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Enquiries:

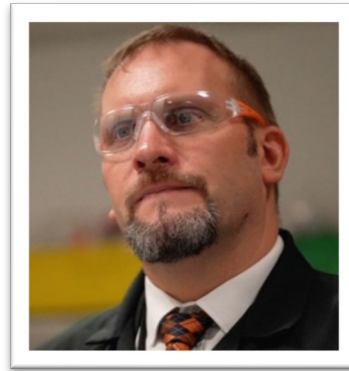
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ISC2024 – Liverpool, UK – 6-10 Oct 2024

M

A Holistic Approach to the Analysis of Novel Psychoactive Substances



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MANDRAKE_LAB



Manchester – Our Journey Begins...



THIS IS NOT A MANCHESTER-CENTRIC ISSUE



MANDRAKE – A Journey through Time and “Spice”



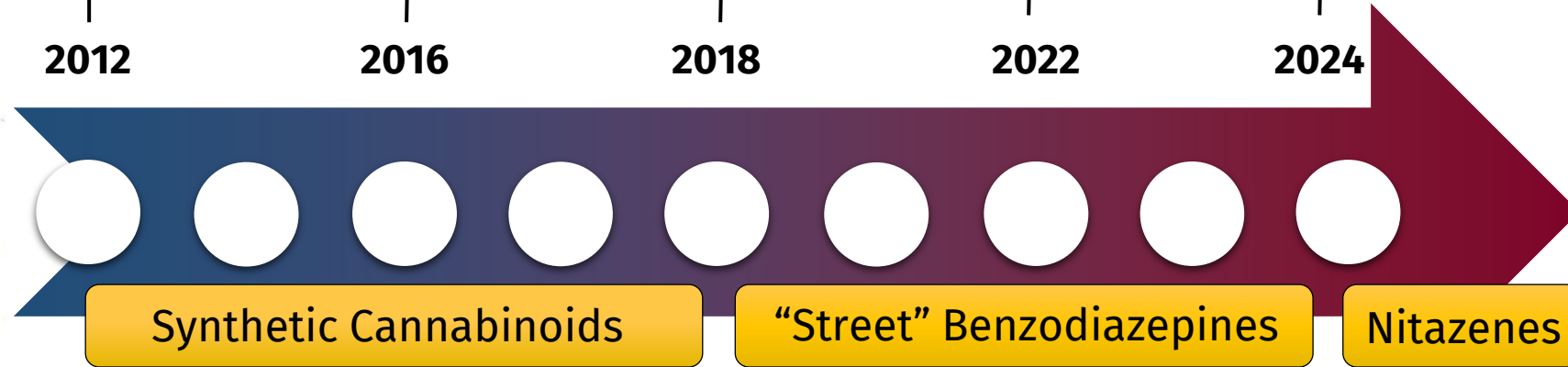
Appointed to Manchester Metropolitan University | 2012

