Chapter 92

25C-NBOMe as a New Hallucinogen

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Abbreviations

25B-N(BOMe)$_2$ 2-(4-Bromo-2,5-dimethoxyphenyl)-*N*,*N*-bis(2-methoxybenzyl)ethanamine

25B-NBOMe 2-(4-Bromo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

25C-NBOMe 2-(4-Chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

25I-NBMD 2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2,3-methylenedioxyphenyl)methyl]ethanamine

25I-NBOMe 2-(2,5-Dimethoxy-4-iodophenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

2C A general name for the family of hallucinogenic derivatives of phenethylamine containing two methoxy groups located on the 2 and 5 positions of a benzene ring

2C-C 4-Chloro-2,5-dimethoxyphenethylamine

2C-H 2,5-Dimethoxy-β-phenethylamine

2C-I 2,5-Dimethoxy-4-iodophenethylamine

3,4-DMA-NBOMe 1-(3,4-Dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]propan-2-amine

4-MMA-NBOMe *N*-(2-methoxybenzyl)-*N*-methyl-1-(4-methylphenyl)propan-2-amine

5-HT$_{2A}$ Subtype 2A of the serotonin (5-hydroxytryptamine) receptor

ACMD Advisory Council on the Misuse of Drugs, an independent expert body that advises British government on drug-related issues in the UK makes recommendations on the control of dangerous or otherwise harmful drugs, including classification and scheduling under the Misuse of Drugs Act 1971 and its regulations.

C30-NBOMe 4-Chloro-2,5-dimethoxy-*N*-[(3,4,5-trimethoxyphenyl)methyl]benzeneethanamine

DEA Drug Enforcement Administration, a federal law enforcement agency under the US Department of Justice tasked with combating drug smuggling and use within the United States

ED Emergency department

EMCDDA European Monitoring Centre for Drugs and Drug Addiction

GC–MS Gas chromatography–mass spectrometry

HPBCD Hydroxypropyl-β-cyclodextrin, the most widely used modified cyclodextrin. The compound is used to change the physicochemical properties of lipophilic compounds for easier diffusion across biological membranes, increase aqueous solubility and stability

LC–MS Liquid chromatography–mass spectrometry

LSD D-Lysergic acid diethylamide

MDPV 3,4-Methylenedioxypyrovalerone,1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one

NBOMe A general name for the family of potent psychedelic substances containing 2-methoxybenzyl moiety substituted at the nitrogen atom of phenethylamines

NFLIS The National Forensic Laboratory Information System, a DEA program that systematically collects drug chemistry analysis results, as well as other related information, from cases analyzed by state, local, and federal forensic laboratories

NPS New psychoactive substances, defined as a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions

PET Positron emission tomography

PFAA Pentafluoroacetic anhydride

QTOFMS Quadrupole-time-of-flight mass spectrometry

SAR Structure–activity relationship, the relationship between the chemical or 3D structure of a molecule and its biological activity

STRIDE The System to Retrieve Information from Drug Evidence, a database of drug exhibits sent to DEA laboratories for analysis

TFAA Trifluoroacetic anhydride

UNODC EWA United Nations Office on Drugs and Crime Early Warning Advisory

"CLASSICAL" AND NOVEL HALLUCINOGENS

Hallucinogens are a wide class of drugs that cause significant distortions in a person's perceptions of reality. When under the influence of this type of drug, people often report experiencing rapid, intense changes in mood, confusion, delusions, and distorted perception, including visual, auditory, time, and space (NIDA, 2014). As presented in previous chapters, hallucinogens can be found in some plants and mushrooms, e.g., mescaline is a psychedelic alkaloid occurring naturally in the peyote cactus (*Lophophora williamsii*), the San Pedro cactus (*Echinopsis pachanoi*), and in the Peruvian torch (*Echinopsis peruviana*), while psilocybin is a compound produced by more than 200 species of mushrooms, including members of the genus *Psilocybe*. D-Lysergic acid diethylamide (LSD) can be synthesized from lysergic acid, a compound derived from a rye fungus. But most hallucinogens marketed in the last two decades are man-made. Many were popularized by Alexander Shulgin, who authored the books entitled *PIHKAL* and *TIHKAL* (standing for *Phenethylamines I Have Known And Loved* and *Tryptamines*

I Have Known And Loved), which extensively described action, dosage, duration, and personal experiences with these two classes of psychoactive drugs (Shulgin & Shulgin, 1991, 1997). Some of Shulgin's noteworthy discoveries included compounds of the 2C family, which have gained popularity on the drug market around the world. The NBOMe compounds, the most recently discovered hallucinogens, are *N*-benzyl derivatives of the 2C family of drugs.

