World Health Organization

Critical review report:

Etazene (etodesnitazene)

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.

Contents

Executive summary

Etazene (IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine, also known, for example, as etodesnitazene, desnitroetonitazene) is a benzimidazole-derived synthetic opioid with a chemical structure and pharmacological similarities to drugs under Schedule I (under the 1961 United Nations Conventions) such as clonitazene, etonitazene and isotonitazene. It corresponds to the *desnitro* analogue of etonitazene in the series of 2-benzylbenzimidazole derivatives with analgesic properties that were originally synthesized in the late 1950s. No medical use of etazene was, however, identified. Etazene has not been reviewed previously by the WHO Expert Committee on Drug Dependence.

Etazene dihydrochloride has been detected in seized material as a white-to-beige powder and in liquid forms, typically of unknown purity or concentration. Etazene citrate sold as a reference material has been described as a crystalline solid. It has also been detected in "m30" pills. Intranasal administration has been reported as the main route used for administration on online forums by people who use drugs.

In silico profiling of the absorption, distribution, metabolism and excretion of etazene indicated that it is three times more lipophilic than morphine, with high gastrointestinal absorption. In contrast to morphine, etazene does not appear to be a substrate for *p*-glycoprotein. Metabolite profiling showed that etazene inhibits CYP1A2, CYP2C19, CYP2D6 and CYP3A4.

In vitro pharmacological studies showed that etazene is an opioid agonist, with higher affinity for μ-opioid receptors than fentanyl and morphine. The potency of etazene at the μ-opioid receptors was about two times higher than that of morphine and similar to that of fentanyl. It was also more potent than morphine (but less potent than fentanyl) in inducing analgesic effects in the warm-water tail-flick assay.

No information was found on the toxicity of etazene, but its recent association with fatalities suggests that this opioid can cause harm and may pose a serious public health threat. Information on the effects of etazene is derived mainly from unverified reports on online forums by people who have used etazene and include typical opioid effects such as itchiness and euphoria. To date, etazene has been confirmed in 10 post-mortem blood and/or urine specimens in Canada and the USA; etazene has also been identified in Europe.

No studies were found of its dependence potential in experimental animals or humans. In drug discrimination studies (two-lever choice method) in animals, etazene fully substituted for the discriminative stimulus effects of morphine, suggesting its potential for abuse. Although no studies were found of the abuse potential of etazene in humans, its structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic μ-opioid receptor agonists (e.g., etonitazene, isotonitazene), which have high potential for abuse, suggest that etazene has potential for abuse; this is supported by descriptions in online reports by people who have used this substance. Such reports suggest that tolerance to etazene may develop, as two people who had used etazene reported having to take increasing doses to achieve the same effects.

There are no known therapeutic or industrial uses of etazene, and there are no marketing authorizations. It is used as a reference material in scientific research and forensic applications.

Reports from Health Canada's Drug Analysis Service, the European Monitoring Center for Drugs and Drug Addiction and the US National Forensic Laboratory Information System

indicate that etazene was first detected in the Canada, Europe (Finland and Poland) and the USA in 2020.

Etazene 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 (CAS) Registry number

14030-76-3 (free base)
1071546-16-1 ((1:1) hydrochloride salt)
2598176-60-2 ((1:2) hydrochloride salt)
100154-69-6 (hydrochloride salt)

C. Other chemical names

2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine (ACI)
Benzimidazole, 1-[2-(diethylamino)ethyl]-2-(*p*-ethoxybenzyl)- (6CI, 7CI, 8CI)
N,*N*-Diethyl-2-{[(4-ethoxyphenyl)methyl]-1*H*-benzimidazol-1-yl}-ethan-1-amine
2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine
2-[2-[(4-Ethoxyphenyl)methyl]benzimidazol-1-yl]-*N*,*N*-diethylethanamine
N,*N*-Diethyl-2-(2-{[4-(ethyloxy)phenyl]methyl}-1H-benzimidazol-1-yl)ethanamine
Etodesnitazene
Etazene
Etazone
Etazen
Desnitroetonitazene

D. Trade names

Etazene is sold as citrate salt under the name "Etodesnitazene (citrate)" *(1)* or as a hydrochloride salt under the name "Etazene hydrochloride" *(2)*. Etazene is sold as a free base under the name 1*H*-benzimidazole-1-ethanamine, 2-[(4-ethoxyphenyl)methyl]-*N*,*N*-diethyl- *(3)*.

