# Chemistry, Pharmacology, Toxicology, and Hepatic Metabolism of Designer Drugs of the Amphetamine (Ecstasy), Piperazine, and Pyrrolidinophenone Types

## *A Synopsis*

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**Abstract:** Designer drugs of the amphetamine type (eg, MDMA, MDEA, MDA), of the new benzyl or phenyl piperazine type (eg, BZP, MDBP, mCPP, TFMPP, MeOPP), or of the pyrrolidinophenone type (eg, PPP, MOPPP, MDPPP, MPPP, MPHP) have gained popularity and notoriety as rave drugs. These drugs produce feelings of euphoria and energy and a desire to socialize. Although in the corresponding drug scene designer drugs have the reputation of being safe, studies in rats and primates in combination with human epidemiologic investigations indicate potential risks to humans. Thus, a variety of adverse effects have been associated with the use/abuse of this class of drugs in humans, including a life-threatening serotonin syndrome, hepatotoxicity, neurotoxicity, and psychopathology. Metabolites were suspected to contribute to some of the toxic effects. Therefore, knowledge of the metabolism is a prerequisite for toxicologic risk assessment. The metabolic pathways, the involvement of cytochrome P450 isoenzymes in the main pathways, and their roles in hepatic clearance are described for designer drugs of different groups. In summary, polymorphically expressed CYP2D6 was the major enzyme catalyzing the major metabolic steps of the studied piperazine- and pyrrolidinophenone-derived designer drugs. However, it cannot be concluded at the moment whether this genetic polymorphism is of clinical relevance.

**Key Words:** designer drug, ecstasy, piperazine, pyrrolidinophenone, metabolism

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Designer drugs of the amphetamine, the new benzyl or phenyl piperazine, and the pyrrolidinophenone type have gained popularity and notoriety as "rave drugs."[1–6] Most designer drugs produce feelings of euphoria and energy and a desire to socialize.[1] They may lead to more or less severe intoxications[7,8] and impairment to drive a car.[9] Although in the corresponding drug scene the designer drugs have the reputation of being safe, several experimental studies in rats and humans and epidemiologic studies indicated risks to humans including a life-threatening serotonin syndrome, hepatotoxicity, neurotoxicity, psychopathology, and abuse potential of such designer drugs.[1,10] Metabolites were suspected to contribute to some of the toxic effects.[2,11] Therefore, knowledge of the metabolism is a prerequisite for toxicologic risk assessment. The metabolic pathways, the involvement of cytochrome P450 isoenzymes in the main pathways, and their roles in hepatic clearances are described for designer drugs of different groups. Implications for pharmacogenetic variations, drug–drug interactions, and for toxicologic risk assessment are discussed.

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## AMPHETAMINE-DERIVED DESIGNER DRUGS

### Chemistry, Pharmacology, and Toxicology

The most important drugs of the amphetamine type are *R,S*-1-(3′,4′-methylenedioxyphenyl)-2-propanamine (MDA), *R,S*-methylenedioxymethamphetamine (MDMA), and *R,S*-methylenedioxyethylamphetamine (MDEA) as well as *R,S*-1-(1′,3′-benzodioxol-5′-yl)-2-butanamine (BDB) or *R,S*-N-methylbenzodioxolylbutanamine (MBDB). Their pharmacologic and toxicologic properties have been reviewed by Kalant.[1]

### Hepatic Metabolism

The metabolism of amphetamine-derived designer drugs has been thoroughly studied in humans[12–15] and recently reviewed by Kraemer and Maurer.[2] In Figure 1, the toxification steps of the methylenedioxyamphetamine derivatives postulated by Hiramatsu et al[11] are shown as well as the major CYP isoforms involved in the initial step.[14,15] Details have recently been discussed elsewhere.[2]

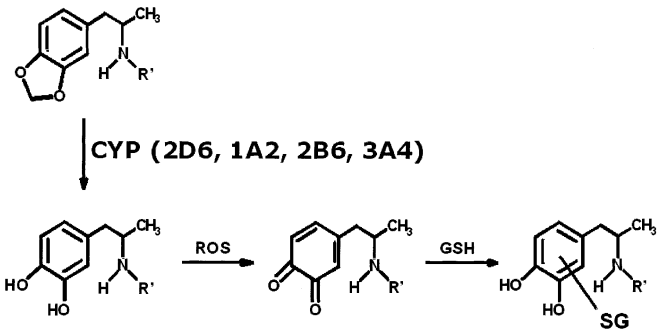


**FIGURE 1.** Postulated major metabolic toxification steps of methylenedioxyamphetamine derivatives (R′ = H, MDA; R′ = $CH_3$, MDMA; R′ = $CH_2CH_3$, MDEA; ROS, reactive oxygen species; GST, glutathione).

