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Small peptide diversification through photoredox-catalyzed oxidative C-terminal modification†

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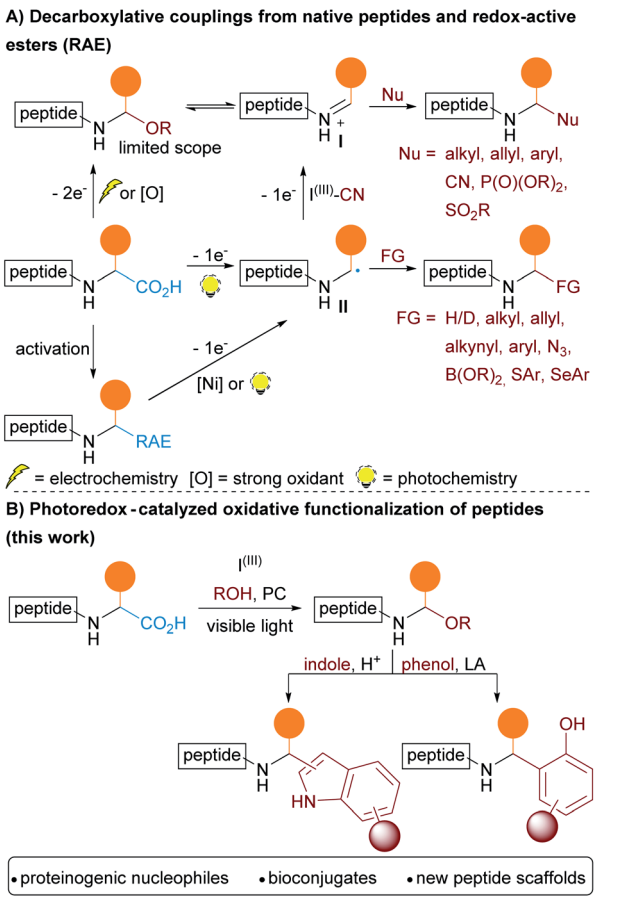
A photoredox-catalyzed oxidative decarboxylative coupling of small peptides is reported, giving access to a variety of *N*,*O*-acetals. They were used as intermediates for the addition of phenols and indoles, leading to novel peptide scaffolds and bioconjugates. Amino acids with nucleophilic side chains, such as serine, threonine, tyrosine and tryptophan, could also be used as partners to access tri- and tetrapeptide derivatives with non-natural cross-linking.

1. Introduction

Bioactive peptides have gained a lot of attention in the past decade as therapeutic compounds interacting with receptors or inhibiting protein–protein interactions. The biological activity and metabolic stability of native peptides is usually improved by the introduction of unnatural amino-acids (UAA) and rigidifying elements.[1] Moreover bioconjugation between peptides and other types of synthetic or natural bioactive molecules opens access to a broader chemical space. This is particularly interesting for drug discovery as it allows combining the best of two worlds, such as the higher target affinity of peptides and the better membrane permeability of small non polar synthetic compounds.[2] This strategy can be used to finely tune the pharmacological properties of drugs.[3] With the ambition to develop an efficient method for the structural diversification of peptides, we were interested in the functionalization of the C-termini of peptides, which can have a fundamental influence on their bioactivity.[4] In addition, as the C-terminus is unique and free in most peptides, such an approach would be at the same time general and selective. Most methods for the modification of native peptides rely on the specific reactivity of nucleophilic residues present in amino acids such as cysteine and lysine, and examples of functionalization of the C-terminus remain scarce.[5]

Recently, decarboxylative coupling has emerged as a method of choice to reach this goal, either *via* one or two-electron processes (Scheme 1A). Concerning the latter, the oxidative decarboxylative conversion of carboxylic acids to alcohols under electrochemical conditions was already reported by Hofer and Moest in 1902.[6] Seebach and coworkers later applied this method to amino acids and small peptides.[7] In the presence of methanol or acetic acid, *N*,*O*-acetals were generated. Activation of the *N*,*O*-acetals to give versatile *N*-acyliminium intermediates **I**[8] then allowed the addition of different nucleophiles (Grignard



Scheme 1 (A) Decarboxylative functionalization of peptides; (B) our photoredox strategy for the synthesis of bioconjugates.

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reagents, phosphites, allylsilanes, terminal alkyne or TMSCN). In 2020, the Malins group reported an extension of this approach to more complex peptides for the total synthesis of analogues of Biseokeaniamides A–C.[9]

The formation of *N*,*O*-acetals could also be achieved using chemical oxidants, in particular hypervalent iodine reagents. The Suárez group investigated the decarboxylative hydroxylation of proline derivatives under visible light using phenyliodine(III) diacetate (PIDA) as oxidant.[10] The strategy was later used by Kita and coworkers on non-cyclic amino-acids, but using heating instead of light to initiate the oxidation step.[11] This method, often coupled with *in situ* functionalization of the acetals, was then applied to amino acids and small peptides.[12]

The advent of photoredox catalysis contributed to the development of new strategies for bioconjugation *via* one–electron processes (Scheme 1A).[13] Starting from native peptides, C-terminal decarboxylative arylation,[14] reduction,[15] allylation,[16] alkynylation,[17] cyanation,[18] azidation[19] and Giese coupling[20] have been described. Decarboxylative coupling reactions can alternatively be performed by activation of the carboxylic acid *via* the formation of a redox-active ester (RAE). Single Electron Transfer (SET) from a metal complex or from a photocatalyst then induces the decarboxylation.[13d] Using nickel complexes, the Baran group elegantly functionalized peptides through decarboxylative alkylation,[21] alkenylation,[22] alkynylation,[23] Giese coupling[24] and borylation.[25] Moreover, photoredox catalyzed decarboxylative arylation,[26] thio-[27] and selenoarylation[28] were also reported. The generation of an α-aminyl radical intermediate **II** was involved in all these processes. However, in the case of the cyanation methodology involving a hypervalent iodine reagent, computation indicated that the radical was further oxidized to form an iminium intermediate, constituting one of the rare cases of two-electron oxidation under photoredox catalysis.[18]

Decarboxylative photoredox catalyzed C–O bonds formation has been described only in a few examples of protected amino acids, and is often associated with overoxidation to give amides.[29] To the best of our knowledge, the generation of peptide derived *N*,*O*-acetals from free carboxylic acids has never been reported using photoredox conditions. When considering that photocatalysis can proceed under milder conditions (room temperature, visible light, weaker oxidants) and requires less technical know-how than electrochemistry, such a method would be highly useful for synthetic and medicinal chemists requiring modified peptides. Furthermore, the method would be complementary to existing one-electron approaches: functional group tolerance would be lower, but access to versatile iminium intermediates would allow extensive diversification of the products with nucleophiles, leading to different types of bond formations.

Herein, we report a photoredox catalyzed oxidative-decarboxylative coupling of small peptides (Scheme 1B). This methodology allowed the synthesis of modified peptides with *N*,*O*-acetals at the C-terminus, which served as intermediates to introduce phenols and indoles *via* Friedel–Crafts reactions. The scope of nucleophiles included alcohols and electron-rich aromatic residues present in natural amino acids such as serine, threonine, tyrosine and tryptophan, giving access to new types of peptide cross-linking for the synthesis of non-natural tri- and tetrapeptides.

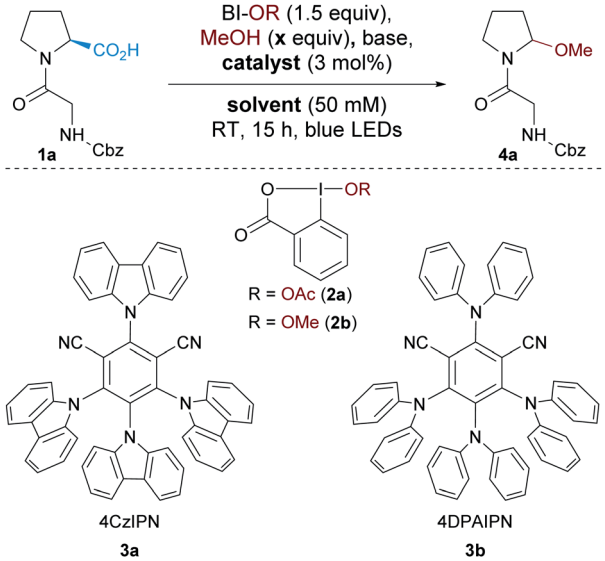
2. Results and discussions

2.1. Discovery and optimization of the reaction

We started our study by exploring the oxidative decarboxylation of Cbz–Gly–Pro (**1a**) in presence of methanol as the model reaction (Table 1). The hypervalent iodine reagent acetoxybenziodoxolone (BI-OAc, **2a**) was selected as oxidant for the optimization, due to its recent success in oxidative decarboxylative reactions.[30]

Based on our work on the alkynylation of peptides using organic photoredox catalysts,[17] 4CzIPN (2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile, **3a**) was selected as photocatalyst and K_2HPO_4 as base. To our delight the desired

Table 1 Optimization of the oxidative decarboxylation of dipeptides



Entry	Solvent	Catalyst	*x*	Base (2 equiv.)	HPLC yield[a] (%)
1[b]	DMF	4CzIPN (**3a**)	50	K_2HPO_4	46 (18)[c]
2[b]	DMF	$Ru(bpy)_3Cl_2$	50	K_2HPO_4	59
3[b]	DMF	$Ru(bpy)_3Cl_2$	10	K_2HPO_4	78
4	DMF	$Ru(bpy)_3Cl_2$	10	K_2HPO_4	82
5	DMF	$Ru(bpy)_3Cl_2$	5	K_2HPO_4	>95
6	DMF	$Ru(bpy)_3Cl_2$	2	K_2HPO_4	>95
7	DMF	Eosin Y	5	K_2HPO_4	17
8[d]	DMF	Rhodamine B	5	K_2HPO_4	27
9[d]	DMF	Rose bengal	5	K_2HPO_4	35
10[d]	DMF	4DPAIPN (**3b**)	5	K_2HPO_4	45
11	MeCN	$Ru(bpy)_3Cl_2$	5	K_2HPO_4	>95
12	**MeCN**	**$Ru(bpy)_3Cl_2$**	**5**	**None**	**>95 (68)[c]**
13	**DCE**	**$Ru(bpy)_3Cl_2$**	**5**	**None**	**>95**
14[e]	**MeCN**	**$Ru(bpy)_3Cl_2$**	**0**	**None**	**>95 (75)[c]**

[a] Ratio of integration at 214 nm by RP-HPLC. [b] Concentration 10 mM. [c] Isolated yield on 0.3 mmol. [d] Green LEDs. [e] BI-OMe (**2b**) instead of BI-OAc (**2a**).

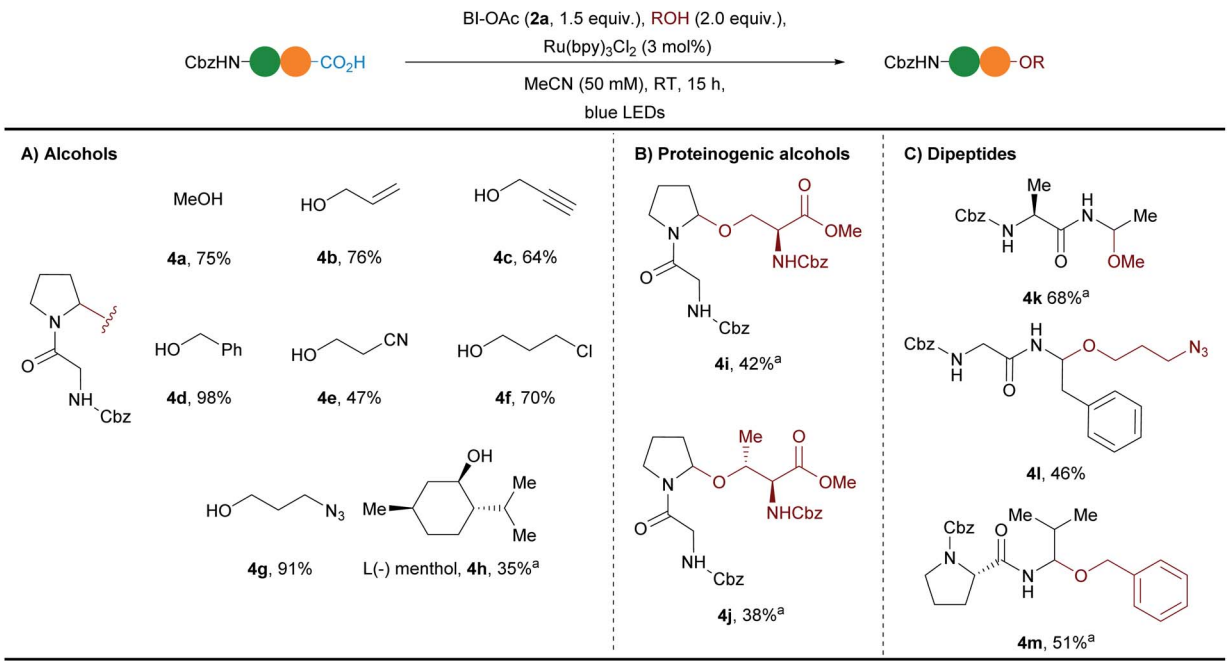
methanol *N*,*O*-acetal **4a** was formed with 50 equivalents of MeOH in DMF in 46% HPLC yield and 18% isolated yield (entry 1). Changing the photocatalyst to $Ru(bpy)_3Cl_2$ slightly increased the yield (entry 2).[31] Decreasing the amount of MeOH in the reaction mixture and increasing the concentration had a beneficial impact on the yield (entries 3 and 4). Full conversion was observed with either 5 or 2 equivalents of methanol (entries 5 and 6). For practical reasons, 5 equivalents of methanol were employed for the rest of the optimization, but 2 equivalents only of alcohols will be used during the investigation of the scope of the reaction.

With those conditions in hand we decided to screen some organic dyes to accomplish a metal-free process. We thus selected organophotocatalysts with similar oxidative properties in the excited state as $Ru(bpy)_3Cl_2$ ($Ru^{II}*/Ru^{I}$: +0.77 V *vs.* SCE).[32] However, neither Eosin Y (EY*/EY$^{\bullet-}$: +0.83 V *vs.* SCE),[33] rhodamine B (RhB*/RhB$^{\bullet-}$: +0.84 V *vs.* SCE)[34] nor rose bengal (RB*/RB$^{\bullet-}$: +0.81 V *vs.* SCE)[34] were suitable for the transformation and degradation of the dyes was observed (entries 7–9). Similarly, despite its promising redox properties, 4DPAIPN (2,4,5,6-tetrakis(diphenylamino)isophthalonitrile, **3b**) (4DPAIN*/4DPAIN$^{\bullet-}$: 0.90 V *vs.* SCE)[17] only afforded the desired product in 45% yield (entry 10). Unfortunately DMF was not a suitable solvent for further functionalization of the *N*,*O*-acetals. Based on the reported use of *N*,*O*-acetals to generate *N*-acyliminiums in MeCN,[35] we tested this solvent and full and clean conversion was observed (entry 11). A control experiment without base was attempted and full conversion to product **4a** was also observed (entry 12). Under these conditions, *N*,*O*-acetal **4a** could be isolated in 68% yield on a 0.3 mmol scale. A similar result was obtained in DCE (entry 13). Interestingly, the reaction was also working with methoxybenziodoxolone (BI-OMe, **2b**) and the corresponding *N*,*O*-acetal **4a** was obtained in 75% isolated yield (entry 14). A slightly higher yield was obtained with **2b** but the necessity to pre-form the hypervalent iodine reagent prior to the reaction is not desirable for more complex alcohols. Finally, control experiments were carried out and only traces of the desired product were observed in the absence of light or catalyst.

2.2. Scope of the oxidative decarboxylation reaction

A robustness test with different protected amino acids present in the reaction mixture showed a moderate functional group tolerance,[36] setting the basis for the investigation of the scope (Scheme 2). Previous works based on electrochemistry or chemical oxidation had focused mostly on the incorporation of simple alcohols as solvents.[7] Our method was already efficient with only two equivalents of methanol, as well as allyl, propargyl and benzyl alcohols, to give *N*,*O*-acetals **4b–d** in 64–98% yield (Scheme 2A). Functional groups such as cyanide, chloride and azide were well tolerated and the corresponding *N*,*O*-acetals **4e–g** were obtained in 47–91% yield. The introduction of bio-orthogonal terminal alkyne or azido groups is highly valuable as it allows to further functionalize the products. The more sterically hindered secondary alcohol (L)-menthol gave the *N*,*O*-acetal **4h** in 35% yield.

The method could be extended to the alcohol-containing amino acids serine and threonine allowing to access a new type of cross-linked peptides **4i** and **4j** in 42% and 38% yield, respectively (Scheme 2B). Finally the conditions were successfully applied to other dipeptides (Cbz–Ala–Ala (**1b**), Cbz–Gly–Phe (**1c**) and Cbz–Pro–Val (**1d**)) with various alcohols and the



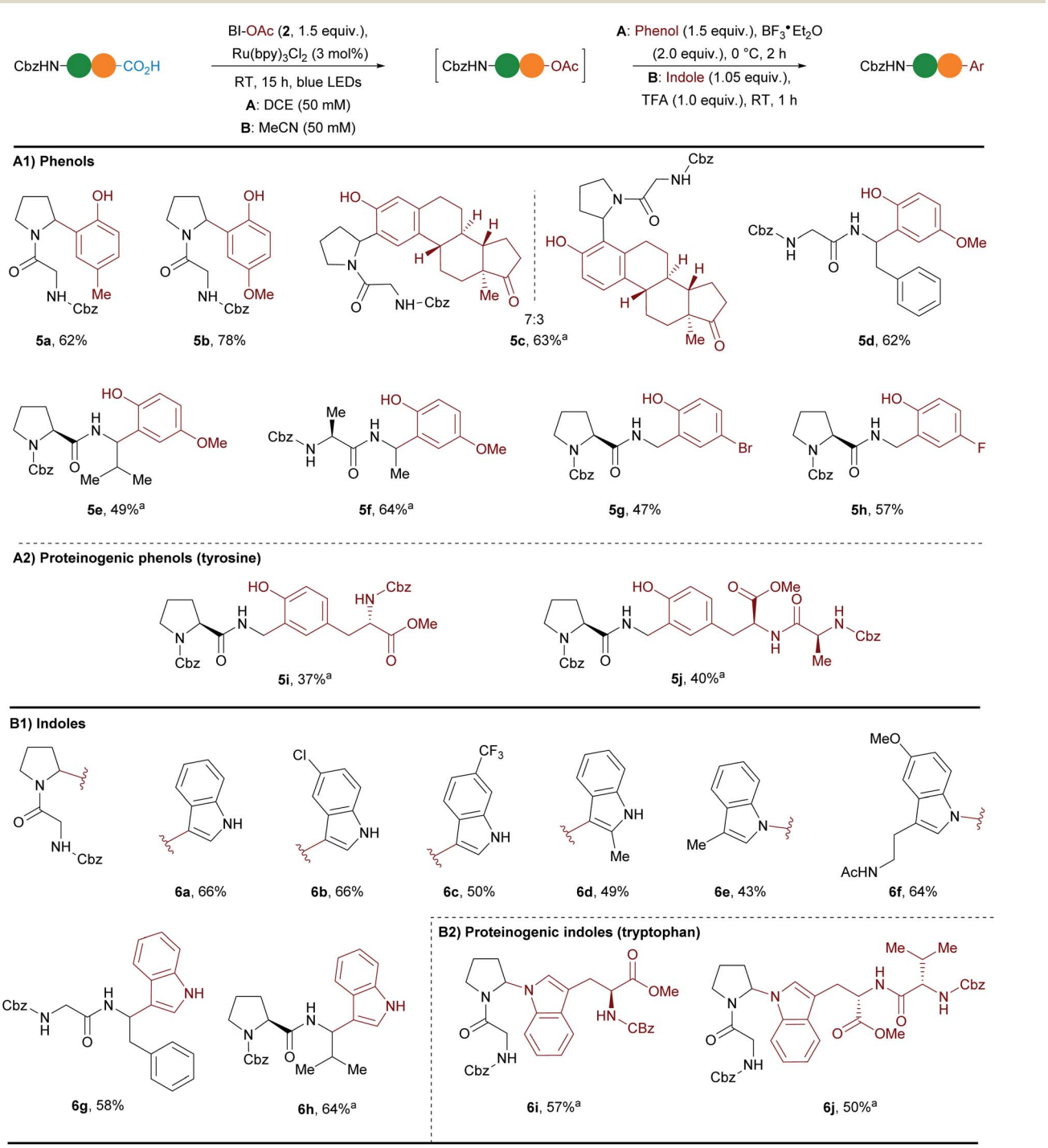
Scheme 2 Scope of obtained *N*,*O*-acetals. Reactions performed on 0.3 mmol scale. Yields of isolated products are given. [a]Compound obtained with a low diastereoselectivity that could not be determined exactly due to the presence of rotamers.

N,*O*-acetals **4k–m** were formed in 46–68% yields as mixtures of diastereoisomers in the case of **4k** and **4m** (Scheme 2C).

2.3. Functionalization of the *N*,*O*-acetals

During our studies on the formation of *N*,*O*-acetals we observed that in absence of alcohol the reaction was still taking place and *N*,*O*Ac-acetals were generated. As we could not isolate these compounds, we wondered whether we could take advantage of their reactivity for the direct reaction with nucleophiles (Scheme 3).

Based on the report of White and coworkers,[37] we examined the addition of *p*-cresol in presence of $BF_3 \cdot Et_2O$ as Lewis acid. While only degradation was observed in MeCN, we were pleased to observe full conversion of Cbz–Gly–Pro (**1a**) to Friedel–Crafts product **5a** in DCE (Scheme 3A(1), conditions A). After the one-pot two steps procedure **5a** could be obtained in 62% yield with

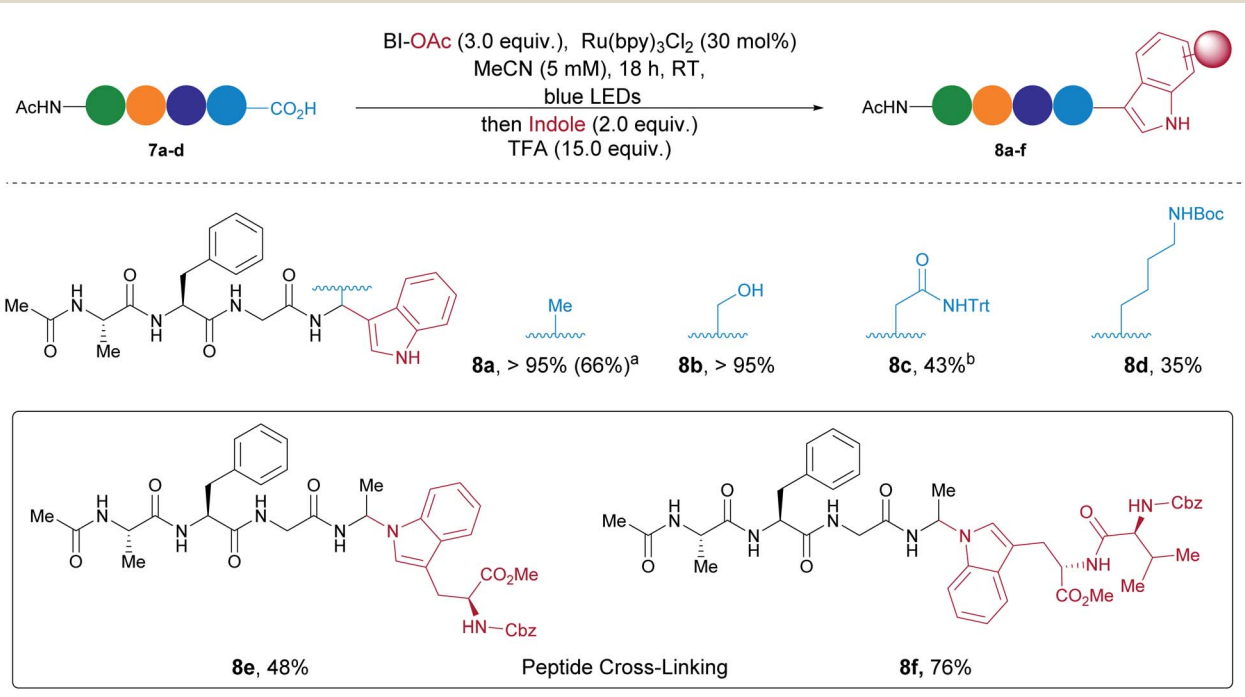


Scheme 3 Scope of the one-pot arylation of dipeptides with phenols and indoles. Reactions performed on 0.3 mmol scale. Yields of isolated products are given. [a]Compound obtained with a low diastereoselectivity that could not be determined exactly due to the presence of rotamers.

complete selectivity for the *ortho* position. Similarly, electron-rich *para*-methoxyphenol could be added to give **5b** in 78% yield. Estrone was also compatible with the reaction conditions: a 7 : 3 mixture of two regioisomers of **5c** was obtained in 63% yield with a preference for the position in *para* to the alkyl donating group. *Para*-methoxyphenol was successfully employed for the arylation of other dipeptides (Cbz–Gly–Phe (**1c**), Cbz–Pro–Val (**1d**) and Cbz–Ala–Ala (**1b**)) to give products **5d–f** in 49–64% yield. Cbz–Pro–Gly (**1e**) could also be arylated at the C-terminal position. Electron-withdrawing groups such as bromine and fluorine were tolerated on the phenol with this more reactive iminium and the corresponding products **5g** and **5h** were obtained in 47% and 57% yield respectively. To our delight phenols in tyrosine were compatible with our method (Scheme 3A(2)). The addition of Cbz–Tyr–OMe and Cbz–Ala–Tyr–OMe led to the formation of unprecedented unnatural tri- and tetrapeptides **5i** and **5j** in 37% and 40% yield respectively.

We were then interested in adding indoles, which are also proteinogenic nucleophiles present in tryptophan. Wang and coworkers recently reported an asymmetric Friedel–Crafts reaction between indoles and *N*-acyl iminiums generated *in situ* by decarboxylation of RAE derived from amino acids.[38] However, this transformation was not extended to peptides and prefunctionalization of the carboxylic acids was needed. Inspired by conditions reported by our group,[35] a one-pot two steps arylation procedure directly from free carboxylic acids was developed using a slight excess of indoles and one equivalent of TFA (Scheme 3B(1), conditions B). Using Cbz–Gly–Pro (**1a**) as model substrate several indoles reacted preferentially at the C3-position. 1*H*-indole afforded **6a** in 66% yield. A chlorine substituent in C6 position and a trifluoromethyl substituent in C7 position were tolerated and led to the formation of the desired products **6b** and **6c** in 66% and 50% yield respectively. 2-Methylindole could be introduced in 49% yield onto dipeptide **1a**. When C3-substituted indoles were employed, N-addition was the major outcome. For instance, 3-methylindole led to the formation of **6e** in 43% yield. C2-addition was also detected in the crude mixture (ratio N/C2-addition 2 : 1), but the corresponding product could not be isolated in pure form. Interestingly, melatonin, which is a hormone helping to regulate the sleep–wake cycle and which can be used for short-term treatment of insomnia, was compatible with the reaction conditions. Product **6f** was obtained in 64% yield. Cbz–Gly–Phe (**1c**) and Cbz–Pro–Val (**1d**) could also be arylated with 1*H*-indole and the corresponding products **6g** and **6h** were obtained in 58% and 64% yields respectively. The tryptophan indoles of Cbz–Trp–OMe and Cbz–Val–Trp–OMe reacted *via* C–N bond formation to give the unprecedented unnatural tri- and tetrapeptides **6i** and **6j** in 57% and 50% yield respectively (Scheme 3B(2)).

Finally, we investigate the extension of our methodology to larger peptides (Scheme 4). Ac–Ala–Phe–Gly–Ala (**7a**) was selected as model substrate. By increasing the amount of oxidant and photocatalyst, indole could be added successfully to **7a**. The desired modified tetrapeptide **8a** was the only product observed by HPLC and was obtained in 66% yield (See ESI† for more details). Serine was also tolerated at the C-terminus and full conversion towards **8b** was observed. A protected amide from asparagine and a protected amine from lysine were moderately tolerated leading to products **8c** and **8d**. Moreover, more complex unnatural peptides could be obtained



Scheme 4 Preliminary results towards arylation of tetrapeptides. Reactions performed on 1 μmol scale. Relative HPLC ratios of the area of the product over remaining starting material and peptide side-products at 214 nm are given. Average of 3 independent trials. [a]Calibrated yield, see SI for details. [b]Compound **8c** could not be fully separated from a side product by HPLC.

by reaction with proteinogenic indoles from Cbz–Trp–OMe and Cbz–Val–Trp–OMe. For instance **8e** and **8f** were formed in moderate to good HPLC ratios. Protected aspartic acid, histidine and arginine were also submitted to the reaction conditions and led to the formation of arylated peptides but with lower HPLC ratios (<25%, see SI for more details).[39] Unfortunately, the current conditions for phenols were not compatible with tetramers and would require further optimization .

3. Conclusion

In summary, we have developed a photoredox-catalyzed oxidative decarboxylative strategy towards the introduction of diverse functional groups on peptides. Under the developed conditions, valuable alcohols were successfully introduced leading to structurally diverse *N*,*O*-acetals. Moreover, the *N*,*O*-acetals were also employed as key reactive intermediates for arylation with phenols and indoles. Bioconjugation of bioactive compounds such as estrone or melatonin with dipeptides was possible. Additionally, serine, threonine, tyrosine and tryptophan derivatives could be used as nucleophilic partners to give new types of cross-linked peptides. As a proof of concept for the arylation of larger peptides, indole and two tryptophan derivatives were successfully added to several tetrapeptides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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39 A mass corresponding to an enamide obtained from deprotonation of the iminium intermediate was often observed in case of lower yields, but further studies will be needed to confirm this structural assignment and to identify other side products.

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1. General methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless for the oxidative decarboxylation and if stated otherwise. For flash chromatography, distilled technical grade solvents were used. THF, CH_3CN, toluene and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, TCI, Merck or Bachem and used as such unless stated otherwise. All dipeptides starting materials 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 and $KMnO_4$ stain. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d^6 or acetonitrile-d^3, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal acetonitrile signal at 1.94 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).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d^6 or acetonitrile-d^3, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal acetonitrile signals at 1.32 and 118.26 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 5µl. 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), which were hold using a rack for test tubes placed at the center of a crystallization flask. 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 approximatively 2 cm for the test tubes

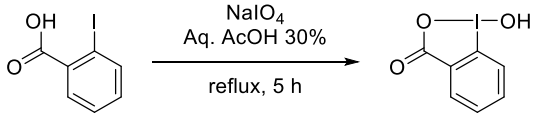
and 5 cm for the Schlenk flasks. Long irradiation resulted in temperature increasing up to 37°C during overnight reactions.

Tetramers peptides were synthesized by solid phase peptide synthesis using a Multipep 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 µm). 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. The column temperature was set up to 25 °C. Low resolution mass spectrometric measurements were acquired using the following parameters: positive electrospray 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.

2. Preparation of reagents and catalysts

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (10)

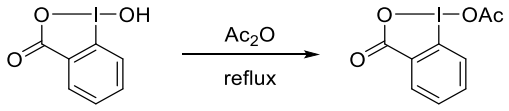


9 **10**

Following a reported procedure,[1] $NaIO_4$ (40.5 g, 189 mmol, 1.05 equiv) and 2-iodobenzoic acid (**9**) (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 (**10**) (44.3 g, 168 mmol, 93%) as a white solid.

^{1}H 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*). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. The values of the NMR spectra are in accordance with reported literature data.[1]

1-Acetoxy-1,2-benziodoxol-3-(1H)-one (BI-OAc, 2)

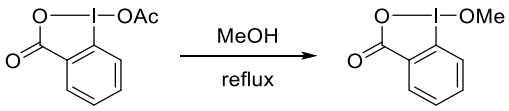


10 **2**

Following a reported procedure,[2] 1-hydroxy-1,2-benziodoxol-3-(1H)-one (**10**, 10.3 g, 39.1 mmol, 1.00 equiv) was suspended in acetic anhydride (35 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording **2** (10.8 g, 35.3 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (dd, 1H, J = 7.6, 1.6 Hz, Ar*H*), 8.00 (dd, 1H, J = 8.3, 1.0 Hz, Ar*H*), 7.92 (ddd, 1H, J = 8.4, 7.2, 1.6 Hz, Ar*H*), 7.71 (td, 1H, J = 7.3, 1.1 Hz, Ar*H*), 2.25 (s, 3H, COCH_3). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[2]

1-Metoxy-1,2-benziodoxol-3-(1H)-one (BI-OMe, 2b)

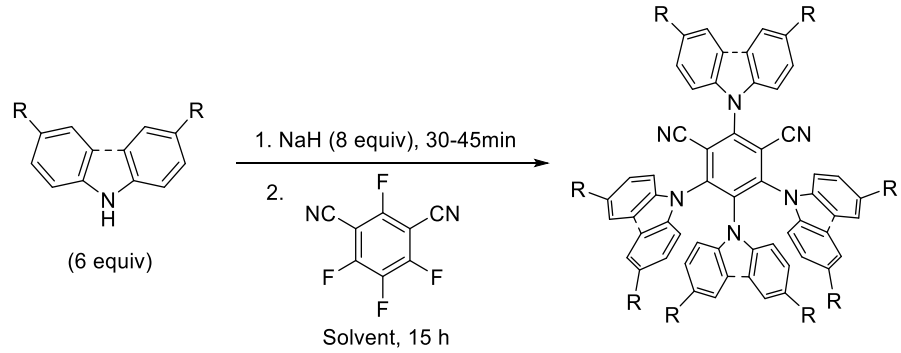


2 **11**

Following a reported procedure,[3] BI-OAc (**2a**, 1.0 g, 3.3 mmol, 1.0 equiv) was refluxed in MeOH (10 mL) for 15 min until a clear, colorless solution was obtained. The mixture was cooled to room temperature and then to -20°C. The precipitate was filtered, washed with a minimal amount of MeOH, and dried under vacuum. BI-OMe **2b**(0.69 g, 2.5 mmol, 76%) was obtained as white crystals.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar*H*), 7.90 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, Ar*H*), 7.76 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar*H*), 7.69 (td, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 4.27 (s, 3H, O*Me*). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.1, 135.2, 133.0, 131.1, 130.7, 126.0, 118.6, 62.4. The values of the NMR spectra are in accordance with reported literature data.[3]

Preparation of catalysts



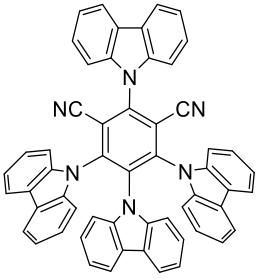
General procedure 1:

Sodium hydride (60% suspension in mineral oil, 8.0 equiv) was added slowly to a stirred solution of substituted-carbazole (5.0 equiv) in dry THF (0.05 M) under a nitrogen atmosphere at RT. After 30 min, 2,4,5,6-tetrafluoroisophthalonitrile (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/CH_2Cl_2 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 (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 (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/CH_2Cl_2 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.

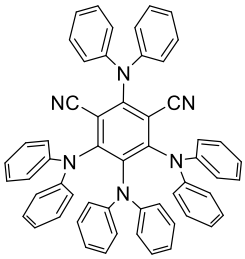
2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN, 3a)



Following the general procedure 1 and starting from 9H-carbazole **12** (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 **13** (0.40 g, 2.0 mmol) in 40 mL of THF. Recrystallization (Hexanes/CH_2Cl_2 (1:1, 90 mL)) afforded the crude product as a yellow powder. Column chromatography afforded 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (**3a**) as a bright yellow crystalline solid (1.14 g, 1.45 mmol, 73 % yield).

Rf (Hexane/DCM 1/1) = 0.29. (yellow spot on TLC). ^{1}H 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*).^{13}C 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. The values of the NMR spectra are in accordance with reported literature data.[4]

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



Following the general procedure 2 and starting from diphenylamine **14** (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 **13** (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 (CH_2Cl_2/pentane (1:2)) gave 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (**3b**) as a yellow-orange crystalline solid (400 mg, 0.502 mmol, 50 % yield).

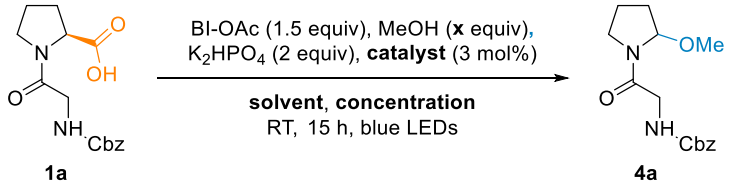
Rf (pentane/DCM 1:1): 0.3. (yellow spot on TLC). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.22 (m, 4H, Ar*H*), 7.12 – 7.05 (m, 12H, Ar*H*), 7.07 – 6.98 (m, 2H, Ar*H*), 6.96 – 6.84 (m, 8H, Ar*H*), 6.73 – 6.63 (m, 10H, Ar*H*), 6.56 (d, *J* = 7.4 Hz, 4H, Ar*H*). ^{13}C NMR (101 MHz, Chloroform-*d*) 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 $C_{56}H_{41}N_6^+$ 797.3387; Found 797.3375. The values of the NMR spectra are in accordance with reported literature data.[5]

3. Peptide synthesis

The used dipeptides were commercially available. 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/triisopropylsilane 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.

4. Optimization

4.1. Optimization of the oxidative decarboxylation



1a **4a**

Degassed solvent was added in a 10 mL test tube containing a teflon coated stirring bar, Z-Gly-Pro (**1a**) (31 mg, 0.10 mmol, 1.0 equiv), R-BX (**2**) (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:

The reaction was monitored by dilution of 50 μL of the crude with 950 μL of acetonitrile. The yield was estimated by the absorbance of product in comparison to the overall absorbance of product, unreacted starting material and side-products if any.

Procedure for isolated yields:

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by preparative TLC (DCM/ethyl acetate 7:3).

Table S1. Optimization of the oxidative decarboxylation on dipeptides

Entry	Solvent	Concentration (mM)	Catalyst	Base (equiv)	Alcohol (equiv)	HPLC yield (%)[a]
1	DMF	10	4CzIPN (**3a**)	K_2HPO_4 (2)	MeOH (50)	46
2	DMF	10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (50)	59
3	DMF	10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (10)	78
4	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (10)	82
5	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (5)	>95
6	DMF	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (2)	>95
7	DMF	50	Eosin Y	K_2HPO_4 (2)	MeOH (5)	17
8[b]	DMF	50	Rhodamine B	K_2HPO_4 (2)	MeOH (5)	27
9[b]	DMF	50	Rose Bengal	K_2HPO_4 (2)	MeOH (5)	35
10[b]	DMF	50	4DPAIPN (**3b**)	K_2HPO_4 (2)	MeOH (5)	45
11	MeCN	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2HPO_4 (2)	MeOH (5)	>95
12	MeCN	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	-	MeOH (5)	>95 (68)[c]
13	DCE	50	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	-	MeOH (5)	>95

[a] Ratio of integration at 214 nm by RP-HPLC, [b] green LEDs, [c] isolated yield.

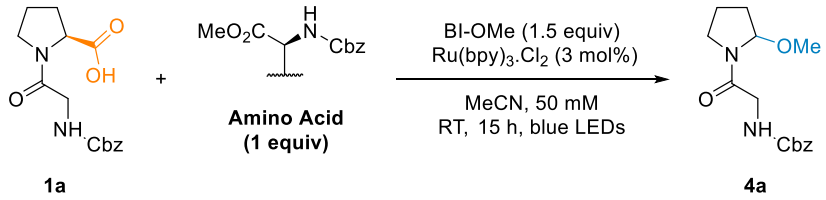
Control experiments were carried out and only traces of the desired product were observed in the absence of light or catalyst.

4.2. Robustness experiments

Degassed MeCN (2 mL) was added in a 5 mL test tube containing Cbz-Gly-Pro (**1a**) (31 mg, 0.10 mmol, 1.0 equiv), the protected amino acid (0.1 mmol, 1 equiv), BI-OMe (**2b**) (42 mg, 0.45 mmol, 1.5 equiv) and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.3 mg, 3.00 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

The reaction was monitored by dilution of 50 µL of the crude with 950 µL of acetonitrile. The yield was estimated by the absorbance of product in comparison to the overall absorbance of product, unreacted starting material and side-products if any.

Table S2. Robustness experiments



Entry	Amino acid (1 equiv)	HPLC yield (%)
1	Cbz-Met-OMe	15
2	Cbz-Ser-OMe	90[a]
3	Cbz-His-OMe	25
4	Cbz-Arg-OMe	>95
5	Cbz-Tyr-OMe	<5
6	Cbz-Trp-OMe	<5
7	Cbz-Gln-OMe	36
8	Cbz-Lys-OMe	<5
9	Cbz-Asp-OMe	>95
10	Cbz-Cys-OMe	62

[a] + 10% of Serine addition on Z-Gly-Pro (**x**).

5. Scope on dipeptides

General procedure 1 for the oxidative decarboxylation of dipeptides

Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), BI-OMe (**2b**) (125 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 2 for the oxidative decarboxylation of dipeptides

Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), BI-OAc (**2a**) (138 mg, 0.450 mmol, 1.50 equiv), the alcohol (0.60 mmol, 2.0 equiv) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 3 for the decarboxylative arylation of dipeptides

Degassed DCE (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), BI-OAc (**2a**) (138 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The phenol (0.45 mmol, 1.5 equiv) was added and the reaction mixture degassed by Ar bubbling before cooling at 0 °C. $BF_3.OEt_2$ (158 µL, 0.600 mmol, 2.00 equiv) was added dropwise and the mixture stirred for 2 h at 0 °C.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

General procedure 4 for the decarboxylative arylation of dipeptides

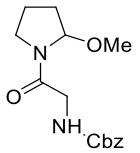
Degassed MeCN (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide (0.30 mmol, 1.0 equiv), BI-OAc (**2a**) (138 mg, 0.450 mmol, 1.50 equiv) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (6.8 mg, 9.0 µmol, 3 mol%) under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs for 15 h at RT.

A solution obtained by dilution of 50 µL of the crude with 950 µL of acetonitrile was injected into the HPLC to monitor the conversion of the starting material.

The indole (0.306 mmol, 1.02 equiv) was added and TFA (23 µL, 0.30 mmol, 1.0 equiv) was added dropwise and the mixture stirred for 1 h at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography DCM to DCM/ethyl acetate on triethylamine deactivated silica (5 vol% in DCM).

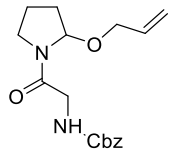
Benzyl (2-(2-methoxypyrrolidin-1-yl)-2-oxoethyl)carbamate (4a)



Following General Procedure 1 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv), **4a** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a pale yellow oil (66 mg, 0.23 mmol, 75%).

Rf (DCM/ethyl acetate 7:3): 0.3. ^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R^1/R^2)) δ 7.40-7.26 (m, 5H, Ar*H* (R^1+R^2)), 5.70 (s, 1H, N*H* (R^1+R^2)), 5.43 (d, *J* = 4.9 Hz, 0.5H, NC*H*COMe (R^1)), 5.12 (s, 2H, OCH_2Ph (R^1+R^2)), 4.96 (d, *J* = 4.5 Hz, 0.5H, NC*H*COMe (R^2)), 4.18-4.05 (m, 1H, NC(O)CH_2NHCbz (R^1)), 4.05-3.91 (m, 1H, NC(O)CH_2NHCbz (R^2)), 3.67 (ddd, *J* = 11.3, 8.4, 2.3 Hz, 0.5H, C(O)NCH_2 (R^1)), 3.58-3.48 (m, 0.5H, C(O)NCH_2 (R^2)), 3.38 (s, 1.5H, OCH_3 (R^1)), 3.43-3.32 (m, 1H, C(O)NCH_2 (R^1+R^2)), 3.31 (s, 1.5H, OCH_3 (R^2)), 2.24-1.66 (m, 4H, $NCH_2CH_2CH_2CH$ (R^1+R^2)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 168.3, 168.2, 156.2, 156.2, 136.4, 136.3, 128.4, 128.0, 127.9, 88.2, 87.5, 66.8, 66.8, 56.6, 54.2, 45.8, 44.8, 43.4, 42.9, 31.2, 30.7, 22.7, 20.7. IR (ν_{max}, cm^{-1}) 3324 (m), 2980 (m), 2886 (m), 2339 (w), 1718 (s), 1655 (s), 1520 (m), 1451 (m), 1246 (s), 1170 (m), 1055 (s), 914 (m), 826 (w), 741 (m), 699 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{20}N_2NaO_4^+$ 315.1315; Found 315.1315.

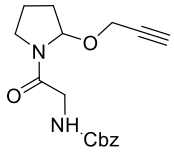
Benzyl (2-(2-(allyloxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4b)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and allyl alcohol (41 μL, 0.60 mmol, 2.0 equiv), **4b** was obtained after column chromatography DCM to DCM/ethyl acetate 9:1 as a pale yellow oil (73 mg, 0.23 mmol, 76%).

Rf (DCM/ethyl acetate 7:3): 0.35. ^{1}H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.42-7.27 (m, 5H, Ar*H* (major+minor)), 5.97-5.81 (m, 1H, CH_2CH=CH_2 (major+minor)), 5.72 (br s, 1H, N*H* (major+minor)), 5.56 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.37-5.20 (m, 1.2H, CH_2CH=CH_2 (major)), 5.17-5.06 (m, 3.2H, CH_2CH=CH_2 (minor), OCH_2Ph (major+minor) and C(O)NC*H* (minor)), 4.22-3.86 (m, 4H, CH_2CH=CH_2 and C(O)CH_2NHCbz (major+minor)), 3.68 (ddd, *J* = 11.3, 8.6, 2.0 Hz, 0.4H, C(O)NCH_2 (minor)), 3.57-3.48 (m, 0.6H, C(O)NCH_2 (major)), 3.44-3.25 (m, 1H, C(O)NCH_2 (major+minor)), 2.30-1.64 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 168.2, 168.1, 156.2, 156.2, 136.4, 136.4, 136.3, 134.7, 133.5, 128.4, 128.0, 127.9, 117.9, 116.6, 86.8, 86.1, 70.2, 68.0, 66.9, 66.8, 66.8, 45.9, 44.9, 43.4, 43.1, 31.7, 31.5, 22.8, 20.7. IR (v_{max}, cm^{-1}) 3331 (m), 2982 (m), 2898 (m), 1720 (s), 1657 (s), 1538 (m), 1451 (m), 1247 (s), 1171 (m), 1052 (s), 915 (m), 740 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_4^+$ 341.1472; Found 341.1476.

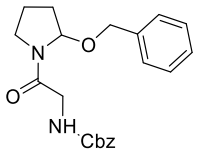
Benzyl (2-oxo-2-(2-(prop-2-yn-1-yloxy)pyrrolidin-1-yl)ethyl)carbamate (4c)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and propargyl alcohol (36 μL, 0.60 mmol, 2.0 equiv), **4c** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (61 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.33. ^{1}H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) *δ* 7.39-7.28 (m, 5H, Ar*H* (major+minor)), 5.69 (br s, 1H, N*H* (major+minor)), 5.66 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.31 (d, *J* = 4.1 Hz, 0.4H, C(O)NC*H*O (minor)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 4.30 (qd, *J* = 15.7, 2.4 Hz, 1.2H, OCH_2CCH (major)), 4.23-4.07 (m, 1.4H, OCH_2CCH (minor) and C(O)CH_2NHCbz (major)), 4.05-3.90 (m, 1.4H, C(O)CH_2NHCbz (major+minor)), 3.71-3.63 (m, 0.4H, C(O)NCH_2 (minor)), 3.53 (t, *J* = 8.8 Hz, 0.6H, C(O)NCH_2 (major)), 3.36 (dq, *J* = 27.4, 9.7, 8.7 Hz, 1H, C(O)NCH_2 (major+minor)), 2.58 (m, 0.4H, OCH_2CCH (minor)), 2.42 (t, *J* = 2.36 Hz, 0.6H, OCH_2CCH (major)), 2.30-1.70 (m, 4H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.7, 168.3, 156.4, 136.6, 136.5, 128.6, 128.2, 128.1, 86.3, 86.1, 80.3, 78.7, 75.9, 73.9, 67.1, 57.1, 54.5, 46.1, 45.1, 43.6, 43.5, 32.0, 31.5, 22.9, 20.8. IR (vmax, cm^{-1}) 3416 (w), 3299 (m), 2973 (w), 2889 (w), 2116 (w), 1720 (s), 1662 (s), 1524 (m), 1430 (s), 1254 (s), 1172 (m), 1058 (s), 911 (m), 737 (s), 700 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_4^+$ 339.1315; Found 339.1315.

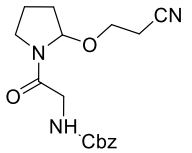
Benzyl (2-(2-(benzyloxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4d)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and benzyl alcohol (65 μL, 0.60 mmol, 2.0 equiv), **4d** was obtained after column chromatography DCM to DCM/ethyl acetate 20:1 as a pale yellow oil (108 mg, 0.293 mmol, 98%).

Rf (DCM/ethyl acetate 7:3): 0.41. ^{1}H NMR (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.40-7.27 (m, 10H, Ar*H* (major+minor)), 5.74-5.63 (m, 1.6H, N*H* (major+minor) and C(O)NC*H* (major)), 5.20 (d, *J* = 4.1 Hz, 0.4H, C(O)NC*H* (minor)), 5.13 (d, *J* = 2.5 Hz, 2H, C(O)OCH_2Ph (major+minor)), 4.70 (br s, 0.6H, NCHOCH_2Ph (major)), 4.67 (d, *J* = 3.0 Hz, 0.6H, NCHOCH_2Ph (major)), 4.56-4.46 (m, 0.8H, NCHOCH_2Ph (minor)), 4.09 (qd, *J* = 17.0, 4.6 Hz, 0.8H, C(O)CH_2NHCbz (minor)), 3.91 (m, 1.2H, C(O)CH_2NHCbz (major)), 3.74-3.65 (m, 0.4H, C(O)NCH_2 (minor)), 3.49 (t, *J* = 8.9 Hz, 0.6H, C(O)NCH_2 (major)), 3.41 (td, *J* = 11.2, 10.5, 7.0 Hz, 0.4H, C(O)NCH_2 (minor)), 3.31 (q, *J* = 9.6 Hz, 0.6H, C(O)NCH_2 (major)), 2.34-1.67 (m, 4H, NCH$_2$CH_2CH_2CH (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.3, 156.4, 156.3, 149.3, 141.0, 138.7, 137.0, 136.6, 136.5, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 87.2, 86.5, 71.3, 69.5, 67.1, 67.0, 65.5, 46.1, 45.0, 43.6, 43.3, 32.0, 31.7, 23.0, 21.0. IR (v_{max}, cm^{-1}) 3418 (w), 3329 (w), 2979 (w), 2881 (w), 1721 (s), 1659 (s), 1524 (m), 1452 (m), 1347 (w), 1253 (m), 1172 (m), 1107 (m), 1054 (s), 914 (m), 740 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^{+}$ Calcd for $C_{21}H_{24}N_2NaO_4^{+}$ 391.1628; Found 391.1633.

