

Fast Response to Emerging Synthetic Opiates: Recent Updates to the RADIANT™ ASAP Seized Drug Library

Emily Lee, Jane Cooper, Michelle Wood

Waters Corporation

This is an Application Brief and does not contain a detailed Experimental section.

For forensic use only.

Abstract

The identification of novel psychoactive substances (NPS) or designer drugs is a major challenge faced by forensic and drug chemistry laboratories. Recently there have been reports of synthetic opioids, specifically benzimidazole-derived opioids, being detected in toxicological and drug seizure samples.¹ The rise of these compounds raises concerns for public health due to their potency and as many drug chemistry laboratories currently do not routinely test for these compounds, there have been challenges in identifying benzimidazoles in samples.

Previously we have described the use of RADIANT™ ASAP for rapid screening for seized materials.² This library has been recently expanded with the addition of data for 12 benzimidazoles. This will enable drug chemistry laboratories to routinely screen for these substances to aid in the control of the use, trafficking, and distribution.

Benefits

Allows forensic drug chemistry laboratories to use the RADIANT ASAP to screen for emerging benzimidazoles.

Introduction

In recent times there has been a significant increase in the number and diversity of NPS and designer drugs. This increase, together with their potential for harm, is a worldwide concern.¹ It also places pressure on the forensic drug chemistry laboratories to keep pace with the ever-changing trends of the illicit drug market.

An emerging drug class are the synthetic opioids, specifically those of the benzimidazole structural class. There has been evidence which indicates that benzimidazoles are being abused through the illicit drug market, due to the identification of these substances in both toxicological and drug seizure samples, and these compounds have no medically approved use.¹ During 2020, the European monitoring Centre for Drugs and Drug Addiction (EMCDDA) received insight relating to the benzimidazole, isotonitazene, which resulted in concern of potential threat in Europe and led to a specific risk assessment of the substance to be carried out in May 2020.³ Since this time, nine additional compounds have been reported to the United Nations Office of Drugs and Crime (UNODC) early warning advisory program.⁴ The rise of these new opioids is of particular concern for public health, due to their strong analgesic potency which has been estimated to be several times more potent than morphine and fentanyl, and therefore have the potential to result in adverse health effects including death.^{5,6}

A widely reported limiting factor in the control of illicit drug use, trafficking, and distribution of NPS is the lack of routine screening analysis for new emerging compounds in laboratories.^{3,7} This causes challenges in identifying and reporting these compounds to early warning programs. Therefore, the ability to quickly update analytical methods with new, emerging and trending analytes is of great benefit for drug chemistry laboratories. Recently we have described how to add new compounds to the RADIANT ASAP seized drug reference library (Figure 1); the process was illustrated using the benzimidazole isotonitazene.⁸ Here we demonstrate the use of that expanded library for the analysis of 11 additional benzimidazoles, enabling drug chemistry laboratories to routinely screen for these substances to aid in the control of the use, trafficking, and distribution.

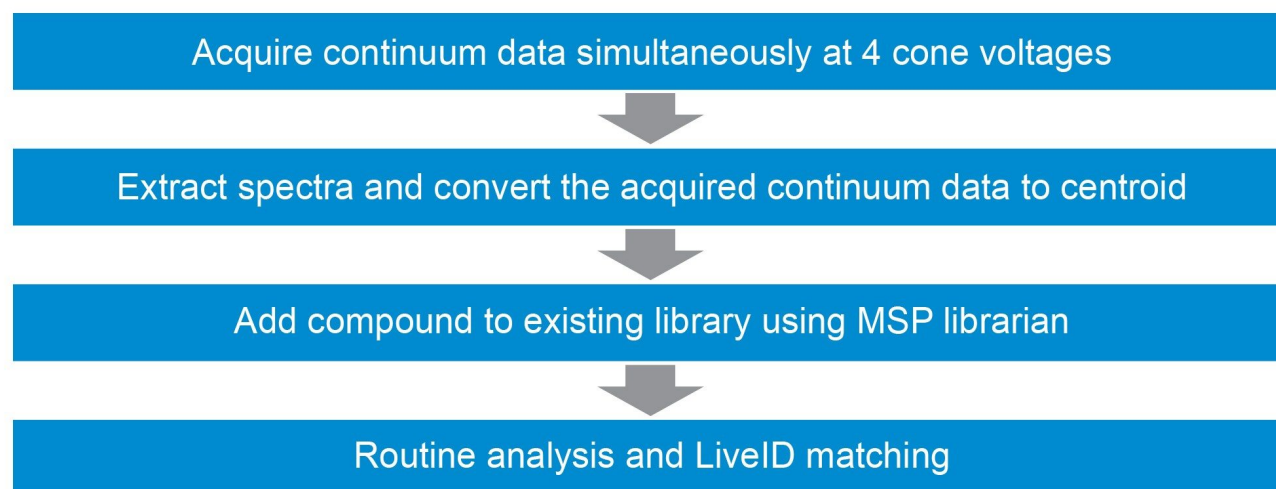


Figure 1. Summary of the steps involved in updating the RADIAN ASAP reference library with new compounds.

