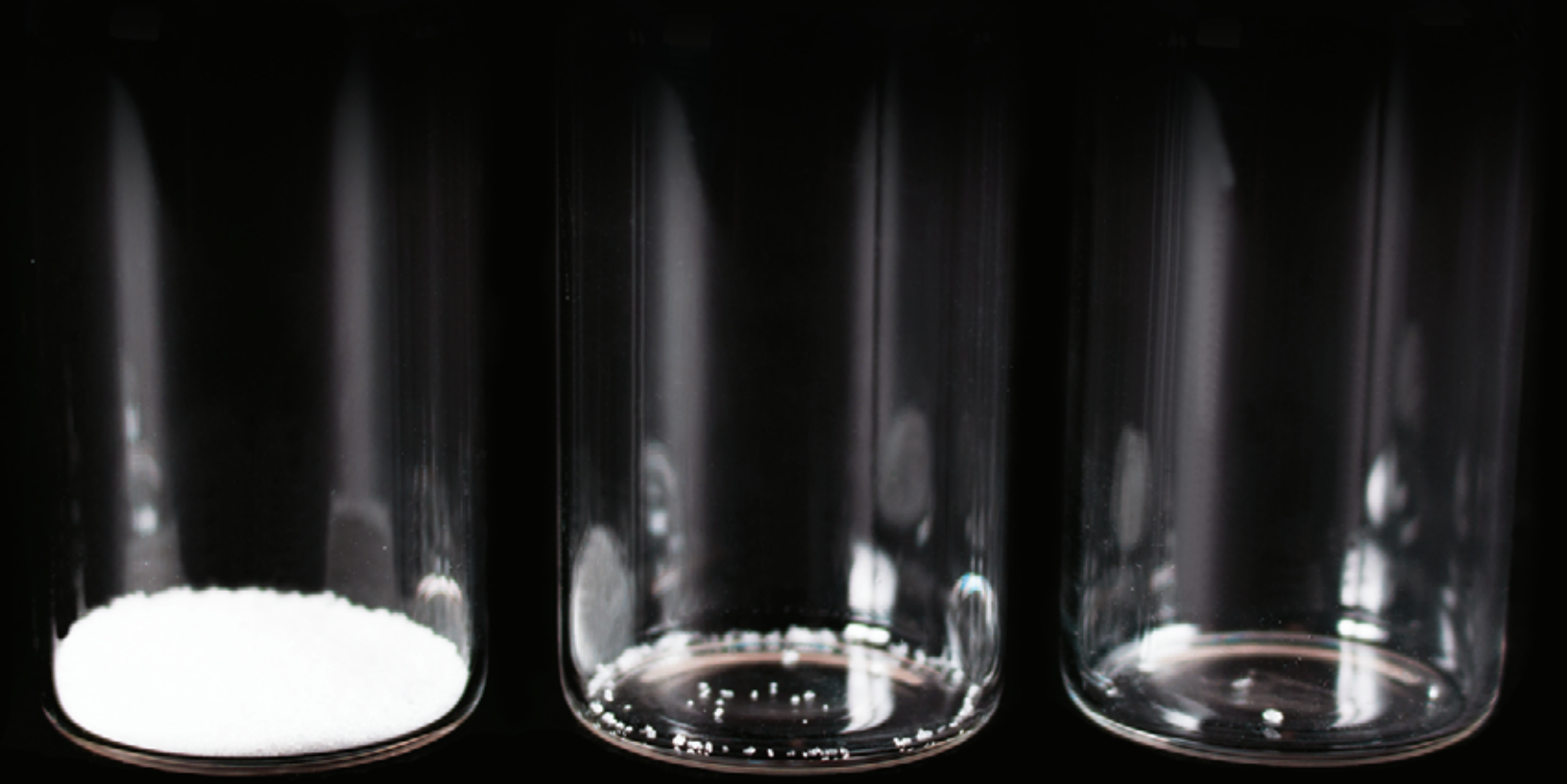
**CAYMAN**CURRENTS
ISSUE 28 | FALL 2017



***From left to right:*** *Representative lethal doses of heroin, fentanyl, and carfentanil*

# *FENTANYL IDENTIFICATION*



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# Tips for Interpreting GC-MS Fragmentation of Unknown Substituted Fentanyls

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Fentanyl is a powerful synthetic opioid developed by Janssen Pharmaceutica in 1959 that has roughly one hundred times the potency of morphine. Due to fentanyl's powerful analgesic properties and wide therapeutic index, it has been safely used by the medical community for decades. Structurally, fentanyl can be described as a 4-anilidopiperidine. Extensive structure-activity relationship (SAR) studies are well documented in scientific and patent literature.[1-3] Some additional 4-anilidopiperidines are safely used in human and/or veterinary medicine (such as alfentanil, sufentanil, and remifentanil) but most have never advanced to clinical trials.[4,5] Until recently, only a handful of 4-anilidopiperidines, such as 3-methyl fentanyl, acetyl fentanyl, and β-hydroxythiofentanyl, were found on the illicit market for recreational drug use within the U.S. and overseas.[6,7] Beginning in late 2015 to early 2016, numerous additional fentanyl-like compounds began to emerge, and there has been no hint of this trend slowing down. The rapid proliferation on the gray market of new molecular entities containing the fentanyl scaffold—designed to skirt existing regulations—has certainly made the identification of new psychoactive substances a challenge (**Figure 1**). The majority of the new fentanyl varieties have been modified at the regions defined on the fentanyl scaffold below.

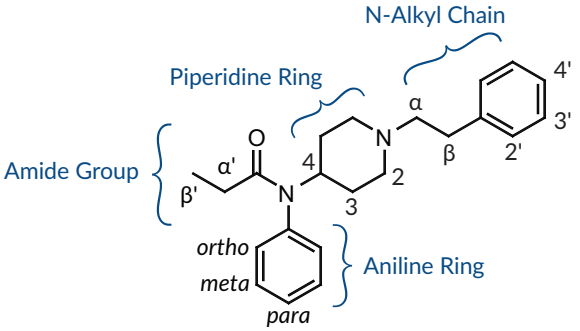


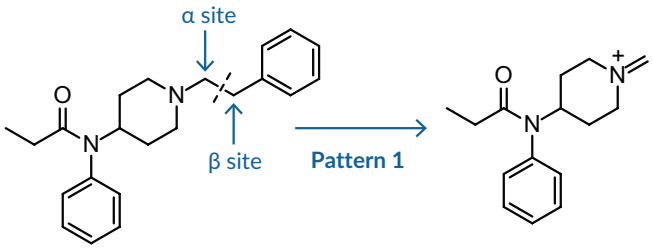

**Figure 1.** Cayman's standardized naming convention differentiates the points of substitution on the fentanyl scaffold by region. Typical variation swaps are noted in the table below.

