

# Disease differentiation and monitoring of anti-TNF treatment in rheumatoid arthritis and spondyloarthropathies

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## Supplemental material

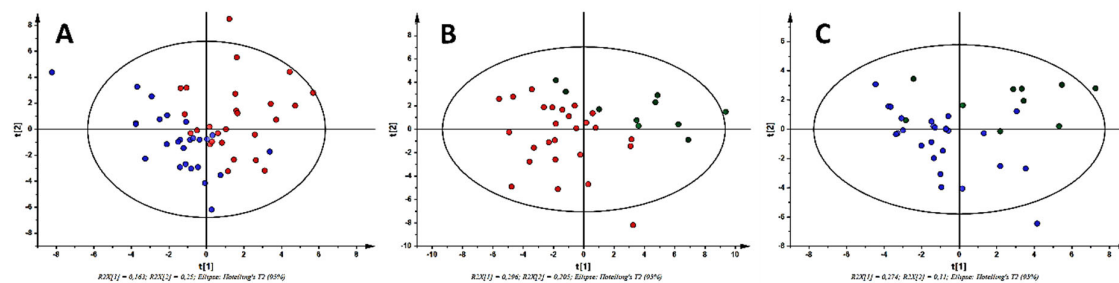
**Table S1.** Demographic data and clinical profiles of patients treated with TNF inhibitors.

Patients	RA	AS	PsA
Number of patients; n	26	29	23 (20 peripheral + 3 axial)
Age, median (range); years	55 (23-74)	45 (26-75)	43 (29-71)
Sex; females/males	21/5	7/22	9/14
Disease duration, median (range); years	9 (1-56)	11 (1-40)	8 (2-41)
Disease onset, median (range); years	43 (4-64)	31 (12-45)	35 (18-56)
Anti-CCP positive, n (%)	18 (69%)	-	-
RF positive, n (%)	20 (77%)	-	-
HLA B27 positive, n (%)	-	27 (93%)	-
<b>Concomitant treatment at the start of biologic treatment:</b>			
MTX, n (%)	17 (65%)	9 (31%)	15 (65%)
Corticosteroids, n (%)	14 (54%)	5 (17%)	2 (9%)
<b>Treatment (anti TNF drug):</b>			
Etanercept, n (%)	14 (54%)	11 (38%)	8 (35%)
Golimumab, n (%)	3 (11.5%)	2 (7%)	3 (13%)
Adalimumab, n (%)	3 (11.5%)	10 (35%)	10 (43%)
Certolizumab, n (%)	6 (23%)	5 (17%)	2 (9%)
Infliximab, n (%)	-	1 (3%)	-

<b>Disease activity:</b>			
DAS28 before treatment, mean $\pm$ SD	6.10 $\pm$ 0.62 (range: 5.12-7.19)	-	6.17 $\pm$ 0.94 (range: 4.4-8.3)
DAS28 at 6 months, mean $\pm$ SD	2.69 $\pm$ 0.84 (range: 0.84-4.93)	-	3.15 $\pm$ 1.44 (range: 1.01-6.06)
Remission at 6 months, n (%) (DAS28<2.6)	9 (35%)	-	8 (40% of peripheral PsA)
Low disease activity at 6 months, n (%) (2.6 $\leq$ DAS28 $\leq$ 3.2)	13 (50%)	-	4 (20% of peripheral PsA)
BASDAI before treatment, median (range)	-	8.2 (5.7-10)	8 (6-9)
BASDAI at 6 months, median (range)	-	2.15 (0.75-9)	2 (0-8)
Remission at 6 months (BASDAI<3), n (%)	-	26 (90%)	3 (100% of 3 axial PsA)
Non-responder at 3 months, n (%)	7 (27%)	3 (10%)	9 (39%)
Non-responder at 6 months, n (%)	4 (15%)	2 (7%)	8 (35%)
Treatment efficacy after 3 months - responders (good and moderate response), n (%)	19 (73%)	26 (90%)	14 (61%)
Treatment efficacy after 6 months - responders (good and moderate response ), n (%)	22 (85%)	27 (93%)	15 (65%)

RA= rheumatoid arthritis, AS= ankylosing spondylitis, PsA= psoriatic arthritis

DAS28 = disease activity score 28; CRP = C-reactive protein; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibodies; SD = standard deviation; TNF = tumor necrosis factor, MTX= methotrexate; NSAIDs= Nonsteroidal anti-inflammatory drugs



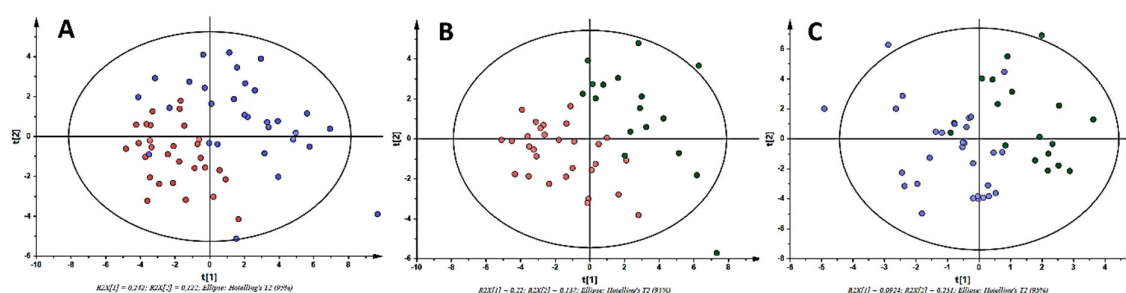
**Figure S1.** PLS-DA model plots for RA treatment at various time points. A – before treatment vs. after 3 months, B – before treatment vs. after 6 months, C – after 3 months vs. after 6 months of therapy with TNFi. Red – RA patients before treatment, Blue – 3 months after initialization of anti-TNF treatment, Green – 6 months after treatment with TNFi.

**Table S2.** The VIP score for discrimination PLS with univariate analysis results for quantified metabolites in comparisons for RA patients.

