SUPPORTING INFORMATION

Chemical Attribution of Fentanyl Using Multivariate Statistical Analysis of Orthogonal Mass Spectral Data

Brian P. Mayer[a,*], Alan J. DeHope[b], Daniel A. Mew[a], Paul E. Spackman[a], Audrey M. Williams[a]

[a]*Forensic Science Center, Lawrence Livermore National Laboratory, 7000 East Ave. L-091, Livermore, CA 94550, United States*

[b]*Materials Science Division, Lawrence Livermore National Laboratory, 7000 East Ave. L-382, Livermore, CA 94550, United States*

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* Corresponding Author
E-mail: mayer22@llnl.gov
Phone: 925-423-1128
Fax: 925-423-9014

1. Synthetic Routes and Observations

Method 1: One-Pot Synthesis

Method 1 was taken from the open literature[1] and uses 4-piperidinone hydrochloride as the piperidine source. Its free base was generated *in situ* and was subsequently reductively aminated with phenylacetaldehyde in the presence of sodium triacetoxyborohydride. A second reductive amination step between NPP and aniline was used to generate ANPP. Repetition of the published one-pot procedure, however, did not result in the addition of the propanal moiety to the aryl amine to generate fentanyl as reported, but instead lead to isolation of the precursor ANPP. It is believed the acidic environment during propionyl chloride addition prevents nucleophilic substitution of the chlorine atom by the secondary amine of ANPP. To correct for this issue and to preserve the one-pot nature of this reaction scheme, the acid was neutralized with base before acylation.

Method 2: "Siegfried" Synthesis

This method is a procedure found on several drug enthusiast websites.[2] Its author is simply listed as "Siegfried," and the procedure is thusly often referenced as such. 4-piperidinone HCl was the piperidine source and was reacted with 2-bromoethylbenzene in the presence of base and a phase transfer catalyst to yield NPP. The procedure for condensation of NPP with aniline was modified slightly from the published route. One equivalent of acetic acid was added to promote condensation, and only one equivalent of aniline in DCM was used as opposed to using aniline as the reaction solvent. This method resulted in the complete conversion of NPP at room temperature. The imine was then reduced to ANPP using sodium borohydride in methanol, then acylated in DCM with propionyl chloride in the presence of pyridine to form fentanyl. The procedure for the isolation of ANPP, however, was simplified from the published method. After evaporation of the reaction mixture, water was added then acidified with 2 N HCl to roughly pH = 7.0. This alteration resulted in the separation of ANPP, which was isolated and carried on to fentanyl.

Method 3: Valdez Synthesis

This method was reported recently by some of the present authors in an open access peer-reviewed journal.[3] The procedure was repeated here but without the reported column chromatography steps. The chemistry is analogous to the other methods although aniline condensation with NPP and the subsequent reduction to ANPP are combined in one synthetic step. The use of STAB, which does not reduce ketones, in the presence of aniline allows for the reductive amination of the NPP directly to ANPP. Fentanyl was generated from ANPP with the use of propionyl chloride and DIPEA.

Method 4: Valdez NPP/Siegfried ANPP→fentanyl ("V-S")

This method represents a hybrid route that uses the Valdez method to generate NPP and the Siegfried method to generated ANPP and fentanyl. It is identical to the Siegfried route except 1) cesium carbonate was used as the base and 2) there was no phase transfer catalyst (PEG). Cesium carbonate was chosen as the base, as it has a higher solubility in organic solvents.

Method 5: Siegfried NPP/Valdez ANPP→fentanyl ("S-V")

This method combines the synthetic procedures from Methods 2 and 3 for NPP and ANPP/fentanyl syntheses, respectively.

Method 6: Alt NPP/Siegfried ANPP→fentanyl ("Alt-S")

Method 6 involves an alternative route for preparing NPP.[4,5] *N*-methylpiperidone is alkylated followed by a ring-opening/ring-closing reaction induced by phenethylamine. The generation of ANPP and fentanyl was performed in accordance with the Siegfried method.

