Electronic Supplementary Material (ESI) for Food & Function.

Supplementary data

Correlating drug-induced and drug-related ultra-high performance liquid chromatography-mass spectrometry serum metabolomic profiles discovers effective constituents of Sini decoction against myocardial ischemia in rats

Guangguo Tan[1, #], Xin Wang[2, #], Kui Liu[3] , Xin Dong[4], Wenting Liao[2,*] Hong Wu[1,*]

1. School of Pharmacy, Fourth Military Medical University, Xi'an 710032, China

2. School of Pharmacy, China Pharmaceutical University, Nanjing 210009, China

3. Student Brigade, College of Basic Medicine, Fourth Military Medical University, Xi'an 710032, China

4. School of Pharmacy, Second Military Medical University, Shanghai 200433, China

[#] These authors contributed equally to this work.

*Corresponding authors: Hong Wu, Email: wuhongfmmu@163.com, Tel: +86-29-84776823; Wenting Liao, Email:lwting84@163.com, Tel: +86-25-83271038.

Supplementary Tables and Figures

Table S1. The perturbed serum metabolites induced by ISO and the regulatory effect of SND on the metabolites

Table S2. Assessment of the protective and regulatory effect of SND based on the relative distance values

Table S3. The absorbed compounds in rat serum after oral administration of SND

Figure S1. Score plots and S-plots generated form OPLS-DA from control and MI groups at 2h and 4h. (A) score plot at 2h, (B) score plot at 4h, (C) S-plot at 2h and (D) S-plot at 4h.

Figure S2. MS/MS mass spectra and predicted structures with expected fragmentation profiles of 21 endogenous metabolite. (A) Valine, (B) Hydroxybutyrylcarnitine, (C) Tyrosine, (D) Isoleucine, (E) Indoleacetic acid, (F) Tryptophan, (G) Hippuric acid, (H) Methylhippuric acid, (I) Indole-3-propionic acid, (J) Sphingosine 1-phosphate, (K) LysoPC(20:5), (L) LysoPC(15:0), (M) LysoPC(18:2), (N) Tetradecanoylcarnitine, (O) LysoPE(20:1(11Z)/0:0), (P) LysoPC(22:5), (Q) Linoleyl carnitine, (R) LysoPC(20:2), (S) Palmitoylcarnitine, (T) Vaccenyl carnitine, and (U) Stearoylcarnitine with or without comparison to commercially available standards.

Figure S3. Base peak ion (BPI) chromatogram of SND (A) and extracted ion chromatogram (XIC) of rat serum after administration of SND (B) as analysed by UHPLC-Q-TOFMS.

Table S1. The perturbed serum metabolites induced by ISO and the regulatory effect of SND on the metabolites

No.	t_R (min)	$[M+H]^+$ m/z	Metabolites[b]	Formula	Fold change and statistic analysis [c]			
					CTR/MI(2h)	SND/MI(2h)	CTR/MI(4h)	SND/MI(4h)
1[a]	0.86	118.0864	*Valine*	$C_5H_{11}NO_2$	(*)1.60	(*)1.42	(*)1.56	(*)1.39
2	1.10	248.1491	Hydroxybutyrylcarnitine	$C_{11}H_{21}NO_5$	(*)0.35	(/)0.74	(*)045	(/)0.75
3[a]	1.20	182.0813	Tyrosine	$C_9H_{11}NO_3$	(*)1.61	(/)1.30	(*)1.45	(/)1.22
4[a]	1.27	132.1037	*Isoleucine*	$C_6H_{13}NO_2$	(*)1.67	(*)1.48	(*)1.55	(*)1.44
5[a]	3.49	176.0738	*Indoleacetic acid*	$C_{10}H_9NO_2$	(*)1.85	(*)1.50	(*)1.68	(*)1.45
6[a]	4.47	205.0990	*Tryptophan*	$C_{11}H_{12}N_2O_2$	(*)1.84	(*)1.42	(*)1.39	(*)1.40
7[a]	5.32	180.0657	Hippuric acid	$C_9H_9NO_3$	(*)2.23	(/)1.34	(*)2.03	(/)1.29
8	5.96	194.0810	Methylhippuric acid	$C_{10}H_{11}NO_3$	(*)1.58	(/)1.31	(*)1.54	(/)1.26
9	9.39	190.0839	*Indole-3-propionic acid*	$C_{11}H_{11}NO_2$	(*)2.39	(*)1.67	(*)2.02	(*)1.50
10[a]	13.42	380.2561	*Sphingosine 1-phosphate*	$C_{18}H_{38}NO_5P$	(*)1.59	(*)1.45	(*)1.52	(*)1.41
11	13.93	542.3240	*LysoPC(20:5)*	$C_{28}H_{48}NO_7P$	(*)2.17	(*)1.62	(*)1.80	(*)1.44
12	14.38	482.3242	LysoPC(15:0)	$C_{23}H_{48}NO_7P$	(*)1.68	(/)1.21	(*)1.47	(/)1.17

