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New designer drugs *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine (PCEEA) and *N*-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA): Studies on their metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques

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Studies are described on the metabolism and the toxicological detection of the phencyclidine-derived designer drugs *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine (PCEEA) and *N*-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA) in rat urine using gas chromatographic/mass spectrometric (GC/MS) techniques. The identified metabolites indicated that PCEEA and PCMEA were transformed to the same metabolites by *N*-dealkylation and *O*-dealkylation partially followed by oxidation of the resulting alcohol to the respective carboxylic acid and hydroxylation of the cyclohexyl ring at different positions and combinations of those. Finally, aromatic hydroxylation of the *O*-dealkylated metabolites was partially followed by hydroxylation of the cyclohexyl ring at different positions. All metabolites were partially excreted in conjugated form. The authors' systematic toxicological analysis (STA) procedure using full-scan GC/MS after acid hydrolysis, liquid–liquid extraction and microwave-assisted acetylation allowed the detection of an intake of a common drug users' dose both of PCEEA and PCMEA in rat urine. Assuming similar metabolism in humans, the STA should be suitable for proof of an intake of PCEEA and PCMEA in human urine, although their differentiation is not possible due to common metabolites. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: PCMEA; PCEEA; metabolism; GC/MS; urinalysis

INTRODUCTION

Several new synthetic drugs from various classes were seized in the German federal state of Hesse and surrounding federal states in the late 1990s. Some of them were phencyclidine derivatives such as *N*-(1-phenylcyclohexyl)-propanamine (PCPR), *N*-(1-phenylcyclohexyl)-3-methoxypropanamine (PCMPA), *N*-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA), and *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine (PCEEA). The seized preparations contained either one compound or mixtures with other designer drugs.[1] So far, little information is available on pharmacological properties of these compounds. However, they might be assumed to be similar to those of the structurally related drugs phencyclidine and ketamine, which both act as antagonists at *N*-methyl-D-aspartate (NMDA) receptors and have psychotomimetic as well as anesthetic properties.[2] Furthermore, it has been reported that (1-phenylcyclohexyl)-amine produced a long-lasting dose-dependent effect on the efflux of dopamine in the rat.[3] This compound is a known metabolite of phencyclidine,[3] PCPR,[4] and the related compound *N*-(1-phenylcyclohexyl)-3-ethoxypropanamine (PCEPA).[5] Certainly, such pharmacological profiles would be in line with abuse of the new phencyclidine-derived compounds as designer drugs. Anticonvulsant activity of (1-phenylcyclohexyl)-amine and some derivatives were reported by Thurkauf *et al*.[6] Only for PCEPA and PCPR, studies on the metabolism and toxicological detection have been described.[4,5] Therefore, the aim of this study was to identify the metabolic pathways of PCEEA and PCMEA using gas chromatography/mass spectrometry (GC/MS) with electron ionization (EI) and positive-ion chemical ionization (PICI) mode. In addition, the detectability of PCEEA, PCMEA,

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and its metabolites within the authors' systematic toxicological analysis (STA) procedure in urine was studied by GC/MS.[5,7–14] This procedure is a widely used very comprehensive screening procedure covering thousands of drugs, poisons and/or their metabolites.[7,9,15,16]

EXPERIMENTAL

Chemicals and reagents

PCEEA HCl and PCMEA HCl were provided by the Hessisches Landeskriminalamt (Wiesbaden, Germany) for research purposes. *N*-Methyl-bis-trifluoroacetamide (MBTFA) and *N*-methyl-*N*-trimethylsilyl trifluoroacetamide (MSTFA) were obtained from Fluka (Taufkirchen, Germany). Bond Elut Certify cartridges were obtained from Varian (Darmstadt, Germany). All other chemicals and biochemicals were obtained from Merck (Darmstadt, Germany). All chemicals and biochemicals were of analytical grade.

Urine samples

The investigations were performed using urine of male Wistar rats (Ch. River, Sulzfleck, Germany) for toxicological diagnostic reasons according to the corresponding German law. They were administered a single 20 mg/kg body mass (BM) dose for metabolism studies or a single 0.1 mg/kg BM dose for STA studies in aqueous suspension by gastric intubation ($n = 3$ each). Urine was collected separately from the faeces over a 24-h period at 20 °C stabilized with sodium fluoride. All samples were directly analyzed. Blank rat urine samples were collected before drug administration to check whether they were free of interfering compounds.

Sample preparation for identification of metabolites by GC/MS

For both compounds, a 3-ml portion of urine was worked-up as previously described for PCEPA.[5] After enzymatic cleavage of the conjugates using glucuronidase (EC no. 3.2.1.31) and arylsulfatase (EC no. 3.1.6.1) from *Helix pomatia*, the solid-phase extract was derivatized by acetylation, trifluoroacetylation, or trimethylsilylation. Aliquots (2 µl) of the derivatized extracts were injected into the GC/MS.

Sample preparation for STA by GC/MS

A 5-ml portion of urine was worked up as described for other designer drugs.[11,13] After cleavage of conjugates by acid hydrolysis using hydrochloric acid and liquid–liquid extraction at pH 8–9 using a mixture of dichloromethane-isopropanol-ethyl acetate, the sample was derivatized by acetylation. Aliquots (2 µl) of the derivatized extracts were injected into the GC/MS.

GC/MS apparatus for identification of metabolites

The extracts were analyzed using a [Hewlett Packard (HP), Agilent, Waldbronn, Germany] 5890 Series II gas chromatograph combined with an HP 5989B MS Engine mass spectrometer and an HP MS ChemStation (DOS series) with HP G1034C software version C03.00. The GC conditions were as follows: splitless injection mode; column, HP-1 capillary (12 m × 0.2 mm I.D.), cross-linked methyl silicone, 330 nm film thickness; injection port temperature, 280 °C; carrier gas, helium; flow-rate 1 ml/min; column temperature, programmed from 100 to 310 °C at 30°/min, initial time 3 min, final time 8 min. The MS conditions were as follows: full-scan mode, m/z 50–800 u; EI mode, ionization energy, 70 eV; PICI mode using methane: ionization energy, 230 eV; ion source temperature, 220 °C; capillary direct interface, heated at 260 °C.

GC/MS apparatus for STA

The extracts were analyzed using a HP 5890 Series II gas chromatograph combined with a HP 5972A MSD mass spectrometer and a HP MS ChemStation (DOS series) with HP G1034C software version C03.00. The GC conditions were as follows: splitless injection mode; column, HP-1 capillary (12 m × 0.2 mm I.D.), cross-linked methyl silicone, 330 nm film thickness; injection port temperature, 280 °C; carrier gas, helium; flow-rate 1 ml/min; column temperature, programed from 100 to 310 °C at 30°/min, initial time 3 min, final time 8 min. The MS conditions were as follows: full-scan mode, m/z 50–550 u; EI mode, ionization energy, 70 eV; ion source temperature, 220 °C; capillary direct interface, heated at 280 °C.

