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Metabolism and toxicological detection of the new designer drug 4′-methoxy-α-pyrrolidinopropiophenone studied in rat urine using gas chromatography–mass spectrometry

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Abstract

R,S-4′-Methoxy-α-pyrrolidinopropiophenone (MOPPP) is a new designer drug with assumed amphetamine-like effects, which has appeared on the illicit drug market. The aim of this study was to identify the MOPPP metabolites using solid-phase extraction, ethylation or acetylation as well as to develop a toxicological detection procedure in urine using solid-phase extraction, trimethylsilylation and GC–MS. Analysis of urine samples of rats treated with MOPPP revealed that MOPPP [limit of detection (*S*/*N* 3) was 100 ng/ml] was completely metabolized by demethylation of the methoxy group, hydroxylation of the pyrrolidine ring with subsequent dehydrogenation to the corresponding lactam and/or oxidative desamination to the corresponding diketo compounds. To some extent, the demethylated MOPPP metabolites were hydroxylated with partial subsequent methylation in position 3′. The hydroxy groups were found to be partly conjugated. Based on these data, MOPPP could be detected in urine via its metabolites by full-scan GC–MS using MS for screening and library search for identification by comparison of the spectra with reference spectra.

Keywords: Designer drug; Metabolism; Toxicological detection; 4′-Methoxy-α-pyrrolidinopropiophenone

1. Introduction

α-Pyrrolidinophenone derivatives like *R,S*-α-pyrrolidinopropiophenone (PPP), *R,S*-4′-methyl-α-pyrrolidinopropiophenone (MPPP), *R,S*-4′-methyl-α-pyrrolidinohexanophenone (MPHP), *R,S*-4′-methoxy-α-pyrrolidinopropiophenone (MOPPP) and *R,S*-3′,4′-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) are new designer drugs which have appeared on the illicit drug market [1–5] and are distributed among drug abusers in tablet form. As the pyrrolidinophenones cannot be detected with usual routine analysis procedures, statements on the frequency of their occurrence cannot be made. Meanwhile, most of these substances are scheduled in the German Controlled Substances Act and possession is strictly prohibited. So far, little information about the dosage as well as the pharmacological and toxicological effects of the pyrrolidinophenones is avail-

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able. The chemical structures of all the α-pyrrolidinophenones are closely related to α-aminopropiophenone anorectics like amfepramone, drugs of abuse like cathinone/methcathinone and antidepressants like bupropion and might therefore evoke similar effects including dopamine release and sympathomimetic properties [6–9]. The metabolism and toxicological detection of MPPP and MPHP have already been described [4,5], but not yet that of MOPPP. However, the knowledge about metabolic steps is a prerequisite for toxicological risk assessment and for developing screening procedures for toxicological detection, as in both cases the metabolites may play a major role. So far, determination or screening procedures for MOPPP and/or its metabolites have not yet been published, although such procedures are necessary for confirmation of the diagnosis of an intoxication or drug abuse.

The aim of the presented study was firstly to identify the MOPPP metabolites in rat urine using gas chromatography–mass spectrometry (GC–MS) in the electron impact (EI) and positive-ion chemical ionization (PICI) modes and secondly to develop a toxicological screening procedure based on the identified metabolites using EI GC–MS.

2. Experimental

2.1. Chemicals and reagents

All chemicals used were obtained from E. Merck (Darmstadt, Germany) and were of analytical grade. *R,S*-MOPPP-HCl was provided from Hessisches Landeskriminalamt (Wiesbaden, Germany) for research purposes.

2.2. Urine samples

The investigations were performed using male rats (Wistar, Ch. River, Sulzfleck, Germany) which were administered a single 20 mg/kg body mass dose (for metabolism studies) or a 1 mg/kg body mass dose (for development of the screening procedure) of MOPPP in an aqueous suspension by gastric intubation. Urine was collected separately from the feces over a 24-h period. All samples were directly analyzed and then stored at −20 °C until further analysis. Blank urine samples were collected before drug administration to check whether the samples were free of interfering compounds.

2.3. Sample preparation for metabolism studies

A 0.5-ml portion of urine was adjusted to pH 5.2 with acetic acid (1 *M*) and incubated at 37 °C for 12 h with 50 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). The urine sample was then diluted with 2.5 ml of water and 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 and 1 ml of 0.01 *M* hydrochloric acid. The retained non-basic compounds were first eluted into a 1.5-ml reaction vial with 1 ml of methanol (fraction 1), whereas the basic compounds were eluted in a second step into a different vial with 1 ml of a freshly prepared mixture of methanol–aqueous ammonia (98:2, v/v, fraction 2). The eluates were gently evaporated to dryness under a stream of nitrogen at 56 °C and derivatized by ethylation or acetylation according to published procedures (Refs. [4] or [10]). Briefly, ethylation was performed after reconstitution in 50 μl of methanol with 50 μl of a solution of diazoethane in diethyl ether, synthesized according to the procedure of McKay et al. [11], the reaction vials were sealed and left at room temperature for 8 h. Thereafter, the mixture was once again gently evaporated to dryness under a stream of nitrogen, redissolved in 100 μl of methanol. Acetylation was conducted with 100 μl of an acetic anhydride–pyridine (3:2, v/v) mixture for 5 min under microwave irradiation at about 440 W [10,12–14]. After evaporation, the residue was dissolved in 100 μl of methanol. A 3-μl aliquot each was injected into the GC–MS system. The same procedure was repeated without the use of enzymatic hydrolysis to study which metabolites of MOPPP are excreted as glucuronides and/or sulfates.

