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Critical Review Report:

Brorphine

1-{1-[1-(4-Bromophenyl)ethyl]piperidin-4-yl}-1,3-dihydro-2*H*-benzimidazol-2-one

Expert Committee on Drug Dependence

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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

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Executive Summary

Brorphine (IUPAC name: 1-{1-[1-(4-bromophenyl)ethyl]piperidin-4-yl}-1,3-dihydro-2*H*-benzimidazol-2-one) is a *N*-benzylpiperidinyl derivative of benzimidazol-2-one and most likely to appear on the streets in the form of a racemate.

Brorphine has not been previously pre-reviewed or critically reviewed by the WHO.

There is no specific information available about the routes of synthesis employed for the brorphine products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally.

It might technically be feasible to convert brorphine into bezitramide (IUPAC name: 4-[4-(2-oxo-3-propanoyl-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]-2,2-diphenylbutanenitrile) which is listed in Schedule I of 1961 Convention (as amended by the protocol of 25 March 1972).

In vitro pharmacological studies have shown that brorphine is qualitatively similar to other synthetic opioids such as morphine, fentanyl and isotonitazene. Brorphine was shown to act as a potent, full agonist at the μ-opioid receptor (MOR) in the [^{35}S]GTPγS binding assay, mini-G_i-, and βarrestin2 recruitment assay.

Information obtained from Internet forums on the effects of brorphine suggests that it induces long-lasting analgesic effects. These reports also suggest that oral administration and inhalation of brorphine by smoking/vaping might be more common than administration by injection and the extent to which this route of administration is used is less clear.

Information on acute or chronic preclinical toxicology studies could not be identified.

In rats, brorphine fully substituted for the discriminative stimulus effects of morphine with a 9-times higher potency and fentanyl was 17-time more potent than brorphine. Naltrexone was shown to block morphine-like discriminative stimulus effects. Brorphine also displayed antinociceptive effects in mice using the warm-water tail flick assay. Brorphine was 12-times more potent than morphine and fentanyl was 1.3-times more potent than brorphine. Naltrexone also blocked the analgesic effects induced by brorphine. These findings suggest that brorphine is likely to display abuse liability similar to other synthetic opioids under international control.

No studies on dependence potential could be identified, although some people who reported brorphine use have also described the development of tolerance and withdrawal symptoms. Based on its MOR agonist activity, use of brorphine would be expected to be associated with the development of opioid tolerance and physical dependence.

Information about therapeutic use could not be identified. Brorphine is not known to have any marketing authorizations and information about any agricultural, industrial or

cosmetic uses could not be identified. Brorphine is used as reference material and for scientific research.

Epidemiological evidence concerning the use of brorphine could not be identified and its use is likely to be limited to recreational substance users rather than the general population. The available information from Internet forums suggests that the use of this substance is associated with individuals who might be using heroin, prescription opioid analgesics and other synthetic opioids. The risk of poisoning includes both current high-risk opioid users and other groups who may have no or limited tolerance to opioids. The mode of use may involve the combinational use (intentionally or unintentionally) of other substances and users may be unaware of the exact dose or compound being ingested (by whatever route).

Epidemiological data on harms associated with brorphine could not be identified but the detection of this substance has been confirmed in at least 60 fatal and non-fatal intoxications involving poly-substance use. Information available from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the scientific literature suggests that brorphine was also detected in falsified oxycodone tablets. People using these products will be unaware of what they contain and the amount, which poses inherent risks to the individual. The risk of poisoning may be greater by the unintentionally high doses that users may take, especially when combined with other substances. Similar to other opioids analgesics, the use of brorphine with other central nervous system depressants can increase the risk of life-threatening respiratory depression and arrest.

The detection of brorphine was first reported to EMCCDA in June 2020. The United Nations Office on Drugs and Crime (UNODC) received first notifications from two UN Member States in 2019. As of 15 July 2021, at least three countries of the EU Early Warning System network and the United Kingdom have reported physical detections of brorphine to the EMCDDA. In detections reported to the EMCDDA, brorphine was found in powders (6 g), in capsules (4 units) and in tablets (2 units). These detections include seizures and collected samples (test purchases and 1 collection associated with a serious adverse event). Since 2019, UNODC's Early Warning Advisory received notifications from 6 countries (as of 25 July 2021).

The U.S. Drug Enforcement Administration reported that at least 20 reports of brorphine have been received by the National Forensic Laboratory Information System (NFLIS) and one of these consisted of 12.533 g of brorphine. It has also been reported that brorphine was found in combination with heroin and fentanyl. Other reports on suspected heroin/fentanyl powders revealed the detection of brorphine in combination with flualprazolam and diphenhydramine. It has been suggested that the appearance of brorphine on the U.S market signaled the replacement of isotonitazene.

Brorphine is not controlled under the 1961, 1971 or 1988 United Nations Conventions but is controlled in some UN Member States.

1. Substance identification

A. International Nonproprietary Name (INN)

Information could not be identified

B. Chemical Abstract Service (CAS) Registry Number

2244737-98-0 (base)

C. Other Chemical Names

1-(1-(1-(4-Bromophenyl)ethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one
1-(1-(1-(4-Bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one
3-[1-[1-(4-Bromophenyl)ethyl]-4-piperidyl]-1H-benzimidazol-2-one

D. Trade Names

Information could not be identified.

E. Street Names

Brorphine; purple heroin.

F. Physical Appearance

Brorphine freebase has been described as a white solid (ADEBAR 2020) and the hydrochloride salt as a neat solid (Cayman Chemical 2021). A collected sample identified as the freebase has also been described as white-off-white (EMCDDA 2021a). Seized brorphine samples have also been reported as white and yellowish powder (EMCDDA 2021a). Brorphine has also been observed as a gray, purple, or white powder, or in crystal form (DEA 2021d).

G. WHO Review History

Brorphine has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and is of no recognized therapeutic use.

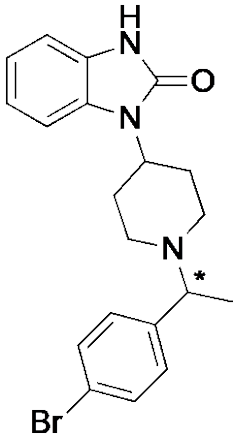
2. Chemistry

A. Chemical Name

IUPAC Name: 1-{1-[1-(4-Bromophenyl)ethyl]piperidin-4-yl}-1,3-dihydro-2*H*-benzimidazol-2-one
CA Index Name: 1-[1-[1-(4-Bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral center

Molecular Formula: $C_{20}H_{22}BrN_3O$
Molecular Weight: 400.32 g/mol

C. Stereoisomers

The presence of a chiral center gives rise to the enantiomeric pair of (S)-brorphine and (R)-brorphine. Brorphine is most likely available as the racemic mixture though the appearance of individual stereoisomers cannot be excluded.

D. *Methods and Ease of Illicit Manufacturing*

Information on the specific routes of synthesis employed for brorphine products circulating on the market could not be identified but straightforward methods for its preparation exist following standard procedures without requiring access to precursors that are controlled internationally. One approach is shown below (Figure 1) (Kennedy et al. 2018). 1-Fluoro-2-nitrobenzene (a) undergoes nucleophilic substitution with *tert*-butyl 4-aminopiperidine-1-carboxylate to give *tert*-butyl 4-((2-nitrophenyl)amino)piperidine-1-carboxylate (b). The nitro group is reduced to the amino group (intermediate c) and then converted into the cyclic urea intermediate (d). Deprotection with trifluoroacetic acid gives 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (e) followed by reductive amination using 1-(4-bromophenyl)ethanone which results in the formation of brorphine (f) (Kennedy et al. 2018).