GC/MS procedure for identification of metabolites and STA by GC/MS

PCEEA, PCMEA, and their metabolites in the derivatized urine extracts were separated by GC and identified by MS. The postulated structures of the (derivatized) metabolites were deduced from the fragments detected in the EI mode which were interpreted in correlation to the fragmentation patterns of the parent compounds which was described by Roesner *et al.*[1] Interpretation of the fragments was performed according to the rules described by e.g. McLafferty and Turecek[17] and Smith and Busch.[18]

For toxicological detection of PCEEA, PCMEA and their metabolites, mass chromatography was used extracting characteristic fragment ions of PCEEA/PCMEA metabolites from the total ion current. The following ions were used for this purpose: m/z 218, 259 and 260. These ions were selected from the mass spectra recorded during this study. The identity of the peaks in the mass chromatograms was confirmed by computerized comparison of the mass spectra underlying the peaks (after background subtraction) with the recorded reference spectra.[15]

RESULTS AND DISCUSSION

Identification of the metabolites

The urinary metabolites of PCEEA and PCMEA were separated by GC and identified by EI MS and PICI MS after gentle enzymatic hydrolysis of glucuronides and/or sulfates, extraction and derivatization as described in detail for PCEPA.[5] PCEEA and PCMEA and their secondary amine metabolites were found to be derivatized only to a minor extent (about 20%) at the amine moiety under the described conditions. This phenomenon, already described for PCEPA and PCPR,[4,5] might be explained by steric hindrance from the neighboring phenyl and cyclohexyl rings and from the side chain, this effect might even be increased by the formation of

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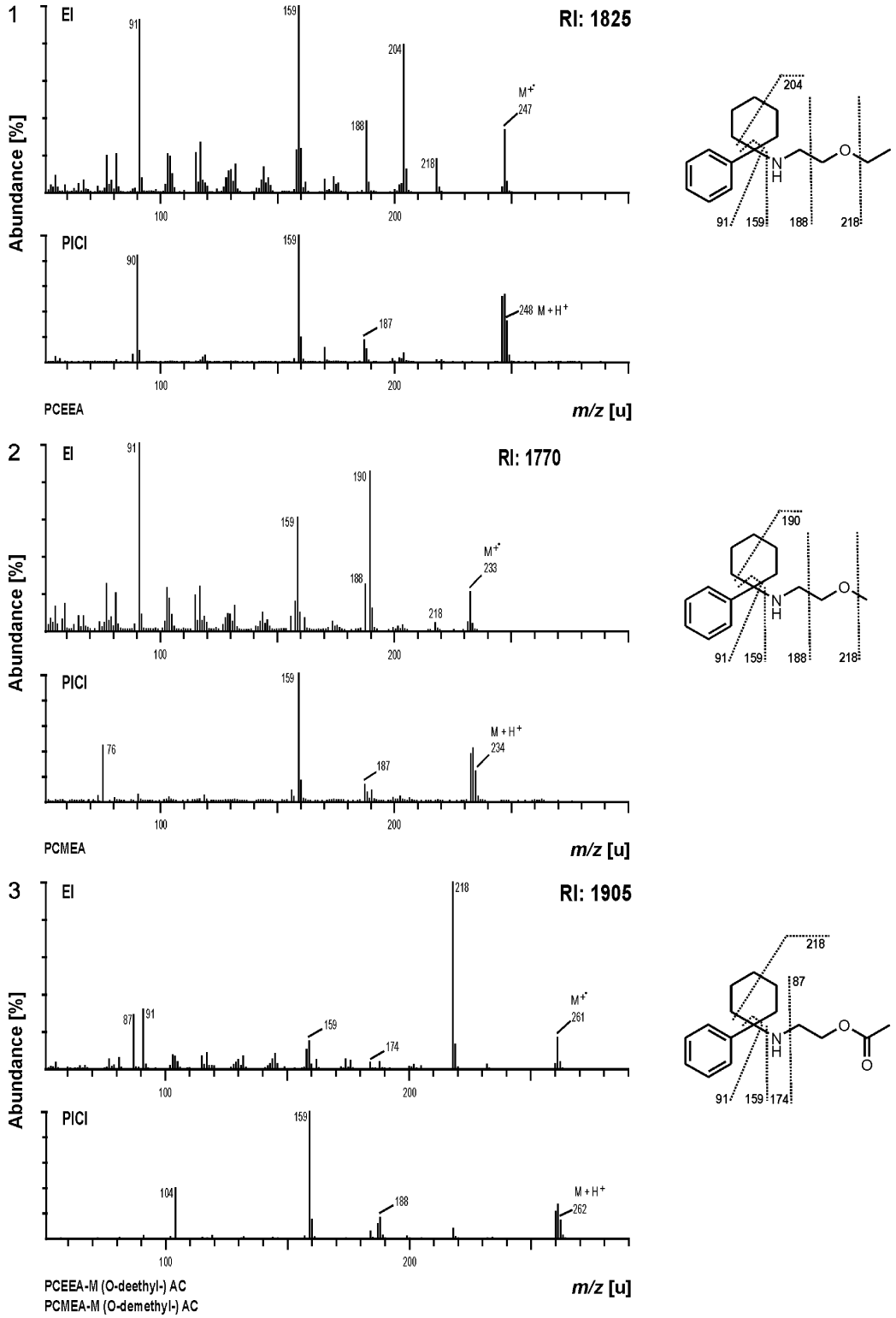

Figure 1. EI and PICI mass spectra, RIs, structures and predominant fragmentation patterns of PCEEA and PCMEA and their metabolites after acetylation or trimethylsilylation.

a hydrogen bond between the hydrogen of the secondary amine function and the other oxygen of the side chain stabilizing as a five-membered ring, or both.

The EI mass spectra, the retention indices (RIs), the structures and predominant fragmentation patterns of PCEEA, PCMEA and their metabolites after derivatization are shown in Fig. 1. In order to verify the molecular mass of the postulated metabolites, PICI mass spectra were recorded, because they usually contain abundant peaks of the protonated molecule $[M + H]^+$ with adduct ions typical for PICI using methane as reagent gas $[M + C_2H_5^+, M + C_3H_5^+]$. While all of the recorded PICI mass spectra contained the respective protonated molecular ions at considerable abundances, the typical adduct ions were absent in about one-third of them.

