

Metal-Mediated Self-Assembled Architectures of Structured Peptides

**विद्या वाचस्पति की
उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध**

**A thesis submitted in partial fulfillment of the requirements
of the degree of Doctor of Philosophy**

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INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE

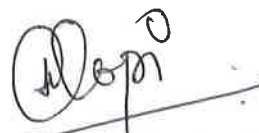
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***Dedicated to My Teachers, Family,
and Friends....***

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled “**Metal-Mediated Self-Assembled Architectures of Structured Peptides**” submitted by **Souvik Roy (ID No. 20183592)** carried out by the candidate at the Indian Institute of Science Education and Research (IISER), Pune, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or Institution.

Date: 13-03-2024



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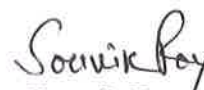
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Declaration

I hereby declare that the thesis entitled “**Metal-Mediated Self-Assembled Architectures of Structured Peptides**” submitted for the degree of Doctor of Philosophy in Chemistry at Indian Institute of Science Education and Research (IISER), Pune has not been submitted by me to any other University or Institution. This work was carried out at Indian Institute of Science Education and Research (IISER), Pune, India under the supervision of Prof. Hosahudya N. Gopi.

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Abbreviations

Ac₂O = Acetic anhydride

ACN = Acetonitrile

AcOH = Acetic acid

Aib = α -Amino isobutyric acid

aq. = Aqueous

Bn = Benzyl

Bpy = Bipyridine

Boc = tert-Butoxycarbonyl

(Boc)₂O = Boc anhydride

^tBu = tertiary Butyl

Calcd. = Calculated

CD = Circular Dichroism

CCDC no. = Cambridge Crystallographic Data Centre number

CIF = Crystallographic Information File

d γ = dehydro gamma

DCC = N, N' –Dicyclohexylcarbodiimide

DBU = 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCM = Dichloromethane

DIPEA = Diisopropylethyl Amine

DMAP = 4-Dimethylaminopyridine

DMF = Dimethylformamide

DMSO = Dimethylsulfoxide

Et = Ethyl

EtOAc = Ethyl acetate

EDC.HCl = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

EtOH = Ethanol

Fmoc = 9-Fluorenylmethoxycarbonyl

Fmoc-OSu = N-(9-Fluorenylmethoxycarbonyloxy) succinimide

g = gram

h = hours

H-bond = Hydrogen bond

HATU = Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

HBTU = 2-(1H-benzotriazol-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate

HCl = Hydrochloric acid

HOAt = 1-Hydroxy-7-azabenzotriazole

HOBt = Hydroxybenzotriazole

IBX = 2-Iodoxybenzoic acid

IR = Infrared Spectroscopy

LAH = Lithium Aluminium Hydride

M = Molar

MALDI-TOF/TOF = Matrix-Assisted Laser Desorption/Ionization-Time of Flight

Me = Methyl

MeOH = Methanol

mg = Milligram

min = Minutes

μL = Micro liter

mL = Milliliter

mM = MilliMolar

mmol = millimoles

MS = Mass Spectroscopy

N = Normal

NHS = N-hydroxy succinimide

NMP = N-methyl pyrrolidone

NMR = Nuclear Magnetic Resonance

ORTEP = Oak Ridge Thermal-Ellipsoid Plot Program

PG = Protecting Group

ppm = Parts per million

Py = Pyridine

PL = Photoluminescence Spectroscopy

R_f = Retention factor

RP- HPLC = Reversed Phase-High Performance Liquid Chromatography

R_t = Retention time

RT = Room Temperature

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

TEM = Transmission Electron Microscopy

UV = Ultraviolet-Visible Spectroscopy

Abstract

Metalloproteins, a fascinating class of biomolecules, incorporate metal ions into their structures to perform critical functions such as catalyzing reactions, transferring electrons, and transporting oxygen. Inspired by the intricate designs and functionalities of metalloproteins, significant efforts have been invested in the literature in emulating their structures and activities. These efforts involve the utilization of both natural and non-natural amino acid building blocks and their intricate interactions with diverse metal ions. Metal-ion-coordinated supramolecular architectures of peptides have attracted considerable attention in recent years due to their close resemblance to metalloproteins and also en route to creating artificial enzymes and catalysts. In the present work, we explored structured peptides as metal coordination templates to understand the supramolecular architectures of protein secondary structure mimetics. The designed short tripeptide 3_{10} -helices terminated by the pyridyl groups displayed remarkably diverse networks upon coordinating with the silver ion. The analysis revealed the anions of silver salts also play a significant role in the formation of diverse networks of 3_{10} -helices and silver ions. The inherent dipoles of the helical peptides in silver-coordinated networks were further explored for the second harmonic generation response. Further, we observed a subtle change in the sequences of peptides that leads to a transformation from helix into beta-turns upon metal coordination. In contrast to 3_{10} -helical structures from α -peptides, the alpha, gamma, alpha-hybrid tripeptides, composed of saturated gamma-amino acids, exhibit stable C_{12} helical structures both in single crystals and the solution state. We further examined the utility of C_{12} -helices in the design of metal-helix networks. Utilizing Ag^+ , Zn^{2+} , Cd^{2+} , and lanthanide ions (Tb^{3+} and Eu^{3+}), we elucidated the organization of helical structures. In the presence of Tb^{3+} and Eu^{3+} ions, the peptides showed photoluminescence properties. Instructively, the same tripeptide helices form gels in active methylene solvents. Overall, the presented research elucidates a novel avenue for the exploration of short helices as innovative tools in the design and development of peptide-based biomaterials and porous networks.

Publications

1. **Souvik Roy**, Aman Chaturvedi, Sanjit Dey, DRGKoppalu R. Puneeth Kumar, Saikat Pahan, Souvik Panda Mahapatra, Pankaj Mandal, and Hosahudya N. Gopi. “Anion Tuned Structural Modulation and Nonlinear Optical Effects of Metal-Ion Directed 3_{10} -Helix Networks.” *Chem. Eur. J.* **2023**, 29, e2023031.
2. **Souvik Roy**, Sanjit Dey, and Hosahudya N. Gopi. “Active Methylene Organic Solvent Driven $\alpha\alpha$ -Hybrid Peptide Based Gelation.” *Manuscript Under Submission*.
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Chapter 1

General Introduction of Metallopeptide Foldamers Composed of Natural and Unnatural Amino Acids

1. Introduction:

Nucleic acids, lipids, carbohydrates, and proteins are among the different biomolecules that perform a variety of biological functions in all living organisms. The most significant biomolecules among them are proteins and metalloproteins.^{1a} The intricate three-dimensional structures of proteins are fundamental in executing their varied biological function. Nature utilized 20 different amino acids to construct proteins, each of the proteins with specific three-dimensional arrangements and functions. Any misfolding or conformational alterations in proteins can result in severe diseases such as Alzheimer's disease, cystic fibrosis, Parkinson's disease, and diabetes.^{1b} Consequently, comprehending the intricate relationship between protein structure and its function is crucial for advancing our understanding of these diseases and developing effective treatments.

1.1. Protein Structure:

Proteins, fundamental macromolecules in living organisms, are composed of amino acid chains folded into intricate three-dimensional structures.² The specific sequence of amino acids in a protein, encoded by genes, dictates its unique structure and function. Proteins exhibit four hierarchical structural levels: primary, secondary, tertiary, and quaternary structures shown in Figure 1.

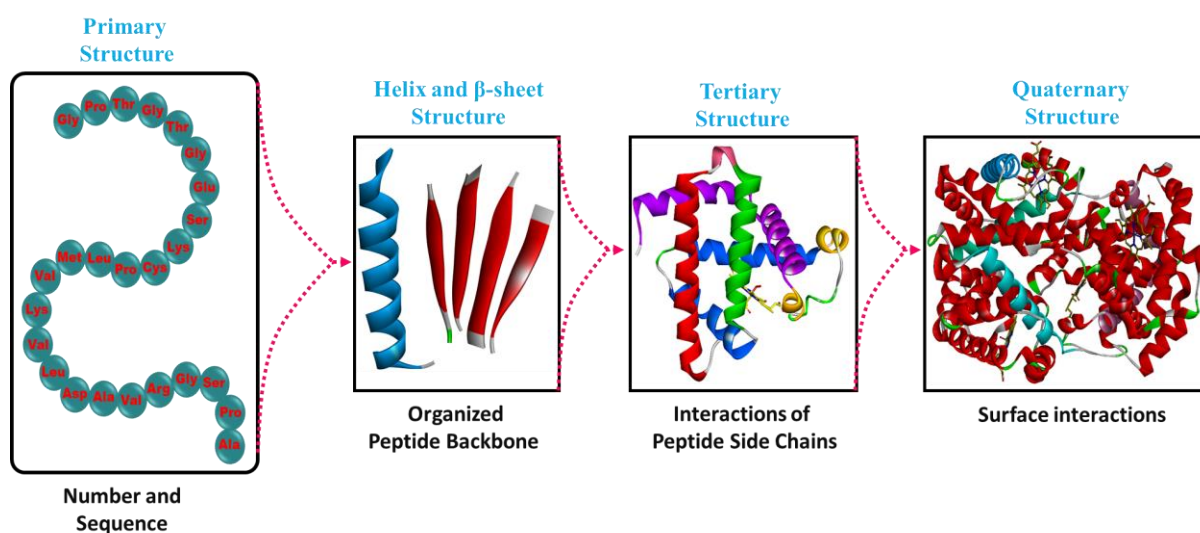


Figure 1: Schematic representation of the four levels of structural arrangement of proteins. (PDB code for Helix and β -sheet structures is 6MRS, Tertiary structure is 1MBO, and Quaternary structure is 3D4X.)

Primary Structure: The primary structure refers to the linear sequence of amino acids in a protein chain. Each amino acid is linked to the next through peptide bonds, forming a polypeptide chain.

Secondary Structure: Protein secondary structure describes the constrain, recurring structural patterns that emerge within a protein chain due to hydrogen bonding interactions between the backbone atoms of amino acids causing the polypeptide chain to fold into specific patterns. Alpha helices and beta sheets are the two most prevalent kinds of protein secondary structures.

Tertiary Structure: Tertiary structure is the unique three-dimensional arrangement of the entire polypeptide chain, enclosing the spatial arrangement of secondary structure elements along with loosely structured loops. These tertiary structures are compact and highly organized, crucial for the functional integrity of proteins. The formation of tertiary structures involves a complex interplay of diverse intermolecular forces like hydrogen bonds, disulfide bridges, van der Waals forces, hydrophobic interactions, and ionic bonds. The tertiary structure determines the protein's overall shape and its functional specificity.

Quaternary Structure: The quaternary structure of a protein refers to the spatial arrangement resulting from the interaction and association of multiple individual subunits. These subunits, often tertiary structural entities in their own right, closely align to form a functional macromolecular complex. The stabilization of these quaternary structures is facilitated by a variety of intermolecular forces, primarily electrostatic interactions.

1.2. Protein Secondary Structure:

The local folded structures that arise within a polypeptide chain are referred to as protein secondary structures. Proteins are made up of long chains of amino acids, and these chains can adopt specific shapes and structures due to interactions between the amino acids. In 1951, Linus Pauling and colleagues identified α -helix and β -sheet structures in protein.³ In proteins, loops are loosely structured peptides that connect the secondary structural units to one another. Two adjacent β -strands that are anti-parallel to one another are joined by loop provinces known as reverse turns. In their seminal research, G. N. Ramachandran and colleagues introduced a groundbreaking analytical tool, commonly referred to as the Ramachandran plot.⁴ This plot was devised to elucidate stable secondary structures by systematically mapping the torsion angle parameters of amino acids within peptide chains. This method has become a cornerstone in the field of structural biology, facilitating a deeper understanding of protein folding and function.

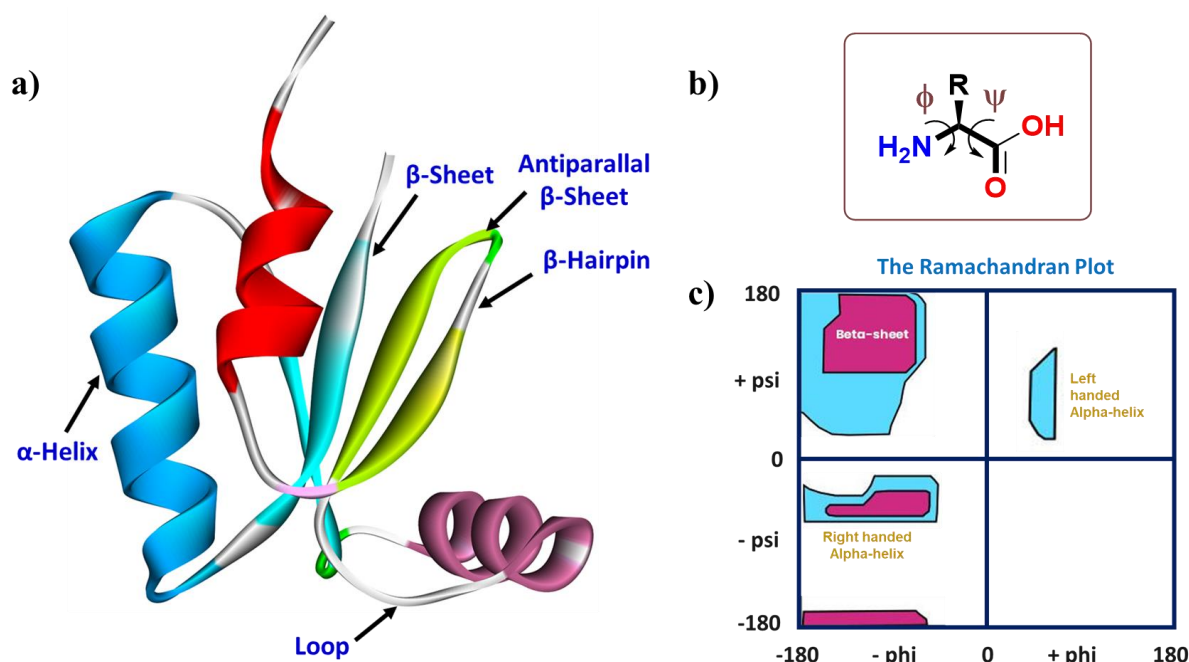
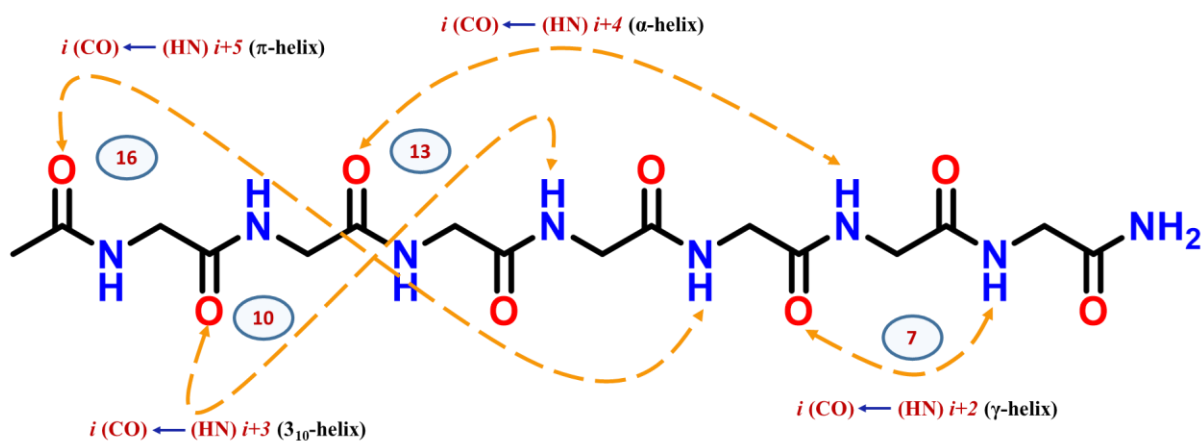


Figure 2: a) A ribbon representation of different protein secondary structures (PDB Code: 1H75). b) Torsion angle parameter of α -amino acids. c) The standard Ramachandran plot and the allowed region for the torsional angles of different secondary structures.

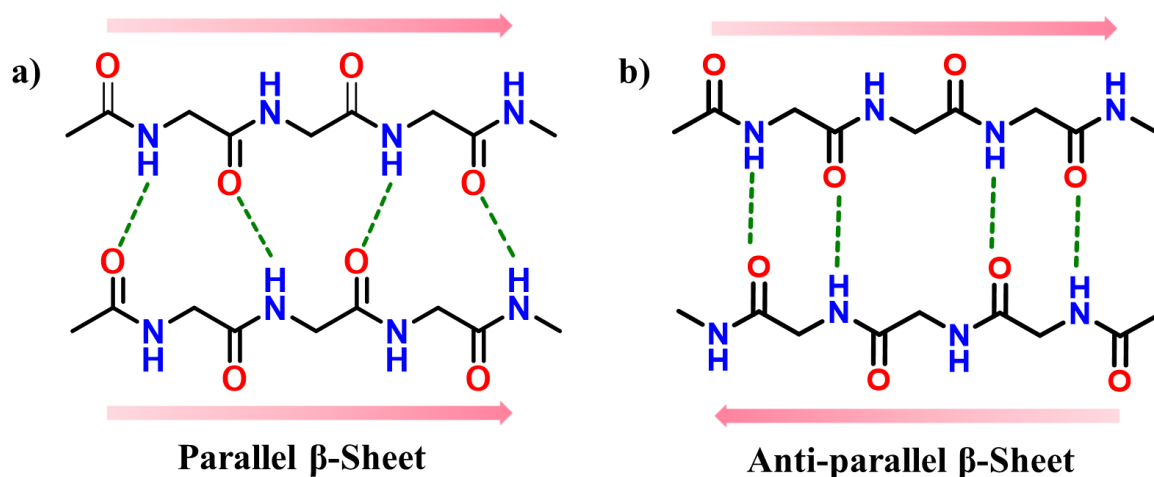
Helices: Helical structures constitute a predominant component of protein secondary structures, crucial for their stability and functionality. The stabilization of helices in proteins and peptides occurs through intermolecular hydrogen bonding interactions involving the carbonyl (CO) and amide (NH) groups of the polypeptide backbone, denoted as CO...HN hydrogen bonds. Helices are methodically categorised into four distinct categories: 2.2_7 -helix (γ -helix), 3_{10} -helix, 3.6_{13} -helix (α -helix), and 4.4_{16} -helix (π -helix). Among these classifications, the α -helix, a fundamental helical structure, was first described by Linus Pauling in 1951.³ The α -helix is stabilized by 13-membered intramolecular hydrogen bonds, where CO groups of the i^{th} amino acid form bonds with NH groups of the $(i+4)^{\text{th}}$ amino acid, denoted as $(i \leftarrow i+4)$ interactions in the polypeptide backbone. This helical structure encompasses 3.6 amino acid residues per turn and is represented as 3.6_{13} -(P)-helix, indicating its right-handedness (P) and average torsion parameters ϕ of approximately -60° and Ψ of -45° in the Ramachandran plot. In contrast, the 3_{10} -helix is a rare helical structure stabilized by 10-membered hydrogen bonding pseudo-cycles. These interactions occur between CO groups of the i^{th} amino acid and NH groups of the $(i+3)^{\text{th}}$ amino acid, denoted as $(i \leftarrow i+3)$ interactions in the polypeptide backbone. The average torsion parameters for the 3_{10} -helical structures are approximately $\phi = -49^\circ$ and $\Psi = -26^\circ$. Additionally, the π -helix is characterized by a 4.4_{16} -(P)-helical structure,



Scheme 1: Representation of different types of helices through its H-bonding

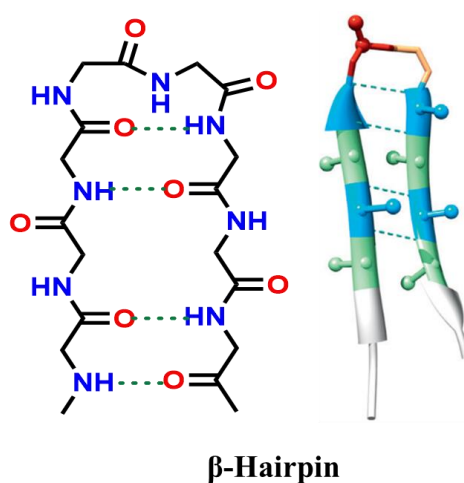
with torsion angles ϕ of approximately -55° and Ψ of -70° , while the γ -helix is represented as 2.2 γ -helix with ϕ of approximately -70° and Ψ of 70° . These diverse helical structures are essential elements of protein folding, each offering unique insights into the intricate hydrogen-bonding patterns governing protein stability. Scheme 1 displays a schematic representation of the various forms of H-bonding in various helical structures.

