# Metabolism of Designer Drugs of Abuse: An Updated Review

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**Abstract:** This paper reviews the metabolism of new designer drugs of abuse that have emerged on the black market during the last years and is an update of a review published in 2005. The presented review contains data concerning the so-called 2C compounds (phenethylamine type) such as 4-bromo-2,5-dimethoxy-beta-phenethylamine (2C-B), 4-iodo-2,5-dimethoxy-beta-phenethylamine (2C-I), 2,5-dimethoxy-4-methyl-beta-phenethylamine (2C-D), 4-ethyl-2,5-dimethoxy-beta-phenethylamine (2C-E), 4-ethylthio-2,5-dimethoxy-beta-phenethylamine (2C-T-2), and 2,5-dimethoxy-4-propylthio-beta-phenethylamine (2C-T-7), beta-keto designer drugs such as 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (butylone, bk-MBDB), 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-one (ethylone, bk-MDEA), 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one (methylone, bk-MDMA), and 2-methylamino-1-p-tolylpropane-1-one (mephedrone, 4-methyl-methcathinone), pyrrolidinophenones such as 4-methyl-pyrrolidinobutyrophenone (MPBP) and alpha-pyrrolidinovalerophenone (PVP), phencyclidine-derived drugs such as *N*-(1-phenylcyclohexyl)-propanamine (PCPr), N-(1-phenyl-cyclohexyl)-2-ethoxyethanamine (PCEEA), N-(1-phenylcyclohexyl)-3-methoxypropanamine (PCMPA), and N-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA), tryptamines such as 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), and finally alpha-methylfentanyl (alpha-MF) and 3-methylfentanyl (3-MF). Papers have been considered and reviewed on the identification of *in vivo* or *in vitro* human or animal metabolites and the cytochrome P450 or monoamineoxidase isoenzyme-dependent metabolism.

**Keywords:** Designer drugs, phenethylamines, beta-keto amphetamines, pyrrolidinophenones, phencyclidines, tryptamines, fentanyls, cytochrome P450, monoamineoxidase.

## INTRODUCTION

In recent years, a series of new drug classes appeared on the illicit drugs market such as 4-substituted or 2,5-dimethoxy amphetamines [1-6], 2,5-phenethylamines (so-called 2Cs) [7-12], beta-keto-amphetamines [13,14], phencyclidine derivatives [15-18], piperazines [19-27], pyrrolidinophenones [19,28-35], and finally tryptamine [36-41] or fentanyl derivatives [42-44]. Although designer drugs have the reputation of being safe, several experimental studies in rats and humans and epidemiological studies indicated risks to humans including a life-threatening serotonin syndrome, hepatotoxicity, neurotoxicity, psychopathology and abuse potential [6,19,45-51]. As metabolites were suspected to contribute to some of the toxic effects [46,52,53], and their knowledge is of importance for developing screening approaches, the main metabolic steps of these new drugs have to be known.

Furthermore, variations in the formation of pharmacologically active metabolites, formation of toxic metabolites, or interactions with other medicaments may have consequences for the assessment of analytical results in clinical or forensic toxicology as well as in doping control. Additionally, there is good evidence that drug metabolism by genetically variable cytochrome P450 (CYP) isoforms 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.

The metabolism of piperazines and some pyrrolidinophenones have already been reviewed by Staack and Maurer in 2005 [28] and the metabolism of amphetamine derivatives and their derived designer drugs will be reviewed elsewhere [54].

The aim of the present paper was to update the previously published review [28] considering English written papers on the human or animal metabolism of 2C drugs such as 4-bromo-2,5-dimethoxy-β-phenethylamine (2C-B), 4-iodo-2,5-dimethoxy-β-phenethylamine (2C-I), 2,5-dimethoxy-4-methyl-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). Papers are also reviewed on beta-keto designer drugs such as 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (butylone, bk-MBDB), 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-one, bk-3,4-methylenedioxyethylamphetamine (ethylone, bk-MDEA), 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one, bk-3,4-methylenedioxymethamphetamine (methylone, bk-MDMA), and mephedrone (2-methylamino-1-p-tolylpropane-1-one, 4-methyl-methcathinone, bk-4-methylmethamphetamine). Furthermore, papers were included on the pyrrolidinophenones 4-methyl-pyrrolidinobutyrophenone (MPBP) and alpha-pyrrolidinovalerophenone (PVP), and phencyclidine-derived drugs such as *N*-(1-phenylcyclohexyl)-propanamine (PCPr), *N*-(1-phenyl-cyclohexyl)-2-ethoxyethanamine (PCEEA), *N*-(1-phenylcyclohexyl)-3-methoxypropanamine (PCMPA), and *N*-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA). Finally, tryptamines such as 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), and the fentanyl-derived drugs alpha-methylfentanyl (alpha-MF) and 3-methylfentanyl (3-MF) were included in the review. Their chemical structures are shown in Figs. (**1a-c, 2a-b, 3, 4**, and **6**-**7**). Papers on the identification of *in vivo* or *in vitro* human or animal metabolites and on the involvement of CYP or monoamineoxidase (MAO) isoenzymes have been considered in the following. The main metabolic reactions and the enzymes involved in the phase-I steps as well as their kinetic constants are summarized in Table **1**.

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

Phenethylamine itself is not a common used drug because it is rapidly metabolized [55], but its derivatives such as 2C-B, 2C-I, 2C-D, 2C-E, 2C-T-2, and 2C-T-7 are often abused [56]. Their chemical structures are shown in Fig. (**1a-c**). They all have in common the phenethylamine backbone with two methoxy groups in positions 2 and 5 of the aromatic ring and they further contain different lipophilic 4-substituents. Introducing new substituents always allows drugs of abuse producers to create "legal" products until they are scheduled as controlled substances. The synthesis of most of the 2Cs were first described in the compilation "PIHKAL" [55]. Although many 2Cs were first synthesized during the 1970s and 1980s and appeared on the illicit drug market, they gained increase

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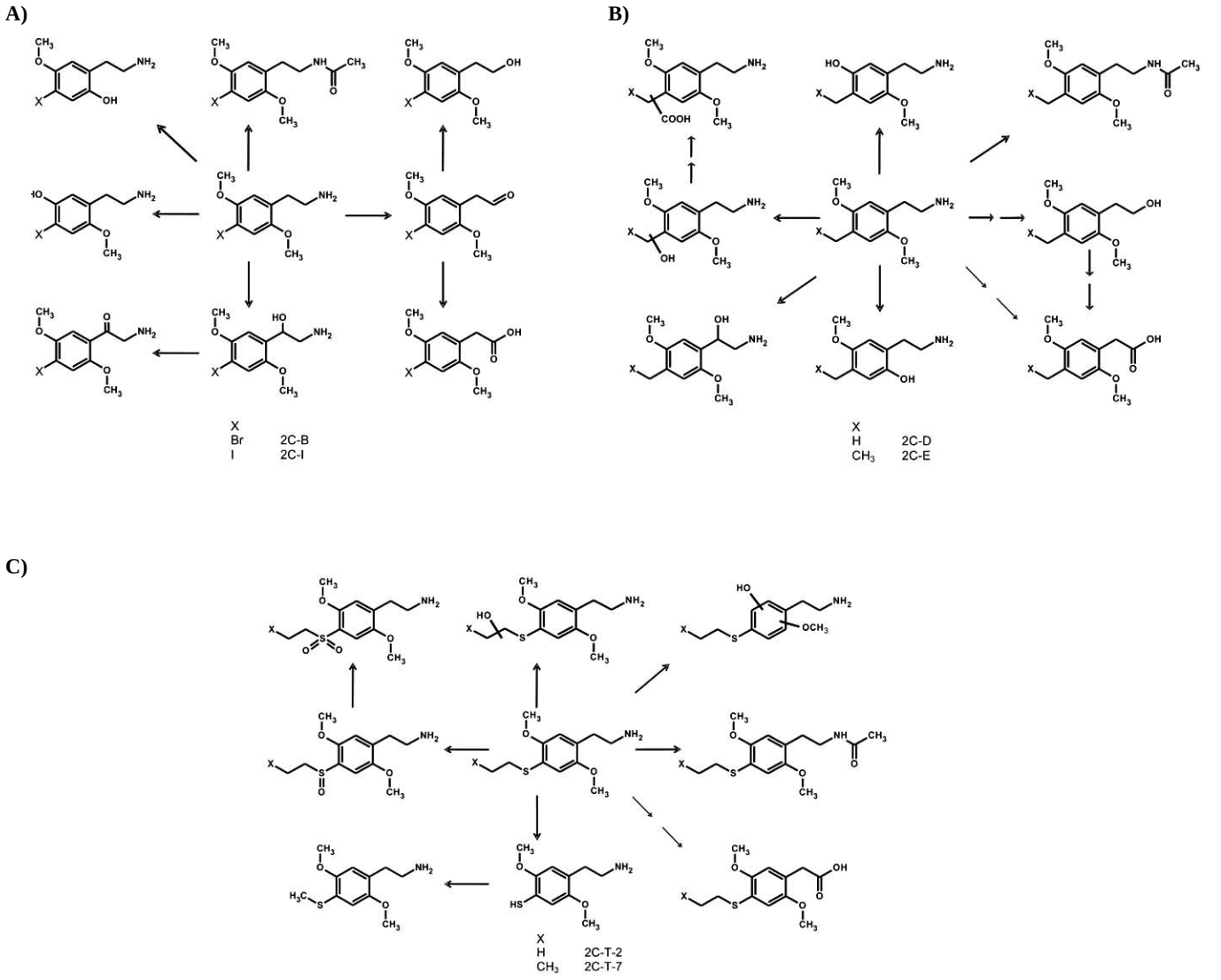



