*Supporting Information*

*for*

# Iridium-catalyzed diacylmethylation of tyrosine and its peptides with sulfoxonium ylides

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## Contents

## 1. General experimental details

Commercially available reagents were used without purification. Solvents were dried by standard procedures prior to use. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer, and chemical shifts are reported in $\delta$ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, and m = multiplet. Coupling constants *J* are reported in Hz. The $^{13}$C NMR spectra are reported in ppm relative to deuterated chloroform (77.3 ppm) or [$d_6$] DMSO (39.5 ppm). Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. High-resolution mass spectra were recorded on Agilent Technologies 6545 Q-TOF LC/MS by using electrospray mode. HPLC chromatograms were recorded on a Water-2998 instrument using CHIRALPAK®IA-3 column, mobile phase $^{n}$hexane/$^{i}$PrOH: 80:20, v/v; Flow rate: 1 mL/min; Detection wavelength: 245 nm. Column chromatography was performed on silica gel (100-200) mesh using varying ratio of ethyl acetate/hexanes as eluent.

## 2. Preparation of starting materials

$\alpha$-Carbonyl sulfoxonium ylides (**2a-k**) were prepared by according to the reported procedures.[1] *N*-Protected *O*-pyridyl tyrosines (**1a-c**)[2] and *N*-protected *O*-pyridyl tyrosine-containing dipeptides (**1d**, **1e**, **1g**)[2], (**1h, 1k, 1m**)[3], tripeptides (**1o-p**)[2] and tetrapeptides (**1q-r**) were prepared according to reported procedures.[3]

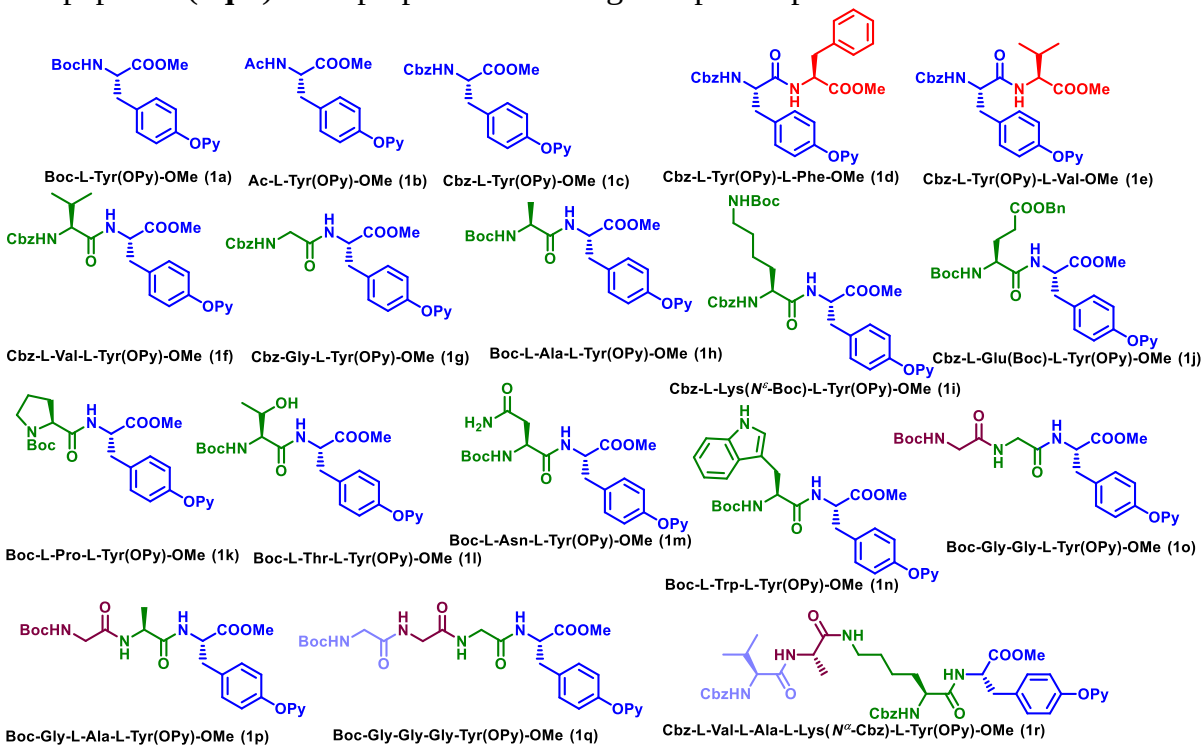
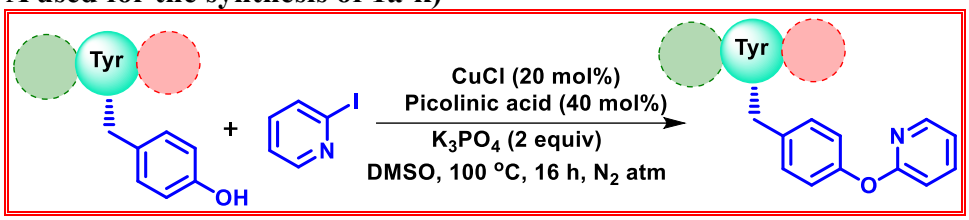



**Figure S1.** *N*-protected *O*-pyridyl tyrosines and *N*-protected *O*-pyridyl tyrosine-containing dipeptides, tripeptides and tetrapeptides used in the present study

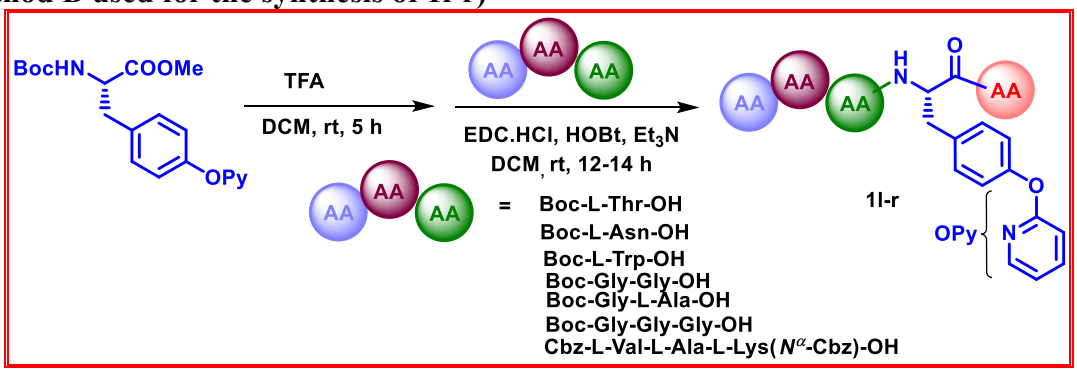
**General procedure for the synthesis of *N*-protected *O*-pyridyl tyrosines and *N*-protected *O*-pyridyl tyrosine-containing dipeptides (Method A or B)**

**(Method A used for the synthesis of 1a-k)**




In a pressure vial containing a stirring bar fitted with a screwed PTFE cap (sealed tube) and purged with nitrogen atmosphere, *N*-protected tyrosine derivative (or *N*-protected tyrosine-containing dipeptide) (1.0 equiv), CuCl (20 mol %), $K_3PO_4$ (2.0 equiv) and 2-picolinic acid (40 mol %) were added. The reaction tube was then evacuated and back-filled with nitrogen gas (this sequence was repeated up to three times). Thereafter, DMSO (2.5 mL/mmol) and 2-iodopyridine (2.0 equiv) were added under nitrogen 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 mixture and the resulting solution was washed with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc (2 × 10 mL). The organic layers were combined and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

**(Method B used for the synthesis of 1l-r)**




**Step-I:** To a stirred solution of Boc-Tyr(OPy)-OMe (1.342 mmol, 0.500 g, 1 equiv) in dichloromethane (20 mL), trifluoroacetic acid (13.42 mmol, 1.027 $\mu$L) was added and the reaction mixture was stirred for 5 h at room temperature. Thereafter, the solvent was evaporated and the crude product was diluted with EtOAc (30 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 25 mL). The organic layer was separated and distilled off to obtain crude product, $NH_2$-Tyr(OPy)-OMe (1.1017 mmol, 0.300 g), which was used as such for the next coupling step.

**Step-II:** Crude $NH_2$-Tyr(OPy)-OMe (approx. 0.300 g, 1 equiv) prepared above was dissolved in freshly distilled dichloromethane (30 mL) at 0 °C under nitrogen atmosphere. To this solution, triethylamine (2.5 equiv), HOBt (1.2 equiv), *N*-protected amino acid/dipeptide/tripeptide (1 equiv) and EDC·HCl (1,2 equiv) were subsequently added, and the reaction mixture was stirred overnight (12-14 h). The resulting mixture was diluted with water and extracted with dichloromethane (2 × 25 mL). The organic layer was separated and evaporated under reduced pressure to afford crude product, which was purified by flash chromatography (hexanes/ethyl acetate = 7:3 or 6:4) to furnish pure **1**.

The characterization of novel starting materials (**1f**, **1i**, **1j**, **1l**, **1n**, **1q**, **1r**) are given below:

**Methyl (*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1f).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **1f** as a colourless sticky semisolid; yield: 0.353 g (63%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 3.6 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.38 – 7.31 (m, 5H), 7.14 (d, $J$ = 7.6 Hz, 2H, 7.06 – 6.99 (m, 3H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.38 (d, $J$ = 8.0 Hz, 1H), 5.38 (d, $J$ = 8.4 Hz, 1H), 5.12 (s, 2H), 4.91 (q, $J$ = 6.4 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.76 (s, 3H), 3.19 – 3.08 (m, 2H), 2.15 – 2.08 (m, 1H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.91 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6, 170.9, 163.6, 156.4, 153.3, 147.7, 139.5, 136.2, 131.9, 130.6, 128.6, 128.2, 128.1, 121.3, 118.6, 111.7, 67.1, 60.3, 53.0, 52.4, 37.3, 40.0, 19.2, 17.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{32}N_3O_6^+$ : 506.2291, found 506.2307 $[M+H]^+$.

**Methyl (*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)-6-((*tert*-butoxycarbonyl)amino)hexanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1i).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ab** as a colourless sticky semisolid; yield: 0.415 g (73%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (dd, $J$ = 4.8, 1.6 Hz, 1H), 7.72 – 7.65 (m, 1H), 7.35 – 7.30 (m, 5H), 7.11 (d, $J$ = 8.0 Hz, 2H), 7.02 (d, $J$ = 8.4 Hz, 2H), 6.99 – 6.97 (m, 1H), 6.90 (d, $J$ = 8.0 Hz, 1H), 6.72 – 6.66 (m, 1H), 5.58 (d, $J$ = 5.6, 1H), 5.10 (s, 2H), 4.88 (q, $J$ = 6.5 Hz, 1H), 4.71 (brs, 1H), 4.15 (q, $J$ = 6.8 Hz, 1H), 3.75 (s, 3H), 3.16 (dd, $J$ = 13.6, 5.6 Hz, 1H), 3.11 – 3.03 (m, 3H), 2.09 – 2.00 (m, 1H), 1.85 – 1.74 (m, 1H), 1.64 – 1.56 (m, 1H), 1.47 – 1.45 (m, 1H), 1.41 (s, 9H), 1.36 – 1.29 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.8, 171.5, 163.6, 156.2, 153.2, 148.9, 147.5, 139.5, 136.2, 132.0, 130.6, 128.5, 128.2, 128.1, 121.4, 118.5, 111.7, 79.1, 67.0, 54.6, 53.0, 52.5, 39.8, 37.2, 31.8, 29.5, 28.4, 22.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{34}H_{43}N_4O_8^+$ : 635.3080, found 635.3097 $[M+H]^+$.

**Benzyl (*S*)-4-((*tert*-butoxycarbonyl)amino)-5-(((*S*)-1-methoxy-1-oxo-3-(4-(pyridin-2-yloxy)phenyl)propan-2-yl)amino)-5-oxopentanoate (1j).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **1j** as a dark bricks semisolid; yield: 0.304 g (53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, J = 3.6 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.37 – 7.35 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.02 – 6.98 (m, 1H), 6.95 – 6.86 (m, 2H), 6.73 (d, J = 8.0 Hz, 1H), 5.35 (t, J = 8.4 Hz, 1H), 5.13 (brs, 2H), 4.86 (q, J = 6.5 Hz, 1H), 4.24 – 4.17 (m, 1H), 3.73 (s, 3H), 3.17 (dd, J = 14.0, 5.6 Hz, 1H), 3.07 (dd, J = 14.0, 6.4 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.16 – 2.09 (m, 1H), 1.96 – 1.87 (m, 1H) 1.43 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.2, 171.7, 171.3, 163.7, 155.6, 153.2, 147.6, 139.5, 135.7, 132.1, 130.6, 130.3, 128.6, 128.3, 128.3, 121.4, 118.5, 115.6, 111.6, 80.1, 66.6, 53.6, 53.6, 52.4, 37.3, 30.4, 28.3, 27.9; HRMS (ESI-TOF) (*m/z*) calculated $C_{32}H_{38}N_3O_8^+$ : 592.2658, found 592.2685 $[M+H]^+$.

**Methyl (*S*)-2-((2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxybutanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1l).** Purified by flash chromatography (hexanes/ethyl acetate = 7:3) afforded compound **1l** as a colourless semisolid; yield: 0.307 g (59%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.12 (s, 1H), 7.71 (t, $J$ = 6.8 Hz, 1H), 7.18 (d, $J$ = 7.6 Hz, 2H), 7.08 – 6.99 (m, 4H), 6.94 (d, $J$ = 8.0 Hz, 1H), 5.47 (d, $J$ = 6.8 Hz, 1H), 4.99 – 4.87 (m, 1H), 4.27 (d, $J$ = 2.8 Hz, 1H), 4.07 (d, $J$ = 6.4 Hz, 1H), 3.77 (s, 3H), 3.29 – 3.19 (m, 1H), 3.05 – 2.96 (m, 1H), 1.45 (s, 9H), 1.16 (d, $J$ = 5.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.8, 171.1, 163.7, 156.3, 153.0, 147.3, 139.7, 132.3, 130.7, 121.5, 118.5, 111.8, 80.3, 66.6, 58.4, 52.9, 52.5, 37.5, 28.3, 18.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{24}H_{32}N_3O_7^+$ : 474.2240, found 474.2259 $[M+H]^+$.

**Methyl (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1n).** Purification by flash chromatography (hexanes/ethyl acetate = 7:3) afforded compound **1n** as a pale yellow semisolid; yield: 0.319 g (52%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.99 (s, 1H), 8.22 (d, $J$ = 3.6 Hz, 1H), 7.83 (t, $J$ = 6.8 Hz, 2H), 7.17 – 7.12 (m, 3H), 7.10 (d, $J$ = 7.6 Hz, 2H), 7.01 (d, $J$ = 7.6 Hz, 2H), 6.86 (brs, 2H), 6.73 (s, 1H), 6.14 (d, $J$ = 6.8 Hz, 1H), 5.45 (brs, 1H), 4.90 (q, $J$ = 6.4 Hz, 1H), 4.54 (brs, 1H), 3.77 (s, 3H), 3.41 (d, $J$ = 13.2 Hz, 1H), 3.11 – 2.98 (m, 2H), 2.96 – 2.86 (m, 1H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.9, 171.6, 163.6, 155.4, 153.1, 146.8, 140.3, 136.4, 132.0, 130.3, 127.2, 123.9, 121.8, 121.5, 119.4, 119.0, 112.6, 111.2, 109.7, 79.8, 54.7, 52.7, 52.4, 36.5, 28.9, 28.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{31}H_{35}N_4O_6^+$ : 559.2556, found 559.2579 $[M+H]^+$.

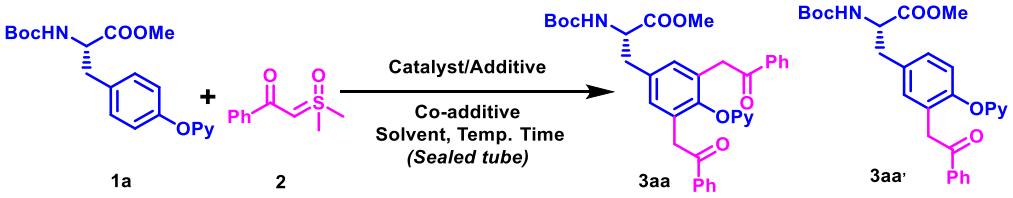
**Methyl (*S*)-2,2-dimethyl-4,7,10,13-tetraoxo-15-(4-(pyridin-2-yloxy)benzyl)-3-oxa-5,8,11,14-tetraazahexadecan-16-oate (1q).** Purification by column chromatography (hexanes/ethyl acetate = 4:6) afforded compound **1q** as a pale yellow semisolid; yield: 0.649 g (65%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 4.0 Hz, 1H), 7.92– 7.86 (m, 1H) , 7.77 – 7.70 (m, 1H), 7.63 – 7.60 (m, 1H), 7.13– 7.09 (m, 2H) (d, $J$ = 8.7 Hz, 2H), 7.05 – 7.01 (m, 1H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.87 (d, $J$ = 7.6 Hz, 1H), 5.49 – 5.40 (m, 1H), 4.91 (q, $J$ = 6.1 Hz, 1H), 4.18– 4.10 (m, 1H) 4.10– 4.03 (m, 1H) , 3.78 (s, 3H), 3.75 (d, $J$ = 5.6 Hz, 2H), 3.70 (d, $J$ = 5.2 Hz, 1H), 3.15 – 3.07 (m, 2H), 2.28 (s, 1H), 1.38 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.2, 171.6, 169.8, 168.7, 163.5, 156.3, 153.1, 146.9, 140.0, 131.9, 131.0, 121.2, 118.8, 112.3, 80.1, 52.7, 52.5, 44.0, 43.7, 42.8, 37.1, 28.2; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{34}N_5O_8^+$ : 544.2407, found 544.2412 $[M+H]^+$.

**Methyl (5*S*,8*R*,15*S*,18*S*)-15-(((benzyloxy)carbonyl)amino)-5-isopropyl-8-methyl-3,6,9,16-tetraoxo-1-phenyl-18-(4-(pyridin-2-yloxy)benzyl)-2-oxa-4,7,10,17-tetraazanonadecan-19-oate (1r).** Purification by column chromatography (hexanes/ethyl acetate = 4:6) afforded compound **1r** as a pale yellow semisolid; yield: 0.890 g (58%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.38 (d, $J$ = 7.2 Hz, 1H), 8.14 (d, $J$ = 3.2 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.84 (t, $J$ = 7.0 Hz, 1H), 7.67 (d, $J$ = 8.8 Hz, 1H), 7.53 (d, $J$ = 7.2 Hz, 1H), 7.37 – 7.35 (m, 4H), 7.35 – 7.32 (m, 4H), 7.31 – 7.29 (m, 2H), 7.26 (d, $J$ = 8.0 Hz, 2H), 7.12 (t, $J$ = 5.8 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.99 – 6.95 (m, 1H), 5.01 (d, $J$ = 8.8 Hz, 4H), 4.48 (q, $J$ = 6.8 Hz, 1H), 4.10 (q, $J$ = 7.7 Hz, 2H), 4.04 – 3.95 (m, 1H), 3.60 (s, 3H), 3.16 – 3.09 (m, 1H), 3.08 – 2.99 (m, 2H), 2.98 – 2.88 (m, 2H), 1.94 – 1.83 (m, 1H), 1.60 – 1.53 (m, 1H), 1.51 – 1.44 (m, 1H), 1.39 – 1.33 (m, 2H), 1.29 – 1.22 (m, 2H), 1.19 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 2.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.7, 172.6, 172.3, 171.0, 163.5, 156.3, 156.1, 153.1, 147.9, 140.6, 137.5, 137.5, 133.7, 130.8, 128.8, 128.8, 128.2, 128.2, 121.3, 119.4, 111.9, 65.9, 65.8, 58.0, 54.8, 54.0, 52.3, 50.6, 38.7, 36.4, 32.0, 31.4, 29.1, 23.2, 19.6, 18.6; HRMS (ESI-TOF) (*m/z*) calculated $C_{45}H_{55}N_6O_{10}^+$ : 839.3979, found 839.3986 $[M+H]^+$.

## 3. Table S1. Detailed optimization studies

The proposed work commenced by optimizing the envisioned $C_{Ar}$–H acylmethylation/diacylmethylation in Boc-L-Tyr(OPy)-OMe (**1a**) with 2-(dimethyl(oxo)-l6-sulfanylidene)-1-phenylethan-1-one (**2a**) as model substrates under diversified Ir-catalyzed conditions (Table S1, ESI). Unfortunately, traces amount of product formation was observed by using $[Cp^*IrCl_2]_2$ in presence of $AgSbF_6$ (20 mol%) in DCE at 60 °C for 36 h (entry 1). In contrast, the use PivOH (2 equiv) as a co-additive initiated the stoichiometric reaction between the model substrates in DCE at 60 °C to afford as a mixture of mono- and diacylmethyl

functionalized products (**3aa** & **3aa′**) in 18% and 12% yields respectively (entry 2). Delightfully, sequential usage of 2 and 3 equivalents of sulfoxonium ylide (**2a**) with 1 equivalent of **1a** using $[Cp^*IrCl_2]_2/AgSbF_6$ catalytic system with PivOH in DCE dramatically elevated the yield of **3aa** to 36% and 58% respectively along with slight increase in the yield of **3aa′** to 17% and 22%, respectively (entries 3-4). Substitution of PivOH with ADA produced **3aa** in 64% along 14% of **3aa′**, while its replacement with AcOH furnishes **3aa** in 72% along with very little (non-isolable) amounts of **3aa′** (entries 5-6). Our solvent screening studies suggested that this transformation is highly solvent-dependent, and the target product could be obtained in better yields using halogenated solvents, such as DCM, $CHCl_3$, TFE and HFIP; TFE being superior yielding 88% of exclusive **3aa**, while HFIP being comparatively less effective (entries 7−10). Notably, no reaction was initiated at all by using non-halogenated solvents including EtOH, DMF and ACN under similar reaction conditions (entry 11). Thereafter, we next integrated our efforts towards modulating catalyst loading from 2.5 mol% to 7.5 mol%; none of these changes were found to be beneficial in terms of obtaining significantly higher yield of **3aa** or greater product's selectivity (entries 12-13). Surprisingly, the process of tuning of $[Cp^*IrCl_2]_2$ catalyst with $[Cp^*RhCl_2]_2$ (5 mol%) under similar conditions resulted in no commencement of the reaction at all, while replacement with $[RuCl_2(p\text{-cymene})]_2$ catalyst reduces the reaction's reactivity and selectivity (entries 14-15). **3aa** is reduced 33% while **3aa'** is 18% (entry 15). It is worth mentioning that increasing the temperature for the aforementioned optimized reaction to 80 °C produced detrimental effects on the yield of **3aa** as a few other minor side products were visible on TLC (entry 16).




| Entry | Catalyst/Additive (mol%) | Co-additive | Solvent | Yield of **3aa** (%)[b] | Yield of **3aa′** (%)[b] |
|---|---|---|---|---|---|
| 1. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | - | DCE | traces | traces |
| 2.[c] | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | PivOH (2 equiv) | DCE | 18 | 12 |
| 3.[d] | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | PivOH (2 equiv) | DCE | 36 | 17 |
| 4. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | PivOH (2 equiv) | DCE | 58 | 22 |
| 5. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | ADA (2 equiv) | DCE | 64 | 14 |
| 6. | $[Cp^*IrCl_2]_2$ (5)/ $AgSbF_6$ (20) | AcOH (2 equiv) | DCE | 72 | <10 |
| 7. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | DCM | 76 | traces |
| 8. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | $CHCl_3$ | 74 | traces |
| 9. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | TFE | 88 | traces |
| 10. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | HFIP | 54 | 16 |
| 11. | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | EtOH/DMF/ACN | -[e] | -[e] |
| 12. | $[Cp^*IrCl_2]_2$ (2.5)/$AgSbF_6$ (20) | AcOH (2 equiv) | TFE | 58 | 11 |
| 13. | $[Cp^*IrCl_2]_2$ (7.5)/$AgSbF_6$ (20) | AcOH (2equiv) | TFE | 89 | traces |
| 14. | $[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | DCE | -[e] | -[e] |
| 15. | $[RuCl_2(p\text{-cymene})]_2$(5)/$AgSbF_6$ (20) | AcOH (2 equiv) | TFE | 33 | 18 |
| 16.[f] | $[Cp^*IrCl_2]_2$ (5)/$AgSbF_6$ (20) | AcOH (2 equiv) | TFE | 72 | traces |

[a]Reaction conditions: The reactions were carried out with **1a** (0.187 mmol) and **2a** (0.561 mmol) with $[Cp^*IrCl_2]_2$ (as indicated in table) in the presence of additive/Co-additive (as indicated in the table) in a solvent (2 mL) at 60 °C for 36 h in a sealed tube. [b]Isolated yields. [c]**2a** (0.187 mmol). [d]**2a** (0.374 mmol). [e]NR = no reaction. [f]Temperature 80 °C (minor additional spots on TLC were observed).

**4. General procedure for the diacylmethylation of *O*-pyridyl tyrosines with sulfoxonium ylides.** To a stirred solution of *N*-protected *O*-pyridyl tyrosine [or *N*-protected *O*-pyridyl tyrosine-containing dipeptide or tripeptide or tetrapeptide] (**1**) (0.070 g, 1 equiv) in TFE (2 mL), $[Cp^*IrCl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%), AcOH (2.0 equiv) and $\alpha$-carbonyl sulfoxonium ylide (**2**) (3.0 equiv) were added under ambient conditions in a pressure vial fitted with a screwed PTFE cap (sealed tube). The reaction was allowed to stir at 60 °C in an oil bath for 36-48 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction was quenched by adding water, and extracted with DCM (3 x 15 mL). The combined organic layers were separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give a crude mixture. The crude mixture was purified by column chromatography on silica gel [using hexanes/ethyl acetate (8:2 or 7:3 or 6:4 or 2:8)] to afford the diacylmethylated product (**3**).

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3aa).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3aa** as a pale yellow semisolid; yield: 0.100 g (88%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 3.6 Hz, 1H), 7.85 (d, $J$ = 7.2 Hz, 4H), 7.57 – 7.48 (m, 3H), 7.42 – 7.35 (m, 4H), 7.04 (s, 2H), 6.89 – 6.84 (m, 1H), 6.72 (d, $J$ = 8.4 Hz, 1H), 5.14 (d, $J$ = 8.0 Hz, 1H), 4.58 (q, $J$ = 6.0 Hz, 1H), 4.11 (brs, 4H), 3.62 (s, 3H), 3.07 (d, $J$ = 5.6 Hz, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.9, 172.2, 162.8, 155.1, 148.7, 147.7, 139.6, 136.5, 133.6, 133.0, 131.3, 129.1, 128.5, 128.4, 118.4, 110.2, 79.9, 54.4, 52.2, 40.3, 37.7, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{37}N_2O_7^+$ : 609.2600, found 609.2607 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-(*p*-tolyl)ethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ab).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ab** as a pale yellow semisolid; yield: 0.096 g (80%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 5.2 Hz, 1H), 7.76 (d, $J$ = 7.6 Hz, 4H), 7.56 (t, $J$ = 7.0 Hz, 1H), 7.18 (d, $J$ = 7.2 Hz, 4H), 7.02 (s, 2H), 6.88 (t, $J$ = 5.2 Hz, 1H), 6.73 (d, $J$ = 8.0 Hz, 1H), 5.11 (d, $J$ = 6.8 Hz, 1H), 4.63 – 4.52 (m, 1H), 4.08 (brs, 4H), 3.63 (s, 3H), 3.10 – 3.02 (m, 2H), 2.39 (s, 6H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.6, 172.2, 162.8, 155.1, 148.7, 147.7, 143.8, 139.6, 134.1, 133.6, 131.2, 129.3, 129.2, 128.6, 118.4, 110.2, 79.9, 54.4, 52.2, 40.2, 37.7, 28.3, 21.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{38}H_{41}N_2O_7^+$ : 637.2913, found 637.2933 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-(4-methoxyphenyl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ac).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ac** as a pale yellow semisolid; yield: 0.097 g (77%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 4.0 Hz, 1H), 7.84 (d, $J$ = 8.4 Hz, 4H), 7.59 – 7.54 (m, 1H), 7.02 (s, 2H), 6.90 – 6.88 (m, 1H), 6.85 (d, $J$ = 8.8 Hz, 4H), 6.73 (d, $J$ = 8.4 Hz, 1H), 5.11 (d, $J$ = 8.4 Hz, 1H), 4.56 (q, $J$ = 6.6 Hz, 1H), 4.05 (brs, 4H), 3.85 (s, 6H), 3.63 (s, 3H), 3.05 (d, $J$ = 5.6 Hz, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.5, 172.2, 163.4, 162.9, 155.1, 148.5, 147.7, 139.6, 133.6, 131.1, 130.8, 129.6, 129.4, 118.4, 113.6, 110.2, 79.9, 55.4, 54.4, 52.2, 40.0, 37.7, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{38}H_{41}N_2O_9^+$ : 669.2812, found 669.2849 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-(4-fluorophenyl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ad).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ad** as a pale yellow semisolid; yield: 0.102

g (84%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 – 8.01 (m, 1H), 7.91 – 7.82 (m, 4H), 7.56 (t, $J$ = 6.2 Hz, 1H), 7.09 – 6.99 (m, 6H), 6.92 – 6.86 (m, 1H), 6.71 (d, $J$ = 7.6 Hz, 1H), 5.08 (d, $J$ = 8.0 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.06 (brs, 4H), 3.65 (s, 3H), 3.12 – 3.01 (m, 2H), 1.44 (s, 9H); NMR (100 MHz, $CDCl_3$) $\delta$ 195.3, 172.1, 165.6 ($^1J_{C\text{-}F}$ = 253.0 Hz), 162.7, 155.1, 148.6, 147.7, 139.7, 133.8, 132.8 ($^4J_{C\text{-}F}$ = 3.0 Hz), 131.3, 131.1 ($^3J_{C\text{-}F}$ = 10.0 Hz), 129.1, 118.5, 115.6 ($^2J_{C\text{-}F}$ = 21.0 Hz), 110.2, 80.0, 54.4, 52.2, 40.3, 37.7, 28.3. HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{35}F_2N_2O_7^+$ : 645.2412, found 645.2417 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ae).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ae** as a pale yellow semisolid; yield: 0.115 g (82%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 3.6 Hz, 1H), 7.94 (d, $J$ = 8.4 Hz, 4H), 7.65 (d, $J$ = 8.4 Hz, 4H), 7.59 – 7.54 (m, 1H), 7.07 (s, 2H), 6.91 – 6.87 (m, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 5.13 (d, $J$ = 8.0 Hz, 1H), 4.60 (q, $J$ = 6.1 Hz, 1H), 4.11 (brs, 4H), 3.67 (s, 3H), 3.11 – 3.06(m, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.8, 172.1, 162.5, 155.1, 148.6, 147.7, 139.8, 139.1, 134.3 (q, $^2J$ = 32.5 Hz), 134.1, 131.5, 128.7, 125.6, (q, $^3J$ = 3.6 Hz), 123.5 (q, $^1J$ = 271 Hz), 118.7, 110.2, 80.0, 54.3, 52.3, 40.6, 37.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{38}H_{35}F_6N_2O_7^+$ : 745.2348, found 745.2376 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-(4-nitrophenyl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3af).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3af** as a colourless semisolid; yield: 0.103 g (79%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.4 Hz, 4H), 8.03 – 7.95 (m, 5H), 7.60 (t, $J$ = 7.8 Hz, 1H), 7.08 (s, 2H), 6.92 (t, $J$ = 6.2 Hz, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H), 5.06 (d, $J$ = 8.4 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.13 (brs, 4H), 3.71 (s, 3H), 3.15 – 3.02 (m, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.2, 172.1, 162.4, 155.0, 150.2, 148.6, 147.7, 140.8, 140.0, 134.3, 131.7, 129.4, 128.5, 123.8, 118.9, 110.2, 80.1, 54.3, 52.3, 40.9, 37.9, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{35}N_4O_{11}^+$ : 699.2302, found 699.2308 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-(4-chlorophenyl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ag).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ag** as a pale yellow semisolid; yield: 0.097 g (76%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 3.2 Hz, 1H), 7.78 (d, $J$ = 8.4 Hz, 4H), 7.57 (t, $J$ = 7.2 Hz, 1H), 7.35 (d, $J$ = 8.0 Hz, 4H), 7.03 (s, 2H), 6.90 (t, $J$ = 6.0 Hz, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 5.06 (d, $J$ = 7.2 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.05 (brs, 4H), 3.66 (s, 3H), 3.11 – 3.03 (m, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.6, 172.1, 162.6, 155.1, 148.6, 147.7, 139.7, 139.5, 134.8, 133.9, 131.3, 129.9, 129.0, 128.8, 118.6, 110.2, 80.0, 54.3, 52.2, 40.4, 37.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{35}Cl_2N_2O_7^+$ : 677.1821, found 677.1859 $[M+H]^+$.

**Methyl 3-(3,5-bis(2-(3-chlorophenyl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ah).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ah** as a pale yellow semisolid; yield: 0.099 g (78%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 2.8 Hz, 1H), 7.81 (s, 2H), 7.71 (d, $J$ = 8.0 Hz, 2H), 7.58 (t, $J$ = 7.4 Hz, 1H), 7.48 (d, $J$ = 7.2 Hz, 2H), 7.33 (t, $J$ = 7.8 Hz, 2H), 7.04 (s, 2H), 6.89 (t, $J$ = 5.8 Hz, 1H), 6.74 (d, $J$ = 8.4 Hz, 1H), 5.11 (d, $J$ = 7.2 Hz, 1H), 4.63 – 4.54 (m, 1H), 4.06 (brs, 4H), 3.67 (s, 3H), 3.08 (d, $J$ = 4.0 Hz 2H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.6, 172.1, 162.6, 155.1, 148.6, 147.8, 139.7, 138.0, 134.8, 133.9, 133.0, 131.5,

129.9, 128.8, 128.4, 126.5, 118.6, 110.3, 80.0, 54.3, 52.3, 40.3, 37.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{35}Cl_2N_2O_7^+$ : 677.1821, found 677.1825 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-(thiophen-2-yl)ethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ai).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ai** as a pale yellow semisolid; yield: 0.084 g (72%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 3.6 Hz, 1H), 7.60 – 7.54 (m, 5H), 7.11 (s, 2H), 7.03 (t, $J$ = 4.2 Hz, 2H), 6.88 (t, $J$ = 5.8 Hz, 1H,), 6.74 (d, $J$ = 8.0 Hz, 1H), 5.13 (d, $J$ = 7.6 Hz, 1H), 4.60 (q, $J$ = 6.8 Hz, 1H), 4.04 – 3.99 (m, 4H), 3.68 (s, 3H), 3.10 (d, $J$ = 6.0 Hz, 2H), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.7, 172.1, 162.7, 155.1, 148.6, 147.7, 143.8, 139.7, 133.9, 133.8, 132.6, 131.5, 128.9, 128.1, 118.5, 110.2, 80.0, 54.4, 52.3, 40.9, 37.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{32}H_{33}N_2O_7S_2^+$ : 621.1729, found 621.1732 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-(furan-2-yl)-2-oxoethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3aj).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3aj** as a pale yellow semisolid; yield: 0.076 g (69%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 – 7.99 (m, 1H), 7.58 (t, $J$ = 5.8 Hz, 1H), 7.49 (s, 2H), 7.14 – 7.02 (m, 4H), 6.91 – 6.84 (m, 1H), 6.73 (d, $J$ = 8.0 Hz, 1H), 6.44 (s, 2H), 5.13 (d, $J$ = 6.0 Hz, 1H), 4.65 – 4.55 (m, 1H), 3.98 – 3.90 (m, 4H), 3.71 (s, 3H), 3.14 – 3.04 (m, 2H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 185.5, 172.2, 162.8, 155.1, 152.1, 148.8, 147.6, 146.5, 139.5, 133.7, 131.6, 128.7, 118.3, 117.9, 112.2, 110.2, 80.0, 54.4, 52.3, 40.0, 37.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{32}H_{33}N_2O_9^+$ : 589.2186, found 589.2196 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxohexyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3ak).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ak** as a pale yellow semisolid; yield: 0.070 g (65%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 3.2 Hz, 1H), 7.68 (t, $J$ = 7.2 Hz, 1H), 7.02 – 6.95 (m, 3H), 6.83 (d, $J$ = 8.4 Hz, 1H), 5.11 (d, $J$ = 6.8 Hz, 1H), 4.65 – 4.56 (m, 1H), 3.74 (s, 3H), 3.45 (brs, 4H), 3.13 – 3.06 (m, 2H), 2.28 (t, $J$ = 7.4 Hz, 4H), 1.43 (s, 9H), 1.42 – 1.38 (m, 4H), 1.20 (q, $J$ = 7.3 Hz, 4H), 0.84 (t, $J$ = 7.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.5, 172.2, 162.7, 155.1, 149.0, 147.6, 139.8, 133.7, 131.6, 129.0, 118.5, 110.3, 80.0, 54.4, 52.3, 44.8, 41.8, 37.8, 28.3, 25.7, 22.2, 13.8; HRMS (ESI-TOF) (*m/z*) calculated $C_{32}H_{45}N_2O_7^+$ : 569.3226, found 569.3256 $[M+H]^+$.

**Methyl (*S*)-2-acetamido-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3ba).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ba** as a pale yellow semisolid; yield: 0.088 g (73%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 4.0 Hz, 1H), 7.86 (d, $J$ = 7.6 Hz, 4H), 7.59 – 7.49 (m, 3H), 7.40 (t, $J$ = 7.6 Hz, 4H), 7.00 (s, 2H), 6.87 (t, $J$ = 6.0 Hz, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H), 6.25 (d, $J$ = 8.0 Hz, 1H), 4.90 (q, $J$ = 6.0 Hz, 1H), 4.11 (q, $J$ = 12.9 Hz, 4H), 3.67 (s, 3H), 3.18 – 3.07 (m, 2H), 1.97 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 171.8, 170.0, 162.8, 148.7, 147.7, 139.7, 136.5, 133.4, 133.2, 131.4, 129.1, 128.6, 128.4, 118.5, 110.2, 52.9, 52.4, 40.0, 37.1, 23.0; HRMS (ESI-TOF) (*m/z*) calculated $C_{33}H_{31}N_2O_6^+$ : 551.2182, found 551.2197 $[M+H]^+$.

**Methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3ca).** Purification by column chromatography (hexanes/ethyl acetate = 8:2) afforded compound **3ca** as a pale yellow semisolid; yield: 0.084 g (76%); $^1$H

NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 4.0 Hz, 1H), 7.84 (d, $J$ = 7.6 Hz, 4H), 7.57 – 7.47 (m, 3H), 7.42 – 7.37 (m, 5H), 7.36 – 7.29 (m, 4H), 7.02 (s, 2H), 6.89 – 6.84 (m, 1H), 6.72 (d, $J$ = 8.4 Hz, 1H), 5.35 (d, $J$ = 8.4 Hz, 1H), 5.14 – 5.11 (m, 2H), 4.66 (q, $J$ = 7.3 Hz, 1H), 4.09 (q, $J$ = 12.4 Hz, 4H), 3.64 (s, 3H), 3.12 (d, $J$ = 5.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.9, 171.7, 162.8, 155.7, 148.8, 147.7, 139.6, 136.5, 136.4, 133.3, 133.0, 131.3, 129.1, 128.5, 128.5, 128.4, 128.2, 128.1, 118.4, 110.2, 67.0, 54.7, 52.3, 40.2, 37.6; HRMS (ESI-TOF) (*m/z*) calculated $C_{39}H_{35}N_2O_7^+$ : 643.2444, found 643.2457 $[M+H]^+$.

**Methyl ((*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-L-phenylalaninate (3da)** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3da** as a pale yellow semisolid; yield: 0.068 g (68%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 3.2 Hz, 1H), 7.84 (d, $J$ = 7.2 Hz, 4H), 7.50 (q, $J$ = 6.8 Hz, 3H), 7.41 – 7.37 (m, 4H), 7.37 – 7.29 (m, 5H), 7.27 – 7.21 (m, 3H), 7.16 (s, 2H), 7.09 (d, $J$ = 6.4 Hz, 2H), 6.83 (t, $J$ = 6.0 Hz, 1H), 6.68 (d, $J$ = 8.0 Hz, 1H), 6.52 (brs, 1H), 5.70 – 5.58 (m, 1H), 5.12 (s, 2H), 4.76 (q, $J$ = 6.0 Hz, 1H), 4.43 (d, $J$ = 4.8 Hz, 1H), 4.11 (brs, 4H), 3.63 (s, 3H), 3.18 – 3.09 (m, 2H), 3.08 – 2.97 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.8, 171.5, 170.3, 162.8, 155.8, 149.0, 147.7, 139.6, 136.6, 136.4, 136.1, 133.9, 133.1, 132.0, 129.3, 129.1, 128.6, 128.5, 128.5, 128.3, 128.1, 128.1, 127.0, 118.3, 110.3, 67.0, 56.1, 53.7, 52.2, 40.1, 38.0, 37.5; HRMS (ESI-TOF) (*m/z*) calculated $C_{48}H_{44}N_3O_8^+$ : 790.3128, found 790.3165 $[M+H]^+$.

**Methyl ((*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-L-valinate (3ea).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ea** as a pale yellow semisolid; yield: 0.072 g (70%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 3.6 Hz, 1H), 7.87 – 7.79 (m, 4H) 7.54 – 7.49 (m, 3H), 7.40 – 7.34 (m, 6H), 7.33 – 7.29 (m, 2H), 7.15 (s, 2H), 6.86 – 6.82 (m, 1H), 6.68 (q, $J$ = 8.9 Hz, 2H), 5.79 (d, $J$ = 7.2 Hz, 1H), 5.14 (s, 2H), 4.55 – 4.48 (m, 1H), 4.46 (dd, $J$ = 8.0, 5.2 Hz, 1H), 4.19 – 3.99 (m, 4H), 3.69 (s, 3H), 3.22 (dd, $J$ = 13.8, 4.6 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.20 – 2.12 (m, 2H), 0.87 (t, $J$ = 6.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.8, 171.8, 170.7, 162.8, 156.1, 149.0, 147.6, 139.6, 136.6, 136.4, 134.0, 133.0, 131.9, 129.1, 128.5, 128.5, 128.3, 128.3, 128.1, 118.3, 110.3, 67.0, 57.6, 56.1, 52.1, 40.2, 37.6, 31.0, 18.9, 17.9; HRMS (ESI-TOF) (*m/z*) calculated $C_{44}H_{44}N_3O_8^+$ : 742.3128, found 742.3148 $[M+H]^+$.

**Methyl (*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3fa).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3fa** as a pale yellow semisolid; yield: 0.067 g (65%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 4.8 Hz, 1H), 7.85 (d, $J$ = 8.0 Hz, 4H), 7.55 – 7.48 (m, 3H), 7.41 – 7.34 (m, 4H), 7.33 – 7.28 (m, 4H), 7.05 (s, 2H), 6.83 (t, $J$ = 6.4 Hz, 2H), 6.67 (d, $J$ = 8.4 Hz, 1H), 6.04 (d, $J$ = 9.2 Hz, 1H), 5.13 – 4.99 (m, 2H), 4.98 – 4.90 (m, 1H), 4.26 – 4.19 (m, 1H), 4.17 – 4.05 (m, 4H), 3.68 (s, 3H), 3.15 (d, $J$ = 5.2 Hz, 2H), 2.35 – 2.23 (m, 1H), 2.02 (brs, 1H), 0.99 (d, $J$ = 6.4 Hz, 3H), 0.85 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.1, 171.4, 171.2, 162.9, 156.8, 148.9, 147.8, 139.6, 136.5, 133.2, 133.0, 131.8, 128.9, 128.5, 128.5, 128.4, 128.0, 127.8, 118.4, 110.1, 66.8, 60.3, 52.9, 52.4, 39.6, 37.2, 30.6, 19.3, 17.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{44}H_{44}N_3O_8^+$ : 742.3128, found 742.3158 $[M+H]^+$.