| Region | Typical Variations |
|---|---|
| Amide Group | • Linear and branched alkyl chains<br>• Heteroatom insertions<br>• Cycloalkanes<br>• Aromatic/heterocyclic rings |
| Aniline Ring | • *Ortho*, *meta*, and *para* substituents<br>• Heterocyclic rings |
| Piperidine Ring | • C-2, C-3, and C-4 piperidine ring substituents |
| N-Alkyl Chain | • Linker chain-length variations<br>• Substitution on the α and β carbons<br>• Non-phenyl ring terminus |

The obvious challenge for law enforcement and border patrol is the ability to identify new unknown substances quickly and accurately. To do so, they often turn to GC-MS libraries for a match. However, if the compound is so novel that mass spectra data has not yet been collected, forensic scientists are left to rely on their chemistry knowledge to decipher clues as to what functional groups have been substituted onto the fentanyl scaffold. Cayman Chemical's scientists work hard to be at the forefront of identifying emerging drugs of abuse by quickly making authentic reference standards available. As new forensic materials go through the quality control process, the GC-MS data are added to the Cayman Spectral Library. By studying the GC-MS spectra of more than 50 fentanyl-like compounds, four major predictive patterns have emerged that provide clues to help in identifying unknown cases.

## Pattern 1:

*Fentanyl-like compounds cleave between the α and β carbons of the ethyl heterocyclic linker, which results in the base peak (BP) ion.*




**Fentanyl, MW 336** **Base Peak Ion 245**

Often with fentanyl compounds, the molecular ion is not detected in the spectra, so the molecular weight (MW) of the compound is not easily discernable. In such cases, the base peak (BP) corresponds to the primary cleavage of the compound, which occurs between the α/β site on the phenethyl moiety or similar chain.

The presence of 91, the tropylium ion, in the spectra of fentanyl-like compounds strongly suggests a phenethyl group. In such cases, the MW of the compound will be equal to the BP plus 91. In the case of fentanyl, the molecular ion (336) is not discernable, but the BP is 245, so 245 + 91 = 336 (BP + $CH_2Ph$ = MW) (**Figure 2**).[8,9] When a linker other than a phenethyl is attached to the piperidine ring such as furanylethyl fentanyl, for example, the ion fragment for 91 is not observed. In this case, an ion fragment at 81 is observed instead for the furanylmethyl ion. A comprehensive list of fentanyl-like compounds with their corresponding MWs, listed in order of descending BPs, can be found on **pages 4 and 5**.

For substituted fentanyls with a hydroxyl group in the β position, such as β-hydroxy fentanyl and β-hydroxythiofentanyl, primary cleavage still occurs between the α/β site, but a smaller fragment peak will be observed as the MW minus 18 (M-18) for the loss of water. For β-hydroxy fentanyl that fragment is 334, and for β-hydroxythiofentanyl that fragment is 340. These peaks have the potential to be confused with the molecular ion, but according to **Pattern 1**, the exact molecular ion is not usually observed.

A noteworthy exception to this first pattern occurs when the phenethyl moiety is replaced with a N-benzyl or N-methyl moiety, as with benzyl fentanyl.[8] In the case of benzyl fentanyl, the molecular ion (322) is noticeable along with the BP of 91, resulting from the cleavage between the piperidine ring and the benzyl group (**Figure 2**). In variations where the compound has a thienyl group instead of a benzyl, such as thienyl fentanyl, the BP is observed at 97.

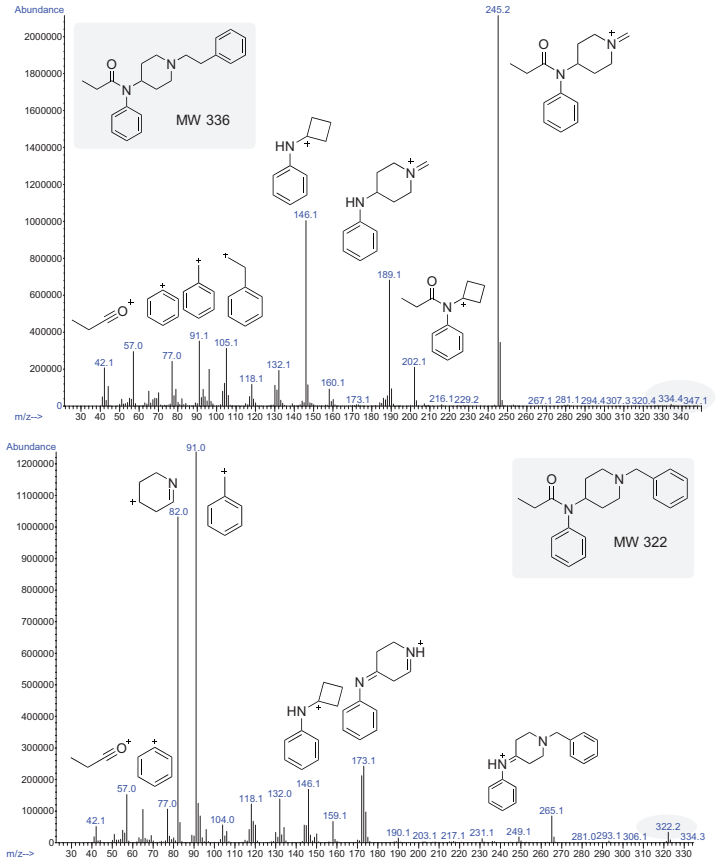
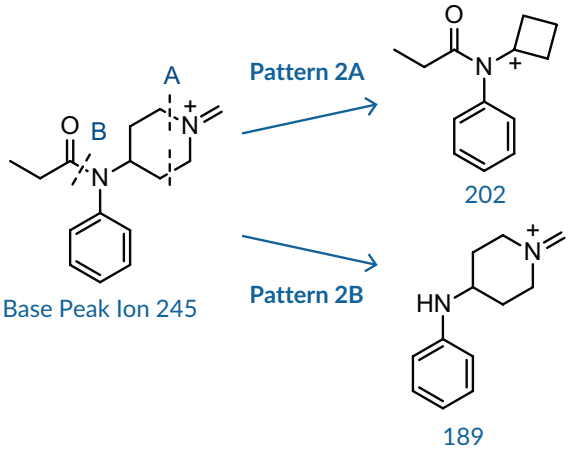



**Figure 2.** A comparison of the GC-MS of fentanyl with its corresponding ion fragments (top) and the GC-MS of benzyl fentanyl (bottom).

