



Critical review report:

Etonitazepyne (*N*-pyrrolidino etonitazene)

**Expert Committee on Drug Dependence
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Executive summary

Etonitazepyne (IUPAC name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole, also known as *N*-pyrrolidino etonitazene) is a benzimidazole-derived synthetic opioid with a chemical structure and pharmacological similarities to Schedule I drugs (under the 1961 United Nations Conventions) such as etonitazene. Etonitazepyne appears to be an analogue of benzylbenzimidazole derivatives with analgesic properties that were originally synthesized in the late 1950s, although it was not described in that series.

No medical use of etonitazepyne was identified. Etonitazepyne has not been reviewed previously by the WHO Expert Committee on Drug Dependence.

Etonitazepyne dihydrochloride supplied as test material from online suppliers has been described as a yellow powder. Reports from the Welsh Emerging Drugs and Identification of Novel Substances project indicate the presence of etonitazepyne in “M30” blue tablets. Snorting, sniffing and oral administration have been described as the main routes for taking etonitazepyne.

No reports on the pharmacokinetics of etonitazepyne were identified.

In-vitro pharmacological studies have shown that etonitazepyne is an opioid agonist, with greater affinity to μ -opioid receptors than to δ - and κ -opioid receptors. Although various inhibitory constants have been reported, both studies showed that etonitazepyne has a higher affinity to μ -opioid receptors and a lower affinity to κ -opioid receptors than fentanyl and morphine. One study indicated a higher affinity, whereas the other revealed a lower affinity, of etonitazepyne to δ -opioid receptors. In other studies, the potency of etonitazepyne at the μ -opioid receptors was greater than that of fentanyl or morphine. Etonitazepyne was more potent in inducing analgesia than morphine and fentanyl in both the warm-water tail-flick assay and the hot-plate latency test.

No studies were found of the toxicity of etonitazepyne, but its association with drug-related deaths and its presence in toxicological cases suggest that it could cause harm and may pose a serious public health threat. The reported effects after etonitazepyne use include euphoria, drowsiness, itchiness, nausea and/or vomiting, sweating and difficulty in breathing.

Etonitazepyne has been analytically confirmed in 21 blood samples and one urine sample from 21 post-mortem cases, of which four were in Canada and 17 in the USA. Etonitazepyne was usually detected with other substances. Etonitazepyne has also been identified in Europe (e.g., Belgium, Slovenia, United Kingdom) and New Zealand.

No studies were identified of the dependence potential of etonitazepyne in experimental animals or humans. In drug discrimination studies (two-lever choice method) in animals, etonitazepyne fully substituted for the discriminative stimulus effects of morphine, suggesting its potential for abuse. Although no studies on the abuse potential of etonitazepyne in humans were identified, its structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic μ -opioid receptor agonists (e.g., etonitazene), which have a high potential for abuse, suggest that etonitazepyne has potential for abuse. In addition, law enforcement data, toxicology case work and reports from online drug forums and websites suggest potential nonmedical use of etonitazepyne. An online forum report by a person who had used etonitazepyne described severe opioid withdrawal.

Etonitazepyne has no known therapeutic or industrial use or any marketing authorization. It is used as a reference material in scientific research and forensic applications.

Etonitazepyne is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions. It is a Schedule I controlled substance in Canada and has been placed temporarily in Schedule I of the Controlled Substances Act in the USA.

1. Substance identification

A. International nonproprietary name

Not available

B. Chemical Abstracts Service registry number

2785346-75-8

C. Other chemical names

2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)benzimidazole
2-(4-Ethoxybenzyl)-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole
2-[[[4-Ethoxy]phenyl]methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole
N-Pyrrolidino etonitazene

D. Trade names

Etonitazepyne is sold as the hydrochloride salt under the name “*N*-pyrrolidino etonitazene” (1).

E. Street names

Etonitazepyne is indicated under its own name or as *N*-pyrrolidino etonitazene.

F. Physical appearance

Etonitazepyne dihydrochloride purchased from online suppliers as a test material has been reported to be a homogeneous yellow powder (2). Etonitazepyne purchased as reference material has been described as a crystalline solid (1).

Reports from the Welsh Emerging Drugs and Identification of Novel Substances project (3) indicated the presence of etonitazepyne in “M30” blue tablets, sold as oxycodone.

