Article

Sensitive Detection of Pharmaceutical Drugs and Metabolites in Serum Using Data-Independent Acquisition Mass Spectrometry and Open-Access Data Acquisition Tools †

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† Authors would like to dedicate this research work to Professor Atta-Ur-Rahman FRS, on his 80th birthday.

SUPPLEMENTARY DATA

Table S1. DIA method Q1 window of 25 and 50 Da

Table S2: 10 pharmaceutical drugs identification by their spectral dot product score using DDA mode in MS-DIAL

Table S3: 23 serum metabolites identification by their spectral dot product score using DDA mode in MS-DIAL

Figure S1 (**A-J**). Identification of all drugs (**A**) Diphenhydramine; (**B**) Atropine; (**C**) Duloxetine; (**D**) Phenylbutazone; (**E**) Ranitidine; (**F**) Finasteride; (**G**) Haloperidol; (**H**) Ranolazine; (**I**) Oxytetracycline; (**J**) Dipyridamole have done by using MS-DIAL software in DDA mode. All identified and matched MS2 spectral information under 5ppm mass difference has given below. A transition list generated from all drugs spectral information and extracted in DIA mode using Skyline software.

Figure S2 (**A-W**). Identified serum metabolites by their MS2 spectra in DDA mode using MS-DIAL software. The software-generated subfigures contain exact mass, retention time and fragments mass of serum metabolites. (**A**) Phenylalanine; (**B**) Di(2-ethylhexyl) phthalate (DEHP); (**C**) Theophylline; (**D**) Tyrosine; (**E**) Atrazine-desethyl; (**F**) Caffeine; (**G**) Tryptophan; (**H**) N, N- Dimethyl dodecyl amine N-oxide; (**I**) Triphenylphosphine oxide; (**J**) Fenpropimorph; (**K**) Phytosphingosine; (**L**) Nadolol; (**M**) DDAO; (**N**) Lupulone; (**O**) Atenolol; (**P**) Di-n-butyl phthalate; (**Q**) Piperine; (**R**) Nordihydroguaiaretic Acid; (**S**) Erucamide; (**T**) NCGC00384769-01; (**U**) NCGC00381156-01; (**V**) Glycochenodeoxycholic Acid; (**W**) Boldenone-Undecylenate.

Figure S3 (**A-E**)**.** DIA MS2 deconvolution results of drug standards were not satisfying for in MS-DIAL. (A) Diphenhydramine; (B) Phenylbutazone; (C) Ranitidine; (D) Ranolazine; (E) Finasteride.

Figure S4 (**A-W**). Identified serum metabolites deconvoluted MS1 (top) and MS2 (bottom) spectra by DIA mode in Skyline. (**A**) Phenylalanine; (**B**) Atrazine-Desethyl; (**C**) Tryptophan; (**D**) Theophylline; (**E**) Caffeine; (**F**) Boldenone-Undecylenate; (**G**) Nadolol; (**H**) DDAO; (**I**) Phytosphingosine; (**J**) N, N-Dimethyl-dodecyl-amine-N-Oxide; (**K**) Piperine; (**L**) NCGC00384769-01; (**M**) NCGC00381156-01; (**N**) Glycochenodeoxycholic Acid; (**O**) Di-N-Butyl Phthalate; (**P**) Nordihydroguaiaretic Acid; (**Q**) Erucamide; (**R**) Di(2-Ethylhexyl) Phthalate; (**S**) Lupulone; (**T**) Atenolol; (**U**) Triphenylphosphine; (**V**) Tyrosine; (**W**) Fenpropimorph.

Table S1. DIA method Q1 window of 25 and 50 Da.

Experiment	MS Type	Min *m/z*	Max *m/z*
0	SCAN	100	1200
1	SWATH	99.5	150.5
2	SWATH	149.5	200.5
3	SWATH	199.5	225.5
4	SWATH	224.5	250.5
5	SWATH	249.5	275.5
6	SWATH	274.5	300.5
7	SWATH	299.5	325.5
8	SWATH	324.5	350.5
9	SWATH	349.5	375.5
10	SWATH	374.5	400.5
11	SWATH	399.5	425.5
12	SWATH	424.5	450.5
13	SWATH	449.5	475.5
14	SWATH	474.5	500.5
15	SWATH	499.5	525.5
16	SWATH	524.5	550.5
17	SWATH	549.5	575.5
18	SWATH	574.5	600.5
19	SWATH	599.5	625.5
20	SWATH	624.5	650.5
21	SWATH	649.5	675.5
22	SWATH	674.5	700.5
23	SWATH	699.5	725.5
24	SWATH	724.5	750.5
25	SWATH	749.5	775.5
26	SWATH	774.5	800.5
27	SWATH	799.5	825.5
28	SWATH	824.5	850.5
29	SWATH	849.5	875.5
30	SWATH	874.5	900.5
31	SWATH	899.5	950.5
32	SWATH	949.5	1,000.50
33	SWATH	999.5	1,050.50
34	SWATH	1,049.50	1,099.50
35	SWATH	1,049.50	1,150.50
36	SWATH	1,199.50	1,200.50

Table S2: 10 pharmaceutical drugs identification based on their spectral dot product score using DDA mode in MS-DIAL.

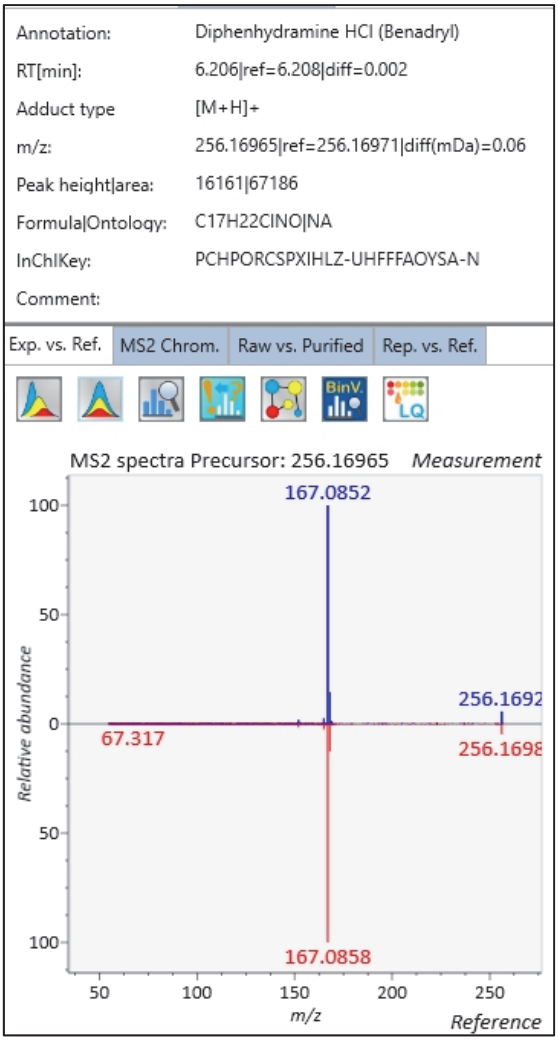
Drugs	Formula	RT	*m/z* $[H]^+$	Fragments	Dot Product *
Ranitidine	$C_{13}H_{22}N_4O_3S$	3.3	315.1485	270.0921, 285.2793	0.90
Oxytetracycline	$C_{22}H_{24}N_2O_9$	4.0	461.1555	426.118, 283.0600	0.36
Ranolazine	$C_{24}H_{33}N_3O_4$	5.3	428.2544	279.1702, 304.2017	0.97
Atropine	$C_{17}H_{23}NO_3$	4.5	290.1745	261.1675, 274.1371	0.88
Diphenhydramine	$C_{17}H_{21}NO$	5.4	256.1696	238.714, 167.085	0.81
Haloperidol	$C_{21}H_{23}ClFNO_2$	5.7	376.1474	358.1369, 360.1338	0.72
Dipyridamole	$C_{24}H_{40}N_8O_4$	6.1	505.3245	429.2723, 460.2896	0.99
Duloxetine	$C_{18}H_{19}NOS$	6.1	298.1260	279.1624, 265.0204	0.3
Finasteride	$C_{23}H_{36}N_2O_2$	8.1	373.2850	317.2222, 305.2585	0.91
Phenylbutazone	$C_{19}H_{20}N_2O_2$	8.2	309.1598	263.1523, 281.1650	0.93

* Dot product calculates the similarity between the experimental MS^2 spectrum and the reference MS^2 spectrum. [18] MS-DIAL software calculates dot product ranges between 0 to 1 of every feature. If the experimental MS^2 information does not match with a library fragment ion, the dot product of that ion will be zero.

Table S3: 23 serum metabolites identification based on their spectral dot product score using DDA mode in MS-DIAL.

Metabolites	Precursor Ions $[M+H]^+$ *m/z*	Product Ions *m/z*	Dot Product
Phenylalanine	166.0862	149.0022, 150.0631	0.93
Atrazine-desethyl	188.0707	144.0803, 146.0598	0.55
Tryptophan	205.0972	146.0595, 159.0915	0.68
Theophylline	181.0720	161.0207, 149.0023	0.81
Caffeine	195.0878	163.9774, 161.0193	0.93
N, *N*- Dimethyl dodecyl amine *N*-oxide	230.2484	228.1788, 212.2365	0.74
Di-n-butyl phthalate	279.1595	150.0269, 223.0971	0.64
Boldenone-Undecylenate	453.3440	435.3339	0.84
Nadolol	310.2019	251.1280, 281.0028	0.64
DDAO	202.2166	173.9622, 184.2054	0.75
Phytosphingosine	318.3007	256.2639, 318,3537	0.77
Piperine	286.1444	262.0576, 250.9922	072
NCGC00384769-01	415.2124	413.2654, 295.1181	0.82
NCGC00381156-01	437.1943	233.0757	0.81
Glycochenodeoxycholic Acid	450.3224	414.3005, 339.2688	0.61
Nordihydroguaiaretic Acid	301.1414	245.0798, 301.3036	0.88
Erucamide	338.3424	295.1956, 321.3159	0.80
Di(2-ethylhexyl) phthalate (DEHP)	391.2853	167.0343, 150.0265	0.80
Lupulone	413.2673	301.1421, 413.3803	0.85
Atenolol	267.1637	237.0144, 265.1491	0.79
Fenpropimorph	304.2615	214.9186, 302.1462	0.74
Tyrosine	182.0811	165.0547, 147.0442	0.68
Triphenylphosphine oxide	279.0937	201.0484, 149.0238	0.77

(A) DDA



DIA

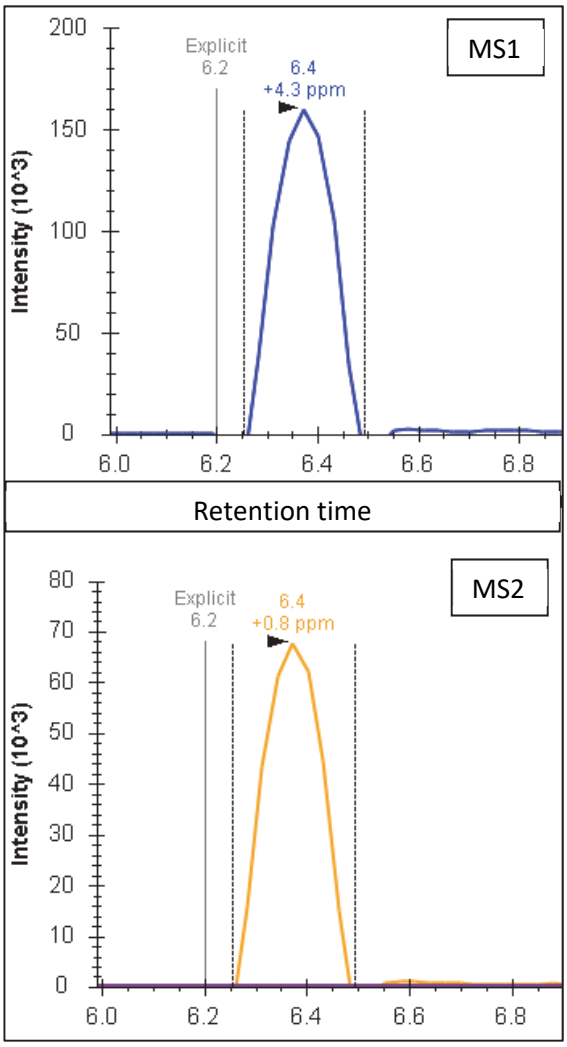
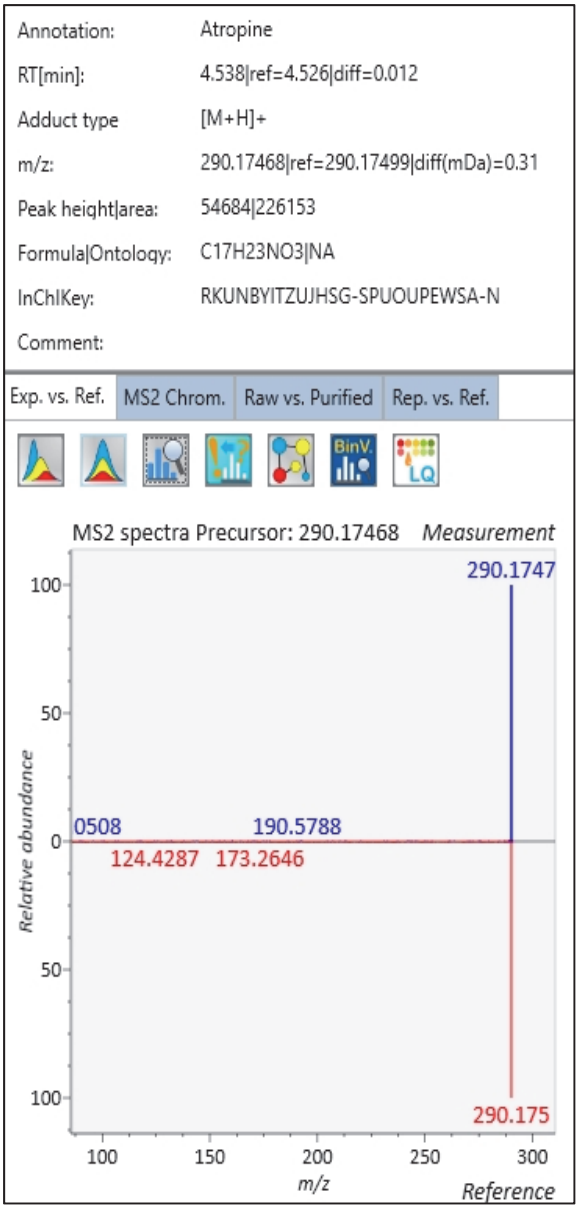


