Chapter 19

Overview of Common Designer Drugs

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INTRODUCTION

Abuse of designer drugs is widespread among young people, especially in the "rave and dance club scene" [1,2]. In the 1990s, consumption of "classic" designer drugs such as ecstasy was peaking but they are still consumed nowadays [3]. For this reason, most of the "classic" designer drugs have been scheduled in many countries [4,5]. As consequence, a wide variety of structural modifications of such drugs have been synthesized and sold in "head shops" or online shops via the Internet [1,6]. These compounds are then called new psychoactive substances (NPS). In this chapter, only classic designer drugs are discussed and their structures are shown in Fig. 19.1. Although designer drugs have the reputation of being safe, several experimental studies in rats and humans and epidemiological studies indicated risks in humans including life-threatening serotonin syndrome, hepatotoxicity, neurotoxicity, psychopathology, and abuse potential [2,6–8]. As metabolites were suspected to contribute to some of the toxic effects and their knowledge is of importance for developing screening approaches, the main metabolic steps of these drugs have to be elucidated [6]. Therefore, this chapter is focused on the chemistry, pharmacology, toxicology, and especially hepatic metabolism of amphetamine-derived, piperazine-derived, pyrrolidinophenone-derived, beta-keto-type, and 2,5-dimethoxy phenethylamine-type designer drugs. Their metabolic pathways are summarized to facilitate the selection of the most suitable target for urine drug testing. Most results were obtained from in vivo studies with rats confirmed by analyses of authentic human urine obtained from case work and/or in vitro by incubation of the drugs with various human liver preparations such as baculovirus-infected insect cell microsomes containing individual human cDNA-expressed cytochrome P450 enzymes (CYP), or human liver microsomes and cytosol [1,2,6,9,10]. Details on the analytical challenge of designer drugs and NPS are published elsewhere [11,12].

AMPHETAMINE-DERIVED DESIGNER DRUGS

The best-known and widespread designer drugs in this class are methylenedioxy-substituted amphetamines, such as MDMA (*R*,*S*-methylenedioxymethamphetamine, "Adam," "ecstasy"), MDA (*R*,*S*-methylenedioxyamphetamine, *R,S*-1 (3′4′-methylenedioxyphen-yl)-2-propanamine, "love pills"), MDEA (*R*,*S*-methylenedioxyethylamphetamine, MDE, "Eve"), BDB (*R*,*S*-benzo-dioxolylbutanamine, *R*,*S*-1(3′,4′-methylenedioxyphenyl)-2-butanamine), and MBDB (*R*,*S*-*N*-methyl-benzo-dioxolylbutanamine), which have a methylenedioxy ($-O-CH_2-O-$) bridge between positions 3 and 4 of the aromatic ring of the amphetamine molecule [1,8].

Their chemistry, pharmacology, and toxicology have been reviewed by Kalant [8] and are summarized in the following section. All these compounds are similar in their chemistry and biological effects. MDMA, as the most frequently consumed drug out of this group, was chosen as an example in the following. Usually, designer drugs are consumed orally in the form of single-dose tablets. The typical dosage ranges of MDMA for recreational use vary between 50 and 150 mg. MDMA does not act by direct serotonin release but by blocking reuptake transporters of serotonin (main effect), noradrenalin, and dopamine. The synthesis products of MDMA and its related compounds are racemic mixtures. The corresponding enantiomers differ, for example, in potency, metabolism, and toxicity. Effects on the users can be divided into single-dose and long-term consumption. The single-dose effects are similar to those of amphetamine with additional entactogenic effects. Physically, they produce a marked increase in wakefulness, endurance and sense of energy, sexual arousal, postponement of fatigue, and sleepiness. According to Kalant [8], the psychological effects are

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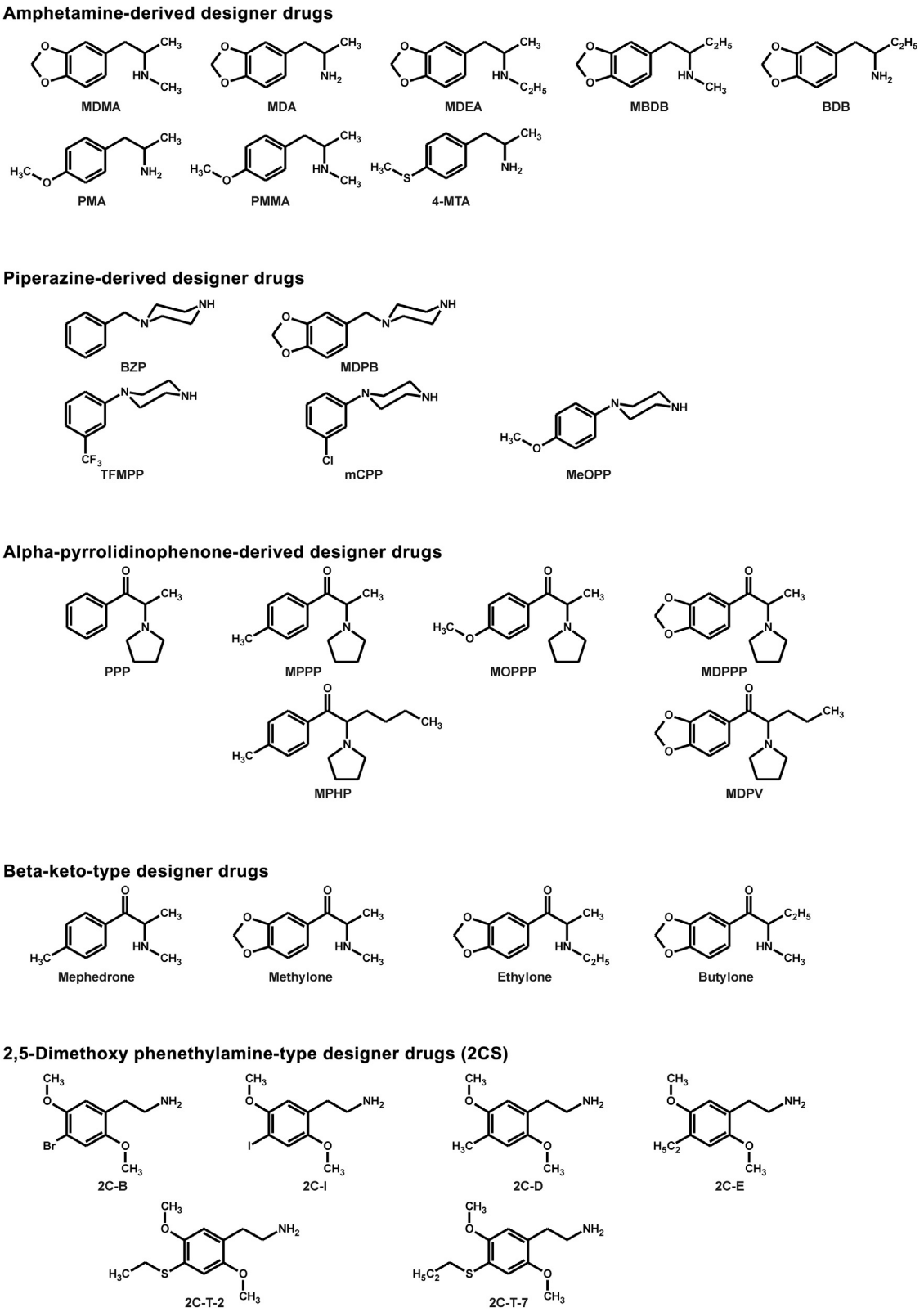