β -Sheets: β -sheets represent a prominent secondary structural motif observed in proteins, constituting the second major structural element after α -helices. Typically, β -sheets consist of 5 to 10 amino acid residues adopting a fully extended conformation. The torsion angles ϕ and Ψ values defining these structures fall within the permissive region of the Ramachandran Map's³ upper left quadrant, adhering to structurally allowed conformations. The concept of β -sheet structures was first introduced by William Astbury in 1931.⁵ However, it was further refined by Linus Pauling and Robert Corey in 1951.⁶ β -sheets are classified into two primary arrangements based on the directionality of the constituent β -strands: (i) parallel β -sheets, where neighboring strands run in the same direction, and (ii) anti-parallel β -sheets, where adjacent strands run in opposite directions. In the tertiary structure of proteins, β -sheets are frequently oriented at approximately 30° angles to each other within the β -sheet structure. This specific arrangement highlights the intricate spatial organization and geometric intricacies governing the formation of β -pleated sheets in proteins, highlights their essential role in the overall architecture and stability of protein tertiary structures.



Scheme 2: Representation of different types of β -sheets through its H-bonding and directionality
a) Parallel β -sheet b) Anti-parallel β -sheet.

Reverse Turns: Reverse turns, recognized as significant secondary structural motifs in proteins, play a crucial role in the overall folding and stability of protein structures. These turns are systematically classified based on the number of amino acid residues involved in inducing the reverse directionality of the polypeptide chain. The classification includes π -turns (involving 6 amino acids), α -turns (involving 5 amino acids), β -turns (involving 4 amino acids), γ -turns (involving 3 amino acids), and δ -turns (involving 2 amino acids).⁷ Among these, β -turns stand out as the most prevalent in protein structures. The occurrence of β -turns is highly influenced by the dihedral angles ϕ (phi) and ψ (psi) of residues at positions $i+1$ and $i+2$ within the polypeptide chain. Based on these angles, β -turns are further subclassified into type I, II, and III, as well as their mirror image counterparts, known as type I', II', and III' turns, respectively.⁸



Scheme 3: Representation of β -Hairpin through its H-bonding and cartoon diagram.

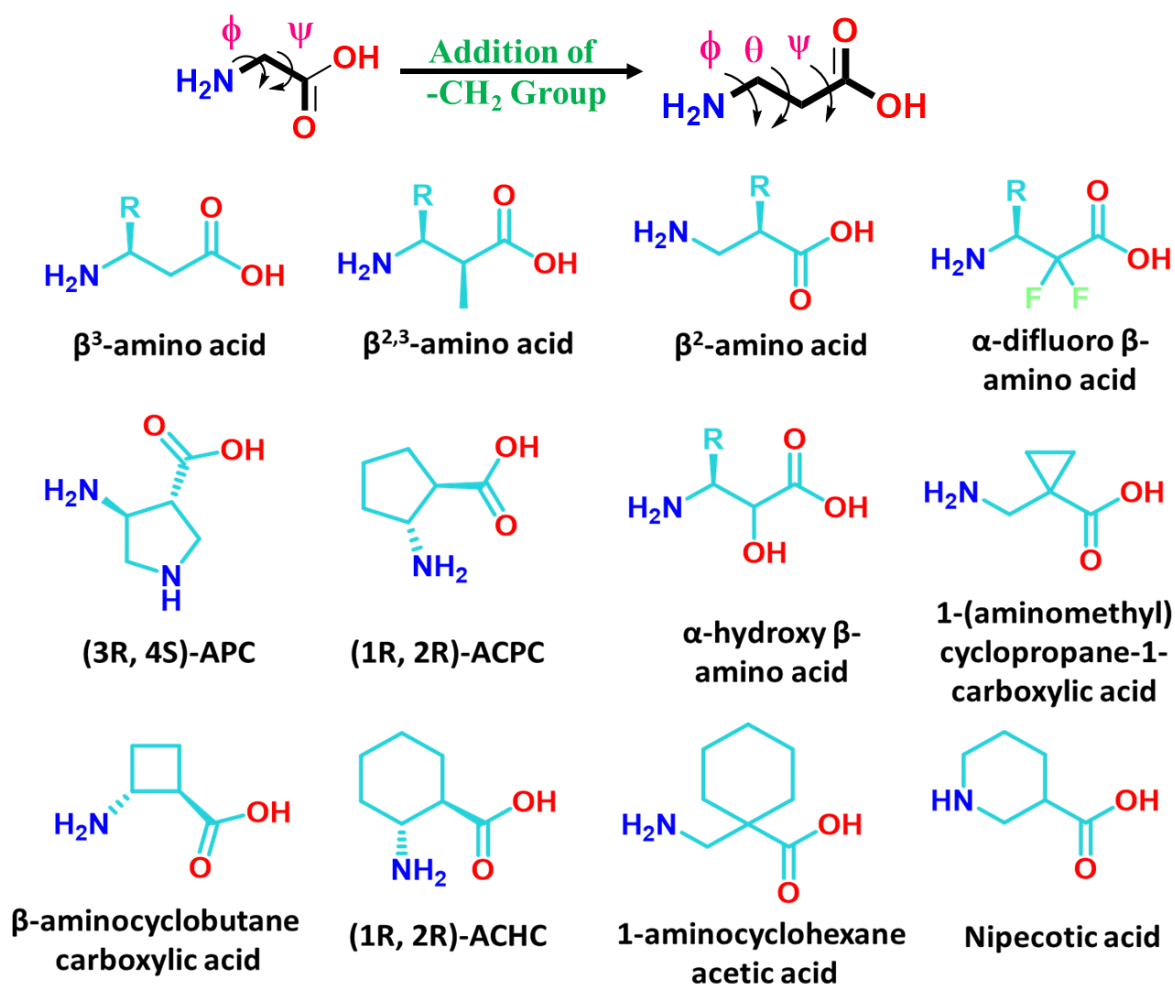
1.3. Mimicking of Protein Secondary Structures:

The intricate exploration of protein structural and functional attributes has attracted chemists to delve into the area of protein structure mimetics, employing non-natural amino acid building blocks. In recent decades, concerted efforts have been devoted to fabricating intricately folded architectures utilizing α -amino acid units.⁹ Numerous functional biomaterials and biologically significant peptide-based drug candidates have been produced by de novo design techniques and the imitation of protein secondary structures. Despite the advancements, inherent limitations such as susceptibility to proteolysis, susceptibility to undesirable protein-protein interactions, and restricted biological activity have encouraged us to integrate non-natural amino acid building blocks.¹⁰ The construction and systematic study of a broad range of protein secondary structures has been made possible by the integration of various non-natural amino acids. Notably, oligomers derived from β - and γ -amino acids have emerged as focal points in the area of designing protein structure mimetics. These non-natural β - and γ -amino acid-based foldamers present a distinctive opportunity for the creation of protein structure mimetics encompassing mixed sequences, including α,β -, α,γ -, and β,γ - sequences. This innovative approach offers nuanced solutions for overcoming the limitations of natural amino acid-based peptides and proteins, thus paving the way for the development of advanced biomaterials and therapeutics.

1.3.1. β -Amino acid mediated Peptide Foldamers:

The nomenclature "Foldamers" was first introduced by Professor Samuel H. Gellman, who defined it as "*any oligomer which can adopt a rigid conformation in solution*".^{10a} Within the domain of foldamers, molecular can adopt diverse structural configurations or geometries, thereby attaining the most thermodynamically stable conformation and minimizing their energy state. β -amino acids, a homologated class of α -amino acids have been extensively employed in the fabrication of distinct protein secondary structural motifs. In β -amino acids, the additional $-\text{CH}_2$ between amine ($-\text{NH}_2$) and carboxyl ($-\text{COOH}$) groups provides an extra torsional parameter θ ($\text{C}^\alpha\text{-C}^\beta$) in addition to ϕ and Ψ angle of α -amino acid. This additional torsional angle parameter provides leverage for the designing of diverse secondary structures of peptides and proteins. β -amino acids, which are also categorized into β^2 and β^3 - amino acids depending on the position of the substituted side chain shown in scheme 4. The distinct folded structures obtained from the β -peptides indicated that the folding of β - and higher homolog peptides are beneficial for comprehending the intricate protein folding process, as well as being an excellent choice for medicinal chemistry and drug discovery. An additional merit of β -amino

acids in comparison to α -amino acids resides in their proteolytic stability, as they demonstrate resilience against various proteases. This attribute has been utilized for applications in intracellular drug delivery.¹¹



Scheme 4: chemical representation of different β -amino acids with their torsion angle different from the α -amino acids used for peptide foldamers.

In their pioneering contributions, Seebach¹² and Gellman¹³ independently advanced the application of acyclic chiral and cyclic β -amino acids, respectively, in the systematic construction of diverse folded architectures. Seebach's pioneering work delved into the utilization of acyclic chiral β -amino acids, while Gellman and colleagues specifically employed cyclic *trans*-2-amino cyclopentanecarboxylic acid (ACPC) and *trans*-2-aminocyclohexanecarboxylic acid (ACHC) (Figure 4). Their investigations revealed that oligomers derived from these cyclic β -amino acids, namely ACPC and ACHC, exhibited a propensity to adopt 12- and 14-helical conformations, respectively. In continuation, Sharma¹⁴ and collaborators contributed to the field by reporting the formation of 10/12 or 12/10 mixed

helical structures derived from carbo- β -amino acid oligomers. This seminal work gives insight into the diverse structural motifs achievable through the strategic incorporation of non-natural amino acids. Additionally, the Atkins¹⁵ and Fulop¹⁶ research groups have made noteworthy contributions by employing various cyclic amino acids as building blocks for the construction of β -peptide foldamers. The structural analysis of β -amino acid-based peptides reveals a distinctive hydrogen-bonding pattern in contrast to that of α -amino acid-based peptides. β -peptides exhibit a capacity for organized secondary structures, including helices, sheets, and turns. Notably, the β -peptide helices manifest diverse folding patterns and hydrogen-bonding arrangements contingent upon the specific β -residue interactions within the polypeptide chain. The noticeable categorizations of β -peptide helices include C₈-, C₁₀-, C₁₂-, and C₁₄- helices, with each designation denoting the respective number of atoms in a helical turn.¹⁷⁻¹⁹ The different H-bonding patterns in helices are shown in Figure 3.

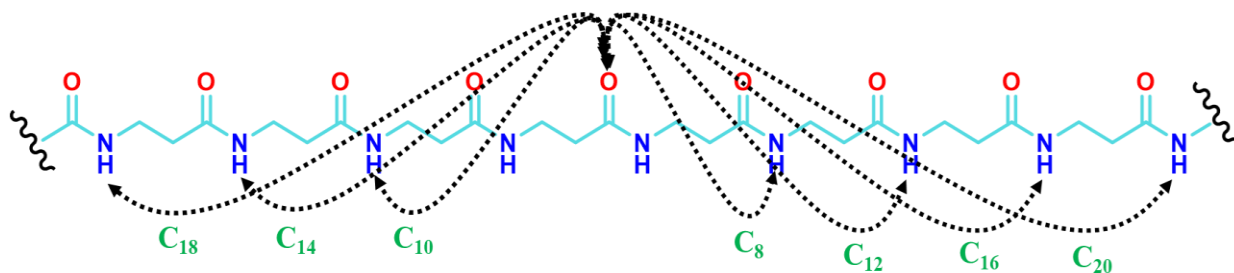


Figure 3: Observed H-bonding patterns for β -peptide-based foldamer.

In addition to helical structures, parallel and antiparallel sheets, as well as β -hairpin structures, have been documented in β -amino acid oligomers. Notably, the conformational landscape of cyclic β -amino acids with distinct ring constraints, such as *trans*-2-aminocyclohexane carboxylic acid,²⁰ exhibits 14-helical conformations, while homooligomers of cyclic β -amino acids constrained by four (e.g., *trans*-2-aminocyclobutane carboxylic acid),¹⁵ five (e.g., *trans*-2-aminocyclopentane carboxylic acid and derivatives),²¹ and a bicyclic [3.3.1] heptane skeleton²² consistently adopt stable 12-helical conformations. Furthermore, pioneering work by Balaram and colleagues underscores the utility of synthetic β -amino acids in the construction of helices and β -hairpins.²³ Their investigations encompass the study of β -hairpin structures^{23a} and three-stranded β -sheets^{23c} achieved through the incorporation of β -Phe residues positioned at opposite faces of anti-parallel β -strands, with the turn facilitated by ^DPro-Gly^{23a, 23b} (Figure 4).

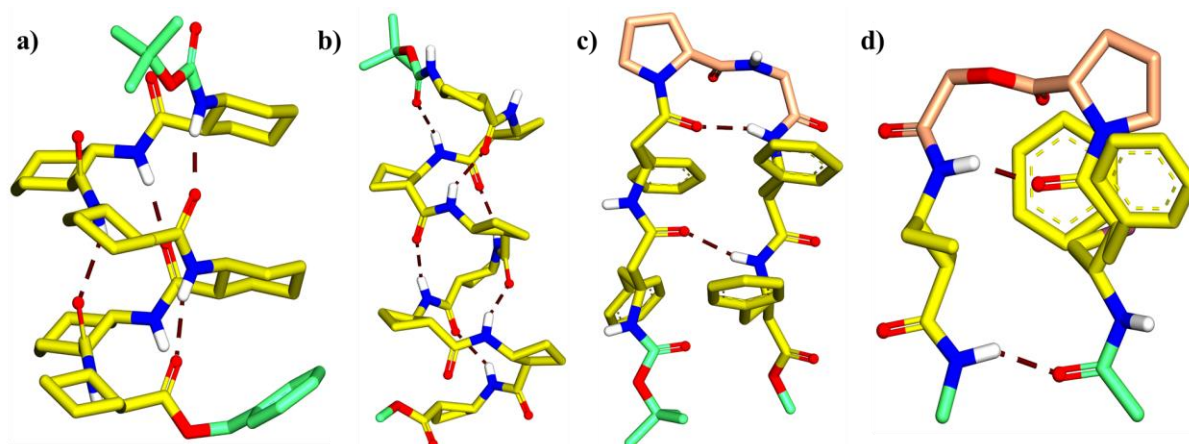


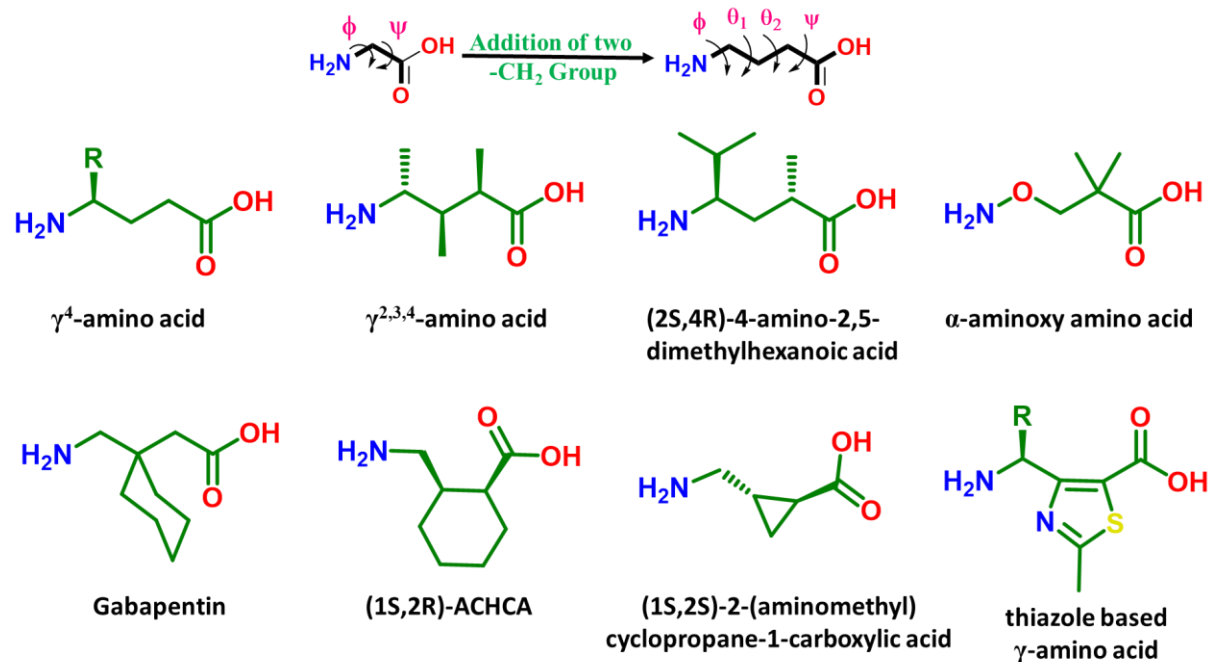
Figure 4: Crystal structure of β -peptide foldamers a) C₁₄ helix from *trans*-ACHA.^{13a} b) C₁₂ helix from cyclobutane β -amino acid.¹⁵ c) β -hairpin conformation constructed from β -amino acids containing α,β -disubstituted β -amino acids,^{23a} and d) β^3 -amino acids.^{13d}

The major distinction within the β -sheets lies in the directionality of the hydrogen bonds, which significantly influences the resultant structural and functional properties of these β -sheet architectures. In the context of α -peptides, the hydrogen bonding patterns manifest alternately in directionality, giving rise to an apolar β -sheet configuration. In contrast, the hydrogen bonding interactions in β -peptides yield a polar sheet wherein the hydrogen bonds are oriented in the same direction. This distinctive disparity in hydrogen bond orientation contributes to the divergent structural characteristics observed between β -sheets formed by α -peptides, which exhibit an apolar nature, and those formed by β -peptides, characterized by a polar sheet configuration.