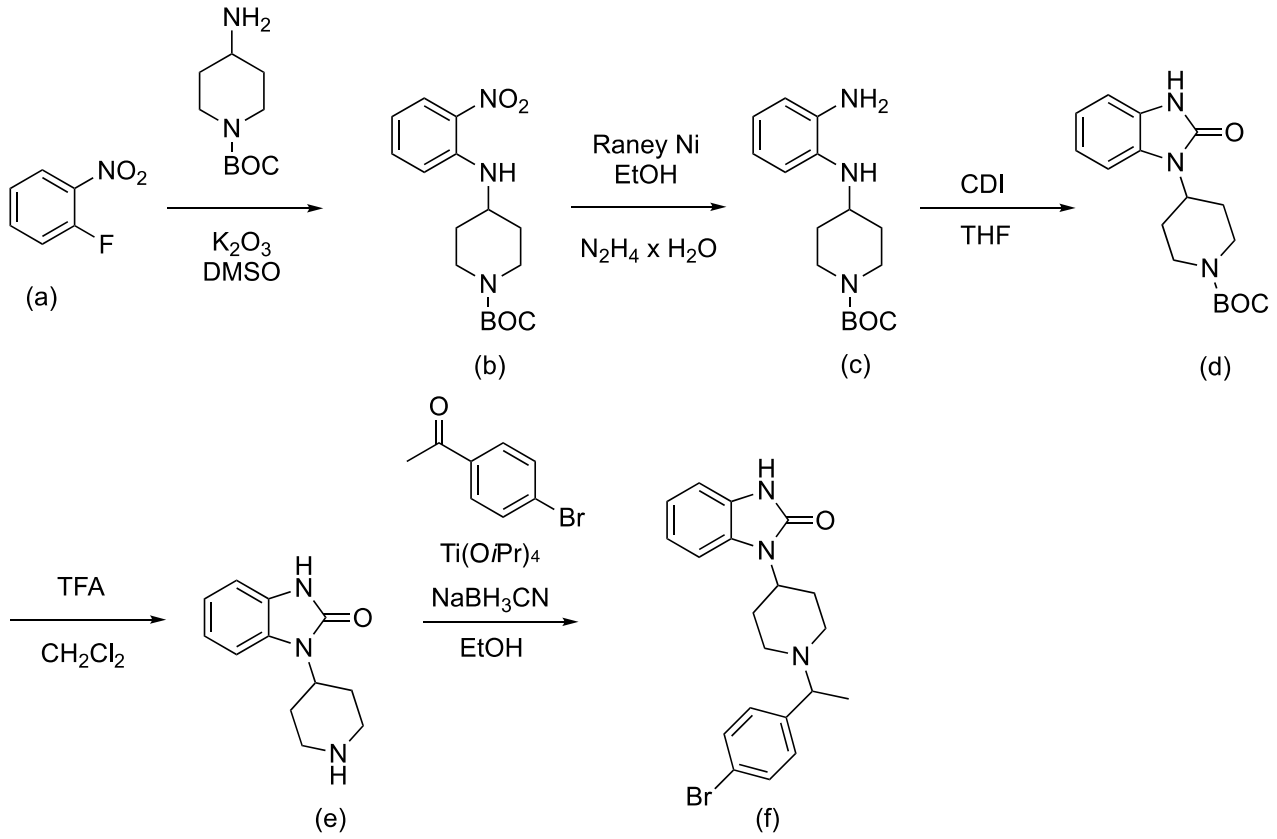


Figure 1. Synthesis of brorphine (modified from Kennedy et al. 2018).

E. Chemical Properties

Melting point

Information could not be identified.

Boiling point

Information could not be identified.

Solubility

Brorphine base was reported to be partially soluble in dichloromethane and methanol but poorly soluble in water (Slovenian National Forensic Laboratory 2020).

F. Identification and Analysis

Identification, especially when available in larger quantities than normally encountered in forensic toxicological work, is straightforward. Analytical data disseminated in scientific publications include those obtained by chromatographic and spectroscopic methods (Kennedy et al. 2018; Krotulski et al. 2021a; Verougstraete et al. 2021). Analytical information available in the public domain includes chromatographic, mass spectral and spectroscopic data (Cayman Chemical 2019; Krotulski, Fogarty and Logan 2020; Slovenian

National Forensic Laboratory 2020). Certified reference material is commercially available for analytical method development and validation. The high potency associated with many synthetic opioids requires the use of sensitive methods of detection that include suitable methods of separation coupled with sensitive detection systems such as mass spectrometry (single or multi stage analysis).

3. Ease of Convertibility Into Controlled Substances

Bezitramide (IUPAC name: 4-[4-(2-oxo-3-propanoyl-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]-2,2-diphenylbutanenitrile) – also containing a piperidine 4-benzimidazolone template – is listed in Schedule I of 1961 Convention (as amended by the protocol of 25 March 1972) (INCB 2020). No specific information on the convertibility of brorphine to bezitramide could be identified. Published reports exist that describe the *N*-debenzylation of substituted piperidines under reductive conditions (e.g. Kawaguchi et al. 1986; Olszewska et al. 2018) and if this is applicable to brorphine then the resulting product from this *N*-debenzylation reaction would be the 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one intermediate (e) shown above (Figure 1) in the synthesis scheme of brorphine. In patents disclosed by the Research Laboratorium Dr. C. Janssen NV (Belgium) on the preparation of bezitramide-type compounds, benzyl group containing intermediates were subjected to similar reductive *N*-debenzylation conditions as well. The 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one intermediate can be converted into bezitramide which is straightforward (Janssen 1963; Janssen 1965).

4. General Pharmacology

A. Routes of administration and dosage

Descriptions encountered in online forums suggest brorphine to be administered preferably orally as a powder (presumably also in capsules or tablets) or inhaled by smoking or vaporizing (e.g. Reddit 2020a; c; 2021a; d). Reports exist that describe the solubility of brorphine base in acidified water (Reddit 2020d; 2021c) or the preparation of emulsions using medium-chain triglyceride/water mixtures (Reddit 2020b). The extent to which such formulations are used for injection is less clear. Some information is available regarding the dose and the dose regimens of brorphine (e.g. Reddit 2020a) (Table 1). 'Typical' dosages depend on factors such as the route of administration, the tolerance of users, the use of other drugs, and the desired effects. Higher single oral doses have also been described (e.g. Bluelight 2021b). Given the difficulties of collecting such data, the doses shown below should be used with caution.

Table 1. Suggested dosages for brorphine (Reddit 2020a) [a]

	'Average beginner'	'Veteran' dosage
Oral	1–2 mg: light 3–5 mg: medium	2–5 mg: light 6–9 mg: medium 10–13: strong

	>6 mg: strong/danger	
Smoked	1 mg: light 2 mg: medium 3 mg: strong/danger	1–2 mg: light 3–5 mg: medium >6 mg: strong
[a] Brorphine was estimated to be 10-times more potent than morphine. Other estimations suggested brorphine to be 3–5 times as potent as morphine based on oral administrations (Bluelight 2021a).		

B. Pharmacokinetics

Data obtained from clinical studies could not be identified. Subjecting brorphine to transformation in pooled human liver microsomes resulted in the detection of six metabolites under the conditions studied (Krotulski et al. 2021a). The detected species represented *N*-debenzylation (plus hydroxylation of this metabolite), hydroxylations at the benzimidazol-2-one and piperidine rings, *O*-methylation of the hydroxylated benzimidazol-2-one metabolite, and oxidation of the piperidine moiety to the 1,2,3,4-tetrahydropyridine analog of brorphine. The *N*-debenzylated and hydroxylated benzimidazol-2-one metabolites have also been detected in blood and urine samples taken from postmortem samples (Krotulski et al. 2021a). A brorphine metabolite hydroxylated at the benzimidazol-2-one moiety was detected in a serum sample obtained from person who used this substance (Verougstraete et al. 2021). Information provided on Internet forums suggest a duration of effects of 3–8 h (Reddit 2020e; 2021a) following oral administration and sometimes longer (Reddit 2020c). A published case report involving a person who started taking brorphine orally 4 four times a day suggested that the effects lasted 'quite long' based on a self-report (Verougstraete et al. 2021). Brorphine was still detected in a serum sample analyzed 60 h after admission to an emergency department (Verougstraete et al. 2021).

C. Pharmacodynamics

Brorphine has been shown to be a potent agonist at the μ-opioid receptor (MOR) (Table 2). Using an in vitro GTPγS binding assay, it has been shown that brorphine was ~7- and 13-times more potent than DAMGO and morphine used as controls. All three compounds acted as full agonists under the same assay conditions. Assessment of βarrestin2 recruitment profiles within the same study also showed that brorphine was equipotent to DAMGO and twice as potent to morphine though the latter only showed a very low efficacy (Table 2) (Kennedy et al. 2018).

Table 2. GTPγS binding and βarrestin2 recruitment activity (Kennedy et al. 2018) [a]

Compound	^{35}S-GTPγS (EC_{50} / nM)	E_{max} (%)	β-arrestin2 (EC_{50} / nM)	E_{max} (%)
DAMGO	33	100	220	100

Morphine	64	83	379	24
Brorphine	4.8	91	182	92

[a] MOR: μ-opioid receptor; MOR-stimulated GTPγS binding: membranes prepared from CHO-hMOR cells; βarrestin2 interactions with MOR: USOS-βarrestin-hMOR-PathHunter cells used by an enzyme fragment complementation assay.