2.4. Sample preparation for toxicological analysis

A 0.5 ml portion of urine was adjusted to pH 5.2 with acetic acid (1 *M*) and incubated at 56 °C for 1 h with 50 μl of a mixture of glucuronidase and

arylsulfatase (same as used in Section 2.3). This sample was diluted with 2.5 ml of water and 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 1 ml of methanol. The retained compounds were then eluted into a 1.5 ml reaction vial with 1 ml of a freshly prepared mixture of methanol–aqueous ammonia (98:2, v/v). The eluate was gently evaporated to dryness under a stream of nitrogen at 56 °C and then reconstituted in 50 μl of ethyl acetate and trimethylsilylated after addition of 50 μl *N*-methyl-*N*-trimethylsilyl-trifluoroacetamide (MSTFA) for 5 min under microwave irradiation at 440 W. A 2-μl aliquot of this mixture was injected into the GC–MS system with an alcohol- and water-free syringe.

2.5. Gas chromatography–mass spectrometry

The MOPPP metabolites were separated and identified in derivatized urine extracts 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. The GC conditions were as follows: splitless injection mode; column, HP-1 capillary (12 m×0.2 mm I.D.), crosslinked methylsilicone, 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 °C/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; chemical ionization using methane, PICI mode: ionization energy, 230 eV; ion source temperature, 220 °C; capillary direct interface heated at 260 °C.

For toxicological detection of MOPPP and its trimethylsilylated metabolites, MS with the selected ions *m/z* 98, 112, 135 and 193 was used. Generation of the mass chromatograms could be started by clicking the corresponding pull down menu which executes the user defined macros [15]. The identity of the peaks in the mass chromatograms was confirmed by computerized comparison [16] of the mass spectra underlying the peaks (after background subtraction) with reference spectra (Fig. 1, mass spectra 1, 5 and 8–10 and Ref. [16]) recorded during this study.

3. Results and discussion

3.1. Sample preparation

Cleavage of conjugates by gentle enzymatic hydrolysis was necessary before extraction and GC–MS analysis of the suspected metabolites in order not to overlook conjugated metabolites. As usual for routine screening procedures, incubation was performed at a higher temperature and for a shorter time in contrast to metabolism studies, in which an almost complete cleavage can be achieved and temperature stress can be avoided. The use of common liquid–liquid extraction under alkaline conditions followed by acetylation [10,13,17–19] was not appropriate, because the majority of the metabolites showed zwitterionic properties. Even MOPPP itself was only poorly extractable under the liquid–liquid extraction procedure applied (pH 8–9, ethyl acetate–isopropanol–dichloromethane, 3:1:1, v/v). In addition, volatility of the free bases and the instability of the analytes under alkaline and high temperature conditions caused difficulties [20,21]. In contrast, solid-phase extraction (SPE) demonstrated acceptable results due to mixed-mode SPE's ability to extract zwitterionic compounds [5].

Derivatization was needed for sensitive detection of metabolites after administration of lower drug doses. For metabolism studies, acetylation has been shown to be preferred for derivatization of metabolites with primary and secondary amino groups as well as of alcoholic and/or phenolic hydroxy groups [17,22,23]. Ethylation was preferred for derivatization of metabolites with phenolic hydroxy and/or vinylogous carboxy groups [4]. In addition, ethylation by diazoethane has the further advantage that phenolic hydroxy groups can be derivatized without affecting alcoholic groups, thereby allowing a distinction between both types of hydroxy groups. Moreover, ethylation is favored over diazomethane methylation, allowing a distinction between metabolic methylation and derivatization. These procedures for sample preparation, extraction and derivatization