2. Sample Chromatograms by Synthetic Route

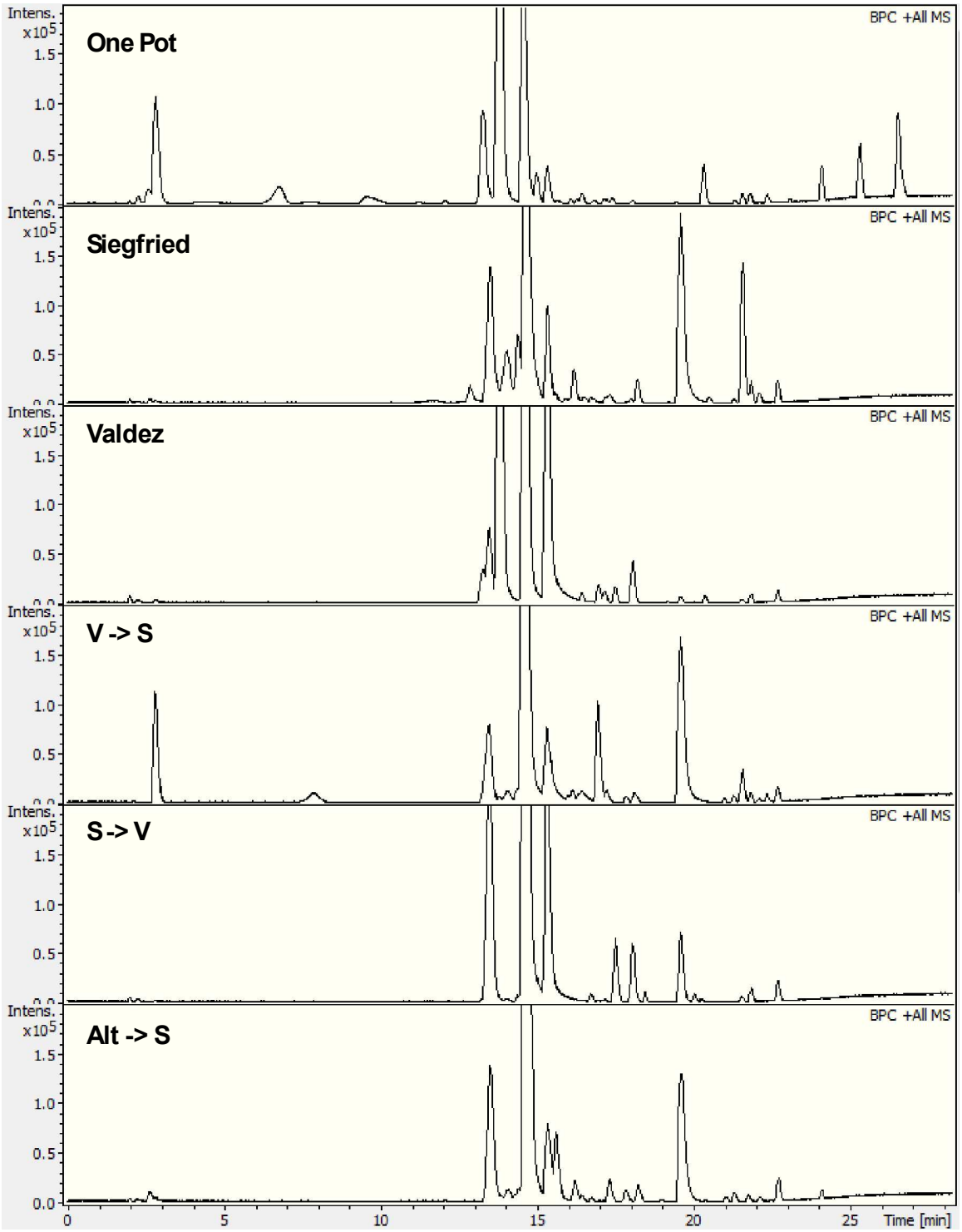


Figure S-1. Representative LC-MS base peak chromatograms for all six routes investigated. The y-axis has been scaled to highlight low-level impurities but is the same for all six traces.

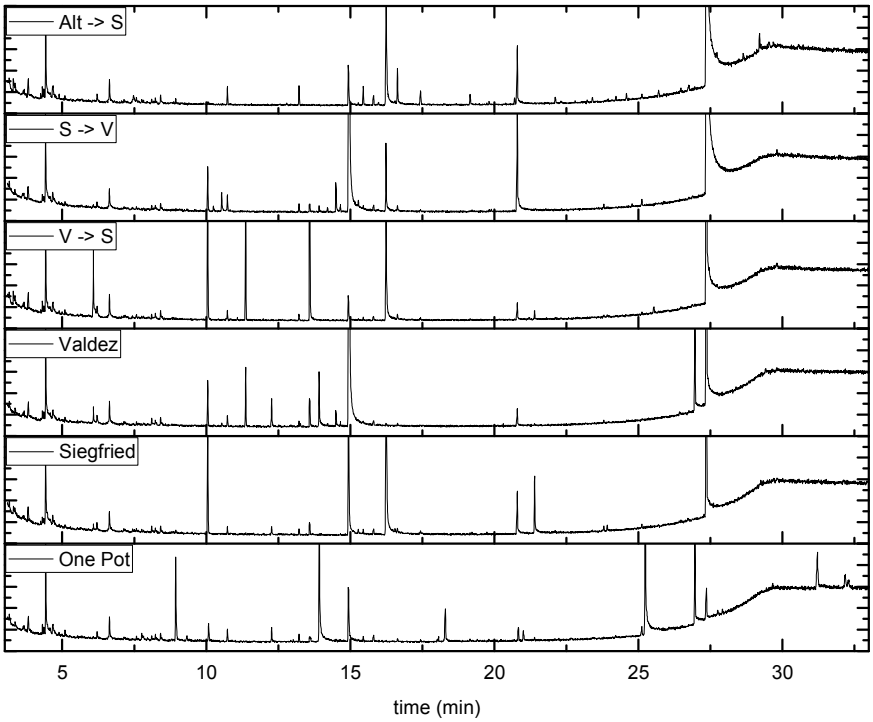


Figure S-2. Representative GC-MS total ion chromatograms for all six routes investigated. The y-axis has been scaled to highlight low-level impurities but is the same for all six traces.

3. Fentanyl CAS Breakdown by Synthetic Route.

Table S-1. Comprehensive list of statistically determined fentanyl CAS categorized by synthesis route. Given are *tentative* compound IDs, formula from TOF data, retention times and compound name, if adequate MS/MS data were available. Masses are given to four significant figures for LC-TOF data (given as [M + adduct]). GC masses are given for EI first and second in parentheses for CI, if detected.

Method 1: One Pot							
ID	**m/z**	**R.T. (min)**	**Compound Name**	**ID**	**m/z**	**R.T. (min)**	**Compound Name**
2	102.1277	2.3	triethylamine	87	360.1954	21.3	$C_{24}H_{26}NO_2$
3	289.2274	2.5	1'-phenethyl-[1,4'-bipiperidin]-4-ol	89	301.1337	21.4	$C_{20}H_{17}N_2O$
4	185.1640	2.6	[1,4'-bipiperidin]-4-ol	95	359.2397	21.8	
6	94.0642	2.8	aniline	98	274.0347	22.1	
7-S	206.1530	2.8	1-phenethylpiperidin-4-ol	99	360.1958	22.4	$C_{24}H_{26}NO_2$
8	406.2795	2.8	*N*-(1'-phenethyl-[1,4'-bipiperidin]-4-yl)-*N*-phenylacetamide	102	240.2322	23.1	$C_{15}H_{30}NO$
9	245.1865	2.8	$C_{12}H_{25}N_2O_3$	103	301.1412	24.1	$C_{16}H_{22}NaO_4$
15-S	206.1554	6.7	1-phenethylpiperidin-4-ol	104	343.1693	25.3	$C_{24}H_{23}O_2$
20	248.1659	12.1	1-phenethylpiperidin-4-yl acetate	105	418.2175	25.3	$C_{30}H_{28}NO$
23	130.1220	13.3	*N*,*N*-diethylpropionamide	D2.7	182.6433	2.7	$C_{24}H_{35}N_3$
24-I	136.0754	13.3	*N*-phenylacetamide	D2.8	177.6509	2.8	$C_{23}H_{37}N_3$
26-AB	323.2120	13.8	*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide (acetylfentanyl)	D2.8-2	203.6497	2.8	$C_{24}H_{41}NO_4$
31	188.1434	14.5	$C_{13}H_{18}N$	A	120 (121/138)	8.936	benzeneacetaldehyde
32-AA	281.2015	14.5	1-phenethyl-*N*-phenylpiperidin-4-amine (ANPP)	G	164 (182)	12.261	phenethyl acetate
33-AC	337.2282	14.6	*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide (fentanyl)	24-I (GC)	135 (136/153)	13.917	*N*-phenylacetamide
36	393.2545	15.0	*N*-(1-phenethylpiperidin-4-yl)-*N*-(propionylphenyl)propionamide	7-S (GC)	205 (206)	18.292	1-phenethylpiperidin-4-ol
48	399.2427	16.1	$C_{27}H_{31}N_2O$	U	135	20.827	
52	401.2572	16.1	$C_{27}H_{33}N_2O$	V	195 (196)	21.009	
54	164.1063	16.4	$C_{10}H_{14}NO$	Z	481	25.110	
59	233.1101	16.9	$C_{16}H_{13}N_2$	32-AA	322 (323)	25.235	ANPP
64	183.9881	17.2	$C_6H_2NO_6$	26-AB	336 (337)	26.957	acetylfentanyl
81	240.1373	20.3	*N*-phenethyl-*N*-phenylacetamide				
Method 2: Siegfried Route							
ID	**m/z**	**R.T. (min)**	**Compound Name**	**ID**	**m/z**	**R.T. (min)**	**Compound Name**

