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The first reported fatality associated with the synthetic opioid 3,4-dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700) and implications for forensic analysis

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Running title: First reported fatality involving the synthetic opioid U-47700

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Introduction

The search for synthetic opioids as alternatives to opium-based derivatives has provided an important impulse to drug development around the globe. An important goal in the systematic evaluation of new drug candidates is the identification of compounds that provide a more favorable side-effect profile, which includes reduced dependence-producing properties and abuse liability. A rich source of information about these research efforts can be found in the scientific literature. However, the exploration of these important discoveries has also been increasingly mined by large-scale producers of these materials, which are then offered for sale. These so-called 'research chemicals' or new psychoactive substances (NPS)^[1] have created challenges to policy makers, clinicians, and law enforcement around the world.^[2]

Recent examples of synthetic opioids that emerged as NPS on the market, and which were associated with severe cases of adverse effects, include 3,4-dichloro-*N*-[1-(dimethylamino)cyclohexylmethyl]benzamide (AH-7921), 1-cyclohexyl-4-(1,2-diphenylethyl)piperazines (MT-45) and *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide (acetylfentanyl), respectively (Figure 1). Following the recommendation provided by the World Health Organization's Expert Committee on Drug Dependence (ECDD),^[3] AH-7921 was placed in Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol in 2015.^[4] Furthermore, ECDD's recommendation to place MT-45 into Schedule I and acetylfentanyl in Schedules I and IV of the same Convention^[5] have been recently confirmed by the Commission on Narcotic Drugs.^[6]

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3 3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700) (Figure
4 1) has recently emerged on the market and can be purchased from various Internet
5 retailers and is a structural isomer of AH-7921 (Figure 1). The preparation of U-
6 47700 and other derivatives was disclosed by the Upjohn Company in the 1970s^[7]
7 followed by the recognition that U-47700 showed increased analgesic properties and
8 morphine-like behavioural features in mice compared to morphine itself.^[8,9] The
9 presence of two chiral centres gives rise to a *cis*- and *trans*- racemic mixture with the
10 *trans*-form being advertised for sale. Binding studies also revealed that U-47700
11 displayed an appreciable selectivity for the μ -opioid receptor over the κ -opioid
12 receptor.^[10,11] A variety of cyclohexyl *trans*-1,2-diamines have been found to be
13 potent analgesics and the vicinal 1,2-diamine pattern has provided access to a large
14 range of substances with diverse biological activities.^[12-14]
15
16

17
18 Since U-47700 did not progress to clinical trials, there is no direct clinical information
19 pertaining to its effects. Keeping in mind the various limitations that may be
20 associated with descriptions obtained from self-reporting users, its effects have been
21 described with various positive and negative symptoms but appeared to be
22 essentially comparable to other opioids. Specifically, euphoria was reported in
23 individuals, sometimes being short-lived, as well as general lift in mood with these
24 desired effects being experienced in waves. The negative effects were also opioid-
25 based, including nausea with some users describing respiratory depression. For
26 some users, U-47700 had a shorter duration of action and the urge to keep re-dosing
27 was stated as being very high.^[15,16]
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31 Case History

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33 In January 2016, a 27-year old male was found dead at home. It was believed he
34 may have snorted mirtazapine (prescribed anti-depressant) and was a user of
35 cannabis, ketamine, "MCAT" (cathinones) and "legal highs". There was evidence of
36 powder in his nasal area, which was obtained for analysis. At autopsy, no natural
37 disease or cause of death was found. At the direction of HM Coroner, toxicological
38 analysis was performed for alcohol and a wide range of drugs.
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41

42 Experimental

43 *Reagents and standards*

44
45 All solvents and chemicals used, e.g. acetonitrile, 1-chlorobutane, sodium carbonate,
46 sulphuric acid, formic acid, triethylammonium phosphate buffer (TEAP) and
47 ammonium formate, were of analytical grade or equivalent from Sigma Aldrich
48 (Dorset, UK) and/or Rathburn Chemicals Ltd. (Walkerburn, Scotland, UK). A sample
49 of *trans*-U-47700 was obtained from Scientific Supplies Ltd. (London, UK).
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52