**Fig. (1). (a).** Main metabolic steps for the phenethylamine-derived designer drugs 2C-B and 2C-I. **(b).** Main metabolic steps for the phenethylamine-derived designer drugs 2C-E and 2C-D. **(c).** Main metabolic steps for the phenethylamine-derived designer drugs 2C-T-2 and 2C-T-7.

ing popularity in the 1990s after the publication of "PIHKAL" [39]. Therefore, it is relatively easy for the illicit drug producers to manufacture a new 2C entity when another one is scheduled.

Only little information is available on the pharmacological and toxicological properties of the members of the 2C series, but it is known, that they show affinity to 5-$HT_2$ receptors and act as agonists or antagonists at different receptor subtypes [57-63]. Several quantitative structure-activity relationships (QSAR) studies were published about hallucinogenic β-phenethylamines [64-71]. For 2C-B, partial agonism at $\alpha_1$-adrenergic receptors was described [72,73]. The chemical structure responsible for hallucinogen-like activity comprises a primary amine functionality separated from the phenyl ring by two carbon atoms (2Cs), the presence of methoxy groups in position 2 and 5 of the aromatic ring, and a hydrophobic 4-substituent (alkyl, halogen, alkylthio, etc.) [51,60]. Using the results of these analyses, predictions of the hallucinogenic potency of new β-phenethylamines should be possible.

2C-B was one of the first compounds of the 2C type entering the illicit drug market in the mid 1980s [74] followed by the *S*-alkyl compounds 2C-T-2 and 2C-T-7 and the iodo analogue 2C-I in the 1990s [56]. They were sold in so-called "smart shops" or "head shops" alone or in mixture with other designer drugs in form of tablets, powder, or liquid preparations [75-80].

## 2C-B

For 2C-B, Kanamori *et al*. investigated the metabolism in rat urine and rat hepatocytes [81-83]. The major metabolites of 2C-B in rat hepatocytes were 2-*O*-desmethyl-2C-B and the carboxylic acid derivative. Other metabolites were the alcohol derivative 2-*O*-demethyl-*N*-acetyl-2C-B and 5-*O*-demethyl-*N*-acetyl-2C-B. This metabolism is similar to that seen in whole rats [81]. Theobald *et al*. could further identify a deaminohydroxy-side chain hydroxy, an *O*-demethyl deaminohydroxy-side chain hydroxy, and an *O*-demethyl-deaminohydroxy-side chain oxo metabolite in rat urine [84].

De Boer *et al*. reported the only human *in vivo* data of metabolites of 2C-B, but only in form of preliminary data [85]. Carmo *et al*. studied the 2C-B metabolism in hepatocytes of six species including humans [86,87]. After incubation of 2C-B with human

**Table 1. Studied Compounds, Metabolic Reactions and Enzymes Involved in the Initial Phase-I Steps. The Kinetic Constants are Given in μM (Km) and pmol/min/pmol (Vmax).**

| Compound | Initial phase-I reactions | Isoform | $K_m$ | $V_{max}$ | Main phase-II reactions | References |
|---|---|---|---|---|---|---|
| **2,5-Dimethoxy phenethylamine-type designer drugs (2Cs)** | | | | | | |
| 2C-B | deamination | MAO-A | 43.8 ± 8.7 | 2.3 ± 0.1 [1] | glucuronidation and/or sulfation* | [81-84,97] |
| | | MAO-B | 63.8 ± 7.7 | 1.7 ± 0.1 [1] | | |
| 2C-I | deamination | MAO-A | 31.1 ± 4.1 | 2.5 ± 0.1 [1] | glucuronidation and/or sulfation* | [11,97] |
| | | MAO-B | 88.3 ± 7.2 | 4.6 ± 0.1 [1] | | |
| 2C-D | deamination | MAO-A | 41.3 ± 3.6 | 1.7 ± 0.04 [1] | glucuronidation and/or sulfation* | [10,97] |
| | | MAO-B | 96.9 ± 9.7 | 2.3 ± 0.1 [1] | | |
| 2C-E | deamination | MAO-A | 49.6 ± 3.3 | 0.7 ± 0.01 [1] | glucuronidation and/or sulfation* | [9,97] |
| | | MAO-B | 187.8 ± 19.1 | 4.3 ± 0.2 [1] | | |
| 2C-T-2 | deamination | MAO-A | 38.8 ± 2.7 | 1.5 ± 0.03 [1] | glucuronidation and/or sulfation* | [7,93,97] |
| | | MAO-B | 146.0 ± 13.0 | 4.3 ± 0.2 [1] | | |
| 2C-T-7 | deamination | MAO-A | 14.4 ± 2.1 | 3.4 ± 0.1 [1] | glucuronidation and/or sulfation* | [8,95,97] |
| | | MAO-B | 108.5 ± 19.2 | 4.5 ± 0.3 [1] | | |
| **Beta-keto-type designer drugs** | | | | | | |
| Methylone | initial reactions not given | no data available | | | glucuronidation and/or sulfation+ | [13] |
| Butylone | initial reactions not given | no data available | | | glucuronidation and/or sulfation* | [14] |
| Ethylone | initial reactions not given | no data available | | | glucuronidation and/or sulfation* | [14] |
| Mephedrone | initial reactions not given | no data available | | | glucuronidation and/or sulfation* | [105] |
| **Pyrrolidinophenone-type designer drugs** | | | | | | |
| MPBP | 4´-hydroxylation | CYP1A2 | 1647 ± 369 | 0.89 ± 0.08 | glucuronidation and/or sulfation* | [29,114] |
| | | CYP2C19 | 9.2 ± 5.3 | 0.14 ± 0.04 | | |
| | | CYP2D6 | 2.4 ± 0.6 | 0.07 ± 0.005 | | |
| PVP | 2´´-oxidation | CYP2B6, CYP2C19, CYP2D6, CYP1A2 | no data available | | glucuronidation and/or sulfation* | [30] |
| Phencyclidine-derived designer drugs | | | | | | |
| PCEPA | O-dealkylation | CYP2B6 | 220 ± 14 | 220 ± 4.3 | glucuronidation and/or sulfation* | [118,119] |
| | | CYP2C19 | 59 ± 10.3 | 41 ± 1.4 | | |
| | | CYP2D6 | 11.0 ± 0.14 | 12.4 ± 0.07 | | |
| | | CYP3A4 | 242 ± 23 | 34.9 ± 1.09 | | |
| PCPr | N-dealkylation, omega-1 hydroxylation, 4-hydroxylation | CYP2B6 | no data available | | glucuronidation and/or sulfation* | [17,120] |
| PCEEA | O-dealkylation | CYP2B6 | 121 ± 7 | 253 ± 4 | glucuronidation and/or sulfation* | [16,120] |
| | | CYP2C9 | 334 ± 22 | 14 ± 0.3 | | |
| | | CYP2C19 | 47 ± 4 | 39 ± 0.7 | | |
| | | CYP3A4 | 550 ± 48 | 27 ± 0.9 | | |
| PCMEA | O-dealkylation | CYP2B6 | 86 ± 8 | 324 ± 7 | glucuronidation and/or sulfation* | [16,120] |
| | | CYP2C19 | 61 ± 11 | 16 ± 1 | | |
| PCMPA | O-dealkylation | CYP2B6 | 248 ± 12.9 | 59 ± 0.98 | glucuronidation and/or sulfation* | [18,119] |
| | | CYP2C19 | 147 ± 8.8 | 15 ± 0.23 | | |
| | | CYP2D6 | 13.6 ± 0.8 | 11.2 ± 0.06 | | |
| **Tryptamine-derived designer drugs** | | | | | | |
| 5-MeO-DIPT | O-demethylation | CYP2D6 | 2.0 [2] | 29.8 [2] | glucuronidation and/or sulfation+ | [130,133] |
| | N-deisopropylation | CYP1A2 | 263 [2] | 9.4 [2] | | |