19	224.1546	11.6	$C_{10}H_{23}KN_3$	D13.7	261.6806	13.7	$C_{35}H_{45}N_3O$
27	278.1744	13.9	$C_{16}H_{24}NO_3$	D13.8	280.7079	13.8	$C_{37}H_{55}NO_3$
28	399.2654	14.1	$C_{24}H_{35}N_2O_3$	D14.1	270.6833	14.1	$C_{35}H_{47}N_3O_2$
43	291.1486	15.4	$C_{19}H_{19}N_2O$	D14.4	261.6806	14.4	$C_{35}H_{45}N_3O$
50	150.0911	16.1	$C_9H_{12}NO$	D14.8	270.6833	14.8	$C_{35}H_{47}N_3O_2$
53	234.1475	16.3	*N*-phenethyl-*N*-propionylpropionamide	D14.8-3	277.6811	14.8	$C_{39}H_{45}N_3$
58	395.2707	16.8	$C_{25}H_{35}N_2O_2$	D15	261.6806	15.0	$C_{35}H_{45}N_3O$
77	363.1675	19.6		D15.4	218.653	15.4	$C_{32}H_{39}N$
82	353.2239	20.5	$C_{22}H_{29}N_2O_2$	D15.7	377.7606	15.7	
91	254.1531	21.6	*N*-phenethyl-*N*-phenylpropionamide	D17.3	248.6721	17.3	$C_{26}H_{47}N_3O_6$
94	439.2424	21.7	$C_{28}H_{33}N_2O_4$	D18	326.7122	18.0	$C_{46}H_{55}NO_2$
97	348.1586	21.9	$C_{22}H_{22}NO_3$				

Method 3: Valdez Route

ID	m/z	R.T. (min)	Compound Name
73	256.1896	18.5	$C_{14}H_{26}NO_3$
67-E (GC)	158	10.532	*N*,*N*-diisopropylpropionamide

Method 4: Valdez→Siegfried

ID	m/z	R.T. (min)	Compound Name
11	184.1117	2.8	1-phenethylpyridin-1-ium
35	335.2118	14.9	$C_{22}H_{27}N_2O$
60	441.2916	16.9	1,1-diphenethyl-4-(*N*-phenylpropionamido)piperidin-1-ium
70	395.2120	18.0	$C_{27}H_{27}N_2O$
84	105.0693	21.0	C_8H_9
100	336.1575	22.4	$C_{19}N_{23}NNaO_3$
B	140	10.045	2-chloroethylbenzene
H	178 (196)	13.583	phenethyl propionate
Y	206	23.918	

Method 5: Siegfried→Valdez

ID	m/z	R.T. (min)	Compound Name
39-K	150.0912	15.3	*N*-phenylpropionamide
71	178.1215	18.1	*N*-ethyl-*N*-phenylpropionamide
D15.3	243.6077	15.3	$C_{33}H_{29}NO_3$
D15.3-2	252.611	15.3	$C_{33}H_{31}NO_4$
J	177 (178)	14.497	
39-K (GC)	149 (150/167)	14.938	*N*-phenylpropionamide

Method 6: Alt NPP→Siegfried

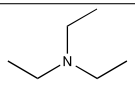
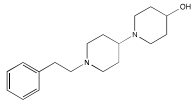
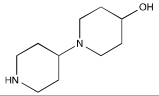
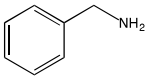
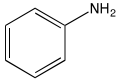
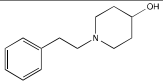
ID	m/z	R.T. (min)	Compound Name
45	210.1391	15.7	
51	423.2750	16.2	$C_{29}H_{35}N_2O$
83	358.2001	21.0	$C_{19}H_{29}NNaO_4$
107	443.2241	26.9	$C_{23}H_{31}N_4O_5$

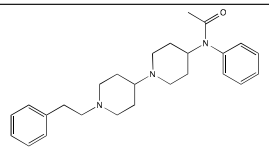
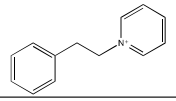
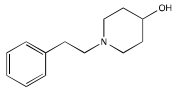
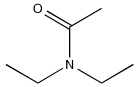
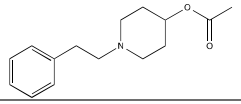
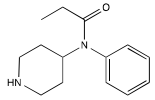
4. Complete LC-MS/MS-TOF and GC-MS Compound Summaries

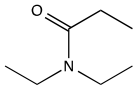
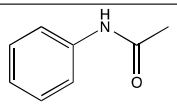
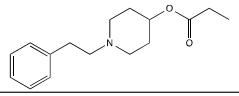
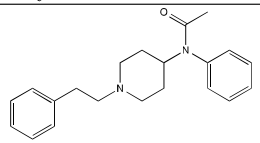
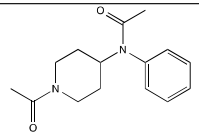
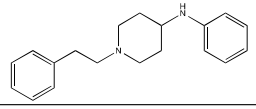
Tables S-2 and S-3 following this page include every compound detected and quantified in the original, unabridged LC and GC chromatograms, respectively. Included are compound ID, name if known, structure if known, and peak area relative to the fentanyl peak area.

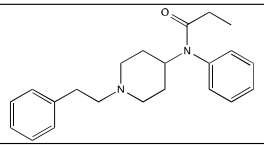
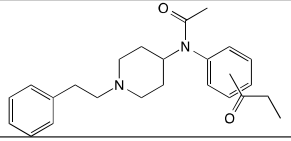
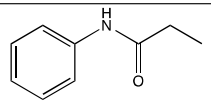
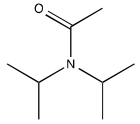
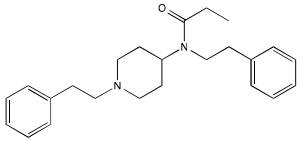
Table S-2. LC-MS/MS-TOF Compound Summary

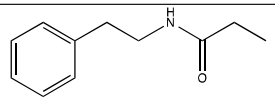
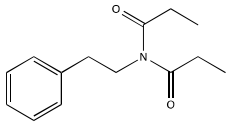
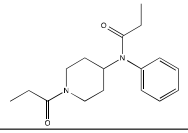
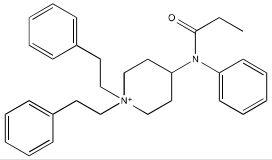
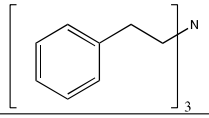
LC-MS Fentanyl CAS