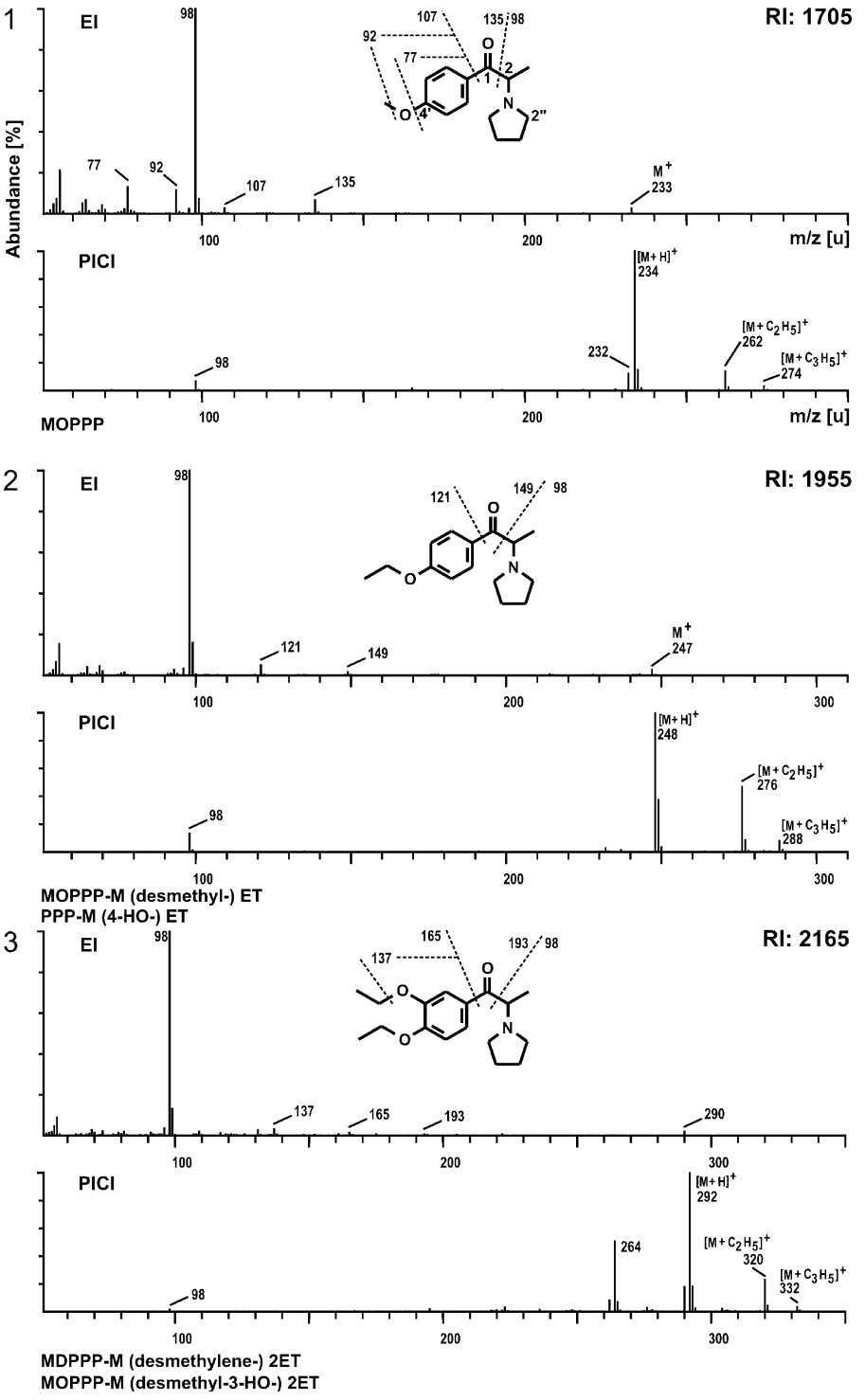


Fig. 1. EI and PICI mass spectra, the gas chromatographic retention indices (RIs), structures and predominant fragmentation patterns of MOPPP and its metabolites after ethylation or trimethylsilylation. The axes are only labelled for 1.

