APPLICATION NOTE

Unraveling the Unknown: Identification of New Psychoactive Substances (NPS) Based on Structural Similarities as in the 2C Family

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Background

The continuing rapid evolution of designer drugs has been an ongoing challenge for law enforcement and public safety. These illegally synthesized and distributed psychoactive substances are often derivatives of controlled substances resembling a similar recreational use experience but not being detected by traditional analytical techniques, which often rely on reference compounds. The 2Cx family, including compounds such as 2C-B, 2C-C, or 2C-D stands out as a concerning group due to their potent psychoactive effects and propensity for abuse. Especially 2C-B has been used as a substitute for ecstasy due to structural and pharmacological similarities. The drug family shares a 2,5-dimethoxyphenylethylamine backbone, and the "2C" refers to the ethylene bridge between amine and benzene ring.[1]

Traditional analytical techniques often rely on reference materials, which might not be available for new designer drugs or highly expensive due to the novelty of the NPS, leaving substance controlling authorities analytically blind to these new substances.[2] In this context, nuclear magnetic resonance (NMR) spectroscopy emerges as a powerful tool in forensic science, offering a distinct advantage over other analytical techniques. Unlike classical methods (chromatography, mass spectrometry, Raman spectroscopy etc.), NMR can recognize derivatives and provides detailed structural information without the need for reference materials, making it particularly valuable in the detection of newly emerging substances.

This study aims to showcase the effectiveness of benchtop NMR to recognize relations and discriminate structural nuances within these compounds. Moreover, this work holds a promising outlook in the ongoing battle against designer drugs. By utilizing the unique capability to identify specific structural motifs and similar compounds, this research not only helps with the detection and discrimination of known substances but also leads towards the recognition of entirely new designer drugs.

Results

In this study, the 60 MHz ^{1}H NMR data of seven derivatives of the 2Cx family, namely 2C-B (**1**), 2C-C (**2**), 2C-D (**3**), 2C-E (**4**), 2C-P (**5**), 2C-T2 (**6**), and 2C-T7 (**7**), are compared and discussed regarding their structural and spectral relations (Figure 1). The differences in the molecular structures of these substituted phenylethylamines **1** - **7** range from as subtle as a formal exchange of a bromine with a chlorine atom to different chain lengths in the alkyl and thioether groups.

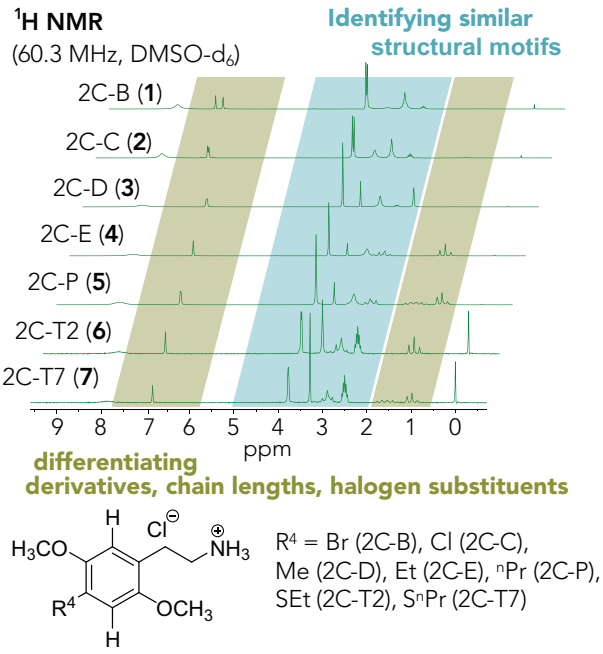


Figure 1. *Stacked 60 MHz ^{1}H NMR spectra of the 2Cx compounds* ***1-7****.*[3]

In our exploration, we focused particularly on previously understudied compounds such as 2C-D (**3**), a representative with a methyl group in the para position relative to the ethylamine substituent. This compound appears as a white powder and readily dissolves in DMSO-d_6.

