

Chemistry, Pharmacology, and Metabolism of Emerging Drugs of Abuse

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Abstract: In recent years, besides the classic designer drugs of the amphetamine type, a series of new drug classes appeared on the illicit drugs market. The chemistry, pharmacology, toxicology, metabolism, and toxicokinetics is discussed of 2,5-dimethoxy amphetamines, 2,5-dimethoxy phenethylamines, beta-keto-amphetamines, phencyclidine derivatives as well as of herbal drugs, ie, Kratom. They have gained popularity and notoriety as rave drugs. The metabolic pathways, the involvement of cytochrome P450 isoenzymes in the main pathways, and their roles in hepatic clearance are also summarized.

Key Words: drugs of abuse, designer drugs, herbal drugs, pharmacology, metabolism

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INTRODUCTION

In recent years, besides the classic designer drugs of the amphetamine-type,^{1–11} a series of new drug classes appeared on the illicit drugs market such as 4-substituted or 2,5-dimethoxy amphetamines,^{12–17} 2,5-phenethylamines (2Cs),^{18–23} beta-keto-amphetamines,^{24,25} and phencyclidine derivatives.^{26–29} Piperazines and pyrrolidinophenones have already been reviewed.^{1,30–32} Although 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.^{1,9,12,33–37} In recent years, new herbal drugs also appeared on the drug scene such as Kratom^{38,39} and Spice.^{40,41} The latter, however, was fortified by synthetic cannabinoids receptor agonists for which metabolic data have not yet been published. Because metabolites were suspected to contribute to some of the toxic effects^{3,34,42} and their knowledge is of importance for developing screening approaches, the main metabolic steps are also described. More detailed reviews will be published elsewhere.⁴³ Procedures for toxicologic analysis of emerging drugs of abuse are discussed by Peters and Martinez-Ramirez elsewhere.⁴⁴

2,5-DIMETHOXY AMPHETAMINE DESIGNER DRUGS

Typical drugs of this class are 4-bromo-2,5-dimethoxyamphetamine (DOB), 4-chloro-2,5-dimethoxyamphetamine (DOC), 4-iodo-2,5-dimethoxyamphetamine (DOI), 2,5-dimethoxy-4-methyl-amphetamine (DOM), 4-bromo-2,5-dimethoxymethamphetamine (MDOB), and 2,4,5-trimethoxyamphetamine (TMA-2). Their chemical structures are shown in Figure 1. Most of these drugs were described by Shulgin.⁴⁵ They were sold in so-called “smart shops” alone or in mixtures with other designer drugs in the form of tablets, powder, liquids, or blotters. This trend was accompanied by seizures by the police of tablets containing 2,5-dimethoxyamphetamines or combinations with other drugs. Because of the high abuse potential of the 2,5-dimethoxyamphetamines, many were scheduled in most countries. Some information is available on pharmacologic properties of the 2,5-dimethoxyamphetamines. They show affinity to 5-HT₂ receptors and act as agonists or antagonists at different receptor subtypes.^{46–51} Because of the high potency and selectivity of DOI as a 5-HT₂ receptor agonist and the fact that it was not scheduled until now and is commercially available, it was used in research when a selective 5-HT₂ receptor agonist was needed.^{52,53} The chemical structure responsible for the hallucinogen-like activity comprises a primary amine functionality separated from the phenyl ring by two carbon atoms, the presence of methoxy groups in positions 2 and 5 of the aromatic ring, and a hydrophobic 4-substituent (alkyl, halogen, alkylthio, etc).⁵¹ The methyl moiety in α -position to the nitrogen atom is reported to be responsible for increased in vivo potency and duration of action.⁵¹ The metabolism of these drugs has been studied in detail.^{13–17,54–56} Although for all of these drugs, demethylation of one of the 2,5 methoxy groups by cytochrome P450 (CYP) 2D6 was observed, these drugs were found to be more or less potent CYP2D6 inhibitors.⁵⁴

