

COMMUNICATION

C-Terminal Bioconjugation of Peptides through Photoredox Catalyzed Decarboxylative Alkynylation

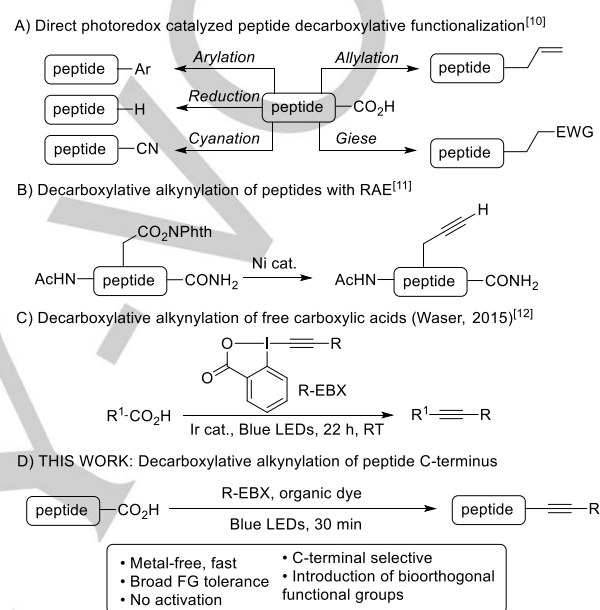
Marion Garreau, Franck Le Vaillant and Jerome Waser^[*]

Abstract: We report the first decarboxylative alkynylation of the C-terminus of peptides starting from free carboxylic acids. The reaction is fast, metal-free and proceeds cleanly to afford alkynylated peptides with a broad tolerance for the C-terminal amino acid. Through the use of hypervalent iodine reagents, the introduction of a broad range of functional groups was successful. C-terminal selectivity was achieved by differentiation of the oxidation potentials of the carboxylic acids based on the use of fine-tuned organic dyes.

Peptides are important in drug discovery, with 140 peptide therapeutics in clinical trials in 2015.^[1] The biological activity and stability of peptides can be further improved by the synthesis of bioconjugates^[2] and macrocycles.^[3] There is thus a need for amino acid selective modification methods.^[4] Progress has been realized through incorporation of unnatural amino acids.^[4,5] However, this strategy implies to know the targeted sequence and requires building blocks compatible with solid-phase synthesis. In contrast, the late-stage functionalization of peptides does not require specialized synthesis methods, but excellent chemoselectivity under mild conditions is needed.^[4,6] If numerous methods for selective modification of lysine, cysteine, or the N-terminal position have been developed,^[7] direct and selective functionalization of the C-terminus remains underexplored. Until recently, available methods relied on amidation reactions or thioester formation.^[8] The selectivity issues encountered between the side-chains of aspartic and glutamic acids and the C-terminal position have limited the use of these strategies.

The emergence of photoredox catalysis has led to novel strategies in biomolecule functionalization, due to mild conditions to generate radicals.^[9] Decarboxylation strategies were developed for C-terminal functionalization (Scheme 1A).^[10a,b] Starting from free carboxylic acids, arylation,^[10c,d] reduction,^[10e,f] allylation,^[10g] cyanation^[10h] and Giese coupling^[10c,i,j] were described. The latter was employed by the MacMillan group to selectively functionalize the C-terminal position of native peptides, taking advantage of the different oxidation potentials of the carboxylic acids.^[10k] Selective functionalizations of peptides were reported using redox-active esters (RAE).^[11a-c] A decarboxylative alkynylation was described by Baran and co-workers (Scheme 1B).^[11d] This approach required pre-functionalization of the carboxylic acid and was employed only for side-chain

modification. A direct decarboxylative alkynylation on peptides starting from free carboxylic acids has not yet been achieved.



Scheme 1. Photoredox-catalyzed decarboxylation strategies for the functionalization of peptides. EWG = Electron-withdrawing group, Phth = phthaloyl, FG = functional group.

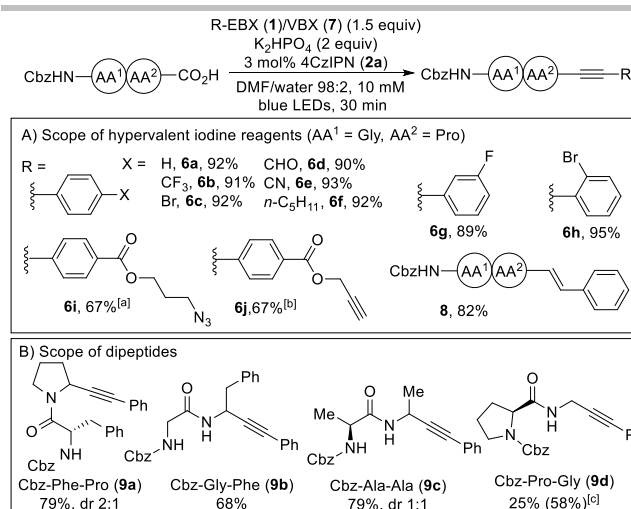
Our group and others developed photoredox-catalyzed decarboxylative alkynylation of amino acids using ethynylbenziodoxolone (EBX) reagents (Scheme 1C).^[12] Peptides could not be functionalized in this work. Nevertheless, EBX reagents have a high potential for biomolecule functionalization. They have been used for the alkynylation of thiols in cysteines^[13] or indoles in tryptophans.^[14] Herein, we report a decarboxylative alkynylation on peptides, which proceeds in 30 min at room temperature under blue LEDs irradiation using EBX reagents and organic dyes as photocatalysts (Scheme 1D). The reaction was selective for the C-terminus, even in the presence of aspartic or glutamic acid residues.

To avoid the use of expensive and toxic transition metals, we focused on organic dyes,^[15] in contrast to previous works based on iridium photocatalysts.^[12a,b] Our group has applied derivatives of 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN, **2a**) in photoredox catalysis.^[16] The introduction of chlorine atoms on the carbazoles (**2b**) gave stronger oxidizing dyes, closing a gap in potential between 4CzIPN (**2a**) and dicyanoanthracene (DCA) (+ 1.35 and 2.06 V, Figure 1). Considering the oxidation potentials of terminal vs-side chain carboxylic acids, it is possible to achieve

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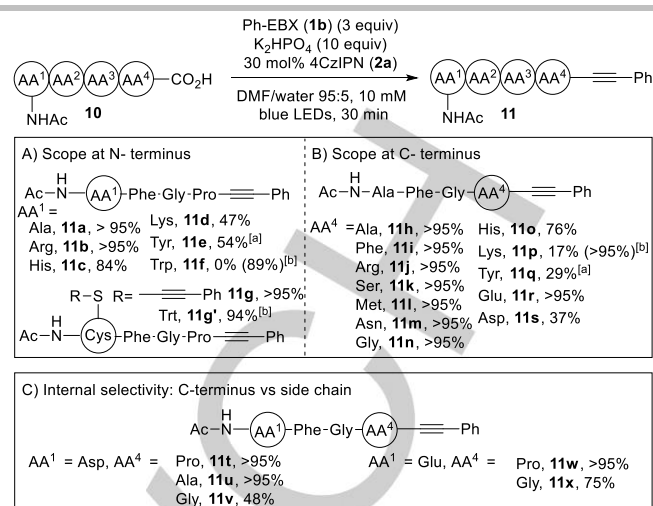
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Scheme 3. Scope of the reaction on dipeptides. Reaction conditions: peptide (1.0 equiv, 0.3 mmol), 4CzIPN (**2a**) (3 mol%), R-EBX (**1**) (1.5 equiv) and K₂HPO₄ (2 equiv) in DMF/water 98:2 (10 mM) at rt for 30 min. Isolated yields are given. ^[a]On 0.05 mmol scale. ^[b]On 0.1 mmol scale. ^[c]With 4CzIPN (**2b**) as catalyst.

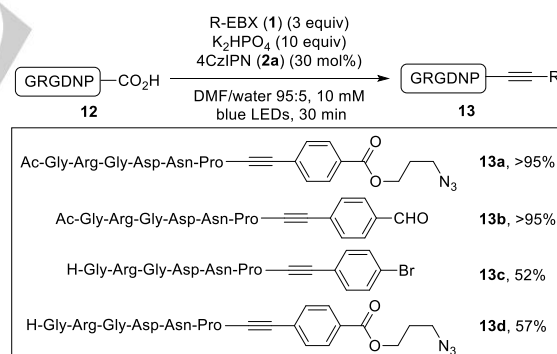
Before expanding the scope to larger peptides, we performed a robustness test:^[26] the alkylation of dipeptide **5a** was repeated in presence of functionalized amino acids, and only for the most electron-rich ones a lower yield was observed.^[24] We then examined variation at the N-terminus of peptide tetramers bearing a C-terminal proline (Scheme 4A). After slight modification of the conditions (increasing of the excess of reagent, base and catalyst loading), full and clean conversion to alkylnated peptides **11a** and **11b** was obtained with alanine or arginine at the N-terminus. Amino acids with basic side-chains such as histidine and lysine led to a lower yield (**11c** and **11d**). With tyrosine and tryptophan, **11e** and **11f** could not be detected.^[27] Gratifyingly, changing the catalyst to the less oxidizing {Ir[dF(CF₃)ppy]₂dtbbpy}PF₆ (**4**), allowed the formation of peptide **11e** in 54% yield. 4tBuCzIPN (**2c**) afforded 20% of yield and the use of 4DPAIPN-derived dyes **3a-c** led to only traces of product **11e**. This approach was not successful with tryptophan, but carrying the reaction prior to deprotection of the indole led to 89% yield. In presence of a cysteine, a very fast thiol-alkynylation takes place first, affording bis-functionalized alkyne **11g** quantitatively. The use of trityl protected peptide gave C-terminus alkylation in 94% yield.

Variation of the C-terminus was then investigated (Scheme 4B). Full and clean conversion to peptides **11h-m** was obtained with alanine, phenylalanine, arginine, serine, methionine, asparagine and glycine. A lower yield was observed for histidine, lysine or tyrosine (**11o-q**). When lysine was protected, the yield was quantitative. Aspartic and glutamic acid were tolerated at the C-terminus. Full and clean conversion was obtained for glutamic acid (**11r**), and 37% of the mono-alkynylated peptide **11s** with aspartic acid. C-terminus selectivity with side-chain carboxylic acids at N-terminus was then investigated (Scheme 4C). In the presence of aspartic acid, selective C-terminus alkylation was observed in the case of proline, alanine and even glycine with good to excellent conversion (**11t** to **11v**). Alkylation at the side chain of aspartic or glutamic acid was never observed in more than 5%. Similar reactivity and selectivity were obtained with an N-terminus glutamic acid (**11w** and **11x**).



Scheme 4. Scope of the reaction on peptide tetramers. Reaction conditions: peptide (1.0 equiv, 1 μmol), 4CzIPN (**2a**) (30 mol%), Ph-EBX (**1b**) (3 equiv) and K₂HPO₄ (10 equiv) in DMF/water 95:5 (10 mM) at rt for 30 min. Yield measured by HPLC as the ratio of the area of the product over remaining starting material and possible side-products at 214 nm. Average of 3 independent trials. All peptides were obtained as non-separable mixtures of diastereoisomers at the propargylic position. ^[a]Using 30 mol% of Ir catalyst **4**. ^[b]Starting from protected peptide.

The methodology was then applied to the N-terminal protected hexamer GRGDNP (**12a**), a potent inhibitor of cell attachment to fibronectin,^[28] which was successfully functionalized with EBX reagents bearing an azide or an aldehyde functional group to give **13a** and **13b** (Scheme 5). Alkylation of N-terminus unprotected peptide **12c** and **12d** was also possible, even if no complete conversion was achieved: Peptides **13c** and **13d** bearing bromide and azide functionalities were obtained in 52 and 57% yield.



Scheme 5. Functionalization of GRGDNP (**12**). Reaction conditions: peptide (1 equiv, 1 μmol), 4CzIPN (**2a**) (30 mol%), R-EBX (**1**) (3 equiv) and K₂HPO₄ (10 equiv) in DMF/water 95:5 (10 mM) at rt for 30 min. Yield measured by HPLC as the ratio of the area of the product over remaining starting material and possible side-products at 214 nm. Average of 3 independent trials. All peptides were obtained as non-separable mixtures of diastereoisomers at the propargylic position.

In summary, a metal-free decarboxylative alkylation of the C-terminus of peptides has been developed. Using organic dyes, alkylnated products were obtained in 30 minutes at room temperature. Complete selectivity for the C-terminus was observed in presence of carboxylic acid side-chains. Most other side-chains were also tolerated, with the exception of tryptophan,

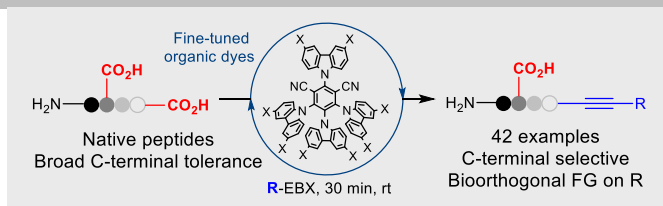
which needed to be protected, resulting in a broadly applicable methodology for modifying peptides.

Acknowledgements

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Only at the end: A decarboxylative alkylation of the C-terminal of peptides starting from free carboxylic acids has been developed. The reaction is fast, metal-free and proceeds cleanly to afford alkynylated peptides bearing a broad range of functional groups. C-terminal selectivity was achieved based on the use of fine-tuned organic dyes.

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1. General methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless for the decarboxylative alkynylation and if stated otherwise. For flash chromatography, distilled technical grade solvents were used. THF, CH₃CN, toluene and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 10 ppm, Karl-Fischer titration). The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, TCI, Merck or Bachem and used as such unless stated otherwise. All dipeptides starting materials and H-GRGDNP-OH were commercially available and used as received. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC aluminum or glass plates and visualized with UV light. ¹H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, CD₃OD, DMSO-d₆ or acetone-d₆, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal methanol signal at 3.30 ppm, the internal DMSO signal at 2.50 ppm or the internal acetone signal at 2.05 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Bruker DPX-400 100 MHz spectrometer in chloroform-d, CD₃OD, DMSO-d₆ or acetone-d₆, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal methanol signal at 49.0 ppm, the internal DMSO signal at 39.5 ppm or the internal acetone signals at 29.84 and 206.26 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, br = broad).

High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. MS-MS analyses were performed on a LTQ Orbitrap FTMS instrument (LTQ Orbitrap Elite FTMS, Thermo Scientific, Bremen, Germany) operated in the positive mode coupled with a robotic chip-based nano-ESI source (TriVersa Nanomate, Advion Biosciences, Ithaca, NY, U.S.A.). A standard data acquisition and instrument control system was utilized (Thermo Scientific) whereas the ion source was controlled by Chipsoft 8.3.1 software (Advion BioScience). Samples were loaded onto a 96-well plate (Eppendorf, Hamburg, Germany) within an injection volume of 5 µL. The experimental conditions for the ionization voltage was +1.4kV and the gas pressure was set at 0.30 psi. The temperature of ion transfer capillary was 275 °C, tube voltages. FTMS spectra were obtained in the 80-1000 *m/z* range in the reduce profile mode with a resolution set to 120,000. In all spectra one microscan was acquired with a maximum injection time value of 1000ms. Typical CID experiments were carried out using Normalized collision energy values of 26-28 and 5 Da of isolation width.

Photoredox catalyzed reactions were performed in test tubes (5 and 10 mL), or Schlenk tubes (50 mL) which were held using a rack for test tubes placed at the center of a crystallization flask. For overnight reactions, the latter was filled by water, in order to keep the temperature as constant as possible, in presence of an air flow. On this flask were attached the blue LEDs (RUBAN LED 5MÈTRES - 60LED/M - 3528 BLEU - IP65 with Transformateur pour Ruban LED 24W/2A/12V, bought directly on RubanLED.com). The distance between the LEDs and the test tubes was approximately 2 cm for the test tubes and 5 cm for the Schlenk flasks. Long irradiation resulted in temperature increasing up to 37°C during overnight reactions.

Tetramers peptides were synthesized by solid phase peptide synthesis using a Multiprep RSi Intavis. Crude products were purified by preparative RP-HPLC on an Agilent 1260 HPLC system with a G2260A 1260 Prep ALS Autosampler, a G1361a 1260 Prep Pump, a G1365C 1260 MWD detector and a G1364B 1260 FC-PS collector, coupled with a Waters XBridge semi-preparative C18 column (19 x 150 mm, 5 µm). Water (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% TFA, were used as the mobile phase at a flow rate of 20 mL.min⁻¹. The following method was used: 100% A to 100% B in 20 minutes.

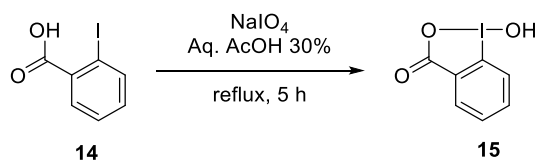
RP-HPLC-MS measurements were performed on an Agilent 1290 Infinity HPLC system with a G4226a 1290 Autosampler, a G4220A 1290 Bin Pump and a G4212A 1290 DAD detector, connected to a 6130 Quadrupole LC/MS MS, coupled with a Waters XBridge C18 column (250 x 4.6 mm, 5 μ m). Water:acetonitrile 95:5 (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase at a flow rate of 0.6 mL/min⁻¹. The gradient was programmed as follows: 100% A to 100% B in 20 minutes then isocratic for 5 minutes (method A). The column temperature was set up to 25 °C. Low resolution mass spectrometric measurements were acquired using the following parameters: positive electrospray ionization (ESI), temperature of drying gas = 350 °C, flow rate of drying gas = 12 L. min⁻¹, pressure of nebulizer gas = 60 psi, capillary voltage = 2500 V and fragmentor voltage = 70 V. In few cases, the gradient was programmed as follows: 100% A to 100% B in 40 minutes, in order to resolve peak overlapping (method B). The other parameters were untouched.

UV/Vis spectroscopy was performed on an Agilent Cary 60 UV-Vis and steady-state luminescence spectroscopy was recorded on a Varian Cary Eclipse spectrophotometer. Cyclic voltammetry experiments were performed on a Biologic SP-150 Potentiostat, with a three-electrode cell configuration: a glassy carbon electrode as the working electrode, Pt wire as a counter electrode and an Ag/AgCl (KCl, 3M) electrode as the reference electrode. Bu₄NPF₆ was employed as the electrolyte (0.1 M).

2. Preparation of hypervalent iodine reagents

The synthesis of reagents **1a-1h** had already been described before by our group. The procedures are taken from the indicated publications to facilitate reproduction of the results by having all data in the same file.

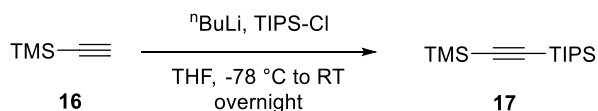
1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**15**)



Following a reported procedure,^[1] NaIO₄ (40.5 g, 189 mmol, 1.05 equiv) and 2-iodobenzoic acid (**14**) (44.8 g, 180 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (350 mL). The mixture was vigorously stirred and refluxed for 5 h. The reaction mixture was then diluted with cold water (250 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 150 mL) and acetone (3 x 150 mL), and air-dried in the dark overnight to afford 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (**15**) (44.3 g, 168 mmol, 93%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.97 (m, 1H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. Consistent with reported data.^[1]

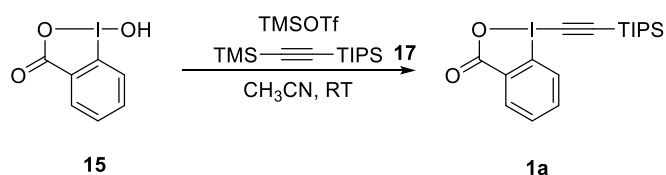
Triisopropylsilyl trimethylsilylacetylene (**17**)



Following a reported procedure,^[2] *n*-butyllithium (2.5 M in hexanes, 28 mL, 70 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**16**) (7.0 g, 71 mmol, 1.0 equiv) in THF (100 mL) at -78 °C. The mixture was warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotriisopropylsilane (15 mL, 71 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (100 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with water and brine, then dried over MgSO₄, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by filtration on silica eluting with pentane (500 mL) to yield **17** (16 g, 64 mmol, 90%) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 1.08 (m, 21H, TIPS), 0.18 (s, 9H, TMS). Consistent with reported data.^[2]

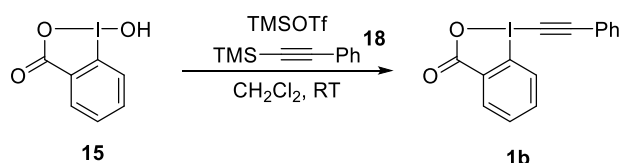
1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one (TIPS-EBX, **1a**)



Following a reported procedure,^[3] 2-iodosylbenzoic acid (**15**) (8.0 g, 30 mmol, 1.0 equiv) was charged in an oven-dried round-bottomed 250 mL flask equipped with a magnetic stirrer. The solid was placed under a nitrogen atmosphere and anhydrous acetonitrile (100 mL) was added. The mixture was cooled to 0 °C. Trimethylsilyltriflate (6.0 mL, 33 mmol, 1.1 equiv) was added dropwise. After 15 min, (trimethylsilyl)(triisopropylsilyl)acetylene (**17**) (8.5 g, 33 mmol, 1.1 equiv) was added dropwise. After 30 min, the suspension became an orange solution. Pyridine (2.7 mL, 33 mmol, 1.1 equiv) was added dropwise. After 15 min, the reaction mixture was transferred in a one-neck 500 mL flask and concentrated under vacuum to afford a yellow solid. The solid was dissolved in DCM (100 mL) and transferred in a 500 mL separatory funnel. The organic layer was washed with a 1 M HCl solution (50 mL) and the aqueous layer was extracted with DCM (100 mL). The organic layers were combined, washed with a saturated solution of NaHCO₃ (2 x 100 mL), dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (40 mL) afforded TIPS-EBX (**3**) (9.2 g, 21.5 mmol, 71%) as colorless crystals.

Mp (Dec.) 170-176 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (m, 1H, ArH), 8.29 (m, 1H, ArH), 7.77 (m, 2H, ArH), 1.16 (m, 21H, TIPS). ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m). Consistent with reported data.^[3]

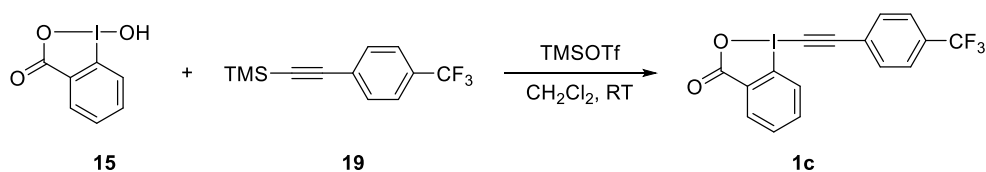
1-[Phenylethynyl]-1,2-benziodoxol-3(1H)-one (Ph-EBX, **1b**)



Following a reported procedure,^[1] trimethylsilyltriflate (7.5 mL, 42 mmol, 1.1 equiv) was added dropwise to a suspension of 2-iodosylbenzoic acid (**15**) (10 g, 38 mmol, 1.0 equiv) in CH₂Cl₂ (100 mL) at 0 °C. The mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**18**) (8.2 mL, 42 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at RT, during this time a white solid was formed. A saturated solution of NaHCO₃ (100 mL) was added and the mixture was stirred vigorously for 5 min. The resulting suspension was filtered on a glass filter. The two layers of the mother liquors were separated and the organic layer was washed with sat. NaHCO₃ (100 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by filtration and boiled in CH₃CN (150 mL). The mixture was cooled down, filtered and dried under high vacuum to afford Ph-EBX (**1b**) (8.6 g, 25 mmol, 65%) as a colorless solid.

Mp (Dec.) 155 – 160 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (m, 1H, ArH), 8.28 (m, 1H, ArH), 7.80 (m, 2H, ArH), 7.63 (m, 2H, ArH), 7.48 (m, 3H, ArH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3, 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2. Consistent with reported data.^[1]

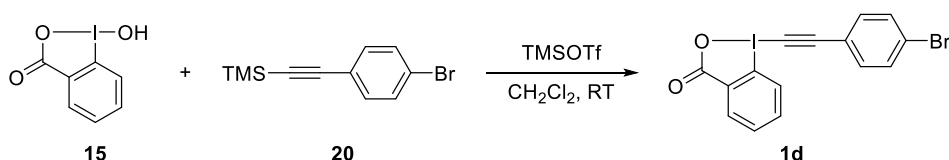
1-[4-Trifluoromethylphenylethynyl]-1,2-benziodoxol-3(1H)-one (**1c**)



Following a reported procedure,^[4] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.3 g, 5.0 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 1 h, followed by the dropwise addition of trimethyl((4-(trifluoromethyl)phenyl)ethynyl)silane (**19**) (1.3 mL, 5.5 mmol, 1.1 equiv), which was dissolved in CH₂Cl₂ (1 mL). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **1c** (1.3 g, 3.2 mmol, 64%) as a pale yellow solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 – 8.38 (m, 1H, ArH), 8.28 – 8.19 (m, 1H, ArH), 7.84 – 7.74 (m, 2H, ArH), 7.74 – 7.65 (m, 4H, ArH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.6, 135.0, 133.0, 132.6, 132.2 (q, *J*_{C-F} = 33.0 Hz), 131.7, 131.2, 126.3, 125.7 (q, *J*_{C-F} = 3.6 Hz), 124.4, 123.4 (q, *J*_{C-F} = 272.6 Hz), 116.1, 104.2, 53.7. Consistent with reported data.^[4]

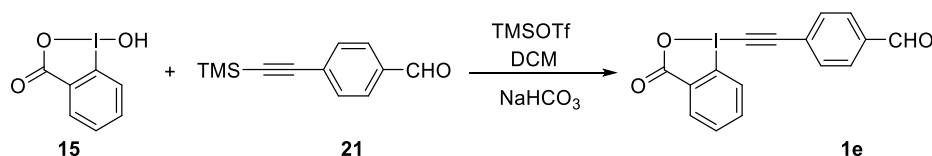
1-[4-Bromophenylethynyl]-1,2-benziodoxol-3(1H)-one (**1d**)



Following a reported procedure,^[5] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.3 g, 5.0 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 1 h, followed by the dropwise addition of ((4-bromophenyl)ethynyl)trimethylsilane (**20**) (1.2 g, 5.5 mmol, 1.1 equiv), which was dissolved in CH₂Cl₂ (1 mL). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 min, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **1d** (1.4 g, 3.3 mmol, 66%) as a pale yellow solid.

Mp 158-163 °C (decomposition). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.30 (m, 1H, ArH), 8.30 – 8.13 (m, 1H, ArH), 7.84 – 7.72 (m, 2H, ArH), 7.58 (d, 2H, *J* = 8.5 Hz, ArH), 7.46 (d, 2H, *J* = 8.5 Hz, ArH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.6, 135.1, 134.3, 132.7, 132.3, 131.9, 131.4, 126.3, 125.7, 119.6, 116.3, 105.4, 52.1. Consistent with reported data.^[6]

1-((4-Formylphenyl)ethynyl)-1,2-benziodoxol-3(1H)-one (**1e**)

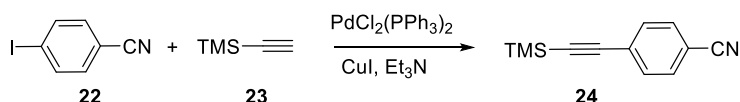


Following a reported procedure,^[7] trimethylsilyl triflate (0.89 mL, 4.9 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.19 g, 4.49 mmol, 1.00 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((4-formylphenyl)ethynyl)trimethylsilane (**21**) (1.00 g, 4.94 mmol, 1.10 equiv), which was dissolved in CH₂Cl₂ (1 mL). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The

mixture was cooled down, filtered and dried under high vacuum to afford **1e** (0.80 g, 2.1 mmol, 41%) as a yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 10.08 (s, 1H, CHO), 8.35 (d, J = 9.1 Hz, 1H, ArH), 8.14 (dd, J = 7.4, 1.7 Hz, 1H, ArH), 8.02 (d, J = 8.5 Hz, 2H, ArH), 7.96 – 7.88 (m, 3H, ArH), 7.82 (t, J = 7.3 Hz, 1H, ArH). ^{13}C NMR (101 MHz, DMSO- d_6) δ 192.6, 166.3, 136.7, 135.3, 133.2, 131.9, 131.4, 129.8, 127.7, 126.1, 116.4, 102.9, 56.6. Consistent with reported data.^[7]

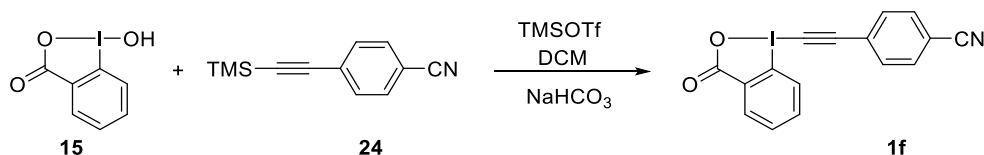
Trimethyl((4-cyanophenyl)ethynyl)silane (**24**)



Following a slight modification of the reported procedure,^[8] 4-iodobenzonitrile (**22**) (1.00 g, 4.37 mmol, 1.0 equiv) was dissolved in triethylamine (10 mL) (without prior drying). After three freeze-thaw-pump cycles, PdCl₂(PPh₃)₂ (92 mg, 0.13 mmol, 3 mol%) and copper iodide (42 mg, 0.22 mmol, 5 mol%) were added under N₂. After the addition of ethynyltrimethylsilane (**23**) (1.2 mL, 8.7 mmol, 2.0 equiv) the green suspension was stirred at RT for 3 h. The reaction mixture was concentrated under vacuum, dissolved in CH₂Cl₂ (30 mL), washed with a saturated ammonium chloride solution (30 mL) and water (30 mL). The organic layers were then dried over MgSO₄, filtered and concentrated under vacuum. The resulting oil was purified by column chromatography (pentane/ethyl acetate 25:1) to afford 4-((trimethylsilyl)ethynyl)benzonitrile (**24**) (847 mg, 4.25 mmol, 97%) as a white solid.

^1H NMR (400 MHz, Chloroform- d) δ 7.59 (d, J = 8.7 Hz, 2H, ArH), 7.53 (d, J = 8.8 Hz, 2H, ArH), 0.26 (s, 9H, SiCH₃). ^{13}C NMR (101 MHz, Chloroform- d) δ 132.6, 132.1, 128.1, 118.6, 111.9, 103.1, 99.7, -0.12. Consistent with reported data.^[9]

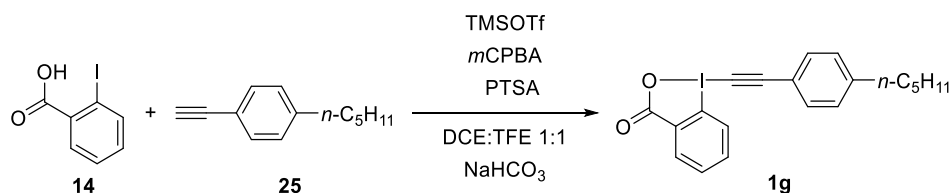
1-[4-Cyanophenylethynyl]-1,2-benziodoxol-3(1H)-one (**1f**)



Following a reported procedure,^[5] trimethylsilyl triflate (0.73 mL, 4.0 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (963 mg, 3.65 mmol, 1.00 equiv) in CH₂Cl₂ (12 mL) at RT. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((4-cyanophenyl)ethynyl)trimethylsilane (**24**) (800 mg, 4.01 mmol, 1.10 equiv), which was dissolved in CH₂Cl₂ (1 mL). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **1f** (865 mg, 2.32 mmol, 64%) as a pale brown solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.34 (d, J = 8.2 Hz, 1H, ArH), 8.13 (dd, J = 7.4, 1.7 Hz, 1H, ArH), 7.99 (d, J = 8.6 Hz, 2H, ArH), 7.90 (d, J = 8.6 Hz, 3H, ArH), 7.81 (t, J = 7.3 Hz, 1H, ArH). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.3, 135.3, 133.3, 132.8, 131.9, 131.4, 131.4, 127.8, 125.3, 118.2, 116.4, 112.7, 102.0, 57.4. Consistent with reported data.^[5]

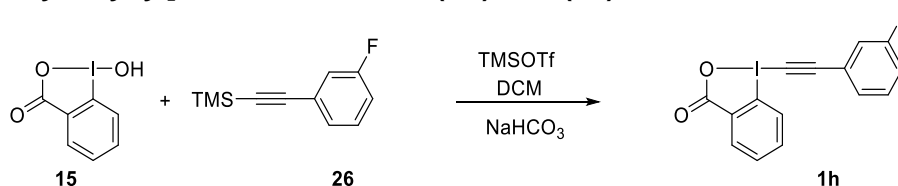
1-((4-Pentylphenyl)ethynyl)-1,2-benziodoxol-3(1H)-one (**1g**)



Following a reported procedure,^[10] in a sealed tube, 2-iodobenzoic acid (**14**) (1.00 g, 4.03 mmol, 1.00 equiv), 4-methylbenzenesulfonic acid (775 mg, 4.03 mmol, 1.00 equiv) and *m*CPBA (994 mg, 4.44 mmol, 1.10 equiv) were suspended in DCE:TFE 1:1 (12 mL) and stirred for 1 h at 55 °C. After 1 h, 1-ethynyl-4-pentylbenzene (**25**) (1.1 mL, 5.6 mmol, 1.4 equiv) was added and the reaction was stirred at 55 °C for 24 h. After 24 h, the solvent was evaporated and the residue was redissolved in CH₂Cl₂ (20 mL) and stirred vigorously with NaHCO₃ sat. (30 mL). After 1 h, the reaction mixture was transferred into a separating funnel and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2x50 mL). The combined organic layers were washed with sat. NaHCO₃, dried over MgSO₄, filtered and concentrated under vacuum. The resulting solid was boiled in MeCN (20 mL), then filtered and the collected solid was further purified by column chromatography using pure ethyl acetate. Trituration in pentane afforded **1g** (191 mg, 0.457 mmol, 11%) as a pale yellow solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.45 – 8.40 (m, 1H, ArH), 8.28 – 8.21 (m, 1H, ArH), 7.79 – 7.74 (m, 2H, ArH), 7.56 – 7.48 (m, 2H, ArH), 7.26 – 7.23 (m, 2H, ArH), 2.71 – 2.60 (m, 2H, ArCH₂), 1.69 – 1.54 (m, 2H, ArCH₂CH₂), 1.40 – 1.27 (m, 4H, CH₂CH₂CH₃), 0.90 (t, *J* = 6.8 Hz, 3H, CH₂CH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.6, 146.7, 135.0, 133.0, 132.6, 131.7, 131.5, 129.0, 126.3, 117.7, 116.4, 107.4, 49.4, 36.2, 31.5, 31.0, 22.6, 14.1. Consistent with reported data.^[10]

1-[3-Fluorophenylethynyl]-1,2-benziodoxol-3(1H)-one (**1h**)

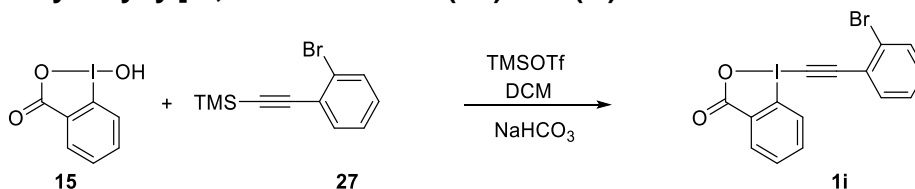


Following a reported procedure,^[10] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.32 g, 5.00 mmol, 1.00 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 1 h, followed by the drop wise addition of ((3-fluorophenyl)ethynyl)trimethylsilane (**26**) (1.1 mL, 5.5 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and the collected solid was dried under high vacuum to afford **1h** (787 mg, 2.15 mmol, 43%) as a colorless solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (dd, *J* = 8.2, 0.8 Hz, 1H, ArH), 8.13 (dd, *J* = 7.4, 1.7 Hz, 1H, ArH), 7.91 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H, ArH), 7.81 (td, *J* = 7.3, 0.9 Hz, 1H, ArH), 7.64 – 7.59 (m, 1H, ArH), 7.58 – 7.53 (m, 2H, ArH), 7.47 – 7.37 (m, 1H, ArH). ¹³C NMR (101 MHz, DMSO-*d*₆)¹ 166.3, 161.8 (d, *J* = 245.6 Hz), 135.3, 131.9, 131.3, 131.2 (d, *J* = 8.7 Hz), 129.0 (d, *J* = 2.9 Hz), 127.7, 122.4 (d, *J* = 9.6 Hz), 119.2 (d, *J* = 23.4 Hz), 118.1 (d, *J* = 21.1 Hz), 116.4, 102.5 (d, *J* = 3.3 Hz), 53.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -111.7. Consistent with reported data.^[10]

¹ One carbon is not resolved.

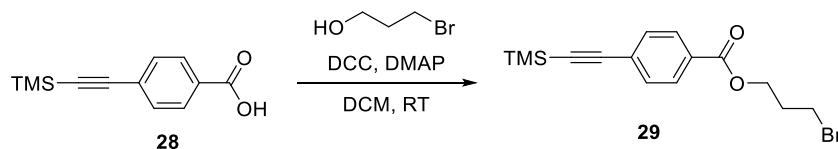
1-[2-Bromophenylethynyl]-1,2-benziodoxol-3(1*H*)-one (**1i**)



Following a reported procedure,^[6] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.32 g, 5.00 mmol, 1.00 equiv) in CH₂Cl₂ (15 mL) at RT. The resulting suspension was stirred for 3 h, followed by the drop wise addition of ((2-bromophenyl)ethynyl)trimethylsilane (**27**) (1.17 g, 5.50 mmol, 1.10 equiv). The resulting suspension was stirred for 6 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (20 mL). The mixture was cooled down, filtered and the collected solid was dried under high vacuum to afford **1i** (1.50 g, 3.51 mmol, 70%) as a colorless solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (td, *J* = 7.3, 2.1 Hz, 2 H, Ar*H*), 7.84 – 7.74 (m, 2 H, Ar*H*), 7.68 (d, *J* = 1.1 Hz, 1 H, Ar*H*), 7.61 (dd, *J* = 7.6, 1.7 Hz, 1 H, Ar*H*), 7.36 (m, 2 H, Ar*H*). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.6, 135.2, 134.7, 133.0, 132.7, 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. Consistent with reported data.^[6]

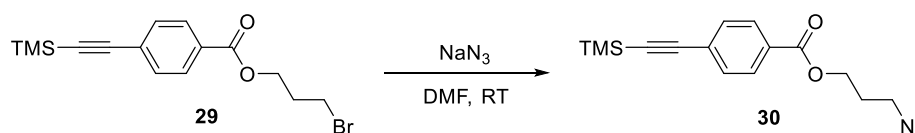
3-Bromopropyl 4-((trimethylsilyl)ethynyl)benzoate (**29**)



4-(Dimethylamino)-pyridine (67 mg, 0.55 mmol, 12 mol%) was added to a stirred reaction mixture of 4-((trimethylsilyl)ethynyl)benzoic acid (**28**) (1.0 g, 4.6 mmol, 1.0 equiv), dicyclohexylcarbodiimide (1.0 g, 5.0 mmol, 1.1 equiv), 3-bromopropan-1-ol (0.62 mL, 6.9 mmol, 1.5 equiv) in dry CH₂Cl₂ (15 mL) at room temperature. The reaction mixture was filtered after 15 h and the solid was rinsed with dichloromethane (2 x 10 mL). The combined filtrates were concentrated under vacuum. Purification by column chromatography pentane/ethyl acetate 9:1 afforded 3-bromopropyl 4-((trimethylsilyl)ethynyl)benzoate (**29**) (1.3 g, 3.8 mmol, 82 %) as a white solid.

Mp 37.2 – 39.3 °C. R_f (pentane/ethyl acetate 9:1): 0.8. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.52 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.46 (t, *J* = 6.0 Hz, 2H, OCH₂), 3.54 (t, *J* = 6.6 Hz, 2H, BrCH₂), 2.32 (p, *J* = 6.4 Hz, 2H, CH₂CH₂), 0.26 (s, 9H, TMS). ¹³C NMR (101 MHz, Chloroform-*d*) δ 165.8, 131.9, 129.5, 129.4, 127.9, 104.0, 97.9, 62.9, 31.8, 29.4, -0.2. IR (ν_{max}, cm⁻¹) 2957 (w), 2926 (w), 2353 (w), 2162 (w), 1725 (s), 1608 (w), 1410 (w), 1269 (s), 1176 (m), 1108 (m), 1016 (w), 868 (s), 769 (m). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₁₅H₁₉⁷⁹BrNaO₂Si⁺ 361.0230, 363.0209; Found 361.0235, 363.0216.

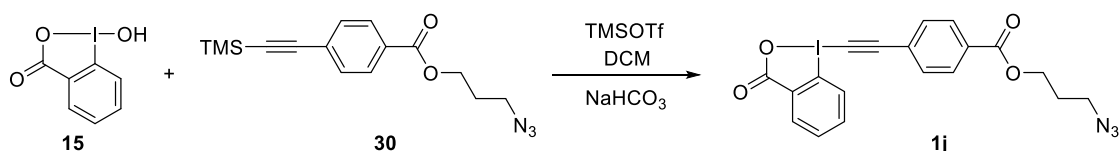
3-Azidopropyl 4-((trimethylsilyl)ethynyl)benzoate (**30**)



NaN₃ (0.25 g, 3.9 mmol, 1.2 equiv) was added to a solution of 3-bromopropyl 4-((trimethylsilyl)ethynyl)benzoate (**29**) (1.1 g, 3.2 mmol, 1.0 equiv) in dry DMF (16 mL) at RT. The mixture was heated at 50 °C overnight. Ice water was added and the aqueous layer was extracted with diethyl ether (3x). The combined organic layers were washed with brine (3x), dried over MgSO₄ and concentrated under vacuum. The crude was purified by column chromatography pentane to pentane/ethyl acetate 95:5 to afford 3-azidopropyl 4-((trimethylsilyl)ethynyl)benzoate (**30**) (0.60 g, 2.0 mmol, 61 % yield) as a pale yellow oil.

Rf: 0.7 (pentane/ethyl acetate 9:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.7 Hz, 2H, ArH), 7.52 (d, *J* = 8.7 Hz, 2H, ArH), 4.41 (t, *J* = 6.2 Hz, 2H, OCH₂), 3.48 (t, *J* = 6.7 Hz, 2H, N₃CH₂), 2.05 (p, *J* = 6.5 Hz, 2H, CH₂CH₂), 0.26 (s, 9H, TMS). ¹³C NMR (101 MHz, Chloroform-*d*) δ 165.8, 131.9, 129.5, 129.4, 128.0, 104.0, 97.9, 62.0, 48.3, 28.2, -0.2. IR (ν_{max}, cm⁻¹) 3666 (w), 2970 (m), 2902 (m), 2101 (s), 1725 (s), 1608 (m), 1472 (w), 1410 (w), 1281 (s), 1115 (m), 1065 (m), 868 (s), 856 (s), 769 (m). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₁₅H₁₉N₃NaO₂Si⁺ 324.1139; Found 324.1137.

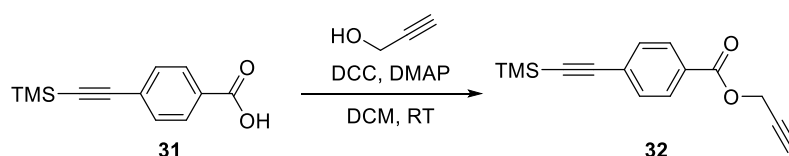
1-((4-(Prop-2-yn-1-yl)benzoate)ethynyl)-1,2-benziodoxol-3(1*H*)-one (**1j**)



Trimethylsilyl triflate (0.34 mL, 1.9 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (454 mg, 1.72 mmol, 1.00 equiv) in CH₂Cl₂ (5 mL) at RT. The resulting suspension was stirred for 1 h, followed by the drop wise addition of 3-azidopropyl 4-((trimethylsilyl)ethynyl)benzoate (**30**) (570 mg, 1.89 mmol, 1.10 equiv), which was dissolved in CH₂Cl₂ (0.5 mL). The resulting suspension was stirred for 4 h at RT. A saturated solution of NaHCO₃ (10 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (10 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH₃CN (10 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **1j** (431 mg, 0.907 mmol, 53%) as a pale brown solid.

Mp (Dec.) 106.4 – 109.3 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 – 8.41 (m, 1H, ArH), 8.34 – 8.20 (m, 1H, ArH), 8.10 (d, *J* = 8.7 Hz, 2H, ArH), 7.87 – 7.76 (m, 2H, ArH), 7.67 (d, *J* = 8.6 Hz, 2H, ArH), 4.46 (t, *J* = 6.2 Hz, 2H, OCH₂), 3.50 (t, *J* = 6.6 Hz, 2H, N₃CH₂), 2.08 (p, *J* = 6.4 Hz, 2H, CH₂CH₂). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.4, 165.3, 135.1, 132.7, 132.6, 131.8, 131.6, 131.2, 129.8, 126.2, 125.1, 116.1, 105.0, 62.4, 54.1, 48.2, 28.2. IR (ν_{max}, cm⁻¹) 3678 (w), 3389 (w), 2988 (s), 2908 (s), 2366 (w), 2101 (m), 1774 (w), 1719 (m), 1638 (m), 1454 (w), 1398 (m), 1281 (m), 1071 (s), 868 (m), 769 (m). HRMS (ESI/QTOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₁₅N₃O₄⁺ 476.0102; Found 476.0112.

Prop-2-yn-1-yl 4-((trimethylsilyl)ethynyl)benzoate (**32**)

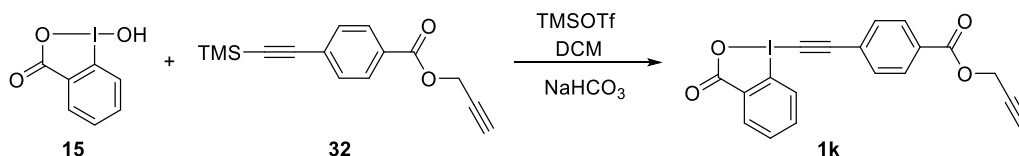


4-(Dimethylamino)-pyridine (27 mg, 0.22 mmol, 12 mol%) was added to a stirred reaction mixture of 4-((trimethylsilyl)ethynyl)benzoic acid (**31**) (0.40 g, 1.8 mmol, 1.0 equiv), dicyclohexylcarbodiimide (0.42 g, 2.0 mmol, 1.1 equiv) and 2-propynol (0.16 mL, 2.8 mmol, 1.5 equiv) in dry CH₂Cl₂ (7 mL) at RT. The reaction mixture was filtered after 15 h and the solid was rinsed with dichloromethane (2 x 5 mL). The combined filtrates were concentrated under vacuum. Purification by column

chromatography pentane/ethyl acetate 9:1 afforded prop-2-yn-1-yl 4-((trimethylsilyl)ethynyl)benzoate (**32**) (375 mg, 1.46 mmol, 80 %) as a white solid.

Mp 58 – 60 °C. Rf (pentane/ethyl acetate 9:1): 0.8. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.7 Hz, 2H, ArH), 7.52 (d, *J* = 8.7 Hz, 2H, ArH), 4.92 (d, *J* = 2.5 Hz, 2H, OCH₂), 2.52 (t, *J* = 2.5 Hz, 1H, CH), 0.26 (s, 9H, TMS). ¹³C NMR (101 MHz, Chloroform-*d*) δ 165.2, 131.9, 129.6, 128.9, 128.2, 103.9, 98.1, 77.5, 75.1, 52.6, -0.2. IR (ν_{max}, cm⁻¹) 3678 (w), 3296 (w), 2963 (m), 2902 (m), 2359 (w), 2162 (w), 2125 (w), 1725 (s), 1608 (m), 1410 (m), 1373 (m), 1262 (s), 1176 (m), 1102 (s), 868 (s), 763 (m). HRMS (APCI/QTOF) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₇O₂Si⁺ 257.0992; Found 257.0995.

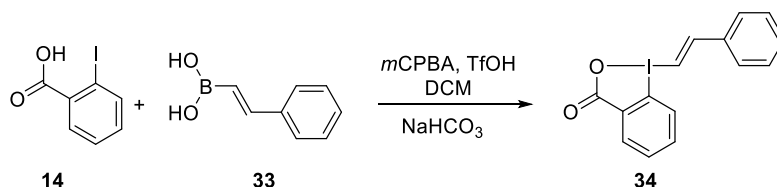
1-((4-(Prop-2-yn-1-yl-benzoate)ethynyl)-1,2-benziodoxol-3(1H)-one (1k)



Trimethylsilyl triflate (0.99 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**15**) (1.32 g, 5.50 mmol, 1.0 equiv) in CH₂Cl₂ (12 mL) at RT. The resulting suspension was stirred for 1 h, followed by the drop wise addition of prop-2-yn-1-yl 4-((trimethylsilyl)ethynyl)benzoate (**32**) (1.41 g, 5.50 mmol, 1.1 equiv), which was dissolved in CH₂Cl₂ (1 mL). The resulting suspension was stirred for 4 h at RT. A saturated solution of NaHCO₃ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. NaHCO₃ (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting solid was purified by column chromatography with pure ethyl acetate to afford **1k** (174 mg, 0.404 mmol, 8%) as a white crystalline solid.

Mp (Dec.) 107 – 118 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (dd, *J* = 6.3, 2.8 Hz, 1H, ArH), 8.28 – 8.21 (m, 1H, ArH), 8.13 (d, *J* = 8.4 Hz, 2H, ArH), 7.88 – 7.74 (m, 2H, ArH), 7.68 (d, *J* = 8.5 Hz, 2H, ArH), 4.96 (d, *J* = 2.5 Hz, 2H, OCH₂), 2.55 (t, *J* = 2.5 Hz, 1H, CH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 166.5, 164.7, 135.1, 132.8, 132.7, 132.6, 131.8, 131.2, 131.0, 130.0, 126.3, 125.4, 116.1, 104.9, 75.4, 54.2, 52.9. IR (ν_{max}, cm⁻¹) 3278 (w), 2988 (m), 2908 (m), 2353 (w), 2119 (w), 1725 (s), 1608 (m), 1577 (w), 1417 (m), 1380 (m), 1262 (s), 1102 (s), 1053 (m), 1016 (m), 967 (w), 868 (w), 868 (w), 739 (m). HRMS (ESI/QTOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₁₂O₄⁺ 430.9775; Found 430.9781.

Ph-VBX (34)

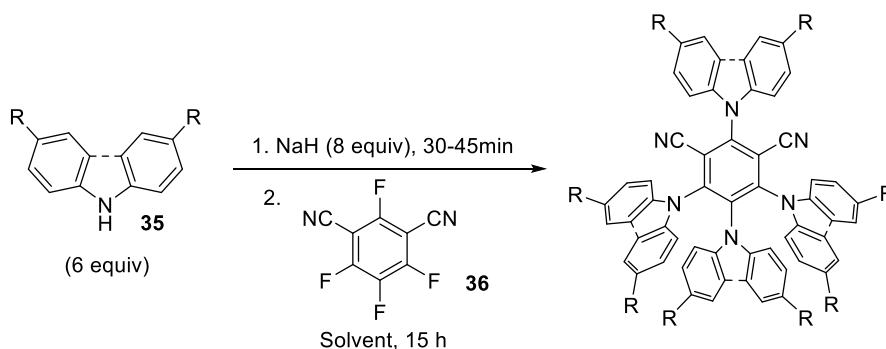


Following a reported procedure,^[11] *m*CPBA (1.25 g, 5.50 mmol, 1.10 equiv) was added to a solution of 2-iodobenzoic acid (**14**) (1.25 g, 5.00 mmol, 1.00 equiv) in CH₂Cl₂ (25 mL). The reaction mixture was cooled to 0 °C and trifluoromethanesulfonic acid (0.66 mL, 7.5 mmol, 1.5 equiv) was added at this temperature before being stirred at r.t for 15 min. The reaction mixture was again cooled to 0 °C over 10 min and (*E*)-styrylboronic acid (**33**) (1.0 g, 7.0 mmol, 1.4 equiv) and the mixture was stirred at r.t for 1 h. A saturated NaHCO₃ solution (25 mL) was added and the mixture was stirred for 1 h. The mixture was diluted with CH₂Cl₂ (25 mL) and H₂O (25 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were washed with brine, dried (Mg₂SO₄) and filtered. The solvent was removed under reduced pressure. The crude

mixture contained a lot of impurities, so purification by column chromatography over silica gel (DCM with 2 to 10% Acetone) afforded 500 mg of pure Ph-VBX **34** as off white crystalline solid (29%).

^1H NMR (400 MHz, Methanol- d_4) δ 8.28 (dd, $J = 5.8, 3.4$ Hz, 1H, ArH), 7.96 (d, $J = 15.4$ Hz, 1H, ArH), 7.74 (dd, $J = 5.9, 3.5$ Hz, 1H, ArH), 7.70 (dd, $J = 7.5, 3.5$ Hz, 4H, ArH), 7.66 (d, $J = 8.7$ Hz, 1H, ArH), 7.49 (dd, $J = 5.1, 2.0$ Hz, 3H, ArH). The NMR shifts match the literature data.^[11]

3. Library of organic dyes



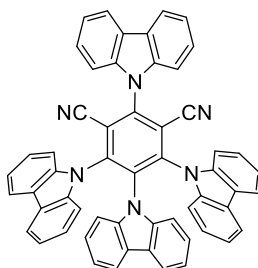
General procedure 1:

Sodium hydride (60% suspension in mineral oil, 8.0 equiv) was added slowly to a stirred solution of substituted-carbazole **35a-d** (5.0 equiv) in dry THF (0.05 M) under a nitrogen atmosphere at RT. After 30 min, 2,4,5,6-tetrafluoroisophthalonitrile **36** (1.0 mmol, 1.0 equiv) was added. After stirring at RT for 15 h, 2 mL water was added to the reaction mixture to quench the excess of NaH. The resulting mixture was then concentrated under reduced pressure. The crude product was purified by recrystallization from hexane/CH₂Cl₂ then filtered. The brown liquid filtrate was concentrated and recrystallized as before. The combined solids were then purified by column chromatography on silica gel with DCM/Hexane.

General procedure 2:

Sodium hydride (60% suspension in mineral oil, 8.0 equiv) was added slowly to a stirred solution of substituted-diphenylamine **35d-f** (6.0 equiv) in dry DMF (0.1 M) under a nitrogen atmosphere at RT. After 45 min - 1 h, 2,4,5,6-tetrafluoroisophthalonitrile **36** (1.0 equiv) was added. After stirring at RT for 15 h, water and ice were added to the reaction mixture to quench the excess of NaH. The precipitate was filtered and purified by recrystallization from pentane/CH₂Cl₂ then filtered. The brown liquid filtrate was concentrated and recrystallized as before. The combined solids were then purified by column chromatography on silica gel with DCM/Hexane.

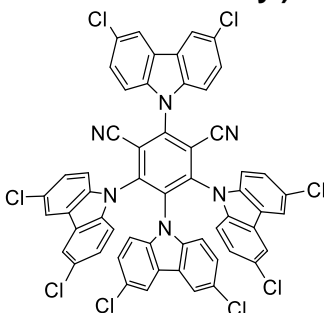
2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN, **2a**)



Following the general procedure 1 and starting from 9*H*-carbazole **35a** (1.67 g, 10.0 mmol, 5.00 equiv), sodium hydride (0.60 g, 15 mmol, 7.5 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (0.40 g, 2.0 mmol) in 40 mL of THF. Recrystallization (Hexanes/CH₂Cl₂ (1:1, 90 mL)) afforded the crude product as a yellow powder. Column chromatography afforded 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (**2a**) as a bright yellow crystalline solid (1.14 g, 1.45 mmol, 73 % yield).

R_f (Hexane/DCM 1/1) = 0.29. (yellow spot on TLC). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.2 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.8 – 7.6 (m, 8H, Ar*H*), 7.5 (ddd, *J* = 8.0, 6.6, 1.6 Hz, 2H, Ar*H*), 7.3 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.2 (dd, *J* = 8.4, 1.5 Hz, 4H, Ar*H*), 7.2 – 7.0 (m, 8H, Ar*H*), 6.8 (t, *J* = 7.8 Hz, 4H, Ar*H*), 6.6 (td, *J* = 7.6, 1.2 Hz, 2H, Ar*H*). ¹³C NMR (101 MHz, Chloroform-*d*) δ 145.2, 144.6, 140.0, 138.2, 136.9, 134.7, 127.0, 125.8, 124.9, 124.7, 124.5, 123.8, 122.4, 121.9, 121.4, 121.0, 120.4, 119.6, 116.3, 111.6, 109.9, 109.5, 109.4. ¹H NMR shift in Chloroform-*d* are consistent with reported data.^[12]

(2r,4s,5r)-2,4,5,6-Tetrakis(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile (4ClCzIPN, 2b)

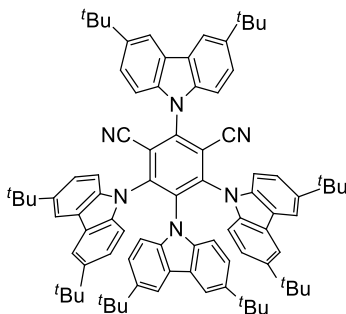


Following the general procedure 1 and starting from 3,6-dichloro-9H-carbazole **35b** (1.96 g, 6.00 mmol, 6.0 equiv), sodium hydride (320 mg, 8.00 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (200 mg, 1.00 mmol) in 20 mL of THF. Recrystallization (Hexanes/CH₂Cl₂ (1:2, 80 mL)) gave 900 mg of yellow powder, then second recrystallization gave 325 mg of brown powder. Column chromatography of the combined solid afforded (2r,4s,5r)-2,4,5,6-tetrakis(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile (**2b**) as a bright yellow crystalline solid (830 mg, 0.780 mmol, 87 % yield).

R_f (Hexane/DCM 1:1): 0.25. (yellow spot on TLC). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (d, *J* = 2.1 Hz, 2H, Ar*H*), 8.15 (d, *J* = 2.1 Hz, 4H, Ar*H*), 8.08 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.87 (dd, *J* = 8.8, 2.1 Hz, 2H, Ar*H*), 7.80 (d, *J* = 2.2 Hz, 2H, Ar*H*), 7.69 (d, *J* = 8.8 Hz, 4H, Ar*H*), 7.46 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.32 (dd, *J* = 8.8, 2.2 Hz, 4H, Ar*H*), 6.93 (dd, *J* = 8.8, 2.2 Hz, 2H, Ar*H*). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 145.0, 144.5, 138.5, 137.4, 136.5, 135.8, 134.5, 127.8, 127.0, 126.4, 125.7, 125.3, 124.2, 123.8, 123.3, 121.6, 120.9, 120.3, 116.8, 112.6, 112.5, 112.3, 111.7. HRMS (ESI) calcd for C₅₆H₂₄Cl₈N₆ [M⁺] 1059.9565; found 1059.9573.

¹H NMR shift in CDCl₃ are consistent with reported data.^[13] However, for better solubility and better resolution new ¹H and ¹³C spectra were recorded in DMSO-*d*₆.

(2r,4s,5r)-2,4,5,6-Tetrakis(3,6-di-*tert*-butyl-9H-carbazol-9-yl)isophthalonitrile (4*t*BuCzIPN, 2c)



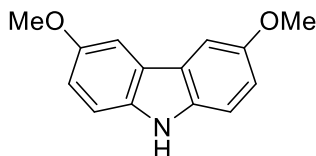
Following the general procedure 1 and starting from 3,6-*tert*-butyl-9H-carbazole **35c** (1.22 g, 4.37 mmol, 5.0 equiv), sodium hydride (280 mg, 7.00 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (175 mg, 0.875 mmol) in 17.5 mL of THF, (2r,4s,5r)-2,4,5,6-tetrakis(3,6-di-*tert*-butyl-9H-carbazol-9-yl)isophthalonitrile (**2c**) was obtained as a yellow (light orange) crystalline solid (940 mg, 0.759 mmol, 87% yield) after recrystallization and column chromatography using dichloromethane:pentane (1:2).

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.42 (d, *J* = 1.8 Hz, 2H, Ar*H*), 7.95 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.87 (d, *J* = 1.9 Hz, 4H, Ar*H*), 7.77 (dd, *J* = 8.6, 2.0 Hz, 2H, Ar*H*), 7.45 (d, *J* = 8.6 Hz, 4H, Ar*H*), 7.42 (d, *J* = 1.9 Hz, 2H, Ar*H*), 7.14 (dd, *J* = 8.7, 2.0 Hz, 4H, Ar*H*), 7.10 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.65 (dd, *J* = 8.7, 2.0 Hz, 2H, Ar*H*), 1.50 (s, 18H, *t*Bu), 1.32 (s, 36H, *t*Bu), 1.24 (s, 18H, *t*Bu). ¹³C NMR (101 MHz, Acetone-*d*₆)² δ 146.0, 144.9, 144.6, 144.1, 143.1, 139.0, 137.6, 136.5, 136.2, 124.6, 124.3, 124.2,

² The signals were not fully resolved.

