



# Common Sense Initiative

Mike DeWine, *Governor*  
Jon Husted, *Lt. Governor*

Joseph Baker, *Director*

**Comments on the proposed rules will be accepted until close of business on January 10, 2025. Please send all comments to the following email address:**

[RuleComments@pharmacy.ohio.gov](mailto:RuleComments@pharmacy.ohio.gov)

**In addition, please copy your comments to:** [CSIPublicComments@governor.ohio.gov](mailto:CSIPublicComments@governor.ohio.gov)

## Business Impact Analysis

Agency, Board, or Commission Name: Ohio Board of Pharmacy

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Regulation/Package Title (a general description of the rules' substantive content):

2-Benzylbenzimidazole "Nitazene" Opioid Pharmacophores

Rule Number(s): 4729:9-1-01

Date of Submission for CSI Review: 12/11/24

Public Comment Period End Date: 1/10/25

**Rule Type/Number of Rules:**

New/\_\_\_ rules

No Change/\_\_\_ rules (FYR? \_\_\_)

Amended/ 1 rules (FYR? \_\_\_)

Rescinded/\_\_\_ rules (FYR? \_\_\_)

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The Common Sense Initiative is established in R.C. 107.61 to eliminate excessive and duplicative rules and regulations that stand in the way of job creation. Under the Common Sense Initiative, agencies must balance the critical objectives of regulations that have an adverse impact on business with the costs of compliance by the regulated parties. Agencies should promote transparency, responsiveness, predictability, and flexibility while developing regulations that are fair and easy to follow. Agencies should prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.

### **Reason for Submission**

1. R.C. 106.03 and 106.031 require agencies, when reviewing a rule, to determine whether the rule has an adverse impact on businesses as defined by R.C. 107.52. If the agency determines that it does, it must complete a business impact analysis and submit the rule for CSI review.

Which adverse impact(s) to businesses has the agency determined the rule(s) create?

The rule(s):

- a.  Requires a license, permit, or any other prior authorization to engage in or operate a line of business.
- b.  Imposes a criminal penalty, a civil penalty, or another sanction, or creates a cause of action for failure to comply with its terms.
- c.  Requires specific expenditures or the report of information as a condition of compliance.
- d.  Is likely to directly reduce the revenue or increase the expenses of the lines of business to which it will apply or applies.

### **Regulatory Intent**

2. Please briefly describe the draft regulation in plain language.  
*Please include the key provisions of the regulation as well as any proposed amendments.*

4729:9-1-01 – Lists the drugs/compounds that are Schedule I controlled substances. Adds all compounds that meet the structural requirements of the 2-benzylbenzimidazole “nitazene” opioids pharmacophores as Schedule I controlled substances.

3. Please list the Ohio statute(s) that authorize the agency, board or commission to adopt the rule(s) and the statute(s) that amplify that authority.

The proposed rules are authorized by sections 3719.44, 3719.41, 3719.45, and 3719.28 of the Ohio Revised Code.

- 4. Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program? If yes, please briefly explain the source and substance of the federal requirement.**

These rules do not implement a federal requirement. However, the rules do incorporate the federal controlled substance schedules.

- 5. If the regulation implements a federal requirement, but includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.**

Not applicable.

- 6. What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?**

ORC 4729.41 requires the Board to adopt controlled substance schedules into administrative rule. Additionally, per ORC 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 8 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.

Further justification for the scheduling of nitazene pharmacophores can be found in the 8-factor analysis included as Appendix I to this BIA.

**7. How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?**

The success of the regulation will be measured by having rules that are enforceable by state and local jurisdictions as well as crime laboratories who process drug evidence.

**8. Are any of the proposed rules contained in this rule package being submitted pursuant to R.C. 101.352, 101.353, 106.032, 121.93, or 121.931?**

*If yes, please specify the rule number(s), the specific R.C. section requiring this submission, and a detailed explanation.*

No.

**Development of the Regulation**

**9. Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.**

*If applicable, please include the date and medium by which the stakeholders were initially contacted.*

The proposed rule was developed by the Ohio Attorney General's Office. The 8-factor analysis and rule were reviewed by the Board's Controlled Substance Advisory Committee. The purpose of the Controlled Substance Advisory Committee is to act in an advisory capacity to the Board by recommending the addition or rescheduling of compounds that meet the scheduling criteria set forth in Chapter 3719. of the Revised Code. The Committee met on November 18, 2024, to review the 8-factor analysis and unanimously recommended its adoption by the Board.

