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Metabolism and toxicological detection of a new designer drug, *N*-(1-phenylcyclohexyl)propanamine, in rat urine using gas chromatography–mass spectrometry☆

Christoph Sauer[a], Frank T. Peters[a], Roland F. Staack[a], Giselher Fritschi[b], Hans H. Maurer[a,*]

[a] *Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, Saarland University, D-66421 Homburg (Saar), Germany*
[b] *Hessisches Landeskriminalamt, D-65187 Wiesbaden, Germany*

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Abstract

Studies are described on the metabolism and the toxicological detection of the phencyclidine-derived designer drug *N*-(1-phenylcyclohexyl)-propanamine (PCPR) in rat urine using gas chromatographic–mass spectrometric techniques. The identified metabolites indicated that PCPR was metabolized by hydroxylation of the cyclohexyl ring at different positions, hydroxylation of the phenyl ring, *N*-dealkylation, and combinations of these steps. Parts of the metabolites were 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 of PCPR in rat urine. Assuming similar metabolism in humans, the STA should be suitable for proof of an intake of PCPR in human urine.

Keywords: *N*-(1-Phenylcyclohexyl)-propanamine; PCPR; Metabolism; GC–MS; Urinalysis

1. Introduction

In the late 1990s, a considerable number of new synthetic drugs from various (new) drug classes were seized in the German federal state of Hesse and surrounding federal states. One of these substances was *N*-(1-phenylcyclohexyl)-propanamine (PCPR, structure depicted next to mass spectrum no. 1 in Fig. 1), a phencyclidine-derived compound. After a short time, further members of this new class of phencyclidine-derived designer drugs appeared on the illicit drug market, namely *N*-(1-phenylcyclohexyl)-3-methoxy-propanamine (PCMPA), *N*-(1-phenylcyclohexyl)-2-methoxy-ethanamine (PCMEA) and *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine (PCEEA). The seized preparations contained either one compound alone or in mixture with other designer drugs [1]. No information is available on pharmacological properties of these compounds. However, due to structural similarities the pharmacological properties might be assumed to be similar to those of phencyclidine or 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, a common metabolite of phencyclidine and metabolite of the above-mentioned phencyclidine-derived compounds, produced a long-lasting dose-dependent effect on the efflux of dopamine in rat [3]. 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. [4].

So far, studies on the metabolism and the toxicological detection have only been described for *N*-(1-phenylcyclohexyl)-3-ethoxypropanamine (PCEPA) [5]. Such studies are necessary for developing toxicological screening procedures in urine, especially if the drugs are excreted primarily or even exclusively in form of metabolites and for toxicological risk assessment, because the metabolites may play a major role in drug toxicity. Therefore, the aim of this study was to identify the metabolic pathways of PCPR using gas chromatography–mass spectrom-

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* Corresponding author. Tel.: +49 6841 16 26050; fax: +49 6841 16 26051.
E-mail address: hans.maurer@uniklinikum-saarland.de (H.H. Maurer).

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etry (GC–MS) with electron ionization (EI) and positive-ion chemical ionization (PICI) mode. In addition, the detectability of PCPR and its metabolites within the authors' systematic toxicological analysis (STA) procedure in urine by GC–MS [5–10] was studied.

2. Experimental

2.1. Chemicals and reagents

PCPR HCl was provided by the Hessisches Landeskriminalamt (Wiesbaden, Germany). *N*-Methyl-bis-trifluoroacetamide (MBTFA) was obtained from Fluka (Taufkirchen, Germany). Isolute Confirm HCX cartridges were obtained from Separtis (Grenzach-Wyhlen, Germany). All other chemicals and biochemicals were obtained from Merck (Darmstadt, Germany). All chemicals and biochemicals were of analytical grade.

2.2. 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).

