Metabolism of Designer Drugs of Abuse

Roland F. Staack and Hans H. Maurer*

Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Saarland, D-66421 Homburg (Saar), Germany

*Address correspondence to this author at the Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Saarland, D-66421 Homburg (Saar), Germany; Tel: +49-6841-16-26050; Fax: +49-6841-16-26051; E-mail: hans.maurer@uniklinik-saarland.de

Abstract: Abuse of designer drugs is widespread among young people, especially in the so-called "dance club scene" or "rave scene", worldwide. Severe and even fatal poisonings have been attributed to the consumption of such drugs of abuse. However, in contrast to new medicaments, which are extensively studied in controlled clinical studies concerning metabolism, including cytochrome P450 isoenzyme differentiation, and further pharmacokinetics, designer drugs are consumed without any safety testing. This paper reviews the metabolism of new designer drugs of abuse that have emerged on the black market during the last years. Para-methoxyamphetamine (PMA), para-methoxymethamphetamine (PMMA) and 4-methlythioamphetamine (4-MTA), were taken into consideration as new "classical" amphetamine-derived designer drugs. Furthermore, N-benzylpiperazine (BZP), 1-(3, 4-methylenedioxybenzyl)piperazine (MDBP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP) and 1-(4-methoxyphenyl)piperazine (MeOPP) were taken into consideration as derivatives of the class of piperazine-derived designer drugs, as well as α-pyrrolidinopropiophenone (PPP), 4'-methoxy-α-pyrrolidinopropiophenone (MOPPP), 3', 4'-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP), 4'-methyl-α-pyrrolidinopropiophenone (MPPP), and 4'-methyl-α-pyrrolidinoethanophenone (MHP) as derivatives of the class of α-pyrrolidinophenone-derived designer drugs. Papers describing identification of in vivo or in vitro human or animal metabolites and cytochrome P450 isoenzyme dependent metabolism have been considered and summarized.

Key Words: Metabolism, Designer Drugs, Amphetamines, Piperazines, Pyrrolidinophenones.

INTRODUCTION

Abuse of designer drugs is widespread among young people, especially in the so-called "dance club scene" or "rave scene", worldwide. A wide variety of structural modifications of amphetamine are known. This group of amphetamine derivatives belongs to the group of so-called "classical" designer drugs. The most known and most widespread compounds are the methylenedioxy-substituted amphetamines, such as MDMA (R, S-methylenedioxyamphetamine, "Adam", "Ecstasy"), MDA (R, S-methylenedioxymethamphetamine, R, S-1-(3', 4'-methylenedioxyphenyl)-2-propynamine, "Love Pills"), MDEA (R, S-methylenedioxymethylamphetamine; MDE; "Eve"), BDB (R, S-benzo-dioxoylbutanamine; R, S-1-(3', 4'-methylenedioxymethyl)-2-butanamine) or MBDB (R, S-N-methyl-benzo-dioxoylbutanamine). However, during the 1990's the illicit drug market for recreational drugs changed considerably. New compounds of the class of "classical" designer drugs such as R, S-para-methoxymethamphetamine (PMA), R, S-para-methoxy-methamphetamine (PMMA) and R, S-4-meththioamphetamine (4-MTA) gained notoriety. Furthermore, so-called piparazines and α-pyrrolidinophenones emerged on the black market as completely new classes of designer drugs [1-6]. Detailed information, e.g. on their synthesis, dosage, pharmacological effects, are given in books specialized on this issue [5, 7, 8] and especially the internet greatly facilitates the free and easy exchange of unedited and non-refereed information [9]. Furthermore, the Internet facilitates the purchase at least of those drugs which are not yet scheduled, as several online shops are specialized in selling such compounds.

In contrast to new medicaments, which are extensively studied in controlled clinical studies concerning metabolism, including cytochrome P450 (CYP) isoenzyme differentiation, and further pharmacokinetics, designer drugs are consumed without any safety testing. The corresponding data on the metabolism is mostly incomplete or even not available at all.

However, data on the metabolism is strongly required. It is a prerequisite for developing toxicological screening procedures, especially in urine, and for toxicological risk assessment. Furthermore variations in the formation of pharmacologically active metabolites, formation of toxic metabolites, or interactions with other medicaments (drug abusers often are polytoxicomaniacs) may have consequences for the assessment of analytical results in clinical or forensic toxicology as well as in doping control. Furthermore, there is good evidence that drug metabolism by genetically variable CYPs can influence the risk of drug dependence, the amount of drug consumed by dependent individuals and some of the toxicities associated with drug taking-behavior [10].

The metabolism of the methylenedioxy substituted amphetamines has recently been reviewed [2]. The aim of the present paper was to review English written papers describing the human or animal metabolism of PMA, PMMA and 4-MTA, as "new classical" designer drugs as well as the metabolism of the piparazines, N-benzylpiperazine (BZP), 1-(3, 4-methylenedioxybenzyl)piperazine (MDBP), 1-(3-
trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP) and 1-(4-methoxyphenyl) piperazine (MeOPP), the α-pyrrolidinophenones R, S-α-pyrrolidinopropiophenone (PPP), R, S-4'-methoxy-α-pyrrolidinopropiophenone (MOPPP), R, S-3', 4'-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP), R, S-4'-methyl-α-pyrrolidinopropiophenone (MPPP), and R, S-4'-methyl-α-pyrrolidinohexanophenone (MPHP). Their chemical structures are shown in Fig. (1).

NEW "CLASSICAL" AMPHETAMINE-DERIVED DESIGNER DRUGS

The new derivatives of the class of "classical" amphetamine-derived designer drugs are all in para position substituted compounds, either with a methoxy group (PMA, PMMA) or with a methylthio group (4-MTA).

R, S-para-Methoxyamphetamine (PMA)

PMA is a scheduled drug in many countries [11, 12]. Its hallucinogenic properties are already known since the late 1960's [13]. PMA is often found in combination with PMMA (see below) and a large number of fatalities worldwide, showing clinical symptoms similar to those reported for other amphetamine derivatives, had been attributed to the consumption of PMA or to this combination [14-25].

Qualitative as well as quantitative stimulus similarity could be shown for PMA, its N-methylated analogue PMMA and its methylthio analogue 4-MTA. To some extent, similarities of R(-)-PMA to the effects of MDMA were found, however, lacking the amphetamine-like character of MDMA [26, 27]. PMA is a serotonergic compound, evoking serotonin release, inhibiting serotonin uptake and showing only little effects on the dopamine system [28-31]. These particular pharmacological properties have been discussed to underlie the higher rate of lethal complications seen with PMA consumption compared with other substituted amphetamines [32]. Inhibition of the monoamine oxidase (MAO) A is a further pharmacological property of PMA [33, 34]. PMA shows neurotoxic effects on serotonin neurons, however being less toxic than MDMA, and on dopamine neurons [35, 36].

