# The Identification of 3,4-MDMA from Its Mass Equivalent Isomers and Isobaric Substances Using Fast LC–ESI-MS–MS

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## Abstract

**3,4-Methylenedioxymethamphetamine (3,4-MDMA, "Ecstacy") and its 17 isomers and isobaric substances are studied using liquid chromatography (LC)–positive electrospray ionization-mass spectrometry (MS). 3,4-MDMA is a controlled substance, whereas in many countries the other studied isobaric compounds are not. A method for confirmation of the presence of 3,4-MDMA in drug seizures is developed and validated. Using single MS, the compounds produce an intense protonated molecule and some characteristic fragments; but tandem MS (MS–MS) is applied to enhance specificity. The MS–MS fragmentation is studied in order to distinguish 3,4-MDMA from the other 17 related compounds. However, the MS–MS spectra of 3,4-MDMA and six related compounds are very similar. Therefore, the LC–MS–MS method is developed for the unambiguous identification of 3,4-MDMA. The use of a monolithic column allows for 5-min gradient runs. This qualitative method is tested with 49 Ecstacy samples seized by the police. All results are congruent with the ones obtained with other methods.**

## Introduction

A few years ago, most so-called "Ecstacy" tablets contained either 3,4-methylenedioxymethamphetamine (3,4-MDMA), *N*-ethyl-3,4-methylenedioxyamphetamine (3,4-MDEA), or a mixture of these two. More recently, however, Ecstacy tablets have often contained complex mixtures of controlled substances, control substance analogues, alternate abused substances, adulterants, diluents, and manufacturing impurities and byproducts (1,2). It is not rare for a skilled clandestine chemist to plan new synthetic strategies to produce slight modifications to an illicit drug molecule in order to overcome legislation of different countries. These mixed component tablets can offer a serious analytical challenge.

The main method for confirming the identity of unknown substances in forensic laboratories is gas chromatography (GC) with electron ionization (EI) mass spectrometry (MS). For 3,4-MDMA there are many positional isomers (regioisomers) in the alkyl side chain or in the aromatic ring substitution pattern, which yield very similar EI mass spectra (3). Methamphetamine and its five side-chain regioisomers have been shown to produce similar EI spectra (4). In this work, we studied 3,4-MDMA and its 17 ring- and side-chain isomers and similar isobaric substances [compounds 1–6 and 8–19, Figure 1, numbering according to earlier publications (5,6)]. In previous studies, different EI-MS spectra were obtained only for the para-ethoxy compounds (nr. 11 and 12), that produced a specific fragment ion with *m/z* 107 (6). In these previous studies, it was observed that EI fragmentation of 3,4-MDMA and its nine regioisomers (compounds 1–10) occurs primarily by α-cleavage, yielding propylimine as a base peak (*m/z* = 58) and methylenedioxyphenyl cation and radical cation (*m/z* = 135/136, respectively) (7). The MS differentiation

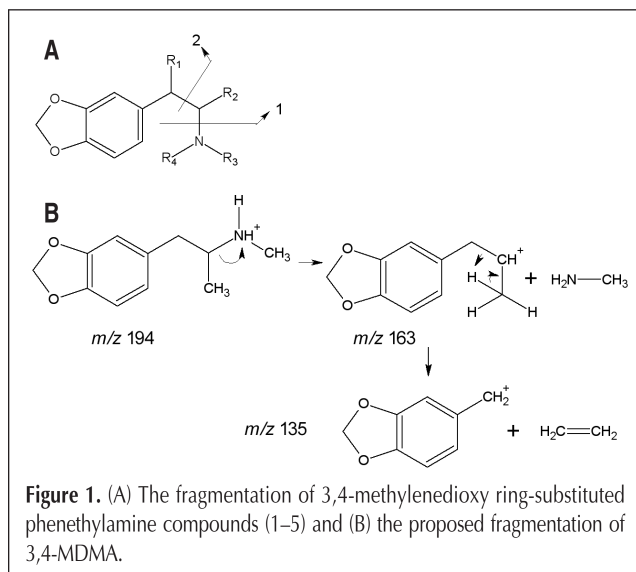


**Figure 1.** (A) The fragmentation of 3,4-methylenedioxy ring-substituted phenethylamine compounds (1–5) and (B) the proposed fragmentation of 3,4-MDMA.