**Methyl (*S*)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3ga).** Purification by column

chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ga** as a pale yellow semisolid; yield: 0.063 g (60%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 – 7.85 (m, 1H), 7.77 – 7.71 (m, 3H), 7.65 – 7.55 (m, 1H), 7.48 – 7.39 (m, 3H), 7.37 – 7.29 (m, 2H), 7.27 – 7.21 (m, 4H), 7.20 (s, 2H), 7.11 – 7.03 (m, 1H), 6.91 (s, 2H), 6.77 – 6.65 (m, 2H), 6.60 (d, $J$ = 8.0 Hz, 1H), 6.21 – 6.08 (m, 1H), 5.04 (q, $J$ = 10.8 Hz, 2H), 4.86 – 4.79 (m, 1H), 4.10 – 3.93 (m, 4H), 3.79 – 3.55 (m, 5H), 3.23 – 3.14 (m, 1H), 3.09 – 2.97 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 171.4, 171.4, 169.1, 162.8, 147.7, 139.7, 136.4, 133.3, 131.8, 129.9, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 118.4, 110.2, 67.0, 52.9, 52.5, 44.6, 39.7, 36.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{41}H_{38}N_3O_8^+$ : 700.2658, found 700.2658 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)propanoate (3ha).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ha** as a pale yellow semisolid; yield: 0.077 g (72%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 2.0 Hz, 1H), 7.86 (d, $J$ = 7.2 Hz, 4H), 7.57 – 7.51 (m, 3H), 7.40 (t, $J$ = 7.6 Hz, 4H), 7.03 (s, 2H), 6.95 – 6.89 (m, 1H), 6.86 (t, $J$ = 5.8 Hz, 1H), 6.70 (d, $J$ = 8.4 Hz, 1H), 5.77 (d, $J$ = 6.8 Hz, 1H), 4.91 (q, $J$ = 5.7 Hz, 1H), 4.33 – 4.21 (m, 1H), 4.17 – 4.10 (m, 4H), 3.68 (s, 3H), 3.21 (dd, $J$ = 13.6, 5.2 Hz, 1H), 3.09 (dd, $J$ = 13.6, 4.8 Hz, 1H), 1.42 (s, 9H), 1.36 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 172.6, 171.4, 162.8, 155.7, 148.7, 147.7, 139.7, 136.5, 133.2, 131.8, 128.8, 128.5, 128.4, 118.4, 110.2, 79.8, 52.9, 52.4, 50.3, 39.8, 37.1, 28.3, 18.1; HRMS (ESI-TOF) (*m/z*) calculated $C_{39}H_{42}N_3O_8^+$ : 680.2971, found 680.2962 $[M+H]^+$.

**Methyl (*S*)-2-((S)-2-(((benzyloxy)carbonyl)amino)-6-((*tert*-butoxycarbonyl)amino)hexanamido)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3ia)** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ia** as a pale yellow semisolid; yield: 0.066 g (69%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 3.6 Hz, 1H), 7.83 (d, $J$ = 7.6 Hz, 4H), 7.57 – 7.50 (m, 3H), 7.49 – 7.45 (m, 1H), 7.38 (t, $J$ = 7.6 Hz, 4H), 7.34 – 7.29 (m, 5H), 7.06 – 6.99 (m, 3H), 6.83 (t, $J$ = 6.0 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 6.11 (d, $J$ = 8.8 Hz, 1H), 5.05 (q, $J$ = 12.2 Hz, 2H), 4.93 (q, $J$ = 6.3 Hz, 1H), 4.73 – 4.61 (m, 1H), 4.36 – 4.19 (m, 2H), 4.17 – 4.08 (m, 4H), 3.72 (s, 3H), 3.22 (dd, $J$ = 13.6, 4.8 Hz, 1H), 3.13 – 3.00 (m, 3H), 1.97 – 1.86 (m, 1H), 1.64 – 1.54 (m, 1H), 1.42 (s, 9H), 1.39 – 1.35 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 171.8, 171.5, 162.6, 156.6, 156.1, 148.8, 147.5, 140.0, 136.4, 136.3, 133.5, 133.4, 132.0, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 118.5, 110.3, 79.0, 66.9, 55.0, 53.0, 52.6, 40.0, 39.8, 37.2, 31.6, 29.3, 28.4, 22.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{50}H_{55}N_4O_{10}^+$ : 871.3918, found 871.3904 $[M+H]^+$.

**Benzyl (*S*)-5-(((*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-1-methoxy-1-oxopropan-2-yl)amino)-4-((*tert*-butoxycarbonyl)amino)-5-oxopentanoate (3ja).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ja** as a pale yellow semisolid; yield: 0.054 g (55%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 3.6 Hz, 1H), 7.86 (d, $J$ = 7.6 Hz, 4H), 7.55 – 7.49 (m, 3H), 7.41 – 7.36 (m, 4H), 7.35 – 7.30 (m, 5H), 7.10 – 7.06 (m, 1H), 7.04 (s, 2H), 6.84 (t, $J$ = 5.8 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 5.84 (d, $J$ = 8.4 Hz, 1H) 5.06 (s, 2H), 4.91 (q, $J$ = 5.7 Hz, 1H), 4.34 – 4.24 (m, 1H), 4.17 – 4.09 (m, 4H), 3.68 (s, 3H), 3.21 – 3.10 (m, 2H), 2.51 (q, $J$ = 7.4 Hz, 2H), 2.08 – 2.02 (m, 1H), 1.97 – 1.89 (m, 1H), 1.41 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 172.9, 171.4, 171.4, 162.8, 155.9, 148.8, 147.7, 139.7, 136.5, 135.9, 133.2, 131.9, 128.9, 128.5, 128.4, 128.2,

128.2, 118.4, 110.2, 79.8, 66.3, 53.8, 53.0, 52.4, 39.8, 37.0, 30.7, 28.3, 27.6; HRMS (ESI-TOF) (*m/z*) calculated $C_{48}H_{50}N_3O_{10}^+$ : 828.3496, found 828.3471 $[M+H]^+$.

***tert*-Butyl (*S*)-2-(((*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3ka). (mixture of rotamers)** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ka** as a pale yellow semisolid; yield: 0.063 g (60%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (brs, 1H), 7.85 (d, $J$ = 7.2 Hz, 4H), 7.58 – 7.47 (m, 3H), 7.45 – 7.35 (m, 4H), 7.17 – 6.98 (m, 3H), 6.89 – 6.82 (m, 1H), 6.70 (d, $J$ = 7.6 Hz, 1H), 4.94 – 4.81 (m, 1H), 4.27 – 4.20 (m, 1H), 4.18 – 4.06 (m, 4H), 3.74 – 3.58 (m, 3H), 3.47 – 3.33 (m, 2H), 3.20 – 3.03 (m, 2H), 2.16 – 1.94 (m, 2H), 1.98 – 1.82 (m, 1H), 1.74 (brs, 1H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.8, 172.3, 171.6, 162.7, 154.8, 156.1, 148.8, 147.6, 139.6, 139.5, 136.5, 133.5, 133.0, 131.7, 129.3, 128.5, 128.4, 118.4, 111.2, 110.2, 102.6, 80.6, 72.0, 61.0, 60.2, 53.2, 52.6, 52.3, 47.0, 40.1, 37.5, 31.6, 28.3, 24.5, 23.6, 8.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{41}H_{44}N_3O_8^+$ : 706.3128, found 706.3146 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxybutanamido)propanoate (3la).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3la** as a pale yellow semisolid; yield: 0.066 g (63%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 4.0 Hz, 1H), 7.86 (d, $J$ = 7.6 Hz, 4H), 7.56 – 7.49 (m, 3H), 7.39 (t, $J$ = 7.6 Hz, 4H), 7.26 (d, $J$ = 8.4 Hz, 1H), 7.08 (s, 2H), 6.88 – 6.83 (m, 1H), 6.69 (d, $J$ = 8.4 Hz, 1H), 5.77 (d, $J$ = 8.0 Hz, 1H), 4.99 – 4.88 (m, 1H), 4.37 – 4.30 (m, 1H), 4.16 (brs, 1H), 4.13 (brs, 4H), 3.73 (s, 3H), 3.24 (dd, $J$ = 13.4, 4.6 Hz, 1H), 3.06 – 2.97 (m, 1H), 1.45 (s, 9H), 1.19 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 171.6, 171.1, 162.7, 156.4, 148.7, 147.5, 139.8, 136.4, 133.4, 133.3, 131.9, 128.9, 128.6, 128.4, 118.5, 110.5, 80.0, 66.9, 58.9, 52.8, 52.5, 40.0, 37.4, 28.3, 19.0; HRMS (ESI-TOF) (*m/z*) calculated $C_{40}H_{44}N_3O_9^+$ : 710.3077, found 710.3085 $[M+H]^+$.

**Methyl (*S*)-2-((S)-4-amino-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanamido)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (3ma).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3ma** as a pale yellow semisolid; yield: 0.055 g (53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 4.0 Hz, 1H), 7.78 (d, $J$ = 7.4 Hz, 4H), 7.48 – 7.41 (m, 3H), 7.34 – 7.29 (m, 4H), 7.19 (s, 1H), 6.96 (s, 2H), 6.73 (t, $J$ = 5.8 Hz, 1H), 6.60 (d, $J$ = 8.4 Hz, 1H), 6.52 (d, $J$ = 8.8 Hz, 1H), 4.87 (q, $J$ = 6.3 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.08 – 4.02 (m, 4H), 3.68 (s, 3H), 3.22 (dd, $J$ = 13.6, 5 .2 Hz, 1H), 3.01 (dd, $J$ = 13.6, 5.2 Hz, 1H), 2.81 (d, $J$ = 5.6 Hz, 2H), 1.38 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.6, 170.2, 167.7, 161.7, 154.8, 147.8, 146.6, 138.7, 135.4, 132.3, 131.8, 131.1, 127.6, 127.5, 127.4, 117.4, 116.3, 109.2, 79.7, 52.2, 51.6, 50.0, 38.5, 35.9, 27.2, 20.0; HRMS (ESI-TOF) (*m/z*) calculated $C_{40}H_{43}N_4O_9^+$ : 723.3030, found 723.3043 $[M+H]^+$.

**Methyl (*S*)-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)propanoate (3na).** Purification by column chromatography (hexanes/ethyl acetate = 7:3) afforded compound **3na** as a pale yellow semisolid; yield: 0.046 g (47%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.48 (brs, 1H), 7.99 (d, $J$ = 3.6 Hz, 1H), 7.87 – 7.79 (m, 5H), 7.58 – 7.51 (m, 3H), 7.40 (t, $J$ = 7.6 Hz, 4H), 7.29 (s, 1H), 7.20 (d, $J$ = 6.8 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.89 – 6.84 (m, 2H), 6.77 (d, $J$ = 8.0 Hz, 2H), 6.44 (d, $J$ = 7.6 Hz, 1H), 5.80 – 5.68 (m, 1H), 4.98 – 4.88 (m, 1H), 4.57 (brs, 1H), 4.10 (d, $J$ = 16.8 Hz,

2H), 3.94 (d, *J* = 16.8 Hz, 2H), 3.71 (s, 3H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.18 – 3.01 (m, 2H), 3.00 – 2.91 (m, 1H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.7, 172.0, 171.5, 162.7, 155.6, 149.0, 147.1, 140.1, 136.5, 136.3, 133.2, 133.0, 131.8, 129.0, 128.6, 128.3, 127.6, 124.4, 121.7, 119.4, 119.2, 118.7, 111.1, 110.8, 110.0, 79.7, 54.9, 52.7, 52.4, 40.0, 36.6, 28.6, 28.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{47}H_{47}N_4O_8^+$ : 795.3393, found 795.3416 $[M+H]^+$.

**Methyl (*S*)-12-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)benzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (3oa).** Purification by column chromatography (hexanes/ethyl acetate = 6:4) afforded compound **3oa** as a pale yellow semisolid; yield: 0.060 g (58%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, *J* = 4.9 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 4H), 7.54 (q, *J* = 7.7, 3H), 7.44 – 7.39 (m, 5H), 7.02 (s, 2H), 6.99 – 6.93 (m, 1H), 6.85 (t, *J* = 6.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.63 (brs, 1H), 4.91 (q, *J* = 6.1 Hz, 1H), 4.20 (d, *J* = 6.4 Hz, 1H), 4.17 – 4.14 (m, 4H), 3.87 – 3.78 (m, 3H), 3.74 (s, 3H), 3.25 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.16 (dd, *J* = 13.8, 5.8 Hz, 1H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 171.6, 170.5, 169.0, 162.7, 156.2, 148.9, 147.5, 139.8, 136.4, 133.4, 133.3, 131.9, 128.8, 128.6, 128.3, 118.5, 110.4, 79.9, 52.8, 52.6, 44.1, 43.0, 39.8, 36.5, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{40}H_{43}N_4O_9^+$ : 723.3030, found 723.3025 $[M+H]^+$.

**Methyl (9*S*,12*S*)-12-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)benzyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (3pa).** Purification by column chromatography (hexanes/ethyl acetate = 6:4) afforded compound **3pa** as a pale yellow semisolid; yield: 0.055 g (53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 – 7.98 (m, 1H), 7.86 (d, *J* = 7.4 Hz, 4H), 7.57 – 7.48 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 4H), 7.01 (s, 2H), 6.87 – 6.81 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.38 – 5.31 (m, 1H), 4.84 (q, *J* = 5.8 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.20 (d, *J* = 16.8 Hz, 2H), 4.16 – 4.05 (m, 3H), 3.24 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.71 (s, 3H), 3.24 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.14 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.44 (s, 9H), 1.29 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.8, 173.5, 171.3, 168.8, 162.7, 155.5, 148.8, 147.7, 139.7, 136.4, 133.4, 133.3, 131.8, 128.8, 128.6, 128.4, 118.5, 110.3, 79.9, 53.1, 52.5, 50.1, 42.8, 39.8, 36.7, 28.4, 18.8; HRMS (ESI-TOF) (*m/z*) calculated $C_{41}H_{45}N_4O_9^+$ : 737.3186, found 737.3185 $[M+H]^+$.

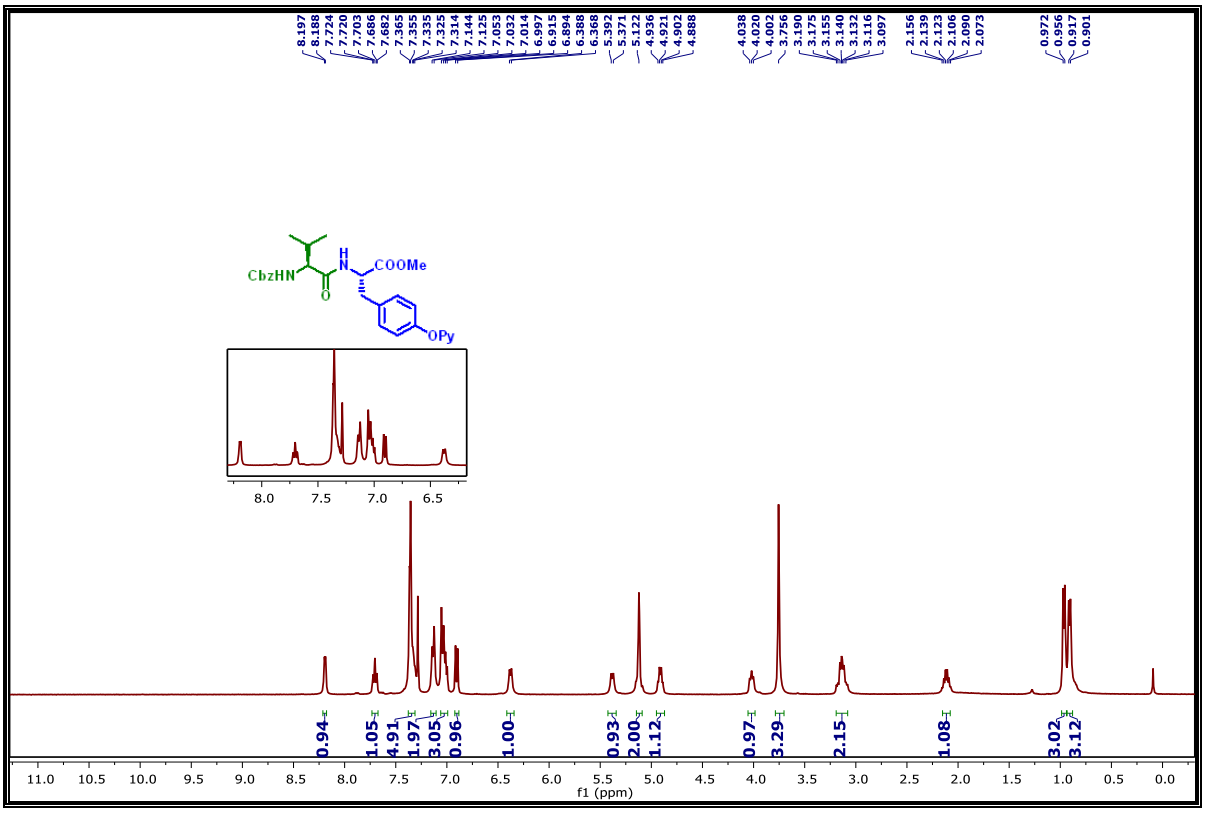
**Methyl (*S*)-15-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)benzyl)-2,2-dimethyl-4,7,10,13-tetraoxo-3-oxa-5,8,11,14-tetraazahexadecan-16-oate (3qa).** Purification by column chromatography (hexanes/ethyl acetate = 2:8) afforded compound **3qa** as a pale yellow semisolid; yield: 0.048 g (48%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, *J* = 5.2 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 4H), 7.73 – 7.67 (m, 1H), 7.66 – 7.60 (m, 1H), 7.58 – 7.50 (m, 3H), 7.41 (t, *J* = 7.4 Hz, 4H), 6.99 (s, 2H), 6.98 – 6.94 (m, 1H), 6.87 (t, *J* = 5.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.61 – 5.49 (m, 1H), 4.91 (q, *J* = 6.1 Hz, 1H), 4.25 – 4.12 (m, 4H), 4.05 (dd, *J* = 16.2, 5.4 Hz, 1H), 3.94 (d, *J* = 6.0 Hz, 2H), 3.85 – 3.77 (m, 3H), 3.75 (s, 3H), 3.23 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.15 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.39 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.9, 171.9, 171.3, 170.1, 169.0, 162.6, 156.3, 149.0, 147.3, 139.9, 136.4, 133.5, 133.3, 132.1, 128.9, 128.7, 128.3, 118.6, 110.7, 79.9, 52.7, 52.6, 44.1, 43.4, 42.9, 40.0, 36.6, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{42}H_{46}N_5O_{10}^+$ : 780.3244, found 780.3243 $[M+H]^+$.

**Methyl (5*S*,8*S*,15*S*,18*S*)-15-(((benzyloxy)carbonyl)amino)-18-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)benzyl)-5-isopropyl-8-methyl-3,6,9,16-tetraoxo-1-phenyl-2-oxa-4,7,10,17-tetraazanonadecan-19-oate (3ra).** Purification by column chromatography (hexanes/ethyl acetate = 2:8) afforded compound **3ra** as a pale yellow

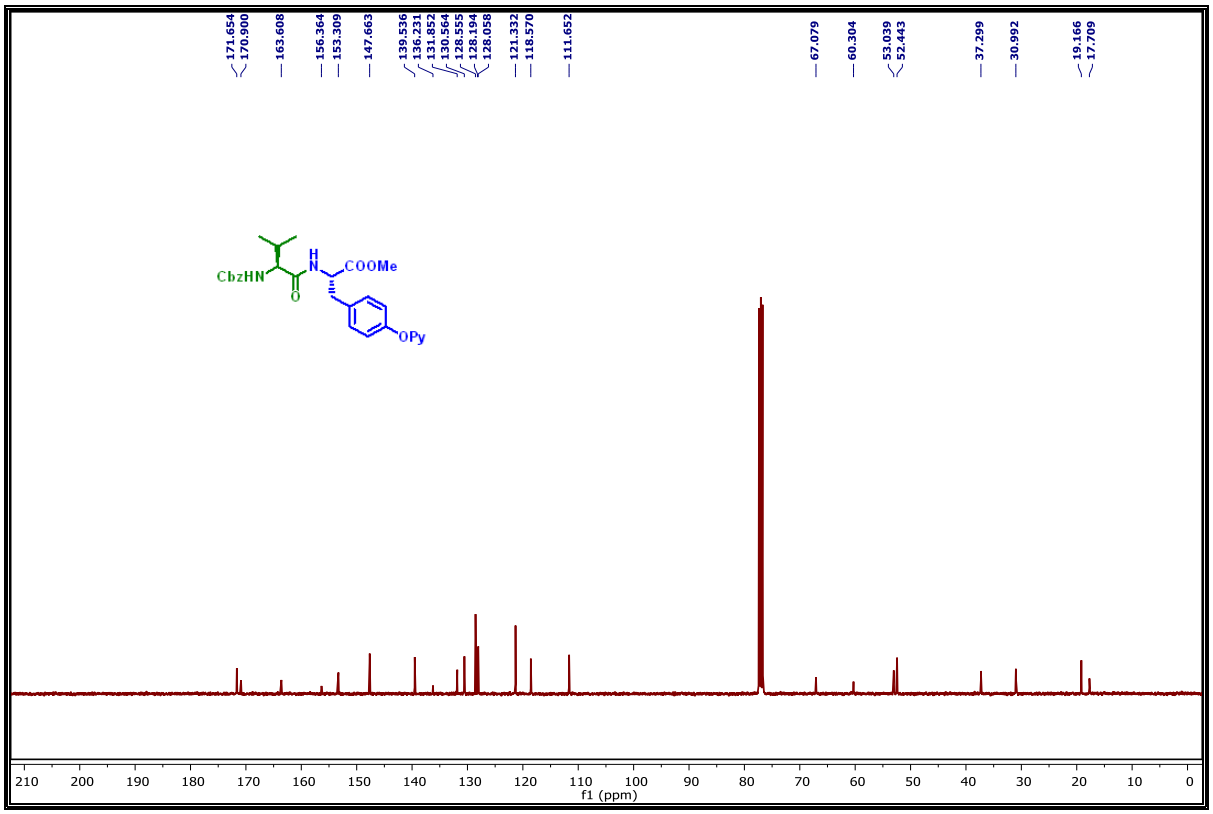
semisolid; yield: 0.038 g (43%); $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.48 (d, $J$ = 6.8 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.94 (d, $J$ = 3.2 Hz, 1H), 7.79 (d, $J$ = 7.6 Hz, 4H), 7.66 (d, $J$ = 9.2 Hz, 1H), 7.62 – 7.51 (m, 4H), 7.46 – 7.38 (m, 5H), 7.37 – 7.29 (m, 9H), 7.27 – 7.23 (m, 1H), 7.15 (s, 2H), 6.93 (t, $J$ = 5.8 Hz, 1H), 6.64 (d, $J$ = 8.4 Hz, 1H), 5.02 (s, 2H), 4.93 (q, $J$ = 11.7 Hz, 2H), 4.49 (q, $J$ = 7.2 Hz, 1H), 4.11 (brs, 4H), 4.09 – 4.02 (m, 3H), 3.56 (s, 3H), 3.50 – 3.44 (m, 2H), 3.14 – 3.06 (m, 1H), 3.00 (d, $J$ = 7.2 Hz, 2H), 2.95 – 2.88 (m, 1H), 1.94 – 1.81 (m, 1H), 1.64 – 1.56 (m, 1H), 1.53 – 1.45 (m, 1H), 1.39 – 1.32 (m, 2H), 1.18 (d, $J$ = 7.2 Hz, 3H), 0.80 (d, $J$ = 3.2 Hz, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 196.9, 172.7, 172.3, 171.0, 162.6, 156.4, 156.1, 149.3, 147.6, 140.3, 137.5, 137.3, 136.8, 134.3, 133.5, 131.7, 131.7, 129.3, 129.0, 128.8, 128.7, 128.4, 128.2, 128.2, 128.1, 128.0, 119.0, 110.5, 65.8, 58.0, 54.8, 53.9, 52.3, 50.9, 50.6, 38.7, 36.3, 31.9, 31.4, 29.1, 23.3, 19.6, 18.6; HRMS (ESI-TOF) (*m/z*) calculated $C_{61}H_{67}N_6O_{12}^+$ : 1075.4816, found 1075.4822 $[M+H]^+$.

## 5. Original NMR spectra of 1

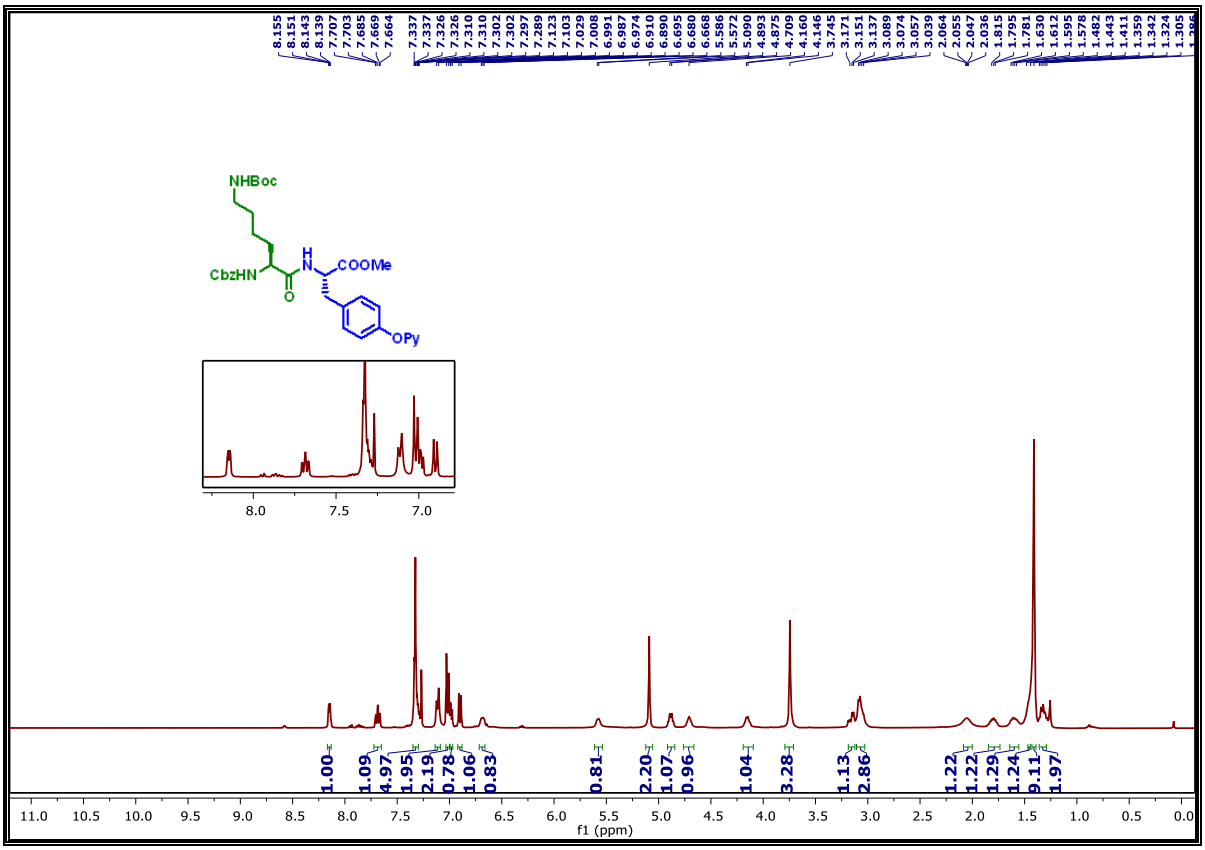
### $^{1}$H NMR of 1f (400 MHz, $CDCl_3$)



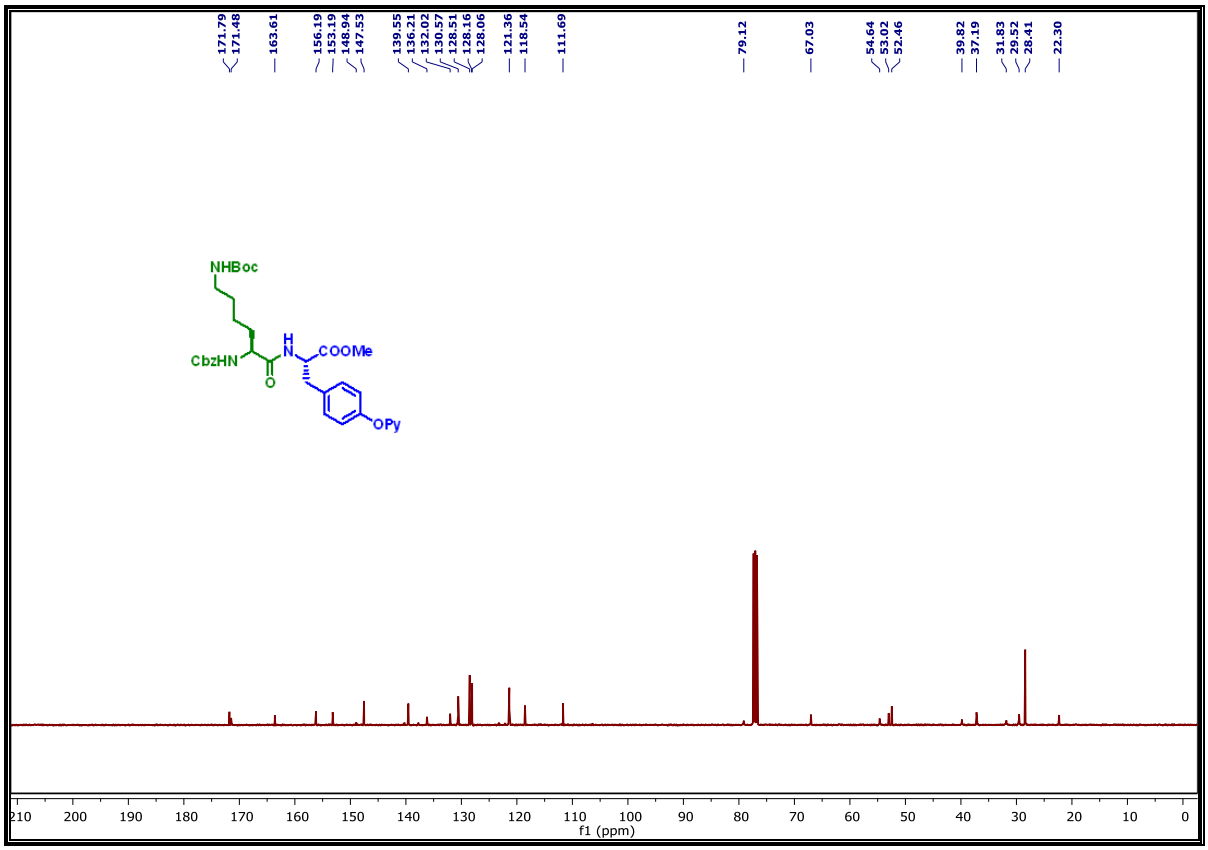

### $^{13}$C NMR of 1f (100 MHz, $CDCl_3$)



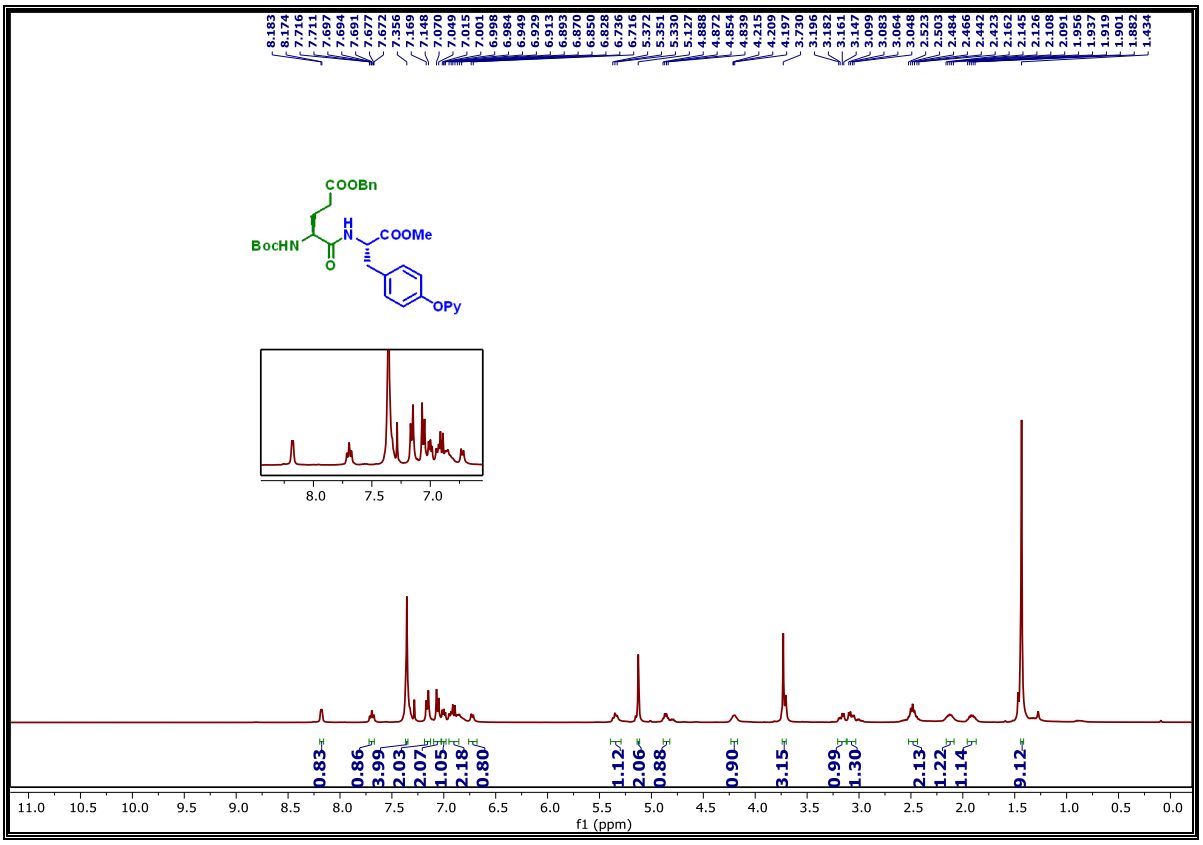
## $^{1}$H NMR of 1i (400 MHz, $CDCl_3$)



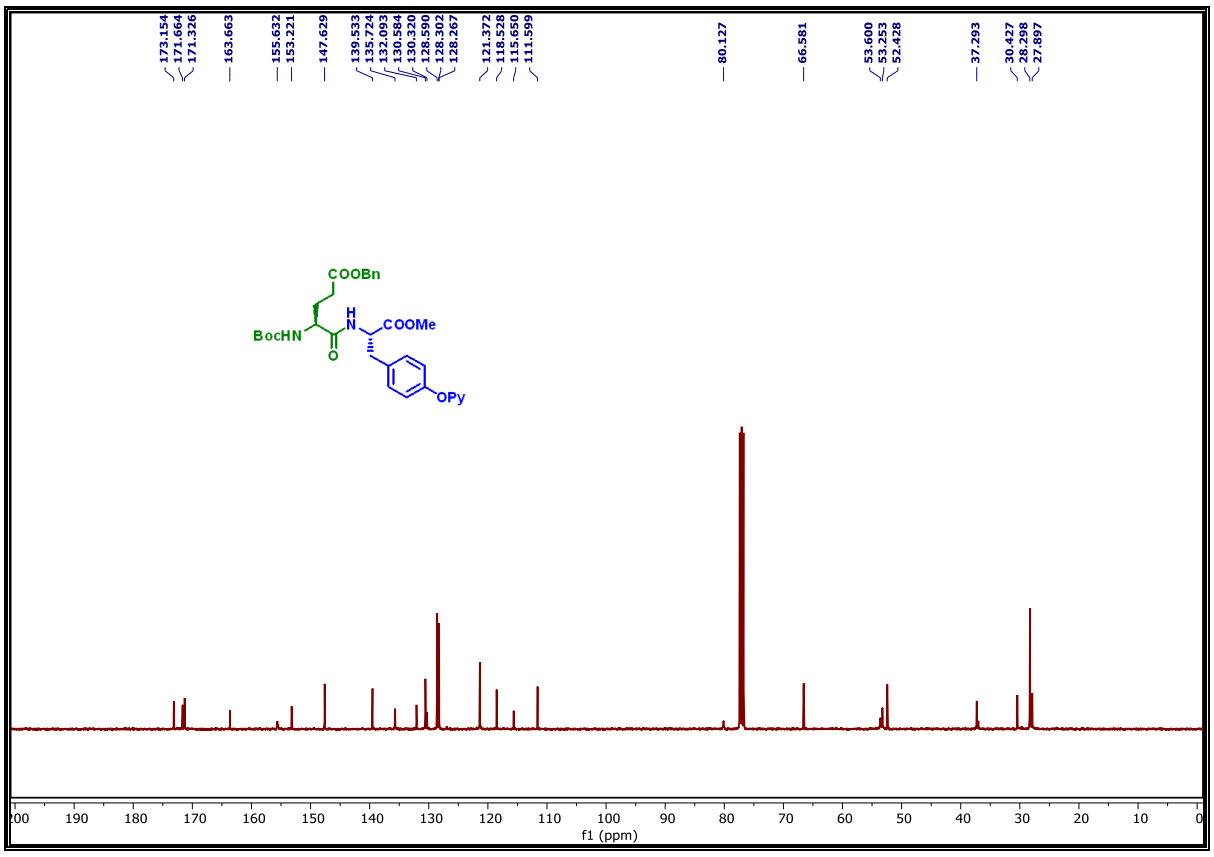

## $^{13}$C NMR of 1i (100 MHz, $CDCl_3$)



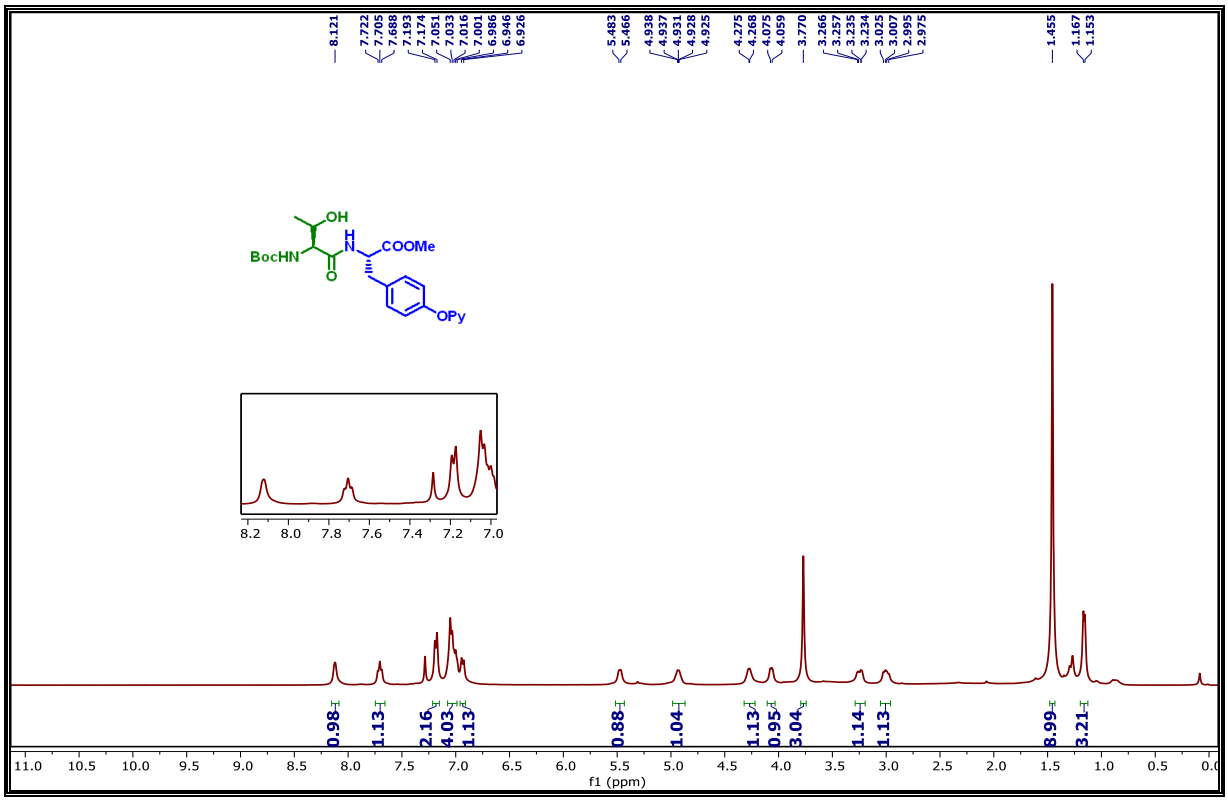
## $^{1}$H NMR of 1j (400 MHz, $CDCl_3$)