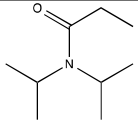
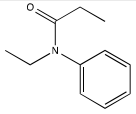
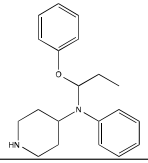
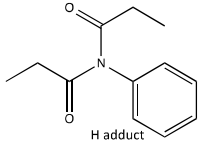
			1	2	3	4	5	6	
Cmpd ID	**Retention time (min)**	**Formula**	**One-pot**	**Siegfried**	**Valdez**	**V->S**	**S->V**	**Alt->S**	**Name**
1	2.1			0.754%		0.241%		0.725%	pyridine
2	2.3		11.521%	0.033%	0.104%	0.004%	0.111%	0.003%	triethylamine
3	2.5		13.371%						1'-phenethyl-[1,4'-bipiperidin]-4-ol
4	2.6		13.631%						[1,4'-bipiperidin]-4-ol
5	2.6			0.644%		0.057%		0.531%	phenylmethanamine
6	2.8		7.892%	0.042%		0.012%		0.068%	aniline
7-S	2.8 (18.292)		89.929%	0.104%	0.029%	0.074%	0.095%	0.174%	1-phenethylpiperidin-4-ol

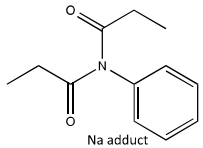
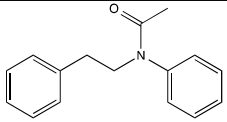
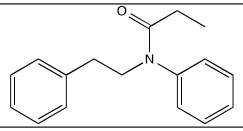
8	2.8		17.266%						*N*-(1'-phenethyl-[1,4'-bipiperidin]-4-yl)-*N*-phenylacetamide
9	2.8	C12H25N2O3	34.695%				0.002%		
10	2.8	C13H14N	0.263%	0.772%		0.107%	0.003%	0.056%	
11	2.8		0.712%	0.561%	0.080%	6.348%	0.211%	0.287%	1-phenethylpyridin-1-ium
12	2.9	C9H12N4O3	0.092%	0.483%	0.014%	0.006%	0.022%	0.063%	
13	2.9	C13H18N	4.672%	0.006%		0.906%	0.003%		
14	4.6	C13H20N				0.402%			
15-S	6.7		36.136%	0.012%		0.016%	0.025%	0.043%	1-phenethylpiperidin-4-ol
16	10.3		122.435%					0.087%	*N*,*N*-diethylacetamide
17	10.8	C13H18N				0.625%			
18	11.2	C13H20N				0.404%			
19	11.6	C10H23KN3		4.757%					
20	12.1		3.062%	0.040%	0.028%	0.004%	0.077%		1-phenethylpiperidin-4-yl acetate
21	12.3		3.947%	2.116%				0.084%	*N*-phenyl-*N*-(piperidin-4-yl)propionamide
22	12.8	C10H18N5O		1.062%					

23	13.3		5.479%		0.034%		0.018%		*N*,*N*-diethylpropionamide
24-I	13.3 (13.917)		82.709%	0.035%	0.821%	0.014%	0.967%	0.014%	*N*-phenylacetamide
25	13.5		3.526%	47.959%	13.154%	10.352%	30.237%	20.744%	1-phenethylpiperidin-4-yl propionate
26-AB	13.8 (26.957)		365.732%	0.601%	0.486%	0.826%	0.467%	0.863%	*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide (acetylfentanyl)
27	13.9	C16H24NO3		1.063%	0.076%	0.085%	0.156%	0.036%	
28	14.1	C24H35N2O3		0.853%					
29	14.3		1.911%				0.335%		
30	14.4	C19H28NO3	0.174%	0.540%		0.201%	0.006%	0.428%	
31	14.5	C13H18N	8.809%	0.094%		0.128%	0.129%	0.193%	
32-AA	14.5 (25.235)		204.624%		0.011%		0.024%	2.605%	1-phenethyl-*N*-phenylpiperidin-4-amine (ANPP)

33-AC	14.6 (27.370)		100.000%	100.000%	100.000%	100.000%	100.000%	100.000%	*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide (fentanyl)
34	14.6		0.290%	0.590%	1.153%	1.045%	1.271%	0.991%	
35	14.9	C22H27N2O		0.160%		1.319%	0.052%	0.292%	
36	15		20.599%		0.074%	0.002%	0.029%		*N*-(1-phenethylpiperidin-4-yl)-*N*-(propionylphenyl)propionamide (unknown Friedl-Crafts site)
37	15	C22H29N2O2	0.251%	1.942%	0.633%	1.170%	0.820%	0.162%	
38	15.2	C19H19N			0.018%	0.400%	0.039%	0.270%	
39-K	15.3 (14.938)		34.651%	17.109%	14.569%	4.398%	22.050%	6.985%	*N*-phenylpropionamide
40	15.3	C16H26NO3		3.342%		4.072%		5.169%	
41-E	15.4 (10.233)		0.327%		1.434%		1.069%		*N*,*N*-diisopropylacetamide
42	15.4	C14H30NO6		2.587%		4.536%		4.386%	
43	15.4	C19H19N2O		0.787%	0.006%	0.152%	0.005%	0.066%	
44	15.5			2.023%	0.109%	0.244%	0.229%	11.051%	*N*-phenethyl-*N*-(1-phenethylpiperidin-4-yl)propionamide
45	15.7	210.1391						0.294%	
46	15.8	C24H40N3O2			0.084%	0.025%	0.219%		

47	15.9			0.489%	0.008%	0.061%	0.027%	0.324%	*N*-phenethylpropionamide
48	16.1	C27H31N2O	2.954%						
49	16.1	C26H35N2O3		4.798%	0.021%	1.323%	0.036%	2.124%	
50	16.1	C9H12NO		0.865%		0.059%		0.020%	
51	16.2	C29H35N2O			#REF!			2.355%	
52	16.3	C27H33N2O	2.980%						
53	16.3			1.481%		0.064%		0.183%	*N*-phenethyl-*N*-propionylpropionamide
54	16.4	C10H14NO	4.258%	0.033%	#DIV/0!	0.050%			
55	16.4	360.2403				1.565%			
56	16.5	C24H32NO2			0.376%	0.475%			
57	16.7		0.230%	1.595%	0.513%	0.290%	0.737%	0.278%	*N*-phenyl-*N*-(1-propionylpiperidin-4-yl)propionamide
58	16.8	C25H35N2O2		0.418%		0.006%			
59	16.9	C16H13N2	3.515%		0.007%		0.025%	0.019%	
60	16.9			0.100%	4.140%	9.081%	0.002%		1,1-diphenethyl-4-(*N*-phenylpropionamido)piperidin-1-ium
61	17.1		0.876%	0.843%	0.482%	0.690%	0.348%		triphenethylamine
62	17.1	C29H36N3O		0.088%	1.338%	1.504%		0.706%	
63	17.1	C25H24N3		0.098%		0.132%		0.012%	

