Supporting Information

Site-Selective Aqueous C–H Acylation of Tyrosine-Containing Oligopeptides with Aldehydes

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1.-General Considerations

Reagents. Commercially available materials were used without further purification. Palladium acetate was purchased from Fluorochem. Luperox® (*tert*-butyl hydroperoxide solution, 70 wt % in water) was purchased from Sigma-Aldrich. All the aldehydes except compound **2t** were commercially available and were used without further purification.

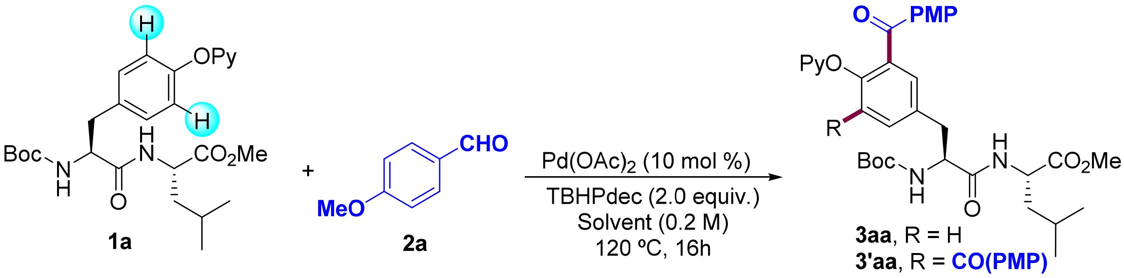
Analytical Methods. ^{1}H NMR and ^{13}C NMR spectra as well as IR, HRMS and melting points (where applicable) are included for all new compounds. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 400 MHz at 20ºC. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm), unless otherwise indicated, and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. High resolution mass spectra (HRMS) were performed by SGIker and were acquired on a LC/Q-TOF mass spectrometer equipped with an electrospray source ESI Agilent Jet Stream. Infrared spectra were recorded on a Bruker Alpha P. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). The yields reported in the manuscript correspond to isolated yields and represent an average of at least two independent runs.

2.-Optimization Details

General Procedure:

A reaction tube containing a stirring bar was charged with **1a** (0.15 mmol, 73 mg), oxidant (0.60 mmol) (if solid) and metal source (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, *p*-anisaldehyde (0.45 mmol, 55µL), oxidant (if liquid), and the corresponding solvent (0.75 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was allowed to cool to room temperature, diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude was either purified by flash chromatography (hexanes/AcOEt, 1/1) or analyzed by ^1H NMR using 1,1-diphenylethylene as internal standard. The purity of the corresponding product **3aa** was verified by ^1H NMR.

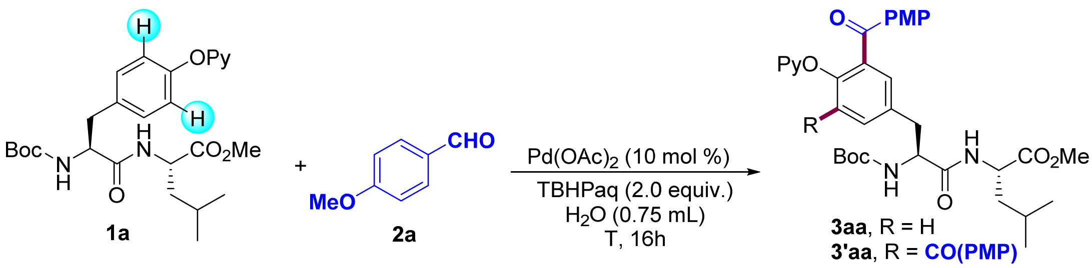
Table S1. Screening of Solvents[a]



Entry	Solvent	Yield(%)[b,c]
1	Toluene	60 (8/2)
2	MeCN	56 (87/13)
3	DMF	traces
4	DMA	traces
5	1,4-Dioxane	traces
6	PhCl	66 (75/25)
7	H_2O	46 (85/15)
8	HFIP	traces

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHP in decane (2.0 equiv.), solvent (0.75 mL), Ar, 16h at 120 °C. [b] Yield of isolated product after column chromatography. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**.

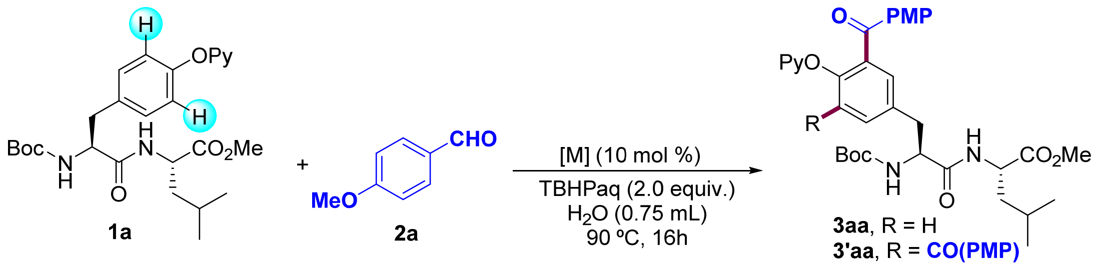
Table S2. Screening of Temperature[a]



Entry	T (°C)	Yield(%)[b,c]
1	rt	no reaction
2	80	56 (95:5)
3	90	65 (93:7)
4	100	69 (88:12)
5	110	70 (88:12)
6	120	74 (87:13)

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHPaq (2.0 equiv.), H_2O (0.75 mL), Ar, 16 h. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**.

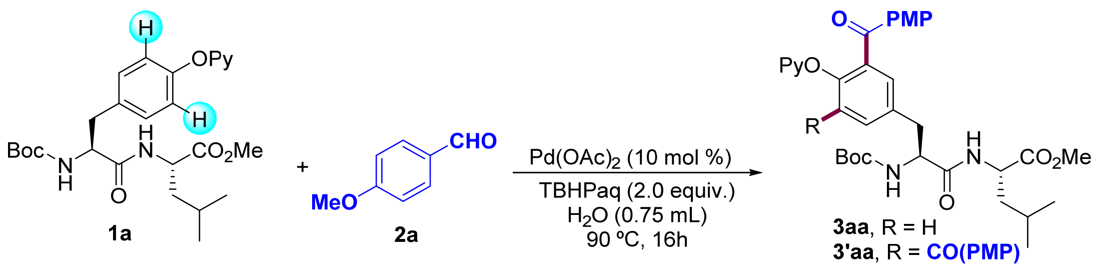
Table S3. Screening of Metal Catalyst[a]



Entry	[M]	Yield(%)[b,c]
1	$Pd(OAc)_2$	65 (93:7)
2	$PdCl_2(MeCN)_2$	15 (100:0)
3	$Pd(TFA)_2$	29 (97:3)
4	$PdCl_2$	23 (95:5)
5	PdI_2	0
6	$PdCl_2(PPh_3)_2$	0
7	$RuCl_2$(*p*-cymene)$_2$	0
8	$NiCl_2(PCy_3)_2$	0
9	$NiCl_2$·DME	0

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), [M] (10 mol %), TBHPaq (2.0 equiv.), H_2O (0.75 mL), Ar, 16 h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**.

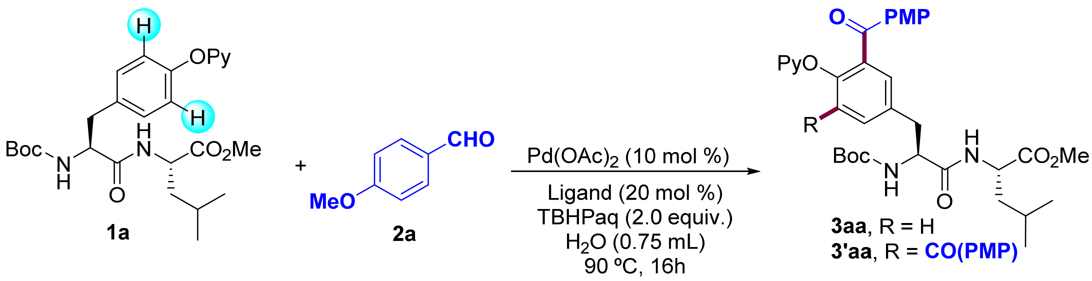
Table S4. Screening of Aldehyde Equivalents[a]

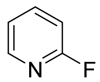
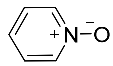


Entry	Equiv. of 2a	Yield(%)[b,c]
1	3	65 (93:7)
2	4	74 (88:12)
3	5	72 (88:12)
4	6	71 (89:11)

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), [Pd] (10 mol %), TBHPaq (2.0 equiv.), H_2O (0.75 mL), Ar, 16 h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa.**

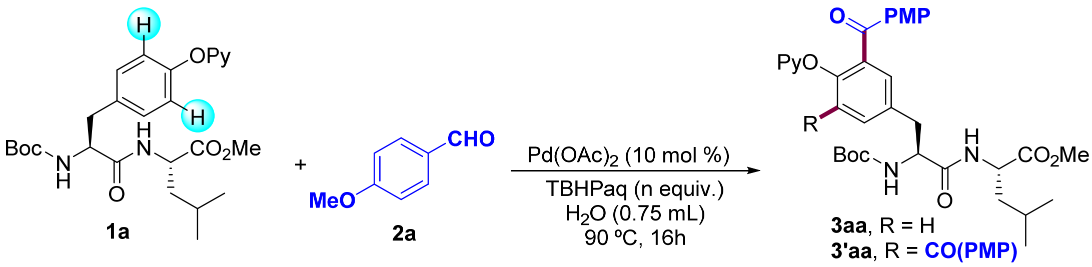
Table S5. Screening of Ligands[a]



none		XPhos	PPh_3	1,10-Phe	
	L1	**L2**	**L3**	**L4**	**L5**
65 (93:7)[b,c]	67 (88:12)[b,c]	63 (9:1)[b,c]	59 (92:8)[b,c]	0	60 (92:8)[b,c]

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHPaq (2.0 equiv.), Ligand (20 mol %), TBHPaq (2.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**.

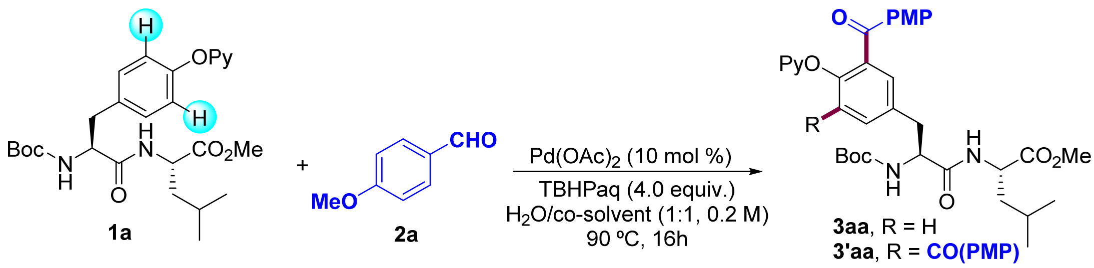
Table S6. Screening of Oxidant Equivalents[a]



Entry	Equiv. of $TBHP_{aq}$	Yield(%)[b,c]
1	2	65 (93:7)
2	3	75 (82:18)
3	4	78 (8:2)[d]

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHPaq (n equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**. [d] Yield of isolated product after column chromatography.

Table S7. Screening of Co-Solvents[a]



Entry	Co-solvent	Yield(%)[b,c]
1	none	78 (8:2)[d]
2	^{t}BuOH	37 (96:4)
3	THF	14 (100:0)
4	MeCN	18 (100:0)

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (4.0 equiv.), H_2O (0.4 mL), co-solvent (0.4 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of mono- and diacylated product **3aa**:**3'aa**. [d] Yield of isolated product after column chromatography.

Table S8. Unsuitable substrates

Tyr-containing Peptides

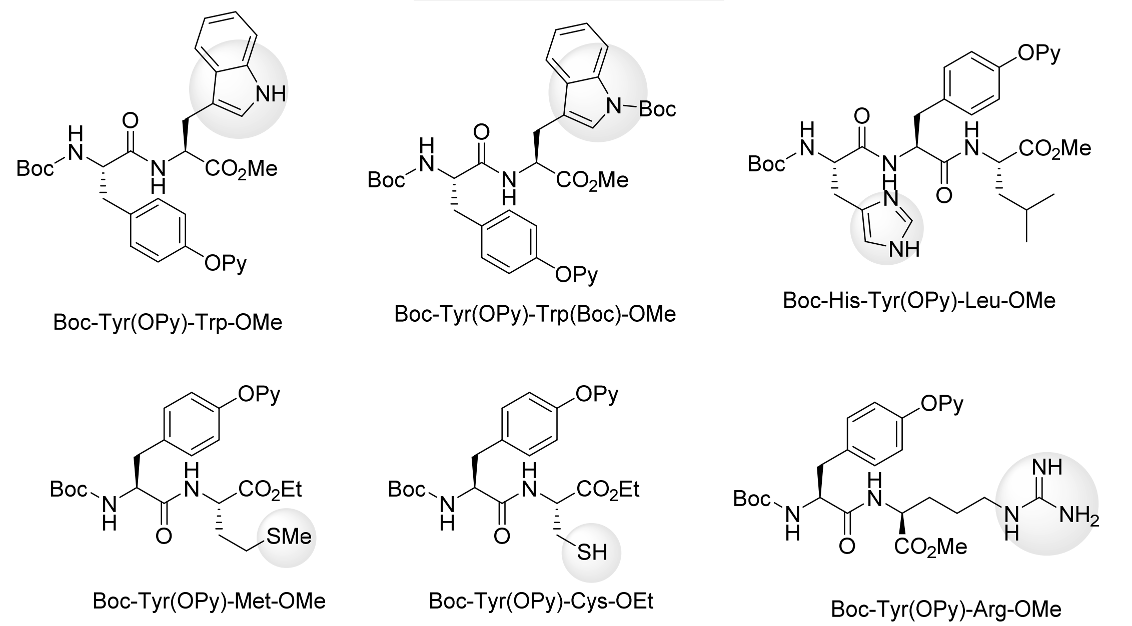
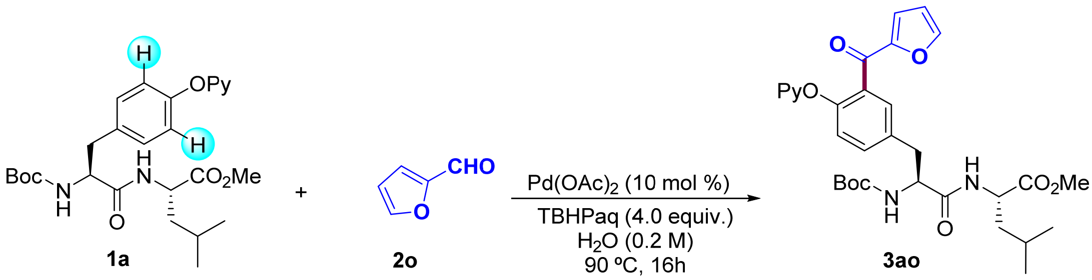


Table S9. Screening with aldehyde 2o

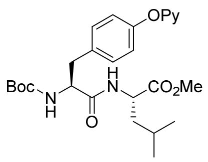


Entry	Variation from the standard conditions	Yield(%)[b,c]
1	none	traces
2	toluene as solvent	48
3	toluene as solvent and PivOH (1.0 equiv.) as additive	31
4	toluene as solvent and XPhos (20 mol %) as additive	35
5	toluene as solvent at 120 ºC	27
6	toluene as solvent at 100 ºC	48
7	toluene as solvent at 100 ºC with 5.0 equiv. of **2o**	55

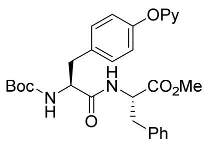
[a]Reaction conditions: **1a** (0.15 mmol), **2o** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHPaq (4.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] Yield of isolated product after column chromatography.

3.-Preparation of the Starting Materials

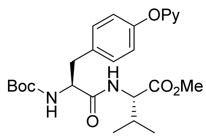
Peptide derivatives



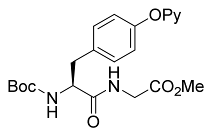
Boc-Tyr(OPy)-Leu-OMe
1a



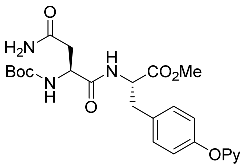
Boc-Tyr(OPy)-Phe-OMe
1b



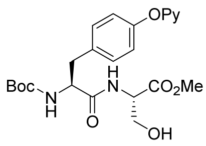
Boc-Tyr(OPy)-Val-OMe
1c



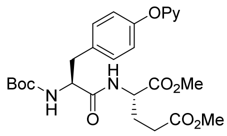
Boc-Tyr(OPy)-Gly-OMe
1d



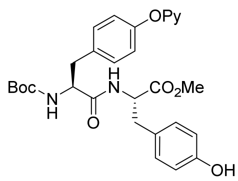
Boc-Asn-Tyr(OPy)-OMe
1e



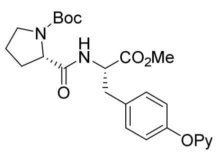
Boc-Tyr(OPy)-Ser-OMe
1f



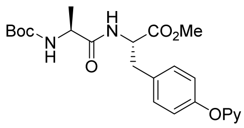
Boc-Tyr(OPy)-Glu(OMe)-OMe
1g



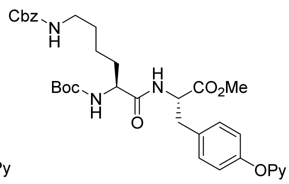
Boc-Tyr(OPy)-Tyr-OMe
1h



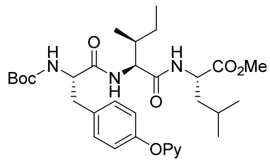
Boc-Pro-Tyr(OPy)-OMe
1i



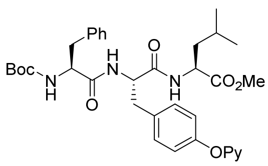
Boc-Ala-Tyr(OPy)-OMe
1j



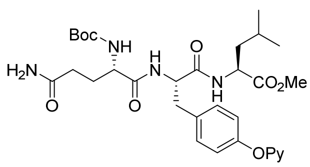
Boc-Lys(Cbz)-Tyr(OPy)-OMe
1k



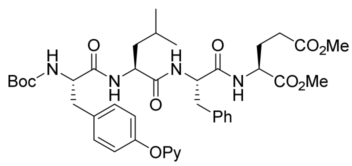
Boc-Tyr(OPy)-Ile-Leu-OMe
1l



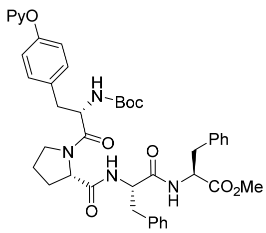
Boc-Phe-Tyr(OPy)-Leu-OMe
1m



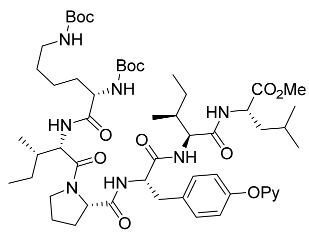
Boc-Gln-Tyr(OPy)-Leu-OMe
1n



Boc-Tyr(OPy)-Leu-Phe-Glu(OMe)-OMe
1o

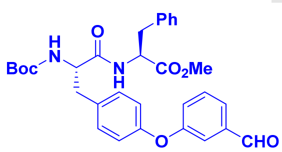


Boc-Tyr(OPy)-Pro-Phe-Phe-OMe
1p

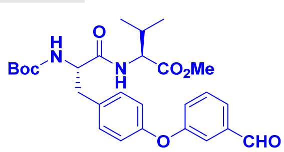


Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe
1q

Aldehydes

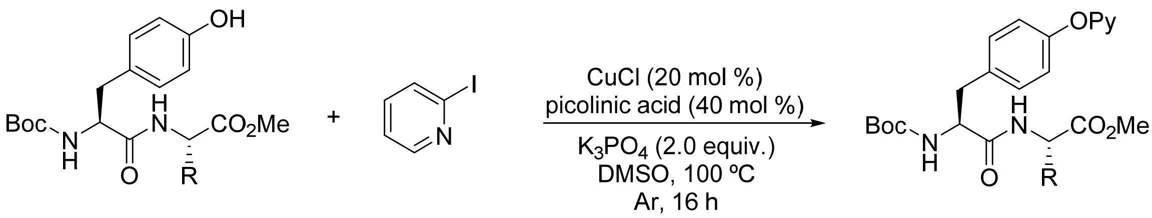


2t

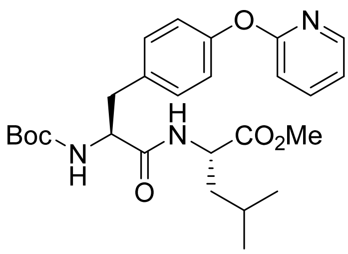


2s

General Procedure for the O-Arylation of Tyr-Containing Peptides[1]



A reaction tube containing a stirring bar was charged with the corresponding tyrosine derivative (1.0 equiv.), CuCl (20 mol %), K_3PO_4 (2.0 equiv.) and 2-picolinic acid (40 mol %). The reaction tube was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). Then DMSO (2.5 mL/mmol) and 2-iodopyridine (2.0 equiv.) were added under argon atmosphere. The reaction tube was next warmed up to 100 °C and stirred for 16 h. After cooling down to room temperature, brine was added to the above solution, washed with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. Organic layers were combined and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

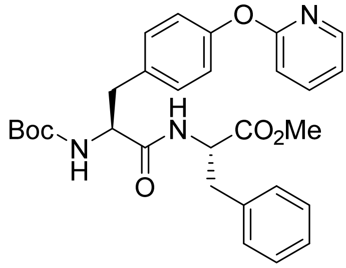


(1a)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl]-*L*-leucinate (1a). Following the general procedure, using Boc-Tyr-Leu-OMe (17.96 mmol, 7.33 g) provided 5.86 g (77% yield) of **1a** as a white solid. Mp 43-45 °C. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.99 (dd, *J* = 6.8, 5.4 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.31 (d, *J* = 8.3 Hz, 1H), 5.01 (s, 1H), 4.66 – 4.51 (m, 1H), 4.34 (d, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 3.08 (dd, *J* = 6.8, 1.8 Hz, 2H), 1.71 – 1.56 (m, 3H), 1.43 (s, 9H), 0.91 (t, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 171.1, 163.8, 155.5, 153.2, 147.7, 139.6, 133.0, 130.8, 121.4, 118.6, 111.6, 80.4, 55.7, 52.4, 50.9, 41.6, 37.5, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}):

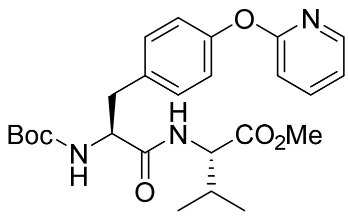
[1] Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. *Organometallics* **2015**, *34*, 953.

3305, 2957, 1744, 1655, 1507, 1467, 1428, 1266, 1245, 1167. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{26}H_{35}N_3O_6$): 485.2526, *found* 485.2532.



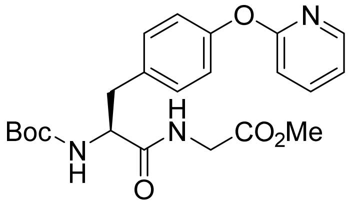
(1b)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl]-*L*-phenylalaninate (1b). Following the general procedure, using Boc-Tyr-Phe-OMe (1.20 mmol, 530.0 mg) provided 530 mg (85% yield) of **1b** as a white solid. Mp 51-53 °C. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.75 – 7.63 (m, 1H), 7.33 – 7.21 (m, 5H), 7.12 – 7.04 (m, 4H), 7.04 – 6.96 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 5.06 (s, 1H), 4.82 (q, *J* = 6.3 Hz, 1H), 4.36 (d, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 3.17 – 3.00 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.9, 163.7, 153.2, 147.7, 139.6, 135.8, 132.9, 130.7, 130.7, 129.3, 128.7, 128.7, 127.3, 127.2, 121.4, 118.6, 111.6, 80.3, 55.7, 53.4, 52.4, 38.0, 37.7, 28.4. IR (cm^{-1}): 3304, 2970, 1741, 1655, 1508, 1467, 1428, 1365, 1266, 1245, 1215, 1168. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{29}H_{33}N_3O_6$): 519.2369, *found* 519.2388.



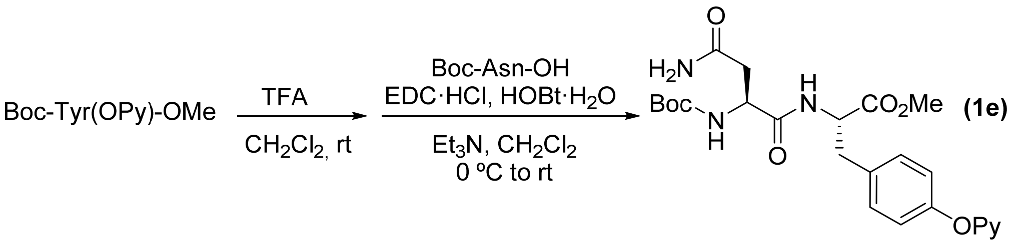
(1c)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl]-*L*-valinate (1c). Following the general procedure, using Boc-Tyr-Val-OMe (1.20 mmol, 473.1 mg) provided 450 mg (80% yield) of **1c** as a white solid. Mp 50-51 °C. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.76 – 7.63 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.01 (dd, *J* = 6.3, 5.0 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 5.12 (d, *J* = 8.0 Hz, 1H), 4.50 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 3.73 (s, 3H), 3.10 (d, *J* = 6.8 Hz, 2H), 2.21 – 2.08 (m, 1H), 1.45 (s, 9H), 0.90 (dd, *J* = 10.7, 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.2, 163.8, 155.5, 153.2, 147.8, 139.6, 133.0, 130.8, 121.4, 118.6, 111.6, 80.4, 57.4, 55.9, 52.3, 37.4, 31.4, 28.4, 19.0, 17.9. IR (cm^{-1}): 3321, 1969, 1740, 1655, 1508, 1467, 1428, 1366, 1215. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{25}H_{33}N_3O_6$): 471.2369, *found* 471.2381.



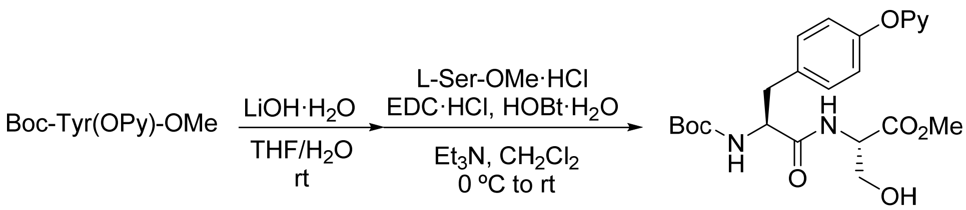
(1d)

Methyl (*S*)-[2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]glycinate (1d). Following the general procedure, using Boc-Tyr-Gly-OMe (1.20 mmol, 422.6 mg) provided 360 mg (70% yield) of **1d** as a yellowish oil. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.70 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.01 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.48 (s, 1H), 5.03 (s, 1H), 4.50 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.09 – 3.91 (m, 2H), 3.74 (s, 3H), 3.10 (d, *J* = 6.8 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.1, 163.8, 153.1, 147.7, 139.6, 133.0, 130.8, 130.5, 121.4, 118.6, 115.7, 80.4, 55.7, 52.5, 41.3, 37.8, 28.4. IR (cm^{-1}): 3305, 2977, 1747, 1663, 1507, 1467, 1428, 1266, 1245, 1207, 1166. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{22}H_{27}N_3O_6$): 429.1900, *found* 429.1905.



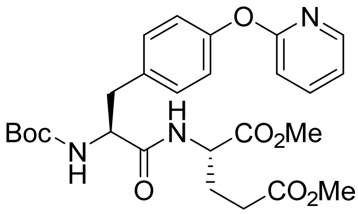
(1e)

Methyl (*S*)-2-[(*S*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanamido)-3-(4-(pyridin-2-yloxy)phenyl]propanoate (1e). Following the general procedure, using Boc-Tyr-OMe (7.20 mmol, 2.13 g) provided 2.50 g (93% yield) of Boc-Tyr(OPy)-OMe as a yellowish oil. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.69 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.01 (ddd, *J* = 7.0, 5.1, 0.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 5.07 (d, *J* = 8.3 Hz, 1H), 4.67 – 4.54 (m, 1H), 3.74 (s, 3H), 3.10 (qd, *J* = 13.9, 6.0 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 163.7, 155.2, 147.8, 139.5, 132.4, 130.6, 121.3, 118.6, 111.6, 80.0, 54.5, 52.4, 37.8, 28.4. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{20}H_{24}N_2O_5$): 372.1685, *found* 372.1696. Then, a solution of Boc-Tyr(OPy)-OMe (3.25 mmol, 1.21 g) in dichloromethane was treated with trifluoroacetic acid (32.50 mmol, 2.43 mL) and stirred for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$. After evaporation of the solvent, the so-obtained crude (without further purification) was dissolved in dichloromethane (10 mL) at 0 ºC. EDC·HCl (3.90 mmol, 748 mg), HOBt (3.90 mmol, 526 mg), Boc-Asn-OH (3.90 mmol, 906 mg) and triethylamine (3.90 mmol, 0.54 mL) were subsequently added and stirred overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (EtOAc) to provide 1.10 g (70% yield) of **1e** as an orange solid. Mp 112-113 °C. ^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ 8.15 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.82 (ddd, *J* = 8.8, 7.4, 2.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.12 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.60 – 4.39 (m, 1H), 3.73 (s, 3H), 3.14 (ddd, *J* = 47.9, 13.9, 6.7 Hz, 2H), 2.69 – 2.55 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, MeOH-*d$_4$*) δ 174.8, 173.6, 172.9, 165.0, 154.5, 148.3, 141.5, 134.4, 131.9, 121.9, 120.1, 112.7, 80.8, 55.0, 52.8, 52.7, 38.2, 37.6, 28.7. IR (cm^{-1}): 3415, 3330, 1733, 1683, 1665, 1637, 1590, 1161. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{24}H_{30}N_4O_7$): 486.2114, *found* 486.2116.



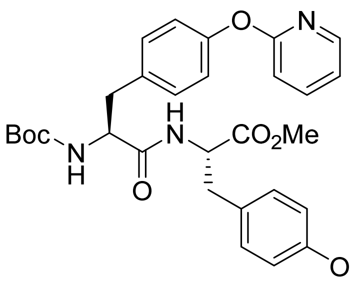
(1f)

Methyl (*S*)-2-[(*S*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanamido)-3-(4-(pyridin-2-yloxy)phenyl]propanoate (1f). To a solution of Boc-Tyr(OPy)-OMe (1.26 mmol, 469 mg) in THF/H_2O (1:1, 20 mL), LiOH·H_2O (1.89 mmol, 79 mg) was added and stirred at room temperature for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc, washed with a solution of HCl 1M and extracted several times with EtOAc. After evaporation of the solvent, the resulting solid was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.1 Hz, 1H), 7.73 (t, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 3H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.18 (d, *J* = 8.0 Hz, 1H), 4.66 (q, *J* = 6.3 Hz, 1H), 3.27 – 3.05 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 163.6, 155.6, 153.1, 147.3, 140.2, 132.9, 131.0, 121.2, 118.8, 111.9, 80.3, 54.3, 37.4, 28.4. Boc-Tyr(OPy)-OH was dissolved in dichloromethane (10 mL) at 0 ºC. EDC·HCl (1.51 mmol, 288 mg), HOBt·H_2O (1.51 mmol, 203 mg), L-Ser-OMe·HCl (1.51 mmol, 235 mg) and triethylamine (1.51 mmol, 0.19 mL) were subsequently added and stirred overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (EtOAc/hexanes, 8:2) to provide 350 mg (57% yield) of **1f** as a white solid. Mp 63-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.07 (m, 1H), 7.71 (ddd, *J* = 8.7, 7.4, 2.0 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 3H), 7.00 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.39 (d, *J* = 7.8 Hz, 1H), 4.62 (dd, *J* = 7.5, 3.7 Hz, 1H), 4.46 (d, *J* = 7.1 Hz, 1H), 3.97 – 3.67 (m, 2H), 3.75 (s, 3H), 3.12 (ddd, *J* = 45.0, 13.9, 6.3 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.7, 163.7, 153.0, 147.3, 139.9, 133.0, 130.9, 121.5, 118.6, 111.9, 80.5, 62.6, 55.8, 54.6, 52.7, 37.7, 28.4. IR (cm^{-1}): 3304, 2977, 1741, 1657, 1590, 1265, 1166. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{23}H_{29}N_3O_7$): 459.2006, *found* 459.2012.



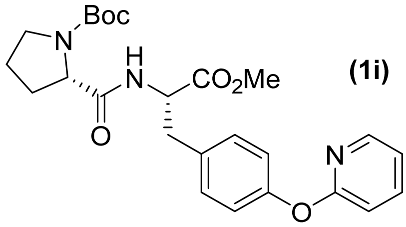
(1g)

Dimethyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl]-*L*-glutamate (1g). Following the synthetic sequence for the synthesis of **1f**, starting from Boc-Tyr-OH (1.43 mmol, 512 mg) and L-Glu(OMe)-OMe·HCl (1.30 mmol, 275 mg) provided 460 mg (69% yield) of **1g** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 3.0 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.40 (dd, *J* = 26.2, 8.3 Hz, 1H), 4.54 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.38 (d, *J* = 7.4 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.13 – 2.91 (m, 2H), 2.40 – 2.05 (m, 3H), 1.97 – 1.81 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.04, 171.70, 171.44, 163.57, 155.36, 152.90, 147.50, 139.45, 132.87, 130.61, 121.13, 118.41, 111.32, 79.99, 55.56, 52.39, 51.66, 51.50, 51.46, 37.45, 29.72, 28.15, 27.05. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{26}H_{33}N_3O_8$): 515.2268, *found* 515.2292.



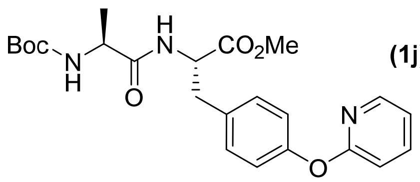
(1h)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-tyrosinate (1h). Following the synthetic sequence for the synthesis of **1f**, starting from Boc-Tyr-OH (1.43 mmol, 512 mg) and L-Tyr-OMe·HCl (1.30 mmol, 301 mg) provided 636 mg (91% yield) of **1h** as a white solid. Mp 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.70 (ddd, *J* = 8.7, 7.4, 2.1 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.06 – 7.02 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 7.9 Hz, 2H), 6.53 (d, *J* = 7.9 Hz, 1H), 5.19 (d, *J* = 8.2 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.12 – 2.87 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.1, 163.6, 155.8, 155.5, 153.2, 147.5, 140.0, 132.8, 130.9, 130.2, 126.6, 120.9, 118.9, 115.8, 111.9, 80.4, 55.6, 53.4, 52.4, 37.6, 37.0, 28.3. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{29}H_{33}N_3O_7$): 535.2319, *found* 539.2332.



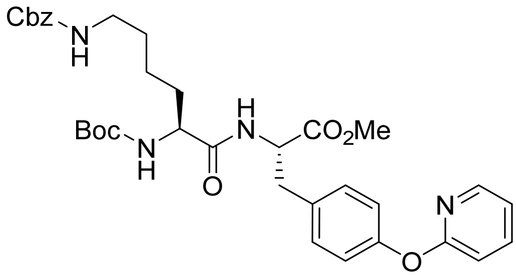
(1i)

***Tert*-butyl (*S*)-2-[((*S*)-1-methoxy-1-oxo-3-(4-(pyridin-2-yloxy)phenyl)propan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (1i).** Following the general procedure, using Boc-Pro-Tyr-OMe (7.65 mmol, 3.00 g) provided 2.57 g (75% yield) of **1i** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 4.9 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.96 (t, *J* = 6.1 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.82 (s, 1H), 4.23 (d, *J* = 30.7 Hz, 1H), 3.71 (s, 3H), 3.41 – 3.26 (m, 2H), 3.18 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.99 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.47 – 2.32 (m, 1H), 2.06 – 1.69 (m, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.7, 163.6, 147.6, 139.4, 130.5, 130.3, 121.3, 121.1, 118.5, 111.4, 80.4, 60.9, 59.9, 53.2, 52.6, 52.3, 46.9, 37.4, 30.7, 28.3, 24.4, 23.4. IR (cm^{-1}): 3279, 2975, 1742, 1677, 1466, 1427, 1390, 1365, 1263, 1243, 1205, 1163, 1119, 728. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{25}H_{31}N_3O_6$): 469.2213, *found* 469.2231.



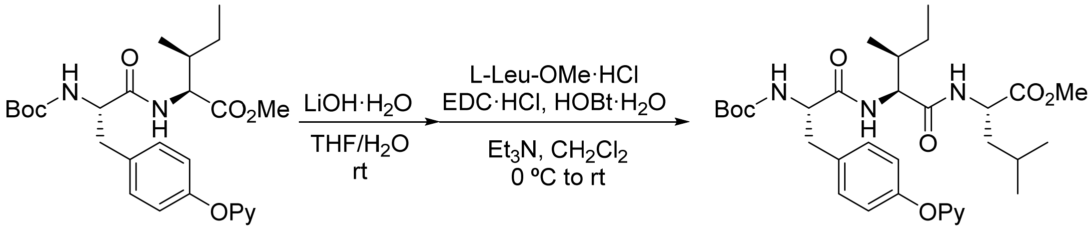
(1j)

Methyl (*S*)-2-[(*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-(pyridin-2-yloxy)phenyl]propanoate (1j). Following the general procedure, using Boc-Ala-Tyr-OMe (4.09 mmol, 1.50 g) provided 1.33 g (73% yield) of **1j** as a yellowish solid. Column chromatography (Hex/EtOAc 4:6). Mp 46-47 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.63 (ddd, *J* = 8.5, 7.2, 2.0 Hz, 1H), 7.15 – 7.04 (m, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.97 – 6.90 (m, 1H), 6.83 (dd, *J* = 8.5, 4.3 Hz, 2H), 5.26 (d, *J* = 7.4 Hz, 1H), 4.82 (q, *J* = 6.7 Hz, 1H), 4.29 – 4.01 (m, 1H), 3.67 (s, 3H), 3.19 – 2.95 (m, 2H), 1.38 (s, 9H), 1.26 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 172.1, 163.9, 155.7, 153.4, 148.0, 147.9, 139.8, 132.5, 130.9, 121.5, 118.8, 111.8, 111.8, 80.2, 53.4, 52.7, 50.3, 37.6, 28.6, 18.5. IR (cm^{-1}): 3303, 1741, 1663, 1427, 1162. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{23}H_{29}N_3O_6$): 443.2056, *found* 443.2064.



(1k)

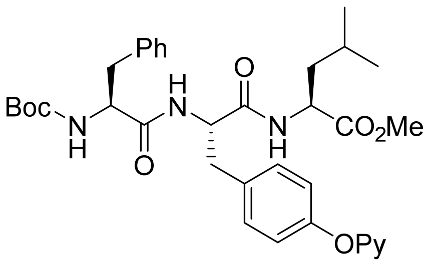
Methyl (*S*)-2-[(*S*)-6-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino) hexanamido]-3-[4-(pyridin-2-yloxy)phenyl]propanoate (1k). Following the general procedure, using Boc-Lyz(Cbz)-Tyr-OMe (3.23 mmol, 1.80 g) provided 1.35 g (68% yield) of **1k** as a yellowish solid. Mp 46-47 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.70 (ddd, *J* = 8.8, 7.3, 2.0 Hz, 1H), 7.36 (s, 4H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.00 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.10 (s, 3H), 4.93 – 4.83 (m, 1H), 4.15 – 4.03 (m, 1H), 3.71 (s, 3H), 3.27 – 3.00 (m, 4H), 1.85 – 1.71 (m, 1H), 1.63 – 1.47 (m, 3H), 1.44 (s, 9H), 1.38 – 1.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 163.6, 156.7, 155.7, 153.3, 147.7, 139.7, 136.7, 132.2, 130.7, 128.6, 128.2, 128.2, 121.3, 118.7, 111.7, 80.1, 66.7, 54.3, 53.1, 52.5, 40.4, 37.4, 31.9, 29.5, 28.4, 22.4. IR (cm^{-1}): 3312, 1702, 1507, 1428, 1428, 1245, 1167. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{34}H_{42}N_4O_8$): 634.3003, *found* 634.3012.



(1l)

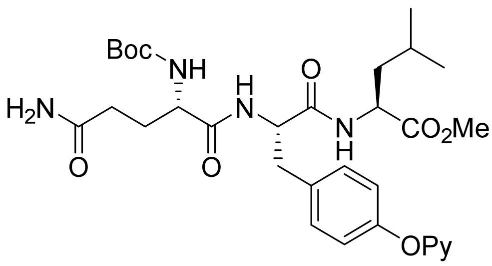
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-isoleucyl-*L*-leucinate (1l). Following the general procedure, using Boc-Tyr-Ile-OMe OMe (10.00 mmol, 4.10 g) provided 2.41 g (50% yield) of Boc-Tyr(OPy)-Ile-OMe as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.72 (ddd, *J* = 8.4, 7.2, 2.1 Hz, 1H), 7.26 (d, *J* = 6.7 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.03 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 5.05 (d, 1H), 4.52 (dd, *J* = 8.5, 5.1 Hz, 1H), 4.35 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.71 (s, 3H), 3.09 (d, *J* =

7.5 Hz, 2H), 1.91 – 1.78 (m, 1H), 1.44 (s, 9H), 1.11 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.0, 163.7, 153.2, 147.7, 139.7, 133.0, 130.8, 121.4, 118.7, 111.7, 80.4, 56.7, 55.9, 52.2, 38.0, 37.4, 28.4, 25.2, 15.5, 11.7. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{26}H_{35}N_3O_6$): 485.2526, *found* 485.2534. Then, starting from Boc-Tyr(OPy)-Ile-OMe (4.18 mmol, 1.97 g) the hydrolysis/peptide coupling sequence was applied to deliver 1.80 g (72% yield) of **1l** as a white solid. Mp 103-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.69 (ddd, *J* = 8.6, 7.2, 2.0 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.00 (dd, *J* = 7.1, 4.9 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.24 (d, *J* = 7.8 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.48 – 4.31 (m, 2H), 3.73 (s, 3H), 3.17 – 2.99 (m, 2H),1.9 (s, 1H), 1.72 – 1.55 (m, 5H), 1.42 (s, 9H), 0.97 – 0.87 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 171.4, 170.8, 163.7, 155.7, 153.2, 147.7, 139.6, 132.9, 130.7, 121.3, 118.6, 111.6, 80.4, 57.9, 55.8, 52.3, 50.9, 41.2, 37.2, 28.3, 24.9, 22.8, 22.0, 15.4, 11.4. IR (cm^{-1}): 3269, 2960, 1746, 1687, 1640, 1507, 1466, 1428, 1245, 1159, 729. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{32}H_{46}N_4O_7$): 598.3366, *found* 598.3410.



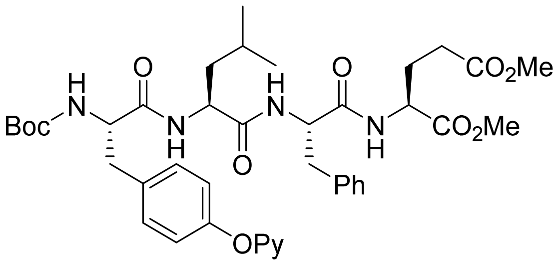
(1m)

Methyl [(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (1m). Following the general procedure, using Boc-Phe-Tyr-Leu-OMe (1.20 mmol, 660 mg) provided 480 mg (63% yield) of **1m** as a white solid. Mp 169-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.68 (ddd, *J* = 8.9, 7.2, 2.0 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.19 (d, *J* = 6.6 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.99 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 5.04 (d, *J* = 7.3 Hz, 1H), 4.70 (q, *J* = 7.0 Hz, 1H), 4.59 – 4.50 (m, 1H), 4.38 (d, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 3.19 – 2.95 (m, 4H), 1.65 – 1.47 (m, 3H), 1.37 (s, 9H), 0.91 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 171.2, 170.2, 163.7, 155.6, 153.2, 147.7, 139.5, 136.5, 132.6, 130.8, 129.3, 128.8, 127.1, 121.4, 118.5, 111.5, 80.5, 55.9, 54.1, 52.4, 51.0, 41.3, 38.0, 37.3, 28.3, 24.7, 22.8, 21.9. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{35}H_{44}N_4O_7$): 632.3210, *found* 632.3235.



(1n)

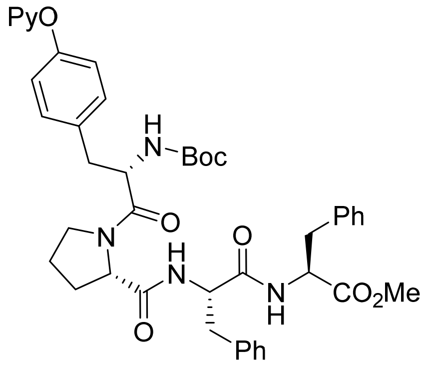
Methyl [(*S*)-2-((*S*)-5-amino-2-((*tert*-butoxycarbonyl)amino)-5-oxopentanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (1n). Following the synthetic sequence for the synthesis of **1e**, starting from Boc-Tyr(OPy)-Leu-OMe (2.06 mmol, 1.00 g) and *L*-Boc-Gln-OH (2.27 mmol, 558 mg) provided 530 mg (69% yield) of **1n** as a white solid. Mp 186-187 °C. ^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ 8.12 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.79 (ddd, *J* = 8.8, 7.3, 2.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.09 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.74 – 4.58 (m, 1H), 4.45 (dd, *J* = 9.3, 5.6 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.68 (s, 3H), 3.29 (p, *J* = 1.6 Hz, 1H), 3.15 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.96 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.21 (t, *J* = 8.2 Hz, 2H), 2.06 – 1.72 (m, 2H), 1.72 – 1.54 (m, 3H), 1.40 (s, 9H), 0.90 (dd, *J* = 16.4, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, MeOH-*d$_4$*) δ 177.8, 174.3, 174.2, 173.2, 165.2, 157.7, 154.5, 148.4, 141.6, 134.7, 132.1, 121.9, 120.1, 112.6, 80.7, 55.5, 52.7, 52.1, 41.5, 38.3, 32.6, 29.2, 28.7, 25.8, 23.3, 21.8. IR (cm^{-1}): 3319, 1714, 1685, 1660, 1635, 1206. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{31}H_{43}N_5O_8$): 613.3112, *found* 613.3112.



(1o)

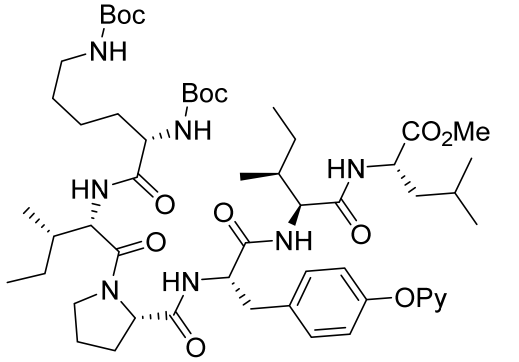
Dimethyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl)-*L*-leucyl-*L*-phenylalanyl-*L*-glutamate (1o). Following the synthetic sequence for the synthesis of **1f**, starting from Boc-Tyr(OPy)-Leu-OMe (1.10 mmol, 533 mg) and using Phe-Glu(OMe)-OMe·HCl (1.30 mmol, 301 mg) provided 700 mg (82 % yield) of **1o** as a white solid. Mp 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz 1H), 7.25 – 7.14 (m, 7H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.01 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 6.4 Hz, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.56 (td, *J* = 8.2, 5.0 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 3.32 (d, *J* = 14.0 Hz, 1H), 3.13 – 3.03 (m, 1H), 3.02 – 2.88 (m, 2H), 2.43 – 2.31 (m, 2H), 2.28 – 2.14 (m, 2H), 2.10 –

1.96 (m, 2H), 1.55 – 1.43 (m, 1H), 1.41 (s, 9H), 0.83 (dd, J = 10.4, 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 172.2, 171.7, 171.5, 171.0, 163.5, 156.3, 153.4, 147.5, 139.9, 137.1, 132.3, 130.6, 129.2, 128.6, 126.9, 121.6, 118.8, 112.0, 81.2, 56.4, 54.0, 52.9, 52.6, 51.9, 40.5, 37.5, 36.8, 30.2, 28.4, 27.2, 24.8, 23.0, 21.8. IR (cm^{-1}): 3277, 2954, 1740, 1687, 1639, 1543, 1429, 1366, 1248, 1170. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{41}H_{53}N_5O_{10}$): 775.3792, *found* 775.3797.



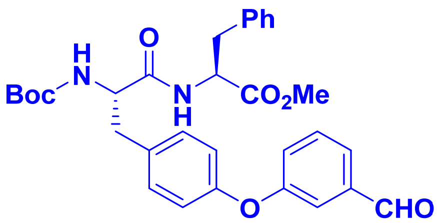
(1p)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl) propanoyl]-*L*-prolyl-*L*-phenylalanyl-*L*-phenylalaninate (1p). Following the general procedure, using Boc-Tyr-Pro-Phe-Phe-OMe (1.46 mmol, 1.00 g) provided 900 mg (81% yield) of **1p** as a white solid. Column chromatography (Hex/EtOAc 2:8). Mp 80-81 °C. ^1H NMR (500 MHz, DMSO-d_6 at 80 ºC) δ 8.15 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.80 (td, J = 7.8, 2.2 Hz, 1H), 7.57 (s, 1H), 7.38 – 7.14 (m, 11H), 7.10 (dd, J = 7.3, 4.9 Hz, 1H), 7.06 – 6.90 (m, 2H), 6.52 (s, 1H), 4.67 – 4.19 (m, 4H), 3.59 (s, 3H), 3.52 – 3.45 (m, 1H), 3.02 – 2.73 (m, 4H), 2.06 – 1.65 (m, 4H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6 at 80 ºC) δ 170.9, 170.5, 170.2, 162.7, 152.3, 147.0, 139.4, 137.2, 136.6, 133.4, 130.0, 128.6, 128.6, 128.5, 128.5, 127.7, 127.5, 127.4, 127.4, 126.0, 125.7, 120.0, 118.4, 111.0, 77.9, 59.3, 53.3, 53.1, 53.0, 51.1, 46.3, 36.9, 36.6, 36.5, 36.0, 28.0, 27.7. IR (cm^{-1}): 3285, 1741, 1633, 1590, 1571, 1427, 1163. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{43}H_{49}N_5O_8$): 763.3581, *found* 763.3596.



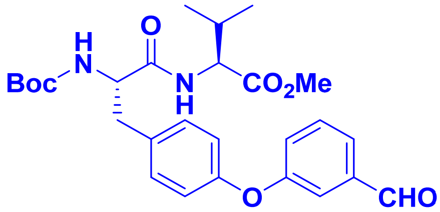
(1q)

Methyl [(*S*)-2-((*S*)-1-(N^2,N^6-bis(*tert*-butoxycarbonyl)-*L*-lysyl-*L*-isoleucyl)pyrrolidine-2-carboxamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-isoleucyl-*L*-leucinate (1q). Following the general procedure, using Boc-Lys(Boc)-Ile-Pro-Tyr-OMe (5.46 mmol, 4.00 g) provided 2.58 g (58% yield) of Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-OMe as a white solid. Then, subsequent hydrolysis/peptide couplings with L-Ile-OMe·HCl and L-Leu-OMe·HCl afforded the target hexapeptide **1q**. Starting from Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-OMe (1.36 mmol, 1.26 g) provided 1.00 g (71%) of **1q** as a white solid. Column chromatography (EtOAc). Mp 115-116 ºC. ^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC) δ 8.16 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.90 – 7.76 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 41.1, 8.8 Hz, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.10 (dd, *J* = 7.2, 4.9 Hz, 1H), 6.96 (p, *J* = 9.3, 8.2 Hz, 3H), 6.52 (s, 1H), 6.30 (s, 1H), 4.62 – 4.51 (m, 1H), 4.51 – 4.30 (m, 4H), 4.26 (t, *J* = 7.9 Hz, 1H), 4.02 – 3.82 (m, 1H), 3.78 – 3.66 (m, 1H), 3.62 (d, *J* = 7.8 Hz, 4H), 3.58 – 3.44 (m, 1H), 2.98 – 2.75 (m, 4H), 2.09 – 1.36 (m, 12H), 1.12 (ddd, *J* = 21.7, 10.6, 5.9 Hz, 2H), 0.97 – 0.71 (m, 26H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6, 171.9, 171.2, 171.0, 170.3, 169.9, 163.1, 155.5, 155.2, 152.3, 147.4, 140.0, 133.7, 130.4, 120.5, 120.4, 118.9, 111.4, 78.0, 77.3, 59.3, 56.4, 54.4, 54.2, 53.6, 52.4, 51.7, 50.2, 47.1, 43.8, 37.0, 36.5, 36.4, 31.5, 29.1, 29.1, 28.3, 28.1, 28.0, 24.2, 24.2, 24.1, 24.1, 23.9, 22.9, 22.8, 22.7, 22.3, 21.8, 21.2, 15.0, 10.9, 10.7. IR (cm^{-1}): 3288, 1740, 1645, 1626, 1591, 1163. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{54}H_{84}N_8O_{12}$): 1036.6209, *found* 1036.6215.



(2t)

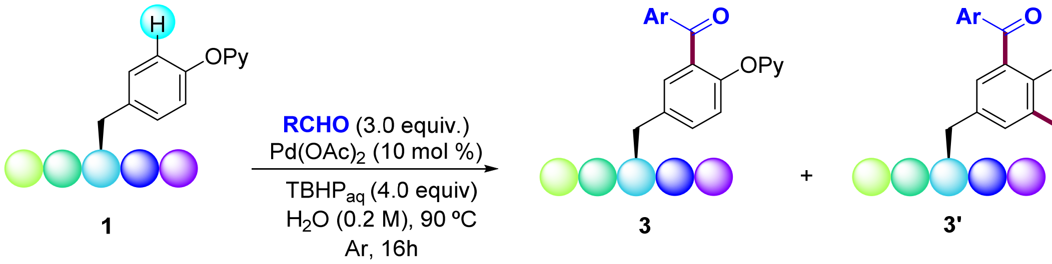
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(3-formylphenoxy)phenyl) propanoyl)-*L*-phenylalaninate (2t). Following the general procedure starting from Boc-Tyr-Phe-OMe (5.10 mmol, 2.26 g) and 3-iodobenzaldehyde (10.20 mmol, 2.35 g) provided 1.24 g (45 % yield) of **2t** as a yellow solid. Mp 54-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.65 – 7.58 (m, 1H), 7.56 – 7.38 (m, 2H), 7.34 – 7.10 (m, 6H), 7.10 – 6.88 (m, 4H), 6.40 (d, *J* = 7.7 Hz, 1H), 5.05 (d, *J* = 8.7 Hz, 1H), 4.85 (dd, *J* = 15.1, 7.3 Hz, 1H), 4.51 – 4.22 (m, 1H), 3.70 (d, *J* = 1.3 Hz, 3H), 3.05 (dddd, *J* = 27.4, 17.5, 11.3, 6.5 Hz, 4H), 1.43 (d, *J* = 9.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 171.7, 171.5, 170.9, 170.8, 158.3, 155.3, 138.1, 135.7, 132.5, 131.2, 131.1, 130.5, 129.3, 129.3, 128.8, 128.7, 127.3, 124.7, 119.6, 118.5, 80.4, 55.7, 53.3, 53.2, 52.5, 38.0, 28.4. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{31}H_{34}N_2O_7$): 546.2366, *found* 546.2369.



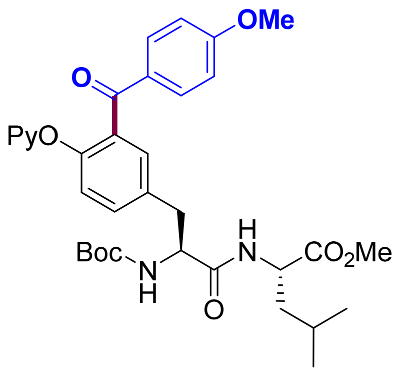
(2s)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(3-formylphenoxy)phenyl) propanoyl]-*L*-valinate (2s). Following the general procedure starting from Boc-Tyr-Val-OMe (2.79 mmol, 1.10 g) and 3-iodobenzaldehyde (5.58 mmol, 1.29 g) provided 500 mg (36 % yield) of **2s** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.60 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.25 – 7.17 (m, 2H), 7.01 – 6.90 (m, 2H), 6.38 (d, *J* = 8.7 Hz, 1H), 5.07 (d, *J* = 8.1 Hz, 1H), 4.48 (dd, *J* = 8.7, 5.0 Hz, 1H), 4.42 – 4.18 (m, 1H), 3.70 (s, 3H), 3.07 (d, *J* = 6.9 Hz, 2H), 2.25 – 2.06 (m, 1H), 1.43 (s, 9H), 0.87 (dd, *J* = 11.2, 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.5, 171.8, 171.1, 158.2, 155.3, 155.0, 137.9, 132.5, 130.8, 130.3, 124.4, 124.3, 119.4, 118.2, 80.0, 57.1, 55.7, 52.0, 37.3, 31.1, 28.1, 18.7, 17.6. IR (cm^{-1}): 3308, 1741, 1696, 1655, 1504, 1246, 1162. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{27}H_{34}N_2O_7$): 498.2366, *found* 498.2366.

4.-Pd-Catalyzed C(sp^2)-H Acylation of Tyr-Containing Oligopeptides

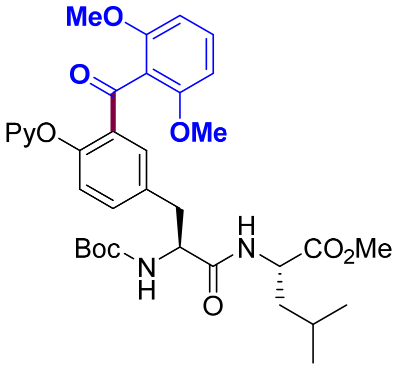


General Procedure: A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol), the aldehyde (0.45 mmol, if solid) and $Pd(OAc)_2$ (10 mol %, 3.4 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, the aldehyde (0.45 mmol, if liquid), a commercially available solution of Luperox® (0.60 mmol, 84 µL) and water (0.75 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.



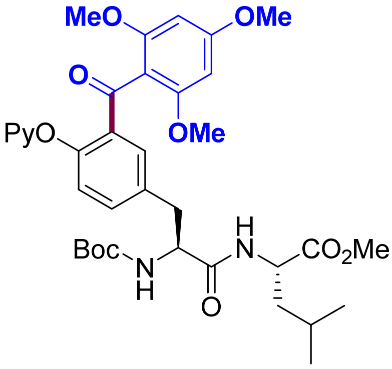
(3aa)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3aa). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and **1a** (0.15 mmol, 73 mg) provided 72 mg (78% yield) (8:2 ratio) of **3aa/3'aa**. The characterization of the major mono-functionalized peptide **3aa** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 5.0, 1.9 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.38 (dd, J = 8.3, 2.3 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.86 (dd, J = 6.3, 5.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 5.16 (d, 1H), 4.61 – 4.52 (m, 1H), 4.38 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.20 – 3.02 (m, 2H), 1.66 – 1.47 (m, 3H), 1.40 (s, 9H), 0.89 (dd, *J* = 6.0, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 173.0, 170.9, 163.6, 163.1, 155.5, 150.4, 147.0, 139.4, 133.2, 132.8, 132.5, 130.9, 130.2, 122.9, 118.6, 113.4, 111.6, 80.4, 55.5, 52.4, 50.9, 41.6, 37.3, 28.3, 24.8, 22.9, 21.9. IR (cm^{-1}): 3289, 2956, 1656, 1596, 1427, 1227, 1253, 1167. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{34}H_{41}N_3O_8$): 619.2894, *found* 619.2906.



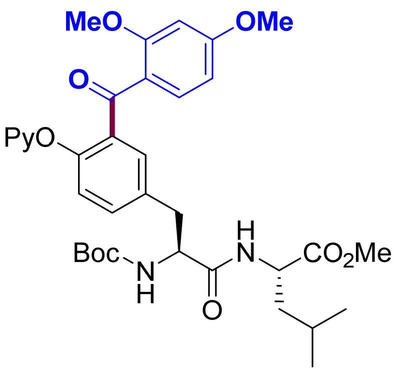
(3ab)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(2,6-dimethoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ab). Following the general procedure, using commercially available 2,6-dimethoxybenzaldehyde (0.45 mmol, 74.8 mg) and **1a** (0.15 mmol, 73 mg) provided 76 mg (74% yield) (8:2 ratio) of **3ab/3'ab**. The characterization of the major mono-functionalized peptide **3ab** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.75 (d, *J* = 3.2 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.15 (d, *J* = 7.1 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.38 (d, *J* = 7.4 Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 3.21 – 3.03 (m, 2H), 1.65 – 1.48 (m, 3H), 1.42 (s, 9H), 0.90 (dd, *J* = 6.0, 4.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 173.0, 171.0, 163.3, 155.5, 153.2, 152.6, 150.8, 146.9, 139.1, 133.8, 133.6, 131.3, 129.9, 123.2, 119.0, 118.1, 114.1, 113.0, 111.0, 80.4, 56.4, 55.8, 55.6, 52.4, 50.9, 41.6, 37.2, 28.3, 24.8, 22.9, 21.9. IR (cm^{-1}): 3316, 2956, 1659, 1593, 1493, 1465, 1426, 1242, 1223, 1170, 1043, 728. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{35}H_{43}N_3O_9$): 649.2999, *found* 649.3014.



(3ac)

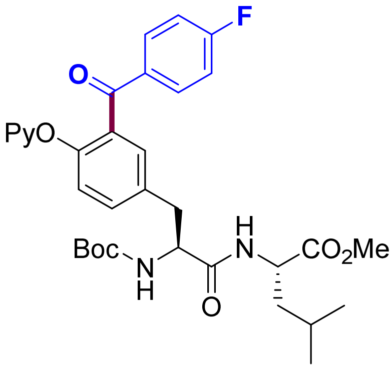
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(2,4,6-trimethoxybenzoyl)phenyl)propanoyl]-*L*-leucinate (3ac). Following the general procedure, using commercially available 2,4,6-trimethoxybenzaldehyde (0.45 mmol, 88.3 mg) and **1a** (0.15 mmol, 73 mg) provided 55 mg (54% yield) of **3ac** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.39 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.86 (dd, *J* = 6.3, 5.0 Hz, 1H), 6.62 – 6.52 (m, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 5.89 (s, 2H), 5.12 (s, 1H), 4.67 – 4.54 (m, 1H), 4.37 (d, *J* = 8.2 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.53 (s, 6H), 3.22 – 3.04 (m, 2H), 1.66 – 1.50 (m, 3H), 1.43 (s, 9H), 0.91 (dd, *J* = 6.0, 4.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 173.0, 171.0, 163.5, 162.5, 159.0, 155.6, 151.3, 146.7, 139.0, 134.2, 133.8, 133.4, 132.0, 124.0, 117.8, 113.3, 111.1, 90.5, 80.5, 55.8, 55.5, 52.4, 50.9, 41.6, 37.2, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3315, 2957, 1664, 1604, 1467, 1427, 1265, 1206, 1158, 1130. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{36}H_{45}N_3O_{10}$): 679.3105, *found* 679.3122.



(3ad)

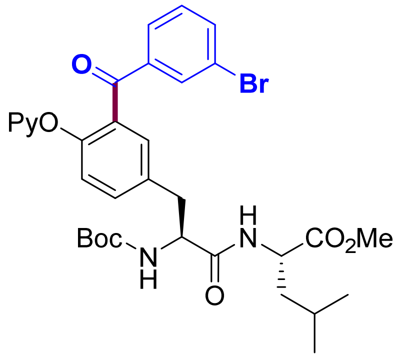
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(2,4-dimethoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ad). Following the general procedure, using commercially available 2,4-dimethoxybenzaldehyde (0.45 mmol, 74.8 mg) and **1a** (0.15 mmol, 73 mg) provided 48 mg (48% yield) (83:17 ratio) of **3ad/3'ad**. The characterization of the major mono-functionalized peptide **3ad** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 4.6 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.46

(s, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 6.8 Hz, 1H), 6.33 (s, 1H), 5.15 (s, 1H), 4.61 (q, *J* = 8.3 Hz, 1H), 4.39 (d, *J* = 6.7 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.14 (qd, *J* = 14.1, 6.7 Hz, 2H), 1.69 – 1.53 (m, 3H), 1.44 (s, 9H), 0.93 (dd, *J* = 5.9, 4.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 173.0, 171.0, 164.2, 163.4, 160.8, 155.5, 150.4, 147.0, 139.1, 134.7, 133.3, 132.8, 131.0, 122.9, 122.0, 118.2, 111.1, 104.6, 98.4, 80.4, 55.7, 55.5, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3315, 2957, 1656, 1598, 1465, 1427, 1265, 1244, 1210, 1161. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{35}H_{43}N_3O_9$): 649.2999, *found* 649.3015.



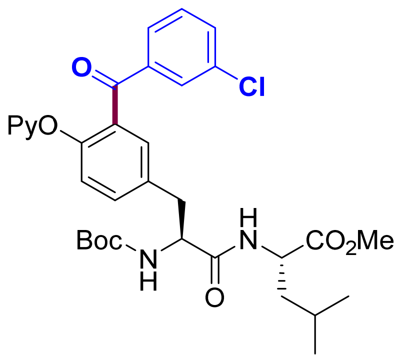
(3ae)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-fluorobenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ae). Following the general procedure, using commercially available 4-fluorobenzaldehyde (0.45 mmol, 48.3 µL) and **1a** (0.15 mmol, 73 mg) provided 73 mg (76% yield) (75:25 ratio) of **3ae/3'ae**. The characterization of the major mono-functionalized peptide **3ae** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.77 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.52 (ddd, *J* = 8.8, 7.2, 2.0 Hz, 1H), 7.41 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.88 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.13 (d, *J* = 8.3 Hz, 1H), 4.64 – 4.51 (m, 1H), 4.38 (d, *J* = 8.7 Hz, 1H), 3.67 (s, 3H), 3.26 – 3.00 (m, 2H), 1.67 – 1.48 (m, 3H), 1.41 (s, 9H), 0.90 (dd, *J* = 6.1, 3.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 173.0, 170.8, 165.75 (d, $J_{C\text{-}F}$ = 252.5 Hz), 162.9, 150.5, 155.5, 147.0, 139.6, 133.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 133.4, 133.3, 132.6 (d, $J_{C\text{-}F}$ = 10.1 Hz), 132.1, 131.0, 123.0, 118.7, 115.3 (d, $J_{C\text{-}F}$ = 20.2 Hz), 111.6, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.3. IR (cm^{-1}): 3314, 2957, 1657, 1596, 1465, 1428, 1241, 1154. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{33}H_{38}FN_3O_7$): 607.2694, *found* 607.2711.



(3af)

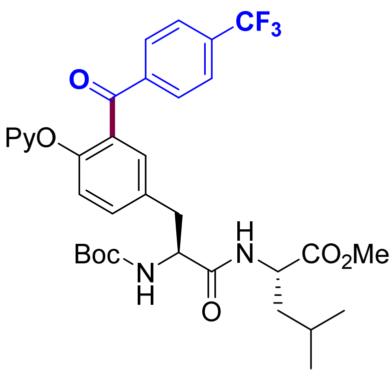
Methyl [(*S*)-3-(3-(3-bromobenzoyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxy carbonyl)amino)propanoyl]-*L*-leucinate (3af). Following the general procedure, using commercially available 3-bromobenzaldehyde (0.45 mmol, 52.7 µL) and **1a** (0.15 mmol, 73 mg) provided 90 mg (58% yield) (8:2 ratio) of **3af/3'af**. The characterization of the major mono-functionalized peptide **3af** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.54 – 7.49 (m, 1H), 7.44 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.89 (dd, *J* = 7.1, 4.9 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 5.14 (d, *J* = 8.3 Hz, 1H), 4.66 – 4.52 (m, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 3.67 (s, 3H), 3.23 – 3.04 (m, 2H), 1.65 – 1.48 (m, 3H), 1.41 (s, 9H), 0.90 (dd, *J* = 6.1, 3.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 173.0, 170.8, 162.8, 155.5, 150.7, 147.1, 139.6, 139.5, 135.6, 133.8, 133.5, 132.5, 131.6, 131.2, 129.7, 128.4, 123.1, 122.4, 118.8, 111.5, 80.5, 55.6, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm^{-1}): 3315, 2957, 1744, 1661, 1428, 1245. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{33}H_{38}BrN_3O_7$): 667.1893, *found* 667.1906.