Established street supply of “Spice” and other NPS | 2016

Greater Manchester Drugs Early Warning System | 2018

Herman-Goldstein Award (2024) **Operation Vulcan** | 2022

Coronial Emergency Departments | 2024



254

2015
GMP begin to experience issues with NPS in City Centre.

2017
MANDRAKE established

2021
GMP Forensic Pathway

2023
MANDRAKE Expansion

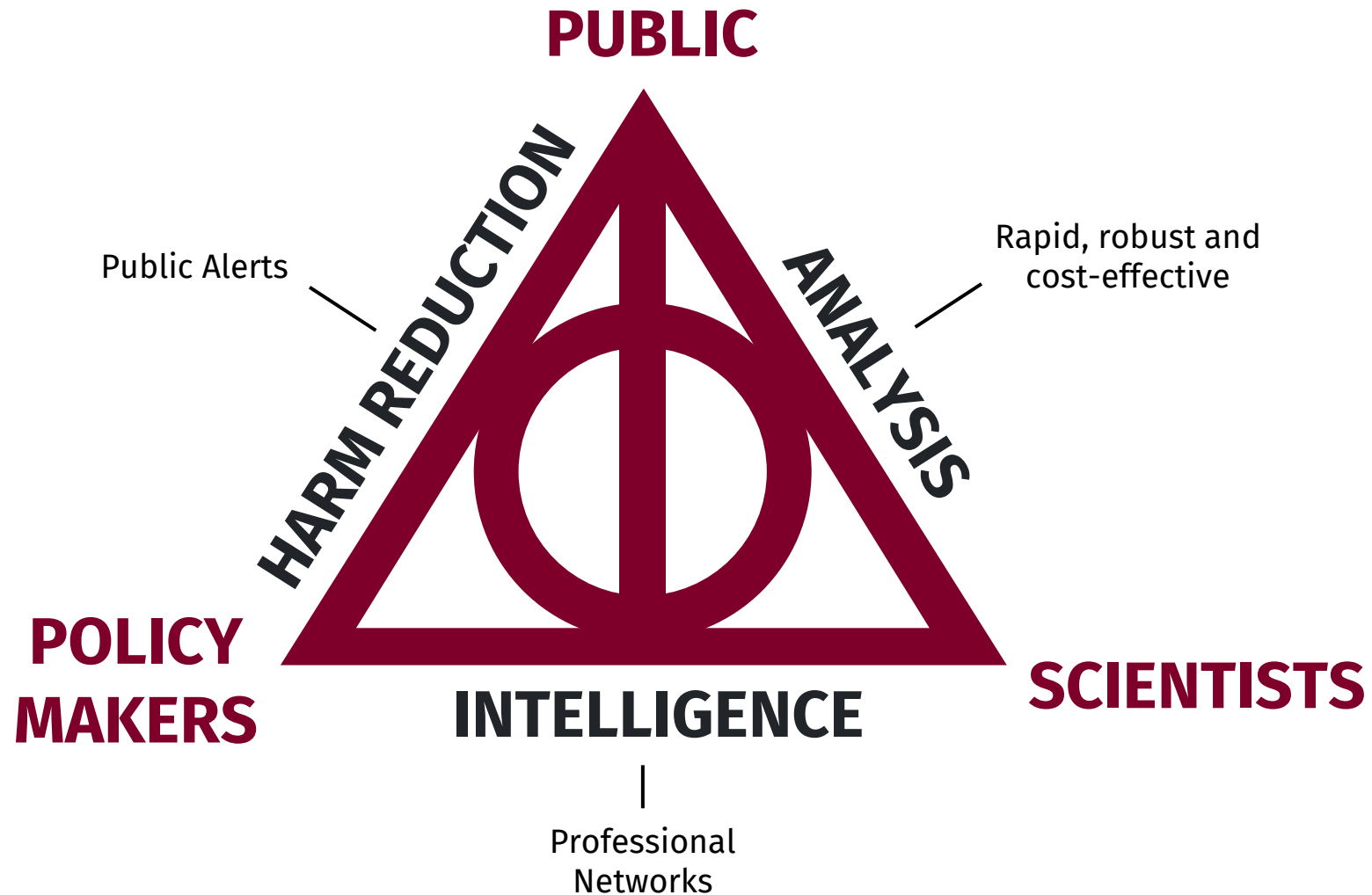
1239

“The MANDRAKE model”



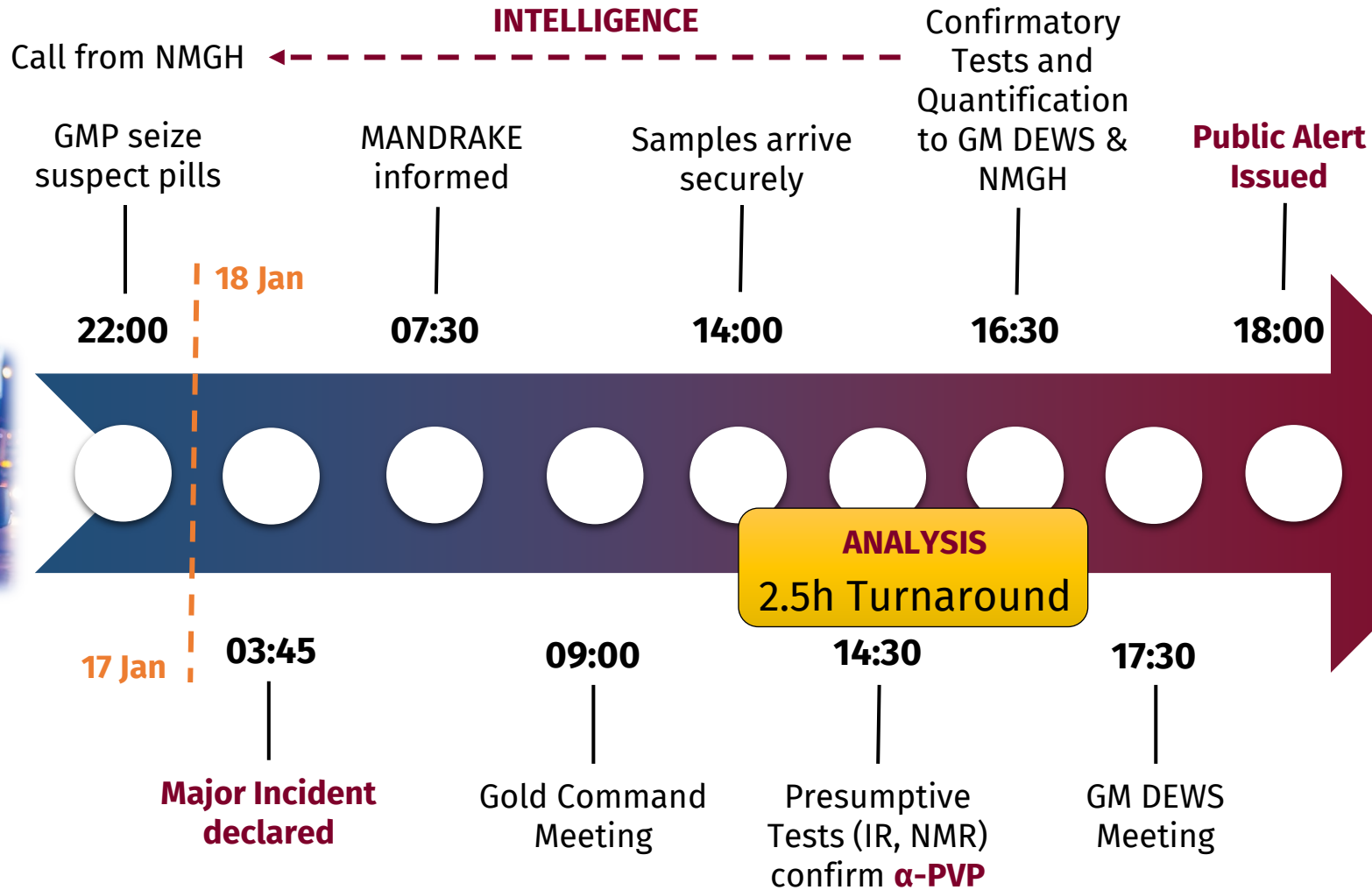


MANDRAKE – Our Focus – The Deathly Hallows





Case Study – The Bury Incident – 17 Jan 2019



Greater Manchester Drug Early Warning System 18.01.2019

WARNING

Dangerous pills in circulation in Greater Manchester

Three young people from Bury are in a serious condition in hospital after taking pills they thought were ecstasy (MDMA)