## Pattern 2:

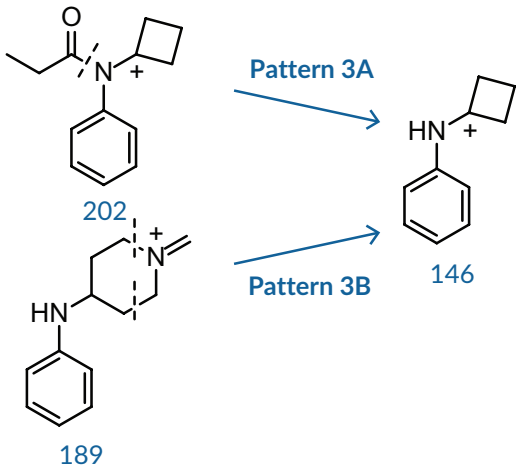
*Additional cleavage of the BP ion occurs along the piperidine ring and at the amide C-N bond.*




The BP ion undergoes additional cleavage in two areas. The first is along the piperidine ring, **Pattern 2A**, eliminating the nitrogen and two carbons to form a cyclobutyl group (mass 202 for fentanyl).[8,10] This is a minor peak in abundance compared to the peak at 189 and 146 for fentanyl. The second cleavage occurs along the C-N amide bond to produce a peak with an abundance of 30-60% of the BP (mass 189 for fentanyl), **Pattern 2B**.[8] These masses will change depending on the substitutions on the piperidine ring, amide group, or aniline ring. Subtracting the mass of this fragment from the BP will yield the mass of the acylium ion.

## Pattern 3:

*Subsequent cleavage at either the piperidine ring or the amide C-N bond of the secondary fragments results in a third characteristic fragment.*




The third characteristic fragment results from cleavage along the amide bond and additional cleavage within the piperidine ring. In the case of fentanyl, cleavage of the amide C-N bond of ion 202, **Pattern 3A**, yields ion fragment 146. Similarly, cleaving the piperidine ring of ion 189, **Pattern 3B**, eliminates the nitrogen and two adjacent carbons, causing the ring to collapse into a cyclobutyl group and yielding the same ion 146.[8,10] The ratio between 146 and 189 is almost always greater than one unless there is a branched alkyl group or a closed alkyl ring system, as seen with isobutyryl fentanyl and cyclopentyl fentanyl (**Figure 3**).

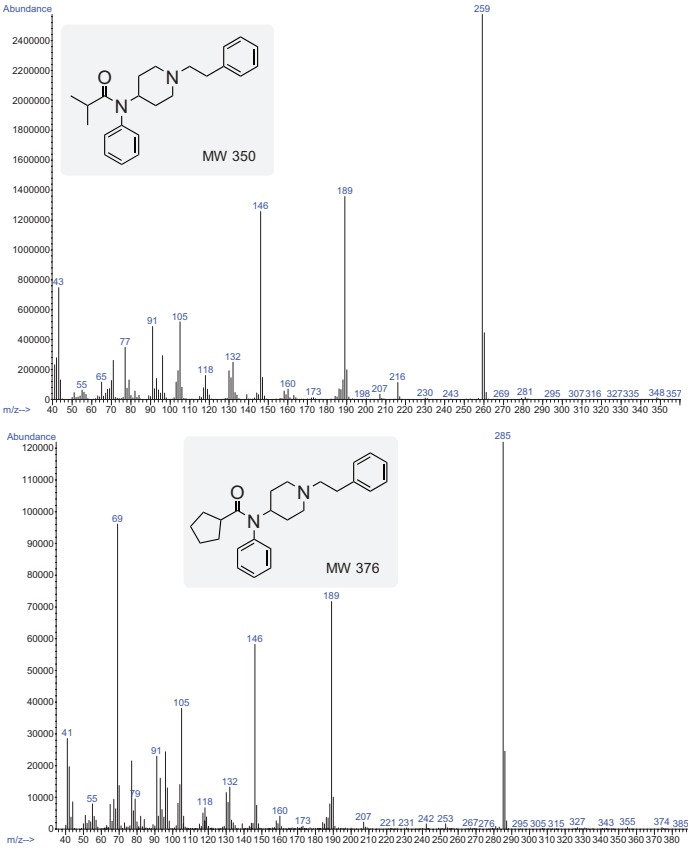
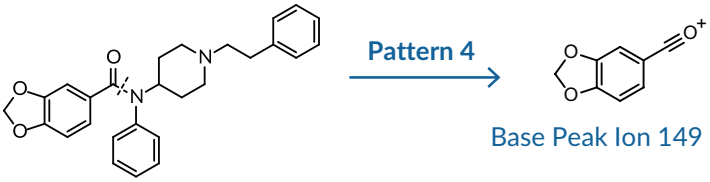



**Figure 3.** The GC-MS for isobutyryl fentanyl (top) is showing a 1:1 ratio of ions 146 to 189, while the GC-MS for cyclopentyl fentanyl (bottom) is showing a ratio of less than one, where the ion 189 is in larger abundance than the ion 146.

Thus, if the 146 and 189 peaks are present in the GC-MS spectra, your unknown will most likely be a fentanyl-like compound without substitutions on the piperidine or aniline regions. If the mass fragments 146 and 189 are absent, this will likely indicate a substitution on the aniline or piperidine ring. Using the major peaks of fentanyl as a foundation, the mass of a substitution can be predicted by calculating the difference. For example, if 146 is not observed yet 160 is, subtracting 146 from 160 will indicate a substitution of a hydrogen by a methyl group. This way, differences in the mass units of the three main peaks within the spectra compared with those of fentanyl may be used to determine the mass of substitutions along the amide, aniline, or piperidine regions of the compound.

## Pattern 4:

*Cleavage at the amide C-N bond will generate the BP if a highly stabilized or highly substituted group is in the acyl region.*




If the primary cleavage occurs along the amide C-N bond to generate the BP, instead of between the α/β site as for **Pattern 1**, then a highly resonance-stabilized group is likely substituted in the $R_1$ position. This is the case for furanyl fentanyl (95) and benzodioxole fentanyl (149) (**Pattern 4**), as well as phenyl fentanyl (105) and thiophene fentanyl (111). Incidentally, cleavage also occurs at the α/β site for furanyl fentanyl and benzodioxole fentanyl, generating less abundant fragments 283 and 337, respectively (**Figure 4**).

It is also imperative to investigate the smaller molecular ion fragments to help identify your unknown because if the acyl amide group contains a different moiety such as a cyclopentyl (69), cyclobutyl (55), methoxyacetyl (45), or a tetrahydrofuran (71), these fragments will help you identify those moieties. For instance, with cyclopentyl fentanyl (**Figure 3**), there is a large fragment peak at 69, indicating cleavage occurs between the C-C bond next to the carbonyl group instead of the amide C-N bond as for furanyl fentanyl. For the most part BP ions are generated by primary cleavage at the α/β site.