(3ag)

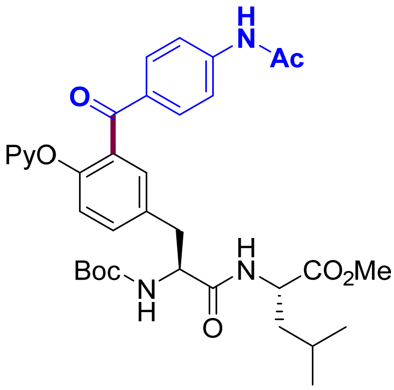
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-chlorobenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-leucinate (3ag). Following the general procedure, using commercially available 3-chlorobenzaldehyde (0.45 mmol, 51.0 µL) and **1a** (0.15 mmol, 73 mg) provided 58 mg (58% yield) (75:25 ratio) of **3ag/3'ag**. The characterization of the major mono-functionalized peptide **3ag** is provided. Colorless oil. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.02 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.73 (t, *J* = 1.9 Hz, 1H), 7.63 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 – 7.40 (m, 3H), 7.32 – 7.26 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 4.66 – 4.53 (m, 1H), 4.41 (d, *J* = 7.5 Hz, 1H), 3.70 (s, 3H), 3.28 – 3.04 (m, 2H), 1.69 – 1.52 (m, 3H), 1.44 (s, 9H), 0.93 (dd, *J* = 6.1, 3.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 173.0, 170.8, 162.8, 147.1, 139.6, 139.3, 134.4, 133.7, 133.5, 132.7, 131.7, 131.2, 129.6, 129.5, 128.0, 123.1, 118.8, 111.5, 80.5, 55.6, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3315, 2957, 1744, 1660, 1466, 1428, 1244. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{33}H_{38}ClN_3O_7$): 623.2398, *found* 623.2411.



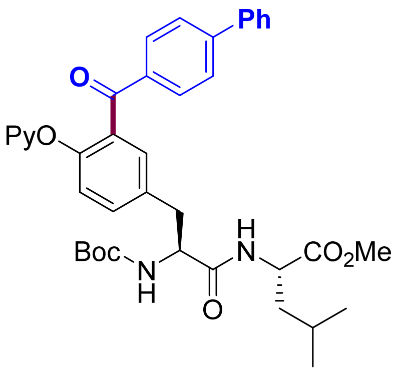
(3ah)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl]-*L*-leucinate (3ah). Following the general procedure, using commercially available 4-trifluoromethylbenzaldehyde (6.15 mmol, 842 μL) and **1a** (2.05 mmol, 1.00 g) provided 759 mg and 294 mg of **3ah**/**3’ah**, respectively, (73% yield) (75:25 ratio). The characterization of the major mono-functionalized peptide **3ah** is provided. White solid. Mp 67-68°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.46 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.88 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 8.3 Hz, 1H), 5.12 (d, *J* = 8.2 Hz, 1H), 4.64 – 4.51 (m, 1H), 4.38 (d, *J* = 7.9 Hz, 1H), 3.67 (s, 3H), 3.25 – 2.99 (m, 2H), 1.67 – 1.49 (m, 4H), 1.41 (s, 9H), 0.90 (dd, *J* = 6.1, 3.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 173.0, 170.7, 162.7, 150.8, 146.9, 140.6, 139.7, 134.0, 133.9 (q, J_{C-F} = 32.5 Hz), 133.6, 131.5, 131.3, 130.0, 125.1 (q, J_{C-F} = 4.0 Hz), 123.3, 123.0 (q, J_{C-F} = 272.6 Hz), 118.8, 111.5, 80.6, 55.6, 52.5, 50.9, 41.6, 37.4, 28.4, 24.8, 22.9, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.08. IR (cm^{-1}): 3313, 2957, 1745, 1659, 1466, 1428, 1325, 1244, 1168, 1131, 1065. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{34}H_{38}F_3N_3O_7$): 657.2662, *found* 657.2676.



(3ai)

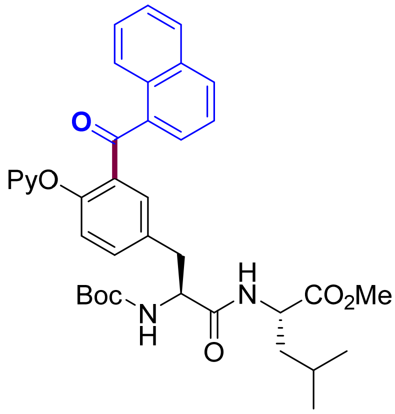
Methyl [(*S*)-3-(3-(4-acetamidobenzoyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-*L*-leucinate (3ai). Following the general procedure *in toluene as solvent*, using commercially available *N*-(4-formylphenyl)acetamide (0.45 mmol, 73.4 mg) and **1a** (0.15 mmol, 73 mg) provided 50 mg (52% yield) of **3ai** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.95 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.49 (dd, *J* = 8.7, 6.8 Hz, 3H), 7.37 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 2H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.61 – 4.51 (m, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 3.09 (ddd, *J* = 46.6, 14.0, 6.8 Hz, 2H), 2.14 (s, 3H), 1.65 – 1.47 (m, 3H), 1.39 (s, 9H), 0.88 (dd, *J* = 6.0, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 173.0, 171.0, 168.9, 163.1, 155.5, 150.5, 147.1, 142.6, 139.6, 133.3, 133.0, 132.7, 132.5, 131.5, 131.0, 122.9, 118.7, 118.5, 111.6, 80.5, 55.5, 52.4, 50.9, 41.5, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm^{-1}): 3307, 2958, 1658, 1591, 1527, 1428, 1287, 1261, 1173, 731. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{35}H_{42}N_4O_8$): 646.3003, *found* 646.3022.



(3aj)

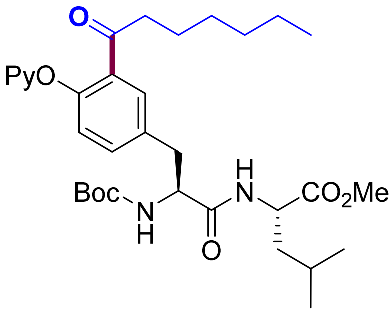
Methyl [(*S*)-3-(3-([1,1'-biphenyl]-4-carbonyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoyl]-*L*-leucinate (3aj). Following the general procedure, using commercially available 4-phenylbenzaldehyde (0.45 mmol, 82.0 mg) and **1a** (0.15 mmol, 73 mg) provided 77 mg (73% yield) (8:2 ratio) of **3aj/3'aj**. The characterization of the major mono-functionalized peptide **3aj** is provided. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.53 – 7.48 (m, 1H), 7.48 – 7.36 (m, 5H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 5.15 (d, *J* = 7.6 Hz, 1H), 4.65 – 4.53 (m, 1H), 4.39 (d, *J* = 7.5 Hz, 1H), 3.67 (s, 3H), 3.22 – 3.06 (m, 2H), 1.64 – 1.50 (m, 3H), 1.41 (s, 9H), 0.90 (dd, *J* = 6.0, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 173.0, 170.8, 163.1, 155.5, 150.6, 147.0, 145.6, 140.1, 139.5, 136.2, 133.4, 133.2, 132.4, 131.1, 130.6, 129.0, 128.3, 127.4, 126.8, 123.1, 118.6, 111.2, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3306, 2957, 1743, 1658, 1599, 1465, 1427, 1243, 1166. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{39}H_{43}N_3O_7$): 665.3101, *found* 665.3118.



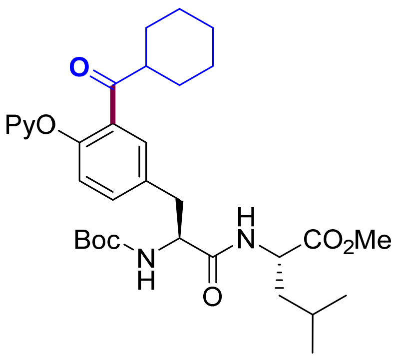
(3ak)

Methyl [(*S*)-3-(3-(1-naphthoyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl) amino)propanoyl)-*L*-leucinate (3ak). Following the general procedure, using commercially available 1-naphthaldehyde (0.45 mmol, 61.1 μL) and **1a** (0.15 mmol, 73 mg) provided 68 mg (68% yield) (84:16 ratio) of **3ak/3'ak**. The characterization of the major mono-functionalized peptide **3ak** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.30 (m, 1H), 7.95 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.67 – 7.57 (m, 2H), 7.52 – 7.45 (m, 3H), 7.35 – 7.30 (m, 1H), 7.30 – 7.25 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.79 – 6.71 (m, 1H), 6.55 (d, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 8.2 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.67 – 4.57 (m, 1H), 4.42 (d, *J* = 7.5 Hz, 1H), 3.69 (s, 3H), 3.28 – 3.05 (m, 2H), 1.70 – 1.52 (m, 3H), 1.44 (s, 9H), 0.93 (dd, *J* = 6.1, 4.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 173.0, 170.8, 162.9, 155.5, 151.1, 146.7, 139.1, 135.9, 134.1, 133.7, 133.6, 132.3, 132.0, 130.8, 130.6, 129.9, 128.2, 127.6, 126.3, 125.7, 124.2, 123.7, 118.4, 111.1, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3307, 2957, 1656, 1427, 1243, 1165, 776, 729. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{37}H_{41}N_3O_7$): 639.2945, *found* 639.2963.



(3am)

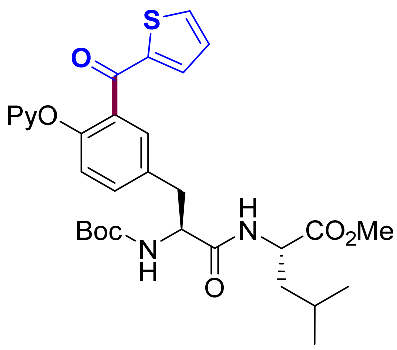
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-heptanoyl-4-(pyridin-2-yloxy) phenyl)propanoyl]-*L*-leucinate (3am). Following the general procedure, using commercially available heptanal (0.45 mmol, 63.0 µL) and **1a** (0.15 mmol, 73 mg) provided 42 mg (47% yield) of **3am** as a colorless oil. The performance of the process in PhCl with 5.0 equiv. of heptanal provided 51 mg (56% yield) of **3am**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 3.1 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 5.12 (d, *J* = 8.4 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H), 3.19 – 3.00 (m, 2H), 2.83 (t, *J* = 7.4 Hz, 2H), 1.65 – 1.48 (m, 5H), 1.41 (s, 9H), 1.25 – 1.12 (m, 6H), 0.90 (dd, *J* = 6.1, 3.4 Hz, 6H), 0.82 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 173.0, 170.9, 163.3, 155.5, 151.3, 147.7, 139.9, 133.9, 133.6, 132.4, 130.8, 123.2, 118.9, 111.8, 80.5, 55.6, 52.4, 50.9, 42.9, 41.6, 37.4, 31.7, 29.0, 28.4, 24.8, 24.1, 22.9, 22.6, 22.0, 14.1. IR (cm^{-1}): 3304, 2955, 2929, 2870, 1744, 1681, 1656, 1466, 1428, 1243, 1167. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{33}H_{47}N_3O_7$): 597.3414, *found* 597.3426.



(3an)

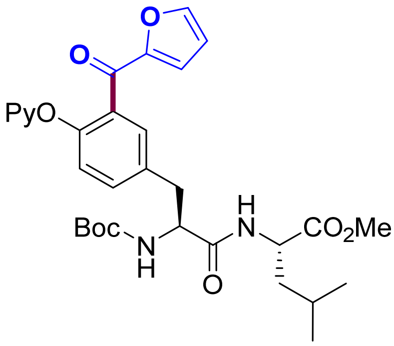
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(cyclohexanecarbonyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3an). Following the general procedure, using commercially available cyclohexylcarboxaldehyde (0.45 mmol, 54.5 µL) and **1a** (0.15 mmol, 73 mg) provided 42 mg (46% yield) of **3an** as a colorless oil. . The performance of the process in PhCl with 5.0 equiv. of aldehyde provided 51 mg (57% yield) of **3an**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 3.3 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.45 (d, *J* =

2.2 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.00 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.54 (s, 1H), 5.14 (d, *J* = 8.4 Hz, 1H), 4.64 – 4.49 (m, 1H), 4.36 (q, *J* = 7.3 Hz, 1H), 3.69 (s, 3H), 3.19 – 2.94 (m, 3H), 1.83 – 1.46 (m, 8H), 1.41 (s, 9H), 1.35 – 1.04 (m, 5H), 0.89 (dd, *J* = 6.0, 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8, 173.0, 170.9, 163.3, 155.5, 150.8, 147.6, 139.8, 133.4, 132.6, 130.7, 123.1, 121.4, 118.9, 118.6, 111.7, 80.5, 55.5, 52.4, 50.9, 49.6, 41.5, 37.3, 28.9, 28.9, 28.3, 26.0, 25.8, 24.8, 22.9, 22.0. IR (cm^{-1}): 3306, 2930, 1744, 1656, 1466, 1428, 1265, 1243, 1164. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{33}H_{45}N_3O_7$): 595.3258, *found* 595.3257.



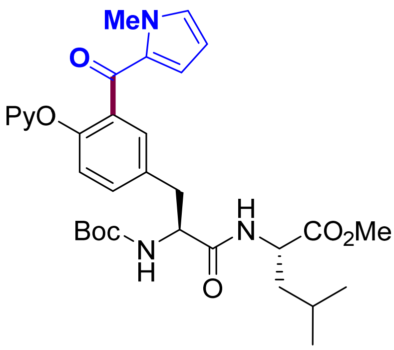
(3ao)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(thiophene-2-carbonyl)phenyl)propanoyl]-*L*-leucinate (3ao). Following the general procedure *in toluene as solvent*, using commercially available 2-thiophenecarboxaldehyde (0.45 mmol, 42.0 µL) and **1a** (0.15 mmol, 73 mg) provided 49 mg (55% yield) of **3ao** as a colorless oil. The performance of the process in toluene at 100 ºC with 5.0 equiv. of aldehyde provided 55 mg (62% yield) of **3ao**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.60 – 7.54 (m, 2H), 7.45 – 7.37 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.04 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 8.2 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.39 (d, *J* = 7.4 Hz, 1H), 3.66 (s, 3H), 3.21 – 3.03 (m, 2H), 1.62 – 1.49 (m, 3H), 1.40 (s, 9H), 0.89 (dd, *J* = 6.0, 3.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7, 173.0, 170.8, 163.2, 155.5, 150.3, 147.0, 144.1, 139.7, 135.8, 134.8, 133.2, 133.2, 132.2, 130.7, 128.1, 123.1, 118.7, 111.8, 80.5, 55.5, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm^{-1}): 3315, 2958, 1742, 1653, 1428, 1243, 1209, 1168, 730. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{31}H_{37}N_3O_7S$): 595.2352, *found* 595.2378.



(3ap)

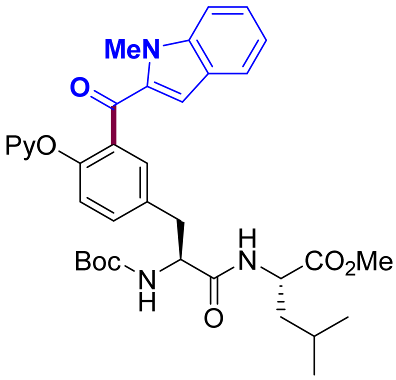
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(furan-2-carbonyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ap). Following the general procedure *in toluene as solvent*, using commercially available 2-furanal (0.45 mmol, 37.3 μL) and **1a** (0.15 mmol, 73 mg) provided 42 mg (48% yield) of **3ap** as a colorless oil. The performance of the process in toluene at 100 ºC with 5.0 equiv. of aldehyde provided 48 mg (55% yield) of **3ap**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.92 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.47 (dd, *J* = 3.6, 1.7 Hz, 2H), 5.13 (d, *J* = 8.4 Hz, 1H), 4.67 – 4.51 (m, 1H), 4.39 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.13 (qd, *J* = 14.0, 6.7 Hz, 2H), 1.64 – 1.47 (m, 3H), 1.41 (s, 9H), 0.89 (dd, *J* = 6.1, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 173.0, 170.8, 163.2, 155.5, 152.4, 150.7, 147.4, 147.1, 139.6, 133.4, 133.2, 131.5, 130.9, 123.1, 121.1, 118.8, 112.4, 111.8, 80.5, 55.5, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm^{-1}): 3324, 2958, 2937, 1742, 1657, 1465, 1428, 1244, 1166. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{31}H_{37}N_3O_8$): 579.2581, *found* 579.2601.



(3aq)

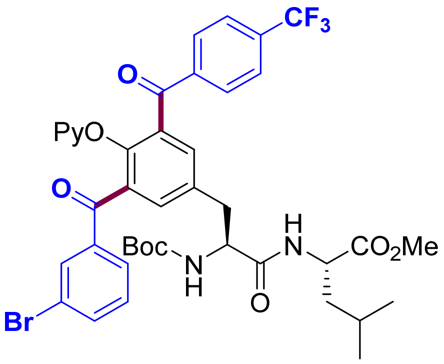
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(1-methyl-1*H*-pyrrole-2-carbonyl) -4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3aq). Following the general procedure *in toluene as solvent*, using commercially available 1-methyl-1*H*-pyrrole-2-carboxaldehyde (0.45 mmol, 49.5 mg) and **1a** (0.15 mmol, 73 mg) provided 33 mg (37% yield) of **3aq** as a colorless oil. The performance of the process in toluene at 100 ºC with

5.0 equiv. of aldehyde provided 39 mg (44% yield) of **3aq**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.36 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.94 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 6.08 (dd, *J* = 4.2, 2.4 Hz, 1H), 5.13 (d, *J* = 7.9 Hz, 1H), 4.61 (td, *J* = 8.5, 4.8 Hz, 1H), 4.40 (d, *J* = 7.4 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 3H), 3.13 (qd, *J* = 14.0, 6.8 Hz, 2H), 1.68 – 1.50 (m, 3H), 1.44 (s, 9H), 0.93 (dd, *J* = 6.1, 3.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 173.0, 170.9, 163.6, 155.6, 150.4, 147.3, 139.4, 133.7, 132.7, 132.2, 131.8, 131.0, 130.9, 123.8, 122.8, 118.5, 111.7, 108.5, 80.5, 55.6, 52.4, 50.9, 41.6, 37.4, 37.2, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3308, 2957, 1659, 1630, 1465, 1427, 1243, 1163, 730. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{32}H_{40}N_4O_7$): 592.2897, *found* 592.2942.



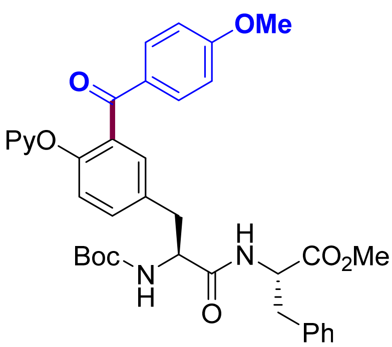
(3ar)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(1-methyl-1*H*-indole-3-carbonyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ar). Following the general procedure *in toluene as solvent*, using commercially available 1-methyl-1*H*-indole-3-carboxaldehyde (0.45 mmol, 42.0 μL) and **1a** (0.15 mmol, 73 mg) provided 60 mg (61% yield) (95:5 ratio) of **3ar/3'ar**. The characterization of the major mono-functionalized peptide **3ar** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.8 Hz, 1H), 8.08 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.38 – 7.28 (m, 4H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 5.22 (d, *J* = 8.3 Hz, 1H), 4.61 (td, *J* = 8.6, 4.6 Hz, 1H), 4.48 (d, *J* = 7.9 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 3.15 (ddd, *J* = 46.4, 14.0, 6.5 Hz, 2H), 1.66 – 1.51 (m, 3H), 1.44 (s, 9H), 0.92 (dd, *J* = 6.1, 4.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5, 173.1, 171.0, 163.6, 155.5, 150.2, 147.1, 140.0, 139.6, 137.7, 134.7, 132.8, 131.9, 130.6, 126.7, 123.5, 122.8, 122.8, 118.6, 116.5, 112.1, 109.6, 80.4, 55.4, 52.4, 50.8, 41.6, 37.5, 33.4, 28.4, 24.8, 22.9, 21.9. IR (cm^{-1}): 3314, 2957, 1666, 1525, 1465, 1428, 1369, 1244, 1207. 733. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{36}H_{42}N_4O_7$): 642.3053, *found* 642.3071.



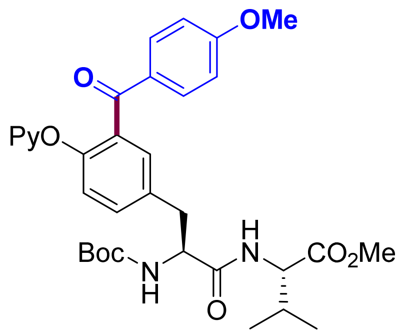
(3as)

Methyl [(*S*)-3-(3-(3-bromobenzoyl)-4-(pyridin-2-yloxy)-5-(4-(trifluoromethyl) benzoyl)phenyl]-2-[(*tert*-butoxycarbonyl)amino)propanoyl]-*L*-leucinate (3as). Following the general procedure *in toluene as solvent*, using commercially available 3-bromobenzaldehyde (0.60mmol, 70 μL) and **3ah** (0.15 mmol, 98.6 mg) provided 69.5 mg (55% yield) of **3as** as a colorless oil. Column chromatography (EtOAc/hexanes, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 3H), 7.75 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.66 – 7.59 (m, 3H), 7.57 – 7.49 (m, 3H), 7.31 – 7.23 (m, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.75 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 6.08 (d, *J* = 8.3 Hz, 1H), 5.20 (d, *J* = 8.3 Hz, 1H), 4.58 (td, *J* = 8.6, 4.5 Hz, 1H), 4.44 (q, *J* = 7.3 Hz, 1H), 3.62 (s, 3H), 3.29 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.12 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.68 – 1.53 (m, 3H), 1.40 (s, 9H), 0.97 – 0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 193.1, 173.0, 170.4, 161.7, 155.4, 147.9, 146.0, 140.2, 139.7, 139.0, 135.8, 134.2, 134.1, 134.0, 133.2, 132.9, 132.4, 129.9, 129.7, 128.3, 125.1, 125.1, 122.4, 118.9, 110.7, 80.6, 55.3, 52.5, 50.9, 41.5, 37.4, 31.1, 28.3, 24.9, 22.9, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.14. IR (cm^{-1}): 3325, 2959, 1666, 1410, 1322, 1240, 1166, 1131, 1109, 1065, 732. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{41}H_{41}BrF_3N_3O_8$): 839.2029, *found* 839.2071.



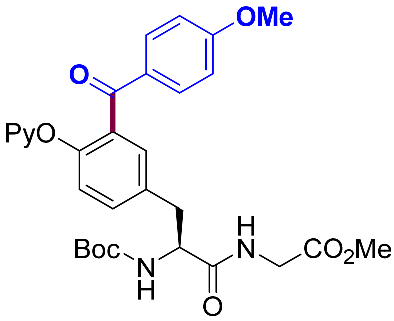
(3ba)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-phenylalaninate (3ba). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 μL) and Boc-Tyr(OPy)-Phe-OMe (**1b**) (0.15 mmol, 77.9 mg) provided 50 mg (49% yield) (8:2 ratio) of **3ba/3'ba**. The characterization of the major mono-functionalized peptide **3ba** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.55 (ddd, *J* = 8.7, 7.2, 2.0 Hz, 1H), 7.38 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 6.4 Hz, 2H), 6.89 (dd, *J* = 6.6, 4.7 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 1H), 4.82 (q, *J* = 6.0 Hz, 1H), 4.51 – 4.30 (m, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.23 – 2.97 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 171.5, 170.7, 163.6, 163.2, 155.4, 150.4, 147.1, 139.5, 135.8, 133.1, 132.8, 132.7, 132.5, 130.9, 130.2, 129.4, 128.7, 127.3, 123.0, 118.6, 113.5, 111.6, 80.5, 55.6, 53.4, 53.3, 52.5, 38.0, 37.6, 28.4. IR (cm^{-1}): 3312, 2970, 1740, 1711, 1658, 1596, 1429, 1385, 1254, 1218, 1168, 908, 728. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{37}H_{39}N_3O_8$): 653.2737, *found* 653.2771.



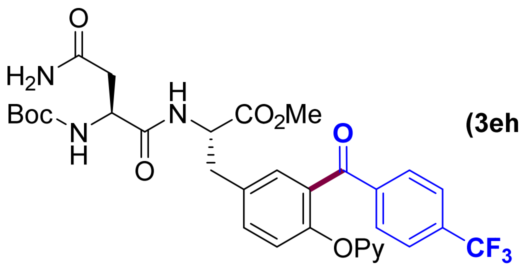
(3ca)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-valinate (3ca). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 μL) and Boc-Tyr(OPy)-Val-OMe (**1c**) (0.15 mmol, 70.7 mg) provided 60 mg (65% yield) (8:2 ratio) of **3ca/3'ca**. The characterization of the major mono-functionalized peptide **3ca** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.57 – 7.48 (m, 1H), 7.38 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 9.2 Hz, 1H), 5.14 (d, *J* = 8.2 Hz, 1H), 4.48 (dd, *J* = 8.7, 5.0 Hz, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.21 – 3.04 (m, 2H), 2.20 – 2.07 (m, 1H), 1.41 (s, 10H), 0.87 (dd, *J* = 10.1, 6.9 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 172.0, 171.0, 163.6, 163.1, 155.6, 147.0, 139.5, 133.2, 132.8, 132.7, 132.5, 132.2, 130.9, 130.2, 123.0, 118.6, 113.5, 111.7, 80.5, 57.4, 55.7, 55.6, 52.3, 37.2, 31.4, 28.4, 19.0, 17.9. IR (cm^{-1}): 3302, 2969, 1739, 1656, 1596, 1465, 1428, 1366, 1255, 1168. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{33}H_{39}N_3O_8$): 605.2737, *found* 605.2759.



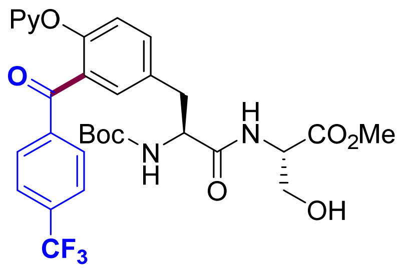
(3da)

Methyl (*S*)-[2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]glycinate (3da). Following the general procedure *in toluene as solvent*, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Gly-OMe (**1d**) (0.15 mmol, 64.0 mg) provided 53 mg (49% yield) (75:25 ratio) of **3da/3'da**. The characterization of the major mono-functionalized peptide **3da** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.58 – 7.50 (m, 1H), 7.40 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.87 (dd, *J* = 6.3, 5.0 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.2 Hz, 2H), 5.18 (d, *J* = 8.1 Hz, 1H), 4.43 (d, *J* = 8.2 Hz, 1H), 4.08 – 3.93 (m, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.19 – 3.07 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 171.4, 170.0, 163.7, 163.1, 155.5, 150.4, 146.9, 139.6, 133.3, 132.9, 132.8, 132.5, 130.9, 130.2, 123.0, 118.6, 113.5, 111.7, 80.6, 55.6, 52.5, 41.3, 37.7, 28.40. IR (cm^{-1}): 3315, 2952, 1743, 1660, 1596, 1428, 1255, 1168. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{30}H_{33}N_3O_8$): 563.2268, *found* 563.2290.



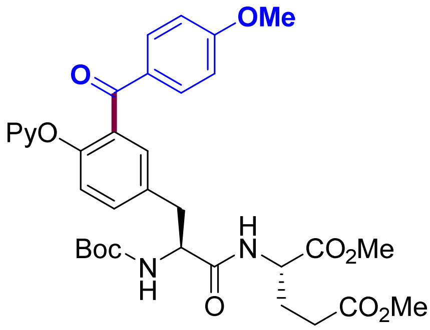
(3eh)

Methyl (*S*)-2-[(*S*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanamido]-3-(4-(pyridin-2-yloxy)-3-[4-(trifluoromethyl)benzoyl)phenyl]propanoate (3eh). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Asn-Tyr(OPy)-OMe (**1e**) (0.15 mmol, 73 mg) provided 39.6 mg and 5 mg of **3eh** and **3'eh**, respectively (44% yield) (9:1 ratio).The characterization of the major mono-functionalized peptide **3eh** is provided. Column chromatography (EtOAc). White solid. Mp 113-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.51 (ddd, *J* = 8.7, 7.2, 1.9 Hz, 1H), 7.48 – 7.28 (m, 3H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.90 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.18 (d, *J* = 7.5 Hz, 1H), 5.95 (d, *J* = 13.8 Hz, 2H), 4.93 – 4.88 (m, 1H), 4.49 – 4.47 (m, 1H), 3.73 (s, 3H), 3.29 (dd, *J* = 14.1, 5.0 Hz, 1H), 3.04 (dd, *J* = 14.2, 8.1 Hz, 1H), 2.95 – 2.72 (m, 1H), 2.48 (dd, *J* = 15.2, 6.1 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 173.4, 171.5, 171.4, 162.53, 155.8, 150.7, 146.7, 140.5, 139.8, 134.0 (q, J_{C-F} = 33.3 Hz), 133.9, 133.1, 131.2 (q, J_{C-F} = 4.0 Hz), 129.9, 125.2, 125.1, 123.6 (q, J_{C-F} = 273.7 Hz), 123.2, 118.9, 111.6, 80.4, 53.2, 52.7, 51.5, 37.3, 36.9, 28.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.07. IR (cm^{-1}): 3320, 3302, 1752, 1685, 1167, 1643, 1466. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{32}H_{33}F_3N_4O_8$): 658.2250, *found* 658.2255.



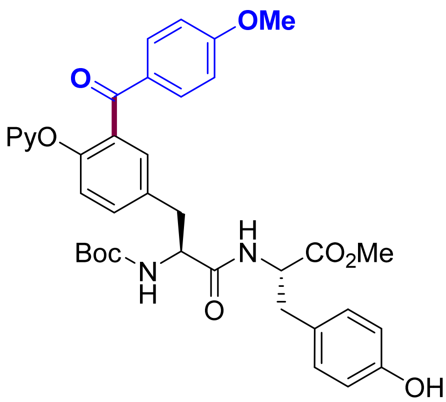
(3fh)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoro-methyl)benzoyl)phenyl)propanoyl]-*L*-serinate (3fh). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.75 mmol, 102 µL) and Boc-Tyr(OPy)-Ser-OMe (**1f**) (0.25 mmol, 138 mg) provided 84 mg and 14 mg of **3fh** and **3fh'**, respectively (60% yield) (9/1 ratio). The characterization of the major mono-functionalized peptide **3fh** is provided. Column chromatography (Hexanes/EtOAc 2:8). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.60 – 7.40 (m, 5H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.32 (d, *J* = 8.0 Hz, 1H), 4.61 – 4.57 (m, 1H), 4.46 (q, *J* = 6.6 Hz, 1H), 3.92 – 3.91 (m, 2H), 3.73 (s, 3H), 3.29 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.10 (dd, *J* = 13.8, 6.2 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 170.9, 170.6, 162.6, 155.6, 150.6, 146.6, 140.4, 140.1, 134.4, 133.8 (q, J_{C-F} = 23.2 Hz), 131.5, 131.4, 129.9, 128.0, 125.2 (q, J_{C-F} = 4.04 Hz), 123.6 (q, J_{C-F} = 273.7 Hz), 123.3, 118.9, 111.7, 80.8, 62.5, 55.7, 54.9, 52.8, 37.5, 28.5, 28.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.11. IR (cm^{-1}): 3304, 1743, 1661, 1594, 1428, 1064. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{31}H_{32}F_3N_3O_8$): 631.2141, *found* 631.2138



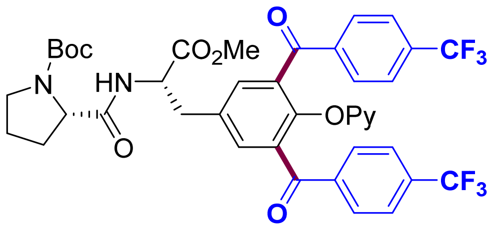
(3ga)

Dimethyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-glutamate (3ga). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Glu(OMe)-OMe (**1g**) (0.15 mmol, 77.3 mg) provided 50 mg (50% yield) (9:1 ratio) of **3ga/3'ga**. The characterization of the major mono-functionalized peptide **3ga** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.41 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.82 – 6.76 (m, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.23 – 5.11 (m, 1H), 4.64 – 4.55 (m, 1H), 4.40 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 3.26 – 3.02 (m, 2H), 2.46 – 2.28 (m, 2H), 2.28 – 2.14 (m, 1H), 2.03 – 1.91 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 173.3, 171.8, 171.1, 163.6, 163.1, 155.5, 150.4, 147.0, 139.5, 133.1, 132.7, 132.6, 132.5, 130.9, 130.2, 123.0, 118.6, 113.4, 111.6, 80.5, 55.7, 55.6, 52.7, 51.9, 51.8, 37.4, 29.9, 28.3, 27.3. IR (cm^{-1}): 3305, 2953, 1737, 1656, 1595, 1427, 1244, 1165, 730. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{34}H_{39}N_3O_{10}$): 649.2635, *found* 649.2674.



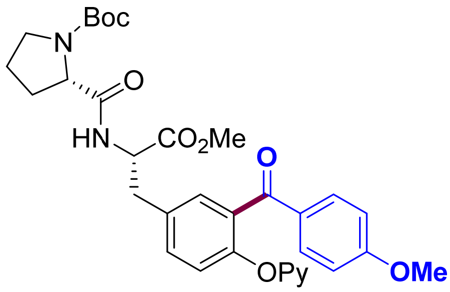
(3ha)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-tyrosinate (3ha). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Tyr-OMe (**1h**) (0.15 mmol, 80.25 mg) provided 51 mg (49% yield) (75:25 ratio) of **3ha/3'ha**. The characterization of the major mono-functionalized peptide **3ha** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.62 – 7.53 (m, 1H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 7.2, 4.9 Hz, 1H), 6.88 – 6.80 (m, 4H), 6.68 (dd, *J* = 8.3, 6.0 Hz, 3H), 6.48 (d, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.82 – 4.71 (m, 1H), 4.46 – 4.32 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.17 – 2.84 (m, 4H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 171.8, 170.7, 163.8, 163.0, 155.6, 155.5, 150.5, 146.9, 139.9, 133.1, 132.6, 132.5, 131.2, 130.3, 130.1, 126.9, 122.5, 118.9, 115.8, 113.6, 113.5, 112.1, 80.5, 55.6, 55.3, 53.3, 52.5, 37.0, 28.4. IR (cm^{-1}): 3325, 1749, 1689, 1167, 1643. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{37}H_{39}N_3O_9$): 669.2686, *found* 669.2711.



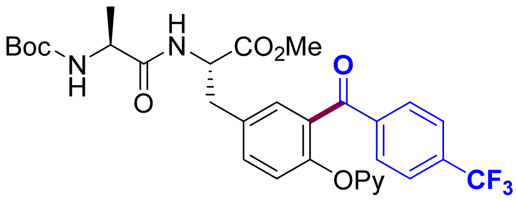
(3'ih)

***Tert*-butyl (*S*)-2-[((*S*)-1-methoxy-1-oxo-3-(4-(pyridin-2-yloxy)-3,5-bis(4-(trifluoromethyl)benzoyl)phenyl)propan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (3'ih).** Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.75 mmol, 102 μL) and Boc-Pro-Tyr(OPy)-OMe (**1i**) (0.25 mmol, 117 mg) provided 160 mg (79% yield) of **3'ih**. Column chromatography (EtOAc/hexanes, 1:1). Yellowish solid. Mp 99-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 4H), 7.69 – 7.61 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 4H), 7.20 (ddd, *J* = 8.7, 7.2, 2.0 Hz, 1H), 6.68 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.02 (d, *J* = 8.3 Hz, 1H), 5.43 (d, *J* = 8.5 Hz, 1H), 4.76 (dt, *J* = 8.6, 6.2 Hz, 1H), 4.48 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.70 (dt, *J* = 10.2, 3.1 Hz, 2H), 3.52 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.41 (s, 3H), 3.25 (dd, *J* = 13.8, 6.2 Hz, 1H), 3.02 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.21 – 2.05 (m, 1H), 2.05 – 1.85 (m, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 172.1, 169.8, 161.6, 155.2, 147.8, 145.9, 140.2, 139.5, 134.4, 134.1, 133.5 (q, J_{C-F} = 28.3 Hz), 132.8, 129.9, 125.0 (q, J_{C-F} = 4.04 Hz), 123.5 (q, J_{C-F} = 272.7 Hz), 118.8, 110.5, 80.0, 58.8, 52.6, 52.1, 47.1, 37.5, 29.0, 28.3, 24.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.16. IR (cm^{-1}): 1744, 1707, 1673, 1643, 1449, 1322, 1064. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{41}H_{37}F_6N_3O_8$): 813.2485, *found* 813.2486.



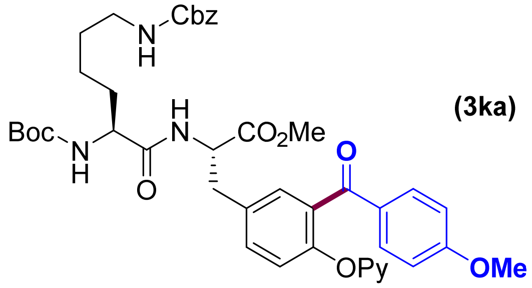
(3ia)

***Tert*-butyl (*S*)-2-[((*S*)-1-methoxy-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy) phenyl)-1-oxopropan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (3ia).** Following the general procedure *in toluene as solvent*, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Pro-Tyr(OPy)-OMe (**1i**) (0.15 mmol, 66.5 mg) provided 77 mg (81% yield) (8:2 ratio) of **3ia/3'ia**. The characterization of the major mono-functionalized peptide **3ia** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.54 (ddd, *J* = 8.7, 7.2, 2.0 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 1H), 4.26 (d, *J* = 29.3 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.41 (m, 2H), 3.26 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.08 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.06 (s, 2H), 1.80 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 171.6, 171.5, 163.5, 162.9, 150.3, 150.3, 146.9, 139.3, 132.5, 132.4, 132.3, 130.5, 130.0, 122.7, 118.5, 113.3, 111.5, 80.4, 61.1, 60.1, 55.4, 53.2, 52.4, 47.0, 37.4, 30.9, 28.2, 24.4, 23.6. IR (cm^{-1}): 2970, 1742, 1687, 1662, 1596, 1427, 1256, 1167. HRMS (ESI) m/z: (M^{+}) *caldc* for ($C_{33}H_{37}N_3O_8$): 603.2581, *found* 603.2616.



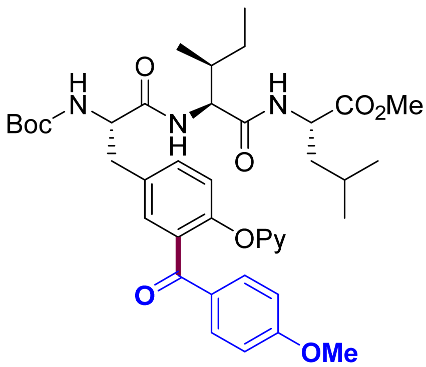
(3jh)

Methyl (*S*)-2-[(*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl]propanoate (3jh). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Ala-Tyr(OPy)-OMe (**1j**) (0.15 mmol, 66 mg) provided 54 mg and 19.5 mg of **3jh** and **3jh'**, respectively, 74% yield (8:2 ratio). The characterization of the major mono-functionalized peptide **3jh** is provided. Column chromatography (EtOAc/hexanes, 1:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.58 – 7.40 (m, 3H), 7.38 – 7.28 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.93 – 6.76 (m, 2H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.23 (d, J = 7.5 Hz, 1H), 4.87 (t, J = 6.7 Hz, 1H), 4.17 (t, J = 7.6 Hz, 1H), 3.71 (s, 3H), 3.27 (dd, J = 13.9, 5.7 Hz, 1H), 3.10 (dd, J = 13.9, 6.2 Hz, 1H), 1.40 (s, 9H), 1.32 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 172.6, 171.6, 162.5, 155.7, 150.8, 146.8, 140.6, 139.7, 134.1 (q, J_{C-F} = 20.2 Hz), 133.0, 131.3, 125.1 (q, J_{C-F} = 4.04 Hz), 124.5 (q, J_{C-F} = 272.7 Hz), 123.2, 118.9, 111.5, 80.2, 53.1, 52.6, 50.2, 37.3, 28.3, 18.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.10. IR (cm^{-1}): 3304, 1742, 1711, 1666, 1428, 1324. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{31}H_{32}F_3N_3O_7$): 615.2192, *found* 615.2201.



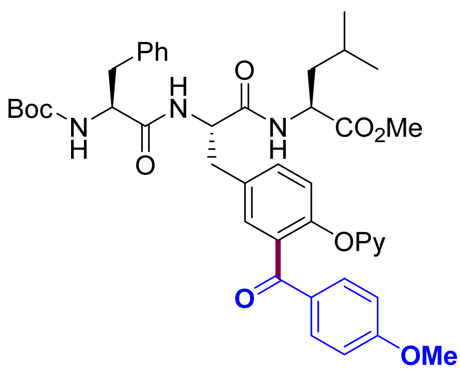
(3ka)

Methyl (*S*)-2-[(*S*)-6-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino) hexanamido]-3-[3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl]propanoate (3ka). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Lys(Cbz)-Tyr(OPy)-OMe (**1k**) (0.15 mmol, 95.1 mg) provided 65 mg (61% yield) of **3ka** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 5.1, 1.9 Hz, 1H), 7.75 (d, J = 8.9 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.41 – 7.27 (m, 6H), 7.23 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.2 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.14 (s, 1H), 5.10 (s, 2H), 4.97 – 4.86 (m, 1H), 4.18 – 4.04 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.31 – 3.01 (m, 4H), 2.19 (s, 1H), 1.82 (d, J = 11.1 Hz, 1H), 1.64 – 1.47 (m, 2H), 1.43 (s, 9H), 1.39 – 1.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 172.0, 171.7, 163.7, 162.9, 156.7, 155.9, 150.4, 147.0, 139.6, 136.7, 132.7, 132.5, 132.5, 130.9, 130.1, 128.6, 128.2, 128.1, 122.9, 118.7, 113.5, 111.7, 80.1, 66.7, 55.6, 54.4, 53.1, 52.6, 40.4, 37.2, 31.7, 29.4, 28.4, 22.5. IR (cm^{-1}): 3322, 2935, 1702, 1657, 1595, 1508, 1427, 1242, 1166, 729. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{42}H_{48}N_4O_{10}$): 768.3370, *found* 768.3398.



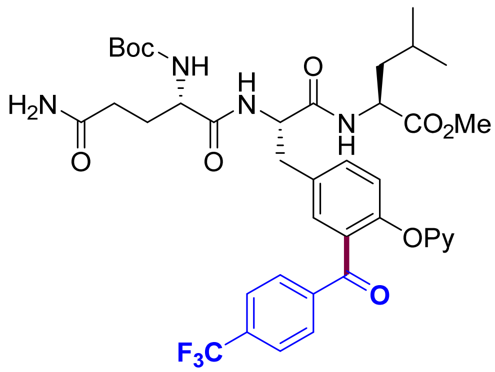
(3la)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-isoleucyl-*L*-leucinate (3la). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Ile-Leu-OMe (**1l**) (0.15 mmol, 89.8 mg) provided 70 mg (62% yield) (85:15 ratio) of **3la/3'la**. The characterization of the major mono-functionalized peptide **3la** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.54 (ddd, *J* = 8.7, 7.2, 2.0 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.89 (dd, *J* = 7.2, 4.9 Hz, 2H), 6.86 – 6.79 (m, 2H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 4.63 – 4.51 (m, 1H), 4.48 – 4.38 (m, 1H), 4.39 – 4.29 (m, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.19 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.08 (dd, *J* = 14.2, 7.9 Hz, 1H), 2.42 (s, 1H), 1.96 – 1.84 (m, 1H), 1.73 – 1.46 (m, 4H), 1.40 (s, 9H), 1.00 – 0.84 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 173.1, 171.2, 170.8, 163.6, 163.0, 155.7, 150.4, 147.0, 139.5, 133.2, 132.6, 132.6, 132.5, 130.9, 130.2, 122.9, 118.6, 113.4, 111.7, 80.5, 57.9, 55.7, 55.5, 52.3, 50.9, 41.2, 37.4, 37.0, 28.3, 24.9, 22.8, 22.0, 15.4, 11.4. IR (cm^{-1}): 3270, 2960, 1641, 1597, 1427, 1253, 1167. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{40}H_{52}N_4O_9$): 732.3734, *found* 732.3769.



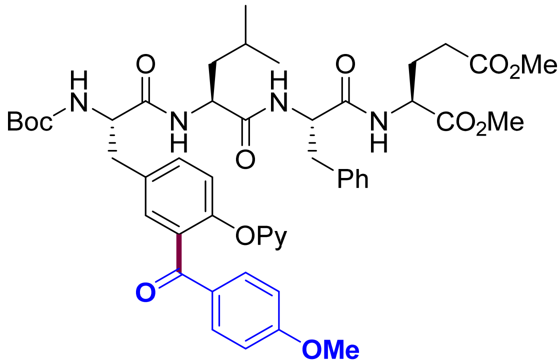
(3ma)

Methyl [(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3ma). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.30 mmol, 36.7 µL) and Boc-Phe-Tyr(OPy)-Leu-OMe (**1m**) (0.10 mmol, 63.0 mg) provided 44 mg (57% yield) of **3ma** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.52 (ddd, *J* = 8.5, 7.2, 2.0 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.26 (d, *J* = 1.8 Hz, 2H), 7.23 – 7.11 (m, 5H), 6.87 (dd, *J* = 6.6, 5.0 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 6.47 (d, *J* = 6.9 Hz, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.74 – 4.63 (m, 1H), 4.56 – 4.46 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.19 – 3.02 (m, 3H), 3.00 – 2.89 (m, 1H), 1.64 – 1.46 (m, 3H), 1.34 (s, 9H), 0.89 (d, *J* = 5.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 172.8, 171.4, 170.1, 163.7, 163.0, 155.8, 150.2, 146.7, 139.8, 136.6, 133.2, 132.9, 132.8, 132.5, 131.0, 130.2, 129.4, 128.8, 127.1, 123.0, 118.6, 113.5, 111.8, 80.5, 56.2, 55.6, 53.9, 52.4, 51.1, 41.2, 37.9, 37.1, 28.3, 24.8, 22.9, 22.0. IR (cm^{-1}): 3295, 2959, 1646, 1597, 1428, 1254, 1168. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{43}H_{50}N_4O_9$): 766.3578, *found* 766.3611.



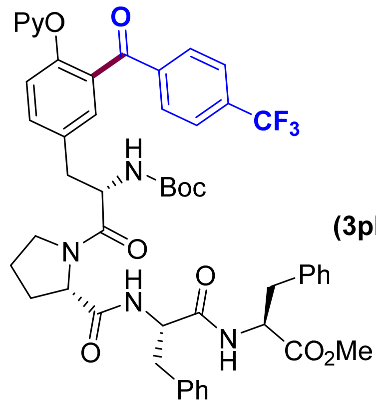
(3nh)

Methyl [(*S*)-2-((*S*)-5-amino-2-((*tert*-butoxycarbonyl)amino)-5-oxopentanamido)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl]-*L*-leucinate (3nh). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 μL) and Boc-Gln-Tyr(OPy)-Leu-OMe (**1n**) (0.15 mmol, 92 mg) provided 50 mg and 12 mg of **3nh** and **3'nh**, respectively, 48% yield (8:2 ratio). The characterization of the major mono-functionalized peptide **3nh** is provided. Column chromatography (EtOAc). Yellow solid. Mp 142-143 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.63 – 7.39 (m, 6H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 6.3 Hz, 1H), 6.91 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.73 (s, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.05 (s, 1H), 5.98 (d, *J* = 6.6 Hz, 1H), 4.88 (td, *J* = 8.1, 5.7 Hz, 1H), 4.57 – 4.45 (m, 1H), 4.14 (d, *J* = 7.4 Hz, 1H), 3.67 (s, 3H), 3.28 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.10 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.48 – 2.18 (m, 3H), 2.11 (dt, *J* = 15.6, 6.2 Hz, 1H), 2.03 – 1.99 (m, 2H), 1.68 – 1.48 (m, 3H), 1.39 (s, 9H), 0.88 (q, *J* = 2.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 175.5, 173.2, 172.2, 170.5, 161.7, 156.2, 147.9, 145.8, 140.0, 139.9, 134.5, 134.1, 134.0, 133.1, 129.9, 128.0, 125.2 (q, J_{C-F} = 3.03 Hz), 123.5 (q, J_{C-F} = 273.7 Hz), 119.1, 110.7, 80.4, 54.2, 54.0, 52.4, 51.2, 41.1, 36.9, 31.4, 29.8, 28.4, 28.0, 26.5, 24.9, 22.8, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.16. IR (cm^{-1}): 3304, 1742, 1666, 1639, 1594, 1428. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{39}H_{46}F_3N_5O_9$): 785.3248, *found* 785.3251.



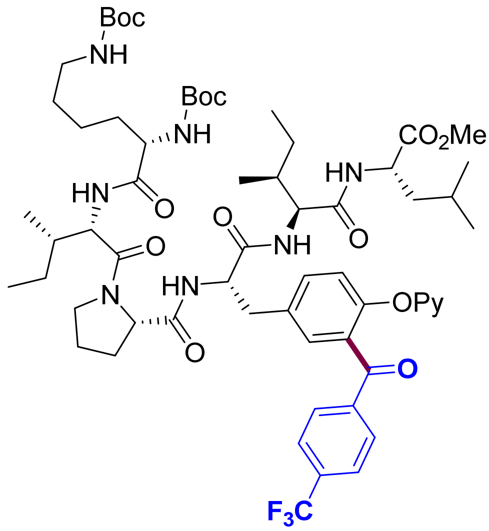
(3oa)

Dimethyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucyl-*L*-phenylalanyl-*L*-glutamate (3oa). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 μL) and Boc-Tyr(OPy)-Leu-Phe-Glu(OMe)-OMe (**1o**) (0.10 mmol, 77.5 mg) provided 60 mg (64% yield) (8:2 ratio) of **3oa/3'oa**. The characterization of the major mono-functionalized peptide **3oa** is provided. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.54 (m, 1H), 7.38 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.14 (m, 6H), 7.06 – 6.96 (m, 1H), 6.92 (dd, *J* = 7.1, 4.6 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.69 (dd, *J* = 13.2, 7.5 Hz, 2H), 5.20 (d, *J* = 6.5 Hz, 1H), 4.85 – 4.72 (m, 1H), 4.61 – 4.52 (m, 1H), 4.40 – 4.26 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 3.27 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.14 (dd, *J* = 14.3, 5.5 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.43 – 2.30 (m, 2H), 2.26 – 2.13 (m, 1H), 2.06 – 1.95 (m, 1H), 1.62 – 1.43 (m, 3H), 1.41 (s, 9H), 0.85 (dd, *J* = 12.6, 5.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 173.3, 172.0, 171.7, 171.6, 170.9, 163.7, 162.8, 156.2, 150.4, 146.6, 139.9, 136.9, 132.8, 132.6, 132.5, 130.8, 130.1, 129.2, 128.7, 128.6, 126.9, 123.0, 118.7, 113.5, 111.9, 81.0, 56.1, 55.6, 54.0, 52.8, 52.6, 51.9, 51.8, 40.6, 37.5, 36.8, 30.1, 28.3, 27.2, 24.7, 22.9, 21.9. IR (cm^{-1}): 3376, 2969, 1739, 1638, 1428, 1255, 1215, 1168. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{49}H_{59}N_5O_{12}$): 909.4160, *found* 909.4187.



(3ph)

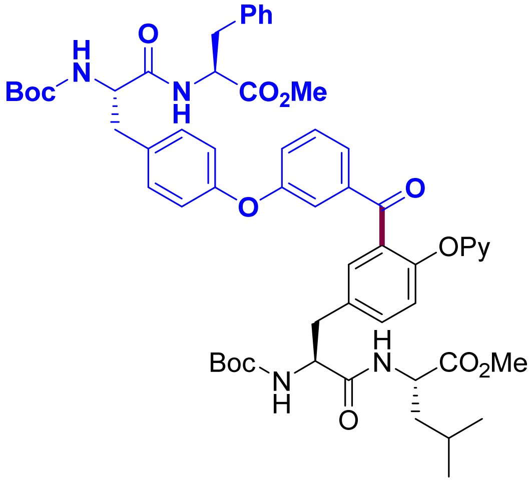
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoro-methyl)benzoyl)phenyl)propanoyl)-*L*-prolyl-*L*-phenylalanyl-*L*-phenylalaninate (3ph). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 μL) and Boc-Tyr(OPy)-Pro-Phe-Phe-OMe (**1p**) (0.15 mmol, 114 mg) provided 67 mg and 21 mg of **3ph** and **3’ph**, respectively, 61% yield (8:2 ratio). The characterization of the major mono-functionalized peptide **3ph** is provided. Column chromatography (EtOAc/hexanes, 8:2). Yellow solid. Mp 97-98 ºC. ^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC) δ 8.01 – 7.91 (m, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.68 – 7.44 (m, 3H), 7.36 – 7.10 (m, 10H), 6.98 (dd, *J* = 7.1, 4.9 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 4.63 – 4.43 (m, 3H), 4.46 – 4.24 (m, 1H), 3.57 (s, 3H), 3.14 – 2.77 (m, 9H), 1.97 – 1.74 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6 at 80 ºC) 193.1, 170.9, 170.5, 170.2, 169.8, 161.9, 154.5, 149.5, 146.3, 140.3, 139.3, 137.2, 136.6, 134.1, 132.0 (q, J_{C-F} = 37.8 Hz), 130.4, 130.1, 129.3, 128.6, 128.6, 128.5, 128.4, 127.7, 127.5, 126.0, 125.6, 124.7 (q, J_{C-F} = 3.78 Hz), 124.7 (q, J_{C-F} = 273.4 Hz), 122.0, 118.5, 110.5, 77.9, 59.4, 53.2, 53.1, 53.0, 51.1, 37.0, 36.8, 36.6, 36.5, 35.8, 28.0, 27.7, 23.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.14. IR (cm^{-1}): 3303, 1742, 1645, 1593, 1428, 1164. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{39}H_{52}F_3N_5O_9$): 935.3717, *found* 935.3725.



(3qh)

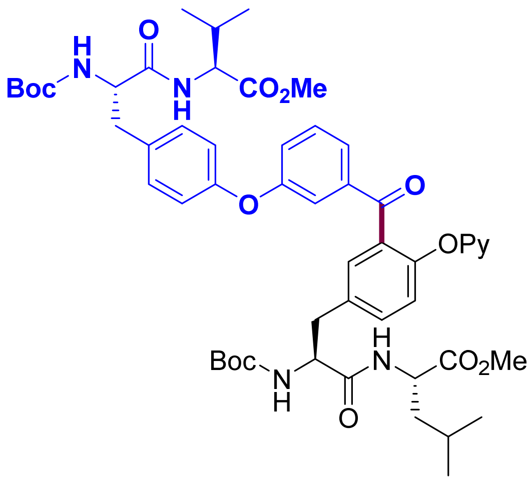
Methyl [(*S*)-2-((*S*)-1-(N^2,N^6-bis(*tert*-butoxycarbonyl)-*L*-lysyl-*L*-isoleucyl)pyrrolidine-2-carboxamido)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl) propanoyl)-*L*-isoleucyl-*L*-leucinate (3qh). Following the general procedure *in toluene as solvent*, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 μL) and Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe (**1q**) (0.15 mmol, 155 mg) provided 81.2 mg and 27.6 mg of **3qh** and **3'qh**, respectively, 58% yield (8:2 ratio). The characterization of the major mono-functionalized peptide **3qh** is provided. Column chromatography (EtOAc/hexanes, 8:2). Yellow solid. Mp 107-108 ºC. ^{1}H NMR (500MHz, DMSO-*d*6) δ 8.30 (d, *J* = 7.3 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.69 – 7.60 (m, 2H), 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.99 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.72 (t, *J* = 5.6 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.59 (td, *J* = 8.3, 5.1 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.27 – 4.14 (m, 2H), 3.87 (q, *J* = 3.9 Hz, 1H), 3.66 (d, *J* = 1.5 Hz, 1H), 3.58 (s, 3H), 3.54 (t, *J* = 6.7 Hz, 1H), 3.05 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.90 – 2.82 (m, 3H), 2.04 – 1.86 (m, 1H), 1.86 – 1.63 (m, 5H), 1.64 – 1.40 (m, 7H), 1.36 (s, 9H), 1.35 (s, 9H), 1.09 – 0.97 (m, 2H), 0.93 – 0.69 (m, 18H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 193.7, 172.7, 171.9, 171.3, 171.0, 170.4, 170.0, 162.2, 155.5, 155.3, 149.7, 146.7, 140.5, 140.0, 134.5, 133.9, 132.1 (q, J_{C-F} = 25.2 Hz), 130.7, 130.6, 129.9, 125.2 (q, J_{C-F} = 3.8 Hz), 123.7 (q, J_{C-F} = 273.4 Hz), 122.5, 118.9, 110.8, 78.0, 77.3, 59.3, 56.4, 54.4, 54.2, 53.6, 51.7, 50.2, 47.1, 37.0, 36.6, 36.3, 31.5, 29.1, 29.0, 28.3, 28.1, 24.2, 24.2, 24.1, 24.0, 23.9, 22.8, 22.6, 21.3, 21.2, 15.0, 15.0, 10.9, 10.9, 10.6. ^{19}F NMR (376 MHz, DMSO-*d*6) δ -63.14. IR (cm^{-1}): 3273, 1744, 1639, 1594, 1428, 1164. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{62}H_{87}F_3N_8O_{13}$): 1208.6345, *found* 1208.6345.

Chemical Ligation (Table 4)



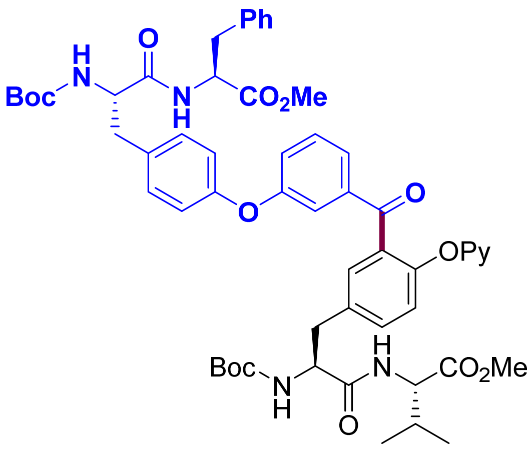
(3at)

Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3at). Following the general procedure in toluene, using aldehyde **2t** (0.45 mmol, 246 mg) and Boc-Tyr(OPy)-Leu-OMe (**1a**) (0.15 mmol, 73.0 mg) provided 92 mg (60% yield) of **3at** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.56 (ddd, *J* = 8.7, 7.4, 2.0 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.30 – 7.23 (m, 4H), 7.22 – 6.99 (m, 7H), 6.95 – 6.81 (m, 3H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.54 (s, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 8.3 Hz, 1H), 5.03 (t, *J* = 8.1 Hz, 1H), 4.90 – 4.77 (m, 1H), 4.60 (td, *J* = 8.5, 4.4 Hz, 1H), 4.48 – 4.25 (m, 2H), 3.70 (s, 6H), 3.21 – 2.91 (m, 6H), 1.69 – 1.52 (m, 3H), 1.43 (s, 9H), 1.40 (s, 9H), 0.98 – 0.87 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 171.5, 171.3, 170.8, 170.7, 162.8, 156.9, 155.7, 155.4, 155.3, 155.2, 150.5, 146.9, 139.3, 139.1, 135.5, 133.2, 133.2, 131.0, 130.7, 129.3, 129.2, 129.1, 128.6, 128.5, 127.1, 127.1, 125.1, 123.1, 122.9, 119.6, 118.8, 118.5, 111.3, 80.3, 80.2, 55.6, 55.3, 53.2, 53.0, 52.3, 50.7, 41.4, 37.9, 37.5, 37.1, 28.2, 24.6, 22.7, 21.8. IR (cm^{-1}): 3304, 2957, 1742, 1656, 1505, 1429, 1243, 1167, 732. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{57}H_{67}N_5O_{13}$): 1029.4735, *found* 1029.4761.



(3as)

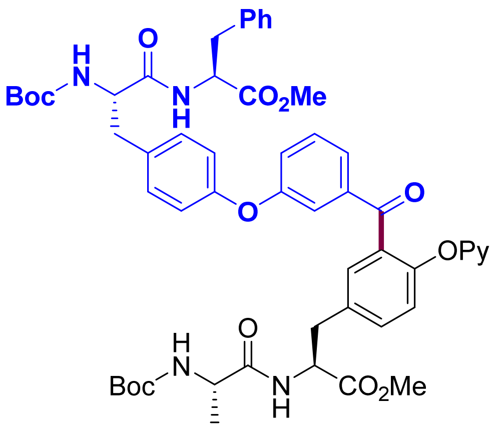
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-leucinate (3as). Following the general procedure in toluene, using aldehyde **2s** (0.45 mmol, 224 mg) and Boc-Tyr(OPy)-Leu-OMe (**1a**) (0.15 mmol, 73.0 mg) provided 76 mg (52% yield) of **3as** as a white solid. Mp 109 -110 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 4.9 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.50 – 7.35 (m, 4H), 7.34 – 7.23 (m, 1H), 7.23 – 7.15 (m, 3H), 7.10 (d, J = 8.3 Hz, 1H), 6.87 (dd, J = 12.1, 7.3 Hz, 3H), 6.66 – 6.53 (m, 3H), 4.66 – 4.53 (m, 1H), 4.53 – 4.22 (m, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.27 – 2.94 (m, 4H), 2.16 – 2.13 (m, 2H), 1.70 – 1.49 (m, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 0.96 – 0.78 (m, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 194.2, 173.0, 171.9, 171.3, 170.9, 163.0, 157.1, 155.9, 155.5, 150.6, 147.0, 139.5, 139.3, 133.4, 131.9, 131.2, 130.8, 130.8, 129.5, 125.2, 123.2, 123.0, 119.7, 119.0, 119.0, 118.6, 111.5, 80.3, 57.3, 56.0, 55.3, 52.4, 52.2, 50.9, 41.5, 37.4, 31.3, 28.4, 28.3, 24.8, 22.9, 21.9, 18.9, 17.9. IR (cm^{-1}): 3305, 1741, 1654, 1580, 1241, 1607. HRMS (ESI) m/z: (M$^+$) *caldc* for ($C_{53}H_{67}N_5O_{13}$): 981.4735, *found* 981.4735.



(3ct)

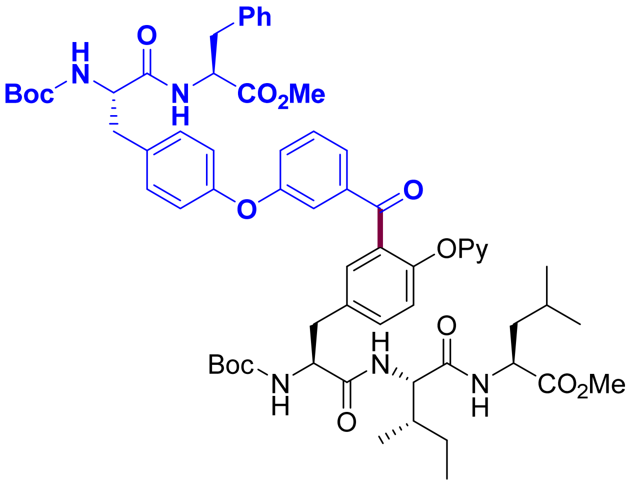
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)

phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-valinate (3ct). Following the general procedure in toluene, using aldehyde **2t** (0.45 mmol, 246 mg) and Boc-Tyr(OPy)-Val-OMe (**1c**) (0.15 mmol, 71.0 mg) provided 89 mg (58% yield) of **3ct** as a white solid. Mp 102 – 103 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 4.9 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.37 (m, 4H), 7.32 – 6.99 (m, 11H), 6.86 (tt, *J* = 14.1, 7.1 Hz, 3H), 6.67 (t, *J* = 9.0 Hz, 2H), 6.45 (d, *J* = 7.6 Hz, 1H), 5.24 (d, *J* = 8.1 Hz, 1H), 5.05 (d, *J* = 9.1 Hz, 1H), 4.82 (dt, *J* = 20.2, 6.8 Hz, 1H), 4.60 – 4.20 (m, 3H), 3.69 (s, 6H), 3.20 – 2.94 (m, 6H), 2.25 – 2.09 (m, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 1.35 – 1.22 (m, 1H), 0.89 (dd, *J* = 13.0, 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 172.2, 171.9, 171.8, 171.3, 171.3, 171.2, 163.2, 157.4, 156.1, 150.9, 147.2, 139.8, 139.6, 139.2, 136.0, 133.7, 133.6, 132.3, 132.1, 131.4, 131.1, 129.7, 129.6, 129.5, 129.0, 128.9, 127.5, 125.4, 123.5, 123.3, 119.9, 119.3, 118.9, 111.8, 80.7, 80.6, 57.6, 53.6, 53.5, 52.7, 52.5, 38.31, 38.2, 37.9, 37.4, 31.6, 28.6, 28.5, 19.2, 18.1. IR (cm^{-1}): 3306, 1740, 1655, 1580, 1427, 1240, 1160. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{56}H_{65}N_5O_{13}$): 1015.4579, *found* 1015.4579.



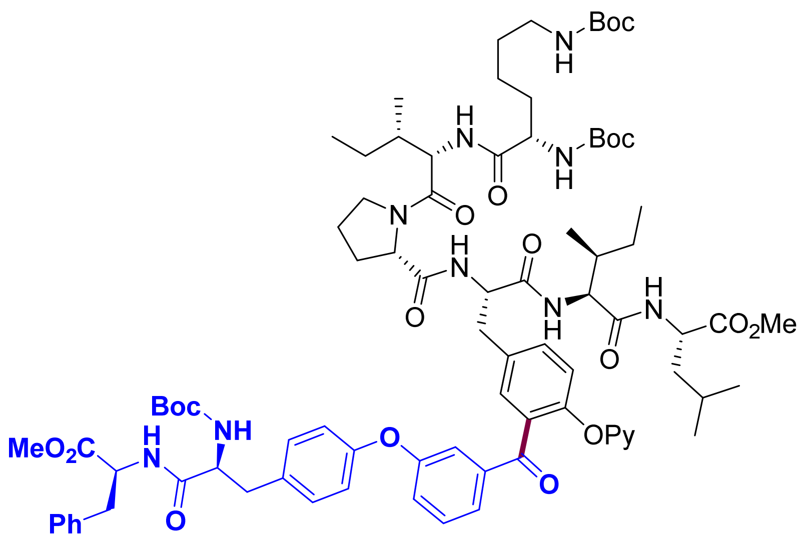
(3jt)

Methyl (*S*)-3-[3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy) phenyl]-2-[(*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido]propanoate (3jt). Following the general procedure in toluene, using aldehyde **2t** (0.45 mmol, 246 mg) and Boc-Ala-Tyr(OPy)-OMe (**1j**) (0.15 mmol, 66.0 mg) provided 96 mg (65% yield) of **3jt** as a white solid. Mp 93 -94 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 4.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.20 (m, 5H), 7.20 – 6.95 (m, 6H), 6.91 (t, *J* = 6.1 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 3H), 6.64 (d, *J* = 8.2 Hz, 1H), 5.26 (s, 1H), 5.01 (s, 1H), 4.90 – 4.79 (m, 2H), 4.38 – 4.35 (m 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.25 (dd, *J* = 14.1, 5.8 Hz, 1H), 3.14 – 2.92 (m, 5H), 1.43 (s, 9H), 1.42 (s, 9H), 1.33 (d, *J* = 7.1 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 194.4, 172.6, 171.7, 171.6, 171.5, 171.5, 171.0, 170.8, 162.8, 157.1, 155.9, 150.7, 147.0, 139.6, 139.3, 135.8, 135.7, 133.4, 132.7, 131.9, 131.2, 131.1, 130.8, 129.5, 129.3, 129.3, 128.8, 128.7, 127.3, 127.2, 125.1, 123.3, 123.1, 123.0, 119.6, 119.0, 118.8, 111.6, 80.4, 80.2, 55.8, 53.4, 53.2, 53.1, 52.6, 52.4, 50.2, 38.1, 38.0, 37.7, 37.3, 29.8, 28.4, 18.0. IR (cm^{-1}): 3306, 1741, 1660, 1504, 1428, 1240, 1162. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{54}H_{61}N_5O_{13}$): 987.4266, *found* 987.4264.



