Supplemental Materials

NMR-Based Metabolomics to Analyze the Effects of a Series of Monoamine Oxidases-B Inhibitors on U251 Cells

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7 Supplementary Figures

5 Supplementary Tables

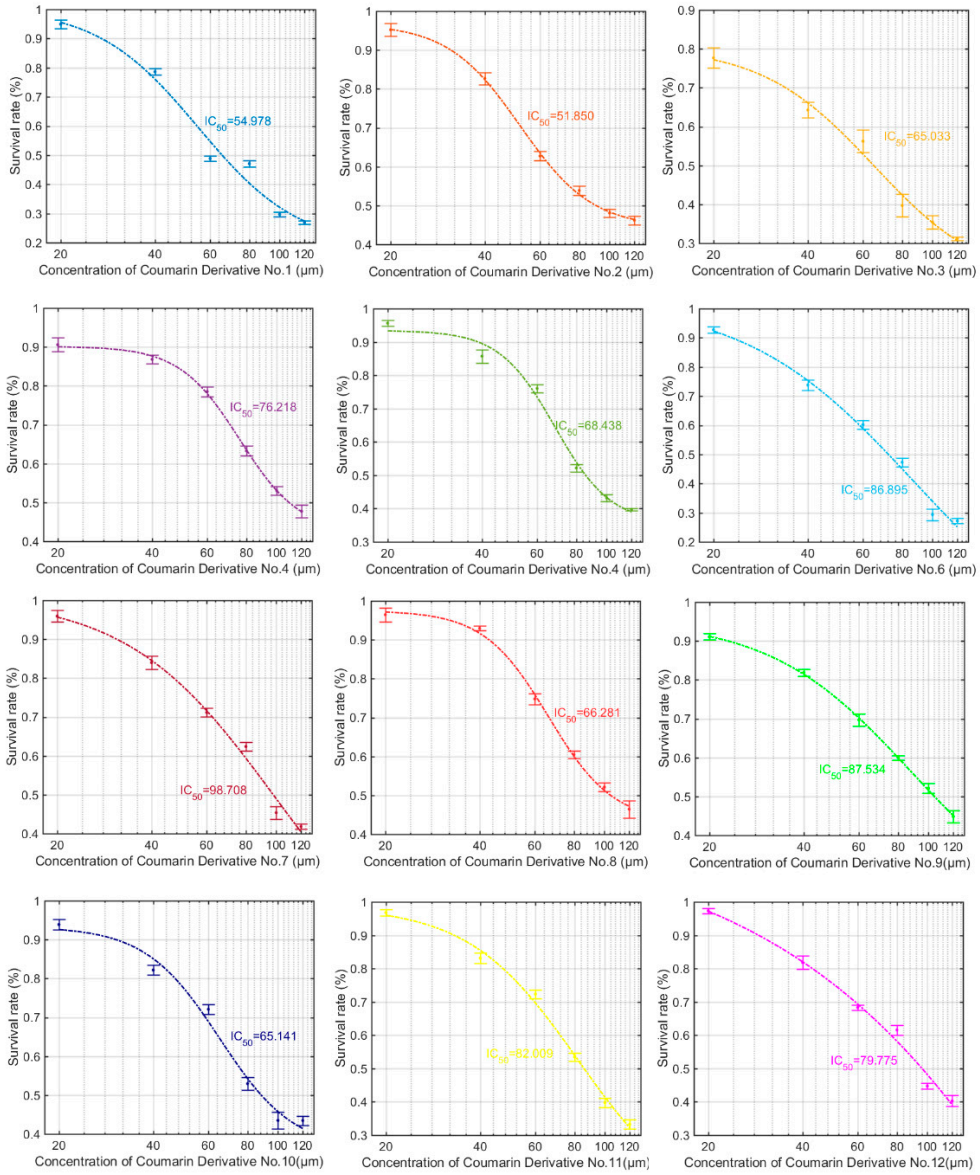


Figure S1. The IC_{50} value of coumarin derivatives in the U251 cells.

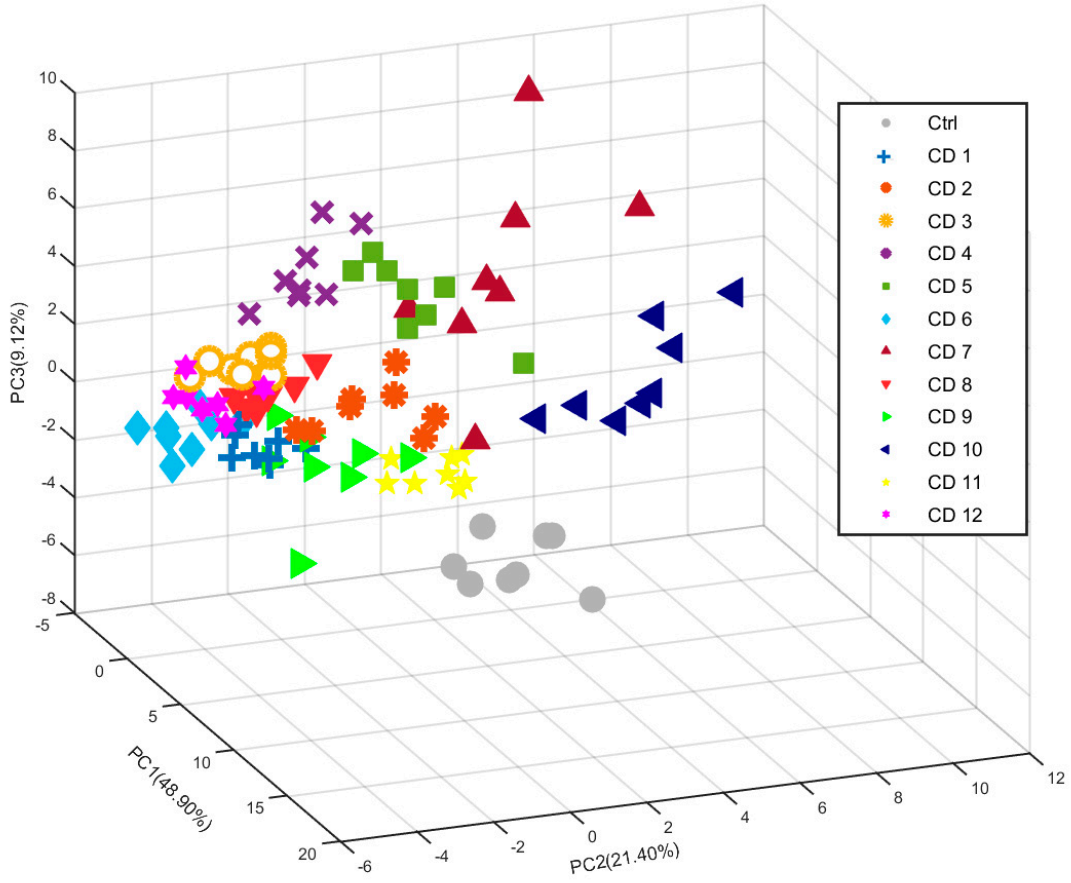


Figure S2. PCA scores plots of relative concentration of metabolites data from twelve coumarin derivatives and control group.