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of the side-chain isomers 3,4-MDMA and 2,3-MDMA (3 and 8) from (3,4-methylenedioxyphenyl)-2-butanamine (3,4-BDB) and 2,3-BDB (5 and 10) has been shown to be possible using derivatization in GC–EI-MS (8,9). In recent studies, 2,3- and 3,4-methylenedioxy substituted ring-isomers 3,4-MDMA and 2,3-MDMA (3 and 8) and 3,4-BDB and 2,3-BDB (5 and 10) (or both) have also been distinguished from each other using GC with either low energy EI or chemical ionization with methane and tandem MS (MS–MS) (10,11) or heptafluorobutyric anhydride derivatives (12) and different product ion intensity patterns. Earlier studies made by using GC–EI-MS and liquid chromatography (LC)–UV (5,6,7) showed that all of the compounds studied in this work can be separated by GC and high-performance liquid chromatography (HPLC) at least partially, but the run times can be long (6). To the best of our knowledge, other separation methods, like capillary electrophoresis, have not been applied for these compounds, with the exception of 3,4-MDMA (13).

This is the initial study involving all of these mass equivalent substances using LC in combination with electrospray ionization (ESI). The first aim was to develop a fast, routine, and qualitative LC–MS–MS method for confirmation of the presence of 3,4-MDMA in the seized drugs. The second aim was to study MS–MS behavior of 3,4-MDMA in order to distinguish it from the other studied compounds.

## Experimental

### Chemicals and sample solutions

HPLC-grade methanol (MeOH) and acetonitrile (ACN) were purchased from Rathburn (Walkerburn, Scotland) and analytical-grade formic acid was purchased from Merck (Darmstadt, Germany). Water was purified with a Milli-Q purifying system (Millipore, Bedford, MA).

3,4-MDMA (RBI, Natick, MA) was purchased as pure reference material. The synthesis and characterization of the compounds studied were carried out according to the earlier works (5–7). The compounds were first dissolved in a 1.0-mg/mL stock solution of $H_2O$–MeOH (1:1). The dilutions for HPLC analysis were performed with deionized water, the working solution being 20 µg/mL. The samples (~ 15 mg) were first extracted to 2 mL MeOH, sonicated for 5 min, diluted to appropriate concentration with deionized water, and filtered (GHP Acrodisc, Pall Gelman Laboratory, Ann Arbor, MI) into autosampler vials. All solutions were stored at –20°C.

### Instrumentation

The LC–MS consisted of an Agilent 1100 Series HPLC system with autosampler and an Agilent 1100 Series LC/MSD trap ion trap MS with Agilent LC/MSD trap software version 4.2 (Bremen, Germany). The column eluent was split 1:10, using an Accurate splitter (LC Packings, San Fransisco, CA).

The eluent A was 0.1% formic acid (FA) with 5% MeOH (v/v) and eluent B was MeOH with 5% $H_2O$ and 0.1% FA in gradient runs. The eluents were degassed by vacuum during use. The gradient used was 10% B in 0–2.0 min and 10%–25% B in 2.0–5.0 min. The column used was a 50- × 4.6-mm endcapped $C_{18}$ reversed-phase Speedrod by Chromolith (Merck KgaA, Darmstadt, Germany). Its temperature was 40°C. The injection volume was 5 µL. The flow rate was 2.5 mL/min, which was split 1:10 after column; 250 µL/min entering the MS. For production of library spectra and generating single MS, the same column with fast isocratic elution with 30:70 0.1% FA–MeOH + 0.1% FA and a flow rate of 0.5 mL/min with 1:10 split ratio were used.