53 *Instrumentation*

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55 HPLC-DAD analysis was performed using a Dionex 3000 Ultimate liquid
56 chromatography system coupled to a UV diode array detector (Thermo Fisher, St
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3 Albans, UK). An ABSciex 3200 QTRAP mass spectrometer coupled to an Agilent
4 1200 HPLC-DAD system (ABSciex, Cheshire, UK) was used for LC-MS/MS analysis.
5 An Agilent UHPLC-high resolution QTOF-MS system was used incorporating an
6 Agilent 6540 UHD Accurate-Mass QTOF LC/MS coupled to an Agilent 1290 Infinity
7 UHPLC system (Agilent, Cheshire, UK). The methodology and instrument
8 parameters have been published previously.^[17]
9

10 11 *Preparation of standards and method characterization*

12
13 U-47700 was used to prepare fresh reference and calibration standards for the
14 formal identification and quantitation in the specimens analyzed. Following
15 determination of limit of detection (LOD) using an extended calibration range (from
16 0.025 and 0.078 mg/L) and limit of quantitation (LOQ), a calibration range of 0.3125,
17 0.625, 1.25, 2.5 and 5 mg/L was produced for U-47700 using blank equine plasma
18 for validation according to Peters *et al.*^[18] Internal quality control standards of 0.5
19 mg/L and 2.5 mg/L were also produced. Intra-day and inter-day precision and
20 accuracy were determined. For quantification, the post-mortem blood case sample
21 was diluted 3-fold in equine plasma for matrix matching and replicate analysis.
22
23

24 25 *Extraction and analysis*

26
27 Basic back extraction using sodium carbonate buffer (with internal standards) and 1-
28 chlorobutane solvent extraction of the calibration and case samples (blood and urine)
29 was performed as previously described.^[17] The chromatographic conditions for
30 qualitative HPLC-DAD, HPLC-MS and UHPLC-QTOF-MS analysis were also based
31 on previously published methods involving an acetonitrile gradient.^[17] Quantitative
32 HPLC-DAD analysis was based on 30% acetonitrile (with 25 mM TEAP buffer) under
33 isocratic elution conditions at a flow rate of 2 mL/min. U-47700 eluted at 2.4 min.
34
35

36 37 **Results and discussion**

38
39 Routine toxicological analysis of the post-mortem urine detected quetiapine (an
40 antipsychotic), amphetamine (a psychostimulant), amitriptyline (an antidepressant),
41 mexedrone (a new psychoactive substance) and ketamine (a dissociative
42 anesthetic). Quetiapine (< 0.05 mg/L) and amphetamine (< 0.1 mg/L) were also
43 detected in the post-mortem blood along with naproxen (an anti-inflammatory drug <
44 0.8 mg/L) representing therapeutic (or recreational in the case of amphetamine)
45 concentrations. No ethanol (alcohol) was detected. Aside from these findings, during
46 HPLC-DAD analysis, initially unidentified compounds were detected in the blood and
47 urine.
48
49

50 51 *Differentiation between U-47700 and AH-7921*

52
53 Subsequent analysis by targeted LC-MS (applied to identify a range of specific NPS)
54 and non-targeted QTOF-MS, originally suggested the primary compound to be
55 consistent with AH-7921 (Figure 1) based on ion transitions m/z 329 > 173 and m/z
56 329 > 284, with only a very slight difference in retention time. The accurate mass of
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3 the protonated molecule at m/z 329.11812 was also consistent with $C_{16}H_{23}Cl_2N_2O^+$.
4 However, both the retention time and UV spectrum differed when analyzed by the
5 HPLC-DAD method. The primary compound with the identical analytical features was
6 also found to be the constituent in the powder recovered from the deceased's
7 nostrils.
8

9
10 Given knowledge of the existence of U-47700 on the NPS market, along with its
11 structural similarity to AH-7921, U-47700 reference material was analyzed using
12 HPLC-DAD, LC-MS and LC-QTOF-MS. Analysis confirmed the primary compound
13 detected in the powder, post-mortem blood and urine to be U-47700 instead of AH-
14 7921. Specifically, under HPLC-DAD conditions, U-47700 eluted at 7.85 min with a
15 maximum peak at 201.7 nm compared to AH-7921 that eluted at 8.26 min with peaks
16 at 205.4 nm and 241.3 nm. Figure 2 shows the overlaid UV spectra and the
17 chromatographic separation of U-47700 from AH-7921. The separate spectra are
18 provided as Supporting Information.
19