Figure S1. Continue

(B) DDA DIA



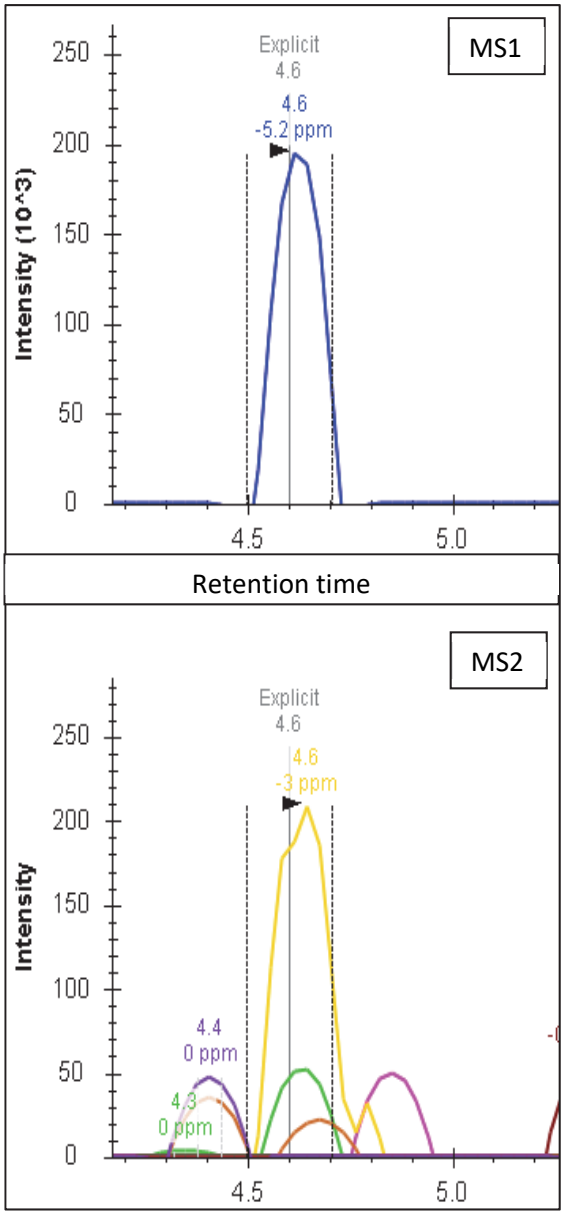


Figure S1. Continue

(**C**) DDA DIA

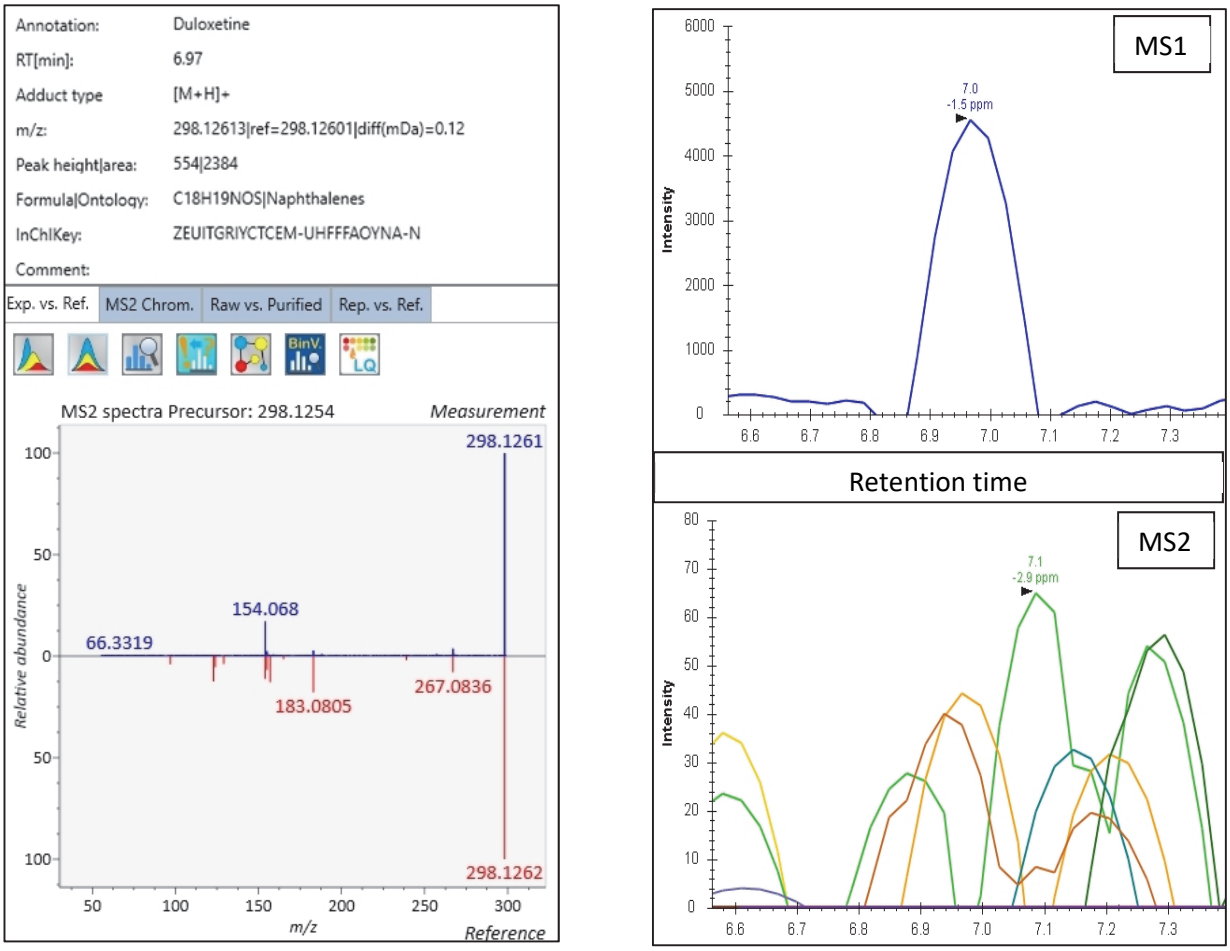
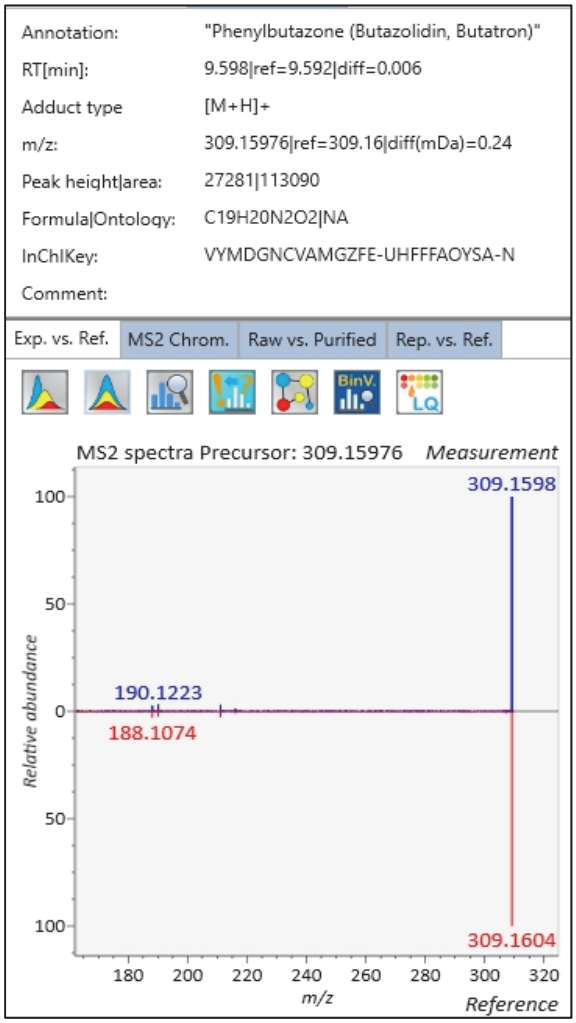