Metabolism of PMA

During the 1970's several studies were conducted on the metabolism of PMA (no. 1 in Fig. (2)) [37-40]. In an in vitro study, 10 000g liver preparations of Guinea pig, rat and...
rabbit were used [37]. Only metabolic alterations of the side chain were found. Deamination to the corresponding ketone 1-(p-methoxyphenyl)-propan-2-one (no. 2 in Fig. (2)) was described for all three species. Using the liver preparations of Guinea pig and rabbit, further reduction of the ketone to the corresponding alcohol (no. 3 in Fig. (2)) was found besides N-hydroxylation (no. 4 in Fig. (2)) and the formation of 1-(p-methoxyphenyl)-propan-2-one oxime (no. 5 in Fig. (2)). Unfortunately, no details on the sex and the specific strain of the used animals were provided.

O-demethylation was reported as the main metabolic pathway in female Dunkin-Hartley Guinea pigs and female Wistar albino rats [39] as well as in male Beagle dogs and Rhesus monkeys [38]. The corresponding metabolite 4-hydroxyamphetamine (no. 6 in Fig. (2)), mainly excreted as conjugate, was the only urinary metabolite of Guinea pigs. In rat urine, 1-(p-methoxyphenyl)-propan-2-one oxime was detected as well as its glucuronide conjugate as minor metabolites, besides 4-hydroxyamphetamine, again mainly conjugated. Concerning conjugation, an interesting species difference could be found, since the Guinea pig utilized glucuronic acid and sulphate for this purpose while the rat used only glucuronic acid [39]. In the same study, the in vivo metabolism in man was also investigated in three subjects, whose oxidation phenotype had been established using debrisoquine. Two of them, showing the extensive metabolizer phenotype, excreted mainly 4-hydroxyamphetamine, free and conjugated, together with small amounts of the oxime metabolite and 4-hydroxynorephedrine (no. 7 in Fig. (2)). The third subject, showing the poor metabolizer phenotype, however, was defective in O-dealkylation. Only very little amounts of 4-hydroxyamphetamine were detected. The main excretion products were the unchanged PMA together with side-chain oxidized metabolites, 1-(p-methoxyphenyl)-propan-2-one oxime, 1-(p-methoxyphenyl)-propan-2-one and, in contrast to the extensive metabolizers, side chain degraded metabolites 4-methoxybenzoic acid (no. 8 in Fig. (2)) and 4-hydroxybenzoic acid (no. 9 in Fig. (2)). The latter

![Proposed scheme for the in vitro and in vivo phase I metabolism of PMA in dogs (D), monkeys (M), pigs (P), rabbits (Rb), rats (R) and humans (H) (according to refs. [37-40]).](image-url)
metabolite could also be identified as urinary metabolite in dogs and Rhesus monkeys [38].

Further in vivo metabolites were described in a study using male Beagle dogs and Rhesus monkeys [40]. Besides 4-hydroxy amphetamine, 4-hydroxy-3-methoxy amphetamine (no. 10 in Fig. (2)) and the corresponding deaminated metabolites 1-(p-hydroxyphenyl)-propan-2-one (no. 11 in Fig. (2)) and 1-(4-hydroxy-3-methoxyphenyl)-propan-2-one (no. 12 in Fig. (2)) were detected. Further hydroxylation of the benzyl carbon of 1-(p-hydroxyphenyl)-propan-2-one (no. 13 in Fig. (2)) was postulated. The in vitro and in vivo metabolism of PMA in the different species is summarized in Fig. (2).

Influence of CYP Isoenzymes on the Metabolism of PMA

The observed differences in O-demethylation of PMA in different human subjects (see above) indicated the influence of the polymorphically expressed CYP2D6 [39]. The influence of this particular isoenzyme was confirmed in two studies [14, 41]. In one of these studies microsomes of human AHH-1 TK+/− cell lines transfected with human cDNA that encoded for CYP2D6 were used as the only enzyme source [14].

In the second study, a panel of human liver microsomes, from CYP2D6 extensive and poor metabolizers, and microsomes from yeast transformed with an expression plasmid containing full-length human CYP2D6 cDNA were used [41]. The latter microsomes were used to show that PMA is a substrate of CYP2D6. Comparison of the metabolite formation rates in microsomes of CYP2D6 extensive and poor metabolizers showed that only trace amounts of 4-hydroxy amphetamine were formed in the CYP2D6 poor metabolizer microsomes at high substrate concentrations. Furthermore, the rates of O-demethylation of PMA and dextromethorphan were highly correlated in the panel of human microsomes and the CYP2D6 inhibitors quinine and quinidine showed significant inhibition of the monitored reaction. Actually, the observation of the deficiency in PMA O-demethylation was one of the observations that led to the discovery of the CYP2D6 polymorphism [41]. In a further study, different enzyme kinetics of PMA O-demethylation between CYP2D6.1 and CYP2D6.10 was shown [42]. PMA showed reduced metabolism and affinity with CYP2D6.10 resulting in a 34-fold reduced in vitro clearance.

The major metabolite, 4-hydroxy amphetamine, is also pharmacologically active [32]. Increased release and inhibition of both serotonin and dopamine has been reported. However, a study in male Sprague-Dawley rats revealed that after peripheral administration of PMA, the concentrations achieved in the brain are unlikely to contribute to the central effects of PMA. The authors concluded that the inability to metabolize PMA due to, e.g. genetic variations or drug interactions, may predispose users to adverse effects of PMA. A connection between PMA fatalities and the inability to metabolize PMA has also been discussed by other authors [39].

R, S-beta-Methoxyamphetamine (PMMA)

PMMA is the N-methylated analogue of PMA and as PMA it is scheduled as a controlled substance in many countries [11, 12, 43]. As already mentioned above, PMA and PMMA are often found together in seized tablets and a large number of fatalities worldwide had been attributed to the consumption of this combination [14-25]. As for its pharmacological properties, quantitative as well as qualitative stimulus similarity between PMMA, PMA and 4-MTA were shown [26]. Furthermore, PMMA shares considerable pharmacological similarities with MDMA, but it lacks the amphetaminergic stimulant component of MDMA. Its stimulant effects were described to be similar to MBDB and dimethoxyamphetamine [44-48]. The only data available on the effects in humans have been published by Shulgin, who described its effects as somewhat different from those of MDMA [49].