The ionization technique used was ESI, operated in a positive ion mode. Operation parameters of the ESI ion source were as follows (values in method for generating library spectra and MS spectra in parentheses): drying gas temperature, 350°C (350°C); drying gas flow, 10.0 L/min (5 L/min); nebulizer gas pressure, 207 kPa (103 kPa); end-plate voltage, –3500 V; and end-plate offset –500 V. Ion trap parameters were as follows: accumulation time was 40 ms (20 ms); averages, 5 (10); rolling averaging, off; and ion charge control, on. Nitrogen produced by a Whatman (Haverhill, MA) model 75-72 nitrogen generator was used as a drying and nebulizing gas. Helium (4.6, 99.996%) was used in the trap as damping and collision gas.

In the gradient LC–MS–MS mode with the library search, the fragmentation amplitude was increased from 30% to 200% from the set value of 1.0 V. The ion optics parameters were optimized for target ions. The scan range and ion optics parameters were as follows: scan *m/z* 50–220; skim1, 17.1 V; octapole delta, 2.62 V; and capillary exit offset, 50.0 V. For the MS experiments, the scan range was *m/z* 50–500.

## Results and Discussion

The mass spectra of the studied compounds (1–6 and 8–19) showed a strong protonated molecule at *m/z* 194 and one or two fragment ions. The main fragment depended on the alkyl chain length at nitrogen and was either *m/z* 177, 163, or 149; or 176, in the case of compound 19. The other fragment ion formed, if present, was *m/z* 121, 133, or 135. 3,4-MDMA produced *m/z* 194 and a fragment ion of *m/z* 163, as did the compounds 8, 11, 13, 16, 17, and 18. Thus, this group of compounds (8, 11, 13, 16, 17, and 18) have similar mass spectra as the controlled drug, 3,4-MDMA (compound 3). The ESI-MS spectrum of compound 13 also showed ion at *m/z* 135 and those of 16, 17, 18, and a weak (relative intensity < 2%) ion at *m/z* 121. No adducts were seen. According to these results, the protonated molecule was chosen for the precursor ion in MS–MS experiments.

### MS–MS experiments

The MS–MS library spectra were produced by increasing the fragmentation amplitude. The fragmentation amplitude is increased in this mode until it reaches the set upper limit or until there is no precursor ion present in the ion trap. Fragments from unknown compounds can be obtained with the used parameters without knowing the optimum fragmentation amplitude in advance. This is because the highest fragmentation energy set is high enough to fragment most molecules. However, in this mode the actual fragmentation energy used to fully fragment a certain compound remains unknown. This makes the

