

MU-OPIOID RECEPTOR ACTIVITY PROFILING OF THE EMERGING GROUP OF NITAZENE NEW SYNTHETIC OPIOIDS

Marthe M. Vandeputte (1), Katleen Van Uytfanghe (1), Nathan K. Layle (2), Danielle M. St. Germaine (2), Donna M. Iula (2) and Christophe P. Stove (1)

(1) Laboratory of Toxicology, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium; (2) Forensic Chemistry Division, Cayman Chemical, Ann Arbor, Michigan, USA

Aims: The illicit drug market is constantly changing, with new synthetic opioids being one of the fastest growing groups. Due to the high potency of many opioids, their use is particularly dangerous. Recently, several benzimidazole opioids (also referred to as nitazenes) have emerged. Isotonitazene, the most frequently encountered member, has been identified in >250 fatalities in the US since it appeared in 2019. While recent scheduling efforts targeted isotonitazene, many other nitazenes remain unregulated. Structurally unrelated to fentanyl or other opioids, little is known about their harm potential. This study provides important new insights into the μ -opioid receptor (MOR) activation of 10 emerging nitazenes and 4 metabolites. **Methods:** The potency and efficacy of the nitazenes was determined via 2 cell-based MOR activation assays (NanoBiT®): activation of MOR, fused to one part of a nanoluciferase enzyme, leads to recruitment of either β -arrestin2 or mini-Gi, fused to the other part. This restores the nanoluciferase activity, yielding a bioluminescent signal upon addition of a substrate. **Results:** Nitazenes are generally highly active, with MOR potencies and efficacies of several analogues exceeding that of fentanyl. Particularly relevant is the unexpected (extremely) high potency of the N-desethyl-isotonitazene metabolite, rivalling the potency of etonitazene and exceeding that of isotonitazene itself. Supported by its identification in fatalities, this likely has in vivo consequences. **Conclusion:** The increasing emergence of nitazenes illustrates the continuously evolving nature of the illicit drug market. Nitazenes are potent MOR agonists. As their use may pose an imminent threat to any user, intensive monitoring and increased awareness are of critical importance.