

‘Synthesise, Characterise, Analyse (SCA)’: A multidisciplinary approach to tackling New Psychoactive Substances (NPS)

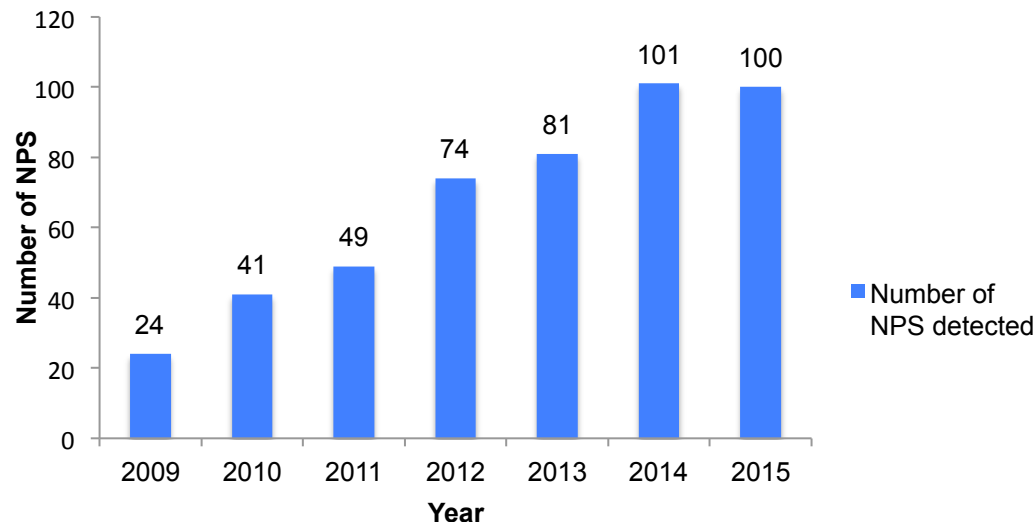
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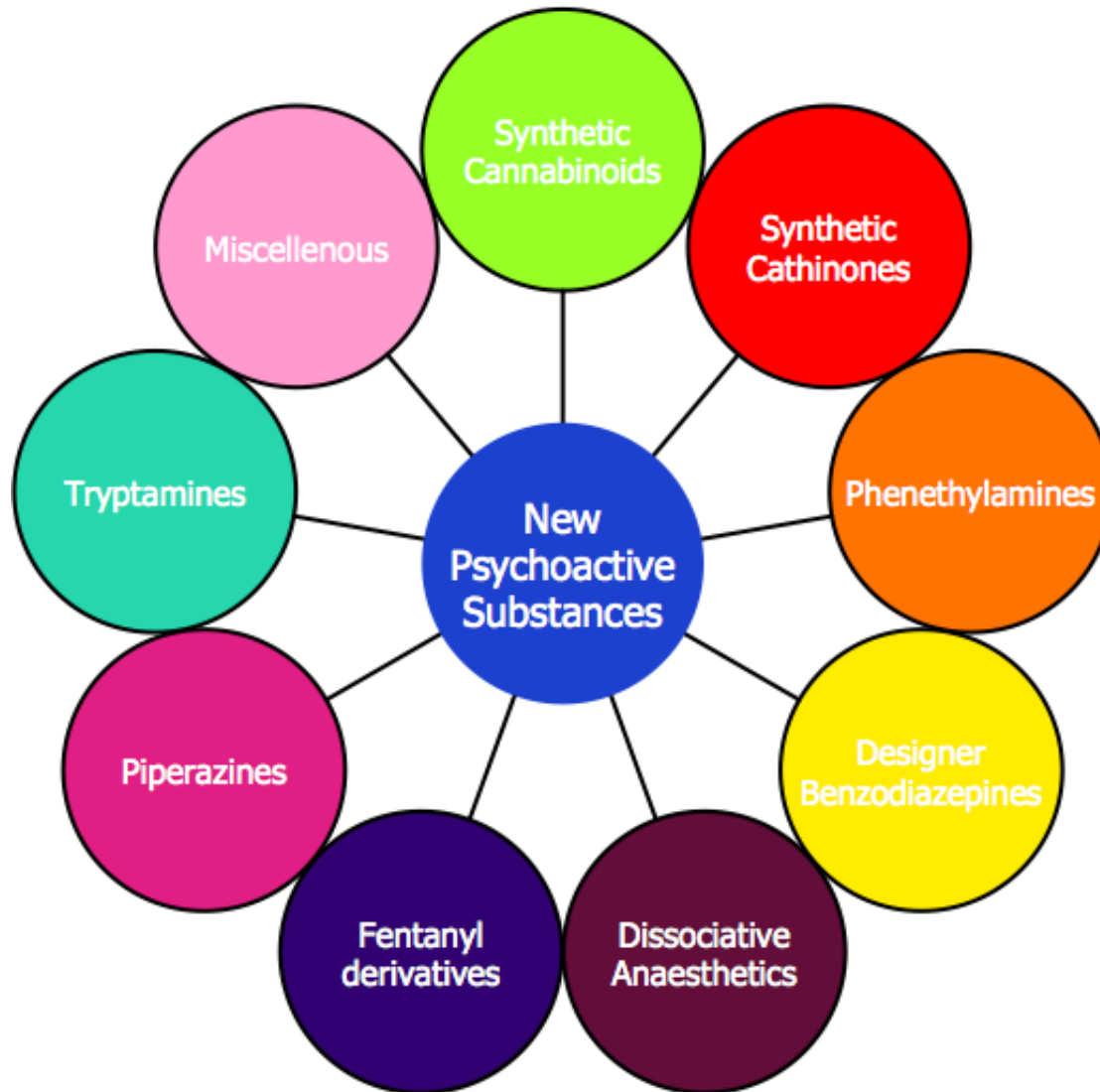
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New Psychoactive Substances (NPS)