Long-term (possibly neurotoxic) effects on brain serotonin neurons were described for PMMA comparable to those of PMA, however, being less potent compared to neurotoxic effects of MDMA [35]. In the same publication, the authors uttered concerns about the possibility of a narrow margin between the behaviorally active and lethal doses of PMMA as described for PMA, due to their observation of a rather high lethality in male Sprague-Dawley rats after the administration of 80 mg/kg body mass.

Metabolism of PMMA

The metabolism of PMMA (no. 1 in Fig. (3)) was studied in male Wistar rats [50]. PMMA was extensively metabolized, mainly being O-demethylation of the methoxy moiety to 4-hydroxy methamphetamine (pholdrine, no. 2 in Fig. (3)). Further aromatic hydroxylation to dihydroxy methamphetamine (no. 7 in Fig. (3)) followed by catechol-O-methyl transferase (COMT) catalyzation methylation to 4'-hydroxy-3'-methoxy methamphetamine (no. 8 in Fig. (3)) was reported. The isomer 3'-hydroxy-4'-methoxy methamphetamine (no. 9 in Fig. (3)) was only formed to a very small extent either by COMT methylation of the 4'-position or by direct hydroxylation of PMMA. A second metabolic pathway, also known from other amphetamine derivatives, was the alteration of the side chain. However, N-demethylation of PMMA to PMMA (no. 5 in Fig. (3)) was only observed to a minor extent and N-demethylation of the major metabolite 4-hydroxy methamphetamine to 4-hydroxy amphetamine (no. 6 in Fig. (3)) could not be observed at all, which was in keeping with the literature [51]. It was concluded that the metabolite 4-hydroxy amphetamine was formed via PMMA N-demethylation to PMMA followed by O-demethylation, especially as 4-hydroxy amphetamine is known as the major metabolite of PMA [38, 39].

Subsequent aromatic hydroxylation of 4-hydroxy amphetamine followed by COMT catalyzed methylation led to the formation of 4'-hydroxy-3'-methoxy amphetamine (no. 10 in Fig. (3)). N-Demethylation of the metabolite 4'-hydroxy-3'-methoxy methamphetamine would also result in the formation of the same compound. Another metabolic alteration of the side chain was hydroxylation at position 1. It could be shown that 1-hydroxylation of hydroxy methamphetamine, which led to the formation of a second chiral center in the molecules, led predominantly to the formation of oxilofrine, the erythro diastereomers (consisting of the pair of enantiomers 1R, 2S and 1S, 2R, no. 3 in Fig. (3)), while the threo diastereomers (consisting of the pair of enantiomers 1R, 2R and 1S, 2S, no. 4 in Fig. (3)) were only
formed to a minor extent. It was not further investigated whether the detected peaks consisted of one or two enantiomers each. Finally, the phenolic metabolites were partially excreted as conjugates. Glucuronide- and sulfate conjugation was postulated as the study was conducted with a mixture of β-glucuronidase and arylsulfatase. Sulfation was already described for 4-hydroxy methamphetamine [52-55]. The proposed scheme for the metabolism of PMMA in male Wistar rats is shown in Fig. (3).

**Influence of CYP Isoenzymes on the Metabolism of PMMA**

The influence of human CYP isoenzymes on the major metabolic reaction, the O-demethylation, was studied in vitro using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs, pooled human liver microsomes (pHLM) and single donor human liver microsomes with CYP2D6 poor metabolizer genotype [56].

CYP2D6 was identified as the only isoenzyme capable of demethylating PMMA, which was further corroborated by significant inhibition of the metabolite formation by CYP2D6 inhibitor quinidine and by significant lower metabolite formation rate in poor metabolizer human liver microsomes. The results were in accordance with the results of studies on the involvement of CYP2D6 in the O-demethylation of other methoxy substituted amphetamine derivatives [14, 41, 57].

**R, S-4-Methylthioamphetamine (4-MTA)**

4-MTA, the methylthio analogue of PMA, initially synthesized as a potential antidepressant [58, 59], has emerged on the illicit drug market in several countries and has recently been submitted to control measures and criminal penalties [11, 12, 43]. As already mentioned above, qualitative and quantitative stimulus similarity could be shown for 4-MTA and the methoxy substituted derivatives PMA and PMMA. To some extent, similarities to the effects of MDMA were found, however, lacking the amphetaminergic character of MDMA [26]. 4-MTA is a very selective serotonergic agent, showing increase in the release of serotonin, inhibition of serotonin reuptake, inhibition of MAO A and only low affinity for noradrenaline and dopamine uptake.
sites and monoamine receptors [59-63]. Due to its pharmacological properties, the induction of a serotonin syndrome is very likely and could be shown in rats [60]. Unlike other amphetamine derivatives, 4-MTA reportedly is non-neurotoxic to serotonergic neurons [60, 64]. Several severe and even fatal poisonings have been reported, and in at least one case 4-MTA was the only drug detected. In these cases, sympathomimetic effects, known for amphetamine derivatives, were observed [65-69]. The slow onset of effects of 4-MTA compared to MDMA has been discussed as a reason for a higher risk of adverse effects. The presumable absence of the effects might encourage the drug abuser to administer further doses, assuming the initial tablet was of poor quality or of a small dose [58, 69].

**Metabolism of 4-MTA**

The metabolism of 4-MTA was studied in CD1 mice [70]. According to this study, 4-MTA was mainly metabolized at the side chain. β-Hydroxylation to 4-methylthiophenylpropanolamine and 4-methylthioca-thine and degradation of the side chain to 4-methylthiobenzoic acid were observed. Furthermore, hydroxylation of the phenyl moiety of the molecule was described. However, this latter hydroxylation could not unequivocally be localized. Hydroxylation at the aromatic ring or at the methylthio group where discussed.

In another study *in vitro* methods were applied [71]. Incubations were performed with primary hepatocytes from male human donors, from male Cynomolgus monkey, male Beagle dogs, male Chincilla rabbits, male Sprague Dawley rats and male CD1 mice. Except for incubations with rabbit hepatocytes, 4-MTA was only poorly metabolized. 4-Methylthiobenzoic acid was identified as the major metabolite in human, monkey, dog, rabbit and mouse hepatocytes but no metabolite was identified in rat hepatocytes indicating qualitative interspecies differences.

