H]^+$	230	213
DOB	$[C_{11}H_{16}BrNO_2 + H]^+$	274	257
25C-NBOMe	$[C_{18}H_{22}ClNO_3 + H]^+$	336	300, 269, 214, 199, 178, 121
	$[C_{18}H_{22}ClNO_3 + H]^+$	336 (isomer)	319, 283, 211
25B-NBOMe	$[C_{18}H_{22}BrNO_3 + H]^+$	380	300, 269, 258, 243, 192, 179, 121
	$[C_{18}H_{22}BrNO_3 + H]^+$	380 (isomer)	363, 283, 255
25I-NBOMe	$[C_{18}H_{22}INO_3 + H]^+$	428	306, 301, 291, 121
		428 (isomer)	411, 284, 272
LSD	$[C_{20}H_{24}IN_3O + H]^+$	324	309, 293, 281, 251, 223, 208, 197, 192

In the CID spectrum of 25C, 25B, and 25I-NBOMe, the loss of NH_3 (17 Da) is observed, being typically found only for primary amines. Thus, this suggests the presence of isomers for these three designer drugs, being their structures shown in mechanism V, **Figure 1S.** It can be observed that after the loss of ammonia and a loss of HX (X = Cl, Br), *m/z* 283 is yielded. The loss of C_7H_8O from *m/z* 319 and 363 leads to the formation of the ions at *m/z* 211 and 255 for 25C and 25B-NOMe, respectively. For 25I-NBOMe, after the loss of ammonia, there is a subsequent loss of iodine radical, leading to the ion at *m/z* 284, mechanism V, **Figure 1S**.

ESI(+)-FT-ICR MS

As the analysis of the blotter paper spray was performed on a low-resolution mass spectrometer, we performed the analysis of extracts from the blotters using an ultra-high resolution mass spectrometer.[23] **Figure 5** shows a typical ESI(+)-FT-ICR mass spectrum for the sample of LSD. The LSD sample was analyzed with ultra-high resolution of R ≈ 670,000 and 1,300,000 (**Figure 5a** and **5b**), being detected as $[M + H]^+$ ion of *m/z* 324.20719 where M = $C_{20}H_{25}N_3O$ and DBE (double bond equivalent) = 10. For an R ≈ 1,300,000, a better signal-to-noise is obtained, resulting in a mass accuracy even lower than 1 ppm throughout the mass spectrum (error = -0.44 ppm, **Figure 5b**).

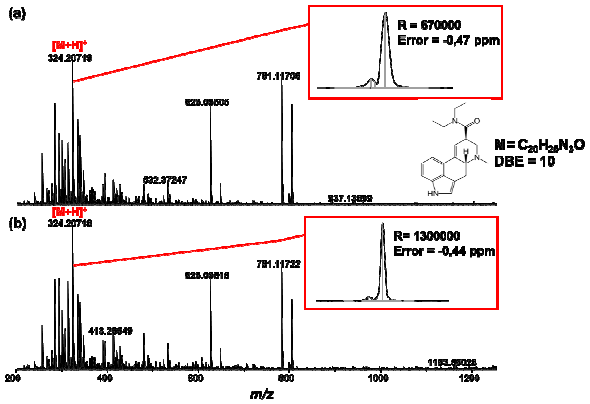

Figure 5. ESI(+)-FT-ICR mass spectrum of the LSD sample.

A more detailed structural elucidation of the LSD sample can be obtained from results of ESI(+)-MSMS, as shown in **Figure 2S** (see supplementary material), in which the ion fragmentation of *m/z* 324 is found to produce the fragments at *m/z* 309, 281, 251, 223, and 208. The formation of fragments *m/z* 309 and 281 indicates losses of the CH_3 and C_2H_5N groups, and the formation of the *m/z* 251 indicates the loss of the diethylamine molecule ($C_4H_{11}N$). The transitions of *m/z* 251 → 223 and *m/z* 223 → 208 reveal the loss of the CO and CH_3 groups, respectively. This fragmentation profile corroborates the PS-MS data, **Figure 4**, and the structure and connectivity of LSD molecule also reported in the literature.[27]

Figure 6 shows the ESI(+)-FT ICR mass spectra of five synthetic drugs using ultra-high mass resolution (on the order of until ≈ 2 millions), in which molecular formulas, measured and theoretical *m/z* values, mass errors, and DBEs are described in **Table 1S** (see supplementary material). Also observed was a good agreement of the chemical profile obtained from PS(+)-MS, **Figure 3**, and ESI(+)-FT-ICR MS data, **Figure 6**.