## PIPERAZINE-DERIVED DESIGNER DRUGS

### Chemistry, Pharmacology, and Toxicology

Since the 1990s, the illicit drug market for recreational drugs has changed considerably. One of these new classes of drugs of abuse are the so-called "piperazines." They can further be divided into two classes, the benzylpiperazines such as N-benzylpiperazine (BZP) itself and its methylene dioxy analogue 1-(3,4-methylenedioxybenzyl)piperazine (MDBP), and the phenylpiperazines 1-(3-chlorophenyl)piperazine (mCPP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP), and 1-(4-methoxyphenyl)piperazine (MeOPP).

Information on human pharmacology can be found for BZP, which produces amphetamine-like effects.[16,17] Central serotoninomimetic action, which involves serotonin (5-HT) uptake inhibition and 5-$HT_1$ receptor agonistic effects, was shown in a further study.[18] A fatality after use of BZP and MDMA has already been reported.[8] For MDBP, weak inhibition of serotonin uptake has been described. Animal studies showed that MDBP pretreatment altered the disposition and metabolism of MDMA in the brain and in peripheral organs.[19] In another study, inhibition of the MDMA-induced neurotoxicity by MDBP was reported.[20] mCPP was found to interact with serotoninergic, adrenergic, and dopaminergic receptor systems.[21,22] The stimulant and hallucinogenic effects of mCPP was comparable to those of MDMA.[23] Serotonin syndrome may occur after mCPP intake.[24] Serotoninergic properties have also been described for TFMPP.[21] Drug users have described similarities between TFMPP and MDMA (www.erowid.org). No information on the human pharmacology is available for MeOPP.