1.3.2. γ -Amino acid-Induced Peptide Foldamers:

γ -amino acids represent homologated analogs of β -amino acids and doubly homologated species of α -amino acids. They are characterized by the extension of the amino acid backbone by two additional $-\text{CH}_2$ groups between $\text{C}=\text{O}$ and C^α carbon which provides extra backbone torsion angles θ_1 ($\text{C}^\beta\text{-C}^\alpha$) and θ_2 ($\text{C}^\gamma\text{-C}^\beta$) along with ϕ and ψ . Due to the incorporation of two additional backbone atoms, γ -peptides are anticipated to exhibit heightened structural diversity relative to their α - and β -peptides counterparts. Prof. Seebach highlighted that *the structural diversity of γ -amino acids and γ -peptides have not been elucidated nearly as well as that of β -peptides: it is expected to be richer.*²⁴ The exploration of foldamers based on γ -amino acids has been relatively limited, likely due to the inherent challenges associated with the synthesis and isolation of stereochemically pure γ -amino acids. There are various types of γ -

amino acid based building blocks that are used for designing of γ -peptide foldamers are shown in Scheme 5.



Scheme 5: chemical representation of different γ -amino acids with their torsion angle different from the α -amino acids used for peptide foldamers.

Seebach²⁵ and colleagues, and Hanessian²⁶ and co-workers have documented stable right-handed 14-helical conformations derived from γ -amino acid oligomers through comprehensive NMR studies. Furthermore, Hoffman and collaborators have contributed to the understanding of helical structures in γ -peptides through *ab initio* theoretical calculations.²⁷ Their findings indicate a broad spectrum of helical conformations, with C_{14} - and C_9 -helices identified as particularly stable structures. Subsequent experimental validation of the predicted C_9 -helical structure was undertaken by Sharma and colleagues, who demonstrated its existence in the context of alternating C-linked carbo- γ^4 -amino acid and γ -aminobutyric acid (GABA) sequences.²⁸ In their detailed investigation, Balaram and colleagues documented the observation of C_9 helical conformations within single crystals of gabapentin (3, 3-dialkyl- γ -amino acid).²⁹ The stability of the C_9 helical structure was attributed to hydrogen-bonding interactions between residues at positions i and $i + 2$. Additionally, Balaram and collaborators reported the identification of C_{14} helical conformation within the oligomer of γ^4 -amino acids featuring proteinogenic side chains (γ^4 -Val, γ^4 -Leu, γ^4 -Ile) in single crystals.³⁰ Again, Gellman and co-workers contributed to the understanding of stable C_{14} helices derived from cyclic γ -

amino acids.^{31, 32} The single crystal structures of C₉- and C₁₄-helices produced from γ -peptide foldamers are shown in Figure 5.

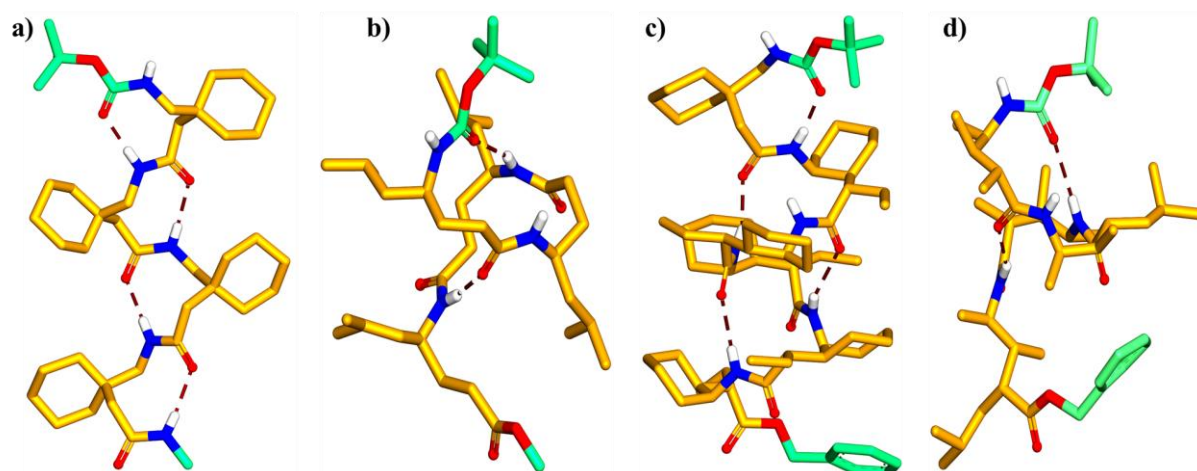


Figure 5: Crystal structure of a) C₉-helix of gabapentin oligomers²⁹ b) C₁₄-helix of γ^4 -peptide oligomer³⁰ c) C₉ helical conformations of heterooligomers of cyclic γ -amino acid³¹ d) C₁₄ helix of the $\gamma^{2,3,4}$ -oligomer peptide.^{24b}

Smith and collaborators conducted a comprehensive study involving the synthesis and conformational analysis of cyclopropane-based γ -amino acids.³³ Their investigation revealed that oligomers of these γ -amino acids adopted parallel-type β -sheet structures, which were stabilized by bifurcated hydrogen bonds involving the carbonyl oxygen, the amide NH group, and one CH of the cyclopropane ring in the solid state. Expanding on these structural insights, the researchers leveraged these amino acids as non-peptidic reverse turns in the design of β -hairpins, showcasing their versatility in contributing to the construction of intricate secondary structures. In addition to cyclic γ -amino acids, diverse backbone architectures featuring oxygen and nitrogen atoms have been investigated for the design of functionally versatile foldamers. Yang and collaborators, for instance, reported the emergence of C₈ helical conformations within α -aminoxy peptides.³⁴ Furthermore, Guichard and colleagues harnessed oligourethane-based peptide foldamers, wherein the γ^3 -carbon in the γ -peptide backbone was replaced with NH, demonstrating an innovative approach to foldamer design.³⁵ In a recent study, Millard and colleagues detailed the formation of C₉ helices within homooligomers of 4-amino-(methyl)-1,3-thiazole-5-carboxylic acids (ATCs), thereby expanding the repertoire of backbone structures explored for functional foldamer architectures.³⁶ The different types of H-bonding patterns in helices containing γ -peptide are shown in Figure 6.

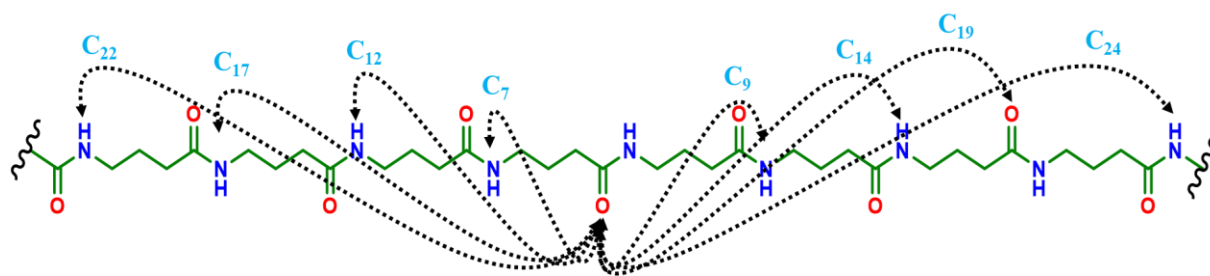


Figure 6: Possible H-bonding patterns for γ -peptide-based foldamer.

1.3.3. Heterogeneous Peptide Foldamers Containing α , β - amino acids:

Because different types of helices with different H-bonding patterns can be derived through proper mixing of different types of amino acids, peptide foldamers with heterogeneous backbones have gained much more momentum in recent years compared to their homogeneous counterparts. In their seminal investigations, Balaram and colleagues pioneered the synthesis of hybrid peptides by strategically incorporating β -amino acids within the framework of host α -peptides.³⁷ Hofmann and coworkers conducted comprehensive quantum mechanical calculations to predict a spectrum of helical conformations accessible to α , β -hybrid peptides. Their theoretical framework proposed the potential generation of various helices, including 9-, 11/9-, 9/11-, 11-, 12/13-, 15/14-, 16/18-, and 18/16-helices, within the context of α , β -hybrid peptide structures.³⁸ Sharma and colleagues reported the presence of an 11/9-helical conformation characterized by alternating hydrogen bonding directions within an α , β -sequence, which incorporated both α - and β -amino acids.^{39, 40} In a distinctive investigation, the research team led by Gellman employed crystal structure to elucidate the conformation of short α , β -hybrid peptides comprised of backbone-constrained trans-ACPC amino acids (trans-2-aminocyclopentane carboxylic acid) and Aib residues. Their findings demonstrated the transformation of 11-helices into 14/15-helices upon the substitution of terminal Aib residues with alanine.⁴¹ This observation suggested minimal energy difference between the two helical types. Again, Gellman and colleagues also demonstrated the formation of $C_{11/11/12}$ and $C_{10/11/11}$ -helices in a 1:2 and 2:1 ratio, respectively, within the context of α , β -hybrid peptides.^{42a} In their investigation, Fulop and colleagues showed the impact of stereochemical patterns in the design of α , β -hybrid peptides, revealing their capacity to adopt diverse helical structures.^{42b} Comparable findings were independently reported by Sharma and collaborators.^{42c-f} Apart from the secondary structural mimetics, Gellman and colleagues reported the formation of helix bundle quaternary structures within hybrid α/β -peptide foldamers specifically the oligomers consisting of β - β - α - β - β and α - α - α - β - α - α - β repeats.^{42g-h} There are some α , β hybride peptide

foldamers are shown in Figure 7.

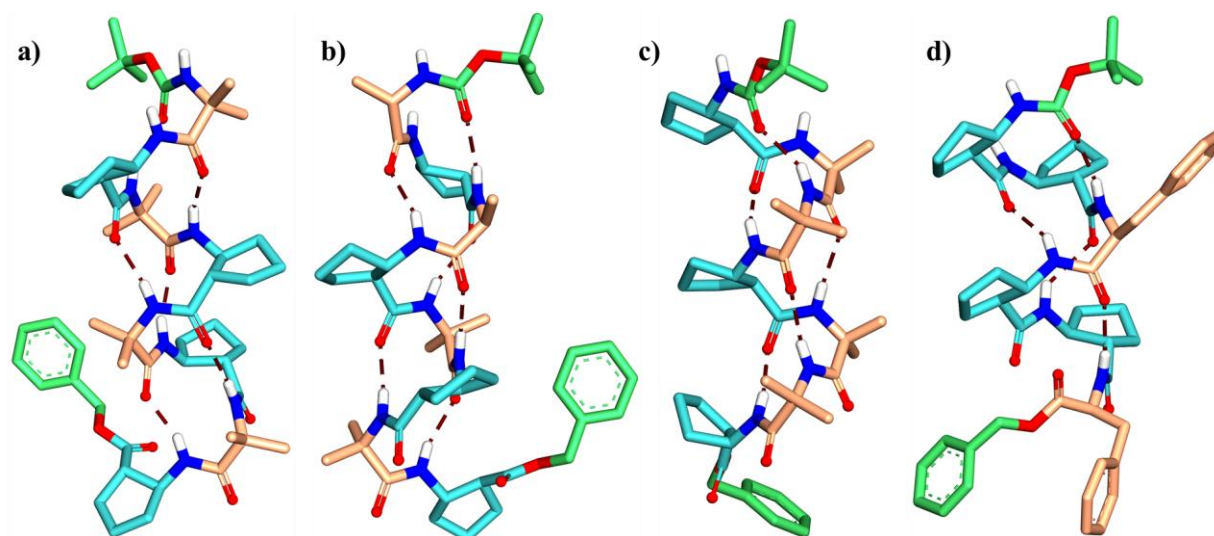


Figure 7: α , β -hybride peptides form different types of helices a) C_{11} helix consisting of Aib and ACPC residues.^{41b} b) 14/15-helical structure consisting of Ala, ACPC, and Aib residues.^{41c} c) 10/11/11-helical structure of 2:1 α,β -hybrid peptide.^{42a} d) 12/11/11-helical structure of 1:2 α,β -hybrid peptide.^{42a}

1.3.4. Heterogeneous Peptide Foldamers Containing α , γ - amino acids:

Analogous to the investigations on mixed α , β -hybrid peptides, research endeavors have been directed towards exploring α,γ -hybrid peptide foldamers in the literature. These hybrid peptides involve a combination of α -amino acids and γ -amino acids in their backbone, presenting a distinct avenue for the design and study of novel peptide architectures with diverse structural and functional properties. Hofmann and colleagues conducted an analysis predicting a range of helical conformations obtainable within 1:1 alternating α - and γ -amino acids.⁴³ Within this spectrum of helix types, their projections indicated that the 12-helix emerged as the most thermodynamically stable, followed by 12/10- or 18/20-helices, thus providing insights into the potential structural preferences within 1:1 α,γ -hybrid peptide sequences. In subsequent investigations, Balaram and co-workers contributed to the understanding of helical conformations within α,γ -hybrid peptides. They reported the stabilization of a stable 12-helix within the α,γ -hybrid peptide comprised of a 1:1 ratio of Aib and gabapentin (Gpn) residues.^{44a} Additionally, they observed a stable 12-helix formation in the context of a 1:1 ratio of α -amino acids and γ -amino acids.^{44b} In both instances, the helical structures were characterized by intramolecular hydrogen bonding between residues at positions i and $i+3$, highlighting the role of such interactions in stabilizing these specific helical configurations. Sharma and colleagues

conducted a study examining various 12/10-helices within the framework of α,γ -hybrid peptides, specifically those composed of L-Ala and γ -Caa (C-linked carbo- γ -amino acid).⁴⁵ In a related endeavor, Gellman's research group demonstrated the design, synthesis, and characterization of diverse α/γ -peptides featuring sterically constrained cyclic γ -amino acids.⁴⁶ Beyond crystallographic characterization, they substantiated the presence of stable 12-helix structures in aqueous buffer through NMR studies, underscoring the versatility and aqueous stability of these α,γ -hybrid peptide architectures.⁴⁷ Furthermore, Balaram and colleagues employed α/γ -peptides to facilitate the stable formation of a reverse turn within a β -hairpin conformation.⁴⁸ In a recent investigation by Misra et al., a co-existence of 12-helices and 15/17-helices was reported in an achiral α/γ -hybrid peptide.⁴⁹ Notably, when the Aib residue in the hybrid peptide was replaced by conventional α -amino acids, the 12-helix underwent a transformation into a 12/10-mixed helical structure.⁵⁰ Several α,γ -hybrid peptide foldamers are shown in Figure 8.

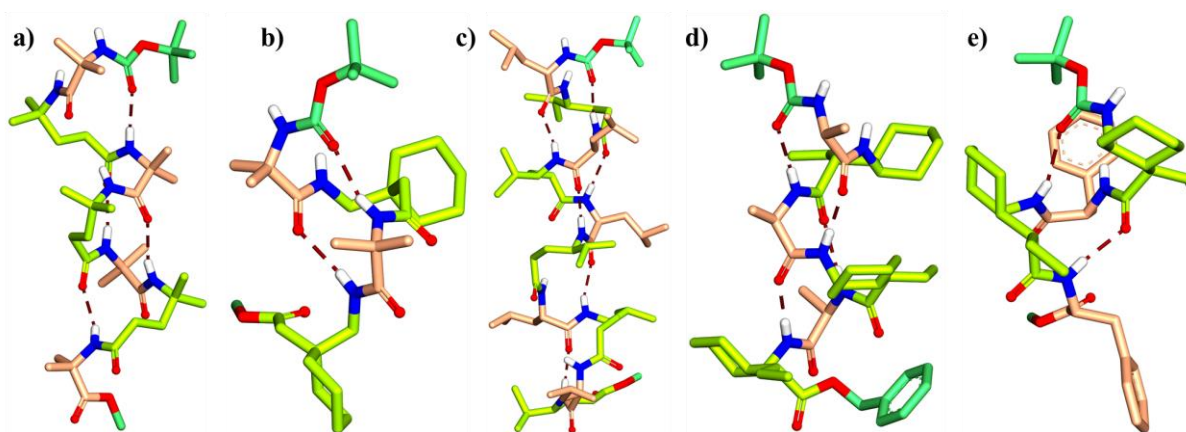


Figure 8: a) 12-helix from achiral α, γ -hybrid peptide consisting of Aib and γ -Aib residues.⁴⁹ b) 12-helix of α,γ -hybrid peptide foldamer.^{44a} c) 12-helix from chiral α, γ -hybrid peptide consisting of Leu and γ -Val residues.^{45c} d) 12-helix from α, γ -hybrid peptide consisting of D Ala and EtACHA residues.^{46b} e) 12-helix from α, γ -hybrid peptide consisting of Phe and EtACHA residues.^{46b}

Beyond the extensively studied α,β - and α,γ -hybrid peptides, limited literature exists regarding the conformational properties of β/γ - hybrid peptides. Additionally, Sharma and Kunwar reported the observation of a mixed 11/13 helical conformation within β/γ - hybrid peptides composed of C-linked carbo- β - and γ -amino acids in solution.⁵¹ Moreover, Balaram and colleagues reported the presence of a 13-helix structure within a short β, γ -hybrid peptide.⁵² Again, Gellman and co-workers demonstrated the formation of a 13-helix in β,γ -hybrid

peptides.⁵³ The helical parameters observed in the 13-helix from β,γ -hybrid peptides exhibit similarities to those characteristic of the α -helix. Additionally, Aitken and colleagues conducted a study on the 9/8-ribbon structure derived from β,γ -hybrid peptides incorporating stereochemically constrained β -amino acids, alongside an investigation into the 13-helix formation facilitated by unconstrained γ^4 -amino acids.⁵⁴

2. Biological Activity of Peptide Foldamers Containing β - and γ - amino acids:

Attributed to their robust proteolytic stability and inherent propensity to adopt distinct and well-defined structures, β,γ -, and the $\alpha\beta,\alpha\gamma$ -hybrid peptide foldamers have emerged as subjects of significant interest within the domains of medicinal chemistry and chemical biology.⁵⁵ Their unique structural characteristics and functional properties make them promising candidates for various applications, including drug development and biomolecular engineering. Gellman and co-workers reported the synthesis of an amphiphilic cationic 14-helical peptide derived from β -amino acids, demonstrating its potent antibacterial activity with notable specificity towards bacteria.⁵⁶ In addition to homooligomers derived from β -amino acids, they successfully designed and characterized amphiphilic α,β -hybrid peptides. These hybrid peptides exhibited significant antibacterial activity against a diverse range of Gram-negative and Gram-positive bacteria, underscoring their potential as effective agents for antibacterial applications.⁵⁷ Schepartz and colleagues conducted innovative research by designing p53 mimetics using β 3-peptides. These mimetics were employed as inhibitors for p53-MDM2 interactions,⁵⁸ showcasing their potential therapeutic relevance in modulating key protein-protein interactions. Additionally, the research group reported the design and synthesis of inhibitors targeting HIV-1 gp41-mediated fusion, presenting a strategic approach for developing therapeutic agents against HIV-1 infection.⁵⁹ Furthermore, investigations have been undertaken into the utilization of α,β -hybrid peptides for the purpose of designing inhibitors targeting the Bak/Bcl-xL interactions.⁶⁰ This approach represents a novel strategy in the development of inhibitors with potential therapeutic implications in the modulation of Bak/Bcl-xL interactions, a critical molecular event in cellular processes. Like β -peptide foldamers, Peptides composed of distinct γ -amino acids, including γ^2 -, γ^3 -, γ^4 -, and $\gamma^{2,3,4}$ -, have exhibited notable proteolytic stability when subjected to the action of 15 proteolytic enzymes, with no discernible degradation observed even after a 48-hour period.^{10b} Moreover, small γ -peptides have demonstrated submicromolar affinity towards various human somatostatin receptors,

highlighting their potential as ligands in receptor-mediated interactions. In addition to this, oligonucleotide analogues derived from γ -peptides and γ/ϵ -peptides have demonstrated robust binding affinity towards DNA or RNA.⁶¹ Furthermore, the exploration of N-functionalized hexamers of cis- γ -aminoproline has been undertaken, revealing their potential for cellular uptake.⁶² Again, the investigation of short α,γ -hybrid peptides has unveiled potent antimicrobial properties,^{63, 64} adding to the diverse range of functional applications attributed to these peptide analogues.