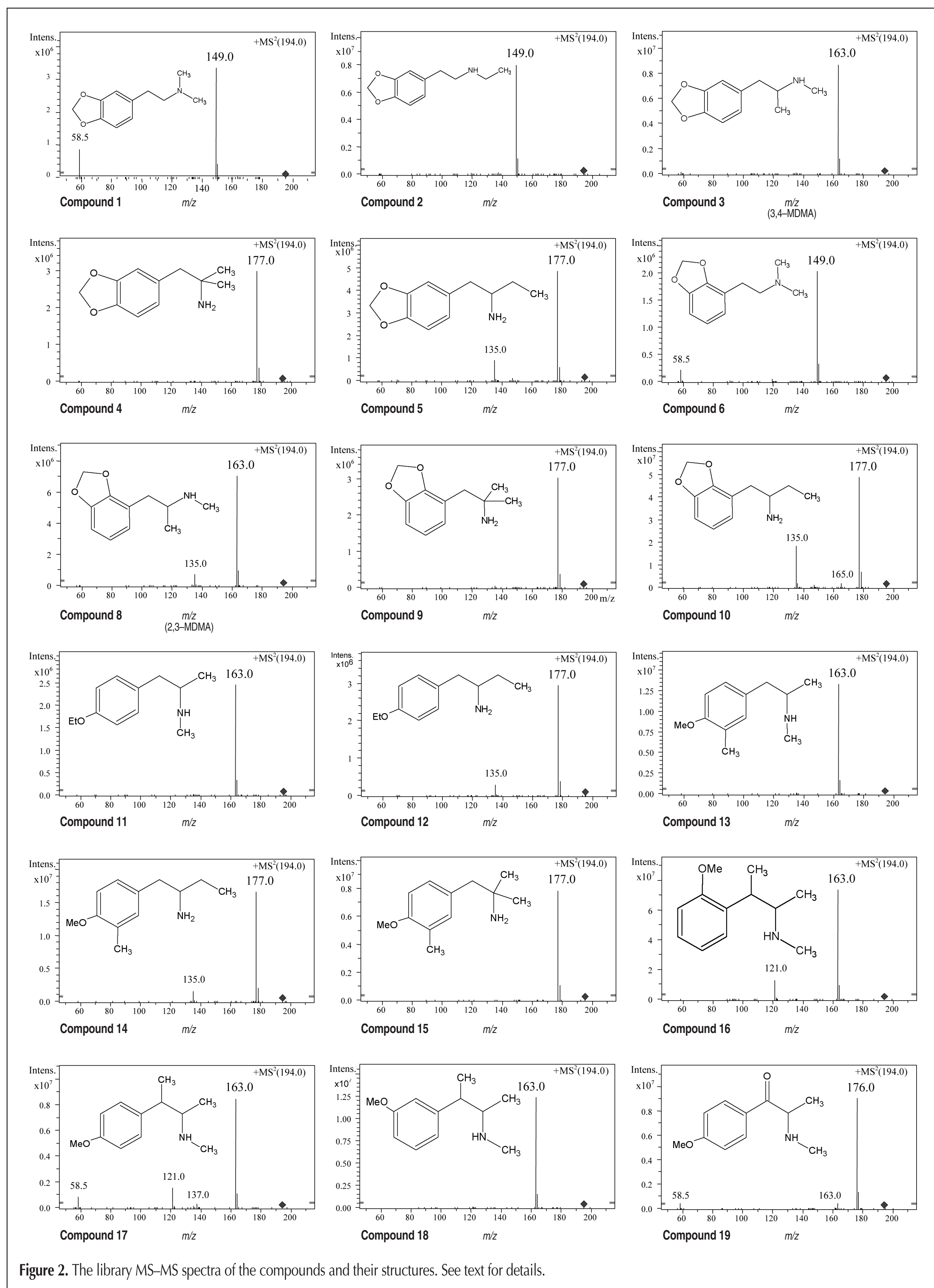


**Figure 2.** The library MS–MS spectra of the compounds and their structures. See text for details.

comparison of the stabilities of the molecules impossible. However, the comparison against the library spectrum of the same compound obtained under similar fragmentation conditions is justified. Therefore, by doing the fragmentation by increasing the energy, the only way to distinguish 3,4-MDMA from the other studied compounds would have to be based on unique product ions or very distinct intensity patterns. The obtained spectra for the library are illustrated in Figure 2.

The proposed MS–MS fragmentation for the amines is presented in Figure 1A. From the protonated molecule, an amine is eliminated to give a benzyl cation (*m/z* 177, 163, or 149) (1), which further eliminates an alkene after an H rearrangement (rH) and inductive cleavage reaction (2) (14), producing ion *m/z* 135 when $R_1$ = H. In Figure 1B, fragmentation is shown with 3,4-MDMA as an example molecule. In addition to the structure presented in Figure 1B, a positively charged seven-ring (tropylium-like) structure is also possible for ion *m/z* 135. Also, an imine ion is observed at *m/z* 58, although sometimes with very low intensity (as in Figure 2 for 3,4-MDMA). Three ions are in many instances agreed to be the minimum for identification purposes (15).

