Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

Benzimidazole-Opioids

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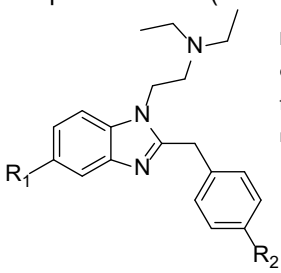
Introduction:

Recently, several synthetic substances of 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 benzimidazole-opioids to include butonitazene, etodesnitazene, flunitazene, metonitazene, metodesnitazene, and protonitazene. Since 2019, the abuse of benzimidazole-opioids as evidenced by their identification in toxicology cases, similar to other synthetic opioids, has resulted in adverse health effects including deaths. 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 including benzimidazole-opioids with no approved medical use are of public health concern.

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 butonitazene, etodesnitazene, flunitazene, metonitazene, metodesnitazene, and protonitazene (shown below):



butonitazene	R_1 = NO_2	R_2 = $OCH_2CH_2CH_2CH_3$
etodesnitazene	R_1 = H	R_2 = OCH_2CH_3
flunitazene	R_1 = NO_2	R_2 = F
metodesnitazene	R_1 = H	R_2 = OCH_3
protonitazene	R_1 = NO_2	R_2 = $OCH_2CH_2CH_3$
metonitazene	R_1 = NO_2	R_2 = OCH_3

Pharmacology:

Data obtained from pre-clinical studies demonstrate that benzimidazole-opioids exhibit pharmacological profile similar to that of etonitazene and other mu-opioid receptor agonists. In antinociceptive study conducted in rodents, flunitazene, metodesnitazene, butonitazene, metonitazene and protonitazene, similar to morphine, produced strong analgesic effects with varying potencies. As compared to morphine, flunitazene and metodesnitazene are equipotent, while butonitazene is about 5-fold more potent, metonitazene is about 100-fold more potent, and protonitazene is about 200-fold more potent as analgesics. Data from in vitro studies showed that butonitazene, etodesnitazene, flunitazene, metonitazene, metodesnitazene, and protonitazene, similar to hydromorphone, fentanyl, and morphine, bound to and activated the mu-opioid receptor, and thus acted 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. Abuse of these benzimidazole-opioids has led to their positive identification in several toxicological cases in the United States. Specifically, metonitazene has been identified in twenty post-mortem 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 isotonitazene 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 end user. Similar to other mu-opioid receptor agonists, the potential health and safety risks for users of these benzimidazole-opioids are high. Recent increase in positive identification of isotonitazene and other benzimidazole-opioids in toxicology and post-mortem cases is a serious concern to the public safety.

Illicit Distribution:

On the illicit drug market, some of these benzimidazole-opioids have been identified in drug seizures. For example, within the National Forensic Laboratory Information System (NFLIS) drug seizure component, preliminary drug report data has been identified since 2020 for metonitazene (94 reports). Also, since 2019, NFLIS has identified schedule I benzimidazole-opioids such as etonitazene and isotonitazene. Furthermore, all of these substances have been positively 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 underscore 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. Benzimidazole-opioids may be treated under 21 U.S.C. 802(32)(A), if intended for human consumption.

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