FORENSICS @ NIST

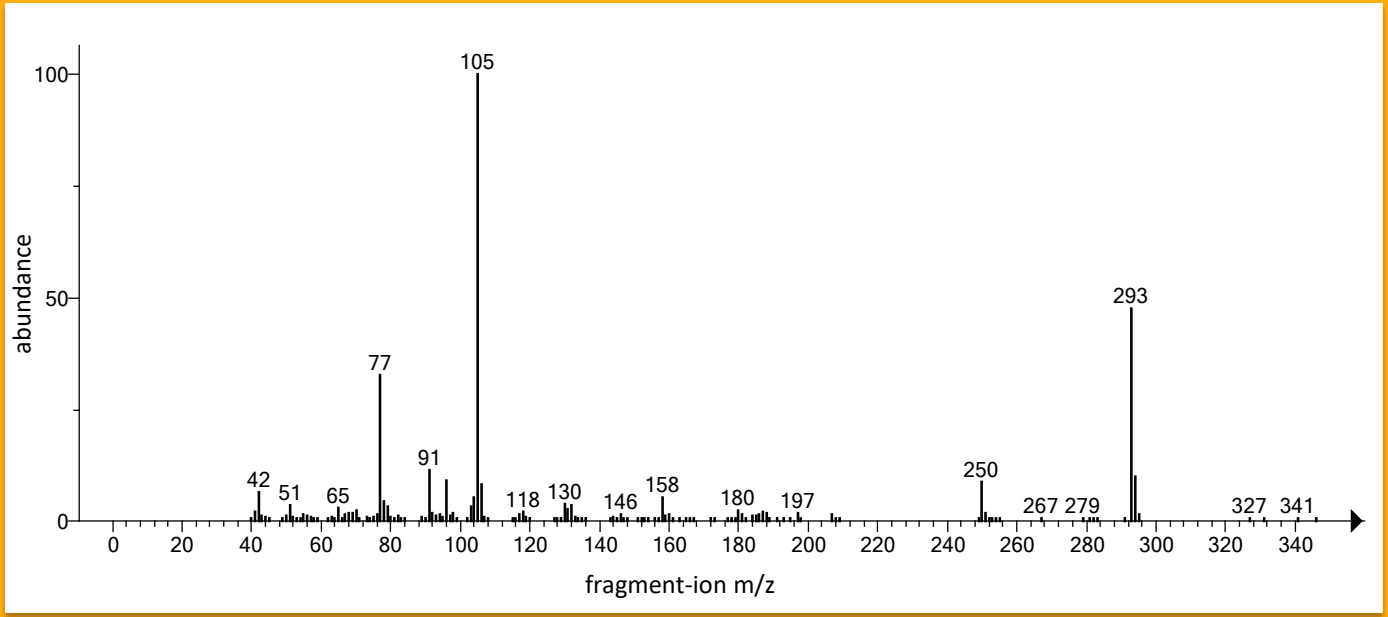
#NISTForensics

Is it a fentanyl?

Arun Moorthy -- asm3@nist.gov
Mass Spectrometry Data Center -- chemdata.nist.gov

Collaborators: WE Wallace, WG Mallard, SE Stein –Mass Spec Data Center, BMD, MML
AJ Kearsley – Applied and Computational Math Division, ITL

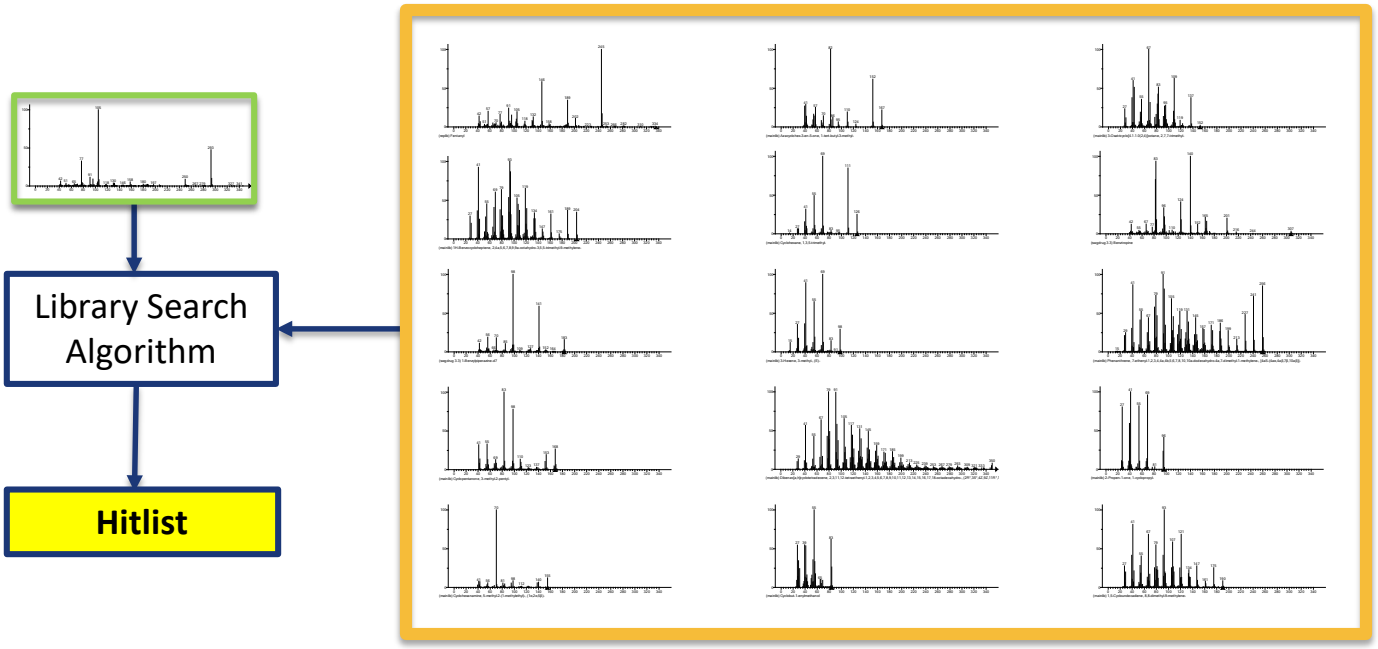
NIST National Institute of Standards and Technology U.S. Department of Commerce



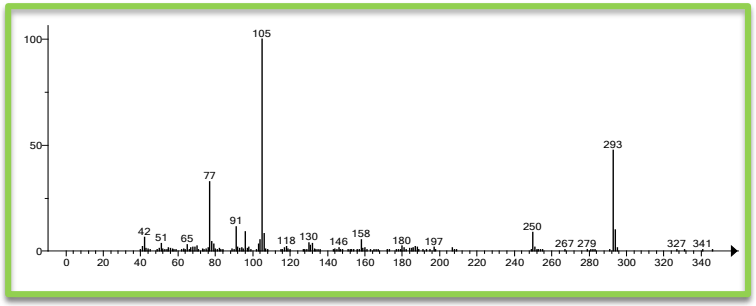
A *mass spectrum* is a histogram detailing the distribution of ***fragment ions*** organized by *mass-to-charge* ratio for a given compound.

Mass Spectral Library Searching

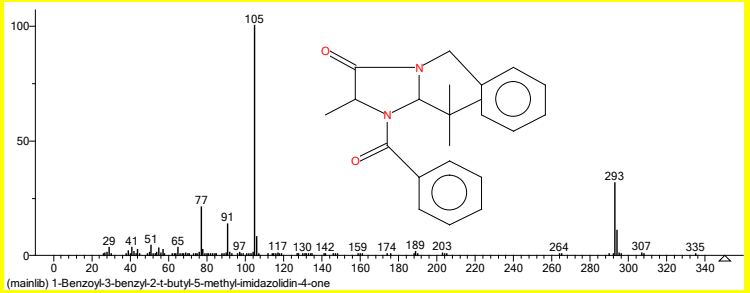
Principle: Given a set (library) of mass spectra for known chemical compounds, the identity of an unknown chemical compound can be *proposed* by comparing the similarity of the spectrum of the unknown with the spectra contained in the library.



