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Research Paper

Chemical modification of peptides by organocopper compounds

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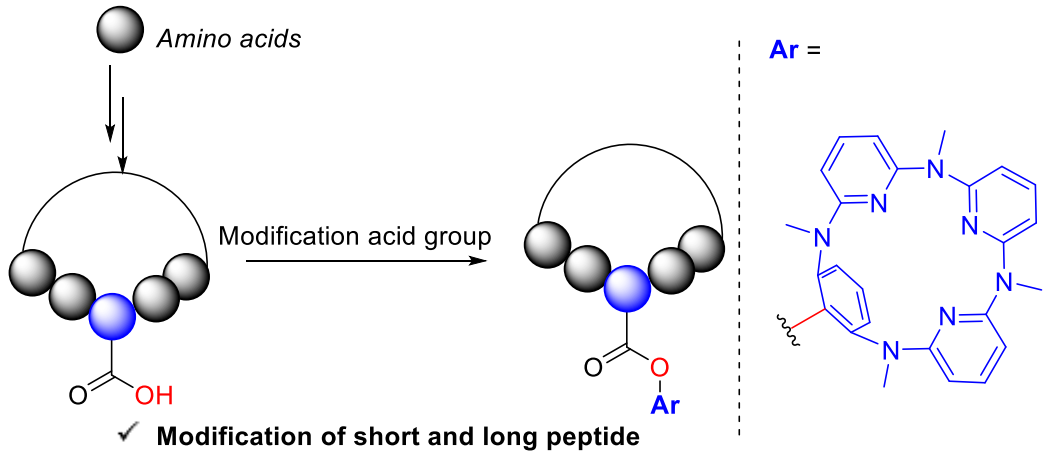
Abstract: *Despite the advancement in metal mediated or organometallic compound involved acid group modification, modification short comings such as long reaction times, expensive catalysts, high temperatures, poor conversion and poor compatibility of functional groups limit the applications of known methods. This study focuses on the modification of linear and cyclic peptides using arylcopper complexes as a key coupling reagent. The objective is the functionalization of carboxylic acid groups within various peptide structures. These groups can be found on aspartic acid (Asp) and glutamic acid (Glu) residues in the backbone of the peptide chain or at the C-terminal end. In order to evaluate the adaptability and effectiveness of these modification reaction, the study investigates various approaches for both linear and cyclic peptide structures. The research also critically assesses the reaction's tolerance to the another fuctional group present in other amino acid as a potential step toward the creation of molecules with therapeutic significance, the present work attempts to produce a strong chemical tool for the selective alteration of peptides.*



Keywords: peptides, arylcopper, organometallic, organocopper

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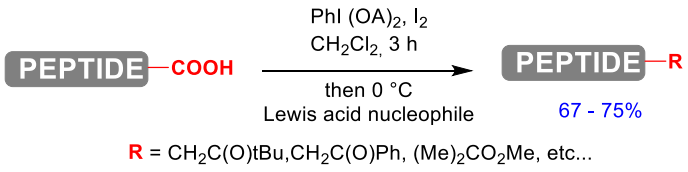
I. Introduction

Peptides are becoming increasingly important pharmaceutical targets as classically « druggable » targets dwindle and methods for peptide synthesis, delivery, and penetration through the cell membrane continue to improve[1]. Relatively minor structural changes can significantly impact the peptide's folding, binding, and pharmacokinetics[2]. Peptide modification using high-valent organocopper compounds is cruticial due to their potential to produce more efficient, selective, and stable bioactive peptides. These modified peptides are essential for therapeutic applications, such as drug development and delivery, due to their enhanced bioavailability and stability against enzymatic degradation[3], [4]. Chemical modification of amino acids in peptides and proteins is essential and attractive for tuning selectivity and efficiency of drugs and understanding the molecular mechanism of their actions[3]· Such chemical modifications are possible by labeling or tagging a suitable moiety at the side chain functionality of amino acids (aspartic acid (Asp), glutamic acid (Glu), lysine (Lys), serine (Ser), etc.) in solution or via solid-phase peptide synthesis (SPPS) technology[5]. For example, cysteine and lysine side chain modifications by installation of various electrophiles are well-known[6], [7]. (Scheme 1.a)

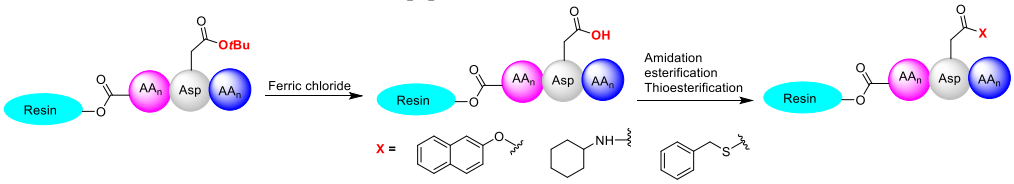
In 2015, Rosendo Hernandez's group reported that the modification of glutamic acid residues through a decarboxylation-alkylation reaction efficiently converts them into α,γ-peptide hybrids containing unnatural γ-amino acids[8] (Scheme 1.b). This process offers the advantage of good overall yields and allows for the sequential protection and deprotection of the carboxyl groups in glutamic units when carried out under mild conditions. This flexible approach enables the generation of structural diversity, providing there by promising potential for creating bioactive peptides.

In 2017, Mandal's group efficient, convenient, and selective Lewis acid-based strategy to achieve a successful on-resin deprotection of the side chain tert-butyl-protected aspartic acid and glutamic acid of a peptide[9] (Scheme 1.c). The method is mild, cost-effective, compatible with fluorenylmethoxycarbonyl (Fmoc) chemistry and allows on-resin incorporation of amides, esters, and thioesters in good yield. This method can be applicable in peptide and protein modification because it enriches the toolbox of orthogonal protection/deprotection techniques.

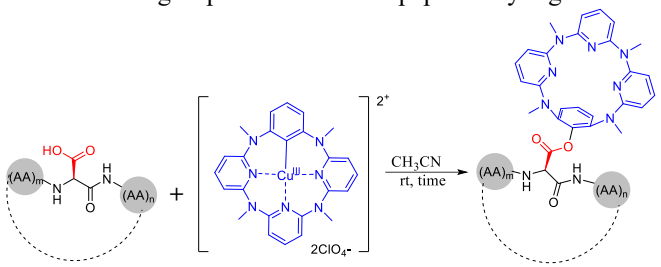
a) **One-Pot Scission Alkylation**[10], [11]



b) **Side Chain Modification on a Solid Phase**[9]



c) This work: Chemoseletive acid group modification of peptides by high-valent copper (III) compound



Scheme 1. Modification of acid group

This research contributes significantly to advancing peptide-based drug design and chemical biology. Research in this field has seen notable progress, particularly through innovative copper catalysis. For instance, Yu was able to ortho-fluorinate triflamide-protected benzylamines using F^+ reagents such N-fluoro-2,4,6-trimethylpyridinium triflate[12], and Shi was able to accomplish Pd(OAc)2-catalyzed ortho-halogenation of acetanilide using CuX_2 (X = Cl, Br)[13]. Copper salts have advantages in promoting C-H functionalizations since they are less expensive and poisonous than noble metal species. $Cu(OAc)_2$ effectively catalyzes the oxidative halogenation of aryl C–H bonds of 2-arylpyridines utilizing dioxygen as an oxidant at a high temperature,

according to Yu's 2006 paper[14]. CuF_2 has been shown to directly fluorinate benzene at 450-550 °C, whereas electron-rich aromatic C–H bonds are chlorinated and brominated in the presence of CuX_2, LiX, and molecular oxygen[15], [16]. Ultimately, these methods, which proceed via high-valent arylcopper(III) intermediates, enable powerful transformation like the direct amination and synthesis of complex azacalix[1]arene[3]pyridine macrocycles, providing valuable tools for molecular design[17], [18]. Domestically, there is growing interest in developing novel copper-based catalysts for selective peptide modification, with a focus on green chemistry and sustainability.

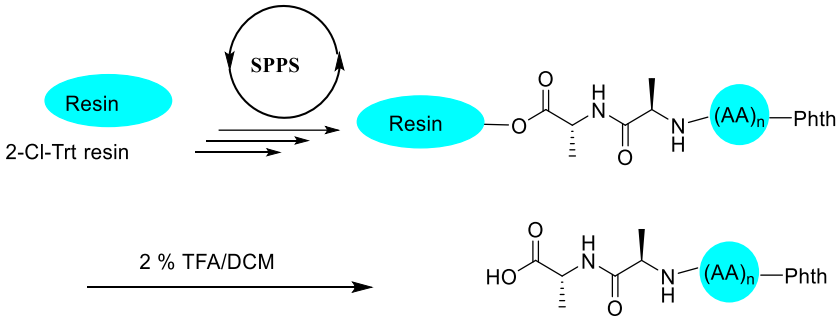
Future trends suggest a continued focus on increasing the efficiency, selectivity, and environmental sustainability of organocopper catalysts. There is a movement towards designing more sophisticated copper(III/II) complexes that can modify peptides under mild conditions, with minimal by products. Additionally, the integration of these methods with automated peptide synthesis technologies is expected to streamline the process of developing peptide-based therapeutics.

II. Experimental section

2.1 General procedure for solid phase peptide synthesis (SPPS)

Method A: Synthesis and characterization of linear peptide substrates with free C-terminal

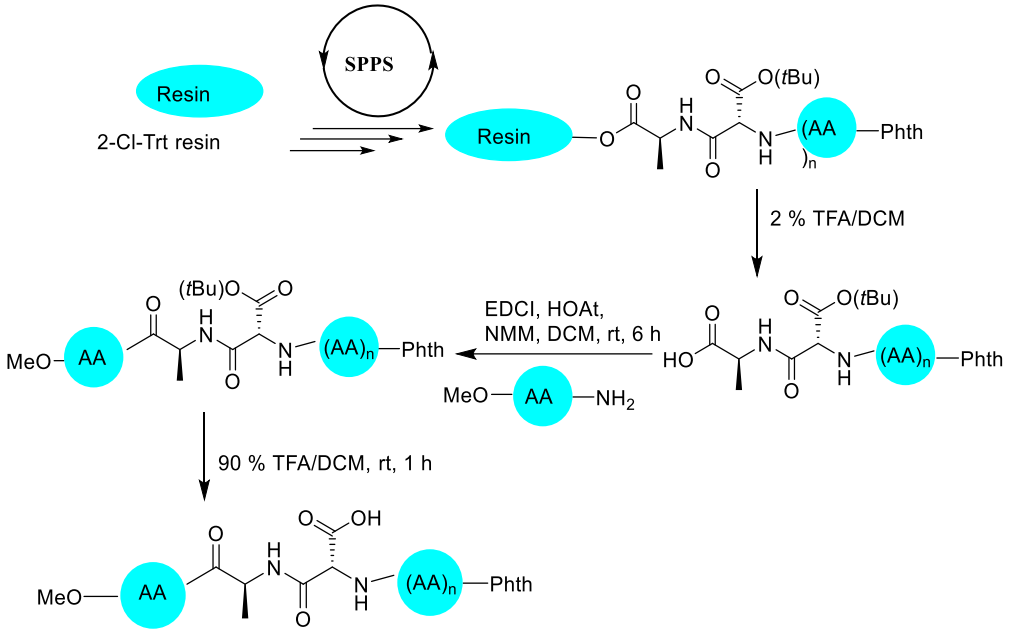
About 862 mg, 1.16 mmol/g of 2-Chlorotrityl chloride resin was swelled in 1% DIPEA/DCM for 30 min in a peptide synthesis tube (25 mL). The resin was drained and treated with a solution of Fmoc amino acid (1.5 mmol, 1.5 equiv) and DIPEA (6.0 mmol, 6.0 equiv) in DCM and shaken for 1 hr 30 min. MeOH (1 mL) and DIPEA (3.0 mmol, 3.0 equiv) were added, and shake for another 30 minutes. The amino acid loading on the resin was estimated via Fmoc determination)[19].The resin was treated with a solution of 20% piperidine in DMF for (20 min) and was successively washed with DMF (2x10 mL) and DCM (2x10 mL). Freshly prepared solution of a Fmoc-protected amino acid (3.0 mmol, 3.0 equiv), Oxyma (3.0 mmol, 3.0 equiv) and DIC (3.3 mmol, 3.3 equiv) in NMP were added to the tube. After completion of the reaction (1-3 hrs), the resin was washed twice with DMF and DCM. The deprotection and coupling steps were repeated to elongate the peptide. The crude peptide was cleaved from the resin by treating it with a solution of 2% TFA/DCM (3x20 mL) for 3x2 h. The combined filtrates were concentrated in vacuo to give the crude peptide with a free carboxylic acid group, which was precipitated by treating it with cold ether[10], [20].



Scheme 2. Synthesis of phthalimide protected peptides

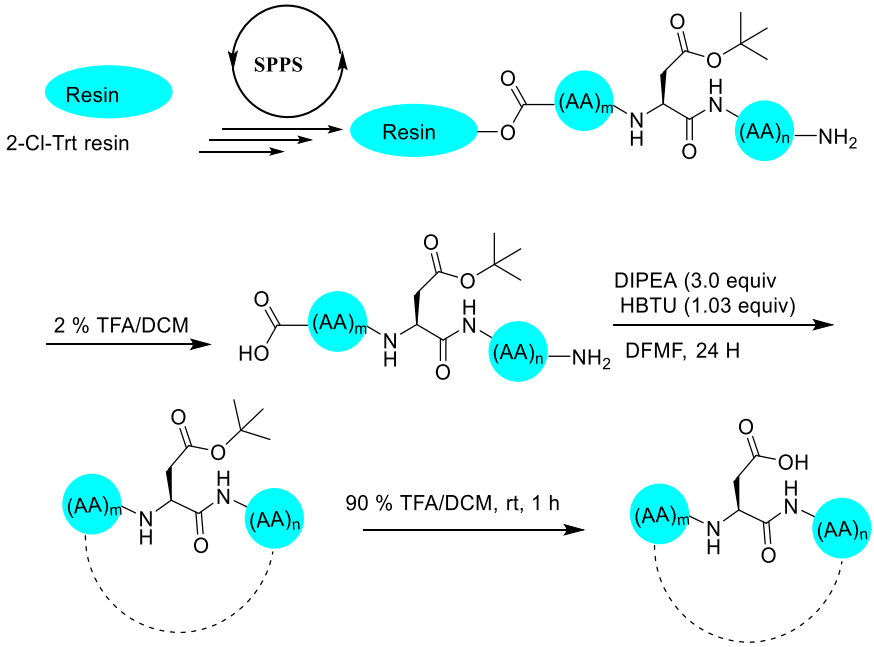
Method B: Synthesis and characterization of linear/ peptide substrates containing Asp/Glu

The crude phthalimide peptide with free carboxylic acid obtained from SPPS (1.0 equiv) was then coupled with an esterified amino acid in the presence of EDCI (1.2 equiv), HOAt (1.2 equiv) and NMM (1.2 equiv) in DCM (3 ml/mmol) for 6-8 hrs. The completion of the reaction was monitored with TLC. The mixture was washed with 1 M HCl, $NaHCO_3$, saturated NaCl, and dried over anhydrous Na_2SO_4. The obtained peptide was treated with 92% TFA/DCM for 1h at room temperature to remove all the protecting groups. The mixture was evaporated, precipitated with Et_2O, and dried under vacuum at 40 °C, followed by column chromatography to obtain the desired linear peptide as a white solid[21].



Scheme 3. Synthesis of phthalimide protected peptides

Method C: Synthesis and characterization of cyclic peptide substrates containing Asp/Glu
For the cyclic peptide, the crude peptide (1.0 equiv) obtained from SPPS was dissolved in dry DMF, DIPEA (3.0 equiv), and HBTU (1.03 equiv) were added and stirred at room temperature overnight. The reaction mixture was concentrated on the rotary evaporator to remove DMF. It was acidified with 1 M HCl and extracted with 30 mL DCM three times.



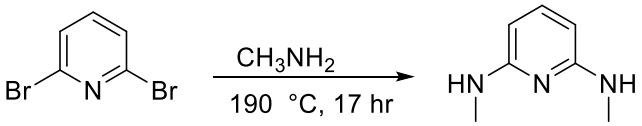
Scheme 4. Synthesis of cyclic peptides

The organic layer was washed with saturated $NaHCO_3$ and brine. It was then dried over anhydrous Na_2SO4, followed by concentration. The crude peptide obtained was purified on column chromatography using DCM/MeOH 30:1 as eluant. Then, the obtained peptide was treated with 90% TFA/DCM for 2h at room temperature to remove all the protecting groups. The mixture was evaporated, precipitated with Et_2O, and dried under vacuum at 40 ºC, followed by column chromatography to obtain the desired cyclic peptide as a white solid[21], [22]

2.2 Preparation of the aryl-copper (III) compound

2.2.1 Synthesis of diamine

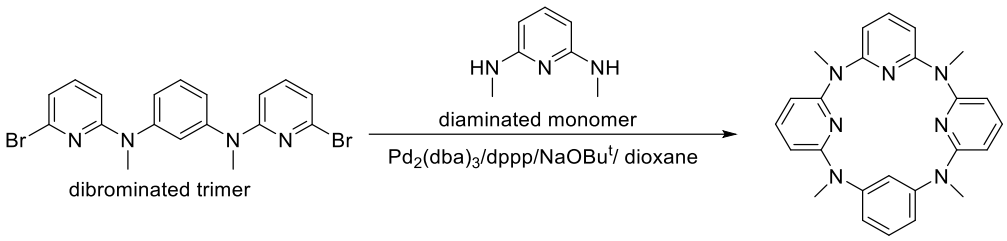
2,6-dibromopyridine (3.56 g, 15 mmol) was transferred into an autoclave with a magnetic stir bar. Methylamine solution (15 mL, 1 mL/mmol) was added, and the autoclave was closed tightly. Then it was heated at 190 °C for 12 hr. After cooling to room temperature, the mixture was filtered to obtain a pure solid crystal of diamine, which was washed with water. The residue was dried while the filtrate was extracted with (2 x 50 mL) CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4. After solvent removal, the residue was chromatographed on a silica gel column with a mixture of petroleum ether and ethyl acetate as the mobile phase to give diamine (1.25 g, 61%) (Scheme 5).



Scheme 5. Synthesis of diamine

2.2.2 Synthesis of azacalix[1]arene[3]pyridine

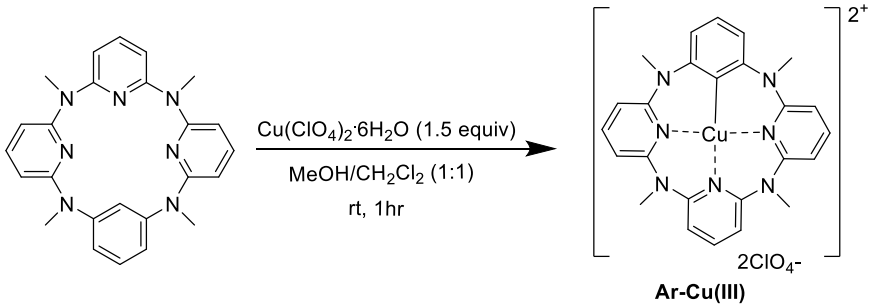
A mixture of the diamine (274 mg, 2 mmol), the dibrominated trimer (899 mg, 2 mmol), $Pd_2(dba)_3$ (276 mg, 0.3 mmol), DPPP (249 mg, 0.6 mmol) and sodium tert-butoxide (578 mg, 6 mmol) was heated at reflux under argon protection in 500 mL anhydrous 1,4-dioxane for 3 hr. After cooling to room temperature, the mixture was filtered through a celite pad. The solvent was removed, and the residue was dissolved in dichloromethane and washed with brine. The organic layer was dried over anhydrous sodium sulfate. After removal of the solvent under vacuum, the residue was subjected to a basic aluminum oxide column with a mixture of petroleum ether and acetone (15:1) as eluent to give the pure product (261.07 mg, 31%) as white crystalline solids (Scheme 6).



Scheme 6. Synthesis of azacalix[1]arene[3]pyridine

2.2.3 Synthesis of Ar-Cu(III)

In an attempt to ascertain if **Ar-Cu(III)** could be useful for the successful modification of the acid group in peptides, we began our study with the synthesis of arylCu(III)compound (Scheme 1.1). Azacalix[1]arene[3]pyridine and $Cu(ClO_4)_2{\cdot}6H_2O$ were dissolved in a mixture of dichloromethane and methanol. The solution turned dark blue immediately and then turned light with the formation of dark purple precipitates[23]. After about 1 hr, the precipitate was filtered and dried to get **Ar-Cu(III)** as a purple solid in almost quantitative yield.



