

Supplemental information

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Material and Methods

Yeast strain and growth conditions

For preculture, the *Saccharomyces cerevisiae* strain S90 (mat α) was grown in Yeast extract, Peptone, Dextrose (YPD) medium containing 10 g/l yeast extract (Merck), 20 g/l peptone (Merck) and 20 g/l D-glucose (Sigma-Aldrich). Yeast Nitrogen Base (YNB) medium was used for the overnight and main cultivation containing 0.67 g/l Difco Yeast Nitrogen Base Without Amino Acids (BD Biosciences) and D-glucose, $c = 60$ mmol/l (Sigma-Aldrich) or [$U\text{-}^{13}\text{C}$] D-glucose, $c = 60$ mmol/l (Cambridge Isotope Laboratories) as sole carbon source, respectively. Aerobic cultures were grown in 25-ml-Erlenmeyer flasks with 5 ml of medium. All cultivations were carried out at 30 °C and 200 rpm on a rotary shaker (Infors Multitron). Cell growth was monitored by the cell density in a cell density meter (Biowave CO8000). To obtain fully labelled extracts two overnight cultivations were applied before main culture.

Cell harvesting and metabolite extraction

For quenching, cells were transferred in 25 ml cold methanol (60%, v/v; -20 °C), followed by centrifugation at 3900×g for 3 min at -10 °C. Cells were washed with pre-cooled 20 ml 0.9% NaCl (w/v) solution and the centrifugation step was repeated. The remaining cell pellet was resuspended in 1 ml 50% cold methanol (v/v) and transferred in a reaction tube, pre-filled with 0.6 g acid-washed glass beads (\varnothing 150-212 μm , Sigma-Aldrich). For cell lysis, a Precellys24 (Bertin) homogenizer was used with the following conditions: 2 x 30 s at 6800 rpm and 30 s pause in-between. The temperature was hold around 0 °C by using the Cryolys cooling option. Then 500 μl chloroform were added followed by 1 min mixing and centrifugation at 14000×g for 5 min at 4 °C. For analysis of polar and non-polar metabolites, 100 μl of the aqueous phase as well as 150 μl of the chloroform phase were transferred to glass vials with micro inserts. Prior to GC/MS analysis, samples were dried using a CentriVap Concentrator (Labconco) at -4 °C.

Metabolite derivatization

Metabolite derivatization was performed by using a multi purpose sampler (Gerstel). For trimethylsilyl (TMS) derivatization, dried samples were dissolved in 15 μ l pyridine (Sigma-Aldrich), containing 20 mg/ml methoxyamine hydrochloride (Sigma-Aldrich), at 40 °C for 60 min under shaking. After adding 15 μ l *N*-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (Sigma-Aldrich) or *N*-Methyl-*N*-(trimethyl-*d*₉-silyl)trifluoroacetamide (Sigma-Aldrich) samples were incubated at 40 °C for 30 min under continuous shaking. For tert-butyldimethylsilyl (TBDMS) derivatization, dried samples were dissolved in 15 μ l pyridine, containing 20 mg/ml methoxyamine hydrochloride, at 55 °C for 60 min under shaking. After adding 15 μ l *N-tert*-Butyldimethylsilyl-*N*-methyltrifluoroacetamide with 1% *tert*-Butyldimethylchlorosilane (Sigma-Aldrich) samples were incubated at 55 °C for 60 min under continuous shaking.

GC/MS analysis

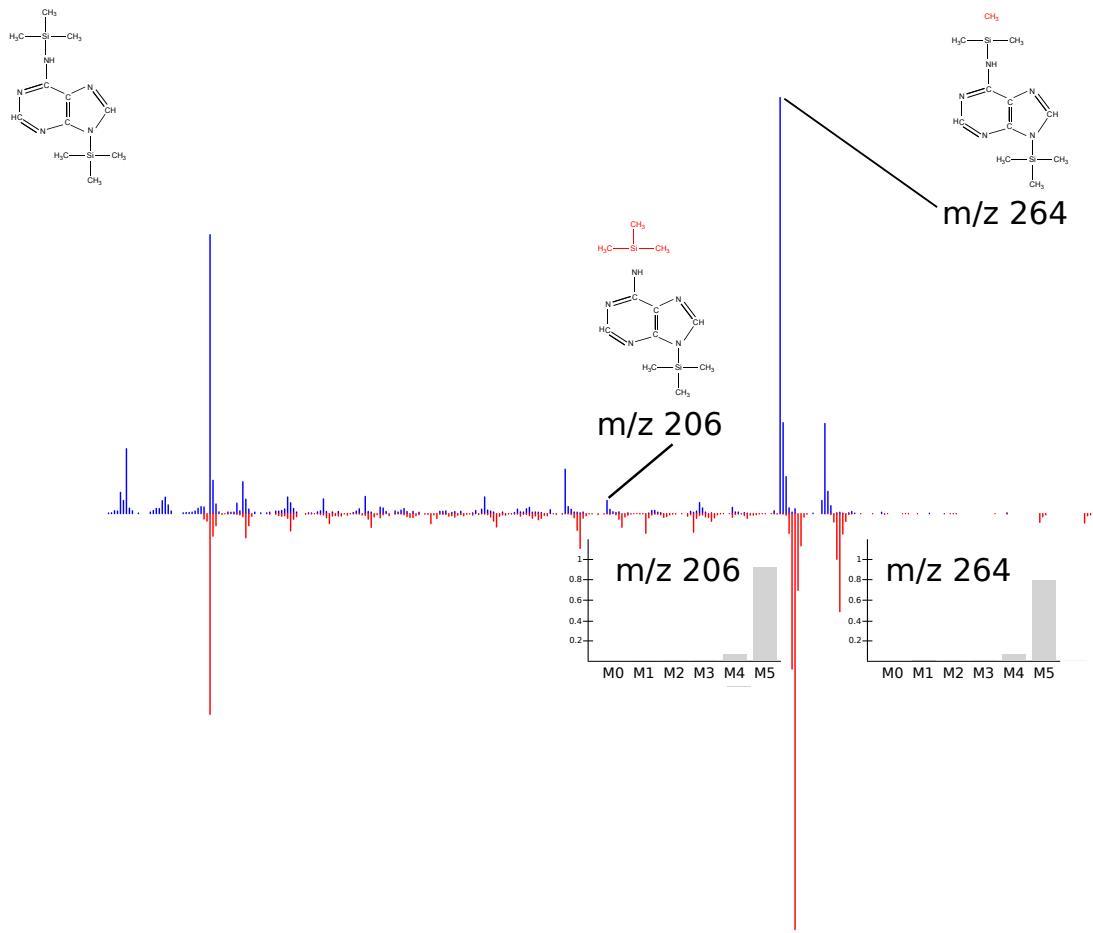
GC/MS analysis was performed by using an Agilent 7890A GC coupled to an Agilent 5975C inert XL MSD. A sample volume of 1 μ l was injected into a Split/Splitless inlet operating in split mode (split ratio 3:1; MeOX/TMS derivatization) or splitless mode (MeOX/TBDMS derivatization) at 270 °C. The gas chromatograph was equipped with a 30 m x 0.25 mm I.D. x 0.25 μ m film thickness DB-35MS capillary column + 5 m DuraGuard capillary in front of the analytical column. Helium was used as carrier gas with a constant flow rate of 1 ml/min. For MeOX/TMS derivatized samples, the GC oven temperature was held at 80 °C for 6 min and increased to 300 °C at 6 °C/min. After 10 min, the temperature was increased at 10 °C/min followed by an additional constant temperature period at 325 °C for 4 min. For MeOX/TBDMS derivatized samples, the GC oven temperature was held at 100 °C for 3 min and increased to 300 °C at 3.5 °C/min. The transfer line temperature was set constantly to 280 °C. The MSD was operating under electron ionization at 70 eV. The MS source was held at 230 °C and the quadrupole at 150 °C. Full scan mass spectra were acquired from m/z 70 to 800. The total run time for MeOX/TMS derivatized samples was 59.167 min and 60.143 min for MeOX/TBDMS derivatized samples.

Results and Discussion

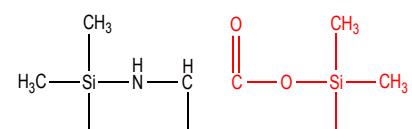
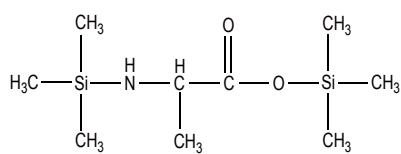
Table 1

Amino acid	m/z	Carbon Atoms	FFC†	Formula	FFC‡
Ala	232	2-3	✓	C ₁₀ H ₂₆ NOSi ₂	✓
	260	1-3	✓	C ₁₁ H ₂₆ NO ₂ Si ₂	✓
Gly	218	2	✓	C ₉ H ₂₄ NOSi ₂	✓
	246	1-2	✓	C ₁₀ H ₂₄ NO ₂ Si ₂	✓
Val	260	2-5	✓	C ₁₂ H ₃₀ NOSi ₂	✓
	288	1-5	✓	C ₁₃ H ₃₀ NO ₂ Si ₂	✓
Leu	200	2-6	✓	C ₁₁ H ₂₆ NSi	✓
	274	2-6	X	C ₁₃ H ₃₂ NOSi ₂	✓
	302	1-6	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
Ile	200	2-6	✓	C ₁₁ H ₂₆ NSi	✓
	274	2-6	X	C ₁₃ H ₃₂ NOSi ₂	✓
	302	1-6	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
Ser	288	2-3	✓	C ₁₄ H ₃₄ NOSi ₂	✓
	302	1-2	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
	362	2-3	✓	C ₁₆ H ₄₀ NO ₂ Si ₃	✓
	390	1-3	✓	C ₁₇ H ₄₀ NO ₃ Si ₃	✓
Thr	376	2-4	X	C ₁₇ H ₄₂ NO ₂ Si ₃	X
	404	1-4	✓	C ₁₈ H ₄₂ NO ₃ Si ₃	✓
Met	218	2-5	✓	C ₁₀ H ₂₄ NSSi	✓
	292	2-5	✓	C ₁₂ H ₃₀ NOSSi ₂	✓
Phe	320	1-5	✓	C ₁₃ H ₃₀ NO ₂ SSI ₃	✓
	234	2-9	✓	C ₁₄ H ₂₄ NSi	✓
	302	1-2	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
	308	2-9	✓	C ₁₆ H ₃₀ NOSi ₂	✓
Asp	336	1-9	✓	C ₁₇ H ₃₀ NO ₂ Si ₃	✓
	302	1-2	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
	376	1-2	✓	C ₁₆ H ₃₈ NO ₃ Si ₃	✓
	390	2-4	X	C ₁₇ H ₄₀ NO ₃ Si ₃	✓
Glu	418	1-4	✓	C ₁₈ H ₄₀ NO ₄ Si ₃	✓
	330	2-5	X	C ₁₆ H ₃₆ NO ₂ Si ₂	✓
Lys	432	1-5	✓	C ₁₉ H ₄₂ NO ₄ Si ₃	✓
	329	2-6	✓	C ₁₇ H ₄₁ N ₂ Si ₂	✓
Tyr	431	1-6	✓	C ₂₀ H ₄₇ N ₂ O ₂ Si ₃	✓
	302	1-2	✓	C ₁₄ H ₃₂ NO ₂ Si ₂	✓
	364	2-8	✓	C ₂₀ H ₃₈ NOSi ₂	✓

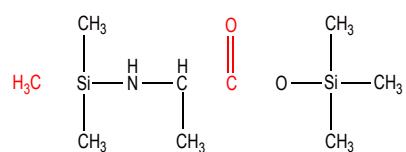
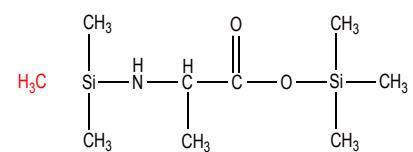
Adenine 2TMS



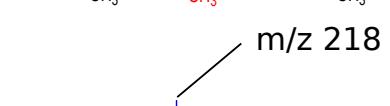
Alanine 2TMS



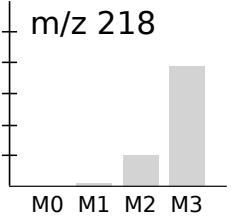
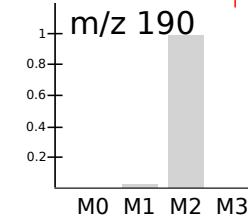
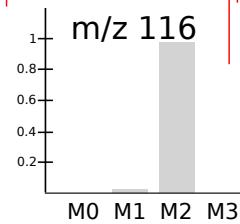
m/z 116



m/z 190

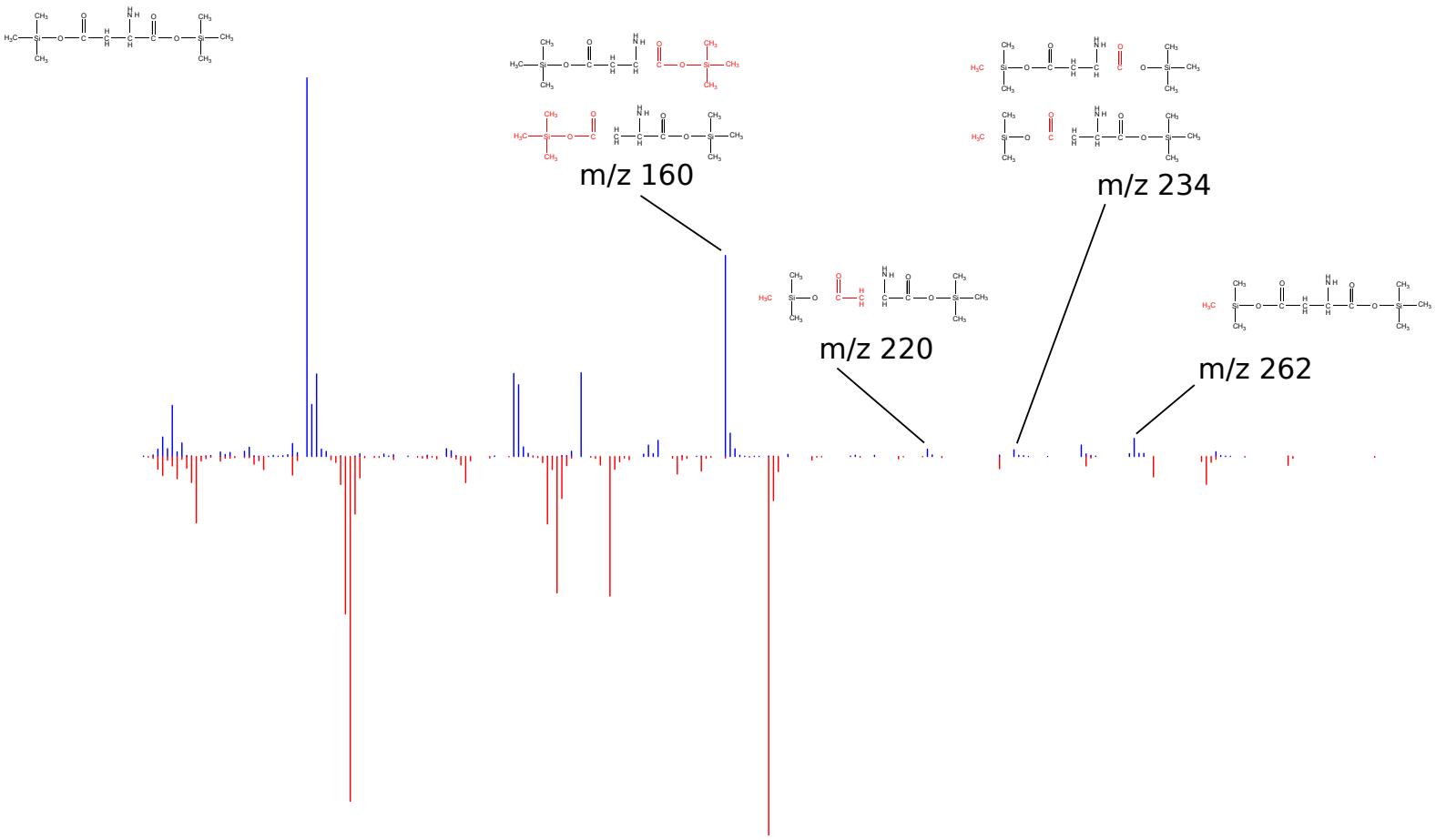


m/z 218



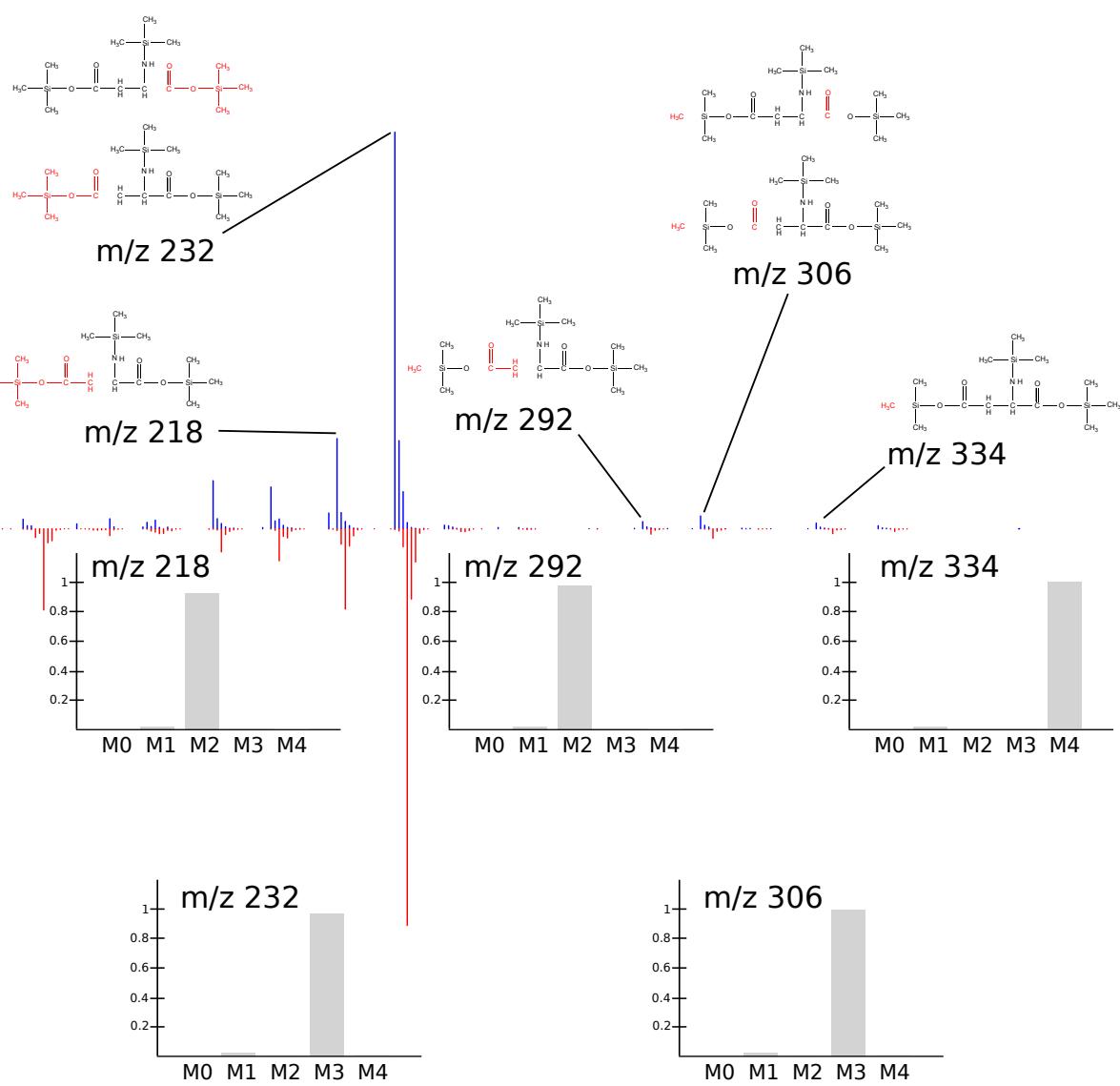
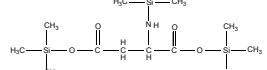
$^{13}\text{C}_3$ Alanine 2TMS