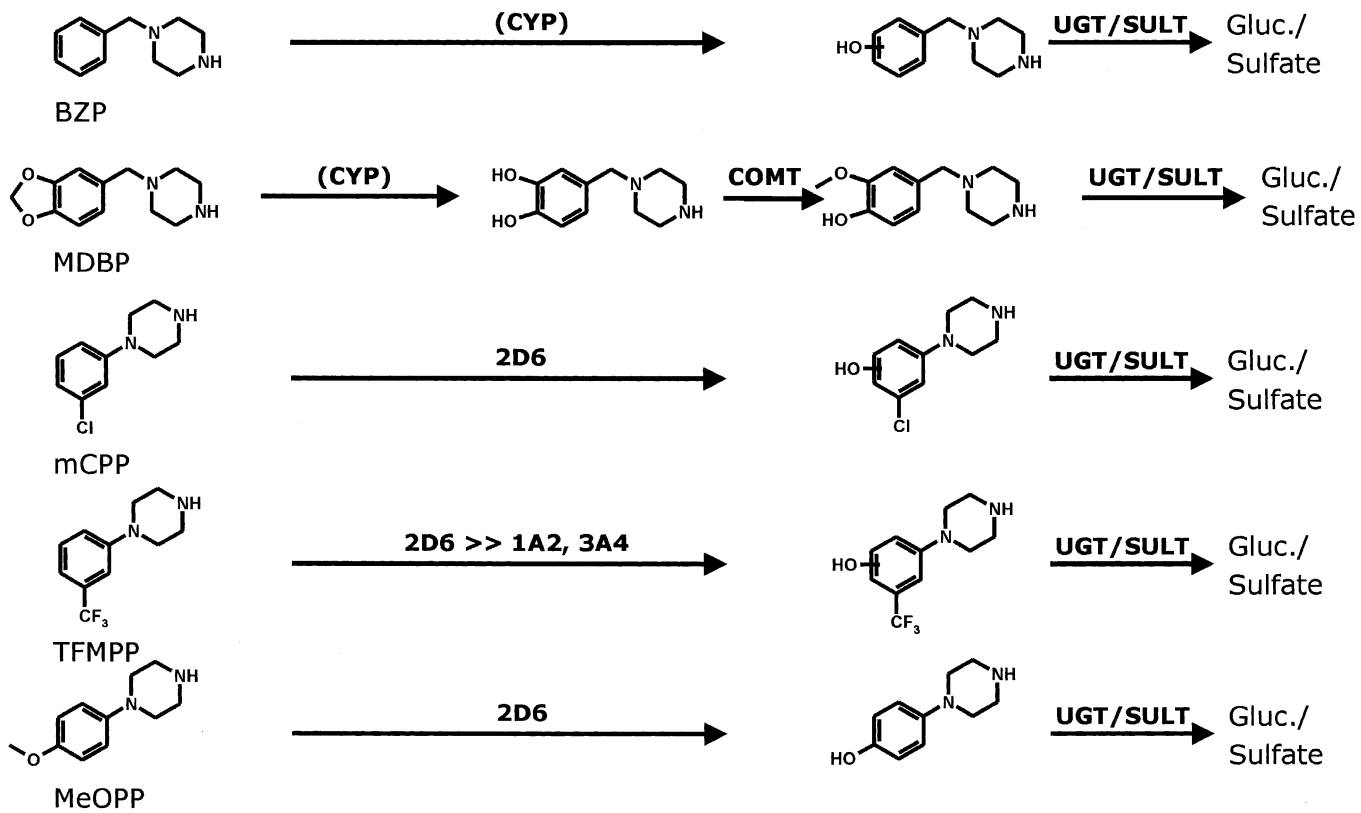


**FIGURE 2.** Major metabolic pathways of common piperazine-derived designer drugs (UGT, UDP glucuronyl transferase; SULT, sulfotransferase; COMT, catechol O-methyl transferase).

## Hepatic Metabolism

The benzylpiperazines were metabolized by alteration of the aromate, either by hydroxylation (BZP) or by demethylenation of the methylenedioxy moiety (MDBP). N-dealkylation to piperazine and metabolic degradation of the piperazine heterocycle to the corresponding ethylenediamine or aniline derivatives were further metabolic reactions.[25,26] The phenylpiperazines were more extensively metabolized than the benzylpiperazines and excreted almost exclusively as metabolites. Metabolic alteration of the aromate, either by hydroxylation (mCPP, TFMPP) or by O-demethylation of the methoxy moiety (MeOPP), were the major metabolic reactions. Metabolic degradation of the piperazine moiety to the corresponding ethylenediamine or aniline derivatives could further be observed. Metabolic phase 2 reactions were partial glucuronidation or sulfation of the phenolic metabolites, methylation of the catechols, and partial acetylation of the aniline derivatives.[27–29] The major metabolic steps are summarized in Figure 2.

Studies on the identification of the CYP isoenzymes involved in the major metabolic steps showed that mCPP hydroxylation as well as MeOPP O-demethylation were catalyzed exclusively by CYP2D6.[29,30] In vivo studies using Wistar and Dark Agouti rats as models of the human CYP2D6 extensive or poor metabolizer phenotypes indicated the involvement of CYP2D6 in TFMPP hydroxylation.[31] In vitro studies showed that three isoforms, CYP1A2, CYP2D6, and CYP3A4, were capable of catalyzing TFMPP hydroxylation, with CYP2D6 being the most important enzyme and accounting for about 80% of the net intrinsic clearance, calculated using the relative activity factor (RAF).[31]

# PYRROLIDINOPHENONE-DERIVED DESIGNER DRUGS

## Chemistry, Pharmacology, and Toxicology

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), and *R,S*-4′-methyl-α-pyrrolidinohexanophenone (MPHP), an MPPP derivative with an elongated side chain.[3]