2,5-DIMETHOXY PHENETHYLAMINE DESIGNER DRUGS

2,5-Dimethoxy phenethylamines, the so-called 2Cs, are analogs of the previously mentioned 2,5-dimethoxyamphetamines (phenylisopropylamines). The chemical structures of the 2Cs 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-

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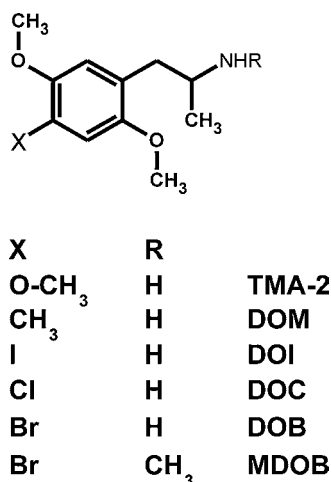


FIGURE 1. Chemical structures of 2,5-dimethoxyamphetamines (TMA-2, 2,4,5-trimethoxyamphetamine; DOM, 2,5-dimethoxy-4-methyl-amphetamine; DOI, 4-iodo-2,5-dimethoxyamphetamine; DOC, 4-chloro-2,5-dimethoxyamphetamine; DOB, 4-bromo-2,5-dimethoxyamphetamine; MDOB, 4-bromo-2,5-dimethoxymethamphetamine).

β -phenethylamine (2C-T-7) are shown in Figure 2. Again, they were described by Shulgin.⁴⁵

Only little information is available on pharmacologic and toxicologic properties of the members of the 2C series, but it is known that they show affinity to 5-HT₂ receptors and act as agonists or antagonists at different receptor subtypes.^{45,50,51,57–60} For 2C-B, partial agonism at α_1 -adrenergic receptors was described.^{61,62} Because of these properties, radioactive 2C-I was synthesized as a label for the 5-HT₂ receptor and as a potential brain scanning agent for nuclear medicine.^{57,63} The chemical structure responsible for the hallucinogen-like activity comprises a primary amine functionality separated from the phenyl ring by two carbon atoms (“2C”), the presence of methoxy groups in positions 2 and 5 of the aromatic ring, and a hydrophobic 4-substituent (alkyl, halogen, alkylthio, etc).⁵¹ Furthermore, several quantitative structure-activity relationships studies were published about hallucinogenic β -phenethylamines.^{64–71} Using the results of these analyses, predictions of the hallucinogenic potency of new β -phenethylamines should be possible.

The 2Cs were mainly metabolized by O-demethylation in positions 2 and 5 of the ring, respectively, 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.^{18–23,72–80} MAO-A and MAO-B were the major enzymes involved in the deamination reaction.⁸⁰ 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.⁸⁰

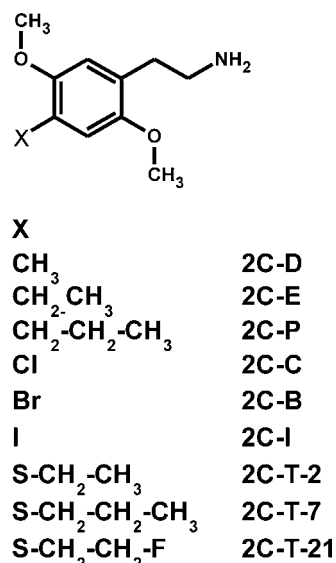


FIGURE 2. Chemical structures of 2,5-dimethoxy phenethylamines (2C-D, 2,5-dimethoxy-4-methyl- β -phenethylamine; 2C-E, 4-ethyl-2,5-dimethoxy- β -phenethylamine; 2C-P, 4-n-propyl-2,5-dimethoxy- β -phenethylamine; 2C-C, 4-chloro-2,5-dimethoxy- β -phenethylamine; 2C-B, 4-bromo-2,5-dimethoxy- β -phenethylamine; 2C-I, 4-iodo-2,5-dimethoxy- β -phenethylamine; 2C-T-2, 4-ethylthio-2,5-dimethoxy- β -phenethylamine; 2C-T-7, 4-propylthio-2,5-dimethoxy- β -phenethylamine; 2C-T-21, 4-(2-fluoroethylthio)-2,5-dimethoxy- β -phenethylamine).