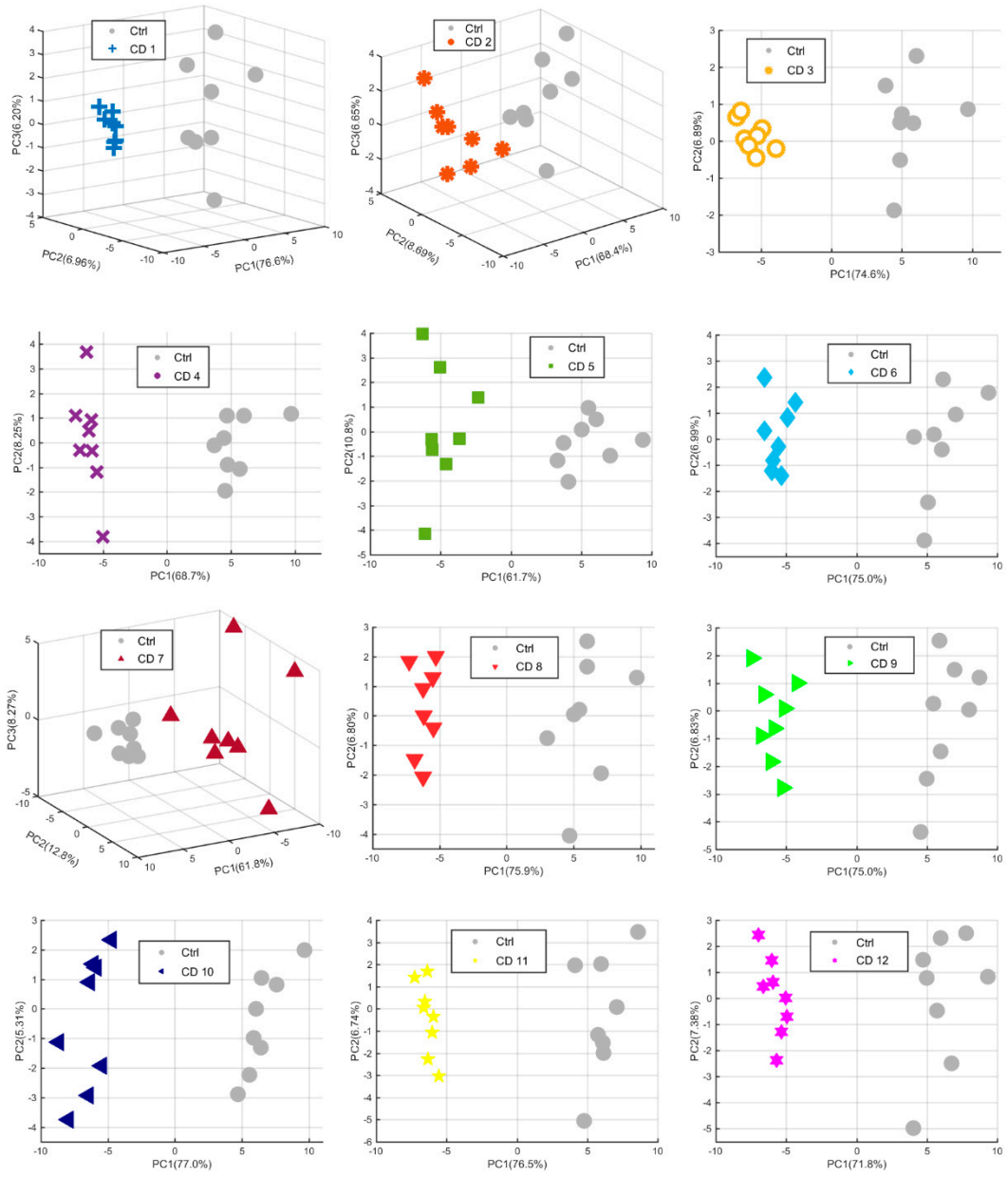


Figure S3. PCA scores plots of relative concentration of metabolites data from each coumarin derivative compared with control group.

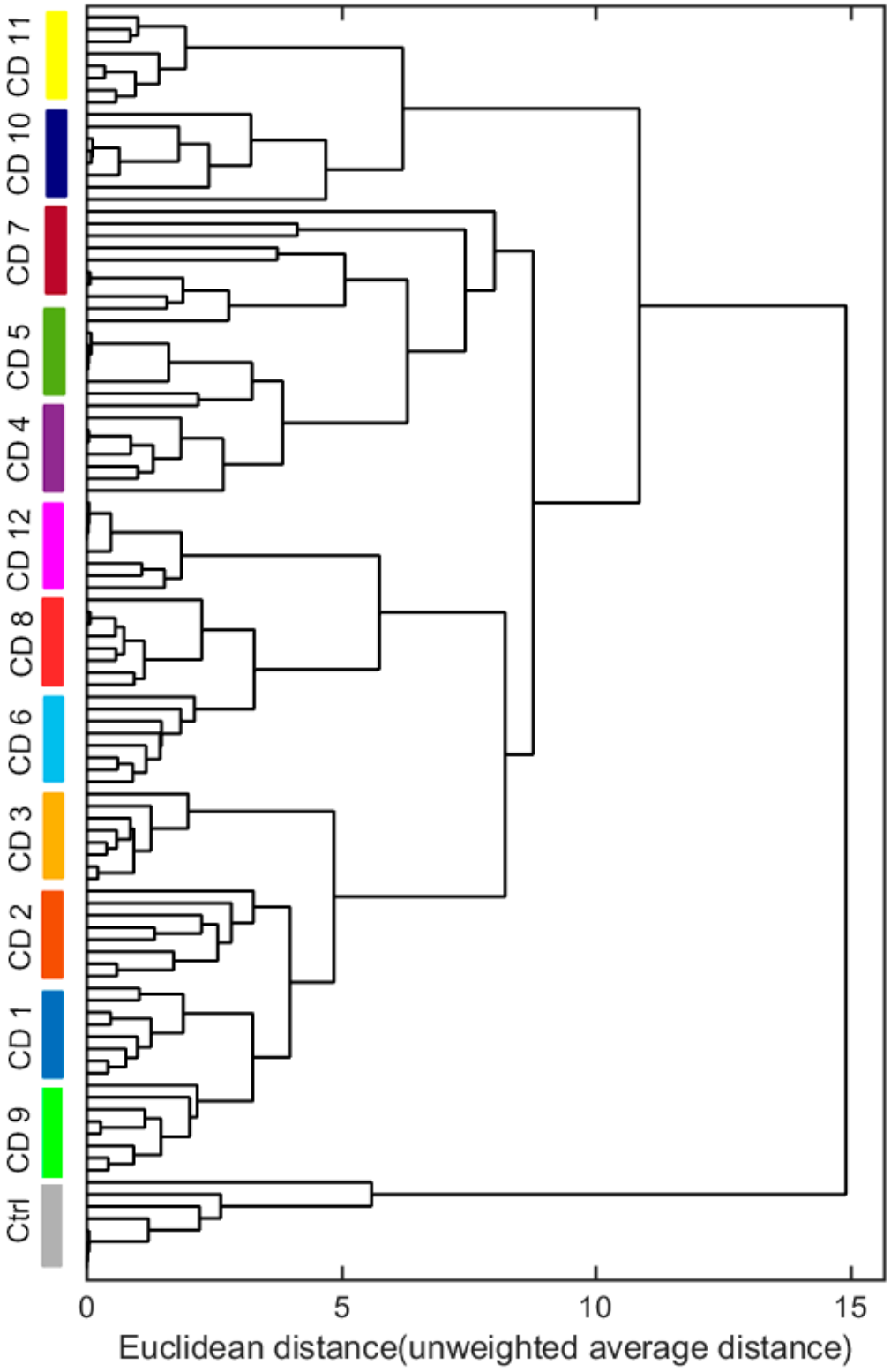


Figure S4. Result of HCA of relative concentration of metabolites data from twelve coumarin derivatives and control group.