Benzyl (2-(2-(2-cyanoethoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4e)

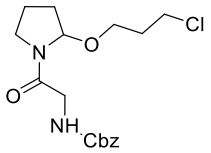


Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-hydroxypropionitrile (41 μL, 0.60 mmol, 2.0 equiv), **4e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (47 mg, 0.14 mmol, 47%).

Rf (DCM/ethyl acetate 7:3): 0.24. ^{1}H NMR (400 MHz, Chloroform-*d,* 8:2 mixture of rotamers (major/minor)) *δ* 7.39-7.28 (m, 5H, Ar*H* (major+minor)), 5.63 (br s, 1H (major+minor)), 5.55 (d, *J* = 4.9 Hz, 0.8H, C(O)NC*H* (major)), 5.12 (m, 2.2H, OCH_2Ph (major+minor) and C(O)NC*H* (minor)), 4.10 (qd, *J* = 16.9, 4.8 Hz, 0.4H, C(O)CH_2NHCbz (minor)), 4.01-3.91 (m, 1.6H, C(O)CH_2NHCbz (major)), 3.83 (tq, *J* = 7.4, 4.0 Hz, 1.6H, OCH_2CH$_2$CN (major)), 3.69 (dq, *J* = 12.9, 5.3, 3.9 Hz, 0.4H, OCH_2CH$_2$CN (minor)), 3.65-3.61 (m, 0.2H, C(O)NCH_2 (minor)), 3.56 (t, *J* = 9.0 Hz, 0.8H, C(O)NCH_2 (major)), 3.45-3.38 (m, 0.2H, C(O)NCH_2 (minor)), 3.34 (q, *J* = 9.8 Hz, 0.8H, C(O)NCH_2 (major)), 2.63 (t, *J* = 6.4 Hz, 0.4H, OCH$_2$CH_2CN (minor)), 2.55 (m, 1.6H, OCH$_2$CH_2CN (major)), 2.31-1.68 (m, 4H, NCH$_2$CH_2CH_2CHO (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 169.0, 168.3, 156.5, 156.4, 136.5, 128.7, 128.3, 128.2, 118.1, 117.5, 87.5, 86.7, 67.1, 63.9, 61.5, 46.1, 45.9, 45.3, 43.6, 43.2, 32.0, 31.7, 23.0, 20.9, 19.3, 19.2. IR (v_{max}, cm^{-1}) 3407 (w), 3329 (w), 2959 (w),

2887 (w), 2251 (w), 1720 (s), 1660 (s), 1525 (m), 1429 (s), 1336 (m), 1254 (s), 1172 (m), 1085 (s), 1060 (s), 914 (m), 739 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{21}N_3NaO_4^+$ 354.1424; Found 354.1422.

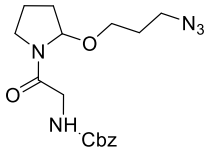
Benzyl (2-(2-(3-chloropropoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4f)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-chloropropan-1-ol (25 μL, 0.60 mmol, 2.0 equiv), **4f** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (74 mg, 0.21 mmol, 70%).

Rf (DCM/ethyl acetate 7:3): 0.29. ^{1}H NMR (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 5.75-5.63 (m, 1H, N*H* (major+minor)), 5.51 (d, *J* = 4.86 Hz, 0.6H, C(O)NC*H* (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 5.07 (d, *J* = 4.2 Hz, 0.4H C(O)NC*H* (minor)), 4.18-4.01 (m, 1H, C(O)CH_2NHCbz (major+minor)), 3.96 (dt, *J* = 17.4, 4.5 Hz, 1H, C(O)CH_2NHCbz (major+minor)), 3.72-3.49 (m, 5H, $OCH_2CH_2CH_2Cl$, $OCH_2CH_2CH_2Cl$ and C(O)NCH_2, (major+minor)), 3.34 (dq, *J* = 26.5, 9.7, 8.6 Hz, 1H, C(O)NCH_2 (major+minor)), 2.33-1.55 (m, 6H, $NCH_2CH_2CH_2CH$ and $OCH_2CH_2CH_2Cl$ (major+minor)). ^{13}CNMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.3, 156.4, 136.5, 128.6, 128.2, 128.1, 87.2, 86.5, 67.0, 65.2, 62.9, 46.1, 45.1, 43.6, 43.2, 42.0, 41.7, 32.7, 32.3, 31.7, 31.6, 23.0, 21.0. IR (v_{max}, cm^{-1}) 3415 (w), 3319 (w), 2959 (m), 2882 (w), 1721 (s), 1660 (s), 1524 (m), 1430 (s), 1246 (m), 1171 (m), 1059 (s), 996 (m), 911 (m), 738 (s), 701 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}ClN_2NaO_4^+$ 377.1239; Found 377.1232.

Benzyl (2-(2-(3-azidopropoxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4g)

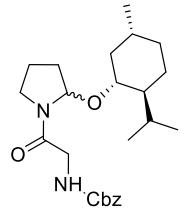


Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-azidopropan-1-ol (600 μL, 1M in DCM, 0.60 mmol, 2.0 equiv), **4g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (99 mg, 0.27 mmol, 91%).

Rf (DCM/ethyl acetate 7:3): 0.38. ^{1}H NMR (400 MHz, Chloroform-*d,* 6:4 mixture of rotamers (major/minor)) *δ* 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 5.75-5.63 (m, 1H, N*H* (major+minor)), 5.50 (d, *J* = 4.9 Hz, 0.6H, C(O)NC*H* (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 5.05 (d, *J* = 4.2 Hz, 0.4H, C(O)NC*H*O (minor)), 4.16-4.01 (m, 0.8H, C(O)CH_2NHCbz (minor)), 4.01-3.91 (m, 1.2H, C(O)CH_2NHCbz (major)), 3.76 (t, *J* = 4.7 Hz, 0.8H, $OCH_2CH_2CH_2N_3$ (minor)), 3.65 (qd, *J* = 6.1, 5.1, 1.8 Hz, 1.2H, $OCH_2CH_2CH_2N_3$ (major)), 3.56-3.26 (m, 4H, $OCH_2CH_2CH_2N_3$ and (CO)NCH_2 (major+minor)), 2.24-1.66 (m, 6H, $NCH_2CH_2CH_2CHO$ and $OCH_2CH_2CH_2N_3$ (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) *δ* 168.4, 168.2, 156.4, 136.5, 128.6, 128.2, 128.1, 87.3, 86.6, 67.0, 65.7, 63.4, 60.1,

48.6, 48.5, 48.4, 46.0, 45.1, 43.6, 43.2, 31.8, 31.6, 31.5, 29.4, 29.2, 23.0, 21.0. IR (v_{max}, cm^{-1}) 3418 (w), 3318 (w), 2952 (m), 2881 (m), 2097 (s), 1721 (s), 1661 (s), 1523 (m), 1452 (s), 1256 (s), 1172 (m), 1056 (s), 912 (m), 739 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}N_5NaO_4^+$ 384.1642; Found 384.1646.

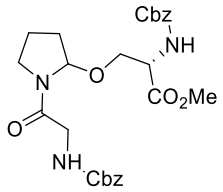
Benzyl (2-(2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)pyrrolidin-1-yl)-2-oxoethyl)carbamate (4h)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and (1R,2S,5R)-(-)-menthol (94 mg, 0.60 mmol, 2.0 equiv), **4h** was obtained after column chromatography DCM to DCM/ethyl acetate 15:1 as a pale yellow oil as an unresolved mixture of diastereoisomers (44 mg, 0.11 mmol, 35%).

Rf (DCM/ethyl acetate 7:3): 0.63. ^{1}H NMR (400 MHz, Chloroform-*d*, unresolved mixture of diastereoisomers and rotamers) δ 7.39-7.28 (m, 5H, Ar*H*), 5.79-5.71 (m, 0.7H, N*H* and C(O)NC*H*), 5.66 (br s, 0.4H, N*H*), 5.58 (m, 0.5H, N*H* and C(O)NC*H*), 5.26 (d, *J* = 4.16 Hz, 0.4H, C(O)NC*H*), 5.19-5.07 (m, 2H, OCH_2Ph), 4.22-3.82 (m, 2H, C(O)CH_2NHCbz), 3.69 (t, *J* = 9.3 Hz, 0.3H, C(O)NCH_2), 3.54 (t, *J* = 9.3 Hz, 0.3H, C(O)NCH_2), 3.51-3.19 (m, 2H, C(O)NCH_2 and NCHOC*H*), 3.12 (tt, *J* = 11.5, 5.7 Hz, 0.3H, C(O)NCH_2), 2.32-1.83 (m, 6H, NCH$_2$CH_2CH_2CH and *H*menthol), 1.79-1.61 (m, 4H, NCH$_2$CH_2CH_2CH and *H*menthol), 1.43-1.07 (m, 3H, *H*menthol), 1.06-0.61 (m, 13H, *H*menthol).^{13}C NMR (101 MHz, Chloroform-*d,* mixture of diastereoisomers and rotamers, signals not fully resolved) δ 168.3, 168.0, 167.7, 156.5, 156.4, 156.3, 136.6, 136.5, 128.6, 128.2, 128.1, 128.0, 85.7, 83.2, 82.8, 77.8, 75.7, 74.9, 67.0, 66.9, 48.8, 48.3, 48.1, 46.0, 45.0, 44.7, 43.7, 43.5, 43.4, 41.8, 41.7, 40.8, 39.7, 34.7, 34.6, 34.4, 32.5, 31.8, 31.7, 31.6, 31.5, 31.4, 25.7, 25.5, 25.2, 25.1, 23.3, 23.2, 23.1, 22.9, 22.5, 22.4, 21.4, 21.3, 21.1, 20.8, 16.2, 16.1, 15.9. IR (v_{max}, cm^{-1}) 3417 (w), 3315 (w), 2954 (m), 2871 (m), 1724 (s), 1661 (s), 1523 (m), 1428 (s), 1242 (m), 1173 (m), 1095 (m), 1049 (s), 915 (m), 736 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{36}N_2NaO_4^+$ 439.2567; Found 439.2567.

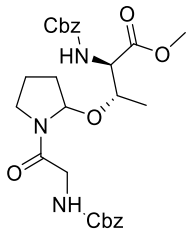
(2S)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-((1-(2-(((benzyloxy)carbonyl)amino)acetyl)pyrrolidin-2-yl)oxy)propanoate (4i)



Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Ser-OMe (114 mg, 0.450 mmol, 1.50 equiv), **4i** was obtained after column chromatography DCM to DCM/ethyl acetate 1:1 as a pale yellow oil and a mixture of diastereoisomers (65 mg, 0.13 mmol, 42%).

Rf (DCM/ethyl acetate 7:3): 0.3. ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers of diastereoisomers)[1] δ 7.40-7.25 (m, 10H, Ar*H*), 6.05 (d, 0.3H, N*H* Ser), 5.93 (d, *J* = 8.4 Hz, 0.1H, N*H* Ser), 5.72 (br s, 1H, N*H* Gly), 5.65 (s, 0.4H, N*H* Ser), 5.47 (d, *J* = 4.8 Hz, 0.3H, C(O)NC*H* Pro), 5.41 (d, *J* = 4.9 Hz, 0.4H, C(O)NC*H* Pro), 5.12 (s, 4H, OCH_2Ph Gly+Ser), 5.09-5.05 (m, 0.3H, C(O)NC*H* Pro), 4.59-4.49 (m, 0.3H, NHC*H* Ser), 4.51-4.41 (m, 0.7H, NHC*H* Ser), 4.12-3.78 (m, 4H, OCH_2 Ser and C(O)CH_2NHCbz Gly), 3.77-3.62 (m, 3H, CO_2CH_3 Ser), 3.59-3.19 (m, 2H, C(O)NCH_2 Pro), 2.19-1.61 (m, 4H, $NCH_2CH_2CH_2CH$ Pro). ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers of diastereoisomers, signals not fully resolved) δ 170.8, 170.7, 170.2, 168.5, 168.2, 156.2, 155.9, 136.3, 136.3, 136.2, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 87.6, 87.2, 87.0, 86.7, 68.9, 68.6, 67.1, 67.0, 66.9, 66.3, 66.2, 54.6, 54.4, 54.3, 54.0, 52.8, 52.7, 52.5, 52.4, 45.9, 45.1, 44.9, 43.4, 43.4, 42.9, 42.8, 33.7, 31.5, 31.4, 31.1, 31.1, 22.7, 22.7, 20.7, 20.6, 20.4. IR (ν_{max}, cm^{-1}) 3324 (m), 2979 (m), 2885 (w), 1718 (s), 1658 (s), 1518 (m), 1436 (m), 1242 (m), 1054 (s), 914 (m), 738 (s), 699 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{31}N_3NaO_8^+$ 536.2003; Found 536.2014.

(2S,3R)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((1-(2-(((benzyloxy)carbonyl)amino) acetyl)pyrrolidin-2-yl)oxy)butanoate (4j)

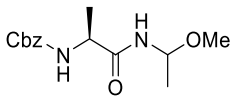


Following General Procedure 2 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Thr-OMe (160 mg, 0.450 mmol, 1.50 equiv), **4j** was obtained after column chromatography DCM to DCM/ethyl acetate 1:1 as a pale yellow oil and a mixture of diastereoisomers (60 mg, 0.11 mmol, 38%).

Rf (DCM/ethyl acetate 7:3): 0.36. ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers of diastereoisomers)[1] δ 7.40-7.28 (m, 10H, Ar*H*), 5.67 (d, *J* = 14.7 Hz, 1H, N*H* Gly), 5.60 (d, *J* = 9.4 Hz, 0.5H, N*H* Thr), 5.55 (d, *J* = 4.7 Hz, 0.6H, C(O)NC*H* Pro), 5.54-5.48 (m, 0.25H, N*H* Thr), 5.43 (d, *J* = 9.7 Hz, 0.25H, N*H* Thr), 5.40 (d, *J* = 4.7 Hz, 0.4H, C(O)NC*H* Pro), 5.17-5.06 (m, 4H, OCH_2Ph Gly and Ser), 4.54-4.37 (m, 0.5H, OC*H* and NHC*H* Thr), 4.37-4.22 (m, 1.2H, OC*H* and NHC*H* Thr), 4.22-4.11 (m, 0.3H, OC*H* and NHC*H* Thr), 3.96 (m, 2H, C(O)CH_2NHCbz Gly), 3.78-3.58 (m, 3H, OCH_3 Thr), 3.47 (dq, *J* = 16.4, 9.5, 8.9 Hz, 0.5H, C(O)NCH_2 Pro), 3.40-3.19 (m, 1.5H, C(O)NCH_2 Pro), 2.15-1.68 (m, 4H, $NCH_2CH_2CH_2CH$ Pro), 1.39-1.16 (m, 3H, OCHCH_3 Thr). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of diastereoisomers and rotamers, signals not fully resolved) δ 171.6, 171.4, 168.7, 168.0, 156.8, 156.7, 156.3, 136.5, 136.4, 136.3, 128.7, 128.6, 128.3, 128.2, 128.1, 86.7, 84.4, 83.9, 74.7, 72.3, 71.3, 67.4, 67.3, 67.2, 67.1, 59.1, 59.0, 52.7, 52.5, 52.4, 46.1, 45.7, 45.0, 44.8, 43.6, 43.5, 43.2, 32.2, 32.1, 31.7, 31.3, 22.9, 22.8, 20.5, 20.4, 17.8, 16.9, 16.0. IR (ν_{max}, cm^{-1}) 3365 (w), 2979 (w), 2890 (w), 2099 (w), 1719 (s), 1663 (m), 1523 (m), 1436 (m), 1318 (m), 1256 (m), 1173 (m), 1065 (s), 1002 (m), 911 (m), 739 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}N_3NaO_8^+$ 550.2160; Found 550.2161.

Benzyl ((2S)-1-((1-methoxyethyl)amino)-1-oxopropan-2-yl)carbamate (4k)

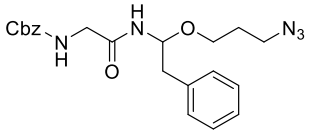
[1] Due to the complexity of the mixture, signals were not attributed to each rotamer and diastereoisomer.



Following General Procedure 1 and starting with Cbz-Ala-Ala (**1b**) (88 mg, 0.30 mmol, 1.0 equiv), **4k** was obtained after column chromatography DCM to DCM/ethyl acetate 8:2 as a white amorphous solid (57 mg, 0.20 mmol, 68%) and as a mixture of unresolved diastereoisomers.

Rf (DCM/ethyl acetate 7:3): 0.25. ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers and rotamers) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, Ar*H*), 6.30 (br s, 1H, N*H*), 5.33 (s, 1H, N*H*Cbz), 5.24 (dqd, *J* = 9.2, 5.9, 3.3 Hz, 1H, C(O)NC*H*COMe), 5.12 (s, 2H, OCH_2Ph), 4.22 (q, *J* = 6.8 Hz, 1H, CbzNC*H*Me), 3.30 (s, 1H, OCH_3), 3.27 (s, 2H, OCH_3), 1.40 (t, *J* = 7.3 Hz, 3H, CbzNCHCH_3), 1.30 (d, *J* = 5.9 Hz, 3H, C(O)NHCHCH_3). δ ^{13}C NMR (101 MHz, Chloroform-*d,* mixture of rotamers, signals not fully resolved) δ 172.3, 156.0, 136.0, 128.6, 128.3, 128.1, 78.4, 67.2, 55.6, 50.7, 28.9, 21.5, 18.7, 18.3. IR (v_{max}, cm^{-1}) 3286 (m), 2981 (w), 1688 (s), 1651 (s), 1540 (s), 1453 (m), 1382 (w), 1324 (m), 1261 (s), 1135 (m), 1070 (m), 914 (m), 738 (s), 699 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{20}N_2NaO_4^+$ 303.1315; Found 303.1315.

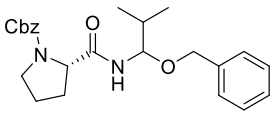
Benzyl (2-((1-(3-azidopropoxy)-2-phenylethyl)amino)-2-oxoethyl)carbamate (4l)



Following General Procedure 2 and starting with Cbz-Gly-Phe (**1c**) (107 mg, 0.30 mmol, 1.0 equiv) and 3-azidopropan-1-ol (600 μL, 1M in DCM, 0.60 mmol, 2.0 equiv), **4l** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colourless oil (57 mg, 0.14 mmol, 46%).

Rf (DCM/ethyl acetate 7:3): 0.52. ^{1}H NMR (400 MHz, Acetonitrile-d_3, 75:25 mixture of rotamers (major/minor)) δ 7.41-7.21 (m, 10H, Ar*H* (major+minor)), 6.88 (d, *J* = 9.4 Hz, 1H, N*H* Phe (major+minor)), 6.02 (m, 0.25H, N*H* Gly (minor)), 5.90 (m, 0.75H, N*H* Gly (major)), 5.28 (dt, *J* = 9.6, 6.3 Hz, 1H, NHC*H* Phe (major+minor)), 5.09 (d, *J* = 9.8 Hz, 2H, OCH_2Ph (major+minor)), 3.81 (d, *J* = 6.1 Hz, 0.5H, NHCH_2 Gly (minor)), 3.66 (dd, *J* = 6.1, 2.8 Hz, 1.5H, NHCH_2 Gly (major)), 3.60-3.51 (m, 1H, OCH_2CH$_2$CH$_2$N$_3$ (major+minor)), 3.42-3.35 (m, 1.5H, OCH_2CH$_2$CH$_2$N$_3$ (major+minor) and OCH$_2$CH$_2$CH_2N$_3$ (minor)), 3.23 (t, *J* = 6.7 Hz, 1.5H, OCH$_2$CH$_2$CH_2N$_3$ (major)), 2.94 (dd, *J* = 13.8, 6.2 Hz, 1H, NHCHCH_2 Phe (major+minor)), 2.83 (dd, *J* = 13.7, 6.3 Hz, 1H, NHCHCH_2 Phe (major+minor)), 1.77-1.63 (m, 2H, OCH$_2$CH$_2$CH_2N$_3$ (major+minor)). ^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 170.5, 168.2, 157.6, 138.1, 138.0, 137.5, 130.6, 129.6, 129.5, 129.2, 128.9, 128.8, 127.4, 126.4, 123.6, 113.5, 81.1, 67.4, 67.3, 65.2, 59.4, 49.1, 44.8, 41.9, 32.4, 29.6. IR (v_{max}, cm^{-1}) 3347 (m), 3064 (m), 2935 (m), 2880 (m), 2097 (s), 1708 (s), 1664 (s), 1517 (s), 1455 (m), 1257 (s), 1155 (m), 1050 (s), 909 (m), 738 (s), 699 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{25}N_5NaO_4^+$ 434.1799; Found 434.1801

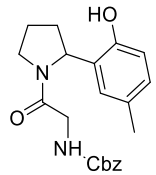
Benzyl (2S)-2-((1-(benzyloxy)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (4m)



Following General Procedure 2 and starting with Cbz-Pro-Val (**1d**) (105 mg, 0.30 mmol, 1.0 equiv) and benzyl alcohol (65 μL, 0.60 mmol, 2.0 equiv), **4m** was obtained after column chromatography DCM to DCM/ethyl acetate 15:1 as a colourless oil (63 mg, 0.15 mmol, 51%).

Rf (DCM/ethyl acetate 7:3): 0.71. ^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$, mixture of rotamers of diastereoisomers) δ 7.45-7.16 (m, 10H, Ar*H*), 6.97-6.70 (m, 1H, N*H*), 5.18-5.05 (m, 1.5H, OC*H*$_2$Ph Cbz), 4.99 (d, *J* = 13.3 Hz, 0.5H, OC*H*$_2$Ph Cbz), 4.91 (m, 1H, NHC*H* Val), 4.54 (m, 0.5H, OC*H*$_2$Ph Val), 4.49-4.33 (m, 1H, OC*H*$_2$Ph Val), 4.26 (m, 1.5H, OC*H*$_2$Ph Val and CbzNC*H* Pro), 3.59-3.40 (m, 2H, CbzNC*H*$_2$ Pro), 2.33-2.19 (m, 1H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro), 2.05-1.95 (m, 1H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro), 1.92-1.73 (m, 3H, CbzNCH$_2$C*H*$_2$C*H*$_2$CH Pro and NHCHC*H* Val), 0.98-0.72 (m, 6H, C*H*$_3$ Val). ^{13}C NMR (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers of diastereoisomers, signals not fully resolved) δ 174.1, 173.8, 173.7, 156.2, 155.5, 139.8, 139.7, 138.1, 129.4, 129.3, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 84.5, 84.3, 70.1, 67.5, 67.4, 62.1, 62.0, 61.6, 61.4, 48.3, 47.8, 33.7, 32.5, 30.8, 25.3, 24.3, 18.6, 18.0, 17.9, 17.8. IR (ν_{max}, cm^{-1}) 3338 (m), 3063 (m), 2929 (m), 1672 (s), 1529 (s), 1417 (s), 1356 (s), 1231 (m), 1119 (s), 1089 (m), 1039 (m), 912 (m), 737 (s), 697 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{24}H_{30}N_2NaO_4^+$ 433.2098; Found 433.2090.

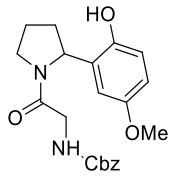
Benzyl (2-(2-(2-hydroxy-5-methylphenyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5a)



Following General Procedure 3 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and *p*-cresol (49 mg, 0.45 mmol, 1.5 equiv), **5a** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow amorphous solid (68 mg, 0.19 mmol, 62%).

Rf (DCM/ethyl acetate 7:3): 0.4. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.94 (s, 1H, O*H* (major+minor)), 7.33 (dt, *J* = 9.1, 4.6 Hz, 5H, Ar*H* (major+minor)), 6.94 (d, *J* = 8.1 Hz, 0.7H, Ar*H* (major)), 6.89 (s, 0.7H, Ar*H* (major)), 6.82 (d, *J* = 7.6 Hz, 0.3H, Ar*H* (minor)), 6.76 (d, *J* = 8.1 Hz, 0.7H, Ar*H* (major)), 6.66 (s, 0.3H, Ar*H* (minor)), 6.51 (d, *J* = 8.0 Hz, 0.3H, Ar*H* (minor)), 5.79 (br s, 0.3H, N*H* (minor)), 5.67 (br s, 0.7H, N*H* (major)), 5.39 (dd, *J* = 7.5, 3.0 Hz, 0.7H, C(O)NC*H* (major)), 5.17 (d, *J* = 7.7 Hz, 0.3H, C(O)NC*H* (minor)), 5.11 (s, 1.4H, OC*H*$_2$Ph (major)), 5.07 (s, 0.6H, OC*H*$_2$Ph (minor)), 4.07 (td, *J* = 20.3, 18.9, 4.6 Hz, 1H, C(O)C*H*$_2$NHCbz (major+minor)), 3.92 (dd, *J* = 17.4, 4.0 Hz, 0.7H, C(O)C*H*$_2$NHCbz (major)), 3.79 (d, *J* = 6.0 Hz, 0.3H, C(O)NC*H*$_2$ (minor)), 3.73 (d, *J* = 8.1 Hz, 0.3H, C(O)NC*H*$_2$ (minor)), 3.67-3.51 (m, 1.4H, C(O)NC*H*$_2$ (major)), 3.43 (dd, *J* = 17.2, 3.3 Hz, 0.3H, C(O)C*H*$_2$NHCbz (minor)), 2.43-2.14 (m, 6H, NCH$_2$C*H*$_2$C*H*$_2$CH and C*H*$_3$ (major+minor)), 1.98-1.82 (m, 1H, NCH$_2$C*H*$_2$C*H*$_2$CH (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.4, 156.6, 156.4, 153.1, 150.7, 136.4, 129.9, 129.6, 129.0, 128.6, 128.3, 128.1, 127.8, 127.4, 126.5, 125.9, 118.4, 115.6, 67.1, 55.9, 55.2, 47.5, 46.2, 43.6, 43.3, 34.4, 31.2, 30.5, 25.2, 21.8, 21.0, 20.9. IR (ν_{max}, cm^{-1}) 3313 (w), 2978 (m), 2899 (w), 2360 (w), 1714 (s), 1640 (s), 1510 (m), 1436 (m), 1269 (m), 1055 (m), 738 (m), 699 (m). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}N_2NaO_4^+$ 389.1472; Found 389.1472.

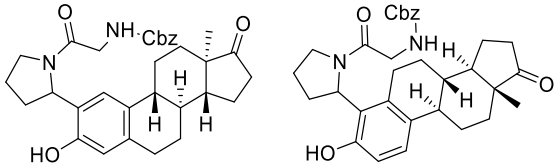
Benzyl (2-(2-(2-hydroxy-5-methoxyphenyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5b)



Following General Procedure 3 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.5 equiv), **5b** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow oil (90 mg, 0.23 mmol, 78%).

Rf (DCM/ethyl acetate 7:3): 0.35. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.73 (s, 1H, O*H* (major+minor)), 7.38-7.28 (m, 5H, Ar*H* (major+minor)), 6.78 (d, *J* = 8.7 Hz, 0.7H, Ar*H* (major)), 6.68 (dd, *J* = 8.7, 2.9 Hz, 0.7H, Ar*H* (major)), 6.65 (d, *J* = 2.8 Hz, 0.7H Ar*H* (major)), 6.57-6.50 (m, 0.6H, Ar*H* (minor)), 6.45 (d, *J* = 2.1 Hz, 0.3H,Ar*H* (minor)), 5.81 (s, 0.3H, N*H* (minor)), 5.66 (s, 0.7H, N*H* (major)), 5.41-5.35 (m, 0.7H, C(O)NC*H* (major)), 5.16 (d, *J* = 7.1 Hz, 0.3H, C(O)NC*H* (minor)), 5.11 (s, 1.4H, OCH_2Ph (major)), 5.08 (s, 0.6H, OCH_2Ph (minor)), 4.16-4.00 (m, 1H, C(O)CH_2NHCbz (major+minor)), 3.93 (dd, *J* = 17.4, 4.2 Hz, 0.7H, C(O)CH_2NHCbz (major)), 3.74 (s, 2.1H, OCH_3 (major)), 3.70 (s, 0.9H, OCH_3 (minor)), 3.62 (dd, *J* = 11.1, 7.1 Hz, 1H, C(O)NCH_2 (major+minor)), 3.59-3.53 (m, 1H, C(O)NCH_2 (major+minor)), 3.46 (dd, *J* = 17.1, 3.6 Hz, 0.3H, C(O)CH_2NHCbz (minor)), 2.40-2.11 (m, 3H, NCH$_2$CH_2CH_2CH (major+minor)), 1.99-1.82 (m, 1H, NCH$_2$CH_2CH_2CH (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 168.0, 167.2, 156.5, 156.3, 153.5, 153.4, 149.2, 147.0, 136.4, 129.2, 128.7, 128.6, 128.3, 128.1, 118.9, 116.3, 113.4, 112.7, 112.6, 111.8, 67.1, 56.0, 55.9, 55.4, 47.5, 46.3, 43.6, 43.3, 34.3, 31.2, 25.1, 21.7. IR (v_{max}, cm^{-1}) 3671 (m), 3320 (m), 2987 (s), 2899 (m), 1717 (s), 1638 (s), 1507 (s), 1453 (s), 1434 (s), 1350 (m), 1286 (s), 1207 (s), 1045 (s), 815 (m), 740 (m). HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{25}N_2O_5^+$ 385.1758; Found 385.1747.

and Benzyl (2-(2-((8S,9R,13R,14R)-3-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)pyrrolidin-1-yl)-2-oxoethyl) carbamate and Benzyl (2-(2-((8S,9R,13R,14R)-3-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-4-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5c)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and estrone (122 mg, 0.450 mmol, 1.50 equiv), **5c** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow amorphous solid (100 mg, 0.188 mmol, 63%, ratio major/minor 7:3).

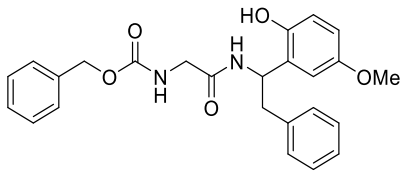
Rf (DCM/ethyl acetate 7:3): 0.32.

Major: ^{1}H NMR (400 MHz, Acetonitrile-d_3, unresolved mixture of rotamers of diastereoisomers) δ 7.31 (m, 5H, Ar*H*), 7.23-7.10 (m, 0.4H, O*H*), 7.10-6.95 (m, 1H, Ar*H*), 6.89-6.73 (m, 0.6H, O*H*), 6.68-6.48 (m, 1H, Ar*H*), 5.89-5.59 (m, 1H, N*H* Gly), 5.17 (m, 1H, C(O)NC*H*), 5.01 (m, 2H, OCH_2Ph), 4.00-3.40 (m, 4H, C(O)CH_2NHCbz and C(O)NCH_2), 3.29-2.97 (m, 1H, ArCH_2 estrone), 2.90-2.60 (m, 1H ArCH_2 estrone), 2.48-2.26 (m, 3H), 2.04 (m, 5H), 1.90-1.73 (m, 2H), 1.67-1.25 (m, 7H), 0.86 (m, 3H, CH_3). ^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of

rotamers of diastereoisomers, signals not fully resolved) δ 166.8, 157.1, 153.2, 153.0, 138.2, 136.5, 132.5, 129.4, 128.8, 128.7, 127.3, 126.4, 125.7, 125.5, 114.8, 114.6, 79.3, 78.6, 67.1, 67.0, 56.8, 56.5, 51.2, 48.7, 48.5, 48.1, 47.3, 47.1, 45.3, 45.1, 44.9, 43.9, 43.8, 43.2, 39.4, 38.3, 36.4, 34.0, 32.6, 32.4, 31.4, 30.4, 29.8, 27.6, 27.4, 27.2, 27.1, 26.8, 26.6, 25.0, 24.8, 22.1, 14.3, 14.2. IR (v_{max}, cm^{-1}) 3305 (m), 2929 (m), 2867 (m), 1726 (s), 1633 (s), 1509 (s), 1451 (s), 1372 (m), 1281 (s), 1257 (s), 1056 (s), 831 (m), 741 (m), 698 (s). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}N_2O_5^+$ 531.2853; Found 531.2840

Minor: ^{1}H NMR (400 MHz, Acetonitrile-d_3, unresolved mixture of rotamers of diastereoisomers) δ 8.26-8.17 (m, 0.2H, O*H*), 8.04-7.93 (m, 0.4H, O*H*), 7.32 (m, 5H Ar*H*), 6.99-6.90 (m, 0.6H, Ar*H*), 6.82 (s, 0.4H, Ar*H*), 6.58-6.45 (m, 1H, Ar*H*), 5.89-5.59 (m, 1H, N*H* Gly), 5.27-5.09 (m, 1H, C(O)NC*H*), 5.03 (m, 2H, OCH_2Ph), 4.00-3.85 (m, 1.6H, C(O)CH_2NHCbz), 3.84-3.74 (m, 0.4H, C(O)CH_2NHCbz), 3.73-3.46 (m, 2H,C(O)NCH_2), 2.88-2.66 (m, 2H, ArCH_2 estrone), 2.47-2.25 (m, 3H), 2.13-1.97 (m, 5H), 1.87-1.72 (m, 2H), 1.67-1.33 (m, 7H), 0.88 (m, 3H, CH_3). ^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of rotamers of diastereoisomers, signals not fully resolved) δ 174.0, 168.6, 153.0, 152.0, 138.3, 137.8, 132.2, 129.4, 129.3, 128.8, 128.7, 127.3, 127.1, 124.1, 123.8, 116.3, 67.1, 56.4, 51.1, 48.7, 47.9, 47.0, 44.9, 44.8, 44.0, 43.8, 39.7, 39.4, 39.2, 36.3, 35.0, 34.5, 32.6, 32.3, 32.1, 31.1, 29.8, 29.6, 27.3, 26.9, 26.8, 25.2, 25.1, 24.5, 23.7, 22.3, 22.2, 14.3, 14.2, 11.3. IR (v_{max}, cm^{-1}) 3337 (m), 2951 (s), 2872 (m), 1733 (s), 1638 (s), 1509 (s), 1454 (s), 1426 (s), 1284 (s), 1254 (s), 1055 (s), 775 (m), 699 (m). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{32}H_{39}N_2O_5^+$ 531.2853; Found 531.2838

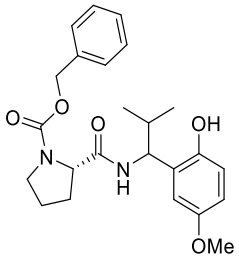
Benzyl (2-((1-(2-hydroxy-5-methoxyphenyl)-2-phenylethyl)amino)-2-oxoethyl) carbamate (5d)



Following General Procedure 3 and starting with Cbz-Gly-Phe (**1c**) (107 mg, 0.300 mmol, 1.00 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5d** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (81 mg, 0.19 mmol, 62%).

Rf (DCM/ethyl acetate 7:3): 0.31. ^{1}H NMR (400 MHz, Chloroform-*d,* unresolved mixture of rotamers) δ 7.98-7.49 (br s, 1H, O*H*), 7.34 (m, 5H, Ar*H*), 7.19 (dq, *J* = 14.2, 7.0 Hz, 4H, Ar*H*), 7.10 (d, *J* = 6.7 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.68 (dd, *J* = 8.7, 2.9 Hz, 1H, Ar*H*), 6.64 (s, 1H, N*H* Phe), 5.40 (s, 1H, N*H* Gly), 5.28 (q, *J* = 8.48 Hz, 1H, NHC*H*Ar), 5.09 (s, 2H, OCH_2Ph), 3.69 (d, *J* = 7.47 Hz, 5H, OCH_3 and NHCH_2), 3.20-3.05 (m, 2H, NHCHCH_2Ph). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 169.8, 156.8, 153.5, 148.4, 137.7, 136.1, 129.2, 128.8, 128.6, 128.5, 128.3, 128.1, 126.8, 118.4, 114.0, 113.4, 67.5, 55.9, 51.1, 44. 6, 40.1. IR (v_{max}, cm^{-1}) 3402 (m), 3065 (m), 2935 (m), 2836 (w), 1707 (s), 1655 (s), 1524 (s), 1455 (m), 1350 (m), 1260 (s), 1211 (s), 1154 (s), 1032 (m), 910 (s), 735 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{26}N_2NaO_5^+$ 457.1734; Found 457.1738.

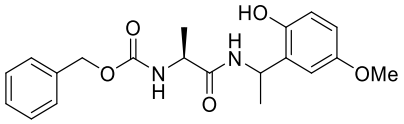
Benzyl (2S)-2-((1-(2-hydroxy-5-methoxyphenyl)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (5e)



Following General Procedure 3 and starting with Cbz-Pro-Val (**1d**) (105 mg, 0.300 mmol, 1.00 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (63 mg, 0.15 mmol, 49%).

Rf (DCM/ethyl acetate 7:3): 0.32. ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers and diastereomers) δ 8.08-7.51 (m, 1H, O*H*), 7.33 (m, 4H, Ar*H*), 7.22 (m, 1H, Ar*H*), 7.09-6.90 (m, 1H, N*H*), 6.78 (d, *J* = 3.7 Hz, 1H, Ar*H*), 6.72-6.59 (m, 2H, Ar*H*), 5.31-4.88 (m, 2H, OCH_2Ph), 4.60 (t, *J* = 8.8 Hz, 1H, NHC*H*Ar), 4.34 (m, 1H, NC*H*C(O)), 3.74 (m, 3H, OCH_3), 3.63-3.32 (m, 2H, CH_2NCbz), 2.38-1.55 (m, 5H, NCH$_2$CH_2CH_2CH and NHCHC*H*), 1.09-0.69 (m, 6H, CH(CH_3)$_2$). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 172.7, 172.6, 156.4, 155.6, 153.7, 153.5, 149.9, 148.9, 128.7, 128.4, 128.0, 116.2, 114.9, 113.7, 113.4, 67.7, 60.6, 55.9, 55.8, 47.6, 31.1, 24.7, 24.6, 20.4, 20.0. IR (ν_{max}, cm^{-1}) 3330 (m), 2958 (m), 2873 (m), 1685 (s), 1530 (s), 1508 (s), 1432 (s), 1356 (s), 1207 (s), 1119 (s), 1040 (m), 911 (s), 735 (s). HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{24}H_{31}N_2O_5^+$ 427.2227; Found 427.2229.

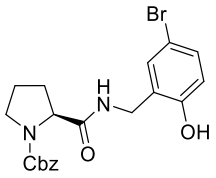
Benzyl ((2S)-1-((1-(2-hydroxy-5-methoxyphenyl)ethyl)amino)-1-oxopropan-2-yl) carbamate (5f)



Following General Procedure 3 and starting with Cbz-Ala-Ala (**1b**) (88 mg, 0.30 mmol, 1.0 equiv) and 4-methoxyphenol (56 mg, 0.45 mmol, 1.50 equiv), **5f** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a colorless oil (71 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.34. ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers and diastereomers) δ 8.23 (br s, 1H, OH), 7.41-7.27 (m, 5H, Ar*H*), 7.07-6.90 (br s, 1H, ArCHN*H*), 6.82 (dd, *J* = 8.7, 4.7 Hz, 1H, Ar*H*), 6.71 (ddd, *J* = 11.6, 6.2, 3.2 Hz, 2H, Ar*H*), 5.50-5.28 (m, 1H, CbzN*H*), 5.17 (dt, *J* = 15.0, 7.2 Hz, 1H, ArC*H*NH), 5.08 (m, 2H, OCH_2Ph), 4.17 (m, 1H, CbzNHC*H*), 3.73 (m, 3H, OCH_3), 1.49 (dd, *J* = 16.9, 6.2 Hz, 3H, ArCHCH_3), 1.37-1.27 (m, 3H, CbzNHCHCH_3). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 173.0, 172.9, 156.2, 156.0, 153.4, 148.5, 135.9, 129.4, 128.6, 128.3, 128.1, 118.6, 118.5, 113.7, 112.3, 67.2, 55.8, 50.4, 50.3, 44.1, 19.6, 18.6, 18.0. IR (ν_{max}, cm^{-1}) 3327 (m), 3079 (m), 2936 (m), 2834 (m), 1705 (s), 1651 (s), 1508 (s), 1453 (s), 1258 (s), 1207 (s), 1030 (m), 910 (m), 734 (s), 699 (m). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{24}N_2NaO_5^+$ 395.1577; Found 395.1582.

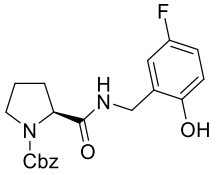
Benzyl (S)-2-((5-bromo-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5g)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**1e**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-bromophenol (78 mg, 0.45 mmol, 1.5 equiv), **5g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (61 mg, 0.14 mmol, 47%).

Rf (DCM/ethyl acetate 7:3): 0.5. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 9.33 (br s, 1H, O*H* (major+minor)), 7.83 (br m, 0.7H, N*H* (major)), 7.44-7.27 (br m, 5H, Ar*H* (major+minor)), 7.19 (br m, 2H, Ar*H* (major+minor)), 7.04-6.91 (br m, 0.3H, N*H* (minor)), 6.80 (d, *J* = 8.6 Hz, 1H, Ar*H* (major+minor)), 5.09 (br m, 2H, OCH_2Ph (major+minor)), 4.44-4.05 (br m, 3H, NC*H*C(O), NHCH_2Ar (major+minor)), 3.46 (br m, 2H, CH_2NCbz (major+minor)), 2.13 (br m, 4H, NCH$_2$CH_2CH_2CH (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 175.0, 174.4, 156.7, 155.2, 136.1, 133.4, 132.8, 128.8, 128.5, 128.1, 126.3, 120.0, 111.5, 67.8, 60.7, 60.2, 47.7, 47.4, 40.2, 28.1, 24.7, 23.9. IR (ν_{max}, cm^{-1}) 3291 (m), 3055 (m), 2933 (w), 1682 (s), 1542 (s), 1481 (s), 1419 (s), 1355 (s), 1275 (s), 1173 (s), 1092 (m), 909 (s), 732 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{21}{}^{(79)}BrN_2NaO_4^+$ 455.0577; Found 455.0579.

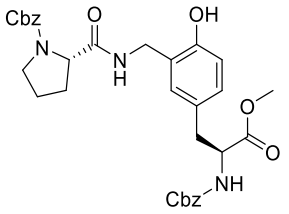
Benzyl (S)-2-((5-fluoro-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5h)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**1e**) (92 mg, 0.30 mmol, 1.0 equiv) and 4-fluorophenol (50 mg, 0.45 mmol, 1.5 equiv), **5h** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (64 mg, 0.17 mmol, 57%).

Rf (DCM/ethyl acetate 7:3): 0.48. ^{1}H NMR (400 MHz, Chloroform-*d*, 1:1 mixture of rotamers (R^1/R^2)) δ 9.02 (br s, 1H, O*H* (R^1+R^2)), 7.82 (br m, 0.5H, N*H* (R^1)), 7.30 (br m, 5H, Ar*H* (R^1+R^2)), 7.18 (br m, 0.5H, N*H* (R^2)), 6.87 (qd, *J* = 8.8, 5.5 Hz, 2H, Ar*H* (R^1+R^2)), 6.72 (br m, 1H, Ar*H* (R^1+R^2)), 5.23-4.91 (br s, 2H, OCH_2Ph (R^1+R^2)), 4.44-4.08 (br m, 3H, NC*H*C(O), NHCH_2Ar (R^1+R^2)), 3.46 (br m, 2H, CH_2NCbz (R^1+R^2)), 2.47-1.79 (br m, 4H, NCH$_2$CH_2CH_2CH (R^1+R^2)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.3, 156.7, 156.3 (d, *J* = 236.7 Hz), 151.9 (d, *J* = 2.0 Hz), 136.2, 128.8, 128.5, 128.1, 125.2, 119.0 (d, *J* = 7.9 Hz), 116.8 (d, *J* = 23.1 Hz), 116.4 (d, *J* = 23.2 Hz), 67.8, 60.2, 59.5, 47.3, 47.0, 40.3, 28.0, 24.7, 23.9, 22.8. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -124.92, -125.08. IR (ν_{max}, cm^{-1}) 3314 (m), 2925 (m), 2853 (m), 1684 (s), 1536 (m), 1508 (s), 1444 (s), 1356 (s), 1256 (s), 1188 (s), 1122 (s), 909 (s), 733 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{21}BrN_2NaO_4^+$ 455.0577; Found 455.0579.

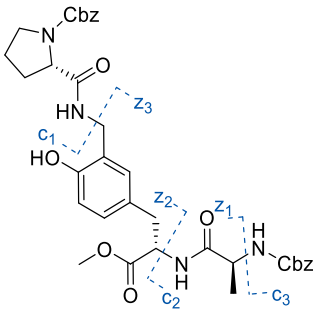
Benzyl(S)-2-((5-((S)-2-(((benzyloxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-2-hydroxy benzyl)carbamoyl)pyrrolidine-1-carboxylate (5i)



Following General Procedure 3 and starting with Cbz-Pro-Gly (**1e**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Tyr-OMe (148 mg, 0.450 mmol, 1.50 equiv), **5i** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (65 mg, 0.11 mmol, 37%).

Rf (DCM/ethyl acetate 7:3): 0.32. ^{1}H NMR (400 MHz, Chloroform-*d*, complex mixture of rotamers) δ 9.05 (br s, 1H, O*H*), 7.68 (br m, 0.5H, N*H* Gly), 7.43-7.27 (m, 10H, Ar*H*), 7.19 (br m, 0.5H, N*H* Gly), 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H, Ar*H*), 6.81 (d, J = 8.2 Hz, 2H, Ar*H*), 5.10 (m, 5H, OC*H*$_2$Ph Pro+Tyr and N*H* Tyr), 4.59 (q, *J* = 5.9 Hz, 0.8H, NHC*H* Tyr), 4.46 (br s, 0.2H, NHC*H* Tyr), 4.33 (br m, 1H, NC*H*C(O) Pro), 4.25 (br m, 0.5H, NHC*H*$_2$Ar Gly), 4.14 (dt, *J* = 12.1, 6.1 Hz, 1.5H, NHC*H*$_2$Ar Gly), 3.71 (s, 3H, OC*H*$_3$ Tyr), 3.44 (br m, 2H, C*H*$_2$NCbz Pro), 2.99 (qd, *J* = 14.0, 5.9 Hz, 2H, NHCHC*H*$_2$ Tyr), 2.44-1.73 (br m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH Pro). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.1, 172.2, 156.6, 155.8, 155.1, 136.4, 136.2, 131.8, 130.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.0, 124.2, 118.2, 67.7, 67.1, 60.3, 55.1, 52.5, 47.3, 40.5, 37.4, 28.1, 24.7. IR (ν_{max}, cm^{-1}) 3317 (m), 3065 (m), 2949 (m), 1693 (s), 1533 (s), 1436 (s), 1355 (s), 1262 (s), 1213 (s), 1121 (m), 911 (s), 732 (s). HRMS (ESI/QTOF) m/z: [M + H]$^{+}$ Calcd for $C_{32}H_{36}N_3O_8^{+}$ 590.2497; Found 590.2490.

Benzyl (S)-2-((5-((S)-2-((S)-2-(((benzyloxy)carbonyl)amino)propanamido)-3-methoxy-3-oxopropyl)-2-hydroxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (5j)



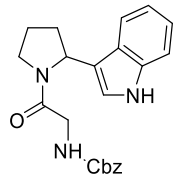
Following General Procedure 3 and starting with Cbz-Pro-Gly (**1e**) (92 mg, 0.30 mmol, 1.0 equiv) and Cbz-Ala-Tyr-OMe (180 mg, 0.450 mmol, 1.50 equiv), **5j** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a white amorphous solid (80 mg, 0.12 mmol, 40%).

Rf (DCM/ethyl acetate 7:3): 0.16. ^{1}H NMR (400 MHz, Acetonitrile-*d*$_3$, complex mixture of rotamers) δ 9.07 (s, 0.3H, O*H*), 8.54 (s, 0.4H, O*H*), 7.74 (s, 1H, N*H* Gly), 7.42-7.23 (m, 9H, Ar*H*), 7.16 (d, *J* = 5.8 Hz, 1H, Ar*H*), 6.99-6.83 (m, 3H, Ar*H* and N*H* Tyr), 6.71 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.18-6.06 (m, 0.7H, N*H* Ala), 5.89 (s, 0.3H, N*H* Ala), 5.19-4.87 (m, 4H, OC*H*$_2$Ph Pro+Ala), 4.57 (ddt, *J* = 10.3, 7.9, 4.0 Hz, 1H, NHC*H* Tyr), 4.31-4.01 (m, 4H, NC*H* Pro, NHC*H*$_2$ Gly and NHC*H* Ala), 3.66 (d, *J* = 3.3 Hz, 3H, OC*H*$_3$ Tyr), 3.46 (m, 2H, NC*H*$_2$ Pro), 3.07-2.96 (m, 1H, NCHC*H*$_2$ Tyr), 2.85 (m, 1H, NCHC*H*$_2$ Tyr), 2.15-2.01 (m, 1H, NCH$_2$C*H*$_2$C*H*$_2$CH Pro), 1.91-1.72 (m, 3H, NCH$_2$C*H*$_2$C*H*$_2$CH Pro), 1.20 (dd, *J* = 16.9, 7.1 Hz, 3H, C*H*$_3$ Ala). ^{13}C NMR (101 MHz, Acetonitrile-*d*$_3$, mixture of rotamers, signals not fully resolved) δ 176.2, 175.5,

173.4, 173.3, 172.8, 172.7, 172.6, 157.1, 156.9, 156.2, 155.6, 155.5, 155.0, 152.2, 138.1, 138.0, 137.9, 133.0, 132.4, 131.5, 131.1, 130.5, 130.4, 130.1, 129.5, 129.4, 128.9, 128.7, 128.6, 128.4, 125.7, 120.6, 117.4, 117.3, 67.7, 67.5, 67.3, 67.1, 61.9, 61.4, 54.6, 54.4, 52.8, 51.5, 48.2, 47.8, 40.2, 39.6, 37.0, 36.9, 32.1, 30.9, 25.1, 24.3, 18.5, 18.3. IR (v_{max}, cm^{-1}) 3317 (s), 2954 (m), 1661 (s), 1535 (s), 1448 (s), 1358 (s), 1256 (s), 1213 (s), 1120 (m), 1059 (m), 910 (s), 773 (m), 735 (s), 698 (s). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{35}H_{41}N_4O_9^+$ 661.2868; Found 661.2883. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 661.2883. Measured c and z ions are reported in the table below

	G	**Y**	**A**
N-terminal	1	2	3
c	249.12	-	-
C-terminal	3	2	1
z	413.17	-	510.22

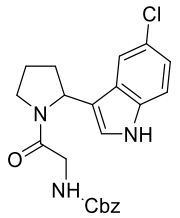
Benzyl (2-(2-(1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6a)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (36 mg, 0.31 mmol, 1.02 equiv), **6a** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow amorphous solid (75 mg, 0.20 mmol, 66%).

