Supplementary Materials

A Quantitative HILIC-MS/MS Assay of the Metabolic Response of Huh-7 Cells Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

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Figure S4: MTT, PCA, heatmap analysis of polar metabolites in Huh-7 cells infected with different concentration of 3-BrPy.

Figure S5: Concentration-dependent effects of 3-BrPy on metabolism of cultured Huh-7 cells.

Figure S6: Protein concentration determination in Huh-7 Cells using the standard BCA Protein Assay

Figure S7: PCA plot of polar metabolites in Huh-7 cells infected with 1 and 10 nM of TCDD in 4 and 24 h treatment.

Figure S8: PCA and PLS-DA plot of polar metabolites in Huh-7 cells infected with 1 and 10 nM of TCDD in 24 h treatment by ^{1}H NMR.

Figure S9: Concentration-dependent effects of TCDD on metabolism of cultured Huh-7 cells by ^{1}H NMR.

Table S1. Validation results (linearity, sensitivity and repeatability) and MRM transitions (MT) of HILIC-MS/MS method for 107 metabolites. Calibration curve: x = concentration μM, y = target peak area relative to internal standards. Linear range (LR), limit of detection (LOD) and limit of quantitation (LOQ) expressed as μM, interday (inter) and intraday (intra) repeatability of "spike-in" samples (5 μM A and 50 μM B polar metabolites mixture) were expressed as the relative standard deviation (%RSD).

No.	Category	Compound*	RT	Area RSD		Calibration curve	R^2	LOD	LOQ	LR	MT	Mode	Internal Standard
			(min)	Inter	Intra								
1	Amino Acid	3-Guanidipropionic	6.57	4.1	9.6	y = 12.121x - 3.4325	0.996	0.20	0.60	LOQ - 50	132.1 > 72.1	ES+	Glutamine (U-^{13}C, U-$^{15}N_2$)
2	Amino Acid	Phenylalanine	5.22	7.1	9.7	y = 0.0958x + 0.0013	0.992	0.03	0.30	LOQ - 20	166.0 > 120.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
3	Amino Acid	Histidine	7.04	5.6	11.8	y = 1.0416x - 0.3014	0.989	0.03	0.15	LOQ - 20	156.2 > 110.2	ES+	Isoleucine ($^{13}C_6$,^{15}N)
4	Amino Acid	Tryptophan	5.10	10.5	14.4	y = 0.0005x - 0.0067	1.000	1.00	3.00	LOQ - 200	205.1 > 188.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
5	Amino Acid	Isoleucine	5.45	2.7	4.5	y = 0.5114x + 0.0257	0.999	0.07	0.21	LOQ - 20	132.1 > 43.3	ES+	Isoleucine ($^{13}C_6$,^{15}N)
6	Amino Acid	leucine	6.53	7.1	10.7	y = 20.363x + 0.4083	0.995	0.10	0.30	LOQ - 20	132.1 > 86.0	ES+	Alanine (2,3-$^{13}C_2$)
7	Amino Acid	Asparagine	6.92	7.0	17.0	y = 0.4603x - 0.19	0.998	0.10	0.30	LOQ - 20	133.2 > 87.2	ES+	Alanine (2,3-13C_2)
8	Amino Acid	Hydroxyproline	6.49	3.9	16.1	y = 0.1758x - 0.0452	0.997	0.33	0.10	LOQ - 20	132.1 > 68.0	ES+	Glutamine (U-^{13}C, U-$^{15}N_2$)
9	Amino Acid	Serine	6.96	9.5	19.3	y = 0.4185x - 0.412	0.998	0.10	0.30	LOQ - 20	106.1 > 60.0	ES+	Alanine (2,3-13C_2)
10	Amino Acid	Glutamine	6.85	9.2	12.2	y = 2.5097x - 0.7179	0.997	0.03	0.09	LOQ - 20	147.1 > 84.01	ES+	Glutamine (U-^{13}C, U-$^{15}N_2$)
11	Amino Acid	Proline	6.19	9.8	14.5	y = 0.5755x + 0.1133	0.997	0.02	0.06	LOQ - 10	116.0 > 70.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
12	Amino Acid	Alanine	6.49	13.1	18.9	y = 1.3002x + 0.0611	0.999	0.08	0.24	LOQ - 20	90.1 > 44.0	ES+	Alanine (2,3-$^{13}C_2$)
13	Amino Acid	Arginine	9.09	8.1	14.0	y = 4.1759x - 1.7646	0.994	0.05	0.15	LOQ - 20	175.2 > 70.2	ES+	Isoleucine ($^{13}C_6$,^{15}N)
14	Amino Acid	Threonine/Homoserine	6.69	9.4	13.1	y = 0.0971x + 0.0668	0.993	0.10	0.30	LOQ - 20	120.1 > 74.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)

15	Amino Acid	Ornithine	4.83	9.9	12.1	y = 0.3646x + 0.0732	0.995	0.15	0.45	LOQ - 20	133.1>70.1	ES+	Alanine (2,3-$^{13}C_2$)
16	Amino Acid	Tyrosine	5.79	8.4	10.8	y = 0.0557x - 0.0156	0.995	0.30	1.00	LOQ - 20	182.0 > 165.0	ES+	Aspartic acid (U-$^{13}C_4$,^{15}N)
17	Amino Acid	Lysine	9.56	7.2	11.8	y = 0.0909x - 0.0267	0.996	0.10	0.30	LOQ - 20	147.2 > 84.2	ES+	Isoleucine ($^{13}C_6$,^{15}N)
18	Amino Acid	Glycine	6.68	12.6	29.2	y = 0.0221x - 0.0213	0.994	1.00	3.00	LOQ - 200	76.1 > 48.0	ES+	Alanine (2,3-$^{13}C_2$)
19	Amino Acid	Aspartic acid	7.65	5.2	9.2	y = 0.0096x - 0.0033	0.990	0.10	0.30	LOQ - 20	134.1 > 88.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
20	Amino Acid	Methionine	5.61	8.0	11.4	y = 0.3657x - 0.0297	0.998	0.10	0.30	LOQ - 20	150.2 > 104.2	ES+	Aspartic acid (U-$^{13}C_4$,^{15}N)
21	Amino Acid	Pyroglutamic acid	6.80	6.8	9.8	y = 1.8862x - 0.9517	0.998	0.01	0.03	LOQ - 20	130.1 > 84.0	ES+	Alanine (2,3-13C_2)
22	Amino Acid	Theanine	5.82	4.2	9.4	y = 4.1865x - 1.1609	0.997	0.02	0.06	LOQ - 20	175.2 > 46.1	ES+	Alanine (2,3-13C_2)
23	Amino Acid	Valine	5.88	4.1	8.7	y = 0.1562x + 0.021	0.994	0.10	0.30	LOQ - 20	118.1 > 72.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
24	Amino Acid derivative	Taurine	6.11	8.4	15.8	y = 0.2052x - 0.2205	0.992	0.20	0.60	LOQ - 20	126.1 > 108.0	ES+	Alanine (2,3-13C_2)
25	Amino Acid derivative	GSSG	7.62	8.6	14.3	y = 0.0482x - 0.0059	0.994	0.15	0.45	LOQ - 20	613.1 > 355.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
26	Amino Acid derivative	GSH	7.62	10.6	26.4	y = 0.0039x - 0.0076	0.992	0.10	0.30	LOQ - 200	308.2 > 179.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
27	Coenzyme	Acetyl CoA	8.12	6.4	12.0	y = 0.1422x - 0.0073	1.000	0.01	0.03	LOQ - 20	810.2 > 303.2	ES+	Isoleucine ($^{13}C_6$,^{15}N)
28	Coenzyme	$NADP^+$	10.23	5.6	11.6	y = 0.9124x + 0.0148	0.997	0.01	0.03	LOQ - 20	744.1 > 136.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
29	Coenzyme	NADPH	9.59	10.9	14.4	y = 1E-04x - 0.0009	0.992	2.00	6.00	LOQ - 200	744.0 > 426.1	ES-	Succinate (^{13}C)
30	Coenzyme	NAD^+	8.30	6.4	9.0	y = 0.3097x - 0.091	0.992	0.01	0.03	LOQ - 20	664.2 > 136.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
31	Coenzyme	NADH	7.55	8.6	14.7	y = 0.0096x - 0.0026	0.995	0.50	1.50	LOQ - 20	666.1 > 649.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
32	Coenzyme	FAD	7.39	7.8	12.1	y = 0.1071x - 0.0069	0.996	0.10	0.30	LOQ - 200	786.2 > 136.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
33	Coenzyme	Palmitoyl CoA	4.85	10.8	19.9	y = 0.0686x - 0.0001	0.998	0.03	0.10	LOQ - 20	1006.5 >499.4	ES+	Palmitoyl-CoA ($^{13}C_{16}$)
34	Nucleotide	cAMP	5.71	6.9	10.1	= 0.1982x + 0.0025	0.995	0.07	0.20	LOQ - 20	330.2 > 136.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)

