

Addressing the Nitazene Threat: Development of Reference Standards.

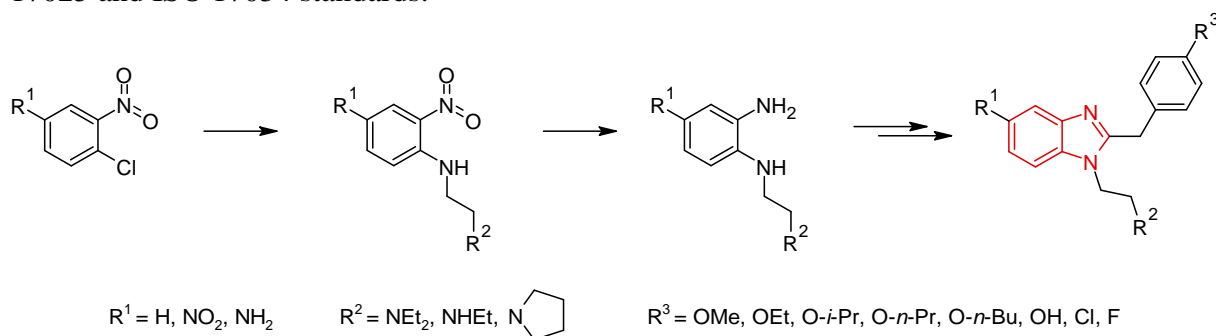
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Benzimidazole derivatives, known as nitazenes, were initially developed as a potential analgesic during the 1950s. They were never approved for therapeutic use due to the risk of adverse events. As a reaction of introduced control measures towards fentanyl in recent years, clandestine labs have started producing nitazenes to diversify their portfolio. In 2019 the first known appearance of isotonitazene was reported, and it has since been identified in several deaths. The original patent reported isotonitazene to be five hundred times more potent than morphine. At Chiron we strive to monitor illicit drug trends and develop reference standards for emerging substances. As part of this we have been utilizing the 4P (Productive, Parallel, Production Platform) strategy to develop a series of nitazenes to address the nitazene threat.

The synthesis of nitazene reference standards involved a multi-step process (Scheme 1), including nucleophilic aromatic substitution; nitro reduction; and benzimidazole formation. Additional protection and deprotection steps were employed with the desethyl derivatives. All synthesized products underwent thorough characterization using nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HR-MS) techniques. Following characterization, the reference materials were certified according to accredited ISO/IEC 17025 and ISO 17034 standards.



Scheme 1: Synthetic overview

A series of nitazenes, including nitazepyne and the metabolites desethyl nitazene and 4-OH-nitazene, have been synthesized with chemical purity of $\geq 98\%$ by HPLC analysis of the final products in most cases. When R^1 is a nitro-group, selective reduction has posed a problem which resulted in mediocre yields. The coupling of phenylacetic acid and the following condensation to give the benzimidazole core was found to work both as a two-step- and one-pot synthesis.

This study demonstrates the critical need for continued monitoring of emerging drug trends, particularly the emerging group of synthetic opioids with high potency. It is important to monitor nitazenes in seized drug samples to efficiently address the issue of trafficking and abuse. Several nitazenes have been developed and are available at Chiron as reference materials.