13[a]	14.68	520.3448	LysoPC(18:2)	$C_{26}H_{50}NO_7P$	(*)1.53	(/)1.32	(*)1.47	(/)1.22
14	14.70	372.3107	*Tetradecanoylcarnitine*	$C_{21}H_{41}NO_4$	(*)0.32	(*)0.62	(*)0.39	(*)0.64
15	14.91	508.3385	LysoPE(20:1(11Z)/0:0)	$C_{25}H_{50}NO_7P$	(*)1.69	(/)1.28	(*)1.51	(/)1.24
16	15.17	570.3553	*LysoPC(22:5)*	$C_{30}H_{52}NO_7P$	(*)1.58	(*)1.43	(*)1.59	(*)1.42
17	15.78	424.3418	*Linoleyl carnitine*	$C_{25}H_{45}NO_4$	(*)0.35	(*)0.63	(*)0.55	(*)0.67
18	16.31	548.3709	*LysoPC(20:2)*	$C_{28}H_{54}NO_7P$	(*)1.85	(*)1.50	(*)1.77	(*)1.46
19[a]	16.44	400.3420	*Palmitoylcarnitine*	$C_{23}H_{45}NO_4$	(*)0.39	(*)0.64	(*)0.48	(*)0.65
20	16.87	426.3575	Vaccenyl carnitine	$C_{25}H_{47}NO_4$	(*)0.37	(/)0.84	(*)0.42	(/)0.83
21	17.67	428.3732	*Stearoylcarnitine*	$C_{25}H_{49}NO_4$	(*)0.44	(*)0.63	(*)0.48	(*)0.69

[a] Identifications confirmed with standard compound. [b]The metabolites in italic type were significantly reversed metabolites by SND.cFold change was calculated from the normalized peak area between control (CTR) group vs myocardial ischemia (MI) group or SND-treated group vs MI group at 2h and 4h. *: $p<0.05$ (one way ANOVA). /: $p>0.05$ (one way ANOVA).

Table S2. Assessment of the protective and regulatory effect of SND based on the relative distance values

Time	Types of distance values	Distance values				Reference
		MI to Control	SND to Control (S-C)	SND to MI (S-M)	S-C/S-M	
2h	Apparent distance values	4.53	3.40	3.40	1.00	Figure 3C
	Relative distance values*	1.00	0.75	0.75		
4h	Apparent distance values	4.44	3.38	2.30	1.47	Figure 3D
	Relative distance values*	1.00	0.76	0.52		

* the normalized relative distance value was calculated by setting the value between the model and the control as 1.