**10. What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?**

The Ohio Attorney General's office provided data to support the adoption of this amended rule. Such data is required by law to justify the scheduling of these compounds. This data can be found in the 8-factor analysis included as Appendix I to this BIA.

**11. What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?**

Please see the 8-factor analysis included as Appendix I to this BIA.

**12. What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn't the Agency consider regulatory alternatives? *Alternative regulations may include performance-based regulations, which define the required outcome, but do not dictate the process the regulated stakeholders must use to comply.***

The Board determined that regulatory alternatives were not appropriate because the addition of these compounds is intended to safeguard public health and safety.

**13. What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?**

The Board of Pharmacy's Director of Policy and Communications reviewed the proposed rule to ensure that the regulation does not duplicate another Ohio Board of Pharmacy regulation.

**14. Please describe the Agency's plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.**

The rule will be posted on the Board of Pharmacy's web site, information concerning the rule will be included in materials e-mailed to licensees, and notices will be sent to associations, individuals, and groups. Board of Pharmacy staff are also available via phone or email to answer questions regarding implementation of the rule.

**Adverse Impact to Business**

**15. Provide a summary of the estimated cost of compliance with the rule(s). Specifically, please do the following:**

**a. Identify the scope of the impacted business community, and**

Persons who manufacture, distribute, dispense, and possess non-FDA approved (e.g. not approved for medical use) nitazene compounds.

**b. Quantify and identify the nature of all adverse impact (e.g., fees, fines, employer time for compliance, etc.).**

Violation of these rules could result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.

***The adverse impact can be quantified in terms of dollars, hours to comply, or other factors; and may be estimated for the entire regulated population or for a representative business. Please include the source for your information/estimated impact.***

**16. Are there any proposed changes to the rules that will reduce a regulatory burden imposed on the business community? Please identify. (*Reductions in regulatory burden may include streamlining reporting processes, simplifying rules to improve readability, eliminating requirements, reducing compliance time or fees, or other related factors*).**

N/A

**17. Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?**

The Board determined that the regulatory intent justifies the impact on business because the regulations protect and promote public safety by classifying compounds that have no medical use in this state as controlled substances.

**Regulatory Flexibility**

**18. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.**

The rule does not provide any exemptions or alternative means of compliance for small businesses. Small businesses are not typically in the business of possessing and distributing Schedule I controlled substances.

**19. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?**

The possession, manufacture, or distribution of Schedule I controlled substances is not considered a paperwork violation.

**20. What resources are available to assist small businesses with compliance of the regulation?**

Board of Pharmacy staff is available by telephone and e-mail to answer questions. Board staff members also provide presentations to licensees as well as trade associations who seek updates on current regulations. Additionally, staff are trained to educate licensees on compliance with all Board of Pharmacy rules and regulations.

Please be advised small businesses are not typically in the business of possessing and distributing Schedule I controlled substances.

## **4729:9-1-01 – Schedule I Controlled Substances (AMEND)**

Pursuant to section [3719.41](#) of the Revised Code, controlled substance schedule I is hereby established, which schedules include the following, subject to amendment pursuant to section [3719.43](#) or [3719.44](#) of the Revised Code.

(A) As used in this rule:

(1) "Synthetic" unless specifically excepted or unless listed in another schedule, means any substance, material, compound, mixture, or preparation that contains any quantity of a substance made artificially by chemical reaction.

(2) "Pharmacophore" means the portion of a chemical structure that confers the activity of the substance.

(3) "A report from an established forensic laboratory" means a laboratory report from the bureau of criminal identification and investigation, or a laboratory operated by another law enforcement agency, or a laboratory established by or under the authority of an institution of higher education that has its main campus in this state and that is accredited by the association of American universities or the north central association of colleges and secondary schools, primarily for the purpose of providing scientific services to law enforcement agencies and signed by the person performing the analysis as defined in division (A) of section [2925.51](#) of the Revised Code.