FIGURE 19.1 Chemical structures of amphetamine-derived, piperazine-derived, pyrrolidinophenone-derived, beta-keto-type, and 2,5-dimethoxy phenethylamine-type designer drugs.

euphoria, well-being, sharpened sensory perception, greater sociability, extraversion, heightened sense of closeness to other people, and greater tolerance of their views and feelings. One of the most important long-term effects is the neurotoxicity of these methylenedioxy derivatives. However, the massive release of serotonin at higher doses not only gives rise to acute psychotic symptoms and serotonin syndrome but also causes chemical damage to the cells that released it. It has been suggested [8] that the demonstrated neurotoxic effects of MDMA on the serotonin system may be the possible cause of a variety of mental and behavioral problems that outlast the actual drug experience by months or years. In addition, hepatotoxicity, cardiovascular toxicity, and cerebral toxicity have been described in the context of ecstasy consumption [8].

The metabolism of these compounds was studied in human and rats and was already reviewed by Kraemer and Maurer [9] and is summarized in Fig. 19.2. Two predominant overlapping pathways were postulated for these compounds. First, demethylenation to catechol derivatives, followed by methylation of one hydroxyl group, catalyzed by the catechol-*O*-methyl-transferase (COMT) and/or glucuronidation via UDP glucuronyltransferases and/or sulfation by sulfotransferases (MDMA, MDA, MDEA, MBDB, BDB). As second pathway, successive degradation of the side chain trough *N*-dealkylation (MDMA, MDEA, MBDB) and deamination (MDMA, MDA, MDEA, MBDB, BDB) was