The results of this effort allowed the division of compounds into four groups according to the main product ion in their MS–MS spectra: (*i*) compounds 4, 5, 9, 10, 12, 14, and 15 produced the *m/z* 177 by the loss of ammonia; (*ii*) compounds 3 (3,4-MDMA), 8, 11, 13, 16, 17, and 18 produced the *m/z* 163 by the loss of methylamine; (*iii*) compounds 1, 2, and 6 produced *m/z* 149 by the loss of primary ethylamine or secondary dimethyl amine; and (*iv*) the ketone compound 19 produced *m/z* 176 by the loss of water. The reproducibility of the spectra was excellent (all relative standard deviations (SDs) < 10% for relative intensities above 5%, $n$ = 4). These results show that 3,4-MDMA can be distinguished from the compounds in groups 1, 3, and 4. Furthermore, within group 2, 3,4-MDMA can be distinguished from compounds 16 and 17, which showed an additional fragment ion at *m/z* 121. This fragment is most likely the result of methyl group migration in the benzylic species to form the methoxybenzyl or methoxytropylium ion (*m/z* 121). 2,3-MDMA, which is structurally the most similar from the studied compounds to 3,4-MDMA, produced the product ion of *m/z* 135, which was not seen here for 3,4-MDMA. The compounds were therefore distinguished from each other. Within group 1, compounds 5, 10, 12, and 14 produced different MS–MS spectra than compounds 4, 9, and 15. The secondary benzylic cations at *m/z* 177 produced by the loss of ammonia in the straight chain 1-phenyl-2-butanamines (compounds 5, 10, 12, and 14) show a more abundant ion at *m/z* 135 than was observed for the branched-chain butanamines (compounds 4, 9, and 15), which yielded the tertiary benzylic cation at *m/z* 177. The only compound that produced unique product ions was compound 19. The unfortunate result of this was that a total of seven different compounds that produced the same intense product ion (i.e., *m/z* 163, compounds 3, 8, 11, 13, 16, 17, and 18) were misidentified as 3,4-MDMA by the settings used in the library search (NIST algorithm) using the ramped fragmentation amplitude and direct introduction of the sample. The library search algorithm compares the unknown spectrum to the spectra in the library (Fit) and the spectra in the library to the unknown (Rfit), from which it generates a value (Purity). The maximum purity value is 1000, indicating perfect correlation between measured and library spectra. Therefore, the unambiguous identification of 3,4-MDMA requires chromatographic separation before MS–MS analysis.

### LC–ESI-MS–MS method

The fast LC separation was optimized to separate 3,4-MDMA from the other compounds studied. The identification of all the compounds studied was not necessary because they are not listed as controlled substances in the United Nations Schedules (16), which are used in many countries. ACN and MeOH were tested and MeOH was found more suitable because it allowed slightly higher organic concentration, which was desirable for ESI performance. Figure 3 shows the LC separation of all the 18 compounds. The seven that were in the scope of the LC separation and misidentified as 3,4-MDMA (compounds in group 2) by the library search are shown in black. This product ion chromatogram represents the precursor ion (*m/z* 194) transition to product ion *m/z* 163 and shows that 3,4-MDMA can be unambiguously identified by LC–ESI-MS–MS. The developed qualitative method was validated according to the recommendations of

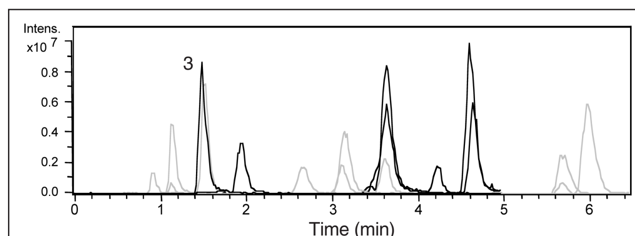


**Figure 3.** The LC separation of the 18 compounds with equivalent mass. The chromatogram for transition *m/z* 194 → 163 for the seven compounds is in black and the other transitions are in grey. 3,4-MDMA is marked with number 3. The concentration of the compounds is 10 or 20 µg/mL.

