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REVIEW ARTICLE

25B-NBOMe and its precursor 2C-B: modern trends and hidden dangers

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Abstract Substituted phenethylamines are a class of designer drugs that hold a significant position in the drug abuse market. The most important substances within this class appear to be 4-bromo-2,5-dimethoxyphenethylamine (2C-B) and its novel derivative 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25B-NBOMe). Intoxications related to 2C-B use are still recorded worldwide, despite the fact that its use and trafficking are banned in many countries. 25B-NBOMe is a highly potent 2C-B derivative that has invaded recently in the "drug arena" and is considered legal to possess and supply in many countries. This manuscript reviews all available information regarding chemistry, availability, pharmacology, and toxicology of 2C-B and 25B-NBOMe. The intoxication and fatal cases reported, as well as the current legislation of these drugs, are also presented.

Keywords 2C-B · Nexus · 25B-NBOMe · New Nexus · Substituted phenethylamines · Toxicology and pharmacology

Introduction

The substituted phenethylamines (2C-X) are a class of designer drugs that contain methoxy groups at the 2 and 5 positions of the benzene ring and a variety of lipophilic substituents at position 4 (see molecular structures shown in Nieddu et al. [1]). All of them appear to have significant psychedelic and hallucinogenic properties [2–5]. 4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a ring-substituted phenethylamine (Fig. 1) that shows a pharmacological action similar to those of other hallucinogens like LSD, mescaline, and psilocybin [6, 7]. 2C-B was first synthesized in 1974 by Alexander Shulgin; it has a phenethylamine structure similar to 3,4-methylenedioxymethamphetamine (MDMA), and is considered to be a partial agonist of serotonin 2A (5-HT_{2A}) and 2C (5-HT_{2C}) receptors [8–10]. Its use was first recorded in the 1980s in the USA as an MDMA replacement [10, 11] and it became popular in many European countries in the 1990s [12, 13]. Nowadays, 2C-B, although a controlled substance worldwide, remains popular among young people who use it in dance clubs and at rave parties [14]. Moreover, new *N*-substituted derivatives of it have emerged on the drug abuse market. The use or possession and supply of these derivatives remains legal until national or international drug laws prohibit them. The simplest among them are the alkyl derivatives; *N*-methyl-2C-B, *N,N*-dimethyl-2C-B, and *N*-ethyl-2C-B. However, these substances are considerably less potent than 2C-B, with affinities for the 5-HT_{2A} receptor being up to 40 times lower [5].

The *N*-benzyl substituted phenethylamines (NBOMes) are much more potent. They are formed by adding a 2-methoxybenzyl (MeOB) group onto the nitrogen of the 2C-X [2]. NBOMes were first synthesized in 2003 by Ralph Heim at Free University of Berlin [15]. They are highly potent hallucinogens, even at microgram-level doses, because the *N*-benzyl substitution of phenethylamine dramatically increases their affinity for the 5-HT_{2A} receptor [2, 16–18]. NBOMes are also agonists for the α-adrenergic receptors. As a result, they can provoke serotonergic and sympathomimetic toxidromes [19].

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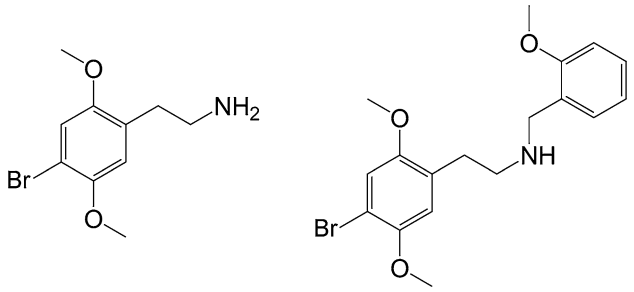

2C-B **25B-NBOMe**

Fig. 1 Chemical structures of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) and 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25B-NBOMe)

Because of this action, they present a significant abuse potential and have been regarded as alternatives to LSD [2, 18]. Among NBOMes, the *N*-benzyl derivative of 2C-B [2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl) ethanamine, 25B-NBOMe] (Fig. 1) shows a much higher binding affinity for the 5-HT_{2A} receptor than 2C-B, and it is also a potent partial agonist [15, 20, 21] explaining its wide use as a hallucinogenic drug of abuse. The use of NBOMes is associated with nonfatal intoxications reported in the scientific literature, but also with deaths according to media reports from the USA and Australia [22].

This review presents all available information regarding the synthesis, prevalence, patterns of use, pharmacology, and toxicology of 2C-B and its derivative 25B-NBOMe. Details of the related cases already published, self-reports from drug users, and the existing legislation that concern these drugs were gathered through PubMed and a World Wide Web search and reviewed.

2C-B

Synthesis

2C-B was first synthesized in 1974 by Alexander Shulgin, and it is described in his later published book "Phenethylamines I Have Known and Loved" (PiHKAL) [6]. The substitution of 2,5-dimethoxyphenethylamine, an already psychoactive compound, at position 4 with bromine produces 2C-B with hallucinogenic effects that are increased when compared with the parent compound [4]. The basic synthesis of 2C-B starts from 2,5-dimethoxybenzaldehyde and includes the condensation of 2,5-dimethoxybenzaldehyde with nitromethane to 2,5-dimethoxynitrostyrene, which is reduced by sodium borohydride to 2,5-dimethoxynitroethane. The crude 2,5-dimethoxynitroethane, through catalytic transfer hydrogenation, gives the 2C-H freebase, which is finally brominated by hydrobromic acid in a hydrogen peroxide environment. There are other routes for the synthesis of 2C-B, but normally they are avoided because they require the use of reagents that are slightly hazardous or difficult to obtain, notably lithium aluminium hydride, pressurized H_2, and Br_2 [23].

Prevalence

2C-B appeared on the drug market in the mid-1980s as a legal MDMA replacement. It has been marketed under different street names over these years, like "Nexus", "Venus", "Bromo", "Eros", "Erox", "Performax", "Spectrum", "Cloud Nine", "Synergy", "Eve", "Zenith", "Utopia", "Afterburner Bromo", "Afro", "Toonies", "Cee-Beetje", "BDMPEA", "MTF", "CB", "CB's", "See Bees", "Bees", "B′s", and "2′s" [24–30]. Sometimes drug users purchase the drug as LSD or psilocybin, while in some cases it is still suggested as an MDMA replacement [25, 28]. Before its scheduling, 2C-B was sold at different "smart-shops", mainly in Germany, as an aphrodisiac under the name "Eros", and was manufactured by the German pharmaceutical company "Drittewelle" [29]. After it was banned, it could still be purchased mainly via the Internet or from drug dealers through illicit channels [27, 28, 31]. During 2013, 2C-B was the most commonly reported of the "new phenethylamines" in the European Union [32]. It became popular in the rave culture internationally due to widely available information on its synthesis on the Internet, its short duration, its mild nature, and its few known side effects. As a consequence today, it is used extensively at parties or music festivals [25, 28]. A survey carried out in the UK focused on the drug-taking habits of young drug users showed that 16.7 % of them were familiar with 2C-B and 7.4 % of the respondents had used it during the past 12 months, while this percentage increased to 12 % among regular clubbers [33]. Another study that examined the prevalence of new psychoactive substances (NPS) in Australia showed that 2C-B was the most prevalent (8 %) among them [34]. 2C-B is commercially available, mainly as powder in small envelopes or as small tablets, which contain the drug at different quantities [27]. The price of a 2C-B tablet varies from country to country; and it can be £2–5 in the UK [30] or $10–30 in the USA [29]. It is also noteworthy that 2C-B was found to be the most frequently detected adulterant of NPS [35].