**(Table 1) contd…..**

| Compound | Initial phase-I reactions | Isoform | $K_m$ | $V_{max}$ | Main phase-II reactions | References |
|---|---|---|---|---|---|---|
| | | CYP2C8 | 291 [2] | 1.7 [2] | | |
| | | CYP2C9 | 1663 [2] | 4.2 [2] | | |
| | | CYP2C19 | 36 [2] | 6.9 [2] | | |
| | | CYP3A4 | 184 [2] | 4.4 [2] | | |
| **Fentanyl-derived designer drugs** | | | | | | |
| alpha-Methylfentanyl | N-dealkylation | no data available | | | no data available | [44] |
| 3-Methylfentanyl | N-dealkylation | no data available | | | no data available | [138] |

* determined indirectly via differences in abundance of metabolites before and after glucuronidase and sulfatase hydrolysis

[+] determined using mass spectrometry

[1] $V_{max}$ given in dimensionless PAR/min and mg protein

[2] standard error not given in reference

hepatocytes, six metabolites could be identified, described to be 4-bromo-2,5-dimethoxyphenylacetic acid, 4-bromo-2-hydroxy-5-methoxyphenylacetic acid, 4-bromo-2,5-dimethoxybenzoic acid, 2-(4-bromo-2,5-dimethoxyphenyl)-ethanol, 2-(4-bromo-2-hydroxy-5-methoxyphenyl)-ethanol and 4-bromo-2,5-dimethoxy-phenol. The main metabolic steps of 2C-B are shown in Fig. (**1a**).

An interesting result was obtained concerning the susceptibility of human hepatocytes to toxic effects of 2C-B [87]. One of the three human donors was found to be much more susceptible. After 2 h of incubation with 1000 μM 2C-B, the ATP content of hepatocytes from human donors 1, 2 and 3 were reduced to 41%, 58%, and 5% of the controls, respectively.

### 2C-I

Because of its affinity to 5-$HT_2$ receptors, radioactive 2C-I was synthesized as a label for the 5-$HT_2$ receptor and as a potential brain scanning agent for nuclear medicine [57,88]. Drees *et al*. reported morbidity involving 2C-I in a 39 years old woman [89].

Theobald *et al*. identified 2C-I metabolites in rat urine using gas chromatography-mass spectrometry (GC-MS) and capillary electrophoresis ion trap (CE-MS) technologies [11]. Unfortunately, CE-ion trap technology could only used for a particular question and not for a determination of phase-II metabolites. As the peak area of the 2C-I parent compound was more abundant after glucuronidase and sulfatase hydrolysis, its *N*-glucuronidation of was concluded.

Finally, they postulated the following metabolic steps: *O*-demethylation of the parent compound in position 2 and 5 of the aromatic ring, respectively, followed either by partial glucuronidation/sulfation or by *N*-acetylation with subsequent partial glucuronidation/sulfation or by deamination to the corresponding aldehyde, which was not detected, followed by oxidation to the corresponding acid or reduction to the corresponding alcohol, followed by partial glucuronidation/sulfation. The latter alcohol was further hydroxylated in beta-position and further oxidized to the corresponding oxo metabolite. Another metabolic pathway was the deamination of the parent compound to the corresponding aldehyde, which was not detected, followed by oxidation to the corresponding acid or reduction to the corresponding alcohol with subsequent partial glucuronidation/sulfation. The proposed metabolic steps of 2C-I are also shown in Fig. (**1a**).

### 2C-D

2C-D was identified on the illicit drug market in the US [90] and partial agonism at $\alpha_1$-adrenergic receptors was described [73]. Compared to other compounds of the class, 2C-D shows a decreased potency concerning hallucinogenic activity, but it has at least about eightfold potency of mescaline [55,69].

Using GC-MS after application of 2C-D to male Wistar rats, the following metabolic steps were postulated as summarized in Fig. (**1b**): *O*-demethylation of the parent compound in position 2 or 5, followed by *N*-acetylation or by deamination with oxidation to the corresponding acid or reduction to the corresponding alcohol [10]. In a second pathway, 2C-D was hydroxylated at the methyl moiety in position 4. In a third pathway, it was deaminated followed by oxidation to the corresponding acid or by reduction to the corresponding alcohol.

### 2C-E

2C-E was identified in several countries on the illicit drug market [79,80]. Lood and Eklund reported that they could identify 2C-E in urine samples of three males [91]. Using GC-MS after application of 2C-E to male Wistar rats, the following metabolic steps could be postulated as also depicted in Fig. (**1b**): *O*-dealkylation of the parent compound in position 2 or 5, followed by *N*-acetylation and hydroxylation at C2´, or by deamination with oxidation to the corresponding acid or reduction to the corresponding alcohol [9]. Second pathway was *N*-acetylation of the parent compound followed on the one hand by hydroxylation at position C1´ of the ethyl side chain with subsequent dealkylation and oxidation to the corresponding ketone and followed on the other hand by beta-hydroxylation. A third pathway was the hydroxylation of the parent compound at position C2´ of the ethyl side chain followed by *N*-acetylation and oxidation of the hydroxy group to the corresponding acid. A further pathway was the deamination of the parent compound followed by reduction to the corresponding alcohol or by oxidation to the corresponding acid. The latter was hydroxylated at position C2´ or C1´ followed by oxidation to the corresponding ketone. Concerning the *O*-demethylation in position 2 or 5 of the aromatic ring, in most cases two isomers were detected, but the exact position of the resulting hydroxy group could not be determined.

### 2C-T-2

2C-T-2 has surfaced in the illicit drug market in the form of tablets containing 2C-T-2 alone or in mixtures with other designer drugs [56,92]. Lin *et al*. described qualitative metabolism for 2C-T-2 in rats and four major metabolites of 2C-T-2 were identified [93]. Two major metabolic pathways were proposed for 2C-T-2 in rats. In the first pathway, 2C-T-2 forms an aldehyde metabolite by deamination and subsequent oxidation and/or reduction whereas the intermediate (4-ethylthio-2,5-dimethoxyphenyl acetaldehyde) was not found. In the second pathway the amino groups is acetylated to form the final metabolites, 1-acetoamino-2-(2-hydroxy-4-ethylthio-5-methoxyphenyl)-ethane and 1-acetoamino-2- (2-methoxy-4-ethylsulfanyl-5-hydroxyphenyl)-ethane. Theobald *et al*. presented the metabolism of 2C-T-2 in more detail and could postulate the following metabolic steps as shown in Fig. (**1c**): sulfoxidation of the parent compound to the corresponding sulfone, followed by N-acetylation and either *O*-demethylation of one methoxy group or hydroxylation of the *S*-alkyl side chain. A second pathway was the

*O*-demethylation of the parent compound, followed by *N*-acetylation and sulfoxidation to the corresponding sulfone. A third pathway was the *N*-acetylation of the parent compound, followed either by *O*-demethylation and sulfoxidation or by *S*-deethylation to the corresponding thiol with subsequent methylation of the thiol moiety [7].

### 2C-T-7

2C-T-7 is another sulfur analogue of 2C-B. After consumption of 2C-T-7, fatalities were reported during 2000 and 2001. Because of these increasing problems with the 2Cs [56,94], many of them were scheduled in most countries. Investigating male rat urine, Theobald *et al*. reported that 2C-T-7 is metabolized by hydroxylation of the propyl side chain followed by *N*-acetylation and sulfoxidation, and by deamination followed by oxidation to the corresponding acid or by reduction to the corresponding alcohol, and by *S*-dealkylation followed by *N*-acetylation, *S*-methylation, and sulfoxidation [8]. Based on the identified compounds, they postulated the following three metabolic pathways. Hydroxylation of the propyl side chain of 2C-T-7 to 2,5-dimethoxy-4-hydroxypropylthio-beta-phenethylamine followed by *N*-acetylation and sulfoxidation should be one possible pathway. The second pathway led to the corresponding acid or (reduced) to the corresponding alcohol, followed by partial glucuronidation and/or sulfation. The third pathway led via *N*-acetylation and *S*-depropylation to the corresponding thiol, followed by methylation of the thiol moiety. Further metabolic steps were the sulfoxidation of the methylated thiol to the corresponding sulfoxide and the corresponding sulfone.

Two years later Kanamori *et al*. presented a study in which 2C-T-7 and its 17 predicted metabolites were synthesized and analyzed by liquid chromatography-mass spectrometry (LC-MS) [95]. Besides this, the drug was administered orally to rats and metabolites were identified. In addition to Theobald *et al*., sulfoxide, sulfones and combinations of them with the previously described metabolic steps were identified. The metabolic steps of 2C-T-7 are also depicted in Fig. (**1c**).