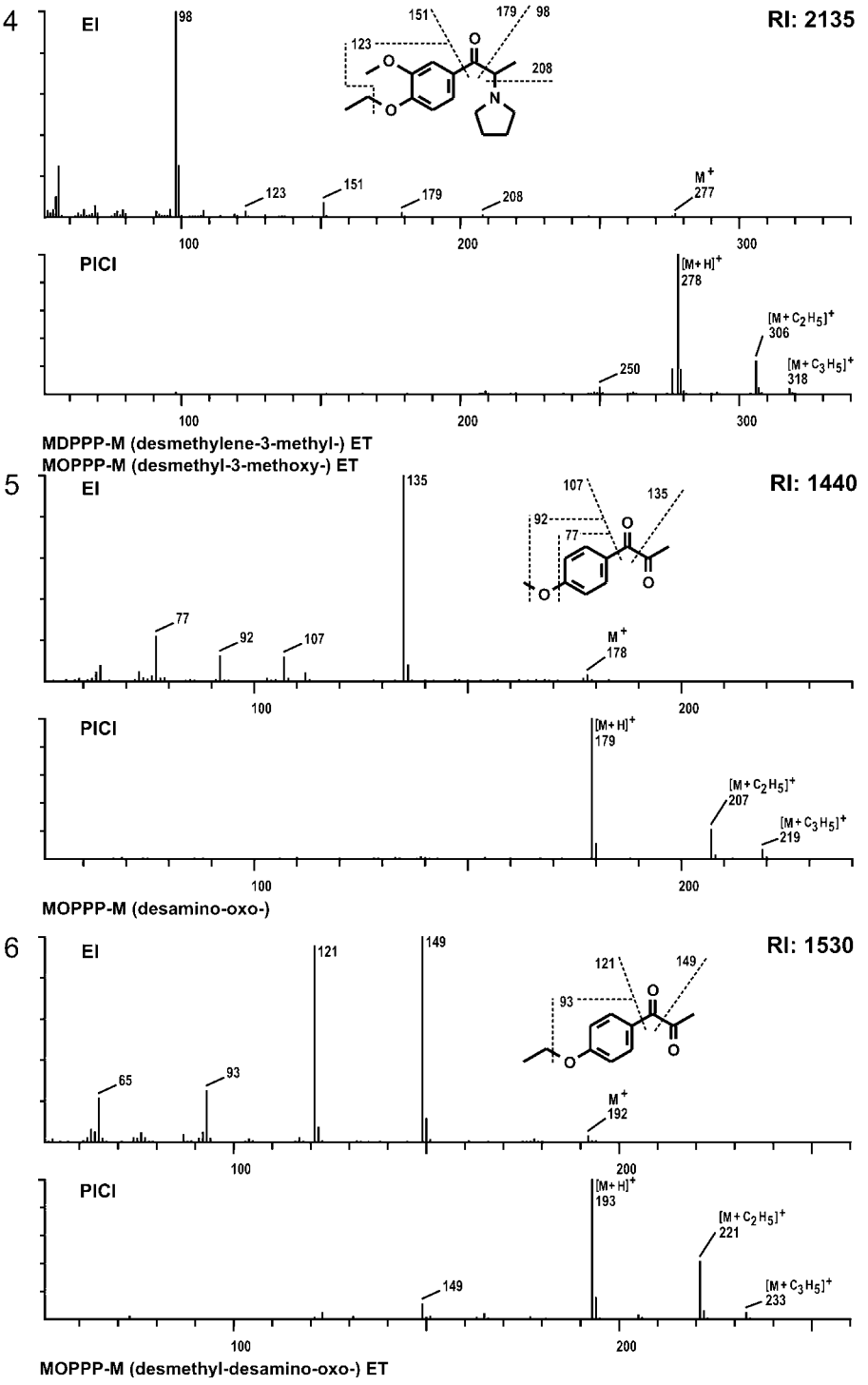
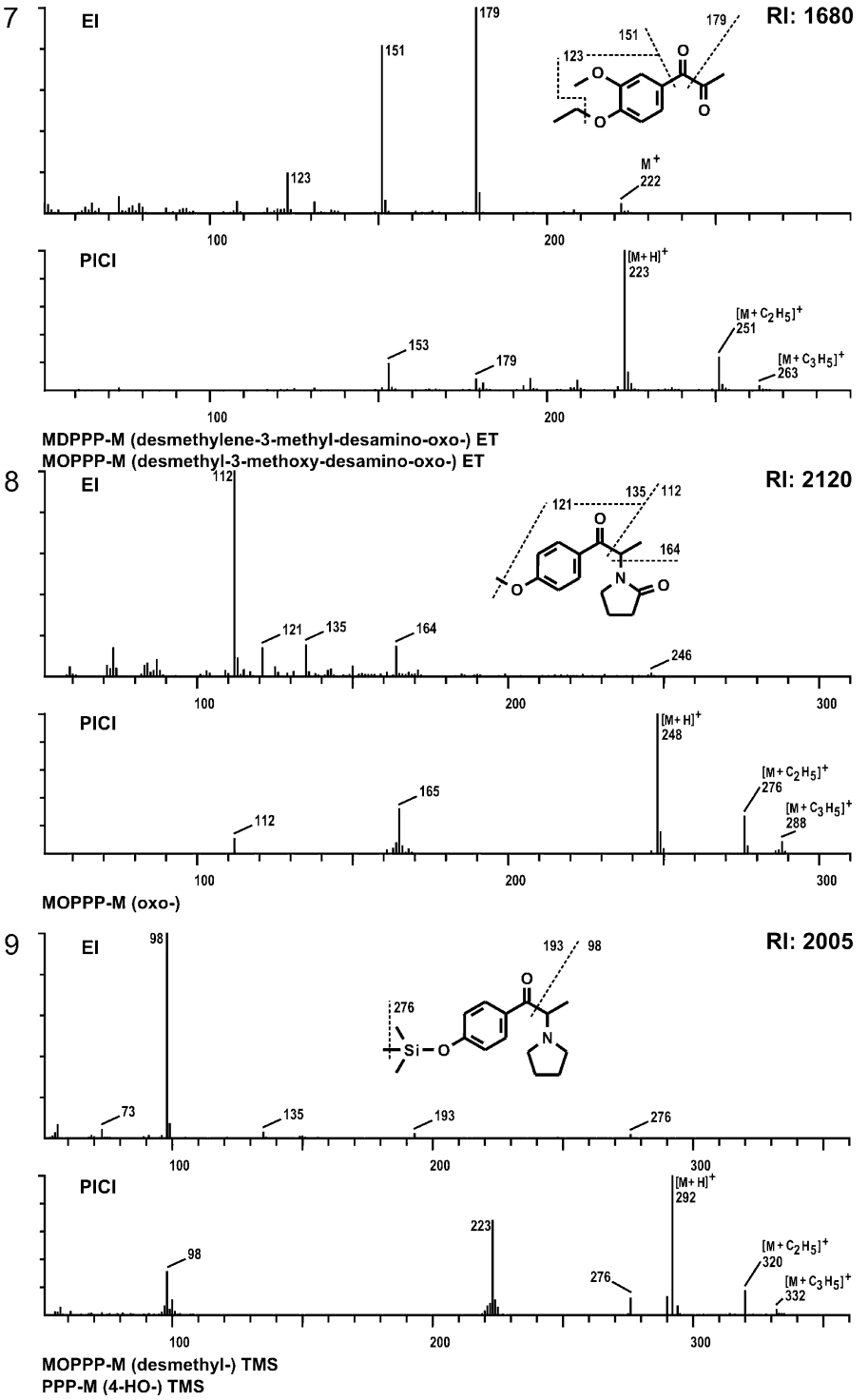