## Exceptions

While most fentanyl-type unknowns may be discerned using these predictive patterns, there are always a few exceptions to the rules. An exception occurs, for instance, when there is a substitution in the 4-position on the piperidine ring, such as with carfentanil. **Pattern 1** still applies because the BP is shown at 303, yet the functional group in the 4-position is either eliminated during fragmentation

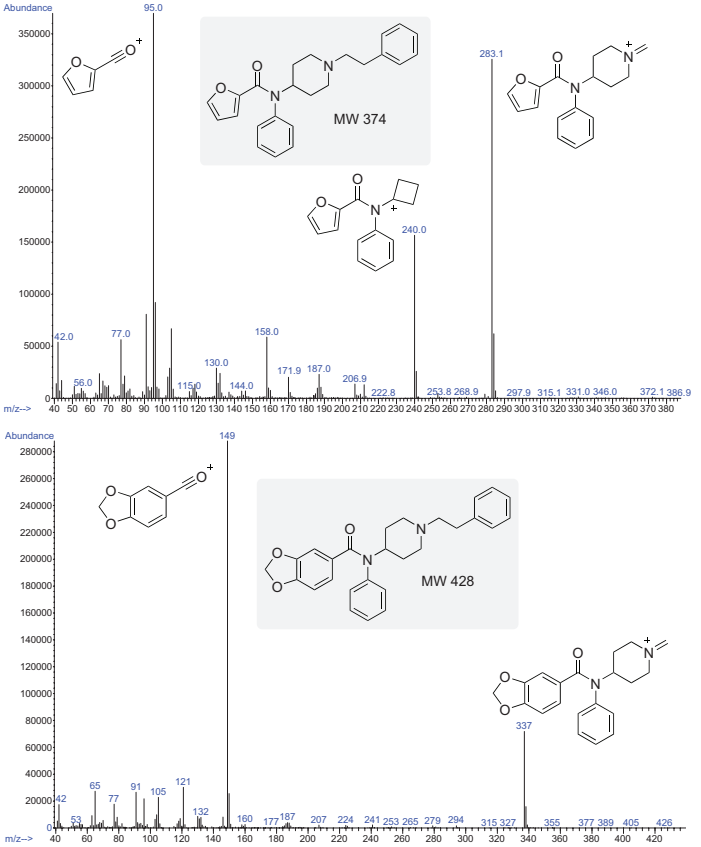



**Figure 4.** Cleavage at the amide C-N bond will generate the BP if a highly stabilized group has been substituted in the acyl region. The primary cleavage of the highly resonance-stabilized ion gives the BP fragments shown at 95 and 149 for furanyl fentanyl (top) and benzodioxole fentanyl (bottom).

or is retained, causing rearrangement leading to other fragments. Further investigation is needed for compounds similar to carfentanil that have substitutions in the 4-position on the piperidine ring. However, even the compounds that do not present all the predictive fragments will still display some areas of cleavage as outlined above.

In summary, by following the patterns outlined above (and taking into consideration notable exceptions), we hope that we have provided useful tips for interpreting the GC-MS of novel 4-anilidopiperidines. Please note that the fragment ion structures proposed in this article are predicted structures only and may not represent the true structures of the ions.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# Designer Fentanyl Compounds

*Listed by base peak in descending order*

| Item No. | Product Name | MW (free base) | Base Peak |
|---|---|---|---|
| 23858 | β'-Phenyl fentanyl | 412.6 | 321 |
| 22752 | *para*-fluoro Tetrahydrofuran fentanyl HCl | 396.5 | 305 |
| 19410 | Carfentanil | 394.5 | 303 |
| 23471 | *para*-methoxy Valeryl fentanyl HCl | 394.5 | 303 |
| 22390 | Cyclohexyl fentanyl HCl | 390.5 | 299 |
| 20018 | *para*-Chloroisobutyryl fentanyl HCl | 384.9 | 293 |
| 19292 | Alfentanil HCl | 416.5 | 289 |
| 18089 | *para*-methoxy-Butyryl fentanyl HCl | 380.5 | 289 |
| 20859 | Tetrahydrofuran fentanyl HCl | 378.5 | 287 |
| 22664 | Tetrahydrofuran fentanyl 3-tetrahydrofurancarboxamide HCl | 378.5 | 287 |
| 20439 | Cyclopentyl fentanyl HCl | 376.5 | 285 |
| 20034 | *para*-Chlorofentanyl HCl | 370.9 | 279 |
| 21740 | *meta*-fluoro Methoxyacetyl fentanyl HCl | 370.4 | 279 |
| 21741 | *para*-fluoro Methoxyacetyl fentanyl HCl | 370.4 | 279 |
| 18583 | Ocfentanil HCl | 370.4 | 279 |
| 19313 | FIBF HCl | 368.5 | 277 |
| 19566 | *meta*-Fluorobutyryl fentanyl HCl | 368.5 | 277 |
| 19567 | *ortho*-Fluorobutyryl fentanyl HCl | 368.5 | 277 |
| 17049 | *para*-Fluorobutyryl fentanyl HCl | 368.5 | 277 |
| 20206 | *meta*-Fluoroisobutyryl fentanyl HCl | 368.5 | 277 |
| 20207 | *ortho*-Fluoroisobutyryl fentanyl HCl | 368.5 | 277 |
| 22749 | *para*-fluoro Cyclopropyl fentanyl HCl | 366.4 | 275 |
| 20035 | *para*-Methoxyfentanyl HCl | 366.5 | 275 |
| 20818 | α-methyl Butyryl fentanyl HCl | 364.5 | 273 |
| 20817 | (±)-*cis*-3-methyl Butyryl fentanyl HCl | 364.5 | 273 |
| 18934 | Valeryl fentanyl HCl | 364.5 | 273 |
| 22389 | Cyclobutyl fentanyl HCl | 362.5 | 271 |
| 21952 | 3-Fluorofentanyl HCl | 354.4 | 263 |
| 19424 | *meta*-Fluorofentanyl HCl | 354.4 | 263 |
| 19425 | *ortho*-Fluorofentanyl HCl | 354.4 | 263 |
| 15496 | *para*-Fluorofentanyl HCl | 354.4 | 263 |
| 21116 | *para*-fluoro Acrylfentanyl | 352.5 | 261 |
| 21932 | *ortho*-fluoro Acrylfentanyl HCl | 352.4 | 261 |
| 20782 | Methoxyacetyl fentanyl HCl | 352.4 | 261 |
| 20821 | α-methyl Thiofentanyl HCl | 356.5 | 259 |
| 22240 | (±)-*cis*-3-methyl Thiofentanyl HCl | 356.5 | 259 |