Dangerous pills sold as MDMA (ecstasy)

The pills are described as badly made and crumbly and were believed to have been "home made". They are beige in colour and stamped with the UPS logo. They are described as smelling of vomit.

The pills contained an extremely high dose of: Alpha-PVP
Alpha-PVP is an hallucinogenic stimulant drug. The dose present in the pills was up to 8 times higher than what is normally considered a strong dose of Alpha-PVP.

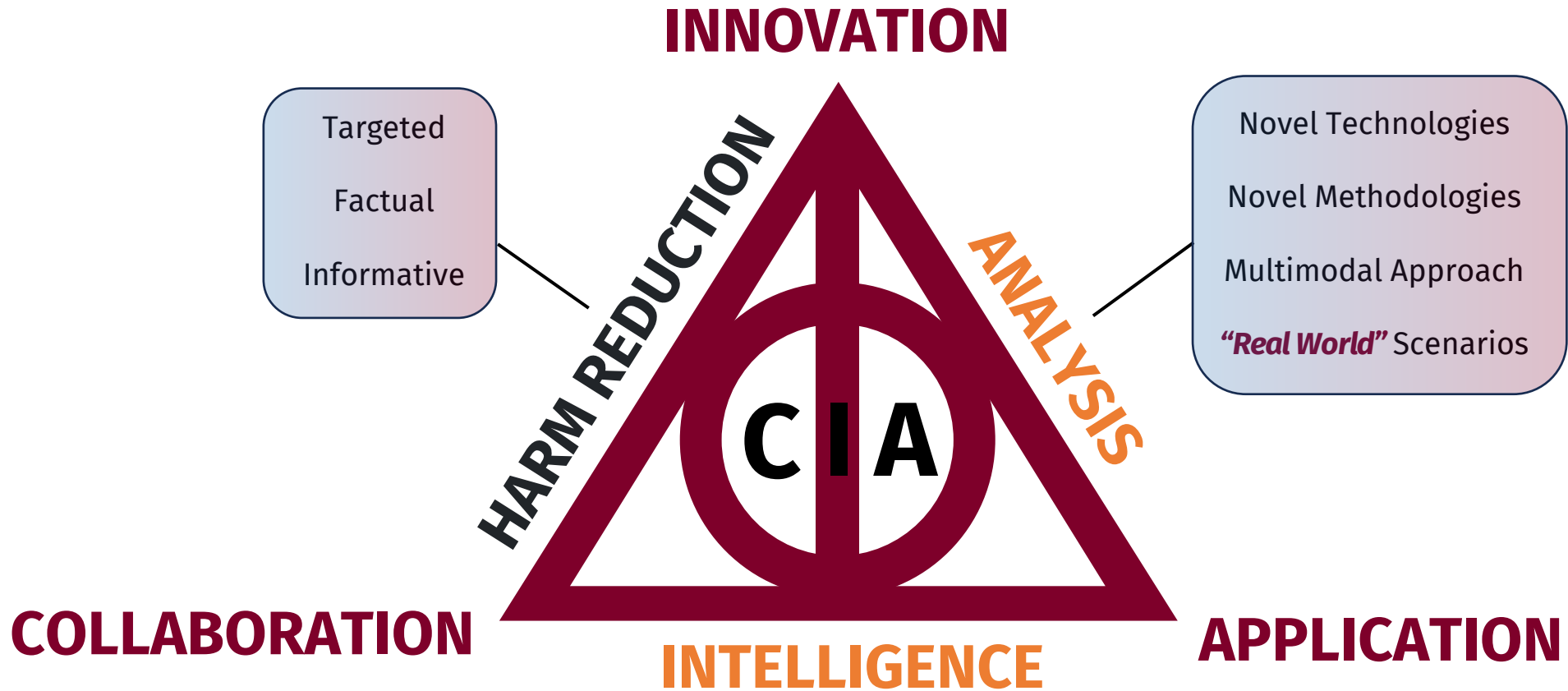
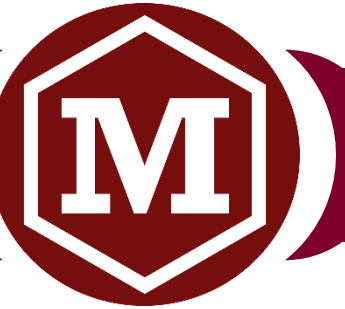
- The three young people experienced a severe adverse reaction that lasted 20 hours. Symptoms included psychosis, distress; severe paranoia. They are still in a serious condition in hospital.
- Alpha-PVP may cause racing heart rate, agitation, high blood pressure, hallucinations and delirium. Alpha-PVP may be fatal especially in combination with other drugs.