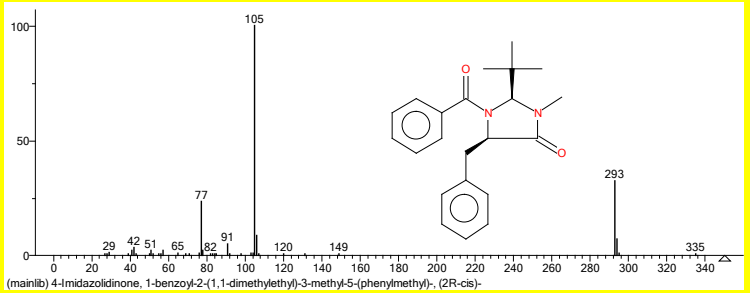
Simple Similarity Search of query against NIST17



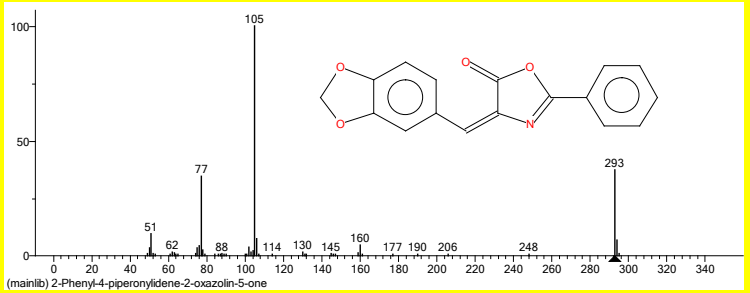
1. (795)



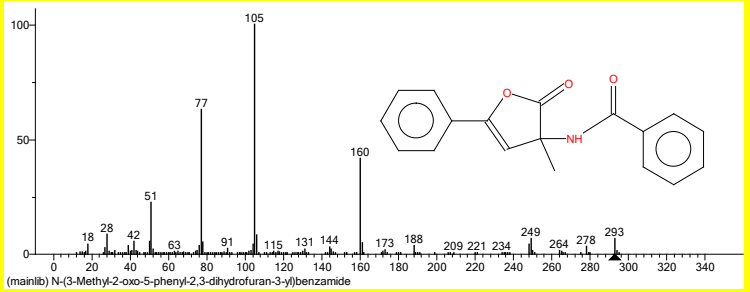
2. (726)



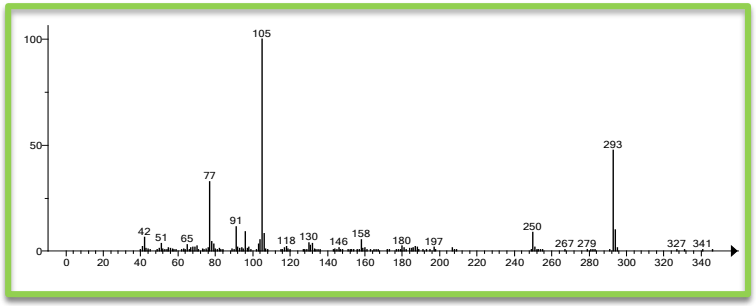
3. (685)



4. (625)

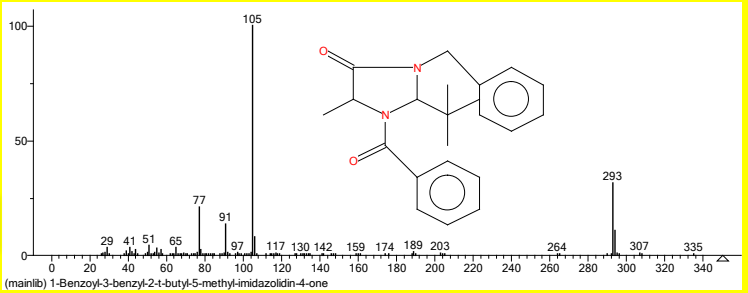


Simple Similarity Search of query against NIST17

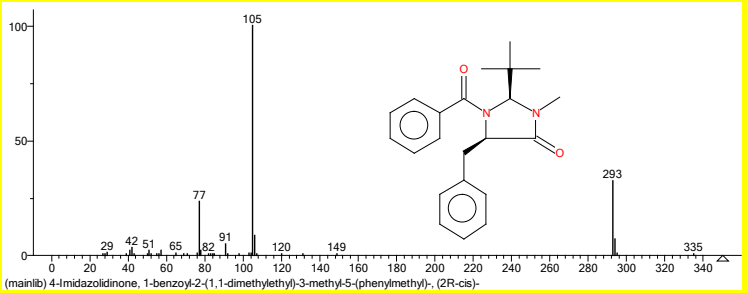


1. (795)

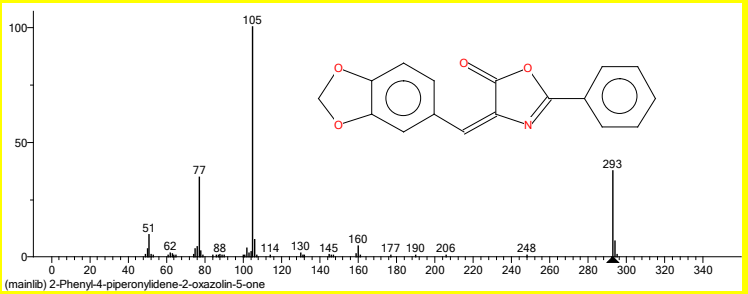
Match Factor



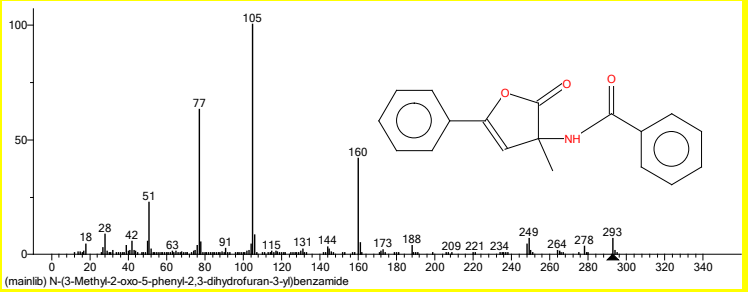
2. (726)



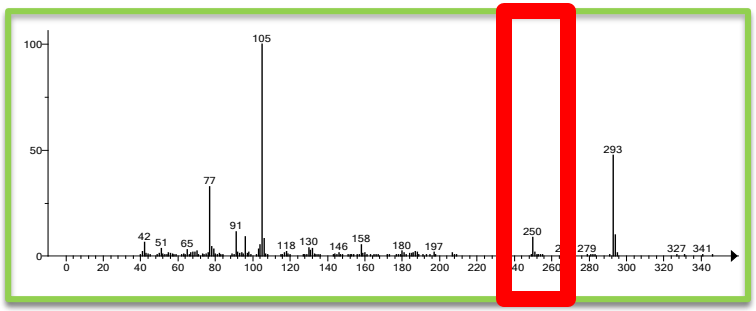
3. (685)



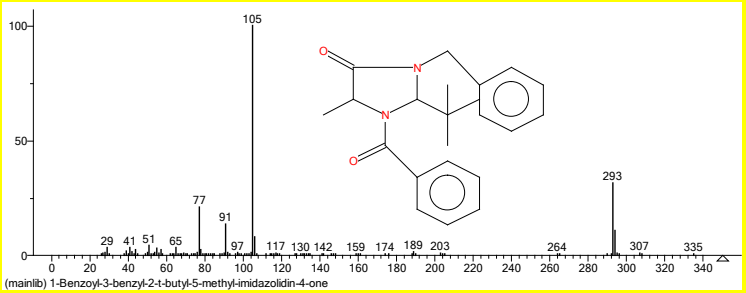
4. (625)



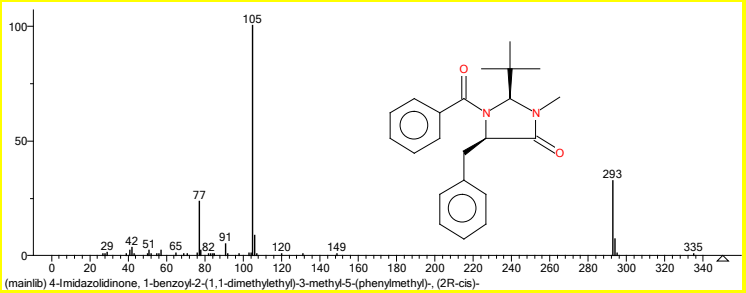
Simple Similarity Search of query against NIST17



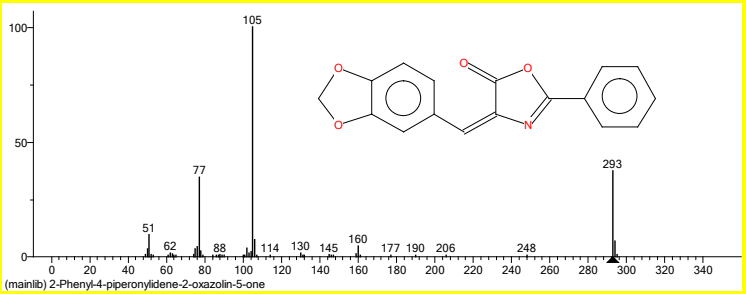
1. (795)



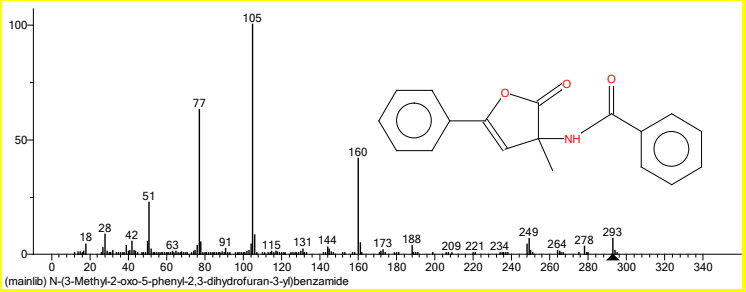
2. (726)



3. (685)



4. (625)