BETA-KETO-AMPHETAMINE DESIGNER DRUGS

The beta-keto (bk) designer drugs butylone (2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one, bk-MBDB), ethylone (3,4-methylenedioxyethylcathinone, bk-3,4-methylenedioxyethylamphetamine, bk-MDEA), methylone (3,4-methylenedioxymethcathinone, bk-3,4-methylenedioxymethamphetamine, bk-MDMA), and mephedrone (2-methylamino-1-p-tolylpropane-1-one, bk-4-methylmethamphetamine) belong to a new class of drugs of abuse. Their chemical structures are shown in Figure 3.

Although no data exist on their pharmacologic and toxicologic properties, their use as alternative drugs for amphetamines allows to conclude that they should have similar stimulant effects. 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.^{24,25} Mephedrone was hydroxylated at the 4-methyl group followed by oxidation to the corresponding 4-carboxy metabolite, N-demethylated finally reduced at the beta-keto group to the corresponding alcohol.⁸¹

PHENCYCLIDINE-DERIVED DESIGNER DRUGS

Several phencyclidine (PCP)-derived designer drugs were seized in Germany, namely, N-(1-phenylcyclohexyl)-propanamine (PCPr), N-(1-phenylcyclohexyl)-3-methoxypropanamine (PCMPA),

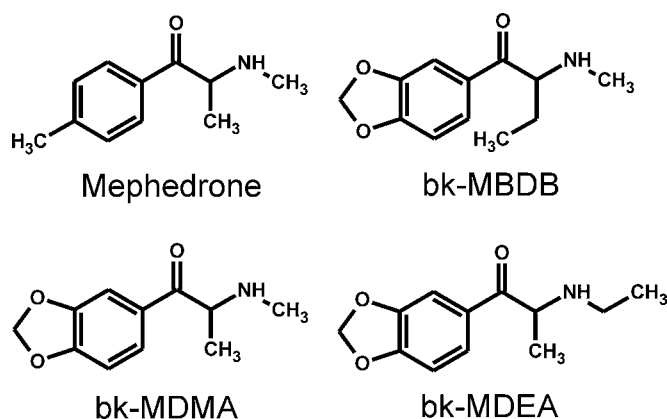


FIGURE 3. Chemical structures of beta-keto amphetamines (bk-MBDB, 2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one; bk-MDMA, beta-keto 3,4-methylenedioxyamphetamine; bk-MDEA, beta-keto 3,4-methylenedioxyethylamphetamine).

N-(1-phenylcyclohexyl)-2-methoxyethanamine (PCMEA), and *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine (PCEEA).⁸² In expectation of its appearance on the illicit drug market, a further homolog, namely, *N*-(1-phenylcyclohexyl)-3-ethoxypropanamine (PCEPA), was synthesized as a reference substance for scientific purposes. Chemical structures of these compounds are shown in Figure 4.

Unfortunately, only little information on the pharmacologic properties of these compounds is available.⁸³ As a result of 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 (NMDA) receptors and have psychotomimetic as well as anesthetic properties.⁸⁴ Furthermore, it has been reported that (1-phenylcyclohexyl)-amine, a known metabolite of PCP and of the previously mentioned PCP-derived compounds,^{26–29} produced a long-lasting dose-dependent effect on the efflux of dopamine in the rat.⁸⁵ A similar pharmacologic profile of the mentioned PCP-derived compounds would clearly be in line with their abuse as designer drugs.