Results from a separate in vitro study on the recruitment of either βarrestin2 or mini-G_i to activated MOR also confirmed that brorphine led to MOR activation similar to other synthetic opioids such as hydromorphone, fentanyl and isotonitazene (Table 3) (Vandeputte, Cannaert and Stove 2020). In the mini-Gi assay, brorphine was found to be ~2.5-times less potent than hydromorphone though it showed an almost 4-times higher efficacy. Isotonitazene was 6.5-times more potent than brorphine and also displayed higher efficacy. Fentanyl was 3-times more potent than brorphine but also showed a lower efficacy though both showed a higher efficacy than hydromorphone (Table 3). In the βarrestin2 recruitment assay, brorphine was 4.7- and 2.2-times less potent than isotonitazene and fentanyl but it showed a slightly higher efficacy. Brorphine was also found to be 1.6-times more potent than hydromorphone with a doubled efficacy (Table 3). The βarrestin2 results for brorphine (EC_{50} = 30.9 nM; E_{max} = 209%) and hydromorphone (EC_{50} = 26.0 nM; E_{max} = 97.5%) were also reported subsequently under similar conditions (Verougstraete et al. 2021).

Table 3. Mini-G_i- and βarrestin2 recruitment (Vandeputte, Cannaert and Stove 2020) [a]

Compound	Mini-G_i (EC_{50} / nM)	E_{max} (%)	βarrestin2 (EC_{50} / nM)	E_{max} (%)
Brorphine	106	385	31.1	226
Hydromorphone	44	100	51.0	100
Fentanyl	32.7	284	14.3	163
Isotonitazene	16.3	484	6.64	159

[a] HEK293T stably expressing either MOR-βarr2-GRK2 (or MOR-mini-G_i system; mini-G_i: GTPase domain of Gαi subunit.

In the three factor analysis documentation for temporary control of brorphine published by the U.S. Drug Enforcement Administration (DEA), it was also reported that brorphine bound to and activated MOR. In the functional [^{35}S]GTPγS binding assay brorphine (EC_{50} = 16.3 nM; E_{max} = 117.6% relative to DAMGO) was stated to be equipotent to fentanyl (EC_{50} = 19 nM; E_{max} = 88.5% relative to DAMGO) with slightly higher efficacy (DEA 2020c).

5. Toxicology

Information on acute or chronic preclinical toxicology studies involving brorphine could not be identified.

6. Adverse Reactions in Humans

Detections of brorphine obtained from biological samples collected during casework formally reported in the scientific literature are summarized in Tables 4 and 5. In the non-fatal intoxication case reported by Razinger et al. (2021), brorphine in combination with chronic serotonergic therapy was thought to account for unconsciousness and severe rhabdomyolysis with acute kidney failure due to serotonergic toxicity. It is currently unknown whether brorphine shows serotonergic effects in vivo. Verougstraete et al. (2021) described a patient who presented at the emergency department querying about admission for detoxification. The patient presented with confusion and bradyphrenia, generalized weakness and cramping and his complaints consisted of generalized pain, situated mainly in the chest, abdomen and muscles. Serum analyses confirmed the detection of brorphine together with prescription medicines. An accidental fatal case involving poly-substance use was also presented by Vohra et al. (2021) (Table 4).

Table 4. Cases involving the detection of brorphine in biological fluids. [a]

Case	Age, sex	Comments	Reference
1	45, M	Non-fatal intoxication: severe rhabdomyolysis and acute kidney failure following ingestion of four crushed 'M30' tablets bought as oxycodone on the Internet. Patient had a history of depression and treated with 25 mg sertraline daily for 6 months; arrived at emergency department (ED) 12 h after ingestion. Became euphoric, dizzy, and lost consciousness 30 min after ingestion of crushed tablets. Patient was shivering and drooling while lying unconscious; woke up after 6 h and was somnolent, confused, and nauseous. He was unable to walk due to diffuse myalgia; reported a small volume of dark urine while urinating. At arrival at ED patient was conscious, confused, diaphoretic, and agitated; he had diffuse myalgia, ocular clonus, tremor, and hyperreflexia. Initial laboratory results revealed severe rhabdomyolysis (serum creatine kinase > 100,000 µkat/L and myoglobin > 20,000 µg/L) and acute kidney failure (serum urea 16.5 mmol/L and creatinine 220 µmol/L). Patient became hypervolemic due to deterioration of renal function with oliguria. Diuretic therapy with furosemide was initiated on the third day and patient developed polyuria on day 4. Serum myoglobin and creatine kinase levels normalized within 2 weeks and serum creatinine level within 3 weeks. Brorphine was detected in blood 12 h post-ingestion and in the tablet (not quantified).	Razinger et al. (2021)
2	24, M	Non-fatal intoxication: Patient presented at emergency department querying an admission for detoxification. Patient presented with normal blood pressure with tachycardia (114 bpm), oxygen saturation of 98% and temperature of 37.3°C. Prescribed medications consisted of sertraline, mirtazapine, methylphenidate and enoxaparin. Two serum samples, taken approximately 60 hours apart, were available: first sample was collected at emergency department (69.4	Verougstraete et al. (2021)

		ng/mL); second during hospitalization in psychiatric ward (7.9 ng/mL). Sertraline and mirtazapine (prescribed) and risperidone detected in subtherapeutic ranges. In the second sample, trazodone and nordiazepam (administered in the hospital context) were detected. A powdered sample brought by the patient was identified as brorphine.	
3	61, F	Fatal intoxication: manner of death – accident; cause of death – combined drug toxicity. Patient with history of obesity, tobacco use, hypertension, chronic obstructive pulmonary disease, schizophrenia, hyperlipidemia, and no documented history of substance use, was found deceased at home. Analytical results cardiac blood: ethanol (27 mg/dL), 4-ANPP (pos.), brorphine (2.0 ng/mL), gabapentin (6.8 mcg/mL), chlorpromazine (82 ng/mL), fentanyl (0.32 ng/mL), benzodiazepines (presumptive pos.), amphetamines (presumptive pos.). Analytical urine results: benzodiazepines (presumptive pos.), amphetamines (presumptive pos.).	Vohra et al. (2021) Vohra and Aaron (2021)
4	NA	Detection of brorphine was described (urine or serum) but no further details were reported.	Verstraete and Hyde (2020)
5	NA	Clinical admission following oral administration of substance. Antemortem serum concentration of brorphine determined at 69 µg/L.	UNODC (2021a)
[a] NA: information not available; pos.: positive			

One country of the EU Early Warning System Network reported one serious adverse event to the EMCDDA in which exposure to brorphine was analytically confirmed from a biological sample. A non-fatal poisoning occurred in 2021 and was linked to the use of falsified oxycodone tablets containing brorphine that had been purchased on the Internet (EMCDDA 2021b). It is possible that this is the same case reported by Razinger et al. (2021) (Table 4).

A series of 20 poly-substance postmortem cases was published by Krotulski et al. (2021a) (Table 5) who presented the analytical findings of cases submitted between June–July 2020. Fentanyl was confirmed in all cases and flualprazolam in 80% of cases. The average concentration of brorphine reported in blood was 2.5 ± 3.1 ng/mL (median: 1.1 ng/mL, range: 0.1–10 ng/mL) and the average concentration of brorphine in urine was found to be 4.6 ± 7.6 ng/mL (median: 1.6 ng/mL, range: 0.2–23 ng/mL). Thirteen decedents were male and seven female; average age: 48 ± 9 yrs (median: 49 yrs; range 29–61 yrs). The majority of cases originated from Midwestern U.S. States, including Illinois (n = 13), Minnesota (n = 5), and Wisconsin (n = 1); one case originated from Arizona (Table 5) (Krotulski, Papsun, Noble, Kacinko and Logan 2021a).