Experimental

Certified reference material for 12 benzimidazoles substances were obtained from Cayman Chemical (Michigan, USA). Certified reference materials were supplied as 1 mg of solid material, each CRM was dissolved in 1 mL of methanol to obtain individual stock solutions at 1 mg/mL. Prior to analysis, the CRM stock solutions were diluted with methanol to a concentration of 50 µg/mL. Data was matched to a reference library that has been previously updated to include 12 benzimidazoles.

Data was acquired using RADIAN ASAP, using a “dip and detect” sampling procedure.² Data was acquired in positive ionization mode for all analytes, with mass detection performed using full scan MS over the range m/z 50–600 in continuum mode. The data was acquired at four differing cone voltages (15, 25, 35, 50) to generate a spectral fingerprint which includes the precursor and product ions.

LiveID™ library matching software is used for the routine analysis of seized drug materials, performing a spectral match between the acquired spectra and the reference library spectra. The software calculates an average match score (maximum 1000) using a reverse fit model for the data acquired at each of the cone voltages. A match score of 850 was used as the reporting cut off for a sample to be deemed positive.

Results and Discussion

Data was processed by using LiveID software in combination with the updated seized drug library. Substances analysed included isotonitazene, etonitazene, clonitazene, metonitazene, flunitazene, etodesnitazene, metodesnitazene, protonitazene, butonitazene, N-pyrrolidino etonitazene, isotodesnitazene, and AP-237. When reanalysed following the library update, all 12 compounds gave match scores > 900 (range 924 to 999). Figure 2 shows an example of the LiveID result obtained for flunitazene CRM.