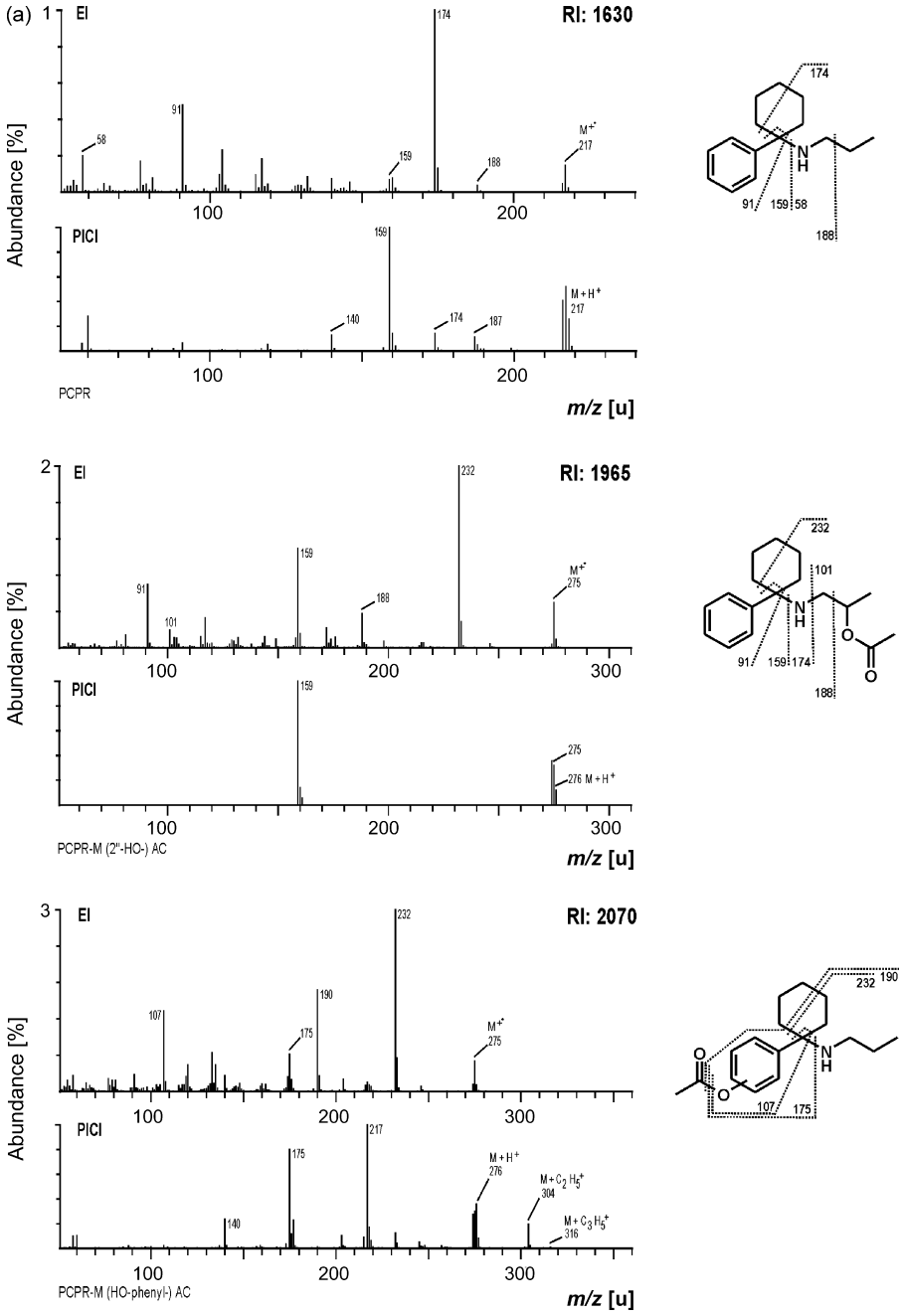


Fig. 1. EI and PICI mass spectra, *I*s, structures and predominant fragmentation patterns of PCPR and its metabolites after acetylation.

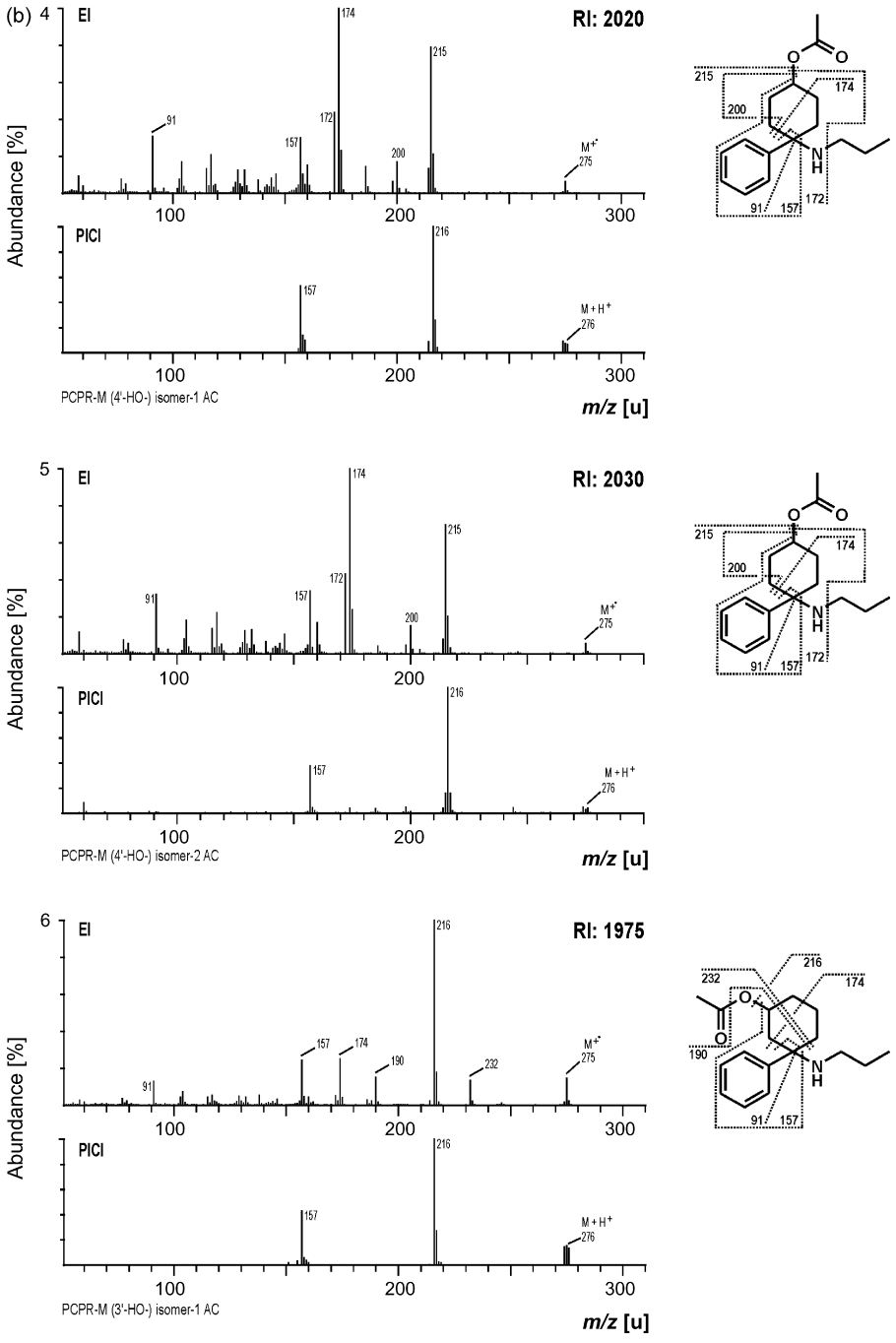


Fig. 1. (*Continued*)

Urine was collected separately from the faeces over a 24 h period. All samples were directly analyzed. Blank rat urine samples were collected before drug administration to check whether they were free of interfering compounds.

2.3. Sample preparation for identification of metabolites by GC–MS

A 3-ml portion of urine was adjusted to pH 5.2 with acetic acid (1 mol/l) and incubated at 50 °C for 1.5 h with 150 μl of a mixture (100 000 Fishman units per ml) of glucuronidase (EC no. 3.2.1.31) and arylsulfatase (EC no. 3.1.6.1) from *Helix pomatia* as described for PCEPA [5]. Then the urine sample was loaded on an Isolute Confirm HCX cartridge (130 mg, 3 ml), previously conditioned with 1 ml of methanol and 1 ml of water. After passage of the sample, the cartridge was washed with 1 ml of water, 1 ml of 0.01 M hydrochloric acid, and 2 ml of methanol. Elution was performed using 1 ml of a freshly prepared mixture of methanol/aqueous ammonia (98:2; v/v). The organic layer was carefully evaporated to dryness at 56 °C under a stream of nitrogen. The residue was derivatized by one of the following procedures. Acetylation was conducted with 100 μl of an

acetic anhydride-pyridine mixture (3:2; v/v) for 5 min under microwave irradiation at about 440 W. After careful evaporation of excess reagent, the residue was dissolved in 100 μl of methanol. Trifluoroacetylation was conducted with 100 μl of MBTFA for 5 min under microwave irradiation at about 440 W. After careful evaporation of excess reagent, the residue was dissolved in 100 μl of ethyl acetate. Aliquots (2 μl) of the acetylated or trifluoroacetylated extracts were injected into the GC–MS apparatus.