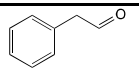
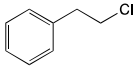
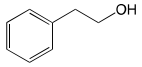
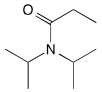
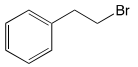
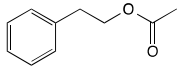
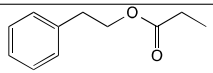
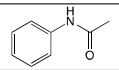
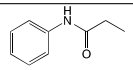
64	17.2	C6H2NO6	4.252%		0.031%		0.093%	0.083%	
65	17.2	C24H28N	0.926%	0.819%	0.502%	0.697%	0.341%		
66	17.2	C32H40N3O2		0.940%	0.038%	1.036%	0.037%	1.185%	
67-E	17.5 (10.532)		0.082%		7.292%		5.506%		*N*,*N*-diisopropylpropionamide
68	17.9	C17H20N3					0.004%	0.514%	
69	18	C9H8N7	0.508%	0.804%	1.015%	0.296%	1.930%	0.129%	
70	18	C27H27N2O				0.575%			
71	18.1		1.711%	0.066%	2.703%		3.990%		*N*-ethyl-*N*-phenylpropionamide
72	18.2			3.171%	0.057%	0.560%	0.015%	1.554%	N-(1-phenoxypropyl)-N-phenylpiperidin-4-amine
73	18.5	C14H26NO3			1.615%		0.863%		
74	19.2	C12H18NO		0.153%	0.020%	0.074%	3.624%		
75	19.5	C15H16NO	2.296%	0.793%		0.382%	0.028%	0.287%	
76	19.6	 H adduct	0.326%	37.341%	3.671%	17.586%	6.001%	14.147%	*N*-phenyl-*N*-propionylpropionamide

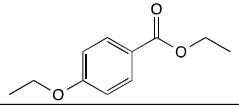
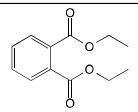
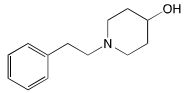
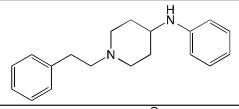
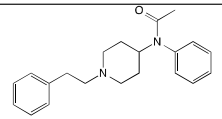
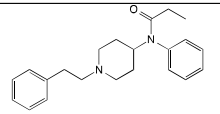
77	19.6	 Na adduct		0.607%		0.016%			*N*-phenyl-*N*-propionylpropionamide
78	19.6	C12H16NO2		3.651%	0.171%	1.759%	0.300%	1.264%	
79	20	C16H20NO	0.117%		0.810%	0.004%	0.598%		
80	20	C25H35N2O3				0.012%		0.200%	
81	20.3		27.204%	0.039%	0.005%	0.004%			*N*-phenethyl-*N*-phenylacetamide
82	20.5	C22H29N2O2		0.381%		0.029%		0.030%	
83	21	358.2001			0.004%			0.535%	
84	21	C8H9		0.033%	0.099%	0.550%	0.018%		
85	21.1	337.2357	3.292%		0.008%			0.006%	
86	21.3	C14H24NO3			0.293%		0.054%		
87	21.3	C24H26NO2	2.757%						
88	21.3	C22H23N2O3		0.710%		0.481%		0.706%	
89	21.4	C20H17N2O	6.301%	0.009%					
90	21.5	C23H29N2O3		0.973%	1.872%	2.801%	0.475%		
91	21.6		7.495%	15.858%	3.459%	1.662%	0.083%	0.005%	*N*-phenethyl-*N*-phenylpropionamide
92	21.6	C26H24NaO		0.288%					
93	21.6	C8H9		0.484%	0.159%	0.379%	0.043%		
94	21.7	C28H33N2O4		0.572%		0.118%		0.174%	
95	21.8	359.2397	7.811%		0.037%		0.094%	0.108%	
96	21.8	C19H24NO		3.138%	0.387%	1.681%	0.944%		
97	21.9	C22H22NO3		0.488%	0.028%	0.214%			
98	22.1	274.0347	2.440%		0.008%				
99	22.4	C24H26NO2	5.681%						
100	22.4	C19N23NNaO3		0.011%		0.524%			
101	22.7	C14H23N2O3	3.052%	0.723%	0.335%	0.637%	0.594%	0.699%	
102	23.1	C15H30NO	3.893%		0.011%		0.038%	0.036%	
103	24.1	C16H22NaO4	26.756%	0.421%	0.504%	0.346%	0.767%	0.541%	
104	25.3	C24H23O2	39.552%						
105	25.3	C30H28NO	15.948%						

106	26	C22H24N	0.180%	0.563%	2.241%	0.119%	0.004%	$	
107	26.9	443.2241	$	0.071%	$	0.083%	$	0.364%	

Table S-3. GC-MS Compound Summary

GC-MS Fentanyl CAS

				1	2	3	4	5	6
Cmpd ID	**Retention time (min)**	**Compound or EI m/z (CI m/z)**	**Structure**	**One-pot**	**Siegfried**	**Valdez**	**V->S**	**S->V**	**Alt->S**
A	8.936	2-phenylacetaldehyde (benzeneacetaldehyde)		14.84%	0.00%	0.00%	0.00%	0.00%	0.00%
B	10.045	2-chloroethylbenzene		0.00%	7.05%	7.05%	11.81%	2.14%	0.00%
C	10.078	2-phenylethan-1-ol		4.78%	0.00%	0.00%	0.00%	0.00%	0.00%
41-D	10.233	N,N-diisopropylacetamide		0.00%	0.00%	0.00%	0.00%	0.29%	0.00%
67-E	10.532	*N,N*-diisopropylpropionamide		0.00%	0.00%	0.00%	0.00%	0.79%	0.00%
F	11.361	2-bromoethylbenzene		0.00%	0.00%	0.00%	12.40%	0.00%	0.00%
G	12.261	phenethyl acetate		1.80%	0.00%	0.00%	0.00%	0.00%	0.00%
H	13.583	phenethyl propionate		0.00%	1.01%	1.01%	20.16%	0.45%	0.00%
24-I	13.917	*N*-phenylacetamide		29.54%	13.31%	13.31%	0.00%	0.75%	0.00%
J	14.497	177 (178)		0.00%	0.00%	0.00%	0.00%	0.87%	0.00%
39-K	14.938	*N*-phenylpropionamide		12.45%	11.04%	11.04%	2.38%	48.24%	10.18%
L	15.112	149 (150/167)		0.00%	0.00%	0.00%	0.00%	7.59%	0.00%
M	15.274	191 (192/209)		0.00%	24.85%	24.85%	0.00%	0.81%	0.00%