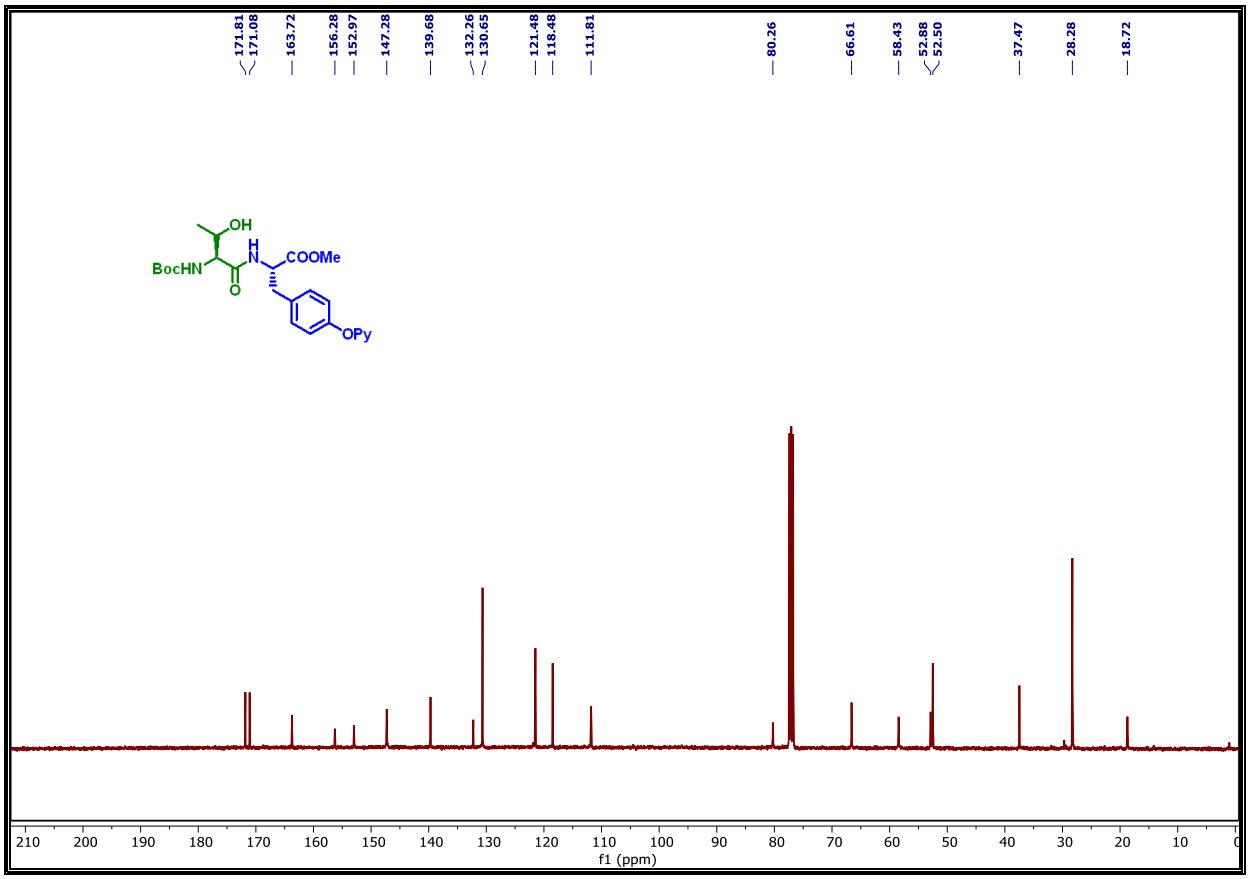

## $^{13}$C NMR of 1j (100 MHz, $CDCl_3$)



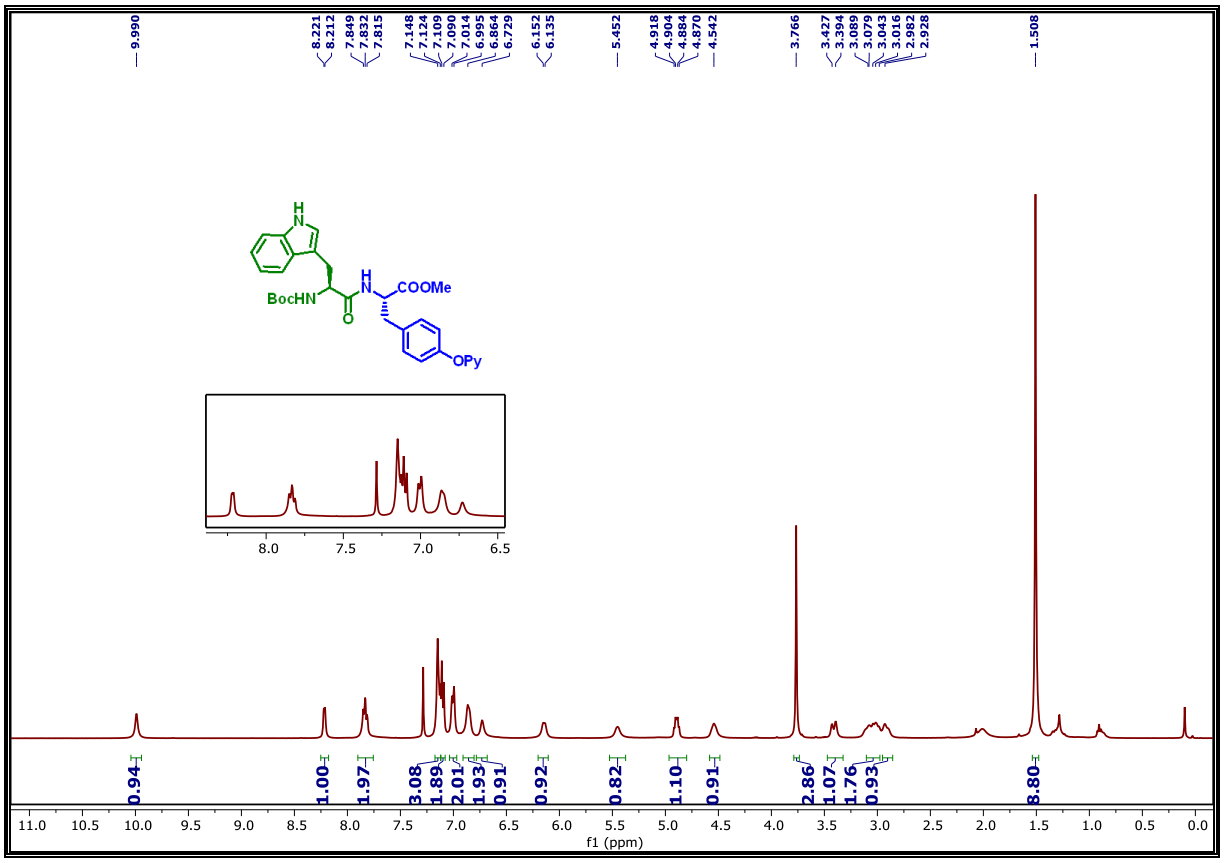
## $^{1}$H NMR of 1l (400 MHz, $CDCl_3$)



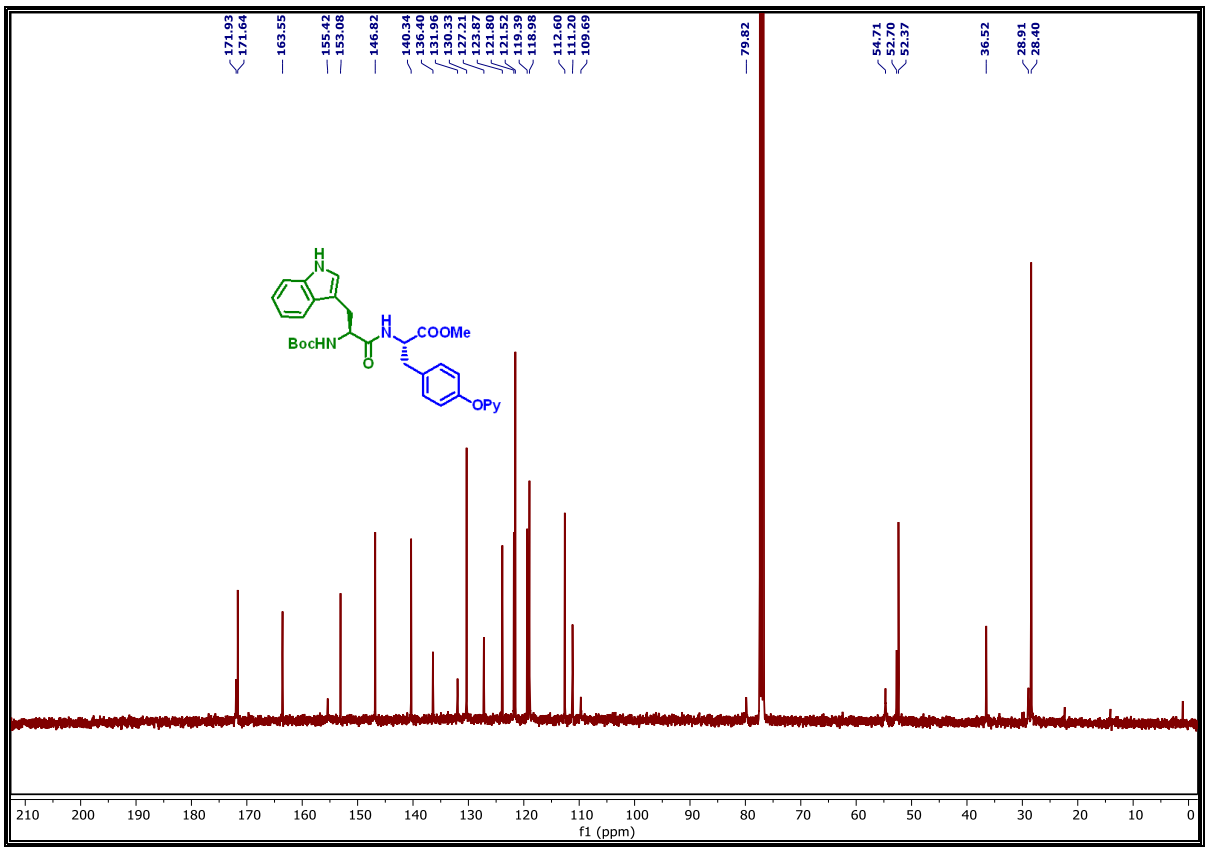

## $^{13}$C NMR of 1l (100 MHz, $CDCl_3$)



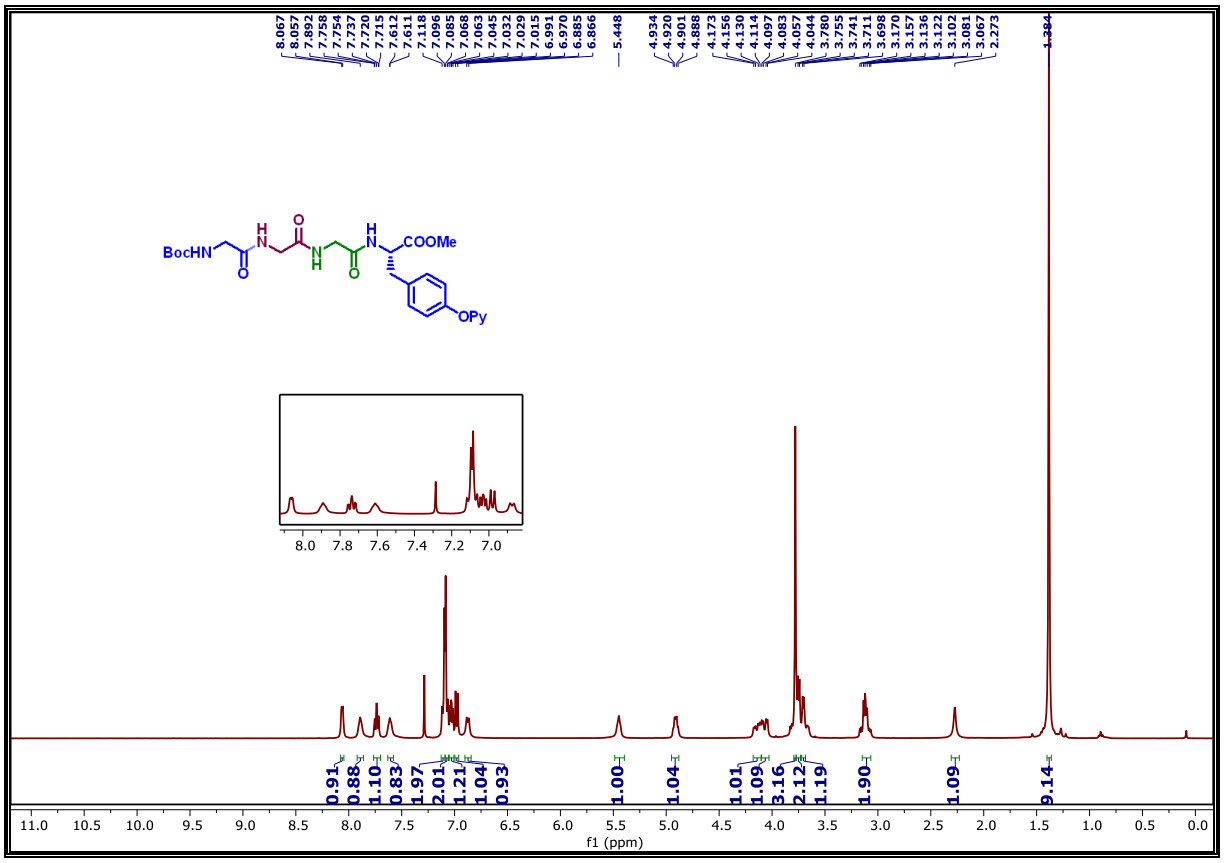
## $^{1}$H NMR of 1n (400 MHz, $CDCl_3$)



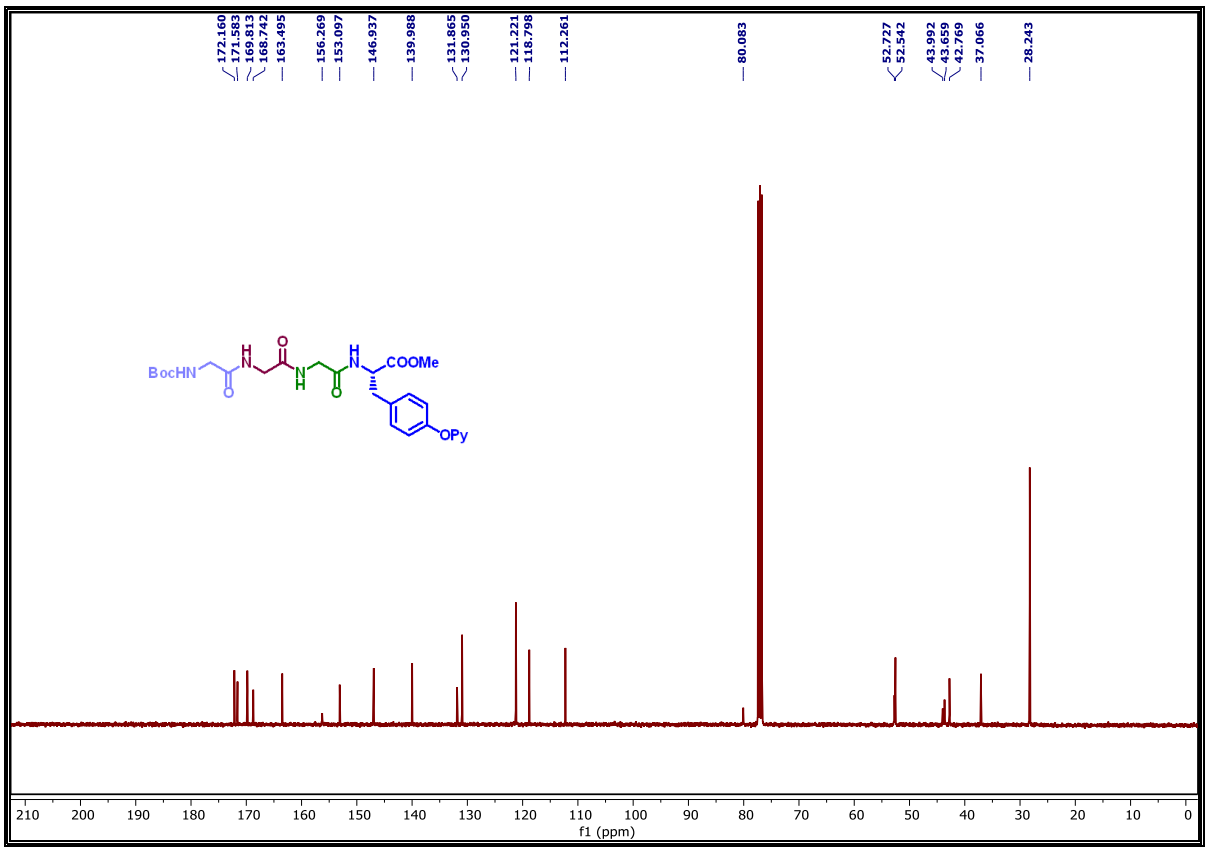

## $^{13}$C NMR of 1n (100 MHz, $CDCl_3$)



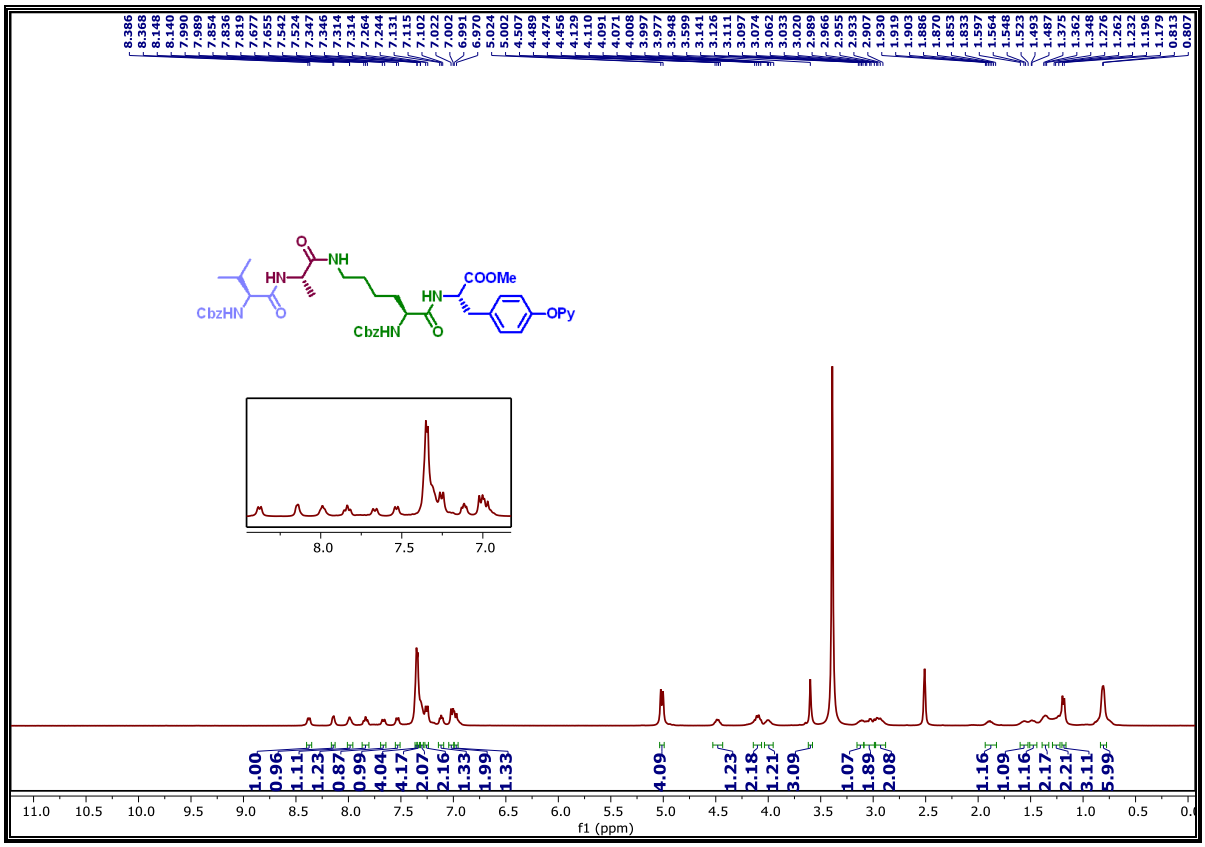
## $^{1}$H NMR of 1q (400 MHz, $CDCl_3$)



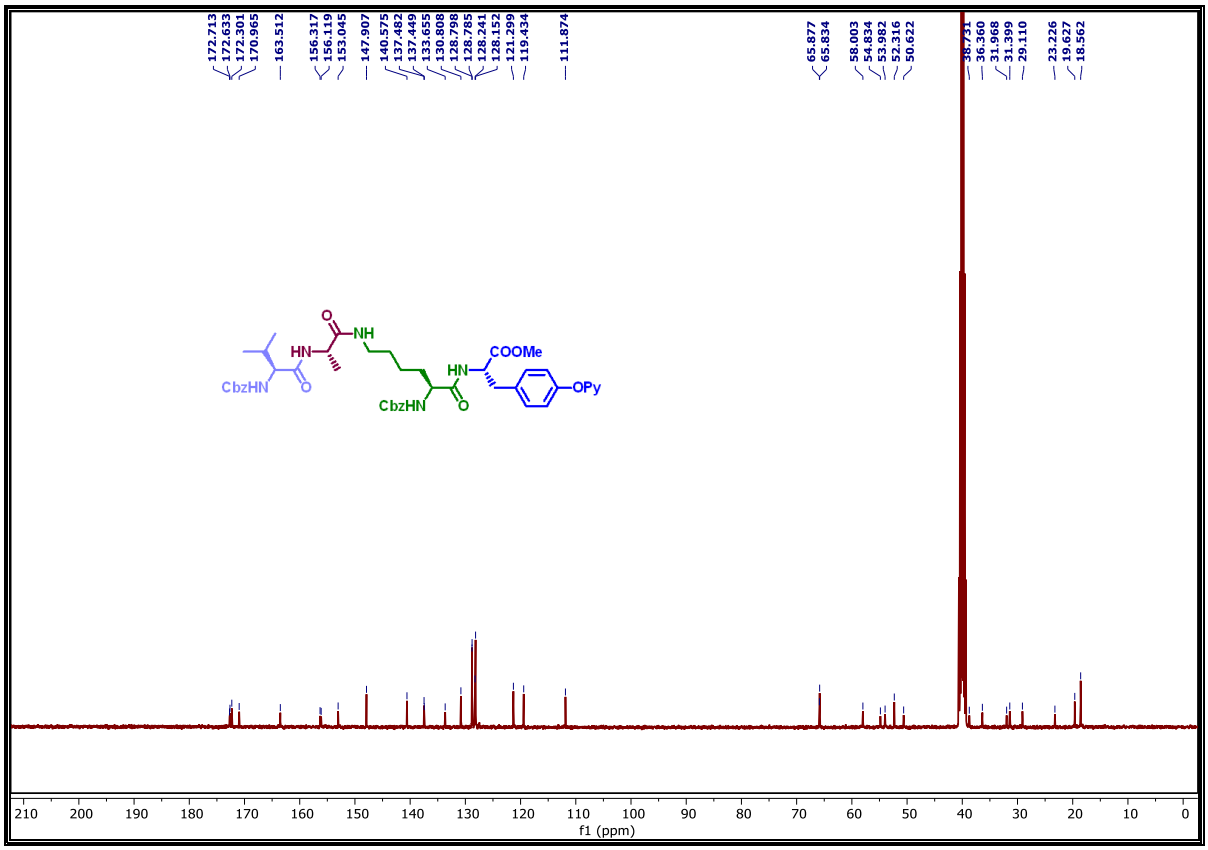

## $^{13}$C NMR of 1q (100 MHz, $CDCl_3$)



## $^{1}$H NMR of 1r (400 MHz, DMSO-$d_6$)

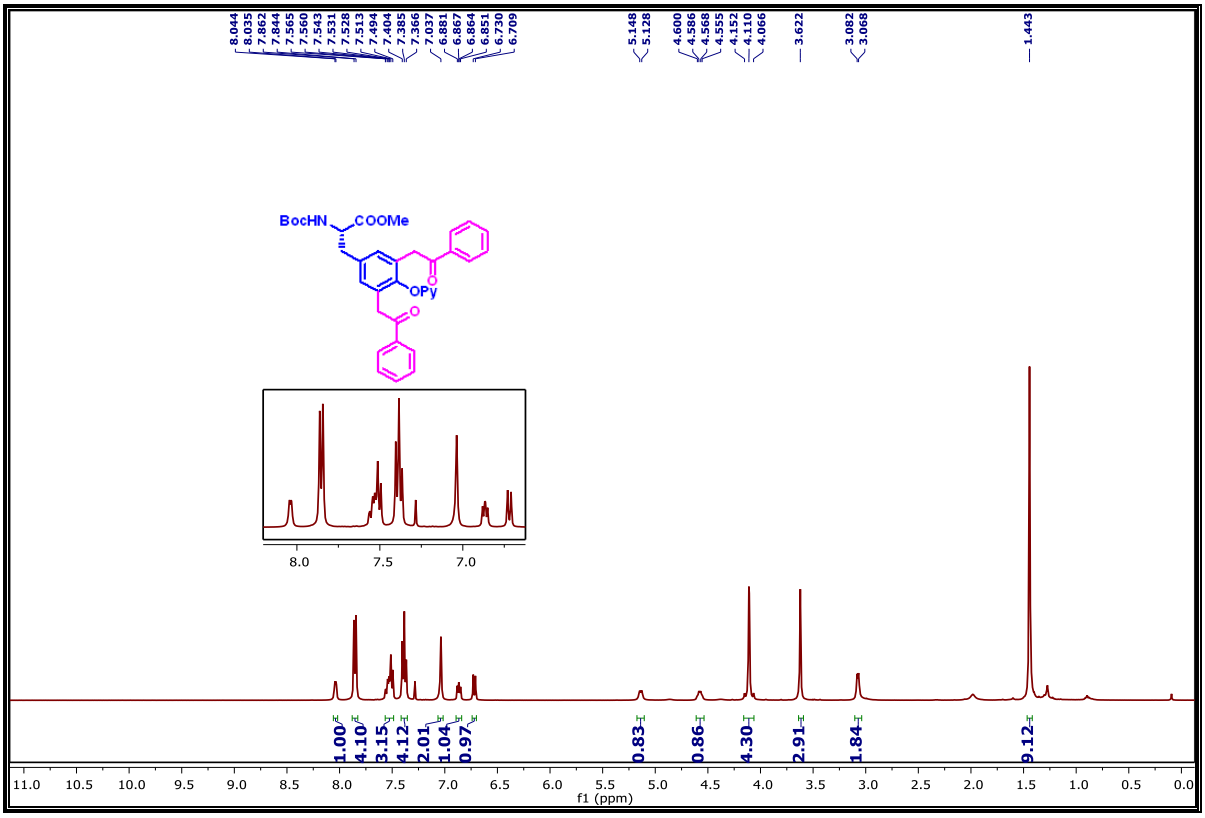



## $^{13}$C NMR of 1r (100 MHz, DMSO-$d_6$)

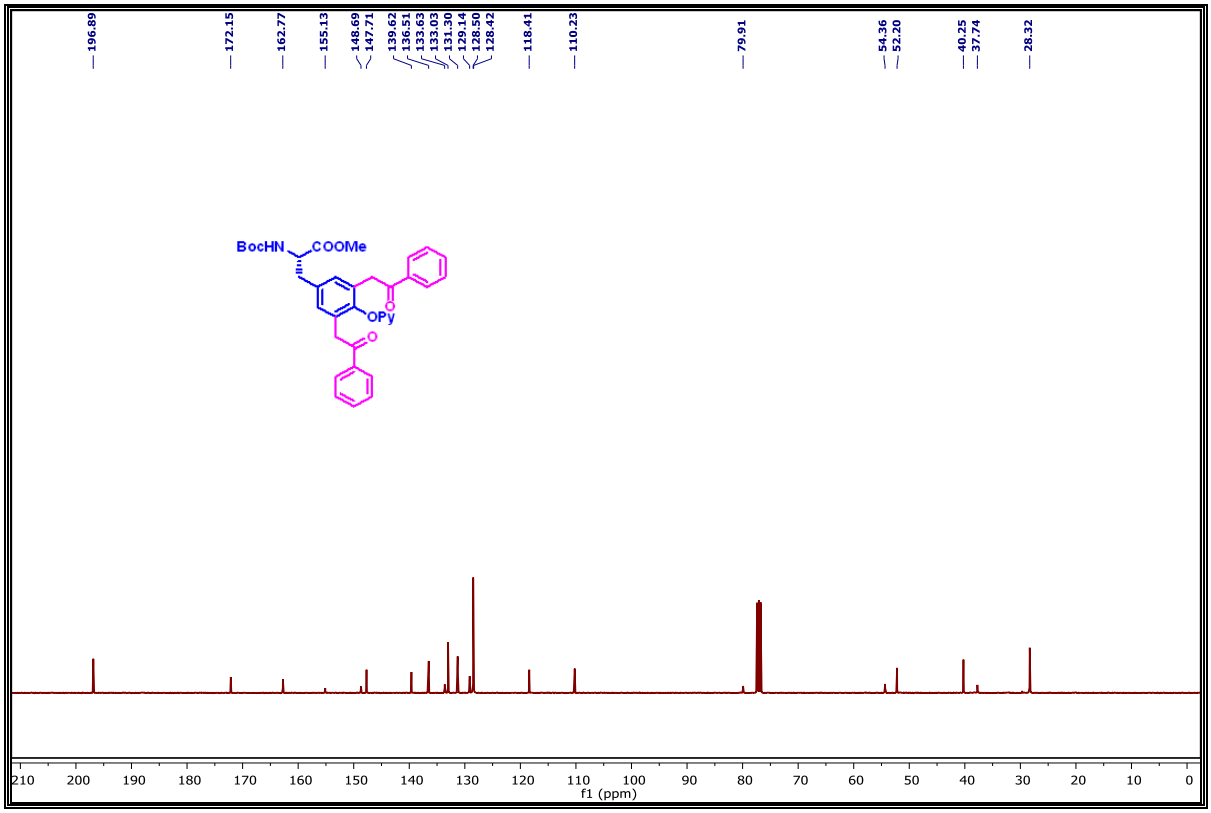


## 6. Original NMR spectra of 3

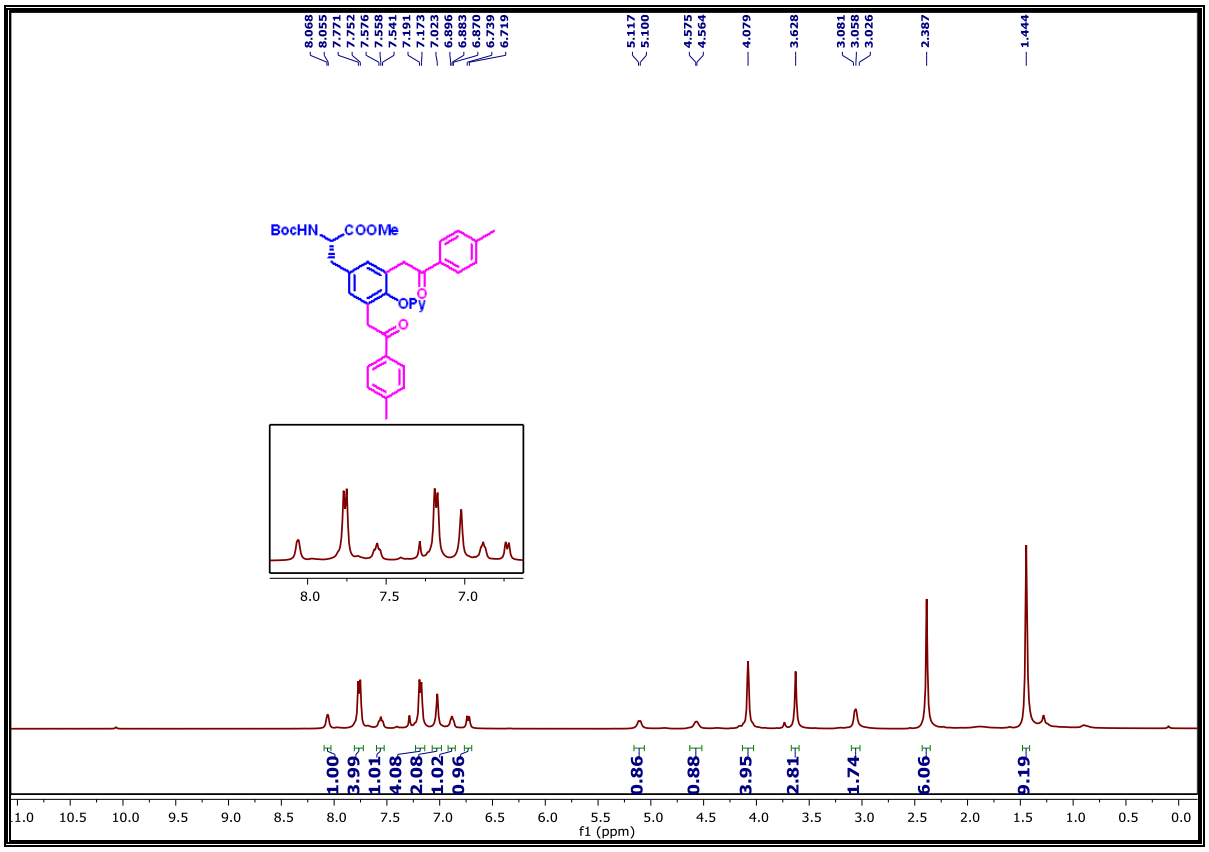
### $^{1}$H NMR of 3aa (400 MHz, $CDCl_3$)



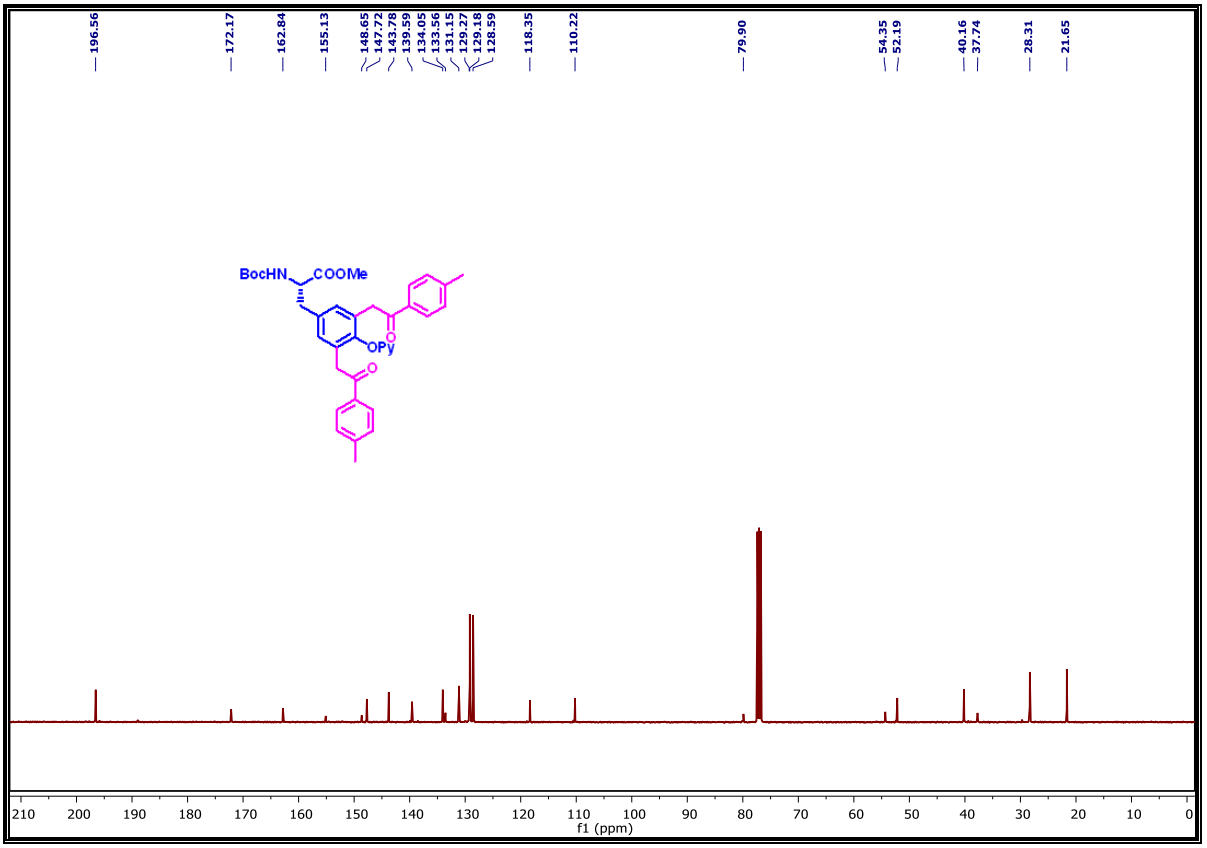

### $^{13}$C NMR of 3aa (100 MHz, $CDCl_3$)



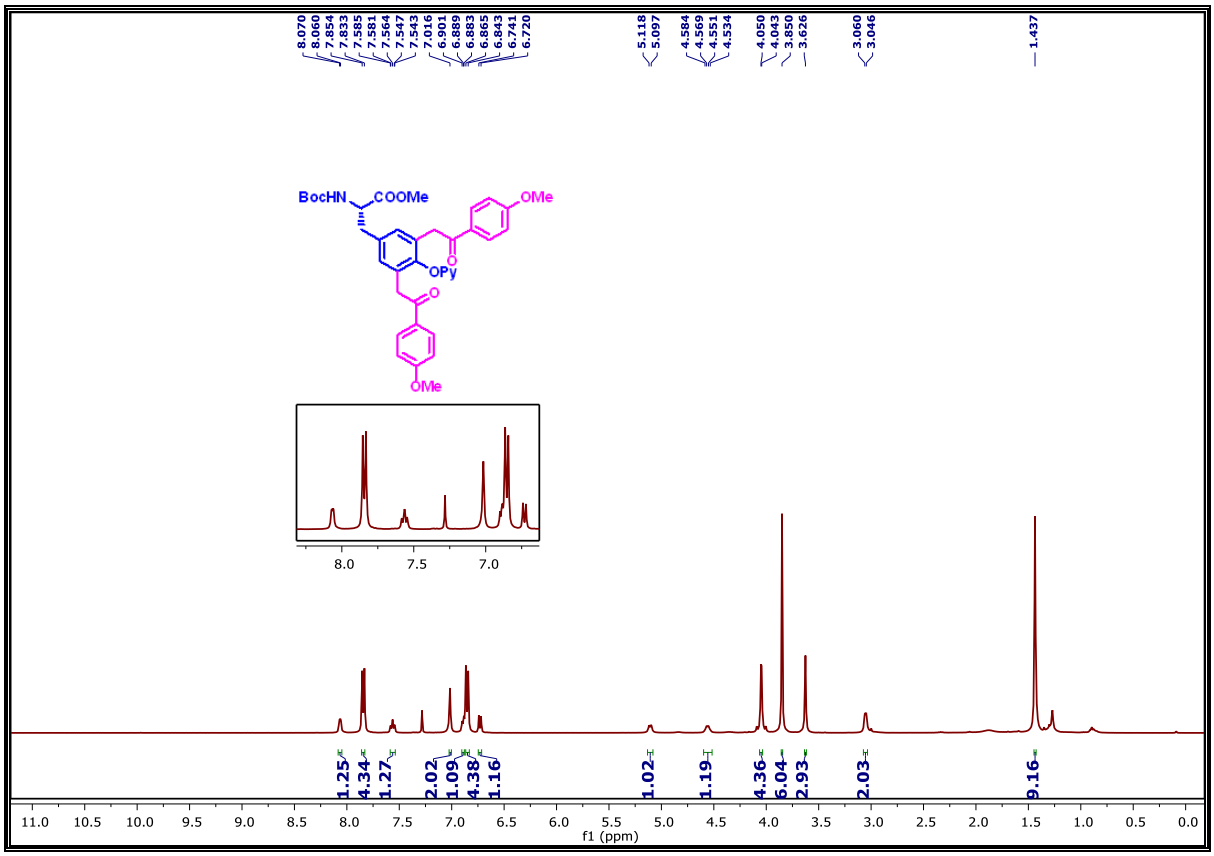
## $^{1}$H NMR of 3ab (400 MHz, $CDCl_3$)



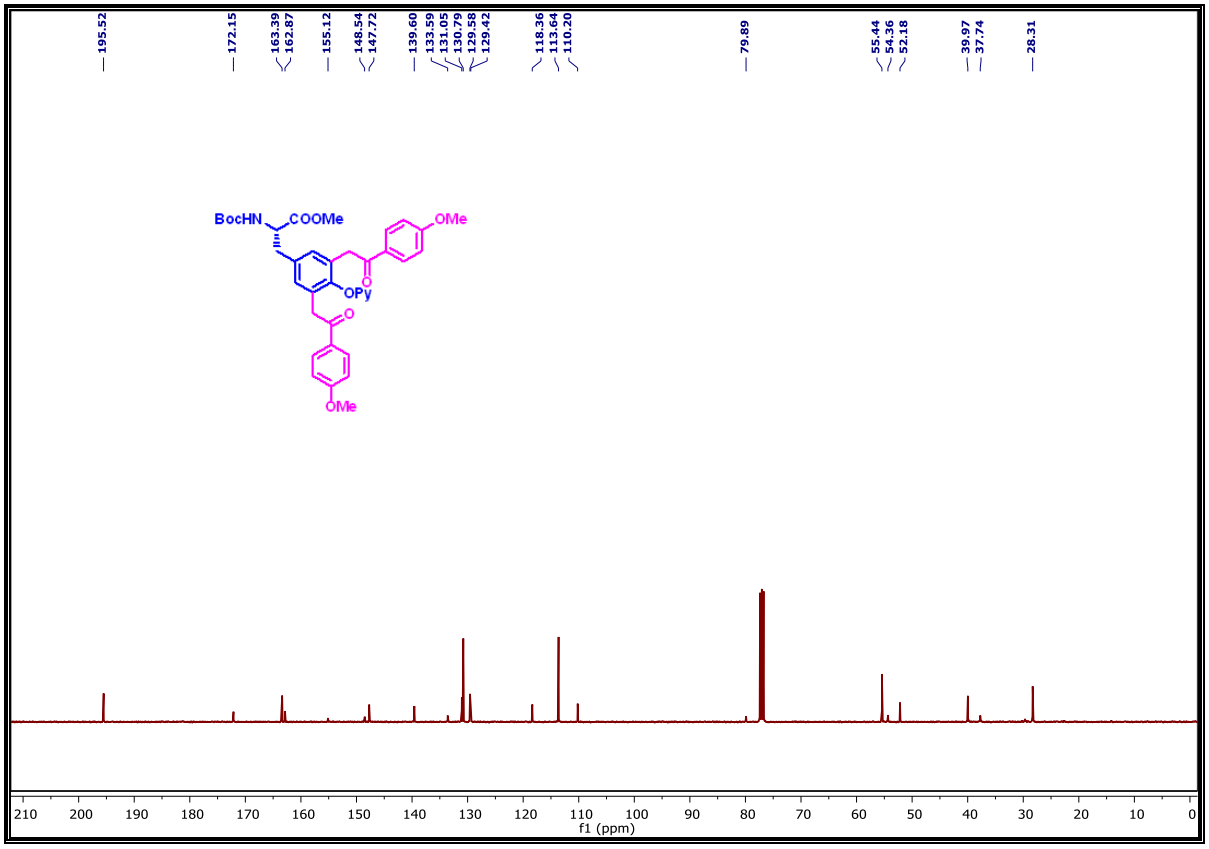

## $^{13}$C NMR of 3ab (100 MHz, $CDCl_3$)



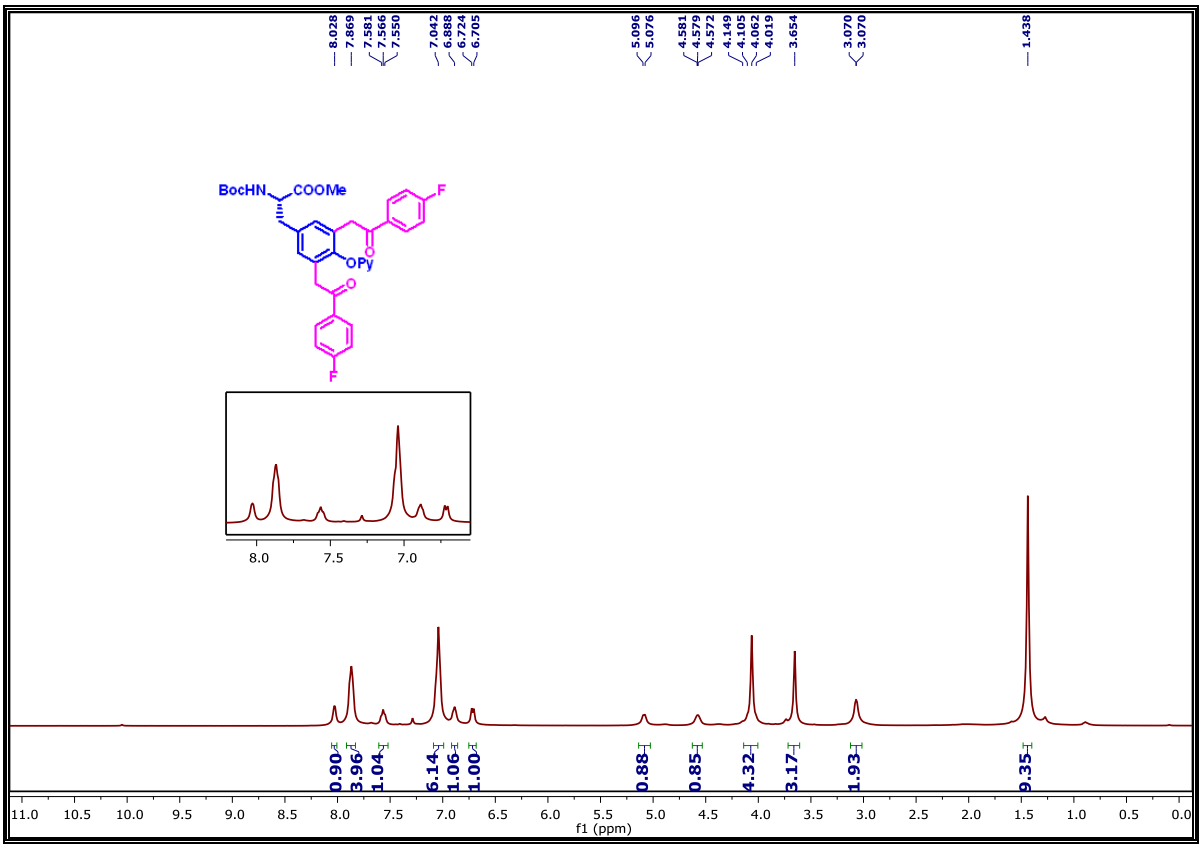
## $^{1}$H NMR of 3ac (400 MHz, $CDCl_3$)



