Rapid Identification of New Psychoactive Substances by Multinuclear NMR Spectroscopy

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Motivation

- Amphetamines eg ICE & Ecstacy, are the most commonly trafficked fully synthetic drugs, but there is an increasing trend towards other so-called 'designer drugs'.
- Typically, ***analogues*** are of prohibited psychoactive drugs; structural changes are aimed at circumventing legal controls whilst retaining psychoactivity.
- Explosion in the number of these new psychoactive substances appearing in Australia and around the world,
- Need for rapid identification and classification in order to assist law enforcement and protect the community.
- Most of these psychoactive compounds contain –N, and here we demonstrate that, together with ^{1}H and ^{13}C Analysis, ^{1}H-^{15}N 2D NMR correlation spectra are especially useful as part of routine screening.

Synthetic Cannabinoids

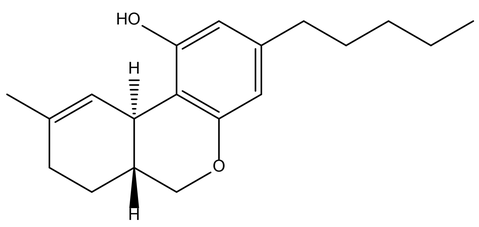


Fig.1 THC

Non-classical cannabinoids, or cannabimimetics, are synthetic compounds that act upon cannabinoid receptors in the brain, but are structurally unrelated to tetrahydrocannabinol (THC, Figure 1). Legitimate research into families of cannabimimetics (like those below) as potential analgesics has spawned less scrupulous interest in similar compounds as potential recreational drugs with cannabis-like effects.[2]

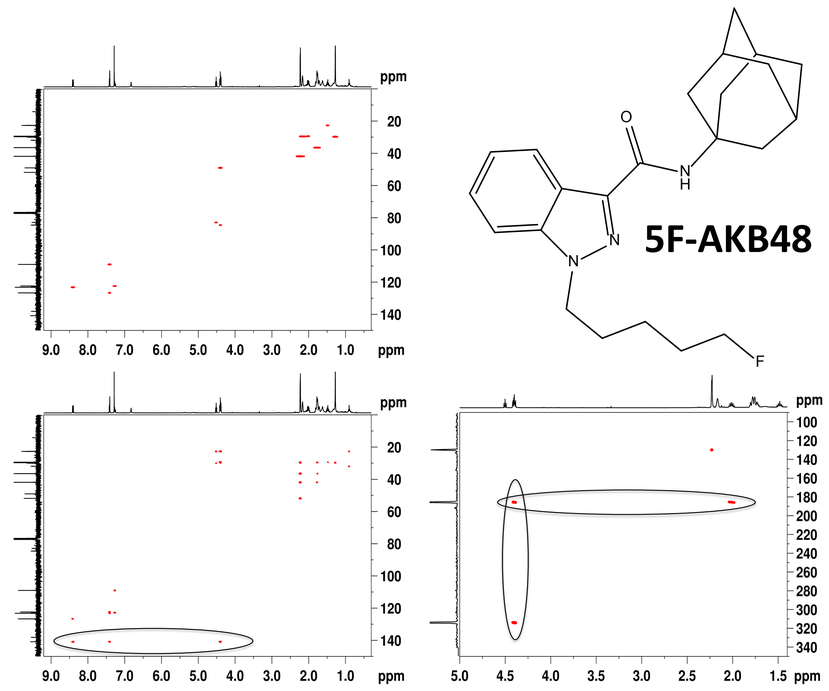


Fig. 2 (anticlockwise from top right) Chemical structure of N-((3s,5s,7s)-adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide; ^{1}H-^{13}C HSQC experiment (105 mins); ^{1}H-^{13}C HMBC experiment (140 mins); ^{1}H-^{15}N HMBC experiment (130 mins). Black ovals identify significant correlations that are indicative of this class of cannabimimetics.