Figure S1. Continue

(D) DDA DIA



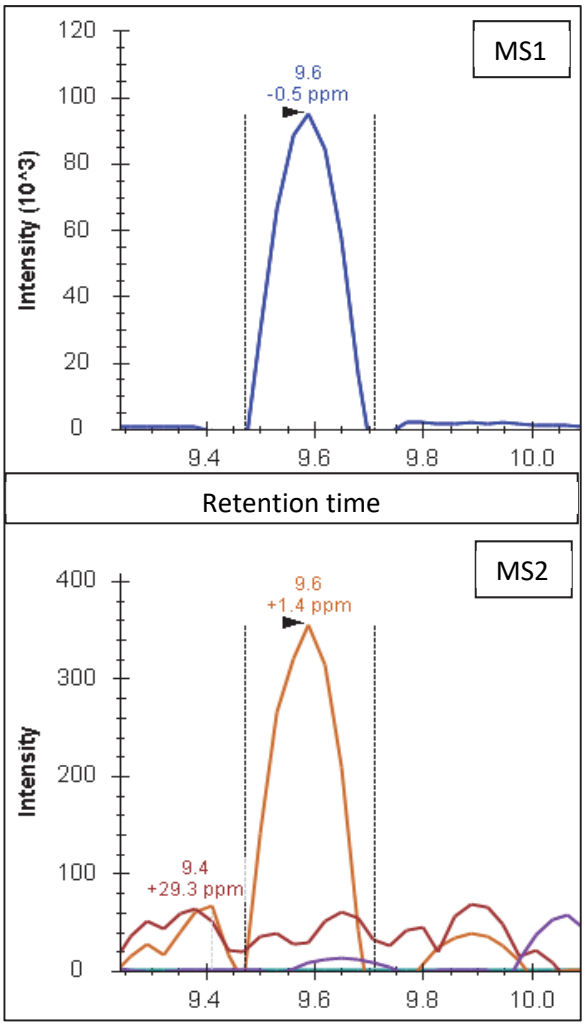


Figure S1. Continue

(E) DDA DIA

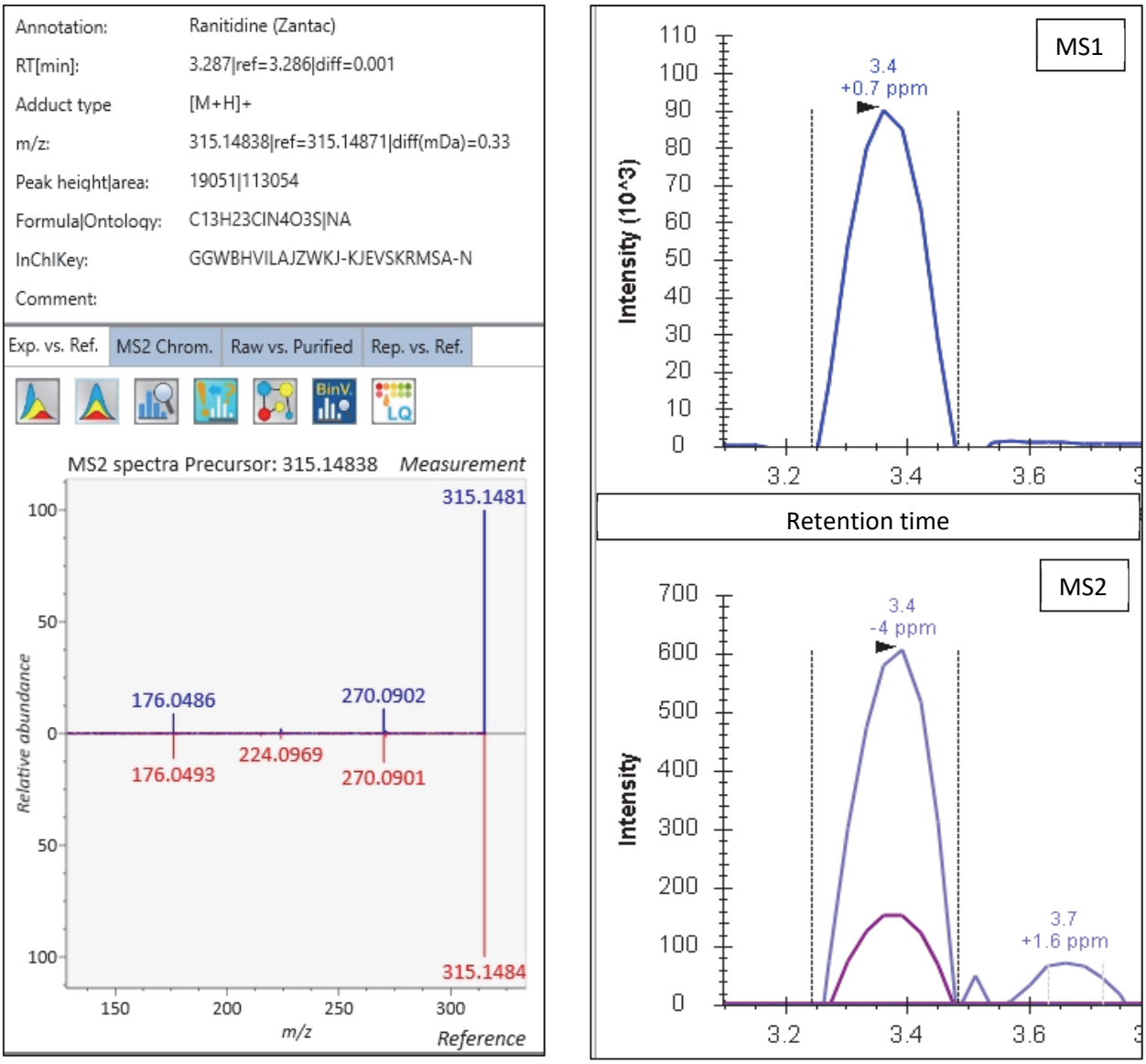
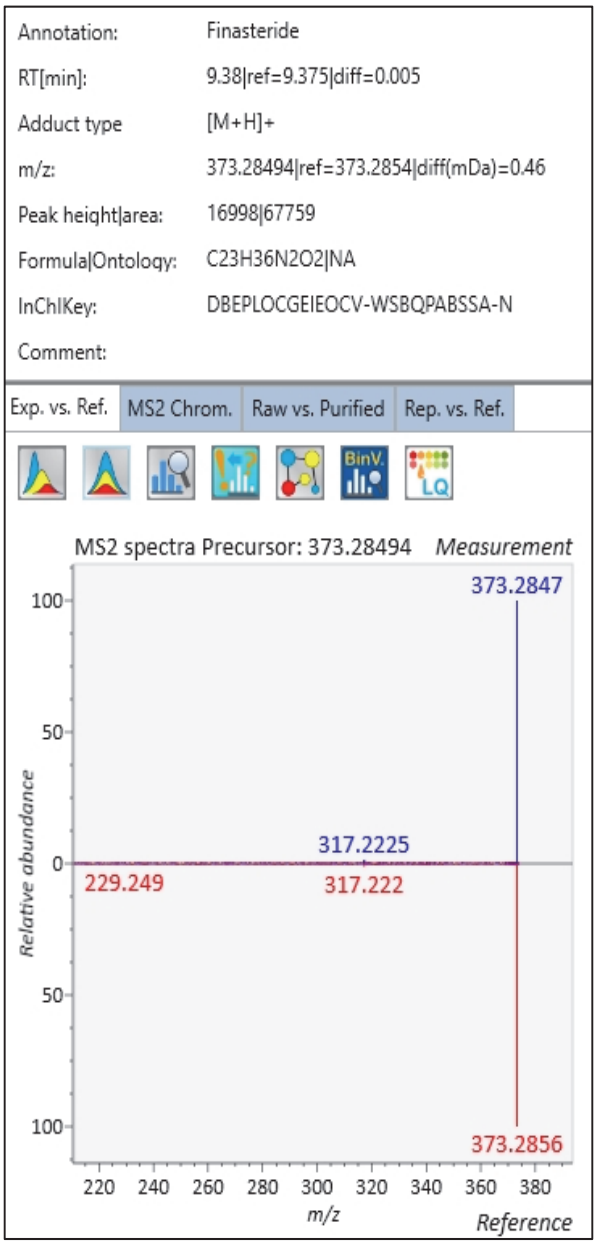


Figure S1. Continue

(F) DDA DIA



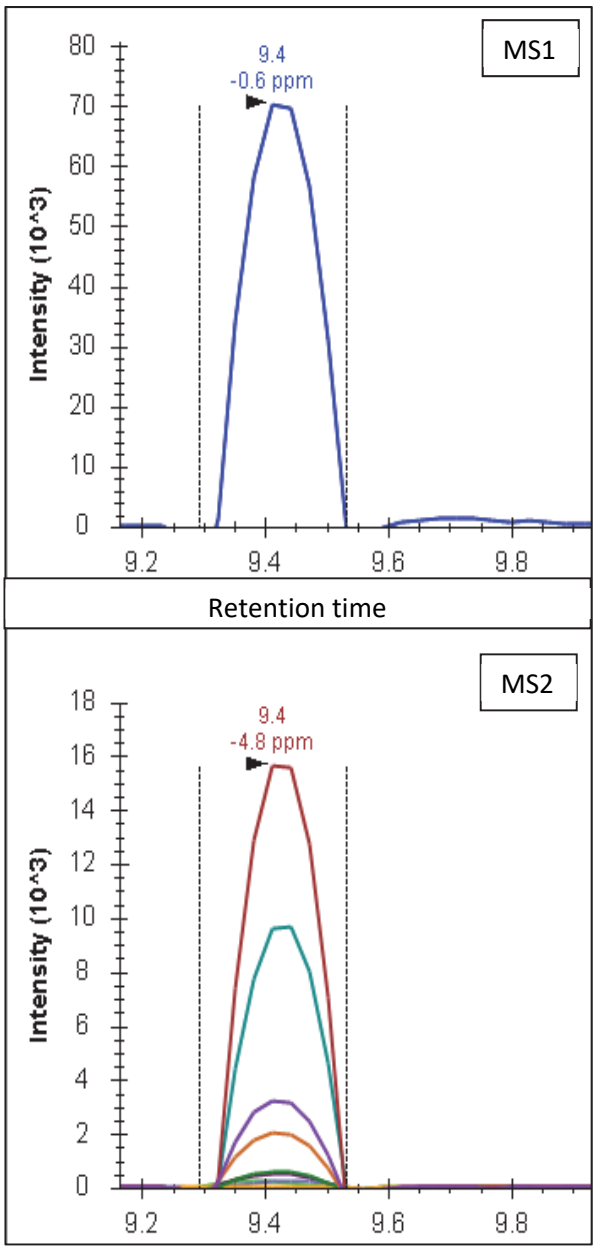


Figure S1. Comtinue

(G) DDA DIA

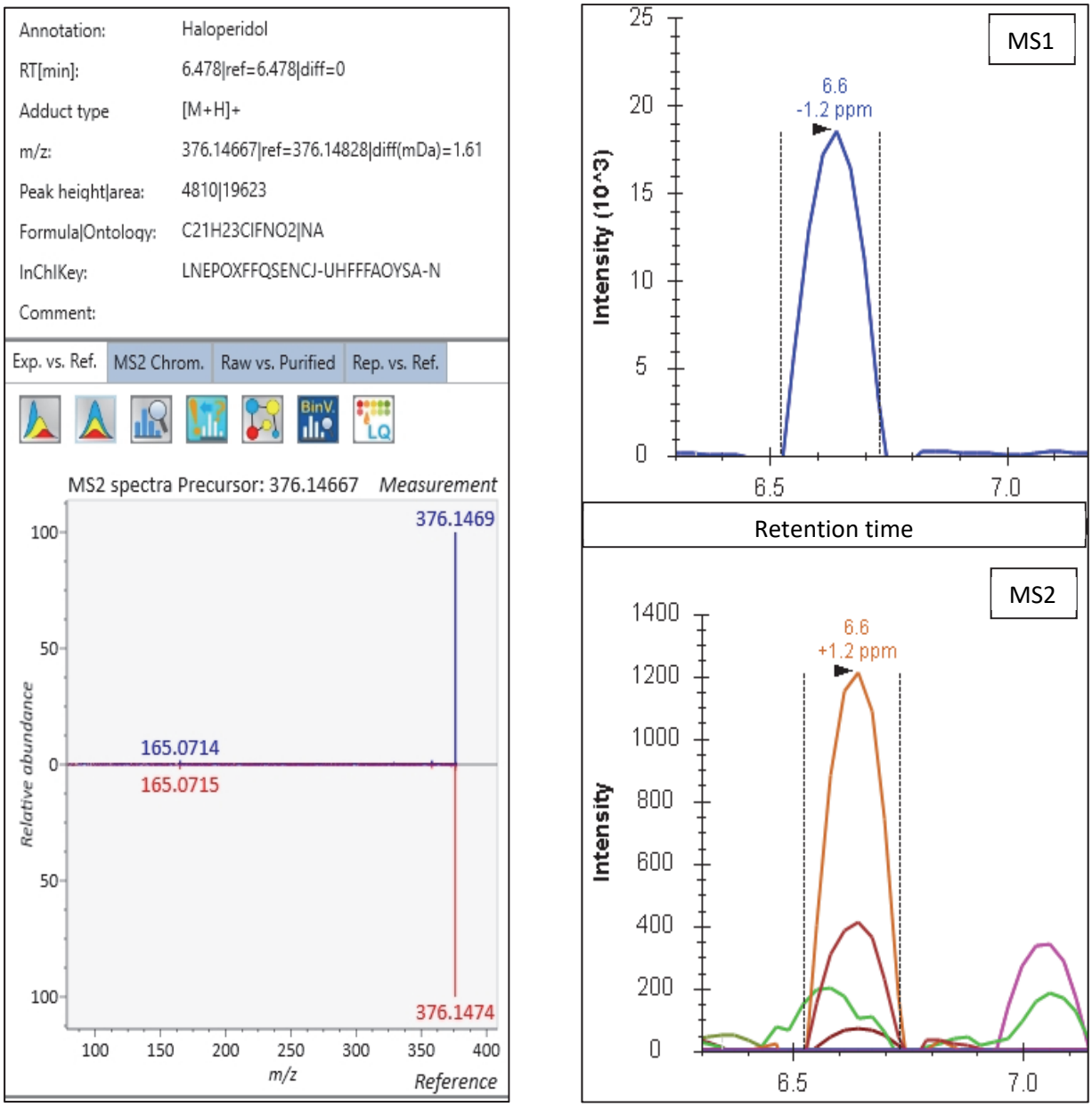
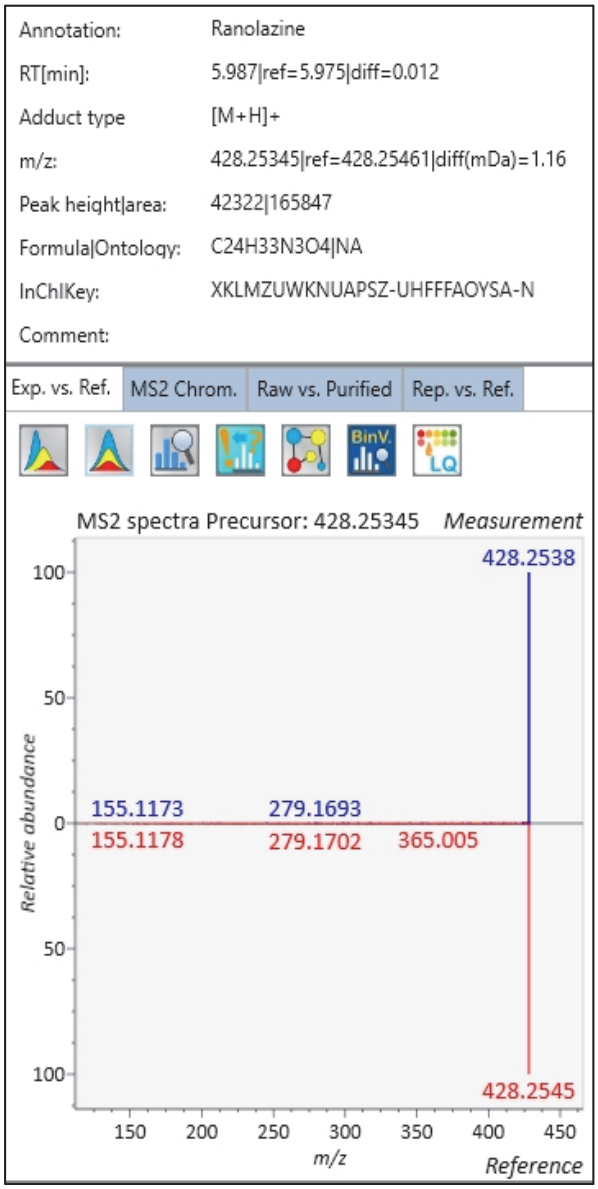