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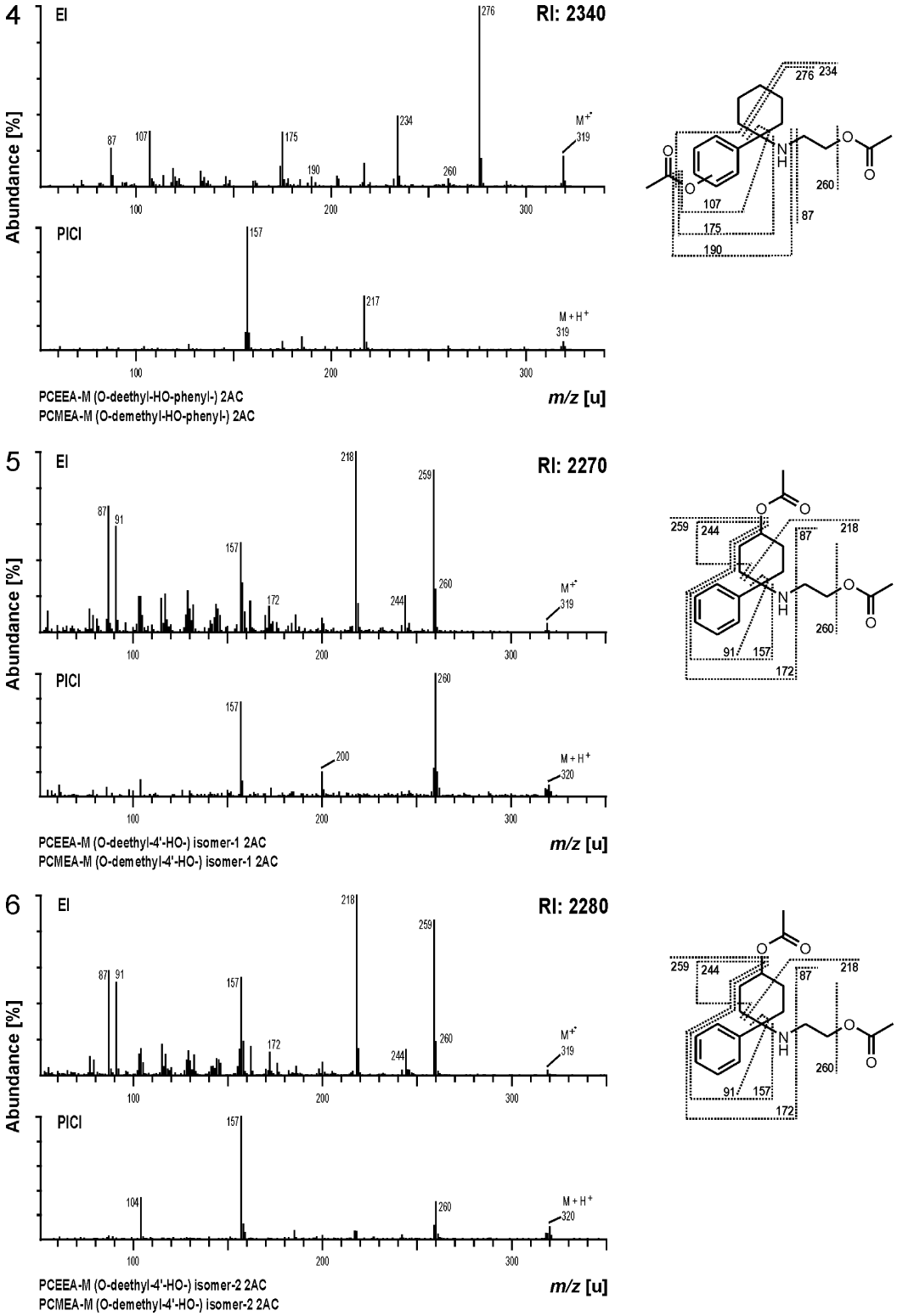

Figure 1. (*Continued*).

Similar observations had been made in the studies of the structurally related drug PCEPA.[5]

In the acetylated urine extract of rats after PCEEA application, PCEEA and the following metabolites could be identified. The numbers of EI spectra in Fig. 1 are given in brackets: PCEEA (1), *O*-deethyl PCEEA (3), *O*-deethyl-hydroxyphenyl PCEEA (4), *O*-deethyl-4′-hydroxy PCEEA isomer 1 (5), *O*-deethyl-4′-hydroxy PCEEA isomer 2 (6), *O*-deethyl-3′-hydroxy PCEEA (7), dehydrated *O*-deethyl-hydroxy PCEEA (common GC artifact of 5, 6 and 7) (8), *O*-deethyl-4′-hydroxy-hydroxyphenyl PCEEA (9), *O*-deethyl-3′-hydroxy-hydroxyphenyl PCEEA (10), *N*-dealkyl PCEEA (11), *N*-dealkyl-4′-hydroxy PCEEA isomer 1 (12), *N*-dealkyl-4′-hydroxy PCEEA isomer 2 (13), *N*-dealkyl-3′-hydroxy PCEEA isomer 1 (14), and *N*-dealkyl-3′-hydroxy PCEEA isomer 2 (15). In the trimethylsilylated urine extract,

