

**Supplementary Table 2.** List of overlapped rat serum metabolites between CSIS+Flx vs. CSIS, and CSIS vs. Control, and Control+Flx vs. Control that had an AUC > 0.90

Metabolites	CSIS+Flx vs. CSIS		CSIS vs. Control		Control+Flx vs. Control	
	AUC	FC	AUC	FC	AUC	FC
5'-Methylthio adenosine	1	2.71	0.97222	0.58		
7-Methylguanine	1	2.63			1	1.88
Stachydrine	1	2.30			1	3.27
Succinate	1	3.04			0.91667	2.42
1-Methylxanthine	0.97917	2.66			0.95833	1.87
Aspartate	0.97917	0.49			0.91667	0.59
Histamine	0.97917	0.51			0.97917	0.38
Hydroxyhippuric acid	0.95833	0.38			0.95833	0.34
Propionylcarnitine	0.95833	1.66			1	2.04
Hydroxyhexa decanoic acid	0.91667	0.75			1	0.45

**Supplementary Table 3.** List of overlapped rat serum predictive metabolites from SVM-LK for classification CSIS+Flx vs. CSIS, CSIS vs. Control and Control+Flx vs. Control

Predictive metabolites	CSIS+Flx vs. CSIS	CSIS vs. Control	Control+Flx vs. Control
	FC	FC	FC
Succinate	3.04		2.42
Stachydrine	2.30		3.27
Amino(iso)butyric acid	1.31	0.82	
Urea	1.14	0.96	1.12
Choline	0.84	1.27	0.84
Histamine	0.51		0.38

**Supplementary Table 4.** List of metabolites for the classification of Control+Flx vs. Control, CSIS vs. Control and CSIS+Flx vs. CSIS obtained by Random Forest

Control+Flx (positive) vs. Control		CSIS (positive) vs. Control		CSIS+Flx (positive) vs. CSIS	
Accuracy	98.00%	Accuracy	75.83%	Accuracy	98.50%
Sensitivity	96.67%	Sensitivity	66.67%	Sensitivity	100.00%
Specificity	100.00%	Specificity	85.00%	Specificity	96.67%

Balanced Accuracy 98.33%

Balanced Accuracy 75.83%

Balanced Accuracy 98.33%

Predictive metabolites			Predictive metabolites			Predictive metabolites		
Name	Importance	FC	Name	Importance	FC	Name	Importance	FC
Hydroxyhexadecanoic acid	0.1354	0.45	5'-Methylthioadenosine	0.1327	0.58	Stachydrine	0.0767	2.30
Histamine	0.0807	0.38	Choline	0.1200	1.27	7-Methylguanine	0.0767	2.63
Stachydrine	0.0800	3.27	N1-Acetyl spermidine	0.0714	0.31	5'-Methylthioadenosine	0.0706	2.71
7-Methylguanine	0.0658	1.88	Myo-Inositol	0.0633	0.71	1-Methylxanthine	0.0662	2.66
1-Methylxanthine	0.0574	1.87	Glutamine	0.0429	0.72	Kynurenic acid	0.0600	2.29
Propionyl carnitine	0.0553	2.04	Lysine	0.0429	0.63	Succinate	0.0600	3.04
3-(4-Hydroxyphenyl)lactate	0.0458	0.64	Cystathionine	0.0386	0.52	Aspartate	0.0554	0.49
Aspartate	0.0413	0.59	Arginine	0.0343	0.72	Guanidinoacetate	0.0412	1.86
Hydroxyhippuric acid	0.0356	0.34	Allantoin	0.0340	0.85	Glycerophosphocholine	0.0317	0.74
Riboflavin	0.0274	1.39	N-Acetylcytidine	0.0302	0.82	Choline	0.0292	0.84
Ala-Pro (Alanyl-Proline)	0.0244	1.65	Methionine	0.0288	0.82	Histamine	0.0281	0.51
Anserine	0.0228	0.59	Indole	0.0286	0.88	N-Acetylglycine	0.0219	0.69
Succinate	0.0228	2.42	Hydroxyhexadecanoic acid	0.0257	0.78	Hydroxyhexadecanoic acid	0.0217	0.75
Urocanate	0.0200	0.60	Asparagine	0.0213	0.78	N1-Acetyl spermidine	0.0200	3.67
Orotic acid	0.0200	0.65	Vanillic acid	0.0143	0.74	Propionyl carnitine	0.0200	1.66
Choline	0.0131	0.85	Cytidine	0.0143	0.89	Hydroxyhippuric acid	0.0183	0.38
Sphingomyelin (d34:1)	0.0126	0.94	Urate	0.0143	0.67	Tauro(cheno) deoxycholic Acid	0.0183	1.57
3-Methylhistidine	0.0101	0.86	Pyridoxic acid	0.0143	0.81	Amino(iso) butyric acid	0.0163	1.31
1-Methylhistidine	0.0100	1.25	Dimethyl arginine	0.0143	0.78	Trimethyllysine	0.0152	1.29
Guanidinoacetate	0.0100	1.55	Pantothenic acid	0.0143	0.72	Cytosine	0.0152	1.14
Glutamine	0.8100	0.81	Histidine	0.0143	0.75	Indoxyl sulfate	0.0150	1.53
Kynurenic acid	0.0100	1.63	N-Acetyl aspartic acid	0.0143	0.70	Urea	0.0106	1.14
Sphingomyelin (d36:1)	0.0100	0.85	Sphingosine (d18:1)	0.0143	1.43	Allantoin	0.0096	1.28