G. WHO review history

Etonitazepyne has not formally been reviewed by WHO and is not currently under international control.

2. Chemistry

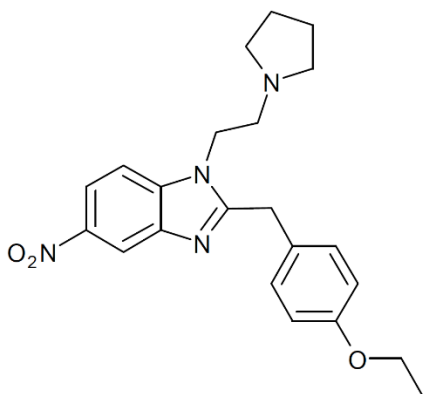
A. Chemical Name

IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole

Chemical Abstracts Service index name: 1*H*-Benzimidazole, 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-[2-(1-pyrrolidinyl)ethyl]- (ACI)

B. Chemical structure

Free base:



Molecular formula: C₂₂H₂₆N₄O₃

Molecular weight: 394.47 g/mol

C. Stereoisomers

No information was available.

D. Methods and ease of illicit manufacture

Etonitazepyne is an opioid 2-benzylbenzimidazole, or “nitazene”, which are compounds developed in the late-1950s as opioid analgesics (4). Unlike its analogues, such as etonitazene, isotonitazene and protonitazene, etonitazepyne has not been reported in the scientific or patent literature (5). An analogue bearing the *N*-pyrrolidino group but lacking the nitro group at the 5-position of the benzimidazole ring (*N*-pyrrolidino etodesnitazene) has been described (6). Related nitazene analogue containing a piperidine substitution, named “etonitazepipne”, was reported recently (7).

Etonitazepyne is a close analogue of etonitazene, carrying a pyrrolidino ring rather than a diethylaminoethyl moiety at the 1-position of the benzimidazole ring.

Synthesis of etonitazepyne has not been reported in the literature. It can be obtained through synthetic routes reported for synthesis of its 5-nitro-2-benzylbenzimidazole analogues, such as etonitazene, by appropriate replacement of reagents (8–12).

Although no information was found on the method and scale of manufacture of etonitazepyne that was recently detected, use of the synthetic methods for its nitazenes analogues should be simple and cost-efficient and does not require regulated precursors.

E. Chemical properties

Melting-point

No information was identified.

Boiling-point

No information was identified.

Solubility

Etonitazepyne has been reported to be soluble in methanol and partially soluble in water; it is not soluble in dichloromethane (13).

Etonitazepyne is soluble in dimethylformamide at 30 mg/mL and in dimethyl sulfoxide at 1 mg/mL. It is soluble at 10 mg/mL in acetonitrile and methanol and at 5 mg/mL in ethanol (1).

F. Identification and analysis

Etonitazepyne is available as a reference material from commercial suppliers for use in routine analysis for forensic and clinical investigations (1).

Analytical methods for the identification of etonitazepyne in seized samples include infrared spectroscopy, proton nuclear magnetic resonance, gas chromatography–mass spectrometry and liquid chromatography–high resolution mass spectrometry (2, 13).

Liquid chromatography coupled with mass spectrometry has been used for identification and quantification of etonitazepyne in biological samples such as human blood and urine (14).

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

Reports from the Welsh Emerging Drugs and Identification of Novel Substances project (3) indicate that snorting or sniffing is the preferred route of administration of etonitazepyne. In one case, the substance was taken orally.

B. Pharmacokinetics

No information was found.

C. Pharmacodynamics

In preclinical studies, the pharmacological profile of etonitazepyne was similar to those of potent Schedule I (under the 1961 United Nations Conventions) synthetic μ -opioid receptor agonists such as etonitazene and isotonitazene (15). Because of these pharmacological similarities, use of etonitazepyne may pose a high risk for abuse and may negatively affect people who use it and their communities.

Data from preclinical studies provided by the US Drug Enforcement Administration (15) on etonitazepyne binding and agonism at the three main opioid receptors (δ , κ , and μ) showed that it had greater binding affinity to μ - and δ -opioid receptors but lower binding affinity to κ -opioid receptors than fentanyl and morphine. Further details on the binding and agonism of etonitazepyne at opioid receptors are presented in Annex 3.