• These pills contain extremely dangerous doses of Alpha-PVP.
• DO NOT TAKE THEM.
• If you have any please dispose of them down the toilet.
• In case of any concerns or emergency ring for an ambulance

HARM REDUCTION

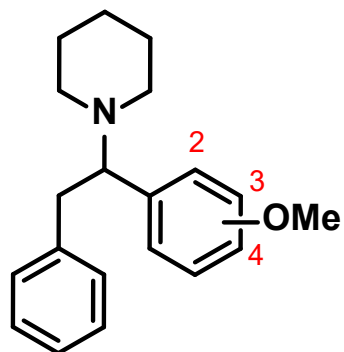


Harm Reduction thro' Excellence in Science





Regioisomeric Discrimination of NPS



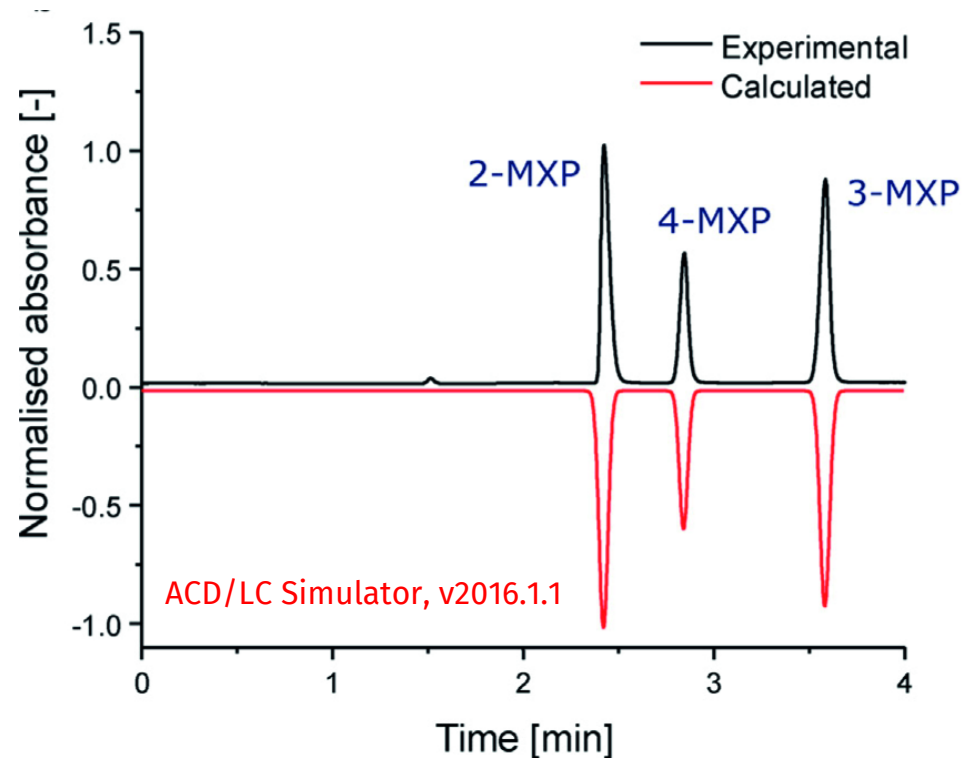
methoxphenidines

NMDAR affinity

2-MXP ($K_i = 36.0$ nM)

3-MXP ($K_i = 19.3$ nM)

4-MXP ($K_i = 461.0$ nM)



Conditions: SP: ACE-C₁₈-AR (50 x 4.6 mm, 3 μ m); Flow rate: 0.3 mL/min, MP: MeCN/10 mM NH₄OAc (pH 6.8) [1]

Thirty-three diphenidine derivatives.

UHPLC-MS/MS

Linear gradient (**10 min**)

Three MRM transitions for each analyte coupled with retention times, allowed for unambiguous identity and confirmation [2]

SFC-UV

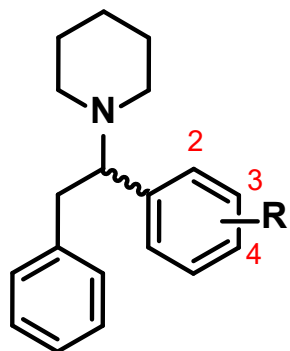
Linear gradient (**<10 min**)

Orthogonal Elution
(3-MXP < 4-MXP < 2-MXP) [3]

[1] Boateng et al., *J. Pharm. Biomed. Anal.*, **2018**, 153, 238; [2] Field et al., *J. Pharm. Biomed. Anal.*, **2022**, 216, 114798; [3] Cochrane et al., *J. Pharm. Biomed. Anal.*, **2022**, 216, 114797; [4] Euerby et al., *ISC2024*, **2024**, "Fentanyl" Board 187 (7 Oct 2024)