Patterns of use

2C-B is usually taken orally in powder or tablet form, in doses of 10–50 mg. Tablets typically contain 5 mg of the drug. A minimum oral dose is considered to be 2–5 mg, a light one 5–15 mg, a common dose 5–25 mg, a high dose 25–40 mg, and a heavy dose higher than 40 mg [25, 36]. Following an onset period of 20–90 min, its action reaches

its maximum in 15–30 min, then plateaus for 2–7 h, and comes down within 1–2 h. The aftereffects may last for 2–4 h [28, 36]. The drug may also be snorted in the powdered form; the doses for this route of administration are approximately one third of the oral ones [25]. The threshold dose for the snorting is approximately 1 mg, a light dose 1–5 mg, a common dose 5–10 mg, a high dose 10–15 mg, and a heavy dose greater than 15 mg. After snorting, the onset period is as short as 1–2 min, the come up lasts 10–20 min, and the action of the drug plateaus for 2–4 h. The comedown lasts 1–2 h and the aftereffects may last 2–4 h [36]. 2C-B can also be smoked [30, 37].

Mechanism of action

2C-B activates 5-HT receptors, and it is characterized as a partial agonist of 5-HT_{2A} and 5-HT_{2C} receptors ($pEC_{50} = 6.8$ for arachidonic acid release) [38]. These receptors are considered to mediate the primary effects of hallucinogenic drugs. 2C-B induces mild activation of 5-HT_{2A} receptors, eliciting weak responses (5–10 %) in both arachidonic acid release and inositol phosphate accumulation. Despite this low efficacy at 5-HT_{2A} receptors, the drug proved to be hallucinogenic. Regarding its effect on head-shaking behavior, 2C-B is considered a "milder" head-shaking inducer than MDMA [39]. This can be explained by the correlation of this behavior (head-shaking) to 5-HT_{2A} agonism [10].

Pharmacology and toxicology

The pharmacokinetics of 2C-B have been studied through animal studies and in vitro experiments. In vivo animal studies and in vitro studies with the use of animal and human hepatocytes [40–44] suggested that the major metabolic steps of 2C-B included *O*-demethylation, *N*-acetylation, and deamination followed by oxidation to the corresponding acids or reduction to the corresponding alcohols. The drug was found to be excreted mainly via several metabolites (4-bromo-2,5-dimethoxyphenylacetic acid, 4-bromo-2,5-dimethoxybenzoic acid, and 4-bromo-5-hydroxy-2-methoxyphenethylamine) in urine, and as the unchanged compound only to a very small extent for up to 3 h after ingestion [25, 26, 41, 44]. In only one pharmacokinetic animal study of 2C-B, the elimination half-life ($T_{1/2}$) was found to be 1.1 h, the distribution volume (V_d) 16 l/kg, and the clearance (CI) 9.8 l/h [26]. Minor interspecies differences were observed in 2C-B metabolism and toxicity, but large interindividual differences in susceptibility of human cultivated hepatocytes suggest that some human subpopulations may show an increased risk for expressing toxicity when exposed to 2C-B [42].

Most available information concerning the pharmacology of 2C-B comes from users who reported their personal drug experience in different blogs, forums, and websites or even in the media. The first reported volunteer experience was that described by Shulgin and his wife in their book PiHKAL [6]. Systematic clinical studies concerning the pharmacological and/or toxicological action of this drug using volunteers remain restricted for ethical reasons and therefore only animal or in vitro studies have been performed to date [7, 9, 45]. In 1992, Lobos et al. [9] found that 2C-B behaves as a partial agonist toward both α_1-adrenergic and 5-HT_2 serotonergic receptors using a rat thoracic aorta model. A few years later, Bronson et al. [7] observed hallucinogenic effects similar to those of mescaline after administration of 2C-B in newly hatched chickens. Palenicek et al. [45] studied the behavioral, neurochemical, and pharmaco-electroencephalography (EEG) profiles of 2C-B in rats. They concluded that "2C-B is a potent centrally active substance which induces behavioral, neurochemical, and electrophysiological changes similar to other psychedelics, entactogens, and stimulants". It shows a time- and dose-dependent biphasic action that is related to its pharmacodynamics. This biphasic action is presumably linked to time differences in the involvement of 5-HT and dopamine systems [45]. The initial effects of the drug are more related to its direct binding at 5-HT receptors [39], while in later stages, especially for high doses of the drug, dopamine plays an important role. More specifically, 2C-B increases dopamine but decreases 3,4-dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens. This action of 2C-B may explain its psychotomimetic and addictive potential. The indications that 2C-B is a monoamine oxidase inhibitor and EEG findings that showed strong effects on the functionality of the brain, might correlate to altered sensorimotor processing and its psychedelic potential. A temporal correlation of 2C-B's effects on locomotion in combination with EEG changes was shown by Palenicek et al. [45].

Different dose-dependant effects have been described by drug users after consumption of 2C-B. When the drug is consumed orally (4–30 mg), it can produce "considerable euphoria and a feeling of energy in the body with increased receptiveness of the visual, auditory, olfactory, and tactile sensations" [26], "feelings of alertness, of being alive and of being in tune with surroundings" [46]. Entactogenic-stimulating effects have been reported after low doses (4–10 mg), while visual hallucinations with intense colors and distortion of objects have been experienced by using moderate doses (10–20 mg). The hallucinations were extremely unpleasant and frightening along with other psychedelic effects after higher ingested doses. In such doses, sympathomimetic effects like tachycardia,

hypertension, hyperthermia, and mydriasis can also appear [6, 8, 10, 26, 28, 42]. Unpleasant stomach effects including nausea, vomiting, diarrhea, cramps, and gas, as well as headaches, confusion, agitation, or even delirious states have also been described by 2C-B users [28, 37, 46]. Several users reported pulmonary reactions that caused increased mucus production, which resulted in intense coughing [28]. The onset of the drug effects usually takes place after 20–90 min, but a full stomach delays it considerably [10, 28]. The average duration of the effects ranges between 4 and 8 h depending on the dose and the susceptibility of an individual [6].

Caudevilla-Galligo et al. [27] registered and studied all acute subjective and unpleasant effects caused by 2C-B, as well as the residual effects during the 48 h following intake reported by recreational users of the drug. The lists of the effects are presented in Table 1.