Table S3. The absorbed compounds in rat serum after oral administration of SND

No.	t_R (min)	Identification	Formula	$[M+H]^+$ *m/z*			MS/MS fragment ions
				Detected	Expected	Error (ppm)	
1	2.68	Chuanfumine	$C_{22}H_{35}NO_5$	394.2601	394.2593	1.9	**376**, 358, 340, 328
2	4.19	Karakoline	$C_{22}H_{35}NO_4$	378.2657	378.2644	3.4	**360**, 342, 328, 314
3	4.38	Mesaconine	$C_{24}H_{39}NO_9$	486.2719	486.2703	3.3	**436**, 454, 468, 422, 404
4	4.75	Isotalatizidine	$C_{23}H_{37}NO_5$	408.2761	408.2750	2.7	**390**, 372, 358
5	5.06	Songorine	$C_{22}H_{31}NO_3$	358.2378	358.2382	-1.2	**342**, 324
6	5.37	Fuziline	$C_{24}H_{39}NO_7$	454.2808	454.2805	0.7	**436**, 404, 386
7	5.61	Neoline	$C_{24}H_{39}NO_6$	438.2866	438.2856	2.4	**420**, 388, 370, 356
8	6.10	Talatizamine	$C_{24}H_{39}NO5$	422.2916	422.2906	2.3	**390**, 372, 358, 340
9	6.60	Chasmanine	$C_{25}H_{41}NO6$	452.3028	452.3012	3.5	**420**, 402, 388, 356, 370
10	7.02	14-acetyltalatizamine	$C_{26}H_{41}NO_6$	464.3005	464.3012	-1.5	**414**, 432, 372, 358
11[a]	7.08	Liquiritigenin	$C_{15}H_{12}O_4$	257.0814	257.0814	0.1	**137**, 239, 229, 213
12[a]	8.02	Benzoylmesaconitine	$C_{31}H_{43}NO_{10}$	590.2986	590.2965	3.5	**540**, 558, 572, 526, 508

13[a]	8.32	Isoliquiritin	$C_{21}H_{22}O_9$	419.1349	419.1342	1.7	**257**, 239, 229, 213, 137
14[a]	8.46	Benzoylaconitne	$C_{32}H_{45}NO_{10}$	604.3125	604.3122	0.5	**554**, 586, 572, 540, 522
15[a]	8.77	Benzoylhypaconitine	$C_{31}H_{43}NO_9$	574.3017	574.3016	0.2	**542**, 524, 510, 492, 478
16	9.34	Benzoyldeoxyaconitine	$C_{32}H_{45}NO_9$	588.3157	588.3173	-2.6	**556**, 524, 538, 506, 492
17[a]	12.28	6-gingerol	$C_{17}H_{26}O_4$	295.1913	295.1909	1.2	**177**, 277, 259, 162
18	15.07	6-shogaol	$C_{17}H_{24}O_3$	277.1808	277.1804	1.6	**137**, 259, 219
19[a]	17.29	Glycyrrhetic acid	$C_{30}H_{46}O_4$	471.3462	471.3469	-1.5	**453**, 437