Fig. 1. (*continued*)



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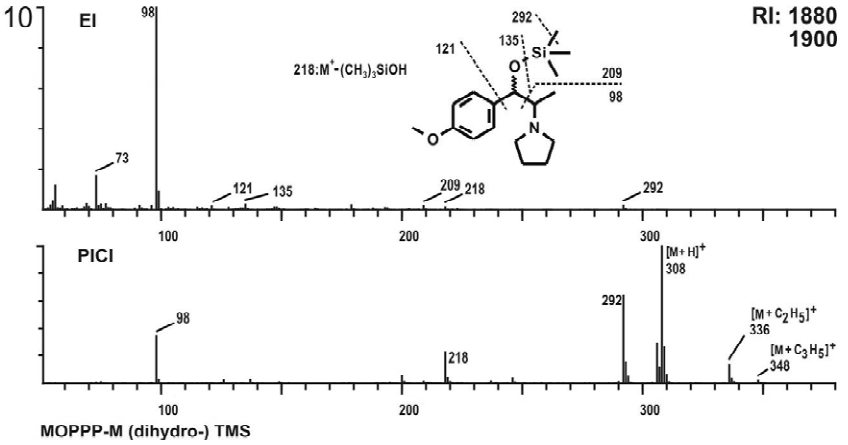

Fig. 1. (*continued*)

have proven to be appropriate for metabolism studies of other pyrrolidinophenone-type designer drugs [4,5].

However, for the toxicological detection procedure, common trimethylsilylation was preferred. In routine work, trimethylsilylation is safer and easier to handle and the reagent is commercially available. All expected target analytes in urine after intake of MOPPP showed good GC properties after trimethylsilylation.

3.2. Identification of metabolites

The urinary metabolites of MOPPP were identified by EI- and PICI-MS after GC separation. The postulated structures of the metabolites were deduced from the fragments detected in the EI mode which were interpreted in correlation to those of the parent compound according to the rules described by, e.g., McLafferty and Turecek [24] or Smith and Busch [25]. In order to verify the molecular mass of the postulated metabolites, PICI mass spectra were recorded, because they contain strong molecular peaks (M+H), in contrast to the EI spectra. In addition, adduct ions are produced typical for PICI using methane as reagent gas.

EI and PICI mass spectra, the gas chromatographic retention indices (RIs), structures and predominant fragmentation patterns of MOPPP and its ethylated or trimethylsilylated metabolites are shown in Fig. 1. No acetylated metabolites were detected, indicating that no primary (i.e., double dealkylation of the pyrrolidine ring) or secondary amines (i.e., ring opening of the pyrrolidine ring) were created. *O*-demethylation of MOPPP leads to the formation of a vinylogous carboxylic acid. Consequently, these metabolites could not be acetylated either. Only one mass spectrum of the diastereomeric compounds (mass spectrum 10) is depicted, as their spectra are very similar, so that one can be used for identification of both peaks considering the given two different retention indices.

The following metabolites of MOPPP (mass spectrum 1 in Fig. 1) could be identified after high dose application: 4′-hydroxy-PPP (mass spectrum 2), 3′,4′-dihydroxy-PPP (mass spectrum 3), 4′-hydroxy-3′-methoxy-PPP (mass spectrum 4), 4′-methoxy-2-oxo-propiophenone (mass spectrum 5), 4′-hydroxy-2-oxo-propiophenone (mass spectrum 6), 4′-hydroxy-3′-methoxy-2-oxo-propiophenone (mass spectrum 7), 2′-oxo-MOPPP (mass spectrum 8). With an estimated share of 70% of the excreted MOPPP metabolites, 4′-hydroxy-PPP was the metabolite in greatest abundance. 4′-hydroxy-3′-methoxy-PPP contributed to about 20%.

Many studies by the authors have demonstrated a high degree of qualitative correspondence of rat and human metabolism [17,18,22,23,26–28]. However, substances like cathinone [20], amfepramone [29] or metamfepramone [30] which are structurally related to MOPPP, were shown to be additionally excreted as dihydro metabolites (diasteromers) in humans to a

considerable extent. Therefore, the data of dihydro-MOPPP (synthesized from MOPPP by sodium borohydride hydration according to Ref. [31]) were included in Fig. 1 (mass spectrum 10). The GC and MS data of those compounds and derivatives, which are not shown in Fig. 1, will also be included in the forthcoming update of the authors' handbook and library [16,32].