SEROTONIN RECEPTOR SUBTYPE 2A AND THE ACTION OF NOVEL HALLUCINOGENS

The exact mechanisms by which hallucinogens cause their effects are not yet clearly understood, but results of many research studies indicate that the action is connected with temporarily disrupting communication between neurotransmitter systems throughout the brain and spinal cord responsible for regulation of vital processes, including mood, perception, sleep, hunger, body temperature, and sexual behavior (NIDA, 2014). It was found that agonist activity at the serotonin (5-hydroxytryptamine) receptor subtype 2A (5-HT_{2A}) is essential for the action of mescaline, psilocin, and LSD, therefore intensive studies on the affinity of different substances for this subtype of the receptor have been performed in recent years. There are three main chemical types that are agonists at this receptor: the phenethylamines, the tryptamines, and the ergolines related to LSD, which can also be considered to be rigidified tryptamines (Nichols, 2012); phenethylamines being the most-rapidly developing class of hallucinogens. It was confirmed that representatives of the 2C family, which are derivatives of phenethylamine containing two methoxy groups substituted at positions 2 and 5 of the benzene ring, interact effectively with serotonin receptors. Typically, a 2C-series member carries a lipophilic substituent in the *para* (4-) position relative to the side chain, which further enhances the 5-HT_{2A} affinity and partial agonistic activity (Clare, 1998; Glennon, Kier, & Shulgin, 1979; Kier & Glennon, 1978; Klopman & Macina, 1985). The most active compounds identified to date possess an ether, alkylthio, alkyl, or halogen group at this position with increasing potency, respectively (Thakur, Thakur, & Khadikar, 2004; Neuvonen, Neuvonen, & Fulop, 2006). Several representatives of the 2C family are listed in Table 1.

Intensive structure–activity relationship (SAR) studies have led to the discovery of agents with nanomolar affinities for the 5-HT_{2A} receptor, some of which are among the most potent hallucinogens known to date (Nichols, 2012; Seggel et al., 1990). It was found that *N*-substitution of common phenethylamines with methyl or ethyl substituents significantly decreases the binding affinity for serotonin receptors, while the addition of an *N*-benzyl moiety affords compounds with remarkable affinity and potency (Braden, Parrish, Naylor, & Nichols, 2006). Substitution of one of the hydrogen atoms attached to the nitrogen in 2,5-dimethoxy-β-phenethylamine (2C-H) by the benzyl moiety led to a 13-fold increase in binding affinity (Braden, 2007). Addition of a hydroxy or methoxy group on the 2 (*ortho*-) position of the *N*-benzyl group enhances the activity even further; *N*-(2-methoxy)benzyl and *N*-(2-hydroxy)benzyl derivatives exhibited 190- and 82-fold increases in affinity in comparison to 2C-H, respectively (Braden, 2007). These derivatives were very selective for 5-HT_{2A} receptors over 5-HT_{1A} and moderately selective over 5-HT_{2C}. It is worth adding that when a hydrogen atom on the α-carbon was substituted by the methyl group, affinity for the 5-HT_{2A} receptor dropped off about 20-fold (Nichols, 2012).

NBOMe COMPOUNDS

The aforementioned SAR studies led to the discovery of the "optimal" substituent at the nitrogen atom of phenethylamines in view of hallucinogenic action, i.e., a 2-methoxybenzyl moiety. An alternative name for this structure is *N*-benzylmethoxyl, abbreviated as NBOMe. 25C-NBOMe was the first representative of this class of substances detected on the drug market. It was identified in a yellow powder seized by the Finnish Customs from the Helsinki incoming mail in January 2011. In the following months other NBOMe compounds were detected in many European countries. Table 1 contains substances that have been notified by the Early Warning System to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) so far and are derivatives of 2C-class compounds containing the 2-methoxybenzyl moiety connected to the amine side chain. Five substances with similar structures

TABLE 1 The NBOMe Compounds Notified by the Early Warning System to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Their 2C-class Counterparts (see Figure 1 for Basic Structures)

Substituent at Position 4	NBOMe Compound	2C-Class Compound
Bromine	25B-NBOMe	2C-B
Chlorine	25C-NBOMe	2C-C
Methyl	25D-NBOMe	2C-D
Ethyl	25E-NBOMe	2C-E
Methyl (+methyl at position 3)	25G-NBOMe	2C-G
No (hydrogen)	25H-NBOMe	2C-H
Iodine	25I-NBOMe	2C-I
Isopropyl	25iP-NBOMe	2C-IP
Nitro (–NO_2)	25N-NBOMe	2C-N

were also reported. 3,4-DMA-NBOMe and 4-MMA-NBOMe are *N*-(2-methoxybenzyl) derivatives of respective amphetamine-type compounds. 25B-N(BOMe)$_2$ can be formed by the dialkylation of 2C-B, while 25I-NBMD and C30-NBOMe are analogs that carry another substituent on the amine side chain, i.e., *N*-(3,4,5-trimethoxybenzyl) and *N*-(2,3-methylenedioxyphenyl). The NBOMe compounds gained popularity around the world in a relatively short time. Since the beginning of 2014, 23 countries and territories have reported the emergence of new psychoactive substances (NPS) to the United Nations Office on Drugs and Crime Early Warning Advisory. By September 2014, 25I-NBOMe was the most frequently reported NPS with 43% of all reports, followed by 25C-NBOMe and the synthetic cathinone, methylone, both of which were reported by an equal number of countries (40%) (UNODC-EWA, 2014).

CHEMISTRY AND DOSAGE FORMS OF 25C-NBOMe

The systematic name for 25C-NBOMe is 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine. The "25C" element of the name refers to the substitution of the chlorine atom on the 2,5-dimethoxyphenethylamine nucleus, while the "NBOMe" component is related to the *N*-(2-methoxybenzyl) part of the molecule. Alternative abbreviations used for this substance are 2C-C-NBOMe and NBOMe-2C-C, while its street names are C-Boom, Pandora, BOM 2-CC, and Dime (Bersani et al., 2014). The structure of 25C-NBOMe is presented in Figure 1.