Cathinones

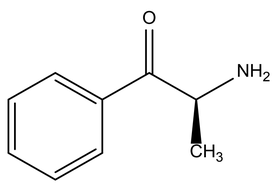


Fig. 3 Cathinone

Cathinone (left) is a stimulant that occurs naturally in the leaves of a plant native to many East African countries, and is an unstable structural analogue of amphetamine.[2]

All cathinone derivatives are examples of keto-phenethylamines, and are distinguished by the ketone functional group adjacent to the phenyl ring.

Numerous analogues of *meth*cathinone are now available, most of which involve substitution of the aromatic ring, or substitution at the amino group.

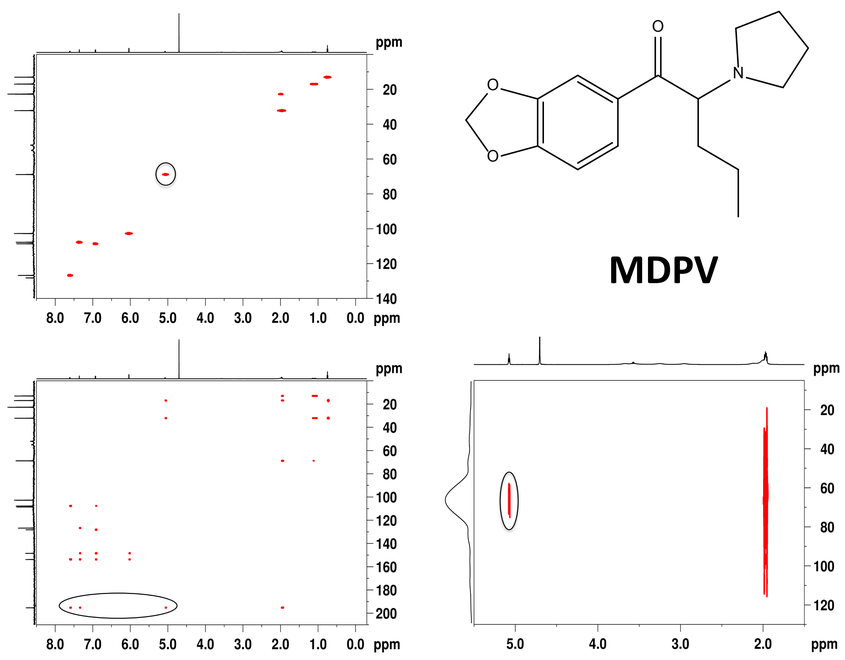


Fig. 4 (anticlockwise from top right) Chemical structure of 3,5-methylenedioxypyrovalerone; ^{1}H-^{13}C HSQC experiment (85 mins); ^{1}H-^{13}C HMBC experiment (360 mins); ^{1}H-^{15}N HMBC experiment (180 mins). Black ovals identify significant correlations that are indicative of cathinone derivatives.

Phenethylamines

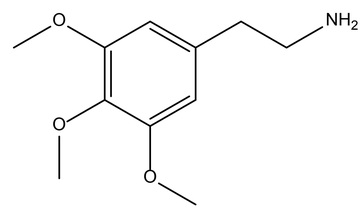


Fig. 5 Mescaline, the hallucinogenic compound found in the peyote cactus.

The phenethylamines include endogenous compounds, such as dopamine, and naturally occurring compounds, such as mescaline (Figure 5). They are known as 2Cs,[3] referring to the two carbon atoms between the amino group and the phenyl ring.

Substitution of methoxy groups at the 2 and 5 positions on the phenyl ring and/or iodine or bromine at the 4 position results in increased hallucinogenic effects.

