



Controlled Substance Advisory Committee

November 18, 2024

1:00 pm – 2:00 pm

Ohio Board of Pharmacy Hearing Room
77 South High Street, 17th Floor
Columbus, OH 43201

Welcome and Introductions	1:00pm
Review of the Committee Responsibilities	1:10pm
Presentation of 8-Factor Analysis – Nitazene Pharmacophore by Jessica A. Toms, Drug Chemistry Manager, Ohio Bureau of Criminal Investigation	1:15pm
Discussion and Review of Nitazene Pharmacophore Proposal	1:35pm
Next Steps / Adjourn	1:55pm

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Proposal to Classify 2-Benzylbenzimidazole “Nitazene” Opioid Pharmacophores as Schedule I Controlled Substances

Section 1: Summary

The Ohio Board of Pharmacy, pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the following into Schedule I:

- All compounds that meet the structural requirements of the 2-benzylbenzimidazole opioids pharmacophores. *For the purposes of this report, these substances will be referred to as 2-benzylbenzimidazole “Nitazene” opioid pharmacophores*

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following eight criteria:

- (1) The actual or relative potential for abuse;
- (2) The scientific evidence of the pharmacological effect of the substance;
- (3) The state of current scientific knowledge regarding the substance;
- (4) The history and current pattern of abuse;
- (5) The scope, duration, and significance of abuse;
- (6) The risk to the public health;
- (7) The potential of the substance to produce psychic or physiological dependence liability; and
- (8) Whether the substance is an immediate precursor.

Section 3: Evaluating 2-benzylbenzimidazole “Nitazene” Opioid Pharmacophores Under the Eight Criteria

(1) The actual or relative potential for abuse.

The 2-benzylbenzimidazole opioids are not structurally related to the traditional phenanthrene (morphine) or fentanyl opioids (Vandeputte et al., 2021). The 2-benzylbenzimidazole opioids were first synthesized in the 1950's and 1960's by the Swiss pharmaceutical company CIBA and one agent, etonitazene, was shown to have an antinociceptive potency 1000-fold greater than that of morphine (Vandeputte et al., 2021). To date, these substances are not approved for medical use anywhere in the world (DEA, 2021). Recent in vitro studies have demonstrated that when compared to fentanyl binding to the μ_1 opioid receptor (MOR), the potency of the 2-benzylbenzimidazole opioids pharmacophores ranged from 20 to 50 times more potent than fentanyl (Vandeputte et al., 2021).

For decades, the regulation of dopamine release in the nucleus accumbens (NAc) has been demonstrated to be central to the euphoria associated with drug reinforcement (Nestler, 2005). The activation of the MOR within the ventral tegmental area results in dopamine release in the NAc (Jalabert et al., 2011; Mori et al., 2016). Therefore, the 2-benzylbenzimidazole opioids pharmacophores have a high potential for abuse (Federal Register, 2021). Recently, nitazenes have been shown to increase dopamine release in the shell of the nucleus accumbens (DeLuca et al., 2022).

(2) The scientific evidence of the pharmacological effect of the substance.

As noted above (Evaluation Criterion 1), the 2-benzylbenzimidazole opioids pharmacophores have been shown to have antinociceptive activity and MOR binding potency greater than that of fentanyl.

(3) The state of current scientific knowledge regarding the substance.

The structure-activity relationship of the 2-benzylbenzimidazole opioids pharmacophores dates back to their discovery in the 1950s (DEA, 2021). Vandeputte et al., (2021) thoroughly characterized the binding potency of the 2-benzylbenzimidazole opioids pharmacophores to the MOR and compared this binding to fentanyl and hydromorphone. The findings from this study clearly demonstrate that these agents activate the MOR with a potency that is much greater than that of fentanyl and hydromorphone.

(4) The history and current pattern of abuse.

The trafficking of counterfeit tablets containing novel opioid agonist is contributing to the drug overdose issue in the United States. In March 2019, isotonitazene first appeared on the drug scene in Canada and Europe (EMCDDA, 2020 and Mueller et al., 2021). Since 2019, over 14 different forms of 2-benzylbenzimidazole opioids pharmacophores have been identified and characterized pharmacologically (Vandeputte et al., 2021). To date, at the federal and state level, 20 of these 2-benzylbenzimidazole opioids pharmacophores have been scheduled (EO-2024-06D and Federal Register, 2024).

(5) The scope, duration, and significance of abuse.

Please see evaluation criterion 3 and 4.

(6) The risk to the public health.

In April 2022, the DEA emergency scheduled seven benzimidazole-opioids: Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-Pyrrolidino Etonitazene, and Protonitazene. Between November 2020 and July 2021, these seven benzimidazoles were identified in 44 toxicology and postmortem cases in the United States (DEA, 2021). To date, isotonitazene has been identified in over 250 deaths in the United States (Vandeputte et al., 2021). Since January 2021, Ohio BCI has identified 16 different benzimidazole opioid compounds in 1062 items (Ohio BCI Laboratory Statistics). Because 2-benzylbenzimidazole opioids pharmacophores activate the MOR leading to their rewarding potential, this also contributes to their ability to induce respiratory depression (Horsfall and Sprague, 2017).