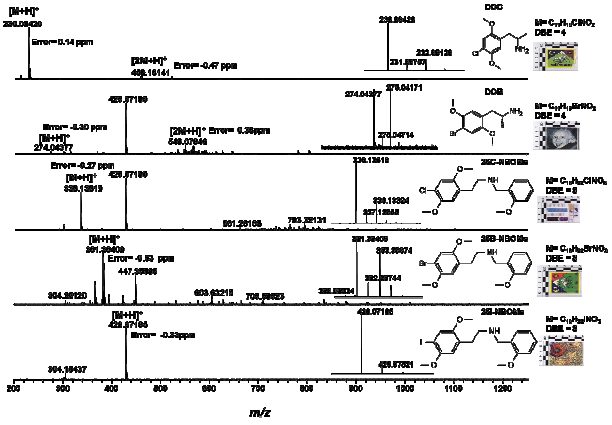

Figure 6. ESI(+)-FT-ICR mass spectra of DOC, DOB, 25C-NBOMe, 25B-NBOME and 25I-NBOMe. The insert show the isotopologue patterns of all designer drugs.

Figure 3S (see supplementary material) shows the ESI(+)MS/MS spectra obtained for five bottle paper samples analyzed. The structural chemical assignments are confirmed via the fragmentation of $[M+H]^+$ ions from typical losses of amine groups (17 Da, NH_3), hydrocarbons (15 Da and 29Da, CH_3 and CH_3CH_2-), and other specific groups of each molecule. The results are in good agreement with PS(+)-MS/MS spectra, **Figure 4**.

Conclusions

The ionization technique of paper spray mass spectrometry is a simple, easy-to-perform, fast, powerful, and open-air ionization technique that can be used for high throughput analysis. The technique does not require sheath gas, heating, or expensive materials for sample analysis and complex sample preparation. In addition, with the improvements of portable mass spectrometers, the proposed method has the potential to be used in forensic laboratories, allowing *in situ* analyses immediately after designer drugs are seized.

Acknowledgments

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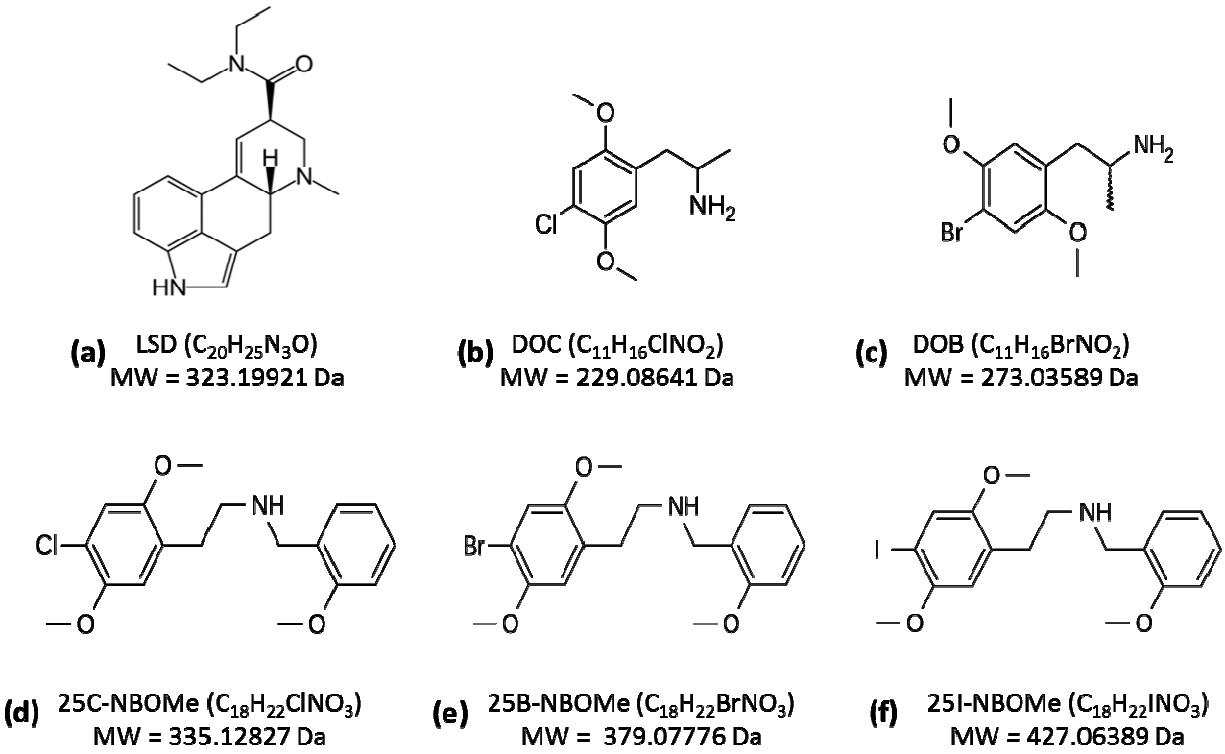


Figure 1.