Scheme 2.3: Preparation of **Ar-Cu(III)**

2.3 General procedure for peptide modification

The peptide (0.05 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile 2 mL or 2 ml acetonitrile, then Cu(III) compound (35 mg, 0.055 mmol, 1.1 equiv or 0.04 mmol, 0.8 equiv) was added into the solution, after 5min the base potassium carbonate (5.52 mg, 0.04 mmol, 0.8 equiv) was added and it was stirred at room temperature. After 15 -30 min, there was an observation of a change in coloration, which indicated the completion of the reaction. 10 mL of sodium bicarbonate solution was added ten aqueous ammonia (1 mL), and the mixture

was extracted with CH_2Cl_2 (3× 5 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a silica gel column to afford the pure product.

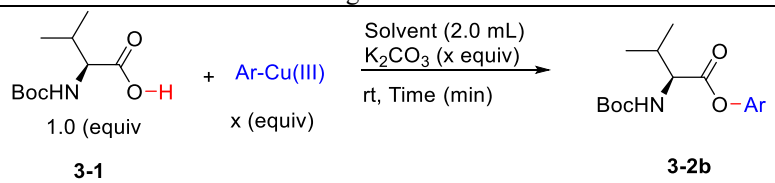
III. Results and discussions

3.1 Optimization of reaction conditions

3.1.1 Screening of base with amino acid

In this reaction, it is crucial to eliminate the proton (H) from the acidic group to form the carboxylate group (COO^-), as this is the species that can react with Ar-Cu(III), a reagent capable of interacting with the COO^- nucleophile. Therefore, the addition of a base for deprotonation is essential to generate COO^-.

Table 3.1 Screening of base with amino acid[a]



Entry	Solvent (mL)	Ar-Cu (III) (equiv)	K_2CO_3 (equiv)	Time (min)	Yield (%)
1	CH_3CN	1.0	0.5	15	48
2	CH_3CN	1.0	1.0	15	58
3	CH_3CN	1.0	0.8	15	92
4	CH_3CN	1.0	0.9	15	89

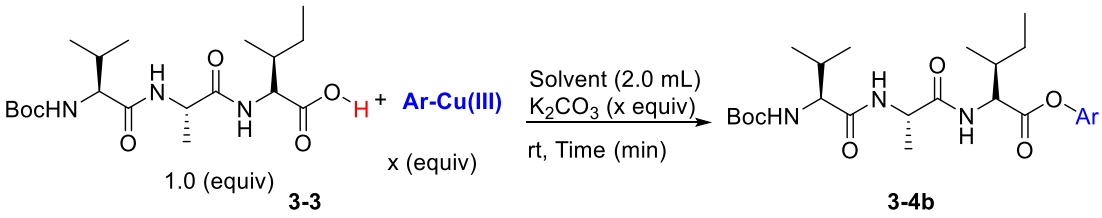
[a]**Conditions:** Ar-Cu(III) (1.0 equiv), CH_3CN, K_2CO_3 (0.8 equiv), room temperature, 15 minutes.

We tested the use of potassium carbonate (K_2CO_3) and observed that the reaction proceeded well, leading us to retain this base while optimizing the equivalence, as shown in the table below (Table 3.1). In entry 1, with a base equivalence of 0.5 equiv, we obtained a yield of 48%. With an equivalence of 1.0 equiv, the yield increased to 58% (Entry 2). By increasing the equivalence to 0.8 and 0.9 equiv, we observed improved yields of 92% and 89%, respectively. We observed that using K_2CO_3 with 0.8 equiv gave the best result, with a yield of 92% (Table 3.1, Entry 3).

3.1.2 Screening of equivalence: Ar-Cu(III), solvent and time with tripeptide

We first maintained the baseline equivalence mentioned above. Then, we continued the optimization of the reaction using a peptide (tripeptide) while keeping the conditions from Entry 1, which gave a yield of 83%.

Table 3.2 Screening of equivalence: Ar-Cu(III), solvent and time with tripeptide[b]



Entry	Solvent (mL)	Ar-Cu (III) (equiv)	K_2CO_3 (equiv)	Time (min)	Yield (%)
1	CH_3CN	1.0	0.8	15	83
2	CH_3CN/H_2O (4:1)	1.0	0.8	15	82
3	CH_3CN/H_2O (9:1)	1.0	0.8	15	74

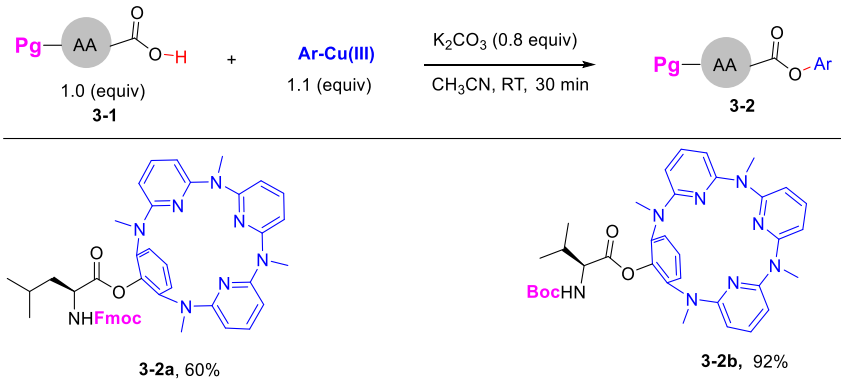
4	CH_3CN/H_2O (20:1)	1.0	0.8	15	82
5	CH_3CN/H_2O (4:1)	1.1	0.8	15	92
6	CH_3CN	1.1	0.8	30	95
7	CH_3CN	1.05	0.8	20	92

[b]**Conditions:** Ar-Cu(III) (1.1 equiv), CH_3CN(2mL), K_2CO_3 (0.8 equiv), room temperature, time (15 min to 1 h)
In the table (Table 3.2), we experimented with a solvent mixture of CH_3CN and water (Entries 2-5). The yields obtained varied, ranging from lower to higher. We then decided to focus on optimizing the Ar-Cu(III) by increasing its equivalence to 1.1 (Entry 5), which improved the yield to 92%, a better result compared to the previous trials. In entry 6, we tried removing the water and using only acetonitrile, which resulted in an even better yield of 95%. However, when continuing the optimization with 1.05 equivalents of Ar-Cu(III), we observed a decrease in yield. In conclusion, the reaction optimization showed that the condition[b] (Entry 6), using only acetonitrile, provided the best yield.

3.2 Investigation of influence of protecting groups

Following reaction optimization, we evaluated the influence of the N-terminal protecting group on the reaction yield after optimization. Using a Boc-protecting group produced an excellent yield of 92% (**3-2b**). In comparison, a significantly lower yield of 60% (**3-2a**) was obtained when an Fmoc-protecting group was used under the same condition reactions. These results demonstrate that this reaction is significantly influenced by the nature of protecting group.

Table 3.3 Investigation of influence of protecting groups[b]

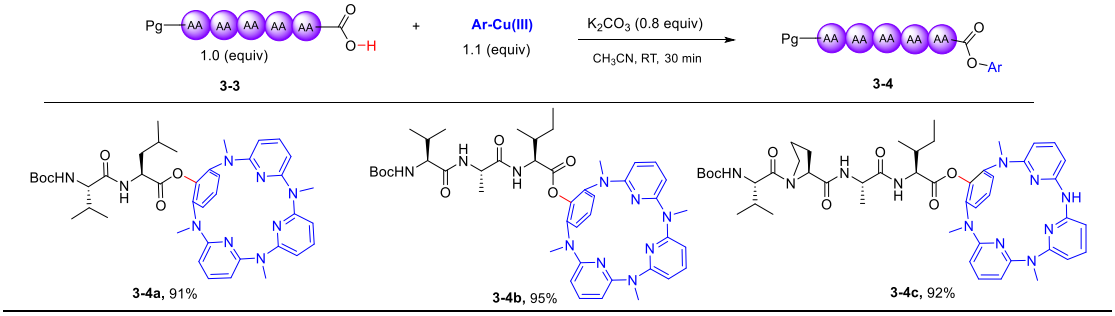


[b]**Conditions:** Ar-Cu(III) (1.1 equiv), CH_3CN(2mL), K_2CO_3 (0.8 equiv), room temperature, time (15 min to 1 h)

3.3 Modification of linear peptide by Ar-cu(III)

Encouraged by these results, and after determining the optimal reaction conditions, we observed that the use of the Boc protecting group provided good yields. We then proceeded with enthusiasm to modify Boc-protected peptides at the N-terminal. The three short peptides namely the dipeptide, tripeptide, and tetrapeptide, all have a free C-terminal group. We then modified the carboxyl (-COOH) groups in these peptides using Ar-Cu(III).

Table 2.4 Modification of short peptides: dipeptide to tetrapeptide[b]

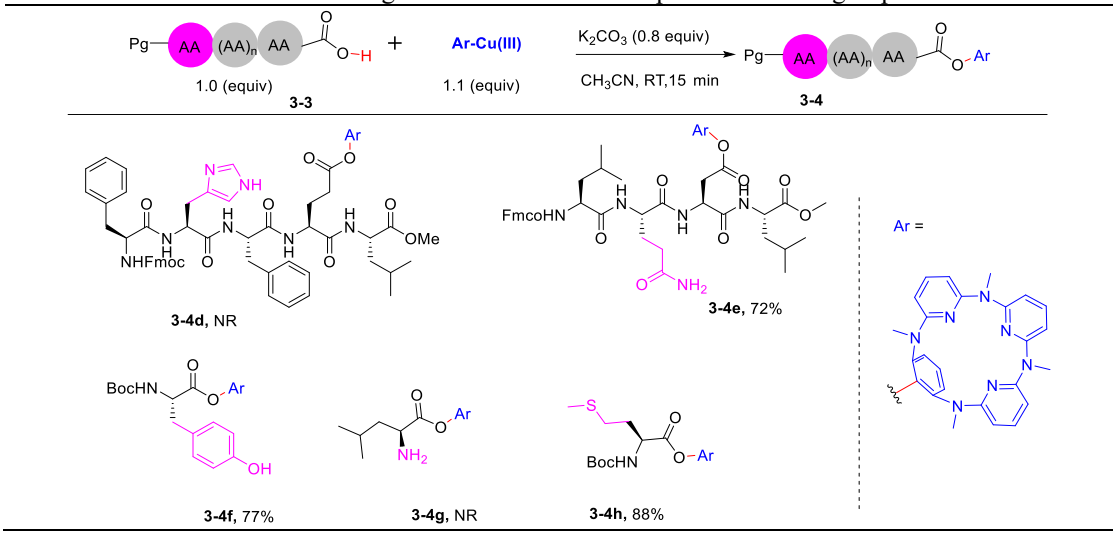


[b]**Conditions:** Ar-Cu(III) (1.1 equiv), CH_3CN(2mL), K_2CO_3 (0.8 equiv), room temperature, time (15 min to 1 h)
The modified peptides are summarized in Table 2.4 below. All yields were excellent: the modified dipeptide yielded 91% (**3-4a**), the modified tripeptide yielded 95% (**3-4b**), and the modified tetrapeptide yielded 92% (**3-4c**).

3.4 Investigation of the tolerance of polar functional groups

We investigated the tolerance of our protocol for the modification of peptides and amino acids in the presence of other nucleophilic functional groups (Table 3.5), as well as carboxylic acids such as aspartic acid and glutamic acid. Tetrapeptides containing

Table 3.5 Investigation of the tolerance of polar functional groups[b]

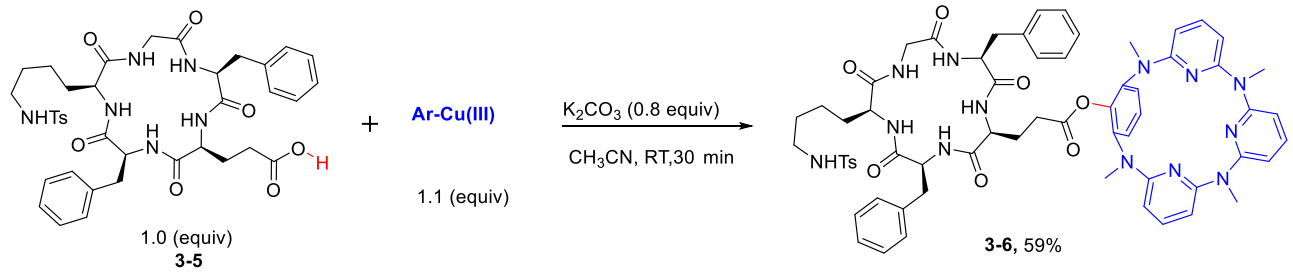


[b]**Conditions:** Ar-Cu(III) (1.1 equiv), CH_3CN(2mL), K_2CO_3 (0.8 equiv), room temperature, time (15 min to 1 h)
aspartic acid and glutamine reacted with Ar-Cu(III), yielding the modified peptides in good yields 72% (**3-4e**) and 77% respectively, with Boc-protected tyrosine (**3-4f**). We also tested the protocol in the presence of methionine, and the yield was excellent at 88% (**3-4h**). However, when histidine was present in the tetrapeptide (**3-4d**), the reaction did not proceed. A similar result was obtained with an amino acid having a free N-terminal.

3.5 Modification of cyclic peptide by Ar-Cu(III)

After successfully performing several types of peptide modifications involving a carboxylic acid group using an aryl-copper(III) complex (1.1 equivalents) with good yields, we decided to take on a more challenging target is the modification of the acid group in cyclic peptides (Table 2.7). We tested this modification method with a cyclic pentapeptide containing an acid group on aspartic acid, and we obtained a modified peptide with a yield that is not bad, 59% (**3-6**).

Table 3.7 Modification of cyclic peptide by Ar-Cu(III)[b]



[b]**Conditions:** Ar-Cu(III) (1.1 equiv), CH_3CN(2mL), K_2CO_3 (0.8 equiv), room temperature, time (15 min to 1 h)

IV. Conclusion

In conclusion, we have developed an innovative and versatile method for the modification of acidic groups in peptides using an aryl-Cu(III) compound. This method is applicable to peptides with acid groups at the C-terminal as well as amino acids like aspartic acid and glutamic acid. The protocol is rapid (30 minutes) and occurs under mild reaction conditions, using acetonitrile as the sole solvent, sometimes mixed with water. It has proven effective for modifying a wide range of peptides, both linear and cyclic.

The method shows broad tolerance to natural amino acids with functional groups, such as tyrosine (Tyr), methionine (Met), and glutamine (Gln). However, there are some limitations with other functional groups, such as histidine (His) and amino acids with amine and carboxyl groups, due to selectivity issues between the acid and amine groups.

The protocol is particularly cost-effective, as it does not require long reaction times or ligands, and it can be carried out in the presence of air without removing water or oxygen. The formed complex is stable and can be stored at room temperature for extended periods.

Peptide modification is a critical area in organic chemistry, especially for bioactive peptides, whether linear or cyclic, that contain acid groups. This method plays a vital role in enhancing and modifying these peptides. Beyond its potential applications in chemical biology and medicinal chemistry, this methodology will significantly contribute to expanding the chemical space of modified peptides and molecular conjugates.

References:

[1]. K. Fosgerau et T. Hoffmann, « Peptide therapeutics: current status and future directions », *Drug Discov. Today*, vol. 20, nº 1, p. 122-128, janv. 2015, doi: 10.1016/j.drudis.2014.10.003.

[2]. C. A. Arbour, L. G. Mendoza, et J. L. Stockdill, « Recent advances in the synthesis of C-terminally modified peptides », *Org. Biomol. Chem.*, vol. 18, nº 37, p. 7253-7272, 2020, doi: 10.1039/D0OB01417F.

[3]. L. Wang *et al.*, « Therapeutic peptides: current applications and future directions », *Signal Transduct. Target. Ther.*, vol. 7, nº 1, p. 48, févr. 2022, doi: 10.1038/s41392-022-00904-4.

[4]. E. Hernando *et al.*, « Palladium-Catalyzed Carbonylative Cyclization of Amines via γ-C(sp^3)–H Activation: Late-Stage Diversification of Amino Acids and Peptides », *ACS Catal.*, vol. 6, nº 10, p. 6868-6882, oct. 2016, doi: 10.1021/acscatal.6b01987.

[5]. P. E. Dawson, T. W. Muir, I. Clark-Lewis, et S. B. H. Kent, « Synthesis of Proteins by Native Chemical Ligation », *Science*, vol. 266, nº 5186, p. 776-779, nov. 1994, doi: 10.1126/science.7973629.

[6]. E. Calce, M. Leone, L. Monfregola, et S. D. Luca, « Chemical Modifications of Peptide Sequences via S-Alkylation Reaction », *Org. Lett.*, vol. 15, nº 20, p. 5354-5357, oct. 2013, doi: 10.1021/ol402637d.

[7]. J. W. Wollack *et al.*, « Multifunctional Prenylated Peptides for Live Cell Analysis », *J. Am. Chem. Soc.*, vol. 131, nº 21, p. 7293-7303, juin 2009, doi: 10.1021/ja805174z.

[8]. C. J. Saavedra, A. Boto, et R. Hernández, « Synthesis of α,γ-Peptide Hybrids by Selective Conversion of Glutamic Acid Units », *Org. Lett.*, vol. 14, nº 13, p. 3542-3545, juill. 2012, doi: 10.1021/ol301552c.

[9]. R. S. Giri, S. R. Manne, G. Dolai, A. Paul, T. Kalita, et B. Mandal, « $FeCl_3$ -Mediated Side Chain Modification of Aspartic Acid- and Glutamic Acid-Containing Peptides on a Solid Support », *ACS Omega*, vol. 2, nº 10, p. 6586-6597, oct. 2017, doi: 10.1021/acsomega.7b01143.

[10]. Y. Weng *et al.*, « Peptide late-stage C(sp^3)–H arylation by native asparagine assistance without exogenous directing groups », *Chem. Sci.*, vol. 11, nº 34, p. 9290-9295, 2020, doi: 10.1039/D0SC03830J.

[11]. X. Chen, B. Li, H. Tong, L. Qi, G. He, et G. Chen, « PALLADIUM-CATALYZED METHIONINE-FACILITATED β and γ C(sp^3)–H Arylation of N-TERMINAL Aliphatic Amino Acids of Peptides », *Chin. J. Chem.*, vol. 40, nº 21, p. 2502-2506, nov. 2022, doi: 10.1002/cjoc.202200340.

[12]. X. Wang, T.-S. Mei, et J.-Q. Yu, « Versatile $Pd(OTf)_2 \cdot 2H_2O$-Catalyzed *ortho* -Fluorination Using NMP as a Promoter », *J. Am. Chem. Soc.*, vol. 131, nº 22, p. 7520-7521, juin 2009, doi: 10.1021/ja901352k.

[13]. A. R. Dick, K. L. Hull, et M. S. Sanford, « A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds », *J. Am. Chem. Soc.*, vol. 126, nº 8, p. 2300-2301, mars 2004, doi: 10.1021/ja031543m.

[14]. X. Chen, X.-S. Hao, C. E. Goodhue, et J.-Q. Yu, « Cu(II)-Catalyzed Functionalizations of Aryl C−H Bonds Using O_2 as an Oxidant », *J. Am. Chem. Soc.*, vol. 128, nº 21, p. 6790-6791, mai 2006, doi: 10.1021/ja061715q.

[15]. M. A. Subramanian et L. E. Manzer, « A “Greener” Synthetic Route for Fluoroaromatics via Copper (II) Fluoride », *Science*, vol. 297, nº 5587, p. 1665-1665, sept. 2002, doi: 10.1126/science.1076397.

[16]. L. Yang, Z. Lu, et S. S. Stahl, « Regioselective copper-catalyzed chlorination and bromination of arenes with O2 as the oxidant », *Chem. Commun.*, nº 42, p. 6460, 2009, doi: 10.1039/b915487f.

[17]. H. Zhang, L. Zhao, D.-X. Wang, et M.-X. Wang, « $Cu(OTf)_2$ -Catalyzed Selective Arene C–H Bond Hydroxylation and Nitration with KNO_2 as an Ambident *O* - and *N* -Nucleophile via a Cu(II)–Cu(III)–Cu(I) Mechanism », *Org. Lett.*, vol. 15, nº 15, p. 3836-3839, août 2013, doi: 10.1021/ol401453f.

[18]. Y. Liu, Q. Zhang, Q.-H. Guo, et M.-X. Wang, « Synthesis of Functionalized Azacalix[1]arene[3]pyridine Macrocycles from Cu(II)-Mediated Direct Amination Reactions of Arene through High Valent Arylcopper(III) Intermediates », *J. Org. Chem.*, vol. 81, nº 21, p. 10404-10410, nov. 2016, doi: 10.1021/acs.joc.6b01448.