(7) The potential of the substance to produce psychic or physiological dependence liability; and

The regulation of dopamine release in the nucleus accumbens (NAc) has been demonstrated to be central to the euphoria associated with drug abuse (Nestler, 2005). The activation of the MOR by the 2-benzylbenzimidazole opioids pharmacophores within the ventral tegmental area would result in dopamine release in the NAc (Jalabert et al., 2011; Mori et al., 2016). Therefore, the 2-benzylbenzimidazole opioids pharmacophores have a high potential for abuse (DEA, 2021). DeLuca et al., (2022) demonstrated that nitazenes do indeed increase the release of dopamine in the nucleus accumbens.

(8) Whether the substance is an immediate precursor.

2-benzylbenzimidazole opioids pharmacophores are not considered immediate precursors.

Section 4: Finding of the Board

Section 3719.44 of the Ohio Revised Codes authorizes the Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a thorough review of all available data, the Ohio Board of Pharmacy finds that all compounds that meet the structural requirements of the 2-benzylbenzimidazole opioids pharmacophores that have not been previously scheduled by the Drug Enforcement Agency (DEA). For the purposes of this report, these substances will be referred to as 2-benzylbenzimidazole “Nitazene” opioid pharmacophores:

1. Have a high potential for abuse;
2. Have no accepted medical use in treatment in this state;
3. Lack accepted safety for use in treatment under medical supervision; and
4. Pose a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that compounds meeting the definition of 2-benzylbenzimidazole opioids pharmacophores warrant control in Schedule I and authorizes the filing of amended rule 4729:9-1-01 of the Administrative Code as found in Section 5 of this document.

Section 5: Proposed Rule

4729:9-1-01 – Schedule I Controlled Substances

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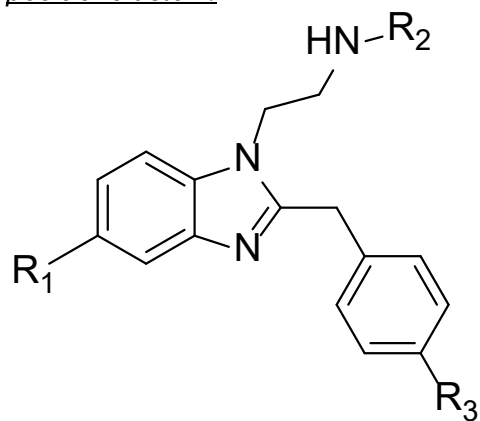
(B) Narcotics-opiates

Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term isomer includes the optical and geometric isomers):

(88) Except as otherwise provided in section 3719.41 of the Revised Code, any compound that meets the following 2-benzylbenzimidazole opioids pharmacophore requirements to bind at the μ receptor, as identified by a report from an established forensic laboratory, is a schedule I controlled substance:

(a) A chemical scaffold consisting of a 2-(benzyl)-1H-benzimidazole-1-ethanamine, whether or not further substituted:

(b) Polar functional group or alkyl or aryl or a halogen substitutions in the R1 or R2 or R3 positions below.



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References:

De Luca MA, Tocco G, Mostallino R, Laus A et al. Pharmacological characterization of novel synthetic opioids: isotonitazene, metonitazene, and piperidylthiambutene as potent μ -opioid receptor agonists. *Neuropharmacol.* 2021;221:109263.

Drug Enforcement Administration, Department of Justice. (2021, December). Schedules of Controlled Substances: Temporary Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-pyrrolidino etonitazene, and Protonitazene in Schedule I. Retrieved from [federalregister.gov](https://www.federalregister.gov)

EMCDDA. (2020) Report on the Risk Assessment of N,N-Diethyl-2-[[4-(1-Methylethoxy)Phenyl]Methyl]-5-Nitro-1Hbenzimidazole-1-Ethanamine (Isotonitazene) in Accordance with Article 5c of Regulation (EC) No 1920/2006 (as Amended), EMCDDA Publications Office, Luxembourg.

EO-2024-06D.

https://content.govdelivery.com/attachments/OHIOGOVERNOR/2024/06/04/file_attachments/2898004/Signed-EO-2024-06D.pdf

Federal Register. Schedules of controlled substances: temporary placement of N-Desethyl Isotonitazene and N-Piperidinyl Etonitazene in Schedule I. DEA. July 29, 2024.

<https://www.federalregister.gov/documents/2024/07/29/2024-16391/schedules-of-controlled-substances-temporary-placement-of-n-desethyl-isotonitazene-and-n-piperidinyl>

Jalabert M, Bourdy R, Courtin J, Veinante P, Manzoni OJ, Barrot M et al. Neuronal circuits underlying acute morphine action on dopamine neurons. *PNAS* 2011;108:16446–50.

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Mueller, F., Bogdal, C., Pfeiffer, B., Andrello, L., Ceschi, A., Thomas, A., and Grata, E. (2021) Isotonitazene: Fatal Intoxication in Three Cases Involving This Unreported Novel Psychoactive Substance in Switzerland. *Forensic Sci. Int.* 320, 110686.

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Vandeputte MM, Uytendange 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 Neuro.* 2021; 12:1241-1251.