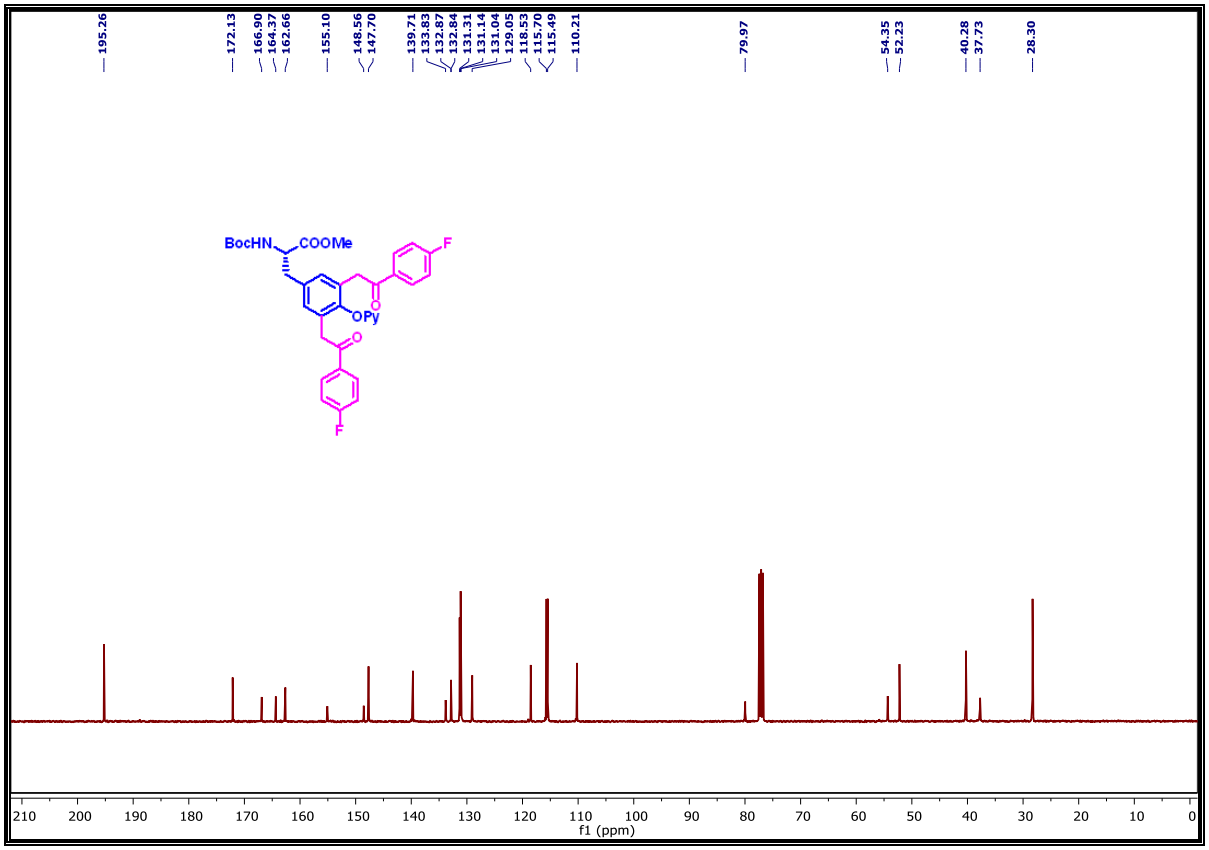

## $^{13}$C NMR of 3ac (100 MHz, $CDCl_3$)



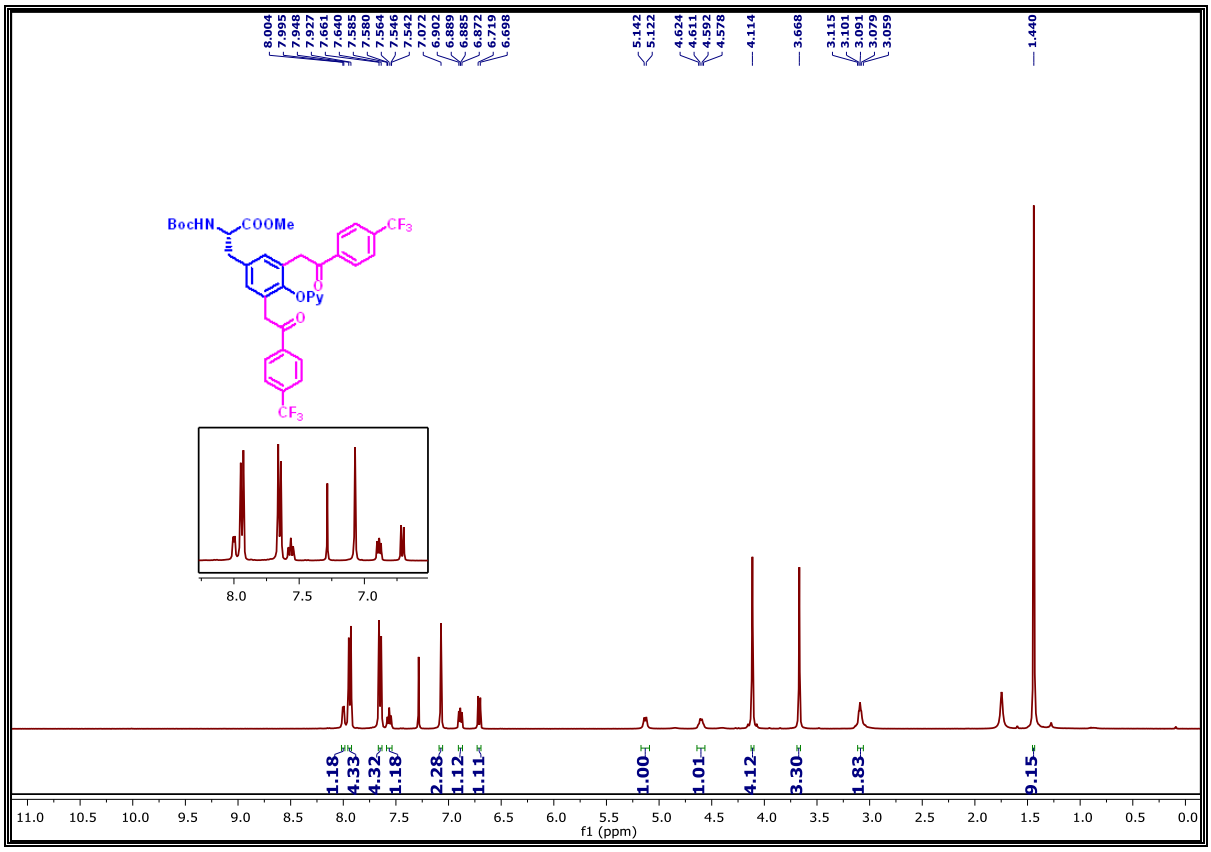
## $^{1}$H NMR of 3ad (400 MHz, $CDCl_3$)



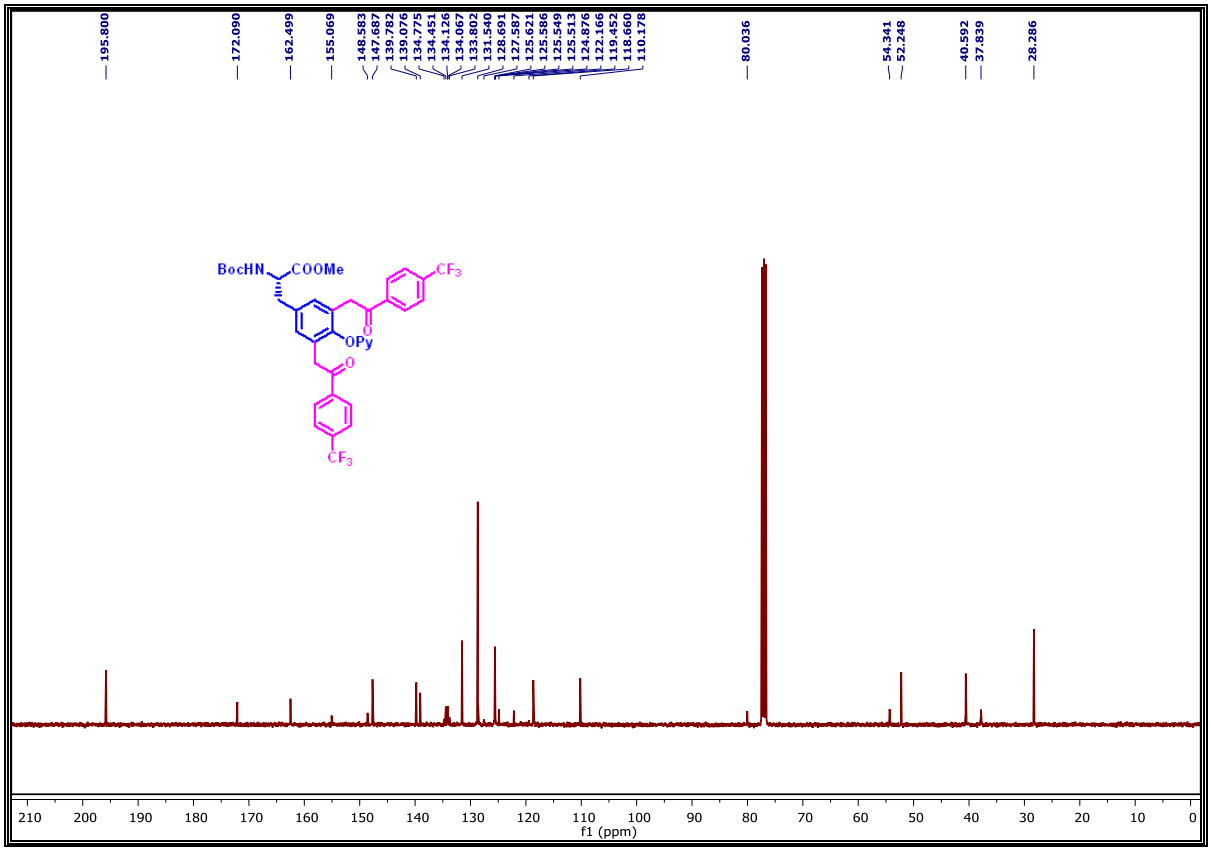

## $^{13}$C NMR of 3ad (100 MHz, $CDCl_3$)



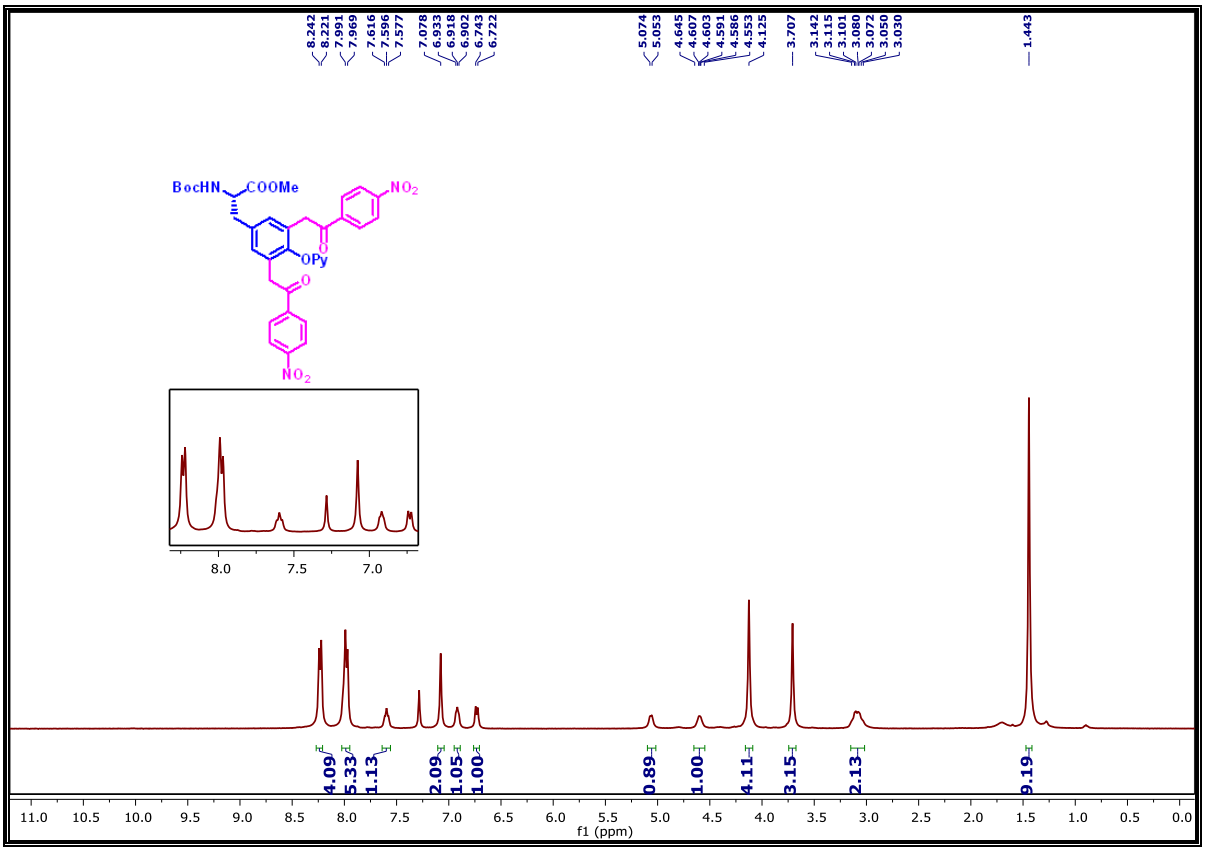
## $^{1}$H NMR of 3ae (400 MHz, $CDCl_3$)



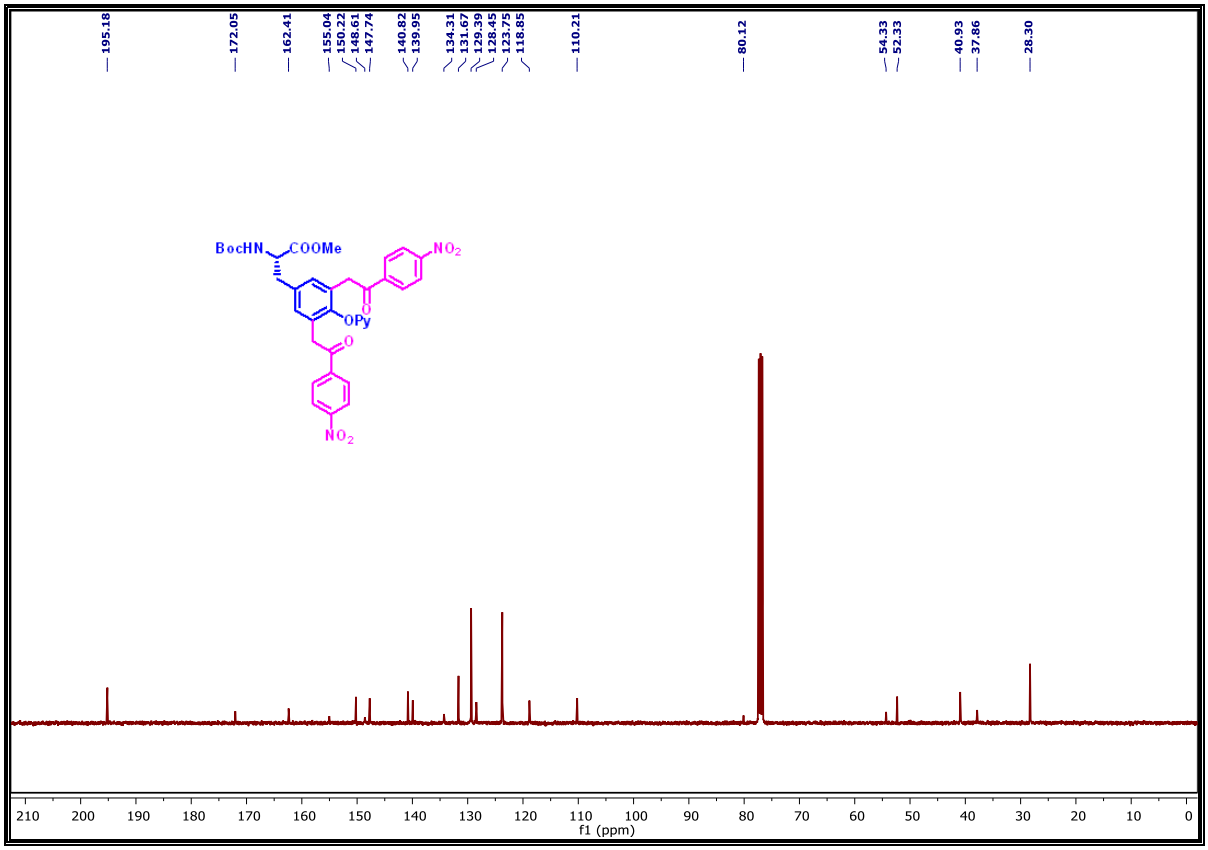

## $^{13}$C NMR of 3ae (100 MHz, $CDCl_3$)



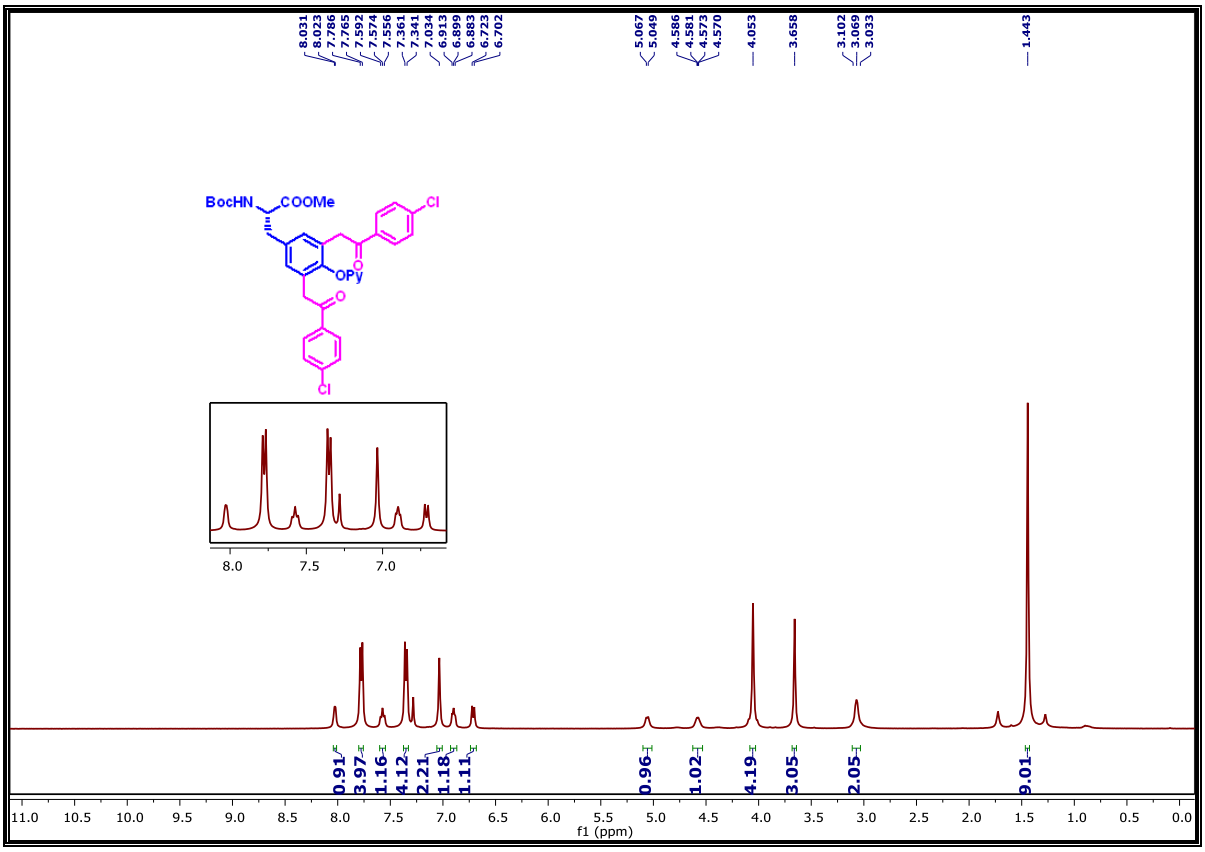
## $^{1}$H NMR of 3af (400 MHz, $CDCl_3$)



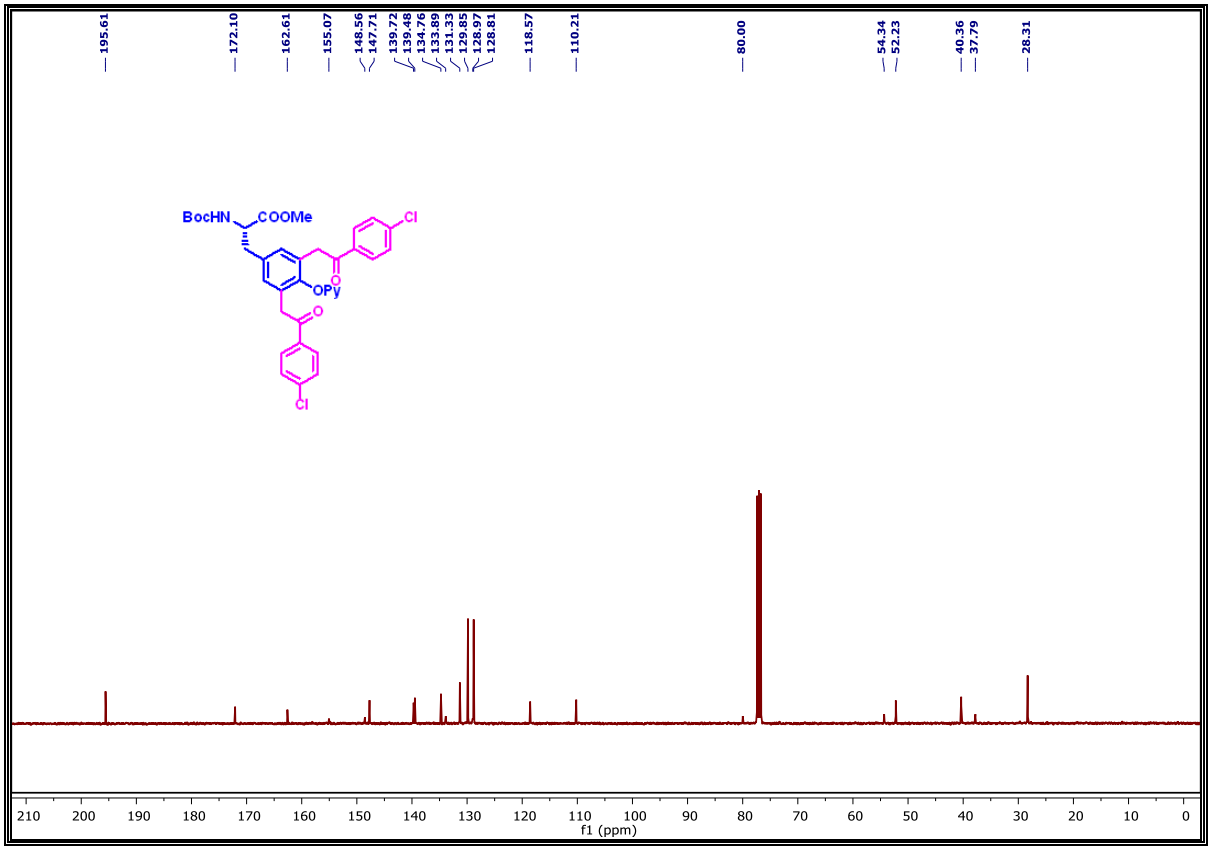

## $^{13}$C NMR of 3af (100 MHz, $CDCl_3$)



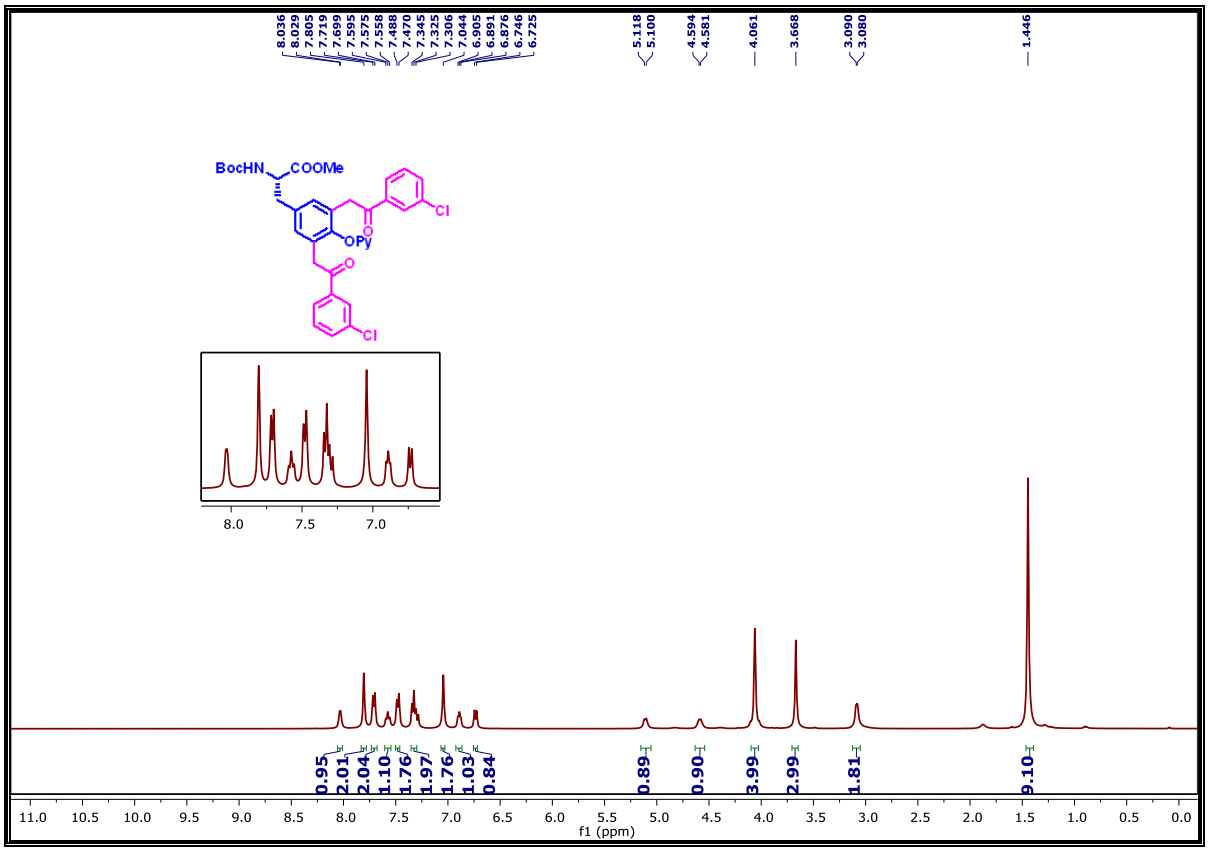
## $^{1}$H NMR of 3ag (400 MHz, $CDCl_3$)



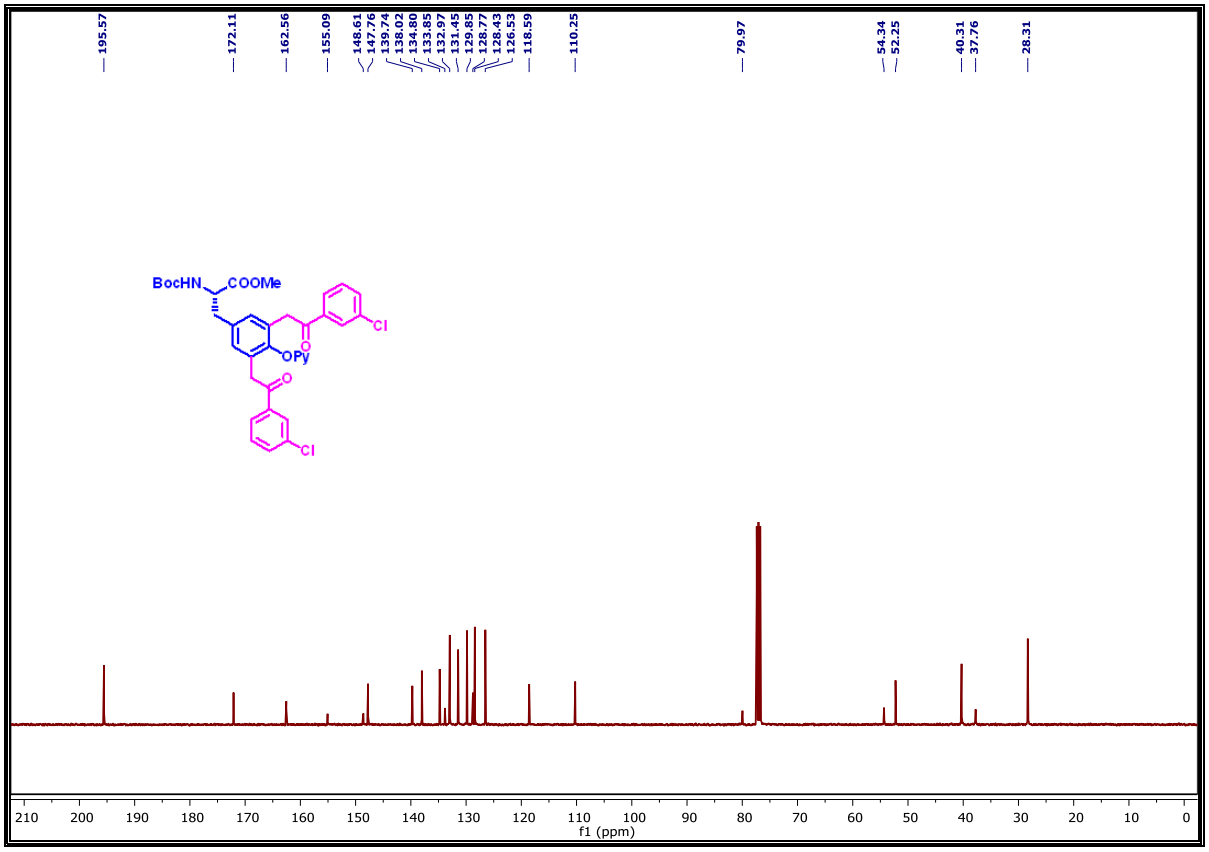

## $^{13}$C NMR of 3ag (100 MHz, $CDCl_3$)



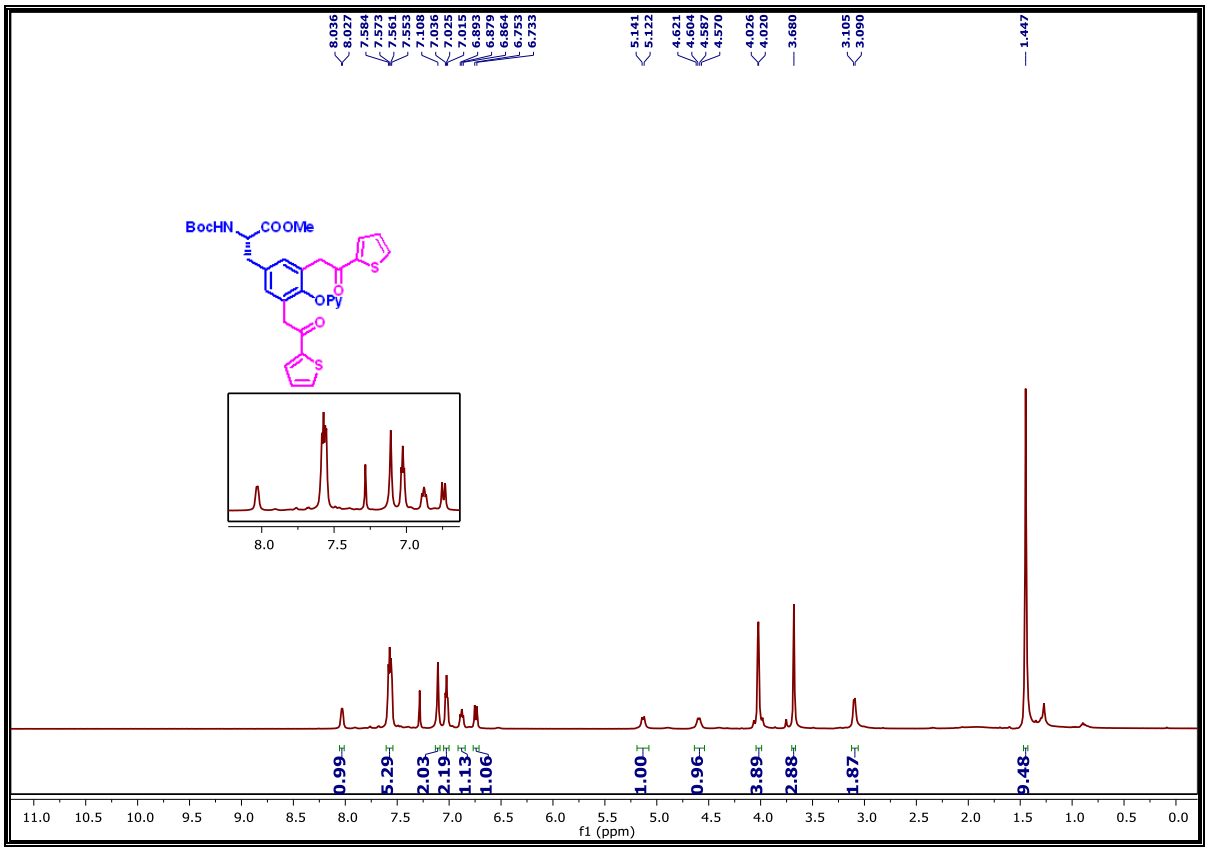
## $^{1}$H NMR of 3ah (400 MHz, $CDCl_3$)



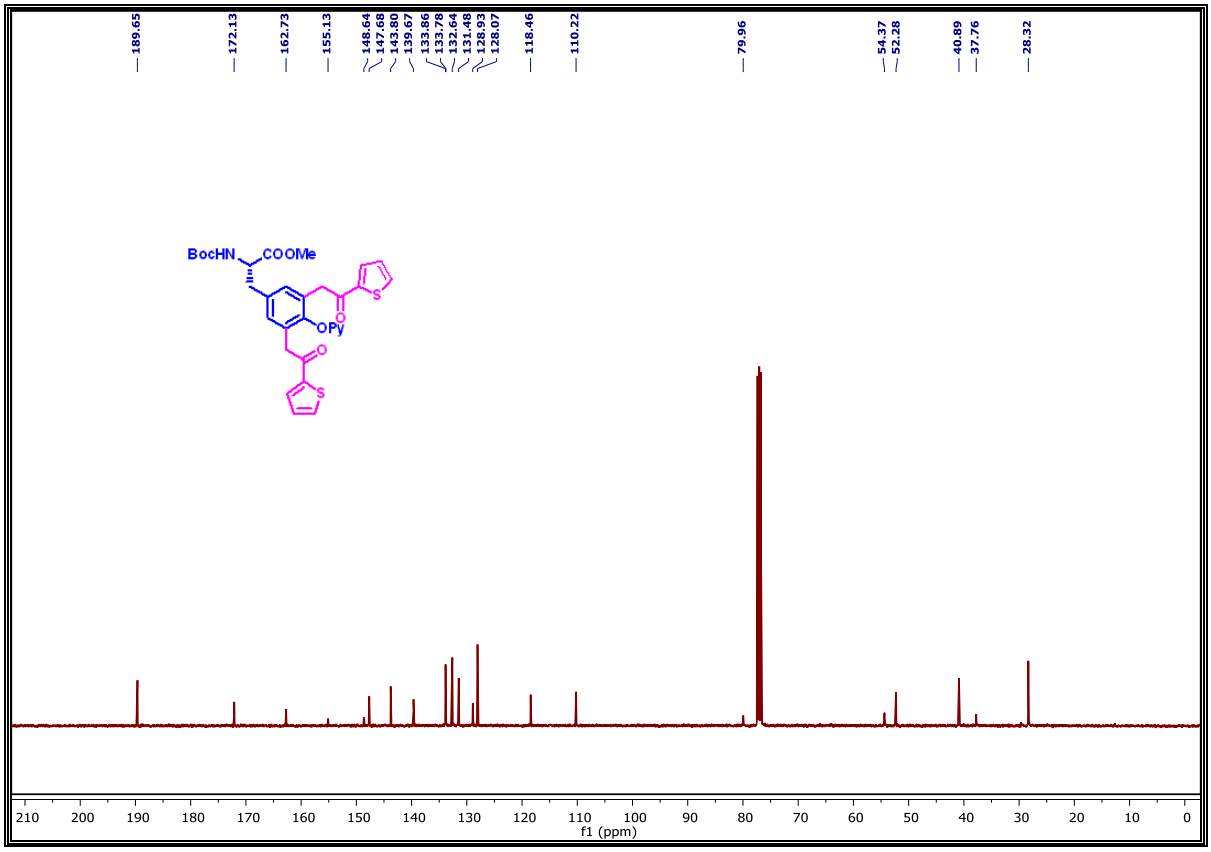

## $^{13}$C NMR of 3ah (100 MHz, $CDCl_3$)



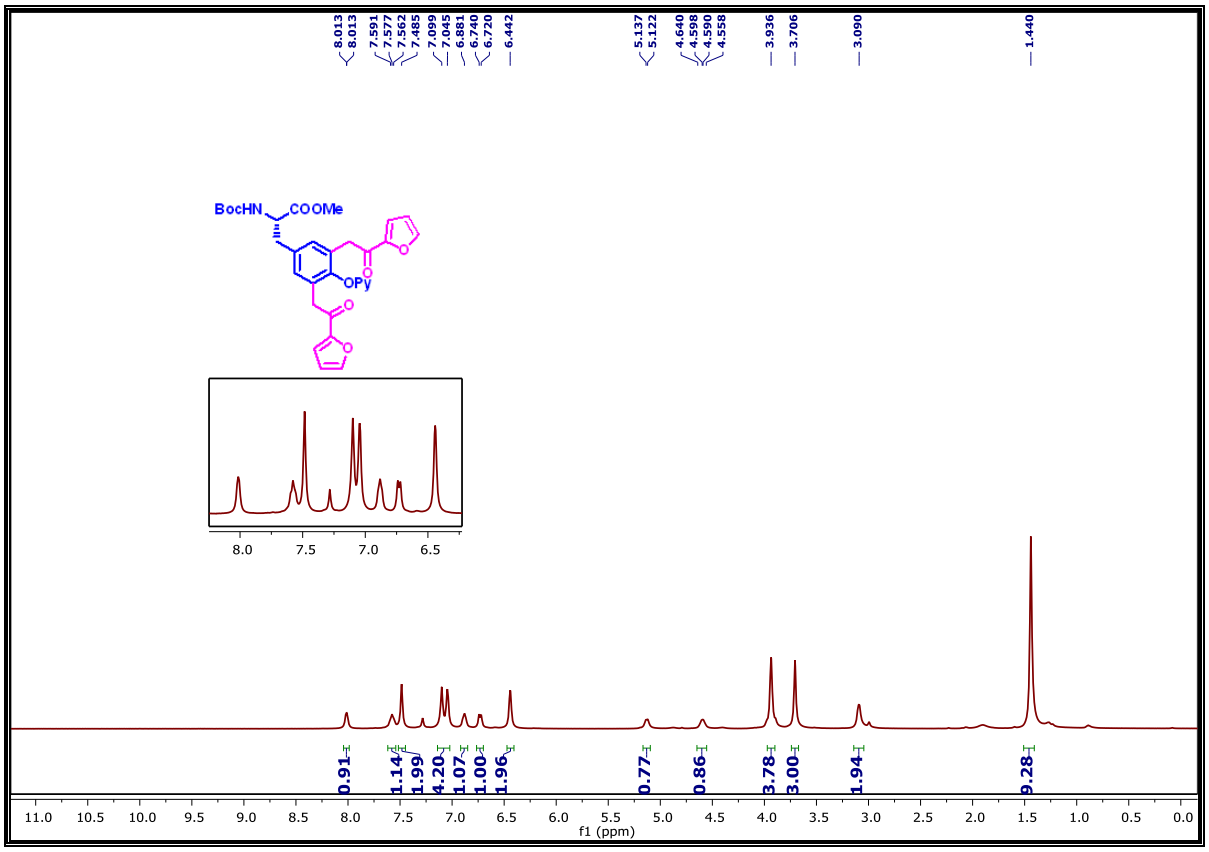
## $^{1}$H NMR of 3ai (400 MHz, $CDCl_3$)