The same procedures with the exception of enzymatic hydrolysis were used to study whether the metabolites were excreted as glucuronide and/or sulfate conjugates. Furthermore, 1 ml of blank rat urine and 1 ml of rat urine containing 100 μl of a methanolic solution of PCPR (0.01 mg/ml) were worked up as described above and 2 μl each were injected into the GC–MS in order to detect possible artifacts.

2.4. Sample preparation for STA by GC–MS

The urine samples (5 ml) were divided into two aliquots. One aliquot was refluxed with 1 ml of 37% hydrochloric acid for 15 min [5,9]. Following hydrolysis, the sample was mixed with 2 ml of 2.3 M aqueous ammonium sulfate and 1.5 ml of 10 M aqueous sodium hydroxide to obtain a pH value of 8–9. Before extraction, the other aliquot of native urine was added. This mixture was extracted with 5 ml of a dichloromethane–isopropanol–ethyl acetate mixture (1:1:3; v/v/v). After phase separation by centrifugation, the organic layer was transferred into a glass flask and evaporated under reduced pressure at 70 °C to dryness. The residue was derivatized by acetylation with 100 μl of an acetic anhydride-pyridine mixture (3:2; v/v) for 5 min under microwave irradiation at about 440 W. After evaporation of the derivatization mixture

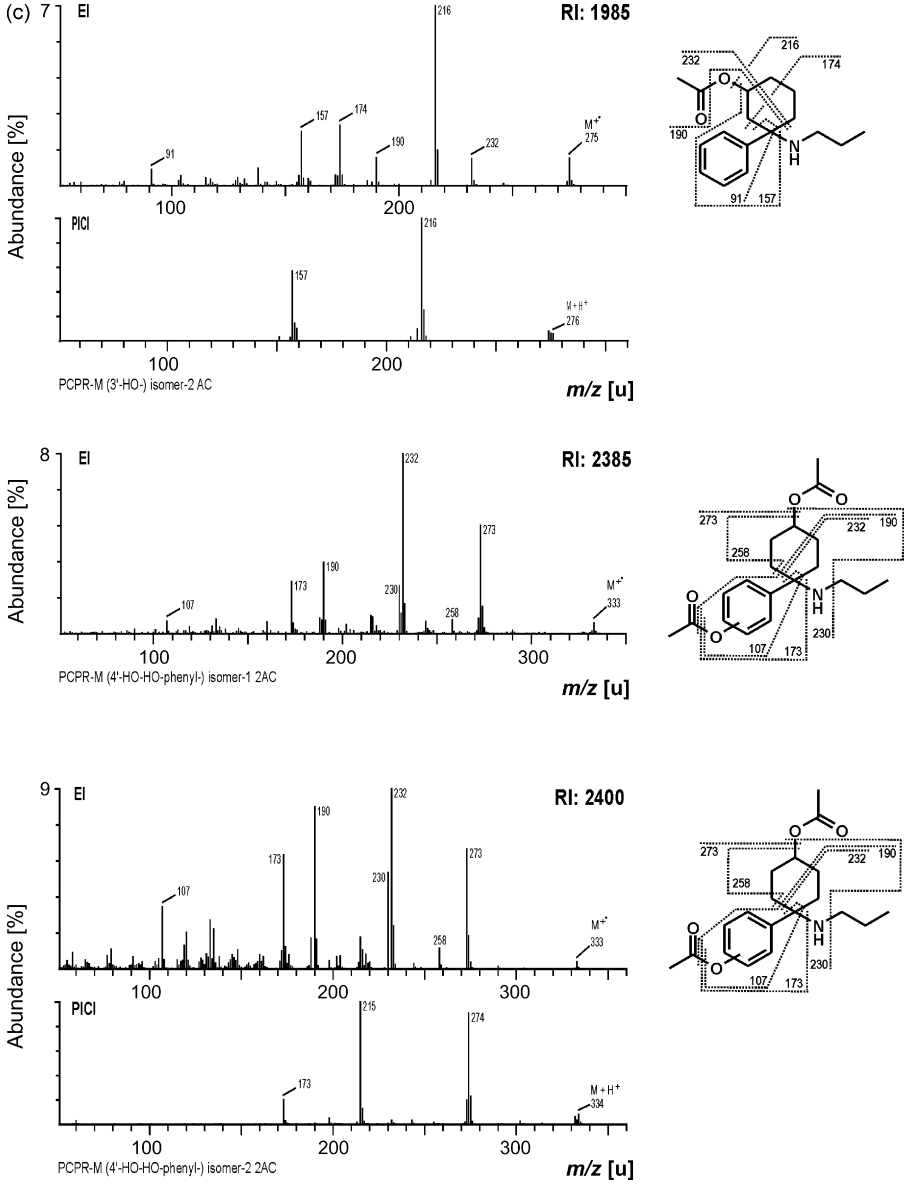


Fig. 1. (*Continued*)