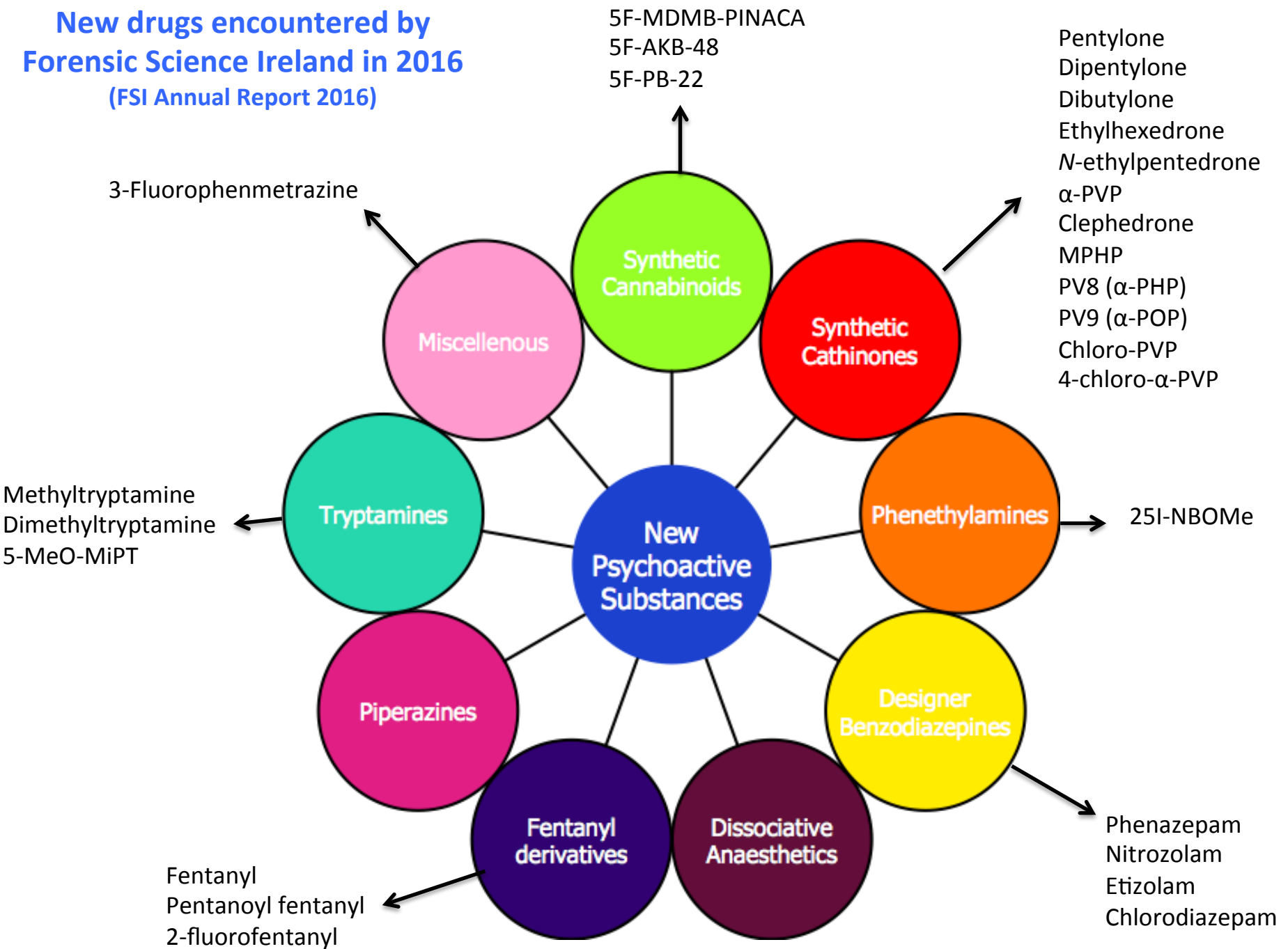
- In recent years, there has been an unprecedented increase in the number, types and seizures of chemicals frequently referred to as new psychoactive substances (NPS).
- The constant release of NPS onto the recreational drug market continues to create challenges for scientists in the forensic, clinical and toxicology disciplines.