4-Methylthiophenylpropanolamin and 4-methylthiocathine, which where identified as putative metabolites in the *in vivo* study in mice [70], and 4-methylthioamphetamine sulfoxide where also detected, but it turned out that these compounds were also formed in the suspension buffer controls without hepatocytes. The only data on the human *in vivo* metabolism can be found in a case report on a fatality after 4-MTA consumption [67]. Besides the presence of unchanged parent compound, two possible metabolites, a hydroxylated metabolite and a sulfoxide were reported.

**Piperazine-Derived Designer Drugs**

The name of this new class of designer drugs derives from the piperazine heterocycle as a common feature. Due to their chemical structures, they can further be divided into two sub-classes, the benzylpiperazines like BZP itself and its methylenedioxy analogue MDBP, and the phenylpiperazines TFMPP, mCPP and MeOPP. Seizures could be made throughout the world [3, 6, 72-78] and even fatalities involving piperazine derived compounds have been reported [79, 80].

In most countries, piperazines are not scheduled drugs. The increasing abuse in the United States of America lead first to the temporary placement of BZP and TFMPP into Schedule I of the Controlled Substance Act (CSA) [81]. Since March 18, 2004 BZP is finally a scheduled drug, whereas TFMPP is no longer controlled under the Controlled Substance Act (CSA) [82]. Since March 1, 2003 BZP is also regulated under the Act on Prohibition of Certain Goods Dangerous to the Health in Sweden [80].

**N-Benzylpiperazine (BZP)**

BZP was originally synthesized as a potential antidepressant agent. Animal studies revealed amphetamine-like effects. Pharmacological studies of BZP showed a central serotoninnomimetic action, which involves serotonin (5-HT) uptake inhibition and 5-HT1 receptor agonistic effects [83]. Furthermore, weak inhibition of serotonin transporters, noradrenaline release and interactions with the dopaminergic system were described [84-87]. Studies with healthy volunteers corroborated the amphetamine-like effects also *in vivo* [88] and a double blind study with former amphetamine addicts showed that BZP and amphetamine produced indistinguishable subjective effects [89]. These studies suggested an approximate ratio of 10:1 (BZP:amphetamine) in the effect potency. As a result of these studies, the authors already predicted a possible abuse in 1973 and advised it to be scheduled.

**Metabolism of BZP**

The metabolism of BZP (no. 1 in Fig. (4)) was studied in male Wistar rats and the identified metabolites were confirmed as human metabolites by analysis of human urine after intake of this designer drug [90]. BZP was not extensively metabolized and mainly excreted as unchanged parent compound. Three metabolic targets could be identified for BZP: the aromatic ring, the benzyl carbon and the piperazine heterocycle. The aromatic ring was metabolically altered by single (nos. 2 and 3 in Fig. (4)) or double hydroxylation followed by catechol-O-methyl-transferase (COMT) catalyzed methylation to N-(4-hydroxy-3-methoxy-benzyl)piperazine (no. 4 in Fig. (4)). As a mixture of β-glucuronidase and arylsulfatase was used for conjugate cleavage, formation of the corresponding glucuronides and/or sulfates was postulated. N-Dealkylation at the benzyl carbon led to the liberation of piperazine (no. 5 in Fig. (4)). Formation of benzoic acid, as described for other BZP derivatives could not unequivocally be confirmed as it is ubiquitous in urine due to its use as food preservative [91]. The piperazine heterocycle was degraded by double N-dealkylation leading either to the formation of benzyamine (no. 6 in Fig. (4)) or to N-benzylethylenediamine (no. 7 in Fig. (4)), depending on the positions of these metabolic reactions. The proposed scheme for the metabolism of BZP in male Wistar rats and in humans is shown in Fig. (4).

**1-(3,4-Methylenedioxybenzyl) Piperazine (MDBP)**

The introduction of a methylenedioxy moiety is a well known structural modification of amphetamines and can likewise be found in the class of benzylpiperazines [4, 5]. MDBP is the corresponding methylenedioxy derivative of BZP. Only very little information can be found on its pharmacological and toxicological properties. Weak inhibition of serotonin uptake has been described [92]. Animal studies showed that MDBP pretreatment altered the disposition and
metabolism of MDMA in the brain and in periphery organs [92] and inhibition of the MDMA-induced neurotoxicity by MDBP was reported [84]. No information on its human pharmacology can be found. Shulgin assumes that the structural variation might provoke slightly different effects compared to the amphetamine-like effects of BZP [4]. Allegedly, higher doses of MDBP are needed to evoke the desired effects [5].

**Metabolism of MDBP**

The metabolism of MDBP was studied in male Wistar rats [93]. This BZP derivative underwent similar, partially overlapping, metabolic pathways with BZP. As described for BZP, MDBP was mainly excreted as unchanged parent compound. Metabolic alteration of the aromatic moiety, the benzyl carbon and the piperazine heterocycle was also described for MDBP. Demethylation of the 3, 4-methylenedioxy moiety to the corresponding catechol and further methylation to N-(4-hydroxy-3-methoxy-benzyl)piperazine followed by partial glucuronidation or sulfation led to formation of metabolites common with BZP. Likewise, N-dealkylation at the benzyl carbon, leading to piperazine, was described. Degradation of the piperazine heterocycle by double N-dealkylation led to the corresponding N-benzylethylenediamine and benzylamine derivatives N-(3, 4-methylenedioxybenzyl)ethylenediamine and 3, 4-methylenedioxybenzylamine. Demethylation of methylenedioxy compounds and subsequent methylation to the corresponding hydroxy-methoxy metabolites are known for several methylenedioxy compounds [94-98].

**1-(3-Trifluoromethylphenyl) Piperazine (TFMPP)**

Although TFMPP is a pharmacologically well characterized compound, showing central activity and serotonergic properties [99-105], no information on the human pharmacology is available. However, its effects in humans should be similar to those of the structurally closely related mCPP, with the chloro moiety exchanged by the bioisosteric trifluoromethyl group.

Owing to its serotonergic properties, TFMPP has widely been used as a pharmacological probe drug for drug discrimination procedures in animals [106-109]. Detailed information on its pharmacological effects can be found in ref [110].

On the internet, drug abusers describe its effects to be similar to those of the classical designer drugs MDMA or MDEA, which could partially be supported by animal studies [107, 109, 111]. Anxiogenic effects and panic reactions were also reported which could be supported by animal studies [112-114] and human studies on structurally related compounds [110, 115].