(3lt)

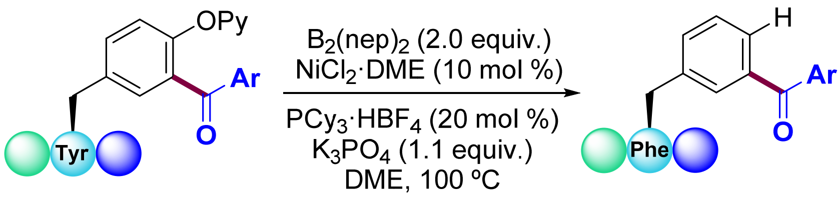
Methyl [(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl) amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl) phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-*L*-isoleucyl-*L*-leucinate (3jt). Following the general procedure in toluene, using aldehyde **2t** (0.45 mmol, 246 mg) and Boc-Ala-Tyr(OPy)-Ile-Leu-OMe (**1l**) (0.15 mmol, 90.0 mg) provided 106 mg (62% yield) of **3jt** as a white solid. Mp 111 – 112 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 4.8 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.51 – 7.35 (m, 4H), 7.33 – 7.19 (m, 5H), 7.17 – 7.01 (m, 6H), 6.87 (dd, *J* = 21.2, 7.0 Hz, 3H), 6.77 – 6.56 (m, 2H), 5.30 (t, *J* = 9.3 Hz, 1H), 5.19 – 5.05 (m, 1H), 4.86 – 4.81 (m, 1H), 4.59 – 4.55 (m, 1H), 4.54 – 4.38 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.25 – 2.76 (m, 6H), 2.32 (s, 2H), 1.88 (s, 1H), 1.76 – 1.48 (m, 4H), 1.41 (s, 9H), 1.39 (s, 9H), 1.15 – 1.10 (m,1H), 0.90 – 0.88 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 172.9, 171.7, 171.5, 171.1, 170.9, 170.7, 162.8, 162.7, 156.9, 155.7, 155.6, 155.5 155.2, 150.5, 150.4, 146.8, 146.8, 139.3, 139.1, 135.6, 135.5, 133.4, 133.2, 133.0, 131.9, 131.8, 131.0, 130.7, 129.3, 129.1, 129.0, 128.5, 128.4, 127.1, 127.0, 125.0, 123.1, 123.0, 122.9, 119.5, 118.8, 118.5, 111.3, 80.3, 80.1, 57.8, 55.5, 53.2, 53.1, 52.2, 52.1, 50.8, 41.0, 37.9, 37.6, 37.2, 28.9, 28.1, 24.7, 22.6, 21.8, 15.1, 11.2. IR (cm^{-1}): 3288, 1743, 1645, 1505, 1240, 1161. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{63}H_{78}N_6O_{14}$): 1142.5576, *found* 1142.5576.



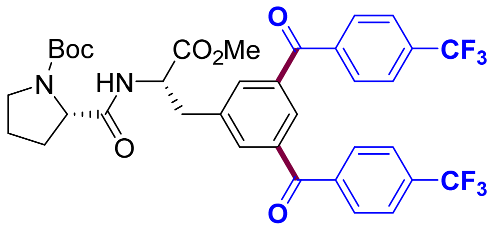
(3qt)

Methyl (*S*)-3-[3-(3-(4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl]-2-[(*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido]propanoate (3qt). Following the general procedure in toluene, using aldehyde **2t** (0.45 mmol, 246 mg) and Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe (**1q**) (0.15 mmol, 155.0 mg) provided 79 mg (33% yield) of **3qt** as a white solid. Mp 68 – 70 ºC. ^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC) δ 8.18 – 7.89 (m, 4H), 7.68 (t, J = 7.7 Hz, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.5 Hz, 5H), 7.33 – 7.07 (m, 11H), 7.00 (t, J = 6.3 Hz, 1H), 6.91 – 6.79 (m, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.51 (s, 1H), 6.29 (s, 1H), 4.61 (dt, J = 14.4, 6.9 Hz, 2H), 4.43 – 4.21 (m, 6H), 3.91 (d, J = 7.1 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.64 (d, J = 1.8 Hz, 2H), 3.60 (d, J = 2.2 Hz, 5H), 3.52 (s, 1H), 3.14 (dd, J = 14.5, 5.1 Hz, 2H), 3.01 – 2.59 (m, 7H), 2.05 – 1.72 (m, 8H), 1.38 (s, 27H), 1.15 – 1.07 (m, 3H), 0.90 – 0.78 (m, 21H). ^{13}C NMR (126 MHz, DMSO-d_6 at 80 ºC) δ 193.2, 172.0, 171.4, 171.1, 171.0, 170.9, 170.8, 170.8, 170.3, 169.8, 169.8, 162.0, 156.5, 155.1, 154.7, 154.3, 154.2, 149.3, 146.4, 139.3, 138.8, 136.6, 133.9, 133.0, 132.5, 130.9, 130.3, 129.7, 129.3, 128.6, 128.5, 127.7, 126.0, 126.0, 124.1, 122.2, 121.6, 118.4, 117.9, 117.8, 117.7, 110.6, 77.9, 77.8, 76.9, 59.2, 56.4, 54.4, 54.2, 54.0, 53.3, 53.0, 52.9, 51.2, 51.2, 51.0, 50.0, 46.6, 36.7, 36.6, 36.2, 36.0, 31.1, 28.8, 28.3, 27.9, 27.7, 27.7, 23.8, 23.8, 23.6, 22.3, 22.1, 21.0, 14.8, 14.7, 10.5, 10.1. IR (cm^{-1}): 3304, 1743, 1647, 1390, 1241, 1162. HRMS (ESI) m/z: (M^{+}) *caldc* for ($C_{85}H_{116}N_{10}O_{9}$): 1580.8418, *found* 1580.8418.

5.-Ni-Catalyzed Reductive Cleavage



General Procedure:[2] A reaction tube containing a stirring bar was charged with peptide **3'ih** (0.25 mmol, 204 mg), $NiCl_2 \cdot DME$ (10 mol %, 5.5 mg), $PCy_3 \cdot HBF_4$ (20 mol %, 18 mg), $B_2(nep)_2$ (0.50 mmol, 113 mg) and K_3PO_4 (0.27 mmol, 175 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, dry 1,2-dimethoxyethane (1 mL) was added by syringe under argon atmosphere. The reaction tube was next warmed up to 100 ºC in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, filtered off through a pad of celite and evaporated under vacuum. The resulting crude was then purified by column chromatography (EtOAc/hexanes, 4:6) to afford 75.2 mg (42% yield) of **4**.



(4)

***Tert*-butyl (*S*)-2-[((*S*)-3-(3,5-bis(4-(trifluoromethyl)benzoyl)phenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (4).** White solid. Mp 89-90 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 1.7 Hz, 1H), 7.99 – 7.88 (m, 4H), 7.78 (t, *J* = 8.5 Hz, 3H), 5.26 (d, *J* = 8.6 Hz, 1H), 4.75 (dd, *J* = 8.6, 6.1 Hz, 1H), 4.52 (dd, *J* = 8.6, 3.7 Hz, 1H), 3.78 – 3.41 (m, 4H), 3.30 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.05 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.17 (dd, *J* = 8.5, 4.9 Hz, 1H), 2.05 – 1.86 (m, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 172.1, 169.8, 161.6, 155.2, 147.8, 145.9, 140.2, 139.4, 134.4, 134.0, 133.7 (q, J_{C-F} = 25.2 Hz), 129.9, 129.8, 127.6, 125.0 (q, J_{C-F} = 4.0 Hz), 123.7 (q, J_{C-F} = 273.7 Hz), 118.8, 110.5, 80.0, 58.9, 52.6, 52.1, 47.1, 37.5, 29.0, 28.3, 24.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.06. IR (cm^{-1}): 1744, 1709, 1645, 1322, 1010. HRMS (ESI) m/z: (M^+) *caldc* for ($C_{36}H_{34}F_6N_2O_7$): 720.2270, *found* 720.2271.

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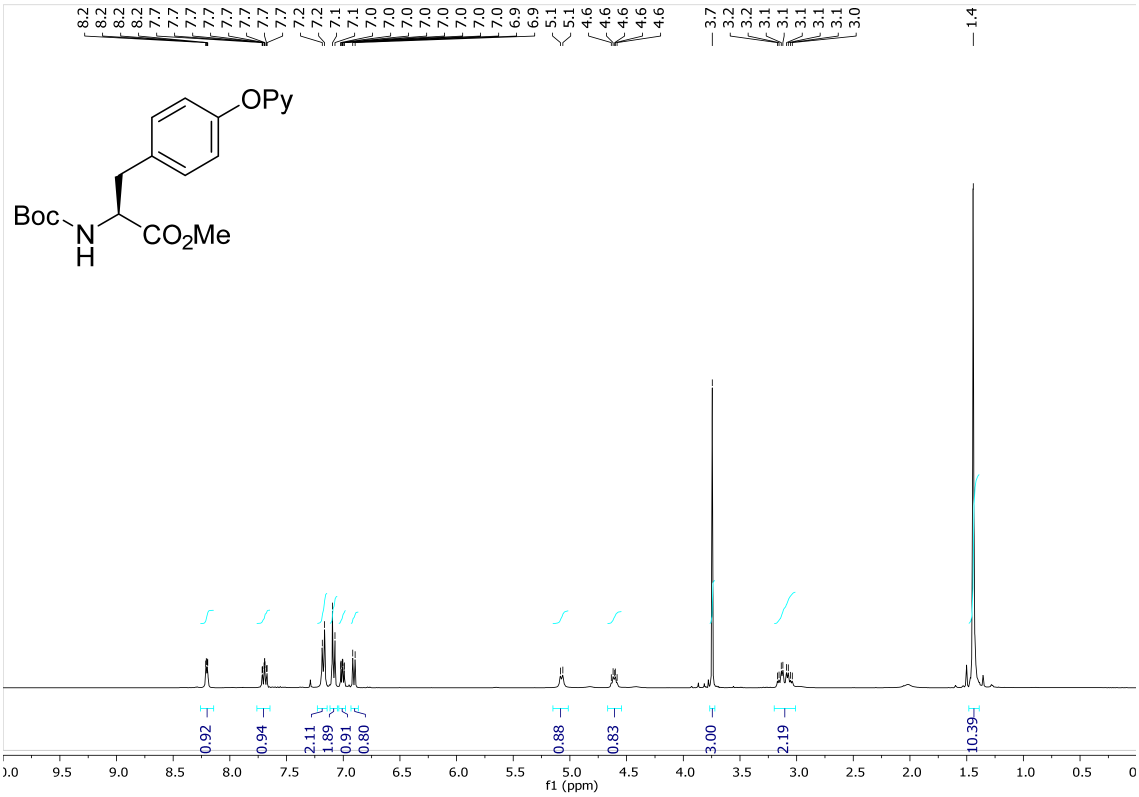
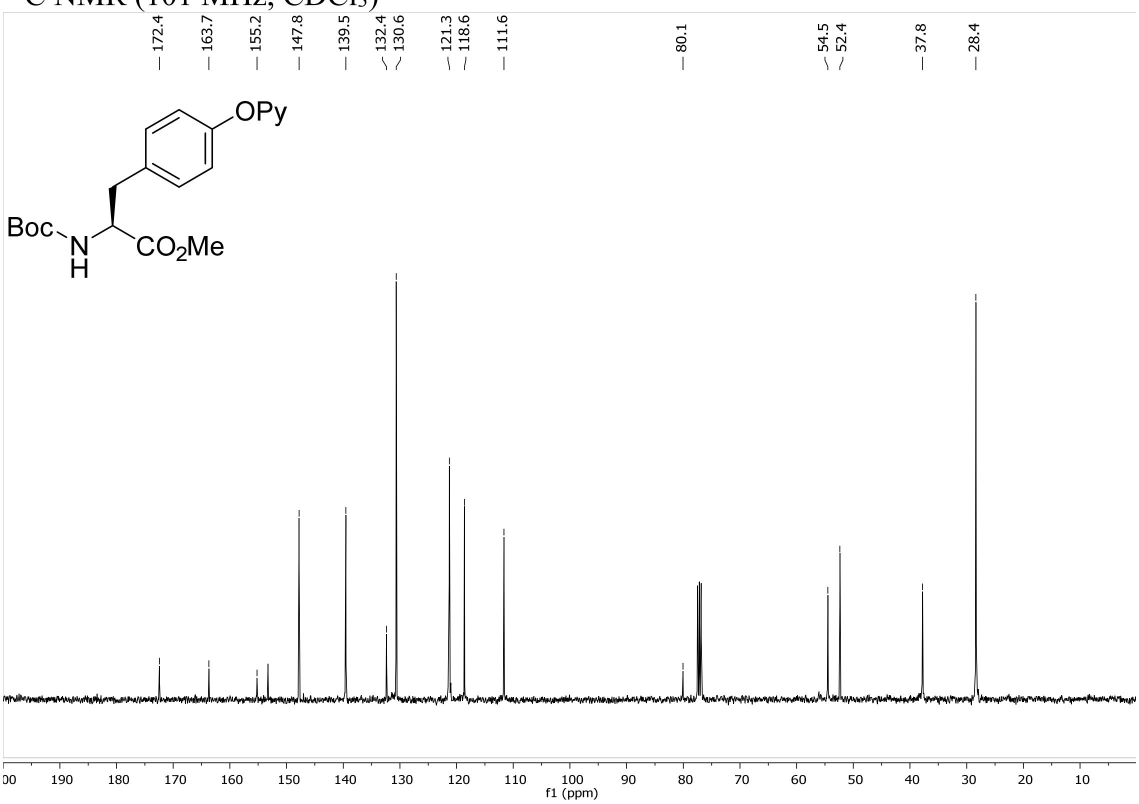
[2] Tobisu, M.; Zhao, J.; Kinuta, H.; Furukawa, T.; Igarashi, T.; Chatani, N. *Adv. Synth. Catal.* **2016**, *358*, 2417.

6.- ^{1}H NMR and ^{13}C NMR Spectra

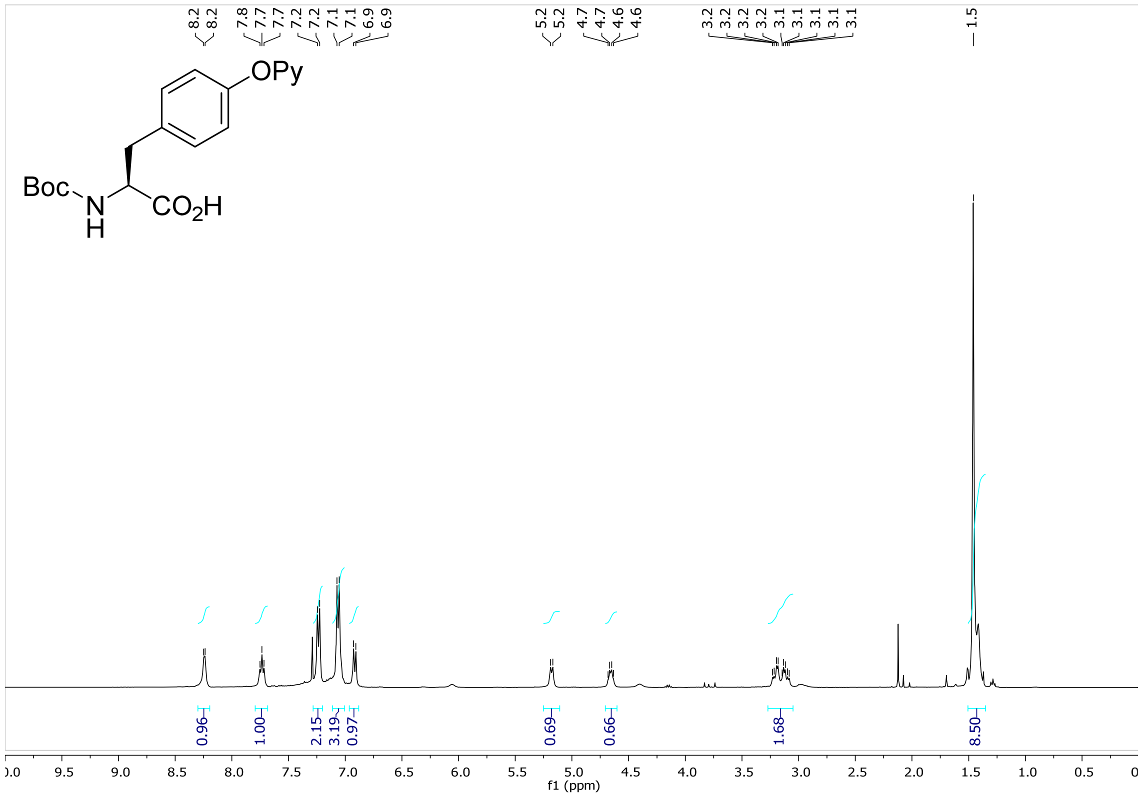
^{1}H NMR (400 MHz, $CDCl_3$)



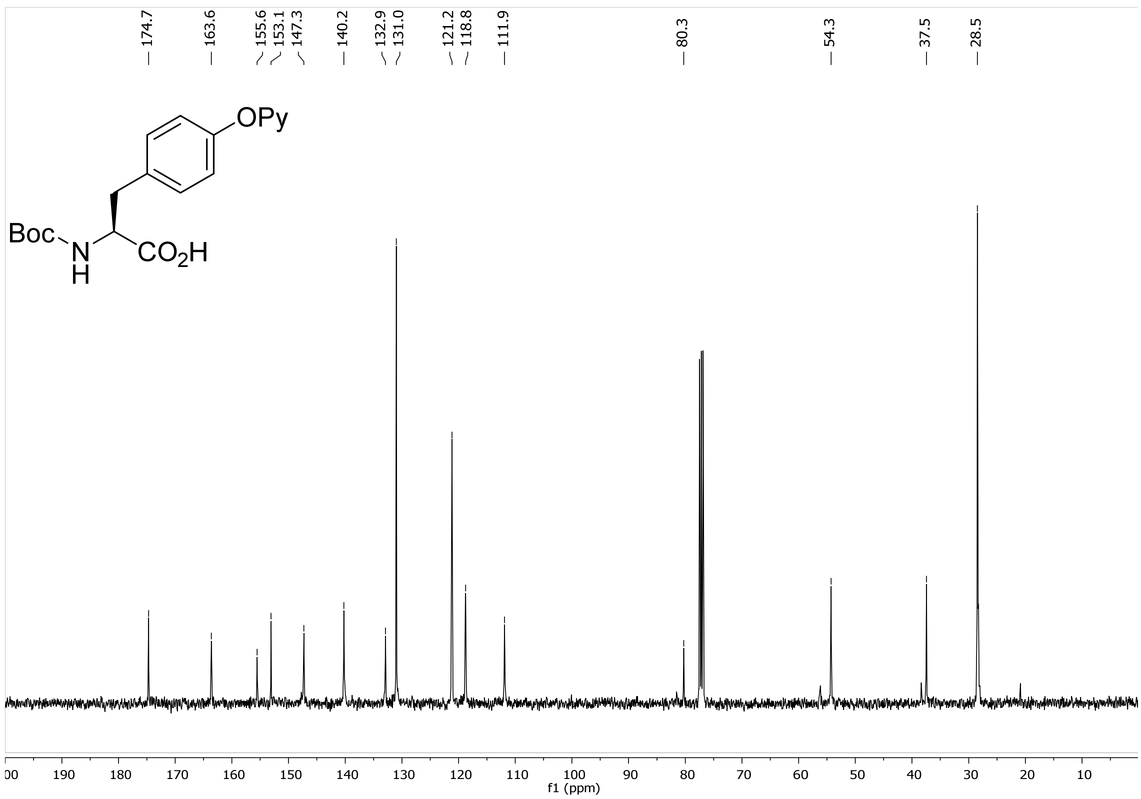
^{13}C NMR (101 MHz, $CDCl_3$)



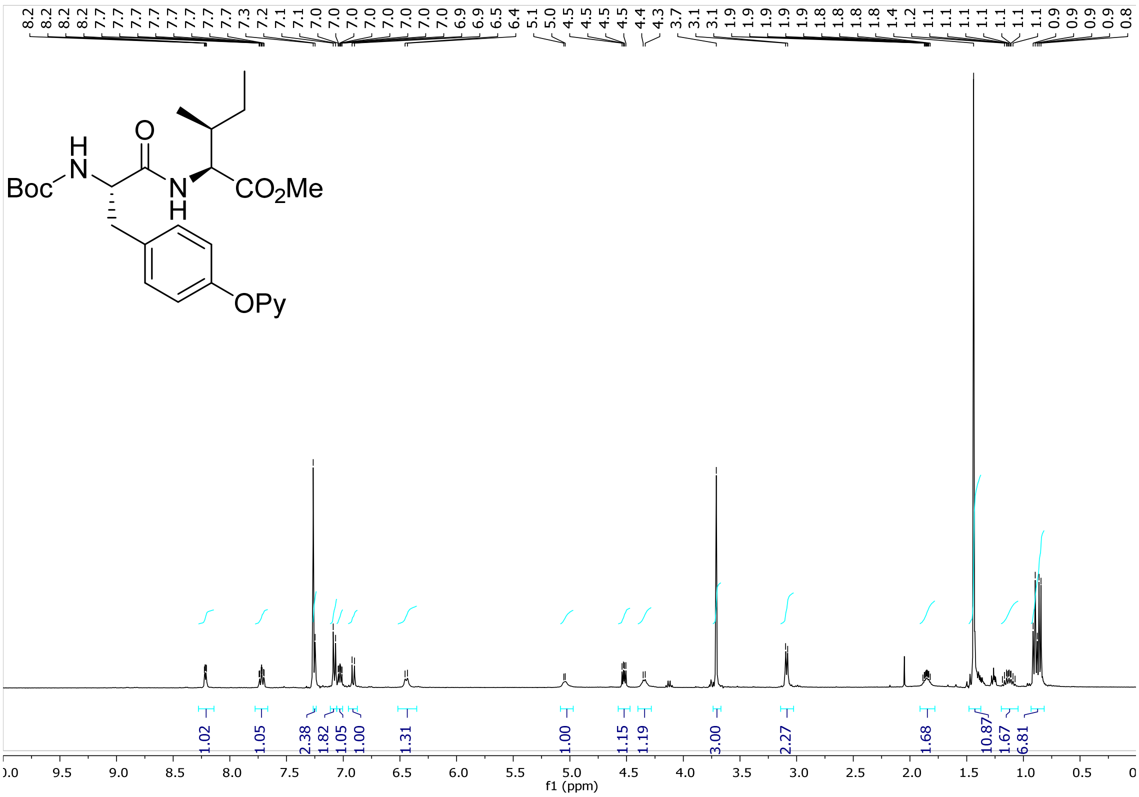
^1H NMR (400 MHz, $CDCl_3$)



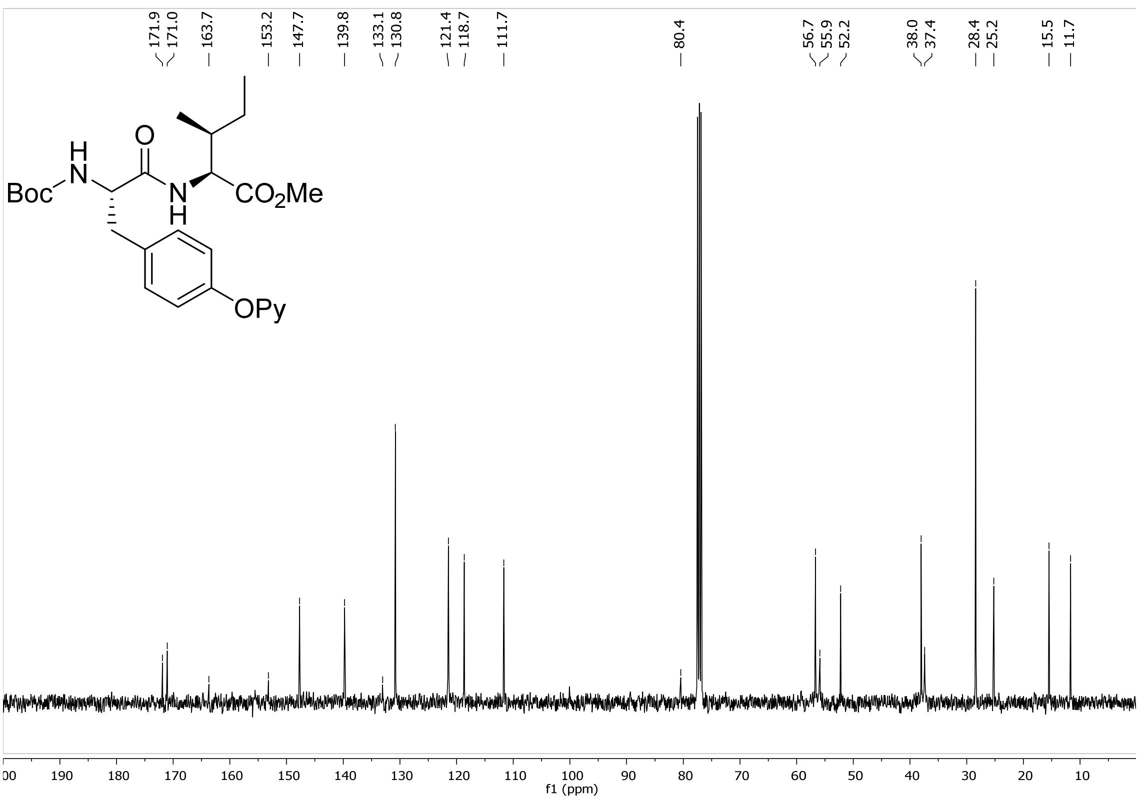
^{13}C NMR (101 MHz, $CDCl_3$)



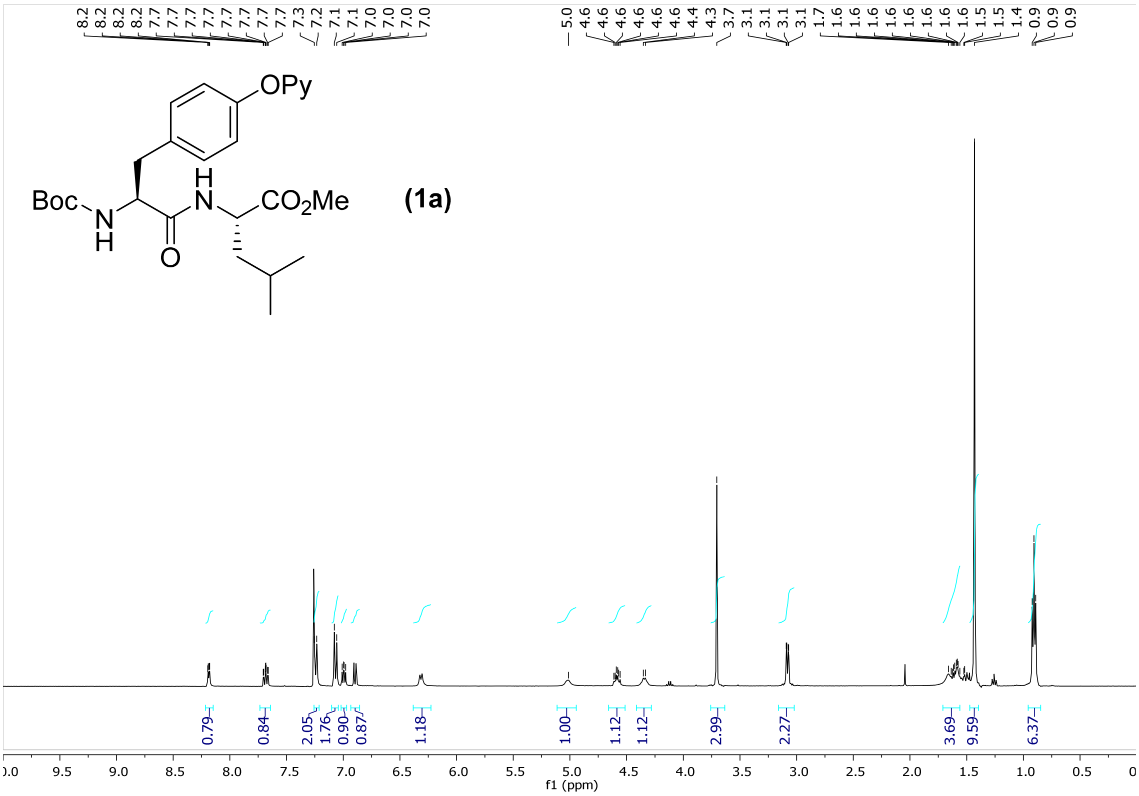
^{1}H NMR (400 MHz, CDCl$_3$)



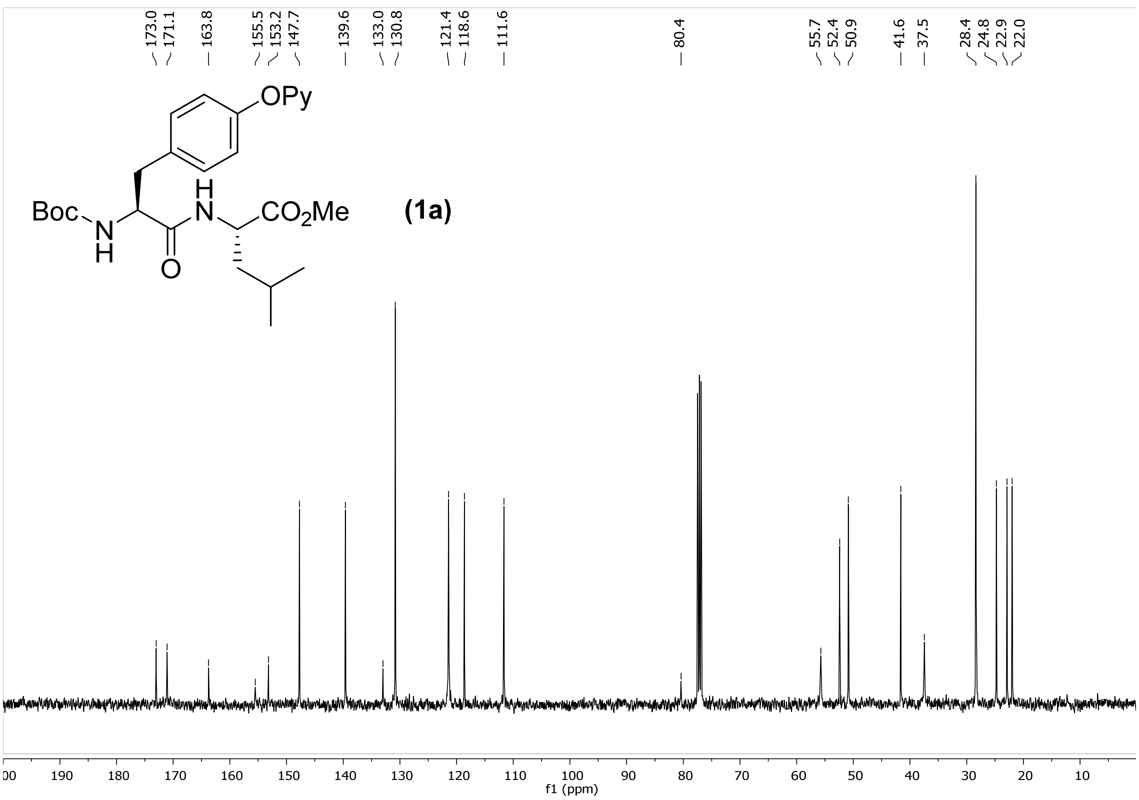
^{13}C NMR (101 MHz, CDCl$_3$)



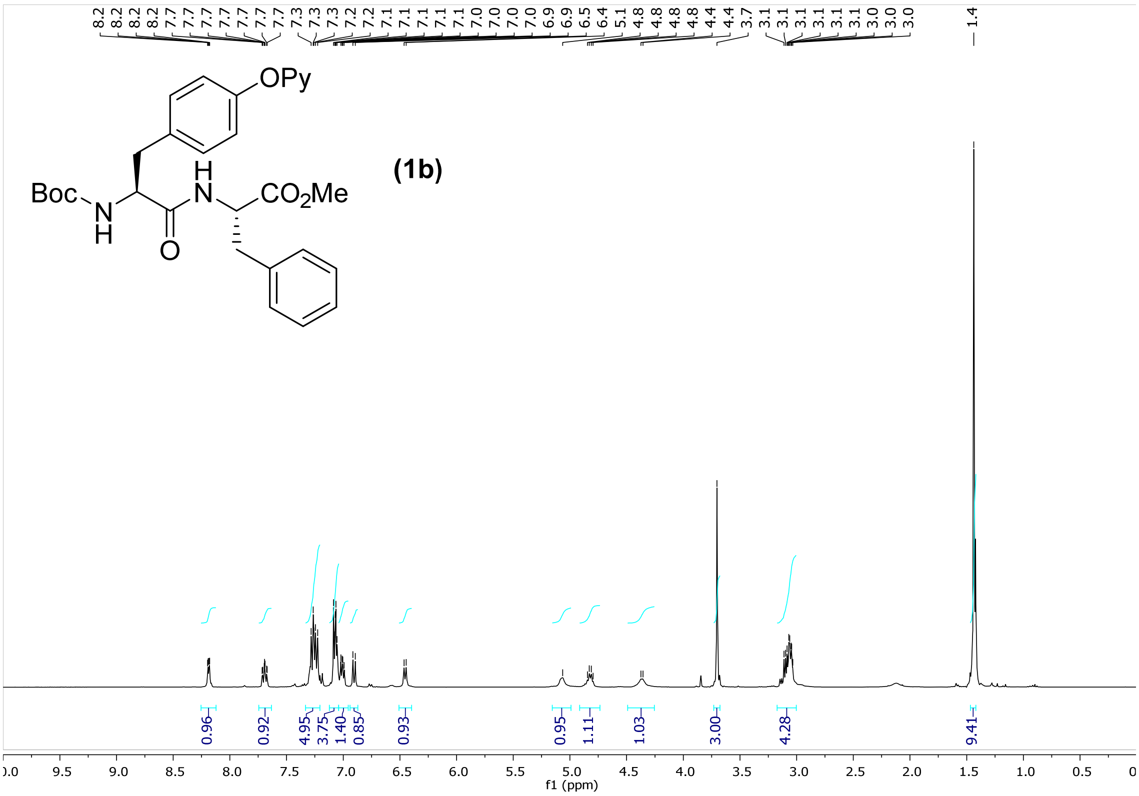
[1]H NMR (400 MHz, CDCl3)



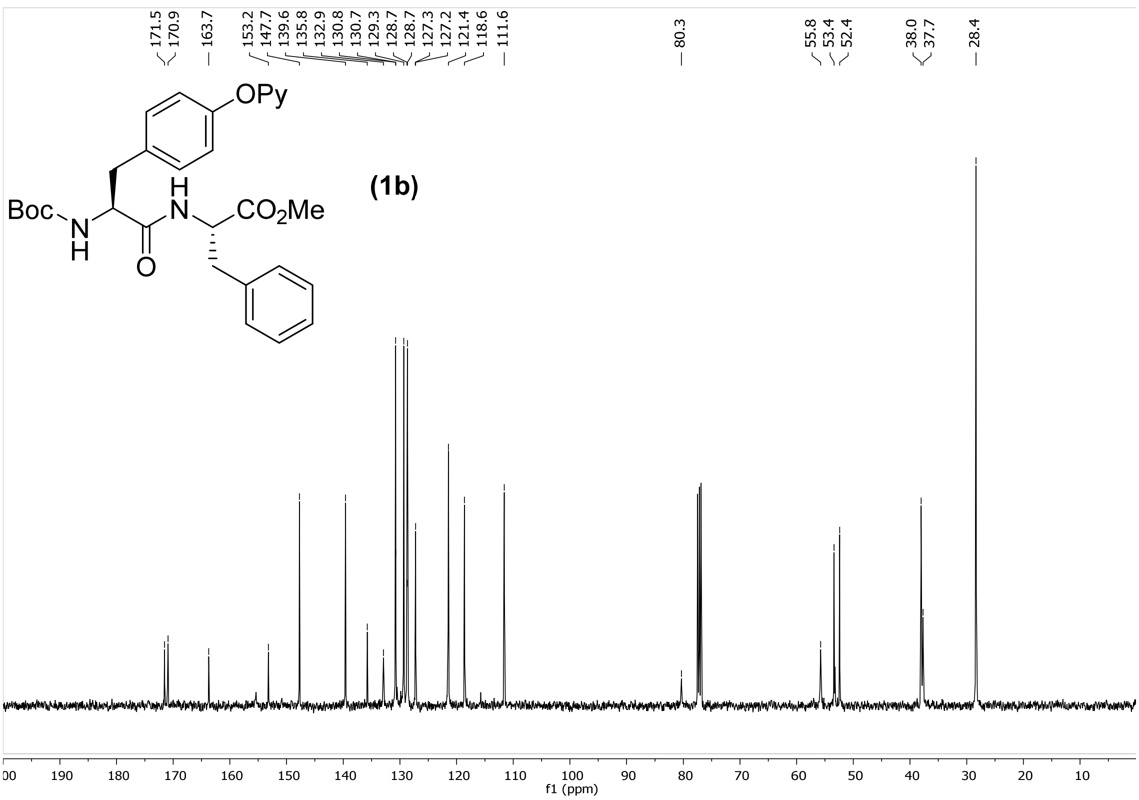
[13]C NMR (101 MHz, CDCl3)



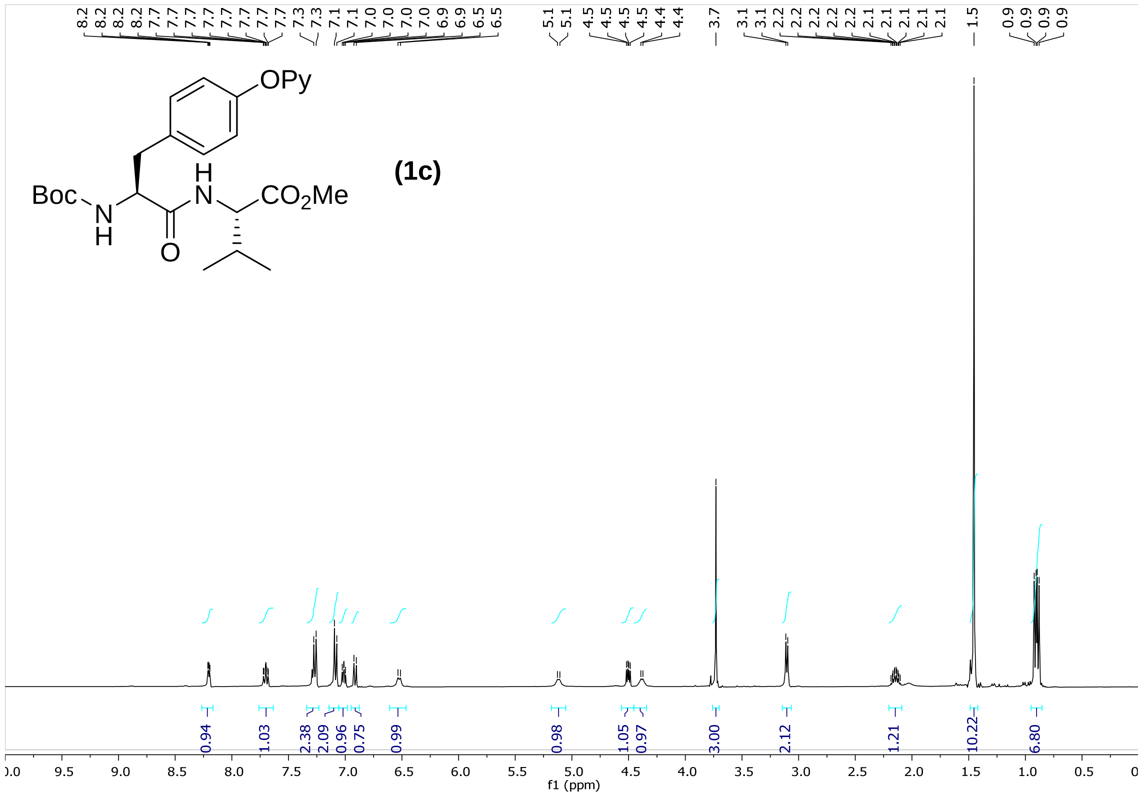
^{1}H NMR (400 MHz, $CDCl_3$)



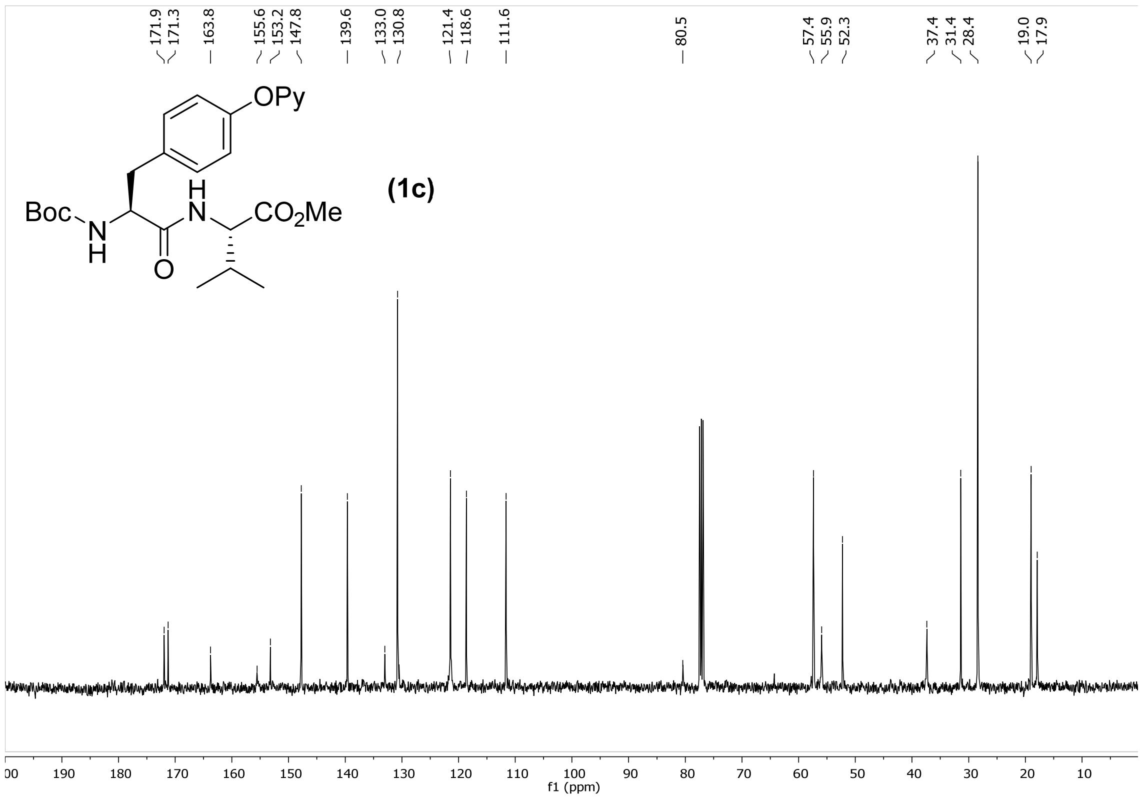
^{13}C NMR (101 MHz, $CDCl_3$)



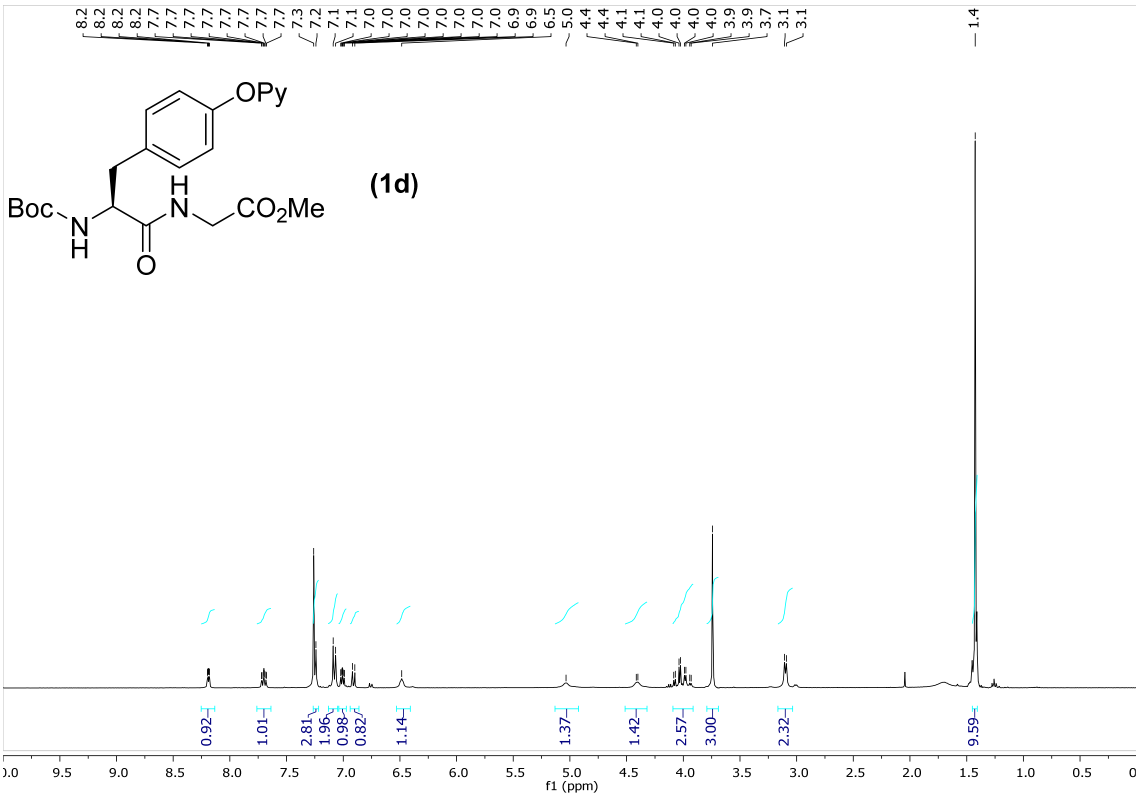
[1]H NMR (400 MHz, $CDCl_3$)



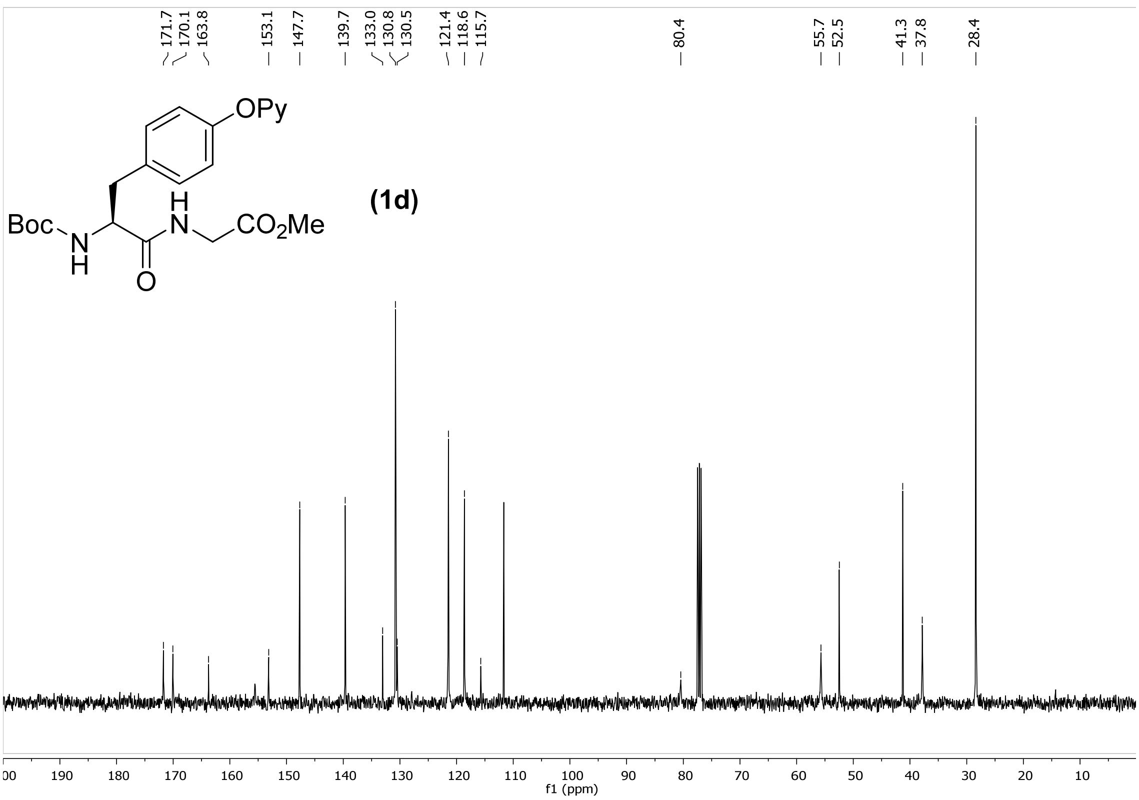
[13]C NMR (101 MHz, $CDCl_3$)



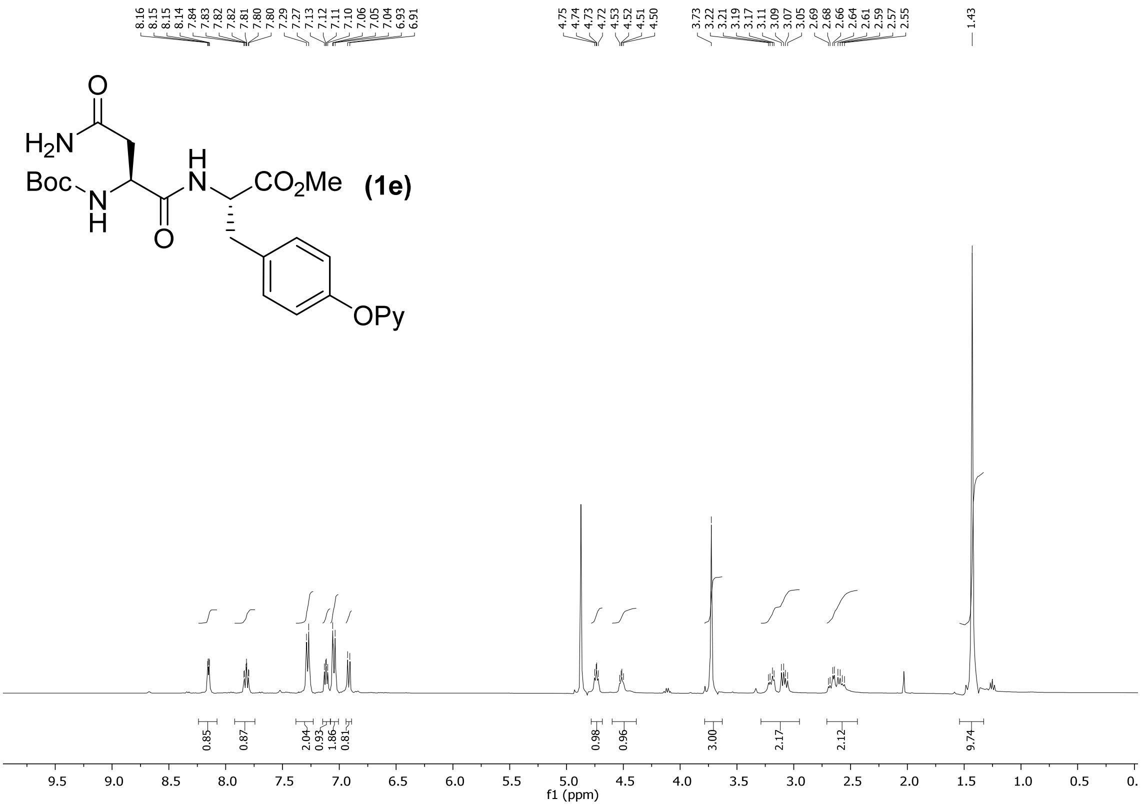
[1]H NMR (400 MHz, $CDCl_3$)



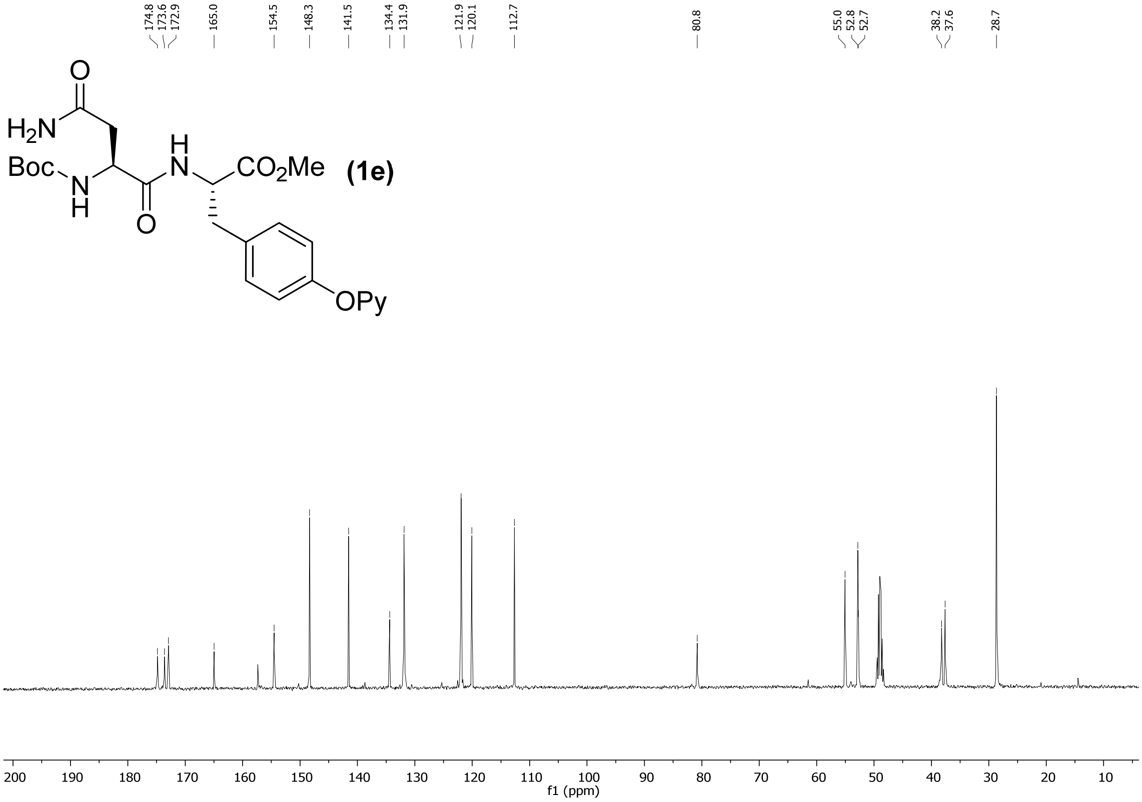
[13]C NMR (101 MHz, $CDCl_3$)



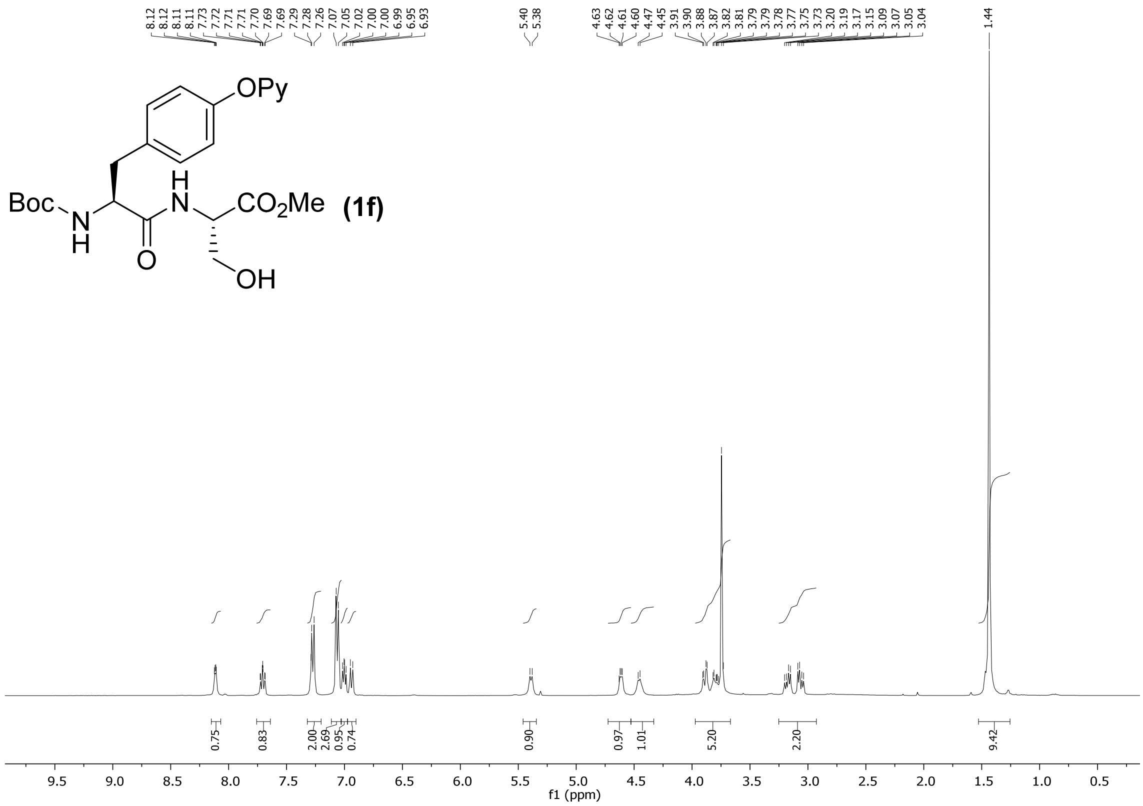
^{1}H NMR (400 MHz, MeOH-d_4)



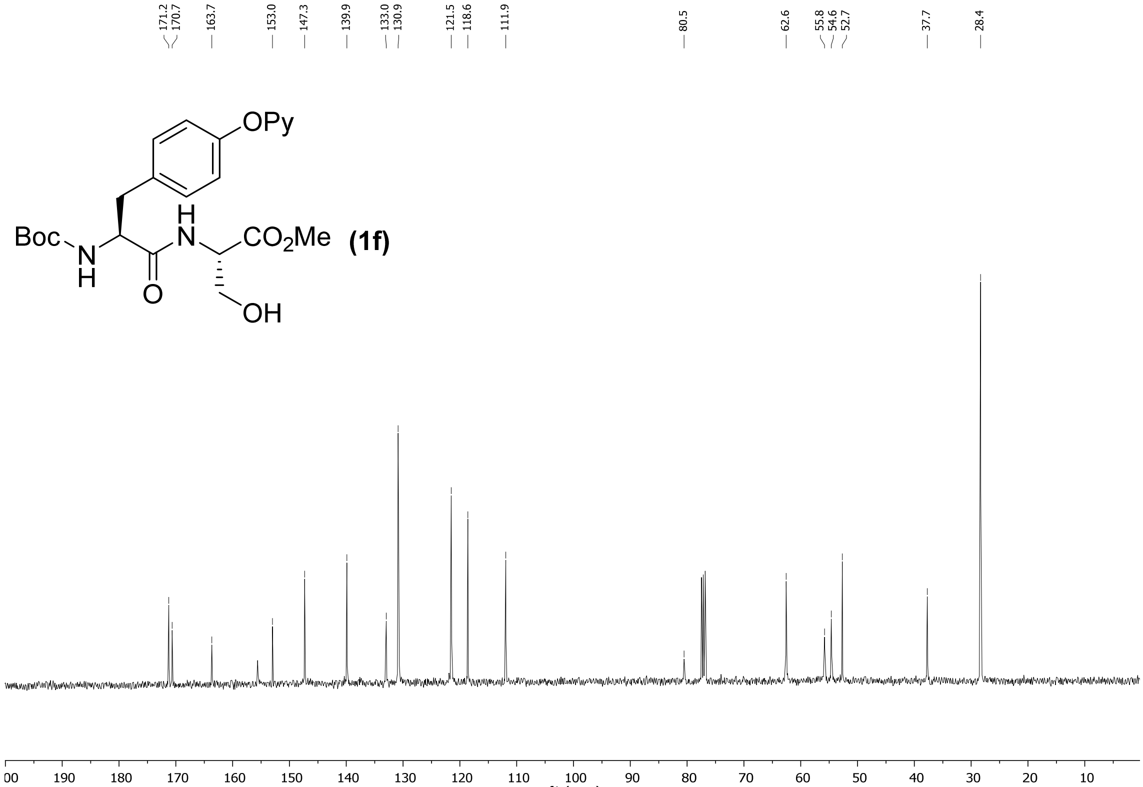
^{13}C NMR (101 MHz, MeOH-d_4)



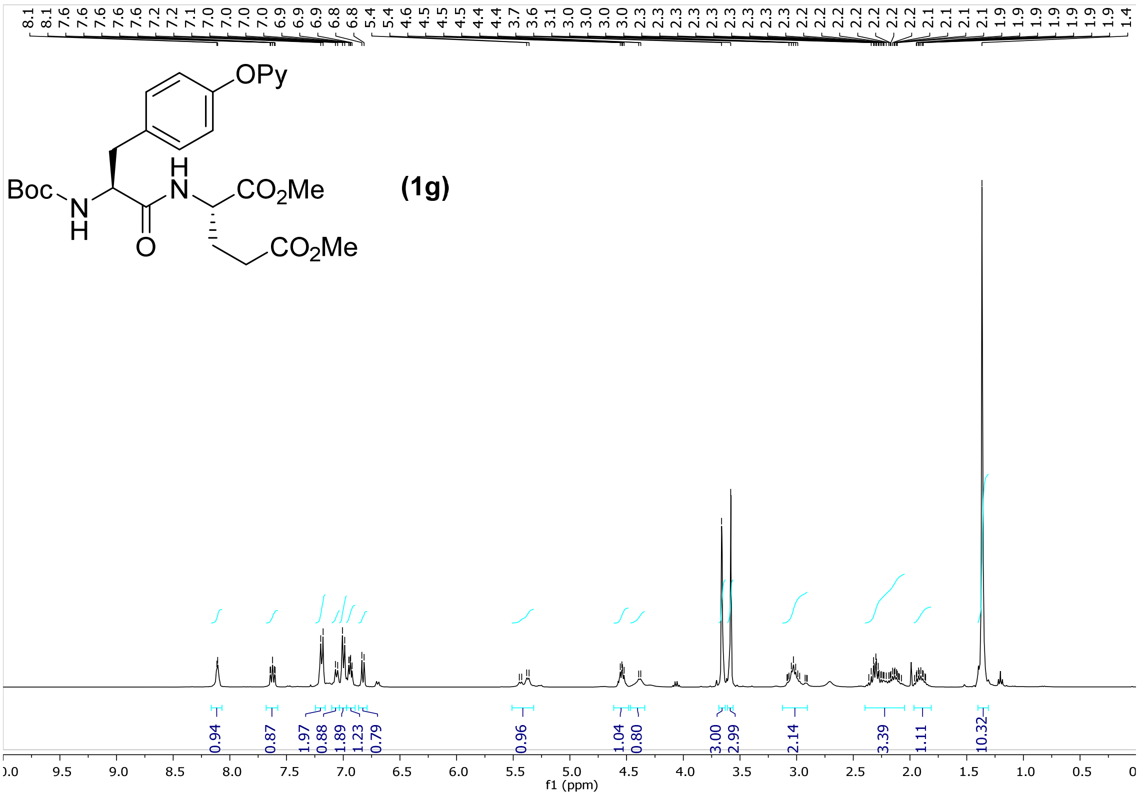
^{1}H NMR (400 MHz, $CDCl_3$)



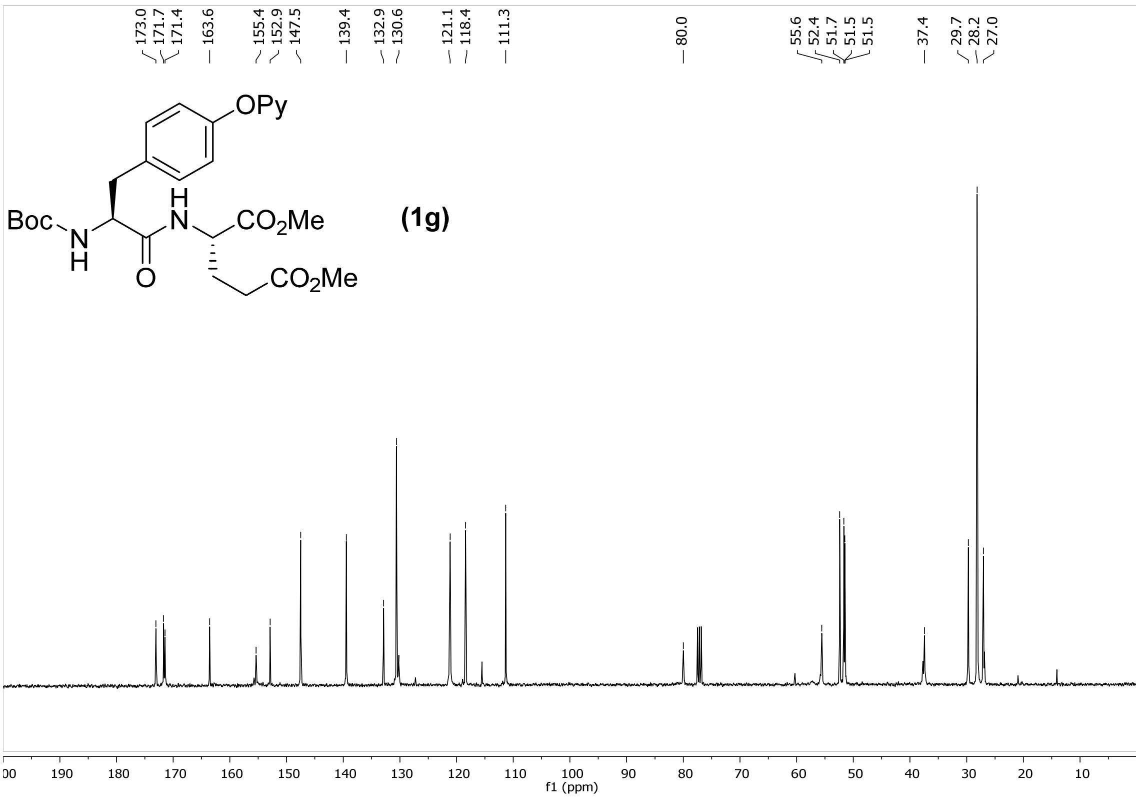
^{13}C NMR (101 MHz, $CDCl_3$)



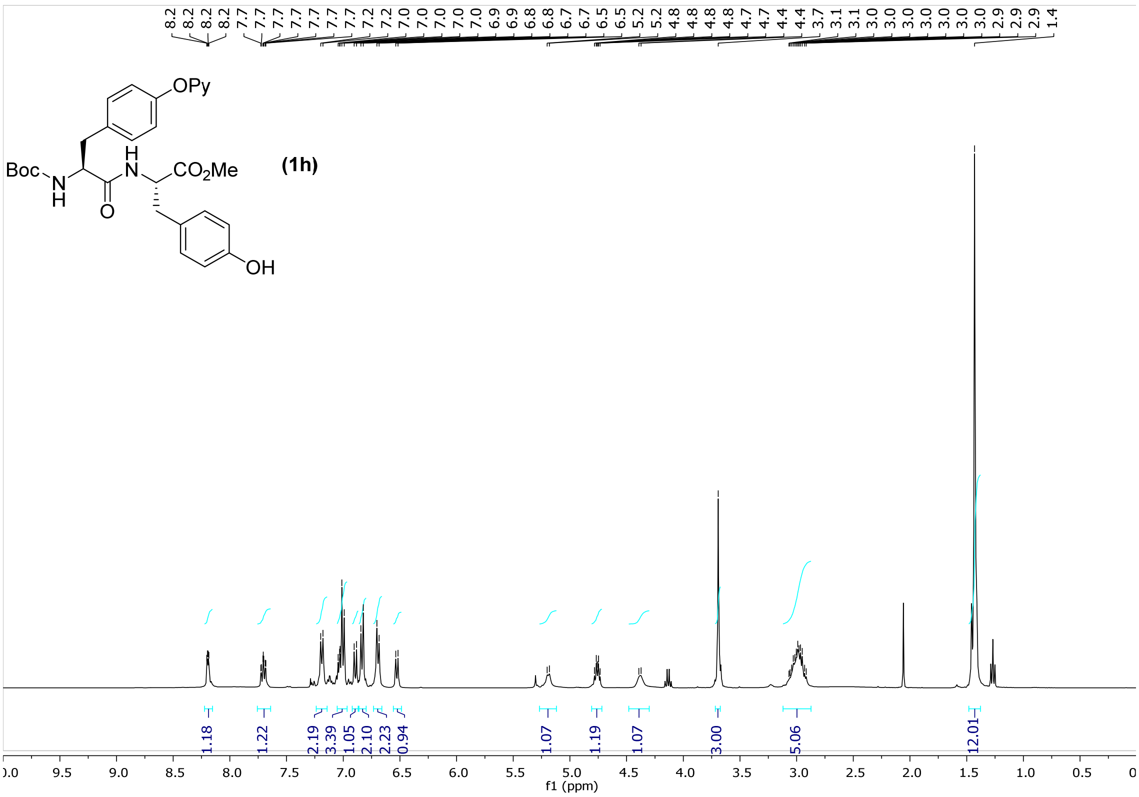
^{1}H NMR (400 MHz, $CDCl_3$)