Figure S1. Continue

(H) DDA DIA



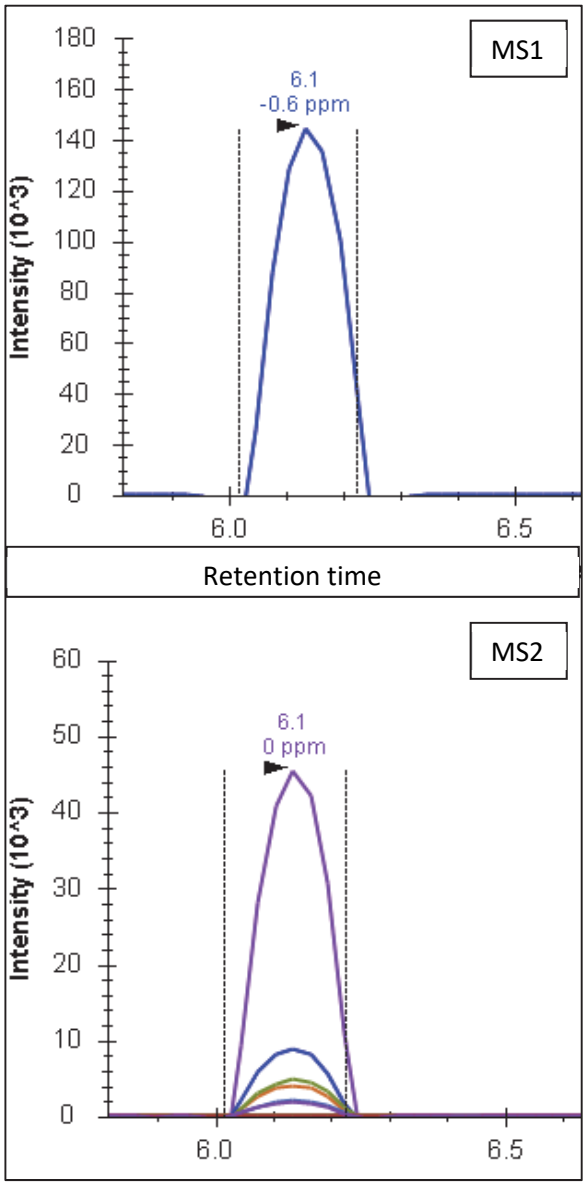
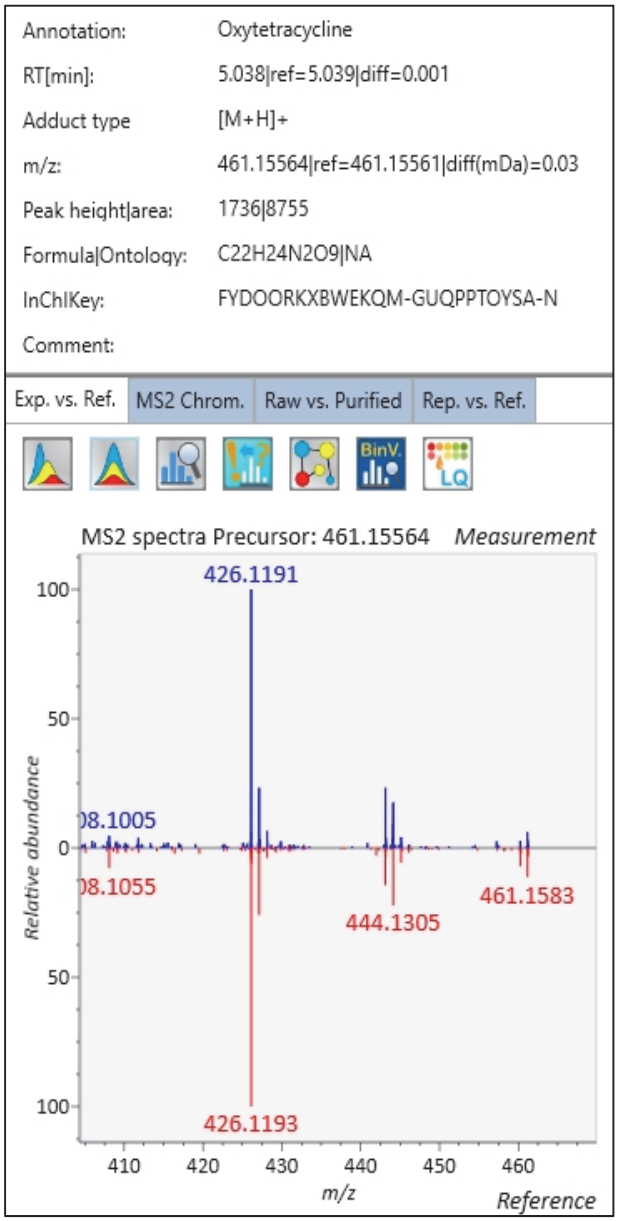


Figure S1. Continue

(I) DDA DIA



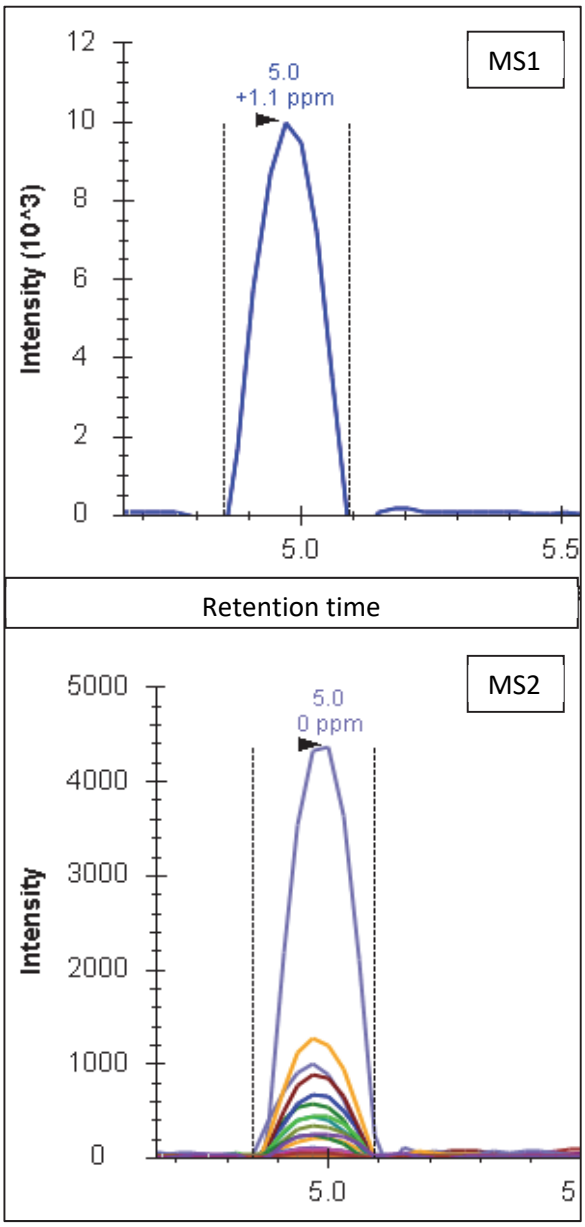


Figure S1. Continue

(J) DDA DIA

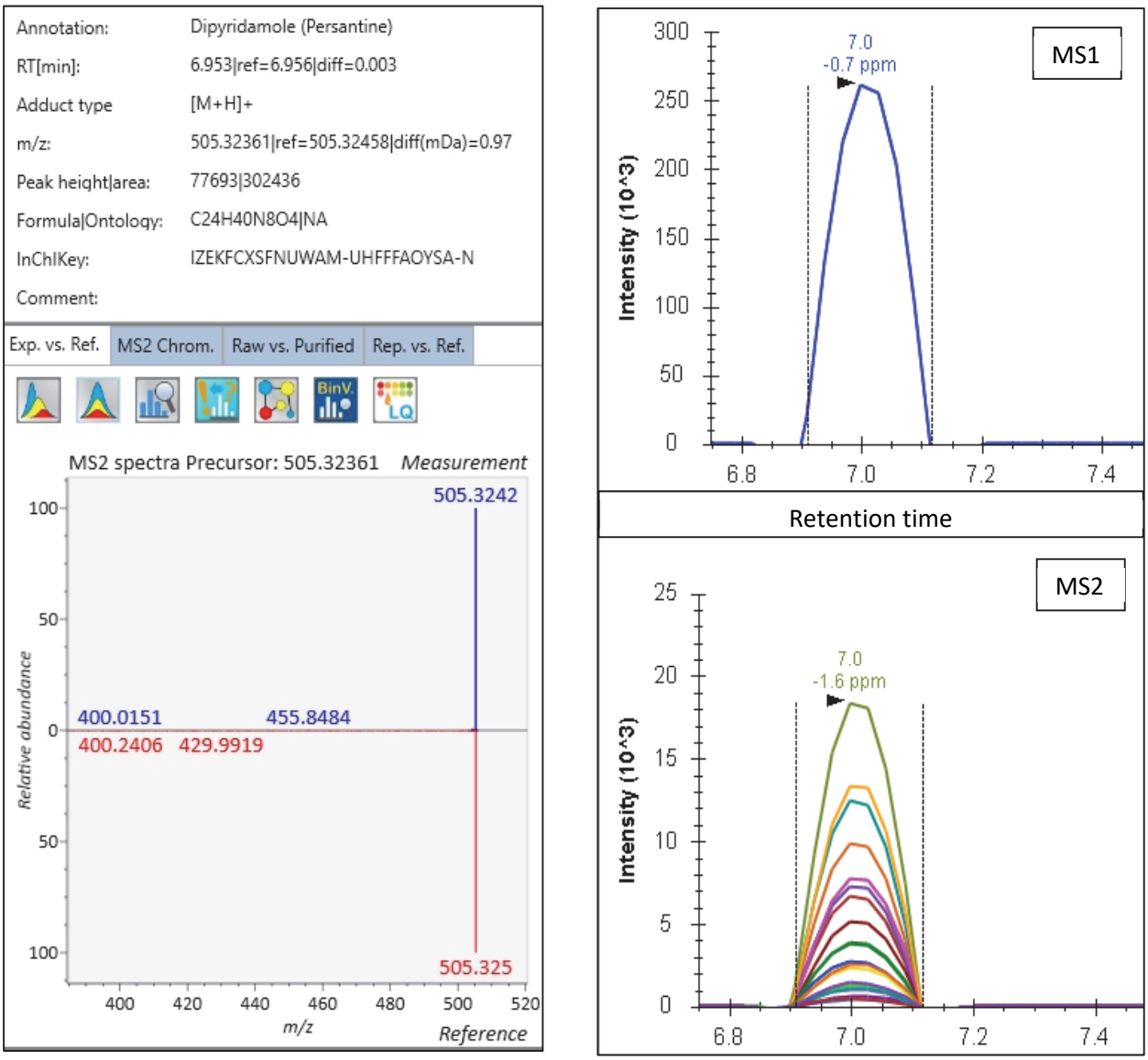
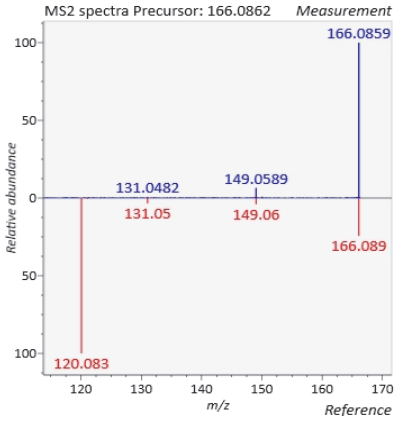


Figure S1. Identification of all drugs (**A**) Diphenhydramine; (**B**) Atropine; (**C**) Duloxetine; (**D**) Phenylbutazone; (**E**) Ranitidine; (**F**) Finasteride; (**G**) Haloperidol; (**H**) Ranolazine; (**I**) Oxytetracycline; (**J**) Dipyridamole have done by using MS-DIAL software in DDA mode. All identified and matched MS2 spectral information under 5ppm mass difference has given below. A transition list generated from all drugs spectral information and extracted in DIA mode using Skyline software.