2C-B users reported that the drug "induces physical effects with a full and complete array of body enhancements which generally includes enhanced tactile sensations, increased bodily awareness and a perception of increased muscle control. The visual effects include increased visual acuity, enhancement of colors and enhanced pattern recognition. The experienced visual distortions and alterations contain visual drifting, tracers, afterimages, texture repetition, color shifting, and scenery slicing. 2C-B users experience a visual geometry similar in appearance to that of LSD, which is described as algorithmic in geometric style, intricate in complexity, large in size, fast and smooth in motion, colorful in scheme, glossy in color, sharp in their edges, and angular in their corners" [36, 47]. Moreover, they claimed that 2C-B can also produce "a full range of low and high level hallucinatory states with transformations, imagery, and hallucinations like other psychedelics. The auditory effects (enhancements, distortions, hallucinations) are more common. The total sum of the cognitive components, regardless of the setting, generally includes entactogenic effects (increased empathy and sociability), sexual arousal, acceleration of thought, enhancement of current mind state, feelings of fascination, importance and awe, introspection, conceptual thinking, connectivity of thought, ego suppression, loss and death feelings, and time distortion" [36, 47].

Positive (desired), neutral, and negative (undesired) effects are described by 2C-B users and intoxicated patients after its use, according to a categorisation made by Erowid. Positive effects include "mood lift, euphoria, increased giggling and laughing, feelings of insight, feelings of love and empathy, brightened colours, enhanced visual perception, mental and physical stimulation, closed- and open-eye visuals (including trails, colour shifts, brightening, etc.), enhanced tactile sensation/eroticism, erotic and sexual thoughts and sensations, and increased

Table 1 Acute subjective, unpleasant and residual effects caused by 4-bromo-2,5-dimethoxyphenethylamine (2C-B) as described by recreational users

Acute subjective effects	Acute unpleasant effects	Residual effects (during the first 48 h)
Enhanced sense of touch and perception of own body	Difficulty focusing gaze	Insomnia
Moving of the walls and floor in waves	Trembling	Involuntary reoccurrence of experiences
More distinct colors and shapes	Sweating	Anxiety
More distinct sounds and music	Nausea	Coughing
With eyes closed, the appearance of images (geometrical patterns, shapes)	Pain in stomach	Difficulty concentrating
Intense feeling of peace and wellbeing	Tachycardia	Depression or sadness
Everything appears funny, causes laughter	Jaw clenching	Lack of appetite
Halos or auras seen around objects	Difficulty breathing	Headache
Everything slower than usual	Coughing	Sweating
Moving objects	Diarrhea	Backache
High sensitivity to cold and heat	Dizziness	
Thoughts coming to mind faster than usual	Muscle or joint pain	
With eyes open, the appearance of images (geometrical patterns, shapes)	Pins and needles in arms or legs	
Feeling of easier communication with others	Urge to defecate, urinate	
Strange and unusual thoughts	Headache	
With eyes open, the appearance of things that are not real	Paresthesia	
Feeling like having sex	Stiff neck	
Objects appearing larger or smaller than usual		
More clouded and slower thoughts		
Being aware of things that I did not remember before		
Feelings of distress		
Any discomfort or small pain being greater		
Everything happening faster than usual		
Being afraid		

Information from Caudevilla-Galligo et al. [27]

access to spiritual ideation". Neutral effects include "a general change in consciousness, decreased appetite, restlessness, unusual thoughts and speech, unusual body sensations (facial flushing, chills, goose bumps, body energy), change in perception of time, change in body temperature regulation, and ego softening". The negative effects that appear after 2C-B use are "uncomfortable changes in body temperature (sweating/chills), nausea, vomiting, tension, muscle twitching, mydriasis, confusion and difficulty in focusing, problems with activities requiring linear focus, insomnia, unpleasant visions, unwanted and overwhelming feelings, paranoia, fear, and panic" [28].

2C-B was previously considered as a safer recreational drug, but recent studies have disclosed remarkable inter-individual differences in human susceptibility to 2C-B toxicity that could be attributed to the various metabolic pathways of 2C-B [10]. 2C-B users also claim that regular use can leave people tired, disorientated, and anxious. Depression, visual illusions, panic attacks, or more serious psychotic illnesses like depersonalization can also appear in vulnerable individuals. Psychological effects of 2C-B can be unpredictable and random, as well as varying greatly from person to person, depending on factors such as previous experiences, state of mind and environment, or dose strength [10, 30, 37].

The long-term effects of 2C-B use are not yet fully known, but there have been cases of associated neurological damage [46, 48], like progressive encephalopathy and quadriparesis caused by diffuse cerebral vasculopathy as an idiosyncratic reaction to 2C-B [49].

There are no current data for the lethal dosage (LD_{50}) of 2C-B, but it is considered to be high [36]. 2C-B has no accepted medical use but shows a high potential for abuse [24]. Despite that, it seems that 2C-B use actually provokes neither physical addiction nor psychological dependence [28]. That is why many drug addicts support the idea that a lack of tolerance causes more intense and uncontrollable experiences when more 2C-B is taken [30]. In some cases, a short period of tolerance after 2C-B use has been observed [28]. Concomitant use of alcohol and other drugs are known to increase the risks of 2C-B use [48].

2C-B related cases reported in scientific literature

There have been no fatal cases directly related to 2C-B use [49]; published cases of intoxication with 2C-B are limited in the scientific literature. This does not mean that cases have not occurred. Intoxications with 2C-B could remain undetected mainly due to the fact that 2C-B and especially its metabolites can easily be missed during routine toxicological analysis [31]. It is noteworthy that the United Nations Office on Drugs and Crime (UNODC) included 2C-B among the test substances for biological samples in its International Collaborative Exercise (ICE) as recently as 2013.

In 2010, Ambrose et al. [49] first reported a case of a 43-year-old woman who ingested liquid 2C-B at a party and presented neurological sequelae. She experienced severe headaches within 48 h. The patient developed progressive encephalopathy and quadraparesis due to diffuse cerebral vasculopathy as an idiosyncratic reaction to 2C-B [49].

The case of an acute psychotic episode of a 27-year-old man that persisted for 2 months was reported in New Zealand after ingestion of a single tablet of 2C-B. The man obtained the tablet from his friends and ingested it. Two days later, he developed auditory hallucinations and paranoid delusions that were followed by increasing irritability, anxiety, and fearfulness. The result was a self-inflicted head injury after fiercely hitting his head on a wall [10]. To our knowledge, no other 2C-B related cases have been reported in the scientific literature.

Analysis of 2C-B

Analytical methods have been developed for the determination of 2C-B in seized materials and biological samples. In 1985, Ragan et al. [11] reported the nuclear magnetic resonance (NMR), ultraviolet (UV), and mass spectral data for 2C-B. Giroud et al. [12] identified 2C-B in seized materials from the Swiss black market, by means of several analytical methods [gas chromatography–mass spectrometry (GC–MS), high-performance liquid chromatography (HPLC)–diode array detection (DAD), capillary electrophoresis–DAD, Fourier-transform infrared (FTIR) spectroscopy, and NMR spectroscopy]. The mass spectra of 2C-B, underivatized and after acetylation and methylation, were presented [12]. A GC–MS determination of 2C-B in human urine was developed by Namera et al. [50] using an automated headspace solid-phase microextraction procedure and in-matrix derivatization. The simultaneous determination of 2C-B with amphetamine derivatives in human urine was also performed after solid-phase extraction (SPE) and HPLC–UV analysis by Soares et al. [51]. Kim et al. [52] determined a number of psychotropic phenylalkylamine derivatives, including 2C-B, in human hair by GC–MS after trifluoroacetyl derivatization. A recently published liquid chromatography–tandem mass spectrometry (LC–MS–MS) method was used to determine 2C-B simultaneously with 14 other psychostimulants in urine samples after SPE [53].