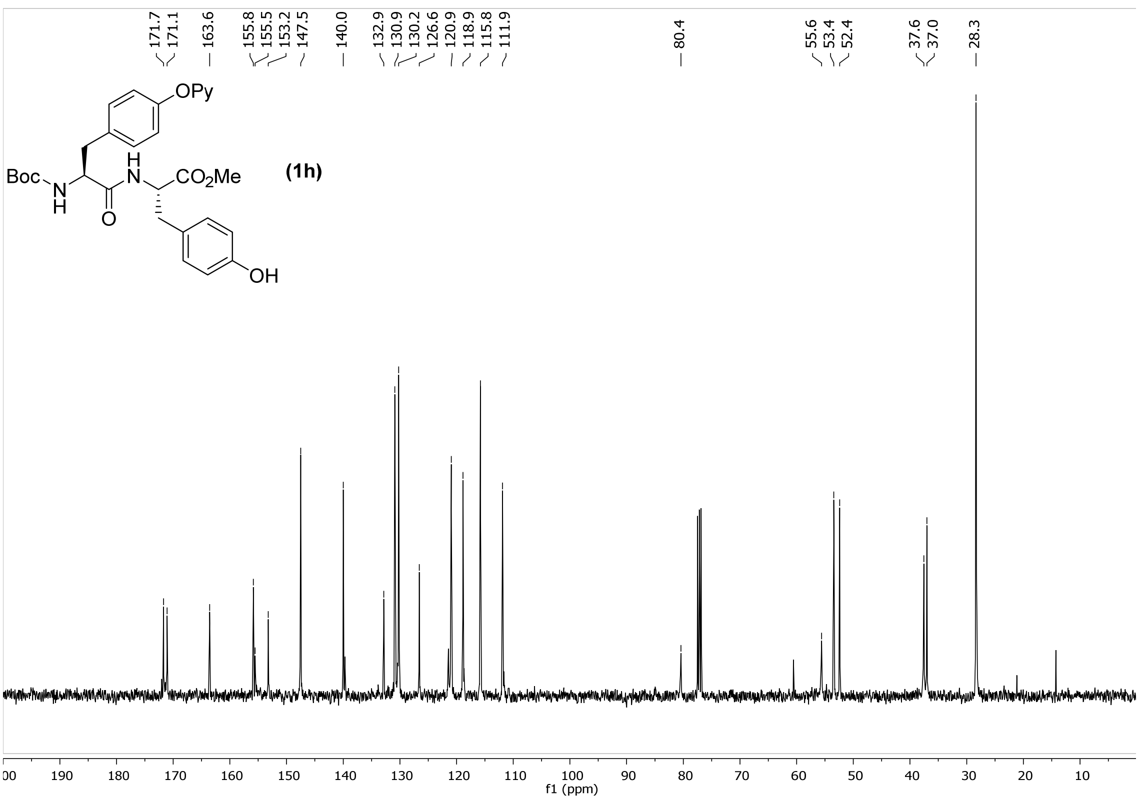
^{13}C NMR (101 MHz, $CDCl_3$)



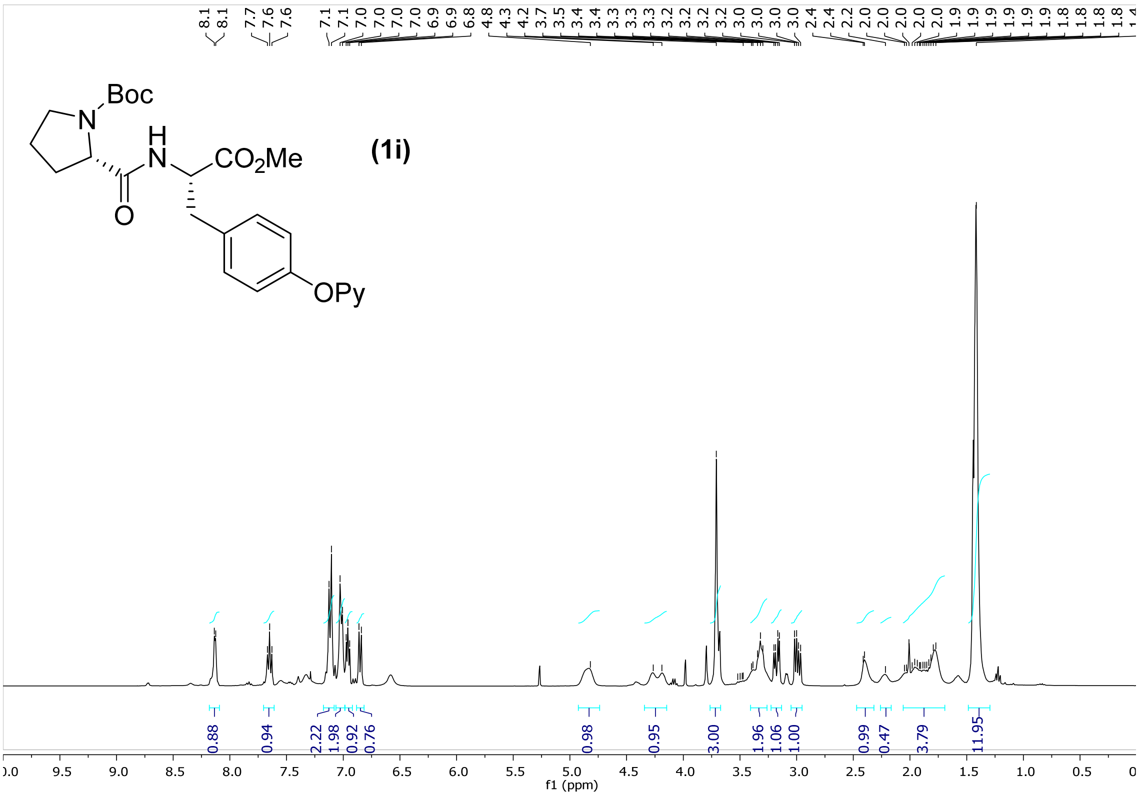
^{1}H NMR (400 MHz, $CDCl_3$)



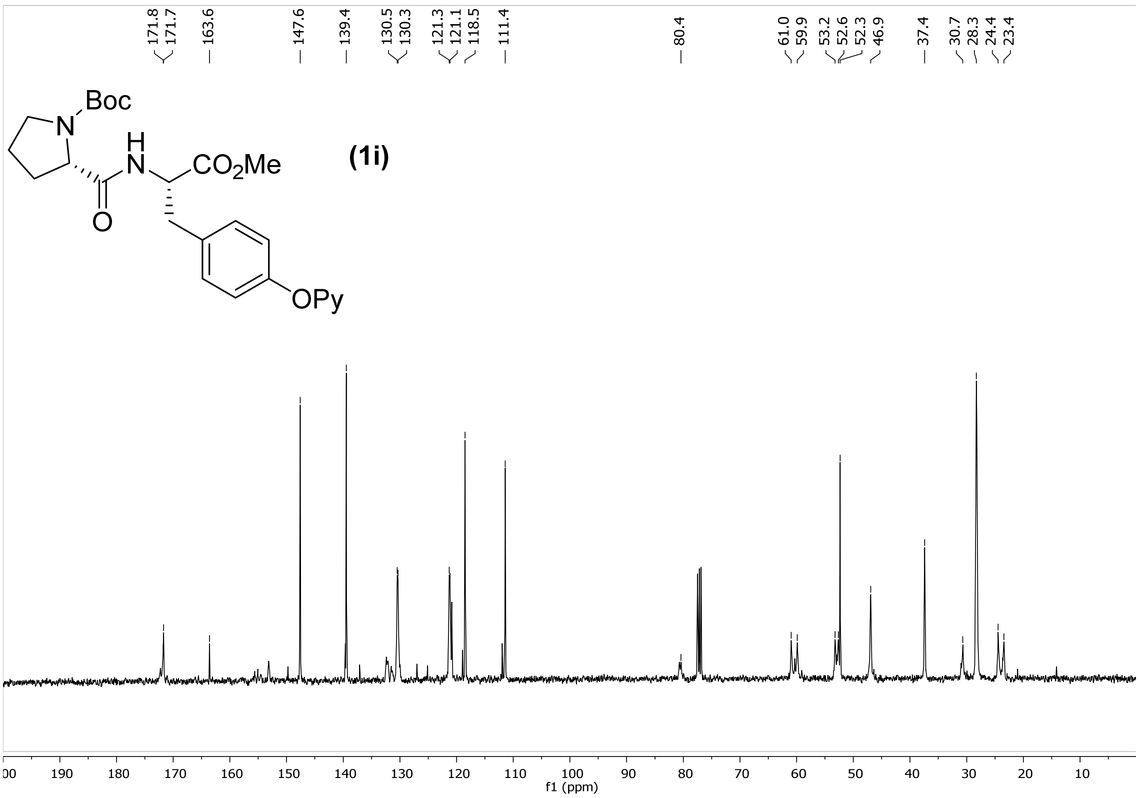
^{13}C NMR (101 MHz, $CDCl_3$)



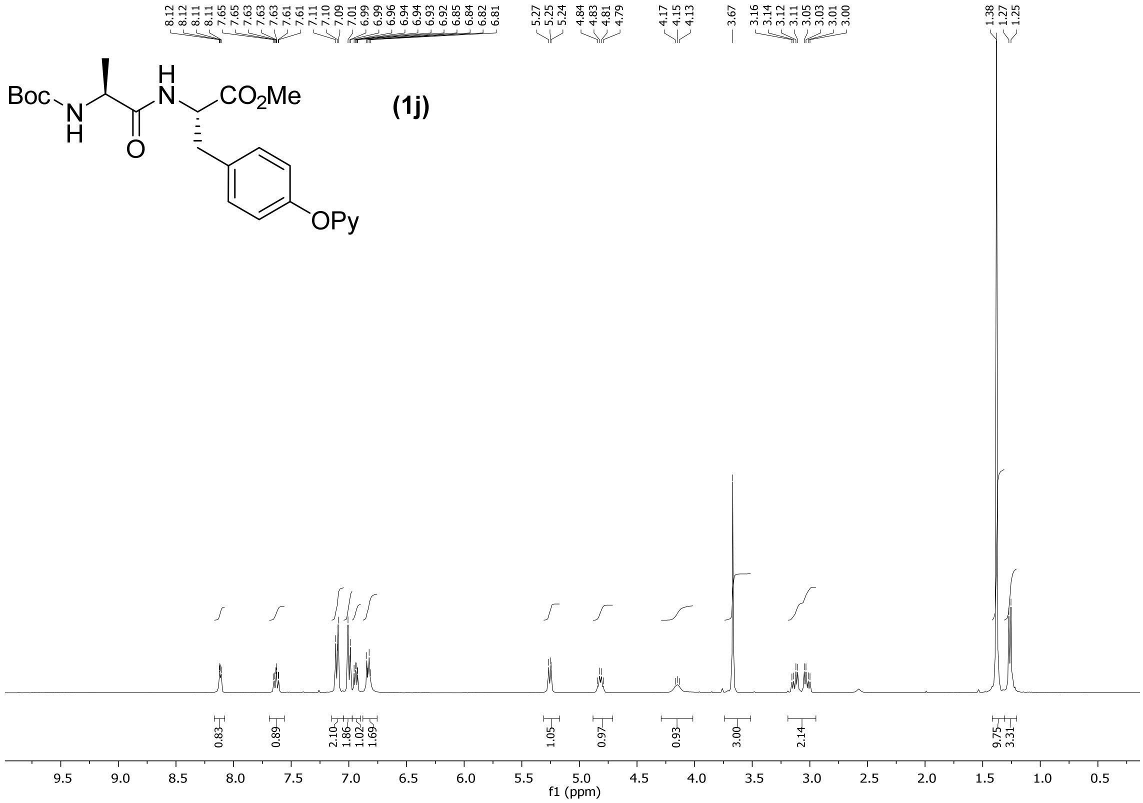
^{1}H NMR (400 MHz, $CDCl_3$)



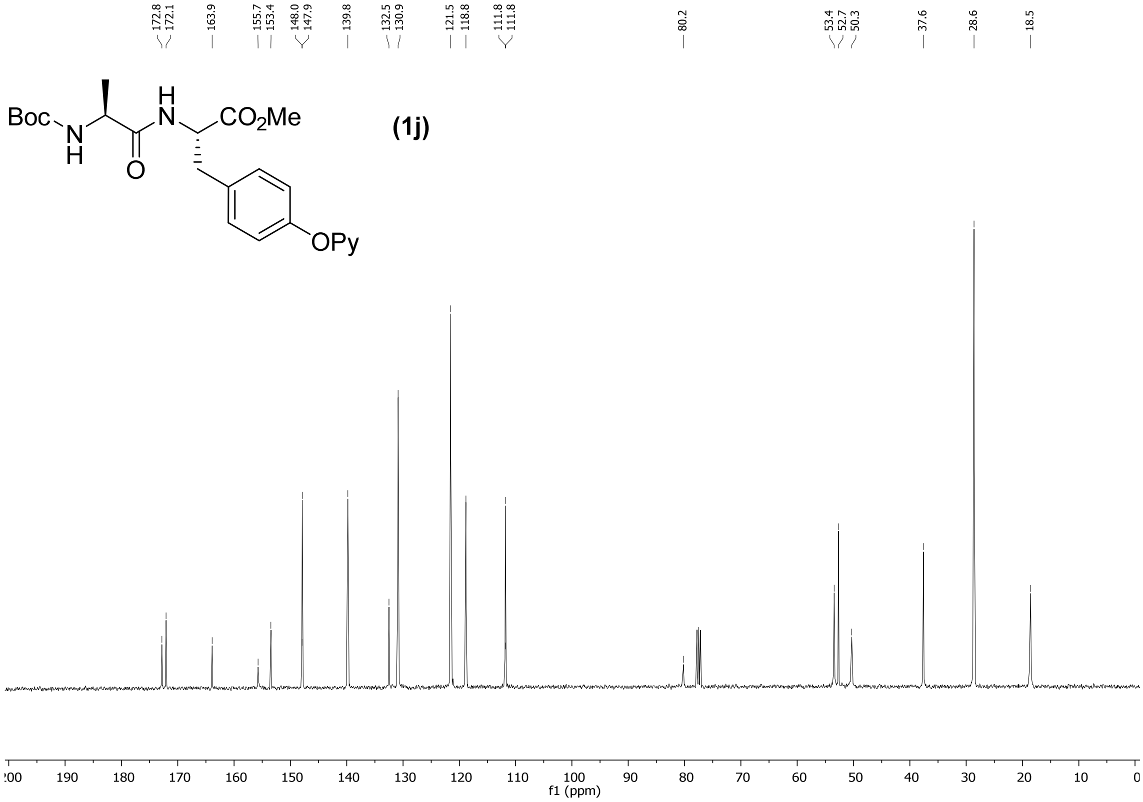
^{13}C NMR (101 MHz, $CDCl_3$)



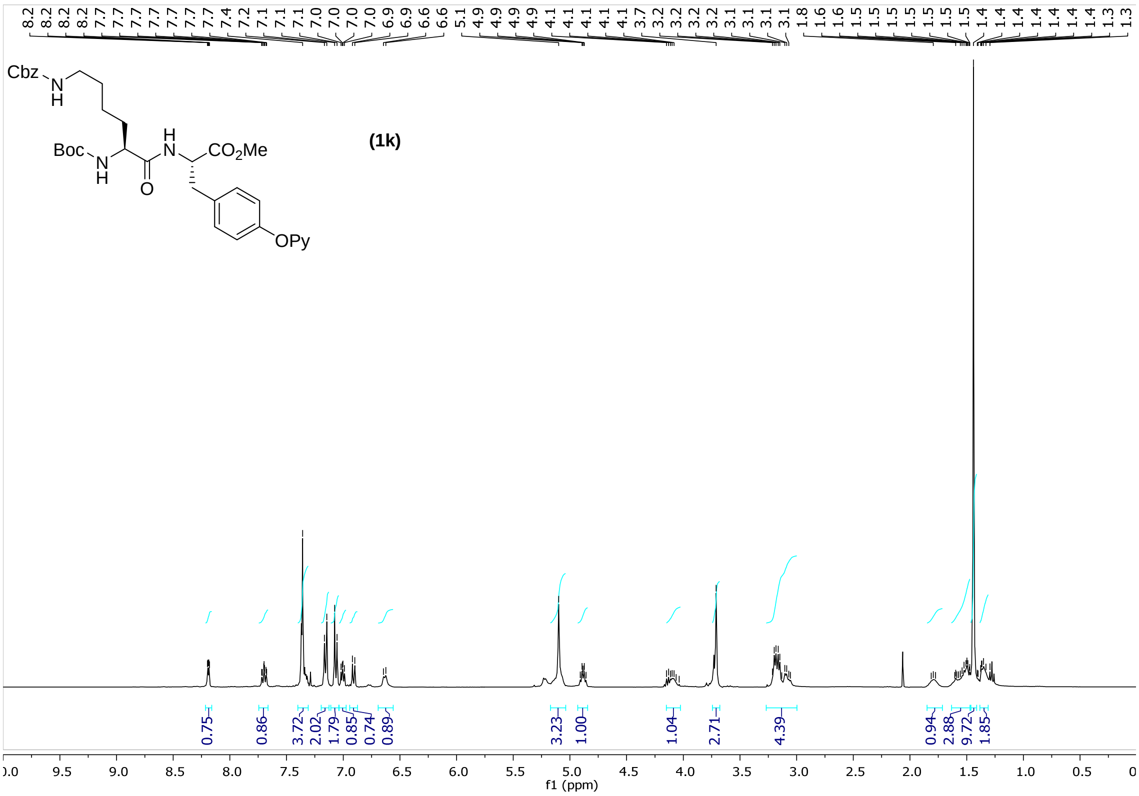
^{1}H NMR (400 MHz, $CDCl_3$)



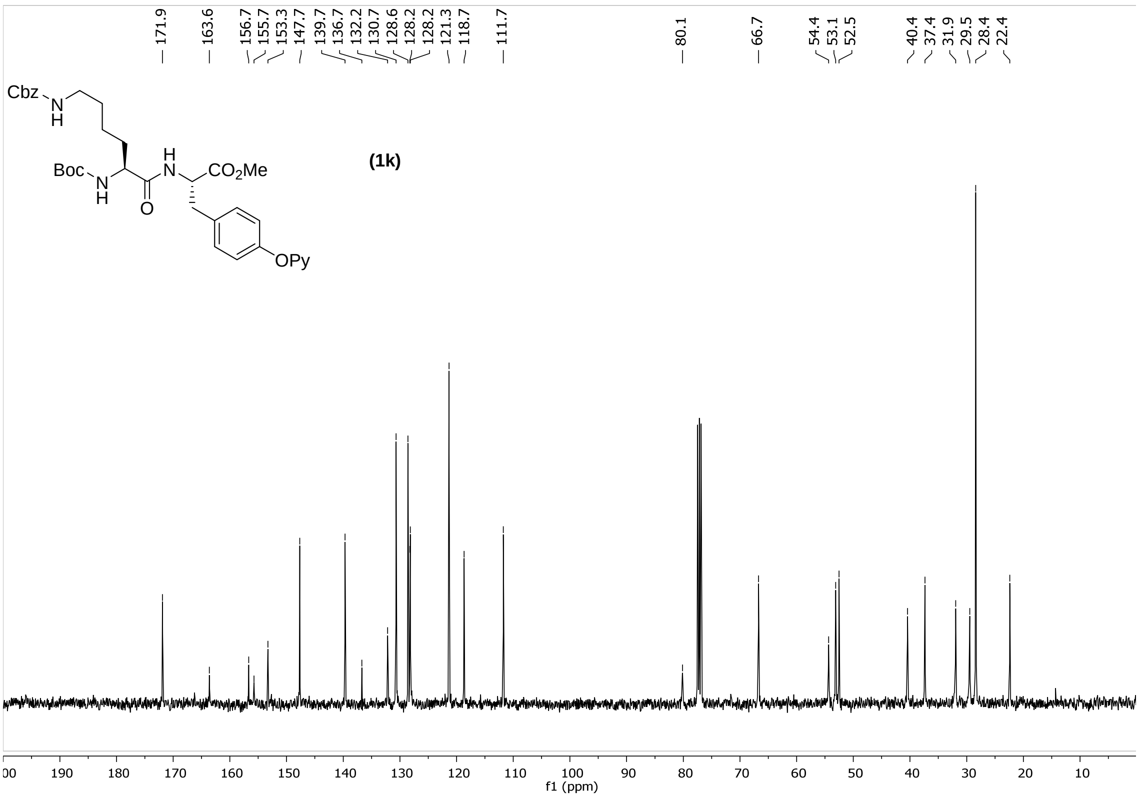
^{13}C NMR (101 MHz, $CDCl_3$)



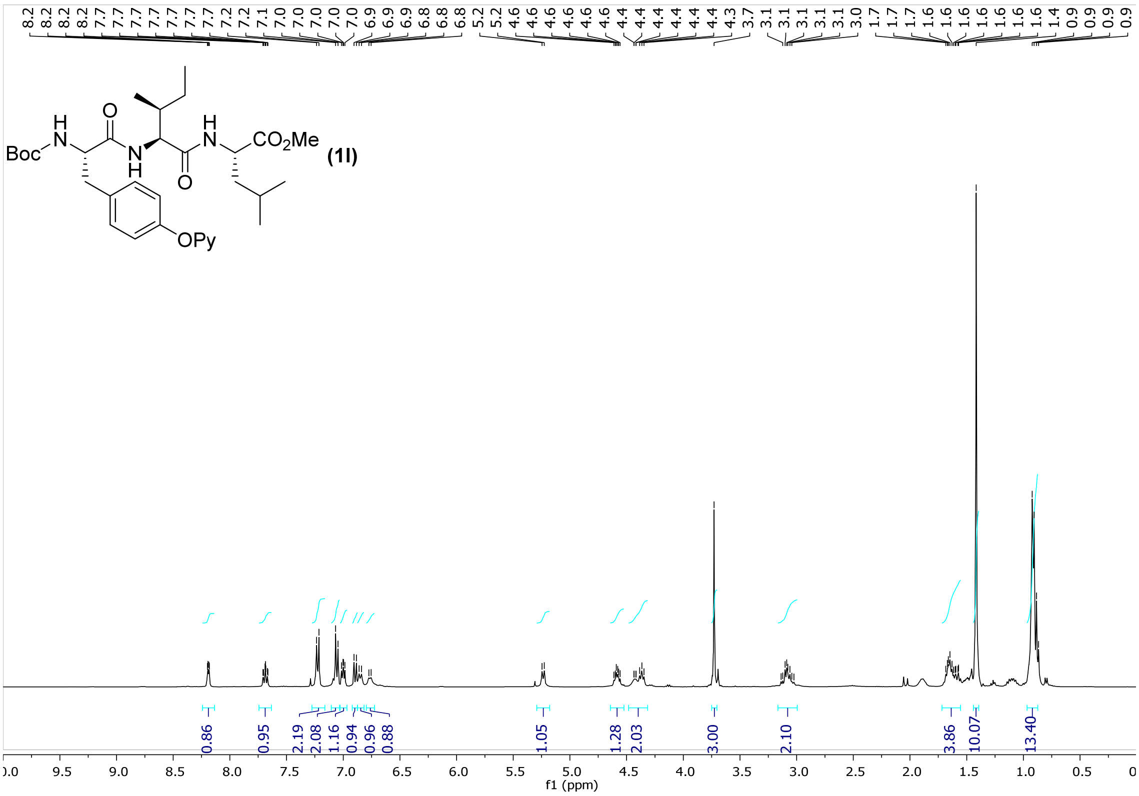
[1]H NMR (400 MHz, CDCl3)



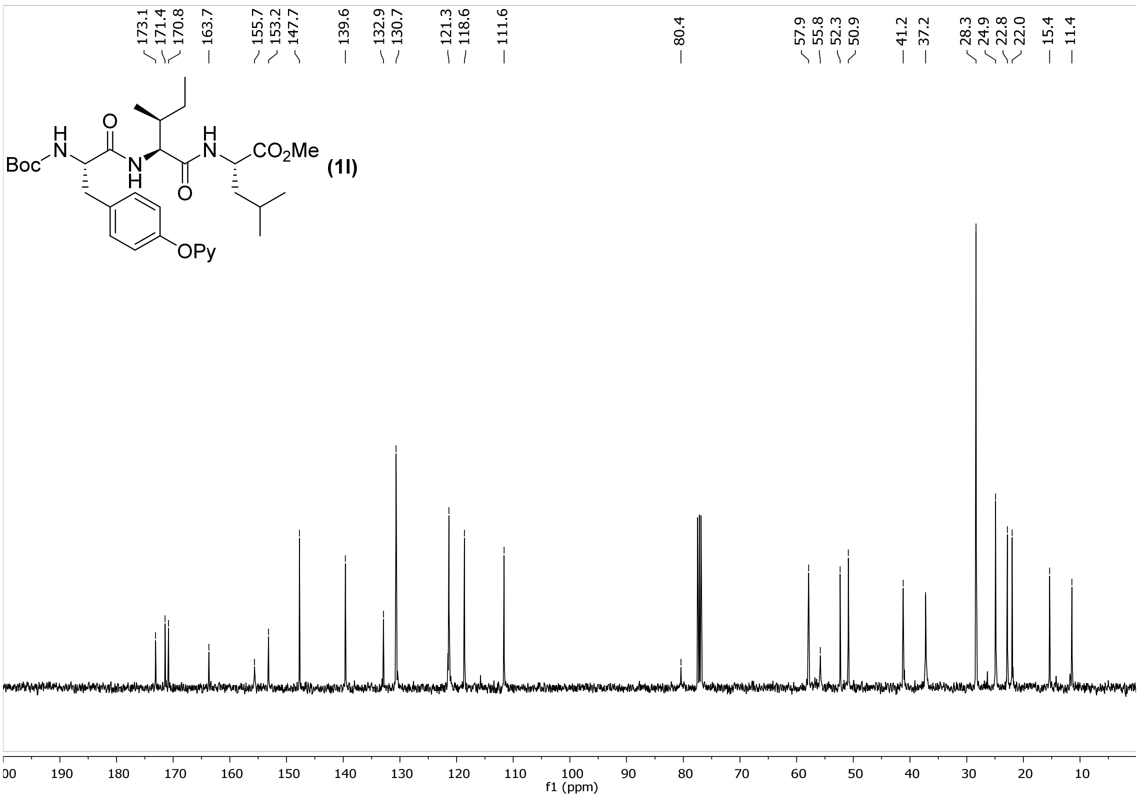
[13]C NMR (101 MHz, CDCl3)



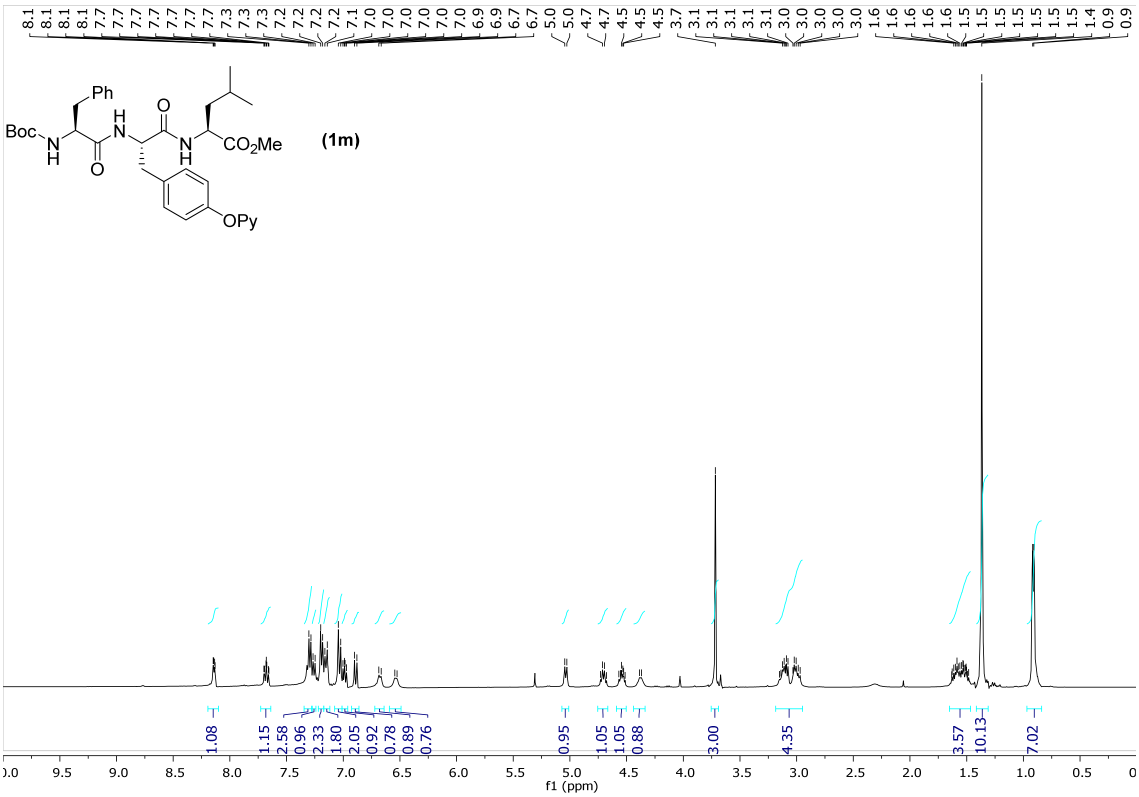
^{1}H NMR (400 MHz, $CDCl_3$)



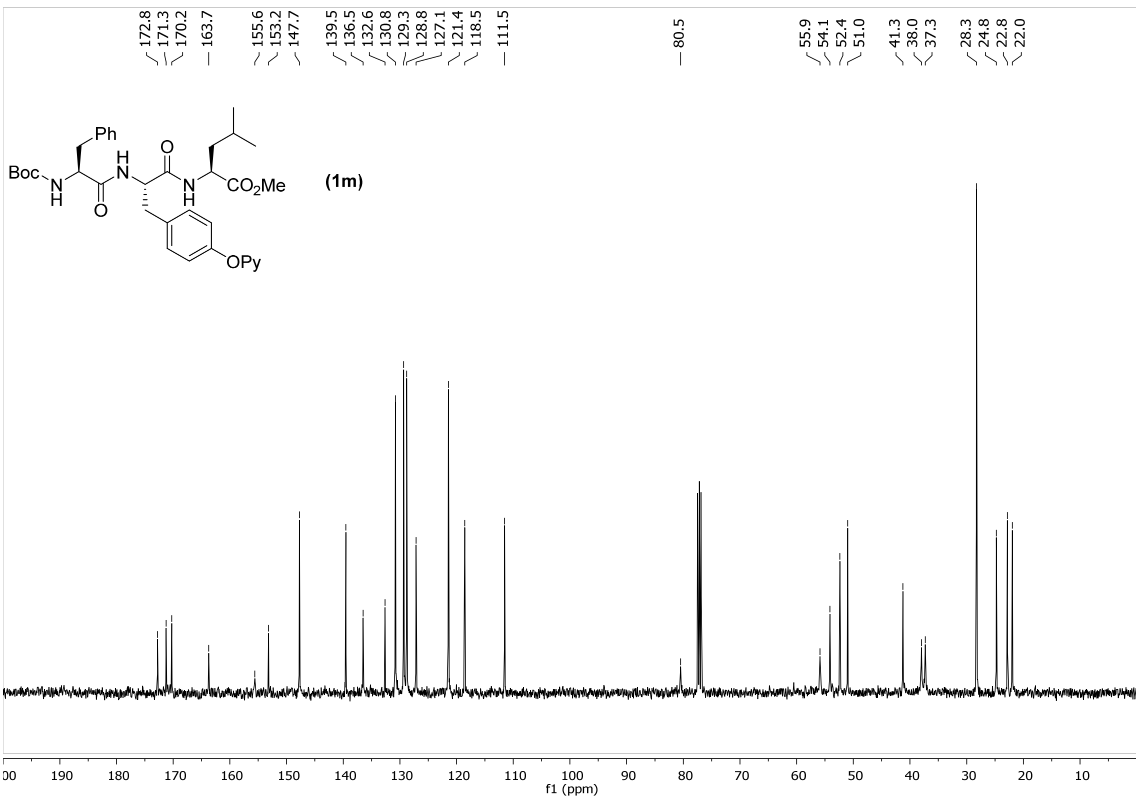
^{13}C NMR (101 MHz, $CDCl_3$)



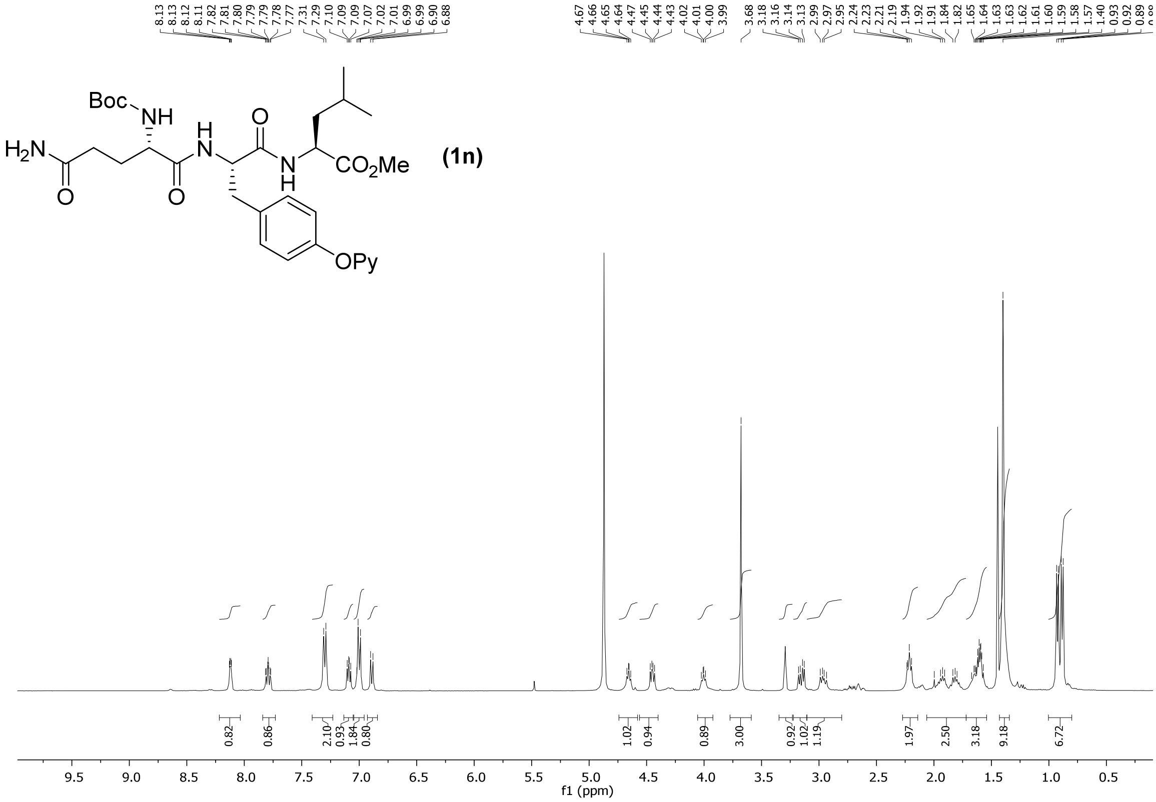
^{1}H NMR (400 MHz, $CDCl_3$)



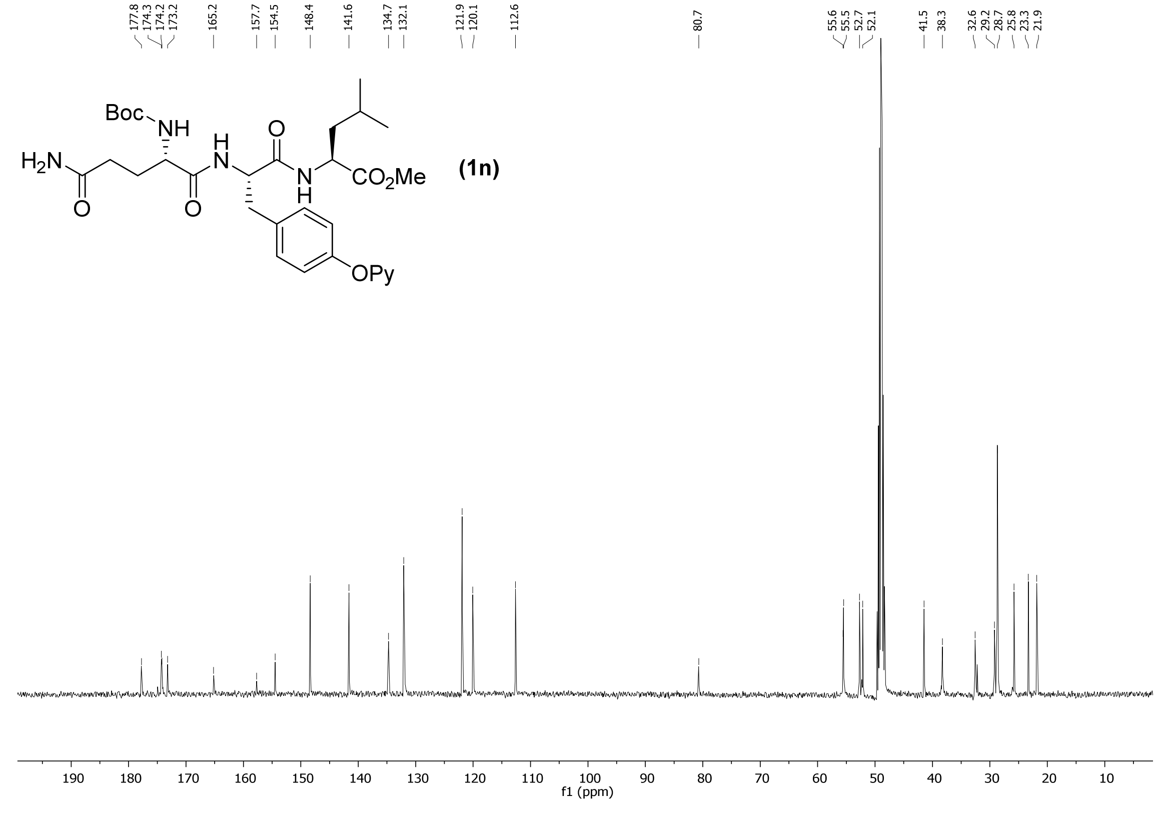
^{13}C NMR (101 MHz, $CDCl_3$)



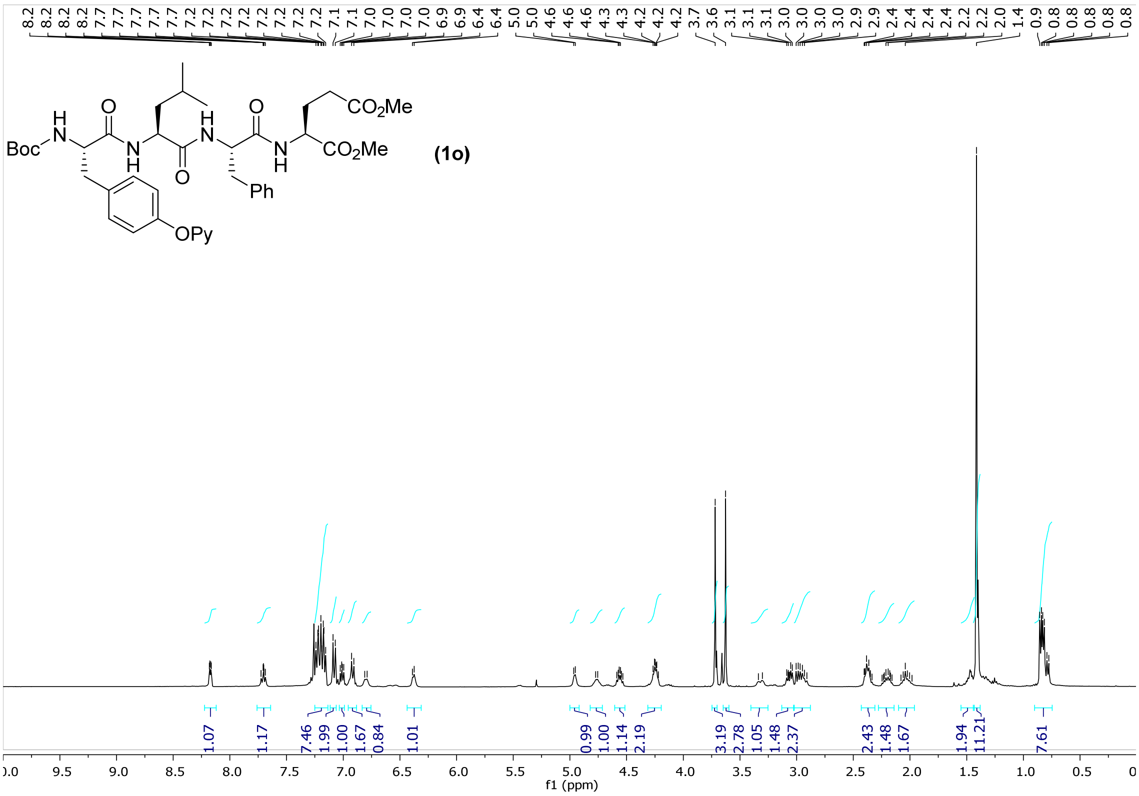
^{1}H NMR (400 MHz, MeOH-d_4)



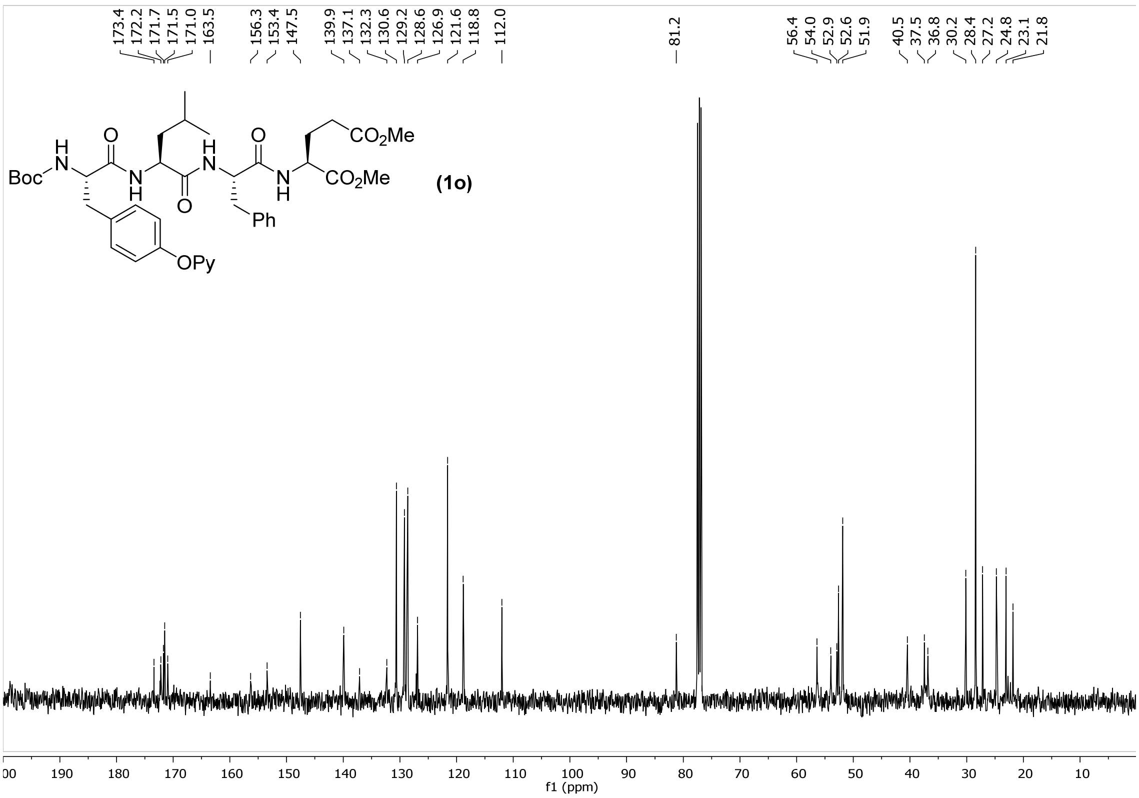
^{13}C NMR (101 MHz, MeOH-d_4)



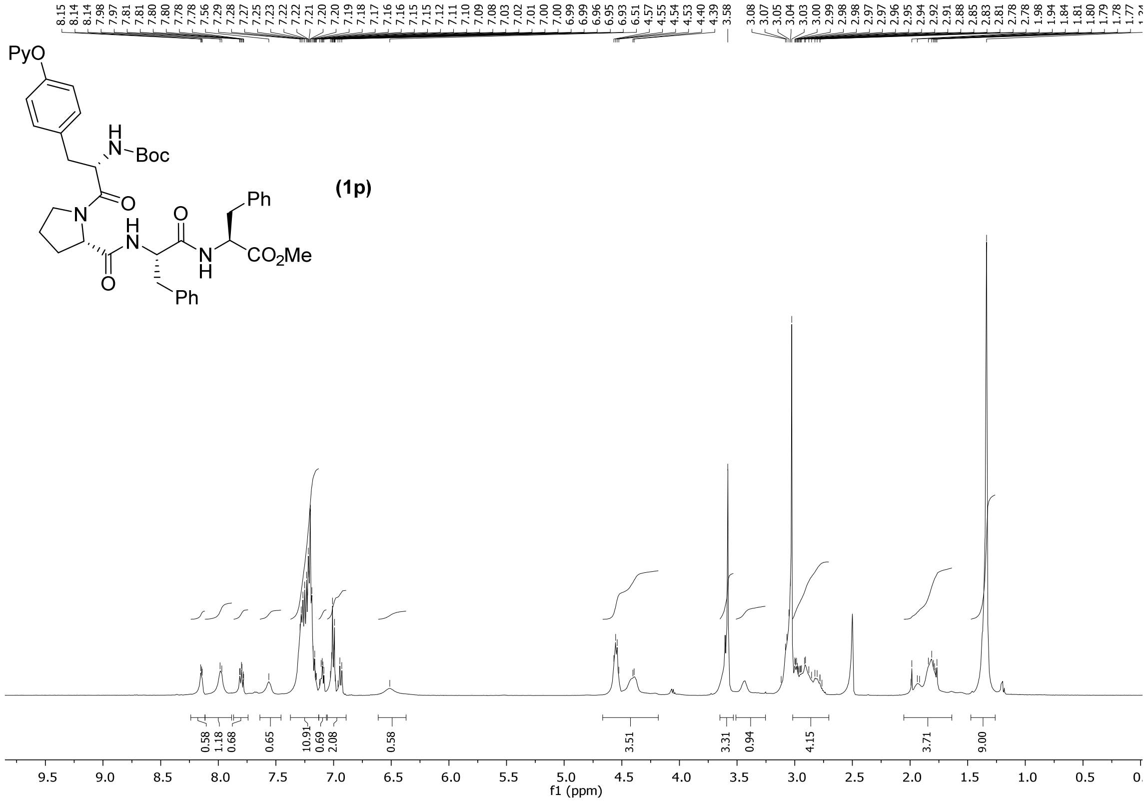
[1]H NMR (400 MHz, $CDCl_3$)



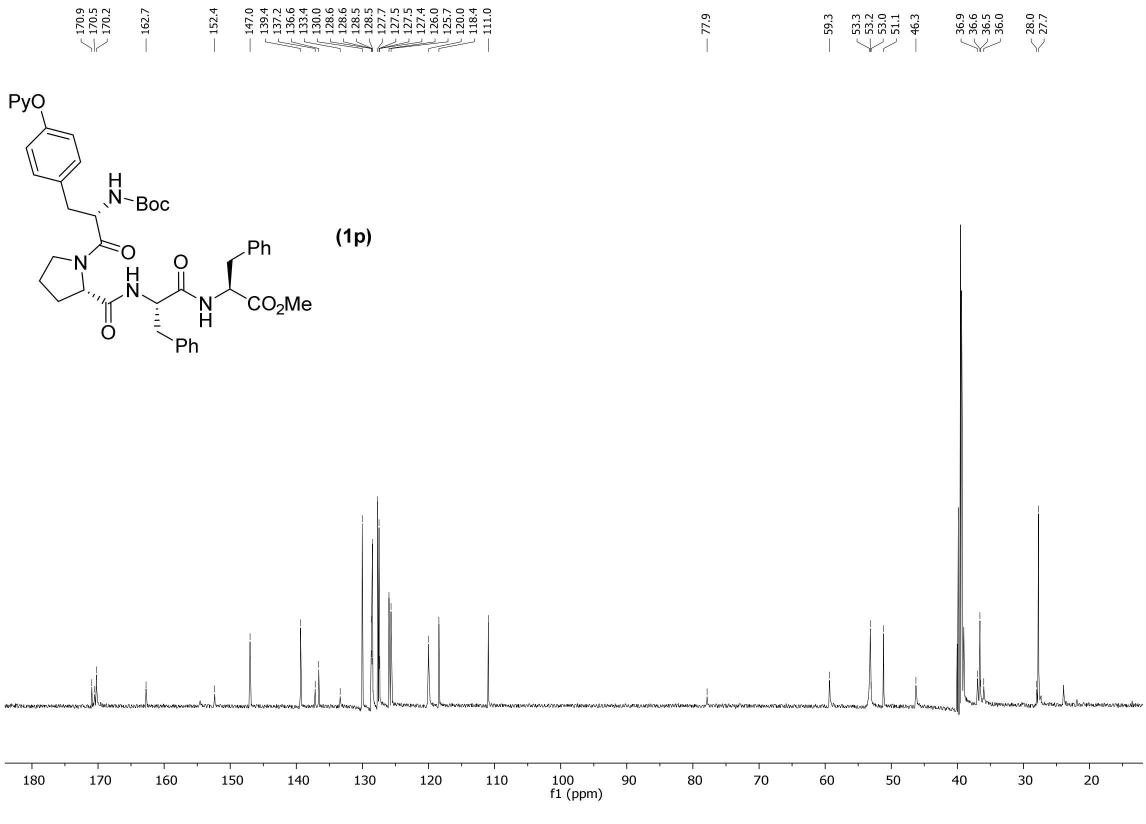
[13]C NMR (101 MHz, $CDCl_3$)



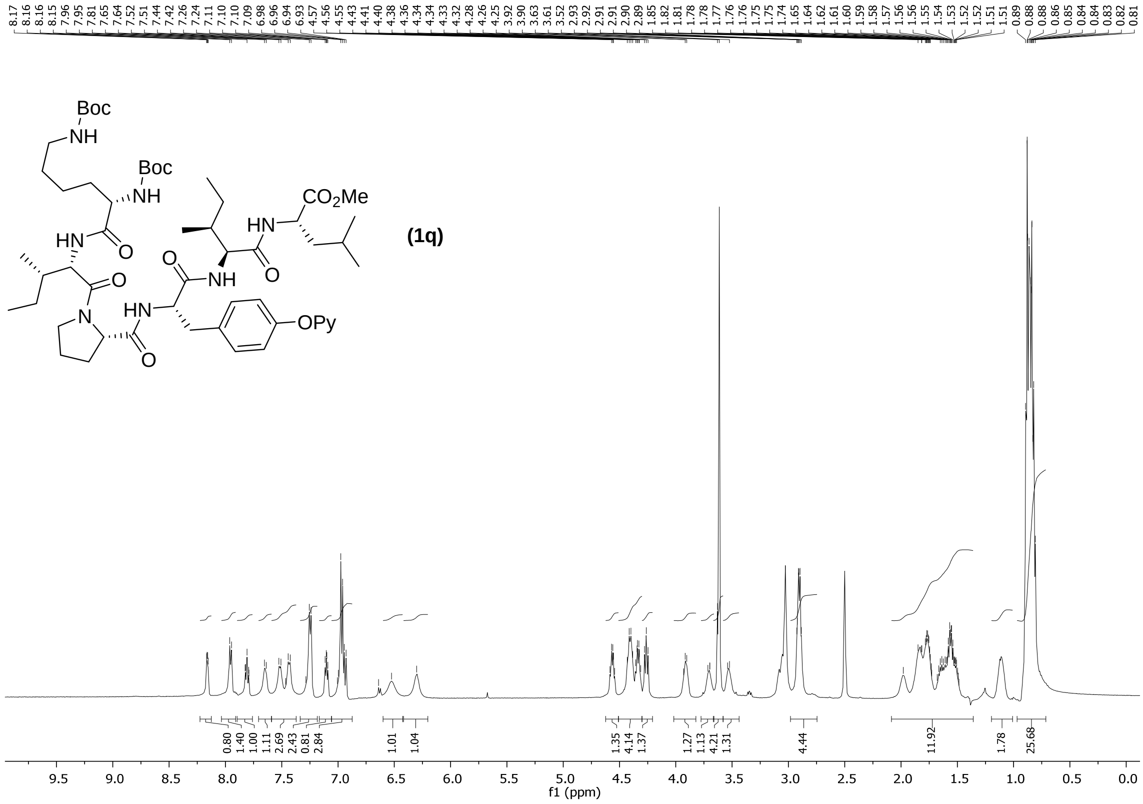
^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC)



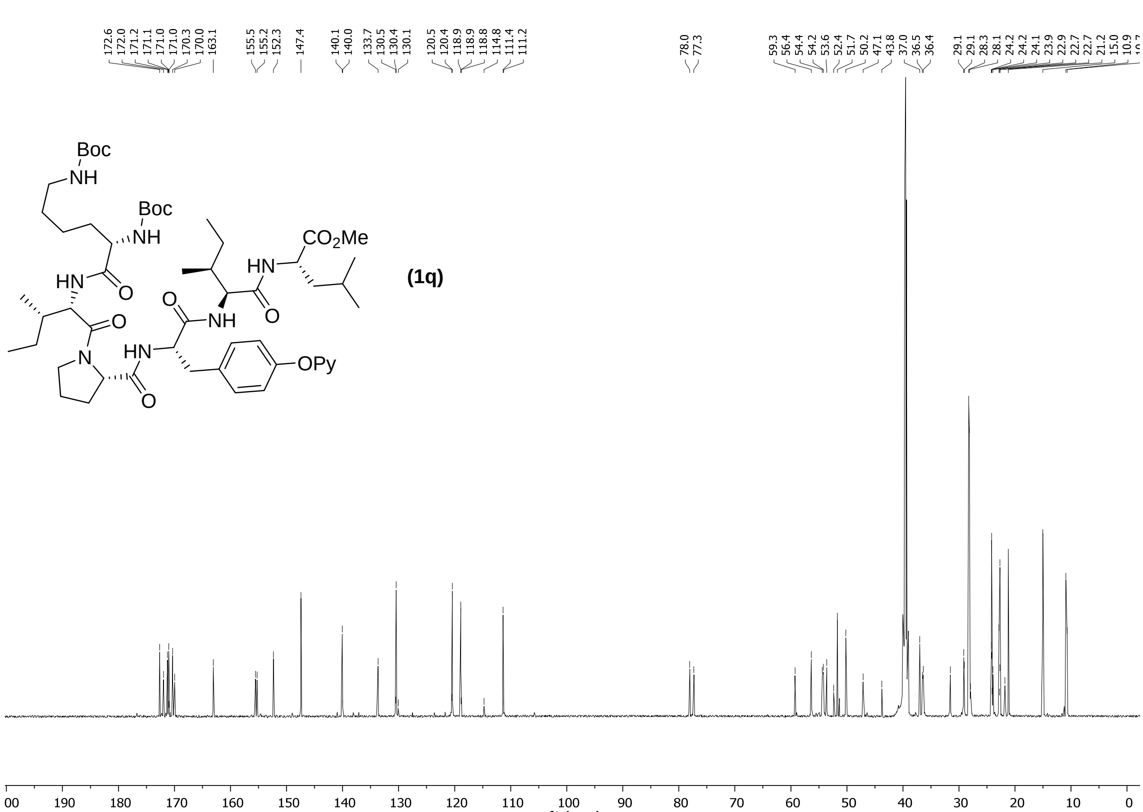
^{13}C NMR (126 MHz, DMSO-d_6 at 80 ºC)



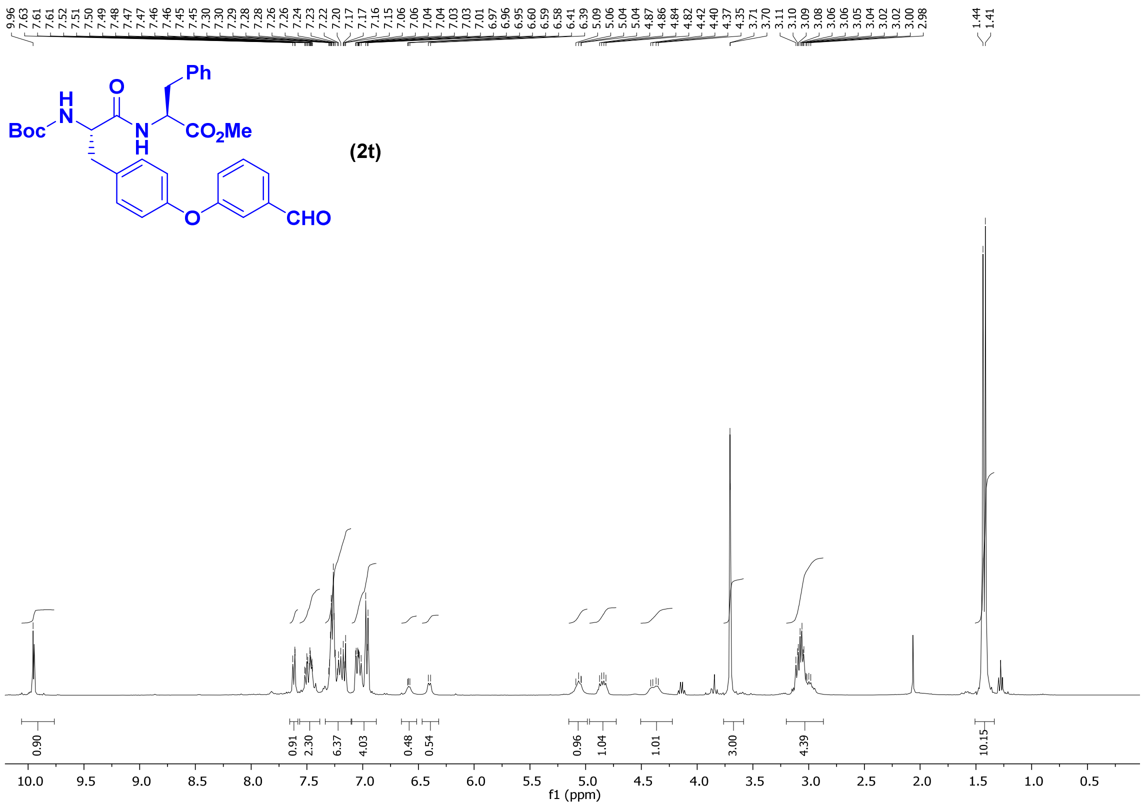
[1]H NMR (500 MHz, DMSO-d_6 at 80 ºC)



[13]C NMR (126 MHz, DMSO-d_6)

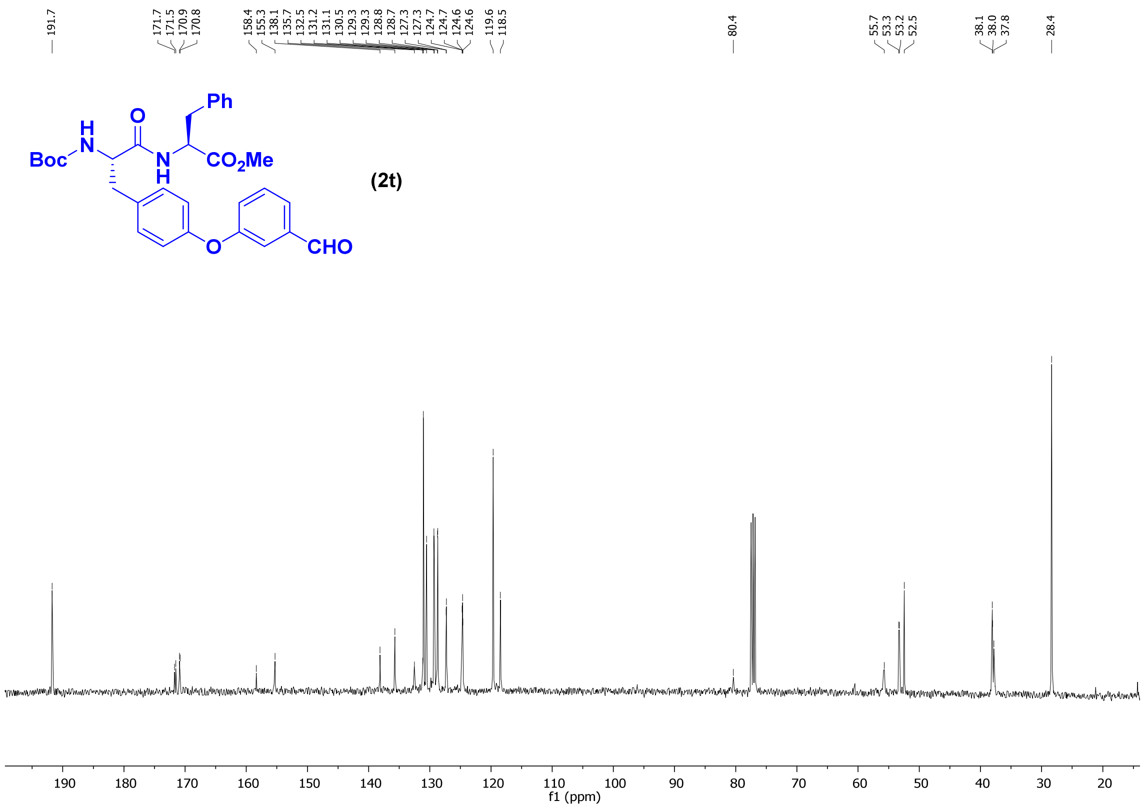


[1]H NMR (400 MHz, CDCl3)



(2t)

[13]C NMR (101 MHz, CDCl3)



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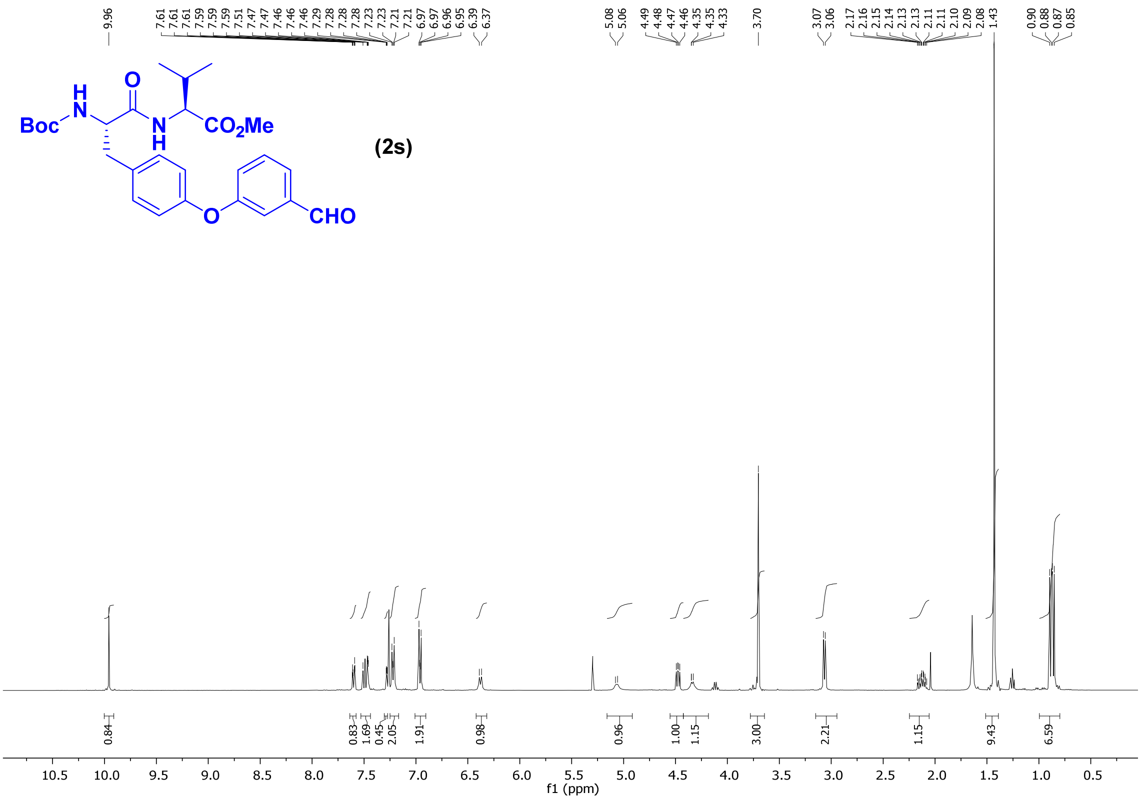
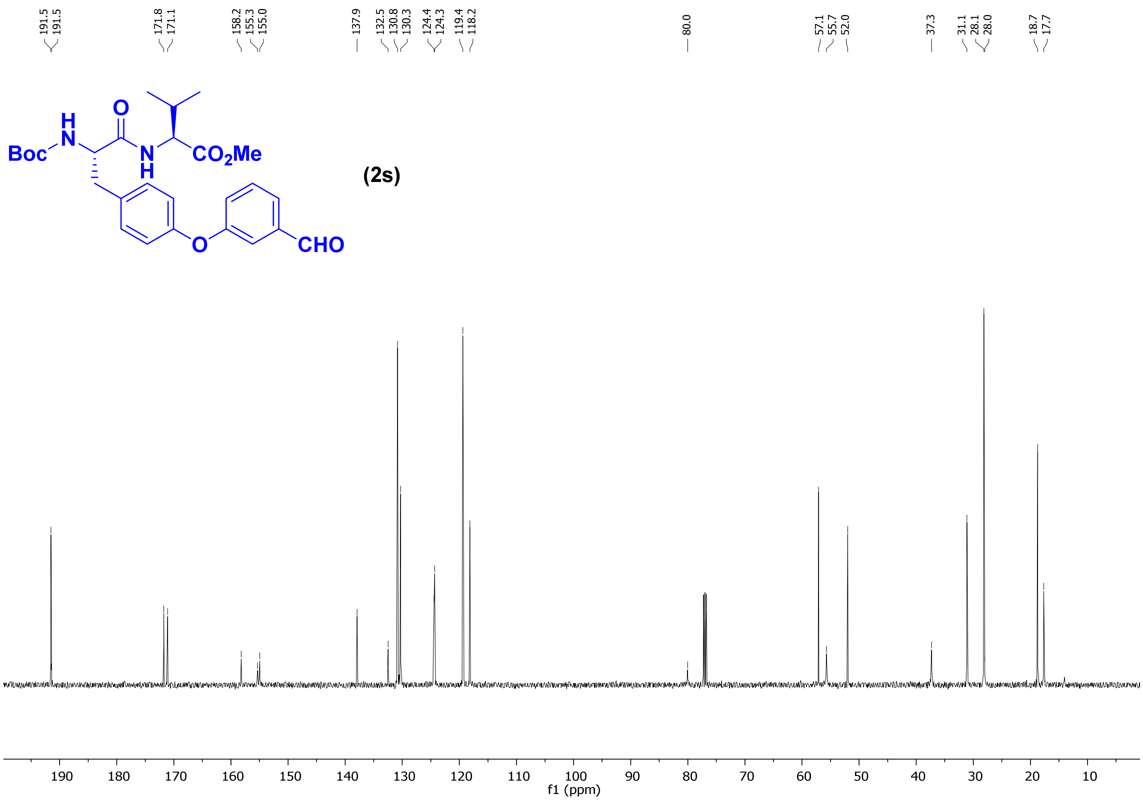
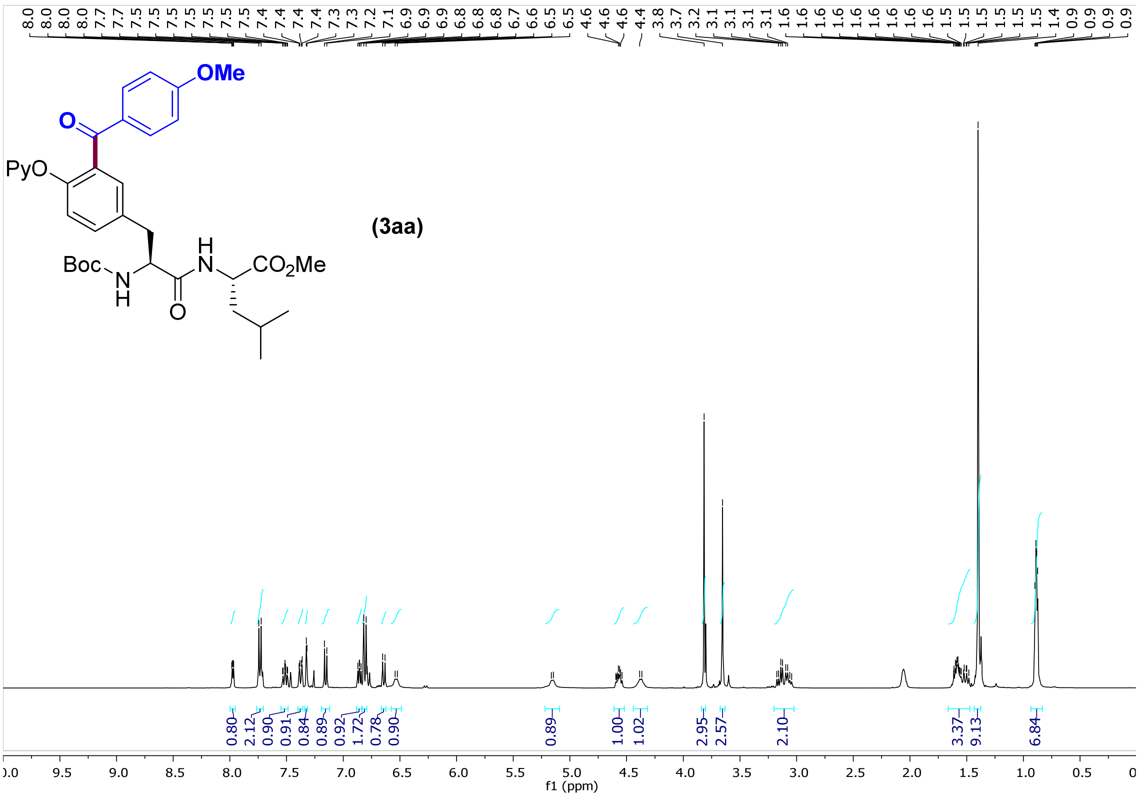
^{1}H NMR (400 MHz, $CDCl_3$)