[19]. M. Li, S. A. Akintelu, et B. Yao, « Post-Assembly Modification of Peptides by Ligand-Enabled β-C(sp^3)–H Arylation of Alanine at the C-Terminus: Overcoming the Inhibition Effect of Peptide Bonds », *Org. Lett.*, vol. 23, nº 12, p. 4807-4812, juin 2021, doi: 10.1021/acs.orglett.1c01481.

[20]. R. Behery *et al.*, « Design, synthesis, and application of modified linear peptides as potential antidiabetic agent », *J. Mol. Struct.*, vol. 1335, p. 141970, juill. 2025, doi: 10.1016/j.molstruc.2025.141970.

[21]. I. Nicolau, A. Paun, C. C. Popescu, N. D. Hădade, et M. Matache, « Solid-Phase Peptide Synthesis – Evaluation of Resin Loading and Preparation of an Amide *C* -Terminal Dipeptide », *J. Chem. Educ.*, vol. 100, nº 6, p. 2430-2434, juin 2023, doi: 10.1021/acs.jchemed.3c00186.

[22]. Y. Yu *et al.*, « Chemoselective Peptide Modification via Photocatalytic Tryptophan β-Position Conjugation », *J. Am. Chem. Soc.*, vol. 140, nº 22, p. 6797-6800, juin 2018, doi: 10.1021/jacs.8b03973.

[23]. Z.-L. Wang, L. Zhao, et M.-X. Wang, « Regiospecific Functionalization of Azacalixaromatics through Copper-Mediated Aryl C–H Activation and C–O Bond Formation », *Org. Lett.*, vol. 13, nº 24, p. 6560-6563, déc. 2011, doi: 10.1021/ol202874n.

SUPPORTING INFORMATION

Chemical modification of peptides by organocopper compounds

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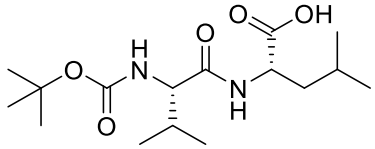
CONTENTS

1. Characterization data of peptide **substrates**

(tert-butoxycarbonyl)-L-valyl-L-leucine was prepared following Method A.

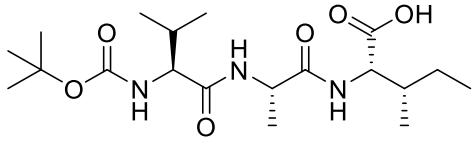


White solid (790.3 mg, 92% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.99 – 6.71 (m, 1H), 5.53 (d, *J* = 8.8 Hz, 1H), 4.62 (s, 1H), 3.99 – 3.85 (m, 1H), 2.07 (dd, *J* = 49.2, 28.5 Hz, 1H), 1.74 – 1.63 (m, 2H), 1.62 – 1.53 (m, 1H), 1.33 (d, *J* = 64.1 Hz, 9H), 0.94 (s, 12H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 175.72, 172.31, 156.28, 80.24, 61.87, 60.15, 50.68, 41.21, 30.73, 28.27, 24.76, 22.86, 21.77, 19.09, 18.26, 17.21.

(tert-butoxycarbonyl)-L-valyl-L-alanyl-L-isoleucine was prepared following Method A.

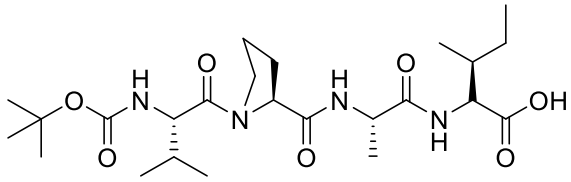


White solid (313.2 mg, 78% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.54 – 7.30 (m, 2H), 5.51 (d, *J* = 8.6 Hz, 1H), 4.81 – 4.65 (m, 1H), 4.59 (dd, *J* = 7.9, 5.1 Hz, 1H), 4.07 (t, *J* = 7.1 Hz, 1H), 2.01 (ddd, *J* = 25.0, 14.5, 11.3 Hz, 2H), 1.57 – 1.11 (m, 14H), 0.92 (dd, *J* = 13.8, 6.5 Hz, 12H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 174.17, 172.50, 172.04, 156.08, 80.08, 59.75, 56.79, 48.84, 37.61, 31.22, 28.32, 25.03, 19.20, 18.41, 17.84, 15.32, 11.55.

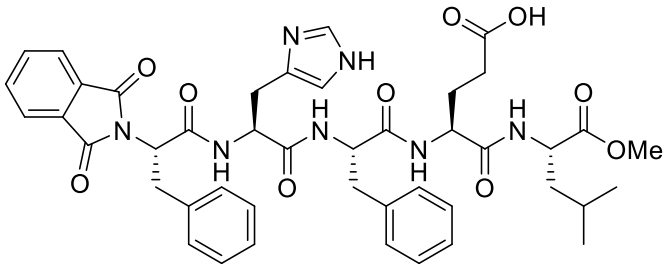
(tert-butoxycarbonyl)-L-valyl-L-prolyl-L-alanyl-L-isoleucine) was prepared following Method A.



White solid (403 mg, 81% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 5.60 (d, *J* = 9.1 Hz, 1H), 4.59 – 4.50 (m, 3H), 4.24 (dd, *J* = 8.5, 7.2 Hz, 1H), 3.78 (d, *J* = 7.1 Hz, 1H), 3.63 (s, 1H), 2.19 – 1.84 (m, 6H), 1.45 – 1.13 (m, 14H), 0.91 (dt, *J* = 19.0, 7.0 Hz, 12H).

(3S)-3-((2S)-5-amino-2-(2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanamido)-5-oxopentanamido)-4-(((S)-1-methoxy-4-methyl-1-oxopentan-2-yl)amino)-4-oxobutanoic acid was prepared following Method B.

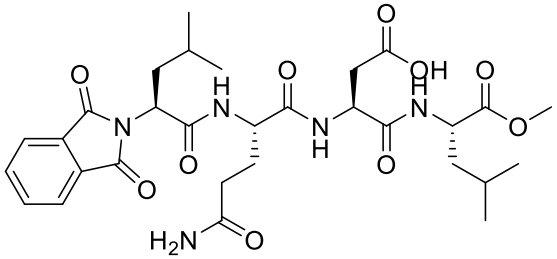


White solid (596.43 mg, 71% yield)

^{1}H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.53 (d, *J* = 8.1 Hz, 1H), 8.37 (d, *J* = 7.4 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 4H), 7.25 (t, *J* = 7.8 Hz, 4H), 7.22 – 7.15 (m, 1H), 7.15 – 7.01 (m, 5H), 6.98 (s, 1H), 4.93 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.58 – 4.51 (m, 1H), 4.37 – 4.25 (m, 2H), 3.61 (s, 3H), 3.46 – 3.40 (m, 2H), 3.17 – 2.96 (m, 4H), 2.89 – 2.77 (m, 2H), 2.28 (t, *J* = 8.1 Hz, 2H), 1.99 – 1.74 (m, 2H), 1.69 – 1.42 (m, 3H), 0.88 (d, *J* = 8.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 174.45, 173.27, 171.62, 171.19, 170.44, 168.48, 167.65, 138.02, 137.90, 134.93, 134.08, 131.68, 129.94, 129.79, 129.23, 128.69, 128.51, 126.95, 126.78, 123.53, 117.15, 55.39, 55.18, 54.53, 54.23, 52.33, 52.15, 50.78, 37.69, 34.34, 30.45, 28.12, 26.64, 24.70, 23.24, 21.70.

(S)-3-((S)-5-amino-2-((S)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanamido)-5-oxopentanamido)-4-(((S)-1-methoxy-4-methyl-1-oxopentan-2-yl)amino)-4-oxobutanoic acid Phth-Leu-Gln-Asp-Leu-OMe was prepared following Method B.

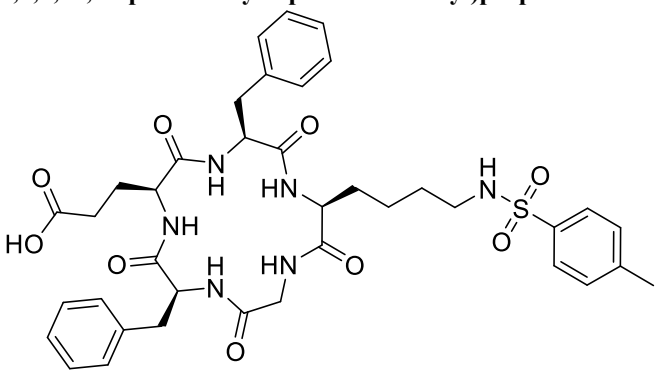


White solid (291.17 mg, 51% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.07 – 7.58 (m, 5H), 7.25 – 7.18 (m, 1H), 6.63 (s, 1H), 4.87 (d, *J* = 8.0 Hz, 2H), 4.39 (s, 1H), 4.17 (d, *J* = 5.9 Hz, 1H), 3.64 (s, 3H), 3.18 – 2.84 (m, 2H), 2.46 (d, *J* = 16.3 Hz, 2H), 2.26 – 1.95 (m, 3H), 1.86 (t, *J* = 10.2 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 2H), 1.35 – 1.15 (m, 2H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.57 (d, *J* = 5.4 Hz, 3H), 0.47 (d, *J* = 4.1 Hz, 3H).

^{13}C NMR (176 MHz, DMSO) δ 174.43, 173.12, 171.67, 171.14, 169.30, 168.27, 135.01, 132.06, 123.64, 53.53, 52.29, 51.65, 50.85, 49.90, 37.33, 31.96, 27.94, 25.08, 24.54, 23.80, 23.21, 21.82, 21.32.

3-((2S,5S,8S,14S)-5,14-dibenzyl-8-(4-((4-methylphenyl)sulfonamido)butyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)propanoic acid was prepared following Method C.



White solid (615.78 mg, 40% yield)

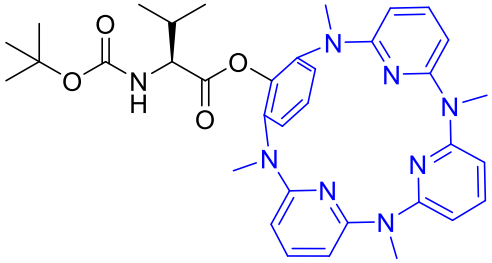
^{1}H NMR (400 MHz, DMSO) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.48 (t, *J* = 5.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.10 (m, 10H), 4.39 – 4.18 (m, 2H), 4.15 – 3.97 (m, 2H), 3.14 – 2.91 (m, 3H), 2.93 – 2.76 (m, 1H), 2.66 (dd, *J* = 13.0, 6.8 Hz, 2H), 2.37 (s, 3H), 2.05 (s, 2H), 1.87 (fs, 2H), 1.69 – 1.46 (m, 2H), 1.43 – 1.27 (m, 2H), 1.23 – 1.08 (m, 2H).

^{13}C NMR (176 MHz, DMSO) δ 170.87, 159.08, 158.83, 158.59, 158.34, 142.97, 138.07, 130.05, 129.46, 129.32, 128.69, 128.64, 126.98, 121.31, 118.92, 116.54, 114.15, 42.92, 29.10, 21.40.

2. Characterisation data of modified peptides

2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-72-yl (tert-

butoxycarbonyl)-L-valinate (2-3b) was synthesized with ArCu(III) compound according to the general procedure

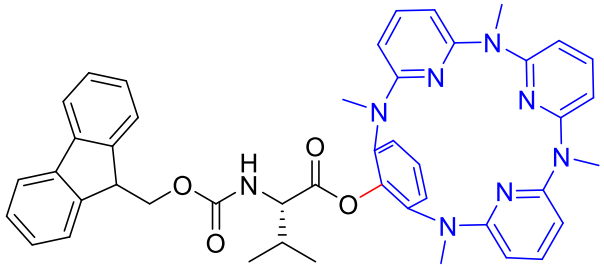


White foam solid (23.5 mg, 92% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.58 (t, *J* = 8.4 Hz, 2H), 6.03 (ddd, *J* = 26.1, 13.0, 5.2 Hz, 4H), 4.87 (d, *J* = 9.8 Hz, 1H), 4.07 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.25 (s, 6H), 3.02 (d, *J* = 2.5 Hz, 6H), 1.86 – 1.73 (m, 2H), 1.40 (s, 9H), 1.25 (s, 2H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 155.45, 145.67, 138.79, 127.91, 120.44, 94.96, 79.31, 58.72, 37.83, 36.28, 30.26, 28.32, 19.41, 16.95.

2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^{2}-yl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-valinate (2-3a) was synthesized with ArCu(III) compound according to the general procedure

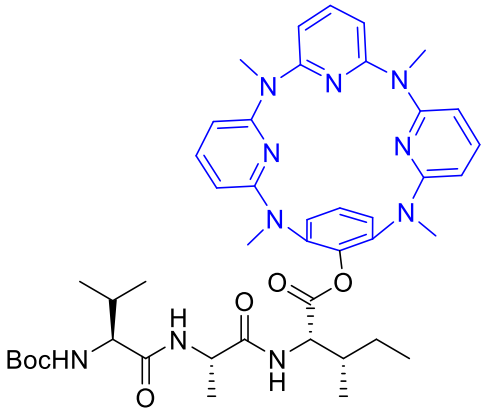


Yellow foam solid (18.6 mg, 60% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.1 Hz, 2H), 7.47 – 7.36 (m, 3H), 7.35 – 7.27 (m, 3H), 7.17 (s, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.90 (s, 2H), 6.58 (s, 2H), 6.10 (d, *J* = 7.9 Hz, 1H), 6.05 – 5.82 (m, 3H), 5.32 (d, *J* = 17.0 Hz, 1H), 4.39 – 4.20 (m, 3H), 4.19 – 4.08 (m, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 3.02 (s, 6H), 1.63 – 1.46 (m, 2H), 1.23 – 1.10 (m, 2H), 0.81 – 0.72 (m, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 155.77, 145.56, 144.10, 143.82, 141.31, 141.25, 127.64, 127.07, 125.30, 125.14, 119.94, 66.78, 52.76, 47.19, 37.92, 37.78, 36.36, 24.61, 22.92, 21.34.

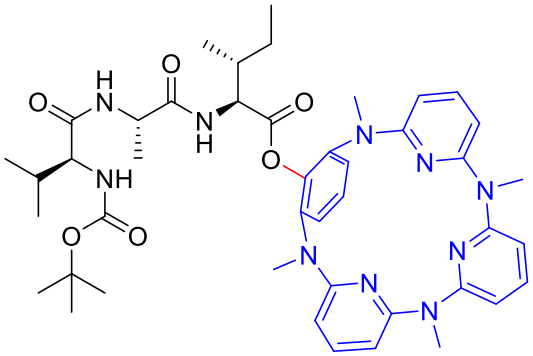
2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^{2}-yl (tert-butoxycarbonyl)-L-valyl-L-alanyl-D-alloisoleucinate (2-4b) was synthesized with ArCu(III) compound according to the general procedure.



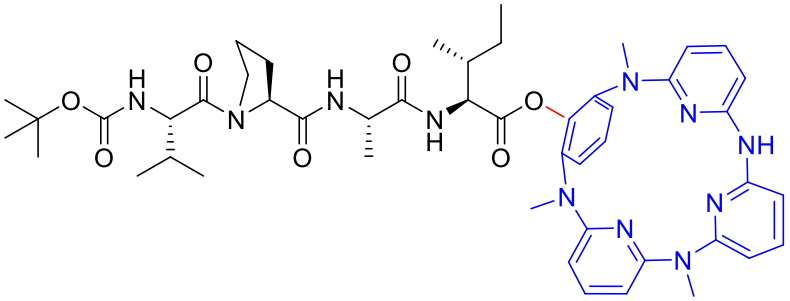
White foam solid (30.2 mg, 92% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.15 – 7.08 (m, 1H), 7.07 – 7.00 (m, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.52 (dd, *J* = 16.9, 7.7 Hz, 3H), 6.14 – 6.05 (m, 2H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 7.6 Hz, 1H), 4.40 (dd, *J* = 9.1, 4.7 Hz, 1H), 4.30 – 4.22 (m, 1H), 3.91 (s, 1H), 3.25 (s, 3H), 3.22 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H), 2.10 – 2.01 (m, 1H), 1.66 – 1.58 (m, 1H), 1.42 (s, 9H), 1.27 (d, *J* = 17.9 Hz, 2H), 1.16 – 1.10 (m, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8

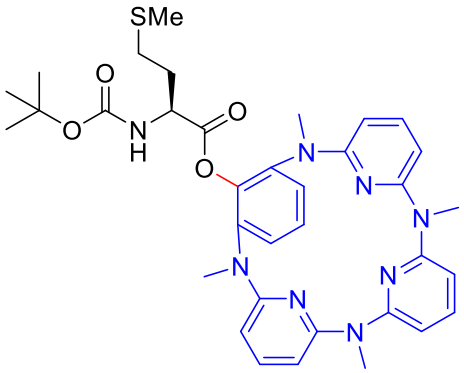
Hz, 3H), 0.73 – 0.67 (m, 6H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 171.60, 171.36, 158.98, 157.12, 155.92, 145.65, 140.80, 139.19, 138.97, 137.52, 128.03, 127.53, 126.42, 120.18, 120.10, 96.36, 96.06, 95.48, 95.19, 79.63, 77.48, 77.36, 77.16, 76.84, 59.50, 50.68, 41.25, 37.84, 36.51, 36.44, 31.26, 28.40, 24.76, 23.09, 21.35, 19.47, 17.58.
2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^2-yl (tert-butoxycarbonyl)-L-valyl-L-alanyl-D-alloisoleucinate



White foam solid (31.37mg, 95% yield)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.15 – 7.08 (m, 1H), 7.07 – 7.00 (m, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.52 (dd, *J* = 16.9, 7.7 Hz, 3H), 6.14 – 6.05 (m, 2H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 7.6 Hz, 1H), 4.40 (dd, *J* = 9.1, 4.7 Hz, 1H), 4.30 – 4.22 (m, 1H), 3.91 (s, 1H), 3.25 (s, 3H), 3.22 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H), 2.10 – 2.01 (m, 1H), 1.66 – 1.58 (m, 1H), 1.42 (s, 9H), 1.27 (d, *J* = 17.9 Hz, 2H), 1.16 – 1.10 (m, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.73 – 0.67 (m, 6H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 171.60, 171.36, 158.98, 157.12, 155.92, 145.65, 140.80, 139.19, 138.97, 137.52, 128.03, 127.53, 126.42, 120.18, 120.10, 96.36, 96.06, 95.48, 95.19, 79.63, 77.48, 77.36, 77.16, 76.84, 59.50, 50.68, 41.25, 37.84, 36.51, 36.44, 31.26, 28.40, 24.76, 23.09, 21.35, 19.47, 17.58.
2,6,8-trimethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^2-yl (tert-butoxycarbonyl)-L-valyl-L-prolyl-L-alanyl-L-isoleucinate was synthesized with ArCu(III) compound according to the general procedure



White foam solid (41.6mg, 92% yield)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 2H), 7.15 – 7.08 (m, 2H), 7.03 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.12 – 6.01 (m, 3H), 5.95 (d, *J* = 8.0 Hz, 1H), 5.24 (d, *J* = 9.2 Hz, 1H), 4.50 (dd, *J* = 7.5, 3.2 Hz, 1H), 4.38 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.23 (ddd, *J* = 20.9, 11.4, 6.5 Hz, 2H), 3.70 (dd, *J* = 16.6, 7.2 Hz, 1H), 3.61 – 3.53 (m, 1H), 3.40 – 3.34 (m, 1H), 3.24 (s, 3H), 3.23 (s, 3H), 2.99 (s, 3H), 2.98 (s, 3H), 2.83 (s, 1H), 2.36 (t, *J* = 8.1 Hz, 1H), 2.20 (dd, *J* = 7.3, 3.6 Hz, 2H), 2.08 – 1.88 (m, 6H), 1.63 (dt, *J* = 23.4, 10.6 Hz, 2H), 1.40 (d, *J* = 8.5 Hz, 9H), 1.25 (s, 1H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.70 – 0.63 (m, 6H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 175.23, 172.42, 171.76, 170.77, 170.23, 158.85, 158.41, 157.29, 157.12, 157.03, 155.99, 145.89, 140.98, 139.24, 138.95, 137.54, 127.71, 127.60, 126.55, 120.52, 119.89, 96.29, 96.18, 95.68, 95.19, 79.70, 59.94, 56.88, 49.57, 49.05, 47.68, 38.11, 38.04, 37.23, 36.60, 36.36, 31.52, 30.81, 29.83, 29.73, 29.45, 28.47, 27.50, 25.25, 24.31, 19.61, 18.06, 17.79, 17.45, 15.43, 14.26, 11.76.
2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^2-yl (tert-butoxycarbonyl)-L-methioninate was synthesized with ArCu(III) compound according to the general procedure

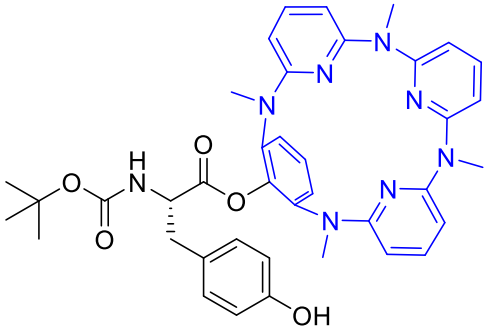


White foam solid (29.51 mg, 88%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 5.7 Hz, 2H), 7.17 (s, 1H), 7.10 – 6.99 (m, 1H), 6.90 (s, 2H), 6.58 (s, 2H), 6.15 – 5.96 (m, 4H), 4.89 (d, *J* = 8.6 Hz, 1H), 4.23 (d, *J* = 4.3 Hz, 1H), 3.25 (s, 6H), 3.02 (s, 6H), 2.41 – 2.22 (m, 2H), 1.91 (s, 3H), 1.72 (d, *J* = 8.9 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 168.18, 139.41, 134.30, 131.82, 129.43, 128.45, 128.16, 127.62, 126.69, 123.60, 120.07, 95.81, 52.11, 38.16, 37.62, 37.41, 36.89, 36.64, 31.93, 29.71, 29.37, 25.29, 24.60, 23.45, 23.10, 22.70, 21.34, 21.17, 18.43, 14.13.