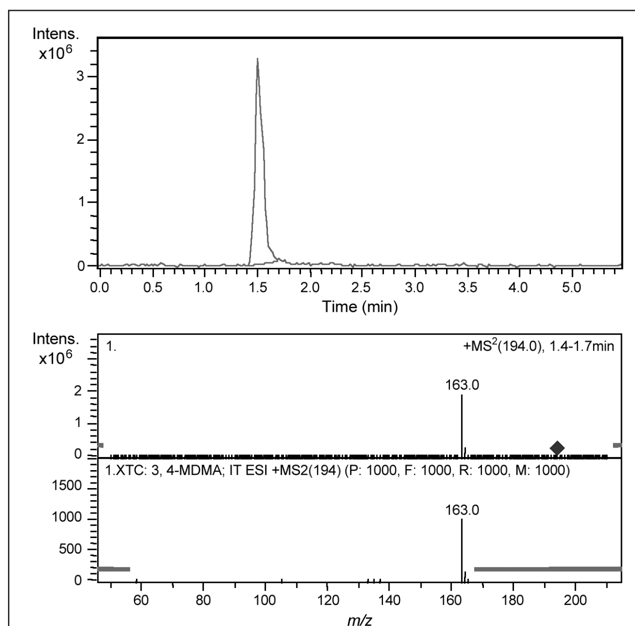


**Figure 4.** A confirmation analysis of an Ecstacy tablet containing 3,4-MDMA; above the total ion chromatogram and below the MS–MS spectrum and its library search result. For details see the text.

Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) Core Committee (17). The validation parameters are shown in Table I. The reproducibility of the retention times was also determined using a concentration range (0.4, 4.0, 20, 40 and µg/mL). The SD of the retention times was mostly below 0.018 min and always well below 0.12 min, which corresponds to 2% variance of the last eluting compound. From these results, the acceptable time window without interfering peaks was determined for the library search. The retention time window in the final method was set to ± 0.2 min (i.e., 24 s).

The developed LC–MS–MS method with the library search was evaluated with 49 authentic samples run in duplicates. A control sample of 3,4-MDMA was always run in the beginning and in the end of the sequence. For example, in forensic toxicology the retention time of the analyte in HPLC can differ by more than 2% from the controls, especially in gradient analyses (18). A 2% deviation for our method means that a deviation of 0.03 min for 3,4-MDMA was acceptable. Also, a negative control (blank) was run between any two samples. An example of an analysis of an Ecstacy tablet and its results are illustrated in Figure 4. The combination of the MS–MS spectrum and the retention time allowed the unambiguous identification of 3,4-MDMA in all samples where present (46/49). One sample contained only methamphetamine, one methamphetamine and caffeine, and one only caffeine. Caffeine is a common adulterant in illicit drug preparations. Other active substances found by GC–MS from the tablets were MDA and MDEA, and they did not affect the specificity of the method. The sensitivity of the method was sufficient for detecting 3,4-MDMA from an Ecstacy tablet when the amount of sample taken for the analysis was 15 mg. The concentration of Ecstacy tablets commonly varies from 50 to 150 mg (in ~ 250 mg total weight of tablet; i.e., 20–60% w/w).

Retention times for the other 11 isomers were also determined because the separation was desirable in order not to obtain too many mixture spectra because the precursor ion is the same for all. Compound 19 coeluted with 3,4-MDMA, but it did not affect identification because of its distinct product ions. These two compounds also are extremely rarely—if ever—present in the same sample. Some of the compounds eluted after the 5 min run time; therefore, the run time was extended for these compounds accordingly (Table I). By using the developed LC–ESI-MS–MS method with the automated library search, unambiguous identification can be obtained for compounds 1, 3 (i.e., 3,4-MDMA), 4, 8, 10, 11, 14, and 19 (Table II, $R_s > 0.5$) from all 18 compounds studied. The remaining 10 were still inseparable because of coelution with another compound with too similar spectrum. However, the scope of this manuscript was to distinguish the controlled drug 3,4-MDMA from the other substances, and this was accomplished.

## Conclusion

The LC–ESI-MS–MS method developed and validated according to SWGDRUG recommendations was shown to be

**Table I. The SD for Retention Times, Main Product Ion, and Resolution ($R_s$) for the Compounds in the Same Main Product Ion Group***