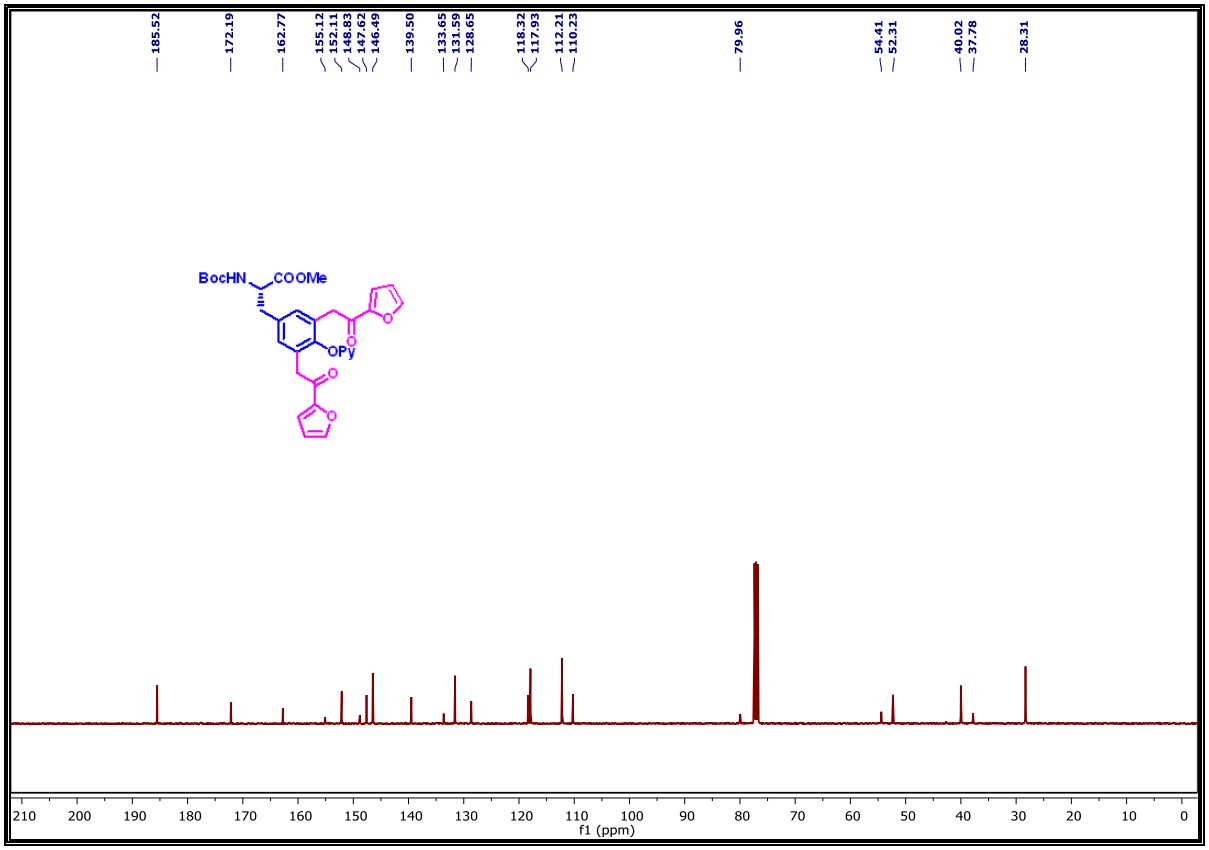

## $^{13}$C NMR of 3ai (100 MHz, $CDCl_3$)



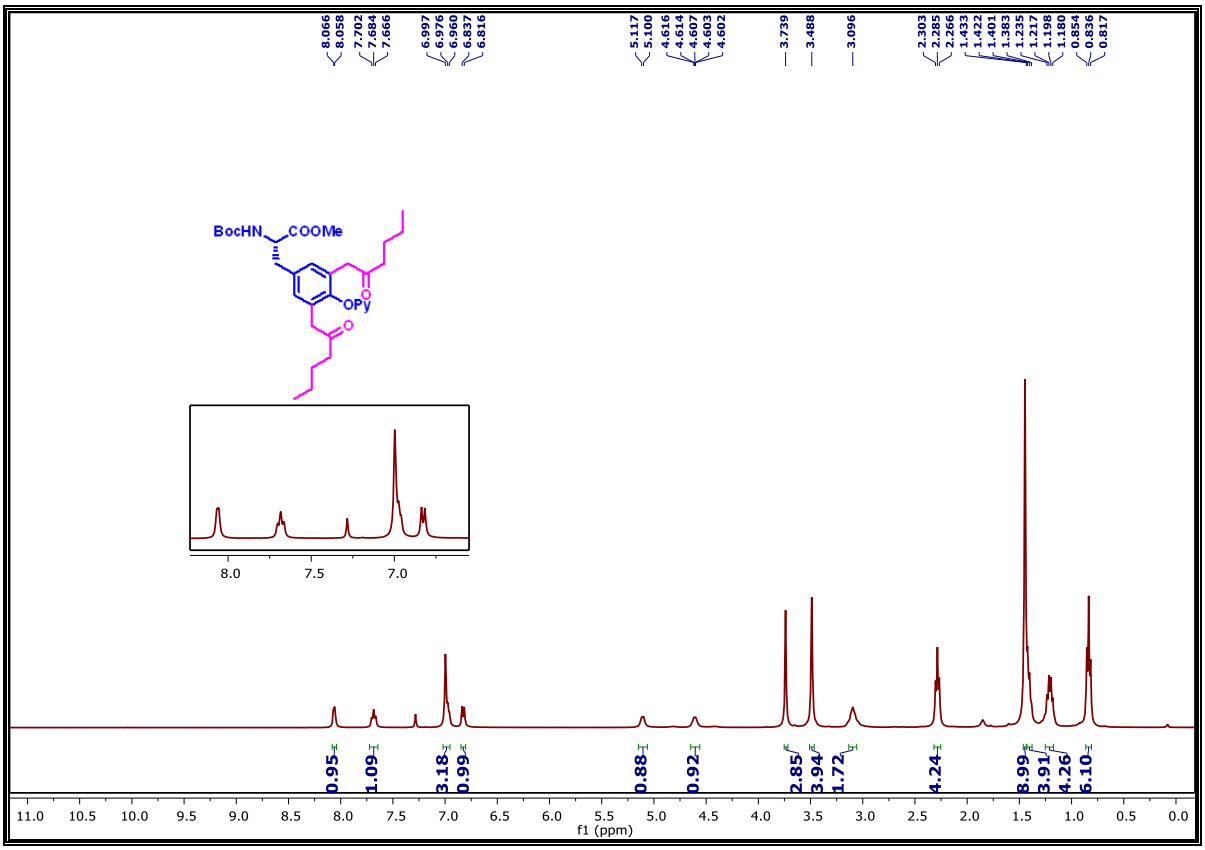
## $^{1}$H NMR of 3aj (400 MHz, $CDCl_3$)



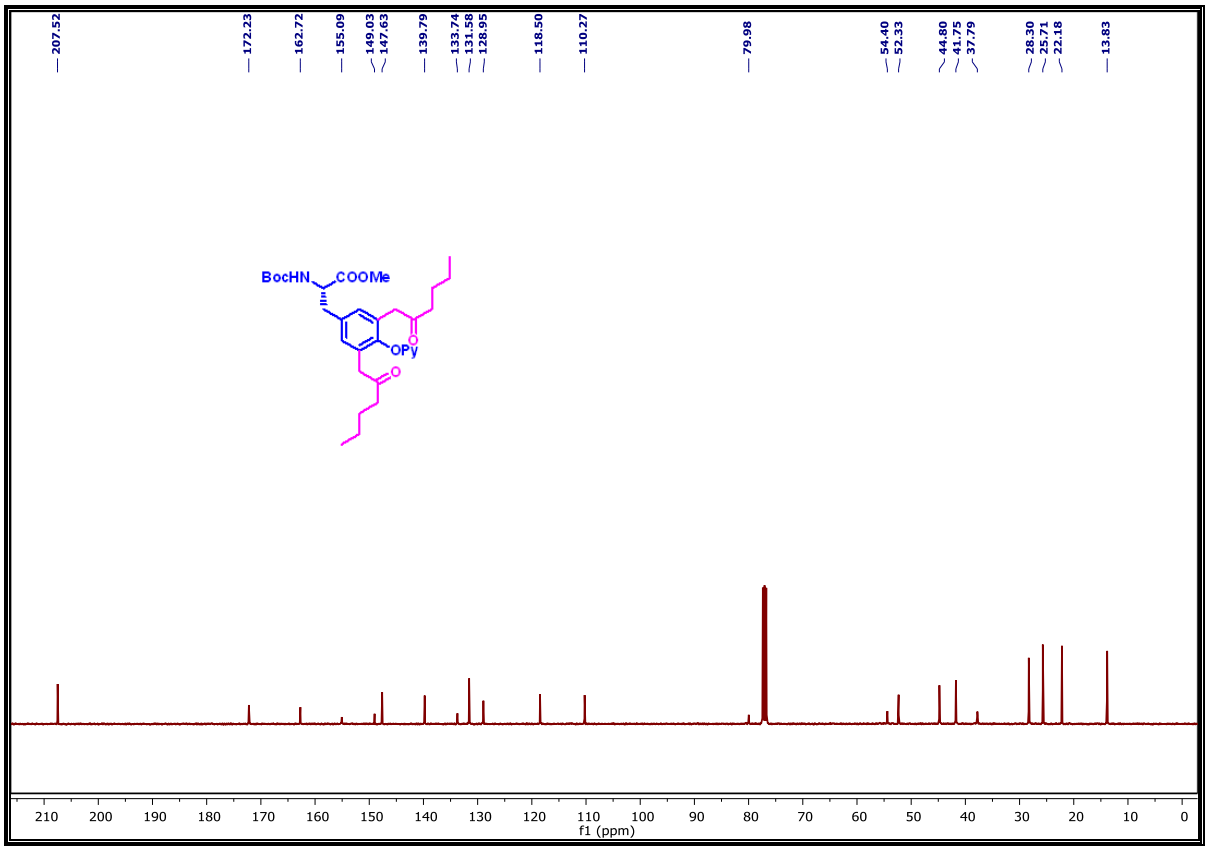

## $^{13}$C NMR of 3aj (100 MHz, $CDCl_3$)



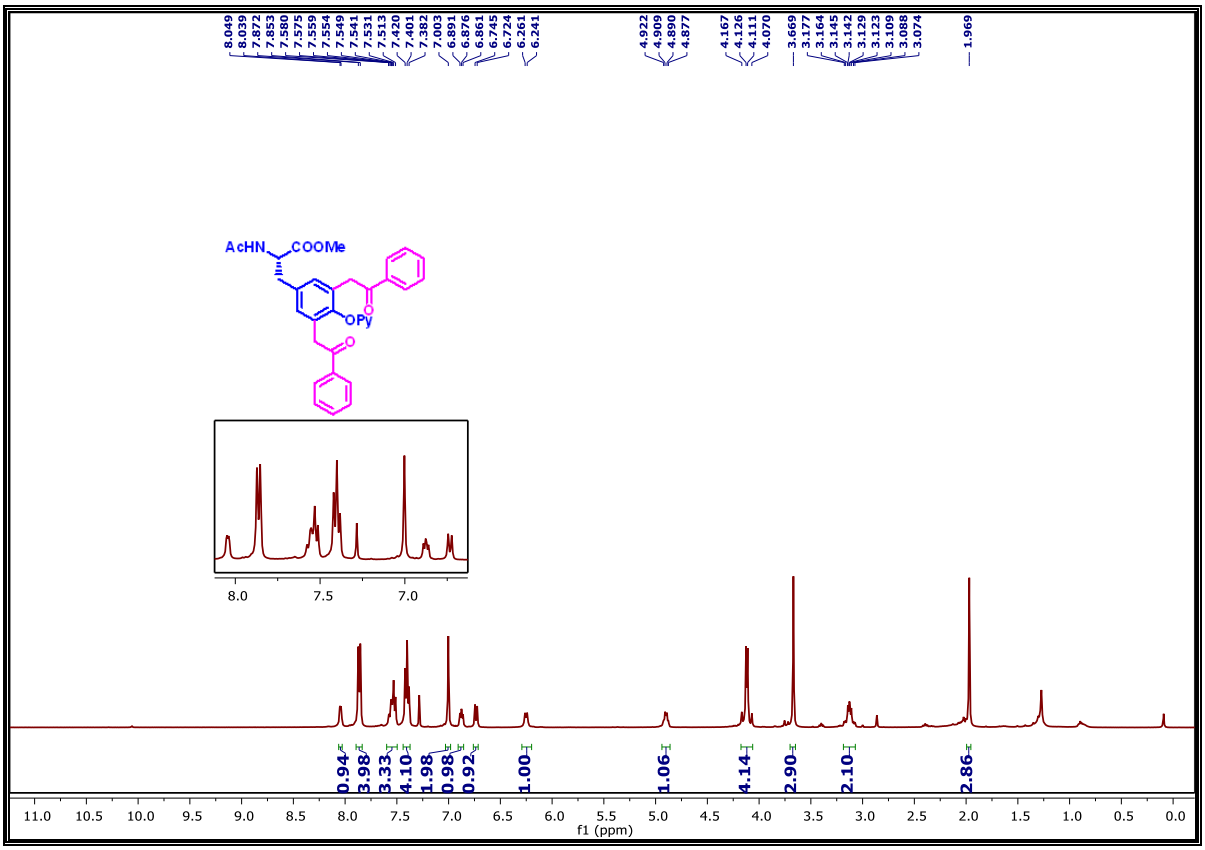
## $^{1}$H NMR of 3ak (400 MHz, $CDCl_3$)



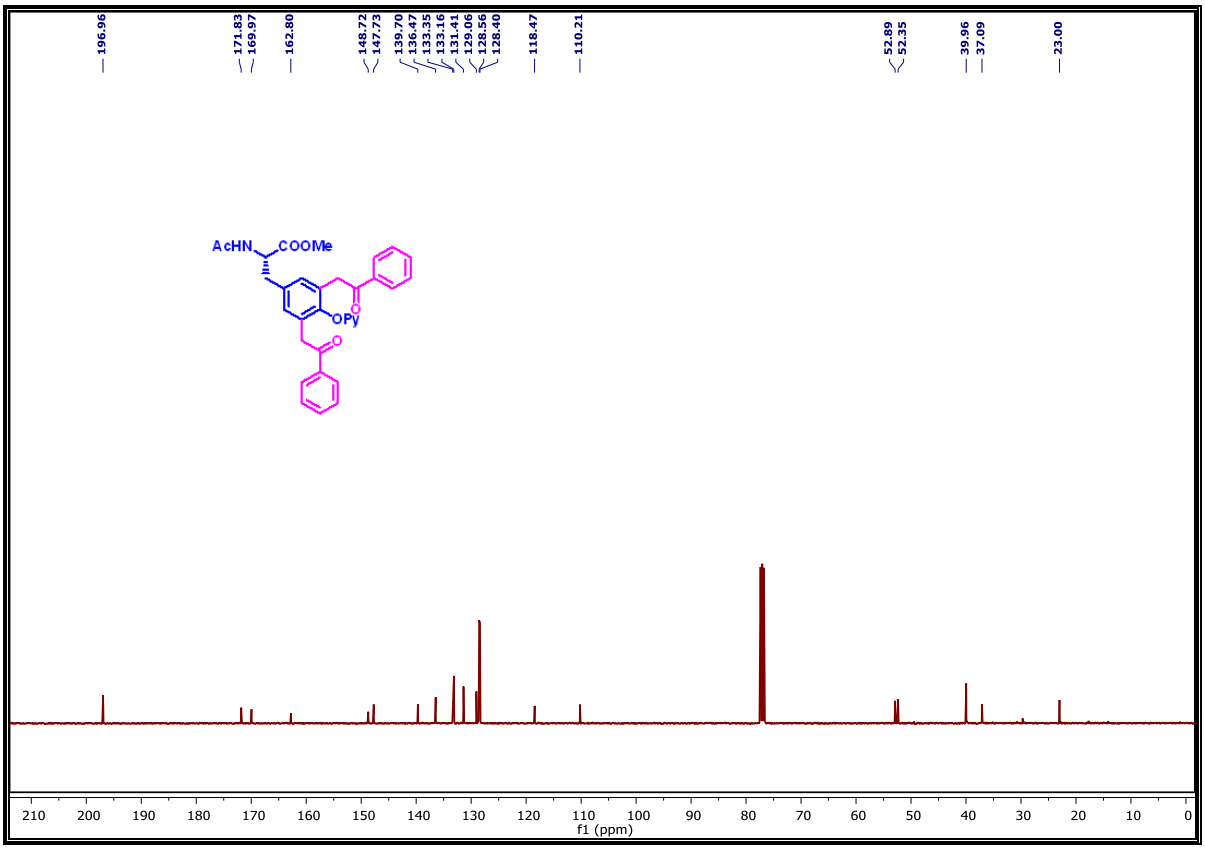

## $^{13}$C NMR of 3ak (100 MHz, $CDCl_3$)



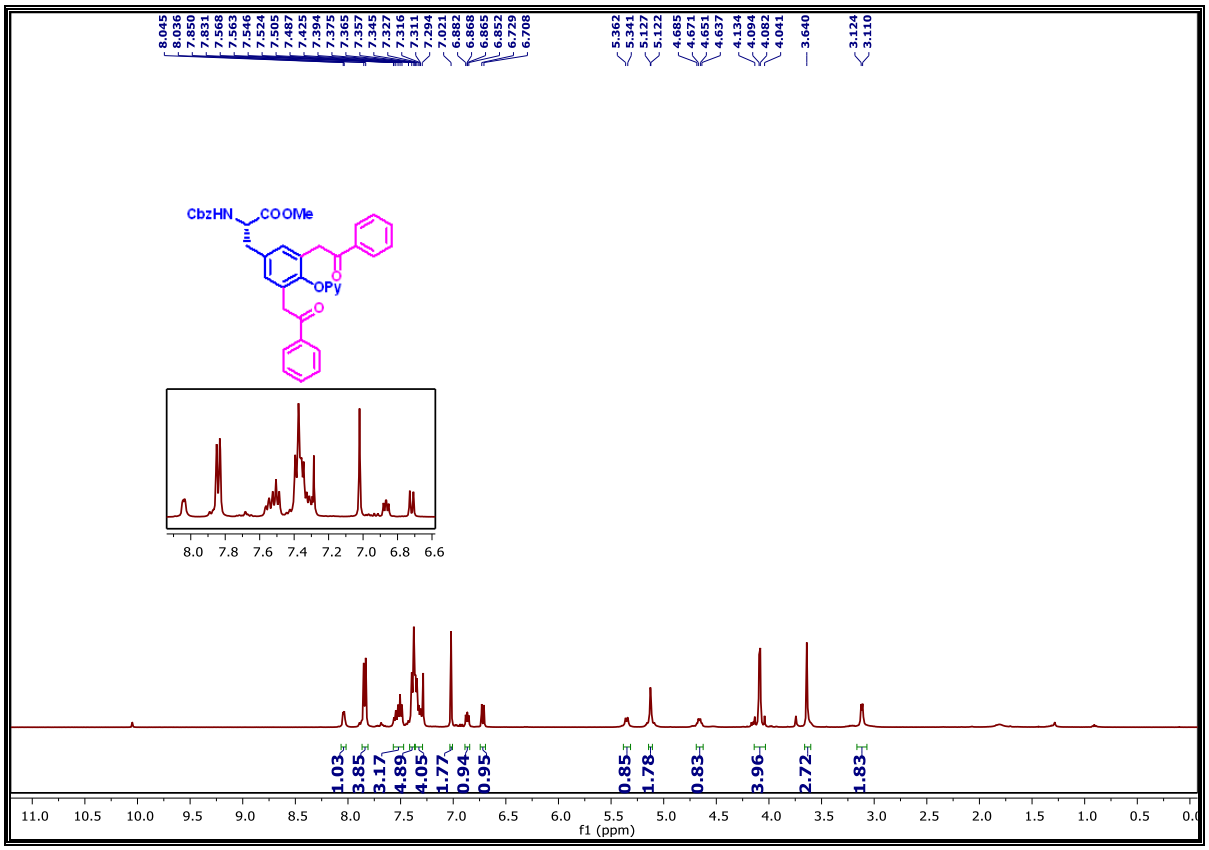
## $^{1}$H NMR of 3ba (400 MHz, $CDCl_3$)



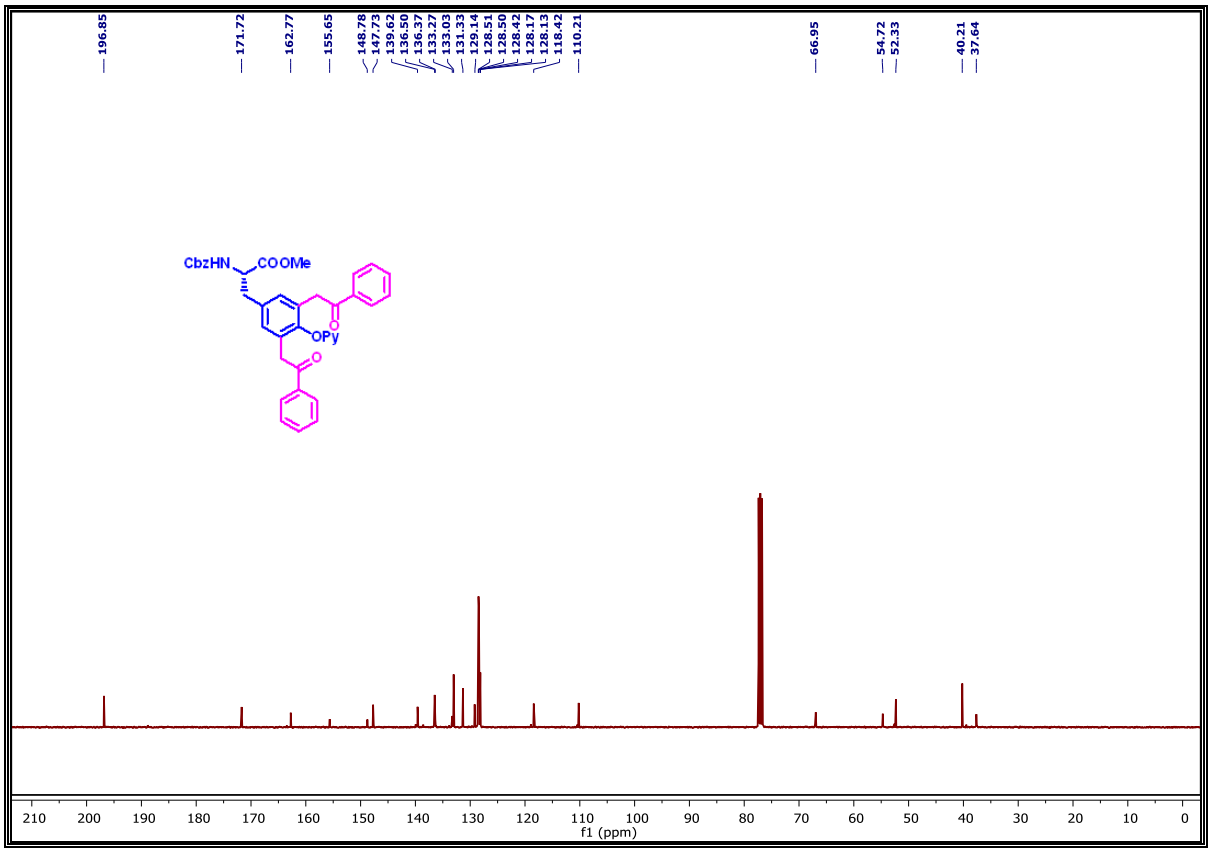

## $^{13}$C NMR of 3ba (100 MHz, $CDCl_3$)



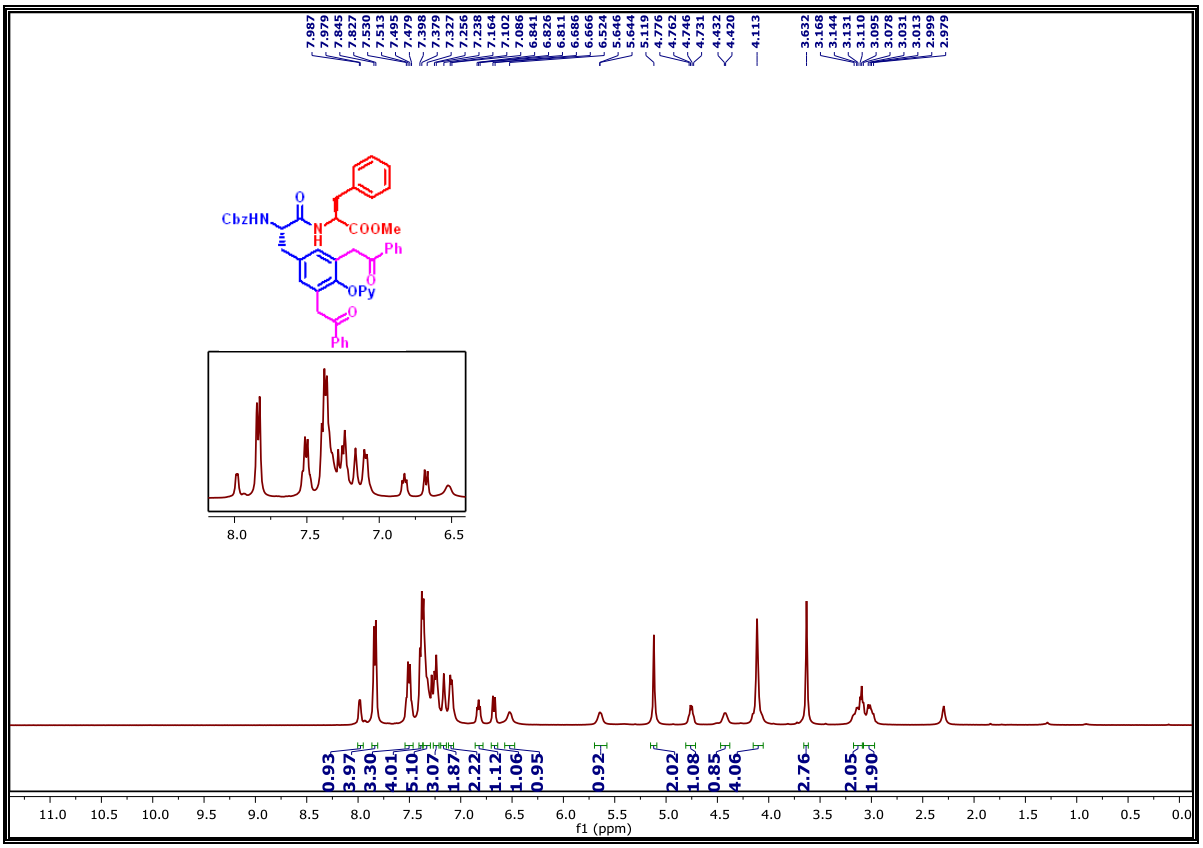
## $^{1}$H NMR of 3ca (400 MHz, $CDCl_3$)



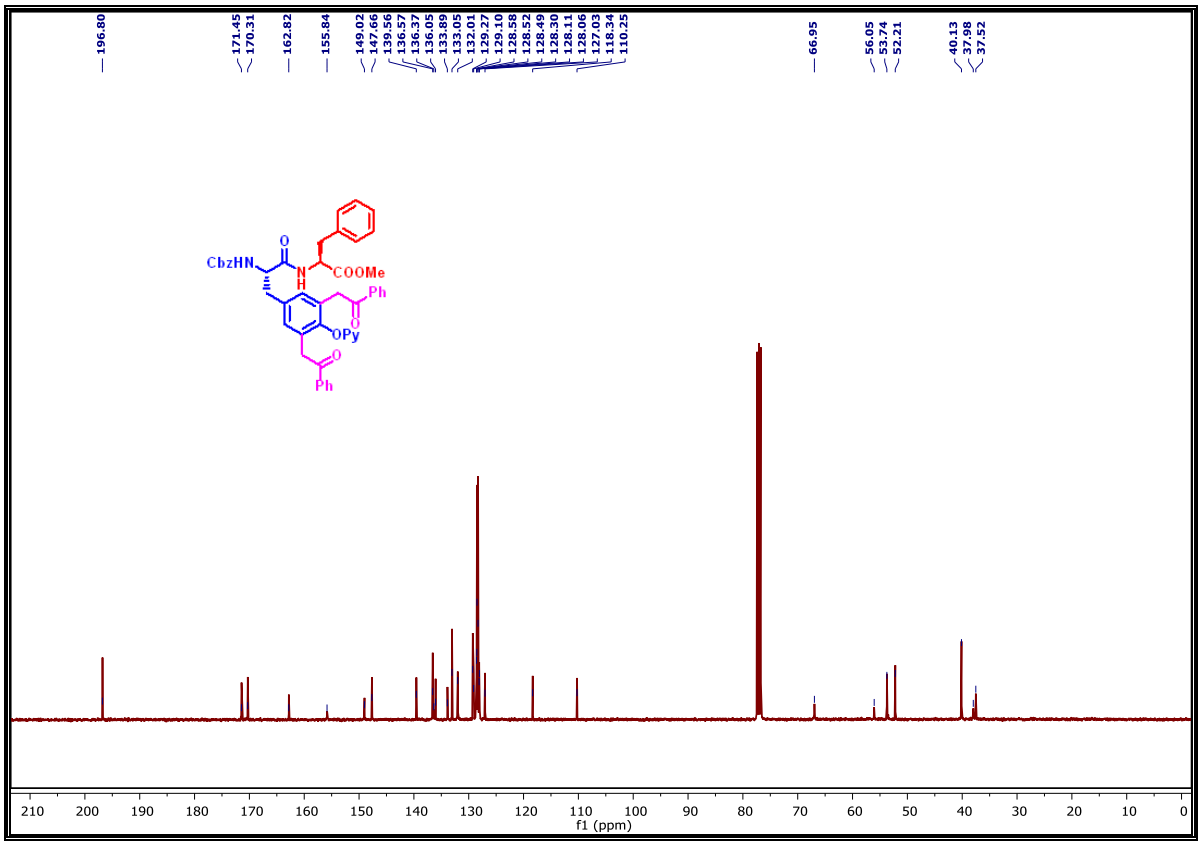

## $^{13}$C NMR of 3ca (100 MHz, $CDCl_3$)



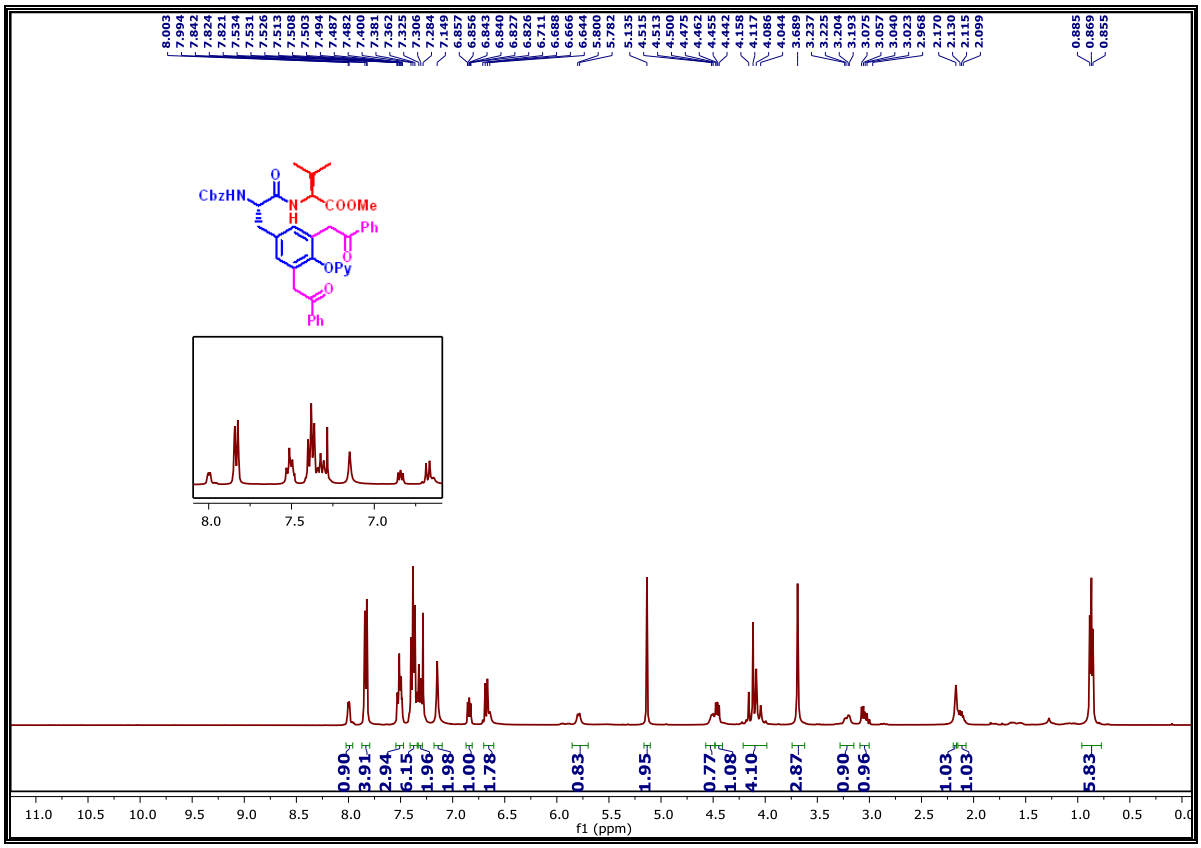
## $^{1}$H NMR of 3da (400 MHz, $CDCl_3$)



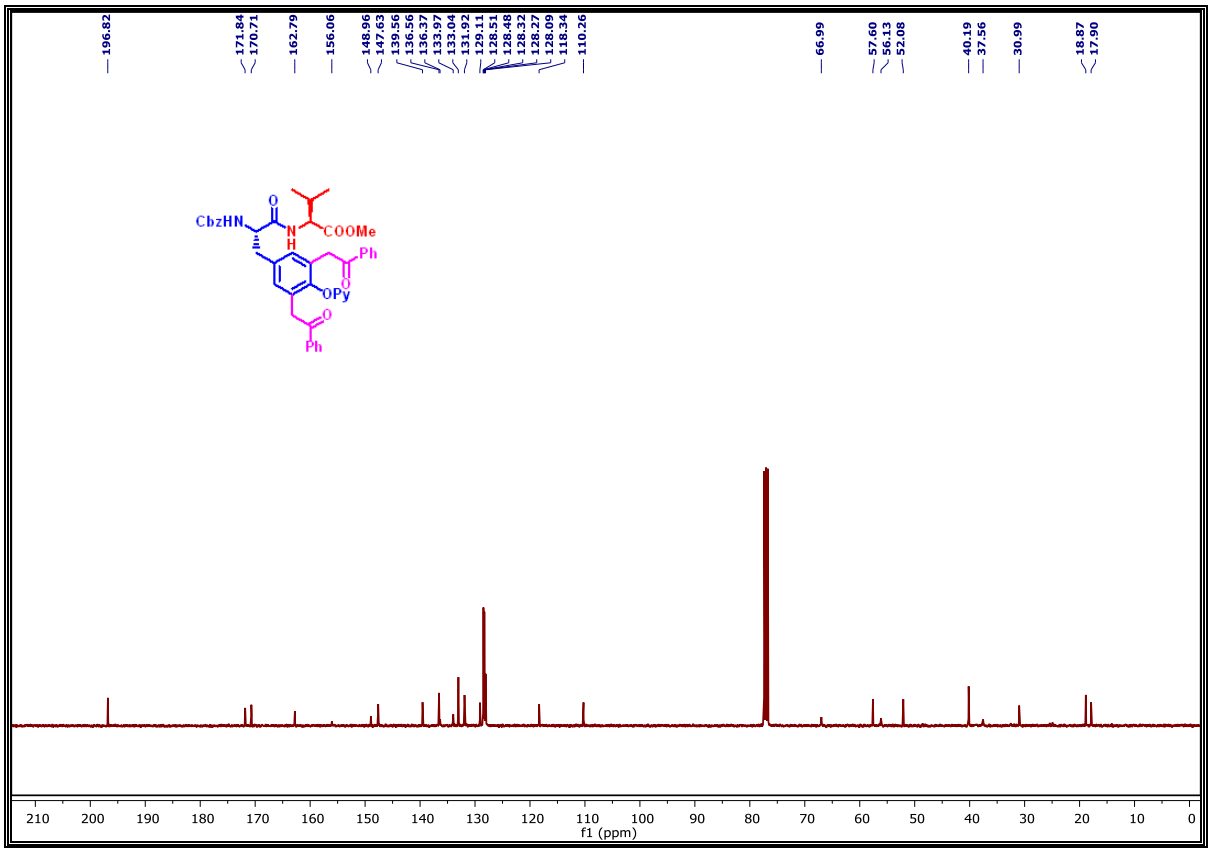

## $^{13}$C NMR of 3da (100 MHz, $CDCl_3$)



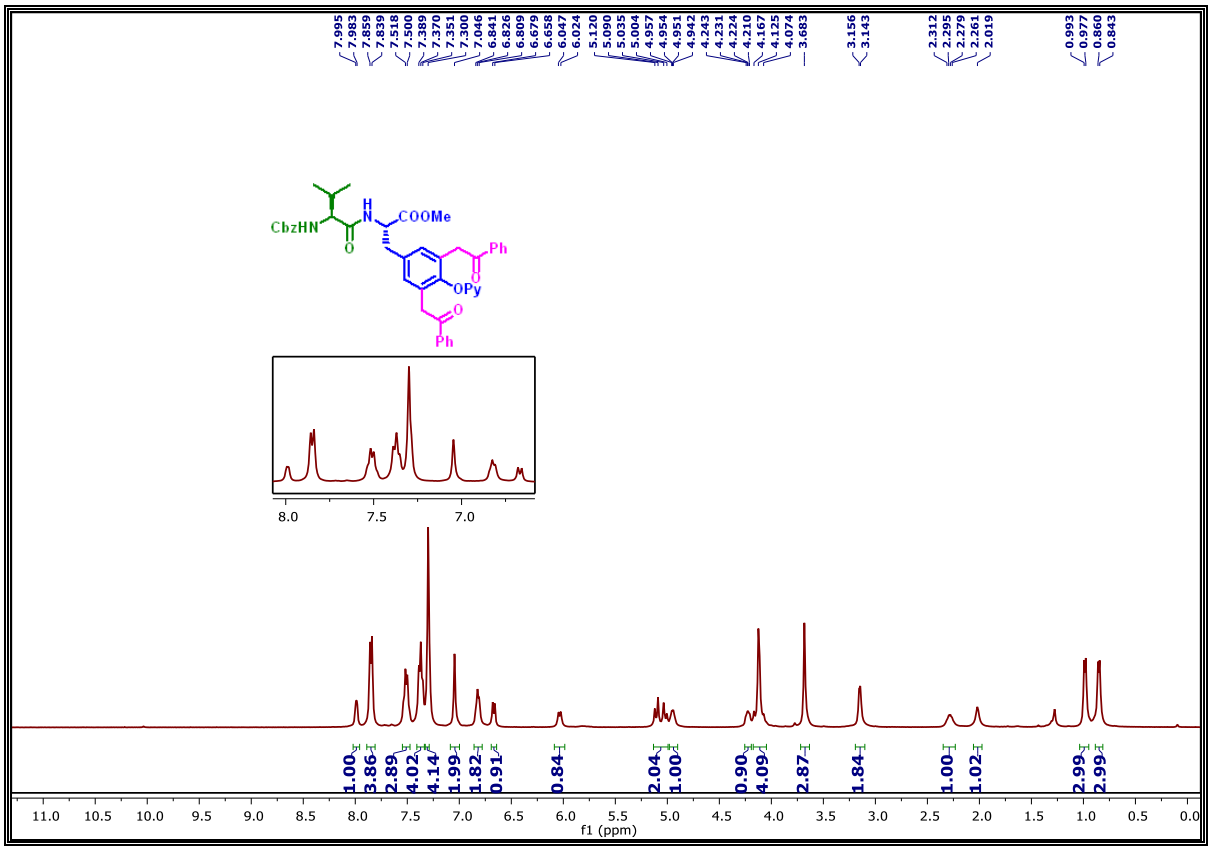
## $^{1}$H NMR of 3ea (400 MHz, $CDCl_3$)



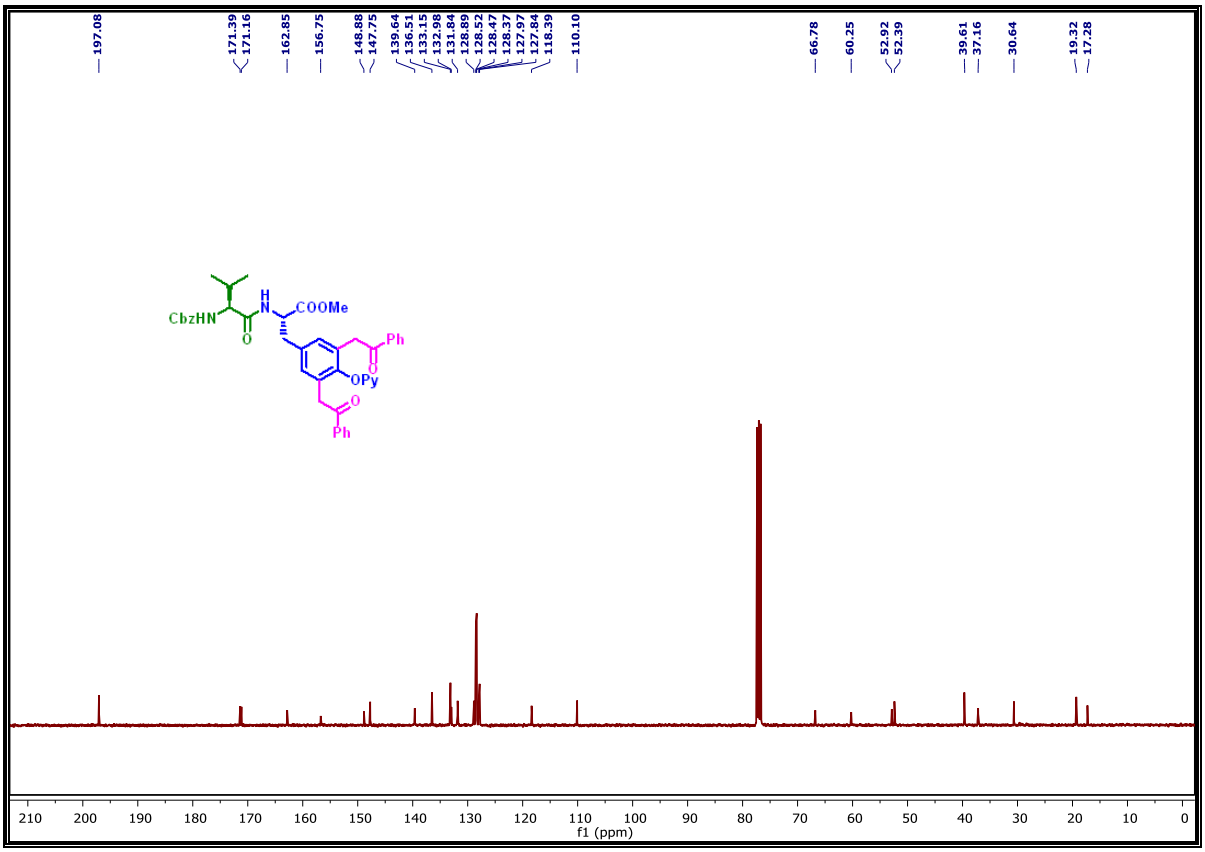

## $^{13}$C NMR of 3ea (100 MHz, $CDCl_3$)



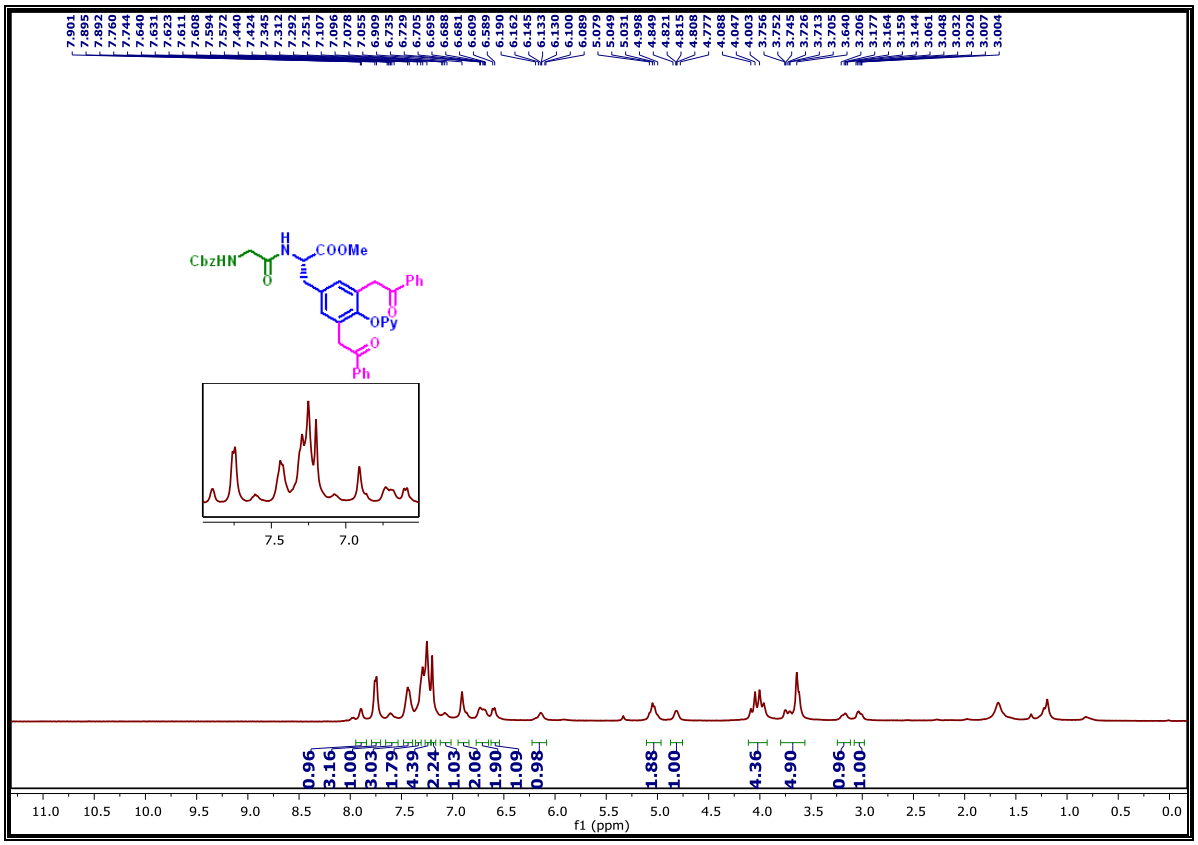
## $^{1}$H NMR of 3fa (400 MHz, $CDCl_3$)



