Supporting information for

Copper (II) Mediated Facile and Ultra Fast Peptide Synthesis in Methanol

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X-Ray Crystal Structure Analysis.

Crystal structure analysis of (Boc-Leu-SH): Crystals of Boc-Leu-SH was grown by on standing gummy Boc-Leu-SH oil. A single crystal (0.27 × 0.24 × 0.22 mm) was mounted in a loop with a small amount of the mother liquor. The X-ray data were collected at 100 K temperature on a Bruker AXS SMART APEX CCD diffractometer using MoK_α radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56°) for a total number of 7001 independent reflections. Space group *P2(1),2(1),2(1)* a = 9.439(3), b = 16.600(4), c = 18.026(4) Å, α = 90.00 , β = 90, γ = 90.00, V= 2824.3(12) $Å^3$ Orthorhombic P, Z=4 for chemical formula $C_{22}H_{40}N_2O_6$, with two molecule in asymmetric unit; ρ_{calcd} =1.159 g cm^{-3}, μ= 0.233 mm^{-1}, F(000) = 1064, R_{int}= 0.0610. The structure was obtained by direct methods using SHELXS-97.[1] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The final R value was 0.0628 ($wR2$= 0.1378) for 4151 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 307 variables, S = 0.934. The largest difference peak and hole were 0.324 and -0.283 e $Å^3$, respectively.

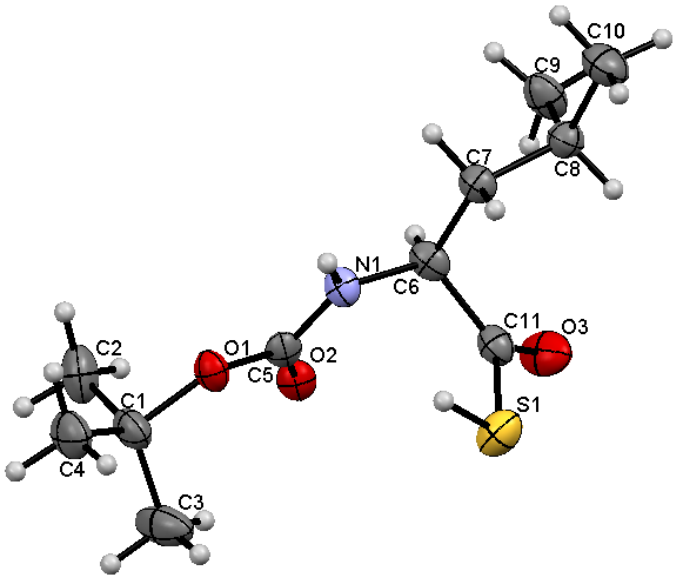
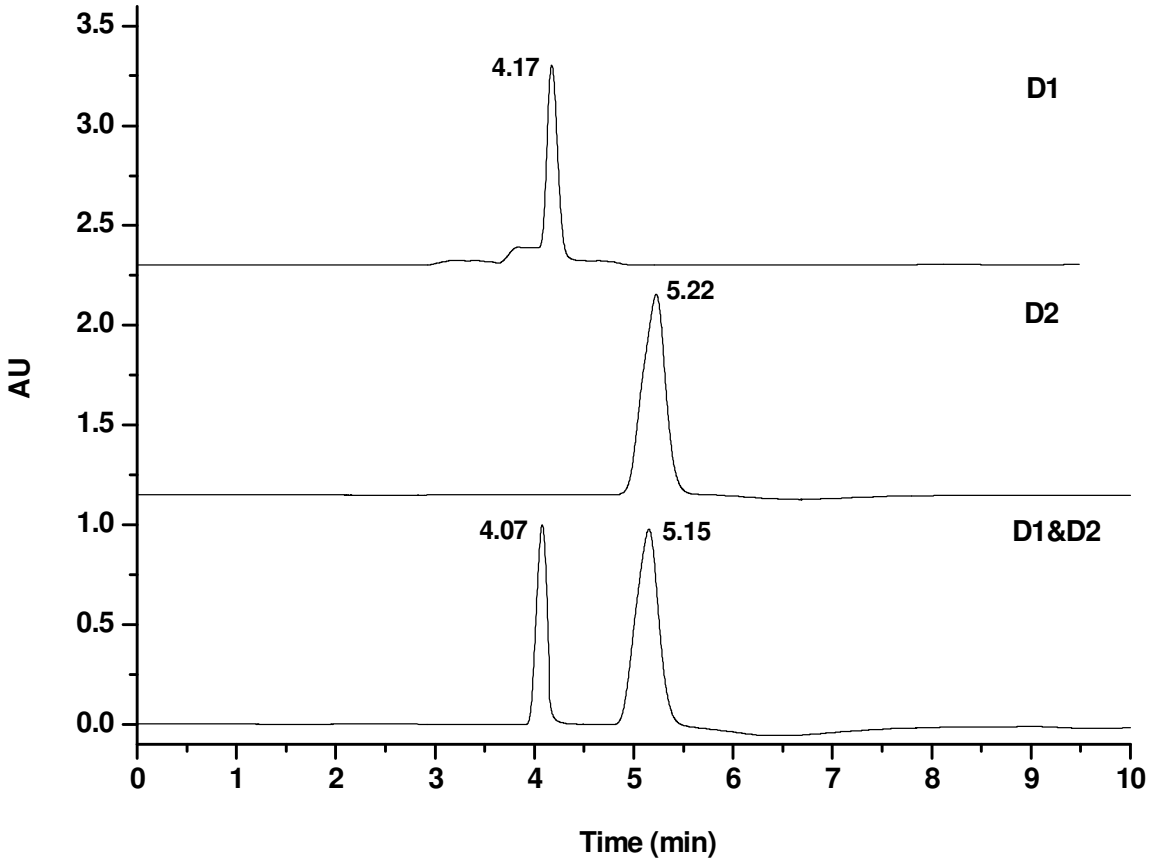


Figure 1: The ORTEP diagram depicting the X-ray structure of Boc-Leu-SH

Racemization Study of Peptides, D1 = Boc-^{L}Ala-Leu-OMe, D2 = Boc-^{D}Ala-Leu-OMe D3= Boc-(±)Ala-Leu-OMe



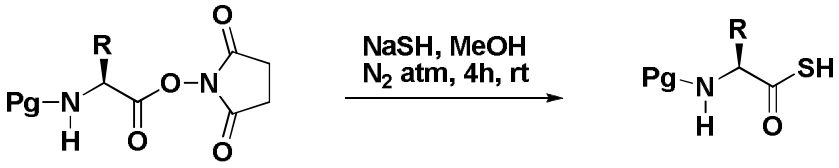
Chiral HPLC of dipeptides D1, D2: HPLC was performed on Daicel CHIRALPAK-AI column using 20% of isopropanol in n-hexane as a solvent system at isocratic mode with the flow rate of 1mL/min.

General Information.

All amino acids, NHS, DCC were purchased from Aldrich. Di-*tert*-butyl dicarbonate were purchased from Spectrochem. NaSH purchased from Acoris. The solvents DMF, DMSO, MeOH, EtOH were purchased from Merck. MeOH was dried over magnesium turnings and distilled prior to use. Column chromatography was performed on Merck silica gel (100-200 mesh). ^{1}H NMR spectra were recorded on Jeol 400 MHz and ^{13}C NMR on 100 MHz spectrometer using residual solvent as internal standard ($CDCl_3$ δ_H, 7.24 ppm, δ_c 77.0 ppm). The chemical shifts (δ) were reported in ppm and coupling constant (J) in Hz. Mass spectra were obtained from MALDI-TOF/TOF (Applied Biosystem).

General Procedure for Synthesis of N-Protected-amino thioacids.

The N-protected thioacids were synthesized using the reported procedure.[2] Briefly, the NHS ester (2 mmol) of protected amino acid was dissolved in distilled MeOH (50 ml). To this stirring solution NaSH (2 mmol) was added under N_2 atmosphere. This reaction mixture was allowed to stir for another 4h. After completion of reaction (monitored by TLC) the solvent MeOH was evaporated under reduced pressure and the residue was dissolved in water (50 ml). This aqueous solution was acidified to $_P$H= 3 with 5% HCl and extracted with ethyl acetate (25 ml x 3). The combined organic layer was then washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get N-protected amino thioacid.



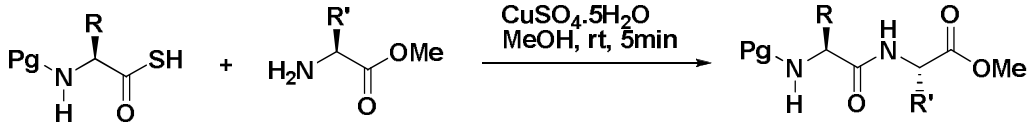
Pg= Boc/Fmoc/Cbz

General Procedure for $CuSO_4.5H_2O$ (or $Cu(OAC)_2.2H_2O$) mediated coupling of N-protected thioacids and amines.

Isolation of Amine Ester from $HCl.NH_2(R)OMe$: Hydrochloride salt of methyl ester of amino acid (2.1 mmol) was dissolved in saturated solution of aq.Na_2CO_3 and extracted with ethyl acetate (30 ml x 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. This organic layer was concentrated to the volume ~2 ml under reduced pressure and directly used for the coupling reaction.

The N-protected thioacid (2 mmol) was dissolved in distilled methanol (2 ml) either in Falcon tube or in RB flask. To this solution, methyl ester of amino acid (2.1 mmol) was added with stirring. This

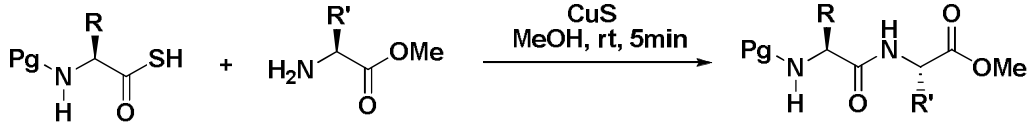
reaction mixture was then treated with 30 mol% of $CuSO_4.5H_2O$(or $Cu(OAc)_2.H_2O$). After 5 min, the clean reaction mixture was converted to dark brown colour turbid solution indicating the completion of the reaction(also by TLC). The reaction mixture was centrifuged and the residue was further washed with methanol. The combined methanol solution was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate (75 ml) and washed with 10% aq.Na_2CO_3, 5% aq. HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography using ethyl acetate and pet. ether.



Pg= Boc/Fmoc/Cbz

General Procedure for CuS mediated coupling of N-protected thioacid and amine

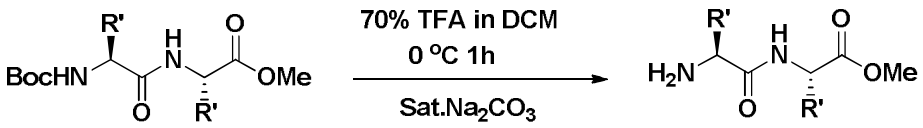
The N-protected thioacid (2 mmol) was dissolved in distilled methanol (2 ml) either in Falcon tube or in RB flask. To this solution, methyl ester of amino acid (2.1 mmol) was added with stirring. This reaction mixture was then treated with 30 mol% of CuS. After 5 min TLC shows the complete disappearance of amine protected thioacid and appearance of amide. The reaction mixture was centrifuged and the residue was further washed with methanol. The combined methanol solution was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate (75 ml) and washed with 10% aq.Na_2CO_3, 5% aq. HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography using ethyl acetate and pet. ether.



Pg= Boc/Fmoc/Cbz

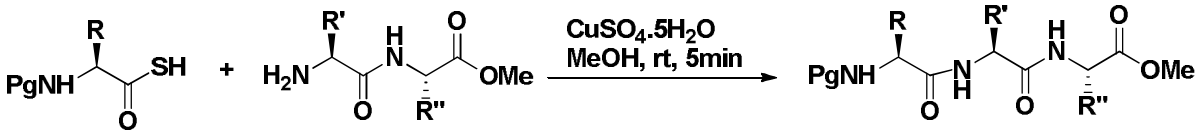
General procedure for synthesis of tri and tetrapeptides

NH_2-X-X-OMe; The dipeptide Boc-X-X-OMe (2.1 mmol) was dissolved in DCM and cooled to 0 ^oC. To this solution TFA (3 ml) was added slowly. The reaction mixture was allowed to stir for 1hr. After completion of reaction (monitored by TLC) the reaction mixture was evaporated under reduced pressure and residue was dissolved in saturated aq. Na_2CO_3. This aqueous solution was then extracted with ethyl acetate (30 ml x 3). The combined ethyl acetate was washed with brine, dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to the volume ~2ml and directly used for the next coupling reaction.



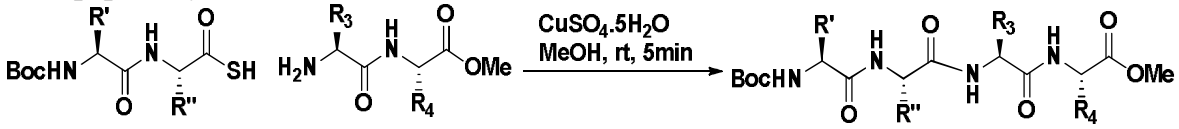
The N-protected thioacid or dipeptide thioacid (2 mmol) was dissolved in distilled MeOH. To this solution dipeptide free amine (2.1 mmol, in ~2 ml EtOAc) was added followed by 30 mol% $CuSO_4.5H_2O$ (or CuS catalyst). After 5 min, the clean reaction mixture was converted to dark brown colour turbid solution, indicating the completion of the coupling reaction. The reaction mixture was centrifuged and the residue was further washed with methanol. The combined methanol solution was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate (75 ml) and washed with 10% aq.Na_2CO_3, 5% aq. HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was further purified by column chromatography using ethyl acetate and pet. ether.

Tripeptide synthesis



Pg = Boc/Cbz

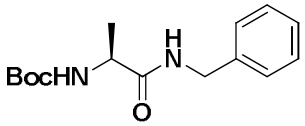
Tetrapeptide synthesis



Spectroscopic Data for Dipeptides, Tripeptides.

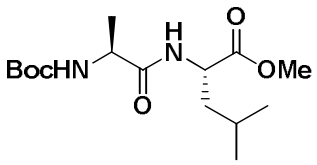
(*S*)-*tert*-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate (Boc-Ala-NHBzl)

White solid, (0.394 g, 71%) **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.320-7.229 (m, 5H, 5 x CH, phenyl), 6.821 (br., 1H, NH, benzylic), 5.201 (br., 1H, NH Boc), 4.412 (br., 2H, -C*H*$_2$Ph), 4.226 (br., 1H αCH, -NHC*H*CH_3), 1.395 (s, 9H, C(CH_3)$_3$ Boc), 1.376-1.357 (d, 3H, J = 7.6, -CHC*H*$_3$); **^{13}C NMR** (100MHz; $CDCl_3$): 172.78, 155.66, 138.19, 128.71, 127.47, 80.16, 50.20, 43.40, 28.35, 18.50. **MALDI-TOF/TOF** m/z Calcd. for $C_{15}H_{22}N_2O_3$ (M + Na) is 301.1528 Observed = 301.1804.



(*S*)-Methyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (Boc-Ala-Leu-OMe, 1); White powder, (0.429 g, 68%) **^{1}H NMR** (400 MHz; $CDCl_3$): δ 6.602-6.592 (d, 1H, J = 4, NH amide), 5.061-5.048 (d, 1H, J = 5.2, NH Boc), 4.624-4.589 (m, 1H, αCH -NHC*H*CH_2, Leu), 4.184-4.167

(m, 1H, δCH, NHC*H*CH_3, Ala), 3.719 (s, 3H, .OCH_3), 1.656-1.623 (m, 2H, CH_2, -CHCH_2CH$(CH_3)_2$ Leu), 1.567-1.524 (m, 1H, CH, -C*H*$(CH_3)_2$), 1.437 (s, 9H, C(C$H_3)_3$, Boc), 1.355-1.338 (d, 3H, *J* = 6.8, CHCH_3, Ala), 0.924-0.910 (d, 6H, *J* = 5.6, CH(C$H_3)_2$ Leu); **^{13}C NMR** (100 MHz, $CDCl_3$) 173.29, 172.49, 155.60, 80.146, 52.343, 50.69, 49.92, 41.51, 28.33, 24.78, 22.90, 21.85, 17.97. **MALDI-TOF/TOF** m/z Calcd. for $C_{15}H_{28}N_2O_5$ (M + Na) is 339.1896 Observed = 339.2333.



(*S*)-Methyl 2-((*R*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (Boc-^{D}Ala-Leu-OMe, 2); White powder, (0.391 g, 62%), **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 6.671-6.661 (d, 1H, *J* = 4, NH amide), 5.037-5.031 (d, 1H, *J* = 2.4, NH, Boc), 4.628-4.574 (m, 1H, αCH, -NHC*H*CH_2-, Leu), 4.225-4.197 (m, 1H, δCH, NHC*H*CH_3, Ala), 3.719 (s, 3H, CH_3, OCH_3), 1.664-1.630 (m, 2H, -CHCH_2CH$(CH_3)_2$), 1.567-1.524 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.447 (s, 9H, C(C$H_3)_3$, Boc), 1.371-1.354 (d, 3H, *J* = 6.8, -CHCH_3, Ala), 0.938-0.916 (dd, 6H, *J* = 6, -CH(C$H_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) 173.40, 172.57, 155.57, 80.24, 52.34, 50.65, 41.47, 28.33, 24.86, 22.91, 21.86, 18.21 **MALDI-TOF/TOF** m/z Calcd .for $C_{15}H_{28}N_2O_5$ (M + Na) is 339.1896 Observed = 339.2218

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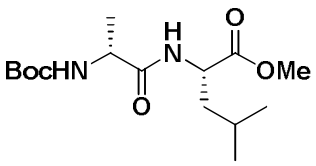
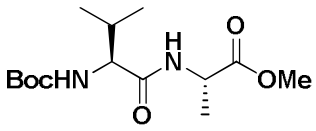
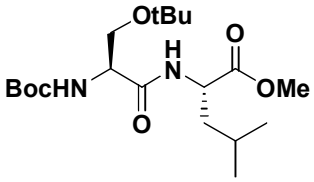


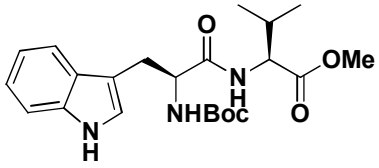
(*S*)-Methyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)propanoate (Boc-Val-Ala-OMe, 3); White solid, (0.459 g, 76%), **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 6.515-6.499 (d, 1H, *J* = 6.4, NH amide), 5.119-5.098 (d, 1H, *J* = 8.4, NH Boc), 4.620-4.548 (m, 1H, αCH Ala), 3.958-3.922 (m, 1H, δCH, Val), 3.745 (s, 3H, OCH_3), 2.146-2.098 (m, 1H, CH, -C*H*$(CH_3)_2$), 1.444 (s, 9H, C(C$H_3)_3$ Boc), 1.420-1.403 (d, 3H, *J* = 6.8, -CHCH_3), 0.982-0.916 (dd, 6H, *J* = 6.8, -CH$(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) 173.25, 171.23, 155.91, 79.97, 59.84, 52.54, 48.05, 31.11, 29.77, 28.37, 19.25, 18.38, 17.79. **MALDI-TOF/TOF** m/z Calcd .for. $C_{14}H_{26}N_2O_5$ (M + Na) is 325.1739 Observed = 325.2072.



(*S*)-Methyl 2-((*S*)-3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)propanamido)-4-methylpentanoate (Boc-Ser(OtBu)-Leu-OMe, 4) White solid, (0.558 g, 72%), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.205 (br., 1H, NH amide), 5.425 (br., 1H, NH Boc), 4.627-4.620 (m, 1H, αCH NHC*H*CH_2), 4.180 (br., 1H, δCH, NHC*H*CH_2-), 3.806-3.782 & 3.392-3.379 (dd, 2H, *J* = 6.8 CHC*H*$_2$O-), 3.717 (s, 3H, -OC*H*$_3$), 1.679-1.616 (m, 2H, -CHC*H*$_2$CH$(CH_3)_2$), 1.560-1.542 (m, 1H, -C*H*$(CH_3)_2$), 1.458 (s, 9H, C(C*H*$_3)_3$), Boc), 1.206 (s, 9H, C(C*H*$_3)_3$ ^{t}Butyl), 0.941-0.921 (dd, 6H, J = 4.4, CH(C*H*$_3)_2$); **^{13}C NMR** (100 MHz; $CDCl_3$): 173.14, 170.57, 155.54, 80.03, 74.14, 61.82, 54.02, 52.26, 50.83, 41.81, 28.37, 27.42, 24.74, 22.93, 21.96. **MALDI-TOF/TOF** m/z Calcd. for $C_{19}H_{36}N_2O_6$ (M + Na) is 411.2471 Observed = 411.2928.

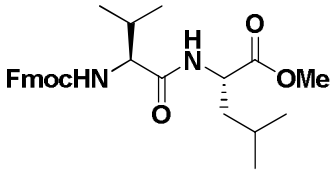


(*S*)-Methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-(*1H*-indol-3-yl)propanamido)-3-methylbutanoate (Boc-Trp-Val-OMe, 5); White solid, (0.525 g, 63%), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.276 (br., 1H, NH, indole), 7.671-.7.656 (d, 1H, *J* = 6, CH aromatic, indole), 7.365-7.348 (d, 1H, *J* = 6.8, CH aromatic, indole), 7.210-7.180 (t, 1H, *J* = 6.4, CH, aromatic), 7.141-7.111 (t, 1H, *J* = 6.4, CH aromatic, indole), 7.085 (br., 1H, CH aromatic, indole), 6.338-6.323 (d, 1H, *J* = 6, NH amide), 5.217 (br., 1H, NH, Boc), 4.459 (br., 1H, αCH, NHC*H*CH-), 4.430-4.403 (q, 1H, *J* =6.8, δCH, NHC*H*CH_2-), 3.636 (s, 3H, OC*H*$_3$), 3.307-3.184 (m, 2H, -CHC*H*$_2$CH-), 2.070-2.018 (m, 1H, -CHC*H*$(CH_3)_2$), 1.443 (s, 9H, C(C*H*$_3)_3$), 0.817-0.775 (dd, 6H, *J* = 5.6, CH(C*H*$_3)_2$), **^{13}C NMR** (100 MHz; $CDCl_3$): 171.84, 171.75, 155.63, 136.32, 127.55, 123.37, 122.23, 119.74, 118.89, 111.25, 110.62, 80.19, 57.34, 55.35, 52.12, 31.29, 28.37, 28.16,18.79, 17.81. **MALDI-TOF/TOF** m/z Calcd. for $C_{22}H_{31}N_3O_5$ (M + Na) is 440.2161 Observed = 440.2792.

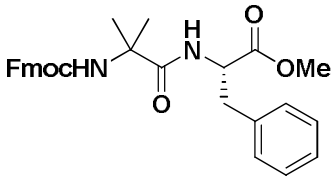


(*S*)-Methyl 2-((*S*)-2-((((*9H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-4-methylpentanoate (Fmoc-Val-Leu-OMe, 6) White solid, (0.717 g, 77%), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.775-7.761 (d, 2H, *J* = 5.6, 2 x CH, Fmoc), 7.606-7.592 (d, 2H, *J* = 5.6, 2 x CH, Fmoc), 7.415-7.388 (t, 2H, *J* = 4.8, 2 x CH, Fmoc), 7.329-7.299 (t, 2H, *J* = 6.4, 2 x CH, Fmoc), 6.366-6.352 (d, 1H, *J* = 5.6, NH

amide), 5.510-5.493 (d, 1H, *J* = 6.8, NH, Fmoc), 4.654-4.610 (m, 1H, αCH, NHC*H*CH_2-), 4.458-4.423 & 4.373- 4.338 (br. 2H, -C*H*$_2$ CH- Fmoc), 4.241-4.213 (t, , 1H, *J* = 5.6, -CH_2C*H*- Fmoc), 4.080-4.050 (t, 1H, *J* = 6, δCH, -NHC*H*CH-), 3.730 (s, 3H, OC*H*$_3$), 2.146-2.108 (m, 1H, -CHC*H*$(CH_3)_2$), 1.673-1.648 (m, 2H, -CHC*H*$_2$CH), 1.566-1.533 (m, 1H, -CH_2C*H*$(CH_3)_2$), 1.0-0.964 (dd, 6H, *J* = 5.2, CH(C*H*$_3$)$_2$), 0.922-0.911 (d, 6H, *J* = 4.4, CH(C*H*$_3$)$_2$ Leu) **^{13}C NMR** (100 MHz; $CDCl_3$): 173.25, 171.31, 156.49, 143.92, 141.35, 127.80, 127.16, 125.16, 120.04, 67.20, 60.25, 52.36, 50.84, 47.20, 41.36, 31.52, 24.89, 22.81, 21.95, 18.07 **MALDI-TOF/TOF** m/z Calcd. for $C_{27}H_{34}N_2O_5$ 489.2365 (M + Na) is Observed = 489.3064.