Enantiomeric Discrimination of NPS

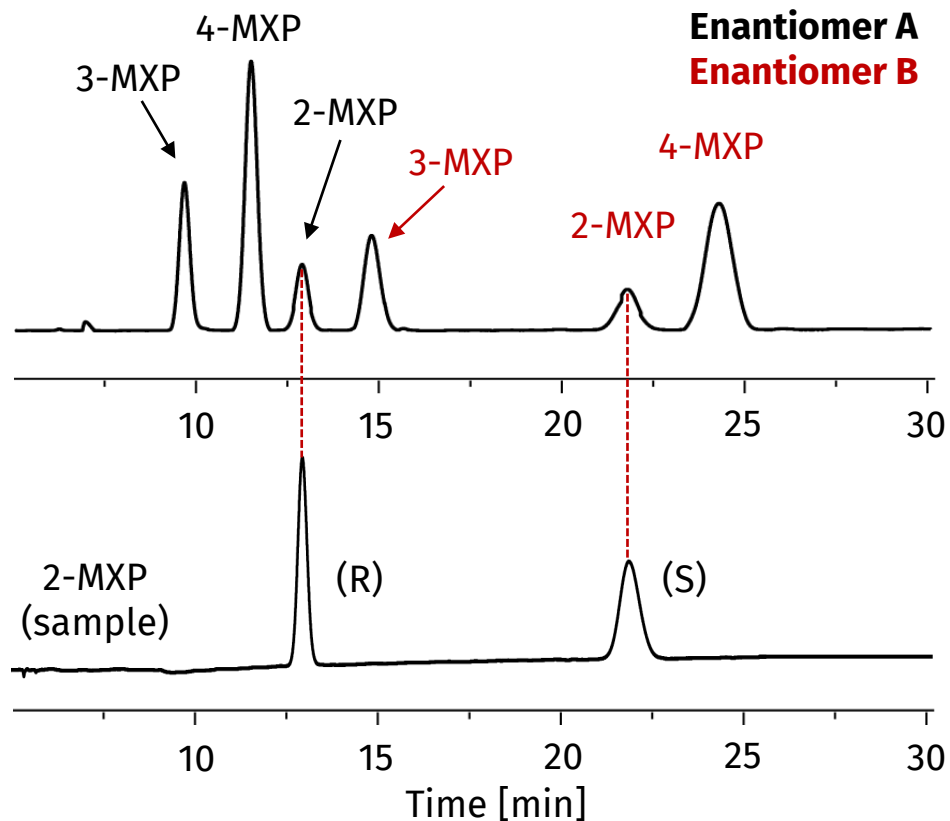


R = H (diphenidine)
R = OMe (methoxphenidines)

NMDAR affinity

(+)-(S)-diphenidine ($K_i = 130$ nM)

(-)-(R)-diphenidine ($K_i = 5.25$ nM)



Conditions: SP: Lux Cellulose-2 (150 x 4.6 mm, 5 μ m);
Flow rate: 1.0 mL/min, MP: 95:5:0.1:0.1 %v/v/v/v
MeCN:IPA:FA:DEA [1]

Lux Cellulose-2

(-)-(R)-2-MXP **before** (+)-(S)-2-MXP

Lux i-Amylose-3

(+)-(S)-2-MXP **before** (-)-(R)-2-MXP

Street samples are **racemic**.

Thirty-two diphenidone derivatives.

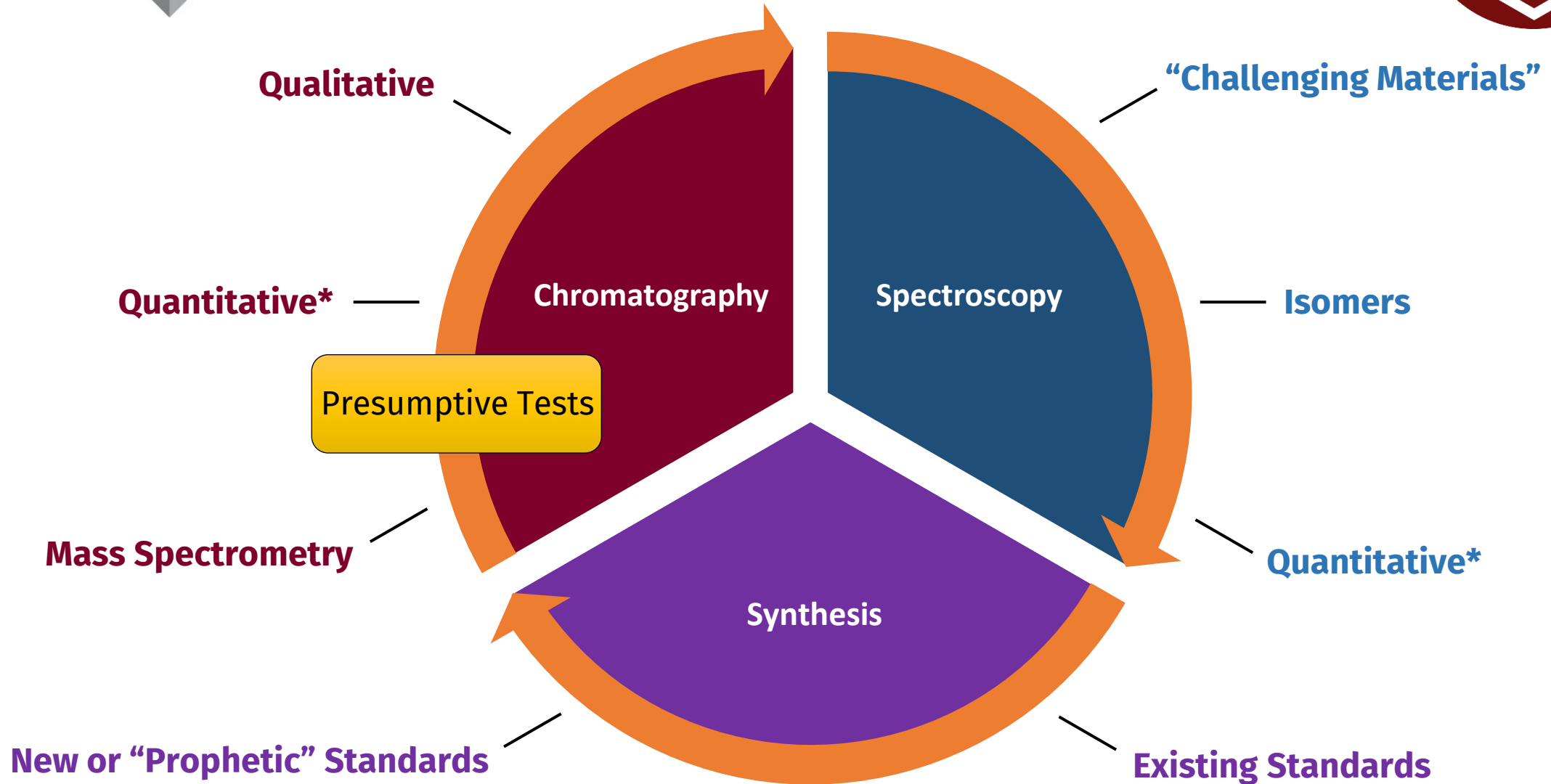
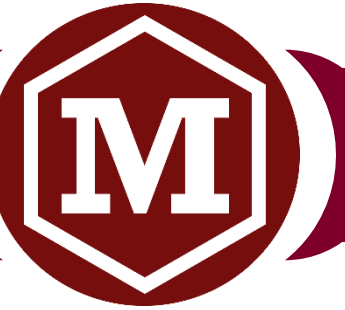
Resolution: *ortho*- < *meta*- < *para*-