122.9, 121.8, 117.3, 116.8, 116.3, 115.3, 112.6, 110.4, 110.2, 109.8, 34.6, 34.3, 34.0, 31.4, 31.2. The characterization data matches the reference.^[14]

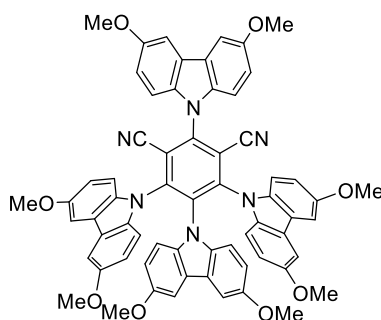
3,6-Dimethoxy-9H-carbazole (**37**)



Following a reported procedure,^[15] in a 25 mL microwave tube were placed 3,6-dibromo-9H-carbazole (975 mg, 3.00 mmol, 1.0 equiv) and copper(I) iodide (1.14 g, 6.00 mmol, 2.0 equiv) under a nitrogen atmosphere. DMF (6 mL) and a 30% solution of NaOMe in MeOH (4 mL) were added. The tube was sealed and heated at 85 °C for 15 h, then at 105 °C for 5 h. The crude mixture was diluted in ethyl acetate and filtered over a silica pad, then concentrated under vacuum. The crude was purified by column chromatography with pentane/dichloromethane 1:1 to afford 3,6-dimethoxy-9H-carbazole (**37**) (477 mg, 2.10 mmol, 70.0 % yield) as a white solid.

R_f (pentane/DCM 1:1): 0.6. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 (bs, 1H, *NH*), 7.51 (d, *J* = 2.5 Hz, 2H, *ArH*), 7.29 (d, *J* = 8.8 Hz, 2H, *ArH*), 7.06 (dd, *J* = 8.8, 2.5 Hz, 2H, *ArH*), 3.94 (s, 6H, *OMe*). ¹³C NMR (101 MHz, Chloroform-*d*) δ 153.6, 135.2, 123.7, 115.2, 111.5, 102.8, 56.0. Consistent with reported data.^[15]

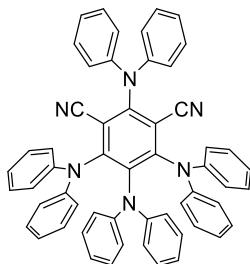
(2*r*,4*s*,5*r*)-2,4,5,6-Tetrakis(3,6-dimethoxy-9H-carbazol-9-yl)isophthalonitrile (4MeOCzIPN, **2d**)



Following the general procedure 1 and starting from 3,6-dimethoxy-9H-carbazole **35d** (443 mg, 1.95 mmol, 6.0 equiv), sodium hydride (104 mg, 2.60 mmol, 8 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (65.0 mg, 0.325 mmol) in 6.5 mL of THF. Recrystallization and column chromatography in pure dichloromethane afforded (2*r*,4*s*,5*r*)-2,4,5,6-Tetrakis(3,6-dimethoxy-9H-carbazol-9-yl)isophthalonitrile (**2d**) as a red crystalline solid (321 mg, 0.312 mmol, 94 % yield).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.5 Hz, 2H, *ArH*), 7.41 (d, *J* = 8.8 Hz, 2H, *ArH*), 7.18 – 7.15 (m, 2H, *ArH*), 7.04 (d, *J* = 2.5 Hz, 4H, *ArH*), 6.93 (d, *J* = 8.9 Hz, 4H, *ArH*), 6.71 (d, *J* = 2.5 Hz, 2H, *ArH*), 6.64 – 6.53 (m, 6H, *ArH*), 6.19 (dd, *J* = 8.9, 2.5 Hz, 2H, *ArH*), 3.87 (s, 6H, *OMe*), 3.67 (s, 12H, *OMe*), 3.57 (s, 6H, *OMe*). ¹³C NMR (101 MHz, Chloroform-*d*) δ 155.6, 155.1, 154.3, 145.0, 144.5, 135.3, 133.7, 133.5, 132.4, 125.6, 125.2, 124.5, 115.7, 114.9, 114.4, 113.6, 112.0, 110.8, 110.5, 110.1, 104.0, 103.4, 102.8, 56.0, 55.8, 55.7. The characterization data matches the reference.^[16]

2,4,5,6-Tetrakis(diphenylamino)isophthalonitrile (4DPAIPN, 3a)

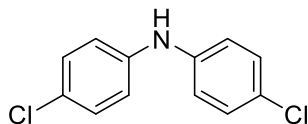


Following the general procedure 2 and starting from diphenylamine **35e** (1.01 g, 6.00 mmol, 6.0 equiv), sodium hydride (320 mg, 8.00 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (200 mg, 1.00 mmol) in 10 mL of DMF. The deprotonation was performed at 50°C for 1 h, followed by stirring at the same temperature for 4 h. Recrystallization (CH₂Cl₂/pentane (1:2)) gave 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (**3a**) as a yellow-orange crystalline solid (400 mg, 0.502 mmol, 50 % yield).

R_f (pentane/DCM 1:1): 0.3. (yellow spot on TLC). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.22 (m, 4H, ArH), 7.12 – 7.05 (m, 12H, ArH), 7.07 – 6.98 (m, 2H, ArH), 6.96 – 6.84 (m, 8H, ArH), 6.73 – 6.63 (m, 10H, ArH), 6.56 (d, *J* = 7.4 Hz, 4H, ArH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 154.2, 151.7, 145.5, 144.6, 143.1, 140.3, 129.4, 128.6, 127.5, 124.2, 123.9, 122.9, 122.6, 122.6, 121.1, 113.1, 113.0. IR (ν_{max}, cm⁻¹) 3065 (w), 3040 (w), 2361 (w), 1586 (m), 1535 (m), 1497 (s), 1415 (s), 1275 (m), 1244 (m), 1028 (w), 907 (m), 742 (s), 698 (s). HRMS (ESI/QTOF) *m/z*: [M + H]⁺ Calcd for C₅₆H₄₁N₆⁺ 797.3387; Found 797.3375.

The data were not in alignment with the reported values,^[17] a crystal structure confirmed the structure (see section 5).

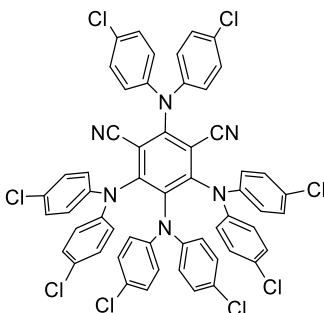
Bis(4-chlorophenyl)amine (38)



Following a reported procedure,^[18] in a 25 mL dry microwave vial was placed Pd₂dba₃ (27.5 mg, 0.0300 mmol, 1 mol%), BrettPhos (48.3 mg, 0.0900 mmol, 3 mol%), 1-chloro-4-iodobenzene (715 mg, 3.00 mmol, 1 equiv), 4-chloroaniline (459 mg, 3.60 mmol, 1.2 equiv), Cs₂CO₃ (2.34 g, 7.20 mmol, 2.4 equiv). The vial was placed under an argon atmosphere and toluene (6 mL) was added. The reaction mixture was stirred at 70 °C overnight and then at 95 °C for 4 h. The mixture was diluted with ethyl acetate, filtered over a celite pad and concentrated under vacuum. The crude was purified by column chromatography pentane/ethyl acetate 100:0 to 95:5 to afford bis(4-chlorophenyl)amine (**38**) (595 mg, 2.50 mmol, 83 % yield) as a yellow-brown solid.

R_f (pentane/ethyl acetate 95:5): 0.45. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.17 (m, 4H, ArH), 7.01 – 6.95 (m, 4H, ArH), 5.71 (s, 1H, NH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.3, 129.4, 126.2, 119.2. Consistent with reported data.^[18]

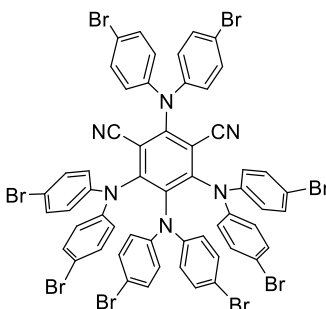
2,4,5,6-Tetrakis(bis(4-chlorophenyl)amino)isophthalonitrile (**4CIDPAIPN**, **3b**)



Following the general procedure 2, and starting from bis(4-chlorophenyl)amine **35f** (550 mg, 2.31 mmol, 6.0 equiv), sodium hydride (123 mg, 3.08 mmol, 8.0 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (77.0 mg, 0.385 mmol) in 4 mL of DMF. Recrystallization (Hexanes/CH₂Cl₂ (1:1)) followed by column chromatography afforded 2,4,5,6-tetrakis(bis(4-chlorophenyl)amino)isophthalonitrile (**3b**) as a bright yellow crystalline solid (332 mg, 0.310 mmol, 80 % yield).

R_f (pentane/DCM 1:1): 0.57. (yellow spot on TLC). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.23 (m, 4H, ArH), 7.13 – 7.07 (m, 8H, ArH), 6.98 – 6.91 (m, 8H, ArH), 6.59 – 6.54 (m, 8H, ArH), 6.46 – 6.40 (m, 4H, ArH). ¹³C NMR (101 MHz, Chloroform-*d*)³ δ 153.2, 143.5, 142.8, 141.3, 138.8, 130.5, 130.2, 129.9, 129.2, 128.6, 128.3, 124.2, 123.6, 121.9, 112.5, 112.4. IR (ν_{max}, cm⁻¹) 2367 (w), 1586 (w), 1535 (w), 1485 (s), 1409 (w), 1282 (m), 1098 (m), 1015 (w), 913 (w), 825 (m), 729 (m), 660 (w). HRMS (APPI/LTQ-Orbitrap) m/z: [M+H]⁺ Calcd for C₅₆H₃₃Cl₈N₆⁺ 1069.0269; Found 1069.0277. A crystal structure confirmed the structure (see section 5).

2,4,5,6-Tetrakis(bis(4-bromophenyl)amino)isophthalonitrile (**4BrDPAIPN**, **3c**)



Following the general procedure 1 and starting from bis(4-bromophenyl)amine **35g** (1.10 g, 4.47 mmol, 5.00 equiv), sodium hydride (0.286 g, 7.16 mmol, 8.00 equiv) and 2,4,5,6-tetrafluoroisophthalonitrile **36** (0.179 g, 0.895 mmol) in 18 mL of THF. Before recrystallization, water (5 mL) was added and the mixture was sonicated for 5 min before being filtered. Two recrystallization (pentane/CH₂Cl₂ 2:1) afforded 2,4,5,6-tetrakis(bis(4-bromophenyl)amino)isophthalonitrile (**3c**) as a bright yellow crystalline solid (1.34 g, 0.938 mmol, 94 % yield).

R_f (pentane/DCM 1:1): 0.6. (yellow spot on TLC). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.37 (m, 4H, ArH), 7.26 – 7.22 (m, 8H, ArH), 7.13 – 7.05 (m, 4H, ArH), 6.93 – 6.82 (m, 4H, ArH), 6.58 – 6.45 (m, 8H, ArH), 6.42 – 6.33 (m, 4H, ArH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 153.1, 151.4, 143.9, 143.2, 141.7, 138.7, 132.9, 132.3, 131.3, 124.6, 124.0, 122.2, 118.3, 118.0, 116.2, 112.6, 112.5. IR (ν_{max}, cm⁻¹) 2367 (w), 1777 (w), 1586 (w), 1523 (w), 1485 (s), 1421 (m), 1389 (m), 1307

³ One carbon is not resolved.

(m), 1282 (m), 1231 (w), 1072 (m), 1009 (m), 818 (m), 710 (w). HRMS (ESI/QTOF) m/z: [M + K]⁺ Calcd for C₅₆H₃₂Br₈KN₆⁺ 1458.5787; Found 1458.5812.

4. Physical measurements

4.1. Spectroscopic characterization

4CZIPN and 4DPAIPN derivatives **2** and **3** were studied at 10 $\mu\text{mol}\cdot\text{L}^{-1}$ in acetonitrile. Absorbance was recorded between 200 and 800 nm. The excitation wavelength for fluorescence was 360 nm.

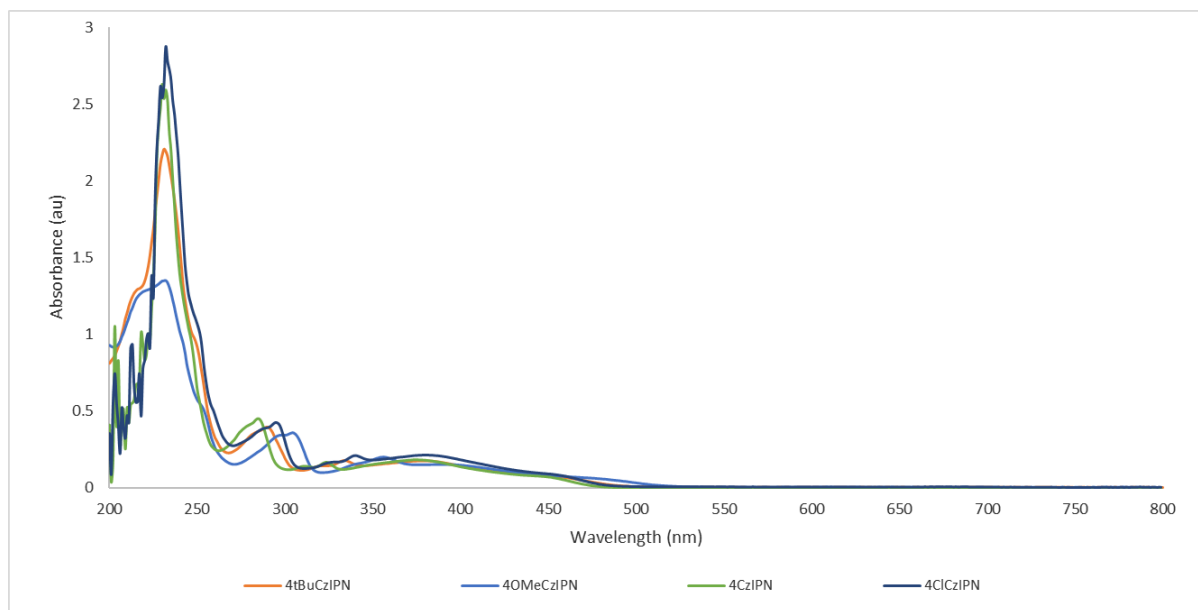


Figure S1: UV-Vis spectra of 4CZIPN derivatives **2** in acetonitrile

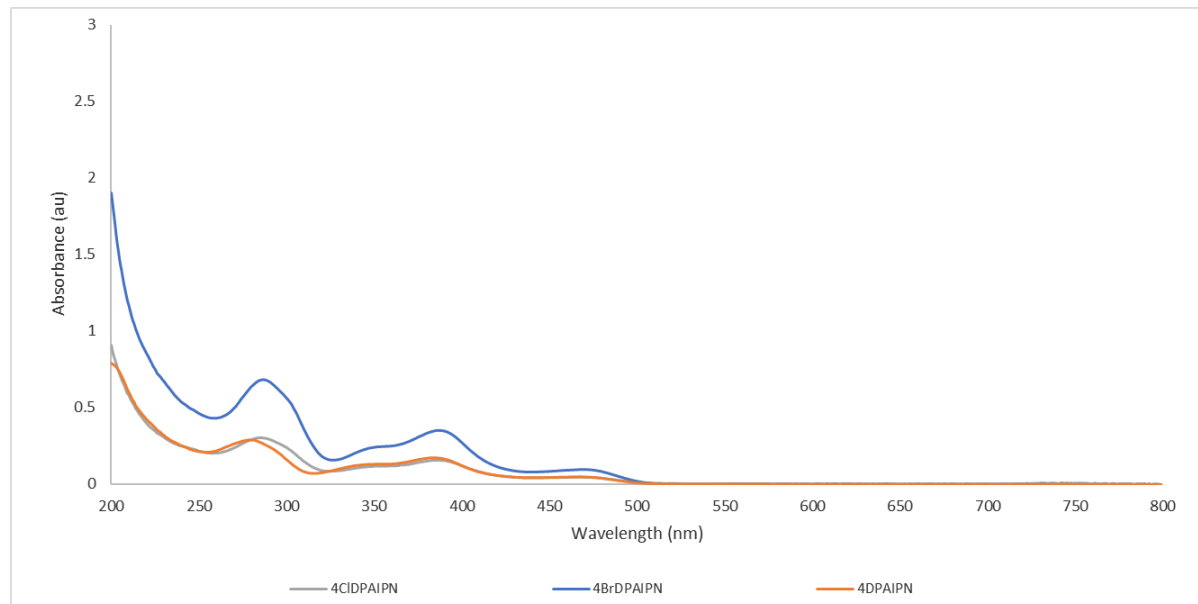


Figure S2: UV-Vis spectra of 4DPAIPN derivatives **3** in acetonitrile

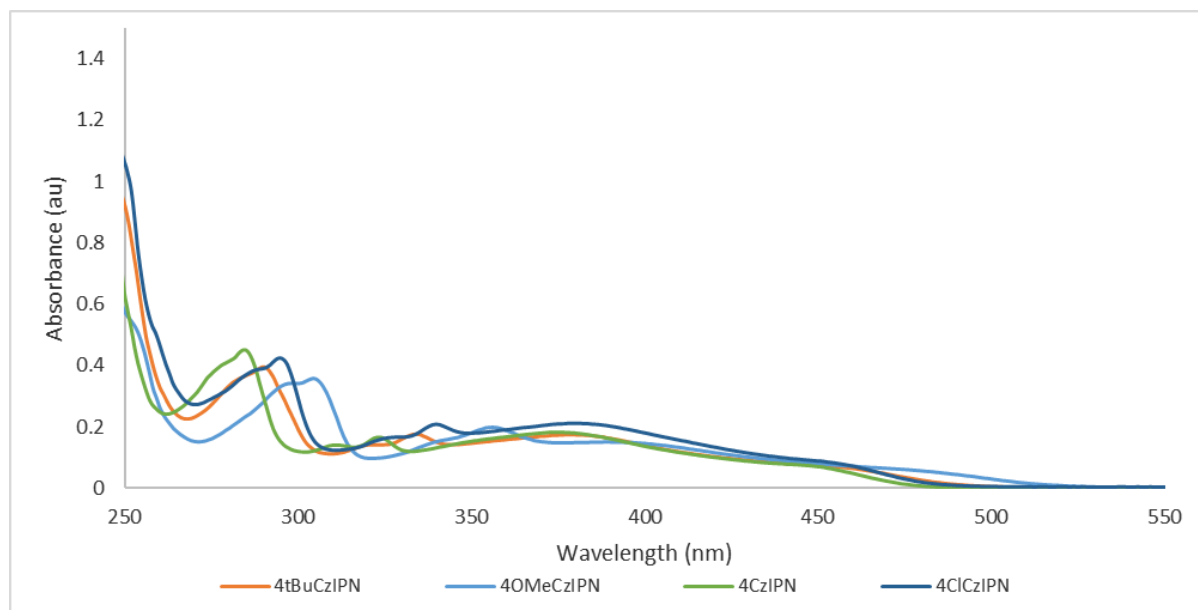


Figure S3: Zoom on the 250-550 nm of the UV-Vis spectra of 4CzIPN derivatives **2** in acetonitrile

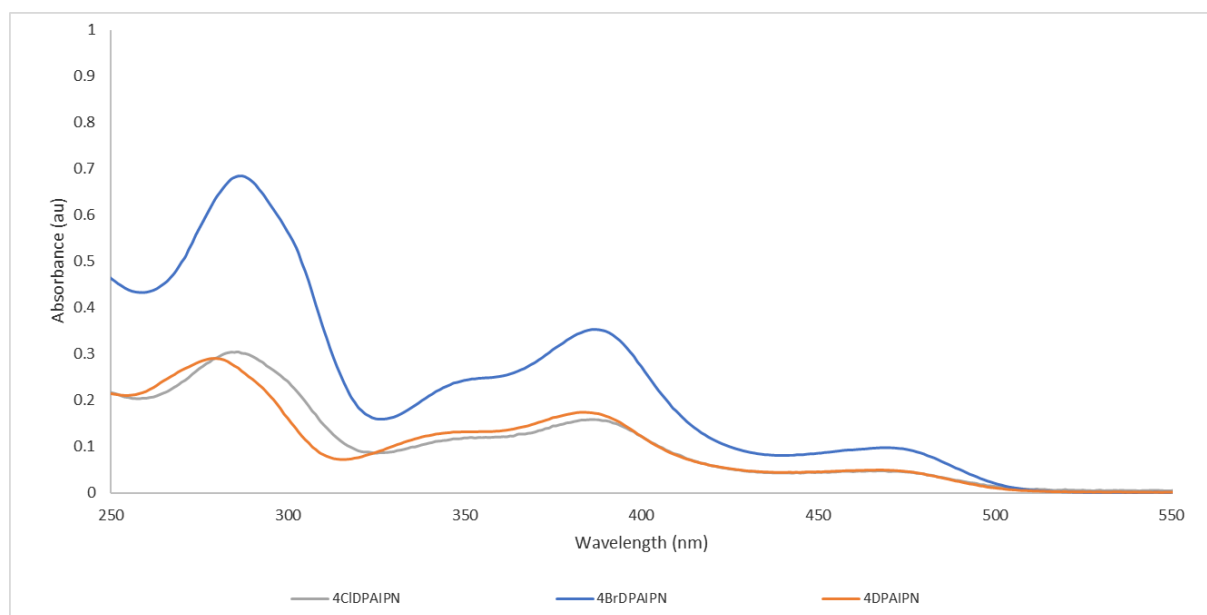


Figure S4: Zoom on the 250-550 nm of the UV-Vis spectra of 4DPAIPN derivatives **3** in acetonitrile

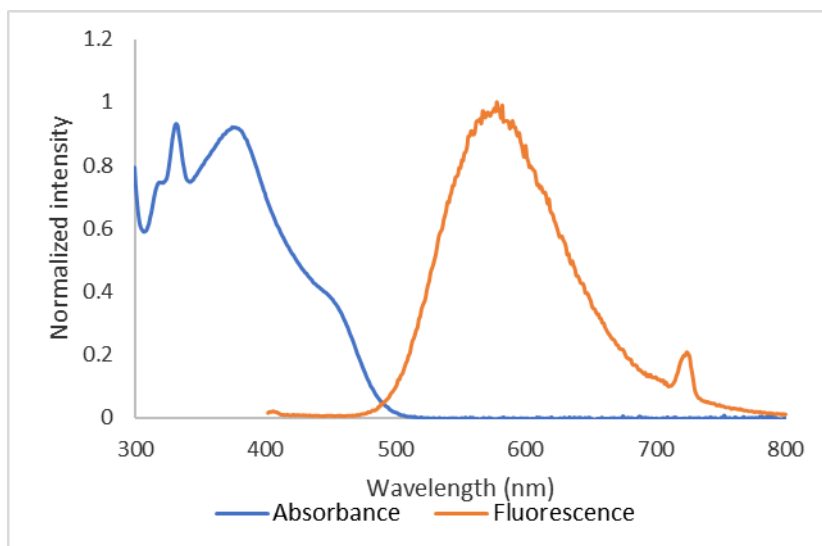


Figure S5 : Absorbance and emission of 4tBuCzIPN (**2c**) at 10 $\mu\text{mol.L}^{-1}$ in acetonitrile

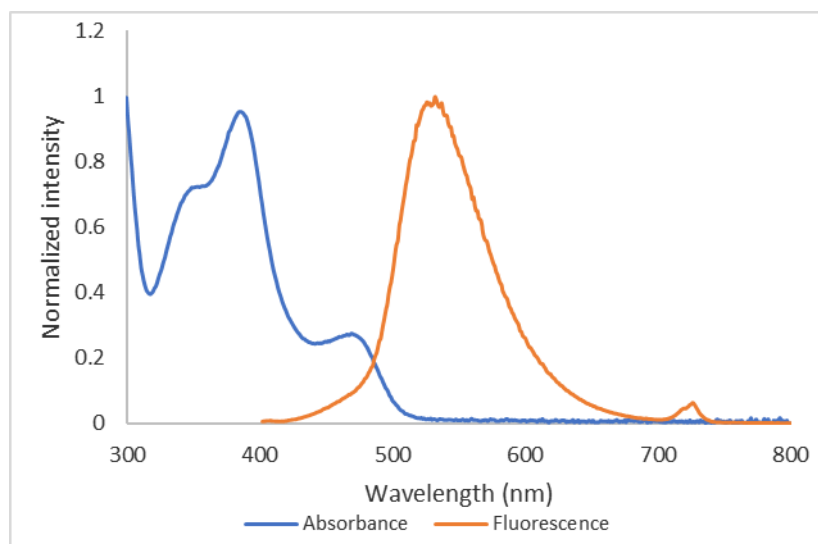


Figure S6 : Absorbance and emission of 4DPAIPN (**3a**) at 10 $\mu\text{mol.L}^{-1}$ in acetonitrile

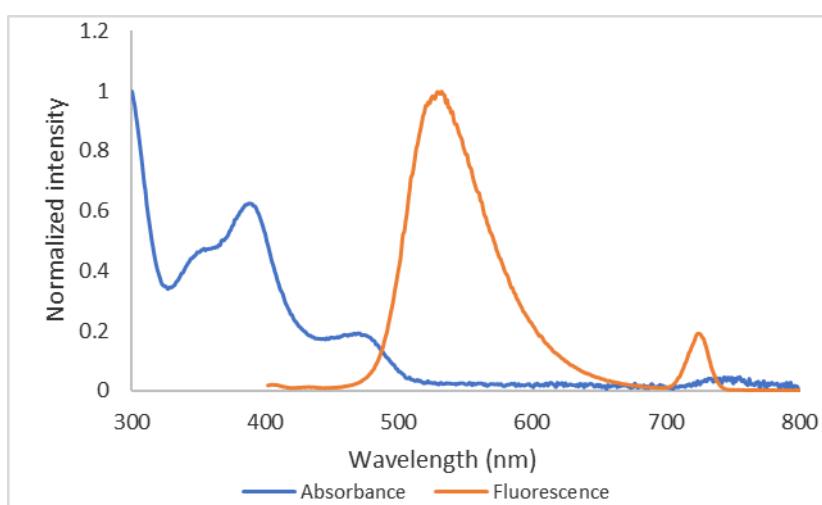


Figure S7 : Absorbance and emission of 4CIDPAIPN (**3b**) at 10 $\mu\text{mol.L}^{-1}$ in acetonitrile

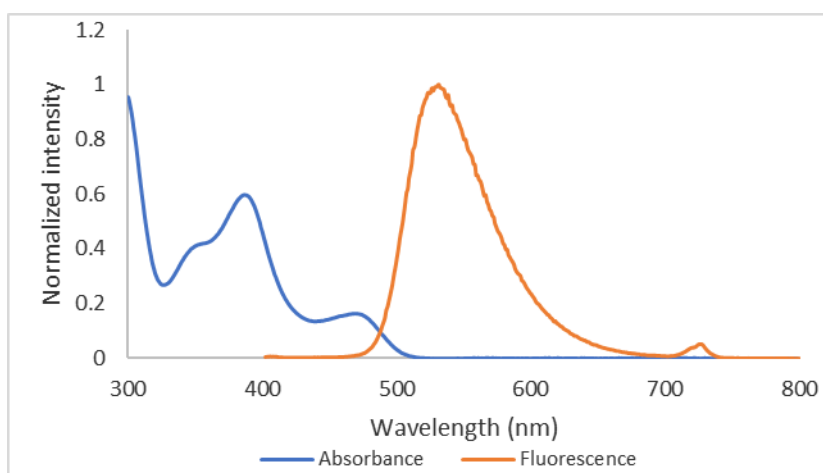


Figure S8: Absorbance and emission of 4BrDPAIPN (**3c**) at 10 $\mu\text{mol.L}^{-1}$ in acetonitrile

4.2. Electrochemical measurements

The cyclic voltammetry of the organic dyes were performed. For comparison, the organic dyes were studied in the same conditions as previous reports on 4CzIPN, at 1mM in degassed acetonitrile at scan rates of 0.1, 0.5 and 1 V/s. ^[10,17,19] For clarity, curves are presented at 0.1 V/s as well as a superposition.

In the case of 4CzIPN derivatives, irreversible waves were observed in the anodic scan and correspond to the oxidation of the carbazole moieties, as reported by Ishimatsu *et al.*^[19] The same group described that the introduction of *t*Bu groups prevents this polymerization.^[14] Reversibility was evaluated through plots of the intensity of the peaks related to the square root of the scan rate.^[20] Reversible waves were observed in the cathodic scans in all cases. They correspond to the reduction of the dicyanobenzene group.^[14] For 4BrDPAIPN (**3b**), higher scan rates gave surprising curves for the reduction, hence the reversibility could not be determined by this method. With a peak to peak separation of 60 mV, this process is quasi-reversible.

In the conditions of this study, the expected anodic and cathodic shifts upon substitution effect were measured (Table S1). The trend in reduction potentials of 4DPAIPN derivatives (**3a**<**3b**<**3c**) follows the electronegativity of the substituents (H<Br<Cl). This can be rationalized by a greater stabilization of the lowest unoccupied molecular orbital (LUMO) with substitution.^[10] Similarly, 4*t*BuCzIPN (**2c**) and 4OMeCzIPN (**2d**) were less oxidant than 4CzIPN (**2a**) by destabilization of the LUMO.

The excitation energy E_{0-0} was estimated by the point of intersection of the normalized absorbance and emission signals (Section 4.1). $E_{1/2}(\text{P}^+/\text{P}^*) = E_{1/2}(\text{P}^+/\text{P}) - E_{0-0}$ and $E_{1/2}(\text{P}^*/\text{P}^-) = E_{0-0} + E_{1/2}(\text{P}/\text{P}^-)$.^[21]

Table S1: Electrochemical properties of 4CzIPN and DPAIPN derivatives **2** and **3**^a

Photocatalyst	E_{0-0} (eV)	$E_{1/2}(\text{P}/\text{P}^-)$	$E_{1/2}(\text{P}^*/\text{P}^-)$	$E_{1/2}(\text{P}^+/\text{P})$	$E_{1/2}(\text{P}^+/\text{P}^*)$
4CzIPN (2a) ^[17]	2.53	-1.21	+1.35	+1.52	-1.04
4CzIPN (2a)	2.64	-1.32	+1.32	+1.39	-1.25
4 <i>t</i> BuCzIPN (2c)	2.53	-1.32	+1.21	+1.22	-1.31
4OMeCzIPN (2d)	2.61 ^[16]	-1.38	+1.23	+1.05	-1.56
4OMeCzIPN (2d) ^[16]	2.61	-1.50	+1.27	+1.11	-1.34
4CIDPAIPN (3b)	2.53	-1.44	+1.09	+1.23	-1.30
4BrDPAIPN (3c)	2.53	-1.55	+0.98	+1.12	-1.41
"4DPAIPN" (3a) ^[17]	2.62	-1.52	+1.10	+1.34	-1.28
4DPAIPN (3a)	2.55	-1.65	+0.90	+1.03	-1.52

^aPotentials in V vs SCE, wavelength in nanometers.

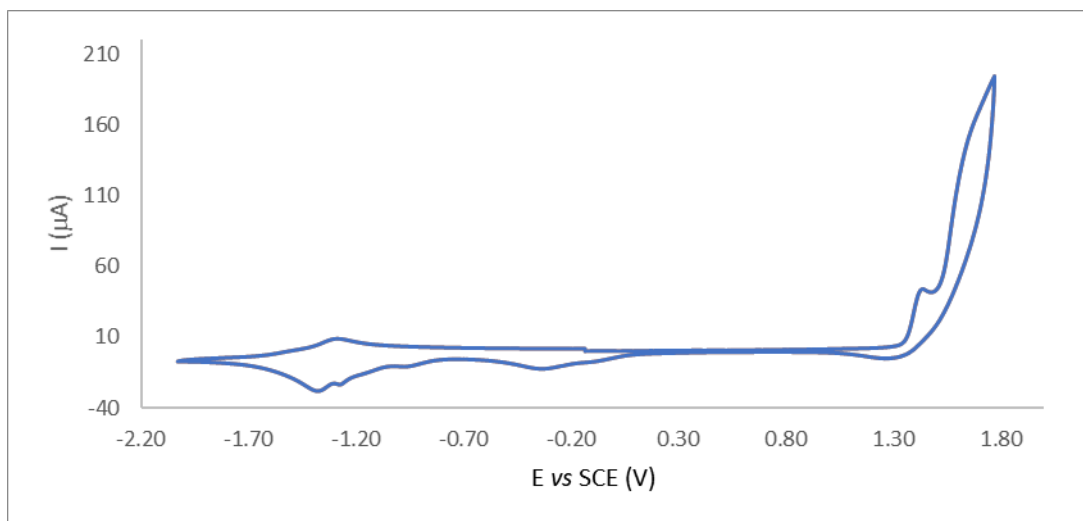


Figure S9: Cyclic voltammetry of 4CzIPN (**2a**) in acetonitrile at 0.1 V/S

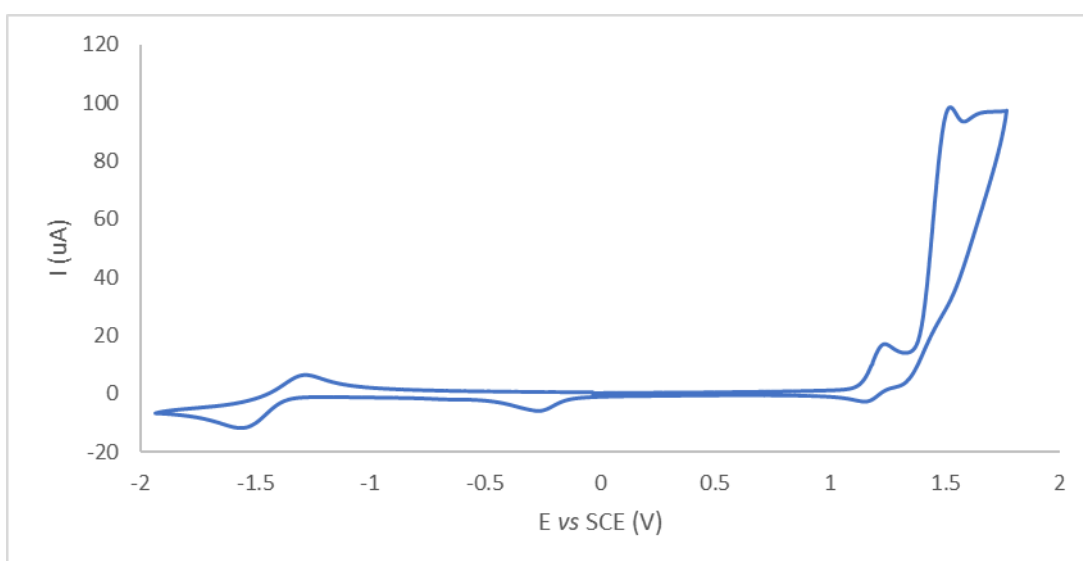


Figure S10 : Cyclic voltammetry of 4tBuCzIPN (**2c**) in acetonitrile 0.1 V/S

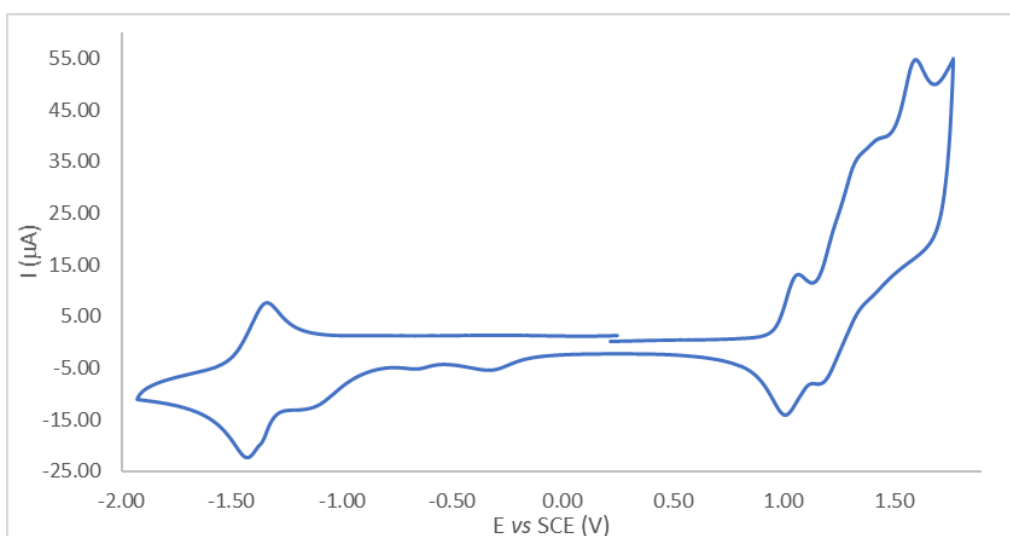


Figure S11: Cyclic voltammetry of 4OMeCzIPN (**2d**) in acetonitrile 0.1 V/S

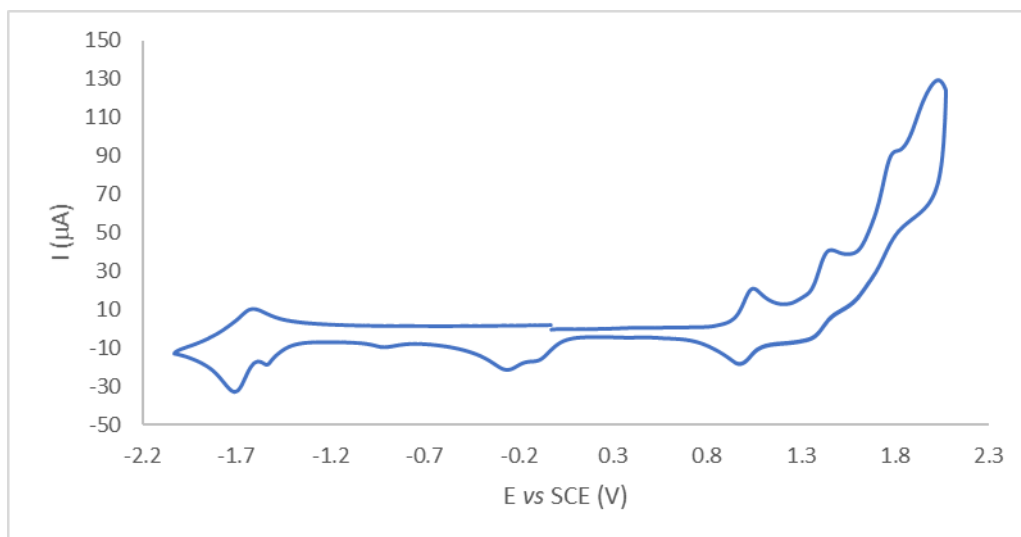


Figure S12: Cyclic voltammetry of 4DPAIPN (**3a**) in acetonitrile 0.1 V/S

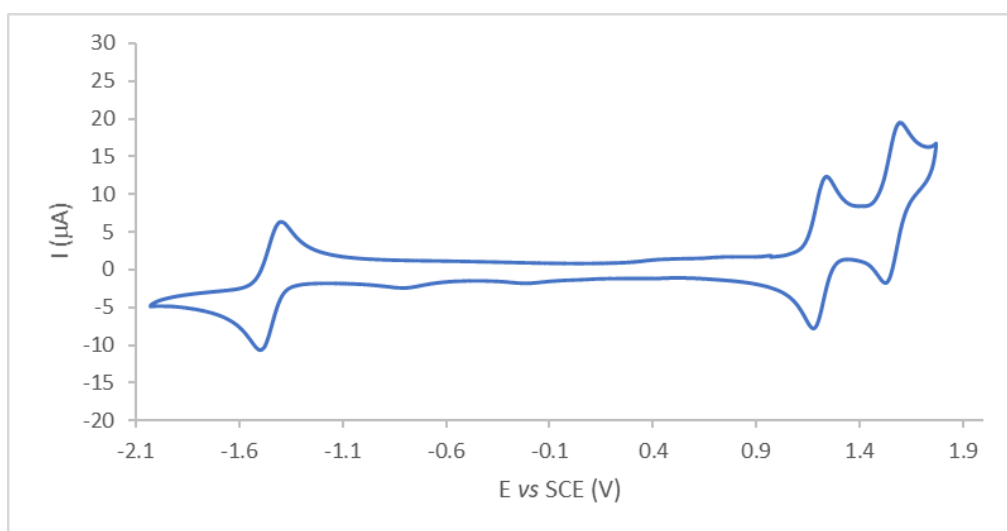


Figure S13: Cyclic voltammetry of 4CIDPAIPN (**3b**) in acetonitrile 0.1 V/S

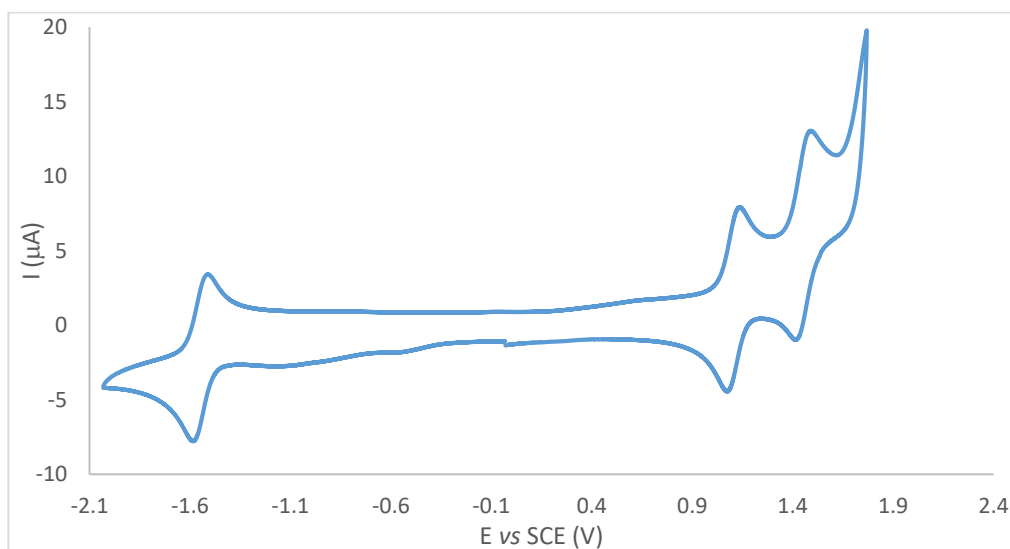


Figure S14 : Cyclic voltammetry of 4BrDPAIPN (**3c**) in acetonitrile 0.1 V/S

Graphs for reversibility determination.

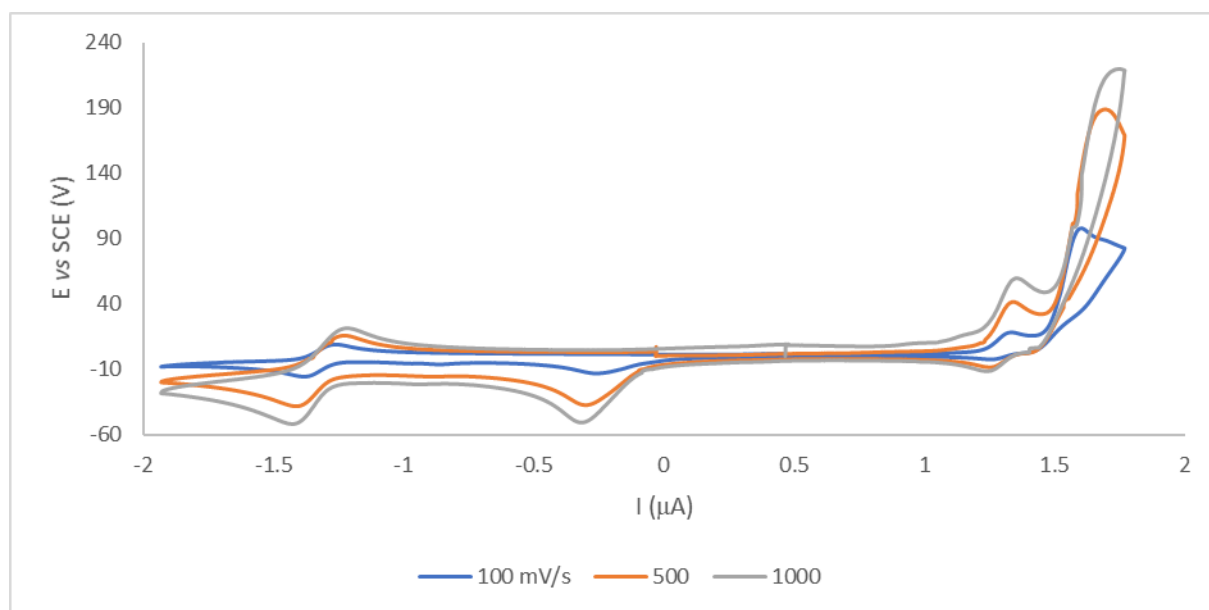


Figure 15: Cyclic voltammetry of 4tBuCzIPN (**2c**)

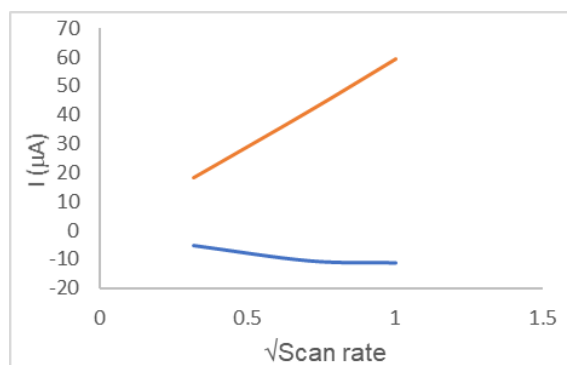


Figure 16: Intensity vs $\sqrt{\text{scan rate}}$, 4tBuCzIPN-Red

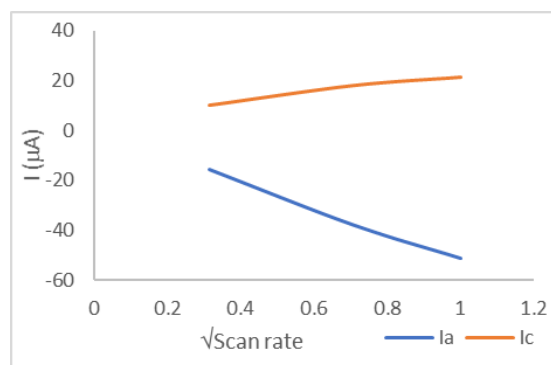


Figure 17: Intensity vs $\sqrt{\text{scan rate}}$, 4tBuCzIPN-Ox

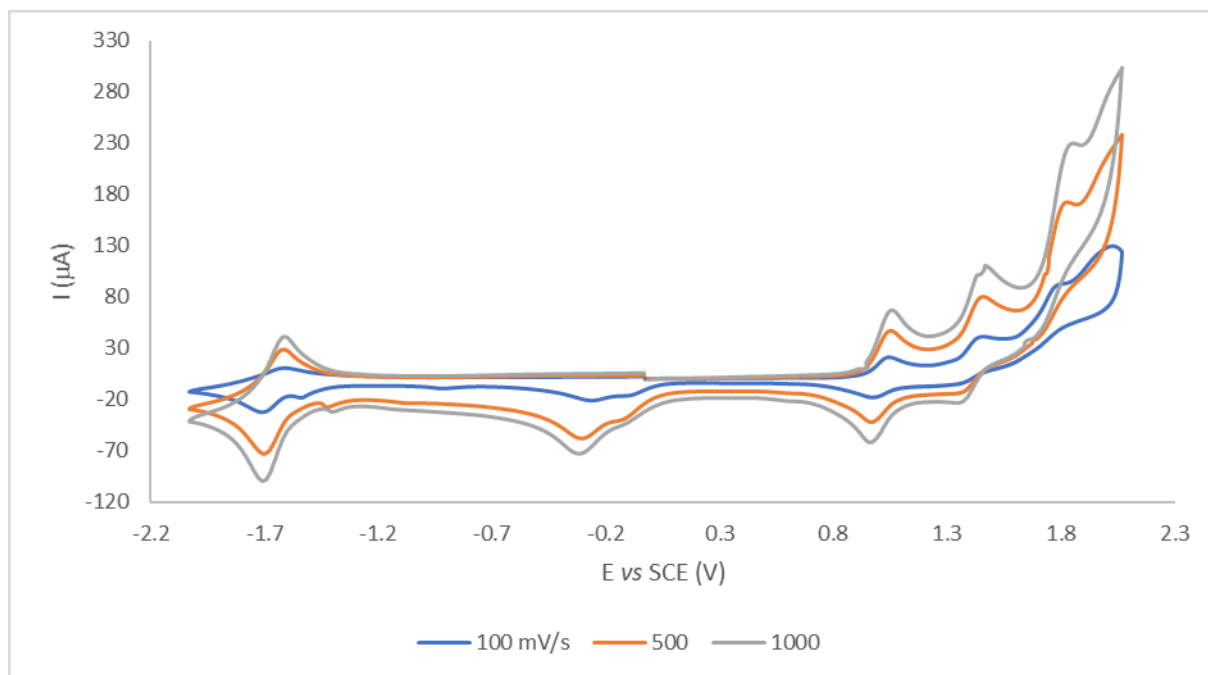


Figure 18: Cyclic voltammetry of 4DPAIPN (3a)

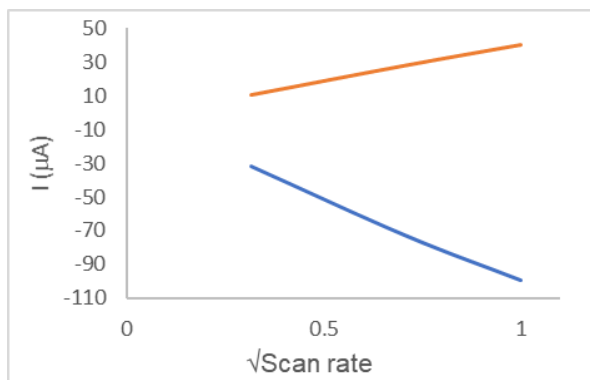


Figure 19: Intensity vs $\sqrt{\text{scan rate}}$, 4DPAIPN-Red

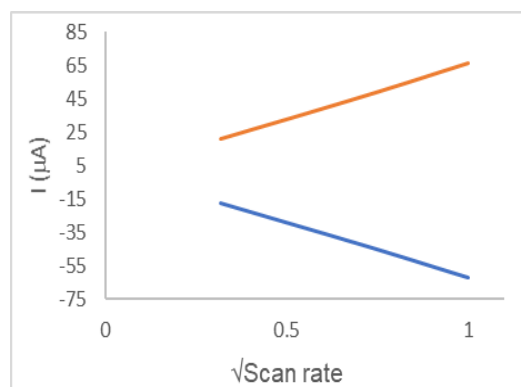


Figure 20: Intensity vs $\sqrt{\text{scan rate}}$, 4DPAIPN-Ox

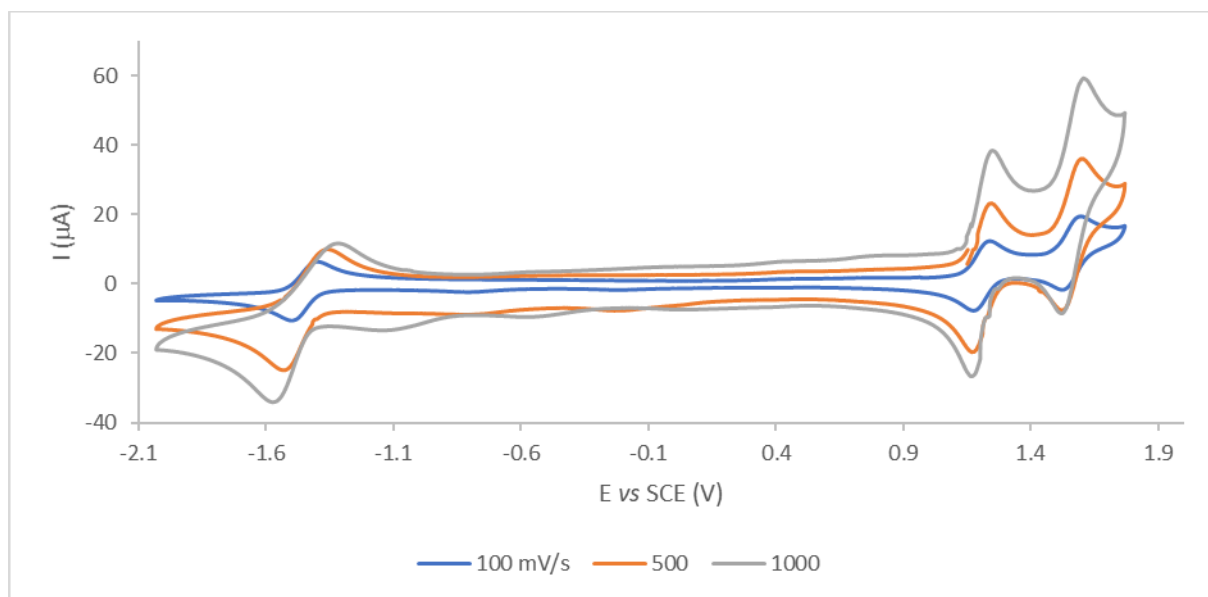


Figure 21: Cyclic voltammetry of 4CIDPAIPN (3b)

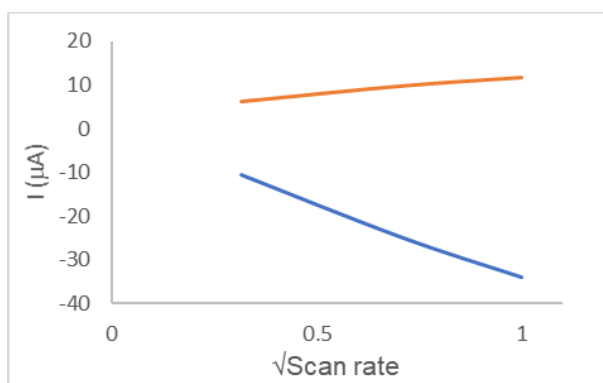


Figure 22: Intensity vs $\sqrt{\text{scan rate}}$, 4CIDPAIPN-Red

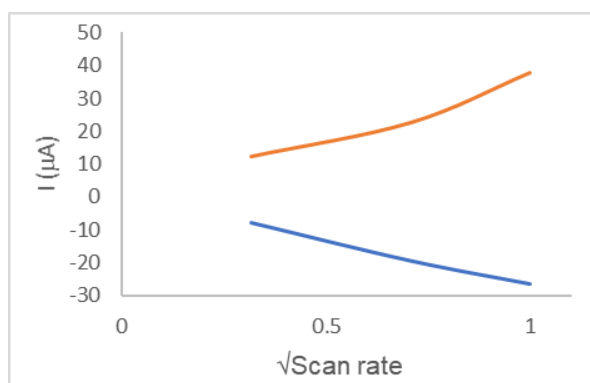


Figure 23: Intensity vs $\sqrt{\text{scan rate}}$, 4CIDPAIPN-Ox

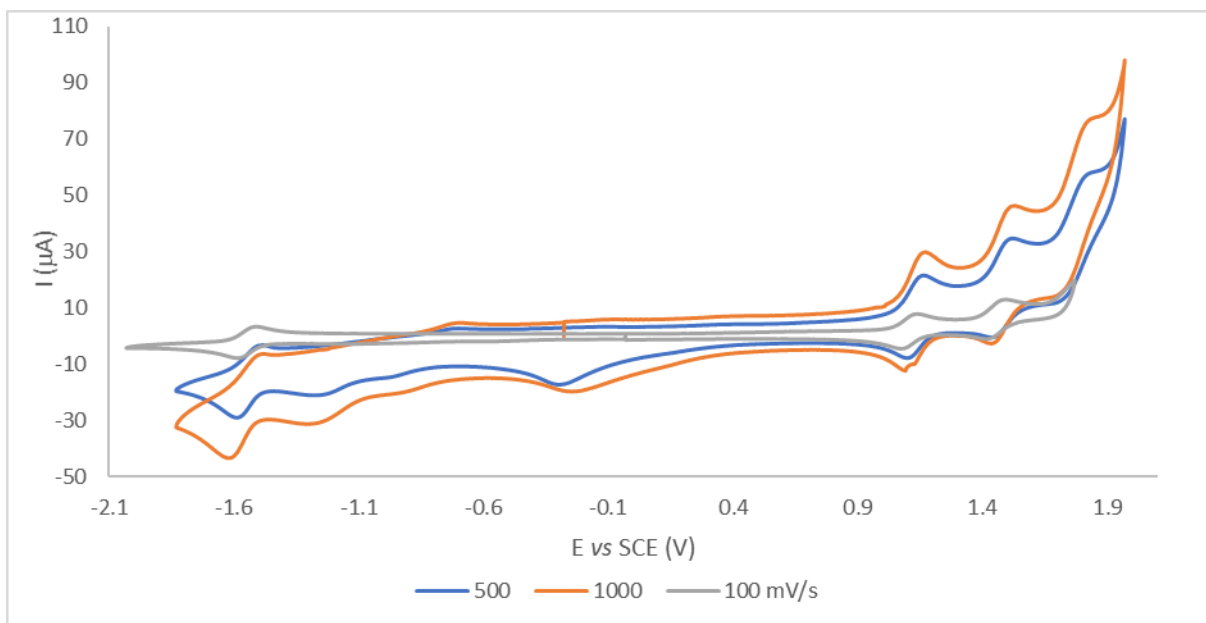


Figure 24: Cyclic voltammetry of 4BrDPAIPN (**3c**)

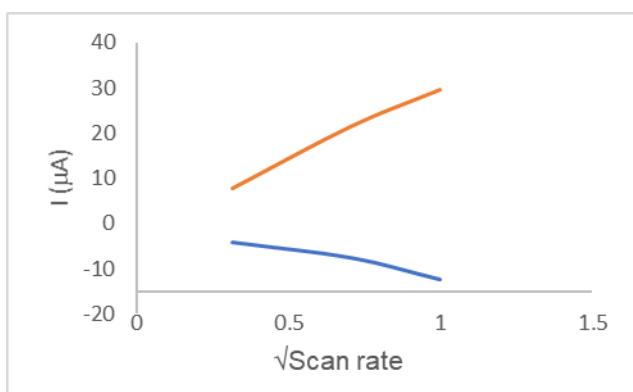


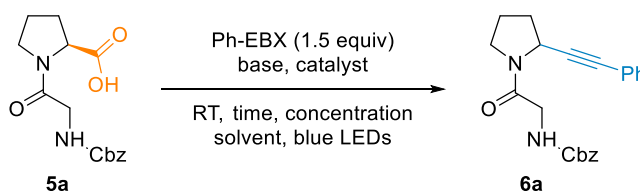
Figure 25: Intensity vs $\sqrt{\text{scan rate}}$, 4BrDPAIPN–Ox

5. Synthesis of peptide tetramers and Ac-GRGDNP

All peptide tetramers were synthesized by solid phase peptide synthesis using a 2-chlorotrityl chloride resin (1.0-1.6 mmol/g, 100-200 mesh). The first amino acid was loaded on the resin by incubation of the Fmoc-protected monomer (3 equiv of the number of active sites on the resin), DIPEA (4 equiv) in dichloromethane for 2 h. A cycle consisted first of the deprotection, achieved by stirring for 20 min with a 20% solution of piperidine in DMF, twice. Then the resin was washed with DMF (7x). Double couplings were performed by adding the Fmoc-protected monomer (4 equiv), HBTU (4 equiv), HOBt (4 equiv), NMM (4 equiv) and stirring for 45 min. Capping was carried out at the end of each cycle, followed by a DMF wash (7x). Acetylation of the N-terminal was achieved by incubating the resin with an Acetic Anhydride/DIPEA/DMF 10/15/75 solution for 30 min, twice. Cleavage of peptides with no protecting groups on the side-chains was performed by stirring the resin in a 20% solution of HFIP in dichloromethane for 30 min. In the presence of protecting groups, a TFA/water/trisopropylsilane 95/2.5/2.5 was used instead and the stirring time increased to 2 h. The cleavage mixture was poured into cold diethyl ether and precipitated peptides were recovered. The crude peptides were purified by preparative RP-HPLC using a gradient water-95% acetonitrile in 20 min. Pure peptides were analyzed by RP-HPLC and HRMS.

6. Decarboxylative alkylation

4.1. Reaction optimization



Degassed solvent (10 mL) was added in a 10 mL test tube containing a teflon coated stirring bar, Z-Gly-Pro (**5a**) (31 mg, 0.10 mmol, 1.0 equiv), Ph-EBX (**1b**) (52 mg, 0.15 mmol, 1.5 equiv), the base and the catalyst under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs at RT.

Procedure for HPLC yields:

0.5 mL of the reaction mixture was diluted with acetonitrile (3 x volume). In the case of metal based catalysts, a filtration over reverse phase silica was performed. The yield was determined using a calibration curve based on absorbance at 214 nm after a linear regression with Excel. The calibration curve was obtained with samples between 0.25 to 1.25 mg/mL using the method A described in the general methods.

Procedure for isolated yields:

The crude mixture was diluted with 10 mL of brine and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over MgSO₄, filtered and concentrated under vacuum. The crude product was purified by preparative TLC (pentane/ethyl acetate 1:1 or DCM/ethyl acetate 8:2).