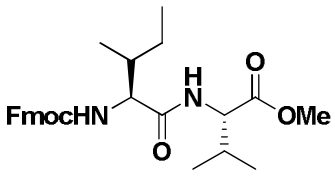


(*S*)-Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methylpropanamido)-3-phenylpropanoate (Fmoc-Aib-Phe-OMe, 7); White solid (0.67 g, 69%), **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 7.768-7.748(d, 2H, *J*= 8, 2 x CH, Fmoc), 7.588-7.561 (dd, 2H, *J*= 7.6, 2 x CH, Fmoc), 7.411-7.375 (t, 2H, *J* = 7.2, 2 x CH, Fmoc), 7.322-7.28 (t, 2H, *J* = 7.2, 2 x CH, Fmoc), 7.224-7.164 (m, 3H, 3 x CH, Phenyl), 7.085-7.068 (d, 2H, *J* = 6.8, 2 x CH, Phenyl), 6.686-6.677 (d, 1H, *J* = 3.6, NH, amide), 5.439 (br. 1H, NH, Aib), 4.848(br. 1H, CH, -C*H*CH_2-, Fmoc), 4.399-4.339 (m, 2H, -CHC*H*$_2$, Fmoc), 4.189-4.156 (t, 1H, J = 6.4, αCH, -NHC*H*CH_2, Phe), 3.683 (s, 3H, OCH_3), 3.126-3.091 (m, 2H, -CHC*H*$_2$Ph), 1.465 (s, 6H, 2 x CH_3, C$(CH_3)_2$, Aib); **^{13}C NMR** (100 MHz, $CDCl_3$) 173.82, 171.79, 154.84, 143.70, 141.19, 135.70, 129.17, 128.39, 126.98, 124.93, 119.89, 66.56, 60.31, 56.68, 52.21, 47.02, 37.66, 30.83, 25.35, 20.95, 14.10. **MALDI-TOF/TOF** m/z Calcd. For $C_{29}H_{30}N_2O_5$ (M + Na) is 509.2052 Observed = 509.2054.

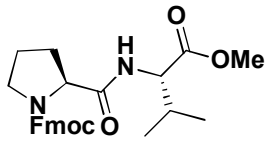


(*S*)-Methyl 2-((*2S,3R*)-2-((((*9H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylpentanamido)-3-methylbutanoate (Fmoc-Ile-Val-OMe, 8); White solid, (0.652 g, 70%) **^{1}H NMR** (400 MHz; $CDCl_3$): *δ* 7.772-7.752 (d, 2H, *J* = 8, 2 x CH, Fmoc), 7.602-7.588 (d, 2H, *J* = 5.6, 2 x CH, Fmoc), 7.415-7.379 (t, 2H, *J* = 7.2, 2 x CH, Fmoc), 7.323-7.286 (t, 2H, *J* = 7.6, 2 x CH, Fmoc), 6.571-6.551 (d, 1H, *J* = 8, NH amide), 5.578-5.557 (d, 1H, *J* = 8.4, NH Fmoc), 4.575-4.540 (dd, 1H, *J* = 5.2, -CH_2C*H*CH-, Fmoc), 4.457-4.412 & 4.380-4.335 (m, 2H, -OC*H*$_2$CH-, Fmoc), 4.238-4.202 (t, 1H, *J* = 7.2, αCH, -NHC*H*CH-), 4.155-4.116 (m, 1H, δCH, -NHC*H*CH- Ile), 3.718 (s, 3H, OC*H*$_3$), 2.207-2.127 (m, 1H, -CHC*H*$(CH_3)_2$

Val), 1.871-1.855 (m, 1H, CH, -CHC*H*CH_3 Ile), 1.594-1.535 & 1.213-1.138 (m, 2H, -CHC$H_2$$CH_3$ Ile), 0.958-0.882 (m, 12H, CH(CH_3)$_2$ Val & CH(CH_3)$_2$ Leu); **^{13}C NMR** (100 MHz, $CDCl_3$) 172.04, 171.37, 156.25, 143.79, 141.20, 127.63, 126.99, 125.03, 119.88, 67,00, 59.54, 57.07, 52.08, 47.05, 37.47, 31.04, 24.78, 18.86, 17.74, 15.28, 11.27. **MALDI-TOF/TOF** m/z Calcd. for $C_{27}H_{34}N_2O_5$ (M + Na) is 489.2365 Observed = 489.2964.

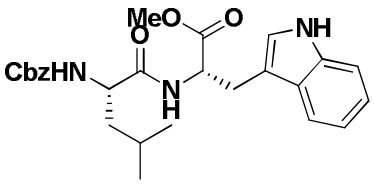


(*S*)-(*9H*-Fluoren-9-yl)methyl 2-(((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (Fmoc-Pro-Val-OMe, 9); White solid, (0.585 g, 65%), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.784-7.766 (d, 2H, *J* = 7.2, 2 x CH, Fmoc), 7.596-7.543 (d, 2H, 2 x CH, Fmoc), 7.427-7.391 (t, 2H, *J* = 6.8, 2 x CH, Fmoc), 7.335-7.301 (t, 2H, *J* = 7.2, 2 x CH, Fmoc), 7.212-7.193 (d, 1H, *J* = 7.6, NH amide), 6.523-6.506 (d,1H, *J* = 6.8, NH Fmoc), 4.482-4.438 (m, 3H, -CH_2C*H*CH- & -OCH_2CHCH-, Fmoc), 4.421-4.391 (m, 1H, CH_2C*H*N- pro), 4.291-4.257 (t, 1H, *J* = 6.4, αCH, -NHC*H*CH-), 3.726 (s, 3H, OCH_3), 3.593-3.554 (t, 2H, *J* = 8.4, -NC$H_2$$CH_2$-, Pro), 2.380.2.365 (br.,1H, -CHC*H*(CH_3)$_2$), 1.957-1.926 (br., 4H, -CH_2CH_2C$H_2$$CH_2$-), 0.916-0.899 (d, 6H, *J* = 6.8,CH(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) 172.26, 171.55, 156.21, 143.98, 141.35, 127.82, 127.15,125.14, 120.07, 67,86, 60.41, 57.41, 52.17, 47.24, 34.19, 31.20, 29.78, 28.11, 25.69, 24.80, 19.11, 17.77. **MALDI-TOF/TOF** m/z Calcd. for $C_{26}H_{30}N_2O_5$ (M + Na) is 473.2052 Observed = 473.2640.

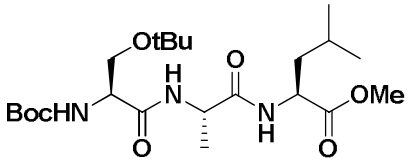


(*S*)-Methyl 2-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-methylpentanamido)-3-(*1H*-indol-3-yl)propanoate (Cbz-Leu-Trp-OMe, 10); White solid, (0.558 g, 60%), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.166 (br. 1H, NH, indole), 7.519-7.499 (d, 1H, *J* = 8, CH, aromatic, indole), 7.338-7.303 (m, 5H, 5 x CH, Phenyl), 7.186-7.073 (m, 2H, 2 x CH aromatic, indole), 6.945 (br., 1H, CH, indole), 6.729-6.711 (d, 1H, *J* = 7.2, NH amide), 5.261-5.240 (d, 1H, *J* = 8.4, NH, Cbz), 5.063-4.984 (m, 2H, -CH_2Ph), 4.953-4.906 (m, 1H, αCH, -NHC*H*CH_2), 4.313-4.280 (m, 1H, δCH, -NHC*H*CH_2- Leu), 3.665 (s, 3H, OCH_3), 3.301-3.295 (d, 2H, *J* = 2.4,-CHCH_2-C-), 1.64 3-1.588 (m, 2H, -CHCH_2CH(CH_3)$_2$), 1.483-1.460 (m, 1H, -CH_2C*H*(CH_3)$_2$), 0.893-0.887 (d, 6H, *J* =6, -CH(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) 172.01, 156.08,

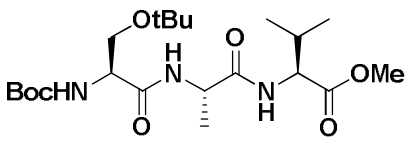
135.97, 128.49, 128.00, 127.39, 123.23, 122.07, 119.50, 118.39, 111.26, 109.33, 66.90, 53.38, 52.77, 52.38, 41.50, 27.43, 24.56, 22.88, 21.80. **MALDI-TOF/TOF** m/z Calcd. for $C_{26}H_{31}N_3O_5$ (M + Na) is 488.2161 Observed = 488.3227.



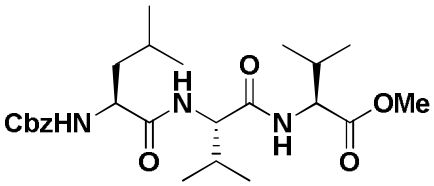
(*6S,9S,12S*)-Methyl 6-(*tert*-butoxymethyl)-12-isobutyl-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (Boc-Ser(O^{t}Bu)-Ala-Leu-OMe, 11) White solid (0.587 g, 64%),), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.162-7.144 (d,1H, *J* = 7.2, NH amide, Leu), 6.716-6.697 (d, 1H, *J* = 7.6, NH amide, Ala), 5.433-5.420 (d, 1H, *J* = 5.2, NH Boc), 4.604-4.476 (m, 2H, -CHCH_2O-), 4.163 (br., 1H, αCH, -NHC*H*CH-, Leu), 3.796-3.766 (m, 1H, δCH, -NHC*H*CH_3), 3.722 (s, 3H, OCH_3), 3.405-3.365 (dd, 1H, *J* = 7.2, -NHC*H*CH_2O-), 1.661-1.596 (m, 2H, -CHCH_2CH$(CH_3)_2$), 1.567-1.524 (m, 1H, -CH_2C*H*$(CH_3)_2$), 1.450 (s, 9H, C(C$H_3)_3$ Boc), 1.389-1.372 (d, 3H, *J* =6.8, -CHCH_3), 1.183 (s, 9H, -C(C$H_3)_3$, tButyl), 0.925-0.901 (dd, 6H, *J* = 6, -CH(C$H_3)_2$). **MALDI-TOF/TOF** m/z Calcd. for $C_{22}H_{41}N_3O_7$ (M + Na) is 482.2842 Observed = 482.3709.



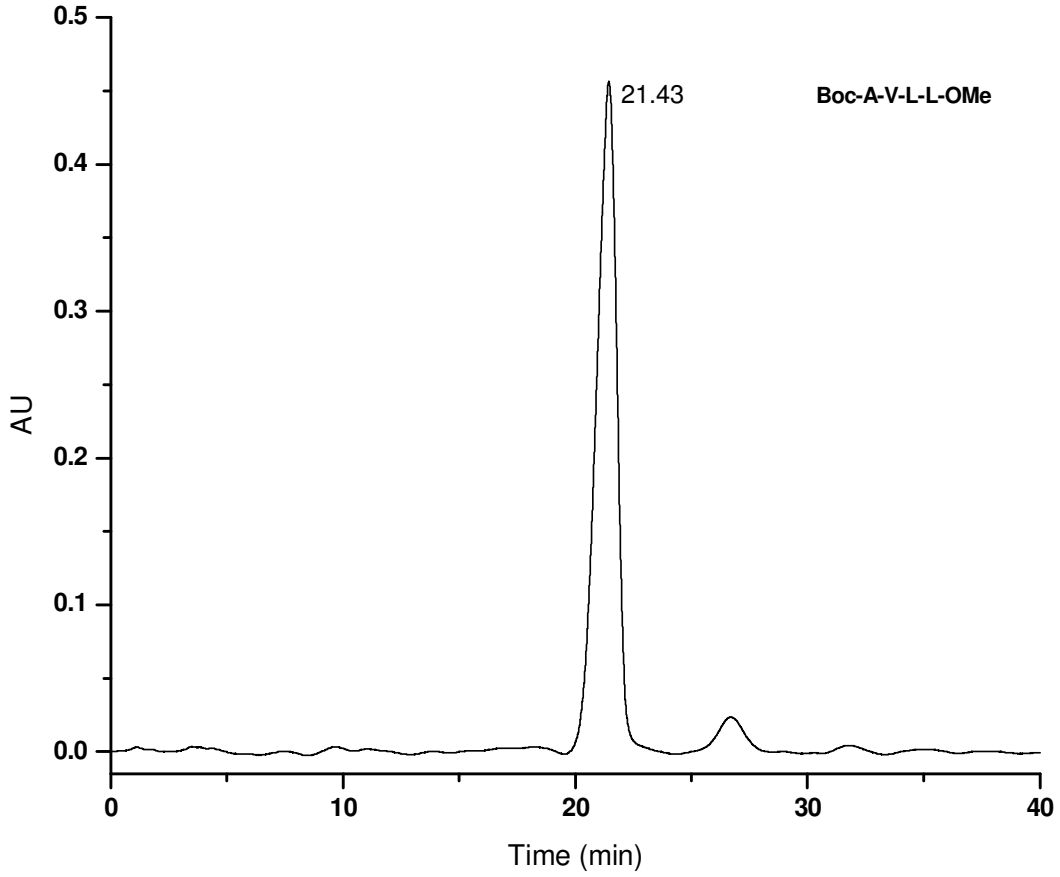
(*6S,9S,12S*)-Methyl 6-(*tert*-butoxymethyl)-12-isopropyl-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (Boc-Ser(O^{t}Bu)-Ala-Val-OMe, 12); White powder (0.542 g, 61%), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.199-7.186 (d, 1H, J = 5.2, NH amide Val), 6.703-6.681 (d,1H, J = 8.8, NH amide, Ala), 5.445-5.434 (d, 1H,J = 4.4 NH Boc), 4.545-4.474 (m, 2H, -CHCH_2O-), 4.187 (br., 1H, αCH, -NHC*H*CH-,Val), 3.814-3.783 (m, 1H, δCH, -NHC*H*CH_3), 3.741 (s, 3H, OCH_3), 3.428-3.362 (m,1H, -NHC*H*CH_2O-, Ser), 2.198-2.129 (m, 1H, -CHC*H*$(CH_3)_2$), 1.453 (s, 9H, -C(C$H_3)_3$ Boc), 1.396-1.378 (d, 3H, J = 7.2, -CHCH_3), 1.192 (s, 9H, C$(CH_3)_3$, ^{t}Butyl); **MALDI-TOF/TOF** m/z Calcd for $C_{21}H_{39}N_3O_7$ (M + Na) is 468.2686 Observed = 468.3583.



(*S*)-Benzyl 2-(((*S*)-1-(((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl)-4-methylpentanoate (Cbz-Leu-Val-Val-OMe, 13);White solid (0.620 g, 65%), **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.328-7.283 (m, 5H, 5 x CH, Phenyl), 7.192-7.170 (d, 1H, J = 8.8, NH amide, Val), 7.016-6.994 (d, 1H, J = 8.8, NH amide, Val), 5.848-5.827 (d, 1H, J = 8.4, NH Cbz), 5.095-5.076 (d, 2H, J = 7.6, CH_2Ph), 4.571-4.537 (m, 1H, αCH, -NHC*H*CH- Val), 4.457-4.415 (m, 1H, δCH, -NHC*H*CH- Val), 4.354-4.319 (m, 1H, CH, -NHC*H*CH_2- Leu), 3.709 (s, 3H, OCH_3), 2.197-2.137 (m, 1H -CHC*H*$(CH_3)_2$), 2.080-2.029 (m, 1H, C*H*$(CH_3)_2$), 1.646-1.510 (m, 3H,-CHCH_2C*H*$(CH_3)_2$), 0.922-0.850 (m,18H, -CH(C$H_3)_2$ x 3 Val, Val, Leu). **MALDI-TOF/TOF** m/z Calcd. for $C_{25}H_{39}N_3O_6$ (M + Na) is 500.2737 Observed = 500.3626.

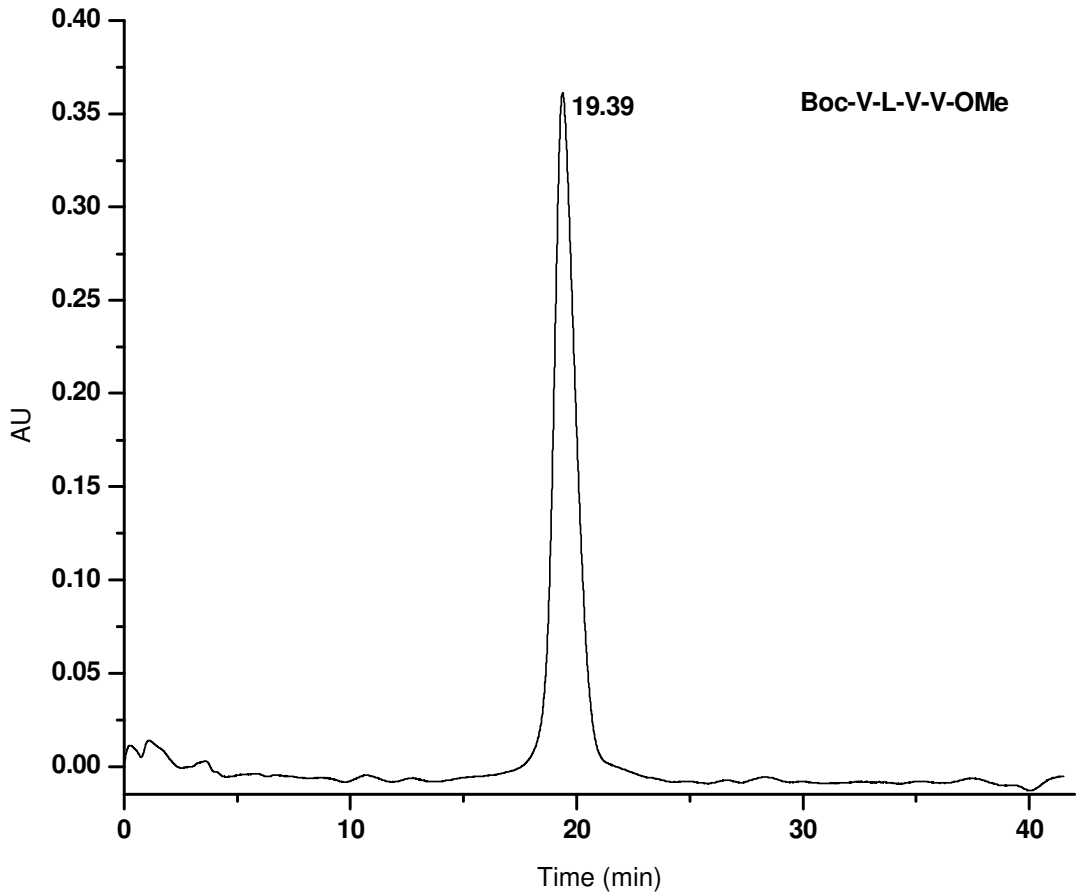


HPLC profile of **Boc-Ala-Val-Leu-Leu-OMe (14).**



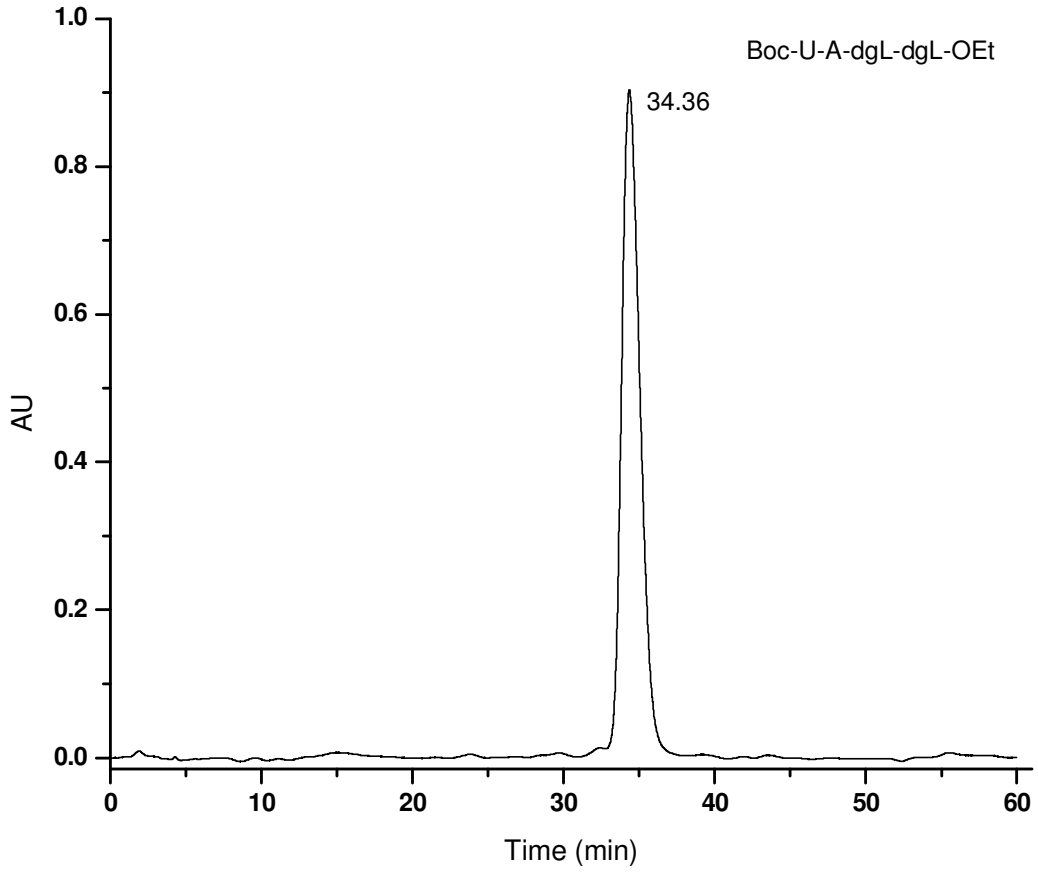
Reverse Phase HPLC profile of crude tetra peptide **14**. Methanol/ H_2O were used as a solvent system at a flow rate of 1.25 mL /Min in a C18 column at 220 nm.

HPLC profile of **Boc-Val-Leu-Val-Val-OMe (15).**



Reverse Phase HPLC profile of crude tetra peptide **15**. Methanol/ H_2O were used as a solvent system at a flow rate of 1.25 mL /Min in a C18 column at 220 nm.

HPLC profile of **Boc-Aib-Ala-dgL-dgL-OMe (16).**



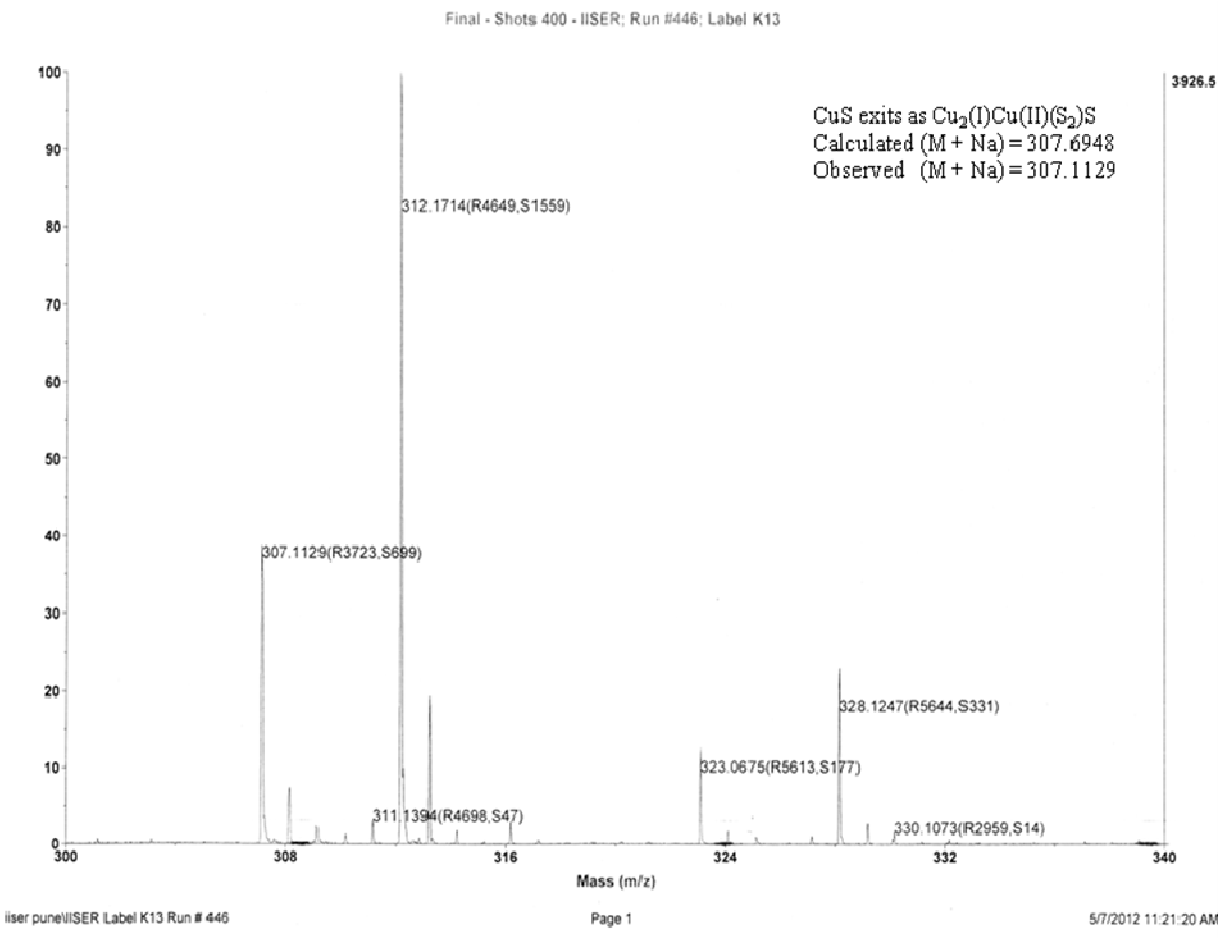
Reverse Phase HPLC profile of crude tetra peptide **16**. Methanol/ H_2O were used as a solvent system at a flow rate of 1.25 mL /Min in a C18 column at 220 nm.