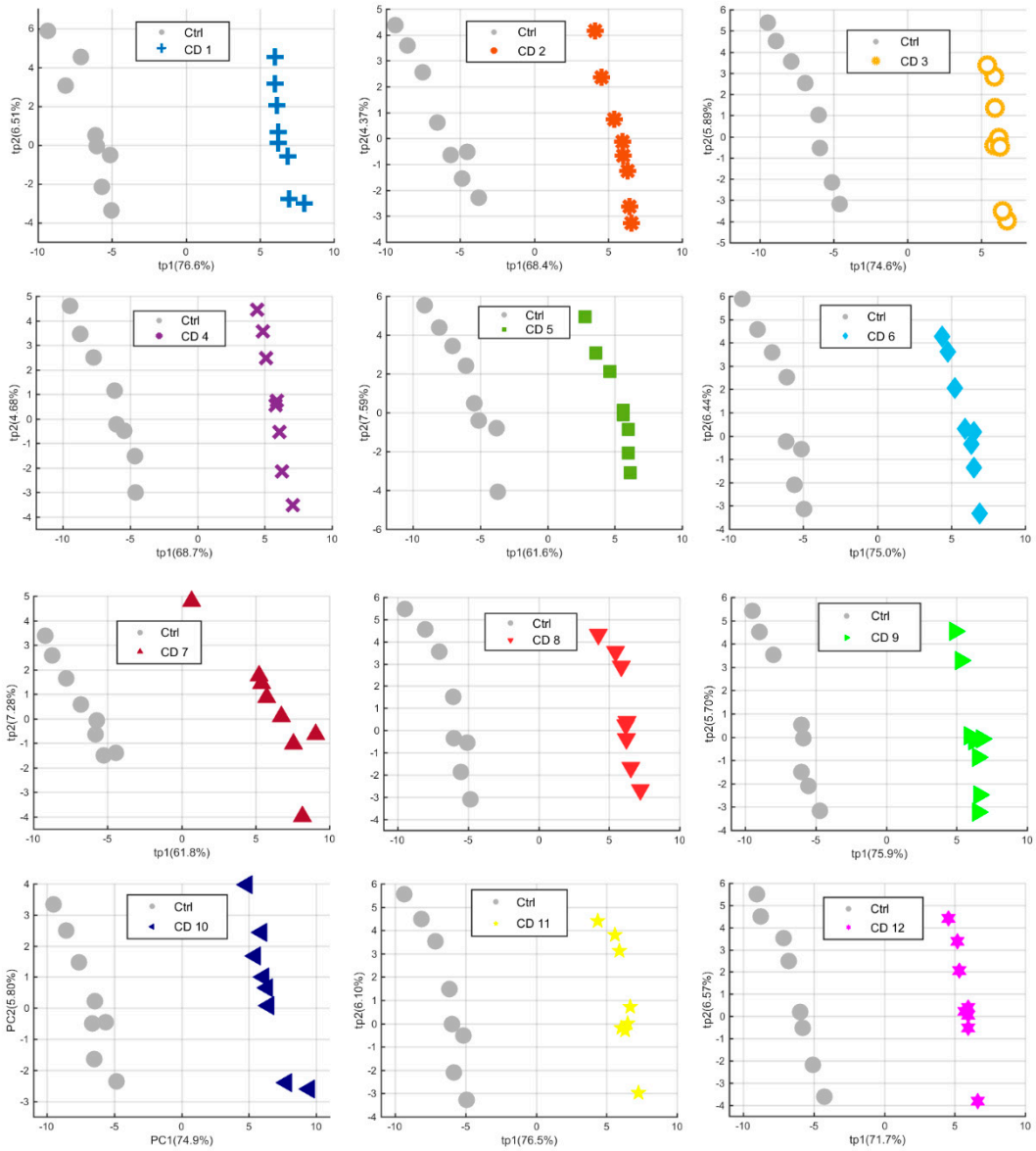


Figure S5. PLS-DA scores plot of relative concentration of metabolites data from each coumarin derivative compared with control group.

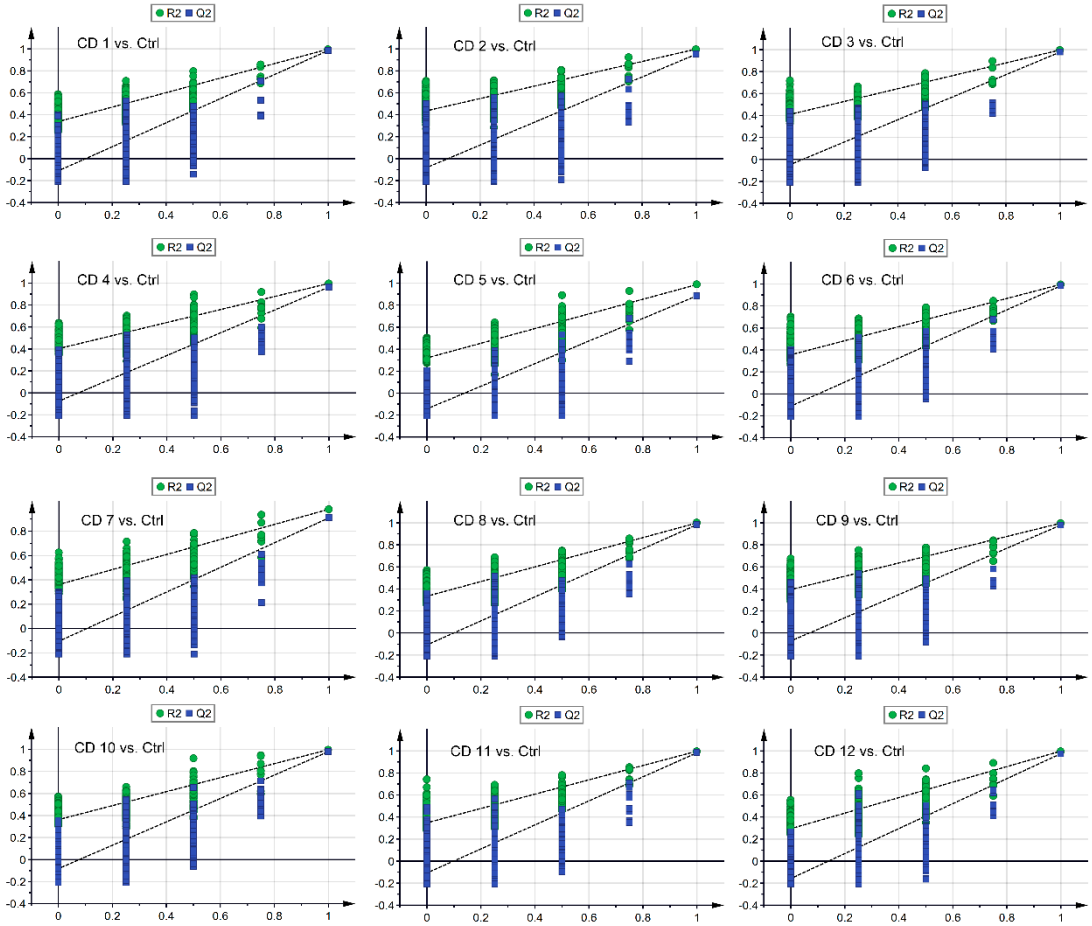


Figure S6. Corresponding permutation tests of PLS-DA models of relative concentration of metabolites data from each coumarin derivative compared with control group.