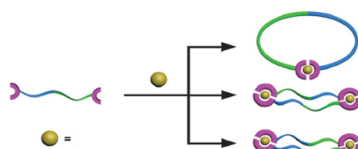
3. Application of Peptide Foldamers: From Biology to Materials:

It is commonly known that metal ions are vital components of many biological systems, taking part in processes like oxidative reactions, electron transfer, and catalysis. Approximately one-third of all known enzymes are classified as metalloenzymes,⁶⁵ characterized by the incorporation of metal ions or metallo-organic cofactors within their protein structures.^{66, 67} Beyond enzymes, various metalloproteins participate in non-enzymatic electron transfer reactions, exemplified by cytochromes. Additionally, certain metalloproteins function in storage roles, as observed in ferritin for iron, or act as transport proteins, such as transferrin for iron. A wide range of possible donor groups are involved in peptide-metal interactions, such as the amino group at the N-terminus, the carboxylate of the C-terminus, the amide carbonyl, and any non-aliphatic functional groups on the side chains.⁶⁸ Through their interactions with side chains, transition metal ions facilitate protein folding in addition to acting as catalysts in a variety of reactions. In their seminal research, Szostak and colleagues reported that peptides incorporating side-arm acidic residues such as Asp and Glu exhibit chelation capabilities with Mg^{2+} ions.⁶⁹ This property allows them to protect RNA molecules from degradation induced by Mg^{2+} ions. In the well-established DNA-binding Zn-finger motifs, zinc (Zn) plays a pivotal role in inducing a specific folding of the polypeptide motif into a compact domain through binding to Cys/His residues. Moreover, zinc ions exhibit noteworthy structural functions and catalytic properties within numerous zinc-containing metalloproteins and enzymes.⁷⁰ Iron-sulfur (FeS) proteins, vital for fundamental life processes, including CO_2 fixation facilitated by proteins like ferredoxin (Fd), rely on a diverse array of cysteine-containing tripeptides to stabilize iron-sulfur clusters.⁷¹ The coordination of metal ions with peptides induces a conformational change in the peptides, contributing to their structural and functional roles. Furthermore, Ghadiri and colleagues have elucidated that peptides featuring His residues can facilitate the conversion of a random coil conformation into an α -helical structure through interactions with imidazole side chains and a tetraammineruthenium (II) moiety.⁷² As a class

of ligands, synthetic peptides are appealing and compelling because they can encompass the characteristics found in both small molecules and proteins. Their attractive qualities include lipophilicity, polarity, charge, and a variety of functional groups. Notably, research has focused on the introduction of different metal-coordinating sites, explaining the ordered self-assembling characteristics of peptides.⁷³ The utilization of metal coordination emerges as a crucial determinant in guiding the systematic assembly of peptide molecules. This strategic approach provides a distinct advantage, allowing for the exploration of the functional attributes inherent in both peptides and metal ions. This exploration, in turn, facilitates the design of innovative self-assembled materials based on peptides and serves as a platform for creating mimetics of metalloproteins. Notably, recent work by Fujita and colleagues has demonstrated the generation of metal-dictated knotted networks through the use of short peptides.⁷⁴ In their pioneering investigations, the research groups led by Chmielewski⁷⁵ and Conticello⁷⁶ systematically examined the protein-like architectures arising from metal-mediated supramolecular assemblies of collagen and coiled-coil peptides. Their work encompassed detailed analyses of the structural intricacies, elucidating the molecular interactions and potential applications in biomolecular mimicry and materials science. In the current investigation, we have undertaken an exploration into the utilization of short tripeptide for the construction of diverse metal-coordinated structural architectures.

3.1. Exploring Metal-Peptide Framework Designs with Helical Peptides and Foldamers:

Peptide-metal assemblies conventionally consist of three principal components: a peptide featuring a designated sequence containing metal binding residues and a specific metal ion. The shape, size, and monodispersity of the resulting self-assemblies are mainly governed by the peptide sequence.⁷⁷ The binding of metals plays a dual role by not only determining the activity of peptides but also serving as linkers between peptides. This is particularly evident when metal-binding residues function as anchors or connectors, fixing a functional group or conjugating another binding motif through one or more metal ions.^{78, 79} The specific type of metal binding site and its position within the peptide not only dictate the structural characteristics of the assemblies but also exert a significant influence on the properties exhibited by these assemblies. In peptide-metal assemblies, metal binding sites can be broadly categorized into two types: artificial ligands and natural ligands shown in Table 1.



Artificial binders		Natural Binders	
Binders	Binding Metals	Binders	Binding Metals
Pyridine	Fe^{2+} , Re^+ , Tc^+ , Cu^{2+} , Pd^{2+} , Ag^+ , Pt^{2+}	Histidine	Zn^{2+} , Cd^{2+} , Cu^{2+} , Ni^{2+} , Ag^+
BiPyridine	Zn^{2+} , Fe^{2+} , Cu^{2+} , Ru^{2+} , Co^{2+} , Ni^{2+}	Cysteine	Hg^{2+} , Pb^{2+} , Zn^{2+} , Cd^{2+}
TerPyridine	Fe^{2+} , Ni^{2+} , Cu^{2+}	Tryptophan	Cu^{2+}
Nitrilotriacetic acid	Ni^{2+} , Zn^{2+} , Cu^{2+} , Co^{2+}	Glutamic acid	La^{3+} , Yb^{3+} , Ca^{2+}
Iminodiacetate	Cu^{2+} , Zn^{2+} , Ni^{2+}	Catecholate	Ti^{4+} , Mo^{6+}
Phosphane ligand	Rh^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Zn^{2+} , Gd^{3+} , Au^+ , Pd^{2+}		
Crown ether	Cs^+ , Zn^{2+}		

Table 1: Artificial and Natural binders with their preferred metal ion.

Artificial metal–ligand residues are custom-synthesized to serve as triggers for the formation of higher-order or specific secondary structure assemblies.⁸⁰ Various ligands, including nitrilotriacetic acid, pyridine, bipyridine, and terpyridine, are frequently utilized to precisely control the structure and properties of peptides in the presence of metal ions.⁸¹ These ligands play a crucial role in orchestrating the self-assembly of peptides and determining the resulting supramolecular architecture. In biological systems, specific amino acid residues, including histidine, cysteine, tryptophan, and glutamic acid, serve as metal-binding sites. The coordination and interaction between these amino acid residues and metal ions induce conformational changes in the peptide or protein structure, ultimately facilitating the formation of intricate supramolecular structures with distinct functions.⁸² So in peptide-metal self-assembly, artificial ligands offer significant advantages over natural ligands owing to their custom-designed chemical structure. The robust strength and precisely defined directionality of metal binding by artificial residues enable meticulous control over the three-dimensional structure and stability of the final assembly.⁸³⁻⁸⁵ In my thesis, we highlight the pivotal role played by artificial ligands in orchestrating the intricate self-assembly processes of peptides. The judicious selection and utilization of these synthetic ligands underscore their significance in influencing the structural and functional attributes of peptide assemblies, providing a nuanced understanding of the self-assembly landscape.

3.1.1. Metal-Peptide Frameworks Derived from Coiled-coil Peptides:

The coiled-coil is a prominent super-secondary protein structure motif characterized by the intertwining or coiling of two or more α -helices, forming a helical supercoil. This unique structural motif plays a pivotal role in numerous biological processes, encompassing essential functions such as protein-protein interactions, transcriptional regulation, and molecular recognition. The intricate nature of coiled-coils underscores their crucial involvement in shaping the molecular landscape that governs various cellular activities and processes.⁸⁶⁻⁸⁹ Furthermore, coiled-coil peptides serve as templates for the construction of metal-driven self-assembled structures. By introducing suitable natural or synthetic metal-binding residues within the folded peptide linkers into a solution containing metal ions, these residues bind to the metal ions, simultaneously leading to the formation of intricate higher-order structures. This utilization of coiled-coil peptides provides a controlled and customized approach to engineer self-assembled architectures driven by metal coordination. The potential of combining coiled-coil peptide self-assembly with metal ions as a means of creating programmable supramolecular one-dimensional (1D) materials has been highlighted by a great deal of research.⁹⁰⁻⁹¹ In their pioneer work, Chmielewski and colleagues⁹² report the programmable metal ion-mediated head-to-tail assembly of a trimeric coiled-coil peptide shown in Figure 9. Depending on the metal ion, this hierarchical peptide assembly has produced nano-sized 3D crystals and nano-to-microspheres. Metal-ligand interactions at the ends of the growing crystal are a notable feature of the head-to-tail crystallization process. Using this characteristic, His-tagged fluorophores have been directed to particular areas of the three-dimensional peptide crystals.

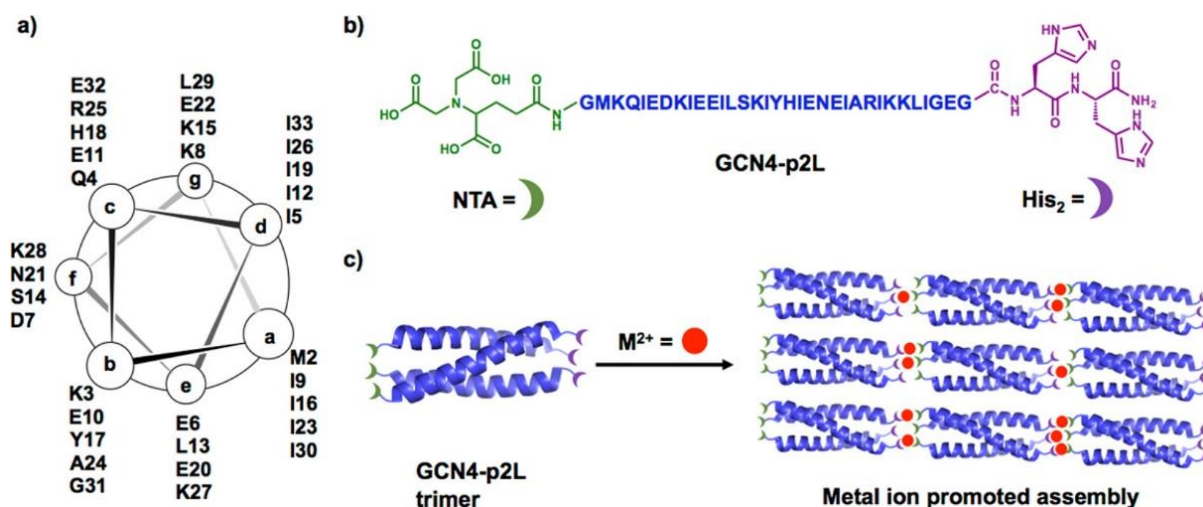


Figure 9: a) Helical wheel representation of coiled-coil peptide. b) Sequence of coiled-coil peptide with the metal binding site of both ends of the peptide. c) Schematic representation of the metal-mediated head-to-tail assembly of trimeric coiled-coil peptide into linear strands, with additional interstrand electrostatic interactions causing an antiparallel framework of the strands.

However, only a limited number of studies have explored their utilization for generating 3D metal peptide frameworks. In a fascinating study, Horne⁹³ and colleagues engineered a distinctive category of crystalline materials featuring coiled-coil peptides specifically designed to facilitate the formation of oligomers. In order to use the peptides as ligands for metal coordination, one or two artificial metal-binding functionalized residues such as 2,2':6',2''-terpyridine (Tpy, X) were carefully added to the surface of each folded peptide which binds with divalent copper ion (Cu^{2+}) to form different types of 2D and 3D metal helix framework shown in Figure 10. The fascinating interplay of metal coordination and coiled-coil peptide-directed self-assembly, as elucidated in this study, holds promise for the innovative design of materials with novel functionalities, offering a spectrum of potential applications.

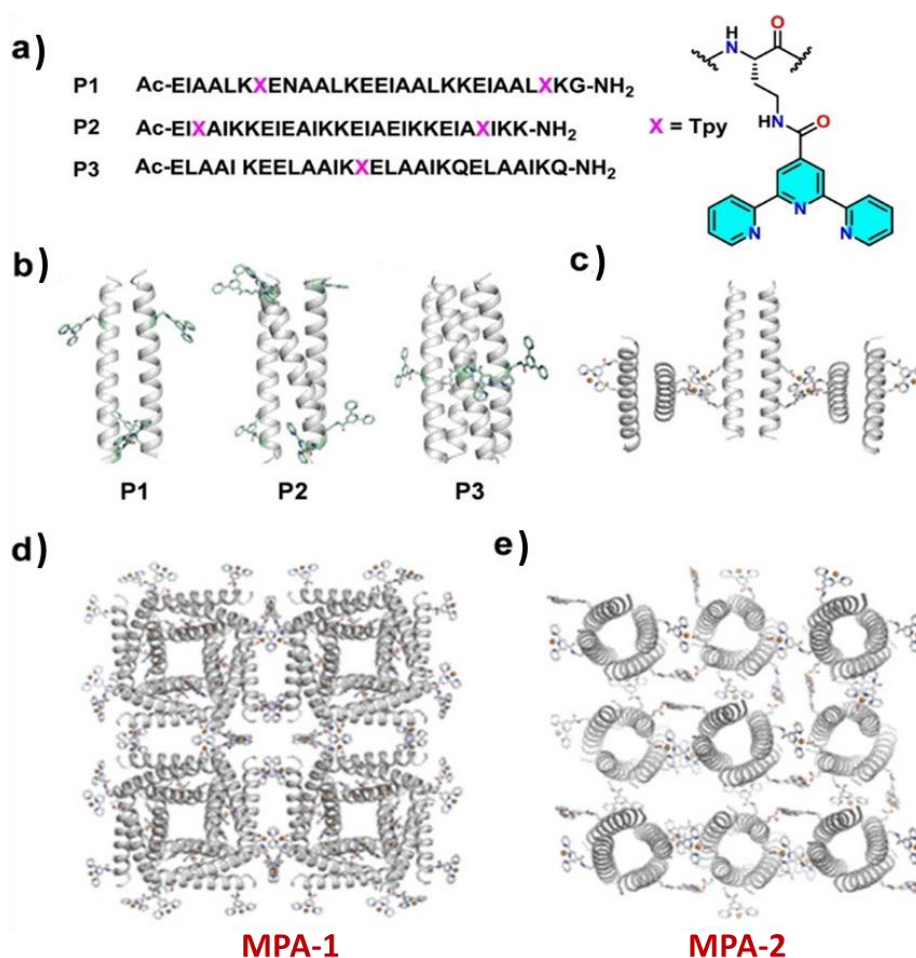


Figure 10: a) Representation of different coiled-coil peptides **P1**, **P2**, and **P3** along with artificial TPy binder. b) Crystal structure of di, tri, and tetrameric coiled-coil peptides of **P1**, **P2**, and **P3**. c) Formation of coordination polymer by coiled-coil peptide **P1** through metal coordination. d), e) Formation of 3D framework and 2D net formed by the coiled-coil peptides of **P2** and **P3** respectively.

3.1.2. Metal-Peptide Frameworks Derived from Collagen-inspired Peptides:

Collagen, a highly abundant structural protein in mammals, exhibits ubiquity across a spectrum of biological structures, encompassing vital tissues like skin, cartilage, connective tissue, blood vessels, and the extracellular matrix.⁹⁴ Its pervasive presence underscores its fundamental role in maintaining tissue integrity and functionality. Collagen manifests as a triple-helical structure, characterized by the assembly of three parallel left-handed PPII helices. These helices consist of a repetitive sequence unit of proline-hydroxyproline-glycine (Pro-Hyp-Gly), intricately intertwined to form a right-handed bundle. The widely recognized significance of collagen fibrils in the extracellular matrix has spurred the development of collagen-mimicking peptides and the exploration of their self-assembly behavior.⁹⁵ Moreover, there is an increasing rapid interest in investigating higher-order structures of collagen through metal-driven self-assembly. Metal ions have been demonstrated to facilitate the swift self-assembly of collagen-mimetic peptides, giving rise to diverse nanostructures.⁹⁶ Not only can metals induce the self-assembly of longer collagen-like peptides into functional nanostructures,⁹⁷ but they can also induce the self-assembly of shorter collagen-inspired peptides into porous 3D crystalline materials. In the study led by Fujita⁹⁸ and colleagues, the researchers explored the metal-driven self-assembly of short synthetic collagen-mimetic peptides. Specifically, they opted for a short peptide sequence containing Gly-Pro-Pro, a repeating unit found in collagen. To enhance metal interaction, modifications were introduced at both termini of the peptide through the incorporation of metal-binding 3-pyridyl groups. An analysis of the metal complex formed through Ag⁺ coordination, conducted using X-ray single-crystal diffraction, revealed that the peptide adopted the Polyproline II (PP II) conformation. Upon extracting the average dihedral angles ϕ and ψ from the single-crystal analysis, it was observed that they closely resembled the angles characteristic of regular PPII helices. The peptide ligand was connected through the nitrogen atoms of the pyridyl (Py) motifs appended at both termini, leading to the formation of Py-Ag⁺-Py coordination modes shown in Figure 11b. Furthermore, the 3D-honeycomb framework MPA-3 with two distinct chiral channels of different pore diameters was produced by the entanglement of the PPII helical peptide chains in the presence of silver ions shown in

Figure 11c. The authors conducted a detailed investigation into the chiral recognition capacity of the larger channel, which has an approximate diameter of 2.2 nm. Notably, this channel exhibited selective encapsulation of the *R*-isomer of 1,1'-bi-2-naphthol over the *S*-isomer, resulting in a 48% enantiomeric excess. Moreover, the larger channel demonstrated exceptional molecular recognition capabilities, particularly for larger biomolecules.