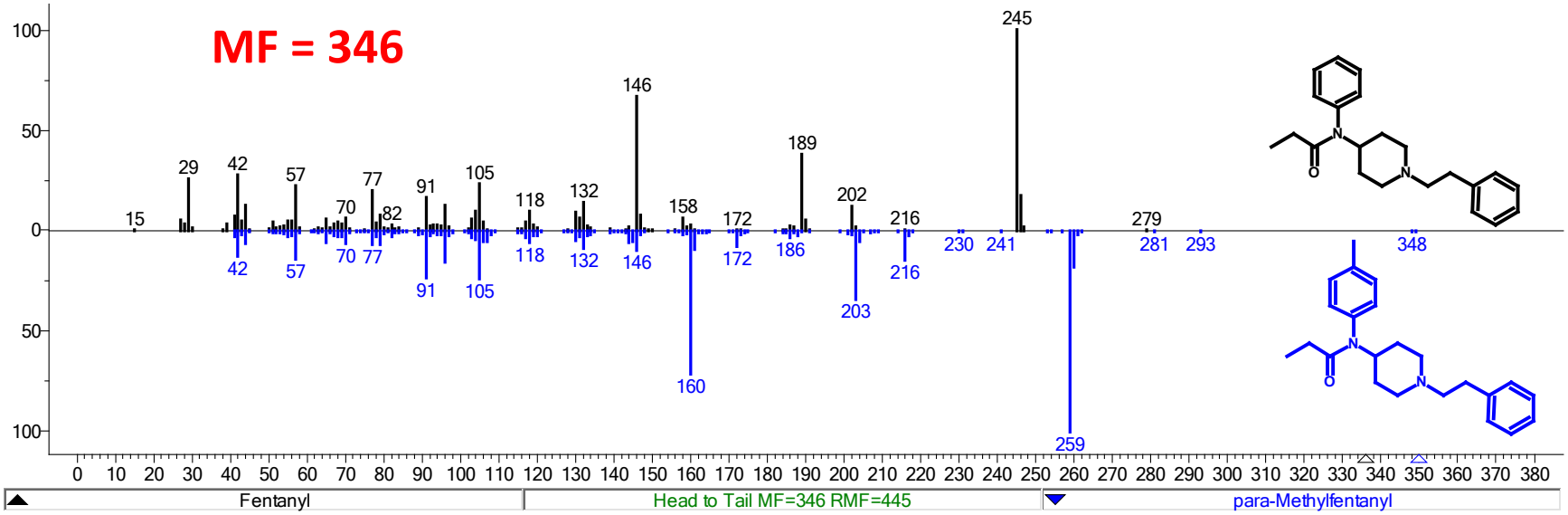
What if a spectrum of the unknown was not contained in the library?

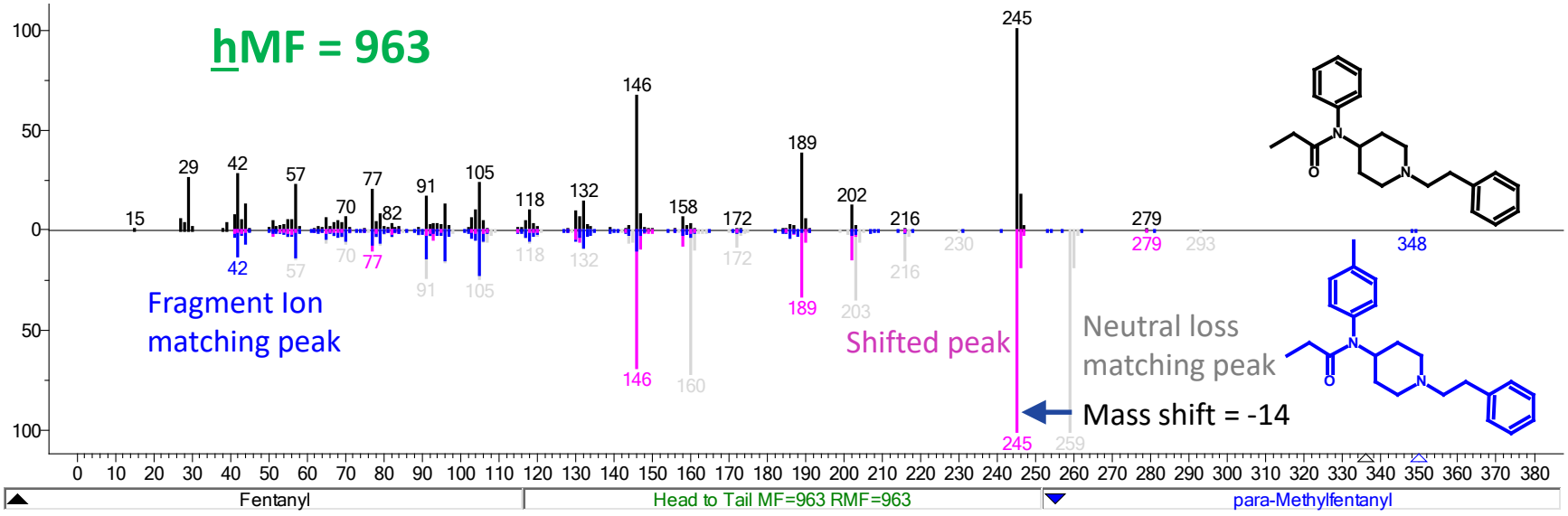
Hybrid Similarity

Hybrid Similarity

- Combines **fragment ion** AND **neutral loss** matching when computing spectral similarity

  - DeltaMass = Δ_m= MW(Query Compound) – MW(Library Compound)
  - Compare each query peak to two peaks in the library spectrum at corresponding:
    - (1) m/z [match suggests compounds form same fragment ion]
    - (2) m/z + DeltaMass [match suggests compounds form same neutral loss]


MF = 346
100
50
0
50
100
15
29
42
57
70
77
82
91
105
118
132
146
158
172
189
202
216
230
241
245
279
281
293
348
42
57
70
77
91
105
118
132
146
160
172
186
203
216
259
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380
Fentanyl
Head to Tail MF=346 RMF=445
para-Methylfentanyl

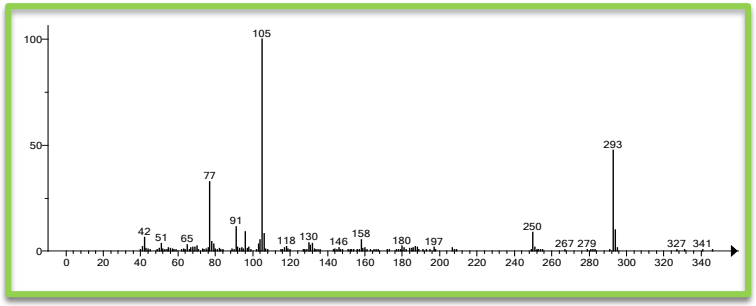

hMF = 963
Fragment Ion matching peak
Shifted peak
Neutral loss matching peak
Mass shift = -14
Fentanyl
Head to Tail MF=963 RMF=963
para-Methylfentanyl

Hybrid Similarity

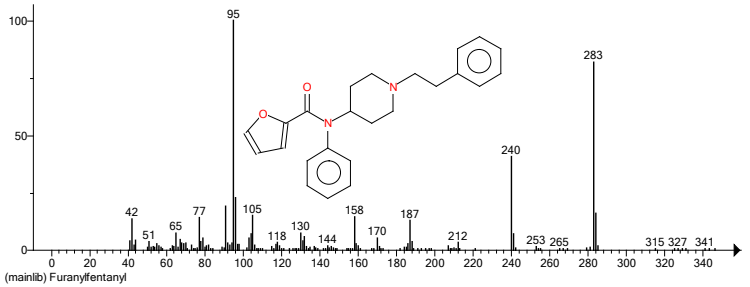
- Combines **fragment ion** AND **neutral loss** matching when computing spectral similarity
  - DeltaMass = Δ_m = MW(Query Compound) – MW(Library Compound)
  - Compare each query peak to two peaks in the library spectrum at corresponding:
    - (1) m/z [match suggests compounds form same fragment ion]
    - (2) m/z + DeltaMass [match suggests compounds form same neutral loss]

- Generates high spectral similarity scores between compounds that differ by the insertion/deletion or replacement of a **single** chemical moiety that does not greatly affect fragmentation mechanism

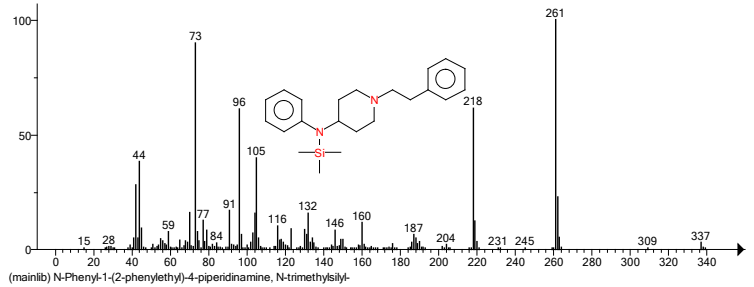
Hybrid Similarity Search of query against NIST17