35	Nucleotide	dUMP	8.03	6.8	14.3	y = 0.0019x + 0.0158	0.997	0.30	1.00	LOQ - 20	309.1 > 81.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
36	Nucleotide	dCMP	8.62	7.6	12.0	y = 0.0151x - 0.0296	0.996	0.10	0.30	LOQ - 20	308.2 > 112.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
37	Nucleotide	cGMP	6.16	8.2	13.5	y = 0.073x - 5E-05	0.993	0.05	0.15	LOQ - 20	346.1 > 152.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
38	Nucleotide	dGMP	8.77	6.7	11.0	y = 0.0458x + 0.0214	0.993	0.03	1.00	LOQ - 20	348.1 > 152.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
39	Nucleotide	ADP	9.20	5.1	12.7	y = 0.1282x - 0.0088	0.998	0.02	0.06	LOQ - 20	428.1 > 136.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
40	Nucleotide	GDP	10.07	4.8	9.4	y = 0.0599x - 0.0026	0.999	0.10	0.30	LOQ - 20	444.1 > 152.0	ES+	AMP ($13C_{10}$,$^{15}N_6$)
41	Nucleotide	UDP	9.63	7.3	12.4	y = 0.0694x - 0.0236	0.997	0.10	0.30	LOQ - 20	405.1 > 97.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
42	Nucleotide	ATP	10.23	3.1	7.1	y = 0.0703x - 0.0034	0.994	0.02	0.06	LOQ - 20	508.1 > 136.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
43	Nucleotide	CTP	10.35	8.1	10.1	y = 0.0789x - 0.0274	0.993	0.15	0.45	LOQ - 20	484.0 > 112.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
44	Nucleotide	GTP	10.42	4.7	9.8	y = 0.0525x - 0.0031	0.998	0.20	0.60	LOQ - 20	524.0 > 152.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
45	Nucleotide	TMP	7.79	14.0	14.3	y = 0.048x + 0.0051	0.996	0.07	0.20	LOQ - 20	323.1 > 81.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
46	Nucleotide	UMP	8.66	3.7	6.4	y = 0.0855x - 0.0091	0.997	0.05	0.15	LOQ - 20	325.2 > 97.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
47	Nucleotide	CMP	9.13	3.7	11.2	y = 0.177x - 0.0948	0.990	0.07	0.20	LOQ - 20	324.1 > 112.04	ES+	Isoleucine ($^{13}C_6$,^{15}N)
48	Nucleotide	GMP	8.85	5.4	14.5	y = 0.0007x - 0.0101	1.000	2.00	6.00	LOQ - 20	362.1 > 211.0	ES-	AMP ($^{13}C_{10}$,$^{15}N_5$)
49	Nucleotide	AMP	8.22	2.5	9.4	y = 0.1643x + 0.0217	0.998	0.02	0.06	LOQ - 20	348.2 > 136.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
50	Nucleotide	XMP	9.23	6.1	14.6	y = 0.0048x + 0.0039	0.991	0.15	0.45	LOQ - 20	365.1 > 153.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
51	Nucleotide	IMP	8.81	9.6	10.5	y = 0.0727x - 0.0061	0.999	0.03	0.09	LOQ - 20	349.1 > 137.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
52	Nucleotide	RMP	7.55	9.1	12.3	y = 0.0423x + 0.0037	0.998	0.01	0.03	LOQ - 20	457.2 > 439.1	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
53	Nucleobase	Creatinine	4.83	5.0	13.4	y = 1.8262x + 0.0374	1.000	0.03	0.10	LOQ - 20	114.1 > 114.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
54	Nucleobase	Inosine	5.37	5.4	14.3	y = 0.0997x - 0.0275	0.995	0.10	0.30	LOQ - 20	269.1 > 137.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)

55	Nucleobase	Guanine	5.58	10.6	16.0	y = 0.3605x + 0.18	0.998	0.33	1.00	LOQ - 20	152.1 > 135.0	ES+	Aspartic acid (U-$^{13}C_4$,^{15}N)
56	Nucleobase	Uridine	4.91	14.6	17.2	y = 0.0252x - 0.0664	0.998	0.30	1.00	LOQ - 20	245.2 > 113.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
57	Nucleobase	Xanthine	5.47	4.8	7.8	y = 0.1449x + 0.1043	0.992	0.39	1.20	LOQ - 25	151.0 > 108.0	ES-	Uracil (1,3-$^{15}N_2$)
58	Nucleobase	Thymine	2.62	8.5	13.2	y = 0.0011x - 0.0018	0.997	0.13	0.39	LOQ - 20	127.1 > 54.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
59	Nucleobase	Uracil	3.04	4.7	8.1	y = 0.0309x - 0.046	0.998	0.10	0.30	LOQ - 200	111.1 > 42.0	ES-	Uracil (1,3-$^{15}N_2$)
60	Nucleobase	Hypoxanthine	5.37	7.5	15.0	y = 0.0162x - 0.0143	0.993	0.02	0.60	LOQ - 20	137.1 > 119.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
61	Nucleobase	Adenine	4.50	4.3	6.0	y = 12.38x - 4.0948	0.998	0.01	0.03	LOQ - 20	136.1 > 119.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
62	Nucleobase	Guanosine	5.58	7.3	9.6	y = 0.1567x - 0.0122	0.995	0.07	0.20	LOQ - 20	284.2 > 152.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
63	Nucleobase	Cytidine	5.52	10.1	14.7	y = 0.2119x - 0.0226	0.999	0.03	0.10	LOQ - 20	244.1 > 112.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
64	Nucleobase	Cytosine	5.06	6.5	22.3	y = 0.1207x - 0.1394	0.992	0.70	2.10	LOQ - 20	112.1 > 69.0	ES+	Alanine (2,3-$^{13}C_2$)
65	Organic Acid	Itaconic acid	6.79	5.1	9.9	y = 0.019x + 0.1103	0.994	0.50	1.50	LOQ - 100	129.0 > 85.0	ES-	Succinate (1,4-$^{13}C_2$)
66	Organic Acid	α-ketoglutaric acid	5.15	6.0	7.5	y = 0.0338x - 0.0083	0.999	0.33	0.10	LOQ - 20	147.1 > 119.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
67	Organic Acid	Fumarate	6.76	6.6	9.4	y = 0.0047x + 0.0037	0.998	0.39	1.20	LOQ - 50	115.0 > 70.0	ES-	Succinate (1,4-$^{13}C_2$)
68	Organic Acid	Hippuric acid	4.82	4.5	5.0	y = 0.0308x + 0.0308	0.996	0.25	0.75	LOQ - 200	178.1 > 134.0	ES-	Succinate (1,4-$^{13}C_2$)
69	Organic Acid	Malic acid	7.34	2.5	3.3	y = 0.1871x + 0.2564	0.995	0.25	0.75	LOQ - 200	133.0 > 115.0	ES-	Malic acid ($^{13}C_4$)
70	Organic Acid	Oritic acid	5.53	4.1	4.8	y = 0.1577x + 0.1494	0.990	0.08	0.24	LOQ - 25	155.1 > 111.0	ES-	Malic acid ($^{13}C_4$)
71	Organic Acid	Lactate	5.68	2.2	8.0	y = 0.0235x - 0.021	0.999	0.20	0.60	LOQ - 200	89.0 > 89.5	ES-	Succinate (1,4-$^{13}C_2$)
72	Organic Acid	Aconitic acid	8.24	7.7	14.5	y = 0.063x - 0.2488	0.997	1.50	4.50	LOQ - 200	173.1 > 129.0	ES-	Malic acid ($^{13}C_4$)
73	Organic Acid	Shikimic acid	6.54	6.9	12.3	y = 0.0035x + 0.0059	0.998	3.00	9.00	LOQ - 200	173.0 > 93.0	ES-	Succinate (1,4-$^{13}C_2$)
74	Organic Acid	Succinate	7.06	2.1	4.7	y = 0.0265x + 0.1029	0.996	0.20	0.60	LOQ - 200	117.1 > 73.1	ES-	Succinate (1,4-$^{13}C_2$)

75	Organic Acid	Pyruvate	4.90	12.7	15.7	y = 0.0065x - 0.0022	0.994	0.39	1.20	LOQ - 200	87.0 > 43.0	ES-	Succinate (1,4-$^{13}C_2$)
76	Organic Acid	Glyceric acid	6.32	10.0	14.6	y = 0.0129x + 0.0614	0.991	0.20	0.60	LOQ - 200	105.0 > 75.0	ES-	Malic acid ($^{13}C_4$)
77	Organic Acid	Citrate/Isocitrate	8.84	4.1	12.3	y = 0.0923x - 1.9041	0.999	1.56	4.68	LOQ - 200	191.1 > 111.0	ES-	Succinate (1,4-$^{13}C_2$)
78	Phosphorylated compound	DHAP	7.96	5.2	9.6	y = 0.0066x - 0.0258	0.998	0.10	0.30	LOQ - 200	169.0 > 79.0	ES-	Malic acid ($^{13}C_4$)
79	Phosphorylated compound	Phosphocreatine	8.69	8.1	23.8	y = 0.0004x + 0.0366	0.996	0.30	1.50	LOQ - 200	212.1 > 90.0	ES+	Aspartic acid (U-$^{13}C_4$,^{15}N)
80	Phosphorylated compound	β-glyceric phosphate	7.62	5.4	12.6	y = 0.0758x - 0.0822	0.997	0.20	0.60	LOQ - 200	173.1 > 99.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
81	Phosphorylated compound	α-glyceric phosphate	7.95	11.8	18.1	y = 0.0452x - 0.1338	0.993	1.0	3.0	LOQ - 200	173.1 > 99.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
82	Phosphorylated compound	KDPG	8.91	5.2	9.2	y = 0.0081x - 0.1144	0.999	3.30	10.00	LOQ - 200	257.1 > 97.0	ES-	Succinate (1,4-$^{13}C_2$)
83	Phosphorylated compound	GA3P	8.84	5.1	9.7	y = 0.0055x - 0.0061	0.992	0.50	1.50	LOQ - 100	171.1 > 99.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
84	Phosphorylated compound	2-PGA/3-PGA	6.01	3.7	10.2	y = 0.0089x + 1.0084	0.998	1.00	3.00	LOQ - 200	187.1 > 105.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
85	Phosphorylated compound	Phosphoenolpyruvate	8.69	6.3	14.8	y = 0.0092x - 0.0236	0.996	1.50	4.50	LOQ - 25	169.0 > 151.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
86	Phosphorylated compound	6-Phosphogluconate	9.71	5.4	6.0	y = 0.0082x - 0.123	0.993	1.56	4.68	LOQ - 200	275.0 > 97.0	ES-	Succinate (1,4-$^{13}C_2$)
87	Phosphorylated compound	E4P	8.88	10.5	14.1	y = 0.0006x + 0.0011	0.992	7.00	21.00	LOQ - 200	201.0 > 103.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
88	Phosphorylated sugar	R5P	8.45	4.6	7.0	y = 0.0096x - 0.0511	0.995	2.00	6.00	LOQ - 200	229.1 > 97.0	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
89	Phosphorylated sugar	Ru5P	8.43	10.5	14.3	y = 0.0128x - 0.0035	0.992	2.00	6.00	LOQ - 200	229.1 > 97.0	ES-	AMP ($^{13}C_{10}$,$^{15}N_5$)
90	Phosphorylated sugar	F1,6BP	10.44	9.8	11.7	y = 0.0044x - 0.0229	0.990	1.00	3.00	LOQ - 200	341.1 > 109.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
91	Phosphorylated sugar	R1,5BP	10.40	12.5	14.3	y = 0.2172x + 0.0327	0.993	0.20	0.60	LOQ - 200	311.1 > 99.2	ES+	Isoleucine ($^{13}C_6$,^{15}N)
92	Phosphorylated sugar	G6P	9.20	3.3	9.1	y = 0.0315x - 0.2521	0.991	0.78	2.34	LOQ - 200	259.1 > 97.0	ES-	Uracil (1,3-$^{15}N_2$)
93	Phosphorylated sugar	F6P	8.63	2.1	3.4	y = 0.0249x - 0.1903	0.996	0.78	2.34	LOQ - 200	259.0 > 97.0	ES-	Uracil (1,3-$^{15}N_2$)
94	Phosphorylated sugar	S7P	8.84	10.5	14.3	y = 0.0074x + 0.0035	0.992	0.39	1.20	LOQ - 200	313.1 > 295.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)