Rf (DCM/ethyl acetate 7:3): 0.25. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers(major/minor)) δ 8.42 (s, 0.3H, N*H* indole (minor)), 8.35 (s, 0.7H, N*H* indole (major)), 7.58 (d, *J* = 7.9 Hz, 0.3H, Ar*H* (minor)), 7.50 (d, *J* = 7.9 Hz, 0.7H, Ar*H* (major)), 7.39-7.27 (m, 6H, Ar*H* (major+minor)), 7.24-7.17 (m, 1H, Ar*H* (major+minor)), 7.17-7.09 (m, 1H, Ar*H* (major+minor)), 6.88-6.80 (m, 1H, Ar*H* (major+minor)), 5.80 (s, 0.3H, N*H* Gly (minor)), 5.66 (s, 0.7H, N*H* Gly (major)), 5.59 (dd, *J* = 7.1, 2.7 Hz, 0.3H, C(O)NC*H* (minor)), 5.23-5.14 (m, 0.7H, C(O)NC*H* (major)), 5.11 (s, 0.6H, OCH_2Ph (minor)), 5.04 (s, 1.4H, OCH_2Ph (major)), 4.04 (dd, *J* = 15.8, 4.6 Hz, 1.3H, C(O)CH_2NHCbz (major+minor)), 3.81 (dt, *J* = 12.0, 5.8 Hz, 0.7H, C(O)NCH_2 (major)), 3.69 (m, 1.7H, C(O)CH_2NHCbz (major) and C(O)NCH_2 (major+minor)), 3.53 (q, *J* = 8.1 Hz, 0.3H, C(O)NCH_2 (minor)), 2.36-1.85 (m, 4H, NCH$_2$CH_2CH_2CH (major+minor)).^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.7, 166.7, 156.5, 156.3, 137.0, 136.6, 128.6, 128.2, 128.1, 125.3, 124.8, 122.7, 122.2, 121.4, 121.3, 120.0, 119.6, 119.0, 118.7, 116.8, 116.7, 111.8, 111.6, 67.0, 66.9, 55.0, 54.9, 46.9, 46.0, 45.9, 43.7, 43.4, 34.5, 32.1, 24.2, 22.2. IR (v_{max}, cm^{-1}) 3311 (m), 3046 (w), 2977 (m), 2876 (w), 1710 (s), 1638 (s), 1521 (m), 1455 (s), 1252 (s), 1165 (m), 1055 (m), 910 (m), 737 (s) HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}N_3NaO_3^+$ 400.1632; Found 400.1629.

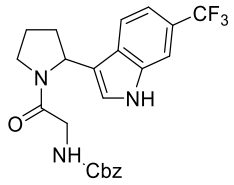
Benzyl (2-(2-(5-chloro-1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6b)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 5-Chloro-1H-indole (46 mg, 0.31 mmol, 1.02 equiv), **6b** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a pale yellow oil (82 mg, 0.20 mmol, 66%).

Rf (DCM/ethyl acetate 7:3): 0.36. ^{1}H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers(major/minor)) δ 8.72 (s, 0.4H, N*H* indole (minor)), 8.59 (s, 0.6H, N*H* indole (major)), 7.51 (d, *J* = 1.7 Hz, 0.4H, Ar*H* (minor)), 7.47-7.41 (m, 0.6H, Ar*H* (major)), 7.36-7.27 (m, 5H, Ar*H* (major+minor)), 7.22 (dd, *J* = 14.1, 8.7 Hz, 1H, Ar*H* (major+minor)), 7.11 (td, *J* = 8.7, 8.0, 1.7 Hz, 1H, Ar*H* (major+minor)), 6.82 (d, *J* = 1.9 Hz, 0.4H, Ar*H* (minor)), 6.73 (d, *J* = 2.4 Hz, 0.6H, Ar*H* (minor)), 5.75 (s, 0.4H, N*H* Gly (minor)), 5.68 (s, 0.6H, N*H* Gly (major)), 5.53-5.47 (m, 0.4H, C(O)NC*H* (minor)), 5.15-4.99 (m, 2.6H, C(O)NC*H* (major) and OCH_2Ph (major+minor)), 4.13-3.93 (m, 1.4H, C(O)CH_2NHCbz (major+minor)), 3.81-3.68 (m, 1.6H, C(O)NCH_2 (major+minor)), 3.64 (dd, *J* = 17.4, 4.5 Hz, 0.6H, C(O)CH_2NHCbz (major)), 3.53 (q, *J* = 7.8 Hz, 0.4H, C(O)NCH_2 (minor)), 2.35-2.16 (m, 1H, NCH$_2$CH_2CH_2CH (major+minor)), 2.06 (dtd, *J* = 17.1, 8.2, 3.7 Hz, 2H, NCH$_2$CH_2CH_2CH (major+minor)), 1.96-1.84 (m, 1H, NCH$_2$CH_2CH_2CH (major+minor)). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.6, 166.9, 156.4, 156.3, 136.4, 135.3, 135.2, 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 126.1, 125.6, 125.5, 125.1, 122.9, 122.7, 122.3, 118.2, 118.0, 116.3, 116.2, 112.8, 112.6, 67.0, 66.9, 54.8, 54.6, 46.8, 46.0, 43.6, 43.3, 34.4, 32.1, 24.0, 22.1. IR (v_{max}, cm^{-1}) 3308 (m), 2927 (m), 1710 (s), 1638 (s), 1520 (m), 1454 (s), 1254 (s), 1173 (m), 1055 (m), 909 (s), 733 (s).HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{22}H_{22}ClN_3NaO_3^+$ 434.1242; Found 434.1253.

Benzyl (2-oxo-2-(2-(6-(trifluoromethyl)-1H-indol-3-yl)pyrrolidin-1-yl)ethyl)carbamate (6c)

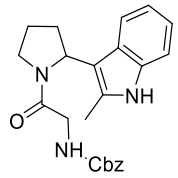


Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 6-trifluoromethyl-1H-indole (57 mg, 0.31 mmol, 1.02 equiv), **6c** was obtained after column chromatography DCM to DCM/ethyl acetate 7:3 as a pale yellow oil (67 mg, 0.15 mmol, 50%).

Rf (DCM/ethyl acetate 7:3): 0.35. ^{1}H NMR (400 MHz, Acetonitrile-d_3, 1:1 mixture of rotamers, (R^1/R^2)) δ 9.69 (s, 0.5H, N*H* indole (R^1)), 9.52 (s, 0.5H, N*H* indole (R^2)), 7.79-7.73 (m, 1H, Ar*H* (R^1+R^2)), 7.73-7.66 (m, 1H, Ar*H* (R^1+R^2)), 7.39-7.26 (m, 5H, Ar*H* (R^1+R^2)), 7.26-7.21 (m, 1H, Ar*H* (R^1+R^2)), 7.19-7.09 (m, 1H, Ar*H* (R^1+R^2)), 5.84 (s, 0.5H, N*H* Gly (R^1)), 5.72 (s, 0.5H, N*H* Gly (R^2)), 5.47-5.39 (m, 0.5H, C(O)NC*H* (R^1)), 5.29 (d, *J* = 5.4 Hz, 0.5H, C(O)NC*H* (R^2)), 5.05 (s, 1H, OCH_2Ph (R^1)), 4.98 (s, 1H, OCH_2Ph (R^2)), 3.96 (d, *J* = 5.3 Hz, 1H, C(O)CH_2NHCbz (R^1+R^2)), 3.89 (dd, *J* = 17.2, 5.3 Hz, 0.5H, NC(O)CH_2NHCbz (R^1)), 3.72 (dt, *J* = 11.7, 6.3 Hz, 1H, C(O)NCH_2 (R^1+R^2)), 3.57 (m, 1H, C(O)NCH_2 (R^1+R^2)), 3.44 (dd, *J* = 17.0, 5.5 Hz, 0.5H,

C(O)CH_2NHCbz (R^2)), 2.39-2.13 (m, 2H, NCH$_2$CH_2CH_2CH (R^1+R^2)), 2.03-1.97 (m, 1H, NCH$_2$CH_2CH_2CH (R^1+R^2)), 1.91-1.82 (m, 1H, NCH$_2$CH_2CH_2CH (R^1+R^2)).^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of rotamers, signals not fully resolved) δ 168.5, 167.8, 157.3 (d, *J* = 12.25 Hz), 138.2, 136.7, 136.4, 129.4, 129.3, 128.8, 128.7, 128.3, 127.8, 126.3, 125.9, 125.1, 124.3, 124.0, 123.8, 123.5, 120.28 (d, *J* = 13.93 Hz), 118.8, 116.4 (dd, *J* = 36.31, 3.45 Hz), 110.12 (dd, *J* = 28.22, 4.43 Hz), 67.1, 67.0, 55.0, 54.8, 47.4, 46.6, 44.1, 43.8, 35.5, 33.0, 30.3, 24.7, 22.8. IR (v_{max}, cm^{-1}) 3365 (s), 3032 (m), 2930 (m), 1710 (s), 1642 (s), 1509 (s), 1454 (s), 1336 (s), 1257 (s), 1157 (s), 1111 (s), 1053 (s), 961 (m), 878 (m), 816 (s), 698 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{22}F_3N_3NaO_3^+$ 468.1505; Found 468.1513.

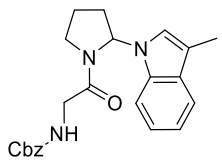
Benzyl (2-(2-(2-methyl-1H-indol-3-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6d)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 2-Methyl-1H-indole (40 mg, 0.31 mmol, 1.02 equiv), **6d** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a brown amorphous solid (58 mg, 0.15 mmol, 49%).

Rf (DCM/ethyl acetate 7:3): 0.36. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 8.25 (s, 0.3H, N*H* indole (minor)), 8.18 (s, 0.7H, N*H* indole (major)), 7.34-7.22 (m, 7H, Ar*H* (major+minor)), 7.16-7.08 (m, 1H, Ar*H* (major+minor)), 7.04 (dd, *J* = 9.3, 6.6 Hz, 1H, Ar*H* (major+minor)), 5.65 (s, 1H, N*H* Gly (major+minor)), 5.32 (t, *J* = 6.9 Hz, 0.3H, C(O)NC*H* (minor)), 5.10-4.98 (m, 2.7H, C(O)NC*H* (major) and OCH_2Ph (major+minor)), 4.10 (dd, *J* = 17.0, 4.5 Hz, 0.3H, C(O)CH_2NHCbz (minor)), 4.00-3.90 (m, 1.7H, C(O)CH_2NHCbz (major+minor) and C(O)NCH_2 (major)), 3.79 (dt, *J* = 12.8, 7.2 Hz, 1H, C(O)NCH_2 (major+minor)), 3.69 (td, *J* = 10.1, 8.0, 5.6 Hz, 0.3H, C(O)NCH_2 (minor)), 3.30 (dd, *J* = 17.3, 3.2 Hz, 0.7H, C(O)CH_2NHCbz (major)), 2.40-2.28 (m, 4H, CH_3 and NCH$_2$CH_2CH_2CH (major+minor)), 2.22-1.84 (m, 3H, NCH$_2$CH_2CH_2CH (major+minor)).^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 167.8, 166.4, 156.3, 156.2, 136.6, 135.5, 131.9, 131.3, 128.6, 128.1, 128.0, 126.2, 125.7, 121.6, 120.9, 119.9, 119.4, 118.1, 117.7, 111.6, 111.1, 110.9, 66.9, 66.8, 55.1, 54.8, 47.8, 47.1, 43.7, 43.3, 35.6, 32.7, 25.4, 23.7, 12.0, 11.8. IR (v_{max}, cm^{-1}) 3393 (m), 3299 (m), 3060 (m), 2965 (m), 2875 (m), 1710 (s), 1637 (s), 1510 (m), 1459 (s), 1237 (m), 910 (m), 737 (s). HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{26}N_3O_3^+$ 392.1969; Found 392.1977

Benzyl (2-(2-(3-methyl-1H-indol-1-yl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (6e)

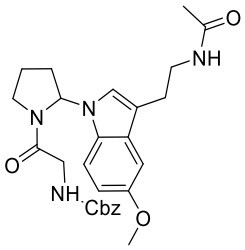


Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and 3-Methyl-1H-indole (40 mg, 0.31 mmol, 1.02 equiv), **6e** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (50 mg, 0.13 mmol, 43%).

Rf (DCM/ethyl acetate 7:3): 0.58. ^{1}H NMR (400 MHz, Chloroform-*d*, 6:4 mixture of rotamers (major/minor)) δ 7.55 (dd, *J* = 17.6, 7.8 Hz, 1H, Ar*H* (major+minor)), 7.43 (d, *J* = 8.2 Hz, 0.4H,

Ar*H* (minor)), 7.31 (*t*, J = 7.3 Hz, 6H, Ar*H* (major+minor)), 7.24-7.08 (m, 1.6H, Ar*H* (major+minor)), 6.76 (d, *J* = 11.0 Hz, 1H, Ar*H* (major+minor)), 6.52-6.45 (m, 0.4H, C(O)NC*H* (minor)), 6.21 (d, *J* = 5.2 Hz, 0.6H, C(O)NC*H* (major)), 5.65 (br s, 0.4H, N*H* (minor)), 5.43 (br s, 0.6H, N*H* (major)), 5.18-4.93 (m, 2H, OCH_2Ph (major+minor)), 4.13 (ddt, *J* = 13.9, 10.6, 5.0 Hz, 1H, C(O)CH_2NHCbz (major+minor)), 3.96 (ddd, *J* = 16.3, 10.9, 4.2 Hz, 1H, C(O)CH_2NHCbz (minor) and C(O)NCH_2 (major)), 3.84 (d, *J* = 10.2 Hz, 0.4H, C(O)NCH_2 (minor)), 3.73 (dt, *J* = 11.6, 8.1 Hz, 0.6H, C(O)NCH_2 (major)), 3.60 (dt, *J* = 18.4, 9.4 Hz, 0.4H, C(O)NCH_2 (minor)), 3.20 (dd, *J* = 17.4, 3.3 Hz, 0.6H,NC(O)CH_2NHCbz (major)), 2.47-2.23 (m, 4H, CH_3 and NCH$_2$CH_2CH_2CH (major+minor)), 2.23-1.96 (m, 3H, NCH$_2$CH_2CH_2CH (major+minor)).^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 168.8, 167.8, 156.4, 156.3, 136.5, 134.9, 129.7, 129.2, 128.7, 128.6, 128.2, 128.1, 128.0, 122.6, 122.0, 121.5, 121.1, 119.9, 119.7, 119.3, 119.2, 112.8, 111.8, 109.8, 109.2, 68.7, 68.1, 67.0, 47.2, 46.1, 43.8, 43.1, 34.8, 32.3, 23.9, 21.7, 9.9. IR (v_{max}, cm^{-1}) 3415 (m), 3053 (m), 2935 (w), 2145 (w), 1714 (s), 1662 (s), 1510 (m), 1432 (m), 1350 (m), 1193 (m), 985 (m), 910 (s), 736 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{25}N_3NaO_3^+$ 414.1788; Found 414.1797.

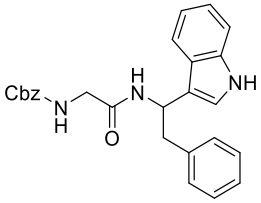
Benzyl (2-(2-(3-(2-acetamidoethyl)-5-methoxy-1H-indol-1-yl)pyrrolidin-1-yl)-2-oxoethyl) carbamate (6f)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and melatonin (71 mg, 0.31 mmol, 1.02 equiv), **6f** was obtained after column chromatography DCM to ethyl acetate as a colorless oil (95 mg, 0.19 mmol, 64% yield).

Rf (DCM/ethyl acetate 7:3): 0.13. ^{1}H NMR (400 MHz, Chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 7.38-7.27 (m, 5.3H, Ar*H* (major+minor)), 7.19 (d, *J* = 8.9 Hz, 0.7H, Ar*H* (major)), 7.03 (d, *J* = 2.3 Hz, 0.7H, Ar*H* (major)), 6.98 (d, *J* = 2.3 Hz, 0.3H, Ar*H* (minor)), 6.90 (dt, *J* = 8.8, 2.9 Hz, 1H, Ar*H* (major+minor)), 6.86 (s, 0.3H, Ar*H* (minor)), 6.82 (s, 0.7H, Ar*H* (major)), 6.40 (d, *J* = 5.3 Hz, 0.3H, C(O)NC*H* (minor)), 6.28 (s, 0.7H, AcN*H* (major)), 6.08 (dd, *J* = 6.0, 2.8 Hz, 0.7H, C(O)NC*H* (major)), 5.65 (s, 0.6H, AcN*H* and CbzN*H* (minor)), 5.48 (s, 0.7H, CbzN*H* (major)), 5.09 (s, 0.6H, OCH_2Ph (minor)), 5.00 (d, *J* = 2.8 Hz, 1.4H, OCH_2Ph (major)), 4.15-3.89 (m, 1.7H, C(O)CH_2NHCbz (major+minor) and C(O)NCH_2 (major)), 3.89-3.70 (m, 4.3H, OCH_3 (major+minor), C(O)CH_2NHCbz (minor) and C(O)NCH_2 (major+minor)), 3.54 (m, 2.3H, C(O)NCH_2 (minor) and CH_2NHAc (major+minor)), 3.17 (dd, *J* = 17.4, 5.6 Hz, 0.7H, C(O)CH_2NHCbz (major)), 2.90 (dt, *J* = 13.9, 7.0 Hz, 2H, CH_2CH$_2$NHAc (major+minor)), 2.47-1.97 (m, 4H, NCH$_2$CH_2CH_2CH (major+minor)), 1.88 (d, *J* = 14.7 Hz, 3H, NHC(O)CH_3 (major+minor)).^{13}C NMR (101 MHz, Chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 170.7, 170.3, 168.6, 168.0, 156.5, 154.6, 154.3, 136.4, 136.2, 130.9, 129.8, 129.6, 128.8, 128.6, 128.3, 128.2, 128.1, 122.9, 122.6, 114.1, 113.0, 112.3, 112.2, 110.8, 110.2, 101.4, 101.1, 69.2, 68.5, 67.1, 56.0, 47.2, 46.1, 43.8, 43.0, 40.2, 39.5, 34.7, 32.2, 25.5, 25.0, 23.9, 23.5, 23.3, 21.8. IR (v_{max}, cm^{-1}) 3330 (m), 3033 (m), 2946 (m), 2833 (m), 1715 (s), 1654 (s), 1542 (s), 1484 (s), 1453 (s), 1220 (s), 1050 (m), 909 (s), 733 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{27}H_{32}N_4NaO_5^+$ 515.2265; Found 515.2276

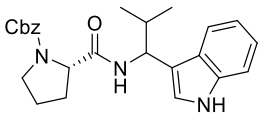
Benzyl (2-((1-(1H-indol-3-yl)-2-phenylethyl)amino)-2-oxoethyl)carbamate (6g)



Following General Procedure 4 and starting with Cbz-Gly-Phe (**1c**) (107 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (36 mg, 0.31 mmol, 1.02 equiv), **6g** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a red amorphous solid (74 mg, 0.17 mmol, 58%).

Rf (DCM/ethyl acetate 7:3): 0.32. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12-7.93 (m, 1H, N*H* indole), 7.64 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.34 (d, *J* = 7.9 Hz, 6H, Ar*H*), 7.24-7.06 (m, 7H, Ar*H*), 6.93-6.88 (m, 1H, Ar*H*), 6.45-6.19 (m, 1H, N*H* Phe), 5.59 (q, *J* = 7.2 Hz, 1H, NHC*H* Phe), 5.45-5.28 (m, 1H, N*H* Gly), 5.08 (s, 2H, OCH_2Ph), 3.74 (t, *J* = 6.9 Hz, 2H, NHCH_2 Gly), 3.26 (tt, *J* = 13.6, 6.7 Hz, 2H, NHCHCH_2 Phe). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.1, 156.7, 138.0, 136.6, 136.2, 129.4, 128.7, 128.4, 128.3, 128.2, 126.6, 125.9, 122.6, 122.1, 120.1, 119.3, 116.0, 111.6, 67.3, 48.1, 44.8, 41.1. IR (ν_{max}, cm^{-1}) 3344 (m), 3032 (m), 2946 (m), 1712 (s), 1661 (s), 1521 (s), 1455 (m), 1339 (m), 1259 (m), 1155 (m), 1075 (m), 910 (s), 740 (s), 699 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{26}H_{25}N_3NaO_3^+$ 450.1788; Found 450.1792

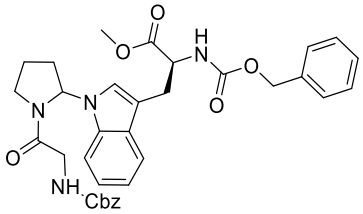
Benzyl (2S)-2-((1-(1H-indol-3-yl)-2-methylpropyl)carbamoyl)pyrrolidine-1-carboxylate (6h)



Following General Procedure 4 and starting with Cbz-Pro-Val (**1d**) (105 mg, 0.30 mmol, 1.0 equiv) and 1H-indole (**x**) (36 mg, 0.31 mmol, 1.02 equiv), **6h** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a red amorphous solid (81 mg, 0.19 mmol, 64%).

Rf (DCM/ethyl acetate 7:3): 0.29. ^{1}H NMR (400 MHz, Chloroform-*d*, complex mixture of diastereomers and rotamers) δ 8.22-7.85 (m, 1H, N*H* indole), 7.62-7.41 (m, 1H, Ar*H*), 7.26 (m, 5H, Ar*H*), 7.14-6.74 (m, 4H, Ar*H*), 6.24 (m, 0.4H, N*H* Val not fully resolved), 5.21-4.86 (m, 3H, OCH_2Ph and NHC*H* Val), 4.47-4.19 (m, 1H, CbzNC*H* Pro), 3.56-3.18 (m, 2H, CbzNCH_2 Pro), 2.42-1.94 (m, 3H, NHCHC*H* Val and NCH$_2$CH_2CH_2CH Pro), 1.89-1.63 (m, 2H, NCH$_2$CH_2CH_2CH Pro), 0.97-0.69 (m, 6H, CH_3 Val). ^{13}C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 171.2, 170.7, 156.4, 155.7, 136.6, 136.5, 128.7, 128.3, 126.3, 122.1, 121.9, 119.5, 116.7, 116.2, 111.4, 67.4, 61.4, 60.8, 52.5, 47.8, 47.1, 32.8, 31.2, 28.1, 24.7, 23.6, 20.2, 19.0, 18.7. IR (ν_{max}, cm^{-1}) 3314 (m), 2962 (m), 2910 (m), 1690 (s), 1660 (s), 1520 (m), 1418 (s), 1356 (s), 1210 (m), 1118 (m), 909 (s), 735 (s), 698 (m). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{29}N_3NaO_3^+$ 442.2101; Found 442.2107.

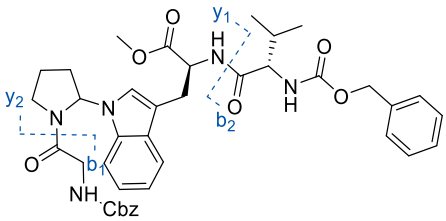
Methyl Nα-((benzyloxy)carbonyl)-1-(1-(((benzyloxy)carbonyl)glycyl)pyrrolidin-2-yl)-L-tryptophanate (6i)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and Z-Trp-OMe (108 mg, 0.306 mmol, 1.02 equiv), **6i** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (105 mg, 0.171 mmol, 57% yield).

Rf (DCM/ethyl acetate 7:3): 0.58. ^{1}H NMR (400 MHz, Chloroform-*d*, complex mixture of diastereomers and rotamers) δ 7.57-7.39 (m, 2H, Ar*H*), 7.38-7.27 (m, 10H, Ar*H*), 7.21-7.06 (m, 2H, Ar*H*), 6.83-6.66 (m, 1H, Ar*H*), 6.45 (d, *J* = 6.2 Hz, 0.4H, C(O)NC*H* Pro), 6.17 (t, *J* = 5.5 Hz, 0.6H, C(O)NC*H* Pro), 5.66-5.22 (m, 2H, N*H* Gly+Trp), 5.05 (m, 4H, OCH_2Ph Gly+Trp), 4.76-4.64 (m, 1H, NHC*H* Trp), 4.18-3.86 (m, 2H, C(O)NCH_2 Pro and NHCH_2 Gly), 3.79-3.50 (m, 4H, OCH_3 Trp and C(O)NCH_2 Pro), 3.41-2.96 (m, 3H, NHCH_2 Gly and NHCHCH_2 Trp), 2.46-1.88 (m, 4H, NCH$_2$CH_2CH_2CH Pro).^{13}C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers and rotamers, signals not fully resolved) δ 172.5, 172.4, 172.2, 168.9, 168.8, 167.8, 156.5, 156.4, 155.9, 155.8, 136.5, 136.2, 135.5, 134.7, 129.2, 128.6, 128.5, 128.2, 128.1, 122.9, 122.8, 122.4, 122.2, 120.6, 119.9, 119.8, 119.6, 119.1, 118.8, 111.3, 110.9, 110.1, 109.8, 109.4, 68.7, 68.3, 67.0, 67.0, 55.1, 54.8, 54.6, 52.6, 52.5, 47.2, 46.1, 43.8, 43.0, 34.8, 32.2, 28.3, 28.1, 23.8, 21.5. IR (ν_{max}, cm^{-1}) 3411 (m), 3280 (m), 3061 (m), 2937 (m), 1716 (s), 1667 (s), 1517 (m), 1437 (m), 1344 (m), 1211 (s), 1060 (m), 911 (m), 738 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{34}H_{36}N_4NaO_7^+$ 635.2476; Found 635.2491.

Methyl Nα-(((benzyloxy)carbonyl)-L-valyl)-1-(1-(((benzyloxy)carbonyl)glycyl)pyrrolidin-2-yl)-L-tryptophanate (6j)



Following General Procedure 4 and starting with Cbz-Gly-Pro (**1a**) (92 mg, 0.30 mmol, 1.0 equiv) and Z-Val-Trp-OMe (138 mg, 0.306 mmol, 1.02 equiv), **6j** was obtained after column chromatography DCM to DCM/ethyl acetate 10:1 as a white amorphous solid (106 mg, 0.149 mmol, 50% yield).

Rf (DCM/ethyl acetate 7:3): 0.48. ^{1}H NMR (400 MHz, Acetonitrile-d_3, complex mixture of diastereomers and rotamers) δ 7.57-7.42 (m, 2H, Ar*H*), 7.38-7.25 (m, 10H, Ar*H*), 7.18 (dt, *J* = 8.1, 4.9 Hz, 1H, Ar*H*), 7.09 (dt, *J* = 15.1, 7.5 Hz, 2H, Ar*H*), 7.04-6.98 (m, 0.5H, N*H* Trp), 6.82 (dd, *J* = 16.7, 7.4 Hz, 0.5H, N*H* Trp), 6.40-6.25 (m, 1H, C(O)NC*H* Pro), 5.91 (d, *J* = 9.0 Hz, 2H, N*H* Gly+Val), 5.12-4.95 (m, 4H, OCH_2Ph Gly+Val), 4.77-4.64 (m, 1H, NHC*H* Trp), 4.10-3.79 (m, 4H, NHCH_2 Gly, NHCH_2 Val and 1H C(O)NCH_2 Pro), 3.68-3.50 (m, 4H, OCH_3 Trp and 1H C(O)NCH_2 Pro), 3.35-2.77 (m, 2H, NHCHCH_2 Trp), 2.48-2.19 (m, 2H, NCH$_2$CH_2CH_2CH Pro), 2.13-2.01 (m, 3H, NCH$_2$CH_2CH_2CH Pro and NHCHC*H* Val), 0.94-0.72 (m, 6H, CH_3 Val).^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of diastereomers and rotamers, signals not fully resolved) δ 173.1, 173.0, 172.9, 172.8, 172.3, 172.1, 169.6, 169.4, 169.2, 157.6, 157.4, 157.3, 157.0, 138.2, 138.0, 136.2, 135.8, 129.4, 129.3, 129.0, 128.8, 128.7,

128.6, 128.5, 125.1, 124.9, 124.7, 124.4, 123.2, 123.1, 122.8, 122.6, 122.5, 120.8, 120.7, 120.2, 120.1, 120.0, 119.7, 119.6, 119.1, 112.1, 111.8, 111.6, 111.1, 111.0, 110.7, 110.5, 110.0, 109.8, 106.9, 69.5, 69.3, 69.1, 67.2, 67.1, 66.9, 61.4, 61.1, 60.9, 60.3, 56.1, 54.6, 54.2, 53.9, 53.8, 53.5, 53.4, 52.7, 47.7, 47.6, 46.9, 46.8, 44.2, 43.5, 43.4, 35.4, 35.2, 33.4, 33.1, 33.0, 32.6, 32.2, 31.8, 31.7, 28.1, 28.0, 27.9, 27.8, 26.6, 25.7, 25.2, 24.3, 22.3, 22.2, 19.6, 19.5, 19.4, 19.2, 18.3, 18.1, 18.0, 17.8. IR (ν_{max}, cm^{-1}) 3307 (m), 2963 (m), 2892 (m), 1714 (s), 1660 (s), 1524 (s), 1438 (s), 1324 (m), 1236 (s), 1055 (m), 910 (m), 735 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{39}H_{45}N_5NaO_8^+$ 734.3160; Found 734.3167. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 734.3167. Measured b and y ions are reported in the table below

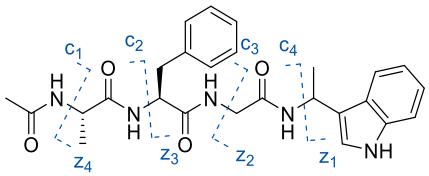
	P	**W**
N-terminal	1	2
b	-	-
C-terminal	2	1
y	521.28	479.23

6. Scope on Tetrapeptides

General procedure 5 for the decarboxylative arylation of Tetrapeptides

A 5 mL test tube was charged under Ar with tetrapeptide (5.0 µmol, 1.0 equiv), BIOAc (4.6 mg, 15 µmol, 3.0 equiv), $Ru(bpy)_3Cl_2$ (1.1 mg, 1.5 µmol, 0.30 equiv) and 1.0 mL of degazed MeCN. The solution was degazed by argon sparging for 5 min. 0.20 mL of the solution were placed into a sealed vial under argon. The reaction mixture was irradiated using blue light LEDs at rt overnight. Then a 41 mM solution of 1H-indole in MeCN (50 µL, 2.0 µmol, 2.0 equiv) and 2,2,2-trifluoroacetic acid (1.2 µL, 15 µmol, 15 equiv) were added. The reaction was let stirring for 1 h. At the end of the reaction, the crude was diluted with 3x the volume of MeCN and injected in RP-HPLC. The yields were determined as the ratio of Aprod/Atotal where Aprod = area in mAU of the product peak (blue arrow in HPLC traces) and Atotal = area in mAU of all peptides products (product, starting material, and side-products if present (red arrow in HPLC traces)). Reported result is an average of 3 independent trials.

(2S)-N-(2-((1-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (8a)



Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**7a**) afforded **8a** in more than 95% HPLC ratio (66% yield with calibration curve) as a mixture of diastereoisomers (retention time 11.299 min).

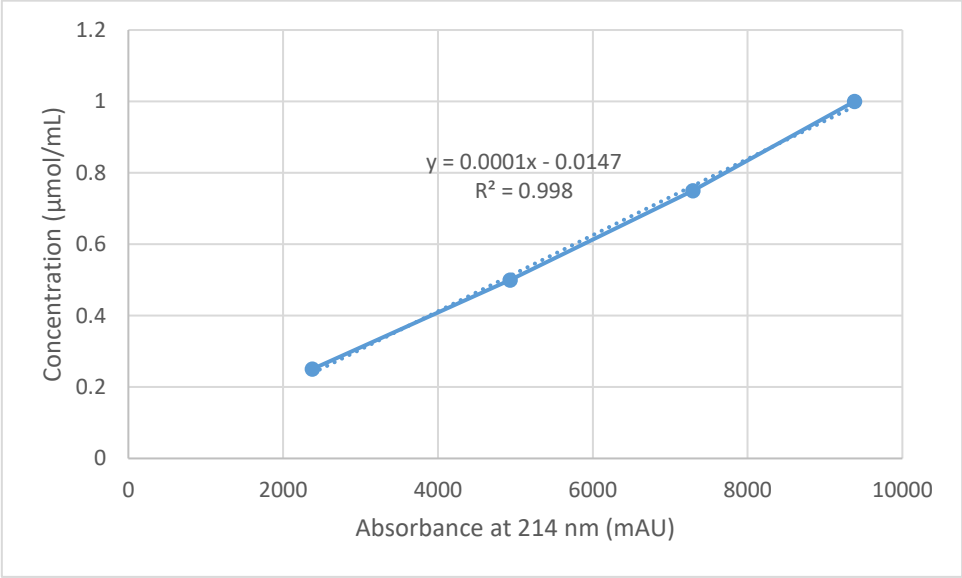
Reaction performed on 20 µmol scale afforded **8a** after purification by preparative RP-HPLC (gradient water-95% acetonitrile in 20 min) as a brown fluffy solid (1.7 mg, 3.6 µmol, 18%).

^{1}H NMR (400 MHz, Acetonitrile-d_3, complex mixture of diastereomers and rotamers) δ 9.21-9.01 (m, 1H, N*H* indole), 7.66-7.56 (m, 1H, Ar*H*), 7.42-7.35 (m, 1H, Ar*H*), 7.34-7.16 (m, 7H, Ar*H*+N*H* Gly), 7.13 (dddd, *J* = 8.2, 7.1, 4.7, 1.1 Hz, 1H, Ar*H*), 7.08-6.91 (m, 3H, Ar*H*+N*H* Ala+Phe), 6.80-6.64 (m, 1H, N*H* Ala), 5.41-5.29 (m, 1H, NHC*H*indole), 4.33 (dddt, *J* = 9.2, 7.1, 5.0, 2.2 Hz, 1H, NHC*H* Phe), 4.10-4.02 (m, 0.5H, AcNHC*H* Ala), 4.01-3.93 (m, 0.5H, AcNHC*H* Ala), 3.77-3.68 (m, 2H, NHCH_2 Gly), 3.17 (dt, *J* = 14.1, 5.0 Hz, 1H, NHCHCH_2Ph Phe), 2.94 (dt, *J* = 10.3, 5.3 Hz, 1H, NHCHCH_2Ph Phe), 1.84 (s, 1.5H C(O)CH_3 Ac-Ala), 1.77 (s, 1.5H, C(O)CH_3 Ac-Ala), 1.55 (dd, *J* = 6.9, 4.8 Hz, 3H, CH_3 Ala-indole), 1.15 (dd, *J* = 7.2, 1.5 Hz, 1.5H, CH_3 Ac-Ala), 1.08 (d, *J* = 7.2 Hz, 1.5H, CH_3 Ac-Ala). ^{13}C NMR (101 MHz, Acetonitrile-d_3, mixture of diastereomers and rotamers, signals not fully resolved) δ 174.3, 174.2, 172.2, 172.2, 168.8, 168.7, 138.6, 138.5, 137.7, 137.6, 130.2, 129.3, 127.6, 122.7, 122.6, 122.6, 120.1, 120.1, 120.0, 120.0, 112.3, 56.2, 56.1, 50.9, 50.9, 43.7, 43.6, 42.6, 42.4, 37.2, 37.1, 22.9, 22.7, 21.6, 21.5, 17.1, 17.0.

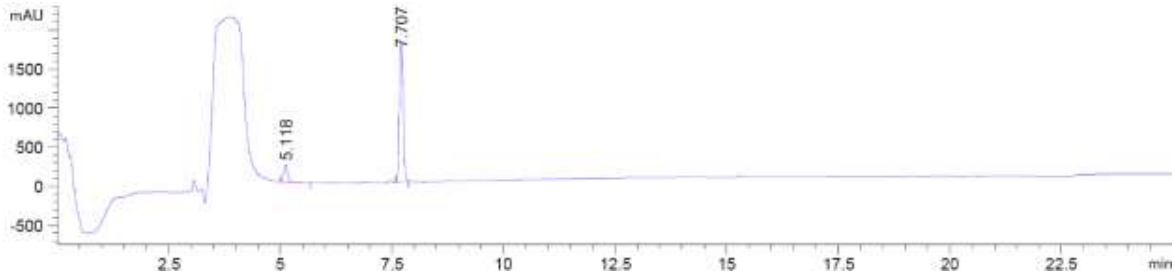
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_5O_4^+$ 478.2449; Found 478.2467. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 478.2467. Measured c and z ions are reported in the table below

	A	F	G	A*
N-terminal	1	2	3	4
c	-	-	-	335.17
C-terminal	4	3	2	1
z	-	-	-	144.08

Calibration with arylated **8a** was achieved through the preparation of several samples of different concentrations and their analysis on RP HPLC. The following linear regression was obtained y = 0,0001x - 0,0147 and R^2 = 0.998, where Y is the concentration in µmol/mL of **8a** and X the absorbance area of the peak at 214 nm.



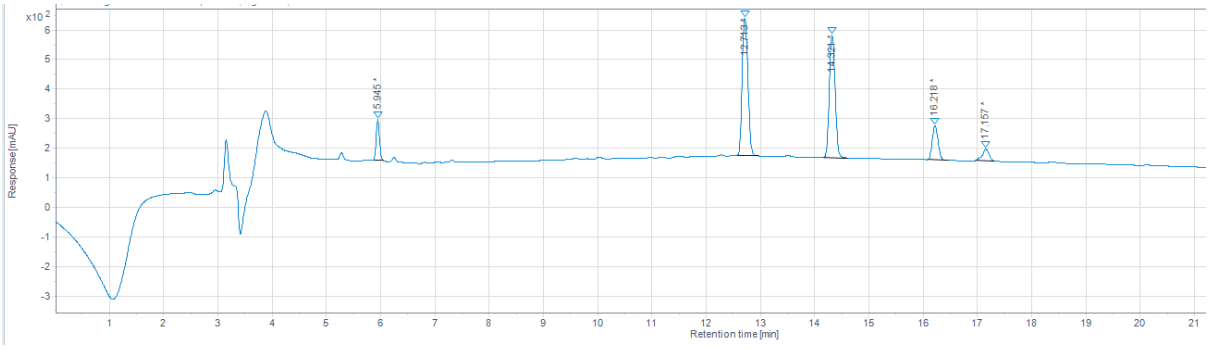
Ac-Ala-Phe-Gly-Ala-OH (**7a**)



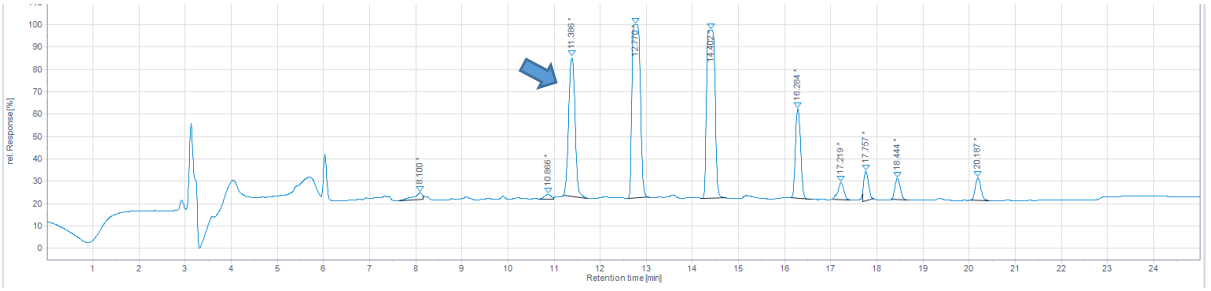
HRMS of **7a** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_6^+$ 429.1745; Found 429.1736.

HPLC-UV chromatogram at 214 nm

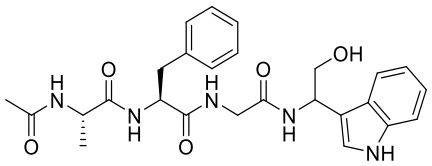
Control experiment without peptide: Iodobenzoic acid (**9**) (12.713 min) and degradation of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (5.945, 14.321, 16.218 min) are observed.



Crude reaction mixture:



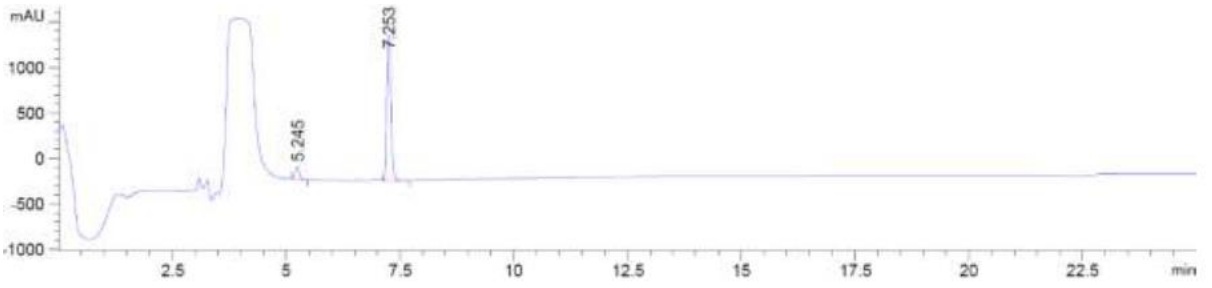
(2S)-2-((S)-2-acetamidopropanamido)-N-(2-((2-hydroxy-1-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-3-phenylpropanamide (8b)



Following general procedure 5, Ac-Ala-Phe-Gly-Ser-OH (**7b**) afforded **8b** in more than 95% HPLC ratio as a mixture of diastereomers (retention time 10.186 min)

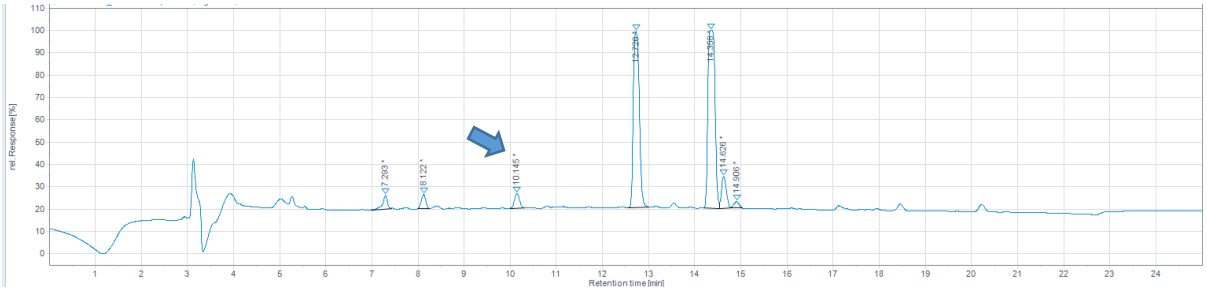
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{31}N_5NaO_5^+$ 516,2217; Found 516,2220

Ac-Ala-Phe-Gly-Ser-OH (**7b**)

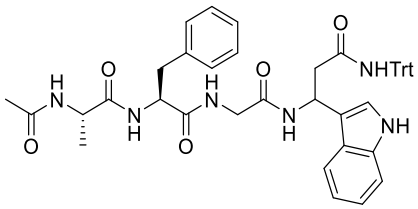


HRMS of **7b** (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_4NaO_7^+$ 445.1694; Found 445.1688.

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



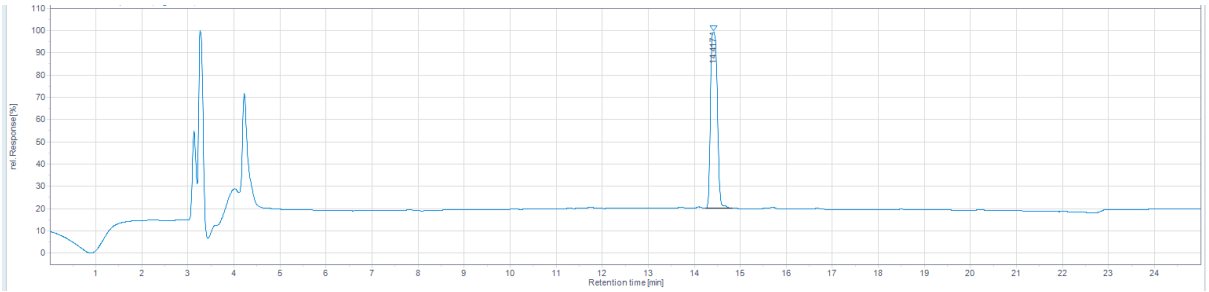
(2S)-N-(2-((1-(1H-indol-3-yl)-3-oxo-3-(tritylamino)propyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (8c)



Following general procedure 5, Ac-Ala-Phe-Gly-Asn(Trt)-OH (**7c**) afforded **8c** in 43% HPLC ratio as a mixture of diastereomers (retention time 16.064 min), which could not be fully separated from a side product.

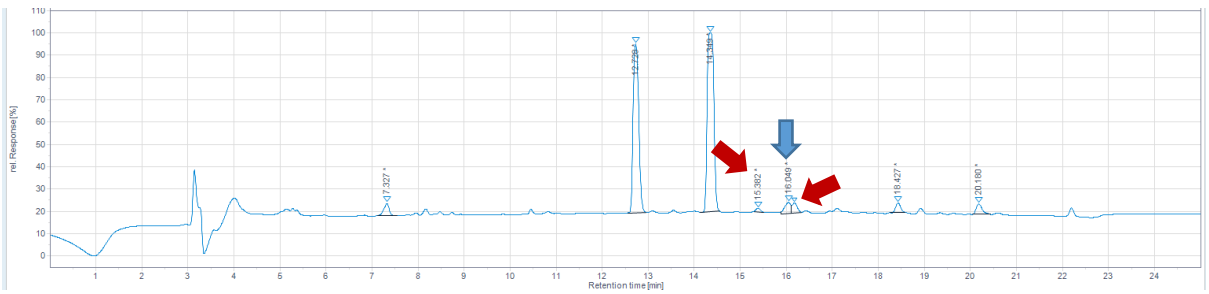
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{46}H_{47}N_6O_5^+$ 763.3602; Found 763.3605.

Ac-Ala-Phe-Gly-Asn(Trt)-OH (**7c**)

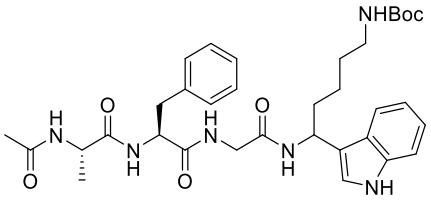


HRMS of **7c** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{39}H_{42}N_5O_7^+$ 692.3079; Found 692.3075.

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



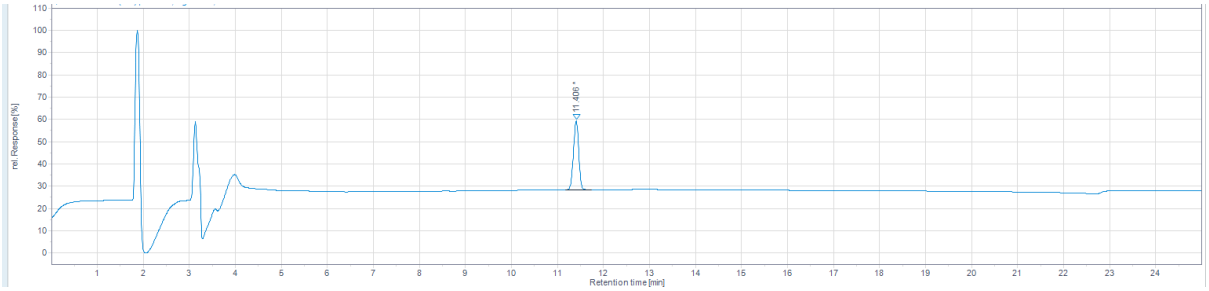
Tert-butyl ((4S,7S)-7-benzyl-13-(1H-indol-3-yl)-4-methyl-2,5,8,11-tetraoxo-3,6,9,12-tetraazaheptadecan-17-yl)carbamate (8d)



Following general procedure 5, Ac-Ala-Phe-Gly-Lys(Boc)-OH (**7d**) afforded **8d** in 35% HPLC ratio as a mixture of diastereomers (retention time 11.683 min)

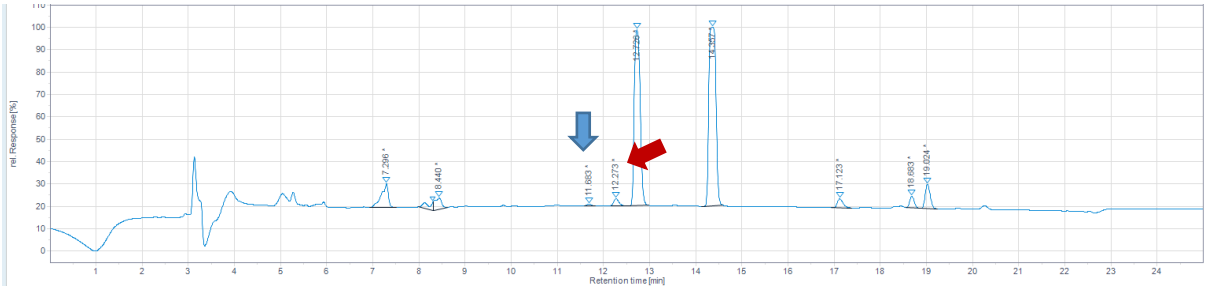
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{34}H_{47}N_6O_6^+$ 635.3552; Found 635.3564.

Ac-Ala-Phe-Gly-Lys(Boc)-OH (**7d**)

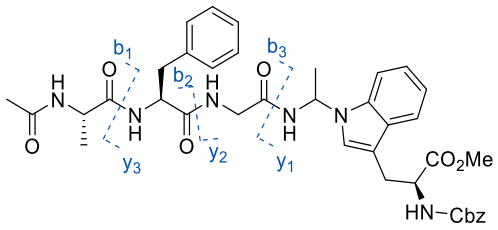


HRMS of **7d** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{27}H_{42}N_5O_8^+$ 564.3028; Found 564.3027.