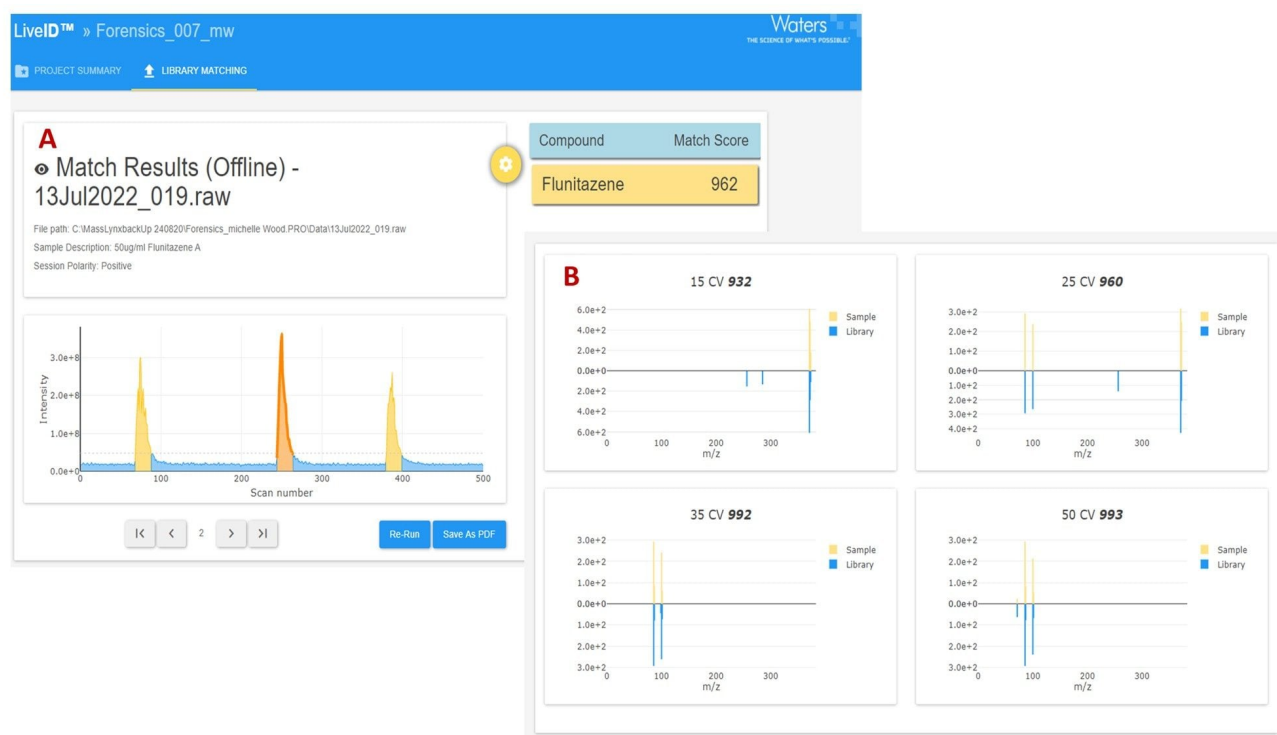


Figure 2. LiveID analysis of reanalysis of flunitazene CRM. Panel A shows triplicate 'dip and detect' analysis for flunitazene reference material and the match factor 962 for the second triplicate. Panel B displays the details for the spectral match with the acquired sample and the new library entry for each cone voltage.

Two of the 12 benzimidazoles added to the library, isotonitazene and protonitazene, are isomers. When these analytes were analysed individually, both analytes were returned as positive matches, with match scores >850 (Figure 3).

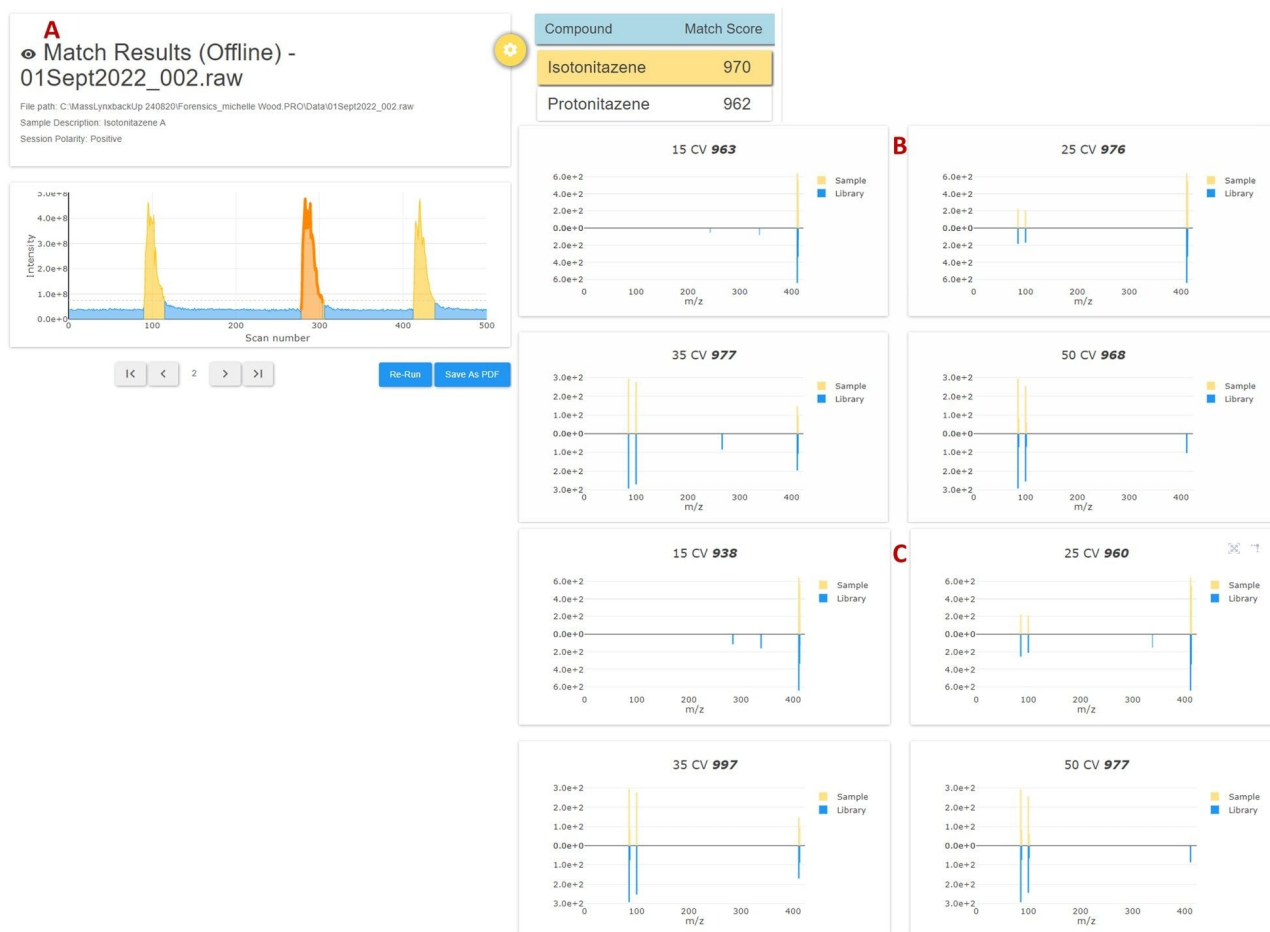


Figure 3. LivedID analysis of isotonitazene CRM. Panel A shows triplicate analysis for isotonitazene reference material and the match factor 970 (isotonitazene) and 962 (protonitazene) for the second triplicate. Panel B displays the details for the spectral match for isotonitazene with the acquired sample and the new library entry. Panel C displays the details for the spectral match for protonitazene with the acquired sample and the new library entry.