# Designer Fentanyl Compounds *Continued*

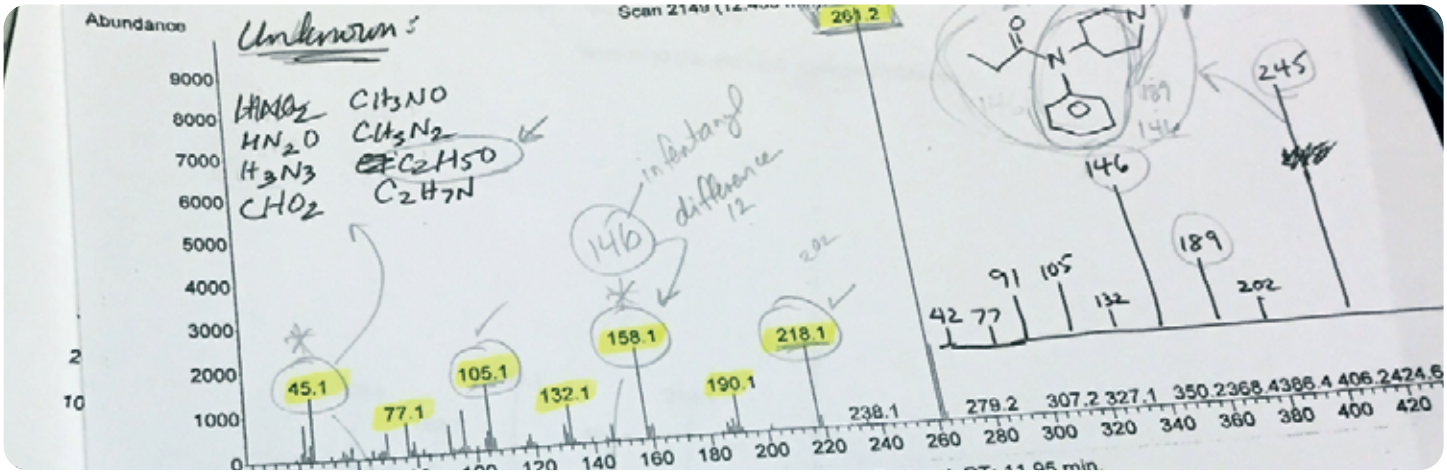
| Item No. | Product Name | MW (free base) | Base Peak |
|---|---|---|---|
| 14728 | Butyryl fentanyl HCl | 350.5 | 259 |
| 18280 | α-methyl Fentanyl HCl | 350.5 | 259 |
| 9002747 | (±)-*cis*-3-methyl Fentanyl HCl | 350.5 | 259 |
| 9002482 | (±)-*trans*-3-methyl Fentanyl HCl | 350.5 | 259 |
| 18584 | Isobutyryl fentanyl HCl | 350.5 | 259 |
| 22633 | *meta*-Methylfentanyl HCl | 350.5 | 259 |
| 22634 | *ortho*-Methylfentanyl HCl | 350.5 | 259 |
| 20038 | *para*-Methylfentanyl HCl | 350.5 | 259 |
| 22801 | Crotonyl fentanyl | 348.5 | 257 |
| 22884 | Methacrylfentanyl | 348.5 | 257 |
| 23036 | *ortho*-methyl Acrylfentanyl HCl | 348.4 | 257 |
| 21739 | Cyclopropyl fentanyl HCl | 348.4 | 257 |
| 17421 | β-Hydroxythiofentanyl HCl | 358.5 | 245 |
| 20789 | β-hydroxy Fentanyl HCl | 352.4 | 245 |
| 9002860 | β-methyl Fentanyl HCl | 350.5 | 245 |
| 21914 | 4'-methyl Fentanyl HCl | 350.5 | 245 |
| 20786 | Thiofentanyl HCl | 342.5 | 245 |
| 20816 | α-methyl Acetyl fentanyl HCl | 336.4 | 245 |
| 14719 | Fentanyl HCl | 336.4 | 245 |
| 20819 | Furanylethyl fentanyl HCl | 326.4 | 245 |
| 19312 | Acrylfentanyl HCl | 334.4 | 243 |
| 9002271 | 4'-methyl Acetyl fentanyl HCl | 336.4 | 231 |
| ISO00128 | Acetyl fentanyl HCl | 322.4 | 231 |
| 19291 | Remifentanil HCl | 376.4 | 168 |
| 20858 | Benzodioxole fentanyl | 428.5 | 149 |
| 22744 | 2,2,3,3-tetramethyl-Cyclopropyl fentanyl HCl | 404.6 | 125 |
| 22802 | Thiophene fentanyl HCl | 390.5 | 111 |
| 22551 | Phenyl fentanyl HCl | 384.5 | 105 |
| 20785 | Thienyl fentanyl HCl | 328.4 | 97 |
| 22750 | *para*-fluoro Furanyl fentanyl HCl | 392.4 | 95 |
| 22779 | *ortho*-methyl Furanyl fentanyl HCl | 388.5 | 95 |
| 22713 | *para*-methyl Furanyl fentanyl HCl | 388.5 | 95 |
| 18705 | Furanyl fentanyl HCl | 374.4 | 95 |
| 21213 | Furanyl fentanyl 3-furancarboxamide isomer HCl | 374.4 | 95 |
| 20350 | Benzyl Carfentanil HCl | 380.4 | 91 |
| 19883 | Benzyl fentanyl HCl | 322.4 | 91 |

*Parent compounds listed, more designer fentanyls and their deuterated standards available online*

# SLEUTHING THE UNKNOWN

*Cayman's pursuit to identify an unknown sample: methoxyacetyl fentanyl*

When an unidentified fentanyl analog appeared related to four separate overdose cases in Alabama, Dr. Rachel Beck, a toxicologist at the University of Alabama at Birmingham who provides forensic services to the Jefferson County Coroner and Medical Examiner's Office, began contacting colleagues across the country. Everyone seemed stumped by what this out-of-the-ordinary opioid could be. Her mass spectrometer was equipped to scan multiple GC-MS spectral databases, including Cayman's Spectral Library, but her compound was too novel to strike a hit. After drawing blanks from her usual go-to resources, Dr. Beck contacted Cayman's forensic scientists to tap into their expertise to help solve the unknown by deciphering the available GC-MS data.




## Examining Base Peak MW

The 261 base peak of this unknown was quite similar to that of fentanyl with a mass difference of +16 amu, and it displayed a fragmentation pattern similar to that of fentanyl. *Para*-fluoro acrylfentanyl, which also has a base peak of 261, was suspected to be the probable match since acrylfentanyl was being observed in many illicit samples at that time. A +16 amu mass difference between fentanyl and the unknown could be accounted for by the subtraction of three hydrogen atoms and the addition of a fluorine atom to the base fentanyl structure. *Para*-fluoro acrylfentanyl was quickly synthesized and sent to Dr. Beck for confirmation. Unfortunately, the retention time of *para*-fluoro acrylfentanyl was off by 0.3 minutes. Also, the m/z and response of some smaller fragments were not fitting the pattern of the mystery compound. It was a very close analog, but not an exact match. When six additional overdose cases related to this same unknown were documented, the identification of this compound became an even more pressing concern.