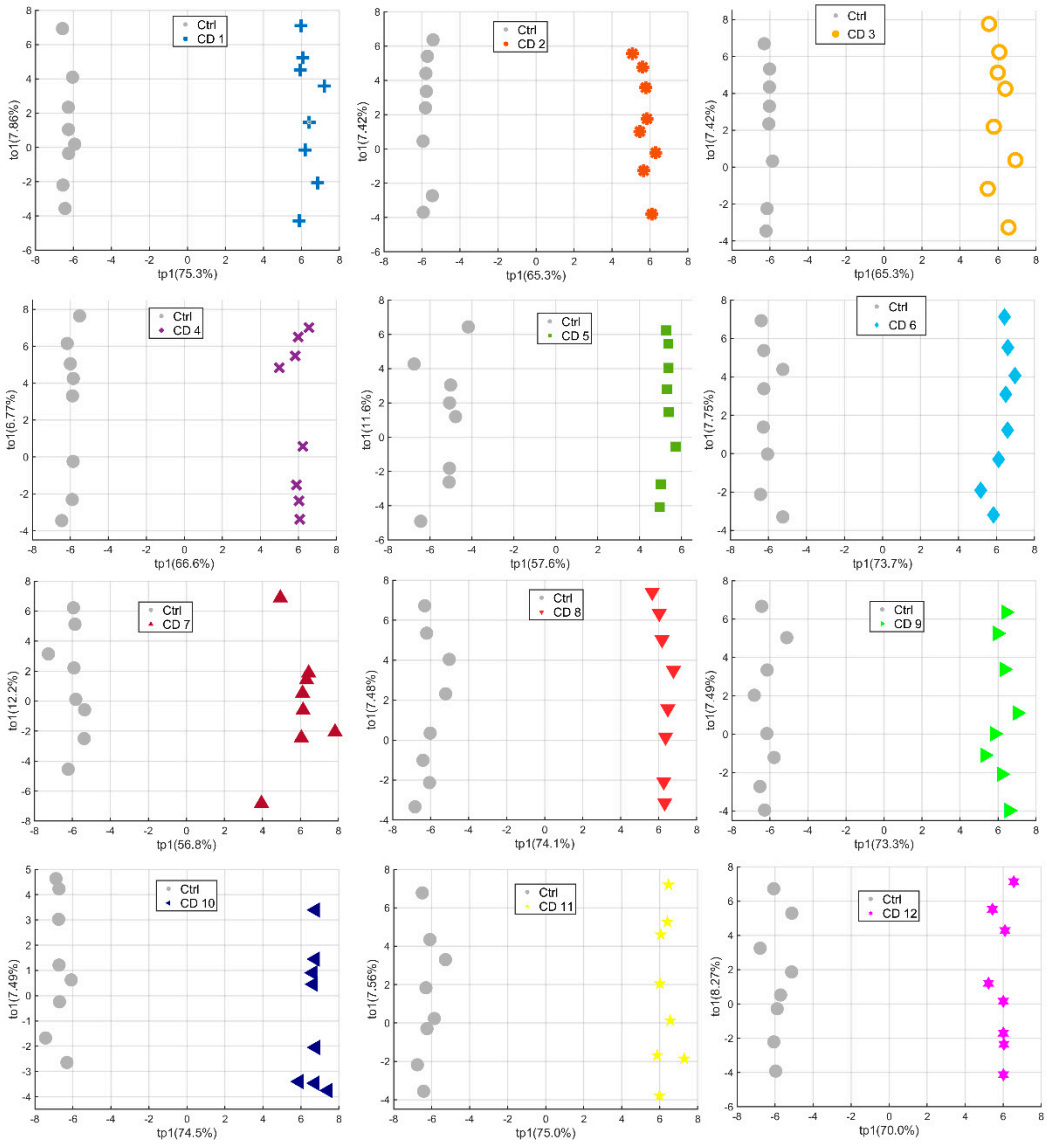
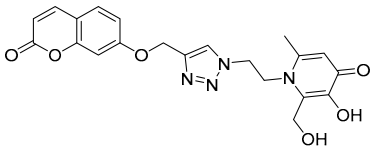
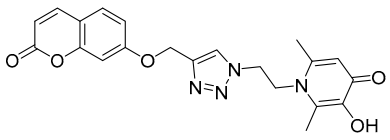
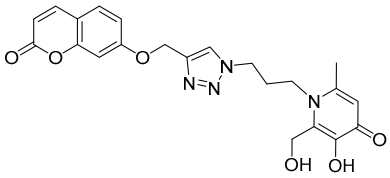
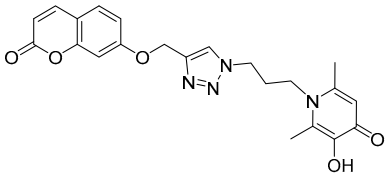
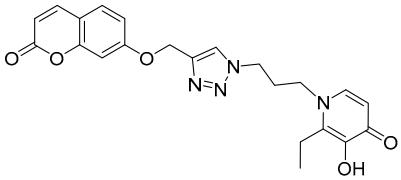
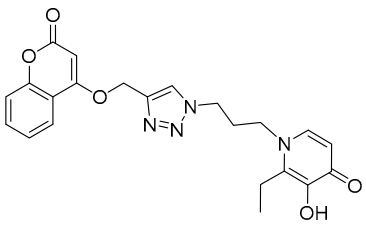
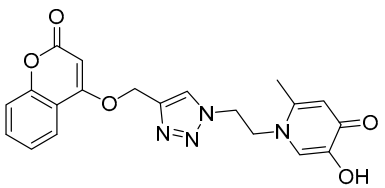


Figure S7. OPLS-DA scores plot of relative concentration of metabolites data from each coumarin derivative compared with control group.

Table S1. The IC_{50} value of coumarin derivatives in the U251 cells

No.	Compound structure	IC_{50} / μm
CD1		54.978
CD2		51.850
CD3		65.033
CD4		76.218
CD5		68.438
CD6		86.896
CD7		98.708

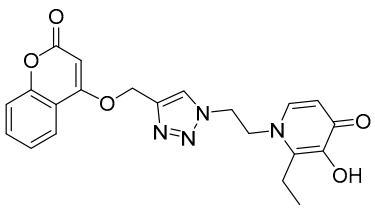
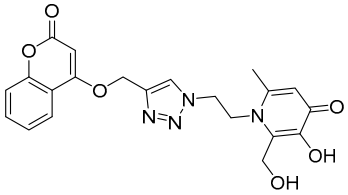
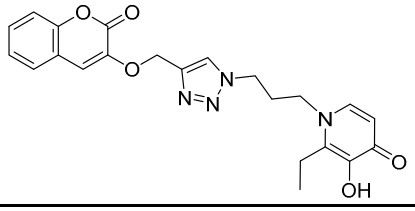
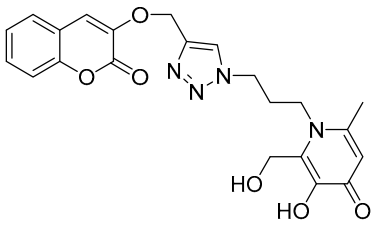
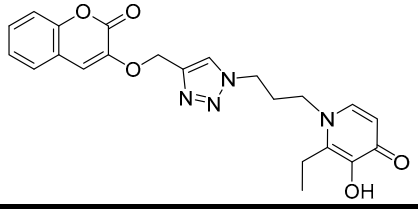
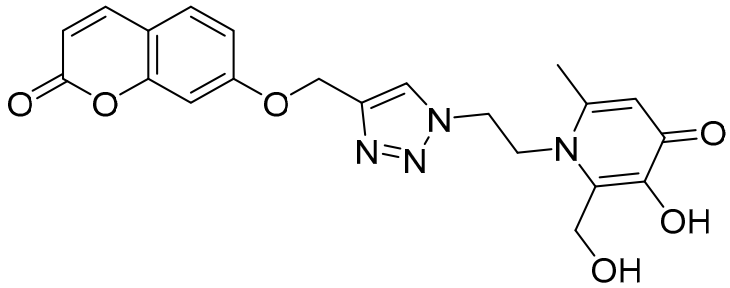
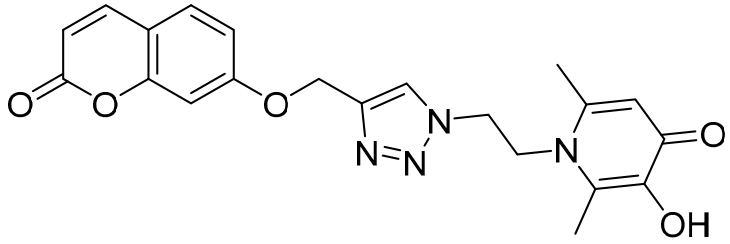
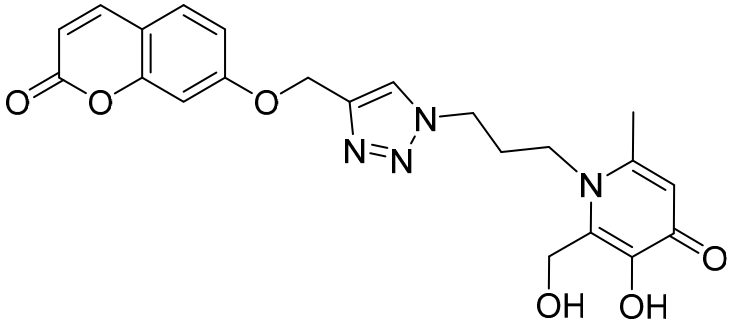
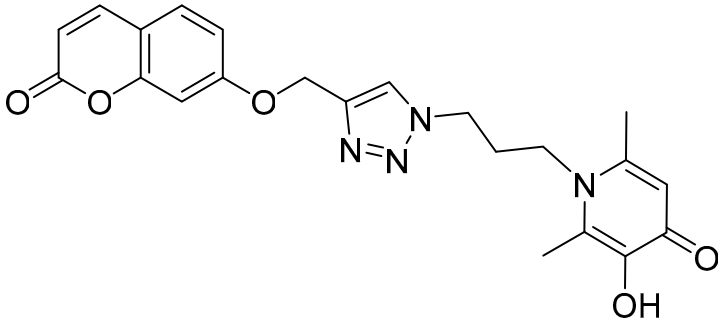
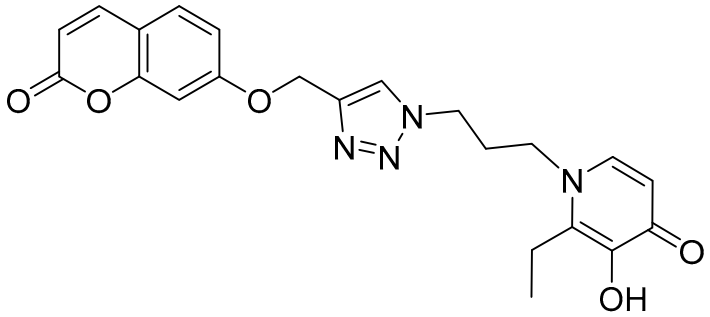
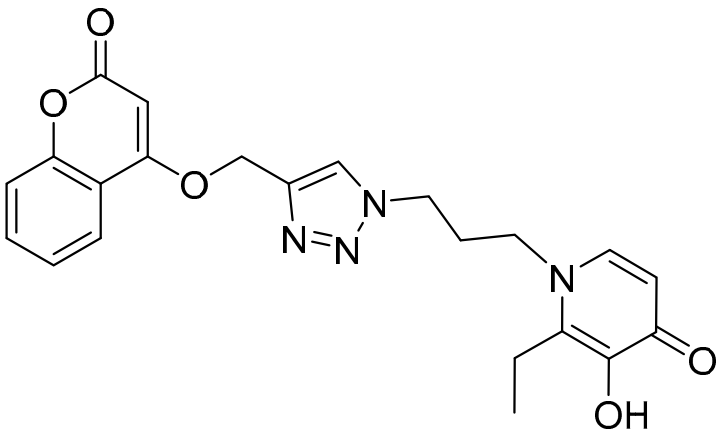
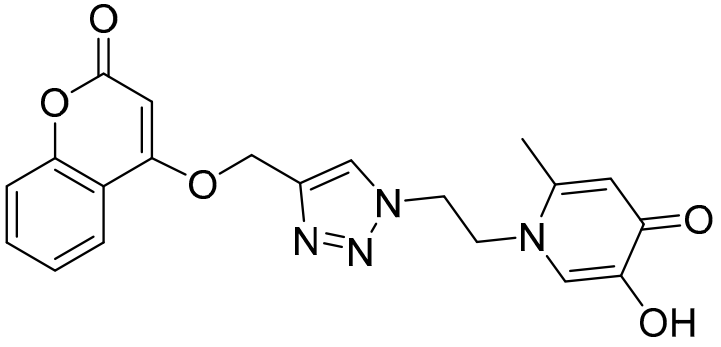
CD8		66.281
CD9		87.534
CD10		65.141
CD11		82.009
CD12		79.775

