BMF 102 I 0922

Nitazenes

Nitazenes (2-benzylbenzimidazoles) are highly potent new synthetic opioids (NSO) that have recently emerged onto the recreational drug market. They were originally developed in the 1950's as analgesics but were never subsequently marketed as human or veterinary medicines. Several international reports of severe toxicity involving nitazenes, especially isotonitazene, have highlighted the significant threat they pose to public health and safety. Toxicology laboratories should ensure that nitazenes are included in forensic testing protocols and remain vigilant in relation to the rapidly expanding class of NSOs.

What are Nitazenes?

Nitazenes (2-benzylbenzimidazoles) are a novel class of highly potent synthetic opioids that have recently emerged on the recreational drug market. Isotonitazene was the first to be notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in August 2019, following a test purchase from an online vendor. However, it is believed to have been available on the European drug market since April 2019. Since then, several other analogues have appeared.

Whilst new to the recreational market, the origin of nitazenes can actually be traced back to the mid-1950's. They were first developed in a search for alternatives to morphine, although they were never clinically approved due to increased risk of adverse events. Nitazenes are mu opioid receptor agonists and thus the risks associated with their use are comparable to opioids. In general, they are highly active, and several analogues have potencies and efficacies of exceeding that of fentanyl.

Presentation and route of administration

Nitazenes can be administered orally as powder, tablets or solution. They can also be administered intranasally by snorting or sublingually via spray. They can be inhaled by 'vaping', smoking or vaporising the 'free base', and injected.

Isotonitazene has been identified in counterfeit hydromorphone tablets in Canada. It has also been used to fortify heroin. Metonitazene has been identified in oxycodone tablets.

Physical, mental and behavioural effects

EUPHORIA

RELAXATION

DROWSINESS& DIZZINESS

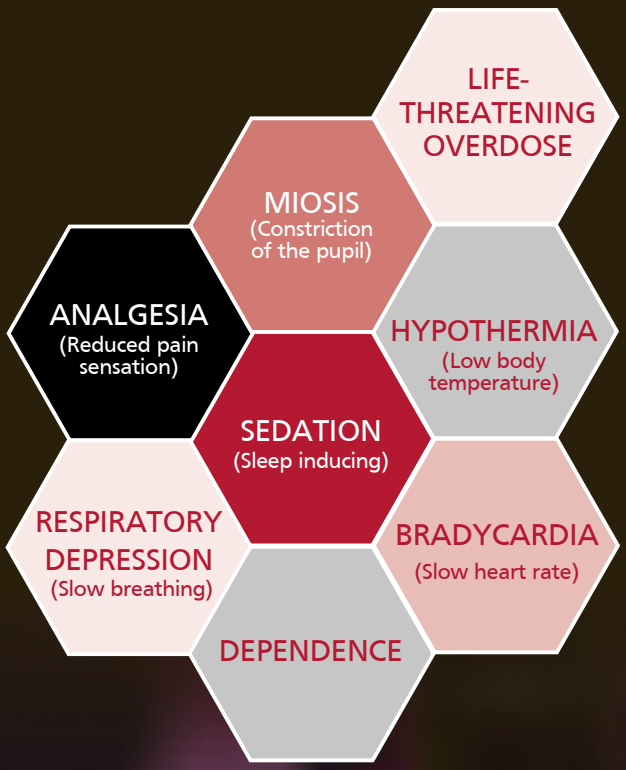
INCOORDINATION & MENTAL CONFUSION

Acute toxicity

There is limited information on the acute toxicity of nitazenes, however, based on the available information, their side effects are expected to be similar to those of other opioid analgesics;

Concomitant use with other CNS depressants is expected to have an additive effect, exacerbating respiratory depression and life-threatening effects.

Given their pharmacological properties, naloxone is expected to be an effective antidote, although due to its short half-life, larger than normal or repeat doses may be required to manage the intoxication in some cases. Extended observation may also be required.



International legal controls

Etonitazene and clonitazene, are long standing inclusions in schedule I of the 1961 Single Convention on Narcotic Drugs because of their 'morphine-like' effects. In April 2021, at the 64th session of the Committee on Narcotic Drugs (CND), a vote was made to also add isotonitazene, following the earlier recommendations made by the 43rd Expert Committee on Drug Dependence (ECDD). Metonitazene was reviewed by the 44th ECDD in October 2021 and a recommendation was put forward to add it to the 1961 Convention. This recommendation was accepted at the 65th CND meeting, which took place in March 2022 and will come into force in November 2022. The ECDD will review a further three nitazenes in October 2022; protonitazene, etazene, and etonitazepyne.