N-Acetylglycine	0.0100	0.82	Methylcytidine	0.0143	0.88	Palmitoyl carnitine	0.0088	1.34
Protoporphyrin	0.0100	0.85	Histamine	0.0143	0.89	Prolylleucine	0.0086	0.71
Proline	0.0100	1.00	Pseudouridine	0.0143	0.77	N-Methyl histamine	0.0085	1.46
Ascorbic Acid-2-sulfate	0.0100	0.81	Stachydrine	0.0127	1.40	Glutamyl-glutamine	0.0077	1.70
Glutamyl-glutamine	0.0100	0.85	Guanidino acetate	0.0102	0.87	Hexanoyl carnitine	0.0067	1.38
Uracil	0.0100	0.54	Citrulline	0.0100	0.76	PLK	0.0067	1.10
N-Acetylserine	0.0097	0.87	Ascorbic Acid-2-sulfate	0.0100	0.73	Deoxy carnitine	0.0067	1.49
Dimethyl arginine	0.0075	0.98	Carnitine	0.0086	0.82	N-Acetyl cytidine	0.0067	1.42
3-Hydroxy-3-methylglutarate	0.0075	0.66	Cytosine	0.0071	0.97	Sphingomyelin (d34:1)	0.0067	0.90
Lactate	0.0075	0.76	Glutamyl-glutamine	0.0071	0.34	Ureido propionic acid	0.0067	1.10
Ureidopropionic acid	0.0074	0.67	Amino(iso)butyric acid	0.0071	0.82	Cystathionine	0.0067	1.50
Acetyl-L-carnitine	0.0072	0.78	Aspartate	0.0048	1.16	Ascorbic Acid-2-sulfate	0.0067	1.02
Glycerophosphocholine	0.0072	0.67	Acetyl-L-carnitine	0.0043	0.95	Creatinine	0.0067	1.10
Cystathionine	0.0067	0.95	Glycerophosphocholine	0.0043	0.99	3-Methyl histidine	0.0065	1.26
Glutamylleucine	0.0067	1.15	N8-Acetyl spermidine	0.0043	0.89	Cytidine	0.0056	1.05
Amino(iso)butyric acid	0.0054	0.96	Creatinine	0.0041	1.03	Xanthosine	0.0054	1.01
Adenosine	0.0046	0.75	Homocitrulline	0.0041	1.03	Acetyl-L-carnitine	0.0048	1.21
Carnosine	0.0044	0.91	Prolylleucine	0.0041	1.17	Lactate	0.0045	1.07
Myo-Inositol	0.0042	1.25	Phenylalanine	0.0041	0.89	Glycine	0.0041	1.12
Betaine	0.0032	0.98				Methionine sulfoxide	0.0036	0.81
Carnitine	0.0028	0.81				Riboflavin	0.0035	1.43
Pyruvate	0.0026	0.82				Methylcytidine	0.0033	1.18
Trimethyllysine	0.0025	1.10				Citrulline	0.0031	0.92
Ornithine	0.0025	0.89				Butanoyl carnitine	0.0031	1.04
						Sphingomyelin (d36:1)	0.0026	0.89
						Uridine	0.0019	1.21
						Urate	0.0017	1.37
						Pseudouridine	0.0017	1.34