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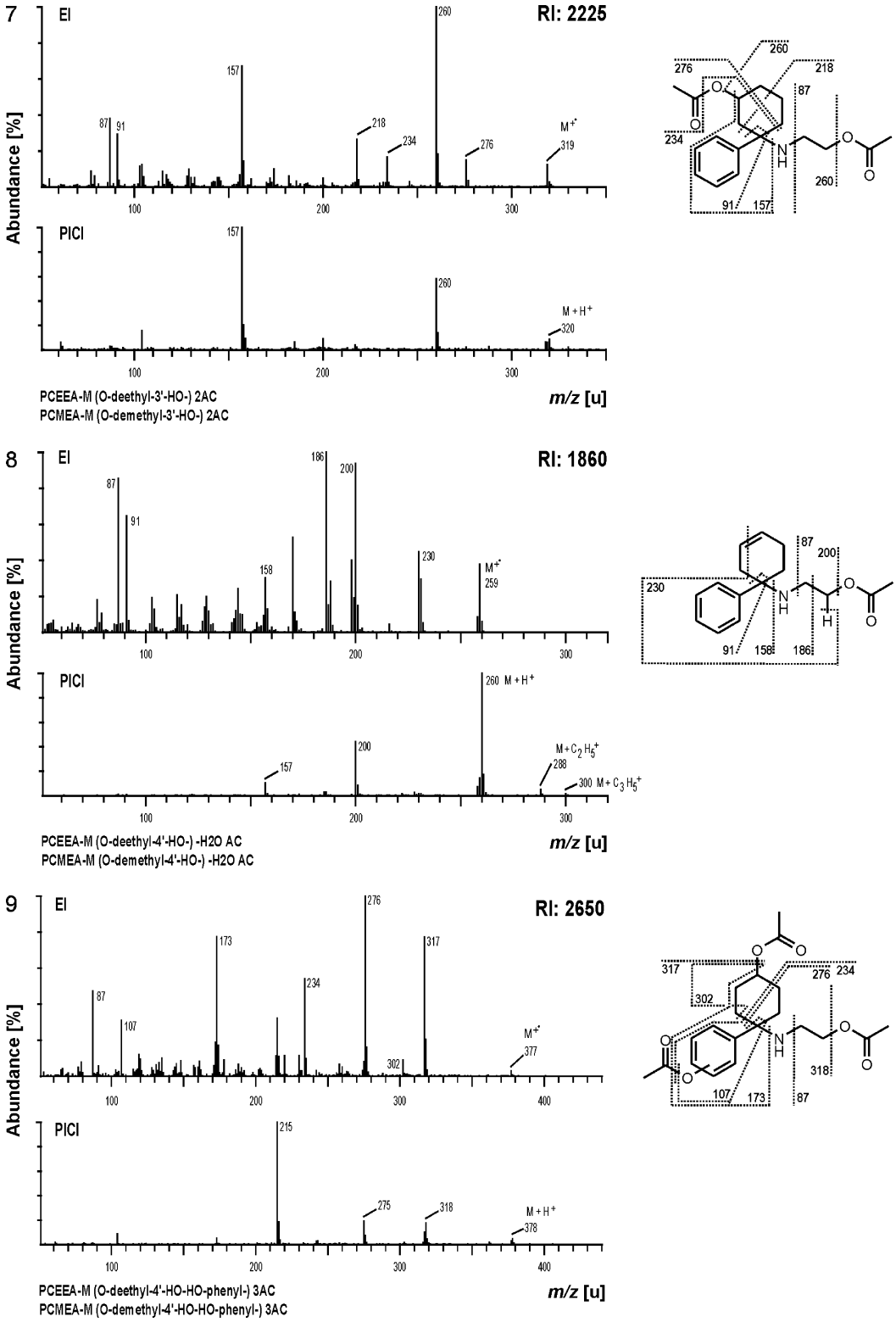

Figure 1. (*Continued*).

PCEEA and the following compounds could additionally be identified: carboxy PCEEA (16), *cis*-carboxy-4′-hydroxy PCEEA (17), *trans*-carboxy-4′-hydroxy PCEEA (18), carboxy-3′-hydroxy PCEEA (19), *O*-deethyl-4′-*cis*-hydroxy PCEEA (20), and *O*-deethyl-4′-*trans*-hydroxy PCEEA (21).

In the acetylated urine extract of rats after PCMEA application, PCMEA and the identical metabolites identified after PCEEA application were detected. Therefore, the names of corresponding *O*-demethyl metabolites were added to the spectra legends in Fig. 1.

Proposed fragmentation patterns

Fragmentation patterns of PCEPA and its metabolites have already been described in detail by Sauer *et al*.[5] In the following, possible fragmentation patterns of the EI mass spectra of PCEEA, PCMEA and their derivatized metabolites

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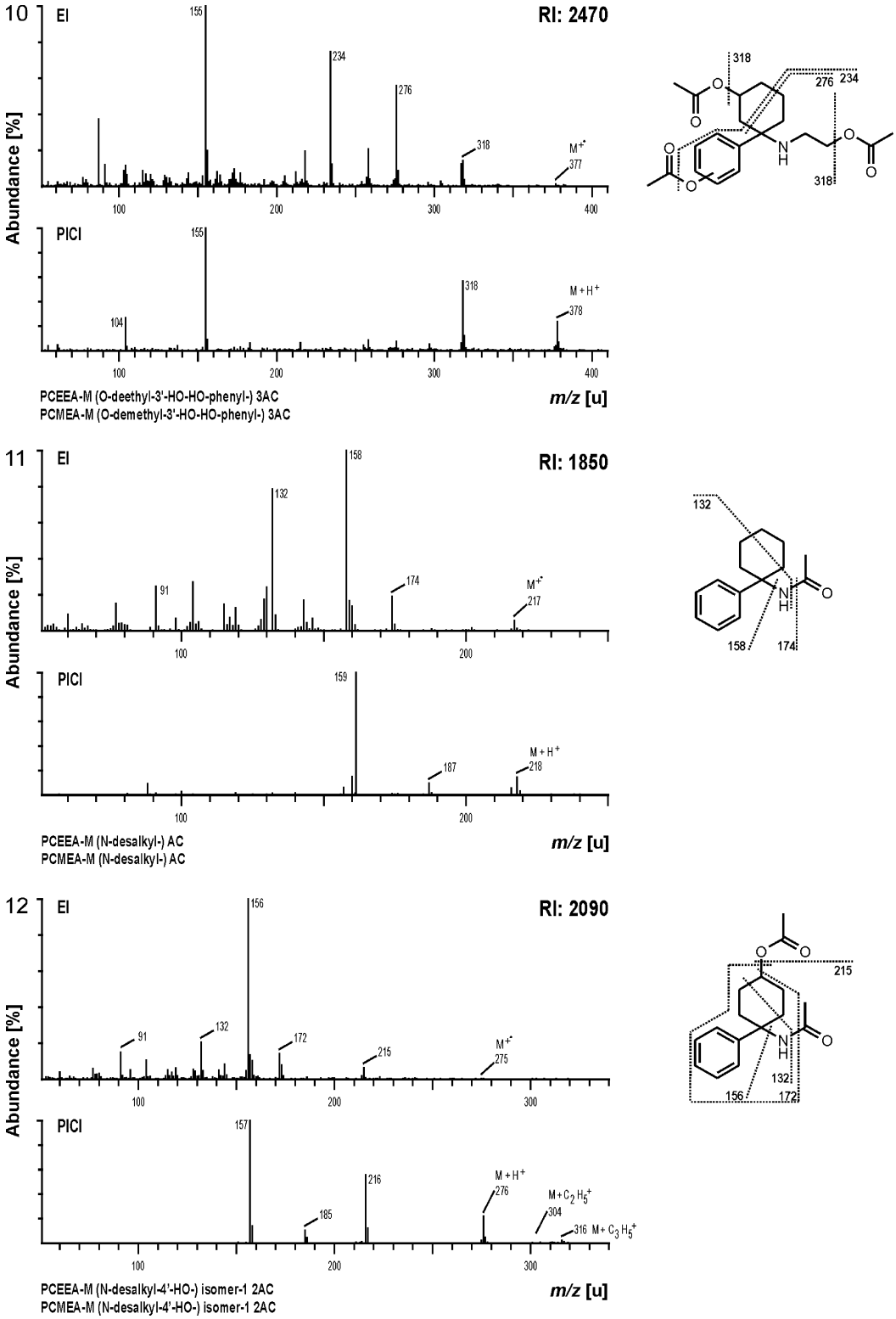