Table S2. Optimization of the decarboxylative alkylation on dipeptides

Entry	Peptide	Solvent	Concentration (mM)	Catalyst (mol%)	Base (equiv)	Time	Ratio SM/P ^[a]	HPLC yield (%)
1 ^[b]	Z-Gly-Pro	DCE ^[c]	200	Ir cat (4) (1)	CsOBz (3)	22 h	-	mixture
2	Z-Gly-Pro	THF ^[c]	10	Ir cat (4) (2)	Cs ₂ CO ₃ (1)	15 h	>5:95	66 ^[d]
3	Z-Gly-Pro	MeCN ^[c]	10	Ir cat (4) (2)	Cs ₂ CO ₃ (1)	15 h	>5:95	55 ^[d]
4	Z-Gly-Pro	DMF ^[c,e]	5	Ir cat (4) (6)	K ₂ HPO ₄ (2)	15 h	>5:95	86
5	Z-Gly-Pro	DMF ^[c,e]	5	4CzIPN (2a) (6)	K ₂ HPO ₄ (2)	15 h	>5:95	86
6	Z-Gly-Pro	DMF ^[c]	5	4CzIPN (2a) (6)	K ₂ HPO ₄ (2)	15 h	>5:95	>95
7	Z-Gly-Pro	DMF ^[c,e]	5	DCA (6)	K ₂ HPO ₄ (2)	15 h	24:76	33
8	Z-Ala-Ala	DMF ^[c,e]	5	4CzIPN (2a) (6)	K ₂ HPO ₄ (2)	2 h	>5:95	83
9 ^[f]	Z-Ala-Ala	DMF ^[c,e]	5	4CzIPN (2a) (6)	K ₂ HPO ₄ (2)	2 h	25:74	27
10	Z-Ala-Ala	DMF ^[c,g]	10	4CzIPN (2a) (3)	K ₂ HPO ₄ (2)	1 h	>5:95	77-90
11	Z-Ala-Ala	DMF ^[c,g]	10	4CzIPN (2a) (0.5-6)	K ₂ HPO ₄ (2)	30 min	>5:95	65-72
12 ^[h]	Z-Ala-Ala	DMF ^[g]	10	4CzIPN (2a) (3)	K ₂ HPO ₄ (2)	30 min	>5:95	86
13 ^[i]	Z-Ala-Ala	DMF ^[g]	10	4CzIPN (2a) (3)	K ₂ HPO ₄ (2)	30 min	>5:95	71

^[a] Ratio of integration at 214 nm by RP-HPLC, ^[b] using TIPS-EBX^[6], ^[c] degassed by nitrogen bubbling, ^[d] isolated yield, ^[e] DMF/H₂O 99:1, ^[f] 40 W CFL household bulb, ^[g] DMF/H₂O 98:2, ^[h] freeze-pump-throw degassing, ^[i] non-degassed solvents.

With the optimized conditions (Table S2, entry 12), a catalyst screening of the novel organic dyes was performed (Table 3). Degassed (by freeze-pump-throw cycles) DMF (10 mL) and degassed water (0.20 mL) were added in a 15 mL microwave tube containing a teflon coated stirring bar, Cbz-Gly-Pro (**5a**) (15.3 mg, 0.0500 mmol, 1.0 equiv), Ph-EBX (**1b**) (26.1 mg, 0.0750 mmol, 1.5 equiv), K₂HPO₄ (17.4 mg, 0.100 mmol, 2.0 equiv) and the organic dye (3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs at RT for 30 min.

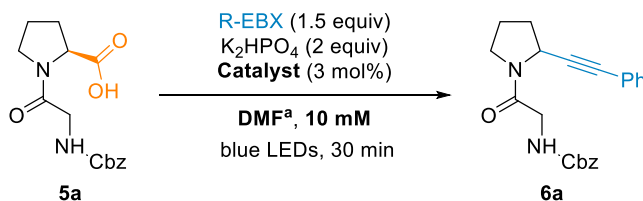


Table 3: Catalyst screening on Z-Gly-Pro

Entry	Catalyst	HPLC yield (%)
1	4CzIPN (2a)	99
2	4ClCzIPN (2b)	89
3	4DPAIPN (3a)	43
4	4BrDPAIPN (3c)	50
5	4ClDPAIPN (3b)	65
6	4tBuCzIPN (2c)	44
7	4MeOCzIPN (2d)	<5
8	4tBuCzIPN (2c) ^[b]	57
9	Ir cat (4)	99
10 ^[c]	4CzIPN (2a)	87

^[a] with 111 equivalents of water, ^[a] 5 mol%, ^[b] non-degassed solvents.

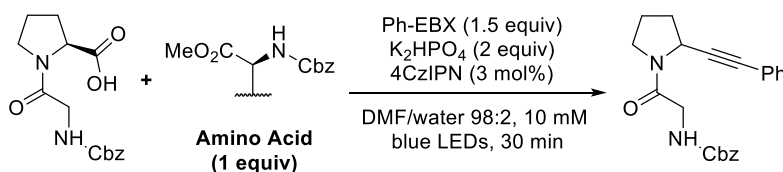
Control experiments were carried out and only traces of the desired product were observed in the absence of light or catalyst. Interestingly, the presence of a base is not required for the transformation as 24% yield was still obtained without addition of base.

4.2. Robustness experiments

Degassed DMF (10 mL) and degassed water (0.20 mL) were added in a 15 mL microwave tube containing a teflon coated stirring bar, Cbz-Gly-Pro (**5a**) (31 mg, 0.10 mmol, 1.0 equiv), the protected amino acid (0.10 mmol, 1.0 equiv), Ph-EBX (**1b**) (52 mg, 0.15 mmol, 1.5 equiv), K₂HPO₄ (35 mg, 0.20 mmol, 2.0 equiv) and 4CzIPN (**2a**) (2.4 mg, 3.0 μmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs at RT for 30 min.

0.5 mL of the crude was filtered under an inverse phase silica pad and eluted with 1.5 mL of acetonitrile. 1 mL was injected into HPLC. The yield was determined using a calibration curve based on absorbance at 214 nm after a linear regression with Excel.

Table 4. Robustness experiments

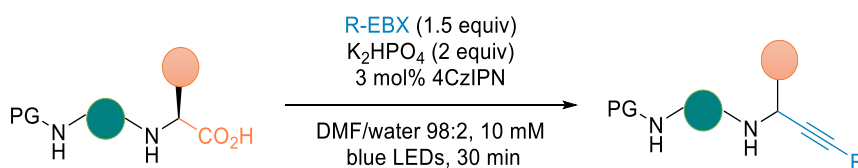


Entry	Amino acid (1 equiv)	Ratio SM/P ^a	HPLC yield (%)
1	Cbz-Met-OMe	>5:95	117
2	Cbz-Ser-OMe	5:95	108
3	Cbz-His-OMe	6:94	81
4	Cbz-Arg-OMe	19:81	79
5	Cbz-Tyr-OMe	43:57	43
6	Cbz-Val-Trp-OMe	65:35	35
7	Cbz-Gln-OMe	55:44	60
8	Cbz-Lys-OMe	42:58	58
9	(Cbz-Cys-OMe) ₂	43:57	50
		2h: 29:71	2h: 71
10	Cbz-Cys-OMe	25:75	62

^a Ratio of product compared to remaining starting material by HPLC analysis.

In all cases the reactions were clean, with no byproducts. Unreacted starting material was detected when the yield were low.

4.3. Dipeptide scope



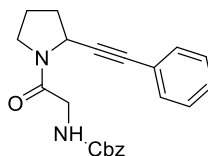
General procedure 3 for the decarboxylative alkylation of dipeptides

Degassed DMF and water (30 mL, 98:2) were added in a 50 mL schlenk flask containing a teflon coated stirring bar, Cbz-Gly-Pro (**5a**) (92 mg, 0.10 mmol, 1.0 equiv), Ph-EBX (**1b**) (0.16 g, 0.45 mmol, 1.5 equiv), K₂HPO₄ (0.11 g, 0.60 mmol, 2.0 equiv) and 4CzIPN (**2a**) (7.1 mg, 9.0 μmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 30 min at RT.

0.5 mL of the crude was filtered under an inverse phase silica pad and eluted with 1.5 mL of acetonitrile. 1 mL was injected into HPLC to determine the conversion.

The crude mixture was diluted with 30 mL of brine and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over MgSO₄, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate 8:2. In some cases a preparative TLC DCM/ethyl acetate 9:1 was performed for characterization.

Benzyl (2-oxo-2-(2-(phenylethynyl)pyrrolidin-1-yl)ethyl)carbamate (**6a**)

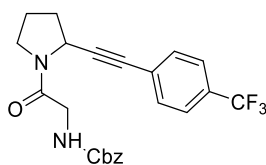


Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv), **6a** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a pale yellow oil (100 mg, 0.276 mmol, 92%).

R_f (DCM/ethyl acetate 95:5): 0.3. ¹H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor))⁴ δ 7.47 – 7.28 (m, 10H, ArH, (major+minor)), 5.84 – 5.55 (m, 1H, NH (major+minor)), 5.13 (s, 2H, OCH₂Ph (major+minor)), 5.01 (dd, *J* = 7.4, 2.3 Hz, 0.4H, NCHC≡C (minor)), 4.69 (t, *J* = 4.9 Hz, 0.6H, NCHC≡C (major)), 4.31 (dd, *J* = 17.2, 3.8 Hz, 0.6H, NC(O)CH₂NHCbz (major)), 4.18 (dd, *J* = 17.2, 5.1 Hz, 0.6H, NC(O)CH₂NHCbz (major)), 4.06 – 3.90 (m, 0.8H, NC(O)CH₂NHCbz (minor)), 3.70 (ddd, *J* = 11.4, 8.0, 3.3 Hz, 0.6H, NCH₂(CH₂)₂CHC≡C (major)), 3.63 – 3.47 (m, 1H, NCH₂(CH₂)₂CHC≡C (major+minor)), 3.44 – 3.31 (m, 0.4H, NCH₂(CH₂)₂CHC≡C (minor)), 2.38 – 1.91 (m, 4H, NCH₂(CH₂)₂CHC≡C (major+minor)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.1, 166.3, 156.2, 136.4, 131.8, 131.7, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 122.7, 121.9, 88.0, 86.8, 84.4, 82.3, 66.8, 48.7, 48.3, 46.1, 45.2, 43.5, 34.5, 32.4, 24.7, 22.9. IR 3293 (w), 2986 (w), 2880 (w), 2362 (w), 2341 (w), 1718 (s), 1648 (s), 1542 (m), 1445 (m), 1263 (m), 1057 (w). HRMS (ESI) calcd for C₂₂H₂₃N₂O₃⁺ [M+H]⁺ 363.1703; found 363.1702.

⁴ The signals of each rotamer were assigned by 2D NMR (see section 7). For clarity, only the spectra of **6a** are presented. Following products were assigned by analogy when a 1:1 ratio was measured.

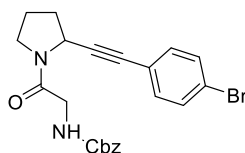
Benzyl (2-oxo-2-(2-((4-(trifluoromethyl)phenyl)ethynyl)pyrrolidin-1-yl)ethyl)carbamate (6b)



Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*CF₃-Ph-EBX (**1c**) (187 mg, 0.450 mmol, 1.50 equiv), **6b** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (124 mg at 95% purity, 0.274 mmol, 91%).

Rf (DCM/ethyl acetate 9:1): 0.3. ¹H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R¹/R²)) δ 7.59 – 7.47 (m, 4H, ArH, (R¹+R²)), 7.45 – 7.27 (m, 5H, ArH, (R¹+R²)), 5.76 (bs, 1H, NH (R¹+R²)), 5.12 (s, 2H, OCH₂Ph, (R¹+R²)), 5.01 (dd, *J* = 7.3, 2.7 Hz, 0.5H, NCHC≡C (R¹)), 4.71 (t, *J* = 4.9 Hz, 0.5H, NCHC≡C (R²)), 4.31 (dd, *J* = 17.1, 3.9 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.15 (dd, *J* = 17.1, 4.7 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 3.99 (d, *J* = 4.3 Hz, 1H, NC(O)CH₂NHCbz (R¹)), 3.75 – 3.66 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R²)), 3.64 – 3.46 (m, 1H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 3.46 – 3.33 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R¹)), 2.39 – 1.93 (m, 4H, NCH₂(CH₂)₂CHC≡C, (R¹+R²)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved)⁵ δ 167.1, 166.4, 162.0, 156.2, 136.4, 132.0 (d, *J* = 3.8 Hz), 130.4 (d, *J* = 33.1 Hz), 129.9 (d, *J* = 32.7 Hz), 128.5, 128.0 (d, *J* = 8.8 Hz), 126.1 (d, *J* = 79.2 Hz), 125.3 (q, *J* = 4.0 Hz), 125.0 (q, *J* = 3.5 Hz), 122.5 (d, *J* = 9.4 Hz), 90.6, 89.2, 83.1, 81.0, 66.9, 48.5, 48.2, 46.2, 45.2, 43.5, 34.4, 32.3, 24.8, 22.9. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -62.8, -62.9. IR 3290 (w), 2986 (w), 2881 (w), 2831 (w), 2362 (m), 2343 (w), 2122 (w), 1717 (m), 1653 (s), 1542 (m), 1457 (w), 1437 (w), 1326 (s), 1263 (w), 1170 (m), 1129 (m), 1068 (m), 845 (w). HRMS (ESI) calcd for C₂₃H₂₁F₃N₂NaO₃⁺ [M+Na]⁺ 453.1396; found 453.1395.

Benzyl (2-(2-((4-bromophenyl)ethynyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6c)

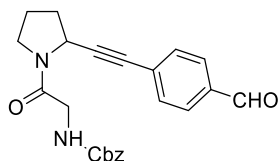


Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*Br-Ph-EBX (**1d**) (192 mg, 0.450 mmol, 1.50 equiv), **6c** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (122 mg, 0.276 mmol, 92%).

Rf (DCM/ethyl acetate 9:1): 0.3. ¹H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R¹/R²)) δ 7.46 – 7.28 (m, 9H, ArH (R¹+R²)), 5.78 (s, 1H, NH, (R¹+R²)), 5.12 (s, 2H, OCH₂Ph, (R¹+R²)), 4.98 (dd, *J* = 7.2, 2.5 Hz, 0.5H, NCHC≡C (R¹)), 4.67 (t, *J* = 5.0 Hz, 0.5H, NCHC≡C (R²)), 4.29 (dd, *J* = 17.1, 4.0 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.14 (dd, *J* = 18.1, 4.2 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.06 – 3.89 (m, 1H, NC(O)CH₂NHCbz (R¹)), 3.74 – 3.63 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R²)), 3.61 – 3.46 (m, 1H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 3.44 – 3.27 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R¹)), 2.38 – 1.90 (m, 4H, NCH₂(CH₂)₂CHC≡C (R¹+R²)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.0, 166.3, 156.2, 136.4, 133.2, 133.1, 131.6, 131.4, 128.4, 128.0, 128.0, 123.0, 122.4, 121.6, 120.9, 89.3, 88.0, 83.4, 81.2, 66.8, 48.5, 48.2, 46.1, 45.2, 43.5, 34.4, 32.3, 24.7, 22.8. IR 3285 (w), 2976 (w), 2880 (w), 2361 (w), 2343 (w), 1718 (s), 1654 (s), 1542 (m), 1437 (m), 1436 (m), 1339 (w), 1260 (m), 1176 (w), 1070 (w), 1011 (w), 830 (w). HRMS (ESI) calcd for C₂₂H₂₁BrN₂NaO₃⁺ [M+Na]⁺ 463.0628; found 463.0612.

⁵ The quadruplets corresponding to the CF₃ couplings were not resolved and appeared as doublets.

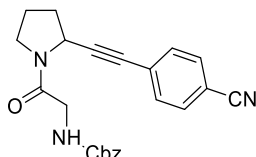
Benzyl (2-(2-((4-formylphenyl)ethynyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6d)



Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*CHO-Ph-EBX (**1e**) (169 mg, 0.450 mmol, 1.50 equiv), **6d** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (105 mg, 0.269 mmol, 90%).

Rf (DCM/ethyl acetate 9:1): 0.33. ¹H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R¹/R²)) δ 9.98 (s, 0.5H, CHO (R¹)), 9.96 (s, 0.5H, CHO (R²)), 7.78 (dd, *J* = 14.0, 8.0 Hz, 2H, ArH (R¹+R²)), 7.53 (t, *J* = 7.6 Hz, 2H, ArH (R¹+R²)), 7.35 – 7.26 (m, 5H, ArH (R¹+R²)), 5.81 (s, 1H, NH (R¹+R²)), 5.11 (s, 2H, OCH₂Ph (R¹+R²)), 5.00 (d, *J* = 4.5 Hz, 0.5H, NCHC≡C (R¹)), 4.72 (t, *J* = 5.0 Hz, 0.5H, NCHC≡C (R²)), 4.29 (d, *J* = 17.1 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.15 (d, *J* = 17.2 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.05 – 3.91 (m, 1H, NC(O)CH₂NHCbz (R¹)), 3.76 – 3.63 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R²)), 3.63 – 3.29 (m, 1.5H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 2.35 – 1.93 (m, 4H, NCH₂(CH₂)₂CHC≡C (R¹+R²)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 191.4, 191.3, 167.1, 166.4, 156.2, 136.3, 135.7, 135.3, 132.3, 132.2, 129.4, 129.3, 128.9, 128.4, 128.0, 128.0, 127.9, 92.2, 90.7, 83.5, 81.4, 66.8, 65.7, 48.5, 48.2, 46.1, 45.2, 43.4, 34.3, 32.2, 24.8, 22.8, 15.2. IR (ν_{max}, cm⁻¹) 3654 (w), 3401 (w), 3321 (w), 2982 (w), 2883 (w), 2729 (w), 2347 (w), 2230 (w), 1700 (s), 1657 (s), 1601 (m), 1515 (m), 1435 (s), 1336 (w), 1262 (m), 1213 (m), 1170 (m), 1053 (m), 985 (w), 911 (w), 825 (m), 733 (s). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₂₃H₂₂N₂NaO₄⁺ 413.1472; Found 413.1478.

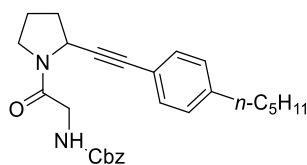
Benzyl (2-(2-((4-cyanophenyl)ethynyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6e)



Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*CN-Ph-EBX (**1f**) (168 mg, 0.450 mmol, 1.50 equiv), **6e** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as an amorphous solid (108 mg, 0.279 mmol, 93%).

Rf (DCM/ethyl acetate 9:1): 0.33. ¹H NMR (400 MHz, Acetonitrile-*d*₃, 55:45 mixture of rotamers (R¹/R²)) δ 7.51 – 7.41 (m, 2H, ArH (R¹+R²)), 7.35 (d, *J* = 8.0 Hz, 1H, ArH (R¹+R²)), 7.28 (d, *J* = 8.1 Hz, 1H, ArH (R¹+R²)), 7.17 – 7.02 (m, 5H, ArH (R¹+R²)), 5.76 – 5.54 (bs, 1H, NH (R¹+R²)), 4.86 (s, 2H, OCH₂Ph (R¹+R²)), 4.70 – 4.64 (m, 0.55H, NCHC≡C (R¹)), 4.59 (dd, *J* = 7.6, 2.4 Hz, 0.45H, NCHC≡C (R²)), 4.01 (dd, *J* = 17.0, 5.8 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 3.78 (dd, *J* = 17.0, 5.5 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 3.74 – 3.56 (m, 1.1H, NC(O)CH₂NHCbz (R¹)), 3.65 (dd, *J* = 5.5, 1.5 Hz, 1.1H, NC(O)CH₂NHCbz (R¹)), 3.41 – 3.26 (m, 1H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 3.24 – 3.11 (m, 1H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 2.14 – 1.66 (m, 4H, NCH₂(CH₂)₂CHC≡C (R¹+R²)). ¹³C NMR (101 MHz, Acetonitrile-*d*₃, mixture of rotamers, signals not fully resolved) δ 168.3, 167.9, 157.5, 157.4, 138.2, 133.3, 133.3, 133.1, 133.0, 129.4, 128.8, 128.7, 128.6, 128.1, 119.3, 119.2, 112.7, 112.3, 94.9, 93.2, 82.9, 80.8, 67.1, 49.2, 48.8, 46.8, 46.1, 44.0, 34.8, 32.9, 25.6, 23.5. IR (ν_{max}, cm⁻¹) 3616 (m), 3398 (w), 2918 (w), 2613 (w), 2370 (m), 2264 (s), 1728 (s), 1659 (s), 1510 (m), 1453 (m), 1348 (w), 1254 (m), 1048 (m), 843 (m), 749 (w). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₂₃H₂₁N₃NaO₃⁺ 410.1475; Found 410.1482.

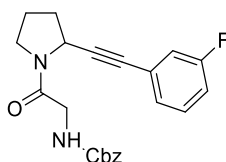
Benzyl (2-oxo-2-(2-((4-pentylphenyl)ethynyl)pyrrolidin-1-yl)ethyl)carbamate (6f)



Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*C₅H₁₁-Ph-EBX (**1g**) (168 mg, 0.450 mmol, 1.50 equiv), **6f** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (119 mg, 0.275 mmol, 92%).

Rf (DCM/ethyl acetate 9:1): 0.36. ¹H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.40 – 7.27 (m, 7H, ArH (major + minor)), 7.09 (dd, *J* = 13.5, 8.0 Hz, 2H, ArH (major + minor)), 5.93 – 5.72 (m, 1H, NH (major + minor)), 5.13 (s, 2H, OCH₂Ph (major+minor)), 5.06 – 4.96 (m, 0.4H, NCHC≡C (minor)), 4.68 (t, *J* = 4.9 Hz, 0.6H, NCHC≡C (major)), 4.31 (dd, *J* = 17.1, 2.6 Hz, 0.6H, NC(O)CH₂NHCbz (major)), 4.18 (dd, *J* = 17.1, 4.0 Hz, 0.6H, NC(O)CH₂NHCbz (major)), 4.07 – 3.87 (m, 0.5H, NC(O)CH₂NHCbz (minor)), 3.74 – 3.61 (m, 0.6H, NCH₂(CH₂)₂CHC≡C (major)), 3.63 – 3.43 (m, 1H, NCH₂(CH₂)₂CHC≡C (major+minor)), 3.44 – 3.24 (m, 0.4H, NCH₂(CH₂)₂CHC≡C (minor)), 2.57 (q, *J* = 7.9 Hz, 2H, ArCH₂ (major+minor)), 2.40 – 1.86 (m, 4H, NCH₂(CH₂)₂CHC≡C (major+minor)), 1.70 – 1.49 (m, 2H, ArCH₂CH₂ (major+minor)), 1.44 – 1.20 (m, 4H, CH₂CH₂CH₃ (major+minor)), 0.97 – 0.76 (m, 3H, CH₂CH₃ (major+minor)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.1, 166.2, 156.2, 143.8, 143.2, 136.4, 131.6, 131.5, 128.4, 128.2, 127.9, 127.9, 127.9, 119.7, 119.0, 87.3, 86.1, 84.5, 82.3, 66.7, 48.5, 48.3, 46.0, 45.1, 43.4, 35.7, 35.7, 34.4, 32.4, 31.3, 30.8, 24.6, 22.8, 22.4, 13.9. IR (ν_{max}, cm⁻¹) 3654 (w), 3407 (m), 3333 (w), 2982 (s), 2926 (s), 2224 (w), 1725 (s), 1657 (s), 1509 (m), 1435 (s), 1336 (w), 1250 (s), 1164 (m), 1059 (s), 917 (w), 837 (m), 745 (m). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₂₇H₃₂N₂NaO₃⁺ 455.2305; Found 455.2310.

Benzyl (2-(2-((3-fluorophenyl)ethynyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6g)

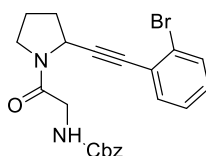


Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *m*F-Ph-EBX (**1h**) (165 mg, 0.450 mmol, 1.50 equiv), **6g** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (101 mg, 0.266 mmol, 89%).

Rf (DCM/ethyl acetate 9:1): 0.25. ¹H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R¹/R²)) δ 7.24 – 6.83 (m, 9H, ArH (R¹+R²)), 5.74 – 5.60 (m, 1H, NH (R¹+R²)), 5.02 (s, 2H, OCH₂Ph (R¹+R²)), 4.89 (dd, *J* = 7.3, 2.5 Hz, 0.5H, NCHC≡C (R¹)), 4.58 (t, *J* = 4.9 Hz, 0.5H, NCHC≡C (R²)), 4.19 (dd, *J* = 17.1, 4.0 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 4.06 (dd, *J* = 17.1, 5.1 Hz, 0.5H, NC(O)CH₂NHCbz (R²)), 3.96 – 3.80 (m, 1H, NC(O)CH₂NHCbz (R¹)), 3.66 – 3.54 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R²)), 3.53 – 3.35 (m, 1H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 3.34 – 3.20 (m, 0.5H, NCH₂(CH₂)₂CHC≡C (R¹+R²)), 2.27 – 1.78 (m, 4H, NCH₂(CH₂)₂CHC≡C (R¹+R²)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.01, 166.3, 162.2 (d, *J* = 246.9 Hz), 162.2 (d, *J* = 246.2 Hz), 156.2, 136.4, 129.9 (d, *J* = 8.6 Hz), 129.7 (d, *J* = 8.7 Hz), 128.4, 128.0, 128.0, 127.9, 127.7 (d, *J* = 3.0 Hz), 127.6 (d, *J* = 3.0 Hz), 124.5 (d, *J* = 9.5 Hz), 123.7 (d, *J* = 9.3 Hz), 118.7 (d, *J* = 6.1 Hz), 118.4 (d, *J* = 6.3 Hz), 116.1 (d, *J* = 21.1 Hz), 115.5 (d, *J* = 21.1 Hz), 89.1, 87.7, 83.2 (d, *J* = 3.5 Hz), 81.1 (d, *J* = 3.1 Hz), 66.8, 48.5, 48.2, 46.1, 45.2, 43.5, 34.4, 32.3, 24.8, 22.8. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -112.6, -113.2. IR (ν_{max}, cm⁻¹) 3426 (m), 3308 (m), 3068 (w), 2976 (m),

2889 (m), 2359 (w), 2329 (w), 1719 (s), 1657 (s), 1583 (m), 1527 (w), 1435 (s), 1343 (m), 1262 (s), 1158 (m), 1059 (s), 991 (m), 868 (m), 794 (m), 739 (m). HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{22}H_{21}FN_2NaO_3^+$ 403.1428; Found 403.1437.

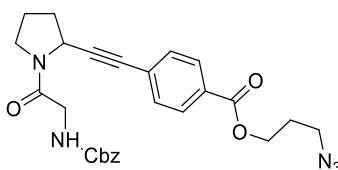
Benzyl (2-(2-((2-bromophenyl)ethynyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6h)



Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and *o*-Br-Ph-EBX (**6i**) (194 mg, 0.450 mmol, 1.50 equiv), **6h** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (127 mg, 0.290 mmol, 95%).

Rf (DCM/ethyl acetate 9:1): 0.34. 1H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.45 (ddd, $J = 9.1, 7.9, 1.3$ Hz, 1H, ArH (major+minor)), 7.33 (dd, $J = 7.7, 1.8$ Hz, 1H, ArH (major+minor)), 7.29 – 6.95 (m, 7H, ArH (major+minor)), 5.70 (d, $J = 14.9$ Hz, 1H, NH (major+minor)), 5.03 (s, 2H, OCH_2Ph (major+minor)), 4.94 (d, $J = 6.1$ Hz, 0.4H, $NCHC\equiv C$ (minor)), 4.63 (dd, $J = 6.6, 2.7$ Hz, 0.6H, $NCHC\equiv C$ (major)), 4.27 (dd, $J = 17.2, 3.9$ Hz, 0.6H, $NC(O)CH_2NHCbz$ (major)), 4.10 (dd, $J = 17.2, 5.2$ Hz, 0.6H, $NC(O)CH_2NHCbz$ (major)), 3.95 – 3.80 (m, 0.8H, $NC(O)CH_2NHCbz$ (minor)), 3.67 – 3.56 (m, 0.6H, $NCH_2(CH_2)_2CHC\equiv C$ (major)), 3.55 – 3.34 (m, 1H, $NCH_2(CH_2)_2CHC\equiv C$ (minor+major)), 3.35 – 3.24 (m, 0.4H, $NCH_2(CH_2)_2CHC\equiv C$ (minor)), 2.39 – 1.78 (m, 4H, $NCH_2(CH_2)_2CHC\equiv C$ (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.1, 166.3, 156.2, 136.4, 136.4, 133.4, 133.3, 132.3, 132.2, 129.8, 129.4, 128.4, 128.0, 127.9, 127.0, 126.9, 125.8, 125.8, 124.7, 124.1, 92.9, 91.4, 83.0, 80.9, 66.8, 48.6, 48.3, 46.1, 45.1, 43.5, 43.5, 34.3, 32.3, 29.6, 24.7, 22.8. IR 3411 (w), 3316 (w), 2953 (w), 2880 (w), 2249 (w), 1717 (m), 1651 (s), 1511 (w), 1435 (s), 1341 (w), 1250 (m), 1175 (w), 1052 (m), 1027 (w), 908 (s). HRMS (ESI) calcd for $C_{22}H_{22}BrN_2O_3^+$ $[M+H]^+$ 441.0808; found 441.0803.

3-Azidopropyl 4-(((1-(2-(((benzyloxy)carbonyl)amino)acetyl)pyrrolidin-2-yl)ethynyl)benzoate (6i)

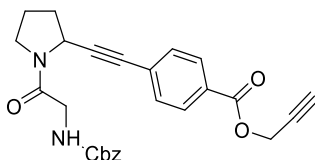


Starting with Cbz-Gly-Pro (**5a**) (15.3 mg, 0.0500 mmol, 1.00 equiv) and **1j** (35.6 mg, 0.0750 mmol, 1.50 equiv), **6i** was obtained after preparative TLC DCM/ethyl acetate 9:1 as a yellow oil (16.3 mg, 0.0330 mmol, 67%).

Rf (DCM/ethyl acetate 9:1): 0.2. 1H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R^1/R^2)) δ 8.02 – 7.91 (m, 2H, ArH (R^1+R^2)), 7.50 – 7.44 (m, 2H, ArH (R^1+R^2)), 7.40 – 7.28 (m, 5H, ArH (R^1+R^2)), 5.75 (bs, 1H, NH (R^1+R^2)), 5.13 (s, 2H, OCH_2Ph (R^1+R^2)), 5.02 (dd, $J = 7.3, 2.6$ Hz, 0.5H, $NCHC\equiv C$ (R^1)), 4.72 (t, $J = 5.0$ Hz, 0.5H, $NCHC\equiv C$ (R^2)), 4.41 (q, $J = 6.1$ Hz, 2H, OCH_2 (R^1+R^2)), 4.30 (dd, $J = 17.1, 4.0$ Hz, 0.5H, $NC(O)CH_2NHCbz$ (R^2)), 4.17 (dd, $J = 17.1, 5.0$ Hz, 0.5H, $NC(O)CH_2NHCbz$ (R^2)), 4.05 – 3.93 (m, 1H, $NC(O)CH_2NHCbz$ (R^1)), 3.71 (ddd, $J = 11.5, 8.0, 3.2$ Hz, 0.5H, $NCH_2(CH_2)_2CHC\equiv C$ (R^2)), 3.61 (t, $J = 9.0$ Hz, 0.5H, $NCH_2(CH_2)_2CHC\equiv C$ (R^1)), 3.57 – 3.35 (m, 1H, $NCH_2(CH_2)_2CHC\equiv C$ (R^1+R^2)), 3.48 (td, $J = 6.7, 2.9$ Hz, 2H, N_3CH_2 (R^1+R^2)), 2.39 – 1.92 (m, 4H, $NCH_2(CH_2)_2CHC\equiv C$ (R^1+R^2)), 2.05 (td, $J = 6.4, 3.8$ Hz, 2H, CH_2CH_2 (R^1+R^2)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.1, 166.4, 166.4, 165.8, 165.7, 156.2, 136.4, 131.8, 131.7, 129.8, 129.5, 129.3, 129.3, 128.5, 128.1, 128.0, 127.6, 126.8,

91.3, 89.9, 83.7, 81.6, 66.9, 62.1, 62.0, 48.6, 48.3, 46.2, 45.3, 43.5, 34.4, 32.3, 29.7, 28.2, 24.8, 22.9. IR (ν_{\max} , cm^{-1}) 3407 (w), 3333 (w), 2951 (w), 2107 (m), 1719 (s), 1657 (s), 1534 (w), 1447 (m), 1275 (s), 1182 (w), 1102 (m), 1053 (m), 862 (w), 776 (m). HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_5\text{NaO}_5^+$ 512.1904; Found 512.1912.

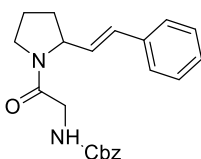
Prop-2-yn-1-yl 4-((1-(2-(((benzyloxy)carbonyl)amino)acetyl)pyrrolidin-2-yl)ethynyl)benzoate (6j)



Starting with Cbz-Gly-Pro (**5a**) (30.6 mg, 0.100 mmol, 1.00 equiv) and **1k** (64.5 mg, 0.150 mmol, 1.50 equiv), **6j** was obtained after preparative TLC DCM/ethyl acetate 8:2 as a yellow oil (31.1 mg pure at 95%, 0.066 mmol, 67%). The isolated product contained traces of alkynylated DMF, a sample for was purified by a second preparative TLC DCM/ethyl acetate 9:1 for characterization.

Rf (DCM/ethyl acetate 9:1): 0.2. ^1H NMR (400 MHz, Chloroform- d , 1:1 mixture of rotamers (R^1/R^2)) δ 7.99 (dd, $J = 13.1, 8.1$ Hz, 2H, ArH (R^1+R^2)), 7.60 – 7.28 (m, 7H, ArH (R^1+R^2)), 5.88 – 5.64 (m, 1H, NH (R^1+R^2)), 5.12 (s, 2H, OCH_2Ph (R^1+R^2)), 5.02 (d, $J = 4.6$ Hz, 0.5H, $\text{NCHC}\equiv\text{C}$ (R^1)), 4.92 (dd, $J = 5.6, 2.4$ Hz, 2H, $\text{CH}_2\text{C}\equiv\text{C}$ (R^1+R^2)), 4.72 (t, $J = 4.8$ Hz, 0.5H, $\text{NCHC}\equiv\text{C}$ (R^2)), 4.29 (d, $J = 18.3$ Hz, 0.5H, $\text{NC(O)CH}_2\text{NHCbz}$ (R^2)), 4.16 (dd, $J = 17.5, 3.7$ Hz, 0.5H, $\text{NC(O)CH}_2\text{NHCbz}$ (R^2)), 4.12 – 3.92 (m, 1H, $\text{NC(O)CH}_2\text{NHCbz}$ (R^1)), 3.78 – 3.65 (m, 0.5H, $\text{NCH}_2(\text{CH}_2)_2\text{CHC}\equiv\text{C}$ (R^2)), 3.66 – 3.46 (m, 1H, $\text{NCH}_2(\text{CH}_2)_2\text{CHC}\equiv\text{C}$ (R^1+R^2)), 3.41 (q, $J = 9.4$ Hz, 0.5H, $\text{NCH}_2(\text{CH}_2)_2\text{CHC}\equiv\text{C}$ (R^1)), 2.52 (dt, $J = 4.7, 2.6$ Hz, 1H, $\text{HC}\equiv\text{C}$ (R^1+R^2)), 2.42 – 1.90 (m, 4H, $\text{NCH}_2(\text{CH}_2)_2\text{CHC}\equiv\text{C}$ (R^1+R^2)). ^{13}C NMR (101 MHz, Chloroform- d , mixture of rotamers, signals not fully resolved) δ 167.1, 166.4, 165.2, 165.1, 156.2, 136.4, 131.8, 131.7, 129.7, 129.5, 129.2, 128.7, 128.5, 128.1, 128.0, 128.0, 127.9, 127.0, 91.5, 90.0, 83.6, 81.5, 75.2, 75.1, 66.9, 52.6, 52.6, 48.6, 48.3, 46.2, 45.3, 43.5, 34.4, 32.3, 24.8, 22.9. IR (ν_{\max} , cm^{-1}) 3660 (w), 3407 (w), 3271 (w), 2982 (m), 1725 (s), 1651 (m), 1515 (w), 1429 (m), 1256 (s), 1102 (s), 1059 (s), 1010 (m), 862 (m), 751 (m), 745 (m). HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{NaO}_5^+$ 467.1577; Found 467.1569.

(E)-Benzyl (2-oxo-2-(2-styrylpyrrolidin-1-yl)ethyl)carbamate (8)

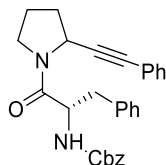


Starting with Cbz-Gly-Pro (**5a**) (92 mg, 0.30 mmol, 1.0 equiv) and Ph-VBX (**34**) (158 mg, 0.450 mmol, 1.50 equiv), **8** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a yellow oil (89.5 mg, 0.246 mmol, 82%).

Rf (DCM/ethyl acetate 9:1): 0.17. ^1H NMR (400 MHz, Chloroform- d , 6:4 mixture of rotamers (major/minor)) δ 7.44 – 7.23 (m, 10H, ArH (major+minor)), 6.42 (dd, $J = 15.8, 7.7$ Hz, 1H, $=\text{CHPh}$ (major+minor)), 6.10 (dd, $J = 15.9, 6.1$ Hz, 1H, $\text{NCHCH}=\text{C}$ (major+minor)), 5.79 (s, 0.4H, NH (minor)), 5.73 (s, 0.6H, NH (major)), 5.12 (s, 0.8H, OCH_2Ph (minor)), 5.09 (s, 1.2H, OCH_2Ph (major)), 4.83 (t, $J = 6.3$ Hz, 0.4H, $\text{NCHC}\equiv\text{C}$ (minor)), 4.50 (t, $J = 7.0$ Hz, 0.6H, $\text{NCHC}\equiv\text{C}$ (major)), 4.17 – 3.84 (m, 2H, $\text{NC(O)CH}_2\text{NHCbz}$ (major+minor)), 3.71 – 3.36 (m, 2H, $\text{NCH}_2(\text{CH}_2)_2$ (major+minor)), 2.27 – 1.83 (m, 4H, $\text{NCH}_2(\text{CH}_2)_2\text{CHC}\equiv\text{C}$). ^{13}C NMR (101 MHz, Chloroform- d , mixture of rotamers, signals not fully resolved) δ 167.3, 166.5, 156.2, 156.1, 136.5, 136.4, 135.8, 133.6, 130.6, 130.2, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.5, 126.5, 126.4, 126.4, 123.9, 123.2, 66.8, 58.8,

46.5, 45.7, 43.5, 43.4, 33.2, 30.7, 23.8, 21.6. IR (ν_{\max} , cm^{-1}) 3666 (w), 3401 (w), 3308 (w), 2982 (s), 2902 (m), 2341 (w), 2187 (w), 1731 (s), 1657 (s), 1509 (m), 1441 (m), 1262 (m), 1164 (w), 1065 (s), 905 (w), 751 (m). HRMS (ESI/QTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{NaO}_3^+$ 387.1679; Found 387.1684.

Benzyl ((2S)-1-oxo-3-phenyl-1-(2-(phenylethynyl)pyrrolidin-1-yl)propan-2-yl)carbamate (9a)



Starting with Cbz-Phe-Pro (**5b**) (119 mg, 0.300 mmol), the crude product was purified by column chromatography DCM to DCM/ethyl acetate 8:2 to afford **9a** as two separable diastereoisomers (ratio 2:1 by RP-HPLC analysis and NMR of the crude mixture): a pale yellow oil (59.7 mg, 0.132 mmol, 44%, major) as fraction 1 and an amorphous solid (47.0 mg, 0.104 mmol, 35%, minor) as fraction 2.

R_f (DCM/ethyl acetate 9:1): 0.44 (fraction 1); 0.32 (fraction 2).

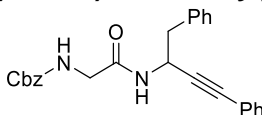
Fraction 1 (major):

¹H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.52 – 7.02 (m, 15H, ArH (major+minor)), 5.81 – 5.62 (m, 1H, NH (major+minor)), 5.13 – 5.03 (m, 2.4H, OCH₂Ph (major+minor) and NC(O)CHN (minor)), 4.98 (dd, J = 6.0, 4.0 Hz, 0.6H, NCHC \equiv C (major)), 4.62 (td, J = 8.5, 5.5 Hz, 0.6H, NC(O)CHN (major)), 3.77 – 3.68 (m, 0.4H, NCHC \equiv C (minor)), 3.67 – 3.57 (m, 0.6H, NCH₂ (major)), 3.43 – 3.22 (m, 1H, NCH₂ (major+minor)), 3.20 (dd, J = 12.7, 4.9 Hz, 0.4H, CH₂Ph (minor)), 3.13 – 3.01 (m, 1.2H, CH₂Ph (major+minor)), 2.95 (dd, J = 12.7, 10.0 Hz, 0.4H, CH₂Ph (minor)), 2.80 – 2.69 (m, 0.4H, NCH₂ (minor)), 2.06 – 1.51 (m, 4H, NCH₂(CH₂)₂CHC \equiv C (major+minor)). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 169.9, 169.5, 155.6, 155.1, 136.4, 136.4, 135.8, 131.9, 131.7, 129.8, 129.5, 128.5, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 127.0, 126.9, 123.0, 122.2, 88.2, 87.0, 84.2, 82.3, 66.8, 66.6, 54.4, 53.8, 48.7, 48.3, 46.0, 45.6, 41.1, 40.0, 33.8, 32.2, 24.8, 22.7. IR (ν_{\max} , cm^{-1}) 3284 (m), 3031 (w), 2963 (w), 2359 (w), 2335 (w), 1712 (s), 1632 (s), 1534 (m), 1435 (s), 1336 (m), 1262 (s), 1041 (m), 763 (m). HRMS (ESI/QTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{NaO}_3^+$ 475.1992; Found 475.2008.

Fraction 2 (minor):

¹H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.45 – 7.09 (m, 15H, ArH (major+minor)), 5.83 – 5.71 (m, 0.4H, NH (minor)), 5.46 (bs, 0.6H, NH (major)), 5.25 (dd, J = 5.9, 3.7 Hz, 0.6H, NCHC \equiv C (major)), 5.15 – 4.95 (m, 2.4H, OCH₂Ph (major+minor) + NC(O)CHN (major)), 4.82 (dd, J = 7.8, 2.0 Hz, 0.4H, NCHC \equiv C (minor)), 4.67 (td, J = 9.0, 5.7 Hz, 0.4H, NC(O)CHN (major)), 3.72 – 3.47 (m, 1.6H, NCH₂ (major+minor)), 3.32 (dd, J = 14.1, 4.1 Hz, 0.6H, CH₂Ph (major)), 3.13 – 2.91 (m, 1.4H, CH₂Ph (major+minor)), 2.54 (td, J = 9.2, 6.9 Hz, 0.4H, NCH₂ (minor)), 2.36 – 1.89 (m, 3.6H, NCH₂(CH₂)₂), 1.63 (dtd, J = 9.7, 6.7, 3.5 Hz, 0.4H, NCH₂(CH₂)₂). ¹³C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 171.0, 169.3, 156.0, 155.5, 136.6, 136.3, 136.2, 131.8, 131.6, 129.5, 129.3, 128.6, 128.4, 128.4, 128.3, 128.0, 128.0, 128.0, 127.9, 127.8, 127.0, 126.6, 122.8, 122.1, 88.4, 88.2, 84.2, 82.1, 66.7, 54.1, 53.7, 49.3, 48.5, 46.1, 45.9, 40.3, 38.3, 34.5, 32.3, 24.3, 23.1. HRMS (ESI/QTOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{NaO}_3^+$ 475.1992; Found 475.1994.

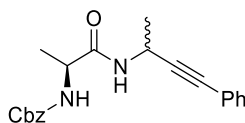
Benzyl (2-((1,4-diphenylbut-3-yn-2-yl)amino)-2-oxoethyl)carbamate (9b)



Starting with Cbz-Gly-Phe (**5c**) (107 mg, 0.300 mmol), the crude product was purified by column chromatography DCM to DCM/ethyl acetate 9:1 to afford **9b** as a pale yellow solid (93 mg, 0.23 mmol, 68%).

Rf (DCM/ethyl acetate 9:1): 0.36. Mp 128.9 – 130.8 °C. ¹H NMR (400 MHz, Chloroform-*d*)⁶ δ 7.33 (m, 15H, ArH), 6.15 (d, *J* = 8.4 Hz, 1H, NH), 5.36 (bs, 1H, NH), 5.29 – 5.20 (m, 1H, NCHC≡C), 5.13 (s, 2H, OCH₂Ph), 3.95 – 3.77 (m, 2H, NC(O)CH₂NHCbz), 3.07 (m, 2H, Ph-CH₂). ¹³C NMR (101 MHz, Chloroform-*d*)⁶ δ 168.7, 167.7, 136.1, 136.1, 131.7, 130.0, 128.6, 128.6, 128.4, 128.3, 128.2, 127.1, 122.3, 87.2, 84.7, 67.4, 43.1, 41.5, 29.7. IR 3316 (w), 2988 (w), 2881 (w), 2361 (s), 2342 (s), 2125 (w), 2086 (w), 1772 (w), 1683 (s), 1542 (s), 1397 (w), 1267 (m), 1138 (w). HRMS (ESI) calcd for C₂₆H₂₄N₂NaO₃⁺ [M⁺Na]⁺ 435.1679; found 435.1682.

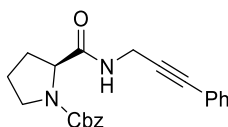
Benzyl (1-oxo-1-((4-phenylbut-3-yn-2-yl)amino)propan-2-yl)carbamate (**9c**)



Starting with Cbz-Ala-Ala (**5d**) (88 mg, 0.30 mmol, 1.0 equiv), **9c** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a white solid (83 mg, 0.24 mmol, 79%) and as a mixture of unresolved diastereoisomers.

Rf (DCM/ethyl acetate 95:5): 0.28. Mp 171 – 172 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 10H, ArH), 6.32 (bs, 1H, NH), 5.30 (bs, 1H, NH), 5.12 (s, 2H, OCH₂Ph), 5.07 – 4.94 (m, 1H, NCHC≡C), 4.24 (m, 1H, CCHNHCbz), 1.46 (d, *J* = 6.9 Hz, 3H, CH₃CHC≡C), 1.40 (d, *J* = 7.0 Hz, 3H, CH₃CHNHCbz). ¹³C NMR (101 MHz, Chloroform-*d*) δ 170.9, 156.0, 136.0, 131.7, 128.6, 128.4, 128.3, 128.1, 128.1, 122.5, 88.9, 82.5, 67.1, 50.5, 37.8, 37.8, 22.4. IR 3294 (m), 3067 (w), 3035 (w), 2984 (w), 2361 (w), 1708 (s), 1656 (s), 1540 (s), 1456 (m), 1330 (w), 1257 (m), 1241 (m), 1135 (w), 1071 (m), 1029 (w), 956 (w), 915 (w). HRMS (ESI) calcd for C₂₁H₂₃N₂O₃⁺ [M+H]⁺ 351.1703; found 351.1697.

(S)-Benzyl 2-((3-phenylprop-2-yn-1-yl)carbamoyl)pyrrolidine-1-carboxylate (**9d**)

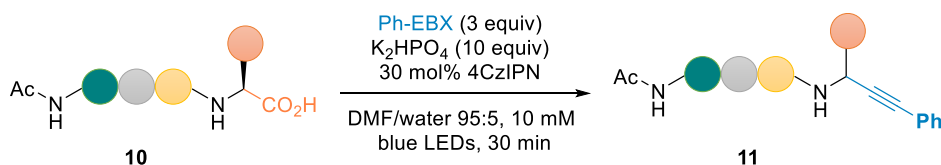


Starting with Cbz-Pro-Gly (**5e**) (92 mg, 0.30 mmol), and using 4ClCzIPN (9.58 mg, 900 μmol, 3.00 mol%) as catalyst, the crude product was purified by column chromatography DCM to DCM/ethyl acetate 85:15 to afford **9d** as a pale yellow solid (63.4 mg, 0.175 mmol, 58%).

Rf (DCM/ethyl acetate 9:1): 0.36. Mp 124.7 – 126.1 °C. ¹H NMR (400 MHz, Acetonitrile-*d*₃, mixture of rotamers, signals not fully resolved) δ 7.18 – 6.88 (m, 10H, ArH), 6.79 (d, *J* = 18.0 Hz, 1H, NH), 4.83 – 4.65 (m, 2H, OCH₂Ph), 3.88 (dd, *J* = 8.8, 3.5 Hz, 1H, NCH), 3.79 (dd, *J* = 14.1, 5.7 Hz, 2H, CH₂C≡C), 3.26 – 3.04 (m, 2H, NCH₂), 1.61 (p, *J* = 2.5 Hz, 2H, NCH₂CH₂), 1.53 (q, *J* = 6.9 Hz, 2H, NCHCH₂). ¹³C NMR (101 MHz, Acetonitrile-*d*₃, mixture of rotamers, signals not fully resolved) δ 173.4, 173.0, 138.1, 132.4, 129.4, 129.4, 129.3, 128.8, 128.6, 128.3, 123.6, 86.8, 82.6, 67.5, 67.4, 61.8, 61.5, 48.1, 47.7, 32.0, 30.6, 29.8, 25.0, 24.2. IR (ν_{max}, cm⁻¹) 3678 (w), 3302 (w), 2982 (s), 2889 (m), 2359 (w), 1700 (s), 1534 (m), 1417 (s), 1349 (m), 1244 (m), 1195 (w), 1115 (m), 1090 (m), 924 (w), 757 (s). HRMS (ESI/QTOF) *m/z*: [M + Na]⁺ Calcd for C₂₂H₂₂N₂NaO₃⁺ 385.1523; Found 385.1519.

⁶ One carbon is not resolved.

4.4. Peptide tetramers scope



General procedure 4 for the decarboxylative alkyne synthesis of tetramers

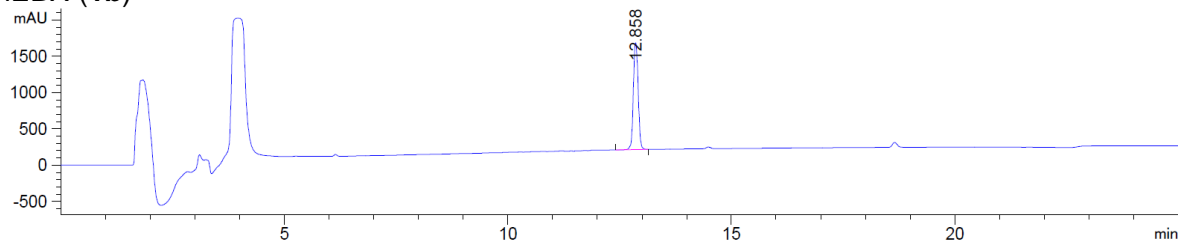
A 20 mM solution of the tetramer in non-degassed DMF (50 μ L, 1.0 μ mol), a 60 μ M solution of Ph-EBX (**1b**) in DMF (25 μ L, 3.0 μ mol, 3.0 equiv), a 15 μ M solution of 4CzIPN (**2a**) in DMF (20 μ L, 0.30 μ mol, 30 mol%) and a 2 M solution of K_2HPO_4 in milli-Q purified water (5 μ L, 10 μ mol, 10 equiv) were placed into a vial. The vial was then capped and degassed by bubbling with argon for 1-2 min and the mixture was irradiated using blue light LEDs for 30 min at RT.

Intermediate samples were prepared by dilution of 10 μ L of the reaction mixture with 30 μ L of MeOH. At the end of the reaction, the crude was diluted with 3x the volume of MeCN/water 1:1 or with 3x the volume of MeCN/water 3:1 and injected in RP-HPLC (volume of injection adapted to the dilution). The yields were determined as the ratio of $A_{\text{prod}}/A_{\text{total}}$ where A_{prod} = area in mAU of the product peak and A_{total} = area in mAU of all peptides products (product, starting material, and side-products if present).

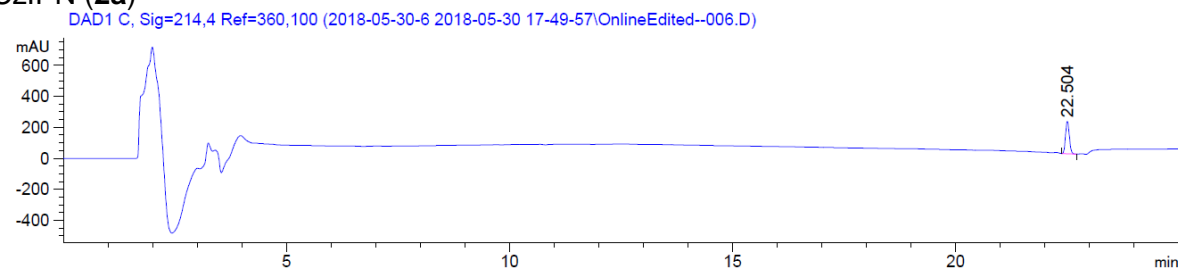
Reported results are an average of a minimum of 3 independent trials. The products are described as peptide-AH.

Reference HPLC-UV chromatograms of reagents at 214 nm

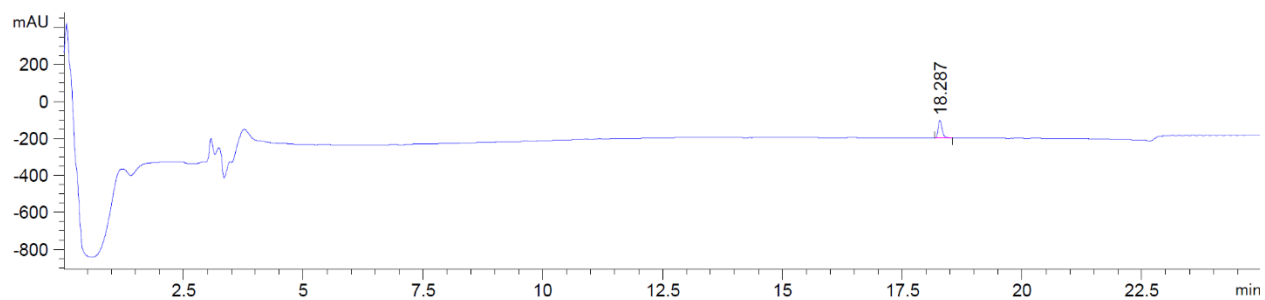
PhEBX (**1b**)



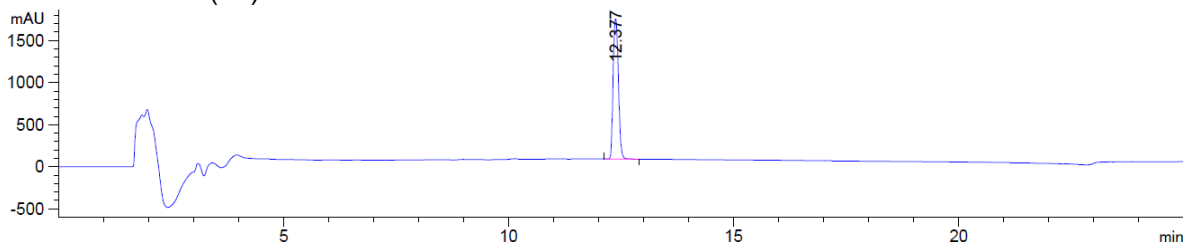
4CzIPN (**2a**)



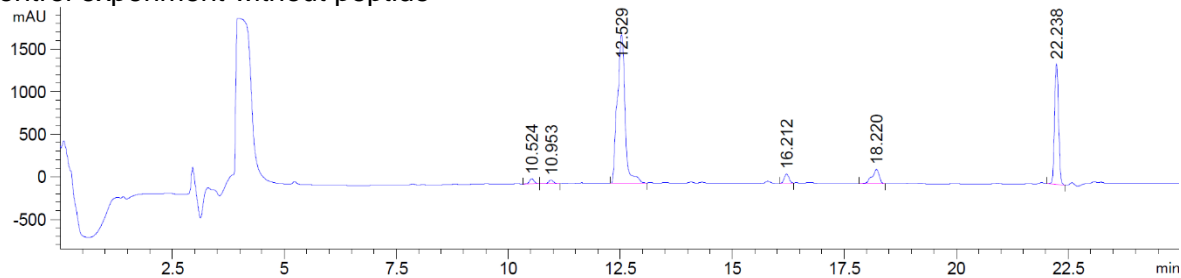
{Ir[dF(CF₃)ppy]₂dtbbpy}PF₆ (**4**)



Iodobenzoic acid (**14**)

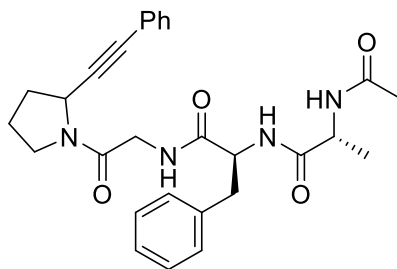


Control experiment without peptide



For clarity in the reaction chromatograms, the peaks of peptide-based products are indicated by an arrow. In all reactions, iodobenzoic acid, Ph-EBX and the catalyst were present, together with side products at 10.524, 16.212 and 18.220 min. The alkyne dimer and alkynylated DMF were identified by NMR but low ionization did not allow confirmation of their retention time.

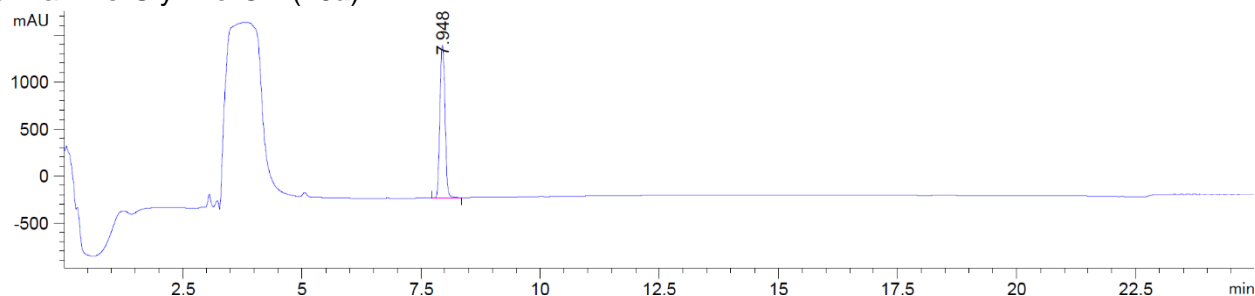
Ac-Ala-Phe-Gly-Pro-AH (11a)



Following the general procedure, Ac-Ala-Phe-Gly-Pro-OH (**10a**) afforded **11a** in more than 95% yield (retention time 13.330).

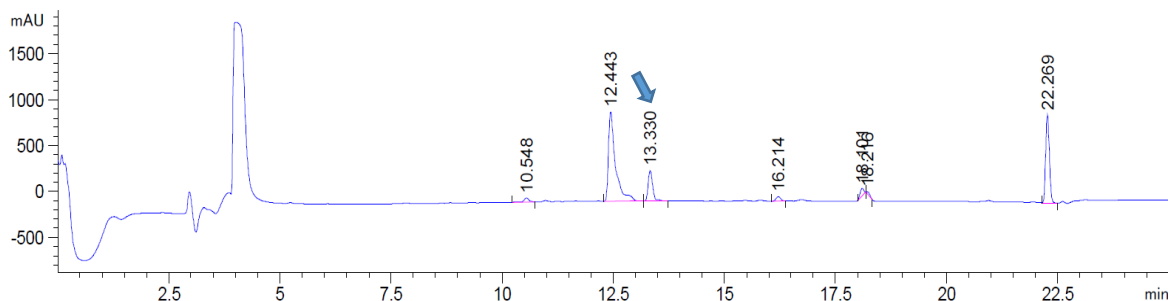
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{28}H_{32}N_4NaO_4^+$ 511.2316; Found 511.2315.

Ac-Ala-Phe-Gly-Pro-OH (10a)

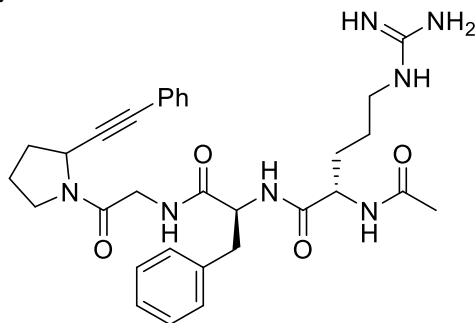


HRMS of **10a** (ESI/QTOF) m/z : $[M + H_1]^-$ Calcd for $C_{21}H_{27}N_4O_6^-$ 431.1936; Found 431.1938.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



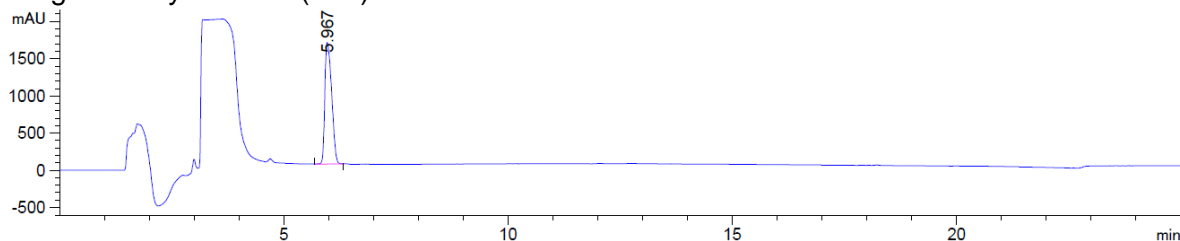
Ac-Arg-Phe-Gly-Pro-AH (11b)



Following the general procedure, Ac-Arg-Phe-Gly-Pro-OH (**10b**) afforded **11b** in more than 95% yield (retention time 10.573).

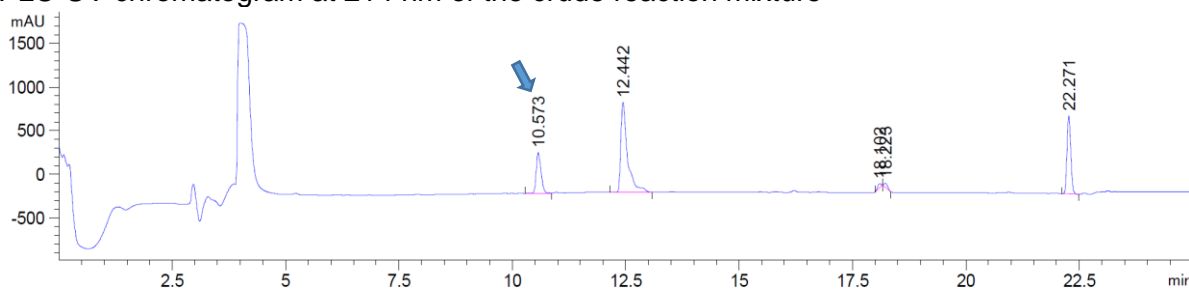
HRMS (ESI/QTOF) m/z: [M]⁺ Calcd for C₃₁H₄₀N₇O₄⁺ 574.3136; Found 574.3151.