E. Street names

Etazene has been identified in m30 pills, as noted on online user forums *(4)*.

F. Physical appearance

Etazene dihydrochloride in seized material has been reported as a grey crystalline powder *(5)* or a light-yellow powder *(6)*. Etazene citrate sold as a reference material has been described as a crystalline solid *(1)*.

Law enforcement agencies have found etazene in several solid forms (e.g., white-to-beige powders and rock) and in liquid forms, typically of unknown purity or concentration *(7)*.

G. WHO review history

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

2. Chemistry

A. Chemical name

IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine

Chemical Abstracts Service index name: 1*H*-Benzimidazole-1-ethanamine, 2-[(4-ethoxyphenyl)methyl]-*N*,*N*-diethyl- (ACI)

B. Chemical structure

Free base:

Molecular formula: $C_{22}H_{29}N_3O$

Molecular weight: 351.494 g/mol

C. Stereoisomers

No information was found.

D. Methods and ease of illicit manufacture

Etazene is the *desnitro* analogue of etonitazene (etodesnitazene) and is thus unsubstituted at C5 of the benzimidazole ring. It is one of a series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics *(8)*. The synthesis of etazene was described by Hunger et al. *(9)* and recently by Vandeputte et al. *(10)*. In the synthesis of protonitazene, the activated chloro atom of 2-nitrochlorobenzene is readily substituted by 2-diethylaminoethylamine. Then, reduction of the nitro group to the resulting amino function and condensation of the *ortho*-phenylenediamine species with ethoxyphenylacetic acid in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline affords etazene. Hydrochloric acid can be used to convert etazene into its corresponding salt forms *(6)*.

Etazene can also be obtained by routes reported for the synthesis of its 5-nitro-2-benzylbenzimidazole analogues, such as etonitazene *(10–14)*.

Although no information was found on the actual method and scale of manufacture of etazene, the synthetic methods are simple and cost–efficient and do not require the use of regulated precursors *(8)*.

E. Chemical properties

Melting-point

65–66 °C (free base) *(15)*
118–120 °C (hydrochloride salt) *(15)*

Boiling-point

No information was found.

Solubility

Etazene hydrochloride salt is reported to be soluble in water and methanol and partially soluble in dichloromethane *(16).*

Etazene citrate salt is soluble in dimethylformamide and in dimethyl sulfoxide at 10 mg/mL. In phosphate-buffered saline (pH 7.2), it is soluble at 1 mg/mL *(1)*.

F. Identification and analysis

Synthetic etazene has been characterized by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), high-performance liquid chromatography coupled to diode-array detection, gas chromatography with mass spectrometry (GC-MS) and liquid chromatography (LC) coupled to high-resolution mass spectrometry *(8)*.

Analytical methods for identification of etazene in seized sample matrices include X-ray crystallography, infrared spectroscopy, ^{1}H-NMR, GC-MS and LC-MS *(5, 16)*. LC coupled with tandem MS was recently reported for identification but not quantification of etazene in biological sample matrices such as human blood and urine *(17)*.

Metabolites of etazene were tentatively identified in the urine and serum of rats by GC–MS and LC-high-resolution MS *(6)*.

3. Ease of conversion into controlled substances

At the time of the writing, no information was available on the conversion of etazene into other controlled substances.