Categories



**New drugs encountered by
Forensic Science Ireland in 2016**
(FSI Annual Report 2016)



Problems

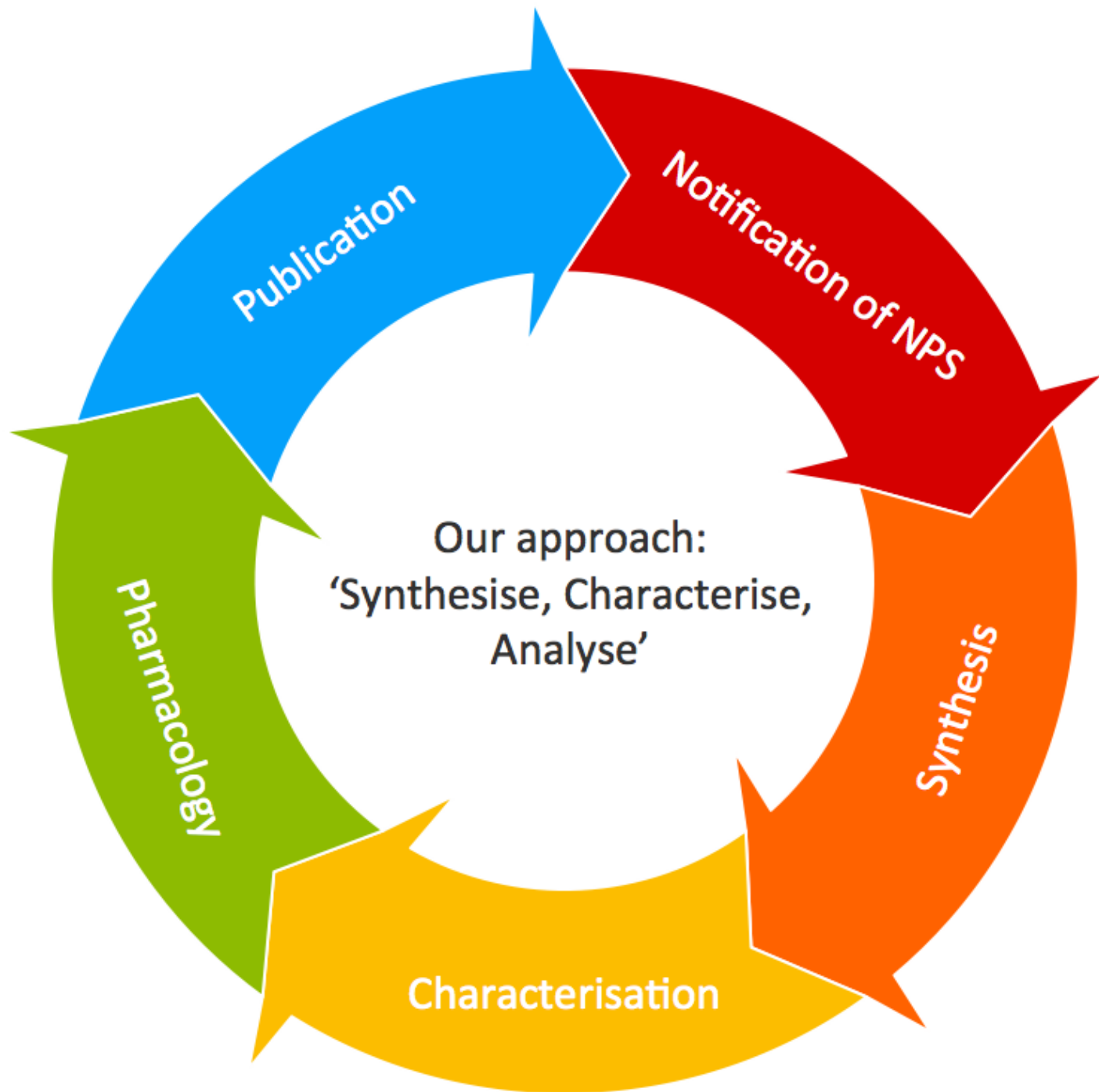
- Main problems:
 - Absence of chemical and pharmacological information
 - Availability (online)
 - Availability of scientific and patent literature
- Forensic Science Laboratories tend to struggle when faced with the challenge of identifying these NPS.
- Most laboratories do not have access to the sophisticated analytical techniques, such as NMR and HR-MS, required for the identification of NPS.
- Absence of chemical reference standards and searchable drug reference libraries.

Current attempts for NPS identification

- Examples: The RESPONSE project & WEDINOS



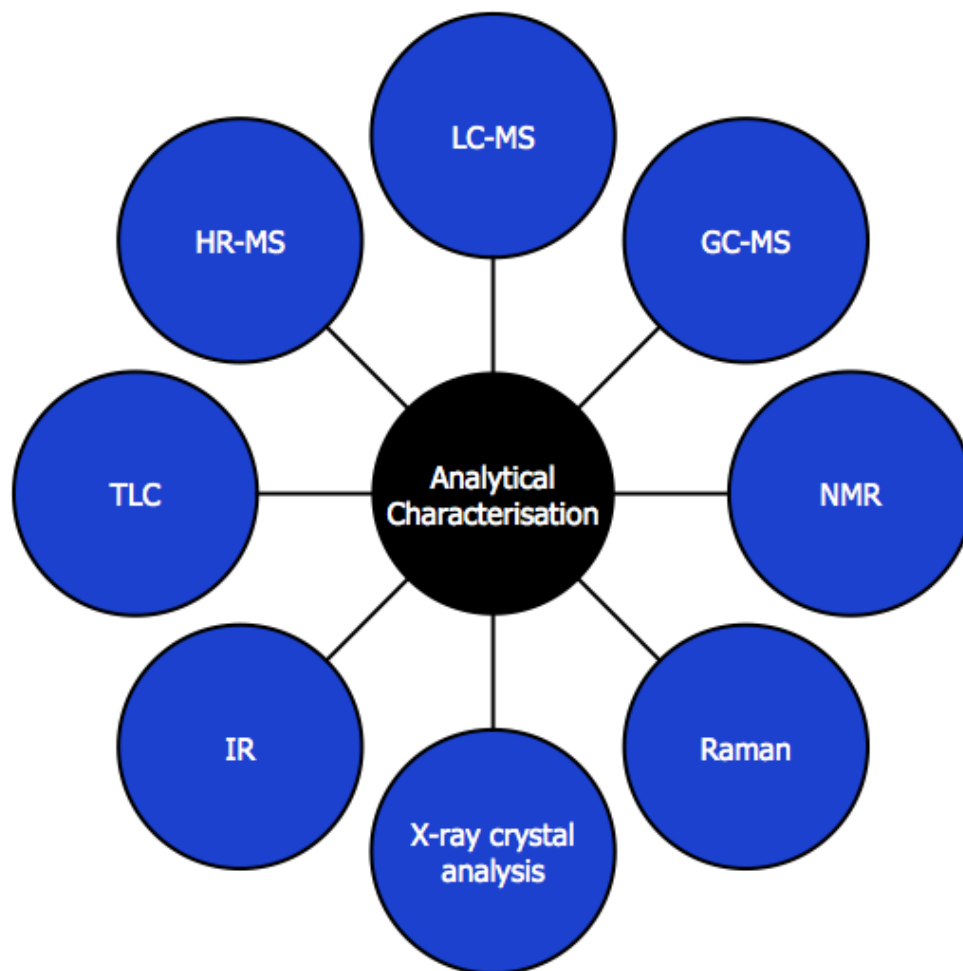
- These projects provide some important analytical details about NPS.
- However, the aims of these projects are not to provide extensive chemical data or pharmacological data on NPS.



Importance of Organic Synthesis

- Facilitates the **unambiguous identification** of an unknown sample through targeted synthesis of all possible isomers.
- Allows synthesis of compounds, which may not be commercially available.
- Allows for the observation of synthesis related **impurities** or route specific **by-products**.
- Extending the synthesis of a currently emerging psychoactive substance to a range of analogues and derivatives provides important **proactive analytical data** to the forensic, law enforcement and clinical communities.
- Once synthesised, these compounds may be used for studies beyond analytical characterisation, such as exploration of pharmacological, metabolism or toxicological features.

