

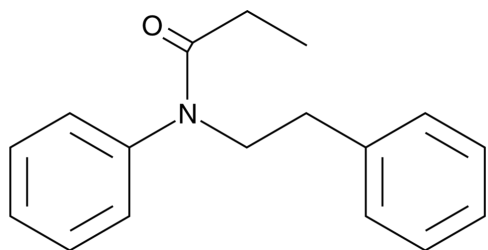
PURPOSE

Samples seized from the Southwest border ports of entry by Customs and Border Protection (CBP) are submitted to the Center for Forensic Science Research and Education (CFSRE) for qualitative and quantitative testing. The purpose of this report is provide information on the identification of precursors, intermediates and by-products identified in tablets and powders containing fentanyl.

BACKGROUND

Seized tablets and powders suspected of containing fentanyl are analyzed using a workflow that includes qualitative analysis by both gas chromatography mass spectrometry (GC/MS) and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF -MS).

N-phenethyl-N-phenylpropionamide



N-phenethyl-N-phenylpropionamide is a by-product in the synthesis of fentanyl.

Formula: C₁₇H₁₉NO

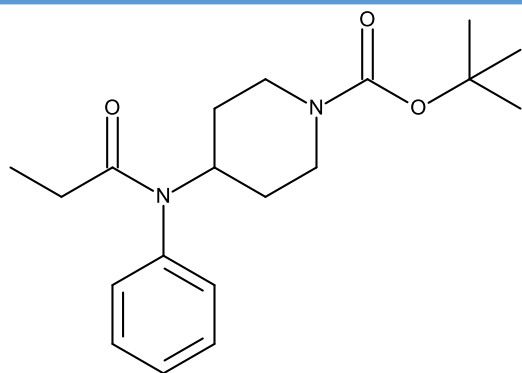
MW: 253.3

[M⁺]: 254

[M+H]⁺: 254.1539

IUPAC: N-phenyl-N-(2-phenylethyl)-propanamide

N-BOC norfentanyl



N-BOC norfentanyl is an intermediate in the synthesis of fentanyl. It is also known as t-BOC-norfentanyl.

Formula: C₁₉H₂₈N₂O₃

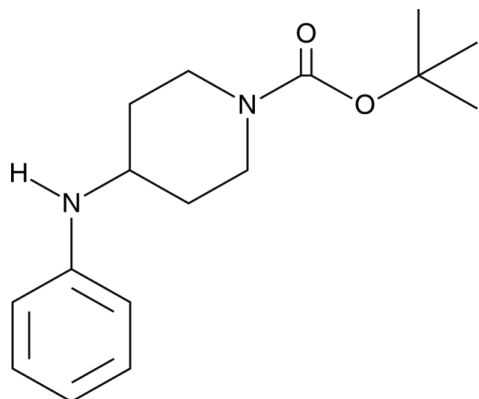
MW: 332.4

[M⁺]: 333

[M+H]⁺: 333.2170

IUPAC: 4-[(1-oxopropyl)phenylamino]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

N-BOC 4-AP



N-BOC 4-AP is a precursor used in the synthesis of fentanyl. It is also known as 4-ANBocP, 4-anilino-1-boc-piperidine, 1-boc-4-(phenylaminopiperdine and tert-butyl 4-(phenylamino)piperdine-1-carboxylate.

