Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

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BENZIMIDAZOLE–OPIOIDS
OTHER NAME: NITAZENES

Introduction:

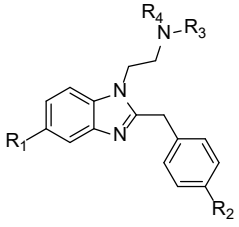
Recently, a number of synthetic substances of the benzimidazole structural class are being trafficked and abused for their opioid-like effects. In the late 1950s, the pharmaceutical research laboratories of the Swiss chemical company CIBA Aktiengesellschaft synthesized numerous substances in this structural class. Since 2019, the abuse of benzimidazole-opioids, as evidenced by their identification in toxicology cases, is similar to other synthetic opioids and has resulted in adverse health effects, including death. As the United States continues to experience an unprecedented epidemic of opioid misuse and abuse, the continued evolution and increased trafficking and popularity of new and deadly synthetic opioids from a variety of structural classes, including benzimidazoles, with no approved medical use are a public health concern.

Licit Uses:

Benzimidazole-opioids are not approved for medical use in the United States.

Chemistry:

This class of substances contains a benzimidazole ring with an ethylamine at its 1-position and a benzyl group at its 2-position. Small structural modifications to this scaffold can produce a series of analogous substances, including (but not limited to) the substances listed below:



	R_1	R_2	R_3	R_4
metonitazene	NO_2	OCH_3	CH_2CH_3	CH_2CH_3
metodesnitazene	H	OCH_3	CH_2CH_3	CH_2CH_3
etonitazene	NO_2	OCH_2CH_3	CH_2CH_3	CH_2CH_3
etodesnitazene	H	OCH_2CH_3	CH_2CH_3	CH_2CH_3
protonitazene	NO_2	$OCH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
butonitazene	NO_2	$OCH_2CH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
isotonitazene	NO_2	$OCH(CH_3)_2$	CH_2CH_3	CH_2CH_3
clonitazene	NO_2	Cl	CH_2CH_3	CH_2CH_3
flunitazene	NO_2	F	CH_2CH_3	CH_2CH_3
etonitazepyne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2-$	
etonitazepipne	NO_2	OCH_2CH_3	$-CH_2CH_2CH_2CH_2CH_2-$	

Pharmacology:

Data obtained from pre-clinical studies demonstrate that benzimidazole-opioids exhibit pharmacological profiles similar to those of etonitazene and other mu-opioid receptor agonists. In an antinociceptive study conducted in rodents, butonitazene, etodesnitazene, etonitazepipne, etonitazepyne, flunitazene, metodesnitazene, metonitazene, and protonitazene produced strong analgesic effects with varying potencies, similar to morphine. Compared to morphine, flunitazene, and metodesnitazene are equipotent, whereas butonitazene, etodesnitazene, etonitazepyne, metonitazene, and protonitazene are more potent as analgesics. Similar to morphine and fentanyl, data from in vitro studies showed that butonitazene, etodesnitazene, etonitazepipne, etonitazepyne, flunitazene, metonitazene, metodesnitazene, and protonitazene bound to and activated the mu-opioid receptor, thus acting as mu-opioid receptor agonists. Activation of the mu-opioid receptor by butonitazene, metonitazene, metodesnitazene, and protonitazene involved interaction with β-arrestin-2. Mu-opioid receptor and β-arrestin-2 interaction has been implicated in adverse health effects of many opioid analgesics. It is well established that mu-opioid receptor agonists have a high potential for addiction and can produce dose-dependent respiratory depression and arrest.

Illicit Uses:

Benzimidazole-opioids are abused for their psychoactive effects. These substances are likely to be abused in the same manner as schedule I opioids, such as etonitazene, isotonitazene, and heroin. Abuse of these benzimidazole-opioids has led to their positive identification in several toxicological cases in the United States. Some of these benzimidazole-opioids have been positively identified in at least 94 toxicology cases.

User Population:

The population likely to abuse benzimidazole-opioids appears to be the same as those abusing prescription opioid analgesics, heroin, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in some of the identified benzimidazole-opioids seizures and in fatal overdose cases. Toxicology analyses co-identified some of these benzimidazole-opioids with other opioids, stimulants, and benzodiazepines. Because abusers of these benzimidazole-opioids are likely to obtain them through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the users. Similar to other mu-opioid receptor agonists, the potential health and safety risks for users of these benzimidazole-opioids are high. Recent increases in positive identification of isotonitazene, metonitazene, and other benzimidazole-opioids in toxicology and post-mortem cases is a serious concern to public safety.

Illicit Distribution:

On the illicit drug market, some of these benzimidazole-opioids have been identified in drug seizures. The Drug Enforcement Administration's National Forensic Laboratory Information System (NFLIS) Drug database is a system that collects drug analysis identification information from participating federal, state, and local forensic drug laboratories. NFLIS-Drug received some reports of benzimidazole-opioids (i.e., clonitazene [8 reports] and etonitazene [18 reports]) from 1999–2004, followed by 0 reports until 2019. Since 2019, NFLIS-Drug has received nearly 7,000 reports of benzimidazole-opioids. Furthermore, substances in this class have been co-identified with other psychoactive substances, including illicit opioids and benzodiazepines, in biological fluids. With no approved medical use, the positive identification of these substances in toxicology cases underscores the public health threat associated with their presence on the illicit drug market.

Control Status:

These benzimidazole-opioids are not approved for medical use in the United States. Twelve benzimidazole-opioids are controlled in schedule I of the Controlled Substances Act. If others are found to meet the criteria outlined in 21 U.S.C. § 802(32) and are intended for human consumption, they may be treated as schedule I controlled substance analogues for the purpose of federal law, pursuant to 21 U.S.C. § 813.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@dea.gov.