In-vitro radioligand binding assays performed in rat brain tissue showed greater affinity of etonitazepyne for μ -opioid receptors ($K_i = 4.09 \pm 0.63$) than for δ - ($K_i = 959 \pm 193$) and κ -opioid receptors ($K_i = 980 \pm 213$) (5), as shown in Table 1.

Table 1. Binding affinities to opioid receptors of etonitazepyne, fentanyl and morphine in three independent experiments

Drug name	δ -OR [^3H]DADLE	κ -OR [^3H]U69,593	μ -OR [^3H]DAMGO
	$K_i \pm \text{SD}$	$K_i \pm \text{SD}$	$K_i \pm \text{SD}$
Etonitazepyne	959 $\pm$ 193	980 $\pm$ 213	4.09 $\pm$ 0.63
Fentanyl	479 $\pm$ 76	224 $\pm$ 33	6.17 $\pm$ 0.82
Morphine	220 $\pm$ 41	74.4 $\pm$ 11.8	3.99 $\pm$ 0.40

Adapted from reference 5

In data provided by the US Drug Enforcement Administration (15), etonitazepyne showed much greater agonism to μ -opioid receptors than fentanyl (about 31 times) and morphine (about 42 times). Its agonism to δ -opioid receptors was similar to that of fentanyl and morphine but lower to κ -opioid receptors (Annex 3).

Etonitazepyne also showed high potency [$\text{EC}_{50} = 0.348 \text{ nM}$ (0.137–0.876)] in a μ -opioid receptor- β -arrestin 2 activation assay. These values exceeded the potencies of both fentanyl [$\text{EC}_{50} = 14.9 \text{ nM}$ (10.6–21.0)] and morphine [$\text{EC}_{50} = 290 \text{ nM}$ (132–668)] (5).

The analgesic properties of etonitazepyne were assessed in the hot-plate test after subcutaneous administration to male Sprague-Dawley rats. Treated rats showed dose-dependent latency of withdrawal, with a potency ($\text{ED}_{50} = 0.0017 \text{ mg/kg}$) 10 and 2000 times those of fentanyl ($\text{ED}_{50} = 0.0209 \text{ mg/kg}$) and morphine ($\text{ED}_{50} = 3.940 \text{ mg/kg}$). The ED_{50} for catalepsy induction (scored on three overt symptoms: immobility, flattened body posture and splayed limbs) was 0.00354 mg/kg (about twice as weak as the antinociceptive potency). The 0.001 and 0.003 mg/kg doses of etonitazepyne slightly but significantly increased the rats' body temperature 60 min after injection, whereas a pronounced, sustained drop in body temperature was noted after injection of the highest dose (0.01 mg/kg). The effects of etonitazepyne on hot-plate latency, catalepsy and body temperature were similar to those of fentanyl and morphine (5).

Etonitazepyne was also tested for its ability to induce analgesic effects in the warm-water tail-flick assay in Swiss-Webster mice with a cumulative dosing procedure (from 0.0001 to 0.01 mg/kg) followed by a time-course of the peak effect of etonitazepyne. Etonitazepyne increased tail-flick latency in a dose-dependent manner. In terms of potency ratios (ED_{50} test compound: ED_{50} reference compound), etonitazepyne was more potent than morphine and fentanyl. In terms of relative efficacy (E_{max} test compound: E_{max} reference compound $\times 100$), etonitazepyne was considered equally efficacious as morphine and fentanyl. The peak analgesic effect of etonitazepyne lasted 30 min.

Subcutaneous injection of naltrexone before administration of 0.01 mg/kg etonitazepyne blocked its analgesic effect, supporting the involvement of opioid receptors on the action of etonitazepyne (16).

5. Toxicology

The peripheral blood concentrations in two post-mortem cases in which etonitazepyne was analytically confirmed were 2.4, and 8.3 ng/mL (17). As the in vivo potency of etonitazepyne is

20 times higher than that of fentanyl in humans, it is reasonable to conclude that these are lethal concentrations (18).