Formula: C₁₆H₂₄N₂O₂

MW: 276.4

[M⁺]: 277

[M+H]⁺: 277.1908

IUPAC: 4-(phenylamino)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester



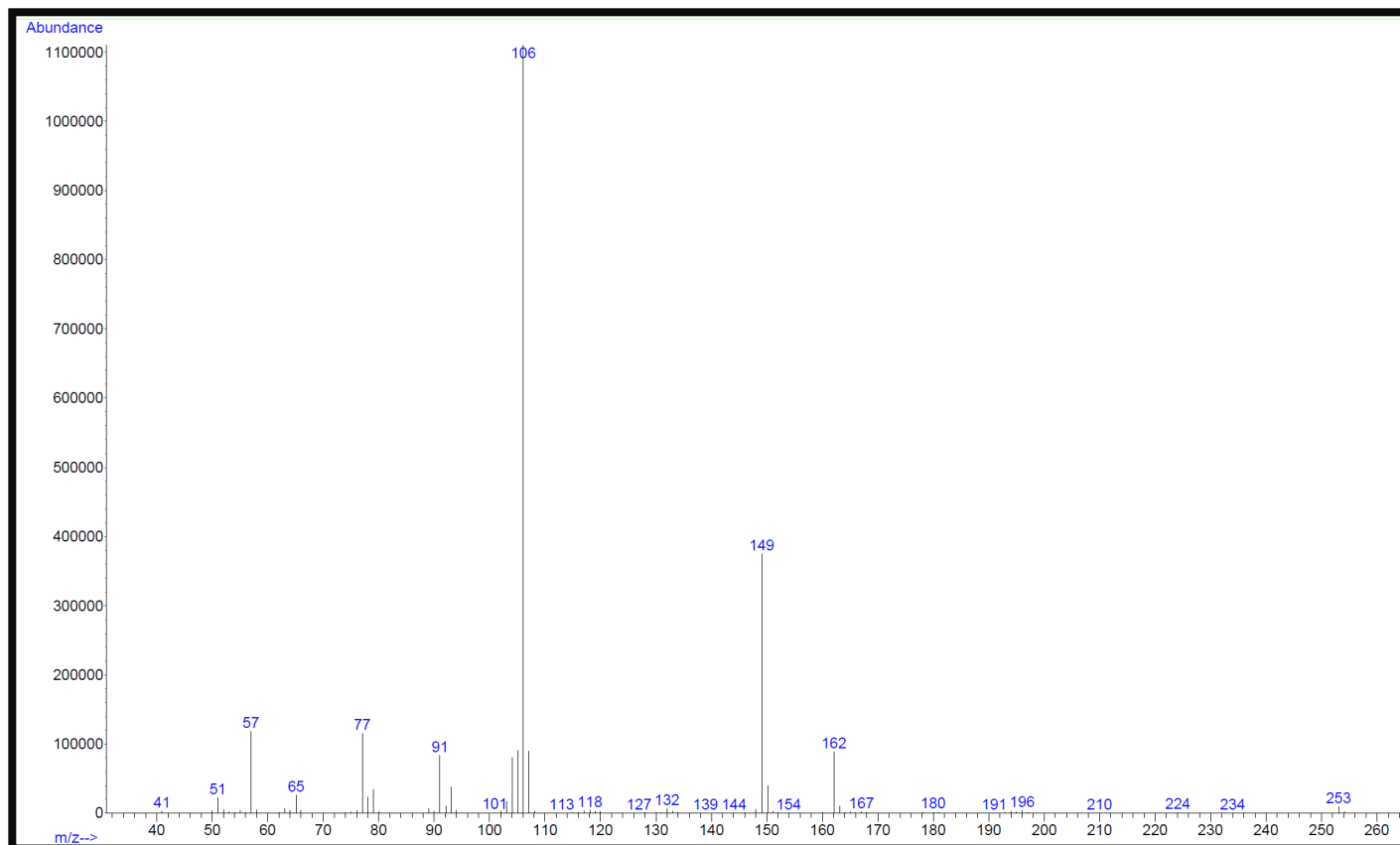
Gas Chromatography Mass Spectrometry (GC-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Agilent 5975 Series GC/MSD

Methods: [GC-MS Method Details](#)

Sample Preparation: Acid-Base Liquid/Liquid Extraction



N-phenethyl-N-phenylpropionamide was previously reported by Mayer *et. al.*, who indicated this compound was a unique by-product in Seigfried route of fentanyl synthesis. Exhibits analyzed at the CFSRE have found the presence of compounds related to Gupta synthesis routes in samples containing N-phenethyl-N-phenylpropionamide including phenethyl 4-ANPP, ethyl 4-ANPP, acetylfentanyl, norfentanyl, and N-propionyl norfentanyl. Some samples also contained N-BOC norfentanyl and N-BOC 4-AP, which may indicate a t-BOC route, but they all also contained phenethyl 4-ANPP suggesting a Gupta route where BOC protected precursors are converted to 4-AP before Gupta synthesis according to Toske *et. al.* A summary of the other synthesis related findings for the 11 exhibits containing N-phenethyl-N-phenylpropionamide is given in Table 1.