Characterisation

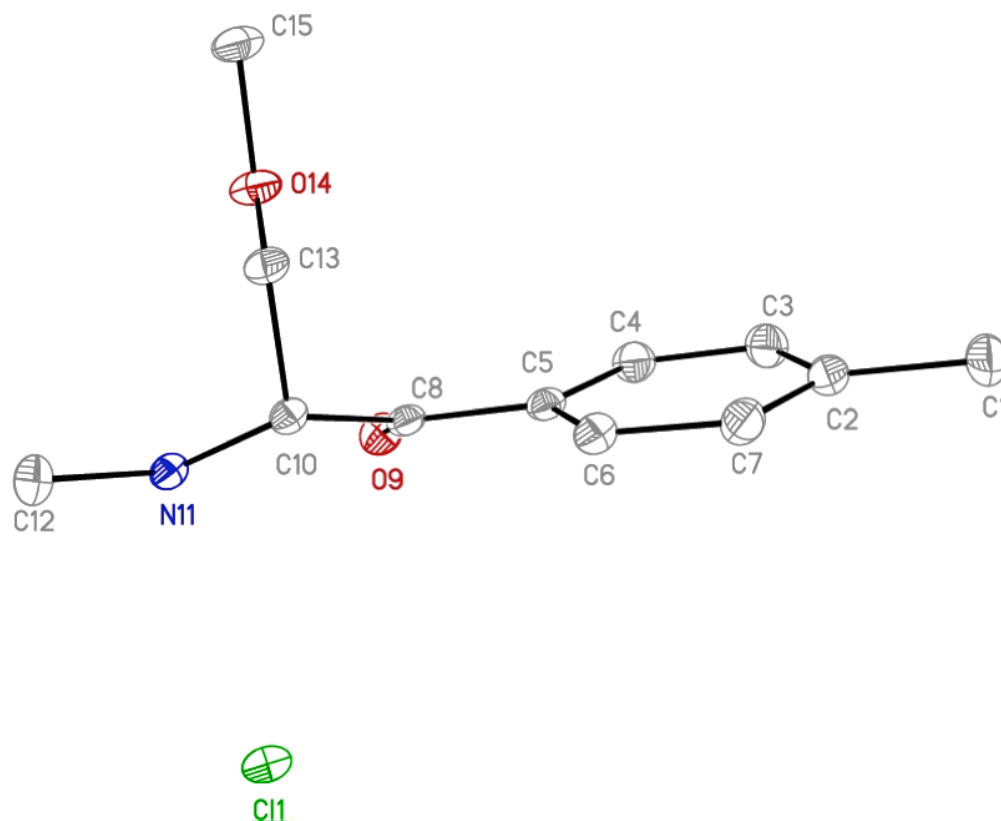


Range of analytical techniques utilised to facilitate the detection, identification and structural elucidation of drugs

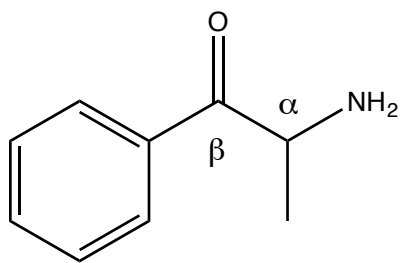
Importance of Pharmacological Evaluation

- **Evaluation of the molecular mechanism of action**
 - ***Technique used:*** *In vitro* Monoamine Transporter Assays in rat brain synaptosomes.
 - ***Information obtained:*** Information on the re-uptake and releasing properties of a selected drug at the dopamine transporters, norepinephrine transporters and serotonin transporters as well as its selectivity for and potency at each transporter.
- **Evaluation of the metabolite profile of NPS**
 - ***Technique used:*** pooled Human Liver Microsomes and LC-MS/MS
 - ***Information obtained:*** Metabolite profile of a selected drug, which aids in the identification of NPS in biological matrices.

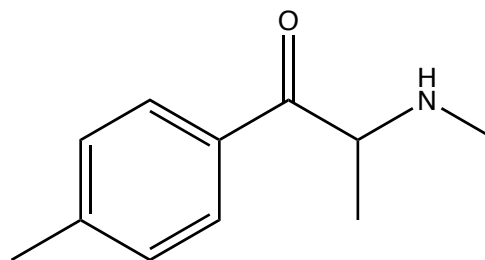
Synthesis, characterisation and monoamine transporter
activity of the New Psychoactive Substance (NPS)
Mexedrone and differentiation from its *N*-methoxy positional
isomer, *N*-methoxymephedrone