Isotonitazene was rapidly controlled in the US through the temporary emergency scheduling procedure in August 2020. It was subsequently added to the Controlled Substances Act (CSA) in June 2021. In December 2021, the DEA gave notice of its intention to place a further seven nitazene variants under temporary control for a period of 2 years; butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, etonitazepyne, protonitazene.

The Canadian Controlled Drugs and Substances Act, schedule 1, part 13, includes a general statement relating to benzimidazoles and their derivatives, including etonitazene and clonitazene, which is interpreted as capturing other nitazene variants.

In the UK, etonitazene and clonitazene are listed as Class A drugs in the Misuse of Drugs Act 1971 and in schedule 2 of the Misuse of Drugs Regulations 2001. On 18th July 2022 the Advisory Council on the Misuse of Drugs (ACMD) recommended these be moved to schedule 1 as they have no medical use. Furthermore, they recommended that the following also be added as Class A, schedule 1 drugs; metonitazene, protonitazene, isotonitazene, butonitazene, flunitazene, metodesnitazene, etodesnitazene, N-pyrrolidino-etonitazene, N-piperidinyl-etonitazene and brorphine. A consultation is proposed in relation recommendations for a generic control on 2-benzyl benzimidazole variants.

In July 2021 Germany adopted a generic control on 2-benzyl benzimidazole synthetic opioids, adding them to the Neue psychoktive Stoffe Gesetz (NpSG).

Sweden has recently added metonitazene to its list of controlled materials.

Japan included isotonitazene in the Shitei Yakubutsu (designated substances) legislation in November 2020 and metonitazene in October 2021.

The NPS REFORM project

New Psychoactive Substances - REferences for the FORensic Market

Despite the presently available Reference Materials (RM) for New Psychoactive Substances (NPS), the rate of emergence of new compounds significantly outpaces the development of counterpart RM for efficient monitoring and testing of these substances – especially for new and extremely potent NSOs, and the synthetic cannabinoid receptor agonists (SCRAs).

NPS Reform – a collaborative Eurostars project between Chiron and Linköping University (LiU) - tackles this problem by developing platforms and proactive methods to predict and monitor the flow of potent NPS onto the market more easily. Using a Predictive Parallel Production Platform (P4), novel reference materials are produced quicker, more efficiently, simultaneously and at a larger scale. By targeting reported NPS, and those which will likely appear in the market based on chemical similarities the platform predicts new compounds and using the parallel synthesis of similar analogous, numerous compounds such as the nitazene analogous presented here can easily be made available with short lead times.

For several compounds, and especially for urine methods, RM for unique and abundant metabolite markers are needed. The second project goal is therefore to improve our understanding of the NPS metabolism – aiming for early identification of metabolites originating from novel drugs of abuse. In many cases, especially for SCRAS, the parent NPS substance cannot be detected in urine and the intake must be proven based on metabolite findings, which also sometimes have extended detection windows as they remain longer in the body. Rapid metabolism studies using human hepatocytes and authentic urine samples identifies potential markers, which are then synthesized using the P4 strategy to also address analogues. Thus, also making RM for unique urine markers more swiftly available.

One of the hazards working with NPS is the unknown potency, especially of NSOs. The final major objective of the NPS reform project is therefore to identify the potency and efficacy of the emerging compounds. Using swift in vitro assays for the activation of the μ-opioid and CB1 receptors, the project also produces safety data for especially NSOs. Figure 1 shows the potency and efficacy of some of the nitazene analogous: etonitazene, metonitazene, isotonitazene, butonitazene and fluonitazene (in order of potency – high to low) produced by the project in relationship to fentanyl.

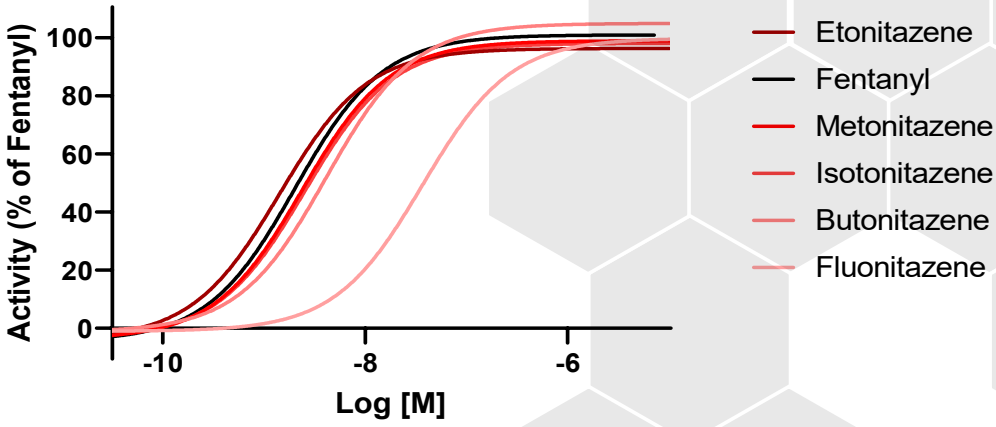


Figure 1.
Dose-response curve for nitazenes relative to fentanyl.