Table 5. Detections of brorphine and other substances in postmortem samples. Modified from Krotulski et al. (2021a) [a]

Case	Age, sex	Brorphine [b] (ng/mL)	Comments [c]
1	53, M	Blood: 10 Urine: 23	Suspected overdose; history of opioid use; "heroin" present at scene. Analytical results: flualprazolam (50 ng/mL), 4-ANPP, caffeine, cotinine, quinine, codeine (6.6 ng/mL), morphine (66 ng/mL), 6-monoacetylmorphine (1.5 ng/mL), citalopram/escitalopram (76 ng/mL), fentanyl (3.4 ng/mL), norfentanyl (0.36 ng/mL), isotonitazene.
2	60, M	Blood: 0.9 Urine: 0.4	Case history information not available. Analytical results: 4-ANPP, caffeine, methadone (160 ng/mL), EDDP (45 ng/mL), morphine (42 ng/mL), bupropion (18 ng/mL), hydroxybupropion (380 ng/mL), duloxetine (520 ng/mL), lamotrigine (6.8 mcg/ mL), gabapentin (15 mcg/mL), fentanyl (14 ng/mL), norfentanyl (11 ng/mL), flualprazolam.
3	45, M	Blood: 1.0 Urine: 1.9	Suspected overdose; manner of death – accident; cause of death – toxic effects of multiple drugs. Analytical results: flualprazolam (2.5 ng/mL), 4-ANPP, caffeine, cotinine, tramadol (33 ng/mL), delta-9 THC (0.62 ng/mL), fentanyl (5.0 ng/mL).
4	57, F	Blood: pos.	Suspected overdose; drug paraphernalia recovered from scene. Analytical results: 4-ANPP, caffeine, cotinine, naloxone, cocaine (110 ng/mL), benzoylecgonine (1300 ng/mL), delta-9 THC (0.88 ng/mL), diphenhydramine (61 ng/mL), fentanyl (31 ng/mL), norfentanyl (5.5 ng/mL), acetylfentanyl (0.13 ng/mL).
5	42, M	Blood: 1.1 Urine: 3.3	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: 4-ANPP, caffeine, cotinine, naloxone, diphenhydramine (620 ng/mL), fentanyl (36 ng/mL), norfentanyl (1.4 ng/mL), morphine (110 ng/mL), 6-monoacetylmorphine (7.3 ng/mL), flualprazolam.
6	60, M	Blood: 8.1 Urine: 21	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: cotinine, sertraline (26 ng/mL), desmethylsertraline (110 ng/mL), verapamil (42 ng/mL), diphenhydramine (960 ng/mL), fentanyl (3.1 ng/mL), morphine (79 ng/mL), 6-monoacetylmorphine (2.5 ng/mL), flualprazolam.
7	47, M	Blood: 2.5	Suspected overdose; sudden death; counterfeit oxycodone pills tested pos. for brorphine. Analytical results: 4-ANPP, naloxone, oxycodone (22 ng/mL), sildenafil (35 ng/mL), *N*-desmethylsildenafil (10 ng/mL), fentanyl (16 ng/mL), norfentanyl

			(1.1 ng/mL).
8	39, M	Blood: 6.7 Urine: 7.3	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: 4-ANPP (pos.), caffeine (pos.), cotinine (pos.), nicotine (pos.), alprazolam (14 ng/mL), tramadol (70 ng/mL), gabapentin (10 mcg/mL), diphenhydramine (1200 ng/mL), fentanyl (45 ng/mL), norfentanyl (2.1 ng/mL), codeine (6.5 ng/mL), morphine (290 ng/mL), hydromorphone (4.7 ng/mL), flualprazolam.
9	37, F	Blood: 0.7	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: ethanol (138 mg/dL), 4-ANPP (pos.), cotinine (pos.), naloxone (pos.), delta-9 carboxy- THC (85 ng/mL), delta-9 THC (18 ng/mL), diphenhydramine (110 ng/mL), fentanyl (22 ng/mL), flualprazolam.
10	48, M	AM blood: 0.6 PM blood: 0.1 Urine: 0.2	Suspected overdose; Puncture marks found at autopsy; cause of death – intoxication from brorphine and other drugs. Analytical results: flualprazolam (5.4 ng/mL), 4-ANPP (pos.), caffeine (pos.), naloxone (pos.), morphine (8.0 ng/ mL), diphenhydramine (190 ng/mL), fentanyl (4.7 ng/mL), norfentanyl (1.6 ng/mL), acetylfentanyl (1.2 ng/mL), clonazolam.
11	47, F	Blood: 6.7 Urine: 2.1	Suspected “heroin” overdose; cause of death – toxic effects of multiple drugs including brorphine. Analytical results: flualprazolam (13 ng/mL), 4-ANPP (pos.), cotinine (pos.), naloxone (pos.), codeine (7.0 ng/mL), morphine (85 ng/mL), 6-monoacetylmorphine (12 ng/mL), xylazine (170 ng/mL), amphetamine (55 ng/mL), methamphetamine (580 ng/mL), fentanyl (190 ng/mL), norfentanyl (5.4 ng/mL), acetylfentanyl (0.15 ng/mL).
12	30, F	Blood: 0.3 Urine: 1.4	Suspected overdose; death occurred at hospital; COVID-19 negative. Analytical results: caffeine (pos.), naloxone (pos.), midazolam (20 ng/mL), amphetamine (110 ng/mL), methamphetamine (1900 ng/mL), MDA (9.8 ng/ mL), MDMA (75 ng/mL), fentanyl (0.37 ng/mL), norfentanyl (0.97 ng/mL).
13	53, M	Blood: neg. Urine: 0.2	Suspected overdose; Cause of death – toxic effects of multiple drugs. Analytical results: flualprazolam (20 ng/mL), 4-ANPP (pos.), caffeine (pos.), naloxone (pos.), morphine (15 ng/ mL), xylazine (30 ng/mL), fentanyl (19 ng/mL), norfentanyl (4.2 ng/mL).
14	57, M	Blood: 0.5	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity.

			Analytical results: 4-ANPP (pos.), cotinine (pos.), naloxone (pos.), tramadol (48 ng/mL), diphenhydramine (950 ng/mL), fentanyl (130 ng/mL), norfentanyl (20 ng/mL), acetylfentanyl (0.10 ng/mL), morphine (21 ng/mL), flualprazolam, isotonitazene.
15	54, F	Blood: Urine:	Suspected overdose; pulmonary and cerebral edema. Analytical results: ethanol (19 mg/dL), codeine (21 ng/mL), morphine (290 ng/mL), 6-monoacetylmorphine (34 ng/mL), lamotrigine (0.60 mcg/mL), topiramate (9400 ng/mL), cyclobenzaprine (38 ng/mL), amphetamine (140 ng/mL), methamphetamine (730 ng/mL), fentanyl (17 ng/mL), flualprazolam.
16	NA	Blood: 0.7 Urine: neg.	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: ethanol (100 mg/dL), 4-ANPP (pos.), caffeine (pos.), cotinine (pos.), naloxone (pos.), nicotine (pos.), nordiazepam (130 ng/mL), chlordiazepoxide (66 ng/mL), lorazepam (9.4 ng/mL), delta-9 THC (0.70 ng/mL), diphenhydramine (53 ng/mL), fentanyl (32 ng/mL), flualprazolam.
17	51, M	Blood: 1.1 Urine: 0.4	Suspected overdose; manner of death – accident; cause of death – combined drug toxicity. Analytical results: ethanol (60 mg/dL), 4-ANPP (pos.), caffeine (pos.), cotinine (pos.), naloxone (pos.), nicotine (pos.), cocaine (71 ng/mL), benzoylecgonine (1600 ng/mL), diphenhydramine (98 ng/mL), fentanyl (9.3 ng/mL), norfentanyl, flualprazolam.
18	49, F	Blood: 3.8 Urine: 1.8	Suspected overdose; cause of death – combined drug toxicity including brorphine. Analytical results: 4-ANPP (pos.), caffeine (pos.), naloxone (pos.), diphenhydramine (260 ng/mL), fentanyl (21 ng/mL), norfentanyl (12 ng/mL), acetylfentanyl (2.0 ng/mL), morphine (70 ng/mL), flualprazolam.
19	29, M	Blood: 1.1 Urine: 0.8	Suspected overdose; illicit drugs found at scene; history of drug use; cause of death – adverse effects of drugs. Analytical results: flualprazolam (3.6 ng/mL), 4-ANPP (pos.), caffeine (pos.), cotinine (pos.), naloxone (pos.), nicotine (pos.), quinine (pos.), acetaminophen (16 mcg/mL), 7-amino-clonazepam (5.2 ng/mL), tramadol (70 ng/mL), diphenhydramine (490 ng/mL), amphetamine (10 ng/mL), methamphetamine (42 ng/mL), fentanyl (37 ng/mL), norfentanyl (1.3 ng/mL).
20	61, F	Blood: 0.4 Urine: 0.2	Suspected overdose; cause of death – multiple drug intoxication. Analytical results: ethanol (57 mg/dL), 4-ANPP (pos.), cotinine (pos.), naloxone (pos.), nicotine (pos.), alprazolam (65 ng/mL), benzoylecgonine

			(330 ng/mL), morphine (33 ng/mL), 6-monoacetylmorphine (2.3 ng/mL), gabapentin (9.9 mcg/mL), fentanyl (21 ng/mL), norfentanyl (1.9 ng/mL).