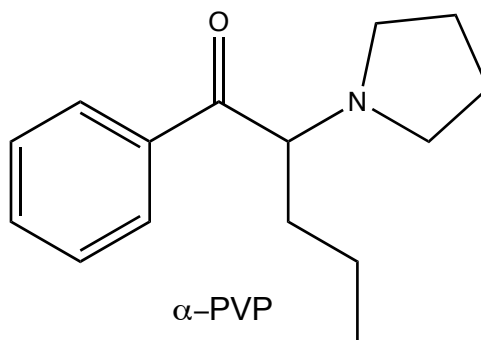
Background



Cathinone

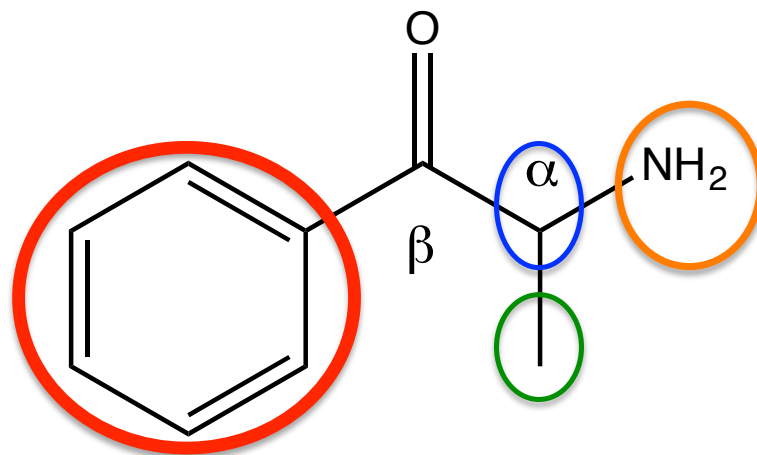


Mephedrone



α -PVP

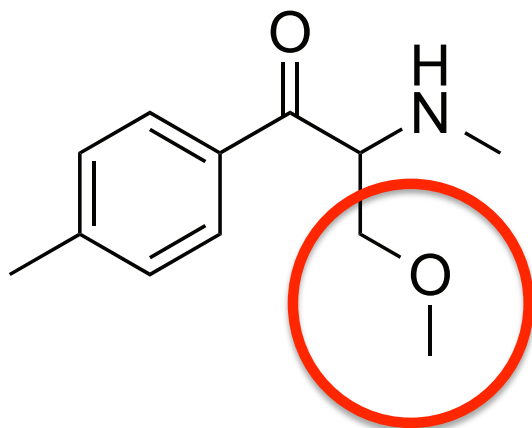
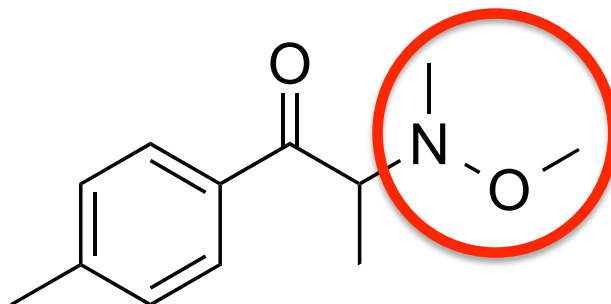
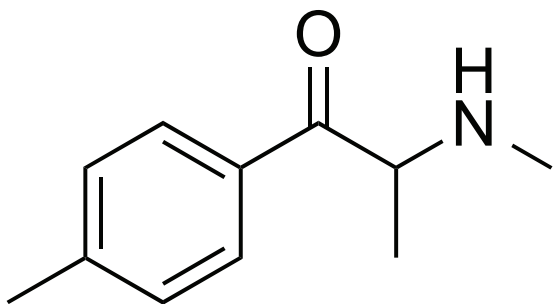
Generic Legislation



Any substance (not being bupropion) structurally derived from 2-amino-1-phenyl-1-propanone by modification in any of the following ways:

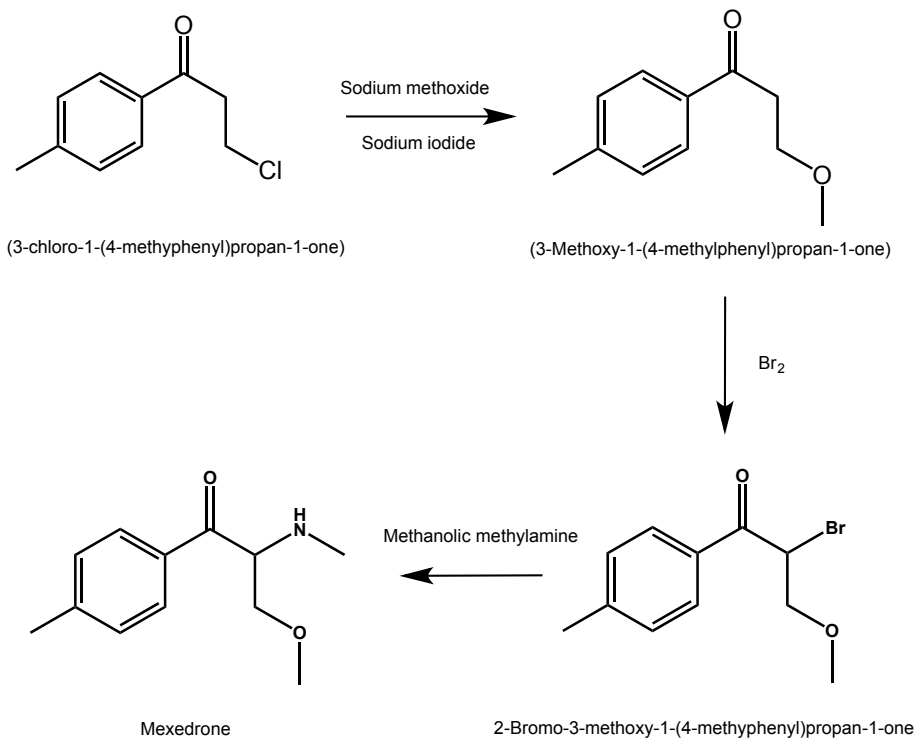
- By substitution in the phenyl ring to any extent with alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylenedioxy, haloalkyl or halo substituents, whether or further in the phenyl ring by one or more other univalent substituents.
- By substitution at the 2- or 3- position of the propanone side chain with alkyl substituents
- By substitution at the nitrogen atom with one or more alkyl or dialkyl groups, or by inclusion of nitrogen atom in a cyclic structure