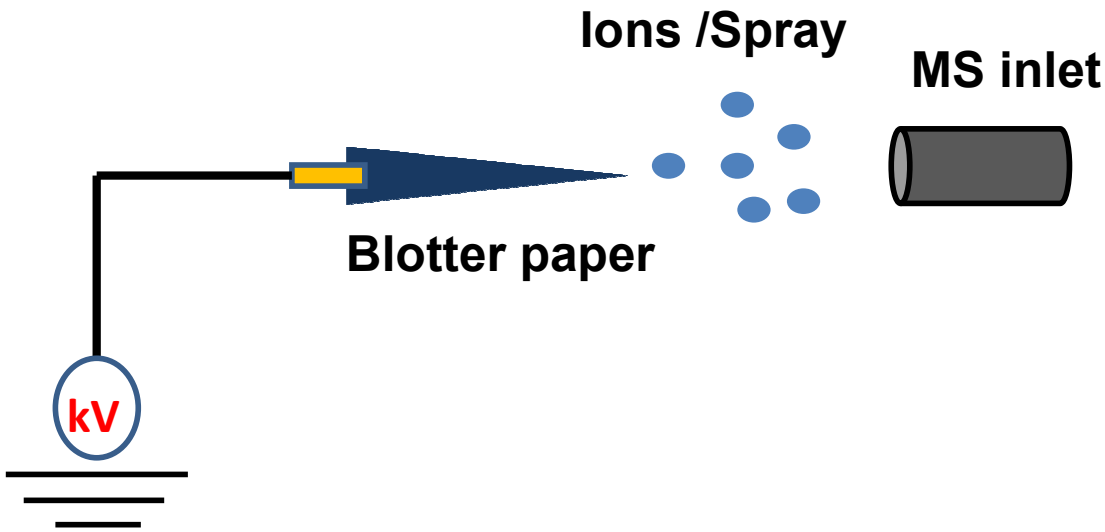


Figure 2.