20
21 Analysis by triple quadrupole/linear ion trap LC-MS showed that both U-47700 and
22 AH-7921 shared some primary product ions, such as m/z 145, 173 and 284, which
23 was in agreement with mass spectral data reported previously.^[17,19,20] However, the
24 product ions of interest, which allowed for the differentiation of both isomers, were
25 detected at m/z 204 and m/z 81 (U-47700) and m/z 190 and m/z 95 (AH-7921),
26 respectively (Figure 3). For example, in the case of AH-7921, the m/z 190 ion would
27 have been consistent with the protonated 3,4-dichlorobenzamide product ion
28 whereas m/z 204 reflected the 3,4-dichloro-*N*-methylbenzamide counterpart found in
29 U-47700 (Figure 1). Correspondingly, the differences between m/z 81 (U-47700) and
30 m/z 95 (AH-7921) reflected the presence of the methylene group in AH-7921 that
31 gave rise to a cyclohex-1-en-1-ylmethyl cation, thus, representing the mass shift of
32 14 amu. It is therefore recommended that if solely relying on a targeted ion transition
33 methodology for the detection of U-47700, the transitions m/z 329 > 81 and m/z 329
34 > 204 will provide the appropriate specificity. Equally, specific transitions m/z 329 >
35 95 and m/z 329 > 190 should be incorporated into any LC-MS method that aims to
36 target the detection of AH-7921.
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41 Analysis of femoral blood by high accuracy mass spectrometry confirmed the
42 protonated molecule of U-47700 at m/z 329.11812 compared to the reference
43 standard at m/z 329.11815 (Figure 4A and B). Both values were within 0.5 ppm of
44 the calculated value at m/z 329.11820. The chlorine related isotopic masses linked to
45 the two chlorine atoms (M+2 and M+4) were also evident (Figure 4A). A
46 representative example of a collision-induced dissociation tandem mass spectrum
47 obtained from the analyte peak of a urine sample is shown in Figure 4C. The specific
48 accurate mass product ions at m/z 81.07023 ($C_6H_9^+$, $\Delta = 4.32$ ppm) and 203.99811
49 ($C_8H_8Cl_2NO^+$, $\Delta = 1.76$ ppm) were consistent with the differentiating ions mentioned
50 above (Figure 3). The suggested structures for these product ions are shown in
51 Figure 4G.
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55 *Detection of metabolites*

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58 During the analysis of the case samples, apparent metabolites of U-47700 were also
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3 detected, with greater abundance in blood compared to urine. Initially, this was
4 observed by HPLC-DAD analysis through UV spectral comparison with the parent
5 molecule and further confirmation was obtained from LC-MS investigations, which
6 pointed towards similar product ions to U-47700 recorded under full scan mass
7 spectrometry conditions. When high accuracy QTOF-MS analysis was carried out,
8 the associated empirical formulae could be determined (Figure 4D-F) which pointed
9 toward *N*-desmethyl and *N,N*-didesmethyl products. The appearance of AH-7921 *N*-
10 desmethyl metabolites was consistent with those observed in the authors' laboratory
11 and those reported in the literature.^[17,19,20] The detection of the *m/z* 204 ion, i.e.
12 protonated 3,4-dichloro-*N*-methylbenzamide (Figure 4G and Supporting Information),
13 suggested that *N*-desmethylation must have occurred on the *N,N*-
14 dimethylcyclohexanamine moiety (Figure 4H). Involvement of the *N*-methyl group
15 would have otherwise given rise to the *m/z* 190 species and this was not observed
16 under the conditions used. QTOF-MS/MS data for *N*-demethyl-U47700 identified in
17 blood are provided as Supporting Information. The detection of the *N,N*-didesmethyl-
18 U-47700 metabolite was based on QTOF-MS alone (Figure 4F) but the signal
19 intensity was not sufficient to obtain acceptable QTOF-MS/MS data. The exact
20 nature of this metabolite remained to be confirmed. The suggested structure (Figure
21 4H) represented the primary amine species, i.e. carrying the *N*-(2-aminocyclohexyl)
22 moiety. However, in the absence of high accuracy MS/MS data, this identification
23 must remain speculative. Similar to CID-MS/MS data recorded for the *N*-desmethyl-
24 U-47700 metabolite (Figure 4D and G), a key product ion that might be expected for
25 the primary amine metabolite would have been at *m/z* 203.99775.
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31 *Quantitative analysis*