References.

1. SHELXS-97: G.M. Sheldrick, *Acta Crystallogr. Sect A*, 1990, **46**, 467-473, b) G.M. Sheldrick, SHELXL-97,Universität Göttingen (Germany) **1997**.

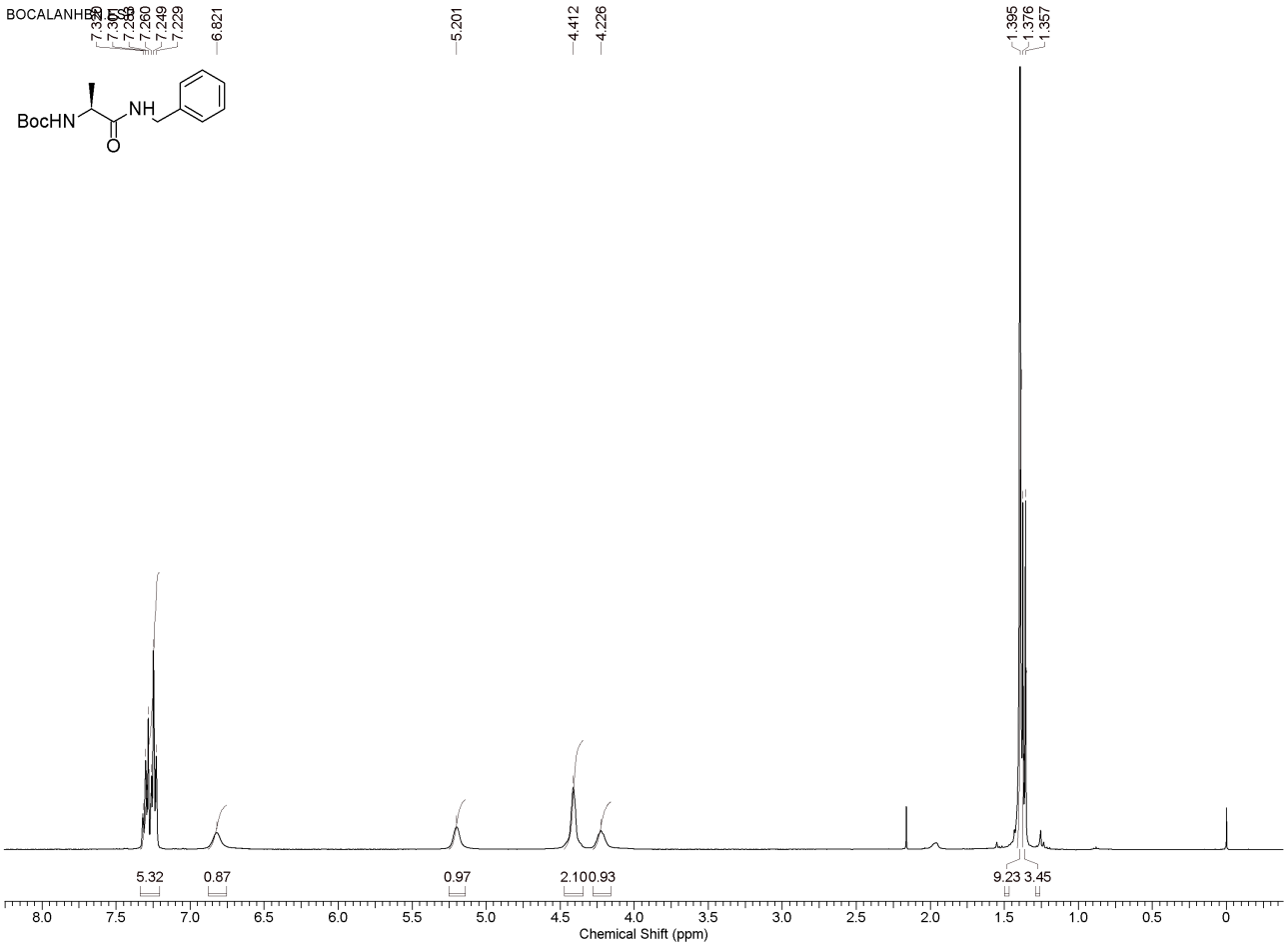
2. Goldstein, A. S.; Gelb, M. H. *Tetrahedron Lett*. 2000, 41, 2797–2800.

MALDI-TOF/TOF Analysis of metal sulfide byproduct (CuS)

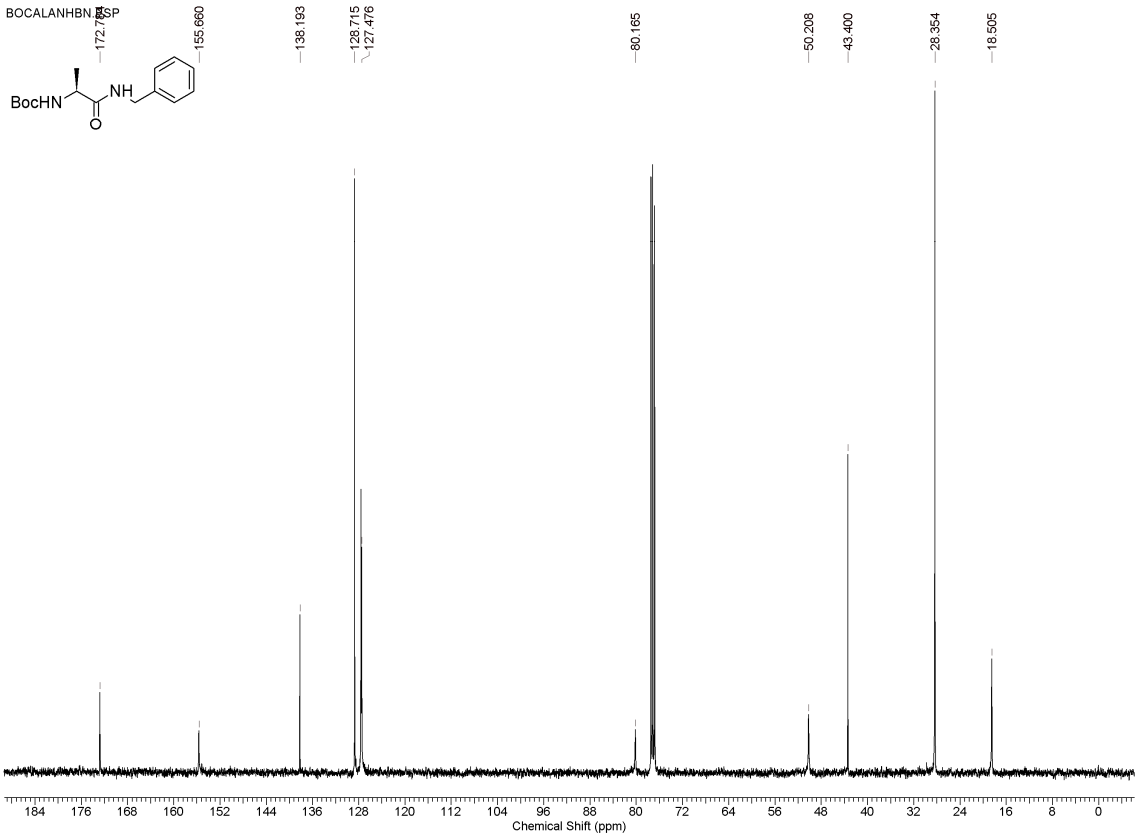


^{1}H, ^{13}C and MALDI-TOF Mass Data

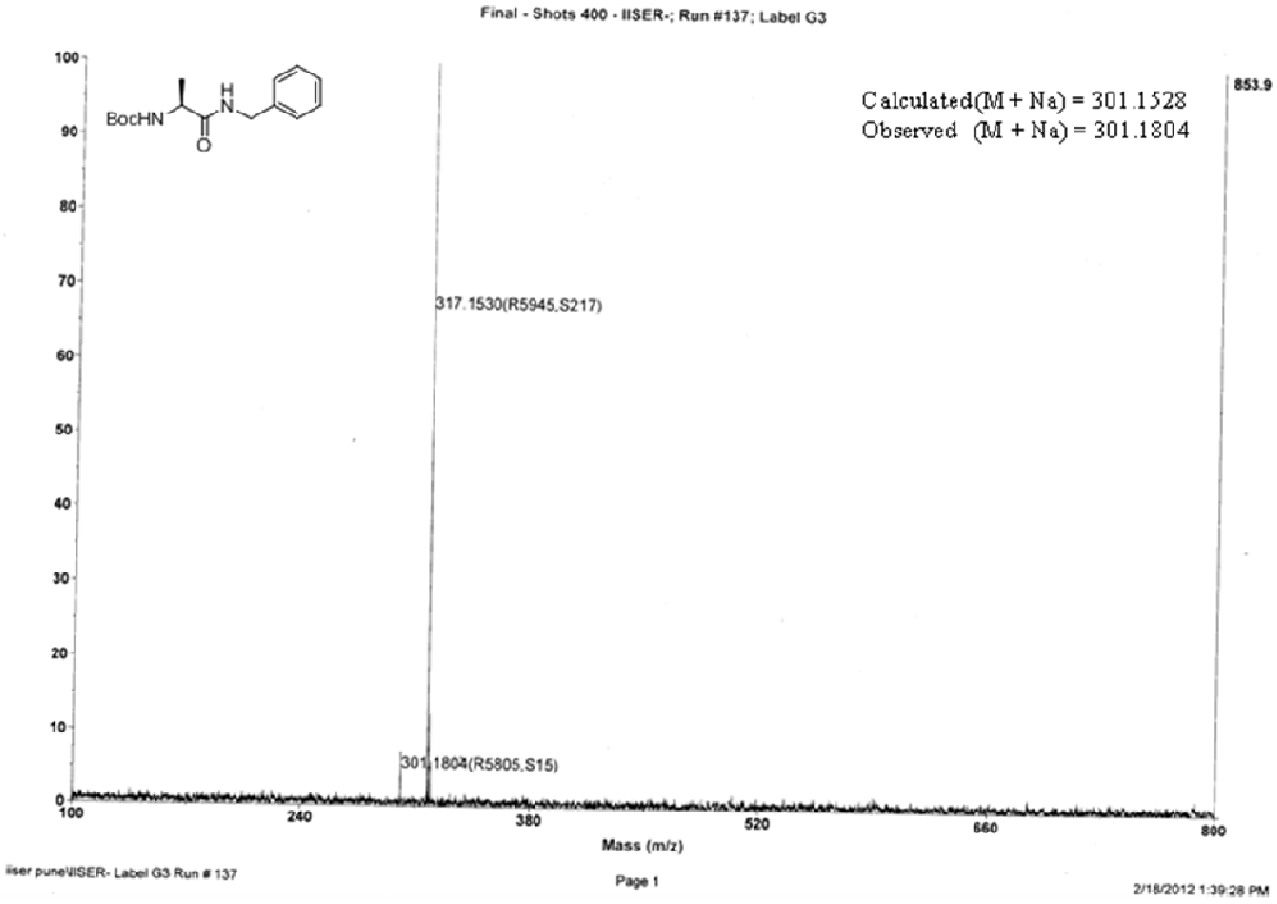
Boc-Ala-NH-Bzl



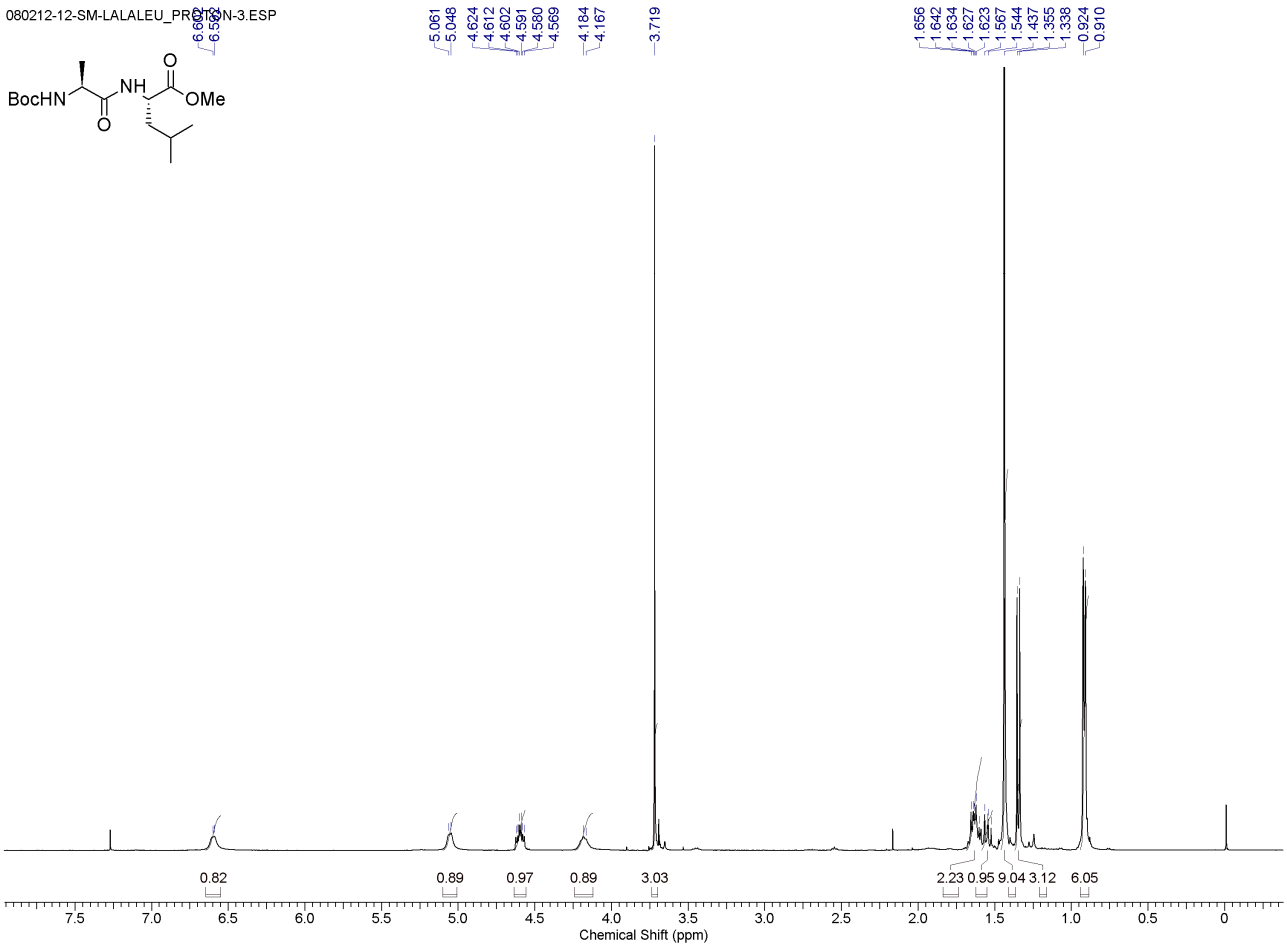
Boc-Ala-NH-Bzl



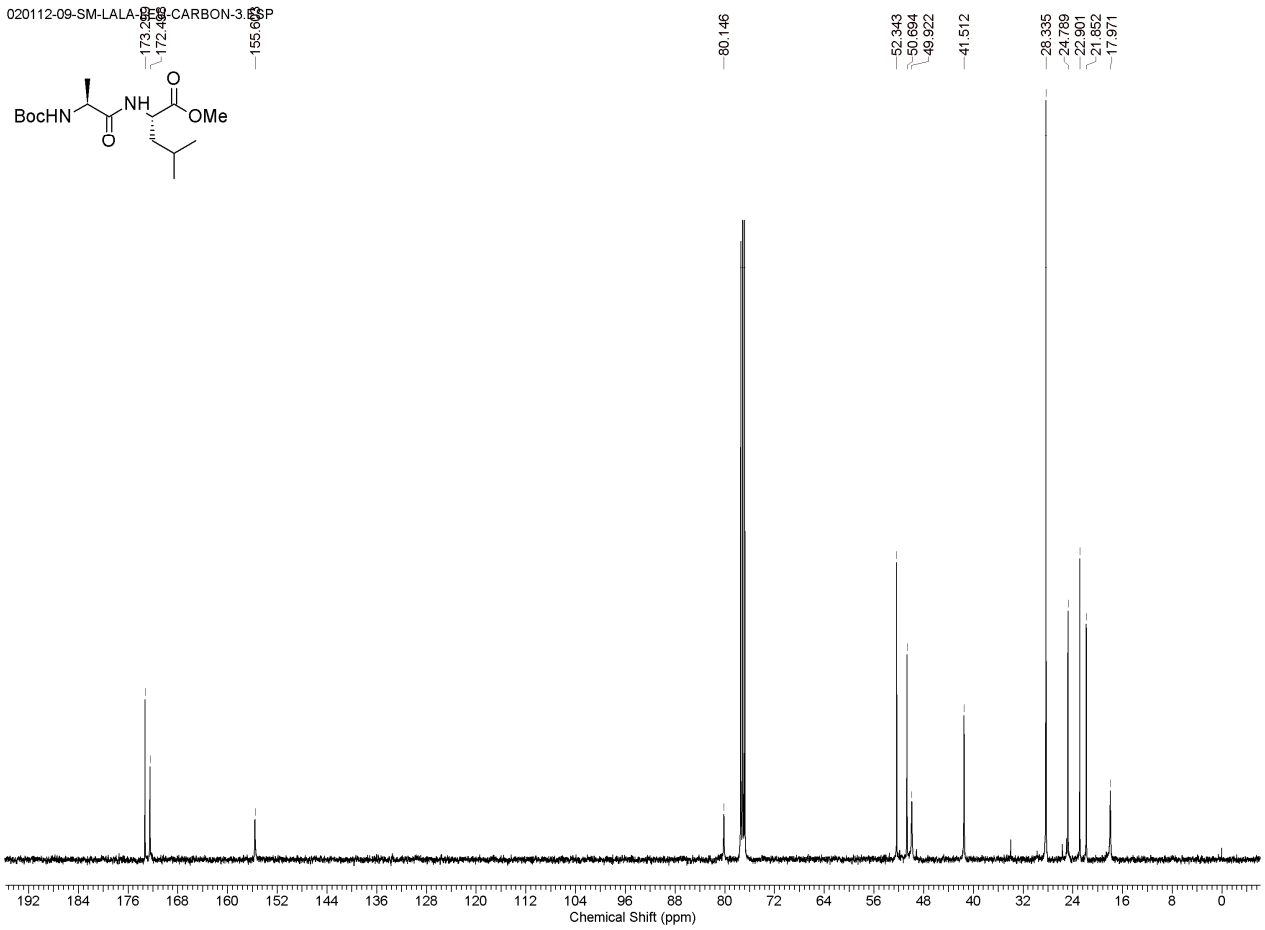
Boc-Ala-NH-Bzl



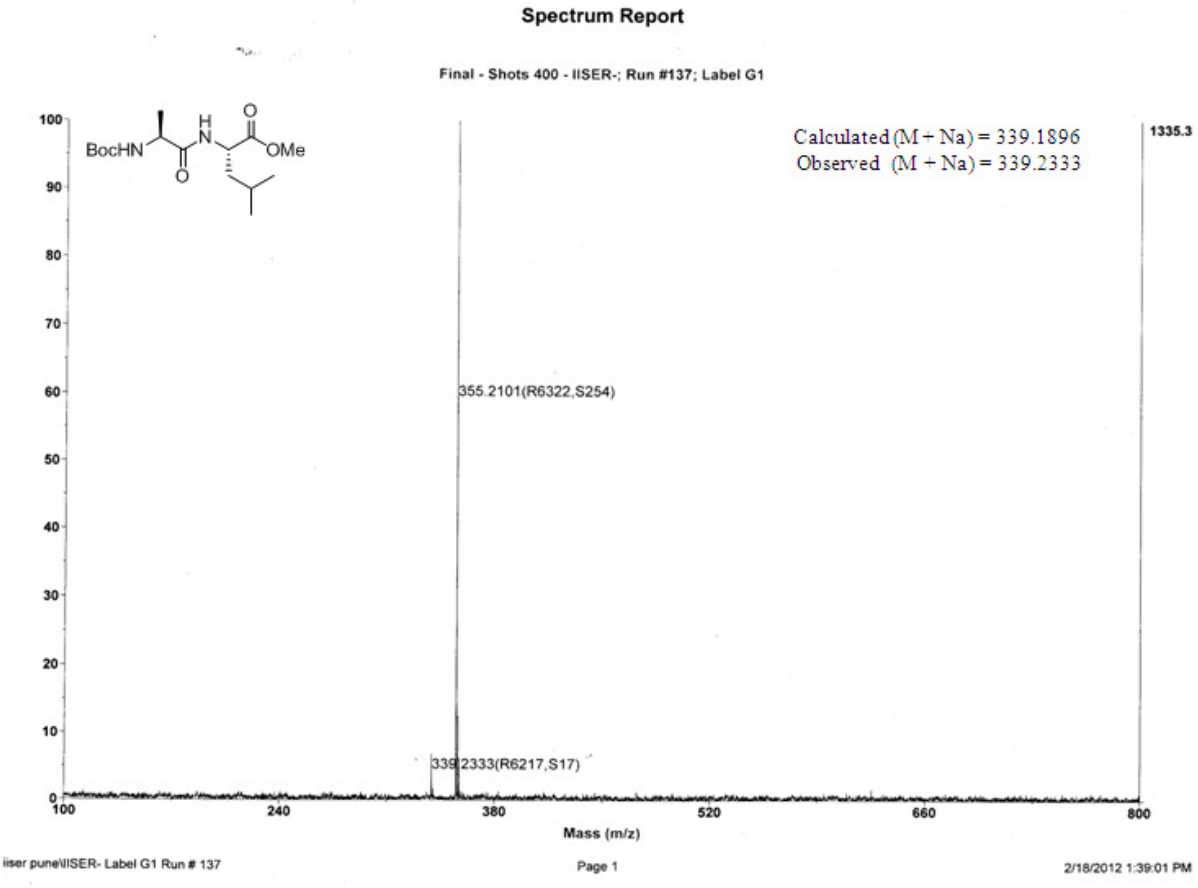
Boc-Ala-Leu-OMe (1)



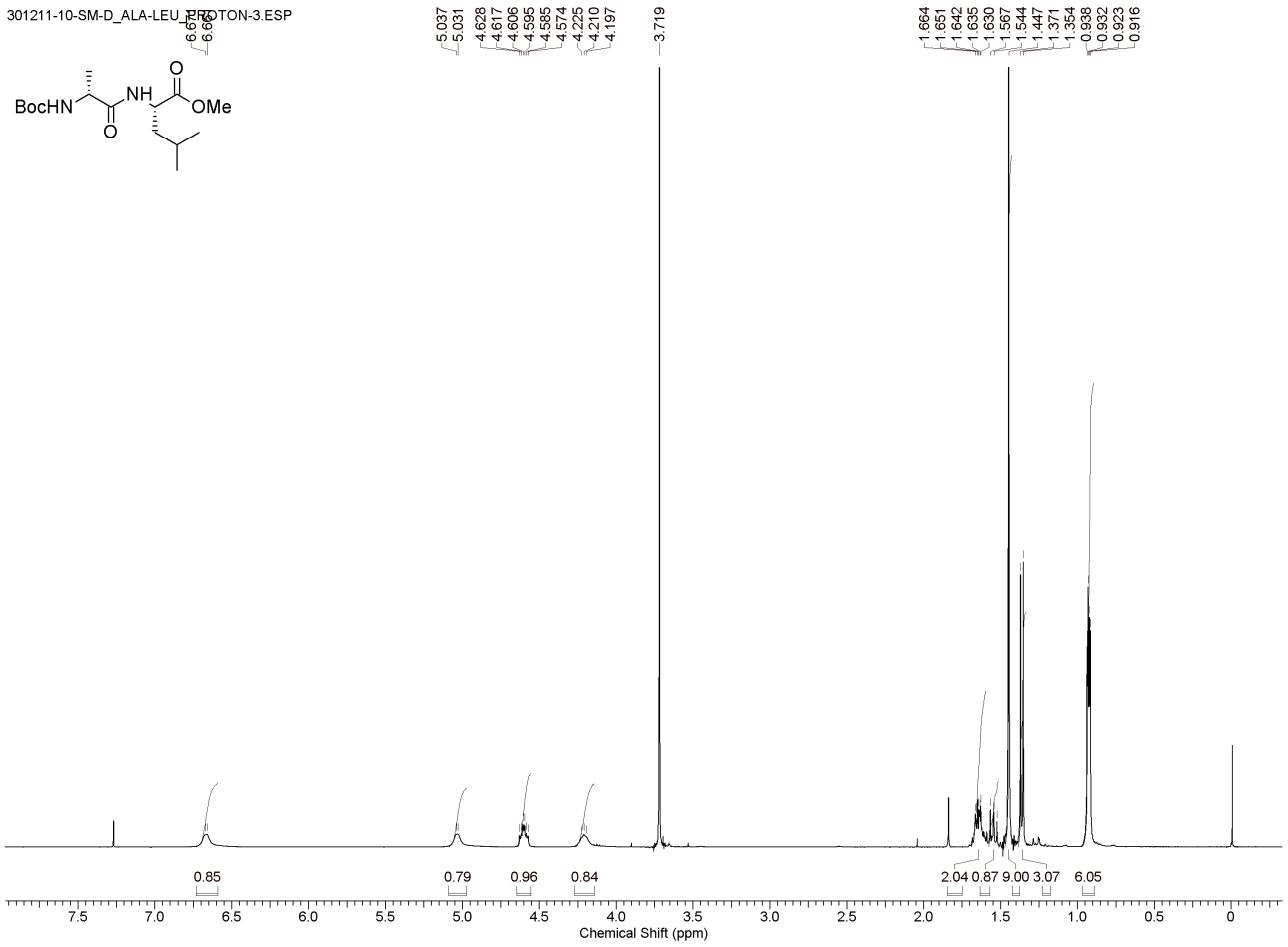
Boc-Ala-Leu-OMe (1)