Rheumatoid arthritis												
Metabolite	VIP score for PLS-DA model			Percentage difference [%]			<i>p</i> value			Adjusted <i>p</i> value		
	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M
2-Hydroxybutyrate	0.923	1.142	0.523	-9.98	3.16	13.13	3.95E-01	9.03E-01	1.13E-01	6.27E-01	9.03E-01	4.77E-01
2-Oxoisocaproate	1.165	1.239	0.898	16.07	30.10	14.21	2.86E-02	8.24E-04	1.16E-01	1.36E-01	8.57E-03	4.77E-01
3-Hydroxybutyrate	0.574	0.958	0.263	-27.70	-50.73	-23.86	4.32E-01	6.05E-02	9.94E-01	6.27E-01	1.42E-01	9.94E-01
3-Methyl-2-oxovalerate	0.996	1.198	0.905	16.21	37.25	21.37	2.05E-01	2.46E-03	1.16E-01	4.63E-01	1.53E-02	4.77E-01
Acetate	0.969	0.879	1.427	-18.72	-30.55	-12.01	7.37E-02	4.79E-03	4.49E-02	2.56E-01	2.49E-02	4.67E-01
Acetone	0.640	0.917	0.652	1.43	9.81	8.38	4.34E-01	2.86E-01	2.26E-01	6.27E-01	3.91E-01	5.68E-01
Alanine	1.643	1.448	0.919	26.23	35.02	9.00	1.27E-05	2.58E-04	5.06E-01	3.31E-04	6.70E-03	6.80E-01
Choline	1.284	1.545	1.353	-14.61	8.29	22.84	1.18E-01	4.34E-01	1.19E-01	2.94E-01	5.25E-01	4.77E-01
Citrate	0.470	0.548	0.564	5.71	12.44	6.74	4.03E-01	4.21E-01	2.50E-01	6.27E-01	5.21E-01	5.68E-01
Creatine	0.530	0.887	1.287	1.05	32.69	31.67	5.27E-01	1.35E-02	7.37E-03	7.05E-01	5.41E-02	2.11E-01
Creatinine	0.708	1.148	0.903	3.01	11.52	8.51	2.62E-01	8.40E-02	2.70E-01	5.05E-01	1.62E-01	5.68E-01
Ethanol	2.603	1.980	1.097	-68.73	-80.27	-13.39	5.28E-07	1.00E-04	2.65E-01	2.75E-05	5.20E-03	5.68E-01
Formate	0.659	0.275	1.705	14.33	-2.32	-16.63	2.78E-01	8.89E-01	8.99E-02	5.16E-01	9.03E-01	4.77E-01
Glucose	0.503	0.557	0.296	7.72	4.19	-3.53	2.58E-01	4.79E-01	9.88E-01	5.05E-01	5.66E-01	9.94E-01
Glutamate	0.495	0.645	1.538	2.59	-6.14	-8.73	7.61E-01	5.69E-01	4.30E-01	8.25E-01	6.30E-01	6.57E-01
Glutamine	1.370	1.213	0.830	14.34	22.63	8.37	2.48E-03	2.65E-03	2.32E-01	4.29E-02	1.53E-02	5.68E-01
Glycerol	0.656	0.619	0.745	-6.90	-2.58	4.32	3.05E-01	4.16E-01	4.52E-01	5.47E-01	5.21E-01	6.71E-01
Glycine	0.835	0.807	0.748	10.16	8.72	-1.44	2.22E-02	7.38E-02	5.10E-01	1.33E-01	1.48E-01	6.80E-01
Histidine	1.121	1.019	0.863	8.88	17.55	8.71	8.14E-02	5.33E-02	3.33E-01	2.65E-01	1.39E-01	6.48E-01
Isobutyrate	1.651	1.105	1.168	-37.59	-65.21	-29.42	6.82E-02	4.63E-02	3.86E-01	2.56E-01	1.27E-01	6.48E-01
Isoleucine	1.003	0.810	1.112	10.28	25.64	15.46	1.19E-01	1.15E-01	3.99E-01	2.94E-01	1.87E-01	6.48E-01
Lactate	0.872	0.853	0.968	19.75	18.67	-1.09	9.45E-02	6.79E-03	7.21E-01	2.79E-01	3.21E-02	7.81E-01
Leucine	0.787	0.876	1.128	6.31	17.32	11.04	2.23E-01	9.36E-02	3.69E-01	4.84E-01	1.68E-01	6.48E-01
Lysine	0.723	0.981	1.432	0.79	21.44	20.66	6.41E-01	2.96E-02	4.25E-02	7.57E-01	9.05E-02	4.67E-01
Lysine + Leucine	0.723	0.939	1.091	-0.40	13.15	13.55	9.76E-01	1.78E-01	3.69E-01	9.76E-01	2.64E-01	6.48E-01
NAC (2.092 ppm) (s)	0.787	0.691	1.110	1.86	4.27	2.41	4.34E-01	2.95E-01	6.26E-01	6.27E-01	3.93E-01	7.40E-01
O-Phosphocholine	0.856	1.193	0.559	-5.28	3.26	8.53	5.42E-01	6.80E-02	5.82E-01	7.05E-01	1.46E-01	7.29E-01
Phenylealanine	0.683	0.715	1.005	2.92	15.07	12.16	6.73E-01	1.04E-01	3.42E-01	7.57E-01	1.74E-01	6.48E-01
Proline	0.981	0.907	1.144	14.74	19.33	4.62	7.36E-02	1.53E-01	7.90E-01	2.56E-01	2.34E-01	8.38E-01
Propylene glycol	1.234	1.135	0.844	22.41	45.86	24.07	1.22E-01	4.08E-04	1.18E-01	2.94E-01	7.07E-03	4.77E-01
Pyruvate	1.105	0.993	0.964	58.44	40.04	-19.54	5.94E-02	9.06E-02	6.80E-01	2.56E-01	1.68E-01	7.68E-01
sn-G3P	0.680	0.942	0.615	5.34	12.90	7.57	1.24E-01	9.67E-02	3.93E-01	2.94E-01	1.68E-01	6.48E-01
Succinate + 3HB	0.535	1.076	0.505	-1.76	-6.28	-4.52	8.65E-01	3.65E-01	6.56E-01	8.82E-01	4.74E-01	7.58E-01
Taurine	1.107	1.019	0.732	10.95	21.15	10.26	2.15E-02	2.76E-02	2.43E-01	1.33E-01	8.96E-02	5.68E-01
Tryptophan	0.711	1.160	1.381	10.44	31.09	20.82	2.57E-01	7.22E-04	1.00E-01	5.05E-01	8.57E-03	4.77E-01
Tyrosine	1.153	1.304	0.968	14.32	30.04	15.89	2.06E-02	2.25E-03	2.56E-01	1.33E-01	1.53E-02	5.68E-01
Unk 4 (1.074 ppm) (s)	1.121	0.571	0.846	2.39	10.37	7.98	5.59E-01	5.15E-01	6.17E-01	7.09E-01	5.90E-01	7.40E-01
Unk 6 (1.23 ppm) (m)	0.807	0.814	0.728	-7.81	1.98	9.78	6.21E-01	5.22E-01	5.72E-01	7.51E-01	5.90E-01	7.29E-01
Unk_10 (2.769 ppm) (s)	1.505	1.125	0.882	-66.95	-38.54	30.36	2.31E-02	6.26E-02	1.13E-01	1.33E-01	1.42E-01	4.77E-01