Between January and October 2021, etonitazepyne was analytically confirmed in 21 blood samples and one urine sample from 21 post-mortem cases in North America: 17 in the USA, in West Virginia (8), Florida (2), Colorado (1), Kentucky (1), Minnesota (1), New Jersey (1), New York (1), Pennsylvania (1) and Tennessee (1); and 4 in Canada, in British Columbia. Seventeen of the decedents were male, and three were female; gender was not reported in one case. The ages ranged from 16 to 61 years. Etonitazepyne was detected with fentanyl in 12 cases, with methamphetamine in 12 and with benzodiazepines such as flualprazolam, etizolam, flubromazepam, clonazepam and desalkylflurazepam in 11 cases. Etonitazepyne was the sole substance detected in seven cases (5).

The US State Unintentional Drug Overdose Reporting System reports data from death certificates, post-mortem testing and death scene and witness findings from medical examiner or coroner reports on deaths related to unintentional drug overdose and those of undetermined intent in 48 US jurisdictions. Etonitazepyne was detected in three cases in all states with usable toxicological reports (i.e., detected non-trend) and in three cases in an analysis limited to states for which data were available for each period and restricted to cases in toxicological reports (i.e., detected trend) between January and June 2021. Etonitazepyne was confirmed as the cause of death in three cases in all states with usable data (i.e., cause-of-death non-trend) and three cases in states with data for each period (cause-of-death trend) between January and June 2021 (19).

A case in the United Kingdom in which etonitazepyne was detected in combination with other substances and caused life-threatening clinical toxicity was published recently (20).

6. Adverse reactions in humans

A self-report on an online forum indicated that the first 30 min after use of etonitazepyne were pleasant, followed by drowsiness. Sweating and shaking were reported to have started 7 h and acid reflux after 9 h after taking one “M30” pill. The same individual reported having woken one night with difficulty in breathing, waking up early and having to dose to avoid withdrawal (21).

Etonitazepyne was analytically confirmed in blood (1.15 h after admission) and urine (5.5 h after admission) in a patient admitted for acute intoxication in the United Kingdom in July 2021 (18). The patient presented with reduced consciousness, miosis, respiratory depression and rhabdomyolysis. Methadone and benzodiazepines were also detected, which possibly contributed to the observed effects.

A “high alert” public notice issued by the New Zealand National Drug Intelligence Bureau for etonitazepyne strongly urged people not to take the substance (22). It described euphoria; drowsiness and wakefulness; temporary relief of pain, stress or low mood; itchiness; severe nausea and/or vomiting; severe sweating or fever; slow and/or difficulty in breathing; blue lips or fingertips; cold, clammy skin; tiny pupils; unresponsiveness and/or loss of consciousness. These reports were not verified, and no further details (e.g., doses taken, use of other substances) was identified.

Self-reports of adverse effects include euphoria (9), relaxation (8), increased confidence (5), increased empathy (2), nausea (2), memory loss (2), loss of consciousness (2), enhanced senses (1), increased libido (1), vomiting (1), tiredness (1) and increased energy (1) (3).

7. Dependence potential

A. *Studies in experimental animals*

No information was found.

B. *Studies in humans*

No information was found.

8. Abuse potential

A. *Studies in experimental animals*

In drug discrimination studies (two-lever choice method), etonitazepyne fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration of etonitazepyne to nine Sprague-Dawley rats at doses of 0.00032–0.0032 mg/kg.

Assessment of potency ratios (ED_{50} test compound: ED_{50} reference compound) showed that etonitazepyne was more potent than morphine or fentanyl and was considered equally efficacious. The results for the first reinforcer measure were similar to those for the total session.

Subcutaneous injection of rats with 1 mg/kg naltrexone before administration of 0.0032 mg/kg etonitazepyne blocked its morphine-like discriminative stimulus, indicating the involvement of opioid receptors in its discriminative stimulus (23). Further details of the discriminative stimulus effects of etonitazepyne are presented in Annex 3.

B. *Studies in humans*

No information was found. Law enforcement data, toxicology case work and reports on online forums and websites suggest potential nonmedical use of etonitazepyne (3, 15, 22).

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

In the late 1950s, the Swiss chemical company CIBA Aktiengesellschaft synthesized a group of benzimidazole derivatives with analgesic properties, which included Schedule I substances such as the synthetic opioids clonitazene, etonitazene and isonitazene. An analogue of etonitazepyne without the nitro group at the 5-position of the benzimidazole ring (*N*-pyrrolidino etodesnitazene) was described, but no reference was made to etonitazepyne (6). Notably, the research did not result in any medically approved analgesic products

Etonitazepyne is not known to have any medical use.