**Supplementary Table 5.** List of overlapped rat serum predictive metabolites from RF for classification CSIS+Flx vs. CSIS, CSIS vs. Control and Control+Flx vs. Control

Predictive metabolites	CSIS+Flx vs. CSIS		CSIS vs. Control		Control+Flx vs. Control	
	Importance	FC	Importance	FC	Importance	FC
Stachydrine	0.0767	2.30	0.0127	1.40	0.0800	3.27
7-Methylguanine	0.0767	2.63			0.0658	1.88
5'-Methylthioadenosine	0.0706	2.71	0.1327	0.58		
1-Methylxanthine	0.0662	2.66			0.0574	1.87
Kynurenic acid	0.0600	2.29			0.0100	1.63
Succinate	0.0600	3.04			0.0228	2.42
Aspartate	0.0554	0.49	0.0048	1.16	0.0413	0.59
Guanidinoacetate	0.0412	1.86	0.0102	0.87	0.0100	1.55
Glycerophosphocholine	0.0317	0.74	0.0043	0.99	0.0072	0.67
Choline	0.0292	0.84	0.1200	1.27	0.0131	0.85
Histamine	0.0281	0.51	0.0143	0.89	0.0807	0.38
N-Acetylglycine	0.0219	0.69			0.0100	0.82
Hydroxyhexadecanoic acid	0.0217	0.75	0.0257	0.78	0.1354	0.45
N1-Acetylspermidine	0.0200	3.67	0.0714	0.31		
Propionylcarnitine	0.0200	1.66			0.0553	2.04
Hydroxyhippuric acid	0.0183	0.38			0.0356	0.34
Amino(iso)butyric acid	0.0163	1.31	0.0071	0.82	0.0054	0.96
Trimethyllysine	0.0152	1.29			0.0025	1.10
Cytosine	0.0152	1.14	0.0071	0.97		
Allantoin	0.0096	1.28	0.0340	0.85		
Prolylleucine	0.0086	0.71	0.0041	1.17		
Glutamyl-glutamine	0.0077	1.70	0.0071	0.34	0.0100	0.85
Cystathionine	0.0067	1.50	0.0386	0.52	0.0067	0.95
Ascorbic Acid-2-sulfate	0.0067	1.02	0.0100	0.73	0.0100	0.81
N-Acetylcytidine	0.0067	1.42	0.0302	0.82		
Creatinine	0.0067	1.10	0.0041	1.03		
Sphingomyelin (d34:1)	0.0067	0.90			0.0126	0.94
Ureidopropionic acid	0.0067	1.10			0.0074	0.67
3-Methylhistidine	0.0065	1.26			0.0101	0.86
Cytidine	0.0056	1.05	0.0143	0.89		
Acetyl-L-carnitine	0.0048	1.21	0.0043	0.95	0.0072	0.78
Lactate	0.0045	1.07			0.0075	0.76
Riboflavin	0.0035	1.43			0.0274	1.39
Methylcytidine	0.0033	1.18	0.0143	0.88		
Citrulline	0.0031	0.92	0.0100	0.76		
Sphingomyelin (d36:1)	0.0026	0.98			0.0100	0.85
Urate	0.0017	1.37	0.0143	0.67		

Pseudouridine	0.0017	1.34	0.0143	0.77		
Myo-Inositol			0.0633	0.71	0.0042	1.25
Glutamine			0.0429	0.72	0.0100	0.81
Dimethylarginine			0.0143	0.78	0.0075	0.98
Carnitine			0.0086	0.82	0.0028	0.81