Mass spectrum 3 and mass spectra 4 and 7 of Fig. 1 do not identify the position of the second hydroxy group and the methoxy group, respectively. However, as catechol-*O*-methyl transferase (COMT) can only methylate the hydroxy groups in position 3 of catechols, the hydroxylation must have taken place in position 3′ of the 4′-hydroxy-PPP. As known from the studies on MDPPP metabolism [3], it is excreted as its demethylene and demethylene-3′-methyl metabolite. These ethylated MDPPP metabolites correspond exactly to those MOPPP metabolites with mass spectra 3 and 4, respectively, and they elute after the same retention times. Ethylated 3′-hydroxy-MOPPP (as well as all other conceivable positional isomers) would probably yield almost the same mass spectrum as mass spectrum 4, but it is likely, that this compound would have a different retention index. A second metabolite was not detected, so that 4′-hydroxy-3-methoxy-PPP was the only positional isomer to be identified. Mass spectrum 8 did not identify the position of the carbonyl group in the pyrrolidine ring. However, as other compounds carrying a pyrrolidine ring are also excreted as their lactam metabolite (e.g., MPPP or nicotine), we postulate the same metabolic pathway for MOPPP. The parent compound MOPPP was not detected, although the limit of detection (S/N 3) was 100 ng/ml. In addition, the extraction efficiency for MOPPP was 91±4% (n=5) measured at 1000 ng/ml.

Based on the identified metabolites of MOPPP, the following partly overlapping metabolic pathways could be postulated (Fig. 2): demethylation of the methoxy group (2–4, 6 and 7), 3′-hydroxylation of these demethylated compounds (3, 4 and 7), mostly followed by COMT catalyzed 3′-methylation to the corresponding demethyl-methoxy compounds (4 and 7), oxidative desamination to the corresponding 2-oxo compounds (5–7) and/or hydroxylation of the 2″-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactam (8). In contrast to the metabolism of the structurally related compound MPHP, reduction of the keto group to the corresponding secondary alcohol or hydroxylation of the side chain did not result in excretion of detectable amounts of metabolite. As the peaks of the metabolites 2–4, 6 and 7 were more abundant after glucuronidase and sulfatase hydrolysis, it can be concluded that they are partly excreted as glucuronides and/or sulfates.

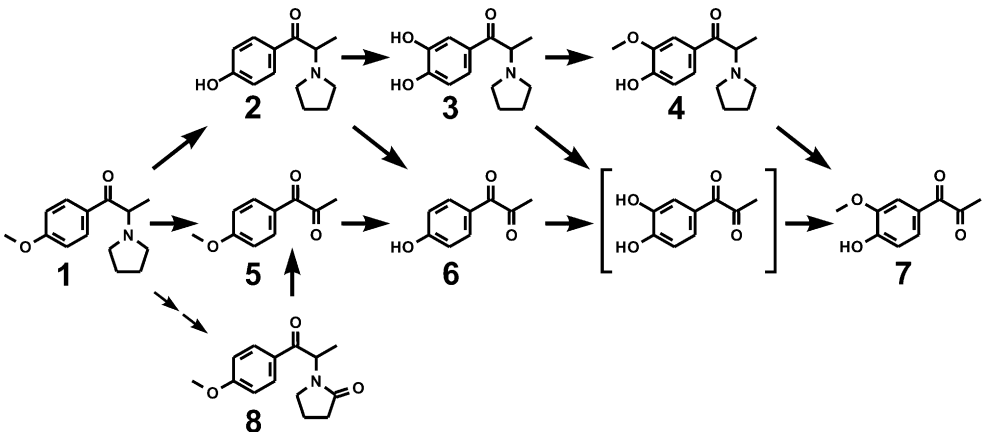

Fig. 2. Proposed scheme for the metabolism of MOPPP in rats. The compound in parentheses is an assumed intermediate. The numbering of the compounds corresponds to that of the mass spectra of the corresponding derivative in Fig. 1.

3.3. Toxicological detection by GC–MS

MOPPP metabolites were separated by GC and identified by full-scan EI-MS after fast enzymatic hydrolysis, SPE and trimethylsilylation. Only fraction 2, where—among others—the MOPPP main metabolite 4′-hydroxy-PPP was eluted, was needed for the toxicological detection. MS with the following ions was used to detect the presence of MOPPP and/or its metabolites: m/z 98, 112, 135 and 193.

The selected ion m/z 98 was used for monitoring the presence of compounds with unchanged pyrrolidine ring (mass spectra 1, 9 and 10 in Fig. 1), m/z 112 for compounds with oxidized pyrrolidine ring (mass spectrum 8 in Fig. 1), m/z 135 for compounds with an unchanged 4′-methoxy-phenylcarbonyl moiety (mass spectra 1, 5 and 8) and m/z 193 for the trimethylsilylated demethyl metabolite (mass spectrum 9 in Fig. 1).