Legal status

2C-B was listed as a Schedule I restricted hallucinogen by the Drug Enforcement Administration (DEA) in 1995 [24].

The World Health Organization recommended international control of 2C-B in 2001 and placed it in Schedule II of the 1971 Convention [54]. Nowadays, the possession, production, and sale of 2C-B are illegal in Argentina, Australia, Belgium, Brazil, Finland, Netherlands, Russia, Switzerland, and Japan. It is also characterized as a class A drug in the UK, which means that possession and supply are banned. In Denmark, it is listed as a category B drug [29]. 2C-B is classified as a Schedule I drug in the USA, Sweden, Italy, Estonia, and Poland, as a Schedule II drug in other EU countries and Norway, and as a Schedule III drug in Canada. It is also listed as a category 2 drug in Spain [28, 36, 46]. The drug is also controlled in Greece, France, Germany, and South Africa [24].

25B-NBOMe

Synthesis

In 2014, new designer drugs with altered hallucinogenic and stimulant activities continue to emerge after synthesis by different substitutions to the 2C phenethylamine structure [4]. According to the 2012 report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 14 new substituted phenethylamines were formally notified to the European Early Warning System (EWS) in 2012. Six of these 14 new phenethylamine derivatives belong to the NBOMe group [22].

25B-NBOMe is a 2C-B derivative that is characterized by the addition of an *N*-benzyl-methoxy group to the amine group. This NBOMe analogue of 2C-B can be synthesized via a reductive alkylation of 2C-B with 2-methoxybenzaldehyde. This synthesis is done stepwise, first by synthesizing the imine, and then by reducing the imine with sodium borohydride or by direct reaction with sodium triacetoxyborohydride [15, 55].

Prevalence

Phenethylamine derivatives have a high prevalence worldwide particularly among young people [56]. 25B-NBOMe has gained recent popularity. It is available under the following street names: 2C-B-NBOMe, "25B", "New Nexus", "BOM 2-CB", "Cimbi-36", and "Holland film" [19, 57, 58]. The drug is encountered as powder, liquid solution, laced on edible items, or soaked onto blotter papers [59]. Users typically use Internet websites and forums for information on these substances that can be easily purchased online [27]. It can be also found in "smartshops" as an aphrodisiac [59, 60]. Most of the packages indicate "not for human consumption". Some suppliers of 25B-NBOMe may also purport it to be or mistake it for LSD or other Schedule I hallucinogens. According to the System to Retrieve Information from Drug Evidence and the National Forensic Laboratory Information System, there were 24 reports for seized powdered materials or laced blotter papers of 25B-NBOMe between June 2011 and June 2013 in the USA [59].

In Europe, quantities of 25B-NBOMe in the form of powder, impregnated paper fragments, perforated paper, or blotters have been seized from December 2012 to March 2014 in different countries like Croatia, Latvia, Hungary, Austria, UK, Germany, Spain, Denmark, and Sweden [57]. A recent report has also detailed the emergence of 25B-NBOMe in Japan after it was detected in illegal products distributed in the country [61].

The annual Global Drug Survey in 2013 showed that 25B-NBOMe was one of the three most popular NBOMes among drug users; 1.2 % of them reported previous use of the drug [62].

Patterns of use

Because 25B-NBOMe is active in doses as low as a few micrograms, small quantities of the drug can provide a large number of doses. It can be taken as a liquid, powder, or tablet or in the form of preloaded paper doses (blotters) [2]. The abuse of 25B-NBOMe can be conducted by nasal snorting of powder, intravenous or intramuscular injection, nasal absorption of liquid solutions, sublingual or buccal administration of blotter papers, and consumption of foods items laced with it [2, 60, 63]. The minimum sublingual dose is 100 μg, while light doses range from 100 to 300 μg. It is frequently used at doses of 350–700 μg or sometimes higher (up to 1,500 μg) [64]. A snorted light dose is 50–200 μg, while middle doses range from 200 to 350 μg. High doses range from 350 to 800 μg, while higher doses up to 1,400 μg and more are characterized as very high and heavy, respectively [63]. The onset of the effects takes place after 15–60 min, and the effects last up to 120 min and then decrease. The plateau lasts for 3–4 h, while the total duration lasts 8–10 h and aftereffects can be observed for 5–24 h [63, 64].

Mechanism of action

There is limited scientific research on the mechanism of action of 25B-NBOMe. The *N*-benzyl-methoxy addition to the amine moiety significantly increases the affinity ($K_i = 1.01$ nM) and activity ($ED_{50} = 0.51$ nM) toward the 5-HT receptor (5-HT_{2A}) [38]. 25B-NBOMe is considered a potent agonist of 5-HT_{2A} receptors because all NBOMes show exceptionally high affinities for these receptors [17, 65]. 5-HT_{2A} receptors were shown to be closely linked to complex activities including working memory, cognitive

processes, and affective disorders such as schizophrenia [66]. The activation of these receptors by 25B-NBOMe results in significant behavioral toxicity that provokes hallucinogenic and stimulant effects, even in low dosages. The potency of 25B-NBOMe is 16-fold higher than that of precursor 2C-B [67].

Pharmacology and toxicology

Despite the recent extensive use of 25B-NBOMe, there is limited published information about its pharmacological effects in humans or animals. However, significant information is emerging from users that report their personal drug experience in different blogs, forums, and websites. 25B-NBOMe, immediately after sublingual use of a blotter paper, unlike LSD, induces a strong, unpleasant metallic chemical taste and a distinctive feeling of general numbness of the tongue and mouth that lasts for up to 1 h [64].

25B-NBOMe is generally considered a stimulant, but it acts in different ways for each user [60, 64, 67]. Its use has been reported to cause "bizarre and irrational behavior, paranoia, fear, confusion, increased body temperature, sweats, and seizures" [68]. 25B-NBOMe users describe "a body enhancement with a euphoric tingling sensation that is also accompanied by spontaneous rushes of euphoria". They also state that "they feel extremely light, often to the point of total weightlessness". Vasoconstriction has also been described by some users, who also complained of temporary difficulty in urinating, mild nausea, and vomiting [64, 67].

The most prominent of the cognitive effects are similar to those of 2C-B and include "introspection, acceleration of thought, ego suppression, loss and death feelings, time distortion, conceptual thinking, increased connectivity of thought, enhancement of current mind state, removal of cultural filter, and entactogenic effects (increased empathy and sociability). Enhanced visual effects are possible like enhancement of colors, increased visual acuity, and pattern recognition. Visual distortions and alterations have been also experienced and include visual drifting, tracers, afterimages, and texture repetition. 25B-NBOMe users experience a visual geometry also similar in appearance to that of 2C-B. 25B-NBOMe consistently produces a full range of hallucinatory states within levels 1–3. However, strong hallucinatory episodes (level 4) are not commonly reported. The most common auditory effects of 25B-NBOMe include enhancements, distortions, and hallucinations" [64, 67].