> Cayman's assistance in the identification of methoxyacetyl fentanyl was invaluable! I could not have identified, confirmed, and quantitated this compound without both their data analysis service and their ability to quickly synthesize a reference standard.
>
> *–Dr. Rachel Beck, Toxicologist at the University of Alabama at Birmingham*

## Deciphering Minor Fragments

Determined to uncover the identity of the molecule, Dr. Donna Iula, the director of Cayman's Forensic Chemistry division, persisted to investigate other substitution options. Knowing now that *para*-fluoro acrylfentanyl was not a match, she compared the spectra of the mystery compound to that of *para*-fluoro acrylfentanyl and other closely related analogs, deciphering many of the minor fragments for clues. Focusing on the smallest minor fragment (45) of the unknown compound, Dr. Iula consulted a mass spec table from her old grad school spectroscopy textbook to get hints as to what a mass of 45 might represent. Was it $HN_2O^+$? $H_3N_3^+$? $CHO_2^+$? $CH_3NO^+$? $CH_3N_2^+$? $C_2H_5O^+$? $C_2H_7N^+$? $C_2H_5O^+$ stood out as a potential option for the fragment given what she knew about the structure-relationship studies around fentanyl. The addition of an oxygen to the amide side chain would account for the mass difference of +16 amu. Also, precedent indicated that an oxygen had been placed within the amide side chain of ocfentanil.

## Substituting $C_2H_5O^+$ on Fentanyl

Coincidently, Dr. Iula's laboratory had just recently synthesized the $C_2H_5O^+$ substitution on fentanyl, methoxyacetyl fentanyl, after seeing chatter surrounding it on an internet forum and notified Dr. Beck that it was available for immediate analysis. This time the GC-MS data matched. Dr. Iula's intuition and perseverance had paid off. Dr. Beck was able to confirm the use of methoxyacetyl fentanyl in all ten cases. The mystery was solved!

# What Do We Know about the Metabolism of the New Fentanyl Derivatives?

*By: Donna M. Iula, Ph.D.*

The metabolism of the pharmaceutical opioid fentanyl has been well studied, but less is known about the metabolism of the newer fentanyl-like compounds that have recently emerged on the scene (*i.e.*, 'designer fentanyls,' 'fentalogs,' or 'fentanyl derivatives').[1-5] Herein we present a brief discussion of what is known about the metabolism of fentanyl and other fentanyl-like opioids. Based on what is currently known, a predictive pattern is evident that can aid in detecting novel fentanyl-like compounds in clinical and post-mortem cases.

Fentanyl is heavily and rapidly metabolized in the liver ('first-pass metabolism') by cytochrome P450 enzymes to several metabolites collectively referred to as phase I metabolites (**Figure 1**). The role of first-pass metabolism is to convert drugs to less lipophilic molecules that are more easily excretable. First-pass metabolites then undergo what is referred to as 'second-pass metabolism', which inactivates the phase I metabolites. Many of these phase II metabolites are in the form of glucuronide or sulfate bioconjugates that are even further hydrophilic. In human plasma, identification of unmetabolized fentanyl is readily possible, whereas in urine, the concentration of fentanyl metabolites often greatly exceeds that of the parent drug. In general, when analyzing urine samples, non-hydrolyzed samples will show the phase II glucuronidation and sulfation products, while hydrolyzed urine samples will only detect the phase I metabolites.

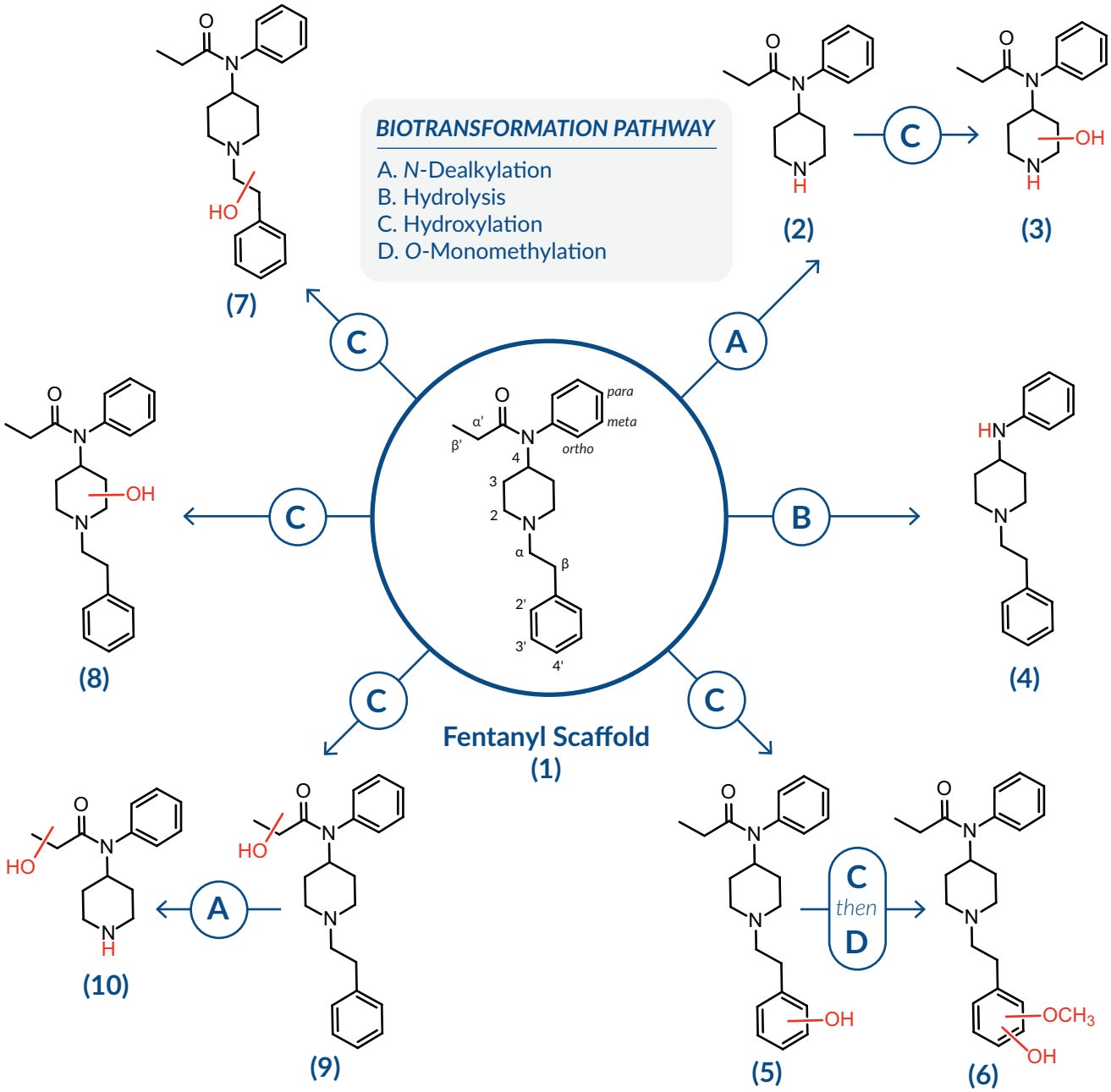
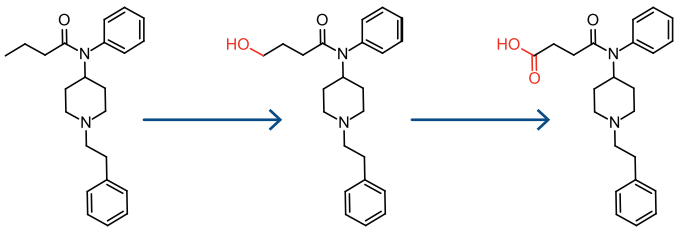