95	Sugar	Mannitol	6.15	5.0	7.5	y = 0.0054x + 0.0043	1.000	0.13	0.39	LOQ - 200	181.2 > 89.0	ES-	Succinate (1,4-$^{13}C_2$)
96	Sugar	Ribose	5.18	9.6	16.3	y = 0.0002x - 0.0029	0.994	0.30	1.00	LOQ - 200	149.1 > 89.0	ES-	Succinate (1,4-$^{13}C_2$)
97	Vitamin	Folic acid	8.52	4.8	7.5	y = 0.007x - 0.0031	0.999	0.33	1.00	LOQ - 200	440.2 > 311.2	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
98	Vitamin	Pyridoxine	3.50	7.0	11.5	y = 0.1982x - 0.6633	0.998	0.15	0.45	LOQ - 200	170.2 > 152.0	ES+	Isoleucine ($^{13}C_6$,^{15}N)
99	Vitamin	Pantothenate	5.76	5.8	8.2	y = 0.0089x - 0.0171	0.995	0.78	2.34	LOQ - 50	220.1 > 90.1	ES+	Isoleucine ($^{13}C_6$,^{15}N)
100	Vitamin	Thiamine	5.52	17.2	19.0	y = 0.3104x - 0.0619	0.999	0.10	0.30	LOQ - 20	267.2 > 122.6	ES+	Alanine (2,3-$^{13}C_2$)
101	Vitamin	Riboflavin	4.85	5.1	10.2	y = 0.084x + 0.0115	0.998	0.02	0.06	LOQ - 20	377.2 > 243.2	ES+	AMP ($^{13}C_{10}$,$^{15}N_5$)
102	Vitamin	Choline	5.30	12.2	19.8	y = 17.15x - 0.3093	0.998	0.03	0.10	LOQ - 20	104.1 > 60.1	ES+	Alanine (2,3-$^{13}C_2$)
103	Vitamin	Vit B_{12}	6.44	9.6	30.6	y = 0.0085x - 0.0191	0.995	1.00	3.00	LOQ - 20	1355.6 > 1209.6	ES+	Alanine (2,3-$^{13}C_2$)
104	Vitamin	Niacinamide	2.47	6.6	12.2	y = 0.9428x + 0.2706	0.998	0.01	0.03	LOQ - 20	123.0 > 80.6	ES+	Isoleucine ($^{13}C_6$,^{15}N)

* **GSSG**: Glutathione oxidized, **GSH**: Glutathione reduced, **NADP$^+$**: *β*-Nicotinamide adenine dinucleotide phosphate oxidized, **NADPH**: *β*-Nicotinamide adenine dinucleotide phosphate reduced, **NAD$^+$**: *β*-Nicotinamide adenine dinucleotide, **NADH**: *β*-Nicotinamide adenine dinucleotide reduced, **FAD**: Flavin adenine dinucleotide, **cAMP**: Cyclic adenosine monophosphate, **dUMP**: Deoxyuridine monophosphate, **dCMP**: Deoxycytidine monophosphate, **cGMP**: Cyclic guanosine monophosphate, **dGMP**: Deoxyguanosine monophosphate, **ADP**: Adenosine 5′-diphosphate, **GDP**: Guanosine 5′-diphosphate, **UDP**: Uridine 5′-diphosphate, **ATP**: Adenosine 5′-triphosphate, **CTP**: Cytidine 5′-triphosphate, **GTP**: Guanosine 5′-triphosphate, **TMP**: Thymidine 5′-monophosphate, **UMP**: Uridine 5′-monophosphate, **CMP**: Cytidine 5′-monophosphate, **GMP**: Guanosine 5′-monophosphate, **AMP**: Adenosine 5′-monophosphate, **XMP**: Xanthosine monophosphate, **IMP**: Inosine 5′-monophosphate, **RMP**: Riboflavin 5′-monophosphate, **DHAP**: Dihydroxyacetone phosphate, **KDPG**: 3-Deoxy-2-keto-6-phosphogluconic, **GA3P**: Glyceraldehyde 3-phosphate, **2-PGA/3-PGA**: 2-Phosphoglyceric acid/3-Phosphoglyceric acid, **E4P**: D-Erythrose 4-phosphate, **R5P**:

Ribose 5-phosphate, **Ru5P**: Ribulose-5-phosphate, **F1,6BP**: Fructose 1,6-bisphosphate, **R1,5BP**: Ribulose-1,5-bisphosphate, **G6P**: Glucose 6-phosphate, **F6P**: D-Fructose 6-phosphate, **S7P**: Sedoheptulose 7-phosphate.

Table **S2**. Retention time (RT), MRM transition (MT) and acquisition mode of ten isotope internal standards in HILIC-MS/MS method.

No.	Category	Compound	RT(min)	MT	Mode
1	Amino Acid	Glutamine (U-$^{13}C_5$, U-$^{15}N_2$)	6.85	154.1 > 89.1	ES+
2	Amino Acid	Isoleucine ($^{13}C_6$,^{15}N)	5.55	139.2 > 92.0	ES+
3	Amino Acid	Alanine (2,3-$^{13}C_2$)	6.49	92.1 > 46.1	ES+
4	Amino Acid	Aspartic acid (U-$^{13}C4$,^{15}N)	7.69	139.2 > 92.1	ES+
5	Nucleotide	AMP ($^{13}C_{10}$,$^{15}N_5$)	8.22	363.1 > 146.1	ES+
6	Organic acid	Malic acid ($^{13}C_4$)	7.35	137.1 > 119.0	ES-
7	Organic acid	Succinate (1,4-$^{13}C_2$)	7.06	119.0 > 74.0	ES-
8	Organic acid	Pyruvate (^{13}C)	4.93	88.0 > 44.0	ES-
9	Coenzyme	Palmitoyl-CoA ($^{13}C_{16}$)	4.82	1022.5 > 515.5	ES+
10	Nucleobase	Uracil (1,3-$^{15}N_2$)	3.02	113.0 > 43.0	ES-

Table **S3**. Details of LC gradients in optimization of HILIC condition.

Gradient A			Gradient B			Gradient C		
Time (min)	Flow (mL/min)	Solvent B (%)	Time (min)	Flow (mL/min)	Solvent B (%)	Time (min)	Flow (mL/min)	Solvent B (%)
0.0	0.15	100	0.0	0.15	100	0.0	0.15	100
0.2	0.15	100	1.0	0.20	100	0.5	0.15	100
10.0	0.25	30	6.0	0.20	30	1.0	0.15	80
15.0	0.30	30	16.0	0.20	30	8.0	0.30	70
16.0	0.30	2	17.0	0.30	2	10.0	0.35	30
18.0	0.30	2	23.0	0.30	2	11.0	0.35	0
19.0	0.30	2	24.0	0.30	100	14.0	0.35	0
25.0	0.40	100	25.0	0.30	100	14.1	0.40	100
30.0	0.40	100	26.0	0.40	100	23.5	0.40	100
			30.0	0.40	100	23.7	0.15	100
						25.0	0.15	100

Table **S4**. Stock and working standard Solutions for HILIC-UPLC-MS/MS method. Metabolites were classified in two different concentration groups (A and B) according to the responds. Stock solutions of analytes should be prepared in concentration of 20 μM for group A and 200 μM for group B in methanol (MeOH)/water, 1:1 (v/v), calibration standards (11 standards) should be prepared by serial dilution of the highest concentration standard.

No.	Category	Compound	Group	No.	Category	Compound	Group
1	Amino Acid	3-Guanidipropionic	B	53	Nucleobase	Uracil	B
2	Amino Acid	Phenylalanine	A	54	Nucleobase	Hypoxanthine	A
3	Amino Acid	Histidine	A	55	Nucleobase	Adenine	A
4	Amino Acid	Tryptophan	B	56	Nucleobase	Guanosine	A
5	Amino Acid	Isoleucine	A	57	Nucleobase	Cytidine	A
6	Amino Acid	leucine	A	58	Nucleobase	Cytosine	A
7	Amino Acid	Asparagine	A	59	Nucleobase	Creatinine	A
8	Amino Acid	Hydroxyproline	A	60	Nucleobase	Inosine	A
9	Amino Acid	Serine	A	61	Nucleobase	Guanine	A
10	Amino Acid	Glutamine	A	62	Nucleobase	Uridine	A
11	Amino Acid	Proline	A	63	Nucleobase	Xanthine	B
12	Amino Acid	Alanine	A	64	Nucleobase	Thymine	A
13	Amino Acid	Arginine	A	65	Organic Acid	Itaconic acid	B
14	Amino Acid	Threonine/Homoserine	A	66	Organic Acid	α-ketoglutaric acid	A
15	Amino Acid	Ornithine	A	67	Organic Acid	Fumarate	B
16	Amino Acid	Tyrosine	A	68	Organic Acid	Hippuric acid	B
17	Amino Acid	Lysine	A	69	Organic Acid	Malic acid	B
18	Amino Acid	Glycine	B	70	Organic Acid	Oritic acid	B
19	Amino Acid	Aspartic acid	A	71	Organic Acid	Lactate	B
20	Amino Acid	Methionine	A	72	Organic Acid	Aconitic acid	B
21	Amino Acid	Pyroglutamic acid	A	73	Organic Acid	Shikimic acid	B
22	Amino Acid	Theanine	A	74	Organic Acid	Succinate	B