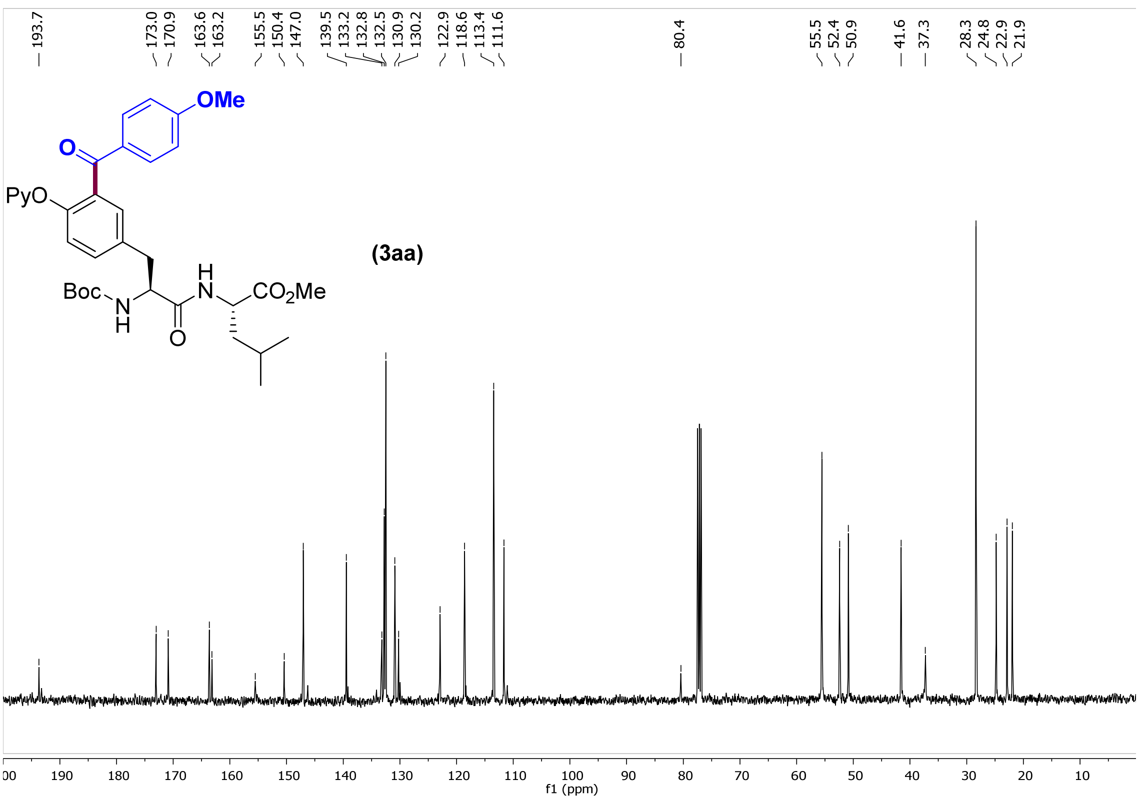
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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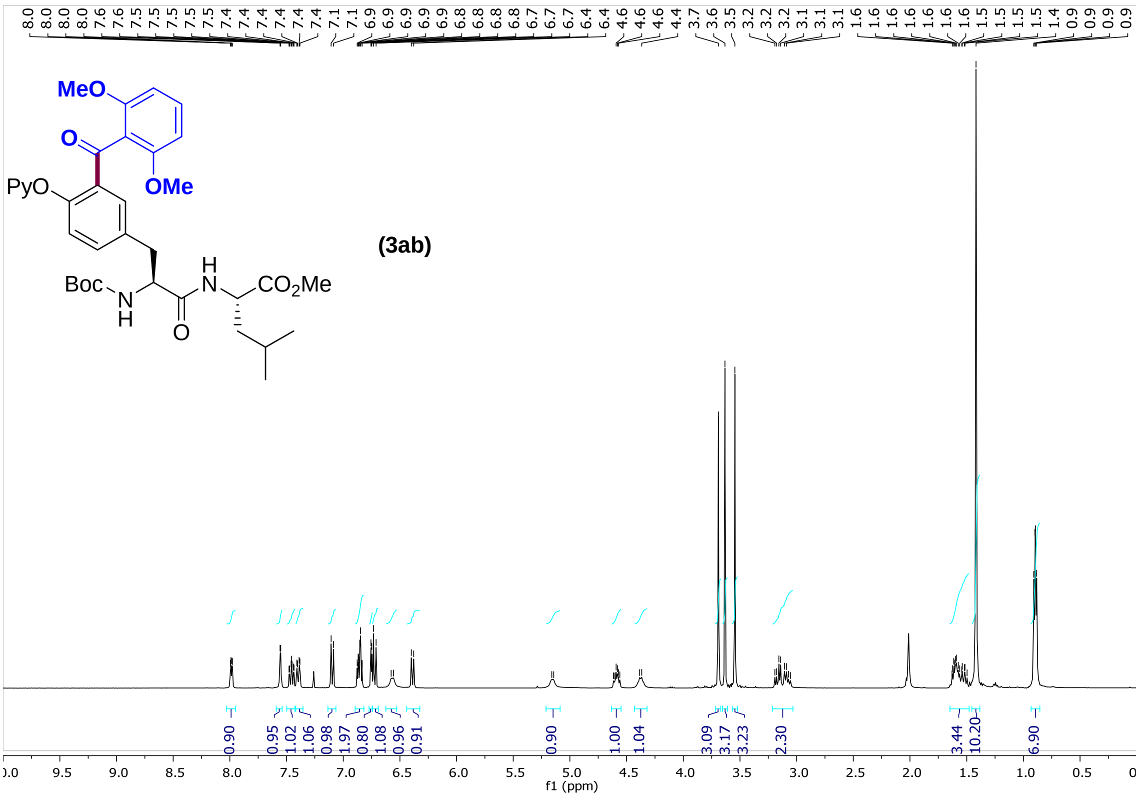

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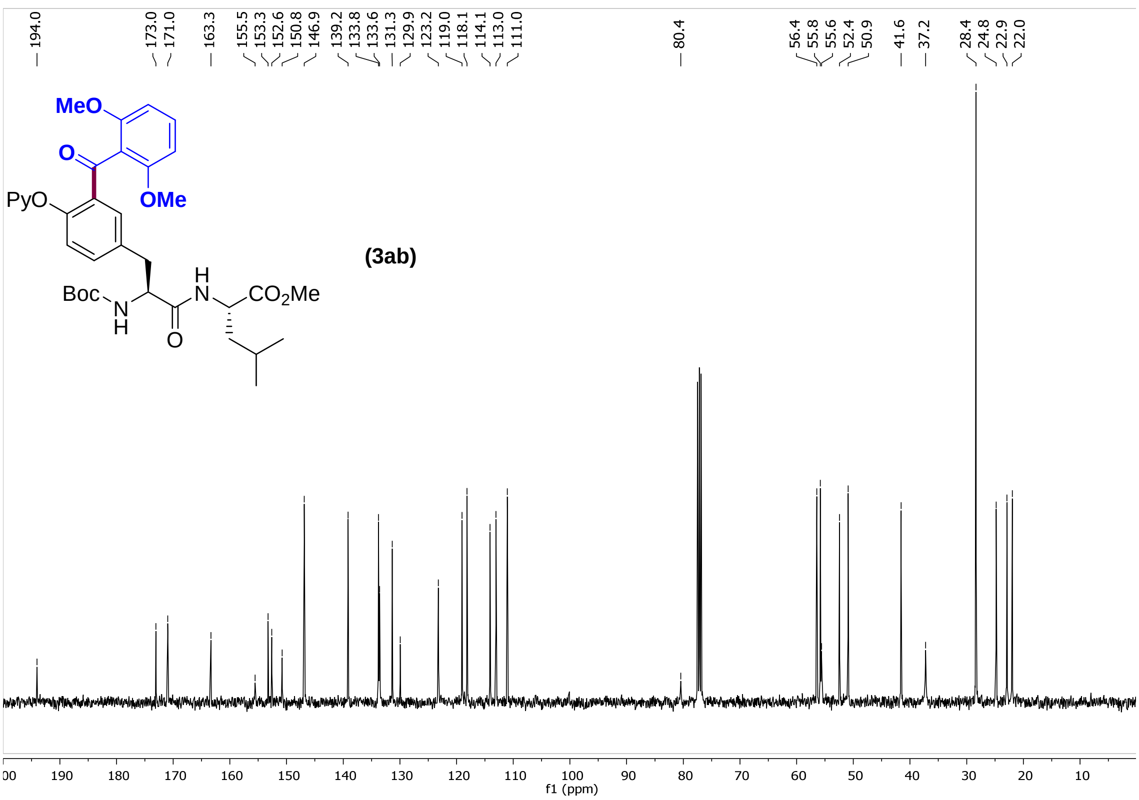

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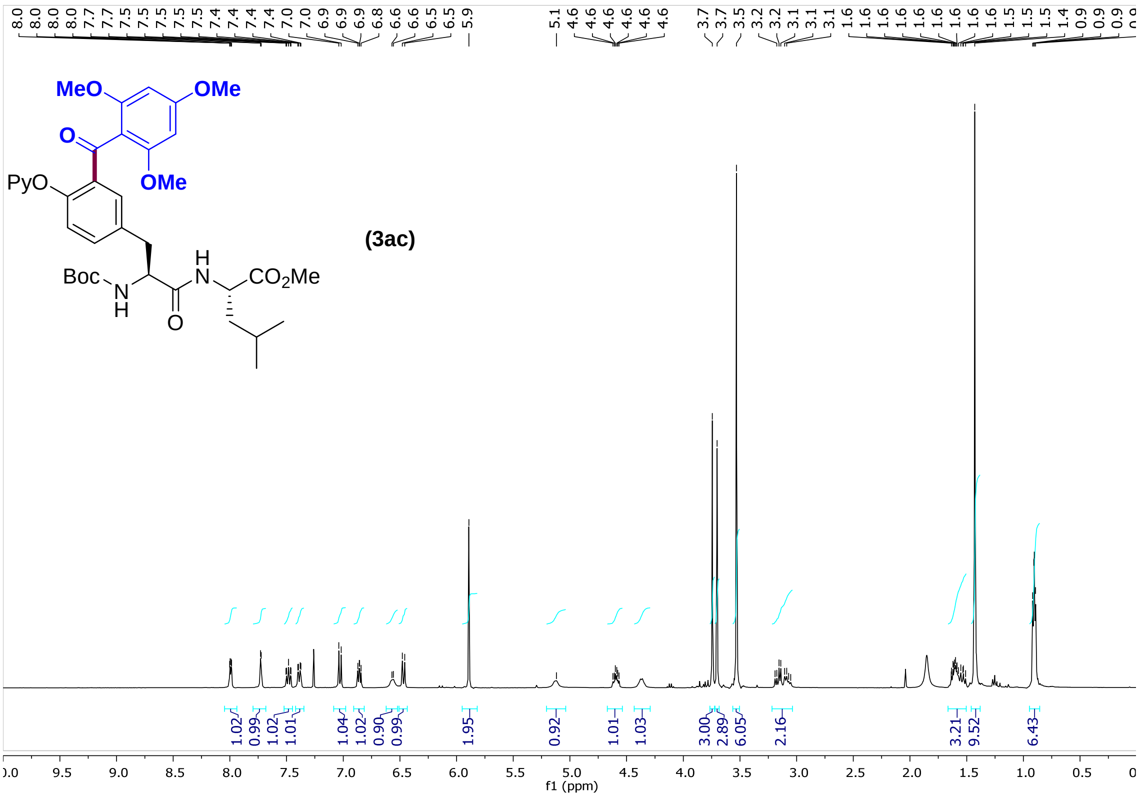

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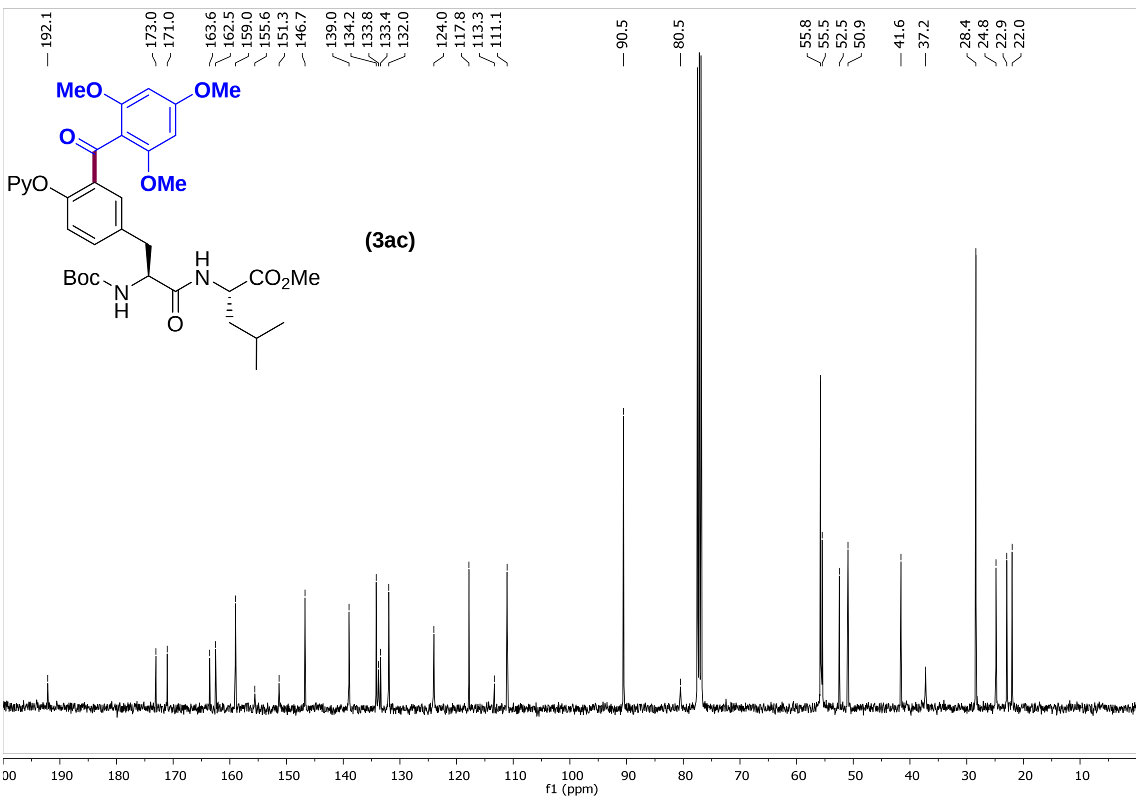

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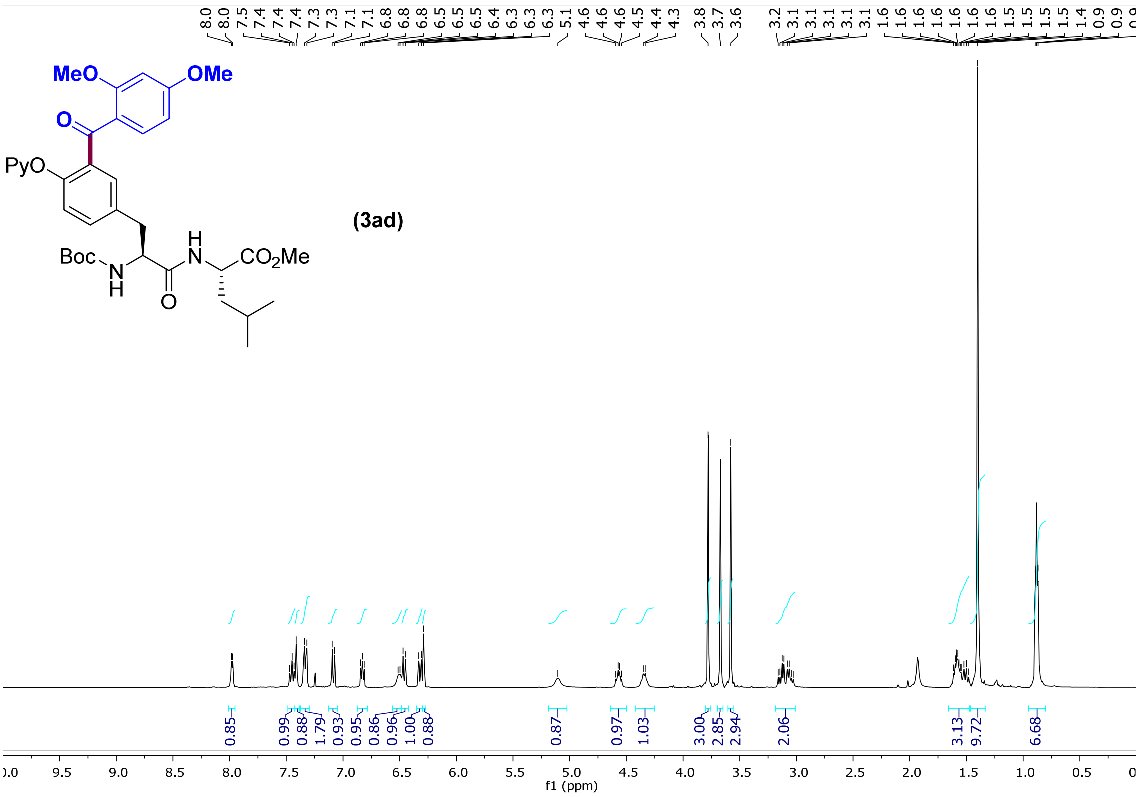

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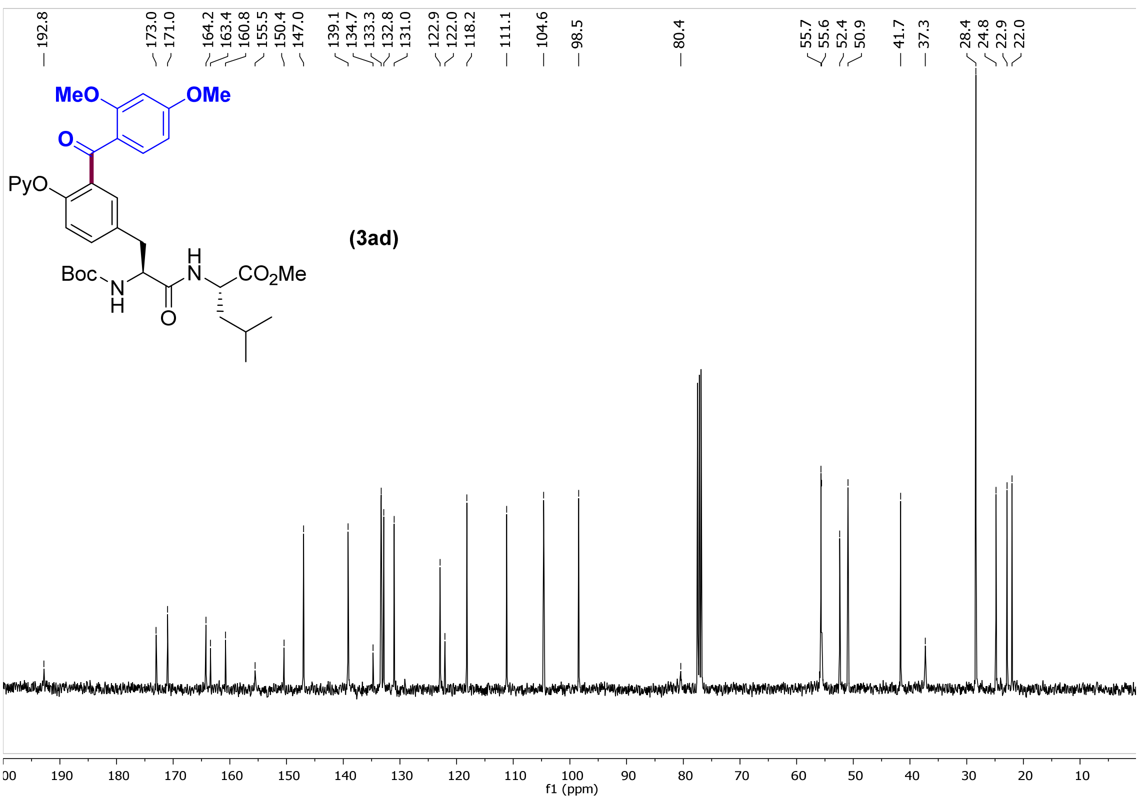

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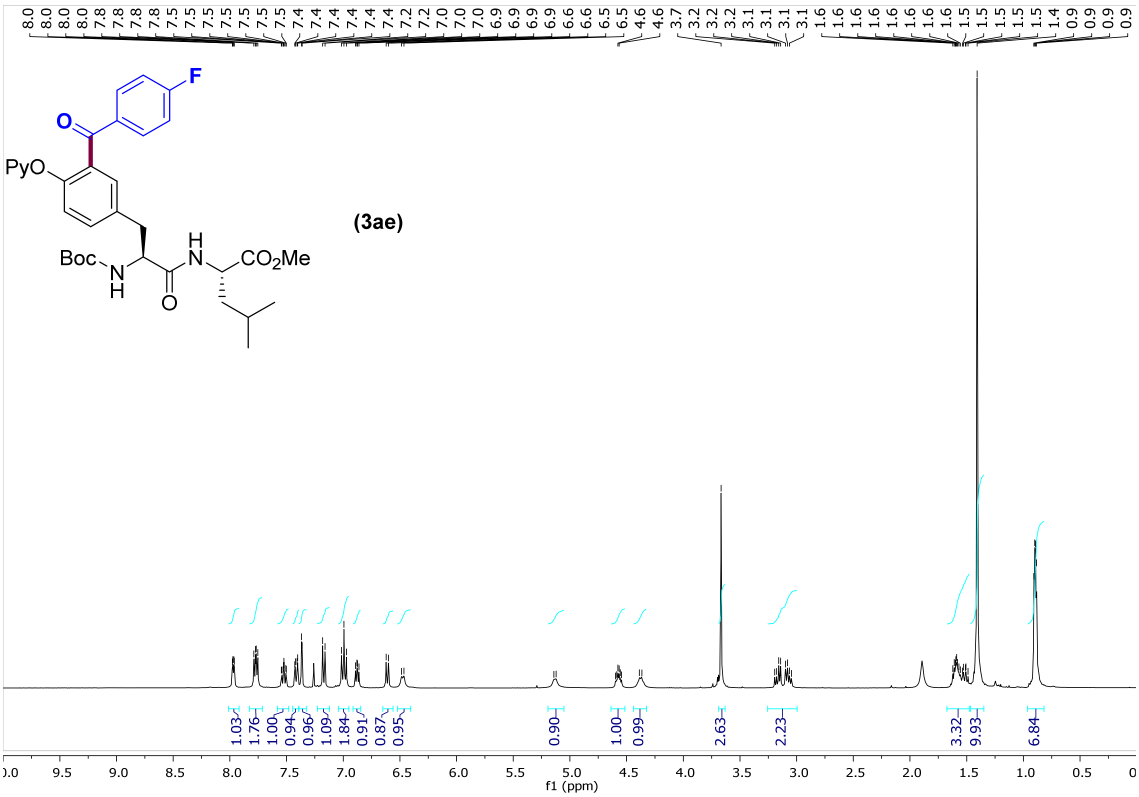

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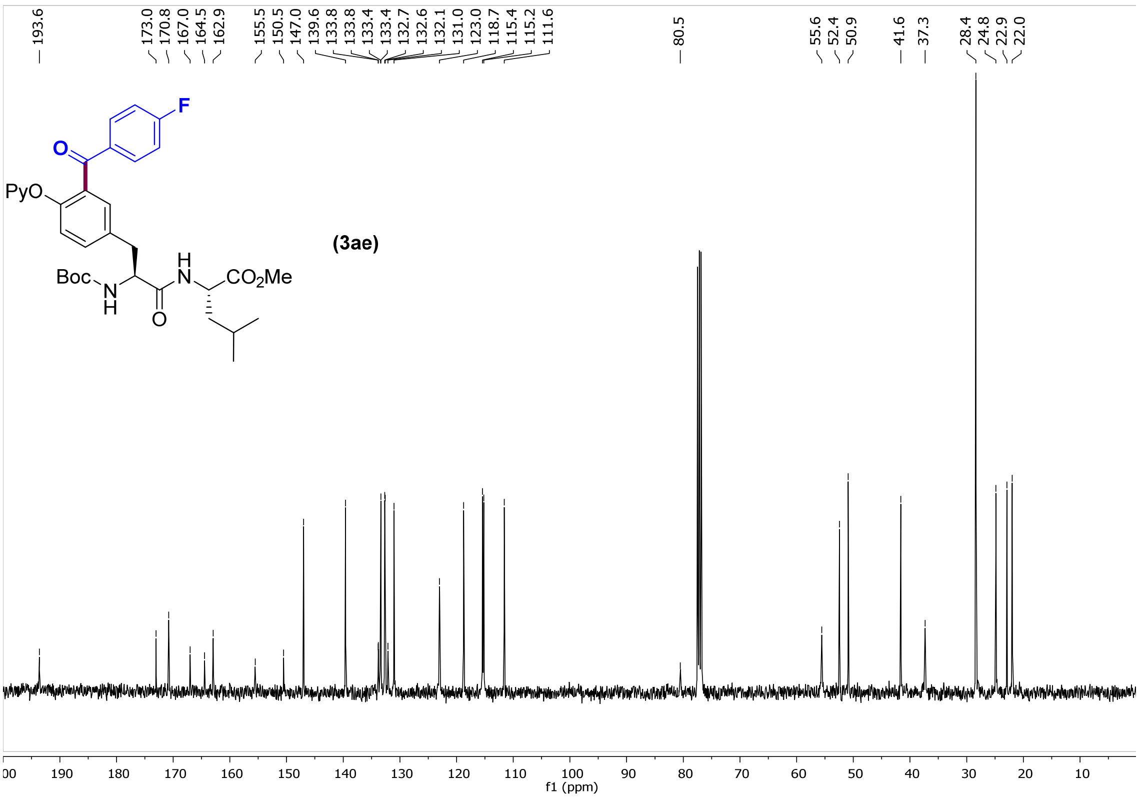

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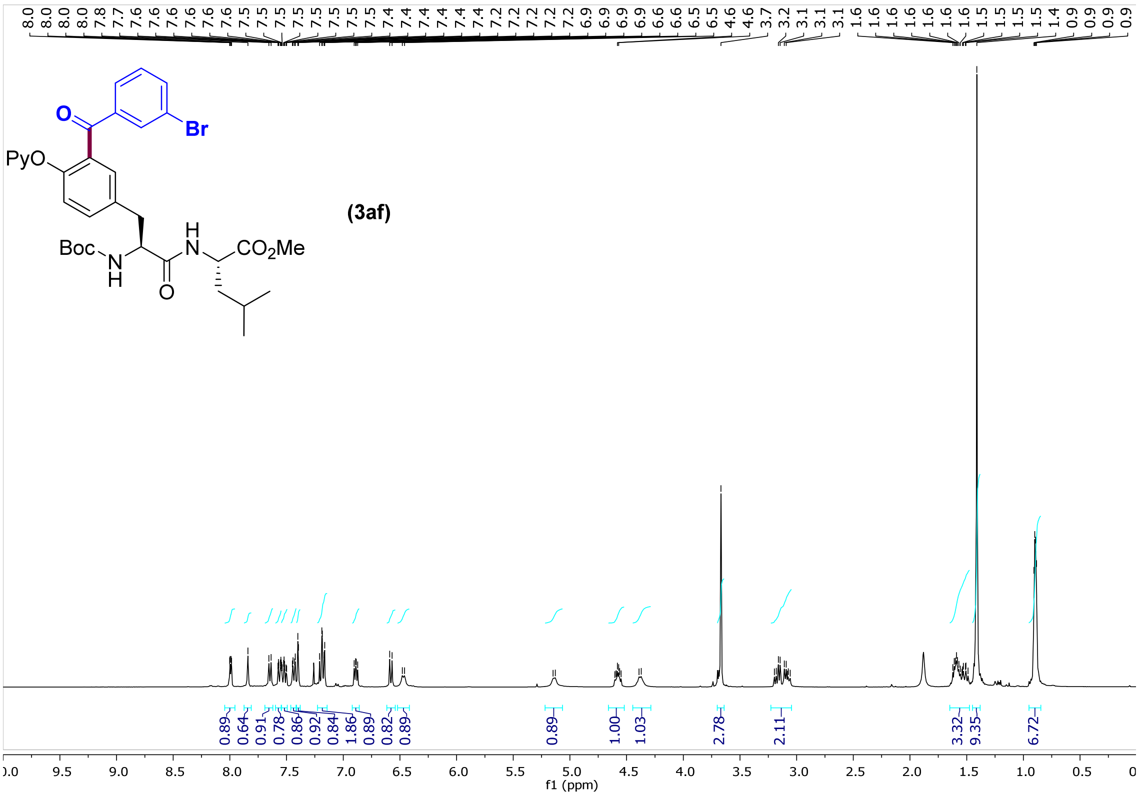

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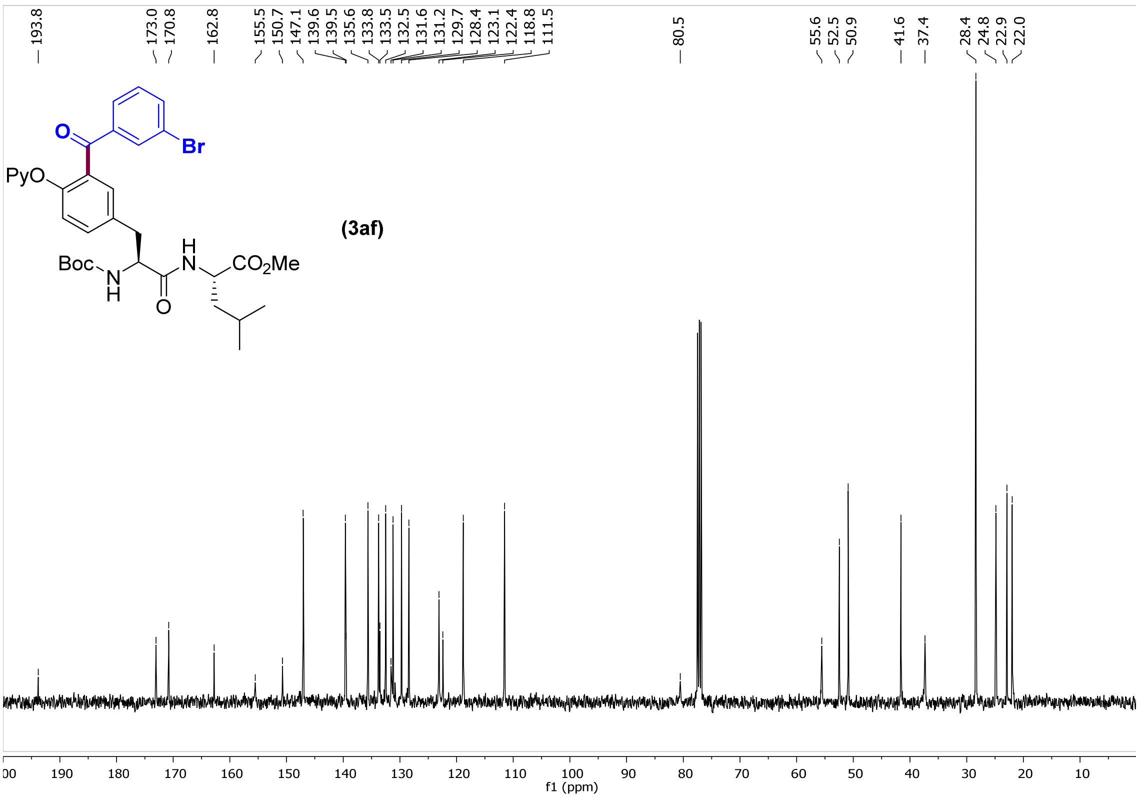

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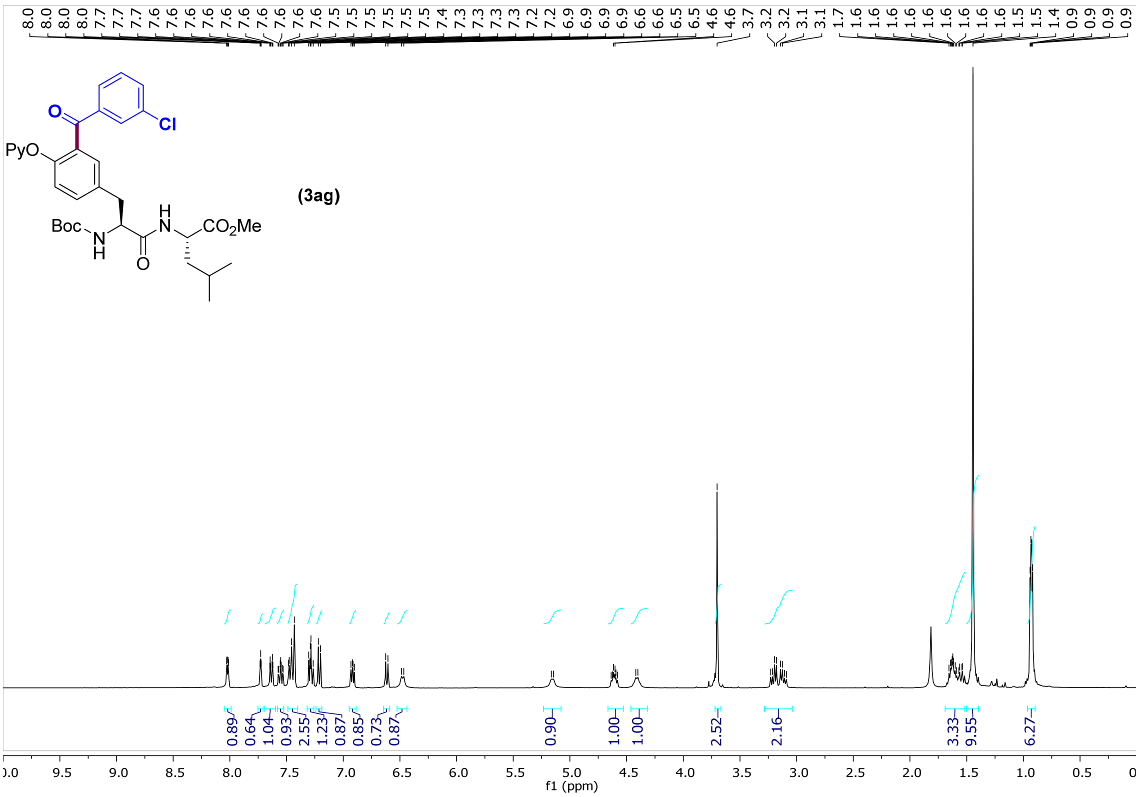

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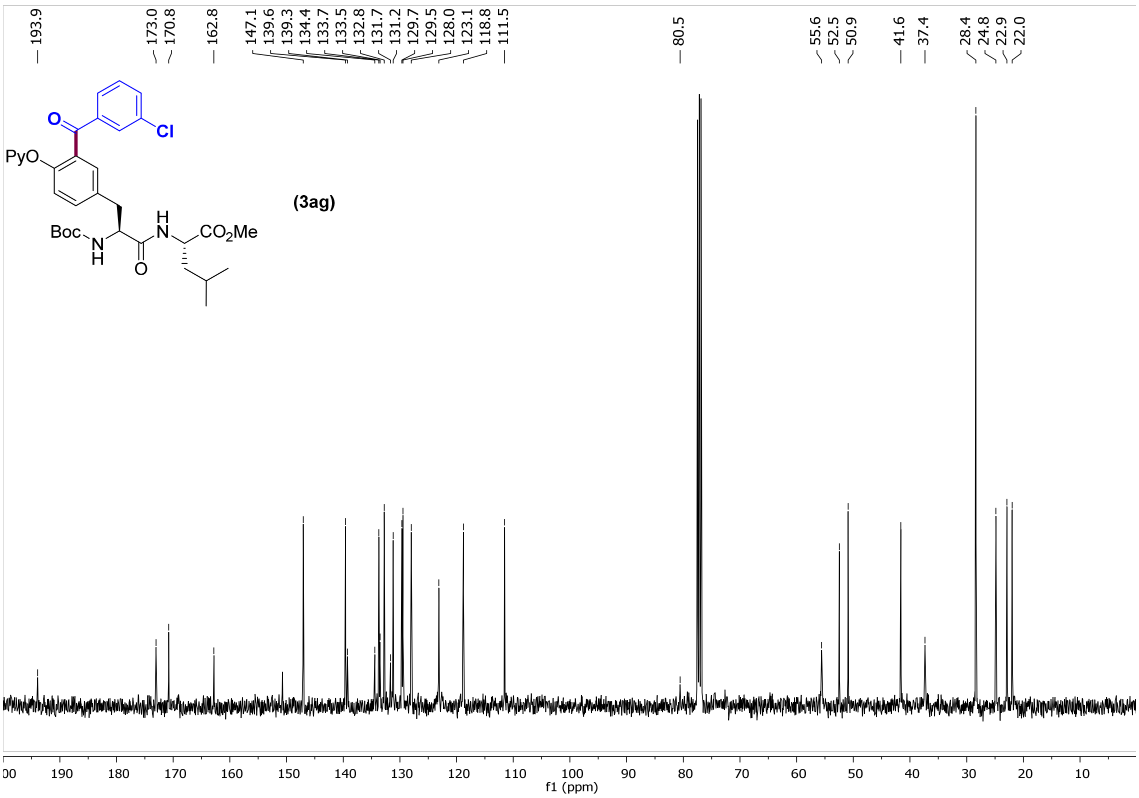

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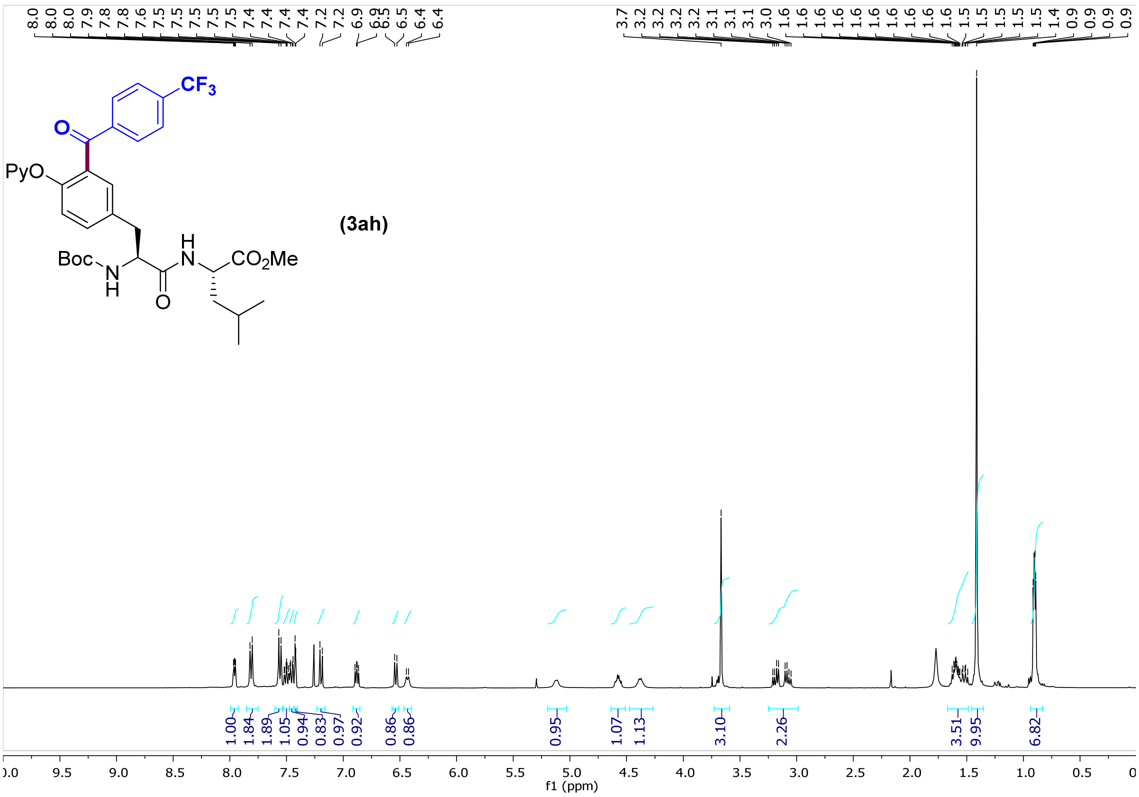

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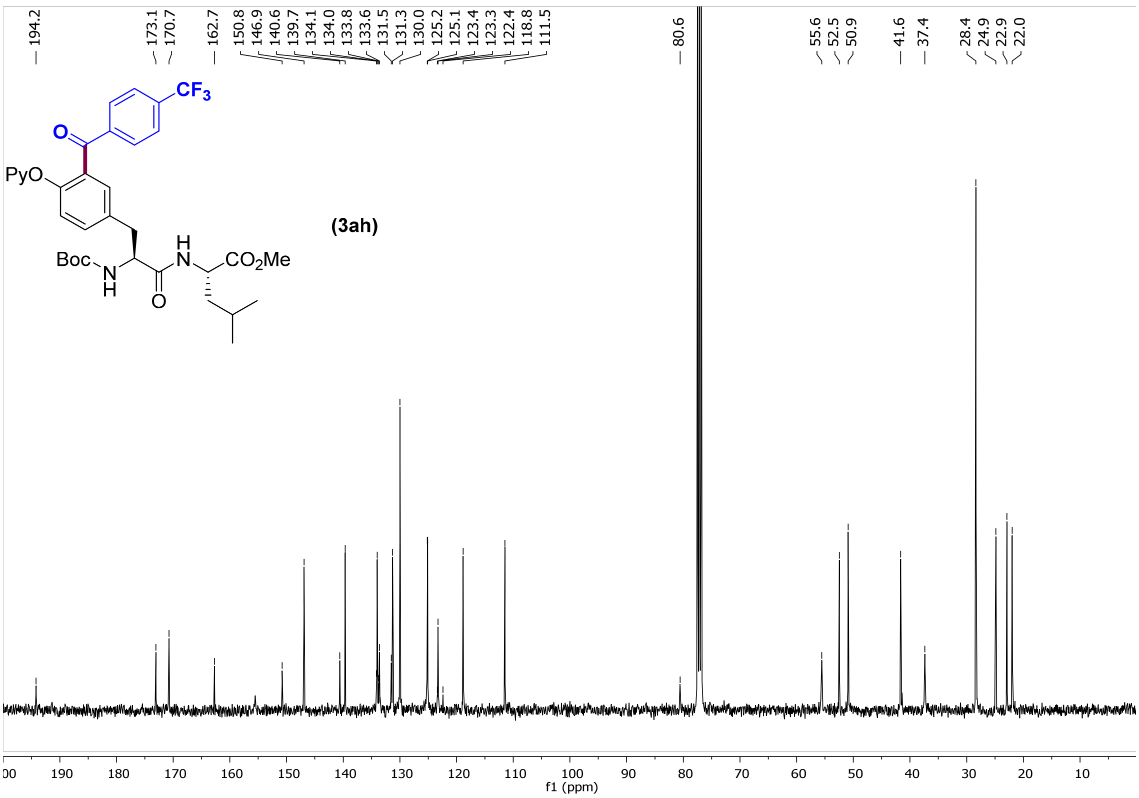

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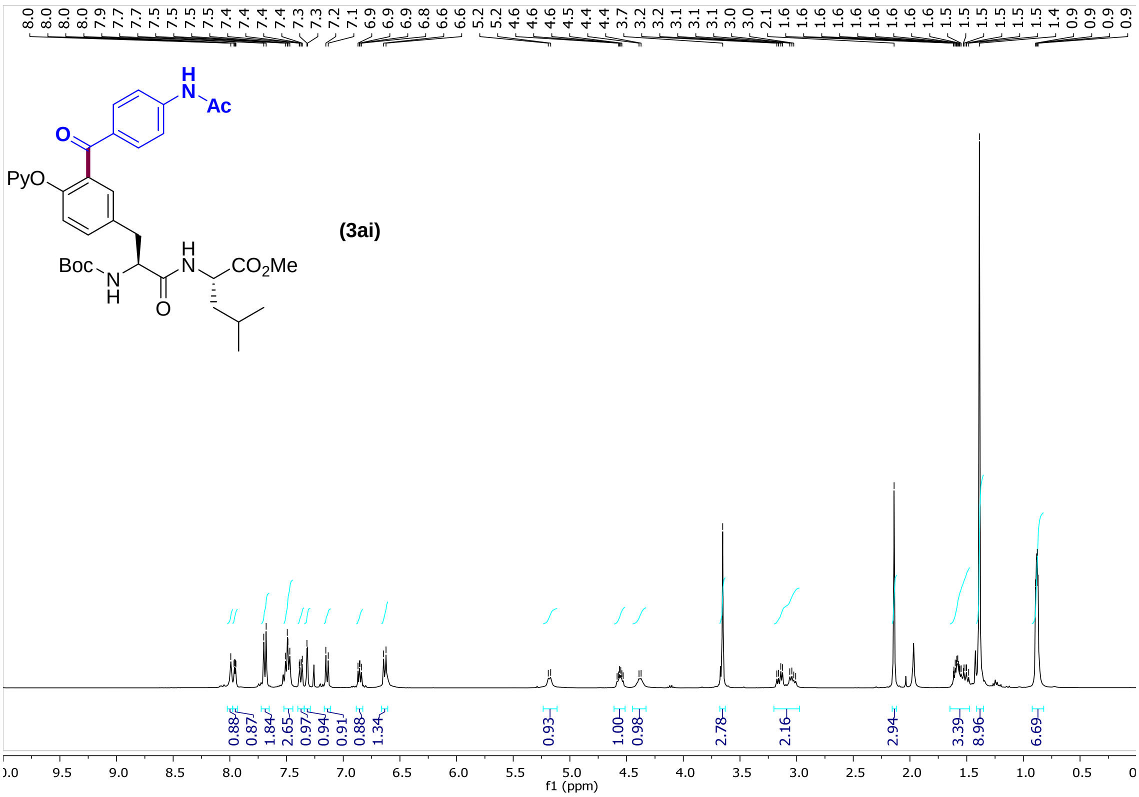

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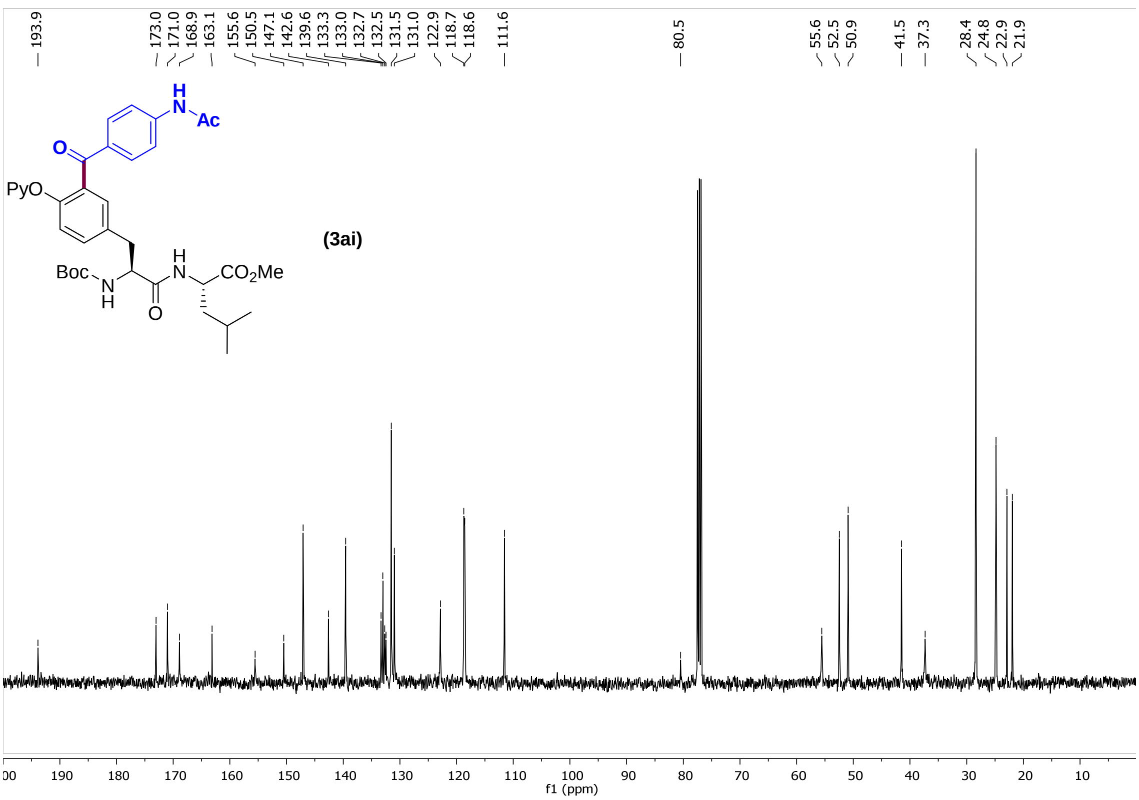

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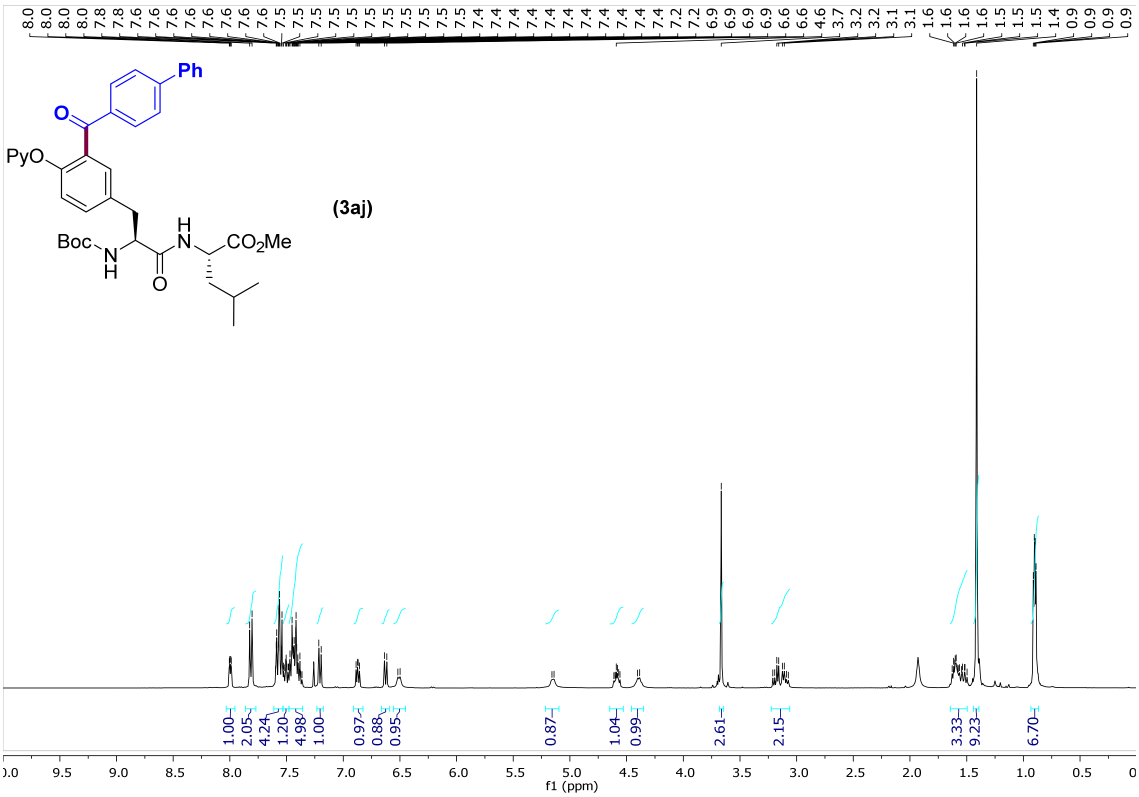

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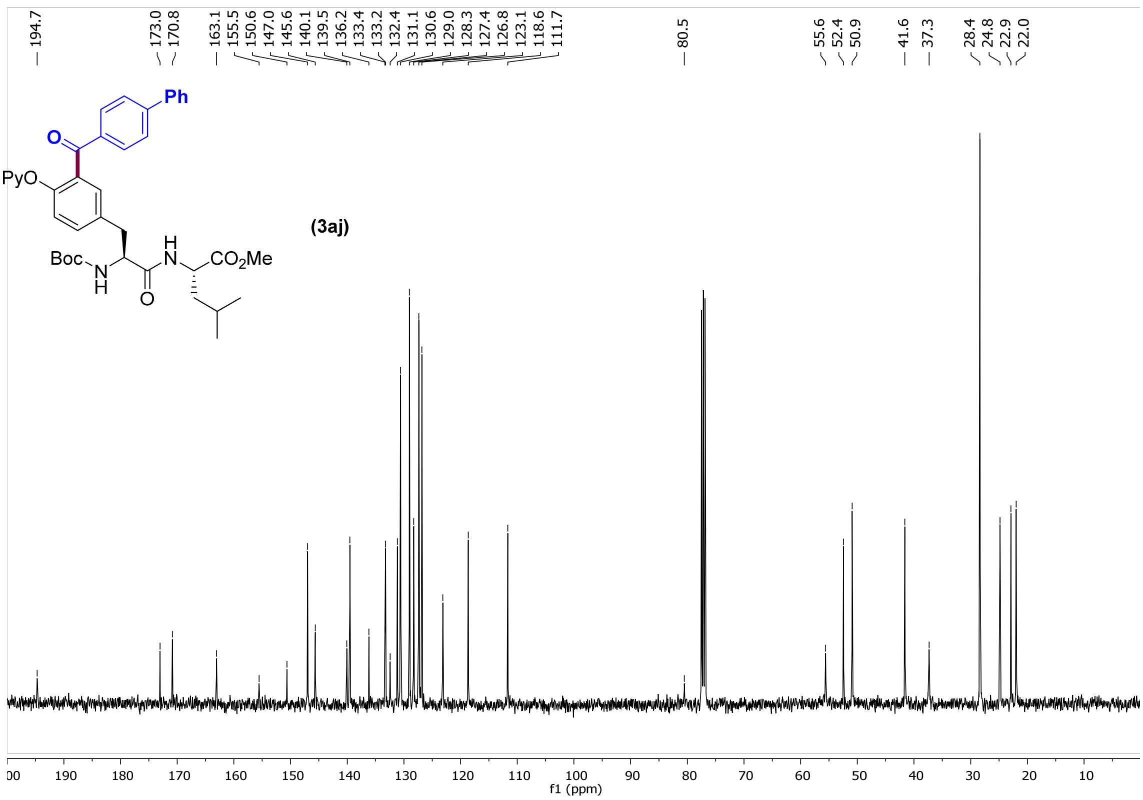

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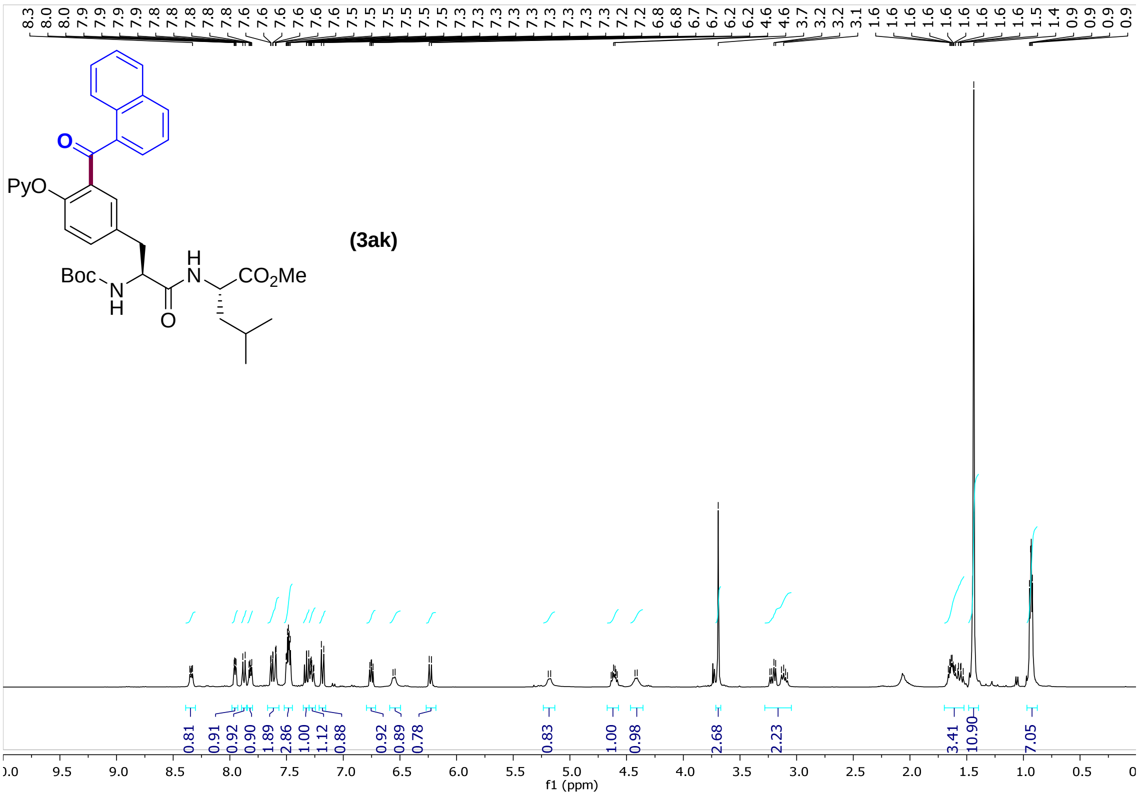

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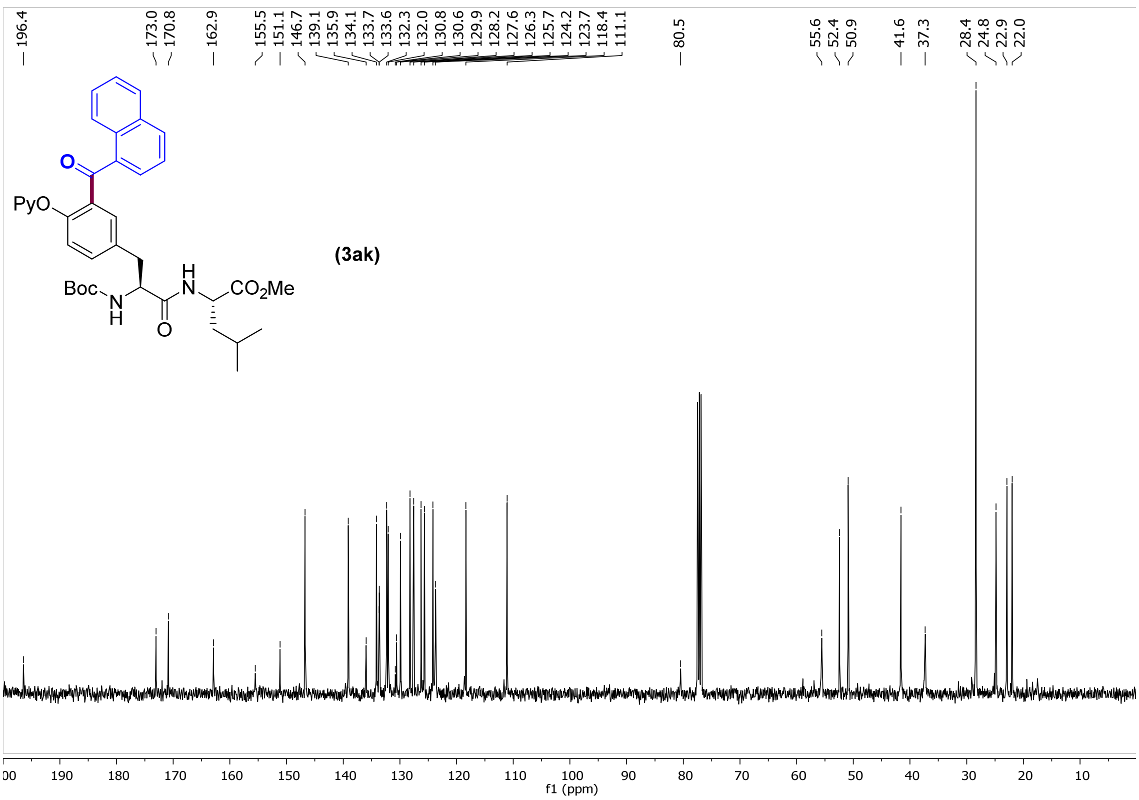

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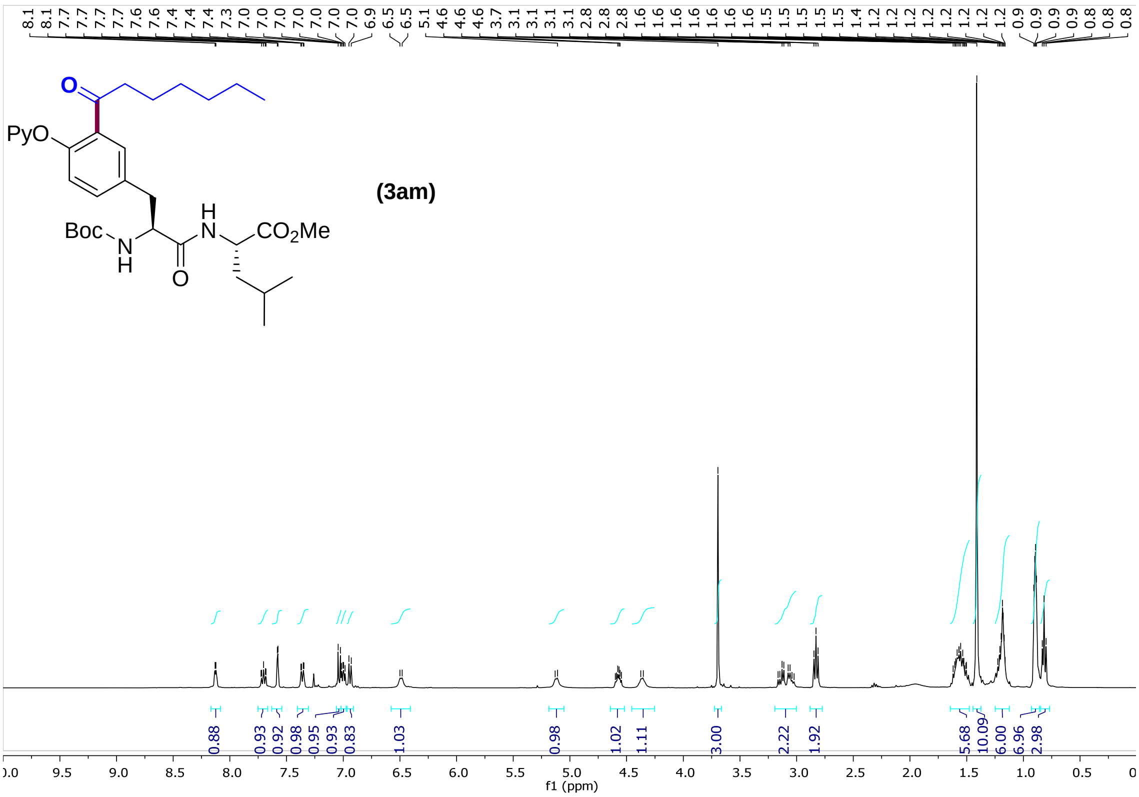

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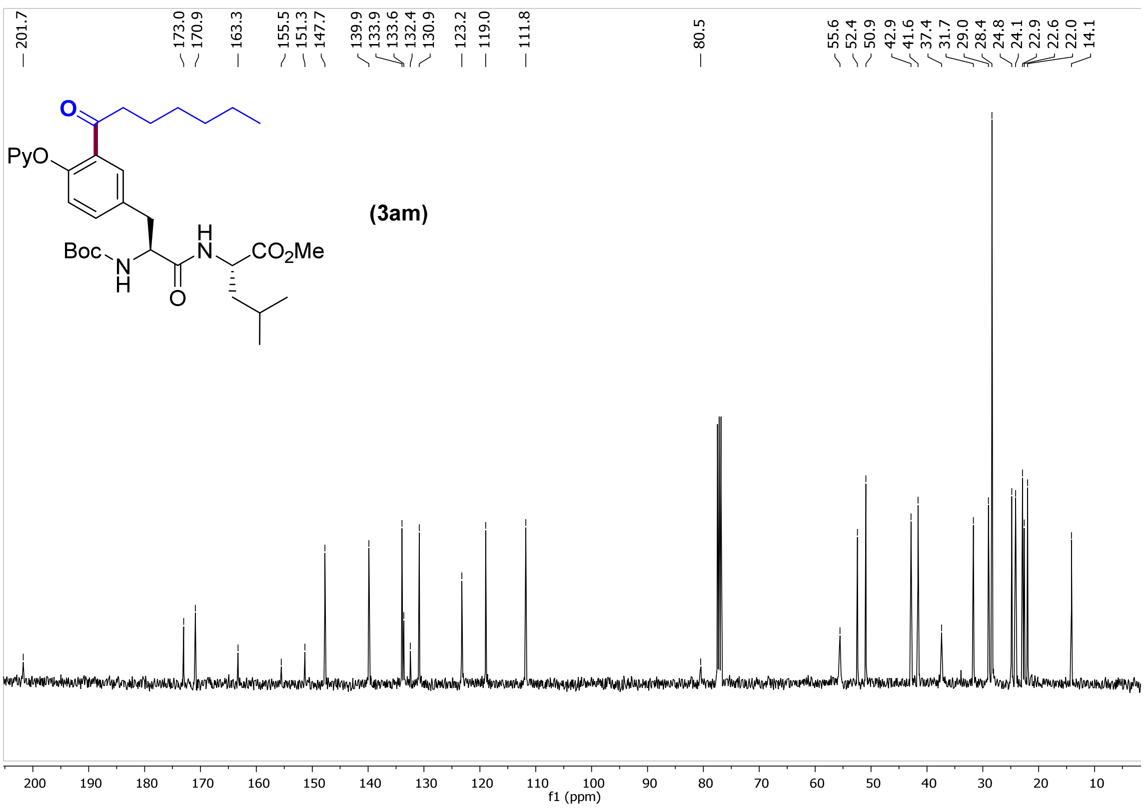