(4) "Synthetic cannabinoids" are drugs commonly found in herbal incense products (common names include but are not limited to: spice, blaze, devil's advocate, genie, smoke, sense, zohai, spike 99, and K2) that may mimic the effects of delta-9-tetrahydrocannabinol (THC), an active central nervous system constituent compound of marijuana.

(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):

(1) Acetyl-alpha-methylfentanyl (N-[1-(1-methyl-2-phenethyl)-4-piperidinyl]-N-phenylacetamide);

- (2) Acetylmethadol;
- (3) Acetyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide);
- (4) Acryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide; other name: acryloylfentanyl);
- (5) AH-7921 (3,4-dichloro-N-[(1-dimethylamino) cyclohexylmethyl]benzamide);
- (6) Allylprodine;
- (7) Alphacetylmethadol (except levo-alphacetylmethadol, also known as levo-alpha-acetylmethadol, levomethadyl acetate, or LAAM);
- (8) Alphameprodine;
- (9) Alphamethadol;
- (10) Alpha-methylfentanyl (N-[1-(alpha-methyl-beta-phenyl)ethyl-4-piperidyl] propionanilide; 1-(1-methyl-2-phenylethyl)-4-(N-propanilido) piperidine);
- (11) Alpha-methylthiofentanyl (N-[1-methyl-2-(2-thienyl)ethyl-4-piperidinyl]-N-phenylpropanamide);
- (12) Benzethidine;
- (13) Betacetylmethadol;
- (14) Beta-hydroxyfentanyl (N-[1-(2-hydroxy-2-phenethyl-4-piperidinyl)-N-phenylpropanamide);
- (15) Beta-hydroxy-3-methylfentanyl (other name: N-[1-(2-hydroxy-2-phenethyl)-3-methyl-4-piperidinyl]-N- phenylpropanamide);
- (16) N-[1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl]-N-phenylpropionamide (other name: beta-Hydroxythiofentanyl);
- (17) Betameprodine;
- (18) Betamethadol;
- (19) Betaprodine;
- (20) Butyryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylbutyramide);



- (21) Clonitazene;
- (22) Dextromoramide;
- (23) Diampromide;
- (24) Diethylthiambutene;
- (25) Difenoxin;
- (26) Dimenoxadol;
- (27) Dimepheptanol;
- (28) Dimethylthiambutene;
- (29) Dioxaphetyl butyrate;
- (30) Dipipanone;
- (31) Ethylmethylthiambutene;
- (32) Etonitazene;
- (33) Etoxidine;
- (34) 4-Fluoroisobutyryl fentanyl (N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide; other name: para-fluoroisobutyryl fentanyl);
- (35) Furanyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylfuran-2-carboxamide);
- (36) Furethidine;
- (37) Hydroxypethidine;
- (38) Ketobemidone;
- (39) Levomoramide;
- (40) Levophenacymorphan;
- (41) 3-methylfentanyl (N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide);
- (42) 3-methylthiofentanyl (N-[3-methyl-1-[2-(thienyl)ethyl]-4-piperidiny]-N-phenylpropanamide);
- (43) Morpheridine;

- (44) MPPP (1-methyl-4-phenyl-4-propionoxypiperidine);
- (45) MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine);
- (46) Noracymethadol;
- (47) Norlevorphanol;
- (48) Normethadone;
- (49) Norpipanone;
- (50) Ocfentanil (N-(2-fluorophenyl)-2-methoxy-N-(1-phenethylpiperidin-4-yl)acetamide);
- (51) Para-fluorofentanyl (N-(4-fluorophenyl)-N-[1-(2-phenethyl)-4-piperidinyl]propanamide);
- (52) PEPAP (1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine);
- (53) Phenadoxone;
- (54) Phenampromide;
- (55) Phenomorphan;
- (56) Phenoperidine;
- (57) Piritramide;
- (58) Proheptazine;
- (59) Properidine;
- (60) Propiram;
- (61) Racemoramide;
- (62) Tetrahydrofuranlyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenyltetrahydrofuran-2-carboxamide);
- (63) Thiofentanyl (N-phenyl-N-[1-(2-thienyl)ethyl-4-piperidinyl]-propanamide);
- (64) Tilidine;
- (65) Trimeperidine;
- (66) U-47700 (3,4-Dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide);

(67) Except as otherwise provided in this chapter, any compound that meets all of the following fentanyl pharmacophore requirements to bind at the mu receptor, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of both of the following:

(i) A five, six, or seven member ring structure containing a nitrogen, whether or not further substituted;

(ii) An attached nitrogen to the ring, whether or not that nitrogen is enclosed in a ring structure, including an attached aromatic ring or other lipophilic group to that nitrogen.