Table 1: N-phenethyl-N-phenylpropionamide identifications. The samples analyzed range in seizure date from June of 2020 to July of 2023.

Total # of Samples	Total # of Exhibits	Exhibit Type	Other Findings
86	11 (Samples seized from July 2022— July 2023)	6 powder cases 5 tablet cases	4-ANPP (n=11) Phenethyl 4-ANPP (n=11) Ethyl 4-ANPP (n=9) N-phenyl-propanamide (n=9) Acetyl Fentanyl (n=8) N-BOC Norfentanyl (n=6) N-propionyl Norfentanyl (n=6) Norfentanyl (n=6) N-BOC 4-AP (n=5) 4-AP (n=1) 4-ANBP (n=1)

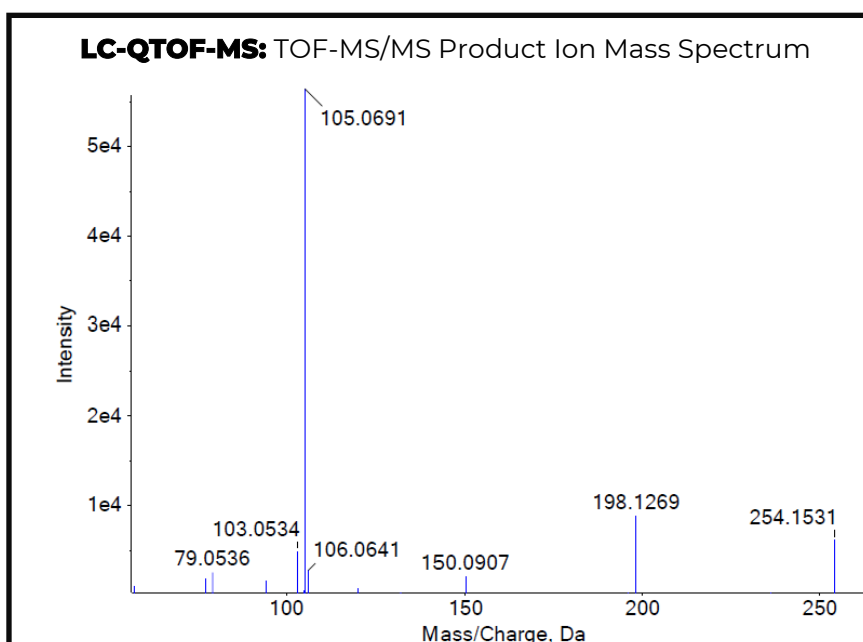
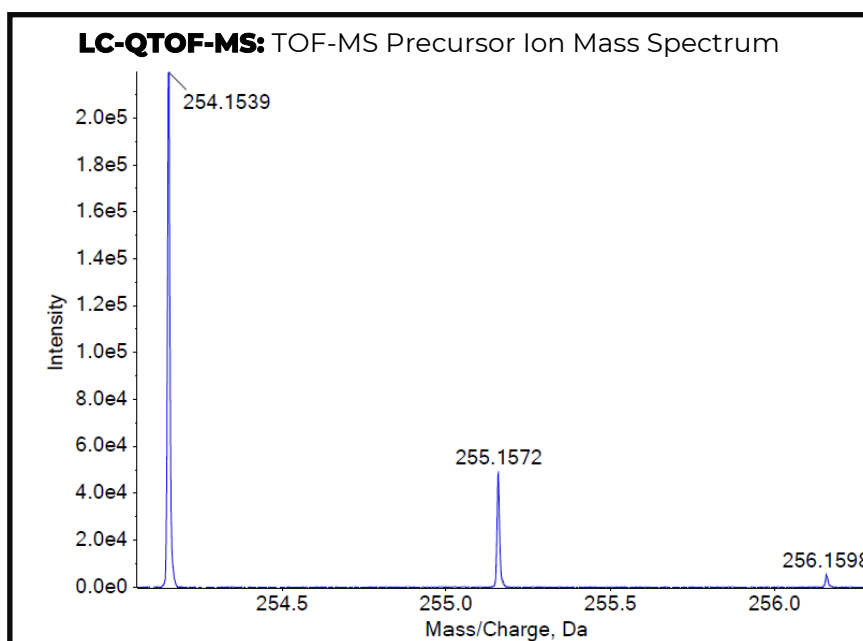
Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry (LC-QTOF-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Sciex Triple TOF® 5600+ LC-QTOF-MS