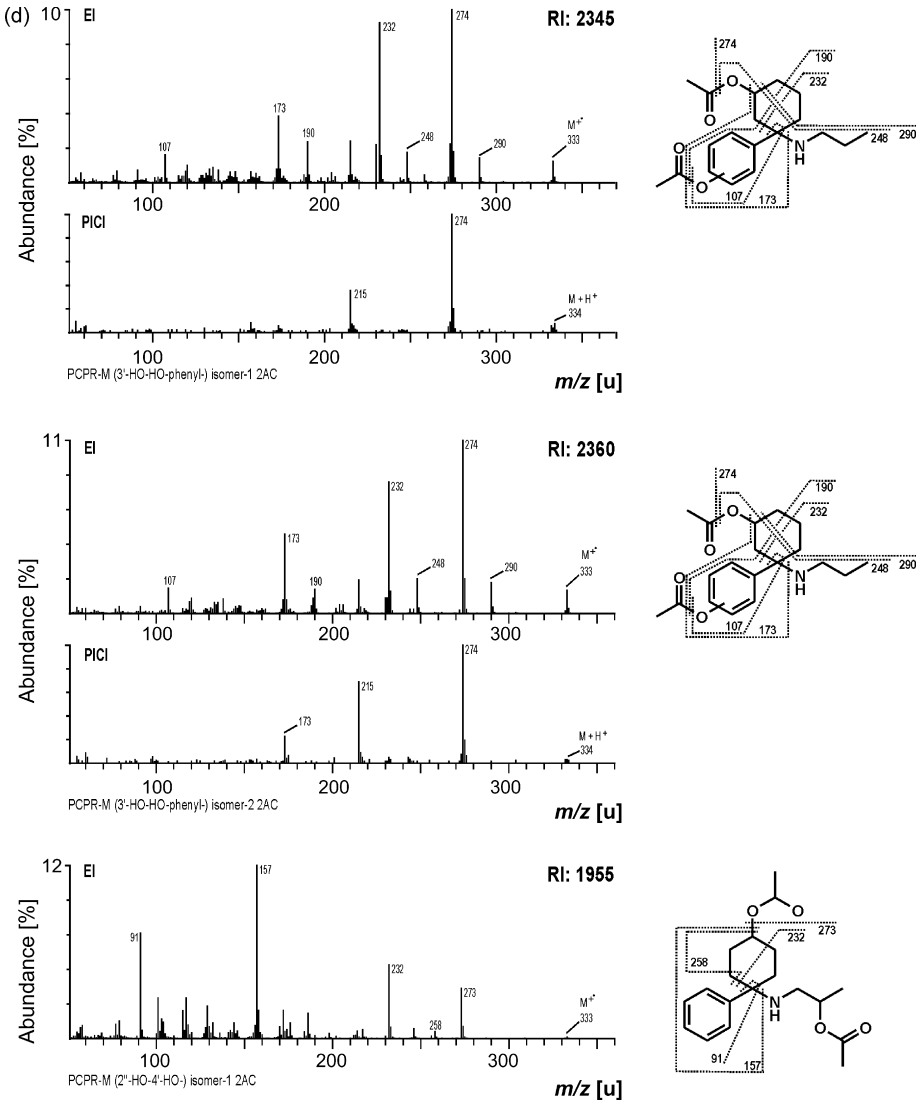


Fig. 1. (*Continued*)

under reduced pressure at 70 °C, the residue was dissolved in 100 μl of methanol and 2 μl were injected into the GC–MS apparatus.

2.5. GC–MS apparatus for identification of metabolites

The extracts were analyzed using a Hewlett-Packard (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-5 capillary (30 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.

2.6. GC–MS apparatus for STA

The extracts were analyzed using a Hewlett-Packard (Agilent) 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, programmed from 100–310 °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.

2.7. GC–MS procedure for identification of metabolites and STA by GC–MS

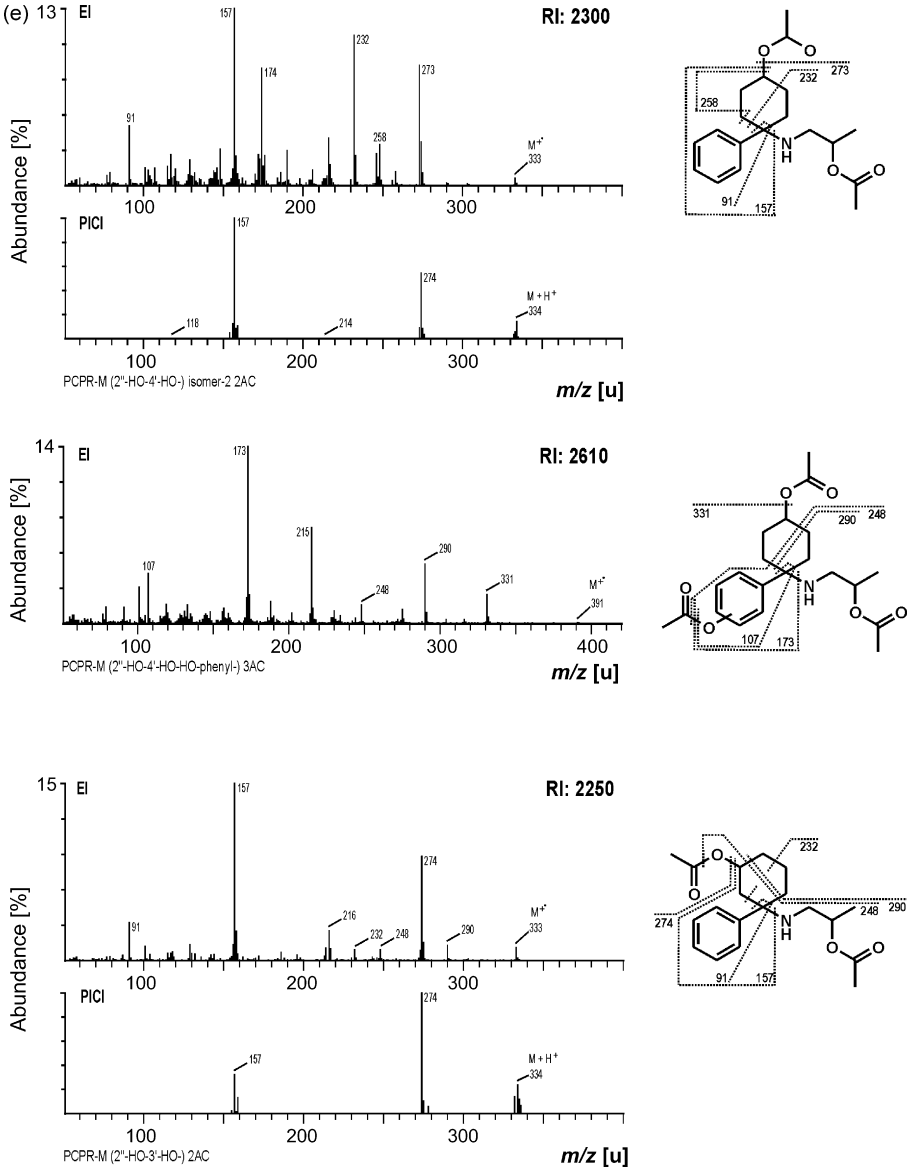
PCPR and its metabolites were separated by GC and identified by MS in the derivatized urine extracts. For toxicological detection of PCPR and its metabolites, mass chromatography was used extracting characteristic fragment ions of PCPR metabolites from the total ion current. The following ions were used for this purpose: *m/z* 156, 174, 232, and 273. 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 [11,12].