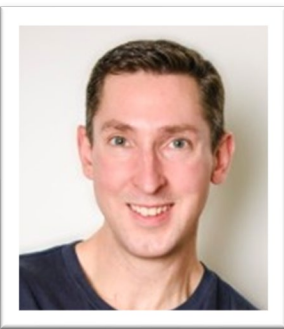
Speculative assignment of enantiomers.

Preparation of enantiopure standards is ongoing.

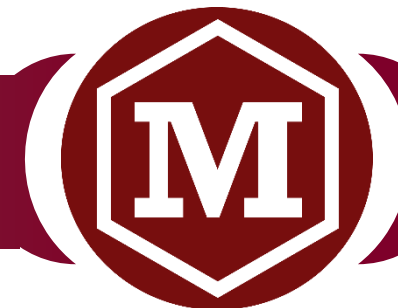


Holistic Approach to the Analysis of Drugs



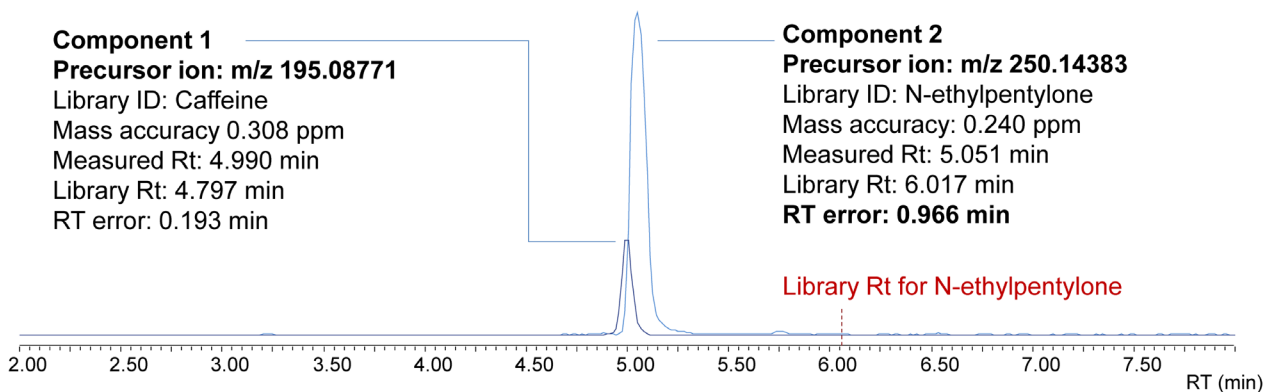


Skeletalisomeric Discrimination of NPS

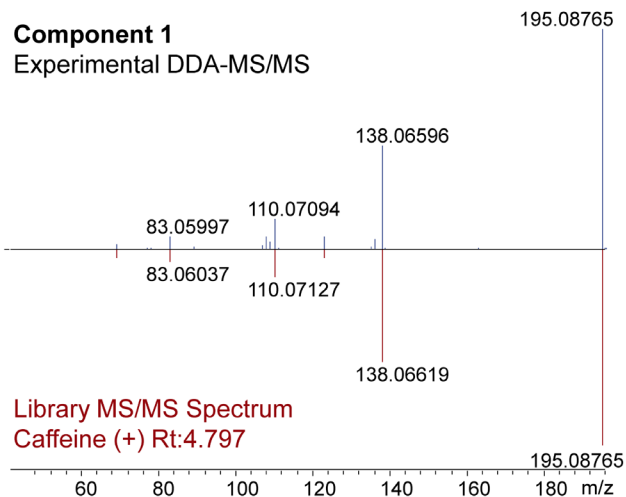


Component 1
Precursor ion: m/z 195.08771
Library ID: Caffeine
Mass accuracy 0.308 ppm
Measured Rt: 4.990 min
Library Rt: 4.797 min
RT error: 0.193 min