Unk_11 (2.945 ppm) (s)	0.832	1.149	1.377	-3.69	22.31	25.95	8.45E-01	7.01E-02	1.18E-02	8.79E-01	1.46E-01	2.11E-01
Unk_12 (3.051 ppm) (s)	0.409	0.884	0.415	11.65	34.56	23.14	4.84E-01	1.25E-02	1.38E-01	6.81E-01	5.41E-02	5.11E-01
Unk_13 (3.112 ppm) (s)	0.341	0.859	0.713	13.17	49.32	36.75	5.31E-01	2.47E-01	2.73E-01	7.05E-01	3.48E-01	5.68E-01
Unk_14 (3.246 ppm) (s)	0.568	0.631	0.646	-2.53	1.73	4.26	5.90E-01	8.60E-01	7.04E-01	7.30E-01	8.94E-01	7.79E-01
Unk_15 (3.63 ppm) (s)	0.738	0.965	1.301	4.24	19.31	15.11	3.23E-01	5.75E-02	1.22E-02	5.60E-01	1.42E-01	2.11E-01
Unk_16 (7.334 ppm) (t)	0.720	1.021	1.098	1.79	17.02	15.24	8.03E-01	2.36E-02	1.75E-01	8.52E-01	8.18E-02	5.68E-01
Unk_18 (8.238 ppm) (s)	0.744	0.593	0.770	15.94	2.18	-13.77	3.36E-01	6.84E-01	4.16E-01	5.64E-01	7.28E-01	6.56E-01
Unk_2 (0.914 ppm) (d)	1.443	1.082	0.515	-30.80	-28.14	2.72	4.41E-03	1.33E-01	5.89E-01	5.73E-02	2.09E-01	7.29E-01
Unk_3 (0.967 ppm) (s)	0.808	0.770	0.885	1.82	16.96	15.15	6.84E-01	3.85E-02	2.41E-01	7.57E-01	1.11E-01	5.68E-01
Unk_7 (1.444 ppm) (d)	1.172	0.866	1.237	23.78	25.44	1.69	1.11E-02	1.16E-03	9.35E-01	1.15E-01	1.00E-02	9.72E-01
Unk_8 (2.050 ppm) (m)	0.802	1.047	1.559	-2.77	-5.94	-3.17	6.74E-01	6.86E-01	4.93E-01	7.57E-01	7.28E-01	6.80E-01
Unk_9 (2.743 ppm) (s)	1.259	0.923	0.796	-21.82	-20.18	1.66	9.65E-02	1.88E-01	5.00E-01	2.79E-01	2.72E-01	6.80E-01
Valine	0.941	0.953	1.130	8.63	23.34	14.79	2.87E-02	1.86E-02	1.51E-01	1.36E-01	6.89E-02	5.22E-01

Grey – Metabolites above VIP 1.00,  $p$  value <0.05, adjusted  $p$  value <0.05



**Figure S2.** PLS-DA model plots for AS treatment at various time points. A – before treatment vs. after 3 months, B – before treatment vs. after 6 months, C – after 3 months vs. after 6 months of therapy with TNFi. Red – AS patients before treatment, Blue – 3 months after initialization of anti-TNF treatment, Green – 6 months after treatment with TNFi.

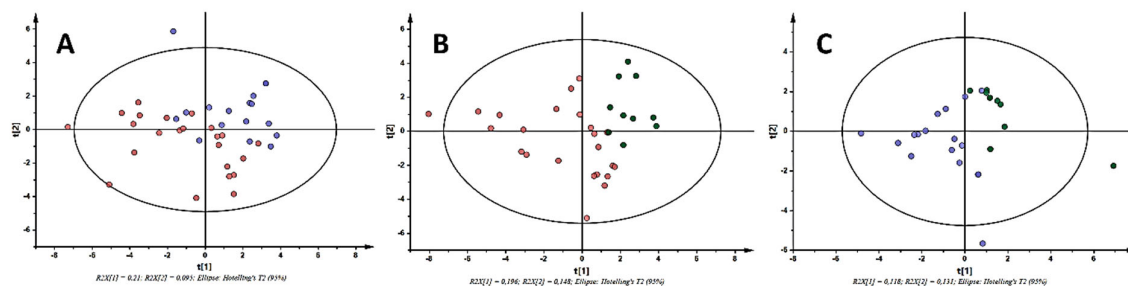
**Table S3.** The VIP score for discrimination PLS with univariate analysis results for quantified metabolites in comparisons for AS patients.

Ankylosing spondylitis												
Metabolite	VIP score for PLS-DA model			Percentage difference [%]			$p$ value			Adjusted $p$ value		
	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M
2-Hydroxybutyrate	0.752	0.728	0.478	-1.32	-7.26	-5.94	8.39E-01	2.18E-01	6.79E-01	8.77E-01	3.00E-01	9.85E-01
2-Oxoisocaproate	1.210	1.291	0.783	32.06	38.28	6.42	1.19E-05	1.22E-02	4.28E-01	1.54E-04	5.76E-02	9.64E-01
3-Hydroxybutyrate	0.448	0.748	0.429	-2.41	-4.51	-2.10	6.46E-01	6.89E-01	9.52E-01	7.31E-01	7.46E-01	9.85E-01
3-Methyl-2-oxovalerate	1.125	1.151	0.330	36.66	35.26	-1.45	5.76E-04	3.99E-02	9.85E-01	2.99E-03	9.82E-02	9.85E-01
Acetate	0.469	0.935	1.859	-2.64	-20.17	-17.55	5.37E-01	1.12E-02	3.52E-02	6.35E-01	5.76E-02	3.17E-01
Acetone	1.532	0.902	0.995	-12.87	-9.73	3.14	2.24E-02	1.90E-01	5.10E-01	4.66E-02	2.82E-01	9.82E-01
Alanine	0.952	0.927	0.309	15.89	14.42	-1.48	1.11E-04	2.42E-02	9.80E-01	8.22E-04	7.48E-02	9.85E-01