3. Result and discussion

3.1. Identification of the metabolites

The urinary metabolites of PCPR were separated by GC and identified by EI MS and PICI MS after gentle enzymatic hydrolysis, extraction, and derivatization. GC–MS was preferred to LC–MS due to the better separation power and the better structural information given by EI fragmentation in contrast to electrospray ionization. This was particularly relevant in this study because several isomers had to be differentiated. Finally, GC–MS is still the most often used technique for urine screening.

Gentle enzymatic cleavage of conjugates at elevated temperature (56 °C) for a short period of time (1.5 h) was necessary before extraction in order not to miss conjugated metabolites.



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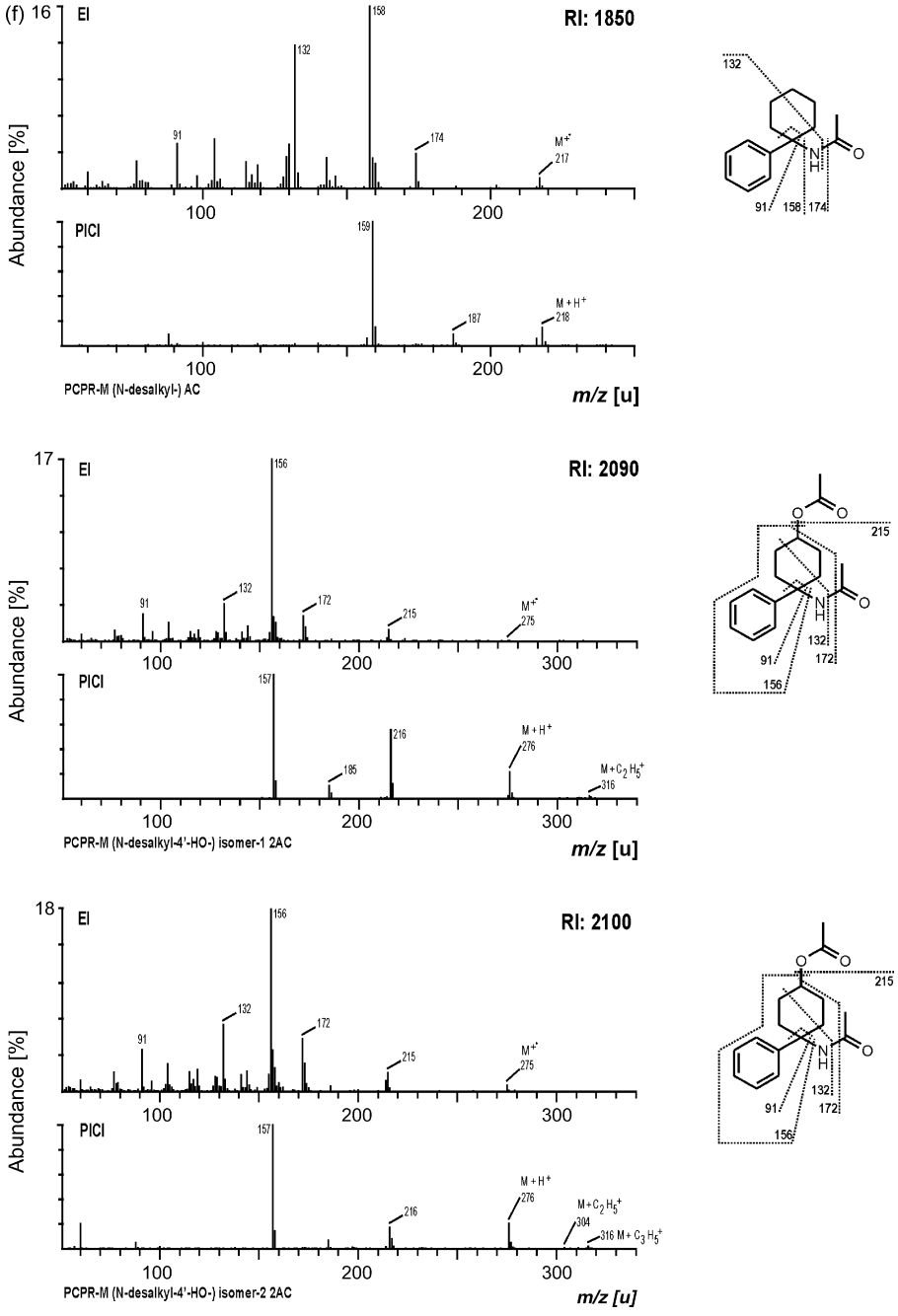

Fig. 1. (*Continued*)

The described mixed-mode solid phase extraction (SPE) had already been used successfully in metabolism studies of other designer drugs in the authors' laboratory [5,7,13–18]. It proved particularly applicable for extraction of basic and amphoteric metabolites and yielded clean extracts, facilitating detection and identification of metabolites. Regarding the structure of PCPR, its metabolites were expected to be either basic or amphoteric, therefore, SPE was preferred to our liquid-liquid extraction procedure under alkaline or acidic conditions [9,11,19–21].

Derivatization was needed to improve the GC properties of these relatively polar metabolites, thus increasing the sensitivity of their detection. Acetylation has proven useful in metabolism studies [9,11,19,21]. It can be employed for derivatization of primary and secondary amino groups as well as alcoholic and/or phenolic hydroxy groups. In the authors' experience, the fragmentation patterns of the resulting derivatives in the EI mode are also easy to interpret facilitating elucidation of metabolite structures [10,19,22–28]. Furthermore, acetylation is the standard derivatization step in the authors' STA. Therefore, the spectra of the acetylated metabolites are needed for the STA. It was observed that under the described conditions the parent drug and its secondary amine metabolites were only derivatized to a minor extent at the amine moiety. This phenomenon has already been observed for PCEPA parent compound [5]. It might be