**Metabolism of TFMPP**

The metabolism of TFMPP (no. 1 in Fig. (5)) was studied in male Wistar rats [116]. In contrast to the two above-mentioned benzylpiperazines, TFMPP was extensively metabolized and almost exclusively excreted as metabolites. The major metabolic reaction was aromatic hydroxylation to hydroxy TFMPP (no. 2 in Fig. (5)) followed by partial glucuronidation (no. 10 and 11 in Fig. (5)) or sulfation (no. 12...
Degradation of the piperazine heterocycle by double N-dealkylation could be observed for the parent compound TFMPP, leading to the formation of N-(3-trifluoromethylphenyl)-ethylenediamine (no. 3 in Fig. (5)) or to 3-trifluoromethylaniline (no. 5 in Fig. (5)), as well as for its hydroxylated metabolite hydroxy TFMPP leading to the formation of N-(hydroxy-3-trifluoromethylphenyl)-ethylenediamine (no. 4 in Fig. (5)) or to hydroxy-3-trifluoromethylaniline (no. 7 in Fig. (5)). Partial N-acetylation was reported as phase II reaction of the aniline derivatives (nos. 6, 8 and 9 in Fig. (5)). The proposed scheme for the metabolism TFMPP in male Wistar rats is shown in Fig. (5).

**Influence of CYP Isoenzymes on the Metabolism of TFMPP**

The influence of human CYP isoenzymes on the major metabolic reaction, the hydroxylation of TFMPP to hydroxy TFMPP was studied in vitro using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs, pHLM and in single donor human liver microsomes with CYP2D6 poor metabolizer genotype [117]. A relative activity factor (RAF) approach [118-123] was used to correct recombinant CYP formation rates for native human liver enzyme activity. According to these studies, CYP2D6 was the most important isoenzyme accounting for 80.9% of predicted total TFMPP hydroxylation clearance by all individual CYPs in pHLM. CYP1A2 and CYP3A4 were responsible for 11.5% and 7.6%, respectively. The importance of CYP2D6 was further confirmed by chemical inhibition studies with CYP2D6 inhibitor quinidine resulting in significant inhibition of metabolite formation. Furthermore, comparison of the metabolite formation rates in pHLM and human liver microsomes with CYP2D6 poor metabolizer genotype revealed a significant lower metabolite formation rate in the microsomes of the poor metabolizer.

In addition, in vivo studies using different rat models were conducted in order to get hints for possible differences in pharmacokinetics in human poor and extensive metabolizer subjects [117]. Female Dark Agouti rats were chosen as a model of the human CYP2D6 poor metabolizer phenotype [124, 125], male Wistar rats as the corresponding model of the human CYP2D6 extensive metabolizer phenotype [125, 126] and male Dark Agouti rats were used as an intermediate model between the poor and extensive metabolizer models [127]. Comparison of the ratio TFMPP vs. hydroxy TFMPP in urine showed that male Wistar rats (extensive metabolizer model) excreted TFMPP mainly as the corresponding hydroxy metabolite. Male Dark Agouti rats (intermediate
model) excreted TFMPP significantly less metabolized, with HO-TFMPP still being the main analyte and female Dark Agouti rats (poor metabolizer model) mainly excreted the unmethylated parent compound TFMPP. Analysis of blood plasma levels was consistent with these findings. Female Dark Agouti rats showed the highest, male Wistar rats showed the lowest TFMPP blood plasma levels at all sample times and the TFMPP plasma levels in male Dark Agouti rats laid between these two groups. In order to confirm that these differences could be attributed to the differences in CYP2D activity in the different rat strains, male Wistar rats were pretreated with the CYP2D specific inhibitor quinine [126, 128], which resulted in a significant increase of TFMPP plasma levels.

1-(3-Chlorophenyl)Piperazine (mCPP)

mCPP is the most extensively characterized compound of the piperazines. It is an active metabolite of therapeutics such as trazodone [129-132], nefazodone [132, 133], etoperidone [129, 134-136], and mepiprazol [129]. mCPP has been found to interact with different serotonin receptors showing mainly nonselective agonistic properties, but antagonistic effects have been described as well [102, 137, 138]. Furthermore, serotonin release by acting as a substrate for serotonin transporters (SERT) proteins [64, 105, 139-141], inhibition of serotonin reuptake [64], slight dopamine release [140], as well as interactions with adrenergic and dopaminergic receptors [142] have been reported. Due to its serotonergic properties, mCPP has widely been used as a clinical tool for investigating pharmacological mechanisms of psychiatric disorders and anxiety [110, 143, 144]. mCPP produced widespread neuroendocrine, physiological and psychological effects, sometimes differing between healthy subjects and people diagnosed with mental illnesses [110, 143, 144].

Concerning drug abuse, its psychological effects are of particular interest. mCPP has been described to produce ethanol-like euphorogenic effects in abstinent alcoholic patients [145] and to lead to derealization [146-149]. “High” feelings, stimulant, and hallucinogenic effects after mCPP administration have been described as similar to those after LSD, mescaline or MDMA use [149-151]. MDMA users showed altered behavioral responses to mCPP, e.g. fewer negative and more positive emotional and physical experiences and less sensitivity to anxiogenic effects [152], which are well known properties of mCPP [110, 144, 146, 153-155]. Induction of migraine-like headaches is another rather undesirable effect of mCPP [110, 147, 156-158]. Furthermore, serotonin syndrome after single administration of mCPP has been reported [159].

Repeated administration of mCPP lead to attenuation especially of its psychological effects [154]. Changes in its pharmacokinetic were ruled out as a possible reason, since mCPP plasma concentrations remained unchanged. Instead, down regulation of serotonin receptors were discussed.

Metabolism of mCPP

In a first study, the metabolism of mCPP was investigated in male Sprague-Dawley rats, which were administered radio-labeled mCPP [160]. Extensive metabolism was reported and no unchanged mCPP could be detected in the urine samples. Para-hydroxy mCPP was identified as the major metabolite, which could not be detected unconjugated. Glucuronidation and sulfation were postulated as the conjugation reactions as shown by studies with β-glucuronidase, with and without the β-glucuronidase inhibitor saccharic acid-1, 4-lactone, or aroylsulfatase.

This working group mentioned the formation of further, not structurally characterized metabolites. Reinvestigation of the metabolism by using male Wistar rats confirmed the finding of extensive metabolism of mCPP and the formation of hydroxy mCPP as the major urinary metabolite [161]. In contrast to the first study, small amounts of unmetabolized mCPP were detected in urine and hydroxy mCPP could also be found unconjugated. In studies on the mCPP precursor drug trazodone, the formation of mCPP N-glucuronides was reported [131, 162].

Moreover, further metabolites were identified. In addition to the aromatic hydroxylation, degradation of the piperazine heterocycle by double N-dealkylation of mCPP to N-(3-chlorophenyl)ethylenediamine or to 3-chloroaniline. Hydroxy-3-chloroaniline was the only metabolite resulting from degradation of the piperazine moiety of hydroxy mCPP. The corresponding ethylenediamine derivative was not detected, in contrast to the metabolism of TFMPP. The aniline metabolites were partially N-acetylated.