4. General pharmacology

A. Routes of administration and dosage

People posting on online forums report mainly intranasal administration as the route of administration of various doses. Participants in forums such as Erowid, Bluelight and Drugs Forum reported using doses of 30–100 mg, dissolved in water or propylene glycol (to avoid burning the nose and throat).

One user reported taking one "m30" pill tested as etazene daily *(4)*.

B. Pharmacokinetics

In silico profiling of the absorption, distribution, metabolism and excretion of etazene showed that it is three times more lipophilic than morphine. The analysis also predicted that, like morphine, etazene has high gastrointestinal absorption and can permeate the blood–brain barrier. Unlike morphine, etazene does not appear to be a substrate for *p*-glycoprotein. Metabolite profiling showed that etazene inhibits CYP1A2, CYP2C19, CYP2D6 and CYP3A4. Etazene, like morphine, had a bioavailability score of 0.55, indicating that it is active in humans when taken orally *(18)*.

The same authors analysed the metabolites of etazene after a 24-h exposure at 28 °C of *Danio rerio* larvae to 75 µM. The results were compared with those for larvae not exposed to etazene and with those exposed to a control medium sample containing only the drug to detect compound degradation during the incubation step. Metabolites were detected in a high-performance LC–electrospray ionization-quadropole time-of-flight-MS system and were identified by comparing their precursor mass, the calculated molecular formulae and the fragmentation patterns with those of the parent compound and of known metabolites of etazene homologues. Fragmentation patterns revealed an imine fragment at m/z 72 and a diethylamine fragment at m/z 100. Further fragmentation of this metabolite resulted in an *N*-ethylethanamine fragment at m/z 253. Further fragments of the etazene metabolite (not identified) were found at m/z 107, 195 and 224 *(18)*.

C. Pharmacodynamics

Preclinical pharmacology studies showed that the pharmacological profile of etazene is similar to those of the potent Schedule I (under the 1961 United Nations Conventions) synthetic opioids etonitazene and isotonitazene and other µ-opioid receptor agonists *(7)*. Because of these pharmacological similarities to etonitazene and isotonitazene, use of etazene may present a high risk of abuse and may negatively affect people who use drugs and their communities, as it is well established that substances that act as µ-opioid

receptor agonists have a high potential for nonmedical use and addiction and can induce dose-dependent respiratory depression.

Data from preclinical studies provided by the US Drug Enforcement Administration *(7)* on etazene binding and agonism at the three main opioid receptors (δ, κ, and μ) showed that etazene has slightly higher binding affinity to μ-opioid receptors than fentanyl and morphine. The affinities of etazene to δ and κ-opoid receptors were lower than those of fentanyl and morphine. Etazene was more potent at μ-opioid receptors than at δ and κ-opioid receptors and showed similar agonism to μ-opioid receptors but lower agonism to δ and κ-opioid receptors than fentanyl and morphine. Further details of the binding and agonism of etazene at opioid receptors are presented in Annex 3.

In the warm-water tail-flick assay with cumulative dosing followed by a time-course of the peak effect of etazene, this opioid had analgesic effects. Etazene increased tail-flick latency to a maximum effect of 100% after administration of 0.32 mg/kg in a dose-dependent manner. Potency ratios (ED_{50} test compound/ED_{50} reference compound) indicated that etazene was more potent than morphine but less potent than fentanyl. Etazene was considered to be as efficacious as morphine and fentanyl. The peak analgesic effects of etazene lasted 15 min.

Subcutaneous injection of naltrexone before administration of 0.32 mg/kg etazene blocked the analgesic effect of etazene, supporting involvement of opioid receptors in the action of etazene *(19)*. Further details of the analgesic effects of etazene are presented in Annex 3.

5. Toxicology

No reports were found on toxic doses of etazene for humans.

