EUDA
EUROPEAN UNION DRUGS AGENCY

# EU Early Warning System: Formal Notification

Formal notification of *N,N*-diethyl-2-(2-{[4-(2-methylpropoxy)phenyl]methyl}-5-nitro-1*H*-1,3-benzimidazol-1-yl)ethan-1-amine (isobutonitazene) by Norway as a new psychoactive substance under the terms of Regulation (EU) No 2023/1322 and Council Framework Decision 2004/757/JHA

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| **Date issued** | **RCS ID** |
| 09.10.2024 | EU-EWS-RCS-FN-2024-0032 |
| **Issued by** | **Transmitted by** |
| EUDA | Action on New Drugs Sector, EUDA |

## 1. Read me first

This document provides formal notification of the analytical identification of *N,N*-diethyl-2-(2-{[4-(2-methylpropoxy)phenyl]methyl}-5-nitro-1*H*-1,3-benzimidazol-1-yl)ethan-1-amine (isobutonitazene) for the first time in Europe.

Please report any additional data you have on this substance to: ews@euda.europa.eu

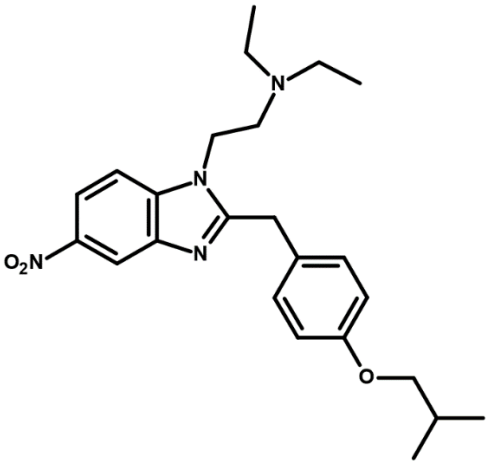
## 2. Data use restrictions

As with all formal notifications issued by the EU Early Warning System (EWS), remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this notification to other groups we would ask that you exercise your best judgment on what information needs to be provided. If you have any questions in this respect, please contact us.

## 3. Names of substance and other identifiers

- **IUPAC name:** *N,N*-diethyl-2-(2-{[4-(2-methylpropoxy)phenyl]methyl}-5-nitro-1*H*-1,3-benzimidazol-1-yl)ethan-1-amine
- **Chemical names:** *N,N*-diethyl-2-[2-[(4-isobutoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine; *N,N*-diethyl-2-(2-(4-isobutoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine; *N,N*-diethyl-2-[2-[[4-(2-methylpropoxy)phenyl]methyl]-5-nitrobenzimidazol-1-yl]ethanamine
- **Common name:** isobutonitazene
- **Other names:** iso-butonitazene; *iso*-butonitazene
- **Chemical formula:** $C_{24}H_{32}N_4O_3$
- **Molecular weight:** 424.54
- **CAS Registry number:** not registered
- **InChIKey:** KQZNQVXEZPNJQC-UHFFFAOYSA-N

**Molecular structure:**




## 4. Substance classification

Opioid

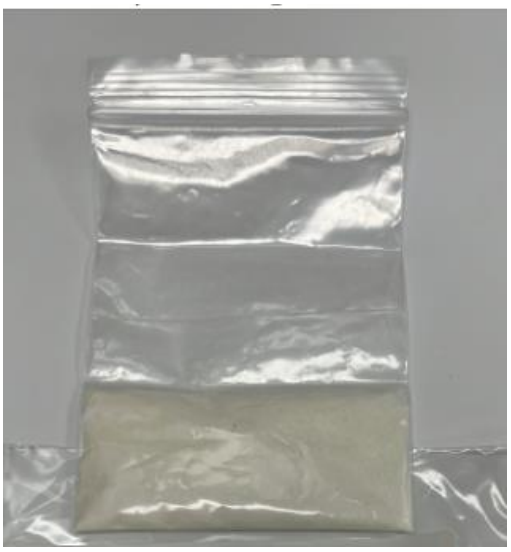
## 5. Detection

**Type:** Seizure

**Case Report identifier:** EDND-CR-2023-1206

**Details:** isobutonitazene was identified in 10.5 grams and 5 grams of white powder, seized by Norwegian Customs at the International Mail Centre in Oslo, in two separate seizures on 4 May 2023 and 18 July 2023, respectively.

The substance was analysed by by Raman spectroscopy (handheld device) and was analytically confirmed by GC-MS,  and FTIR by the Norwegian Customs.



## 6. Chemistry and Analysis

**Chemical classification:** azacyclic; azole; benzimidazole

Isobutonitazene, which can also be known as iso-butonitazene/*iso*-butonitazene, is an opioid of the 2-benzylbenzimidazole family.