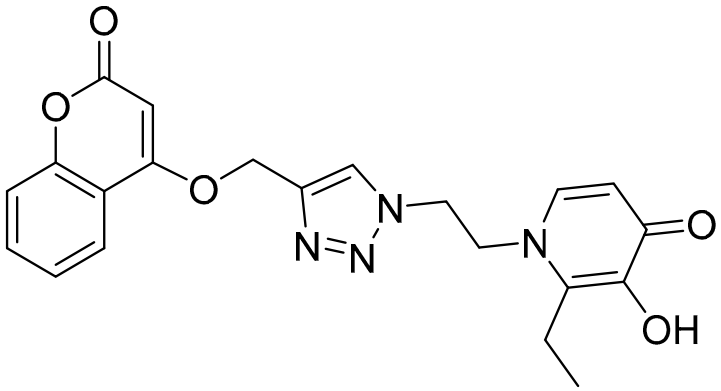
Table S2. The detailed information of twelve coumarin derivatives in our work.

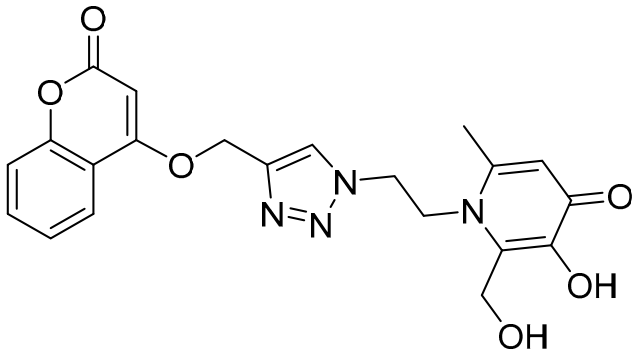
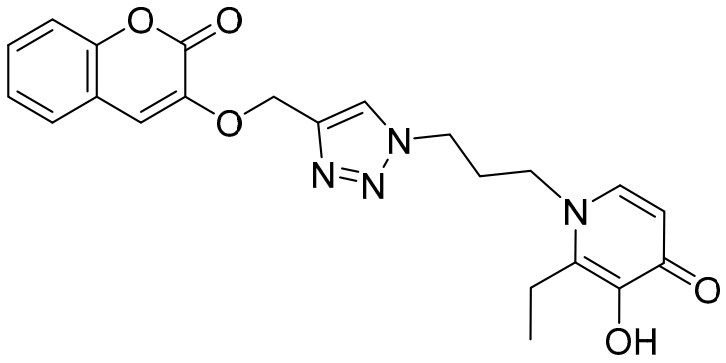
No.	Compound structure	Data Representation
CD1		**3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2-(4-(((2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** yellow solid, yield: 81%; m.p.: 212-215 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.10 (s, 1H), 7.02 (dd, J = 8.6, 2.4 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 5.30 (s, 2H), 4.98 (d, J = 5.9 Hz, 2H), 4.95 (d, J = 5.9 Hz, 2H), 4.60 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.4, 160.7, 160.6, 155.7, 149.6, 144.7, 142.9, 142.8, 142.6, 130.0, 126.3, 113.5, 113.3, 113.2, 113.1, 102.1, 61.9, 53.1, 50.5, 48.4, 20.1. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_6$ $[M+H]^+$: 425.1456; found: 425.1439.
CD2		**3-hydroxy-2,6-dimethyl-1-(2-(4-(((2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** white solid, yield: 93%; m.p.: 256-249 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 7.01 (dd, J = 8.6, 2.5 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 5.30 (s, 2H), 4.93 (t, J = 6.3 Hz, 2H), 4.80 (t, J = 6.2 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.4, 160.7, 159.1,

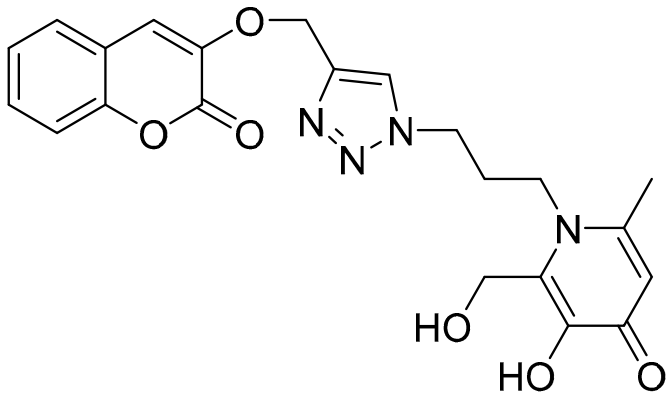
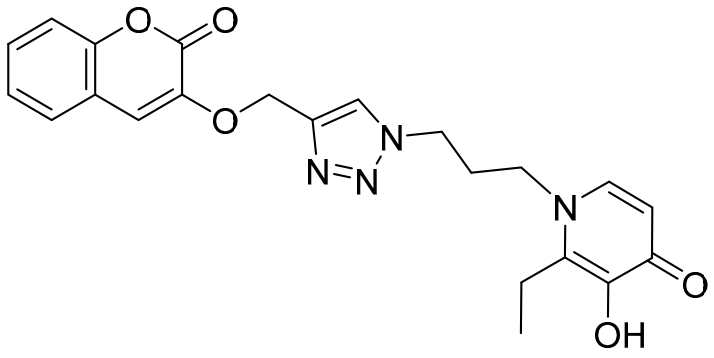
		155.7, 148.4, 144.8, 143.1, 142.9, 141.9, 130.0, 126.4, 113.4, 113.2, 113.1, 112.6, 102.1, 61.9, 51.1, 47.7, 20.3, 13.6. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_5$ $[M+H]^+$: 409.1518; found: 409.1506.
CD3		**3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(3-(4-(((2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)pyridin-4(*1H*)-one:** yellow solid, yield: 84%; m.p.: 189-192 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.15 (s, 1H), 7.12 (s, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.31 (dd, J = 9.4, 1.7 Hz, 1H), 5.29 (s, 2H), 4.76 (s, 2H), 4.61 (t, J = 6.7 Hz, 2H), 4.45 (t, J = 8.5 Hz, 2H), 2.54 (s, 3H), 2.40 (dq, J = 13.3, 6.9 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 163.5, 161.5, 160.7, 160.0, 155.7, 148.8, 144.7, 142.7, 142.5, 142.3, 130.0, 125.5, 113.5, 113.3, 113.1, 102.0. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_6$ $[M+H]^+$: 439.1612; found: 439.1606.
CD4		**3-hydroxy-2,6-dimethyl-1-(3-(4-(((2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)pyridin-4(*1H*)-one:** white solid, yield: 87%; m.p.: 263-265 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.01 (d, J = 9.4 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.15 (s, 1H), 7.06 (s, 1H), 7.02 (d, J = 8.7 Hz, 1H), 6.30 (d, J = 9.4 Hz, 1H), 5.30 (s, 2H), 4.62 (t, J = 6.7 Hz, 2H), 4.34-4.18 (m, 2H), 2.51 (d, J = 7.0