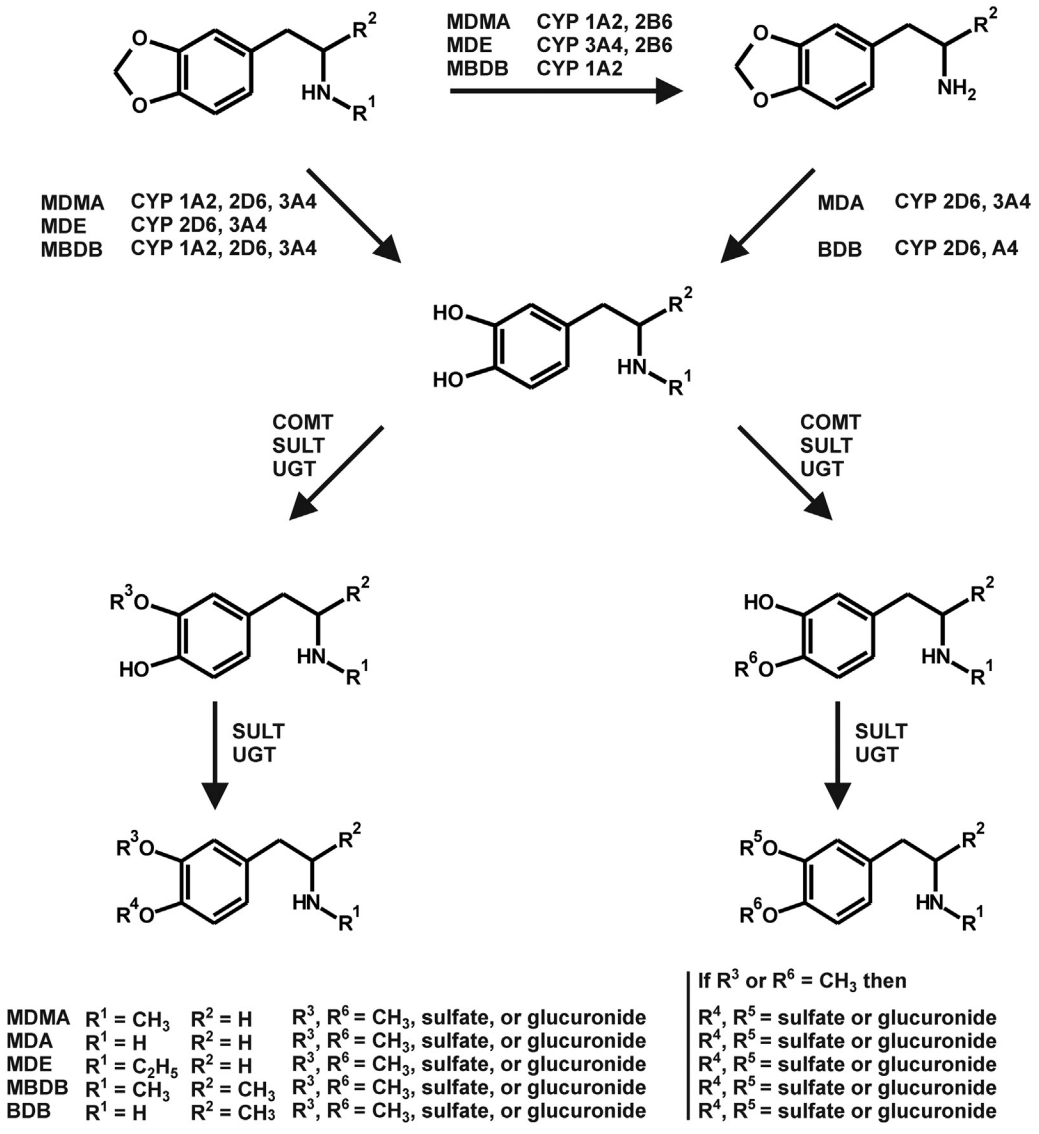

FIGURE 19.2 Main metabolic pathways of the racemic MDMA, MDA, MDE, MBDB, and BDB with involved enzymes. *SULT*, Sulfotransferase; *UGT*, UDP glucuronyltransferase.

described. According to in vitro studies using human liver microsomes and specific inhibitors for the main isoenzymes [7], formation of the catechol derivatives was mainly catalyzed by CYP3A4 and the polymorphically expressed CYP2D6. CYP1A2 was also involved in this metabolic step for MDMA and MBDB, but to a minor extent. In contrast, *N*-dealkylation of MDMA and MBDB was catalyzed by CYP1A2 and of MDE by CYP3A4. CYP2D6 contributed only to a minor extent, but at this time CYP2B6 was not yet integrated in the CYP testing. Kreth et al. [13] described CYP2B6 as main enzyme catalyzing the *N*-dealkylation. This was confirmed by Meyer et al. [14] studying the enantioselective metabolism of MDMA. *N*-demethylation was mainly catalyzed by CYP2B6 (*R*,*S*-MDMA), CYP1A2 (*R*-MDMA), and CYP2B6 (*S*-MDMA), while for demethylenation, the isozyme with the highest contribution to net clearance for *R*,*S*-MDMA, *R*-MDMA, and *S*-MDMA was CYP2D6.

Schwaninger et al. [15] have investigated the urinary excretion kinetic of MDMA and its phase I and II metabolites in human urine after controlled MDMA administration. According to this study, the main excretion products were MDMA itself and 3,4-dihydroxymethamphetamine and 4-hydroxy-3-methoxymethamphetamine conjugated to sulfates or glucuronides with sulfates present at higher concentrations. This indicated that the *O*-methylation was preferred at hydroxyl group in position 3 of the aromatic ring [15].

PMA, PMMA, AND 4-MTA

Chemistry, pharmacology, toxicology, and hepatic metabolism of *R*,*S*-para-methoxyamphetamine (PMA), *R*,*S*-para-methoxy methamphetamine (PMMA), and *R*,*S*-4-methylthioamphetamine (4-MTA) were summarized by Staack and Maurer [1] and were reported as follows. During the 1990s, the illicit drug market changed and new compounds such as PMA, PMMA, and 4-MTA appeared and were consumed orally. In the meantime, they were scheduled in most countries. Their hallucinogenic properties were already known since the late 1960s. PMA, PMMA, and 4-MTA showed similar pharmacological and toxicological effects to those of MDMA but with minor stimulating amphetamine-like effects. PMA is a serotonergic compound, evoking serotonin release, inhibiting its uptake with a minor influence of the dopamine system. It was reported that after PMA consumption, a higher rate of lethal complications may occur in comparison to other substituted amphetamine derivatives, what can be probably explained by its pharmacological and toxicological properties.

As depicted in Fig. 19.3, PMA and PMMA have mainly been metabolized by *O*-demethylation. Aromatic hydroxylation to the corresponding catechol followed by *O*-methylation by COMT and/or glucuronidation and sulfation were described as minor pathways as well as alteration of the side chain through aliphatic hydroxylation (PMA, PMMA, 4-MAT), *N*-hydroxylation to the corresponding oxime (PMA, 4-MAT), oxidative deamination followed by oxidation to carboxylic acid (PMA), and *N*-dealkylation (PMMA). For 4-MTA, no demethylation of the methylthio group but hydroxylation at the aromatic ring was described. Its main metabolic pathway studied in mice and primary human hepatocytes was the degradation of the side chain, comparable to PMA. Incubations using human liver microsomes and baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYP enzymes indicated that the *O*-demethylation of PMA and PMMA was exclusively metabolized by CYP2D6.

PIPERAZINE-DERIVED DESIGNER DRUGS

Chemistry, pharmacology, toxicology, and hepatic metabolism of the piperazine-derived designer drugs were already reviewed by Maurer et al. [2] and Staack and Maurer [1] and will be discussed in the following. Since the 1990s, the so-called piperazines emerged on the black market as completely new class of designer drugs. They can be divided into two classes, the benzylpiperazines such as *N*-benzylpiperazine (BZP) itself, and its methylenedioxy analogue 1-(3,4-methylenedioxybenzyl)piperazine (MDBP, MDBZP), and the phenylpiperazines 1-(3-chlorophenyl)piperazine (mCPP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP), and 1-(4-methoxyphenyl)piperazine (MeOPP). For all compounds except for MeOPP, serotonergic properties and amphetamine-like effects have been described.