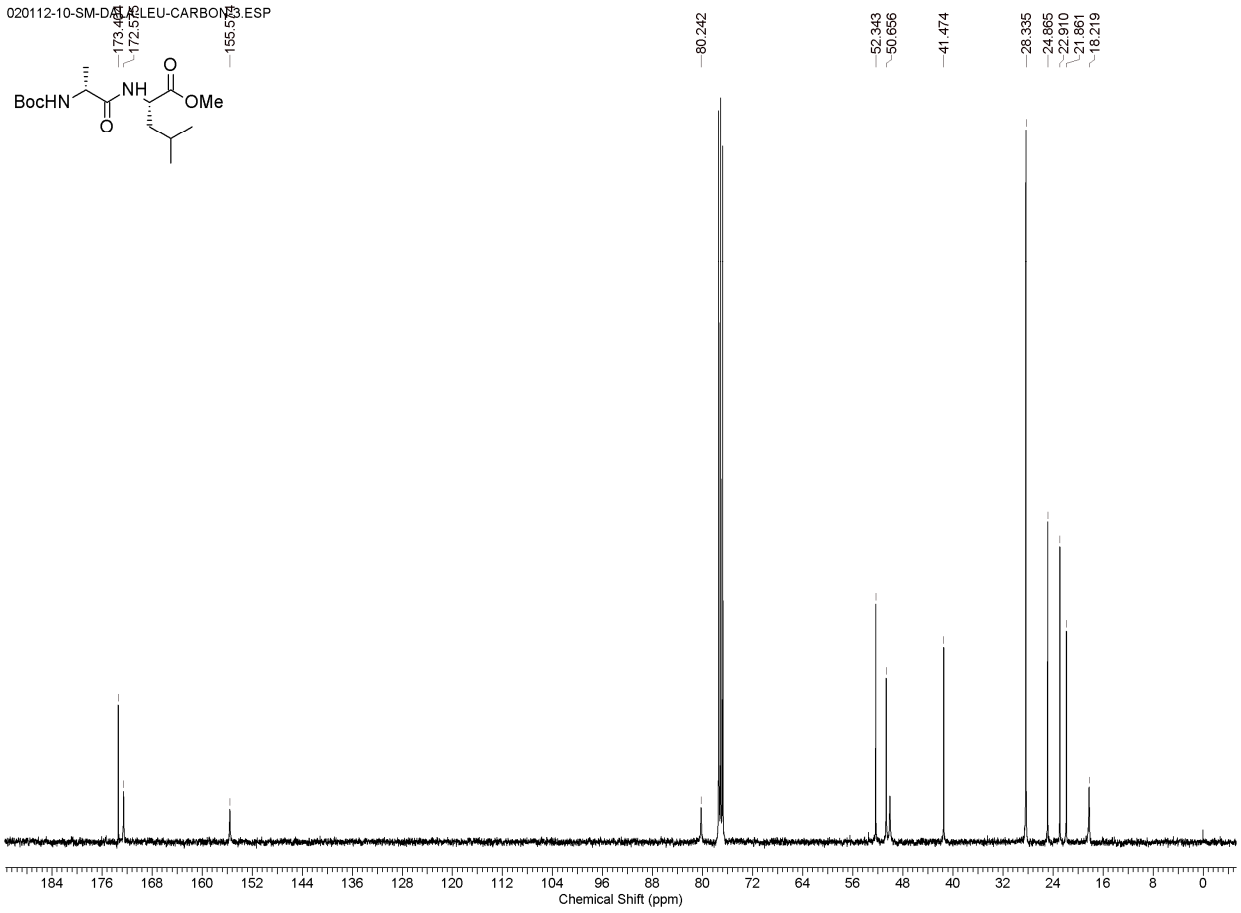
Boc-Ala-Leu-OMe (1)



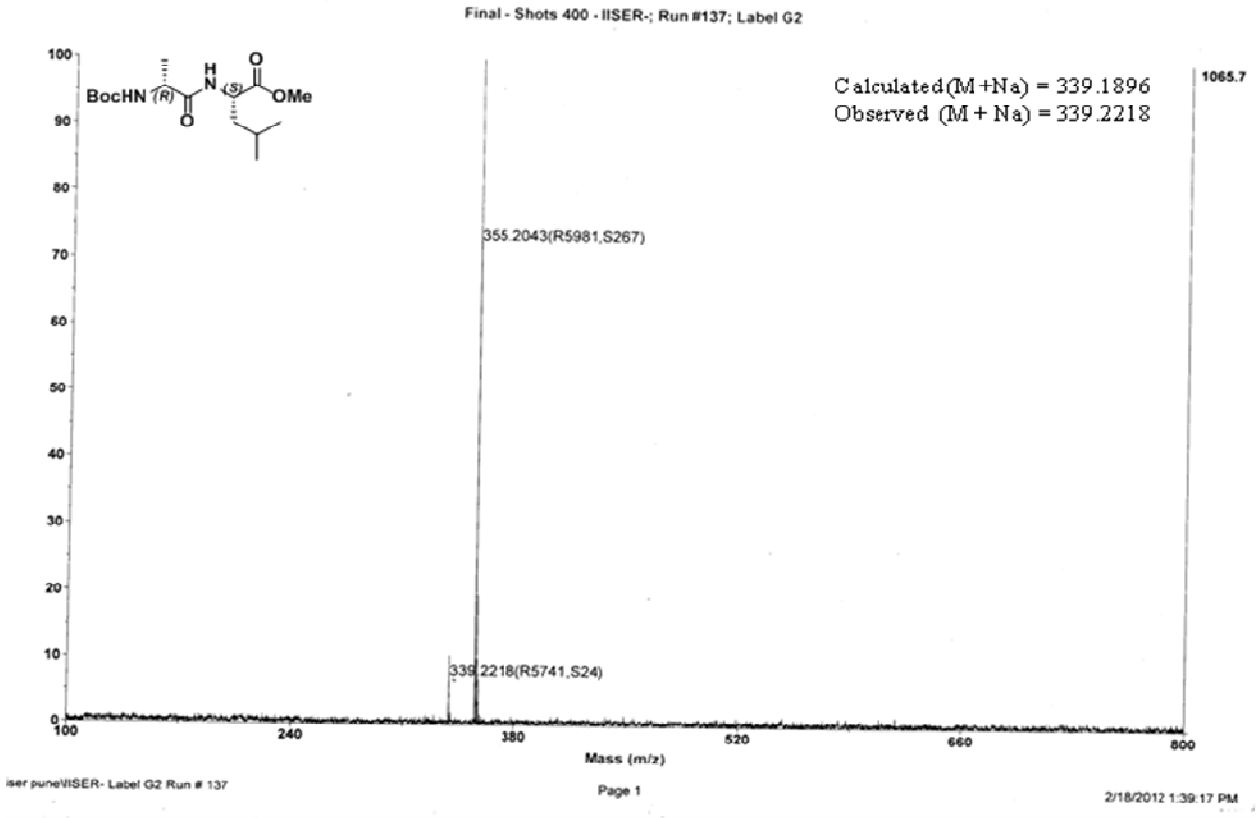
Boc-^{D}Ala-Leu-OMe (2)



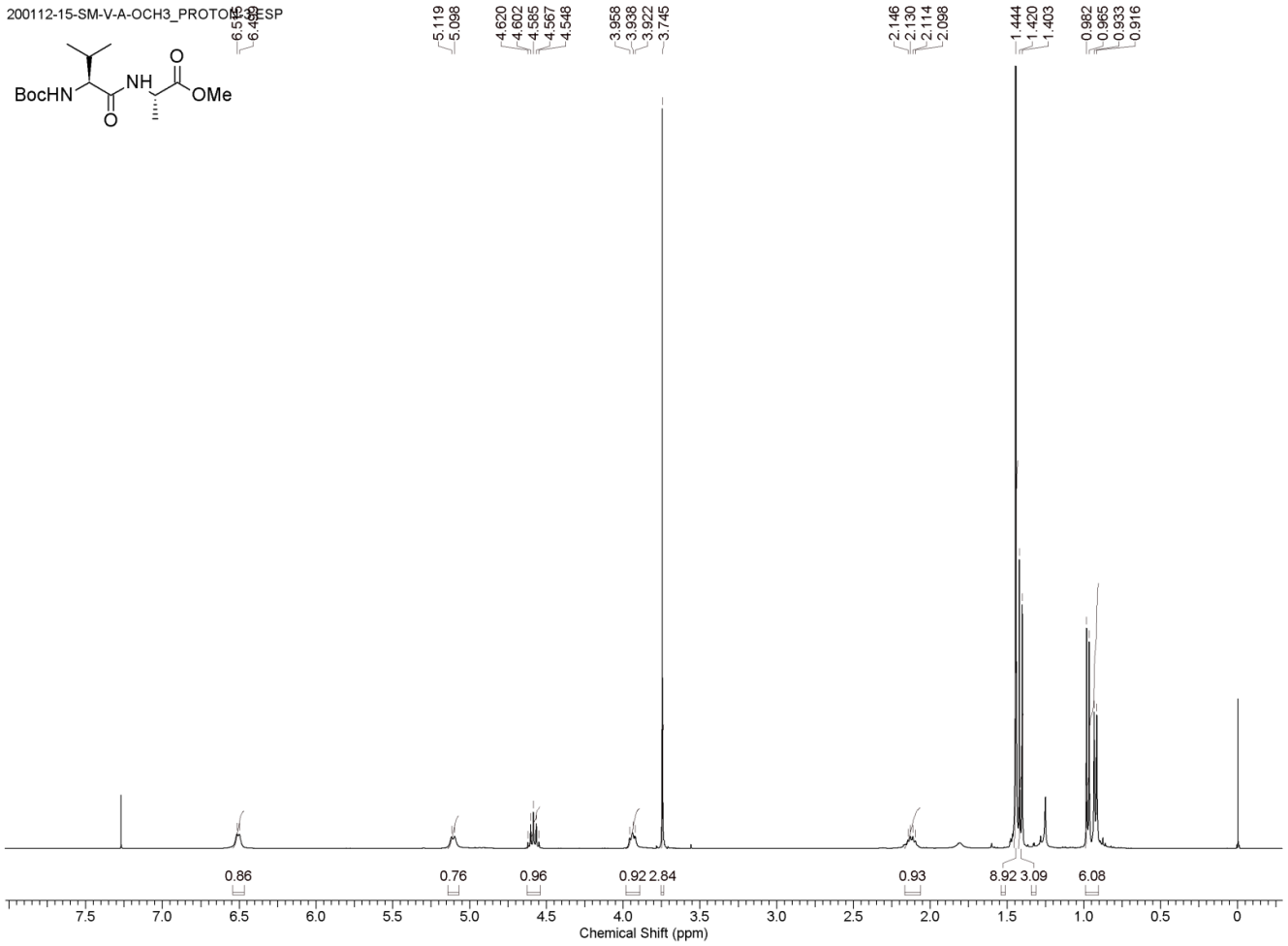
Boc-^{D}Ala-Leu-OMe (2)



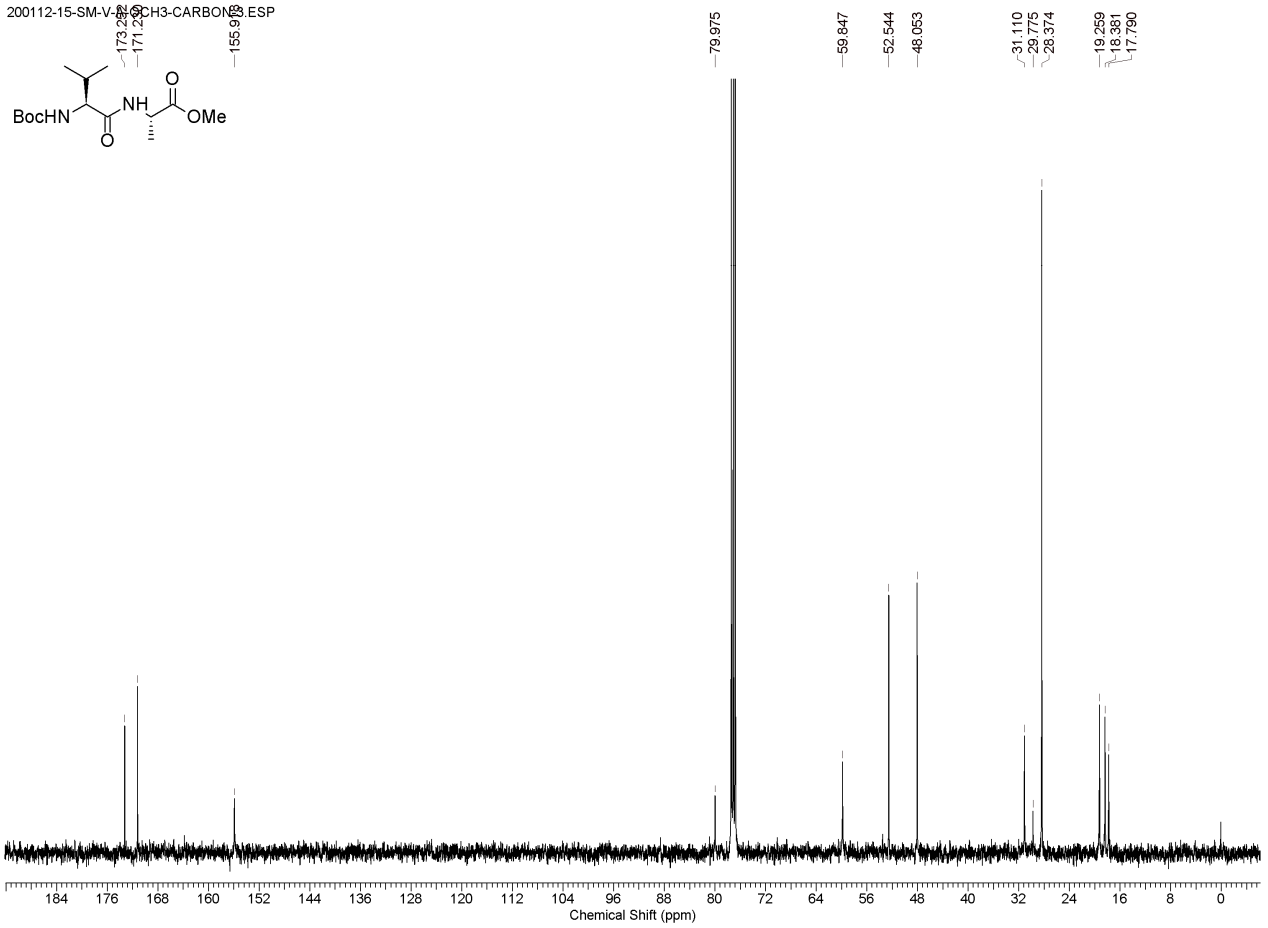
Boc-^{D}Ala-Leu-OMe (2)



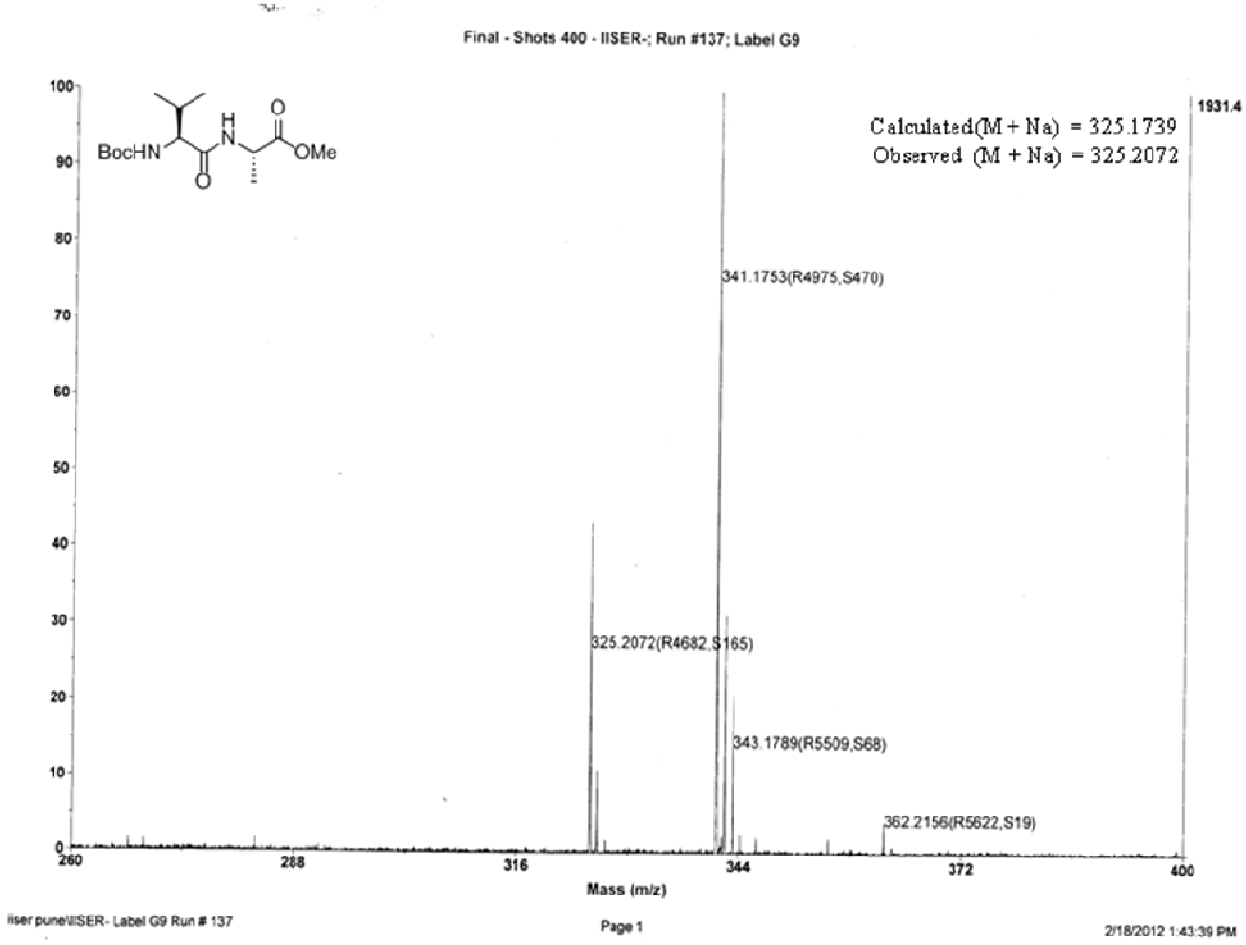
Boc-Val-Ala-OMe (3)



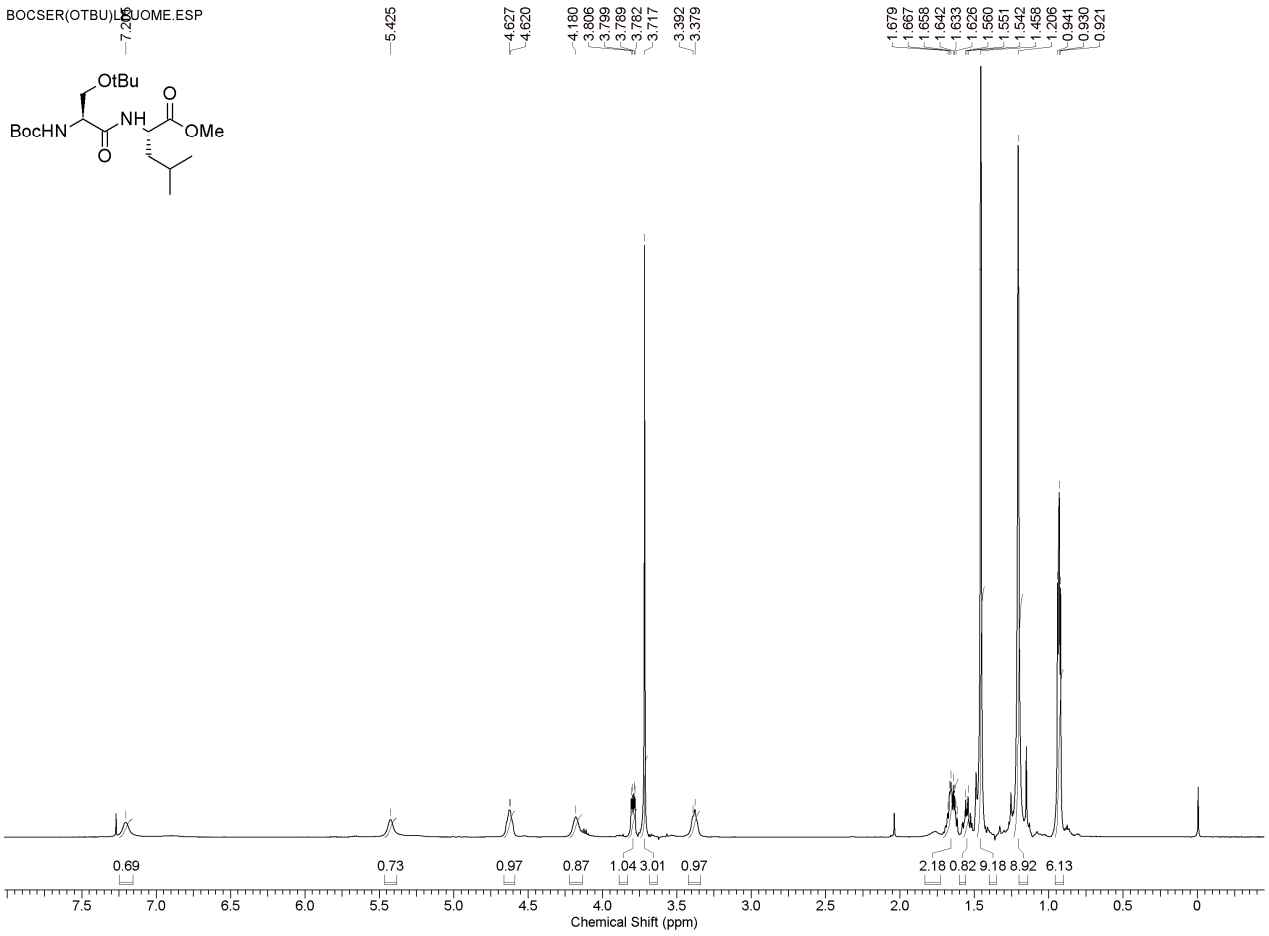
Boc-Val-Ala-OMe (3)