N	15.585	212 (150/167)		0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
O	15.799	ethyl 4-ethoxybenzoate		2.55%	0.00%	0.00%	0.24%	0.41%	0.63%
P	15.955	187 (188)		0.00%	0.00%	0.00%	0.76%	0.00%	0.00%
Q	16.239	205 (206/223)		0.00%	29.41%	29.41%	33.74%	1.68%	39.93%
R	16.635	diethyl phthalate		4.49%	0.00%	0.00%	0.69%	0.68%	2.33%
7-S, 15-S	18.292	1-phenethylpiperidin-4-ol		4.95%	0.00%	0.00%	0.00%	0.00%	0.00%
T	20.788	327 (262)		0.00%	4.16%	4.16%	0.72%	4.98%	8.66%
U	20.827	135 (240)		1.70%	0.00%	0.00%	0.00%	0.00%	0.00%
V	21.009	195 (196)		0.34%	0.00%	0.00%	0.00%	0.00%	0.00%
W	21.397	149 (254)		0.00%	3.09%	3.09%	0.69%	0.00%	0.00%
X	22.233	218 (219)		0.03%	0.00%	0.00%	0.00%	0.00%	0.00%
Y	23.918	206 (NC)		0.00%	0.00%	0.00%	0.47%	0.00%	0.00%
Z	25.110	481 (289)		0.09%	0.00%	0.00%	0.00%	0.00%	0.00%
32-AA	25.235	1-phenethyl-N-phenylpiperidin-4-amine (ANPP)		14.10%	0.00%	0.00%	0.00%	0.00%	4.34%
26-AB	26.957	N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide (acetylfentanyl)		6.82%	0.00%	0.00%	0.00%	0.00%	0.00%
33-AC	27.370	N-(1-phenethylpiperidin-4-yl)-N-phenylpropionamide (fentanyl)		1.53%	6.09%	6.09%	15.92%	30.33%	33.93%

5. Reproducibility of Synthetic Replicates

Below is a chart giving raw area counts from LC-MS/MS data (singly charges species) for the three synthetic replicates performed using the One Pot Method. This chart's aim is:

1) To demonstrate that there exists relatively high consistency between such syntheses, (an observation consistent for all synthetic routes performed) and
2) To show that for this one pot method, the preferential generation of acetylfentanyl over the intended fentanyl product is not merely a result of a synthetic "accident."

Note that for the sake of brevity we have not shown raw peak areas for the other five routes.

Table S-4. Peak area counts for three replicates of the One Pot synthesis. Retention times in minutes and exact mass associated with the peak are given along side their chemical ID refered to in the main article.

Chemical ID	Ret. Time (min)	exact mass	Sample ID (One Pot Synth)			Chemical ID	Ret. Time (min)	exact mass	Sample ID (One Pot Synth)		
			FSC-35	FSC-61	FSC-63				FSC-35	FSC-61	FSC-63
1	2.1	80.0497	0	0	0	55	16.4	360.2403	0	0	0
2	2.3	102.1277	157453	92633	248246	56	16.5	366.2423	0	0	0
3	2.5	289.2274	183093	184973	210328	57	16.7	289.1905	7952	801	1202
4	2.6	185.164	165185	176160	248296	58	16.8	395.2707	0	0	0
5	2.6	108.0807	0	0	0	59	16.9	233.1101	47843	45845	58369
6	2.8	94.0642	77784	148871	114716	60	16.9	441.2916	0	0	0
7-S	2.8	206.153	1402256	1131166	1356568	61	17.1	330.2207	32648	2360	2904
8	2.8	406.2795	181994	292214	272635	62	17.1	442.2879	0	0	0
9	2.8	245.1865	355492	552505	592756	63	17.1	366.1968	0	0	0
10	2.8	205.146	0	7803	3583	64	17.2	183.9881	54039	73222	56645
11	2.8	184.1117	12151	6588	12069	65	17.2	330.2221	34777	2360	2904
12	2.9	233.1601	1952	0	2034	66	17.2	498.3126	0	0	0
13	2.9	188.1424	52231	76928	72925	67-E	17.5	158.1531	0	2124	1406
14	4.6	190.1583	0	0	0	68	17.9	266.1655	0	0	0
15-S	6.7	206.1554	522690	471550	568842	69	18	214.0834	0	20857	1126
16	10.3	116.1078	5200013	46036	50026	70	18	395.212	0	0	0
17	10.8	188.1424	0	0	0	71	18.1	178.1215	4685	45671	23659
18	11.2	190.1583	0	0	0	72	18.2	309.1961	0	0	0
19	11.6	224.1546	0	0	0	73	18.5	256.1896	0	0	0
20	12.1	248.1659	20450	47751	64234	74	19.2	192.1376	0	0	0
21	12.3	233.1642	153416	5468	11839	75	19.5	226.1205	33177	23479	42678
22	12.8	244.1536	0	0	0	76	19.6	228.0989	1988	9039	3068
23	13.3	130.122	139062	40769	57178	77	19.6	363.1675	0	0	0
24-I	13.3	136.0754	1024343	1297784	1255522	78	19.6	206.1135	0	0	0
25	13.5	262.1797	17030	61245	74229	79	20	242.1526	5040	0	0
26	13.8	323.212	5307097	5312959	5200075	80	20	411.266	0	0	0
27	13.9	278.1744	0	0	0	81	20.3	240.1373	285566	354676	536508
28	14.1	399.2654	0	0	0	82	20.5	353.2239	0	0	0
29	14.3	261.1589	72152	3773	6756	83	21	358.2001	0	0	0
30	14.4	318.2066	2354	2074	3084	84	21	105.0693	0	0	0
31	14.5	188.1434	104238	140302	136509	85	21.1	337.2357	0	16985	125435
32-AA	14.5	281.2015	2580905	3094288	3176037	86	21.3	254.1757	0	0	0
33-AC	14.6	337.2282	1274445	1613273	1437887	87	21.3	360.1954	31702	34581	52990
34	14.6	359.2099	0	6924	5613	88	21.3	363.1682	0	0	0
35	14.9	335.2118	0	0	0	89	21.4	301.1337	130013	12527	130034
36	15	393.2545	269397	326773	294881	90	21.5	381.2181	0	0	0
37	15	353.2237	3612	2742	4486	91	21.6	254.1531	76594	97851	149773
38	15.2	275.1535	0	0	0	92	21.6	381.186	0	0	0
39-K	15.3	150.0912	556370	430945	511530	93	21.6	105.0693	0	0	0
40	15.3	280.1939	0	0	0	94	21.7	439.2424	0	0	0
41	15.4	144.1377	2930	5310	5888	95	21.8	359.2397	125762	96984	115142
42	15.4	308.2072	0	0	0	96	21.8	282.1852	0	0	0
43	15.4	291.1486	0	0	0	97	21.9	348.1586	0	0	0
44	15.5	365.2603	0	0	0	98	22.1	274.0347	53648	1605	50273
45	15.7	210.1391	0	0	0	99	22.4	360.1958	63544	93141	89055
46	15.8	462.3115	0	0	0	100	22.4	336.1575	0	0	0
47	15.9	178.1224	0	0	0	101	22.7	267.1716	80394	9223	42404
48	16.1	399.2427	29261	50203	48293	102	23.1	240.2322	54642	50855	62919
49	16.1	423.2668	0	0	0	103	24.1	301.1412	399222	337162	420956
50	16.1	150.0911	0	0	0	104	25.3	343.1693	571429	548811	590612
51	16.2	423.275	0	0	0	105	25.3	418.2175	231240	237994	220606
52	16.3	401.2572	35543	64821	30663	106	26	302.1905	0	3247	4549
53	16.3	234.1475	0	0	0	107	26.9	443.2241	0	0	0
54	16.4	164.1063	22756	110136	59828						