Choline	0.915	0.565	1.898	-17.00	9.85	26.74	8.22E-02	1.60E-01	9.33E-02	1.26E-01	2.52E-01	4.86E-01
Citrate	1.460	0.858	1.406	36.08	19.67	-16.71	8.55E-07	3.39E-02	8.25E-02	4.44E-05	9.26E-02	4.86E-01
Creatine	1.018	1.094	0.592	19.54	26.35	6.90	2.41E-05	8.02E-03	3.56E-01	2.39E-04	5.76E-02	9.64E-01
Creatinine	0.895	0.859	0.516	11.87	11.62	-0.26	5.44E-04	2.82E-02	9.64E-01	2.99E-03	8.16E-02	9.85E-01
Ethanol	2.288	2.496	0.381	-31.22	-30.42	0.82	4.73E-06	1.00E-04	9.73E-01	8.19E-05	4.12E-03	9.85E-01
Formate	1.166	0.969	0.267	28.30	24.75	-3.62	8.69E-03	1.32E-01	3.61E-01	2.38E-02	2.21E-01	9.64E-01
Glucose	0.488	0.946	0.583	1.24	1.89	0.66	6.78E-01	9.09E-01	7.78E-01	7.50E-01	9.27E-01	9.85E-01
Glutamate	0.678	0.818	0.701	3.03	6.69	3.66	4.64E-01	6.62E-01	4.43E-01	5.74E-01	7.36E-01	9.64E-01
Glutamine	1.247	0.961	0.932	17.87	12.55	-5.35	1.78E-06	1.89E-01	4.21E-02	4.62E-05	2.82E-01	3.17E-01
Glycerol	0.495	0.375	0.392	8.55	4.28	-4.27	1.83E-02	4.74E-01	3.83E-01	3.96E-02	5.74E-01	9.64E-01
Glycine	0.845	0.510	0.707	11.61	6.02	-5.60	5.78E-03	2.16E-01	2.85E-01	1.77E-02	3.00E-01	9.27E-01
Histidine	1.054	1.094	0.153	16.77	15.59	-1.18	2.76E-05	1.39E-02	9.68E-01	2.39E-04	5.91E-02	9.85E-01
Isobutyrate	0.795	1.223	2.901	-10.88	-89.48	-80.56	4.23E-01	7.39E-04	1.00E-04	5.36E-01	7.97E-03	5.20E-03
Isoleucine	0.855	0.859	0.827	13.07	4.47	-8.61	4.75E-02	5.37E-01	5.04E-01	7.96E-02	6.21E-01	9.82E-01
Lactate	0.895	1.301	1.101	16.88	31.58	14.91	5.32E-03	1.11E-02	2.51E-01	1.73E-02	5.76E-02	8.70E-01
Leucine	1.012	0.997	0.592	12.85	13.49	0.65	1.15E-02	1.19E-02	6.86E-01	2.86E-02	5.76E-02	9.85E-01
Lysine	0.788	0.740	0.723	10.85	7.35	-3.50	3.46E-02	1.39E-01	8.17E-01	6.20E-02	2.26E-01	9.85E-01
Lysine + Leucine	0.822	0.792	0.693	5.21	3.13	-2.07	2.70E-01	4.40E-01	9.17E-01	3.70E-01	5.72E-01	9.85E-01
NAC (2.092 ppm) (s)	1.045	0.941	0.539	0.79	0.63	-0.16	6.21E-01	8.74E-01	9.67E-01	7.17E-01	9.09E-01	9.85E-01
O-Phosphocholine	0.607	0.603	0.701	-0.71	6.52	7.22	9.58E-01	9.69E-01	5.88E-01	9.58E-01	9.69E-01	9.85E-01
Phenylealanine	0.868	1.269	1.393	11.61	20.89	9.34	5.26E-02	7.66E-04	1.44E-01	8.54E-02	7.97E-03	6.25E-01
Proline	1.032	0.805	0.550	10.95	9.42	-1.54	2.78E-02	2.19E-01	9.31E-01	5.15E-02	3.00E-01	9.85E-01
Propylene glycol	1.177	1.183	1.489	29.49	51.72	23.11	1.03E-02	4.94E-02	1.73E-01	2.67E-02	1.10E-01	6.91E-01
Pyruvate	1.045	1.166	0.909	40.83	75.20	37.23	9.40E-02	5.08E-02	4.55E-01	1.40E-01	1.10E-01	9.64E-01
sn-G3P	1.414	1.115	1.788	21.17	7.39	-13.83	5.20E-04	2.51E-01	1.11E-02	2.99E-03	3.35E-01	2.89E-01
Succinate + 3HB	0.856	0.806	0.750	11.32	5.75	-5.58	6.95E-02	4.86E-01	3.40E-01	1.10E-01	5.75E-01	9.64E-01
Taurine	0.921	0.870	0.465	9.71	14.75	5.06	2.58E-02	8.89E-02	6.10E-01	4.97E-02	1.65E-01	9.85E-01
Tryptophan	1.082	1.107	0.363	20.16	23.81	3.69	2.95E-03	1.55E-02	5.94E-01	1.02E-02	5.91E-02	9.85E-01
Tyrosine	0.825	1.135	0.511	13.63	17.82	4.22	6.76E-03	1.59E-02	5.84E-01	1.95E-02	5.91E-02	9.85E-01
Valine	0.958	0.977	0.591	12.39	12.64	0.25	1.43E-02	4.15E-02	6.89E-01	3.24E-02	9.82E-02	9.85E-01
Unk_4 (1.074 ppm) (s)	0.666	0.684	0.668	7.11	-0.82	-7.93	5.12E-01	7.36E-01	7.24E-01	6.19E-01	7.81E-01	9.85E-01
Unk_6 (1.23 ppm) (m)	0.653	0.634	1.088	0.16	15.43	15.27	9.53E-01	9.87E-02	1.04E-01	9.58E-01	1.71E-01	4.94E-01
Unk_10 (2.769 ppm) (s)	0.881	1.052	1.525	-55.25	-86.99	-36.07	1.40E-02	2.16E-03	2.66E-02	3.24E-02	1.87E-02	3.17E-01
Unk_11 (2.945 ppm) (s)	1.134	1.165	0.538	29.84	27.28	-2.61	9.09E-04	1.59E-04	5.91E-01	3.84E-03	4.12E-03	9.85E-01
Unk_12 (3.051 ppm) (s)	0.659	0.806	0.165	20.81	24.36	3.59	7.07E-04	2.42E-02	4.64E-01	3.34E-03	7.48E-02	9.64E-01
Unk_13 (3.112 ppm) (s)	0.748	0.645	0.290	31.63	30.01	-1.66	1.67E-01	4.68E-01	9.22E-01	2.34E-01	5.74E-01	9.85E-01
Unk_14 (3.246 ppm) (s)	0.692	1.042	1.814	4.01	-13.19	-17.18	3.65E-01	5.28E-02	3.71E-02	4.75E-01	1.10E-01	3.17E-01
Unk_15 (3.63 ppm) (s)	1.232	0.974	0.934	14.22	9.43	-4.80	9.61E-04	2.44E-02	2.24E-01	3.84E-03	7.48E-02	8.31E-01
Unk_16 (7.334 ppm) (t)	0.737	0.780	0.923	5.14	8.41	3.27	2.80E-01	6.71E-02	4.33E-01	3.73E-01	1.29E-01	9.64E-01
Unk_18 (8.238 ppm) (s)	0.359	0.340	0.546	0.59	10.12	9.54	8.43E-01	4.57E-01	9.09E-01	8.77E-01	5.74E-01	9.85E-01
Unk_2 (0.914 ppm) (d)	1.174	1.345	1.479	-28.50	-56.70	-29.39	2.57E-03	3.50E-04	9.34E-02	9.56E-03	6.06E-03	4.86E-01
Unk_3 (0.967 ppm) (s)	0.743	0.659	0.683	8.32	5.19	-3.14	1.60E-01	6.65E-01	9.19E-01	2.30E-01	7.36E-01	9.85E-01
Unk_7 (1.444 ppm) (d)	1.090	1.032	0.324	15.65	18.41	2.78	4.46E-02	6.49E-02	6.64E-01	7.73E-02	1.29E-01	9.85E-01