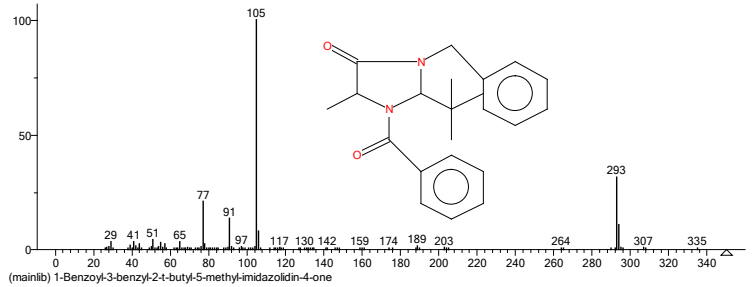
1. (934)
$\Delta_m = 10$



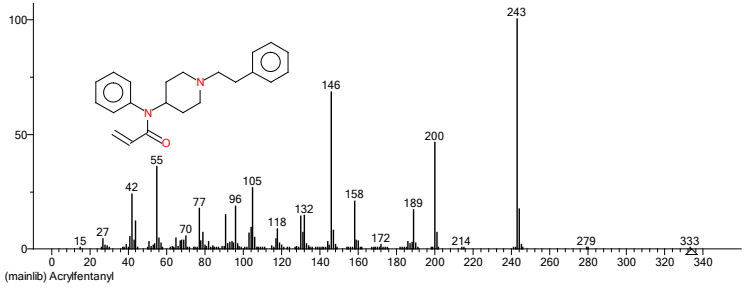
2. (822)
$\Delta_m = 32$



3. (820)
$\Delta_m = 34$

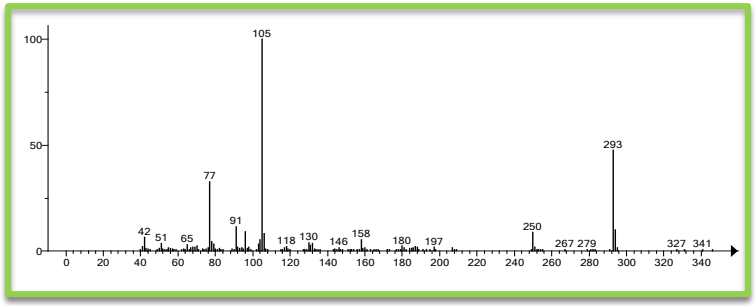


6. (787)
$\Delta_m = 50$

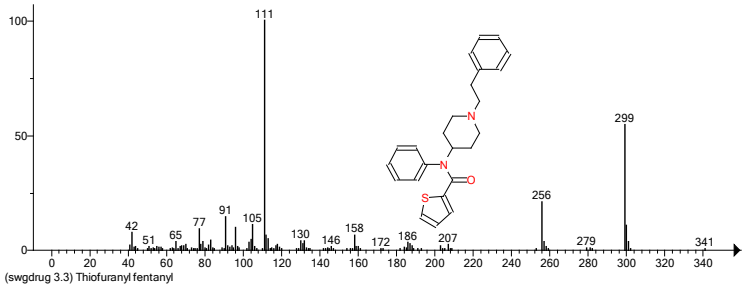


Libraries matter!

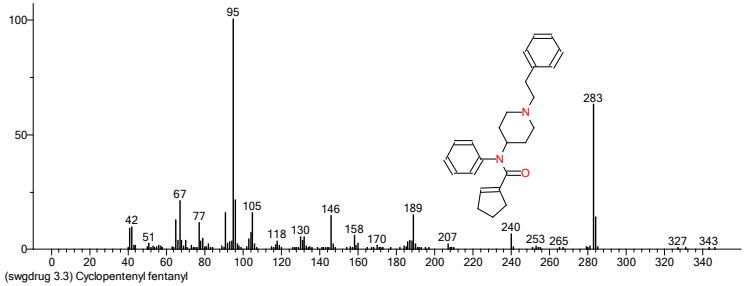
Hybrid Similarity Search of query against SWGDRUG 3.3



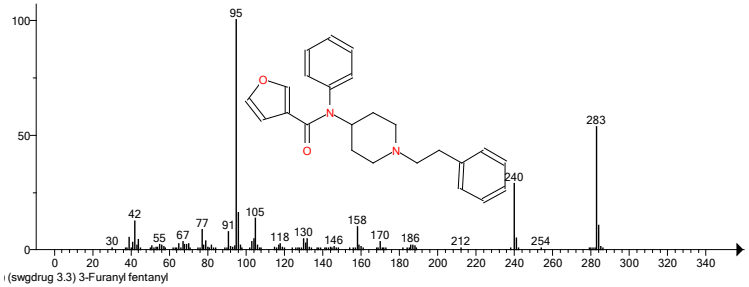
1. (962)
$\Delta_m = -6$



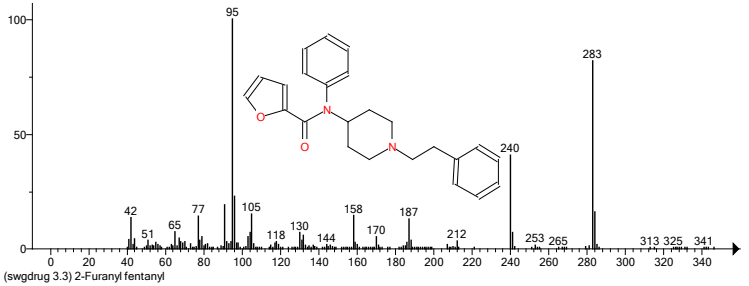
2. (938)
$\Delta_m = 10$



3. (937)
$\Delta_m = 10$



4. (936)
$\Delta_m = 10$



Can we do more?

Fentanyl ClassifieR

Fentanyl ClassifieR (prototype)

Fentanyl ClassifieR (prototype)

Objective: Make mass spectral library searching “easier” by re-casting our search question.

Fentanyl ClassifieR (prototype)

Objective: Make mass spectral library searching “easier” by re-casting our search question.

Trivial example:

Here is an exotic fruit, what is it?

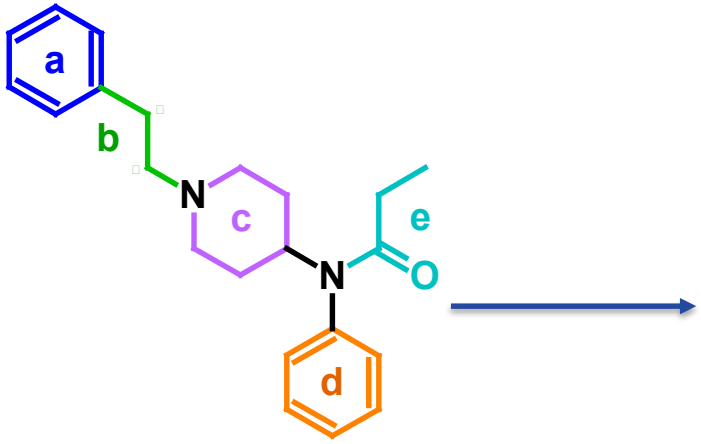
Hard question – requires knowledge of *all* fruit

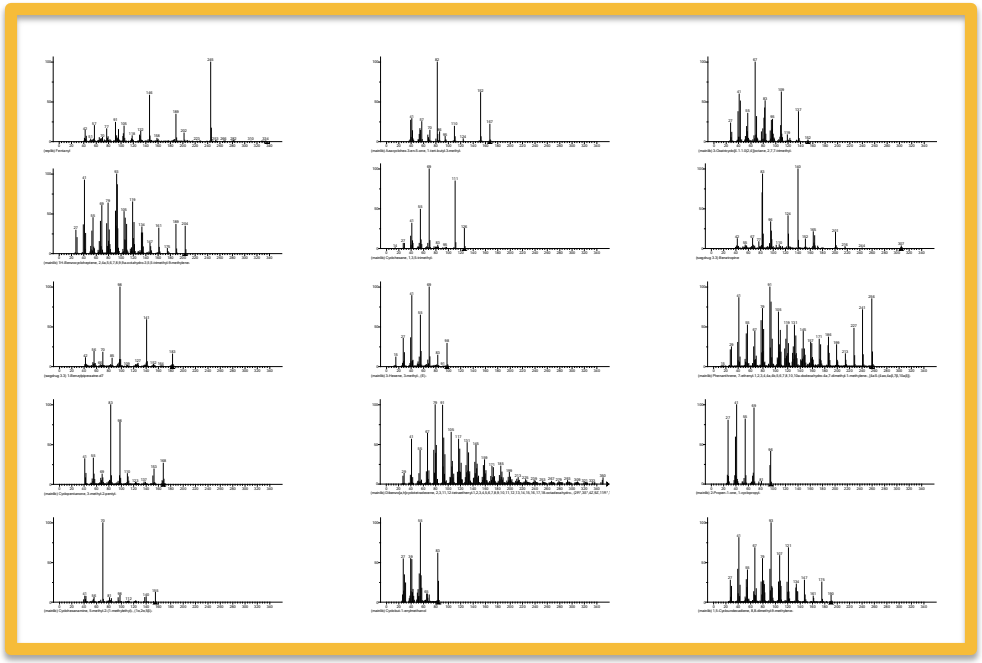
Here is an exotic fruit, is it an apple?