Component 2
Precursor ion: m/z 250.14383
Library ID: N-ethylpentylone
Mass accuracy: 0.240 ppm
Measured Rt: 5.051 min
Library Rt: 6.017 min
RT error: 0.966 min

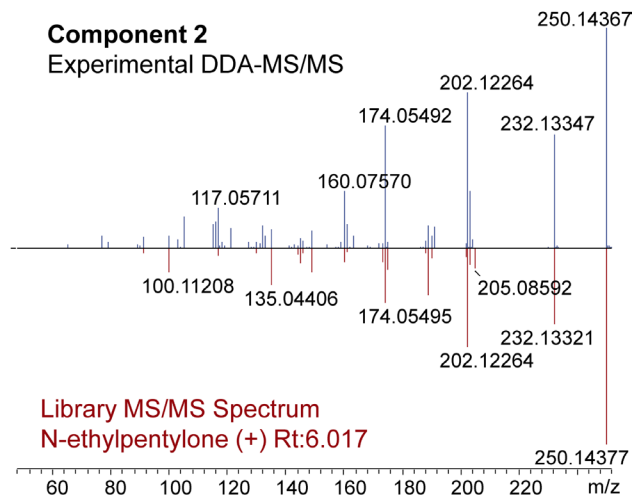


Component 1
Experimental DDA-MS/MS



Library MS/MS Spectrum
Caffeine (+) Rt: 4.797

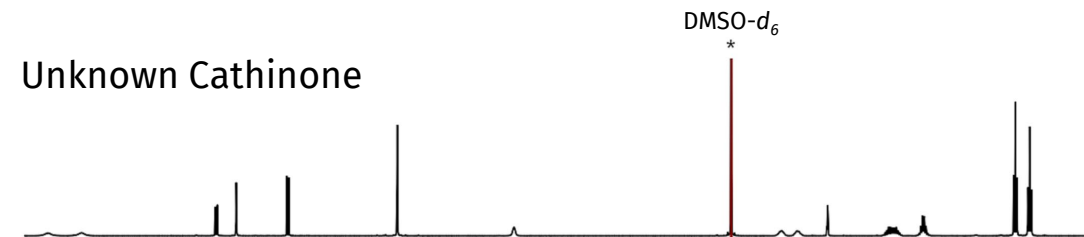
Component 2
Experimental DDA-MS/MS



Library MS/MS Spectrum
N-ethylpentylone (+) Rt: 6.017

NMR (500 MHz) Analysis:

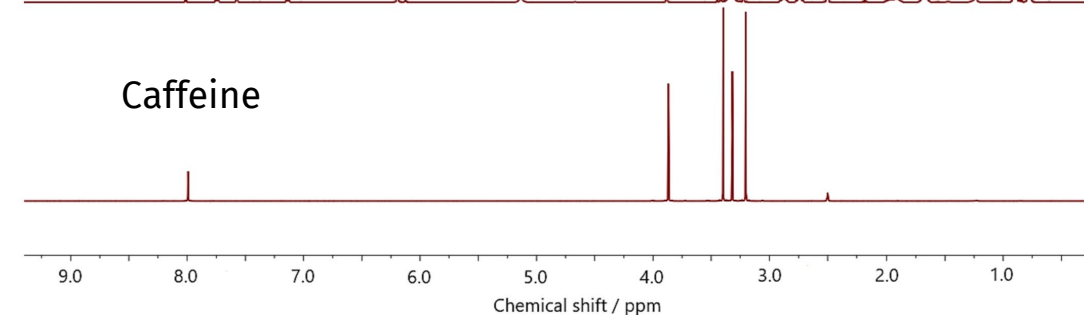
Unknown Cathinone



"Seized tablets"



Caffeine



GC-EI-MS analysis indicates N-ethylpentylone
NMR **does not** match literature for N-ethylpentylone

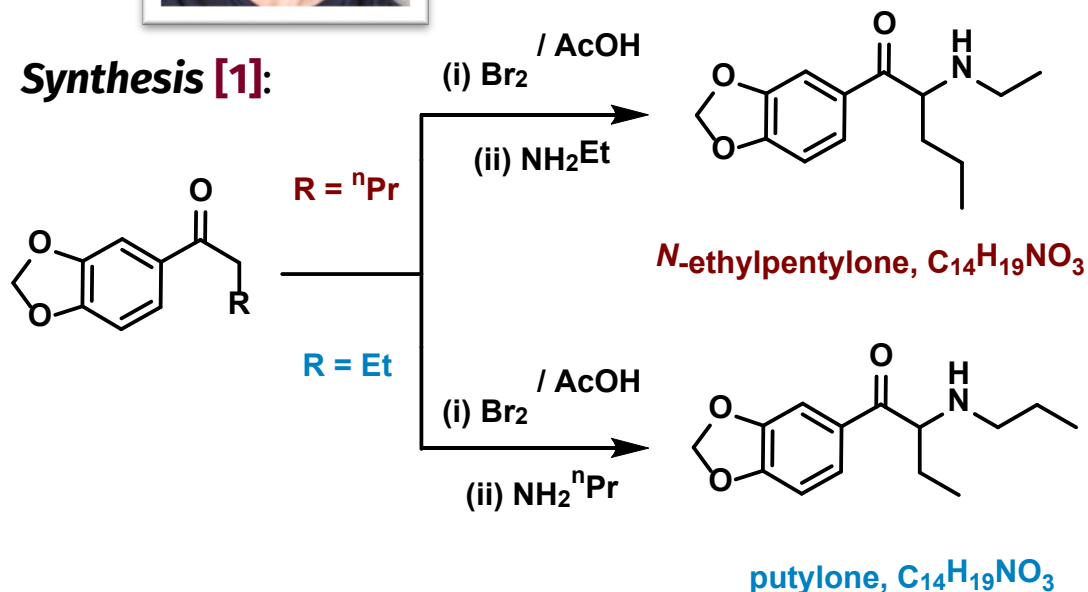
Conditions: SP: Shim-pack Velox Biphenyl (100 x 2.1 mm, 2.7 μ m); Temp. 40 $^{\circ}$ C, Flow rate: 0.3 mL/min, MP: MeOH/2 mM NH_4HCO_2 /0.002% HCOOH