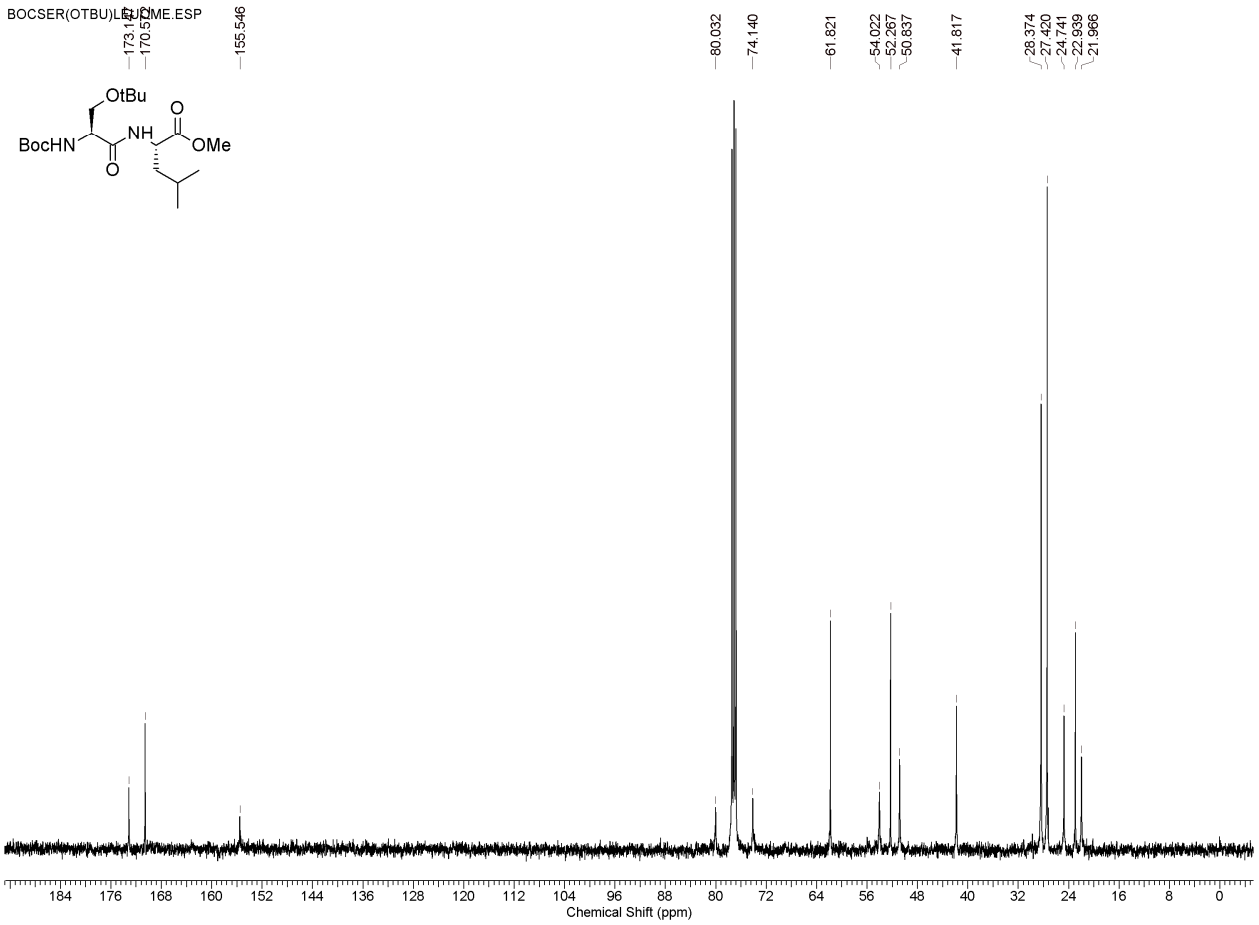
Boc-Val-Ala-OMe (3)



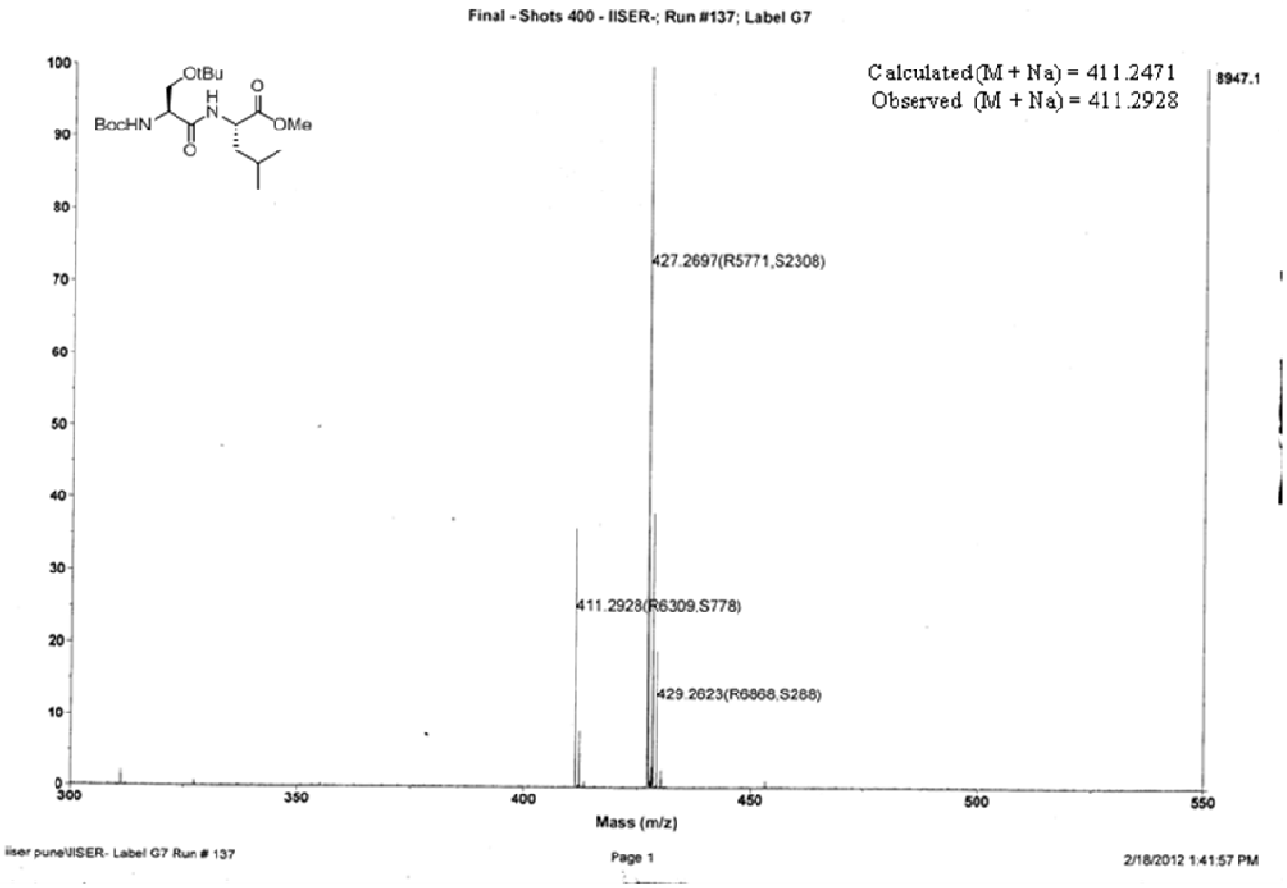
Boc-Ser(OBu^t)-Leu-OMe (4)



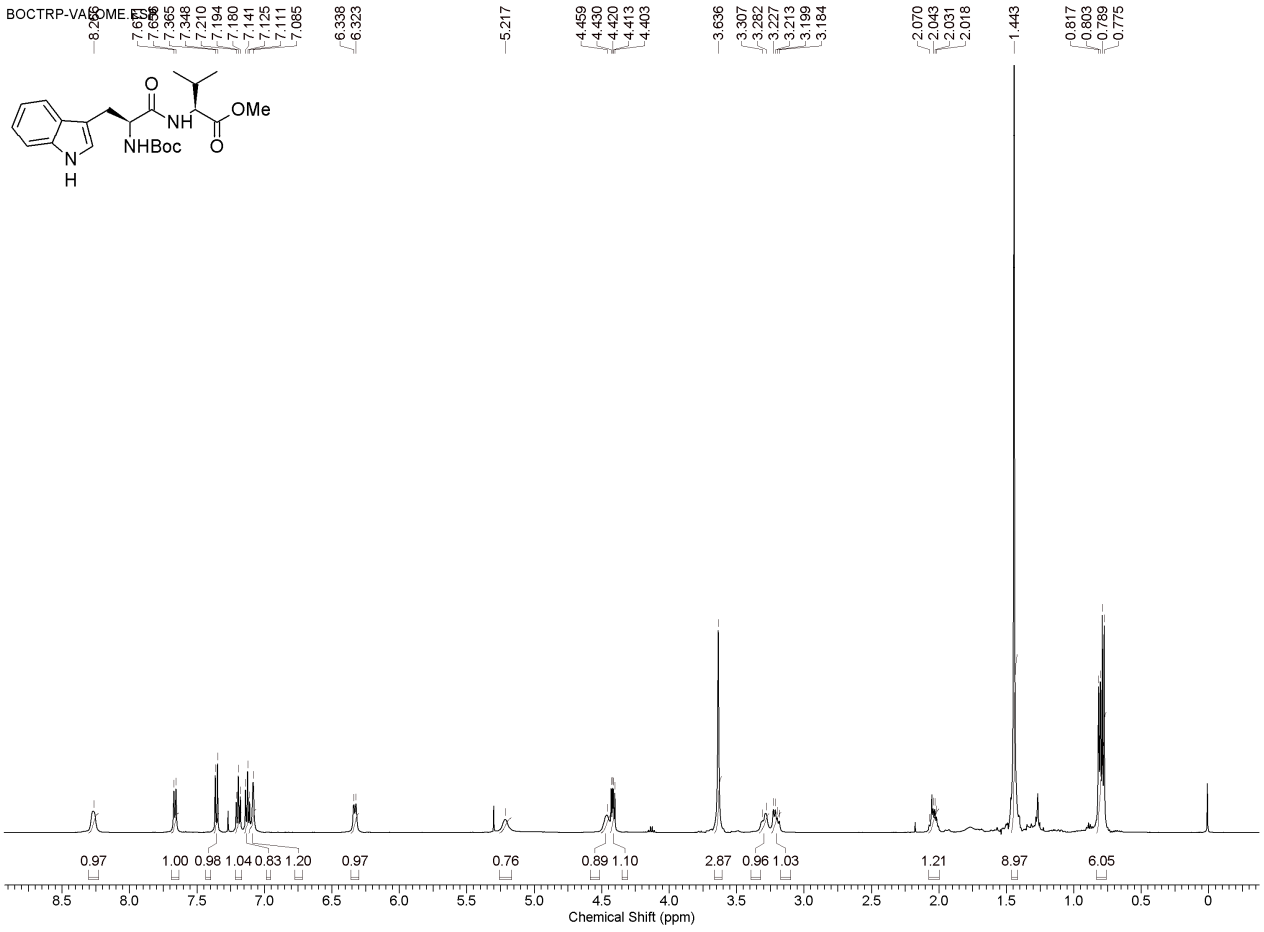
Boc-Ser(OBu^t)-Leu-OMe (4)



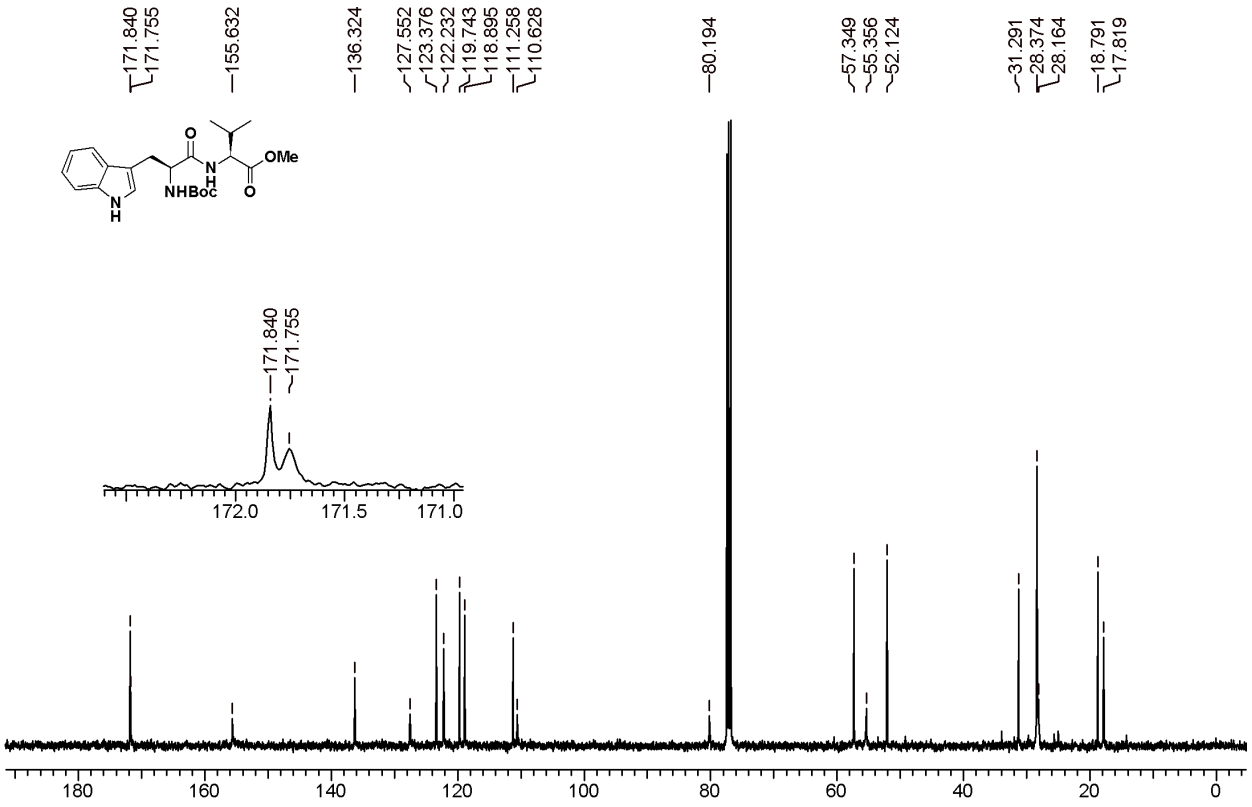
Boc-Ser(OBu^t)-Leu-OMe (4)



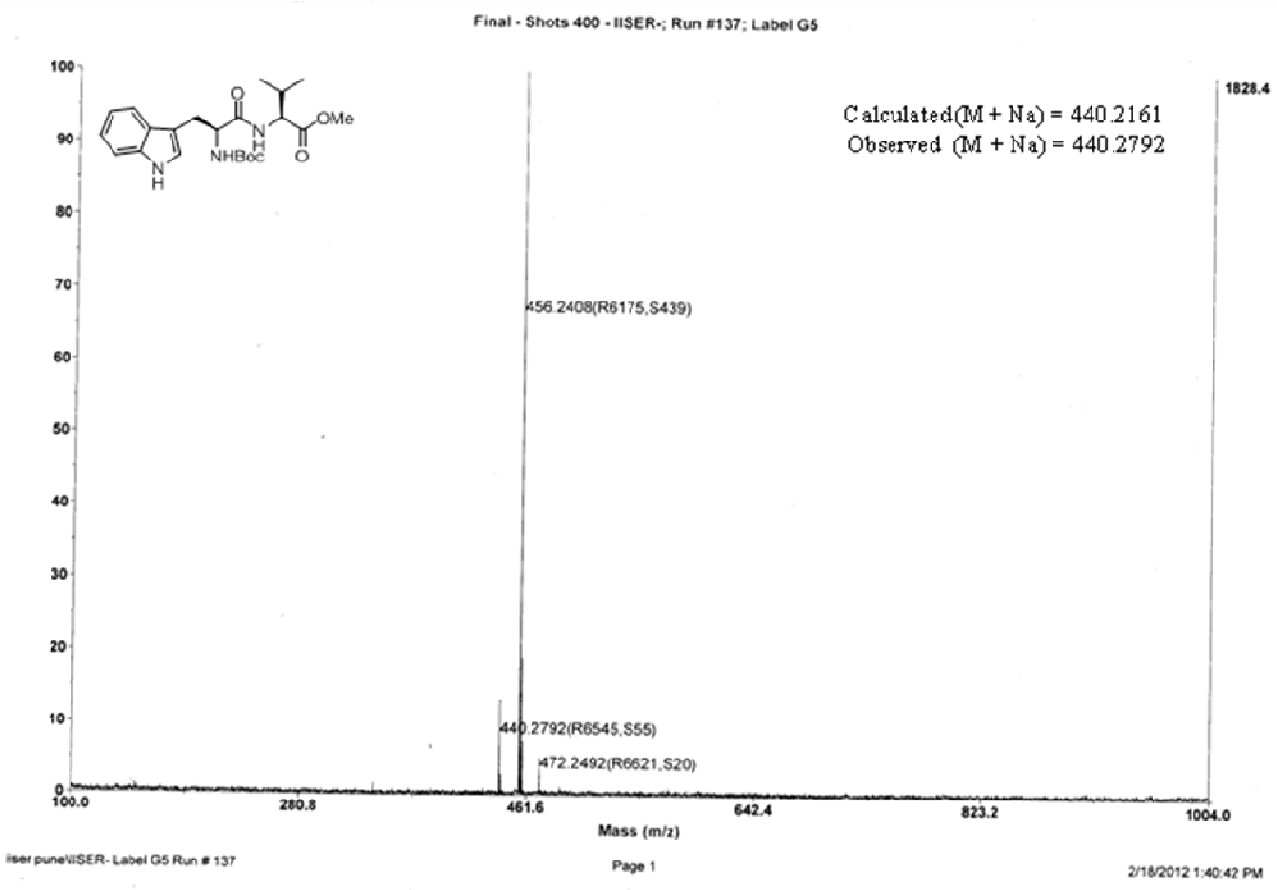
Boc-Trp-Val-OMe (5)



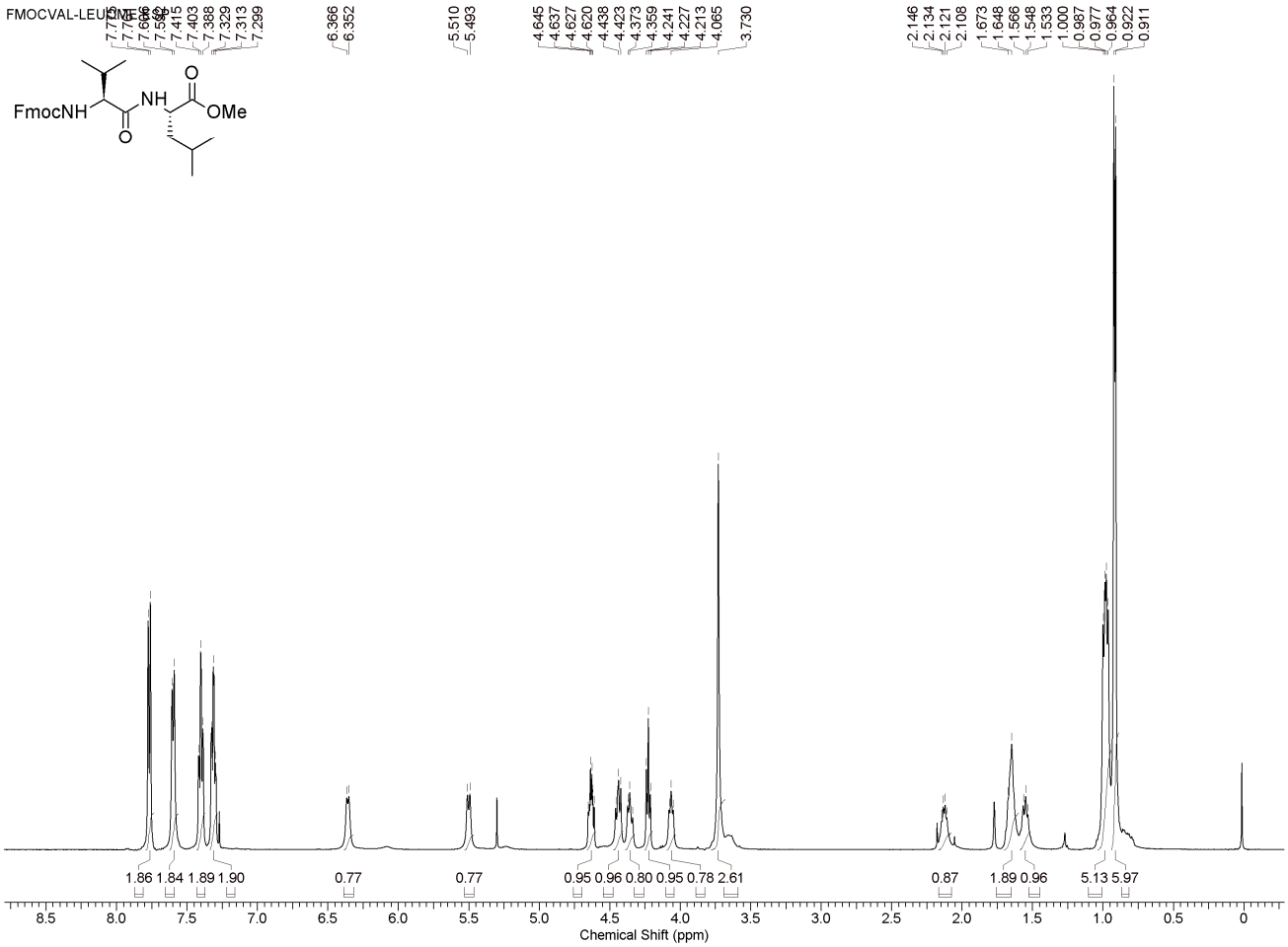
Boc-Trp -Val-OMe (5)



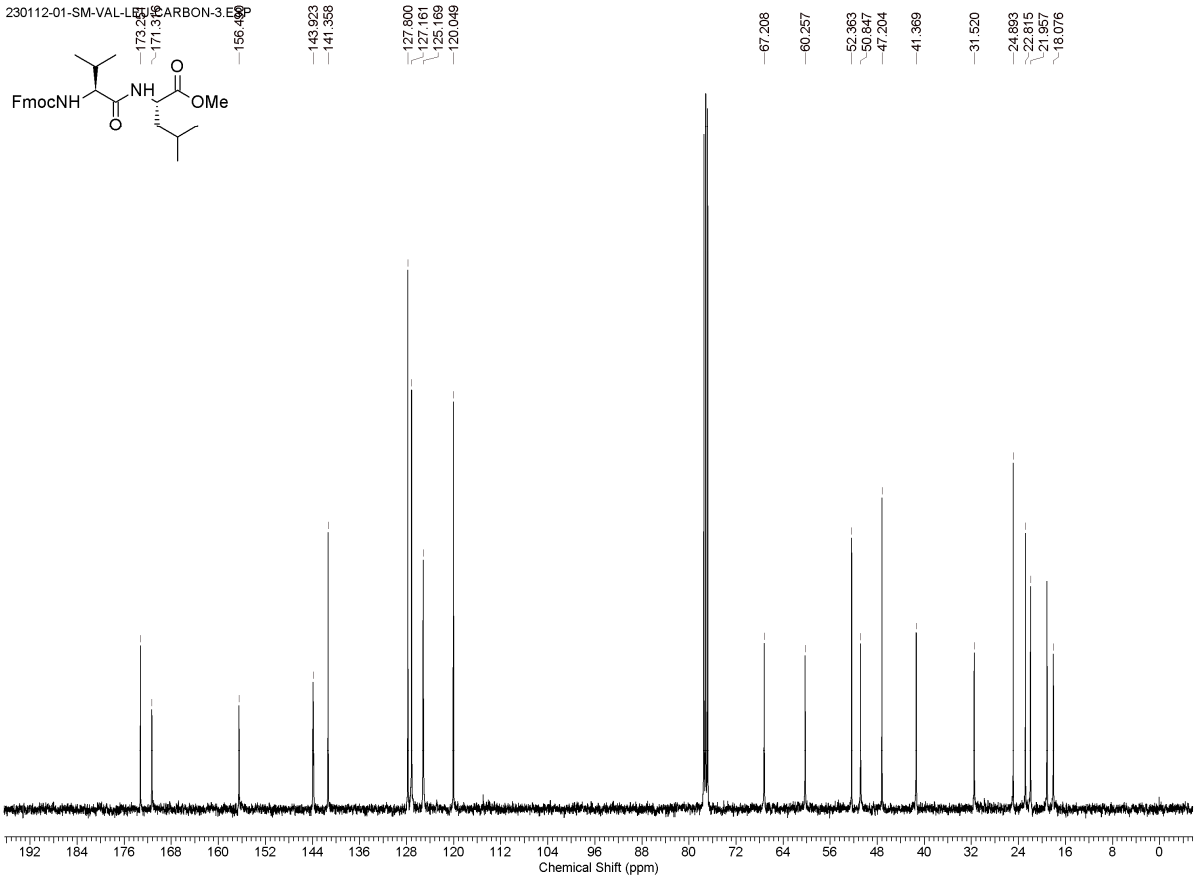
Boc-Trp-Val-OMe (5)