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



Methyl1-(1-(2-((S)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamido)acetamido) ethyl)-N*α*-((benzyloxy)carbonyl)-L-tryptophanate (8e)

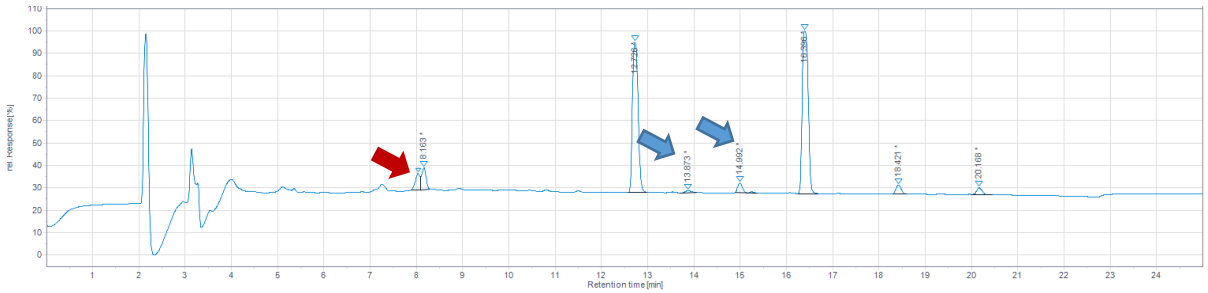


Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**7a**) afforded **8e** in 48% HPLC ratio as a mixture of isomers (retention time 13.873 min + 14.992 min)

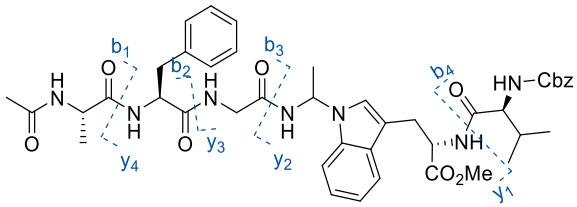
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{38}H_{45}N_6O_8^+$ 713.3293; Found 713.3287. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 713.3287. Measured b and y ions are reported in the table below

	A	F	G	A*
N-terminal	1	2	3	-
b	-	261.12	318.15	-
C-terminal	3	2	1	-
y	600.28	453.21	396.19	-

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



Methyl1-(1-(2-((S)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamido)acetamido) ethyl)-Na-(((benzyloxy)carbonyl)-L-valyl)-L-tryptophanate (8f)

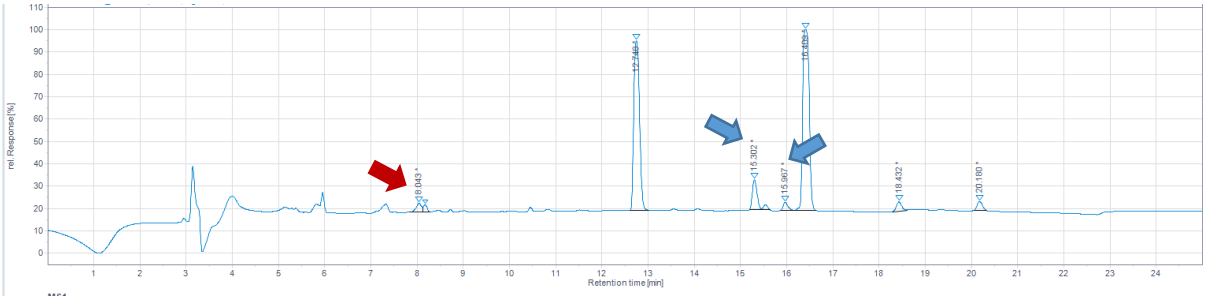


Following general procedure 5, Ac-Ala-Phe-Gly-Ala-OH (**7a**) afforded **8f** in 76% HPLC ratio as a mixture of isomers (retention time 15.302 min + 15.965 min)

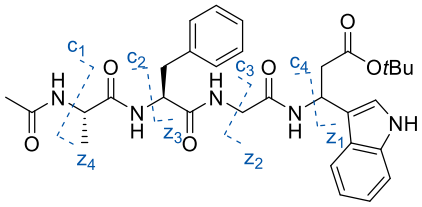
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{43}H_{54}N_7O_9^+$ 812.3978; Found 812.3973. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 812.3973. Measured b and y ions are reported in the table below

	A	F	G	A*	W*	V
N-terminal	1	2	3	-	4	-
b	-	261.12	318.15	-	-	-
C-terminal	3	2	1	-	1	-
y	-	552.28	495.26	-	579.29	-

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



Tert-butyl (4S,7S)-7-benzyl-13-(1H-indol-3-yl)-4-methyl-2,5,8,11-tetraoxo-3,6,9,12-tetraazapentadecan-15-oate (8g)

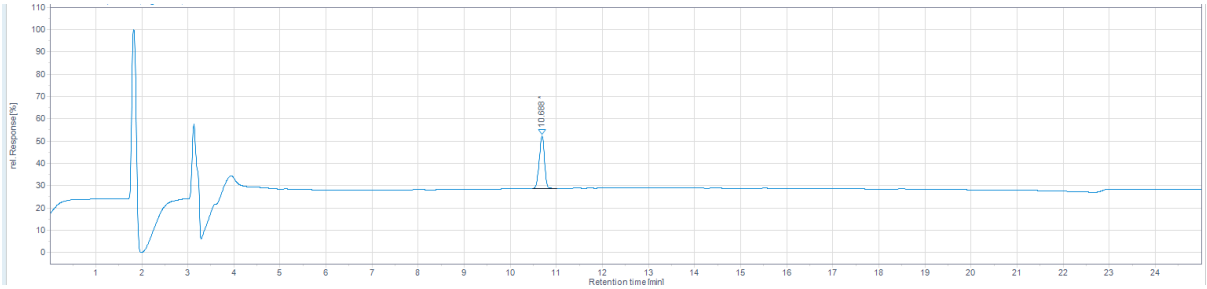


Following general procedure 5, Ac-Ala-Phe-Gly-Asp(O*t*Bu)-OH (**7e**) afforded **8g** in 26% HPLC ratio as a mixture of diastereomers (retention time 13.457 min)

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{31}H_{40}N_5O_6^+$ 578.2973; Found 578.2982. MS-MS (nanochip-ESI/LTQ-Orbitrap): selected ion 578.2982. Measured c and z ions are reported in the table below

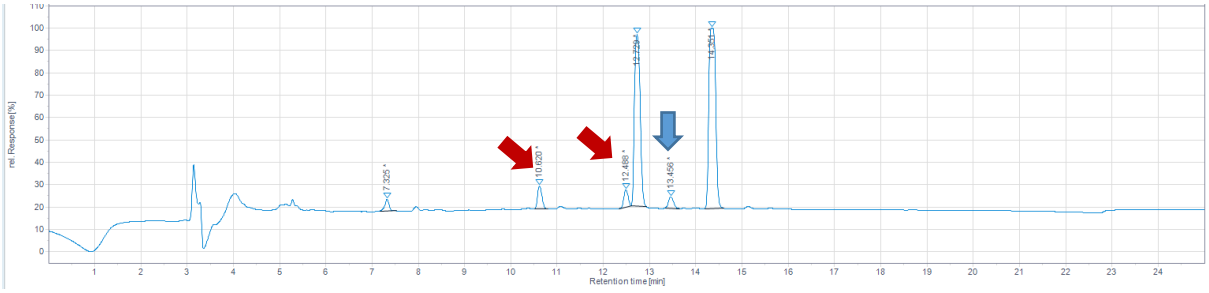
	A	**F**	**G**	**A***
N-terminal	1	2	3	4
c	-	-	278.15	335.17
C-terminal	4	3	2	1
z	519.26	-	-	244.13

Ac-Ala-Phe-Gly-Asp(O*t*Bu)-OH (**7e**)

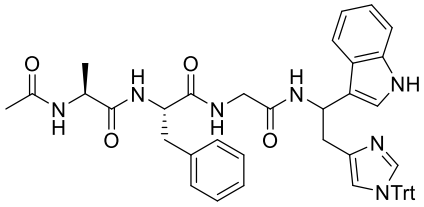


HRMS of **7e** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{24}H_{35}N_4O_8^+$ 507.2449; Found 507.2448.

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



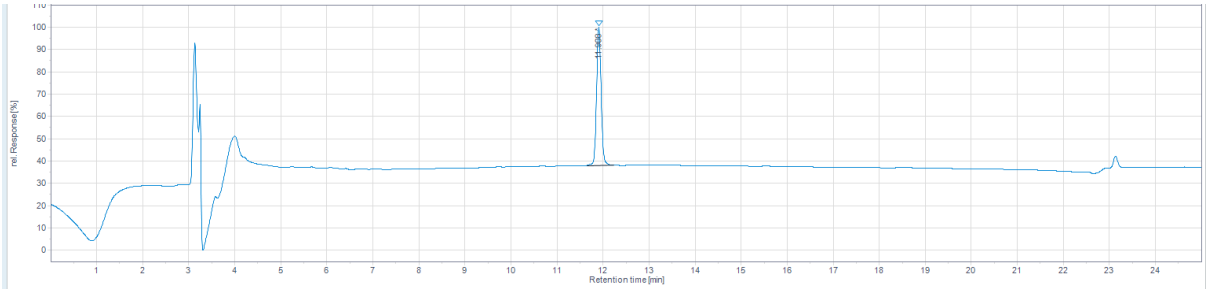
(2S)-N-(2-((1-(1H-indol-3-yl)-2-(1-trityl-1H-imidazol-4-yl)ethyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (8h)



Following general procedure 5, Ac-Ala-Phe-Gly-His(Trt)-OH (**7f**) afforded **8h** in 13% HPLC ratio as a mixture of diastereomers (retention time 13.098 min)

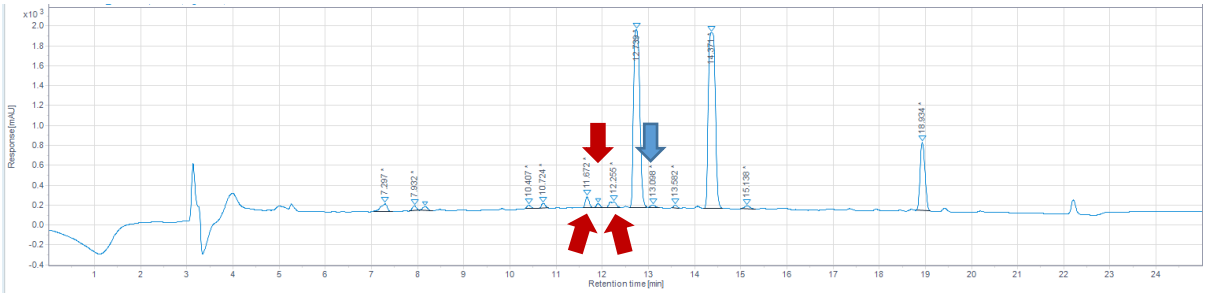
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{48}H_{48}N_7O_4^+$ 786.3762; Found 786.3744.

Ac-Ala-Phe-Gly-His(Trt)-OH (**7f**)

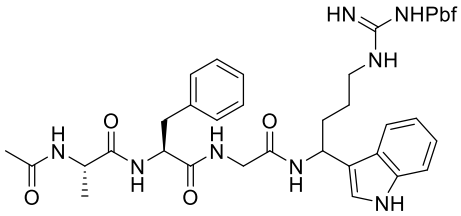


HRMS of **7f** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{41}H_{43}N_6O_6^+$ 715.3239; Found 715.3237.

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



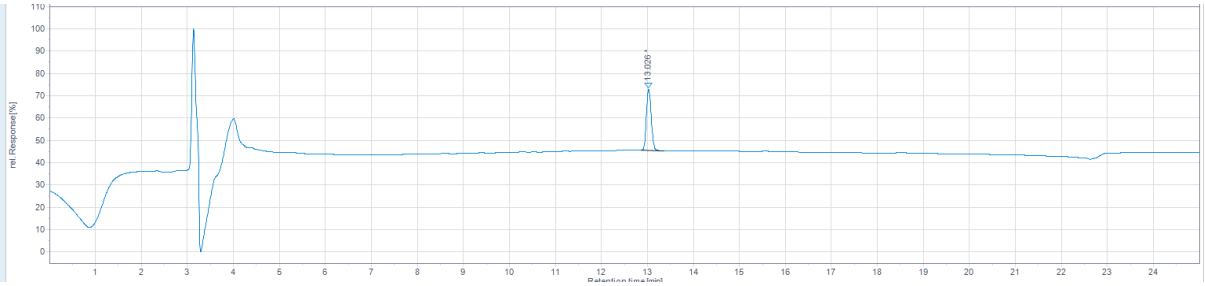
(2S)-N-(2-((1-(1H-indol-3-yl)-4-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)butyl)amino)-2-oxoethyl)-2-((S)-2-acetamidopropanamido)-3-phenylpropanamide (8i)



Following general procedure 5, Ac-Ala-Phe-Gly-Arg(Pbf)-OH (**7g**) afforded **8i** in 11% HPLC ratio as a mixture of diastereomers (retention time 16.150 min)

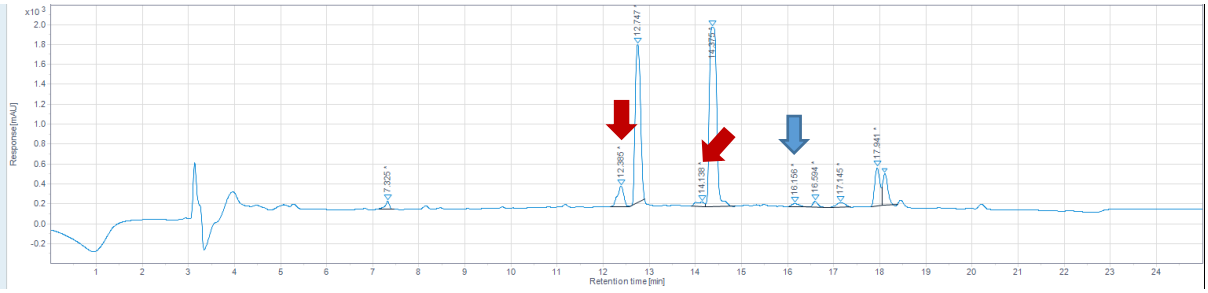
HRMS (ESI/QTOF) m/z: $[M + H_{-1}]^-$ Calcd for $C_{42}H_{53}N_8O_7S^-$ 813.3763; Found 813.3754.

Ac-Ala-Phe-Gly-Arg(Pbf)-OH (**7g**)



HRMS of **7g** (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{35}H_{50}N_7O_9S^+$ 744.3385; Found 744.3383.

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



7. References

[1] J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666.

[2] F. Le Vaillant, M. D. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790–1800.

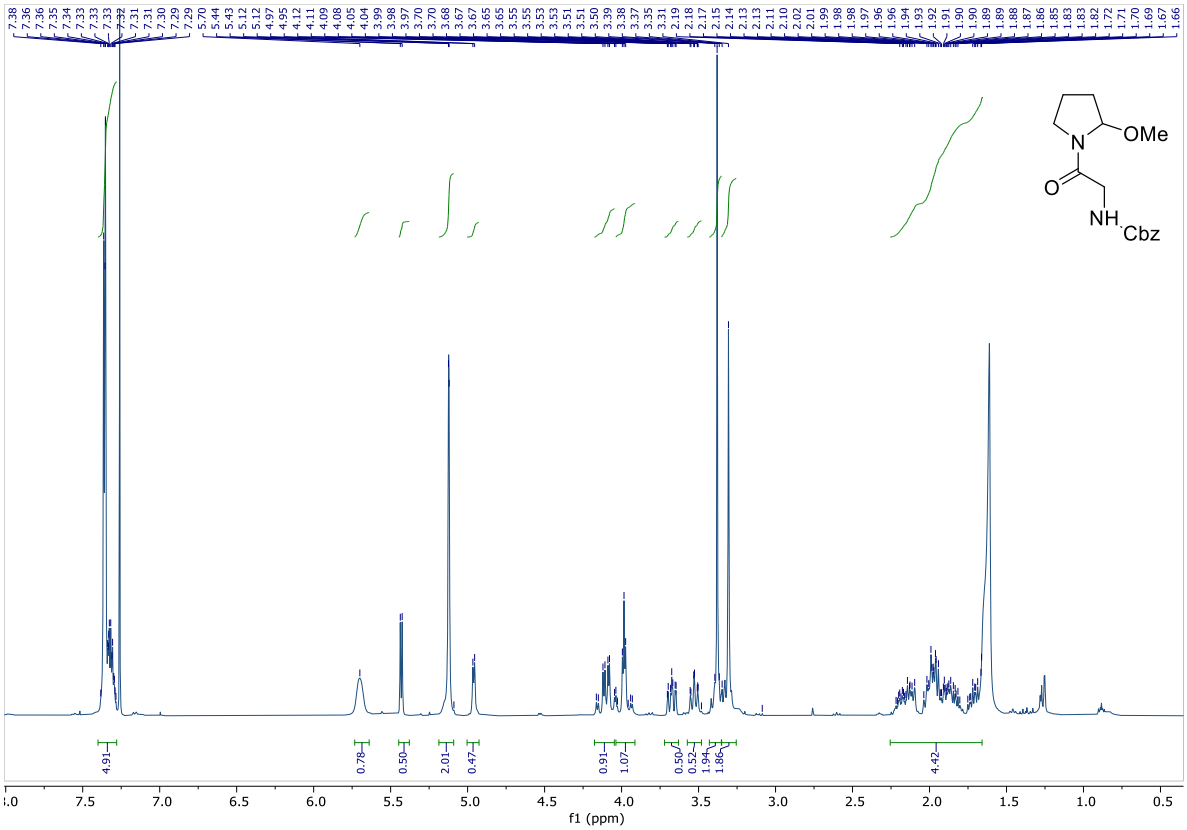
[3] J. Hu, T. Lan, Y. Sun, H. Chen, J. Yao, Y. Rao, *Chem. Commun.* **2015**, *51*, 14929–14932.

[4] H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, *492*, 234–238.

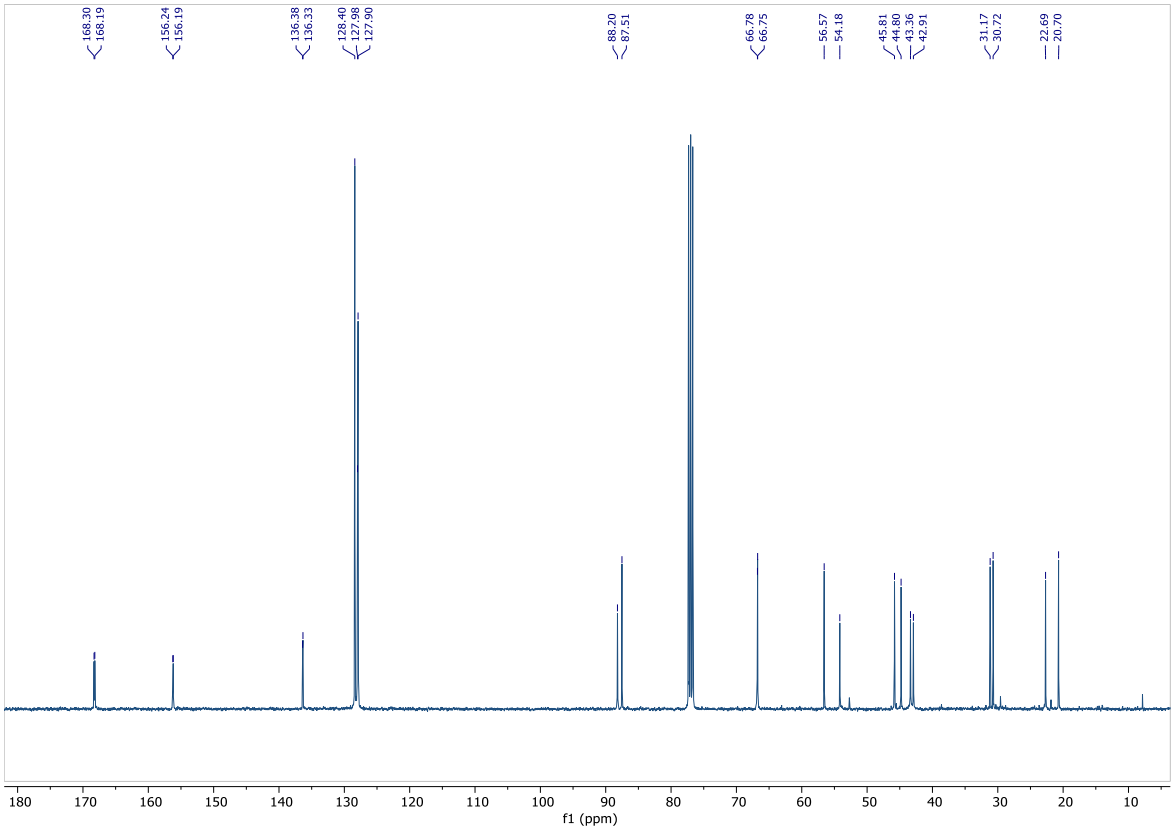
[5] M. Garreau, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 8182–8186.

8. NMR spectra

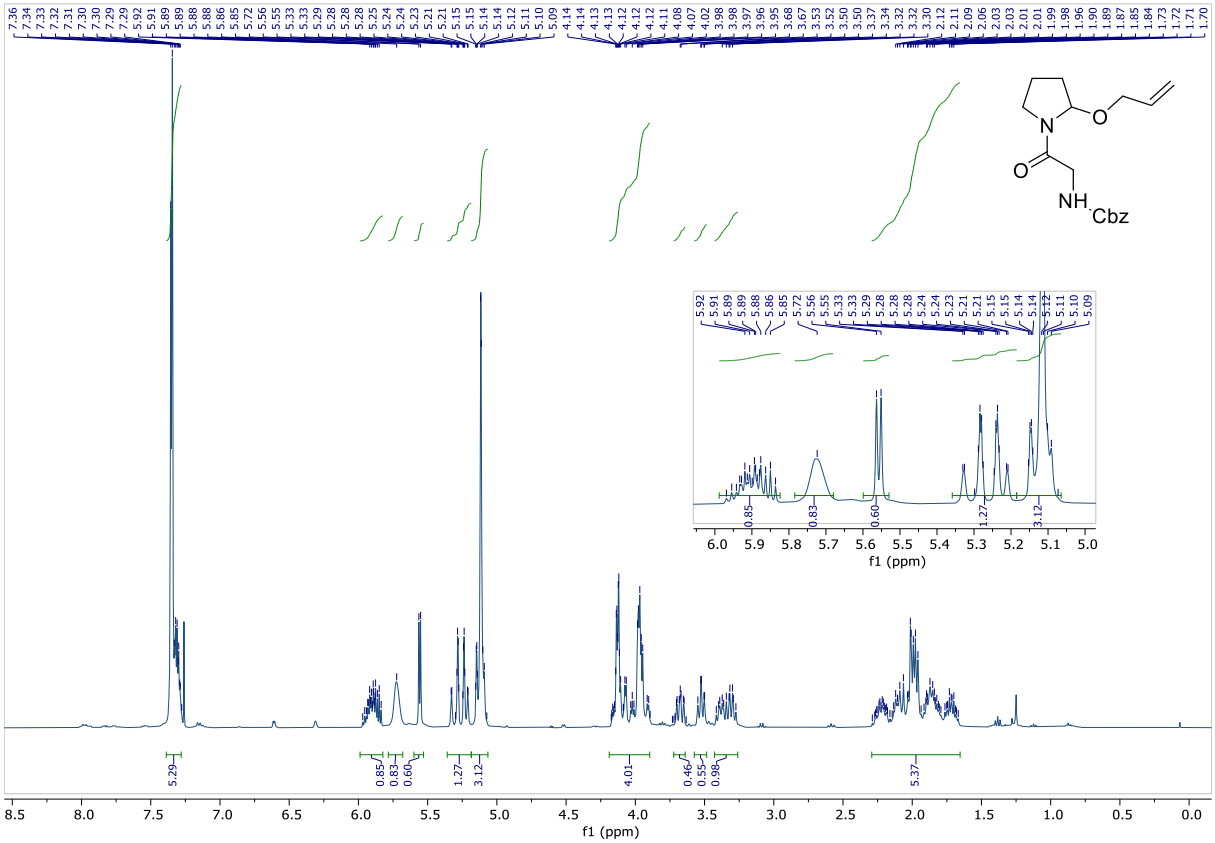
^{1}H-NMR (400 MHz, Chloroform-*d*) (4a)



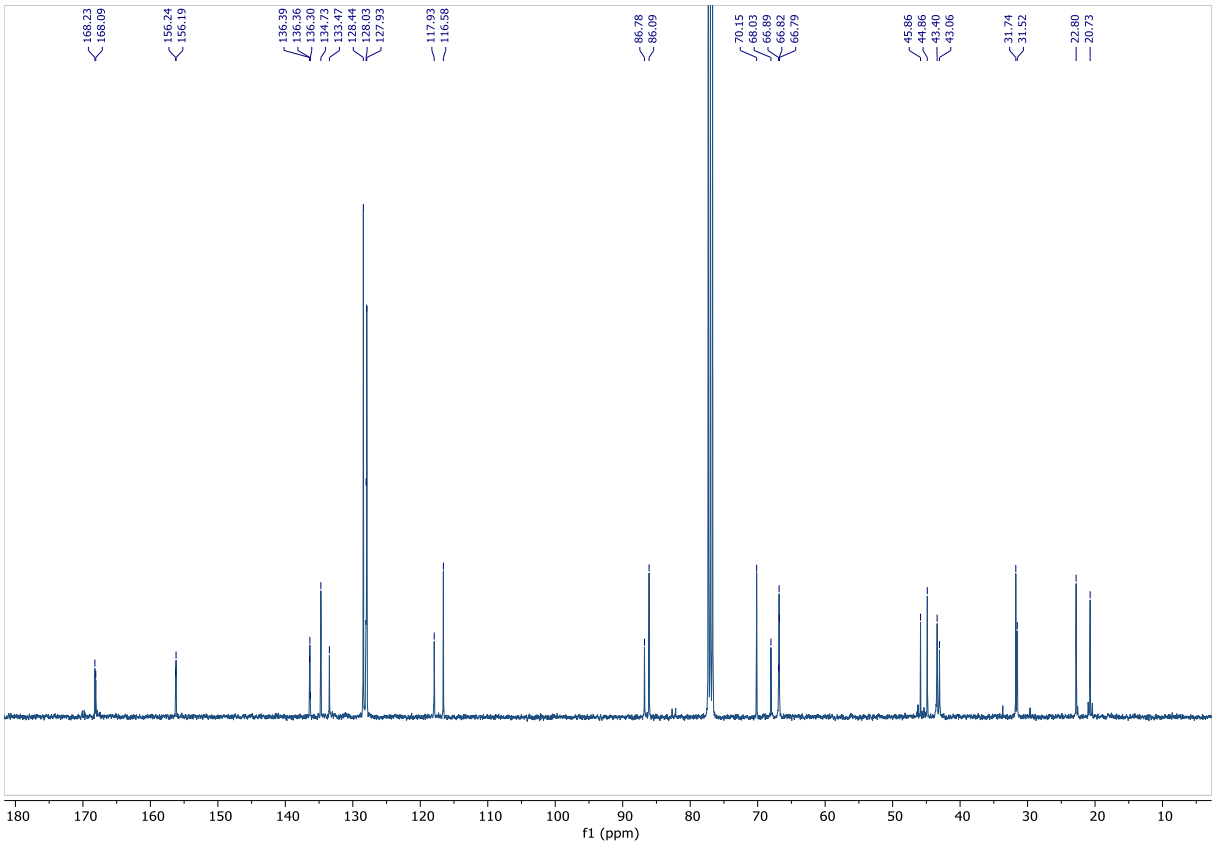
^{13}C-NMR (101 MHz, Chloroform-*d*) (4a)



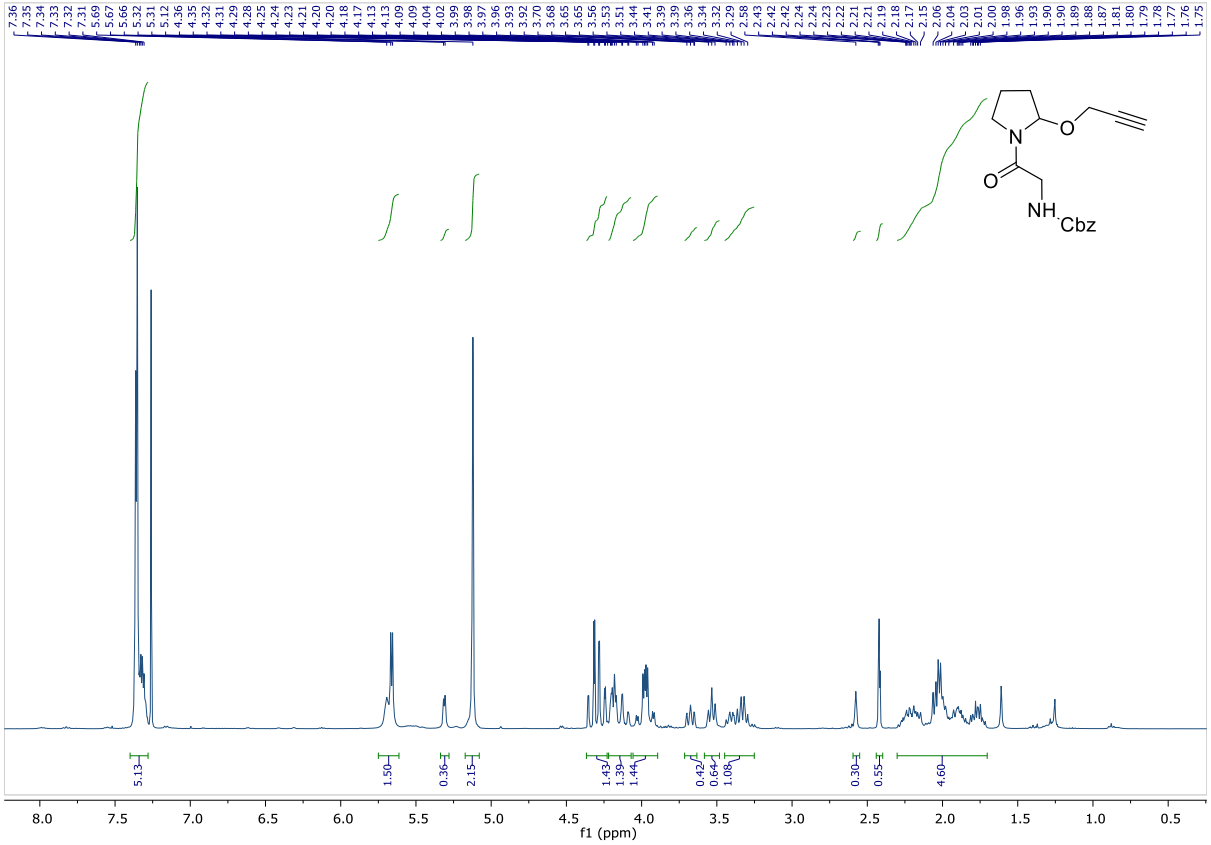
^{1}H-NMR (400 MHz, Chloroform-*d*) (4b)



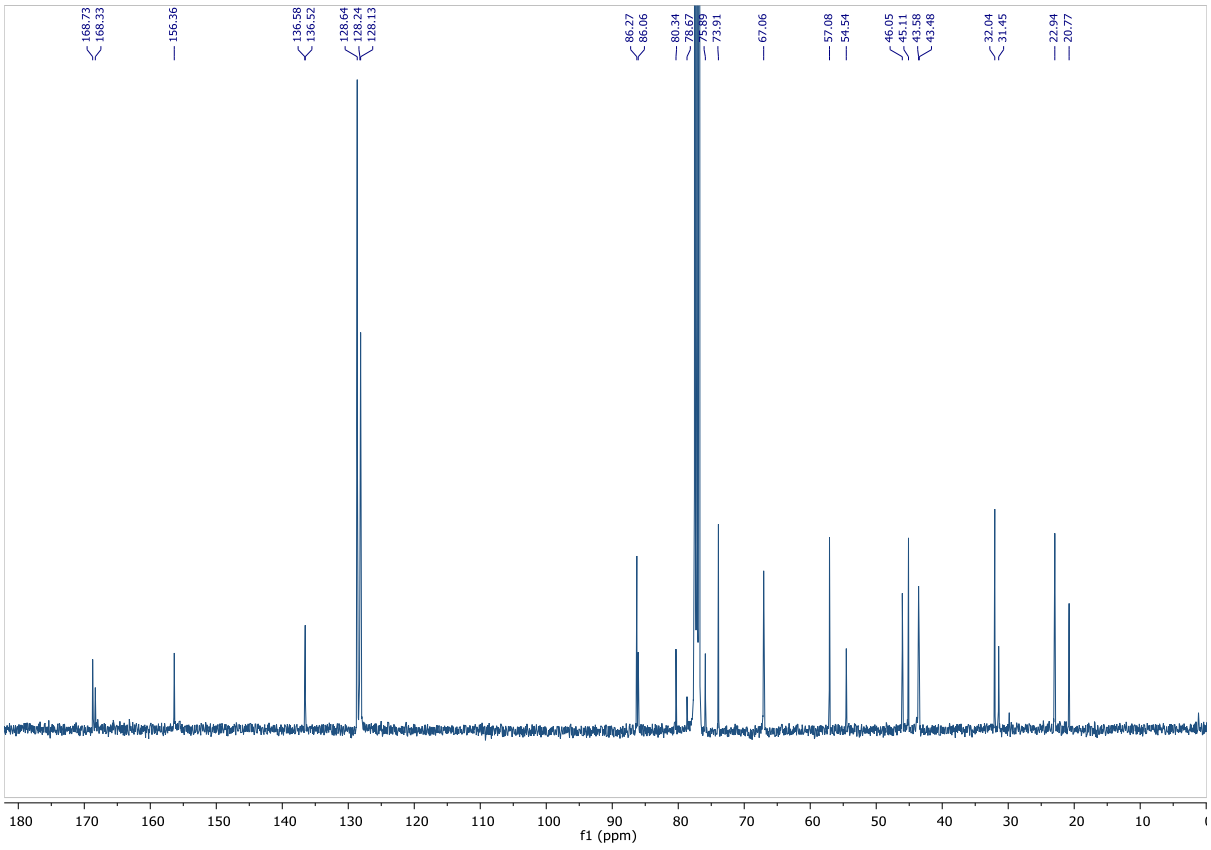
^{13}C-NMR (101 MHz, Chloroform-*d*) (4b)



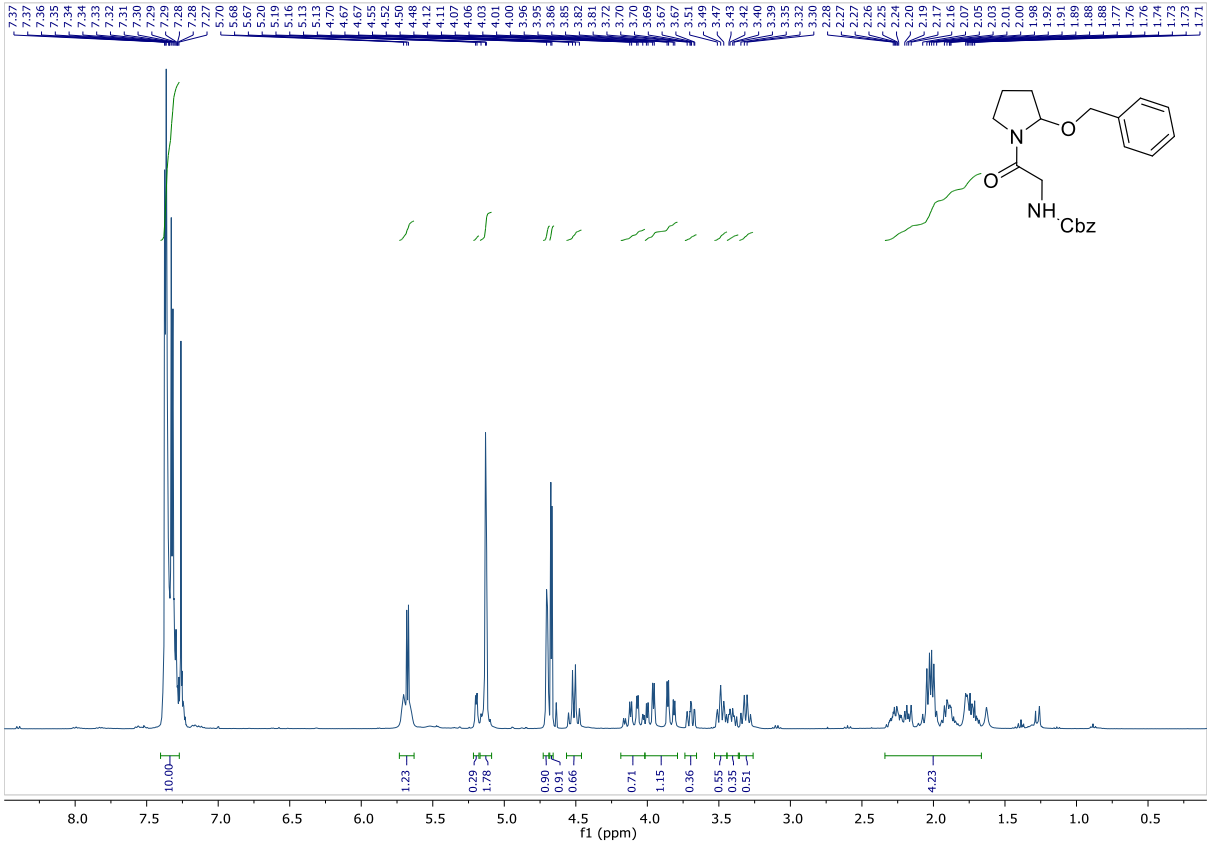
^{1}H-NMR (400 MHz, Chloroform-*d*) (4c)



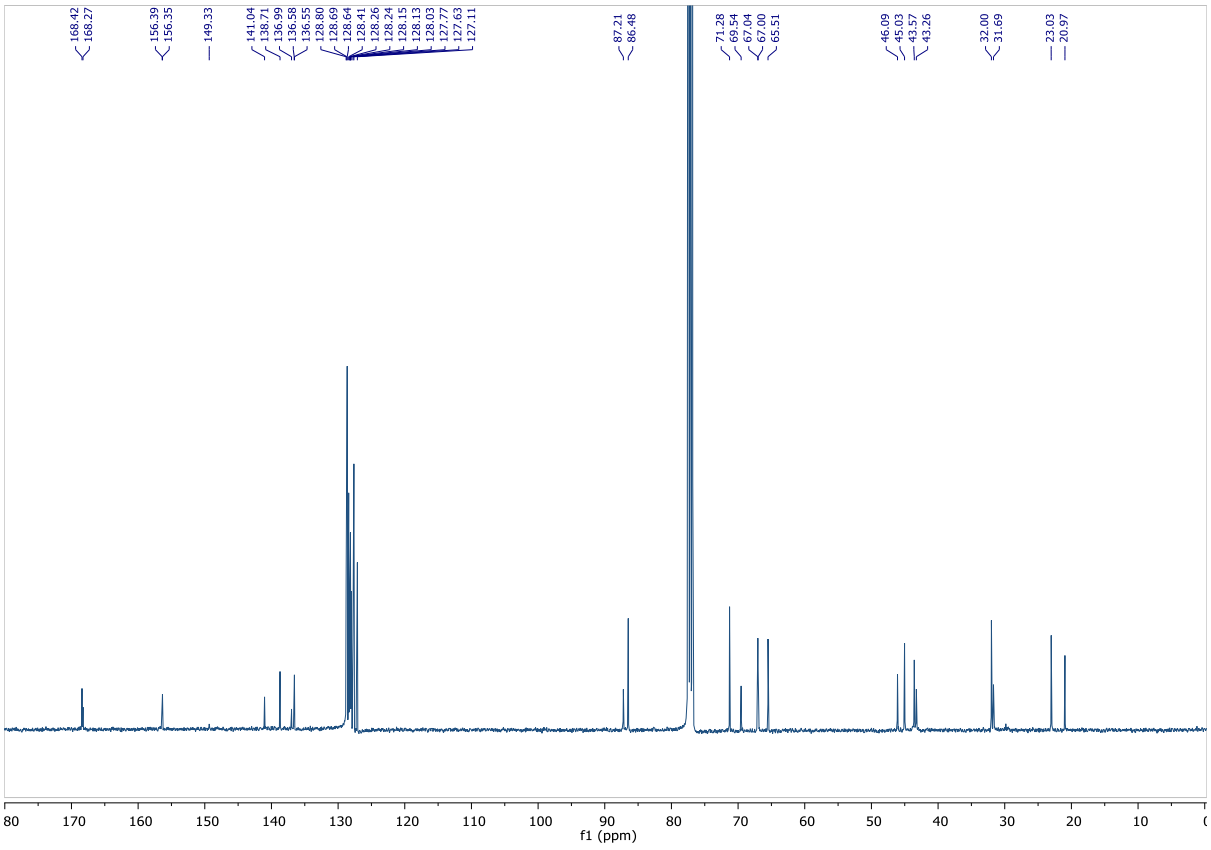
^{13}C-NMR (101 MHz, Chloroform-*d*) (4c)



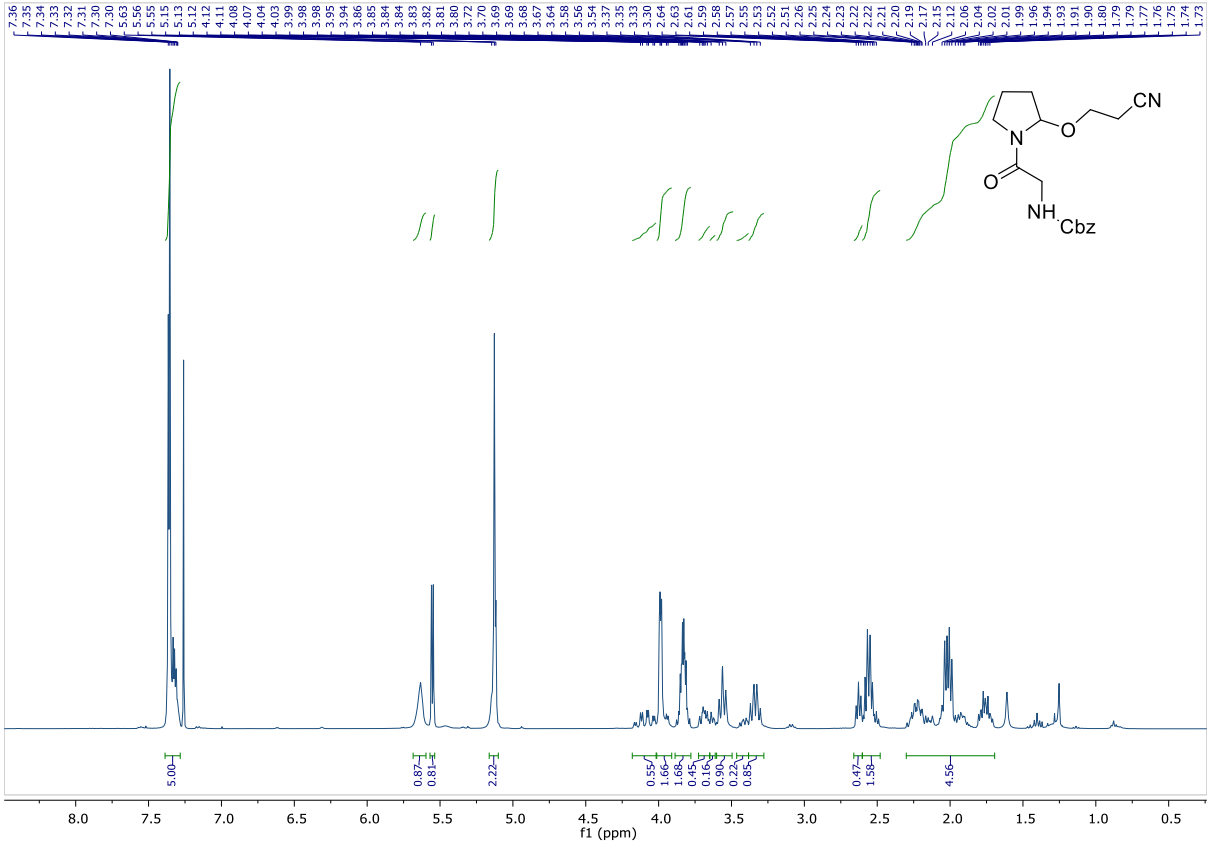
^{1}H-NMR (400 MHz, Chloroform-*d*) (4d)



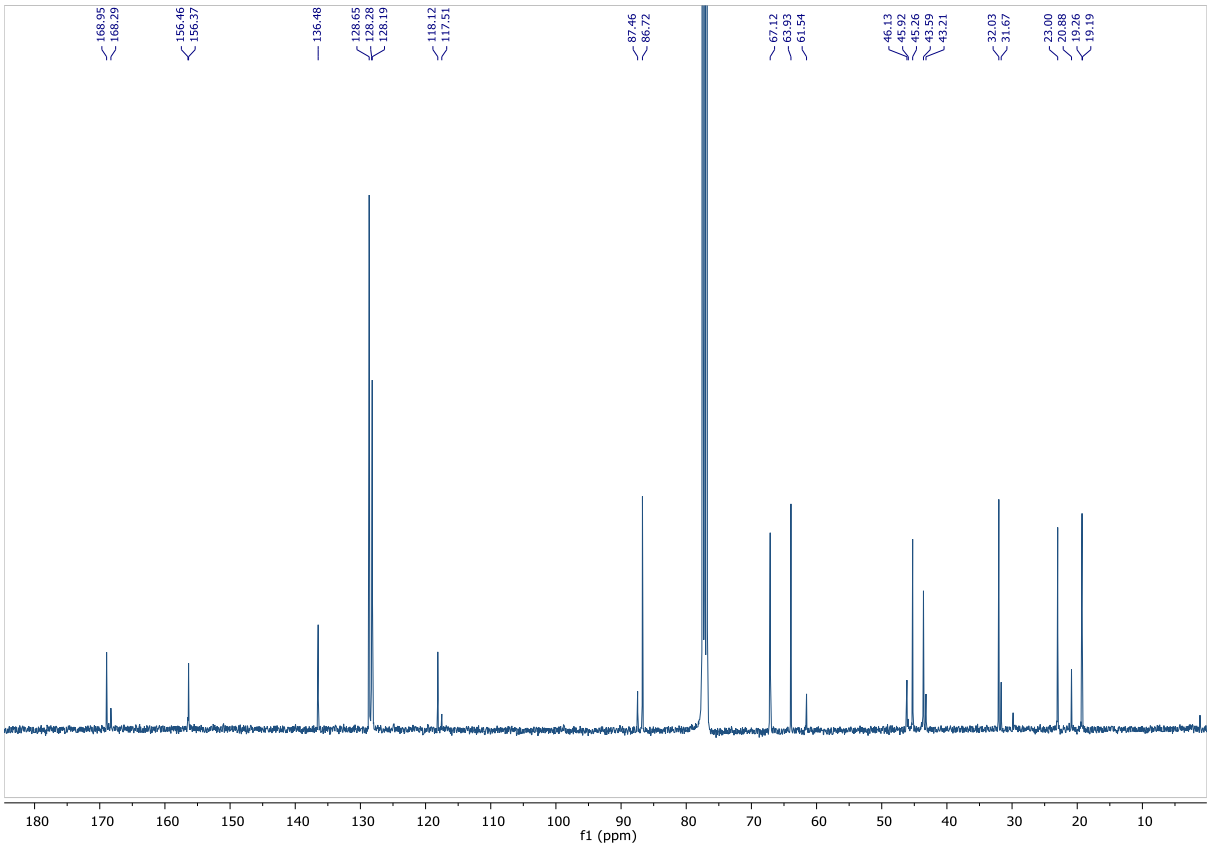
^{13}C-NMR (101 MHz, Chloroform-*d*) (4d)



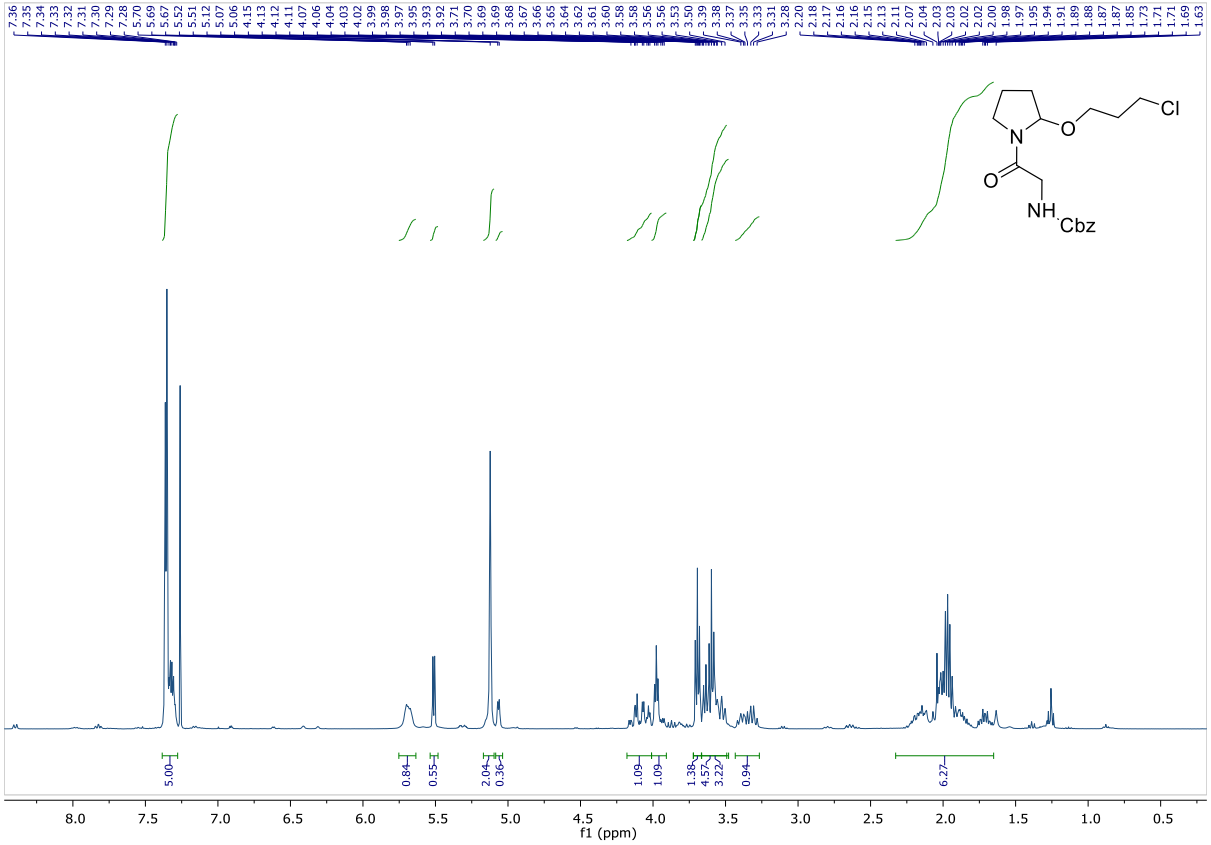
^{1}H-NMR (400 MHz, Chloroform-*d*) (4e)