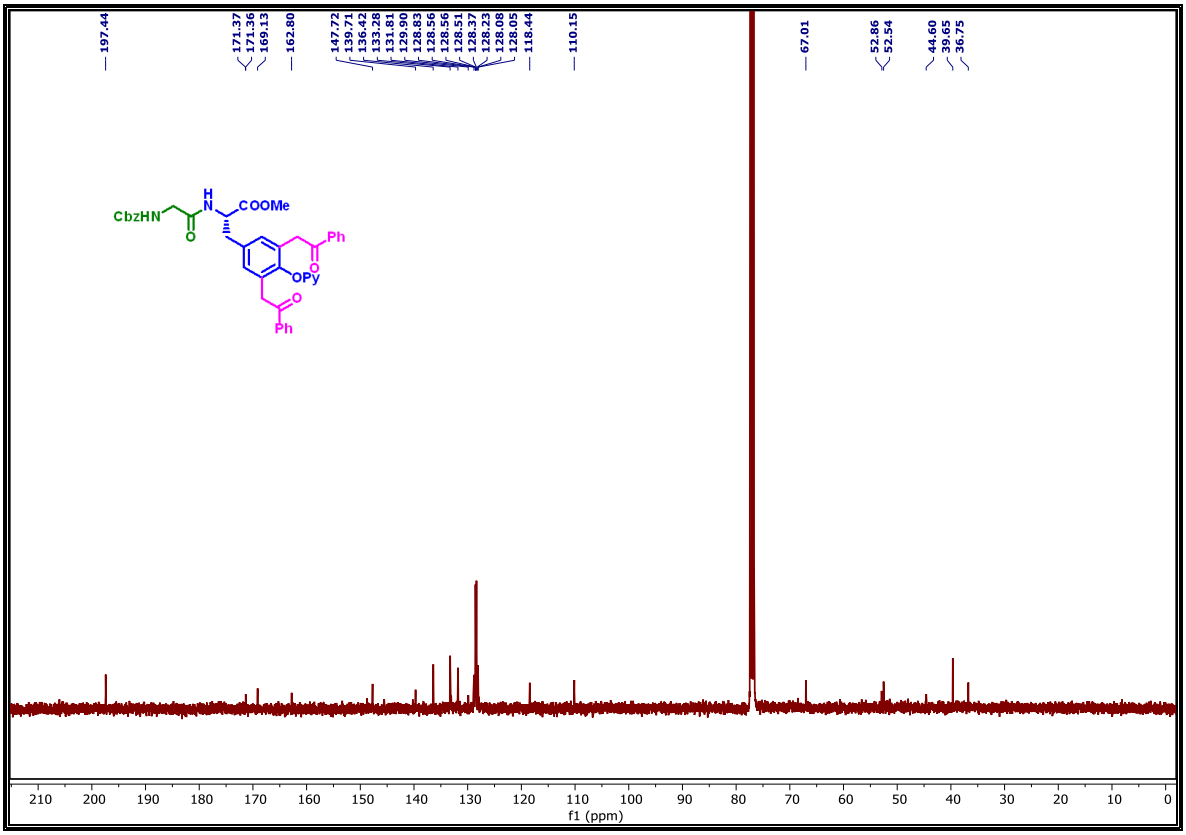

## $^{13}$C NMR of 3fa (100 MHz, $CDCl_3$)



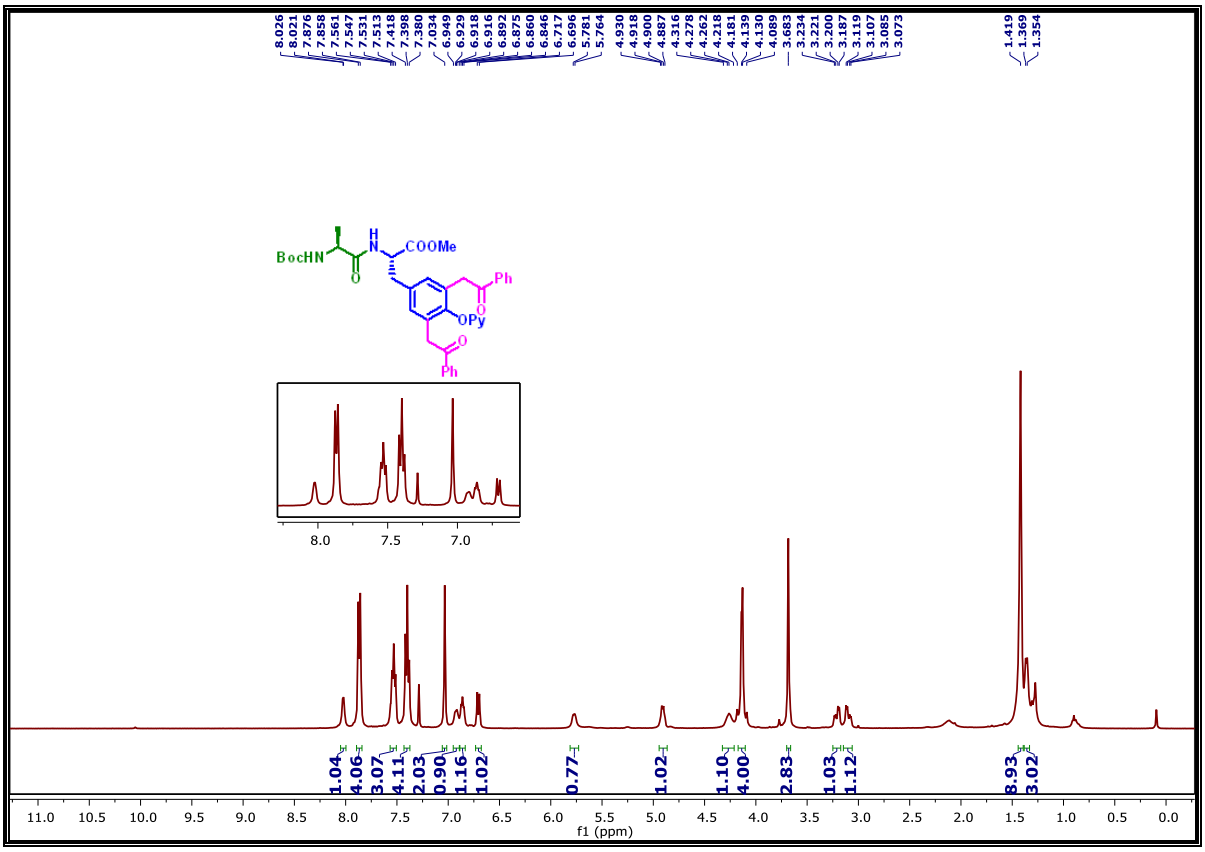
## $^{1}$H NMR of 3ga (400 MHz, $CDCl_3$)



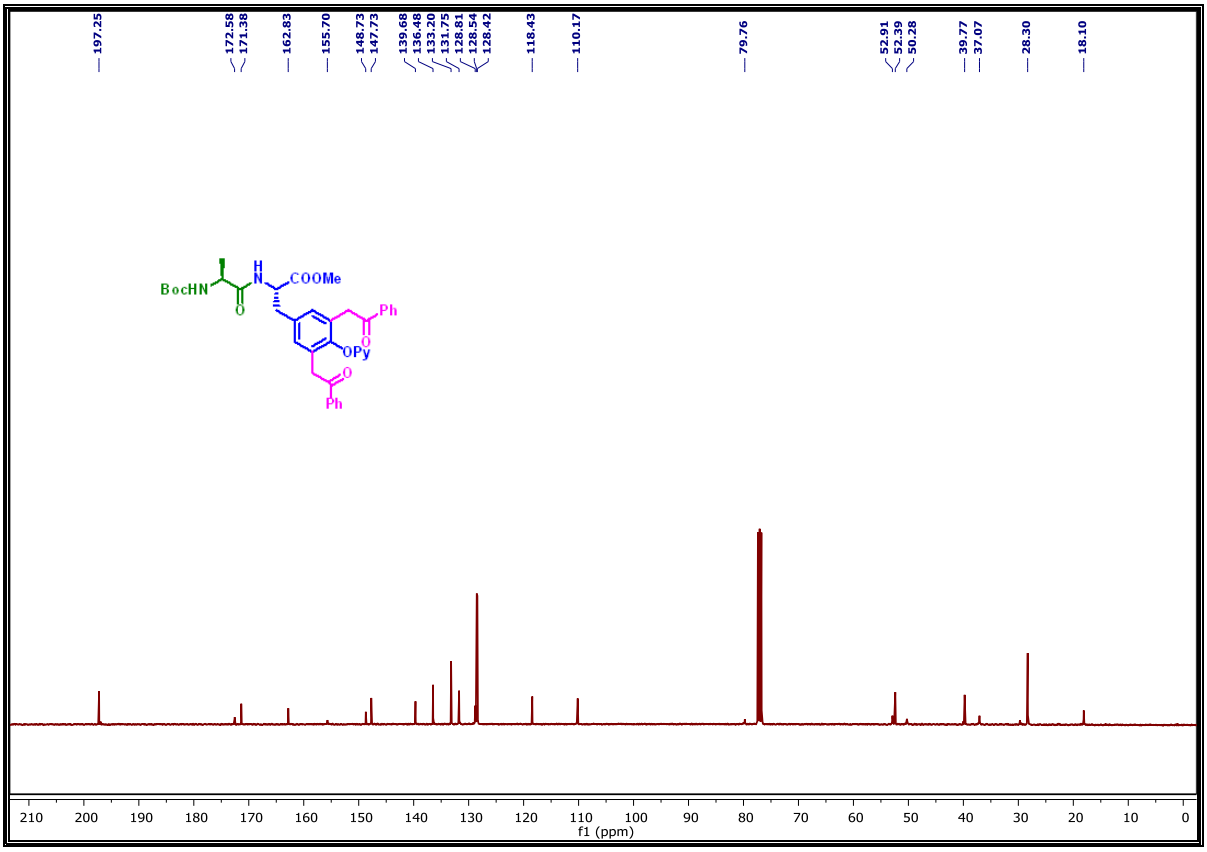

## $^{13}$C NMR of 3ga (100 MHz, $CDCl_3$)



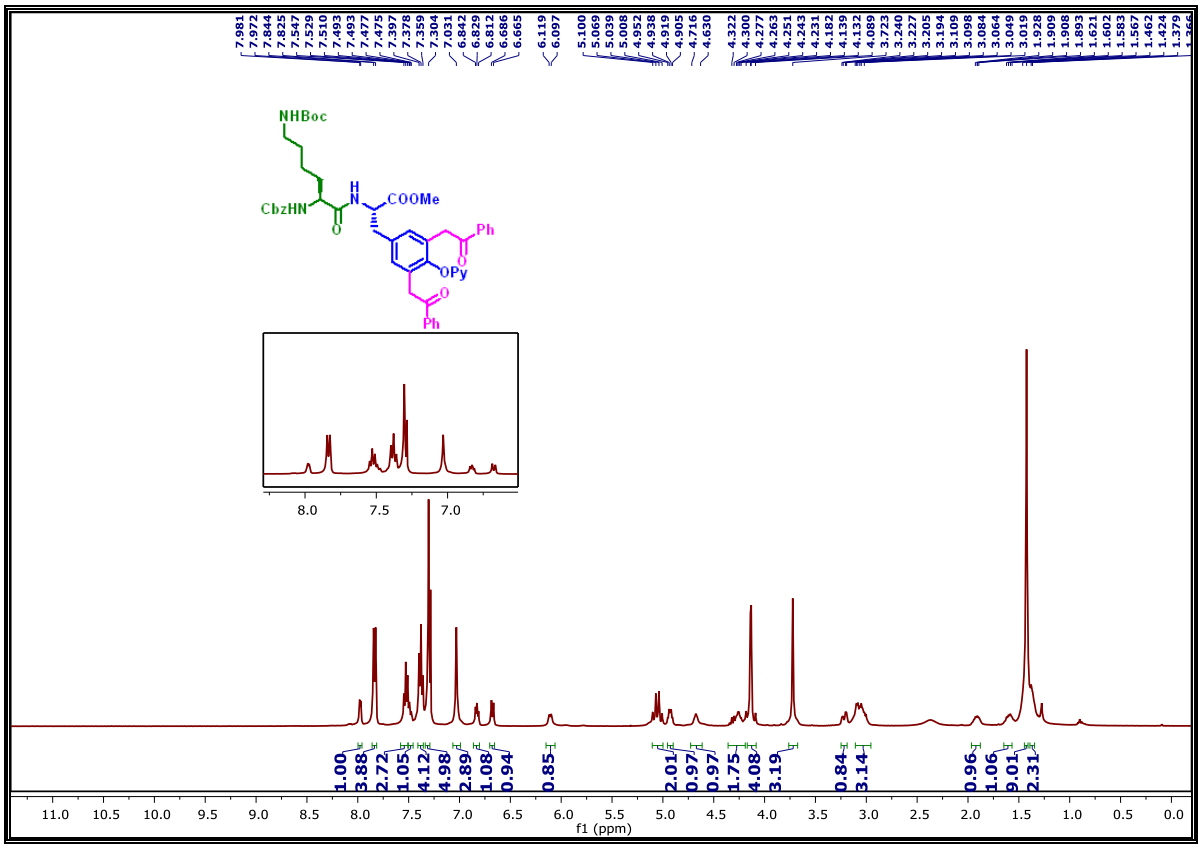
## $^{1}$H NMR of 3ha (400 MHz, $CDCl_3$)



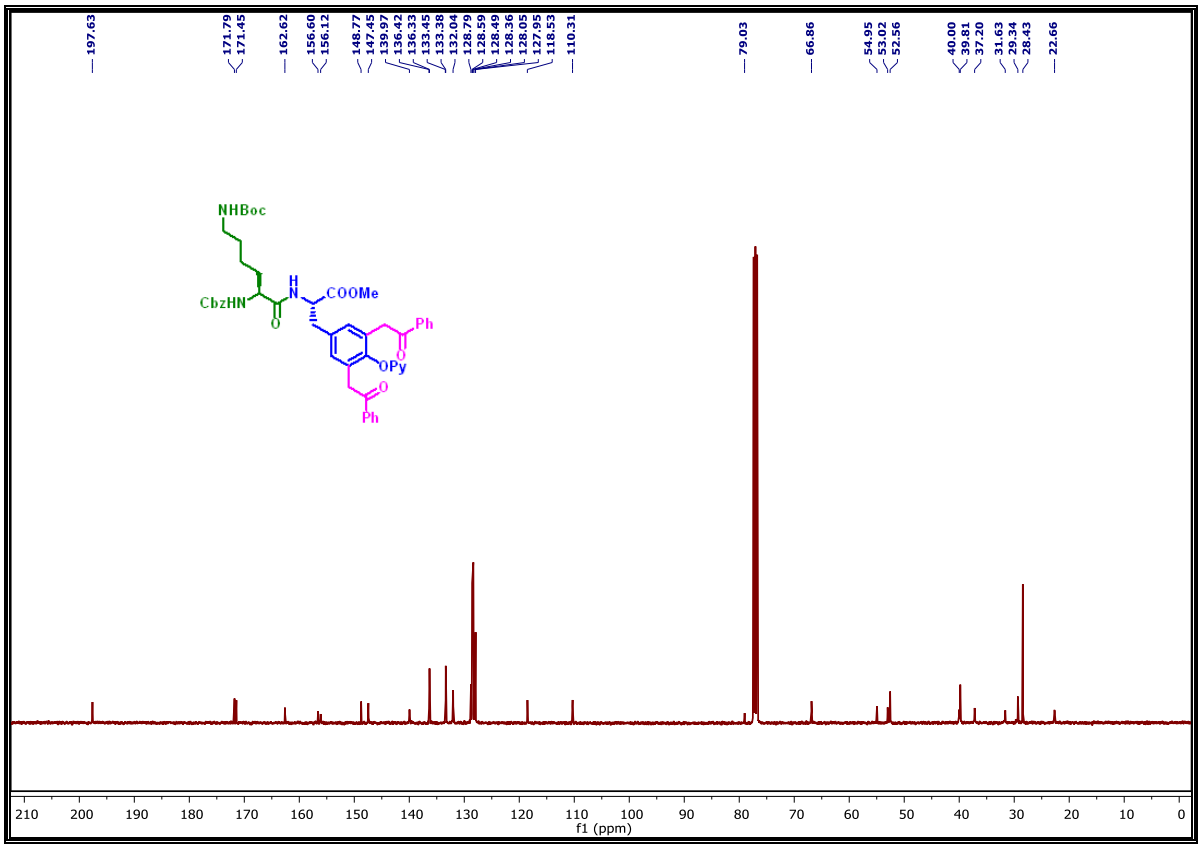

## $^{13}$C NMR of 3ha (100 MHz, $CDCl_3$)



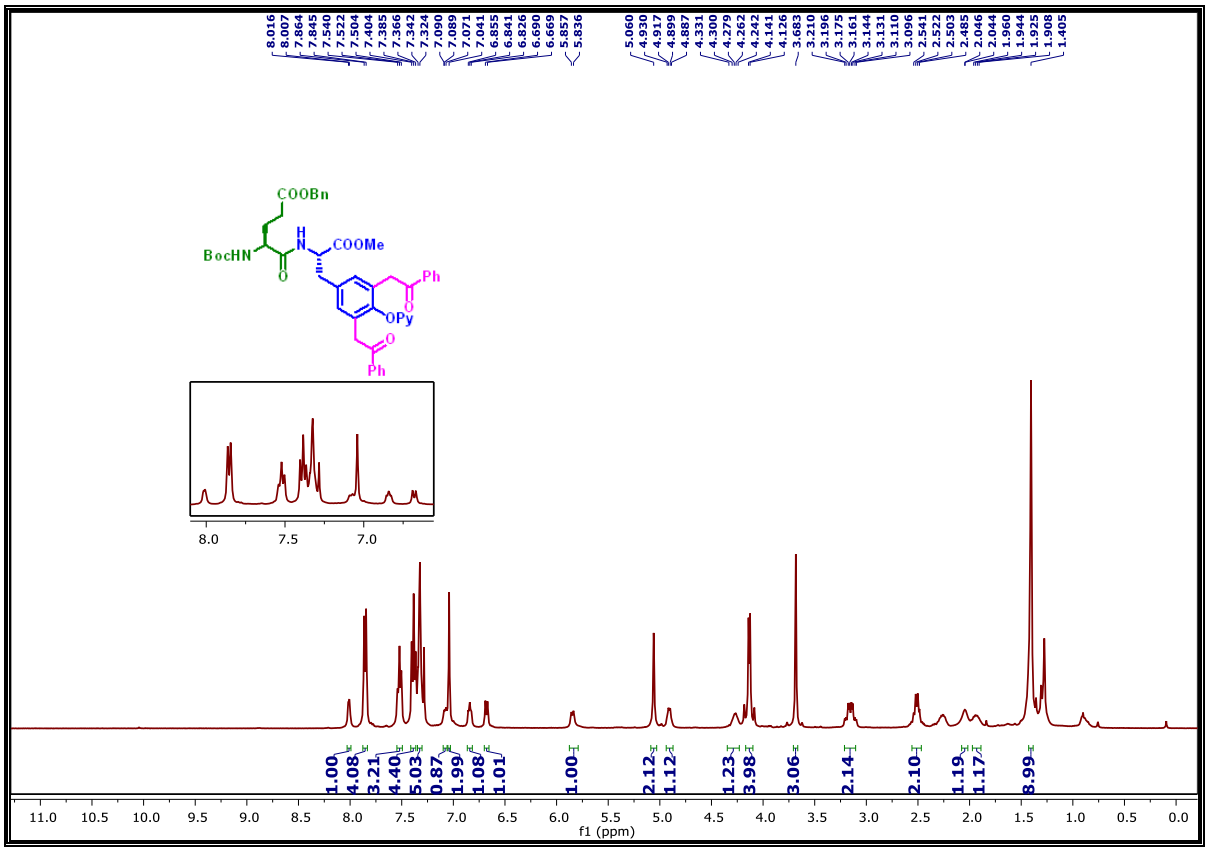
## $^{1}$H NMR of 3ia (400 MHz, $CDCl_3$)



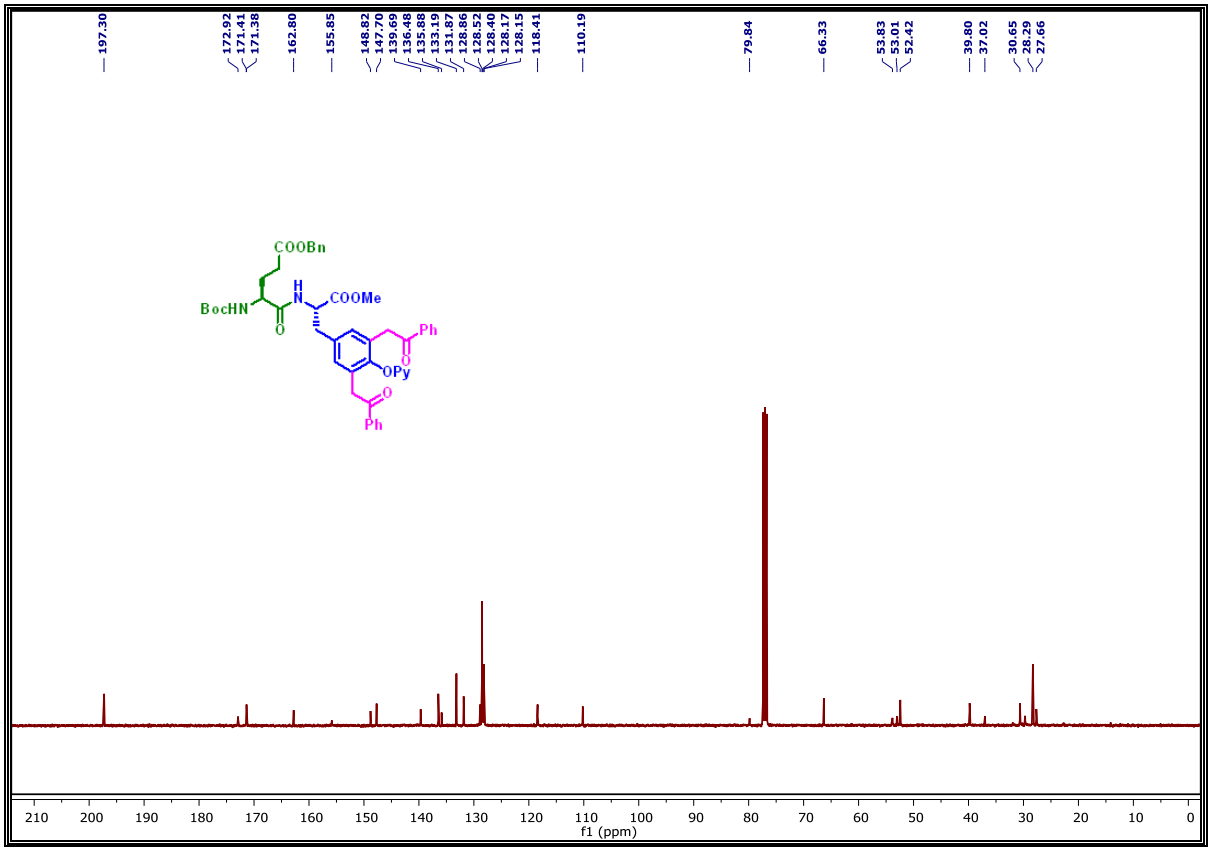

## $^{13}$C NMR of 3ia (100 MHz, $CDCl_3$)



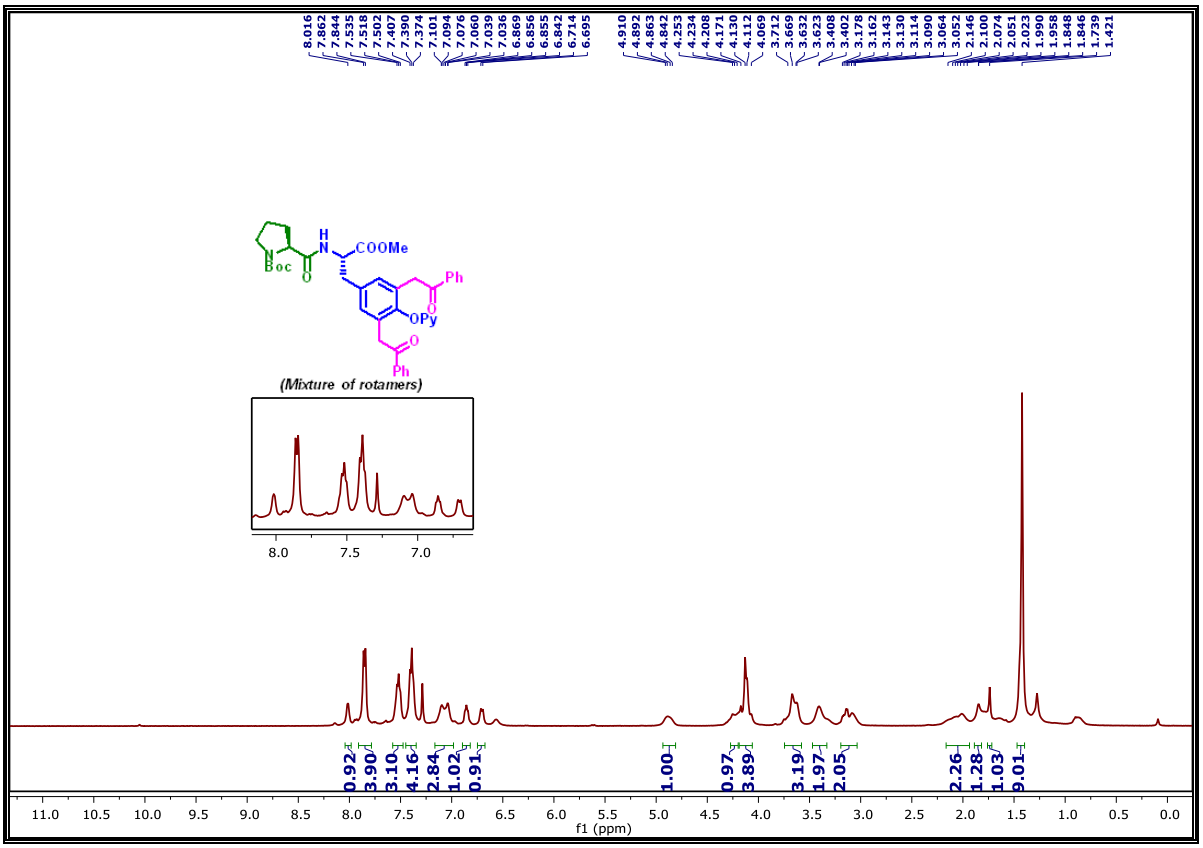
## $^{1}$H NMR of 3ja (400 MHz, $CDCl_3$)



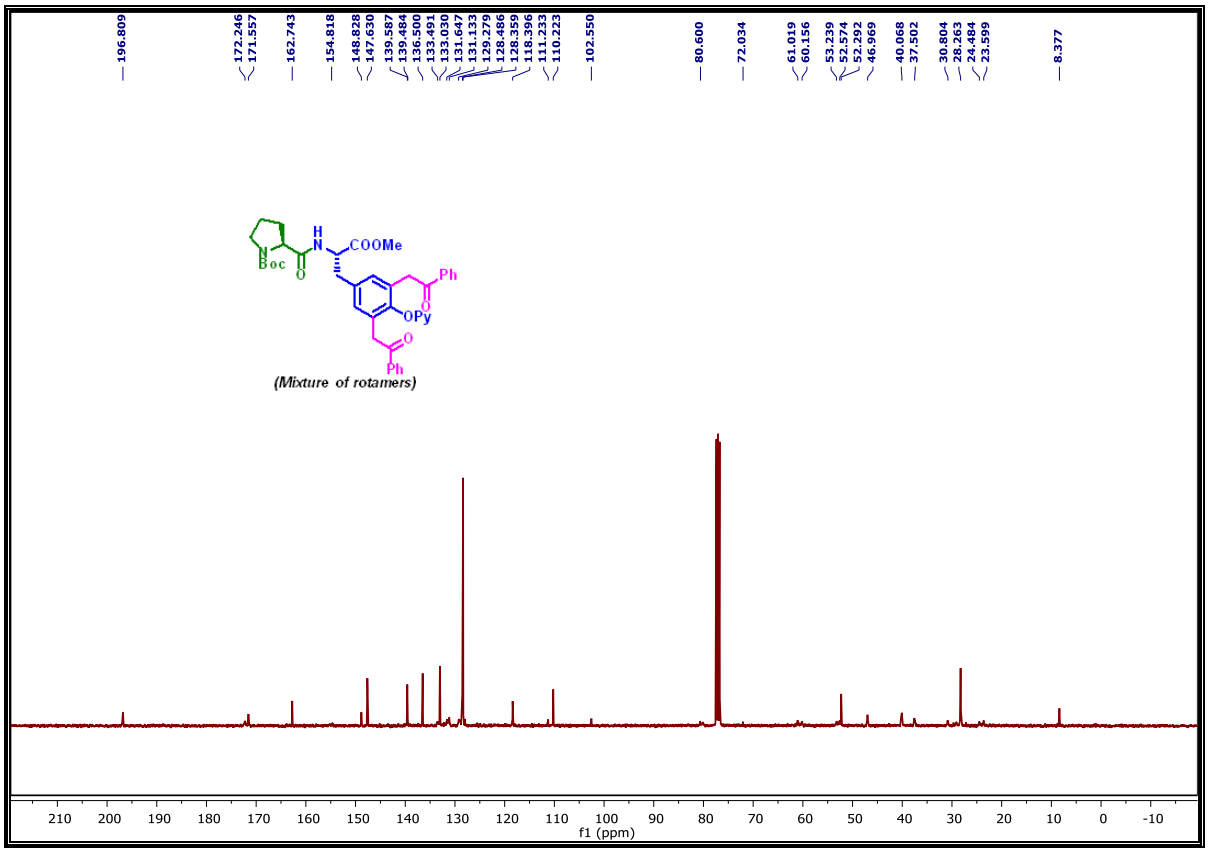

## $^{13}$C NMR of 3ja (100 MHz, $CDCl_3$)



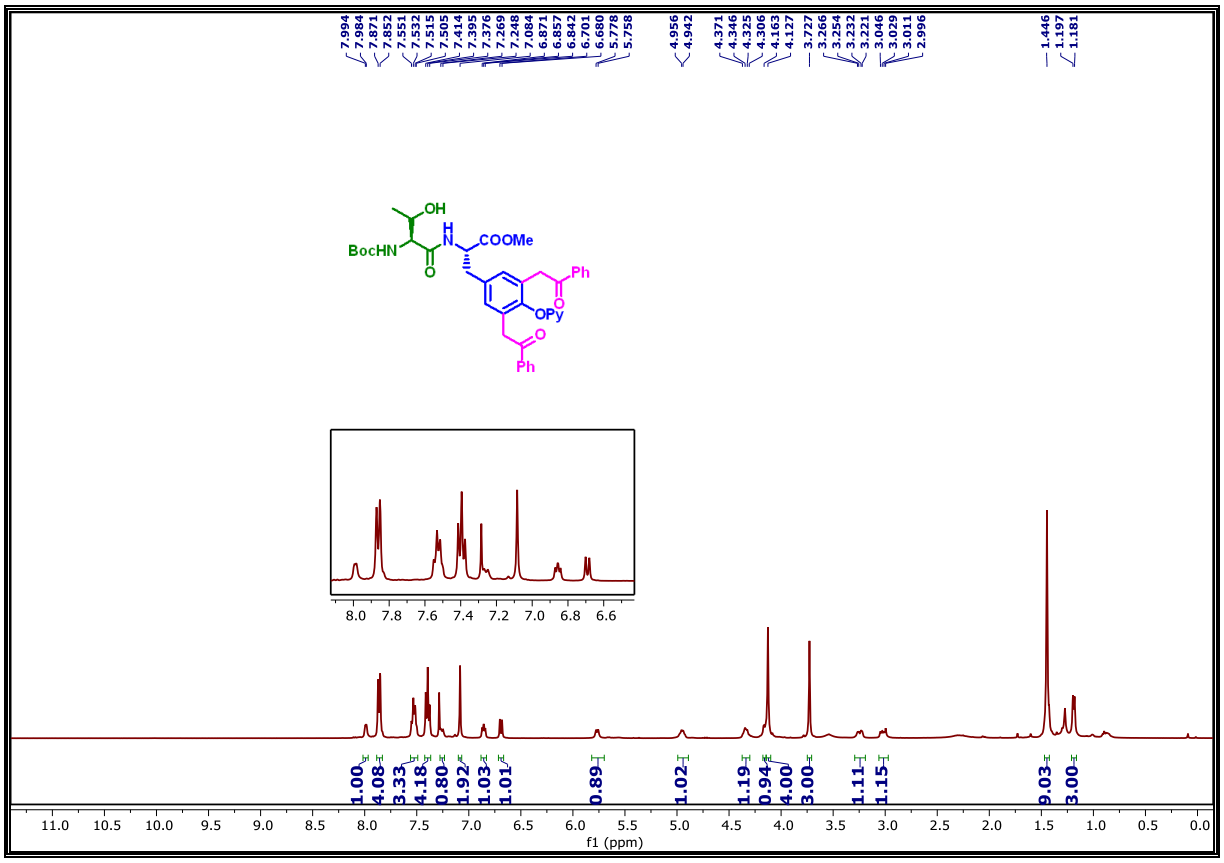
## $^{1}$H NMR of 3ka (400 MHz, $CDCl_3$)



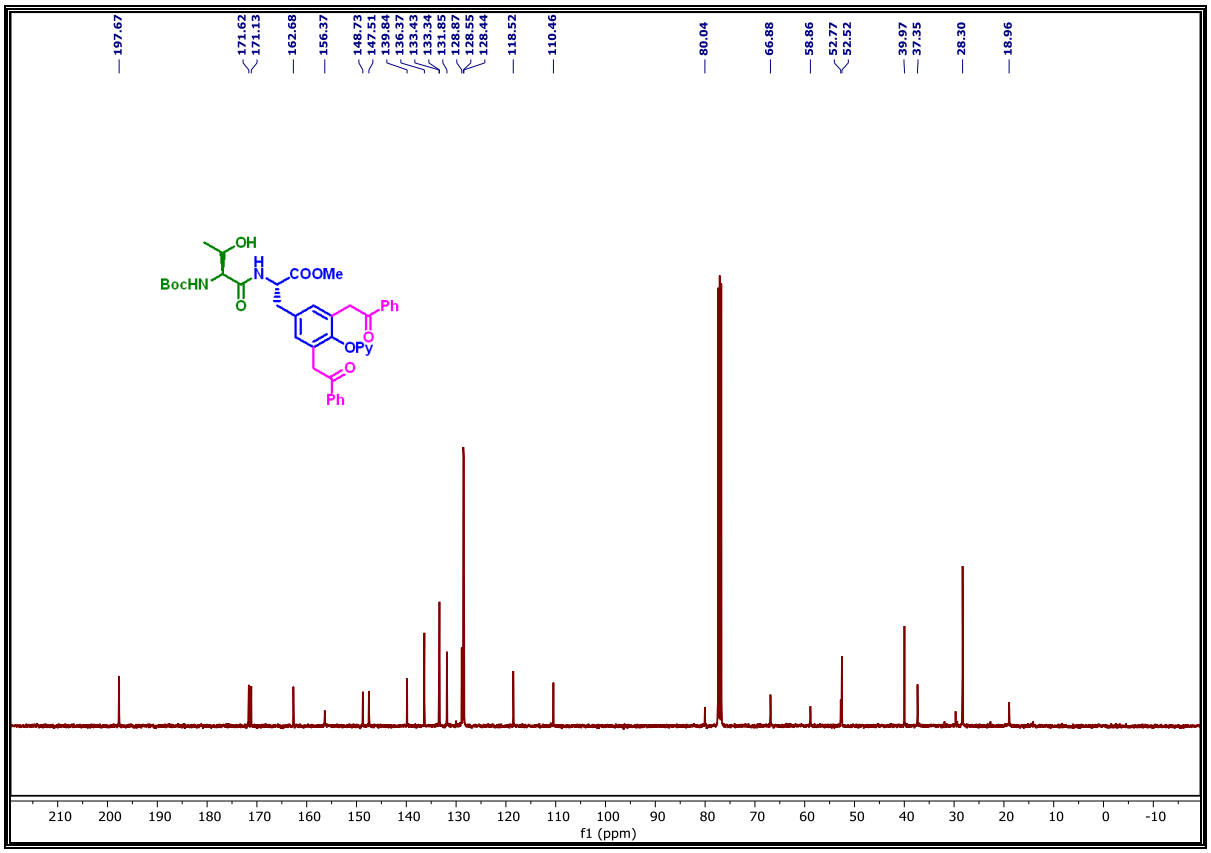

## $^{13}$C NMR of 3ka (100 MHz, $CDCl_3$)



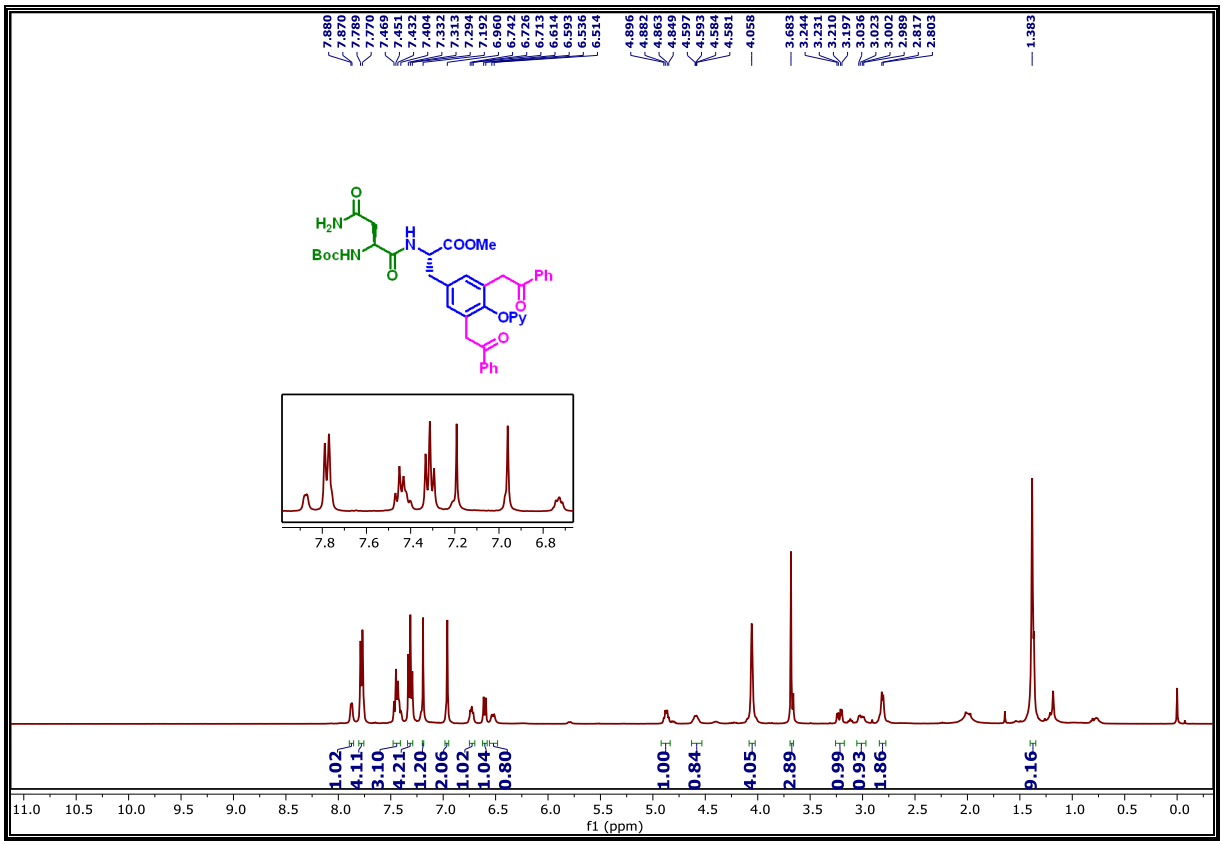
## $^{1}$H NMR of 3la (400 MHz, $CDCl_3$)