[a] identifications confirmed with standard compound

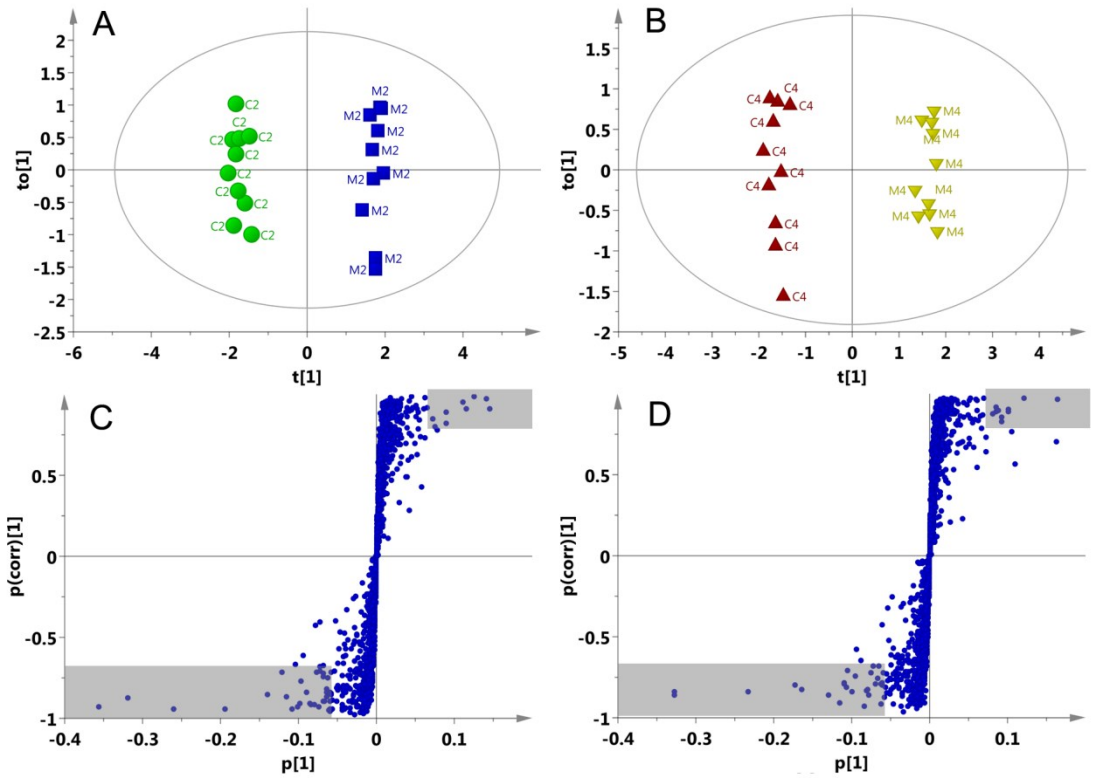

Figure S1. Score plots and S-plots generated form OPLS-DA from control and MI groups at 2h and 4h. (A) score plot at 2h, (B) score plot at 4h, (C) S-plot at 2h and (D) S-plot at 4h.