Influence of CYP Isoenzymes on the Metabolism of mCPP

The influence of human CYPs on the hydroxylation of mCPP, the major metabolic reaction was investigated in vitro by two working groups [163, 164]. In the first study human liver microsomes and microsomes from metabolically competent cell lines expressing cDNA for human CYPs were used [163]. Incubations with single cDNA -expressed human CYPs, inhibition studies using CYP2D6 inhibitor quinidine and correlation analysis of isoenzyme activities in a panel of human liver microsomes with hydroxy mCPP production where performed to prove CYP2D6 being the only isoenzyme catalyzing the monitored reaction. The second study corroborated these results by performing incubations with human liver microsomes, microsomes of cDNA-transfected lymphoblastoid cells expressing individual human CYPs and by inhibition studies with quinidine [164]. Both working groups concluded that this finding is consistent with clinical studies demonstrating increased steady-state plasma mCPP concentrations in CYP2D6 poor metabolizers receiving treatment with the mCPP precursor drug nefazodone [165] and with the observation of higher mCPP levels in patients receiving trazodone, another mCPP precursor drug, in combination with the CYP2D6 inhibitor fluoxetine [166]. increased mCPP plasma concentrations under co-administration of trazodone and thioridazine was also found [167] and a significant increase of the mean mCPP plasma concentration when haloperidol was co-administered with trazodone [168]. In another study of the same working group, steady-state plasma concentrations of mCPP after administration of trazodone were compared between different groups of patients showing different CYP2D6 genotypes. However, no significant differences were found [169].

1-(4-Methoxyphenyl)Piperazine (MeOPP)

MeOPP, the methoxy-substituted phenylpiperazine derivative, can be considered as the analogue piperazine to PMA
and PMMA of the class of amphetamines. Only very little is known on the pharmacology and toxicology of MeOPP. Its two-methoxy isomer is known to show serotonergic and dopamine antagonistic properties and its effects have been described as similar to those of TFMPP [99, 104, 110, 170, 171]. Therefore, in analogy to other 1-arylpiperazines, especially to the above-mentioned compounds, similar effects might be assumed for MeOPP.

**Metabolism of MeOPP**

The metabolism of MeOPP was studied in male Wistar rats [172]. As the two other phenylpiperazines, MeOPP was extensively metabolized. O-Demethylation of the methoxy moiety was the major metabolic step, as known from the methoxy-substituted amphetamine derivatives PMA and PMMA. The formed metabolite hydroxyphenylpiperazine was subsequently conjugated by partial glucuronidation or sulfation as concluded from studies with a mixture of β-glucuronidase and arylsulfatase. N-(4-Methoxyphenyl) ethylenediamine and 4-methoxyaniline were formed by degradation of the piperazine moiety of MeOPP and 4-hydroxyaniline could be detected as the piperazine-degraded metabolite of hydroxyphenylpiperazine. As described for mCPP, the corresponding ethylenediamine metabolite of the major metabolite could not be detected, in contrast to the findings of the metabolism of TFMPP. 4-hydroxyaniline was found to be partially glucuronidated or sulfated. Furthermore, it could be shown to be N-acetylated to N-acetyl-4-hydroxyaniline, which actually is the analgesic drug acetaminophen (paracetamol).

**Influence of CYP Isoenzymes on the Metabolism of MeOPP**

The influence of human CYP isoenzymes on the major metabolic reaction, the O-demethylation of MeOPP was studied in vitro using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs, pHLM and in single donor human liver microsomes with CYP2D6 poor metabolizer genotype [172].

CYP2D6 was identified as the only isoenzyme capable of demethylating MeOPP, further corroborated by significant inhibition of the metabolite formation by CYP2D6 inhibitor quinidine and by significant lower metabolite formation rate in poor metabolizer human liver microsomes. This result was in accordance with the results of studies on the involvement of CYP2D6 in the O-demethylation of other methoxy substituted compounds such as amphetamines, β-carbolines and tryptophane [14, 41, 56, 173, 174].

**α-PYRROLIDINOPHENONE-DERIVED DESIGNER DRUGS**

The common feature of this new class of designer drugs is the α-pyrolidinophenone structure. As the piperazines, this class can also be further divided into sub-classes, the α-pyrolidinophenopropiophenones, PPP, as the basic structure, MOPPP, MDPPP, MPPP and the α-pirrolidinohexanophenones. Up to now, MPHP, a MPPP derivative with elongated side chain, is the only member of this second class. The α-pyrolidinophenones, with the exception of MOPPP, are scheduled in the German Controlled Substances Act.

In contrast to the other designer drug classes, no experimental data at all on pharmacology and toxicology of this drug class have been published. Drugs of abuse like cathinone, anorectics like amfepramone and antidepressants like bupropion all incorporate an α-amino-propiophenone partial structure. They are known to evoke amphetamine-like effects [175-177] including dopamine release and indirect sympathomimetic properties. With the amino group being replaced by a pyrrolidine ring as virtually the only difference in chemical structure, pyrrolidinophenones may be assumed to cause similar effects.

**R, S-α-Pyrrolidinopropiophenone (PPP)**

**Metabolism of PPP**

The metabolism of PPP (no. 1 in Fig. (6)) was studied in male Wistar rats [178]. PPP was extensively metabolized and almost exclusively excreted as metabolites. The major metabolic target was the pyrrolidine ring, in contrast to all other PPP derivatives, which were mainly metabolized at their aromatic substituents. The pyrrolidine ring of PPP was either hydroxylated at the 2'-position followed by dehydrogenation to the corresponding lactam (no. 2 in Fig. (6)) or metabolically degraded by double dealkylation to the corresponding primary amine, which actually is cathinone (no. 3 in Fig. (6)), the main psychoactive alkaloid of kath (Catha edulis FORSK) [179, 180]. Partial subsequent reduction of the keto group to the corresponding secondary alcohol introduced a second chiral center into the molecule creating the corresponding norephedrine diastereomers (no. 4 in Fig. (6)). Hydroxylation of PPP in position 4' led to the formation of a vinylogous carboxylic acid metabolite (no. 5 in Fig. (6)). This latter metabolite as well as the norephedrine metabolites was shown to be partially conjugated. In contrast to its derivatives described below, oxidative deamination to the corresponding 2-oxo metabolites was not observed for PPP. The proposed scheme for the metabolism of PPP in male Wistar rats is shown in Fig. (6).