These phencyclidine-derived compounds were mainly metabolized by *O*-dealkylation, followed by oxidation to the

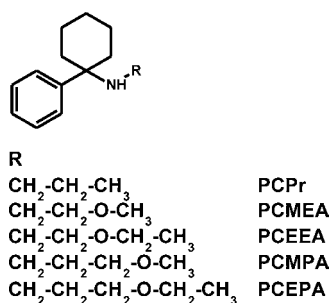


FIGURE 4. Chemical structures of phencyclidine-derived designer drugs (PCPr, *N*-(1-phenylcyclohexyl)-propanamine; PCMEA, *N*-(1-phenylcyclohexyl)-2-methoxyethanamine; PCEEA, *N*-(1-phenylcyclohexyl)-2-ethoxyethanamine; PCMPA, *N*-(1-phenylcyclohexyl)-3-methoxypropanamine; PCEPA, *N*-(1-phenylcyclohexyl)-3-ethoxypropanamine).

corresponding acid, hydroxylation of the cyclohexyl ring in different positions, hydroxylation of the phenyl ring, *N*-dealkylation, and combinations of these steps. Phase II reactions consisted of partial glucuronidation and/or sulfation of some Phase I metabolites.^{26–29} The main metabolic step of PCEPA, PCMPA, PCEEA, and PCMEA was catalyzed by different CYP isoforms.^{86,87}

HERBAL DRUG KRATOM

The plant *Mitragyna speciosa* Korth. (Rubiaceae) is native in Thailand and other southeast Asian countries and its Thai name is "*Kratom*."^{88,89} The leaves of *Mitragyna speciosa* have been used in Thailand for its opium-like effect and its coca-like ability to combat fatigue of and enhance tolerance to hard workers under a scoring sun.⁹⁰ In addition, it has been used as a traditional medicine for common illnesses such as coughing, diarrhea, muscle pain, hypertension, and to cure morphine addicts.^{91,92} The main alkaloids are mitragynine (MG, approximately 60% based on the crude base), paynantheine (PAY, approximately 10%), and speciogynine (SP, 5%–10%).⁹³ Chemical structures of these compounds are shown in Figure 5. Because of its stimulant and euphoric effects, *Kratom* is misused as an herbal drug of abuse, which has been illegal in Thailand since 1946 and in Australia since 2005. The wide availability of *Kratom* through the Internet reflects extensive demand for this product. For example, opiate addicts may attempt to mitigate opioid withdrawal symptoms.⁹⁴

The Phase I and II metabolism of MG and PAY in rats and humans was extensively studied using liquid chromatography–mass spectrometry with a linear ion trap analyzer providing detailed structure information in the MSⁿ mode and using high-resolution mass spectrometry with an Orbitrap analyzer providing the empiric formula of the corresponding fragments for confirmation.^{38,39} MG and PAY were metabolized by hydrolysis of the methylester in position 16, *O*-demethylation of the 9-methoxy group and of the 17-methoxy group, followed, through the corresponding aldehydes, by oxidation to carboxylic acids or reduction to alcohols and combinations of some steps. In rats, four metabolites were additionally conjugated to glucuronides and one to sulfate, but in humans, three metabolites to glucuronides and three to sulfates.

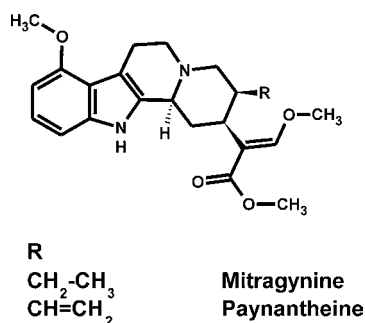


FIGURE 5. Chemical structures of the *Kratom* alkaloids mitragynine and paynantheine.

CONCLUSIONS

The drugs of abuse market is dynamic with new drugs always appearing. Toxicologists must follow up these trends and have to investigate the chemical, analytical, toxicologic, and metabolic properties of these emerging drugs. Finally, clinical case data are necessary to assess the impact of these drugs to human health.

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