[a] Submitted for analysis between June–July 2020.

[b] Blood sample matrices: femoral, peripheral, iliac, or hospital blood; pos: positive; neg: negative; AM: antemortem; PM: postmortem.

[c] pos.: positive

A separate set of aggregated data involving brorphine detections in various forensic case types were disseminated in the form of trend reports published by the U.S. Center for Forensic Science Research & Education (CFSRE). These trend reports covering the period between Q3/2020 and Q2/2021 showed 58 detections of brorphine that included detections of other substances (Table 6), which have now been confirmed to reach over 60 detections (Krotulski, pers. commun.). Between Q3/2020 and Q1/2021, the brorphine positivity results in CFSRE cases were as follows: ~3.70% (Q3/2020); ~1.25% in Q4/2020, and ~0.9% in Q1/2021 (Krotulski et al. 2021b). At the time of writing, NMS Labs have identified brorphine in ~200 cases overall during screening though analytical confirmations might not have occurred in all cases (Krotulski, pers. commun.). This represented an increase of the identifications reported up to Q4/2020 (Vandeputte et al. 2021) and the initial screening results (120 cases) reported between June–October 2020 (DEA 2021d). The exact number of confirmed identifications may be lower than those initially identified during screening.

Table 6. NPS Opioids in the United States. Trend Reports published by NPS Discovery. The Center for Forensic Science Research & Education (CFSRE). [a]

Quarter	Brorphine	Fentanyl	Combinations [b]	Frequency	Reference
Q3 2020	44	361	Brorphine + fentanyl Brorphine + flualprazolam Brorphine + stimulant (Cocaine and/or meth) Brorphine + tramadol Brorphine + isotonitazene	39 39 18 9 6	Krotulski, Mohr and Logan (2020)
Q4 2020	9	392	Brorphine + fentanyl Brorphine + flualprazolam Brorphine + stimulant (Cocaine and/or meth)	8 8 7	Krotulski et al. (2020)
Q1 2021	4	249	–	–	(Krotulski et al. 2021c)
Q2 2021	1	306	–	–	(Krotulski et al. 2021d)

[a] Forensic case types linked to these results include illicit drug investigations, medicolegal death investigations, and/or driving under the influence of drugs (DUID) investigations. Total number of NPS identifications at CFSRE during this quarter (in collaboration with NMS Labs), including those from sample-mining, data-mining, and/or esoteric testing.

[b] Meth: methamphetamine

7. Dependence Potential

A. Animal Studies

Information could not be identified.

B. Human Studies

Information concerning clinical studies on withdrawal and physical dependence could not be identified. Self-reports from people reported to have used brorphine suggest that regular consumption was associated with the development of tolerance (Reddit 2021c; d; Verougstraete, Vandeputte et al. 2021) and withdrawal symptoms (Reddit 2021b).

8. Abuse Potential

A. Animal Studies

Drug discrimination studies:

Using a two-lever discrimination task (10 male Sprague-Daley rats (morphine sulfate training dose 3.2 mg/kg) under a fixed-ratio (FR10) schedule of reinforcement, brorphine (test doses ranging from 0.1 to 0.32 mg/kg) fully substituted (ED_{50} = 0.16 mg/kg) for the discriminative stimulus effects of morphine (ED_{50} = 1.46 mg/kg). The ED_{50} for a fentanyl standard was 0.0090 mg/kg. Peak morphine-appropriate responding (E_{max}) was 99 ± 1%. The response rate decreased to 74% of vehicle control following 0.32 mg/kg brorphine. Naltrexone (1 mg/kg) blocked the morphine-like discriminative stimulus effects of brorphine, reducing morphine-appropriate responding to 26 ± 12%. Brorphine was 9-times more potent than morphine based on the differences in ED_{50} values (Gatch 2020b).

Warm-water tail flick assay:

Analgesic effects were tested in 10 Swiss-Webster mice for baseline tail withdrawal latency using 50° C water. Brorphine was tested in doses from 0.01 to 3.2 mg/kg (s.c.). Brorphine (ED_{50} = 0.11 mg/kg) dose-dependently increased tail-flick latencies to a maximum defined as 100% maximum peak effects (MPE). The ED_{50} for the morphine standard was 1.31 mg/kg (E_{max} = 98 %MPE). The ED_{50} for the fentanyl standard was 0.084 mg/kg (E_{max} = 100 %MPE). Peak analgesic effects of brorphine lasted 75 min, and returned to baseline within 120 min. Naltrexone (1 mg/kg) blocked the analgesic effects of brorphine, reducing tail-flick

latencies to 14.9 ± 3.3 %MPE. Based on ED_{50} values brorphine was 12-times more potent than morphine and fentanyl was 1.3-times more potent than brorphine (Gatch 2020a).

B. Human Studies

Information from clinical studies could not be identified.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Information about therapeutic use could not be identified.

10. Listing on the WHO Model List of Essential Medicines

Brorphine is not listed on the 21st WHO Essential Medicines List or the 7th WHO Essential Medicines List for Children.

11. Marketing Authorizations (as a Medicinal Product)

Information on marketing authorization of brorphine as a medicinal product could not be identified.

12. Industrial Use

Information about recorded industrial use could not be identified.

13. Non-Medical Use, Abuse and Dependence

Epidemiological evidence concerning the use of brorphine could not be identified. Its use is likely to be limited to recreational substance users rather than the general population. The detection of brorphine in biological fluids confirms that this substance is used recreationally. The available information obtained from Internet forums suggest that the use of this substance might be associated with individuals who might be using heroin, prescription opioid analgesics and other synthetic opioids. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and people using this substance may be unaware of the exact dose or compound being ingested (by whatever route). Brorphine is available in its own right and is advertised for sale by some Internet retailers including those operating on the 'dark web' (Lamy et al. 2021). Current information so far available suggests that brorphine shows abuse liability and that this is likely extend to dependence-producing properties. Discussions on online forums involving brorphine appear to have been available since at least early 2019 (Barenholtz et al. 2021; Catalani et al. 2021; Vandeputte et al. 2021).

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Epidemiological data on harms associated with brorphine could not be identified. The information available on fatal and non-fatal intoxications (Section 6) suggests involvement

of poly-substance use. Data on the effects of brorphine on the ability to drive and operate machines could not be identified. Since it is well established that opioid analgesics impact on the mental and physical ability required for driving and operating machinery, it is likely that this will also extend to brorphine. In the U.S., it has been suggested that the introduction of brorphine to the market reflected the replacement of isotonitazene, another synthetic opioid (Vandeputte et al. 2021).

Marginalized and vulnerable opioid users including those who inject such substances might also use synthetic opioid 'research chemicals'. However, people who are using these substances may not be aware of using them and the high potency associated with some synthetic opioids might result in increased risks of life-threatening overdoses. Brorphine has been detected in falsified oxycodone tablets and implicated in fatal and non-fatal intoxications (EMCDDA 2021b; Krotulski et al. 2021a; Razinger et al. 2021). There is evidence to suggest that these falsified products may also be purchased via the Internet (EMCDDA 2021b). As highlighted by the EMCDDA, falsified medicines are commonly visually indistinguishable from legitimate products and people using these products will be unaware of what they contain and the amount, which poses inherent risks to the individual. The risk of poisoning may be greater by the unintentionally high doses that users may take, especially when combined with other substances. Similarly to other opioids analgesics, the use of brorphine with other central nervous system depressants can increase the risk of life-threatening respiratory depression and arrest. The risk of poisoning includes both current high-risk opioid users and other groups who may have no or limited tolerance to opioids, including recreational users. Recreational users are less likely to be aware of the risk of overdose and are unlikely to have access to community opioid overdose prevention programs, including take-home naloxone programs (EMCDDA 2021b; c). As highlighted by the EMCDDA, falsified medicines are commonly visually indistinguishable from legitimate products and people using these products will be unaware of what they contain and the amount, which poses inherent risks to the individual. The risk of poisoning may be greater by the unintentionally high doses that users may take, especially when combined with other substances. Similarly to other opioids analgesics, the use of brorphine with other central nervous system depressants can increase the risk of life-threatening respiratory depression and arrest. The risk of poisoning includes both current high-risk opioid users and other groups who may have no or limited tolerance to opioids, including recreational users. Recreational users are less likely to be aware of the risk of overdose and are unlikely to have access to community opioid overdose prevention programs, including take-home naloxone programs (EMCDDA 2021b; c).