**R, S-4'-Methoxy-α-Pyrrolidinopropiophenone (MOPPP)**

**Metabolism of MOPPP**

MOPPP is the methoxy-substituted α-pyrrolidinophenone, corresponding to the methoxy substituted derivatives of the classes of amphetamines or piperazines. The metabolism of MOPPP was studied in male Wistar rats [181]. As PPP, the lead structure of this new class of designer drugs, MOPPP was also extensively metabolized. However, as already mentioned before, in contrast to PPP the aromatic substituent was mainly metabolically altered. O-Demethylation of the methoxy group led to the formation of 4'-hydroxy-pyrrolidinopropiophenone, a common metabolite with PPP, followed by aromatic hydroxylation at position 3' to the corresponding catechol and subsequently by COMT catalyzed 3'-methylation to 4'-hydroxy-3'-methoxy-pyrrolidinophenone, two metabolites common with MDPPP.

Oxidative deamination of MOPPP or its metabolites resulted in the formation of 4'-methoxy-2-oxo-propiophenone, 4'-hydroxy-2-oxo-propiophenone, 4'-hydroxy-3'-methoxy-2-oxo-propiophenone, also a metabolite common with MDPPP. Hydroxylation of the 2'-position of the pyrrolidine
ring followed by dehydrogenation to the corresponding lactam was also reported. The phenolic metabolites were partially excreted as glucuronides and/or sulfates, again as concluded from studies with a mixture of β-glucuronidase and arylsulfatase. Reduction of the keto group to the corresponding secondary alcohol was not observed.

Influence of CYP Isoenzymes on the Metabolism of MOPPP

The influence of human CYP isoenzymes on the major metabolic reaction O-demethylation of MOPPP to 4'-hydroxy-pyrrolidinopropiophenone was studied in vitro using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs and pHLM [123]. CYP2C19 and CYP2D6 were identified to be able to catalyze the monitored reaction. Calculations using a relative activity factor (RAF) approach [118-123] to correct recombinant CYP formation rates for native human liver enzyme activity showed that CYP2D6 accounted for about 80-95% of the net intrinsic clearance of MOPPP depending on the data applied for the calculation. As a biphasic profile was detected in the studies using CYP2D6 as single enzyme source, the corresponding kinetic data were also estimated by fitting a Michaelis Menten equation for a two-site binding model. The importance of CYP2D6 for this reaction was further confirmed by inhibition studies using CYP2D6 inhibitor quinidine.

R, S-3', 4'-Methyleneoxy-α-Pyrrolidinopropiophenone (MDPPP)

Metabolism of MDPPP

MDPPP (no. 1 in Fig. 7) is the α-pyrrolidino-propiophenone derivative corresponding to the "ecstasy" class of amphetamines. The metabolism of MDPPP was studied in male Wistar rats [182]. MDPPP was extensively metabolized. Similar to the other aromatic ring substituted PPP derivatives, this substrate was the major metabolic target, i.e. demethylation (no. 2 in Fig. 7)) of the methylenedioxy followed by COMT catalyzed methylation to 4'-hydroxy-3'-methoxy-pyrrolidinopropiophenone (no. 3 in Fig. 7)), common metabolites with MOPPP, was the major metabolic pathway. Furthermore, MDPPP and its at the methylenedioxy moiety altered metabolites were either oxidative deaminated to the corresponding 2-oxo compounds 3', 4'-methylenedioxy-2-oxo-propiophenone (no. 4 in Fig. 7)), 3', 4'-dihydroxy-2-oxo-propiophenone (no. 5 in Fig. 7)), 4'-hydroxy-3'-methoxy-2-oxo-propiophenone (no. 6 in Fig. 7)), or its pyrrolidine ring was oxidized to the corresponding lactams 2''-oxo-MDPPP (no. 7 in Fig. 7)), 3', 4'-dihydroxy-2''-oxo- pyrrolidinopropiophenone (no. 8 in Fig. 7)) and 3'- hydroxy-4'-methoxy-2''-oxo-pyrrolidinopropiophenone (no. 1 in Fig. 7)). Oxidative deamination of these lactams would also yield the before mentioned 2-oxo compound. The phenolic metabolites were partially excreted as glucuronides and/or sulfates, again as concluded from studies with a mixture of β-glucuronidase and arylsulfatase. As for MOPPP, reduction of the keto group to the corresponding secondary alcohol was not observed. The proposed scheme for the metabolism of MDPPP in male Wistar rats is shown in Fig. 7).

Influence of CYP Isoenzymes on the Metabolism of MDPPP

The influence of human CYP isoenzymes on MDPPP demethylation to 3', 4'-dihydroxy-pyrrolidinopropiophenone, the major metabolic reaction of MDPPP, was studied in vitro using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs and pHLM [183, 184]. As described for MOPPP O-demethylation, CYP2C19 and CYP2D6 were identified to be able to catalyze MDPPP.
demethylenation. Based on kinetic data corrected for the relative activity factors, CYP2D6 could be identified to be the enzyme mainly responsible for the monitored reaction, accounting for about 55% of the net intrinsic clearance of MDPPP, which could be confirmed by inhibition studies using CYP2D6 inhibitor quinidine.

**R, S-4'-Methyl-α-Pyrrolidinopropiophenone (MPPP)**

*Metabolism of MPPP*

The metabolism of MPPP was studied in Wistar rats [185]. MPPP was extensively metabolized. Besides oxidation of the tolyl methyl group to the corresponding carboxylic acid and/or hydroxylation of the 2"-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactam, the side chain is mainly metabolically altered. Oxidative deamination of the carboxylic acid metabolite 2"-oxo-4'-carboxy-pyrrolidinopropiophenone and/or of the further at the pyrrolidine ring oxidized metabolite 2"-oxo-4'-carboxy-pyrrolidinopropiophenone to 2-oxo-4'-carboxy propiophenone, which was further metabolized by side chain degradation to the 4'-carboxybenzoic acid was observed. The carboxy acid metabolites were partially excreted as conjugates, probably as acyl glucuronides as concluded by the authors.

**Influence of CYP isoenzymes on the metabolism of MPPP**

The influence of human CYP isoenzymes on hydroxylation of the tolyl methyl group of MPPP, the initial oxidation step, was studied *in vitro* using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs and pHLM [122]. Calculations using a relative activity factor (RAF) approach [118-123] to correct recombinant CYP formation rates for native human liver enzyme activity showed that CYP2D6 accounted for about 80% of the net intrinsic clearance of MPPP besides CYP2C19. Only very marginal turnover rates could also be detected for CYP1A2, CYP2B6 and CYP2C9. The importance of CYP2D6 was further confirmed by inhibition studies using CYP2D6 inhibitor quinidine. For CYP2C19, atypical, biphasic kinetics were observed.