Metabolism studies were performed in vivo using rats. Benzylpiperazines were not extensively metabolized and thus excreted mainly as unchanged parent compound in contrast to phenylpiperazines, which were extensively metabolized as shown in Fig. 19.4. It is important to know that mCPP is also a metabolite of therapeutics such as trazodone, nefazodone, etoperidone, and mepiprazol, and that interpretation of the analytical result must consider the presence or absence of unique metabolites of the therapeutics [16]. Piperazine-derived designer drugs were metabolized by alteration of the aromatic ring by hydroxylation (BZP, mCPP, TFMPP) or demethylation (MeOPP) followed by conjugation to sulfates or glucuronides. The metabolic pathways of MDBP were similar to those of methylenedioxy-substituted amphetamines, namely demethylenation followed by *O*-methylation in position 3 or 4 and/or sulfation or glucuronidation. Further

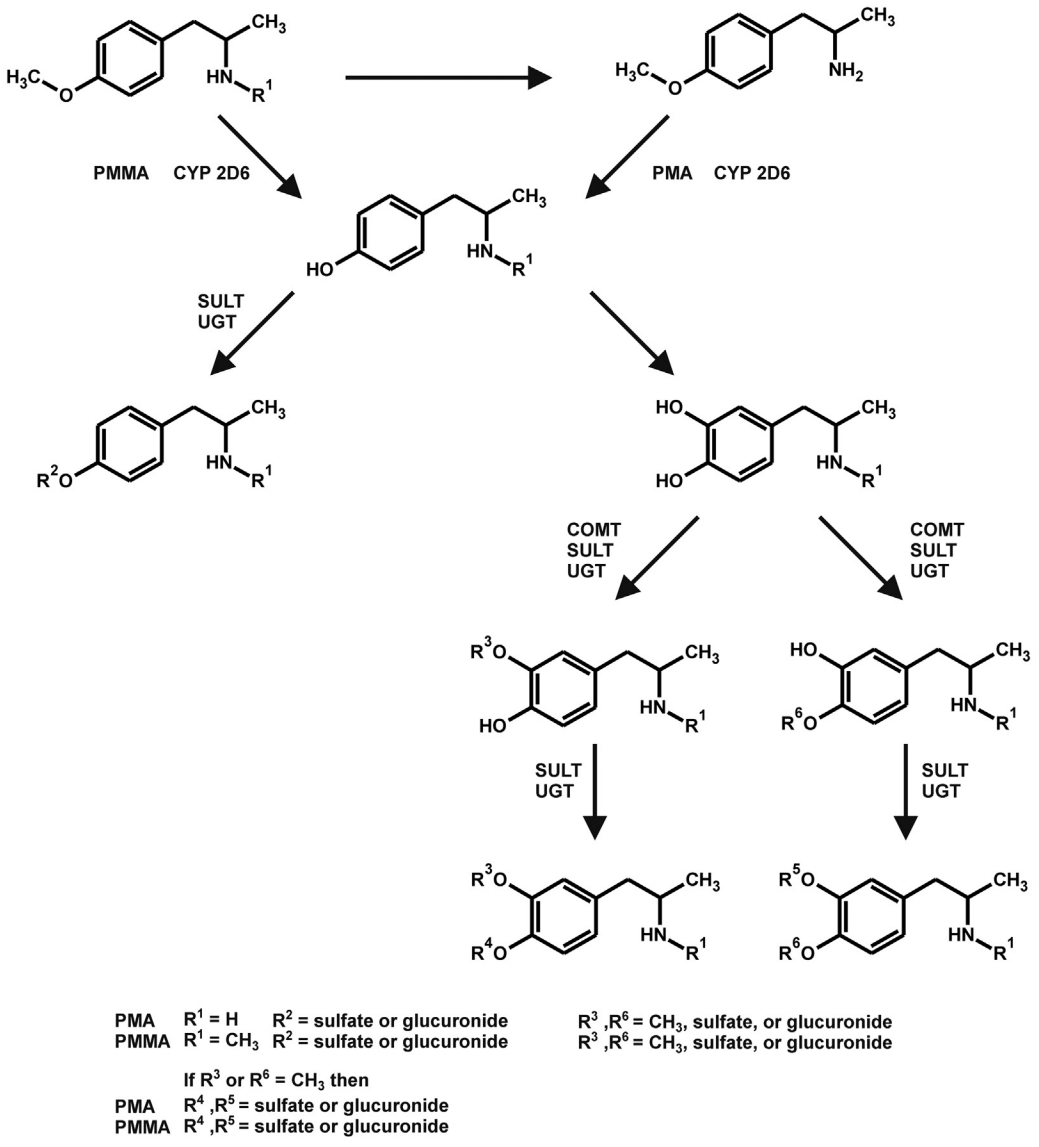

FIGURE 19.3 Main metabolic pathways of the racemic PMA and PMMA with involved enzymes, if they are known. *SULT*, Sulfotransferase; *UGT*, UDP glucuronyltransferase.

metabolic steps were *N*-dealkylation to piperazine and degradation of the piperazine heterocycle to the corresponding ethylenediamine or aniline derivatives followed by *N*-acetylation (BZP, MDBP, mCPP, TFMPP, MeOPP). *O*-Demethylation of MeOPP and hydroxylation of mCPP and TFMPP were mainly catalyzed by CYP2D6. In addition, TFMPP hydroxylation was catalyzed by CYP1A2 and 3A4 to a minor extent.