25C-NBOMe has no known legitimate uses as a research, industrial, cosmetic, or medicinal compound, except for study into its potential use as a tracer in positron emission tomography imaging studies (Ettrup et al., 2011). The synthesis of 25C-NBOMe was first reported in the scientific literature in 2011 (Ettrup et al., 2011). This substance was derived from the psychedelic phenethylamine 2C-C (4-chloro-2,5-dimethoxylphenethylamine) by substitution of the hydrogen atom located on the nitrogen with a 2-methoxybenzyl group. Synthesis can be achieved in two alternative ways: by reductive amination of 2-methoxybenzaldehyde with 2C-C using sodium borohydride (Heim, 2003); or reductive amination of 2-hydroxybenzaldehyde with 2C-C and further methylation of the hydroxy group (Ettrup et al., 2011).

In a pure form, 25C-NBOMe is available as a white powder, and is mixed in single doses with a carrier powder (also as capsules filled with powder). Reports of seizures have noted that 25C-NBOMe has also been sold in the form of tablets (usually containing 300–350 μg) or dissolved in liquids. But the typical form of distribution is "blotters." These are sheets of absorbent paper divided into squares with distinctive, often cartoon-based designs, like postage stamps or transfers. Examples of blotter papers containing 25C-NBOMe seized by the police are presented in Figure 2. Blotters are designed for sublingual or buccal administration. The paper sheets are perforated so they can be torn into small, single-dose units (typically 5–10 mm squares). Blotters are created by soaking the sheet of paper in a dilution of the active substance. Unfortunately, this process can create significant batch to batch variability and there is no easy way for users to determine the exact dosage of a particular tab (square). Due to extremely low doses of 25C-NBOMe, usually containing less than 1 mg (i.e., less than 1000 μg), the risk of overdosing is serious. An additional complication is that some 25C-NBOMe is sold as freebase, some as hydrochloride, and some as "precomplexed" material that is mixed with hydroxypropyl-β-cyclodextrin purported to make 25C-NBOMe more soluble in water and therefore bioavailable. These different forms will all have different total masses per active dose. Information from seizures, analysis of products offered in online stores, and Internet drug forums suggest that 25C-NBOMe may have been sold as a "legal" replacement for LSD or sold as LSD or a compound from the 2C group directly on the illicit drug market. In the latter case users may be unaware that they are using 25C-NBOMe. Nevertheless, "tabs" of this substance are also purchased as "research chemicals" or equivalent products via the Internet. It is common that 25C-NBOMe is sold as a mixture with other substances.

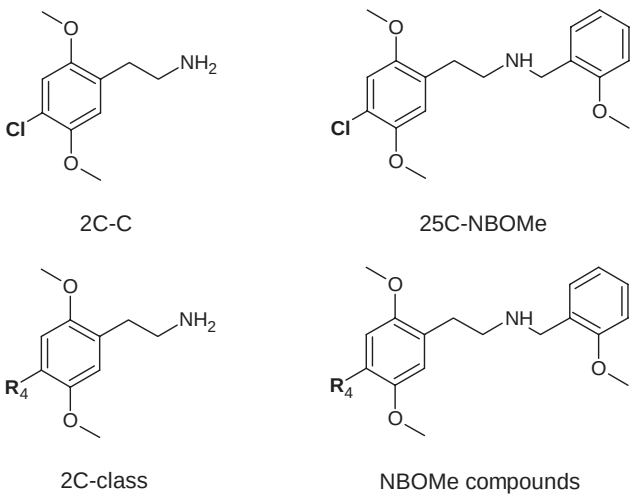

FIGURE 1 Structure of 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe), its precursor 4-chloro-2,5-dimethoxyphenethylamine (2C-C), and general structures of the NBOMe and 2C-class compounds.

FIGURE 2 Package seized by the police containing blotter papers with 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe).

PREVALENCE OF USE

Prevalence of use of 25C-NBOMe and other NBOMe compounds was assessed through an online survey on drugs (Lawn, Barratt, Williams, Horne, & Winstock, 2014). Over 20,000 responses were collected, mainly from the United Kingdom, Australia, and the United States. Lifetime prevalence of NBOMe compounds was nearly 3%. The most popular was 25I-NBOMe, followed by 25B-NBOMe and 25C-NBOMe. Most of the respondents indicated a website as the source of the drug. According to their statements, the NBOMe drugs were administered mainly orally or sublingually/buccally and the effects were similar to those observed after other serotonergic hallucinogens, though were reported to be "greater negative while high." Users found NBOMe-series drugs to be extremely good value for money. In the United States, the System to Retrieve Information from Drug Evidence, a federal database for the seized drugs analyzed by DEA forensic laboratories, and the National Forensic Laboratory Information System, a system that collects drug analysis information from state and local forensic laboratories, contained 849 reports for 25I-NBOMe, 171 reports for 25C-NBOMe, and 24 reports for 25B-NBOMe between June 2011 and June 2013. Bulk quantities of powdered material and blotter paper laced with some combination of 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe have also been encountered (DEA, 2013b). The NBOMe compounds were the fourth most popular drugs in 2013 on "Silk Road," an online platform selling drugs, with 29% of surveyed drug users reporting that they used the marketplace to procure it (Ferdman, 2013). In contrast, the Advisory Council on the Misuse of Drugs (ACMD) in the United Kingdom suggested that 25C-NBOMe did not seem to be a drug of choice, was not particularly prevalent, and there was no evidence that it was associated with criminal behavior, either through violent or acquisitive crime (ACMD, 2013). Notwithstanding, the ACMD has recommended that the NBOMe compounds should be scheduled under Schedule I of the Misuse of Drugs Regulations and now these substances are banned in the United Kingdom.