A recent study showed that etazene dose-dependently (doses of 10–300 μM) caused developmental toxicity in *Danio rerio* larvae by increasing their mortality, developmental malformations and cardiotoxic effects to a greater extent than morphine (doses of 1–50 mM) *(18)*.

In three post-mortem cases in which etazene was analytically confirmed, the blood concentrations were 1.8, 39 and 60 ng/mL *(20)*.

The UNODC Early Warning Advisory Tox-Portal of the United Nations Office on Drugs and Crome *(21)* included three reports in which etazene was identified. In Australia in 2021, etazene was detected in the femoral blood of a deceased 41-year-old male, but no data were provided on the probable contribution of etazene to the death. Etazene was identified in the urine of a 38-year-old male the USA in 2021 in a case of driving under the influence of drugs, in combination with methadone and bupropion. It was considered that there was a strong probability that etazene contributed to the clinical status of the individual. In another case in the USA in 2021, etazene was found in the peripheral blood of a deceased 21-year-old male, in combination with 26 ng/mL fentanyl. The possibility that etazene contributed to the death was considered to be medium. No data on the doses of etazene were available in any of the cases.

6. Adverse reactions in humans

Most adverse reactions after etazene use have been reported on unverified online forums. For example, one person described itchiness and a “nice euphoric glow”, in

addition to pain relief and a sense of well-being, after taking 1 mg of etazene *(22)*. Another user reported a feeling of euphoria similar to that induced by isotonitazene (*23*). Most of the effects induced by etazene appear to occur almost immediately after administration *(22)*.

Data collected between May 2020 and July 2021 confirmed the presence of etazene in 10 post-mortem specimens of blood and/or urine associated with death investigations (9) or clinical intoxications (1) in Canada and the USA.

In the US Center for Disease Control State Unintentional Drug Overdose Reporting System, which contains data from death certificates, post-mortem toxicology testing and death scene and witness findings from medical examiner or coroner reports on deaths related to unintentional drug overdoses and those of undetermined intent in 48 US jurisdictions, etazene was listed as the cause of death in one case from all states for which there were usable data (i.e., no trend in causes of death) between July and December 2020 and one case between January and June 2021. In no cases was etazene listed as the cause of death in states for which data were available in each period (6–10 for January 2019–June 2021). It should be noted that data on trends and non-trends in causes of death do not necessarily imply confirmation of etazene as the cause of death in a toxicological report. In cases from toxicological reports (i.e., detected non-trend) from all states with usable data, etazene was detected in one case between July and December 2020 and in two cases between January and June 2021. Etazene was not detected in any post-mortem case in an analysis limited to states with data for each period (6–10 in January 2019–June 2021) *(24)*.

7. Dependence potential

A. Studies in experimental animals

No studies were identified.

B. Studies in humans

No studies were identified.

8. Abuse potential

A. Studies in experimental animals

In drug discrimination studies (two-lever choice method), etazene fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration to 10 Sprague-Dawley rats at doses of 0.01–0.32 mg/kg. Assessment of the potency ratio (ED_{50} test compound:ED_{50} reference compound) showed that etazene was more potent than morphine but less potent than fentanyl; etazene was considered to be as efficacious as morphine and fentanyl.

Subcutaneous injection to rats of naltrexone before administration of 0.32 mg/kg etazene blocked the morphine-like discriminative stimulus effects of etazene, indicating involvement of opioid receptors in the discriminative stimulus effects of etazine *(25)*. Details of the discriminative stimulus effects of etazene are presented in Annex 3.

B. Studies in humans

No studies were identified. Potential nonmedical use of etazene is described in online forums.

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

In the late 1950s, the Swiss pharmaceutical company CIBA Aktiengesellschaft synthesized a group of benzimidazole derivatives with analgesic properties *(9)*. These derivatives included Schedule I (under the 1961 United Nations Conventions) synthetic opioids such as clonitazene, etonitazene and istonitazene. None of the derivatives was medically approved.

Etazene is not known to have any medical use.