Brorphine was reported to be one of the constituents in poly-substance mixtures called 'purple heroin' and such mixtures have been found to include benzodiazepines, acetaminophen, anti-depressants, and fentanyl together with brorphine (DEA 2021d).

15. Licit Production, Consumption and International Trade

Brorphine is used as reference material for scientific research. It is not known to have any agricultural, industrial or cosmetic uses.

16. Illicit Manufacture and Traffic and Related Information

Brorphine was formally notified to the EU Early Warning System Network by the EMCDDA on behalf of the Sweden on 4 June 2020 based on a sample seized in March 2020. Brorphine has been available on the drug market in Europe since at least March 2020. As of 15 July 2021, a total of three countries of the EU Early Warning System network have reported a total of five physical detections of brorphine to the EMCDDA, two of which were seizures. The last detection reported occurred in January 2021. In detections reported to the EMCDDA, brorphine was found in powders (6 g), in capsules (4 units) and in tablets (2 units). These detections include seizures and collected samples (test purchases and 1 collection associated with a serious adverse event). From the limited data available, brorphine can be purchased under its own name. In at least one case brorphine was missold as oxycodone tablets (EMCDDA 2021b).

The number of countries that reported brorphine detections to the United Nations Office on Drugs and Crime (UNODC) as of 25 July 2021 is as follows: two countries in 2019, two countries in 2020, and two countries in 2021 (UNODC 2021b).

The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, has registered reports involving the detection of brorphine. According to the three-factor analysis documentation for temporary control of brorphine published by the DEA published in August 2020, twenty reports of brorphine have been received and one of these consisted of 12.533 g of brorphine. At the time of the query (18 August 2020), it was stated that the DEA were aware of 11 more seizures of brorphine that were not yet reported to NFLIS at that time. Some of these reports originated in 2019 (DEA 2020c) and it appeared that these 20 seizures occurred between June 2019 and August 2020 (DEA 2021c). Brorphine numbers could neither be identified in the NFLIS-DRUG 2019 annual report (DEA 2020b) nor the NFLIS-DRUG 2020 midyear report (DEA 2021b). Brorphine was however included in the NFLIS-DRUG snapshot report of March 2021 that featured NFILS report numbers of selected substances (Table 7) (DEA 2021a). It has also been reported that brorphine was featured in a NFLIS-DRUG snapshot report of December 2019 (Krotulski, Papsun, Noble, Kacinko and Logan 2021a).

Table 7. U.S. National Forensic Laboratory Information System (NFLIS) snapshot report – top five drugs in the category 'selected narcotic analgesics' (DEA 2021a) [a]

Compound	No of reports
Phenylfentanyl	151
Fluorofentanyl [b]	77
Brorphine	28
Isotonitazene	26
Metonitazene	23

Total	42,384

[a] Top five drug reports received by NFLIS-Drug between 01 January 2021 and 31 March 2021.

[b] Includes all positional and non-specified isomers as reported by participating laboratories.

Some cases were reported where brorphine was found in combination with heroin and fentanyl. Other reports on suspected heroin/fentanyl powders revealed the detection of brorphine in combination with flualprazolam and diphenhydramine (DEA 2021c).

In the DEA emerging threat reports covering drug reports collected from the DEA's laboratory system, brorphine was not included in the 2019 annual report (DEA 2019). In the 2020 annual report, there were 4862 identifications of fentanyl, fentanyl-related compounds and other new synthetic opioids. Fentanyl accounted for approximately 89% of the identifications (4323 times). Brorphine was reported two times and indicated as being reported for the first time (in 2020) (DEA 2020a). A DEA bulletin publication published in July 2021 contains updated NFLIS-Drug data (queried 6 July 2021) that suggests that 131 reports were received between June 2019–June 2021 and a rise in mid-2020 (DEA 2021d). The reported numbers covered in this section are likely to change due to delays related to the Covid-19 pandemic.

17. Current International Controls and Their Impact

Brorphine is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Refer to 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

Detections of brorphine may be under-reported if this substance is not routinely screened for in all laboratories receiving samples for analysis.

References

ADEBAR (2020) Analytical Report. Brorphine. 1-[1-[1-(4-Bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one. Ausbau analytischer Datenbanken, Erhebung und bundesweite Bereitstellung von analytischen Daten, pharmakologischen Daten, Verfahrensvorschriften und Referenzmaterialien für neu auf dem Drogenmarkt auftretende Stoffe. Available at: https://www.projekt-adebar.eu/index.php?id=11

Barenholtz E, Krotulski AJ, Morris P, Fitzgerald ND, Le A, Papsun DM, Logan BK, Hahn WE, Goldberger BA, Cottler LB, Palamar JJ (2021) Online surveillance of novel psychoactive substances (NPS): Monitoring Reddit discussions as a predictor of increased NPS-related exposures. International Journal of Drug Policy 98 103393. https://doi.org/10.1016/j.drugpo.2021.103393

Bluelight (2021a) Brorphine is the tofu of opioids: Available at: https://www.bluelight.org/xf/threads/brorphine-is-the-tofu-of-opioids.885922/ - post-15078584 (last accessed 24 July 2021).

Bluelight (2021b) Warning: brorphine is a severe overdose risk. Available at: https://www.bluelight.org/xf/threads/warning-brorphine-is-a-severe-overdose-risk.886363/ - post-15061994 (last accessed 24 July 2021).

Catalani V, Arillotta D, Corkery JM, Guirguis A, Vento A, Schifano F (2021) Identifying new/emerging psychoactive substances at the time of COVID-19; a web-based approach. Frontiers in Psychiatry 11 1638. https://doi.org/10.3389/fpsyt.2020.632405

Cayman Chemical (2019) Brorphine hydrochloride. GC-MS data sheet. Cayman Chemical Company. Ann Arbor. Michigan. USA. Available at: https://www.caymanchem.com/gcms/27816-0567046-GCMS.pdf

Cayman Chemical (2021) Brorphine (hydrochloride). Product Information. Item No. 27816. 28 April 2021. Cayman Chemical Company. Ann Arbor. Michigan. USA. Available at: https://www.caymanchem.com/pdfs/27816.pdf

DEA (2019) DEA emerging threat report: Annual 2019. U.S. Drug Enforcement Administration Special Testing and Research Laboratory. Available at: https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2019-Annual.pdf

DEA (2020a) DEA emerging threat report: Annual 2020. U.S. Drug Enforcement Administration Special Testing and Research Laboratory. Availabale at: https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2020-Annual.pdf

DEA (2020b) NFLIS-Drug 2019 Annual report. National Forensic Laboratory Information System (NFLIS). Drug Enforcement Administration. Diversion Control Division. Springfield, Virginia, USA. Available at: https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-DRUG_2019_Annual_Report.pdf

DEA (2020c) Temporary Schedule I placement of 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (Brorphine). Background, data, and analysis: three factor analysis pursuant to 21 U.S.C. 811(h)(3). August 2020. Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration, Washington, DC, USA. Available at: https://www.regulations.gov/document/DEA-2020-0038-0003

DEA (2021a) NFLIS Drug Snapshot (March 2021). Reported to NFLIS-Drug for the first time between 01 January 2021 and 31 March 2021. National Forensic Laboratory Information System. Drug Enforcement Administration. Diversion Control Division. Springfield, Virginia, USA. Available at: https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS_Snapshot_032021.pdf

DEA (2021b) NFLIS-Drug 2020 Midyear report. National Forensic Laboratory Information System (NFLIS). Drug Enforcement Administration. Diversion Control Division. Springfield, Virginia, USA. Available at: https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/13915NFLISdrugMidYear2020.pdf

DEA (2021c) Schedules of Controlled Substances: temporary placement of brorphine in Schedule I. Federal Register 86 (38):11862-11867. Available at: https://www.govinfo.gov/content/pkg/FR-2021-03-01/pdf/2021-04242.pdf

DEA (2021d) (U) Indicators point to rise in brorphine's domestic availability. DEA Bulletin. DEA-DCI-BUL-076-21 (July 2021).