Fig. 3 shows reconstructed mass chromatograms indicating the presence of MOPPP metabolites in a trimethylsilylated extract of rat urine after administration of 1 mg/kg body mass of MOPPP. This dose was chosen as it should approximately correspond to a dose ingested by abusers. Seized tablets of the related designer drug PPP always have been shown to contain approximately 40 mg. In addition, the chosen dose is in the same range as that of the structurally related medicament amfepramone. The identity of the peak in the mass chromatograms was confirmed by computerized comparison of the underlying mass spectrum with reference spectra recorded during this study [16]. Fig. 4 illustrates the mass spectrum underlying the marked peak in Fig. 3,

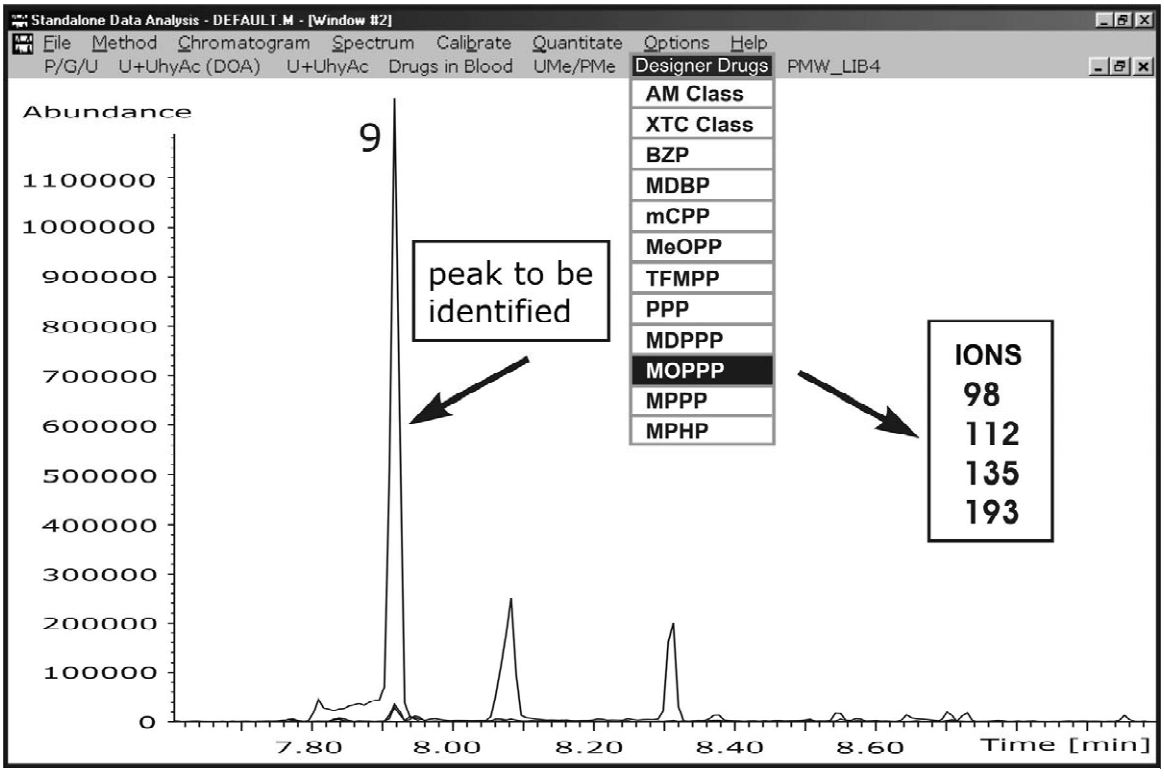

Fig. 3. Typical mass chromatograms with the ions m/z 98, 112, 135 and 193. They indicate the presence of MOPPP metabolites in a trimethylsilylated extract of a rat urine sample collected over 24 h after ingestion of 1 mg/kg body mass of MOPPP. The numbering of the peaks corresponds to that of the mass spectra of the corresponding derivative in Fig. 1. The merged chromatograms can be differentiated by their colors on a color screen.