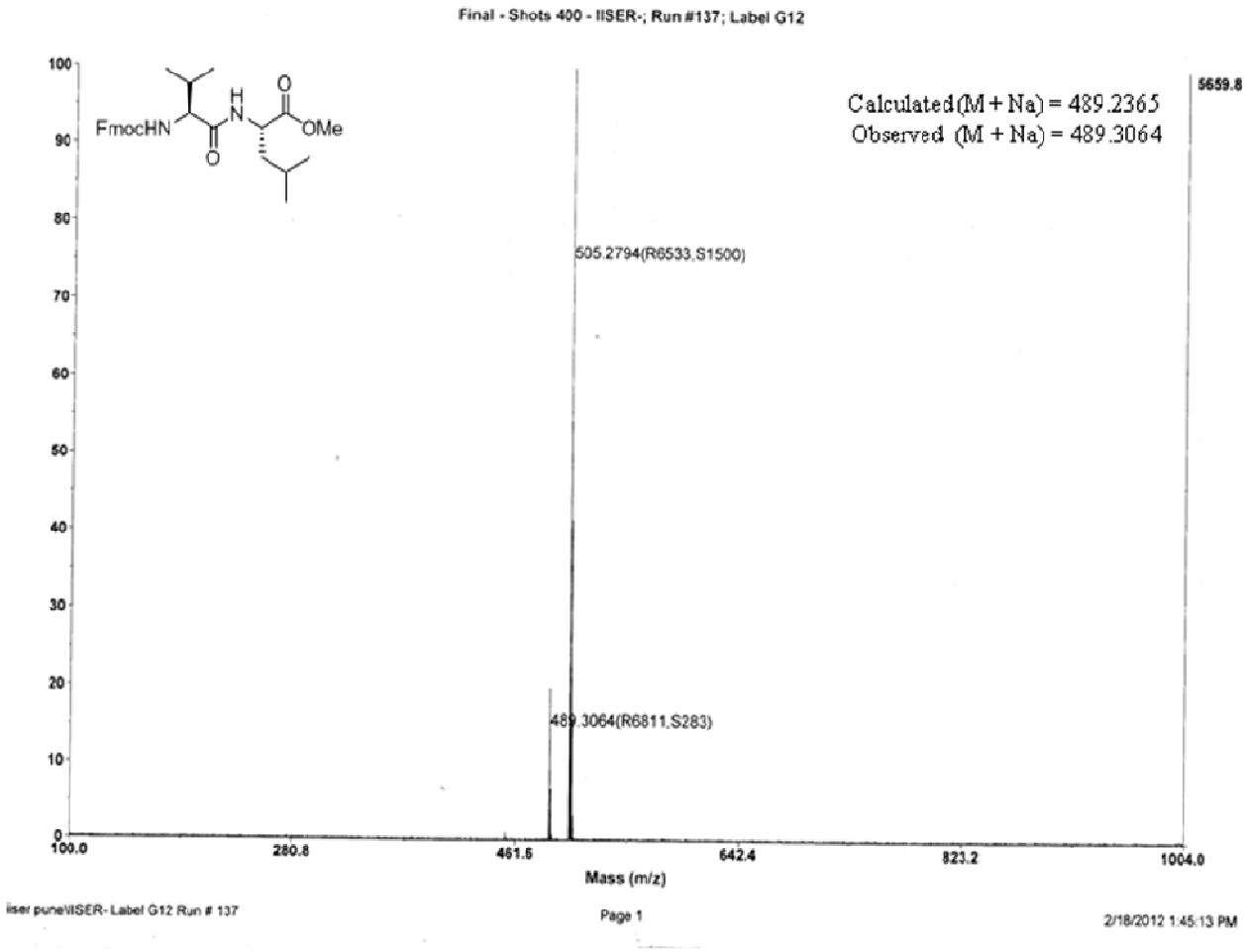
Fmoc-Val-Leu-OMe (6)



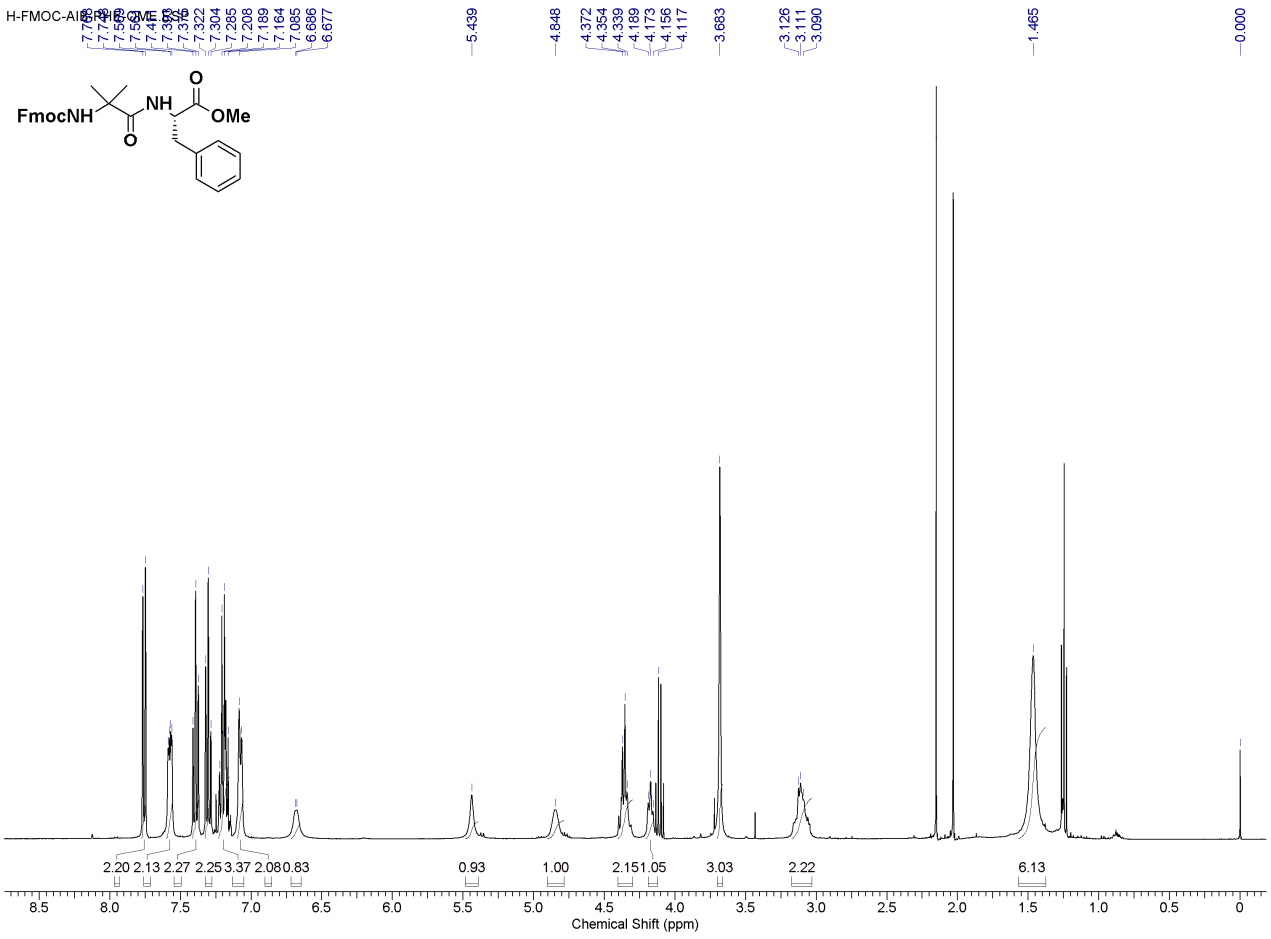
Fmoc-Val-Leu-OMe (6)



Fmoc-Val-Leu-OMe (6)



Fmoc-Aib-Phe-OMe (7)



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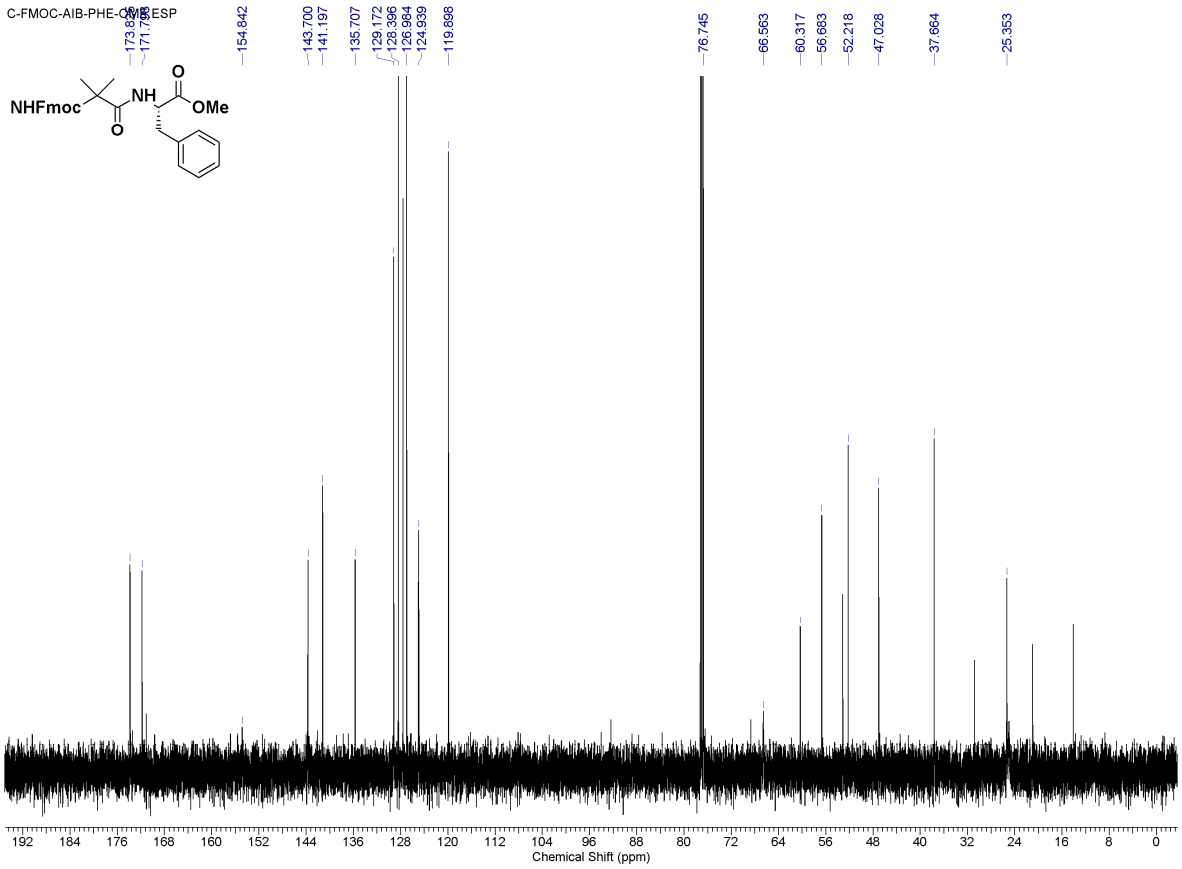

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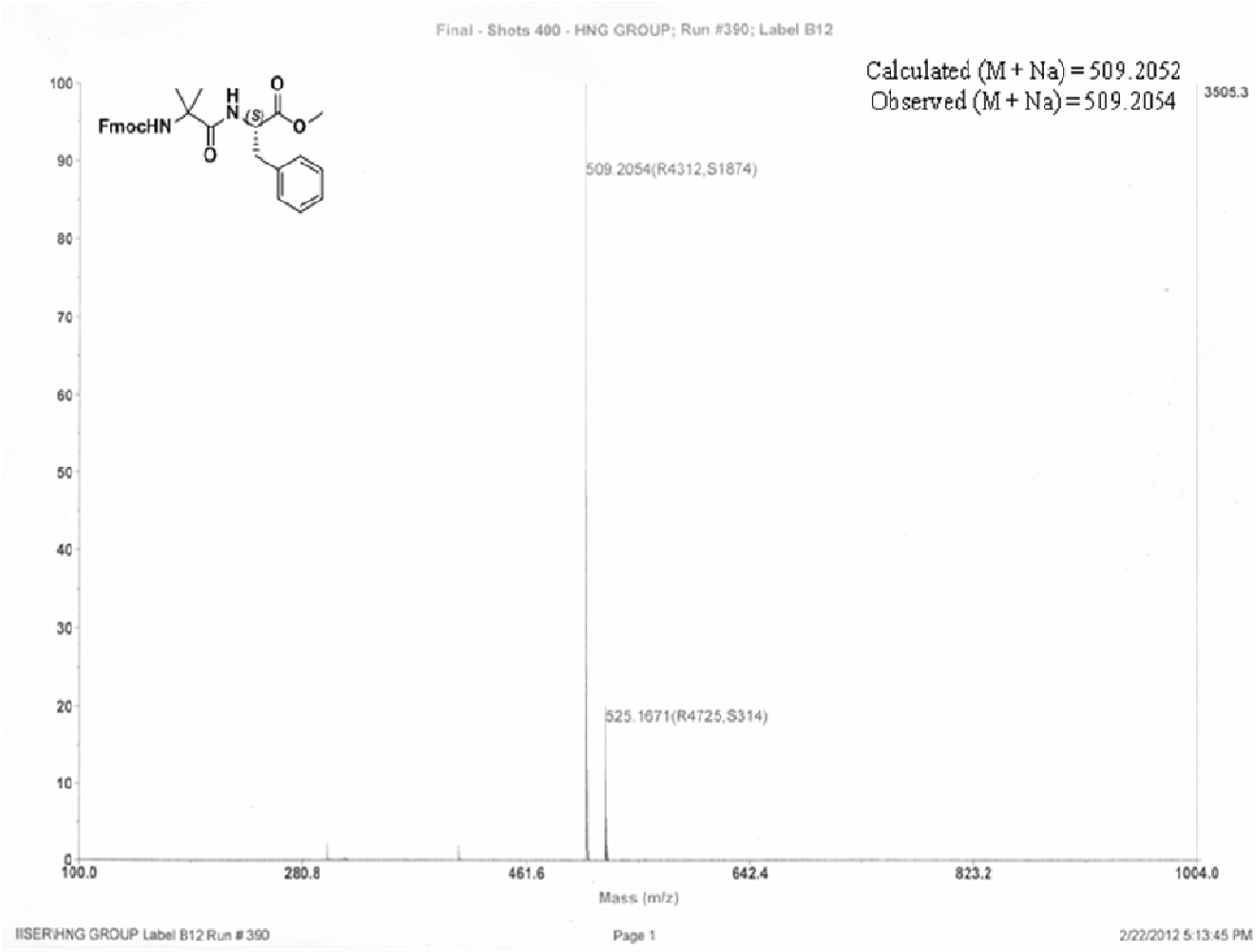
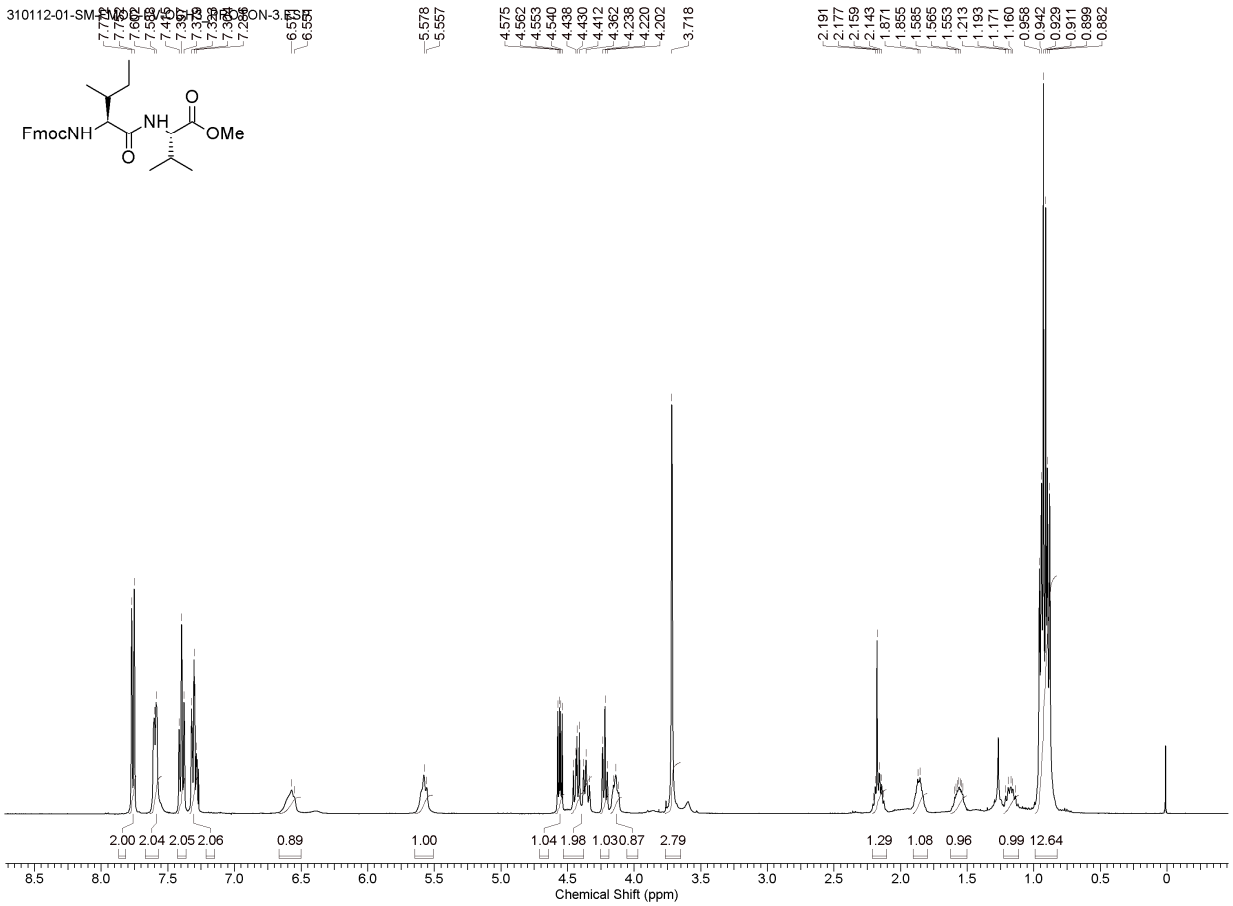


Fmoc-Ile-Val-OMe (8)



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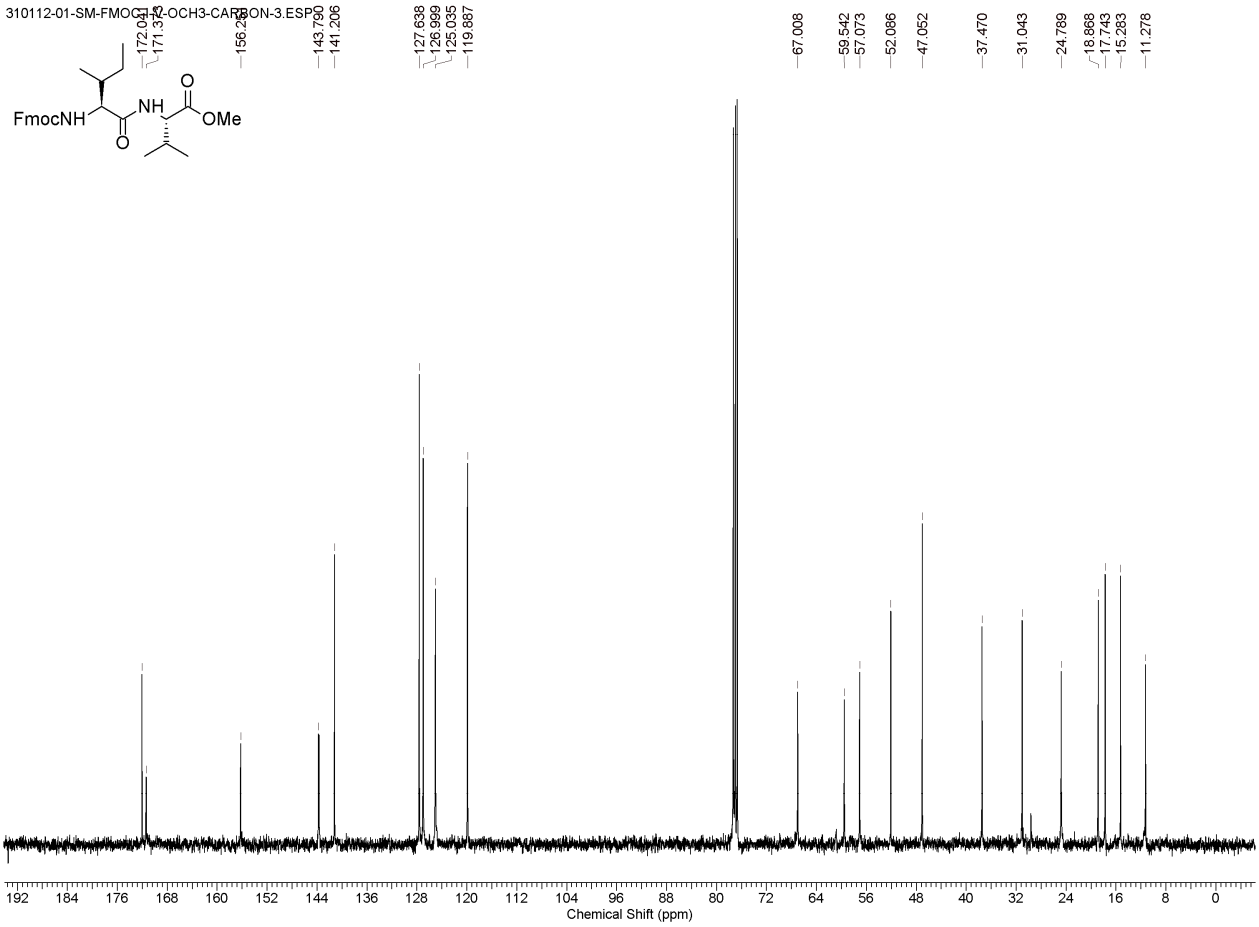

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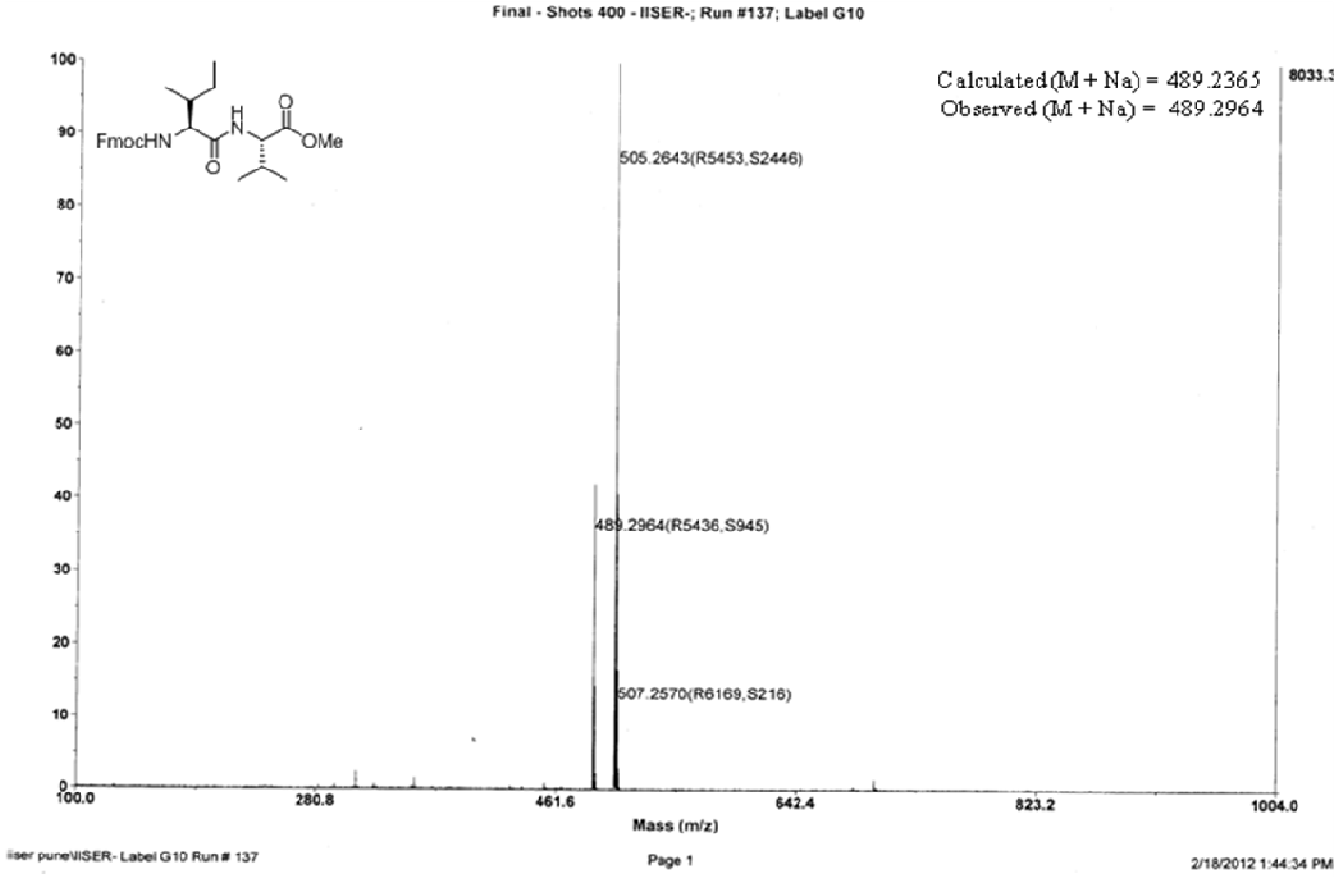
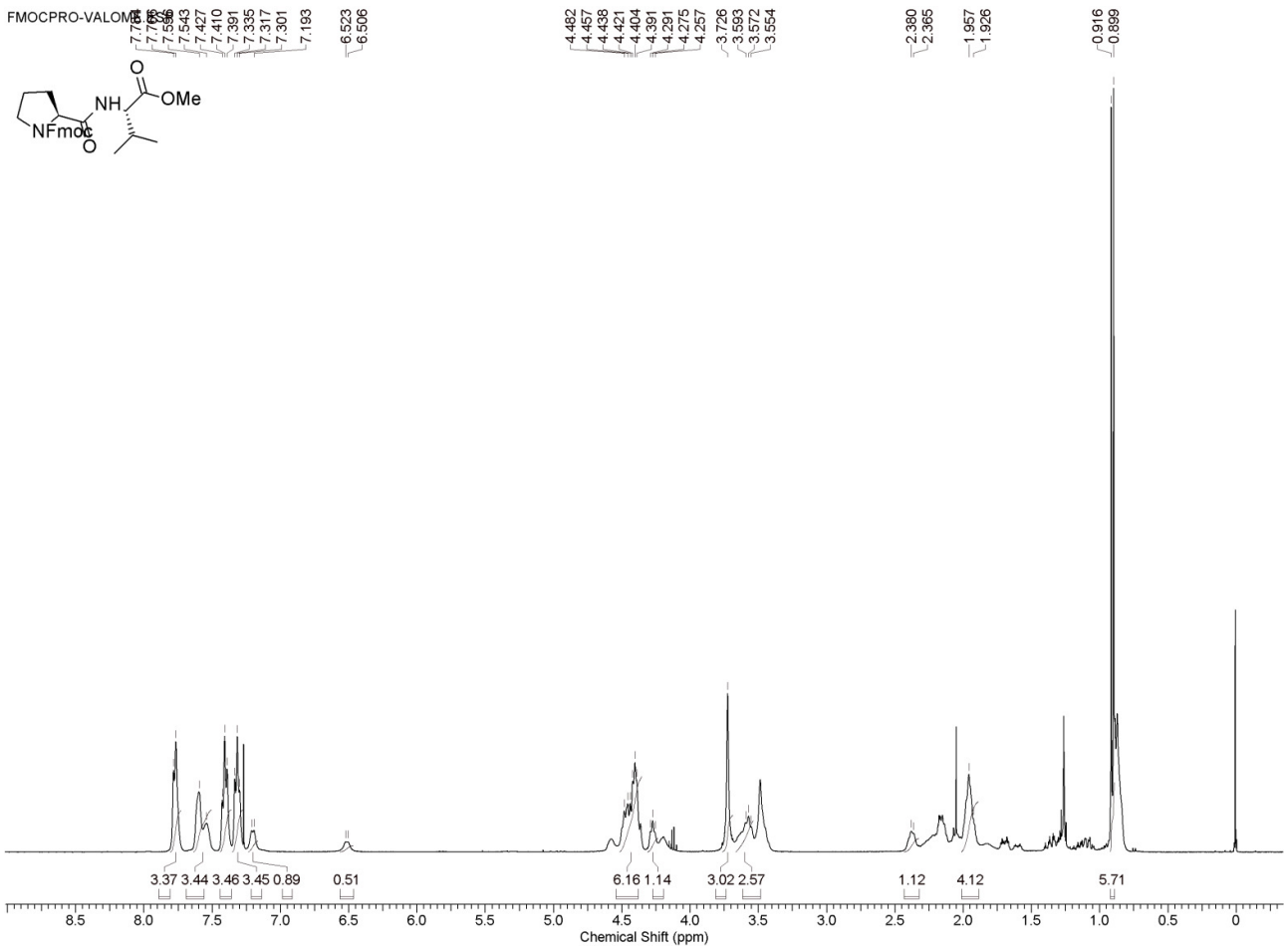