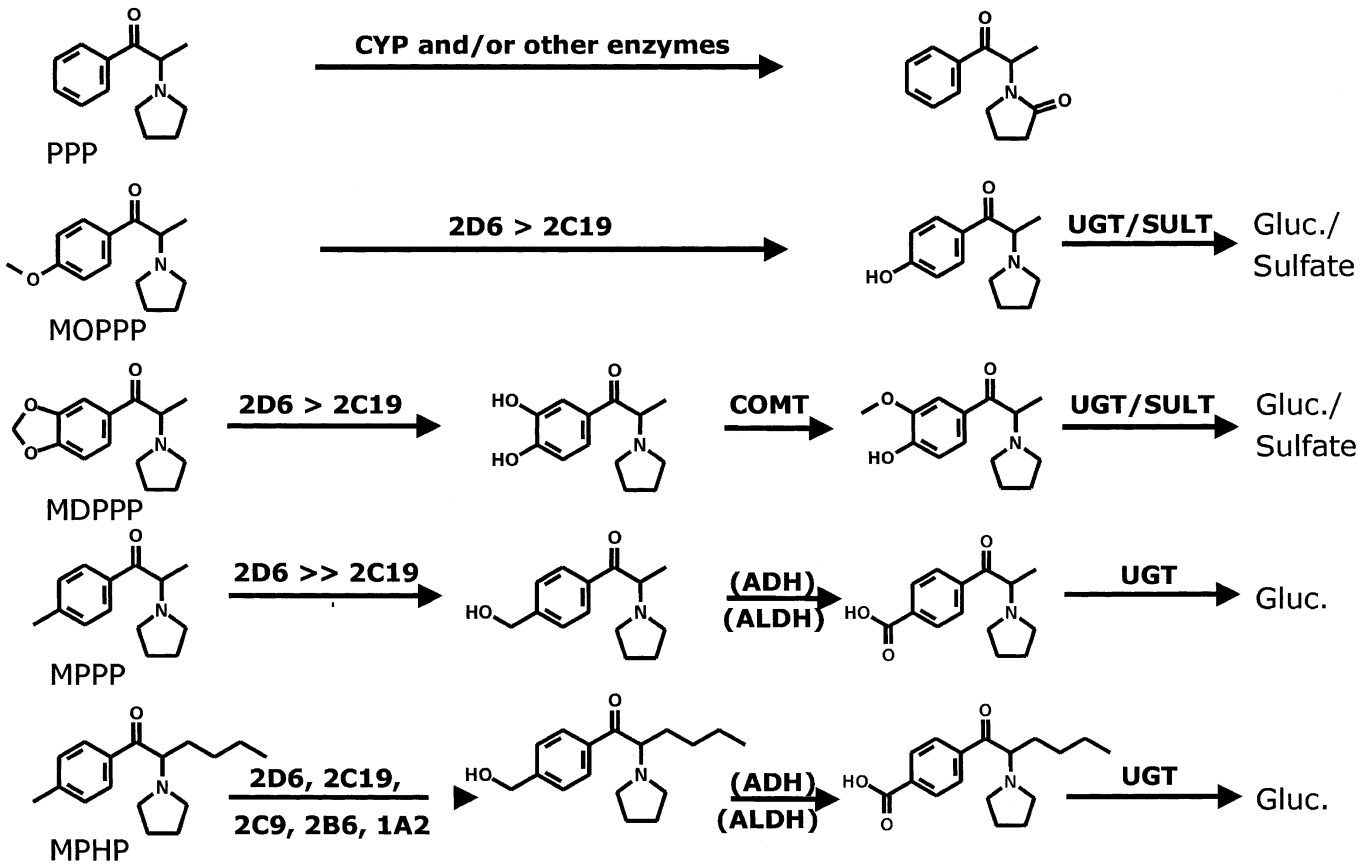


**FIGURE 3.** Major metabolic pathways of common pyrrolidinophenone-derived designer drugs (UGT, UDP glucuronyl transferase; SULT, sulfotransferase; COMT, catechol O-methyl transferase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase).

Unfortunately, until now, no experimental data on pharmacology and toxicology of this drug class have been published. Drugs of abuse such as cathinone, anorectics such as amfepramone, and antidepressants such as bupropion all incorporate an α-aminopropiophenone partial structure. They are known to evoke amphetamine-like effects[32–34] 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.

## Hepatic Metabolism

PPP was shown to be metabolically altered mainly on the pyrrolidine ring, which was oxidized to its corresponding lactam or metabolically degraded by double dealkylation to cathinone followed by reduction of the keto group. In contrast to its derivatives, oxidative desamination to the corresponding 2-oxo metabolites was not observed for PPP. All other drugs were mainly metabolized at their aromatic substituents, by oxidation of the methyl groups to the corresponding carboxylic acid (MPPP, MPHP), by O-demethylation of the methoxy moiety (MOPPP), or by demethylenation of the methylenedioxy moiety (MDPPP). Hydroxylation of the side chain could be observed only for the derivative with elongated side chain (MPHP). Metabolic phase 2 reactions were methylation of the catechols, partial glucuronidation or sulfation of the hydroxy metabolites, and partial glucuronidation of the carboxy metabolites.[35–39] The major metabolic steps are summarized in Figure 3.

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 were catalyzed by CYP2D6 and CYP2C19, with CYP2D6 being the major enzyme according to calculations using the RAF approach. CYP1A2, CYP2B6, and CYP2C9 were additionally involved in MPPP and MPHP hydroxylation to a minor extent.[40–42]

## CONCLUSIONS

Detailed knowledge of the metabolic steps of designer drugs is an important prerequisite for assessing possible interactions with other drugs or food ingredients as well as interindividual pharmacogenetic differences. Although the polymorphically expressed CYP2D6 was the major enzyme catalyzing the major metabolic steps of the studied piperazine- and pyrrolidinophenone-derived designer drugs, it cannot be concluded at the moment whether this genetic polymorphism is of clinical relevance. Further studies on the pharmacology and toxicology of the metabolites together with well-documented clinical data will be necessary.

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