Ac-Arg-Phe-Gly-Pro-OH (**10b**)

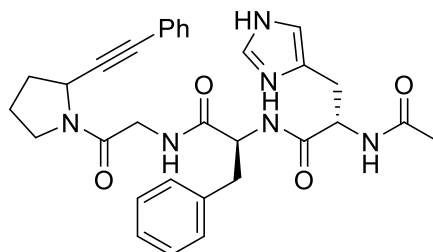


HRMS of **10b** (ESI/QTOF) m/z: [M + H₋₁]⁻ Calcd for C₂₄H₃₄N₇O₆⁻ 516.2576; Found 516.2579.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



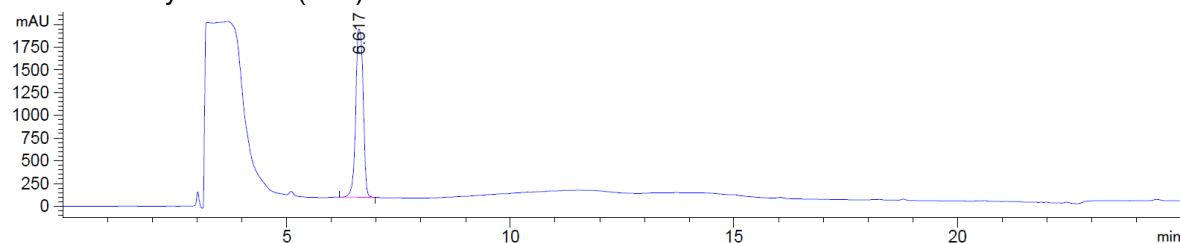
Ac-His-Phe-Gly-Pro-AH (**11c**)



Following the general procedure, Ac-His-Phe-Gly-Pro-OH (**10c**) afforded **11c** in 84% yield (retention time 10.778 with method A, 17.054 with method B for a better separation).

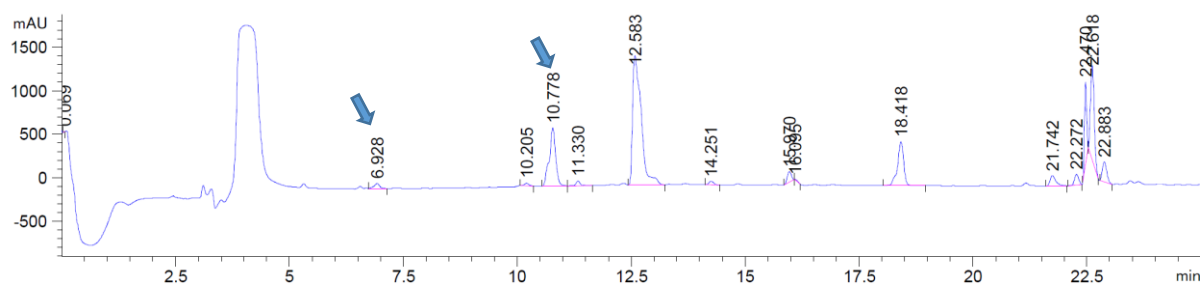
HRMS (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₃₁H₃₅N₆O₄⁺ 555.2714; Found 555.2722.

Ac-His-Phe-Gly-Pro-OH (**10c**)

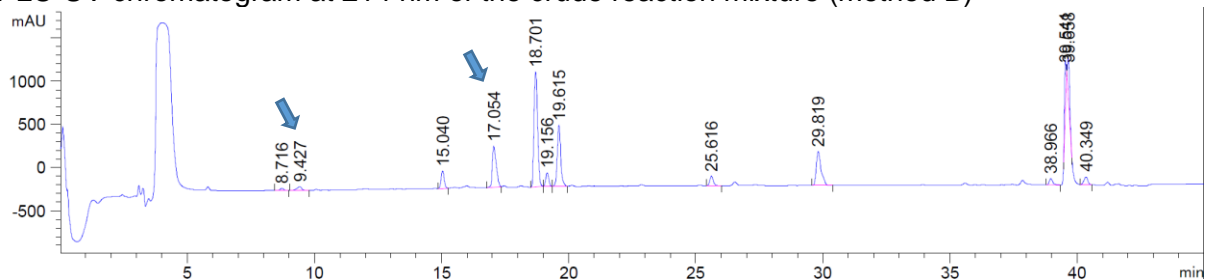


HRMS of **10c** (ESI/QTOF) m/z: [M + H₋₁]⁻ Calcd for C₂₄H₂₉N₆O₆⁻ 497.2154; Found 497.2147.

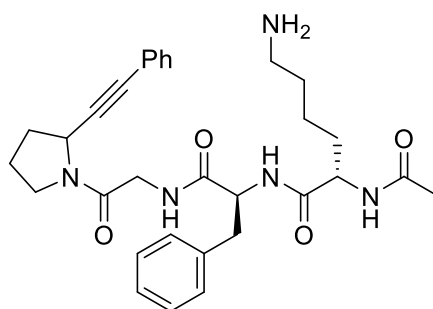
HPLC-UV chromatogram at 214 nm of the crude reaction mixture (method A)



HPLC-UV chromatogram at 214 nm of the crude reaction mixture (method B)



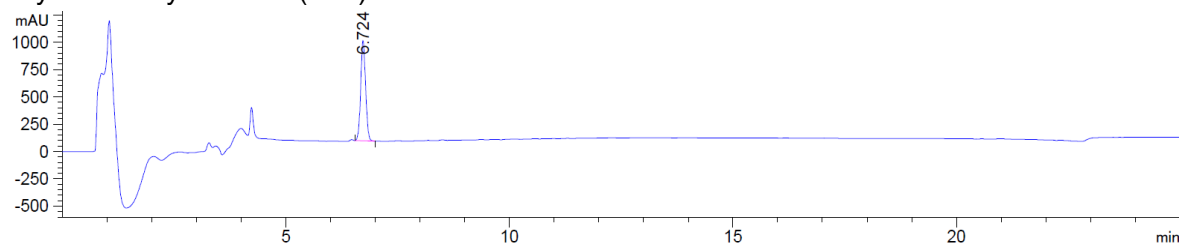
Ac-Lys-Phe-Gly-Pro-AH (11d)



Following the general procedure, Ac-Lys-Phe-Gly-Pro-OH (**10d**) afforded **11d** in 47% yield (retention time 10.670).

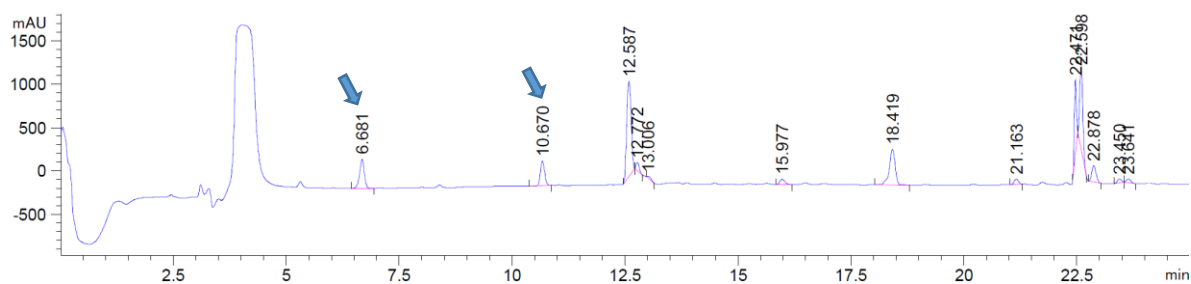
HRMS (ESI/QTOF) m/z : $[M]^+$ Calcd for $C_{31}H_{40}N_5O_4^+$ 546.3075; Found 546.3071.

Ac-Lys-Phe-Gly-Pro-OH (**10d**)

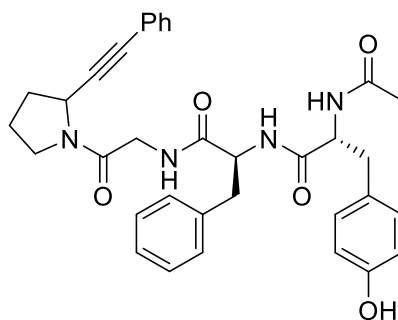


HRMS of **10d** (ESI/QTOF) m/z : $[M + H_{-1}]^-$ Calcd for $C_{24}H_{34}N_5O_6^-$ 488.2515; Found 488.2518.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



Ac-Tyr-Phe-Gly-Pro-AH (11e)

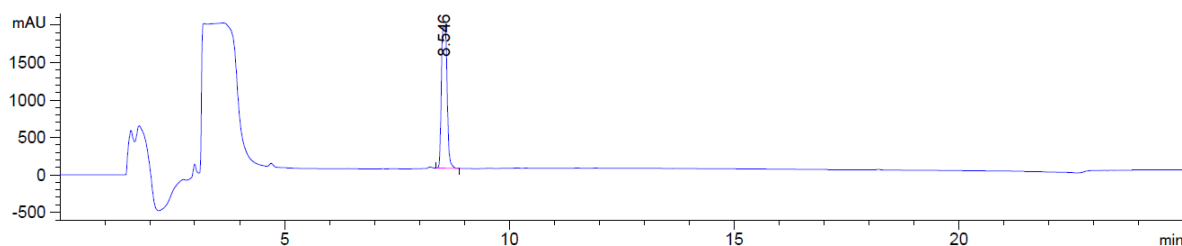


Following the general procedure and using 4tBuCzIPN (**2c**) as catalyst, Ac-Tyr-Phe-Gly-Pro-OH (**10e**) afforded **11e** in 20% yield (retention time 13.942).

Following the general procedure and using Ir (**4**) as catalyst, Ac-Tyr-Phe-Gly-Pro-OH (**10e**) afforded **11e** in 54% yield (retention time 13.937).

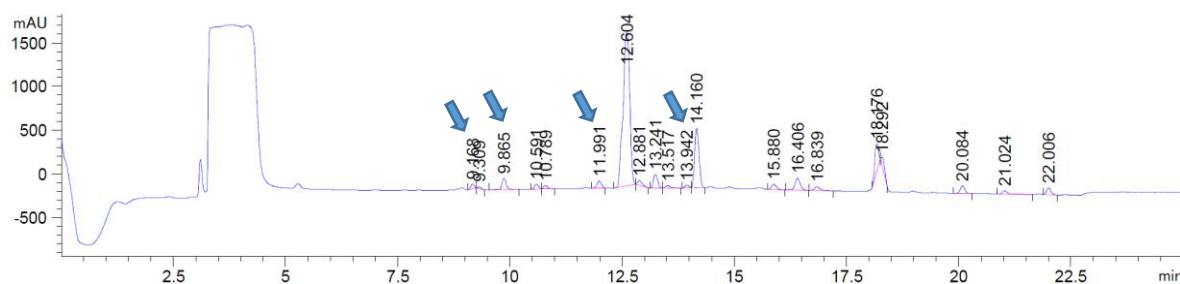
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{34}H_{36}N_4NaO_5^+$ 603.2578; Found 603.2580.

Ac-Tyr-Phe-Gly-Pro-OH (10e)

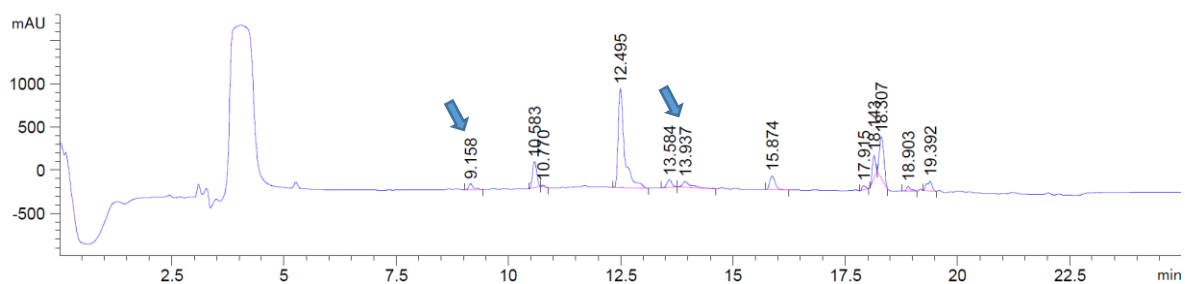


HRMS of **10e** (ESI/QTOF) m/z : $[M + H_1]^-$ Calcd for $C_{27}H_{31}N_4O_7^-$ 523.2198; Found 523.2205.

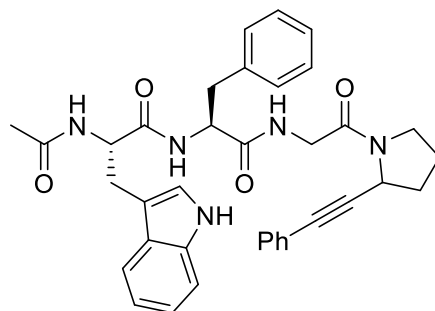
4tBuCzIPN (**2c**) as the catalyst



{Ir[dF(CF₃)ppy]₂dtbbpy}PF₆ (**4**) as the catalyst

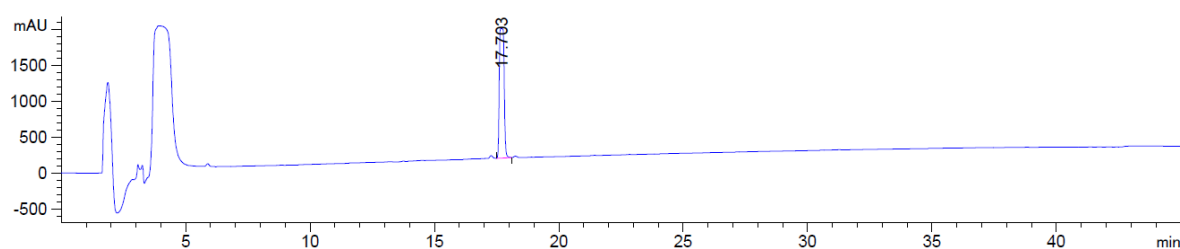


Ac-Trp-Phe-Gly-Pro-AH (11f)



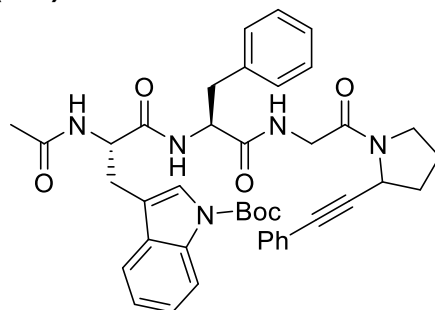
Following the general procedure, no desired product was detected from Ac-Trp-Phe-Gly-Pro-OH (**10f**) neither with 4CzIPN (**2a**), 4*t*BuCzIPN (**2c**) nor Ir cat (**4**).

Ac-Trp-Phe-Gly-Pro-OH (10f)



HRMS of **10f** (ESI/QTOF) m/z : $[M + H_1]^-$ Calcd for $C_{29}H_{32}N_5O_6^-$ 546.2358; Found 546.2357.

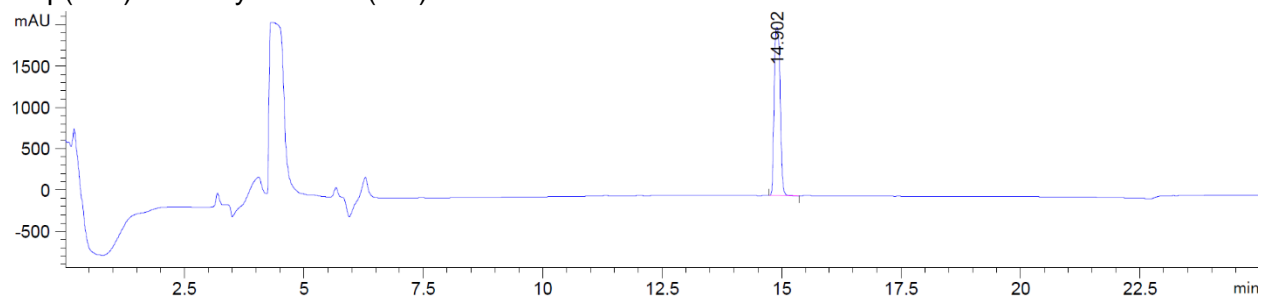
Ac-Trp(Boc)-Phe-Gly-Pro-AH (11f')



Following the general procedure, Ac-Trp(Boc)-Phe-Gly-Pro-OH (**10f'**) afforded **11f'** in 89% yield (retention time 18.973).

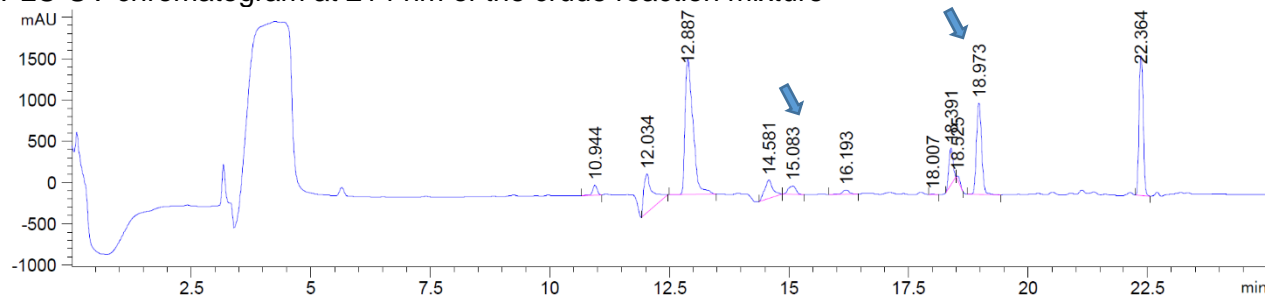
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z : $[M + H]^+$ Calcd for $C_{41}H_{46}N_5O_6^+$ 704.3443; Found 704.3460.

Ac-Trp(Boc)-Phe-Gly-Pro-OH (**10f**)

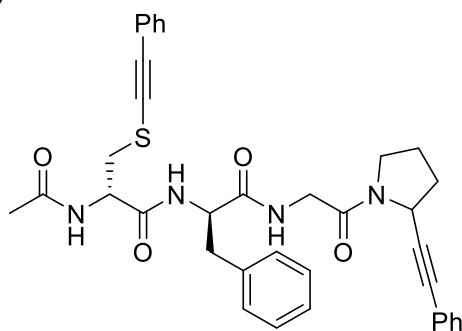


HRMS of **10f** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{34}H_{42}N_5O_8^+$ 648.3028; Found 648.3050.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



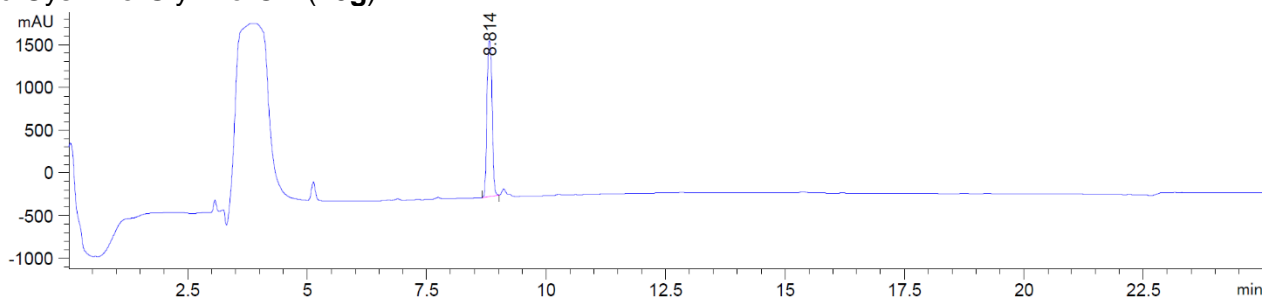
Ac-Cys-Phe-Gly-Pro-AH (**11g**)



Following the general procedure, Ac-Cys-Phe-Gly-Pro-OH (**10g**) afforded **11g** in more than 95% yield (retention time 17.432).

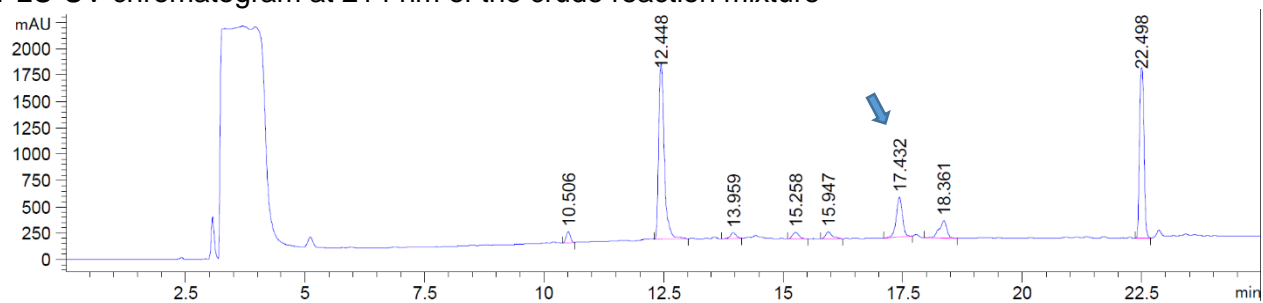
HRMS (QTOF) m/z: $[M + K]^+$ Calcd for $C_{36}H_{36}KN_4O_4S^+$ 659.2089; Found 659.2091.

Ac-Cys-Phe-Gly-Pro-OH (**10g**)

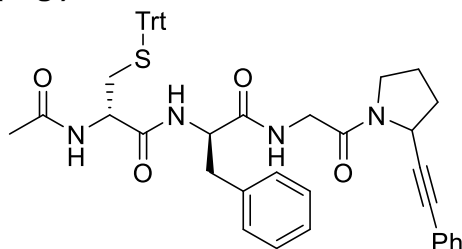


HRMS of **10g** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{28}N_4NaO_6S^+$ 487.1622; Found 487.1632.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



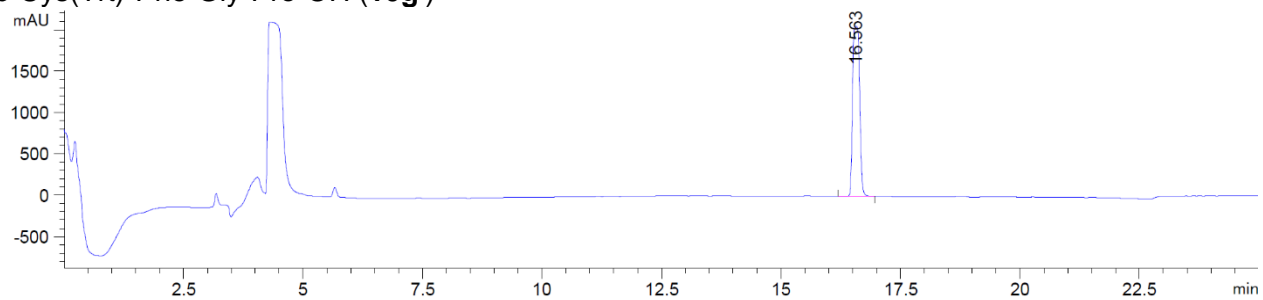
Ac-Cys(Trt)-Phe-Gly-Pro-AH (11g')



Following the general procedure, Ac-Cys(Trt)-Phe-Gly-Pro-OH (**10g'**) afforded **11g'** in 94% yield (retention time 20.083).

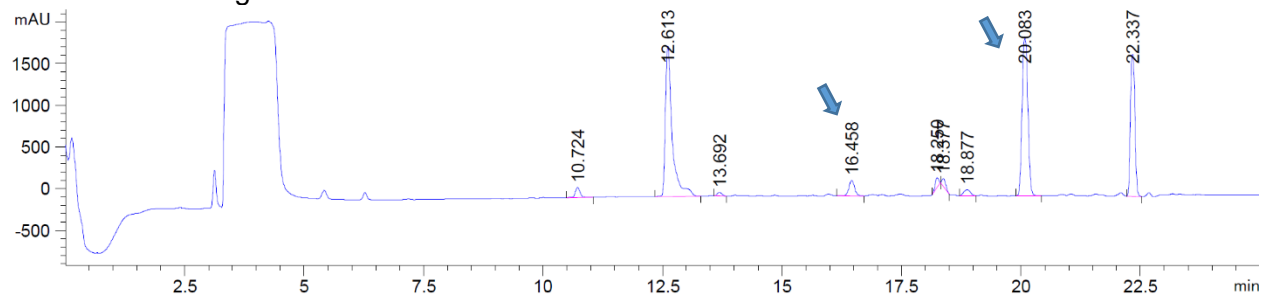
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]⁺ Calcd for C₄₇H₄₇N₄O₄S⁺ 763.3313; Found 763.3333.

Ac-Cys(Trt)-Phe-Gly-Pro-OH (10g')

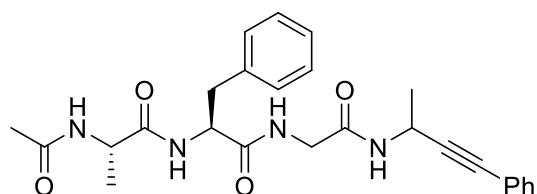


HRMS of **10g'** (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]⁺ Calcd for C₄₀H₄₃N₄O₆S⁺ 707.2898; Found 707.2909.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



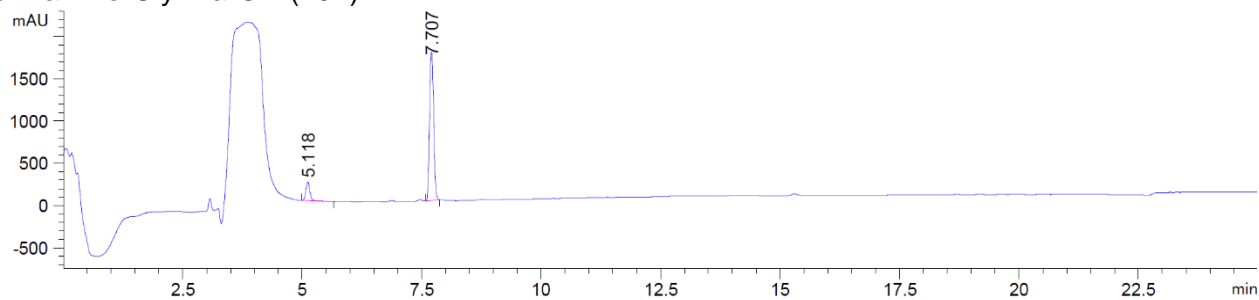
Ac-Ala-Phe-Gly-Ala-AH (11h)



Following the general procedure, Ac-Ala-Phe-Gly-Ala-OH (**10h**) afforded **11h** in more than 95% yield (retention time 12.755).

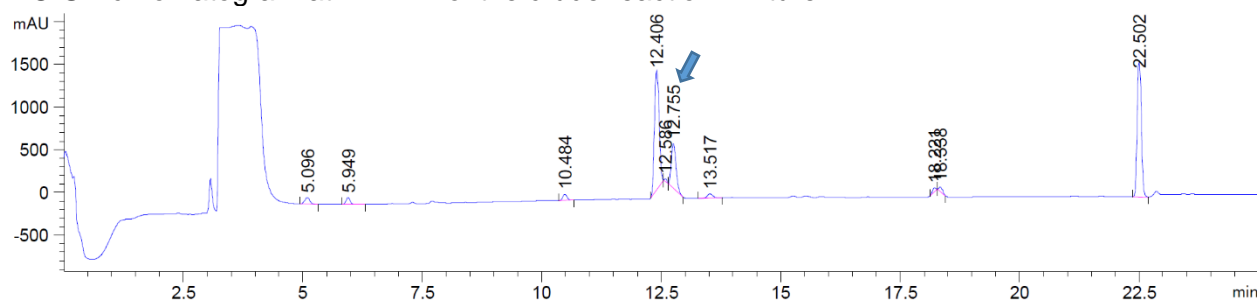
HRMS (ESI/QTOF) m/z: $[M + K]^+$ Calcd for $C_{26}H_{30}KN_4O_4^+$ 501.1899; Found 501.1908.

Ac-Ala-Phe-Gly-Ala-OH (**10h**)

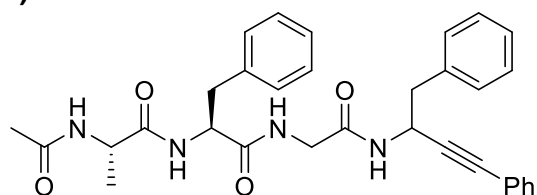


HRMS of **10h** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_6^+$ 429.1745; Found 429.1736.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



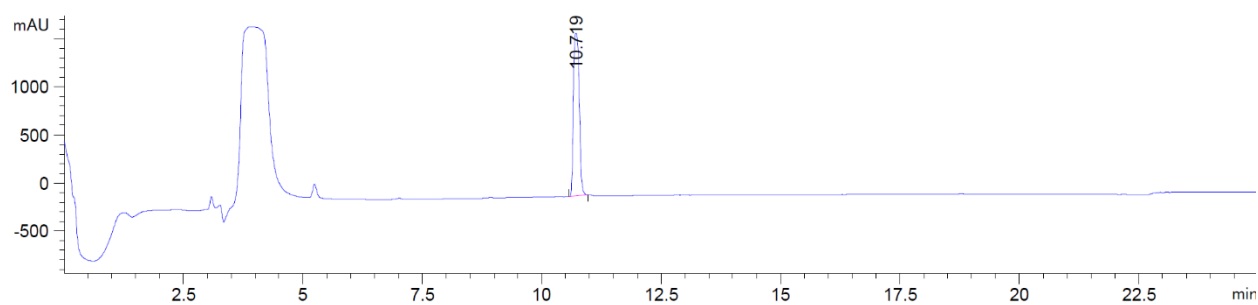
Ac-Ala-Phe-Gly-Phe-OH (**11i**)



Following the general procedure, Ac-Ala-Phe-Gly-Phe-OH (**10i**) afforded **11i** in more than 95% yield (retention time 15.242).

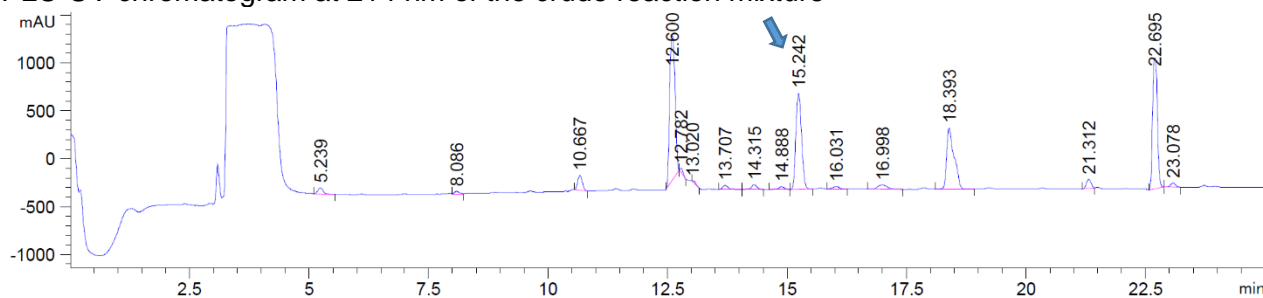
HRMS (QTOF) m/z: $[M + K]^+$ Calcd for $C_{32}H_{34}KN_4O_4^+$ 577.2212; Found 577.2225.

Ac-Ala-Phe-Gly-Phe-OH (**10i**)

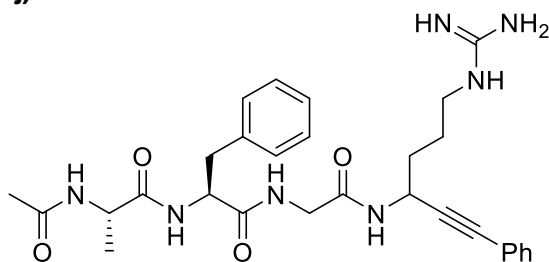


HRMS of **10i** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{30}N_4NaO_6^+$ 505.2058; Found 505.2069.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



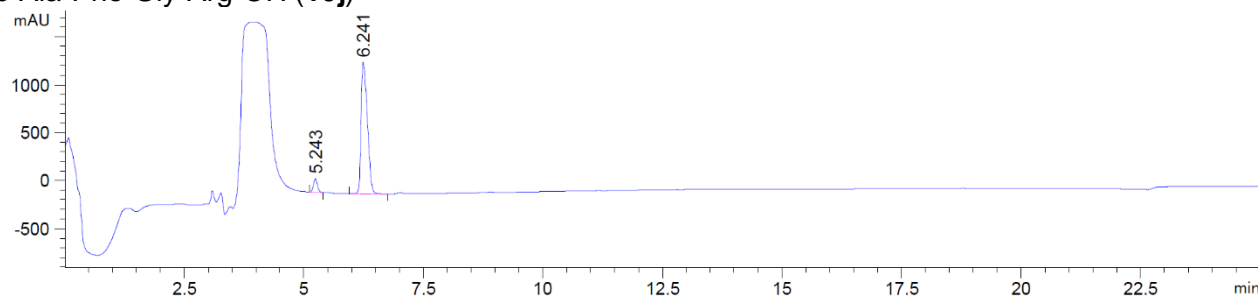
Ac-Ala-Phe-Gly-Arg-AH (**11j**)



Following the general procedure, Ac-Ala-Phe-Gly-Arg-OH (**10j**) afforded **11j** in more than 95% yield (retention time 9.735).

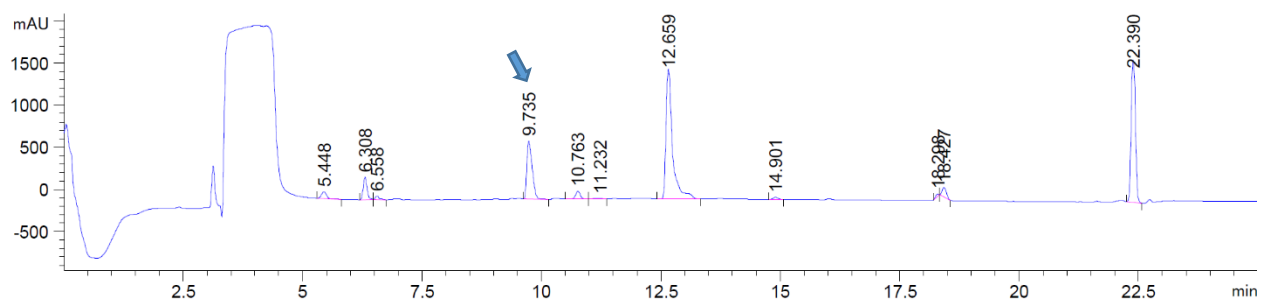
HRMS (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{29}H_{38}N_7O_4^+$ 548.2980; Found 548.2988.

Ac-Ala-Phe-Gly-Arg-OH (**10j**)

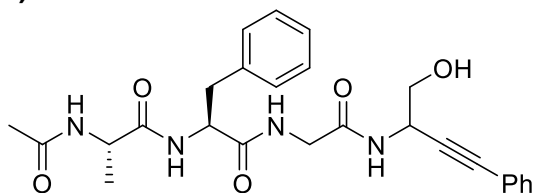


HRMS of **10j** (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{22}H_{34}N_7O_6^+$ 492.2565; Found 492.2576.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



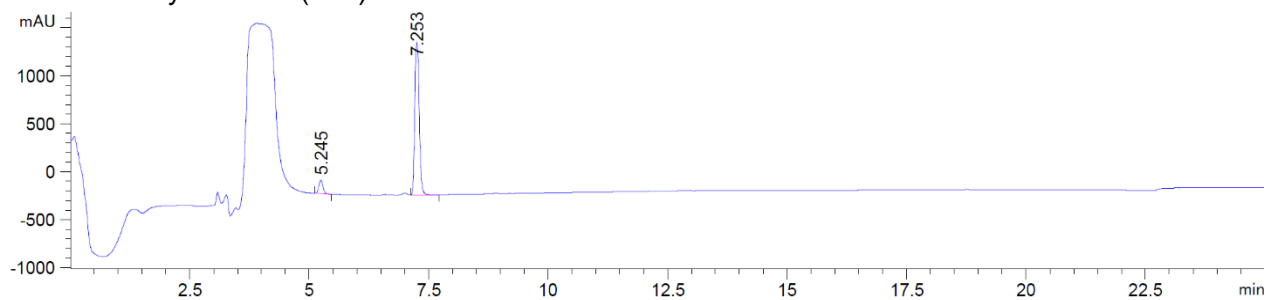
Ac-Ala-Phe-Gly-Ser-AH (11k)



Following the general procedure, Ac-Ala-Phe-Gly-Ser-OH (**10k**) afforded **11k** in more than 95% yield (retention time 11.436).

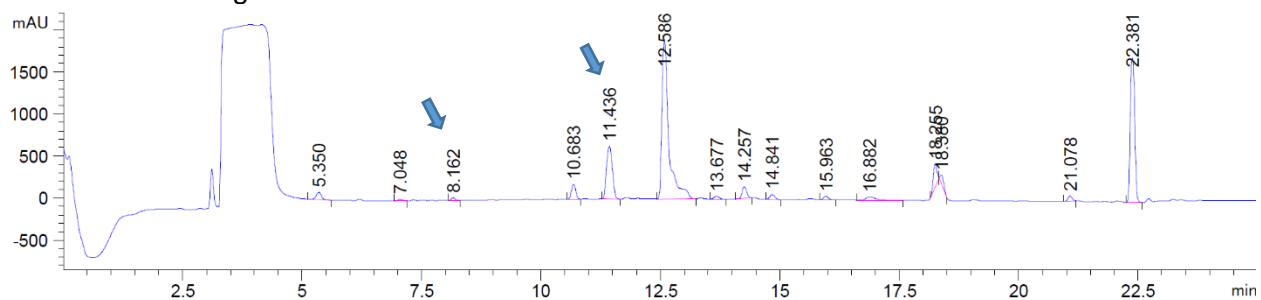
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{26}H_{30}N_4NaO_5^+$ 501.2108; Found 501.2107.

Ac-Ala-Phe-Gly-Ser-OH (10k)

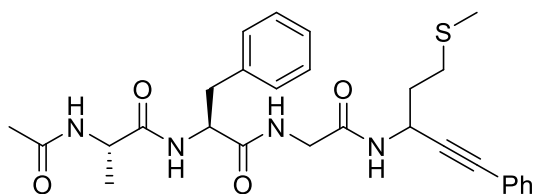


HRMS of **10k** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_7^+$ 445.1694; Found 445.1688

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



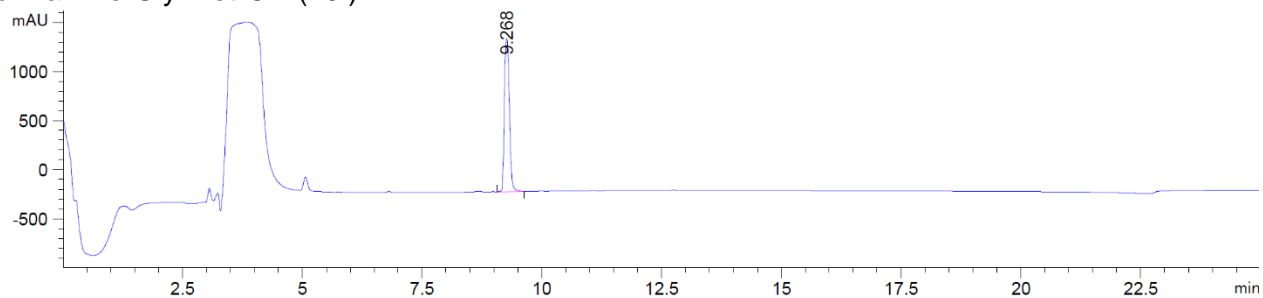
Ac-Ala-Phe-Gly-Met-AH (11l)



Following the general procedure, Ac-Ala-Phe-Gly-Met-OH (**10l**) afforded **11l** in more than 95% yield (retention time 12.124).

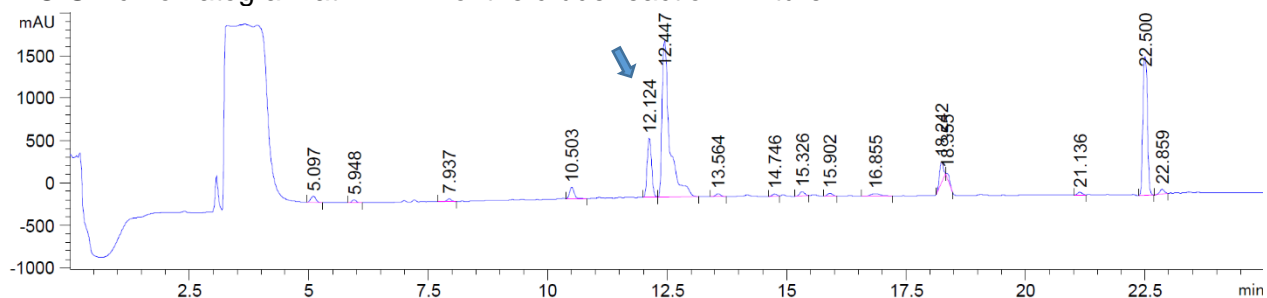
HRMS (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{28}H_{35}N_4O_4S^+$ 523.2374; Found 523.2375

Ac-Ala-Phe-Gly-Met-OH (**10l**)

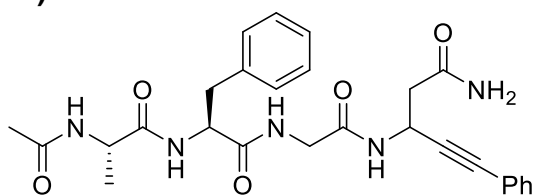


HRMS of **10l** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{21}H_{30}N_4NaO_6S^+$ 489.1778; Found 489.1774.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



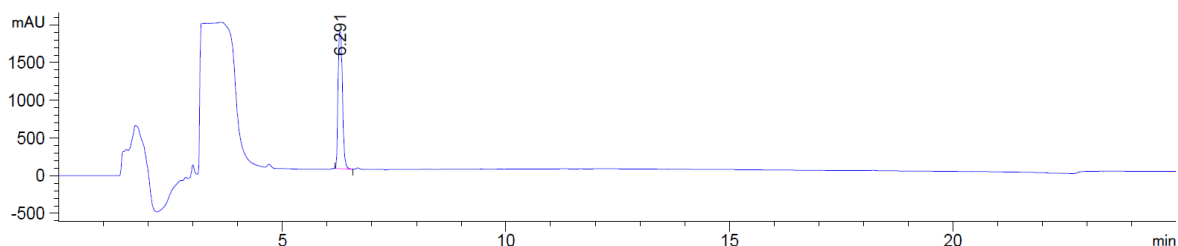
Ac-Ala-Phe-Gly-Asn-OH (**11m**)



Following the general procedure, Ac-Ala-Phe-Gly-Asn-OH (**10m**) afforded **11h** in more than 95% yield (retention time 10.724).

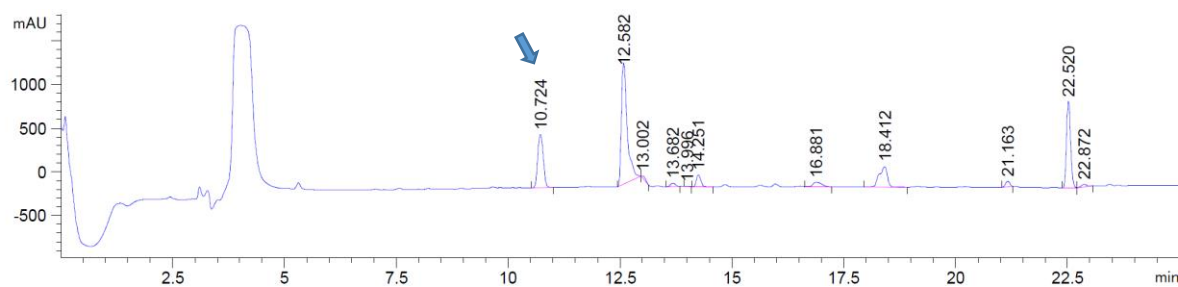
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{27}H_{31}N_5NaO_5^+$ 528.2217; Found 528.2223.

Ac-Ala-Phe-Gly-Asn-OH (**10m**)

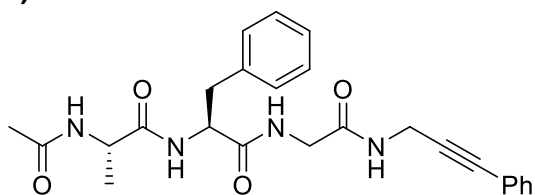


HRMS of **10m** (ESI/QTOF) m/z: $[M + H_1]^-$ Calcd for $C_{20}H_{26}N_5O_7^-$ 448.1838; Found 448.1830.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



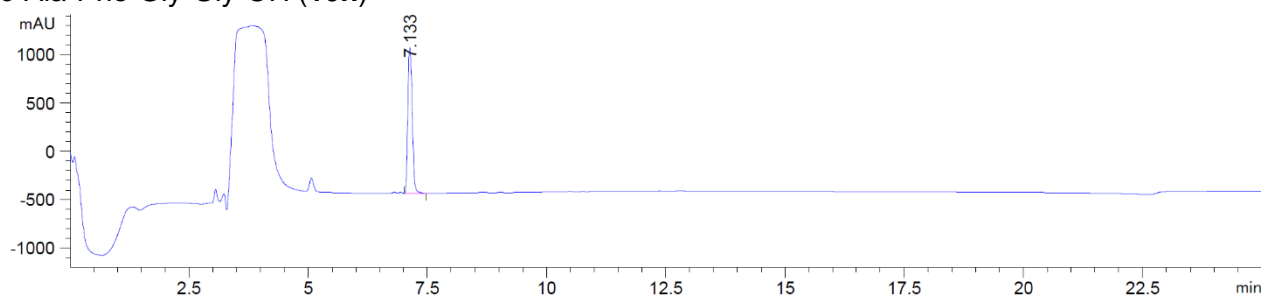
Ac-Ala-Phe-Gly-Gly-AH (**11n**)



Following the general procedure, Ac-Ala-Phe-Gly-Gly-OH (**10n**) afforded **11n** in more than 95% yield (retention time 11.995).

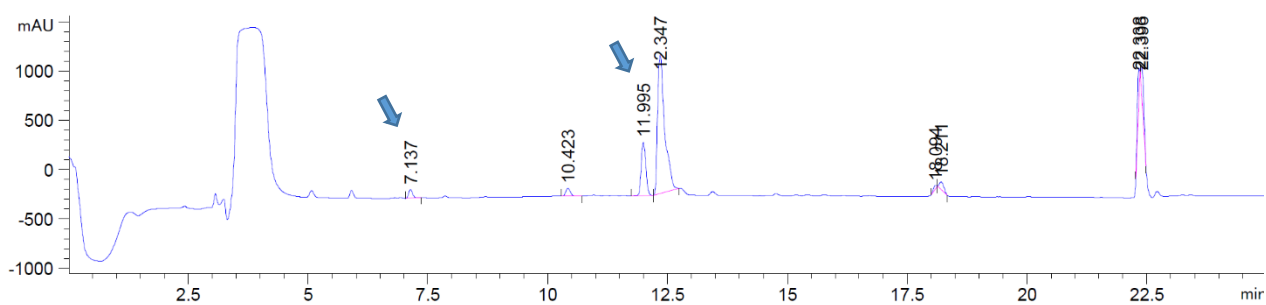
HRMS (ESI/QTOF) m/z: $[M + K]^+$ Calcd for $C_{25}H_{28}KN_4O_4^+$ 487.1742; Found 487.1757.

Ac-Ala-Phe-Gly-Gly-OH (**10n**)

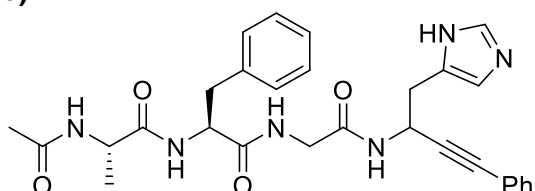


HRMS of **10n** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_4NaO_6^+$ 415.1588; Found 415.1585.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



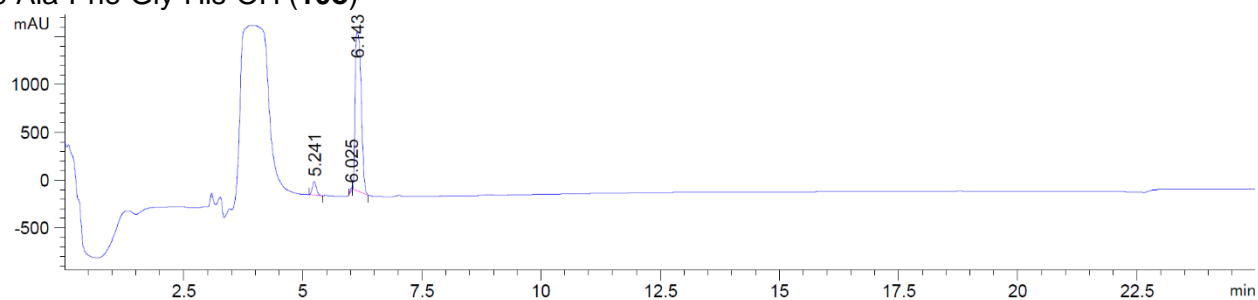
Ac-Ala-Phe-Gly-His-AH (11o)



Following the general procedure, Ac-Ala-Phe-Gly-His-OH (**10o**) afforded **11o** in an average of 76% yield (retention time 9.386).

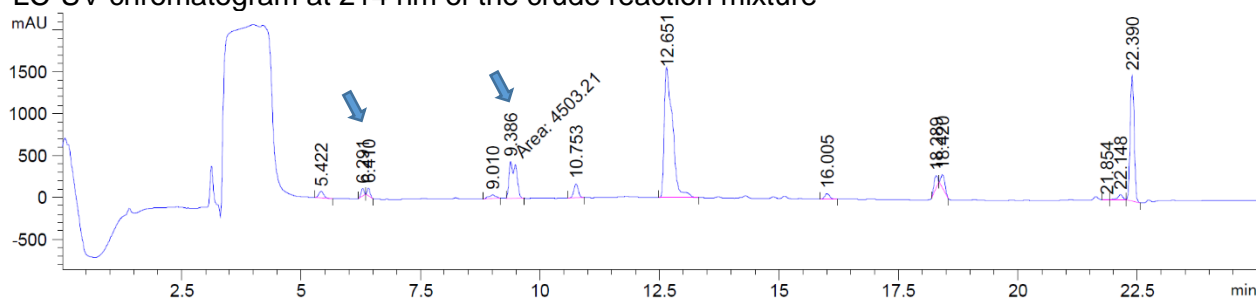
HRMS (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{29}H_{33}N_6O_4^+$ 529.2558; Found 529.2566.

Ac-Ala-Phe-Gly-His-OH (10o)

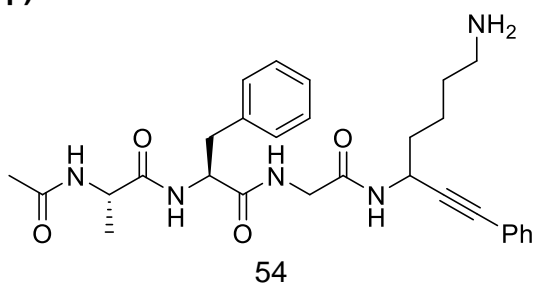


HRMS of **10o** (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{22}H_{29}N_6O_6^+$ 473.2143; Found 473.2148.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



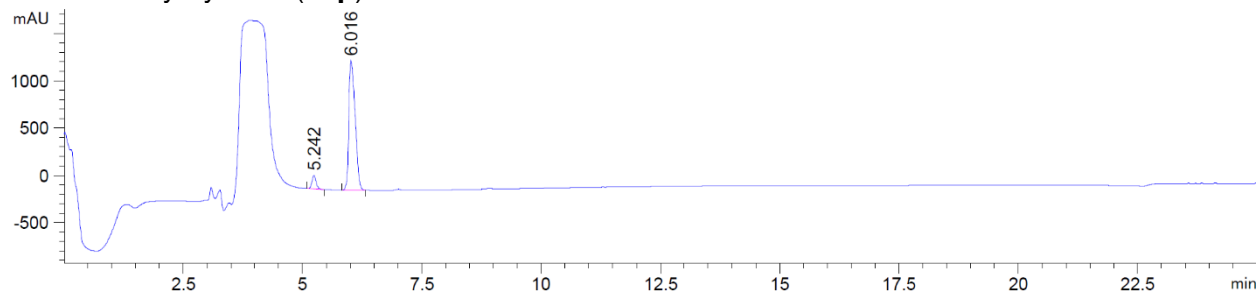
Ac-Ala-Phe-Gly-Lys-AH (11p)



Following the general procedure, Ac-Ala-Phe-Gly-Lys-OH (**10p**) afforded **11p** in an average of 17% yield (retention time 9.432).

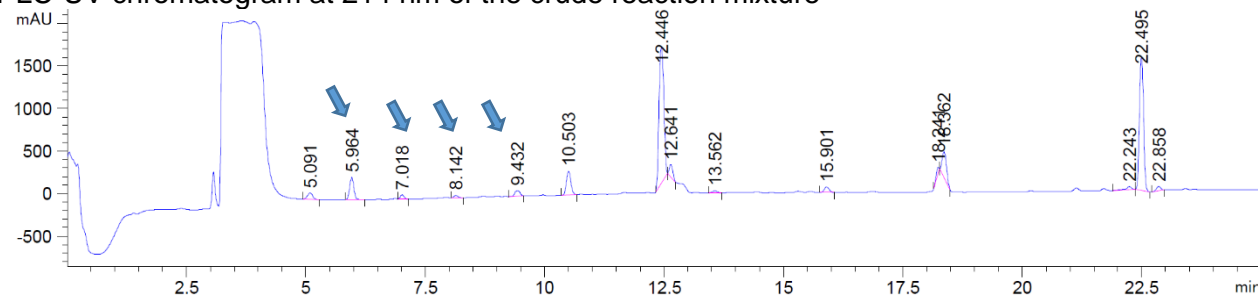
HRMS (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₂₉H₃₈N₅O₄⁺ 520.2918; Found 520.2922.

Ac-Ala-Phe-Gly-Lys-OH (**10p**)

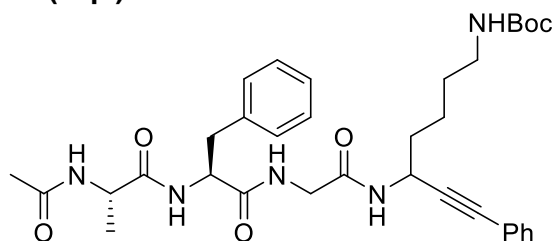


HRMS of **10p** (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₂₂H₃₄N₅O₆⁺ 464.2504; Found 464.2514.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



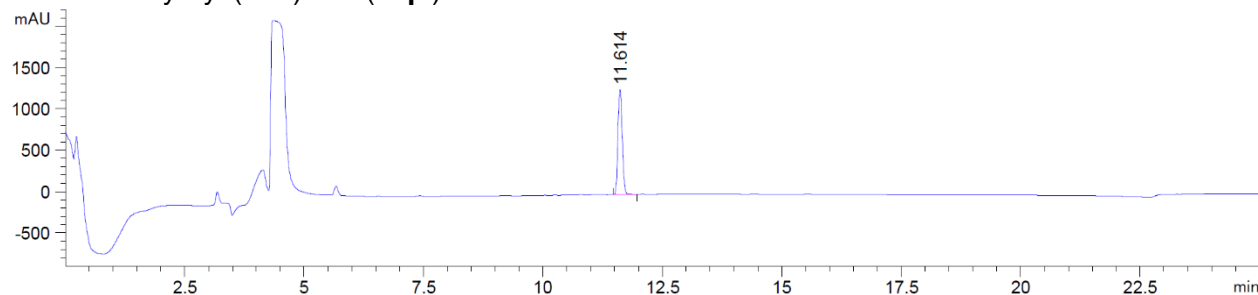
Ac-Ala-Phe-Gly-Lys(Boc)-AH (**11p'**)



Following the general procedure, Ac-Ala-Phe-Gly-Lys(Boc)-OH (**10p'**) afforded **11p'** in more than 95% yield (retention time 15.359).

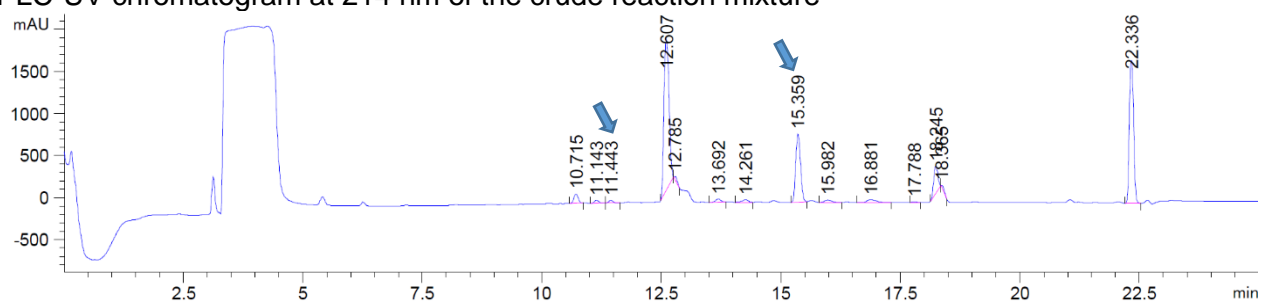
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]⁺ Calcd for C₃₄H₄₆N₅O₆⁺ 620.3443; Found 620.3455.

Ac-Ala-Phe-Gly-Lys(Boc)-OH (**10p'**)

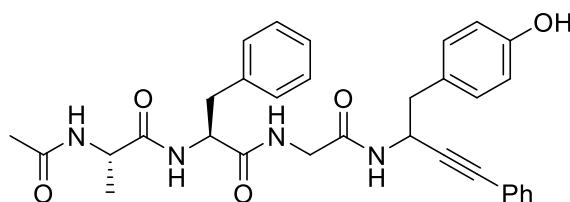


HRMS of **10p'** (ESI/QTOF) m/z: [M + Na]⁺ Calcd for C₂₇H₄₁N₅NaO₈⁺ 586.2847; Found 586.2860.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



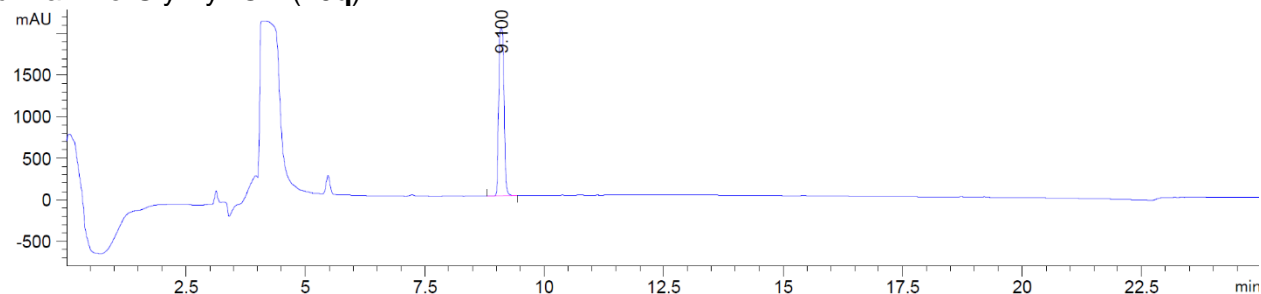
Ac-Ala-Phe-Gly-Tyr-AH (11q)



Following the general procedure and using Ir (**4**) as catalyst, Ac-Ala-Phe-Gly-Tyr-OH (**10q**) afforded **11q** in an average of 29% yield (retention time 13.243).

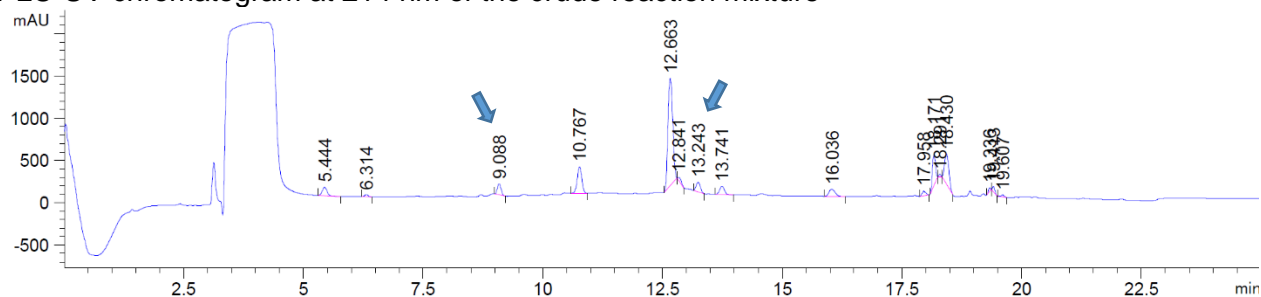
HRMS (ESI/QTOF) m/z: [M + K]⁺ Calcd for C₃₂H₃₄KN₄O₅⁺ 593.2161; Found 593.2172.