Aspartic acid 2TMS



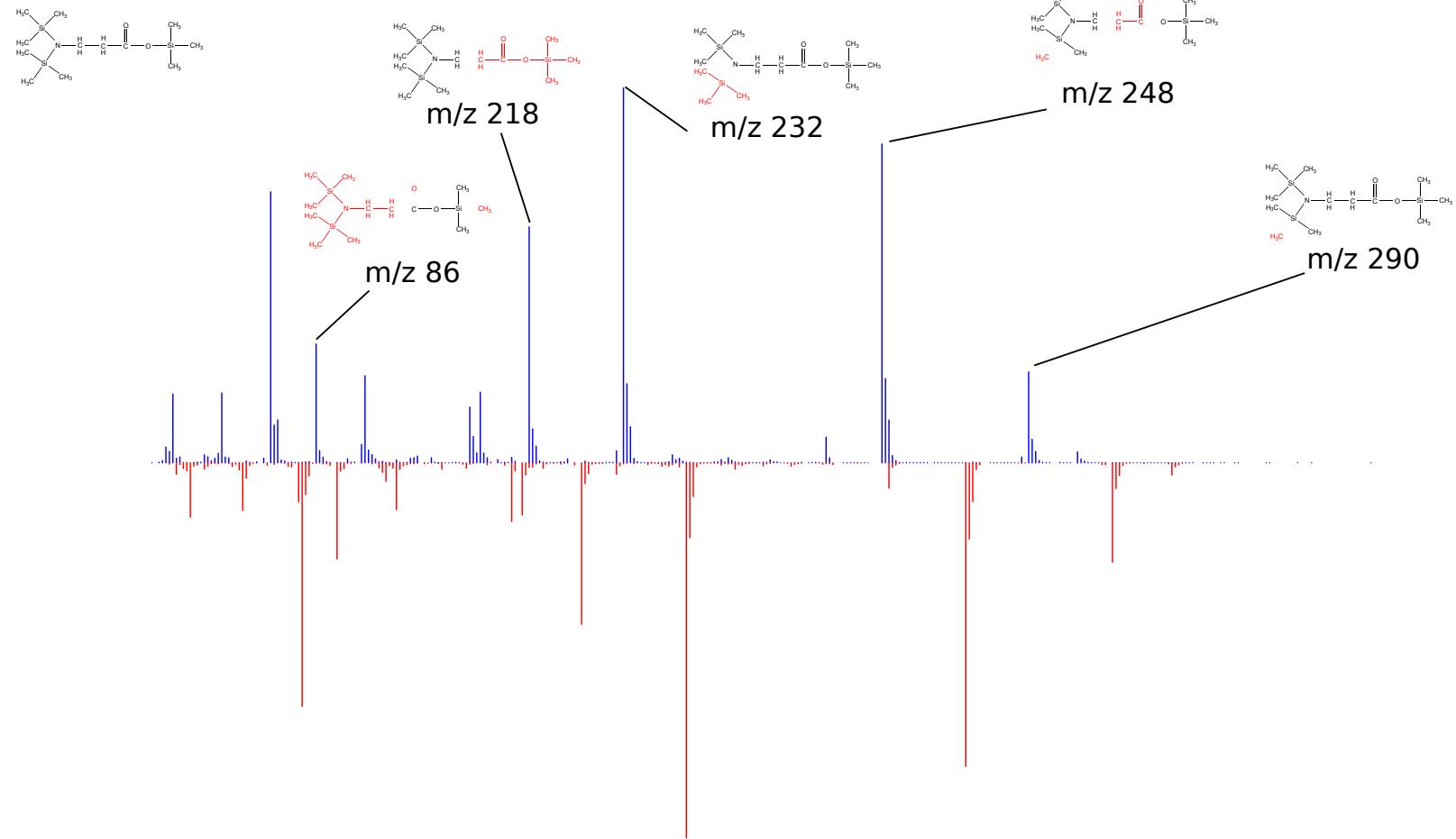
Aspartic acid d_9 -2TMS

Aspartic acid 3TMS



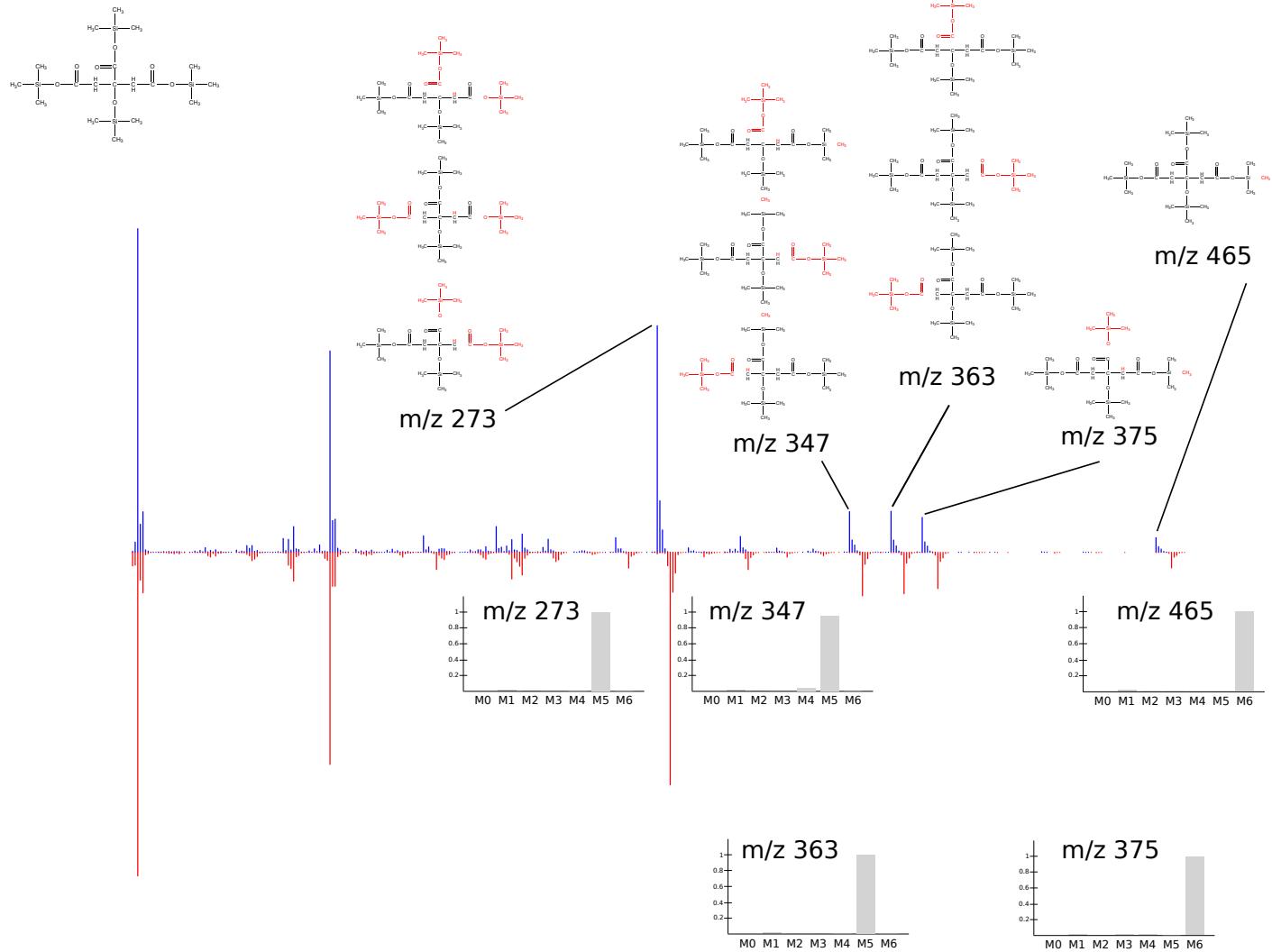
$^{13}\text{C}_4$ Aspartic acid 3TMS

beta-Alanine 3TMS



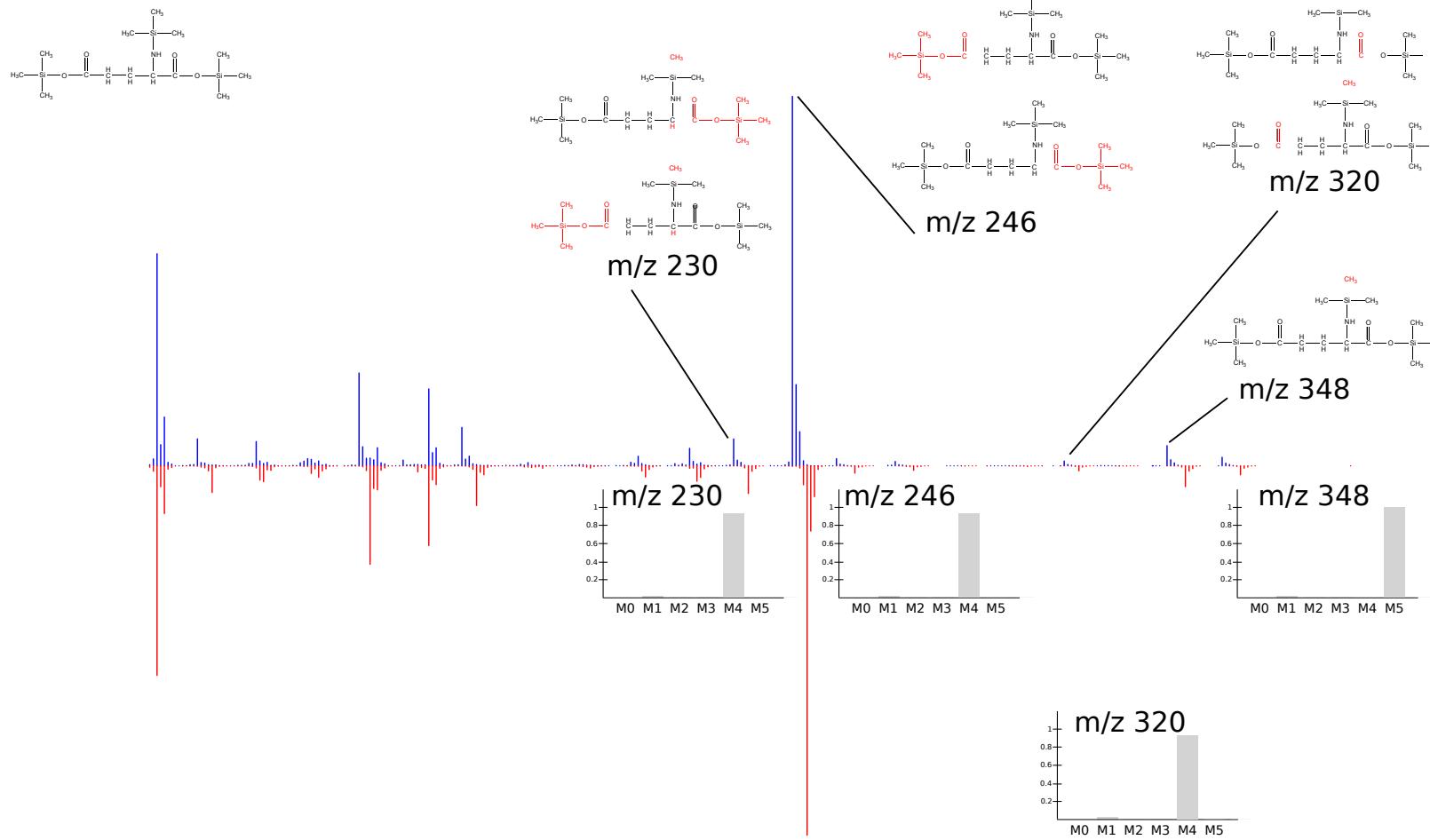
beta-Alanine d_9 -3TMS

Citric acid 4TMS



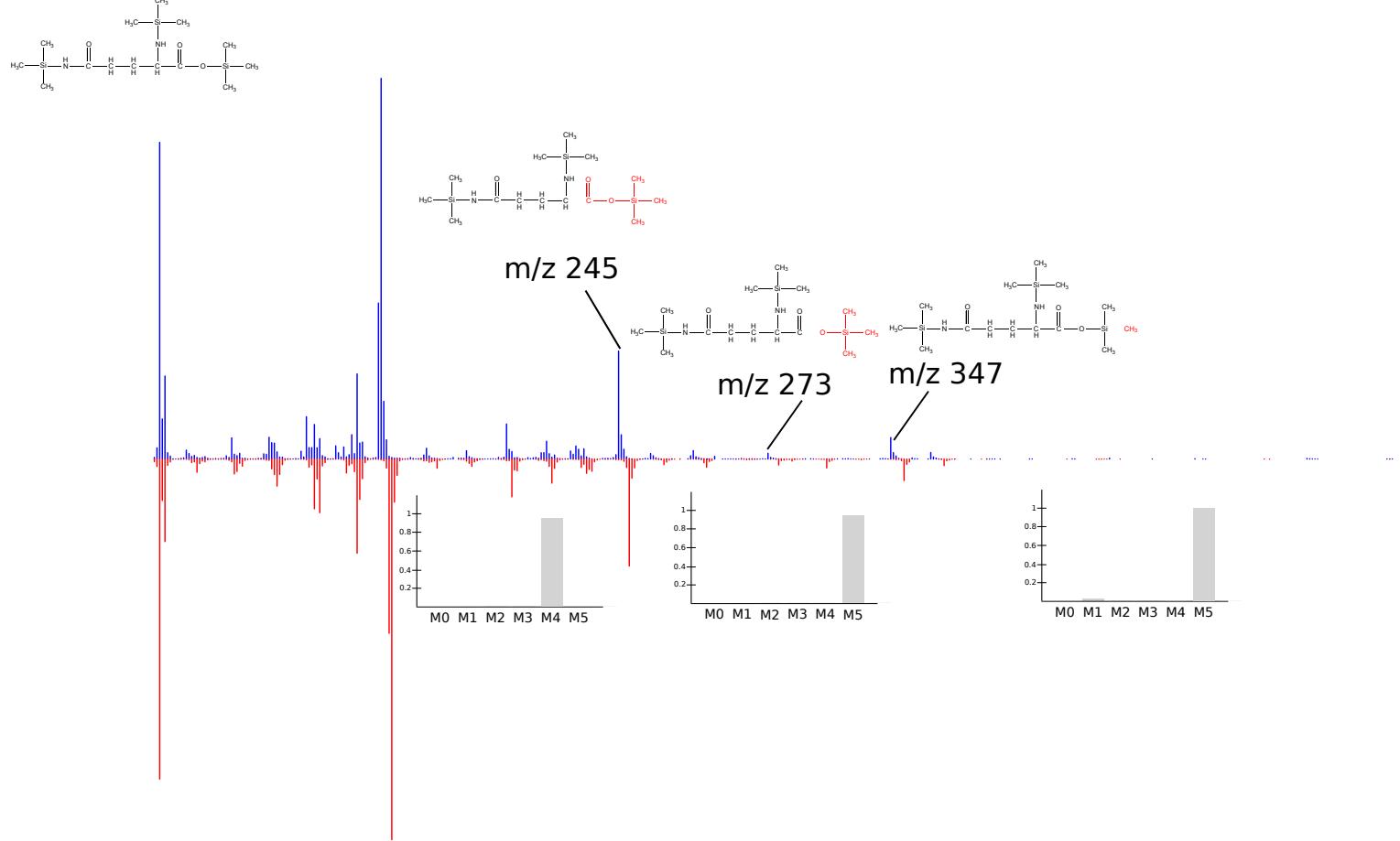
$^{13}\text{C}_6$ Citric acid 4TMS

Glutamic acid 3TMS



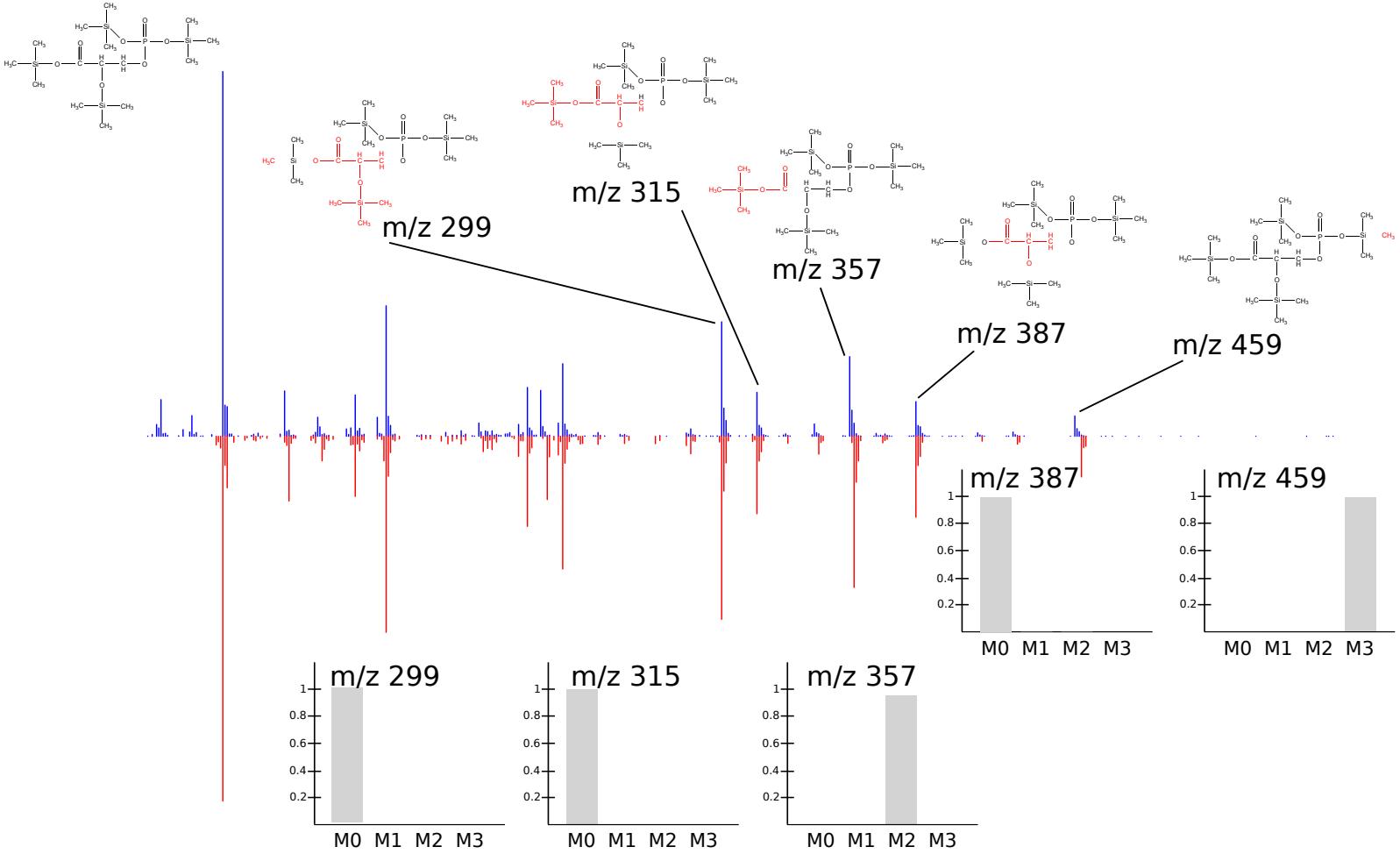
¹³C₅ Glutamic acid 3TMS

Glutamine 3TMS



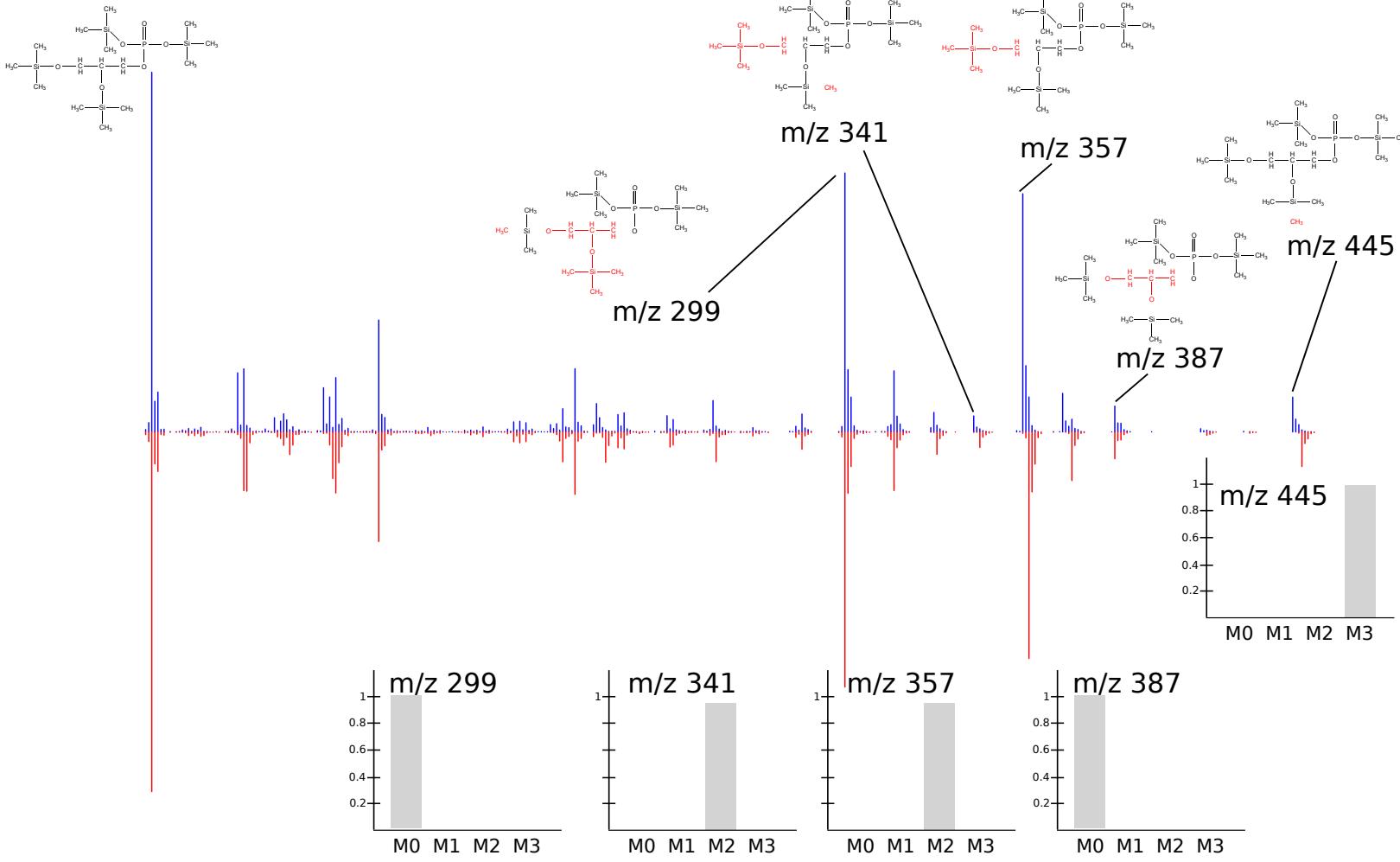
$^{13}\text{C}_5$ Glutamine 3TMS

3-phosphoglycerate 4TMS



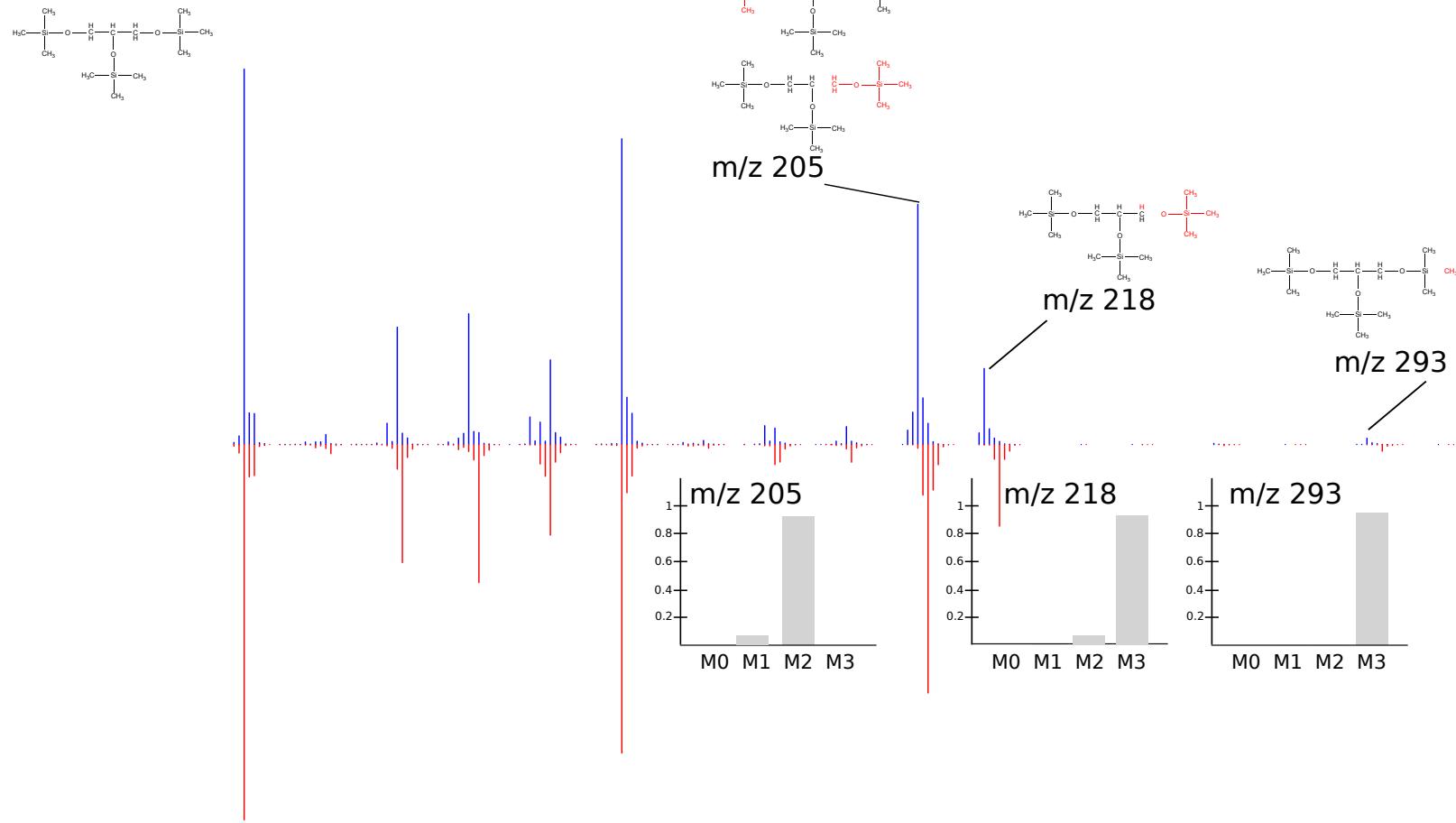
$^{13}\text{C}_3$ 3-phosphoglycerate 4TMS