2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^{2}-yl (tert-butoxycarbonyl)-L-tyrosinate was synthesized with ArCu(III) compound according to the general procedure.

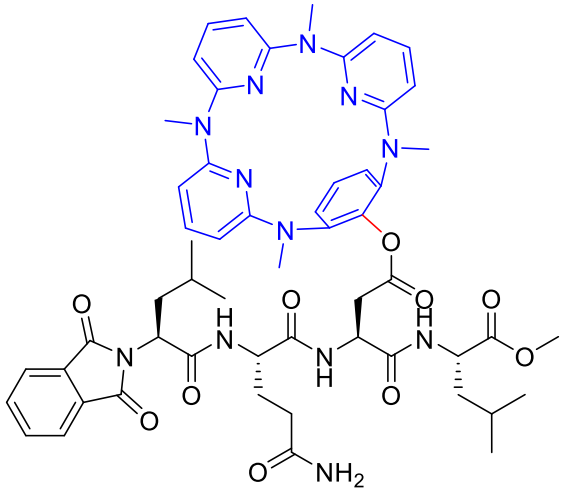


White foam solid (27.05 mg, 77% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 12.0, 7.9 Hz, 2H), 6.68 – 6.55 (m, 4H), 6.46 (s, 2H), 6.07 (dd, *J* = 19.0, 7.5 Hz, 4H), 4.79 (d, *J* = 8.2 Hz, 1H), 4.24 (td, *J* = 8.8, 5.1 Hz, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 3.05 (s, 2H), 3.03 (s, 3H), 2.53 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.43 – 2.27 (m, 1H), 1.35 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.34, 155.32, 155.15, 145.99, 139.12, 138.08, 129.89, 127.67, 127.46, 121.01, 120.34, 115.62, 95.63, 95.15, 79.38, 54.67, 37.98, 37.83, 36.52, 36.33, 36.01, 29.71, 28.31.

methyl ((2S)-2-((2S)-5-amino-2-(2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanamido)-5-oxopentanamido)-4-oxo-4-((2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane-7^{2}-yl)oxy)butanoyl)-L-leucinate was synthesized with ArCu(III) compound according to the general procedure

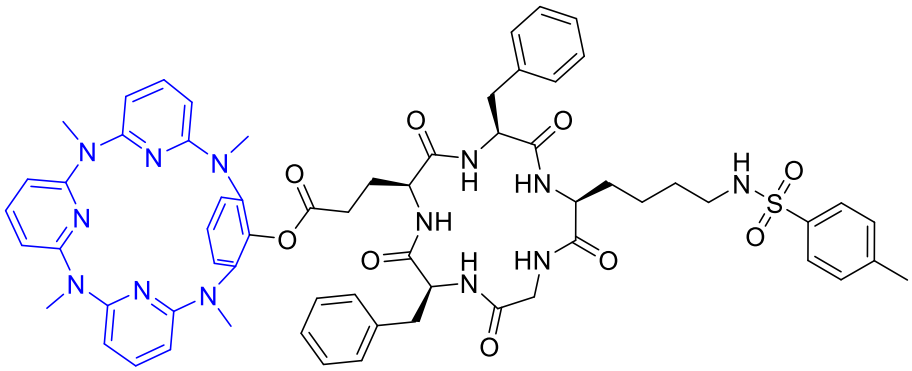


White foam solid (53.4mg, 72% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.85 – 7.70 (m, 4H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.22 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.99 – 6.74 (m, 3H), 6.60 (dd, *J* = 17.9, 7.6 Hz, 2H), 6.48 (s, 1H), 6.05 (d, *J* = 7.6 Hz, 2H), 6.03 – 5.94 (m, 2H), 5.31 (s, 1H), 4.88 (dd, *J* = 11.7, 4.2 Hz, 1H), 4.51 – 4.32 (m, 2H), 4.24 (dd, *J* = 13.9, 8.0 Hz, 1H), 3.61 (s, 3H), 3.24 (s, 3H), 3.23 (s, 3H), 3.10 (s, 3H), 2.98 (s, 3H), 2.90 (dd, *J* = 18.9, 4.8 Hz, 1H), 2.61 (dd, *J* = 18.6, 7.0 Hz, 1H), 2.37 – 2.08 (m, 4H), 2.07 – 1.97 (m, 1H), 1.86 (t, *J* = 9.9 Hz, 1H), 1.42 (ddt, *J* = 17.9, 13.6, 8.9 Hz, 4H), 1.26 (d, *J* = 12.0 Hz, 1H), 0.97 (t, *J* = 6.4 Hz, 6H), 0.67 (dd, *J* = 20.0, 6.0 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 175.92, 172.75, 171.69, 170.60, 170.34, 169.94, 168.23, 159.11, 158.73, 157.84, 157.22, 156.94, 146.50, 140.33, 140.14, 139.49, 138.40, 134.45, 131.73, 128.54, 127.82, 125.85, 123.74, 121.19, 119.15, 96.62, 96.23, 95.72, 95.46, 53.90, 52.29, 52.13, 51.16, 49.59, 40.85, 37.63, 37.45, 37.29, 37.13, 36.46, 34.12, 31.24, 29.79, 27.78, 25.33, 24.67, 23.51, 22.69, 21.75, 21.27.

2,4,6,8-tetramethyl-2,4,6,8-tetraaza-1,3,5(2,6)-tripyridina-7(1,3)-benzenacyclooctaphane 7^{2}-yl3-((2S,5S,8S,14S)-5,14-dibenzyl-8-(4-((4-methylphenyl)sulfonamido)butyl) 3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)propanoate was synthesized with ArCu(III) compound according to the general procedure

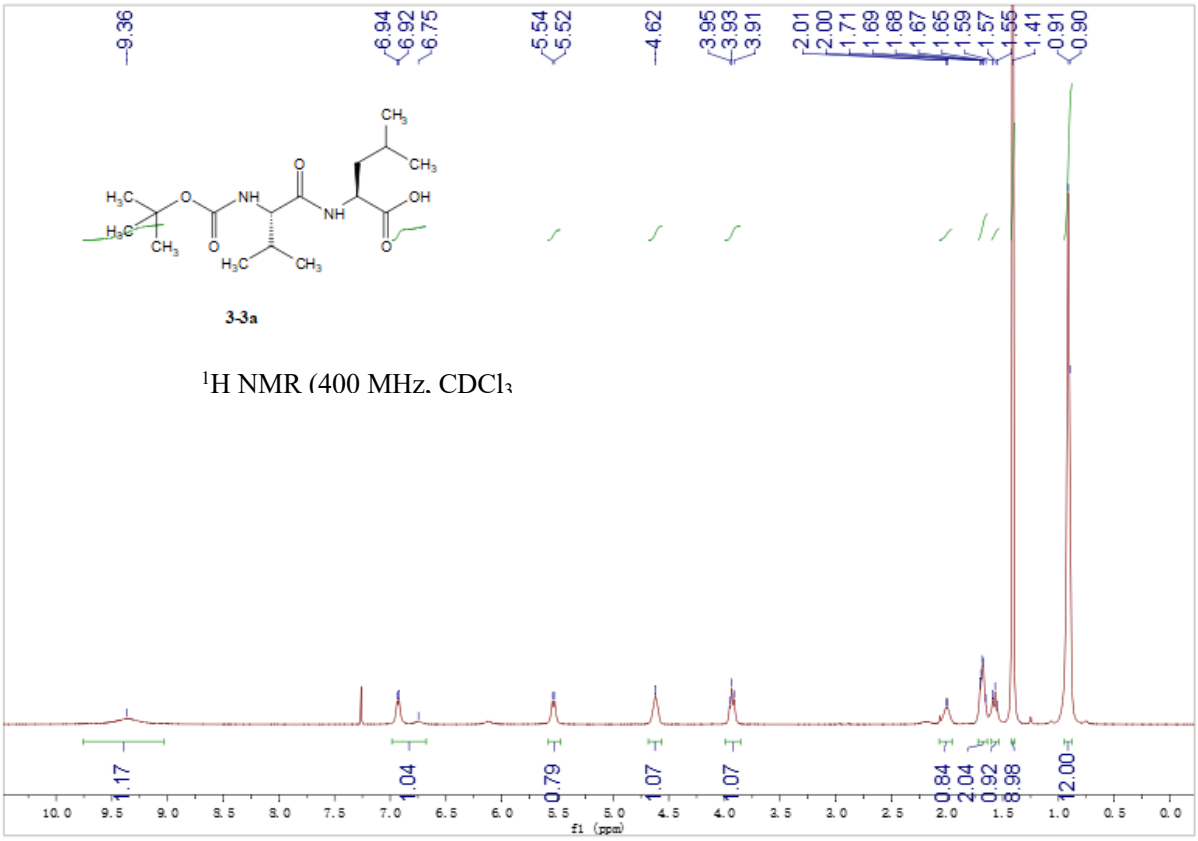


White foam solid, (41.62mg, 59% yield)

^{1}H NMR (400 MHz, DMSO) δ 8.40 (t, *J* = 5.6 Hz, 1H), 8.23 (t, 2H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 5.8 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.26 – 7.09 (m, 11H), 7.09 – 7.02 (m, 1H), 6.88 (d, *J* = 7.9 Hz, 2H), 6.50 (d, *J* = 7.6 Hz, 2H), 6.19 – 5.99 (m, 4H), 4.36 – 4.20 (m, 1H), 4.14 – 3.91 (m, 3H), 3.82 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.28 (d, *J* = 5.5 Hz, 1H), 3.11 (d, *J* = 3.7 Hz, 6H), 3.07 – 2.98 (m, 3H), 2.95 (d, *J* = 1.3 Hz, 6H), 2.79 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.64 (dd, *J* = 13.1, 6.8 Hz, 2H), 2.37 (s, 3H), 1.96 – 1.83 (m, 2H), 1.80 – 1.69 (m, 2H), 1.65 – 1.43 (m, 2H), 1.32 (dd, *J* = 12.6, 5.5 Hz, 2H), 1.23 (s, 1H), 1.18 – 1.03 (m, 2H).

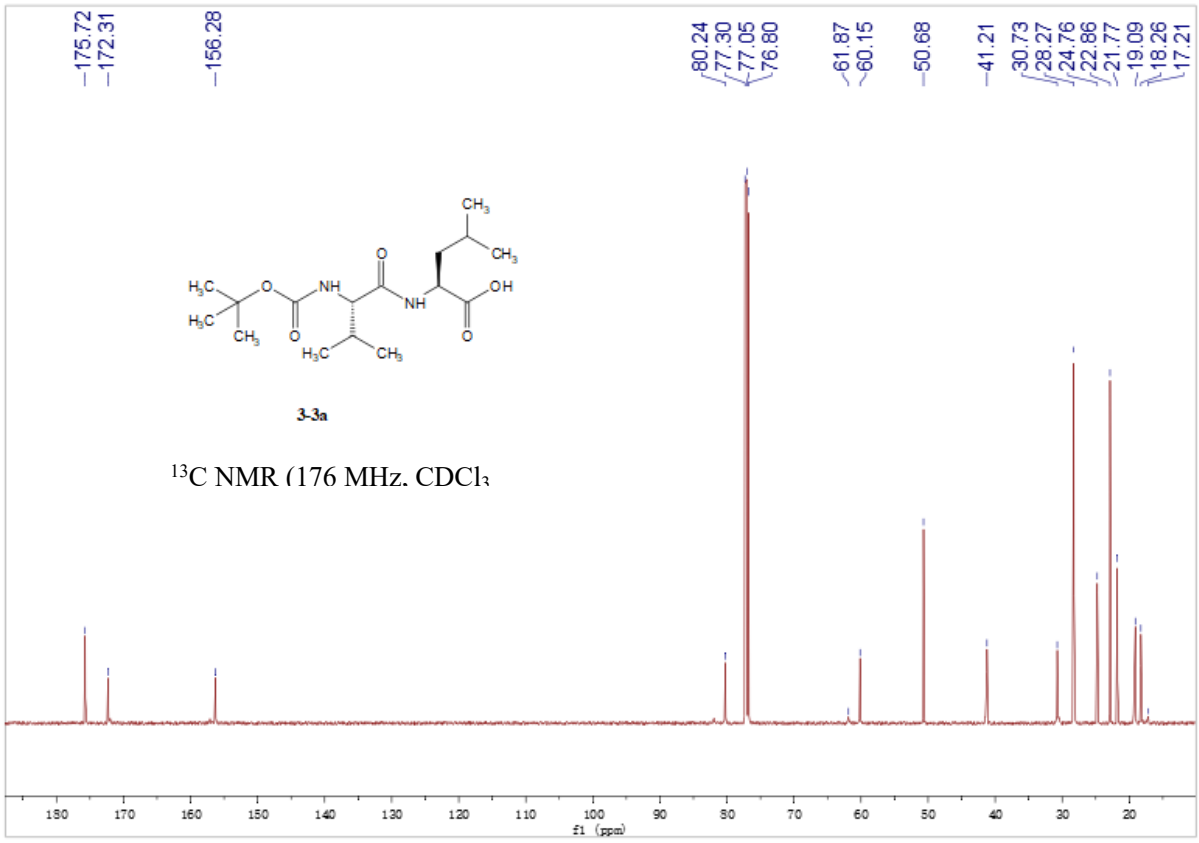
^{13}C NMR (176 MHz, $CDCl_3$) δ 172.57, 171.90, 171.36, 171.33, 170.95, 169.72, 158.77, 157.11, 145.52, 142.99, 140.54, 139.45, 138.06, 138.02, 137.81, 130.08, 129.35, 129.28, 128.79, 128.70, 128.00, 126.99, 126.54, 120.07, 96.43, 95.60, 57.86, 56.19, 53.60, 53.27, 43.69, 42.93, 37.94, 37.35, 36.61, 31.05, 29.71, 29.11, 26.67, 23.16, 21.43.