Methods: [LC-QTOF-MS Method Details](#)

Sample Preparation: Dilution in mobile phase



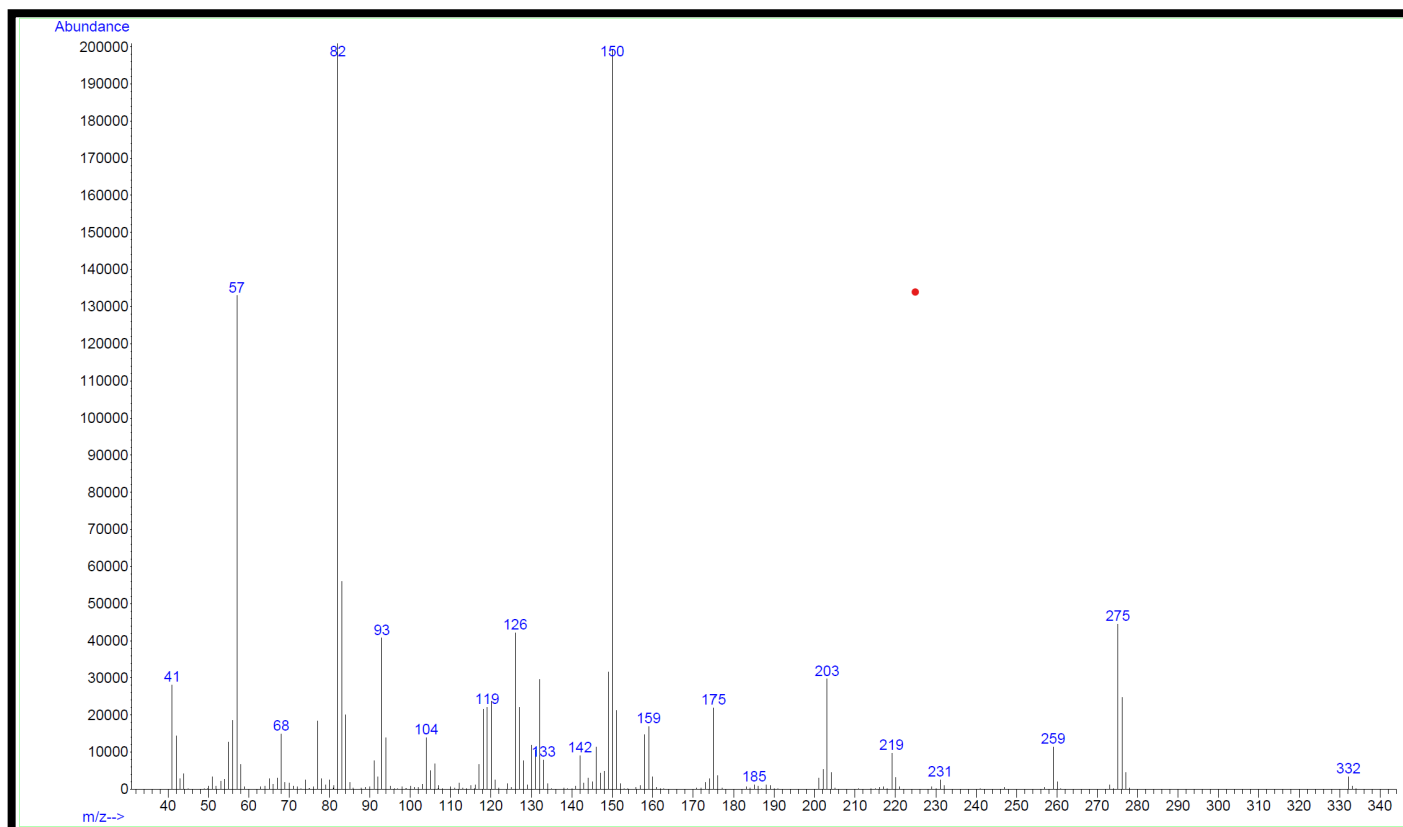
Gas Chromatography Mass Spectrometry (GC-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Agilent 5975 Series GC/MSD