		Hz, 5H), 2.47 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.5, 160.7, 158.6, 155.7, 147.6, 144.7, 142.6, 142.5, 141.8, 130.0, 125.6, 113.4, 113.1, 113.1, 112.6, 102.1, 62.2, 49.1, 47.1, 28.8, 20.3, 13.4. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_5$ $[M+H]^+$: 423.1663; found: 423.1676.
CD5		**2-ethyl-3-hydroxy-1-(3-(4-(((2-oxo-2H-chromen-7-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)pyridin-4(*1H*)-one:** white solid, yield: 91%; m.p.: 204-206 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.02 (d, J = 9.5 Hz, 1H), 7.88 (d, J = 7.1 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 6.6 Hz, 1H), 7.00 (dd, J = 8.6, 2.4 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 5.27 (s, 2H), 4.92 (dd, J = 6.8, 4.5 Hz, 2H), 4.86 (d, J = 5.8 Hz, 2H), 2.69 (q, J = 7.4 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.4, 160.7, 159.5, 155.7, 146.9, 144.7, 143.2, 142.8, 138.8, 130.2, 126.7, 113.3, 113.2, 113.1, 111.3, 102.1, 61.9, 55.1, 49.8, 19.8, 12.1. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_5$ $[M+H]^+$: 409.1506; found: 409.1512.

CD6		**2-ethyl-3-hydroxy-1-(3-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)pyridin-4(*1H*)-one:** white solid, yield: 90%; m.p.: 192-195 ºC; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.12 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.21 (s, 1H), 5.38 (s, 2H), 4.51 (t, J = 6.6 Hz, 2H), 4.41-4.37 (m, 2H), 2.87 (q, J = 7.5 Hz, 2H), 2.32–2.28 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.6 , 161.5, 158.3, 152.8, 145.3, 141.7, 140.1, 138.5, 131.2, 126.7, 123.4, 125.1, 116.1, 114.6, 112.7, 92.7, 64.6, 51.2, 46.4, 30.8, 20.2, 12.5. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_5$ $[M+H]^+$: 423.1815; found: 423.1826.
CD7		**5-hydroxy-2-methyl-1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** white solid, yield: 86%; m.p.: 235-237ºC; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.99 (dd, J = 2.0, 8.4 Hz, 1H), 6.30 (d, J = 9.2 Hz, 1H), 5.26 (s, 2H), 4.92 (d, J = 6.0 Hz, 4H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.7, 161.9, 160.5, 153.2, 148.0, 144.2, 141.6, 133.3, 131.7, 125.7, 124.7, 123.3, 116.9, 115.5,

		114.5, 91.8, 63.2, 53.1, 47.0, 30.1, 18.8. HRMS (ESI) calcd for $C_{20}H_{19}N_4O_5$ $[M+H]^+$: 395.1315; found: 395.1321.
CD8		**2-ethyl-3-hydroxy-1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:**;white solid, yield: 90%; m.p.: 253-256 ºC ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.13 (d, J = 7.0 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 8.4, 7.2, Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.18 (s, 1H), 5.45 (s, 2H), 4.58 (t, J = 6.9 Hz, 2H), 2.87 (q, J = 7.5 Hz, 2H), 2.44 (t, J = 6.6 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.1, 163.0, 159.3, 152.2, 145.6, 143.8, 140.7, 138.2, 133.7, 126.1, 124.3, 123.3, 116.7, 111.6, 110.7, 91.3, 62.3, 51.3, 47.3, 32.1, 12.6. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_5$ $[M+H]^+$: 409.1506; found: 409.1500.

CD9		**3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2-(4-(((2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** white solid, yield: 89%; m.p.: 142-148 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 6.6 Hz, 1H), 7.26 (s, 1H), 7.13 (d, J = 8.4Hz, 1H), 6.21 (d, J = 8.4 Hz, 1H), 5.43 (s, 2H), 4.95 (d, J = 6.0 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 4.60 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.3 , 162.1 , 161.4 , 152.7, 141.7, 144.5, 143.1, 142.7, 142.3, 131.1, 128.6, 111.4, 113.3, 112.0, 113.1, 101.5, 63.7, 52.9, 50.3, 47.4, 20.5. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_6$ $[M+H]^+$: 425.1415; found: 425.1418.
CD10		**3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2-(4-(((2-oxo-2H-chromen-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** white solid, yield: 85%; m.p.: 168-170 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 6.9 Hz, 1H), 6.12 (s, 1H), 5.43 (s, 2H), 4.96 (t, J = 6 Hz, 2H), 4.89 (t, J = 6 Hz, 2H), 2.73 (q, J = 7.8 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H). NMR (150 MHz, DMSO-d_6) δ 165.7, 163.8, 160.5, 151.1, 142.8, 145.1, 142.7, 146.2, 141.5, 131.9, 128.4, 110.3, 113.5, 113.8, 111.9, 101.7,

		63.4, 52.1, 50.4, 45.1, 20.6. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_5$ $[M+H]^+$: 409.1612; found: 409.1607.
CD11		**2-ethyl-3-hydroxy-1-(3-(4-(((2-oxo-2H-chromen-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)pyridin-4(*1H*)-one:** white solid, yield: 92%; m.p.: 195-198 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.11 (s, 1H), 6.17 (s, 1H), 5.46 (s, 2H), 4.76 (s, 2H), 4.63 (t, J = 6.6 Hz, 2H), 2.56 (s, 3H), 2.55 (s, 2H), 2.39-2.45 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.4, 165.7, 160.3, 154.2, 140.8, 143.6, 142.7, 141.9, 141.2, 130.7, 128.5, 122.5, 117.1, 116.5, 112.3, 103.7, 63.3, 51.5, 50.2, 46.8, 31.2. 19.2. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_6$ $[M+H]^+$: 439.1616; found: 439.1603.
CD12		**3-hydroxy-2-(hydroxymethyl)-6-methyl-1-(2-(4-(((2-oxo-2H-chromen-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)pyridin-4(*1H*)-one:** white solid, yield: 85%; m.p.: 168-170 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 6.9 Hz, 1H), 6.12 (s, 1H), 5.43 (s, 2H), 4.96 (t, J = 6 Hz, 2H), 4.89 (t, J = 6 Hz, 2H), 2.73 (q, J = 7.8 Hz, 2H), 1.10 (t, J = 7.4 Hz,

		3H). NMR (150 MHz, DMSO-d_6) δ 165.7, 163.8, 160.5, 151.1, 142.8, 145.1, 142.7, 146.2, 141.5, 131.9, 128.4, 110.3, 113.5, 113.8, 111.9, 101.7, 63.4, 52.1, 50.4, 45.1, 20.6. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_5$ $[M+H]^+$: 409.1612; found: 409.1607.