### Enzymes Involved in the Phase-I Metabolism of Phenethylamines

One major metabolic step of the phenethylamines is the deamination to the corresponding aldehyde. These aldehydes were not detected in urine, most probably because they are rapidly reduced or oxidized to the respective alcohols or carboxylic acids, which are present in urine [7-12,81-83,96]. Isoenzymes of the MAO and CYP types were studied concerning their ability to catalyze this deamination [97]. The initial screening studies with the two human hepatic MAOs and nine most abundant human hepatic CYPs were performed to identify their possible role in 2C deamination. For 2C-D, 2C-E, 2C-T-2, and 2C-T-7, CYP2D6 was involved in deamination but with low formation rates. Therefore, kinetic data were only determined for both MAO isoforms. The apparent $K_m$ values determined in this study show that the 2Cs have a slightly higher affinity for MAO-A than for MAO-B. Furthermore, the differences of the $K_m$ values between MAO-A and -B are getting greater by an increasing 4-substituent size. The reason for this might be a large binding pocket for 4-substituents in the case of MAO-A, whereas MAO-B should contain a small hydrophobic binding pocket for 4-substituents [98]. Furthermore, MAO-B showed increased $V_{max}$ values compared to MAO-A. However, interpretation of the measured $V_{max}$ values in this study is difficult, because quantification of metabolites was not possible since there were no metabolite standards available for quantification. As MAO-A and MAO-B are involved in one of the major metabolic steps of the 2Cs, the 2Cs might be susceptible for drug-drug interactions with MAO inhibitors possibly leading to elevated plasma concentrations of the 2Cs. Such inhibitors are used as antidepressants such as tranylcypromine and moclobemide or as anti-parkinsonians such as selegiline. Additionally, authors stated that due to the relatively high apparent $K_m$ values of the 2Cs, further studies on their MAO inhibitory potential are required. However, the question whether drug interactions are of relevance for 2C pharmacokinetics and/or clinical outcome of intoxications cannot be answered at the moment due to lack of sufficient authentic human data.

### Overview

The 2Cs were mainly metabolized by *O*-demethylation in position 2 or 5 of the aromatic ring and by deamination followed by oxidation to the corresponding acid or reduction to the corresponding alcohol. Further metabolic steps were side chain hydroxylation and in the case of sulfur containing 2Cs, sulfoxidation. Metabolic phase II reactions were partial glucuronidation or sulfation and *N*-acetylation. Combinations of these steps and minor metabolites could also be detected [7-12,81-83,85-87,93,96,97]. MAO-A and MAO-B were the major enzymes involved in the deamination reaction [97]. For 2C-D, 2C-E, 2C-T-2, and 2C-T-7, CYP2D6 was also involved, but only to a small extent. All studied 2Cs have a slightly higher affinity for MAO-A than for MAO-B, which can be explained by the size of the binding pocket of the enzyme for the 4-substituent of the 2Cs [97].

## BETA-KETO-TYPE DESIGNER DRUGS

The so-called beta-ketos (bk) namely butylone (bk-MBDB), ethylone (bk-MDEA), methylone (bk-MDMA), and mephedrone (4-methylmethcathinone) have appeared as a new class of designer drugs on the black market in many countries [13,99,100]. Due to their chemical similarity to amphetamines or methcathinone and the use as alternatives for these drugs, a similar stimulant effect of the bk-designer drugs could be postulated.

### Methylone

Methylone showed strong inhibitory effects on the re-uptake of dopamine, serotonin and norepinephrine [101]. It increased serotonin and norepinephrine release, but had little effect on dopamine release using rat brain synaptosomes. Shimizu *et al*. described an intoxication of a 27-year-old male patient after a single ingestion of the mixture of methylone and 5-MeO-MIPT [102]. Metabolism of methylone was investigated using rat and human urine samples [13]. The human urine specimens were collected 36 h after oral application and the rat urine samples were collected over 24 h after intraperitoneal administration. Additionally, the expected major urinary metabolites were synthesized as standards, namely 3,4-methylenedioxycathinone (MDC), 4-hydroxy-3-methoxymethcathinone (HMMC), 3-hydroxy-4-methoxymethcathinone (3-OH-4-MeO-MC), and 3,4-methylenedioxyephedrine (MDEP). The metabolic steps postulated according to the metabolites identified by GC-MS and LC-MS are shown in Fig. (**2a**). In rat urine, all aforementioned metabolites were detected with exception of the reduced compound MDEP which is in line with other findings concerning similar beta-keto compounds [30-35,103,104]. The cumulative amount of the most abundant characteristic metabolite HMMC excreted within the first 48 h was approximately 26% of the dose. In addition, over 80% of the excreted urinary HMMC and 3-OH-4-MeO-MC were found to be conjugated. In human urine, methylone, MDC, HMMC, and 3-OH-4-MeO-MC were detected. The authors concluded after quantification of the investigated metabolites that HMMC is an abundant characteristic metabolite and that MDC and 3-OH-4-MeO-MC are minor metabolites for methylone in humans. Unfortunately, they have not checked for other metabolites than the synthesized one. For instance metabolites resulting from overlapping metabolic steps such as 3-hydroxy-4-methoxycathinone or 3,4-methylenedioxynorephedrine. The latter one is of particular interest since other authors concluded that the reduction of the oxo group is the predominant step for the *N*-dealkyl metabolites of beta-keto drugs [105].

### Butylone

The metabolites of bk-MBDB were identified in abusers' urine by GC-MS and LC-MS and the structures were confirmed by chemical synthesis [14]. Based on the identified metabolites, the following metabolic steps could be postulated Fig. (**2a**): *N*-demethylation, demethylenation followed by methylation, and reduction of the keto group. In analogy to MDMA, MDEA and MBDB, *N*-demethylation was the minor step and demethylenation followed by methylation the predominant one. In contrast to MDMA, MDEA and MBDB, methylation in position 4 was higher than in position 3. This might be caused by affinity differences of the demethylenated compounds to the catechol *O*-methyltransferase (COMT) or by individual differences. Metabolites containing hydroxy groups were excreted in conjugated form.

### Ethylone

Using GC-MS and LC-MS, metabolites of ethylone (bk-MDEA) in abusers' urine were identified using the synthesized metabolites 2-amino-1-(3,4-methylenedioxyphenyl)propan-1-one (bk-MDA), 2-ethylamino-1-(4-hydroxy-3-methoxyphenyl)propan-1-one (bk-4,3-HMEA), 2-ethylamino-1-(3-hydroxy-4-methoxy phenyl)propan-1-one (bk-3,4-HMEA), and 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-ol (beta-hydroxy-MDEA) [14]. Metabolic steps identified are shown in Fig. (**2a**). In addition conjugates were determined on the basis of enzymatic hydrolysis and direct analyses of conjugates by LC-MS.

In the study by Zaitsu *et al*. bk-MDA, bk-4,3-HMEA, bk-3,4-HMEA, and beta-hydroxy-MDEA were determined as metabolites for bk-MDEA. Based on the quantitative measurement, bk-4,3-HMEA was the most abundant for bk-MDEA among the identified metabolites and, as for bk-MBDB, the N-dealkylation seemed to be a minor pathway. Again, the urinary levels of the 3-OH-4-MeO metabolites were comparatively high as described for bk-MBDB metabolites. Furthermore, the urinary levels of bk-4,3-HMEA, bk-3,4-HMEA increased after acidic hydrolysis. Finally, the same pathways as described for bk-MBDB were determined for bk-MDEA.

As already mentioned in context with the methylone metabolism study, authors have not checked for other metabolites than the synthesized ones. In consequence, such study design impedes the elucidation of uncommon pathways in designer drug metabolism.

### Mephedrone

Mephedrone was recently scheduled in Germany because of its potential for addiction and the associated health risks. Meyer *et al*. studied the metabolism of mephedrone in rat and human urine using GC-MS and identified the following metabolites: nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone, and nor-hydroxytolyl mephedrone depicted in Fig (**2b**). Besides these metabolites, the parent drug mephedrone was also detected [105]. The following metabolic pathways were postulated: *N*-demethylation to the primary amine, reduction of the keto moiety to the respective alcohol and oxidation of the tolyl moiety to the corresponding alcohols and the carboxylic acid. Hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone were partly excreted as glucuronides and/or sulfates. In human urine samples a further metabolite namely 4-carboxy-dihydro mephedrone could be identified by these authors. Additionally, they concluded that only the primary amines were reduced to both diastereomic alcohols and that only one diastereomer was detectable in the case of the dihydro metabolites of the secondary amines. This should be due to the fact that the *N*-methyl group is sterically hindering the enzymatic reaction to one of the isomers.