(b) A polar functional group attached to the chemical scaffold, including but not limited to, a hydroxyl, ketone, amide, or ester;

(c) An alkyl or aryl substitution off the ring nitrogen of the chemical scaffold; and

(d) The compound has not been approved for medical use by the United States food and drug administration.

(68) N,N-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene).

(69) 2-Methyl-AP-237 (1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one).

(70) AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone).

(71) Tianeptine.

(72) N,N-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (metonitazene).

(73) 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzimidazole (N-pyrrolidino etonitazene; etonitazepyne).

(74) N,N-diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (protonitazene).

(75) 2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (etodesnitazene; etazene).

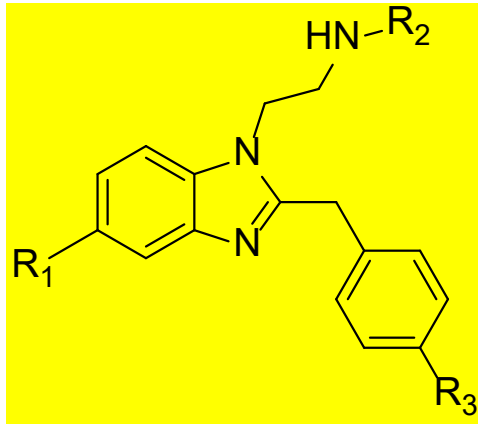
(76) 2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (butonitazene).

- (77) N,N-diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (flunitazene).
- (78) N,N-diethyl-2-(2-(4-methoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (metodesnitazene).
- (79) N-Pyrrolidino metonitazene (2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate).
- (80) N-Pyrrolidino protonitazene (5-nitro-2-(4-propoxybenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole).
- (81) Ethyleneoxynitazene (2-(2-((2,3-dihydrobenzofuran-5-yl)methyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid).
- (82) N-Desethyl isotonitazene (N-(2-(3-ethyl-2-oxoimidazolidin-1-yl)-5-nitrophenyl)-2-(4-isopropoxyphenyl)acetamide).
- (83) 5-Methyl etodesnitazene (2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-5-methyl-1H-benzimidazole-1-ethanamine, 2-hydroxypropane-1,2,3-tricarboxylic acid).
- (84) 3', 4'-Methylenedioxyntazene (2-(2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine).
- (85) N-Pyrrolidino isotonitazene (2-(4-isopropoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate).
- (86) Ethylene etonitazene (2-(2-(4-ethoxyphenethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid).
- (87) N-Desethyl etonitazene (2-[(4-ethoxyphenyl)methyl]-N-ethyl-5-nitro-1H-benzimidazole-1-ethanamine).

**(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  $\mu$  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.**



(C) Narcotics-opium derivatives

Any of the following opium derivatives, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation:

- (1) Acetorphine;
- (2) Acetyldihydrocodeine;
- (3) Benzylmorphine;
- (4) Codeine methylbromide;
- (5) Codeine-n-oxide;
- (6) Cyprenorphine;
- (7) Desomorphine;
- (8) Dihydromorphine;
- (9) Drotebanol;
- (10) Etorphine (except hydrochloride salt);
- (11) Heroin;
- (12) Hydromorphinol;

- (13) Methyldesorphine;
- (14) Methyldihydromorphine;
- (15) Morphine methylbromide;
- (16) Morphine methylsulfonate;
- (17) Morphine-n-oxide;
- (18) Myrophine;
- (19) Nicocodeine;
- (20) Nicomorphine;
- (21) Normorphine;
- (22) Pholcodine;
- (23) Thebacon;
- (24) 6-monoacetylmorphine (6-MAM).

(D) Hallucinogens

Any material, compound, mixture, or preparation that contains any quantity of the following hallucinogenic substances, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation. For the purposes of this division only, "isomer" includes the optical isomers, position isomers, and geometric isomers.