Fmoc-Pro-Val-OMe (9)



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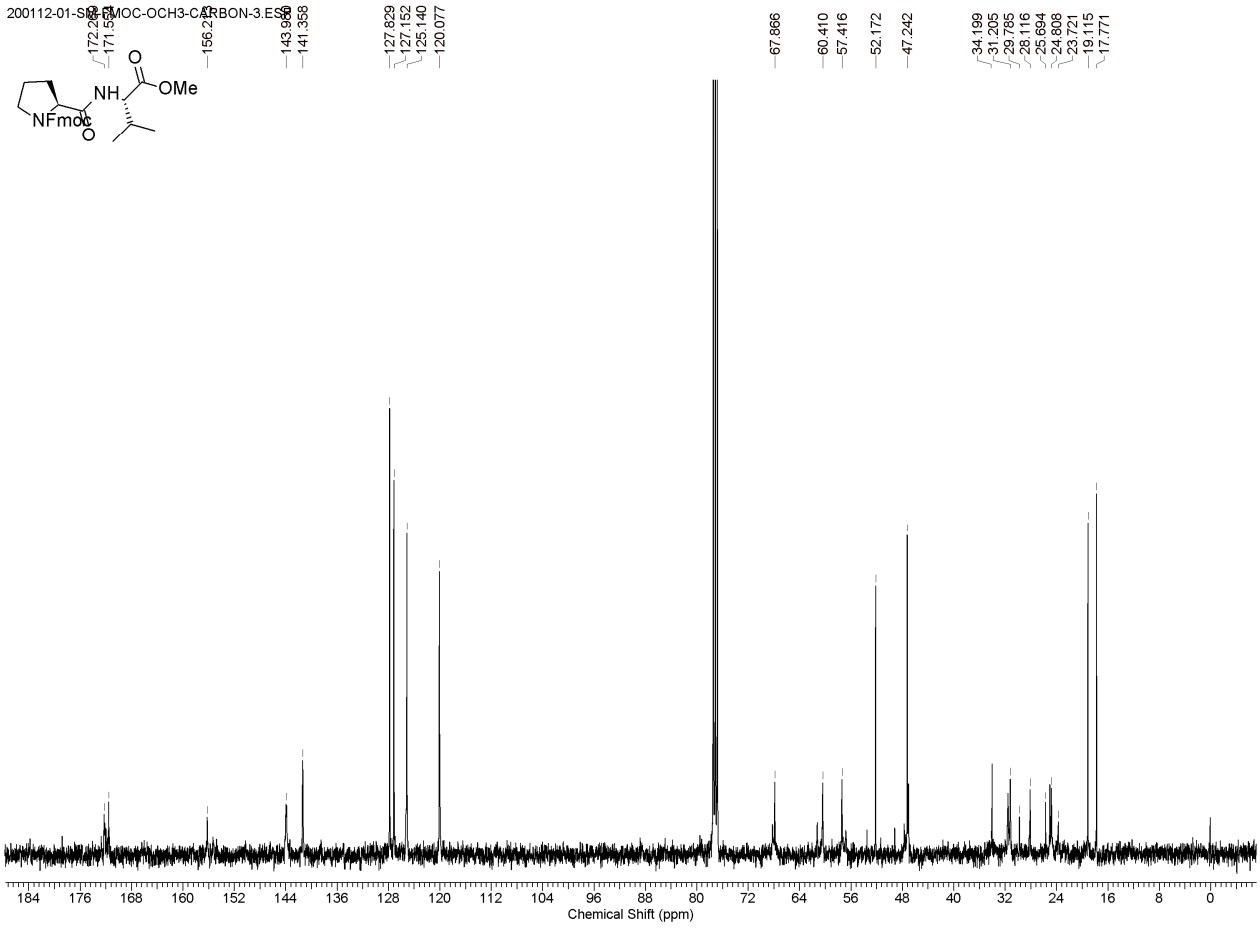

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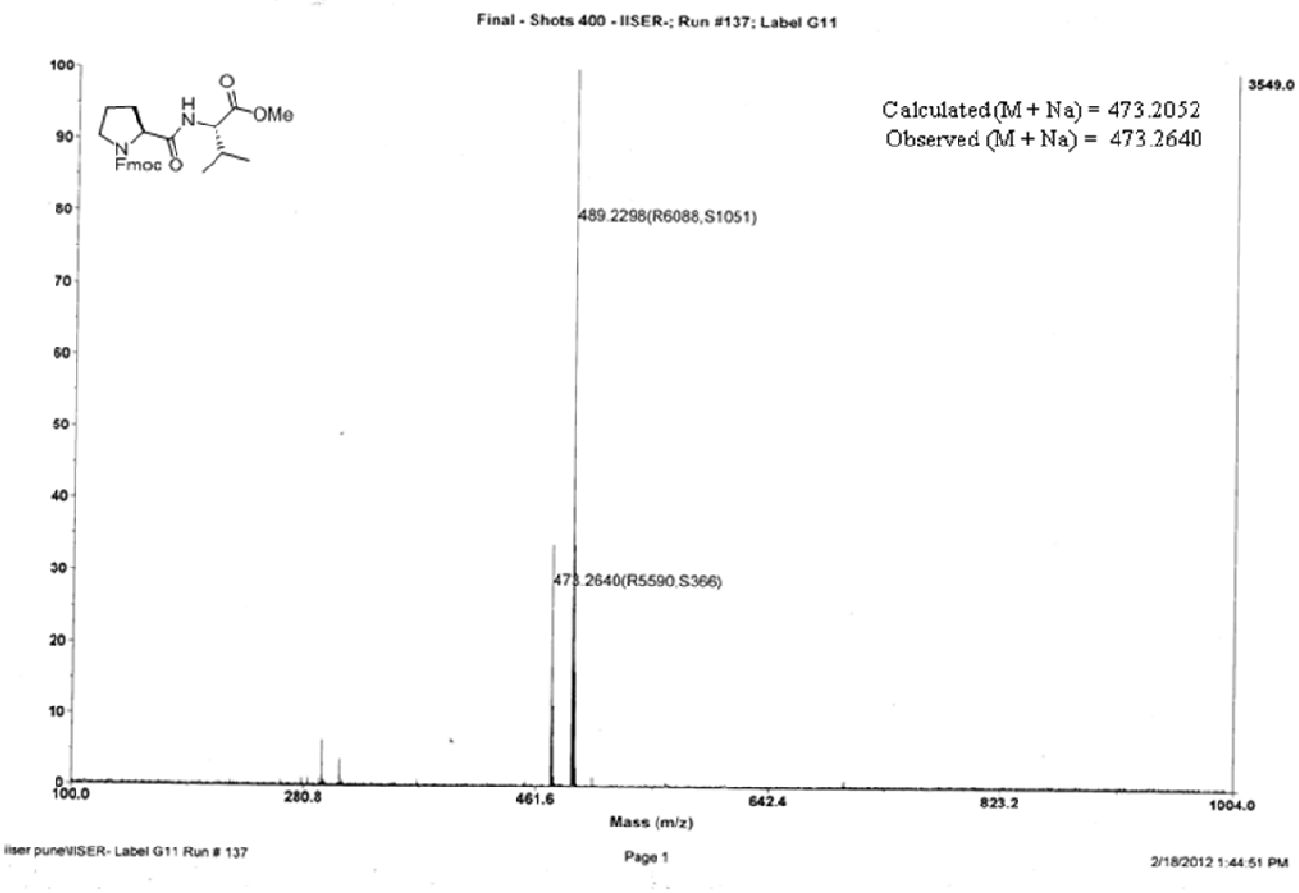
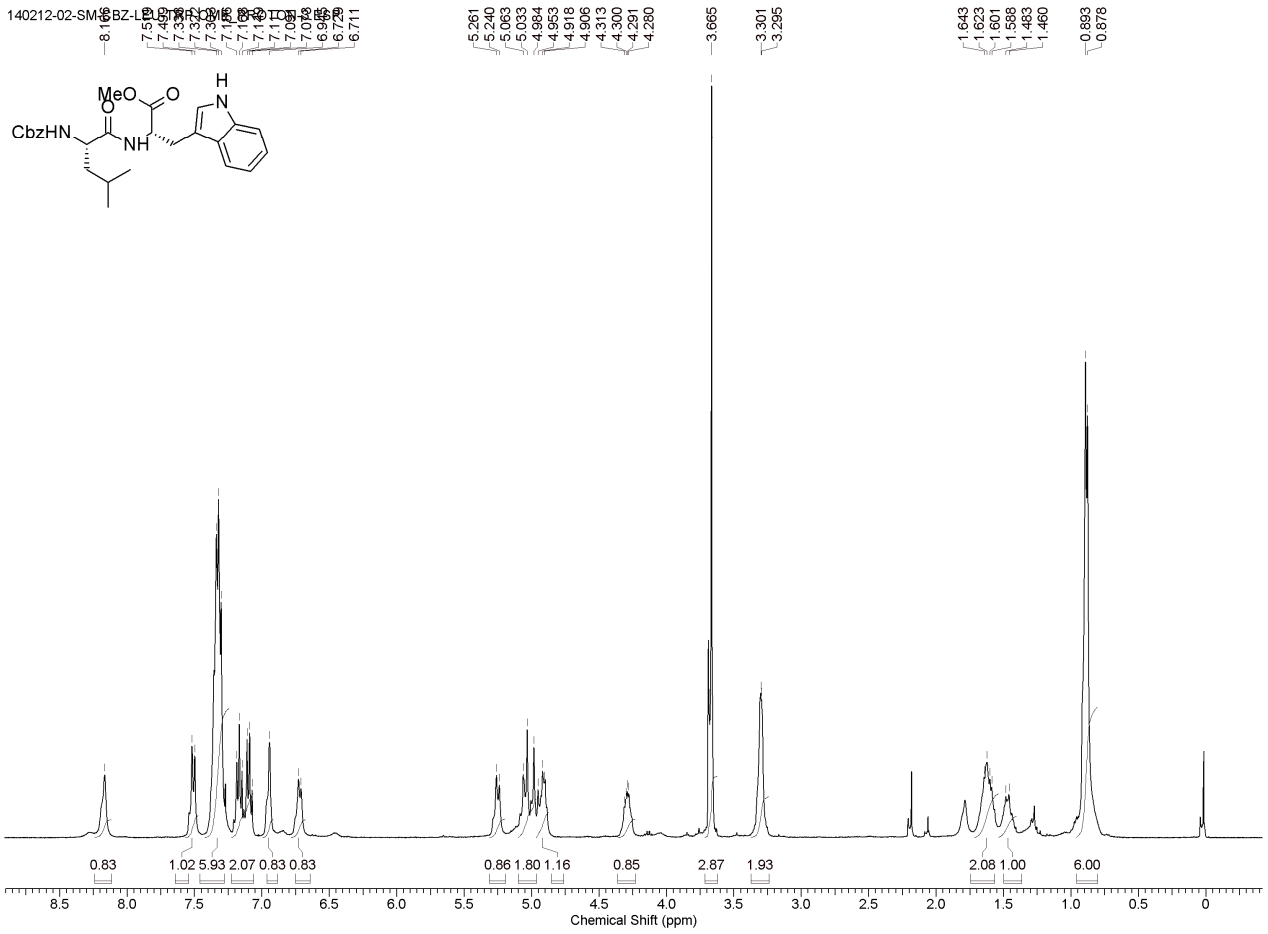


Cbz-Leu-Trp-OMe (10)



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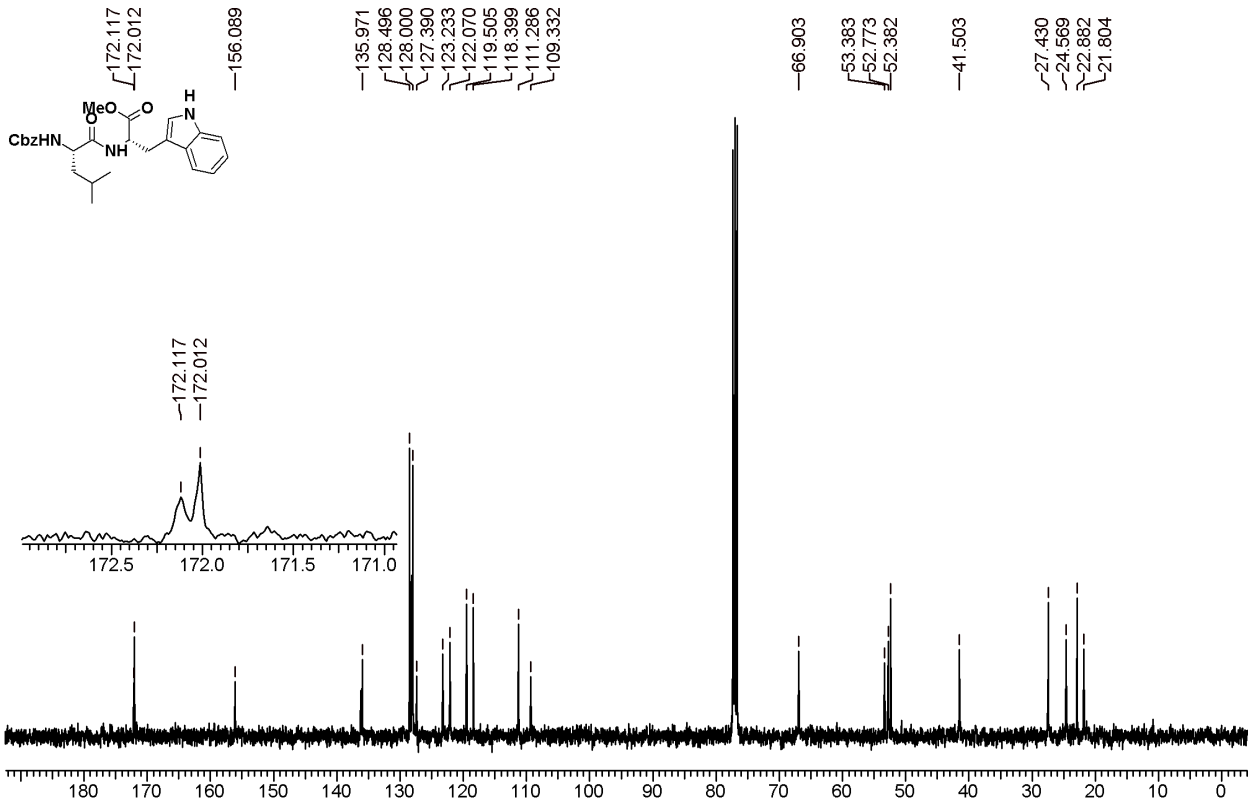
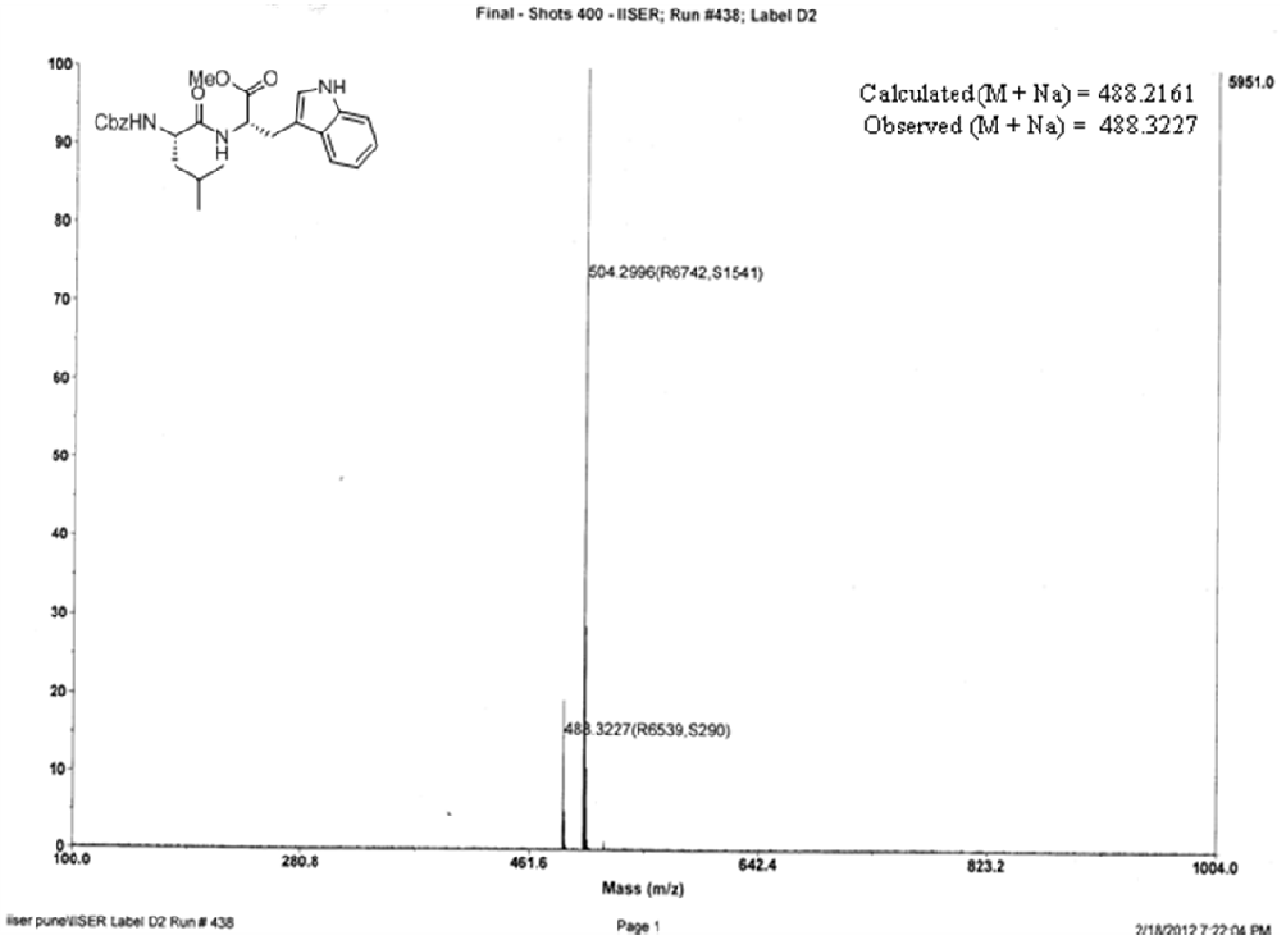
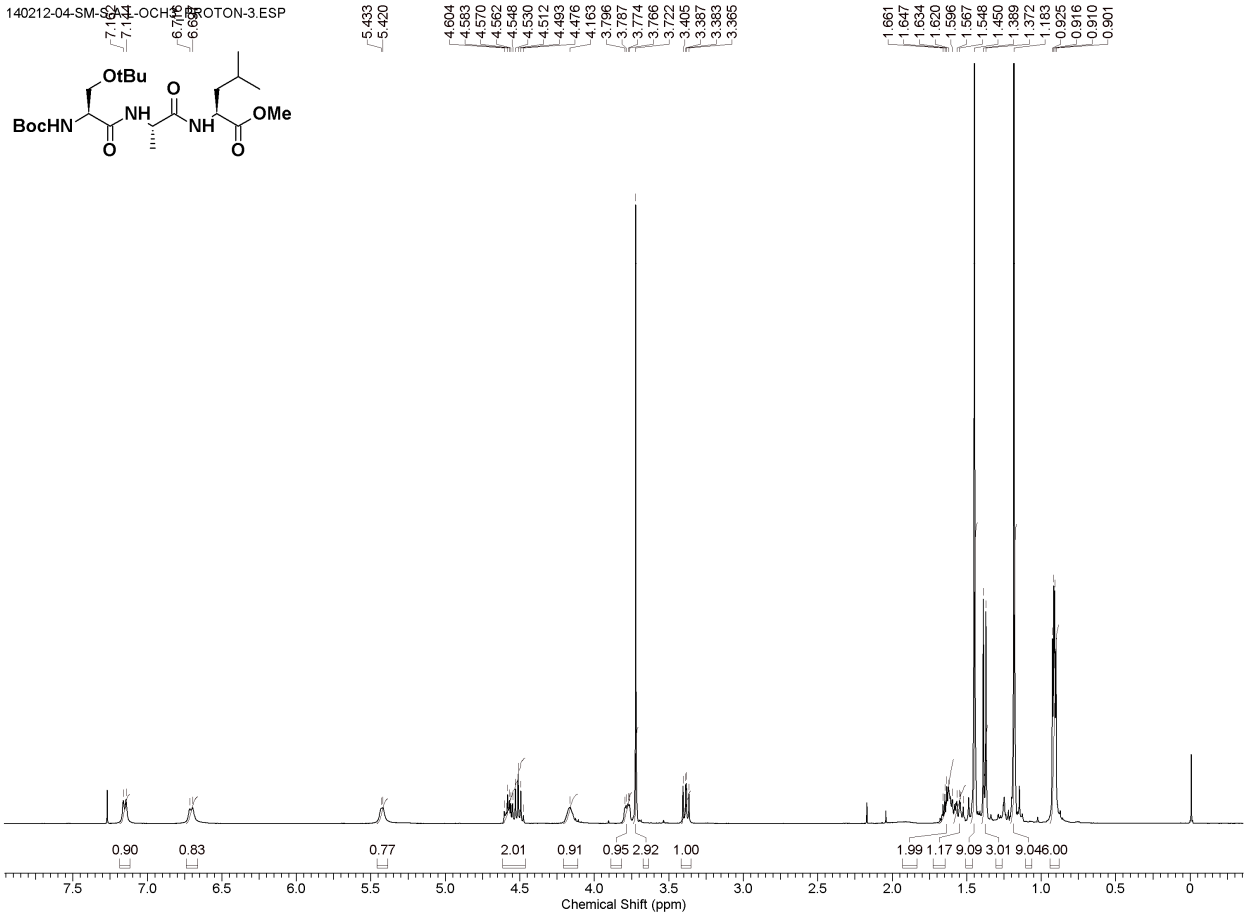