Glycerol-3-phosphate 4TMS



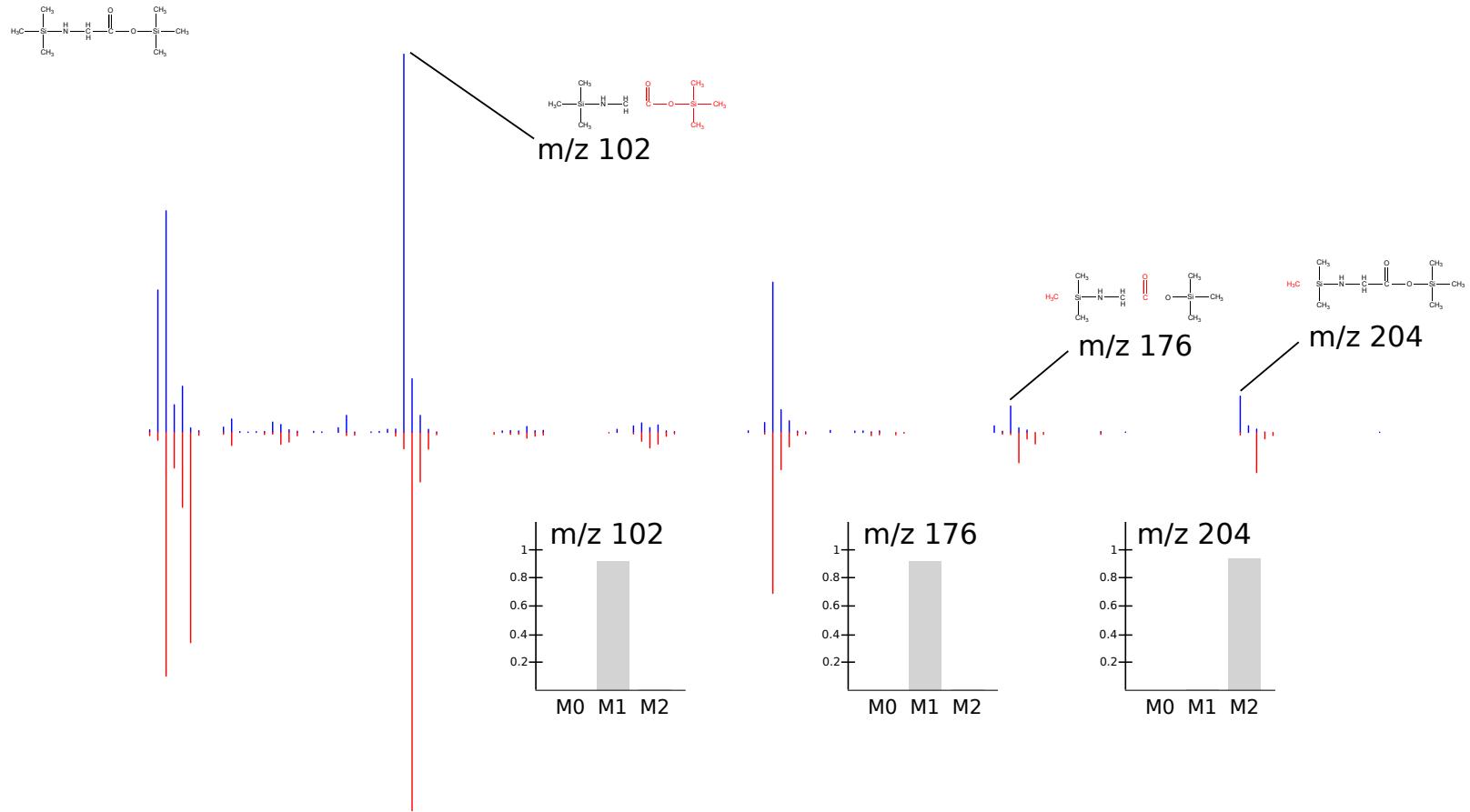
¹³C₃ Glycerol-3-phosphate 4TMS

Glycerol 3TMS



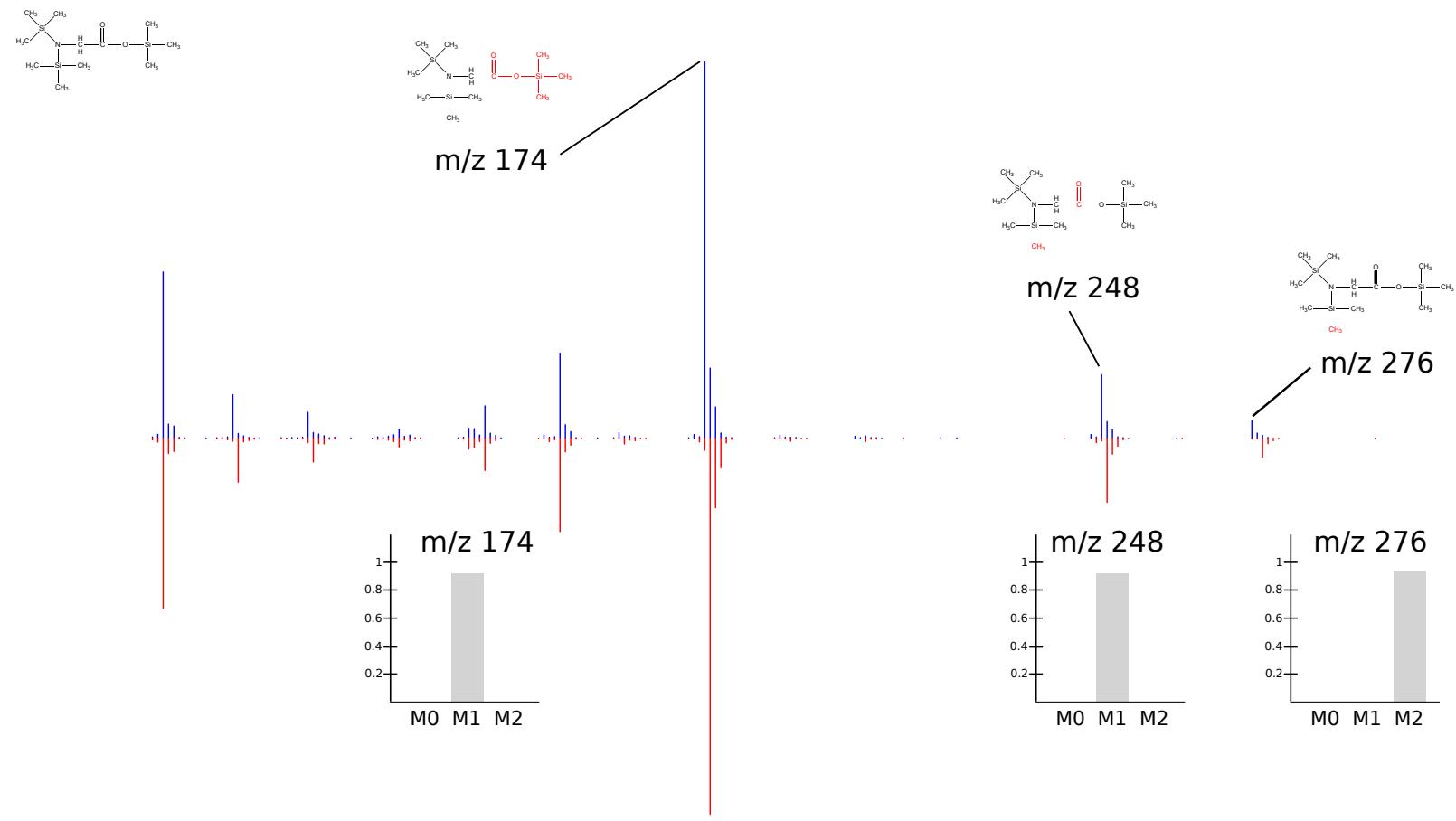
$^{13}\text{C}_3$ Glycerol 3TMS

Glycine 2 TMS



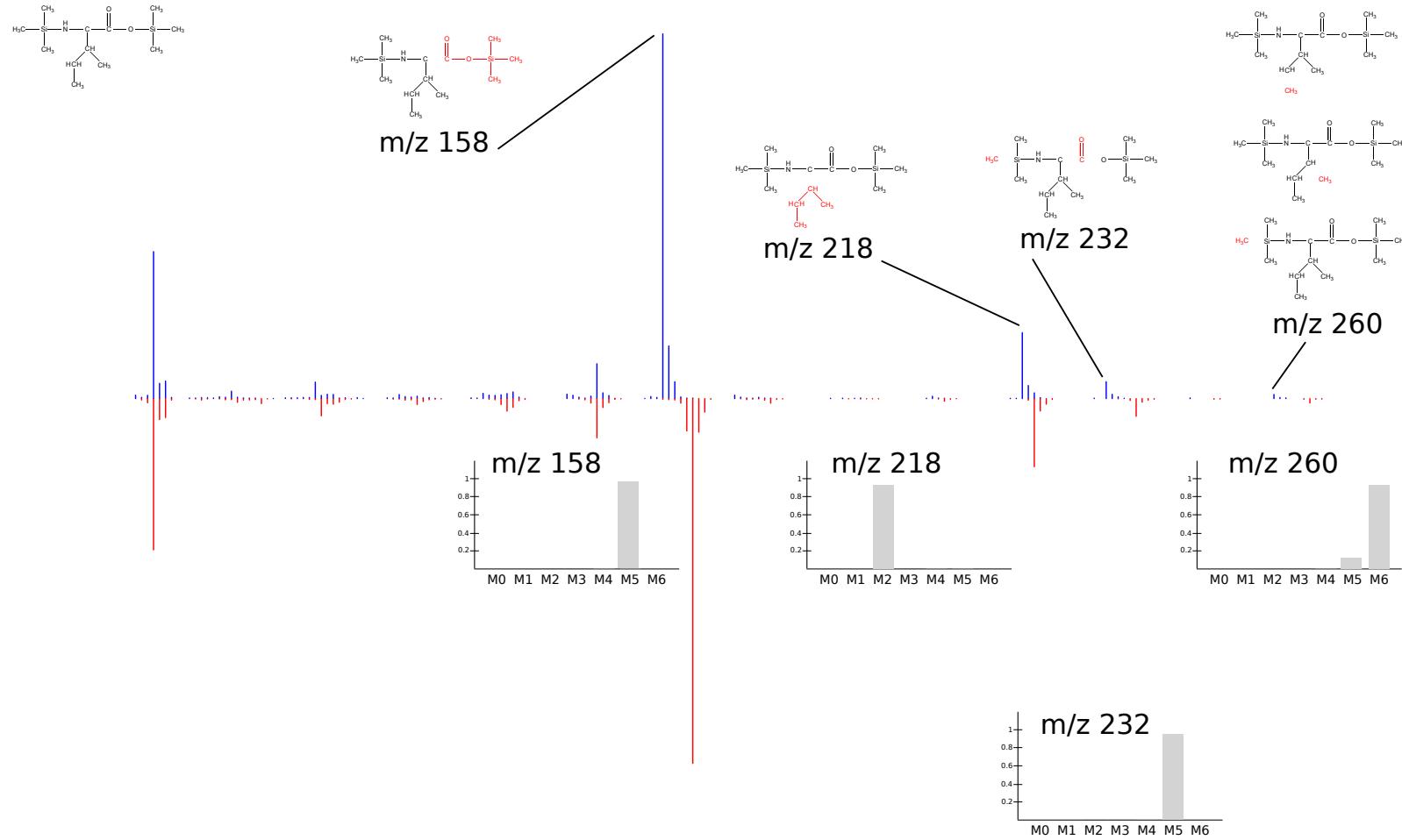
$^{13}\text{C}_2$ Glycine 2 TMS

Glycine 3TMS



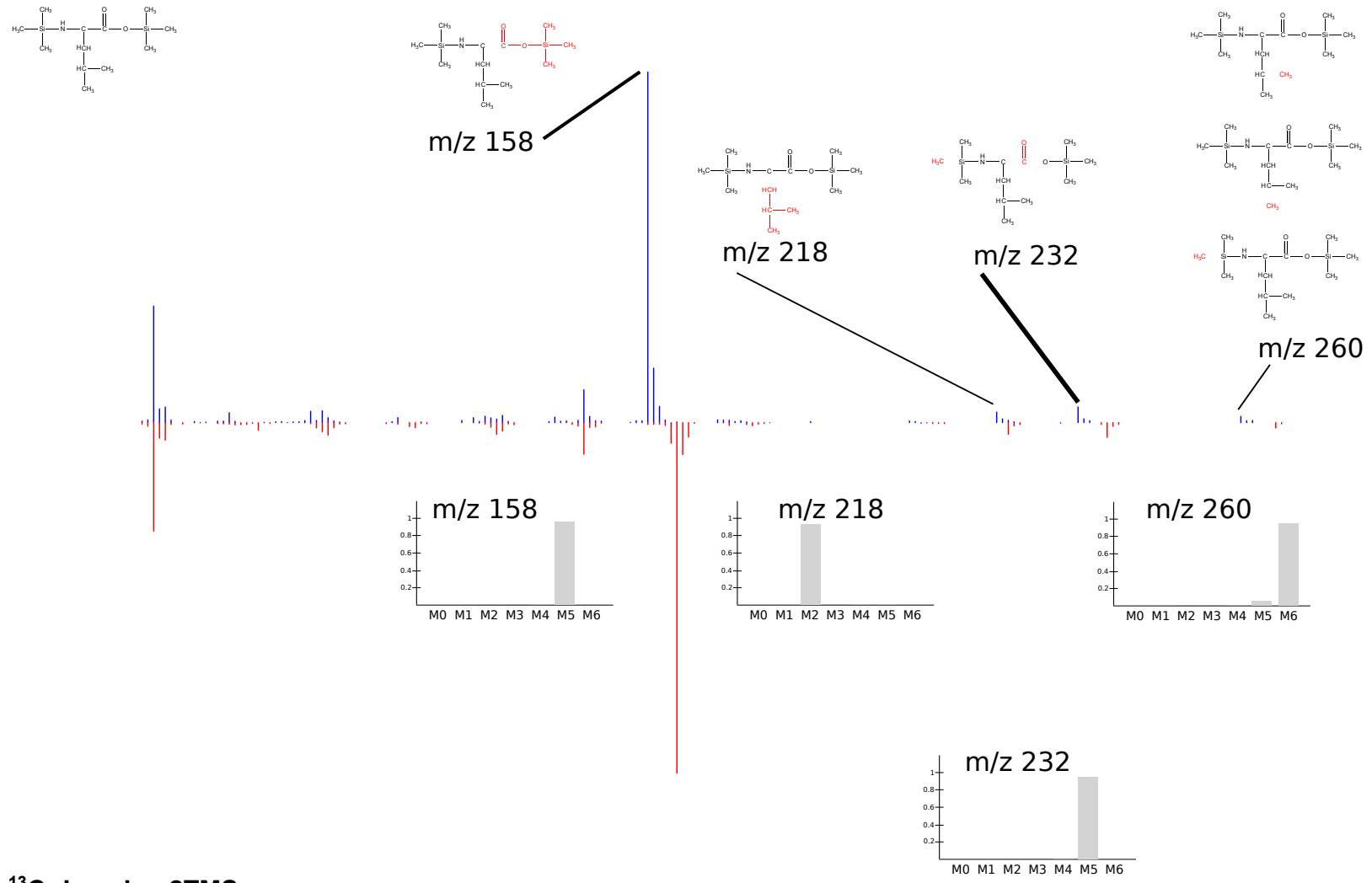
$^{13}\text{C}_2$ Glycine 3 TMS

Isoleucine 2TMS



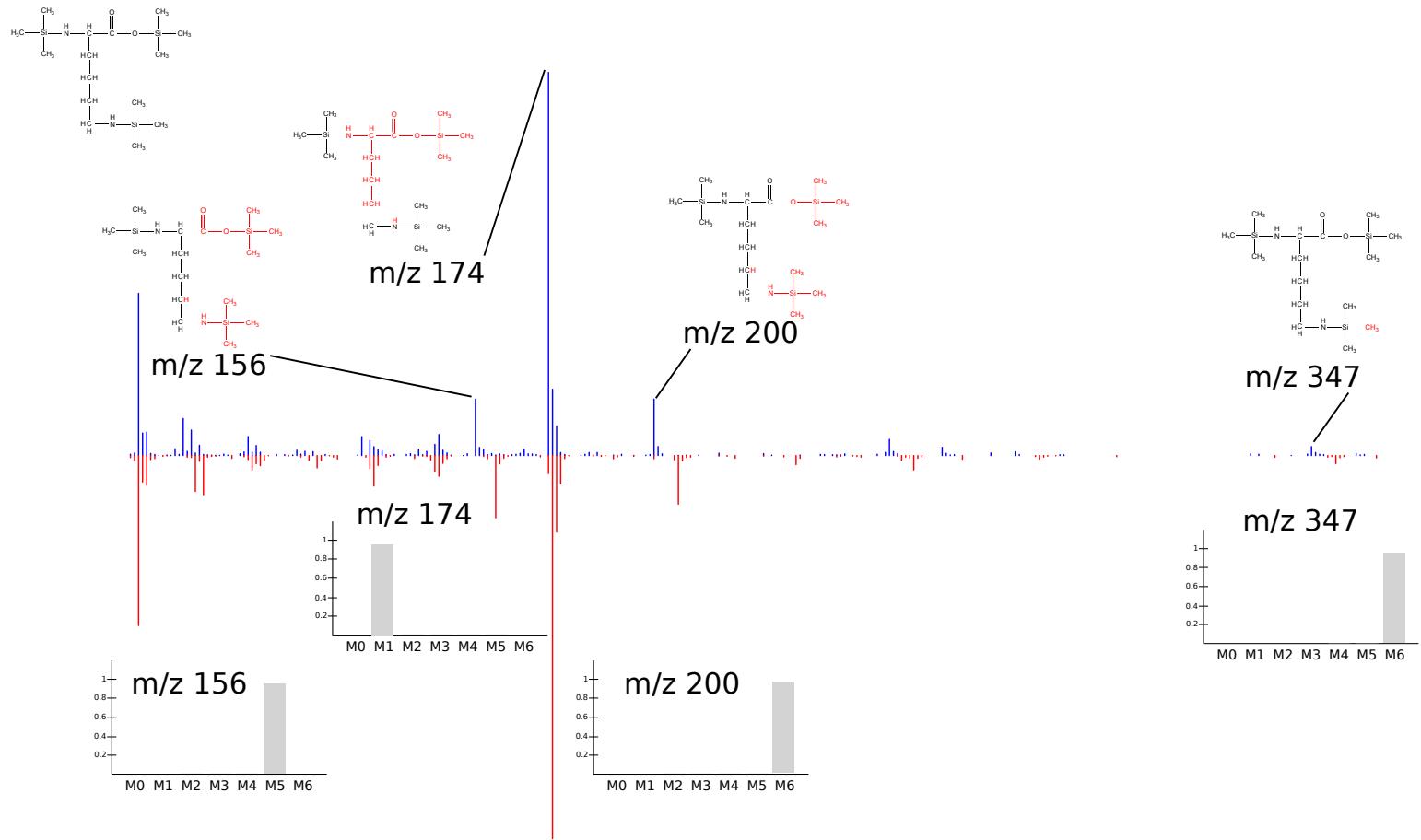
$^{13}\text{C}_6$ Isoleucine 2TMS

Leucine 2TMS



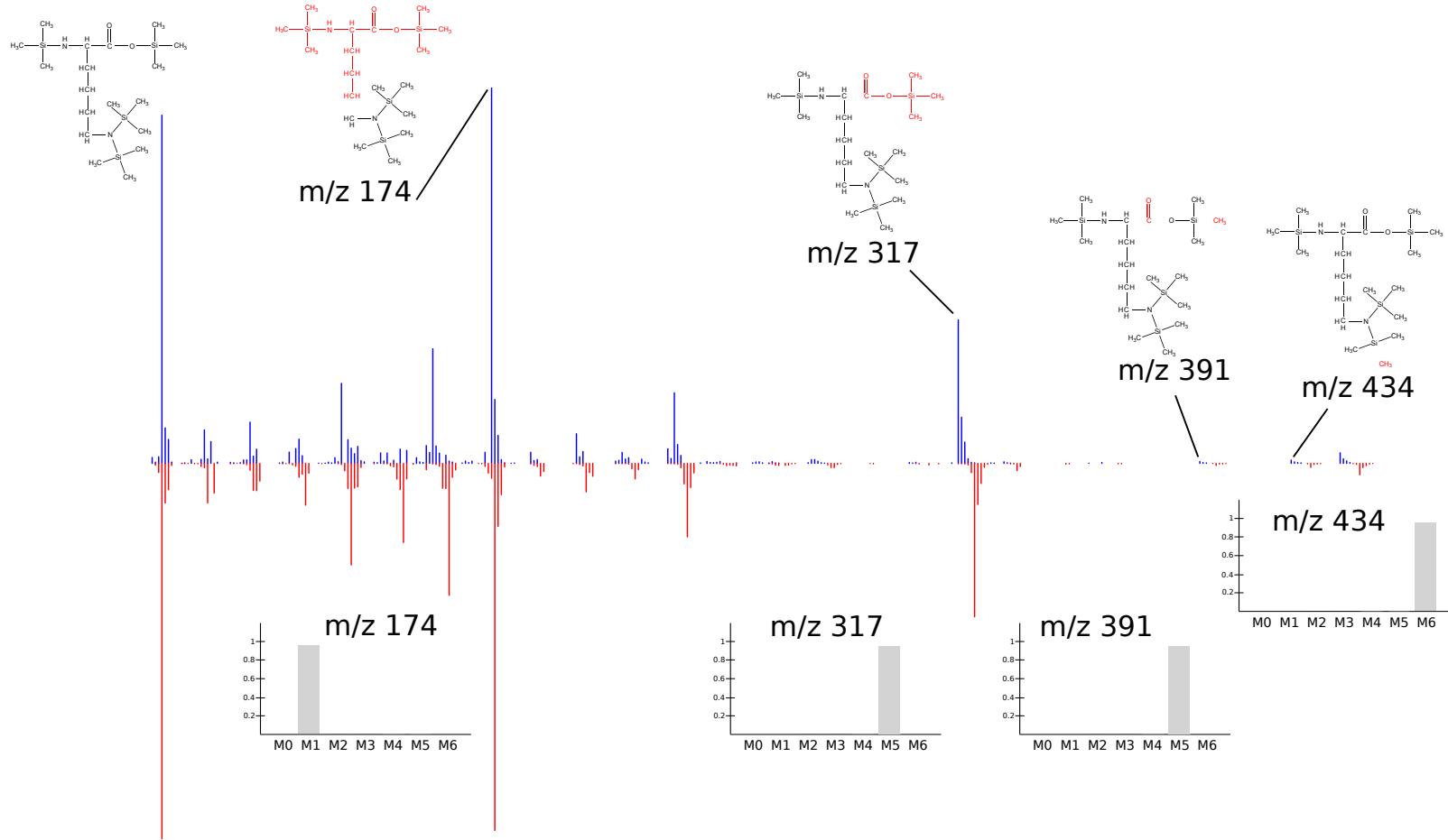
$^{13}\text{C}_6$ Leucine 2TMS

Lysine 3TMS



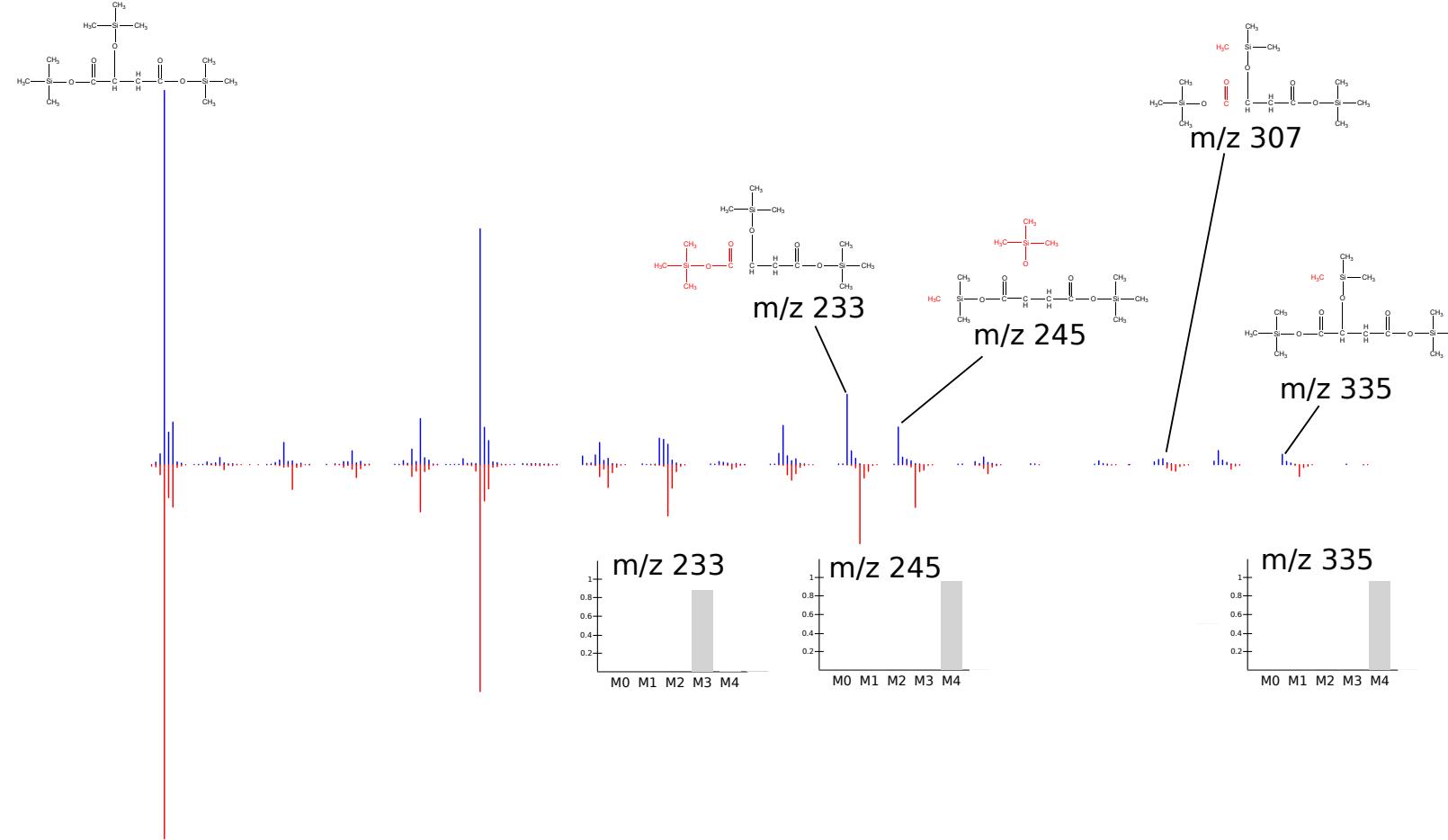