10. Listing on the WHO Model Lists of Essential Medicines

Etonitazepyne is not listed on the 22nd WHO List of Essential Medicines or the 8th WHO List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Etonitazepyne is not known to have any marketing authorizations.

12. Industrial use

Etonitazepyne is not known to have any industrial use.

13. Non-medical use, abuse and dependence

No studies were found of the abuse and dependence potential of etonitazepyne in humans. A few self-reports of intentional etonitazepyne use are found on online user forums (e.g., 3).

Although no studies of the abuse potential of etonitazepyne in humans were found, its structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic μ -opioid receptor agonists (e.g., etonitazene), which have high potential for abuse, suggest that etonitazepyne has potential for abuse in humans.

One person on an online forum reported rapidly escalating tolerance and described taking half to one pill every 7 h to avoid withdrawal. He stated that switching to large doses of oxycodone was insufficient to prevent or reduce withdrawal symptoms. The individual described withdrawal (including sweating and leg restlessness) that was so severe that he was unable to go to work (21).

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

No information was found on the nature or magnitude of public health problems associated with etonitazepyne use. Adverse effects experienced by people who have taken etonitazepyne are described in section 6.

Detection of etonitazepyne in post-mortem cases and toxicology reports and evidence of its illicit distribution on the drug market suggest that etonitazepyne use may cause serious harm and represents a public health concern.

15. Licit production, consumption and international trade

Etonitazepyne is used as a reference material in scientific research and forensic applications (1).

16. Illicit manufacture and traffic and related information

The European Monitoring Centre for Drugs and Drug Addiction reported identification of etonitazepyne in some European countries in either seizures or test purchases from online suppliers (24).

The Early Warning System Tox-Portal of the United Nations Office on Drugs and Crime reported the presence of etonitazepyne in Belgium, the United Kingdom (both in 2021), the USA (2021), Canada (2021 and 2022) and New Zealand (2022) (25). In February 2021,

the presence of etonitazepyne was confirmed by forensic testing in a 1-g test purchase from China, which was communicated to the Belgian focal point within the SCANNER Project (26). In March 2022, the New Zealand National Drug Intelligence Bureau issued a public notice confirming the presence of etonitazepyne in a tablet sold as oxycodone (21); the source of the tablet was not identified. In November 2021, an NPS Early Warning System public notice from Slovenia identified etonitazepyne in a falsified “Percocet” (sold as oxycodone) blue tablet (purchased on the Darknet) in Maribor (27).

In March 2021, the Scanning Novel Opioids on Online Platforms (SNOOP) of the International Narcotics Control Board detected vendors of a substance purported to be etonitazepyne on e-commerce platforms. As of April 2022, six platforms in South, East, and South-East Asia had identified eight vendors offering the substance as powders in bulk via SNOOP. One of the vendors advertised a wholesale price per kilogram of US\$ 60–80 for a minimum 1-kg purchase (26).

Data from law enforcement agencies indicate that etonitazepyne appeared on the illicit drug market in the USA in 2021 (15). A public alert issued in June 2021 by the Center for Forensic Science Research and Education New Psychoactive Discovery programme reported that the substance had been associated with eight overdose deaths in the USA (17). Health Canada’s Drug Analysis Service first detected etonitazepyne in four overdose deaths due to several substances in British Columbia during the third quarter of 2021. The number of detections in 2021–2022 in Canada subsequently increased to 128 (28).

17. Current international controls and their impact

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

18. Current and past national controls

Etonitazepyne is a schedule I controlled substance in Canada. It has been temporarily placed in Schedule I in the USA, effective 12 April 2022 until 12 April 2024 (29).

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

As etonitazepyne has been identified in products sold as oxycodone (3, 21), it is reasonable to expect that the prevalence of intoxications due to etonitazepyne and related to etonitazepyne may be under-reported.

References

1. *N*-Pyrrolidino etonitazene (item no. 33169). Ann Arbor (MI): Cayman Chemical Co.; 2022 (<https://www.caymanchem.com/product/33169/n-pyrrolidino-etonitazene>, accessed 3 July 2022).
2. Blanckaert P, Balcaen M, Vanhee C, Risseeuw M, Canfyn M, Desmedt B et al. Analytical characterization of “etonitazepyne”, a new pyrrolidiny-containing 2-benzylbenzimidazole opioid sold online. *Drug Test Anal.* 2021;13(9):1627–34 (doi: 10.1002/dta.3113).