Table S3. The tagged chemical shifts (ppm) and function groups from the indicated metabolites

No.	HMDB No.	Metabolites Name	Tagged chemical shift (ppm)	Function groups
1	HMDB0001857	1,3-dimethylurate	3.308	CH_3
2	HMDB0001860	1,7-dimethylxanthine	7.830	NH
3	HMDB0000008	2-hydroxybutyrate	0.887	CH_3
4	HMDB0000694	2-hydroxyglutarate	4.017	CH_2
5	HMDB0001863	2-hydroxyvalerate	0.900	CH_3
6	HMDB0000208	2-oxoglutarate	2.429, 2.997	CH_2, CH_2
7	HMDB0000357	3-hydroxybutyrate	1.188	CH_3
8	HMDB0000042	acetate	1.908	CH_3
9	HMDB0000060	acetoacetate	2.272	CH_3
10	HMDB0001659	acetone	2.225	CH_3
11	HMDB0001341	ADP	8.254, 8.507	NH
12	HMDB0000161	alanine	1.469	CH_3
13	HMDB0000045	AMP	8.247, 8.576	NH
14	HMDB0000191	aspartate	2.669, 2.801	CH_2
15	HMDB0000538	ATP	8.245, 8.500	NH
16	HMDB0000043	betaine	3.252	CH_3
17	HMDB0000039	butyrate	0.882	CH_3
18	HMDB0000097	choline	3.189	CH_3
19	HMDB0000094	citrate	2.526	CH_3
20	HMDB0000193	isocitrate	2.990	CH_3
21	HMDB0000064	creatine	3.025	CH_3
22	HMDB0000064	creatine phosphate	3.940	CH_3
23	HMDB0000562	creatinine	4.047	CH_3
24	HMDB0000087	dimethylamine	2.715	CH_3
25	HMDB0000108	ethanol	1.173	CH_3
26	HMDB0001887	ethylene glycol	3.662	CH_3
27	HMDB0000142	formate	8.444	H
28	HMDB0000134	fumarate	6.509	=CH
29	HMDB0000107	galactitol	3.688	CH
30	HMDB0000122	glucose	4.637, 5.226	CH
31	HMDB0000148	glutamate	2.348	CH_2
32	HMDB0000641	glutamine	2.445	CH_2
33	HMDB0000125	glutathione	2.965	CH_2
34	HMDB0000123	glycine	3.575	CH_2
35	HMDB0000128	guanidoacetate	3.785	CH_2

36	HMDB0000177	histidine	7.082, 7.822	=CH
37	HMDB0000157	hypoxanthine	8.179, 8.201	=CH
38	HMDB0000195	inosine	8.224, 8.333	=CH
39	HMDB0000172	isoleucine	0.926, 0.998	CH_3, CH_2
40	HMDB0000190	lactate	4.118	CH
41	HMDB0000687	leucine	0.948	CH_3
42	HMDB0000182	lysine	1.715	CH_2
43	HMDB0000691	malonate	3.119	CH_2
44	HMDB0001138	N-acetylglutamate	2.021	CH_3
45	HMDB0006029	N-acetylglutamine	2.025	CH_3
46	HMDB0000532	N-acetylglycine	2.028	CH_3
47	HMDB0000902	NAD+	9.329	CH
48	HMDB0001406	niacinamide	8.929	NH_2
49	HMDB0001565	phosphocholine	3.206	CH_3
50	HMDB0000210	pantothenate	0.883, 0.918	CH_3
51	HMDB0000159	phenylalanine	7.318, 7.367, 7.419	CH
52	HMDB0000243	pyruvate	2.363	CH_3
53	HMDB0000086	glycero-3-phosphocholine	3.215	CH_3
54	HMDB0000254	succinate	2.394	CH_2
55	HMDB0000251	taurine	3.417	CH_2
56	HMDB0000925	trimethylamine-N-oxide	3.253	CH_3
57	HMDB0000158	tyrosine	6.887, 7.182	CH
58	HMDB0000883	valine	1.030	CH_3

Table S4. Detailed statistical information for each group of differential metabolites.

CD1 vs. Ctrl				
	p	FC	VIP	p(corr)
glycine	0.0004	1.2891	1.4341	0.8899
guanidoacetate	0.0131	1.1860	1.0232	0.6426
lysine	0.0234	1.1903	1.1271	0.5334
aspartate	0.0037	-1.1800	1.1183	-0.7673
galactitol	0.0481	-1.1578	1.2110	-0.6207
taurine	0.0323	-1.1877	1.2788	-0.6144
CD2 vs. Ctrl				
	p	r	VIP	p(corr)
galactitol	0.0469	1.1739	1.1184	0.5297
glutamate	0.0264	1.3199	1.9076	0.7066
glutamine	0.0156	1.2160	1.4088	0.5259
taurine	0.0004	-1.2242	1.4384	-0.7824
inosine	0.0052	-1.1828	1.1209	-0.9053
lysine	0.0099	-1.1788	1.3903	-0.6761
CD3 vs. Ctrl				
	p	FC	VIP	p(corr)
phenylalanine	0.0000	1.2826	1.3158	0.8671
glutamate	0.0135	1.3637	1.8608	0.6218
glutamine	0.0076	1.3618	2.0673	0.6957
NAD+	0.0347	1.2587	1.6972	0.6305
taurine	0.0000	-1.7013	2.9456	-0.9636
aspartate	0.0000	-1.1881	1.6817	-0.9370
lysine	0.0080	-1.2176	1.1799	-0.6805
CD4 vs. Ctrl				
	p	FC	VIP	p(corr)
galactitol	0.0000	1.7099	1.4126	0.9057
glutamate	0.0010	1.6298	1.3248	0.8152
glutamine	0.0007	1.9457	1.5801	0.8393
glutathione	0.0015	10.5329	2.9545	0.8150
NAD+	0.0001	2.1130	1.6017	0.7937
taurine	0.0000	-2.3755	1.8588	-0.9813
lysine	0.0000	-1.6173	1.3681	-0.9545
CD5 vs. Ctrl				
	p	FC	VIP	p(corr)
glutamate	0.0013	1.7729	1.2967	0.4243
glutamine	0.0011	2.1033	1.5150	0.9699
ADP	0.0002	1.4419	1.0858	0.8865
taurine	0.0000	-2.2449	1.7107	-0.9668
lactate	0.0222	-1.9491	1.2174	-0.5926

CD6 vs. Ctrl				
	p	FC	VIP	p(corr)
glycine	0.0000	1.1602	1.2528	0.8705
lactate	0.0230	1.7565	2.0297	0.6077
aspartate	0.0000	-1.2253	1.4525	-0.9353
taurine	0.0000	-1.3156	1.6988	-0.8718
glutathione	0.0458	-1.8059	2.1434	-0.6081
CD7 vs. Ctrl				
	p	FC	VIP	p(corr)
glutamate	0.0048	2.2818	1.6714	0.7408
glutamine	0.0017	2.0868	1.7074	0.8359
glutathione	0.0436	5.4437	2.7678	0.6284
lactate	0.0439	7.4065	2.9879	0.5870
taurine	0.0000	-1.6553	1.4108	-0.9416
inosine	0.0005	-1.3202	1.0602	-0.8677
CD8 vs. Ctrl				
	p	FC	VIP	p(corr)
phenylalanine	0.0007	1.2713	1.0910	0.7036
glutamate	0.0408	1.2283	1.9236	0.5611
lactate	0.0380	2.1439	3.9894	0.5583
taurine	0.0000	-1.3363	2.5242	-0.8967
aspartate	0.0000	-1.1715	1.9275	-0.9245
CD9 vs. Ctrl				
	p	FC	VIP	p(corr)
galactitol	0.0033	3.5407	1.6754	0.7464
glutathione	0.0000	26.6600	2.8216	0.9351
glycine	0.0000	3.0527	1.6592	0.9629
guanidoacetate	0.0000	2.6467	1.5585	0.9734
ethanol	0.0000	3.2240	1.7033	0.9809
aspartate	0.0000	-1.6037	1.0783	-0.9844
taurine	0.0000	-2.0226	1.3253	-0.9890
inosine	0.0000	-1.8396	1.2343	-0.9908
glutamate	0.0000	-2.6561	1.5144	-0.8956
lactate	0.0000	-3.7449	1.7378	-0.8381
CD10 vs. Ctrl				
	p	FC	VIP	p(corr)
galactitol	0.0000	1.4696	1.4135	0.8900
glutamate	0.0000	2.5836	2.3099	0.8945
glutamine	0.0000	2.9352	2.5162	0.9211
glutathione	0.0000	35.4889	4.5058	0.9305
glycine	0.0050	1.3031	1.1898	0.7633
guanidoacetate	0.0003	1.2462	1.0552	0.8145
butyrate	0.0002	1.2645	1.1557	0.8751

ethanol	0.0001	1.3796	1.3377	0.9163
leucine	0.0001	1.2226	1.0031	0.8273
NAD+	0.0006	-1.6655	1.6371	-0.8757
CD11 vs. Ctrl				
	p	FC	VIP	p(corr)
taurine	0.0000	1.3117	2.1857	0.8085
inosine	0.0148	1.3594	1.0711	0.7328
lactate	0.0394	-1.4575	3.0995	-0.7218
CD12 vs. Ctrl				
	p	FC	VIP	p(corr)
phenylalanine	0.0000	1.3169	1.3661	0.9218
3-hydroxybutyrate	0.0021	1.3813	1.1157	0.8541
isoleucine	0.0025	1.2886	1.9347	0.7812
lactate	0.0214	1.8251	2.5595	0.6218
leucine	0.0037	1.4152	2.2915	0.7795
lysine	0.0401	1.1815	1.4645	0.5843
taurine	0.0000	-1.5662	2.5460	-0.9320
aspartate	0.0000	-1.2643	1.9503	-0.9598
glutamine	0.0428	-1.2472	1.5466	-0.5901