10. Listing on the WHO Model Lists of Essential Medicines

Etazene 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)

Etazene is not known to be authorized for marketing.

12. Industrial use

Etazene is not known to have any industrial use.

13. Non-medical use, abuse and dependence

No information was found. There are only a few self-reports of intentional etazene use on online forums (e.g., Erowid, Bluelight).

Although no studies on the abuse potential of etazene 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, isotonitazene), which have high potential for abuse, suggest that etazene has a similar potential for abuse in humans. This is supported by online reports by people who used this substance.

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

No information was found. Adverse effects experienced by people who have taken etazene are described in section 6.

Reports on online forums suggest the development of tolerance to etazene. For example, one person reported a "strong desire to redose" *(22)*. This 16-year-old male, weighing 85 kg, started by taking 500 μg of etazene and 10 min later took 1 mg more; 15 min after the

last dose, he took 1.5 mg and repeated this dose every half hour until he went to sleep about 6 h after the first dose. All the doses were taken intranasally. He used etazene every day (about 5–10 doses a day) for the following 2 weeks. Another user reported experiencing cravings and the desire to frequently re-dose, consuming an average of one pressed "m30" pill (tested for etazene) per day for 11 days *(4)*. Another individual reported having to take 150–180 mg of oxycodone-equivalent single dose to "get high" *(4)*.

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

15. Licit production, consumption and international trade

Etazene is used as a reference material in scientific research and forensic applications.

16. Illicit manufacture and traffic and related information

Etazene was first detected in Canada in 2020, and 333 identifications of this substance by GC-MS plus Fourier transform IR were reported in 2021–2022 by Health Canada's Drug Analysis Service *(26)*.

According to the European Monitoring Center for Drugs and Drug Addiction, etazene has been identified in some European countries either in seizures or test purchases from online suppliers. For example, on 30 March 2020, a grey powder identified as etazene was seized in Poland, and in June 2020 a liquid form (nasal spray) of etazene was seized by customs police in Finland. The origin of the packages in both cases was Poland, and the destination was an individual in Finland *(7, 27)*. Etazene was also detected in 2020 in Austria, Czechia, Estonia and Sweden *(21)*.

Reports from the US National Forensic Laboratory Information System indicate that etazene was first detected in the USA on 1 October 2020, in Ohio, with 12 reports in 2021 from Florida (1), Missouri (1), Ohio (9) and Pennsylvania (1). Weights were reported in only 9 cases, totaling 3.35 g *(7)*.

17. Current international controls and their impact

Etazene is not currently controlled under the 1961, 1971 or 1988 United Nations Convention.

18. Current and past national controls

Etazene is a schedule I controlled substance in Canada. It has also been placed temporarily in Schedule I in the USA, effective from 12 April 2022 to 12 April 2024 *(28)*.

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

The absence of medical approval for etazene, abuse and identification of this opioid in toxicology case work, its presence on the illicit market and reports from law enforcement

agencies suggest that etazene poses a threat to public health. Moreover, people who use etazene are likely to obtain it from unregulated sources; therefore, the identity, purity and doses of these substances are uncertain and likely to be inconsistent, posing serious adverse health risks to the end user *(7)*.