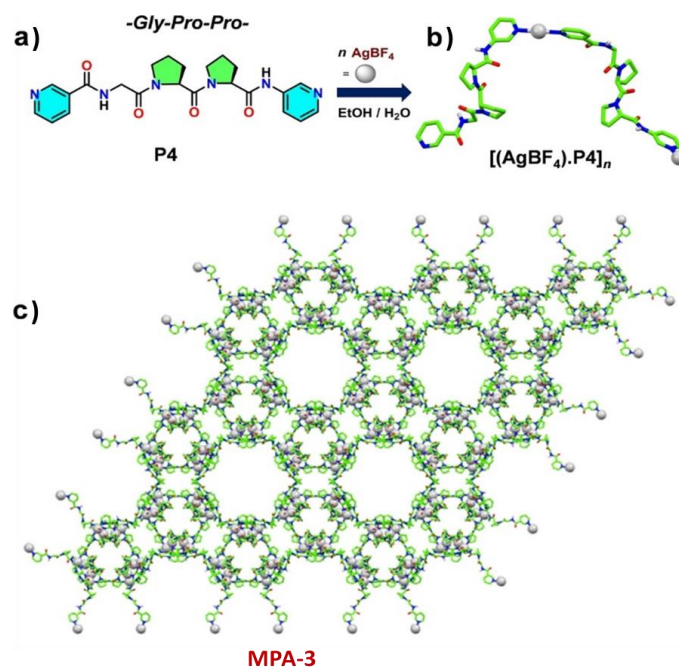


Figure 11: a) Chemical structure of collagen mimetic ³Py-Gly-Pro-Pro-³Py peptide. b) Head-to-tail coordination of peptide in the presence of AgBF₄ through single crystal diffraction. c) A 3D porous framework structure showing the higher-order arrangement along the c-axis of the [(AgBF₄) P4]_n.

3.1.3. Metal-Peptide Catenanes Derived from Short Peptides:

A catenane is a type of mechanically interlocked molecular architecture consisting of two or more interlocked macrocycles or molecular rings. In a catenane, the rings are threaded through one another, much like links in a chain. The distinctive feature of catenanes is the topological constraint imposed by the interlocking arrangement. Catenanes can be synthesized through various methods, including template-directed synthesis or self-assembly processes. The resulting structures exhibit unique properties and behaviors due to their interlocked nature. The study and design of catenanes have applications in diverse fields, including supramolecular chemistry, materials science, and nanotechnology. These mechanically interlocked molecules serve as models for understanding molecular recognition, host-guest interactions, and the dynamic behavior of interlocked structures. Fujita⁹⁹ and co-workers designed the tripeptide

ligand, exhibiting intrinsic folding characteristics, has been designed through the incorporation of pyridine groups as coordination sites. The combination of the Pro-Gly-Pro sequence-based peptide linker and linear Ag (I) results in the formation of a three-membered metallacycle denoted as $\text{Ag}_3(\text{P5})_3$. In this molecular architecture, the peptide backbone adopts an Ω -shaped loop conformation. Simultaneously, four rings self-assemble into a highly interlocked structure, facilitating the creation of an unprecedented metal-peptide [4] catenane shown in Figure 12b. In this unique arrangement, each ring is spontaneously threaded by the other three, resulting in a crossing number of 12. A minute modification of the previous tripeptide has resulted in the formation of a distinct topologically inequivalent framework, maintaining identical ring- and crossing-numbers. The newly designed tripeptide featuring a Thr-Pro-Pro sequence facilitated the generation of a similar [4] catenane.¹⁰⁰ This [4] catenane exhibits a roughly spherical structure with a molecular size of approximately 2 nm (Figure 12d), comprising four $\text{Ag}_3(\text{P6})_3$ rings arranged in T symmetry with respect to each other. This arrangement displays a three crossed tetrahedral link, distinctly different from MPA-4, which exhibits a T2-tetrahedral link. The conformational change is attributed to the formation of a hydrogen-bonded cyclic trimer within MPA-5, leading to the stabilization of the three-crossed junction. Consequently, it has been proposed that peptide side-chain chemistries have a significant impact on peptide assembly and folding.

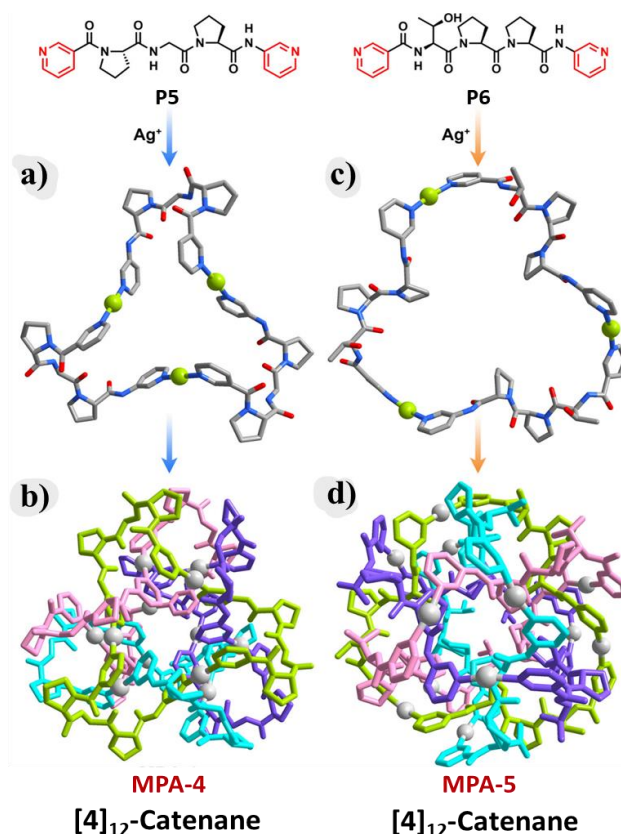


Figure 12: a), b) Self-assembly and crystal structure of MPA-4. c), d) Self-assembly and crystal structure of MPA-5.

3.1.4. Metal-Peptide Knots Derived from Short Peptides:

The synthesis of molecular knots represents a significant milestone in the field of chemical topology, recognizing knots as fundamental structural elements with crucial roles in natural phenomena.¹⁰¹ Molecular-level knotting, observed in flexible polymer chains, exerts a substantial impact on the physical and chemical properties of materials. This influence spans diverse aspects, including chirality expression, elasticity, mechanical strength, and biological activity.¹⁰² The ability to manipulate molecular knots at the atomic and molecular scale offers avenues for tailoring materials with precise and desired characteristics, contributing to advancements in various scientific and technological domains. The design and development of structurally well-defined molecular knots, achieved through processes involving twisting, folding, and/or threading molecular building blocks, present a formidable challenge. This challenge is likely attributed to the entropic (and/or kinetic) disadvantages associated with self-threading processes. However, the utilization of metal-ion templates emerges as a promising strategy to overcome these challenges and construct topologically complex structures with precision and defined architectures.¹⁰³ In this context, Leigh and colleagues have successfully engineered a range of precisely defined molecular knots through coordination-driven self-assembly.¹⁰⁴ The flexibility of the constituent strands is a crucial determinant for the formation of these knotted structures, facilitated by the cooperative engagement of multiple interstrand interactions. Peptides, characterized by dynamic and flexible linkers, emerge as promising candidates for steering the creation of intricately entangled nanostructures with potential bioactivity. As an illustrative example, Fujita et al. engineered a tripeptide ligand featuring a Gly-Gly-Gly (**P7**) sequence. The assembly of **P7** and Ag (I) culminates in the creation of an intricately entangled structure (MPA-6) interconnected through a head-to-tail arrangement (Figure 13b).¹⁰⁵ The stability of the complex is orchestrated through the cooperative interplay of hydrogen bonds, secondary coordination, and π - π stacking interactions between the interstrands. This concerted molecular assembly results in the formation of a 7_1 torus knot characterized by a total of seven crossings. Remarkably, this complex can undergo further expansion into an 8-crossing torus link (8^2_1 link, denoted as MPA-7) through the substitution of the counteranion NTf_2^- with PF_6^- during the self-assembly process. The structural transformation induced by this change in anion is likely attributed to the improved crystal packing observed in MPA-6 with PF_6^- . The metamorphosis of achiral metal-peptide knots into

topologically chiral architectures could yield a captivating chiral microenvironment conducive to enzyme-mimicking biomolecular recognition. Through the substitution of achiral glycine with chiral L-alanine in **P7**, the strategically designed tripeptide **P8**, featuring an Ala-Gly-Gly sequence, can be utilized to generate a geometrically analogous 8-crossing link denoted as MPA-8 (Figure d). MPA-8, distinguished by its superior chiral microenvironment featuring both polar and apolar moieties, holds the promise of facilitating remarkable enantioselective recognition and separation across a diverse array of biomolecules. This unique property positions it as a potentially powerful tool in various applications requiring precise chiral discrimination and selective separation processes.

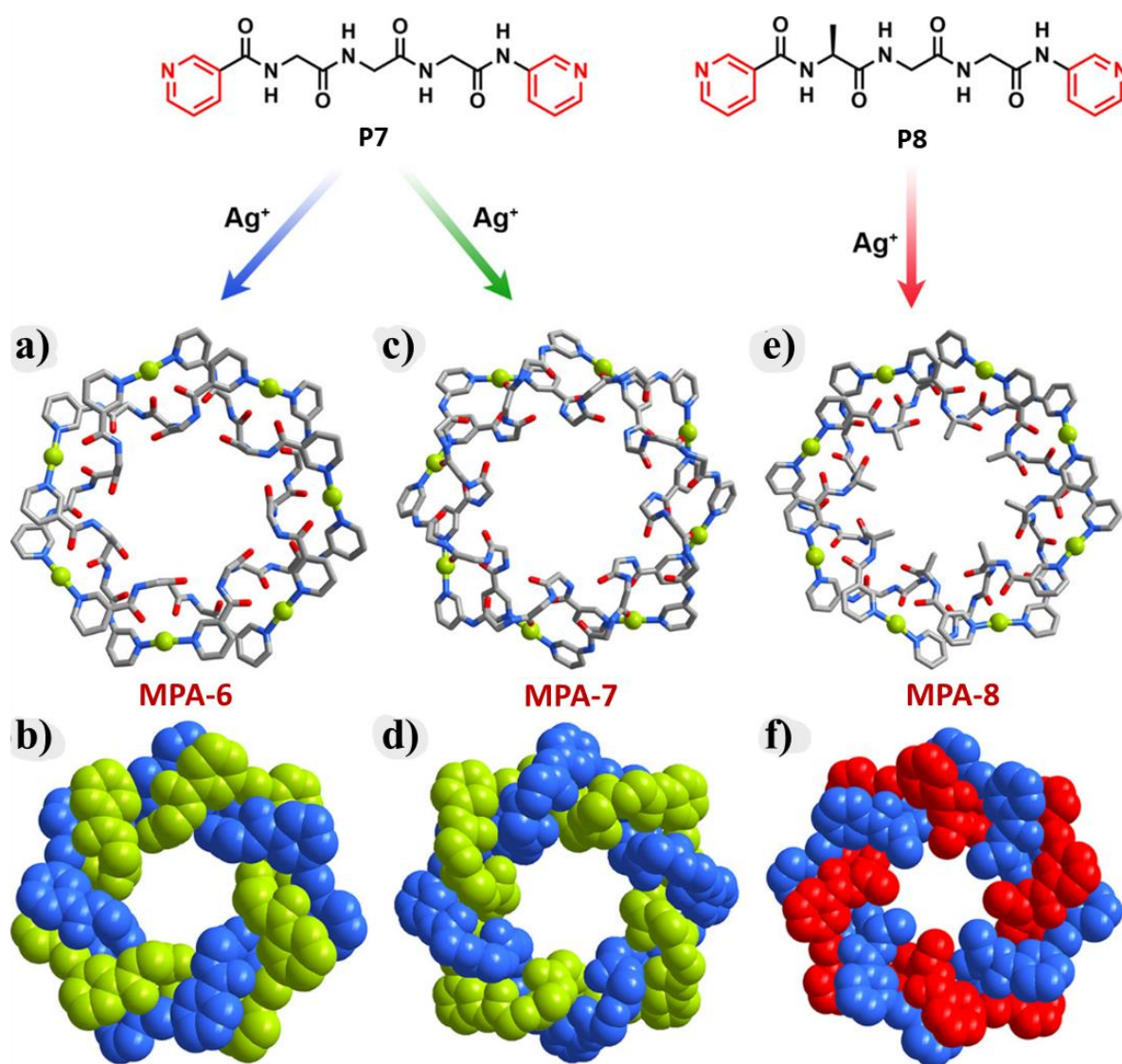


Figure 13: Self-assembly and crystal structure of MPA-6 (a, b), MPA-7 (c, d), and MPA-8 (e, f) respectively.

3.1.5. Metal-Peptide Frameworks Derived from Peptide Foldamers:

Foldamers refer to synthetic peptidic or abiotic oligomers or discrete chain molecules characterized by their ability to adopt a rigid conformation in a solution state. These molecules are designed to mimic the structures and functions of proteins, demonstrating a unique capacity for controlled folding reminiscent of natural biomolecules.¹⁰⁶ Peptidic foldamers provide distinct advantages over natural peptides, characterized by heightened stability, customizable folding attributes, and the capacity to finely regulate structure-properties relationships. In recent studies, β -peptide foldamers have emerged as versatile spacers, playing a pivotal role in the systematic design of a varied repertoire of metal-peptide hybrid frameworks. This innovative approach involves leveraging the unique properties of β -peptide foldamers to engineer and tailor MHFs for specific applications in materials science and related fields. Lee and colleagues undertook the design of a series of β -peptides, denoted as **P9–P12**, incorporating *trans*-2-aminocyclopentanecarboxylic acid (*trans*-ACPC) modified with 4-pyridyl moieties at both the N- and C-termini for the purpose of metal-binding coordination.¹⁰⁷ The single crystal structures of the shorter oligomers **P9** to **P11** in the absence of metal revealed a right-handed 12-helical conformation stabilized by *i* to *i*+3 intramolecular hydrogen bonds involving the carbonyl oxygen (C=O) and the amide hydrogen (H-N). In contrast, the **P12** hexamer exhibited an unusual 16-helical conformation. Upon complexation of the **P9** trimer with Ag⁺, two distinct helical conformations were observed, comprising 12- and 8-helix architectures (Figure 14b). These diverse helical conformations of the peptide ligand were made visible by the higher-order self-assembly. The peptide ligand alternately bound to the metal ion via Py-Ag⁺-Py linkages to form porous coordination frameworks. Notably, the 3D-porous network MPA-9 was further stabilized by classical hydrogen bonds of the helices, metal coordination, and aromatic pi-stacking of the pyridyl linkers.

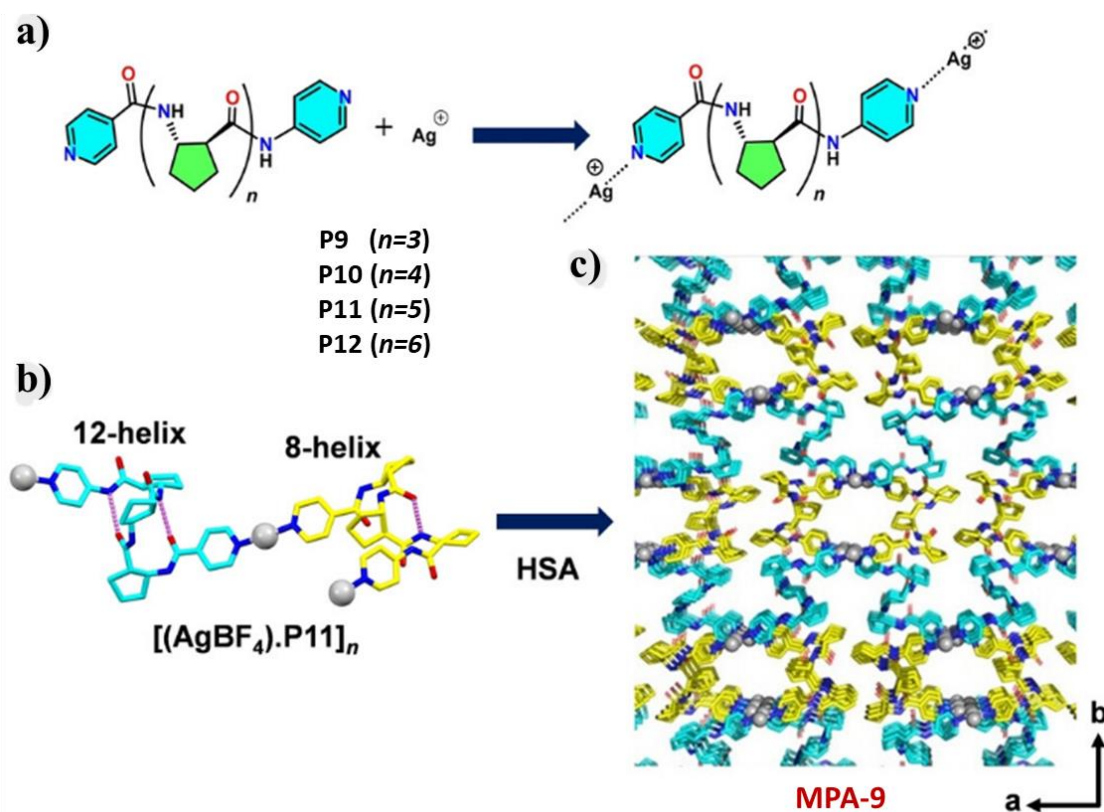


Figure 14: a) Sequence of different β -peptide oligomers along with its Ag^+ coordinating site. b) X-ray diffracted structure of **P9** in the presence of $AgBF_4$. c) 3D metal peptide porous framework along the c-axis leads to the formation of nano-channel.