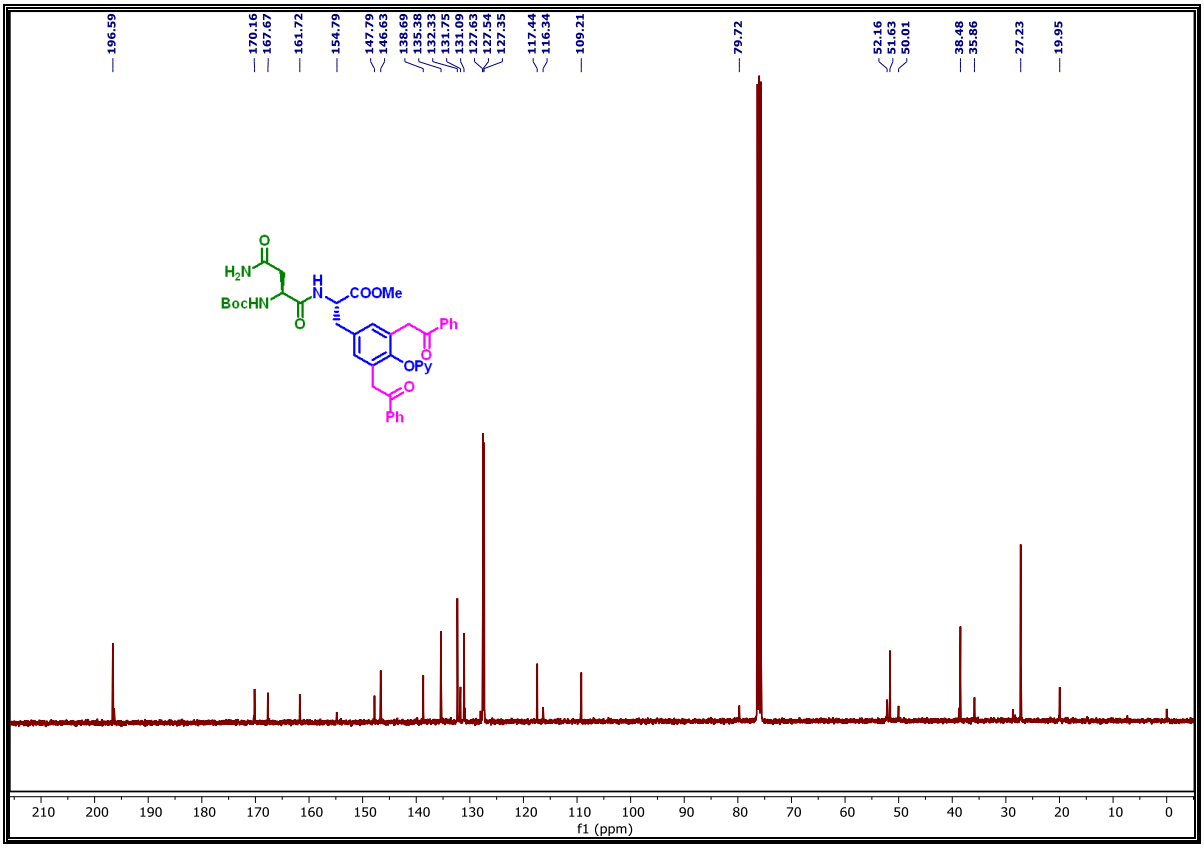

## $^{13}$C NMR of 3la (100 MHz, $CDCl_3$)



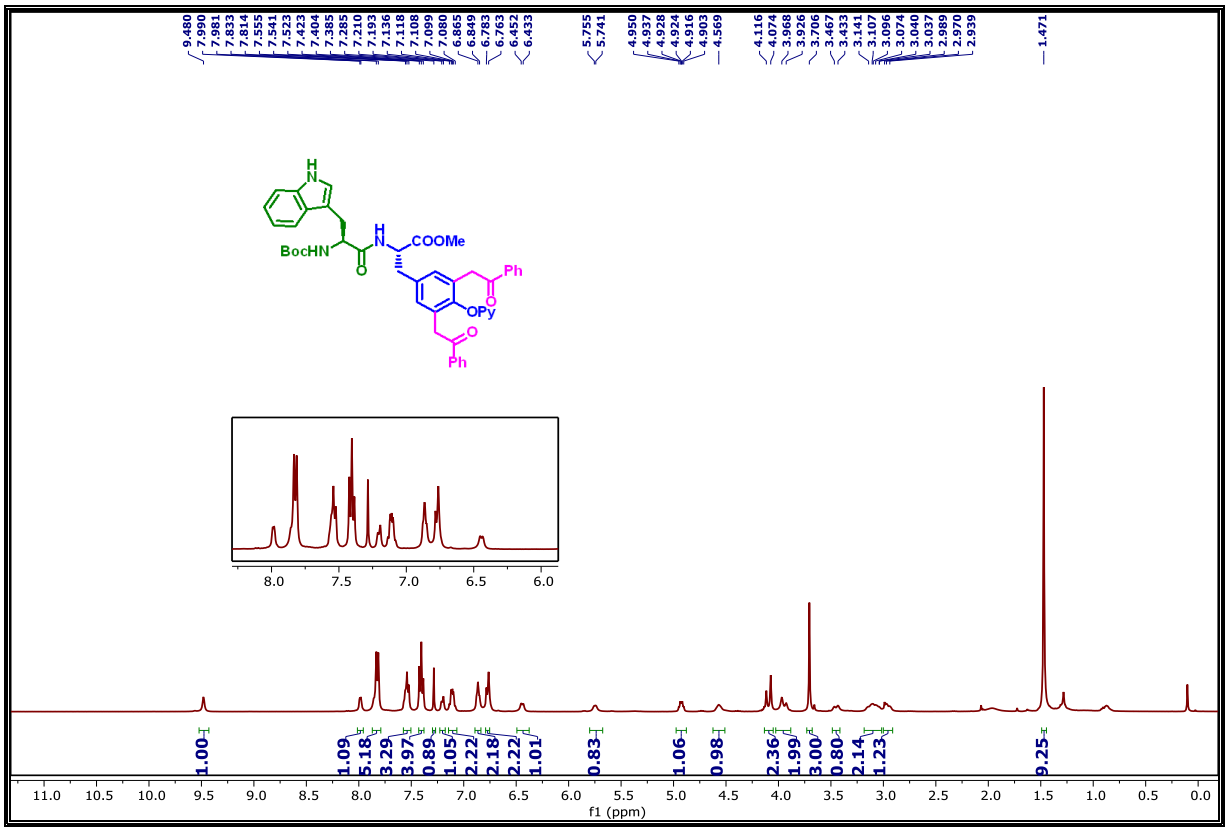
## $^{1}$H NMR of 3ma (400 MHz, $CDCl_3$)



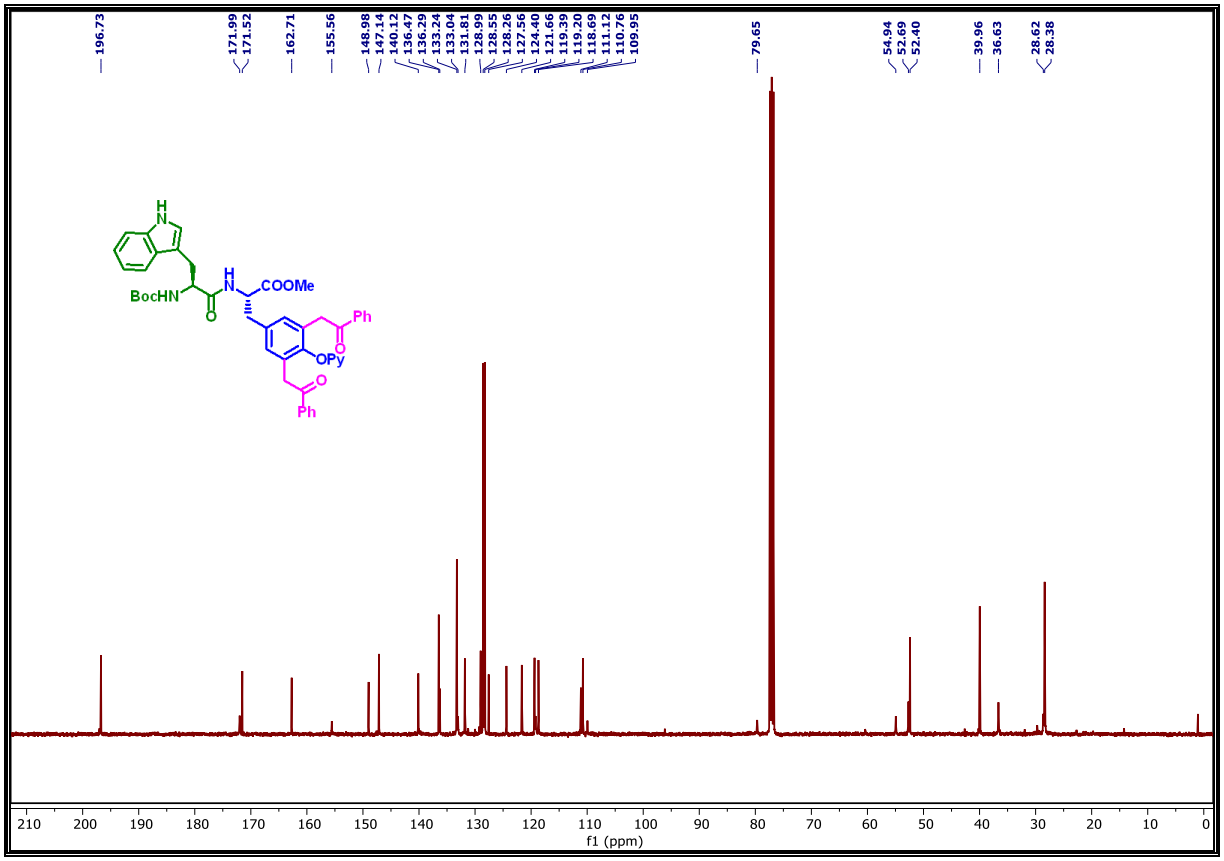

## $^{13}$C NMR of 3ma (100 MHz, $CDCl_3$)



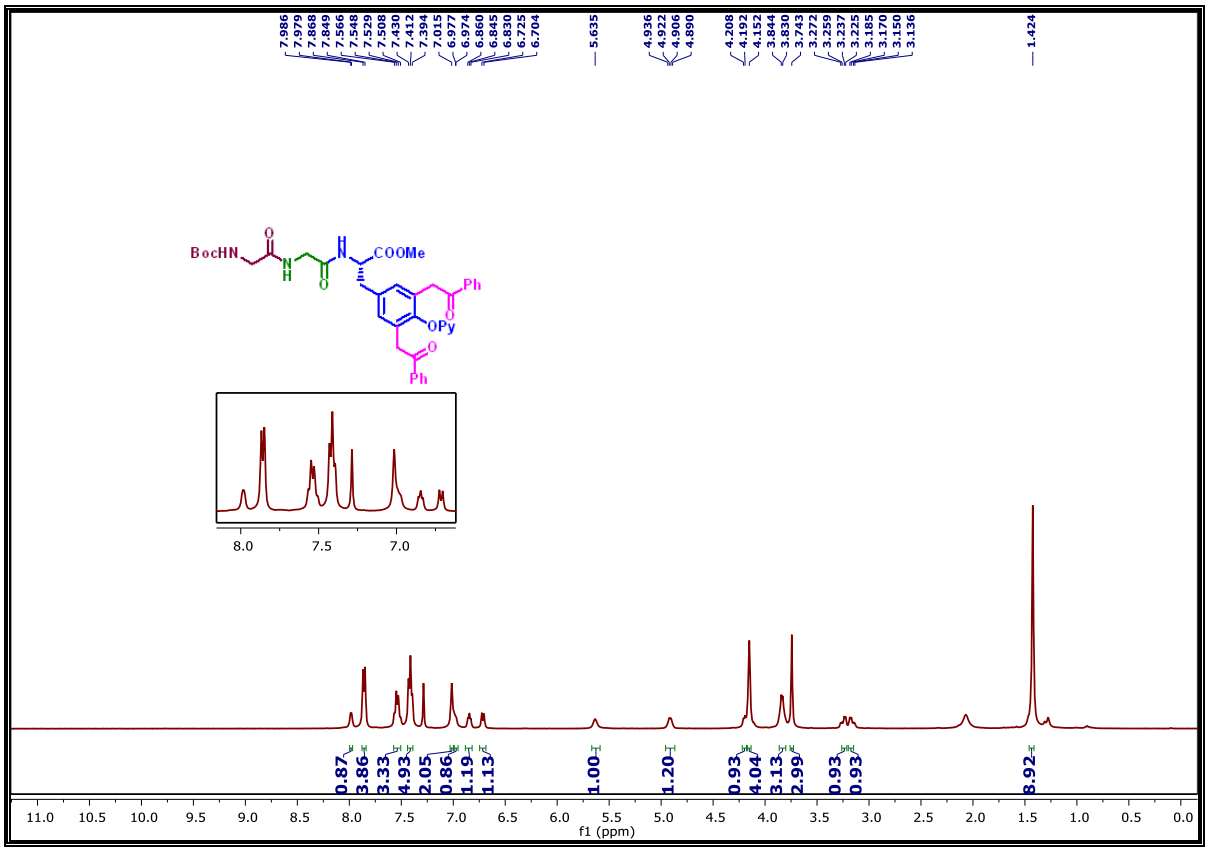
## $^{1}$H NMR of 3na (400 MHz, $CDCl_3$)



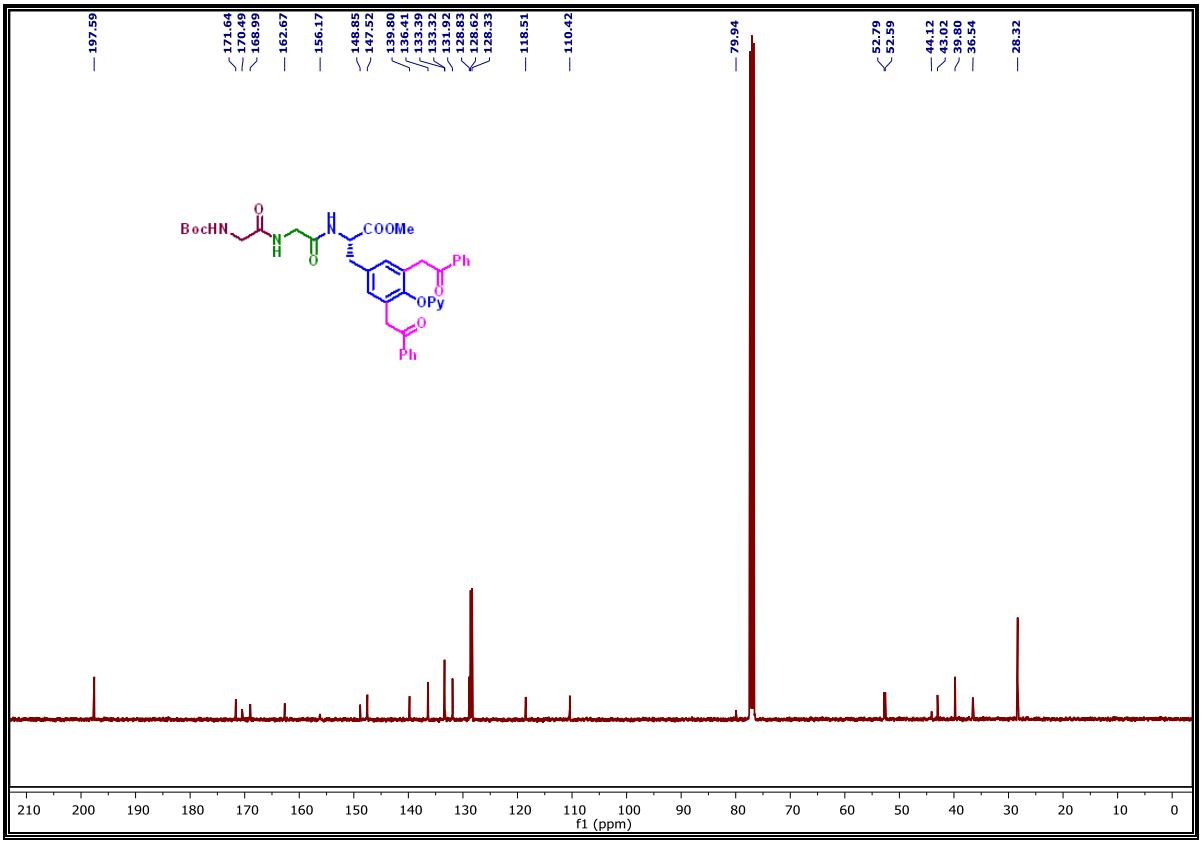

## $^{13}$C NMR of 3na (100 MHz, $CDCl_3$)



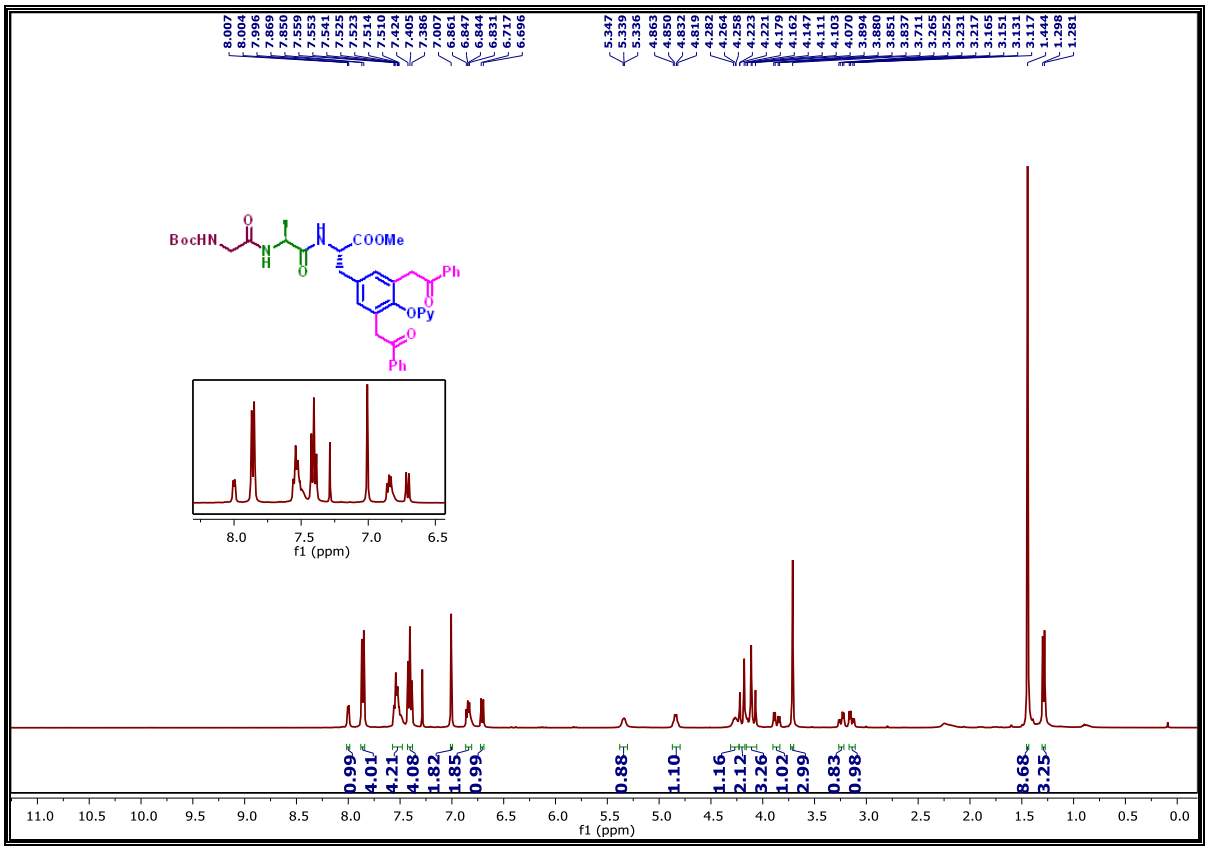
## $^{1}$H NMR of 3oa (400 MHz, $CDCl_3$)



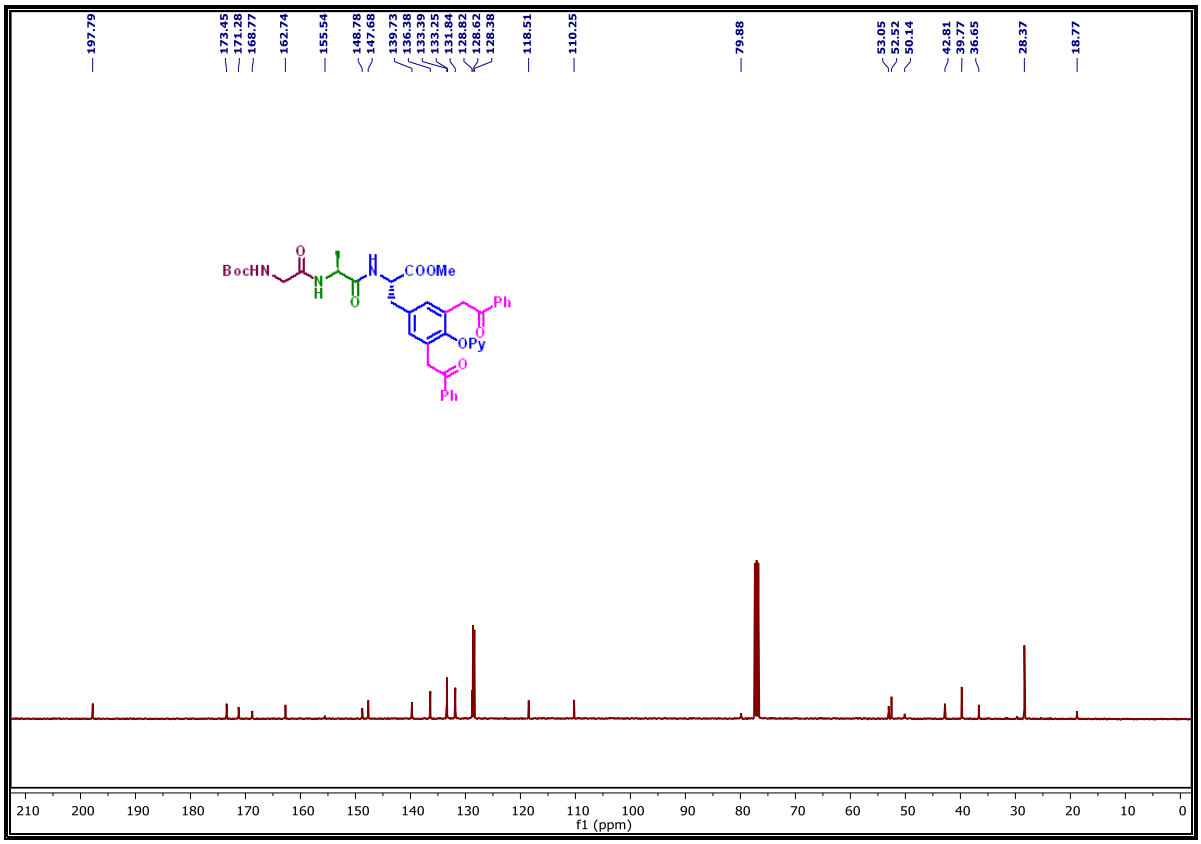

## $^{13}$C NMR of 3oa (100 MHz, $CDCl_3$)



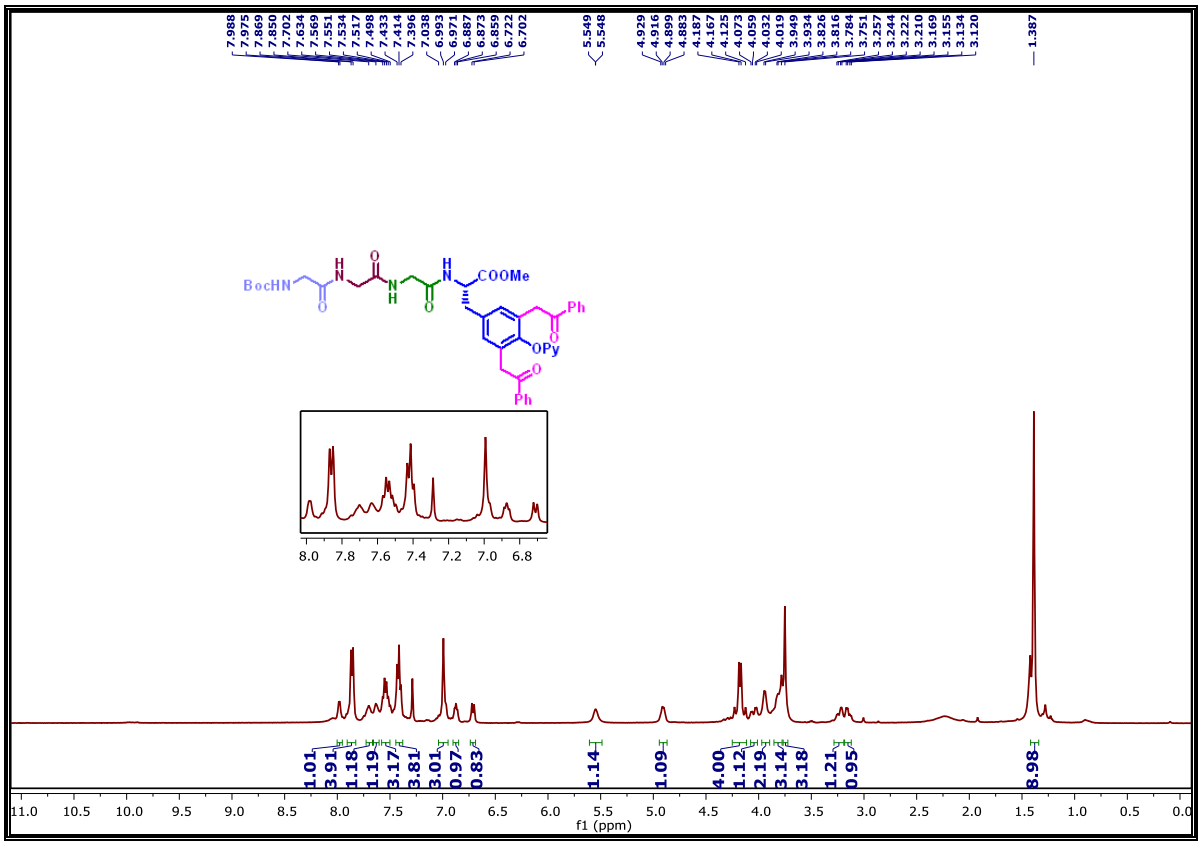
## $^{1}$H NMR of 3pa (400 MHz, $CDCl_3$)



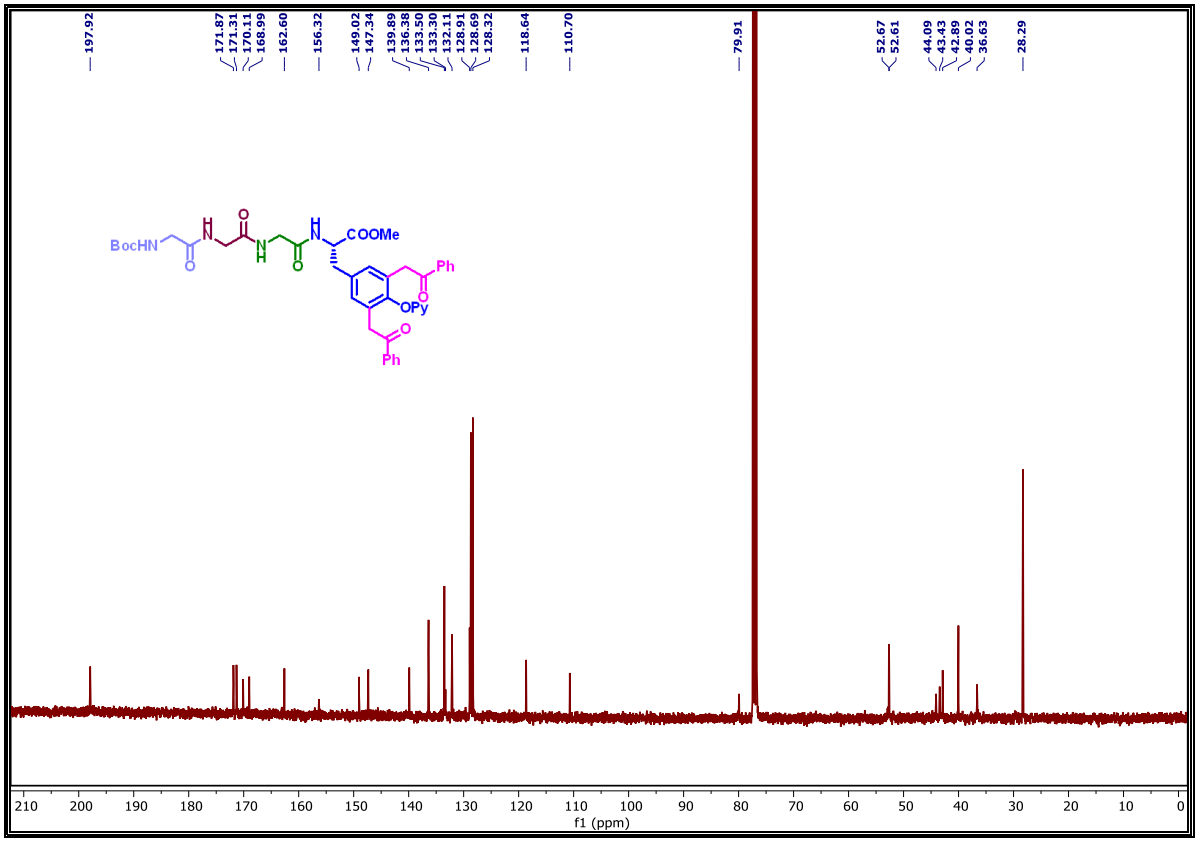

## $^{13}$C NMR of 3pa (100 MHz, $CDCl_3$)



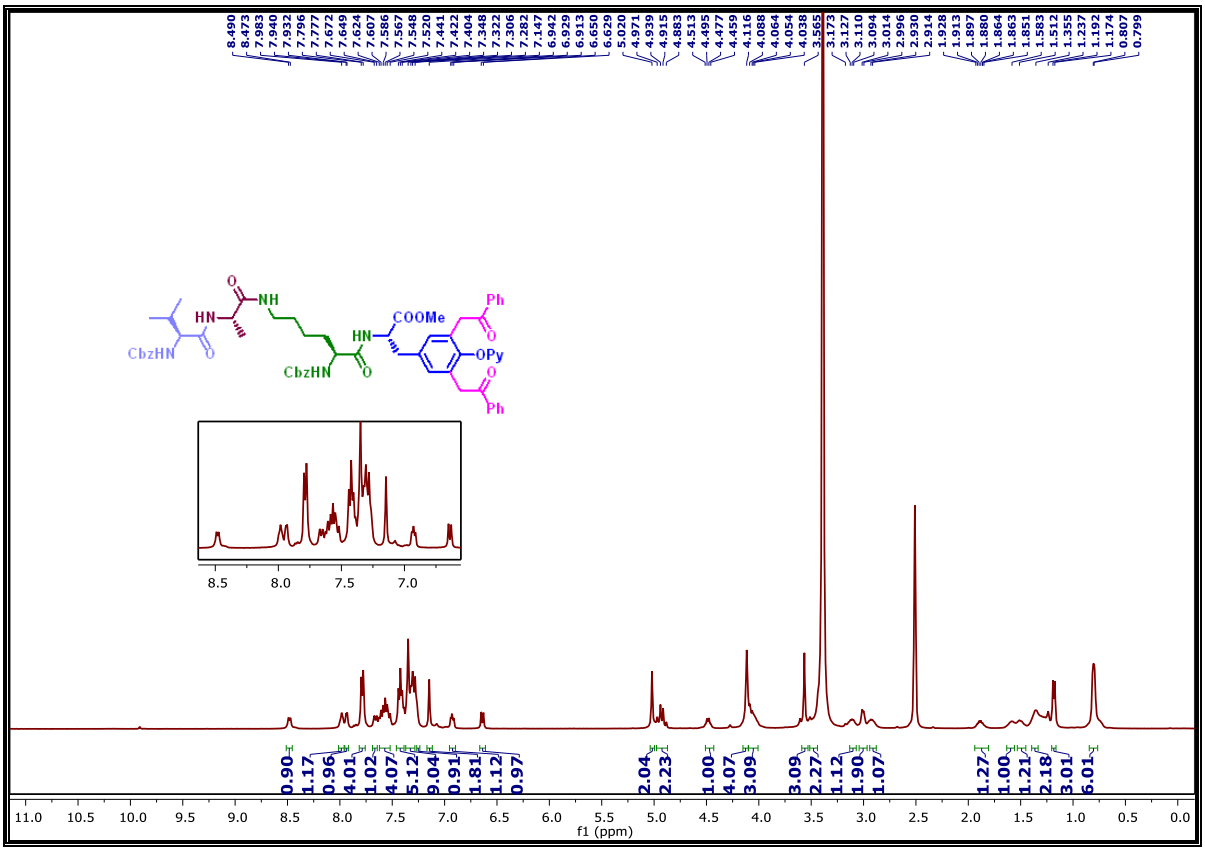
## $^{1}$H NMR of 3qa (400 MHz, $CDCl_3$)



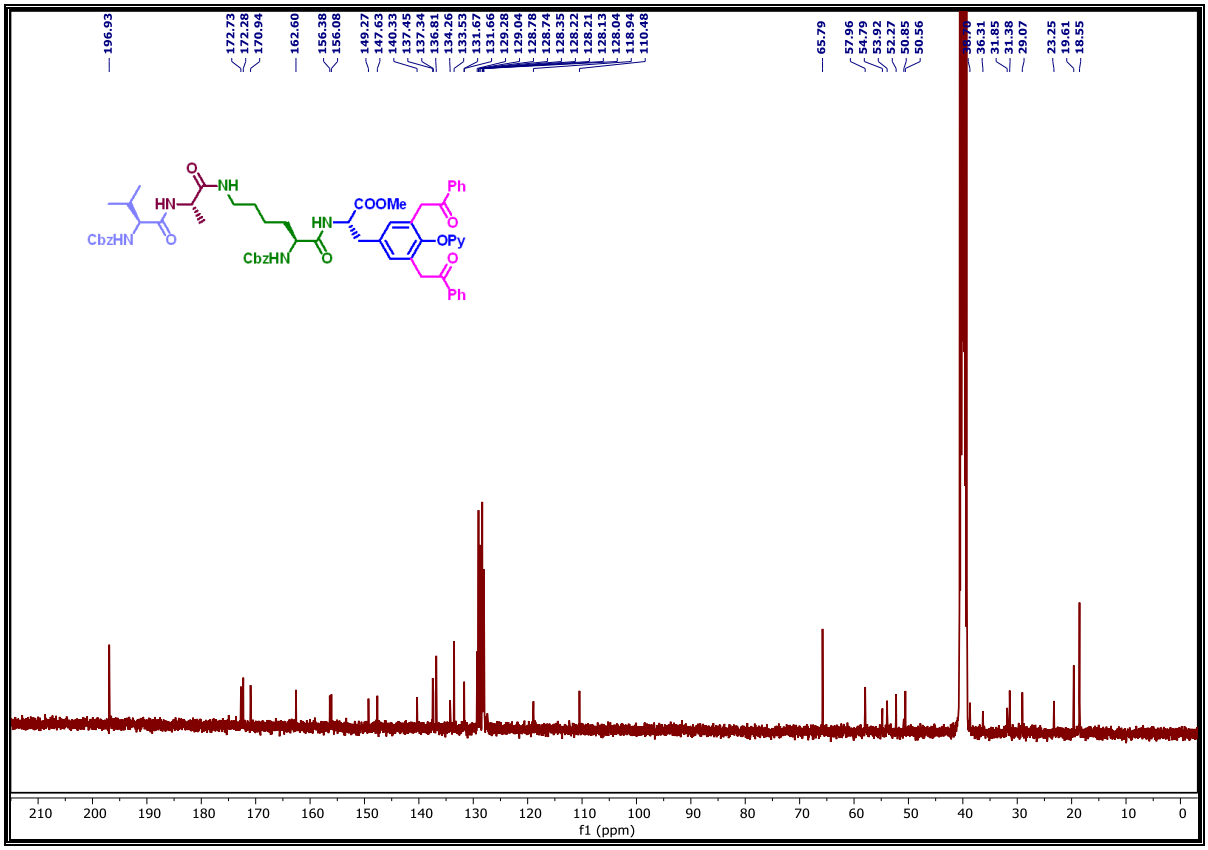

## $^{13}$C NMR of 3qa (100 MHz, $CDCl_3$)



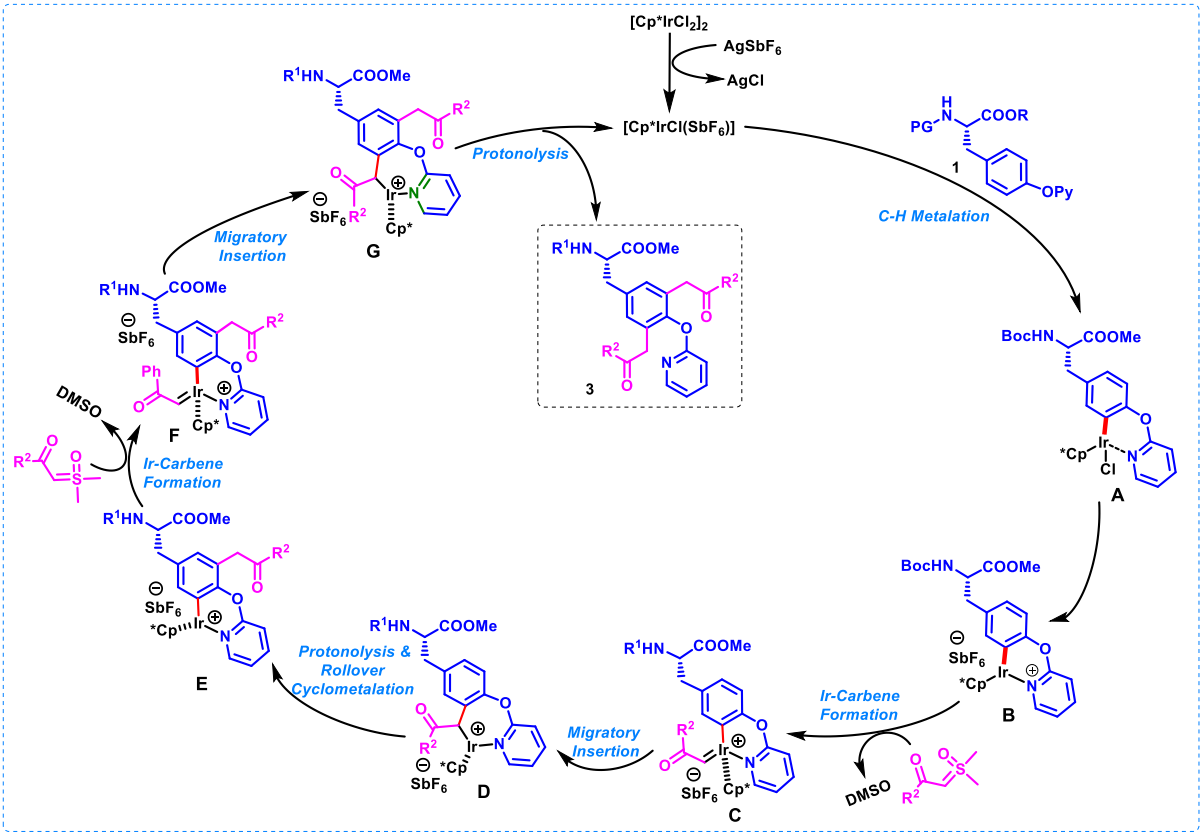
## $^{1}$H NMR of 3ra (400 MHz, DMSO-$d_6$)



## $^{13}$C NMR of 3ra (100 MHz, DMSO-$d_6$)



**7. Scheme S1.** Plausible mechanism

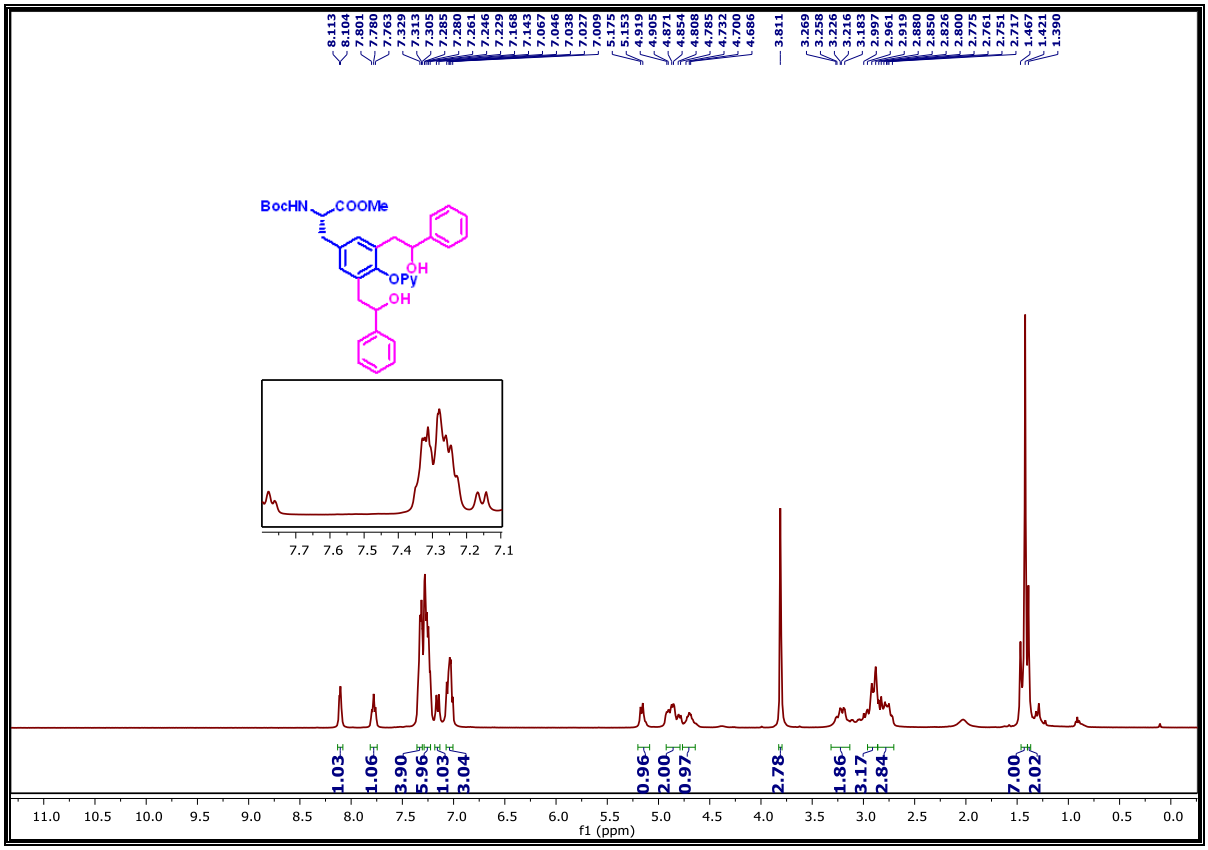



## 8. Procedure for reduction of the two ketonic carbonyls in 3aa

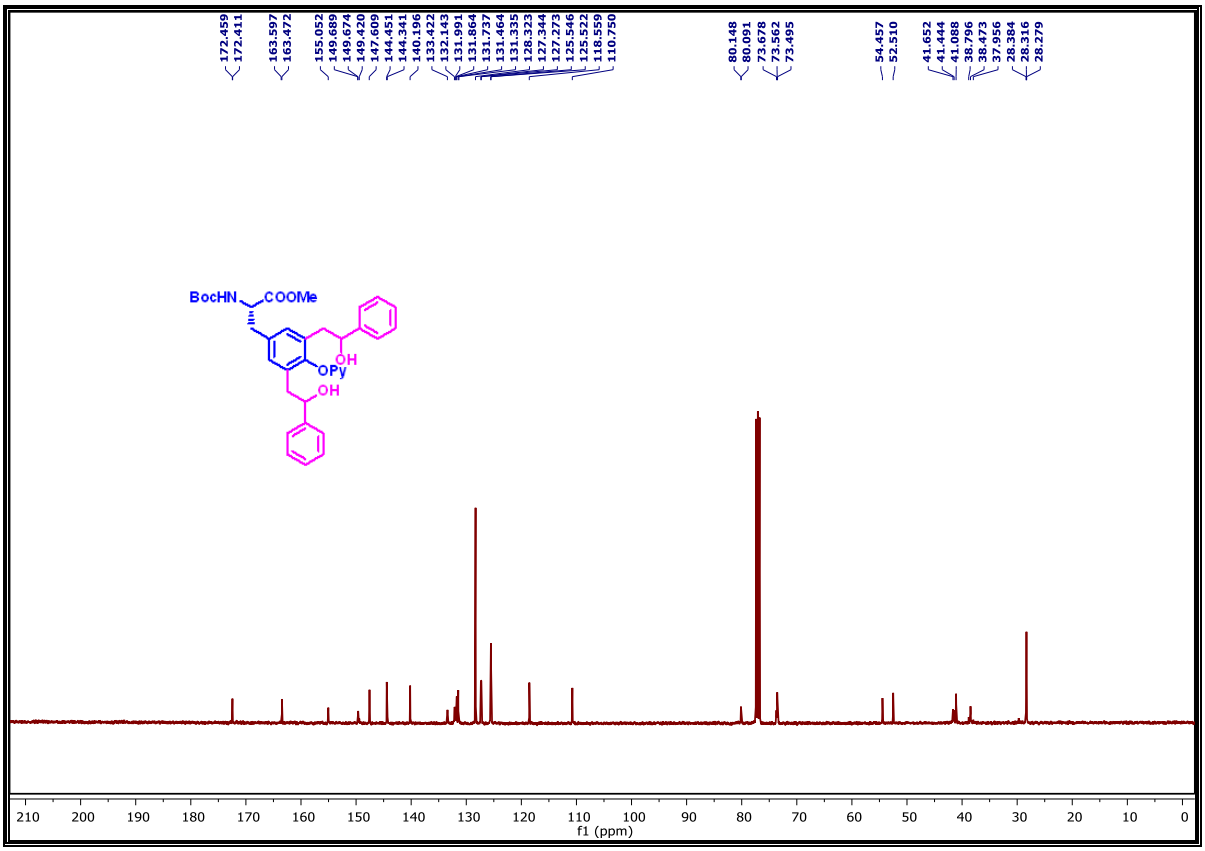
To a stirred solution of **3aa** (0.070 mg, 0.1151 mmol) in MeOH (2 mL), $NaBH_4$ (0.018 g, 0.4604 mmol) was slowly added at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 15 minutes, and then at room temperature for 3 hours. Water was later added to the reaction and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure, and the residue obtained was purified by silica gel chromatography (hexanes/ethyl acetate = 7:3) to afford **4aa**.