23	Amino Acid	Valine	A
24	Amino Acid derivative	Taurine	A
25	Amino Acid derivative	GSSG	A
26	Amino Acid derivative	GSH	B
27	Coenzyme	Acetyl CoA	A
28	Coenzyme	$NADP^+$	A
29	Coenzyme	NADPH	B
30	Coenzyme	NAD^+	A
31	Coenzyme	NADH	A
32	Coenzyme	FAD	B
33	Coenzyme	Palmitoyl CoA	A
34	Nucleotide	cAMP	A
35	Nucleotide	dUMP	A
36	Nucleotide	dCMP	A
37	Nucleotide	cGMP	A
75	Organic Acid	Pyruvate	B
76	Organic Acid	Glyceric acid	B
77	Organic Acid	Citrate/Isocitrate	B
78	Phosphorylated compound	DHAP	B
79	Phosphorylated compound	Phosphocreatine	B
80	Phosphorylated compound	β-glyceric phosphate	B
81	Phosphorylated compound	α-glyceric phosphate	B
82	Phosphorylated compound	KDPG	B
83	Phosphorylated compound	GA3P	B
84	Phosphorylated compound	2-PGA/3-PGA	B
85	Phosphorylated compound	Phosphoenolpyruvate	B
86	Phosphorylated compound	6-Phosphogluconate	B
87	Phosphorylated compound	E4P	B
88	Phosphorylated sugar	R5P	B
89	Phosphorylated sugar	Ru5P	B

38	Nucleotide	dGMP	A	90	Phosphorylated sugar	F1,6BP	B
39	Nucleotide	ADP	A	91	Phosphorylated sugar	R1,5BP	B
40	Nucleotide	GDP	A	92	Phosphorylated sugar	G6P	B
41	Nucleotide	UDP	A	93	Phosphorylated sugar	F6P	B
42	Nucleotide	ATP	A	94	Phosphorylated sugar	S7P	B
43	Nucleotide	CTP	A	95	Sugar	Mannitol	B
44	Nucleotide	GTP	A	96	Sugar	Ribose	B
45	Nucleotide	TMP	A	97	Vitamin	Folic acid	B
46	Nucleotide	UMP	A	98	Vitamin	Pyridoxine	B
47	Nucleotide	CMP	A	99	Vitamin	Pantothenate	B
48	Nucleotide	GMP	A	100	Vitamin	Thiamine	A
49	Nucleotide	AMP	A	101	Vitamin	Riboflavin	A
50	Nucleotide	XMP	A	102	Vitamin	Choline	A
51	Nucleotide	IMP	A	103	Vitamin	Vit B_{12}	A
52	Nucleotide	RMP	A	104	Vitamin	Niacinamide	A

Table **S5**. Quantitation of polar metabolites in each sample treated by 3-BrPy with different concentration.

Value are expressed as nmol per 2.50 E+06 cells (N = 6).

No.	Class	compound	Quantitation (nmol)											
			Control		5 μM 3-BrPy		15 μM 3-BrPy		50 μM 3-BrPy		100 μM 3-BrPy		Positive control	
			mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
1	Amino Acid	Arginine	0.38	0.07	0.37	0.07	0.48	0.11	0.44	0.13	0.28	0.04	0.41	0.05
2	Amino Acid	Asparagine	0.14	0.02	0.13	0.01	0.14	0.02	0.12	0.01	0.11	0.03	0.21	0.02
3	Amino Acid	Aspartic acid	5.89	1.26	8.05	1.86	8.60	1.67	5.47	0.98	4.99	0.41	11.89	2.04
4	Amino Acid	Alanine	0.47	0.06	0.46	0.08	0.43	0.10	0.49	0.09	0.30	0.06	0.34	0.13
5	Amino Acid	Glutamine	13.10	3.07	12.72	1.96	10.57	2.08	8.38	1.89	7.01	1.08	8.39	1.94
6	Amino Acid	Leucine	0.03	0.02	0.04	0.02	0.04	0.02	0.09	0.01	0.08	0.01	0.13	0.03
7	Amino Acid	Isoleucine	1.98	0.29	2.02	0.36	2.90	0.68	2.95	0.62	2.08	0.22	3.44	0.42
8	Amino Acid	Histidine	2.38	0.42	1.96	0.28	2.62	0.31	2.51	0.82	2.42	0.16	2.50	0.51
9	Amino Acid	Phenylalanine	2.50	0.40	2.23	0.28	3.17	0.52	2.90	0.82	2.38	0.26	2.93	0.32
10	Amino Acid	Methionine	10.22	1.55	10.22	1.61	12.54	3.00	13.42	2.32	9.62	1.70	14.40	2.25
11	Amino Acid	Hydroxyproline	0.10	0.03	0.11	0.06	0.11	0.03	0.09	0.04	0.04	0.01	0.12	0.03
12	Amino Acid	Proline	0.12	0.02	0.10	0.02	0.14	0.04	0.10	0.03	0.05	0.02	0.10	0.04
13	Amino Acid	Serine	7.68	2.22	7.22	0.60	7.01	0.65	6.27	1.24	5.81	0.33	6.62	0.96
14	Amino Acid	Lysine	2.22	0.50	2.14	0.43	2.86	0.72	2.47	0.71	1.68	0.23	2.39	0.27
15	Amino Acid	Ornithine	0.07	0.02	0.06	0.01	0.08	0.01	0.05	0.01	0.05	0.01	0.06	0.02
16	Amino Acid	Threonine	0.94	0.22	0.87	0.27	1.35	0.39	1.38	0.14	0.79	0.08	1.47	0.28
17	Amino Acid	Tryptophan	7.24	1.65	7.99	1.62	10.50	2.67	9.15	2.51	10.34	1.13	10.35	2.35
18	Amino Acid	Tyrosine	3.63	1.62	3.50	1.29	4.29	1.65	5.59	1.97	4.80	0.79	4.37	1.38
19	Amino Acid	Pyroglutamic acid	4.40	0.88	3.75	0.43	4.20	0.45	3.01	0.65	2.38	0.21	2.98	0.63
20	Amino Acid	Valine	0.60	0.11	0.60	0.13	0.79	0.11	0.80	0.21	0.56	0.09	0.87	0.17
21	Amino Acid derivative	GSH	163.37	27.20	175.19	33.04	202.72	26.16	134.51	31.82	129.87	15.88	73.09	15.42
22	Amino Acid derivative	GSSG	1.15	0.15	0.98	0.26	0.93	0.21	1.07	0.14	0.94	0.08	1.01	0.10
23	Amino Acid derivative	Taurine	6.34	1.09	6.90	1.88	9.01	2.38	6.53	1.31	3.60	1.73	10.65	2.39
24	Coenzyme	NAD^+	0.67	0.08	0.75	0.11	0.92	0.19	1.02	0.27	0.53	0.04	0.84	0.10
25	Coenzyme	NADH	2.07	0.54	1.72	0.36	1.50	0.37	1.12	0.51	1.08	0.21	0.28	0.06
26	Coenzyme	NADP	0.02	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.01	0.00	0.01	0.00
27	Coenzyme	FAD	0.13	0.05	0.14	0.09	0.15	0.05	0.10	0.02	0.11	0.04	0.10	0.02
28	Coenzyme	Acetyl CoA	0.07	0.01	0.07	0.02	0.07	0.03	0.04	0.02	0.01	0.00	0.08	0.01
29	Coenzyme	Pamitoyl-CoA	0.02	0.00	0.02	0.00	0.01	0.00	0.01	0.01	0.00	0.00	0.01	0.01

30	Nucleobase	Adenine	0.01	0.00	0.01	0.00	0.02	0.01	0.02	0.00	0.02	0.00	0.02	0.00
31	Nucleobase	Cytidine	0.01	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.03	0.01	0.01	0.00
32	Nucleobase	Creatinine	0.06	0.01	0.06	0.02	0.08	0.01	0.06	0.02	0.03	0.02	0.06	0.01
33	Nucleobase	Guanine	0.11	0.06	0.09	0.03	0.11	0.07	0.16	0.08	0.21	0.15	0.05	0.03
34	Nucleobase	Guanosine	0.06	0.03	0.06	0.02	0.06	0.03	0.09	0.04	0.12	0.06	0.04	0.03
35	Nucleobase	Inosine	0.03	0.01	0.04	0.01	0.03	0.01	0.03	0.01	0.03	0.01	0.03	0.00
36	Nucleobase	Hypoxanthine	0.19	0.04	0.19	0.04	0.21	0.02	0.19	0.04	0.17	0.03	0.21	0.02
37	Nucleobase	Thymine	0.12	0.01	0.13	0.01	0.17	0.08	0.14	0.01	0.15	0.03	0.16	0.01
38	Nucleobase	Uracil	0.12	0.01	0.14	0.05	0.13	0.01	0.15	0.02	0.12	0.01	0.14	0.01
39	Nucleobase	Uridine	0.22	0.02	0.24	0.03	0.25	0.06	0.27	0.03	0.31	0.08	0.24	0.02
40	Nucleotide	ADP	2.37	0.52	2.43	0.27	2.60	0.33	2.44	0.49	2.53	0.49	1.43	0.19
41	Nucleotide	UDP	0.41	0.15	0.37	0.08	0.36	0.11	0.39	0.12	0.46	0.10	0.10	0.02
42	Nucleotide	GDP	0.67	0.13	0.67	0.07	0.74	0.07	0.65	0.11	0.66	0.09	0.44	0.06
43	Nucleotide	ATP	9.28	0.75	8.11	1.41	8.26	1.42	6.59	0.97	6.40	0.39	6.68	0.77
44	Nucleotide	GTP	1.80	0.35	1.73	0.49	1.64	0.39	1.21	0.32	0.98	0.15	1.01	0.23
45	Nucleotide	CTP	1.90	0.60	1.82	0.45	1.70	0.27	1.35	0.20	1.22	0.16	0.96	0.22
46	Nucleotide	dCMP	0.01	0.00	0.02	0.01	0.02	0.01	0.02	0.00	0.01	0.00	0.02	0.00
47	Nucleotide	IMP	0.03	0.01	0.03	0.01	0.03	0.01	0.02	0.00	0.02	0.01	0.02	0.00
48	Nucleotide	AMP	0.59	0.15	0.62	0.21	0.97	0.24	1.02	0.33	0.47	0.12	0.29	0.06
49	Nucleotide	CMP	0.05	0.01	0.05	0.01	0.05	0.00	0.05	0.00	0.05	0.01	0.06	0.00
50	Nucleotide	UMP	0.09	0.02	0.09	0.02	0.08	0.02	0.07	0.01	0.03	0.00	0.04	0.01
51	Nucleotide	XMP	0.10	0.03	0.13	0.04	0.20	0.06	0.16	0.04	0.08	0.02	0.13	0.03
52	Organic acid	Pyruvate	0.80	0.39	0.98	0.76	0.57	0.33	0.68	0.38	1.29	0.18	1.09	0.52
53	Organic acid	Fumarate	1.34	0.14	2.09	0.50	1.87	0.53	2.51	0.50	0.98	1.00	0.51	0.12
54	Organic acid	Succinate	1.48	0.32	1.50	0.31	1.42	0.21	1.50	0.19	1.10	0.23	1.11	0.24
55	Organic acid	Aconitic acid	0.66	0.10	0.75	0.13	0.68	0.15	0.84	0.18	1.07	0.17	0.46	0.05
56	Organic acid	Citrate (Isocitrate)	5.59	1.02	6.17	0.45	5.59	0.44	5.43	1.54	5.85	0.50	4.18	0.55
57	Organic acid	Malic acid	3.93	0.83	4.54	0.74	4.02	0.61	4.23	0.77	3.26	0.75	0.91	0.28
58	Organic acid	Shikimic acid	0.12	0.00	0.12	0.00	0.13	0.00	0.13	0.00	0.13	0.00	0.15	0.01
59	Organic acid	Lactate	9.84	1.54	10.97	1.58	18.57	4.94	26.74	7.72	14.60	4.43	3.00	0.90
60	Organic acid	α-ketoglutaric acid	0.07	0.03	0.12	0.05	0.16	0.08	0.12	0.08	0.06	0.03	0.09	0.04
61	Phosphorylated compound	2-PGA (3-PGA)	24.43	6.25	21.41	5.33	19.40	2.70	15.04	4.60	16.88	2.40	17.98	1.93
62	Phosphorylated compound	α-glycerol phosphate	0.09	0.01	0.12	0.05	0.11	0.02	0.11	0.02	0.09	0.01	0.12	0.01
63	Phosphorylated compound	GA3P	0.25	0.12	0.23	0.08	0.26	0.12	0.26	0.03	0.17	0.07	0.06	0.05
64	Phosphorylated compound	RMP	0.03	0.00	0.03	0.00	0.03	0.00	0.02	0.00	0.02	0.00	0.03	0.01
65	Phosphorylated compound	Phosphoenolpyruvate	0.03	0.02	0.02	0.01	0.03	0.01	0.02	0.01	0.01	0.01	0.03	0.01

