

25B-NBOMe
Critical Review Report
Agenda item 4.17

Expert Committee on Drug Dependence
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Summary

25B-NBOMe is a substituted phenethylamine and derivative of 2C-B. It is a potent partial agonist of the serotonin 5-HT_{2A} receptor in particular and appears to have stimulant and particularly hallucinogenic effects. It has been associated with a few reported non-fatal intoxications and some deaths, with seized material and use reported in many countries. It has been reportedly sold as LSD or as a 'legal' alternative to LSD or "research chemical" usually via Internet websites. The variation in formulations and resultant dosage coupled with its potency results in health risks to the individual. There are not much data concerning the abuse or dependence potential of 25B-NBOMe.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

1026511-90-9

C. Other Names

2C-B-NBOMe; 25B-NBOMe; 25B; 2CBNBOMe; 2C-B-NBOMe; NBOMe-2C-B; NBOMe-2CB;

2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine

2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethan-1-amine

4-bromo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine

4-bromo-2,5-dimethoxy-N-(o-methoxybenzyl)phenethylamine

4-bromo-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]-benzeneethanamine

N-(2-methoxybenzyl)-2,5-dimethoxy-4-bromophenethylamine

N-(2-methoxybenzyl)-4-bromo-2,5-dimethoxyphenethylamine

Cimbi-36 (¹¹C radiolabelled for PET scanning) - Center for Integrated Molecular Brain Imaging (CIMBI)

D. Trade Names

None

E. Street Names

Nova; 25B; legal acid; NBomb; NE-BOME; New Nexus; NBOMe-2C-B, BOM 2-CB

The drug is most often listed on “research chemical” websites as 25B-NBOMe. 25B- refers to the 2,5-dimethoxy-4-bromophenethylamine (2C-B) portion of the structure with NBOMe referring to the N-Benzoylmethoxy moiety (methoxy being OMe in chemical shorthand).

F. Physical properties

25B-NBOMe hydrochloride is a powder.

G. WHO Review History

25B-NBOMe was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that 25B-NBOMe is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

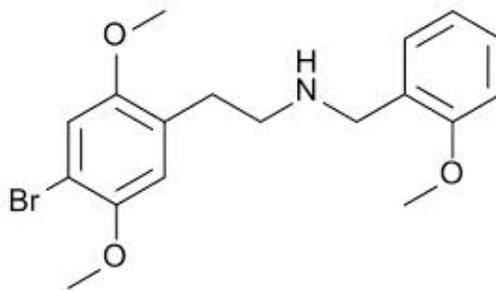
A. *Chemical Name*

IUPAC Name: 2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine

CA Index Name: Not applicable

B. *Chemical Structure*

Free base:



Molecular Formula: C₁₈H₂₂BrNO₃

Molecular Weight: Free base = 380.2762

Melting point: 156°C (HCl salt) – Heim (2003)

Boiling point: not known

Fusion point: not known

C. *Stereoisomers*

25B-NBOMe has no chiral centres and therefore no stereoisomers.

D. *Synthesis*

The synthesis of 25B-NBOMe was first mentioned by Heim in a thesis at the Free University of Berlin (2003). It is a stepwise reductive alkylation where the reducing agent (NaBH₄) is added after the imine intermediate is formed first by the addition of 2-methoxybenzaldehyde to the starting 2C-B compound (Abdel-Magid *et al.* 1996). Various researchers have used this process to synthesise a variety of NBOMe structures for chemical testing, including 25B-NBOMe (Casale and Hays, 2012; Hansen *et al.*, 2014). The free base product is a colourless oil. Published methods typically produced the hydrochloride salt.

E. *Chemical description*

25B-NBOMe is a derivative of 2C-B (4-bromo-2,5 dimethoxyphenethylamine), a known synthetic derivative of phenethylamine with stimulant and hallucinogenic properties. 25B-NBOMe contains the 2C-B substructure, substituted with a 'N-(2-methoxy)benzyl' group.