EVALUATION OF DOSAGES AND ROUTES OF ADMINISTRATION

25C-NBOMe is most commonly administered sublingually, buccally, and orally, less commonly smoked (as a freebase), taken intrarnasally, rectally, vaginally, and through injection. The parenteral route of administration is preferred, because the activity of 25C-NBOMe when taken orally is considered as weak. The range of doses depends on the route of administration (Table 2). The threshold doses are 25–50 μg and heavy as high as 1200 μg. When 25C-NBOMe is nasally insufflated (dissolved in water) threshold doses are reported to be 50–200 μg, common doses 200–350 μg, strong doses 350–700 μg, and heavy doses >700 μg. When taken sublingually the threshold doses are 100–250 μg, common 250–450 μg, strong 450–800 μg, and heavy >800 μg. Hallucinogenic effects can be achieved at a dose of 200–1000 μg when administered intranasally or sublingually, and from 50 to 500 μg when smoked. For smoking, 25C-NBOMe may be dissolved in isopropanol and then 300 μg doses applied to the plant material, which is subsequently smoked (in cigarettes, spliffs, or pipes). In cases of less popular routes of administration the doses described by the users were 400 μg (rectally), 500 μg (vaginally), and 830 μg (injected). Onset of action is observed after 0–15 min (sublingual) or 0–5 min (insufflated), coming up after 30–90 min (sublingual) or 15–30 min (insufflated), and coming down after 1–4 h (sublingual) or 1–3 h (insufflated) (Table 3). The total duration of action is reportedly up to 4–10 h. Insufflation leads to more rapid and probably more severe and toxic consequences than oral or sublingual intake. As mentioned, 25C-NBOMe may be used on its own as well as in combination with other drugs, which is an important consideration when assessing effects and combinational toxicity (Bersani et al., 2014; WHO, 2014; Zuba, Sekuła, & Buczek, 2013).

TABLE 2 Typical Doses of 25C-NBOMe

Dose	Route/Dose (μg)	
	Insufflated/Nasal	Sublingual
Threshold	50–200	100–250
Common	200–350	250–450
Strong	350–700	450–800
Heavy	>700	>800

PHARMACODYNAMICS

25C-NBOMe is a potent partial agonist of the 5-HT_{2A} receptor. Data from in vitro studies have shown that this substance has nanomolar affinity for this receptor; its binding (K_i) at the rat 5-HT_{2A} receptor was reported to be 2.89 ± 1.05 nM with activation (ED_{50}) of 2.31 ± 0.11 nM and intrinsic activity of 88% (Ettrup et al., 2011). These data indicate great the potential of 25C-NBOMe as a hallucinogen. It should be noted, however, that K_i values for 25I-NBOMe and 25B-NBOMe are lower (0.044 nM and 0.51 ± 0.19 nM, respectively), which means that these substances bind stronger to the receptor (Braden, 2007; Lawn et al., 2014). As the 5-HT_{2A} affinity of NBOMe compounds is over 10 times greater than the 5-HT_{2A} affinity of their 2C-series counterparts, the NBOMe drugs produce greater behavioral responses in animals (Halberstadt & Geyer, 2014) and require lower doses to produce subjective effects in humans. There are no published studies assessing the psychological and/or behavioral effects of 25C-NBOMe, but some of the effects have been self-reported by users on Internet drug discussion forums. Anecdotal hallucinogenic effects of 25C-NBOMe include extreme patterning, vibrant coloring, strong sound distortion,

TABLE 3 Duration of Action of 25C-NBOMe

	Time of Action (min)	
	Insufflated	Sublingual/Buccal
Onset	0–5	0–15
Coming up	15–30	30–90
Plateau	120–240	240–360
Coming down	60–180	60–240
Total duration	240–480	360–480

as well as open and closed eye visuals. The positive effects reported by users include euphoria, sociability, mood lift, dissociation, mental and physical stimulation, increased empathy, conceptual thinking, time distortion, and increased appreciation of music. Described adverse effects were feelings of confusion and paranoia, anxiety, panic attacks, insomnia, headache, sweating, body tremors, and nausea. Other effects as reported by physicians include increased heart rate and blood pressure, agitation, aggression, seizures, fever, and high body temperature (Bersani et al., 2014; WHO, 2014; Zuba et al., 2013; www.talktofrank.com, n.d.).

ABUSE AND DEPENDENCE POTENTIAL

There is a paucity of data concerning the abuse and dependence potential of 25C-NBOMe with no experimental studies conducted in animals or humans having been published so far. Case reviews in the scientific literature, information from local or national drug treatment agencies, or user reports on the Internet forums describing dependence potential are also not available. However, some sources indicate that 25C-NBOMe as well as 25I-NBOMe and 25B-NBOMe have a high potential for abuse (DEA, 2013a). There is a lack of data about long-term effects of 25C-NBOMe, but some of the symptoms were observed by users even after several months following consumption (www.bluelight.org, n.d.).