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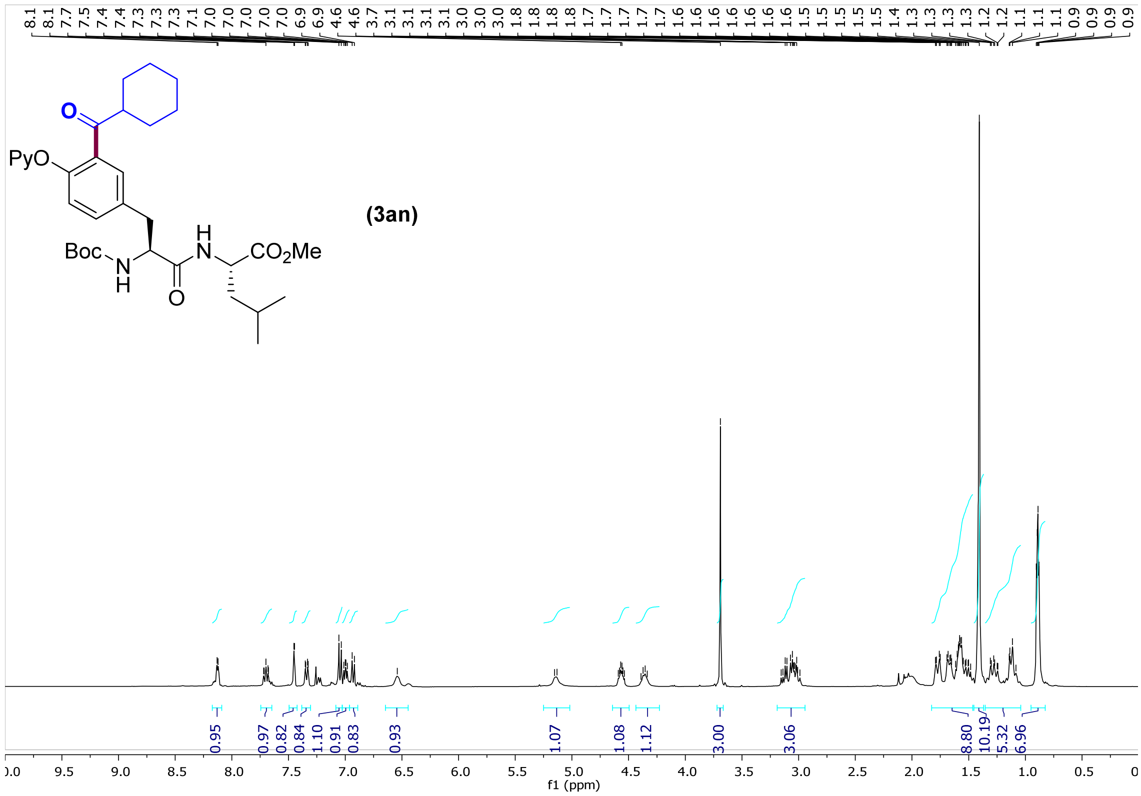

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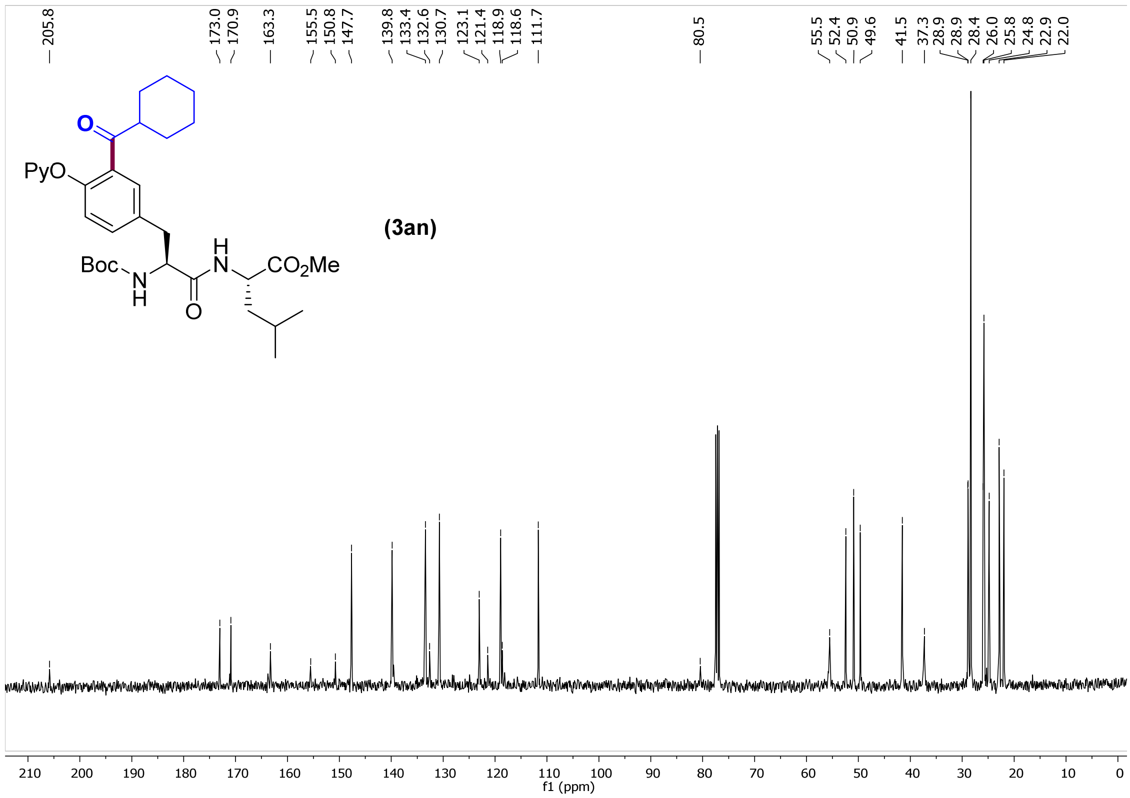

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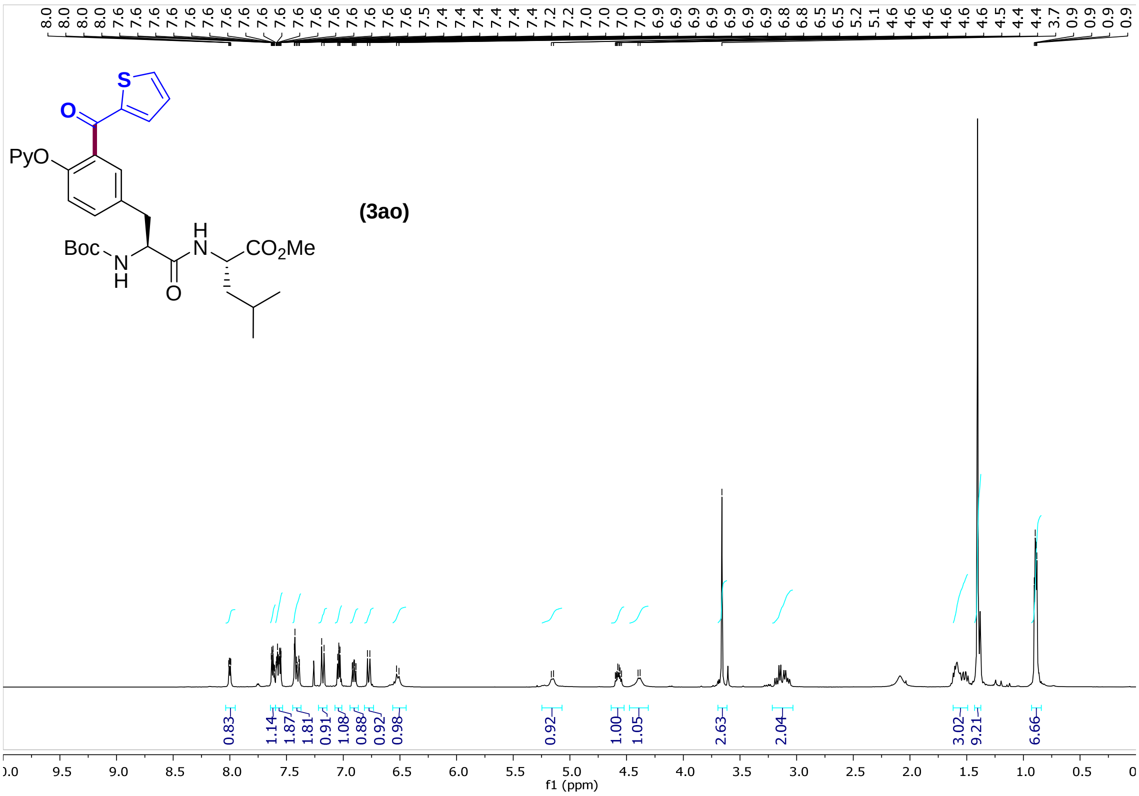

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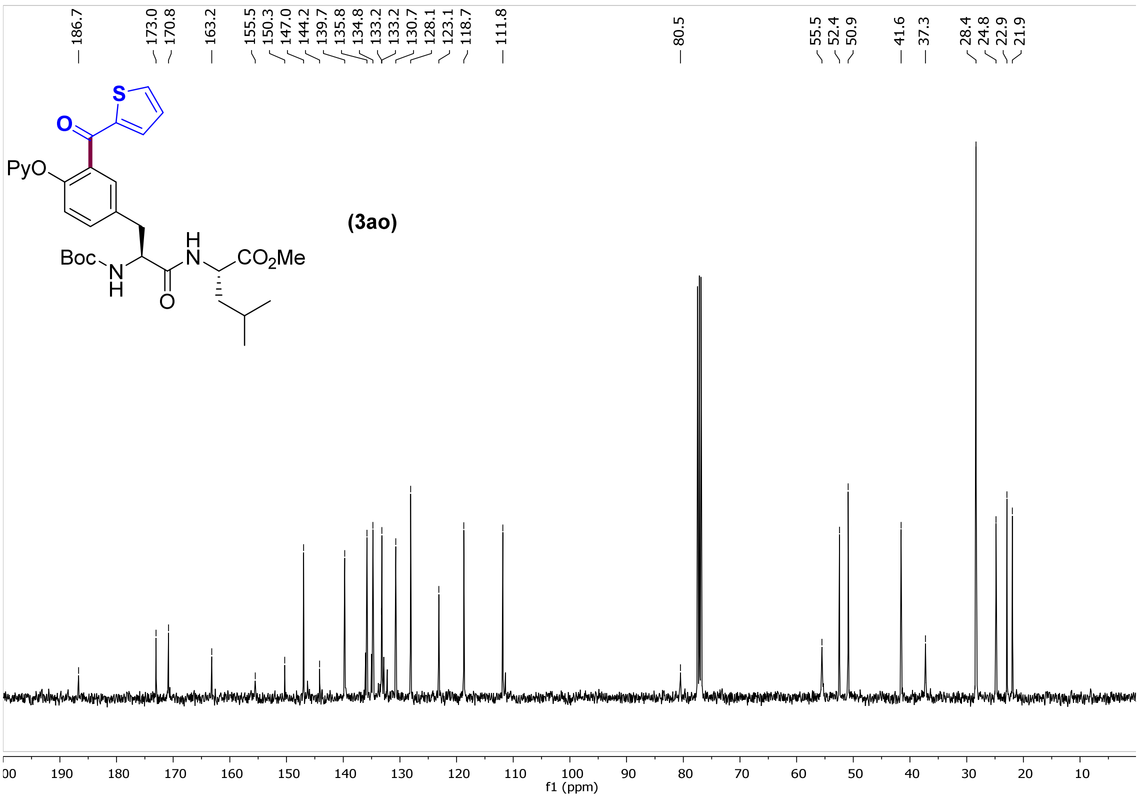

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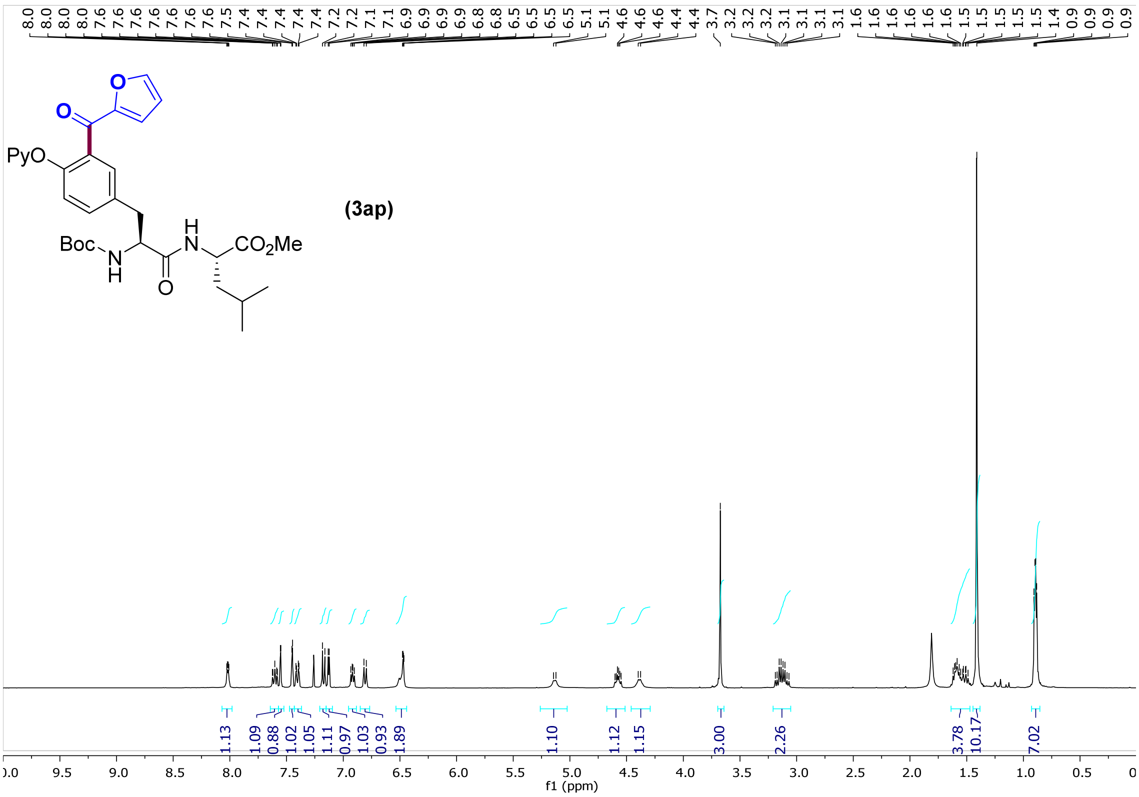

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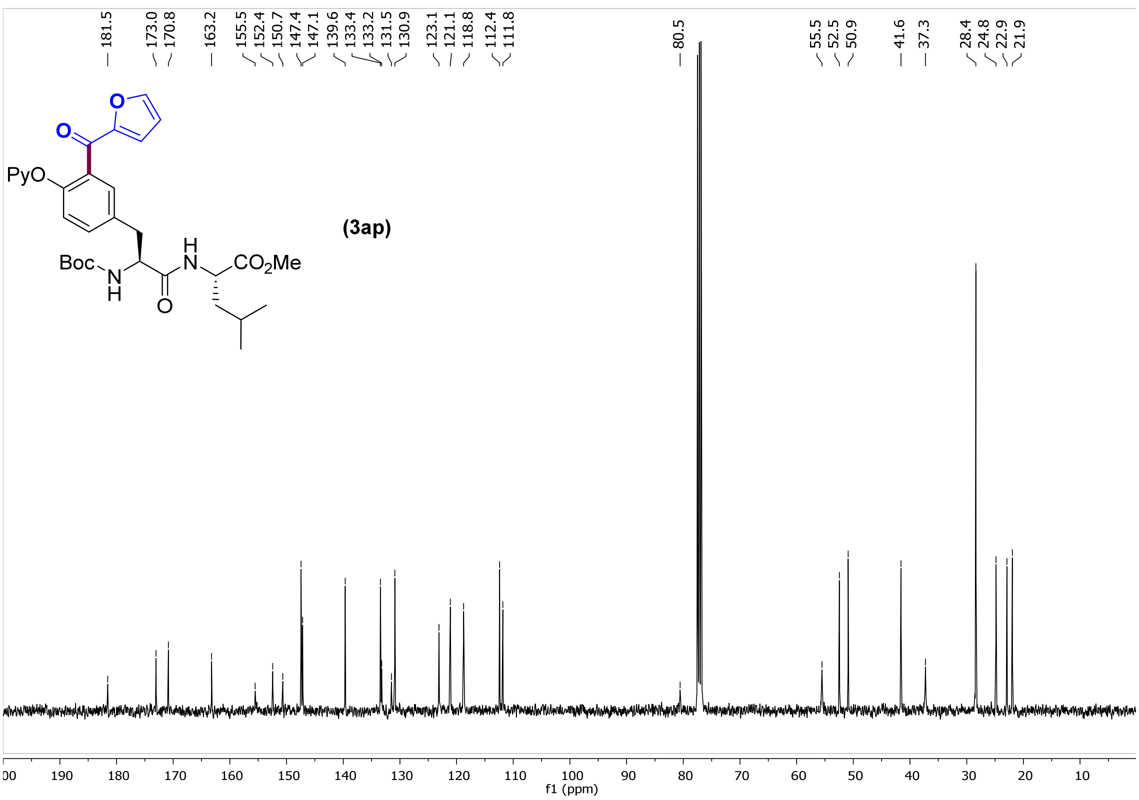

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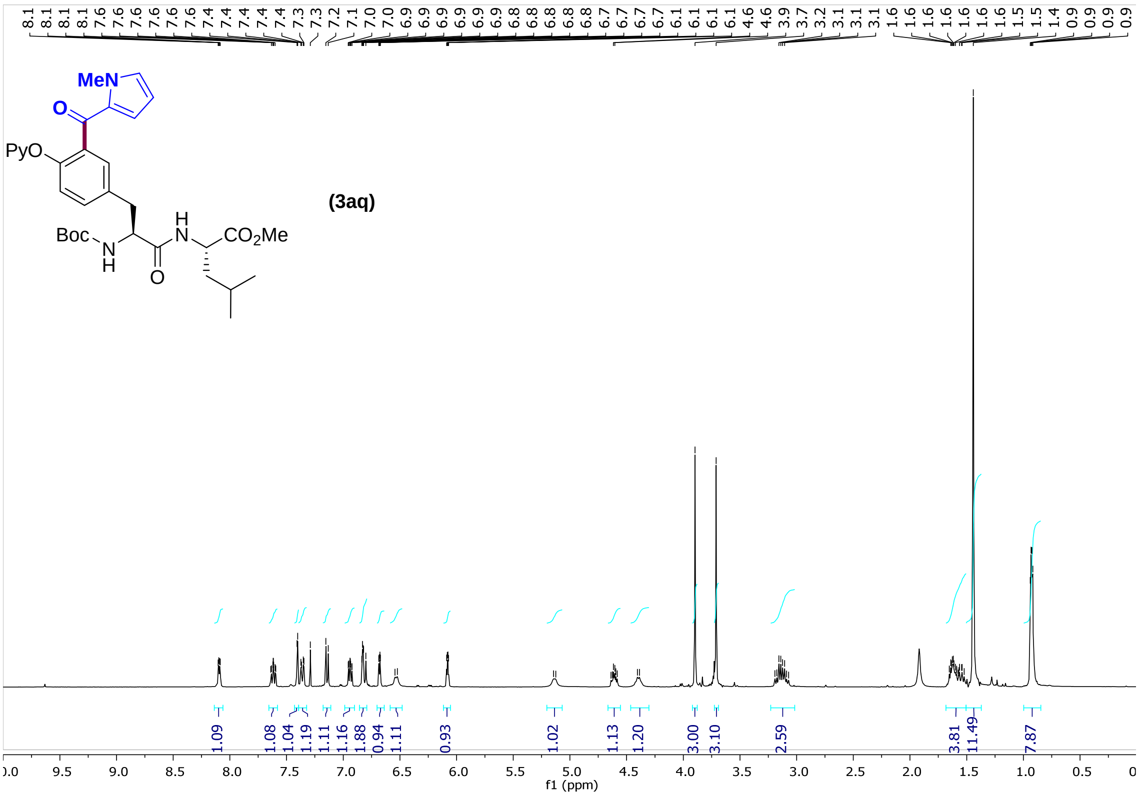

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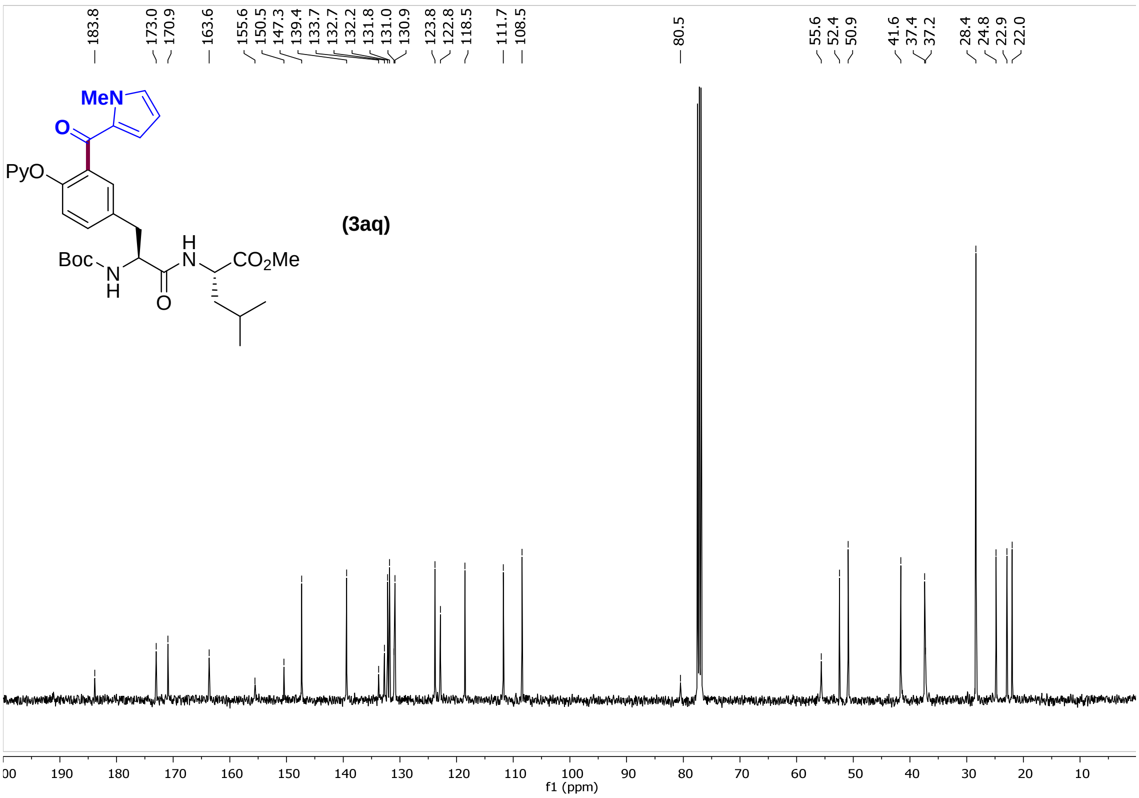

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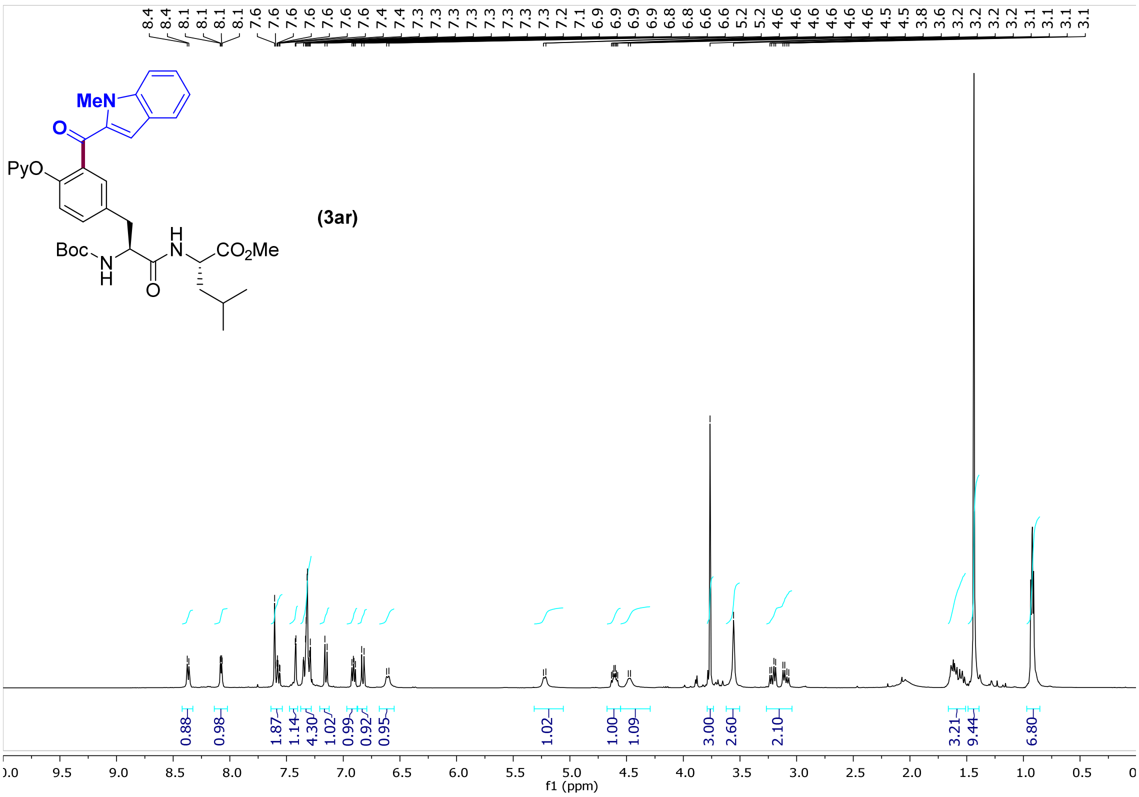

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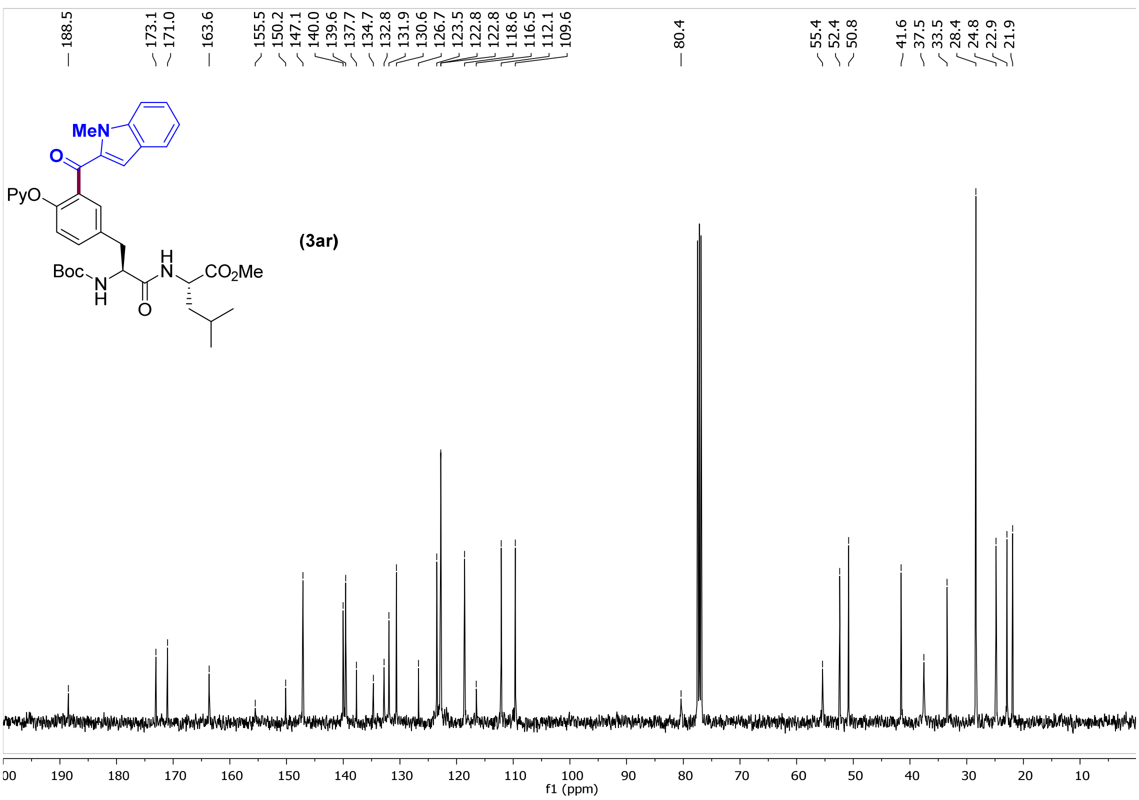

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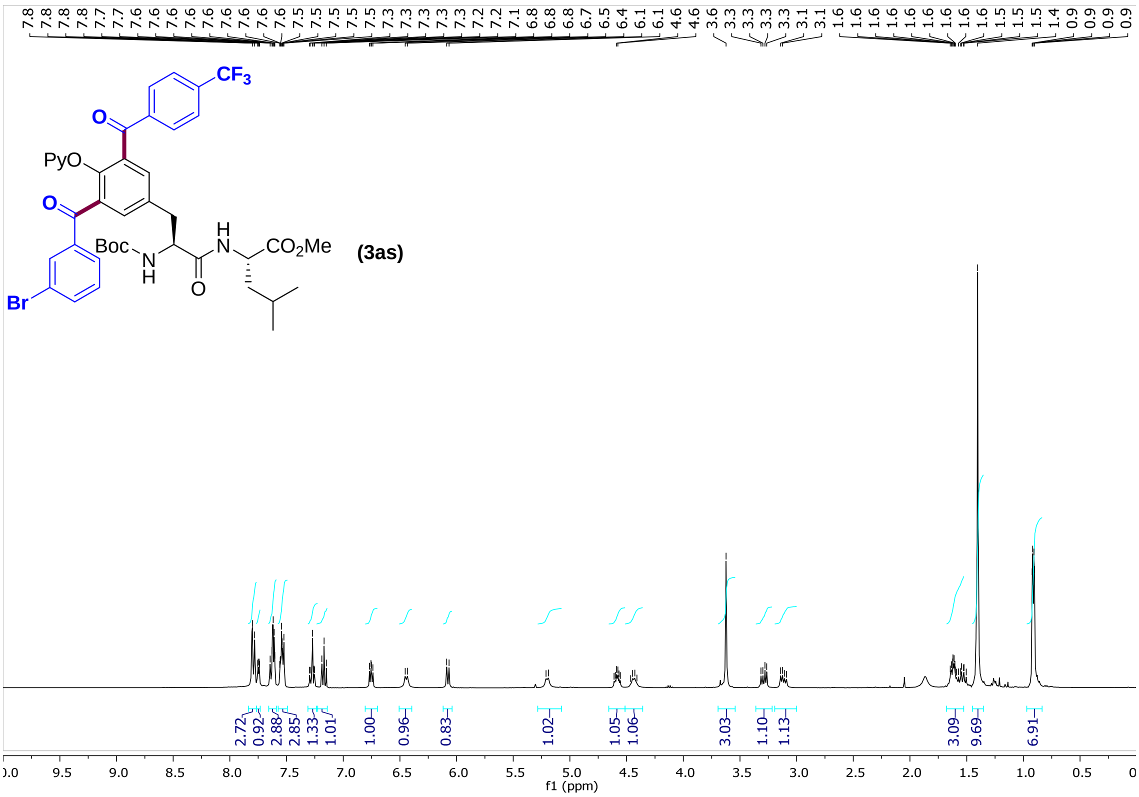

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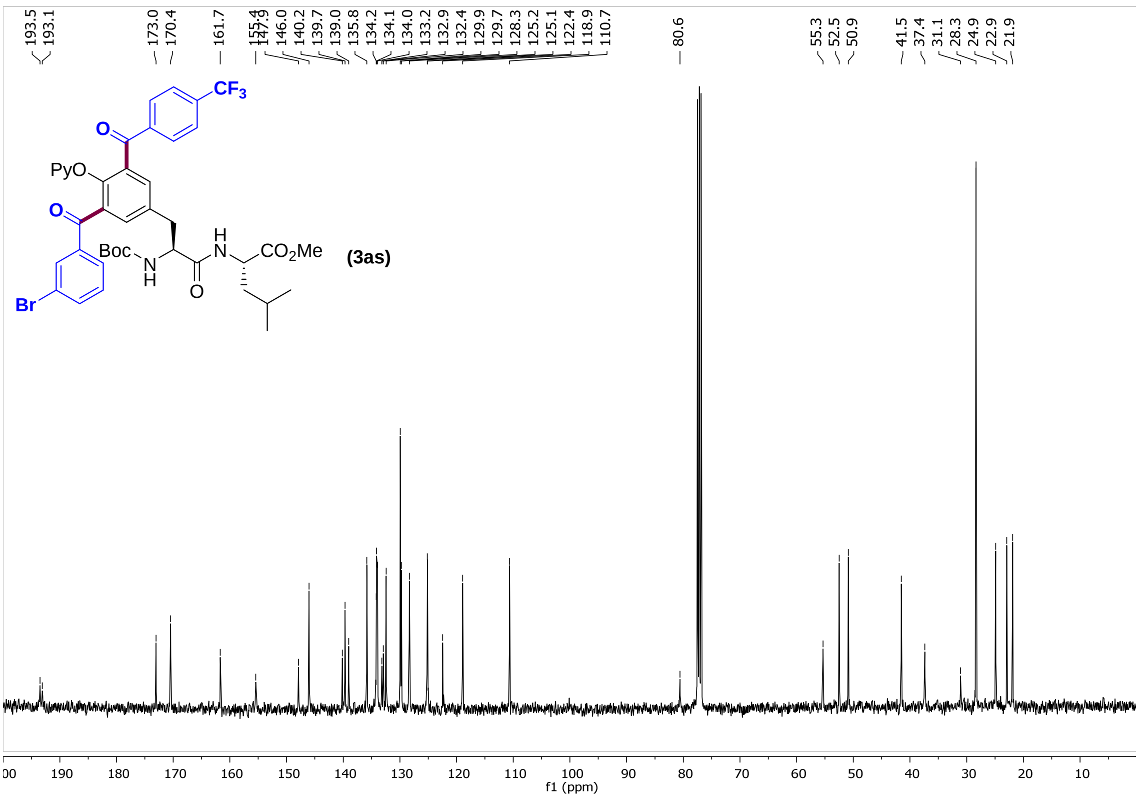

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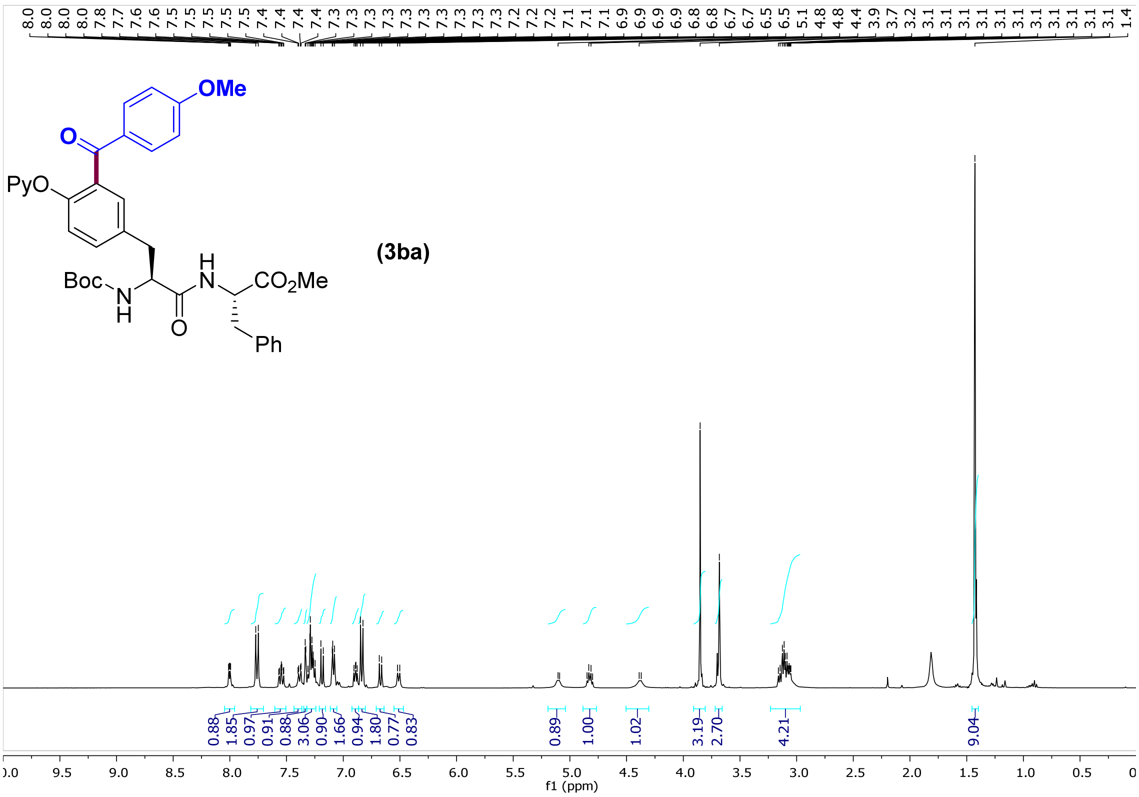
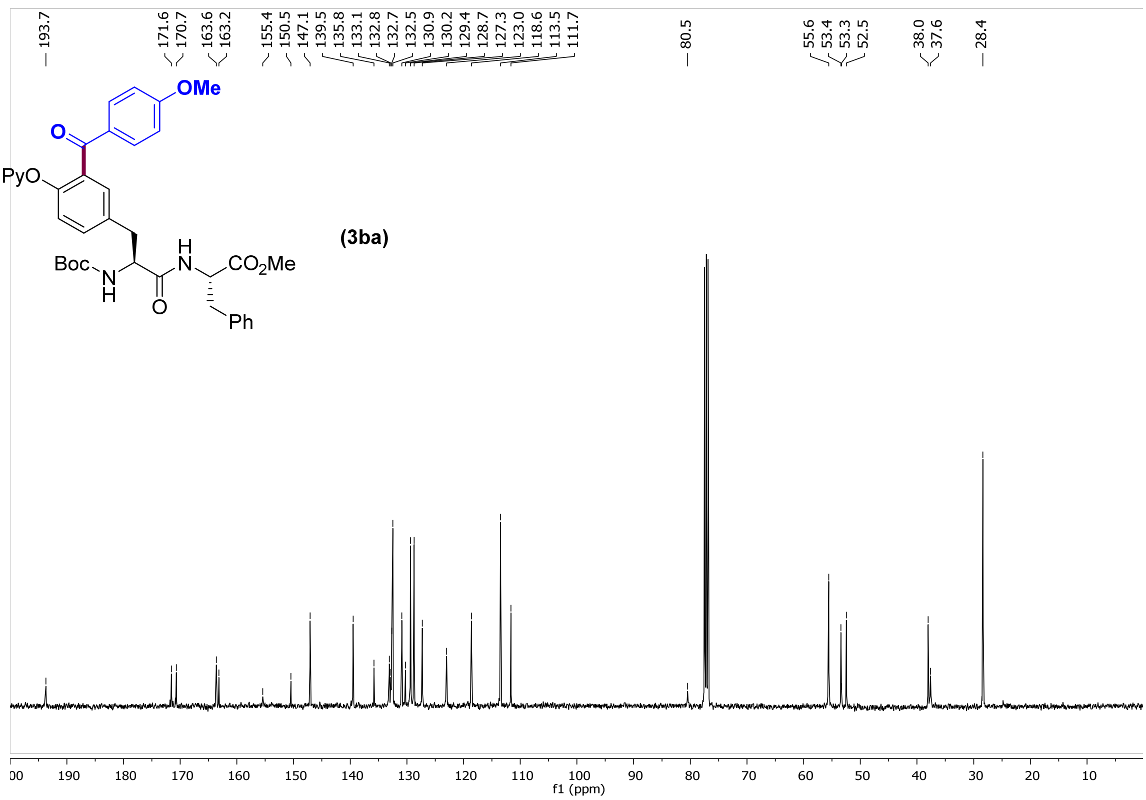
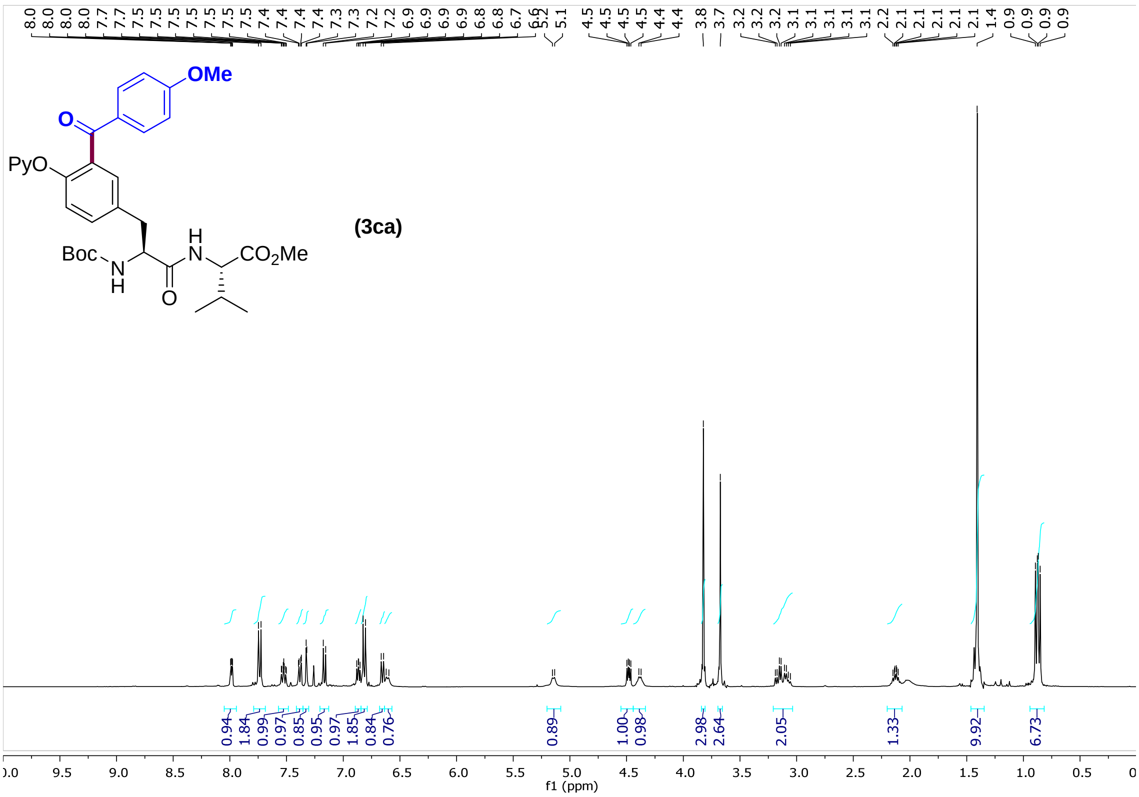


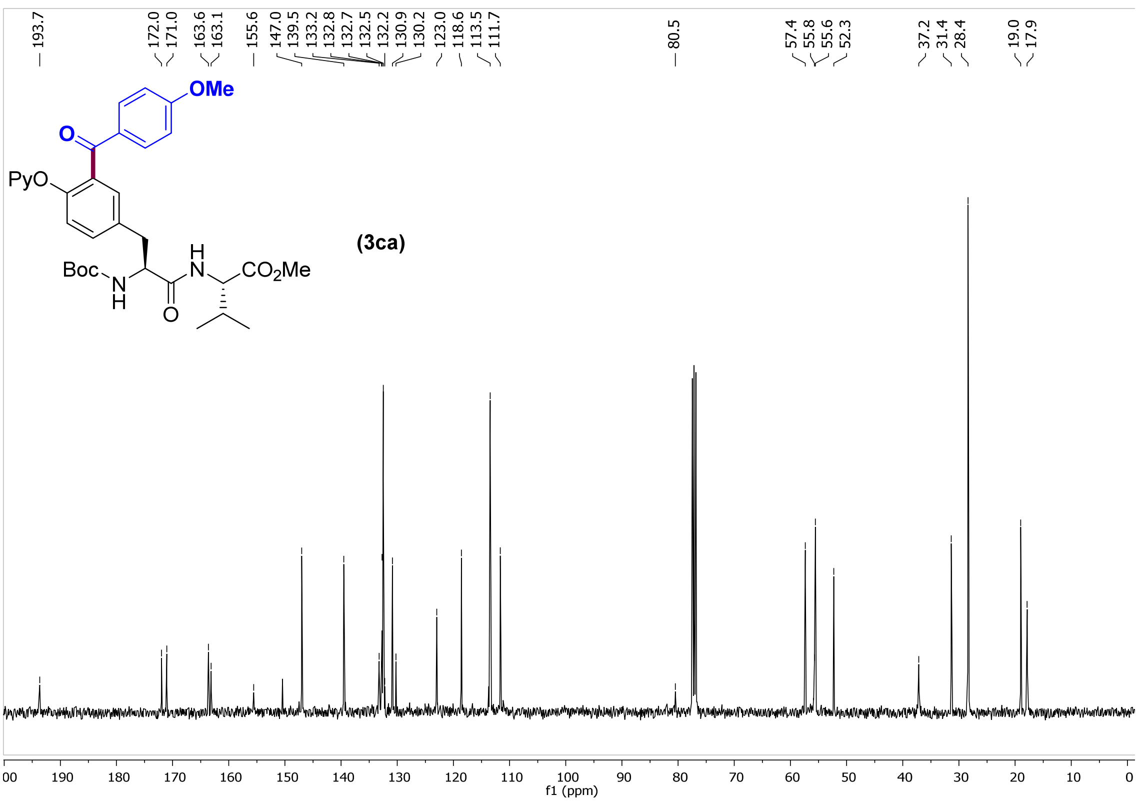
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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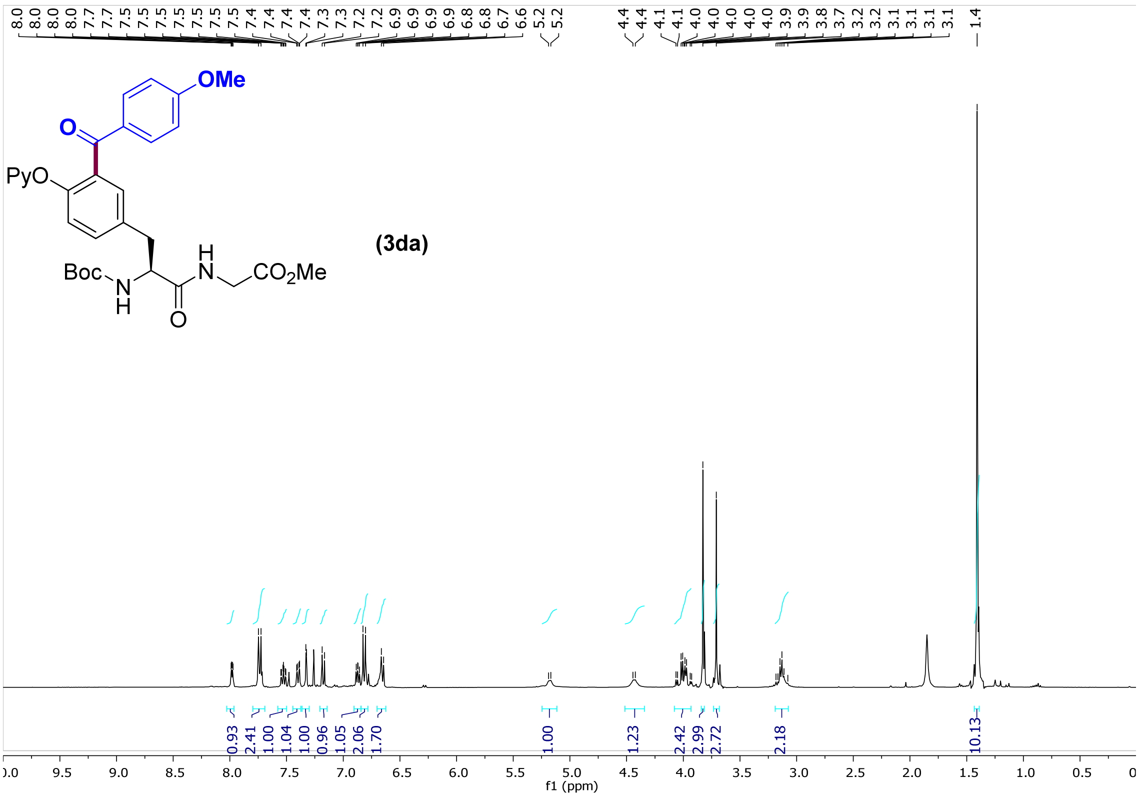
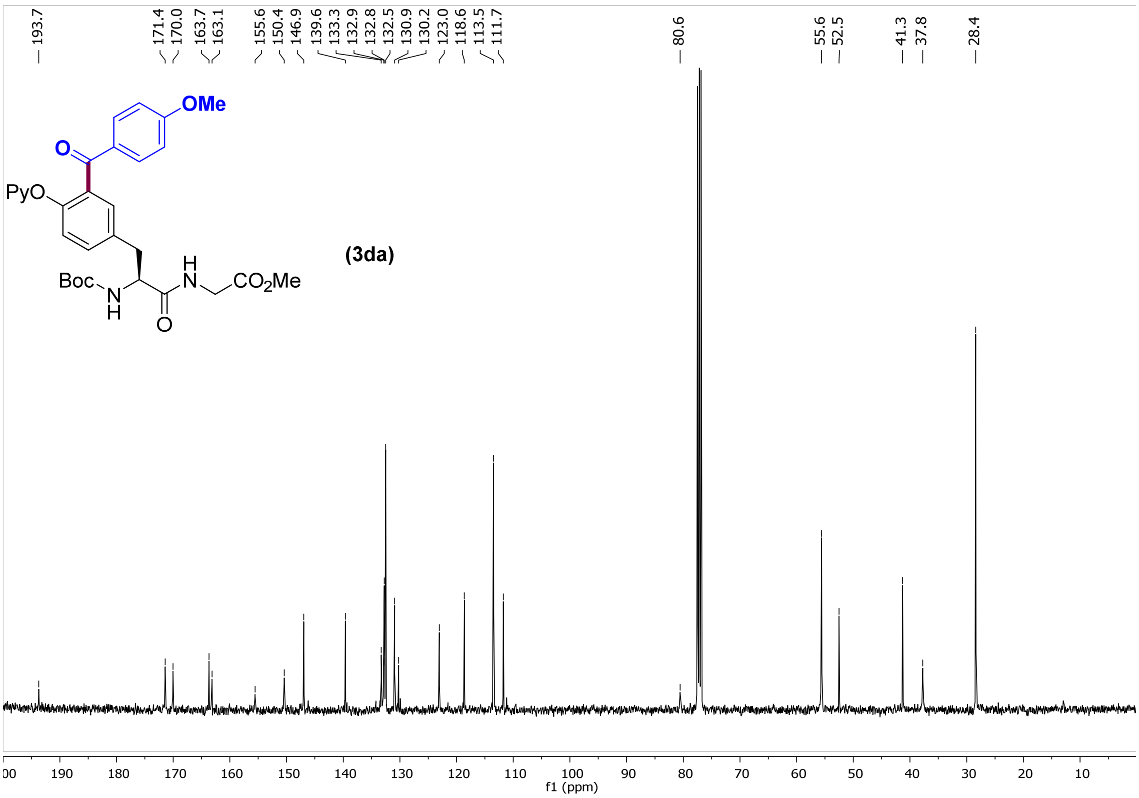


^{13}C NMR (101 MHz, $CDCl_3$)



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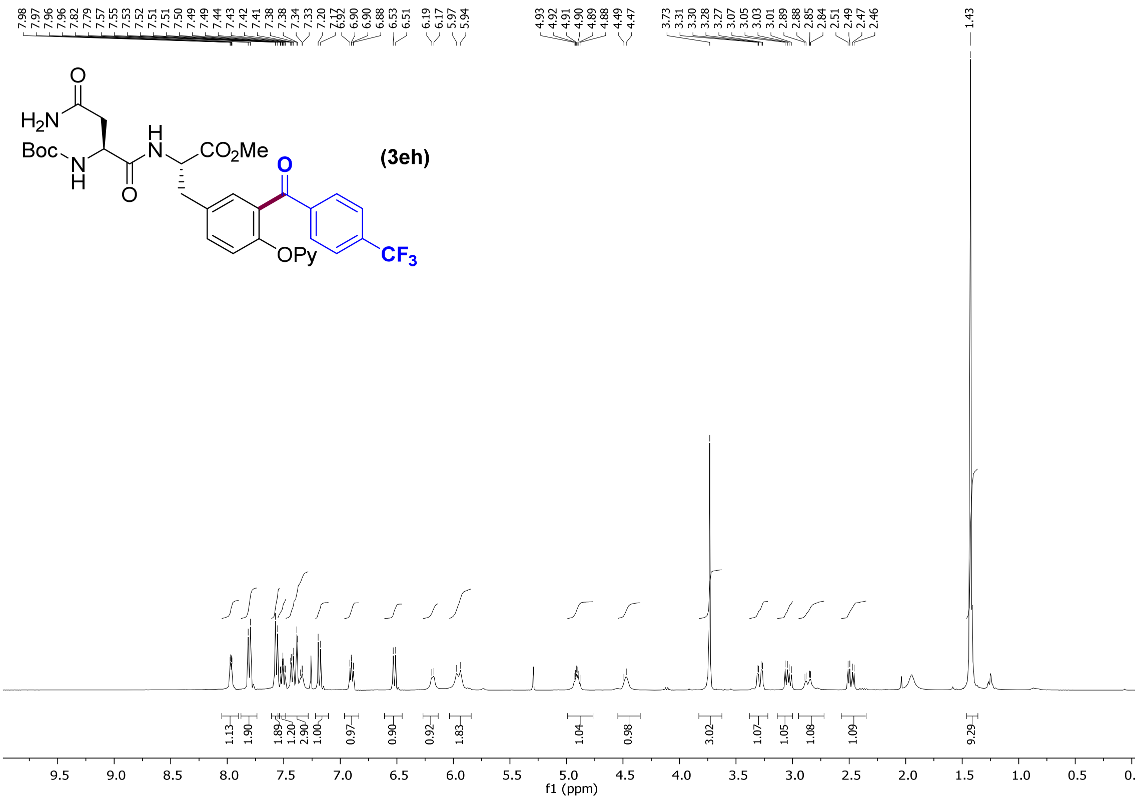

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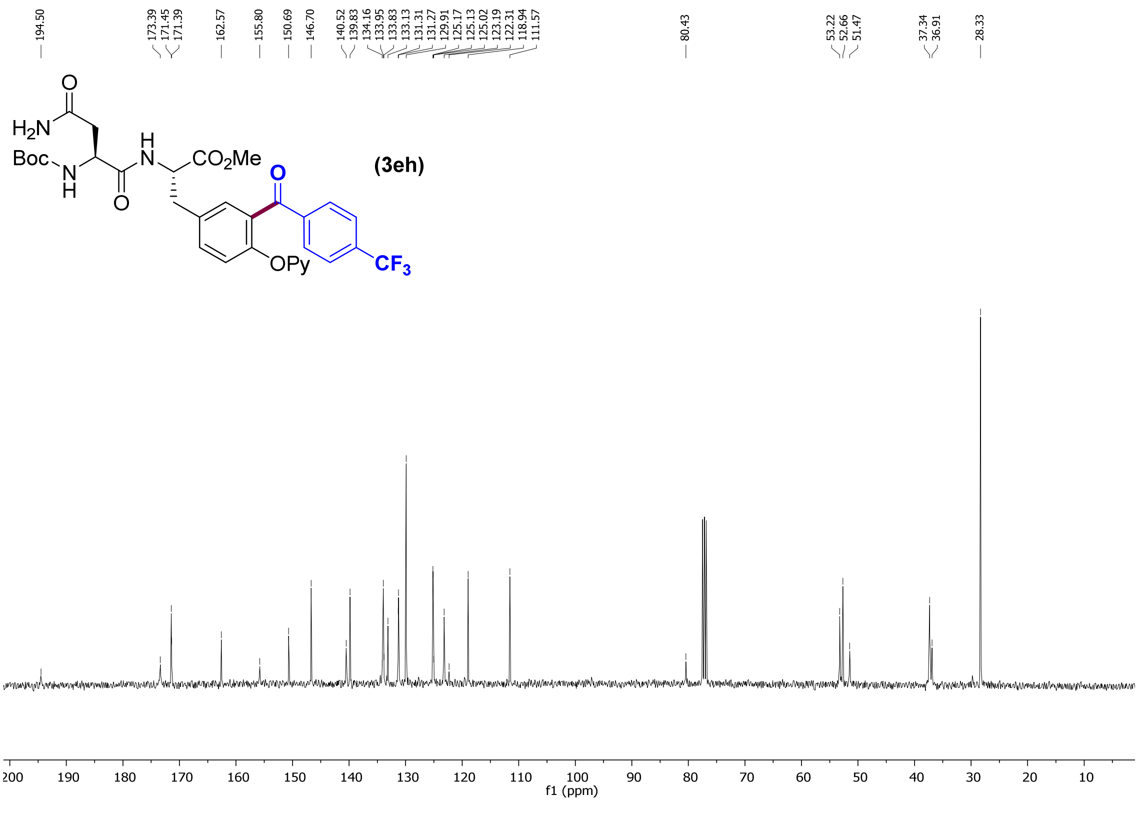

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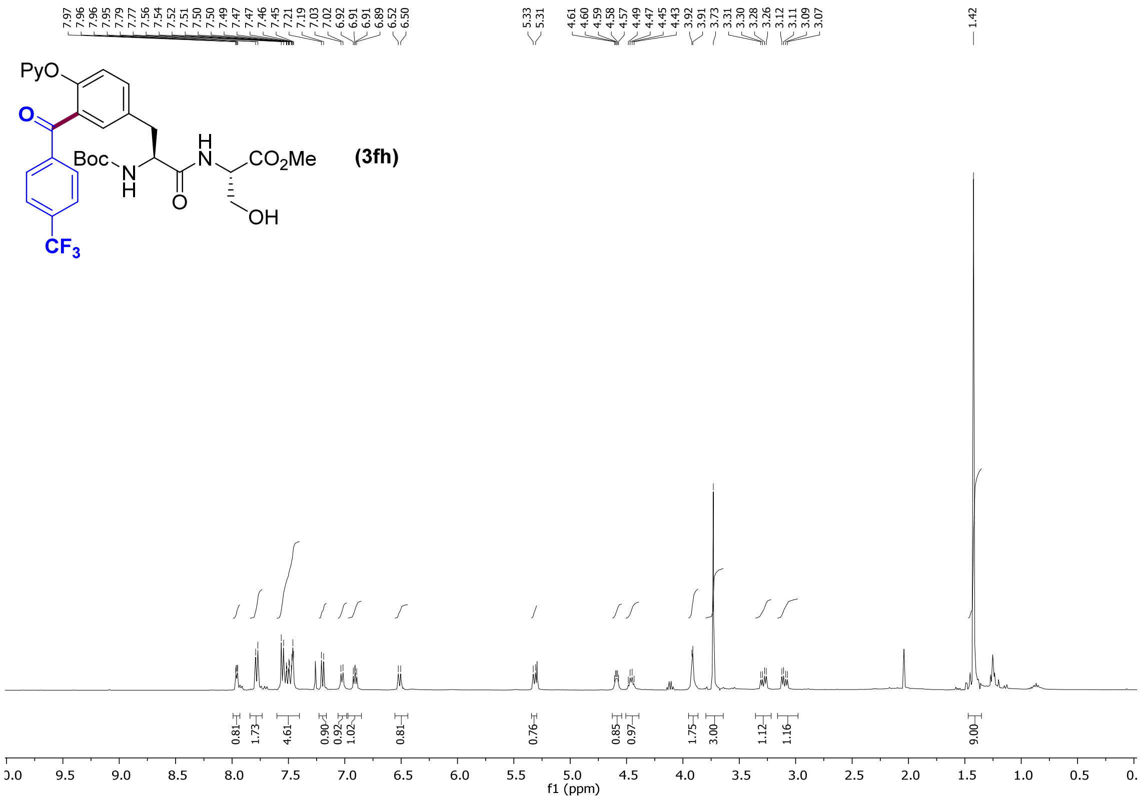

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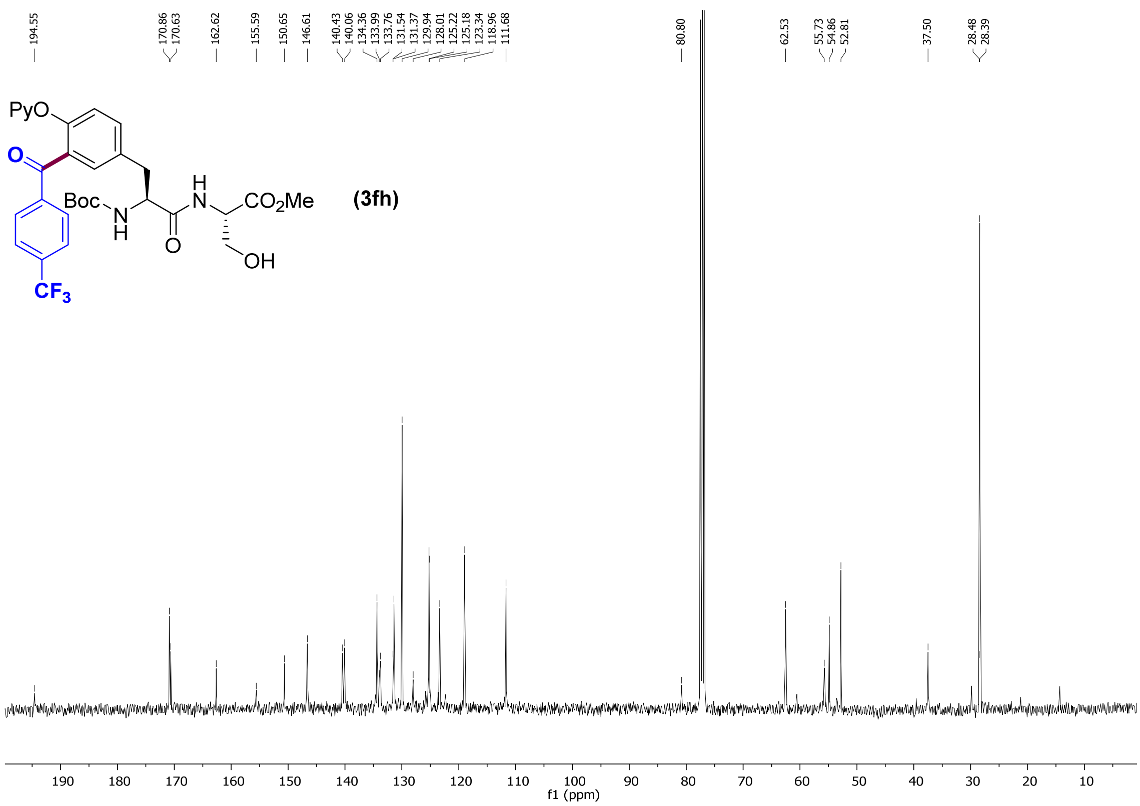

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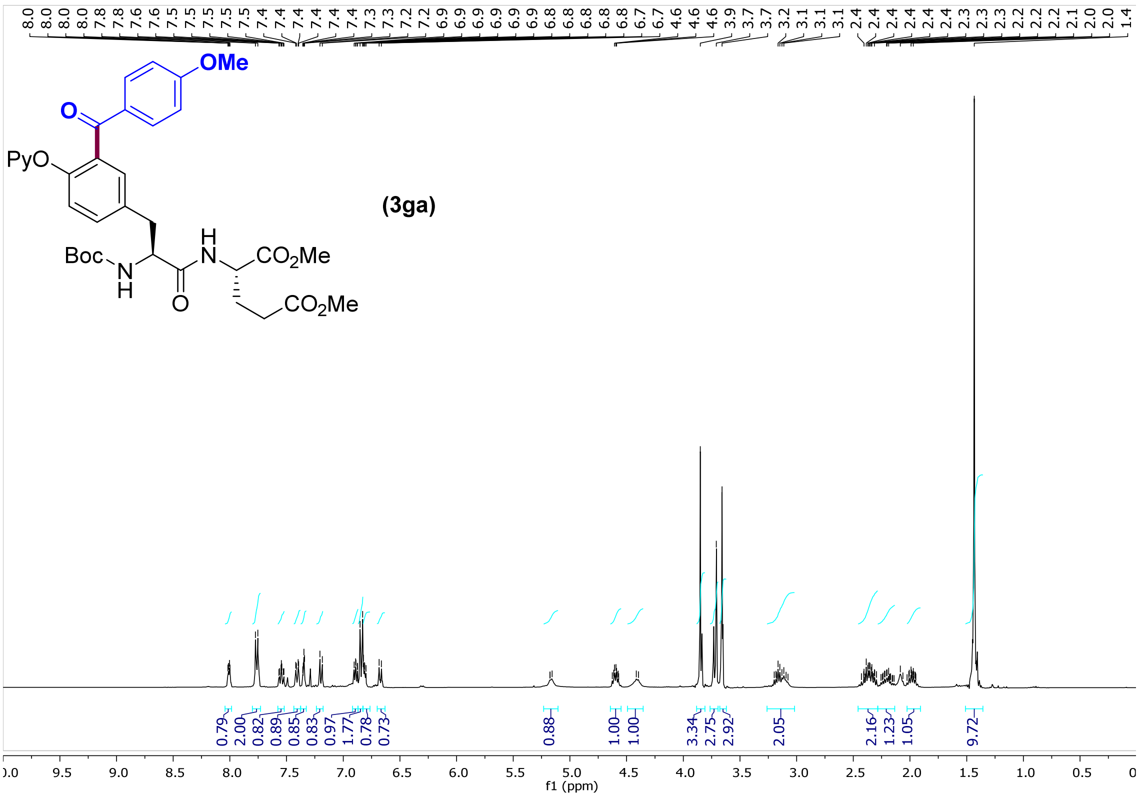

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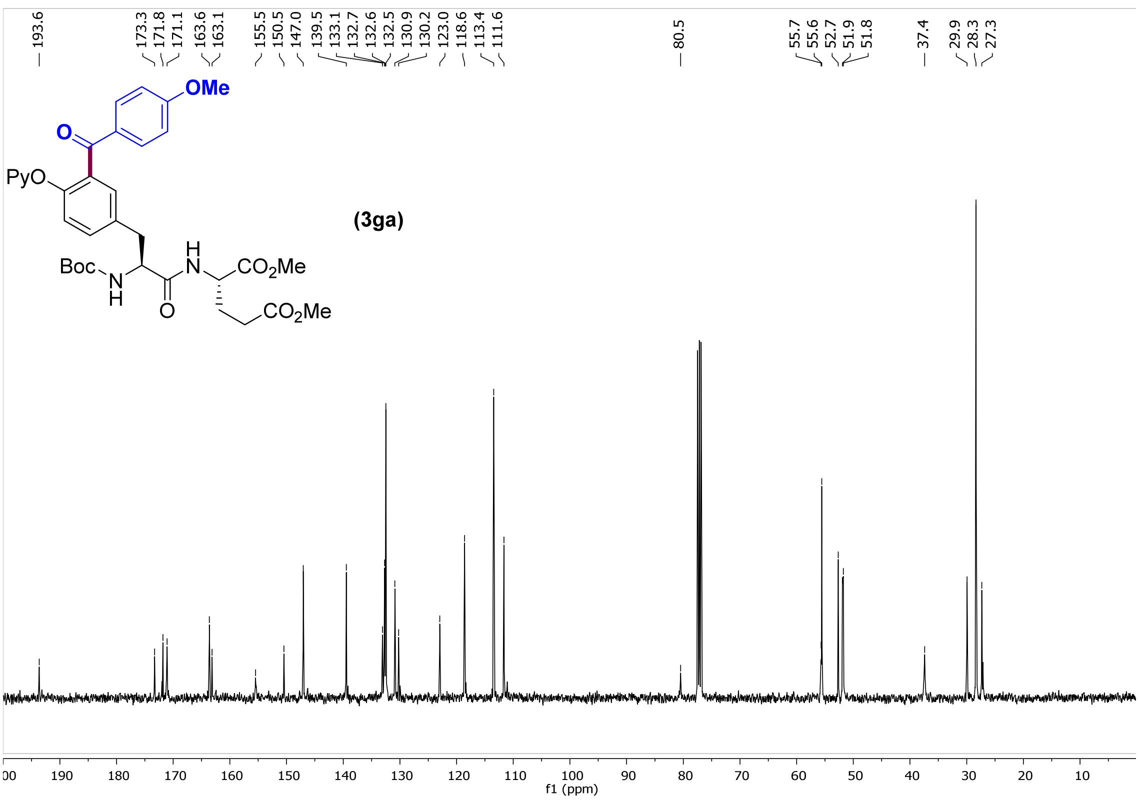