Methods: [GC-MS Method Details](#)

Sample Preparation: Acid-Base Liquid/Liquid Extraction



According to Toske *et al.*, N-BOC norfentanyl is a t-BOC synthesis route intermediate and can be an impurity in fentanyl synthesized via a Gupta route when N-BOC 4-AP is used to generate unprotected 4-AP starting material. t-BOC is a protecting group that can be added to a molecule. Adding protecting groups can allow precursors that would otherwise be subject to control avoid regulation due to the change in the molecular structure. Protecting groups also play a role in synthesis by preventing reactions at certain sites until the group is removed. The samples analyzed contained other compounds often seen in Gupta synthesis routes. A summary of the other synthesis related findings for the 12 exhibits containing N-BOC norfentanyl is given in Table 2.

Table 2: N-BOC norfentanyl identifications. The samples analyzed range in seizure date from June of 2020 to July of 2023.

Total # of Samples	Total # of Exhibits	Exhibit Type	Other Findings
60	12 (Samples seized from July 2022— June 2023)	9 powder cases 3 tablet cases	4-ANPP (n=12) Phenethyl 4-ANPP (n=11) Ethyl 4-ANPP (n=10) Acetyl Fentanyl (n=10) N-phenyl-propanamide (n=9) Norfentanyl (n=8) N-BOC 4-AP (n=8) N-propionyl Norfentanyl (n=5) 4-ANBP (n=1) 4-AP (n=1)

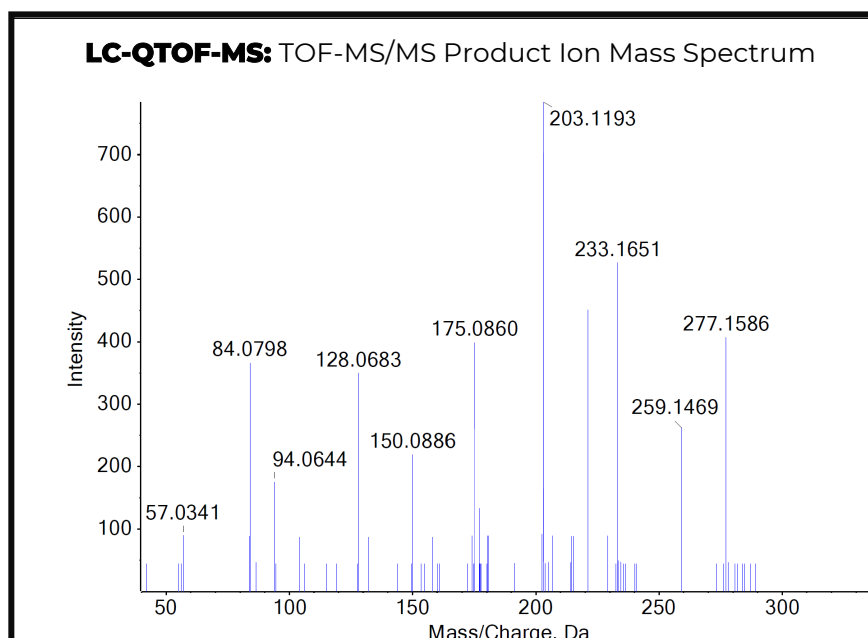
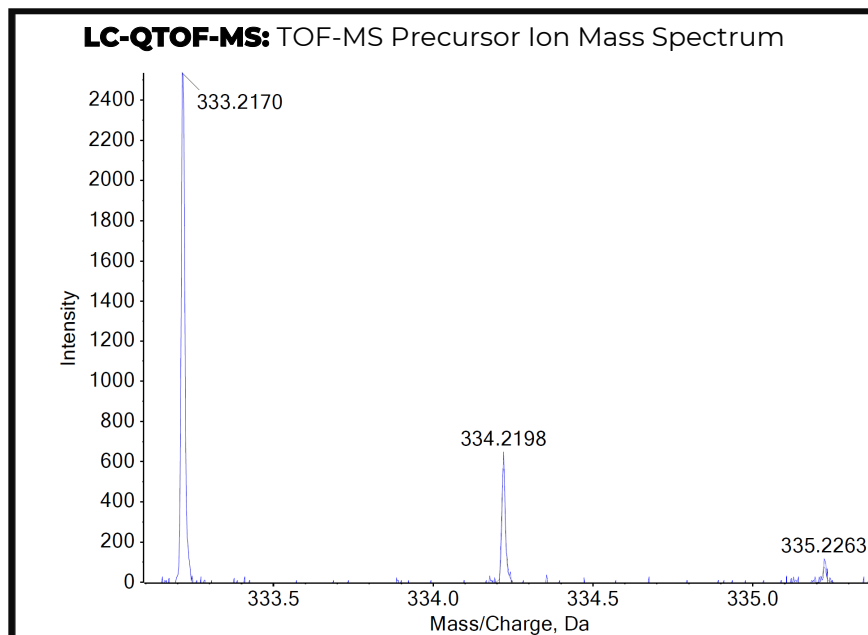
Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry (LC-QTOF-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Sciex Triple TOF® 5600+ LC-QTOF-MS