Courtesy of Prof. Henrik Green, Division of Clinical Chemistry and Pharmacology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden

Nitazenes product listing

ISO 17034
ISO/IEC 17025
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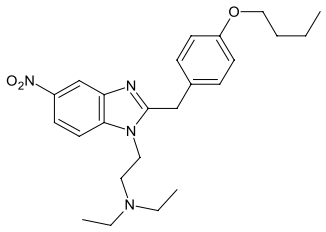
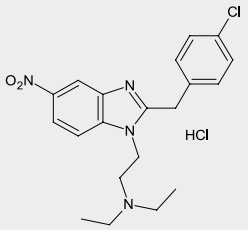
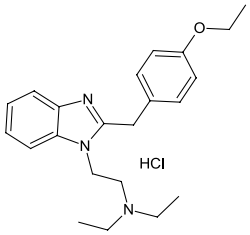
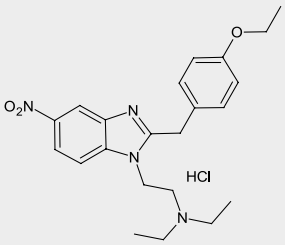
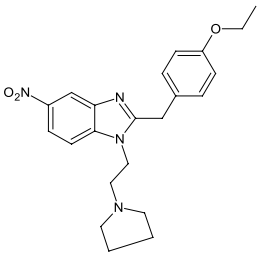
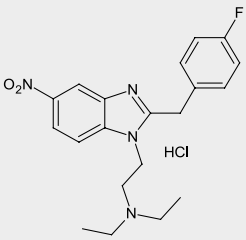
Chiron No.	Name	Structure	CAS
14877.24	**Butonitazene** *(Butoxynitazene)*		95810-54-1
14454.20	**Clonitazene hydrochloride** *(C193901)*		2053-24-9
14321.22	**Etazene hydrochloride** *(Etodesnitazene hydrochloride)*		1071546-16-1
14195.22	**Etonitazene hydrochloride** *(NIH 7607)*		2053-25-0
14971.22	**N-Pyrrolidino Etonitazene** *(Etonitazepyne)*		N/A
14455.20	**Fluonitazene hydrochloride** *(Flunitazene hydrochloride)*		2728-91-8

Nitazenes product listing

ISO 17034
ISO/IEC 17025
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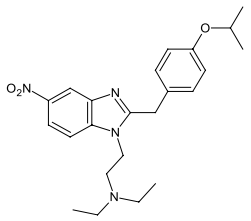
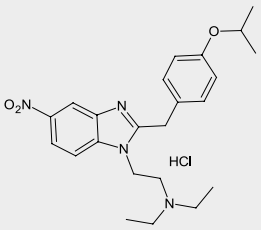
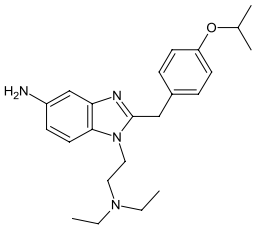
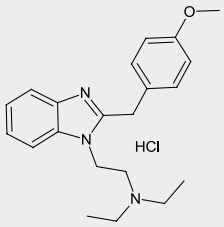
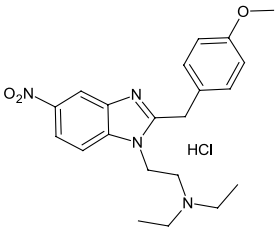
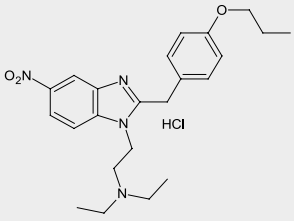
Chiron No.	Name	Structure	CAS
14118.23	**Isotonitazene**		14188-81-9
15270.23	**Isotonitazene hydrochloride**		119276-00-5
14970.23	**5-Aminoisotonitazene**		N/A
14453.21	**Metodesnitazene hydrochloride**		1071546-40-1
14456.21	**Metonitazene hydrochloride**		3983-24-2
14621.23	**Protonitazene hydrochloride** *(Pronitazene hydrochloride)*		119276-01-6

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