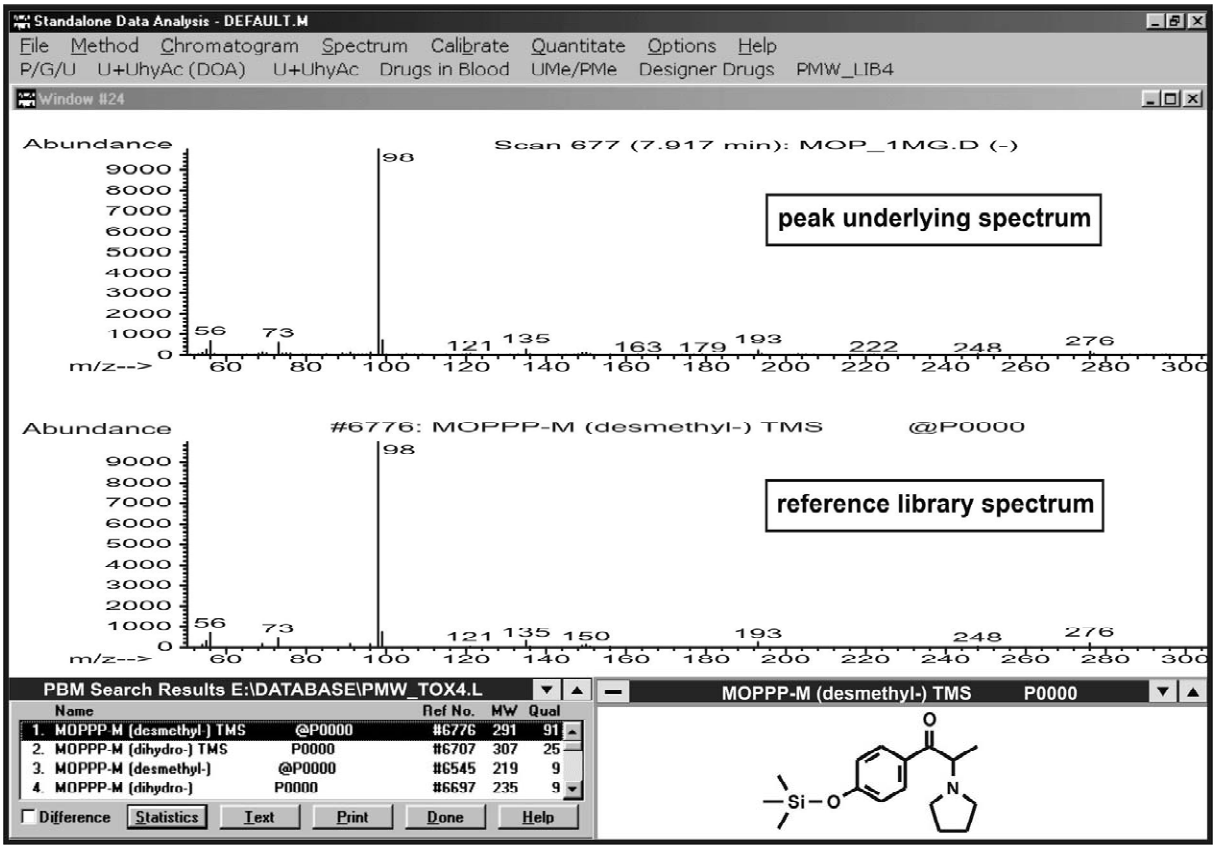

Fig. 4. Mass spectrum underlying the marked peak in Fig. 3, the reference spectrum, the structure, and the hit list found by computer library search.

reference spectrum (9 in Fig. 1), structure, and the drug list found by computer library search. The gas chromatographic RIs provide preliminary indications, allow one to distinguish between the above mentioned positional isomers and/or diastereomers and may be useful to gas chromatographers without an MS facility. Therefore, RIs are also provided in Fig. 1. They were recorded during the GC–MS procedure (Section 2.5) and calculated in correlation with the Kovats' indices [33] of the components of a standard solution of typical drugs which is measured daily for testing the GC–MS performance [34,35]. The reproducibility of retention indices measured on capillary columns was better using a mixture of drugs than that of the homologous hydrocarbons recommended by Kovats.

Unfortunately, no authentic human urine samples after intake of MOPPP were available. However, the same metabolites found in rat urine are also likely to be in human urine samples. As already discussed above, the diasteromeric dihydro metabolites (mass spectrum 10) might additionally be detectable in human urine. However, as mass m/z 98 would also indicate the presence of dihydro-MOPPP, its mass spectrum was included in Fig. 1. This metabolite is also likely to be detectable in human urine. The extraction efficiency for trimethylsilylated dihydro-MOPPP was 63±5% measured at 1000 ng/ml and the limit of detection (S/N 3) was 50 ng/ml (n=4). Extrapolating the rat data, the described screening procedure should be sensitive enough to detect an intake of an illicit dose of MOPPP.

It should be mentioned that MOPPP has common metabolites with PPP [2] and MDPPP [3]. The

common metabolite with PPP is 4′-hydroxy-PPP. Yet, differentiation of the intake of PPP besides MOPPP should be possible via the unique PPP metabolite 2′-oxo-PPP. Differentiation of the intake of small doses of MOPPP taken in combination with PPP might become difficult, if 4′-hydroxy-PPP as the MOPPP main metabolite was present, as 4′-hydroxy-PPP is also detectable after the intake of PPP alone. Special attention must be paid to the detection of unique MOPPP metabolites in this case. The common metabolites with MDPPP are 3′,4′-dihydroxy-PPP, 3′-methoxy-4′-hydroxy-PPP and 3′-methoxy-4′-hydroxy-2-oxo-propiophenone [3]. Intake of small doses of MOPPP with MDPPP can easily be differentiated via the unique main metabolite of MOPPP, 4′-hydroxy-PPP. Differentiation of the ingestion of small doses of MDPPP with MOPPP might be hard, if 3′-methoxy-4′-hydroxy-PPP as the MDPPP main metabolite was present, as 3′-methoxy-4′-hydroxy-PPP is also detectable after the intake of MOPPP alone. Special attention must be paid to the detection of unique MDPPP metabolites in this instance. If all members of the pyrrolidinophenone designer drug class were excreted as their respective dihydro metabolites to a considerable extent in humans, as discussed above, incontestable statements on the ingested parent compound(s) can be made. The presented screening procedure should also be suitable for other designer drugs of the α-pyrrolidinophenone type.

4. Conclusions

The presented studies revealed that the new designer drug MOPPP was extensively metabolized by the rat. Screening must, therefore, be focused on metabolites. The described screening procedure should be suitable for detection of MOPPP and/or its metabolites in human urine in clinical or forensic cases.

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