Ac-Ala-Phe-Gly-Tyr-OH (10q)

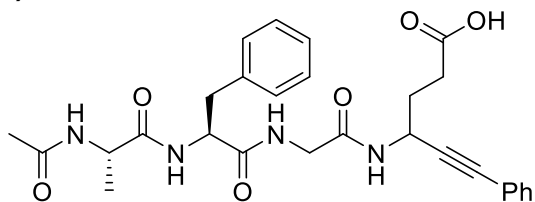


HRMS of **10q** (ESI/QTOF) m/z: [M + H]⁺ Calcd for C₂₅H₃₁N₄O₇⁺ 499.2187; Found 499.2187.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



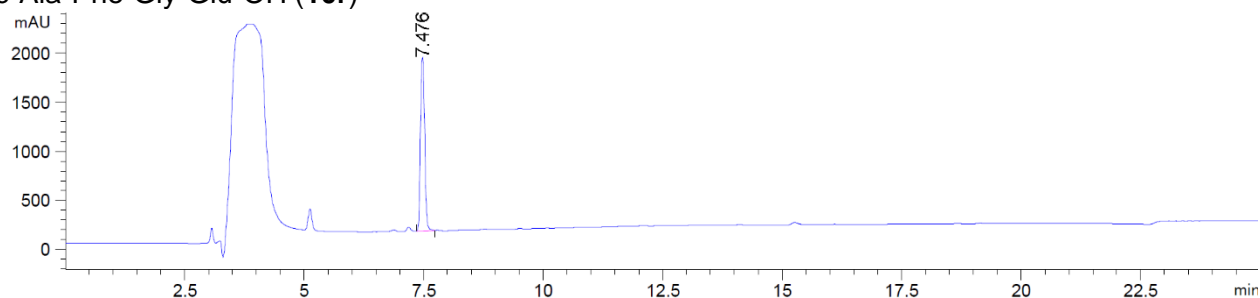
Ac-Ala-Phe-Gly-Glu-AH (11r)



Following the general procedure, Ac-Ala-Phe-Gly-Glu-OH (**10r**) afforded **11r** in more than 95% yield (retention time 11.730). The product with double alkylation was detected at a retention time of 16.9 as less than 5% as the single alkylation at the C-terminal position.

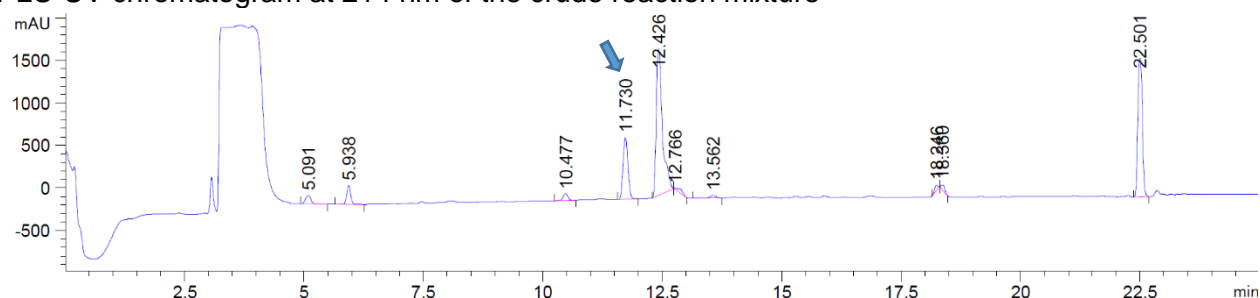
HRMS (ESI/QTOF) m/z : $[M + K]^+$ Calcd for $C_{28}H_{32}KN_4O_6^+$ 559.1953; Found 559.1962.

Ac-Ala-Phe-Gly-Glu-OH (**10r**)



HRMS of **10r** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{21}H_{28}N_4NaO_8^+$ 487.1799; Found 487.1807.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



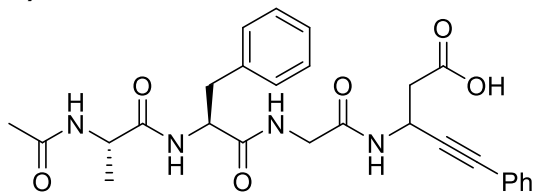
The 3 independent trials were gathered and purified by preparative HPLC using a gradient of 100% A to 100% B in 20 minutes (see general methods). The desired peptide was obtained as a mixture at 40% pure together with iodobenzoic acid. The site of decarboxylative alkylation was assigned by NMR. The signal in α position of the alkyne was attributed with the 1H and the HMBC NMR. As an integration of 1 was measured, selective alkylation at the C-terminal position was achieved. The signals are reported below, with signals of iodobenzoic acid in italics in brackets.

1H NMR (800 MHz, $DMF-d_7$, 1:1 mixture of diastereoisomers, signals only partially resolved, only relevant protons were attributed) δ 8.29 – 8.10 (m, 4H, ArH), (8.07 (dd, $J = 7.9, 1.1$ Hz, 2H), 8.03 (s, 4H), 7.85 (dd, $J = 7.7, 1.7$ Hz, 2H), 7.55 (td, $J = 7.5, 1.2$ Hz, 2H),) 7.46 (tdd, $J = 4.8, 3.1, 1.9$ Hz, 2H, ArH), 7.42 – 7.37 (m, 3H, ArH), (7.32 – 7.27 (m, 6H),) 7.24 – 7.18 (m, 1H, ArH), 5.08 – 4.97 (m, 1H, $NC(H)C\equiv C$), 4.56 (ddd, $J = 9.5, 7.5, 4.8$ Hz, 0.5H, $NC(O)CH_2NH$), 4.52 (ddd, $J = 9.6, 7.4, 4.8$ Hz, 0.5H, $NC(O)CH_2NH$), 4.32 – 4.24 (m, 1H, $NC(O)CHCH_3NH$), 3.97 (dd, $J = 6.3, 1.6$ Hz, 1H), 3.95 (dd, $J = 6.3, 1.5$ Hz, 1H), 3.82 (dd, $J = 16.7, 5.6$ Hz, 0.5H), 3.79 (dd, $J = 16.7, 5.6$ Hz, 0.5H), 3.25 (ddd, $J = 14.0, 6.8, 4.8$ Hz, 1H), 3.06 – 2.97 (m, 1H), 2.59 – 2.48 (m, 2H, $CHCH_2CH_3$), 2.12 – 2.02 (m, 2H, $NHCHCH_2$), 1.90 (d, $J = 3.4$ Hz, 3H, Ac-NH), 1.22 (t, $J = 6.8$ Hz, 3H, $NC(O)CHCH_3NH$).

^{13}C NMR (201 MHz, $DMF-d_7$) δ 174.3, 174.2, 173.6, 173.5, 171.8, 170.6, 170.5, 168.7, (168.3, 141.4), 138.6, 138.6, (137.4, 132.8), 132.6, 131.9, 131.9, (130.8), 129.6, 129.3, 128.9, 128.9, 128.9,

128.6, (128.5), 126.6, 123.0, (93.9), 89.5, 89.5, 82.6, 82.6, 55.4, 55.3, 49.7, 42.8, 40.9, 40.9, 37.2, 31.2, 22.4, 17.3, 17.3.

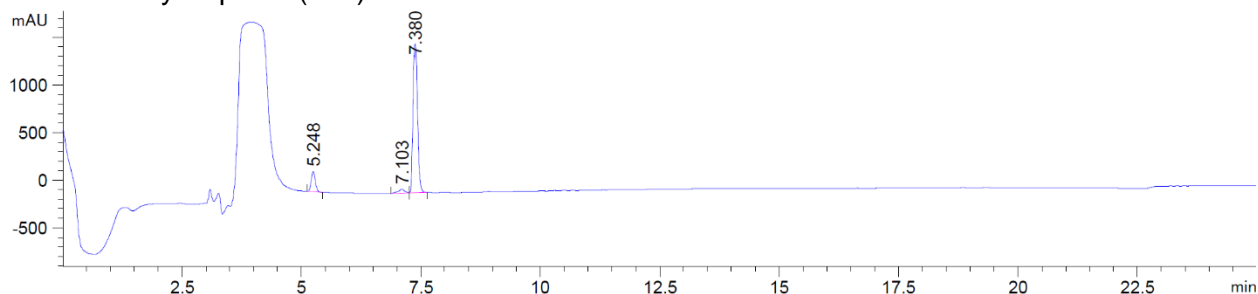
Ac-Ala-Phe-Gly-Asp-AH (11s)



Following the general procedure, Ac-Ala-Phe-Gly-Asp-OH (**10s**) afforded **11s** in an average of 37% yield (retention time 11.684). The product with double alkylation was not detected in the HPLC chromatogram.

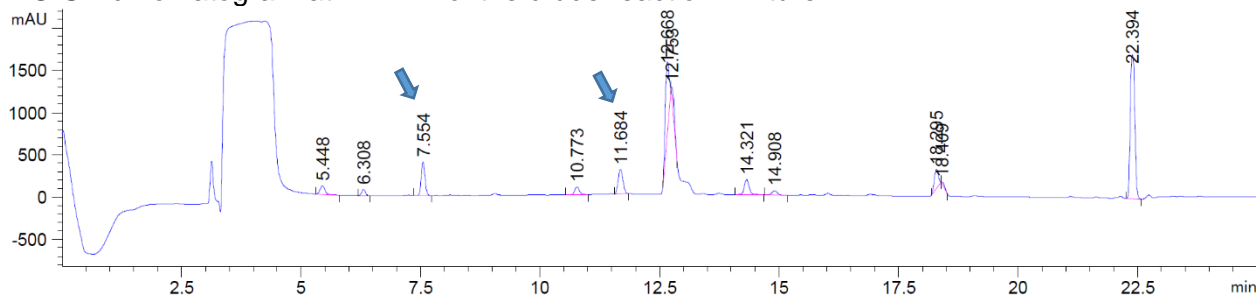
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z : $[M]^-$ Calcd for $C_{27}H_{29}N_4O_6^-$ 505.2093; Found 505.2077.

Ac-Ala-Phe-Gly-Asp-OH (10s)



HRMS of **10s** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{20}H_{26}N_4NaO_8^+$ 473.1643; Found 473.1646.

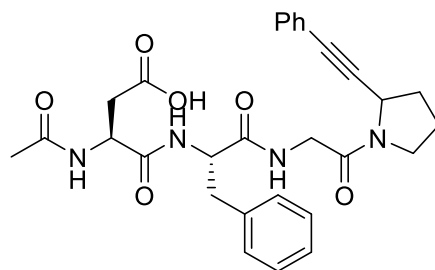
HPLC-UV chromatogram at 214 nm of the crude reaction mixture



The 3 independent trials were gathered and purified by preparative HPLC using a gradient of 100% A to 100% B in 20 minutes (see general methods). The desired peptide was obtained as a mixture at 75% pure together with iodobenzoic acid. The site of decarboxylative alkylation was assigned by NMR by analogy to Ac-Ala-Phe-Gly-Glu-AH (**11r**) as not enough material was obtained to record an interpretable ^{13}C or HMBC NMR. The signal in α position of the alkyne was attributed with the 1H NMR. As an integration of 1 was measured, selective alkylation at the C-terminal position was achieved. The signals are reported below, with signals of iodobenzoic acid in italics in brackets.

1H NMR (800 MHz, $DMF-d_7$, 1:1 mixture of diastereoisomers, signals only partially resolved, only relevant protons were attributed) δ 8.32 – 8.18 (m, 2H, ArH), (7.81 (d, $J = 7.5$ Hz, 0.3H), 7.54 – 7.49 (m, 0.3H)), 7.46 – 7.38 (m, 5H, ArH), 7.33 – 7.26 (m, 2H, ArH (and 2H)), 7.24 – 7.19 (m, 1H, ArH), 5.33 – 5.23 (m, 1H, $NCHC\equiv C$), 4.58 (ddd, $J = 9.2, 7.6, 4.7$ Hz, 1H, $NC(O)CH_2NH$), 4.31 – 4.21 (m, 1H, $NC(O)CH_2NH$), 4.00 – 3.97 (m, 0.5H), 3.97 – 3.95 (m, 0.5H), 3.81 (dd, $J = 16.7, 5.5$ Hz, 0.5H), 3.77 (dd, $J = 16.7, 5.2$ Hz, 0.5H), 3.27 (dt, $J = 14.0, 4.6$ Hz, 1H), 3.06 – 2.99 (m, 2H), 1.93 (d, $J = 14.2$ Hz, 3H, Ac-NH), 1.22 (t, $J = 7.5$ Hz, 3H, $NC(O)CHCH_3NH$).

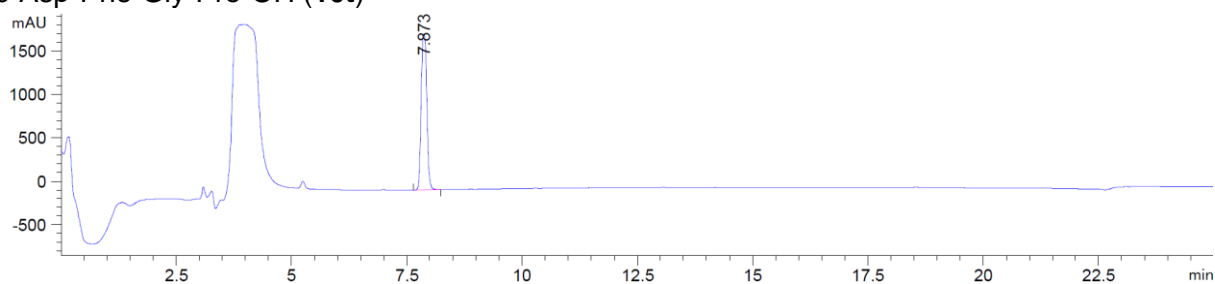
Ac-Asp-Phe-Gly-Pro-AH (11t)



Following the general procedure, Ac-Asp-Phe-Gly-Pro-OH (**10t**) afforded **11t** in more than 95% yield (retention time 13.020).

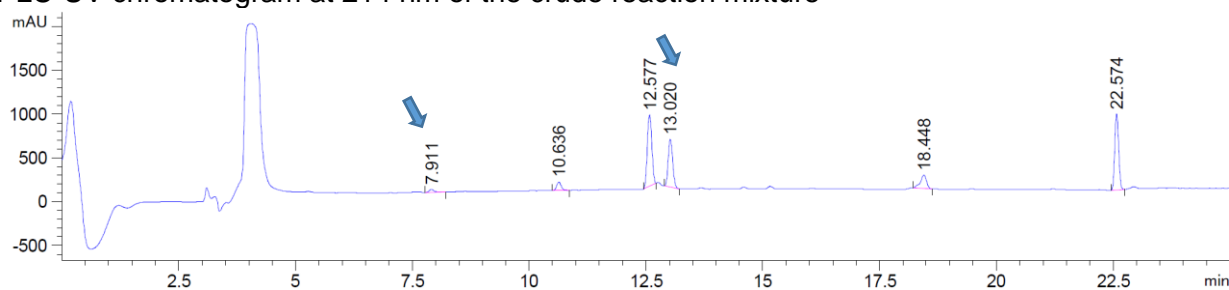
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{22}H_{27}N_4O_8^-$ 555.2214; Found 555.2218.

Ac-Asp-Phe-Gly-Pro-OH (10t)



HRMS of **10t** (ESI/QTOF) m/z : $[M + H_1]^-$ Calcd for $C_{24}H_{34}N_7O_6^-$ 475.1834; Found 475.1832.

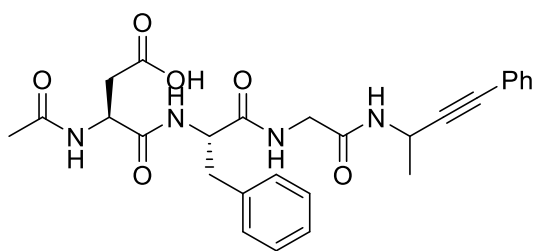
HPLC-UV chromatogram at 214 nm of the crude reaction mixture



MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 533.2399. Measured **b** and **y** ions are reported in the table below.

	D	F	G	P*
N-terminal	1	2	3	4
b	-	305.11	362.13	-
C-terminal	4	3	2	1
y	-	-	376.20	229.13

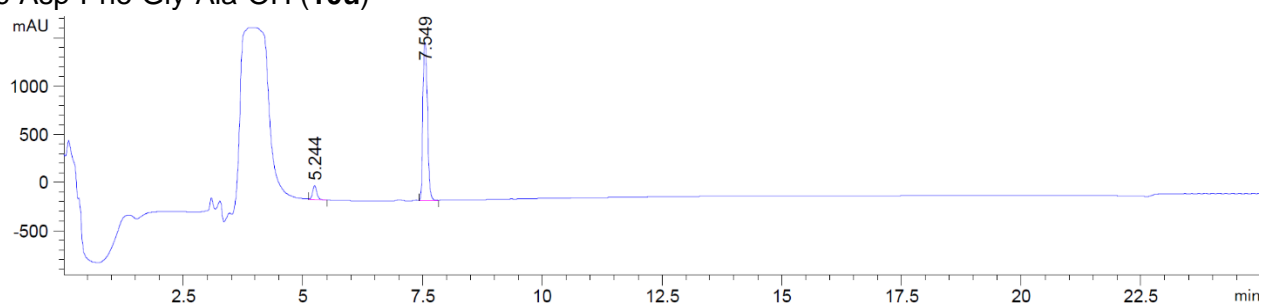
Ac-Asp-Phe-Gly-Ala-AH (11u)



Following the general procedure, Ac-Asp-Phe-Gly-Ala-OH (**10u**) afforded **11u** in more than 95% yield (retention time 12.426). The product with double alkylation was detected at a retention time of 15.88 as less than 5% as the single alkylation at the C-terminal position.

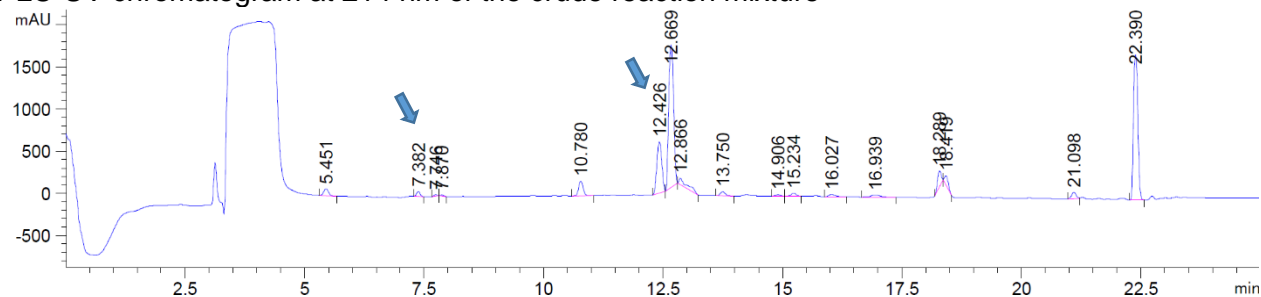
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z : $[M + H]^+$ Calcd for $C_{27}H_{31}N_4O_6^+$ 507.2238; Found 507.2235.

Ac-Asp-Phe-Gly-Ala-OH (**10u**)

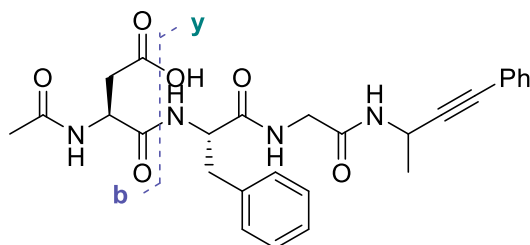


HRMS of **10u** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{20}H_{26}N_4NaO_8^+$ 473.1643; Found 473.1646.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture

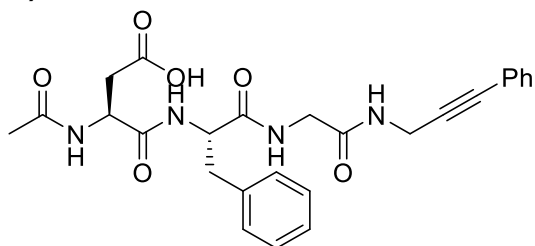


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 507.2235. Measured **b** and **y** ions are reported in the table below.



	D	F	G	A*
N-terminal	1	2	3	4
b	158.0448	305.1134	362.1348	-
C-terminal	4	3	2	1
y	-	350.1863	203.1178	-

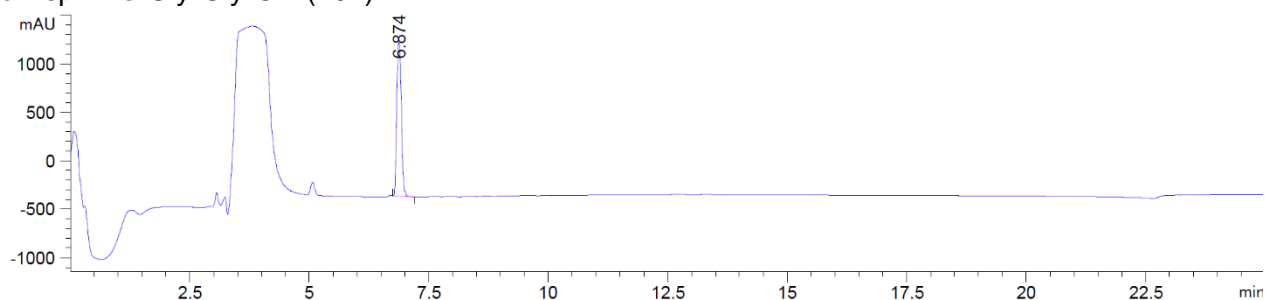
Ac-Asp-Phe-Gly-Gly-AH (11v)



Following the general procedure, Ac-Asp-Phe-Gly-Gly-OH (**10v**) afforded **11v** in an average of 48% yield (retention time 11.503). The product with double alkylation was detected at a retention time of 15.38 as less than 5% as the single alkylation at the C-terminal position.

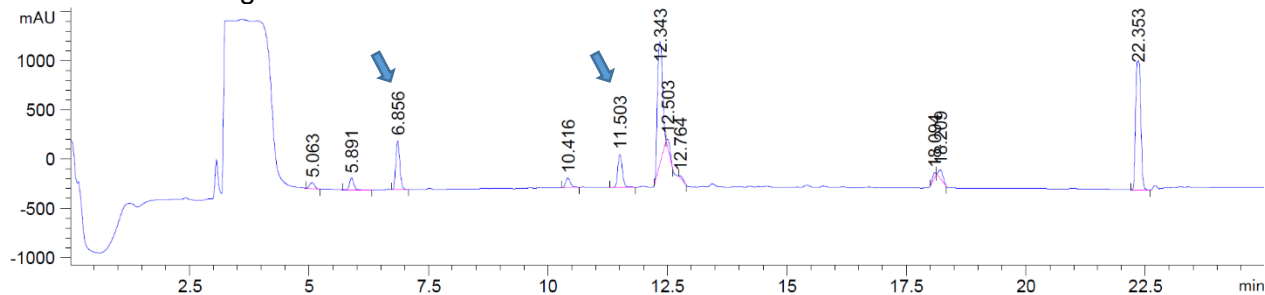
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{26}H_{28}N_4NaO_6^+$ 515.1901; Found 515.1896.

Ac-Asp-Phe-Gly-Gly-OH (10v)

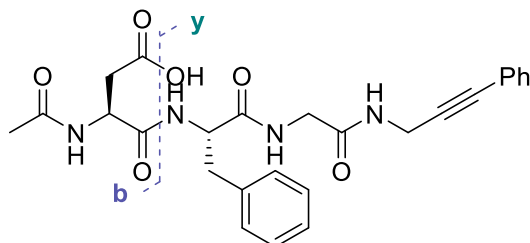


HRMS of **10v** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{19}H_{24}N_4NaO_8^+$ 459.1486; Found 459.1481.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture

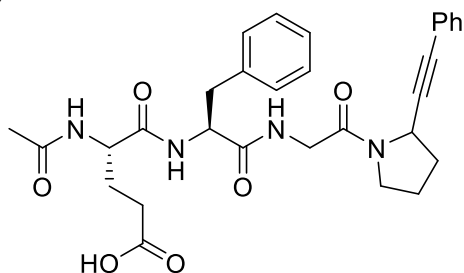


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 493.2085. Measured **b** and **y** ions are reported in the table below.



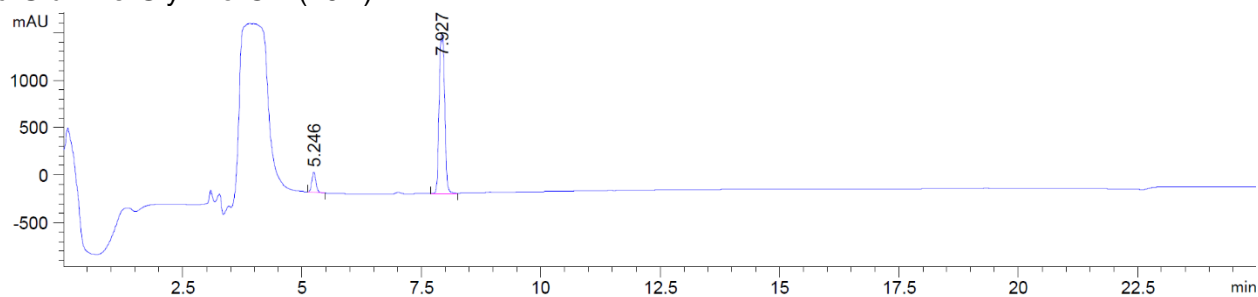
	D	F	G	G*
N-terminal	1	2	3	4
b	-	305.1134	362.1347	-
C-terminal	4	3	2	1

Ac-Glu-Phe-Gly-Pro-AH (11w)



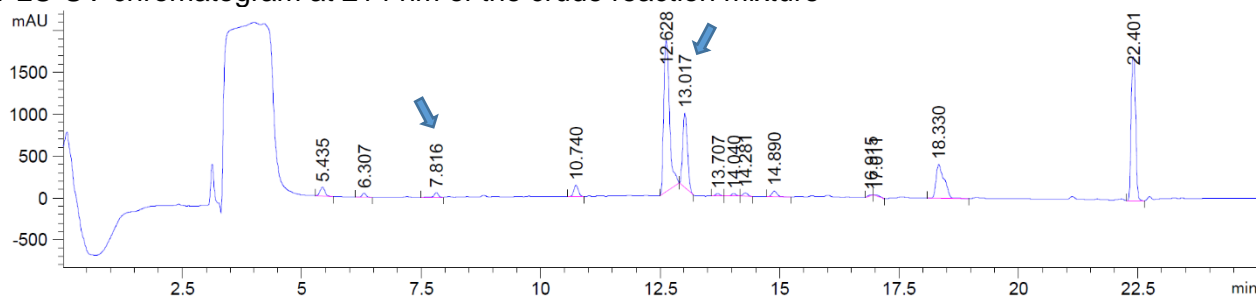
Following the general procedure, Ac-Glu-Phe-Gly-Pro-OH (**10w**) afforded **11w** in more than 95% yield (retention time 13.017). The product with double alkylation was not detected.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z : $[M + H]^+$ Calcd for $C_{30}H_{35}N_4O_6^+$ 547.2551; Found 547.2547.

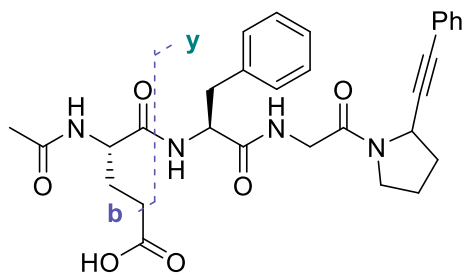
Ac-Glu-Phe-Gly-Pro-OH (**10w**)

HRMS of **10w** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{30}N_4NaO_8^+$ 513.1956; Found 513.1958.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture



MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 547.3604. Measured **b** and **y** ions are reported in the table below.



E

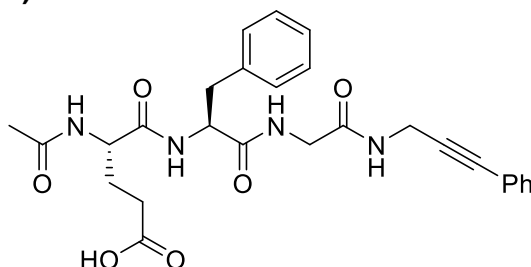
F

G

P*

N-terminal	1	2	3	4
b	172.0606	319.1288	376.1500	-
C-terminal	4	3	2	1
y	-	376.2023	229.1334	-

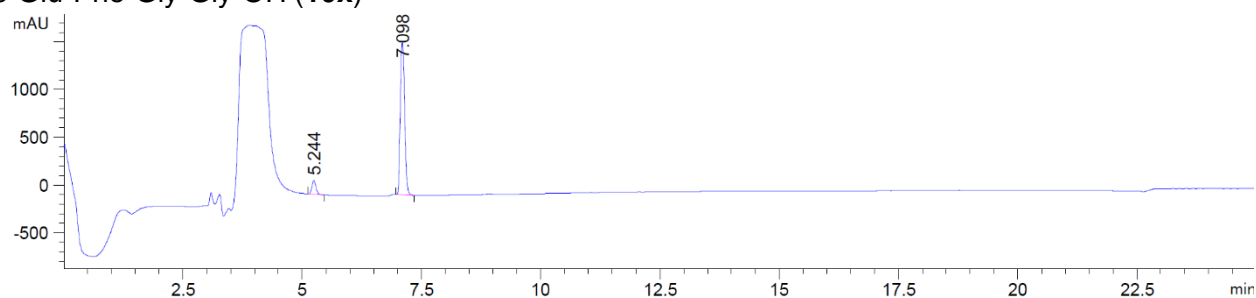
Ac-Glu-Phe-Gly-Gly-AH (11x)



Following the general procedure, Ac-Glu-Phe-Gly-Gly-OH (**10x**) afforded **11x** in an average of 75% yield (retention time 11.738). The product with double alkylation was only detected in HRMS of the crude, not in the HPLC chromatogram.

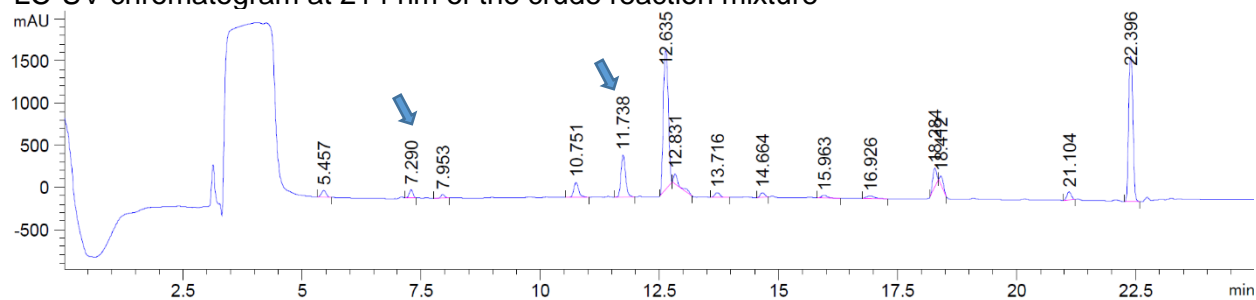
HRMS (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{27}H_{30}N_4NaO_6^+$ 529.2058; Found 529.2059.

Ac-Glu-Phe-Gly-Gly-OH (**10x**)

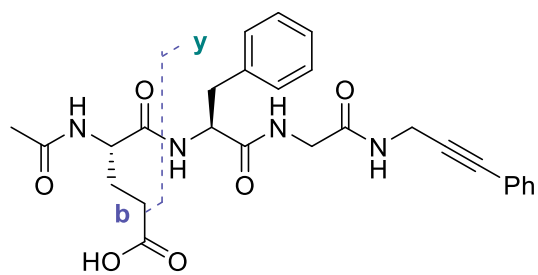


HRMS of **10x** (ESI/QTOF) m/z : $[M + Na]^+$ Calcd for $C_{20}H_{26}N_4NaO_8^+$ 473.1643; Found 473.1648.

HPLC-UV chromatogram at 214 nm of the crude reaction mixture

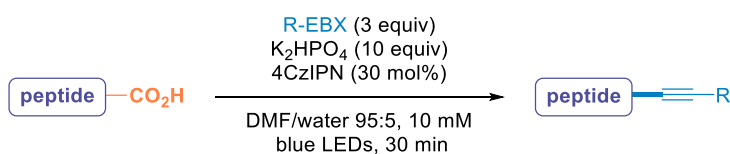


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 507.2235. Measured **b** and **y** ions are reported in the table below.



	E	F	G	G*
N-terminal	1	2	3	4
b	172.0605	319.1289	376.1503	-
C-terminal	4	3	2	1
y	-	336.1708	189.1023	-

4.5. Scope on Gly-Arg-Gly-Asp-Asn-Pro-OH



General procedure 5 for the decarboxylative alkylation of Gly-Arg-Gly-Asp-Asn-Pro-OH

A 20 mM solution of the peptide in non-degassed DMF (50 μ L, 1.0 μ mol), a 60 μ M solution of R-EBX (**1**) in DMF (25 μ L, 3.0 μ mol, 3.0 equiv), a 15 μ M solution of 4CzIPN (**2a**) in DMF (20 μ L, 0.30 μ mol, 30 mol%) and a 2 M solution of K₂HPO₄ in milli-Q purified water (5 μ L, 10 μ mol, 10 equiv) were placed into a vial. The vial was then capped and degassed by bubbling with argon for 1-2 min and the mixture was irradiated using blue light LEDs for 30 min at RT.

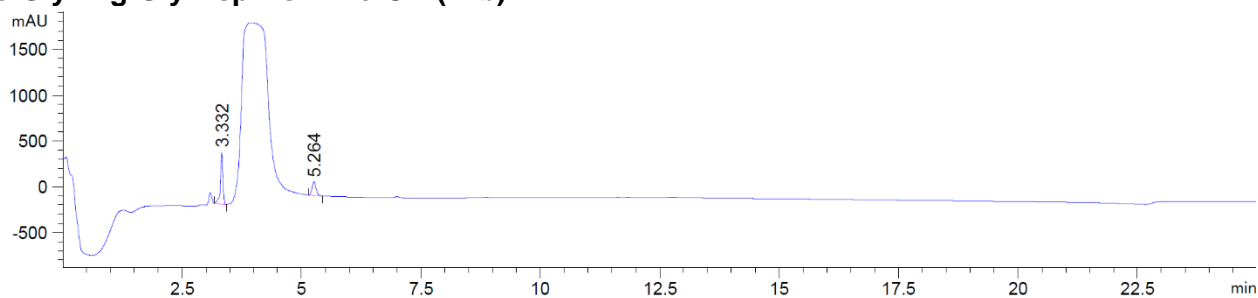
At the end of the reaction, the crude was diluted with 3x the volume of MeCN/water 1:1 and injected in RP-HPLC. The yields were determined as the ratio of $A_{\text{prod}}/A_{\text{total}}$ where A_{prod} = area in mAU of the product peak and A_{total} = area in mAU of all peptides products (product, starting material, and side-products if present).

Reported results are an average of 3 independent trials.

The products are described as peptide-AR with R standing for the substitution on the aryl ring.

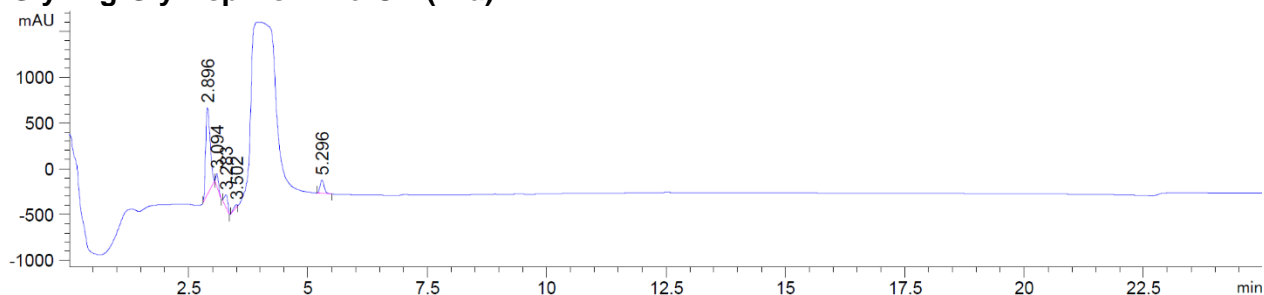
Reference HPLC-UV chromatograms of reagents at 214 nm (Iodobenzoic acid, and 4CzIPN in section 0)

Ac-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12b**)

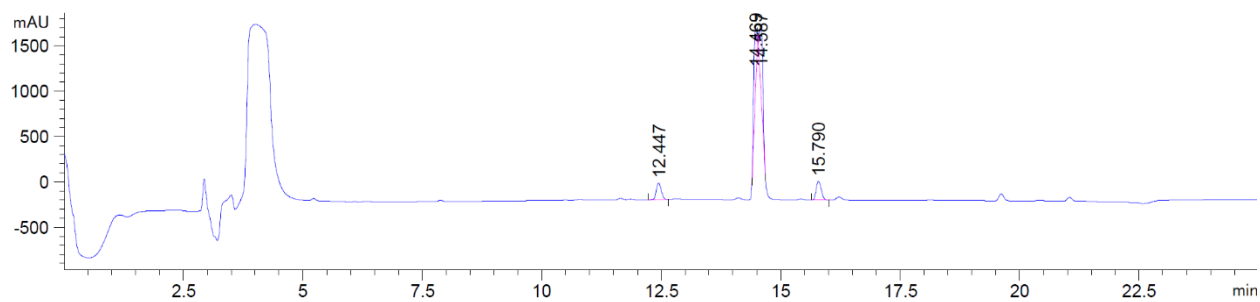


HRMS (ESI/QTOF) m/z : $[M + H_1]^-$ Calcd for C₂₅H₃₉N₁₀O₁₁⁻ 655.2805; Found 655.2802.

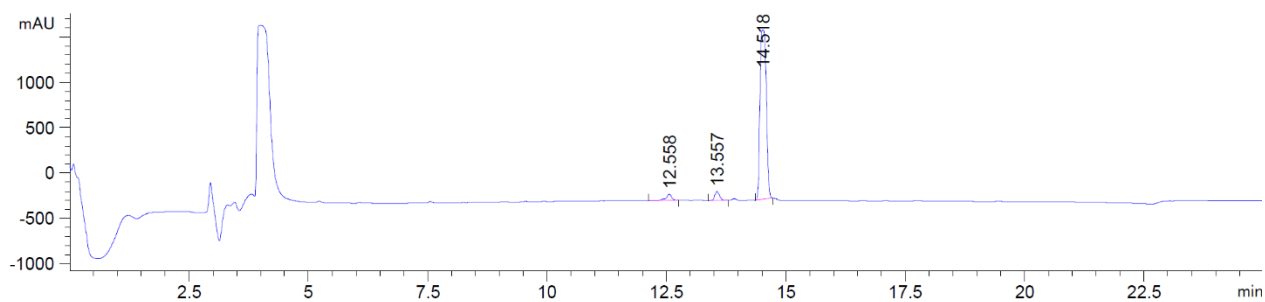
H-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12a**)



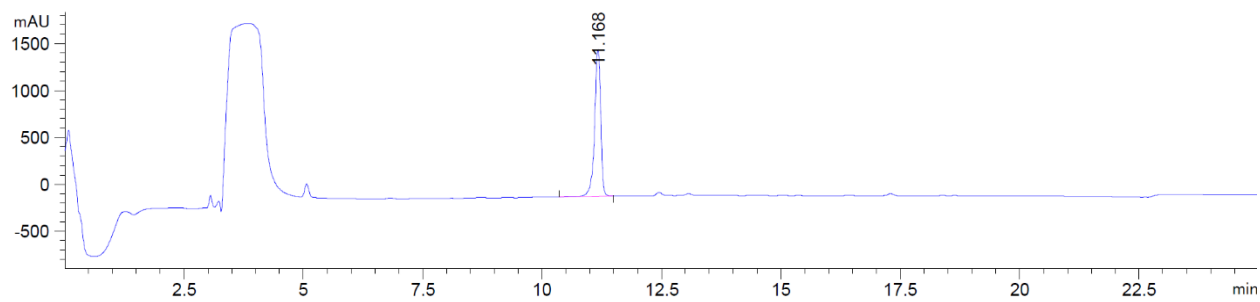
1-[4-Bromophenylethynyl]-1,2-benziodoxol-3(1H)-one (*p*Br-Ph-EBX, 1d)



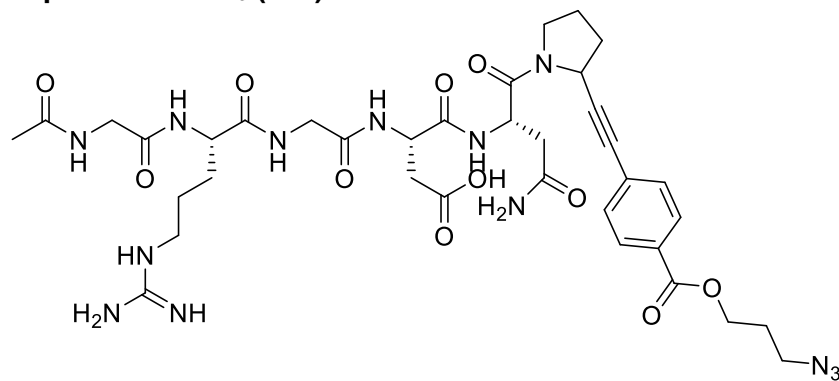
1-((4-(Prop-2-yn-1-yl)benzoate)ethynyl)-1,2-benziodoxol-3(1H)-one (N₃-Ar-EBX, 1j)



1-((4-Formylphenyl)ethynyl)-1,2-benziodoxol-3(1H)-one (CHO-Ph-EBX, 1e)



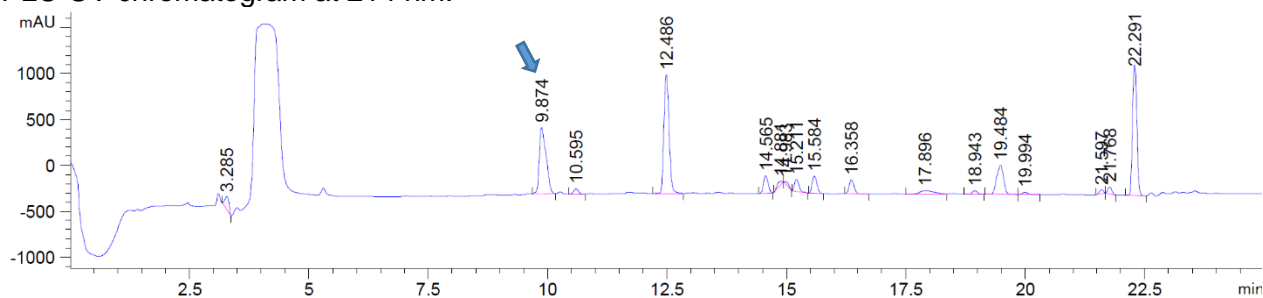
Ac-Gly-Arg-Gly-Asp-Asn-Pro-AN₃ (13a)



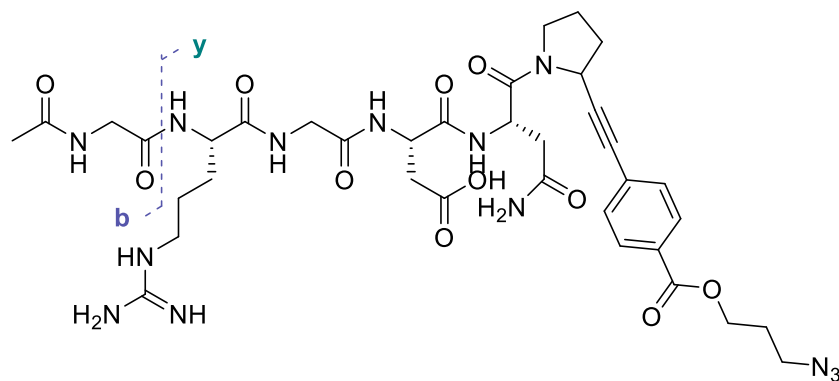
Following the general procedure, Ac-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12a**) afforded **13a** in quantitative yield (retention time 9.874).

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: [M + H]⁺ Calcd for C₃₆H₅₀N₁₃O₁₁⁺ 840.3747; Found 840.3739.

HPLC-UV chromatogram at 214 nm:

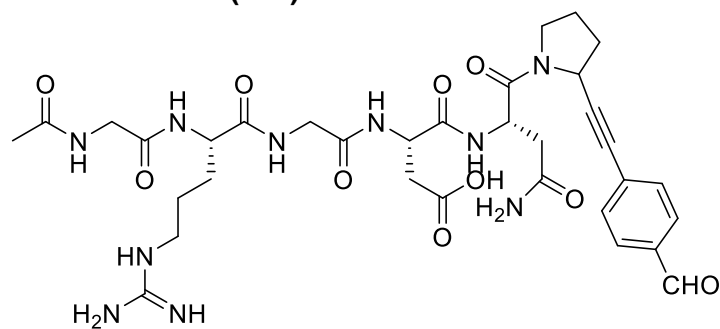


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 840.3739. Identified **b** ions are reported in the table below. **y** ions could not be identified due to non-controlled fragmentation.



	G	R	G	D	N	P*
N-terminal	1	2	3	4	5	6
b	100.03	256.14	313.16	428.19	542.23	-

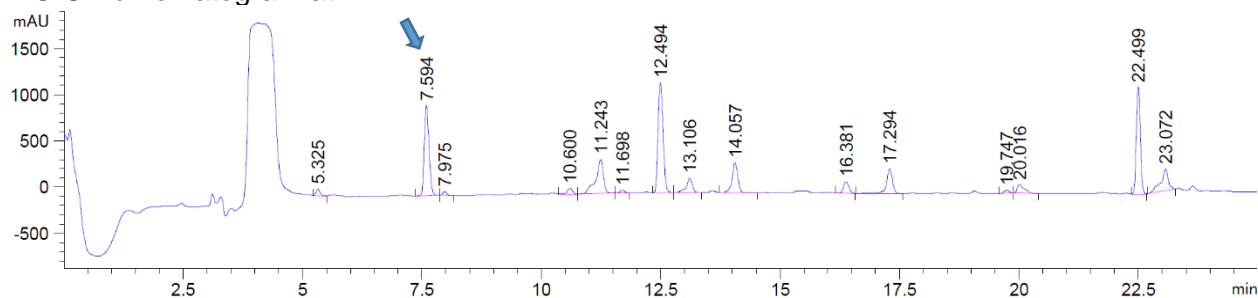
Ac-Gly-Arg-Gly-Asp-Asn-Pro-ACHO (**13b**)



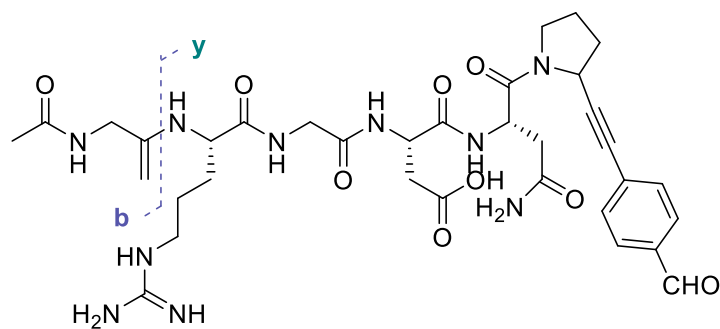
Following the general procedure, Ac-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12a**) afforded **13b** in quantitative yield (retention time 7.594).

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{33}H_{45}N_{10}O_{10}^+$ 741.3315; Found 741.3302.

HPLC-UV chromatogram at 214 nm:

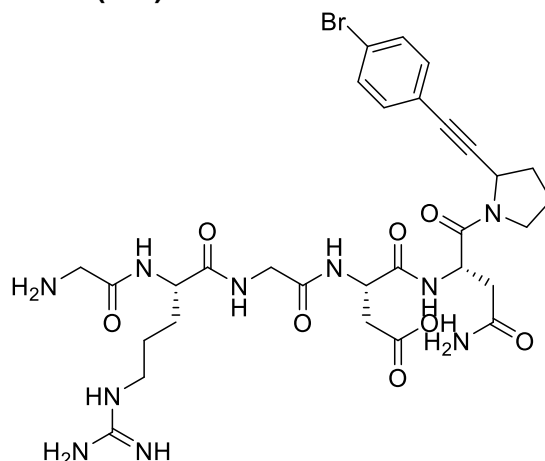


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 741.3302. Identified **b** and **y** ions are reported in the table below.



	G	R	G	D	N	P*
N-terminal	1	2	3	4	5	6
b	100.03	256.14	313.16	428.19	542.23	-
C-terminal	6	5	4	3	2	1
y	-	642.30	486.20	429.18	314.15	-

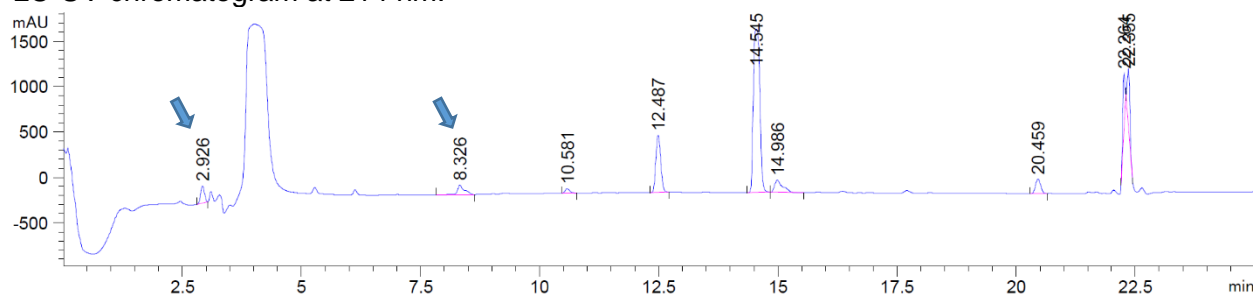
H-Gly-Arg-Gly-Asp-Asn-Pro-ABr (13c)



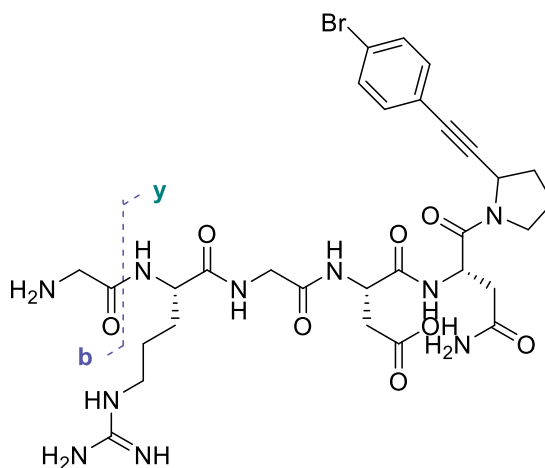
Following the general procedure, H-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12b**) afforded **13c** in 52% yield (retention time 8.326).

HRMS (ESI/QTOF) m/z : $[M + H]^+$ Calcd for $C_{30}H_{42}^{79}BrN_{10}O_8^+$ 749.2365, 751.2345; Found 749.2350, 751.2342.

HPLC-UV chromatogram at 214 nm:

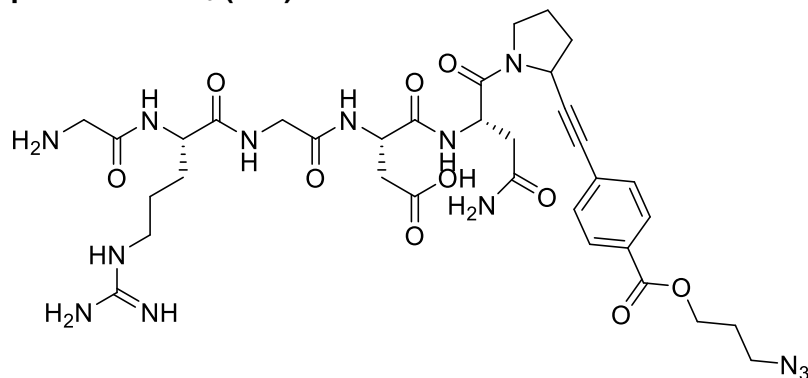


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 749.2350. Identified **b** and **y** ions are reported in the table below.



	G	R	G	D	N	P*
N-terminal	1	2	3	4	5	6
b	-	214.13	271.15	386.18	500.22	-
C-terminal	6	5	4	3	2	1
y	-	692.21	536.11	479.09	364.07	250.02

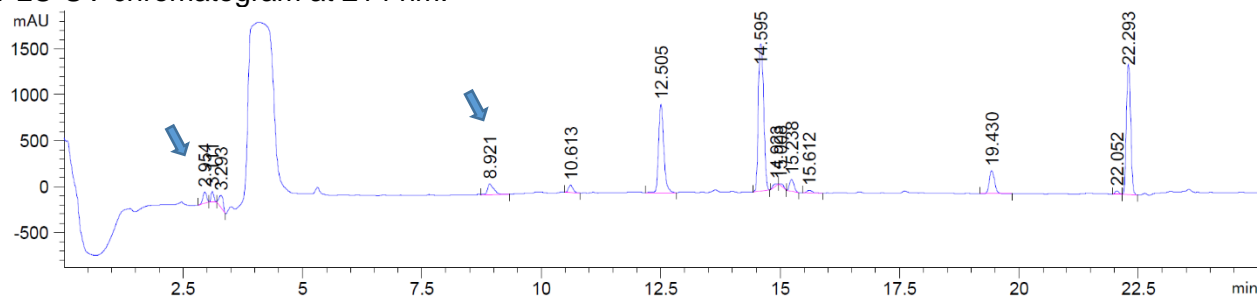
H-Gly-Arg-Gly-Asp-Asn-Pro-AN₃ (13d)



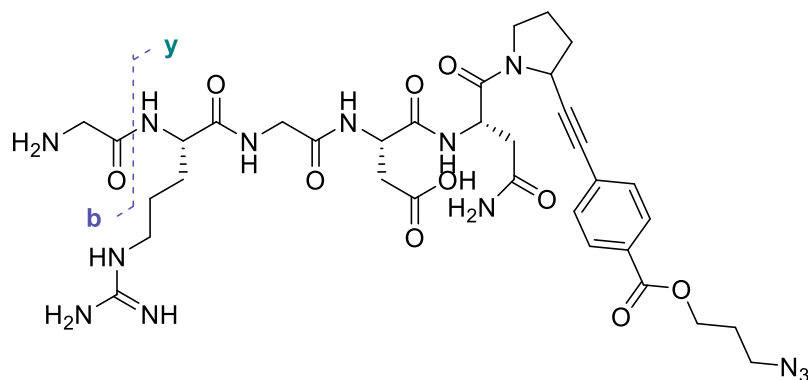
Following the general procedure, H-Gly-Arg-Gly-Asp-Asn-Pro-OH (**12b**) afforded **13c** in 57% yield (retention time 8.921).

HRMS (QTOF) m/z : $[M + H]^+$ Calcd for $C_{34}H_{48}N_{13}O_{10}^+$ 798.3642; Found 798.3640.

HPLC-UV chromatogram at 214 nm:

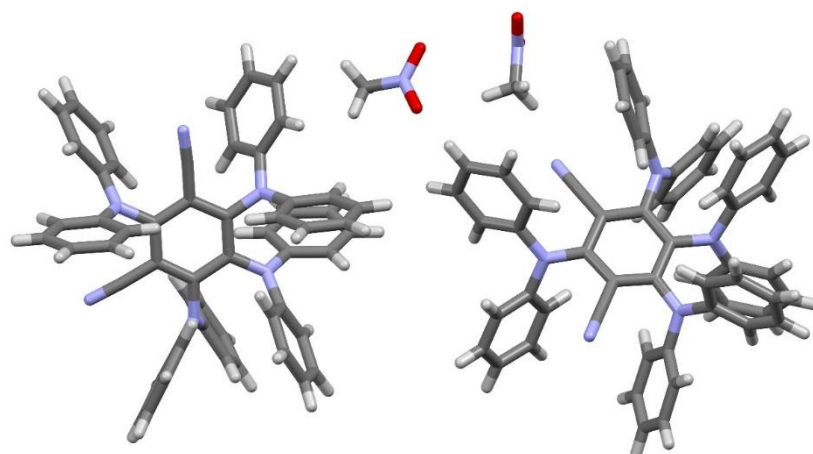


MSMS (nanochip-ESI/LTQ-Orbitrap): selected ion 798.3640. Identified **b** ions are reported in the table below. **y** ions could not be identified due to non-controlled fragmentation.

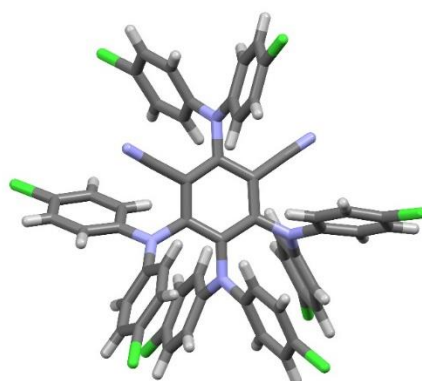


	G	R	G	D	N	P*
N-terminal	1	2	3	4	5	6
b	-	214.12	271.15	386.17	500.22	-

5. Crystal structures



A single crystal was grown by slow diffusion of a solution of **3a** in nitromethane. Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (**CCDC 1879098**) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.