The only experimental animal study available on the pharmacology of 25B-NBOMe was carried out by Ettrup et al. [65], who administered two different doses of 25B-NBOMe (0.05 and 0.5 mg/kg) in rats and pigs, and studied the effects on head twitch response (HTR), a high-frequency paroxysmal head rotation that occurs after 5-HT_{2A} receptor activation. They found that 25B-NBOMe induces the HTR only when the high dose was used [65]. When the results of this study were compared with those of related studies of other *N*-benzylphenethylamines, it was confirmed that 25B-NBOMe was highly potent [18].

There are no published studies on the safety of 25B-NBOMe in humans, but the available data suggests that even extremely small amounts can cause seizures, sympathomimetic symptoms and signs, rhabdomyolysis, impaired renal and liver function, cardiac and respiratory arrest, and even death [19, 59, 69–71]. The LD_{50} of 25B-NBOMe has not been determined. Because drug users obtain 25B-NBOMe, like most new designer drugs, through unknown sources, its identity, purity, and concentration are uncertain and inconsistent, thus posing significant risk of adverse health effects to users [64]. 25B-NBOMe use causes immediate tolerance that lasts up to 2–3 weeks, but its addiction potential has not been substantially studied [64].

25B-NBOMe related intoxication or fatal cases

There are some 25B-NBOMe related intoxication or fatal cases that have been reported in websites and forums for drug users or in published studies. The first intoxication case after 25B-NBOMe use appeared in the scientific literature in 2013 [70]. A 19-year-old man was found unresponsive with generalized tonic–clonic seizure activity. The patient arrived at the emergency department in status epilepticus (with generalized tonic–clonic jerking movements), with hyperthermia (40 °C), tachycardia (152 bpm), blood pressure at 145/90 mmHg, respiratory rate at 22 rpm, and oxygen saturation at 97 % on ventilator. He required intubation, seizure control, and paralysis. During the next day, a period of forgetfulness followed. The reported intoxication was documented to be due to 25B-NBOMe by toxicological analysis of the material provided by his friend and of biological samples of his own. The concentration of 25B-NBOMe in a serum sample 39 h after admission was found to be 180 pg/ml, while the respective concentration in urine samples obtained 25–48 h after his admission decreased from 2,700 to 250 pg/ml [70].

Another recently published study reported two NBOMe intoxication cases that occurred in China [19]. A 17-year-old man with a history of recreational use of cannabis was admitted to an Accident and Emergency Department, initially for confusion and agitation (Glasgow Coma Scale 13: E3V4M6) after ingestion of one "happy pill". Then the patient developed convulsions, other sympathomimetic symptoms, and signs like hypertension (215/94 mmHg), tachycardia (140 bpm), sweating, hyperthermia (38.4 °C), and mydriasis. High doses of diazepam were administered

to him. The CT brain scan was clear. He required intubation, seizure control with sedation by midazolam and rocuronium, as well as cyproheptadine as antidote for possible 5-HT syndrome. The patient was discharged after 5 days. The 25B-NBOMe intoxication was confirmed by the toxicological analysis of a urine sample collected 40 min after admission. Another 31-year-old man, who had a history of substance abuse, was also admitted to the Accident and Emergency Department due to sympathomimetic symptoms and signs like agitation, tachycardia (162 bpm), hypertension (160/123 mmHg), dilated pupils, hyperthermia (39.6 °C), and sweating. Treatments with intravenous lorazepam and ice packs for physical cooling were required. The patient had impaired renal function due to rhabdomyolysis and deranged liver function. He admitted to consumption of half a packet of a drug named "Holland film" sublingually. Both 25B-NBOMe and 25C-NBOMe were found in a urine sample collected 7 h after his admission [19].

Another case of 25B-NBOMe intoxication was reported on the Internet [72] in April 2013 in the USA. A man consumed one piece of an LSD-like blotter, and became very paranoid and anxious. After initially enjoying his experience, he then started to repeat phrases spoken by others, and he tried to commit suicide by falling from the second floor of a building. Not seriously hurt, he then ran away and climbed a barbed-wire fence without noticing that he was injured. He stripped off all his clothes and then attempted to dive in front of cars on a freeway. He jumped off a small bridge and started throwing large rocks at his friends who were trying to help him. The man was hospitalized for his injuries. It was found that 25B-NBOMe was responsible for his behavior [72].

A good number of 25B-NBOMe related fatal cases have been reported via the Internet. Thus, NBOMes including 25B-NBOMe have been linked to the deaths of at least 19 people, aged 15–29 years, in the USA between March 2012 and August 2013 according to the Drug Enforcement Administration (DEA) [59].

The only publication of a 25B-NBOMe related fatal case came from Switzerland [71]. A 20-year-old man with no medical history was found dead near a psychiatric hospital. A pump spray containing 10 ml of a clear odorless liquid was found nearby. The toxicological analysis of the pump spray liquid was performed by GC–MS and FTIR and NMR spectroscopy, and revealed the presence of 25B-NBOMe as the only active compound. The confirmation of 25B-NBOMe in the blood of the victim was carried out by LC–MS–MS without quantification of the substance because of the absence of a reference standard. Amphetamine and cannabinoids were also determined in his blood [71].

In March 2012 in South Australia, a man who ingested 25B-NBOMe, along with 25I-NBOMe, died from injuries sustained after running and beating himself against fixed objects including trees and power poles [68, 69, 73]. During the next few days in the same area, two nonfatal overdoses were reported of young adults that were related to each other. According to Acting Detective Superintendent Derryn Philips of the Drug Investigation Branch, 25B-NBOMe or/and 25I-NBOMe were responsible for the incidents. The drug was possibly produced in China and purchased via the Internet [68, 69].

The forensic investigation of intoxications or fatalities due to new psychoactive substances like 25B-NBOMe is relatively difficult, because such cases can remain undetermined mainly due to a lack of reference standards or as a result of a lack of proper methodology for the determination of NBOMe drugs and their metabolites [19]. Screening tests for NBOMes like 25B-NBOMe are not included in the routine analysis of a toxicological laboratory, because such analyses are not scheduled in most countries. Specific assays for the determination of drugs are usually performed only when its use is documented repeatedly.

Analysis of 25B-NBOMe

Emerging new designer drugs tend to show new clinical profiles, and they are difficult to identify in laboratories, because these drugs or their metabolites cannot be detected in routine rapid drug screening by urine immunoassays [4]. The difficulty in identification of these drugs, like 25B-NBOMe, during the investigation of different forensic cases leads to the necessity of the development of analytical methodology to determine these drugs or their metabolites in biomedical samples.