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33 For quantitative analysis by HPLC-DAD, validation of the method showed intra-day
34 accuracy and precision values of < 2% (at 0.5 and 2.5 mg/L), inter-day accuracy and
35 precision values of < 18% and < 6%, respectively (at 0.5 and 2.5 mg/L), a limit of
36 detection of 0.05 mg/L and a limit of quantitation of 0.3125 mg/L utilizing the lowest
37 calibrator. U-47700 was subsequently measured at a concentration of 1.46 mg/L in
38 post-mortem femoral blood.
39

40
41 As there are currently no other published fatalities involving U-47700, concentration
42 data obtained from post-mortem blood cannot be used for comparison. However, if
43 related to morphine or AH-7921 blood concentrations, a femoral blood concentration
44 of 1.46 mg/L could be considered excessive. During the investigation of AH-7921
45 deaths by this laboratory, post-mortem femoral blood AH-7921 concentrations of
46 0.05, 0.35, 0.58, 0.84 and 4.46 mg/L were found. Other drugs and/or alcohol were
47 detected in all of the cases but only contributed or provided an alternative cause of
48 death in two of the cases (associated with femoral blood concentrations of 0.05 and
49 0.35 mg/L). Other deaths in Europe reported by various researchers involved AH-
50 7921 concentrations between 0.03 and 0.99 mg/L.
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53
54 Nevertheless, as with all fatalities involving opiates and opioids, the toxicological
55 significance will depend on the degree of any acquired tolerance through regular use.
56 In the case described here, there was no information or evidence of regular
57 opiate/opioid use and it was not clear whether the deceased would have known that
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3 the powder used was an opioid, irrespective of the exact composition (i.e. U-47700).
4 Even if it were known to be an opioid, the purity of the substance would have most
5 likely been unknown to the user, creating a dose-safety risk. As nasal insufflation of
6 synthetic opioids (i.e. AH-7921) has been previously reported (and is also commonly
7 associated with other drugs especially cocaine and synthetic stimulants), the route of
8 administration in this case did not provide an inference of user knowledge as to the
9 nature of the powder. Nonetheless, the major risk to life from opioids is their
10 depressant effect on the central nervous system, notably causing respiratory
11 depression, and in the absence of any other significant pathological or toxicological
12 findings, fatal U-47700 toxicity was a likely outcome.
13
14

15 16 Conclusion

17
18 The new psychoactive substance U-47700, a synthetic μ -opioid receptor agonist and
19 related to AH-7921, has recently emerged on the “research chemical” market. The
20 fatality identified in this case presents for the first time a post-mortem femoral blood
21 concentration, namely 1.46 mg/mL, and characterized metabolites. The combination
22 of HPLC-DAD analysis with triple quadrupole/linear ion trap mass spectrometry (MS)
23 and high accuracy QTOF-MS/MS allowed for an unambiguous identification. Given
24 that U-47700 is a structural isomer of AH-7921, another synthetic opioid that has
25 emerged in previous years, care has to be taken if relying solely on accurate mass
26 (without fragmentation) and when choosing ion transitions for targeted analysis, in
27 order to avoid misidentification.
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31 Acknowledgement

32
33 The authors thankfully acknowledge the support from Scientific Supplies Ltd.
34 (London, UK) and Dr. Pierce V. Kavanagh (Dublin, Ireland).
35
36