3. Copies of 1H and 13C NMR Spectra of peptide substrates



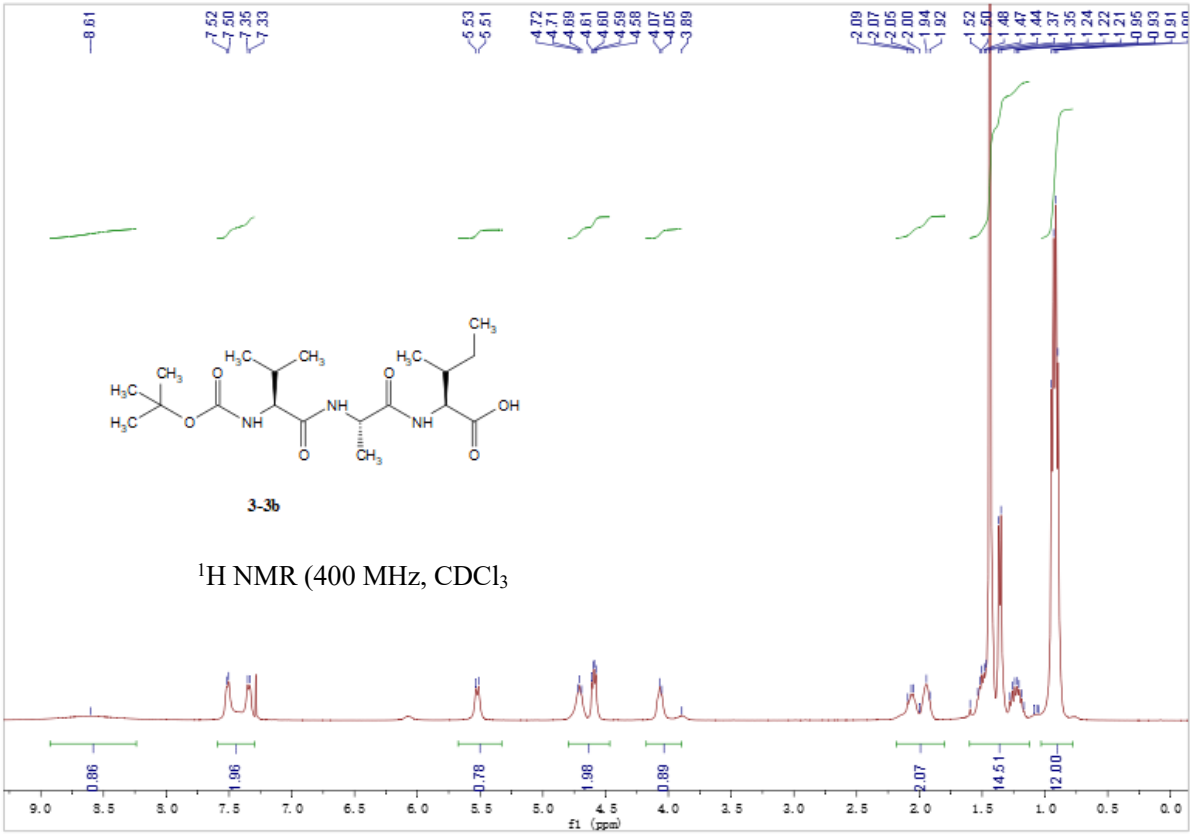
3-3a

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



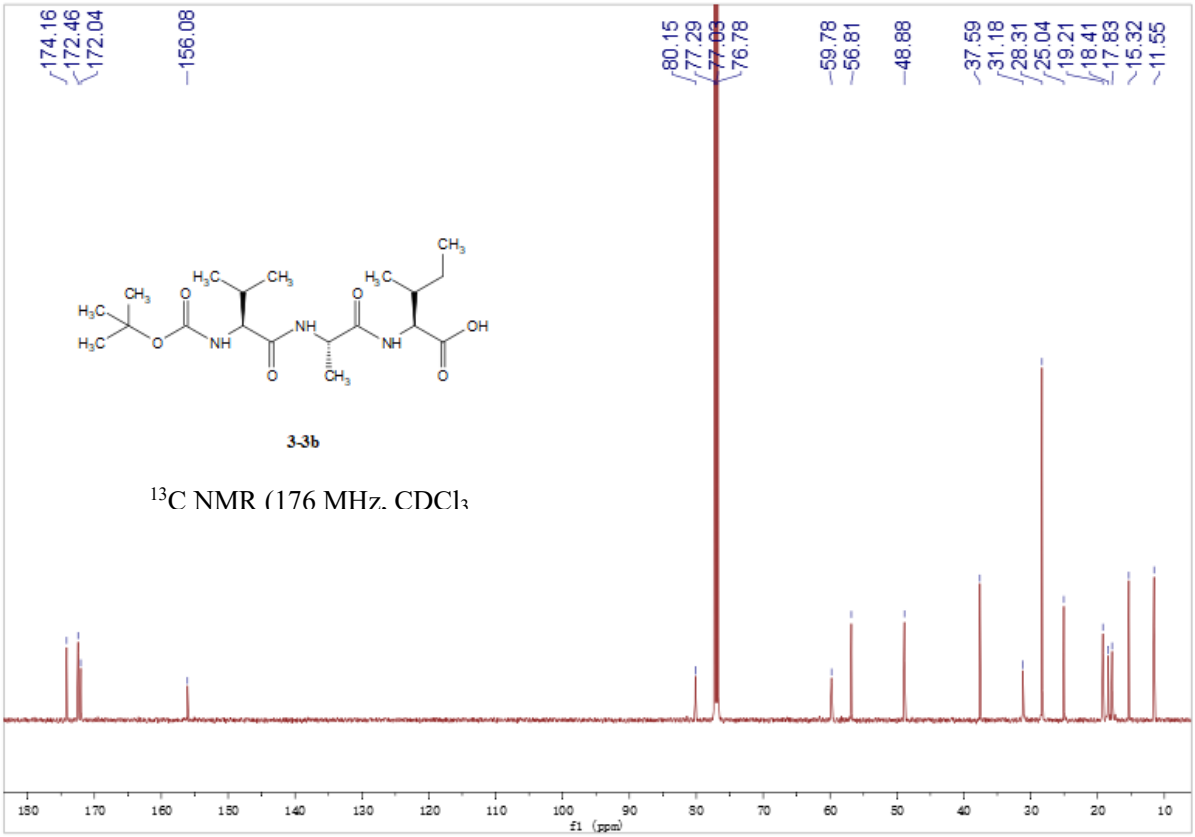
3-3a

^{13}C NMR (176 MHz, $CDCl_3$



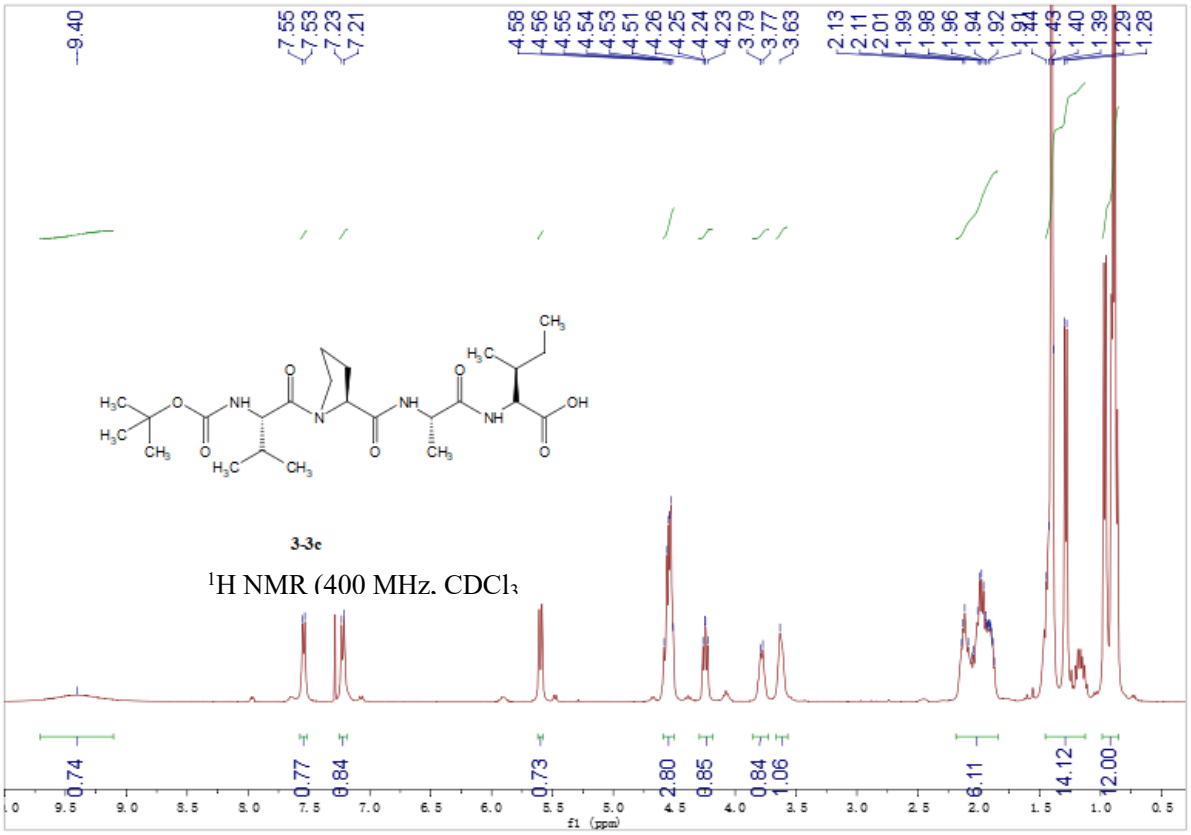
3-3b

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



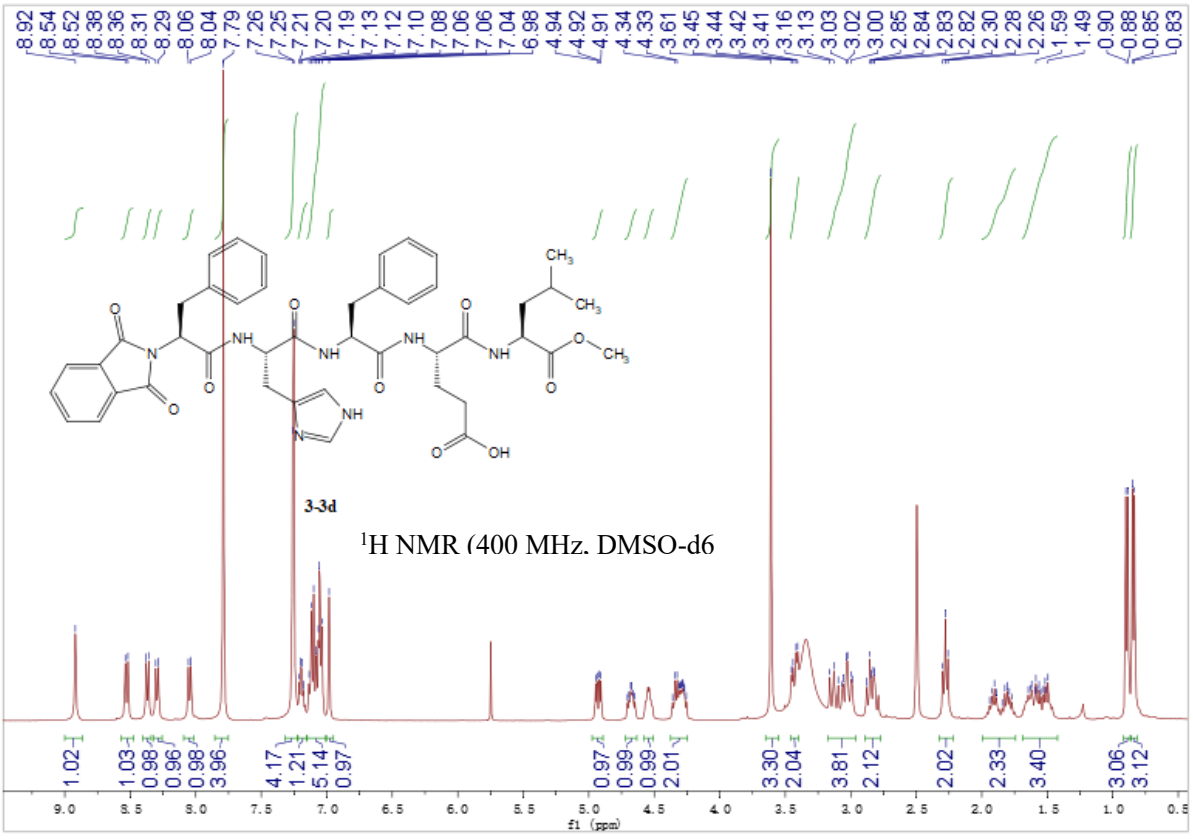
3-3b

^{13}C NMR (176 MHz, $CDCl_3$



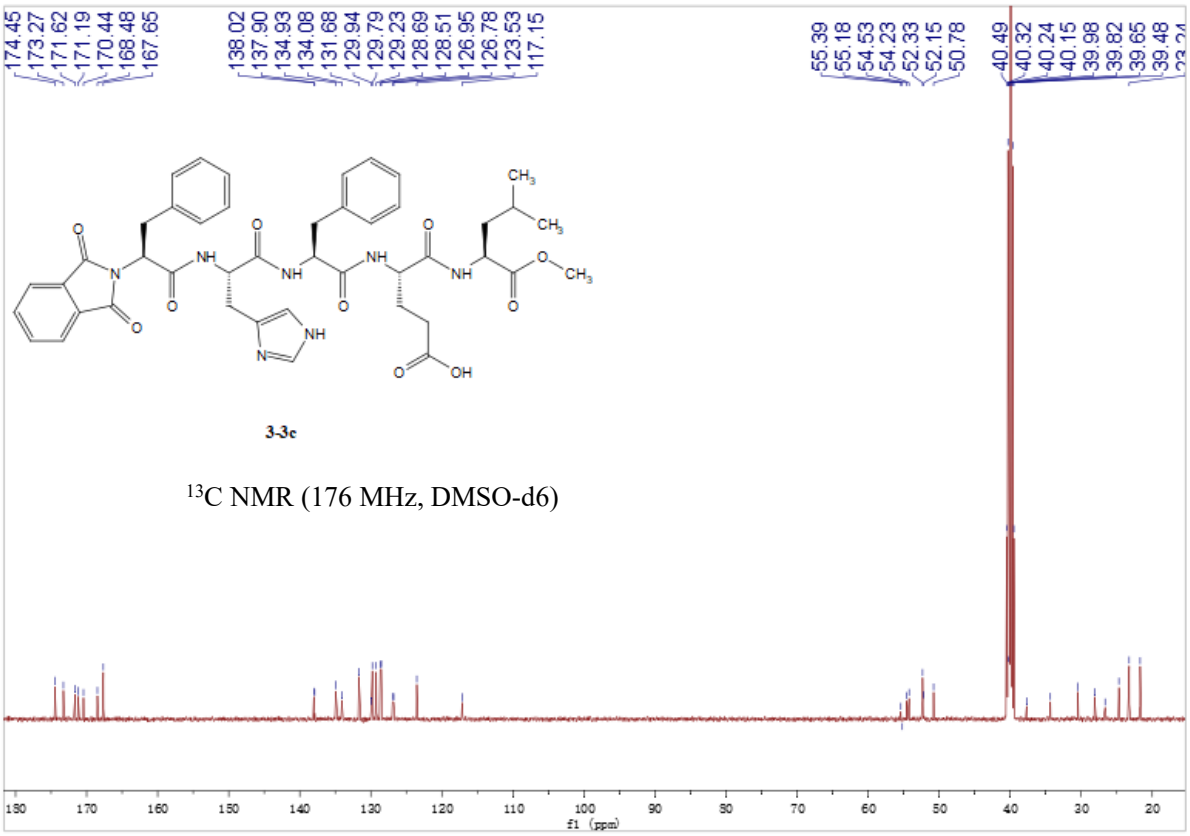
3-3c

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



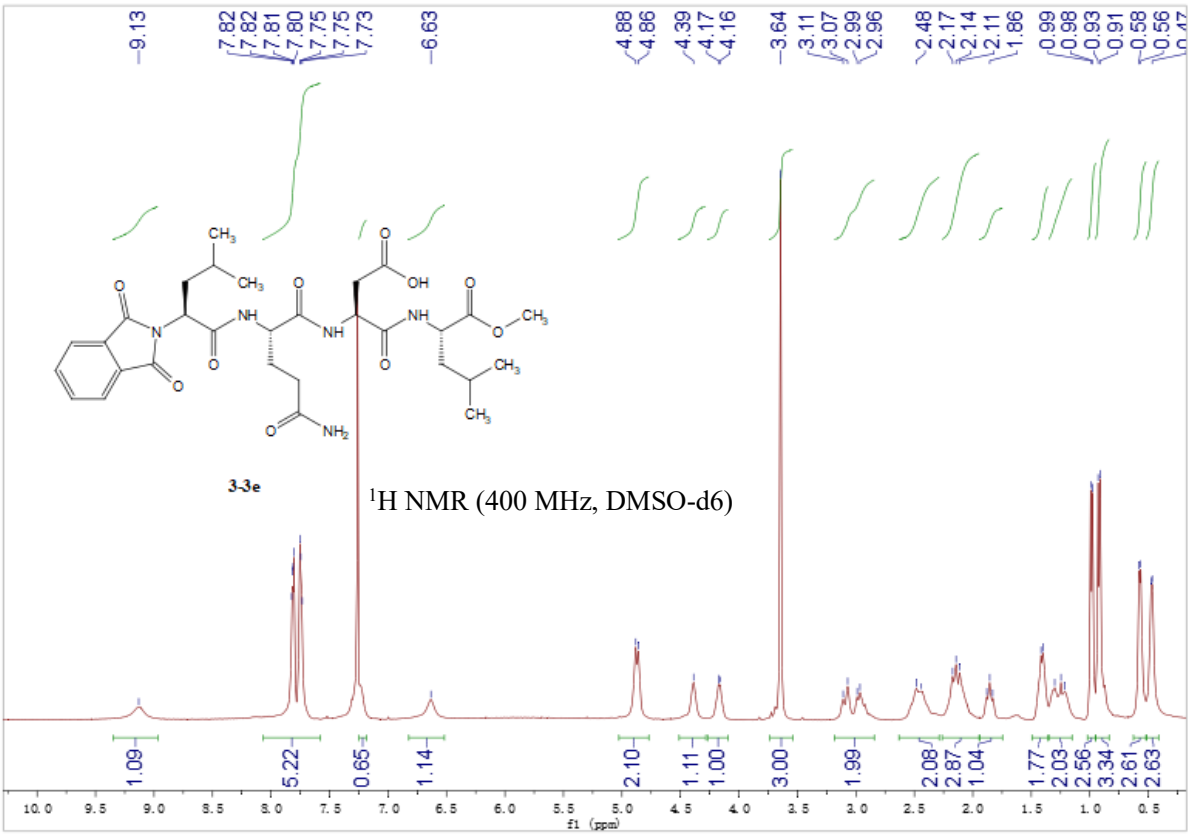
3-3d

^{1}H NMR (400 MHz. DMSO-d6



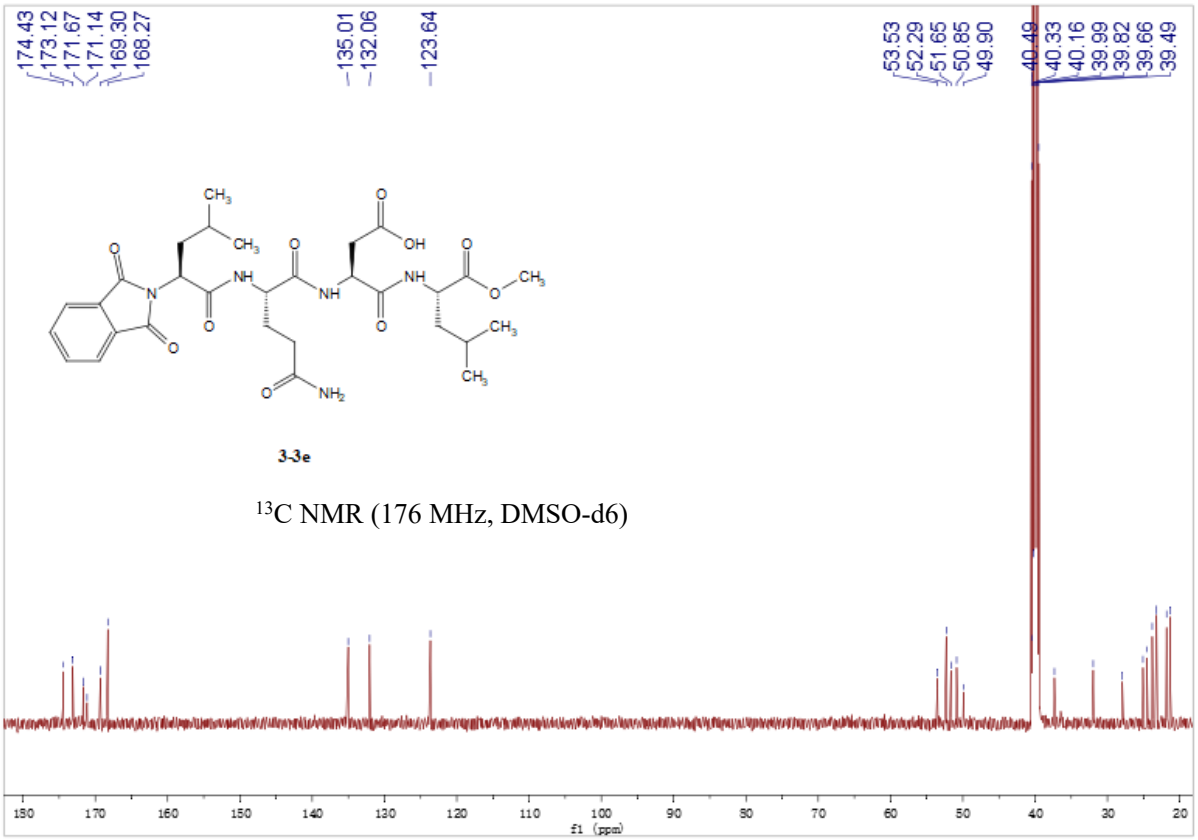
3-3c

^{13}C NMR (176 MHz, DMSO-d6)



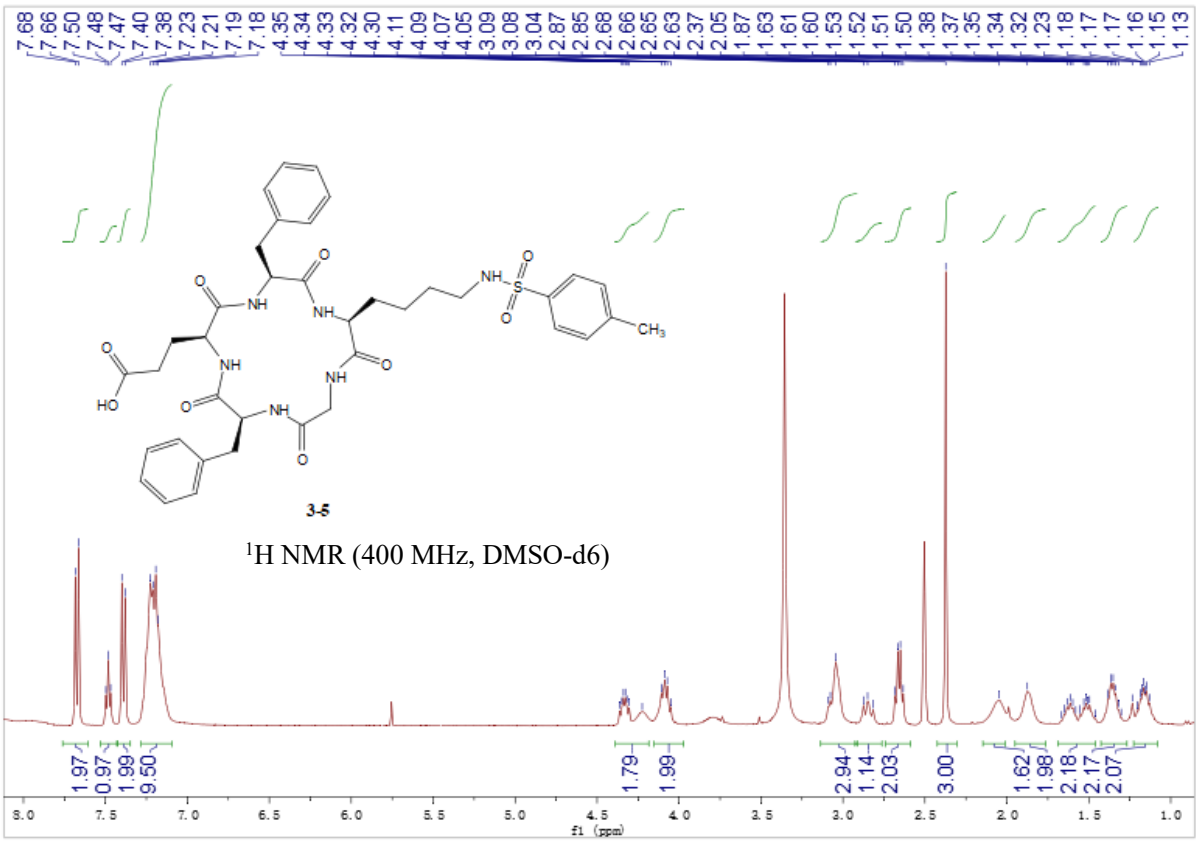
3-3e

^{1}H NMR (400 MHz, DMSO-d6)