Easier question – requires knowledge of *all* apples

Fentanyl ClassifieR (prototype)

1) Build a highly curated library of JUST fentanyl analogs

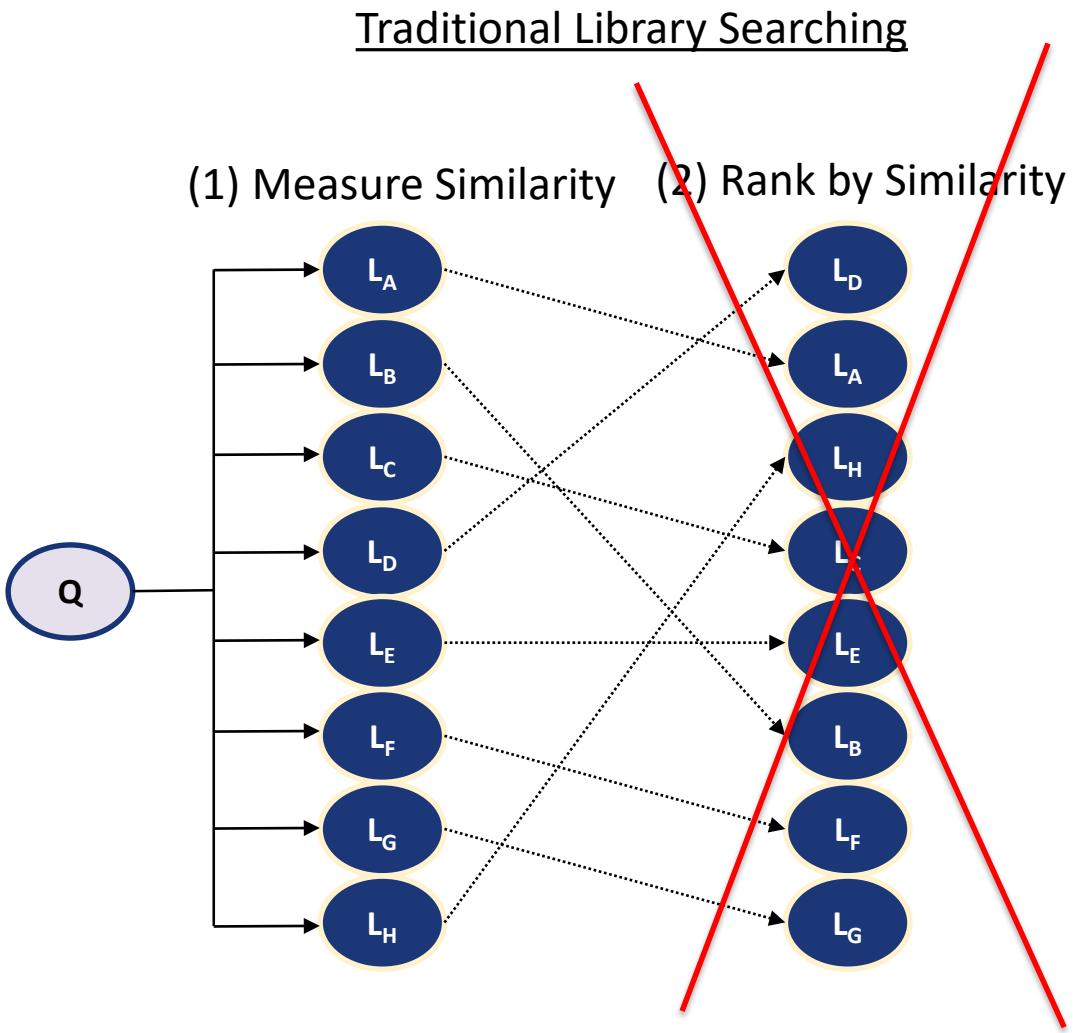




Fentanyl ClassifieR (prototype)

1) Build a highly curated library of JUST fentanyl analogs

2) Measure similarity between the query spectrum and the library spectra

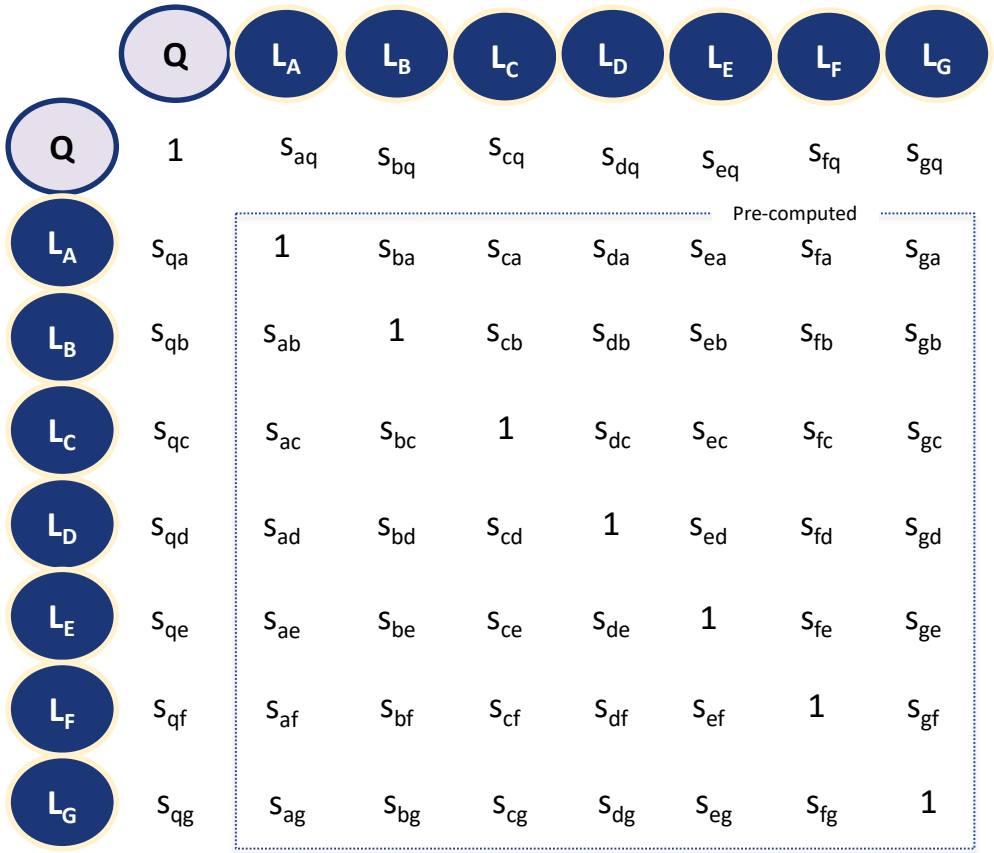


Fentanyl ClassifieR (prototype)

1) Build a highly curated library of JUST fentanyl analogs

2) Measure similarity between the query spectrum and the library spectra

3) Measure similarity between ALL of the fentanyl analog spectra in the library



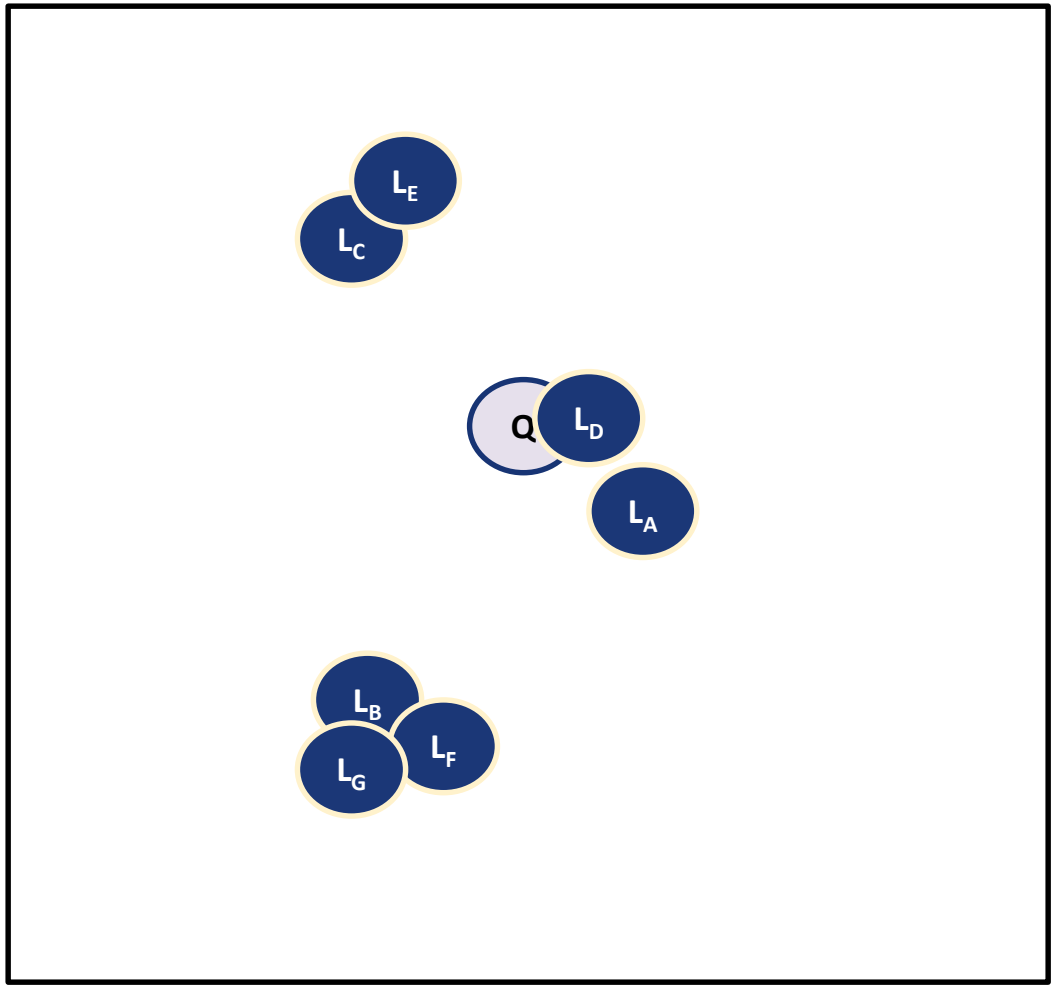
Fentanyl ClassifieR (prototype)