ALPHA-PYRROLIDINOPHENONE-DERIVED DESIGNER DRUGS

Chemistry, pharmacology, toxicology, and hepatic metabolism of the alpha-pyrrolidinophenone-derived designer drugs was summarized by Maurer et al. [2] and Staack and Maurer [1]. The following pyrrolidinophenone-derived designer drugs have appeared on the illicit drug market: *R,S*-α-pyrrolidinopropiophenone (PPP) as the basic structure of this new class, *R,S*-4′-methoxy-α-pyrrolidinopropiophenone (MOPPP), *R,S*-3′,4′-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP), *R,S*-4′-methyl-α-pyrrolidinopropiophenone (MPPP), *R,S*-4′-methyl-α-pyrrolidinohexanophenone (MPHP), a MPPP derivative with an elongated side chain. In recent years, 3,4-methylene-dioxypyrovalerone (MDPV) became the most common pyrrolidinophenone-derived drugs of abuse and is therefore included in this chapter although being

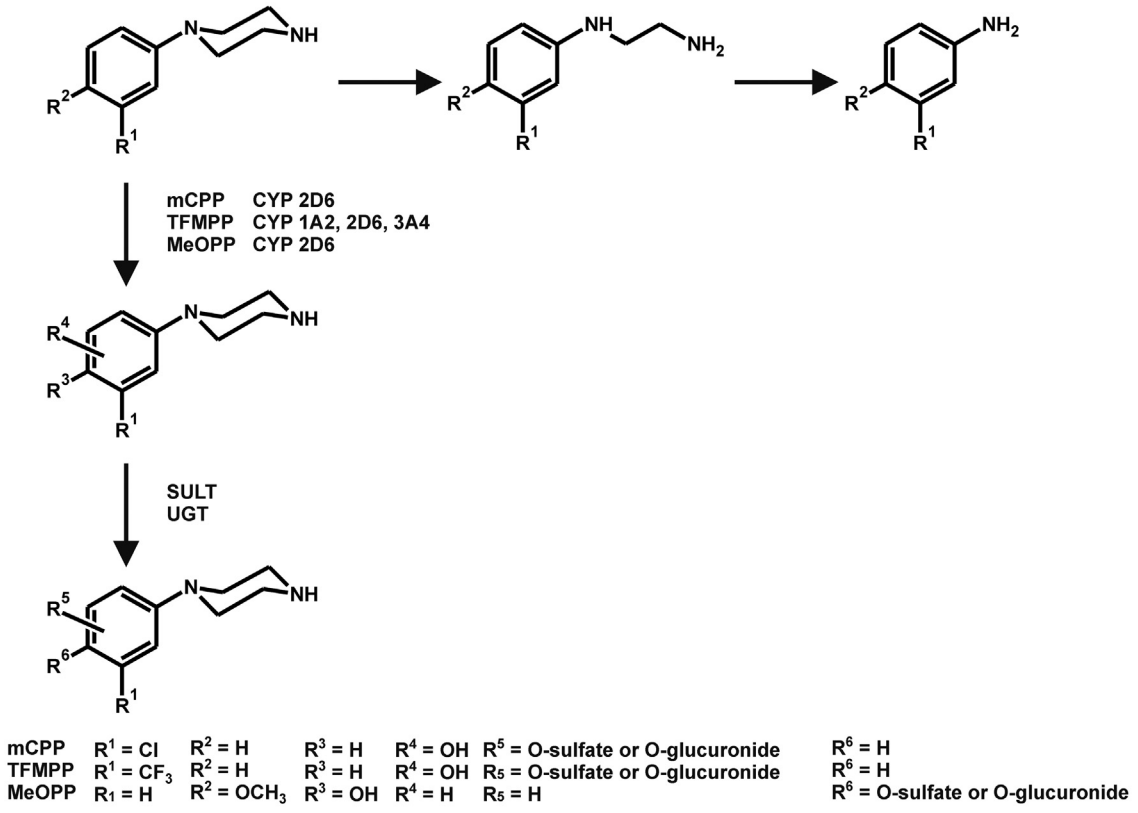

FIGURE 19.4 Main metabolic pathways of the mCPP, TFMPP, and MeOPP with involved enzymes, if they are known. *SULT*, Sulfotransferase; *UGT*, UDP glucuronyltransferase.

classified as NPS [3]. All alpha-pyrrolidinophenone-derived designer drugs have replaced the amino group by a pyrrolidine ring, which probably produce amphetamine-like effects including dopamine release and indirect sympathomimetic properties.

All these compounds were extensively metabolized at least in rats [1,2,17]. The main pathways are shown in Fig. 19.5. In contrast to the other pyrrolidinophenones, PPP was mainly altered at pyrrolidine ring by oxidation to the corresponding lactam or by double dealkylation to cathinone, the main psychoactive alkaloid of Kath (*Catha edulis*), followed by reduction of the keto group. All other drugs were mainly metabolized by oxidation at the tolyl position to the corresponding carboxylic acids (MPPP, MPHP), by *O*-demethylation of the methoxy moiety (MOPPP), or by demethylenation of the methylenedioxy moieties (MDPPP, MDPV). Hydroxylation of the side chain could be observed only for the derivative with elongated side chain (MPHP, MDPV) and hydroxylation of the aromatic ring only for MOPPP. Resulting catechols were methylated and/or glucuronidated or sulfated. In addition, reduction of the keto group (PPP) and oxidation of the pyrrolidine ring to the corresponding lactam (MOPPP, MDPPP, MPPP, MPHP, MDPV) were described as well as oxidative deamination to the corresponding 2-oxo metabolite (MDPPP). Studies on the identification of the CYP isoenzymes involved in the major metabolic steps showed that initial hydroxylation of the 4′-methyl moiety of MPPP and MPHP, *O*-demethylation of MOPPP, and demethylenation of MDPPP and MDPV were catalyzed by CYP2D6 and CYP2C19, with CYP2D6 being the major enzyme according to calculations using the relative activity factor (RAF) approach. The RAF approach can be used for the in vitro-in vivo scaling of pharmacokinetic clearance from in vitro intrinsic clearance measurements in heterologous expression systems. CYP1A2, CYP2B6, and CYP2C9 were additionally involved in MPPP and MPHP hydroxylation of the tolyl methyl group to a minor extent.