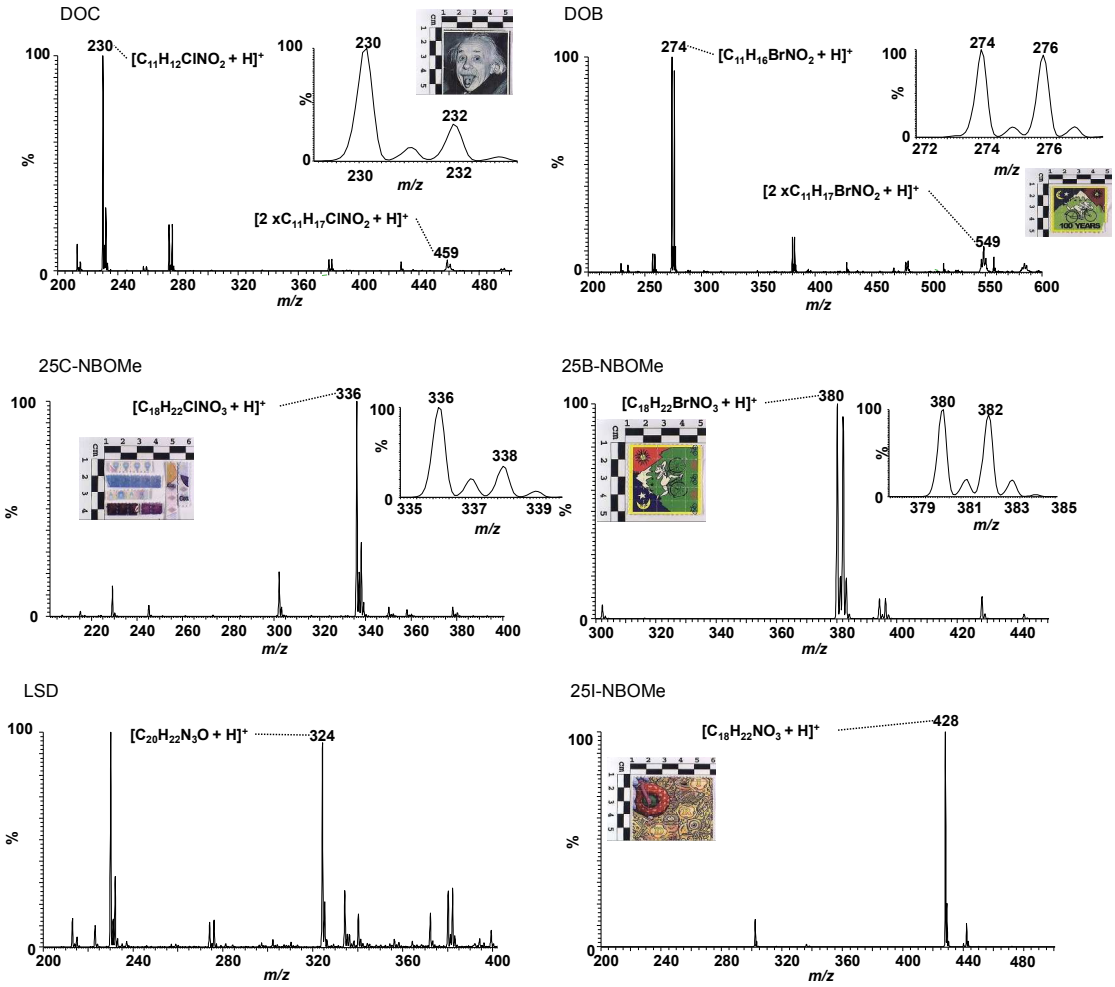


Figure 3

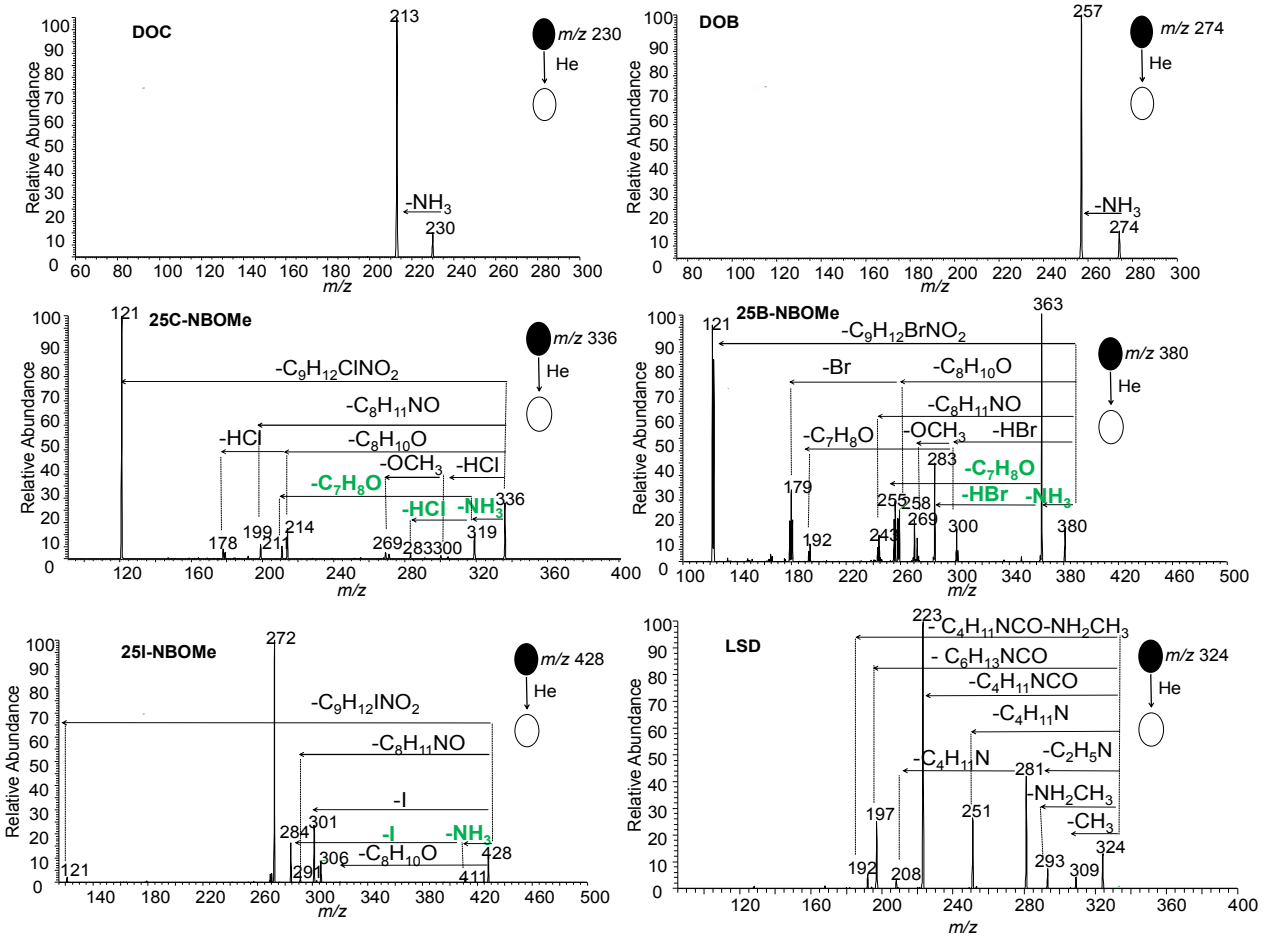


Figure 4