A recent study on nitazene analogues and their positional isomers has referred to isonitazenes as nitro group positional isomers of nitazenes [1]. The prefix iso- has therefore been used to describe both positional isomers that have the nitro group at the 6-position of the benzimidazole ring (e.g. iso-metonitazene (iso-MetN), *N*,*N*-diethyl-2-[2-(4-methoxybenzyl)6-nitro-1*H*-benzimidazol-1-yl]ethanamine) [1] and also for structural isomers that contain a dimethyl branched alkoxy side chain in the para-substitution at the benzyl moiety (as in isotonitazene, *N*,*N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine).

Isobutonitazene is structurally related with the internationally controlled isotonitazene (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs). Isobutonitazene differs from isotonitazene by the substitution of the isopropoxy group by an isobutoxy group in the *para*-substitution at the benzyl moiety.

Isobutonitazene, butonitazene (formally notified in February 2021 and under intensive monitoring since March 2021) and *sec*-butonitazene (not monitored by the EU EWS) are structural isomers. The identification and discrimination of these isomers can pose analytical challenges due to the fact that these substances have the same molecular weight and may have similar fragmentation patterns. As a result, in addition to GC-MS, other analytical techniques, such as FTIR or NMR, may be required.

Reference standards are available for isobutonitazene (citrate) [2], butonitazene [3] and *sec*-butonitazene (citrate) [4]. A λmax (ultraviolet wavelength of maximum absorbance) of 240 nm is reported for isobutonitazene (citrate) [2]. A λmax of 242 nm and 239 nm is reported for butonitazene and *sec*-butonitazene (citrate), respectively [3, 4]

Isobutonitazene (citrate) is reportedly soluble in DMF (10 mg/ml), DMSO (10 mg/ml) and PBS (pH 7.2) (1 mg/ml) [2]. Butonitazene is reportedly soluble in DMF (25 mg/ml), DMF:PBS (pH7.2) (1:1) (0.5 mg/ml), DMSO (20 mg/ml) and ethanol (10 mg/ml) [3]. *Sec*-Butonitazene (citrate) is reportedly soluble in DMF (10 mg/ml), DMSO (10 mg/ml) and PBS (pH 7.2) (1mg/ml) [4].

## 7. Pharmacology and toxicology

**Pharmacological classification:** opioid

There is limited information available on the pharmacology and toxicology of this substance. Based on its chemical structure, the substance is expected to be a μ-opioid receptor (MOR) agonist and have opioid narcotic analgesic effects.

A recent structure-activity relationship study has shown that *para*-alkoxy side chain length influences the subnanomolar affinity at MOR [5]. Nitazenes presenting one or four carbon chain showed to have a decreased affinity when compared with nitazenes with intermediate chain lengths (two or three carbon chains) [5]. The use of an *in vitro* μ-opioid receptor (MOR) activation assay has shown that the *para*-alkoxy side chain branching influences MOR activation potential, with isobutonitazene (and sec-butonitazene) being more potent in activating MOR than butonitazene [6].

A study on human metabolism of the synthetic benzimidazole opioids isotonitazene, metonitazene, etodesnitazene, and metodesnitazene reported *O*-dealkyl and *N*-deethyl-*O*-dealkyl metabolites and glucuronides as predominant in urine samples [7]. The metabolisation of 2-benzimidazole structural analogues that differ solely in the composition of the alkoxy side chain is foreseen to form similar *O*-dealkyl metabolites [7]. Phase II conjugates of *O*-dealkyl and *N*-deethyl-*O*-dealkyl metabolites are suitable additional targets for proving consumption without glucuronide hydrolysis in urine [7].

## 8. Further information

Further information on this substance is available on the EDND profile:
https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1508

## 9. Acknowledgements

The Norwegian National Focal Point and the Directorate of Norwegian Customs are kindly acknowledged for the information and analytical data provided.

## 10. Attachments

None.

## 11. References

[1] Kanamori T et al. Analysis of highly potent synthetic opioid nitazene analogs and their positional isomers. Drug Test Anal. 2023; 15:449-457

[2] https://www.caymanchem.com/product/35107

[3] https://www.caymanchem.com/product/30278/butonitazene

[4] https://www.caymanchem.com/product/34856/sec-butonitazene-(citrate)

[5] Kozell LB *et al*. Pharmacologic Characterization of Substituted Nitazenes at μ, κ, and Δ Opioid Receptors Suggests High Potential for Toxicity. J Pharmacol Exp Ther. 2024; 389(2): 219–228

[6] Vandeputte M & Stove C, Ghent University, personal communication, September 2024

[7] Taoussi O *et al*. Human metabolism of four synthetic benzimidazole opioids: isotonitazene, metonitazene, etodesnitazene, and metodesnitazene. Arch of Toxicology. 2024; 98:2101–2116