1) Build a highly curated library of JUST fentanyl analogs

2) Measure similarity between the query spectrum and the library spectra

3) Measure similarity between ALL of the fentanyl analog spectra in the library

4) Learn (*e.g. cluster*)

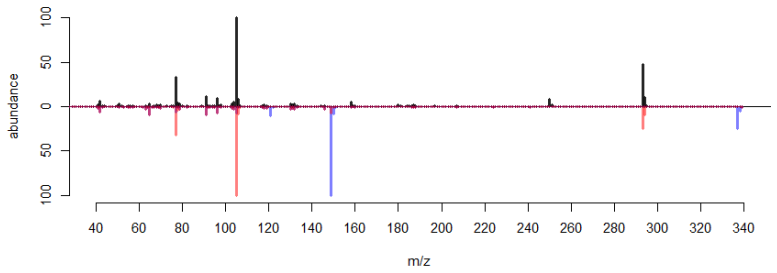


Search | Details | Instructions

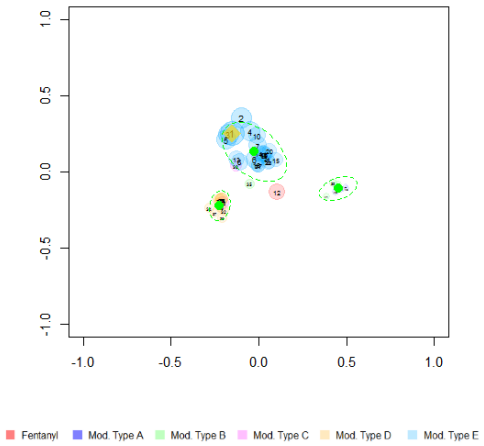
Press F11 to exit full screen

Fentanyl Classifier (MS Search Details)

Molecular weight information was contained in the Query MSP. The nominal MW of 384 Da was employed in the Hybrid Search.

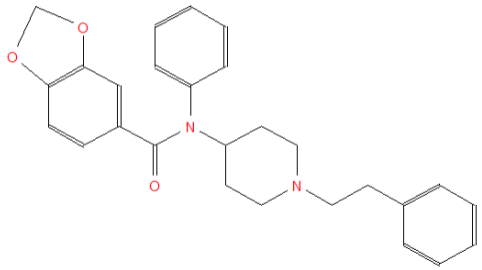


Hit List | Hit Map

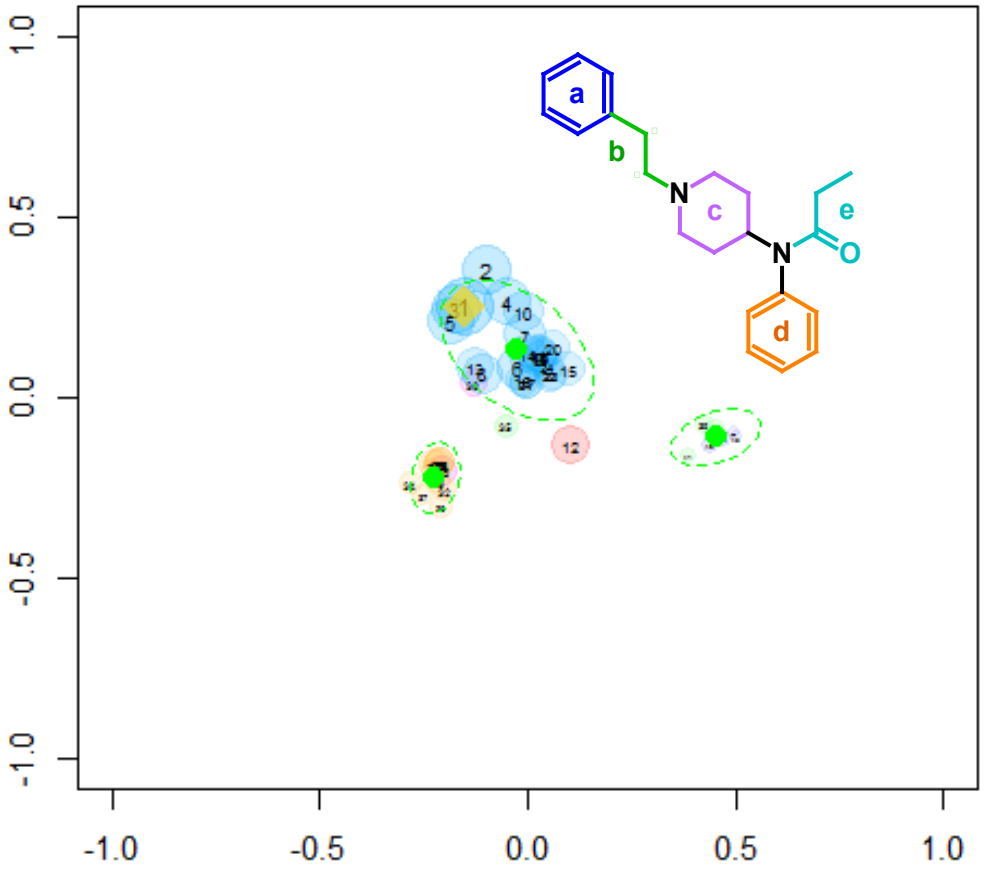


Proposed Hit Details

Name:	Benzodioxole fentanyl
Formula:	C27H28N2O3
Exact Mass:	428.21
MW:	428
InChIKey:	ZFAAZMIOHJNKGD-UHFFFAOYSA-N
Confidence:	0.42

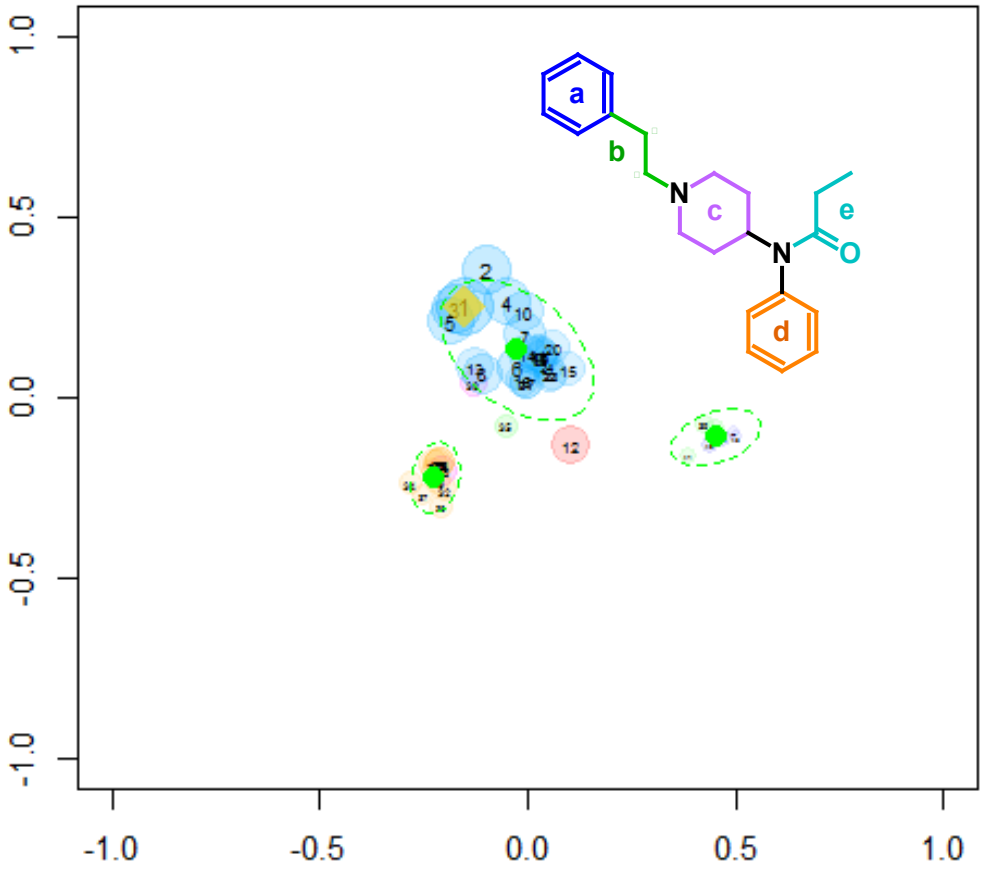


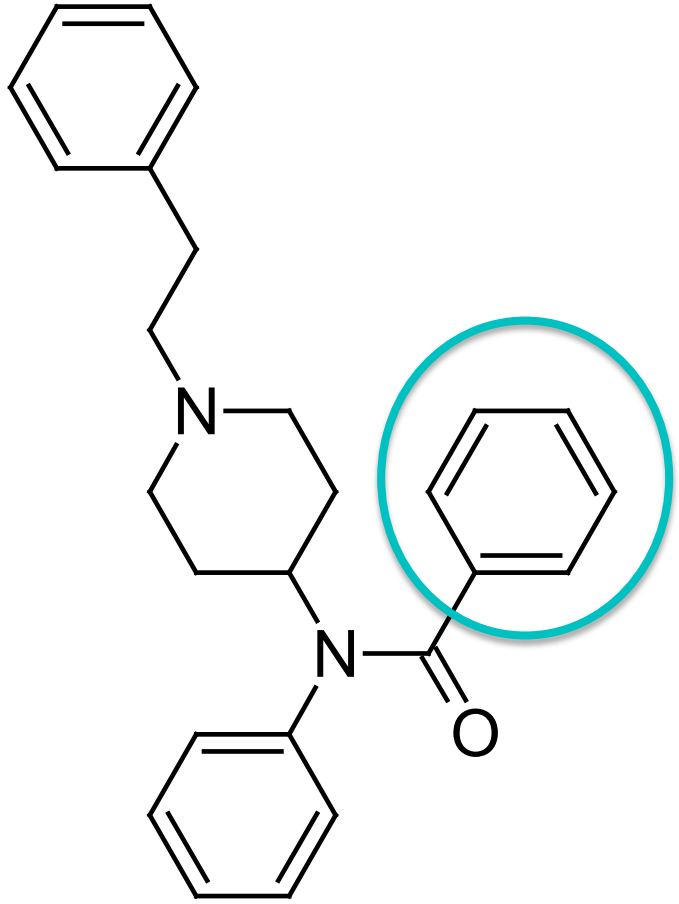
Fentanyl ClassifieR (prototype)