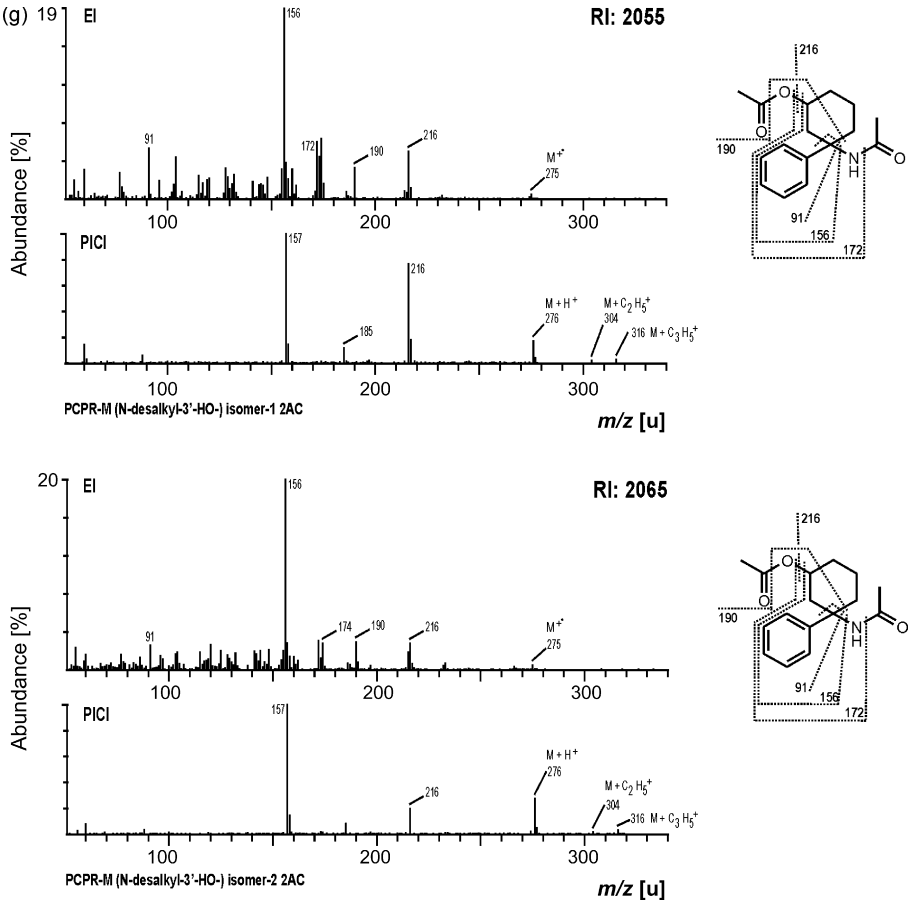

Fig. 1. (*Continued*).

explained by steric hindrance from the neighboring phenyl and cyclohexyl rings and from the side chain. A major extent of this effect could be observed for PCEPA. The side chain of PCEPA is able to form a six-membered ring stabilized by a hydrogen bond. As PCPR does not contain this structure this might explain why a greater extent of acetylation could be observed for PCPR as compared to PCEPA.

A disadvantage of using acetylation in metabolism studies is the problem that physiologically acetylated metabolites cannot be differentiated from acetyl derivatives. The presence of such physiologically acetylated metabolites was checked for in urine extracts after trifluoroacetylation. 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 compound which was described by Roesner at al. [1]. Interpretation of the fragments was performed according to the rules described by e.g. McLafferty and Turecek [29] and Smith and Busch [30]. The EI mass spectra, the retention indices (*I*), the structures and predominant fragmentation patterns of PCPR and its 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 half of them (nos. 1, 2, 4–16). Similar observations had been made in studies of the structurally related drug PCEPA [5]. This phenomenon can be partly explained by the structures of the respective compounds. As the adduct formation of PCEPA and its metabolites would be expected to take place mainly at the nitrogen atom of the amine moiety [5], the adduct formation is probably sterically hindered by the neighboring phenyl and cyclohexyl rings. An additional effect of steric hindrance might be caused by the hydroxylated side chain, because the above-mentioned adducts were absent in the PICI spectra of the corresponding metabolites (nos. 2, 12–15). A further possible effect of steric hindrance might be caused by the hydroxyl moieties at cyclohexyl ring. As the cyclohexyl ring is able to change its conformation, a hydrogen bond might be formed between the hydroxyl moiety at the cyclohexyl ring and the secondary amine. None of the at the cyclohexyl ring hydroxylated metabolites, but with an unchanged or hydroxylated side chain, showed the above mentioned adducts (nos. 4–7, 9–11, 13–15).

In the acetylated urine extract, PCPR and the following metabolites (and also some artifacts formed during GC injection) could be identified. The numbers of the spectra in Fig. 1 are given in brackets: PCPR (1), 2″-hydroxy-PCPR (2), hydroxyphenyl PCPR (3), 4′-hydroxy PCPR isomer 1 (4), 4′-hydroxy PCPR isomer 2 (5), 3′-hydroxy PCPR isomer 1 (6), 3′-hydroxy

PCPR isomer 2 (7), 4′-hydroxy-hydroxyphenyl PCPR isomer 1 (8), 4′-hydroxy-hydroxyphenyl PCPR isomer 2 (9), 3′-hydroxy-hydroxyphenyl PCPR isomer 1 (10), 3′-hydroxy-hydroxyphenyl PCPR isomer 2 (11), 2″-hydroxy-4′-hydroxy PCPR isomer 1 (12), 2″-hydroxy-4′-hydroxy PCPR isomer 2 (13), 2″-hydroxy-4′-hydroxy-hydroxyphenyl PCPR (14), 2″-hydroxy-3′-hydroxy PCPR (15), *N*-dealkyl PCPR (16), *N*-dealkyl-4′-hydroxy PCPR isomer 1 (17), *N*-dealkyl-4′-hydroxy PCPR isomer 2 (18), *N*-dealkyl-3′-hydroxy PCPR isomer 1 (19) and *N*-dealkyl-3′-hydroxy PCPR isomer 2 (20).