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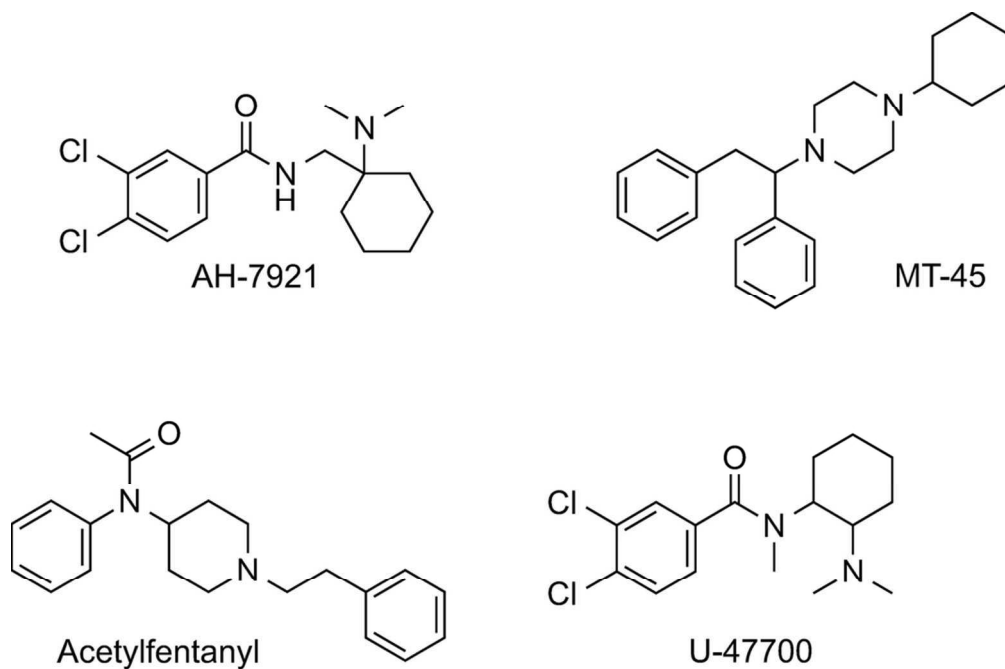
Figure captions

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2
3 **Figure 1.** Examples of synthetic opioids that have emerged on the “research
4 chemical” market. U-47700 has only emerged very recently but AH-7921, MT-45 and
5 acetylfentanyl have been placed under international control.
6

7 **Figure 2.** High performance liquid chromatography photodiode array detection data
8 obtained from U-47700 and AH-7921 standards.
9