Figure 1. (*Continued*).

will analogously be discussed in relation to the postulated metabolite structures depicted in Fig. 1. The numbers of the metabolites are assigned to the mass spectra in Fig. 1. PCEEA (1), PCMEA (2), and their metabolites with an unchanged double-ring system (3, 16) showed the fragment ion m/z 159 or 158 for those with amide structure (11). The hydroxyphenyl metabolite (4) showed a respective fragment ion m/z 175 after further neutral loss of the acetyl moiety, while 3′- and 4′-hydroxy metabolites showed a fragment m/z 157 resulting from elimination of acetic acid (5–7) or m/z 156 for those with amide structure (12–15). In addition, a fragment ion m/z 173 was observed for metabolites hydroxylated at both rings (9, 10). Benzyl-like cleavage of PCEEA (1), PCMEA (2), and all of their metabolites led to the formation of the tropylium ion m/z 91 for all compounds with an unchanged aromatic ring (1–3, 5–8,

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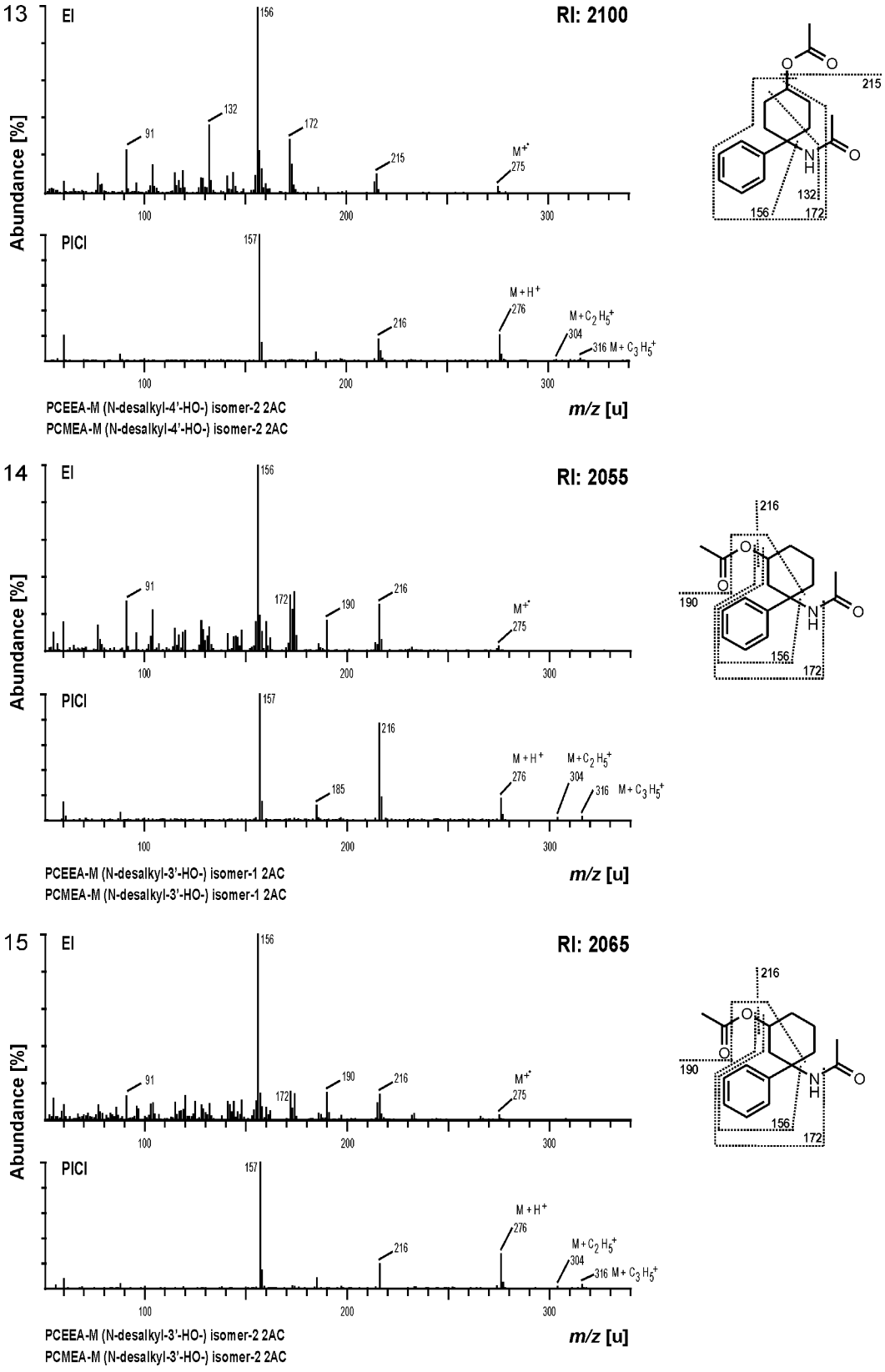

Figure 1. (*Continued*).

11–21) and to a corresponding fragment ion m/z 107 for the respective hydroxyphenyl metabolites (4, 9) after loss of the respective acetyl moiety. PCEEA (1), PCMEA (2), and all of their metabolites containing a secondary amine but no hydroxy group at the cyclohexyl ring showed a loss of 43 u leading to fragment ions m/z 204 (1), 190 (2), 218 (3), and 276 (4). In the case of the 3′-hydroxy metabolite (7), two different positions of the β-cleavage were possible: on the one hand, an acetylated enol immonium cation with m/z 276 (7) formed by the above-mentioned loss of 43 u. This could