$^{13}\text{C}_6$ Lysine 3TMS

Lysine 4TMS



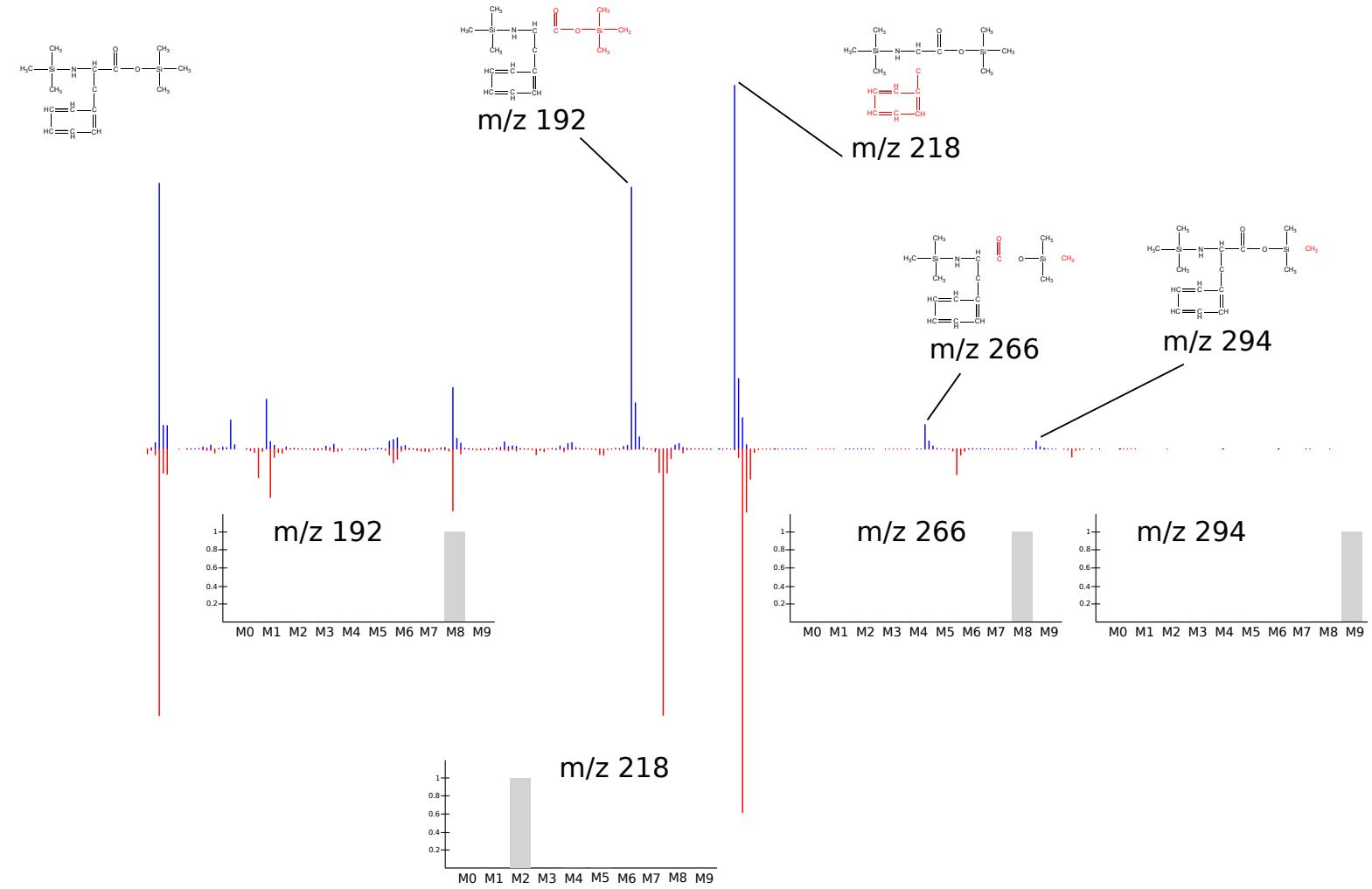
$^{13}\text{C}_6$ Lysine 4TMS

Malic acid 3TMS



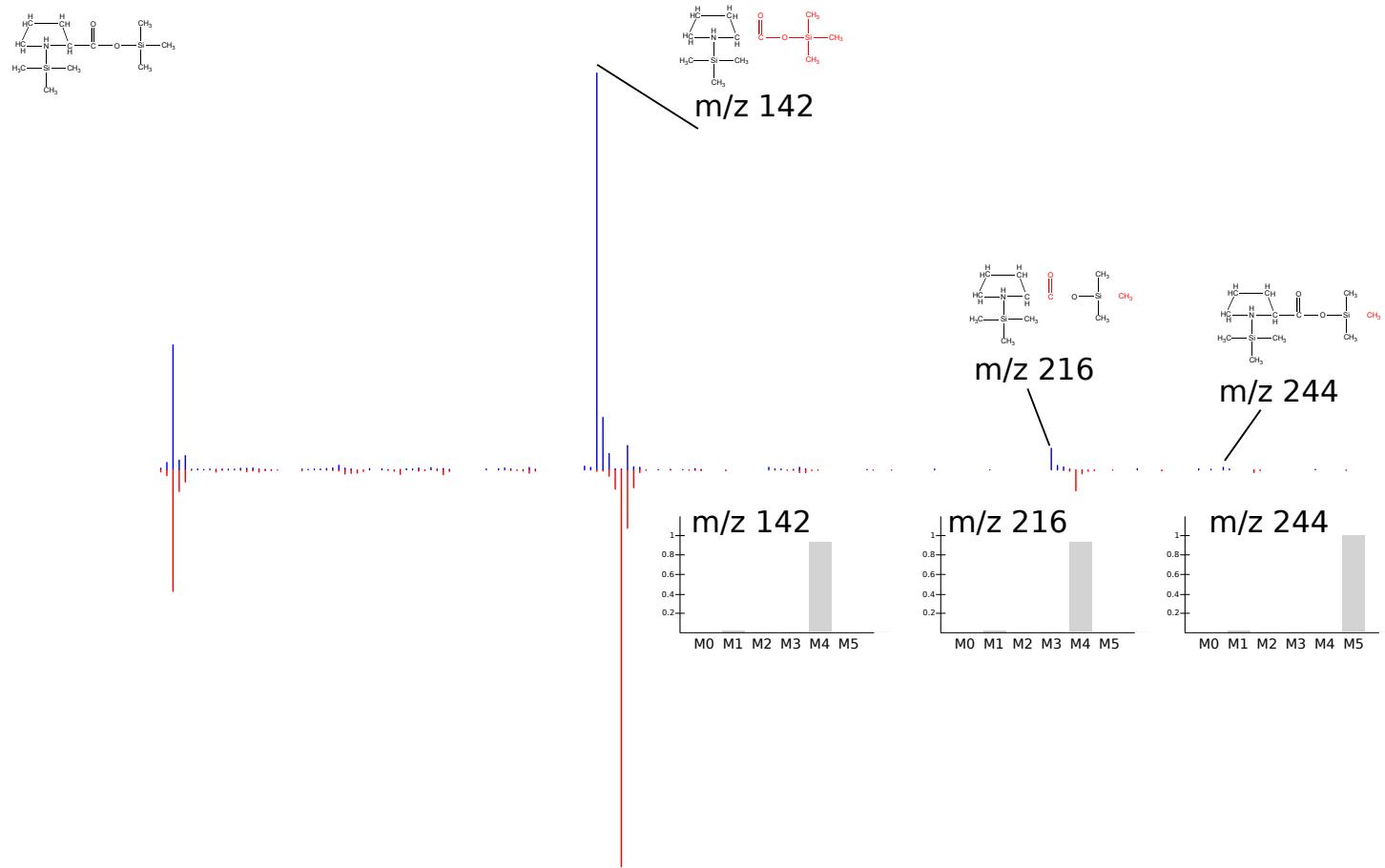
$^{13}\text{C}_4$ Malic acid 3TMS

Phenylalanine 2TMS



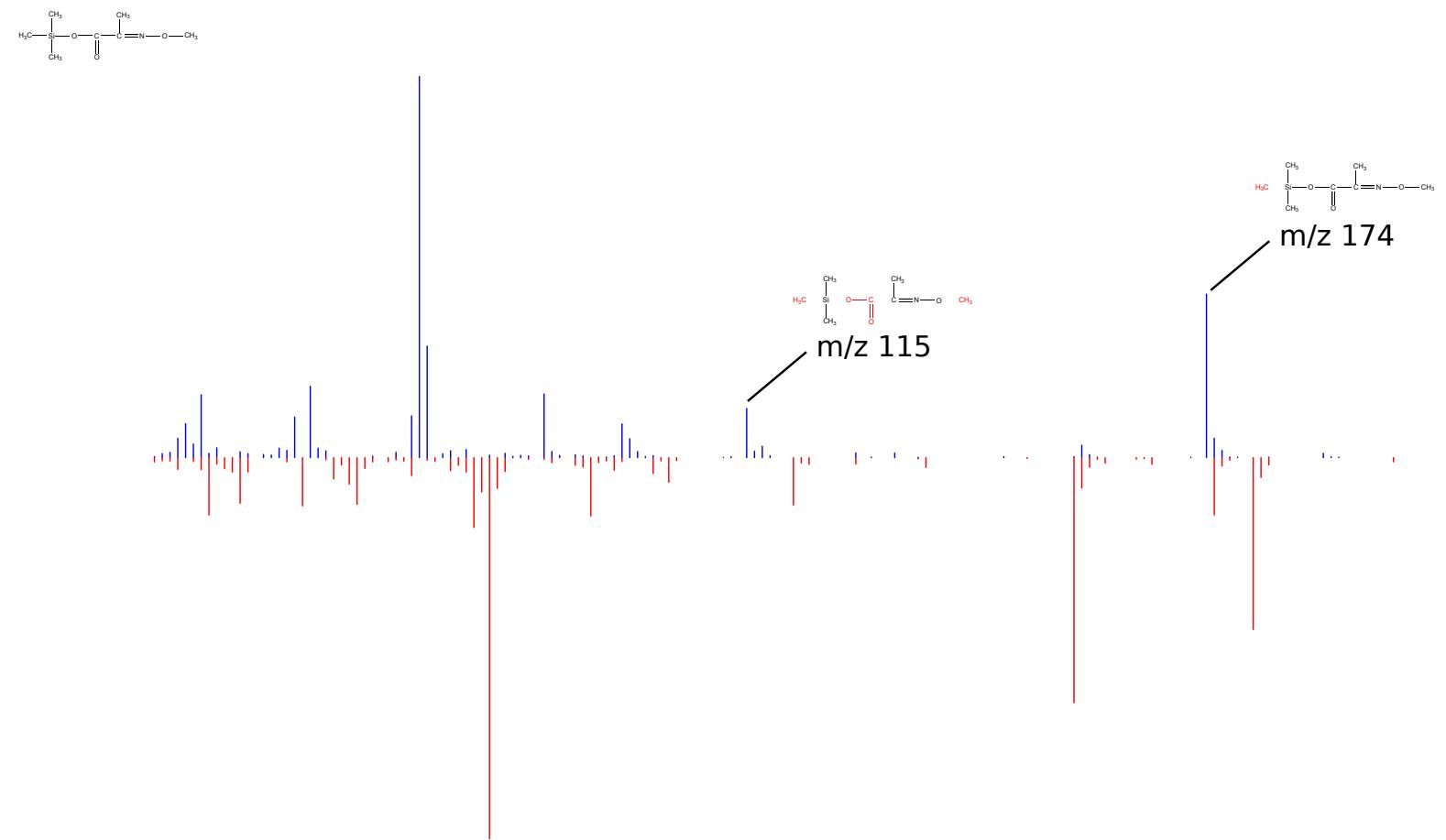
¹³C₉ Phenylalanine 2TMS

Proline 2TMS



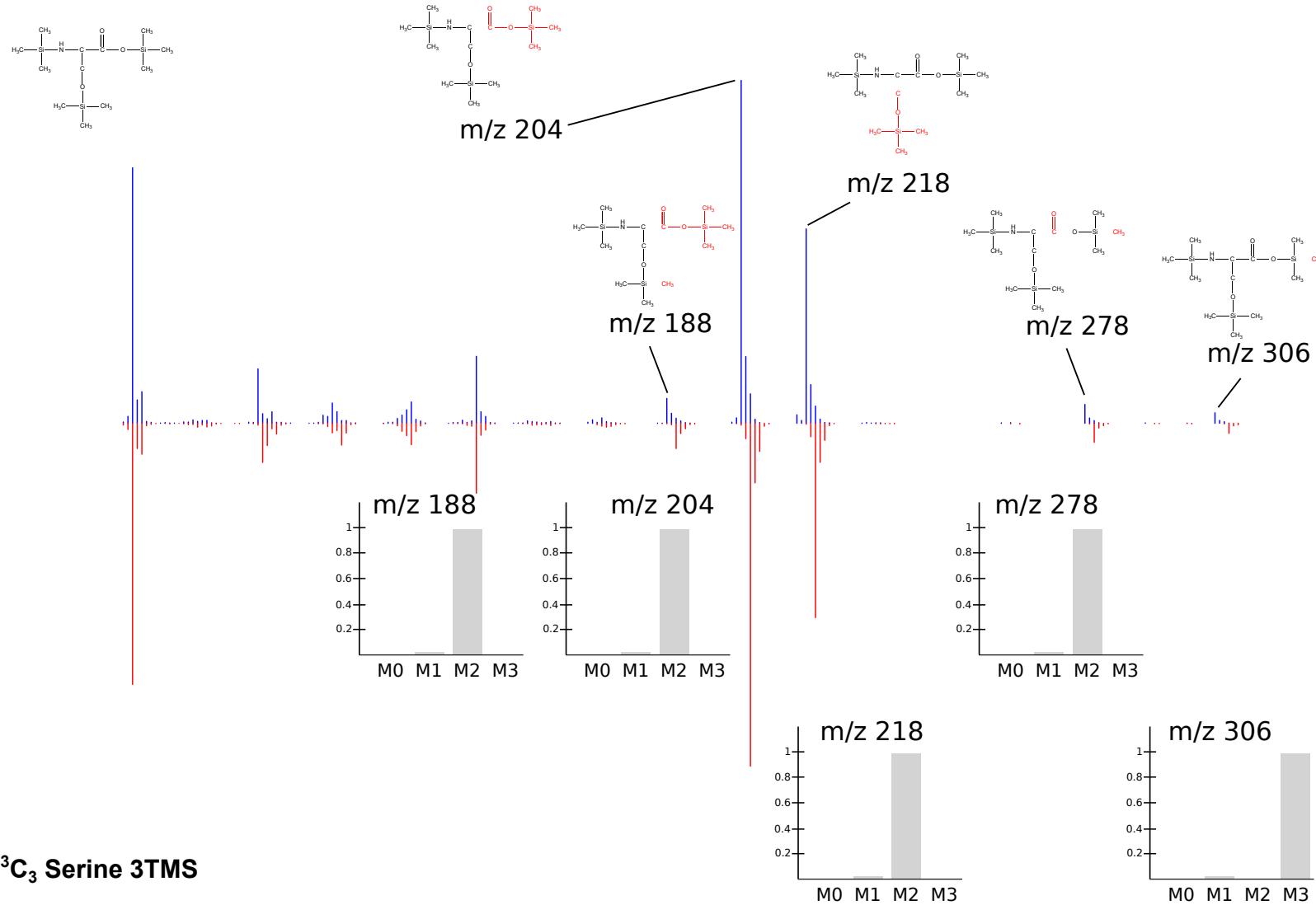
$^{13}\text{C}_5$ Proline 2TMS

Pyruvic acid 1TMS 1MEOX



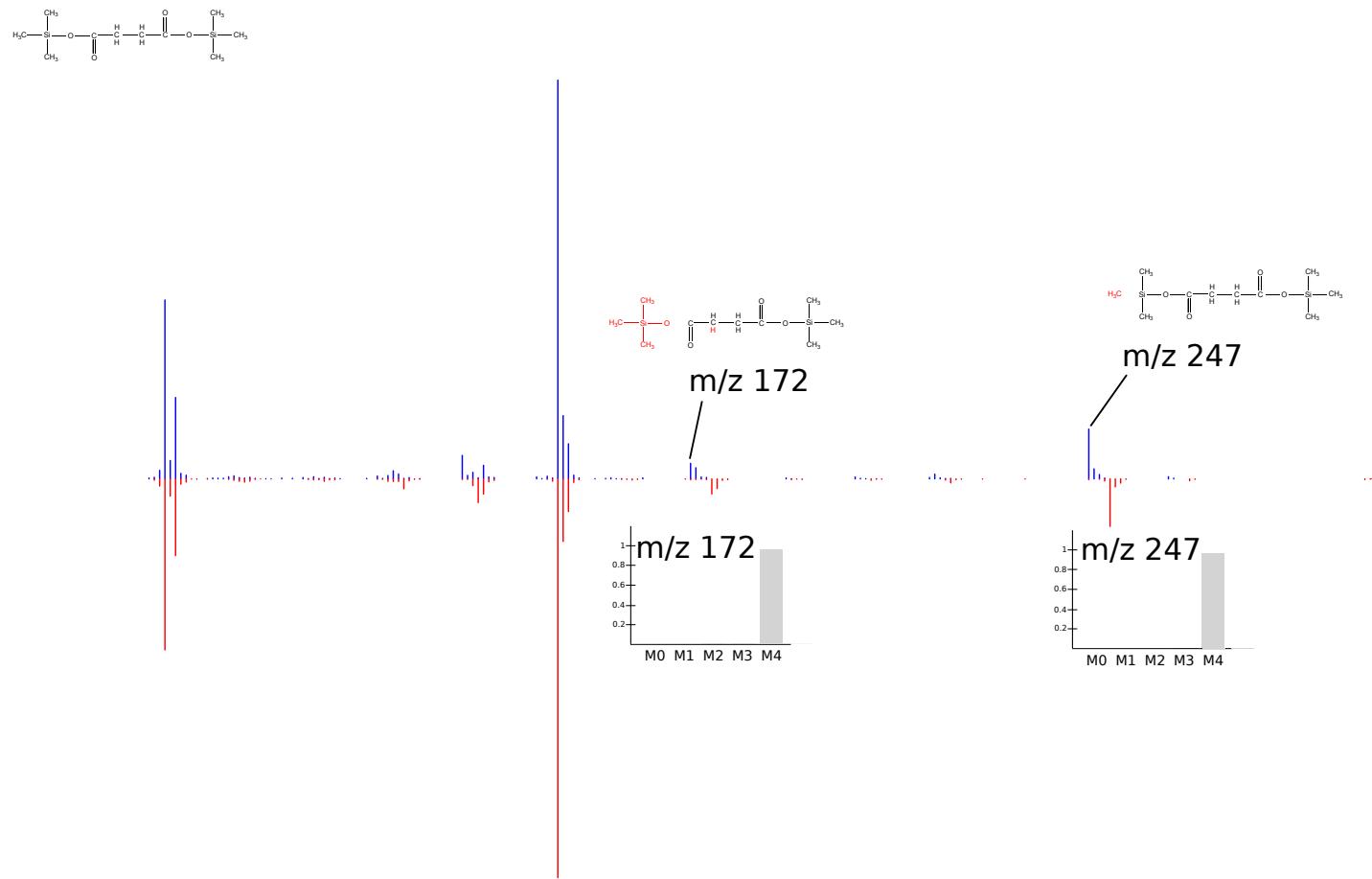
Pyruvic acid d₉-1TMS 1MEOX

Serine 3TMS



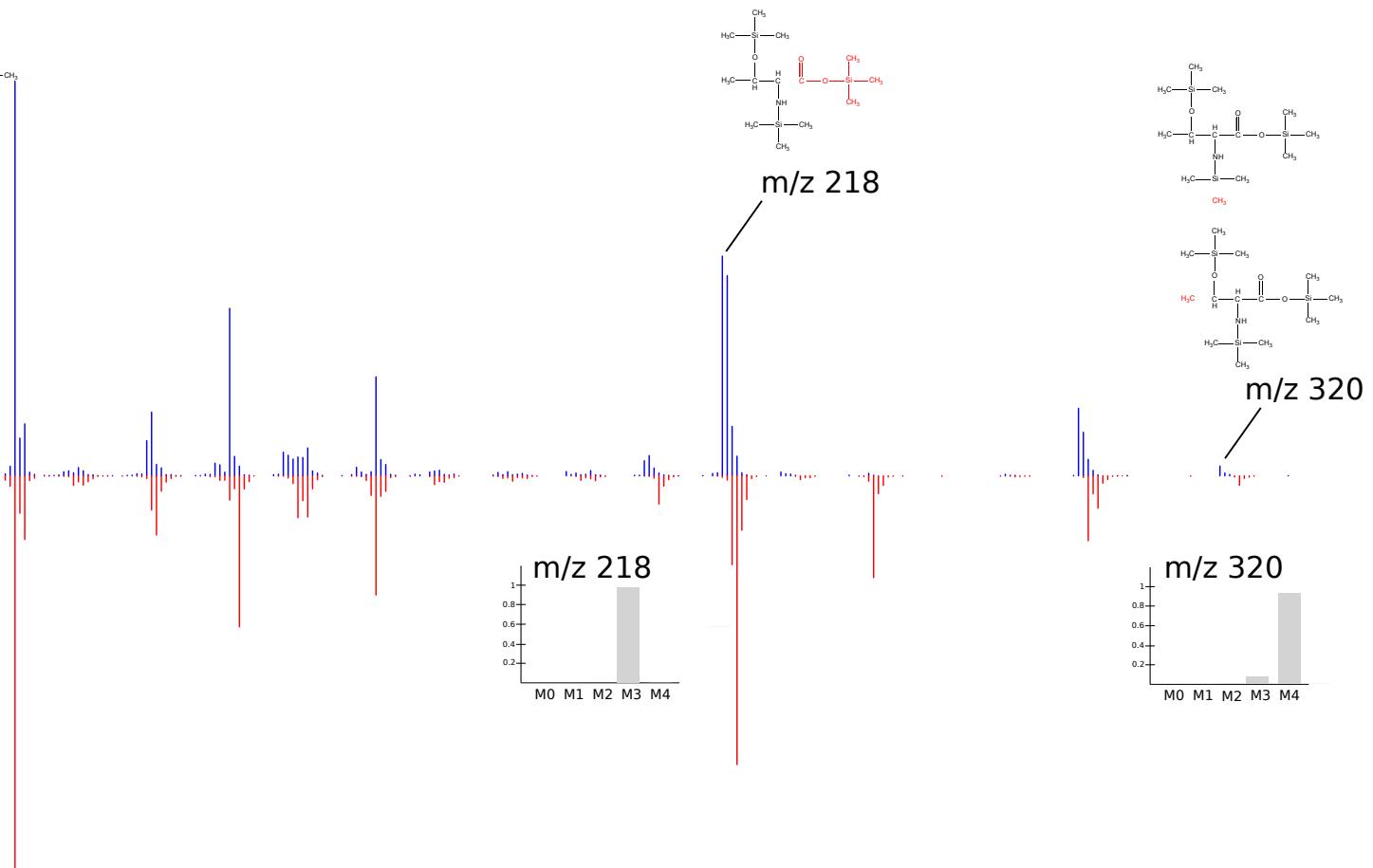
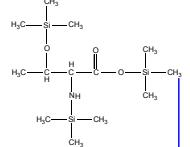
$^{13}\text{C}_3$ Serine 3TMS