66	Phosphorylated sugar	G6P	1.93	0.74	1.97	0.40	3.30	1.10	2.60	0.78	2.11	1.78	0.76	0.08
67	Phosphorylated sugar	R5P	0.35	0.09	0.37	0.18	0.40	0.18	0.41	0.11	0.45	0.10	0.25	0.01
68	Phosphorylated sugar	S7P	0.28	0.03	0.28	0.03	0.26	0.05	0.27	0.04	0.24	0.06	0.22	0.02
69	Phosphorylated sugar	F1,6BP	5.70	1.82	4.46	0.94	4.45	1.08	2.66	0.37	2.21	0.68	0.19	0.04
70	Phosphorylated sugar	F6P	0.99	0.22	0.91	0.13	0.99	0.13	0.82	0.09	0.60	0.09	0.50	0.01
71	Sugar	Mannitol	0.08	0.04	0.14	0.08	0.31	0.27	0.35	0.25	0.05	0.05	0.50	0.49
72	Vitamin	Niacinamide	0.03	0.02	0.04	0.01	0.09	0.04	0.06	0.02	0.12	0.08	0.06	0.01
73	Vitamin	Pyridoxine	1.17	0.24	1.32	0.27	2.08	0.23	1.59	0.45	0.78	0.63	1.62	0.25
74	Vitamin	Riboflavin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75	Vitamin	Pantothenate	7.03	5.38	5.66	1.85	6.18	1.20	7.25	2.64	5.00	6.24	3.26	0.80
76	Vitamin	Choline	0.61	0.14	0.83	0.09	0.92	0.06	0.95	0.17	0.76	0.05	1.00	0.16
77	Vitamin	Folic acid	0.62	0.13	0.74	0.04	0.88	0.21	0.89	0.15	0.69	0.07	1.11	0.13
78	Vitamin	Thiamine	0.04	0.02	0.05	0.02	0.03	0.01	0.06	0.03	0.01	0.01	0.07	0.02

Table **S6**. Quantitation of polar metabolites in each sample treated by TCDD with different concentration with 4 hours and 24 hours. Value are expressed as pmol, the cell number for each sample was approximately 1.0 E+06 (N = 6).

No.	Class	Compound	Quantitation (pmol)					
			DMSO_4 h		1 nM_4 h		10 nM_4 h	
			mean	SD	mean	SD	mean	SD
1	Amino Acid	Alanine	26.07	26.91	11.71	6.91	19.68	12.92
2	Amino Acid	Serine	375.65	260.77	462.74	270.83	702.17	391.30
3	Amino Acid	Proline	612.11	207.35	704.30	337.39	532.89	172.38
4	Amino Acid	Valine	472.75	210.38	618.94	114.64	564.99	329.35
5	Amino Acid	Threonine	375.59	81.65	492.65	80.23	714.23	215.94
6	Amino Acid	Pyroglutamic acid	16170.69	4318.92	15255.17	815.24	21301.88	4343.70
7	Amino Acid	Isoleucine	1234.91	663.12	1753.07	588.86	2941.08	1549.52
8	Amino Acid	Hydroxyproline	177.33	77.12	168.35	82.64	155.88	40.26
9	Amino Acid	Asparagine	204.83	75.02	209.20	76.85	295.30	84.42
10	Amino Acid	Aspartic acid	2598.65	726.55	2824.75	747.84	3706.93	698.46
11	Amino Acid	Glutamine	13133.63	3935.16	12084.56	881.14	17350.44	3340.89
12	Amino Acid	Lysine	531.80	231.61	902.91	323.50	1461.52	1084.24
13	Amino Acid	Methionine	17885.33	3405.82	25928.75	7334.92	36297.18	13069.66
14	Amino Acid	Histidine	1256.55	631.77	1419.50	625.80	2748.08	1296.25
15	Amino Acid	Phenylalanine	720.46	143.10	1097.83	252.14	1525.21	686.42

16	Amino Acid	Arginine	55.49	19.87	98.65	18.39	194.36	179.66
17	Amino Acid	Tyrosine	1301.39	243.87	1896.74	406.31	3227.50	1889.43
18	Amino Acid	Tryptophan	412.44	143.91	597.69	181.06	711.26	438.24
19	Amino Acid derivative	Taurine	5340.18	1137.09	6258.98	2130.57	5492.20	1243.31
20	Amino Acid derivative	GSSG	4041.01	1359.41	3660.92	1114.88	5390.80	1391.51
21	Amino Acid derivative	GSH	543945.28	243820.86	590689.82	160092.84	579492.81	153398.04
22	Nucleobase	Adenine	11.21	3.30	8.86	1.72	10.51	3.02
23	Nucleobase	Creatinine	50.15	24.56	48.52	11.55	61.14	24.20
24	Nucleobase	Xanthine	18.08	6.98	18.74	10.02	21.68	5.94
25	Nucleotide	Cytidine	8.79	1.94	7.21	0.57	9.93	3.97
26	Nucleotide	Guanosine	18.72	1.18	19.08	1.89	18.74	1.08
27	Nucleotide	Uracil	26.11	20.69	13.76	4.99	11.45	5.36
28	Nucleotide	GMP	296.85	4.83	296.53	5.77	299.67	7.89
29	Nucleotide	CMP	39.68	3.67	40.02	6.99	37.28	2.85
30	Nucleotide	UMP	293.33	78.30	300.60	102.17	271.64	54.14
31	Nucleotide	AMP	835.41	566.04	1007.10	869.68	1967.63	1625.36
32	Nucleotide	IMP	33.75	13.48	27.94	8.14	30.82	12.18
33	Nucleotide	RMP	110.55	31.65	115.15	27.51	148.49	29.98
34	Nucleotide	XMP	8.21	1.97	9.63	3.35	8.07	2.58
35	Nucleotide	dUMP	260.14	160.97	317.07	131.86	269.83	75.99

36	Nucleotide	cAMP	2.32	0.40	2.26	0.42	2.33	0.32
37	Nucleotide	dGMP	26.67	1.30	25.37	1.69	25.62	2.89
38	Nucleotide	UDP	3030.89	1383.71	3509.01	1695.00	5838.16	3160.42
39	Nucleotide	ADP	7390.50	3143.66	8635.94	4493.89	15114.87	9551.01
40	Nucleotide	GDP	1134.31	349.30	1152.67	305.02	1196.06	191.78
41	Nucleotide	CTP	7474.37	3468.33	7655.18	2680.49	14485.88	7937.00
42	Nucleotide	ATP	25693.21	10500.79	28480.17	11390.20	47650.92	24081.01
43	Nucleotide	GTP	9360.11	4597.01	10773.01	4694.61	19224.17	10436.86
44	Coenzyme	NAD^+	868.48	169.53	878.19	197.07	1073.25	69.62
45	Coenzyme	$NADP^+$	15.67	8.92	16.35	10.71	16.80	7.32
46	Coenzyme	FAD	95.17	12.66	98.79	19.46	105.19	3.80
47	Coenzyme	NADH	6436.31	4451.45	8028.38	3468.92	11191.08	3031.42
48	Coenzyme	Acetyl-CoA	71.36	15.30	76.78	11.06	81.37	12.09
49	Coenzyme	Palmitoyl-CoA	23.37	3.00	22.49	2.09	22.76	0.81
50	Coenzyme	Stearoyl-CoA	8.66	1.37	11.25	4.41	9.81	2.63
51	Organic Acid	Lactate	3696.71	2189.71	6744.70	966.56	8730.32	2629.83
52	Organic Acid	Succinate	282.91	65.38	392.74	183.83	438.98	95.78
53	Organic Acid	Malic acid	3985.61	1032.22	5175.18	1976.22	8108.87	2315.05
54	Organic Acid	Hippuric acid	204.59	11.30	200.81	3.91	202.62	5.74
55	Organic Acid	Itaconic acid	221.36	176.99	272.91	279.71	406.51	143.08