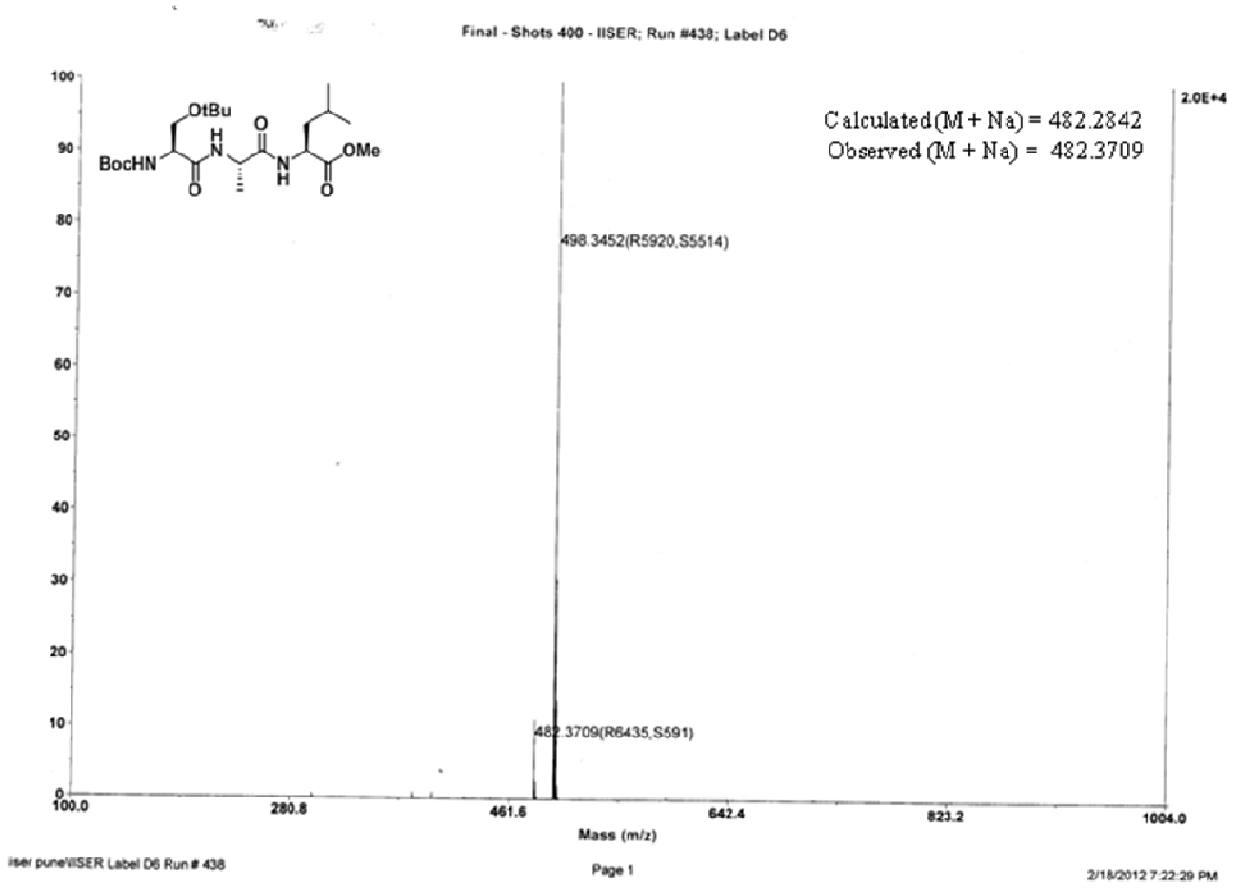
Cbz-Leu-Trp-OMe (10)



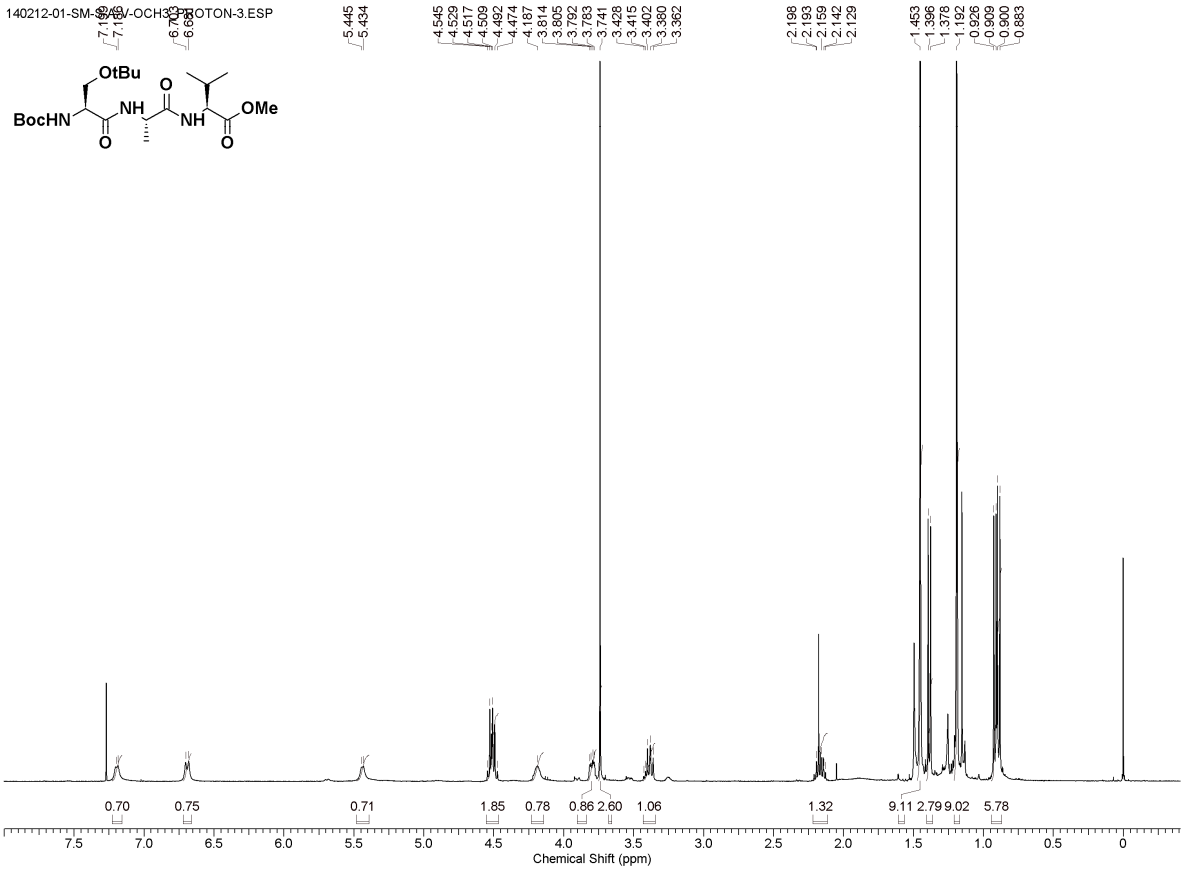
Boc-Ser(OBu^t)-Ala-Leu-OMe (11)



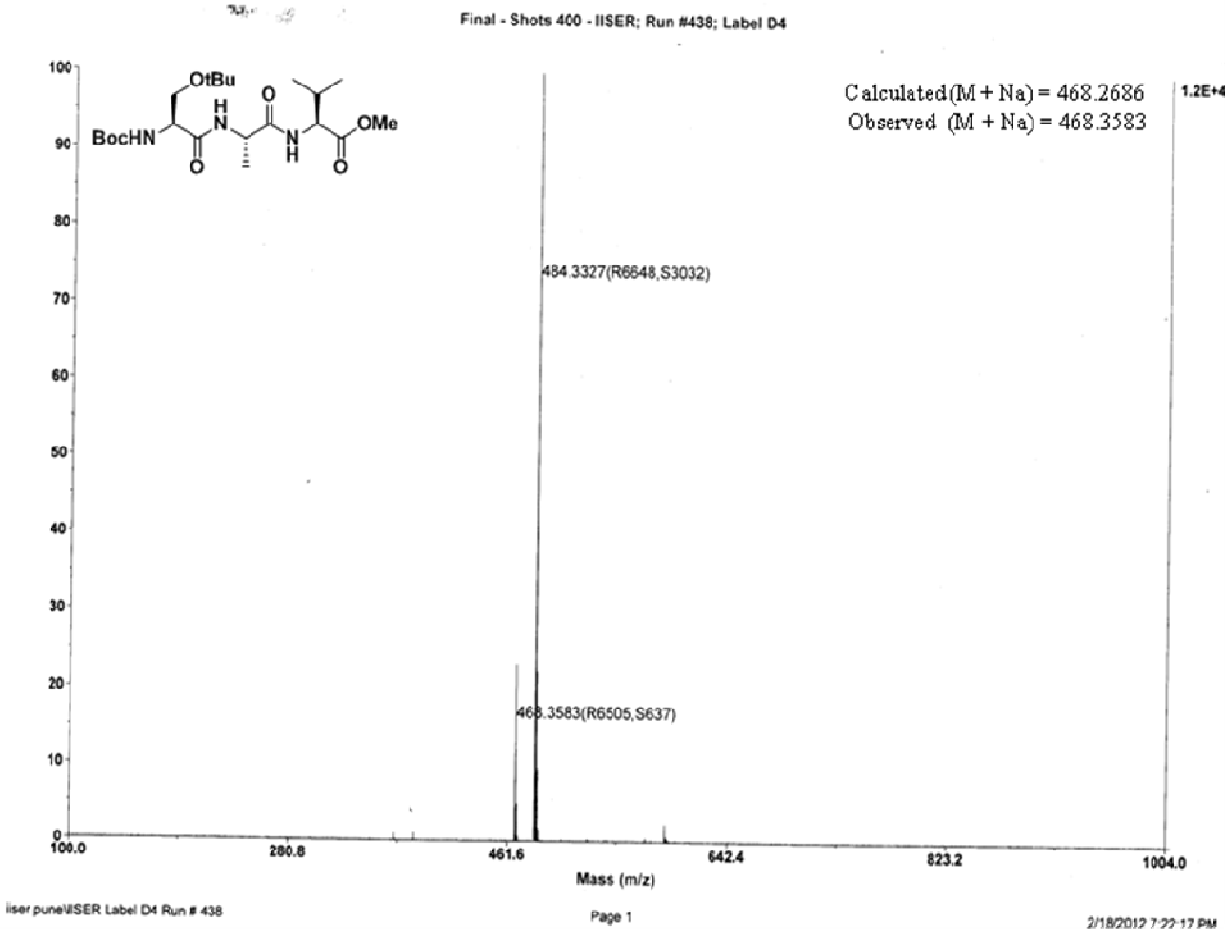
Boc-Ser(OBu^t)-Ala-Leu-OMe (11)



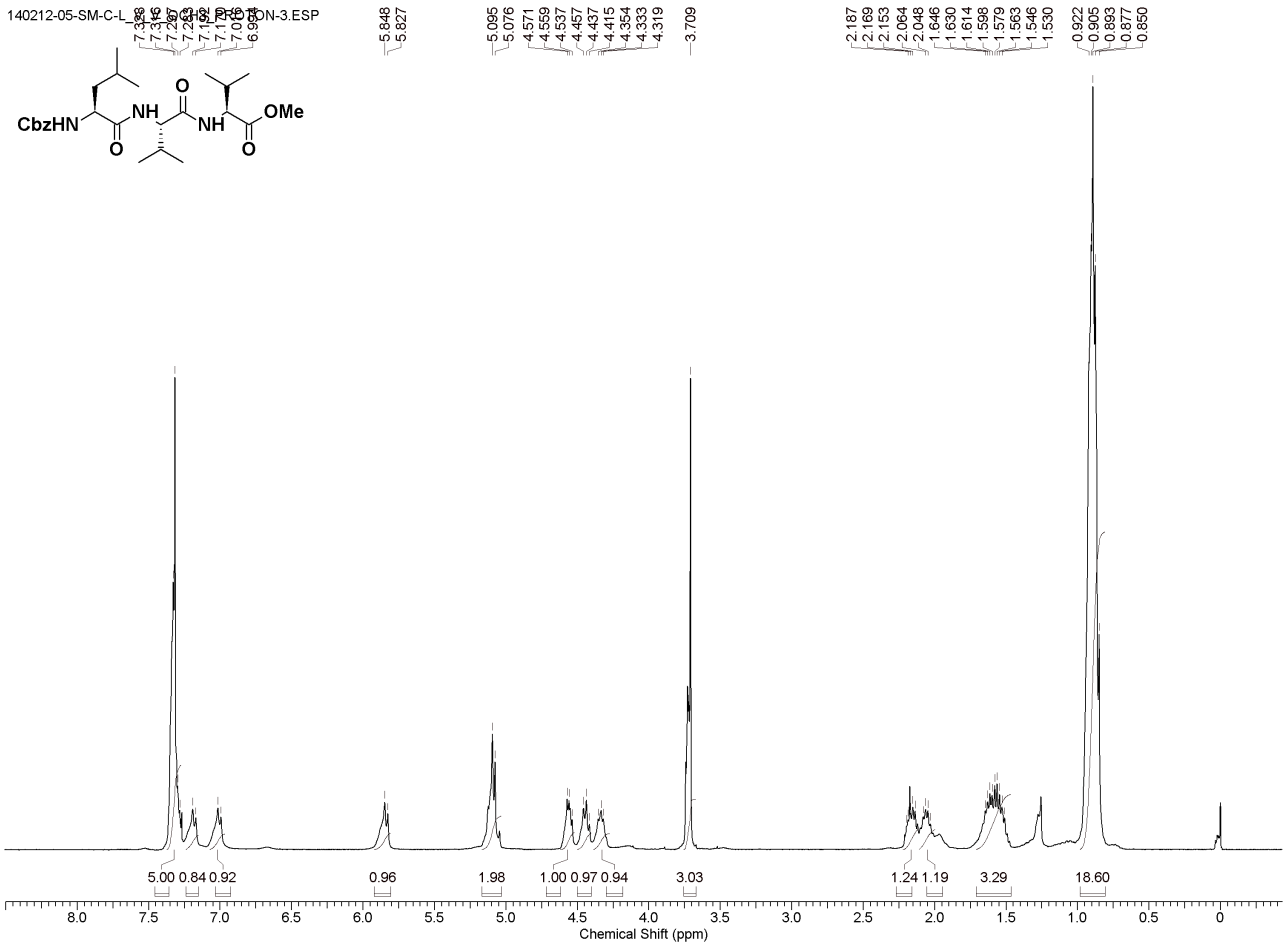
Boc-Ser(OBu^t)-Ala-Val-OMe (12)



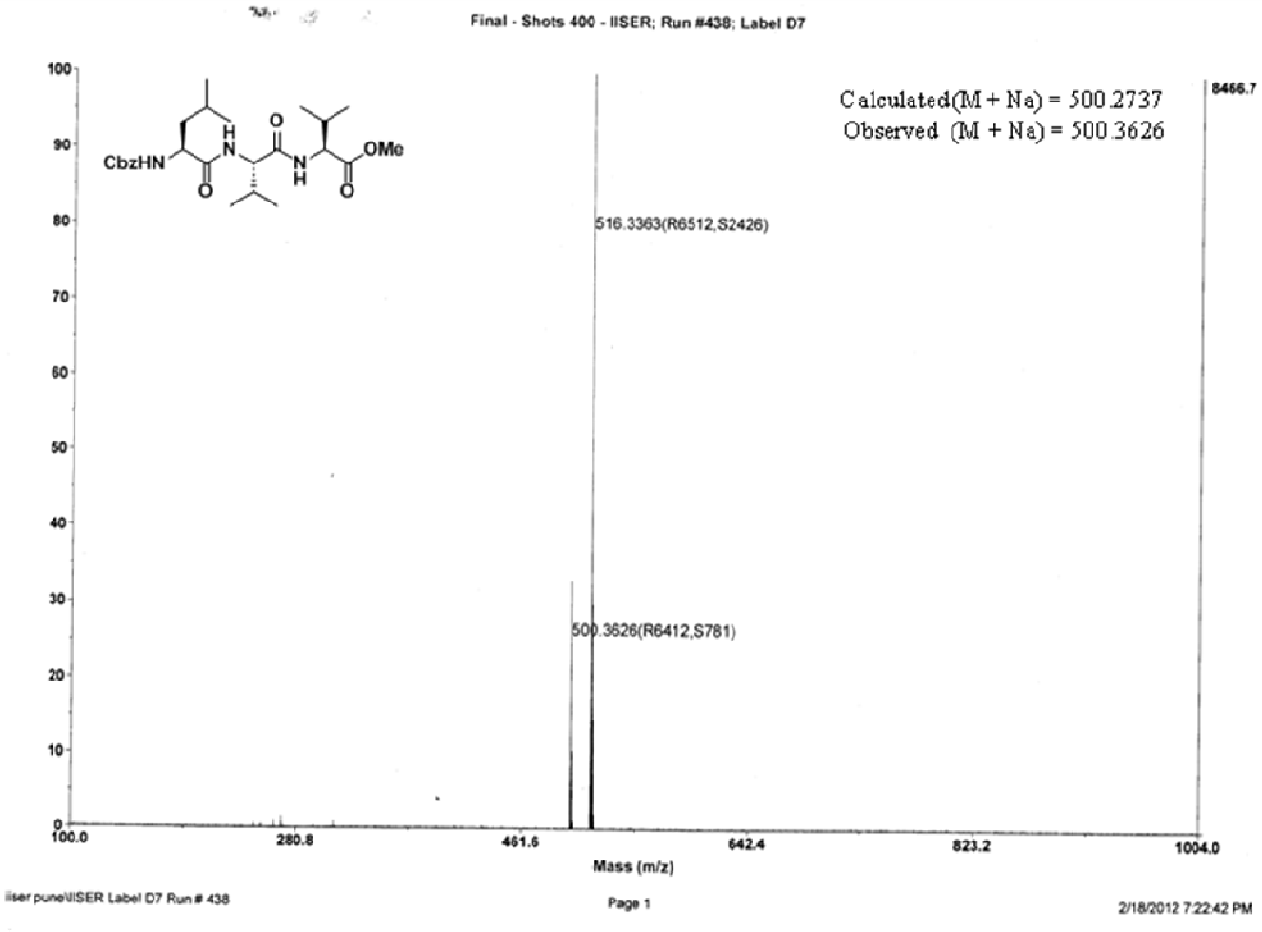
Boc-Ser(OBu^t)-Ala-Val-OMe (12)



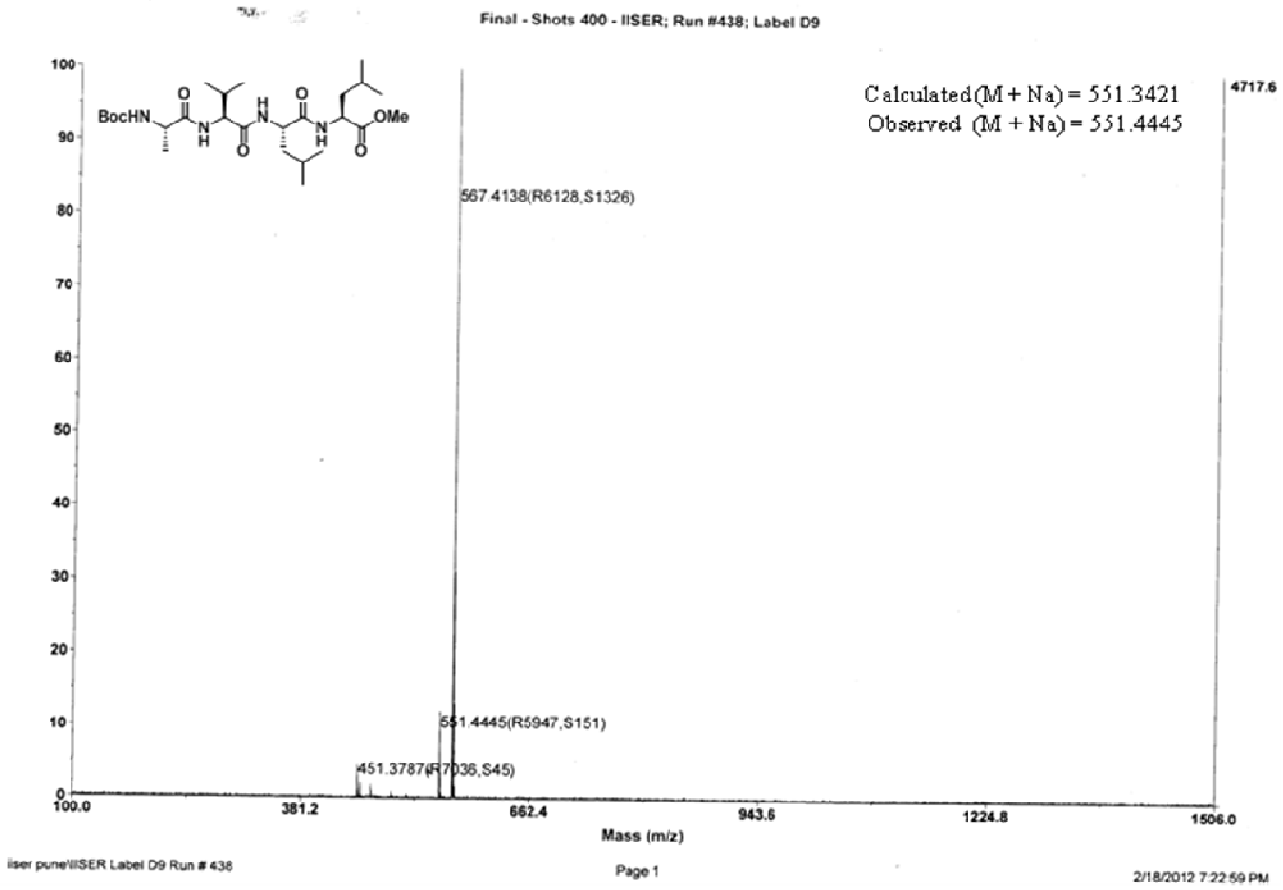
Cbz-Leu-Val-Val-OMe (13)



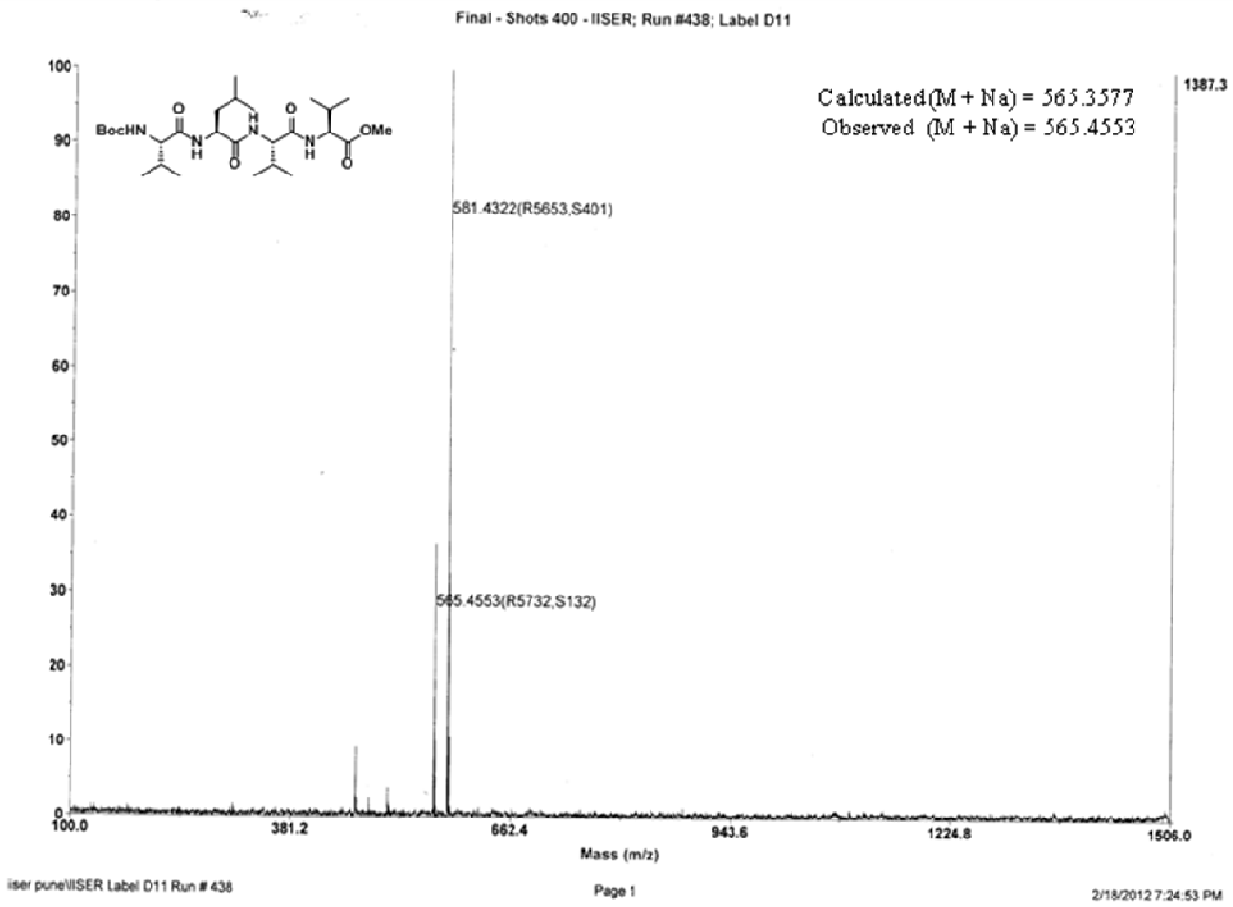
Cbz-Leu-Val-Val-OMe (13)



Boc-Ala-Val-Leu-Leu-OMe (14)



Boc-Val-Leu-Val-Val-OMe (15)



Boc-Aib-Ala-dgL-dgL-OEt (16)