Succinic acid 3TMS



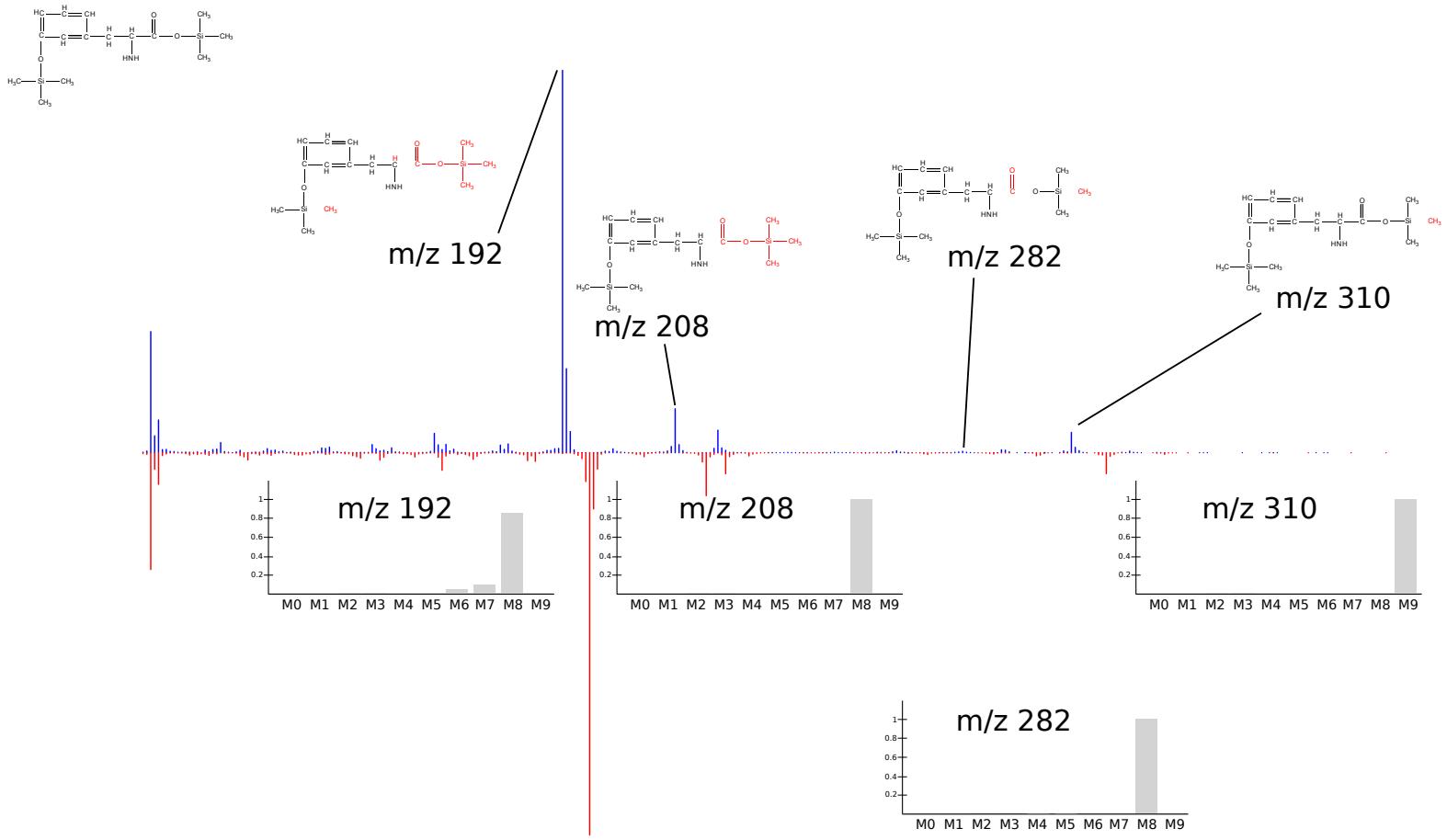
$^{13}\text{C}_4$ Succinic acid 3TMS

Threonine 3TMS



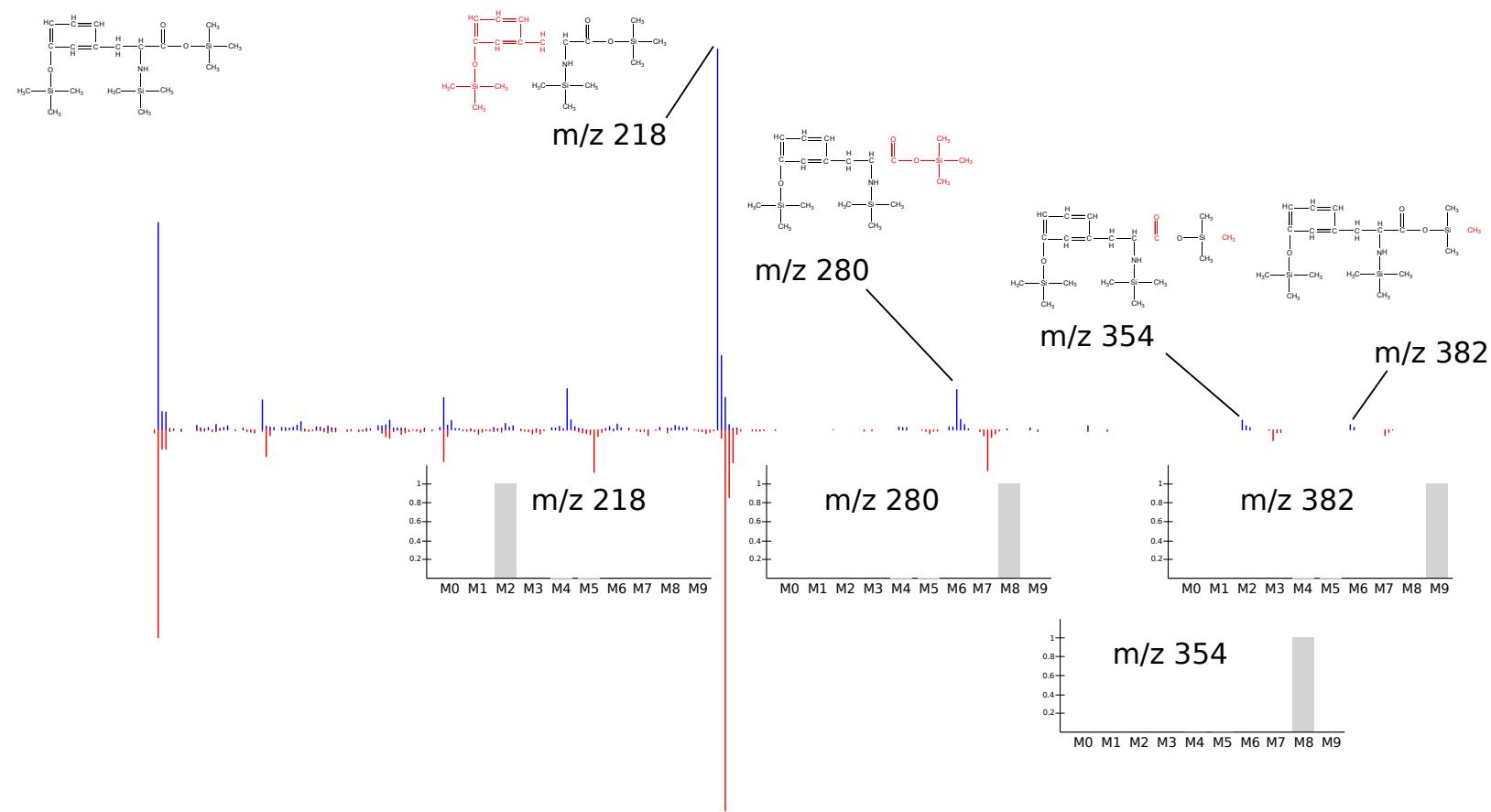
$^{13}\text{C}_4$ Threonine 3TMS

Tyrosine 2TMS



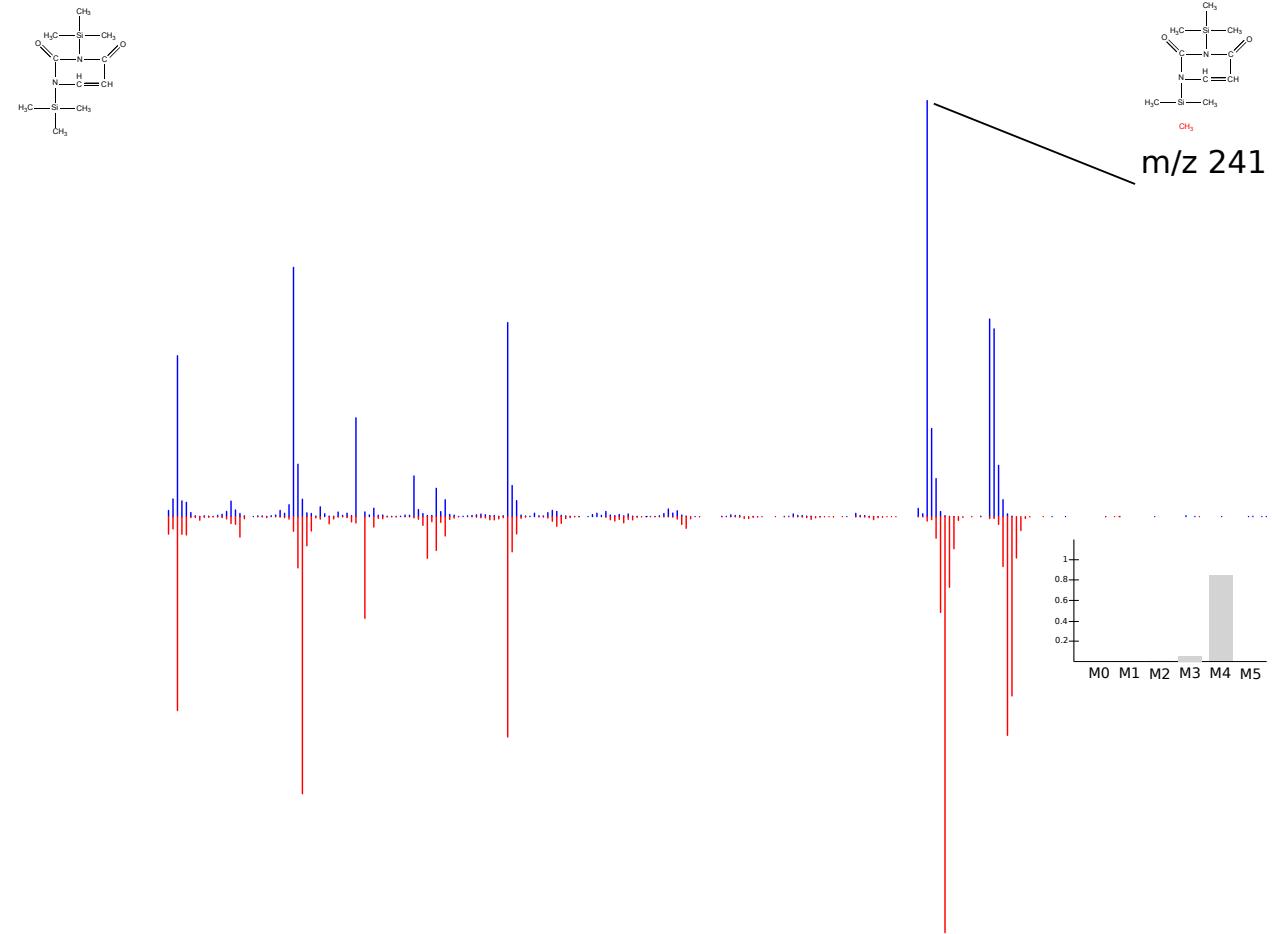
¹³C₉ Tyrosine 2TMS

Tyrosine 3TMS



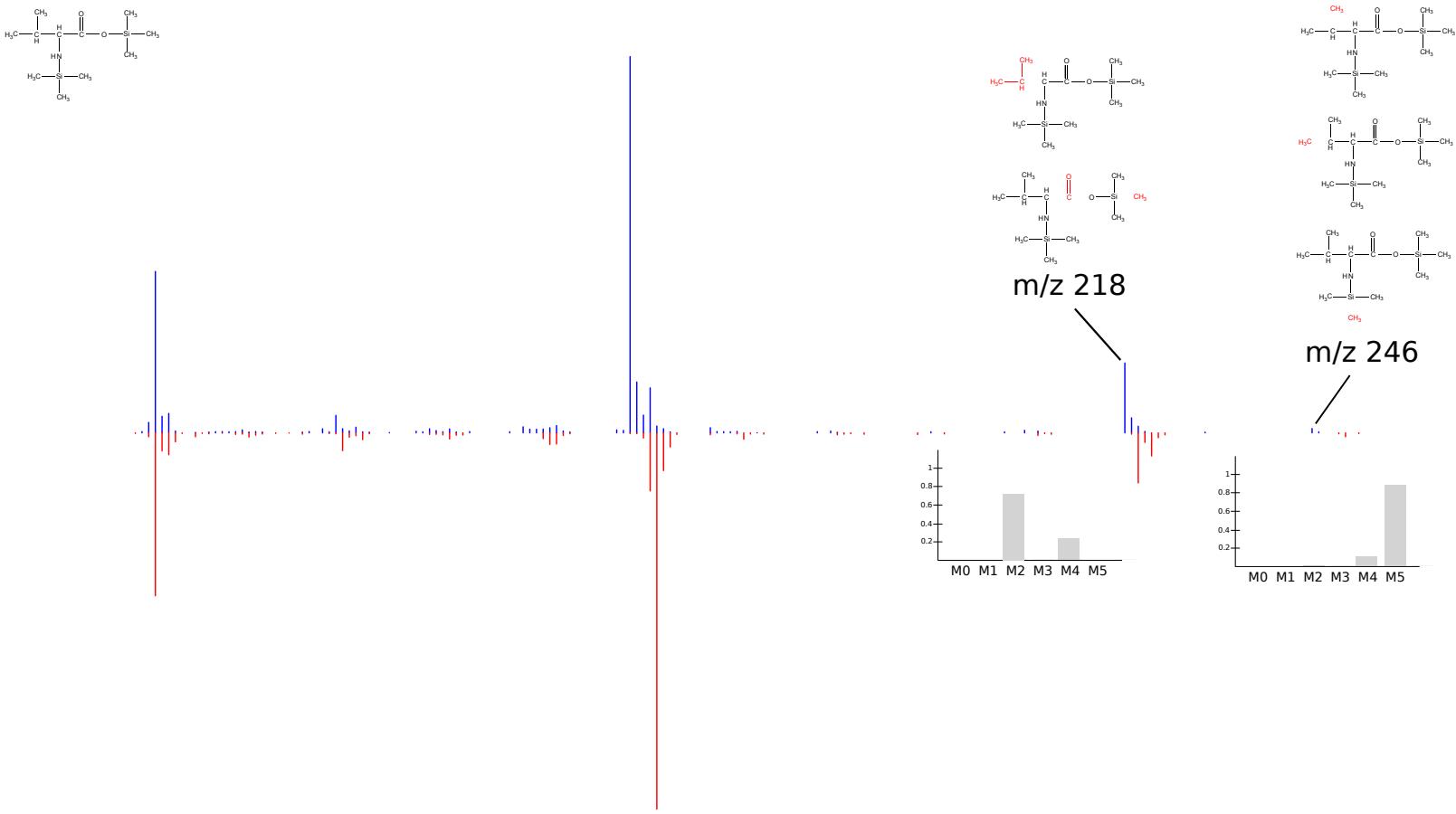
$^{13}\text{C}_9$ Tyrosine 3TMS

Uracil 2TMS



$^{13}\text{C}_4$ Uracil 2TMS

Valine 2TMS



$^{13}\text{C}_5$ Valine 2TMS

Table 2: TBDMS Derivatized Fragment Ions

Compound	m/z	m/z ^{13}C	Formula
Alanine 2TBDMS	317	-	$\text{C}_{15}\text{H}_{35}\text{NO}_2\text{Si}_2$
	302	305,306	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
	274	276	$\text{C}_{13}\text{H}_{32}\text{NOSi}_2$
	260	263	$\text{C}_{11}\text{H}_{26}\text{NO}_2\text{Si}_2$
	232	234	$\text{C}_{10}\text{H}_{26}\text{NOSi}_2$
Aspartic acid 3TBDMS	475	-	$\text{C}_{22}\text{H}_{49}\text{NO}_4\text{Si}_3$
	460	464	$\text{C}_{21}\text{H}_{46}\text{NO}_4\text{Si}_3$
	418	422	$\text{C}_{18}\text{H}_{40}\text{NO}_4\text{Si}_3$
	390	393	$\text{C}_{17}\text{H}_{40}\text{NO}_3\text{Si}_3$
	376	378	$\text{C}_{16}\text{H}_{38}\text{NO}_3\text{Si}_3$
	316	319	$\text{C}_{15}\text{H}_{34}\text{NO}_2\text{Si}_2$
	302	304	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
Citric acid 4TBDMS	648	-	$\text{C}_{30}\text{H}_{64}\text{O}_7\text{Si}_4$
	633	639	$\text{C}_{29}\text{H}_{61}\text{O}_7\text{Si}_4$
	501	507	$\text{C}_{23}\text{H}_{45}\text{O}_6\text{Si}_3$
	459	465	$\text{C}_{20}\text{H}_{39}\text{O}_6\text{Si}_3$
Fumaric acid 2TBDMS	344	-	$\text{C}_{16}\text{H}_{32}\text{O}_4\text{Si}_2$
	329	333	$\text{C}_{15}\text{H}_{29}\text{O}_4\text{Si}_2$
	287	291	$\text{C}_{11}\text{H}_{20}\text{O}_4\text{Si}_2$
γ -Aminobutyric acid 2TBDMS	331	-	$\text{C}_{16}\text{H}_{37}\text{NO}_2\text{Si}_2$
	316	320	$\text{C}_{15}\text{H}_{34}\text{NO}_2\text{Si}_2$
	274	278	$\text{C}_{12}\text{H}_{28}\text{NO}_2\text{Si}_2$
Glutamine 3TBDMS	488	-	$\text{C}_{23}\text{H}_{52}\text{N}_2\text{O}_3\text{Si}_3$

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Table 2 – *Continued from previous page*

Compound	m/z	m/z ^{13}C	Formula
	473	478	$\text{C}_{22}\text{H}_{49}\text{N}_2\text{O}_3\text{Si}_3$
	431	436	$\text{C}_{19}\text{H}_{53}\text{N}_2\text{O}_3\text{Si}_3$
	357	362	$\text{C}_{17}\text{H}_{37}\text{N}_2\text{O}_2\text{Si}_2$
	329	333	$\text{C}_{16}\text{H}_{37}\text{N}_2\text{OSi}_2$
Glutamic acid 3TBDMS	489	-	$\text{C}_{23}\text{H}_{51}\text{NO}_4\text{Si}_3$
	474	479	$\text{C}_{22}\text{H}_{48}\text{NO}_4\text{Si}_3$
	432	437	$\text{C}_{19}\text{H}_{42}\text{NO}_4\text{Si}_3$
	358	363	$\text{C}_{17}\text{H}_{36}\text{NO}_3\text{Si}_2$
	330	334	$\text{C}_{16}\text{H}_{36}\text{NO}_2\text{Si}_2$
	272	276	$\text{C}_{12}\text{H}_{26}\text{NO}_2\text{Si}_2$
Histidine 3TBDMS	497	-	$\text{C}_{24}\text{H}_{51}\text{N}_3\text{O}_2\text{Si}_3$
	482	488	$\text{C}_{23}\text{H}_{48}\text{N}_3\text{O}_2\text{Si}_3$
	440	446	$\text{C}_{20}\text{H}_{42}\text{N}_3\text{O}_2\text{Si}_3$
	412	417	$\text{C}_{19}\text{H}_{42}\text{N}_3\text{OSi}_3$
	280	285	$\text{C}_{14}\text{H}_{28}\text{N}_2\text{Si}_2$
Isoleucine 2TBDMS	359	-	$\text{C}_{18}\text{H}_{41}\text{NO}_2\text{Si}_2$
	302	304,308	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
	274	279	$\text{C}_{13}\text{H}_{32}\text{NOSi}_2$
	200	205	$\text{C}_{11}\text{H}_{26}\text{NSi}$
Leucine 2TBDMS	359	-	$\text{C}_{18}\text{H}_{41}\text{NO}_2\text{Si}_2$
	302	304,308	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
	274	279	$\text{C}_{13}\text{H}_{32}\text{NOSi}_2$
	200	205	$\text{C}_{11}\text{H}_{26}\text{NSi}$
Lysine 3TBDMS	488	-	$\text{C}_{24}\text{H}_{56}\text{N}_2\text{O}_2\text{Si}_3$

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Table 2 – *Continued from previous page*