**Figure 1.** The major proposed routes of metabolism for fentanyl and designer fentanyls.

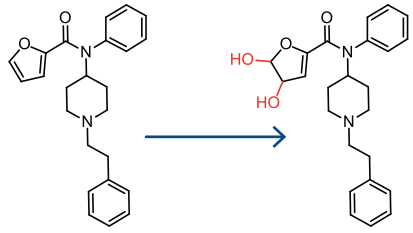
The major route of fentanyl metabolism is *via* oxidative *N*-dealkylation to the inactive desphenethyl metabolite norfentanyl (**2**). Another known (but minor) human metabolite is despropionyl fentanyl (**4**), which is also known as 4-ANPP. This amide hydrolysis metabolite can coincidentally be formed as a metabolic product of several different fentanyl analogs, so its presence isn't particularly diagnostic. It is also a precursor contaminant found in seized illicit fentanyl and fentanyl analog powders, further adding to the complexity of identifying it in urine analysis. There are numerous hydroxylated compounds that are typically less abundant (**3**, **5**, **7**, **8**, **9**, and **10**). It has been reported, for example, that hydroxylation can occur on the ethyl linker of the phenethyl moiety (either at the α or β position), at the 2 or 3 position on the piperidine ring, along the amide alkyl chain, or on the phenyl ring of the phenethyl moiety. Some of these hydroxylated metabolites, such as 4'-hydroxy fentanyl (**5**), are potentially bioactive, but most are believed to be inactive. Hydroxy fentanyls like **5** can be further biotransformed *via* a second hydroxylation to afford a catechol that is then *O*-monomethylated to yield metabolite **6**. This methylation conjugation reaction is presumably catalyzed by the enzyme catechol-O-methyltransferase and is believed to occur at the 3' position. This is technically a phase II metabolic product, but it is detected in both hydrolyzed and non-hydrolyzed urine specimens due to its stability. Norfentanyl (**2**) is also further oxidized (**Figure 1**). Keep in mind that most of the metabolites depicted in **Figure 1** can potentially undergo further transformations to yield additional metabolites and often the exact positioning of the hydroxyl group is unknown.




**Butyryl Fentanyl (11)** **(12)** **(13)**

**Figure 2.** Major human metabolites of butyryl fentanyl.

Biotransformation studies on several fentanyl derivatives such as acetyl fentanyl,[6,7] furanyl fentanyl,[7,8] *para*-fluoroisobutyryl fentanyl (FIBF),[7] 3-methyl fentanyl,[9] isofentanyl,[9] α-methyl fentanyl,[10] butyryl fentanyl,[11] acrylfentanyl,[7,12] and carfentanil[13,14] have been reported. While *in vivo* and *in vitro* studies utilizing human liver hepatocytes or microsomes can identify up to 32 primary and secondary metabolites for a particular fentanyl derivative, actual human urine specimens typically show the number to be far less. For the sake of simplicity, only phase I metabolites will be discussed in this review of the literature. What has been documented for fentanyl metabolism typically translates to the new designer fentanyls. The various pathways described in **Figure 1** are followed to varying degrees. For example, while screening for designer fentanyl metabolites in urine specimens, one can expect to find the *N*-dealkylation metabolite to typically predominate. Notable exceptions, however, are butyryl fentanyl and furanyl fentanyl. In those cases, the oxidative *N*-dealkylation metabolic pathway and subsequent hydroxylation do not dominate. While butyryl fentanyl (**11, Figure 2**) is only one carbon longer than fentanyl, unexpectedly, the added lipophilicity is enough to steer metabolism to the butanamide side chain. Here, both the hydroxylation metabolite (**12, Figure 2**) and its secondary oxidation product (**13**, **Figure 2**), the corresponding carboxylic acid, are both dominant metabolites (**Figure 2**). The expected desphenethyl nor-metabolite that occurs with most fentanyl derivatives is actually present in very low abundance in furanyl fentanyl cases. The metabolism of furanyl fentanyl (**14, Figure 3**), which differs substantially from fentanyl in that the ethyl chain of the propanamide is replaced with an aromatic heterocyclic furan moiety, does not follow the typical fentanyl metabolic routes either. As described in two recent studies, it was observed that the furanyl ring system is heavily targeted for metabolism.[7,8] Like butyryl fentanyl, the corresponding typical *N*-dealkylated nor-metabolite is present in very low concentrations (if at all) in urine samples. Instead, metabolite 4-ANPP (**4**) is detected along with a unique dihydrodiol (**15, Figure 3**).




**Furanyl Fentanyl (14)** **(15)**

**Figure 3.** A unique human phase I metabolite of furanyl fentanyl.

In summary, if a novel fentanyl derivative is very close in structure to fentanyl itself, the corresponding 'nor-fentanyl' metabolite (**2**) is typically one of the major breakdown products. The other structures illustrated in **Figure 1** are often present but will differ in relative abundance. Examples of analogs following this path include FIBF, 3-methyl fentanyl, acetyl fentanyl, α-methyl fentanyl, and acrylfentanyl. However, if the acyl alkyl chain is longer, such as in butyryl fentanyl, the majority of the metabolism will occur at this lipophilic site. When unique ring systems are present, such as in furanyl fentanyl, extensive metabolism of that ring system occurs in preference to *N*-dealkylation.