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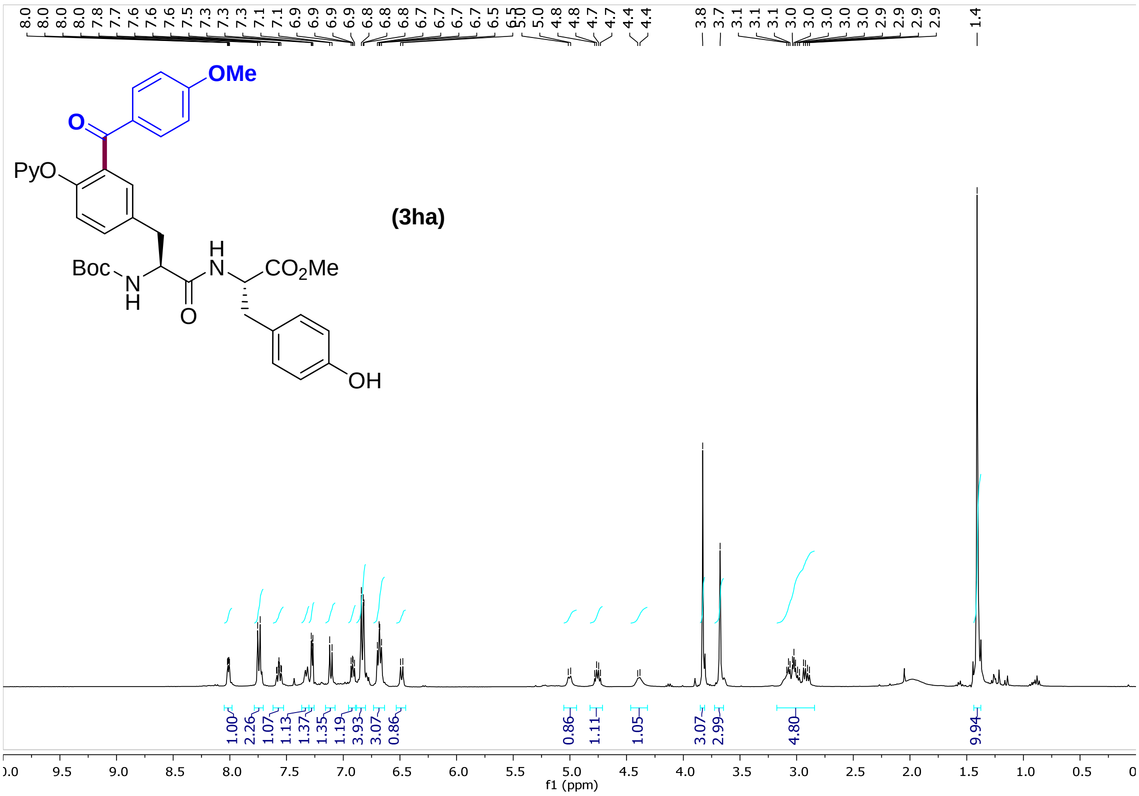
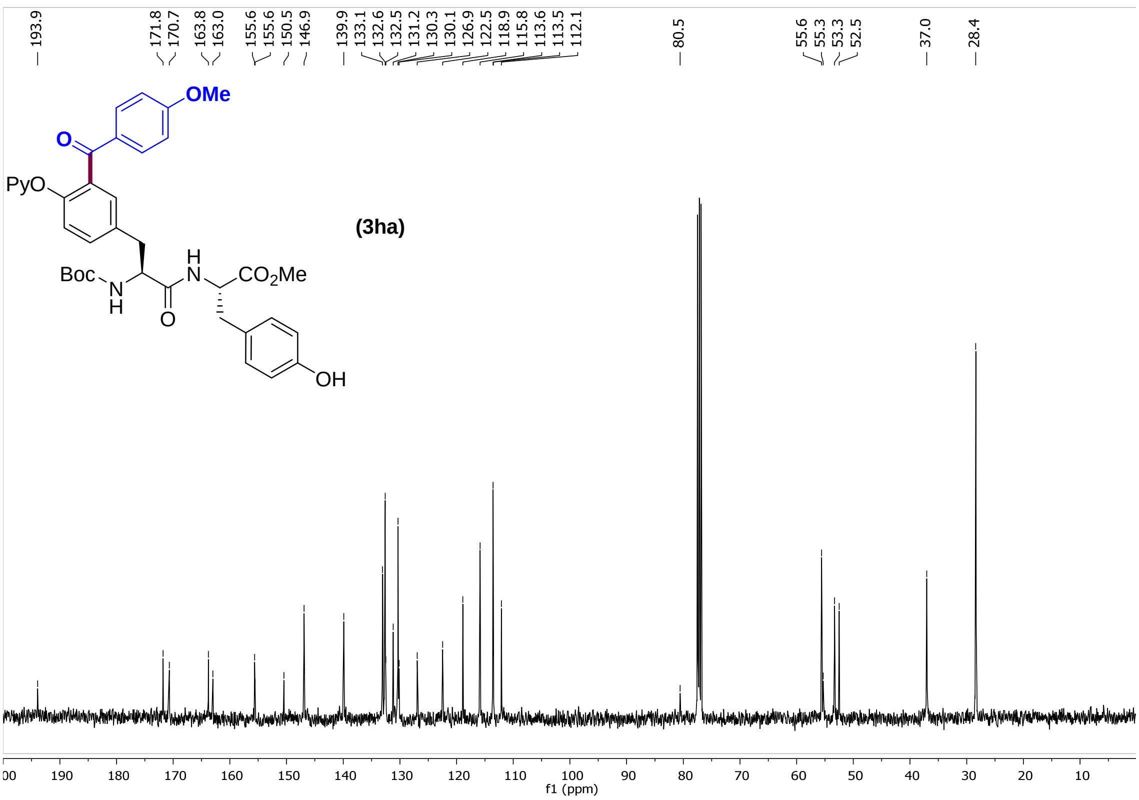
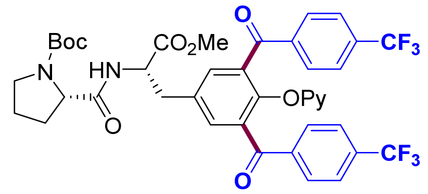


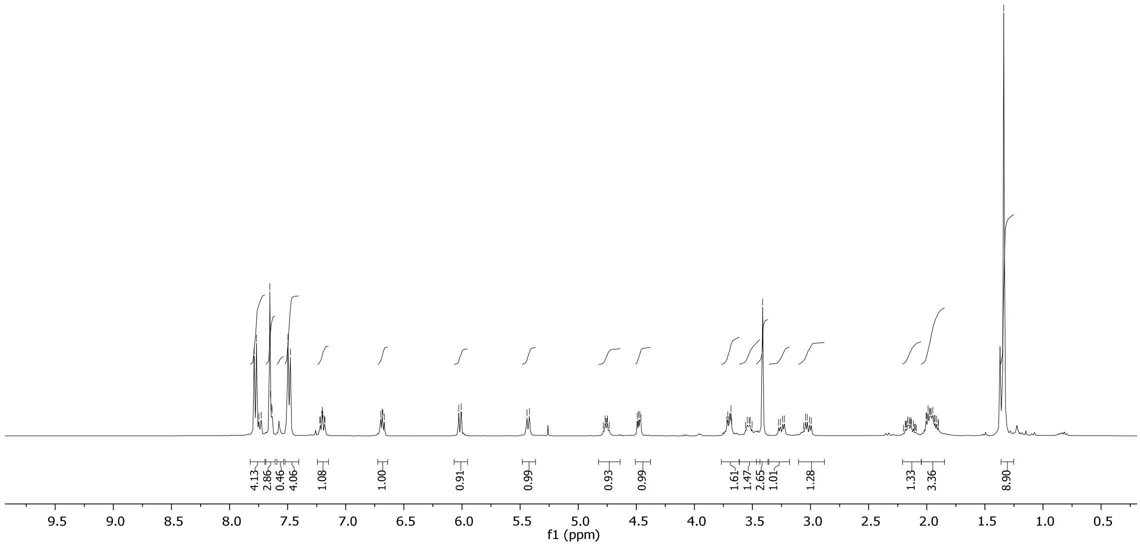
^{13}C NMR (101 MHz, $CDCl_3$)



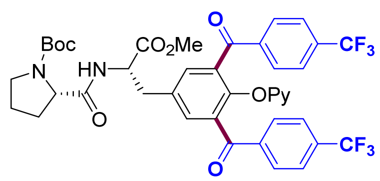
^{1}H NMR (400 MHz, $CDCl_3$)



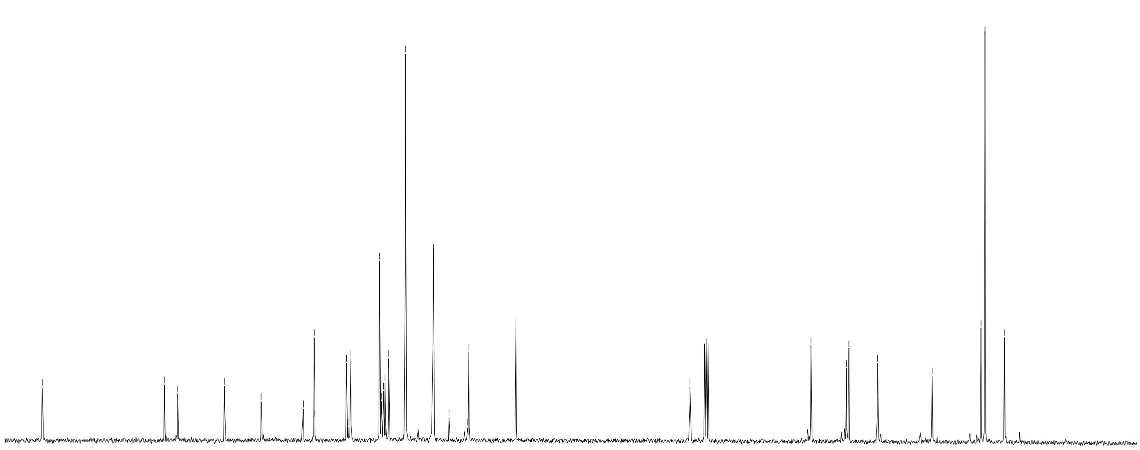
(3'ih)



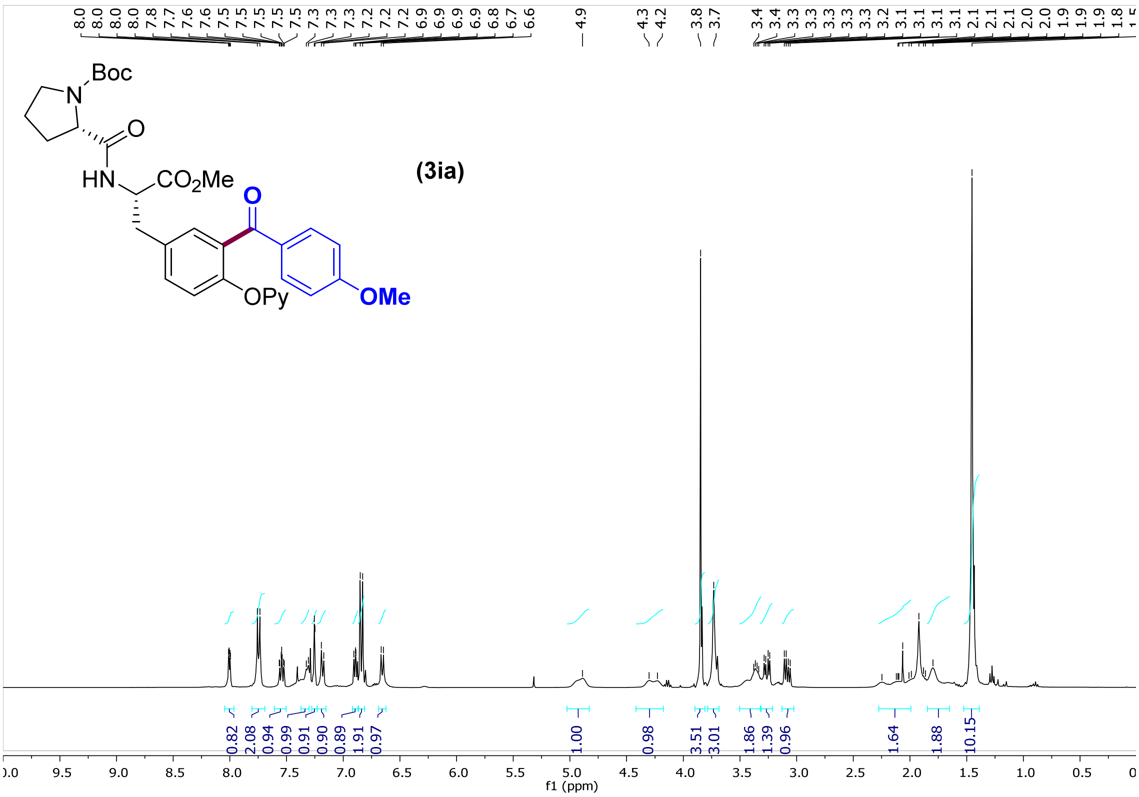
^{13}C NMR (101 MHz, $CDCl_3$)



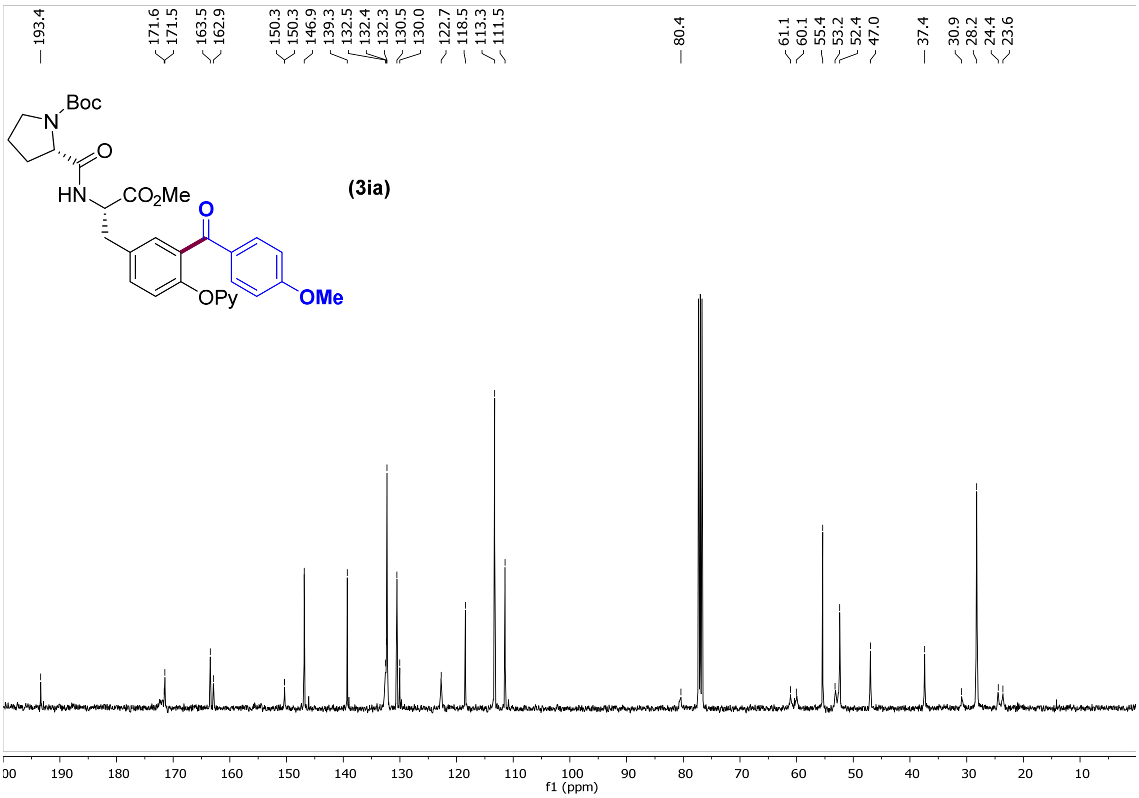
(3'ih)



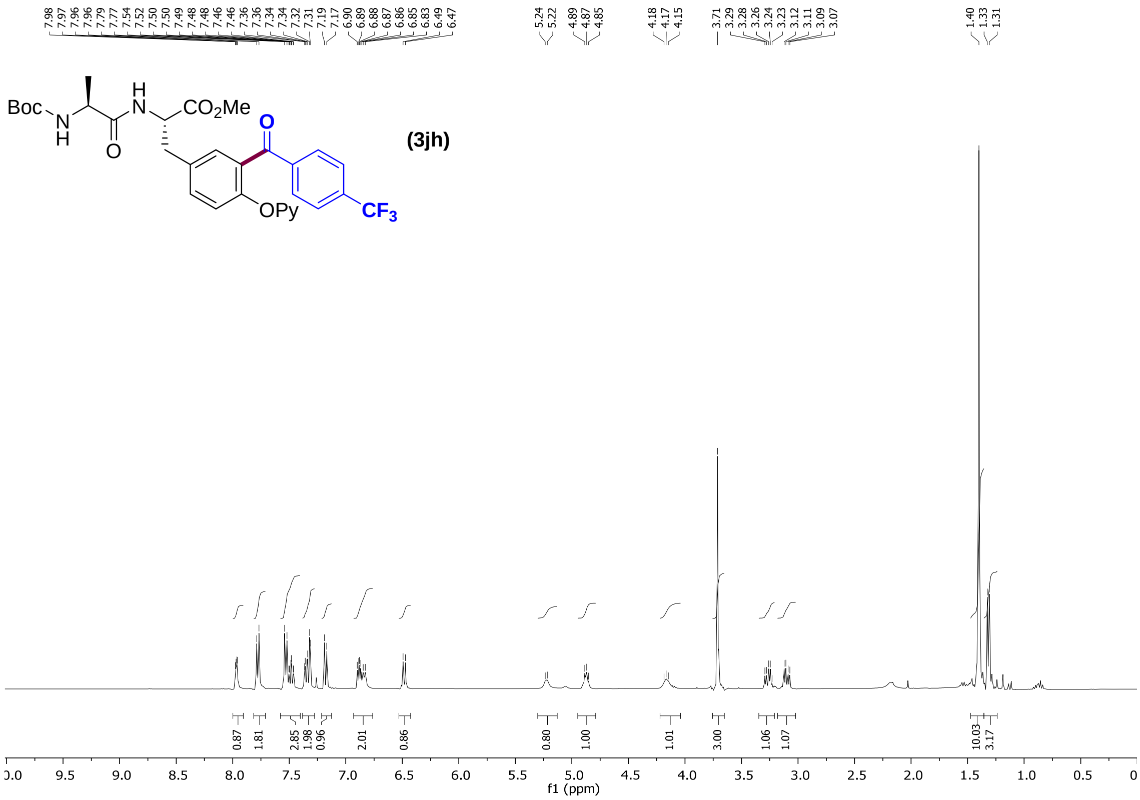
^{1}H NMR (400 MHz, $CDCl_3$)



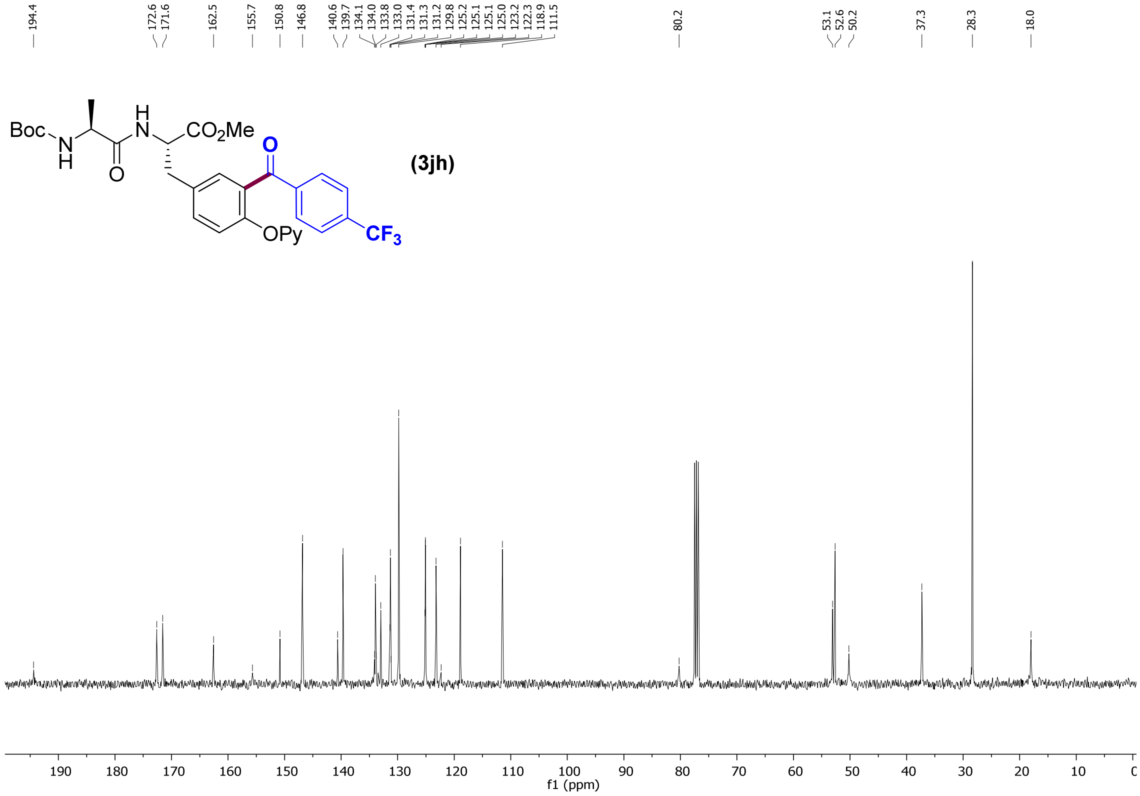
^{13}C NMR (101 MHz, $CDCl_3$)



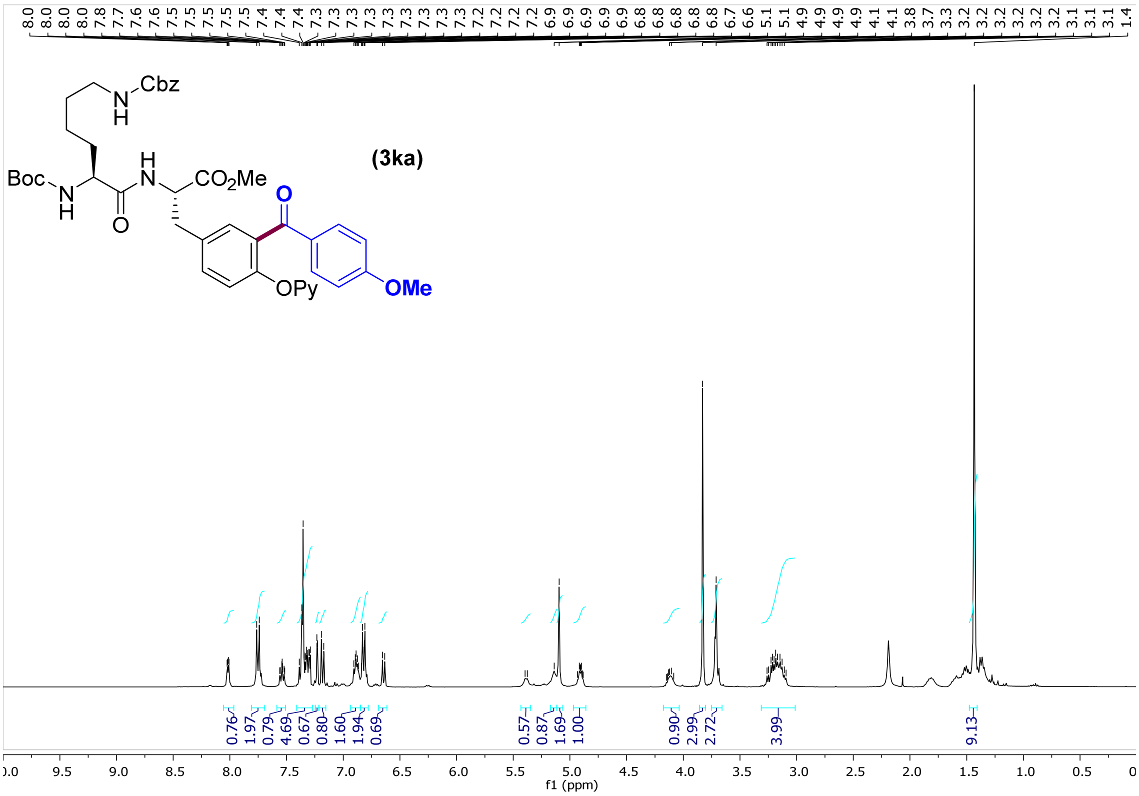
^{1}H NMR (400 MHz, $CDCl_3$)



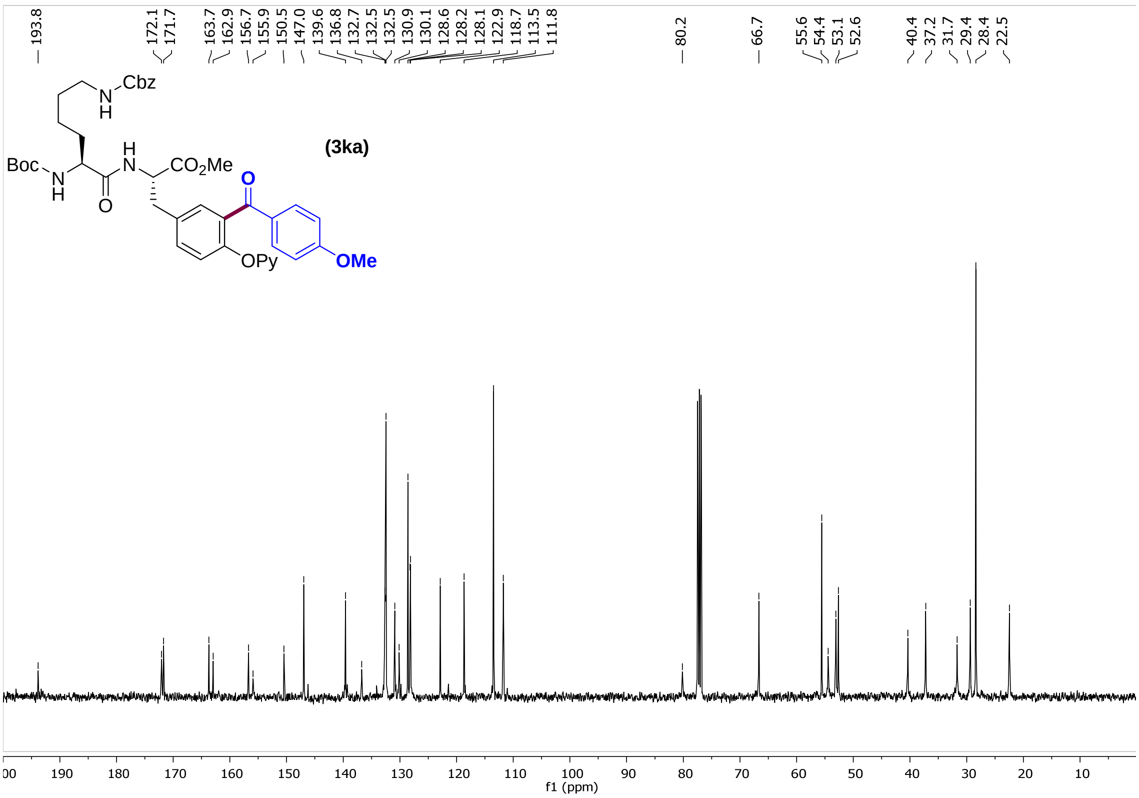
^{13}C NMR (101 MHz, $CDCl_3$)



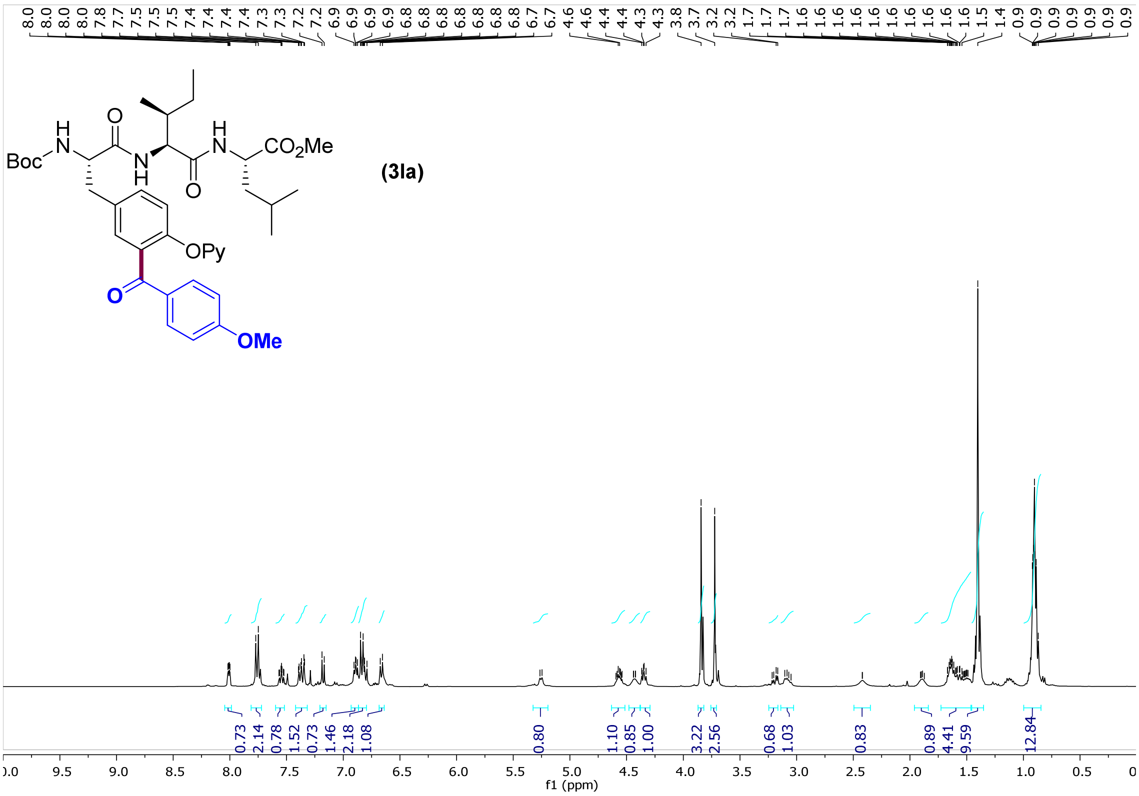
[1]H NMR (400 MHz, $CDCl_3$)



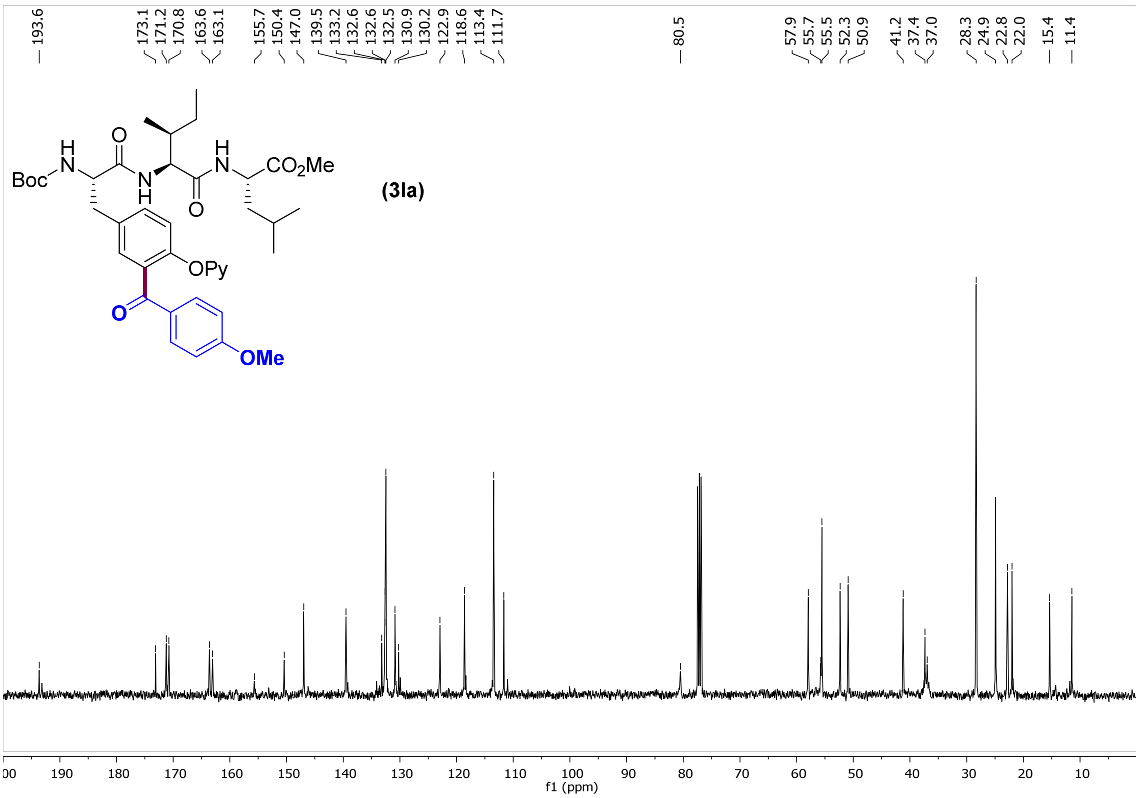
[13]C NMR (101 MHz, $CDCl_3$)



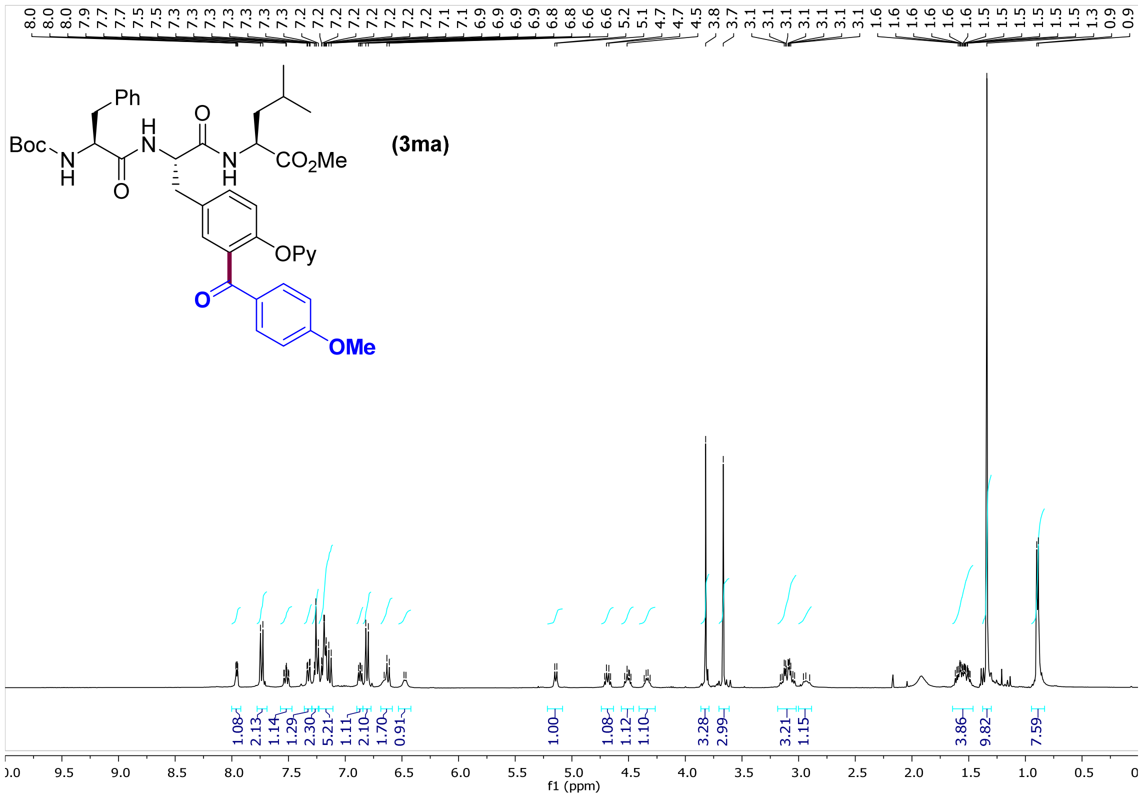
[1]H NMR (400 MHz, CDCl3)



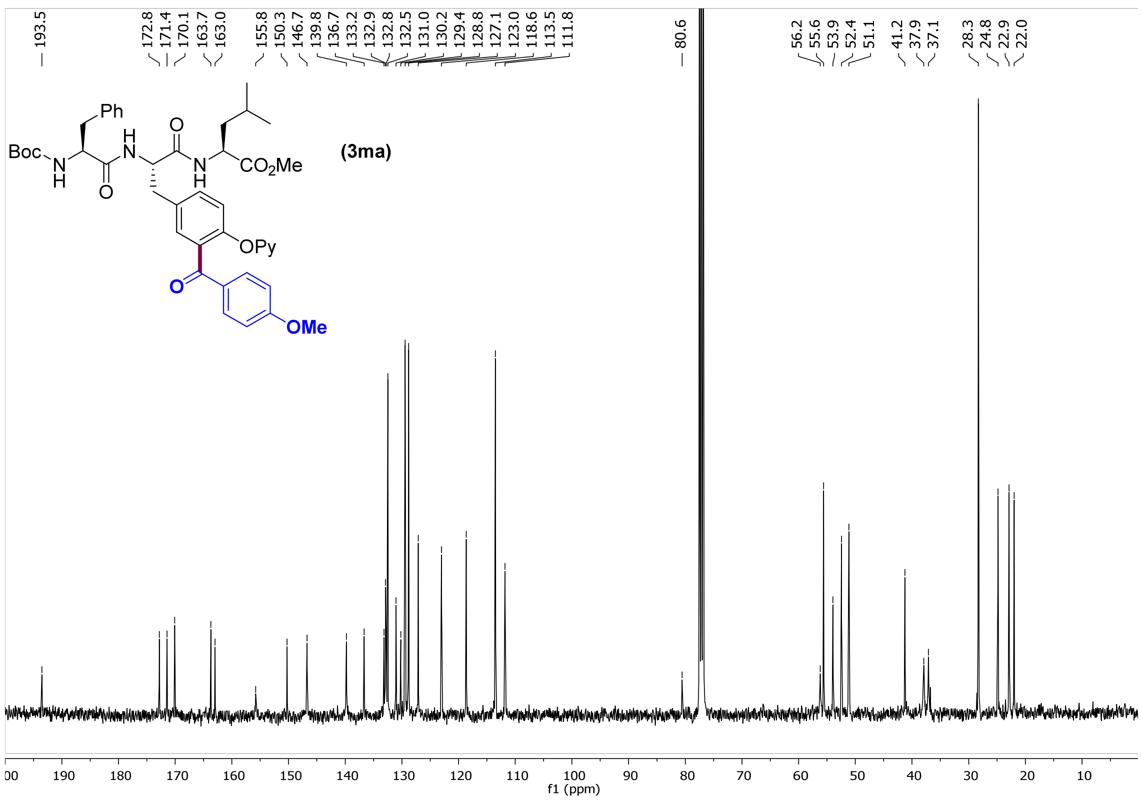
[13]C NMR (101 MHz, CDCl3)



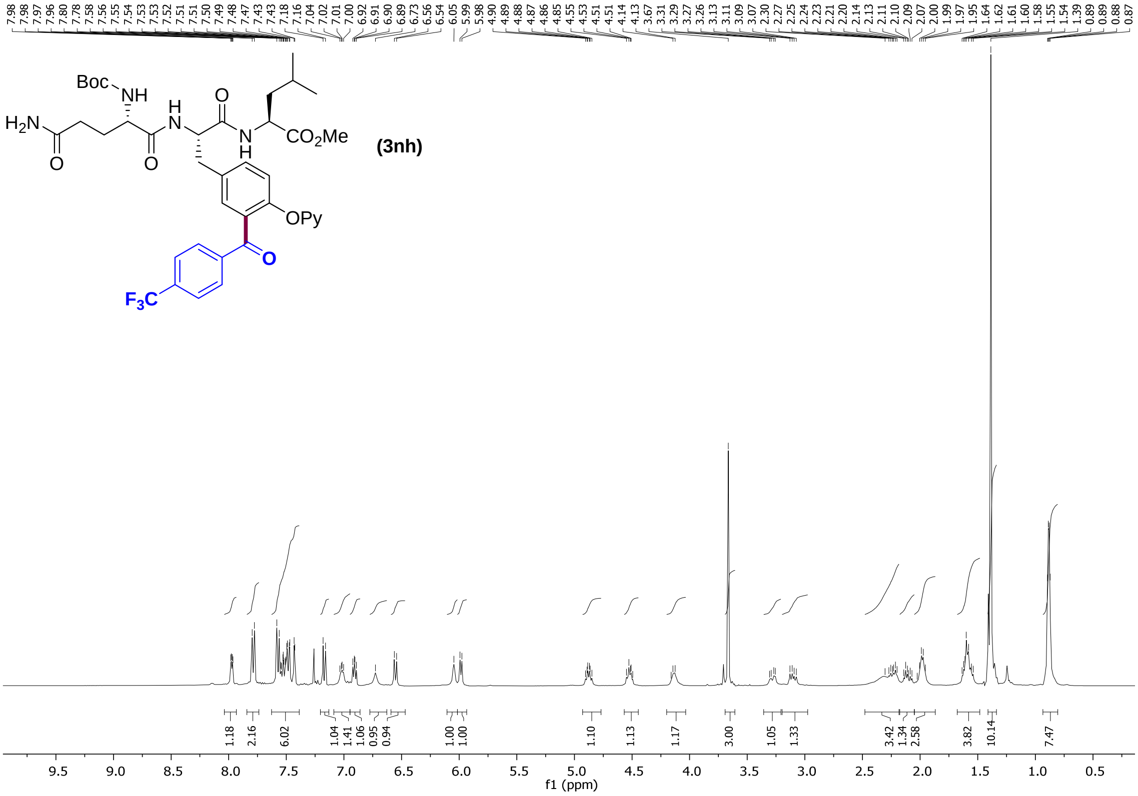
^{1}H NMR (400 MHz, $CDCl_3$)



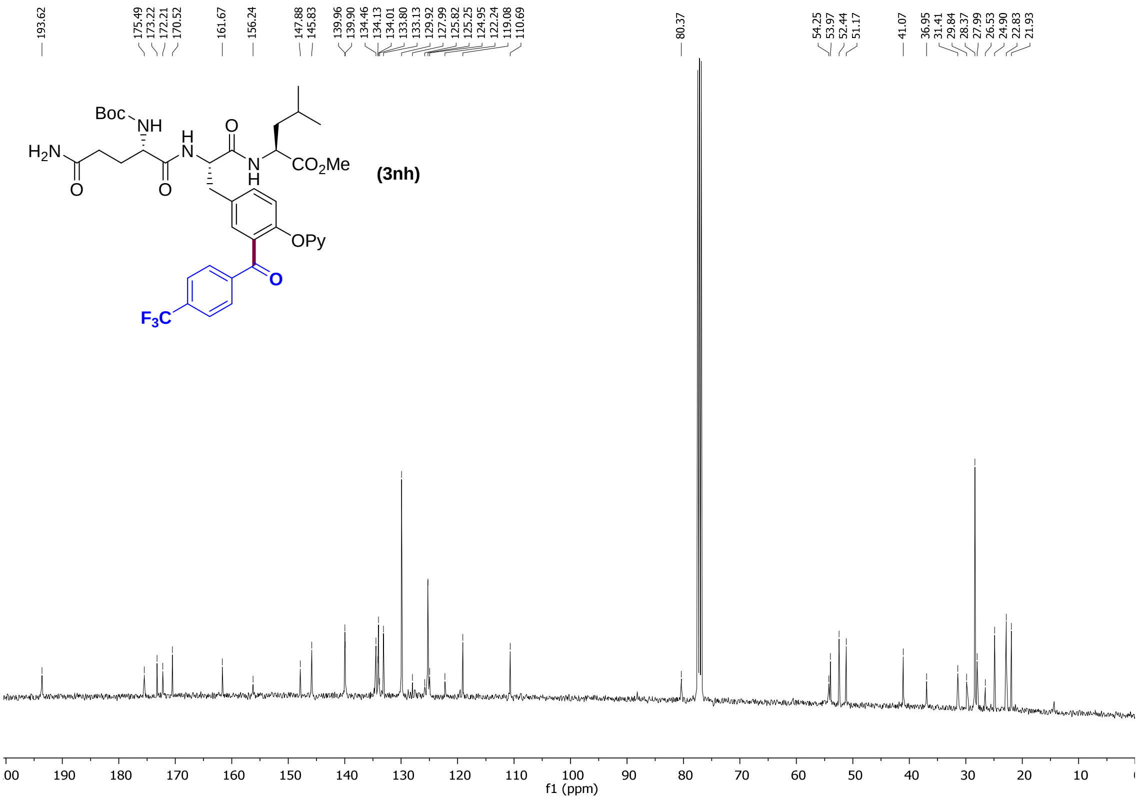
^{13}C NMR (101 MHz, $CDCl_3$)



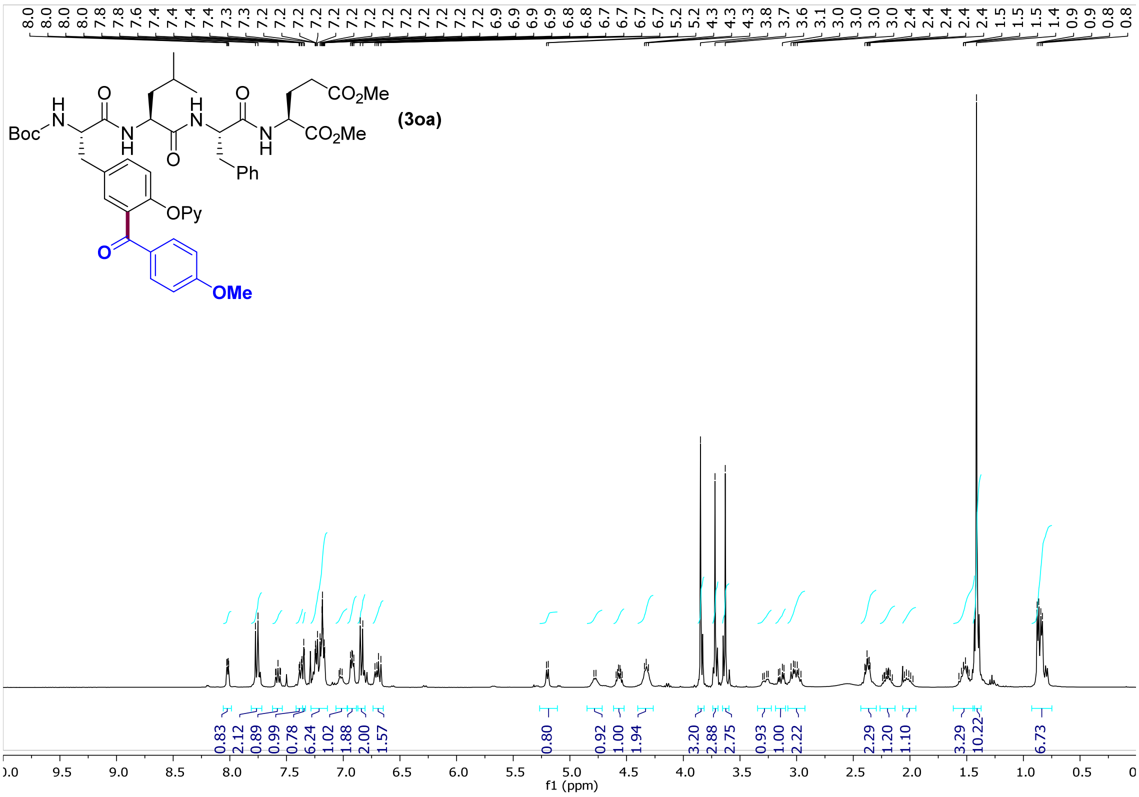
[1]H NMR (400 MHz, $CDCl_3$)



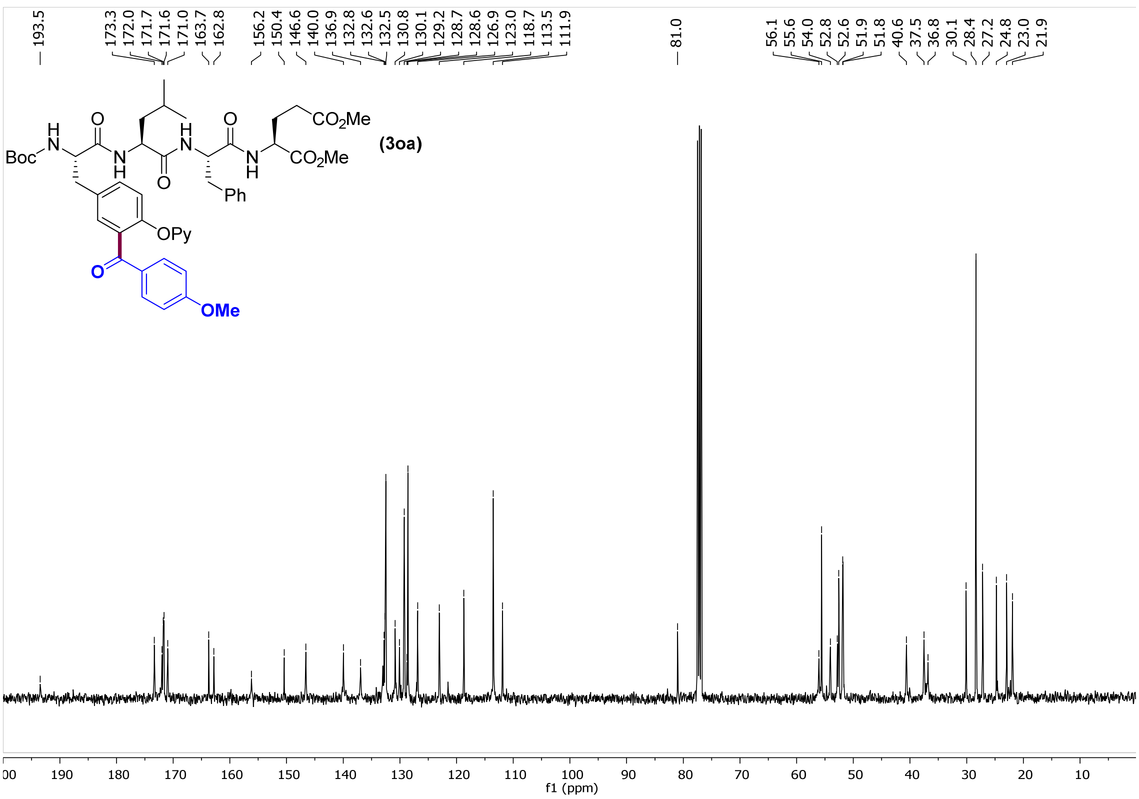
[13]C NMR (101 MHz, $CDCl_3$)



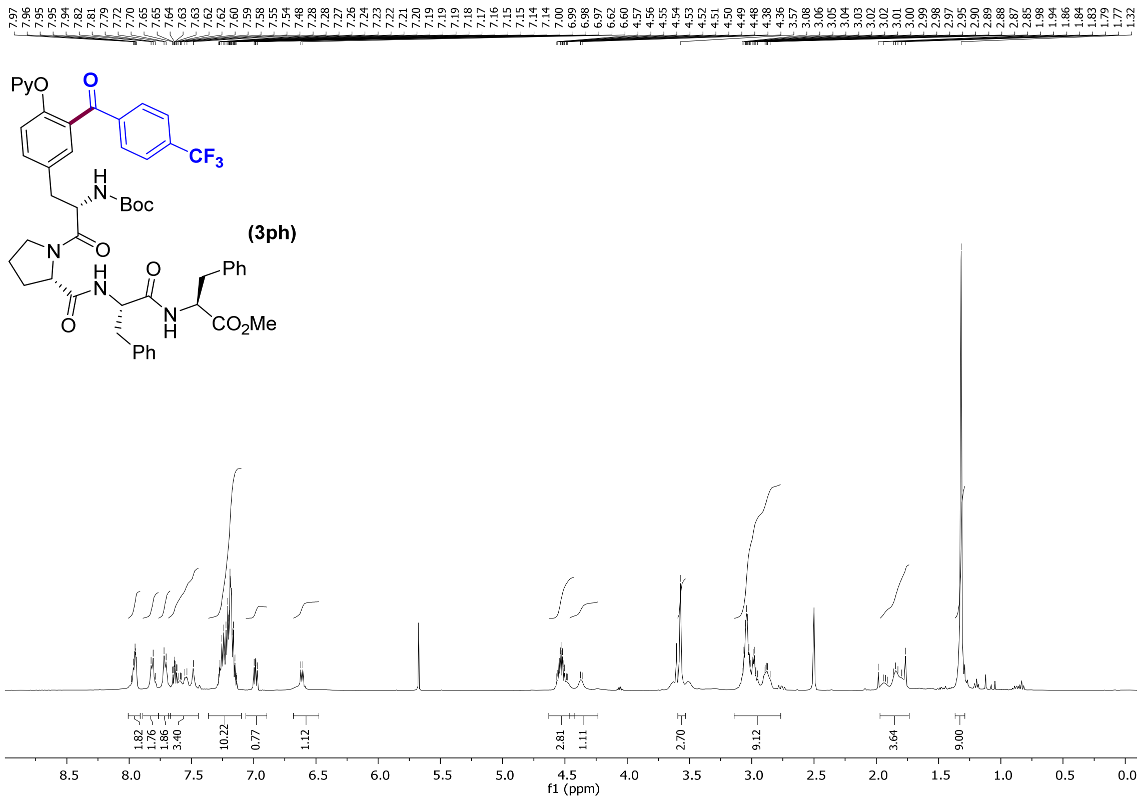
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

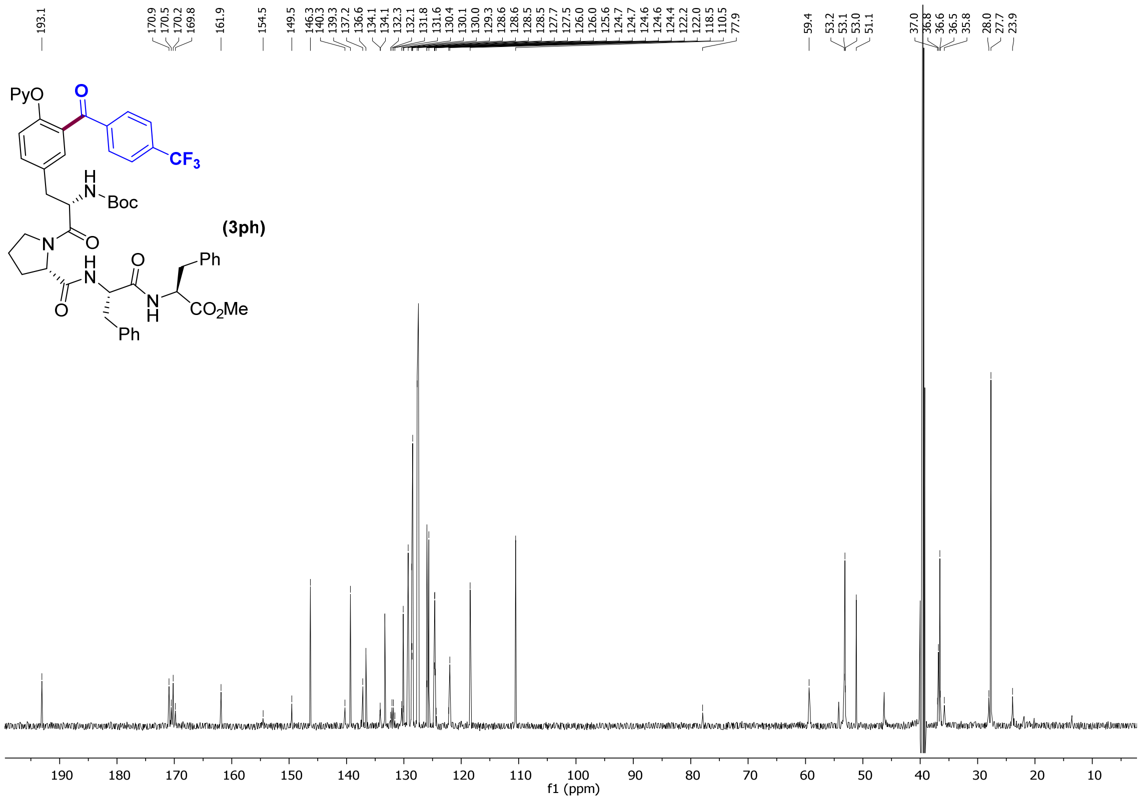


^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC)



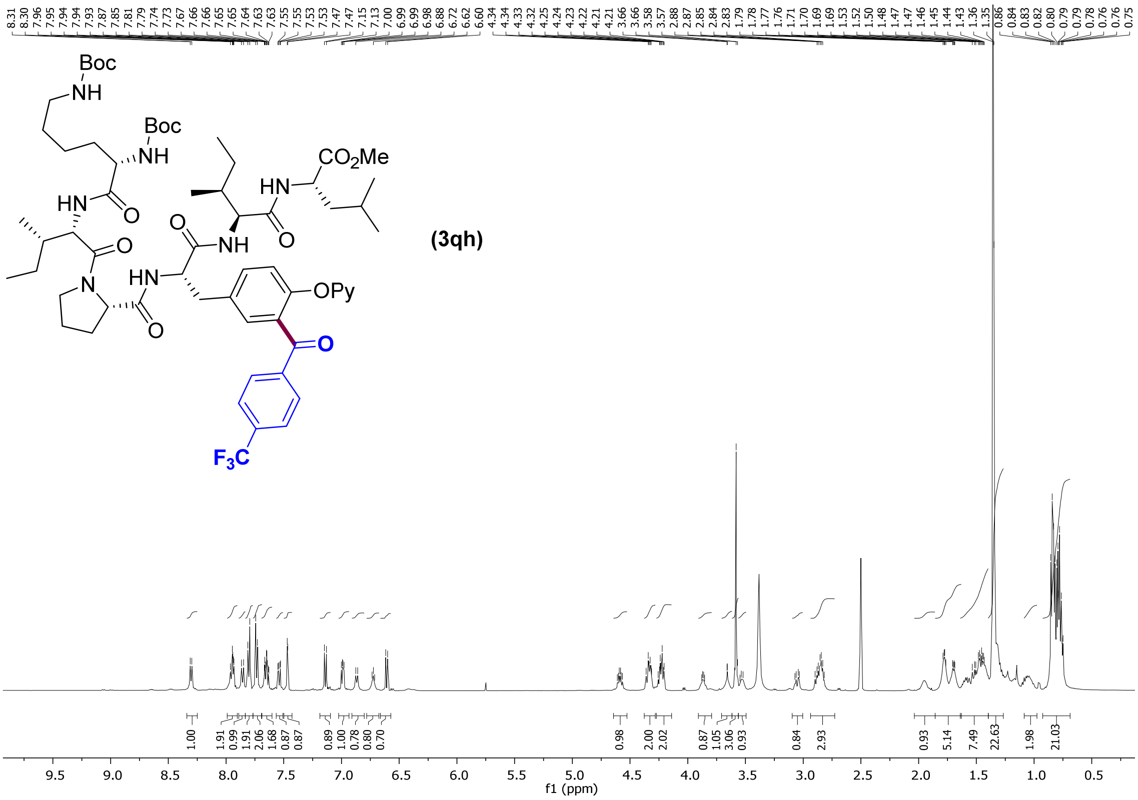
(3ph)

^{13}C NMR (126 MHz, DMSO-d_6 at 80 ºC)

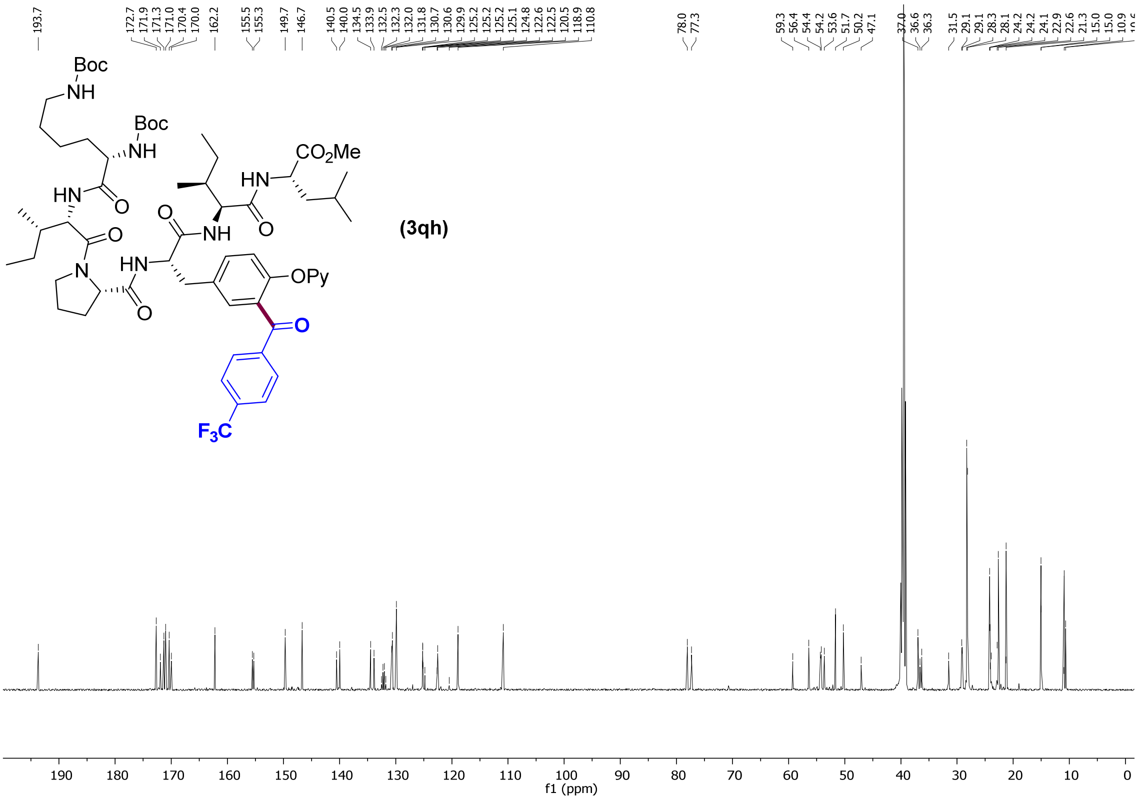


(3ph)

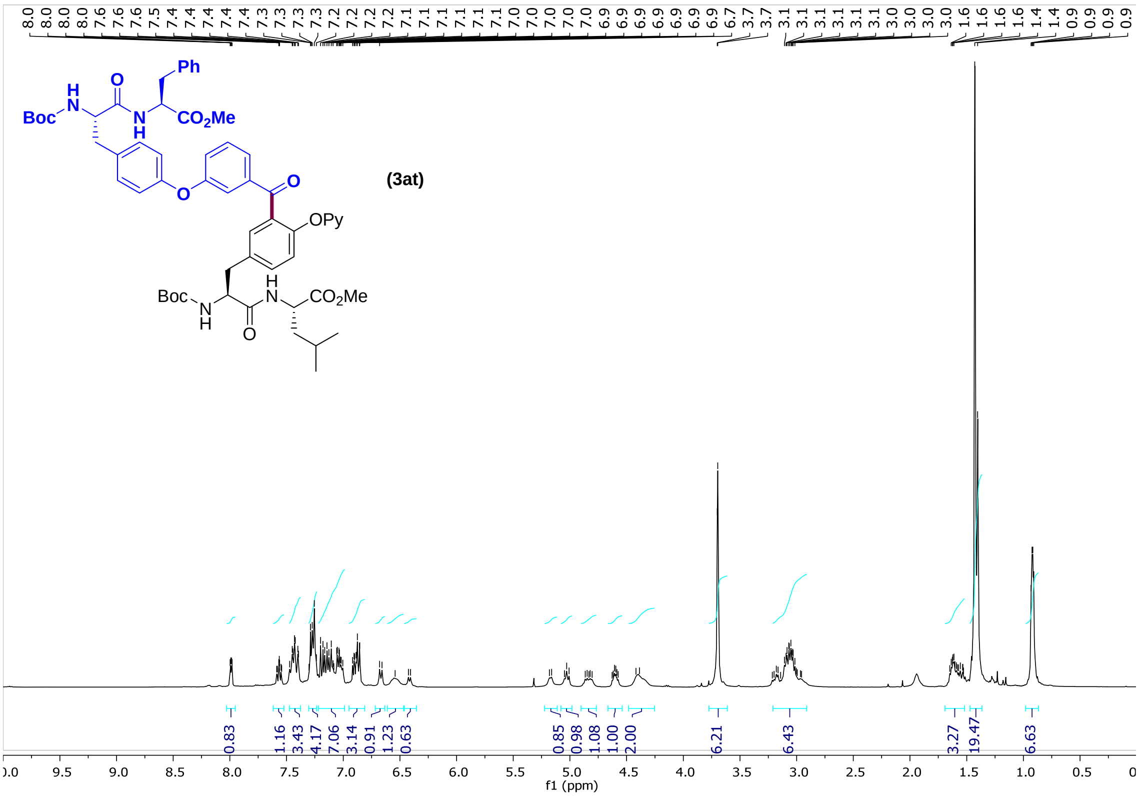
^{1}H NMR (500 MHz, DMSO-d_6 at 80 ºC)



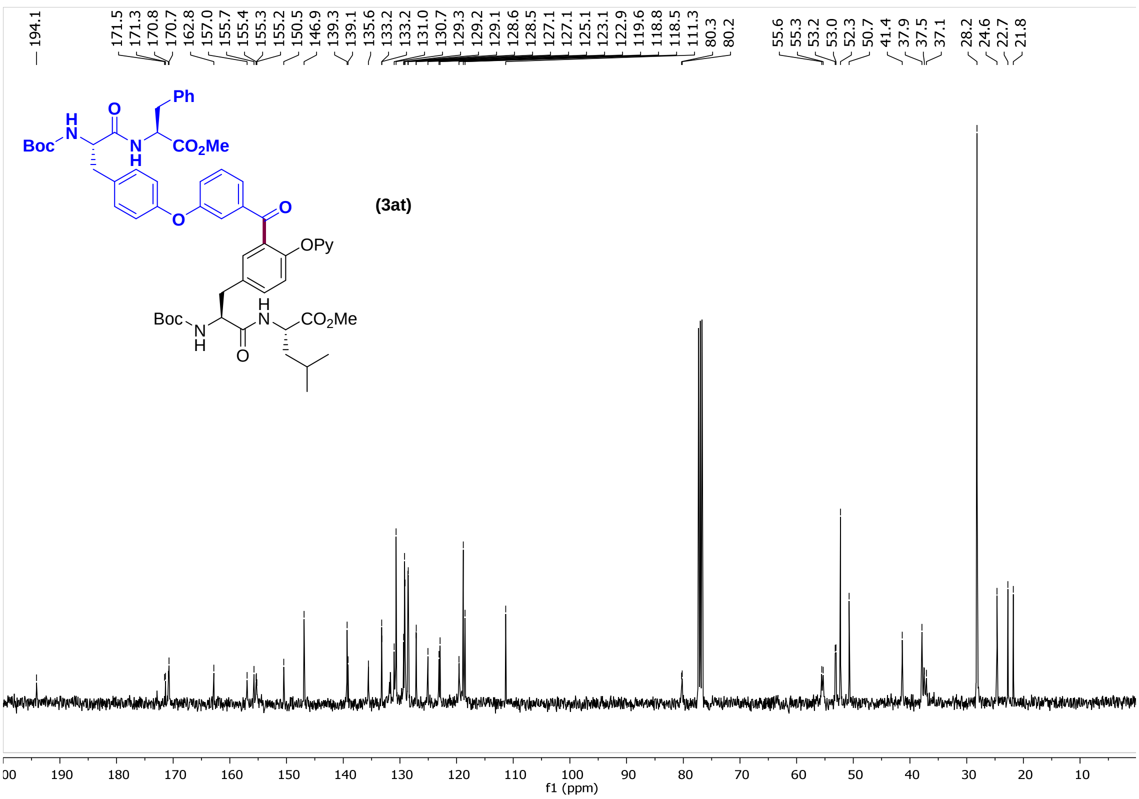
^{13}C NMR (126 MHz, DMSO-d_6)