- (1) Alpha-ethyltryptamine (some trade or other names: etryptamine; Monase; alpha-ethyl-1H-indole-3-ethanamine; 3-(2-aminobutyl) indole; alpha-ET; and AET);
- (2) 4-bromo-2,5-dimethoxyamphetamine (some trade or other names: 4-bromo-2,5-dimethoxy- alpha-methylphenethylamine; 4-bromo-2,5-DMA);
- (3) 4-bromo-2,5-dimethoxyphenethylamine (some trade or other names: 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane; alpha-desmethyl DOB; 2C-B, Nexus);
- (4) 2,5-dimethoxyamphetamine (some trade or other names: 2,5-dimethoxy-alpha-methylphenethylamine; 2,5-DMA);

- (5) 2,5-dimethoxy-4-ethylamphetamine (some trade or other names: DOET);
- (6) 2,5-dimethoxy-4-(n)-propylthiophenethylamine (other name: 2C-T-7);
- (7) 4-methoxyamphetamine (some trade or other names: 4-methoxy-alpha-methylphenethylamine; paramethoxyamphetamine; PMA);
- (8) 5-methoxy-3,4-methylenedioxy-amphetamine;
- (9) 4-methyl-2,5-dimethoxy-amphetamine (some trade or other names: 4-methyl-2,5-dimethoxy- alpha-methylphenethylamine; "DOM" and "STP");
- (10) 3,4-methylenedioxy amphetamine (MDA);
- (11) 3,4-methylenedioxymethamphetamine (MDMA);
- (12) 3,4-methylenedioxy-N-ethylamphetamine (also known as N-ethyl-alpha-methyl-3,4(methylenedioxy)phenethylamine, N-ethyl MDA, MDE, MDEA);
- (13) N-hydroxy-3,4-methylenedioxyamphetamine (also known as N-hydroxy-alpha-methyl-3,4(methylenedioxy)phenethylamine and N-hydroxy MDA);
- (14) 3,4,5-trimethoxy amphetamine;
- (15) 5-methoxy-N,N-dimethyltryptamine (some trade or other names: 5-methoxy-3-[2-(dimethylamino)ethyl]indole; 5-MeO-DMT);
- (16) Alpha-methyltryptamine (other name: AMT);
- (17) Bufotenine (some trade or other names: 3-(beta-dimethylaminoethyl)-5-hydroxyindole; 3-(2- dimethylaminoethyl)-5-indolol; N, N-dimethylserotonin; 5-hydroxy-N, N-dimethyltryptamine; mappine);
- (18) Diethyltryptamine (some trade or other names: N, N-diethyltryptamine; DET);
- (19) Dimethyltryptamine (some trade or other names: DMT);
- (20) 5-methoxy-N,N-diisopropyltryptamine (other name: 5-MeO-DIPT);
- (21) Ibogaine (some trade or other names: 7-ethyl-6,6beta,7,8,9,10,12,13-octahydro-2-methoxy- 6,9-methano- 5H-pyrido[1',2':1,2] azepino [5, 4-b] indole; tabernanthe iboga);
- (22) Lysergic acid diethylamide;

(23) Marihuana;

(24) Mescaline;

(25) Parahexyl (some trade or other names: 3-hexyl-1- hydroxy-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran; synhexyl);

(26) Peyote (meaning all parts of the plant presently classified botanically as "Lophophora williamsii Lemaire," whether growing or not, the seeds of that plant, any extract from any part of that plant, and every compound, manufacture, salts, derivative, mixture, or preparation of that plant, its seeds, or its extracts);

(27) N-ethyl-3-piperidyl benzilate;

(28) N-methyl-3-piperidyl benzilate;

(29) Psilocybin;

(30) Psilocyn;

(31) Tetrahydrocannabinols (synthetic equivalents of the substances contained in the plant, or in the resinous extractives of Cannabis, sp. and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity such as the following: delta-1- cis or trans tetrahydrocannabinol, and their optical isomers; delta-6-cis or trans tetrahydrocannabinol, and their optical isomers; delta-3,4-cis or trans tetrahydrocannabinol, and its optical isomers. (Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions, are covered.)), excluding any of the following:

(a) Tetrahydrocannabinols found in "hemp" and "hemp products" as those terms are defined in section [928.01](#) of the Revised Code; and

(b) Any other substance containing tetrahydrocannabinols as authorized in this chapter of the Administrative Code.