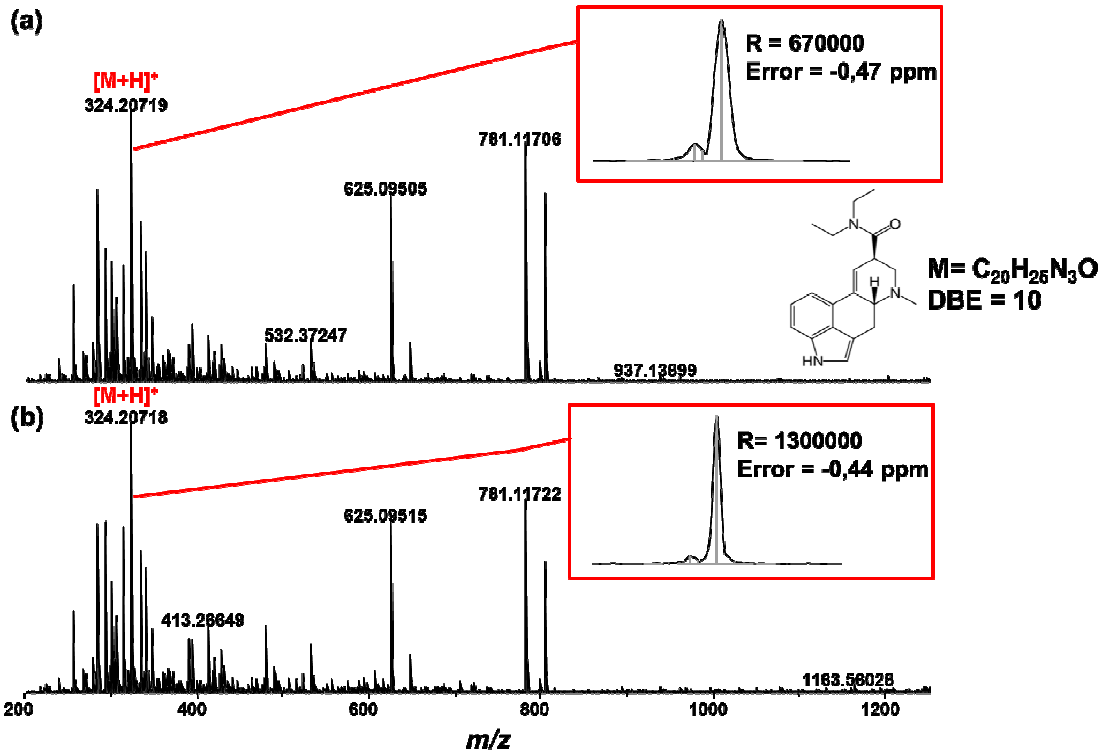


Figure 5

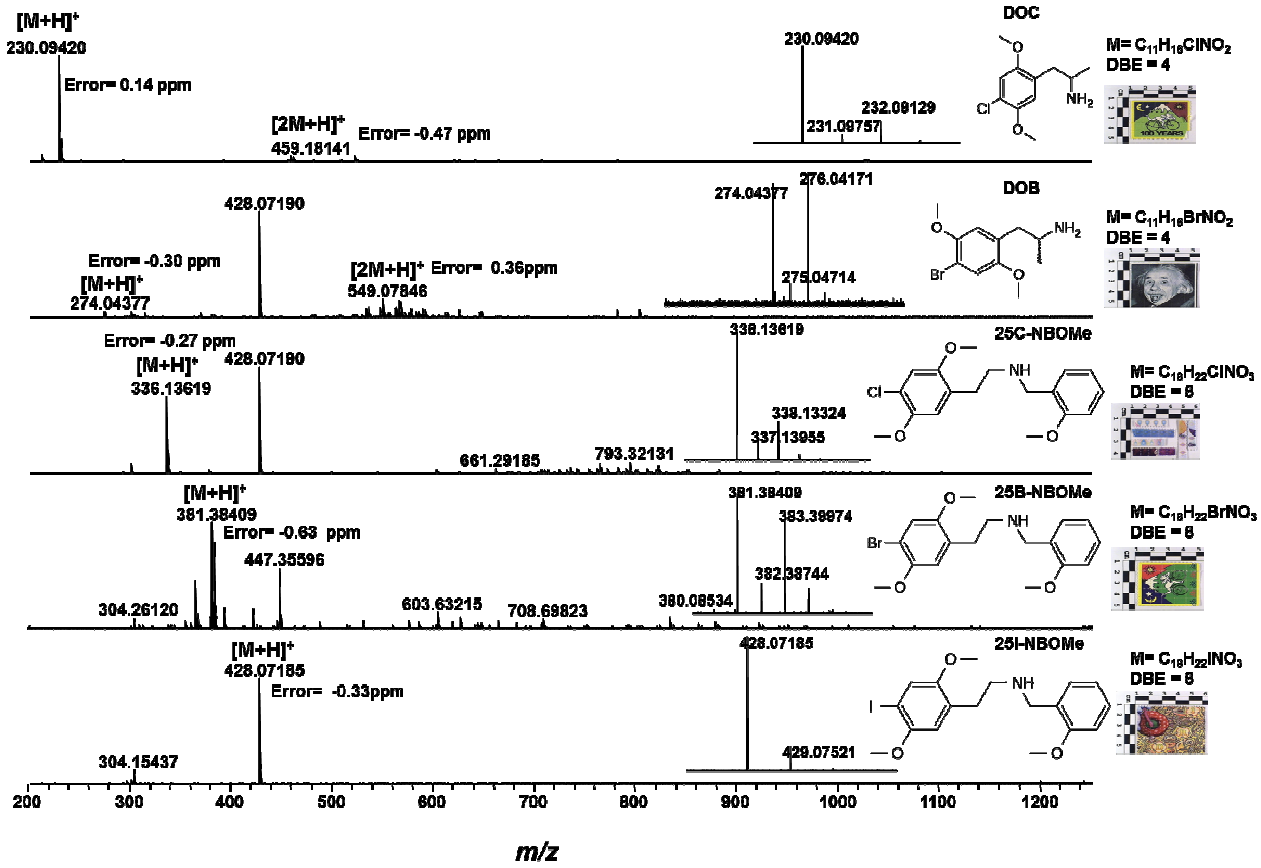