3.2. Proposed fragmentation patterns

Fragmentation patterns of PCEPA and its metabolites have been described in detail by Sauer at al. [5]. Fragmentation patterns of PCPR and its derivatized metabolites are depicted in Fig. 1. The numbers of the corresponding mass spectra in Fig. 1 are given in brackets. PCPR (1) and its metabolites with an unchanged double ring system showed the fragment ion *m/z* 159 (1, 2) as depicted in Fig. 2, pattern A, cleavage I, or 158 for those with amide structure (16). Fragmentation patterns of the amide structures have been described by Sauer et al. [5]. The hydroxyphenyl metabolite (3) showed a respective fragment ion *m/z* 175 after further neutral loss of the acetyl moiety (Fig. 2A, I) while 3′- and 4′-hydroxy metabolites showed a fragment *m/z* 157 (Fig. 2B and C, I) resulting from elimination of acetic acid (4–7, 12, 13, 15) or *m/z* 156 for those with amide structure (17–20). Accordingly, a fragment ion *m/z* 173 was observed for metabolites hydroxylated at both rings (8–11) (Fig. 2B and C, I). Benzyl-like cleavage of PCPR and all of its metabolites led to formation of the tropylium ion *m/z* 91 for all compounds with an unchanged aromatic ring (1, 2, 4–7, 12, 13, 15–20) and to a corresponding fragment ion *m/z* 107 for the respective hydroxyphenyl metabolites (3, 8–11, 14) after loss of the respective acetyl moiety (Fig. 2A–C, II). PCPR (1) and all of its metabolites containing a secondary amine but no hydroxy group at the cyclohexyl ring showed a loss of 43 (Fig. 2A, III) leading to fragment ions *m/z* 174 (1) and *m/z* 232 (2, 3). In case of the 3′-hydroxy metabolites (6, 7, 10, 11, 15), two different positions of the β-cleavage were possible: on the one hand, an acetylated enol immonium cation with *m/z* 232 (6,7) and *m/z* 290 (10, 11, 15) was formed by the above-mentioned loss of 43 u (Fig. 2B, IV). This could be followed by an α-cleavage resulting in a neutral loss of the acetyl moiety corresponding to 42 u (Fig. 2B, V) and formation of an enol immonium cation *m/z* 190 (6, 7) and *m/z* 248 (10, 11, 15). 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 (Fig. 2B, VI, VII) resulting in fragment ions *m/z* 216 (6, 7) and *m/z* 274 (10, 11, 15). β-Cleavage between position 1′ and 2′ followed by an cleavage between position 3′ and 4′ led to a neutral loss of 101 u (Fig. 2B, III) leading to fragment ion *m/z* 174 (6, 7) and *m/z* 232 (10, 11, 15). In case of the 4′-hydroxy metabolites (4, 5, 8, 9, 12–14), β-cleavage between positions 1′ and 2′ or between 1′ and 6′ followed by a cleavage between position 3′ and 4′ or position 4′ and 5′ led to neutral loss of 101 u (Fig. 2C, III) and formation of fragment ions *m/z* 174 (4, 5), *m/z* 232 (8, 9, 12, 13), and *m/z* 290 (14), respectively. Another important fragmentation pattern of the 4′-hydroxy metabolites was the elimination of acetic acid resulting in a loss of 60 u (Fig. 2C, VIII) and formation of fragment ions *m/z* 215 (4, 5), *m/z* 273 (8, 9, 12, 13), or *m/z* 331(14). As described for other cyclohexenyl rings [29,30], this was followed by loss of a methyl radical from the cyclohexyl ring leading to fragment ions *m/z* 200 (4, 5) and *m/z* 258 (8, 9, 12, 13) (Fig. 2C, IX). Similar differentiation of isomeric hydroxycyclohexyl metabolites has already been described for phencyclidine [31,32].

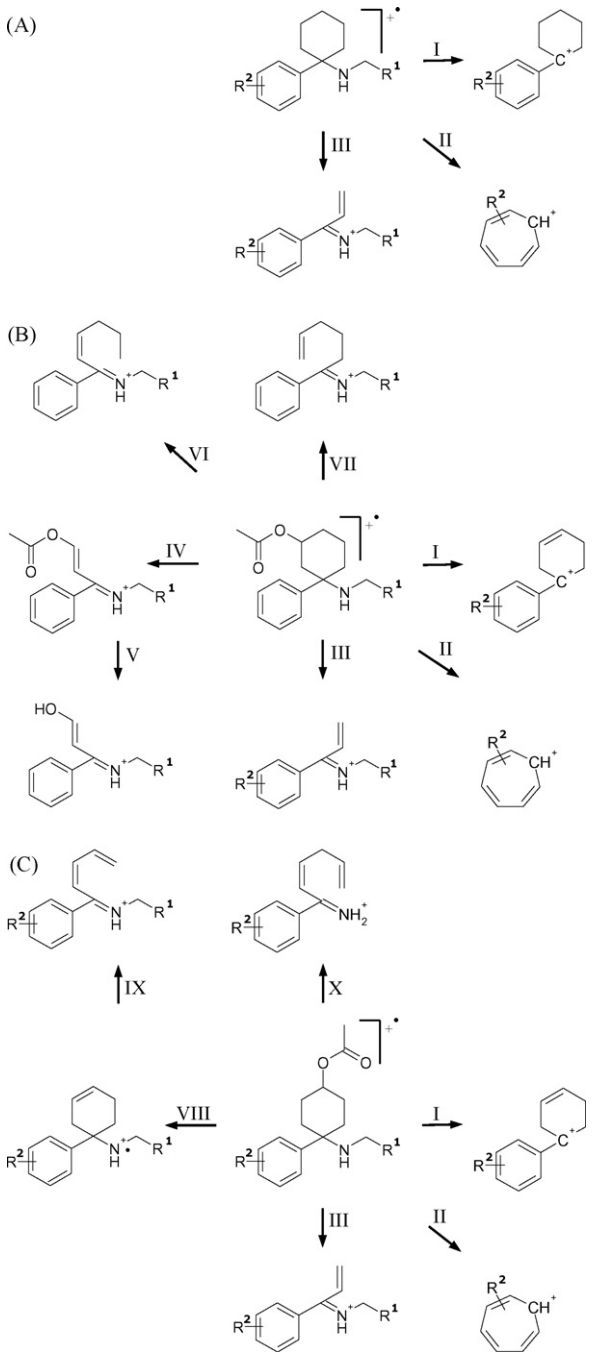

Fig. 2. Proposed fragmentations characterizing the different metabolites (the numbers correspond to the respective spectra in Fig. 1).