(32) N-ethyl-1- phenylcyclohexylamine (1-phenylcyclohexyl)ethylamine; N-(1-phenylcyclohexyl)ethylamine; cyclohexamine; PCE);

(33) 1-(1- phenylcyclohexyl)pyrrolidine (PCPy; PHP);

(34) 1-[1-(2-thienyl)-cyclohexyl]- piperidine (2-thienyl analog of phencyclidine; TPCP; TCP);



- (35) 1-[1-(2-thienyl)cyclohexyl]pyrrolidine (some other names: TCPy);
- (36) 4-methylmethcathinone (mephedrone);
- (37) 3,4-methylenedioxypropylvalerone (MDPV);
- (38) 3,4-Methylenedioxy-N-methylcathinone (Methylone);
- (39) Hashish;
- (40) Salvia divinorum;
- (41) Salvinorin A;
- (42) (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144);
- (43) 1-pentyl-3-(1-adamantoyl)indole (AB-001);
- (44) N-adamantyl-1-pentylindole-3-carboxamide (APICA, 2NE1);
- (45) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB- FUBINACA);
- (46) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA);
- (47) N-adamantyl-1-pentylindazole-3-carboxamide (APINACA, AKB48);
- (48) 2-ethylamino-2-(3-methoxyphenyl)cyclohexanone (methoxetamine);
- (49) N,N-diallyl-5-methoxytryptamine (5MeO-DALT);
- (50) [1-(5-fluoropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoropentyl-UR-144; XLR11);
- (51) [1-(5-chloropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-chloropentyl-UR-144);
- (52) [1-(5-bromopentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-bromopentyl-UR-144);
- (53) {1-[2-(4-morpholinyl)ethyl]indol-3-yl}-(2,2,3,3-tetramethylcyclopropyl) methanone (A-796,260);
- (54) 1-[(N-methylpiperidin-2-yl)methyl]-3-(1-adamantoyl)indole (AM1248);

- (55) N-adamantyl-1-(5-fluoropentylindole)-3-carboxamide (5F-APICA, STS135);
- (56) 5-(2-aminopropyl)benzofuran (5-APB);
- (57) 6-(2-aminopropyl)benzofuran (6-APB);
- (58) 5-(2-aminopropyl)-2,3-dihydrobenzofuran (5-APDB);
- (59) 6-(2-aminopropyl)-2,3-dihydrobenzofuran (6-APDB);
- (60) Benzothiophenylcyclohexylpiperidine (BTCP);
- (61) 2-(2,5-Dimethoxy-4-ethylphenyl)ethanamine (2C-E);
- (62) 2-(2,5-Dimethoxy-4-methylphenyl)ethanamine (2C-D);
- (63) 2-(4-Chloro-2,5-dimethoxyphenyl)ethanamine (2C-C);
- (64) 2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine (2C-I);
- (65) 2-[4-(Ethylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-2);
- (66) 2-[4-(Isopropylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-4);
- (67) 2-(2,5-Dimethoxyphenyl)ethanamine (2C-H);
- (68) 2-(2,5-Dimethoxy-4-nitro-phenyl)ethanamine (2C-N);
- (69) 2-(2,5-Dimethoxy-4-(n)-propylphenyl)ethanamine (2C-P);
- (70) 4-methoxymethamphetamine (PMMA);
- (71) 5,6 - Methylenedioxy-2-aminoindane (MDAI);
- (72) 5-iodo-2-aminoindane (5-IAI);
- (73) 2-(4-iodo-2,5-dimethoxyphenyl)-N- [(2-methoxyphenyl)methyl]ethanamine(25I-NBOMe);
- (74) 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25C-NBOMe, 2C-C-NBOMe);
- (75) 2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25B-NBOMe, 2C-B-NBOMe);
- (76) 4-methyl-N-ethylcathinone (4-MEC);
- (77) 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP);