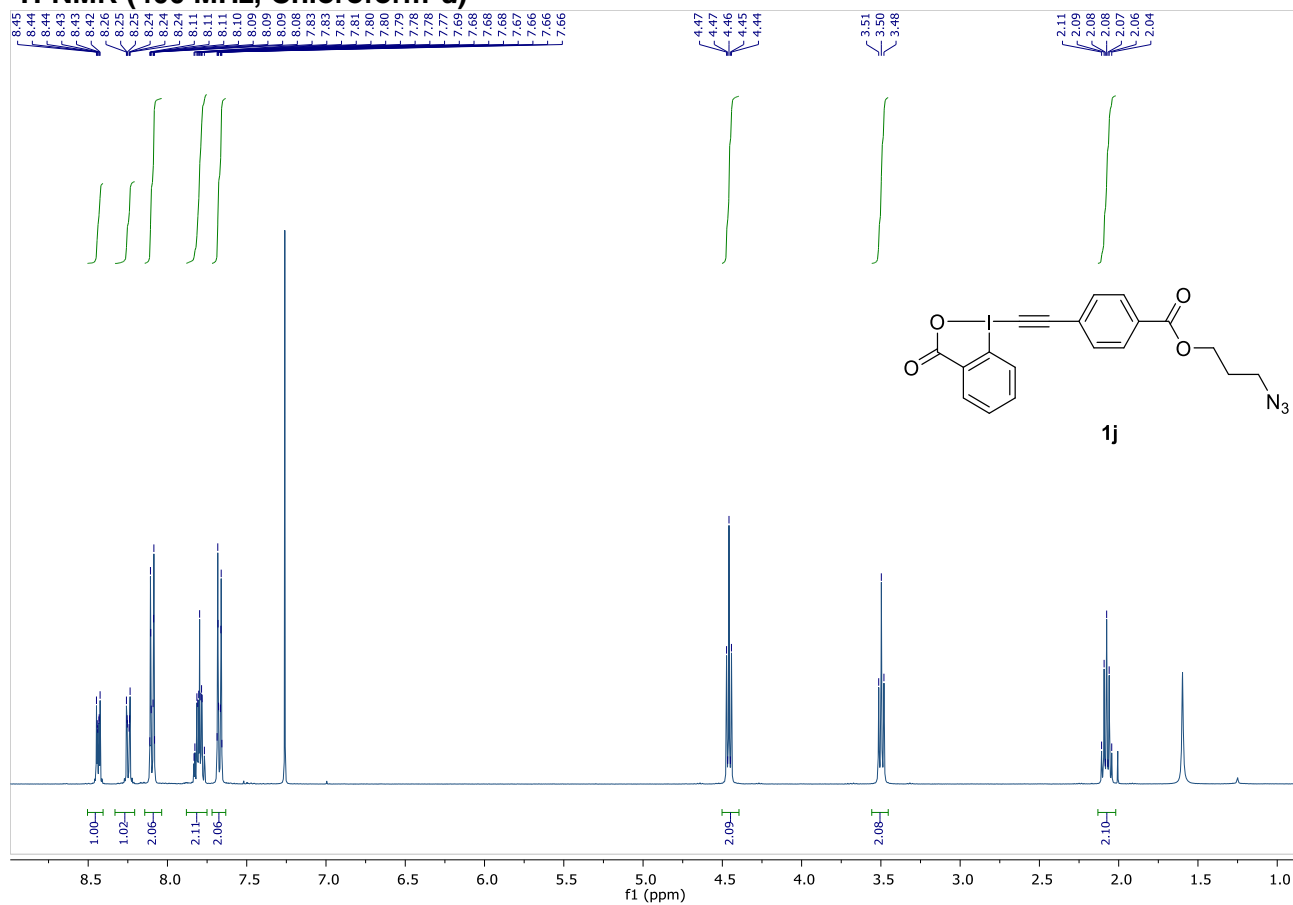
A single crystal was grown by slow diffusion of a solution of **3b** in CDCl_3 . Supplementary crystallographic data for this compound have been deposited at Cambridge Crystallographic Data Centre (**CCDC 1879097**) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

6. Bibliography

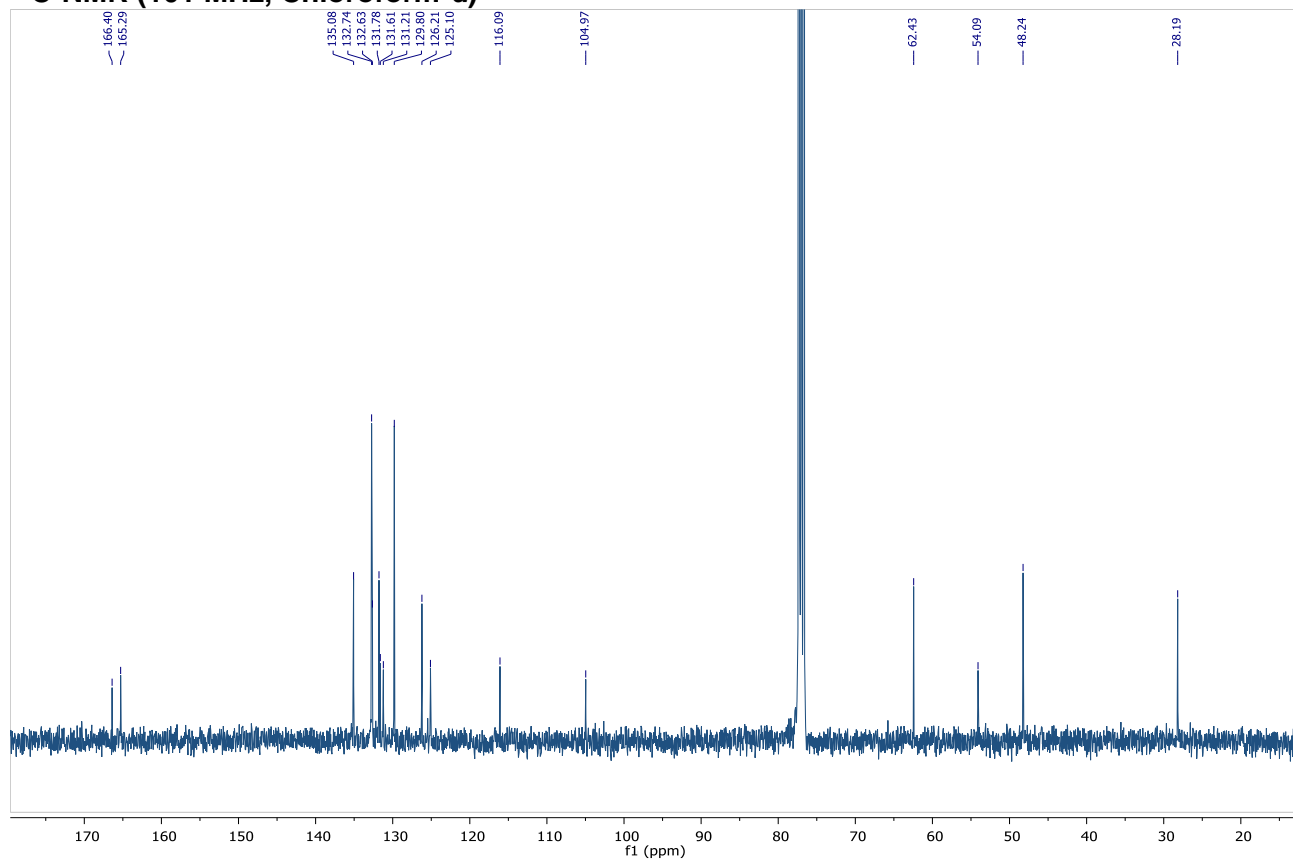
- [1] J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666.
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- [20] N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart, J. L. Dempsey, *J. Chem. Educ.* **2018**, 197–206.
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7. NMR spectra

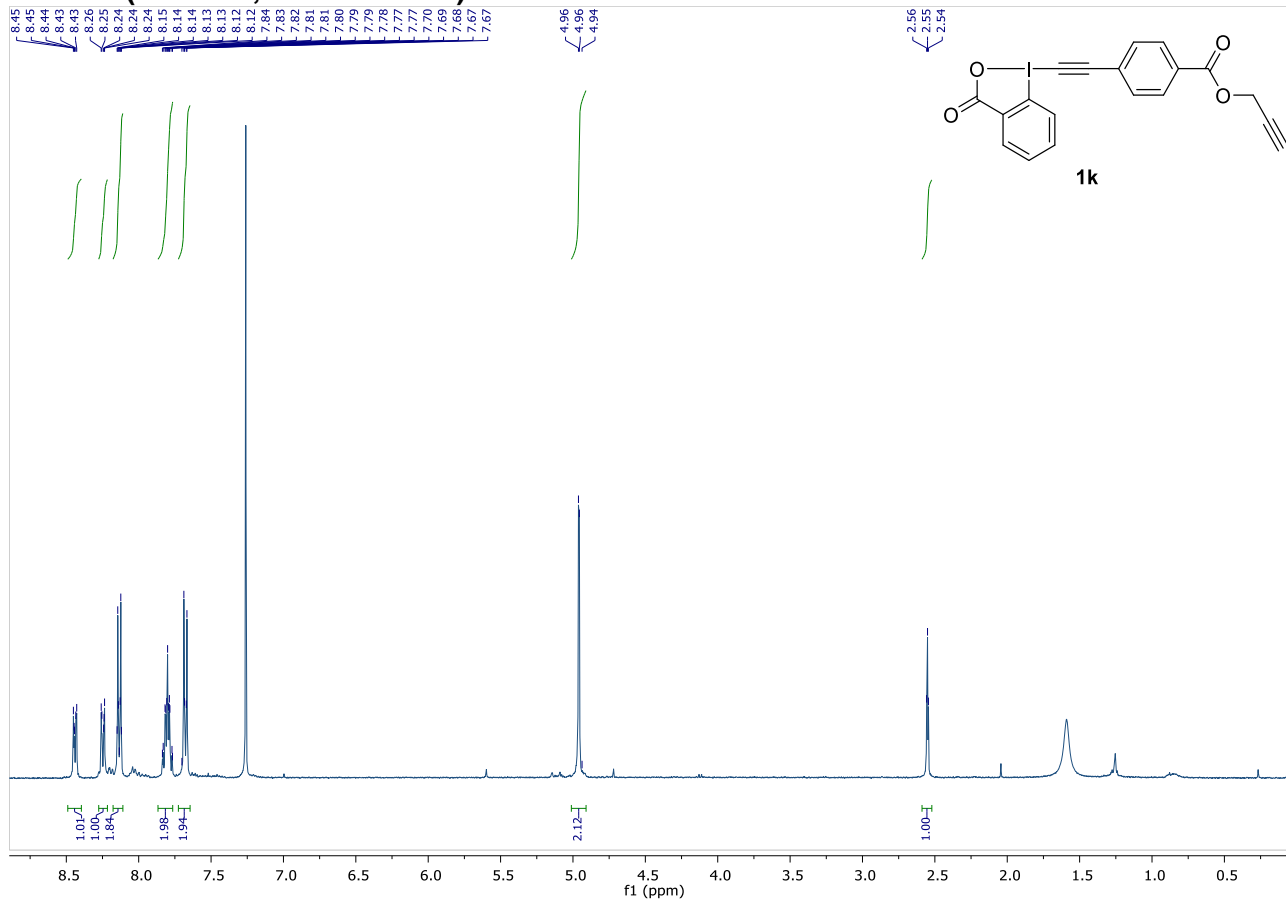
¹H-NMR (400 MHz, Chloroform-d)



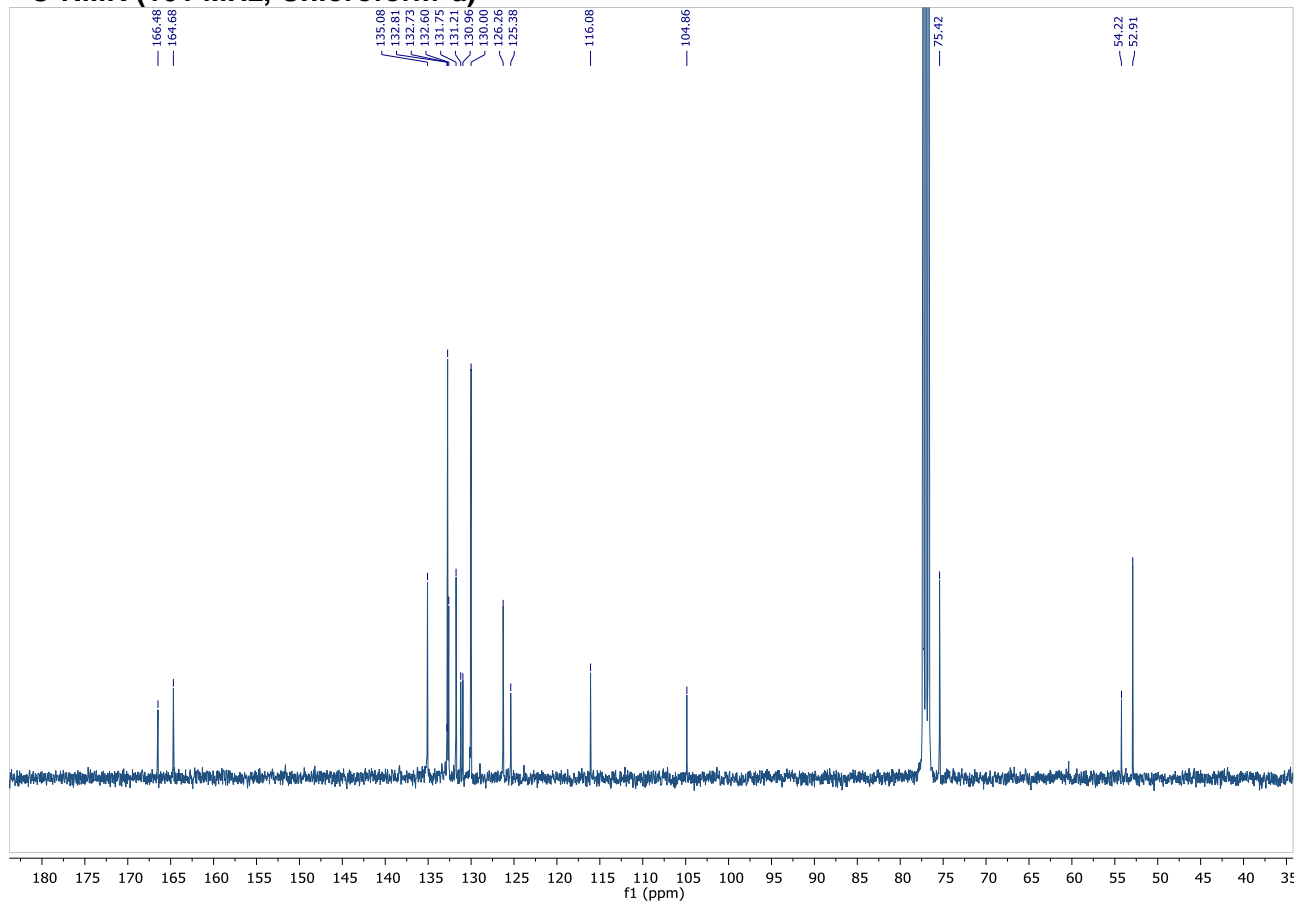
¹³C-NMR (101 MHz, Chloroform-d)



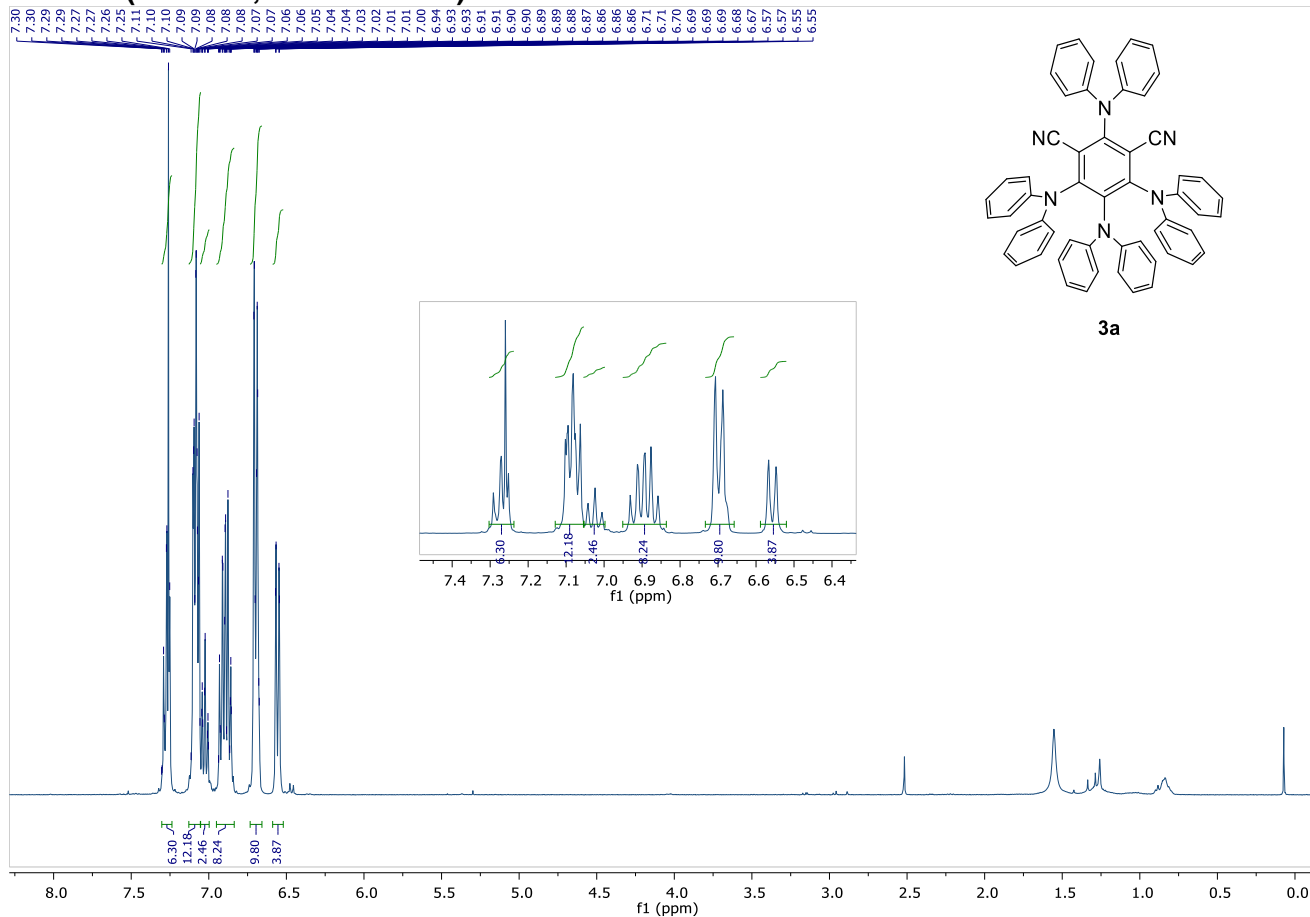
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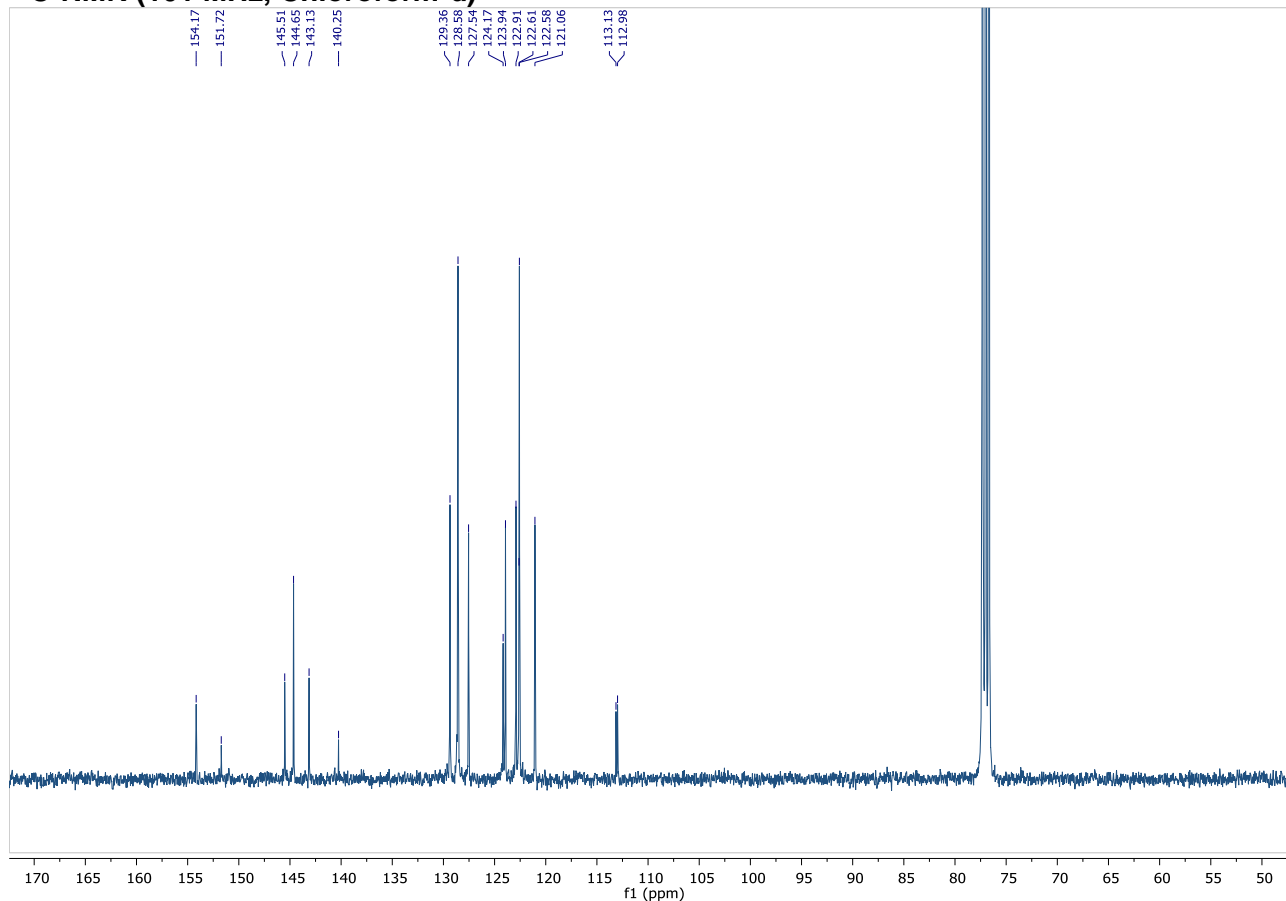
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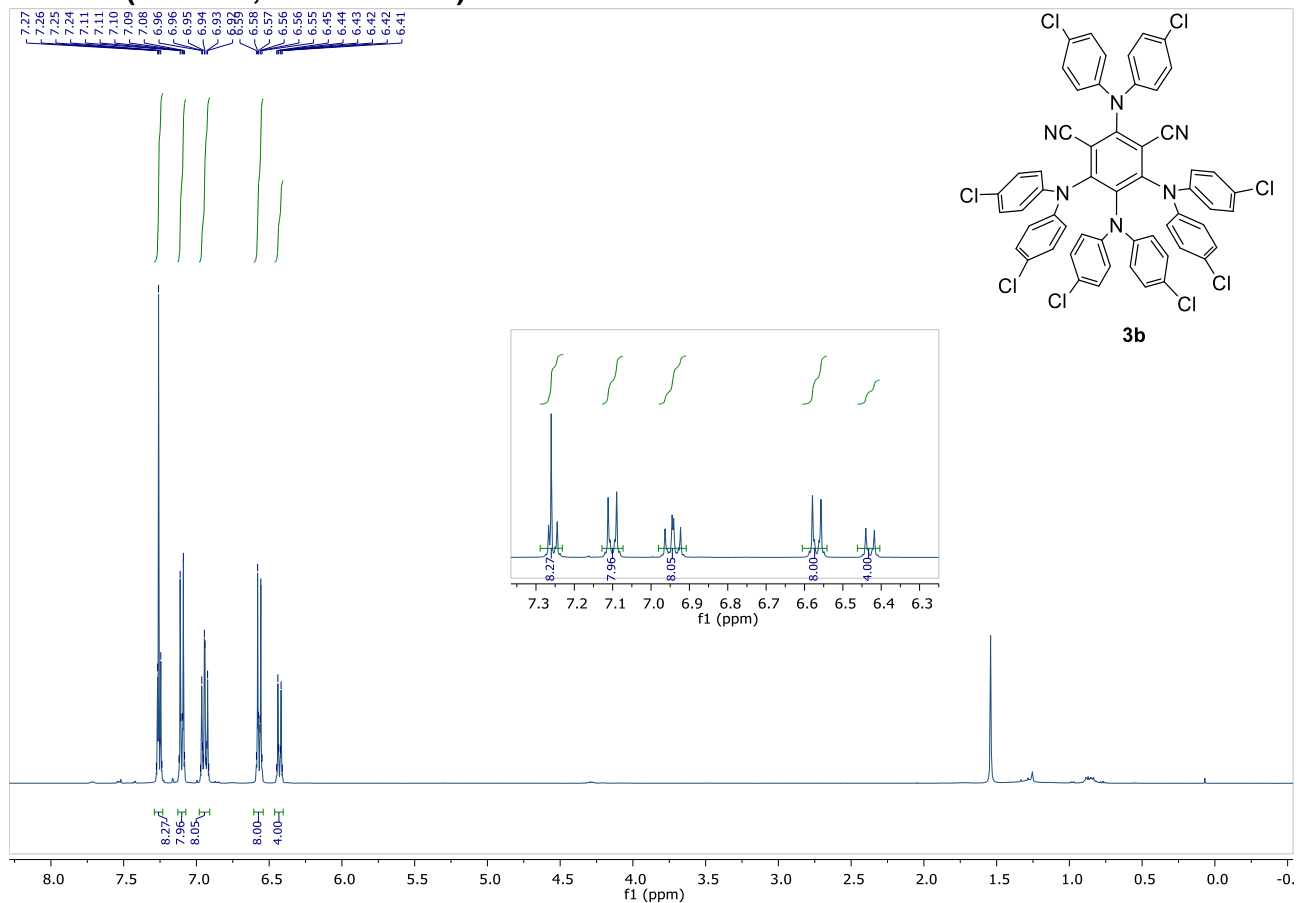
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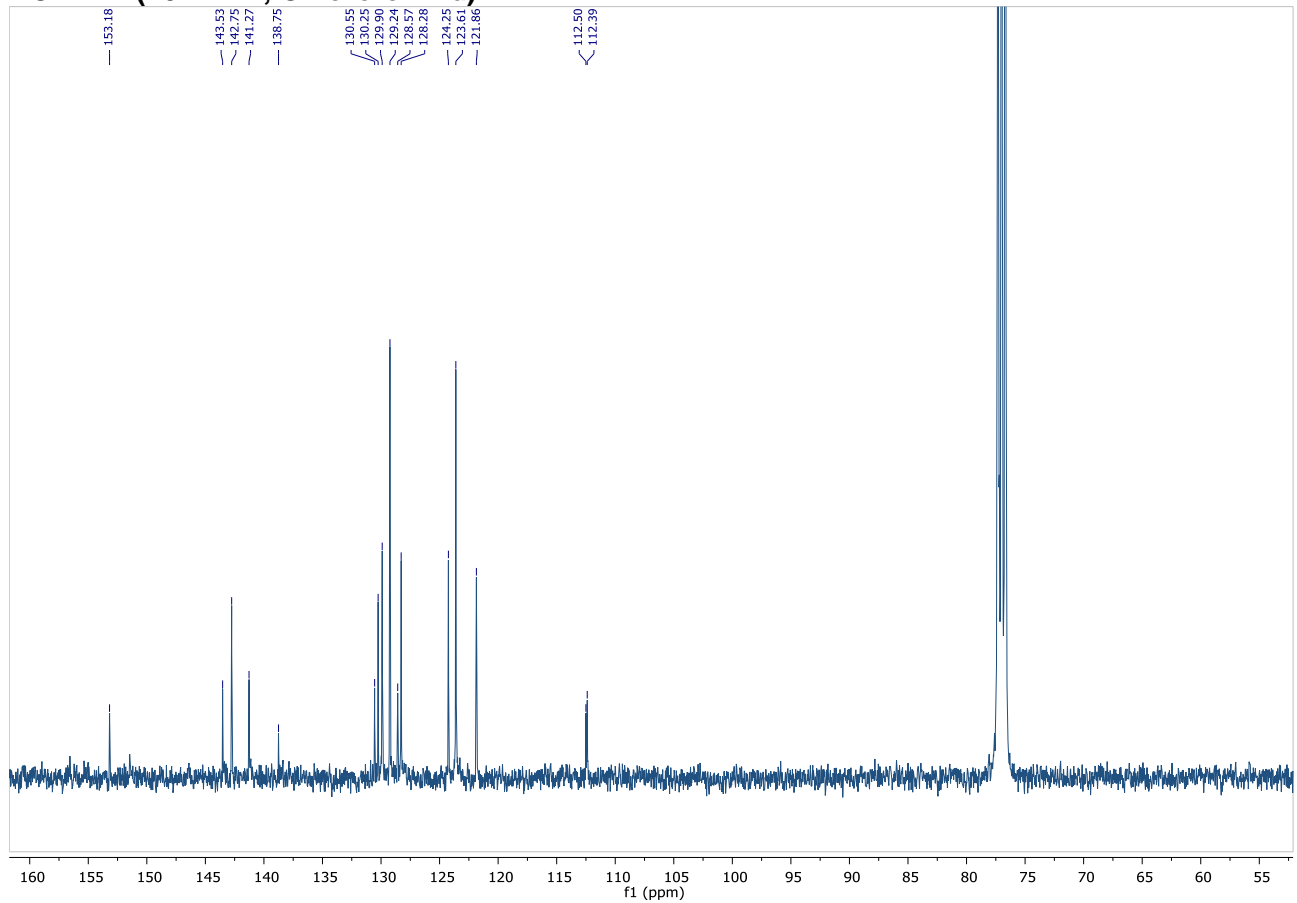
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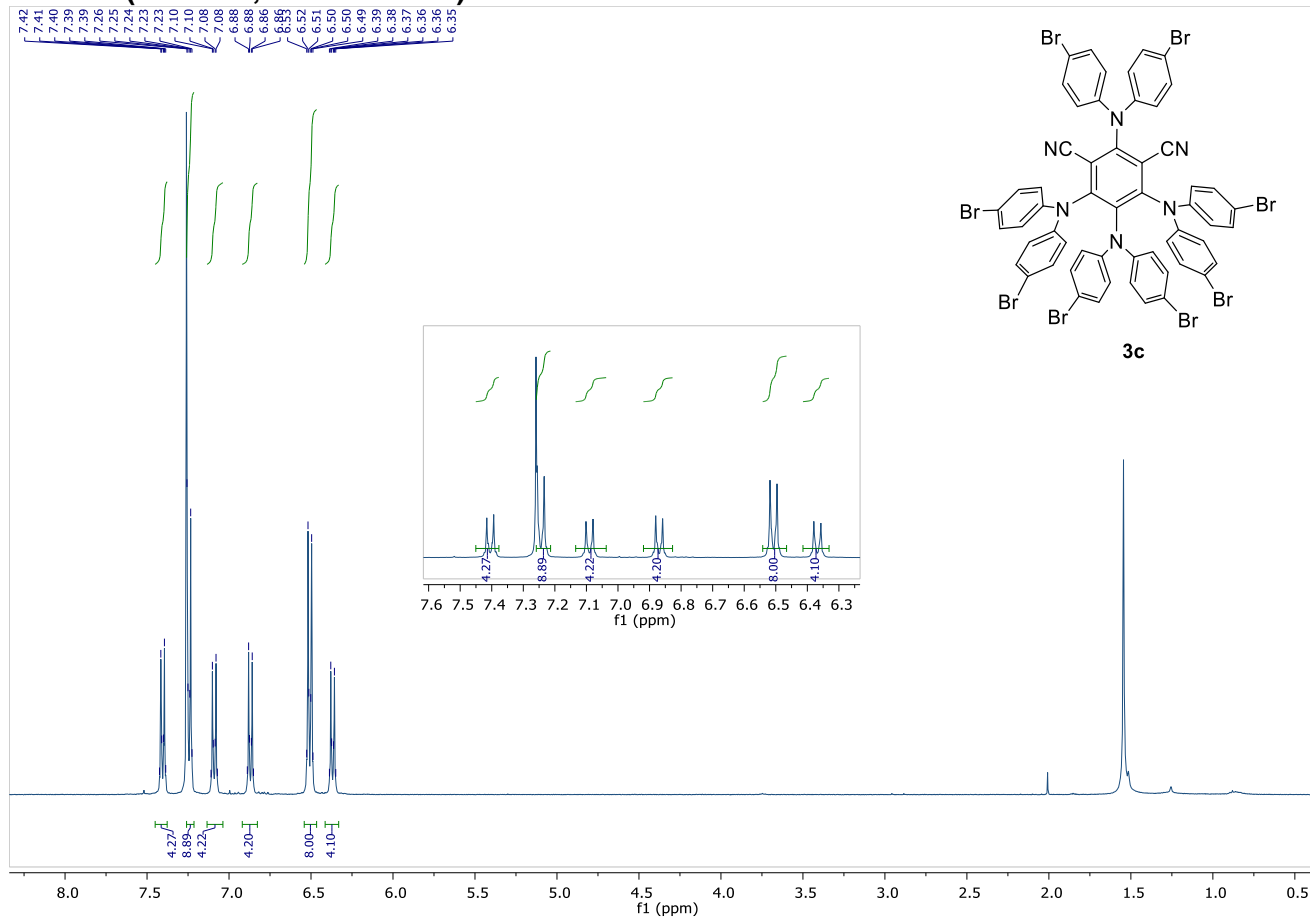
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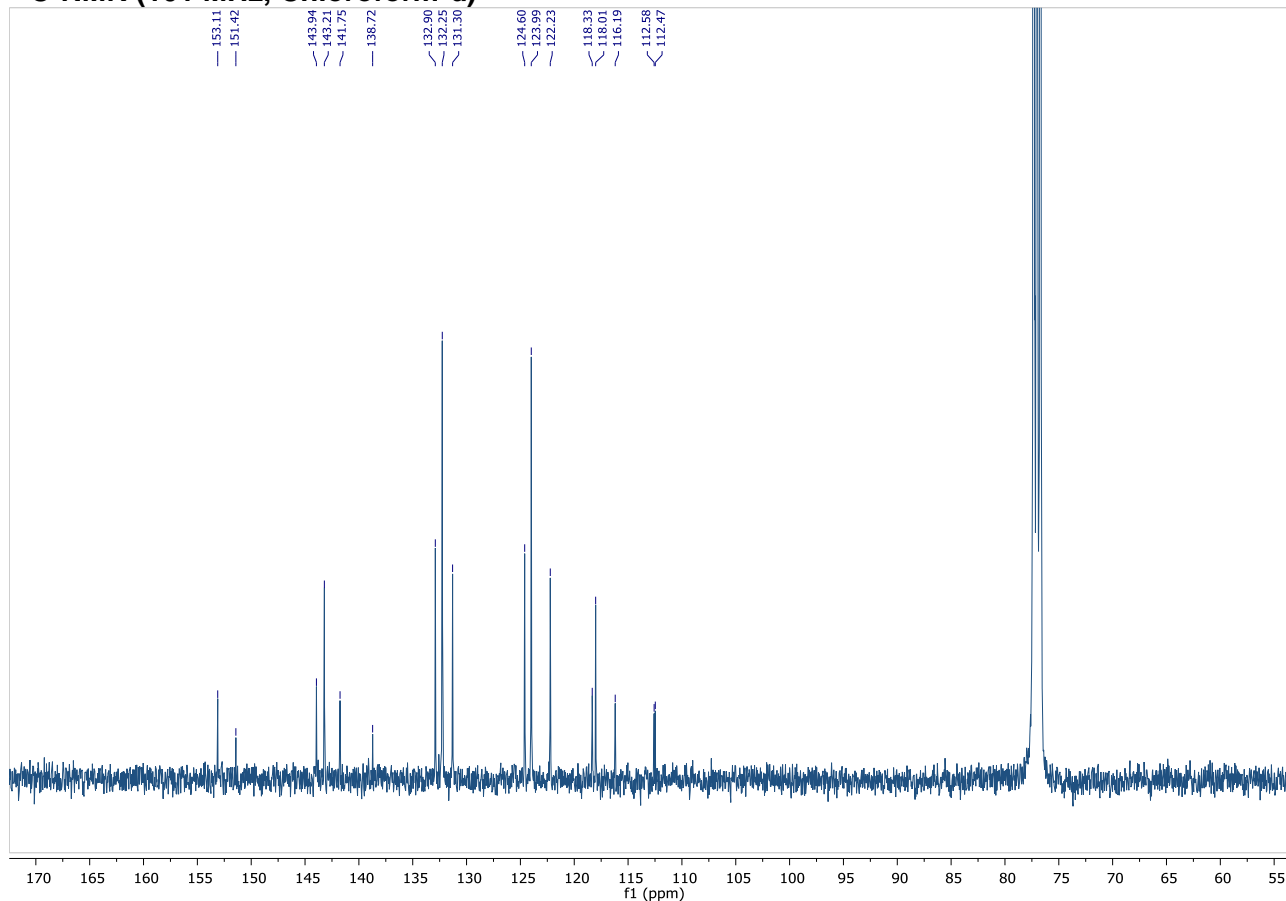
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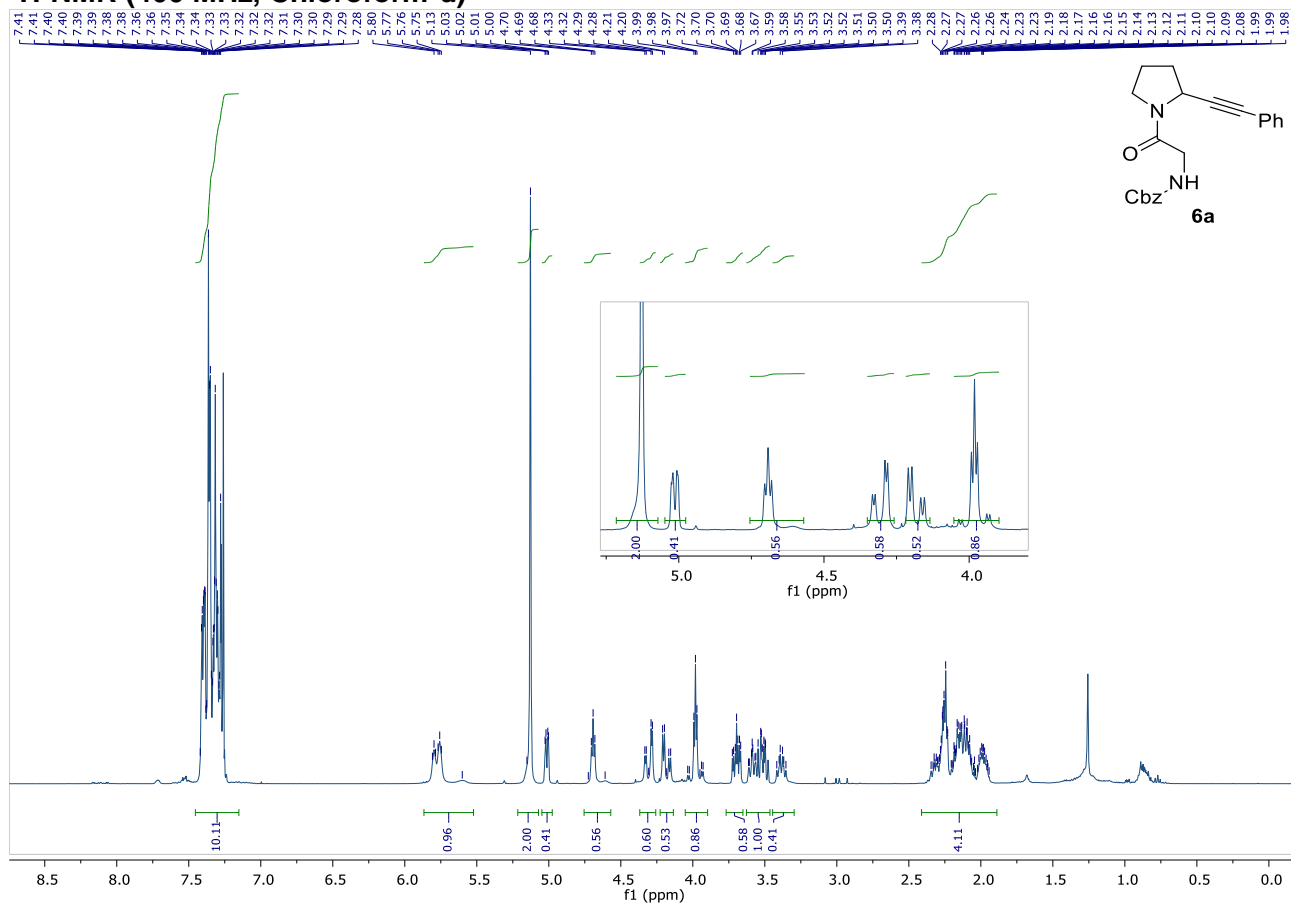
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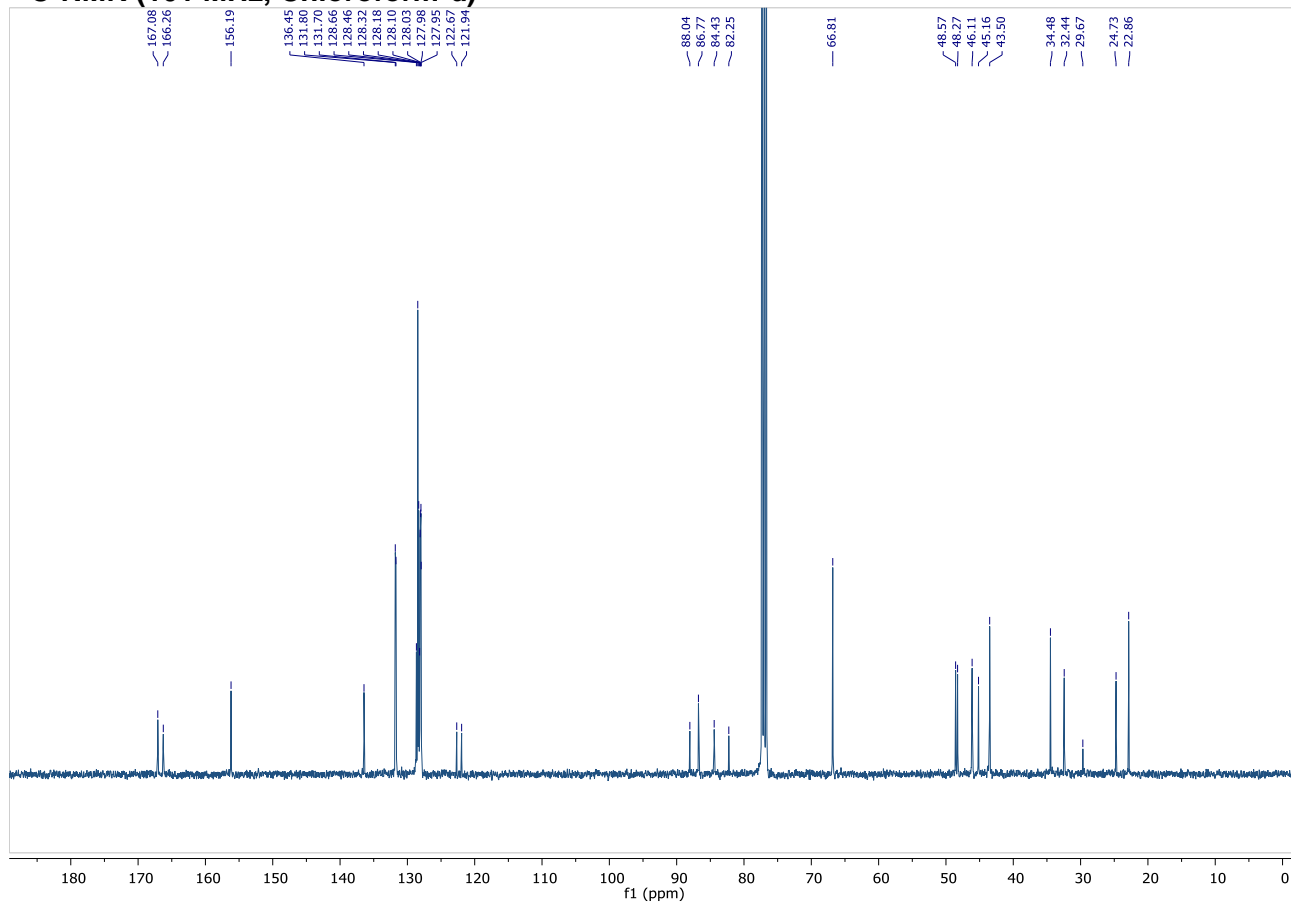
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¹H-NMR (400 MHz, Chloroform-d)



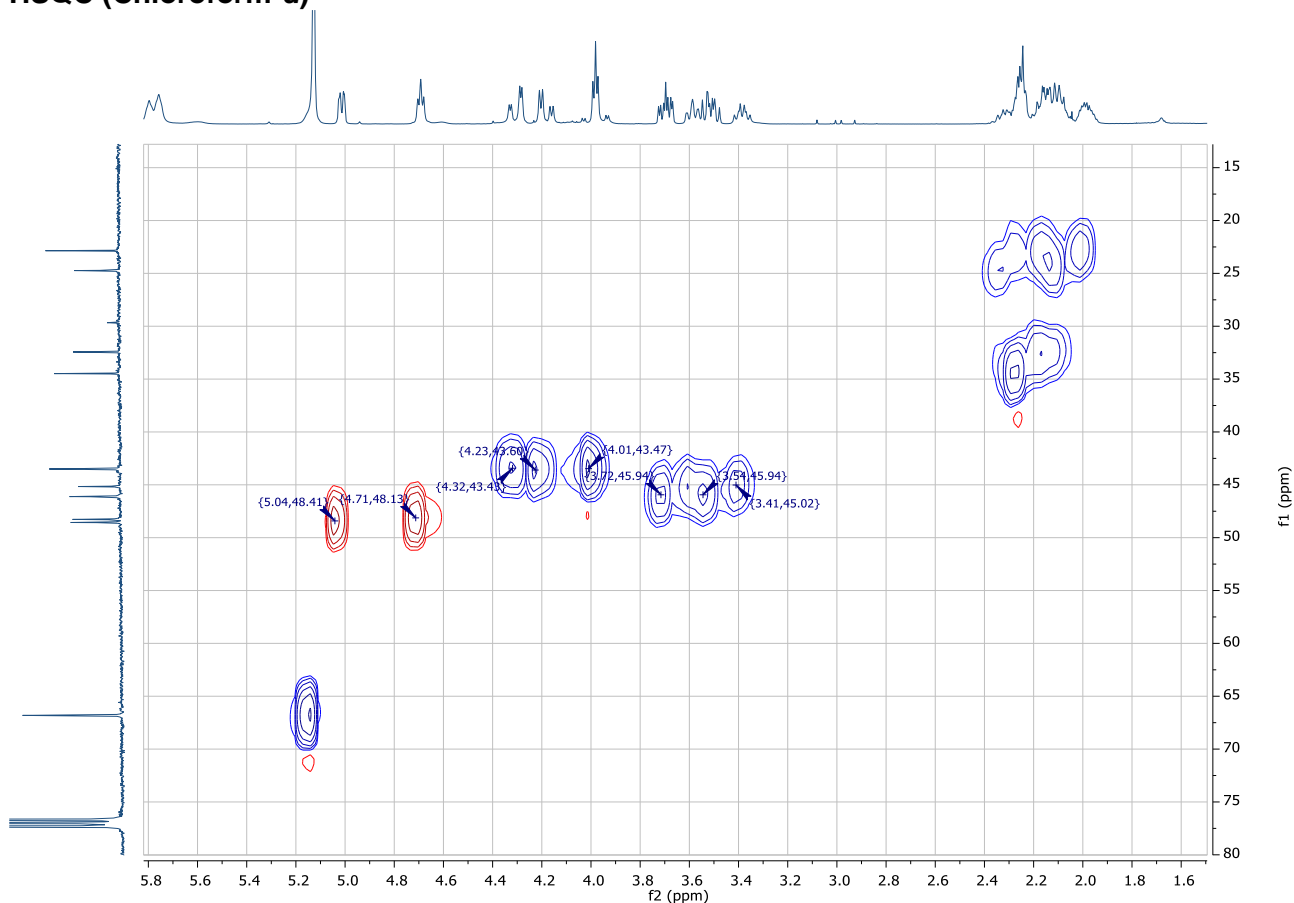
¹³C-NMR (101 MHz, Chloroform-d)



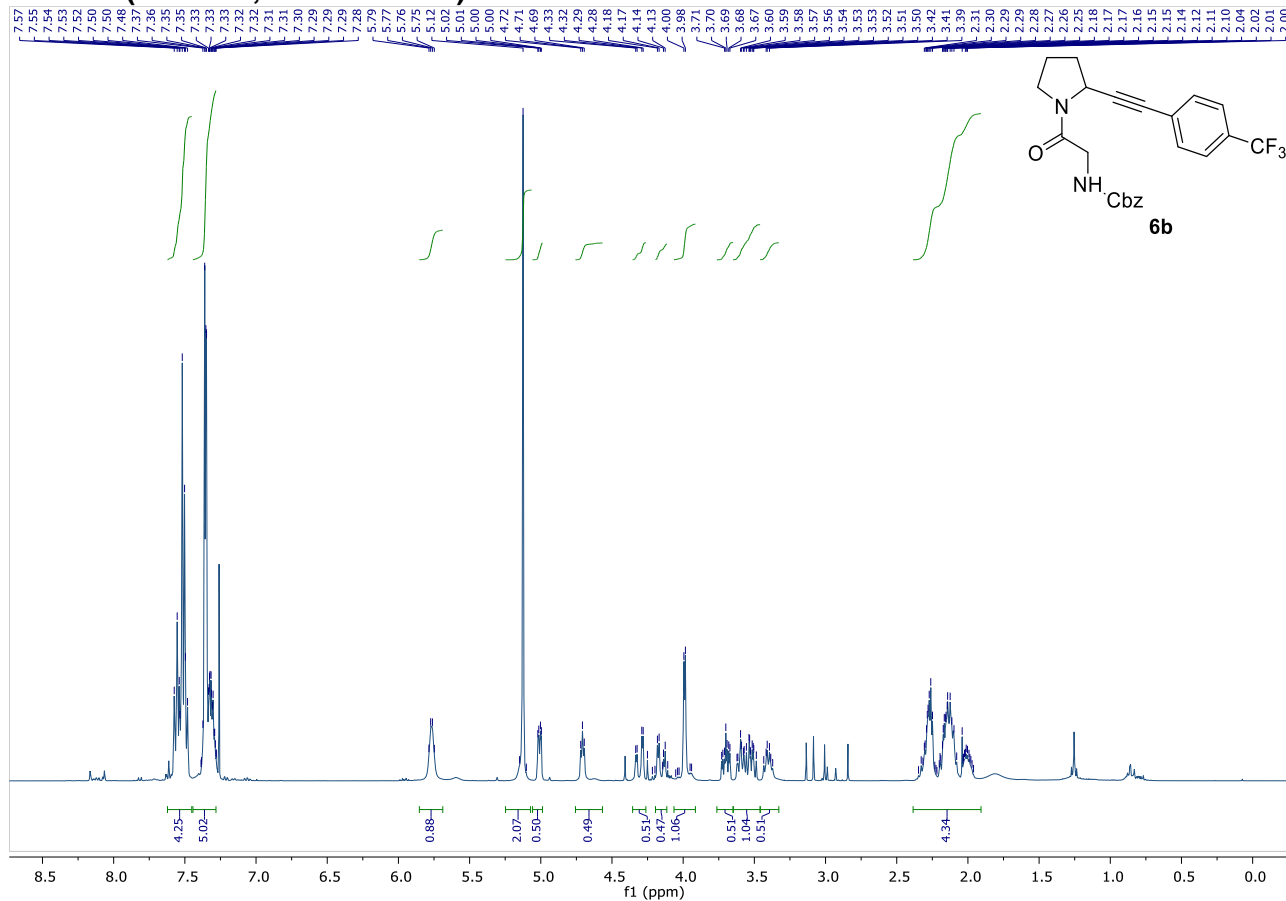
COSY (Chloroform-d)



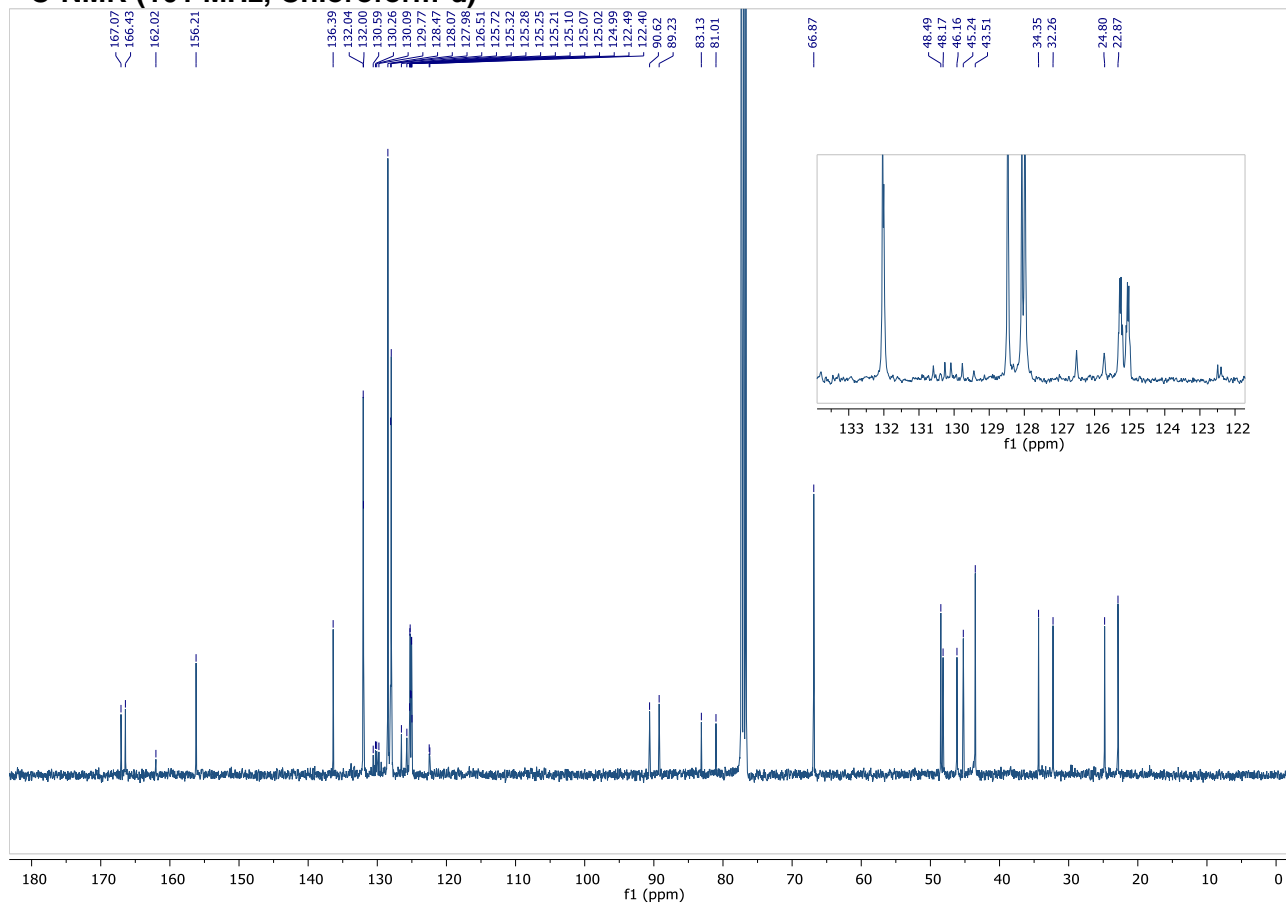
HSQC (Chloroform-d)



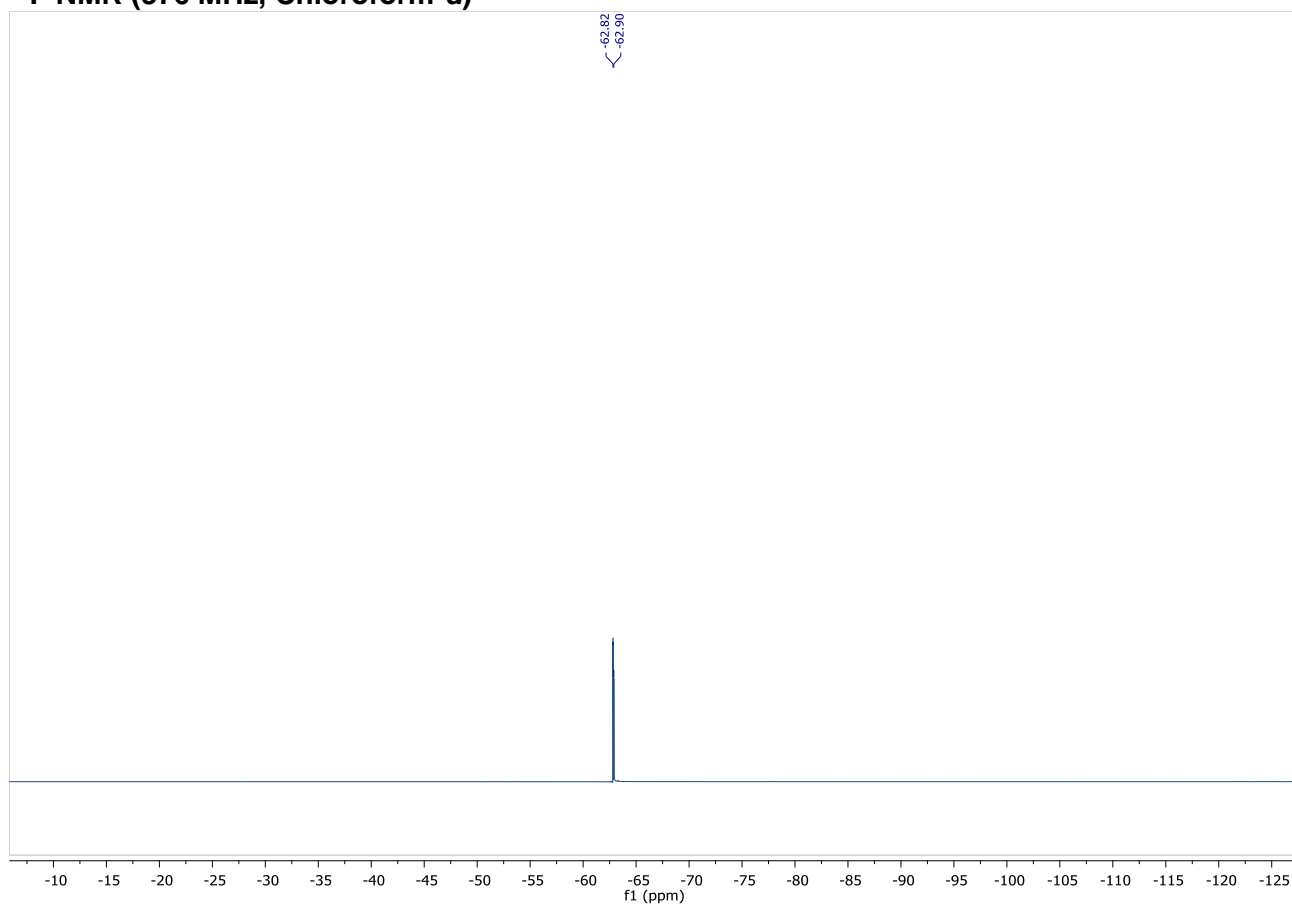
¹H-NMR (400 MHz, Chloroform-d)