There is only one validated method for the determination of 25B-NBOMe by LC–MS–MS in biological fluids. This method was used successfully to determine 25B-NBOMe in human serum and urine samples after liquid–liquid extraction with hexane/ethyl acetate (9:1, v/v). It was applied in the investigation of an intoxication case where 25B-NBOMe was involved, and the drug use was confirmed by analyzing serum and urine samples [70]. The presence of 25B-NBOMe has been also confirmed by LC–MS–MS in postmortem blood after identification of this substance as the only active compound in a pump spray liquid found near the victim [71]. In a recently published study, 25B-NBOMe was identified by GC–MS and LC–MS in seized materials [61]. Tang et al. [19] presented the analysis of urine samples using LC–MS–MS following glucuronidase digestion and SPE during the investigation of two NBOMe intoxication cases. A full range of the analytical parameters of 25B-NBOMe including the mass spectra of this substance using GC–MS and NMR and FTIR spectroscopy were presented by Casale and Hays [55], the Scientific Group for the Analysis of Seized Drugs

[74], and the Southern Association of Forensic Scientists [75].

Legal status

In many jurisdictions, *N*-benzyl substituted phenethylamines are not usually included with other phenethylamines, leading to scheduling problems of substances like 25B-NBOMe [2]. In the UK, the Misuse of Drugs Act, Schedule 2 Part 1 (c) considered the phenethylamine derivatives as class A substances. Because of the high risk of overdose with 25B-NBOMe, the Advisory Council on the Misuse of Drugs suggested in May 2013 that urgent measures should be taken. The increased recreational use of the drug forced the British Government to issue a temporary class drug order on a list of emerging recreational drugs including this substance in June 2013. This order was to last for up to 12 months and prohibited the production, import, and sale of 25B-NBOMe [2, 76].

In the USA, the Deputy Administrator of the DEA decided in October 2013 to temporarily place 25B-NBOMe and two other similar synthetic phenethylamines (25I-NBOMe and 25C-NBOMe) into Schedule I "to avoid an imminent hazard to the public safety". Any subsequent final order for temporarily scheduling of these substances will be effective on the data of publication in the Federal Register and will be in effect for a period of 2 years, with possible extension of one additional year, pending completion of the permanent or regular scheduling process. Therefore, 25B-NBOMe was classified as a Schedule I controlled substance under the Federal Controlled Substances Act in the USA in November 2013 [59, 77].

However, the drug is not subject to international controls [62]. Despite this, 25B-NBOMe has been scheduled in Sweden since August 2013 [78], in Denmark since October 2013 [79], and it is also illegal in New Zealand, Poland, Hungary, and Israel [57, 62]. In Australia, even though 25B-NBOMe is not regulated, it is a chemical analogue of the regulated 2C-B; anybody purchasing it runs the risk of being charged with trafficking of a controlled drug [68].

In any case, because 25B-NBOMe is a chemical analogue of 2C-B, it should be considered as an internationally controlled substance. In such a case, sale or possession of 25B-NBOMe intended for human consumption should be considered illegal.

Conclusions

Adolescents, young people, and others who are curious about drugs sometimes search on the Internet to purchase drugs and especially new designer drugs. This is typical in the case of the phenethylamine 2C-B, which has been popular in rave parties and clubs. This is also the case for the NBOMe derivative 25B-NBOMe. These drugs are usually trafficked via the Internet through websites or forums for drug users, with only the positive effects being emphasized. Little scientific information is available on the pharmacokinetics, pharmacological properties, and toxicological effects of these phenethylamines. The main sources of information are the self-reports from drug users. The recreational use of 2C-B is still of concern for the forensic community, and 25B-NBOMe use has increased in the past 3 years especially among young people. The uncontrolled manufacture, distribution, importation, exportation, and abuse of 2C-B and especially 25B-NBOMe pose an imminent hazard to public safety. Available data and information indicate that these two designer drugs have a high potential for abuse and a lack of safety.

Clinical and forensic toxicologists must remain alert against various new substituted phenethylamines that continue to appear. Methods for the determination of phenethylamine drugs and their metabolites need to be developed for use in cases of emergency and forensic toxicology. When newly introduced drugs become scheduled, newer drugs emerge to take their place because clandestine chemists are often one step ahead. As a consequence, newer NBOMe analogues are expected to emerge onto the drug market following the recent scheduling of NBOMes in many countries worldwide.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

References

1. Nieddu M, Trignano C, Burrai L, Pirisi MA, Boatto G (2013) Cross-reactivities of 41 new amphetamine designer drugs to EMIT® immunoassays. Forensic Toxicol 31:133–137
2. Advisory Council on the Misuse of Drugs (ACMD) (2013) "NBOMe" compounds: a review of the evidence of use and harm. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/204808/J_TCDO_report_on_5-6APB_and_NBOMe_compounds.pdf. Accessed 5 May 2014
3. Dean BV, Stellpflug SJ, Burnett AM, Engebretsen KM (2013) 2C or not 2C: phenethylamine designer drug review. J Med Toxicol 9:172–178
4. Stellpflug SJ, Kealey SE, Hegarty CB, Janis GC (2014) 2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe): clinical case with unique confirmatory testing. J Med Toxicol 10:45–50
5. Wikipedia (2014) 2C (psychedelics). http://en.wikipedia.org/wiki/2C_(psychedelics). Accessed 8 May 2014
6. Shulgin A, Shulgin A (1991) PiHKAL: a chemical love story. Transform Press, Berkeley
7. Bronson ME, Jiang W, DeRuiter J, Clark CR (1995) A behavioral comparison of Nexus, cathinone, BDB, and MDA. Pharmacol Biochem Behav 51:473–475