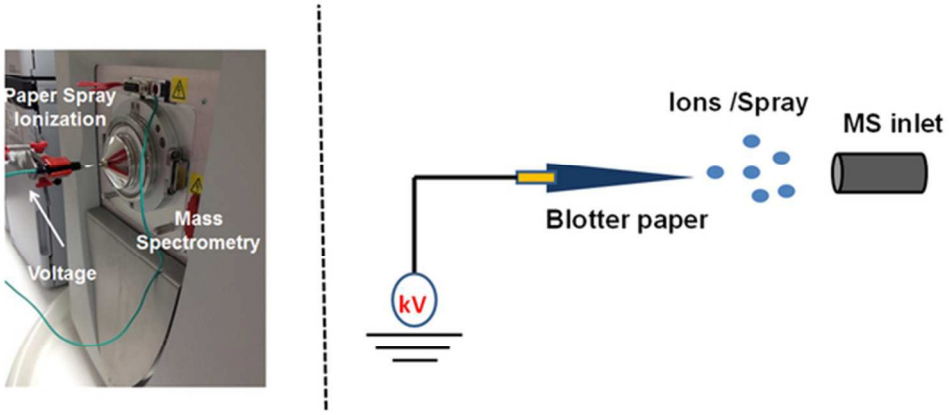


Figure 6



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