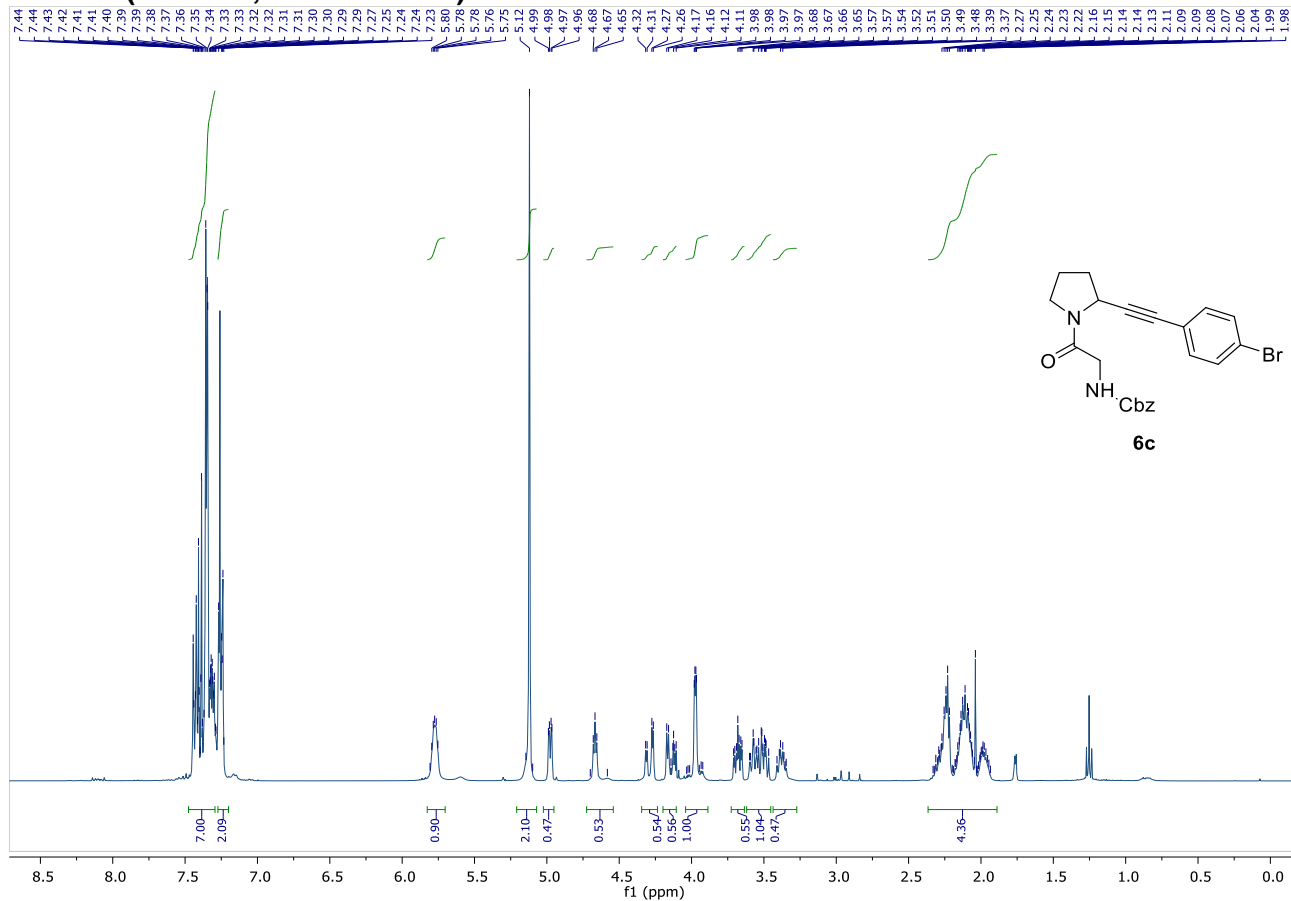
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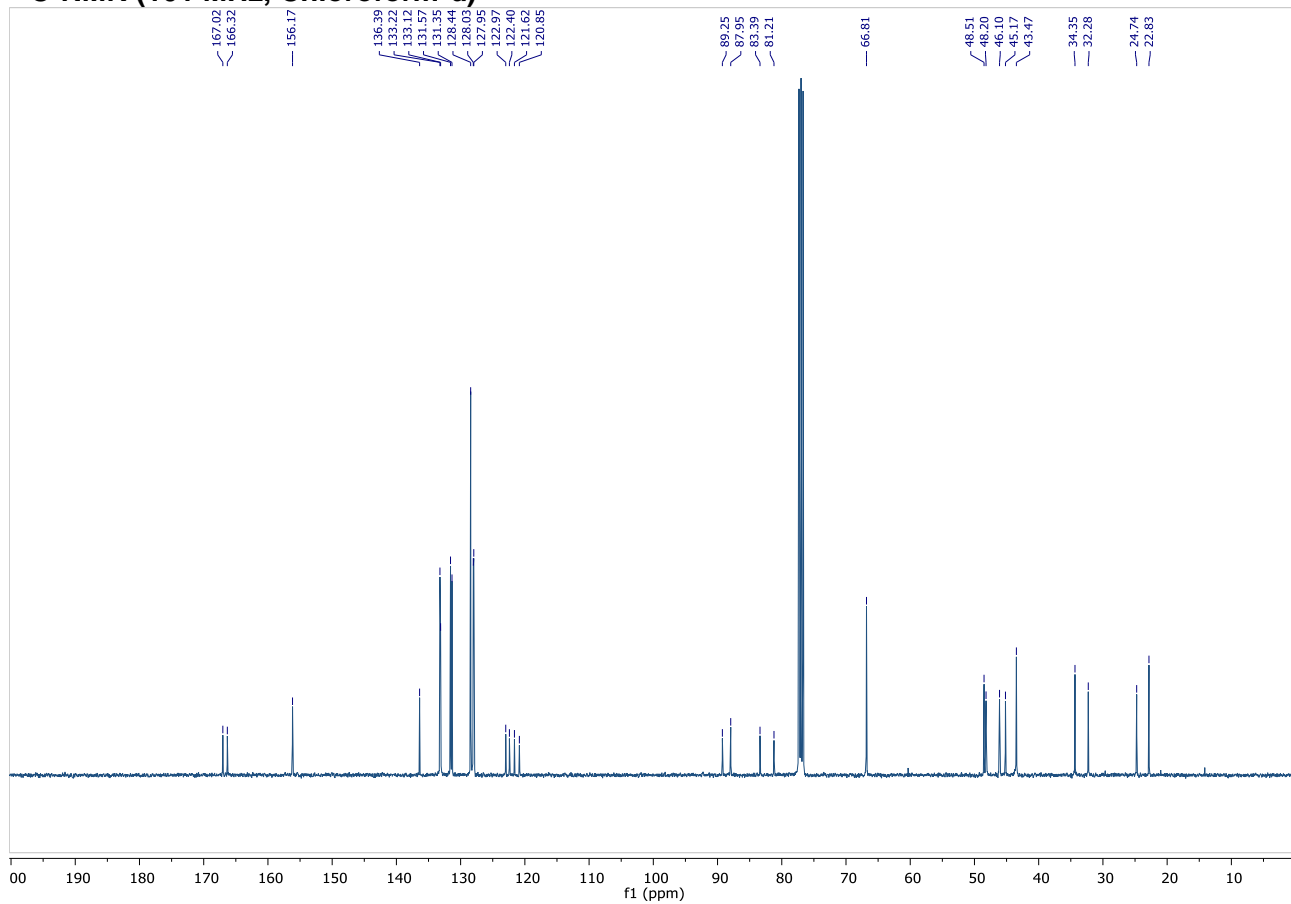
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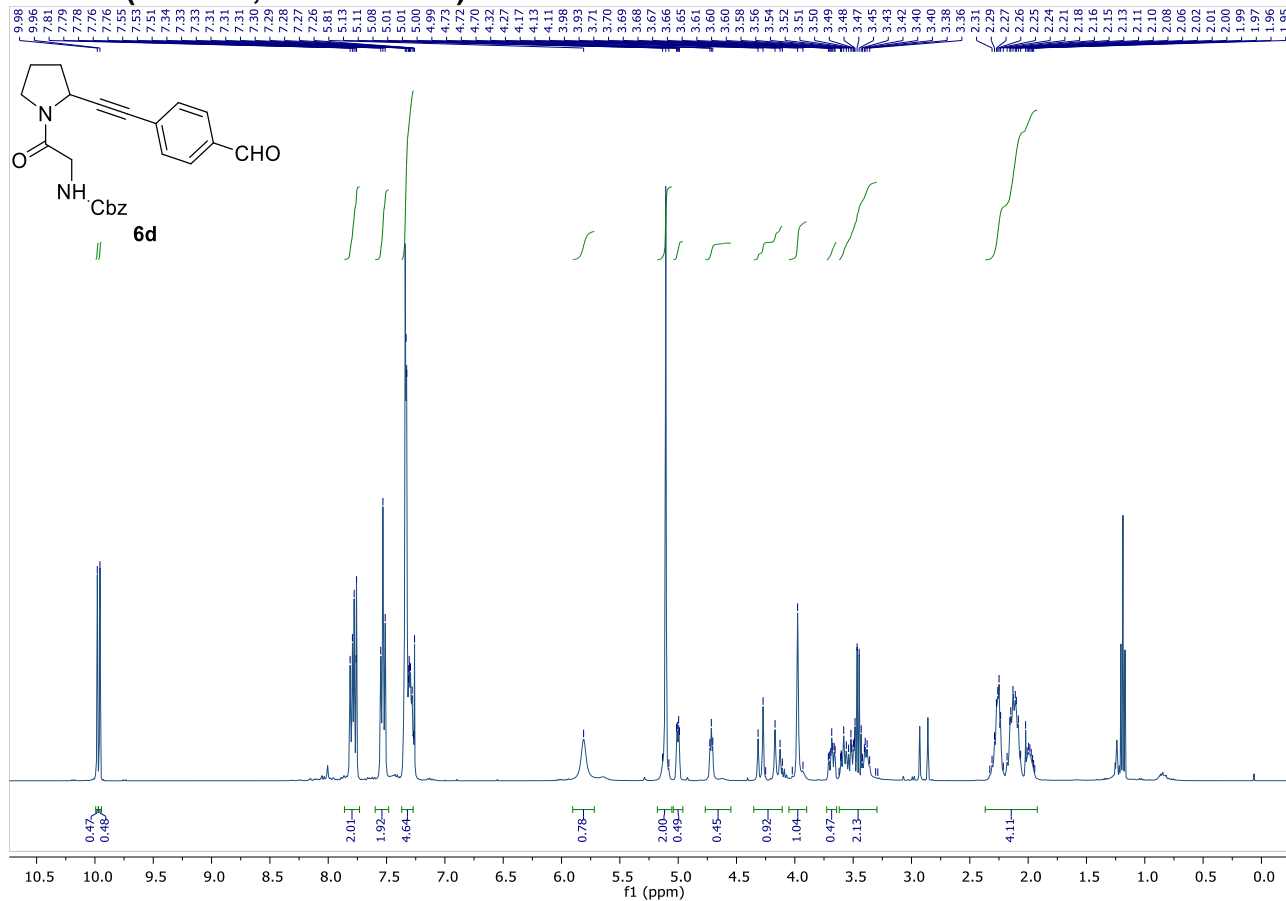
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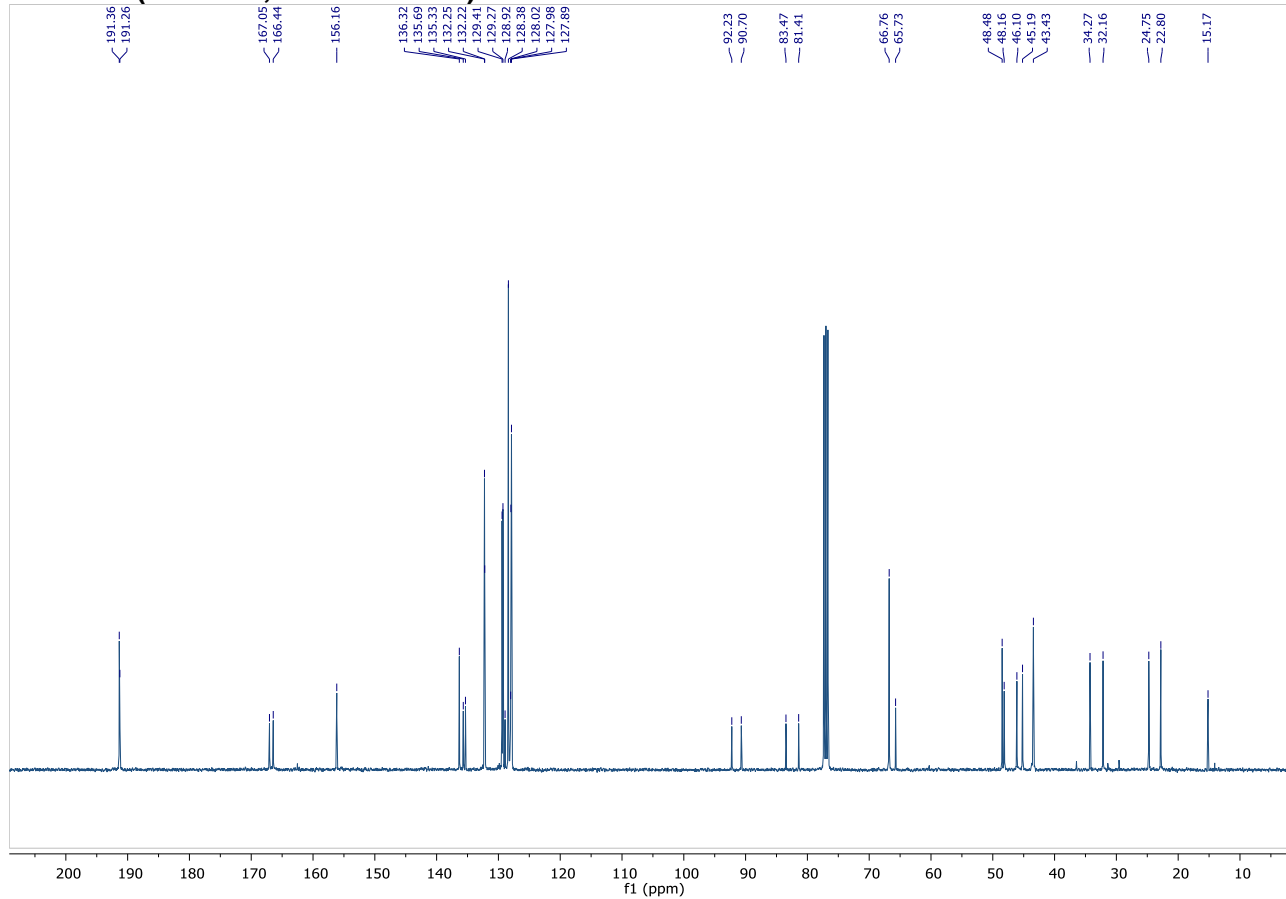
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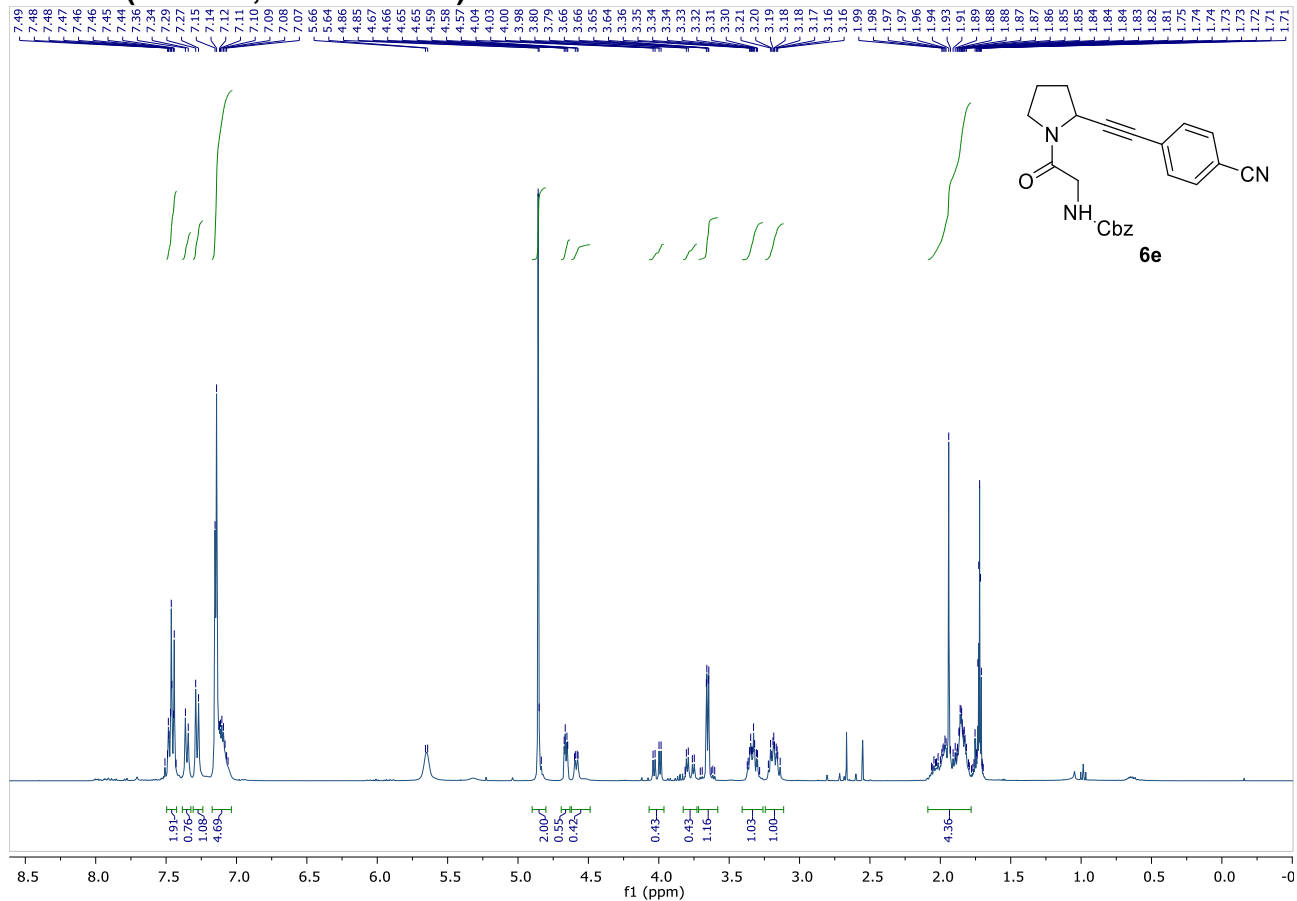
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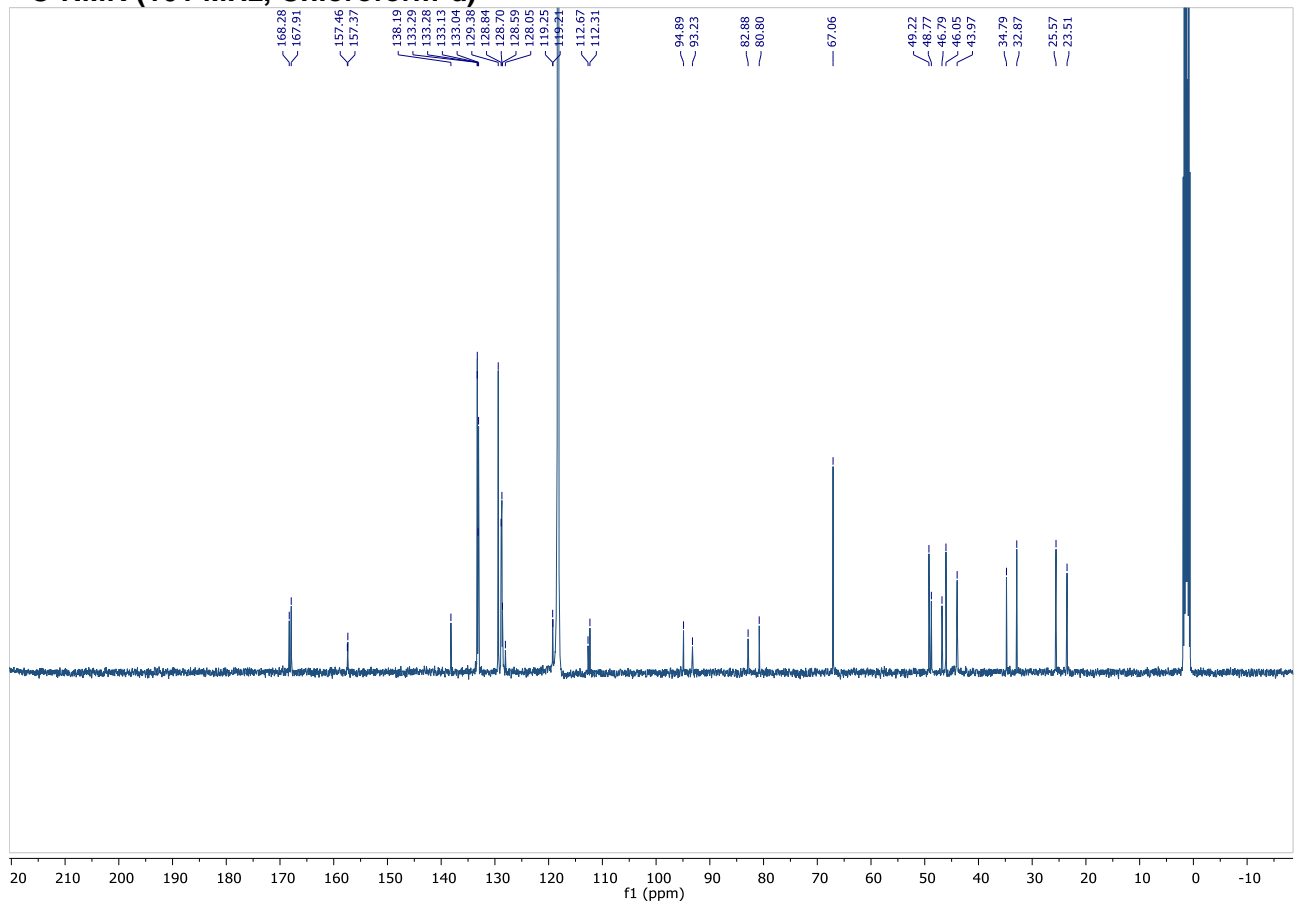
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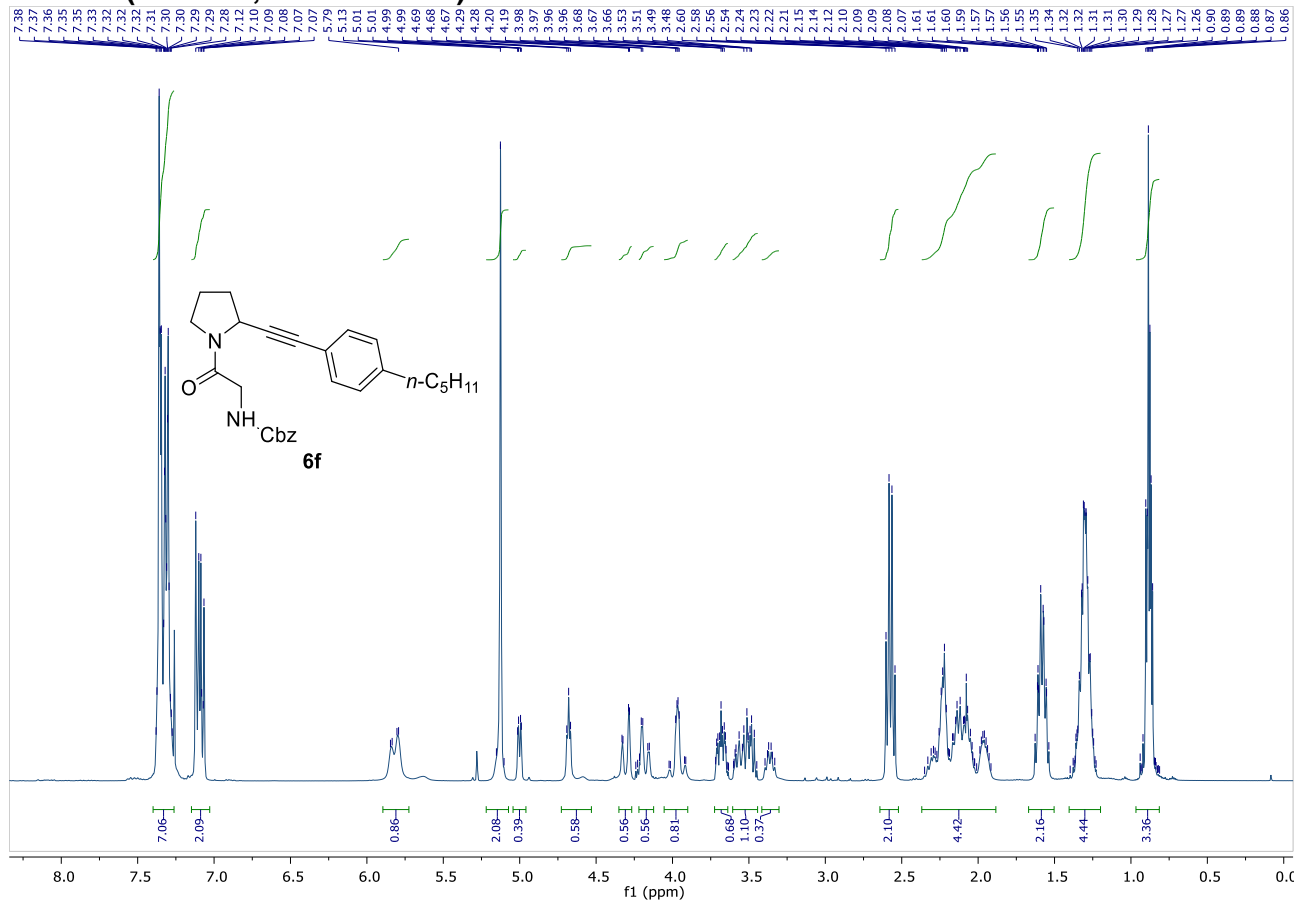
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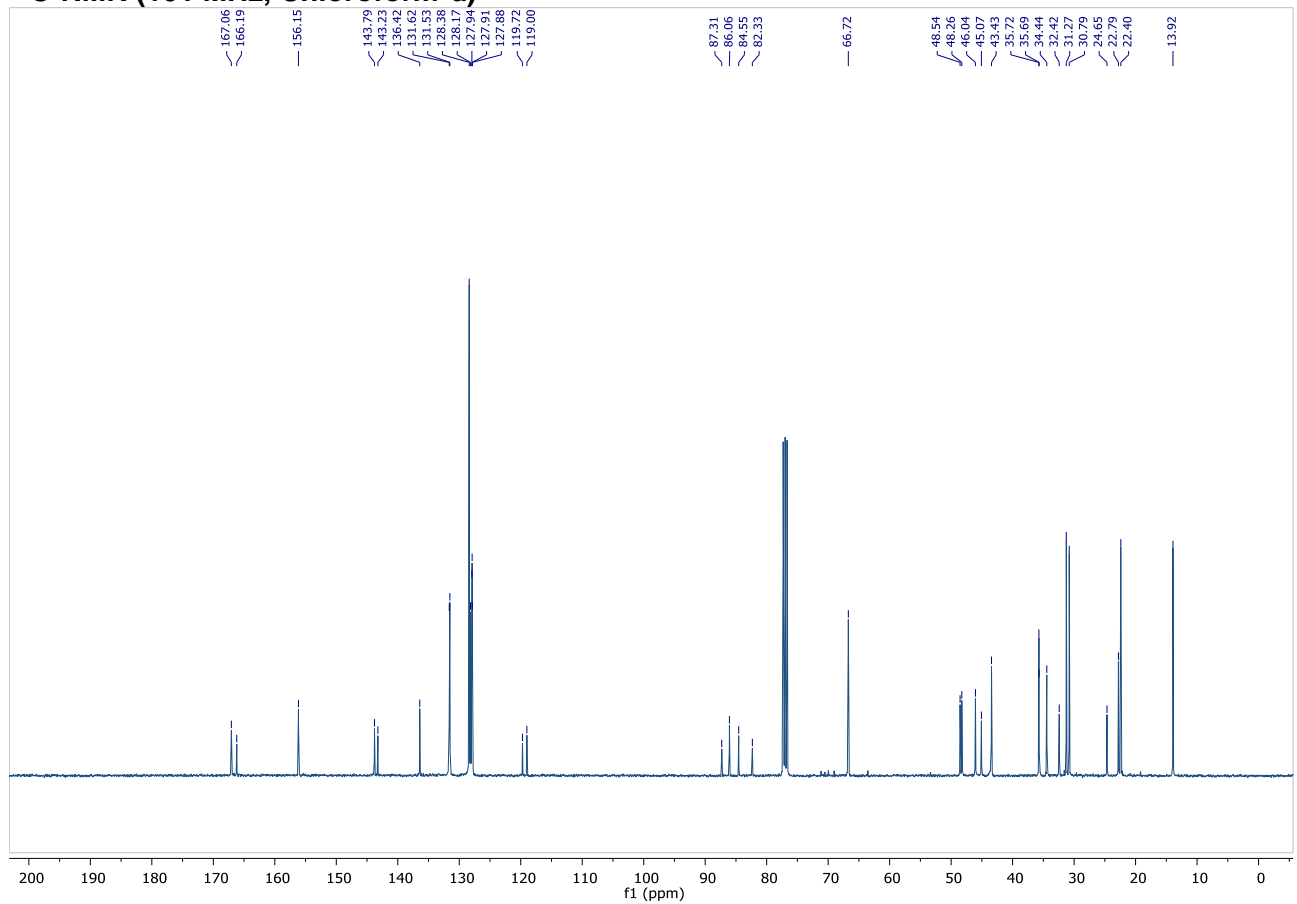
¹³C-NMR (101 MHz, Chloroform-d)



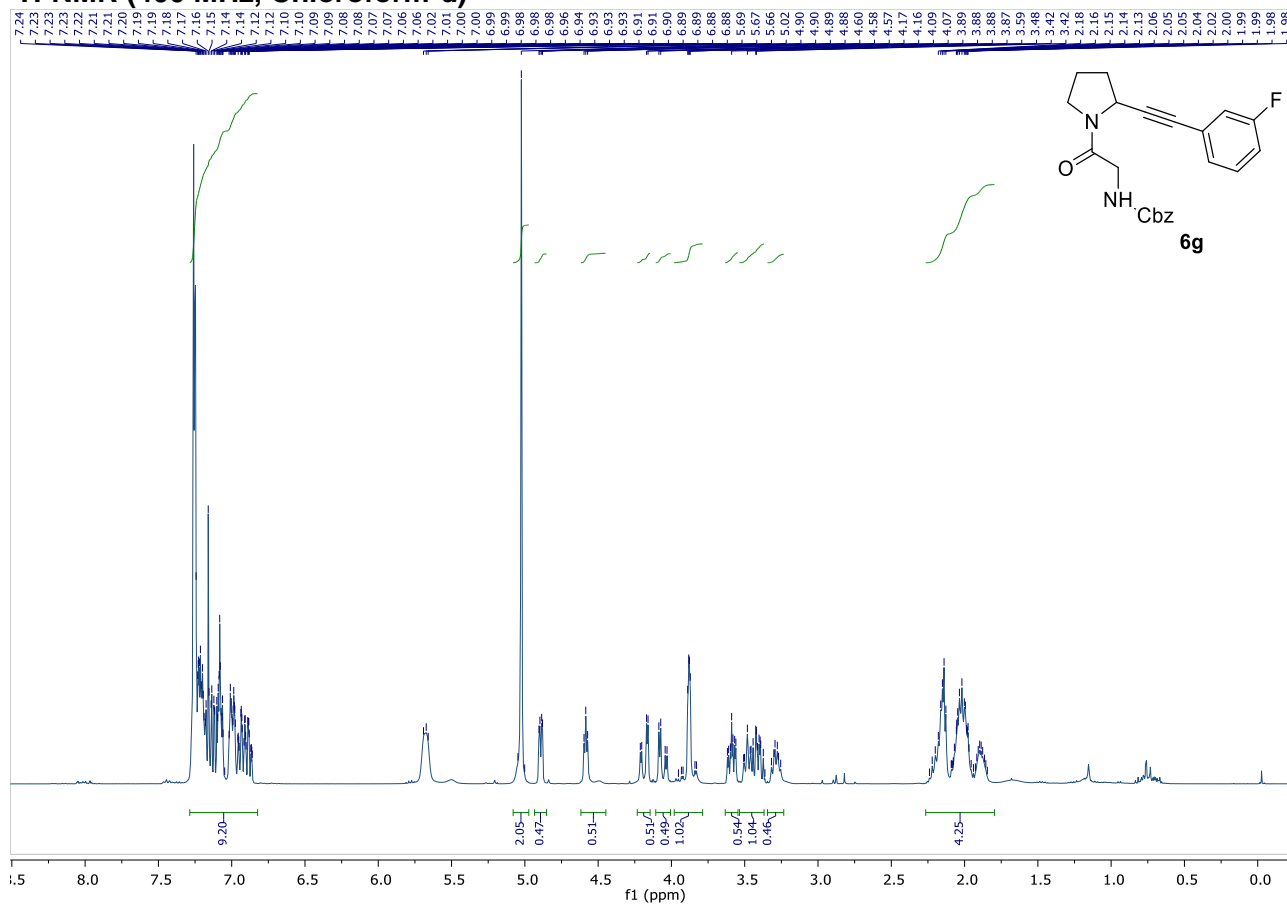
¹H-NMR (400 MHz, Chloroform-d)



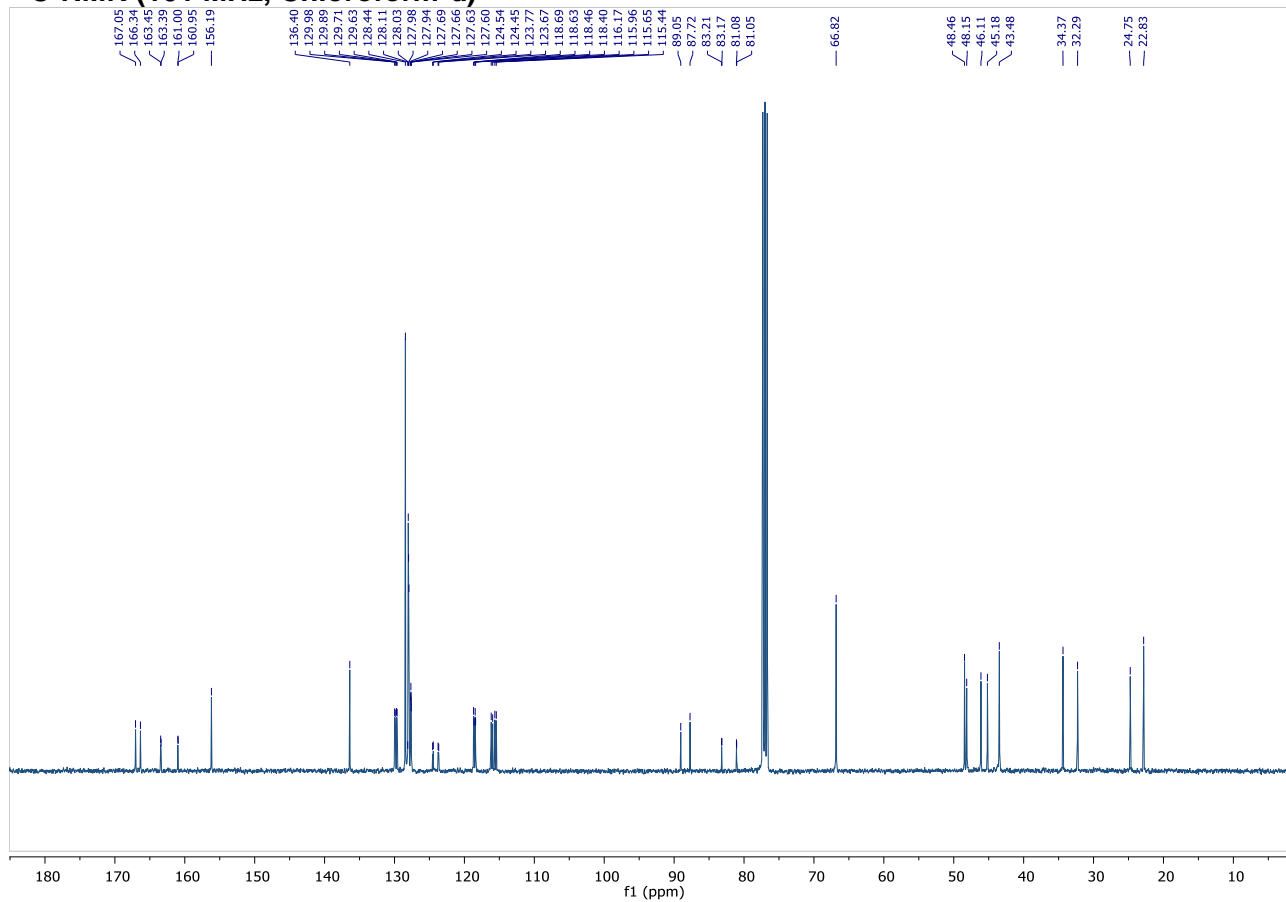
¹³C-NMR (101 MHz, Chloroform-d)



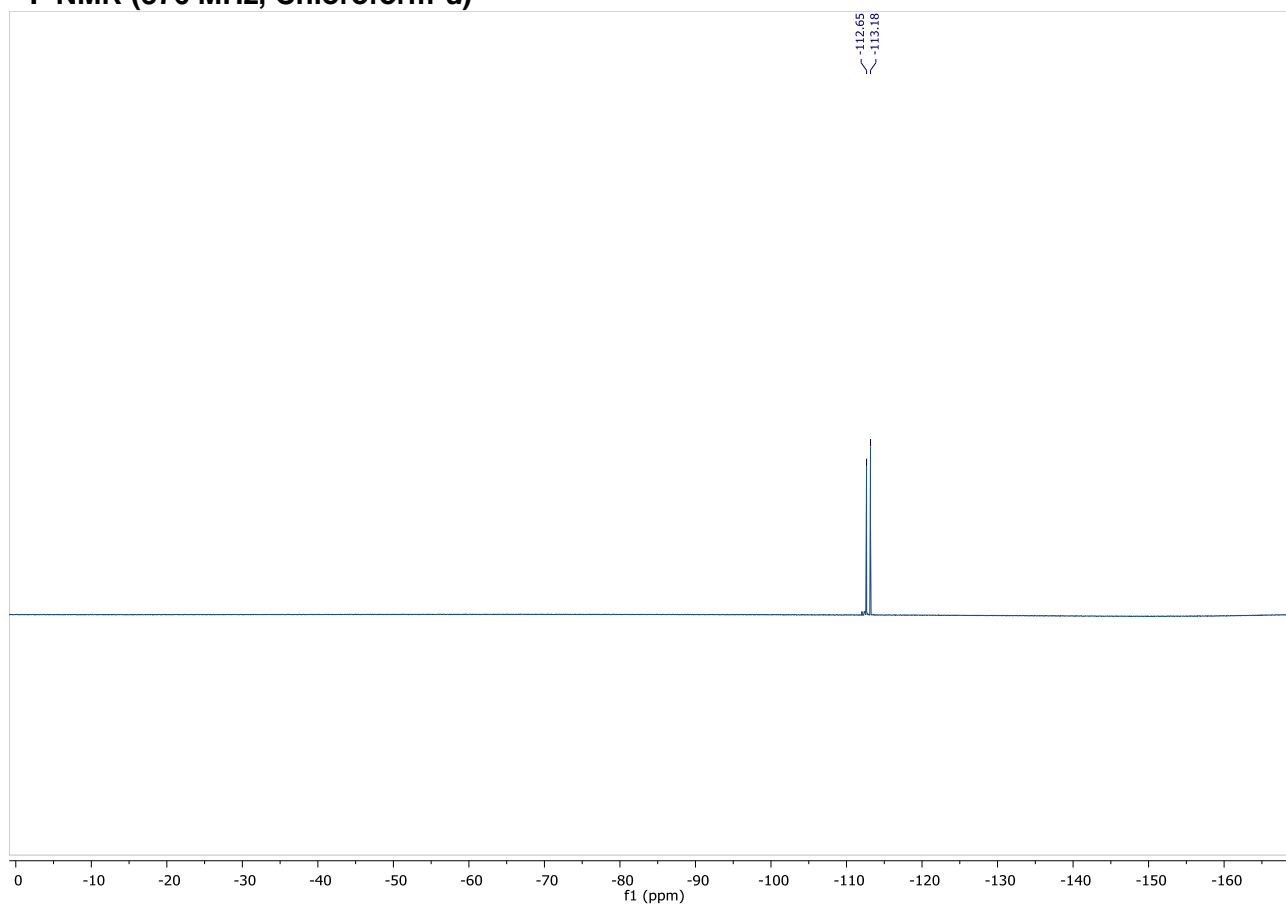
¹H-NMR (400 MHz, Chloroform-*d*)



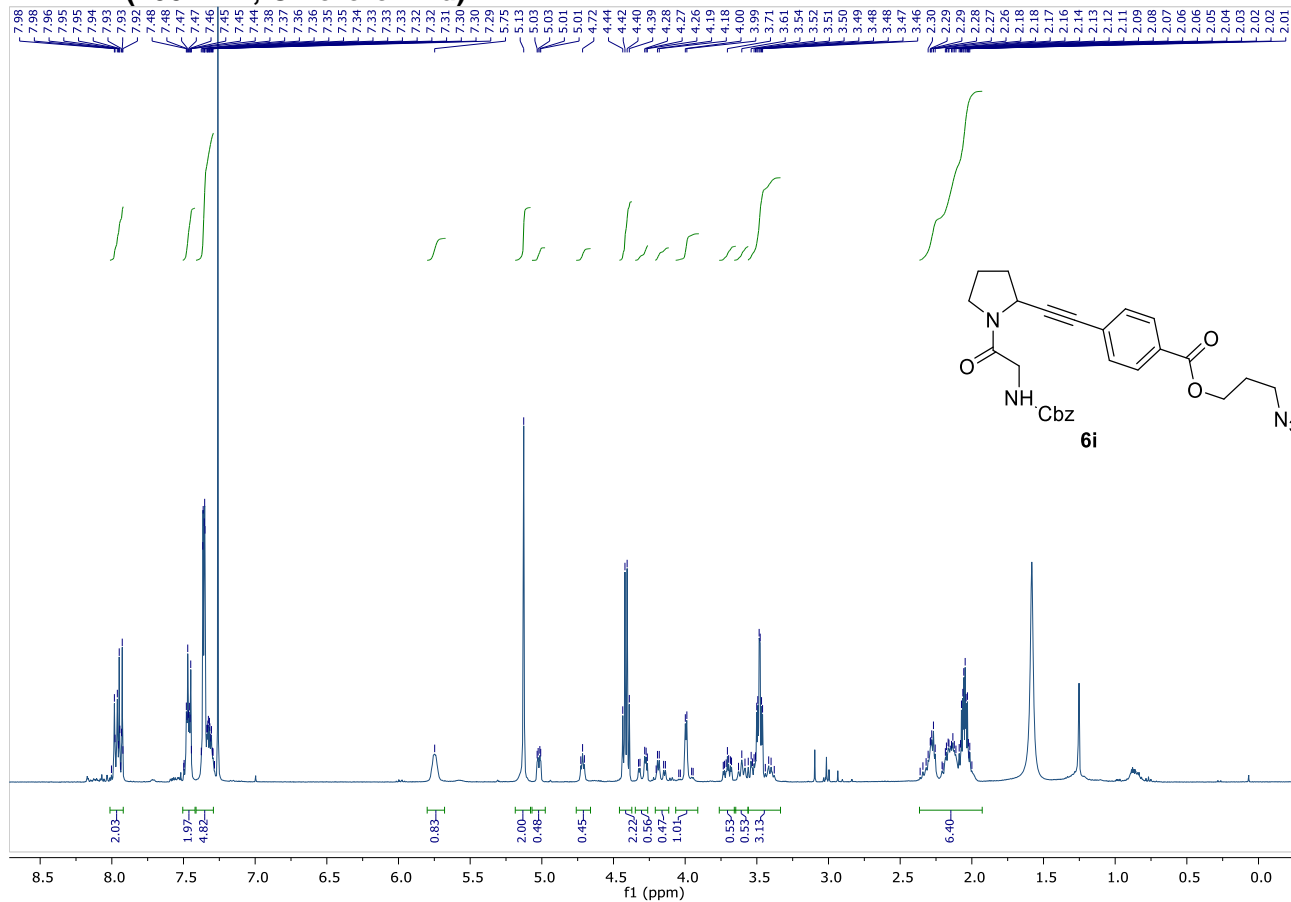
¹³C-NMR (101 MHz, Chloroform-*d*)



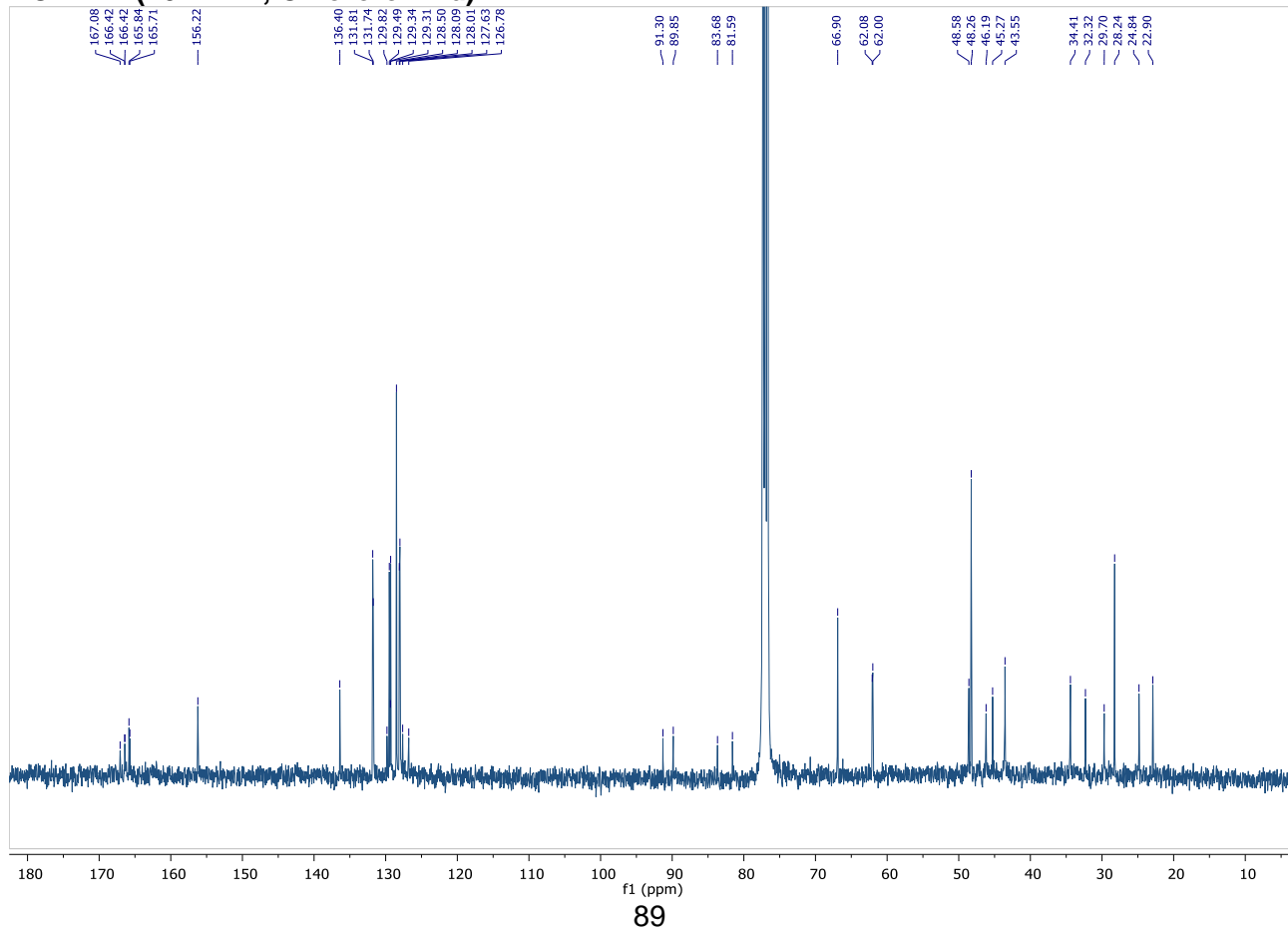
¹⁹F NMR (376 MHz, Chloroform-*d*)



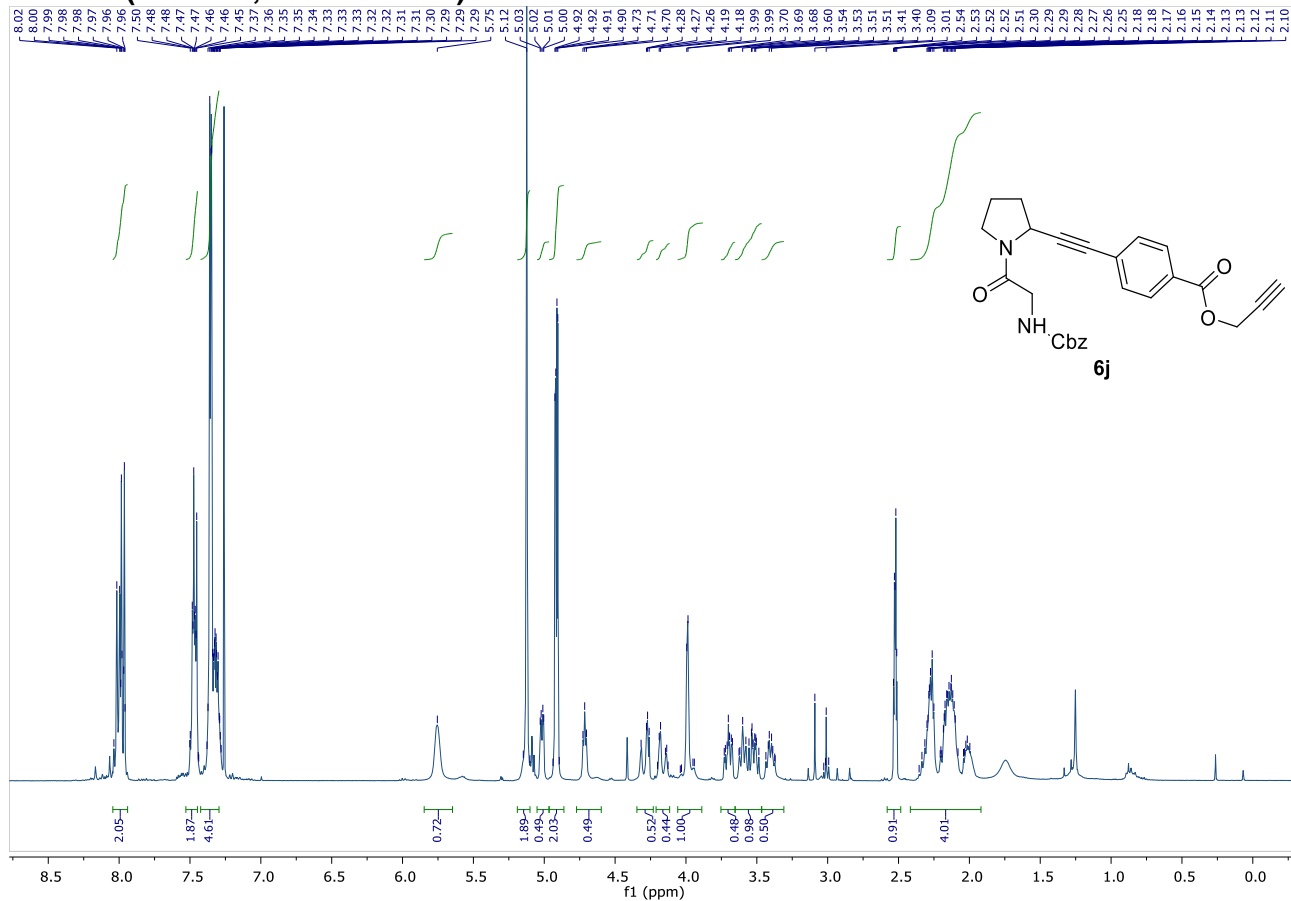
¹H-NMR (400 MHz, Chloroform-d)



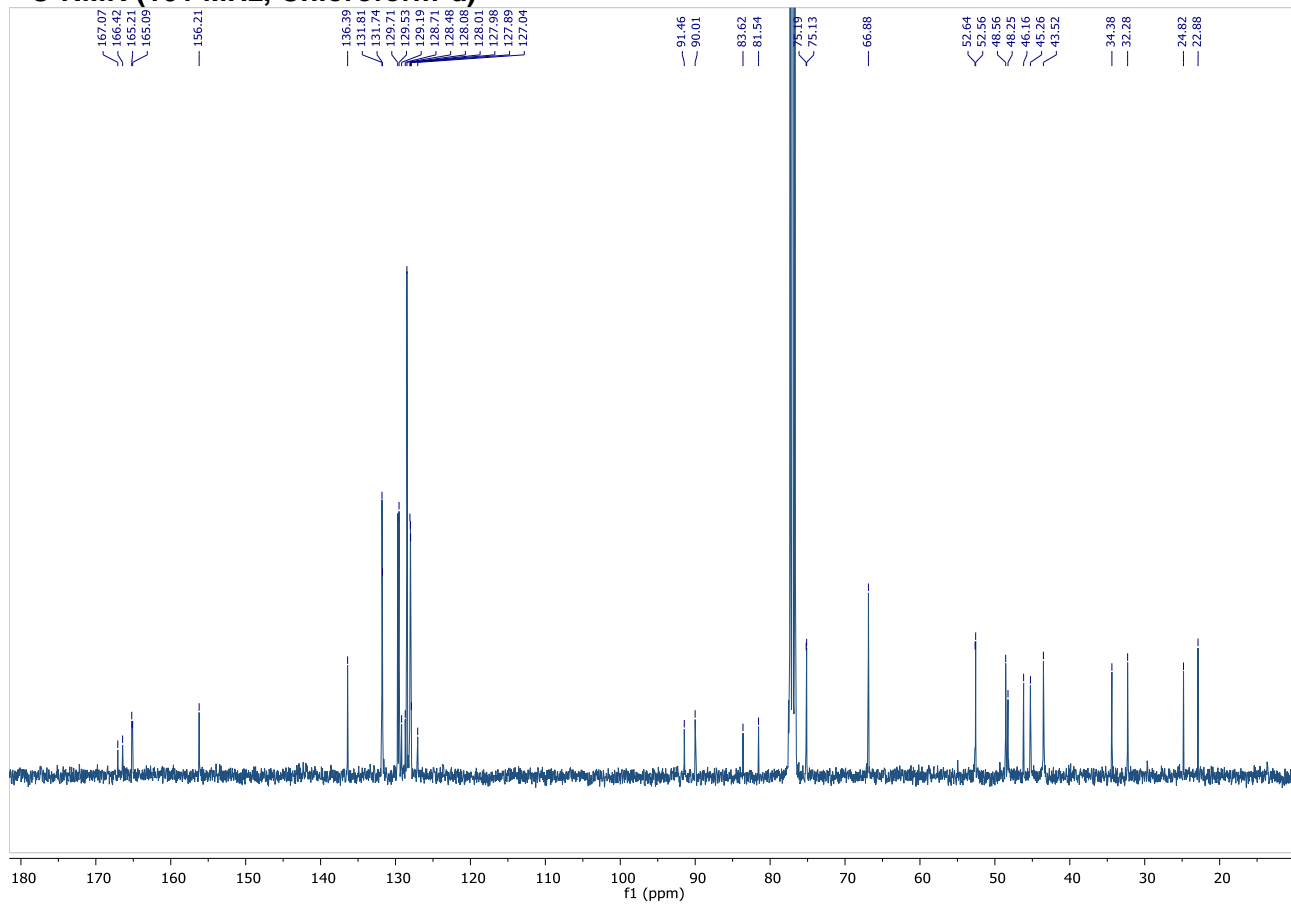
¹³C-NMR (101 MHz, Chloroform-d)



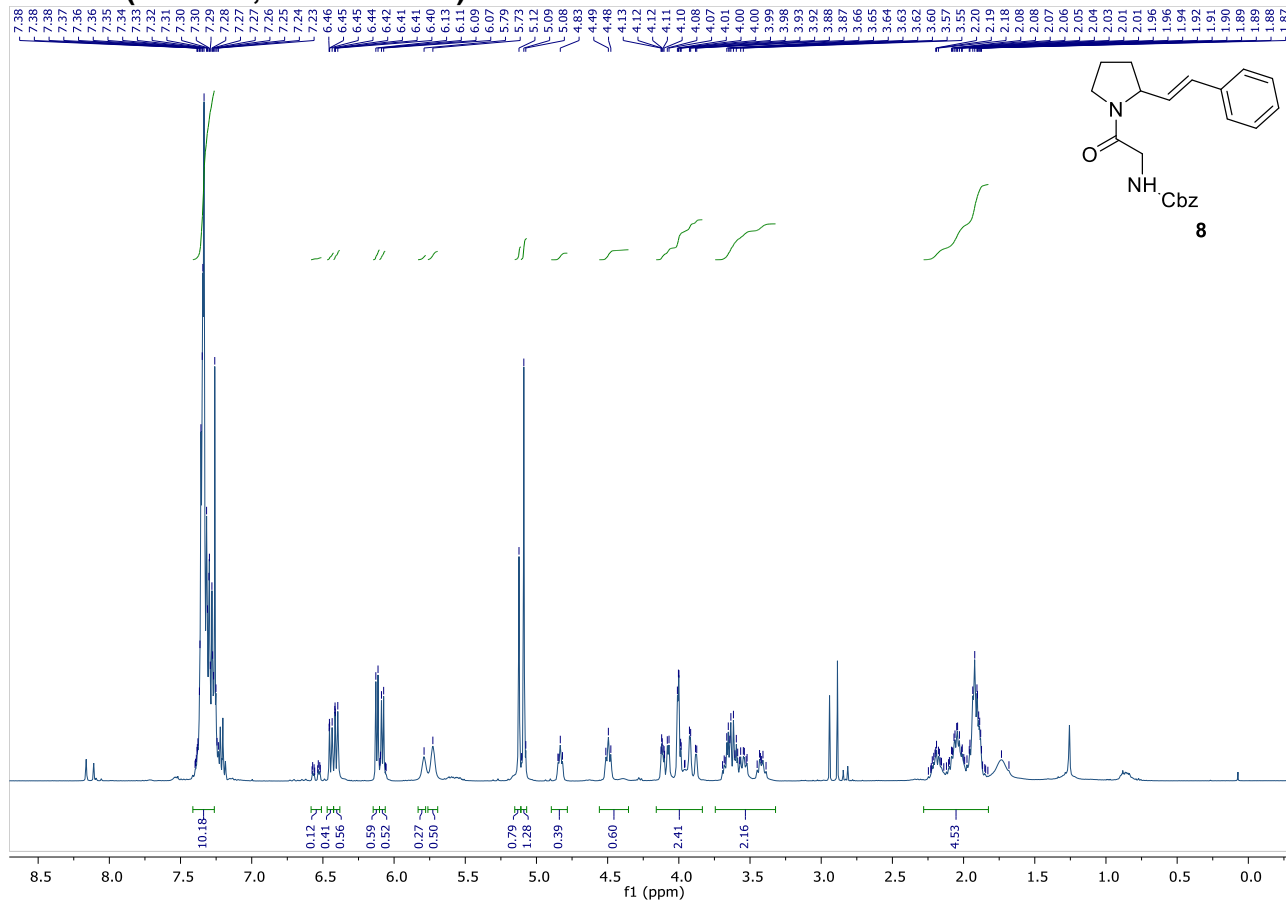
¹H-NMR (400 MHz, Chloroform-d)



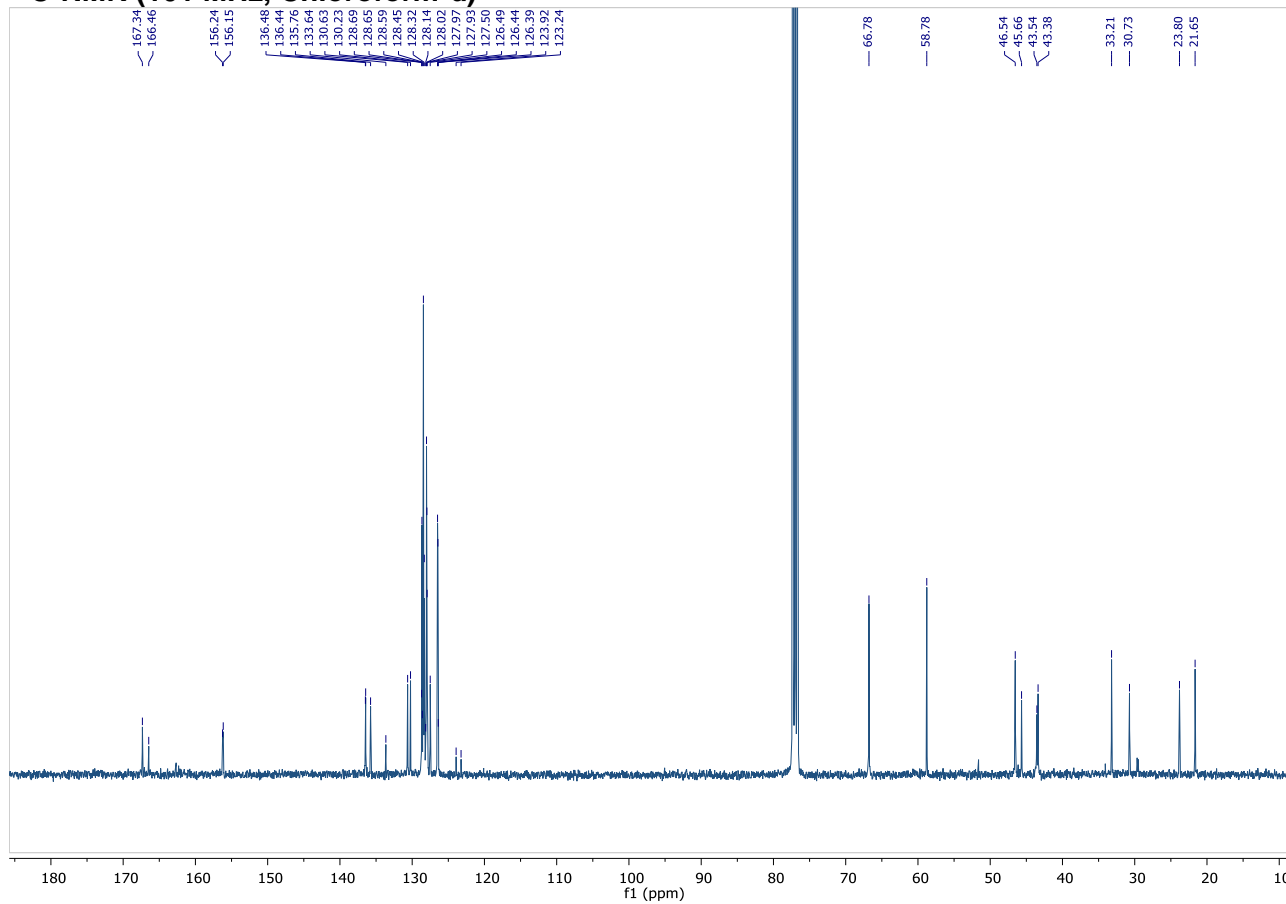
¹³C-NMR (101 MHz, Chloroform-d)



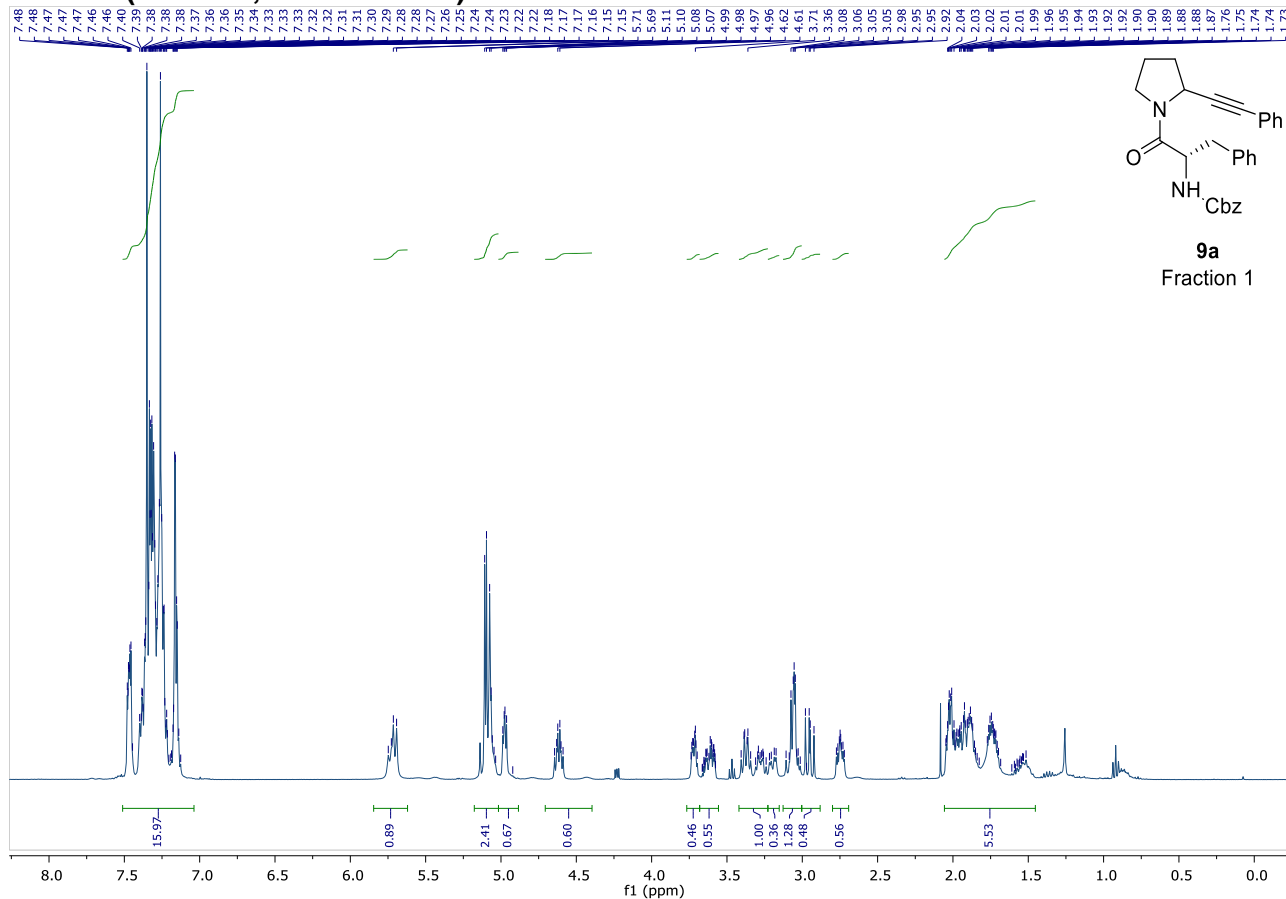
¹H-NMR (400 MHz, Chloroform-d)