6. Classification Probabilities for Cross-Validated Training Set

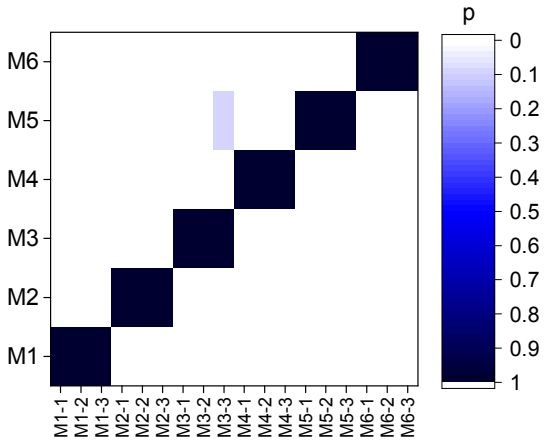


Figure S-3. Class prediction for cross-validated calibration set. All samples have been correctly classified by cross-validation of the PLS-DA model using 5 components. On-diagonal intensity reflects probability of correct classification. Off-diagonal intensities indicate that there is non-zero likelihood of that sample to be misclassified.

7. LC Chromatograms for Surface Data: Exposure Time Dependence

Below are two graphs showing chromatograms for stainless steel (SS, Figure S-4) and vinyl tile (VT, Figure S-5) data as a function of exposure time. Note that there is very little difference in both relative and absolute intensities of relevant peaks over the course of a 24 hour exposure. The introduction of new peaks associated with extracted matrix components (particularly for vinyl tile) did not interfere with the ability to extract peak areas for compounds of interest to the chemometric model.

Figure S-4. Stainless steel signature data for 2 hour exposure (top) to 24 hour exposure (bottom).

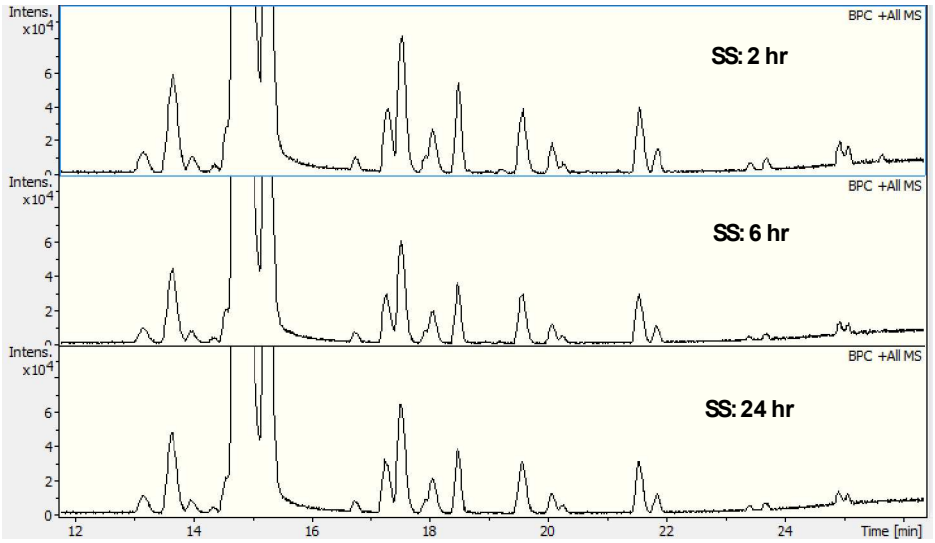
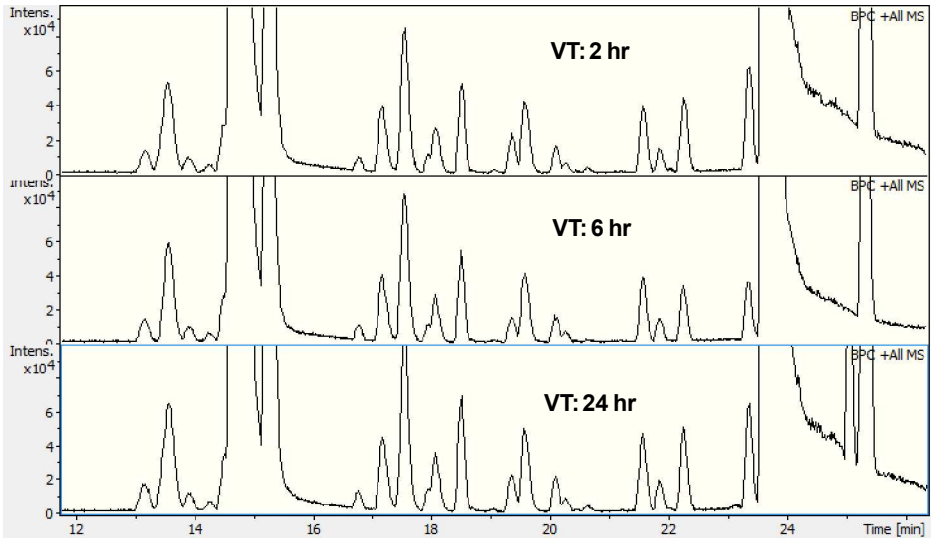


Figure S-5. Vinyl tile signature data for 2 hour exposure (top) to 24 hour exposure (bottom).