56	Organic Acid	Aconitic acid	19.56	15.91	16.27	6.25	34.41	11.84
57	Organic Acid	Citric acid	1431.29	76.68	1395.86	38.93	1501.05	63.30
58	Sugar	Ribose	8038.43	2156.39	13590.40	4558.65	17072.86	7096.13
59	Sugar	Mannitol	52.07	12.43	70.25	25.13	83.18	39.67
60	Phosphorylated sugar	Ru5P (R5P)	1861.86	5.04	1867.98	6.77	1861.31	3.64
61	Phosphorylated sugar	F6P	620.81	49.67	682.41	102.05	641.81	34.53
62	Phosphorylated sugar	G6P	202.55	46.48	239.11	30.04	312.87	90.52
63	Phosphorylated sugar	S7P	387.41	68.44	482.45	33.70	461.91	70.33
64	Phosphorylated sugar	F1,6BP	2899.79	796.95	2968.42	785.98	3825.52	923.75
65	Phosphorylated compound	GA3P	100.29	45.41	133.98	82.86	182.17	85.41
66	Phosphorylated compound	*α*-glyceric phosphate	658.42	175.38	778.27	210.22	817.57	296.43
67	Phosphorylated compound	2-PGA (3-PGA)	126481.82	18891.01	129873.47	12180.42	127414.91	18856.31
68	Phosphorylated compound	Phosphoenolpyruvate	370.84	6.22	381.07	20.31	398.05	38.99
69	Vitamin	Pyridoxine	23.40	7.84	26.77	7.73	46.55	20.59
70	Vitamin	Riboflavin	11.05	1.35	12.44	1.08	13.74	2.51
71	Vitamin	Pantothenate	1768.26	678.92	1543.98	403.15	2032.49	429.18
72	Vitamin	Niacinamide	14.33	4.02	19.98	8.14	31.58	20.48
73	Vitamin	Choline	380.67	137.99	358.39	199.87	395.35	65.96
74	Vitamin	Thiamine	127.56	42.39	199.54	96.43	184.84	33.40

No.	**Class**	**Compound**	**DMSO_24 h**		**1 nM_24 h**		**10 nM_24 h**	

			mean	SD	mean	SD	mean	SD
1	Amino Acid	Alanine	64.83	27.57	38.35	25.30	28.28	17.97
2	Amino Acid	Serine	2186.73	830.97	1102.20	531.24	617.87	428.15
3	Amino Acid	Proline	1072.58	369.43	667.87	123.69	731.52	201.34
4	Amino Acid	Valine	695.96	206.16	609.41	148.80	579.67	285.08
5	Amino Acid	Threonine	1001.58	159.08	707.31	195.39	604.42	91.40
6	Amino Acid	Pyroglutamic acid	32191.68	3225.50	23642.65	5885.62	15203.48	2853.11
7	Amino Acid	Isoleucine	3844.80	576.37	2481.98	501.15	2074.63	487.98
8	Amino Acid	Hydroxyproline	437.74	99.17	183.75	21.49	208.94	82.35
9	Amino Acid	Asparagine	1284.38	514.66	387.32	300.22	241.62	124.23
10	Amino Acid	Aspartic acid	4665.38	575.76	3238.41	802.43	2763.35	843.10
11	Amino Acid	Glutamine	28760.63	3379.73	20914.67	5565.04	12669.03	1701.51
12	Amino Acid	Lysine	1604.00	660.01	942.85	300.52	872.51	363.52
13	Amino Acid	Methionine	52180.95	6607.05	32535.46	3863.59	27067.46	2923.63
14	Amino Acid	Histidine	4179.44	1112.61	2952.17	866.80	1782.87	364.43
15	Amino Acid	Phenylalanine	1891.04	380.19	1215.32	195.39	1150.78	226.85
16	Amino Acid	Arginine	27.07	13.84	42.20	19.41	56.88	16.64
17	Amino Acid	Tyrosine	2614.35	450.13	2092.72	559.17	2046.17	912.46
18	Amino Acid	Tryptophan	822.86	124.22	553.97	170.68	484.38	217.22
19	Amino Acid derivative	Taurine	7277.23	2229.74	5607.35	926.15	7062.56	1618.63

20	Amino Acid derivative	GSSG	5819.16	2239.13	5126.11	774.57	5238.39	1147.79
21	Amino Acid derivative	GSH	659128.64	292416.10	783888.54	170497.73	785053.50	108184.15
22	Nucleobase	Adenine	13.25	4.30	10.07	2.88	9.82	1.82
23	Nucleobase	Creatinine	91.38	23.19	71.98	6.86	64.66	10.92
24	Nucleobase	Xanthine	16.34	3.52	19.71	6.84	18.99	3.62
25	Nucleotide	Cytidine	9.96	1.17	8.39	1.29	7.97	0.98
26	Nucleotide	Guanosine	23.57	4.00	19.90	1.66	18.20	1.45
27	Nucleotide	Uracil	8.67	1.89	8.42	2.24	8.14	2.03
28	Nucleotide	GMP	303.99	8.66	299.10	4.56	301.90	9.51
29	Nucleotide	CMP	48.40	8.31	37.08	3.47	40.04	4.04
30	Nucleotide	UMP	431.70	104.49	302.47	61.56	272.74	62.60
31	Nucleotide	AMP	1577.36	906.52	1402.06	786.63	1161.38	579.89
32	Nucleotide	IMP	22.08	8.55	18.07	6.52	33.21	12.02
33	Nucleotide	RMP	202.03	20.31	178.81	34.28	159.84	42.24
34	Nucleotide	XMP	14.24	3.29	8.83	2.90	10.31	3.65
35	Nucleotide	dUMP	215.91	85.39	282.59	50.84	373.40	105.30
36	Nucleotide	cAMP	3.12	0.62	2.44	0.28	2.42	0.38
37	Nucleotide	dGMP	28.39	3.76	27.24	2.02	24.26	1.43
38	Nucleotide	UDP	6682.12	1616.66	5902.14	2830.01	5905.20	1818.07
39	Nucleotide	ADP	19225.68	8319.67	16109.67	7162.01	12872.87	3952.15

40	Nucleotide	GDP	2549.80	408.61	1524.88	457.49	1769.35	218.94
41	Nucleotide	CTP	21831.31	8971.33	16536.23	7621.93	15611.21	4883.92
42	Nucleotide	ATP	91296.00	30135.80	63812.10	26947.34	53247.40	8753.39
43	Nucleotide	GTP	30756.41	7847.43	23177.71	9978.37	21329.36	5490.31
44	Coenzyme	NAD^+	1975.15	328.29	1348.66	126.01	1310.83	151.41
45	Coenzyme	$NADP^+$	37.88	15.96	22.59	11.92	28.32	8.67
46	Coenzyme	FAD	166.72	24.65	120.32	20.11	131.88	13.13
47	Coenzyme	NADH	27860.83	5775.18	21057.99	6072.07	17528.72	6132.44
48	Coenzyme	Acetyl-CoA	118.05	26.31	93.14	11.28	94.20	14.34
49	Coenzyme	Palmitoyl-CoA	35.58	6.19	31.16	7.71	27.16	2.78
50	Coenzyme	Stearoyl-CoA	19.20	2.34	14.30	2.27	10.55	2.44
51	Organic Acid	Lactate	12622.26	2967.07	10801.42	3510.44	14600.93	4786.93
52	Organic Acid	Succinate	504.05	141.16	491.98	135.51	538.75	105.28
53	Organic Acid	Malic acid	9724.17	1091.37	9727.80	2610.34	10513.18	2457.49
54	Organic Acid	Hippuric acid	200.39	1.47	201.36	3.89	199.29	1.26
55	Organic Acid	Itaconic acid	530.48	242.51	460.33	112.61	292.73	185.92
56	Organic Acid	Aconitic acid	82.35	28.52	50.72	10.39	37.11	4.42
57	Organic Acid	Citric acid	1695.51	79.15	1567.62	65.23	1507.82	31.92
58	Sugar	Ribose	26514.72	5192.75	22123.98	8614.85	18295.21	5042.65
59	Sugar	Mannitol	48.55	9.87	48.99	6.19	56.40	11.34

60	Phosphorylated sugar	Ru5P (R5P)	1871.72	8.60	1865.13	10.25	1863.59	8.76
61	Phosphorylated sugar	F6P	695.80	93.35	629.32	26.09	636.93	35.56
62	Phosphorylated sugar	G6P	335.08	119.87	284.49	101.27	256.10	41.35
63	Phosphorylated sugar	S7P	788.07	262.95	570.95	79.62	498.08	68.61
64	Phosphorylated sugar	F1,6BP	5201.27	1401.45	4188.83	752.47	3764.52	1058.80
65	Phosphorylated compound	GA3P	170.17	86.28	154.20	86.09	160.09	66.37
66	Phosphorylated compound	*α*-glyceric phosphate	1225.47	388.04	841.14	145.20	768.75	158.33
67	Phosphorylated compound	2-PGA (3-PGA)	141466.60	19580.92	122705.57	11820.21	137117.04	25425.32
68	Phosphorylated compound	Phosphoenolpyruvate	409.94	28.02	405.55	19.64	380.25	14.33
69	Vitamin	Pyridoxine	50.06	5.26	45.23	5.98	34.77	7.05
70	Vitamin	Riboflavin	13.04	1.79	12.30	0.65	13.15	1.68
71	Vitamin	Pantothenate	2793.58	445.41	2495.93	719.67	1679.33	276.85
72	Vitamin	Niacinamide	24.41	5.78	22.58	9.73	17.81	7.27
73	Vitamin	Choline	713.09	166.98	382.08	120.61	238.09	69.25
74	Vitamin	Thiamine	168.91	45.75	145.51	34.19	170.72	57.23

Table S7. Metabolites significantly affected by TCDD exposure by 4 h treatment. The fold changes are given as the ratio of the average content in TCDD and in DMSO.

Metabolites	Fold change (LC-MS $p < 0.05$)	
	1 nM	10 nM
Aspartic acid	1.09	1.43
F1,6BP	1.02	1.05
G6P	1.18	1.55
Histidine	1.13	2.19
Isoleucine	1.42	2.38
Lactate	1.82	2.36
Malic acid	1.3	2.03
Methionine	1.45	2.03
Phenylalanine	1.52	2.12
Pyroglutamic acid	0.94	1.32
S7P	1.25	1.19
Threonine	1.31	1.9
Tyrosine	1.46	2.48

Table S8. Metabolites significantly affected by TCDD exposure by 24 h treatment. The fold changes are given as the ratio of the average content in TCDD and in DMSO.