BETA-KETO-TYPE DESIGNER DRUGS

Methylone (bk-MDMA), ethylone (bk-MDEA), butylone (bk-MBDB), and mephedrone (4-methylmethcathinone) are beta-keto-substituted analogues of the corresponding amphetamines and appeared as new class on the illicit drug

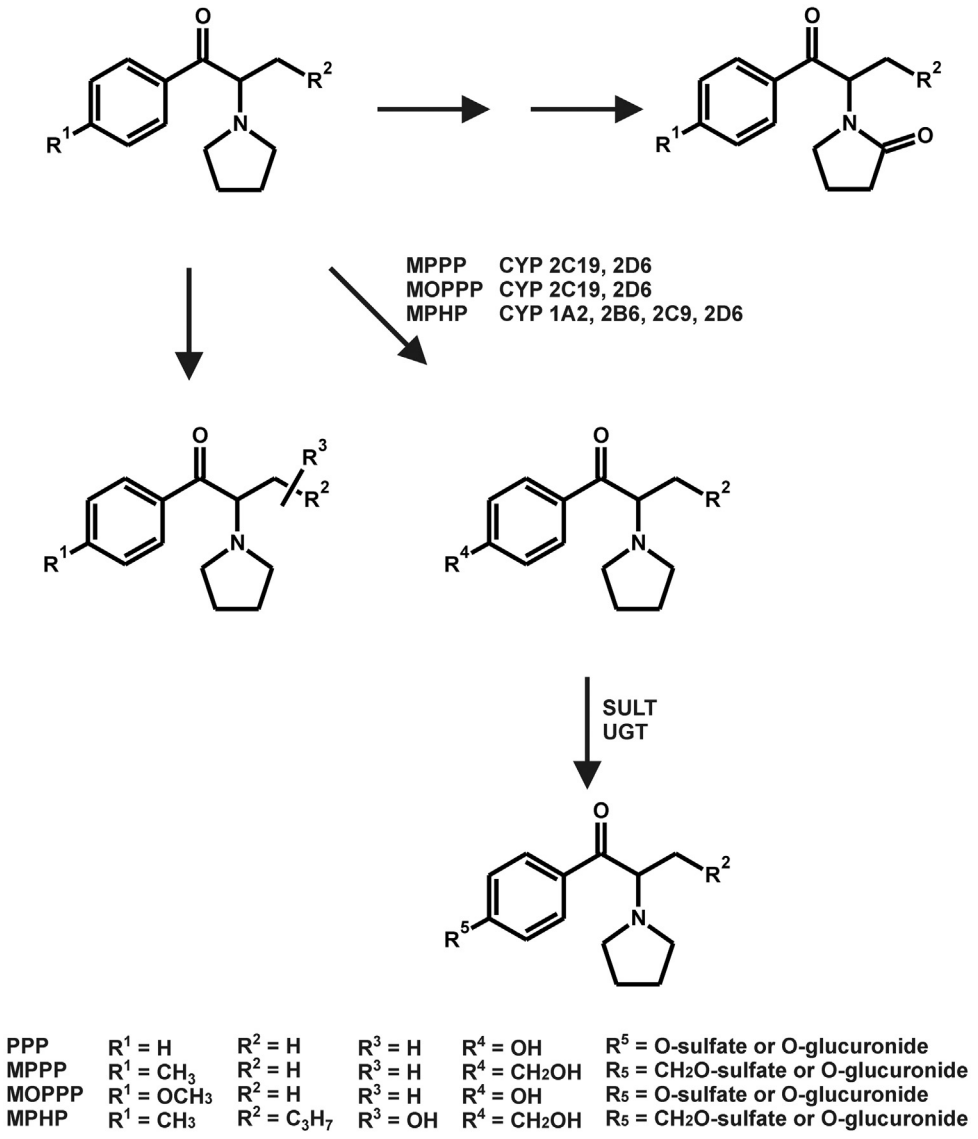

FIGURE 19.5 Main metabolic pathways of the racemic PPP, MPPP, MOPPP, and MPHP with involved enzymes, if they are known. *SULT*, Sulfotransferase; *UGT*, UDP glucuronyltransferase.

market. Due to their chemical similarity to amphetamines or methcathinone and the use as alternatives of these drugs, similar pharmacological and toxicological effects as described above could be postulated [6]. Metabolism of methylone and mephedrone was investigated in rat and abuser's urine and the metabolism of ethylone and butylone only in abuser's urine [6]. Methylone, ethylone, and butylone were metabolized similar to their methylenedioxy-substituted amphetamine analogues (Fig. 19.6), namely by *O*-demethylenation followed by methylation of one of the hydroxy groups. As minor metabolic steps, *N*-demethylation and reduction of the keto group were described. Mephedrone was degraded by reduction of the keto group, *N*-demethylation, and oxidation of the tolyl group to the corresponding alcohol and carboxylic acid. Metabolites of all drugs containing hydroxy groups were conjugated to sulfates or glucuronides. CYP enzyme kinetic data of methylone and in vitro incubations of mephedrone with specific CYP inhibitor showed that CYP2D6, CYP1A2, 2B6, and 2C19 were more or less involved in the initial metabolic steps [18,19].