Unk_8 (2.050 ppm) (m)	1.619	1.039	0.713	-12.17	-10.84	1.34	2.33E-02	9.78E-02	7.84E-01	4.66E-02	1.71E-01	9.85E-01
Unk_9 (2.743 ppm) (s)	0.620	1.051	1.466	3.43	-19.68	-23.07	7.47E-01	3.65E-02	4.27E-02	8.09E-01	9.48E-02	3.17E-01

Grey – Metabolites above VIP 1.00,  $p$  value <0.05, adjusted  $p$  value <0.05



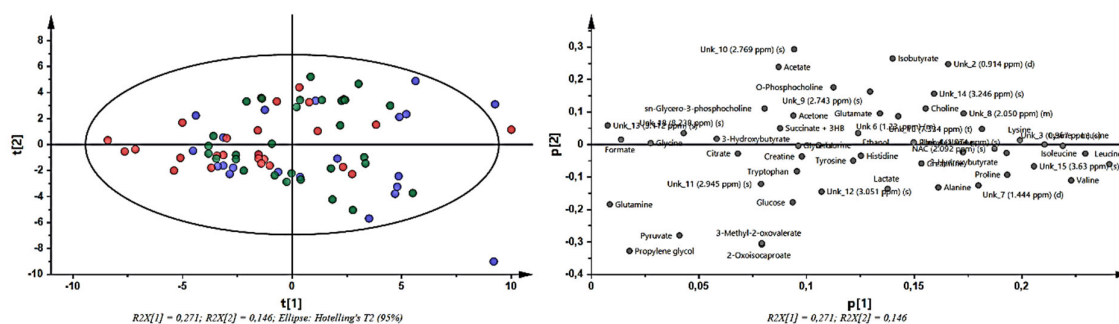
**Figure S3.** PLS-DA model plots for PsA treatment at various time points. A – before treatment vs. after 3 months, B – before treatment vs. after 6 months, C – after 3 months vs. after 6 months of therapy with TNFi. Red – PsA patients before treatment, Blue – 3 months after initialization of anti-TNF treatment, Green – 6 months after treatment with TNFi.

**Table S4.** The VIP score for discrimination PLS with univariate analysis results for quantified metabolites in comparisons for PsA group.