PHARMACOKINETICS

Data on the pharmacokinetics of NBOMe compounds in animals and humans are limited. Stellpflug, Kealey, Hegarty, and Janis (2014) predicted that metabolism can occur through O-demethylation and reported such a metabolite for 25I-NBOMe. Soh and Elliott (2014) identified the desmethyl and possible didesmethyl metabolites of 25C-NBOMe in casework biological fluid. It is worth noting that *N*-(2-hydroxybenzyl) derivatives of 2C-class phenethylamines are also potent ligands of 5-HT receptors (Hansen et al., 2014), therefore their role in the hallucinogenic action of NBOMe compounds needs further study. An alternative suggested route of metabolism is removal of the halogen atom. 25H-NBOMe was detected after administration of both 25C-NBOMe and 25I-NBOMe, although it is not clear whether it was formed during metabolism or whether it was present as a contaminant in the consumed product (Soh & Elliott, 2014; Stellpflug et al., 2014).

ACUTE TOXICITY ASSOCIATED WITH 25C-NBOMe

Emergency departments continue to report cases of severe toxicity due to new hallucinogens. Reports from medical examiners and toxicology laboratories link 25I-NBOMe, 25C-NBOMe, and/or 25B-NBOMe to the death of at least 19 individuals, aged 15–29 years, in the United States between March 2012 and August 2013 (DEA, 2013b).

So far, only several cases of lethal poisonings with 25C-NBOMe have been described. Two cases were reported in 2013 and involved two young men (16- and 18-year-olds) that died after having inhaled the drug (Bersani et al., 2014). In the first case, the involvement of 25C-NBOMe powder was confirmed but the concentration of this substance in the blood of the deceased was not known. The cause of death was reported to be cardiac arrest (Gerber, 2013). In the second case, the deceased took 25C-NBOMe liquid possibly thinking it was 2C-I. Analysis of postmortem biological fluid showed the presence of cannabinoids and 25C-NBOMe, and excluded 2C-I. The concentrations of 25C-NBOMe in blood and urine were determined to be less than 6.25 ng/ml (Soh & Elliott, 2014; WHO, 2014). Two separate subsequent fatalities occurred in 2014 in the United States. They concerned a young girl and a young man who bought capsules of 2C. Toxicological research revealed the presence of 25C-NBOMe (15–25 mg) in each capsule. The autopsy reports stated that they died from "apparent intake of 25C1-NBOMe," "complications of anoxic brain injury," and "25C1-NBOMe toxicity." The concentrations of the 25C-NBOMe in biological material were not given (Nienaber, 2014). A report from Australia indicated that 25C-NBOMe was encountered in a series of three cases. The blood concentrations ranged from less than 0.5 to 8 ng/ml (Stockham, Partridge, Kostakis, & Rogers, 2014).

Several nonfatal poisonings with 25C-NBOMe are also described in the literature. Grautoff and Kähler (2014) presented the case of a 19-year-old male who had nasally administered 2 mg (2000 μg) of 25C-NBOMe. Two hours after ingestion the man experienced seizures and loss of consciousness. Although by the second day of hospitalization it seemed that the patient would return to health quickly, on the third day an acute kidney failure occurred followed by acute lung failure on the fourth day. Finally, after 13 days in the intensive care unit the man recovered. Two cases of acute intoxication associated with 25B-NBOMe and 25C-NBOMe were reported by Tang, Ching, Tsui, Chu, and Mak (2014). The presence of both compounds was analytically confirmed in the urine. The patients developed confusion, agitation, hypertension, tachycardia, hyperthermia, sweating, dilated pupils, rhabdomyolysis, and deranged liver function. Confusion, agitation, hypertension, and tachycardia have also been observed in other cases. Armenian and Gerona (2014) described a case of intoxication of a 24-year-old female. She ingested three doses on blotter paper thinking that it was LSD. The woman was confused and thought that she was being attacked by invisible assailants. The adverse effects were characterized by agitated delirium and tachycardia consistent with a sympathomimetic syndrome. The woman's pupils were dilated, and her skin was moist and hot. She was not oriented to person, place, or time. Three other nonfatal poisonings with 25C-NBOMe were mentioned by Forrester (2014).

It seems that the main cause of poisoning with this substance is the lack of knowledge about its identity and dosage, which makes overdoses more likely. Due to its extremely high potency, misjudging the dose of 25C-NBOMe carries very real risks to the user. A substantial dosage mistake could result in undesirable or threatening effects. Effects of 25C-NBOMe at high doses seem to include delirious, dangerous behavior with some accidents resulting in death, as well as the possibility of death from direct pharmacological effects. Dangerous doses may be 3–5 mg, very low compared to many other "recreational" drugs. 25C-NBOMe is often bought and unwittingly taken as LSD or a drug from the 2C family. LSD is perceived by many drug users as a safe drug, as no documented deaths from an LSD overdose have been reported. Recreational doses of 2C-class compounds are higher and range from several to tens of mg. Unintentional ingestion of 25C-NBOMe instead of LSD or 2C compounds can be disastrous. If 25C-NBOMe is taken in pure powder form, accidental inhalation or contact with the eyes or mouth after handling could lead to severe dose-related effects.