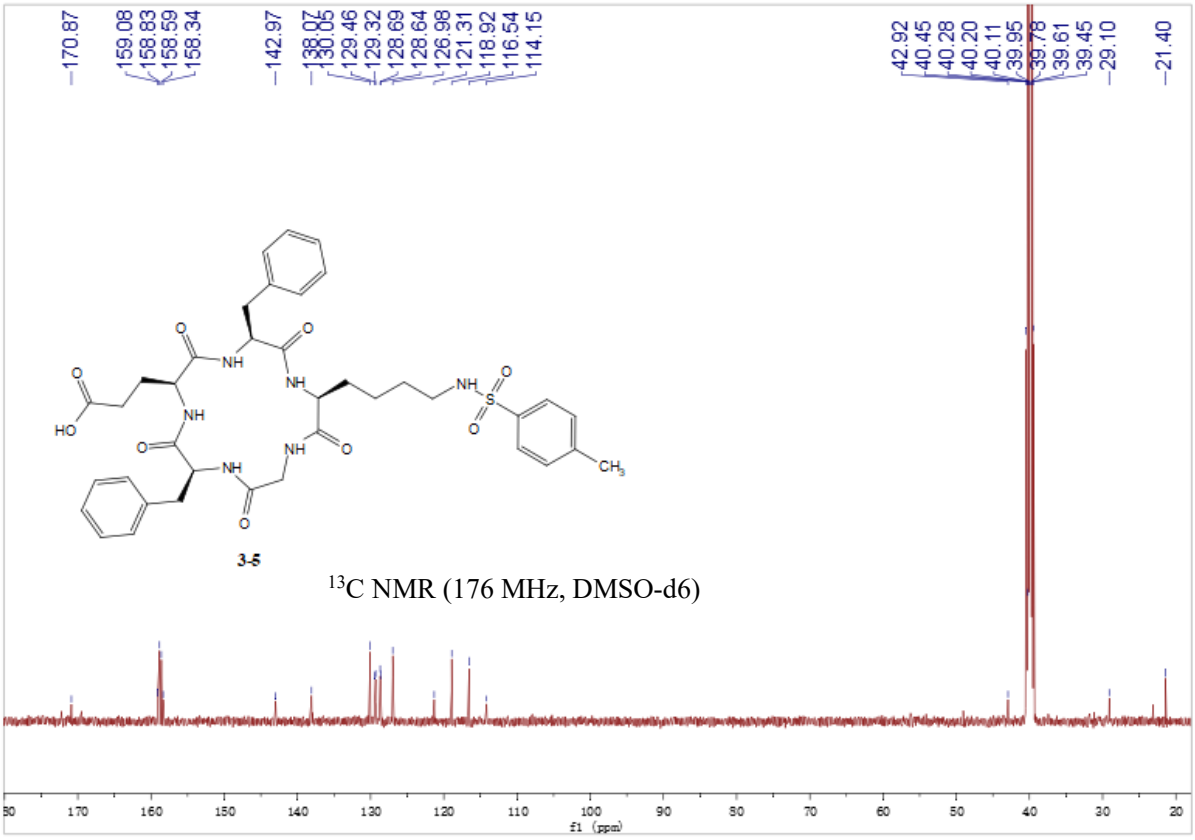
3-3e

^{13}C NMR (176 MHz, DMSO-d6)



3-5

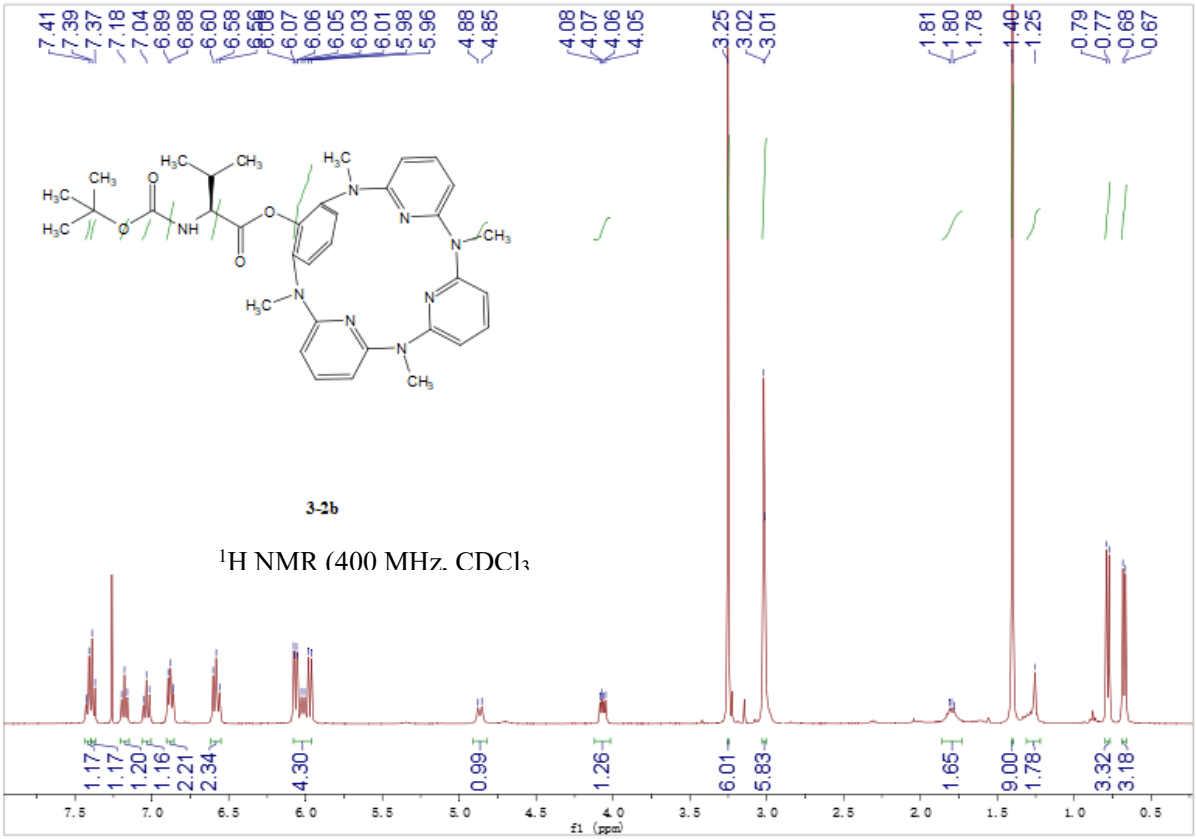
^{1}H NMR (400 MHz, DMSO-d6)



3-5

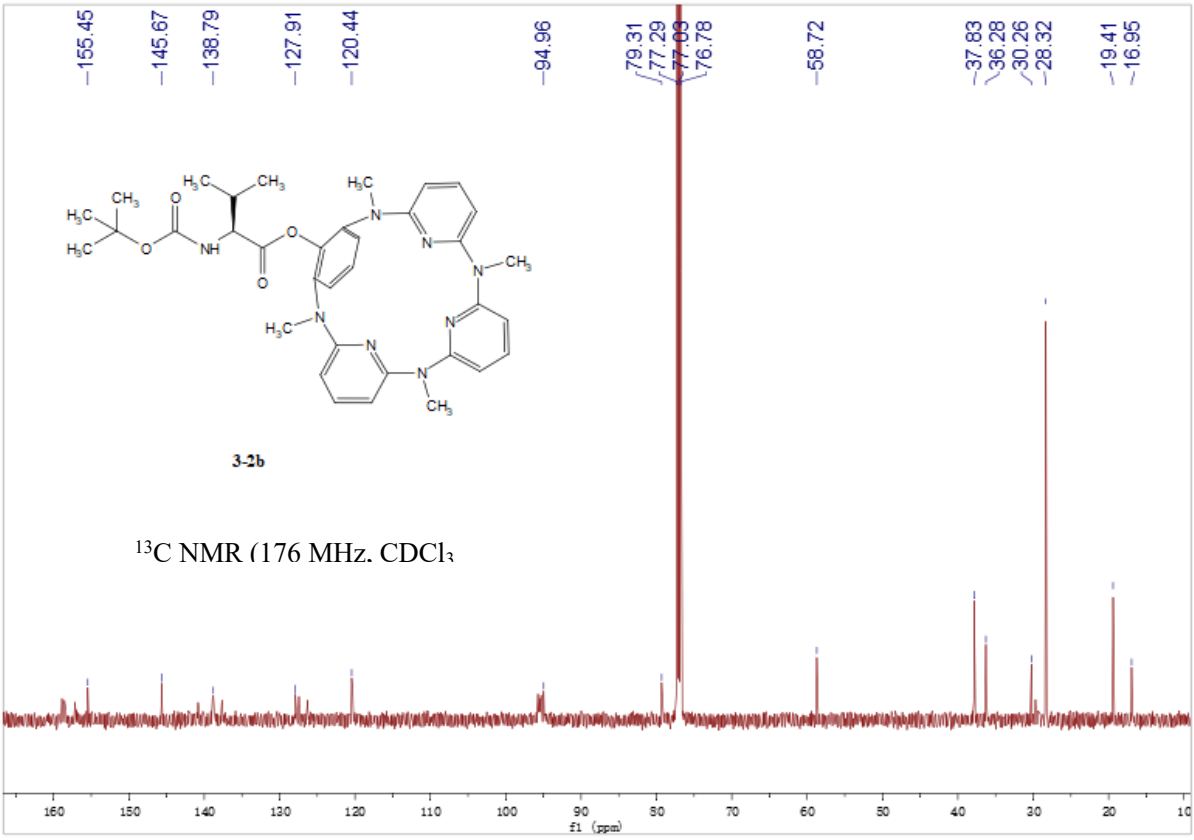
^{13}C NMR (176 MHz, DMSO-d6)

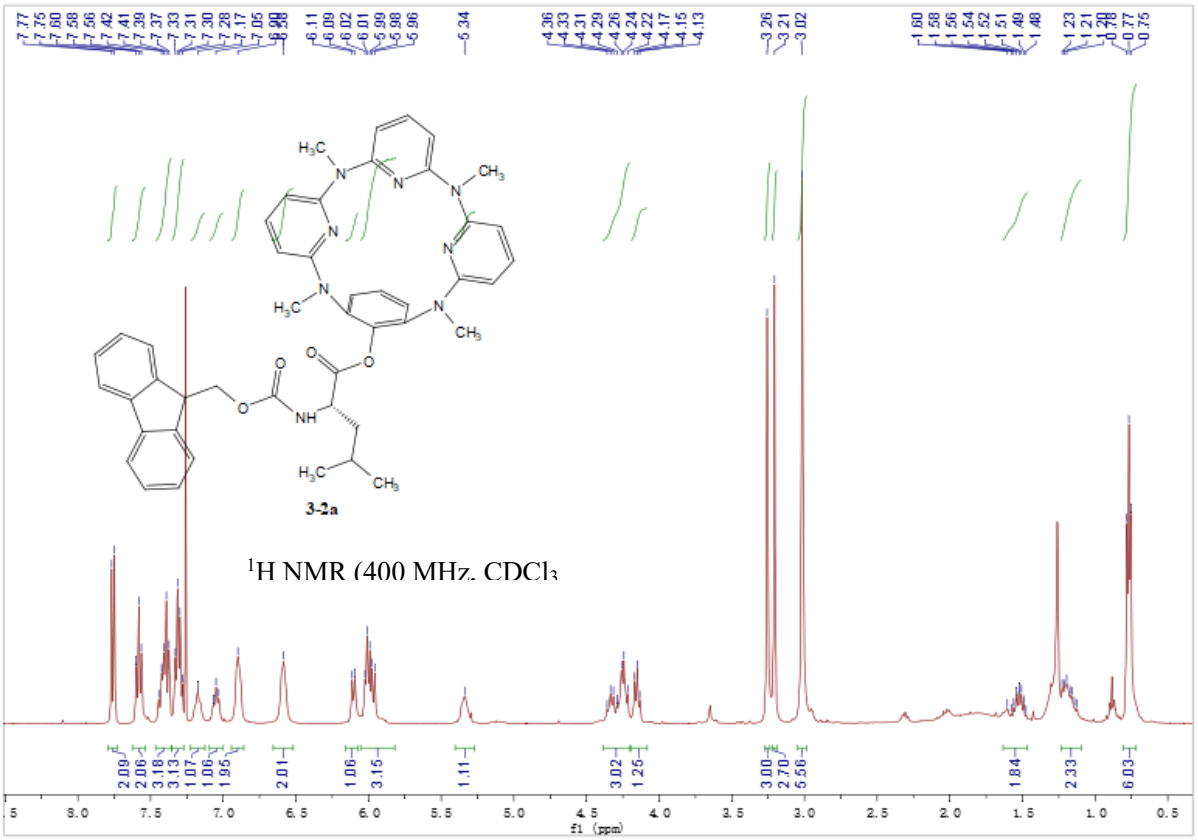
4. Copies of 1H and 13C NMR Spectra of modified peptides

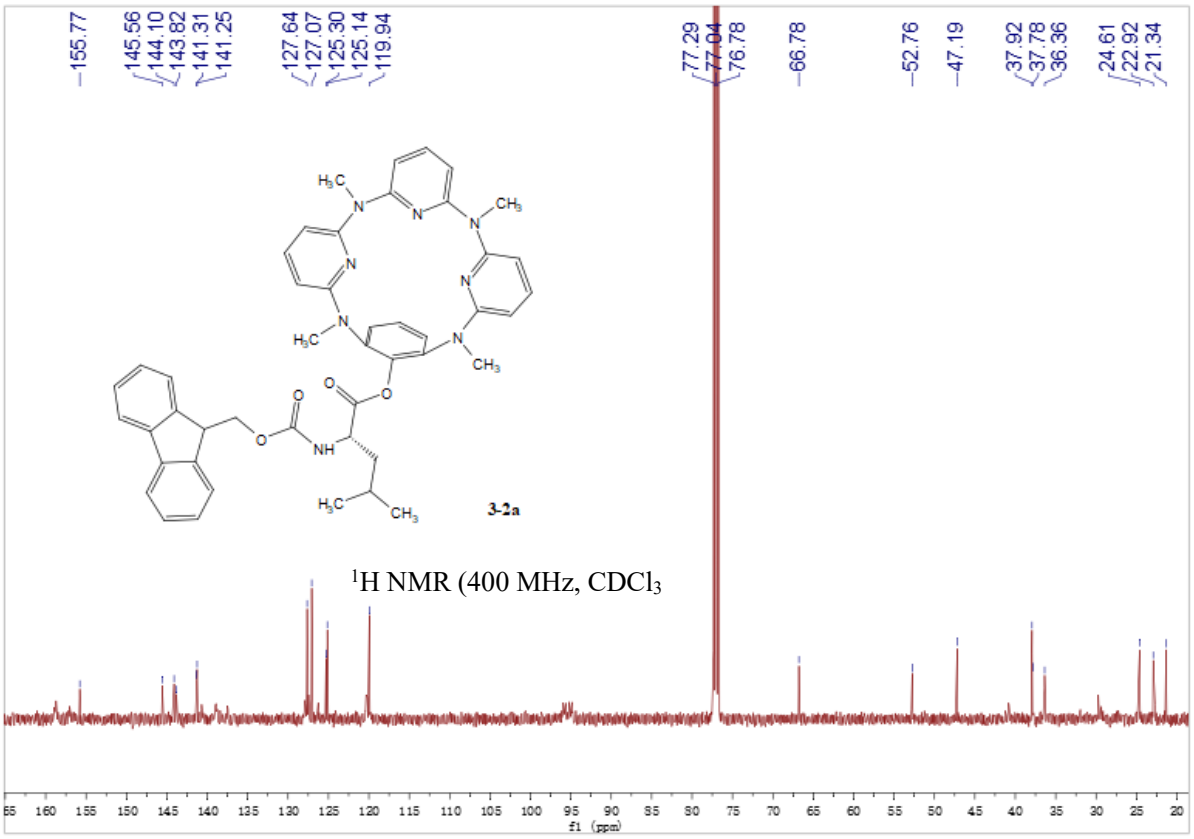


3-2b

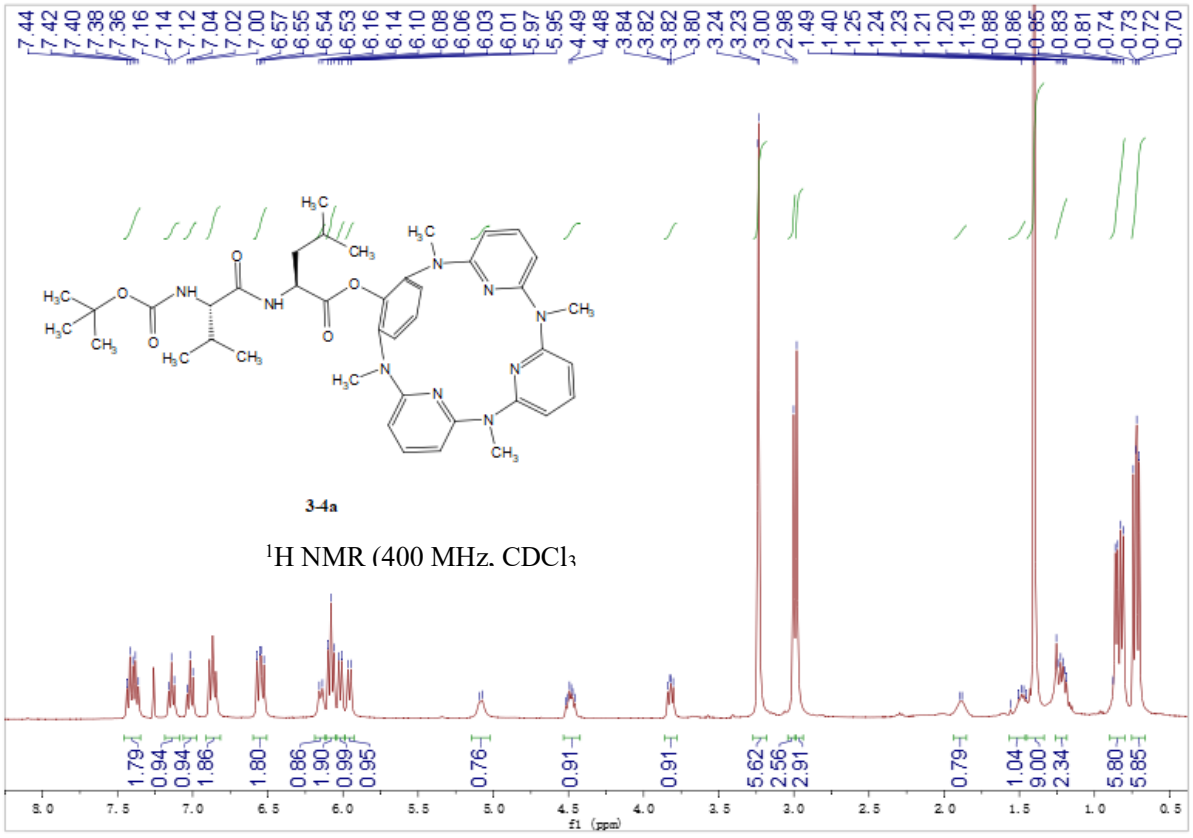
^{1}H NMR (400 MHz, CDCl$_3$


155.45
145.67
138.79
127.91
120.44
94.96
79.31
77.29
77.03
76.78
58.72
37.83
36.28
30.26
28.32
19.41
16.95
3-2b
13C NMR (176 MHz, CDCl3
f1 (ppm)

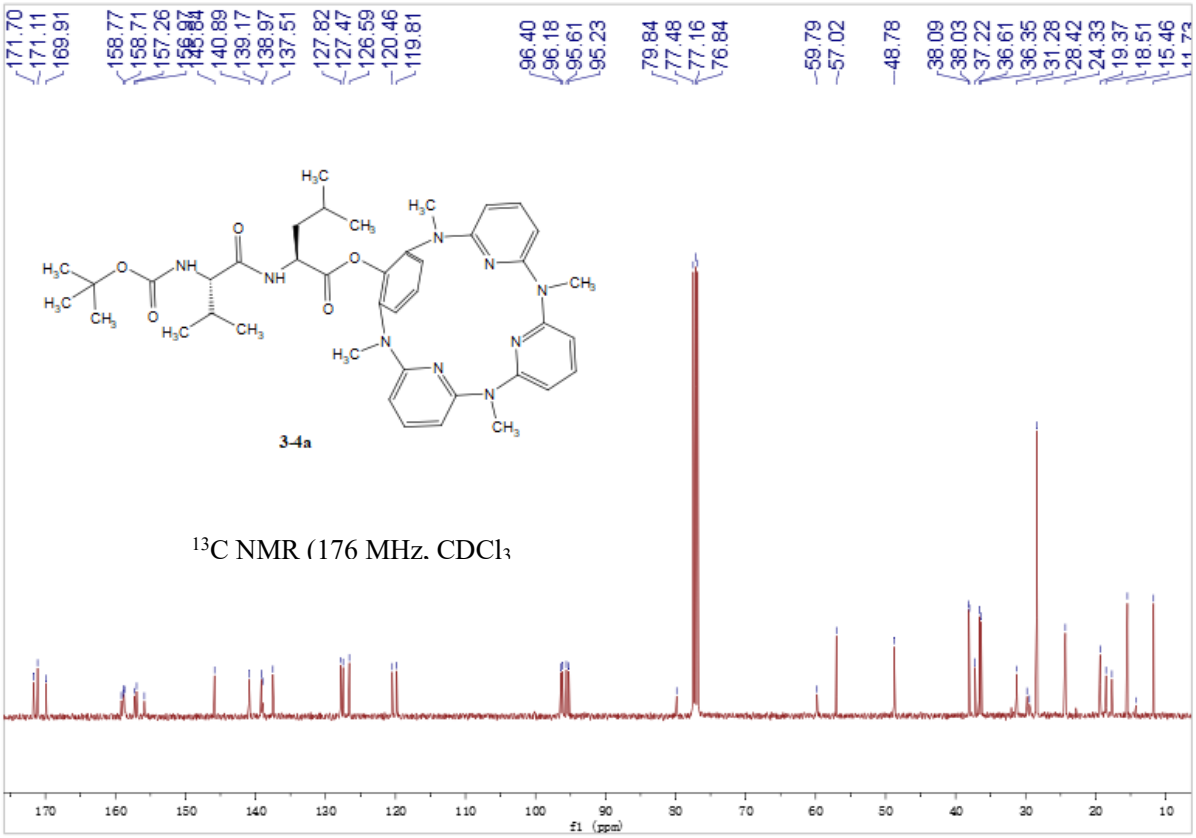

3-2a
1H NMR (400 MHz, CDCl3
f1 (ppm)