Compared to β -peptides, γ -peptides have received comparatively less attention, primarily due to challenges associated with the synthesis of stereochemically pure γ -amino acids.^{12b} In their seminal work, Seebach²⁵ and Hanessian²⁶ elucidated the formation of helical secondary structures using γ -peptides. Additionally, Hoffman and colleagues employed quantum chemical computations to predict a broad spectrum of helical architectures achievable with γ -peptides.²⁷ This pioneering research significantly contributed to our understanding of the structural potential of γ -peptides. Recently, there has been a notable surge of interest in hybrid peptides, combining both α - and γ -amino acids, beyond homooligomers. This heightened attention is attributed to the prospect of forming a diverse array of helical structures through the strategic manipulation of stoichiometries and arrangements of monomer units.^{55c} Balaram^{45c} and Gopi¹⁰⁸ groups demonstrated the stability of 12-helix secondary structures in α,γ -hybrid peptides, comprising various proteinogenic side chains with γ -amino acids. These hybrid peptides exhibit a remarkable ability to adopt a helical structure with a short sequence due to the strong helical propensity of γ -amino acids. These unique structural characteristics of

α,γ -peptides are leveraged as spacers in constructing Metal-Peptide Frameworks. In their study, Gopi and colleagues engineered an ultrashort α,γ -hybrid peptide that terminated at both ends with a 4-pyridyl residue.⁷⁵ This designed tripeptide, denoted as P13, was composed of stereochemically-constrained Aib residues, flexible γ -amino acids, and natural leucine residues. The strategic inclusion of Aib residues in the peptide facilitated the adoption of a helical secondary structure. Detailed crystallographic analysis further elucidated that the peptide adopted a 12-helix conformation, which was stabilized by intramolecular hydrogen bonding between the *i* and *i*+3 residues. Upon complexation with AgBF₄, the 12-helix structure of the peptide remained intact. Two 12-helix peptides were observed to associate in a head-to-tail fashion through silver ion coordination, forming a linear coordination polymer. Notably, the two N-terminal amide NH groups and the two C-terminal amide CO groups were involved in intermolecular head-to-tail hydrogen bonding with other helices. The infinite silver ion coordination-mediated helical polymerization along the horizontal direction, combined with extended head-to-tail intermolecular hydrogen bonds along the vertical direction, resulted in the formation of a 3D-porous MPA-10 network with a pore size of 5.9 Å (Figure 15c). Intriguingly, these Metal-Peptide Frameworks (MPFs) exhibited the capability to capture CO₂ at 195 K, suggesting their potential application as materials for future energy storage.

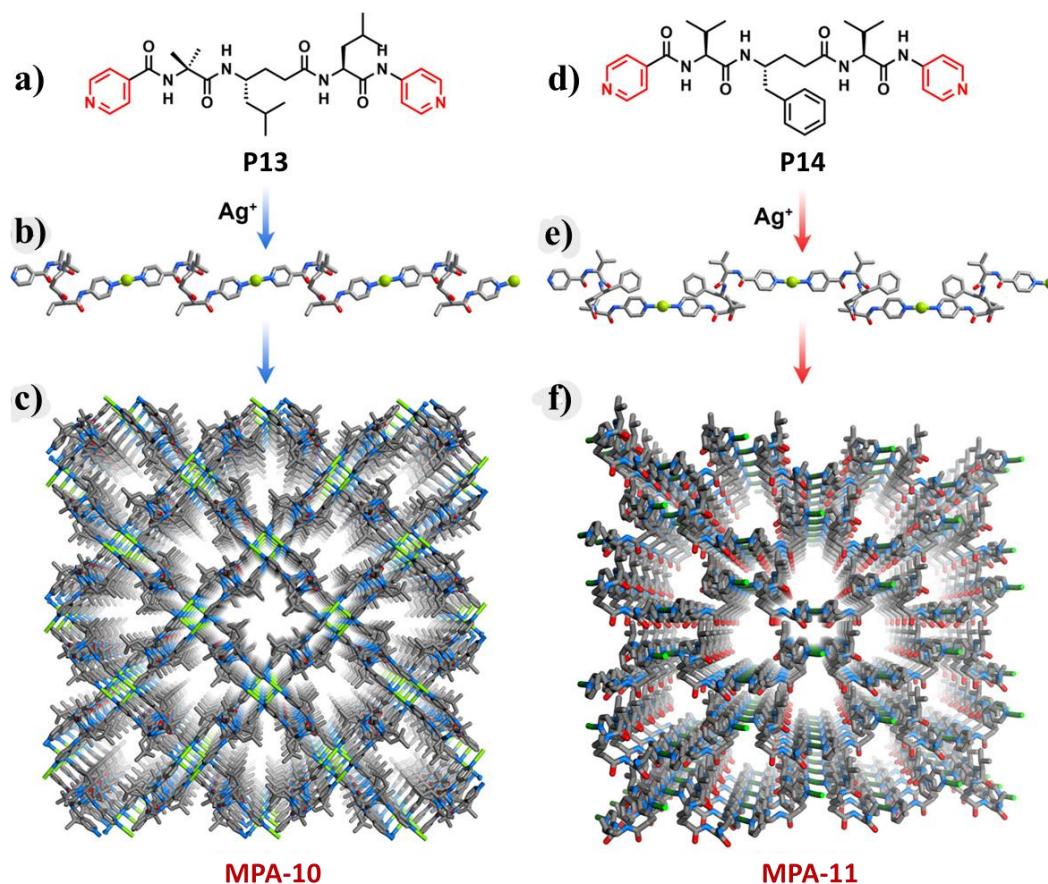


Figure 15: a) Chemical structure of short hybrid peptide **P13** b) X-ray diffracted crystal structure of Silver coordinated peptide in a head-to-tail fashion. c) The 3D metal-peptide porous network observed along the c-axis. d) Chemical structure of short hybrid peptide **P14**. e) X-ray diffracted crystal structure of Silver coordinated peptide in a head-to-head fashion. f) The 3D metal-peptide porous network observed along the c-axis.

In a recent study, Gopi and colleagues showcased the ability of an short α,γ -tripeptide, namely **P14**, to spontaneously adopt a 12-helix conformation even in the absence of steric constraints.¹⁰⁹ The design of **P14** involved incorporating two β -sheet inducing valine residues along with flexible γ -phenylalanine (γ -Phe) amino acids. Both ends of the tripeptide were equipped with metal-coordinating 4-pyridyl ligands. Upon exposure to Ag^+ and Cu^{2+} ions, the hybrid peptide underwent gelation, forming metallogels. Intriguingly, crystallographic analysis of the AgBF_4 -induced metallogel unveiled the preservation of the 12-helix structure in the gel phase. The helices were interconnected through silver ion coordination, resulting in the formation of a linear coordination polymer. On the other hand, complexation with AgPF_6 induced the creation of MPA-11, a 3D porous coordination polymer where two 12-helices were linked in a head-to-head configuration. The extraordinary metal-driven self-assembly of 12-helix peptide templates holds significant promise for advancing the field. This innovative approach is poised to inspire the creation of novel metal-driven foldamer frameworks with diverse functionalities. The potential applications could be broadened by exploring variations in the side chain composition and length of the peptide sequence. Such tailoring possibilities hold great promise for the development of functional materials with versatile applications across various scientific and technological domains.

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Accessing Three-Dimensional Crystals with Incorporated Guests through Metal-Directed Coiled-Coil Peptide Assembly



Author: Manish Nepal, Michael J. Sheedlo, Chittaranjan Das, et al

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Supramolecular Metal-Coordination Polymers, Nets, and Frameworks from Synthetic Coiled-Coil Peptides



Author: Nathan A. Tavenor, Matthew J. Murnin, W. Seth Horne

Publication: Journal of the American Chemical Society

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Artificial Metal-Peptide Assemblies: Bioinspired Assembly of Peptides and Metals through Space and across Length Scales



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Chapter 2

Anion Tuned Structural Modulation of Metal-Ion Directed 3₁₀-Helix Networks

1. Introduction:

In recent years, the exploration of metal-ion coordinated supramolecular architectures of peptides has emerged as a prominent area of research, drawing substantial attention within the scientific community. This heightened interest is primarily driven by the remarkable structural similarities these peptide architectures share with natural metalloproteins. The intricate interplay between metal ions and peptides has not only fascinated researchers for its biological relevance but has also paved the way for innovative applications in the development of artificial enzymes and catalysts.¹ Furthermore, the utilization of metal ions in the realm of peptide chemistry extends to their role in orchestrating the induction of specific secondary structures from the linear primary sequences of peptides² and also for the transformation of coiled-extended-coiled structures,³ and double hairpin⁴ into helical conformations. This transformative process represents a key aspect of bioinspired design, where metal ions act as molecular architects, guiding peptides into well-defined three-dimensional arrangements. Moreover, metal ions have been investigated for their role in catalyzing the conversion of a single helix into a double helix⁵ and promoting the formation of helix duplexes.⁶ Beyond structural transformations, the coordinated action of metal ions is also employed in the fabrication of protein-like structures through the self-assembly of collagen mimetics⁷ and coiled-coil peptides.^{8,9} This intricate process showcases the versatility of metal-ion interactions in guiding the hierarchical assembly of peptides, yielding biomimetic structures with controlled features. Significant advancements have been made in constructing notable porous networks,¹⁰ cages, and coordinated polymers using short peptides.¹¹ In continuation, the exploration of stable 12-helix structures derived from α,γ -hybrid peptides,¹² and β -peptides¹³ has been undertaken, specifically for the purpose of fabricating metal ion-mediated molecular architectures. Beyond peptides, metal ions have been instrumental in the design and construction of notable structures and assemblies from abiotic foldamers.^{14,15} Such endeavors highlight the versatility of metal-ion interactions in orchestrating the self-assembly and organization of foldameric structures with tailored functionalities. Continuing our endeavors to fabricate metal-coordinated assemblies from short and structured peptides, we aimed to explore the potential for constructing metal-ion-coordinated structures involving α -peptide helices. The 3_{10} -helix, emerging as the third prevalent secondary structure following the α -helix and β -sheets in proteins, assumes a distinctive role in this investigation.¹⁶ Notably, 3_{10} -helices are characterized by their brevity, spanning approximately 3 to 4 residues, and are predominantly situated at the N- and C-termini of α -helices. The groups of Balaram, Karle, and

Toniolo have conducted extensive investigations into the conformations of α -helices and 3_{10} -helices. Their focus has centered on synthetic peptides comprising sterically constrained α,α -dialkyl amino acids, utilizing Aib residues as key elements in the design of short helical peptides.^{17, 18} In this study, we present our findings on the anion-tuned silver ion-mediated synthesis, revealing coordination site-dependent porous networks, coordination polymers characterized by opposite helix chirality, right-handed superhelices, and macrocyclic structures. Additionally, we investigate the non-linear optical effects exhibited by these constructs. This preliminary report serves to elucidate the extensive structural diversity observed and the remarkable second harmonic generation (SHG) properties inherent to the metal-coordinated 3_{10} -helices of α -peptides. These observations provide valuable insights into the potential applications of such peptide-metal complexes in advanced materials and nonlinear optical systems.

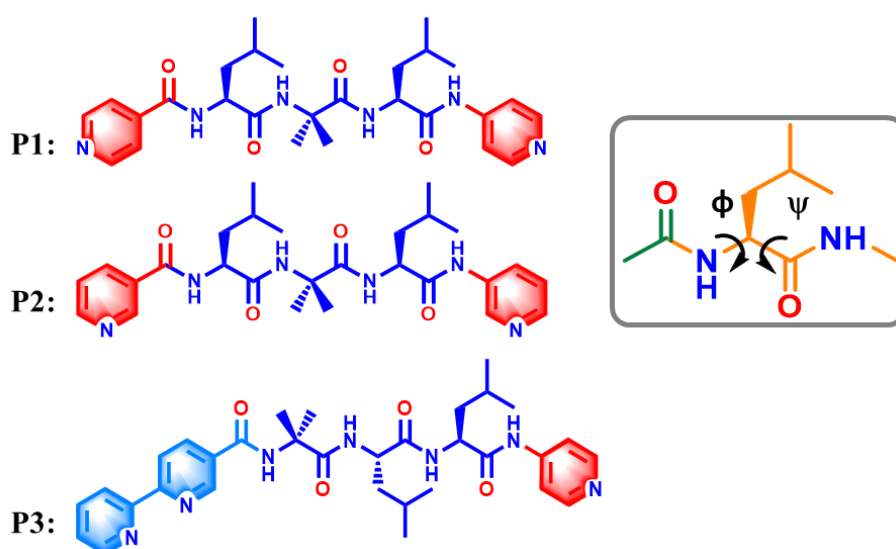
2. Scope and Aim of the Current Work:

The fabrication of structure-based supramolecular architectures, predominantly utilizing biomolecules, has garnered considerable attention. Peptides, in particular, emerge as promising templates for such architectures due to their inherent biocompatibility, functional diversity, flexibility, hydrophobicity, structural adaptability, and chirality.¹⁹ The peptide backbone's conformational adaptability, manifesting as helices or sheets and their self-assembly properties, opening new avenues for diverse applications. Inspired by the pivotal roles of metal ions in biological systems, endeavors have been directed towards emulating metalloproteins and metalloenzymes. The combination of metal ions and peptide-building units as linkers have been extensively explored to construct various metal-peptide coordination assemblies, particularly porous architectures, garnering significant attention for their versatile applications.²⁰ Fujita²¹ and colleagues involved in the design of short tripeptides featuring α -amino acids terminated with pyridine binders at both C- and N-terminal ends. These peptides exhibited the ability to coordinate with metal ions, giving rise to supramolecular architectures such as porous frameworks, catenanes, and various knot structures. Notably, in their design, all peptide backbones maintained an unstructured conformation. In light of this, our study seeks to innovate by introducing helicity into short tripeptide sequences through the incorporation of α,α -dialkyl amino acids.^{17, 18} Building upon previous work, we aim to investigate the impact of metal binding on the coordination assembly of these peptides.

3. Results and Discussion:

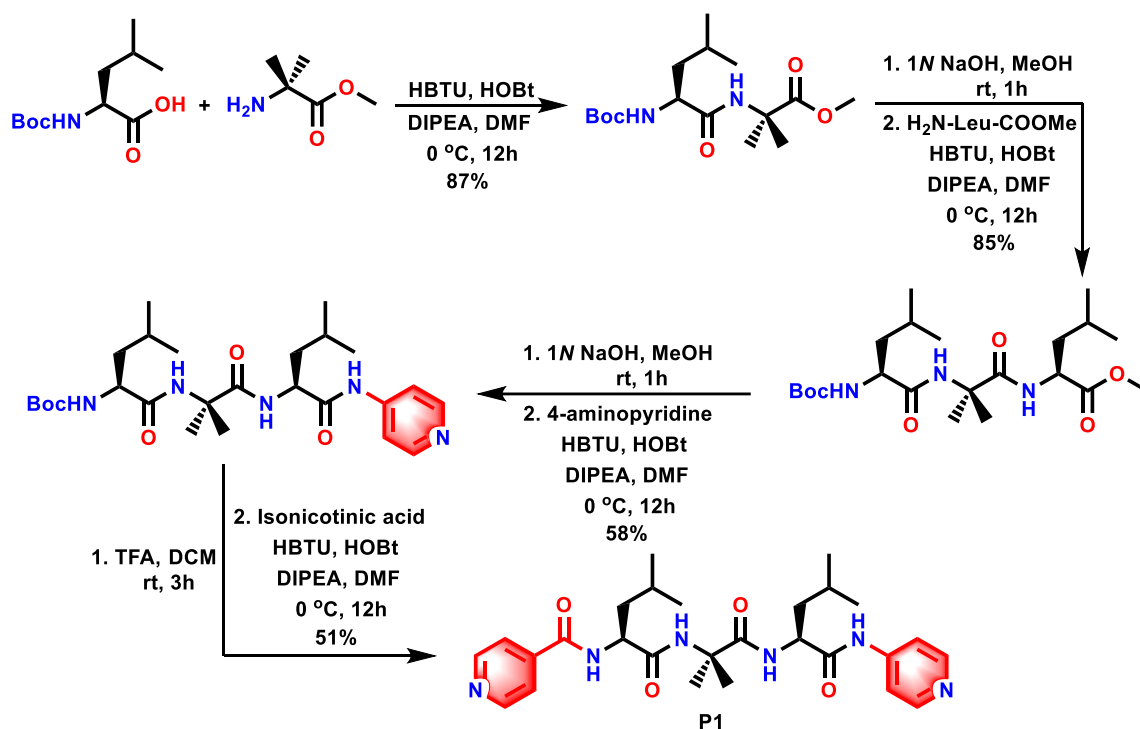
3.1. Design and Synthesis of Peptides:

In the pursuit of expanding the potential for novel metal-coordination architectures arising from peptide helical secondary structures, we designed two short tripeptides, denoted as **P1** and **P2**, featuring α -amino acids. The specific peptide sequences are shown in Scheme 1. To confer structural stability, Aib was strategically positioned within the peptide sequences, occupying a central role in the formation of robust helical structures. The termini of these peptides were conjugated to either 3-pyridyl or 4-pyridyl groups, serving as metal-coordinating entities. The notion of utilizing pyridyl groups is to keep the structure away from the metal-coordination site.



Scheme 1: Sequences of short tripeptides **P1**, **P2**, and **P3**. Local torsion variables of α -residue are also shown.

The synthesis of all tripeptides was executed employing a conventional solution-phase strategy, encompassing Boc-chemistry and coupling methodologies. The synthetic procedure is shown in Scheme 2. The tripeptides, denoted as **P1** and **P2**, were synthesized through solution-phase techniques and subsequently subjected to purification via column chromatography, following the delineated procedures in Scheme 2 with 48% to 60% yield respectively.



Scheme 2: Synthesis of short α - tripeptide **P1**.

3.2. Crystal Structures Analysis of Peptide **P1** and **P2**:

In the pursuit of elucidating the potential metal-coordinated assemblies accessible to **P1** and **P2**, and to gain insights into the conformational influence during metal coordination, we subjected these peptides to crystallization using diverse metal salts and solvent combinations. Notably, single crystals were exclusively obtained at the interface of a peptide solution in methanol/ethanol and an aqueous solution containing various silver salts. No crystals were observed when employing metal salts other than those of silver. Subsequently, the single crystals formed through silver coordination were systematically analysed via X-ray diffraction, revealing detailed structural information, which is expounded upon below.

3.2.1. Crystal Structures Analysis of **P1**-AgOTf Complex:

We started our investigation with peptide **P1** with the treatment of AgOTf salt. Peptide **P1** gave single crystals at the interface of ethanol/water upon treatment of AgOTf at ambient temperature. The X-ray diffracted single crystal structure of **P1**-AgOTf complex is shown in Figure 1a. The structural analysis revealed that **P1**-AgOTf complex crystallized in the space group of $P 2_1$. The **P1** adopted a classical right-handed 3_{10} -helix conformation in single crystals. The short helix structure is stabilized by two incipient 10-membered intramolecular hydrogen bonds between the residues of CO (i) to NH ($i+3$) residues. The

average ϕ and ψ torsion angles of Leu residues are $-53\pm 2^\circ$ and $-38\pm 2^\circ$ respectively, while Aib displayed -66° and -5° respectively.