| Compound nr[†] | Compound name | $t_R$ (min) | SD ($t_R$) ($n$ = 5)[‡] | LOD (µg/mL)[§] | Main product ion | $R_s$ (pre/post)** |
|---|---|---|---|---|---|---|
| Compound 1 | *N,N*-dimethyl-3,4-methylenedioxyphenyl-2-ethanamine | 0.91 | 0.007 | n.m.[††] | 149 | n.a.[‡‡]/0.65 |
| Compound 6 | *N,N*-dimethyl-2,3-methylenedioxyphenyl-2-ethanamine | 1.13 | 0.009 | n.m. | 149 | 0.65/0.01 |
| Compound 2 | *N*-ethyl-3,4-methylenedioxyphenyl-2-ethanamine | 1.15 | 0.016 | n.m. | 149 | 0.01/n.a. |
| Compound 3 | 3,4-MDMA | 1.51 | 0.009 | 0.4 | 163 | n.a./1.28 |
| Compound 19 | *p*-methoxymethcathinone | 1.52 | 0.017 | 0.4 | 176 | n.a./n.a. |
| Compound 8 | 2,3-MDMA | 1.95 | 0.015 | 0.4 | 163 | 1.28/4.90 |
| Compound 4 | α,α-dimethyl-1-(3,4-methylenedioxyphenyl)-2-ethanamine | 2.64 | 0.013 | n.m. | 177 | n.a./1.36 |
| Compound 9 | α,α-dimethyl-1-(2,3-methylenedioxyphenyl)-2-ethanamine | 3.10 | 0.027 | n.m. | 177 | 1.36/0.11 |
| Compound 5 | (3,4-methylenedioxyphenyl)-2-butanamine, 3,4-BDB | 3.14 | 0.018 | n.m. | 177 | 0.11/1.39 |
| Compound 10 | (2,3-methylenedioxyphenyl)-2-butanamine, 2,3-BDB | 3.61 | 0.008 | n.m. | 177 | 1.39/6.01 |
| Compound 17 | 2-(3-methoxyphenyl)-*N*-methyl-3-butanamine | 3.62 | 0.017 | 0.4 | 163 | 4.90/0.02 |
| Compound 18 | 2-(4-methoxyphenyl)-*N*-methyl-3-butanamine | 3.63 | 0.011 | 0.4 | 163 | 0.02/1.73 |
| Compound 11 | *p*-ethoxymethamphetamine | 4.21 | 0.013 | 1.0 | 163 | 1.73/1.11 |
| Compound 13 | *p*-methoxy-*m*-methylmethamphetamine | 4.59 | 0.009 | 0.4 | 163 | 1.11/0.13 |
| Compound 16 | 2-(2-methoxyphenyl)-*N*-methyl-3-butanamine | 4.63 | 0.009 | 0.4 | 163 | 0.13/n.a. |
| Compound 12 | 1-(4-ethoxyphenyl)-2-butanamine | 5.66 | 0.021 | n.m. | 177 | 6.01/0.07 |
| Compound 15 | 4-methoxy-3-methylphentermine | 5.67 | 0.021 | n.m. | 177 | 0.07/0.75 |
| Compound 14 | 1-(4-methoxy-3-methylphenyl)-2-butanamine | 5.94 | 0.014 | n.m. | 177 | 0.75/n.a. |

* LODs are presented only for the seven compounds with similar fragmentation pattern to 3,4-MDMA.
† Compound nr. 7 (*N*-ethyl-2,3-methylenedioxyphenyl-2-ethanamine) was absent from the study.
‡ Concentration = 20 µg/mL.
§ LOD from total ion chromatogram (s/n > 3).
** $R_s = 1.176(t_{R,2} - t_{R,1})/(w_{1/2,1} + w_{1/2,2})$; $w_{1/2}$ = 0.2 min is used in calculations and $R_S$ is calculated for compounds that have the same product ion.
†† n.m. = not measured.
‡‡ n.a. = not applicable because of no preceding or following peak with the same product ion.

applicable for identification of the illicit drug 3,4-MDMA from its mass equivalent isomers and isobaric substances. This is very significant improvement to the present routine methods because the misidentification of these compounds in some GC–MS procedures may exist because of spectral and chromatographic similarities. The use of a fast gradient with a monolithic column, together with MS–MS detection, also provided significantly shorter analysis times than with GC–MS and LC–UV methods developed earlier (6). An in-house library, which included the obtained MS and MS–MS spectra and retention times, provided fast and unambiguous identification of the controlled substance also from authentic sample material.

## Acknowledgments

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