8. Shulgin AT, Carter MF (1975) Centrally active phenethylamines. Psychopharmacol Commun 1:93–98
9. Lobos M, Borges Y, Gonzalez E, Cassels BK (1992) The action of the psychoactive drug 2C-B on isolated rat thoratic aorta. Gen Pharmacol 23:1139–1142
10. Huang HH, Bai YM (2011) Persistent psychosis after ingestion of a single tablet of "2C-B". Prog Neuropsychopharmacol Biol Psychiatry 35:293–294
11. Ragan FA, Hite SA, Samuels MS, Garey RE (1985) 4-Bromo-2,5-dimethoxyphenethylamine: identification of a new street drug. J Anal Toxicol 9:91–93
12. Giroud C, Augsburger M, Rivier L, Mangin P, Sadephipour F, Varesio E, Veuthey JL, Kamalaprija P (1998) 2C-B: a new psychoactive phenethylamine recently discovered in ecstasy tablets sold on the Swiss black market. J Anal Toxicol 22:345–354
13. deBoer D, Gijzels MJ, Bosman IJ, Maes RA (1999) More data about the new psychoactive drug 2C-B. J Anal Toxicol 23:227–228
14. Kanamori T, Nagasawa K, Kuwayama K, Tsujikawa K, Iwata YT, Inoue H (2013) Analysis of 4-bromo-2,5-dimethoxyphenethylamine abuser's urine: identification and quantitation of urinary metabolites. J Forensic Sci 58:279–287
15. Heim R (2003) Synthese und Pharmakologie potenter 5-HT_{2A}-Rezeptoragonisten mit *N*-2-Methoxybenzyl-Partialstruktur. Entwicklung eines neuen Struktur-Wirkungskonzepts (in German). http://www.diss.fu-berlin.de/diss/receive/FUDISS_thesis_000000001221. Accessed 9 May 2014
16. Blaazer AR, Smid P, Kruse CG (2008) Structure–activity relationships of phenylalkylamines as agonist ligands for 5-HT(2A) receptors. ChemMedChem 3:1299–1309
17. Nichols DE, Frescas SP, Chemel BR, Rehder KS, Zhong D, Lewin AH (2008) High specific activity tritium-labeled *N*-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (INBMeO): a high-affinity 5-HT_{2A} receptor-selective agonist radioligand. Bioorg Med Chem 16:6116–6123
18. Halberstadt AL, Geyer MA (2014) Effects of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent *N*-benzyl derivatives on the head twitch response. Neuropharmacology 77:200–207
19. Tang MHY, Ching CK, Tsui MSH, Chu FKC, Mak TWL (2014) Two cases of severe intoxication associated with analytically confirmed use of the novel psychoactive substances 25B-NBOMe and 25C-NBOMe. Clin Toxicol 52:561–565
20. Silva ME (2008) Theoretical study of the interaction of agonists with the 5-HT2A receptor. http://epub.uni-regensburg.de/12119/1/Maria_Elena_Silva_Doctor_Tesis.pdf. Accessed 8 May 2014
21. Silva ME, Heim R, Strasser A, Elz S, Dove S (2011) Theoretical studies on the interaction of partial agonists with the 5-HT2A receptor. J Comput Aided Mol Des 25:51–66
22. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2012) New drugs in Europe. EMCDDA-Europol 2012 annual report on the implementation of council decision 2005/387/JHA. http://www.emcdda.europa.eu/publications/implementation-reports/2012. Accessed 10 May 2014
23. Erowid (2005) 2C-B synthesis without LAH. http://www.erowid.org/archive/rhodium/chemistry/2cb.beaker.html. Accessed 8 May 2014
24. National Drug Intelligence Center (NDIC) (2001) Information bulletin 2C-B (Nexus) reappears on the club drug scene. http://www.justice.gov/archive/ndic/pubs0/665/index.htm. Accessed 9 May 2014
25. Cole MD, Lea C, Oxley N (2002) 4-Bromo-2,5-dimethoxyphenethylamine (2C-B): a review of the public domain literature. Sci Just 42:223–224
26. Rohanova M, Palenicek T, Balikova M (2008) Disposition of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) and its metabolite 4-bromo-2-hydroxy-5-methoxyphenethylamine in rats after subcutaneous administration. Toxicol Lett 178:29–36
27. Caudevilla-Galligo F, Riba J, Ventura M, Gonzalez D, Farre M, Barbanoj MJ, Bouso JC (2012) 4-Bromo-2,5-dimethoxyphenethylamine (2C-B): presence in the recreational drug market in Spain, pattern of use and subjective effects. J Psychopharmacol 26:1026–1035
28. Erowid (2014) 2C-B. http://www.erowid.org/chemicals/2cb/2cb.shtml. Accessed 8 May 2014
29. Wikipedia (2014) 2C-B. http://en.wikipedia.org/wiki/2CB. Accessed 8 May 2014
30. Leicester City Council (2014) Drug data, contents of section 5, general information. http://www.leicester.gov.uk/EasySiteWeb/GatewayLink.aspx?alId=74760. Accessed 2 May 2014
31. deBoer D, Bosman I (2004) A new trend in drugs-of-abuse; the 2C-series of phenethylamine designer drugs. Pharm World Sci 26:110–113
32. King LA (2014) New phenethylamines in Europe. Drug Test Anal 6:808–818
33. MixMag (2012) Global drug survey. http://issuu.com/mixmagfashion/docs/drugs_survey_2012_2?e=1541988/2686928#search. Accessed 9 May 2014
34. Burns L, Roxburgh A, Matthews A, Bruno R, Lenton S, Van Buskirk J (2014) The rise of new psychoactive substance use in Australia. Drug Test Anal 6:846–849
35. Gine CV, Espinosa IF, Vilamala MV (2014) New psychoactive substances as adulterants of controlled drugs. A worrying phenomenon? Drug Test Anal 6:819–824
36. PsychonautWiki (2014) 2C-B. http://psychonautwiki.org/wiki/2C-B. Accessed 10 May 2014
37. Red Button Forum (2014) 2CB. http://red-button.org/a-z/2cb/. Accessed 2 May 2014
38. Cayman Chemical (2014) Item number 12047, 25B-NBOMe (hydrochloride). https://www.caymanchem.com/app/template/Product.vm/catalog/12047;jsessionid=24B0B4AEB5BAD0573691AEFFF54C2622. Accessed 6 May 2014
39. Moya PR, Berg KA, Gutierrez-Hernandez MA, Saez-Briones P, Reyes-Parada M, Cassels BK, Clarke WP (2007) Functional selectivity of hallucinogenic phenethylamine and phenylisopropylamine derivatives at human 5-hydroxytryptamine (5-HT)$_{2A}$ and 5-HT_{2C} receptors. J Pharmacol Exp Ther 321:1054–1061
40. Kanamori T, Inoue H, Iwata Y, Ohmae Y, Kishi T (2002) In vivo metabolism of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in the rat: identification of urinary metabolites. J Anal Toxicol 26:61–66
41. Carmo H, deBoer D, Remiao F, Carvalho F, dos Reys LA, Bastos ML (2004) Metabolism of the designer drug 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in mice, after acute administration. J Chromatogr B 811:143–152
42. Carmo H, Hengstler JG, deBoer D, Ringel M, Remiao F, Carvalho F, Fernandes E, dos Reys LA, Oesch F, Bastos ML (2005) Metabolic pathways of 4-bromo-2,5-dimethoxyphenethylamine (2C-B): analysis of phase I metabolism with hepatocytes of six species including human. Toxicology 206:75–89
43. Kanamori T, Tsujikawa K, Ohmae Y, Iwata YT, Inoue H, Kishi T, Nakahama T, Inouye Y (2005) A study of the metabolism of methamphetamine and 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in isolated rat hepatocytes. Forensic Sci Int 148:131–137
44. Theobald DS, Fritschi G, Maurer HH (2007) Studies on the toxicological detection of the designer drug 4-bromo-2,5-dimethoxy-β-phenethylamine (2C-B) in rat urine using gas chromatography-mass spectrometry. J Chromatogr B 846:374–377
45. Palenicek T, Fujakova M, Brunovsky M, Horacek J, Gorman I, Balikova M, Rambousek L, Syslova K, Kacer P, Zach P, Bubenikova-Valesova V, Tyls F, Kubesova A, Puskarcikova J, Hoschl C (2013) Behavioral, neurochemical and pharmaco-EEG profiles