### Overview

The bk designer drugs were metabolized by humans in analogy to corresponding amphetamines and additionally reduced at the beta-keto group to the corresponding alcohol. bk-MBDB, bk-MDEA, and bk-MDMA are mainly demethylenated and subsequently *O*-methylated as well as *N*-dealkylated and finally, the keto groups reduced with exception of bk-MDMA [13,14]. Mephedrone was hydroxylated at the 4-methyl group followed by oxidation to the corresponding 4-carboxy metabolite, *N*-demethylated and finally reduced at the beta-keto group to the corresponding alcohol [105].

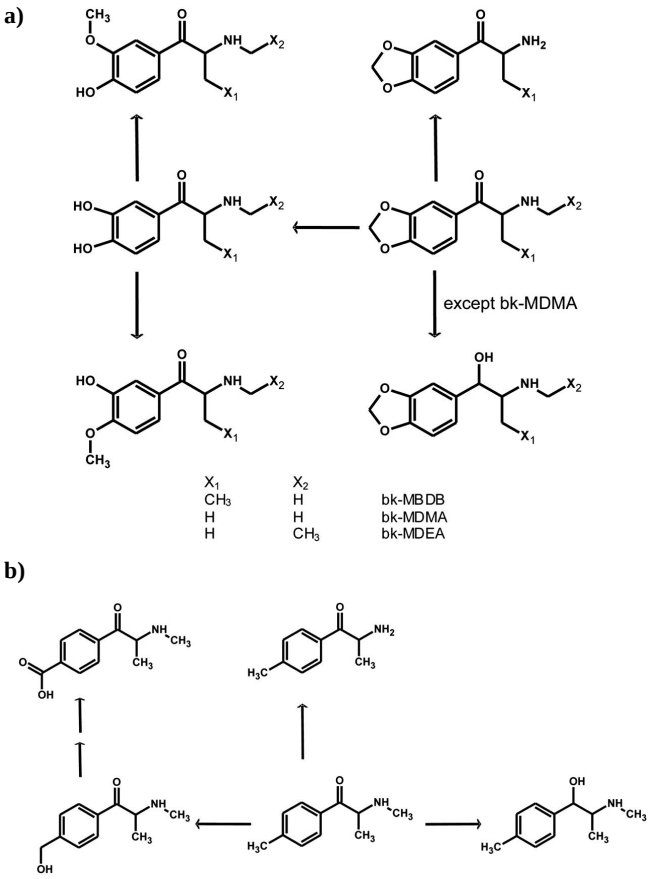



**Fig. (2). (a).** Main metabolic steps for the beta-keto designer drugs bk-MBDB, bk-MDMA, and bk-MDEA. **(b).** Main metabolic steps for the beta-keto designer drug mephedrone.

No studies are published yet dealing with enzymes involved in the aforementioned metabolic steps of the bk-designer drug family.

## PYRROLIDINOPHENONE-DERIVED DESIGNER DRUGS

MPBP and PVP are new designer drugs of the pyrrolidinophenones type which have been mentioned in a former review article [28]. MPBP and PVP were seized as powder by the German police. It is assumed to be taken orally as the other pyrrolidinophenones, which are distributed among drug abusers as tablets, capsules, or powders [28,106]. So far, little information about the dosage as well as the pharmacological and toxicological effects of the pyrrolidinophenones is available. However, they may be expected to be very similar to those of pyrovalerone (4-methyl-pyrrolidinovalerophenone) due to their close structural relation to this drug. Pyrovalerone is a psychostimulant which acts by releasing dopamine and norepinephrine from the respective nerve terminals [107-109].

In 2006, Meltzer *et al* reported that pyrovalerone and several structural analogs, among them PVP, are inhibitors of dopamine, serotonin, and norepinephrine transporters [110]. In the early 1960s, pyrovalerone was pharmacologically characterized in animal ex-

periments by Stille *et al*. [111]. Pyrovalerone had been studied as a therapeutic drug, but was withdrawn from the market and scheduled as a controlled substance after reports of its intravenous abuse by polytoxicomaniacs [112].

**MPBP**

The urinary metabolites of MPBP were identified by full-scan EI-MS after GC separation [29]. From these mass spectra, the following metabolites could be deduced: 4´-hydroxymethyl-PBP, 2´´-oxo-MPBP, 4´-carboxy-PBP, 4´-carboxy-2´´-oxo-PBP, 2-oxo- 4´-carboxy-BP, 1-dihydro-4´-carboxy-PBP, 1-dihydro-4´-carboxy-2´´-oxo-PBP Fig (**3**). Degradation of the pyrrolidino-moiety of MPBP to secondary or primary amine structures obviously did not occur. With an estimated extent of 40% of the excreted MPBP metabolites, 4´-carboxy-PBP was the metabolite of greatest abundance.

The exact position of the oxo group in the pyrrolidino-oxo metabolites of MPBP was not determined. However, the 2´´-position seems to be the most likely as lactam formation is common in the metabolism of pyrrolidino compounds such as prolintane and nicotine [113]. Only one peak was detected for the diastereomeric dihydro metabolites. This might be explained by stereoselective formation of only one diastereomer or more than one diastereomer might have been formed which were, however, not separated under the applied chromatographic conditions.

Based on the identified metabolites of MPBP, the following partly overlapping metabolic pathways could be postulated: hydroxylation of the 4´-methyl group to the corresponding alcohol followed by oxidation to the corresponding carboxylic acid; hydroxylation of the 2´´-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactams; reduction of the keto group of 4´-carboxy metabolites to the corresponding secondary alcohols; and oxidative deamination of 4´-carboxy-PBP to the corresponding 2-oxo compound. The 4´-carboxy-2-oxo-, 4´-hydroxy-, and the 1-dihydro-4´-carboxy-2´´-oxo-metabolites were partly excreted as glucuronides and/or sulfates.

**PVP**

The urinary metabolites of PVP were also identified by full-scan EI and PICI MS after GC separation [30]. From the recorded mass spectra, the following metabolites could be deduced in rat urine extract: PVP, N,N-bis-dealkyl-PVP, 2´´-oxo-PVP, hydroxyalkyl-PVP, hydroxyphenyl-N,N-bis-dealkyl-PVP, hydroxyphenyl-PVP, hydroxyalkyl-2´´-oxo-PVP, carboxy-4- oxo-PVP, hydroxyphenyl-2´´-oxo-PVP, di-hydroxy-PVP, hydroxyphenyl-carboxy-4-oxo-PVP, and hydroxyphenyl-carboxy-4-oxo-PVP Fig. (**3**).

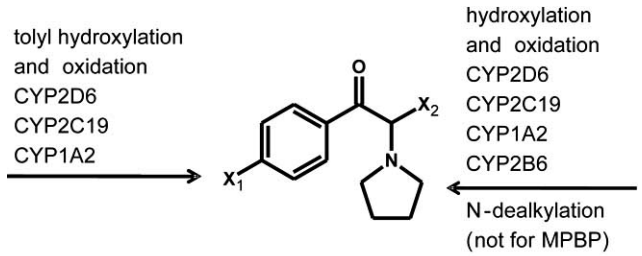



**Fig. (3).** Chemical structures of the alpha-pyrrolidinophenone-derived designer drugs MPBP and PVP. Arrows indicate the corresponding metabolic steps.

On the basis of the identified metabolites of PVP, the following partly overlapping metabolic pathways could be postulated: hydroxylation of the side chain followed by dehydrogenation to the corresponding ketone; hydroxylation of the 2´´-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactams or followed by ring opening to the respective aliphatic aldehyde and further oxidation to the respective carboxylic acid; degradation of the pyrrolidine ring to the corresponding primary amines; hydroxylation of the phenyl ring, most probably in the 4´-position resulting in a phenylogous carboxylic acid. HO-phenyl-PVP, hydroxyphenyl- 2´´-oxo-PVP, di-HO-PVP, HO-phenyl-amino-PVP, and HO-alkyl-PVP were more were partly excreted as glucuronides and/or sulfates.

**Influence of CYP Isoenzymes on the Metabolism of MPBP and PVP**

*In vitro* initial screening studies with the 10 most abundant human hepatic CYPs using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs and pooled human liver microsomes (pHLM) were performed for identification of the main metabolite of MPBP in microsomes and to clarify their role in metabolism of the drugs [114]. This study showed that the 4´-hydroxy metabolite was the product of the main metabolic step.