Several NBOMe derivatives exist where the bromine atom is exchanged for another halide element, hydrogen atom or organic functional group, i.e. iodine (25I-NBOMe), chlorine (25C-NBOMe), hydrogen atom (25H-NBOMe), -

methyl (25DNBOMe), -ethyl (25E-NBOMe), -nitro (25N-NBOMe) or -isopropyl (25iP-NBOMe).

F. Chemical properties

See Section B and G.

G. Chemical identification

Given its chemically basic nature, the extraction of 25B-NBOMe is relatively straightforward as is direct analysis of the compound itself (e.g. as a powder or in liquid form) by a number of techniques. However, as detailed elsewhere, in biological fluid, concentrations present after use may be very low and therefore require the application of very sensitive techniques (e.g. tandem mass-spectrometry). Detection methods such as gas chromatography with mass-spectrometry (GC-MS), high performance liquid chromatography with diode-array detection (HPLC-DAD) and/or mass-spectrometry (LC-MS) and accurate mass spectrometry have been published as part of case studies (Soh and Elliott 2013, Casale and Hays 2012, Poklis *et al.*, 2013, 2014). The detection outputs depend on the technique used but for 25I-NBOMe with LC-MS, the protonated molecular ion [M+H] of 380 m/z is observed with fragmentation resulting in a predominant 121 m/z ion of the N-(2-methoxy)-benzyl fragment as well as a 91 m/z fragment ion (Soh and Elliott 2013, Elliott 2014, Casale and Hays 2012, Poklis *et al.*, 2013, 2014). No presumptive test data (including Marquis field tests) exist. There is no known cross-reactivity with commercially-available urine immunoassay tests for the standard drugs of abuse.

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4.1. Pharmacodynamics

Animal studies

Data from in vitro studies have shown that 25B-NBOMe has nanomolar affinity for the serotonin 5-HT_{2A} receptor and is a partial agonist, with less affinity for the 5-HT_{2C} receptor (Hansen *et al.*, 2014; Ettrup *et al.*, 2010 and 2011; Finnema *et al.*, 2014, Juncosa *et al.*, 2013). The addition of the 2-methoxybenzyl group significantly enhances the affinity and potency of 25B-NBOMe compared to 2C-B (Blaazer *et al.*, 2008; Juncosa *et al.*, 2013). Stimulation of the 5-HT_{2A} receptors appears to be essential for the hallucinogenic effects of drugs such as LSD (Egan *et al.* 1998, Marek & Aghajanian, 1996; González-Maeso *et al.*, 2007; Hanks & González-Maeso, 2013; Nelson *et al.*, 1998). Binding (K_i) at the rat 5-HT_{2A} receptor was reported to be 1.01±0.17 nM with activation (ED₅₀) of 0.51±0.19 nM and intrinsic activity of 87% (Ettrup *et al.*, 2011). As part of preclinical assessment of dosage for 25B-NBOMe in PET scanning, and as a potent full agonist for the 5-HT_{2A} receptor Ettrup *et al.* (2013) studied the effect of 25B-NBOMe on the head twitch behavioural response (HTR) in mice which is used as a surrogate marker of the hallucinogenic effect of 5-HT_{2A} receptor activation in humans (Hanks & González-Maeso, 2013). The study found that

25B-NBOMe induces HTR in mice in a dose dependent manner, with a dose of 0.5 mg/kg i.p inducing significant HTR compared to a saline control. A significant HTR was not elicited by 0.05 mg/kg 25B-NBOMe relative to saline, while doses at and above 2.5 mg/kg had prominent sedative effects.