(A)

Annotation:	Phenylalanine
RT[min]:	3.385
Adduct type	[M+H]+
m/z:	166.0862|ref=166.08626|diff(mDa)=0.06
Peak height|area:	142784|833542
Formula|Ontology:	C9H11NO2|NA
InChIKey:	COLNVLDHVKWLRT-UHFFFAOYSA-N
Comment:	

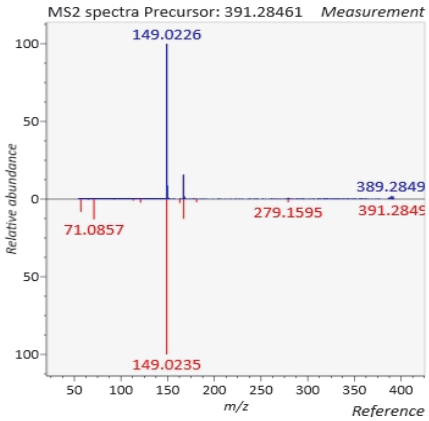
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(B)

Annotation:	Di(2-ethylhexyl)phthalate (DEHP)
RT[min]:	11.432
Adduct type	[M+H]+
m/z:	391.28461|ref=391.2843|diff(mDa)=0.31
Peak height|area:	42440|358116
Formula|Ontology:	C24H38O4|NA
InChIKey:	BJQHLKABXJIVAM-UHFFFAOYSA-N
Comment:	

Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(C)

Annotation:	Theophylline
RT[min]:	4.719
Adduct type	[M+H]+
m/z:	181.07187|ref=181.07201|diff(mDa)=0.14
Peak height|area:	19415|77346
Formula|Ontology:	C7H8N4O2|NA
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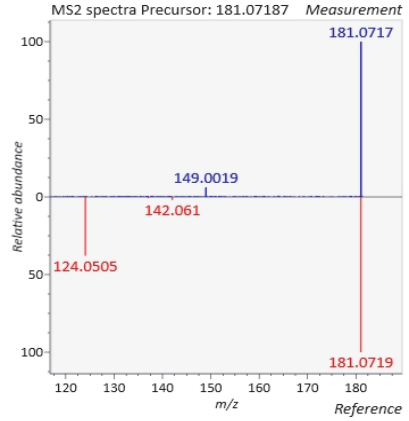
Comment:	

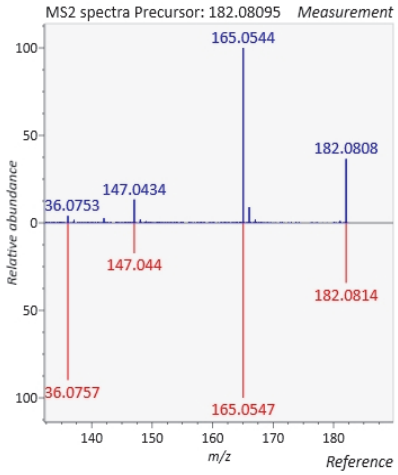
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(D)

Annotation:	Tyrosine
RT[min]:	1.568
Adduct type	[M+H]+
m/z:	182.08095|ref=182.08118|diff(mDa)=0.23
Peak height|area:	28371|320943
Formula|Ontology:	C9H11NO3|NA
InChIKey:	OUYCCCASQSFEME-UHFFFAOYSA-N
Comment:	

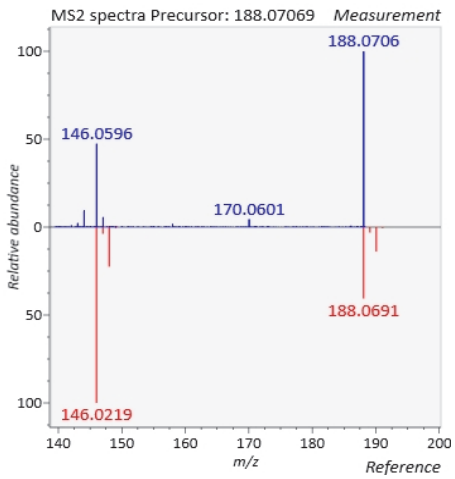
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(E)

Annotation:	Atrazine-Desethyl
RT[min]:	4.236
Adduct type	[M+H]+
m/z:	188.07069|ref=188.0697|diff(mDa)=0.99
Peak height|area:	199813|883057
Formula|Ontology:	C6H10ClN5|NA
InChIKey:	DFWFIQKMSFGDCQ-UHFFFAOYSA-N
Comment:	

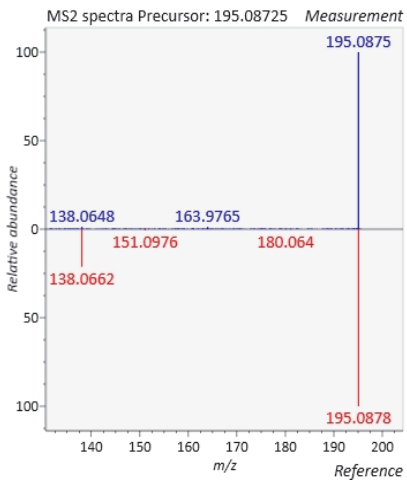
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(F)

Annotation:	Caffeine
RT[min]:	5.453
Adduct type	[M+H]+
m/z:	195.08725|ref=195.08771|diff(mDa)=0.46
Peak height|area:	64177|276681
Formula|Ontology:	C8H10N4O2|NA
InChIKey:	RYYVLZVUVIJVGH-UHFFFAOYSA-N
Comment:	

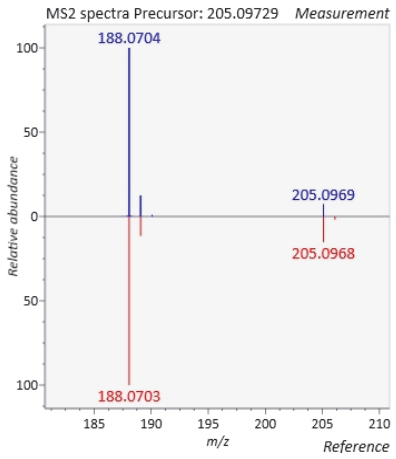
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(G)

Annotation:	Tryptophan
RT[min]:	4.236
Adduct type	[M+H]+
m/z:	205.09729|ref=205.09715|diff(mDa)=0.14
Peak height|area:	84966|371912
Formula|Ontology:	C11H12N2O2|NA
InChIKey:	QIVBCDIJIAJPQS-VIFPVBQESA-N
Comment:	

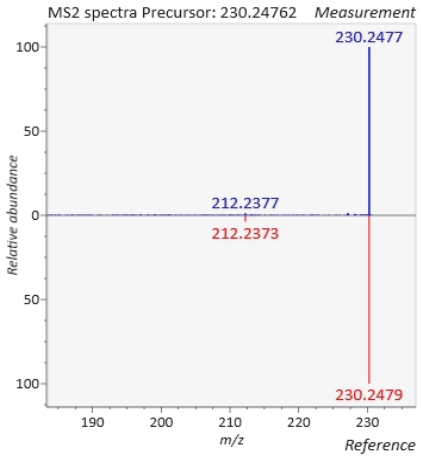
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(H)

Annotation:	N,N-Dimethyldodecylamine N-oxide
RT[min]:	8.09
Adduct type	[M+H]+
m/z:	230.24762|ref=230.2478|diff(mDa)=0.18
Peak height|area:	17332|72019
Formula|Ontology:	C14H31NO|NA
InChIKey:	SYELZBGXAIXKHU-UHFFFAOYSA-N
Comment:	

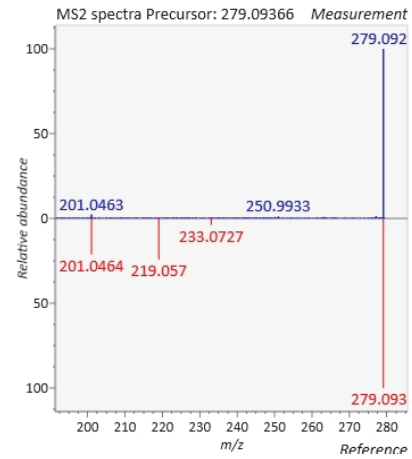
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(I)

Annotation:	Triphenylphosphine oxide
RT[min]:	8.954
Adduct type	[M+H]+
m/z:	279.09366|ref=279.09329|diff(mDa)=0.37
Peak height|area:	5764|28550
Formula|Ontology:	C18H15OP|NA
InChIKey:	FIQMHBFVRAXMOP-UHFFFAOYSA-N
Comment:	

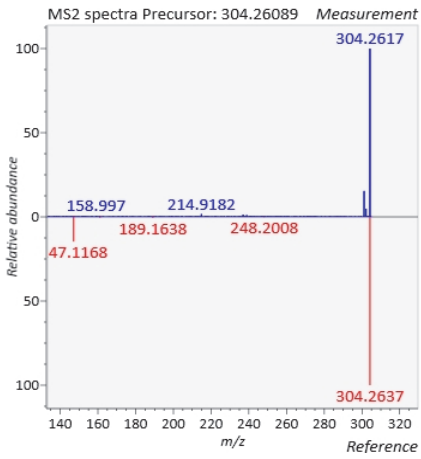
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(J)

Annotation:	Fenpropimorph
RT[min]:	11.838
Adduct type	[M+Na]+
m/z:	304.26089|ref=304.26349|diff(mDa)=2.6
Peak height|area:	28556|127706
Formula|Ontology:	C20H33NO|NA
InChIKey:	RYAUSSKQMZRMAI-ALOPSCKCSA-N
Comment:	

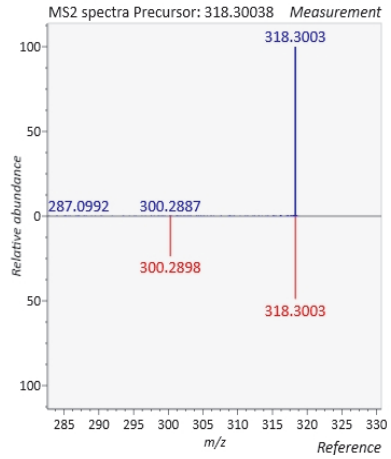
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(K)

Annotation:	Phytosphingosine
RT[min]:	8.02
Adduct type	[M+H]+
m/z:	318.30038|ref=318.3002|diff(mDa)=0.18
Peak height|area:	18029|70442
Formula|Ontology:	C18H39NO3|NA
InChIKey:	AERBNCYCJBRYDG-KSZLIROESA-N
Comment:	

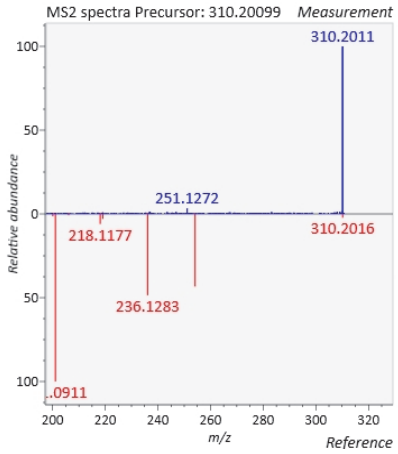
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(L)

Annotation:	Nadolol
RT[min]:	6.669
Adduct type	[M+H]+
m/z:	310.20099|ref=310.20129|diff(mDa)=0.3
Peak height|area:	4011|24184
Formula|Ontology:	C17H27NO4|NA
InChIKey:	VWPOSFSPZNDTMJ-UCWKZMIHSA-N
Comment:	

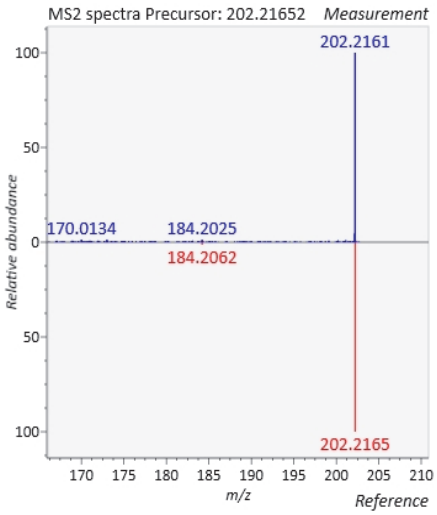
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(M)

Annotation:	DDAO
RT[min]:	7.282
Adduct type	[M+H]+
m/z:	202.21652|ref=202.21651|diff(mDa)=0.01
Peak height|area:	5419|26341
Formula|Ontology:	C12H27NO|NA
InChIKey:	ZRKZFNZPJKEWPC-UHFFFAOYSA-N
Comment:	