IDENTIFICATION OF 25C-NBOMe IN BIOLOGICAL AND NONBIOLOGICAL SAMPLES

25C-NBOMe is distributed mainly in paper "blotters." Extraction of the active compound can be carried out with a variety of organic solvents, including methanol and acetone. Liquids containing 25C-NBOMe can be analyzed directly or after evaporation and dissolution in an appropriate solvent. A basic analytical technique used in forensic laboratories for identification of the composition of seized drugs is gas chromatography coupled with mass spectrometry (GC–MS). The GC–MS spectrum of 25C-NBOMe is presented in Figure 3. The electron impact mass spectra of most NBOMe compounds have a characteristic pattern of dominant ions, which are observed at $m/z = 121$, 150, and 91. These ions originate from the decay of the (2-methoxy)benzyl moiety. The other ions in the GC–MS spectrum of 25C-NBOMe are of low intensity and the molecular ion is not observed. Fortunately, as this compound has a chlorine atom in the structure, the characteristic isotope distribution is observed for many minor fragment ions. The molecular mass can be determined after derivatization, e.g., with trifluoro- or pentafluoroacetic anhydride or when a soft ionization method is applied, for example chemical ionization in GC–MS, and atmospheric pressure chemical ionization or electrospray ionization in liquid chromatography with mass spectrometry. The latter technique is now a common tool in forensic toxicology laboratories dealing with biosamples. Due to the low concentrations of 25C-NBOMe commonly encountered in biological fluids, its detection requires the implementation of sensitive tandem mass spectrometry. Accurate mass spectrometry, e.g., quadrupole-time-of-flight mass spectrometry, has also been applied in several case studies. This technique allows for accurate mass determination of molecular and fragmentation ions. The protonated molecule $[M+H]^+$ is observed at m/z 336.1361 with commonly observed product ions at m/z 121.0648 [(2-methoxy)benzyl fragment] as well as m/z 91.0542, which represents the tropylium species.

LEVELS OF 25C-NBOMe AND OTHER NBOMe COMPOUNDS IN BIOLOGICAL MATERIAL

Published data concerning the concentrations of 25C-NBOMe in blood, serum, and/or urine after administration of this substance are limited. This is caused primarily by a lack of routine methods used for the detection of new hallucinogens in samples collected from individuals including hospitalized patients, drivers, etc. Traditional screening tests are generally not suitable for such purposes due to limited selectivity and sensitivity. Small doses of 25C-NBOMe produce very low expected concentrations in the blood. It is therefore necessary to use sensitive targeted screening methods, preferably chromatographic techniques coupled with tandem mass spectrometry.

As the doses and physicochemical properties of 25C-NBOMe are similar to those of 25B-NBOMe and 25I-NBOMe, it is likely that all compounds would have similar blood and urine