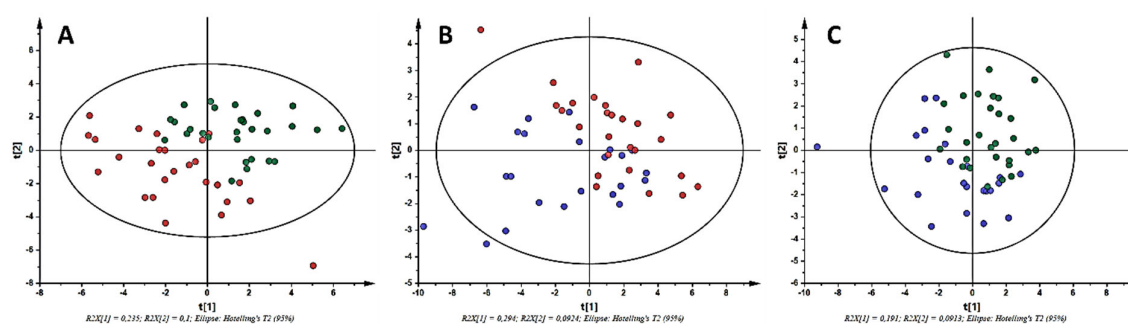
Metabolite	VIP score for PLS-DA model			Percentage difference [%]			$p$ value			Adjusted $p$ value		
	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M	BT vs 3M	BT vs 6M	3M vs 6M
2-Hydroxybutyrate	0.903	0.744	0.452	-19.13	-24.93	-5.87	3.07E-01	2.43E-01	7.64E-01	7.25E-01	5.41E-01	9.26E-01
2-Oxoisocaproate	0.145	0.892	1.384	-3.59	19.97	23.52	4.48E-01	1.49E-01	6.37E-02	8.31E-01	4.83E-01	6.62E-01
3-Hydroxybutyrate	0.458	0.365	0.322	-33.14	-14.14	19.23	9.96E-01	9.15E-01	6.75E-01	9.96E-01	9.66E-01	9.26E-01
3-Methyl-2-oxovalerate	0.362	0.427	0.653	7.67	14.14	6.49	8.21E-01	6.26E-01	6.03E-01	9.27E-01	8.26E-01	9.26E-01
Acetate	0.833	1.619	1.613	-13.75	-44.14	-30.85	1.55E-02	2.70E-04	3.65E-02	1.61E-01	7.49E-03	6.32E-01
Acetone	1.016	1.664	0.899	-9.74	-17.44	-7.73	1.04E-01	5.80E-03	4.03E-01	4.50E-01	6.03E-02	9.15E-01
Alanine	1.042	0.668	0.537	-4.83	0.36	5.19	6.43E-01	5.83E-01	4.66E-01	9.07E-01	8.19E-01	9.15E-01
Choline	0.857	1.051	0.595	-6.32	-11.49	-5.18	3.97E-01	2.00E-01	6.14E-01	8.25E-01	5.32E-01	9.26E-01
Citrate	0.553	1.437	1.453	-6.36	27.87	34.08	4.96E-01	1.38E-01	1.44E-01	8.46E-01	4.78E-01	8.12E-01
Creatine	0.515	0.800	1.250	-1.84	-14.43	-12.60	9.63E-01	2.01E-01	4.05E-01	9.82E-01	5.32E-01	9.15E-01
Creatinine	1.152	0.901	0.379	1.71	3.43	1.72	5.04E-01	3.49E-01	7.10E-01	8.46E-01	6.25E-01	9.26E-01
Ethanol	3.287	2.410	0.444	-50.49	-48.67	1.94	1.00E-04	9.27E-04	7.86E-01	5.20E-03	1.61E-02	9.26E-01
Formate	0.380	1.178	2.162	-3.31	-11.76	-8.46	2.43E-01	3.92E-01	4.75E-01	6.32E-01	6.57E-01	9.15E-01
Glucose	1.027	0.197	1.430	-16.53	3.70	20.20	1.93E-01	5.01E-01	1.43E-01	6.30E-01	7.23E-01	8.12E-01
Glutamate	1.059	0.672	0.731	-19.32	-9.67	9.69	3.50E-02	2.45E-01	3.68E-01	2.40E-01	5.41E-01	9.15E-01
Glutamine	0.591	0.670	1.174	-0.78	9.11	9.89	4.32E-01	4.51E-01	2.45E-01	8.31E-01	6.90E-01	9.15E-01
Glycerol	1.770	0.860	0.904	-19.54	-12.12	7.47	1.19E-02	2.15E-01	4.29E-01	1.55E-01	5.32E-01	9.15E-01
Glycine	0.676	0.136	0.645	-5.57	-0.40	5.17	2.36E-01	8.90E-01	3.29E-01	6.32E-01	9.66E-01	9.15E-01
Histidine	0.882	1.256	0.925	-2.70	3.33	6.03	5.56E-01	7.70E-01	2.57E-01	9.04E-01	9.48E-01	9.15E-01
Isobutyrate	1.064	1.272	1.700	-2.21	-61.23	-59.22	7.08E-02	1.67E-02	1.14E-03	3.35E-01	1.24E-01	5.93E-02

Isoleucine	0.941	0.924	1.167	-0.76	-15.92	-15.16	8.69E-01	3.66E-02	3.00E-01	9.27E-01	1.90E-01	9.15E-01
Lactate	0.959	0.094	0.630	2.41	0.11	-2.29	6.86E-01	6.51E-01	7.64E-01	9.07E-01	8.26E-01	9.26E-01
Leucine	0.981	1.015	0.533	-4.54	-4.67	-0.13	7.29E-01	7.91E-01	9.95E-01	9.25E-01	9.48E-01	9.95E-01
Lysine	1.106	1.084	0.547	-7.41	-12.76	-5.37	2.18E-01	7.08E-02	5.81E-01	6.30E-01	3.07E-01	9.26E-01
Lysine + Leucine	1.130	1.085	0.481	-11.00	-12.79	-1.79	1.57E-01	1.14E-01	7.94E-01	6.26E-01	4.36E-01	9.26E-01
NAC (2.092 ppm) (s)	1.306	1.283	0.538	-6.05	-6.74	-0.69	3.19E-02	2.12E-02	9.75E-01	2.40E-01	1.38E-01	9.94E-01
O-Phosphocholine	0.738	0.809	0.581	-2.13	-10.04	-7.92	6.90E-01	2.12E-01	4.09E-01	9.07E-01	5.32E-01	9.15E-01
Phenylealanine	0.845	0.586	1.141	-8.48	1.23	9.71	2.09E-01	8.02E-01	2.60E-01	6.30E-01	9.48E-01	9.15E-01
Proline	1.119	0.450	1.164	-15.81	-3.20	12.62	4.15E-02	9.39E-01	1.56E-01	2.40E-01	9.66E-01	8.12E-01
Propylene glycol	0.427	0.743	1.501	-8.78	29.98	38.51	3.79E-01	3.44E-01	1.26E-01	8.20E-01	6.25E-01	8.12E-01
Pyruvate	0.953	0.413	1.009	32.05	15.20	-17.06	4.96E-01	6.06E-01	9.45E-01	8.46E-01	8.26E-01	9.94E-01
sn-G3P	0.418	0.458	0.454	0.69	2.66	1.97	7.60E-01	4.90E-01	5.56E-01	9.27E-01	7.23E-01	9.26E-01
Succinate + 3HB	0.636	0.392	0.451	-10.98	-7.71	3.27	8.72E-01	9.47E-01	7.45E-01	9.27E-01	9.66E-01	9.26E-01
Taurine	0.456	0.251	0.599	-4.89	-2.41	2.48	2.83E-01	8.48E-01	6.31E-01	7.00E-01	9.66E-01	9.26E-01
Tryptophan	0.502	0.599	0.941	-2.32	2.07	4.39	6.77E-01	9.42E-01	3.42E-01	9.07E-01	9.66E-01	9.15E-01
Tyrosine	1.026	1.122	0.859	2.19	11.42	9.24	7.85E-01	3.27E-01	3.38E-01	9.27E-01	6.25E-01	9.15E-01
Valine	1.094	1.013	0.393	1.71	1.77	0.07	6.98E-01	3.46E-01	9.30E-01	9.07E-01	6.25E-01	9.94E-01
Unk_4 (1.074 ppm) (s)	0.910	0.963	0.679	-1.00	13.80	14.79	8.14E-01	4.44E-01	5.08E-01	9.27E-01	6.90E-01	9.26E-01
Unk_6 (1.23 ppm) (m)	1.045	0.944	0.821	-8.02	-20.20	-12.23	6.45E-01	1.65E-01	4.60E-01	9.07E-01	5.03E-01	9.15E-01
Unk_10 (2.769 ppm) (s)	0.772	1.246	1.463	-20.16	-88.36	-71.38	1.86E-01	3.20E-02	5.63E-02	6.30E-01	1.85E-01	6.62E-01
Unk_11 (2.945 ppm) (s)	0.177	0.150	1.035	-1.75	2.43	4.18	5.98E-01	3.66E-01	5.99E-01	9.07E-01	6.34E-01	9.26E-01
Unk_12 (3.051 ppm) (s)	0.464	1.026	1.346	-9.42	49.01	57.76	9.46E-01	2.50E-01	2.21E-01	9.82E-01	5.41E-01	9.15E-01
Unk_13 (3.112 ppm) (s)	0.650	0.535	1.389	-36.94	-47.80	-11.36	3.43E-01	4.10E-01	8.70E-01	7.75E-01	6.66E-01	9.63E-01
Unk_14 (3.246 ppm) (s)	1.147	1.503	1.474	-16.78	-30.70	-14.11	4.03E-02	1.25E-02	9.08E-02	2.40E-01	1.08E-01	7.87E-01
Unk_15 (3.63 ppm) (s)	0.771	0.395	0.891	-1.50	0.40	1.90	8.08E-01	6.46E-01	5.64E-01	9.27E-01	8.26E-01	9.26E-01
Unk_16 (7.334 ppm) (t)	1.214	1.051	0.161	-9.82	-8.49	1.33	5.10E-02	2.93E-01	8.70E-01	2.65E-01	6.09E-01	9.63E-01
Unk_18 (8.238 ppm) (s)	0.574	1.065	0.666	-7.87	3.63	11.49	5.85E-01	8.79E-01	4.17E-01	9.07E-01	9.66E-01	9.15E-01
Unk_2 (0.914 ppm) (d)	1.085	1.618	1.723	-27.34	-68.57	-43.26	3.91E-03	2.88E-04	1.85E-02	6.77E-02	7.49E-03	4.81E-01
Unk_3 (0.967 ppm) (s)	0.757	0.932	0.431	-9.86	-14.41	-4.57	4.37E-01	1.17E-01	7.38E-01	8.31E-01	4.36E-01	9.26E-01
Unk_7 (1.444 ppm) (d)	0.912	0.289	0.907	-0.76	-6.07	-5.32	8.74E-01	9.72E-01	9.66E-01	9.27E-01	9.72E-01	9.94E-01
Unk_8 (2.050 ppm) (m)	1.475	1.673	0.580	-20.35	-24.40	-4.09	2.30E-03	3.31E-03	7.69E-01	5.98E-02	4.30E-02	9.26E-01
Unk_9 (2.743 ppm) (s)	0.940	1.067	0.405	-13.92	-21.06	-7.19	1.96E-01	5.14E-02	8.01E-01	6.30E-01	2.43E-01	9.26E-01