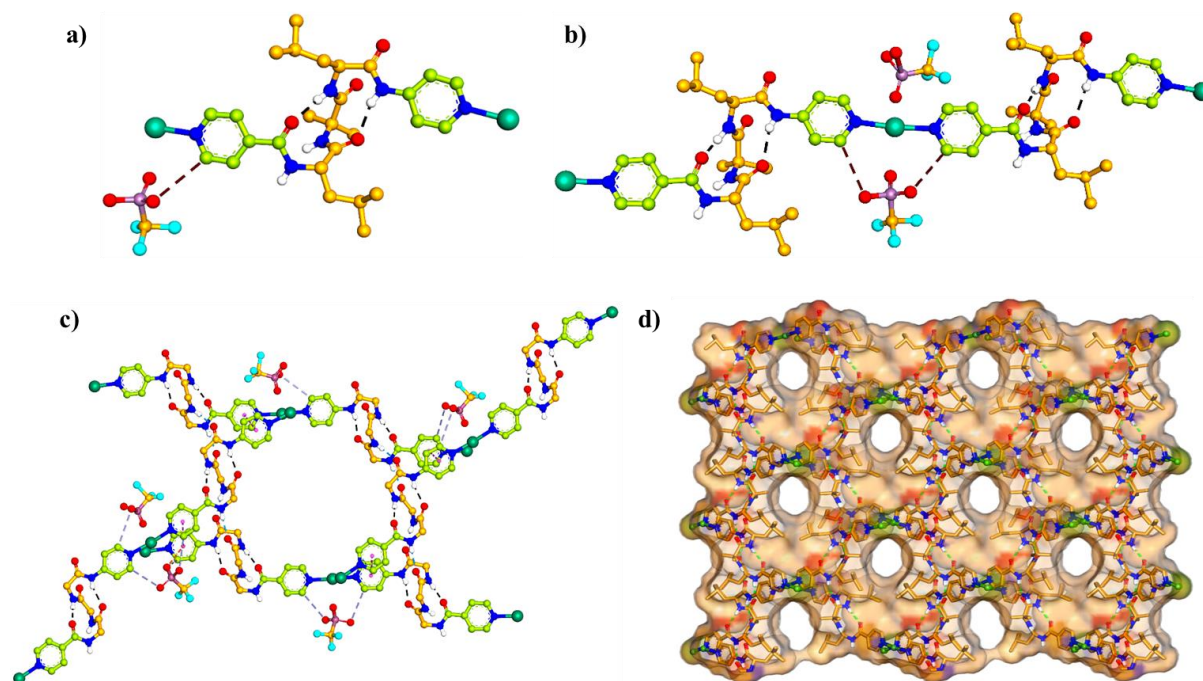


Figure 1: a) The X-ray diffraction structure of silver coordinated **P1** in the presence of AgOTf. b) The ‘Head to tail’ silver ion coordination between helices and the interaction with OTf anion in the crystal packing. c) Hydrogen-bonding driven porous network of **P1** (for clarity side-chain residues have been omitted). d) The metal peptide porous framework along the a-axis.

Further, the terminal 4-pyridyl groups are engaged in silver ion coordination which connected the two helical peptides in a head-to-tail fashion as shown in Figure 1b. The trifluoromethanesulfonate is interacting with 4-pyridyl coordinated Ag^+ through a salt bridge and also interacts with 4-pyridyl groups through $\text{CH}\cdots\text{O}$ H-bonds. The two N-terminal amide NH groups are involved in the intermolecular H-bonds with the two C-terminal CO groups of the other helix. Four different silver-coordinated helices are interacted through H-bonds to form a porous network (Figure 1c). The continuous intermolecular H-bonds between the 3_{10} -helices, cation- π interaction between Ag (I) and 4-pyridyl groups, π - π interactions between two pyridyl groups, and anion- π interactions between 4-pyridyl groups and triflate ion lead to a 3-dimensional porous network (Figure 1d) with a pore size of $6.6 \times 6.5 \text{ \AA}^2$. The counter anion plays a significant role in the formation of a 3-dimensional polymeric structure.

The torsion angles and H-bond parameters of the **P1**-AgOTf complex are given in Table 1-2.

Table 1: Torsion Angle Parameters of **P1**-AgOTf.

Peptide		Residue	ϕ	Ψ
P1 -AgOTf	Molecule 1	Leu	-58	-26
		Aib	-50	-26
		Leu	-55	-39
	Molecule 2	Leu	-52	-37
		Aib	-66	-5
		Leu	-55	-39

Table 2: H-bond Parameters of **P1**-AgOTf.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P1- AgOTf	Molecule 1	Py CO ← NH Leu	3.02	3.03	82
		Leu CO ← NH Py	2.11	2.87	147
	Molecule 2	Py CO ← NH Leu	2.15	2.99	167
		Leu CO ← NH Py	2.09	2.85	148
Complex		Hydrogen bond (intermolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P1- AgOTf	Molecule 1	Leu CO(2) ← NH Aib(1)	2.10	2.93	159
		Aib CO(2) ← NH Leu(1)	2.06	2.91	171
		Leu CO(1) ← NH Aib(2)	2.18	2.96	152
		Aib CO(1) ← NH Leu(1)	2.09	2.94	169

3.2.2. Crystal Structures Analysis of **P1**-AgPF₆ Complex:

Motivated by the porous network exhibited by **P1** in the presence of AgOTf, we conducted X-ray analysis on single crystals formed from the interaction of **P1** with AgPF₆. Peptide **P1** gave single crystals at the interface of ethanol/water upon treatment of AgPF₆ at ambient

temperature. The resulting **P1**-AgPF₆ complex crystallized in the P 2₁ space group. In sharp contrast to the distinctive right-handed 3₁₀-helix and porous network observed in the **P1**-AgOTf complex, the coordination with Ag (I) from AgPF₆ induced a novel scenario characterized by a coexistence of both right and left-handed 3₁₀-helical conformations within **P1** shown in Figure 2a. These helical structures are stabilized by two successive intramolecular 10-membered hydrogen bonds. Notably, the Ag (I) ions exhibited coordination with either two left-handed helices or two right-handed helices (see Figure 2b), displaying a preference for homochiral coordination rather than a combination of left and right-handed helices. The left and right-handed 3₁₀-helices were arranged in an alternating fashion, further stabilized by intermolecular hydrogen bonds between the N-terminal amide NH groups of one helix and the C-terminal CO groups of another helix (see Figure 2c).

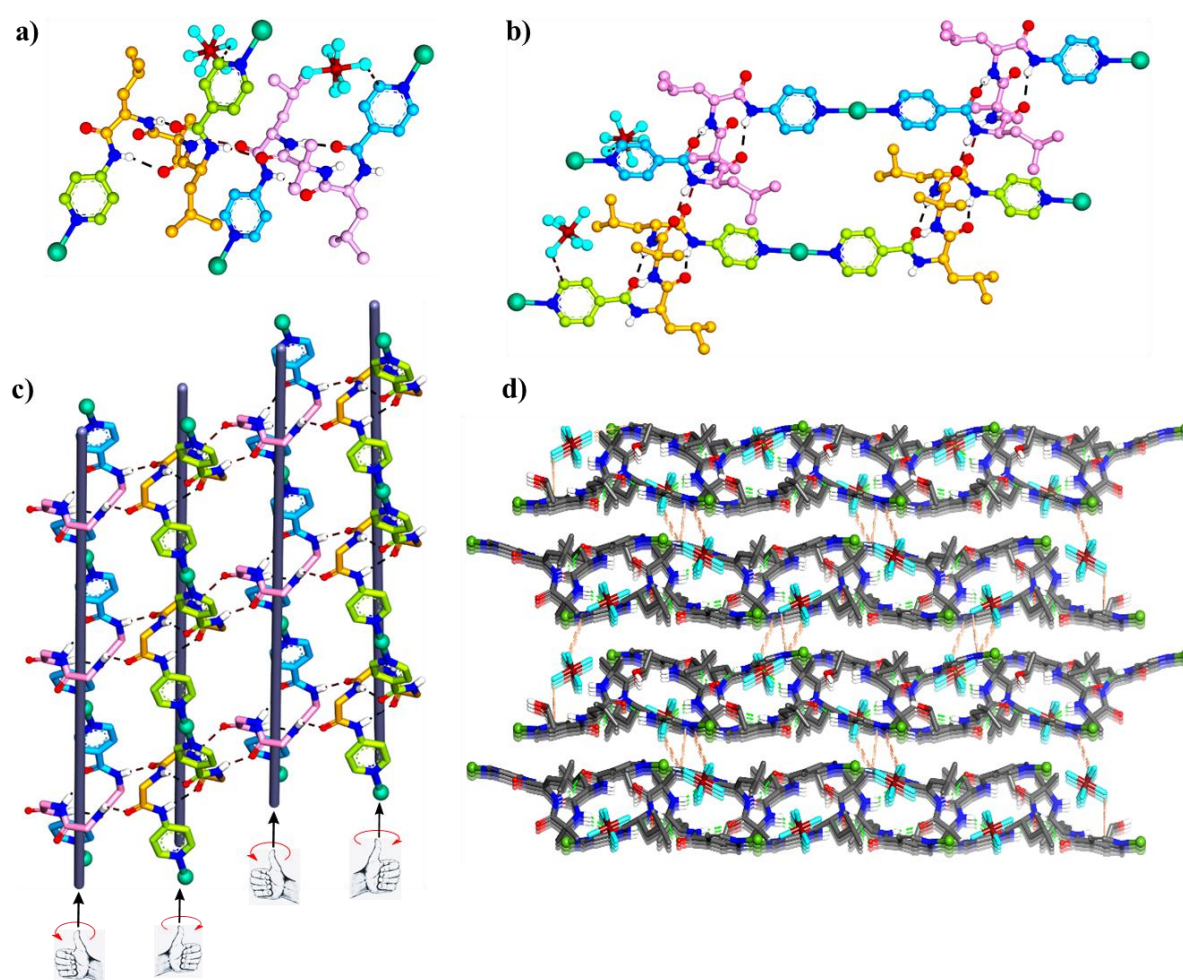


Figure 2: a) The X-ray diffraction structure of Silver coordinated **P1** in the presence of AgPF₆. b) The 'head-to-tail' Silver ion directed peptide assembly and the intermolecular H-bonding with PF₆⁻ anion in crystal packing. c) The continuous linear left- and right-handed helical

polymeric structures observed in the single crystals (for clarity side-chain residues have been omitted). d) The continuous linear polymeric structure along a-axis.

Though the left-handed short 3_{10} -helices have been found in the protein structures,¹⁶ it is quite surprising to note that short peptide with two L- α -residues adopted left-handed conformation. The transformative force exerted by metal coordination and other interacting forces inducing the transition from a right-handed helix to a left-handed helix bears conceptual similarity to proteins inherently possessing left-handed conformations within their three-dimensional structures. Analysis of the average ϕ and ψ angles for the left and right-handed helices revealed values of 54 ± 10 and 34 ± 14 , and -61 ± 12 and -24 ± 12 , respectively. Noteworthy structural alterations were attributed to the influence of the bulky PF_6^- anion, along with anion- π and aromatic CH---F interactions, collectively playing a significant role in facilitating the formation of metal-coordinated left- and right-handed helical polymers (see Figure 2c).

The torsion angles and H-bond parameters of the **P1**-AgPF₆ complex are given in Table 3-4.

Table 3: Torsion Angle Parameters of **P1**-AgPF₆.

Peptide		Residue	ϕ	Ψ
P1 -AgPF ₆	Molecule 1	Leu	-58	-34
		Aib	-53	-29
		Leu	-73	-12
	Molecule 2	Leu	45	48
		Aib	53	29
		Leu	64	25

Table 4: H-bond Parameters of **P1**-AgPF₆.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle \text{O}...\text{H}-\text{N}$
			in angstroms		in degrees
P1 -AgPF ₆	Molecule 1	Py CO $\leftarrow$ NH Leu	2.19	3.00	158
		Leu CO $\leftarrow$ NH Py	2.03	2.83	155
		Py CO $\leftarrow$ NH Leu	2.15	2.93	151

	Molecule 2	Leu CO $\leftarrow$ NH Py	2.14	2.92	151
Complex	Hydrogen bond (intermolecular)	C=O...H-N	C=O...N-H	$\angle$O...H-N	
		in angstroms			in degrees
P1-AgPF₆	Leu CO $\leftarrow$ NH Aib	2.21	2.88	135	
	Aib CO $\leftarrow$ NH Leu	2.05	2.87	162	

3.2.3. Crystal Structures Analysis of P1-AgNTf₂ Complex:

Encouraged by the structural divergence of **P1** in the presence of AgOTf and AgPF₆, we further sought to investigate the influence of a much bulkier anion on the structure and the assembly of **P1**. The peptides crystallized in the presence of AgNTf₂ salt. The single crystals were obtained at the interface of an aqueous solution of AgNTf₂ and the solution of peptide in ethanol at ambient temperature. The crystal structure of **P1-AgNTf₂** is shown in Figure 3a. The **P1-AgNTf₂** crystallized in the space group of P 2₁2₁2₁. In contrast to the previous structures described above, the peptide **P1** adopted a distorted helical structure. The helical structure is stabilized by two intramolecular 10-membered H-bonding between residues of CO (*i*) to NH (*i*+3) residues, however, the distance of the H-bond between the CO of the 4-pyridyl group and Leu3 NH is longer than the actual H-bond. The torsion angles of Leu1 were found to be -54 (ϕ) and +136 (ψ) and the next two residues adopted left-handed helix conformation. In their survey of protein structures, Basu and Chakrabarti^{22, 23} defined this type of folded structures as 3₁₀^{EL}-helices, where the first residue is in the extended region (E) and the next two residues in the left-handed conformation. Here, **P1** adopted 3₁₀^{EL}-helix conformation. Two 3₁₀^{EL}-helices are interconnected by the silver ion in a head-to-tail fashion. Besides the ionic interaction with silver ion, bis(trifluoromethanesulfonyl)imide is involved in intermolecular H-bonding with the Leu1 NH and also brings two helices closer together through intermolecular CH---O interaction with three 4-pyridyl groups of the two helices. The silver ion coordinate with **P1** in a head to tail fashion and displayed a right-handed infinite superhelical coordinated polymer (Figure 3c). The centre of the superhelix is occupied by the bis(trifluoromethanesulfonyl)imide anions.

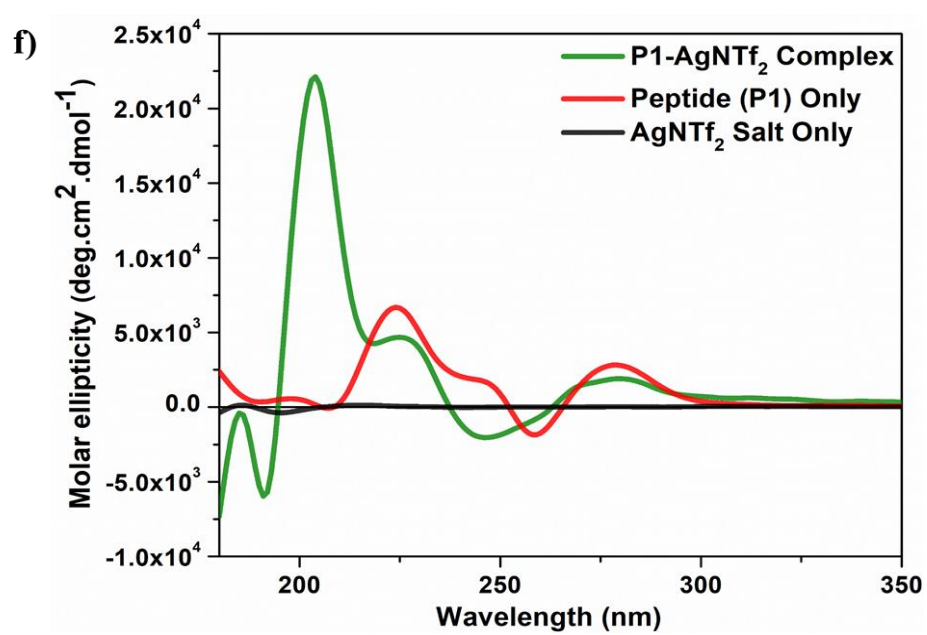
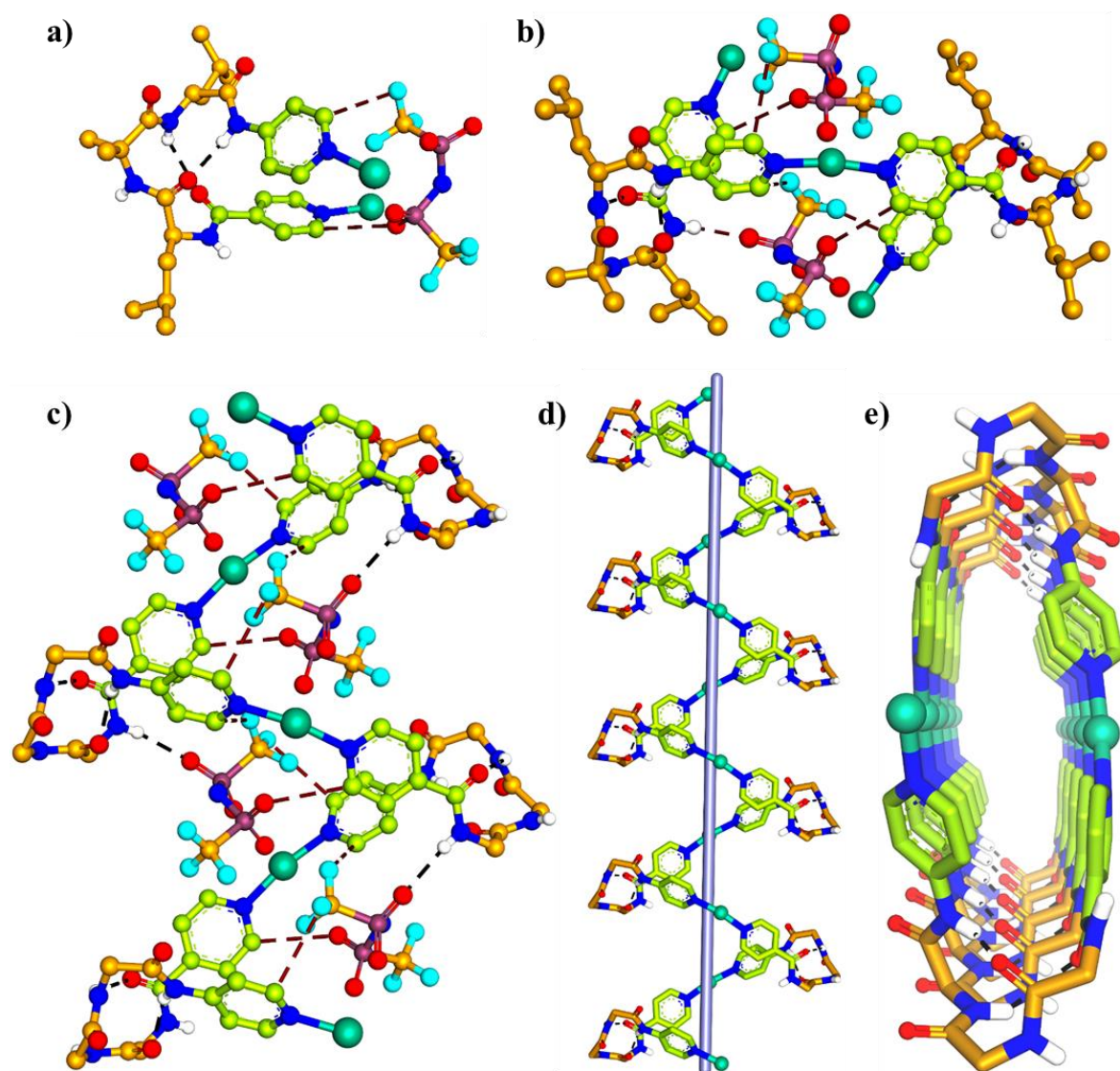


Figure 3: a) Crystal structure of silver coordinated **P1** in the presence of AgNTf₂ derived from single crystal X-ray diffraction data. b) The ‘head-to-tail’ Silver ion-directed peptide assembly and c) The interaction with NTf₂ anion in the crystal packing. d) and e) Side and upper view of superhelical structure along the vertical direction (for clarity side-chain residues have been omitted). f) CD spectra analysis of the peptide **P1** with AgNTf₂ salt.