**Methyl (2*S*)-3-(3,5-bis(2-hydroxy-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (4aa). (mixture of diastereomers)** Purification by of crude mixture by column chromatography (hexanes/ethyl acetate = 3:7) afforded compound **4aa** as a colourless semisolid; yield: 0.058 g (82%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.11 (d, $J$ = 3.6 Hz, 1H), 7.78 (t, $J$ = 7.6 Hz, 1H), 7.36 – 7.30 (m, 4H), 7.29 – 7.22 (m, 6H), 7.15 (d, $J$ = 10.0 Hz, 1H), 7.07 – 7.00 (m, 3H), 5.16 (d, $J$ = 8.8 Hz, 1H), 4.93 – 4.79 (m, 2H), 4.77 – 4.64 (m, 1H), 3.81 (s, 3H), 3.32 – 3.14 (m, 2H), 2.96 – 2.86 (m, 3H), 2.86 – 2.69 (m, 3H), 1.42 (s, 7H), 1.39 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.5, 172.4, 163.6, 163.5, 155.1, 149.7, 149.7, 149.4, 147.6, 144.5, 144.3, 140.2, 133.4, 132.1, 132.0, 131.9, 131.7, 131.5, 131.3, 128.3, 127.3, 127.3, 125.5, 125.5, 118.6, 110.8, 80.2, 80.1, 73.7, 73.6, 73.5, 54.5, 52.5, 41.7, 41.4, 41.1, 38.8, 38.5, 37.9, 28.4, 28.3, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{41}N_2O_7^+$ : 613.2913, found 613.2927 $[M+H]^+$.

## $^{1}$H NMR of 4aa (400 MHz, $CDCl_3$)




## $^{13}$C NMR of 4aa (100 MHz, $CDCl_3$)

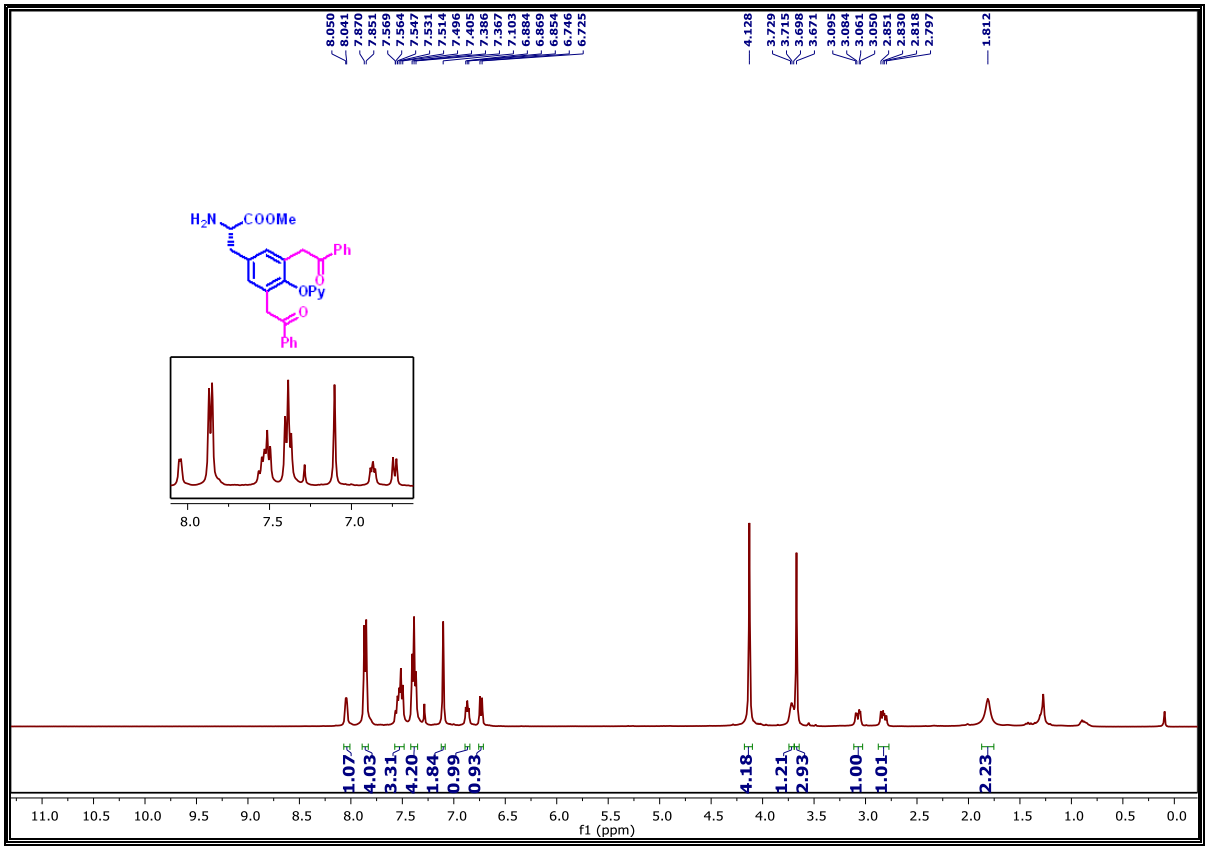


## 9. Procedure for deprotection of Boc group in 3aa

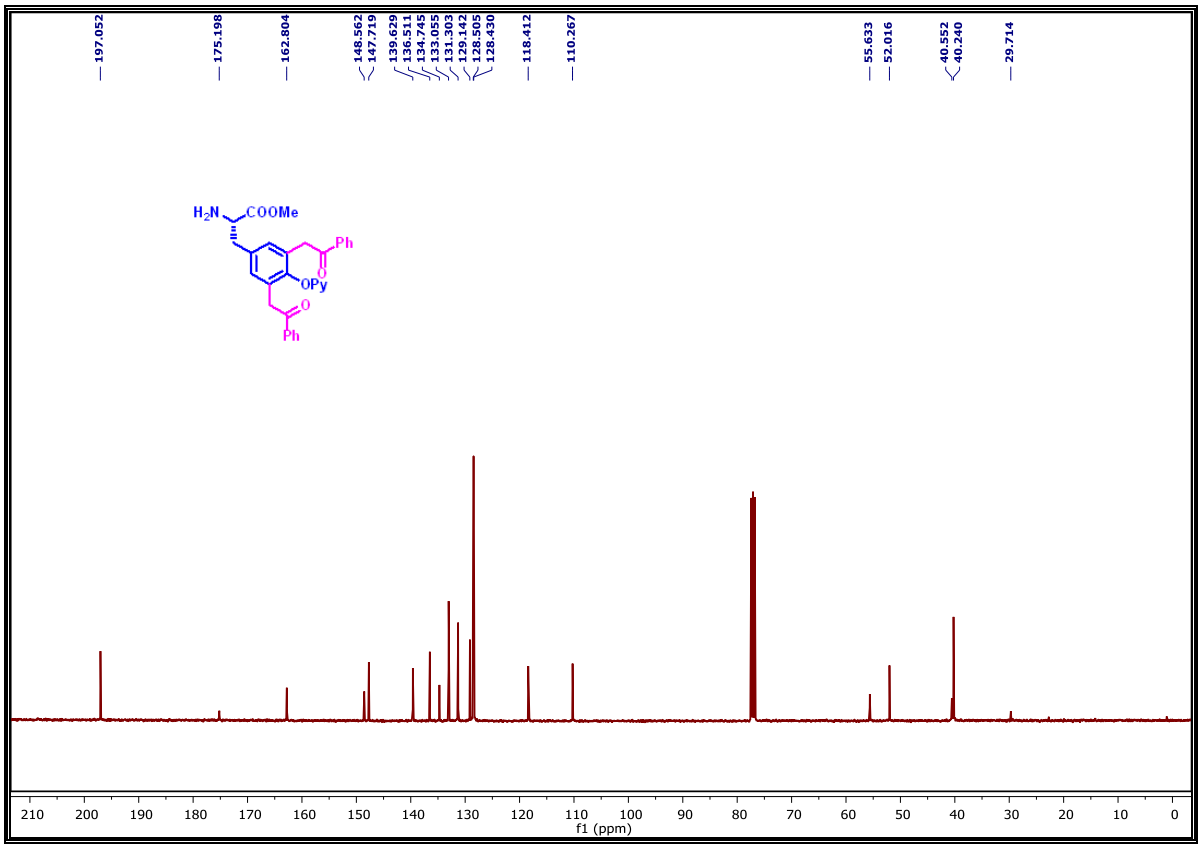
To a stirred solution of **3aa** (0.070 g, 0.1151 mmol) in dichloromethane (2 mL), trifluoroacetic acid (131 $\mu$L, 1.1513 mmol) was added drop-wise at room temperature. The reaction was stirred at room temperature for 12 hours. The reaction mixture was diluted with DCM (15 mL) and the mixture was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford **5aa**.

**Methyl (*S*)-2-amino-3-(3,5-bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)propanoate (5aa).** Compound **5aa** was obtained as a pale yellow semisolid; yield: 0.031 g (53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J$ = 3.6 Hz, 1H), 7.86 (d, $J$ = 7.6 Hz, 4H), 7.57 – 7.48 (m, 3H), 7.39 (t, $J$ = 7.6 Hz, 4H), 7.10 (s, 2H), 6.87 (t, $J$ = 6.0 Hz, 1H), 6.74 (d, $J$ = 8.4 Hz, 1H), 4.13 (s, 4H), 3.74 – 3.69 (m, 1H), 3.67 (s, 3H), 3.07 (dd, $J$ = 13.6, 4.4 Hz, 1H), 2.82 (dd, $J$ = 13.2, 8.4 Hz, 1H), 1.81 (brs, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 175.2, 162.8, 148.6, 147.7, 139.6, 136.5, 134.8, 133.1, 131.3, 129.1, 128.5, 128.4, 118.4, 110.3, 55.6, 52.0, 40.6, 40.2, 29.7; HRMS (ESI-TOF) ($m/z$) calculated $C_{31}H_{29}N_2O_5^+$ : 509.2076, found 509.2063 $[M+H]^+$.

**$^1$H NMR of Crude 5aa (400 MHz, $CDCl_3$)**



**$^{13}$C NMR of Crude 5aa (100 MHz, $CDCl_3$)**

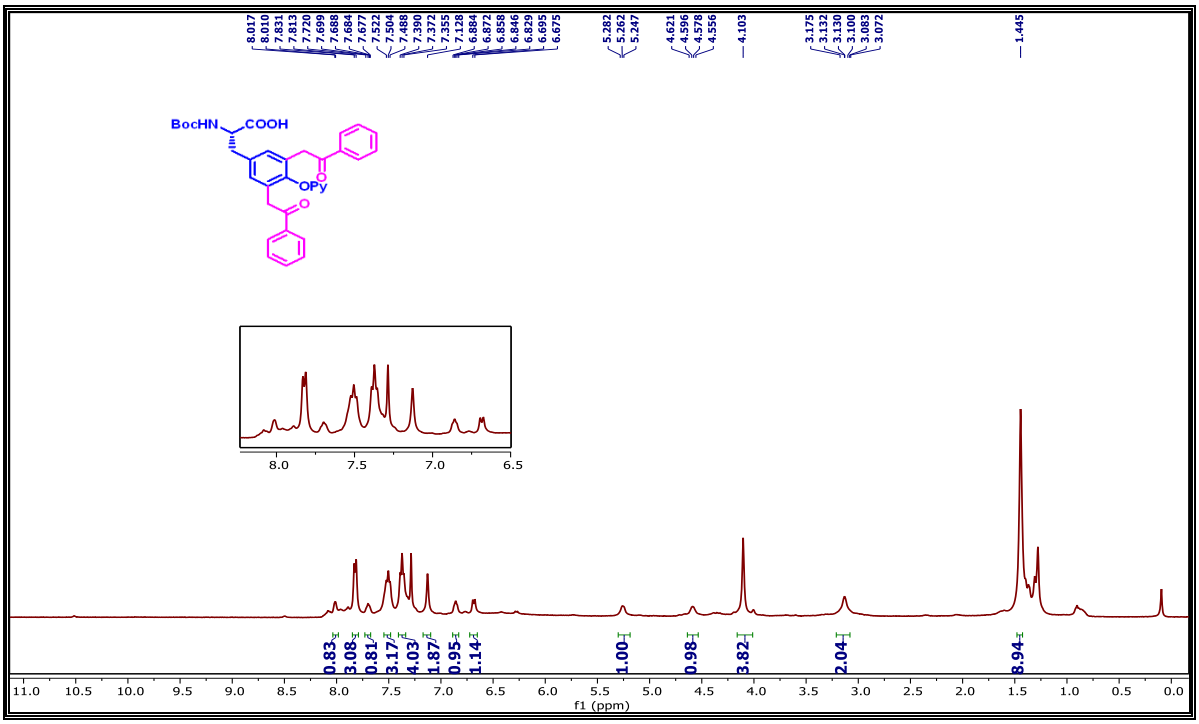



## 10. Procedure for hydrolysis of ester in 3aa

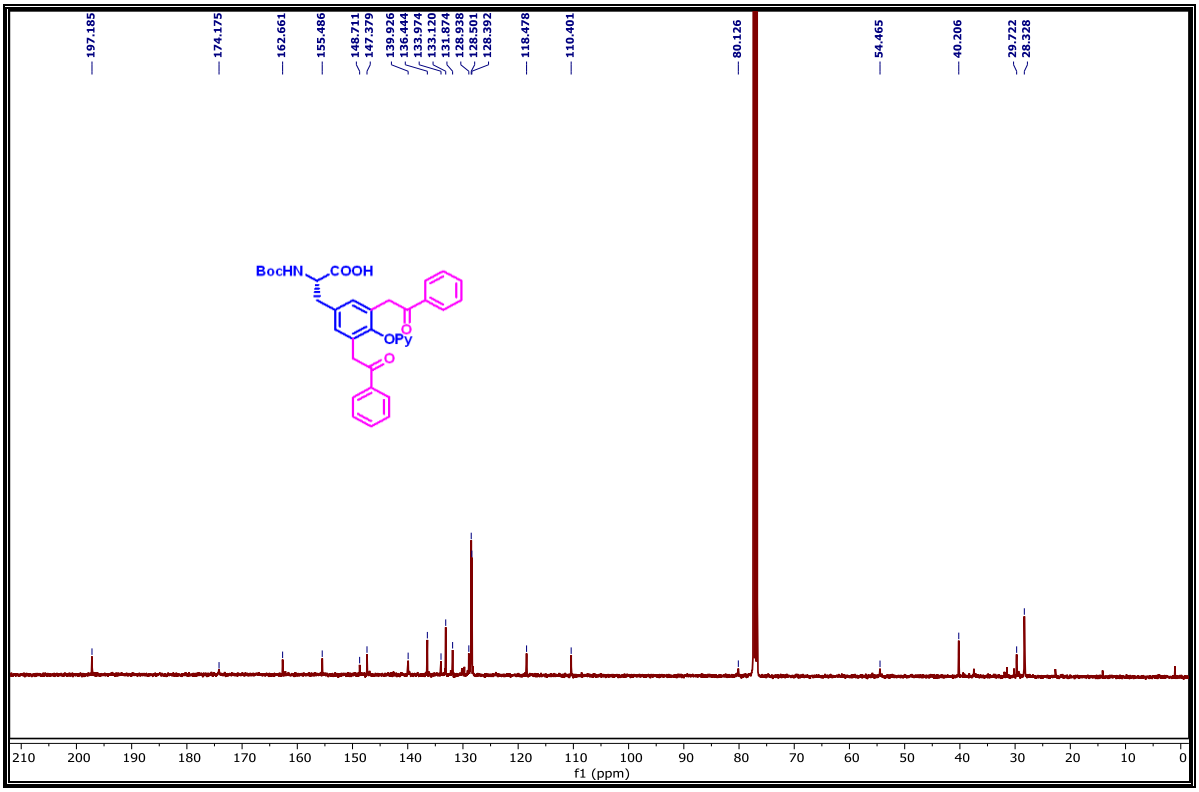
To a solution of **3aa** (0.070 g, 0.1151 mmol) in THF/$H_2O$ (1:1, 4 mL), LiOH·$H_2O$ (0.008 g, 0.1726 mmol) was added, and the reaction mixture was stirred at room temperature for 6 hours. Thereafter, the reaction mixture was concentrated under reduced pressure and the residue was diluted with EtOAc (15 mL), washed with a solution of 1M HCl (20 mL). The organic layer was separated and concentrated under reduced pressure to afford **6aa**.

**(*S*)-3-(3,5-Bis(2-oxo-2-phenylethyl)-4-(pyridin-2-yloxy)phenyl)-2-((*tert*-butoxycarbonyl) amino)propanoic acid (6aa).** Compound **6aa** was obtained as a pale yellow semisolid; yield: 0.051 g (63%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 – 7.98 (m, 1H), 7.82 (d, $J$ = 7.2 Hz, 3H), 7.73 – 7.68 (m, 1H), 7.55 – 7.48 (m, 3H), 7.41 – 7.34 (m, 4H), 7.13 (s, 2H), 6.89 – 6.83 (m, 1H), 6.69 (d, $J$ = 8.0 Hz, 1H), 5.30 – 5.19 (m, 1H), 4.64 – 4.54 (m, 1H), 4.16 – 4.01 (m, 4H)), 3.21 – 3.08 (m, 2H), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 174.2, 162.7, 155.5, 148.7, 147.4, 139.9, 136.4, 134.0, 133.1, 131.9, 128.9, 128.5, 128.4, 118.5, 110.4, 80.1, 54.5, 40.2, 29.8, 28.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{35}H_{35}N_2O_7^+$ : 595.2444, found 595.2461 $[M+H]^+$.

## $^{1}$H NMR of 6aa (400 MHz, $CDCl_3$)




## $^{13}$C NMR of 6aa (100 MHz, $CDCl_3$)



## 11. Procedure for isolation of iridium-complex (7a)

A mixture of Boc-L-Tyr(OPy)-OMe (**1a**, 0.035 g, 0.0939 mmol), $[Cp^*IrCl_2]_2$ (0.037 g, 0.0939 mmol), NaOAc (0.092 g, 2.254 mmol) and DCM (3.0 mL) were added to a Schlenk tube under $N_2$ atmosphere. The mixture was stirred at 60 $^0$C for 18 h, then cooled to room temperature. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography on (hexanes/ethyl acetate = 7:3) to afford a pale yellow semisolid **[Mixture of (A′+B′) in the ratio 1:1]**; yield: 0.027 g; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.63 (d, $J$ = 5.6 Hz, 2H), 7.69 (t, $J$ = 7.8 Hz, 2H), 7.36 (s, 1H), 7.08 (s, 1H), 7.09 (d, $J$ = 8.0 Hz, 2H), 6.99 (t, $J$ = 6.6 Hz, 2H), 6.91 (t, $J$ = 8.2 Hz, 2H), 6.63 (d, $J$ = 8.4 Hz, 1H), 6.56 (d, $J$ = 8.4 Hz, 1H), 5.06 – 4.89 (m, 2H), 4.67 – 4.57 (m, 1H), 4.52 – 4.42 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.14 – 3.06 (m, 1H), 3.04 – 2.86 (m, 3H), 1.53 (s, 30H), 1.44 (s, 9H), 1.41 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.0, 172.7, 163.1, 163.1, 155.3, 155.2, 153.6, 153.6, 153.3, 153.2, 141.0, 140.9, 1140.2, 140.2, 133.0, 132.9, 124.9, 124.9, 120.6, 120.5, 115.0, 120.5, 115.0, 114.9, 114.3, 87.9, 87.8, 79.7, 79.6, 60.4, 54.9, 54.4, 52.3, 52.2, 37.4, 37.3, 29.7, 28.3, 22.4, 14.1, 8.8; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{38}N_2O_5IrClNa^+$ (**A′**): 757.1996, found 757.1990 $[M+Na]^+$ and $C_{30}H_{38}N_2O_5Ir^+$ (**B′**): calculated 699.2410, found 699.2412 $[M]^+$.

**HRMS of Ir-Complex (7a: A′+B′) (100 MHz, $CDCl_3$)**

<table>
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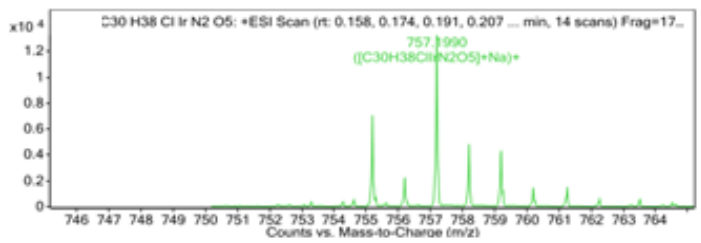
<td> 
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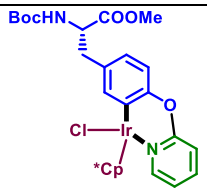
<td> 

detected as $[M]^+$ in HRMS<br>Cacl.: 757.1996, Found.: 757.1990</td>
</tr>
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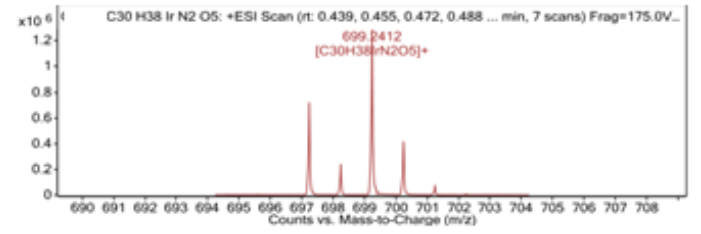
<td> 
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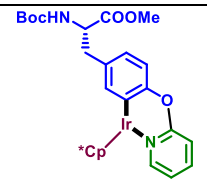
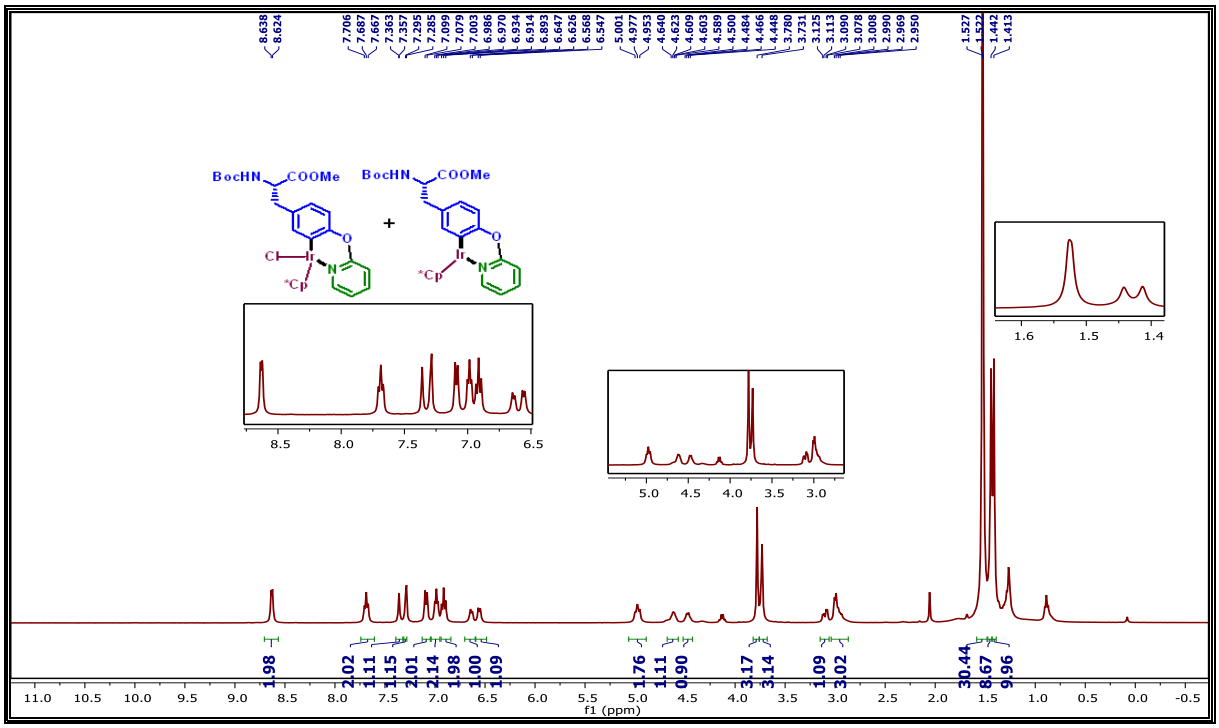
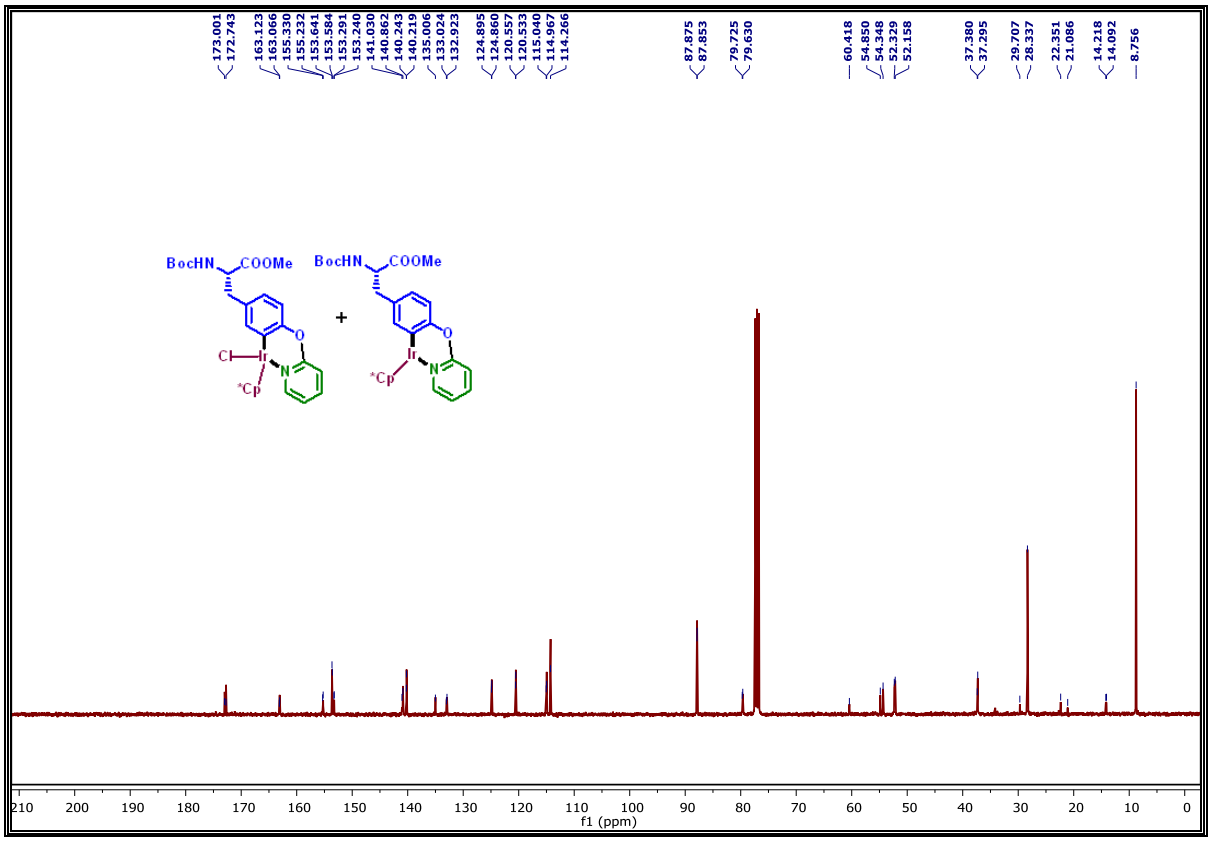
<td> 

detected as $[M]^+$ in HRMS<br>Cacl.: 699.2410, Found.: 699.2412</td>
</tr>
</table>

## $^{1}$H NMR of Ir-Complex (7a: A′+B′) (400 MHz, $CDCl_3$)

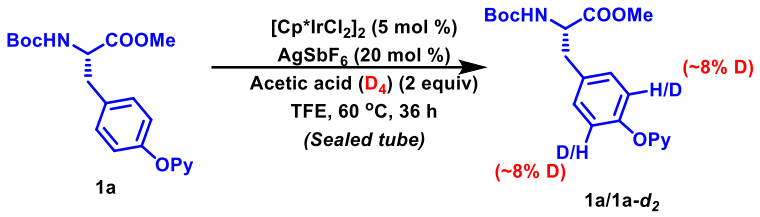


## $^{13}$C NMR of Ir-Complex (7a: A′+B′) (100 MHz, $CDCl_3$)

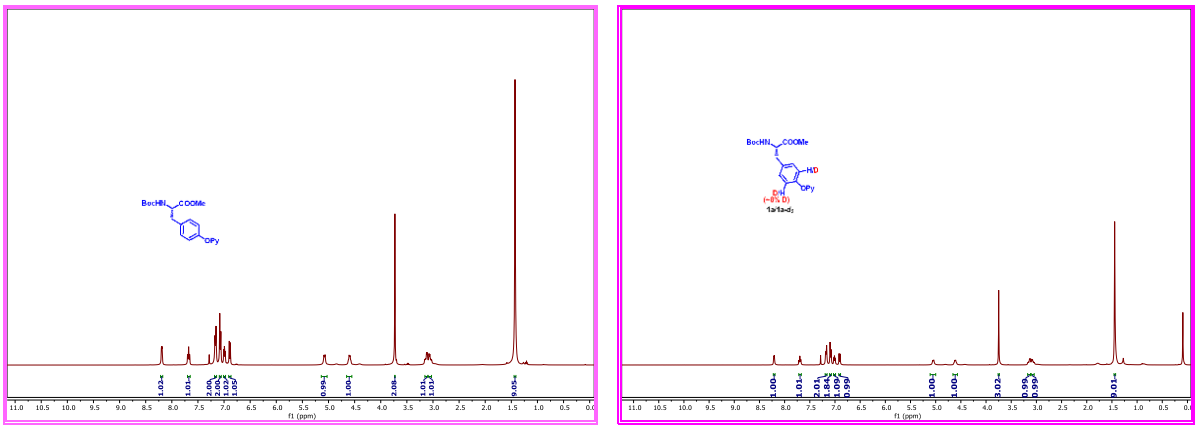


## 12. Deuterium labelling study

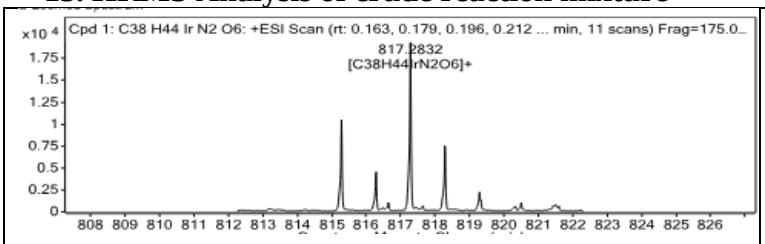
To an oven-dried round-bottom flask charged with 2 mL of TFE (2 mL), **1a** (1 equiv), $[Cp^*IrCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), acetic acid-$d_4$ (2 equiv) were added. The reaction was allowed to stir at 60 ºC for 36 h. The reaction was cooled to room temperature, quenched with water and extracted with DCM (2 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Purification by column chromatography using ethyl acetate/hexanes (2:8) as eluent afforded the desired product (**1a** + **1a-*d*$_2$**); $^1$H NMR of this product indicated approximately 8% deuteration scrambling on both terminal *ortho* aryl protons when compared with the $^1$H NMR of **1a**.

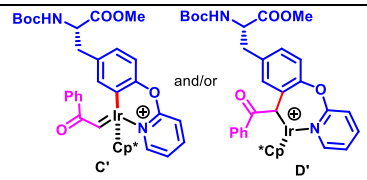



**$^1$H NMR of 1a and 1a + 1a-*d*$_2$ (400 MHz, CDCl$_3$)**



## 13. HRMS Analysis of crude reaction mixture

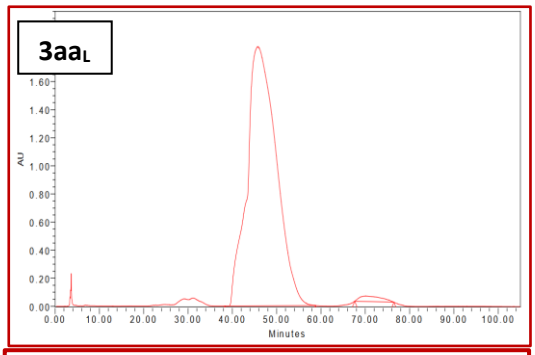


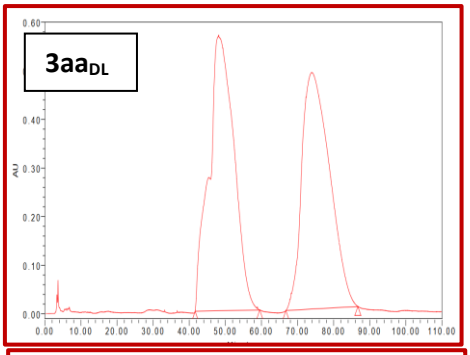




detected as [M]+ in HRMS
Cacl.:817.2828, Found.: 817.2832

## 14. HPLC chromatograms of 3aa$_L$ and 3aac$_{DL}$

HPLC separation of **3aa$_L$** (Chiralpak® IA-3, $^n$hexane/$^i$PrOH: 80:20, v/v, Detection wavelength: -245 nm), 1.0 mL/min.): $t_r$ (major) = 45.8 min, $t_r$ (minor) = 70.2 min, >98% ee. HPLC separation of **3aa$_{DL}$** (Chiralpak® IA-3, $^n$*h*exane/$^i$PrOH: 80:20, v/v), 1.0 mL/min., Detection wavelength: 245 nm): $t_r$ = 48.1 min, $t_r$ = 73.9 min.




Peak Results

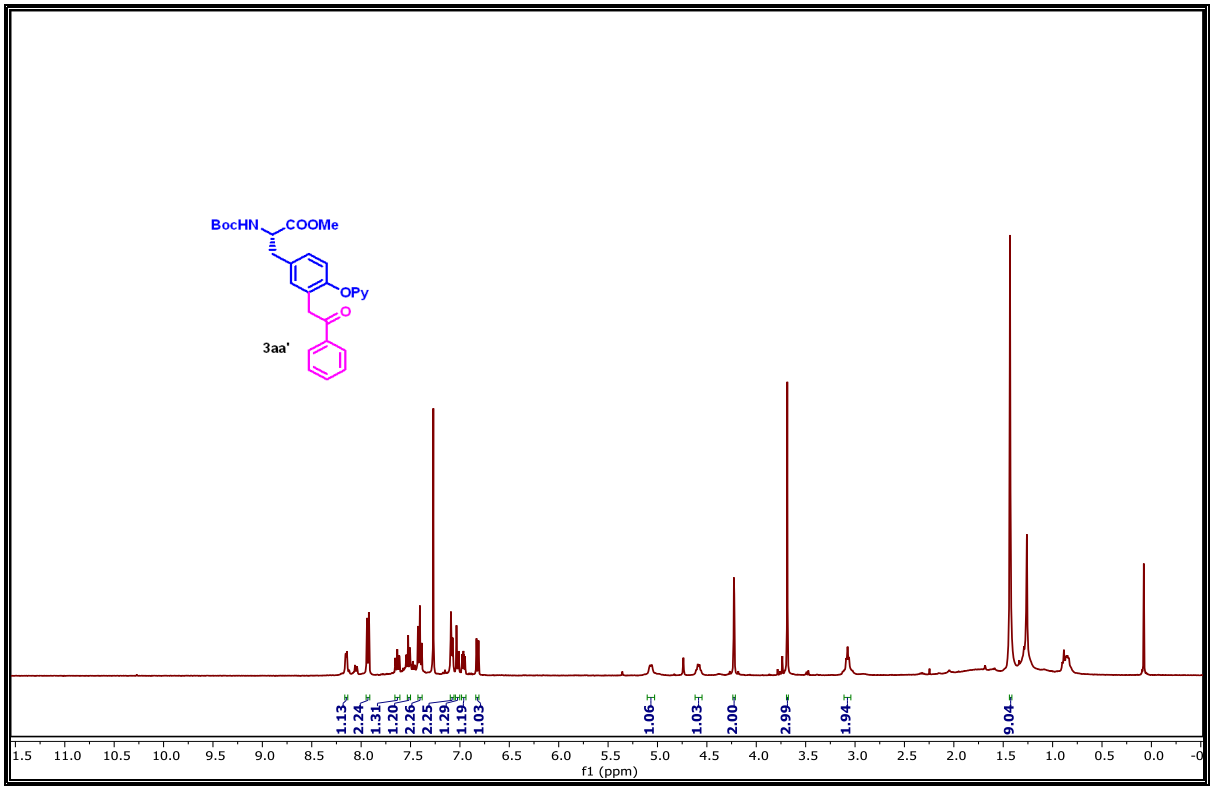
| | Processed Channel Descr. | SampleName | RT | Area |
|---|---|---|---|---|
| 1 | 2998 PDA 245.0 nm (2998 (210-400)nm) | NK 818 CHI 2 | 45.828 | 848811375 |
| 2 | 2998 PDA 245.0 nm (2998 (210-400)nm) | NK 818 CHI 2 | 70.239 | 13813764 |

Peak Results

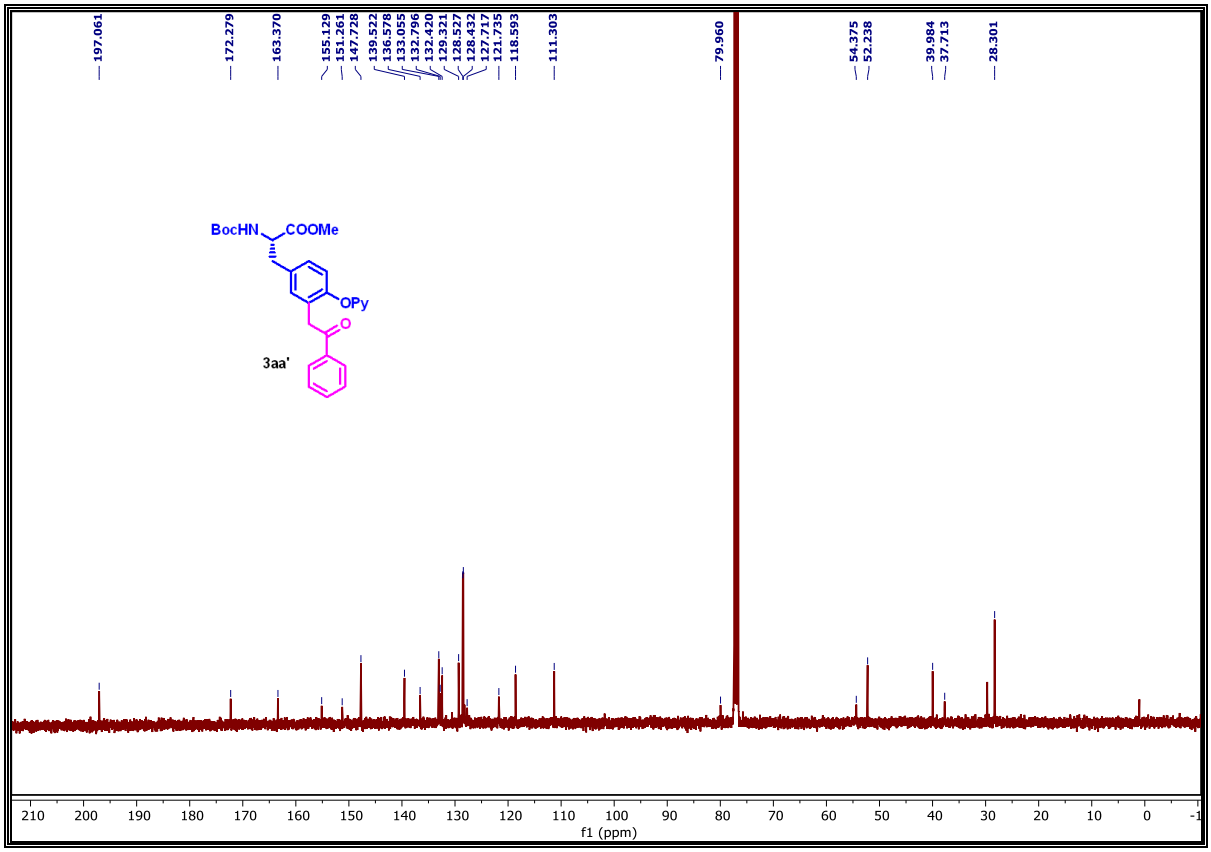
| | Processed Channel Descr. | SampleName | RT | Area |
|---|---|---|---|---|
| 1 | 2998 PDA 245.0 nm (2998 (210-400)nm) | NK 915 RAC 2 | 48.154 | 273395995 |
| 2 | 2998 PDA 245.0 nm (2998 (210-400)nm) | NK 915 RAC 2 | 73.933 | 261715192 |

## 15. $^{1}$H and $^{13}$C NMR spectra of 3aa′

### $^{1}$H NMR of 3aa′ (400 MHz, $CDCl_3$)



**$^{13}$C NMR of 3aa′ (100 MHz, $CDCl_3$)**




## 16. References


1. S. Zhu, K. Shi, H. Zhu, Z.-K. Jia, X.-F. Xia, D. Wang and L.-H. Zou, *Org. Lett.,* 2020, **22**, 1504-1509.

2. N. D. Kharat, S. Naharwal, D.Tank, S. S. Panda, K. Bajaj and R. Sakhuja, *Org. Lett.,* 2023, **25**, 7673-7677.

3. M. San Segundo and A. Correa, *Chem.Sci.,* 2020, **11**, 11531-11538.