2,5-DIMETHOXY PHENETHYLAMINE-TYPE DESIGNER DRUGS (2CS)

Chemistry, pharmacology, toxicology, and hepatic metabolism of 2,5-dimethoxy phenylamphetamine-type designer drugs (2Cs) were summarized by Meyer and Maurer [6]. The main representatives of this group are 4-bromo-2,5-dimethoxy-β-phenethylamine (2C-B), 4-iodo-2,5-dimethoxy-β-phenethylamine (2C-I), 2,5-dimethoxy-4-methyl-

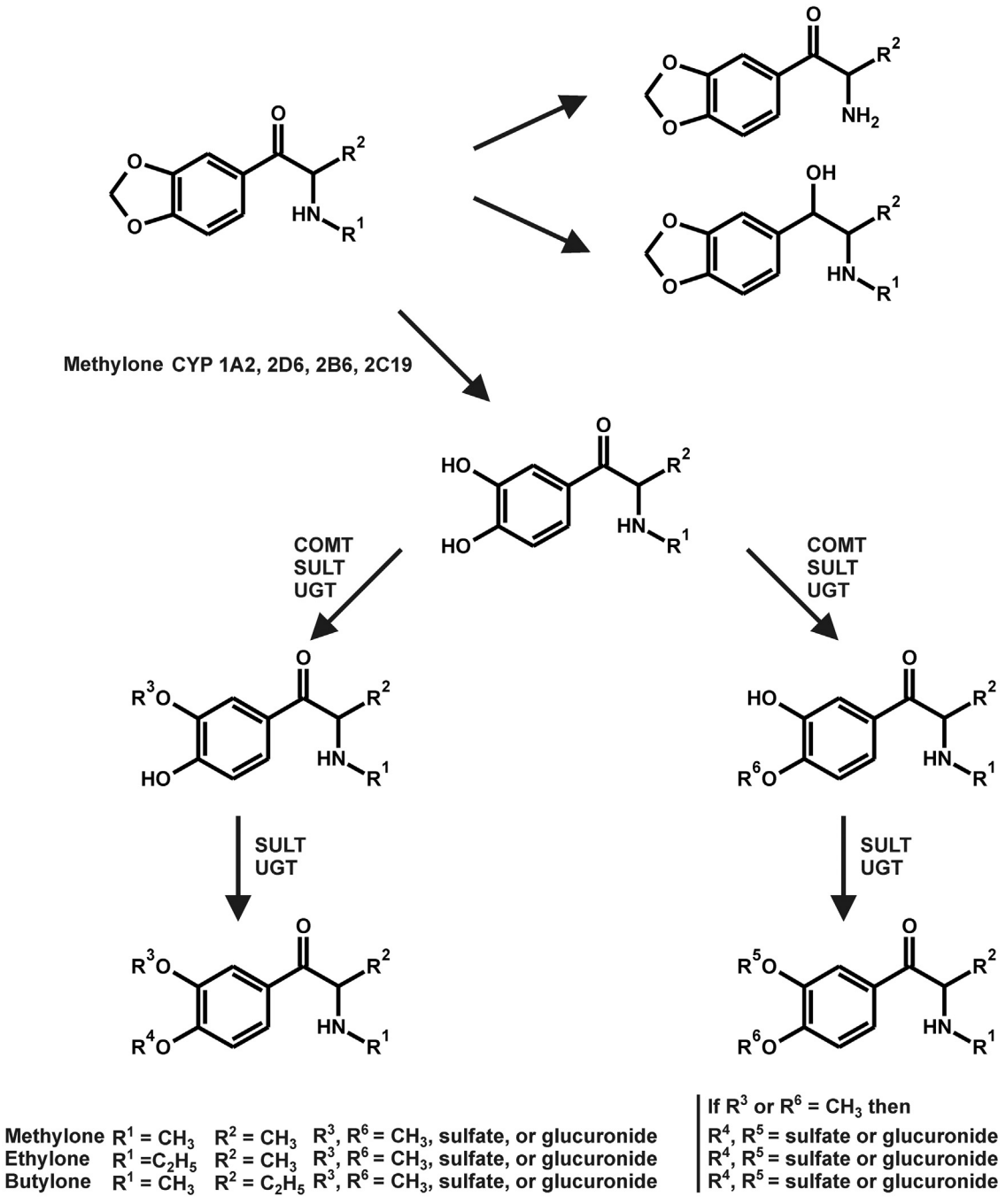

FIGURE 19.6 Main metabolic pathways of the racemic methylone, ethylone, and butylone with involved enzymes, if known. *SULT*, Sulfotransferase; *UGT*, UDP glucuronyltransferase.

β-phenethylamine (2C-D), 4-ethyl-2,5-dimethoxy-β-phenethylamine (2C-E), 4-ethylthio-2,5-dimethoxy-β-phenethylamine (2C-T-2), and 2,5-dimethoxy-4-propylthio-β-phenethylamine (2C-T-7). All these derivatives have a phenethylamine backbone with two methoxy groups in positions 2 and 5 of the aromatic ring and they further contain different lipophilic substituents in position 4. Many 2Cs were first synthesized during the 1970s and 1980s and appeared on the illicit drug market but an enormous increase in consumption was observed during the 1990s after the publication of PiHKAL [20] where their synthesis and pharmacology were described. 2C-B appeared first on the illicit drug market in the mid of 1980s and 2C-T-2, 2C-T-7, and 2C-I a few years later, sold as tablets, powder, or liquids alone or in mixture with other designer drugs. 2Cs shows affinity to 5-HT_2 receptors and act as agonist or antagonists at different receptor

subtypes. The 2Cs have hallucinogen-like effects due to their primary amine functionality separated from the phenyl ring by two carbon atoms (2Cs) and the presence of methoxy groups on positions 2 and 5 of the aromatic ring, and a hydrophobic 4-substituent. 2C-D showed less hallucinogenic properties than the other 2Cs, but eightfold higher potency than mescaline.