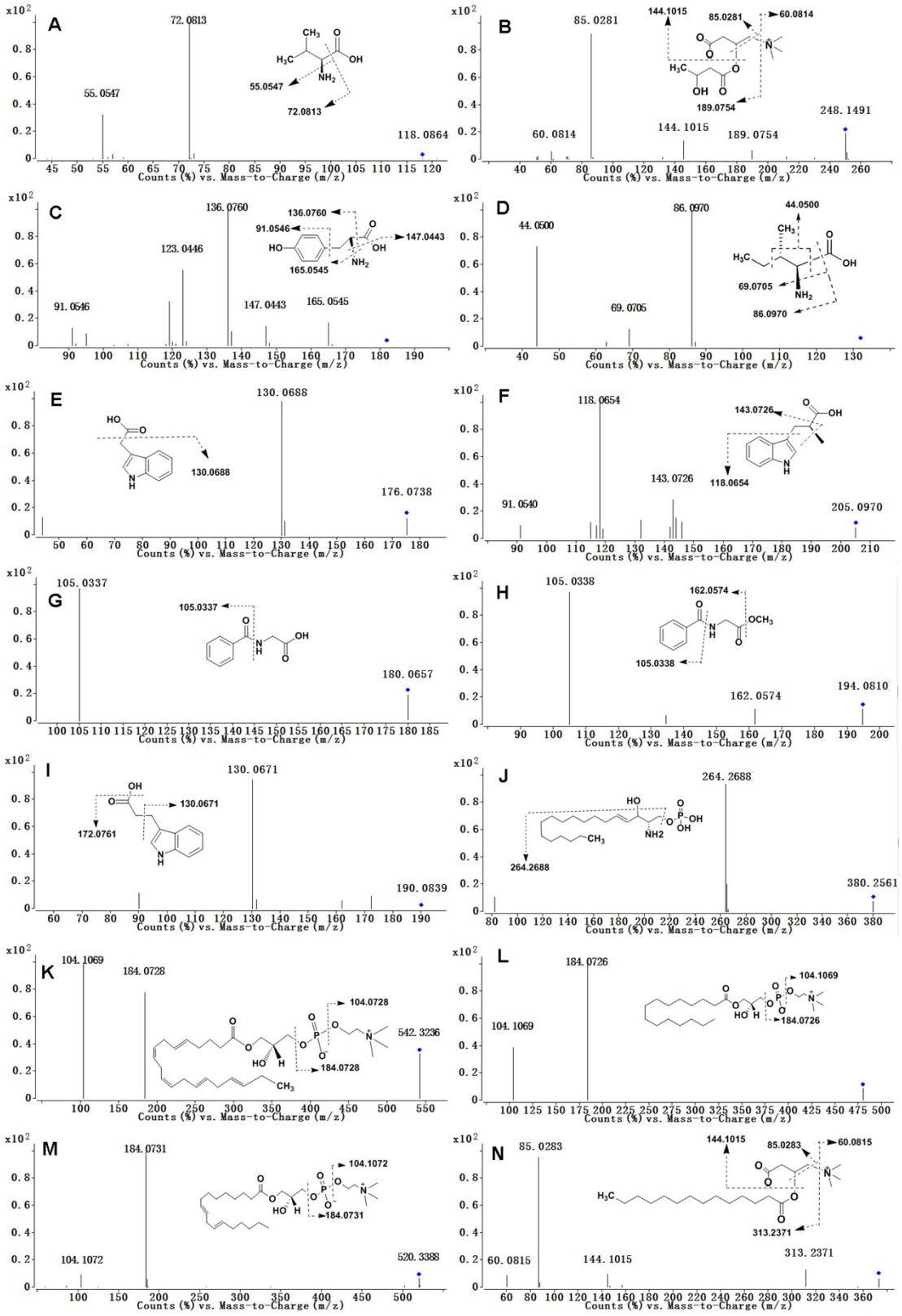

Figure S2. MS/MS mass spectra and predicted structures with expected fragmentation profiles of 21 endogenous metabolite. (A) Valine, (B) Hydroxybutyrylcarnitine, (C) Tyrosine, (D) Isoleucine, (E) Indoleacetic acid, (F) Tryptophan, (G) Hippuric acid, (H) Methylhippuric acid, (I) Indole-3-propionic

acid, (J) Sphingosine 1-phosphate, (K) LysoPC(20:5), (L) LysoPC(15:0), (M) LysoPC(18:2), (N) Tetradecanoylcarnitine, (O) LysoPE(20:1(11Z)/0:0), (P) LysoPC(22:5), (Q) Linoleyl carnitine, (R) LysoPC(20:2), (S) Palmitoylcarnitine, (T) Vaccenyl carnitine, and (U) Stearoylcarnitine with or without comparison to commercially available standards.