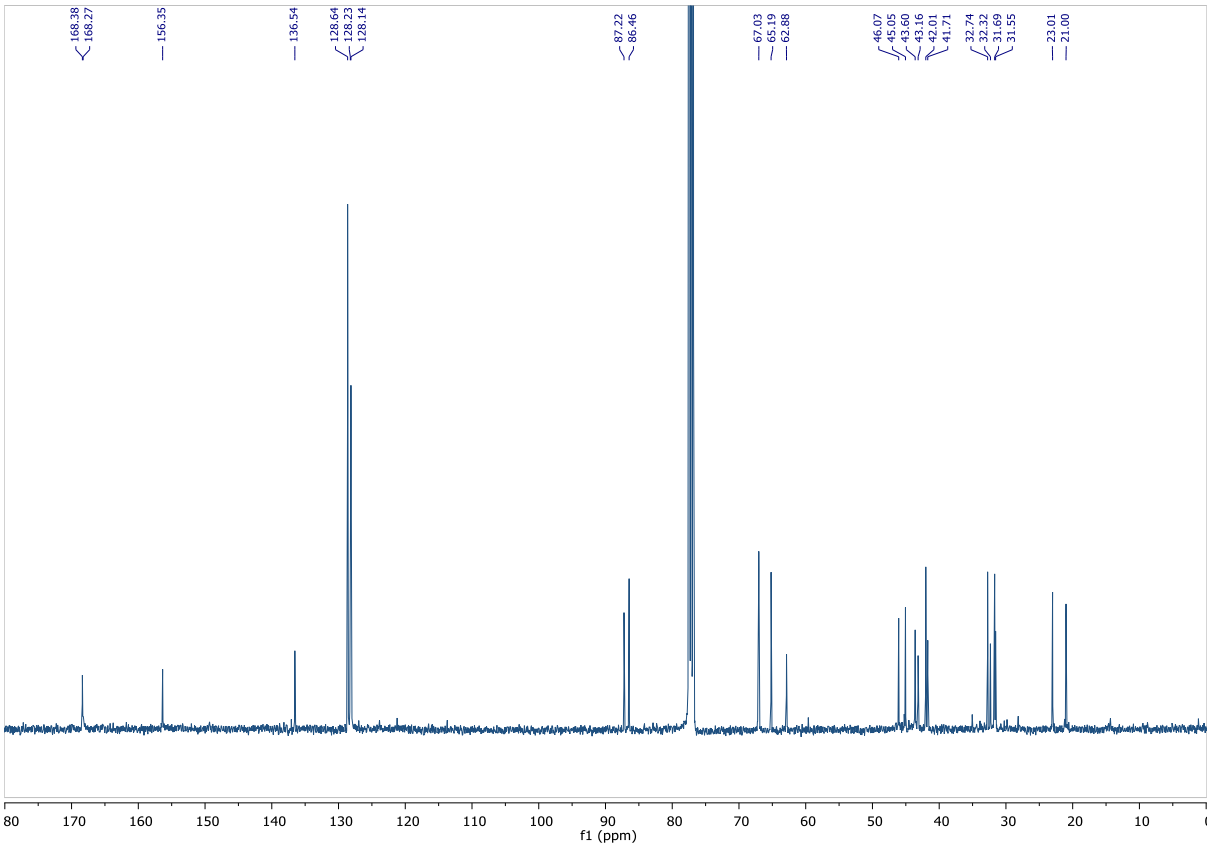
^{13}C-NMR (101 MHz, Chloroform-*d*) (4e)



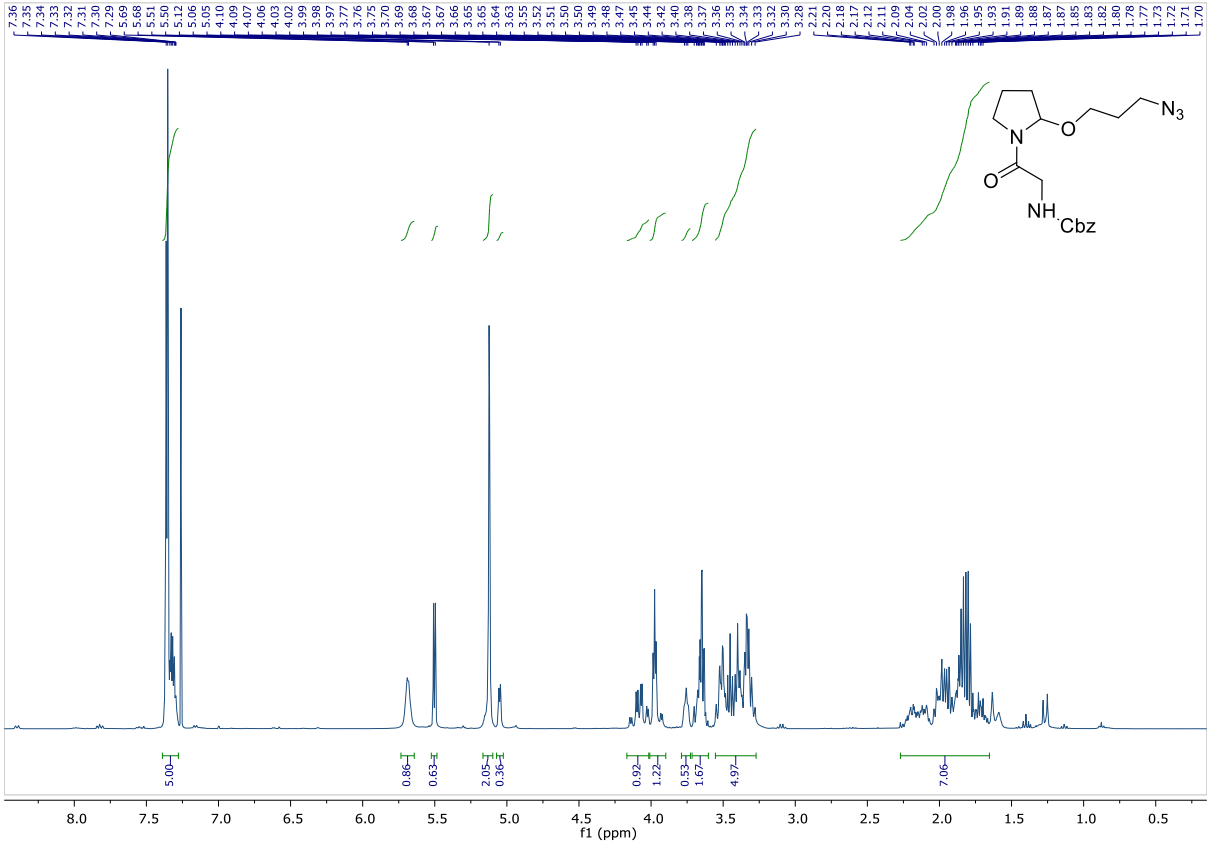
^{1}H-NMR (400 MHz, Chloroform-*d*) (4f)



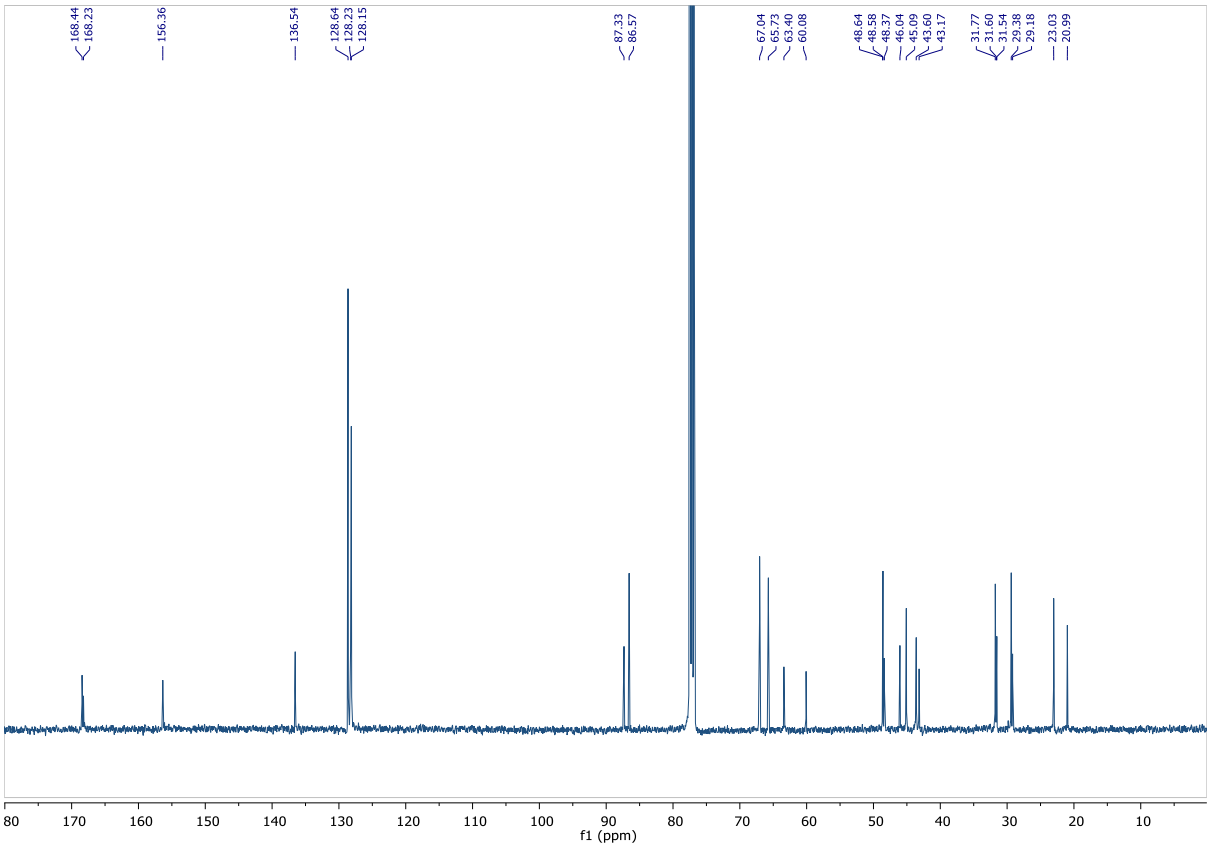
^{13}C-NMR (101 MHz, Chloroform-*d*) (4f)



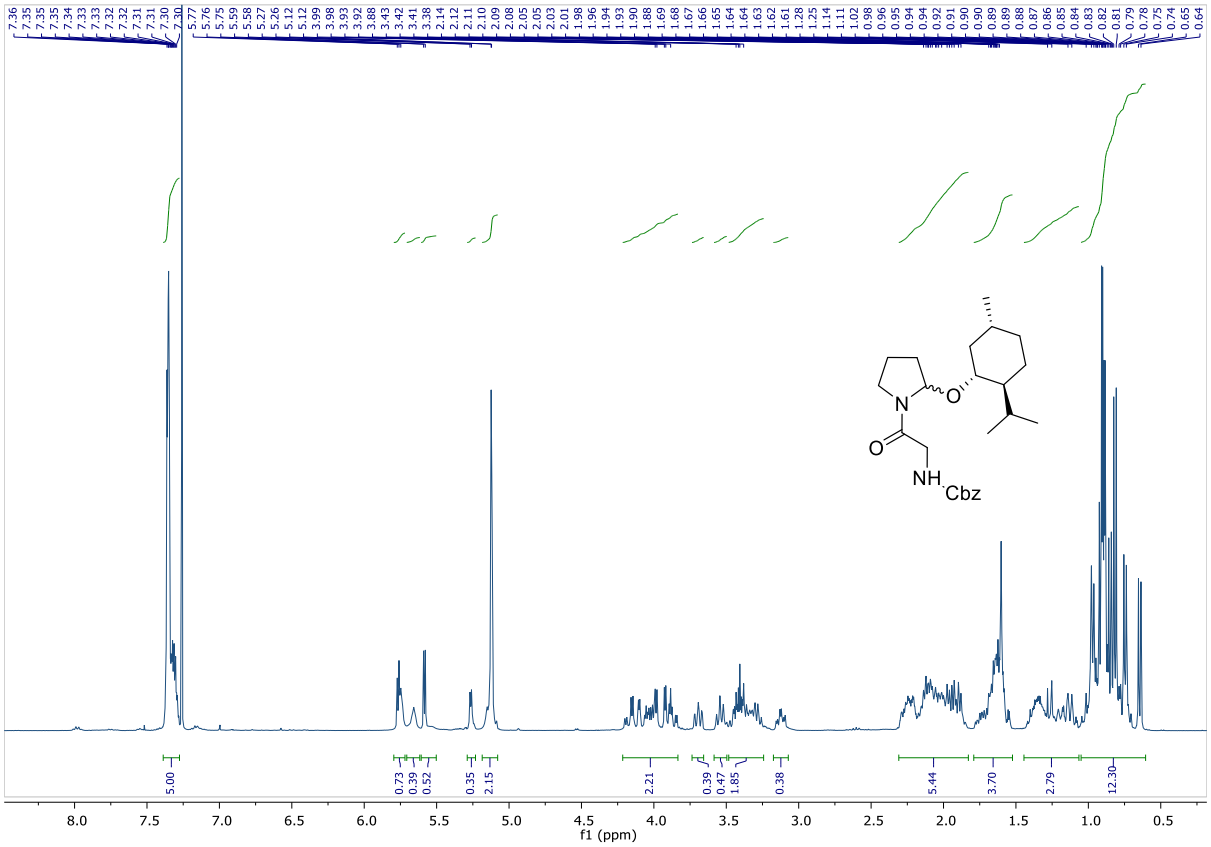
^{1}H-NMR (400 MHz, Chloroform-*d*) (4g)



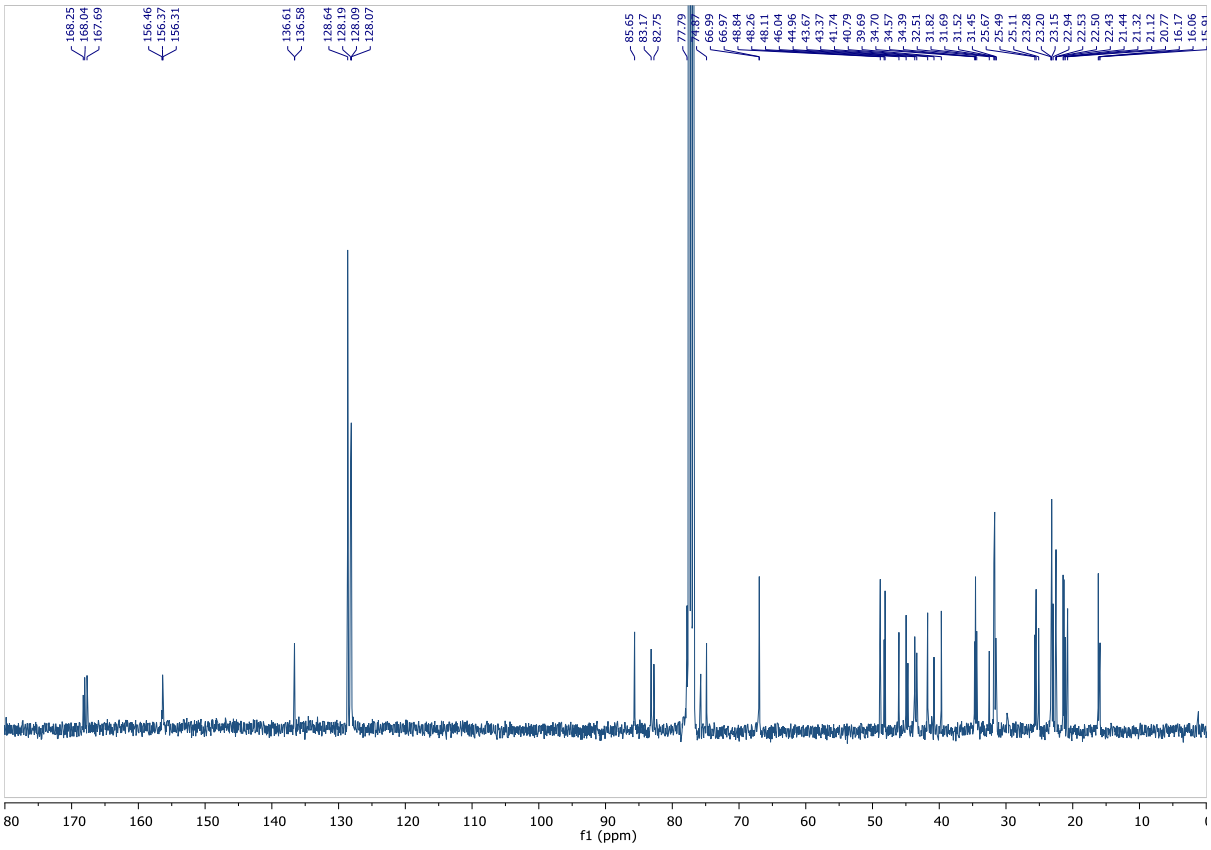
^{13}C-NMR (101 MHz, Chloroform-*d*) (4g)



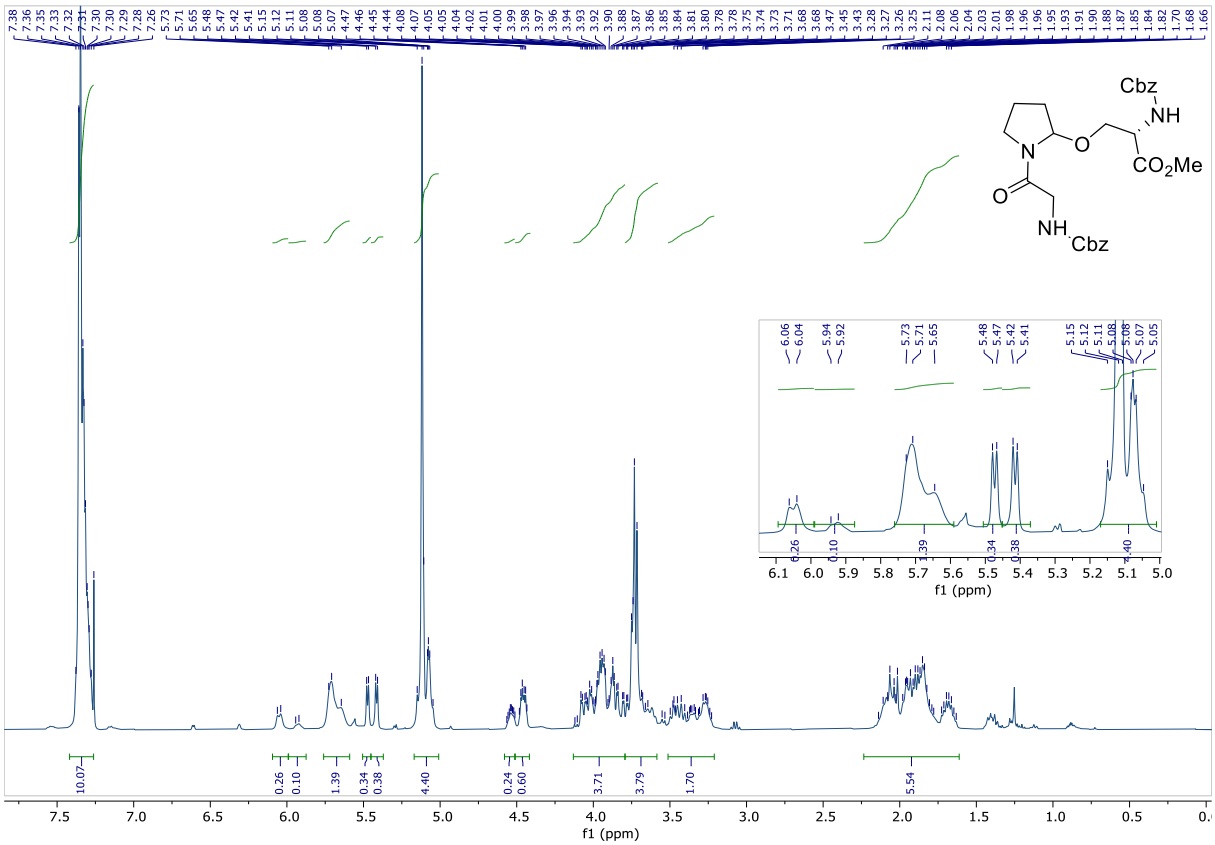
^{1}H-NMR (400 MHz, Chloroform-*d*) (4h)



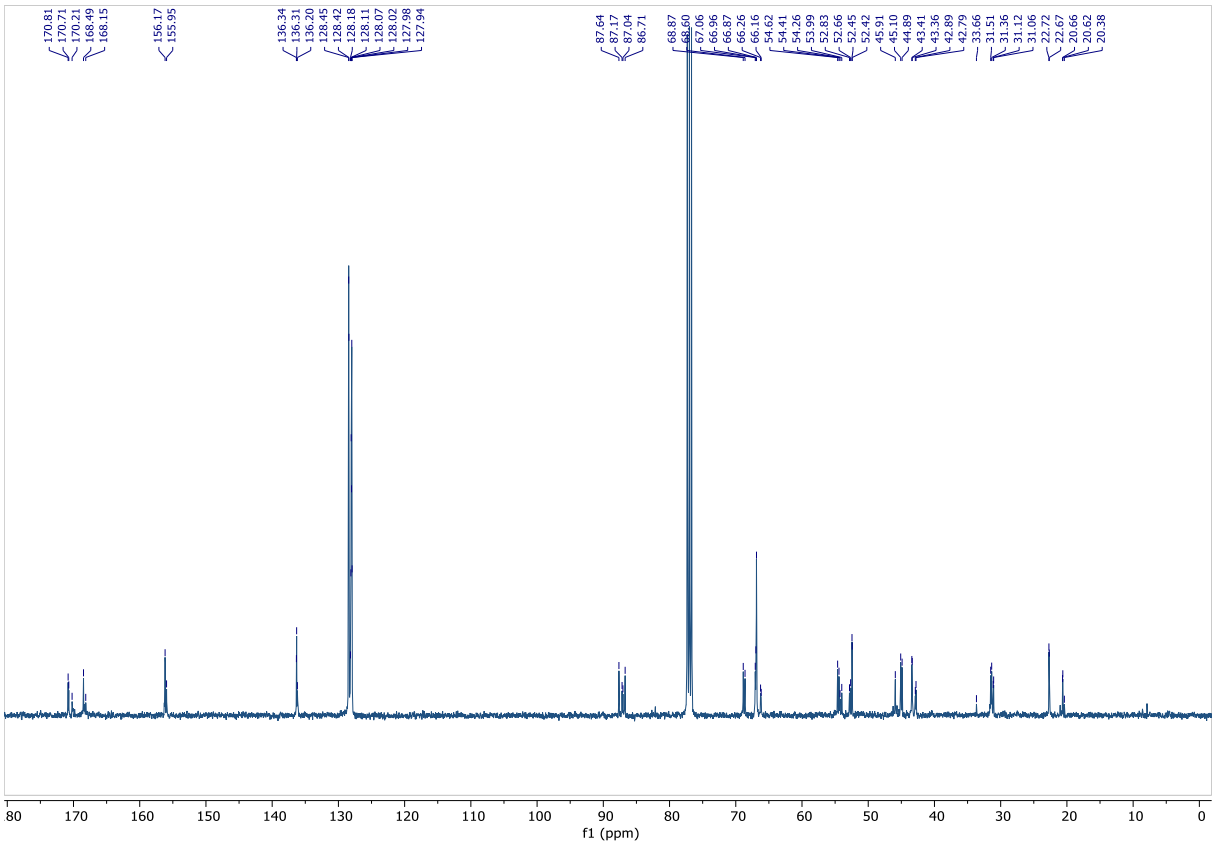
^{13}C-NMR (101 MHz, Chloroform-*d*) (4h)



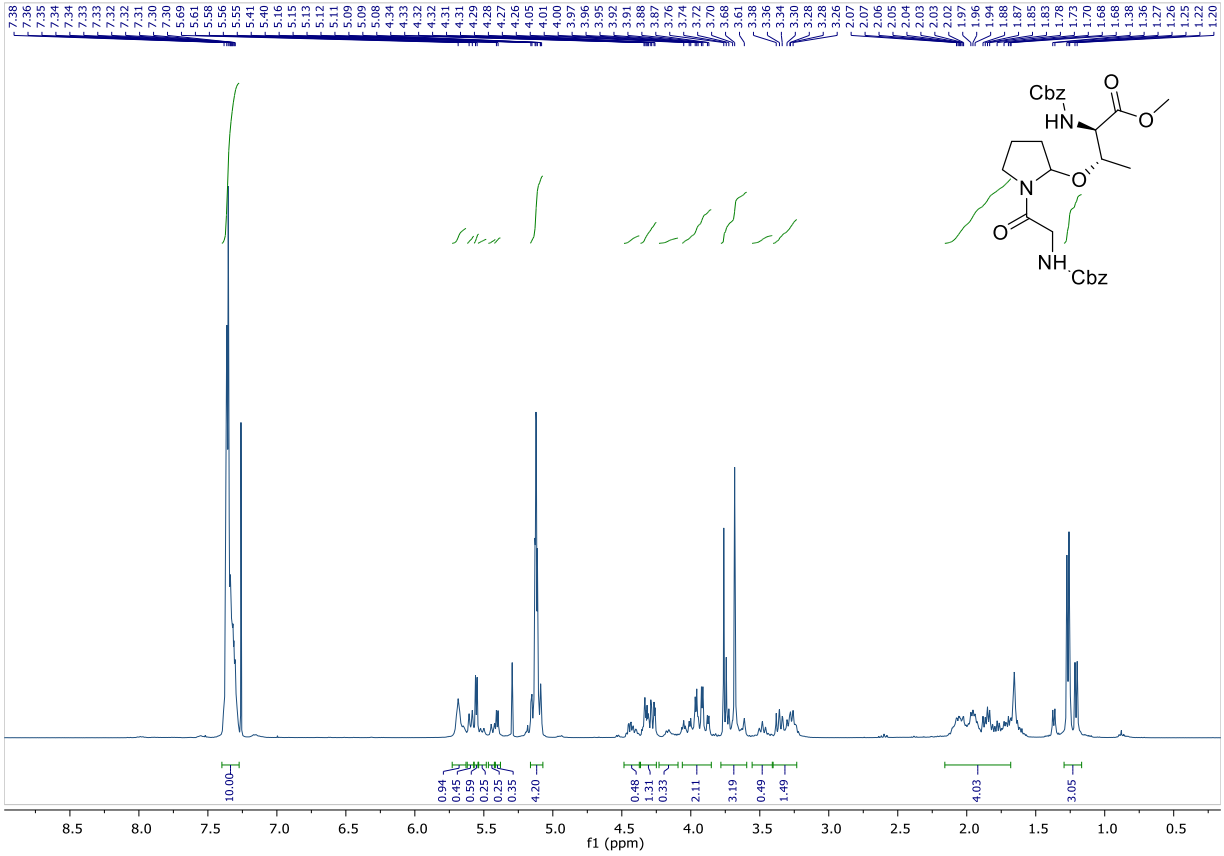
^{1}H-NMR (400 MHz, Chloroform-*d*) (4i)



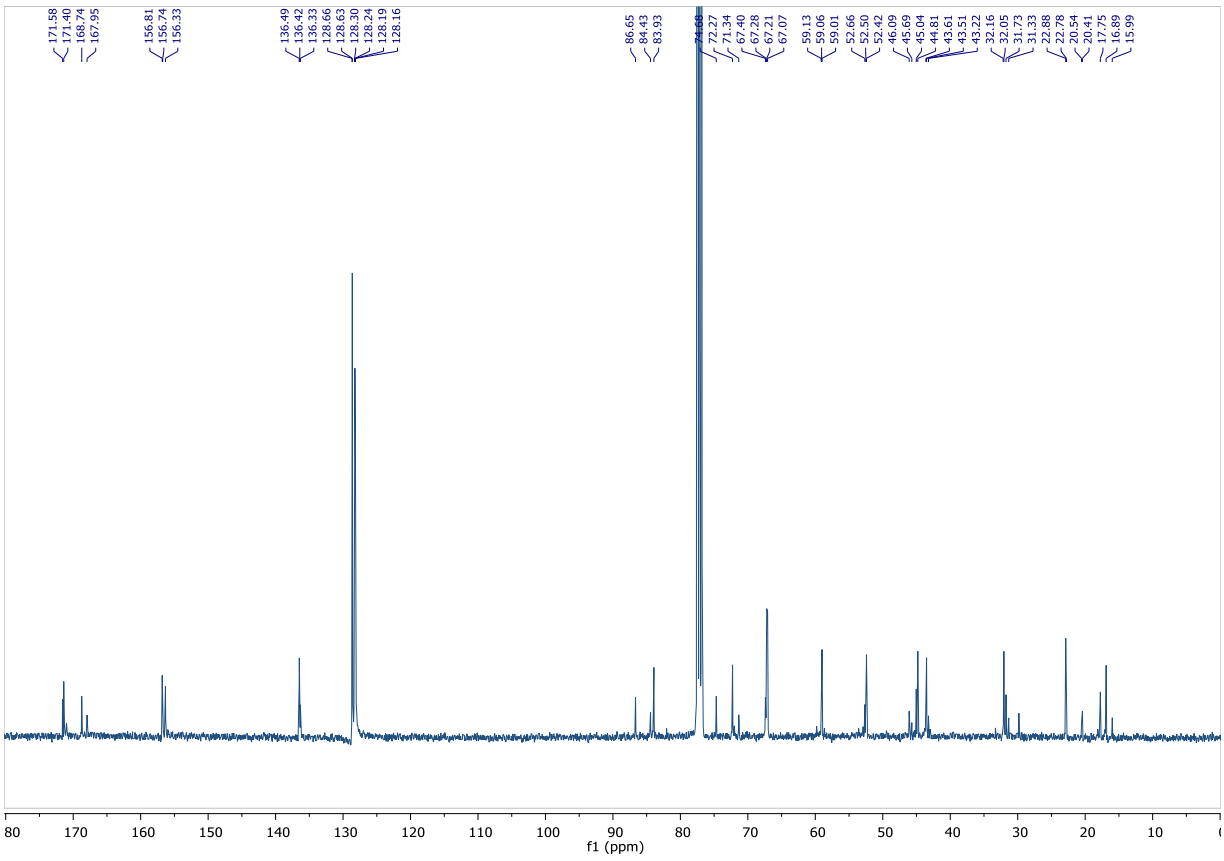
^{13}C-NMR (101 MHz, Chloroform-*d*) (4i)



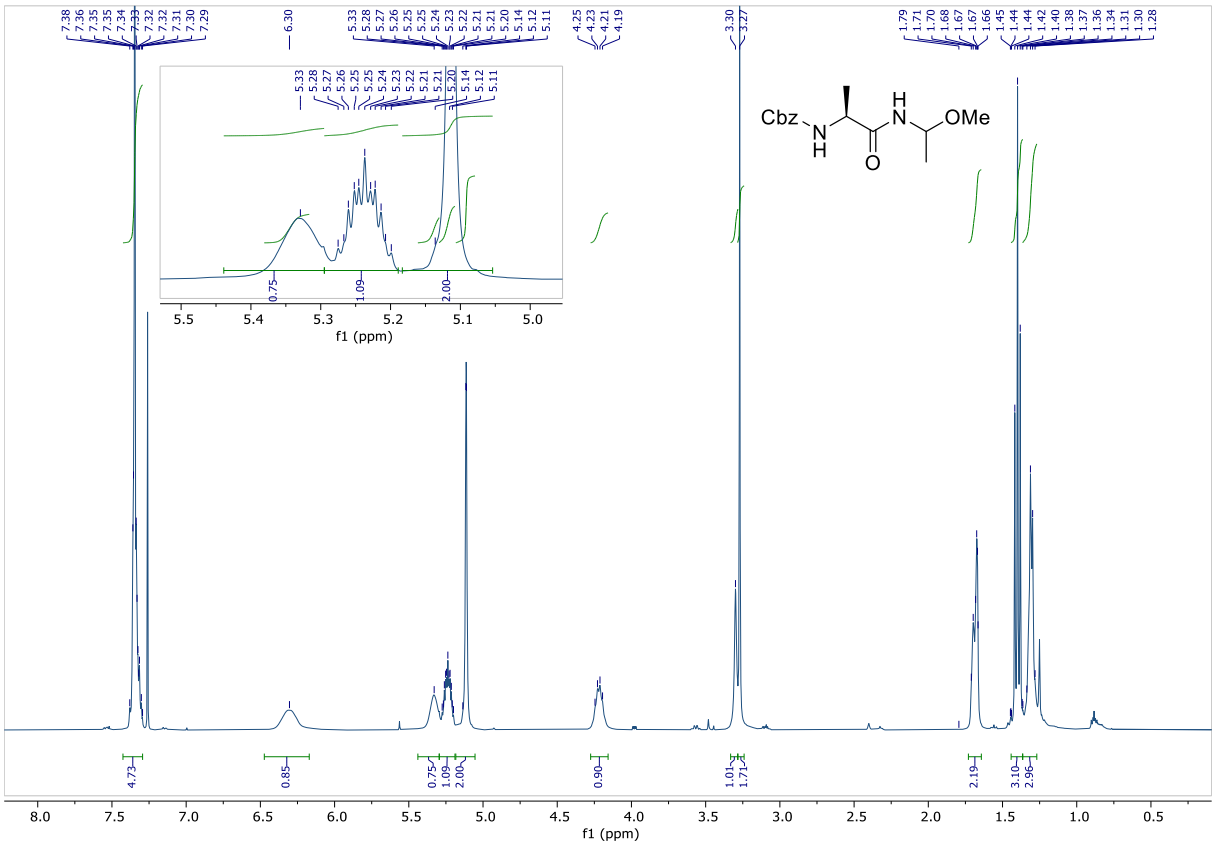
^{1}H-NMR (400 MHz, Chloroform-*d*) (4j)



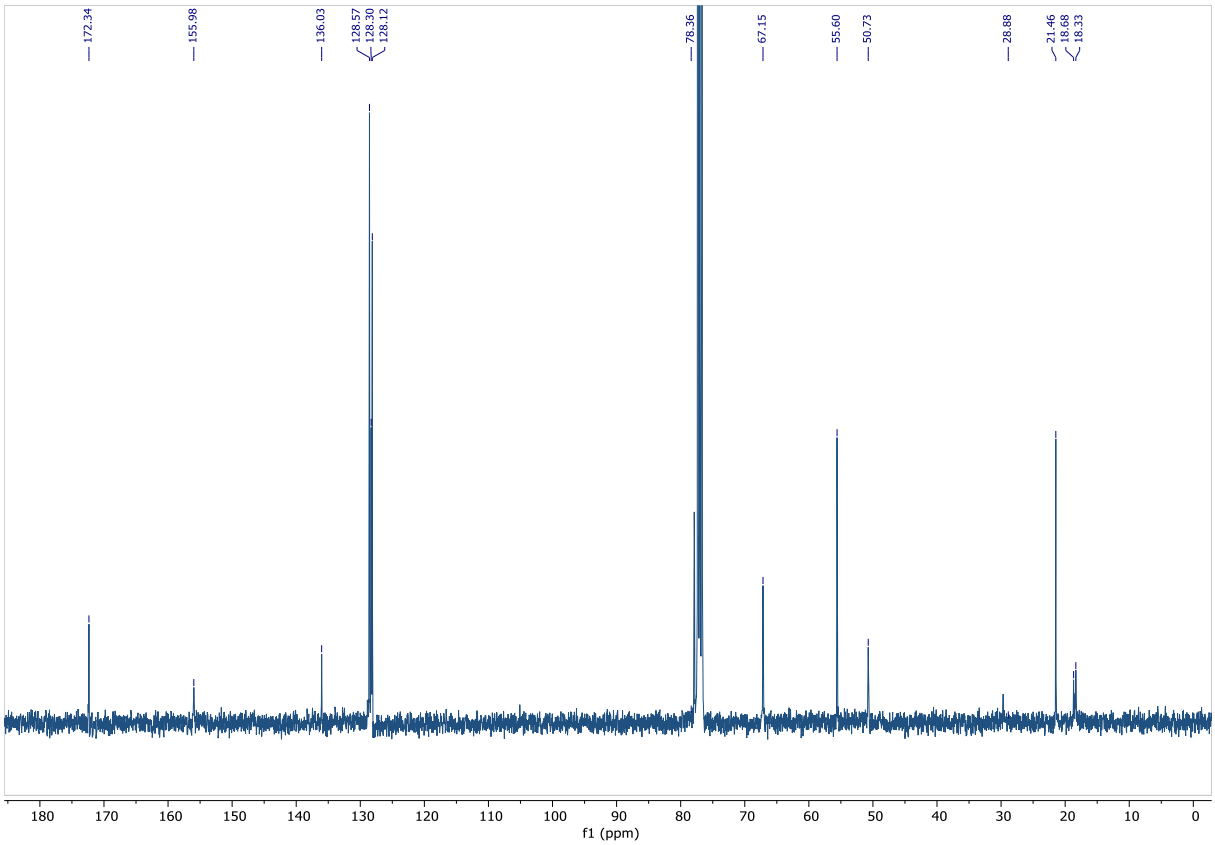
^{13}C-NMR (101 MHz, Chloroform-*d*) (4j)



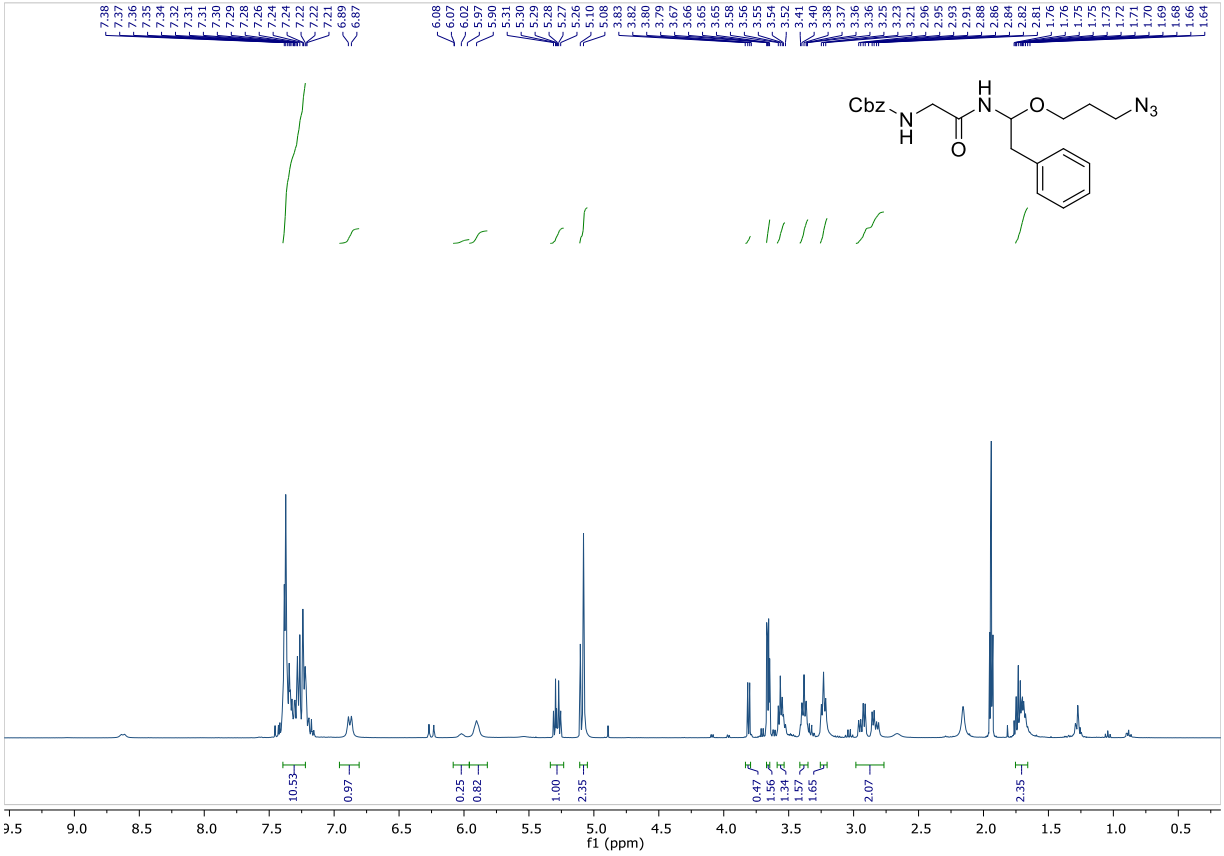
^{1}H-NMR (400 MHz, Chloroform-*d*) (4k)



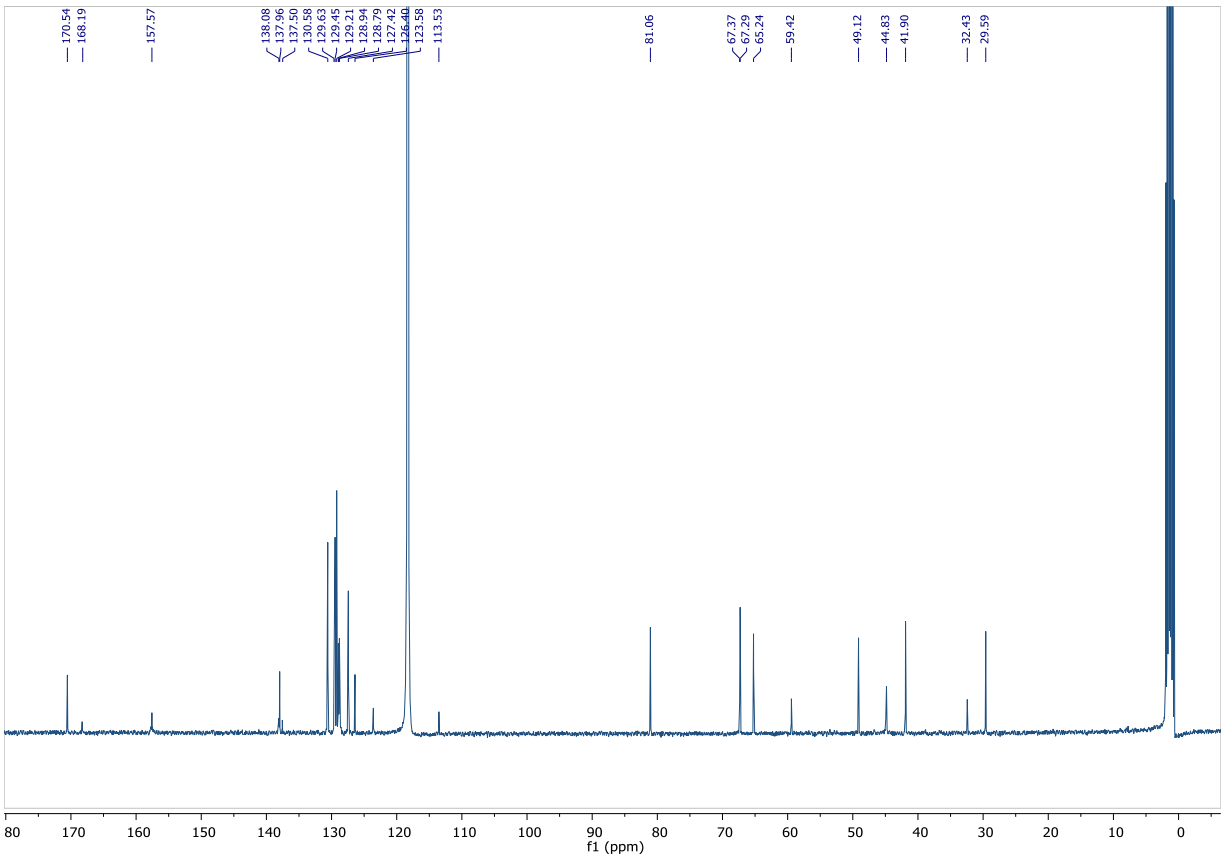
^{13}C-NMR (101 MHz, Chloroform-*d*) (4k)



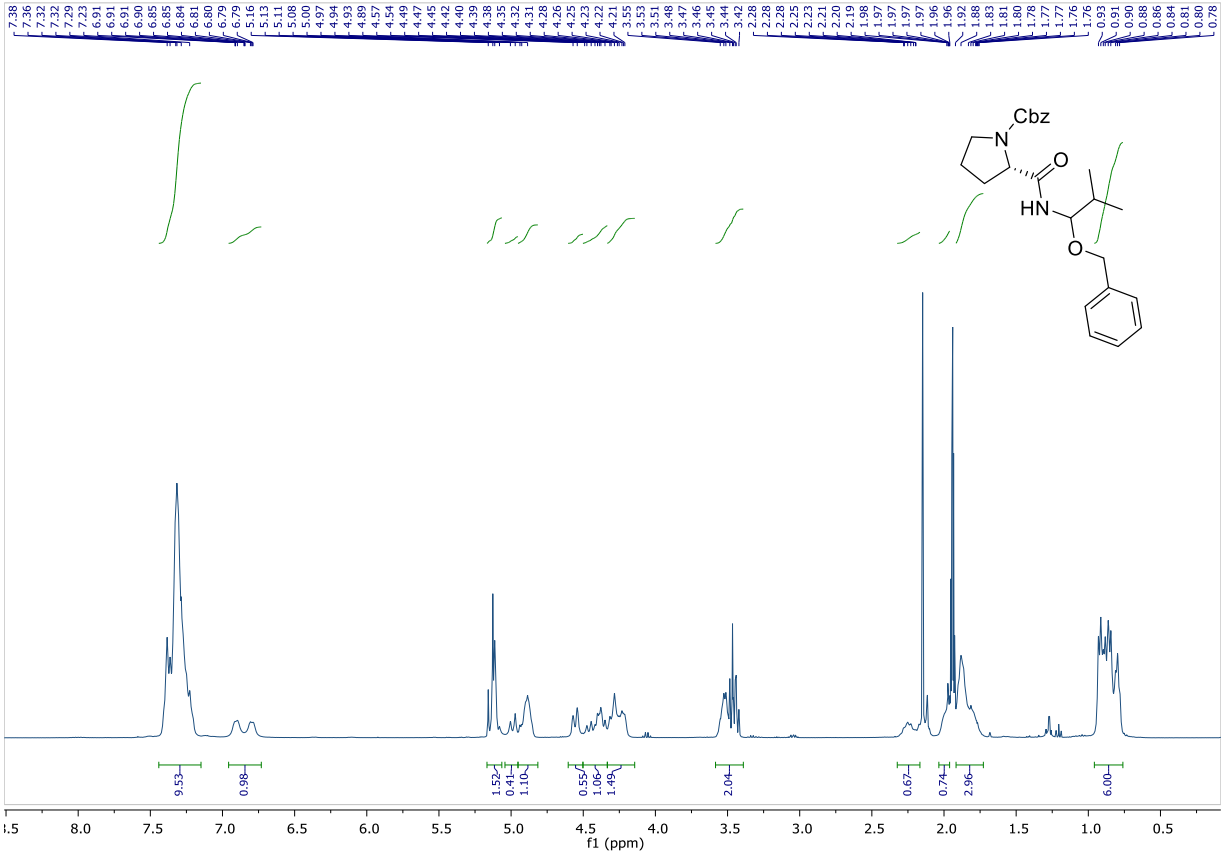
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (4l)



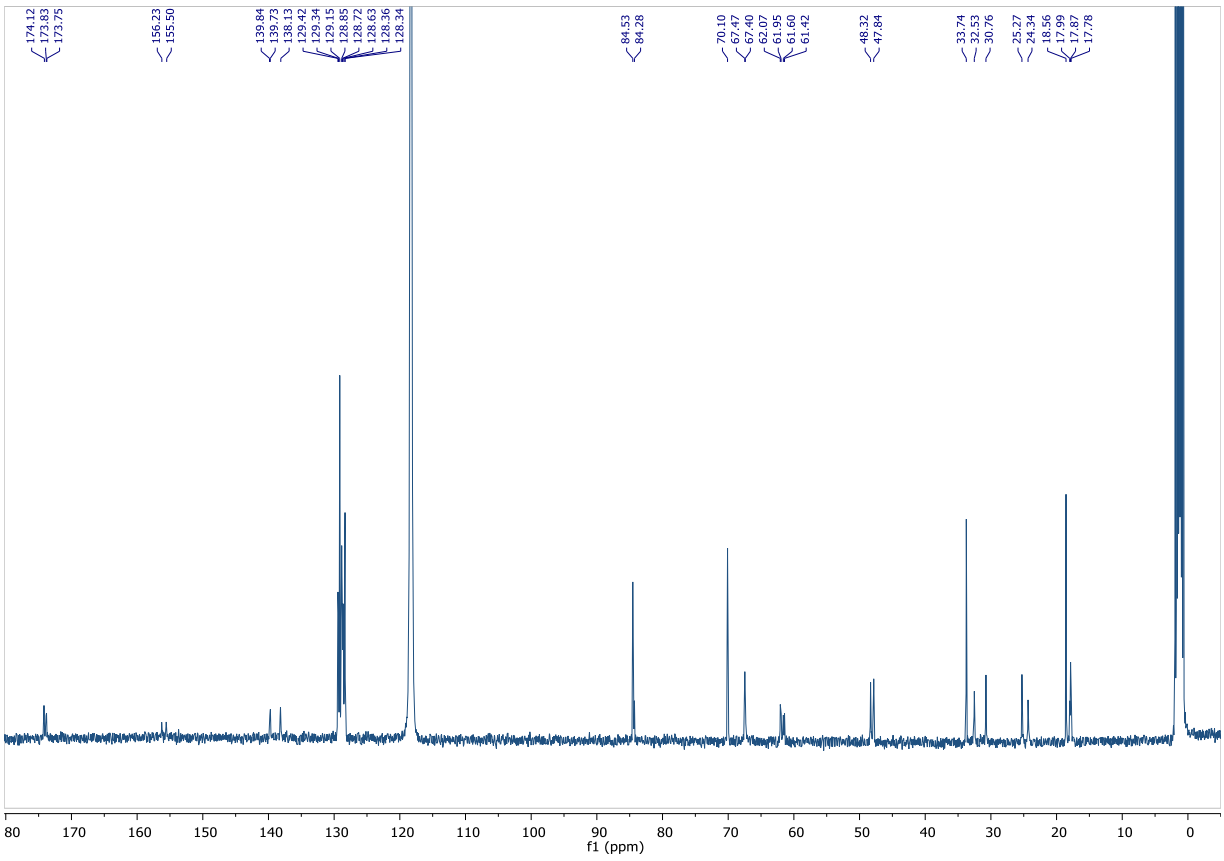
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (4l)