Among the ten CYPs tested, only CYP2C19, CYP2D6, and CYP1A2 were markedly capable of catalyzing the hydroxylation of the 4´-methyl moiety of MPBP. In the incubations of the other CYPs, only very little (CYP2B6) or no HO-MPBP was detectable. Because of the very low activity of CYP2B6 with respect to MPBP 4´-methyl hydroxylation, only CYP2C19, CYP2D6, and CYP1A2 were characterized by their kinetic profiles in the study by Peters *et al*. The kinetic data for CYP2D6 and CYP1A2 followed the expected classic hyperbolic Michaelis-Menten plots. In contrast, CYP2C19 revealed a biphasic kinetic profile. This is in accordance with previous findings where a biphasic kinetic profile of CYP2C19 had also been observed when studying 4´-hydroxylation of the MPBP analog MPPP [35]. CYP2D6 ($K_m$ 2.4 μM) and CYP2C19 (K*m1* 9.2 μM) turned out to have the highest affinity towards MPBP with apparent $K_m$ values markedly lower than the $K_m$ of CYP1A2 ($K_m$ 1674 μM ), whereas the capacity of CYP1A2 ($V_{max}$ 0.89 pmol/min/pmol) was considerably higher than those of the CYP2D6 and CYP2C19 (0.07 and 0.14 pmol/min/pmol, respectively). However, with respect to expected plasma concentrations of MPBP, CYP1A2 should only play a minor role in MPBP metabolism because of its extremely high $K_m$ value. According to the results of the relative activity factor (RAF) approach, CYP2D6 (54%) and CYP2C19 (30%) accounted for more than 80% of the net clearance. The metabolite formation in CYP2D6 and CYP2C19 poor metabolizer microsomes was almost 80% lower than in pHLM indicating that the *in vivo* hepatic clearance can be expected to be considerably lower in CYP2D6 and CYP2C19 poor metabolizer subjects. Inhibition experiments with the inhibitors quinidine (CYP2D6), fluconazole (CYP2C19), and naphthoflavone (CYP1A2) were additionally performed. The effects of the inhibitors fluconazole and naphthoflavone were essentially the same with inhibition of HO-MPBP formation of approximately 50%. Formation of HO-MPBP was inhibited by quinidine at about 83% (1 μM MPBP) and 59% (50 μM MPBP).

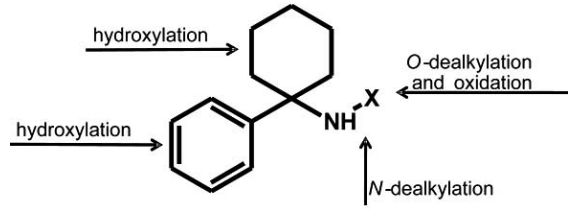
Concerning PVP solely initial screening studies with nine human hepatic CYPs were performed [30].

**Overview**

The alpha-pyrrolidinophenone designer drugs MPBP and PVP were metabolized by humans in analogy to the previously reported ones [28]. The main metabolic step for MPBP is the hydroxylation of the tolyl group and PVP is primarily oxidized to the 2´-oxo compound which is also the main metabolic step of the similar compound alpha-pyrrolidinopropiophenone (PPP) [33]. In general, CYP2B6, CYP2C19, CYP2D6, and CYP1A2 are capable to catalyze both metabolic steps. In the case of MPBP, CYP2B6 seems to play a minor role, whereas CYP2D6 and CYP2C19 seem to be the most important enzymes for its biotransformation.

## PHENCYCLIDINE-DERIVED DESIGNER DRUGS

In the late 1990s, PCPr, a phencyclidine (PCP)-derived compound was seized in Germany [15-18]. Within a short period of time, further members of this new class of PCP-derived designer drugs appeared in the illicit drug market, namely PCMPA, PCMEA, and PCEEA. The seized preparations contained either one compound alone or mixtures with other designer drugs [106]. In expectance of its appearance on the illicit drug market, a further homologue, namely, *N*-(1-phenylcyclohexyl)-3-ethoxypropanamine (PCEPA), was synthesized as a reference substance for scientific purposes. Chemical structures of these compounds are shown in Fig. (**4**).




| X | |
|---|---|
| $CH_2$-$CH_2$-$CH_3$ | PCPr |
| $CH_2$-$CH_2$-O-$CH_3$ | PCMEA |
| $CH_2$-$CH_2$-O-$CH_2$-$CH_3$ | PCEEA |
| $CH_2$-$CH_2$-$CH_2$-O-$CH_3$ | PCMPA |
| $CH_2$-$CH_2$-$CH_2$-O-$CH_2$-$CH_3$ | PCEPA |

**Fig. (4).** Chemical structures of the phencyclidine-derived designer drugs PCPr, PCMEA, PCEEA, PCMPA, and PCEPA. Arrows indicate the corresponding metabolic steps.

Only little information on the pharmacological properties of these compounds is available [115]. Due to structural similarities, they might be assumed to be similar to those of PCP or ketamine, which both act as antagonists at *N*-methyl-D-aspartate receptors and have psychotomimetic as well as anesthetic properties [116]. Furthermore, it has been reported that (1-phenylcyclohexyl)-amine, a known metabolite of PCP and of the above-mentioned PCP-derived compounds [15-18], produced a long-lasting dose-dependent effect on the efflux of dopamine in the rat [117].

Sauer *et al.* [15-18] studied the metabolism of the above-mentioned phencyclidine derivatives in rat urine after oral administration of the corresponding drug using GC-MS techniques. On the basis of the identified compounds, the metabolic steps summarized in Fig. (**4**) have been postulated.

### PCEPA

For PCEPA, the following metabolic steps were postulated Fig. (**4**): *N*-dealkylation; *O*-deethylation partially followed by oxidation to the corresponding acids; hydroxylation of the cyclohexyl ring at different positions [118]. After *O*-deethylation and oxidation to the corresponding acid, the side chain of the acid could also be hydroxylated. Further possible pathways are the following: *O*-deethylation followed by *N*-dealkylation; *O*-deethylation followed by hydroxylation of the cyclohexyl ring and *N*-dealkylation; *O*-deethylation followed by hydroxylation of the cyclohexyl ring and aromatic hydroxylation and oxidation to the corresponding acid; and *O*-deethylation followed by oxidation to the corresponding acid and aromatic hydroxylation followed by hydroxylation of the cyclohexyl ring.

### PCPr

For PCPr, the following metabolic steps were postulated Fig. (**4**): *N*-dealkylation, hydroxylation of the cyclohexyl ring at different positions and of the aromatic system as well as of the side chain [17]. Furthermore, combinations of the different possibilities of hydroxylation of the cyclohexyl ring, the aromatic system and the side chain could be identified. Metabolites hydroxylated at the side chain were postulated to be hydroxylated in omega-1 position based on the fragmentation pattern in electron ionization (EI) MS. Almost all non-*N*-dealkylated metabolites were excreted in conjugated form.

### PCEEA AND PCMEA

Due to their structural similarity, PCEEA and PCMEA were investigated in one study [16] and the following metabolic steps could be postulated Fig. (**4**): *N*-dealkylation, *O*-dealkylation partially followed by oxidation to the corresponding acid, hydroxylation of the cyclohexyl ring at different positions of *N*-dealkyl metabolites, *O*-dealkyl metabolites and of the corresponding acids, and finally aromatic hydroxylation of the *O*-dealkyl metabolites. However, there is no inherent difference in the metabolism of both compounds indicating that there is no influence of the *O*-substituent on general enzyme activity.

### PCMPA

PCMPA was mainly metabolized to the same metabolites as PCEPA [18]. Therefore, common metabolic pathways of PCMPA and PCEPA were concluded with exception of mono hydroxylation of the parent drug, which was observed for PCEPA, but not for PCMPA.

### Influence of CYP Isoenzymes on the Metabolism of Phencyclidine-Derived Designer Drugs

*In vitro* initial screening studies were performed with the 10 most abundant human hepatic CYPs using different microsomal preparations, baculovirus-infected insect cell microsomes containing individual human cDNA-expressed CYPs, and pHLM. They allowed to identify the main metabolite of PCEPA, PCMPA, PCEEA, and PCMEA in microsomes and to clarify their role in metabolism of the aforementioned drugs [119,120]. The results are summarized in Fig. (**5**) and Table **1**.

In these studies, the kinetics of metabolite formation by active enzymes were also determined and used to estimate the percentages of net clearance of each individual CYP. The RAF approach [121-123] was used for this purpose. According to the results of the RAF approach, CYP2B6 should be the most relevant CYP for *O*-dealkylation of PCEEA and PCMEA accounting for 53% (PCEEA) and 91% (PCMEA) of the net clearance. Concerning PCEPA and PCMPA, CYP2D6 was the most important enzyme and accounted for 30% (PCEPA) and 40% (PCMPA) of the net clearance. The authors concluded that the decreasing side-chain length of the compounds was associated with a higher contribution of CYP2B6. In accordance with the decreasing involvement of CYP2B6, the number of CYPs involved and their contributions increased with increasing side-chain length Fig. (**5**), right [120].