Methods: [LC-QTOF-MS Method Details](#)

Sample Preparation: Dilution in mobile phase



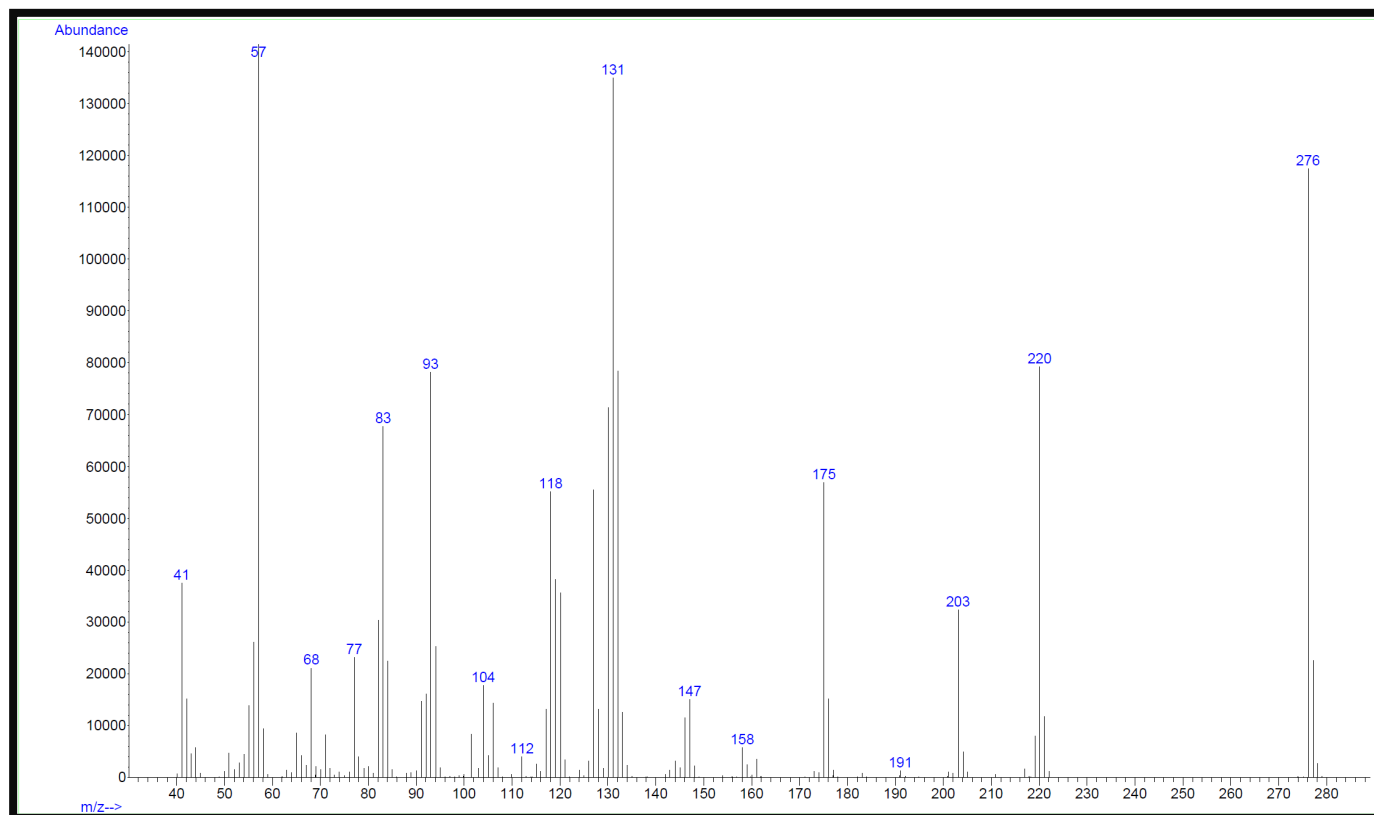
Gas Chromatography Mass Spectrometry (GC-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Agilent 5975 Series GC/MSD