**R, S-4'-Methyl-α-Pyrrolidinohexanophenone (MPHP)**

*Metabolism of MPHP*

MPHP is the side chained elongated analogue of MPPP. The metabolism of MPHP was studied in male Wistar rats [186]. MPHP was extensively metabolized. As described for the other methyl phenyl derivative MPPP, hydroxylation of the tolyl methyl group mostly followed by dehydrogenation to the corresponding carboxy compounds and hydroxylation of the 2"-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactam was observed. Reduction of the keto group to the corresponding secondary alcohol diastereomers, known from the metabolism of PPP could also be detected. In contrast to the metabolisms of the pyrrolidinopropiophenone derivatives, this pyrrolidinohexanophenone derivative is further hydroxylated of the side
chain leading to diastereomers and possibly to positional isomers. Oxidative deamination and further biotransformation to the corresponding benzoic acid in analogy to the pyrrolidinopropiophenones was not observed. The hydroxylated metabolites and the carboxy metabolites were excreted as glucuronides and/or sulfates, again as concluded from studies with a mixture of β-glucuronidase and arylsulfatase.

Influence of CYP Isoenzymes on the Metabolism of MPHP

As for its α-pyrrolidinopropiophenone analogue MPPP, the influence of CYP isoenzymes on the hydroxylation of the tolyl methyl group was investigated [183, 187]. Different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs and pHLM were used for this investigation. CYP1A2, CYP2B6, CYP2C9 and CYP2D6 were capable of catalyzing this reaction, with CYP2D6 and CYP2C19 having the highest affinity towards MPHP. In addition, CYP2C19 exhibited the highest turnover rate and CYP2D6, the enzyme with the highest affinity showed the lowest capacity. As the apparent \( K_m \) values of CYP1A2, CYP2B6, and CYP2C9 were roughly one order of magnitude lower than those of CYP2C19 and CYP2D6 and as their \( V_{max} \) values were only in the low or intermediate range, it was concluded that they should not play a major role in MPHP clearance. The influence of CYP2D6 was also emphasized by inhibition studies with CYP2D6 inhibitor quinidine.

Furthermore, CYP2B6, CYP2C9 and CYP2C19 were identified to be capable of hydroxylating the side chain. However, as side chain hydroxylation was only a minor metabolic pathway, the kinetic parameters of the CYPs involved in this reaction were not determined.

CONCLUSIONS

Identification of metabolites of the amphetamine-, piperazine and α-pyrrolidinophenone-derived designer drugs of abuse is well described. This data is of crucial importance for forensic and clinical toxicologists, as it is a prerequisite for developing toxicological screening procedures, thus allowing the detection of an intake of these compounds.

The CYP dependent metabolism of these drugs has been studied for most of these new compounds during the last years. The particular importance of the polymorphically expressed CYP2D6 for the major metabolic steps of the new designer drugs of abuse could be shown. Especially this finding demands further studies in order to elucidate whether there are inter-individual different toxicological risks and whether these findings lead to pharmacokinetic variations that has consequences for the assessment of analytical results in clinical or forensic toxicology as well as in doping control.

More studies on the formation of toxic metabolites, or interactions with other medicaments are necessary in order to entirely understand their toxicity and the influence of metabolism on this toxicity.

ACKNOWLEDGEMENTS

The authors thank Denis S. Theobald for his suggestions.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDB</td>
<td>( R, S )-benzodioxoylbutanamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-1-(3', 4'-methylenedioxyphenyl)-2-butanamine</td>
</tr>
<tr>
<td>BZP</td>
<td>N-benzylpiperazine</td>
</tr>
<tr>
<td>mCPP</td>
<td>1-(3-chlorophenyl)piperazine</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine oxidase</td>
</tr>
<tr>
<td>MBDB</td>
<td>( R, S )-methylbenzodioxylbutanamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-N-methyl-1-(3', 4'-methylenedioxyphenyl)-2-butanamine</td>
</tr>
<tr>
<td>MDA</td>
<td>( R, S )-methylendioxyamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-1-(3', 4'-methylendioxyphenyl)-2-propanamine</td>
</tr>
<tr>
<td>MDBP</td>
<td>1-(3, 4-methylendioxybenzyl)piperazine</td>
</tr>
<tr>
<td>MDEA</td>
<td>( R, S )-methylendioxyethylamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-N-ethyl-1-(3', 4'-methylendioxyphenyl)-2-propanamine</td>
</tr>
<tr>
<td>MDMA</td>
<td>( R, S )-methylendioxyamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-N-methyl-1-(3', 4'-methylendioxyphenyl)-2-propanamine</td>
</tr>
<tr>
<td>MDPPP</td>
<td>( R, S )-3', 4'-methylendioxy-( \alpha )-pyrrolidinophenophenone</td>
</tr>
<tr>
<td>MeOPP</td>
<td>1-(4-methoxyphenyl)piperazine</td>
</tr>
<tr>
<td>MOPPP</td>
<td>( R, S )-4'-methoxy-( \alpha )-pyrrolidinophenophenone</td>
</tr>
<tr>
<td>MPHP</td>
<td>( R, S )-4'-methyl-( \alpha )-pyrrolidinohexanophenone</td>
</tr>
<tr>
<td>MPPP</td>
<td>( R, S )-4'-methyl-( \alpha )-pyrrolidinophenophenone</td>
</tr>
<tr>
<td>4-MTA</td>
<td>( R, S )-4-methylthioamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-1-(4-methylthiophenyl)-2-aminopropane</td>
</tr>
<tr>
<td>pHLM</td>
<td>Pooled human liver microsomes</td>
</tr>
<tr>
<td>PMA</td>
<td>( R, S )-para-methoxyamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-1-(4-methoxyphenyl)-2-aminopropane</td>
</tr>
<tr>
<td>PMMA</td>
<td>( R, S )-para-methoxymethamphetamine</td>
</tr>
<tr>
<td></td>
<td>( R, S )-N-methyl-1-(4-methoxyphenyl)-2-aminopropane</td>
</tr>
<tr>
<td>PPP</td>
<td>( R, S )-( \alpha )-pyrrolidinophenophenone</td>
</tr>
<tr>
<td>TFMPP</td>
<td>1-(3-trifluoromethylphenyl)piperazine</td>
</tr>
</tbody>
</table>

REFERENCES