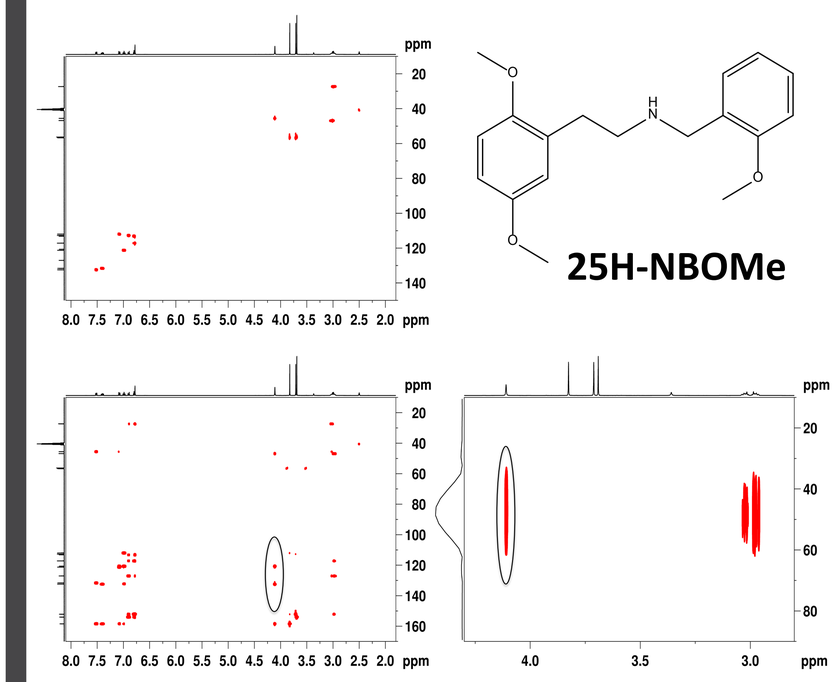


Fig. 6 (anticlockwise from top right) Chemical structure of 2-(2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine; ^{1}H-^{13}C HSQC experiment (15 mins); ^{1}H-^{13}C HMBC experiment (20 mins); ^{1}H-^{15}N HMBC experiment (50 mins). Black ovals identify significant correlations that are indicative of phenethylamine derivatives.

Classification and Identification of Two Unknowns

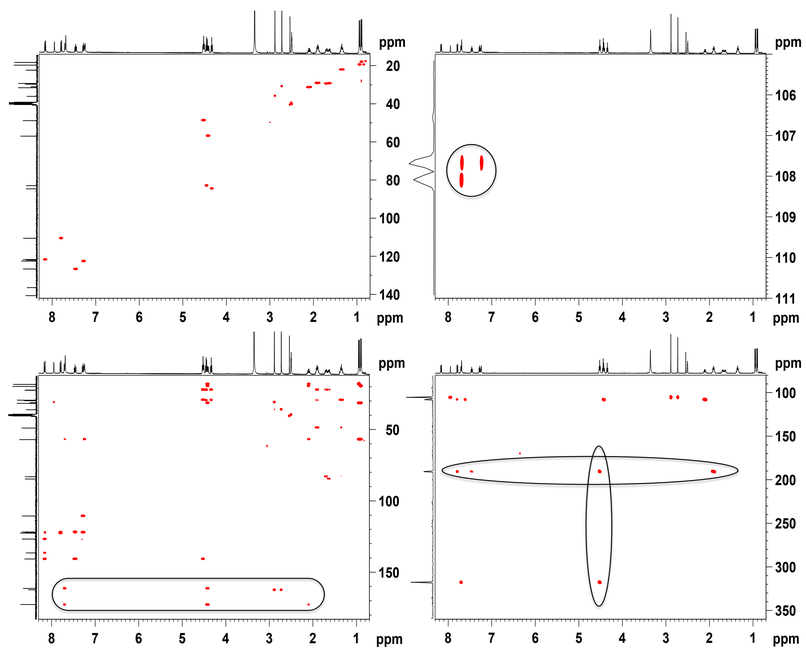
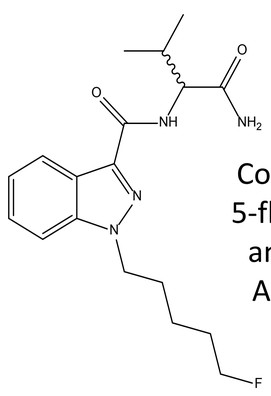
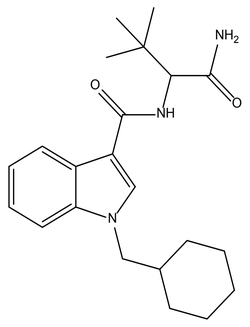