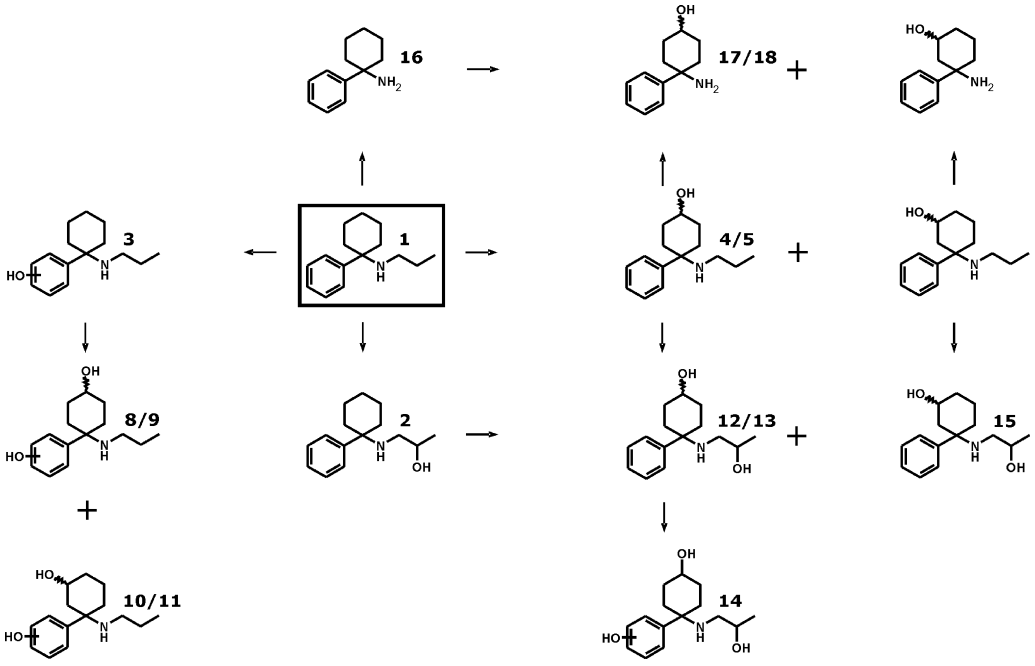

Fig. 3. Metabolic pathways of PCPR (the numbers correspond to the respective metabolites in Fig. 1).

In case of 4′-hydroxy metabolites with an unchanged side chain, a cleavage between the nitrogen and position one of the side chain followed by a loss of acetic acid (Fig. 2C, X) led to fragment ions *m/z* 172 (4, 5) and *m/z* 230 (8, 9). β-Cleavage between position 1″ and 2″ of the side chain of PCPR led to fragment ion *m/z* 188 that was mainly observed for the parent compound itself. As the *N*-dealkyl-metabolites of PCPR are the same as formed by PCEPA, the interpretation of their mass spectra can be found in ref. [5].

Metabolites hydroxylated at the side chain are postulated to be hydroxylated in ω-1 position. In contrast, the *O*-deethyl metabolites of PCEPA carry the hydroxyl moiety at the ω-position of the side chain. The mass spectra of the respective *O*-deethyl metabolites of PCEPA and the postulated ω-1 hydroxy metabolites of PCPR were compared. Their fragmentation patterns as well as the GC retention were different. As hydroxylation next to the nitrogen can be excluded because this would result in an *N*-dealkylation, hydroxylation only in ω-1 position should explain the differences of the above mentioned mass spectra.

3.3. Proposed metabolic pathways

Based on the identified compounds, the following metabolic pathways, shown in Fig. 3 could be postulated: *N*-dealkylation (16), hydroxylation of the cyclohexyl ring at different positions (4–7), of the aromatic system (3) and of the side chain (2). Furthermore, combinations of the different possibilities of hydroxylation of the cyclohexyl ring, the aromatic system and the side chain could be identified (8–15, 17–20). Comparison of enzymatically cleaved and non-enzymatically cleaved portions of rat urine indicated that almost all non-*N*-dealkylated metabolites were excreted in conjugated form.

3.4. Detection by GC–MS within the STA

The authors' STA procedure allowed the detection of an intake of a dose of PCPR that corresponds to a common drug users' dose in urine. Fig. 4 shows typical reconstructed mass chromatograms with the ions *m/z* 156, 174, 232, and 273 an acetylated extract of a rat urine sample collected over 24 h after

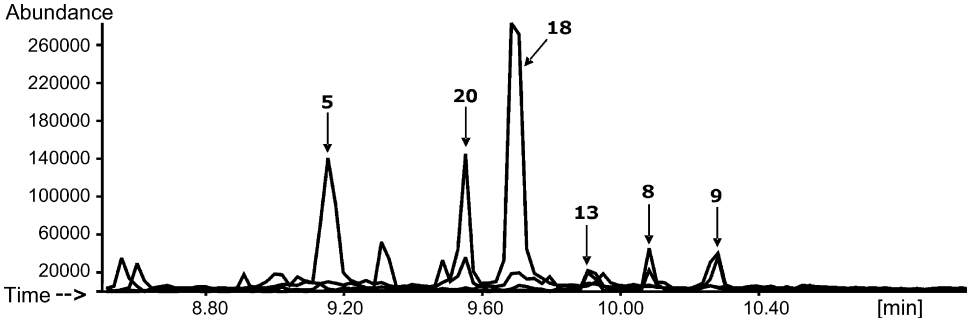

Fig. 4. Typical reconstructed mass chromatograms with ions *m/z* 156, 174, 232, and 273 of an acetylated extract of a rat urine sample collected over 24 h after application of 0.1 mg/kg BM of PCPR corresponding to a common drug users' dose (the numbers of the peaks correspond to the respective spectra in Fig. 1).

application of a single dose of 0.1 mg/kg BM of PCPR which corresponded to a dose of about 7 mg corresponding to that of seized tablets containing other phencyclidine derivatives. They indicate 4′-hydroxy PCPR isomer 2 (5), 4′-hydroxy-hydroxyphenyl PCPR isomer 1 (8), 4′-hydroxy-hydroxyphenyl PCPR isomer 2 (9), 2″-hydroxy-4′-hydroxy PCPR isomer 2 (13), *N*-dealkyl-4′-hydroxy PCPR isomer 2 (18). Their identity was confirmed by computerized comparison of the underlying mass spectrum with the reference spectra recorded during this study.

4. Conclusions

The metabolism studies presented here showed that the designer drug PCPR was mainly metabolized by hydroxylation of the cyclohexyl ring in different positions, hydroxylation of the phenyl ring, *N*-dealkylation, and combinations of these steps. As other studies have shown [6,19,33–35], it can be assumed that the metabolites found in rat urine should also be present in human urine. Therefore, it can be concluded that the procedure should also be applicable for human urine screening for PCPR in clinical or forensic cases (Fig. 4).

Acknowledgements

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