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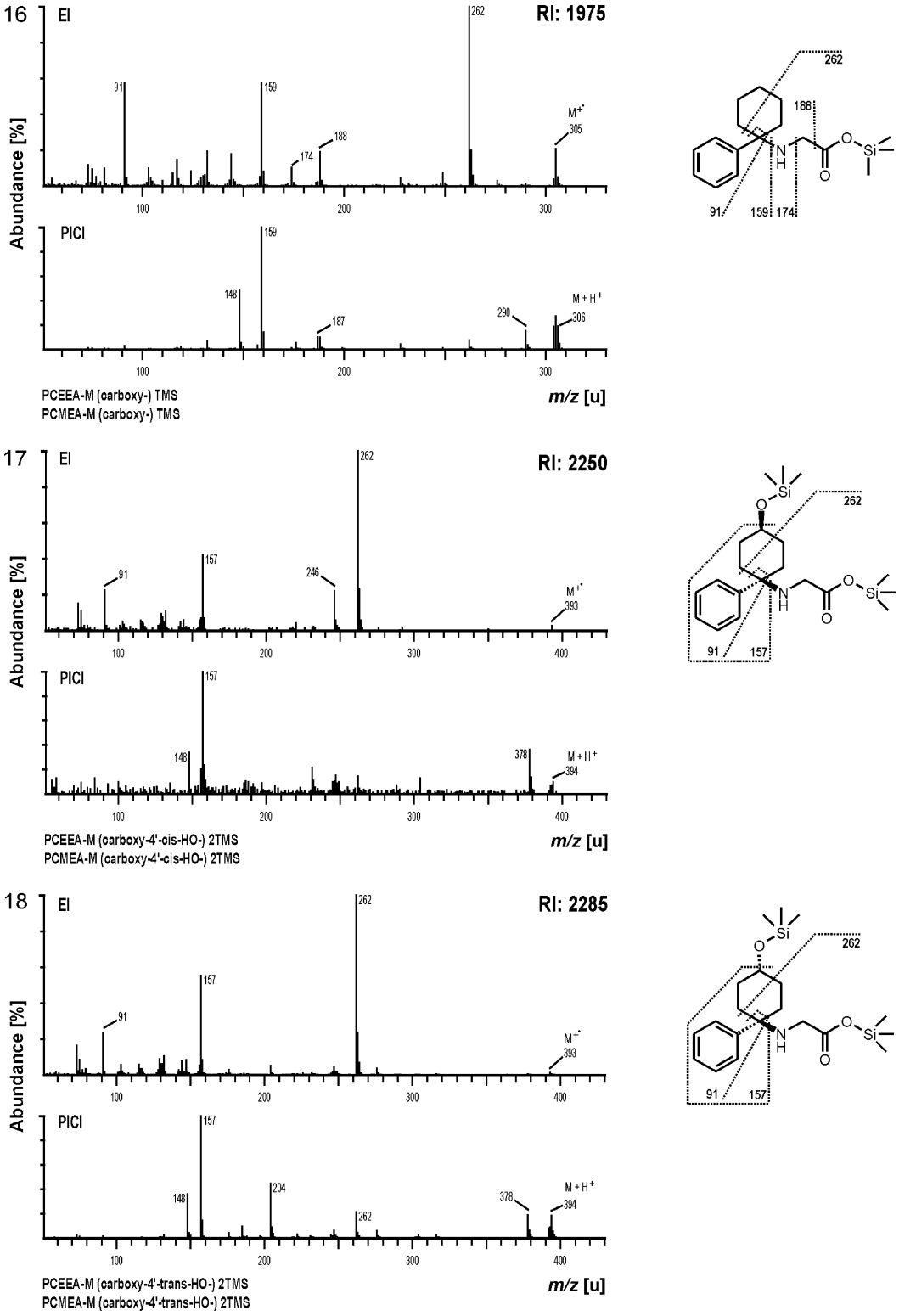

Figure 1. (*Continued*).

be followed by an α-cleavage resulting in a neutral loss of the acetyl moiety corresponding to 42 u and the formation of an enol immonium cation m/z 234 (7). On the other hand, homolytic cleavage of the carbon–oxygen bond in position 3′ led to the loss of an acetyloxyl radical corresponding to 59 u resulting in fragment ion m/z 260 (7). Following β-cleavage between position 1′ and 2′ led to a neutral loss of 101 u and the formation of fragment ion m/z 218 (7).

In the case of the 4′-hydroxy metabolites (5, 6, 9), β-cleavage between positions 1′ and 2′ or between 1′ and 6′ led to neutral loss of 101 u and formation of fragment ions m/z 218 (5, 6) and 276 (9), respectively. Another important fragmentation pattern of the 4′-hydroxy metabolites was the elimination of acetic acid resulting in a loss of 60 u and formation of fragment ions m/z 259 (5, 6) or 317(9). As previously described in literature for other cyclohexenyl

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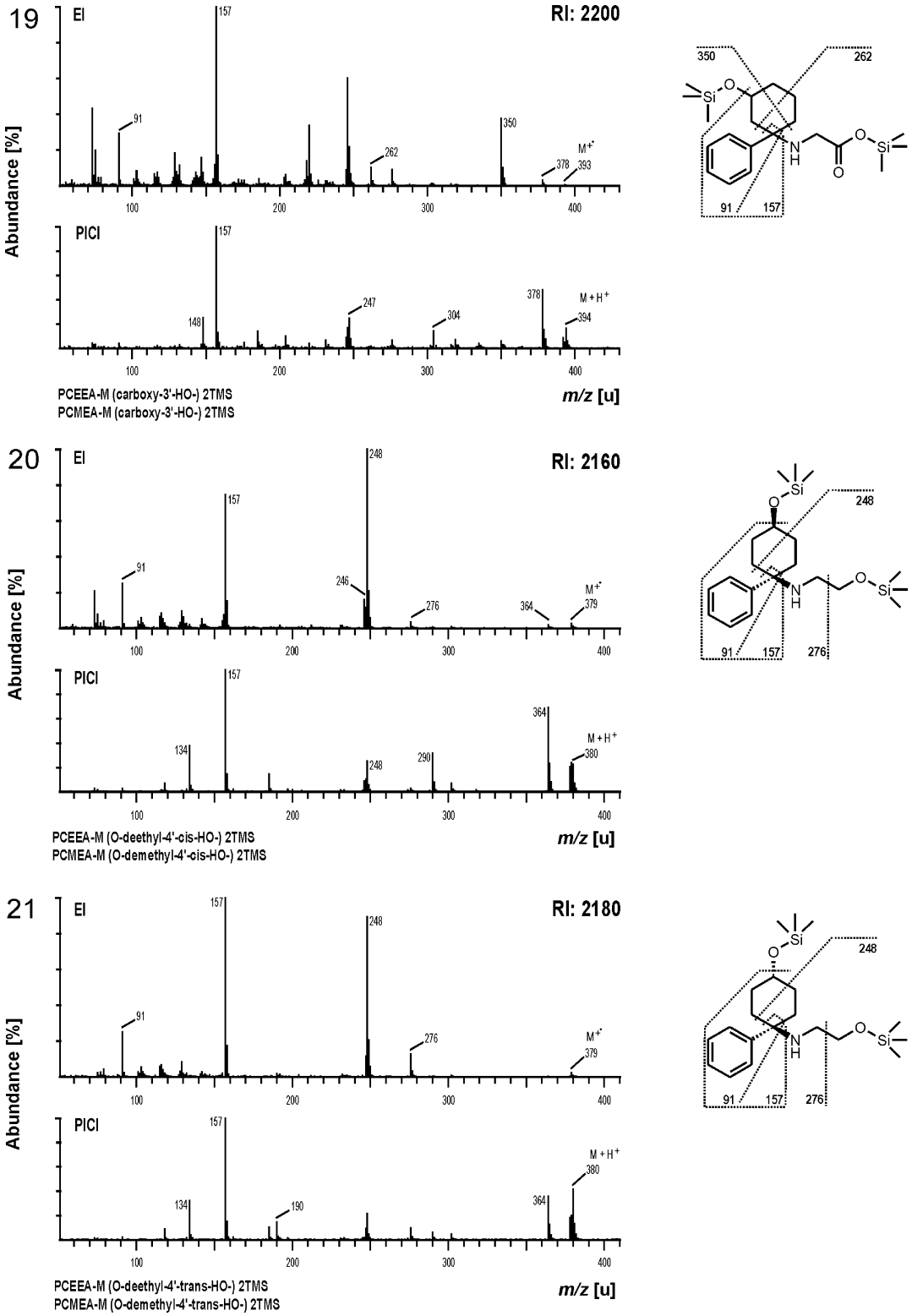