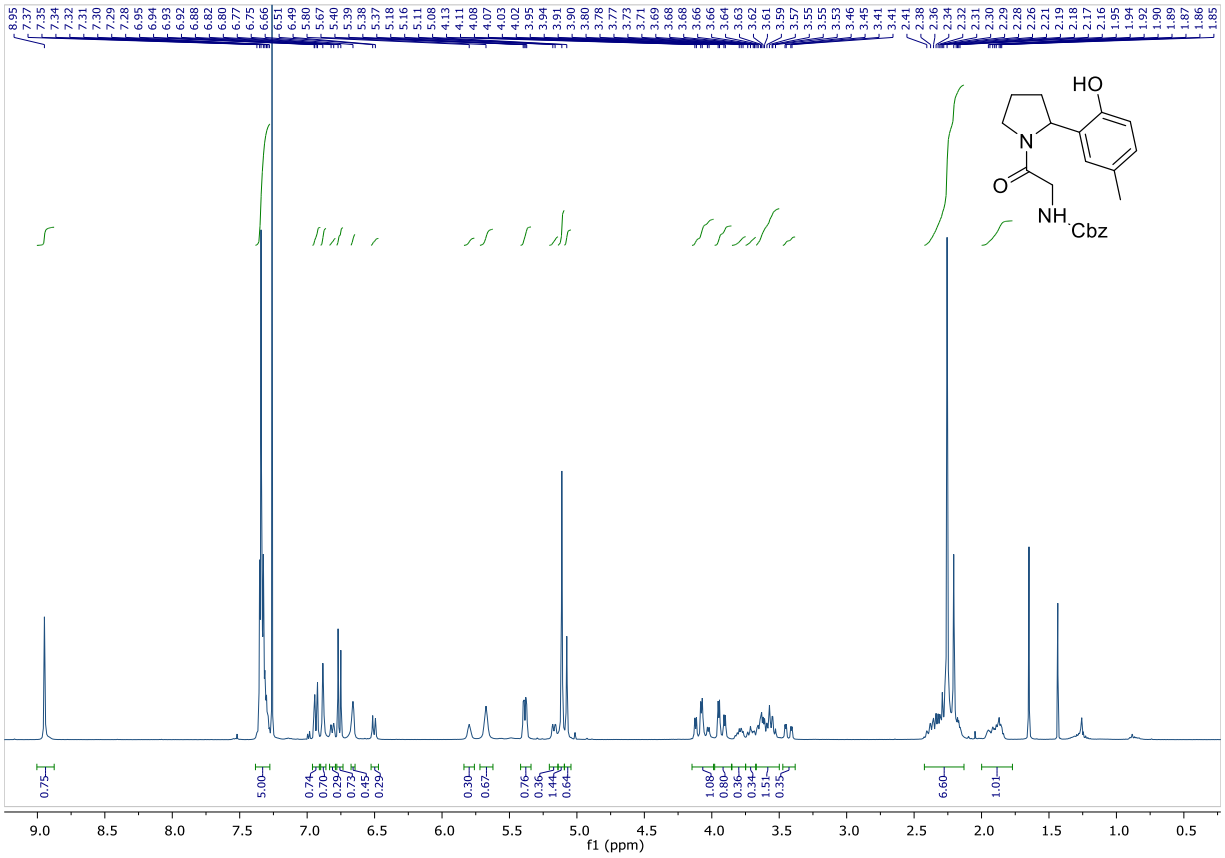
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (4m)



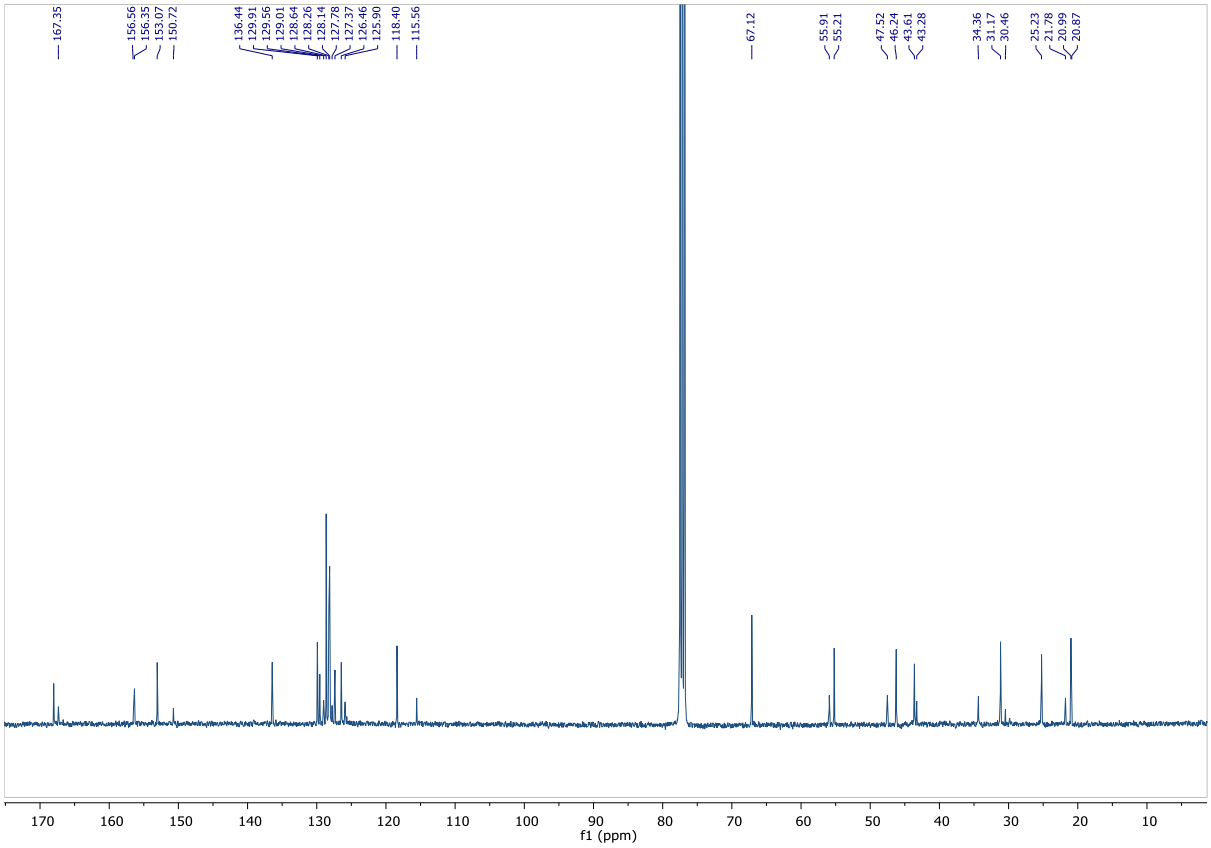
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (4m)



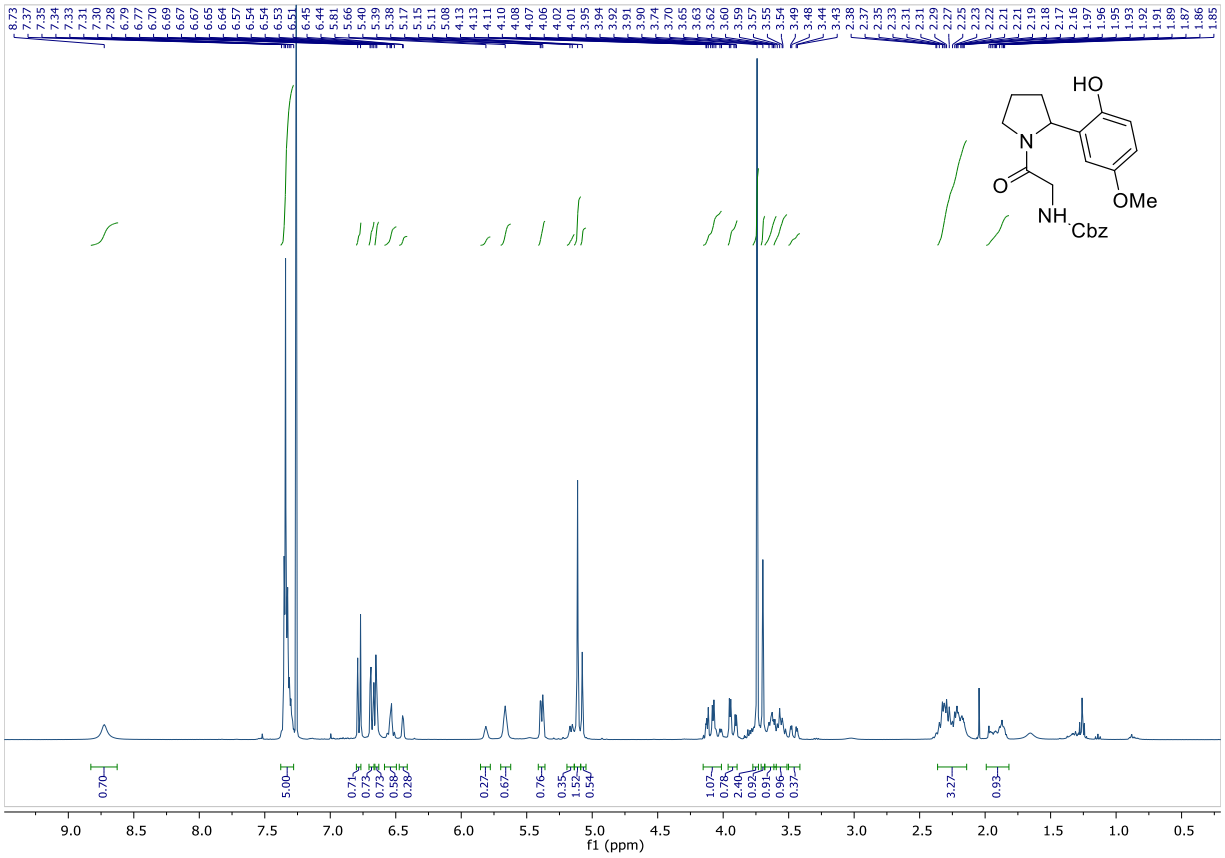
^{1}H-NMR (400 MHz, Chloroform-*d*) (5a)



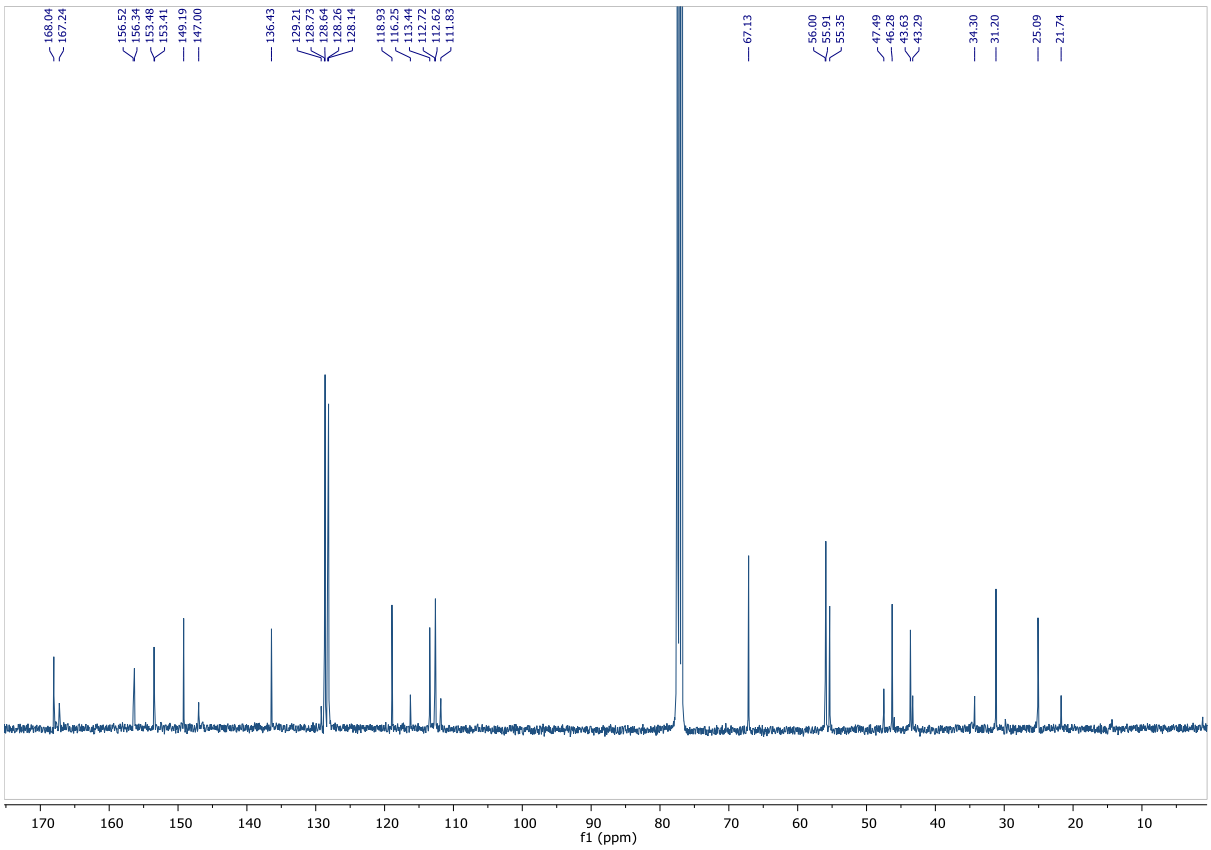
^{13}C-NMR (101 MHz, Chloroform-*d*) (5a)



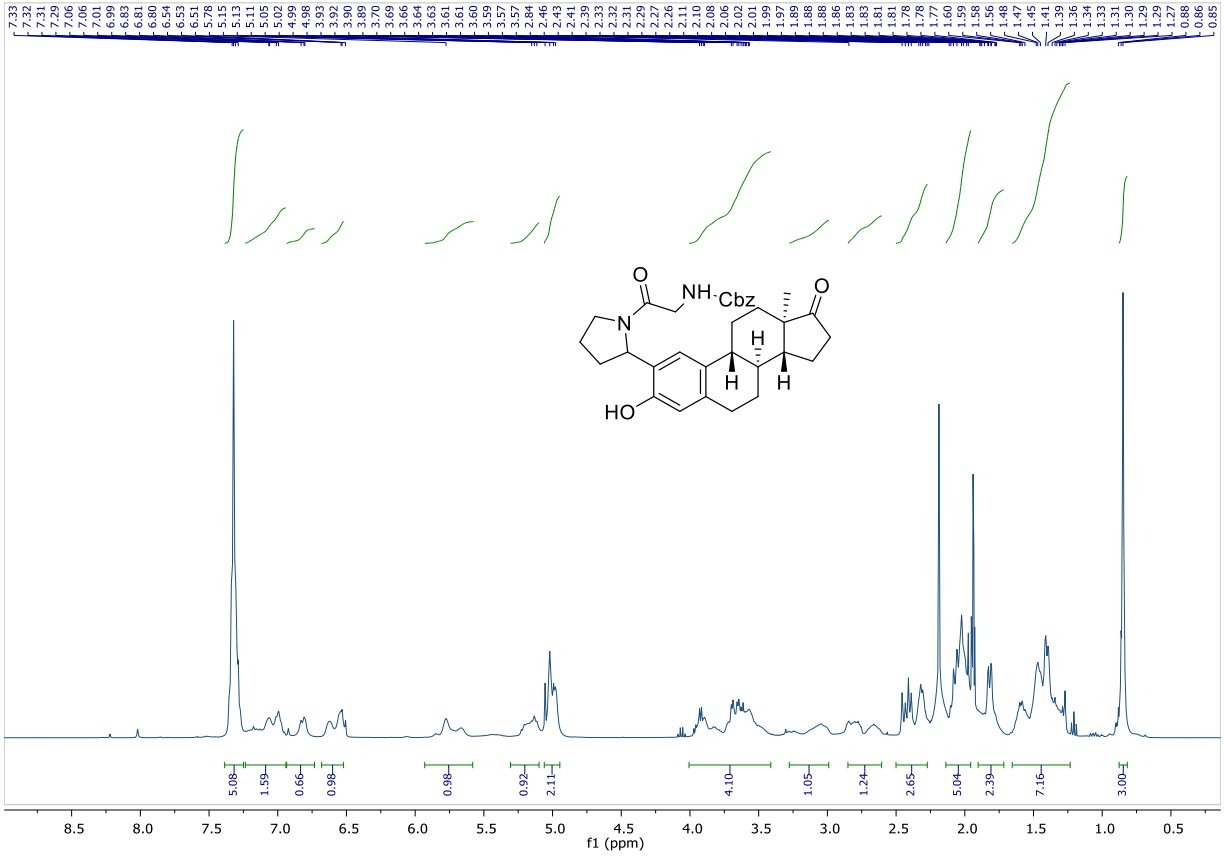
^{1}H-NMR (400 MHz, Chloroform-*d*) (5b)



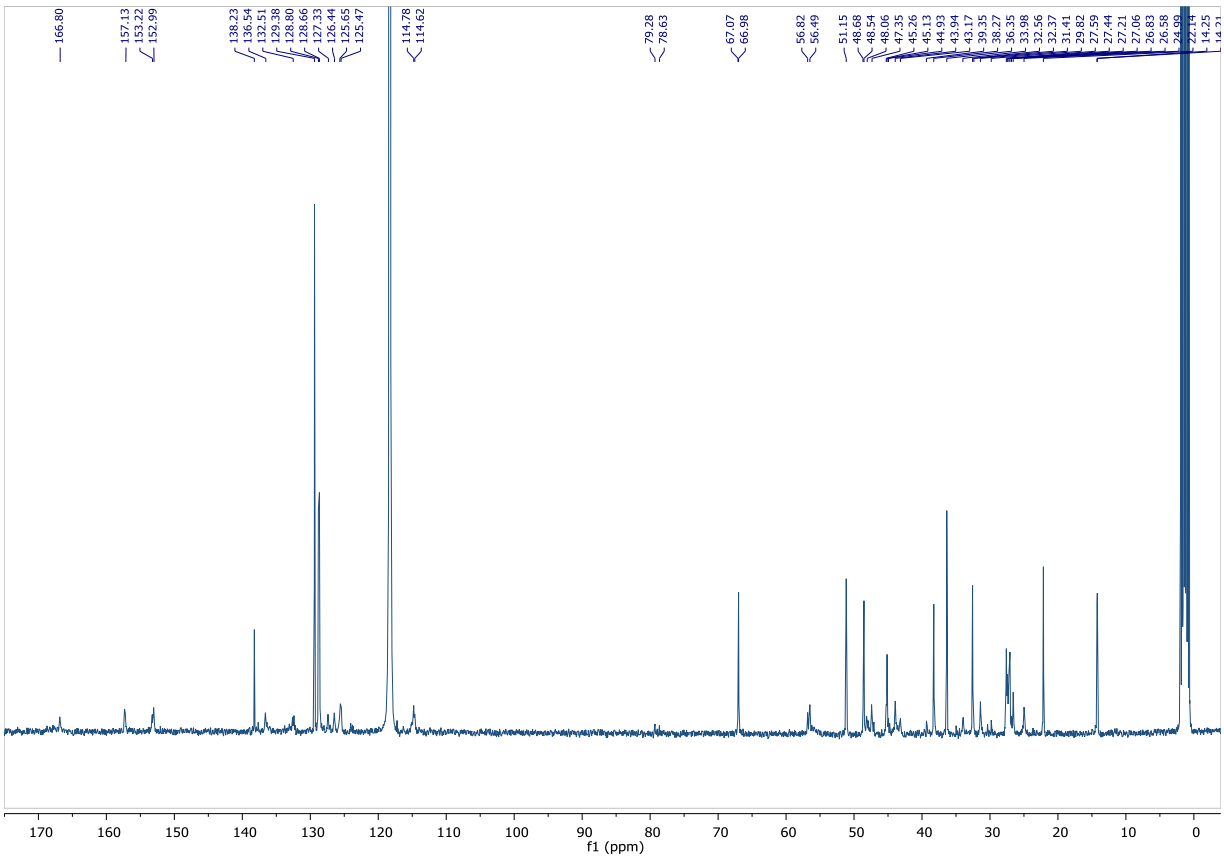
^{13}C-NMR (101 MHz, Chloroform-*d*) (5b)



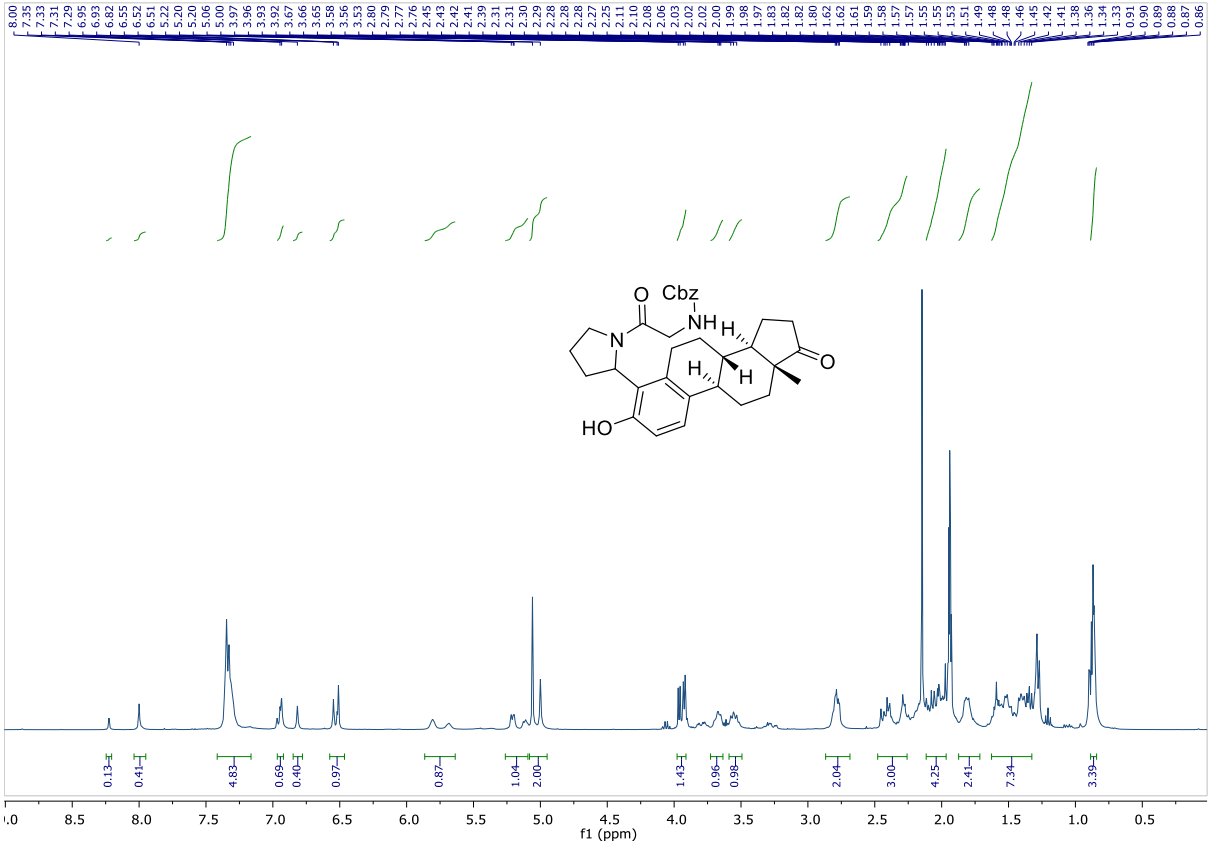
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (5c major)



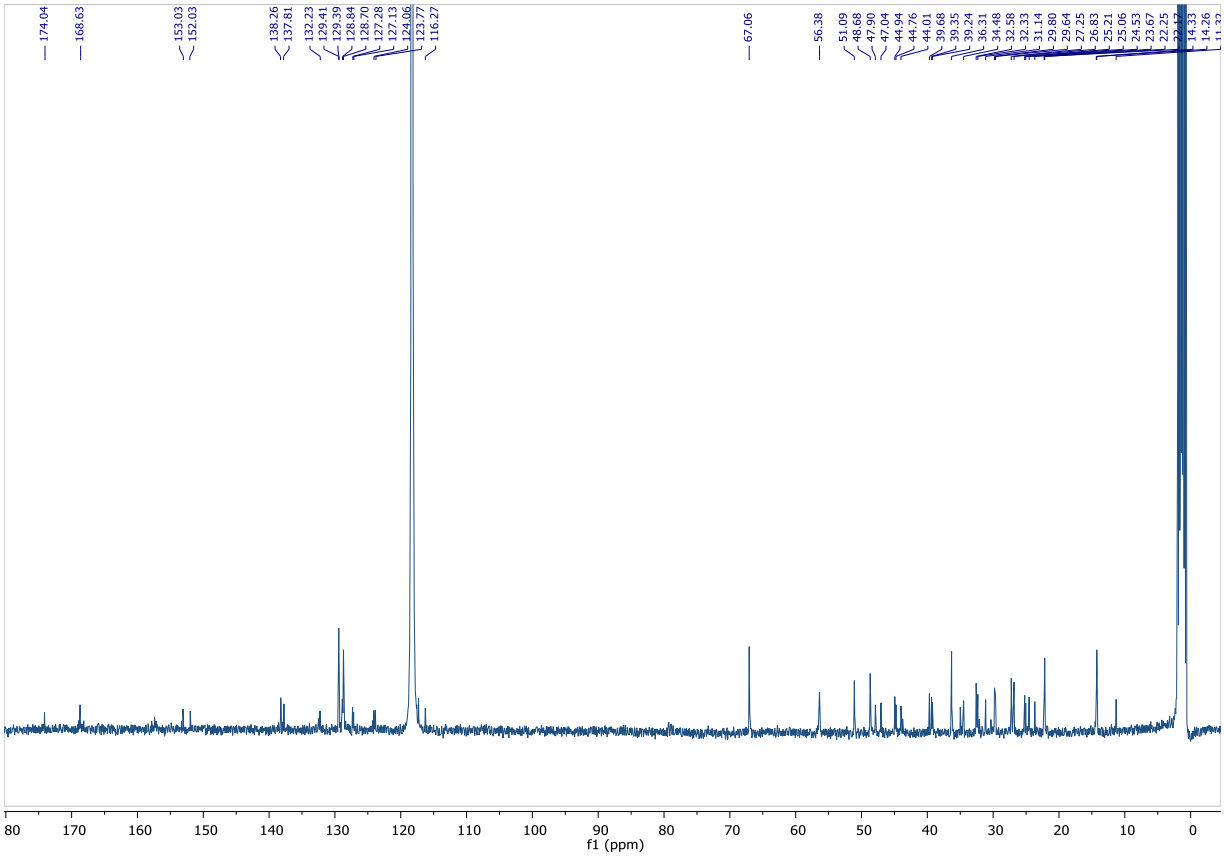
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (5c major)



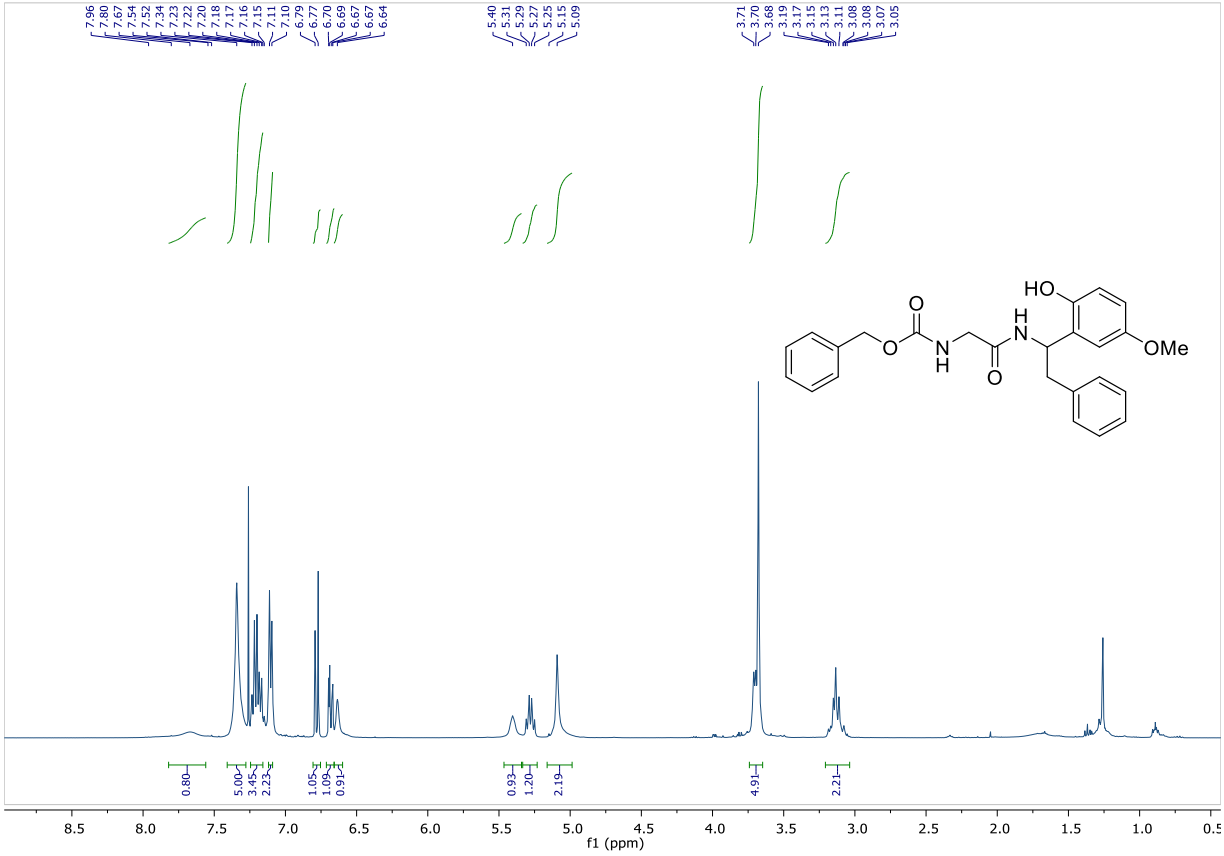
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (5c minor)



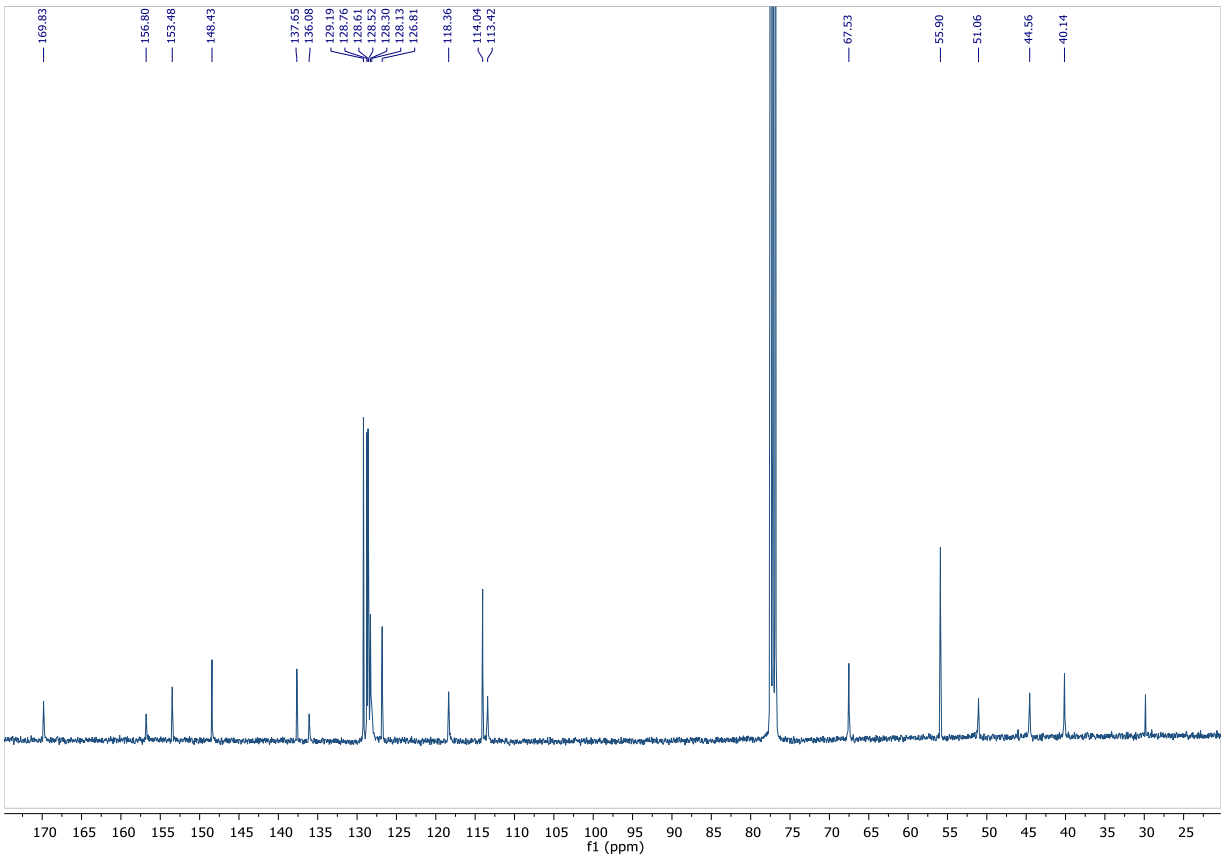
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (5c minor)



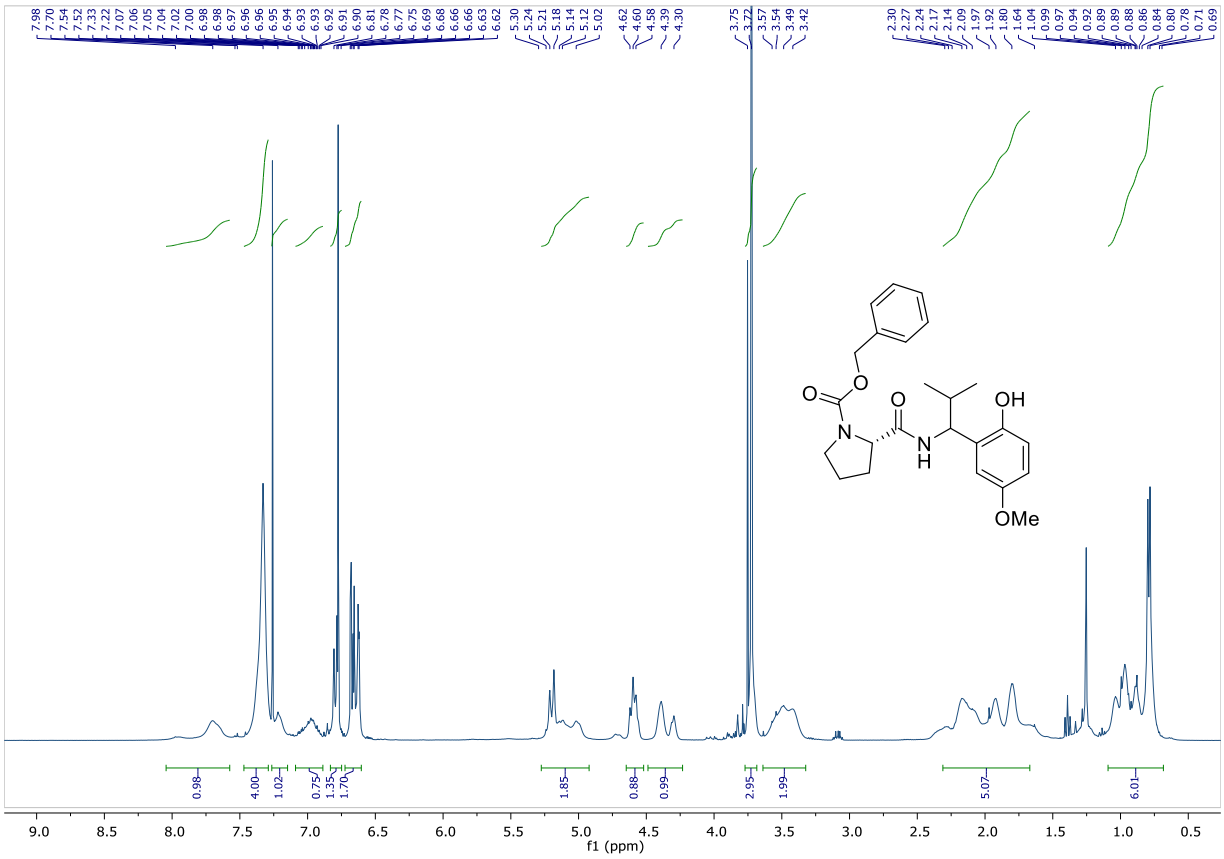
^{1}H-NMR (400 MHz, Chloroform-*d*) (5d)



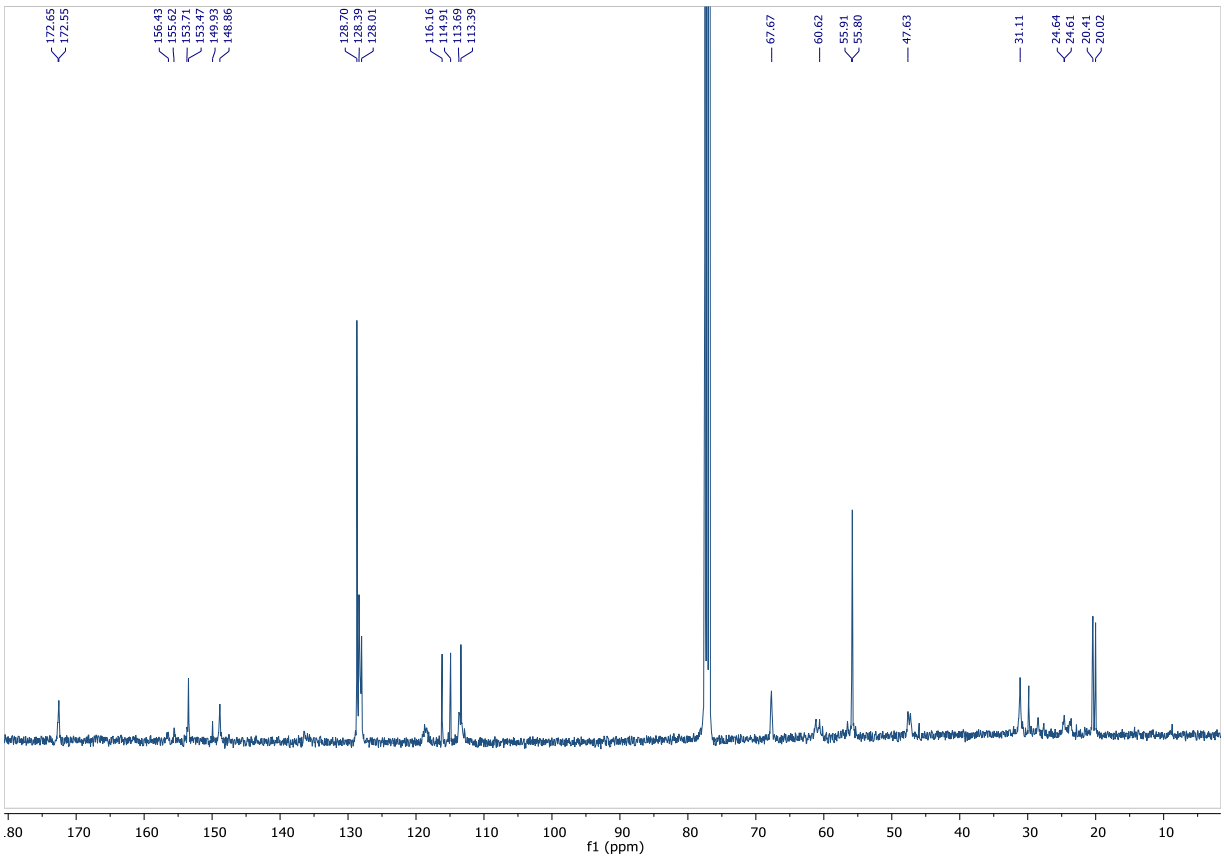
^{13}C-NMR (101 MHz, Chloroform-*d*) (5d)



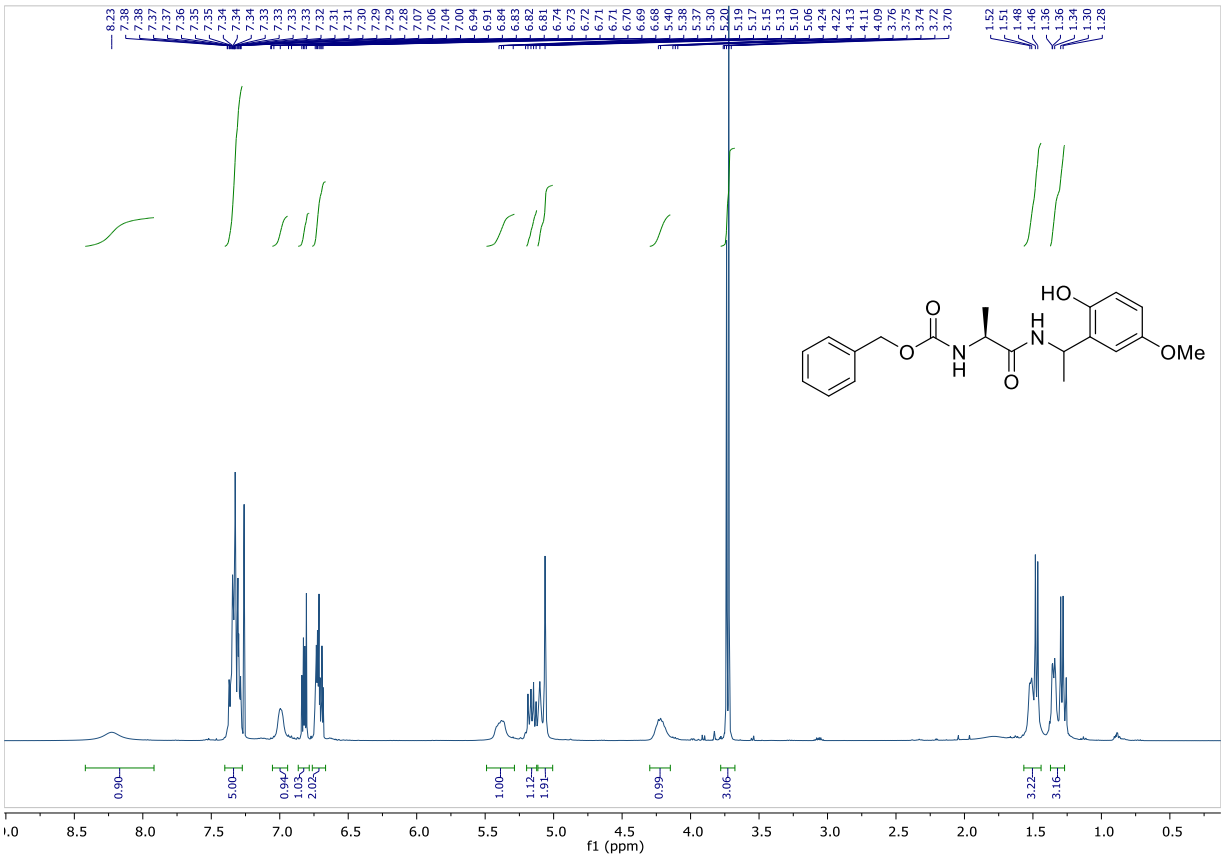
^{1}H-NMR (400 MHz, Chloroform-*d*) (5e)



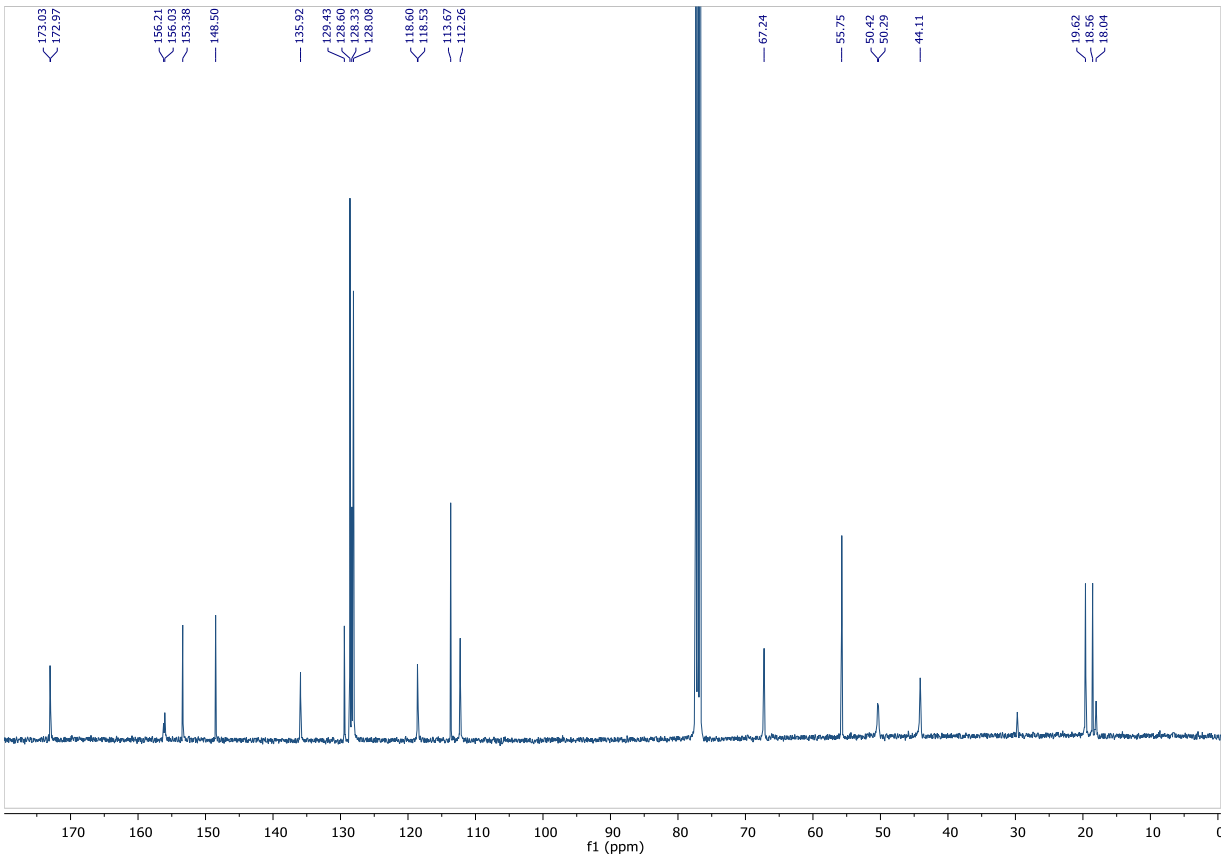
^{13}C-NMR (101 MHz, Chloroform-*d*) (5e)



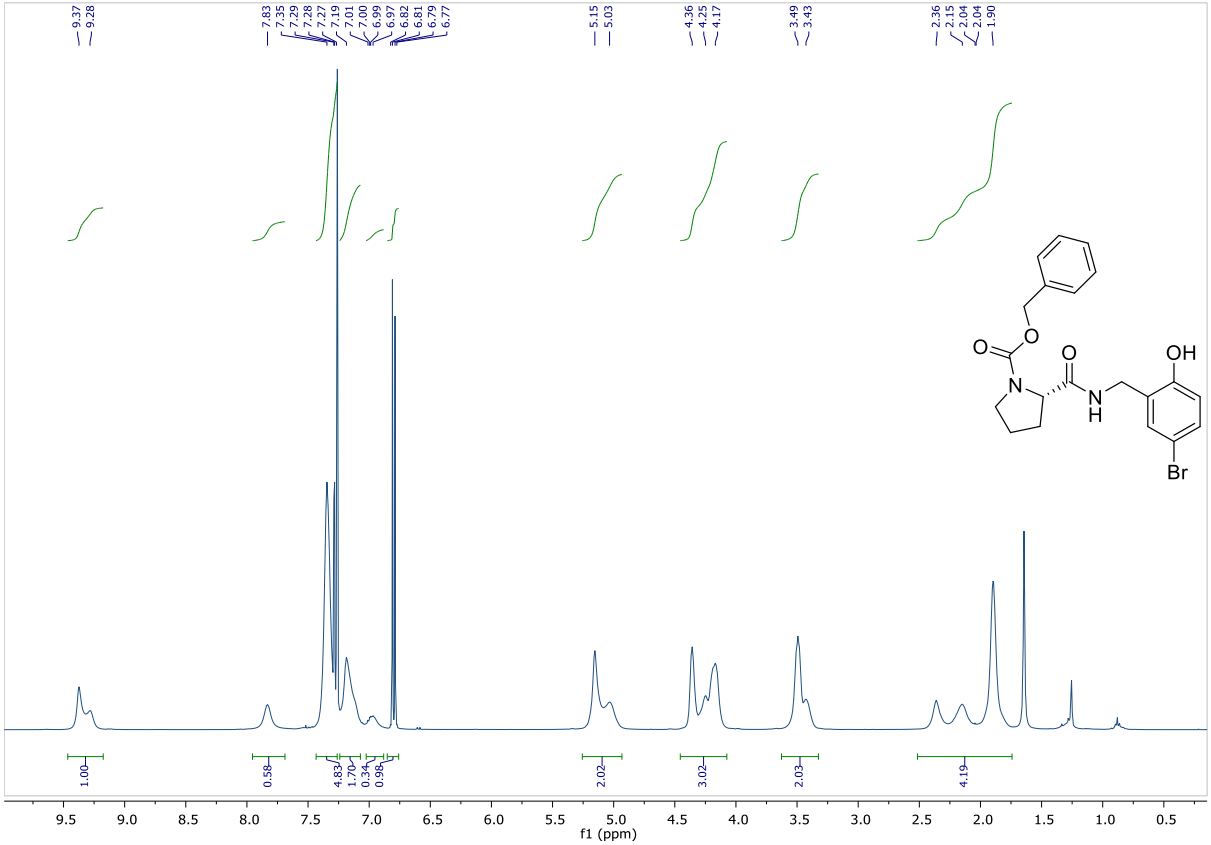
^{1}H-NMR (400 MHz, Chloroform-*d*) (5f)