Grey – Metabolites above VIP 1.00,  $p$  value <0.05, adjusted  $p$  value <0.05



**Figure S4.** PCA model plot and corresponding loading plot for the RA, AS and PsA groups of patients before treatment. Red – RA before treatment Green – AS before treatment, Blue – PsA before treatment.

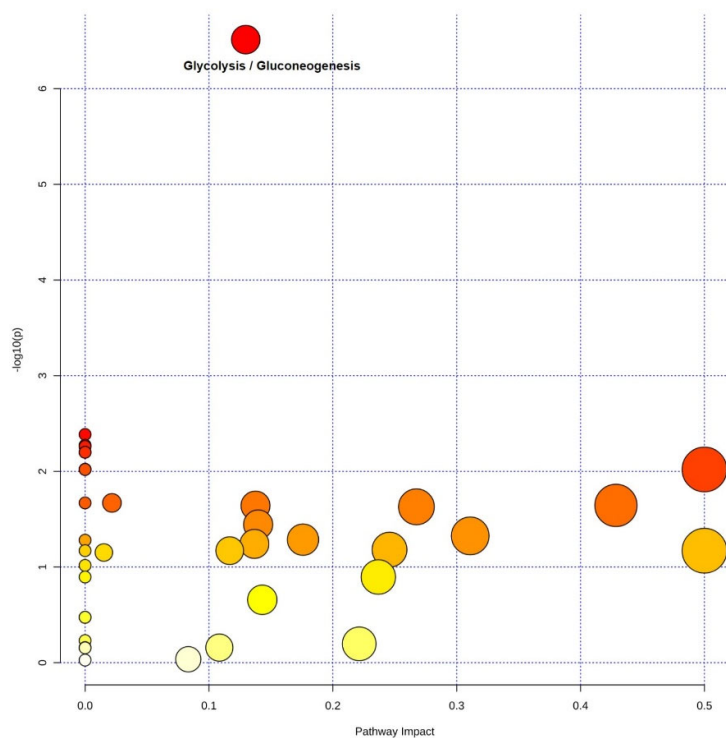


**Figure S5.** PCA model plot and corresponding loading plot for the RA, AS and PsA groups of patients before treatment. A – RA vs. AS, B – RA vs. PsA, C – AS vs. PsA. Red – RA before treatment Green – AS before treatment, Blue – PsA before treatment.