EMCDDA (2021a) Brorphine. European Database on New Drugs (EDND). European Monitoring Centre for Drugs and Drug Addiction. Available at: https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1108

EMCDDA (2021b) EMCDDA response to request for information on the new psychoactive substance brorphine for a WHO critical review. European Monitoring Centre for Drugs and Drug Addiction. Lisbon, Portugal.

EMCDDA (2021c) Fake oxycodone tablets containing brorphine - Slovenia, 2021. EU Early Warning System Advisory. European Monitoring Centre for Drugs and Drug Addiction. Date issued: 22 January 2021. RCS ID: EU-EWS-RCS-AD-2021-0001.

Gatch MB (2020a) Final study report. Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Test of analgesic effects alone and in combination with naltrexone.

Gatch MB (2020b) Final study report. Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Test of substitution for the discriminative stimulus effects of morphine.

INCB (2020) International Narcotics Control Board. Yellow List. Annex to Forms A, B and C, 59th edition, July2020. List of narcotic drugs under international control. Single Convention on Narcotic Drugs, 1961. Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs. Available at: https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/59_edition/59_YL_2020_EN.pdf

Janssen C (1963) Nieuwe reeks van organische verbindugen. Research Laboratorium Dr. C. Janssen NV, Belgium. BE633495.

Janssen PAJ (1965) Benzimidazolinyl piperidines. Research Laboratorium Dr. C. Janssen NV, Belgium. US3196157A. Available at: https://worldwide.espacenet.com/patent/search/family/026897320/publication/US3196157A?q=pn%3DUS3196157A

Kawaguchi M, Hayashi O, Sakai N, Hamada M, Yamamoto Y, Oda Ji (1986) An asymmetric synthesis of 2-substituted piperidines through ozonolysis of cyclopentenes and reductive aminocyclization. Agricultural and Biological Chemistry 50 (12):3107-3112. https://doi.org/10.1271/bbb1961.50.3107

Kennedy NM, Schmid CL, Ross NC, Lovell KM, Yue Z, Chen YT, Cameron MD, Bohn LM, Bannister TD (2018) Optimization of a series of mu opioid receptor (MOR) agonists with high G protein signaling bias. Journal of Medicinal Chemistry 61 (19):8895-8907. https://doi.org/10.1021/acs.jmedchem.8b01136

Krotulski AJ, Fogarty MF, Logan BK (2020) Brorphine Monograph. Latest revision: 17 July 2020. NMS Labs; Center for Forensic Science Research & Education. Willow Grove, Pennsylvania, USA. Available at: https://www.npsdiscovery.org/wp-content/uploads/2020/07/Brorphine_071720_CFSRE-Toxicology_Report.pdf

Krotulski AJ, Mohr ALA, Logan BK (2020) NPS Opioids in the United States. Trend Report: Q3 2020. NPS Discovery. The Center for Forensic Science Research & Education. Willow Grove, Pennsylvania. Available at: https://www.npsdiscovery.org/wp-content/uploads/2020/10/2020-Q3_NPS-Opioids_Trend-Report.pdf

Krotulski AJ, Papsun DM, Noble C, Kacinko SL, Logan BK (2021a) Brorphine - Investigation and quantitation of a new potent synthetic opioid in forensic toxicology casework using liquid chromatography-mass spectrometry. Journal of Forensic Sciences 66 (2):664-676. https://doi.org/10.1111/1556-4029.14623

Krotulski AJ, Papsun DM, Walton SE, Logan BK (2021b) Metonitazene in the United States - forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. Drug Testing and Analysis. https://doi.org/10.1002/dta.3115

Krotulski AJ, Walton SE, Mohr ALA, Logan BK (2020) NPS Opioids in the United States. Trend Report: Q4 2020. NPS Discovery. The Center for Forensic Science Research & Education. Willow

Grove, Pennsylvania. Available at: https://www.npsdiscovery.org/wp-content/uploads/2021/01/2020-Q4_NPS-Opioids_Trend-Report.pdf

Krotulski AJ, Walton SE, Mohr ALA, Logan BK (2021c) NPS Opioids in the United States. Trend Report: Q1 2021. NPS Discovery. The Center for Forensic Science Research & Education. Willow Grove, Pennsylvania. Available at: https://www.npsdiscovery.org/wp-content/uploads/2021/04/2021-Q1_NPS-Opioids_Trend-Report.pdf

Krotulski AJ, Walton SE, Mohr ALA, Logan BK (2021d) NPS Opioids in the United States. Trend Report: Q2 2021. NPS Discovery. The Center for Forensic Science Research & Education. Willow Grove, Pennsylvania. Available at: https://www.npsdiscovery.org/wp-content/uploads/2021/07/2021-Q2_NPS-Opioids_Trend-Report.pdf

Lamy FR, Daniulaityte R, Barratt MJ, Lokala U, Sheth A, Carlson RG (2021) "Etazene, safer than heroin and fentanyl": non-fentanyl novel synthetic opioid listings on one darknet market. Drug and Alcohol Dependence 225 108790. https://doi.org/10.1016/j.drugalcdep.2021.108790

Olszewska B, Jab, ska A, Zawisza A (2018) Diastereoselective synthesis of 2-vinylpyrrolidines and 2-vinylpiperidines by the palladium-catalysed cyclization of amino-allylic carbonates containing a chiral protecting group. ARKIVOC 2018 (5):254-271. https://doi.org/10.24820/ark.5550190.p010.591

Razinger G, Grenc D, Brvar M, Pezdir T, Kranvogl R, Brvar M (2021) Severe rhabdomyolysis and acute kidney failure due to synthetic opioid brorphine exposure in combination with chronic sertraline therapy. European Journal of Clinical Pharmacology. https://doi.org/10.1007/s00228-021-03136-7

Reddit (2020a) Beginner and veteran brorphine guide and overview. Available at: https://www.reddit.com/r/researchchemicals/comments/j3nn92/beginner_and_veteran_brorphine_guide_and_overview/ (last accessed 23 July 2021)

Reddit (2020b) Brorphine. Available at: https://www.reddit.com/r/researchchemicals/comments/fd5337/brorphine/ (last accessed 24 July 2021).

Reddit (2020c) My experience with brorphine. Available at: https://www.reddit.com/r/researchchemicals/comments/j03l4m/my_experience_with_brorphine/ (last accessed 24 July 2021).

Reddit (2020d) Volumic dosing for Brorphine. Available at: https://www.reddit.com/r/researchchemicals/comments/ixasyk/volumic_dosing_for_brorphine/ (last accessed 24 July 2021).

Reddit (2020e) Whats with all the brorphine hate ? Available at: https://www.reddit.com/r/researchchemicals/comments/hzoxlr/whats_with_all_the_brorphine_hate/ (last accessed 23 July 2021)

Reddit (2021a) Brorphine. Available at: https://www.reddit.com/r/Opioid_RCs/comments/kphokj/brorphine/gkm4stc/?utm_source=share&utm_medium=web2x&context=3 (last accessed 23 July 2021).

Reddit (2021b) Brorphine. Avaulable at: https://www.reddit.com/r/fentanyl/comments/of8mjo/brorphine/ (last accessed 25 July 2021)

Reddit (2021c) My experience with Brorphine. Available at: https://www.reddit.com/r/researchchemicals/comments/j03l4m/my_experience_with_brorphine/ (last accessed 25 July 2021)

Reddit (2021d) Suggest brorphine oral or vaped? Avaiable at: https://www.reddit.com/r/researchchemicals/comments/l1yg55/suggest_brorphine_oral_or_vaped/ (last accessed 24 July 2021).

Slovenian National Forensic Laboratory (2020) Analytical report. Brorphine (C20H22BrN3O). Sample ID: 2178-20. European project RESPONSE. Available at: https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/Brorphine-ID-2178-20_report.pdf

UNODC (2021a) Early Warning Advisory (Tox-Portal). https://www.unodc.org/tox/__-/admin/incident/view/1935 Available at: (last accessed 25 July 2021)

UNODC (2021b) UNODC Early Warning Advisory (EWA) on new psychoactive substances (NPS) database. United Nations Office on Drugs and Crime. Available at: https://www.unodc.org/LSS/NPSFinding/List (last accessed 25 July 2021)

Vandeputte MM, Cannaert A, Stove CP (2020) *In vitro* functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Archives of Toxicology 94 (11):3819-3830. https://doi.org/10.1007/s00204-020-02855-7

Vandeputte MM, Krotulski AJ, Papsun DM, Logan BK, Stove CP (2021) The rise and fall of isotonitazene and brorphine: two recent stars in the synthetic opioid firmament. Journal of Analytical Toxicology. In press. https://doi.org/10.1093/jat/bkab082

Verougstraete N, Vandeputte MM, Cannaert A, Stove C, Verougstraete N, Verstraete AG, Lyphout C, Hulpia F, Van CS, Verstraete AG (2021) First report on brorphine: the next opioid on the deadly new psychoactive substance horizon? Journal of Analytical Toxicology 44 (9):937-946. https://doi.org/10.1093/jat/bkaa094

Verstraete A, Hyde E (2020) Une méthode de dépistage des NPS utilisant les plateformes collaboratives HighresNPS et Mzcloud. Toxicologie Analytique et Clinique 32 (4, Supplement):S47-S48. https://doi.org/10.1016/j.toxac.2020.09.017

Vohra V, Aaron C (2021) The color purple: death associated with brorphine, an emerging novel synthetic opioid. Clinical Toxicology 59 (6):556-557.