Metabolites	Fold change (LC-MS $p < 0.05$)	
	1 nM	10 nM
Acetyl CoA	0.79	0.8
Aconitic acid	0.62	0.45
Alanine	0.59	0.44
Arginine	1.56	2.1
Asparagine	0.3	0.19
Aspartic acid	0.69	0.59
ATP	0.7	0.58
cAMP	0.78	0.77
Choline	0.54	0.33
Citric acid	0.92	0.89
CMP	0.77	0.83
Creatinine	0.79	0.71
Cytidine	0.84	0.8
dGMP	0.96	0.85
FAD	0.72	0.79
GDP	0.6	0.69
Glutamine	0.73	0.44
Histidine	0.71	0.43
Hydroxyproline	0.42	0.48
Isoleucine	0.65	0.54
Lysine	0.59	0.54
Methionine	0.62	0.52
NAD^+	0.68	0.66
NADH	0.76	0.63
Pantothenate	0.89	0.6

Phenylalanine	0.64	0.61
Phosphoenolpyruvate	0.99	0.93
Proline	0.62	0.68
Pyroglutamic acid	0.73	0.47
S7P	0.72	0.63
Serine	0.5	0.28
Stearoyl-CoA	0.74	0.55
Threonine	0.71	0.6
Tryptophan	0.67	0.59
UMP	0.7	0.63
XMP	0.62	0.72

Figure S1. **A)** Chromatography comparison for selected 12 metabolites on three LC gradients on a Waters BEH Amide column. **B)** Effect of changes in column temperature on selected polar metabolites. Waters BEH Amide column temperature was 20°C, 30°C, and 40°C. **C)** Comparison of chromatography for selected 12 metabolites using a Waters BEH Amide and Waters BEH HILIC columns (1.7 µm; 2.1 x 100 mm). **D)** Effect of increasing mobile phase buffer concentration on polar metabolites chromatogram. **E)** Effect of changes in pH value on selected polar metabolites. pH values were adjusted to 5, 7, and 9 by acetic acid or ammonium hydroxide. Mobile phase A consisted of 90:10 water:acetonitrile containing 20 mM ammonium acetate, Mobile phase B consisted of 10:90 water:acetonitrile containing 20 mM ammonium acetate. Unless otherwise stated, the pH of mobile phase A and B were adjusted to 9.0, Waters BEH Amide Column (1.7 µm; 2.1 x 100 mm) were employed and the temperature was set as 30°C.

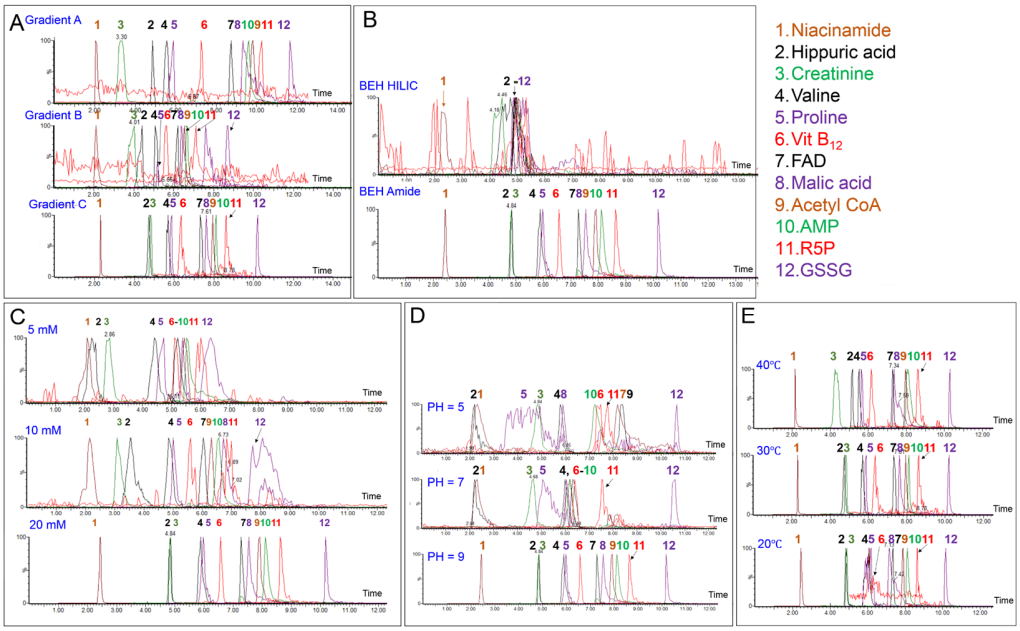

Figure S2. Separation of five pairs of isomers by gradient C. Processed using Waters BEH Amide column. Mobile phase A consisted of 90:10 water:acetonitrile containing 20 mM ammonium acetate (pH = 9.0). Mobile phase B consisted of 10:90 water: acetonitrile containing 20 mM ammonium acetate (pH = 9.0). Waters BEH Amide Column (1.7 µm; 2.1 x 100 mm) were employed and the temperature was set as 30°C.

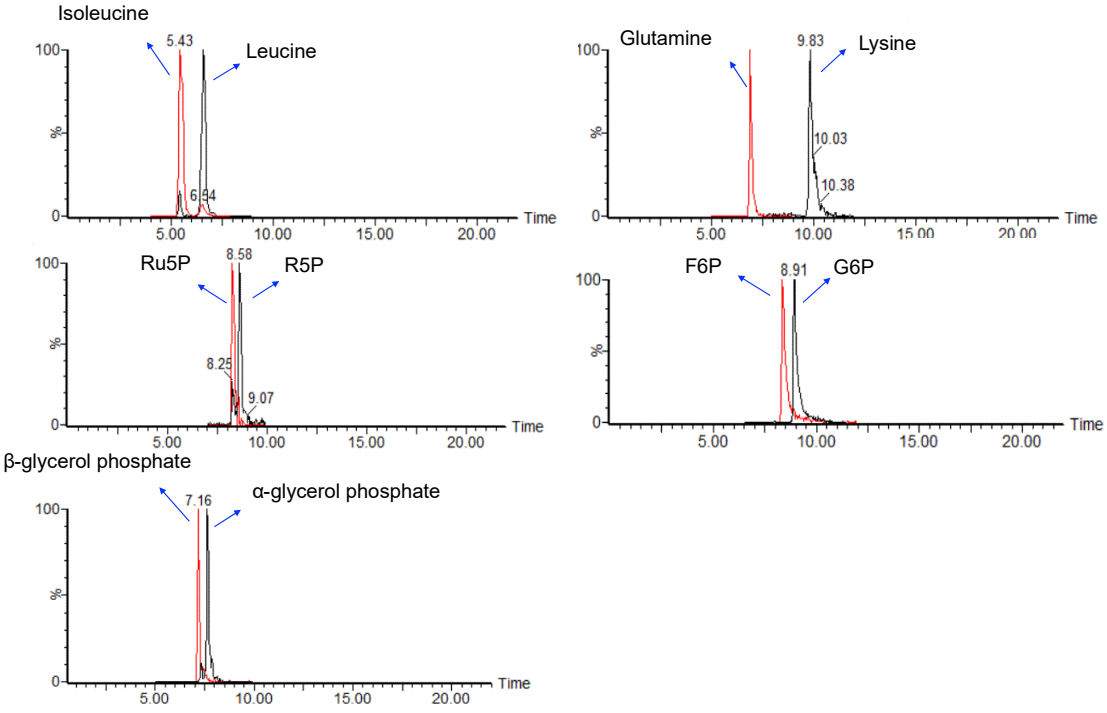

Figure S3. Pharmacologic targeting of aerobic glycolysis in Huh-7 cells. The glycolytic pathway (orange) and its metabolic interconnections with the pentose phosphate pathway (PPP) (blue) and the tricarboxylic acid (TCA) cycle (green) are shown. Pyruvate and glutamine were added in media to survive the cells. Red and blue color of the metabolites represent increasing or decreasing in treatment group comparing with control group, 3-BrPy blocked on HK-ii and GAPDH, most of the changes were in glycolytic pathway, indicating it was inhibited by 3-BrPy.

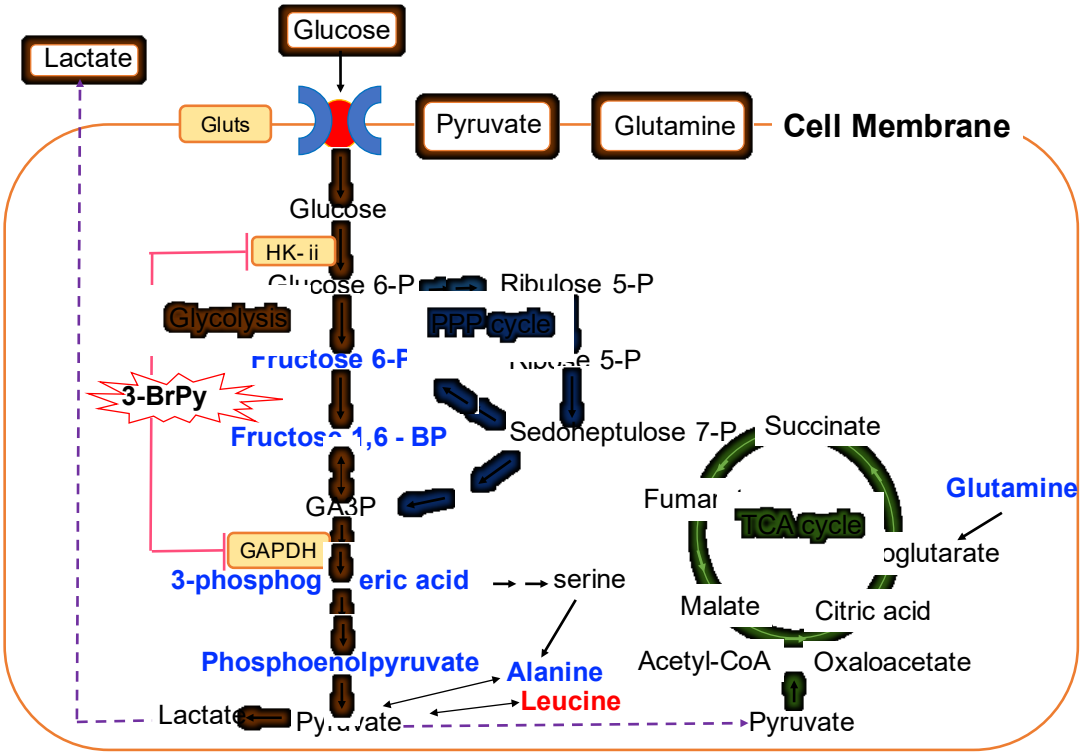

Figure S4. **A)** %Cytotoxicity of each group by MTT assay at 560 nm wave length. **B)** Scores plot of principal components analysis of polar metabolites in Huh-7 cells infected with different concentration of 3-BrPy. **C)** Variation patterns of polar metabolites involved in glycolysis metabolism in presence of 3-BrPy, representing the significant increasing (red) or decreasing (blue) quantitated metabolites. The same with Figure 2, The z-scores were imported into R and the heatmap.2 command from the G plots package was used to create the heatmaps. The metabolites were not sorted but were separated into groups based on metabolite category.