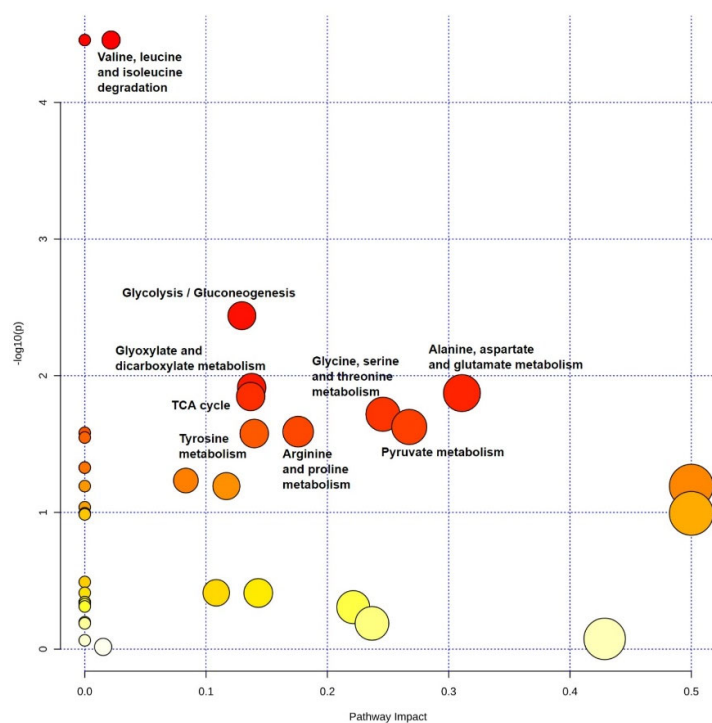


**Figure S6.** The MetPA analysis within the most perturbed biochemical pathways in: a) RA, b) AS, c) PsA

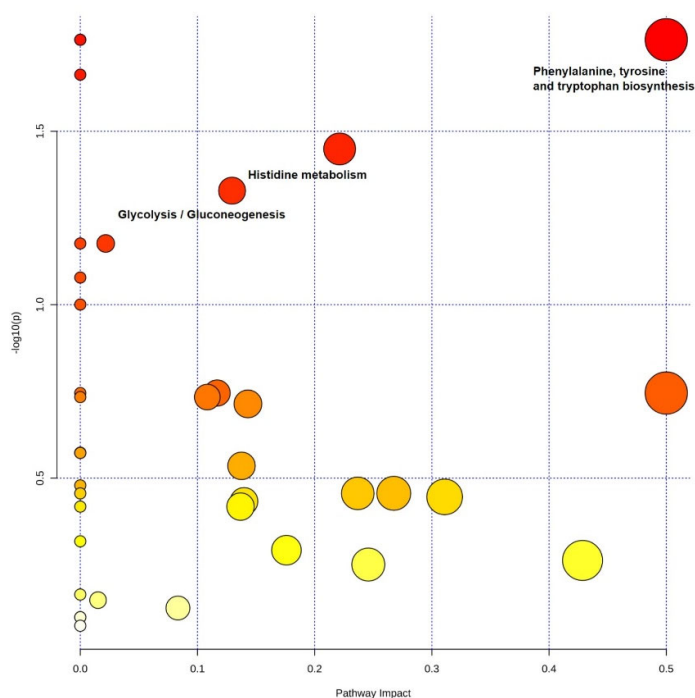
a)



b)



c)



**Table S5.** List of assignments of  $^1\text{H}$  NMR resonance signals with chemical shift, KEGG and HMDB ID. Presented in alphabetical order list of compounds spin systems that were used in multivariate and univariate analysis.

Name	Chemical shift [ppm]	Multiplicity	HMDB ID	KEGG ID
2-Oxoisocaproate	0.924; 2.623	(d), (d)	HMDB00695	C00233
2-Hydroxybutyrate	0.904	(s)	HMDB00008	C05984
3-Hydroxybutyrate	1.207; 2.324	(d), (dd)	HMDB00357	C01089
3-Methyl-2-oxovalerate	1.101	(d)	HMDB00491	C03465
Acetate	1.932	(s)	HMDB00042	C00033
Acetone	2.248	(s)	HMDB01659	C00207
Alanine	1.492	(d)	HMDB00161	C00041
Choline	3.199	(s)	HMDB00097	C00114
Citrate	2.557	(dd)	HMDB00094	C00158
Creatine	3.046; 3.942	(s); (s)	HMDB00064	C00300
Creatinine	3.061; 4.076	(s); (s)	HMDB00562	C00791
Ethanol	1.189	(t)	HMDB00108	C00469
Formate	8.464	(s)	HMDB00142	C00058
Glycine	3.582	(s)	HMDB00123	C00037
Glucose	3.275; 3.522; 3.895; 5.263	(m); (m); (d); (d)	HMDB00122	C00031
Glutamate	2.349	(m)	HMDB00148	C00025
Glutamine	2.152; 2.45	(m); (m)	HMDB00641	C00064
Glycerol	3.588	(m)	HMDB00131	C00116
Isobutyrate	1.078	(s)	HMDB01873	C02632
Isoleucine	0.998	(d)	HMDB00172	C00407

<b>Lactate</b>	1.338; 4.133	(d); (q)	HMDB00190	C00186
<b>Leucine</b>	0.951	(t)	HMDB00687	C00123
<b>Lysine + Leucine</b>	1.737	(m)	-	-
<b>Lysine</b>	1.92; 3.033	(m); (t)	HMDB00182	C00047
<b>NAC</b>	2.092	(s)	-	-
<b>O-Phosphocholine</b>	3.211	(s)	HMDB00284	C00588
<b>Histidine</b>	8.178	(s)	HMDB00177	C00135
<b>Phenylealanine</b>	7.437	(m)	HMDB00159	C00079
<b>Proline</b>	2.017	(m)	HMDB00162	C00148
<b>Propylene glycol</b>	1.128	(d)	HMDB01881	C02912
<b>Pyruvate</b>	2.391	(s)	HMDB00243	C00022
<b>sn-Glycero-3-phosphocholine</b>	3.235	(s)	HMDB00086	C00670
<b>Succinate + 3HB</b>	2.409	(s)	-	-
<b>Taurine</b>	3.296	(s)	HMDB00251	C00245
<b>Tryptophan</b>	7.562	(d)	HMDB00883	C00183
<b>Tyrosine</b>	6.925	(m)	HMDB00158	C00082
<b>Valine</b>	0.977	(d)		
<b>Unk_2</b>	0.914	(d)	-	-
<b>Unk_3</b>	0.967	(s)	-	-
<b>Unk_4</b>	1.074	(s)	-	-
<b>Unk_6</b>	1.23	(m)	-	-
<b>Unk_7</b>	1.444	(d)	-	-
<b>Unk_8</b>	2.05	(m)	-	-
<b>Unk_9</b>	2.743	(s)	-	-
<b>Unk_10</b>	2.769	(s)	-	-
<b>Unk_11</b>	2.945	(s)	-	-
<b>Unk_12</b>	3.051	(s)	-	-
<b>Unk_13</b>	3.112	(s)	-	-
<b>Unk_14</b>	3.246	(s)	-	-
<b>Unk_15</b>	3.63	(s)	-	-
<b>Unk_16</b>	7.334	(t)	-	-
<b>Unk_18</b>	8.238	(s)	-	-