Figure 1. (*Continued*).

rings,[17,18] this was followed by the loss of a methyl radical from the cyclohexyl ring leading to fragment ions m/z 244 (5, 6) or 302 (9). Similar differentiation of isomeric hydroxycyclohexyl metabolites has already been described for phencyclidine.[19,20]

PCEEA (1), PCMEA (2), and all of their metabolites with an *O*-dealkylated side chain (3–7, 9, 10) showed a cleavage between the nitrogen atom and position 1 of the side chain. The resulting fragment ions have m/z values of 87 u representing the *O*-dealkylated side chain. The fragment ions representing the other part of the molecule were m/z 174 in the case of an unchanged double- ring system (3), m/z 190 for hydroxyphenyl metabolites after loss of the acetyl moiety (4), and m/z 172 for the 3′- or 4′-hydroxy metabolites (5–7) after elimination of acetic acid. β-Cleavage between position 1′ and 2′ of the side chain of PCEEA and PCMEA

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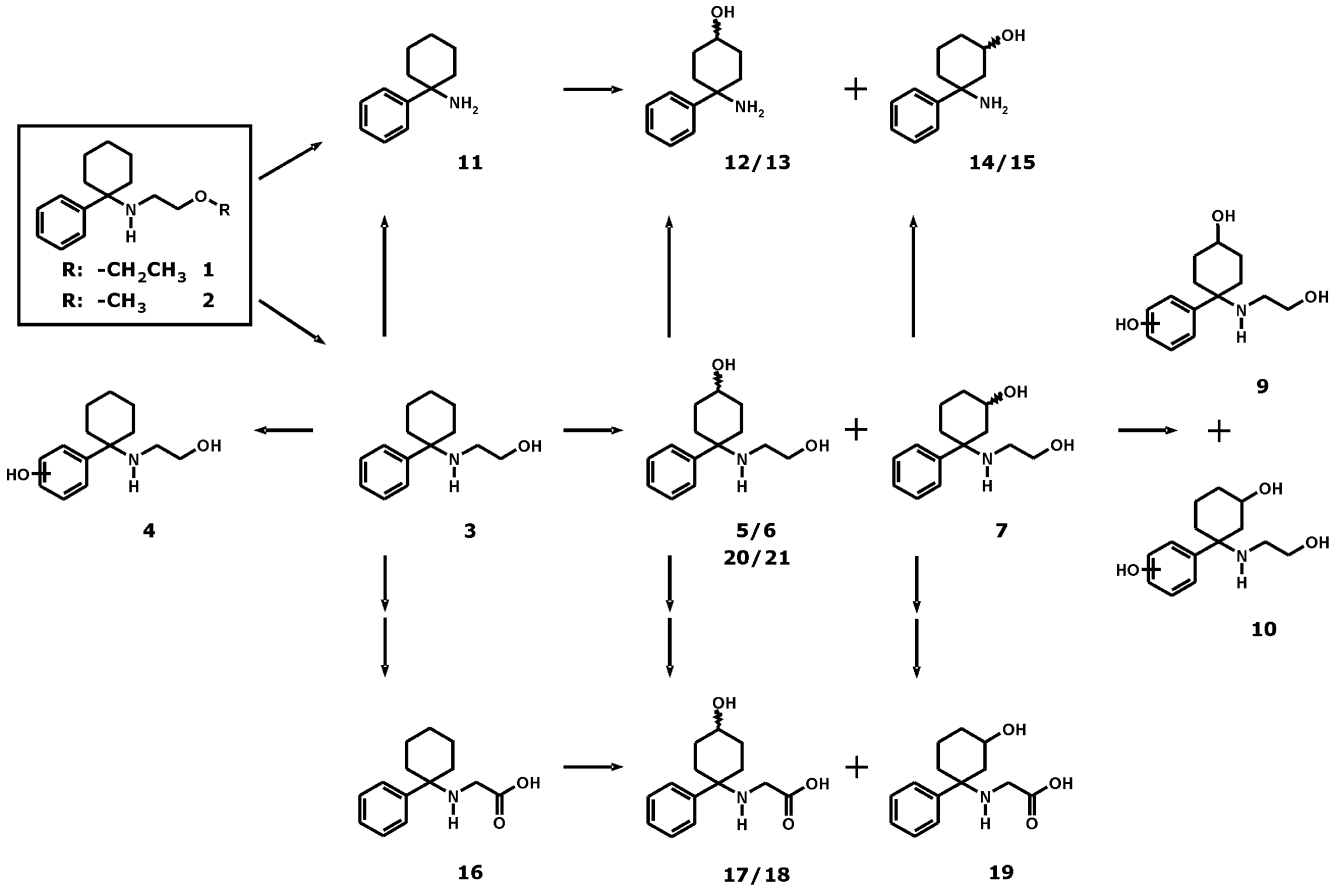

Figure 2. Metabolic pathways of PCEEA or PCMEA.