Replacement for Mephedrone

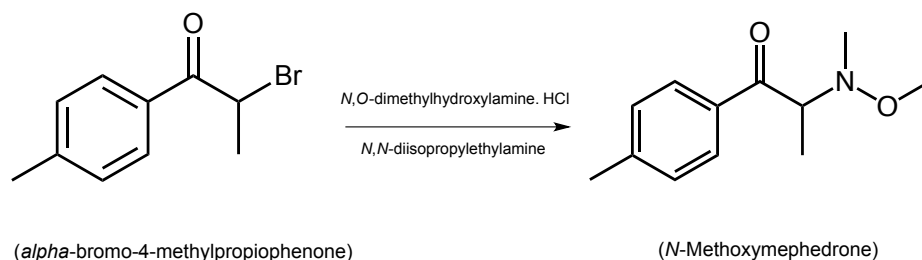


Synthesis of Mexedrone & *N*-methoxymephedrone

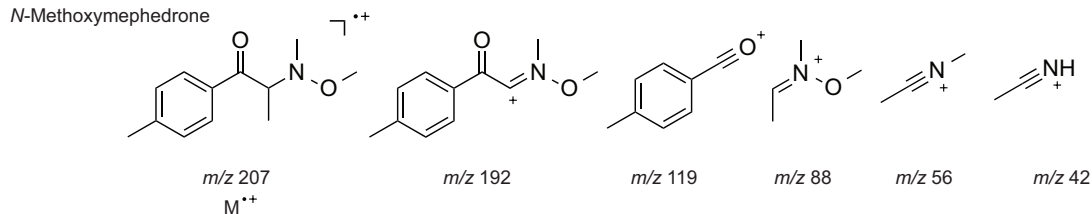
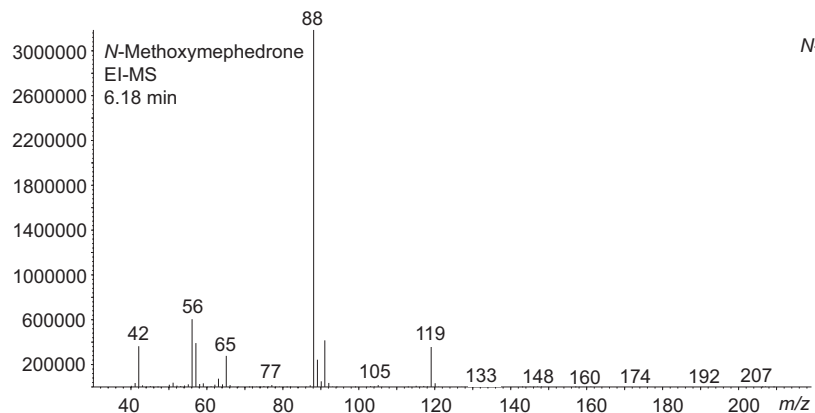
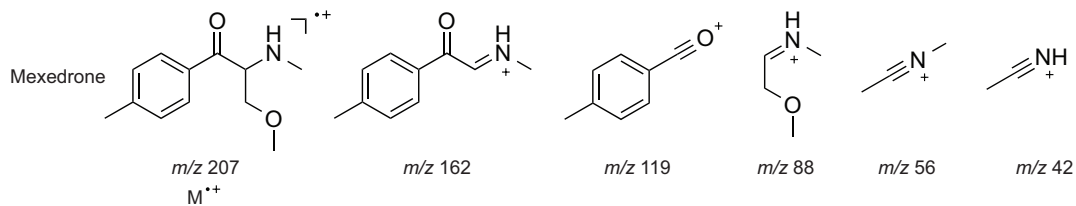
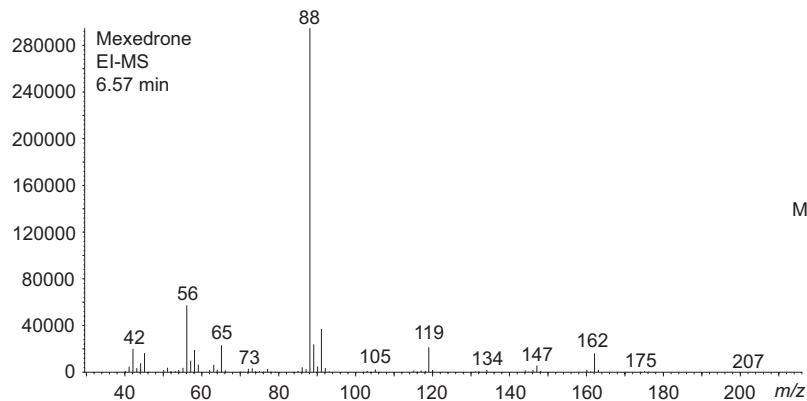
Mexedrone