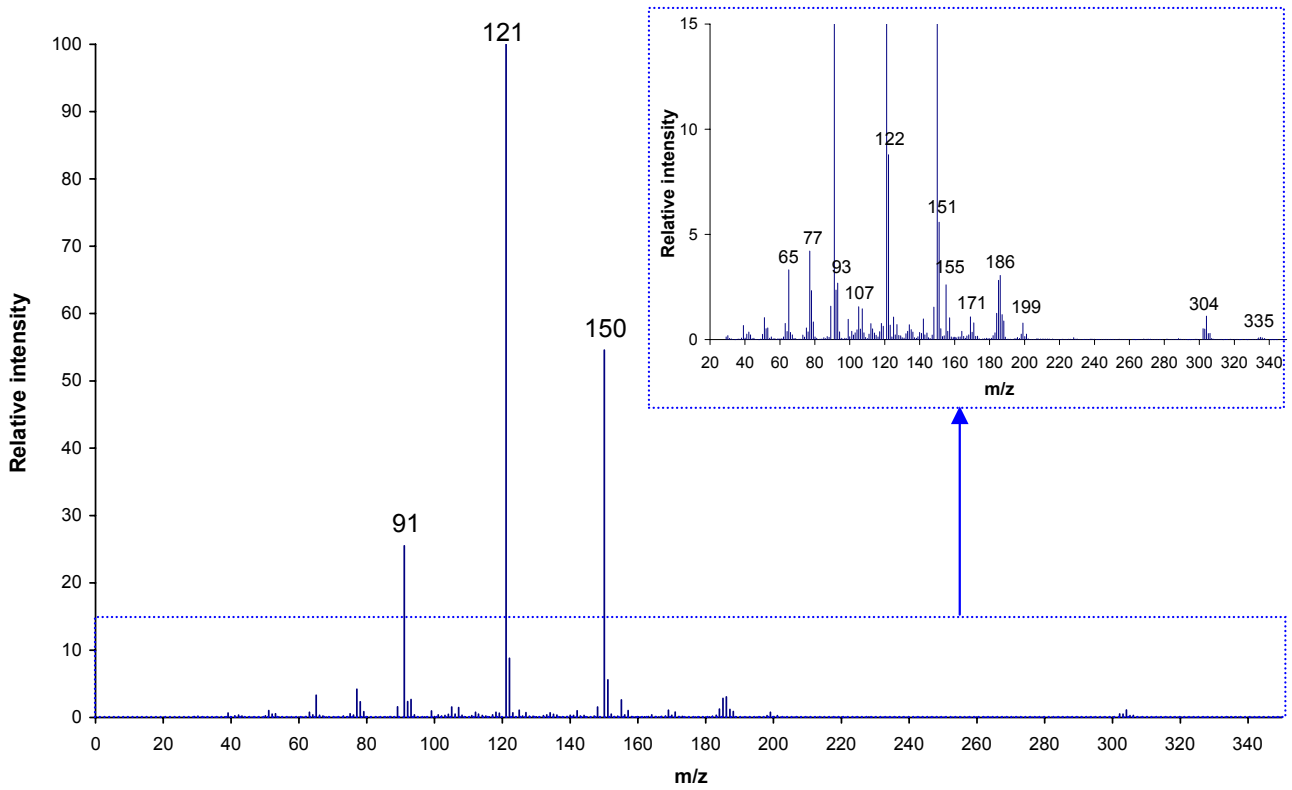

FIGURE 3 The gas chromatography–mass spectrometry (GC–MS) spectrum of 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe).

concentrations. Several well-documented cases are presented below. Poklis, Nanco, Troendle, Wolf, and Poklis (2014c) reported a case of 25B-NBOMe intoxication of a 19-year-old male who was found unresponsive and with generalized grand mal seizure activity. The serum and urine specimens collected 39 h post admission to the emergency department (ED) contained 25B-NBOMe at concentrations of 0.18 and 1.90 ng/ml, respectively. The patient fully recovered after 6 days of hospitalization. The concentration of 25B-NBOMe in urine was similar to the urinary concentrations of 25I-NBOMe determined by other authors in patients that ranged from 2 to 36 ng/ml (Kelly, Eisenga, Riley, & Judge, 2012; Hill et al., 2013). Poklis, Charles, Wolf, and Poklis (2013), Poklis, Clay, and Poklis, (2014) and Poklis, Devers, et al., (2014) analyzed serum samples collected from over 20 individuals who had taken 25I-NBOMe. Serum (drawn 25–48 h after admission to the ED) concentrations of 25I-NBOMe were within the range 0.25–2.78 ng/ml (Poklis et al., 2013; Poklis, Clay, et al., 2014; Poklis, Devers, et al., 2014). Rose, Poklis, and Poklis (2013) presented a case of an 18-year-old male with serve agitation and hallucinations after jumping out of a moving car. The patient had sympathomimetic toxidrome and diagnosed tachycardia and hypertension. 25I-NBOMe was found in the serum at a concentration of 0.76 ng/ml. Stellpflug et al. (2014) reported a case concerning the intoxication of an 18-year-old female with 25I-NBOMe. She administered sublingually one dose of an unspecified amount and exhibited seizure, tachycardia, hypertension, agitation, and confusion. The urine concentration of 25I-NBOMe was 7.5 ng/ml, and 25H-NBOMe was detected below 0.9 ng/ml as well as 2C-I at a concentration of 1.8 ng/ml. Poklis, Devers, et al., 2014 also reported a case of fatal behavioral intoxication due to the ingestion of 25I-NBOMe with laboratory confirmation in postmortem samples. The individual ingested blotter paper, which was later established to contain approximately 500 μg of 25I-NBOMe. His friends noticed that he began to display strange and paranoid behavior, leading to a fatal consequence. The decedent apparently jumped or fell accidentally from his apartment balcony. Toxicology findings in postmortem material were as follows: peripheral and heart blood 0.41 ng/ml, urine 2.86 ng/ml, vitreous humor 0.1 ng/ml, liver 7.2 ng/g, brain 2.54 ng/g, bile 10.9 ng/g, and gastric content 7.1 μg total.

Overall, in relation to all the above data it can be concluded that the expected concentrations of 25C-NBOMe in blood are very low, ranging from about 0.1 to several ng/ml, while the concentrations in urine are up to several tens of ng/ml.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

25C-NBOMe is a representative of the NBOMe compounds, a family of very potent hallucinogens that have appeared on the drug market in the last 4 years. These compounds are derivatives of psychedelic phenethylamines from the 2C family, but their affinity for the 5-HT_{2A} receptor is much higher in comparison to respective counterparts, which is reflected in lower active doses.

25C-NBOMe is often advertised as "legal LSD," which suggests to potential users that the action is similar to this psychedelic drug. But reports from clinical and forensic toxicologists indicate that consumption of 25C-NBOMe and related compounds poses much higher risk. Overdose of 25C-NBOMe leads to severe serotonin toxidrome and the most important and critical adverse effects are related to the cardiovascular system. In some presentations the effects were typical for sympathomimetic toxidrome observed after consumption of stimulants such as amphetamine or cocaine. Many fatalities were notified after administration of 25C-NBOMe despite its relatively low prevalence, which is in strong contrast with "classical" hallucinogens such as LSD, mescaline, or tryptamines.