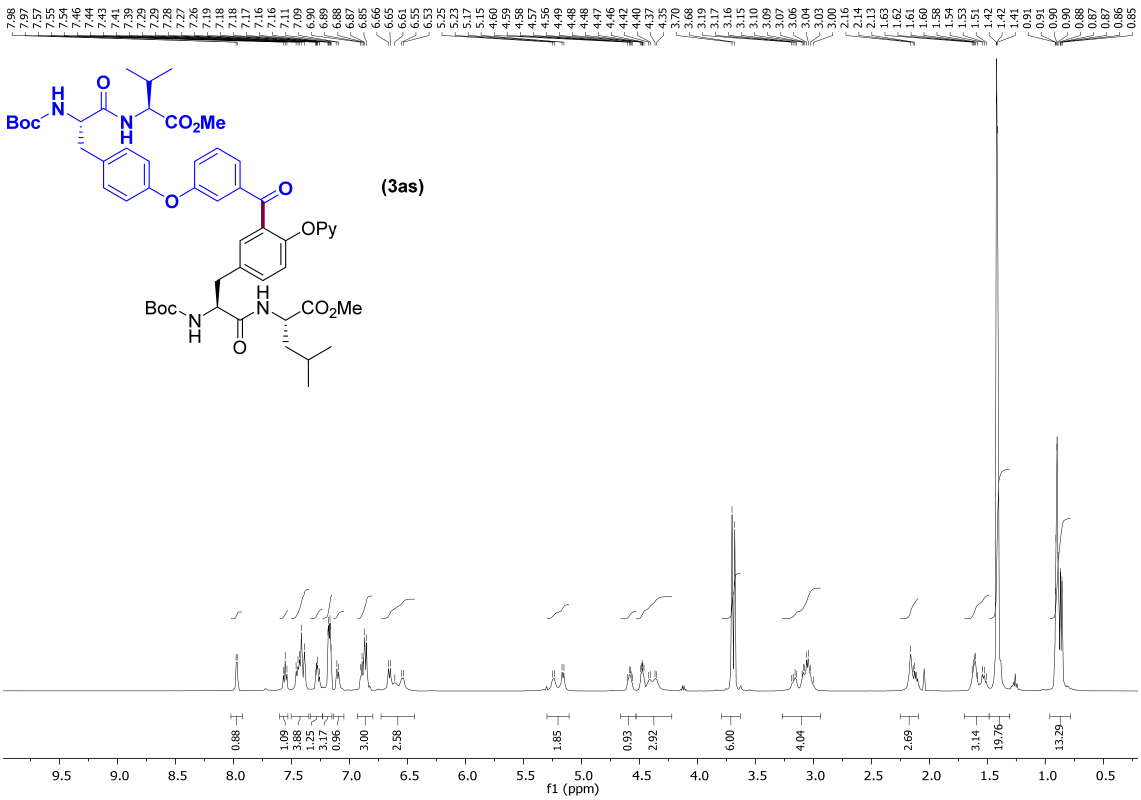
[1]H NMR (400 MHz, CDCl3)



[13]C NMR (101 MHz, CDCl3)

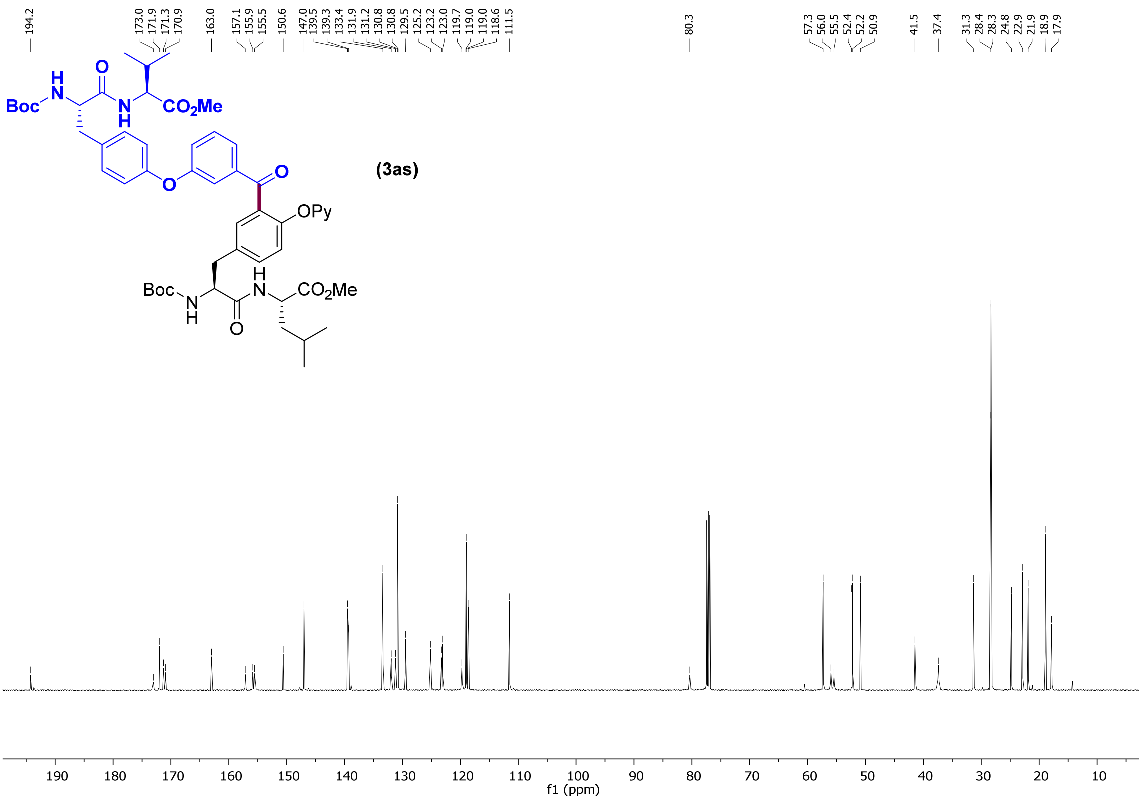


^{1}H NMR (400 MHz, $CDCl_3$)



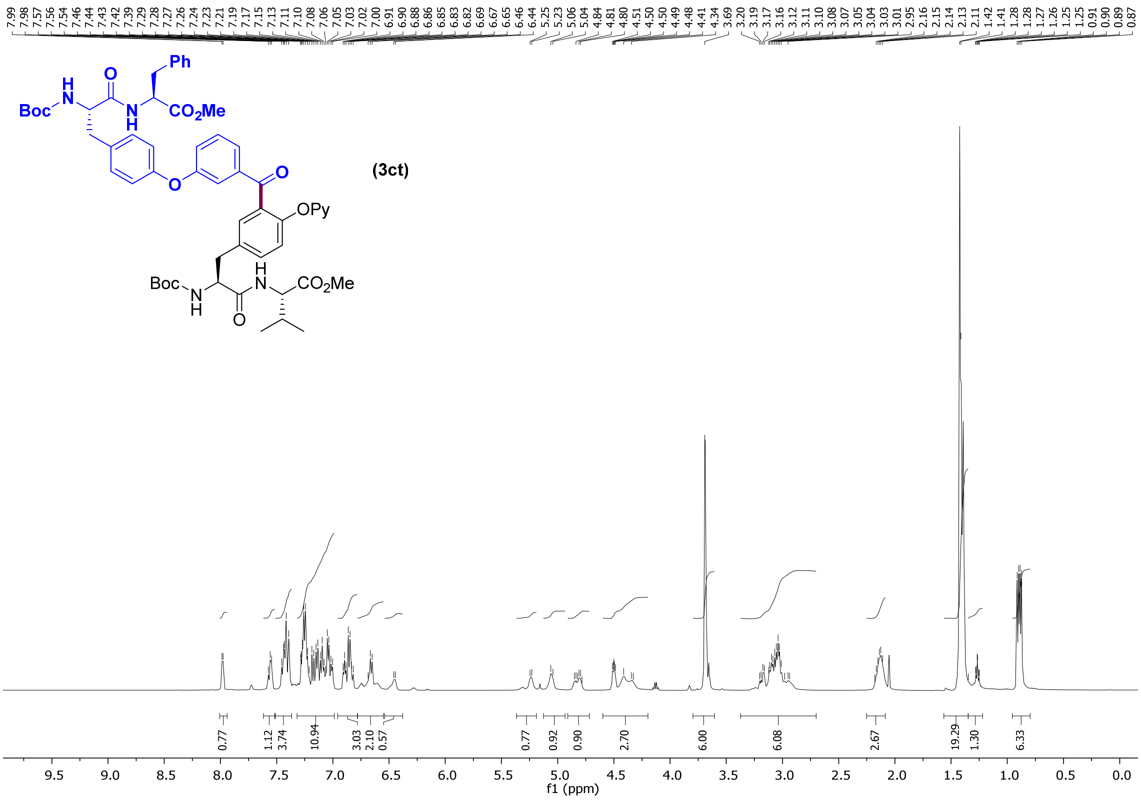
(3as)

^{13}C NMR (126 MHz, $CDCl_3$)

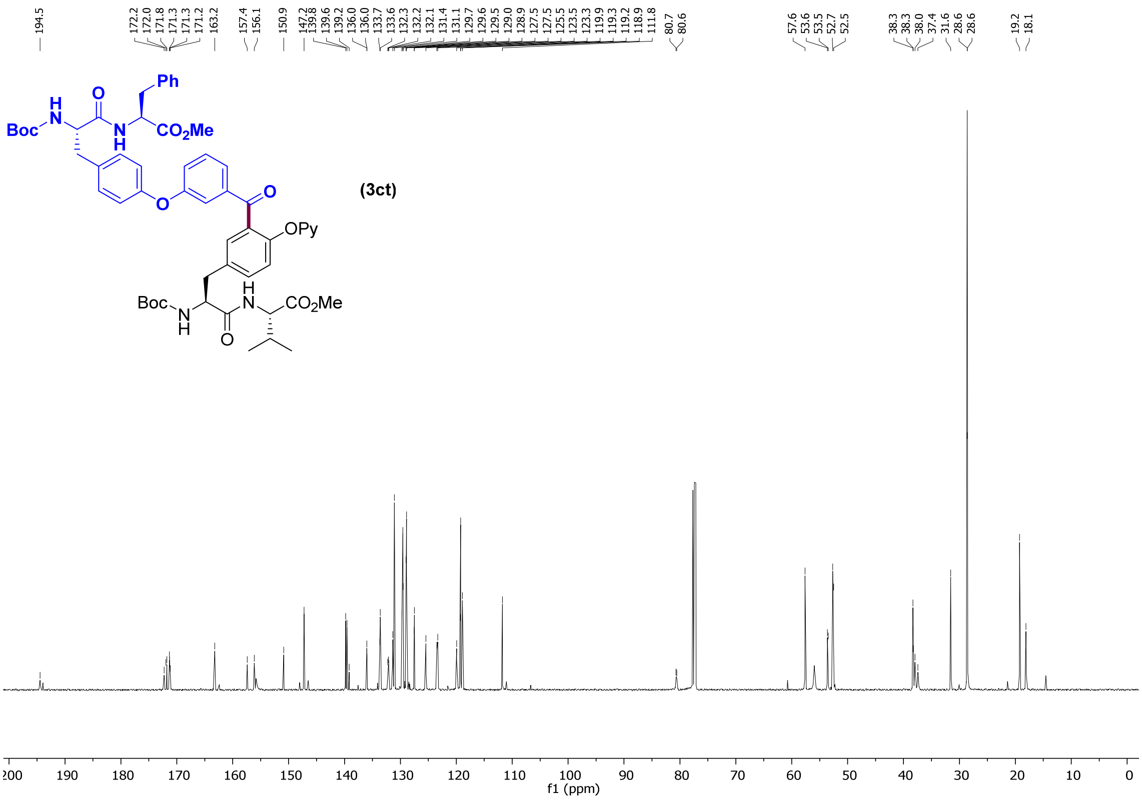


(3as)

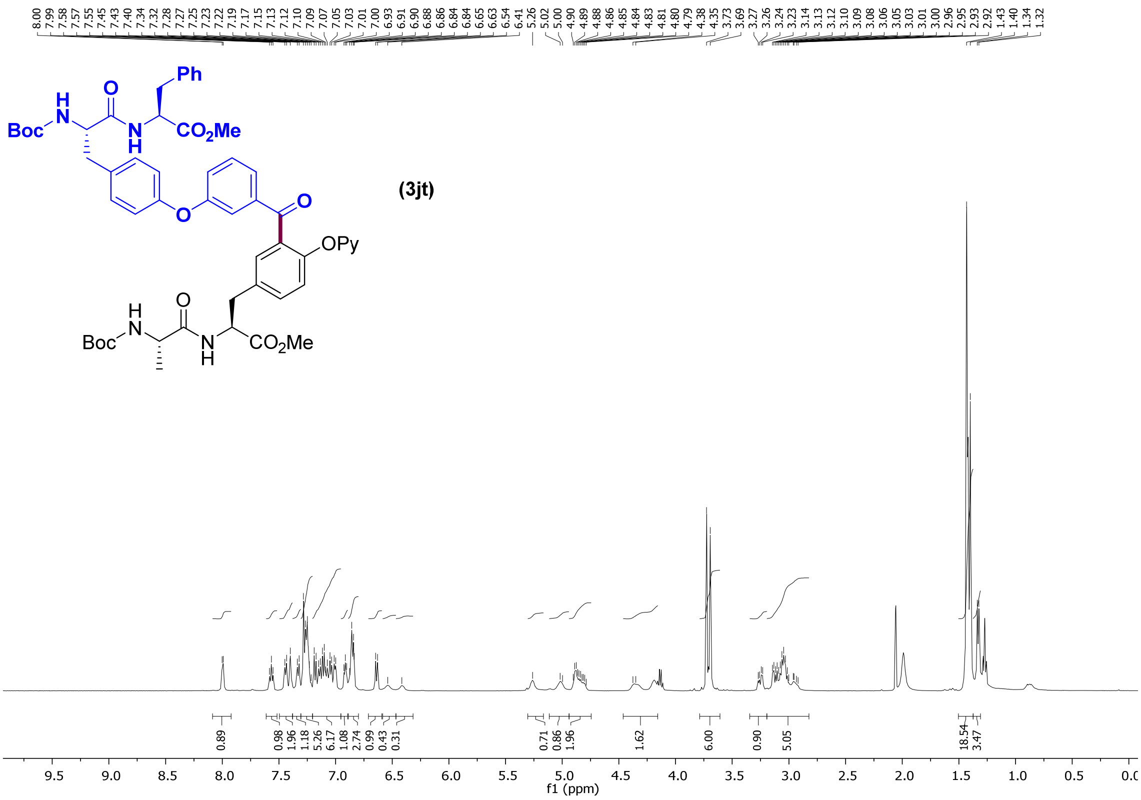
^{1}H NMR (500 MHz, $CDCl_3$)



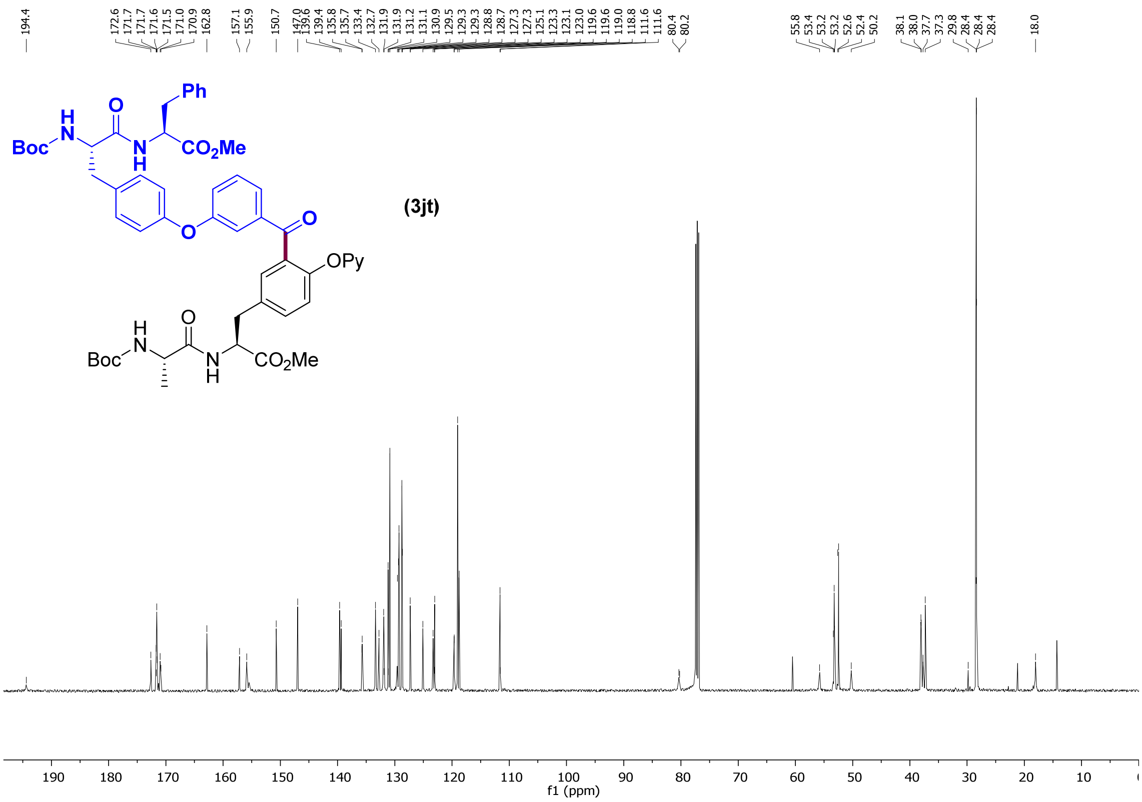
^{13}C NMR (126 MHz, $CDCl_3$)



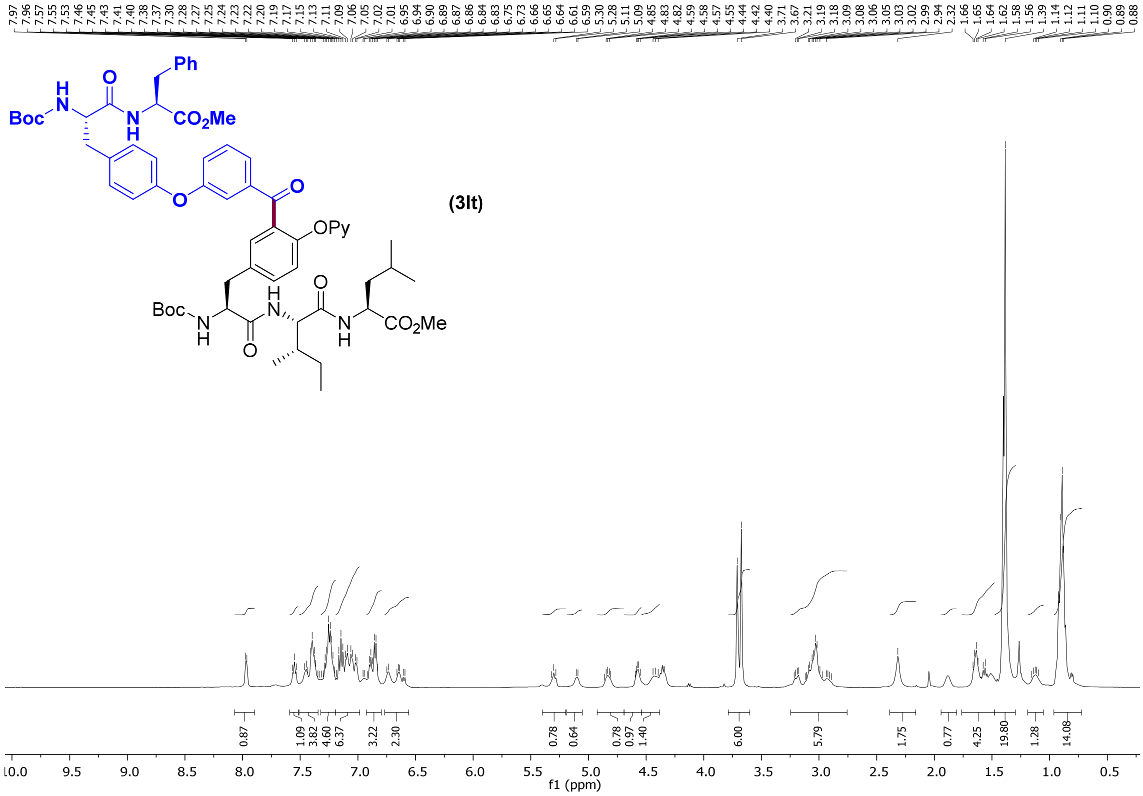
^{1}H NMR (500 MHz, $CDCl_3$)



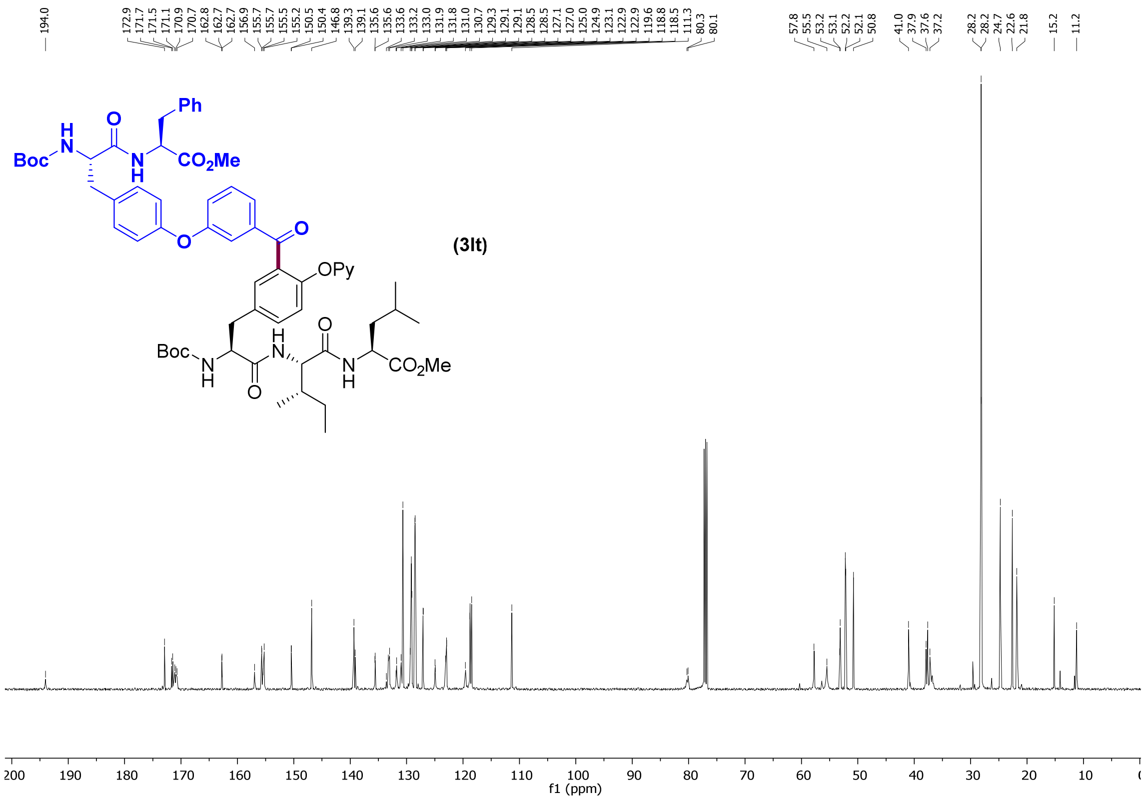
^{13}C NMR (126 MHz, $CDCl_3$)



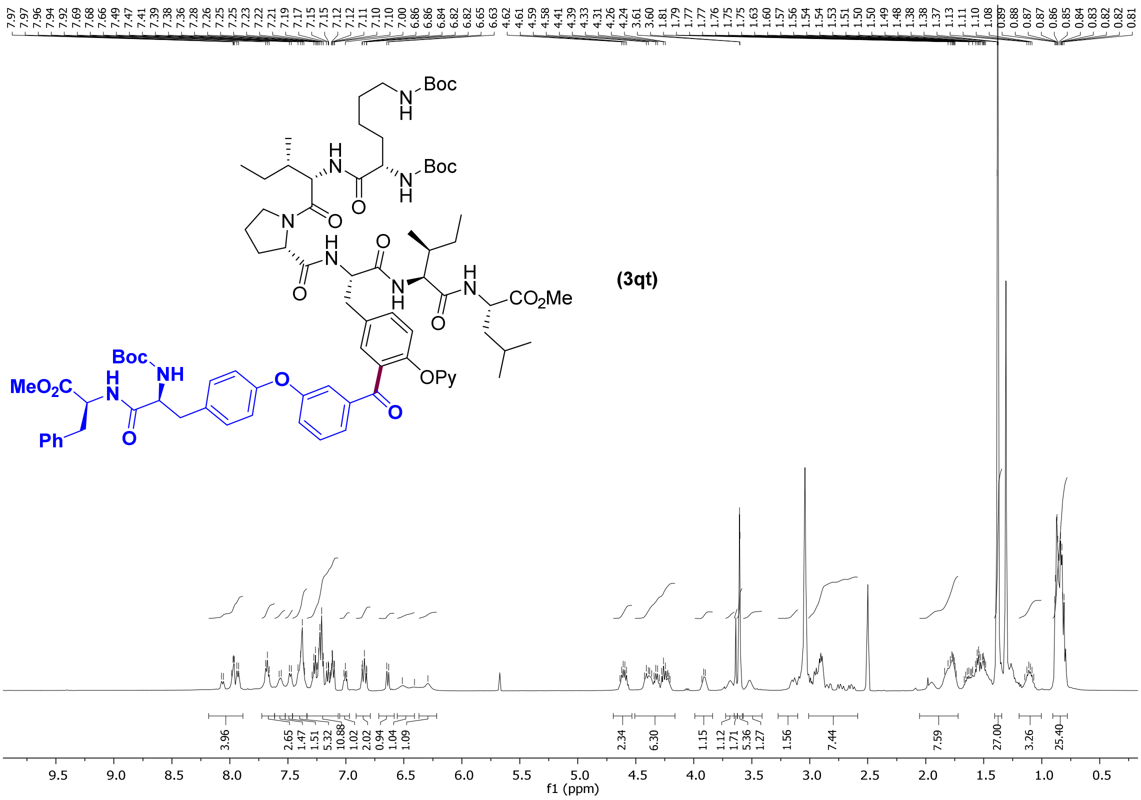
[1]H NMR (500 MHz, CDCl3)



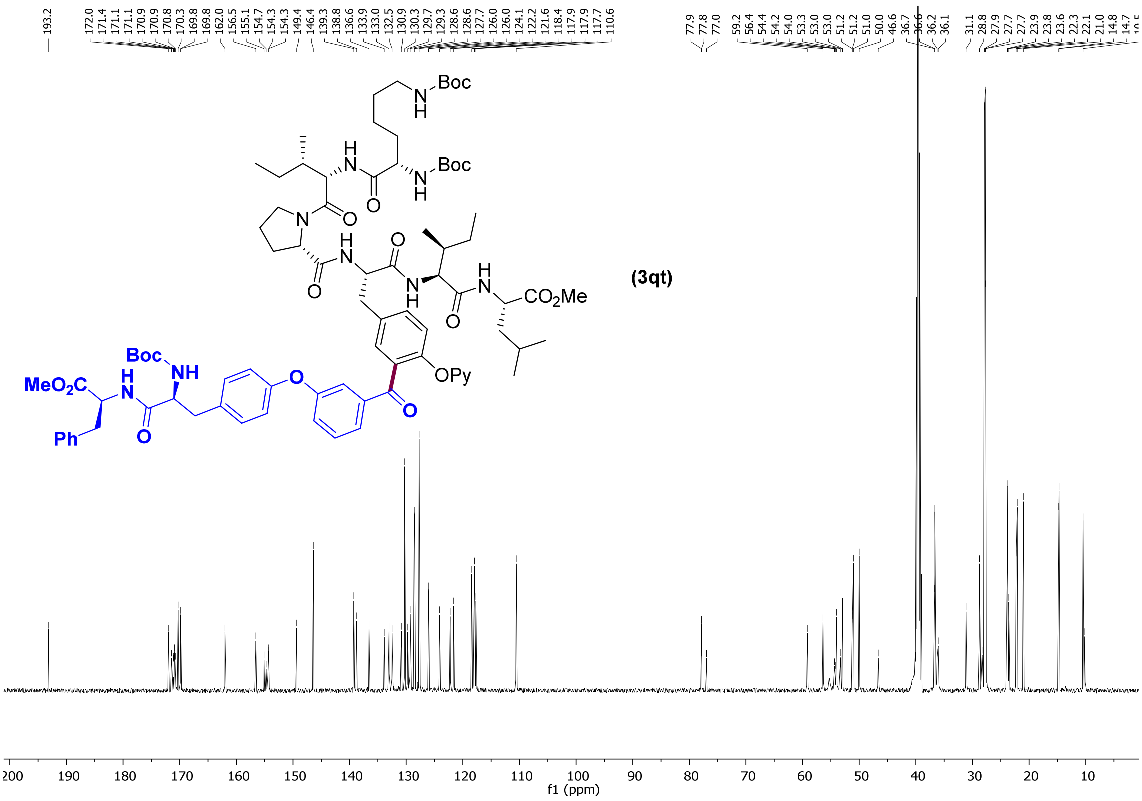
[13]C NMR (126 MHz, CDCl3)



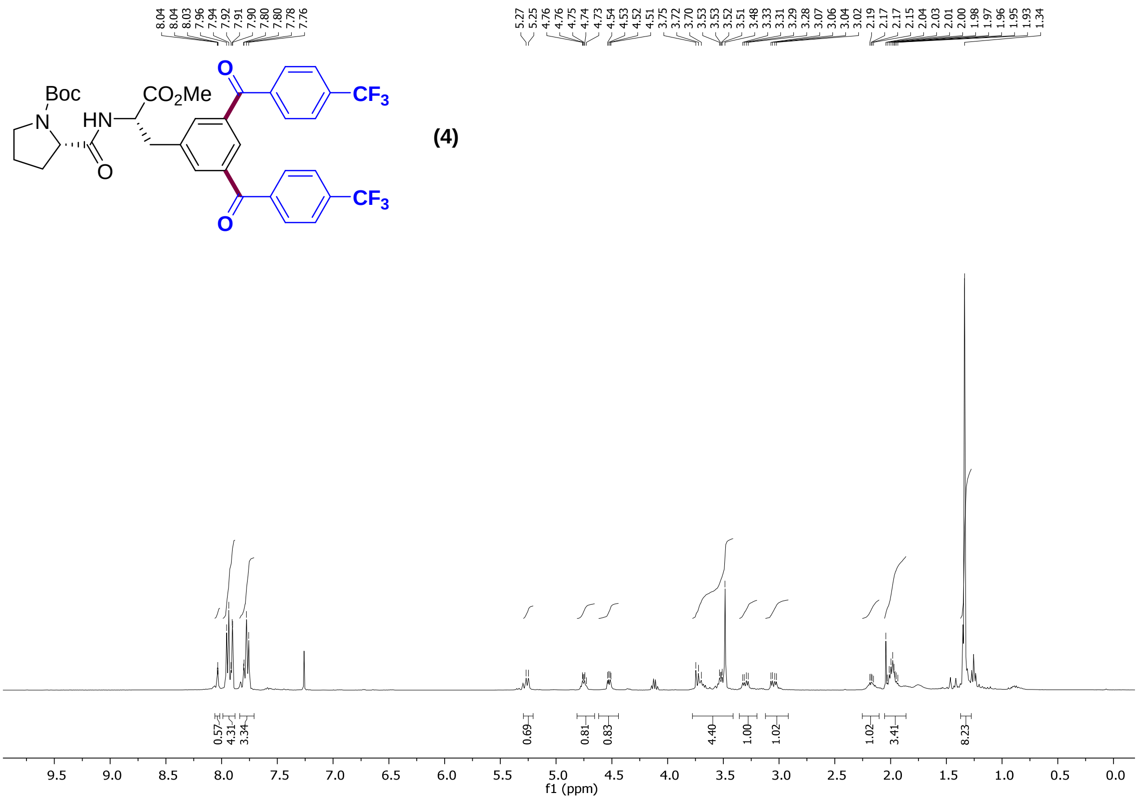
[1]H NMR (500 MHz, DMSO-d_6 at 80 ºC)



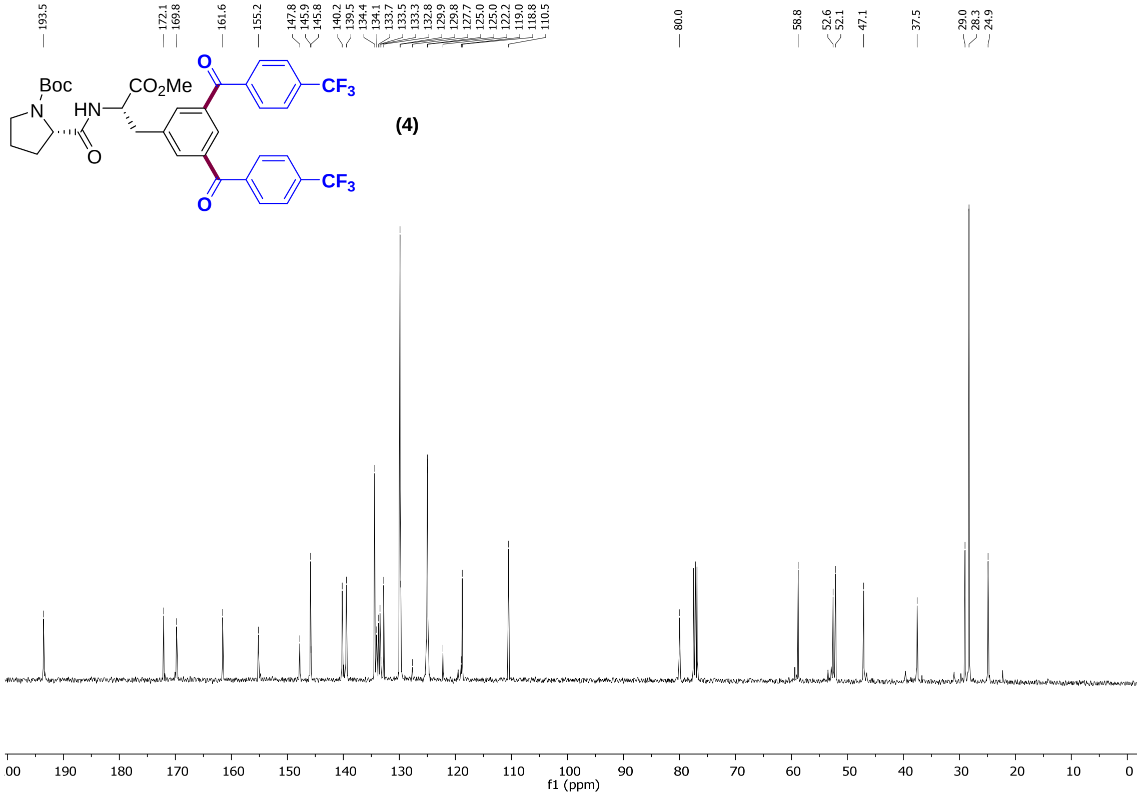
[13]C NMR (126 MHz, DMSO-d_6 at 80 ºC)



^{1}H NMR (400 MHz, $CDCl_3$)

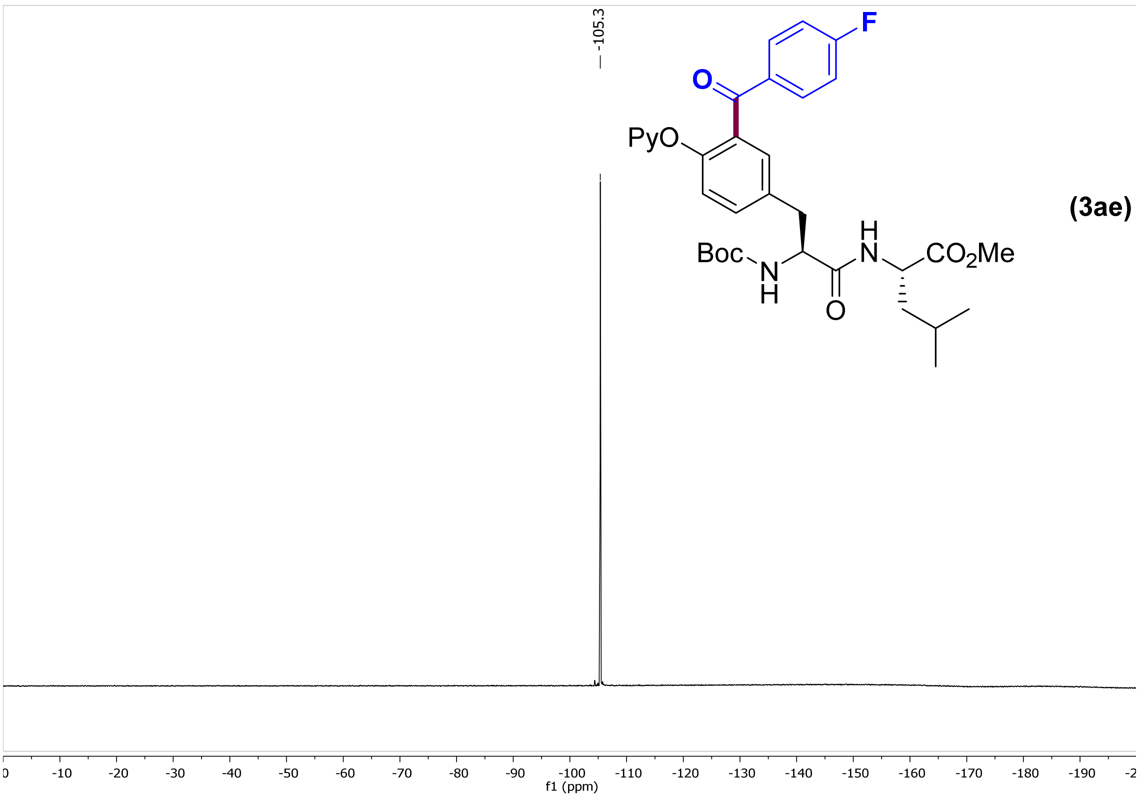


^{13}C NMR (101 MHz, $CDCl_3$)

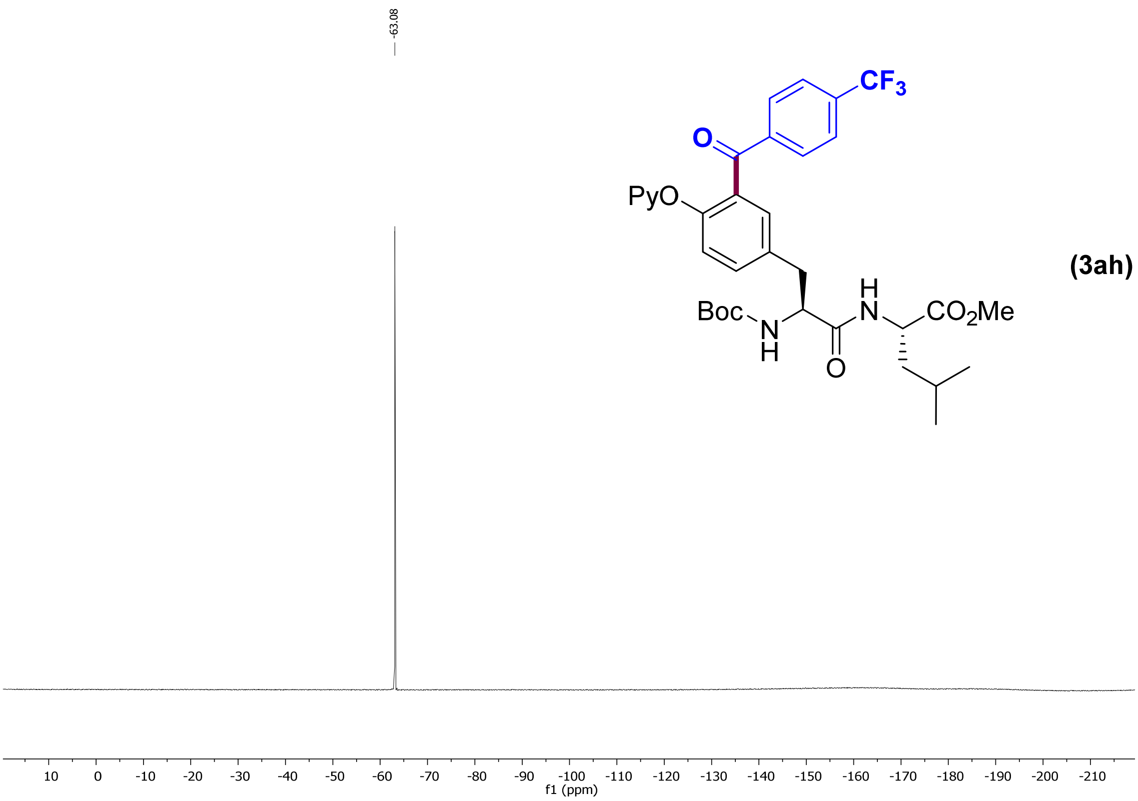


6.- ^{19}F NMR Spectra

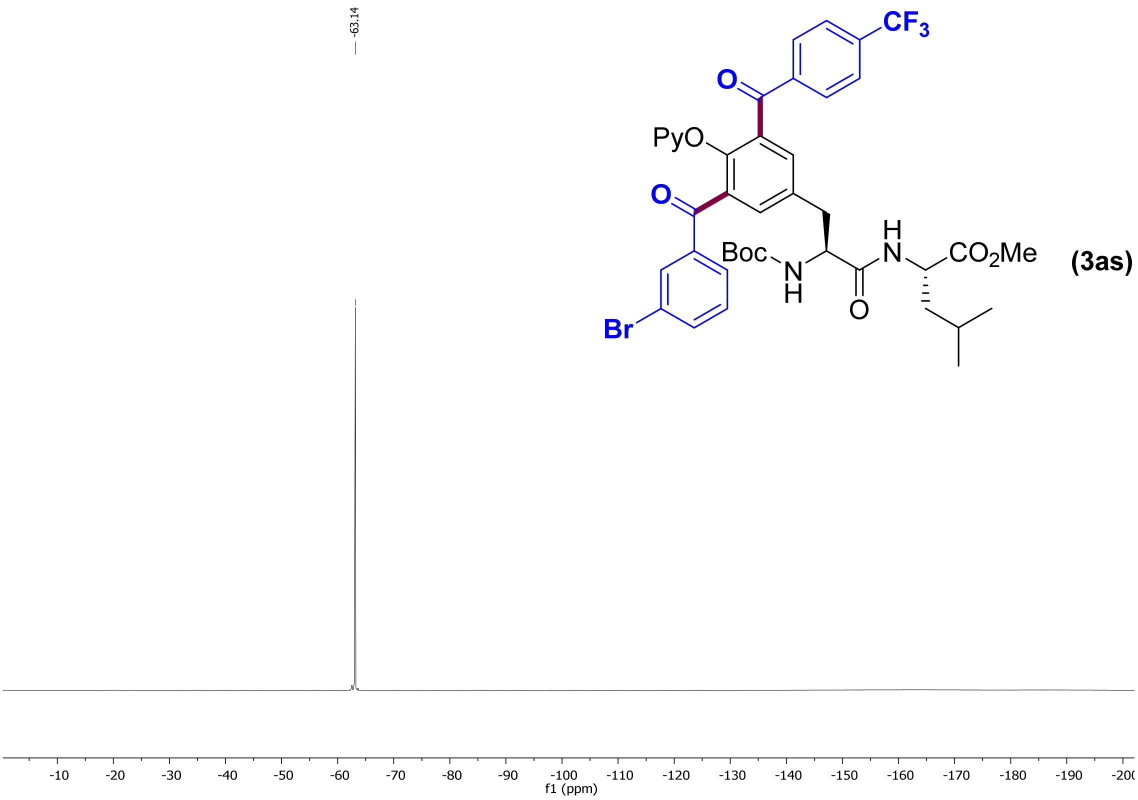
^{19}F NMR (376 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

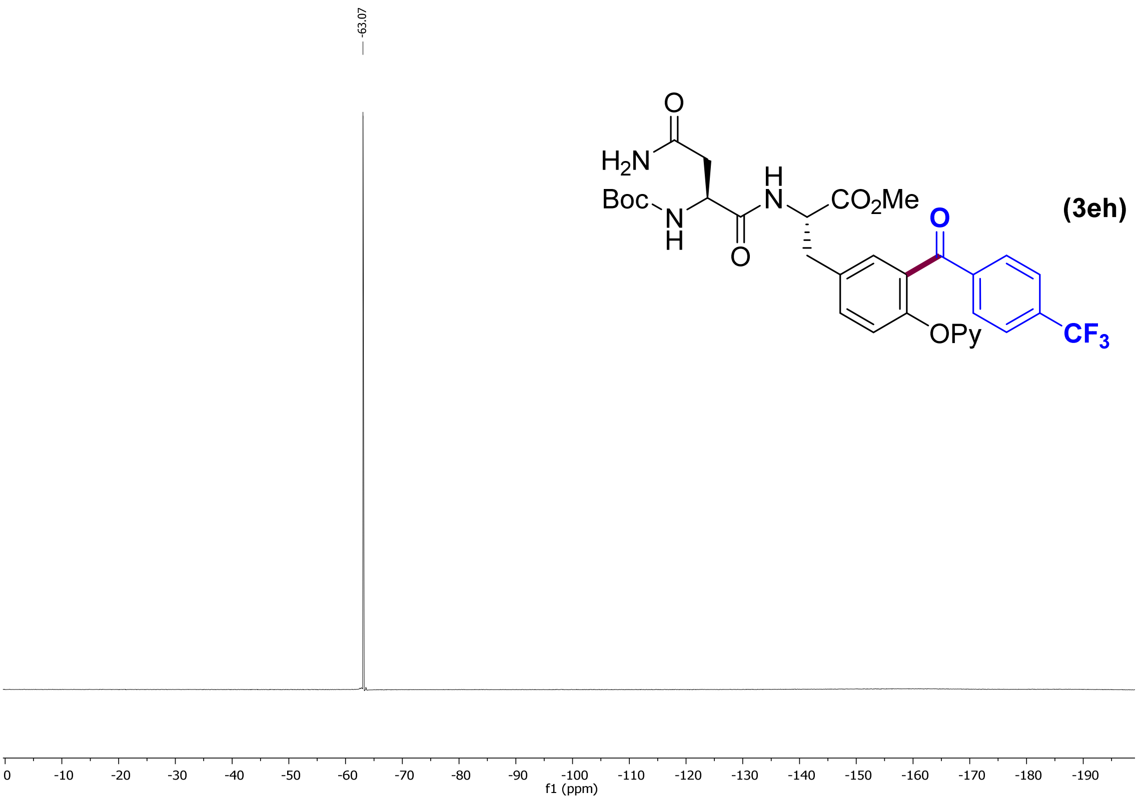


^{19}F NMR (376 MHz, $CDCl_3$)



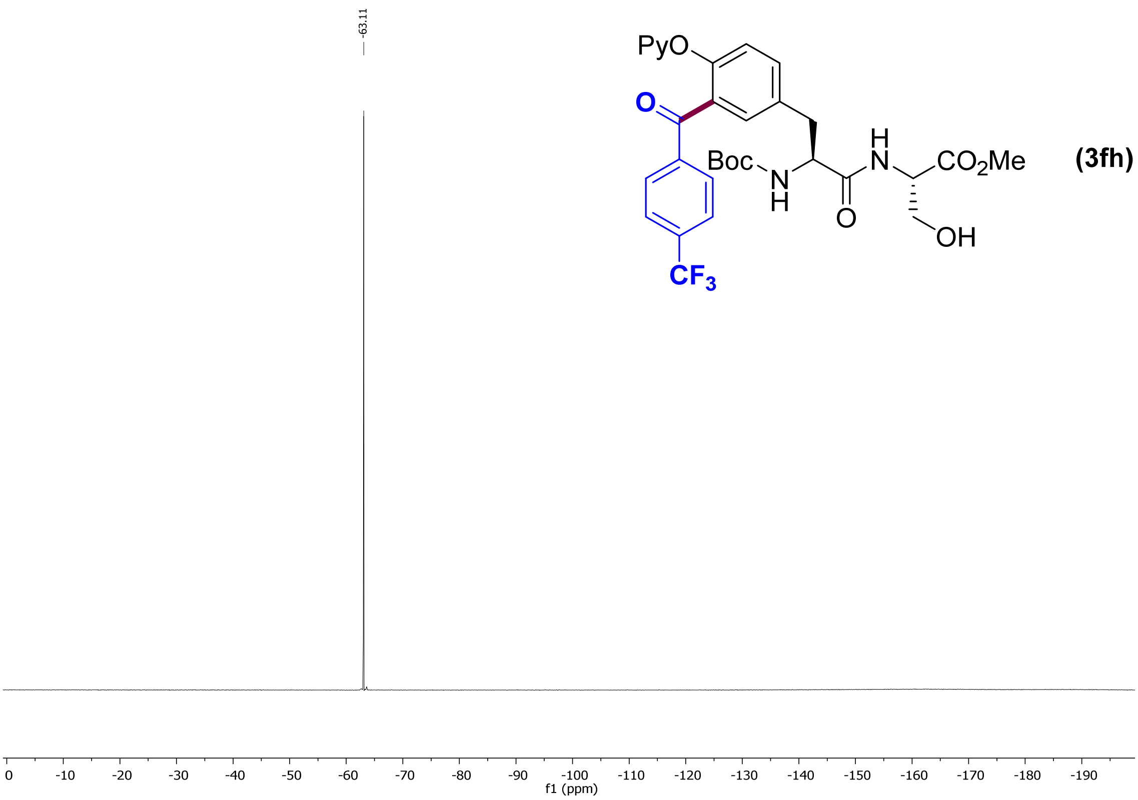
(3as)

^{19}F NMR (376 MHz, $CDCl_3$)

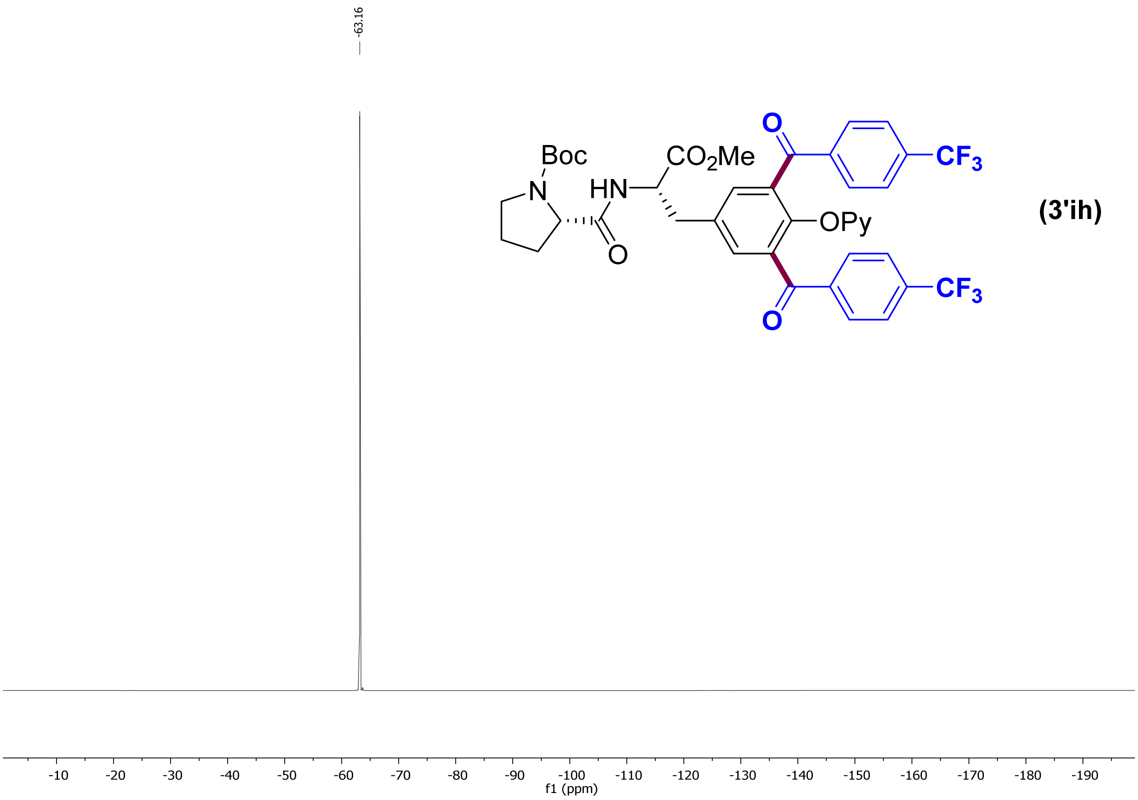


(3eh)

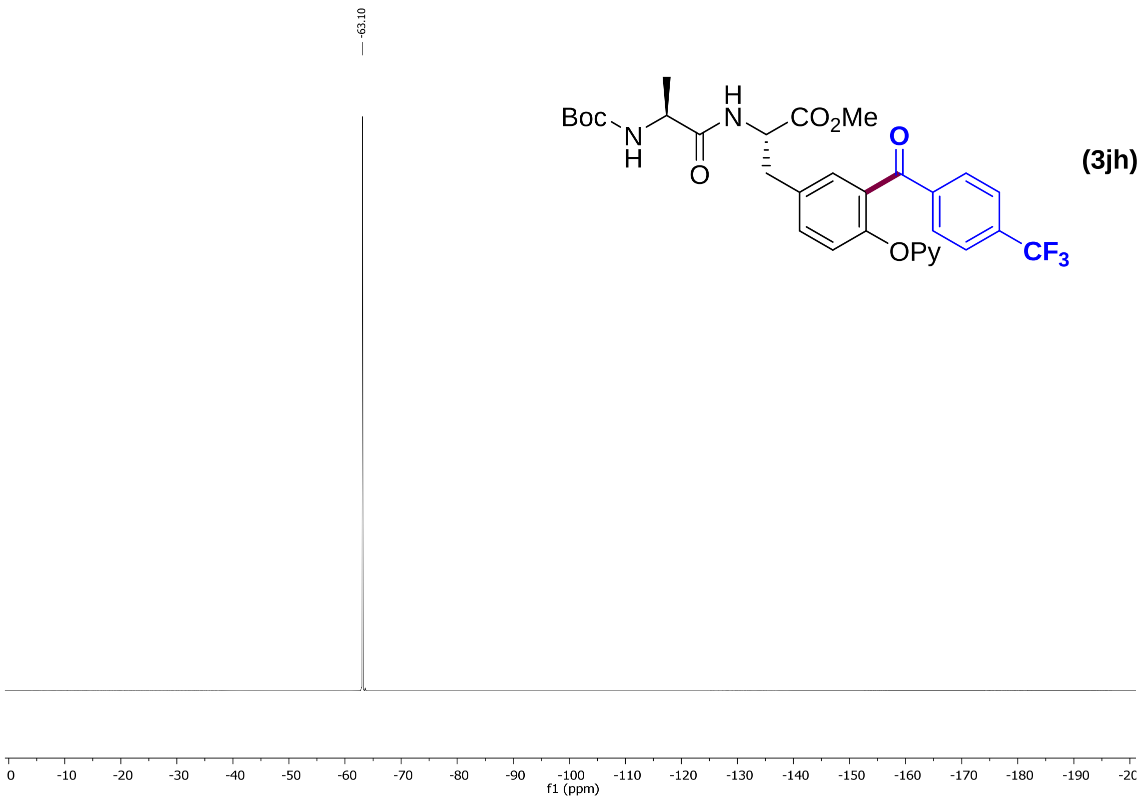
^{19}F NMR (376 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

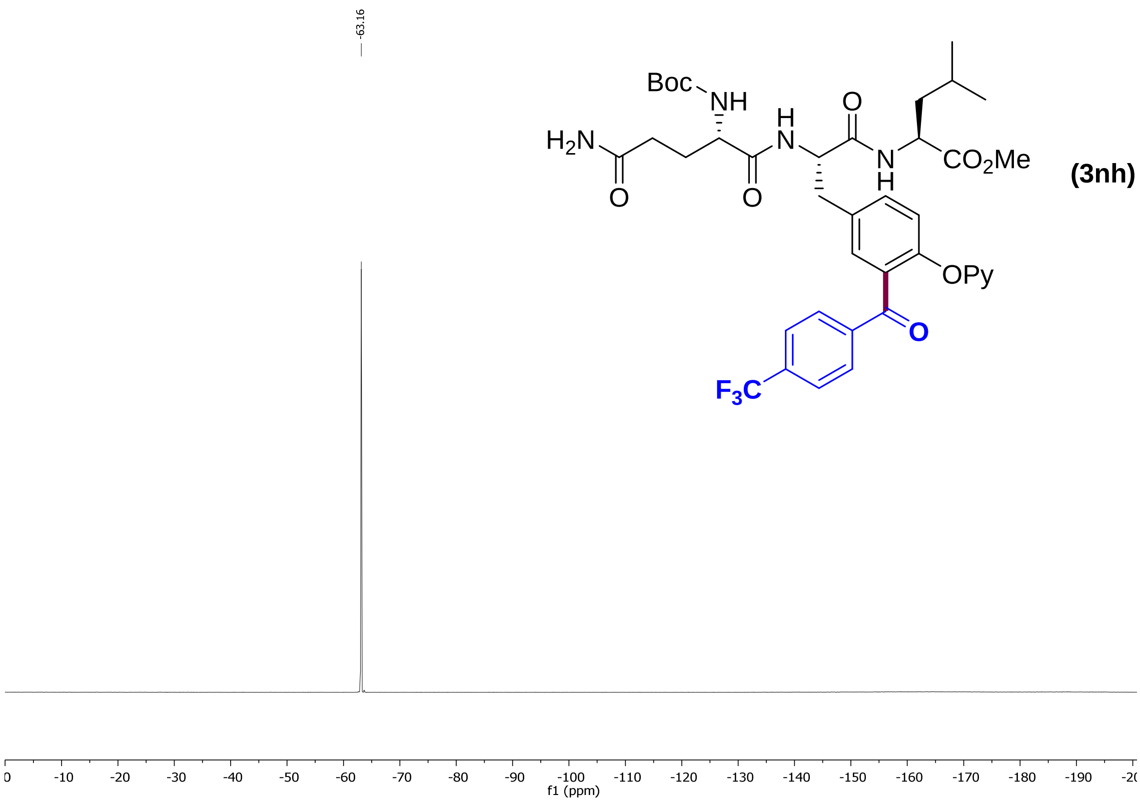


^{19}F NMR (376 MHz, $CDCl_3$)



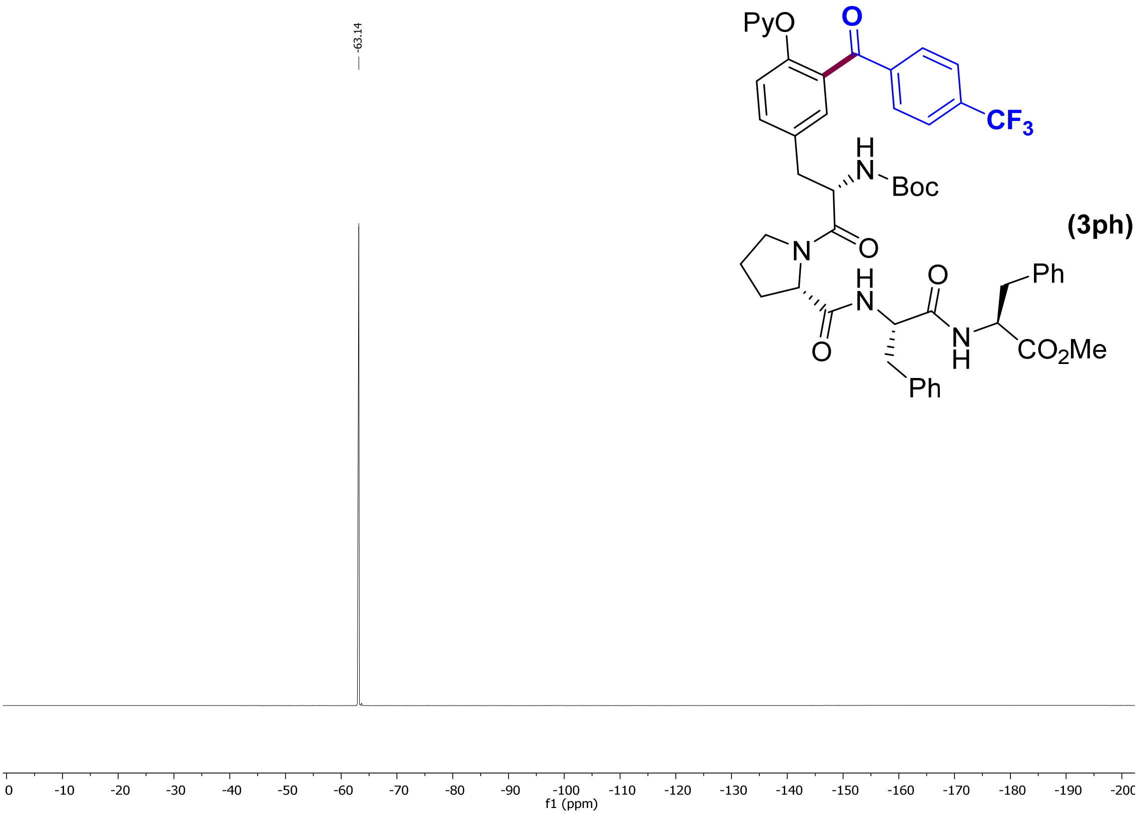
(3jh)

^{19}F NMR (376 MHz, $CDCl_3$)



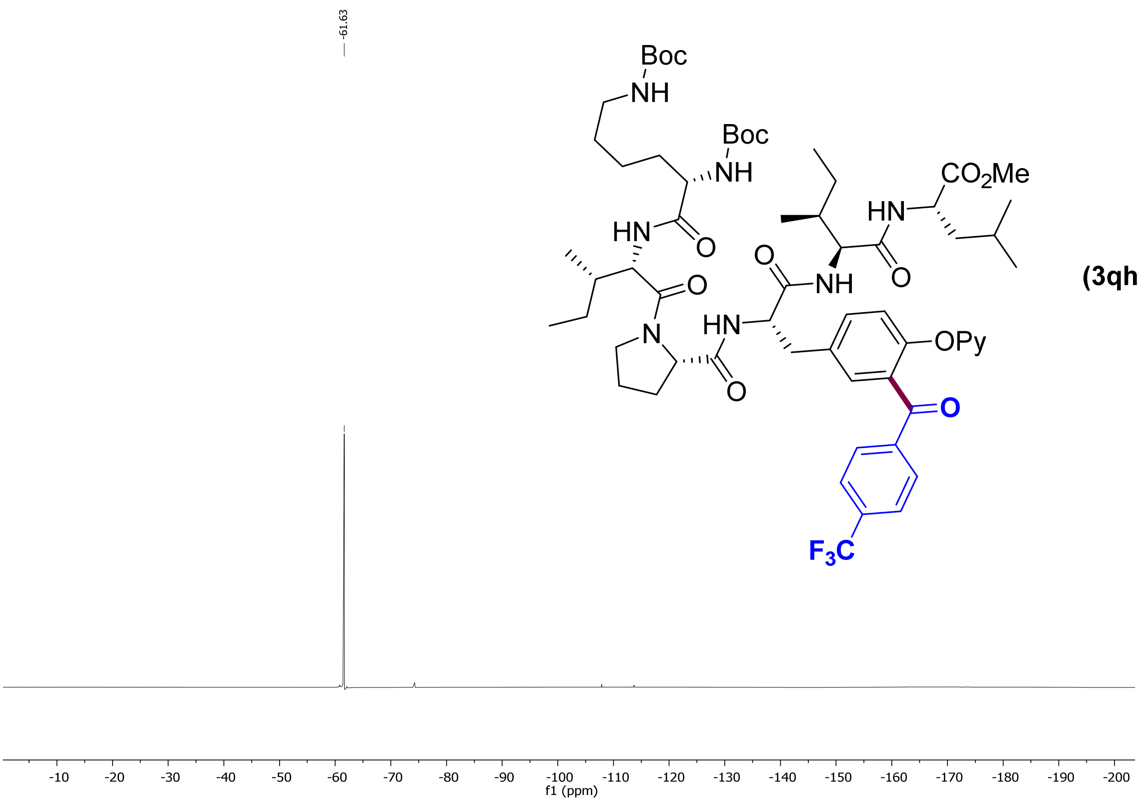
(3nh)

^{19}F NMR (376 MHz, CDCl$_3$)



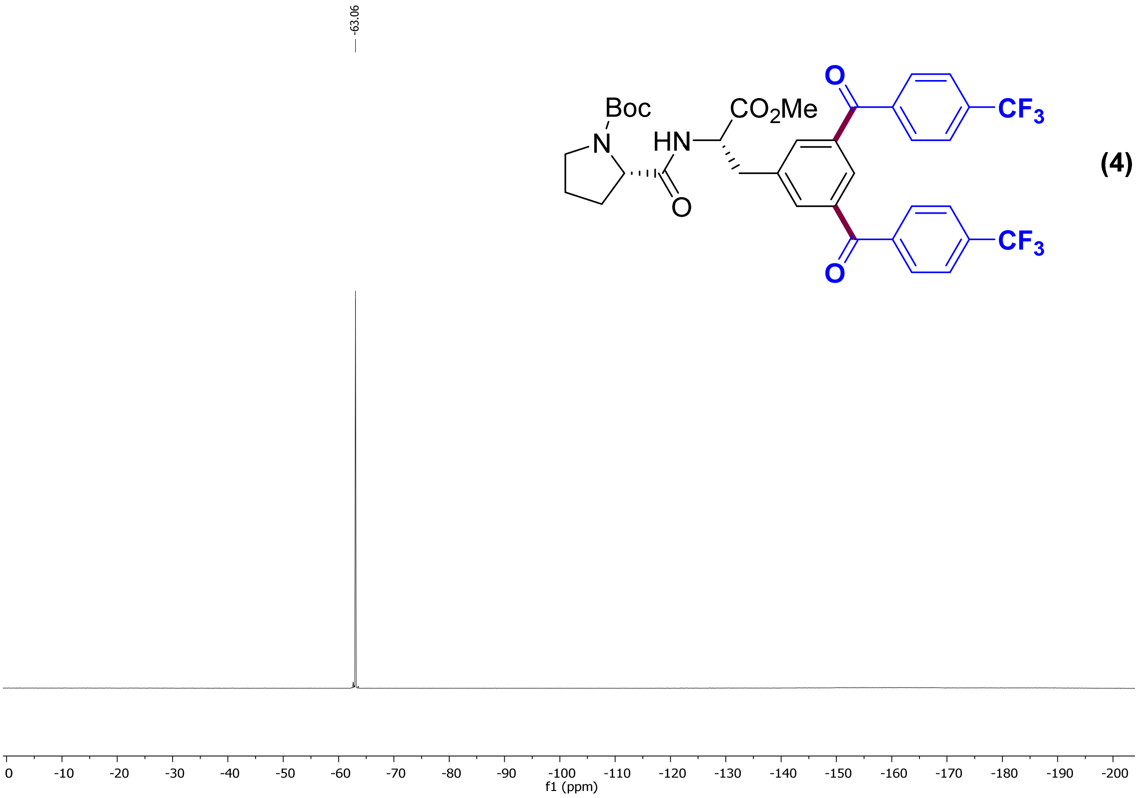
(3ph)

^{19}F NMR (376 MHz, DMSO-d_6)



(3qh)

^{19}F NMR (376 MHz, $CDCl_3$)



(4)