3. Sample results for etonitazepyne. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances, Public Health Wales; 2022 (<https://www.wedinos.org/sample-results#mylocation>, accessed 29 July 2022).
4. Ujváry I, Christie R, Evans-Brown M, Gallegos A, Jorge R, de Morais J et al. DARK classics in chemical neuroscience: Etonitazene and related benzimidazoles. *ACS Chem Neurosci*. 2021;12(7):1072–92 (doi: 10.1021/acscchemneuro.1c00037).
5. Vandeputte MM, Krotulski AJ, Walther D, Glatfelter GC, Papsun D, Walton SE et al. Pharmacological evaluation and forensic case series of N-pyrrolidino etonitazene (etonitazepyne), a newly emerging 2-benzylbenzimidazole “nitazene” synthetic opioid. *Arch Toxicol*. 2022;96(6):1845–63 (doi: 10.1007/s00204-022-03276-4).
6. Hunger A, Kebrle J, Rossi A, Hoffmann K. Benzimidazol-Derivate und verwandte Heterocyclen. II. Synthese von 1-Aminoalkyl-2-benzyl-benzimidazolen [Benzimidazole derivatives and related heterocycles III. Synthesis of 1-aminoalkyl-2-benzyl-nitro-benzimidazoles]. *Helv Chim Acta*. 1960;43 (3):800-809. doi: 10.1002/hlca.19600430323
7. Vandeputte MM, Krotulski AJ, Walther D, Glatfelter GC, Papsun D, Walton SE, Logan BK, Baumann MH, Stove CP. Pharmacological evaluation and forensic case series of N-pyrrolidino etonitazene (etonitazepyne), a newly emerging 2-benzylbenzimidazole ‘nitazene’ synthetic opioid. *Arch Toxicol*. 2022;96 (6):1845-1863. (doi: 10.1007/s00204-022-03276-4)
8. Thomas JB, Fall MJ, Cooper JB, Burgess JP, Carroll FI. Rapid in-plate generation of benzimidazole libraries and amide formation using EEDQ. *Tetrahedron Lett*. 1997;38(29):5099–102 (doi: 10.1016/S0040-4039(97)01136-2).
9. Kim Y, Kumar MR, Park N, Heo Y, Lee S. Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and C–N bond formation. *J Organic Chem*. 2011;76(23):9577–83 (doi: 10.1021/jo2019416).
10. Renton P, Green B, Maddaford S, Rakhit S, Andrews JS. NOpiates: Novel dual action neuronal nitric oxide synthase inhibitors with μ -opioid agonist activity. *ACS Medicinal Chem Lett*. 2012;3(3):227–31 (doi: 10.1021/ml200268w).
11. Bucha M, Eppakayala L, Chary MT. A facile synthesis and molecular docking for anti-inflammatory activity of 2-(4-chlorobenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-5-amine and 2-(4-chlorobenzyl)-1-((1-ethylpyrrolidin-2-yl)methyl)-1H-benzo[d]imidazol-5-amine. *Indian Jo Heterocyclic Chem*. 2018;28:321. ISSN (Online): 2456-431.
12. Vandeputte MM, Van Uytfaenghe K, Layle NK, St Germaine DM, Iula DM, Stove CP. Synthesis, chemical characterization, and μ -opioid receptor activity assessment of the emerging group of “nitazene” 2-benzylbenzimidazole synthetic opioids. *ACS Chemical Neurosci*. 2021;12(7):1241–51 (doi: 10.1021/acscchemneuro.1c00064).
13. Analytical report. Etazene ((2-{2-[(4-ethoxyphenyl)methyl]-1H-1,3-benzodiazol-1-yl}ethyl)diethylamine). Vodovodna, Ljubljana: Slovenian National Forensic Laboratory; 2021 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/Etazene-ID-2206-20_report.pdf, accessed 09 September 2022)
14. Vandeputte MM, Verougstraete N, Walther D, Glatfelter GC, Malfliet J, Baumann MH et al. First identification, chemical analysis and pharmacological characterization of N-piperidiny etonitazene (etonitazepipne), a recent addition to the 2-benzylbenzimidazole opioid subclass. *Arch Toxicol*. 2022;96(6):1865–80 (doi: 10.1007/s00204-022-03294-2).
15. Temporary Schedule I placement of butonitazene (2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine); etodesnitazene (2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine); flunitazene (N,N-diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine); metonitazene (N,N-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine); metodesnitazene