Despite their structural similarity, 2C-B and 2-C with bromine and chlorine in *para* position to the "2C" ethylene bridge, the aromatic proton 2 signal in 2C-B is shifted by $\Delta\delta$ = 0.11 ppm to higher frequency compared to the respective signal of 2C-C (Figure 2). This results in baseline separation of the aromatic singlets, a spectral feature that differenciates 2C-B (**1**) from the other derivatives **2-7**. The two haloarene compounds clearly differentiate from 2C-D by the absence of the methyl signal 6 of the 2C-D spectrum.

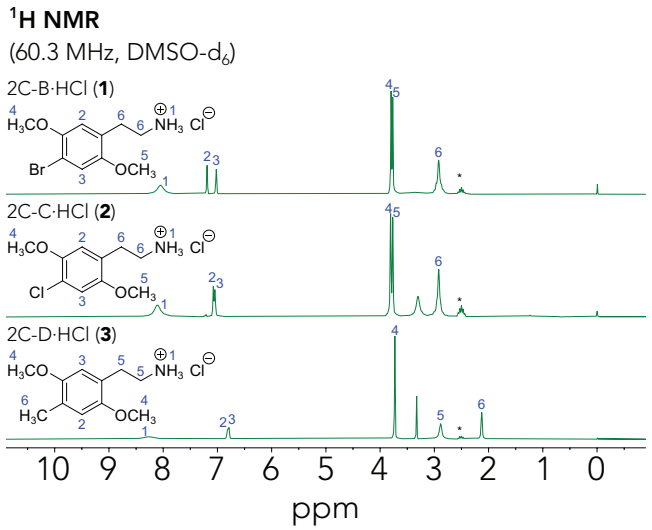


Figure 2. *Stacked 60 MHz ^{1}H NMR spectra of the 2C-B (**1**, top) and 2C-C (**2**, middle) in comparison with 2C-D (**3**, bottom).*[3]

In contrast, compounds like 2C-E (**4**), 2C-P (**5**), 2C-T2 (**6**), and 2C-T7 (**7**) show very similar chemical shifts for the aromatic proton signals. However, the different alkyl chain lengths result in a shift of the terminal CH_3 group signal as well as the additional methylene group signals make the differentiation of 2C compounds **3** - **5** very easy (Figure 3).

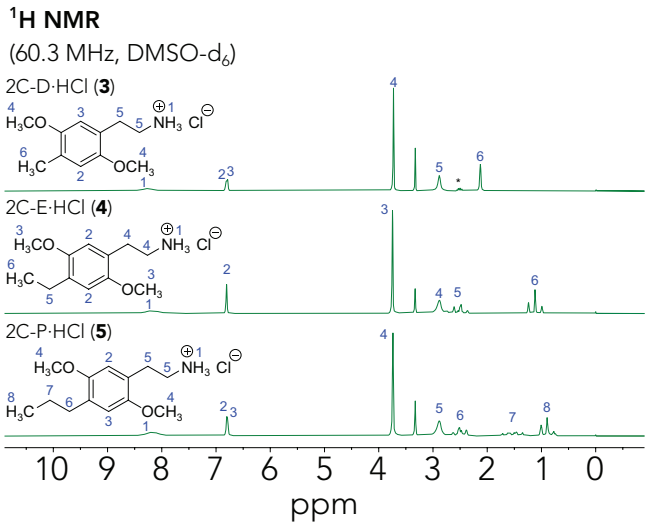
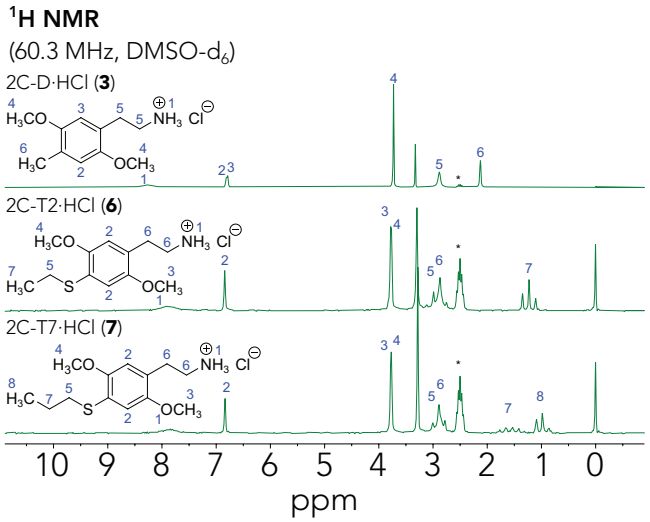