10 **Figure 3.** Enhanced product ion scans of U-47700 and AH-7921 using electrospray
11 ionization HPLC linear ion trap mass spectrometry. Both structural isomers were
12 differentiated based on distinct product ions as indicated by the arrows.
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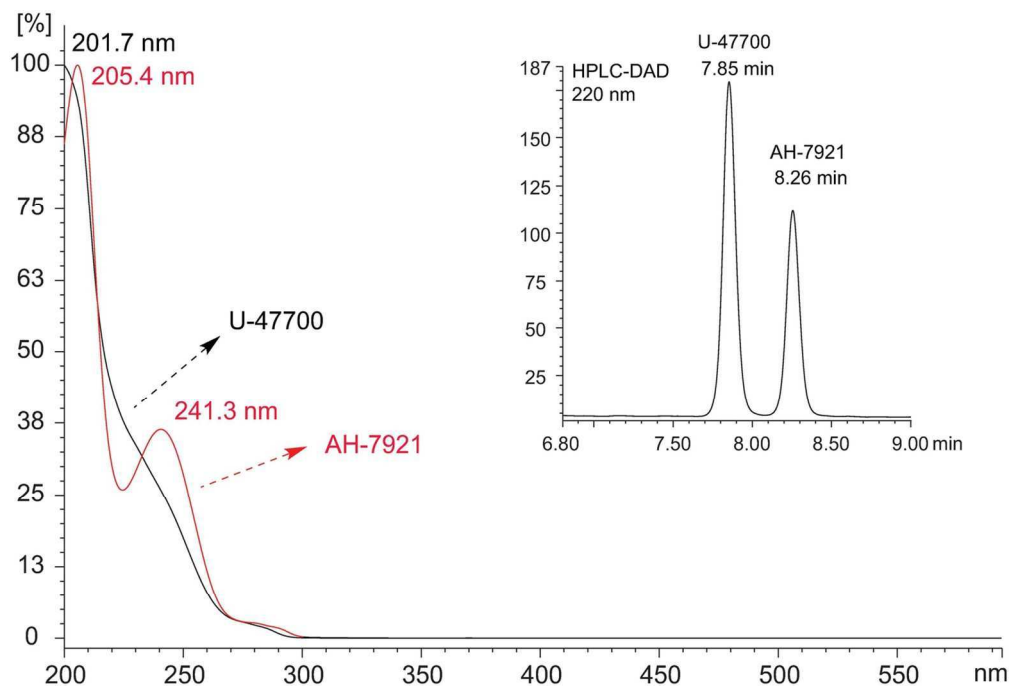
14 **Figure 4.** A–F: UHPLC high accuracy QTOF-MS and MS/MS data recorded for U-
15 47700 and metabolites detected in post-mortem blood and urine. H: Structures of
16 suggested CID-MS/MS key ions recorded for U-47700 and *N*-desmethyl-U-47700.
17 These two key ions would not be detected in the tandem mass spectrum of its
18 structural isomer AH-7921. H: Suggested structures for *N*-desmethyl-U-47700 and
19 *N,N*-didesmethyl-U-47700.
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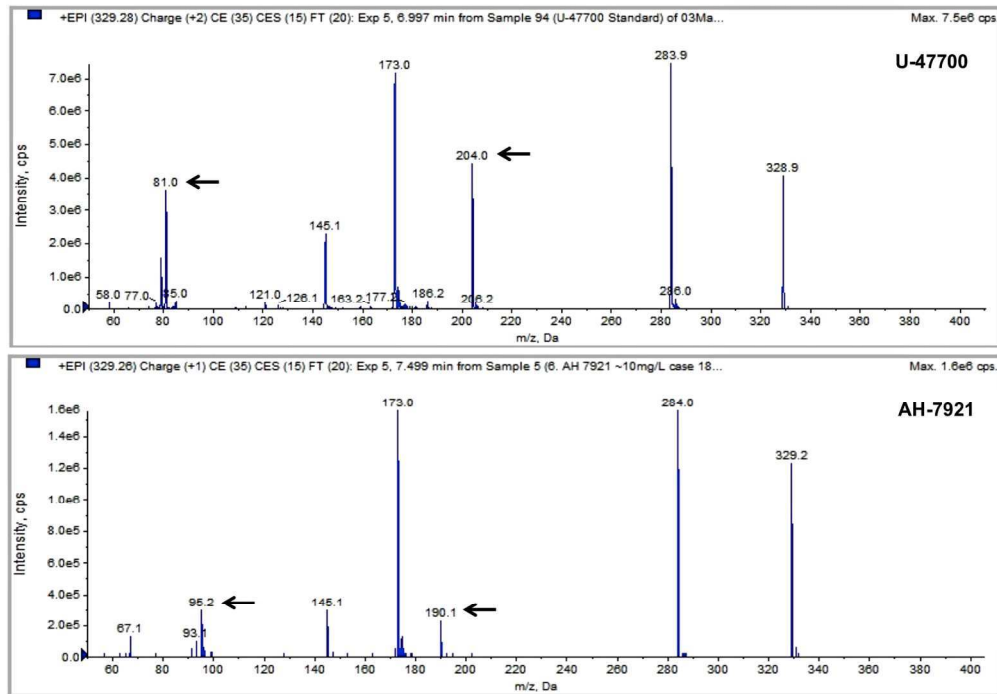
Figure 1. Examples of synthetic opioids that have emerged on the "research chemical" market. U-47700 has only emerged very recently but AH-7921, MT-45 and acetylfentanyl have been placed under international control.