- (N,N-diethyl-2-(2-(4-methoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine); N-pyrrolidino etonitazene (2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzimidazole); and protonitazene (N,N-diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine). Background, data, and analysis: Three factor analysis pursuant to 21 U.S.C. 811(h)(3). Washington DC: Drug Enforcement Administration, Drug and Chemical Evaluation Section, Diversion Control Division; 2021 (<https://www.govinfo.gov/content/pkg/FR-2022-04-12/pdf/2022-07640.pdf>, accessed 09 September 2022).
16. Gatch MB. Test of analgesic effects alone and in combination with naltrexone. Compound: N-Pyrrolidino etonitazene. In: Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Fort Worth (TX): University of North Texas, Health Science Center; 2020; Call Order: 15DDHQ22F00000029.
 17. Krotulski A, Papsun D, Walton S, Logan B. NPS discovery: New high potency synthetic opioid N-pyrrolidino etonitazene (etonitazepyne) linked to overdoses across United States. Willow Grove (PA): Center for Forensic Science Research & Education, 2021 (https://www.npsdiscovery.org/wp-content/uploads/2021/06/Public-Alert_N-Pyrrolidino-Etonitazene_NPS-Discovery_061721.pdf, accessed 09 September 2022)
 18. Montanari E, Madeo G, Pichini S, Busardò FP, Carlier J. Acute intoxications and fatalities associated with benzimidazole opioid (nitazene analog) use: A systematic review. *Ther Drug Monit.* 2022;44(4):494–510 (doi: 10.1016/j.tdm.2021.10.001).
 19. FDA_NPS May2022 updated. Atlanta (GA): US Center for Disease Control and Prevention, State Unintentional Drug Overdose Reporting System; 2022.
 20. Pucci M, Hudson S, Hill SL, Thomas SHL. Severe toxicity involving N-pyrrolidino etonitazene in the United Kingdom – A case report. *Clin Toxicol.* 2022;60(4):533–4 (doi: 10.1080/15563650.2021.1979235).
 21. Bluelight; 2022 (<http://www.bluelight.org/>, accessed 20 July 2022).
 22. High Alert. Highly potent opioid found in fake oxycodone tablets. Wellington: Drug Information and Alerts Aotearoa New Zealand; 2022 (<https://www.highalert.org.nz/alerts-and-notifications/highly-potent-opioid-found-in-fake-oxycodone-tablets/>, accessed 29 July 2022).
 23. Gatch MB. Test of substitution for the discriminative stimulus effects of morphine: Compound: N-Pyrrolidino etonitazene. In: Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Fort Worth (TX): University of North Texas, Health Science Center, 2020; Call order: 15DDHQ22F00000029.
 24. EU Early Warning System Situation Reports. ELisbon: European Monitoring Center for Drugs and Drug Addiction; 2022.
 25. Tox-Portal. Early Warning Advisory. Vienna: United Nations Office on Drugs and Crime; 2022 (<https://www.unodc.org/tox/#/login>, accessed 27 July 2022).
 26. Special notice: Emergence of potentially dangerous synthetic opioids: etonitazepyne. Vienna: International Narcotics Control Board; 2022.
 27. Obvestilo Sistema za zgodnje opozarjanje na pojav NPS: Okrogla modra tabletko Percocet s potentnim sintetičnim opioidom [NPS early warning system notice: Round blue pill Percocet with potent synthetic opioid]. Ljubljana: DrogArt Association; 2021 (<https://www.drogart.org/opozorila/7271/obvestilo-sistema-za-zgodnje.html>, accessed 30 July 2022).
 28. Canada prioritization table. Health Canada, Drug Analysis Servis; 2022.
 29. Schedules of controlled substances: Temporary placement of butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, N-pyrrolidino etonitazene, and protonitazene in Schedule I. CFR Part 1308. Arlington (VA): Drug Enforcement Administration; 2022 (<https://www.govinfo.gov/content/pkg/FR-2022-04-12/pdf/2022-07640.pdf>, accessed 09 September 2022).