Figure 3. *Stacked 60 MHz ^{1}H NMR spectra of the 2C-D (**3**, top) in comparison with 2C-E (**4**, middle) and 2C-P (**5**, bottom).*[3]

Similar to their alkyl analogues, the terminal methyl group signals 7 and 8 of the thioether derivatives 2C-T2 (**6**) and 2C-T7 (**7**), respectively, differ in both, multiplicity and chemical shift from the respective CH_3 group signal 6 of 2C-D (**3**) (Figure 4, top). This allows for unambiguous differentiation between these derivatives. The presence of sulfur atoms induced high-frequency shifts in the CH_3 group signals of the ethyl and propyl fragments in 2C-T2 (**6**) and 2C-T7 (**7**) compared to their counterparts in 2C-E (**4**) and 2C-P (**5**), respectively. This shift also provides a distinctive marker, enabling unambiguous differentiation between alkyl and thioether substituted 2Cx compounds (Figure 4, bottom).



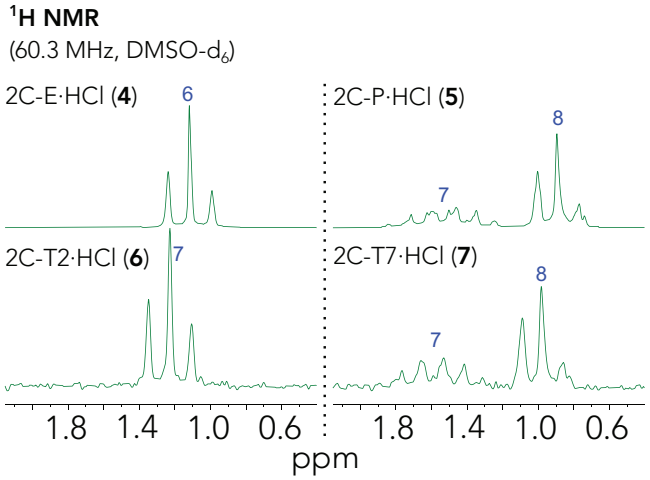


Figure 4. *Top: Stacked 60 MHz ^{1}H NMR spectra of the 2C-D (**3**, top) in comparison with 2C-T2 (**6**, middle) and 2C-T7 (**7**, bottom); bottom: comparison of 2C-E (**4**) and 2C-T2 (**6**), and 2C-P (**5**) and 2C-T7 (**7**).*[3]

Conclusions

In our study, benchtop ^{1}H NMR spectroscopy was successfully employed to fully discriminate seven very structural similar 2C NPS drugs. This resembles the possibility of automated structural motif detection, which allows for flagging new designer drugs. With the foundational knowledge gained from our exploration of the 2Cx family, we have collected a database of known illicit drugs to create an intelligent automation software for flagging NPS substances that may emerge on the black market. This innovative approach will simplify the detection of designer drugs in the near future.

The reader is highly encouraged to view our original publication[3] in *Magnetic Resonance Chemistry* for more details. If you have any questions about forensic NMR analysis or illicit drug detection, please don't hesitate to contract us via sales@nanalysis.com.

References

[1] B. V. Dean, S. J. Stellpflug, A. M. Burnett, K. M. Engebretsen, *J. Med. Toxicol.* **2013**, *9*, 172.

[2] G. Dowling, P. V. Kavanagh, H.-G. Eckhardt, B. Twamley, G. Hessman, G. McLaughlin, J. O'Brien, S. D. Brandt, *Drug Test. Anal.* **2018**, *10*, 1198.

[3] J. F. Araneda, M. Baumgarte, M. Lange, A. F. G. Maier, S. D. Riegel, *Magn. Reason. Chem.* **2023**, *61*, 66.

Bay 1, 4600 – 5 Street NE
Calgary, Alberta, Canada
T2E 7C3

Tel: +1.403.769.9499

nanalysis.com

sales@nanalysis.com