Methods: [GC-MS Method Details](#)

Sample Preparation: Acid-Base Liquid/Liquid Extraction



N-BOC 4-AP is also a t-BOC protected molecule that is an intermediate in the t-BOC synthesis route and a pre-precursor to 4-AP for Gupta routes. Samples analyzed at CFSRE contained compounds that indicate Gupta synthetic routes. A summary of the other synthesis related findings for the 9 exhibits containing N-BOC 4-AP is given in Table 3.

Table 3: N-BOC 4-AP identifications. The samples analyzed range in seizure date from June of 2020 to July of 2023.

Total # of Samples	Total # of Exhibits	Exhibit Type	Other Findings
37	9 (Samples seized from July 2022—June 2023)	6 powder cases 3 tablet cases	N-BOC Norfentanyl (n=9) 4-ANPP (n=9) Phenethyl 4-ANPP (n=8) N-phenyl-propanamide (n=7) Acetyl Fentanyl (n=7) Ethyl 4-ANPP (n=7) N-phenethyl-N-phenylpropionamide (n=6) Norfentanyl (n=5) N-propionyl Norfentanyl (n=5) 4-ANBP (n=1)

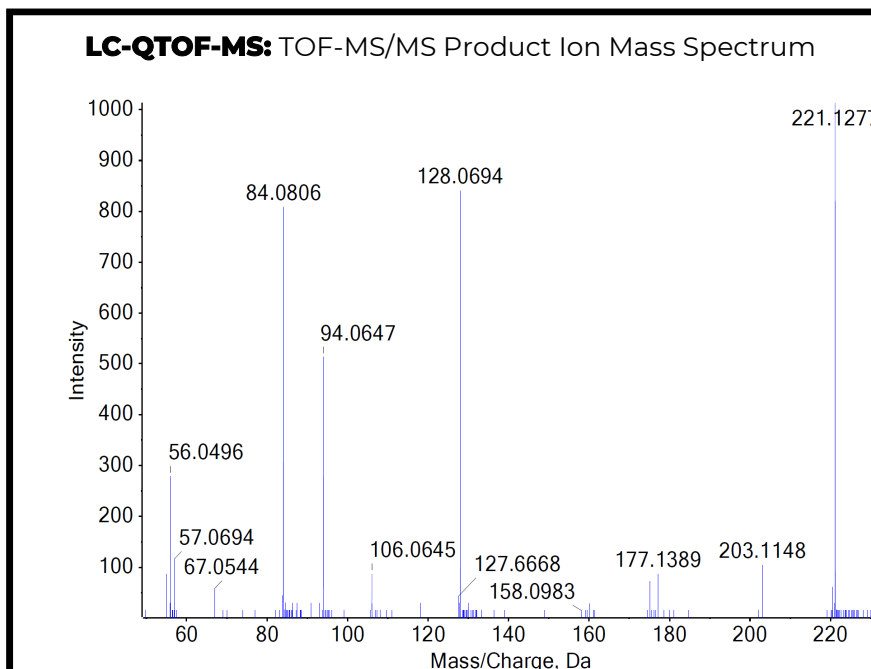
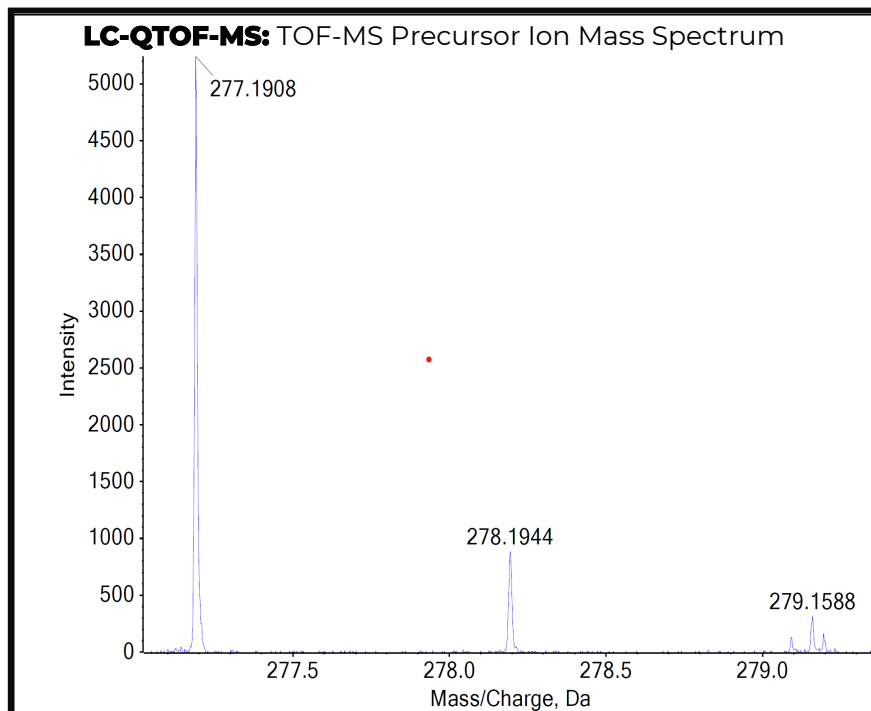
Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry (LC-QTOF-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Sciex Triple TOF® 5600+ LC-QTOF-MS