Compound	hMF	Δ_m	Relatedness Index
Benzodioxole fentanyl – E	861	-44	0.42
3-Furanyl fentanyl – E	839	10	0.57
Cyclopentyl fentanyl – E	819	10	0.48
2-Furanyl fentanyl – E	816	10	0.51
Acryl fentanyl – E	775	50	0.25

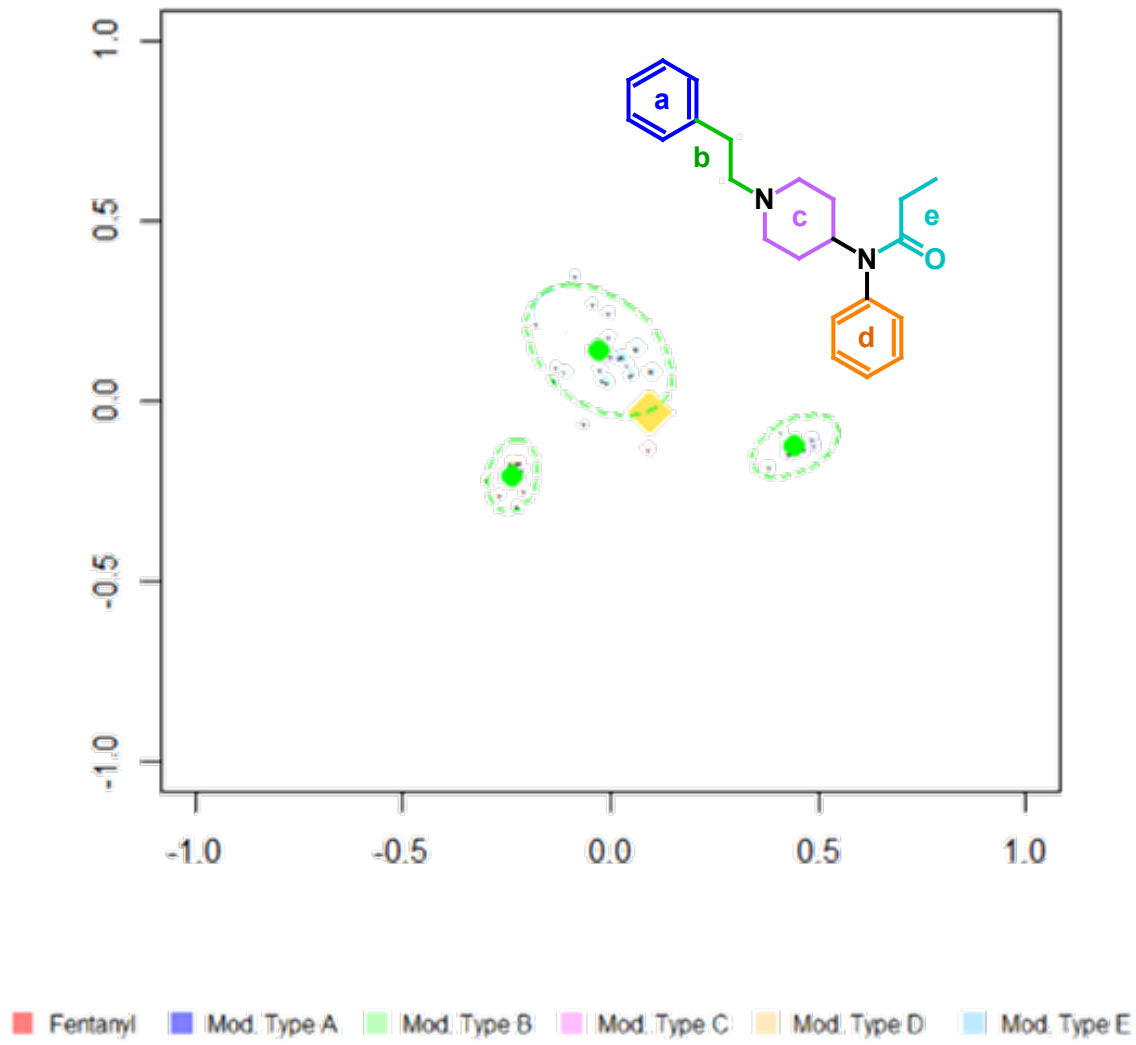
Fentanyl ClassifieR (prototype)





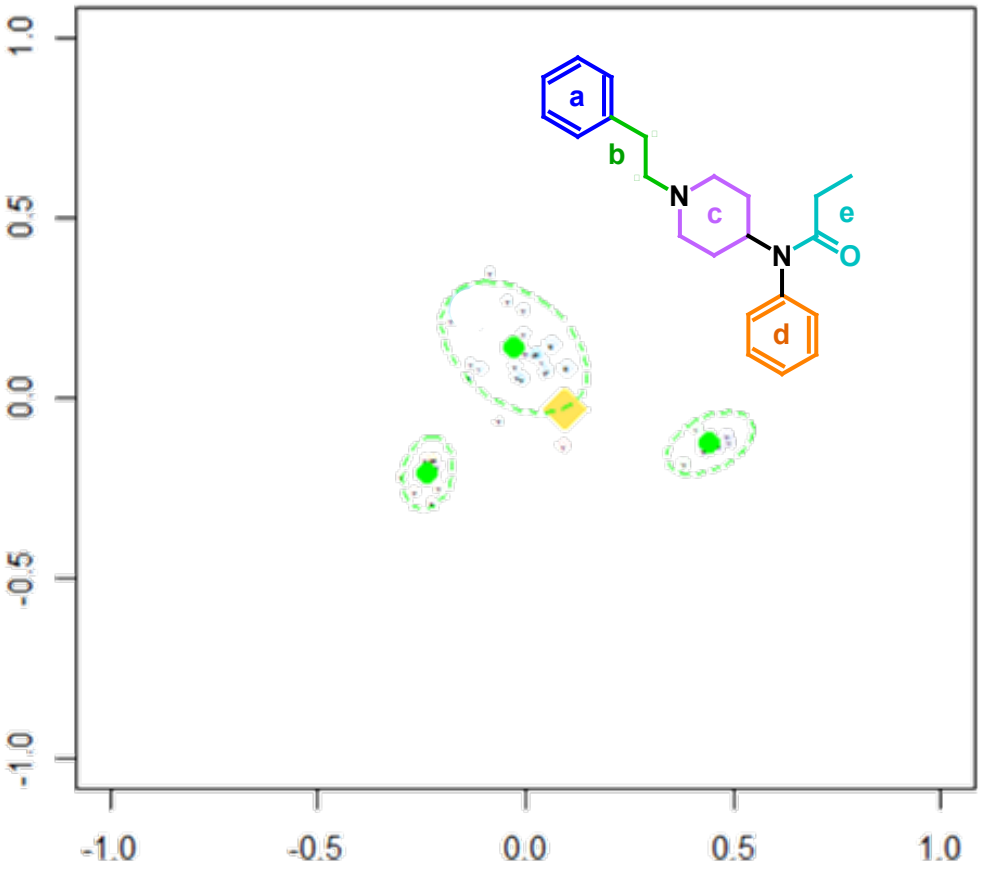
Fentanyl Mod. Type A Mod. Type B Mod. Type C Mod. Type D Mod. Type E

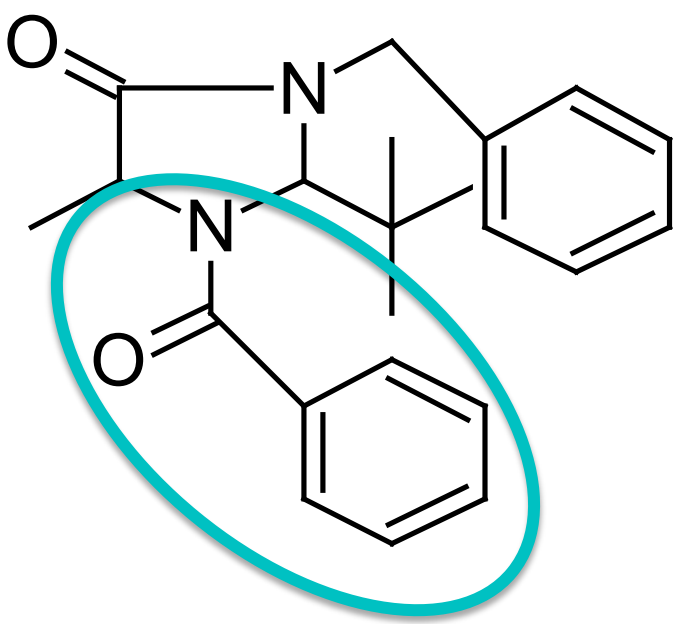
Fentanyl ClassifieR (prototype)