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

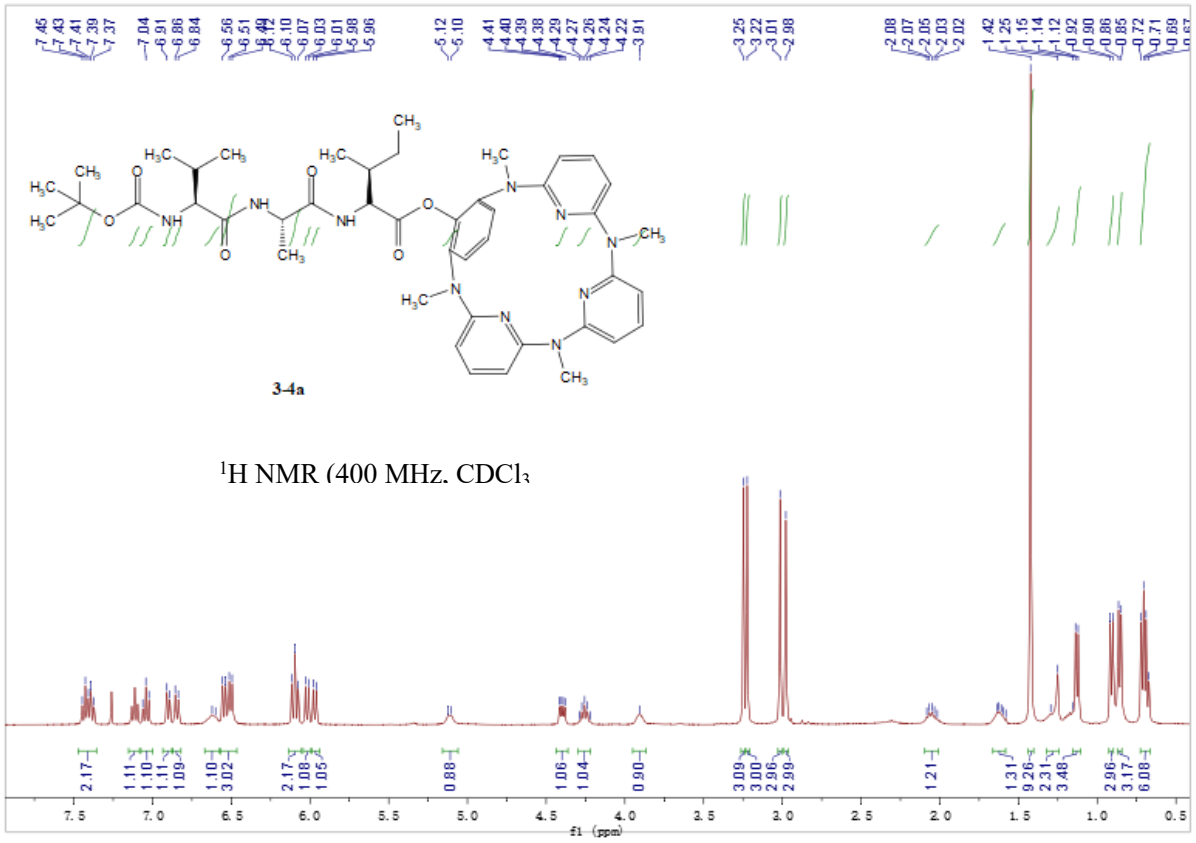


^{1}H NMR (400 MHz, $CDCl_3$



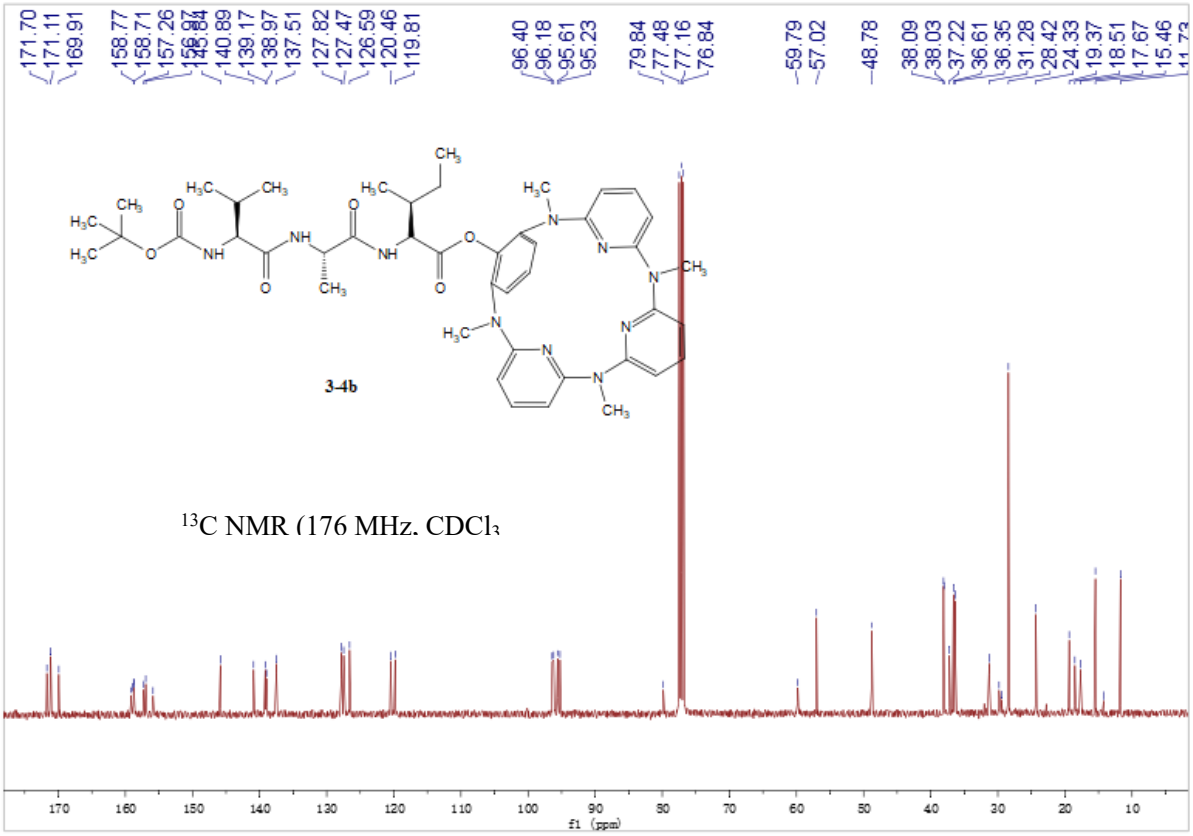
3-4a

^{13}C NMR (176 MHz, $CDCl_3$

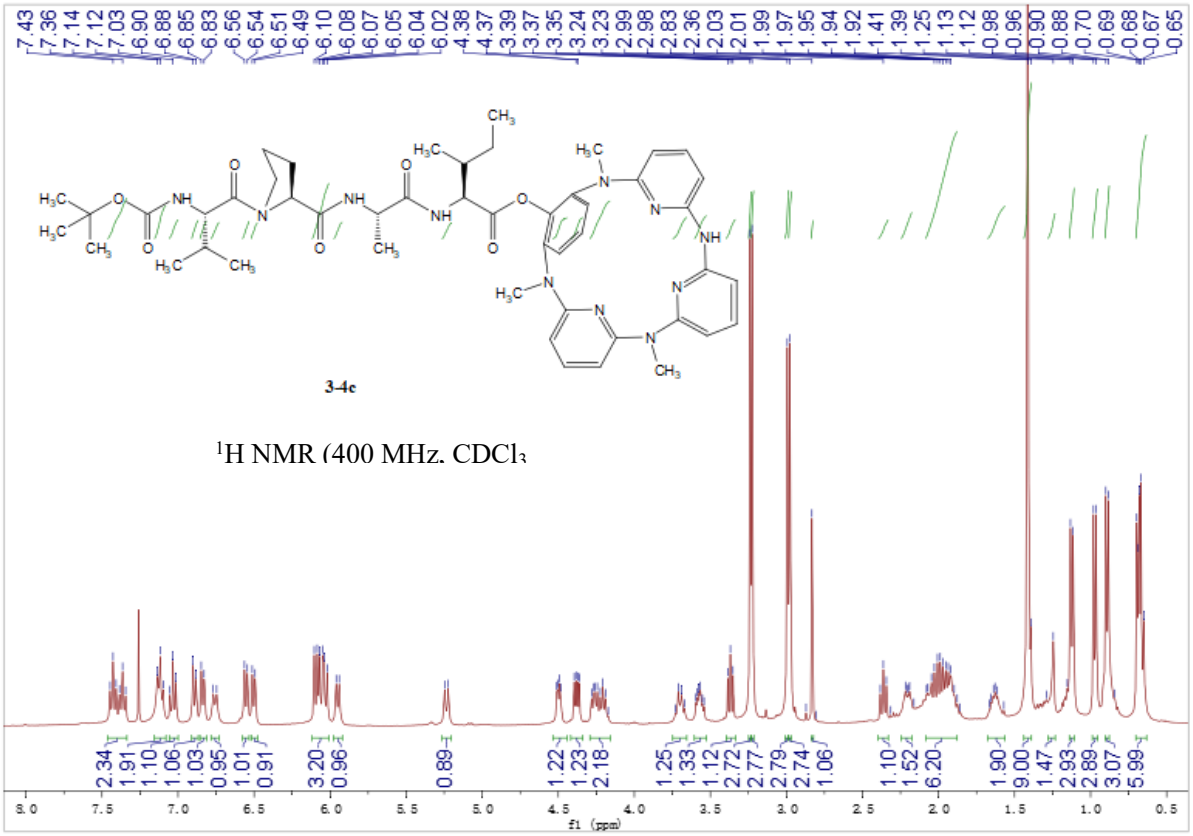


3-4a

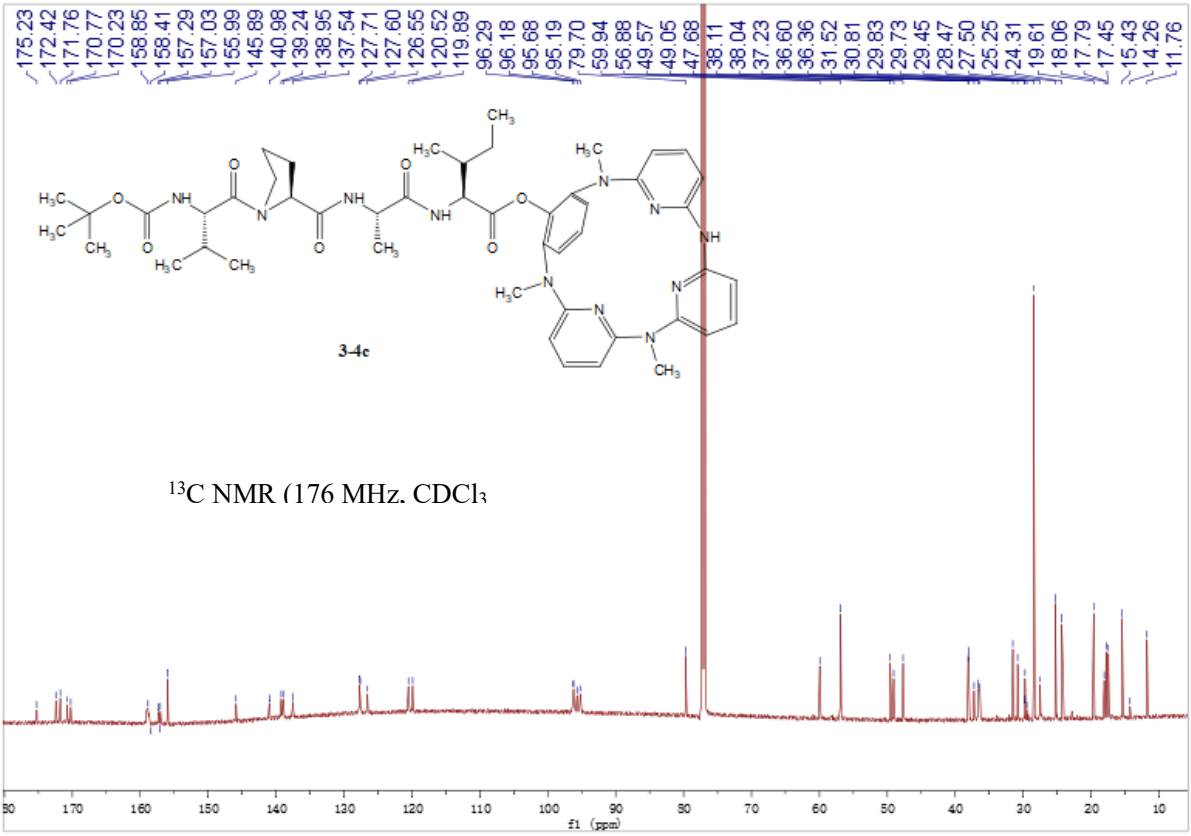
^{1}H NMR (400 MHz, $CDCl_3$



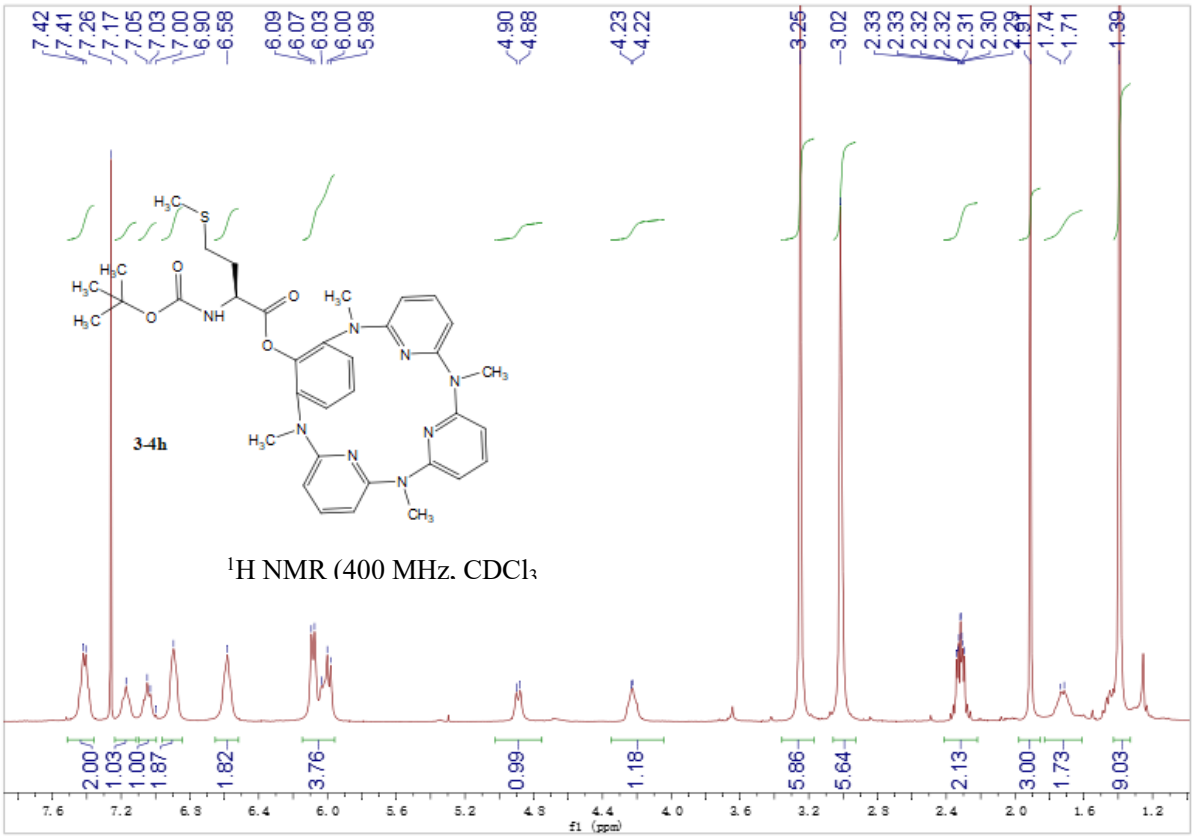
^{13}C NMR (176 MHz, $CDCl_3$



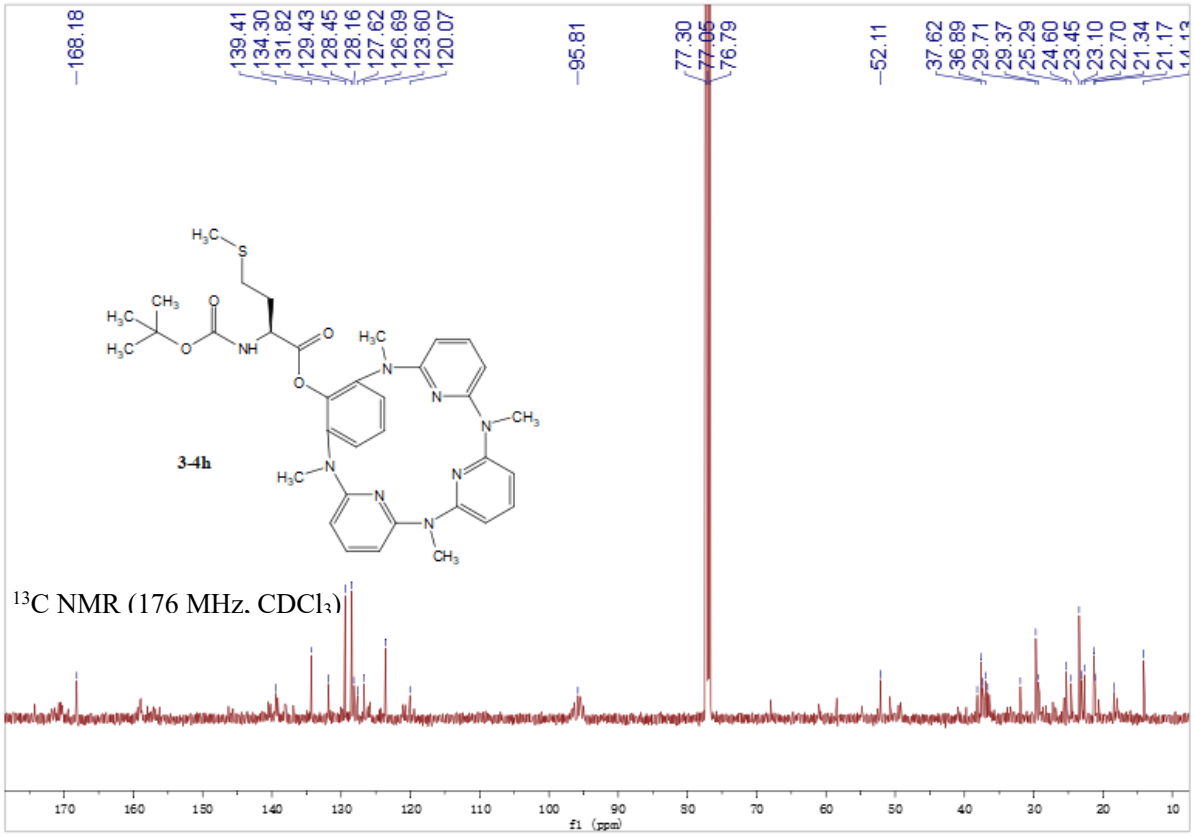
^{1}H NMR (400 MHz, $CDCl_3$



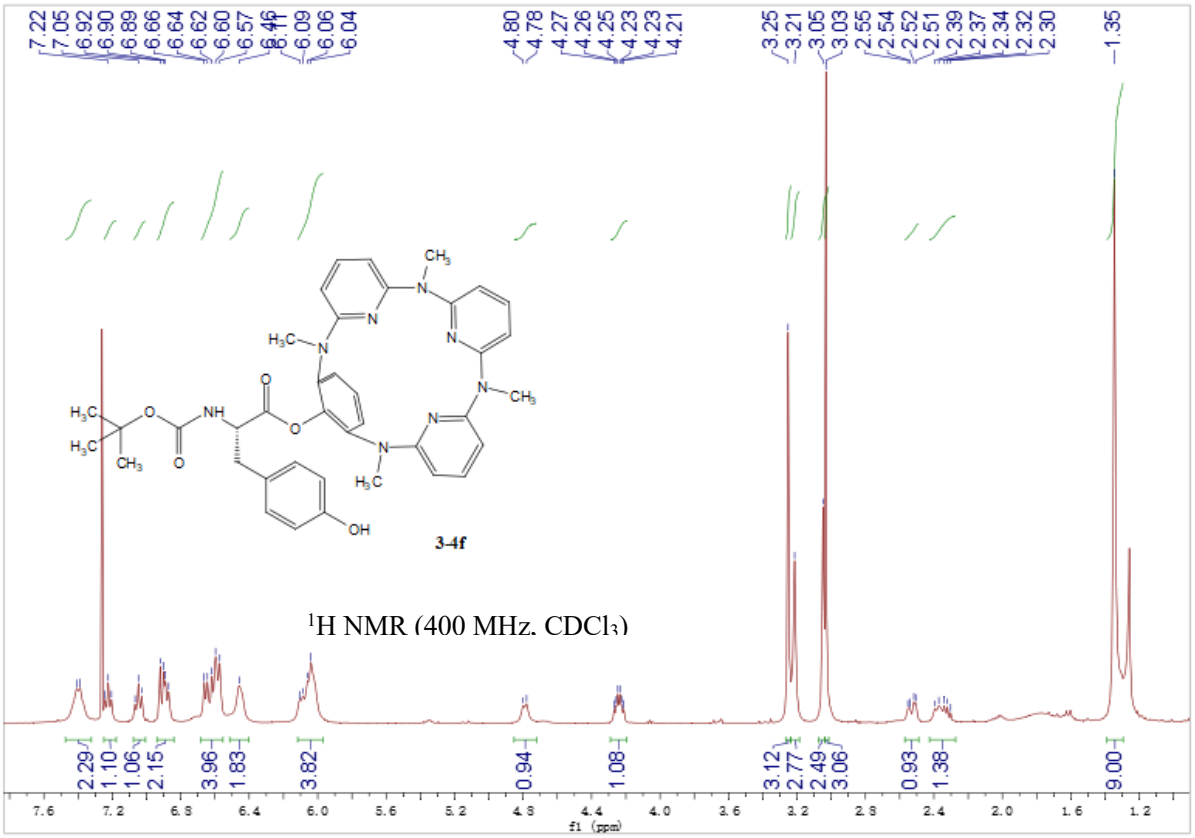
^{13}C NMR (176 MHz, $CDCl_3$



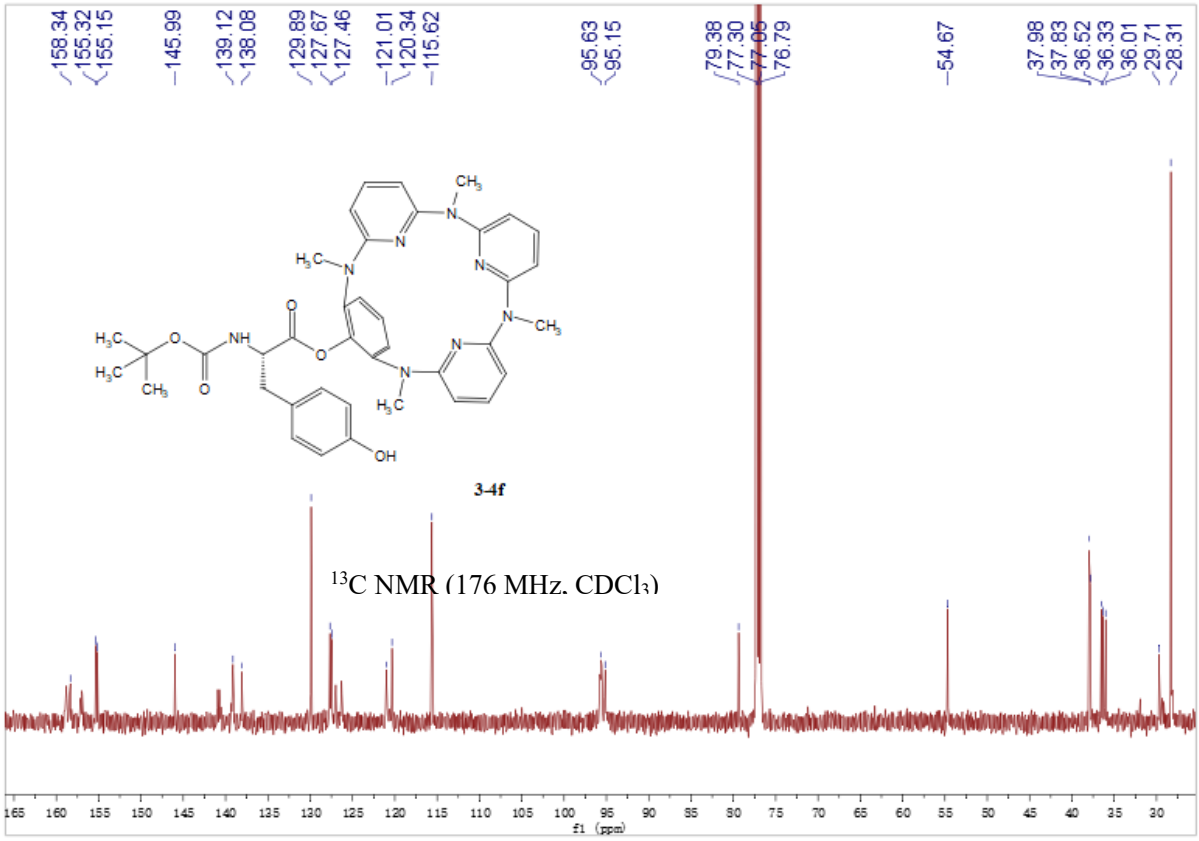
^{1}H NMR (400 MHz, $CDCl_3$



^{13}C NMR (176 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)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155.15
145.99
139.12
138.08
129.89
127.67
127.46
121.01
120.34
115.62
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95.15