Human data

Although tested in animals, there are no reported human clinical trials with 25B-NBOMe in the scientific literature. However, Juncosa et al. (2013) reported, using human embryonic kidney (HEK) 293 cells expressing wild-type human 5-HT_{2A} receptors, binding (K_i) of 0.19±0.01 nM. Separately, whilst 25B-NBOMe is considered to be not orally active, there are no current human data to confirm or refute this. This perception has seemingly affected the routes of administration of user products (Section 4.2). Based on user reports (Erowid), the initial effects are felt within 15 minutes (sublingual/buccal/insufflated) with a duration of effects of up to 12 hours (no information on dose). Further, unconfirmed timelines following use from collation of the Bluelight forum reports are;

Total duration:	8-10 hours (sublingual/buccal)	6-10 hours (insufflated)
Onset:	20-70 minutes (sublingual/buccal)	5-20 minutes (insufflated)
Coming up:	30-60 minutes (sublingual/buccal)	20-40 minutes (insufflated)
Plateau:	120-240 minutes (sublingual/buccal)	90-240 minutes (insufflated)
Coming down:	1-5 hours (sublingual/buccal)	1-5 hours minutes (insufflated)

4.2. Routes of administration and dosage

Reported routes of administration for 25B-NBOMe include sublingual (especially “blotter” paper), buccal, nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking. Information from case reports and user websites suggest a range of doses are used that may depend on the route of administration. Example doses reported on the Erowid user website include: ‘400 µg, sublingual’; ‘1250 µg, insufflated liquid’; ‘1250 µg, sublingual’; ‘500 µg, buccal’; ‘400 µg in liquid ethanol, vapourised’; (Erowid). Further examples are provided in Section 6 (see also: Blue Light Forum, Drug Forum).

Information from user websites suggest that 25B-NBOMe may be used on its own as well as in combination with other new psychoactive substances and/or controlled drugs (Erowid, Blue Light Forum, Drug Forum). This is supported by reported non-fatal intoxications and deaths following analysis of biological samples (Section 6).

4.3. Pharmacokinetics

Animal studies

There do not appear to be any published pharmacokinetic data for 25B-NBOMe in animals.

Human studies

Whilst there do not appear to be any published pharmacokinetic data for 25B-NBOMe in humans, Stellpflug et al (2013) and Soh and Elliott (2013) reported the presumed detection of a desmethyl- metabolite of 25I-NBOMe and 25C-NBOMe, respectively (through predicted O-demethylation) in casework biological fluid and it would seem likely that 25B-NBOMe may exhibit a similar metabolic route. Although 25H-NBOMe was detected in a case involving 25B-NBOMe (Soh and Elliott, 2013) and also by Stellpflug et al. (2013) in a case involving 25I-NBOMe, this may not be through metabolism (due to the unclear existence of a metabolic pathway that would remove the halogen) and could be due to 25H-NBOMe being present as a contaminant in the product consumed (Stellpflug et al., 2013).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of 25B-NBOMe. However, as part of preclinical assessment of dosage for 25B-NBOMe in PET scanning, Etrup et al. (2013) extrapolated from animal data that the effective dose of [¹¹C]25B-NBOMe was 5–8 µSv/MBq with 1.5 µg of 25B-NBOMe ultimately administered as part of PET studies.

User reports from Erowid described the following subjective effects of self-reported 25B-NBOMe;

“Positive” (including; strong open and closed eye visuals, mood lift, euphoria, empathy, mental and physical stimulation), “Neutral” (including; general change in consciousness, Change in perception of time, time dilation, sleepiness) and “Negative” (including; confusion, nausea and vomiting, paranoia, unwanted and overwhelming feelings).

Adverse effects reported in a single non-fatal case report included; tachycardia, hypertension, seizures, hyperpyrexia (Poklis et al. 2013). In a fatality reported by Soh and Elliott (2013), the deceased was reported to have vomited before becoming unconscious (Elliott 2014).

6. Adverse reactions in humans

A single non-fatal intoxication and a death associated with 25B-NBOMe have been reported in the USA (Poklis et al. 2013) and the United Kingdom (Soh and Elliott 2013), respectively. A further death was reported from Switzerland. All cases were analytically confirmed.