Table S5. The results of significantly disturbed metabolic pathways for each coumarin derivative affecting the celluar U251metabolic pathways

	Total	Expected	Hits	Raw p	-log(p)	Holmadjust	FDR	Impact
CD1 vs. Ctrl								
Aminoacyl-tRNA biosynthesis	48	0.19	3	5.23×10^{-4}	3.28	4.39×10^{-2}	4.39×10^{-2}	0.10
Glycine, serine and threoninemetabolism	33	0.13	2	6.25×10^{-3}	2.20	5.19×10^{-1}	2.63×10^{-1}	0.23
Taurine and hypotaurine metabolism	8	0.03	1	3.06×10^{-2}	1.51	1.00	6.19×10^{-1}	0.33
CD2 vs. Ctrl								
D-Glutamine and D-glutamate metabolism	6	0.02	2	1.86×10^{-4}	3.73	1.56×10^{-2}	7.82×10^{-3}	0.25
Aminoacyl-tRNA biosynthesis	48	0.19	3	5.23×10^{-4}	3.28	4.29×10^{-2}	1.46×10^{-2}	0.10
Arginine biosynthesis	14	0.05	2	1.11×10^{-3}	2.95	9.02×10^{-2}	2.34×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.11	2	4.52×10^{-3}	2.35	3.61×10^{-1}	7.59×10^{-2}	0.28
Taurine and hypotaurine metabolism	8	0.03	1	3.06×10^{-2}	1.51	1.00	3.22×10^{-1}	0.33
CD3 vs. Ctrl								
Aminoacyl-tRNA biosynthesis	48	0.22	5	4.63×10^{-7}	6.33	3.89×10^{-5}	3.89×10^{-5}	0.17
Arginine biosynthesis	14	0.06	3	2.01×10^{-5}	4.70	1.67×10^{-3}	8.46×10^{-4}	0.25
Alanine, aspartate and glutamate metabolism	28	0.13	3	1.76×10^{-4}	3.75	1.45×10^{-2}	4.37×10^{-3}	0.47
D-Glutamine and D-glutamate metabolism	6	0.03	2	2.60×10^{-4}	3.58	2.11×10^{-2}	4.37×10^{-3}	0.50
Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.02	1	1.80×10^{-2}	1.75	1.00	1.68×10^{-1}	0.50
CD4 vs. Ctrl								
D-Glutamine and D-glutamate metabolism	6	0.03	2	2.60×10^{-4}	3.58	2.19×10^{-2}	1.09×10^{-2}	0.50
Aminoacyl-tRNA biosynthesis	48	0.22	3	8.95×10^{-4}	3.05	7.34×10^{-2}	2.51×10^{-2}	0.10
Arginine biosynthesis	14	0.06	2	1.55×10^{-3}	2.81	1.26×10^{-1}	3.26×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.13	2	6.25×10^{-3}	2.20	5.00×10^{-1}	8.75×10^{-2}	0.28

Glutathione metabolism	28	0.13	2	6.25×10^{-3}	2.20	5.00×10^{-1}	8.75×10^{-2}	0.19
Taurine and hypotaurine metabolism	8	0.04	1	3.56×10^{-2}	1.45	1.00	3.74×10^{-1}	0.33
CD5 vs. Ctrl								
D-Glutamine and D-glutamate metabolism	6	0.02	2	1.24×10^{-4}	3.91	1.04×10^{-2}	5.22×10^{-3}	0.50
Arginine biosynthesis	14	0.05	2	7.46×10^{-4}	3.13	6.12×10^{-2}	2.09×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.09	2	3.04×10^{-3}	2.52	2.47×10^{-1}	6.39×10^{-2}	0.28
Taurine and hypotaurine metabolism	8	0.03	1	2.56×10^{-2}	1.59	1.00	2.69×10^{-1}	0.33
CD6 vs. Ctrl								
Glutathione metabolism	28	0.09	2	3.04×10^{-3}	2.52	2.56×10^{-1}	2.48×10^{-1}	0.19
Aminoacyl-tRNA biosynthesis	48	0.15	2	8.85×10^{-3}	2.05	7.26×10^{-1}	2.48×10^{-1}	0.07
Taurine and hypotaurine metabolism	8	0.03	1	2.56×10^{-2}	1.59	1.00	5.37×10^{-1}	0.33
CD7 vs. Ctrl								
D-Glutamine and D-glutamate metabolism	6	0.02	2	1.86×10^{-4}	3.73	1.56×10^{-2}	1.56×10^{-2}	0.5
Arginine biosynthesis	14	0.05	2	1.11×10^{-3}	2.95	9.12×10^{-2}	9.12×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.11	2	4.52×10^{-3}	2.35	7.59×10^{-2}	7.59×10^{-2}	0.28
Glutathione metabolism	28	0.11	2	4.52×10^{-3}	2.35	7.59×10^{-2}	7.59×10^{-2}	0.19
Taurine and hypotaurine metabolism	8	0.03	1	3.06×10^{-2}	1.51	2.86×10^{-1}	2.86×10^{-1}	0.33
CD8 vs. Ctrl								
Arginine biosynthesis	14	0.05	2	7.46×10^{-4}	3.13	6.19×10^{-2}	2.75×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.05	2	3.04×10^{-3}	2.52	2.47×10^{-2}	6.39×10^{-2}	0.31
Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.01	1	1.29×10^{-2}	1.89	1.00	2.16×10^{-1}	0.50
CD9 vs. Ctrl								
Glutathione metabolism	28	0.18	3	5.83×10^{-4}	3.23	4.90×10^{-2}	4.90×10^{-2}	0.22
Aminoacyl-tRNA biosynthesis	48	0.31	3	2.87×10^{-3}	2.54	2.38×10^{-1}	9.00×10^{-2}	0.10

Arginine biosynthesis	14	0.09	2	3.27×10^{-3}	2.49	2.68×10^{-1}	9.00×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.18	2	1.30×10^{-2}	1.89	1.00	1.66×10^{-1}	0.31
Glycine, serine and threonine metabolism	33	0.21	2	1.78×10^{-2}	1.75	1.00	1.66×10^{-1}	0.23
Taurine and hypotaurine metabolism	8	0.05	1	5.06×10^{-2}	1.30	1.00	3.03×10^{-1}	0.33
CD10 vs. Ctrl								
Aminoacyl-tRNA biosynthesis	48	0.31	4	1.49×10^{-4}	3.83	1.25×10^{-2}	1.22×10^{-2}	0.14
D-Glutamine and D-glutamate metabolism	6	0.04	2	5.55×10^{-4}	3.26	4.06×10^{-2}	1.22×10^{-2}	0.50
Glutathione metabolism	28	0.18	3	5.83×10^{-4}	3.23	4.72×10^{-2}	1.22×10^{-2}	0.22
Arginine biosynthesis	14	0.09	2	3.27×10^{-3}	2.49	2.59×10^{-1}	4.52×10^{-2}	0.19
Alanine, aspartate and glutamate metabolism	28	0.18	2	1.30×10^{-2}	1.89	9.97×10^{-1}	1.36×10^{-1}	0.28
Glycine, serine and threonine metabolism	33	0.21	2	1.78×10^{-2}	1.75	1.00	1.49 x 10-1	0.23
Valine, leucine and isoleucine biosynthesis	8	0.05	1	5.06×10^{-2}	1.30	1.00	3.54×10^{-1}	0.25
CD11 vs. Ctrl								
Taurine and hypotaurine metabolism	8	0.02	1	1.54×10^{-2}	1.81	1.00	1.00	0.33
CD12 vs. Ctrl								
Aminoacyl-tRNA biosynthesis	48	0.28	6	5.03×10^{-8}	7.30	4.23×10^{-6}	4.23×10^{-6}	0.21
Valine, leucine and isoleucine biosynthesis	8	0.05	2	8.25×10^{-4}	3.08	6.84×10^{-2}	3.46×10^{-2}	0.25
Alanine, aspartate and glutamate metabolism	28	0.16	2	1.05×10^{-2}	1.98	8.49×10^{-1}	2.20×10^{-1}	0.34
Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.02	1	2.30×10^{-2}	1.64	1.00	3.21×10^{-1}	0.50