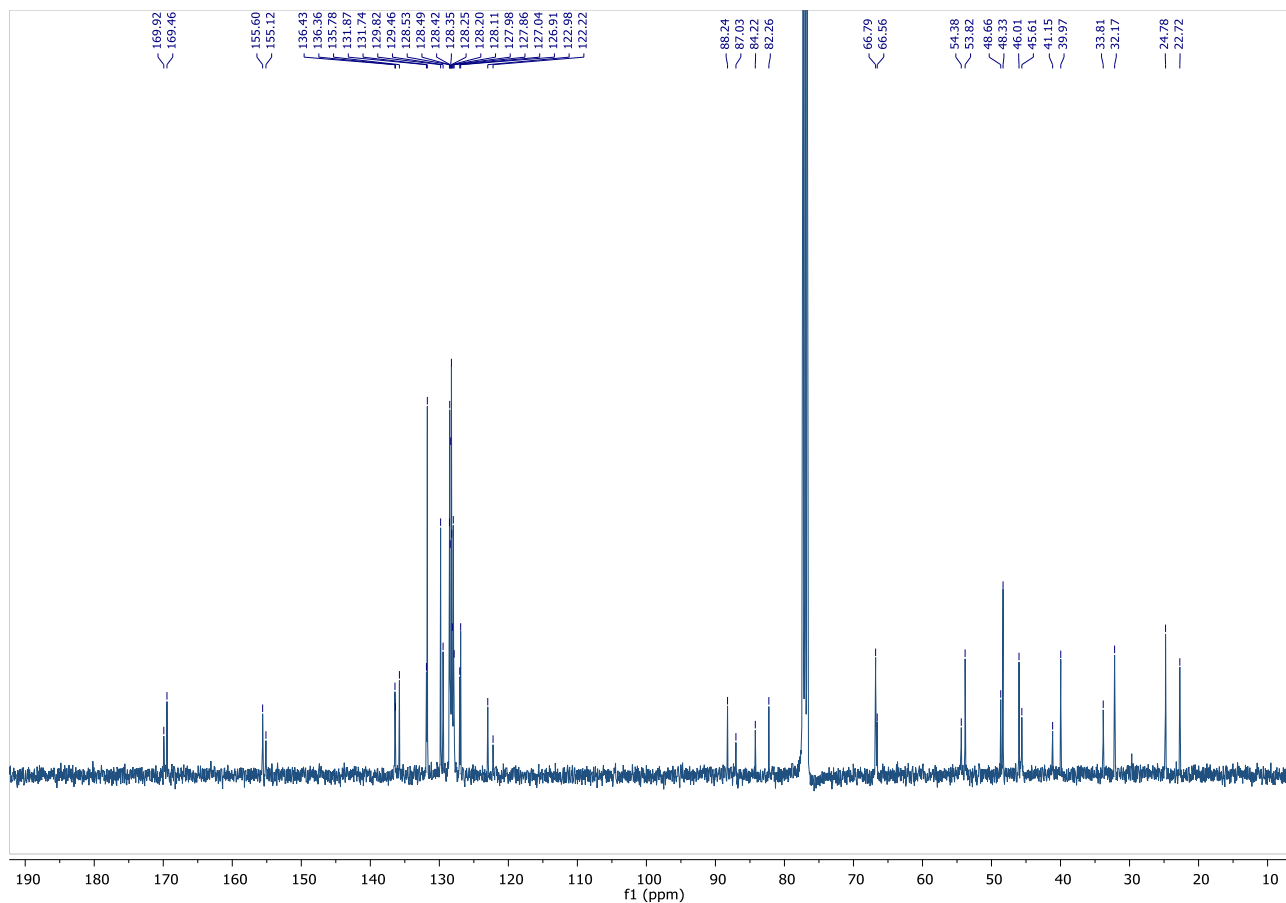
¹³C-NMR (101 MHz, Chloroform-d)



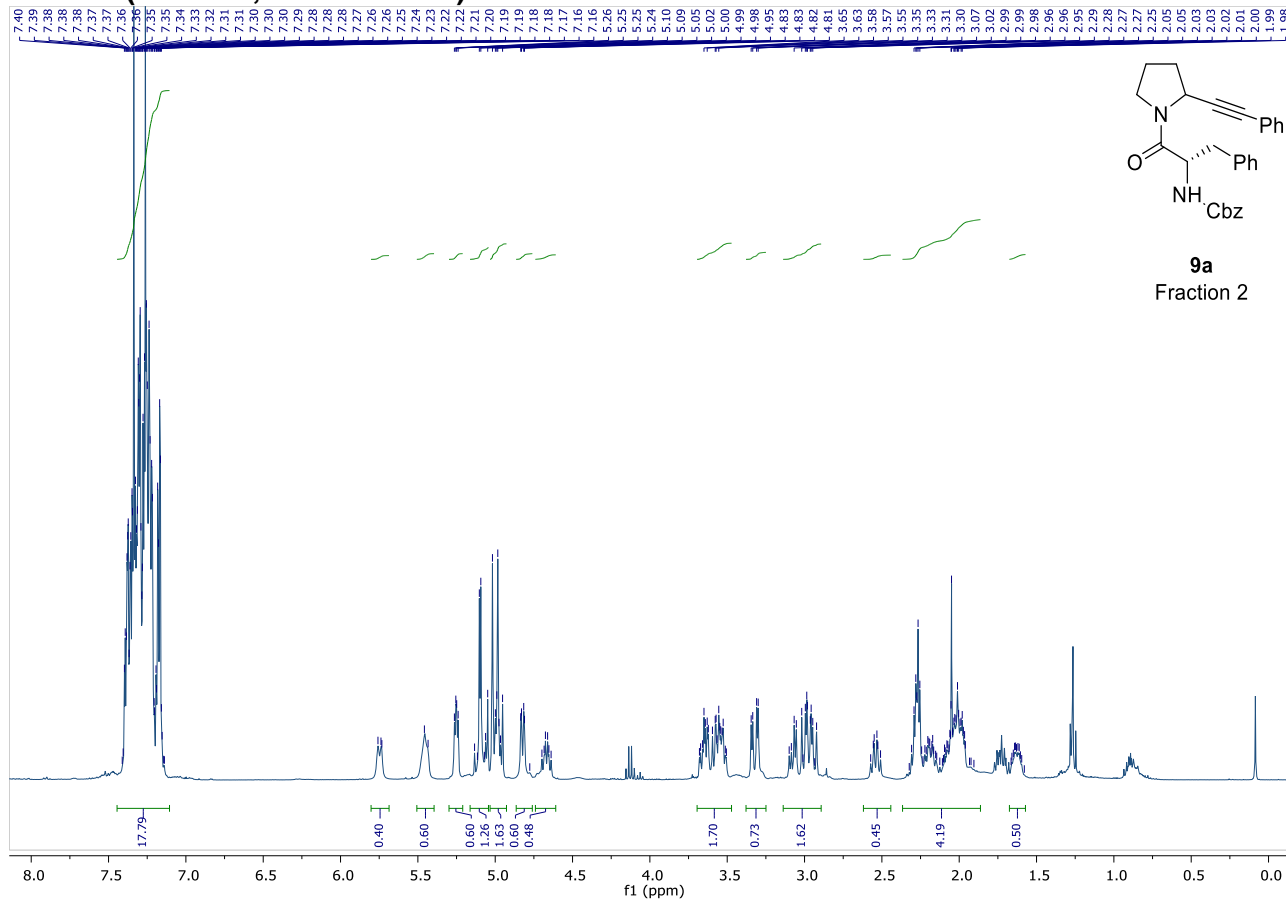
¹H-NMR (400 MHz, Chloroform-*d*)



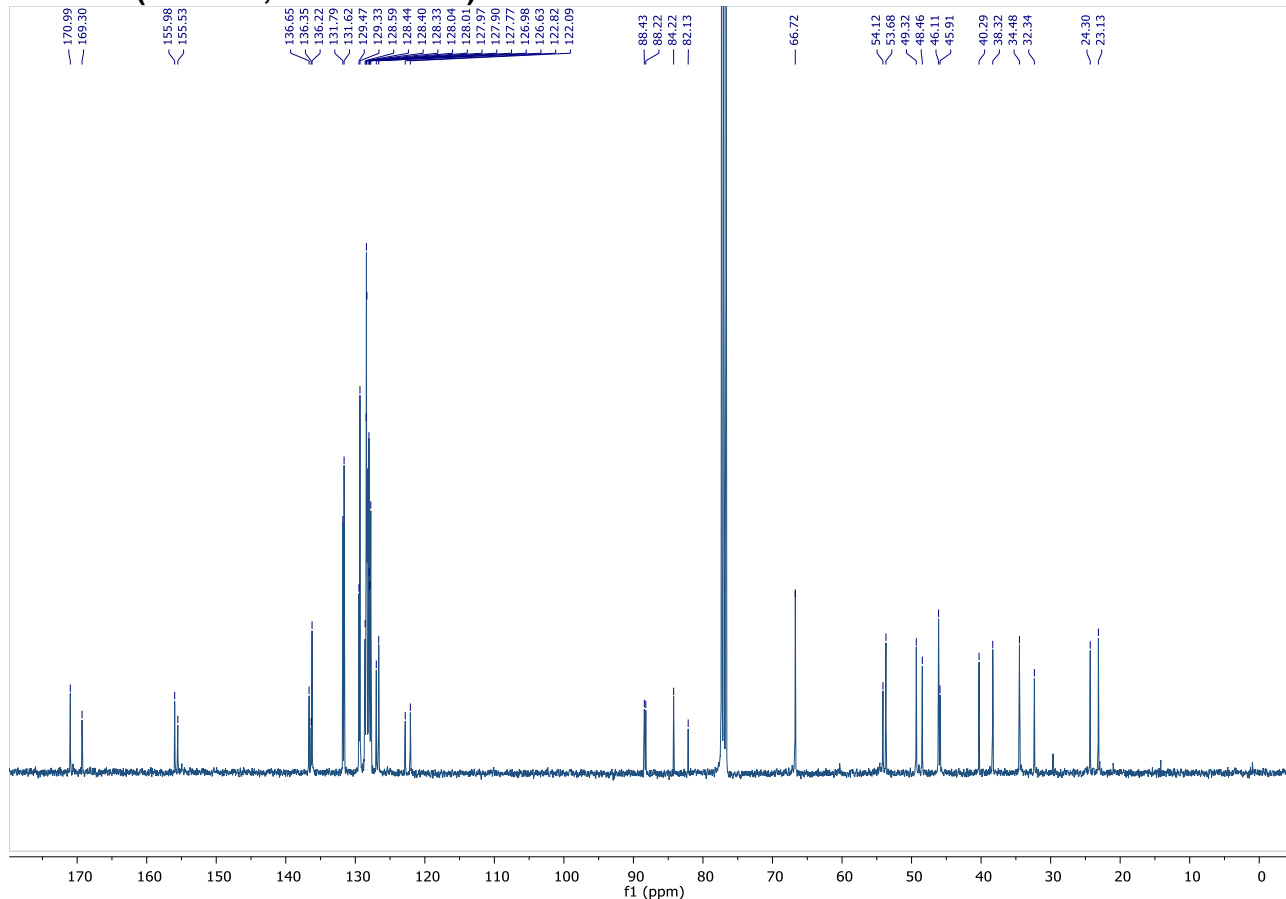
¹³C-NMR (101 MHz, Chloroform-*d*)



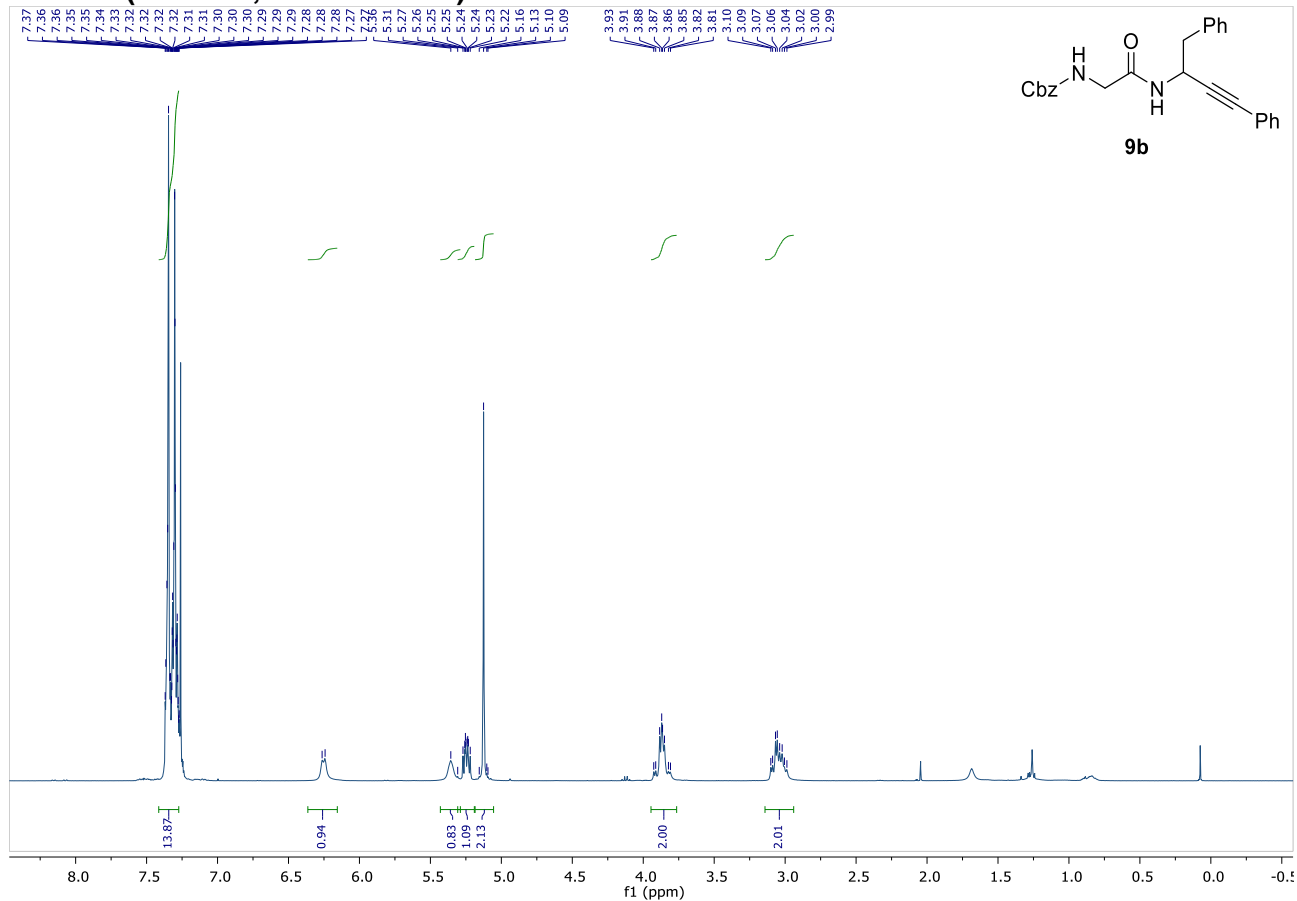
¹H-NMR (400 MHz, Chloroform-d)



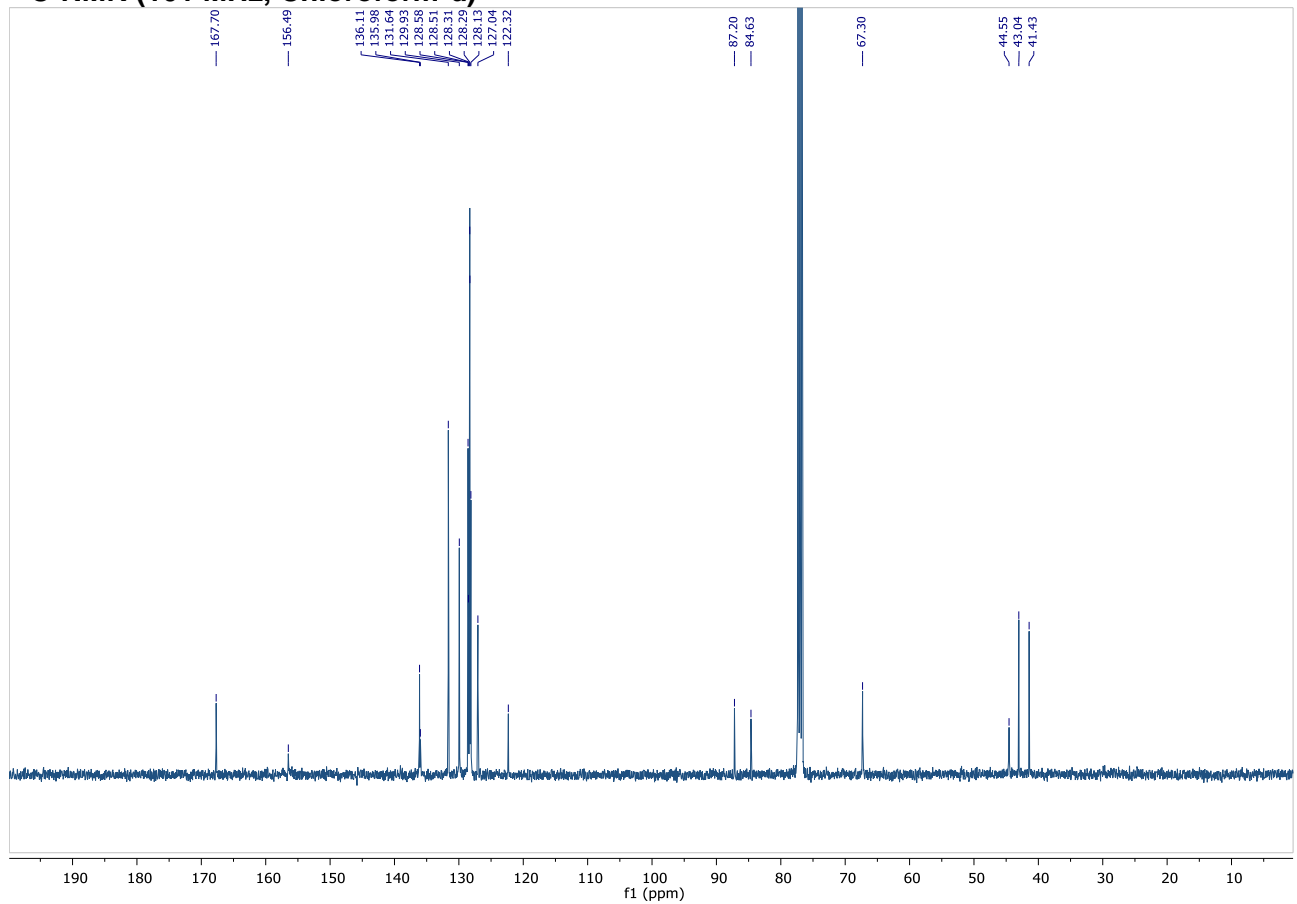
¹³C-NMR (101 MHz, Chloroform-d)



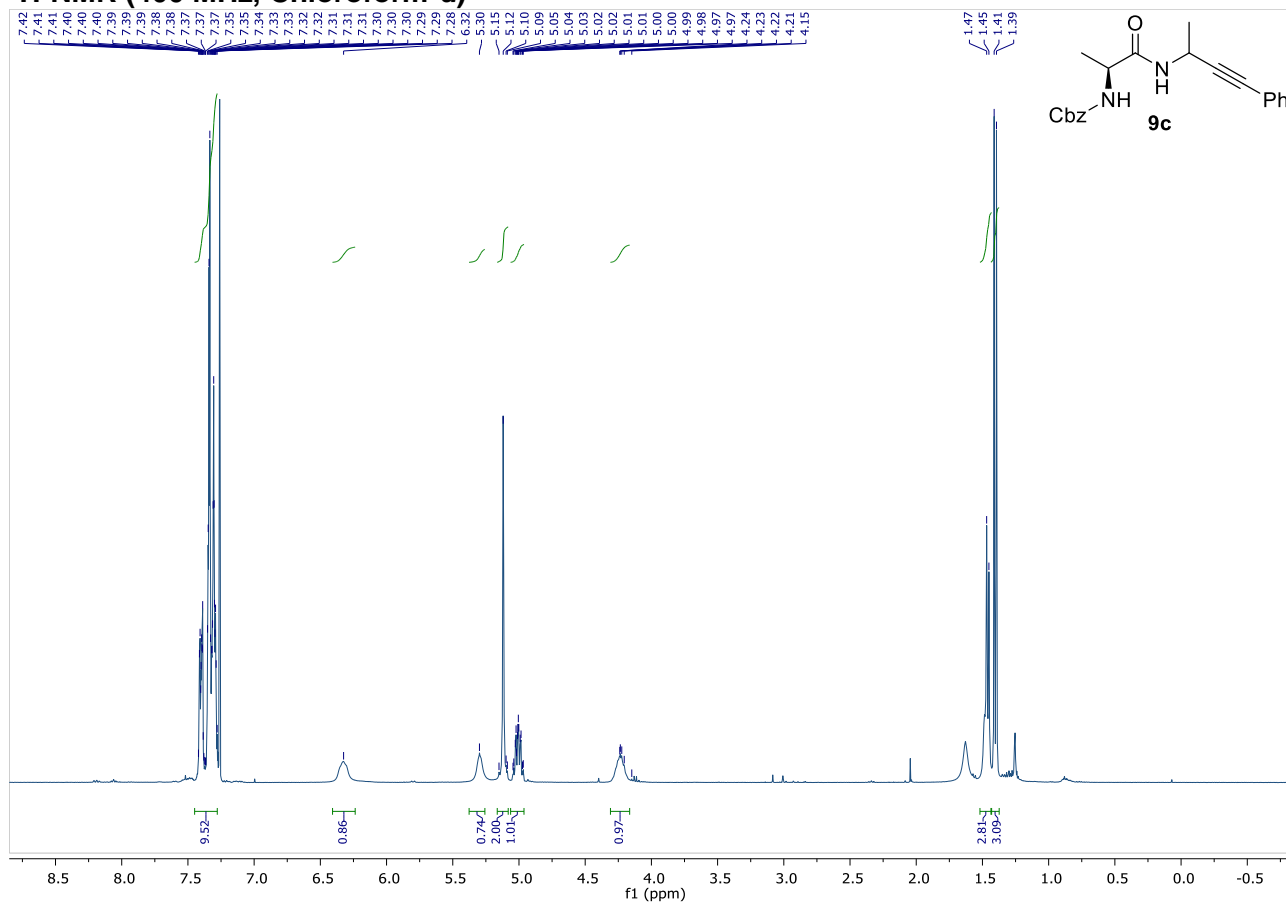
¹H-NMR (400 MHz, Chloroform-*d*)



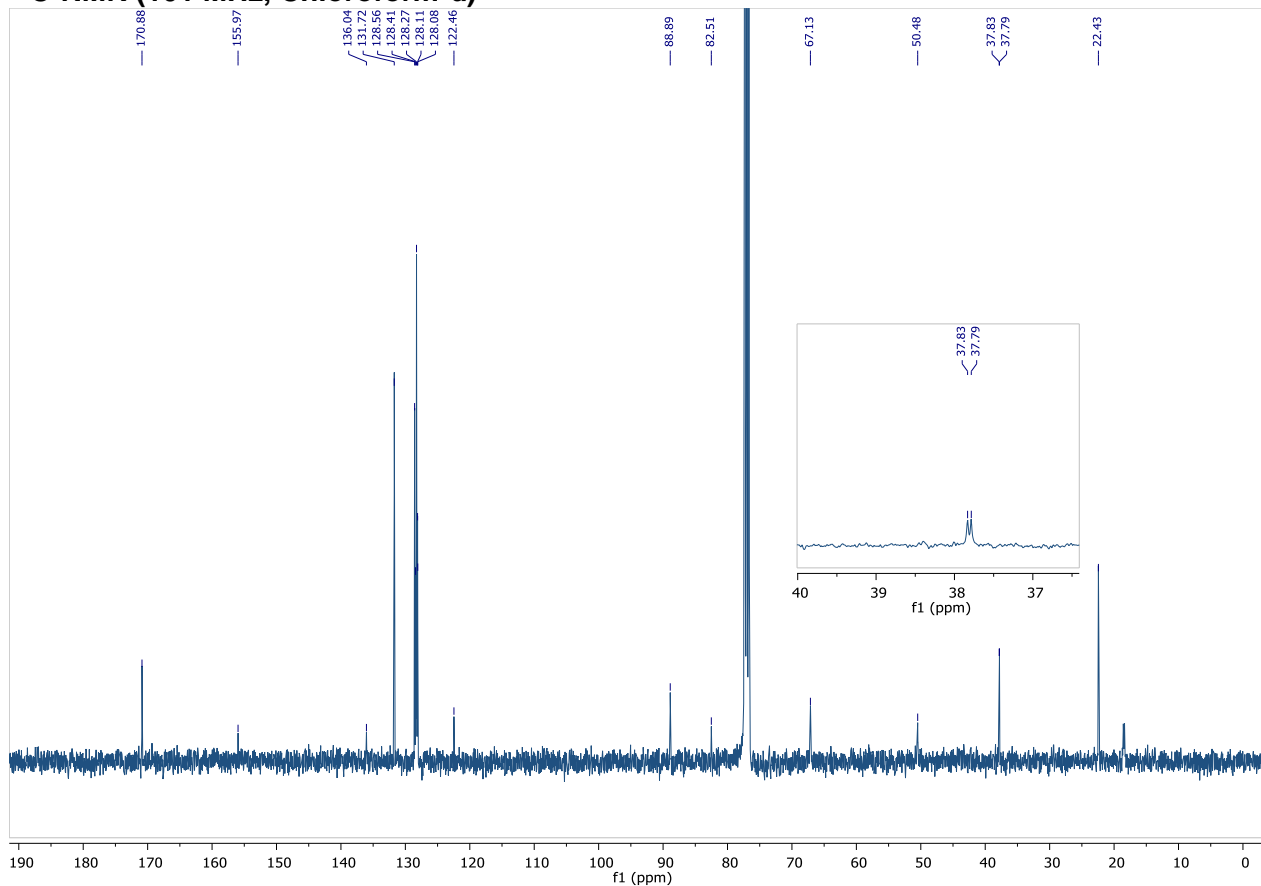
¹³C-NMR (101 MHz, Chloroform-*d*)



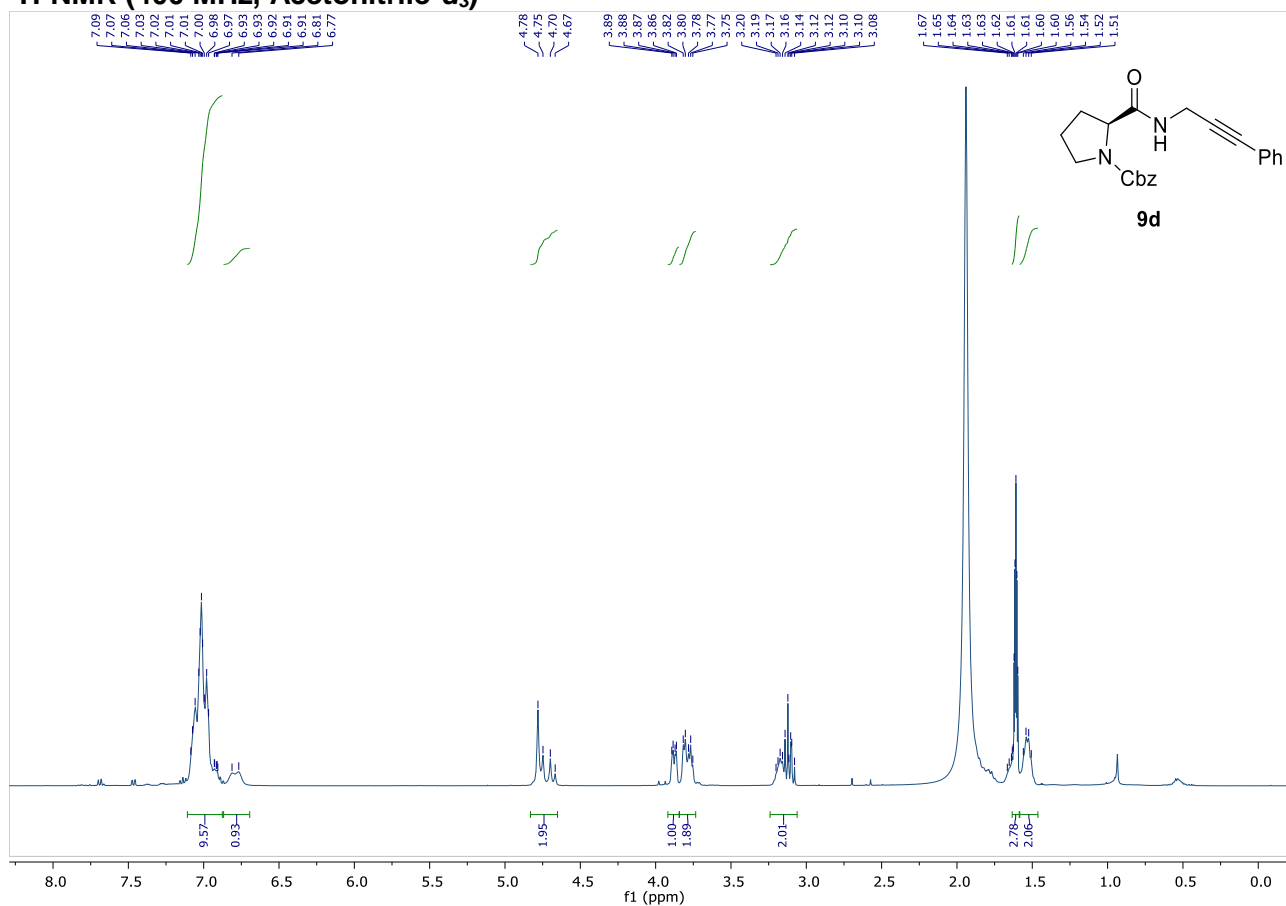
¹H-NMR (400 MHz, Chloroform-d)



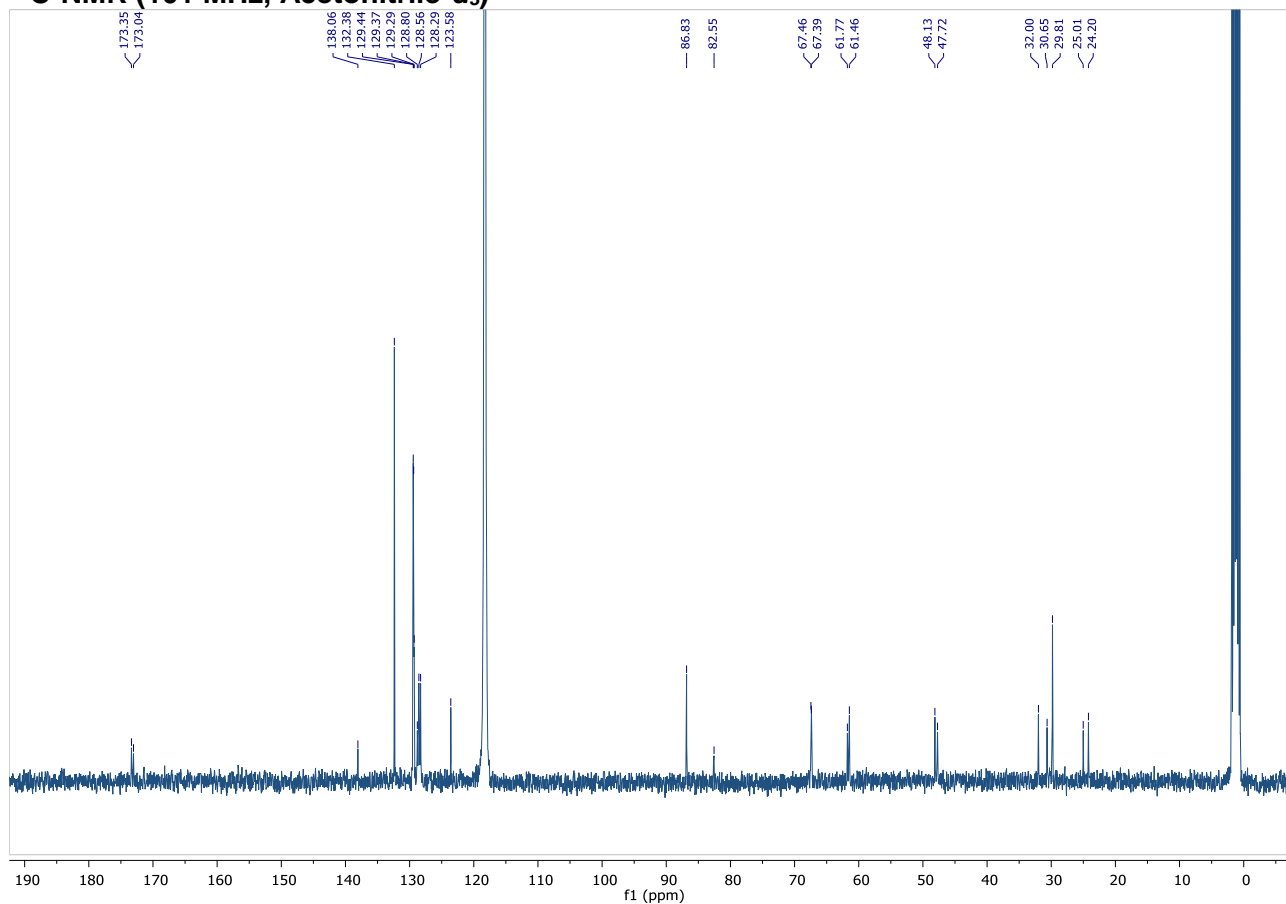
¹³C-NMR (101 MHz, Chloroform-d)



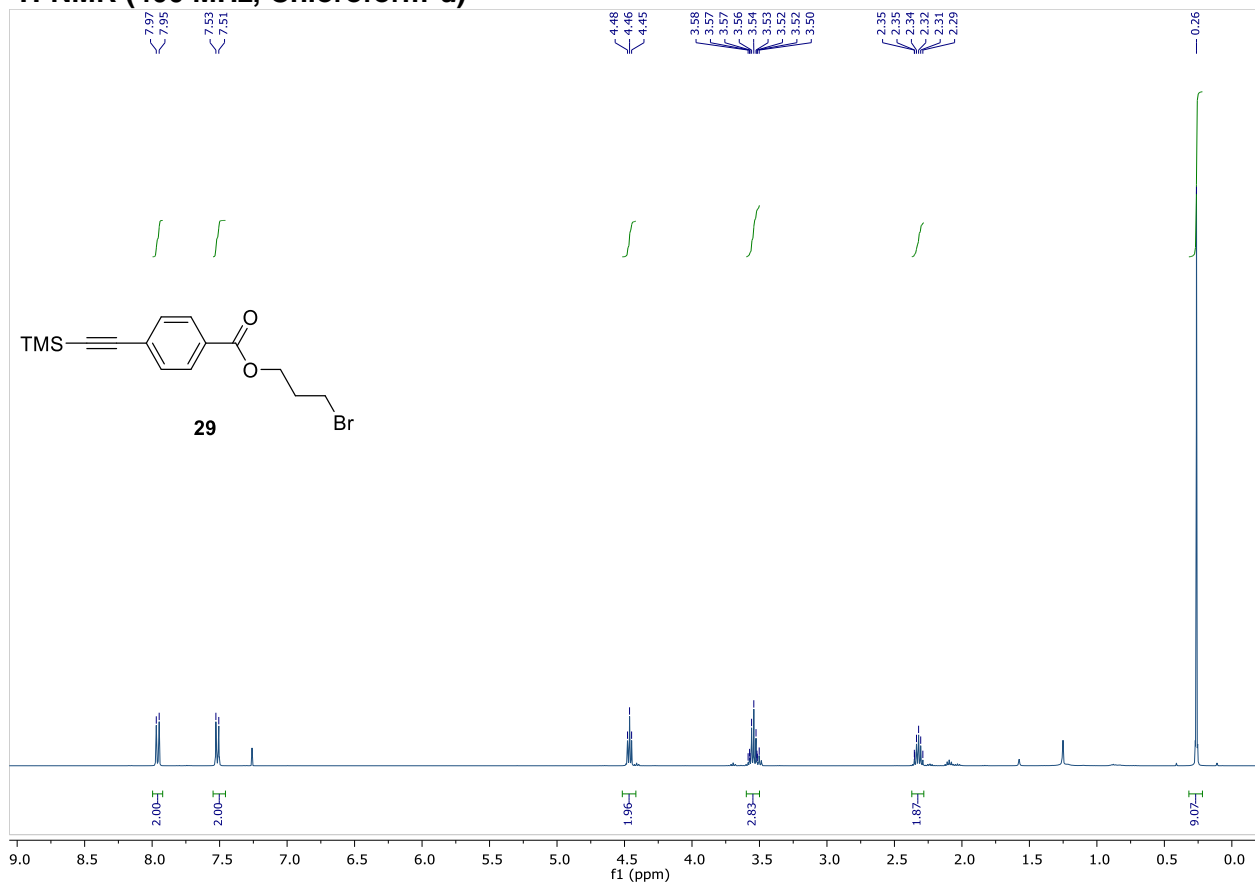
¹H-NMR (400 MHz, Acetonitrile-d₃)



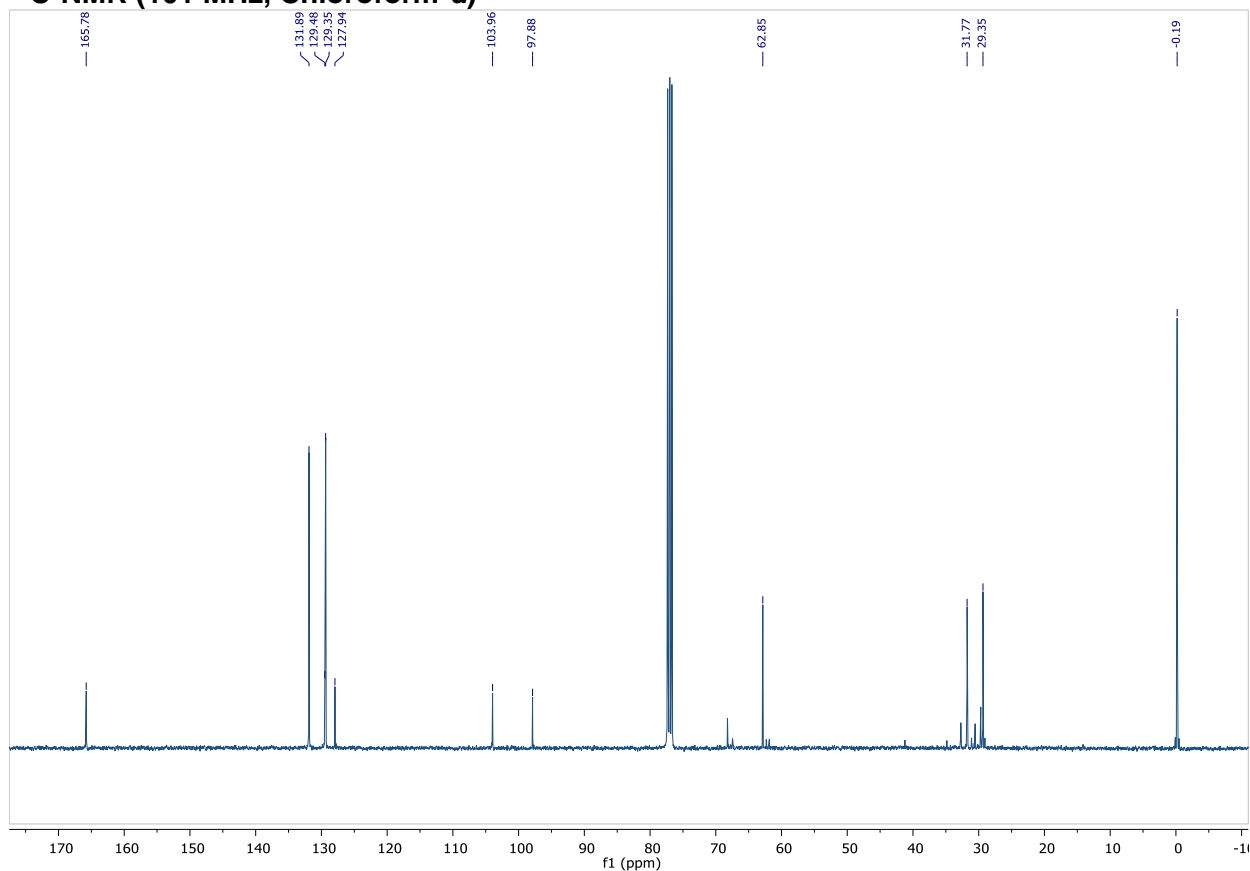
¹³C-NMR (101 MHz, Acetonitrile-d₃)



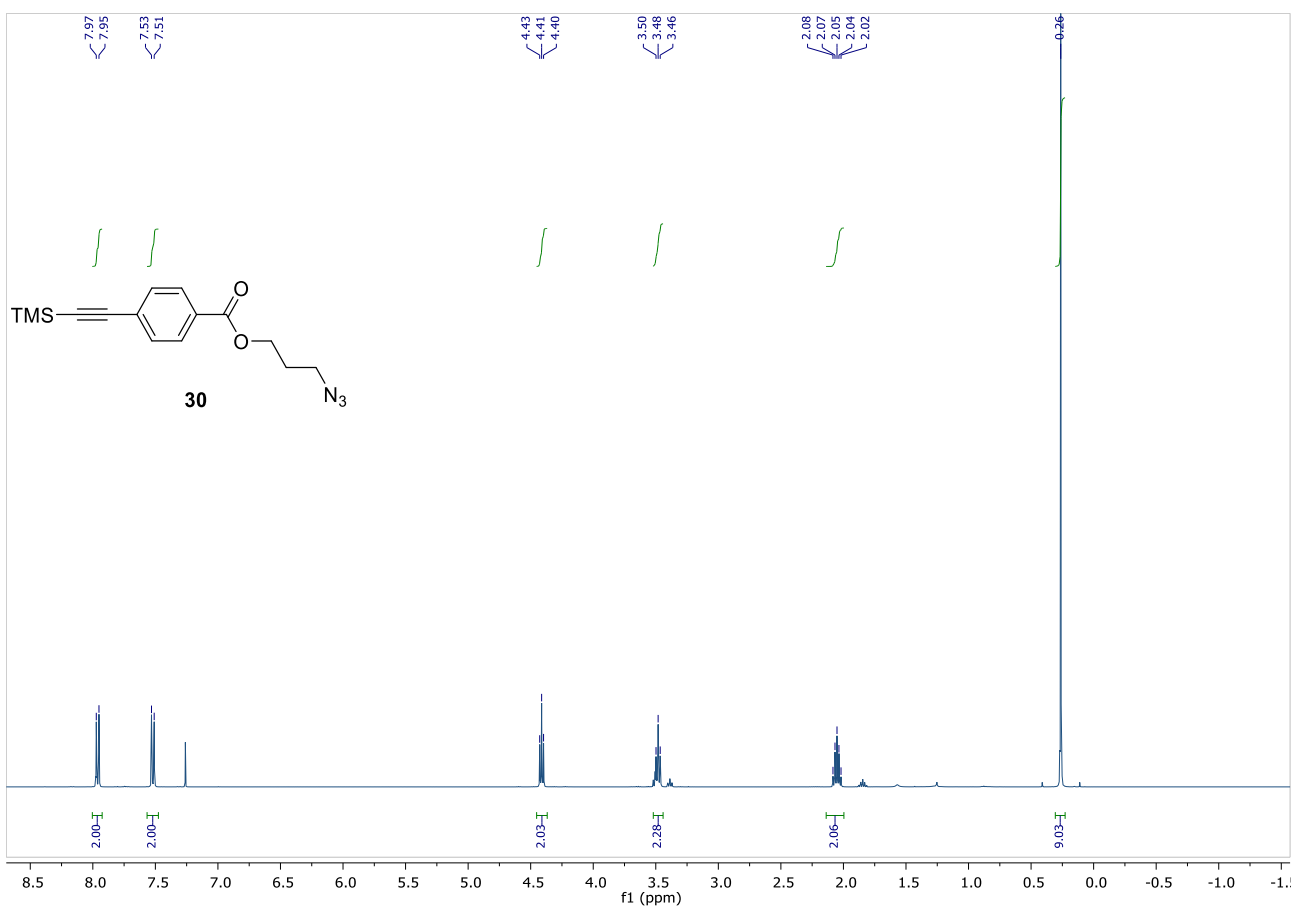
¹H-NMR (400 MHz, Chloroform-*d*)



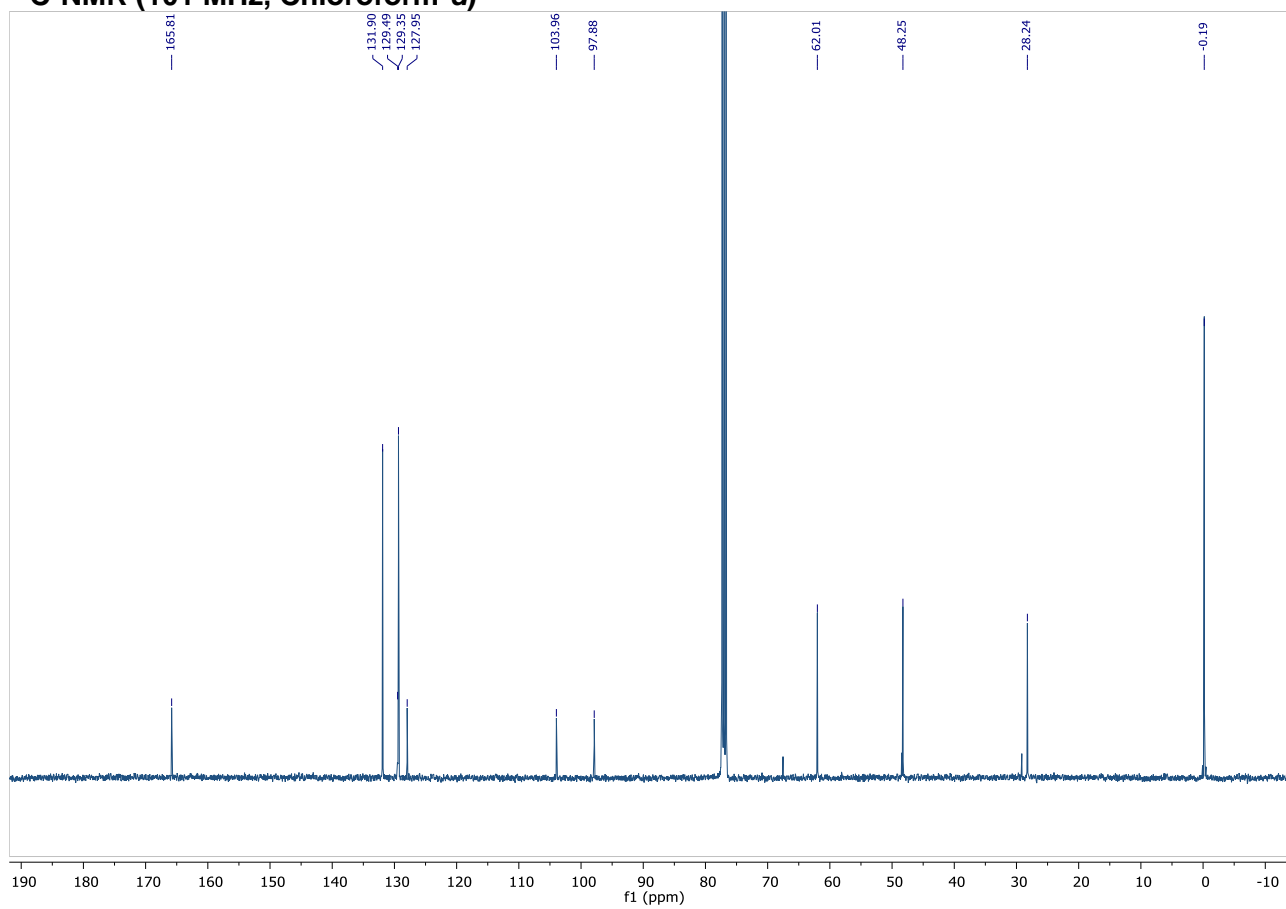
¹³C-NMR (101 MHz, Chloroform-*d*)



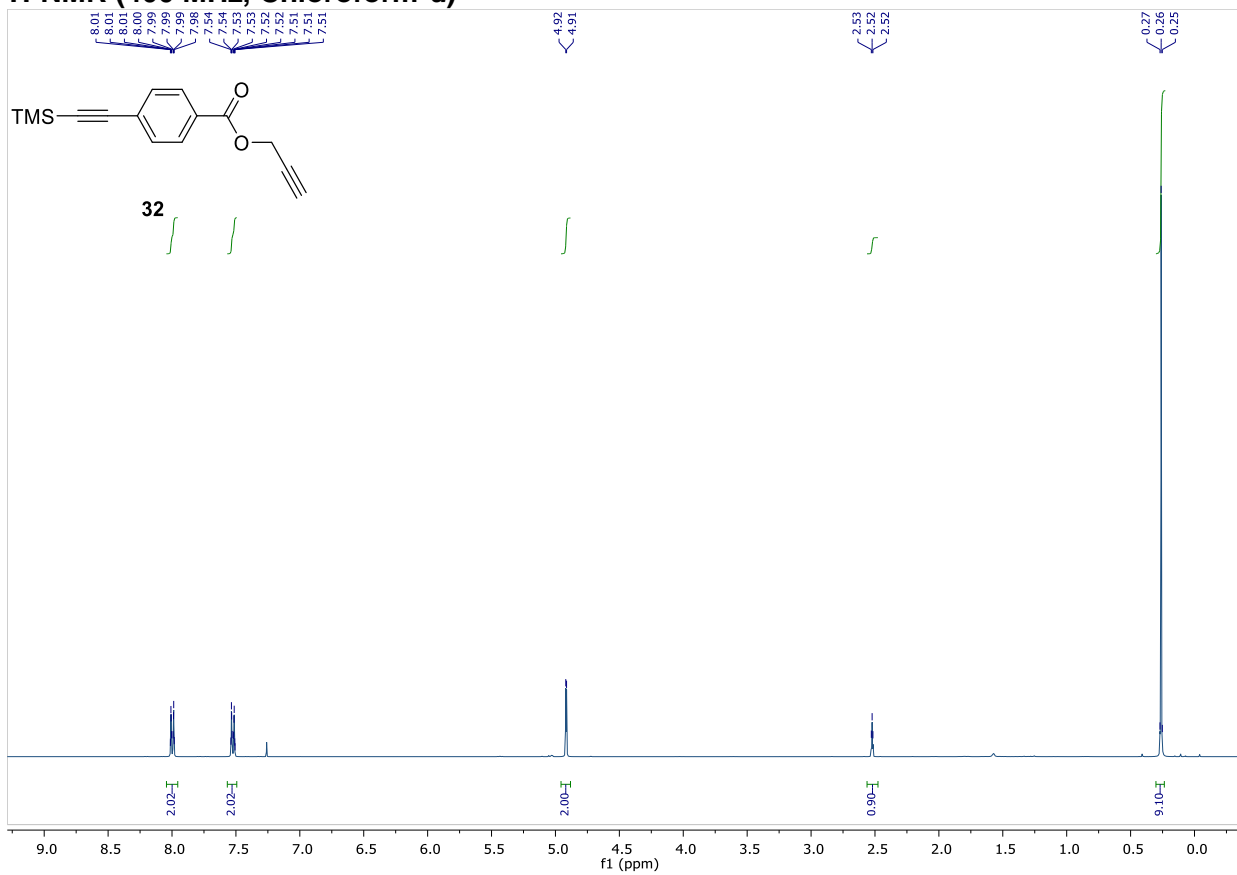
¹H-NMR (400 MHz, Chloroform-*d*)



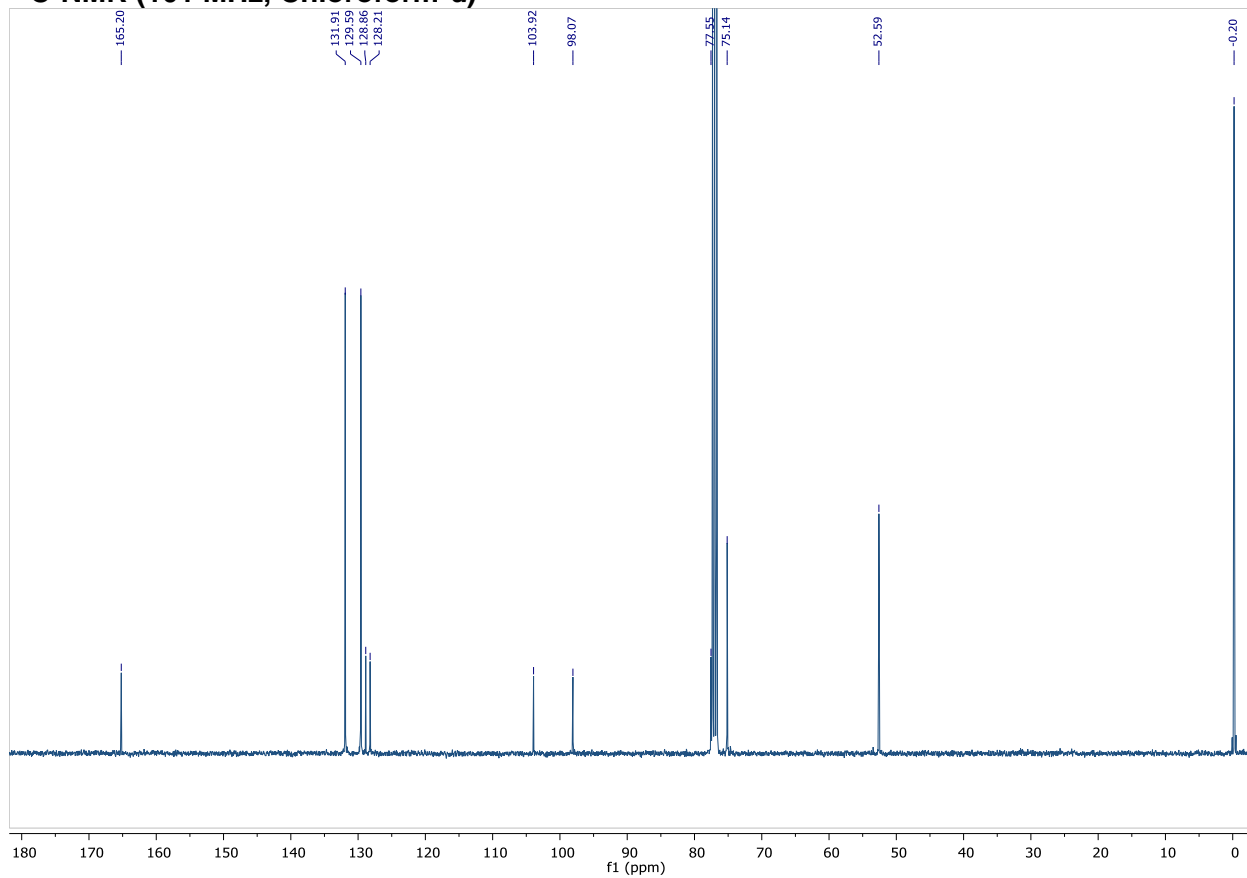
¹³C-NMR (101 MHz, Chloroform-*d*)



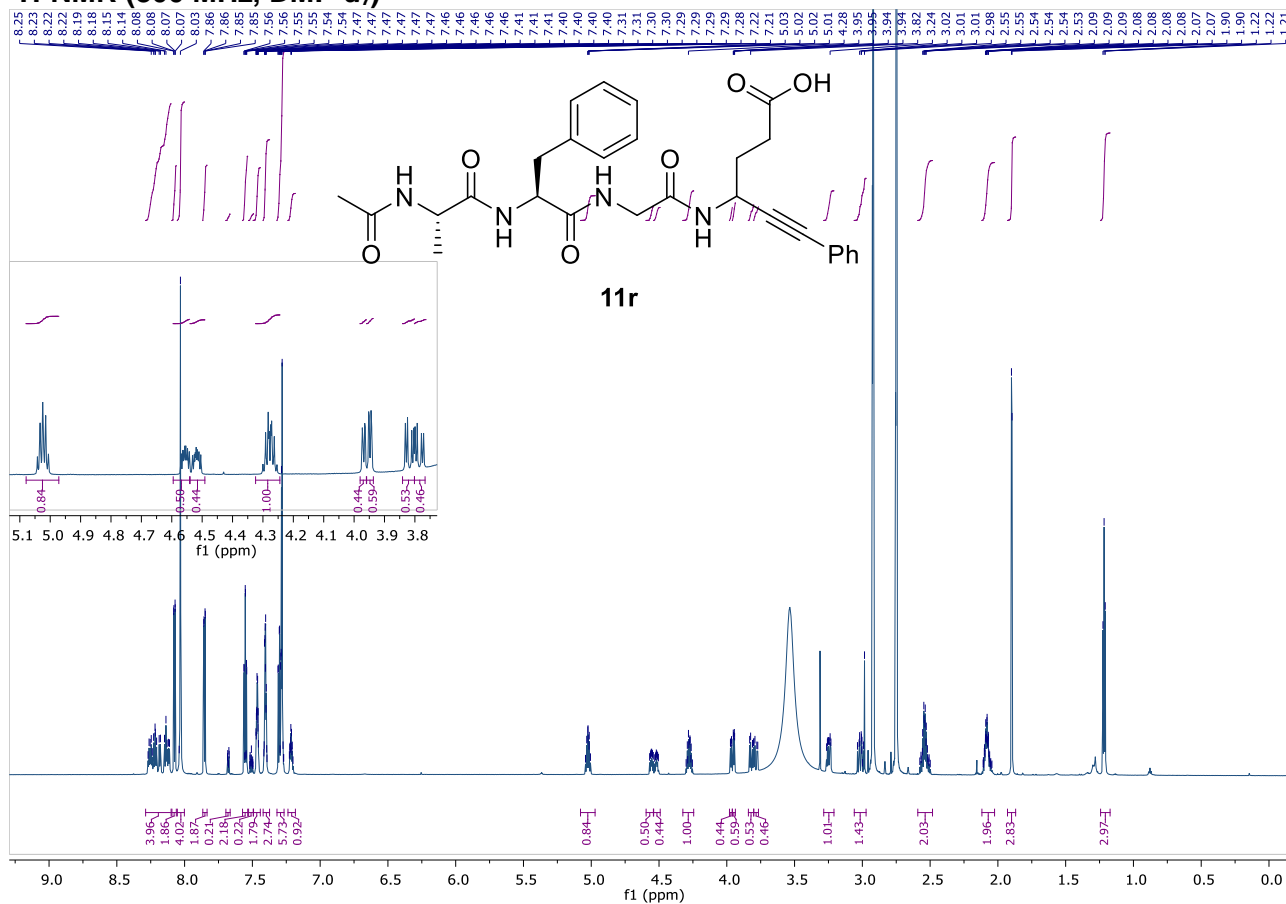
¹H-NMR (400 MHz, Chloroform-*d*)



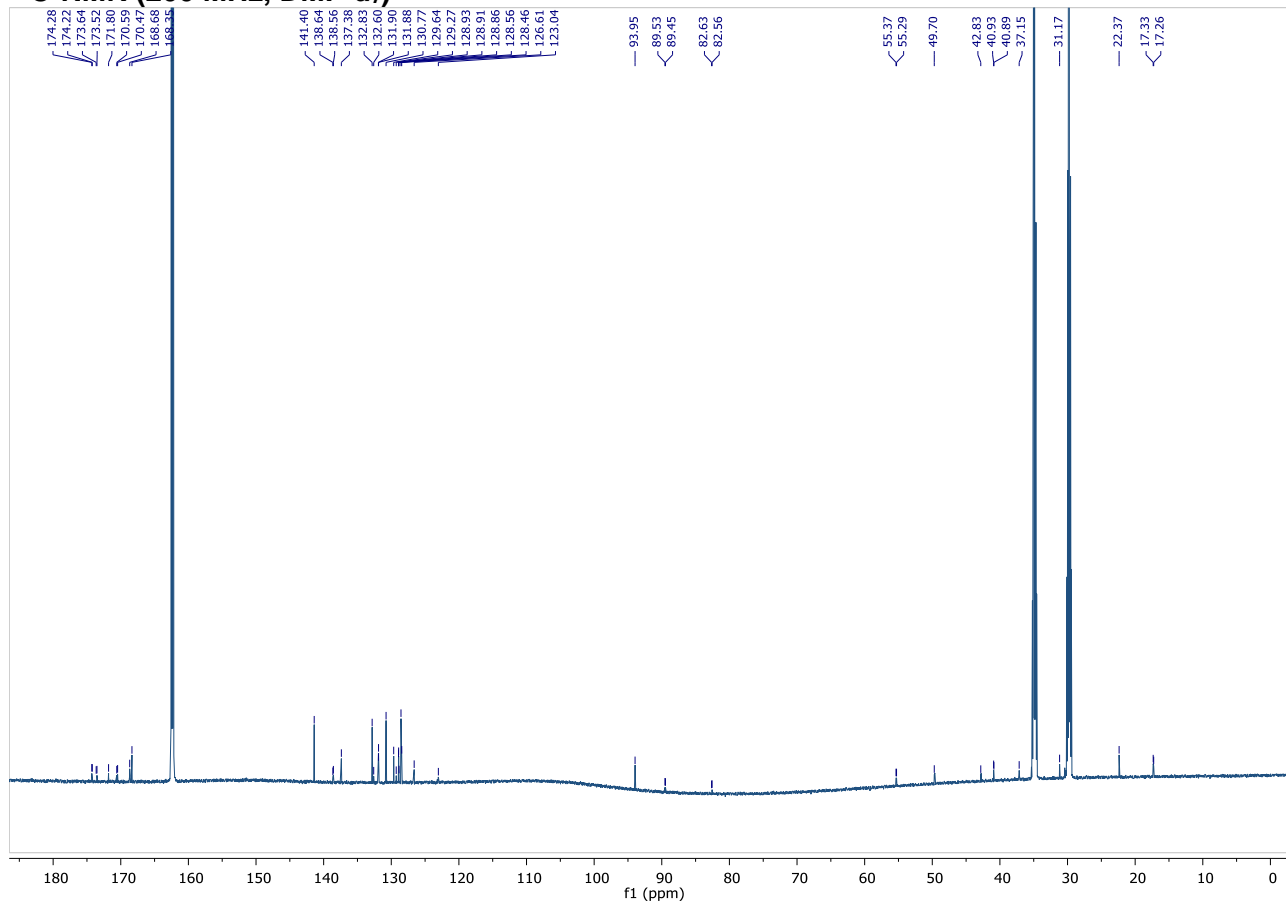
¹³C-NMR (101 MHz, Chloroform-*d*)



¹H-NMR (800 MHz, DMF-d₇)



¹³C-NMR (200 MHz, DMF-d₇)



HMBC (DMF-d₇)