Skeletalisomeric Discrimination of NPS



Synthesis [1]:



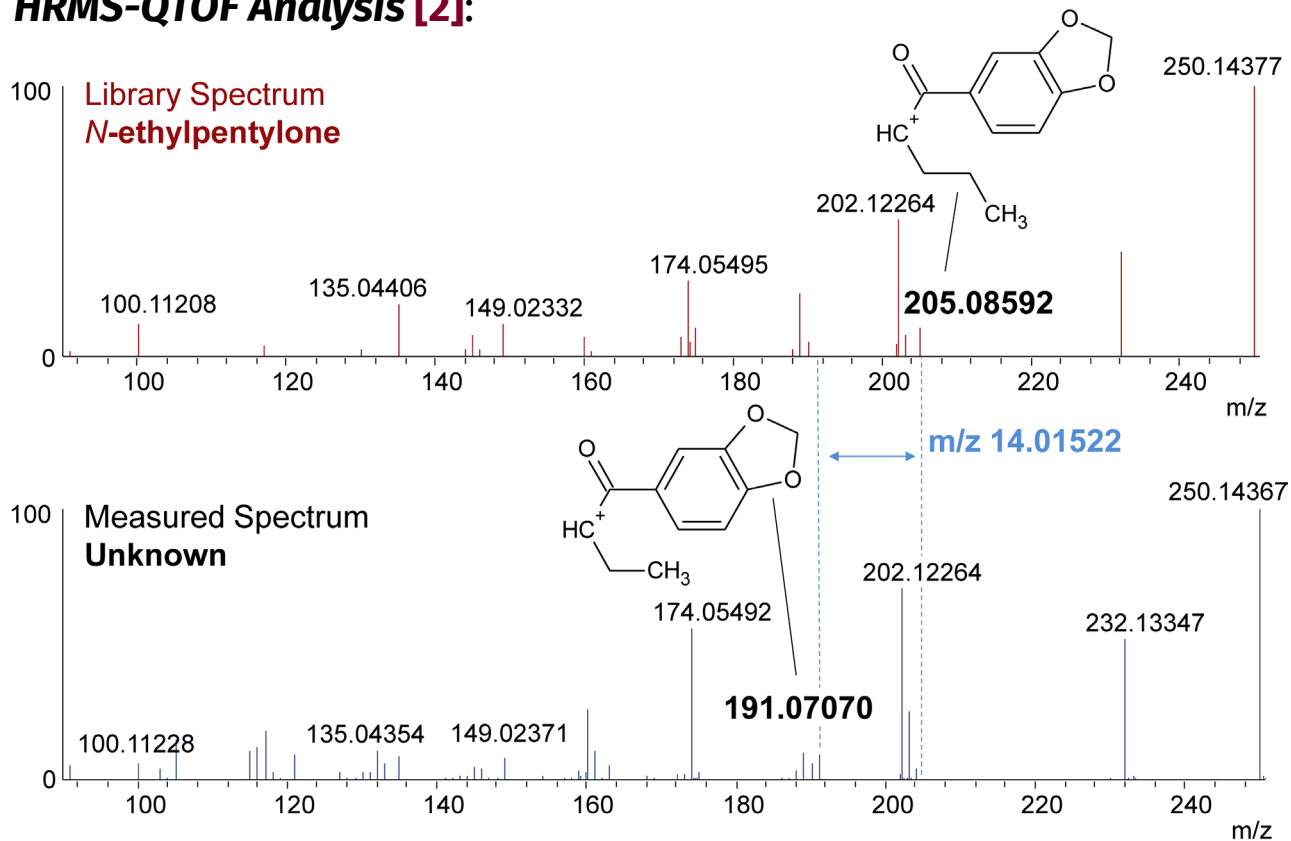
Synthesised **putylone** reference standard has $t_R = 5.05$ min

The standard was used to quantify the seized tablets

Putylone (130.6–135.5 mg/tablet)

Caffeine (40.2–43.4 mg/tablet).

HRMS-QTOF Analysis [2]:



Applied to other examples of **novel cathinones**



Manchester – Our Journey Continues...



THIS IS A MANCHESTER-LED SOLUTION



Acknowledgements



Manchester Metropolitan University

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Ms Emily Dawber
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Thank you for your attention

*Affiliated to Shimadzu UK Limited