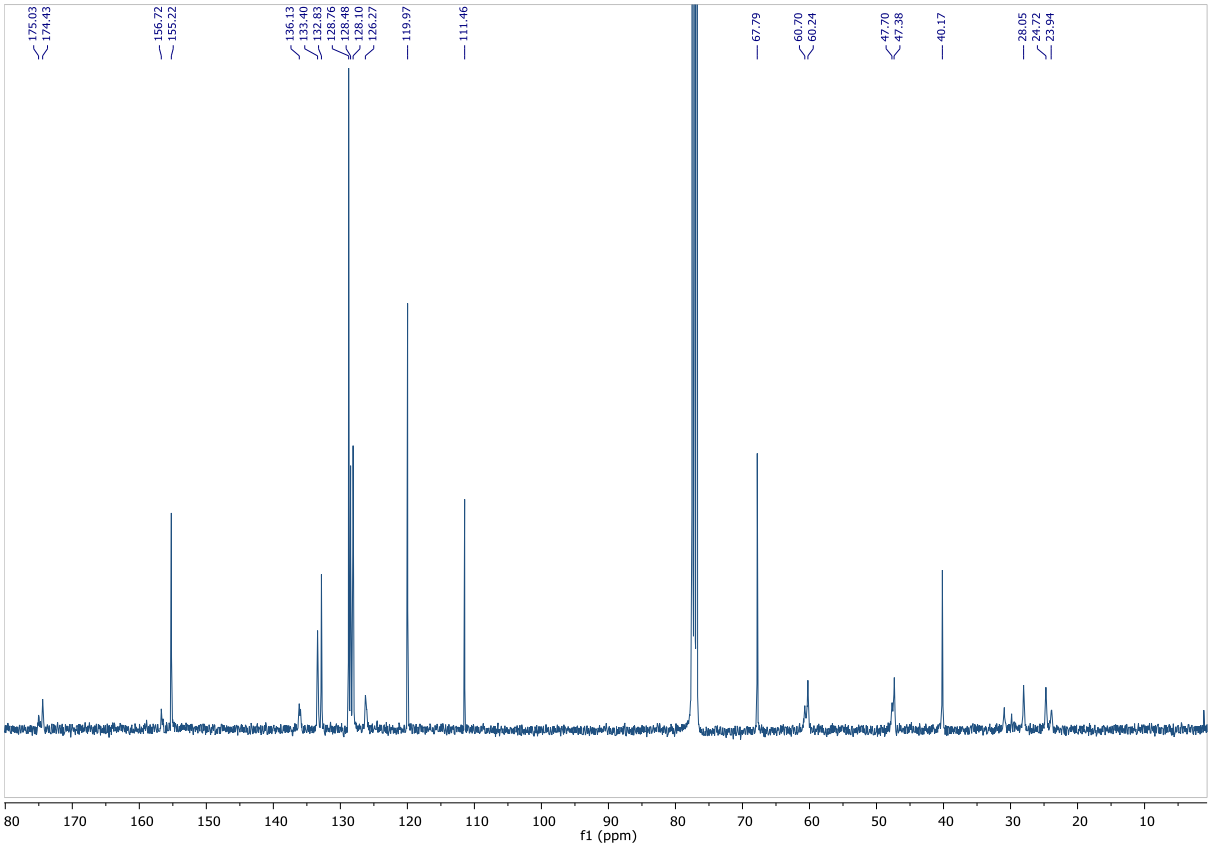
^{13}C-NMR (101 MHz, Chloroform-*d*) (5f)



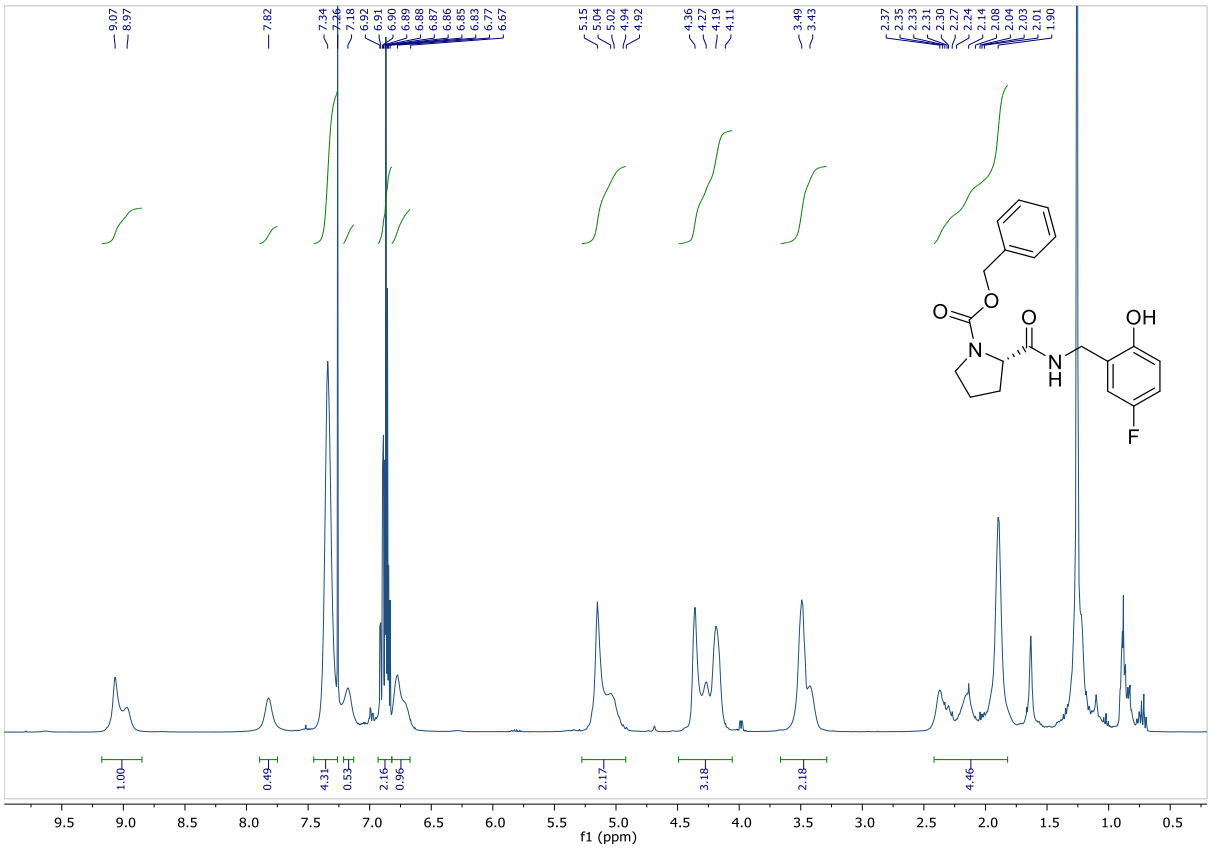
^{1}H-NMR (400 MHz, Chloroform-*d*) (5g)



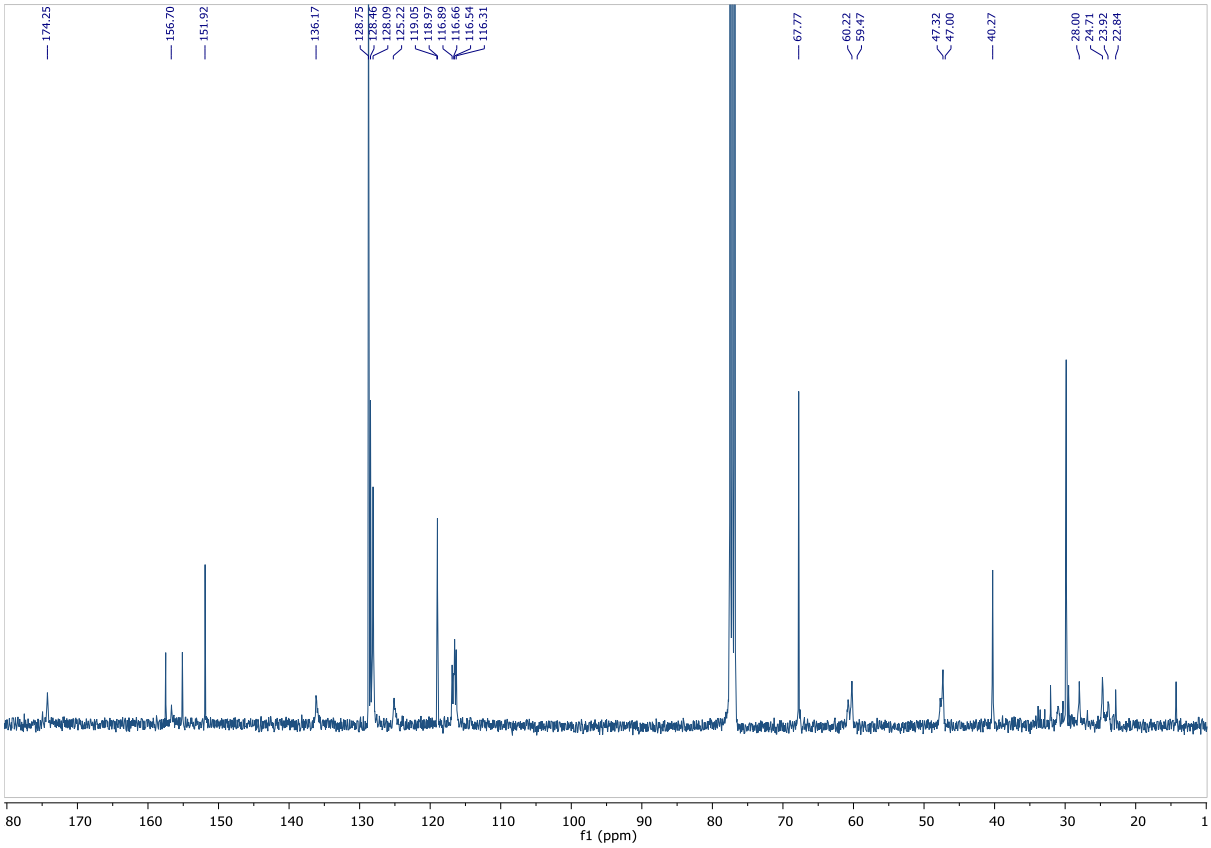
^{13}C-NMR (101 MHz, Chloroform-*d*) (5g)



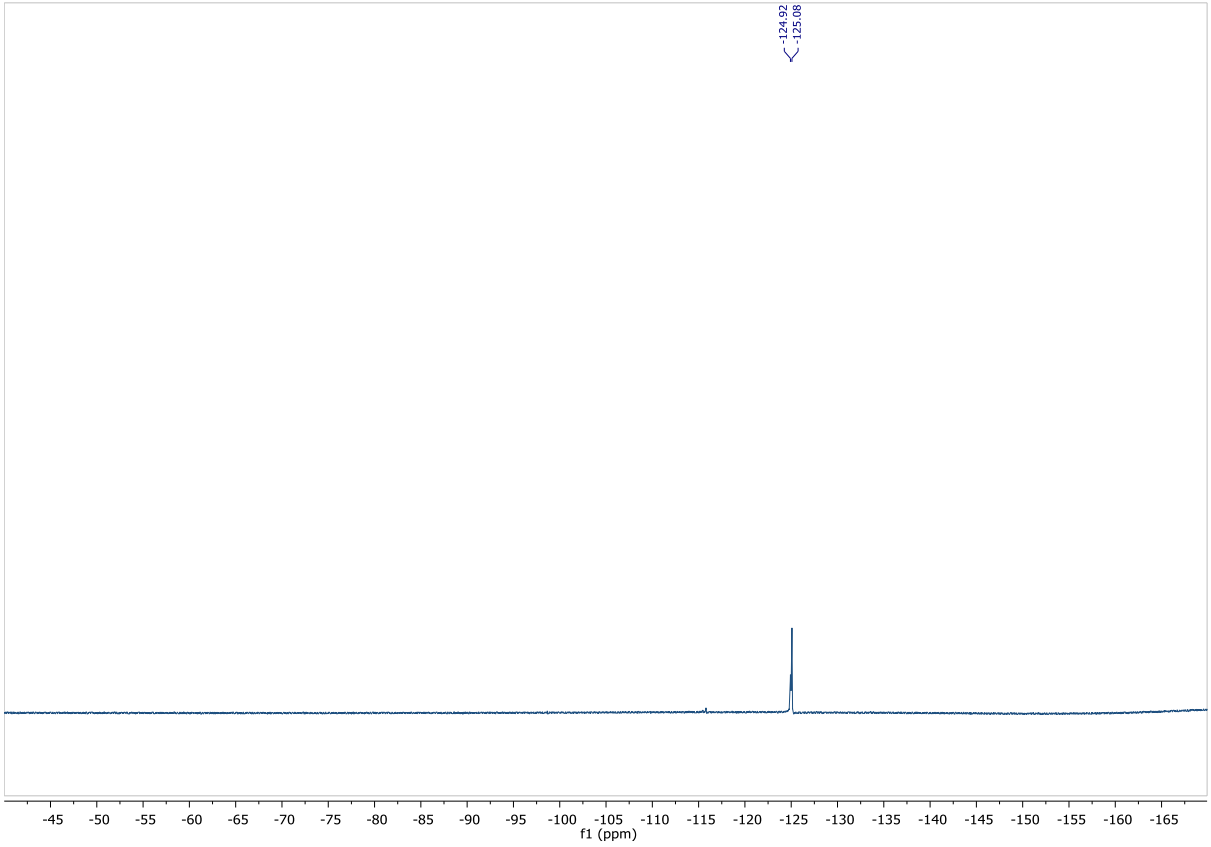
^{1}H-NMR (400 MHz, Chloroform-*d*) (5h)



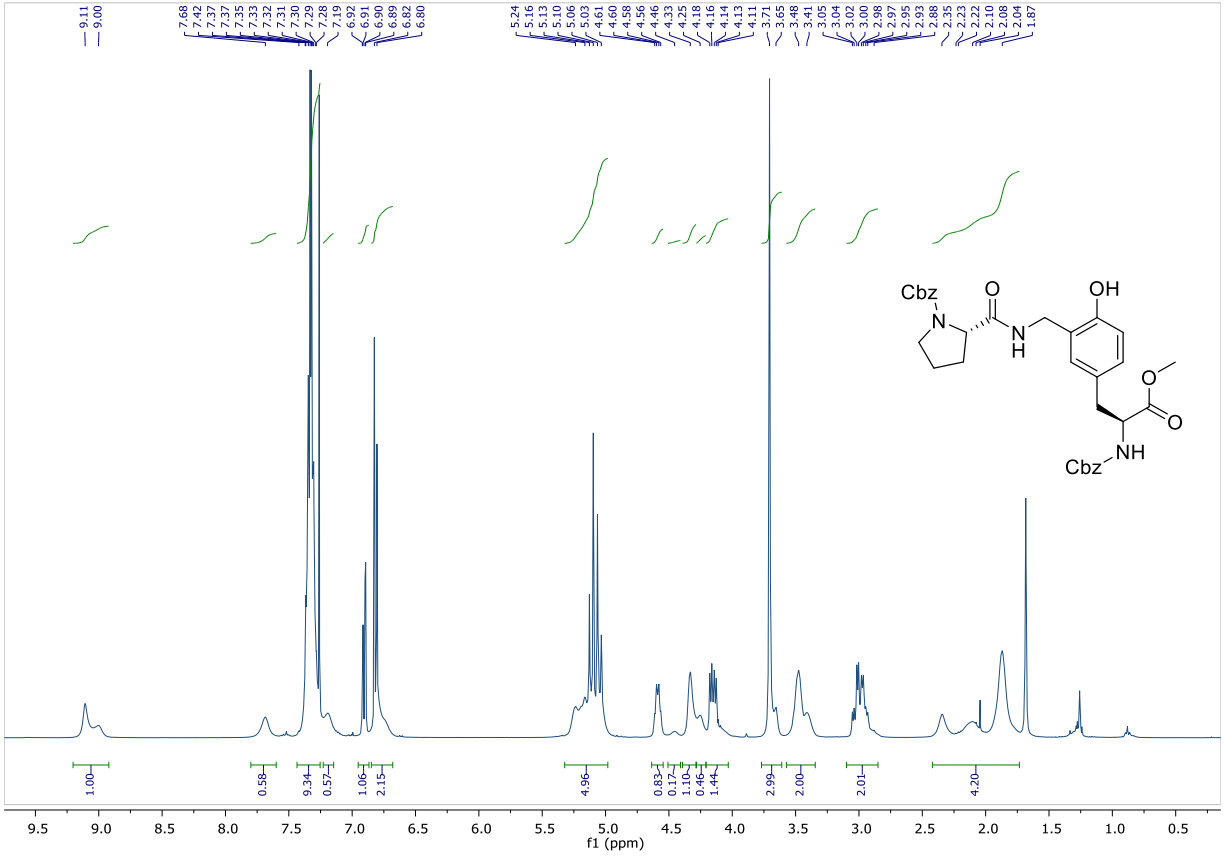
^{13}C-NMR (101 MHz, Chloroform-*d*) (5h)



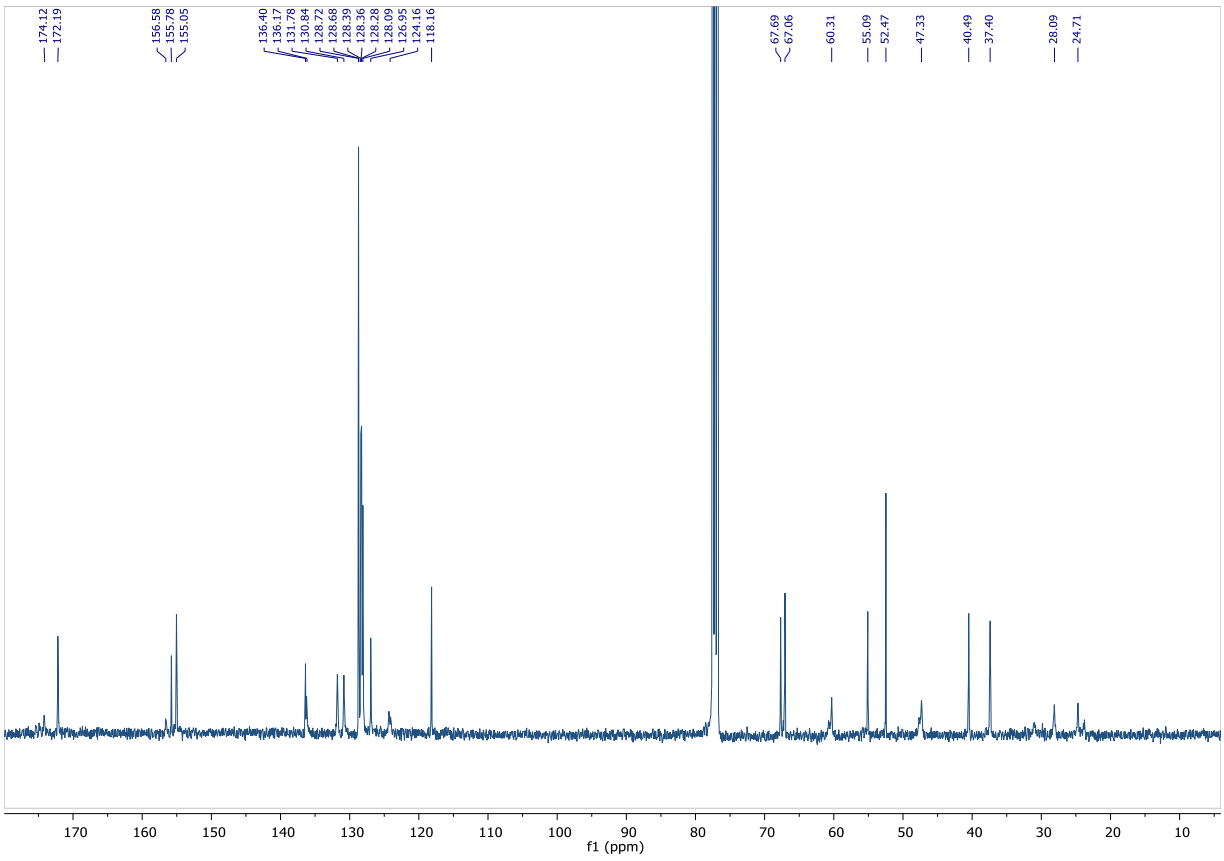
^{19}F-NMR (376 MHz, Chloroform-*d*) (5h)



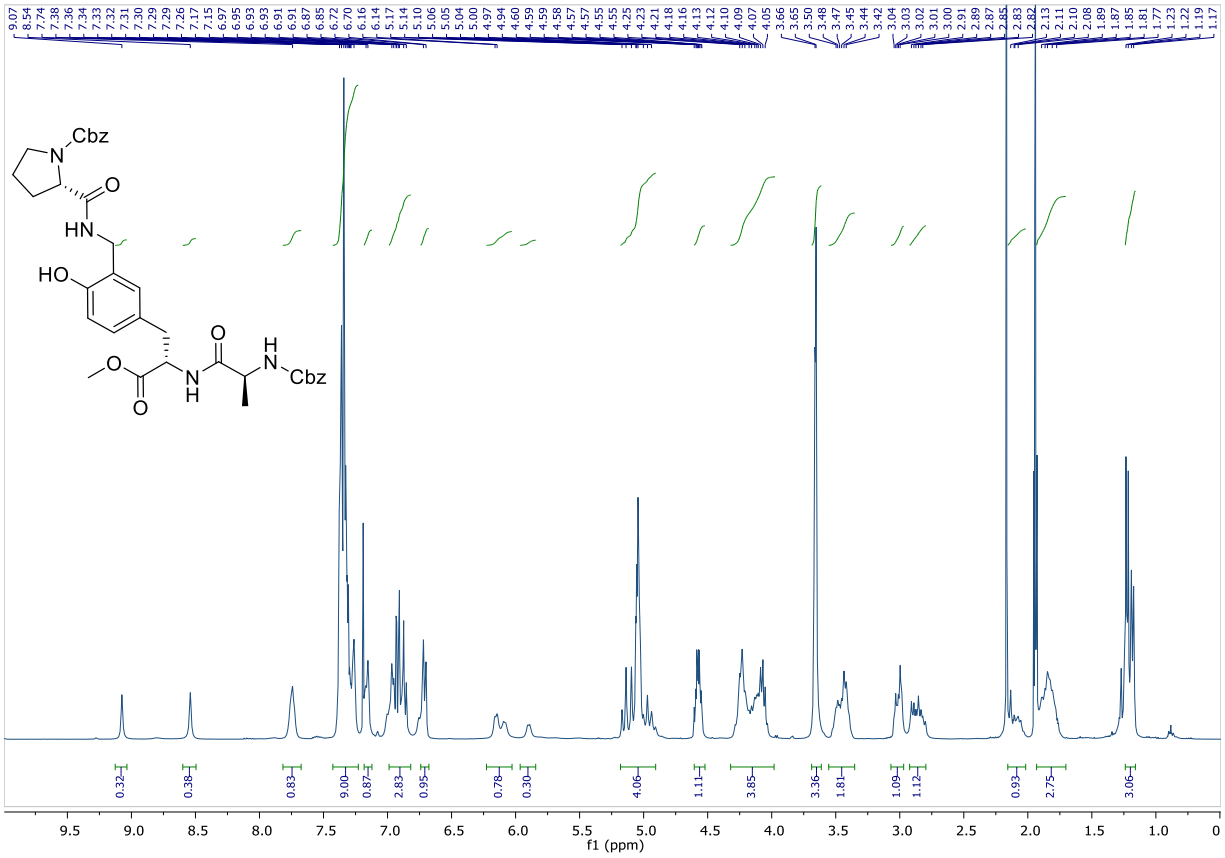
^{1}H-NMR (400 MHz, Chloroform-*d*) (5i)



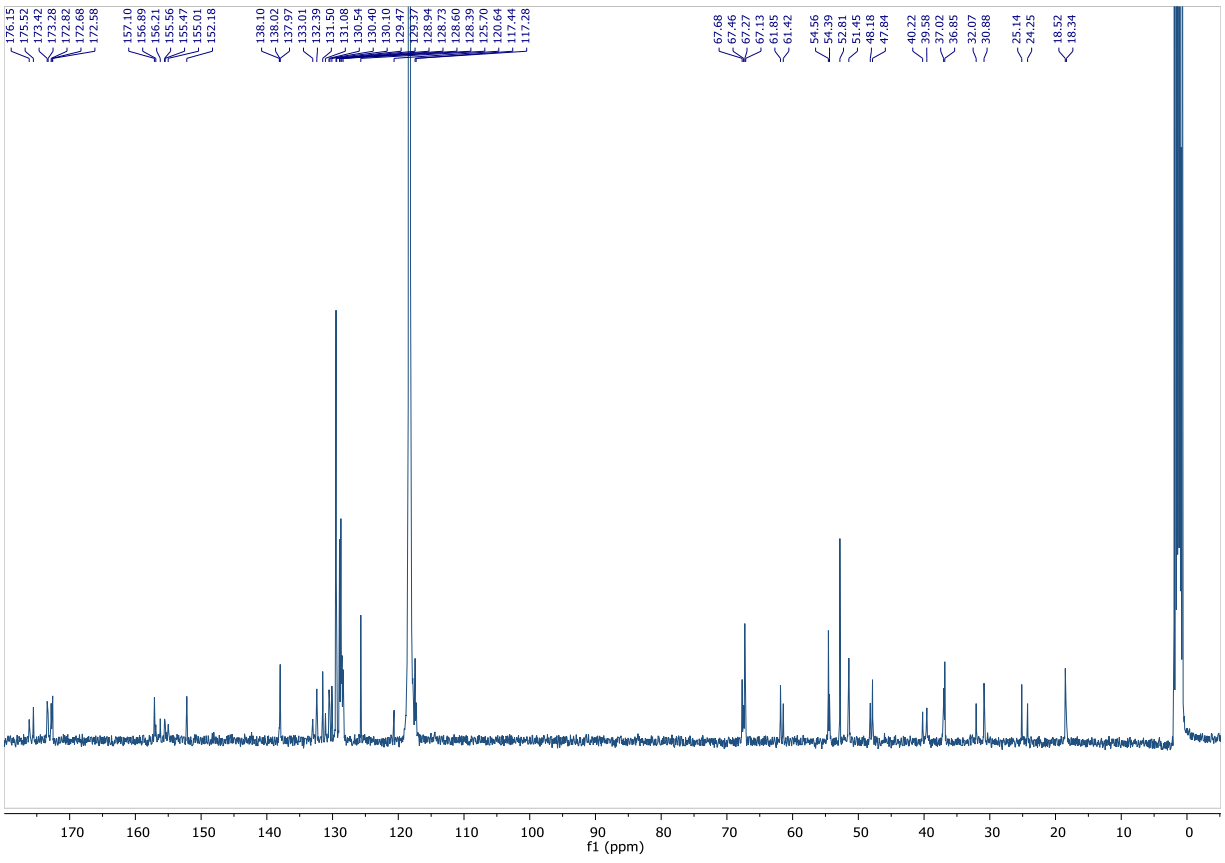
^{13}C-NMR (101 MHz, Chloroform-*d*) (5i)



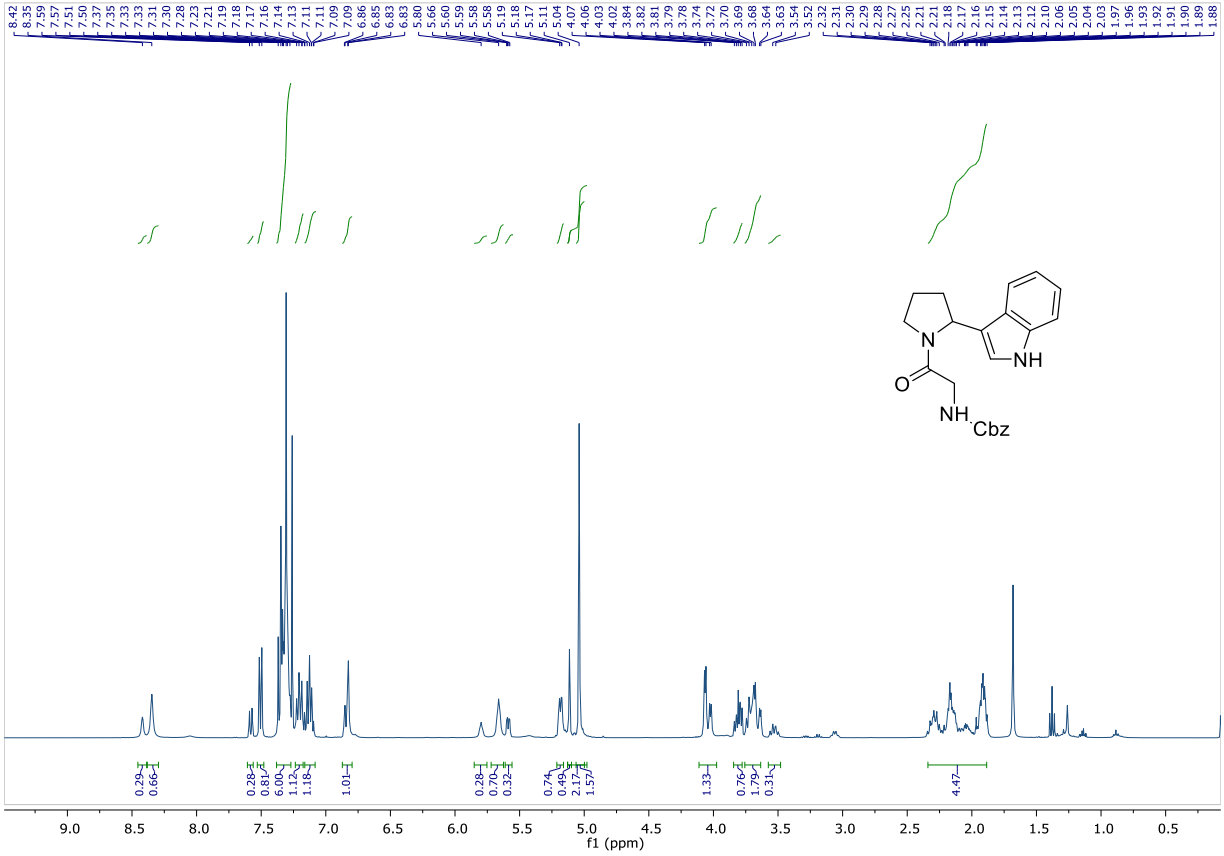
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (5j)



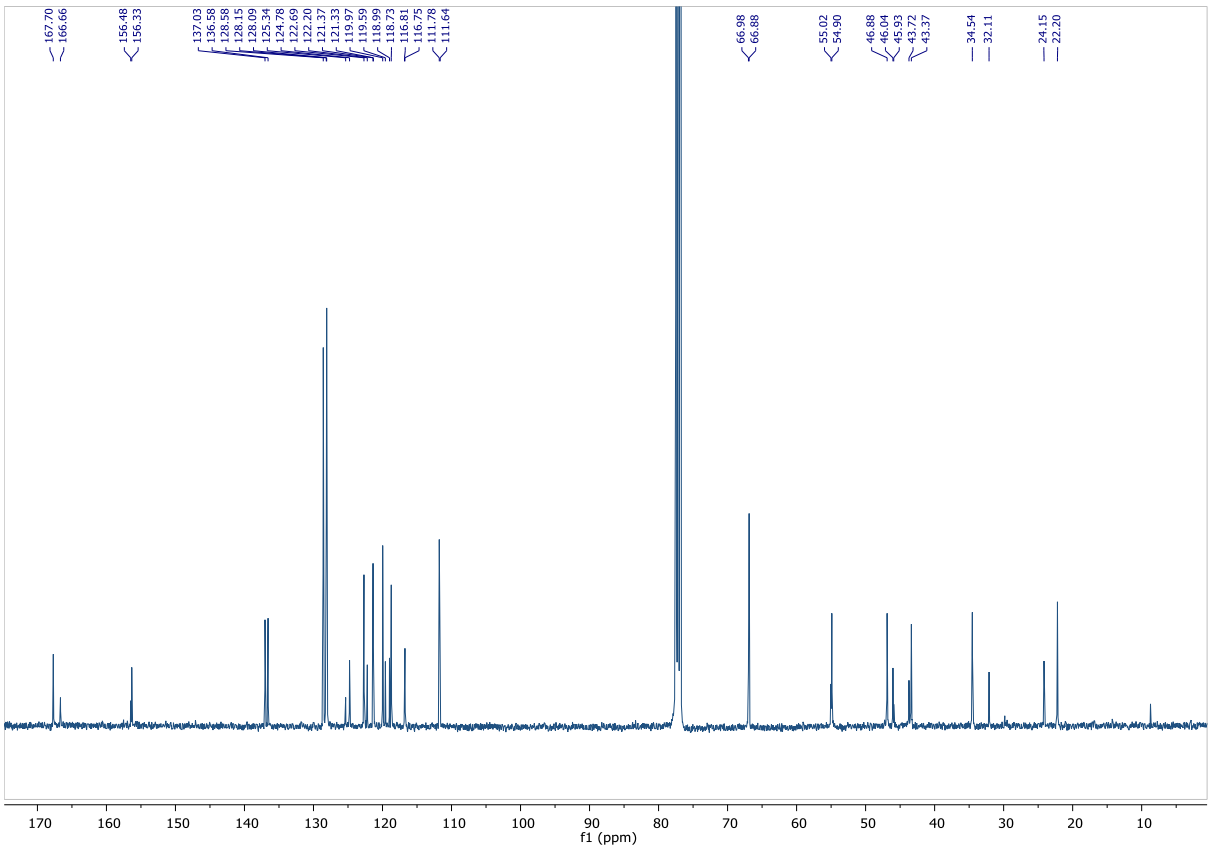
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (5j)



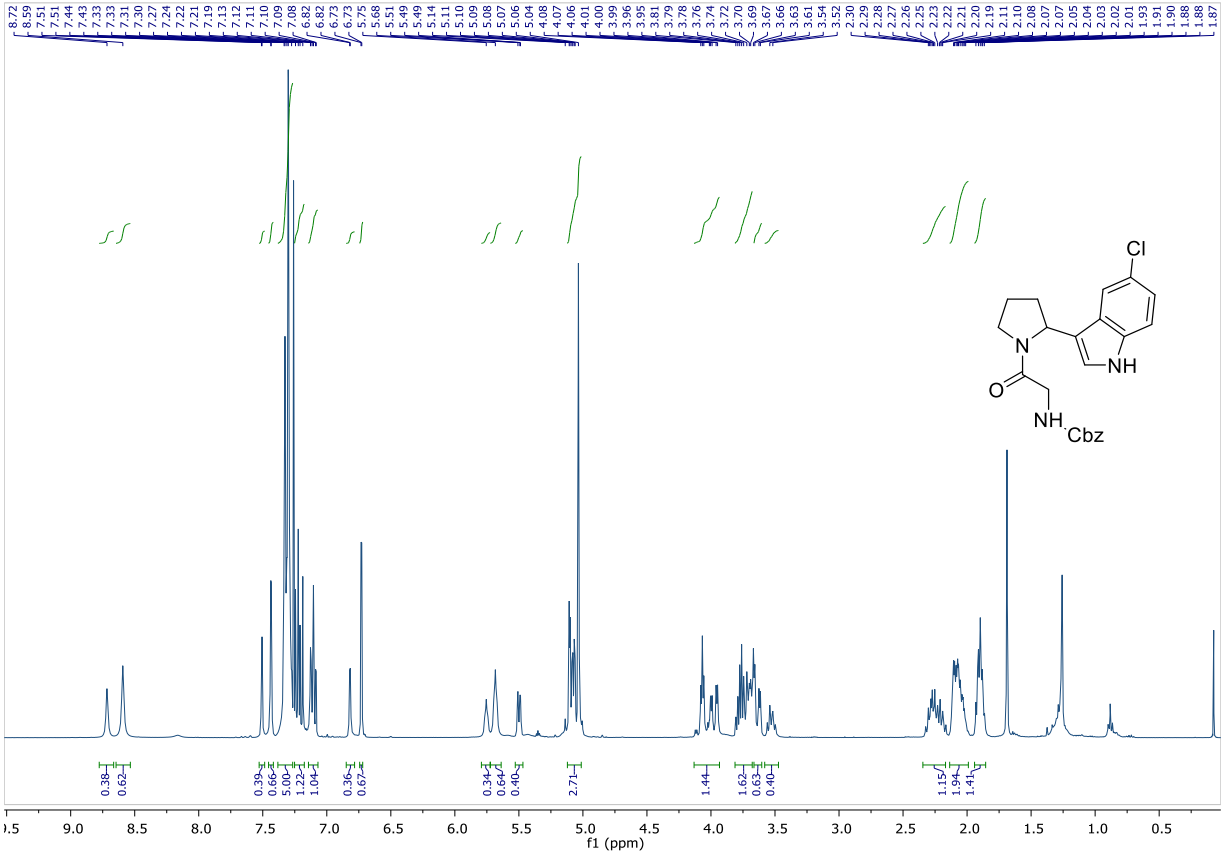
^{1}H-NMR (400 MHz, Chloroform-*d*) (6a)



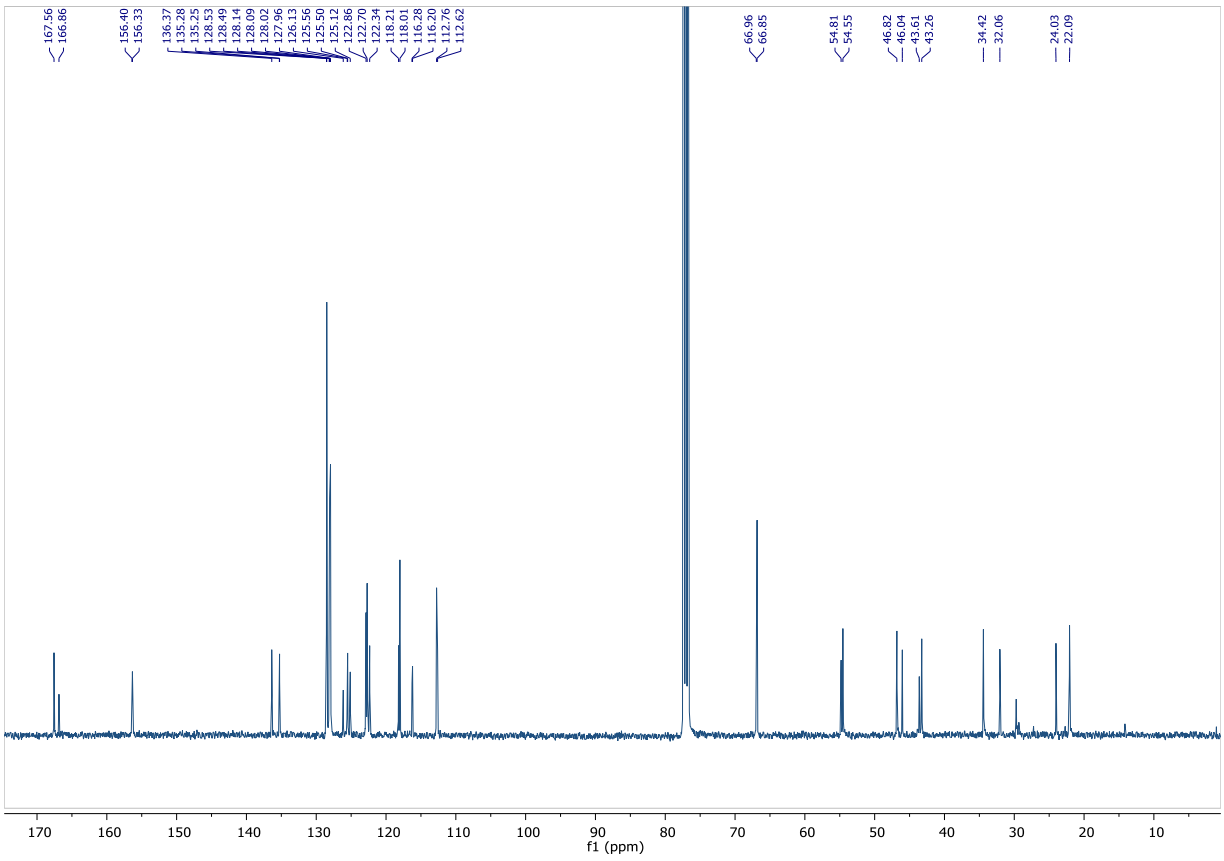
^{13}C-NMR (101 MHz, Chloroform-*d*) (6a)



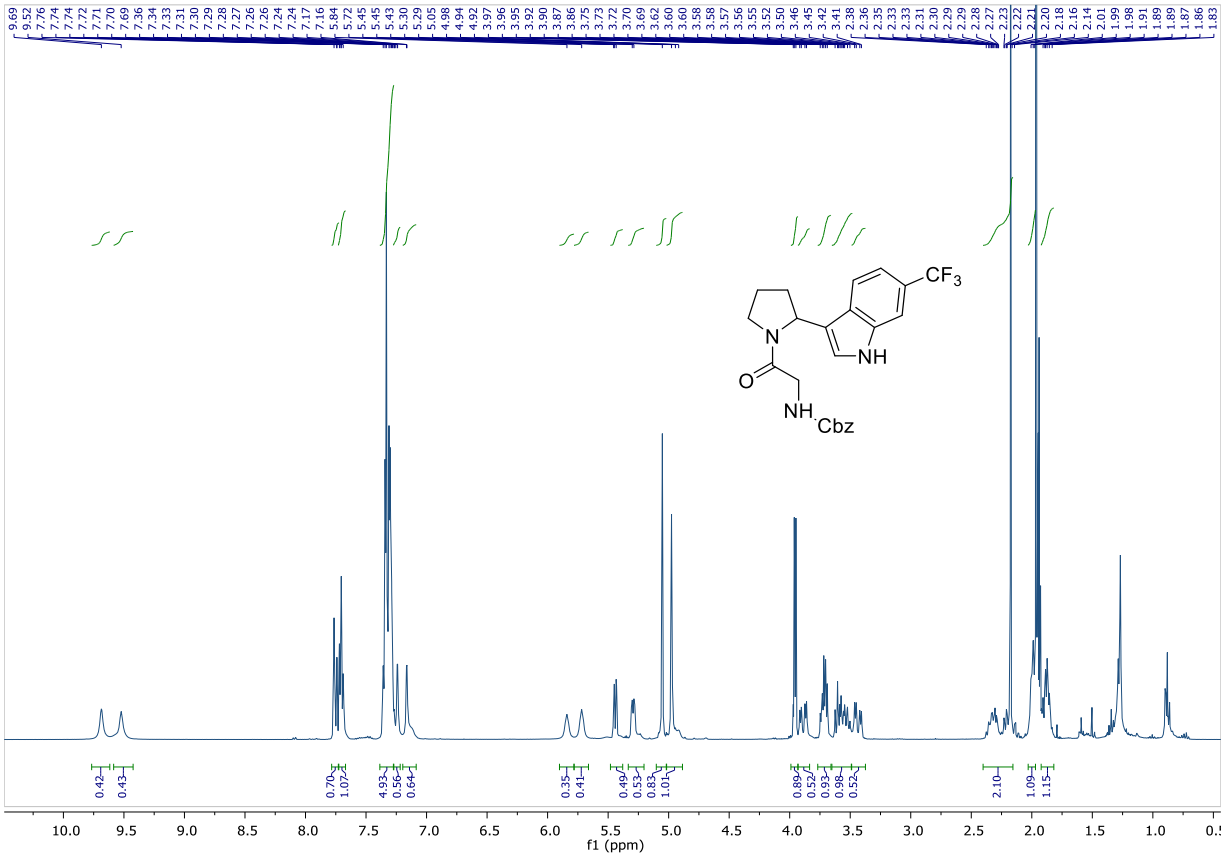
^{1}H-NMR (400 MHz, Chloroform-*d*) (6b)



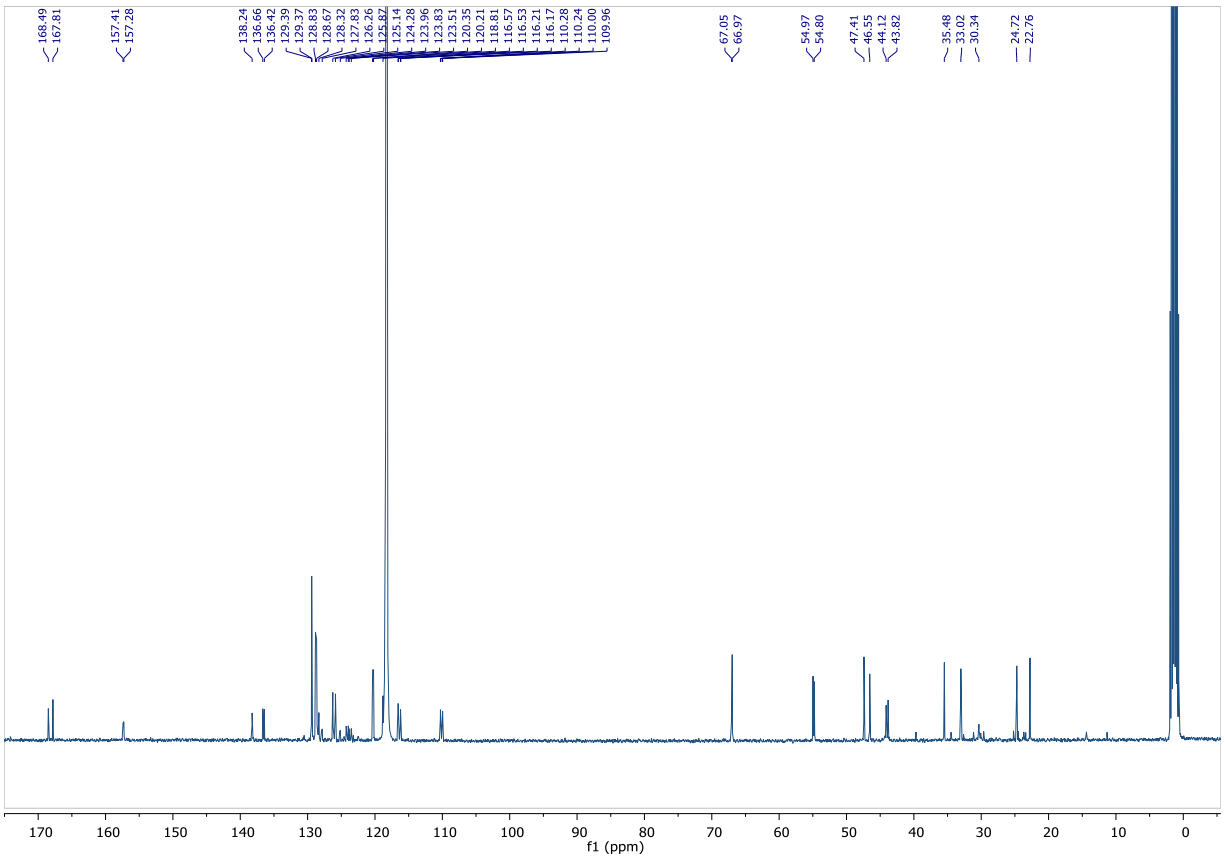
^{13}C-NMR (101 MHz, Chloroform-*d*) (6b)



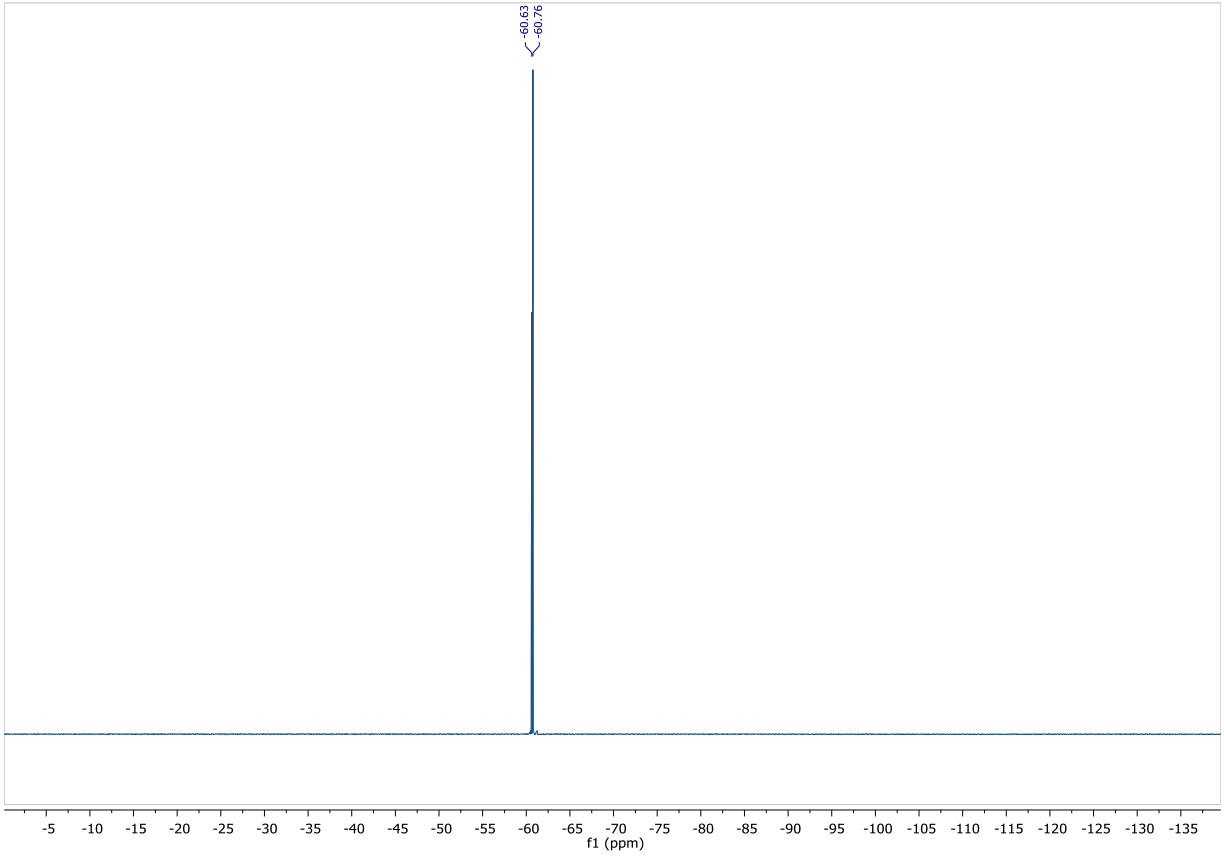
^{1}H-NMR (400 MHz, Acetonitrile-d_3) (6c)