90x59mm (300 x 300 DPI)



High performance liquid chromatography photodiode array detection data obtained from U-47700 and AH-7921 standards.
125x85mm (300 x 300 DPI)

Review



Enhanced product ion scans of U-47700 and AH-7921 using electrospray ionization HPLC linear ion trap mass spectrometry. Both structural isomers were differentiated based on distinct product ions as indicated by the arrows.
614x433mm (72 x 72 DPI)

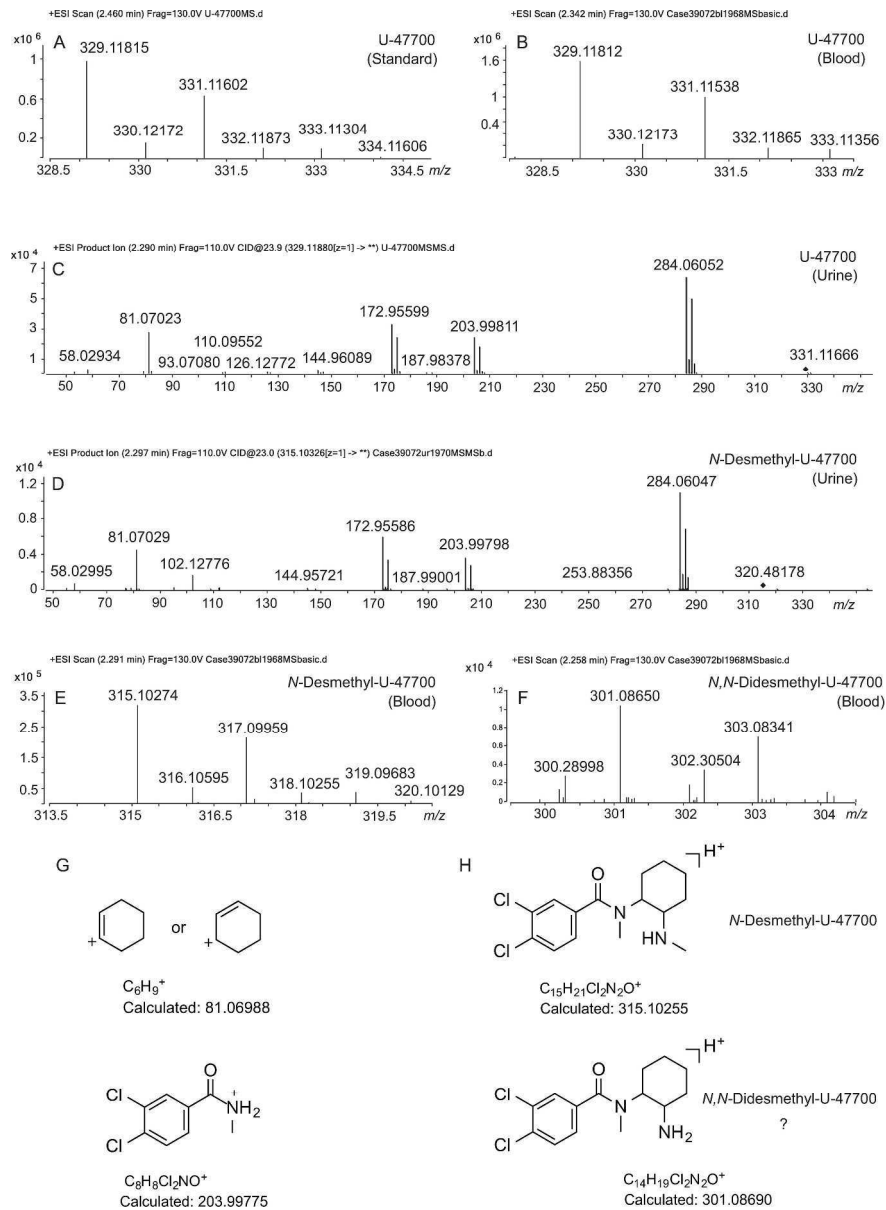


Figure 4. A–F: UHPLC high accuracy QTOF-MS and MS/MS data recorded for U-47700 and metabolites detected in post-mortem blood and urine. H: Structures of suggested CID-MS/MS key ions recorded for U-47700 and *N*-desmethyl-U-47700. These two key ions would not be detected in the tandem mass spectrum of its structural isomer AH-7921. H: Suggested structures for *N*-desmethyl-U-47700 and *N,N*-didesmethyl-U-47700.

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