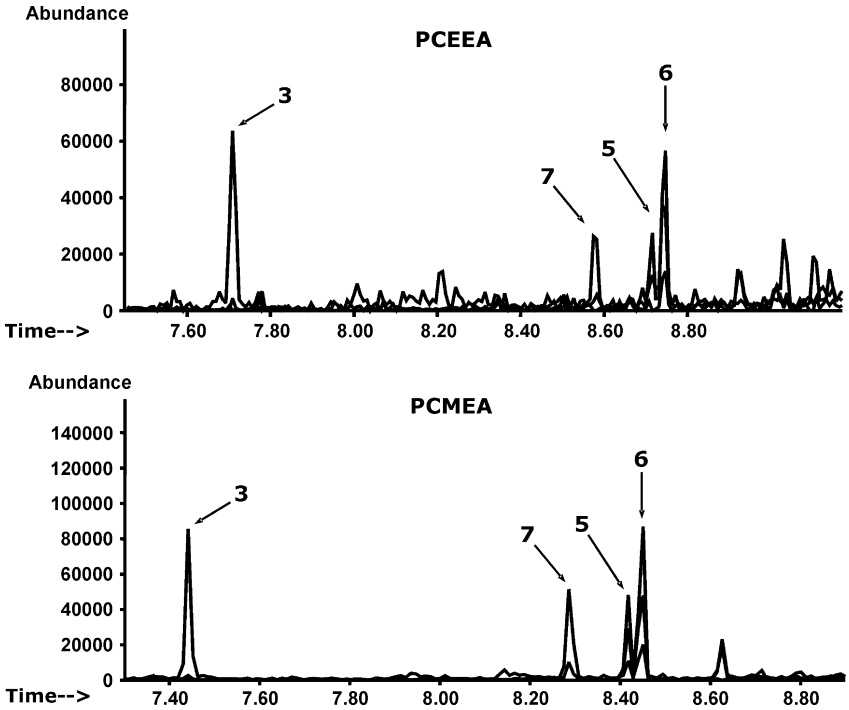

Figure 3. Typical reconstructed mass chromatograms with ions *m/z* 218, 259 and 260 of an acetylated extract of a rat urine sample collected over 24 h after application of 0.1 mg/kg BM of PCEEA (upper part) or PCMEA (lower part). The numbers of the peaks correspond to the respective spectra in Fig. 1.

led to fragment ion *m/z* 188 that was mainly observed for the parent compounds themselves. PCEEA, PCMEA and PCEPA formed identical *N*-dealkyl-metabolites, so elucidations to these metabolites can be found in literature.[5] Other expected metabolites were the carboxylic acids formed by oxidation of the respective *O*-dealkylated metabolites. In analogy to

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previous metabolism studies of the authors' working group, methylation and ethylation, alone and in combination with acetylation were performed.[21,22] This lead to derivatives, which were attributable likely to these expected carboxylic acids, but were also positional isomers of other metabolite derivatives. Since the observed fragmentation patterns were also quite similar, unambiguous attribution of certain metabolite structures through interpretation of the EI mass spectra was not possible, so that silylation experiments were performed for confirmation. In the following, possible fragmentation patterns of PCEEA and PCMEA metabolites after silylation will be discussed in relation to the postulated metabolite structures. However, this discussion will be limited to the mass spectra of those metabolites which provided additional structural information. Again, the numbers of the corresponding mass spectra in Fig. 1 are given in brackets. The main fragmentation patterns of the silylated *O*-dealkyl-carboxy metabolites were the same as described in the previous paragraphs and the respective fragment ions confirmed their structures. Cleavage between the nitrogen atom and the quaternary carbon atom of the phenylcyclohexyl double-ring system resulted in fragment ions m/z 159 in the case of carboxy PCEEA/PCMEA (16), m/z 157 in the case of metabolites hydroxylated at the cyclohexyl ring after loss of trimethylsilanol corresponding to 90 u (17–21). The benzyl-like cleavage led to the formation of tropylium ions with m/z 91 for metabolites with an unchanged phenyl ring (16, 17–21). Finally, β-cleavage of the cyclohexyl ring yielded fragment ions m/z 262 for metabolites with an unchanged (16), 3′- (19) or 4′-hydroxylated (17, 18) cyclohexyl ring.

A closer look at the structures of the 3′- and 4′-hydroxy metabolites shows that in both positions there is a possibility for *cis–trans* isomerism, as it was previously described for the corresponding metabolites of phencyclidine.[20] In the case of the 4′-hydroxylation, for each of the respective metabolites, two peaks with virtually identical mass spectra were detected in acetylated extracts. These were most likely attributable to corresponding *cis*- and *trans*- isomers. However, unambiguous assignment of the acetylated isomers to a certain peak was not possible via their mass spectra and therefore, the isomers are referred to as isomer 1 and isomer 2. In the silylated extracts, two peaks were also detected for each of the 4′-hydroxy metabolites, which could be determined as *cis*- and *trans*- isomers as discussed in detail for PCEPA.[5]

Postulated metabolic pathways

On the basis of the identified compounds, the following metabolic pathways, shown in Fig. 2 could be postulated: *N*-dealkylation, *O*-dealkylation partially followed by oxidation to the corresponding acid, hydroxylation of the cyclohexyl ring at different positions of *N*-dealkyl metabolites, *O*-dealkyl metabolites and of the corresponding acids, and finally aromatic hydroxylation of the *O*-dealkyl metabolites. All metabolites were partially excreted in conjugated forms.

Detection by GC/MS within the STA

The authors' STA procedure allowed the detection of an intake of a dose of PCEEA or PCMEA that corresponds to common drug users' doses[1] in urine. Figure 3 shows the typically reconstructed mass chromatograms with the ions m/z 218 for all the target metabolites, 259 for dealkyl-4′-hydroxy metabolites, and 260 for dealkyl-3′-hydroxy metabolites of an acetylated extract of a rat urine sample collected over 24 h after application of a single dose of 0.1 mg/kg BM of PCEEA (upper part) or PCMEA (lower part). They indicate *O*-dealkyl PCEEA/PCMEA (3), *O*-dealkyl-4′-hydroxy PCEEA/PCMEA isomer 1 (5), *O*-dealkyl-4′-hydroxy PCEEA/PCMEA isomer 2 (6), and *O*-dealkyl-3′-hydroxy PCEEA/PCMEA (7). Their identity was confirmed by a computerized comparison of the underlying mass spectrum with the reference spectra recorded during this study. As neither of the parent drugs could be detected after a common drug user's dose and as they formed identical urinary metabolites, a differentiation of their intake would not be possible unless the parent drugs or unique metabolites are present in the human urine in contrast to the rat urine.

CONCLUSIONS

The metabolism studies presented here showed that the designer drugs PCEEA and PCMEA were mainly metabolized by *O*-dealkylation, hydroxylation of the cyclohexyl ring in different positions, hydroxylation of the phenyl ring, oxidation to the carboxylic acid, *N*-dealkylation, and combinations of these steps.

The authors' experience in metabolism and analytical studies on rats and humans support the assumption that the metabolites found in rat urine should also be present in human urine.[10,23–26] Therefore, it can be concluded that the procedure described here should also be applicable for human urine screening for PCEEA and/or PCMEA in clinical or forensic cases. However, their differentiation would only be possible through detection of the respective parent drug or unique metabolites.

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