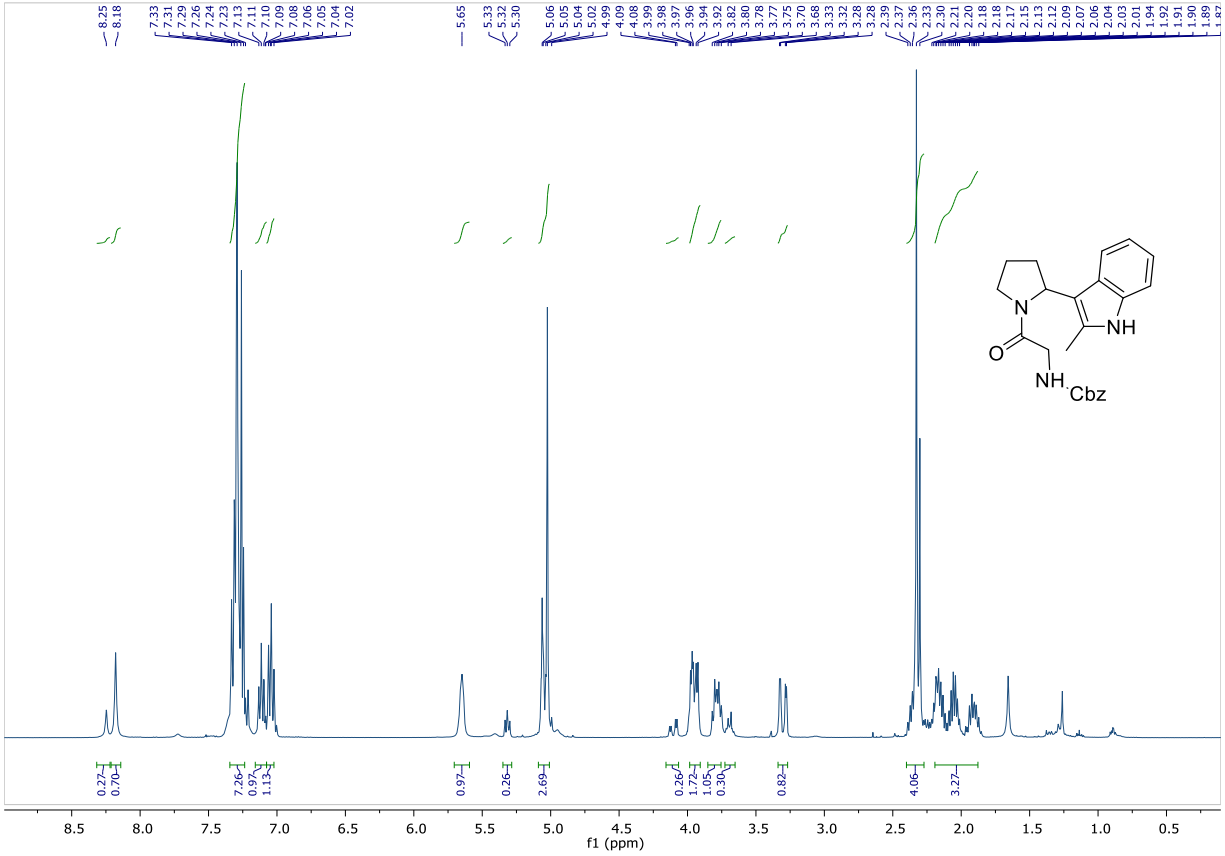
^{13}C-NMR (101 MHz, Acetonitrile-d_3) (6c)



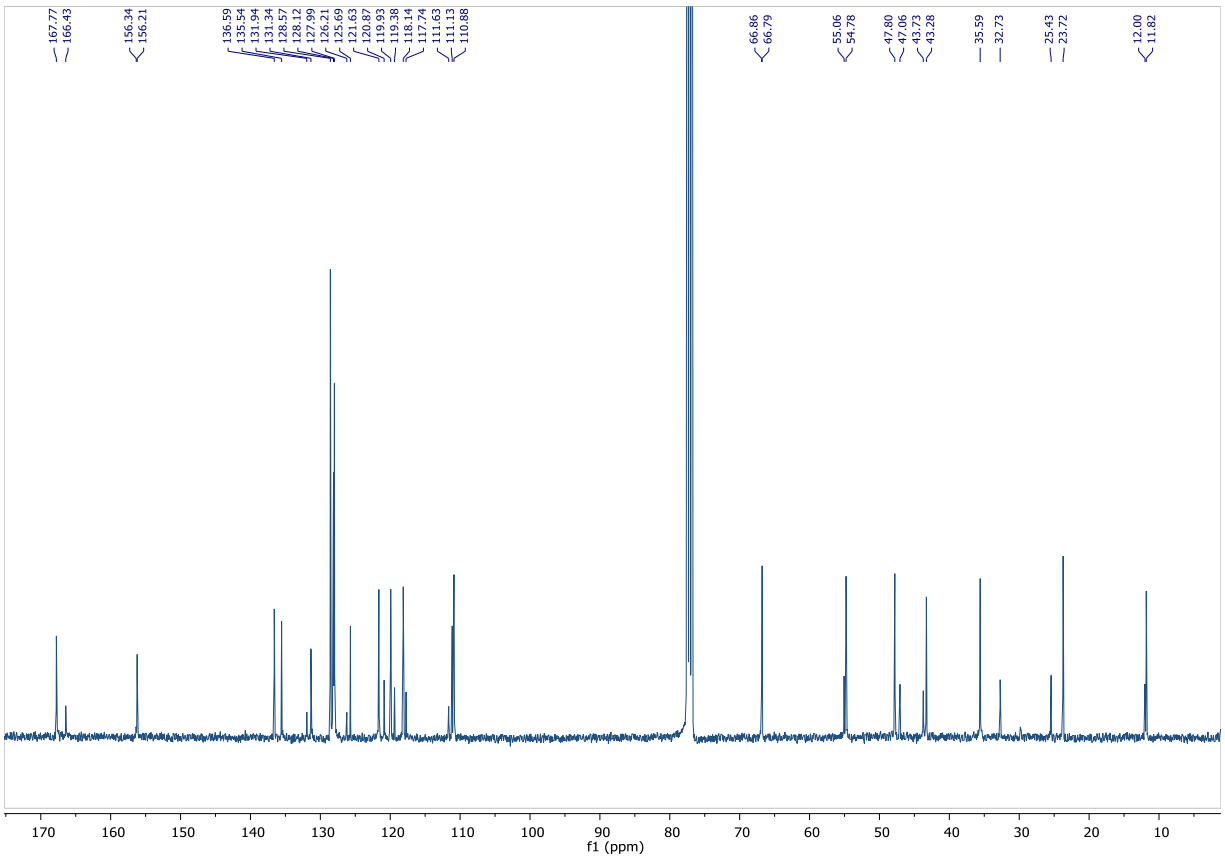
^{19}F-NMR (376 MHz, Acetonitrile-d_3) (6c)



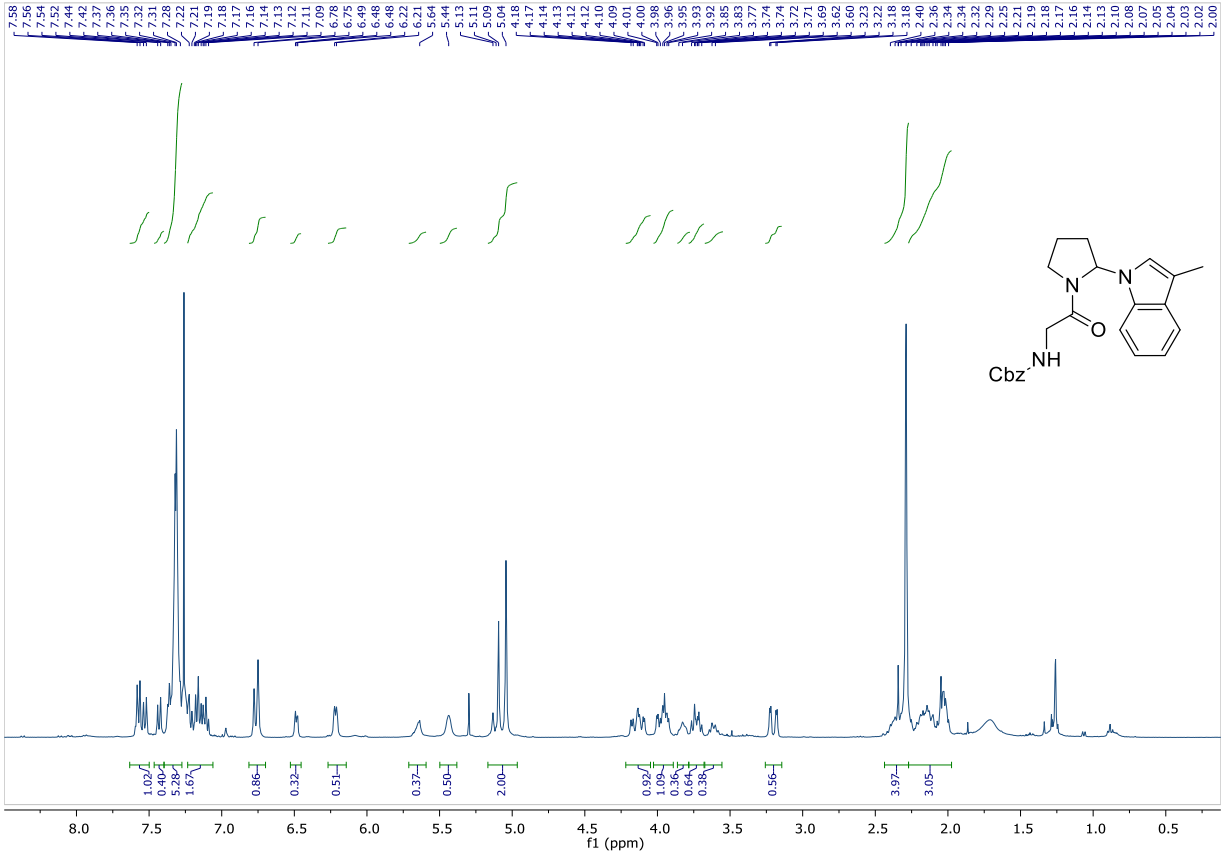
^{1}H-NMR (400 MHz, Chloroform-*d*) (6d)



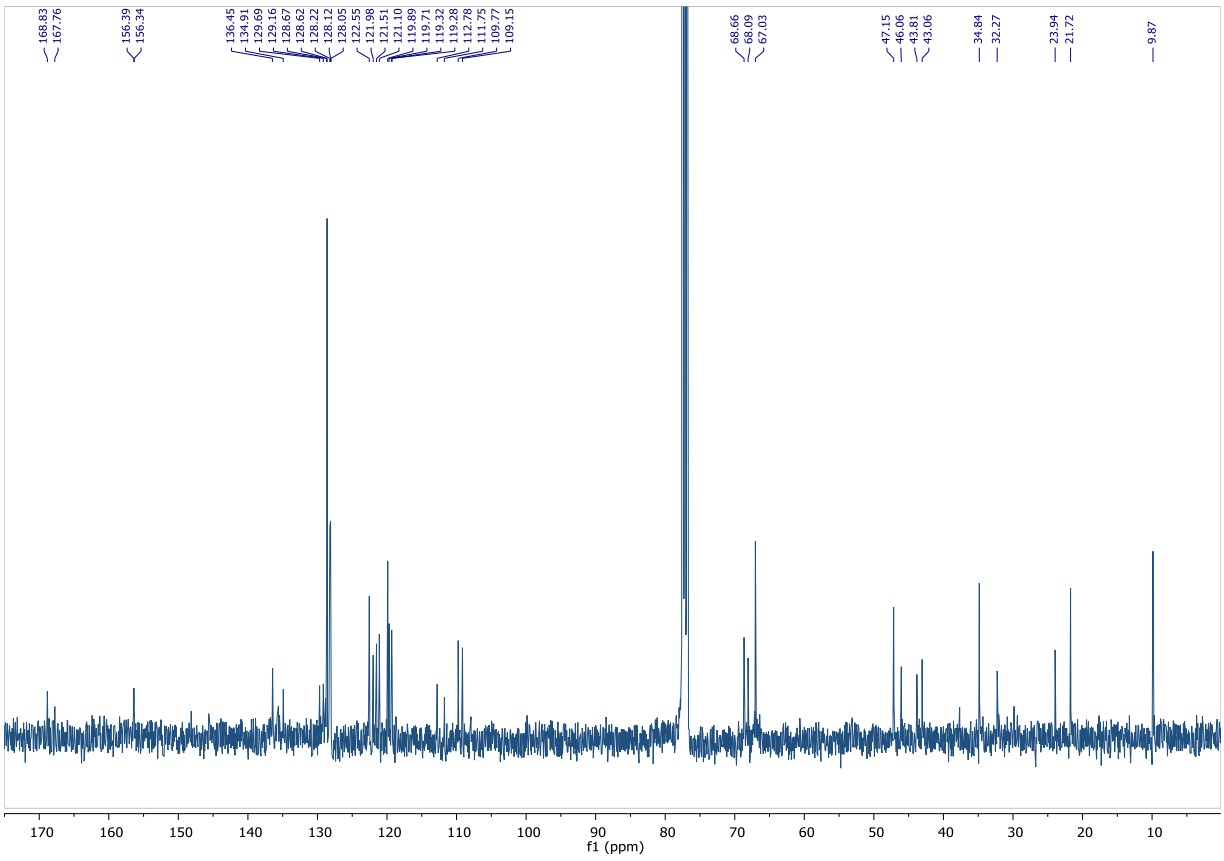
^{13}C-NMR (101 MHz, Chloroform-*d*) (6d)



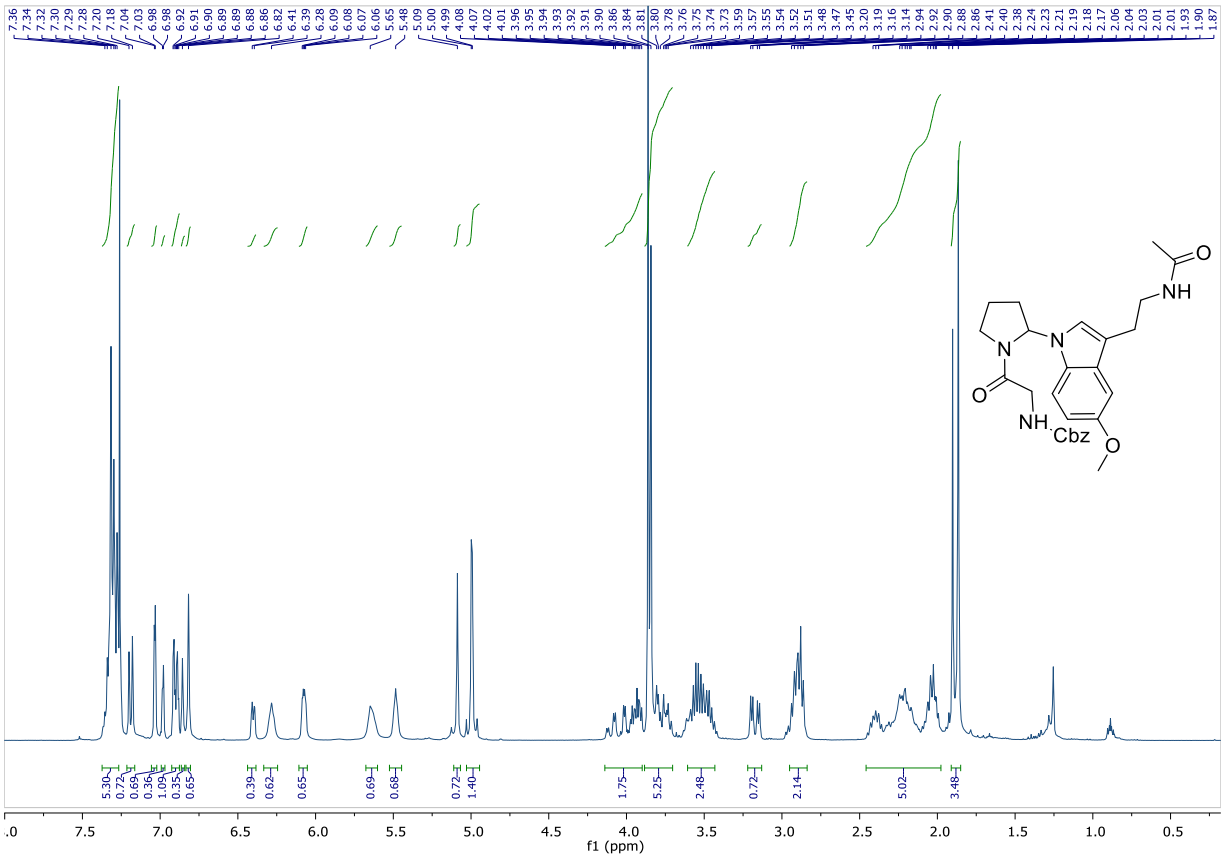
^{1}H-NMR (400 MHz, Chloroform-*d*) (6e)



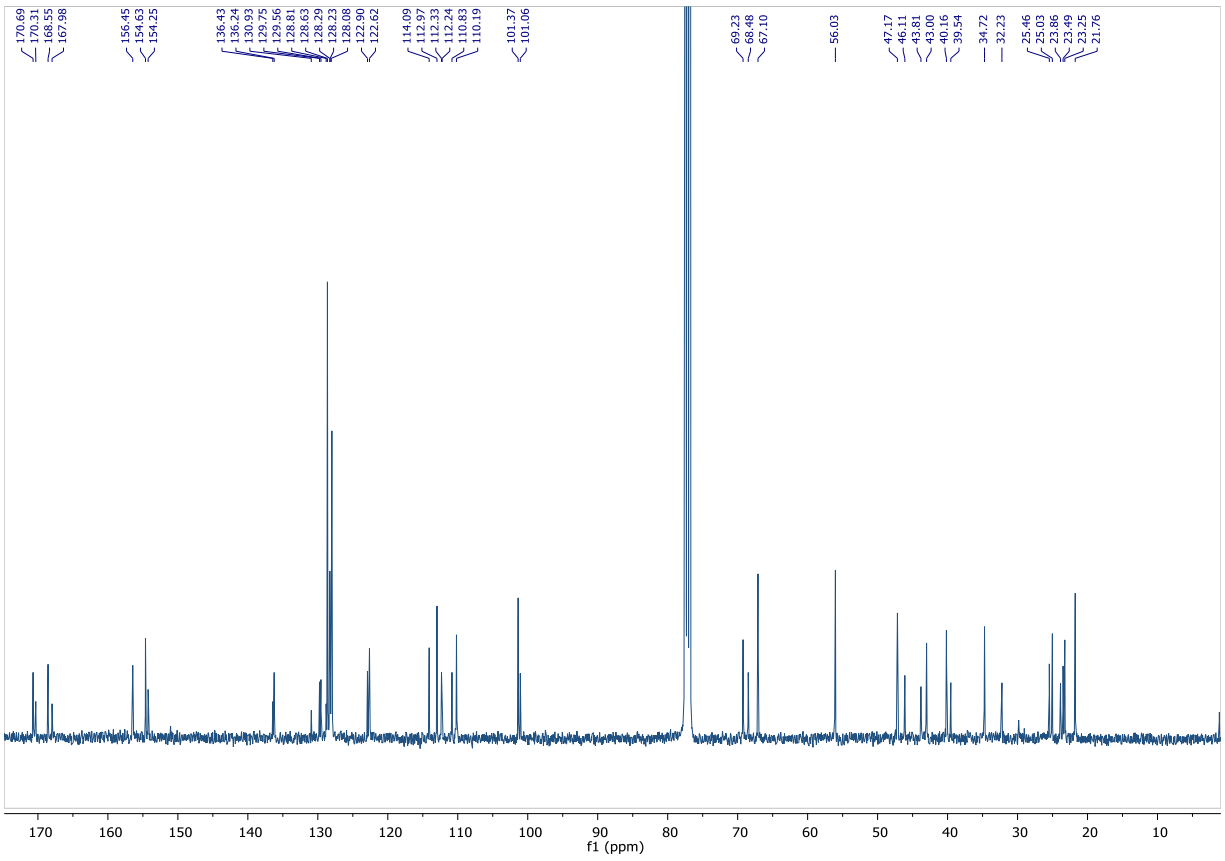
^{13}C-NMR (101 MHz, Chloroform-*d*) (6e)



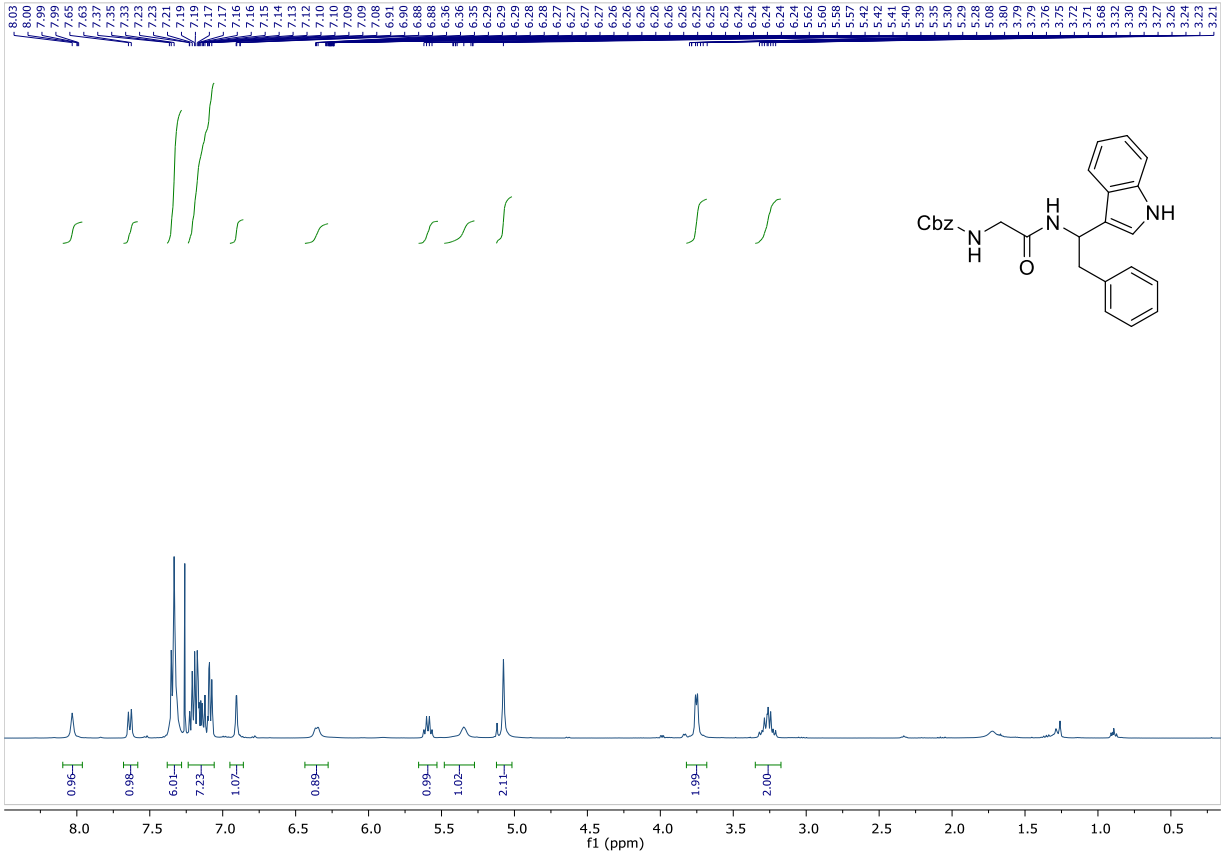
^{1}H-NMR (400 MHz, Chloroform-*d*) (6f)



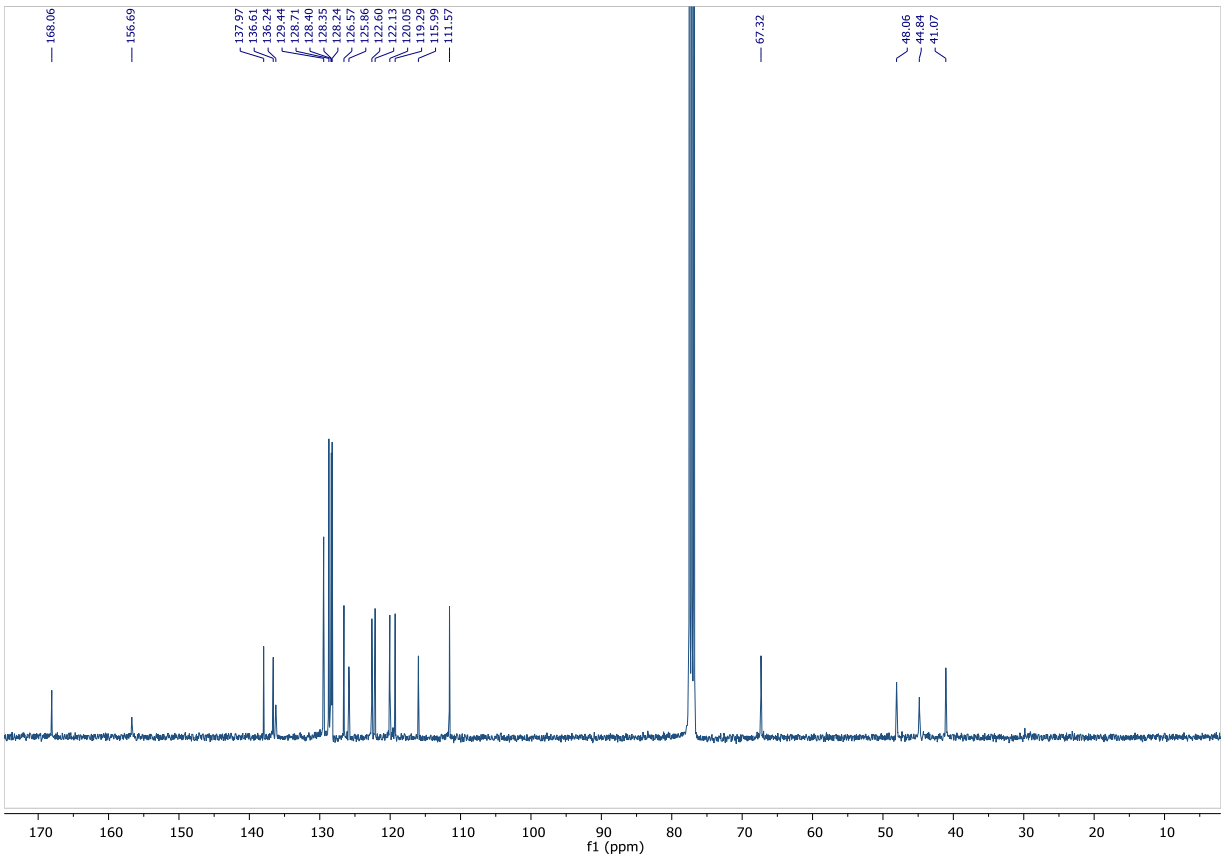
^{13}C-NMR (101 MHz, Chloroform-*d*) (6f)



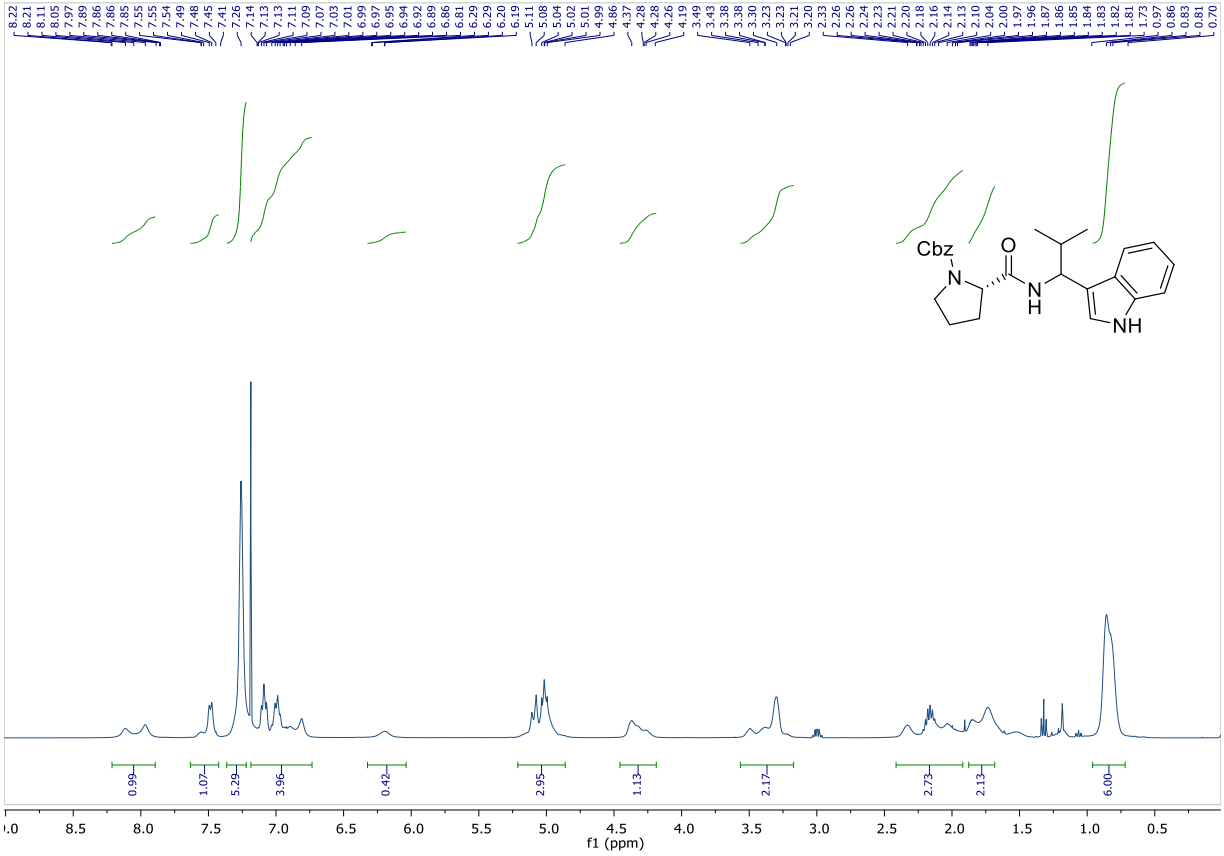
^{1}H-NMR (400 MHz, Chloroform-*d*) (6g)



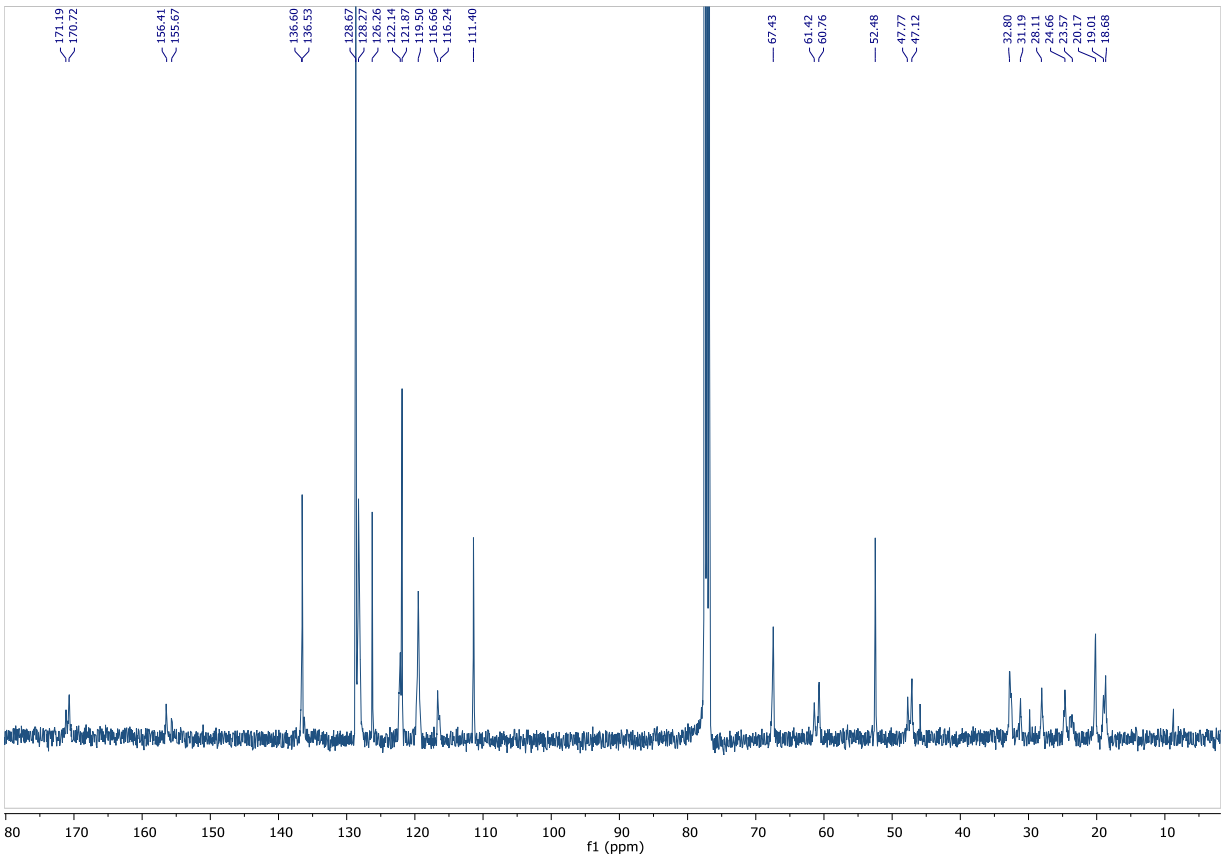
^{13}C-NMR (101 MHz, Chloroform-*d*) (6g)



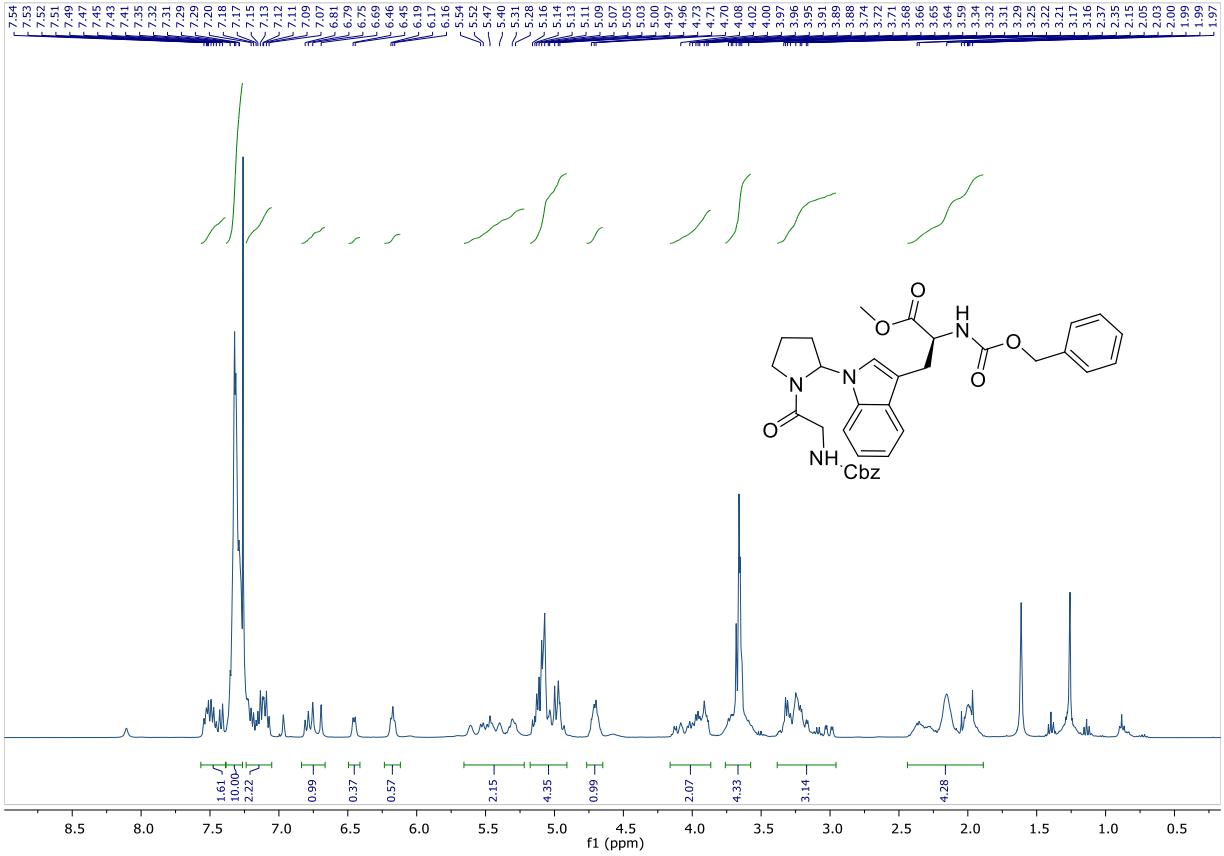
^{1}H-NMR (400 MHz, Chloroform-*d*) (6h)



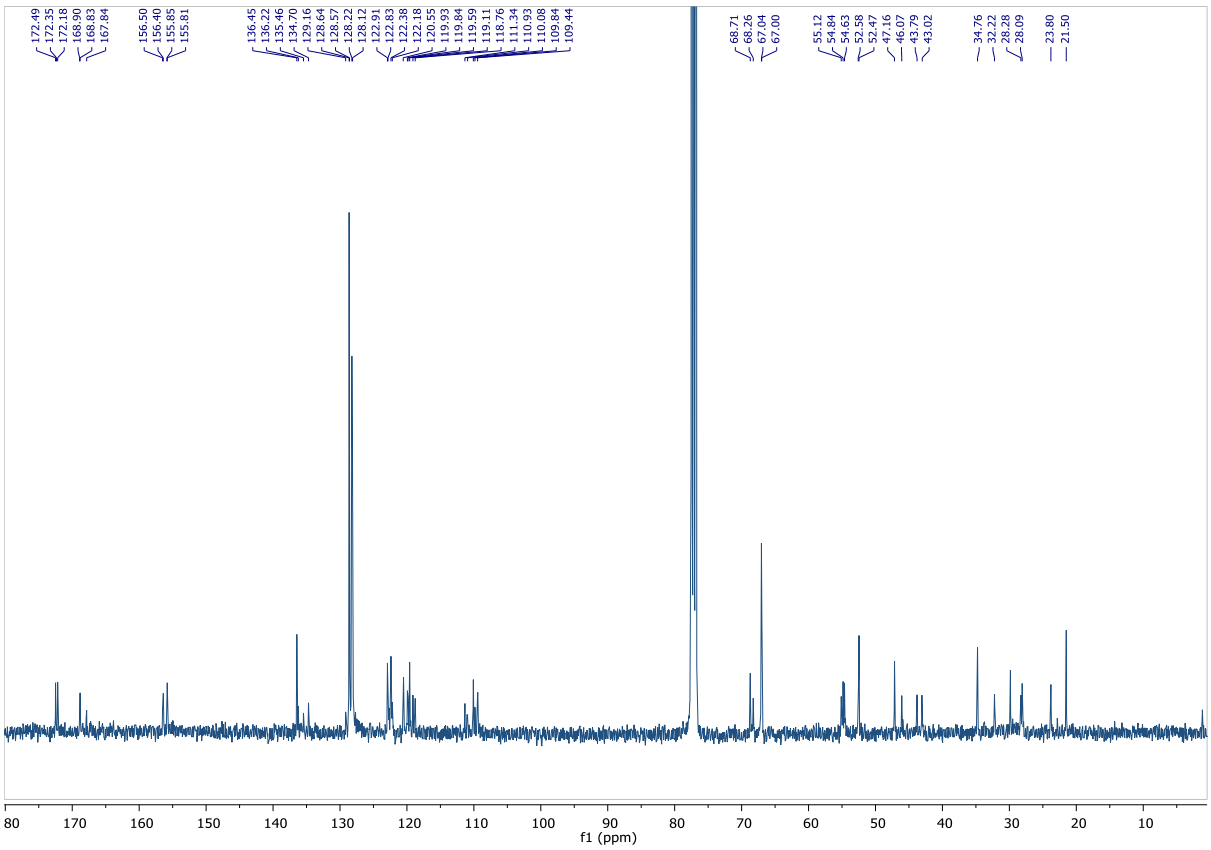
^{13}C-NMR (101 MHz, Chloroform-*d*) (6h)



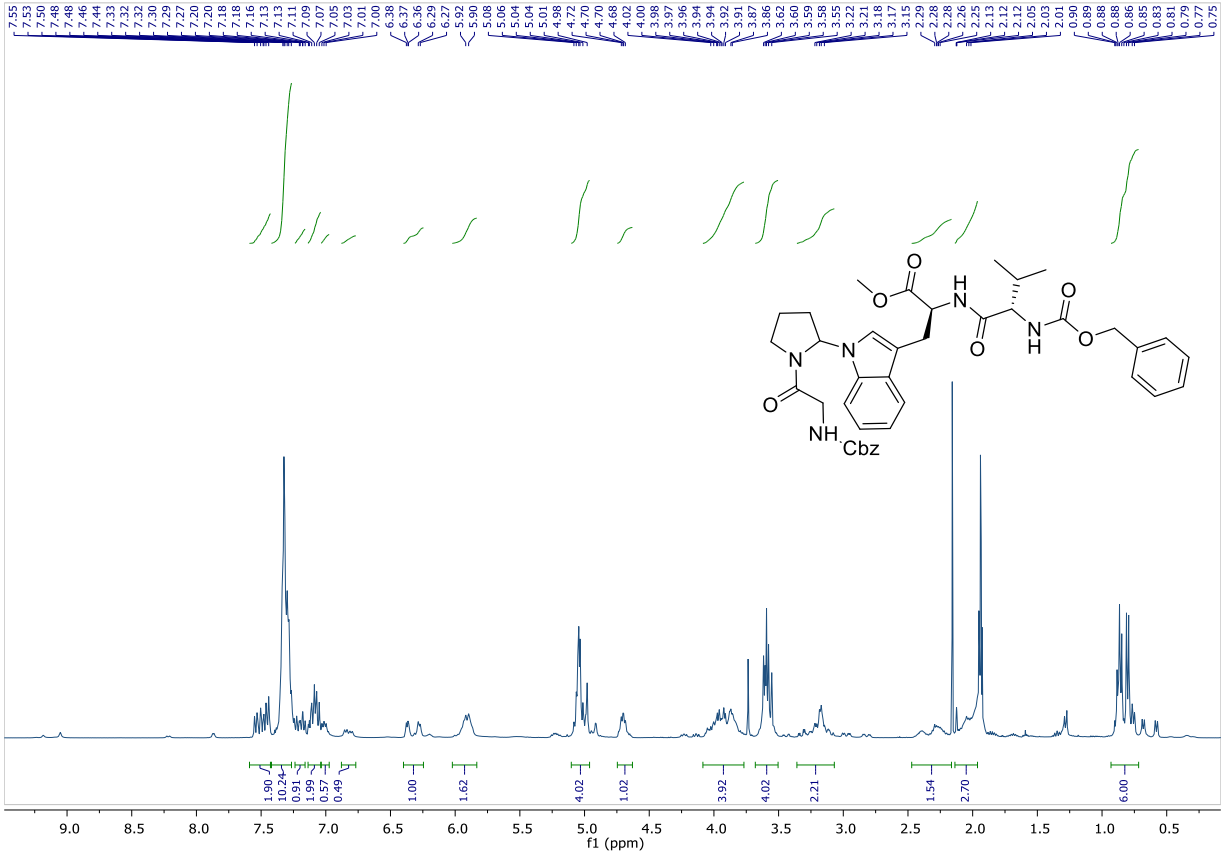
^{1}H-NMR (400 MHz, Chloroform-*d*) (6i)



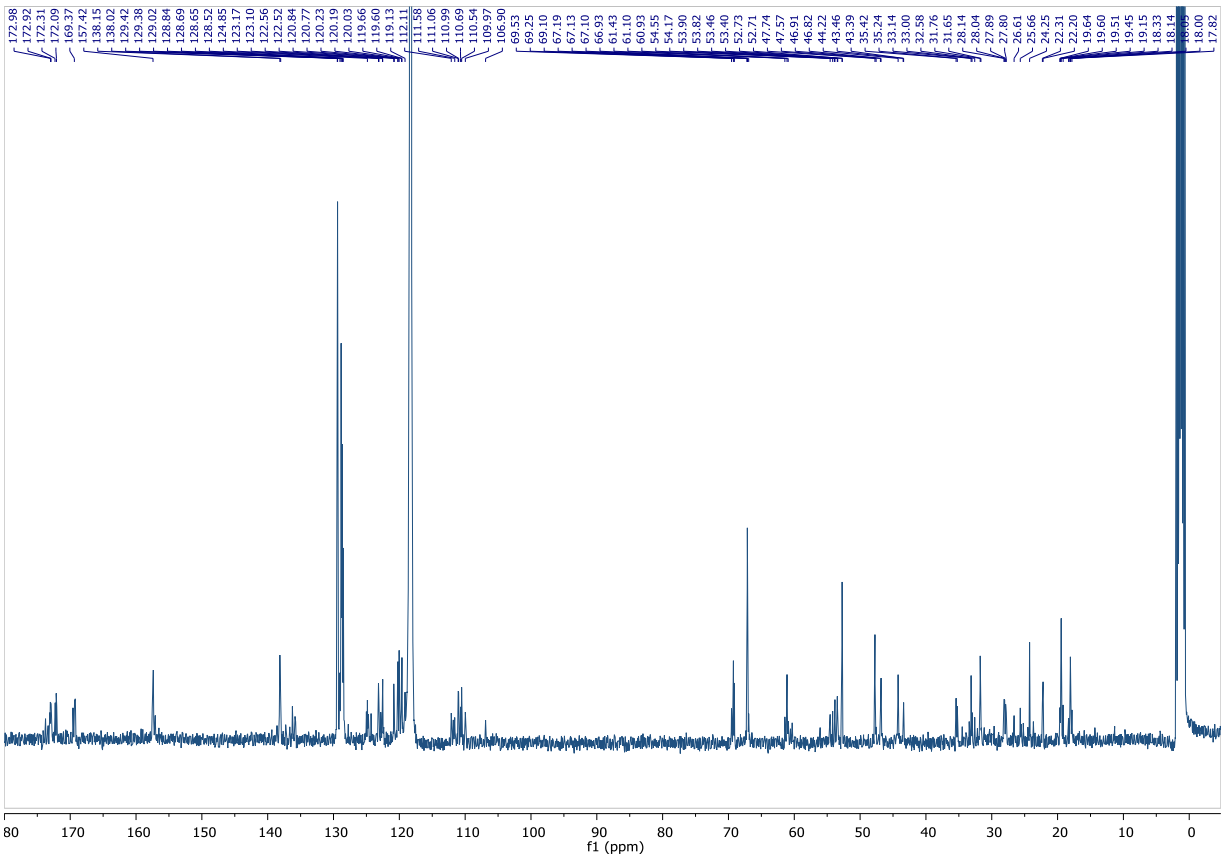
^{13}C-NMR (101 MHz, Chloroform-*d*) (6i)



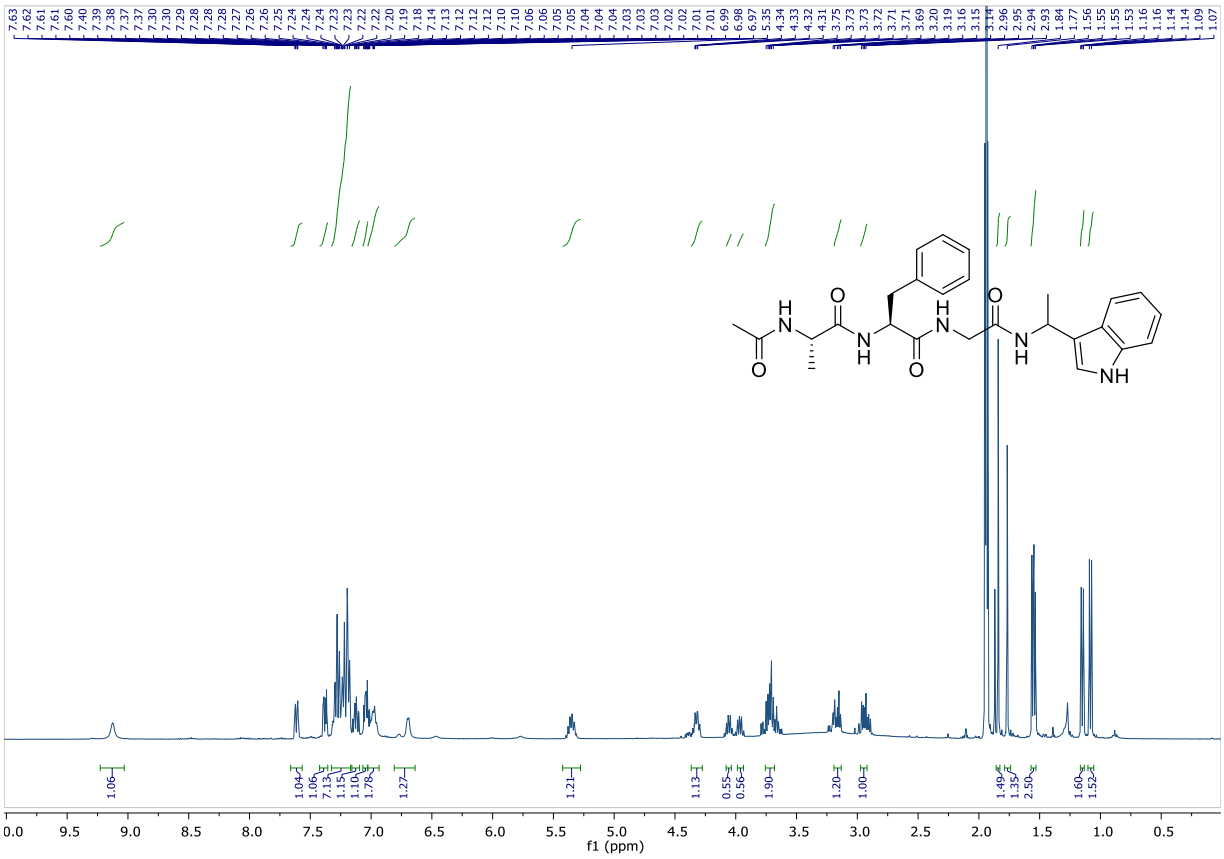
^{1}H-NMR (400 MHz, Acetonitrile-*d*$_3$) (6j)



^{13}C-NMR (101 MHz, Acetonitrile-*d3*) (6j)



^{1}H-NMR (400 MHz, Acetonitrile-*d_3*) (8a)



^{13}C-NMR (101 MHz, Acetonitrile-*d3*) (8a)