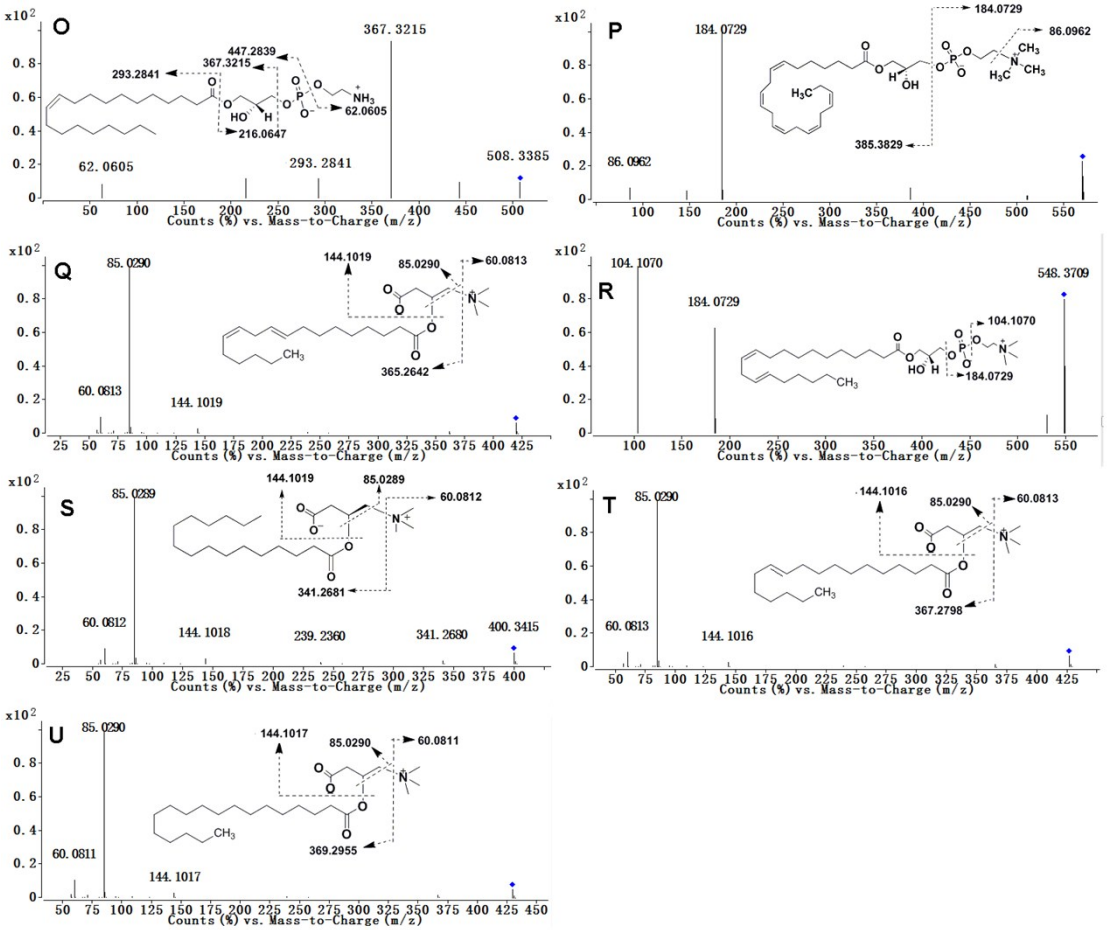

Figure S2. *Cont.*

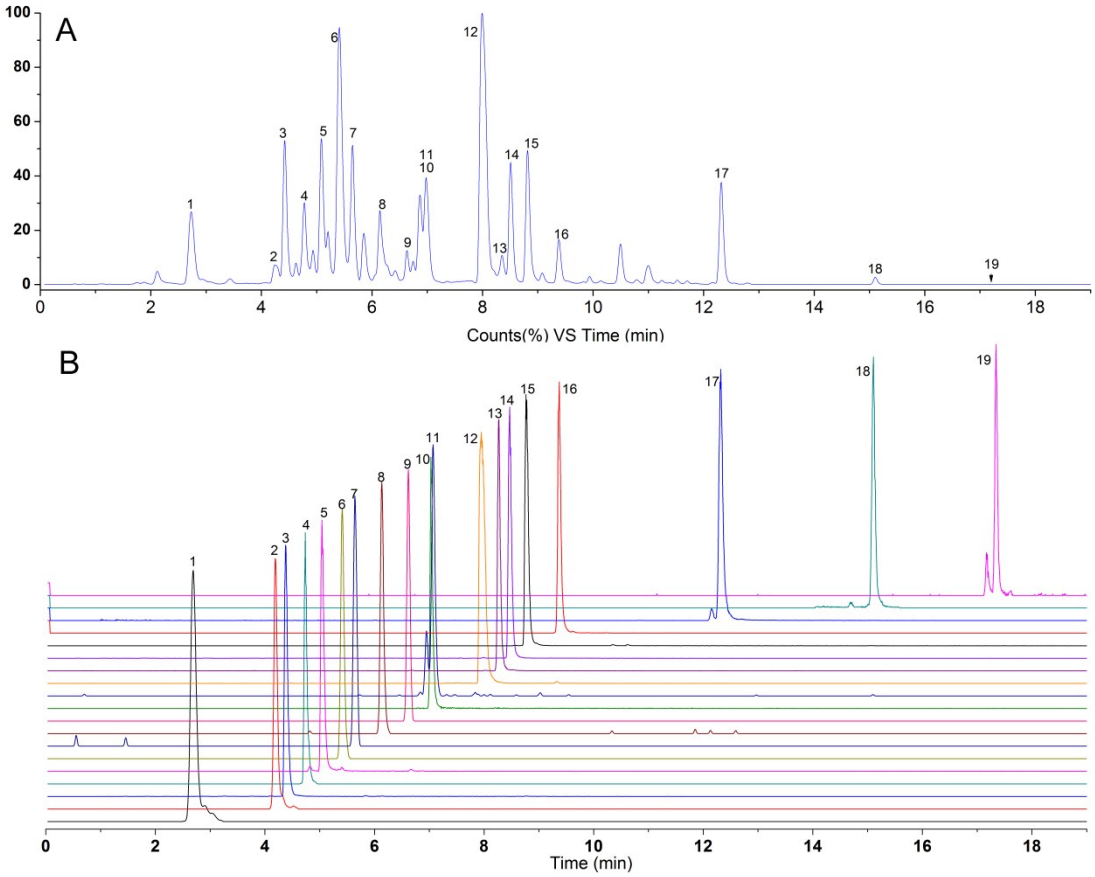

Figure S3. Base peak ion (BPI) chromatogram of SND (A) and extracted ion chromatogram (XIC) of rat serum after administration of SND (B) as analysed by UHPLC-Q-TOFMS.