of the psychedelic drug 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in rats. Psychopharmacology 225:75–93
46. Talk to Frank Forum (2013) 2CB: random letters and numbers or something more serious? http://www.talktofrank.com/news/2cb-random-letters-and-numbers-or-something-more-serious. Accessed 9 May 2014
47. Disregard Everything I Say (DEIS) (2013) 2C-B, broken down and described. http://www.disregardeverythingisay.com/post/60184360278/2c-b-broken-down-and-described. Accessed 14 May 2014
48. Youth Rise Forum (2014) Phenethylamines (2CX, DOX, 25IX, etc.). http://www.youthrise.org/our-issues/harm-reduction/nightlife-and-party-drug-harm-reduction/Phenethylamines. Accessed 5 May 2014
49. Ambrose JB, Bennet BA, Lee HS, Josephson SA (2010) Cerebral vasculopathy after 4-bromo-2,5-dimethoxyphenethylamine ingestion. Neurologist 16:199–202
50. Namera A, Yashiki M, Kojima T, Ueki M (2002) Automated headspace solid-phase microextraction and in-matrix derivatization for the determination of amphetamine-related drugs in human urine by gas chromatography–mass spectrometry. J Chromatogr Sci 40:19–25
51. Soares ME, Carvalho M, Carmo H, Remiao F, Carvalho F, Bastos ML (2004) Simultaneous determination of amphetamine derivatives in human urine after SPE extraction and HPLC-UV analysis. Biomed Chromatogr 18:125–131
52. Kim JY, Jung KS, Kim MK, Lee JII, In MK (2007) Simultaneous determination of psychotropic phenylalkylamine derivatives in human hair by gas chromatography/mass spectrometry. Rapid Commun Mass Spectrom 21:1705–1720
53. Kerrigan S, Mott A, Jatzlau B, Ortiz F, Perrella L, Martin S, Bryand K (2014) Designer psychostimulants in urine by liquid chromatography-tandem mass spectrometry. J Forensic Sci 59:175–183
54. World Health Organization (WHO) (2001) WHO expert committee on drug dependence. Thirty second report. http://whqlibdoc.who.int/trs/WHO_TRS_903.pdf. Accessed 8 May 2014
55. Casale JF, Hays PA (2012) Characterization of eleven 2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine (NBOMe) derivatives and differentiation from their 3- and 4-methoxybenzyl analogues–Part I. Microgram J 9:84–109
56. United Nations Office on Drugs and Crime (UNODC) (2013) Global smart update. http://www.unodc.org/documents/scientific/Global_SMART_Update_9_web.pdf. Accessed 9 May 2014
57. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2014) European database on new drugs (EDND), phenethylamines, 25B-NBOMe. https://ednd.emcdda.europa.eu/html.cfm/index7246EN.html. Accessed 6 May 2014
58. Wikipedia (2014) 25B-NBOMe. http://en.wikipedia.org/wiki/25B-NBOMe. Accessed 9 May 2014
59. Drug Enforcement Administration (DEA) (2013) 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe (street names: N-bomb, Smiles, 25I, 25C, 25B). http://www.deadiversion.usdoj.gov/drug_chem_info/nbome.pdf. Accessed on 6 May 2014
60. Erowid (2012) 2C-B-NBOMe reports (also 25B-NBOMe). http://www.erowid.org/experiences/subs/exp_2CBNBOMe.shtml. Accessed 3 May 2014
61. Uchiyama N, Shimokawa Y, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y (2014) Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products. Forensic Toxicol 32:105–115
62. Lawn W, Barratt M, Williams M, Horne A, Winstock A (2014) The NBOMe hallucinogenic drug series: patterns of use, characteristics of users and self-reported effects in a large international sample. J Psychopharmacol 28:780–788
63. Drugs Forum (2014) 25B-NBOMe. http://www.drugs-forum.com/forum/showwiki.php?title=25B-NBOMe. Accessed 9 May 2014
64. PsychonautWiki (2014) 25B-NBOMe. http://psychonautwiki.org/wiki/25B-NBOMe. Accessed 10 May 2014
65. Ettrup A, Holm S, Hansen M, Wasim M, Santini MA, Palner M, Madsen J, Svarer C, Kristensen JL, Knudsen GM (2013) Preclinical safety assessment of the 5-HT_{2A} receptor agonist PET radioligand [^{11}C]Cimbi-36. Mol Imag Biol 15:376–383
66. Poklis JL, Charles J, Wolf CE, Poklis A (2013) High-performance liquid chromatography tandem mass spectrometry method for the determination of 2CC-NBOMe and 25I-NBOMe in human serum. Biomed Chromatogr 27:1794–1800
67. Disregard Everything I Say (DEIS) (2014) 25B-NBOMe, broken down and described. http://www.disregardeverythingisay.com/post/83025698345/25b-nbome-broken-down-and-described. Accessed 14 May 2014
68. Shroomery Forum (2012) New hallucinogenic drug 25B-NBOMe and 25I-NBOMe led to South Australian man's bizarre death. http://www.shroomery.org/forums/showflat.php/Number/16834552. Accessed 9 May 2014
69. Rice S (2012) New hallucinogenic drug 25B-NBOMe and 25I-NBOMe led to South Australian man's bizarre death. http://www.news.com.au/national-news-2/south-australia/new-hallucinogenic-drug-25b-nbome-and-25i-nbome-led-to-south-australian-mans-bizarre-death/story-fndo4dzn-1226472672220. Accessed 8 May 2014
70. Poklis JL, Nanco CR, Troendle MM, Wolf CE, Poklis A (2014) Determination of 4-bromo-2,5-dimethoxy-*N*-[(2-methoxyphenyl) methyl]-benzeneethanamine (25B-NBOMe) serum and urine by high performance liquid chromatography with tandem mass spectrometry in a case of severe intoxication. Drug Test Anal 6:764–769
71. Sporkert F, Augsburger M, Vilarino R, Michaud K, Schlapfer M, Marcourt L (2013) Identification and implication of the phenethylamine derivative 25B-NBOMe in a case of an unresolved fatality. The 51st annual meeting of the International Association of Forensic Toxicologists, Madeira
72. Neurosoup Forum (2013) 25B-NBOMe (2C-B-NBOMe) hospitalization. http://www.neurosoup.com/25b-nbome-2c-b-nbome-hospitalization/. Accessed 8 May 2014
73. Erowid (2012) 25I-NBOMe. http://www.erowid.org/chemicals/2ci_nbome/. Accessed 3 May 2014
74. Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) (2013) 25B-NBOMe. http://www.swgdrug.org/Monographs/25B-NBOMe.pdf. Accessed 9 May 2014
75. Forendex Forum (2014) Southern Association of Forensic Scientists. http://forendex.southernforensic.org/index.php/detail/index/1246. Accessed 5 May 2014
76. Home Office (2013) 'NBOMe' and 'Benzofury' banned. https://www.gov.uk/government/news/nbome-and-benzofury-to-be-banned. Accessed 14 May 2014
77. Drug Enforcement Administration (DEA), Department of Justice (2013) Schedules of controlled substances: temporary placement of three synthetic phenethylamines into Schedule I. Final Order. Fed Reg 78:68716–68719
78. Läkemedelsverkets författningssamling (2013) Föreskrifter om ändring i Läkemedelsverkets föreskrifter (LVFS 2011:10) om förteckningar över narkotika (in Swedish). http://www.lakemedelsverket.se/upload/lvfs/LVFS_2013-15.pdf. Accessed 8 May 2014
79. Sundhedsstyrelsen (2013) Health and treatment/narcotico (in Danish). file:///C:/Users/user/Downloads/DK_NBOMe%20substances%20risk%20assessment%20(3).pdf. Accessed 8 May 2014