- (78) Alpha-pyrrolidinopentiophenone (alpha-PVP);
- (79) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one (butylone, bk-MBDB);
- (80) 2-(methylamino)-1-phenylpentan-1-one (pentedrone);
- (81) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)pentan-1-one (pentylone, bk-MBDP);
- (82) 4-fluoro-N-methylcathinone (4-FMC; flephedrone);
- (83) 3-fluoro-N-methylcathinone (3-FMC);
- (84) 1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)pentan-1-one (naphyrone);
- (85) Alpha-pyrrolidinobutiophenone (alpha-PBP);
- (86) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA);
- (87) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA);
- (88) [1-(5-fluoropentyl)-1H-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201);
- (89) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: MAB-CHMINACA; ADB-CHMINACA);
- (90) Diphenylprolinol (diphenyl(pyrrolidin-2-yl)methanol, D2PM);
- (91) Desoxypipradrol (2-benzhydrylpiperidine);
- (92) Synthetic cannabinoids - unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of a synthetic cannabinoid found to be in any of the following chemical groups or any of those groups which contain any synthetic cannabinoid salts, isomers, or salts of isomers, whenever the existence of such salts, isomers, or salts of isomers is possible within the specific chemical groups:
- (a) Naphthoylindoles: any compound containing a 3-(1-naphthoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-

morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylindoles include, but are not limited to, 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200); 1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM2201), 1-pentyl-3-(1-naphthoyl)indole (JWH-018), and 1-butyl-3-(1-naphthoyl)indole (JWH-073).

(b) Naphthylmethylindoles: any compound containing a 1H-indol-3-yl-(1-naphthyl)methane structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindoles include, but are not limited to, (1-pentylindol-3-yl)(1-naphthyl)methane (JWH-175).

(c) Naphthoylpyrroles: any compound containing a 3-(1-naphthoyl)pyrrole structure with or without substitution at the nitrogen atom of the pyrrole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the pyrrole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylpyrroles include, but are not limited to, 1-hexyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-147).

(d) Naphthylmethylindenes: any compound containing a naphthylmethylideneindene structure with or without substitution at the 3-position of the indene ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indene group to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindenes include, but are not limited to, (1-[(3-pentyl)-1H-inden-1-ylidene)methyl]naphthalene (JWH-176).

(e) Phenylacetylindoles: any compound containing a 3-phenylacetylindole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-

morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Phenylacetylindoles include, but are not limited to, 1-pentyl-3-(2-methoxyphenylacetyl)indole (JWH-250), and 1-(2-cyclohexylethyl)-3-(2-methoxyphenylacetyl)indole (RCS-8); 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203).

(f) Cyclohexylphenols: any compound containing a 2-(3-hydroxycyclohexyl)phenol structure with or without substitution at the 5-position of the phenolic ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the cyclohexyl group to any extent. Cyclohexylphenols include, but are not limited to, 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (some trade or other names: CP-47,497) and 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (some trade or other names: cannabicyclohexanol; CP-47,497 C8 homologue).

(g) Benzoylindoles: any compound containing a 3-(1-benzoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Benzoylindoles include, but are not limited to, 1-pentyl-3-(4-methoxybenzoyl)indole (RCS-4), 1-[2-(4-morpholinyl)ethyl]-2-methyl-3-(4-methoxybenzoyl)indole (Pravadoline or WIN 48,098).

(93) Quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate (PB-22; QUPIC);

(94) Quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22);

(95) Except as otherwise provided in this rule, any compound that meets at least three of the following cannabinoid pharmacophore requirements to bind at the CB1 and CB2 receptors, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of substituted or non-substituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles or other ring types);

(b) Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors;

(c) Carbonyl or ester or equivalent for hydrogen bonding;

(d) Cyclohexane, naphthalene ring, substituted butanamide or equivalent for steric requirements for CB1 and CB2 receptor binding.