For the non-fatal case, a 19 year old male in prior good health was found by his room-mates having “jerking movements”. He was taken to hospital. Observed adverse effects (as stated above) included tachycardia, hypertension, seizures and hyperpyrexia (Poklis et al. 2013). The patient required intensive medical treatment including intubation and sedation. He eventually recovered and was fully alert and orientated by day 6. A serum and urine specimen was obtained 39 hours after admission with 25B-NBOMe concentrations measured to be 180 pg/mL (0.18 ng/mL) in the serum and 1900 pg/mL (1.9 ng/mL) in the urine.

For the UK fatal case, in April 2013, a 19 year old male was reported to have vomited before becoming unconscious whereupon an ambulance was called but he was pronounced dead shortly after arrival. 25B-NBOMe was tentatively identified on a DVD (disc) thought to have been used to “snort” a substance. No further case information was available. Analysis of a post-mortem blood and urine specimen detected cannabinoids, paracetamol and 25B-NBOMe (Soh and Elliott 2013, Elliott 2014). The concentrations of 25B-NBOMe in the blood and urine were determined to be less than 6.25 ng/mL, the limit of detection of the assay (Elliott 2014).

In October 2013 in Switzerland, a 20 year old male (with psychiatric problems) died having thought to have used a pump spray containing 10 mL of an odourless liquid identified as 25B-NBOMe. 25B-NBOMe as well as cannabinoids and amphetamine were found in the post-mortem blood in concentrations indicating recent cannabis and amphetamine consumption without being clearly responsible for the death.

7. Dependence potential

No studies have examined the dependence potential of 25B-NBOMe in vitro, in animals or in humans.

8. Abuse potential

No studies have examined the abuse potential of 25B-NBOMe in vitro, in animals or in humans.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

25B-NBOMe has no recorded therapeutic applications or medical use. The use of radio-labelled 25B-NBOMe in medical research is discussed elsewhere.

10. Listing on the WHO Model List of Essential Medicines

25B-NBOMe is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

25B-NBOMe has never been marketed as a medicine.

12. Industrial use

25B-NBOMe has no industrial use.

13. Non-medical use, abuse and dependence

25B-NBOMe use and/or seized material has been reported in Austria, Denmark, Germany, Hungary, Latvia, Spain, Sweden, Switzerland, the United Kingdom and the USA.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Lawn et al undertook a study to examine the characteristics of users of 25B-NBOMe, 25C-NBOMe and 25I-NBOMe through the Global Drugs Survey (Lawn et al., 2014). A total of 22,289 responses were collected in late 2012. One-third (n = 7,360; 33.9%) of respondents were from the UK, 7,784 (35.9%) were from Australia, 3,756 (17.3%) were from the USA, 2,164 (10.0%) were from the rest of Europe, and 618 (2.9%) were from Canada. Most (68.6%) respondents were male and the mean age was 31.4 years (SD = 12.4; range 16 – 100). 2.6% of respondents (n = 582) reported having ever tried one of the three NBOMe drugs and that at 2.0%, 25I-NBOMe was the most popular (n = 442) followed by 25B-NBOMe (n = 267; 1.2%) and 25C-NBOMe (n = 65; 0.8%). Almost all (93.5%) respondents whose last new drug tried was a NBOMe drug and 81.2% of this group administered the drug orally or sublingually/buccally. Subjective effects were similar to comparison serotonergic hallucinogens, though higher 'negative effects while high' and greater 'value for money' were reported. The most common (41.7%) drug source was via a website. Information from seizures, collected samples and user websites suggest that 25B-NBOMe has been commonly sold as a 'legal' replacement for LSD or sold as LSD directly on the illicit drug market. In the latter case users may be unaware that they are using 25B-NBOMe. Nevertheless, it also appears to be associated with the purchase of "research chemicals" or equivalent products via the Internet as well clearly stated to be 25B-NBOMe "tabs". Instances of misuse, abuse and dependence would be limited to such individuals rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs. However, analysis of various products have shown that the composition can differ (including between that claimed by the retailer) and the user is unlikely to be aware of the exact dose or compound being ingested (by whatever route) which presents an inherent risk to the individual.

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Not applicable in relation to affecting impact of medical use.