The CYP2B6-specific chemical inhibitor 4-(4-chlorobenzyl) pyridine reduced metabolite formation in pHLM in the case of PCEPA, PCMPA, PCEEA, and PCMEA. The CYP2D6-specific chemical inhibitor quinidine reduced metabolite formation in pHLM in case of PCEPA and PCMPA. Examinations with HLMs from CYP2D6-poor metabolizers showed a reduction of metabolite formation for PCEPA and PCMPA. In the case of the *O*-dealkylation of PCMEA and PCPr in humans, CYP2B6 showed a major or even exclusive involvement [124]. Considering this major involvement of CYP2B6, simultaneous intake of potent CYP2B6 inhibitors such as triethylenethiophosphoramide (thiotepa), ticlopedine, clopidogrel [125,126], or several antidepressants [127] might lead to a decreased clearance of PCMEA or PCPr and, consequently, to elevated plasma concentrations. However, the clinical relevance of such interactions remains to be established [119,120].

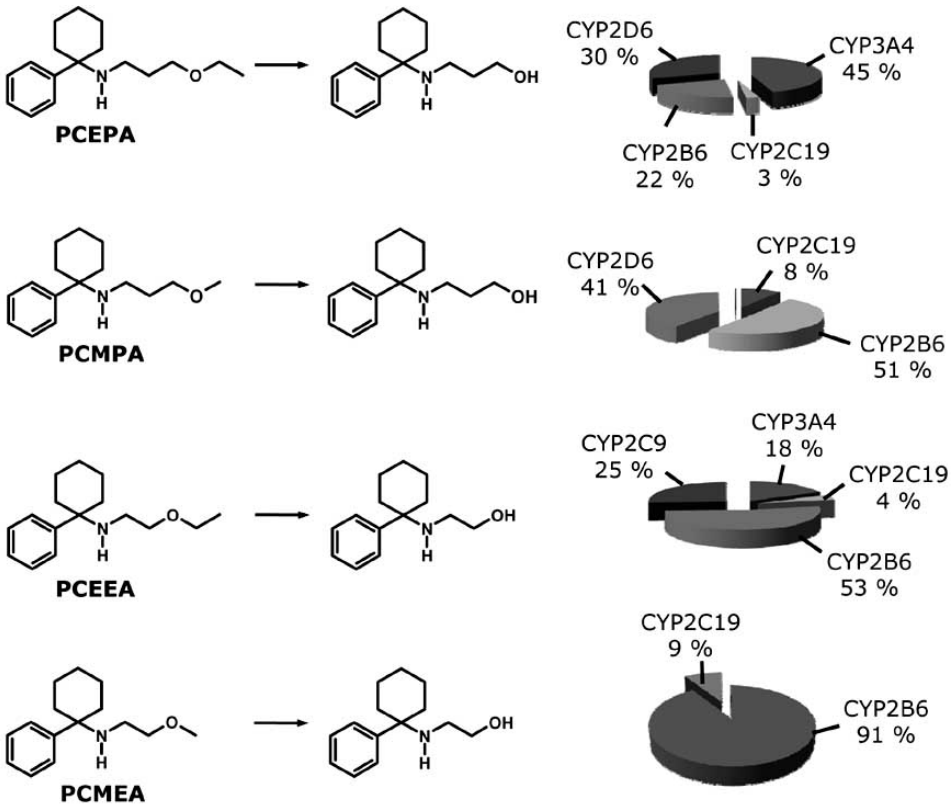



**Fig. (5).** Main metabolic steps for PCEPA, PCMPA, PCEEA, PCMEA (left) and the contribution of the given CYPs to these steps (right).

### Overview

The phencyclidine-derived compounds were mainly metabolized by *O*-dealkylation, followed by oxidation to the corresponding acid, hydroxylation of the cyclohexyl ring in different positions, hydroxylation of the phenyl ring, *N*-dealkylation, and combinations of these steps Fig. (**4**). Phase II reactions consisted of partial glucuronidation and/or sulfation of some phase I metabolites. The main metabolic steps of PCEPA, PCMPA, PCEEA, and PCMEA were catalyzed by different CYP isoforms. CYP2B6 should be the most relevant CYP for *O*-dealkylation of PCEEA and PCMEA. CYP2D6 plays the major role in phase-I metabolism of PCEPA and PCMPA.

## TRYPTAMINE-DERIVED DESIGNER DRUGS

Besides phenethylamines, indoleamines belong to the hallucinogenic drugs. Among the indoleamines, *N*,*N*-dimethyltryptamine is the prototypical drug of the tryptamine subgroup. Tryptamines represent a cross-section of compounds that cause hallucinations in humans by putative activation of the 5-$HT_2$A receptor [40,128]. In general, tryptamines have high affinity for the serotonin 5-$HT_2$ receptors; hallucinogenic potency is well correlated with the relative affinity of these compounds for the 5-$HT_2$ receptor [129]. Tryptamine derivatives that have been identified as synthetic hallucinogenic designer drugs include 5-MeO-DIPT (Foxy, Foxy Methoxy). Other derivatives such as *N*,*N*-dimethyltryptamine and 5-MeO-DMT are naturally occurring tryptamines found in plants and animals and are therefore not discussed in this review dealing with designer drugs of abuse.

### 5-MeO-DIPT

5-MeO-DIPT is a tryptamine-type designer drug that is used world-wide particularly by young people [36-39]. Users of 5-MeO-DIPT reported effects of euphoria, empathy, visual and auditory distortions, feelings of love and emotional distress as well as nausea, vomiting and diarrhea [40,41]. The *in vivo* and *in vitro* metabolic profiles of 5-MeO-DIPT in humans and animals have been reported [130-132]. The metabolite structures were identified in humans by GC-MS and LC-MS and confirmed by chemical synthesis [133]. The following metabolic steps of 5-MeO-DIPT were deduced from the identified structures Fig. (**6**): *O*-demethylation to 5-hydroxy-DIPT and hydroxylation at position 6 to 6-hydroxy-5-MeO-DIPT, both steps followed by conjugation to sulfates and glucuronides. *N*-Dealkylation of the side chain led to the corresponding secondary amine. 5-Hydroxy-DIPT and 6-hydroxy-5-MeO-DIPT were found to be the major metabolites. Further expected metabolites such as 5-methoxyindoleacetic acid and 5-hydroxyindoleacetic acid formed by the oxidative deamination were not found during this human study. Kanamori *et al.* [134], however, could identify in rat urine 5-methoxyindoleacetic acid in addition to the *O*-demethyl and *N*-dealkyl metabolites.

Narimatsu *et al.* studied the oxidative metabolism of 5-MeO-DIPT in pHLM and rat liver microsomes [130,131]. In pHLM, *O*-demethylation was the major step and *N*-dealkylation the minor one. In rat liver microsomes, *O*-demethylation was predominant in a low substrate concentration range while *N*-dealkylation became important in a high substrate concentration range.

### Influence of CYP Isoenzymes on the Metabolism of 5-MeO-DIPT

Narimatsu *et al.* studied the influence of microsomes prepared from rat livers and human livers as well as of recombinant CYP enzymes from rats and humans on the metabolism of 5-MeO-DIPT [130,131]. Unfortunately, the enzyme kinetics of metabolite formation were not correlated with the expected activity of each individual CYP for *in vivo* systems using e.g. the RAF approach [121-123]. Therefore, it is not surprising that the CYP2C19 inhibitor omeprazole showed no effect on the 5-MeO-DIPT oxidation in HLM which is in contrast to the comparably low $K_m$ value determined using recombinant CYP2C19 [130]. Human liver microso-

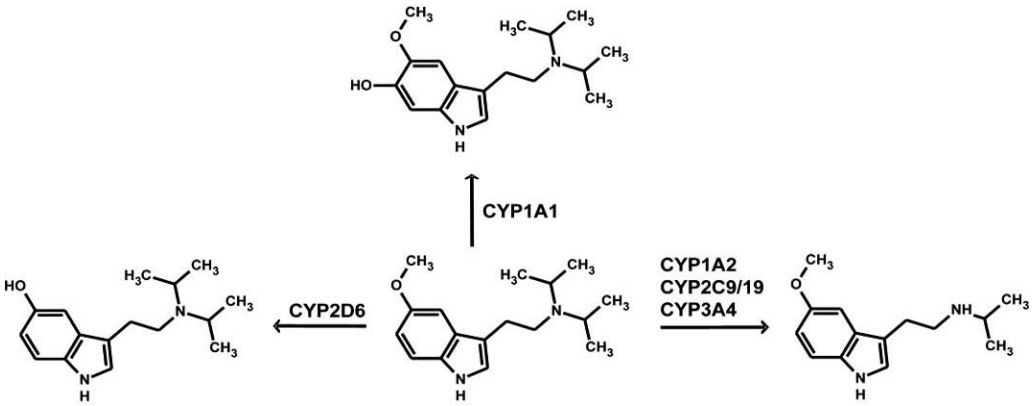



**Fig. (6).** Main metabolic steps for the tryptamine-derived designer drug 5-MeO-DIPT (Foxy).

mal *O*-demethylation was monophasic, whereas the *N*-deisopropylation was triphasic. Experimental evidence obtained using enzyme inhibitors and recombinant enzymes indicated that CYP2D6 is the major and preferred human CYP enzyme for the *O*-demethylation of 5-MeO-DIPT. Studies using rat CYP inhibitors and recombinant rat enzymes indicated that CYP2D2 was responsible for the low-$K_m$ phase *O*-demethylation and CYP1A1 and/or CYP2C6 for the high $K_m$-phase reaction in rat liver microsomes. Although *N*-deisopropylation in untreated male rat liver microsomes yielded monophasic kinetics, CYP2C11 and CYP3A2 seem to be involved in this reaction.