(E) Depressants

Any material, compound, mixture, or preparation that contains any quantity of the following substances having a depressant effect on the central nervous system, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Mecloqualone;

(2) Methaqualone;

(3) Except as listed in rule [4729:9-1-03](#) of the Administrative Code, gamma-hydroxybutyric acid (some other names include GHB; gamma-hydroxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid; sodium oxybate; sodium oxybutyrate);

(4) Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine);

(5) Except as otherwise provided in this chapter, any compound that contains the following structural requirements of a benzodiazepine pharmacophore, as identified by a report from an established forensic laboratory:

A core structure consisting of a benzene ring fused to the seven-membered diazepine ring with a 5-aryl substituent aka 5-aryl-1,4-benzodiazepine for binding to the GABA receptor. Regardless of impact on the lipophilic properties of the compound, a benzodiazepine pharmacophore may contain a variety of functional groups including, but not limited to, aldehydes, ketones, esters, and amides.

This paragraph only applies to a compound that has not been approved for medical use by the United States food and drug administration.

(F) Stimulants

Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of the following substances having a stimulant effect on the central nervous system, including their salts, isomers, and salts of isomers:

- (1) Aminorex (some other names: aminoxaphen; 2-amino-5-phenyl-2-oxazoline; or 4,5-dihydro-5- phenyl-2-oxazolamine);
- (2) N-Benzylpiperazine (some other names: BZP, 1-benzylpiperazine);
- (3) Cathinone (some trade or other names: 2-amino-1-phenyl-1-propanone, alpha-aminopropiophenone, 2-aminopropiophenone, and norephedrone);
- (4) Fenethylamine;
- (5) Methcathinone (some other names: 2-(methylamino)-propionophenone; alpha-(methylamino)propionophenone; 2-(methylamino)-1-phenylpropan-1-one; alpha-N-methylaminopropiophenone; monomethylpropion; ephedrone; N-methylcathinone; methylcathinone; AL-464; AL-422; AL-463 and UR1432), its salts, optical isomers and salts of optical isomers;
- (6) (+/-)cis-4-methylaminorex ((+/-)cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine);
- (7) N-ethylamphetamine;
- (8) N,N-dimethylamphetamine (also known as N,N-alpha-trimethyl-benzeneethanamine; N,N-alpha-trimethylphenethylamine);
- (9) N-methyl-1-(thiophen-2-yl) propan-2-amine (methio-propamine);
- (10) Substituted cathinones - any compound except bupropion or compounds listed under a different schedule, structurally derived from 2-aminopropan-1-one by substitution at the 1-position with either phenyl, naphthyl, or thiophene ring systems, whether or not the compound is further modified in any of the following ways:
  - (a) By substitution in the ring system to any extent with alkyl, alkylendioxy, alkoxy, haloalkyl, hydroxyl, or halide substituents, whether or not further substituted in the ring system by one or more other univalent substituents;
  - (b) By substitution at the 3-position with an acyclic alkyl substituent;

(c) By substitution at the 2-amino nitrogen atom with alkyl, dialkyl, benzyl, or methoxybenzyl groups;

(d) By inclusion of the 2-amino nitrogen atom in a cyclic structure.

(11) Except as otherwise provided in this rule, any compound that contains the structural requirements of the cathinone pharmacophore, as identified by a report from an established forensic laboratory.

(G) For the purpose of complying with federal law, all materials, compounds, mixtures or preparations which contain any substance temporarily placed in schedule I pursuant to 21 U.S.C. 811 by the United States drug enforcement administration (~~7/19/2024~~ 12/11/2024).





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

Approved 12/9/2024

### 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.

## **Appendix I**

### **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  $\mu_1$  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.

## **Appendix I**

### **(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.

# Appendix I

## 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 previous 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*

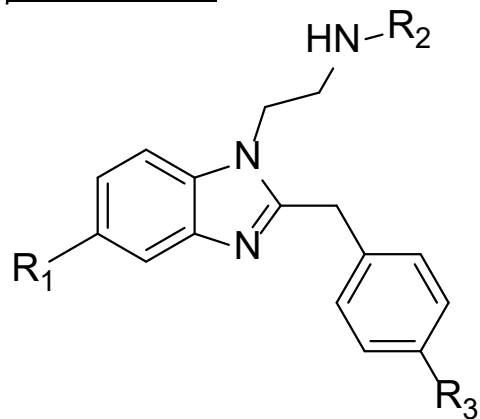
*Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (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  $\mu$  receptor, as identified by a report from an established forensic laboratory, is a schedule I controlled substance:*

## Appendix I

(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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## Appendix I

### References:

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