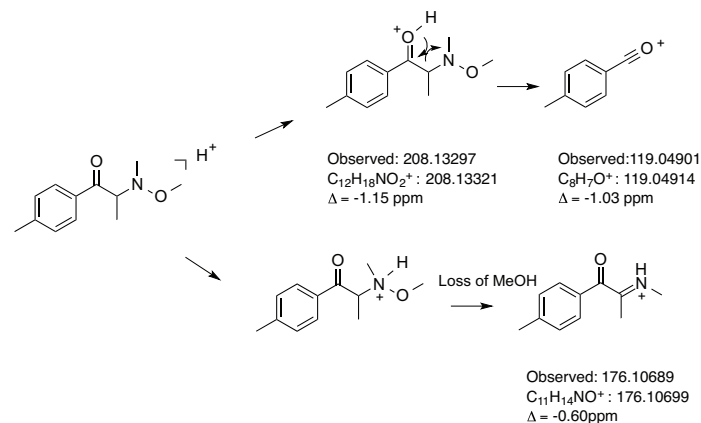
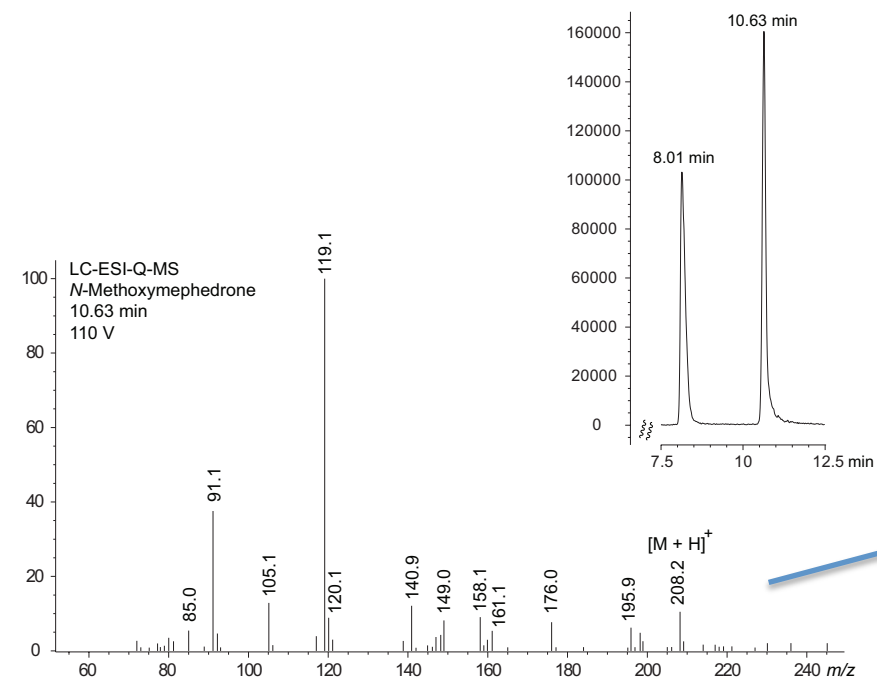
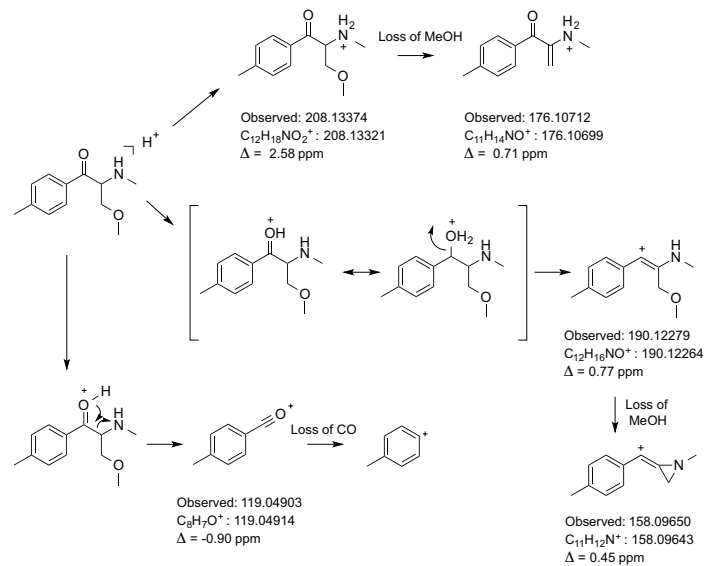
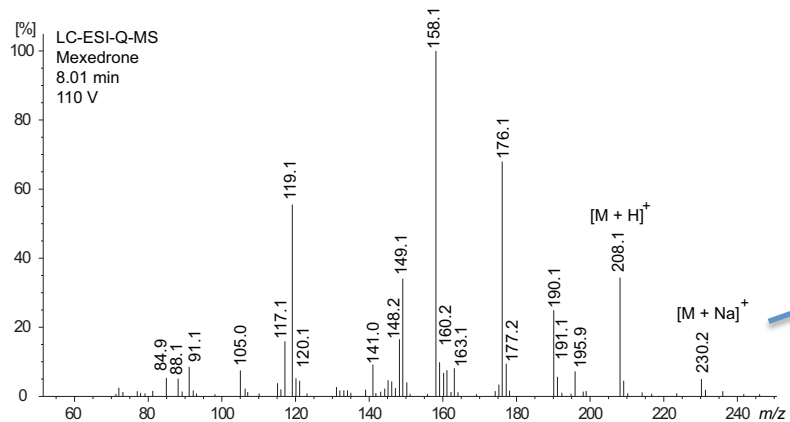
N-methoxymephedrone



Characterisation: GC-MS



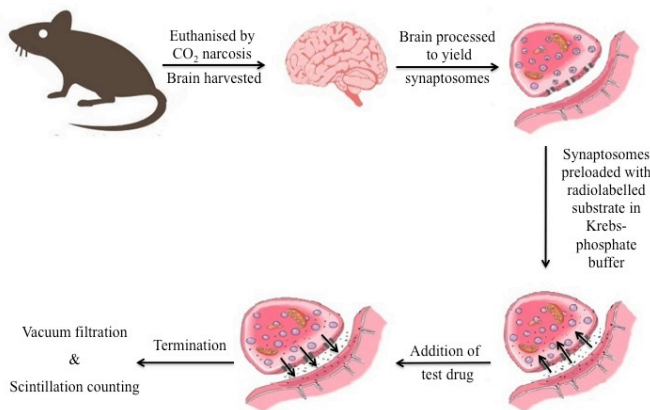
Characterisation: LC-MS



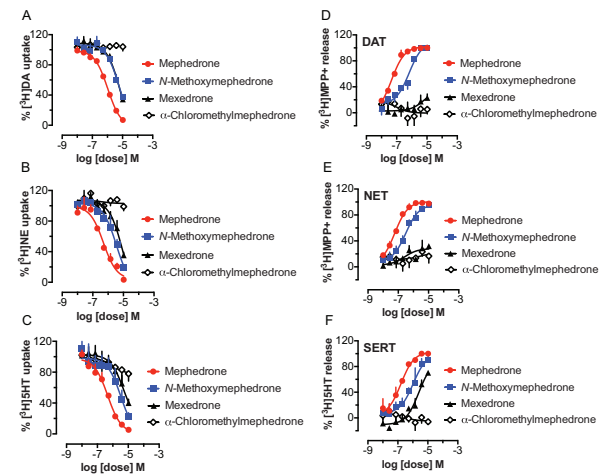
Monoamine Transporter Activity

Pharmacology summary:

- *N*-Methoxymephedrone showed a transporter-mediated releasing profile comparable to mephedrone, although much lower in potency.
- By contrast, mexedrone was found to be a weak monoamine transporter uptake blocker and weak serotonin releasing agent – ‘hybrid’ activity.
- This might explain why this substance received mixed reviews on psychonaut forums.



Schematic representation of the release assay method



Effects of Mexedrone, *N*-methoxymephedrone and mephedrone on inhibition of uptake and stimulation of release at DAT, SERT and NET in rat brain synaptosomes.

Mexedrone: Conclusion

- Chemical profile of mexedrone ascertained.
- Pharmacological evaluation of **mexedrone** concluded it is **much less potent** than **mephedrone**.
- Vendor sample found to contain mexedrone.
- This was the first study on mexedrone, which reiterates the continuous need to remain vigilant on the availability of newly emerging psychoactive substances.

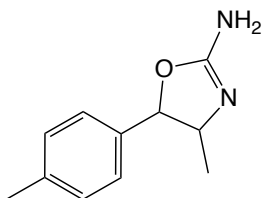
Overall Conclusion

- This approach of combining chemistry with pharmacology allows for the generation of essential data and is an effective approach to tackling an increasingly complex area of investigation where growing demands are placed on investigators in the field of NPS.