## FENTANYL-DERIVED DESIGNER DRUGS

Known modifications of fentanyl are formed by methylation of both, the alpha-position of the phenethyl group (alpha-methylfentanyl) and the 3-position of the piperidine ring (3-methylfentanyl). They show the same analgesic activities as fentanyl and were called bogus "China White" [42-44]. The term of "China White" was the street name of heroin originally but today fentanyl analogues are called "China White". Alpha-methylfentanyl appeared on the illicit drug market in California in 1979. In 1984, 3-methylfentanyl was identified and the drug was involved in overdoses in California in 1984–1985 [135]. The cis-(+)-isomer of 3-methylfentanyl is approximately 7000 times as potent as morphine while the trans-(±)-isomer is approximately 1000 times as potent [136].

Metabolism and metabolite quantification of alpha-methylfentanyl was investigated using GC-MS and synthesized metabolites by Higashikawa *et al*. after injection of alpha-methylfentanyl in rats [44]. The following metabolites of alpha-methylfentanyl were described: main metabolites identified were nor-fentanyl, omega-hydroxy-nor-fentanyl and omega-1 hydroxy-nor-fentanyl. Furthermore, omega hydroxy methylfentanyl, omega-1-hydroxy methylfentanyl, omega-hydroxy-4-hydroxyphenyl methylfentanyl, and 4-hydroxyphenyl methylfentanyl were detected as shown in Fig (**7**). In another study, besides the aforementioned metabolites, unchanged alpha-methylfentanyl was detected and quantified with 2.9% of the total metabolite pool [137]. Hammargren et el. used GC with electron capture detection to detect the nor metabolite of 3-methylfentanyl, nor-3-methylfentanyl, in human urine Fig. (**7**) [138]. Studies concerning CYP isozymes involved in the mentioned main metabolic steps are missing.

### Overview

Fentanyl-derived designer drugs are metabolized similar to fentanyl itself. The main metabolic steps is the *N*-dealkylation to the respective nor-metabolites, namely nor-fentanyl in the case of alpha-methylfentanyl and nor 3-methylfentanyl in the case of 3-methylfentanyl.

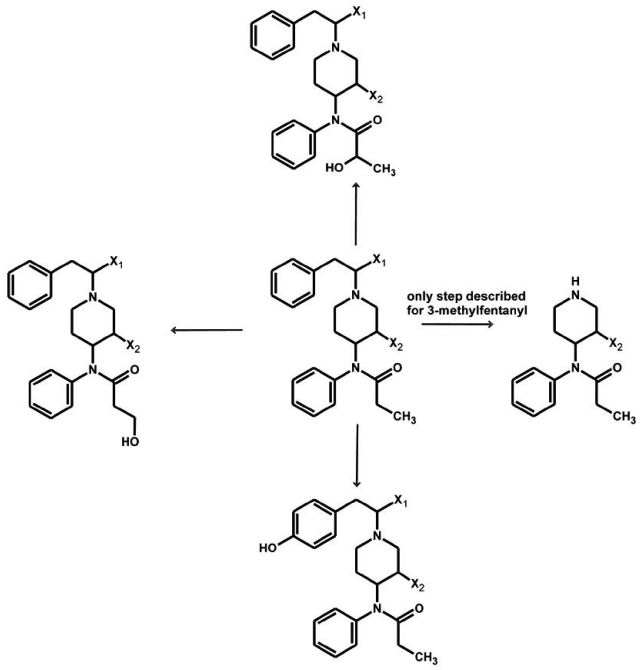



**Fig. (7).** Main metabolic steps for the fentanyl-derived designer drugs 3-methylfentanyl and alpha-methylfentanyl.

## CONCLUSION

Identification of metabolites of the so-called 2C compounds (phenethylamine type), beta-keto designer drugs, two pyrrolidinophenones, phencyclidine-derived drugs, tryptamines, and fentanyl-derived drugs is well described. Papers describing identification of *in vivo* or *in vitro* human or animal metabolites and CYP isoenzyme-dependent metabolism have been considered and summarized.

This data is of importance for forensic and clinical toxicologists, as it is a prerequisite for developing toxicological screening procedures especially in urine based on metabolites, allowing the detection of an intake of these compounds. The CYP-dependent metabolism of these drugs has been studied as basis of the assessment of potential pharmacogenomic variations or drug/drug interactions. This could have consequences for the interpretation of analytical results in clinical and forensic toxicology as well as in doping control. Indeed, most major metabolic steps were shown to be catalyzed by the polymorphically expressed CYP2D6 and CYP2B6. 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.

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## ABBREVIATIONS

| | | |
|---|---|---|
| 2C-B | = | 4-bromo-2,5-dimethoxy-beta-phenethylamine |
| 2C-I | = | 4-iodo-2,5-dimethoxy-beta-phenethylamine |
| 2C-D | = | 2,5-dimethoxy-4-methyl-beta-phenethylamine |
| 2C-E | = | 4-ethyl-2,5-dimethoxy-beta-phenethylamine |
| 2C-T-2 | = | 4-ethylthio-2,5-dimethoxy-beta-phenethylamine |
| 2C-T-7 | = | 2,5-dimethoxy-4-propylthio-beta-phenethylamine |
| butylone | = | 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one |
| ethylone | = | 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-one |
| methylone | = | 2-methylamino-1-(3,4-methylenedioxy-phenyl)propan-1-one |
| mephedrone | = | 2-methylamino-1-p-tolylpropane-1-one |
| MPBP | = | 4-methyl-pyrrolidinobutyrophenone |
| PVP | = | alpha-pyrrolidinovalerophenone |
| PCEEA | = | N-(1-phenyl cyclohexyl)-2-ethoxyethanamine |
| PCMPA | = | N-(1-phenylcyclohexyl)-3-methoxypropanamine |
| PCMEA | = | N-(1-phenylcyclohexyl)-2-methoxyethanamine |
| 5-MeO-DIPT | = | 5-methoxy-*N*,*N*-diisopropyltryptamine |
| 5-MeO-DMT | = | 5 -methoxy-*N*,*N*-dimethyltryptamine |
| alpha-MF | = | alpha-methylfentanyl |
| 3-MF | = | 3-methylfentanyl |
| 2Cs | = | 2,5-phenetyhlamines |
| CYP | = | cytochrome P450 |
| QSAR | = | Quantitative structure-activity relationships |
| GC-MS | = | Gas chromatography-mass spectrometry |
| CE-MS | = | Capillary electrophoresis-mass spectrometry |
| MAO | = | Monoamineoxidase |
| bk | = | Beta-keto |
| 5-MeO-MIPT | = | 5-methoxy-*N*-methyl-*N*-isopropyltryptamine |
| MDC | = | 3,4-methylenedioxycathinone |
| HMMC | = | 4-hydroxy-3-methoxymethcathinone |
| 3-OH-4-MeO-MC | = | 3-hydroxy-4-methoxymethcathinone |
| MDEP | = | 3,4-methylenedioxyephedrine |
| COMT | = | catechol *O*-methyltransferase |
| LC-MS | = | Liquid chromatography-mass spectrometry |
| bk-MDA | = | 2-amino-1-(3,4-methylenedioxyphenyl) propan-1-one |
| bk-4,3-HMEA | = | 2-ethylamino-1-(4-hydroxy-3-methoxyphenyl)propan-1-one |
| bk-3,4-HMEA | = | 2-ethylamino-1-(3-hydroxy-4-methoxy phenyl)propan-1-one |
| beta-hydroxy-MDEA | = | 2-ethylamino-1-(3,4-methylenedioxyphenyl)propan-1-ol |
| EI | = | Electron ionization |
| PICI | = | Positive-ion chemical ionization |
| pHLM | = | Pooled human liver microsomes |
| MPPP | = | 4-methyl-pyrrolidinopropiophenone |
| RAF | = | Relative activity factor |
| PcPr | = | *N*-(1-phenylcyclohexyl)-propanamine |

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