Methods: [LC-QTOF-MS Method Details](#)

Sample Preparation: Dilution in mobile phase





References and Related Articles

Krotulski, AJ, Shinefeld, J, DeBord, J, Logan, BK (2022), Fentanyl Purity, Potency, & Synthesis: Real-Time Testing of Opioid Drug Products in the United States, Center for Forensic Science Research and Education, United States of America.

Mayer, BP, DeHope, AJ, Mew, DA, Spackman, PE, Williams, AM. Chemical Attribution of Fentanyl Using Multivariate Statistical Analysis of Orthogonal Mass Spectral Data. *Anal Chem.* 2016; 88:4303-4310.

Toske, SG, Mitchell, JR, Myslinski, JM, Walz, AJ, Guthrie, DB, Guest, EM, Corbett, CA, Lockhart, ED. Organic Impurity Profiling of Fentanyl Samples Associated with Recent Clandestine Laboratory Methods. *J Forensic Sci.* 2023, 68:1470-1483.

Vandeputte, MM, Krotulski, AJ, Hulpia, F, Van Calenbergh, S, Stove, CP. Phenethyl-4-ANPP: A Marginally Active By-product Suggesting a Switch in Illicit Fentanyl Synthesis Routes. *J Anal Toxicol.* 2022;46(4):350-357 .

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