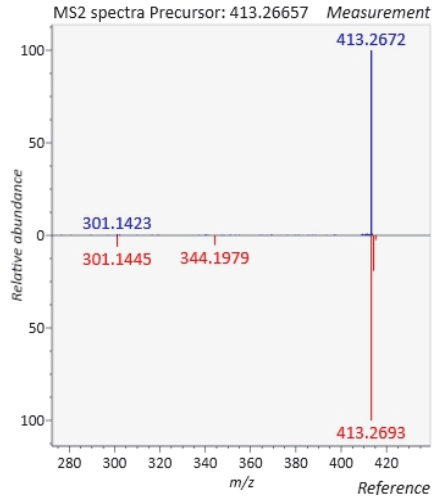
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(N)

Annotation:	Lupulone
RT[min]:	11.432
Adduct type	[M+Na]+
m/z:	413.26657|ref=413.26929|diff(mDa)=2.72
Peak height|area:	149356|1305127
Formula|Ontology:	C26H38O4|NA
InChIKey:	WPVSVIXDXMNGGN-UHFFFAOYSA-N
Comment:	

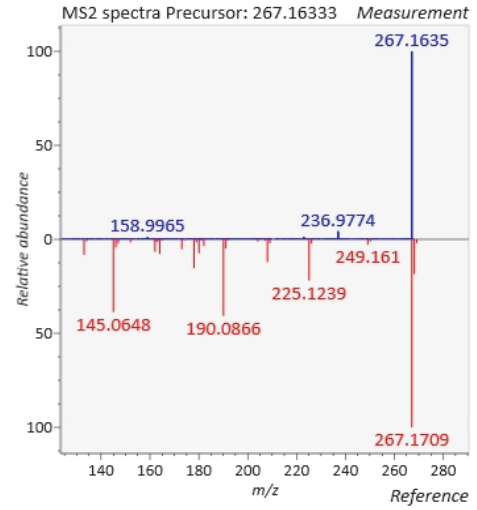
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(O)

Annotation:	Atenolol
RT[min]:	11.661
Adduct type	[M+H]+
m/z:	267.16333|ref=267.17029|diff(mDa)=6.96
Peak height|area:	45759|257158
Formula|Ontology:	C14H22N2O3|NA
InChIKey:	METKIMKYRPQLGS-UHFFFAOYSA-N
Comment:	

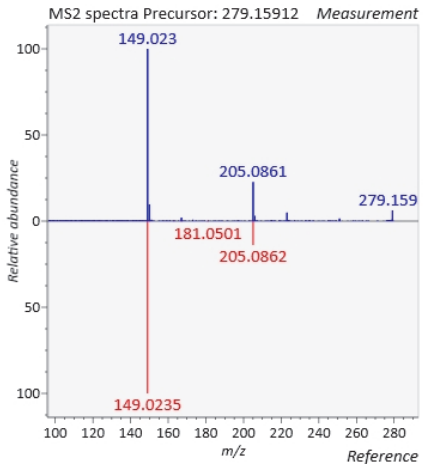
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(P)

Annotation:	Di-n-butyl phthalate
RT[min]:	10.35
Adduct type	[M+H]+
m/z:	279.15912|ref=279.15909|diff(mDa)=0.03
Peak height|area:	22151|93192
Formula|Ontology:	C16H22O4|NA
InChIKey:	DOIRQSBPFJWKBE-UHFFFAOYSA-N
Comment:	

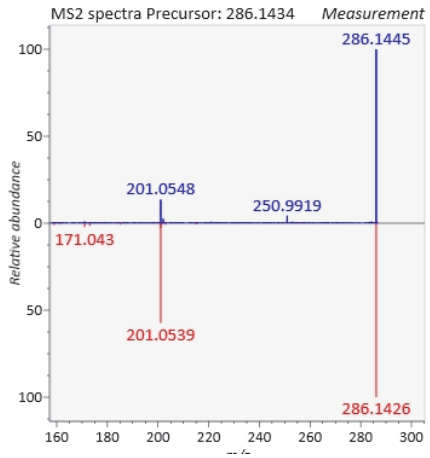
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(Q)

Annotation:	Piperine
RT[min]:	9.474
Adduct type	[M+H]+
m/z:	286.1434|ref=286.1438|diff(mDa)=0.4
Peak height|area:	11141|47501
Formula|Ontology:	C17H19NO3|NA
InChIKey:	MXXWOMGUGJBKIW-SRRWRRMSSA-N
Comment:	

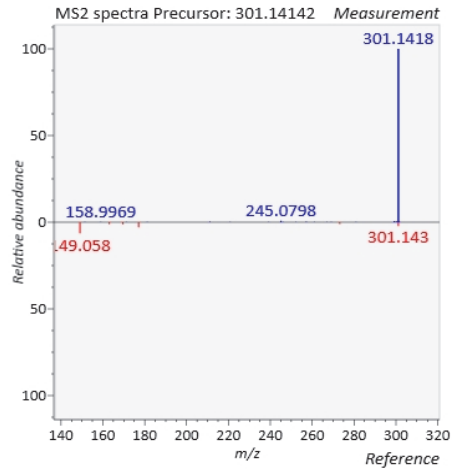
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(R)

Annotation:	Nordihydroguaiaretic acid
RT[min]:	10.353
Adduct type	[M+Na]+
m/z:	301.14142|ref=301.1445|diff(mDa)=3.08
Peak height|area:	154945|695456
Formula|Ontology:	C18H22O4|NA
InChIKey:	HCZKYJDFEPMADG-UHFFFAOYSA-N
Comment:	

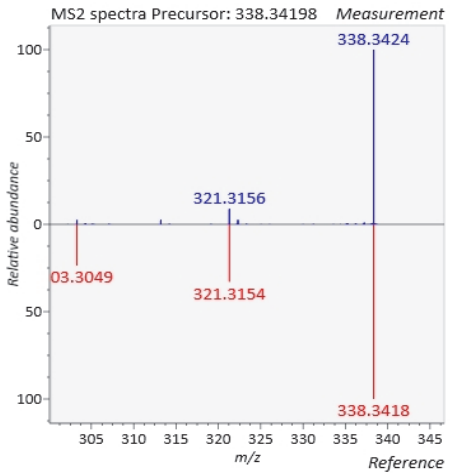
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(S)

Annotation:	Erucamide
RT[min]:	10.878
Adduct type	[M+H]+
m/z:	338.34198|ref=338.34161|diff(mDa)=0.37
Peak height|area:	105621|882770
Formula|Ontology:	C22H43NO|NA
InChIKey:	UAUDZVJPLUQNMU-KTKRTIGZSA-N
Comment:	

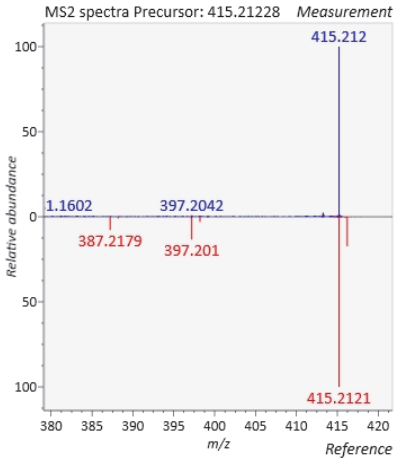
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(T)

Annotation:	NCGC00384769-01!6,8-dihydroxy-2,2,4,4-tet
RT[min]:	9.612
Adduct type	[M+H]+
m/z:	415.21228|ref=415.211|diff(mDa)=1.28
Peak height|area:	35700|154691
Formula|Ontology:	C24H30O6|NA
InChIKey:	AYAUOXWJIWVPSO-UHFFFAOYSA-N
Comment:	

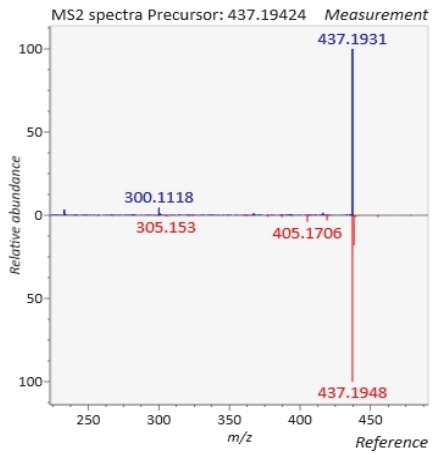
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(U)

Annotation:	NCGC00381156-01_C24H30O6_Methyl 3-[(1
RT[min]:	9.612
Adduct type	[M+Na]+
m/z:	437.19424|ref=437.19299|diff(mDa)=1.25
Peak height|area:	32688|163818
Formula|Ontology:	C24H30O6|NA
InChIKey:	VYXBNIDRQOAAHX-RQADFKIXSA-N
Comment:	

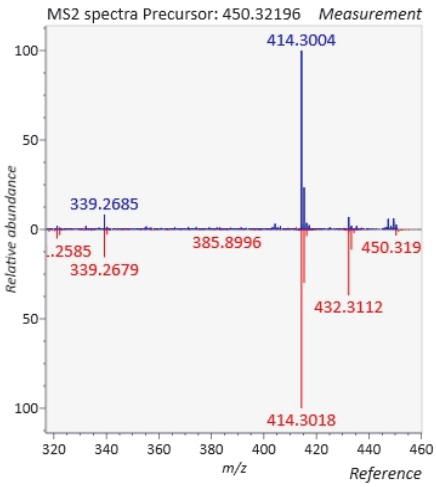
Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(V)

Annotation:	GLYCOCHENODEOXYCHOLIC ACID
RT[min]:	10.24
Adduct type	[M+H]+
m/z:	450.32196|ref=450.32199|diff(mDa)=0.03
Peak height|area:	3569|14505
Formula|Ontology:	C26H43NO5|NA
InChIKey:	GHCZAUBVMUEKKP-GYPHWSFCSA-N
Comment:	

Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.



(W)

Annotation:	Boldenone_Undecylenate
RT[min]:	6.573
Adduct type	[M+H]+
m/z:	453.34399|ref=453.33698|diff(mDa)=7.01
Peak height|area:	51103|238632
Formula|Ontology:	C30H44O3|NA
InChIKey:	AHMMSNQYOPMLSX-KEZAGTACSA-N
Comment:	

Exp. vs. Ref. | MS2 Chrom. | Raw vs. Purified | Rep. vs. Ref.

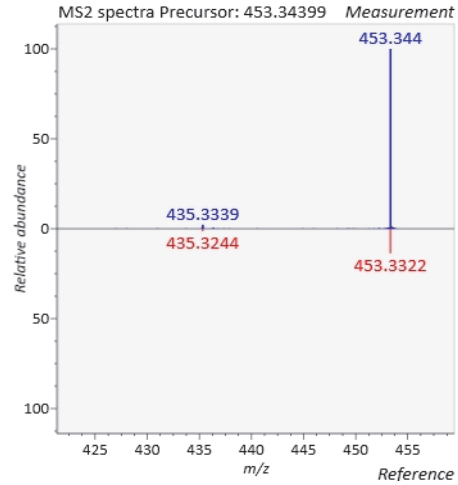
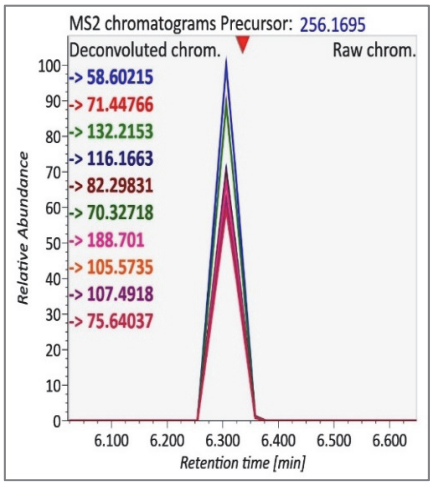
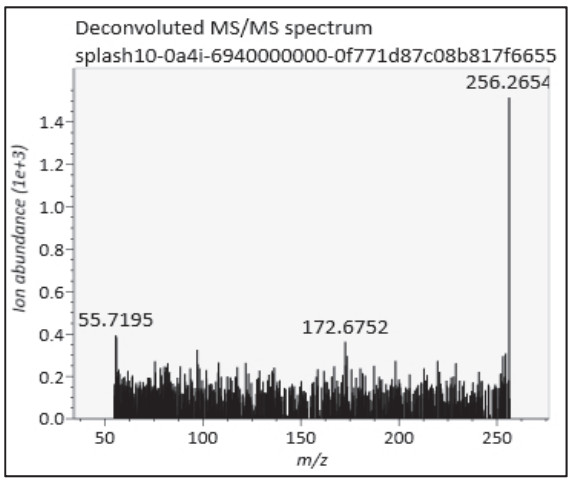


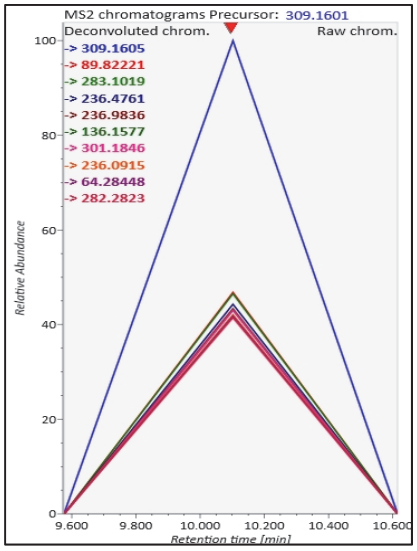
Figure S2. Identified serum metabolites by their MS2 spectra in DDA mode using MS-DIAL software. The software-generated subfigures contain exact mass, retention time and fragments mass of serum metabolites. (**A**) Phenylalanine; (**B**) Di(2-ethylhexyl) phthalate (DEHP); (**C**) Theophylline; (**D**) Tyrosine; (**E**) Atrazine-desethyl; (**F**) Caffeine; (**G**) Tryptophan; (**H**) N, N- Dimethyl dodecyl amine N-oxide; (**I**) Triphenylphosphine oxide; (**J**) Fenpropimorph; (**K**) Phytosphingosine; (**L**) Nadolol; (**M**) DDAO; (**N**) Lupulone; (**O**) Atenolol; (**P**) Di-n-butyl phthalate; (**Q**) Piperine; (**R**) Nordihydroguaiaretic Acid; (**S**) Erucamide; (**T**) NCGC00384769-01; (**U**) NCGC00381156-01; (**V**) Glycochenodeoxycholic Acid; (**W**) Boldenone-Undecylenate.