Main metabolic pathways are similar for all 2Cs (Fig. 19.7). They were investigated in rat urine and for 2C-B and 2C-E in consumer urine, too with the following results: *O*-demethylation in position 2 or 5 of the aromatic ring, deamination to the corresponding aldehyde, which was not detectable, followed by oxidation to the corresponding carboxylic acid or reduction to the corresponding alcohol, partial glucuronidation or sulfation, and *N*-acetylation. Combinations of

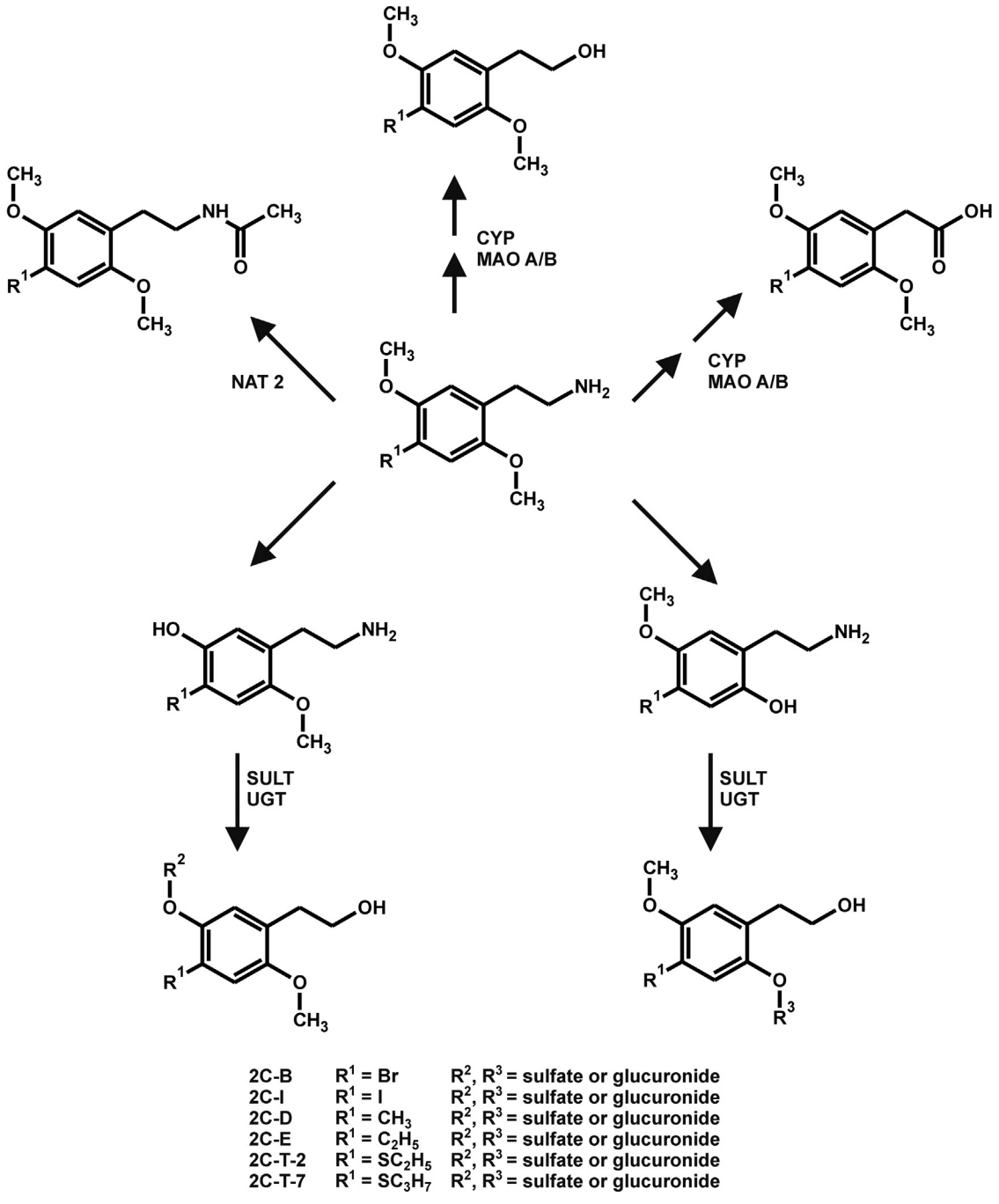

FIGURE 19.7 Main metabolic pathways of the 2C-B, 2C-I, 2C-D, 2C-E, 2C-T-2, and 2C-T-7 with involved enzymes. *NAT*, *N*-acetyltransferase; *SULT*, sulfotransferase; *UGT*, UDP glucuronyltransferase.

these steps have also been observed. 2Cs with nonhalogenic substituents in position 4 of the aromatic ring showed hydroxylation at these substituents and, in case of sulfur containing compounds, sulfoxidation. Investigation with baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYP, monoamine oxidase (MAO) enzymes revealed that the oxidative deamination of all 2Cs was catalyzed by MAO A and B, with higher affinity to MAO A, or to a minor extendt by CYP2D6 for 2C-D, 2C-E, 2C-T-2, and 2C-T-7. The differences of the K_m values between MAO A and B increased with the size of the 4-substituent. Interactions should be considered if 2Cs are taken in combination with therapeutic MAO inhibitors. Studies using recombinant human *N*-acetyltransferase showed that *N*-acetylation was mainly catalyzed by the polymorphically expressed *N*-acetyltransferase 2 [21]. In the meantime, highly potent derivatives occurred on the NPS marked, the so-called NBOMes with an *N*-2-methoxy-benzyl rest at the primary amine group of the corresponding 2Cs [22].

CONCLUSIONS

Most of the discussed designer drugs have similar pharmacological effects such as stimulating, entactogenic, and partly hallucinogenic effects. The main acute toxicological risk is the serotonin syndrome. They are extensively metabolized with the exception of benzylpiperazines and the polymorphically expressed CYP2D6 is one important enzyme in phase I metabolism. It must be kept in mind that some designer drugs have common metabolites or are metabolites of therapeutic drugs. Thus, differentiation needs detection of unique metabolites.

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