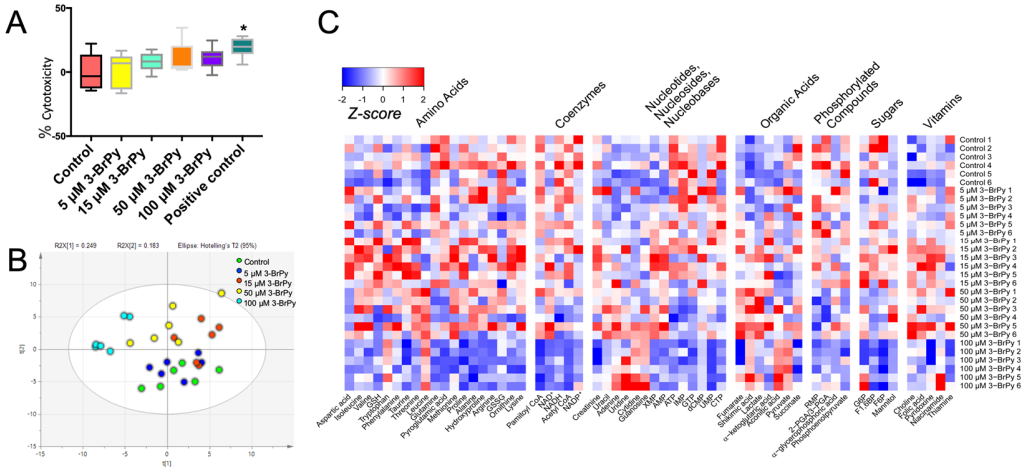

Figure S5. Concentration-dependent effects of 3-BrPy on metabolism of cultured Huh-7 cells. Metabolites are distributed in energy metabolism (NADH, ATP), oxidative stress (GSH, GSSG), glycolytic metabolism (F6P, F1,6BP, 3-phosphogluceric acid, phosphoenolpyruvate), TCA cycle (citric acid, succinate, malic acid), PPP cycle (S7P) and amino acid metabolism (glutamine, serine, alanine, leucine). Cells were incubated for 24 h with the concentration indicated. Controls: 0 μM 3-BrPy; positive controls: 2 mM glucose in media and 0 μM 3-BrPy. Significant difference among groups is analyzed by one-way ANOVA with Dunnett's test, *p*-value was adjusted for multiple comparisons. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; and ****, $p < 0.0001$. The cell number was normalized to 2.50E+06 per sample.

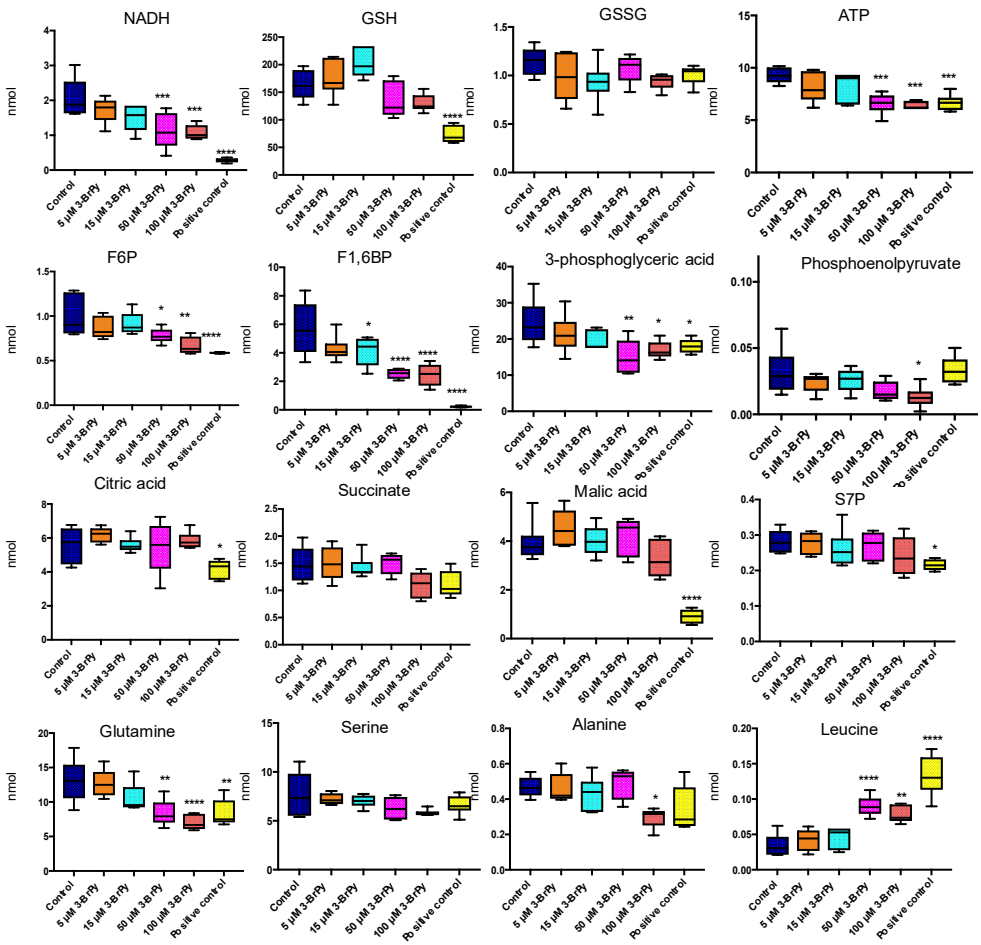

Figure S6. Protein concentration determination in Huh-7 Cells using the standard BCA Protein Assay.

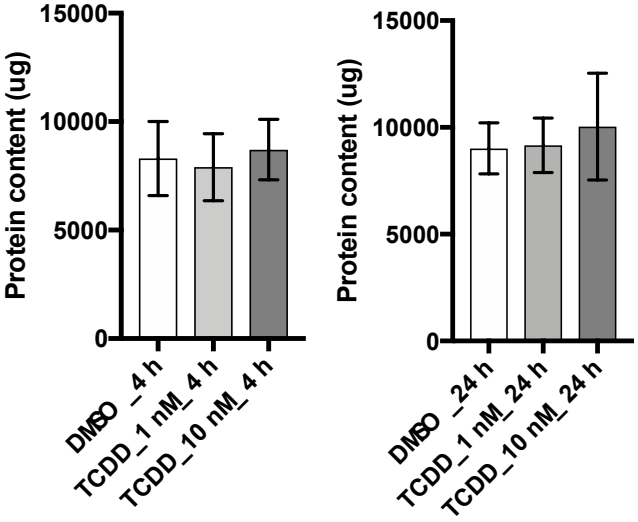

Figure S7. Scores plot of principal components analysis of polar metabolites in Huh-7 cells infected with 1 nM and 10 nM of TCDD in 4 h and 24 h treatment.

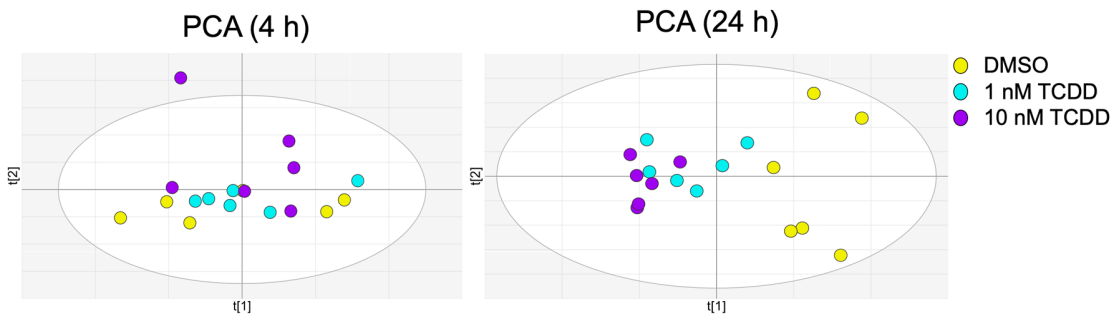

Figure S8. A) PCA plot of polar metabolites in Huh-7 cells treated with 1 and 10 nM TCDD for 24 h by ^{1}H NMR. B) PLS-DA plot of polar metabolites in Huh-7 cells treated with 1 nM and 10 nM of TCDD for 24 h.

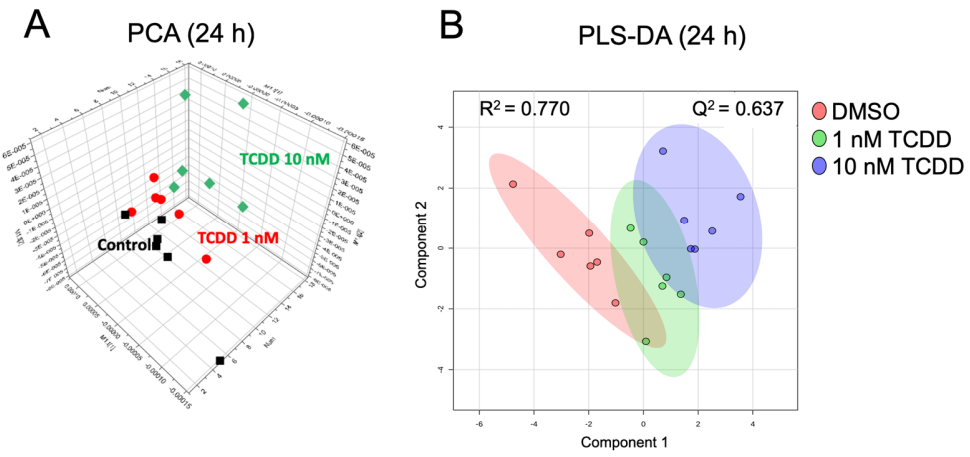

Figure S9. Concentration-dependent effects of TCDD on the metabolism of cultured Huh-7 cells as detected by ^{1}H NMR. Huh-7 cells were treated with 1 and 10 nM TCDD for 4 h and 24 h. DMSO (vehicle) served as control. Significant differences among groups was determined by one-way ANOVA with Dunnett's test, *p*-value was adjusted for multiple comparisons. *, $p < 0.05$; **, $p < 0.01$.