Dosage, form of distribution, and hallucinogenic action of 25C-NBOMe are similar to LSD. Anecdotal reports of users indicate that the substances can be differentiated in taste; genuine LSD blotters are either tasteless or have a mild "metallic" flavor, while most people describe an intense bitterness when holding a 25C-NBOMe blotter in their mouths. But even experienced users can mistakenly overdose with novel drugs. 25C-NBOMe and other NBOMe compounds, despite the demonstrated toxicity, have increased popularity on the drug market. Novel hallucinogens have partially displaced LSD and other scheduled psychedelics. The most common reasons include simple synthesis leading to low prices, stability, and easy availability, mainly via online stores. The growing popularity of 25C-NBOMe and related chemicals poses a serious risk due to limited knowledge of the impact of new substances on the human body.

The appearance of 25C-NBOMe on the drug market is associated with the broader phenomenon of "legal highs." Hundreds of NPS have been marketed in the past several years without research on their toxicity, pharmacokinetics, pharmacodynamics, interactions, etc. Limited or no data are available on their long-term effects, genotoxicity, carcinogenicity, and teratogenicity. Easy access to NPS has significantly changed the drug market and some new substances, e.g., mephedrone or MDPV (3,4-methylenedioxypyrovalerone,1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one), are popular even after their scheduling. Therefore, detailed studies on the toxicity, abuse, and dependence potential of NPS are highly desired.

DEFINITION OF TERMS

Agonist A substance capable of combining with a receptor on a cell to produce a physiologic reaction typical of a naturally occurring substance.

Blotters Sheets of absorbent paper divided into squares with distinctive designs used for sublingual administration.

Buccal Route of administration by which drugs diffuse through the oral mucosa (tissues that line the mouth) and enter directly into the bloodstream.

Electron impact An ionization method widely used in mass spectrometry in which electrons interact with gas phase atoms or molecules to produce ions.

Electrospray ionization A technique used in mass spectrometry to produce gas phase ions (without fragmentation) using an electrospray in which a high voltage is applied to a liquid to create an aerosol.

Partial agonist A substance that can activate a receptor but is unable to elicit the maximal response of the receptor system irrespective of the concentration applied. The maximum response produced by a partial agonist is called its intrinsic activity and may be expressed on a percentage scale where a full agonist produced a 100% response.

Serotonin toxidrome A syndrome caused by excessive stimulation of serotonergic receptors. Drugs involved in the development of

the syndrome act by inhibiting the reuptake of serotonin, causing the release of serotonin into synapses, directly stimulating serotonin receptors, or decreasing the metabolism of serotonin. Mild signs and symptoms include anxiety, diaphoresis, and gastrointestinal complaints. Severe cases can present with confusion, hypertension, hyperthermia, hyperreflexia, and seizures.

Spliff One of the slang terms used for a cigarette made from smoking herbal material, e.g., cannabis or synthetic cannabinoids.

Sublingual Route of administration by which drugs diffuse into the blood through tissues located under the tongue.

Sympathomimetic toxidrome A syndrome caused by a dangerous level of substances that stimulate the sympathetic nervous system. The signs and symptoms include tachycardia, tachypnea, hypertension, central nervous system excitation, delusions, paranoia, hyperthermia, sweating, and dilation of the pupils.

KEY FACTS ON NEW PSYCHOACTIVE SUBSTANCES

- NPS are a range of man-made chemicals that have been designed to imitate the effects of illicit drugs, such as cannabis, amphetamine, cocaine, or LSD, by either mimicking the pharmacological effects of a specific drug, or by slightly modifying the chemical structure of existing controlled drugs.
- The number of reported NPS is growing rapidly, and has surpassed the total number of drugs under international control.
- These substances have been known by terms such as "designer drugs," "legal highs," "herbal highs," "bath salts," and "research chemicals."
- There is no scrutiny or quality control in the production of NPS in clandestine laboratories.
- Manufacturers of NPS do not perform any studies on their toxicity, pharmacokinetics, or pharmacodynamics, therefore the consequences of consumption are unpredictable.
- NPS users have frequently been hospitalized with severe intoxications.
- Fatalities have been associated even with hallucinogenic substances like 25C-NBOMe.
- There are medical difficulties in treating the adverse effects of NPS on the users due to the lack of knowledge about their action on humans.
- The difference between the real content of packages of NPS and the declared composition poses a serious threat for potential users.
- As manufacturers of NPS try to stay ahead of the law, they often change the content of the products. Consequently, the composition may be different from batch to batch, even if the packaging and name are the same.
- Many NPS are not under international control, but many countries have established permanent control measures for some substances or issued temporary bans.

SUMMARY POINTS

- This chapter focuses on 25C-NBOMe and related compounds, which appeared on the drug market in the past few years.
- The NBOMe compounds are very potent partial agonists of serotonin receptor subtype 2A. High affinity for this receptor is crucial in the hallucinogenic action of substances.
- 25C-NBOMe is sold online as "legal LSD" or as "research chemical."
- Novel hallucinogens are distributed in the form of paper blotters, a liquid, or tablets.
- 25C-NBOMe is much more toxic than "classical" hallucinogens such as LSD or mescaline.
- Common doses of 25C-NBOMe are at microgram levels. Administration of higher doses carries very real risk.
- The side effects include agitation, confusion, paranoia, insomnia, nausea, anxiety, and panic attacks.
- Long-term effects, abuse, or dependence potential of 25C-NBOMe have not been investigated.
- Concentrations of this substance after consumption are very low; less than 10 ng/ml in blood and less than 100 ng/ml in urine.

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