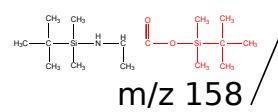
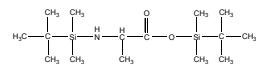
Compound	m/z	m/z ^{13}C	Formula
	473	479	$\text{C}_{23}\text{H}_{53}\text{N}_2\text{O}_2\text{Si}_3$
	431	437	$\text{C}_{20}\text{H}_{47}\text{N}_2\text{O}_2\text{Si}_3$
	329	334	$\text{C}_{17}\text{H}_{41}\text{N}_2\text{Si}_2$
Malic acid 3TBDMS	476	-	$\text{C}_{22}\text{H}_{48}\text{O}_5\text{Si}_3$
	461	465	$\text{C}_{21}\text{H}_{45}\text{O}_5\text{Si}_3$
	419	423	$\text{C}_{18}\text{H}_{39}\text{O}_5\text{Si}_3$
	391	394	$\text{C}_{17}\text{H}_{39}\text{O}_4\text{Si}_3$
	375	378	$\text{C}_{17}\text{H}_{39}\text{O}_3\text{Si}_3$
	287	291	$\text{C}_{12}\text{H}_{23}\text{O}_4\text{Si}_2$
Ornithine 3TBDMS	474	-	$\text{C}_{23}\text{H}_{54}\text{N}_2\text{O}_2\text{Si}_3$
	459	464	$\text{C}_{22}\text{H}_{51}\text{N}_2\text{O}_2\text{Si}_3$
	417	422	$\text{C}_{19}\text{H}_{45}\text{N}_2\text{O}_2\text{Si}_3$
Serine 3TBDMS	447	-	$\text{C}_{21}\text{H}_{49}\text{NO}_3\text{Si}_3$
	432	435	$\text{C}_{20}\text{H}_{46}\text{NO}_3\text{Si}_3$
	404	406	$\text{C}_{19}\text{H}_{46}\text{NO}_2\text{Si}_3$
	390	393	$\text{C}_{17}\text{H}_{40}\text{NO}_3\text{Si}_3$
	362	364	$\text{C}_{16}\text{H}_{40}\text{NO}_2\text{Si}_3$
	302	304	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
	288	290	$\text{C}_{14}\text{H}_{34}\text{NOSi}_2$
	230	232	$\text{C}_{10}\text{H}_{24}\text{NOSi}_2$
Succinic acid 2TBDMS	346	-	$\text{C}_{16}\text{H}_{34}\text{O}_4\text{Si}_2$
	331	335	$\text{C}_{15}\text{H}_{31}\text{O}_4\text{Si}_2$
	289	293	$\text{C}_{12}\text{H}_{25}\text{O}_4\text{Si}_2$
	215	219	$\text{C}_{10}\text{H}_{19}\text{O}_3\text{Si}$

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Table 2 – *Continued from previous page*

Compound	m/z	m/z ^{13}C	Formula
Tyrosine 3TBDMS	523	-	$\text{C}_{27}\text{H}_{53}\text{NO}_3\text{Si}_3$
	508	517	$\text{C}_{26}\text{H}_{50}\text{NO}_3\text{Si}_3$
	466	475	$\text{C}_{23}\text{H}_{44}\text{NO}_3\text{Si}_3$
	438	346	$\text{C}_{22}\text{H}_{44}\text{NO}_2\text{Si}_3$
	364	372	$\text{C}_{20}\text{H}_{38}\text{NOSi}_2$
	302	304	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
Valine 2TBDMS	345	-	$\text{C}_{17}\text{H}_{39}\text{NO}_2\text{Si}_2$
	302	304, 306	$\text{C}_{14}\text{H}_{32}\text{NO}_2\text{Si}_2$
	288	293	$\text{C}_{13}\text{H}_{30}\text{NO}_2\text{Si}_2$
	260	264	$\text{C}_{12}\text{H}_{30}\text{NOSi}_2$

Alanine 2TBDMS



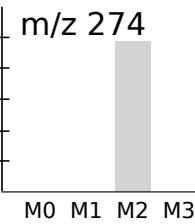
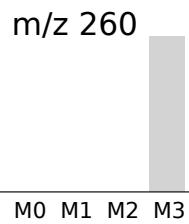
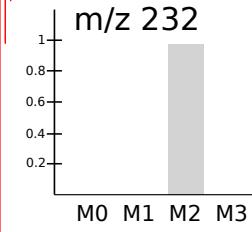
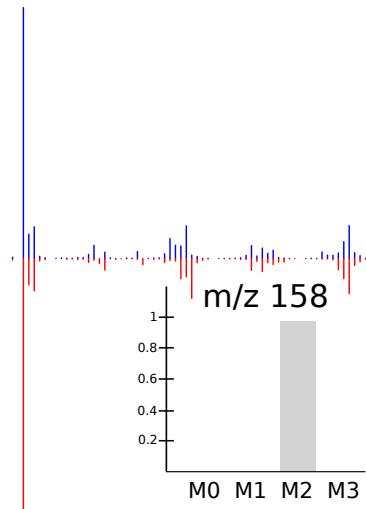
$m/z 232$

$m/z 260$

$m/z 302$

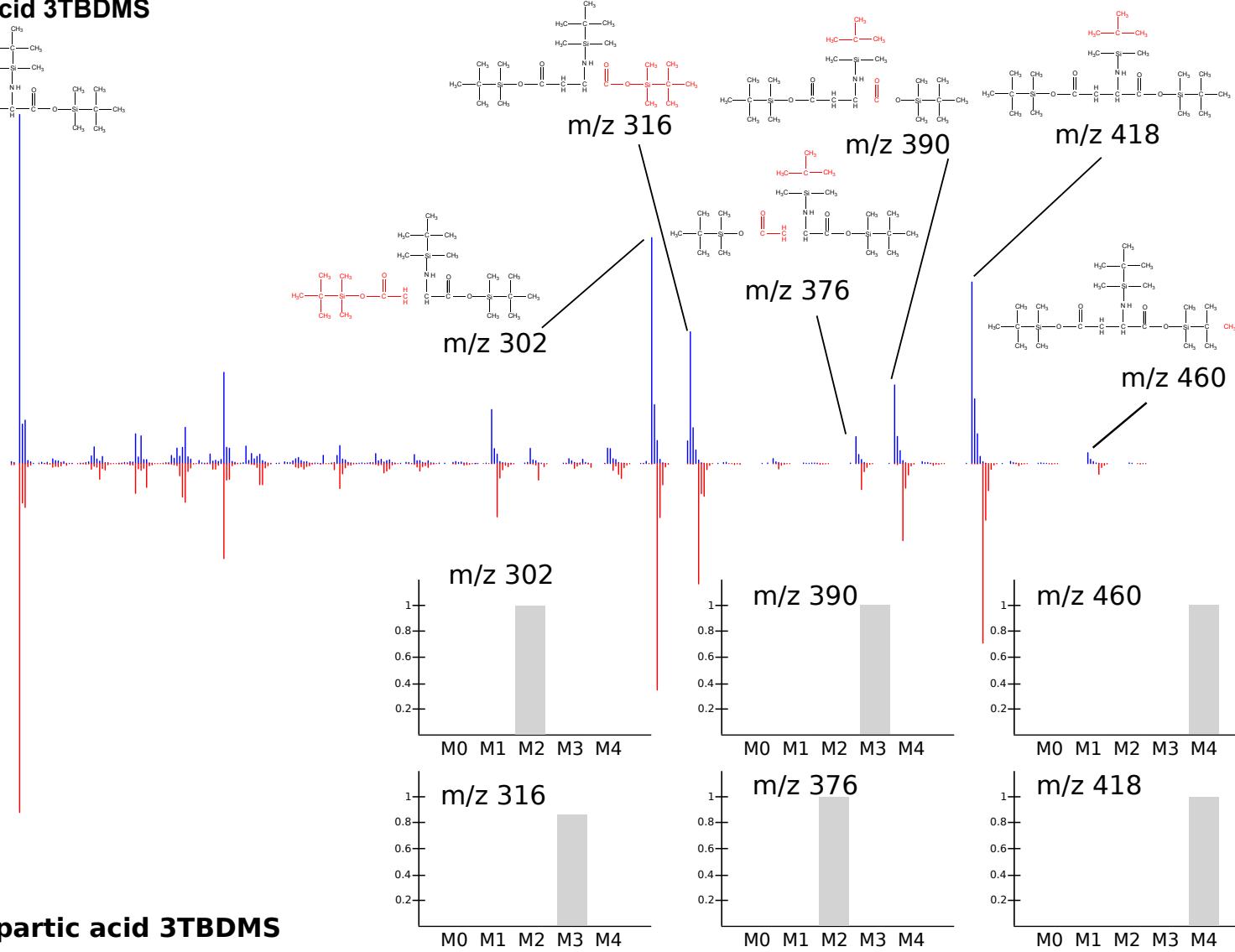
$m/z 274$

$m/z 302$



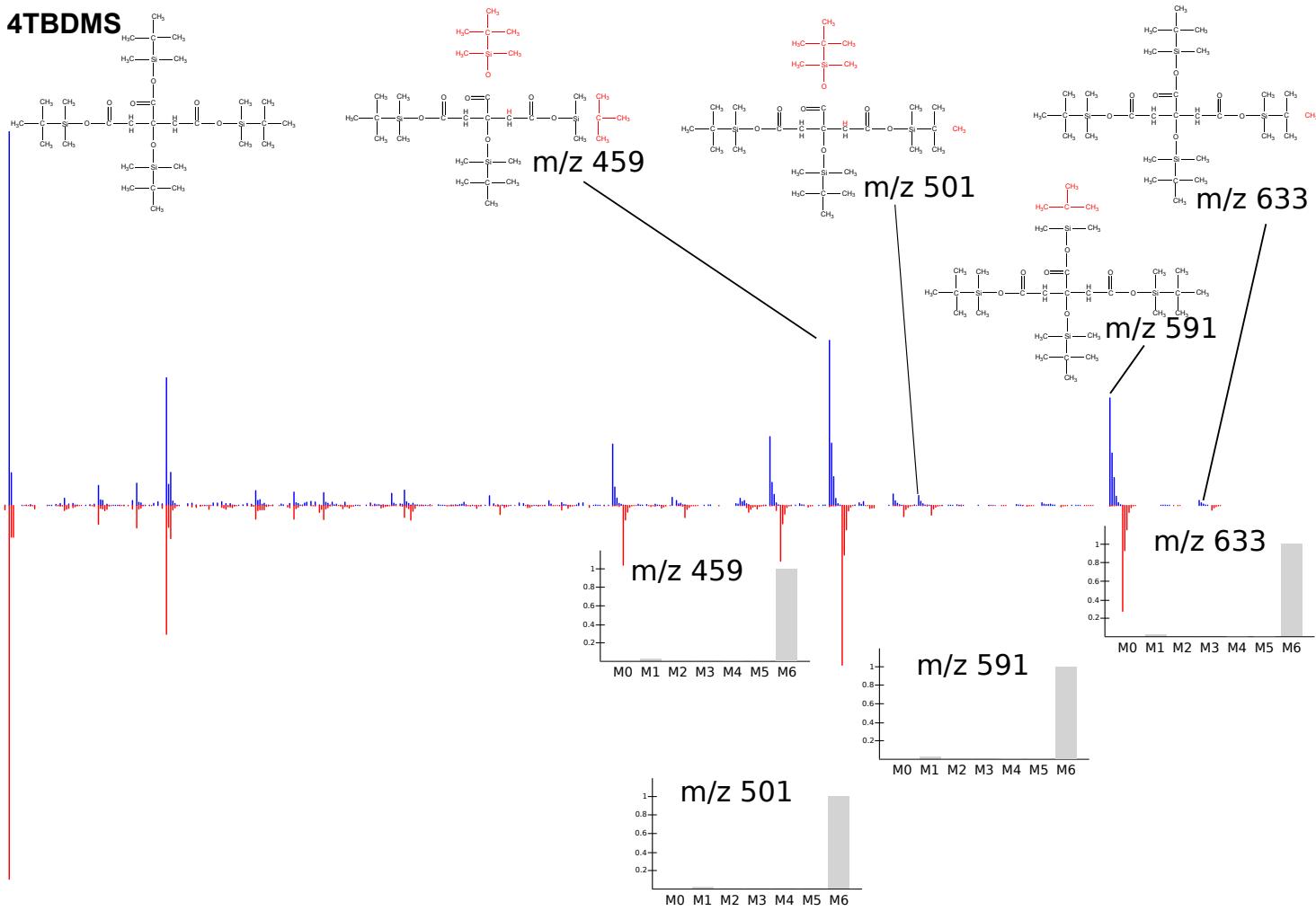
$^{13}\text{C}_3$ Alanine 2TBDMS

Aspartic acid 3TBDMS



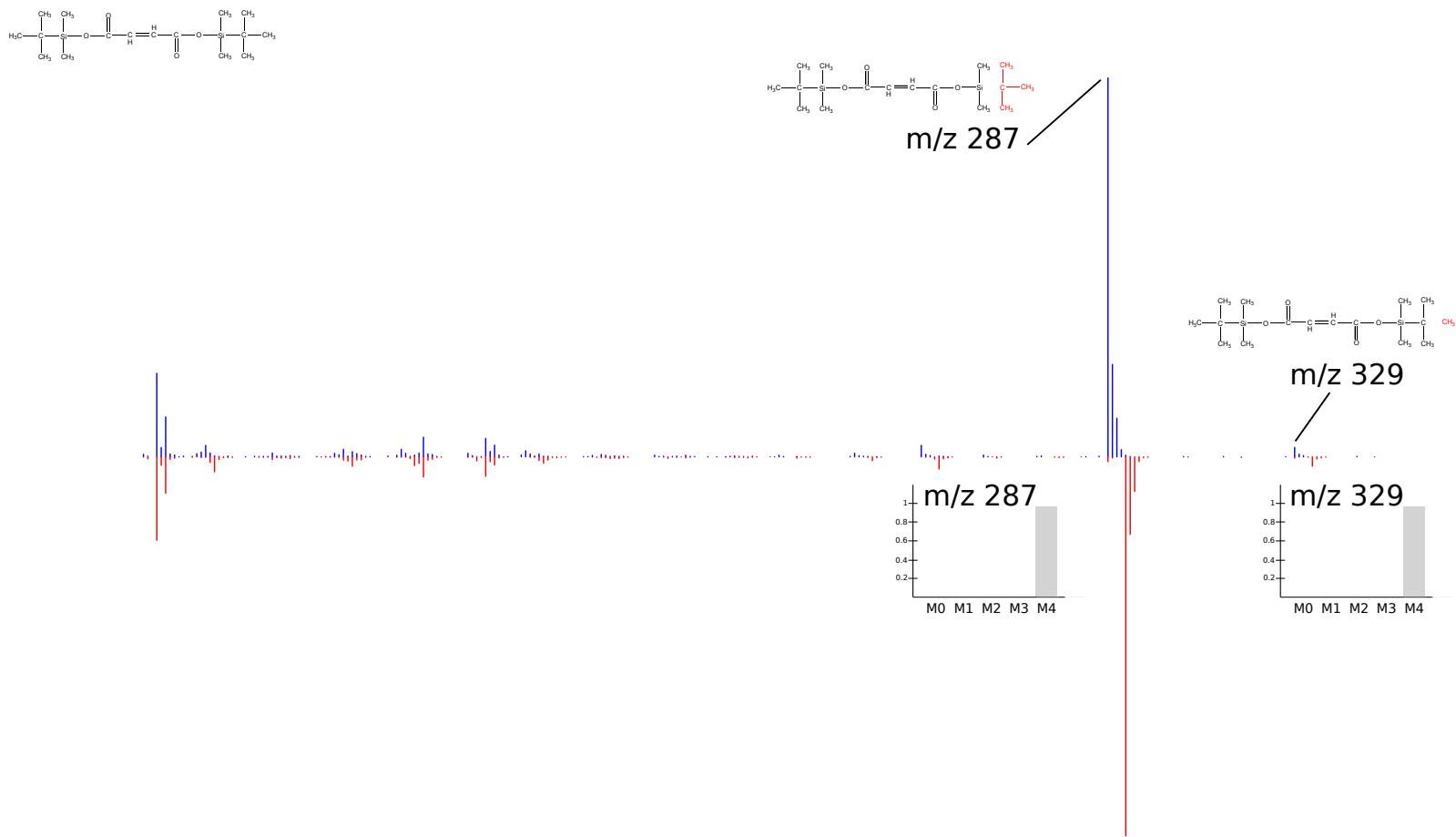
$^{13}\text{C}_4$ Aspartic acid 3TBDMS

Citric acid 4TBDMS



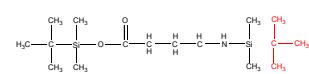
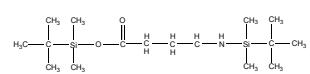
$^{13}\text{C}_6$ Citric acid 4TBDMS

Fumaric acid 2TBDMS

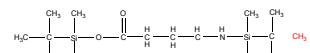


$^{13}\text{C}_4$ Fumaric acid 2TBDMS

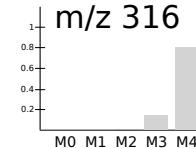
gamma-Aminobutyric acid 2TBDMS



m/z 274



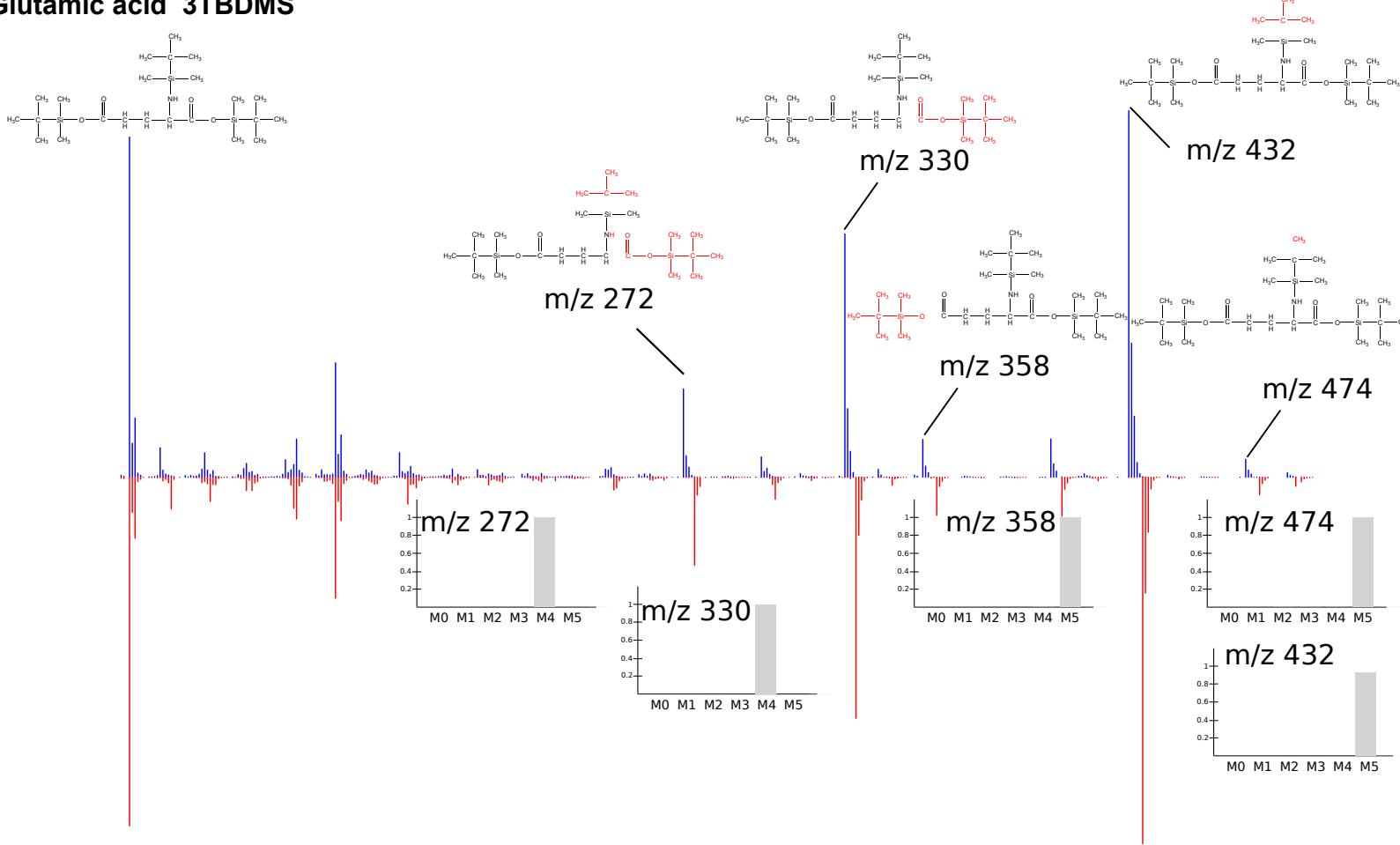
m/z 316



m/z 274

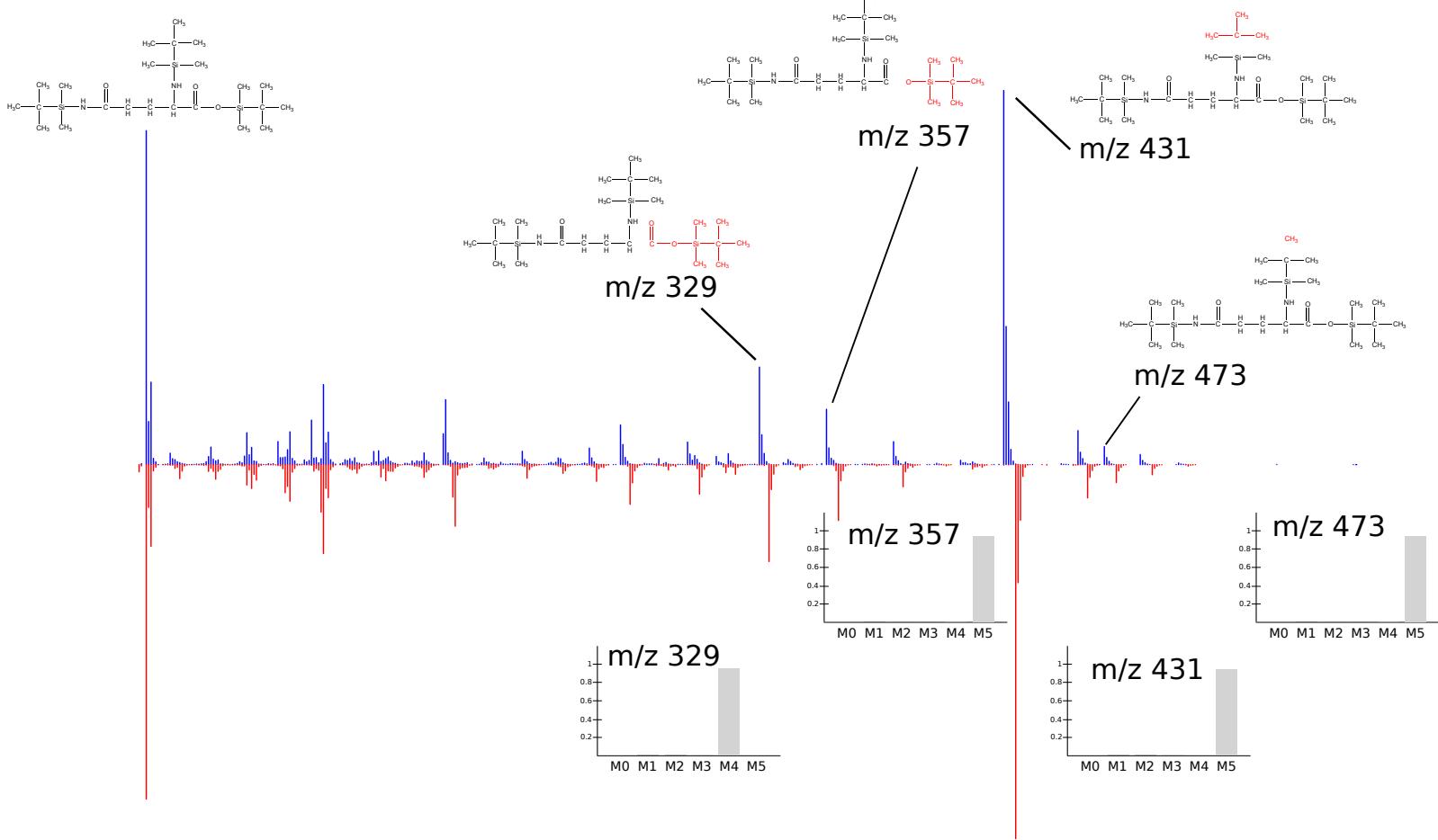
$^{13}\text{C}_4$ gamma-Aminobutyric acid 2TBDMS