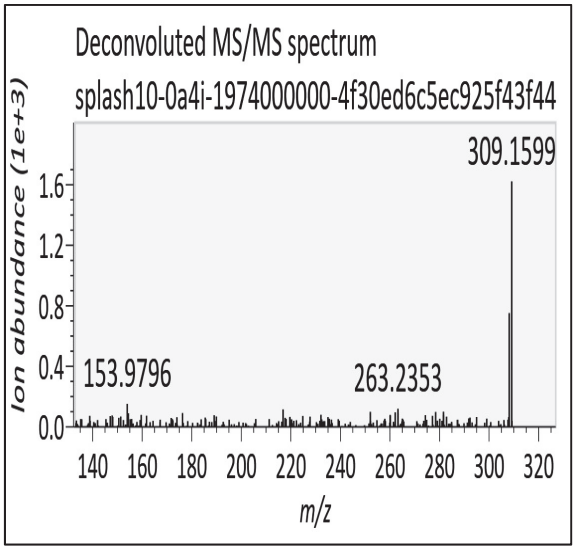
(**A**) DIPHENHYDRAMINE



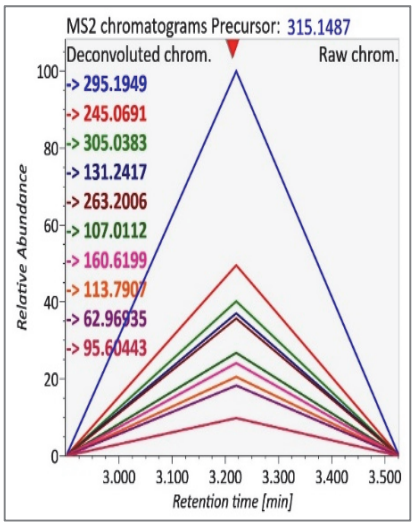


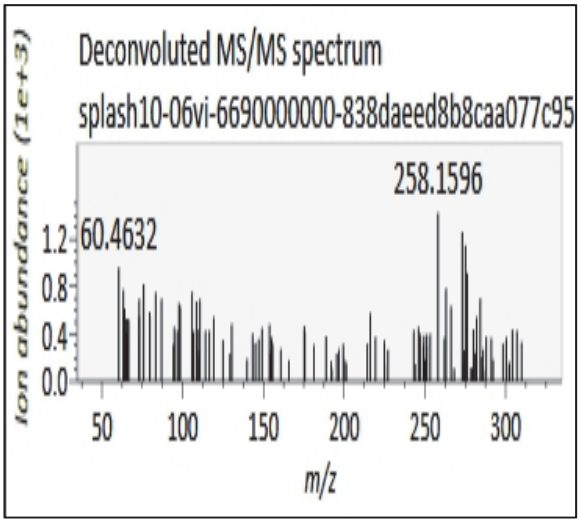
(**B**) PHENYLBUTAZONE



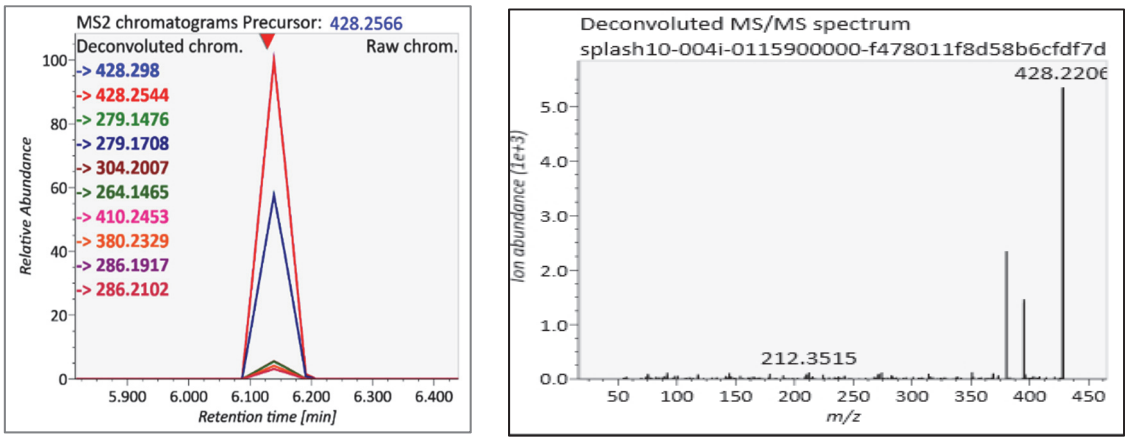


(**C**) RANITIDINE





(**D**) RANOLAZINE



(**E**) FINASTERIDE

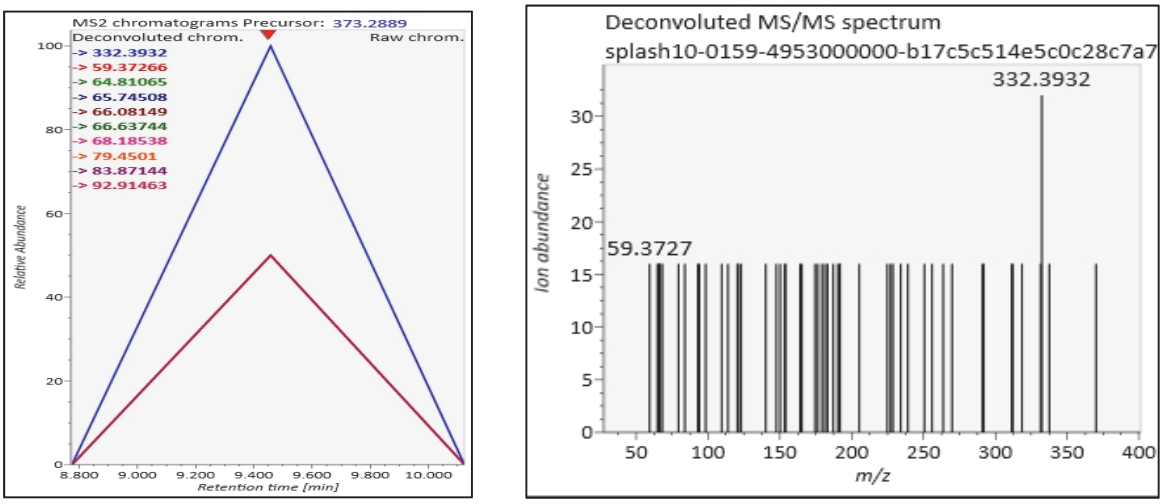
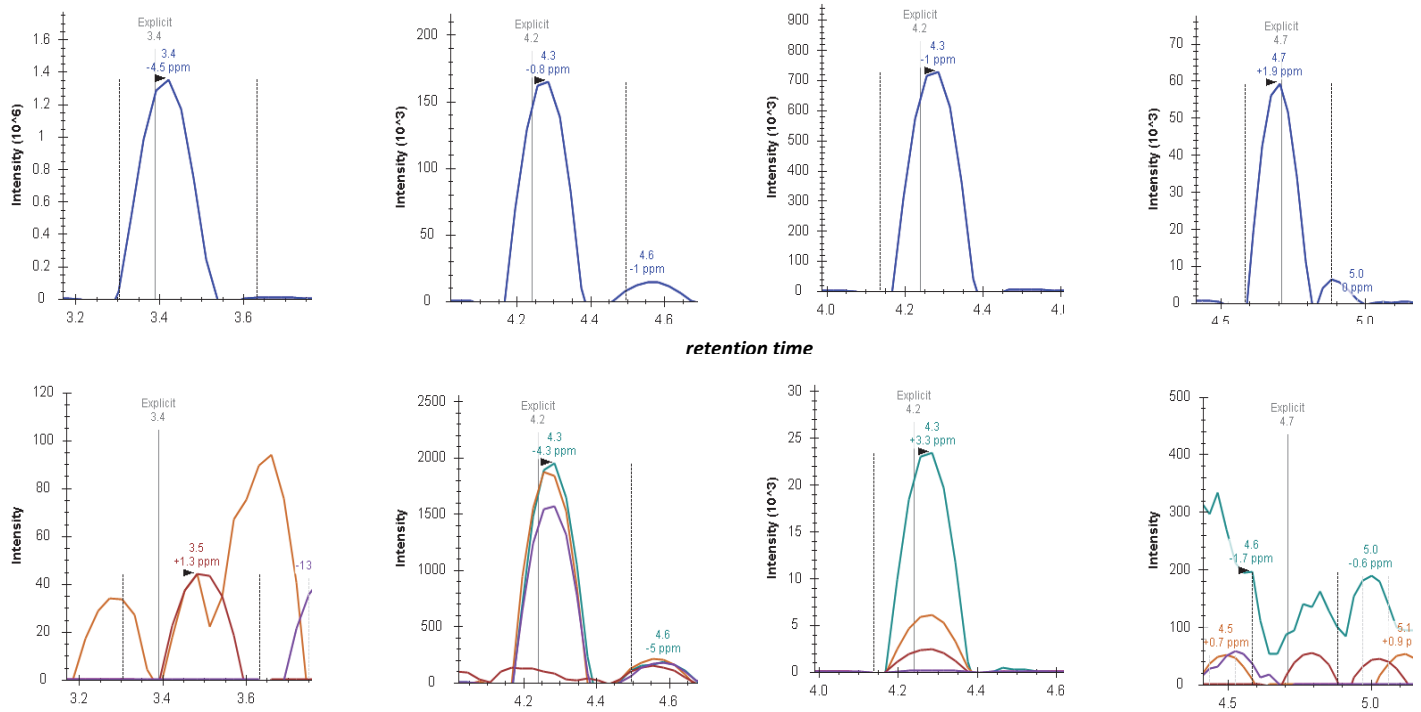
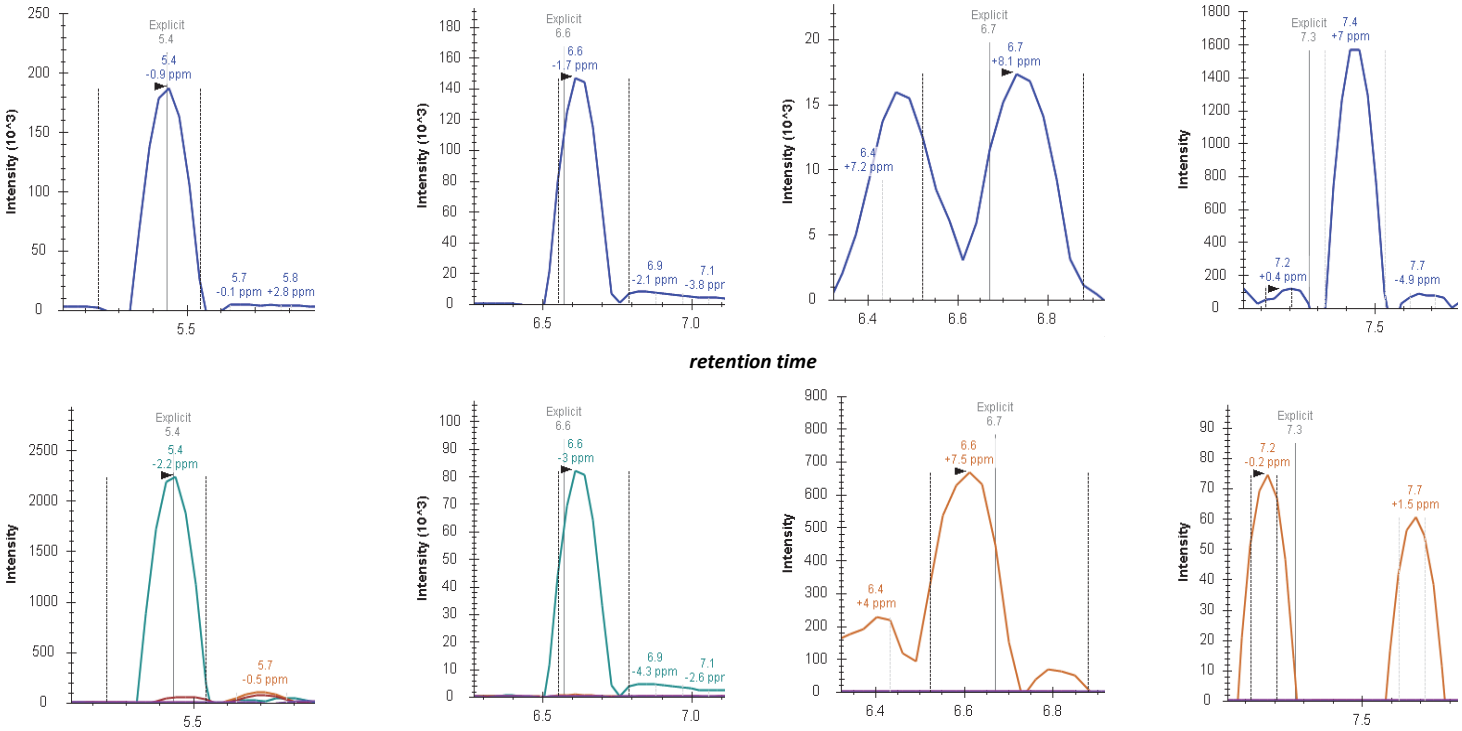


Figure S3. DIA MS^2 deconvolution results of drug standards were not satisfying for in MS-DIAL. (**A**) Diphenhydramine; (**B**) Phenylbutazone; (**C**) Ranitidine; (**D**) Ranolazine; (**E**) Finasteride.