79.38
77.30
77.05
76.79
54.67
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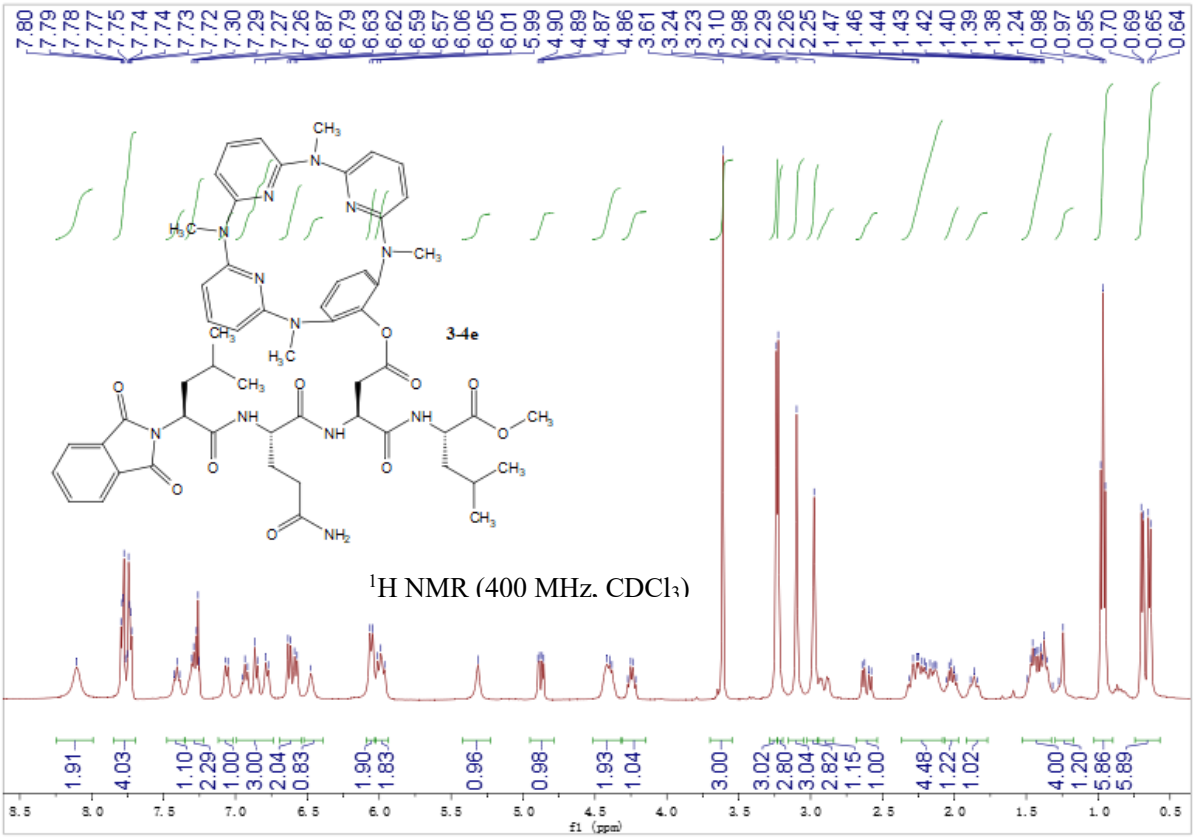
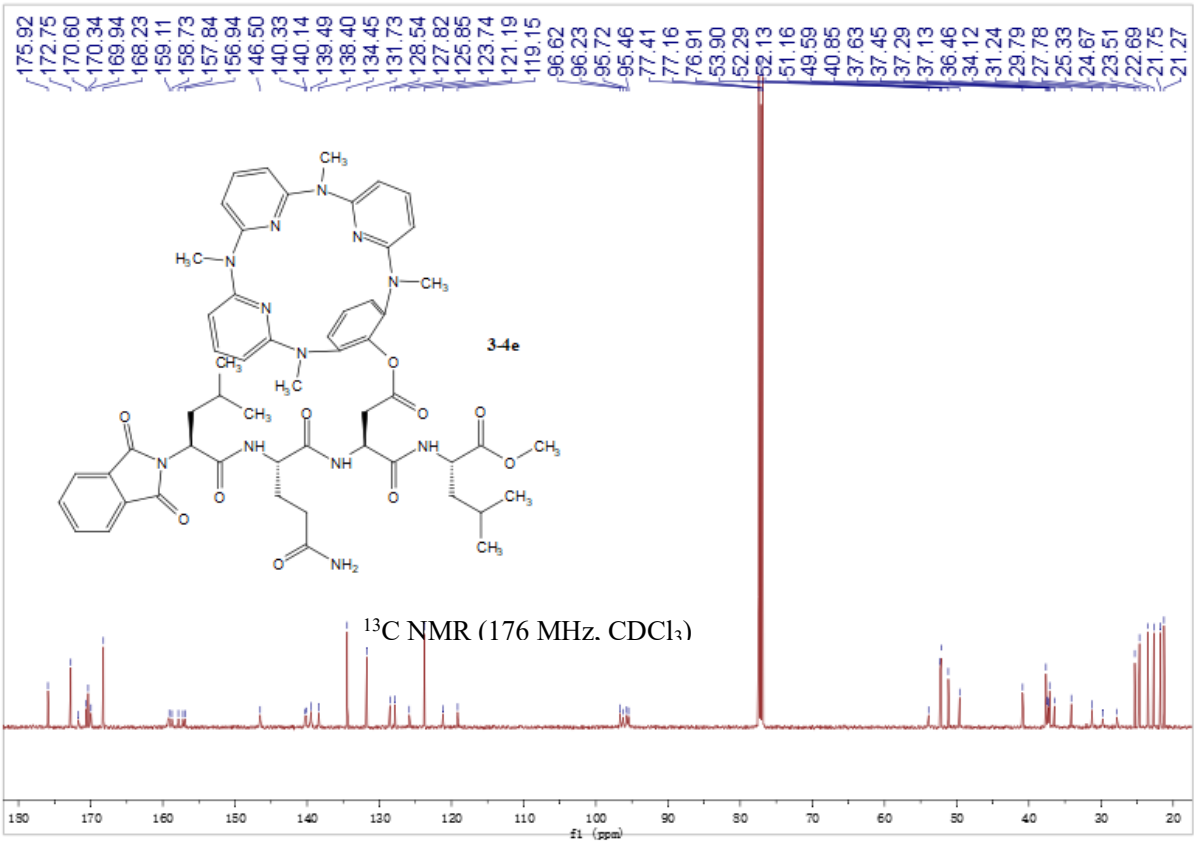
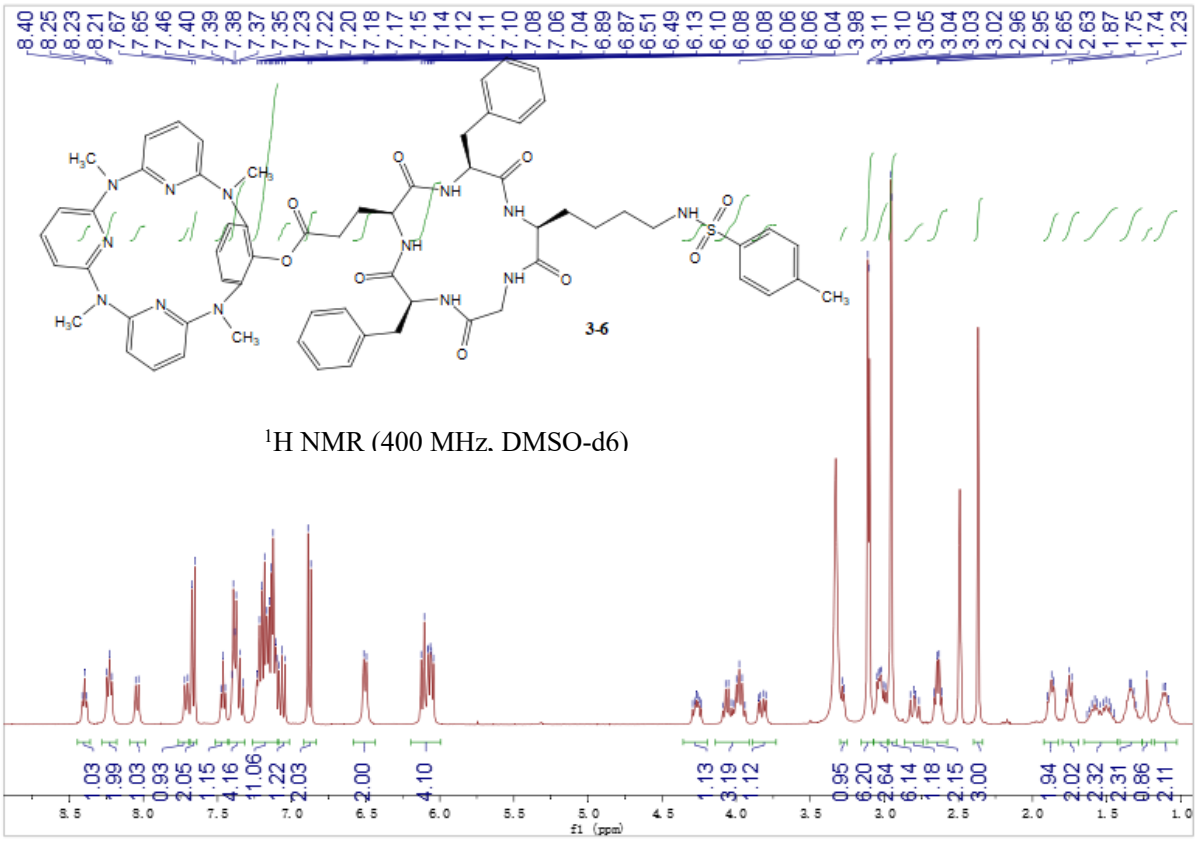
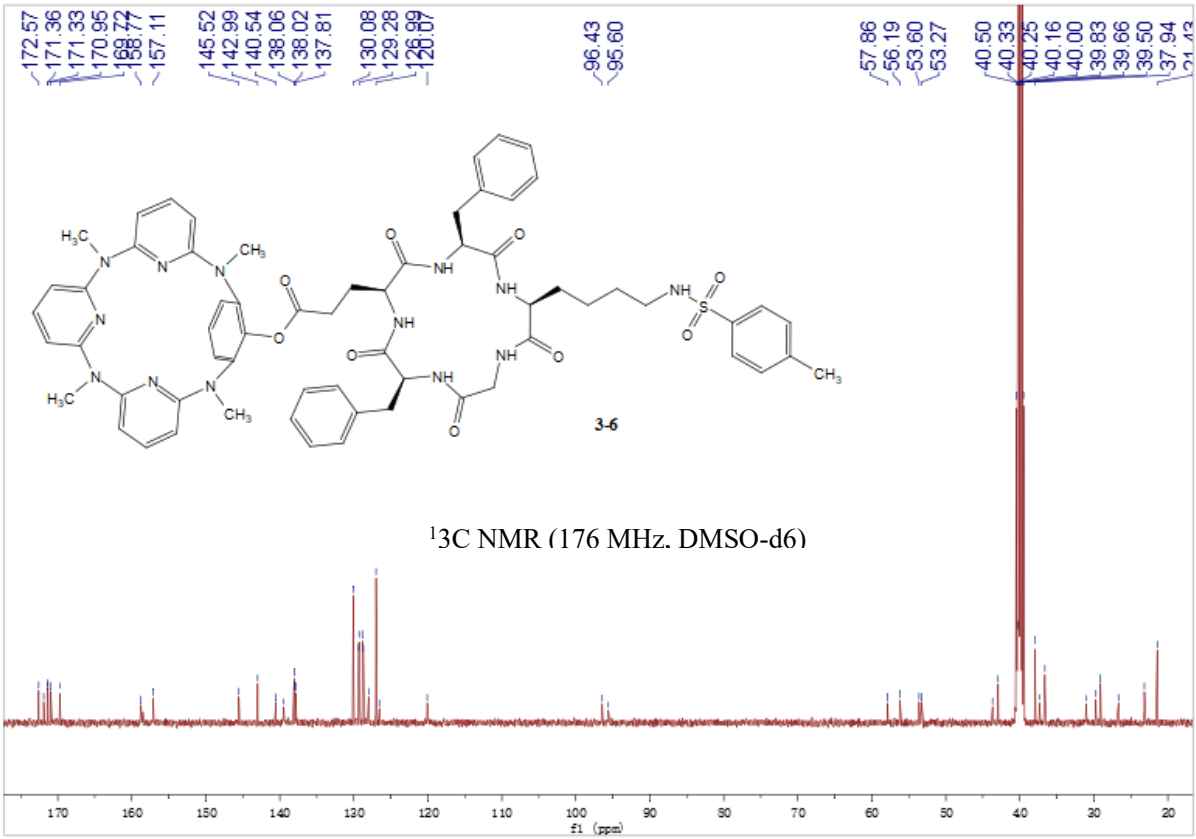
36.01
29.71
28.31
3-4f
13C NMR (176 MHz, CDCl3)
f1 (ppm)


7.80
7.79
7.78
7.77
7.75
7.74
7.74
7.73
7.72
7.30
7.29
7.27
7.26
6.87
6.79
6.63
6.62
6.59
6.57
6.06
6.05
6.01
5.99
4.90
4.89
4.87
4.86
3.61
3.24
3.23
3.10
2.98
2.29
2.26
2.25
1.47
1.46
1.44
1.43
1.42
1.40
1.39
1.38
1.24
0.98
0.97
0.95
0.70
0.69
0.65
0.64
3-4e
1H NMR (400 MHz, CDCl3)
1.91
4.03
1.10
2.29
1.00
3.00
2.04
0.83
1.90
1.83
0.96
0.98
1.93
1.04
3.00
3.02
2.80
3.04
2.82
1.15
1.00
4.48
1.22
1.02
4.00
1.20
5.86
5.89
f1 (ppm)


3-4e
^{13}C NMR (176 MHz, CDCl$_3$)


3-6
^{1}H NMR (400 MHz, DMSO-d6)



^{1}3C NMR (176 MHz, DMSO-d6)