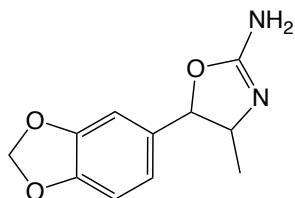
Overall Conclusion

- This 'SCA' approach has been used for several other NPS including:

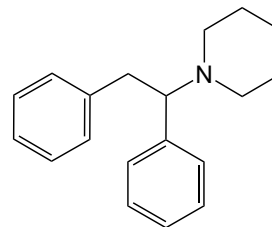
4,4-dimethylaminorex



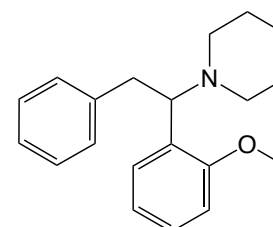
3',4'-methylenedioxy-4-methylaminorex



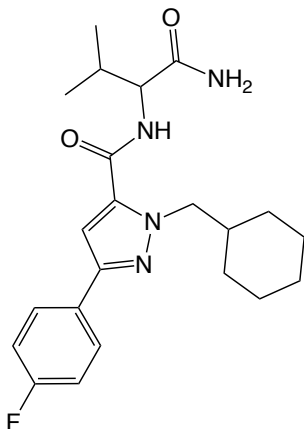
Diphenidine



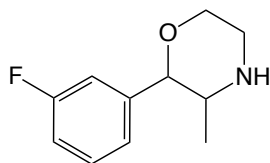
2-Methoxydiphenidine



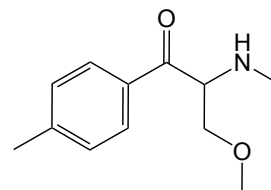
AB-CHMFUPPYCA



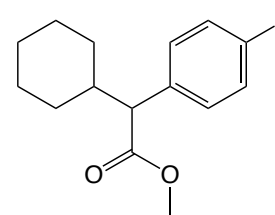
3-Fluorophenmetrazine



Mexedrone



4-Fluoromethylphenidate



Acknowledgements

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- Dr. Rachel Christie (EMCDDA)
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- Dr. Volker Aüwarter and his colleagues (University Medical Center Freiburg)

Publication list

1. Gavin McLaughlin, Noreen Morris, Pierce V. Kavanagh, John D. Power, Geraldine Dowling, Brendan Twamley, John O'Brien, Gary Hessman, Brian Murphy, Donna Walther, John S. Partilla, Michael H. Baumann, Simon D. Brandt. Analytical characterization and pharmacological evaluation of the new psychoactive substance 4-fluoromethylphenidate (4F-MPH) and differentiation between the (\pm)-threo and (\pm)-erythro diastereomers. *Drug Testing and Analysis*. 2017, 9, 347-357. DOI: 10.1002/dta.2167
2. John D. Power, Pierce V. Kavanagh, Gavin McLaughlin, Michael Barry, Geraldine Dowling, Simon D. Brandt. 'APAAN in the neck' – A reflection on some novel impurities found in seized materials containing amphetamine in Ireland during forensic analysis. *Drug Testing and Analysis*. 2017. DOI: 10.1002/dta.2194
3. Geraldine Dowling, Pierce V. Kavanagh, Brian Talbot, John O'Brien, Gary Hessman, Gavin McLaughlin, Brendan Twamley, Simon D. Brandt. Outsmarted by nootropics? An investigation into the thermal degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and CRL-40,941 in the GC injector: formation of 1,1,2,2-tetraphenylethane and its tetra fluoro analog. *Drug Testing and Analysis*. 2017, 9, 446-452. DOI: 10.1002/dta.2142
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5. Florian Franz, Verena Angerer, Simon D. Brandt, Gavin McLaughlin, Pierce V. Kavanagh, Bjoern Moosmann, Volker Auwärter. In vitro metabolism of the synthetic cannabinoid 3,5-AB-CHMFUPPYCA and its 5,3-regioisomer and investigation of their thermal stability. *Drug Testing and Analysis*. 2017, 9, 311-316. DOI: 10.1002/dta.1950.
6. Gavin McLaughlin, Noreen Morris, Pierce V. Kavanagh, Geraldine Dowling, John D. Power, Brendan Twamley, John O'Brien, Brian Talbot, Harald H. Sitte, Simon D. Brandt. Test purchase, synthesis and characterization of 3-fluorophenmetrazine (3-FPM) and differentiation from its ortho- and para-substituted isomers. *Drug Testing and Analysis*. 2017, 9, 369-377. DOI: 10.1002/dta.1945.

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10. John D. Power, Pierce Kavanagh, Gavin McLaughlin, John O'Brien, Brian Talbot, Michael Barry, Brendan Twamley, Geraldine Dowling, Simon D. Brandt. Identification and characterization of an imidazolium by-product formed during the synthesis of 4-methylmethcathinone (mephedrone). *Drug Testing and Analysis*. 2015, 7, 894-902. DOI: 10.1002/dta.1789.
11. Gavin McLaughlin, Noreen Morris, Pierce V. Kavanagh, John D. Power, Brendan Twamley, John O'Brien, Brian Talbot, Geraldine Dowling, Olivia Mahony, Simon D. Brandt, Julian Patrick, Roland P. Archer, John S. Partilla, Michael H. Baumann. Synthesis, characterization and monoamine transporter activity of the new psychoactive substance 3',4'-methylenedioxy-4-methylaminorex (MDMAR). *Drug Testing and Analysis*. 2014, 7, 555-564. DOI: 10.1002/dta.1732.
12. Jason Wallach, Pierce V. Kavanagh, Gavin McLaughlin, Noreen Morris, John D. Power, Simon P. Elliott, Marion S. Mercier, David Lodge, Hamilton Morris, Nicola M. Dempster, Simon D. Brandt. Preparation and characterization of the 'research chemical' diphenidine, its pyrrolidine analogue, and their 2,2-diphenylethyl isomers. *Drug Testing and Analysis*. 2014, 7, 358-367. DOI: 10.1002/dta.1689