A phenomenon frustrating to forensic and clinical toxicologists is that given the strong structural similarity among emerging designer fentanyls, many are coincidentally biotransformed to the exact same molecule. This fact can make pinpointing the specific parent drug in a case difficult. The ability to identify minor metabolites that are unique to the parent drug is therefore of considerable importance. Cayman offers many of these major and minor metabolites (**see page 9**). If you cannot find a particular compound, our skilled scientists can propose the synthesis of any phase I or phase II metabolite you might be interested in studying.


**References**

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# Fentanyl and Designer Fentanyl Metabolites

| Item No. | Product Name | Known or Presumptive Metabolite of: |
|---|---|---|
| ISO00130 | Acetyl norfentanyl (hydrochloride) | Acetyl fentanyl |
| ISO60130 | Acetyl norfentanyl (hydrochloride) (CRM) | |
| ISO60131 | Acetyl norfentanyl-$d_5$ (hydrochloride) (CRM) | |
| 18810 | 4-ANPP | Acetyl fentanyl, Acrylfentanyl, Butyryl fentanyl, Cyclopentyl fentanyl, Fentanyl, Furanyl fentanyl, Isobutyryl fentanyl, Valeryl fentanyl, and most other fentanyl varieties |
| 22700 | 4-ANPP (CRM) | |
| 19232 | 4-ANPP-$d_5$ | |
| 19233 | 4-ANPP-$d_5$ (CRM) | |
| 20494 | Butyryl fentanyl carboxy metabolite | Butyryl fentanyl |
| 19428 | Butyryl norfentanyl (hydrochloride) | Butyryl fentanyl |
| 19561 | Butyryl norfentanyl (hydrochloride) (CRM) | |
| 24061 | Cyclopropyl norfentanyl (hydrochloride) | Cyclopropyl fentanyl |
| 20789 | β-hydroxy Fentanyl (hydrochloride) | Fentanyl |
| 20125 | Despropionyl *meta*-Fluorofentanyl | *meta*-Fluorobutyryl fentanyl, *meta*-Fluorofentanyl, *meta*-Fluoroisobutyryl fentanyl, *meta*-fluoro Methoxyacetyl fentanyl, and other *meta*-fluorinated varieties |
| 20126 | Despropionyl *ortho*-Fluorofentanyl | *ortho*-Fluorobutyryl fentanyl, *ortho*-Fluorofentanyl, Ocfentanil, and other *ortho*-fluorinated varieties |
| 20104 | Despropionyl *para*-Fluorofentanyl | FIBF, *para*-fluoro Acrylfentanyl, *para*-Fluorofentanyl, *para*-fluoro Methoxyacetyl fentanyl, and other *para*-fluorinated varieties |
| 19429 | Furanyl norfentanyl (hydrochloride) | Furanyl fentanyl |
| 19559 | Furanyl norfentanyl (hydrochloride) (CRM) | |
| 17421 | β-Hydroxythiofentanyl (hydrochloride) | Thiofentanyl |
| 19736 | β-Hydroxythiofentanyl (hydrochloride) (CRM) | |
| 19598 | β-Hydroxythiofentanyl-$d_5$ (hydrochloride) | |
| 19947 | β-Hydroxythiofentanyl-$d_5$ (hydrochloride) (CRM) | |
| 20204 | Isobutyryl norfentanyl | Isobutyryl fentanyl |
| 20205 | Isobutyryl norfentanyl (CRM) | |
| 22422 | Methoxyacetyl norfentanyl (hydrochloride) | Methoxyacetyl fentanyl |
| 19859 | Norcarfentanil (hydrochloride) | Carfentanil |
| 22182 | Norcarfentanil (hydrochloride) (CRM) | |
| 15899 | Norfentanyl | Fentanyl, Furanylethyl fentanyl, Thiofentanyl |
| ISO60195 | Norfentanyl (CRM) | |
| 18729 | Norfentanyl-$d_5$ (CRM) | |
| 22617 | (±)-*cis*-3-methyl Norfentanyl | (±)-*cis*-3-methyl Fentanyl |
| 22695 | (±)-*trans*-3-methyl Norfentanyl | (±)-*trans*-3-methyl Fentanyl |
| 9001142 | Norsufentanil | Sufentanil |
| 9001143 | Norsufentanil-$d_3$ | |
| 21926 | Remifentanil Acid (trifluoroacetate salt) | Remifentanil |
| 20497 | Valeryl fentanyl carboxy metabolite | Valeryl fentanyl |

*View a complete list of metabolites and their deuterated standards online*

# TOOLS AND RESOURCES

*to assist in the identification of emerging drugs of abuse*

## Cayman Spectral Library

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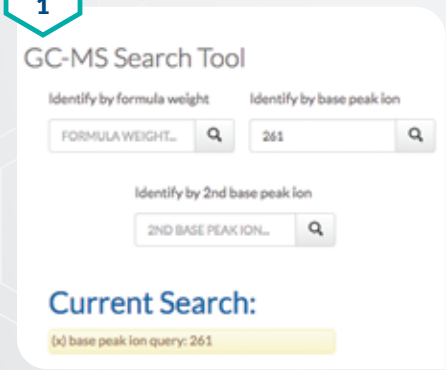
## GC-MS Search Tool

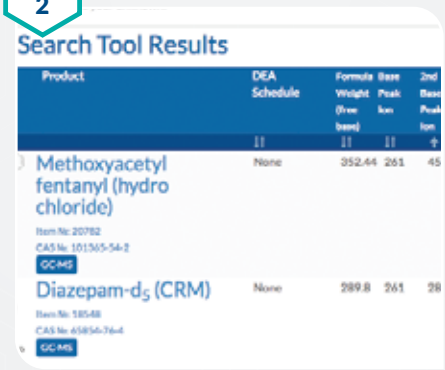
Search unknowns by formula weight, base peak, or 2nd base peak ion

**STEP 1**



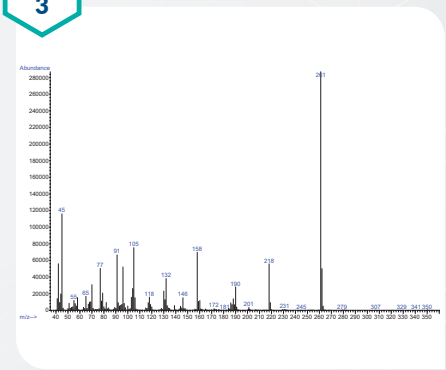

*Search by FW, Base Peak, or 2nd Base Peak Ion*

**STEP 2**




*Select Product*

**STEP 3**



*View GC-MS*

### Available online at www.caymanchem.com/forensics

If you can't find your unknown, submit your GC-MS data and any relevant information (suspected chemical class, matrix, solvent, GC parameters, *etc.*) to techserv@caymanchem.com for our scientists to investigate.

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Revised March 2018