Compound	hMF	Δ_m	Relatedness Index
Cyclopropyl fentanyl – E	274	2	0.02
Valeryl fentanyl – E	268	-14	0.02
Fentanyl	212	14	0.02
Cyclohexyl fentanyl – E	211	-40	0.01
Pivaloyl fentanyl – E	208	-14	0.01

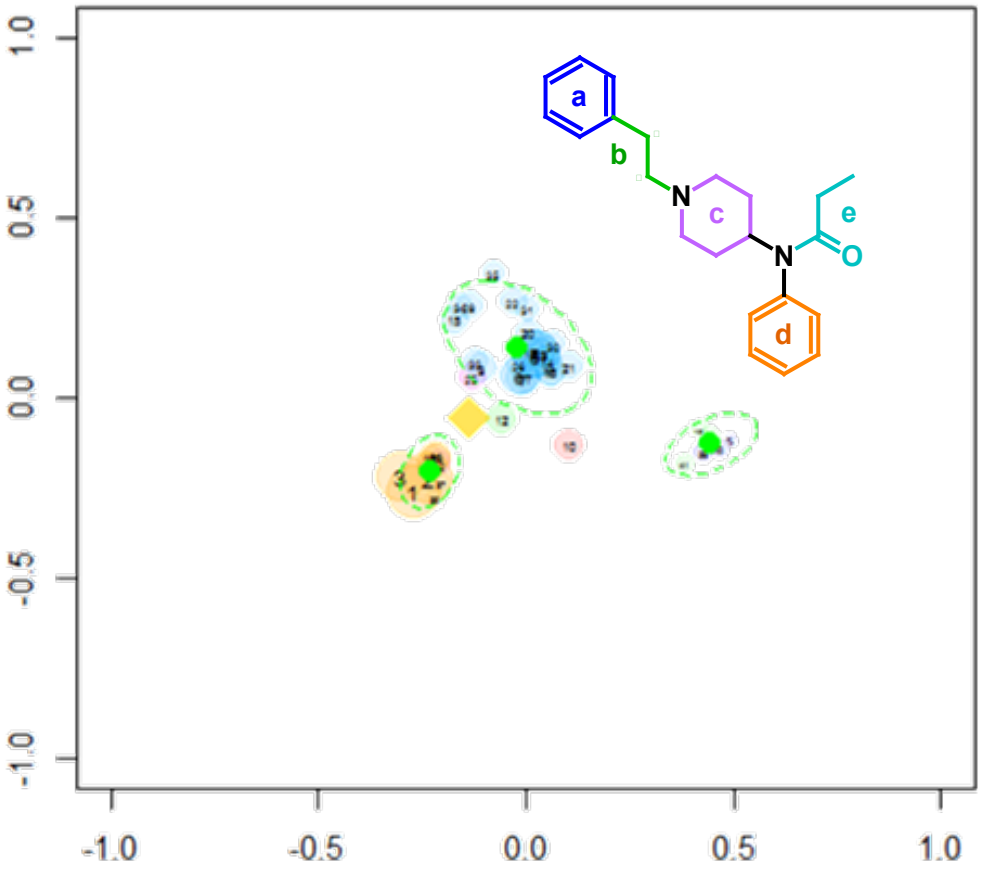
Fentanyl ClassifieR (prototype)





Fentanyl Mod. Type A Mod. Type B Mod. Type C Mod. Type D Mod. Type E

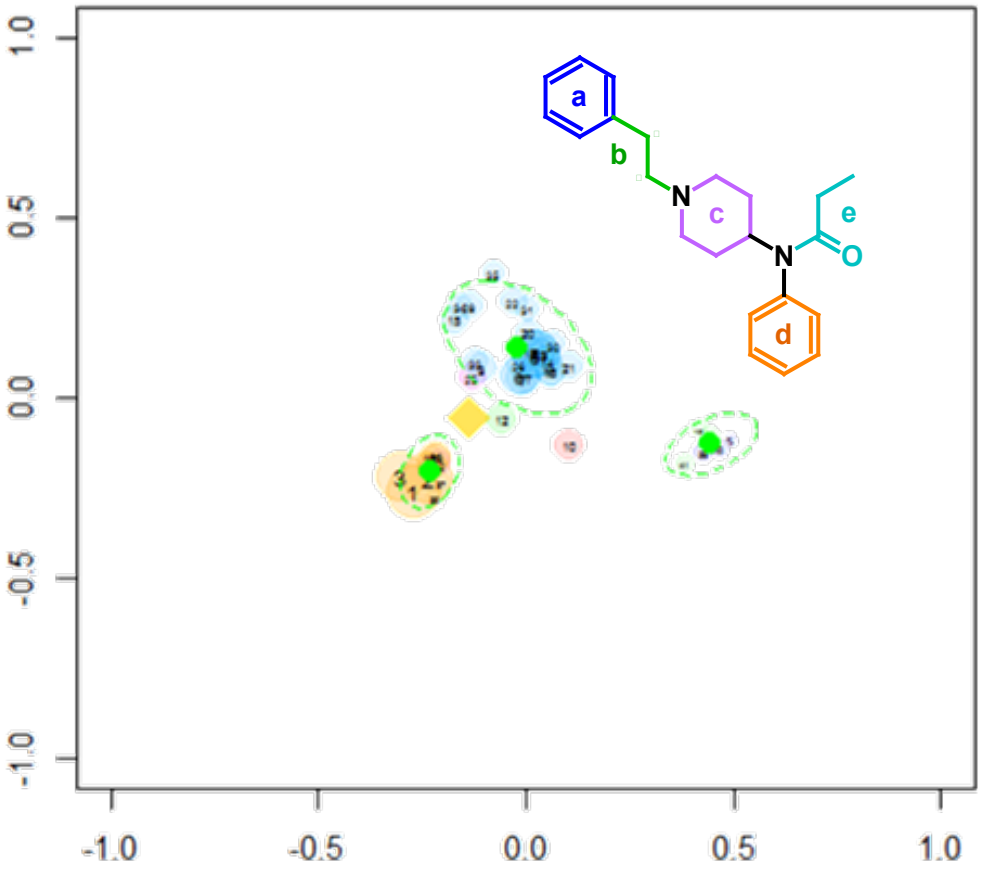
Fentanyl ClassifieR (prototype)

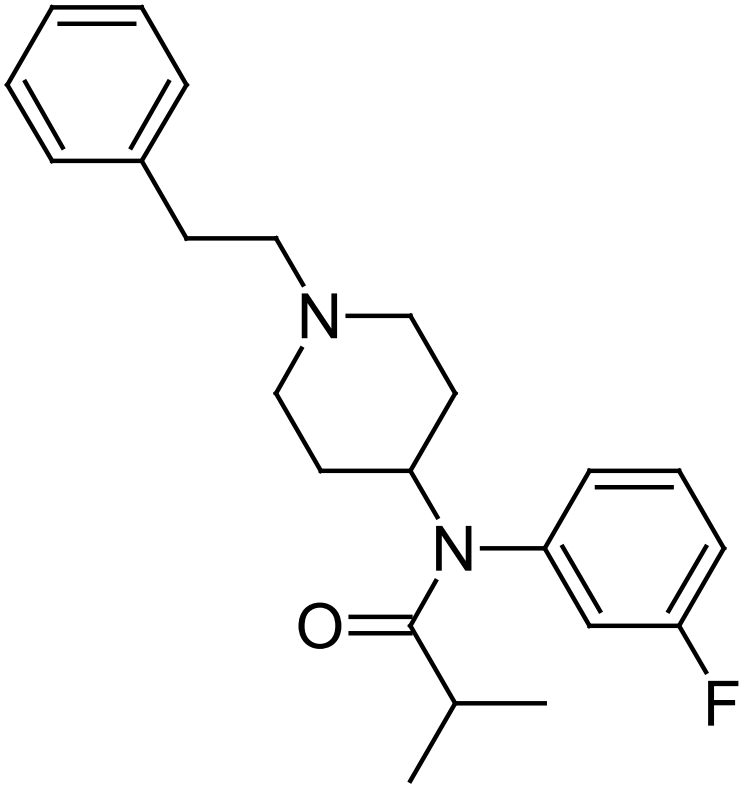


Compound	hMF	Δ_m	Relatedness Index
m-fluoro fentanyl – D	908	14	0.56
p-fluoro fentanyl – D	890	14	0.56
o-fluoro fentanyl – D	856	14	0.47
isobutyryl fentanyl – E	806	18	0.38
butyryl fentanyl – E	796	18	0.37

Fentanyl Mod. Type A Mod. Type B Mod. Type C Mod. Type D Mod. Type E

Fentanyl ClassifieR (prototype)





Fentanyl Mod. Type A Mod. Type B Mod. Type C Mod. Type D Mod. Type E

Can we extend this to other classes of drugs?

Questions?

arun.moorthy@nist.gov
chemdata.nist.gov