Glutamic acid 3TBDMS



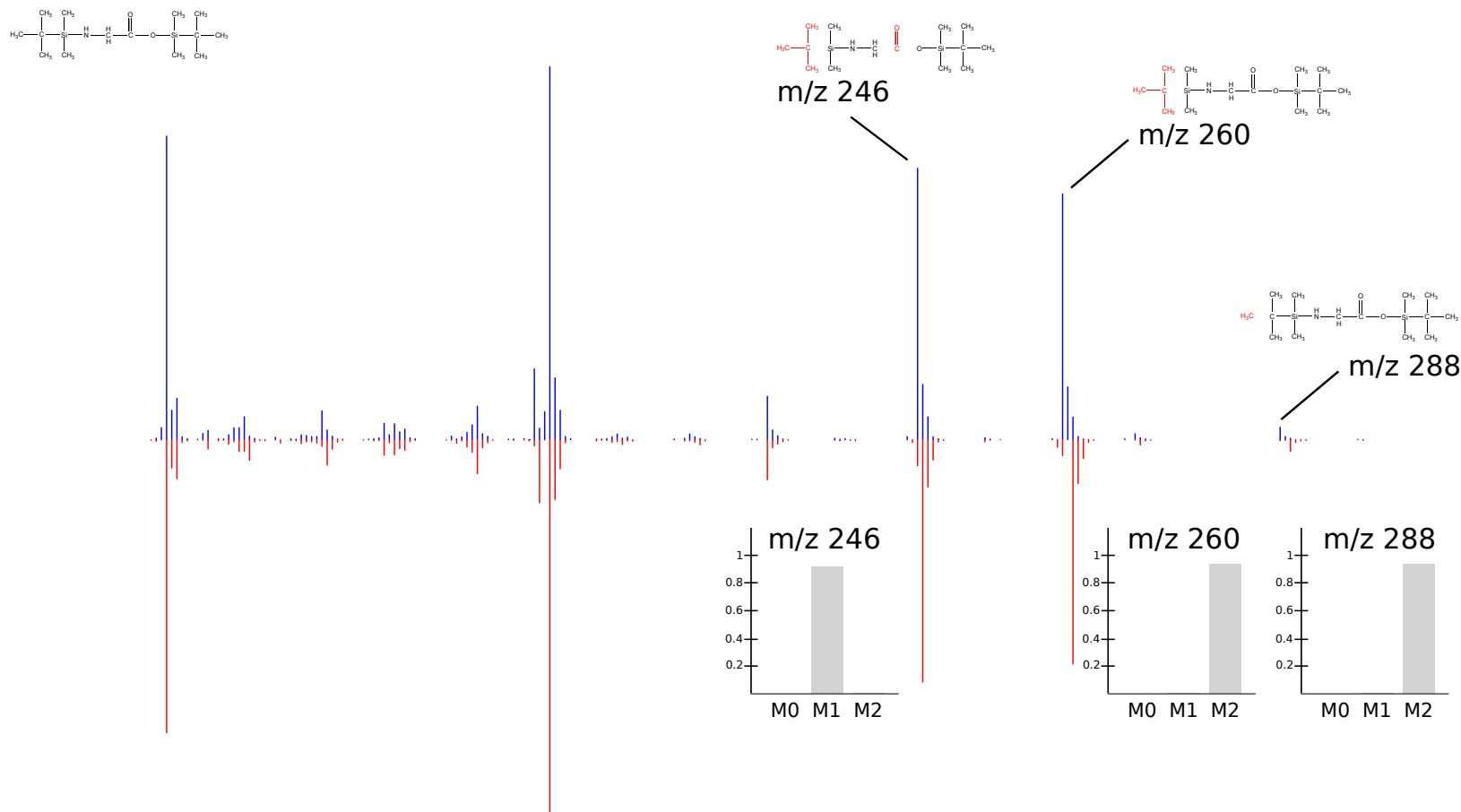
$^{13}\text{C}_5$ Glutamic acid 3TBDMS

Glutamine 3TBDMS



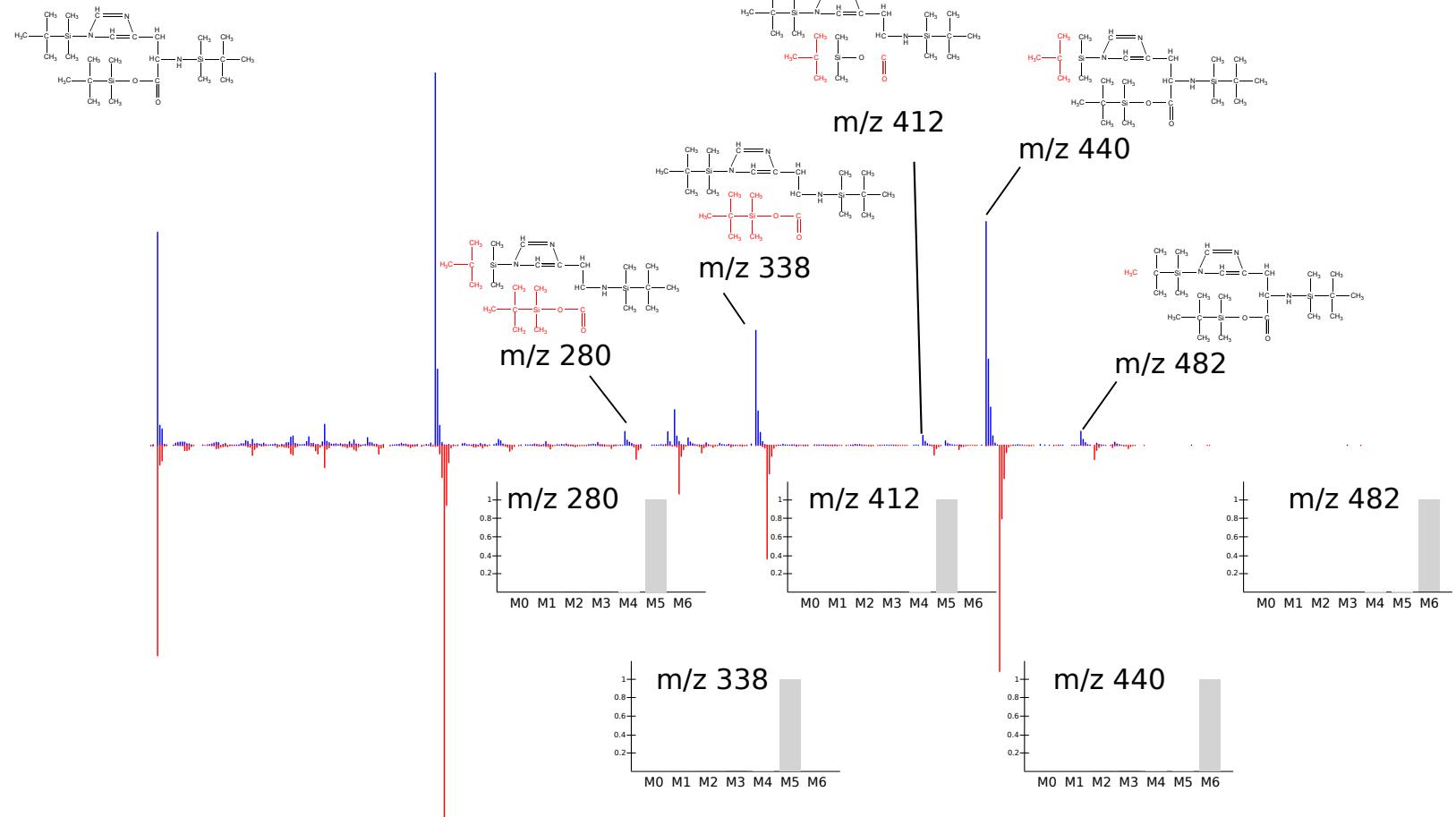
$^{13}\text{C}_5$ Glutamine 3TBDMS

Glycine 2TBDMS



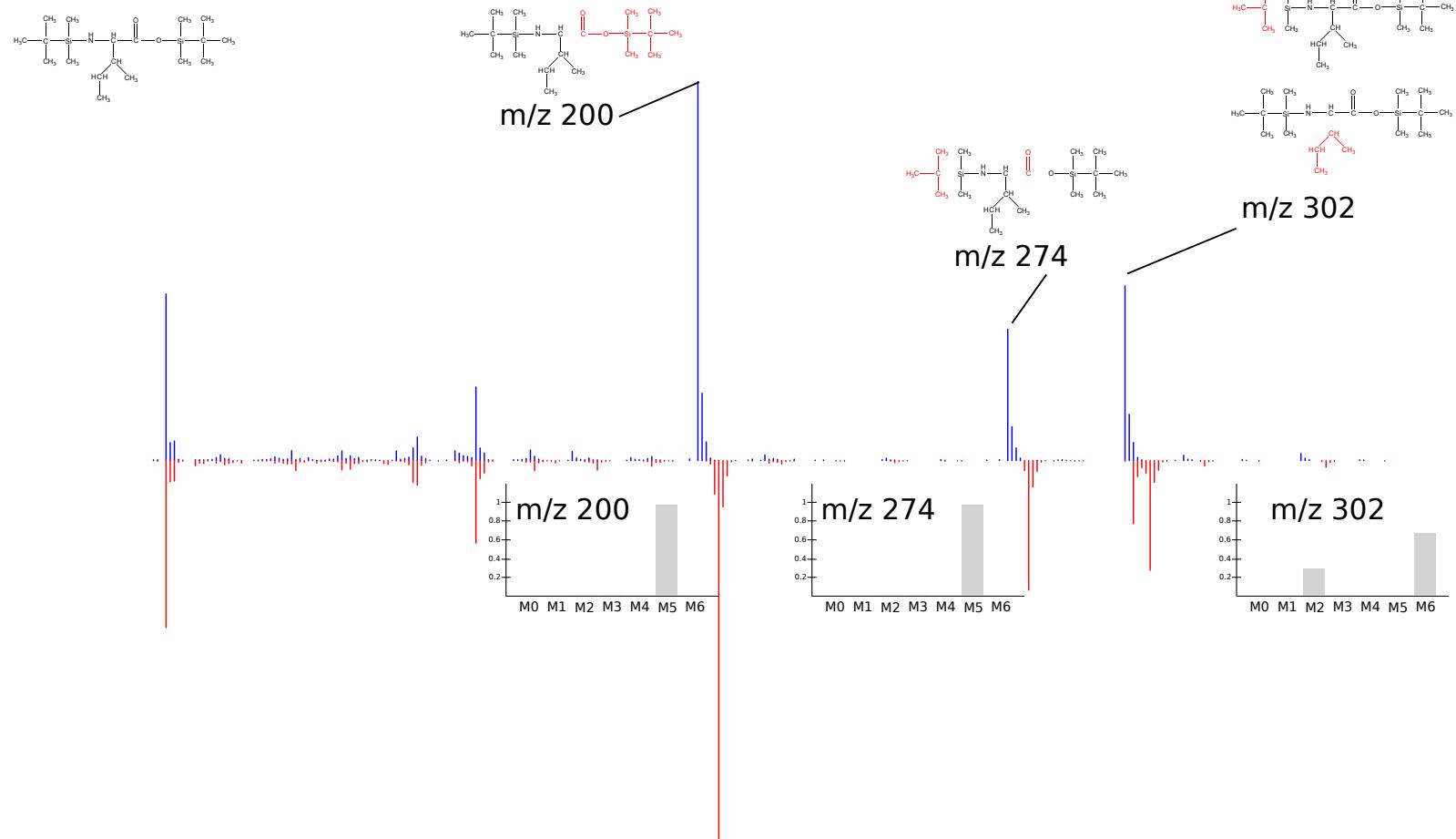
$^{13}\text{C}_2$ Glycine 2TBDMS

Histidine 3TBDMS



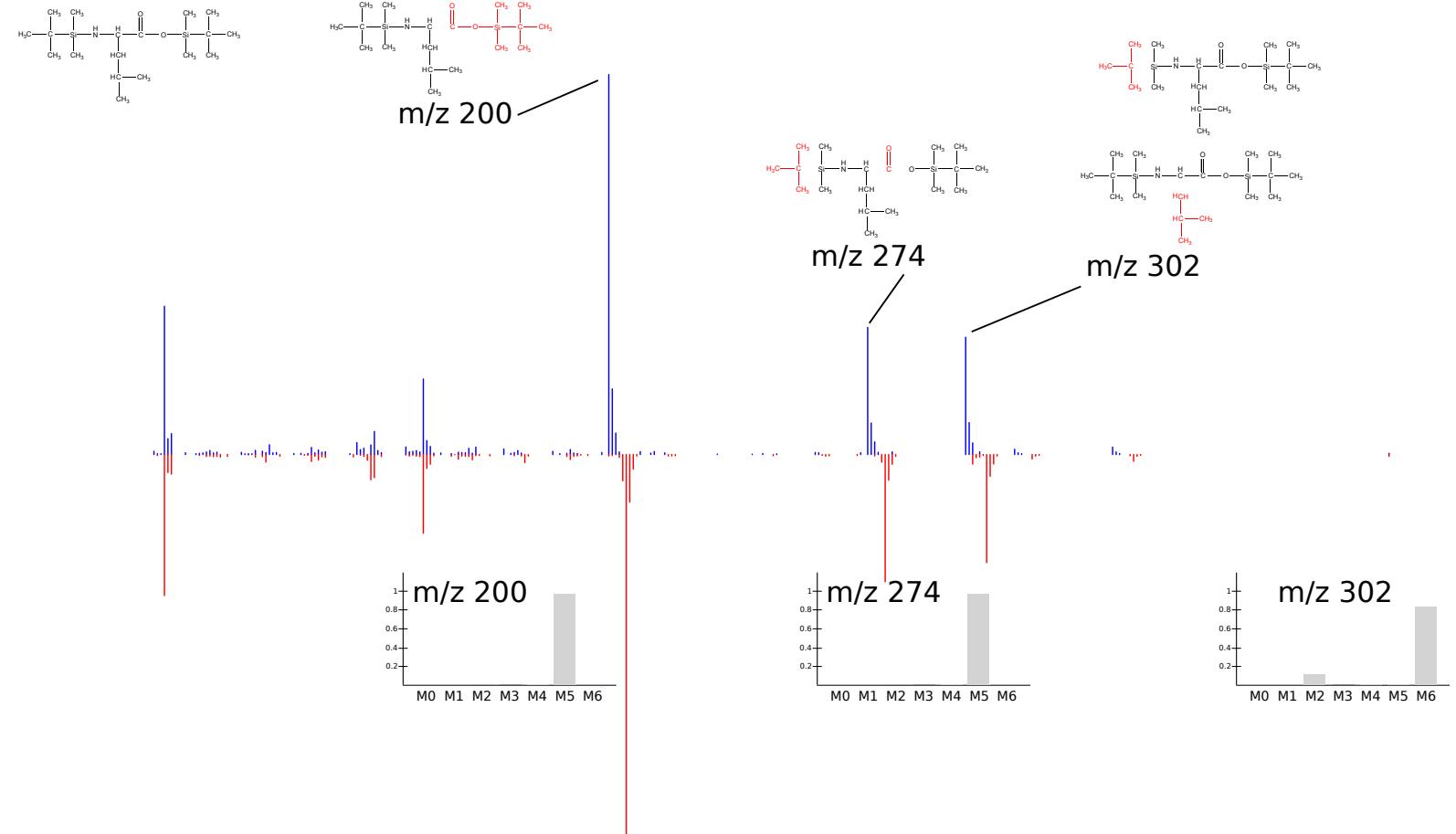
$^{13}\text{C}_6$ Histidine 3TBDMS

Isoleucine 2TBDMS



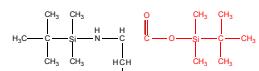
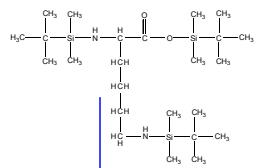
$^{13}\text{C}_6$ Isoleucine 2TBDMS

Leucine 2TBDMS

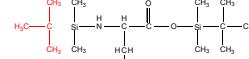


$^{13}\text{C}_6$ Leucine 2TBDMS

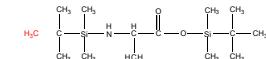
Lysine 3TBDMS



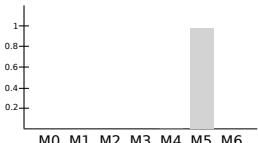
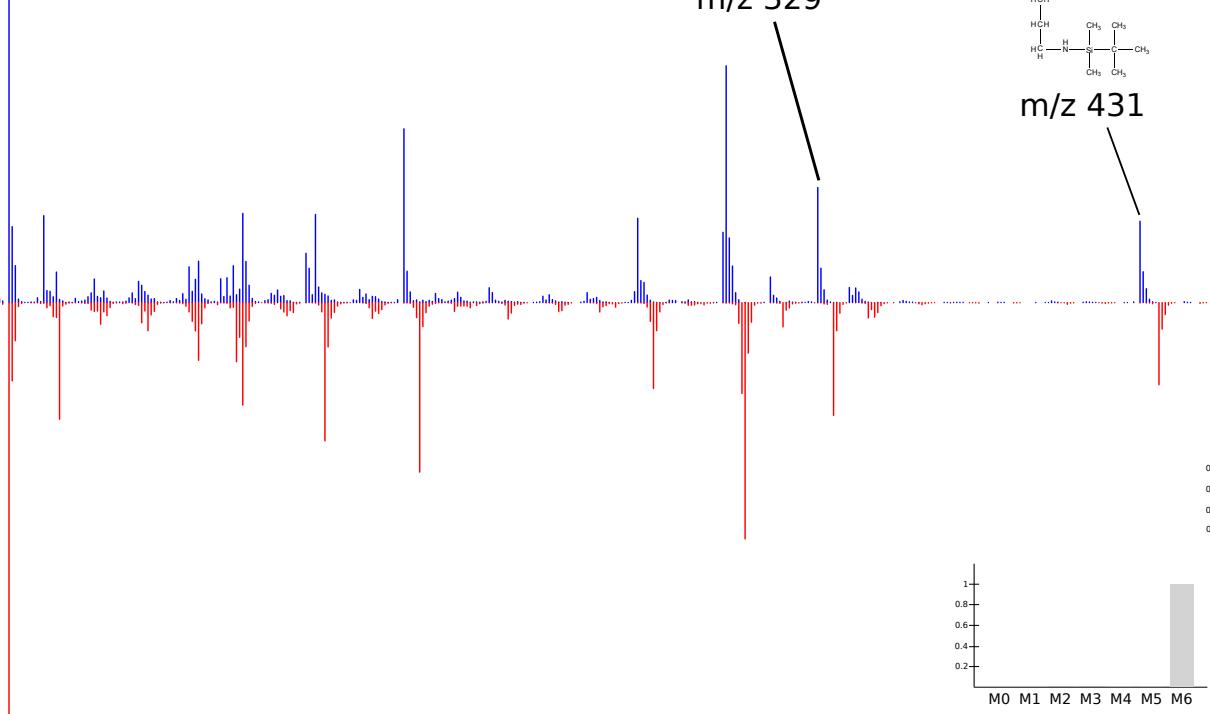
m/z 329