Fig. 7 (anticlockwise from top right) Compound **1** 2D correlation experiments: ^{1}H-^{15}N HSQC (60 mins); ^{1}H-^{13}C HSQC (100 mins); ^{1}H-^{13}C HMBC (140 mins); ^{1}H-^{15}N HMBC (130 mins).
Black ovals highlight some significant correlations, including the indazole and amide nitrogens, and the carbonyl carbons



Compound **1**: 5-fluoropentyl analogue of AB-PINACA



Compound **2:**
N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamide

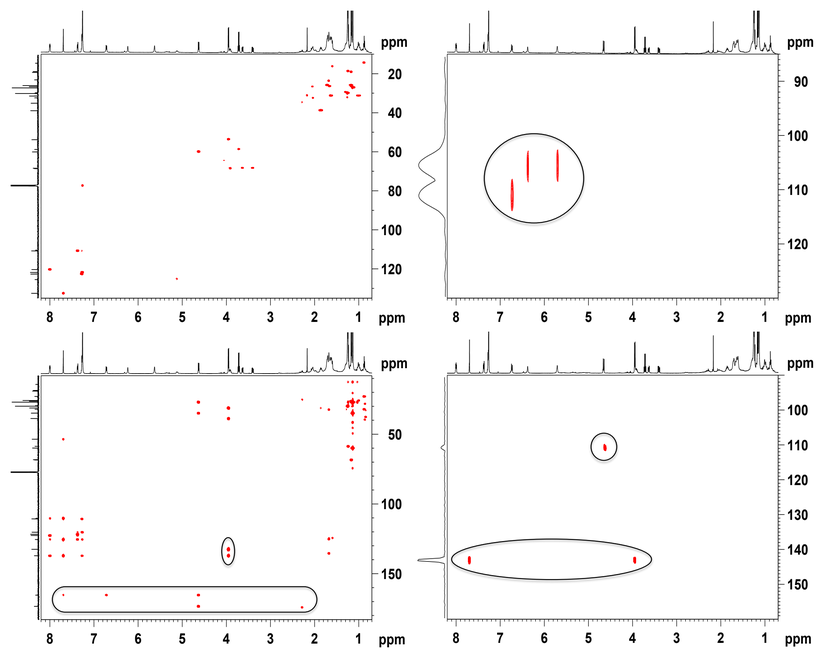


Fig. 8 (anticlockwise from top right) Compound **2** 2D correlation experiments: ^{1}H-^{15}N HSQC (60 mins); ^{1}H-^{13}C HSQC (180 mins); ^{1}H-^{13}C HMBC (360 mins); ^{1}H-^{15}N HMBC (130 mins).
Black ovals highlight some significant correlations, including the indole and amide nitrogens, and the carbonyl carbons.

Concluding Remarks

As more and more structural variations of known psychoactive compounds are produced to avoid specific legislation, forensic analysts are faced with the increasingly daunting task of identifying them in the absence of a reference material.[2] The structure of the unknown must therefore be determined from `first principles', exploiting multinuclear magnetic resonance spectroscopy and, in particular, looking beyond the typical 1D ^{1}H and ^{13}C experiments to the valuable information contained in correlation spectra, especially ^{1}H-^{15}N.

References

1. Uchiyama, N. *et al*. Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative a-PVT and an opioid receptor agonist AH-7921 identified in illegal products. *Forensic Toxicol.* 2013 31:223-240.
2. Collins, M. Some new psychoactive substances: Precursor chemicals and synthesis-driven end-products. *Drug Test. Analysis* **2011** 3:404-416.
3. Vang Dean, B. *et al*. 2C or Not 2C: Phenethylamine Designer Drug Review. *J. Med. Toxicol.* **2013** 9:172-178.