18. Current and past national controls

25B-NBOMe is currently controlled under drug control legislation in Brazil, Denmark, Hungary, Israel, Romania, Russia, Sweden and areas of Australia (Queensland and New South Wales). Furthermore it is party to a temporary class order in the United Kingdom (from June 2013 to be reviewed in June 2014) and under temporary Schedule I control in the USA (November 2013).

Also refer, Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Researchers have used radiolabelled 25B-NBOMe as a tool to study the serotonergic system in the brain (Ettrup et al., 2010, 2011 and 2013) as part of work that ultimately aims to further the understanding of the pathogenesis of human disease in which the serotonergic system may play a role. This includes research into its potential use as a tracer in Positron Emission Tomography (PET) imaging studies (Ettrup et al., 2010, 2011 and 2013).

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of 25B-NBOMe

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 65 Member States answered the questionnaire for **25 B NBOMe**. Of these only 20 respondents (AMR 4, EUR 13, WPR 3) had information on this substance.

LEGITIMATE USE

No respondent reported that 25 B NBOMe was currently authorized or was in the process of being authorized/registered as a medical product in their country nor that it had any other use in health care. Four respondents stated that this substance was used in medical and scientific research. There was no use stated for animal/veterinary care. For legitimate use one each responded only importing, only manufacturing and both manufacturing and importing.

HARMFUL USE

Fourteen respondents confirmed recreational/harmful use; the common route of administration was oral in eight responses and for three this was by oral, inhaling/sniffing. For such use, 11 reported sourcing only via trafficking and one each via diversion plus trafficking and via clandestine manufacturing. Ten respondents reported on the common formulations available - two liquid, two powder, three powder and liquid, one powder and tablet and two tablet forms. Seven respondents described that it was used on blotter paper. Adulteration of other products is also reported. Four responded that it was used only in clubs, three only by the general population and one both by the general population and in clubs. In general population, adolescents and young adults are specially mentioned. Three countries reported withdrawal, tolerance and other adverse effects or medical illnesses caused by 25 B NBOMe. These included intoxication, dizziness, head ache, difficulty to sleep, agitation, death due to injuries related to intoxication.

One respondent mentions that higher doses of 25B-NBOMe may result in overdose and death. Three deaths were associated with 25B-NBOMe exposure in 2013. Drug induced toxicity and violent, erratic behaviour due to the abuse of 25I-NBOMe, 25C-NBOMe and 25B-NBOMe synthetic substances has led to numerous reports of emergency department admissions and deaths (Kelly et al., 2012; Rose et al., 2012; Rose et al., 2013; Hill et al., 2013; Stellpflug et al., 2013).Deaths have been reported for most routes of administration, including nasal insufflation, liquid solutions applied to nasal membrane, sublingual or buccal administration of blotter paper, and consumption of adulterated food items. Youth appear to be the primary abusers of these synthetic substances, as supported by the available emergency department reports and reports of death. The average age of decedents where 25I-NBOMe, 25C-NBOMe or 25B-NBOMe was confirmed to be a contributing factor in the death is 20 years (n=14). (See also information provided for 25 I and C NBOMe – these may have similar effects)

CONTROL

Of those with information on this substance, 14 reported that 25B NBOMe was controlled under legislation that was intended to regulate its availability; eight under “controlled substance act”, two under “medicines law”, one each as “temporary ban”, under “generic legislation” and under “analogue legislation”. Another one specified that this was included in a specific section of the national medicines law. Four respondents stated that there were problems with the implementation of this legislation. On illicit activities, two respondents reported processing into the consumer product, 11 reported trafficking, one diversion and 10 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	No data	5 (4)
Total quantity seized (kg)	No data	No data
Total quantity seized (other)	No data	Blotters – 280 (3) Tablets - 4,860 (200 mg) in 2013

IMPACT OF SCHEDULING

Nineteen respondents reported that if 25 B NBOMe was placed under international control, they would have the laboratory capacity to identify the substance. This substance has no medical use reported.