While the RADIAN ASAP screen did not allow for differentiation of these two isomers, this can be achieved if required through subsequent application of a technique which utilizes chromatographic separation. For example, application of the Waters™ MRM based screening method which is based on UPLC separation coupled with the TQS-micro tandem mass spectrometer, provides clear differentiation of these two substances owing to a difference in chromatographic retention time of over 0.4 minutes.⁹

Conclusion

The seized drug reference library, for use with the RADIAN ASAP and LiveID has been updated with 12 benzimidazole substances. The seized drug reference library can be downloaded from Waters Marketplace, in the LiveID resources section (<https://marketplace.waters.com/apps/170156/liveid#!resources> < <https://marketplace.waters.com/apps/170156/liveid#!resources> >). These additional analytes in the library increase the number of NPS, specifically synthetic opioids, that the RADIAN ASAP with LiveID can be used to screen for. This enables users to keep their screening methods up to date with these trending and emerging synthetic opioid substances.

References

1. European Monitoring Centre for Drugs and Drug Addiction (2020). *New psychoactive substances: global markets, global threats and COVID-19 pandemic. An update from the EU Early warning System* (December 2020), Publications of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/rapid-communication/new-psychoactive-substances-global-markets-glocal-threats-and-covid-19-pandemic_en < https://www.emcdda.europa.eu/publications/rapid-communication/new-psychoactive-substances-global-markets-glocal-threats-and-covid-19-pandemic_en > (accessed 24 Aug 2022).
2. Wood M. Radian ASAP with LiveID – Fast, Specific, and Easy Drug Screening. Waters Application Note. [720007125](#), 2021.
3. Evans-Brown M., *et al.* EMCDDA Technical Report on the New Psychoactive Substance *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (isotonitazene). https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en < https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en > (accessed 24 Aug 2022).
4. Advisory Council on the Misuse of Drugs. ACMD report – A Review of the Evidence on the Use and harm of 2-Benzyl Benzimidazole ('nitazene') and Piperidine Benzimidazolone ('bromphine-like') Opioids. July 2022. <https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids-accessible-version> <[https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-](https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids-accessible-version)

[and-piperidine-benzimidazolone-oids/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-oids-accessible-version](#) > (accessed 24 Aug 2022).

5. Drug Enforcement Administration, Diversion Control Division, Drug and Chemical Evaluation Section, May 2022. https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-oids.pdf <
https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-oids.pdf> (accessed 24 Aug 2022).
6. Canadian Centre on Substance Use and Addiction. CCENDU Drug Alert Nitazenes. March 2022.
https://www.ccsa.ca/sites/default/files/2022-03/CCSA-CCENDU-Drug-Alert-Nitazenes-2022-en_0.pdf <
https://www.ccsa.ca/sites/default/files/2022-03/CCSA-CCENDU-Drug-Alert-Nitazenes-2022-en_0.pdf>
(accessed 24 Aug 2022).
7. Di Trana A, *et al.* Synthetic Benzimidazole Opioids: The Emerging Health Challenge for European Drug Users. *Frontiers in Psychiatry*. 13:858234. 2022.
8. Lee E, Cooper J, Martin N, Wood M. Updating the RADIANT ASAP seized drug reference library, Waters White paper, [720007838](#) <<https://www.waters.com/webassets/cms/library/docs/720007838en.pdf>> 2023.
9. Mistry N.S, Cooper J, Wood M. Expansion of the MRM Toxicology Screening Methodology for use with Waters Xevo TQ-S Micro. Waters Application Note. [720007748](#). 2022.

Featured Products

[RADIANT ASAP Direct Mass Detector](https://www.waters.com/waters/nav.htm?cid=135073413) <<https://www.waters.com/waters/nav.htm?cid=135073413>>

[LiveID Software](#) <

https://www.waters.com/waters/nav.htm?cid=134939519&alias=AEMredirectForBaseID_134939519>

720007839, January 2023



© 2023 Waters Corporation. All Rights Reserved.

[Terms of Use](#) [Privacy](#) [Trademarks](#) [Sitemap](#) [Careers](#) [Cookies](#) [Preferências de cookies](#)