m/z 431

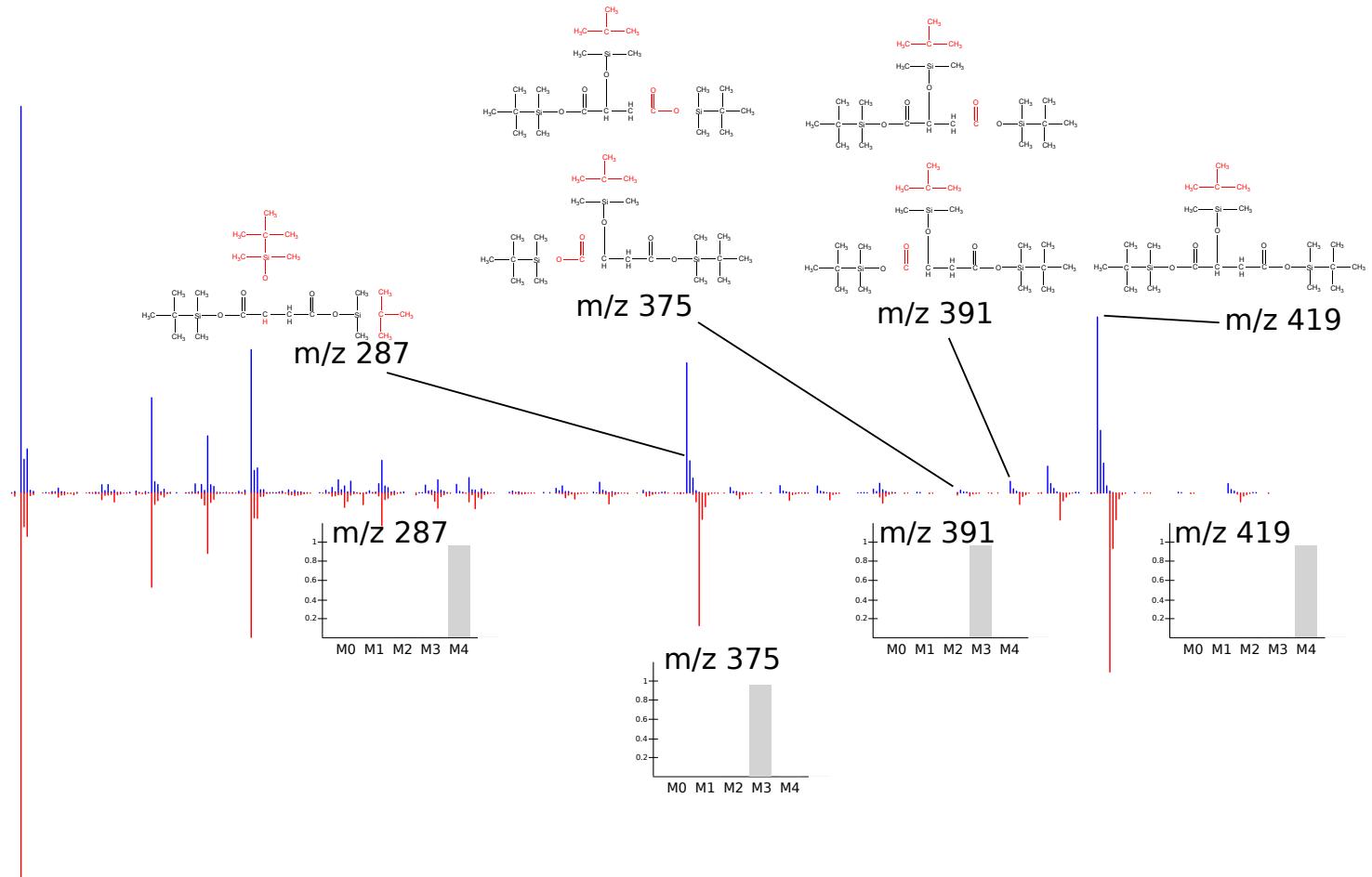


m/z 473



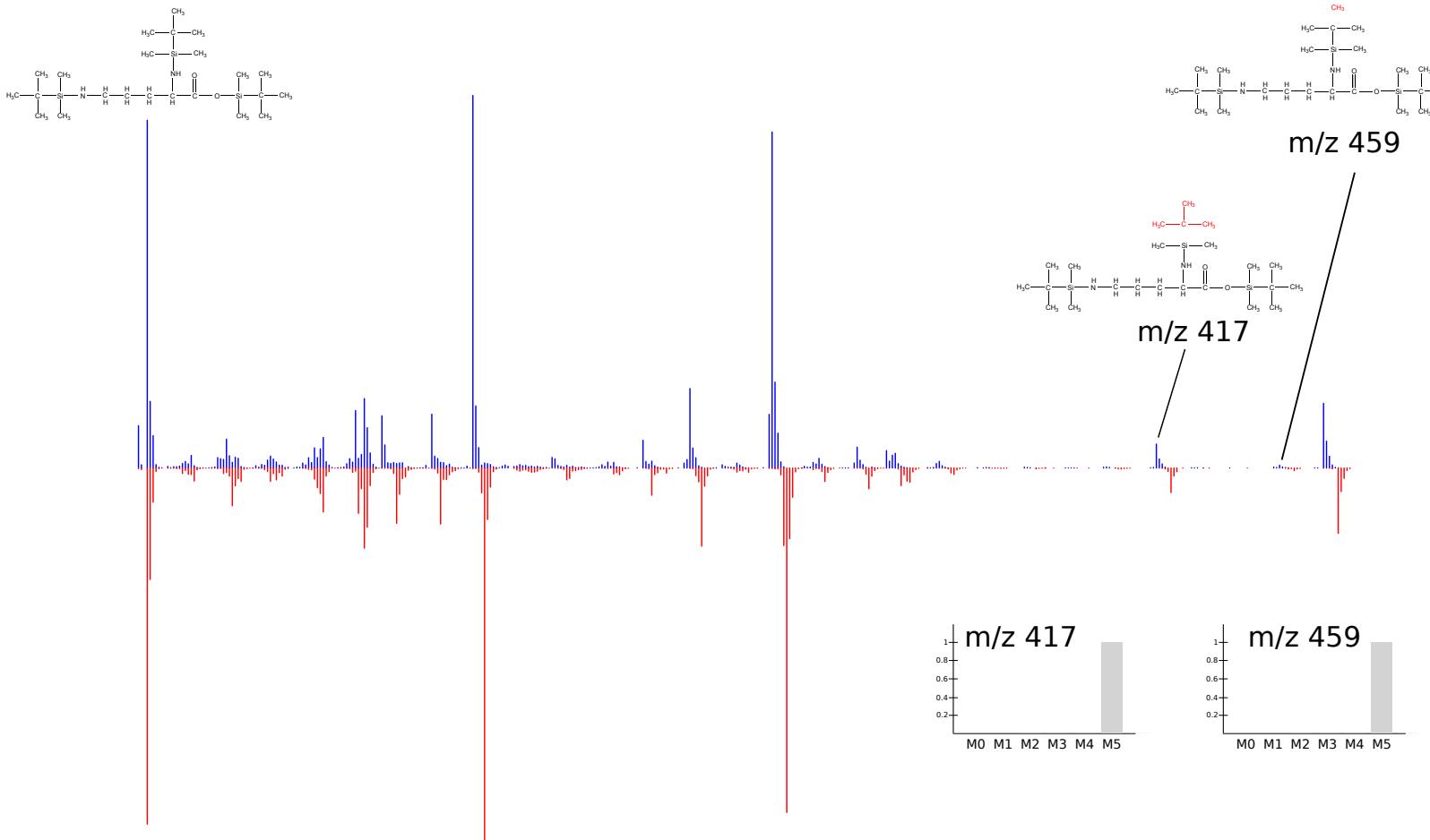
$^{13}\text{C}_6$ Lysine 3TBDMS

Malic acid 3TBDMS



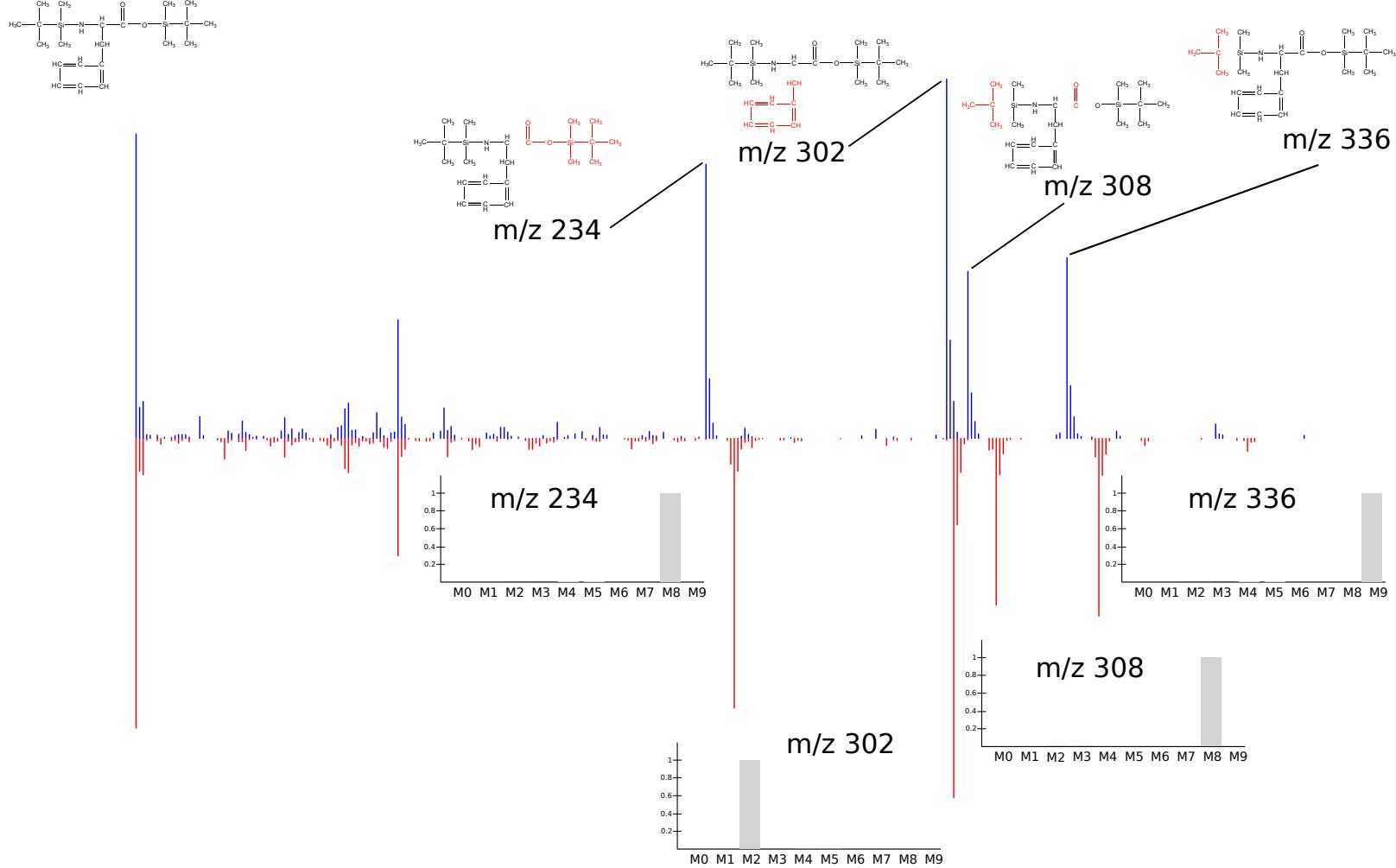
$^{13}\text{C}_4$ Malic acid 3TBDMS

Ornithine 3TBDMS



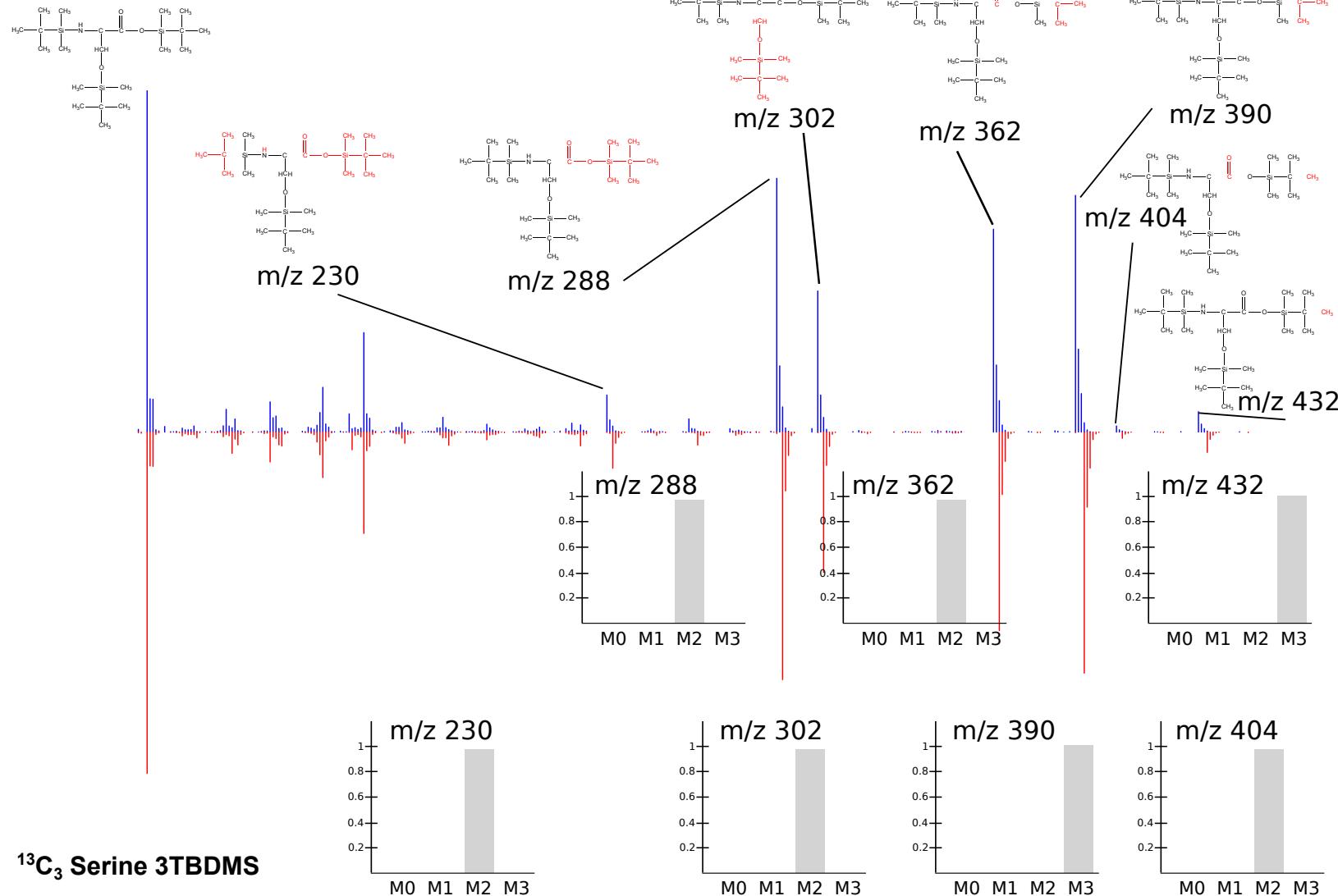
$^{13}\text{C}_5$ Ornithine 3TBDMS

Phenylalanine 2TBDMS



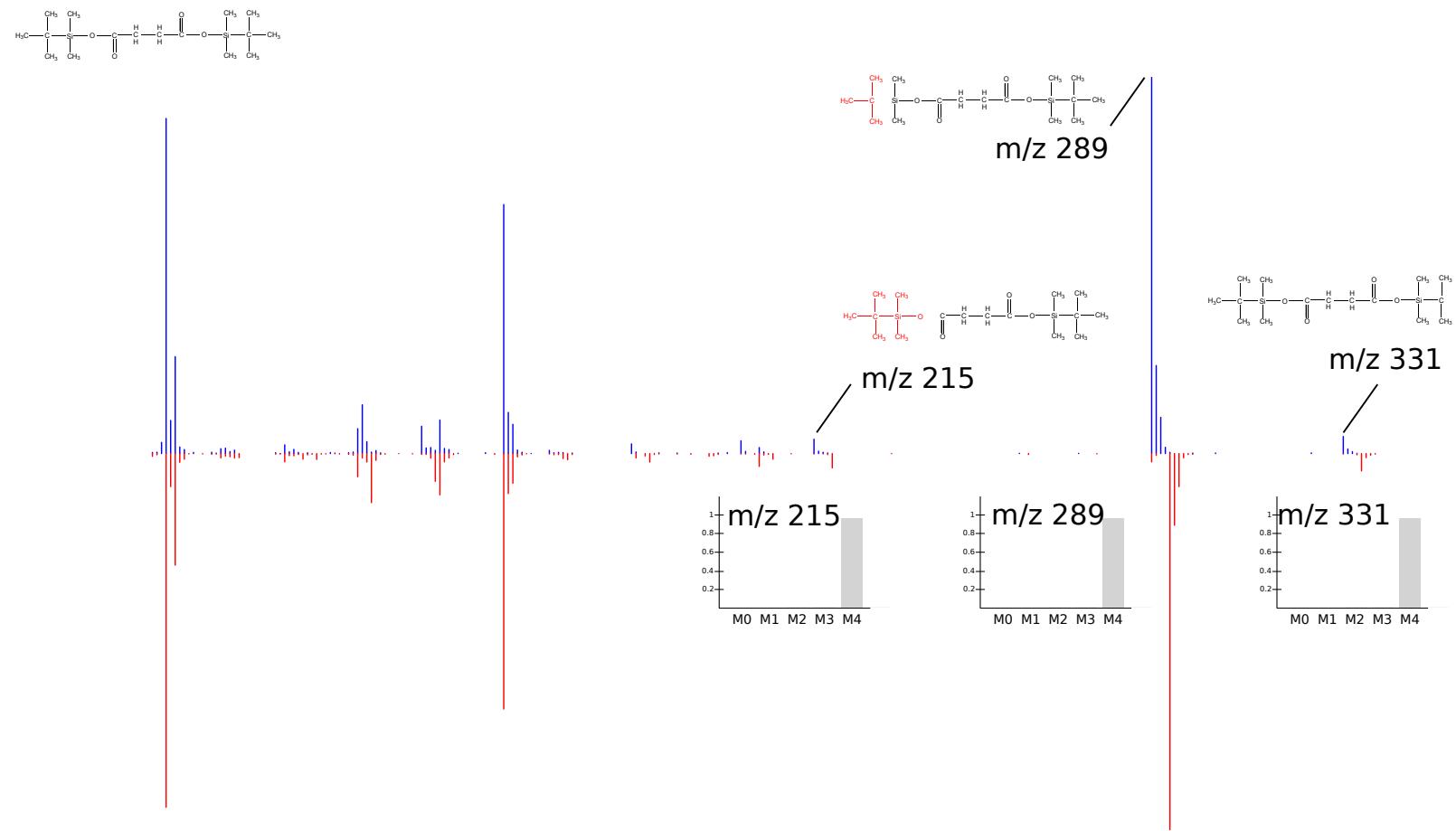
Phenylalanine 4TBDMS ^{13}C

Serine 3TBDMS



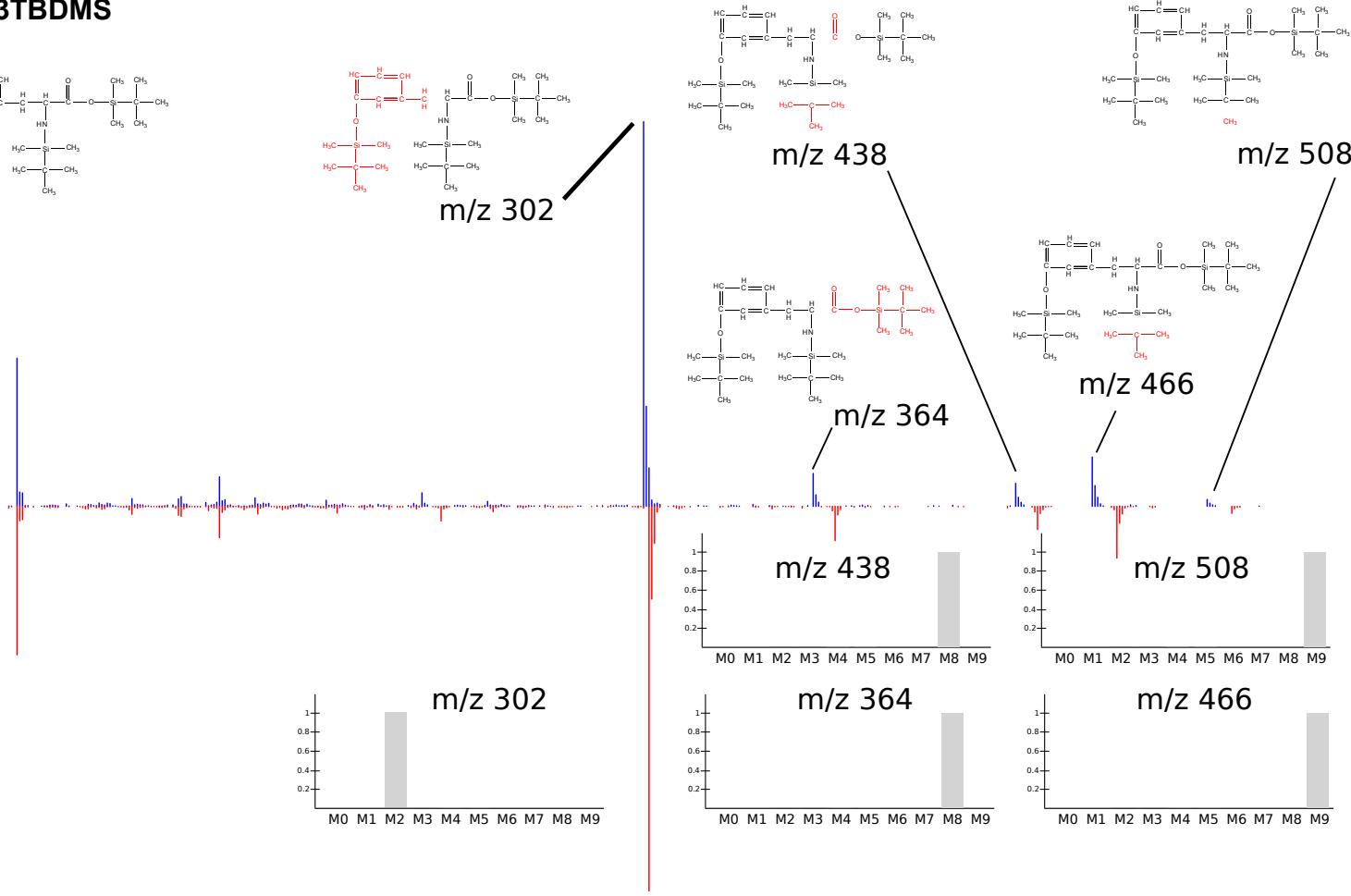
$^{13}\text{C}_3$ Serine 3TBDMS

Succinic acid 2TBDMS



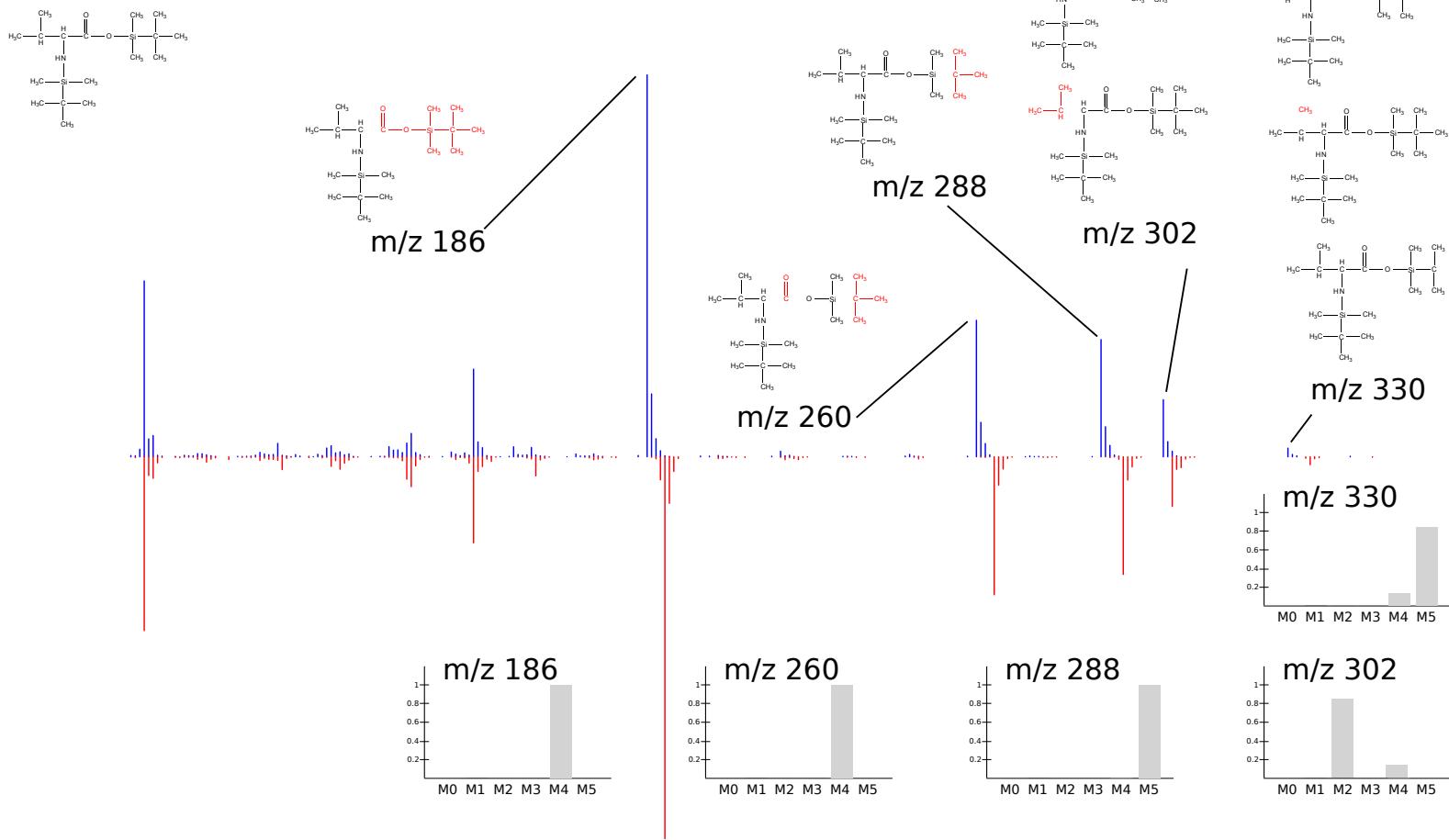
$^{13}\text{C}_4$ Succinic acid 2TBDMS

Tyrosine 3TBDMS



$^{13}\text{C}_9$ Tyrosine 3TBDMS

Valine 2TBDMS



$^{13}\text{C}_5$ Valine 2TBDMS