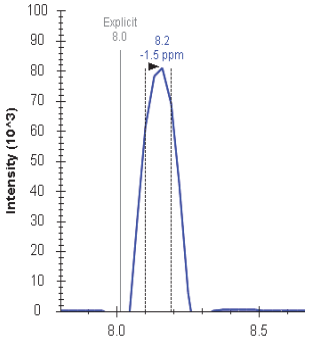
(A) PHENYLALANINE **(B) ATRAZINE-DESETHYL** **(C)TRYPTOPHAN** **(D) THEOPHYLLINE**



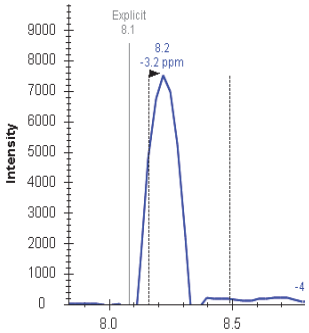
(E) CAFFEINE **(F) BOLDENONE_UNDECYLENATE** **(G) NADOLOL** **(H) DDAO**



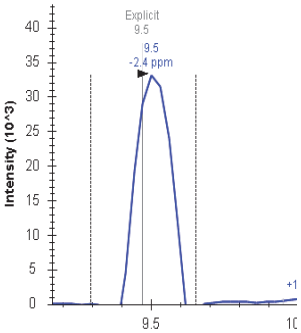
(I) PHYTOSPHINGOSINE



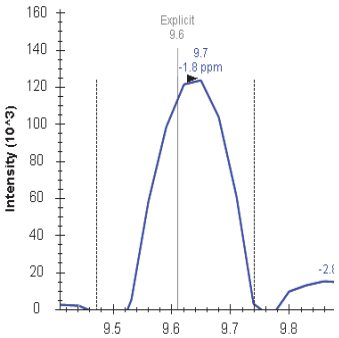
(J) N, N-DIMETHYLDODECYLAMINE N-OXIDE



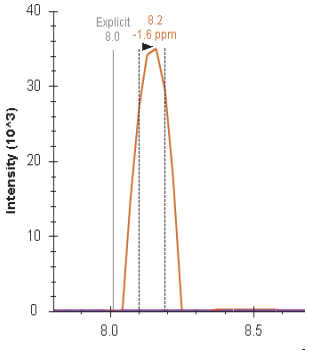
(K) PIPERINE

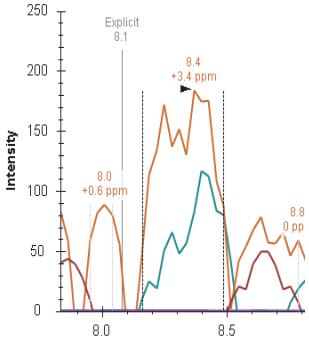


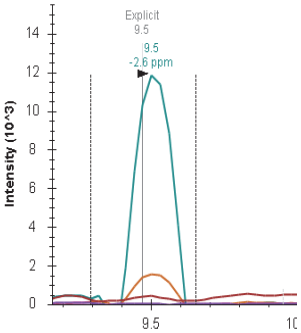
(L) NCGC00384769-01

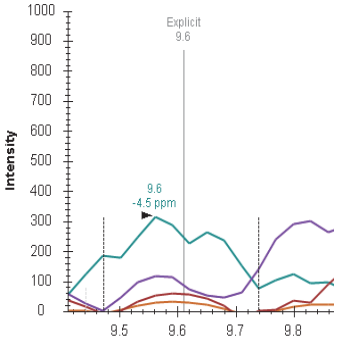


retention time

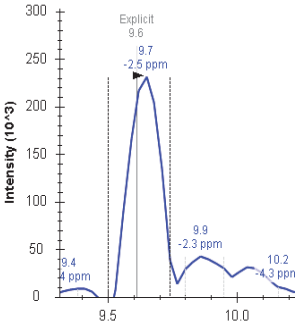




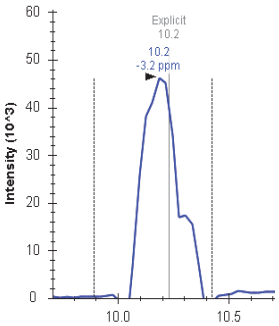




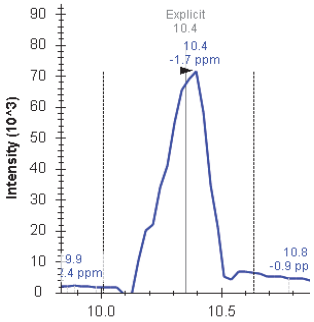
(M) NCGC00381156-01



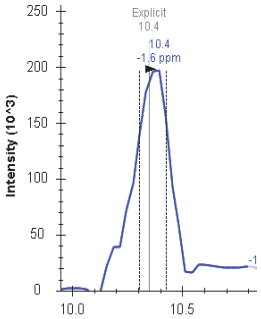
(N) GLYCOCHENODEOXYCHOLIC ACID



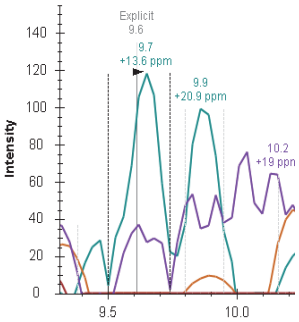
(O) DI-N-BUTYL PHTHALATE

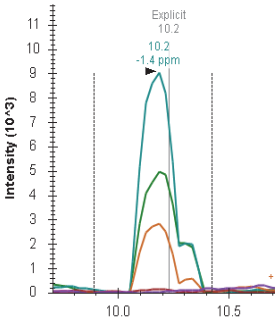


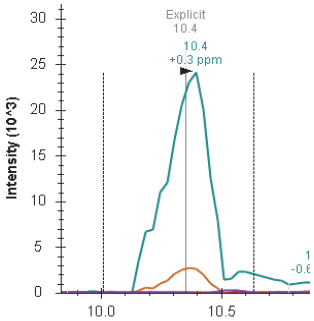
(P) NORDIHYDROGUAIARETIC ACID

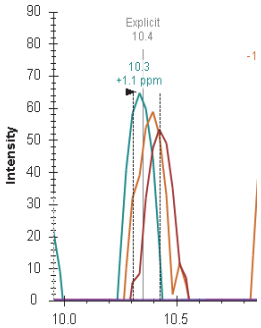


retention time









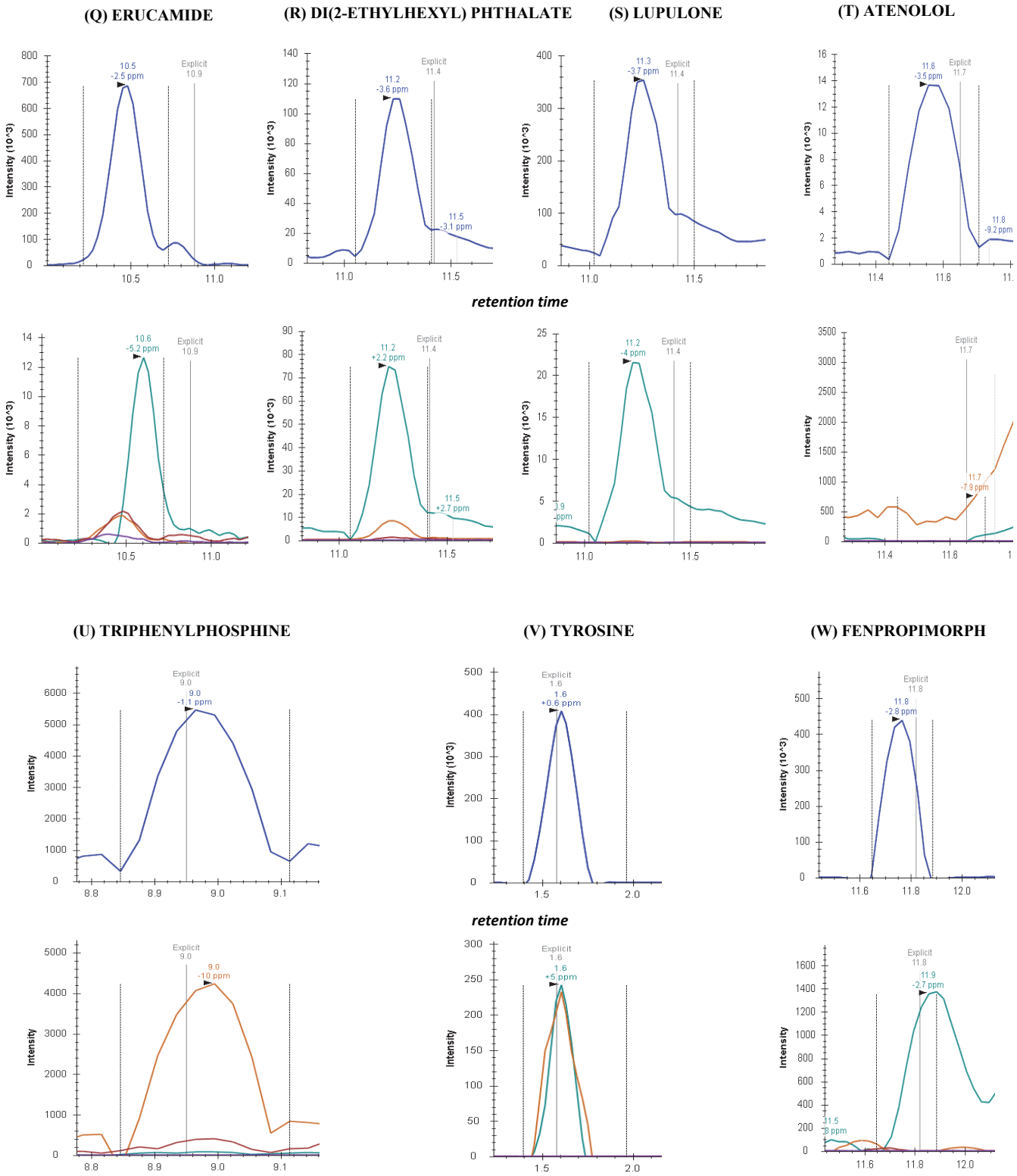


Figure S4. Identified serum metabolites deconvoluted MS1 (top) and MS2 (bottom) spectra by DIA mode in Skyline. (**A**) Phenylalanine; (**B**) Atrazine-Desethyl; (**C**) Tryptophan; (**D**) Theophylline; (**E**) Caffeine; (**F**) Boldenone-Undecylenate; (**G**) Nadolol; (**H**) DDAO; (**I**) Phytosphingosine; (**J**) N, N-Dimethyl-dodecyl-amine-N-Oxide; (**K**) Piperine; (**L**) NCGC00384769-01; (**M**) NCGC00381156-01; (**N**) Glycochenodeoxycholic Acid; (**O**) Di-N-Butyl Phthalate; (**P**) Nordihydroguaiaretic Acid; (**Q**)

Erucamide; (**R**) Di(2-Ethylhexyl) Phthalate; (**S**) Lupulone; (**T**) Atenolol; (**U**) Triphenylphosphine; (**V**) Tyrosine; (**W**) Fenpropimorph.