References

1. Etodesnitazene (citrate) Item No. 29916. Ann Arbor (MI): Cayman Chemical Co.; 2022 (https://www.caymanchem.com/product/29916/etodesnitazene-(citrate), accessed 21 June 2022).
2. Etazene hydrochloride. Dandenong South (VIC): Chiron Chemicals; 2022 (http://shop.chiron.no/main.aspx?page=articlelist&requery=1&searchstr=etazene&searchfld=, accessed 21 June 2022).
3. 1H-Benzimidazole-1-ethanamine, 2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-. Zhejiang: Sagechem; 2022 (http://www.sagechem.com/product/1761430, accessed 21 June 2022).
4. Bluelight; 2022 (http://www.bluelight.org/, accessed 20 July 2022).
5. Siczek M, Zawadzki M, Siczek M, Chłopaś-Konowałek A, Szpot P Etazene (N,N-diethyl-2-{[(4-ethoxyphenyl)methyl]-1H-benzimidazol-1-yl}-ethan-1-amine (dihydrochloride)): A novel benzimidazole opioid NPS identified in seized material: Crystal structure and spectroscopic characterization. Forensic Toxicol. 2021;39(1):146–55 (doi: 10.1007/s11419-020-00552-9).
6. Grigoryev A, Kavanagh P, Dowling G, Rodin I. Tentative identification of etazene (etodesnitazene) metabolites in rat serum and urine by gas chromatography–mass spectrometry and accurate mass liquid chromatography–mass spectrometry. J Anal Toxicol. 2022 (doi: 10.1093/jat/bkac001).
7. 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.
8. 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/acschemneuro.1c00037).
9. Hunger A, Kebrle J, Rossi A, Hoffmann K. Benzimidazol-Derivate und verwandte Heterocyclen III. Synthese von 1-Aminoalkyl-2-nenzyl-nitro-benzimidazolen [Benzimidazole derivatives and related heterocycles III. Synthesis of 1-aminoalkyl-2-nenzyl-nitro-benzimidazoles]. Helv Chim Acta. 1960;43(4):1032–46 (doi: 10.1002/hlca.19600430412).
10. Vandeputte MM, Van Uytfanghe 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 Chem Neurosci. 2021;12(7):1241–51 (doi: 10.1021/acschemneuro.1c00064).

11. 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).
12. 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).
13. 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).
14. 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 J Heterocyclic Chem. 2018;28:321.
15. Hoffmann K, Hunger A, Rossi A. New basically substituted benzylbenzimidazoles. US Patent number: US2980690A; 1961.
16. 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 9 September 2022)
17. Walton SE, Krotulski AJ, Logan BK. A forward-thinking approach to addressing the new synthetic opioid 2-benzylbenzimidazole nitazene analogs by liquid chromatography-tandem quadrupole mass spectrometry (LC-QQQ-MS). J Anal Toxicol. 2022;46(3):221–31 (doi: 10.1093/jat/bkab117).
18. Kurach Ł, Chłopaś-Konowałek A, Budzyńska B, Zawadzki M, Szpot P, Boguszewska-Czubara A. Etazene induces developmental toxicity in vivo *Danio rerio* and in silico studies of new synthetic opioid derivative. Sci Rep. 2021;11(1):24269 (doi: 10.1038/s41598-021-03804-9).
19. Gatch MB. Test of analgesic effects alone and in combination with naltrexone 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; 2022.
20. NPS discovery: Etodesnitazene – New synthetic opioid identified during forensic death investigations in the United States and Canada. Willow Grove (PA): Center for Forensic Science Research and Education; 2021.
22. Grass Valley (CA): Exploring a Not Very Known Opioid Etodesnitazene. Erowid Center; 2022 (https://erowid.org/experiences/exp_front.shtml, accessed 20 July 2022).
23. Drugs Forum (online forum). Available at: https://drugs-forum.com/. Accessed on 20.07.2022.
24. FDA_NPS May2022 updated. Atlanta (GA): State Unintentional Drug Overdose Reporting System, US Centers for Disease Control and prevention; 2022.
25. Gatch MB. Test of substitution for the discriminative stimulus effects of morphine 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, 2022.
26. Canada prioritization table. Ottawa: Health Canada, Drug Analysis Service; 2022.
27. EU Early Earning System Situation Reports. ELisbon: European Monitoring Center for Drugs and Drug Addiction; 2022.
28. Schedules of controlled substances: Temporary placement of butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, N-pyrrolidino etonitazene,

and protonitazene in Schedule I. CFR Part 1308. Springfield (VA): Drug Enforcement Administration; 2022.