8. Scores Plot for Vinyl Tile Samples

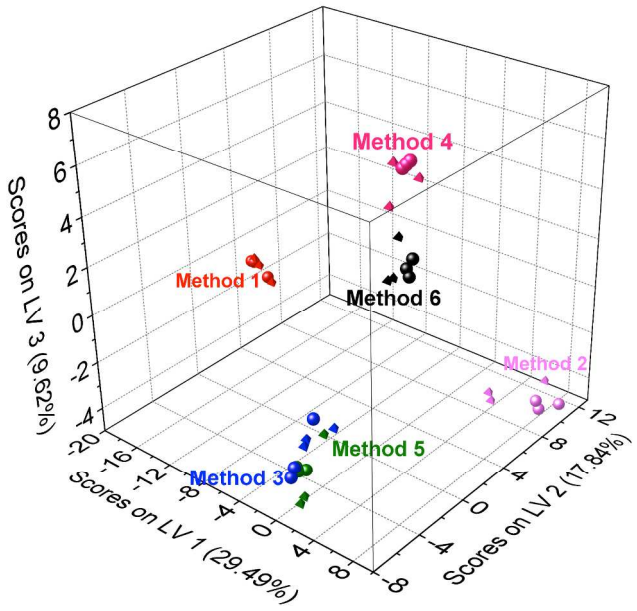


Figure S-6. PLS-DA scores from vinyl tile surface data color-coded by the predicted "most probable" class. Spheres are the surface data sets, whereas pyramids represent data from the calibration sets taken from Figure 3 in the main text.

9. Scores Plots for PLS-DA Analyses of GC, LC, and GC+LC Data Sets

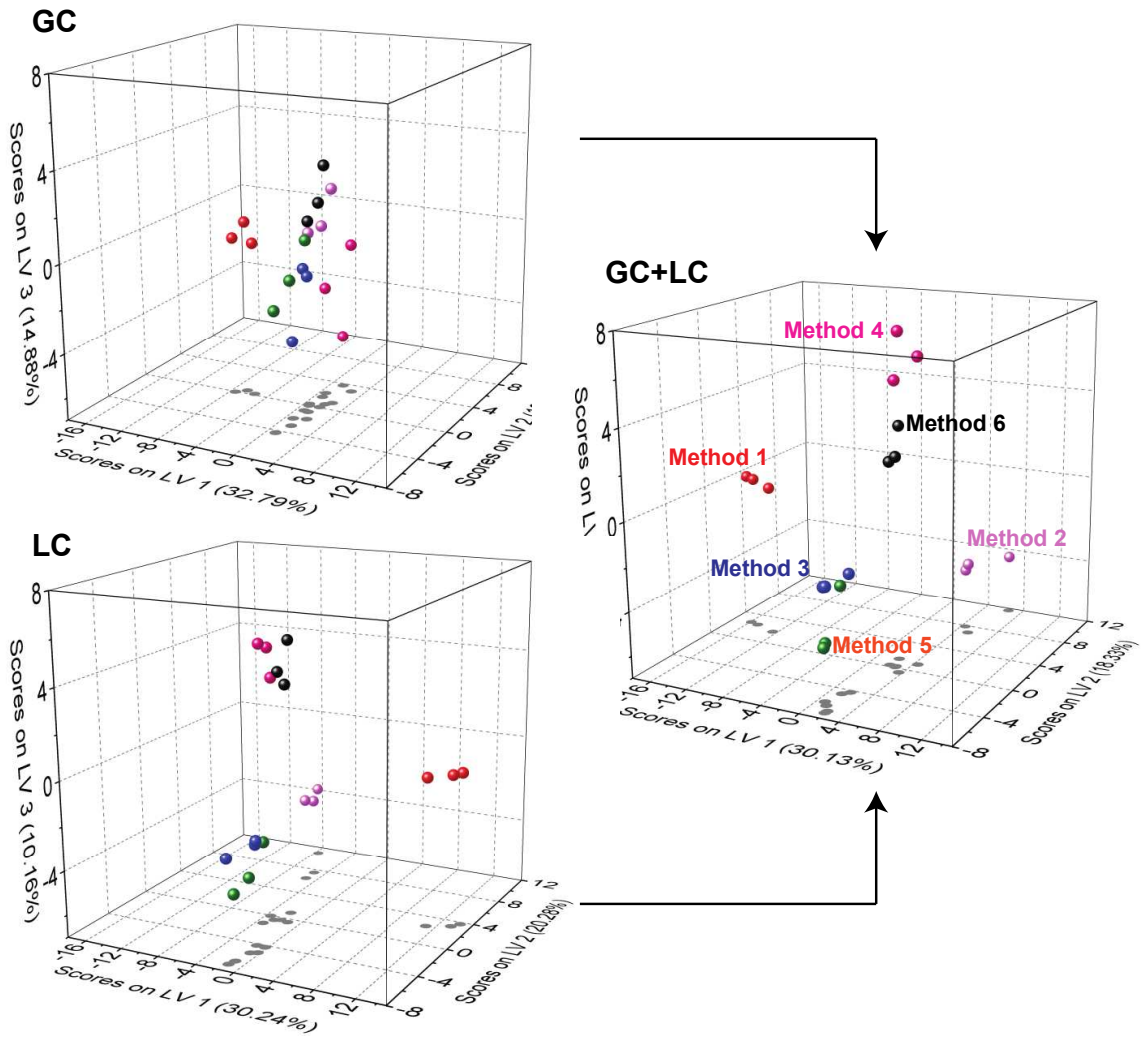


Figure S-7. Three-dimensional scores plots showing qualitative discriminatory ability among classes for GC, LC, and GC+LC data sets. Increased separation occurs for the combined chromatographic data. Plots are shown with equal axes scales to emphasize trends.

10. References

[1] Gupta, P. K.; Ganesan, K.; Pande, A.; Malhotra, R. C. *J. Chem. Res-S* **2005**, *2005*, 452-453.

[2] Seigfried. Synthesis of Fentanyl. https://www.erowid.org/archive/rhodium/chemistry/fentanyl.html (accessed Aug 31, 2015).

[3] Valdez, C. A.; Leif, R. N.; Mayer, B. P. *PLoS ONE* **2014**, *9*, e108250.

[4] Mustazza, C.; Borioni, A.; Sestili, I.; Sbraccia, M.; Rodomonte, A.; Ferretti, R.; Del Giudice, M. R. *Chem. Pharm. Bull.* **2006**, *54*, 611-622.

[5] Grishina, G. V.; Potapov, V. M.; Abdulganeeva, S. A.; Korchagina, E. Y. *Chem. Heterocyc. Compd.* **1985**, *21*, 1355-1362.