Vohra V, King AM, Jacobs E, Aaron C (2021) Death associated with brorphine, an emerging novel synthetic opioid. Clinical Toxicology. In press. https://doi.org/10.1080/15563650.2021.1879111

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 17 countries had information on brorphine (Table 1).

Table 1. Numbers of countries providing information on brorphine

Region	Number of countries without information	Number of countries with information on substance
African	5	0
Eastern Mediterranean	8	0
European	18	12
Region of the Americas	9	3
South-East Asia	4	0
Western Pacific	10	2
Total (71)	54	17

APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

No countries reported any approved human medical products, therapeutic indications, scientific use or industrial use relating to brorphine.

EPIDEMIOLOGY OF NON-MEDICAL USE

Five countries (3 European, 2 Region of the Americas) described seizures, reports from health professionals and reports from toxicology laboratories as evidence of non-medical use of brorphine in their country (use outside of the medical, industrial or scientific context).

Routes of administration and formulations

The most commonly reported routes of brorphine administration was oral and injection (Table 2).

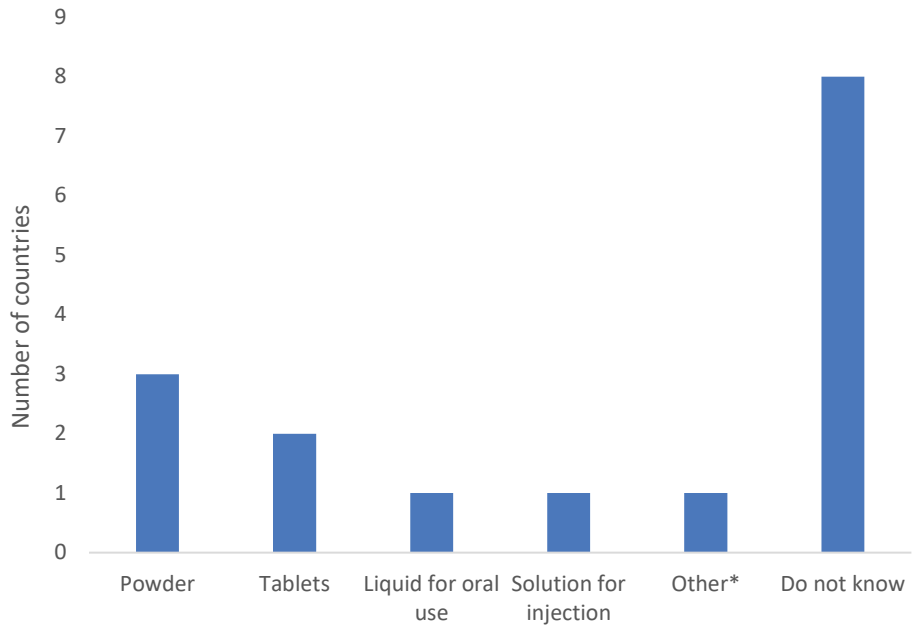
Table 2. Reported routes of brorphine administration

Route of administration	Number of countries
Oral	3
Injection	2
Sniffing	1
Smoking	1
Do not know	9
Other*	1

* Rectal route of brorphine administration

The most commonly reported formulation of brorphine was powder (Figure 1).

Figure 1. Formulations of brorphine

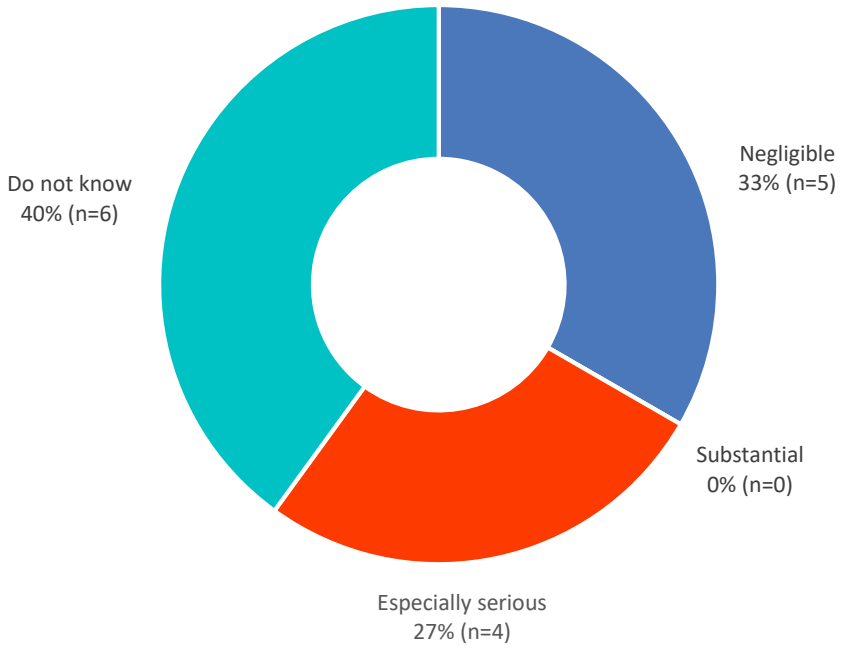


* Other brorphine formulation included "rock, capsule, unspecified liquid".

Perceived negative health impact

Four countries (4 European, 1 Region of the Americas, 1 Western Pacific) reported the level of negative health impact due to brorphine's non-medical consumption as "especially serious" (Figure 2). One country (Region of the Americas) noted "Brorphine has been encounter[ed] on the illicit market and has been positively identified in over 120 toxicology cases".

Figure 2. Countries reporting negative health impact of the non-medical consumption of brorphine



Emergency Department visits

No countries were aware of emergency room/department visits related to brorphine.

Deaths

No countries reported any deaths where brorphine was the only substance involved. One country (Region of the Americas) reported 120 deaths in 2020 where brorphine and another substance(s) were involved. One country (European) reported a total of 1809 brorphine related deaths in 2019 (where it was not reported whether brorphine was the only substance or one of multiple substances involved).

Drug Dependence

Two countries (European) reported they were aware of people presenting to drug dependence treatment in their country due to use of brorphine.

CURRENT DRUG CONTROL

Ten countries (8 European, 2 Region of the Americas) reported brorphine is currently controlled under national legislation to regulate its availability. One country (European) remarked brorphine "has been placed under control as a narcotic substance due to the potential risks posed by the opioid receptor activity and due to the documented fatalities in other countries. The assessment and control has been made and placed nationally."

Table 3 shows reported activities involving brorphine.

Table 3. Reported activities involving brorphine for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Trafficking	2
Internet sales (seller or website located in respondent's country)	2
Smuggling (from other countries)	1
Internet sales (from abroad to buyers in respondent's country)	1
Internet sales (other or location of sellers and website unknown)	1
Other*	1
Do not know	9

* "Other activities are present as brorphine has been identified in seized samples"

Seizures

Two countries (2 Region of Americas) reported seizures of brorphine in 2021. Seizure numbers ranged from 1 to 12 (Table 4).

Three countries (5 European, 2 Region of Americas) reported seizures of brorphine in 2020. Seizure numbers ranged from 1 to 112, and seizure quantities ranged from 0.05 to 1717 grams.

Two countries (2 Region of the Americas) reported seizures of brorphine in 2019. Seizure numbers ranged from 6 to 8.

Table 4. Reported seizures of brorphine

Year	Number of countries reporting seizures	Number of seizures
2021	2	13
2020	3	117
2019	2	14

Fourteen countries (11 European, 2 Region of the Americas, 1 Western Pacific) reported having the forensic laboratory capacity to analyze brorphine.