The side-view and top view of the superhelix without amino acid side-chains are shown in Figures 3d and 3e, respectively. The helical conformation exhibited by the **P1**-AgNTf₂ complex was verified through comparative analysis of circular dichroism (CD) spectra with those of the native helical peptide **P1**, as shown in Figure 3f. The CD spectra of Peptide **P1** reveal characteristic maxima at 224 nm and 246 nm, indicative of its inherent helical structure. In contrast, the CD spectra of the **P1**-AgNTf₂ complex manifest altered features, with maxima observed at 204 nm and 226 nm. These spectral shifts provide spectroscopic evidence affirming the modification in helical structure induced by the coordination of **P1** with AgNTf₂. Overall **P1**-silver ion displayed remarkable structural plasticity to accommodate different sizes and the nature of the counter anions.

The torsion angles and H-bond parameters of the **P1**-AgNTf₂ complex are given in Table 5-6.

Table 5: Torsion Angle Parameters of **P1**-AgNTf₂.

Peptide	Residue	ϕ	Ψ
P1 -AgNTf ₂	Leu	-54	136
	Aib	52	37
	Leu	76	21

Table 6: H-bond Parameters of **P1**-AgNTf₂.

Complex	Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O...H-N
		in angstroms		in degrees
P1 -AgNTf ₂	Py CO ← NH Leu	2.53	3.26	142
	Leu CO ← NH Py	2.12	2.85	144
Complex	Hydrogen Bond (intermolecular)	C=O...H-N	C=O...N-H	∠O...H-N
		in angstroms		in degrees

P1-AgNTf₂	Aib CO(2) ← NH Aib(1)	2.26	2.84	124
	Aib CO(1) ← NH Aib(3)	2.26	2.84	124

3.2.4. Crystal Structures Analysis of P2-AgPF₆ Complex:

The structural diversity of **P1** in the presence of different counter anions of silver salt motivated us to investigate the possible structures and assemblies of the same peptide with different coordination sites. In this context, **P2** consisting of 3-pyridyl groups at the C- and N-terminus was designed and subjected to crystallization in the presence of various silver salts. Peptide **P2** gave single crystals at the interface of methanol/water in the presence of AgPF₆ at ambient temperature. In contradistinction to the dual-handed helical silver ion-coordinated polymers observed in the context of **P1** with AgPF₆, single crystal analysis of **P2** in the presence of AgPF₆ elucidated an exclusive adoption of a right-handed 3₁₀-helical conformation by the peptide. The silver ions facilitated the linkage of two helices in a ‘head-to-tail’ arrangement shown in Figure 4a. Concurrently, the hexafluorophosphate anion engaged in intermolecular C-F---H-N and C-F---H-C (3-pyridyl) interactions with distinct helices within the crystal packing (Figure 4b).

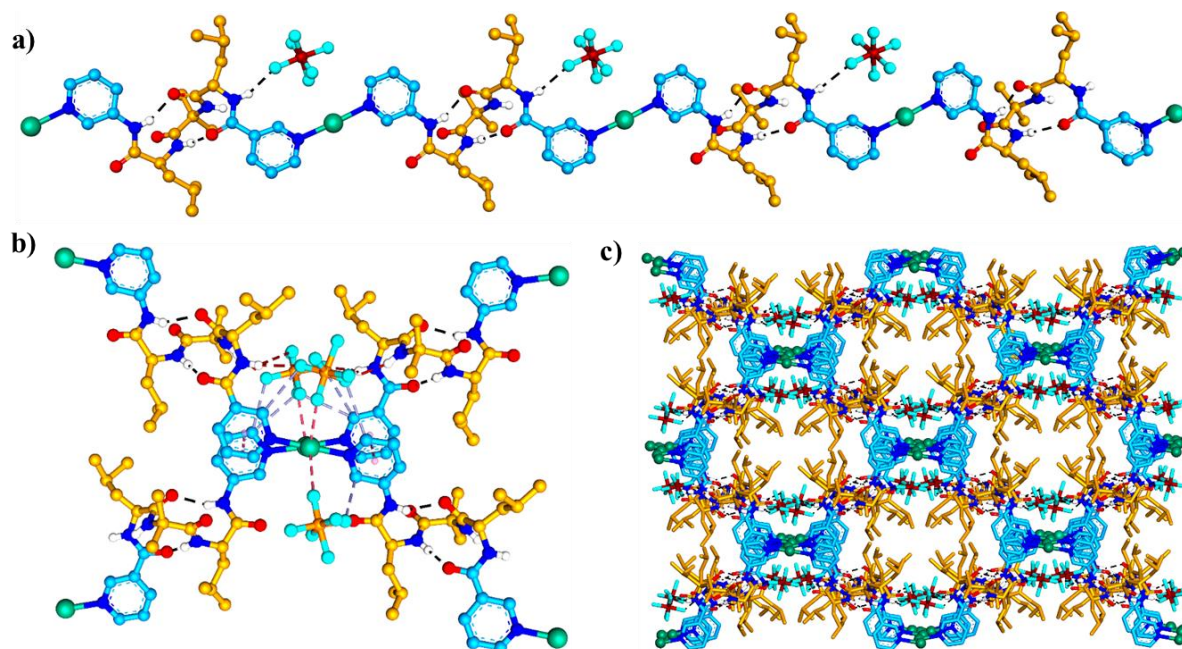


Figure 4: a) The ‘head-to-tail’ Silver ion directed peptide assemble crystal structure of **P2** in the presence of AgPF₆. b) Different interaction between anion and pyridine-containing peptide in metal coordination. c) The metal peptide closely packed porous structure along the c-axis.

These anion-peptide interactions served to bring the helices into closer proximity, with the silver ions maintained at a separation of 3.4 Å. The amalgamation of silver ion coordination and the diverse non-covalent interactions between peptides and anions collectively contributed to the establishment of a densely packed porous structure, as depicted in Figure 4c. These findings underscore the pronounced influence of the coordination site in dictating the supramolecular assembly, particularly in concert with counter anions.

The torsion angles and H-bond parameters of the **P2**-AgPF₆ complex are given in Table 7-8.

Table 7: Torsion Angle Parameters of **P2**-AgP₆.

Peptide		Residue	ϕ	Ψ
P2 -AgPF ₆	Molecule 1	Leu	-59	-37
		Aib	-58	-26
		Leu	-59	-29
	Molecule 2	Leu	-54	-30
		Aib	-54	-34
		Leu	-54	-33

Table 8: H-bond Parameters of **P2**-AgPF₆.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O...H-N
			in angstroms		in degrees
P2 -AgPF ₆	Molecule 1	Py CO ← NH Leu	2.20	3.02	154
		Leu CO ← NH Py	2.02	2.84	154
	Molecule 2	Py CO ← NH Leu	2.94	3.01	86
		Leu CO ← NH Py	2.11	2.90	150

3.2.5. Crystal Structures Analysis of **P2**-(AgPF₆+AgBF₄) Complex:

Inspired by the porous network evident in **P2** upon interaction with AgPF₆, we conducted an X-ray analysis on single crystals generated through the interaction of **P2** with a 1:1 mixture of AgPF₆ and AgBF₄. The formation of single crystals by Peptide **P2** was achieved at the

methanol/water interface, initiated by treating a mixture of AgPF₆ and AgBF₄ at ambient temperature. The ensuing X-ray diffraction analysis revealed the adoption of a C₁₀ helical structure by Peptide **P2**, shown in Figure 5a. The single crystal structure exhibited the coexistence of both BF₄ and PF₆ anions within the asymmetric unit, with conformational analysis confirming the right-handed helical nature of both helices present in the asymmetric unit. Silver ions facilitated the linkage of two helices in a ‘head-to-tail’ arrangement shown in Figure 5a. The average ϕ and ψ torsion angles of Leu residues were found to be $-65\pm5^\circ$ and $-25\pm5^\circ$, respectively, while Aib displayed angles of -55° and -28° , respectively. Simultaneously, both BF₄ and PF₆ anions participated in intermolecular C-F---H-N and C-F---H-C (3-pyridyl) interactions with distinct helices within the crystal packing, as delineated in Figure 5b. The continuous ‘head-to-tail’ coordination with silver ions, combined with intra- and intermolecular hydrogen bonding and π - π stacking interactions, culminated in the formation of a three-dimensional Metal-peptide framework along the c-axis, shown in Figure 5c.

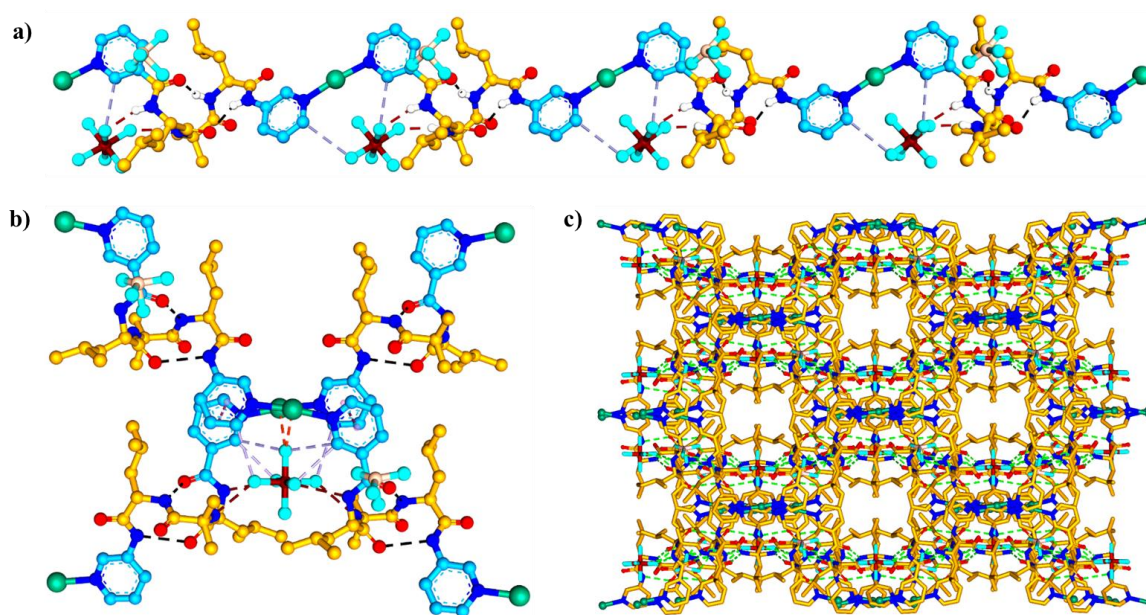


Figure 5: a) The ‘head-to-tail’ Silver ion-directed peptide assemble crystal structure of **P2** in the presence of both AgBF₄ and AgPF₆ salts. b) Interaction between anions and pyridine-containing peptide in metal coordination. c) The metal peptide porous network along the c-axis.

The torsion angles and H-bond parameters of the **P2**-(AgPF₆+AgBF₄) complex are given in Table 9-10.

Table 9: Torsion Angle Parameters of **P2**-(AgBF₆+AgBF₄).

Peptide		Residue	ϕ	Ψ
P1 -AgPF ₆ +AgBF ₄	Molecule 1	Leu	-59	-38
		Aib	-55	-28
		Leu	-69	-20
	Molecule 2	Leu	-65	-24
		Aib	-57	-26
		Leu	-86	-26

Table 10: H-bond Parameters of **P2**-(AgBF₆+AgBF₄).

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O....H-N
			in angstroms		in degrees
P2 -AgPF ₆ +AgBF ₄	Molecule 1	Py CO $\leftarrow$ NH Leu	2.14	2.91	145
		Leu CO $\leftarrow$ NH Py	2.07	2.88	152
	Molecule 2	Py CO $\leftarrow$ NH Leu	2.17	3.00	158
		Leu CO $\leftarrow$ NH Py	2.12	2.87	143

3.2.6. Crystal Structures Analysis of **P2**-AgNO₃ Complex:

Further, we examined the **P2** structure and assembly in the presence of AgNO₃. The crystal structure analysis of the **P2**-AgNO₃ complex revealed a remarkable 2:2 macrocycle of peptide and silver ions. The structure is shown in Figure 6a. In the presence of AgNO₃, **P2** adopted the left-handed 3₁₀^{EL}-helical structure similar to the structure of **P1** in the presence of AgNTf₂. The two helical units are held together by two silver ions in a ‘head to tail’ fashion. The structure is stabilized by two incipient 10-membered H-bonds, however, the distance of N-terminal 3-pyridyl amide CO (*i*) and Leu3 NH (*i*+3) is longer (2.56 Å) than the regular H-bonds. Further, the CO of Leu1 is involved in the 10-membered H-bonding with the C-terminal 3-pyridyl NH with a regular distance of 2.10 Å. The analysis of the crystal structure revealed that the nitrate anion interacts with both Ag (I) ions in the macrocycle and bringing them closer together. In

addition, Aib 2 CO also interacts with Ag (I) and this interaction leads to continuous bridged macrocycles (Figure 6c).

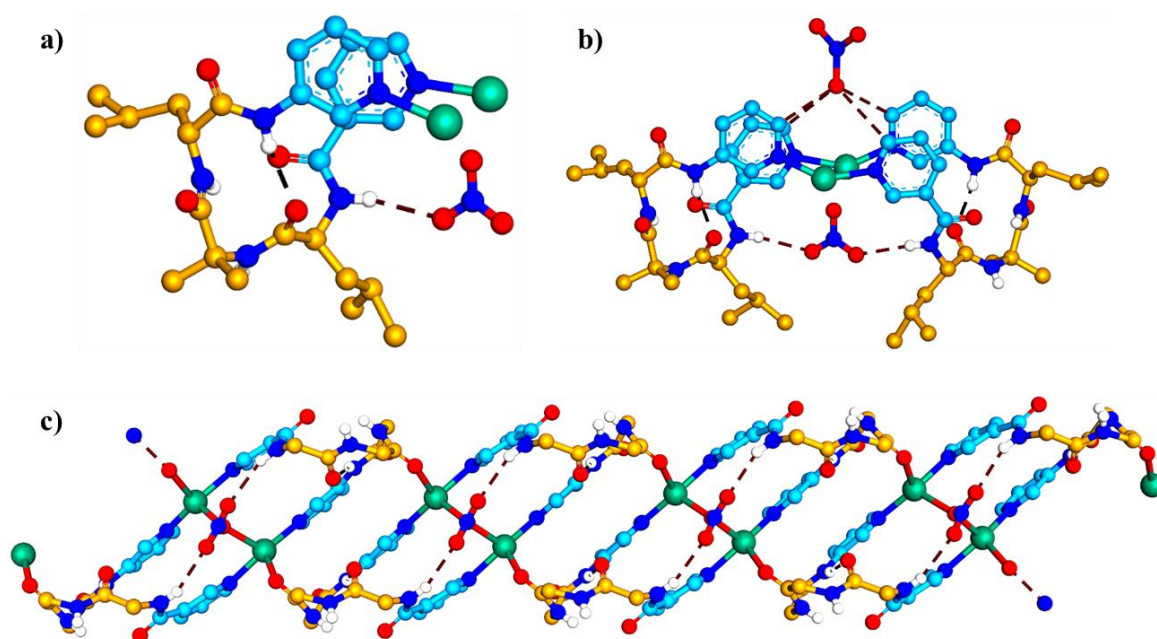


Figure 6: a) Crystal structure of silver coordinated **P2** in the presence of AgNO₃ derived from single crystal X-ray diffraction data. b) The macrocyclic structure of **P2** in the presence of AgNO₃. c) Continuous bridge polymeric structure along the horizontal direction (for clarity side-chain residues have been omitted).

The torsion angles and H-bond parameters of the **P2**-AgNO₃ complex are given in Table 11-12.

Table 11: Torsion Angle Parameters of **P2**-AgNO₃.

Peptide		Residue	ϕ	Ψ
P1 -AgNO ₃	Molecule 1	Leu	-60	152
		Aib	53	29
		Leu	79	20
	Molecule 2	Leu	-60	150
		Aib	57	26
		Leu	76	22

Table 12: H-bond Parameters of **P2**-AgNO₃.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O...H-N
			in angstroms		in degrees
P2- AgNO ₃	Molecule 1	Py CO ← NH Leu	2.99	3.23	113
		Leu CO ← NH Py	2.89	2.95	88
	Molecule 2	Py CO ← NH Leu	2.60	3.25	131
		Leu CO ← NH Py	2.12	2.98	163

Overall, these results revealed a remarkable structural flexibility of the tripeptide. It can adopt right-handed, left-handed 3_{10} -helix conformations, 3_{10}^{EL} conformation in the presence of various anions. In contrast to the stable 12-helix displayed α,γ -hybrid peptides in the absence or presence of metal salts, to the α -peptide adopted diverse conformations.

3.2.7. Structural Analysis of **P2**-AgOTf and **P2**-AgNTf₂ Complex:

Motivated by the observed structural divergence of **P2** in the presence of AgBF₄, AgPF₆, and AgNO₃, we embarked on an investigation to discern the impact of substantially bulkier anions on the structural framework and assembly of **P2**. To this end, we endeavored to crystallize peptide **P2** in the presence of AgOTf and AgNTf₂ salts, employing the layering method in methanol/water or ethanol/water solvent systems. Notably, the crystallization attempts yielded small, thin, and fragile crystals at the ethanol/water interface in the presence of the respective metal salts. Unfortunately, the tiny size of these crystals precluded successful diffraction analysis. To avoid this limitation and derive structural insights, Powder X-ray Diffraction (PXRD) experiments were conducted on the **P2**-AgOTf and **P2**-AgNTf₂ complexes at a temperature of 150 K, as shown in Figure 7. After obtaining the PXRD data, structural elucidation of these peptide-metal complexes was pursued using the McMaille method, facilitated by the Highscore Plus software. The comprehensive structural details are given in Table 13-14, providing valuable insights into the intriguing behavior of **P2** in the presence of AgOTf and AgNTf₂.

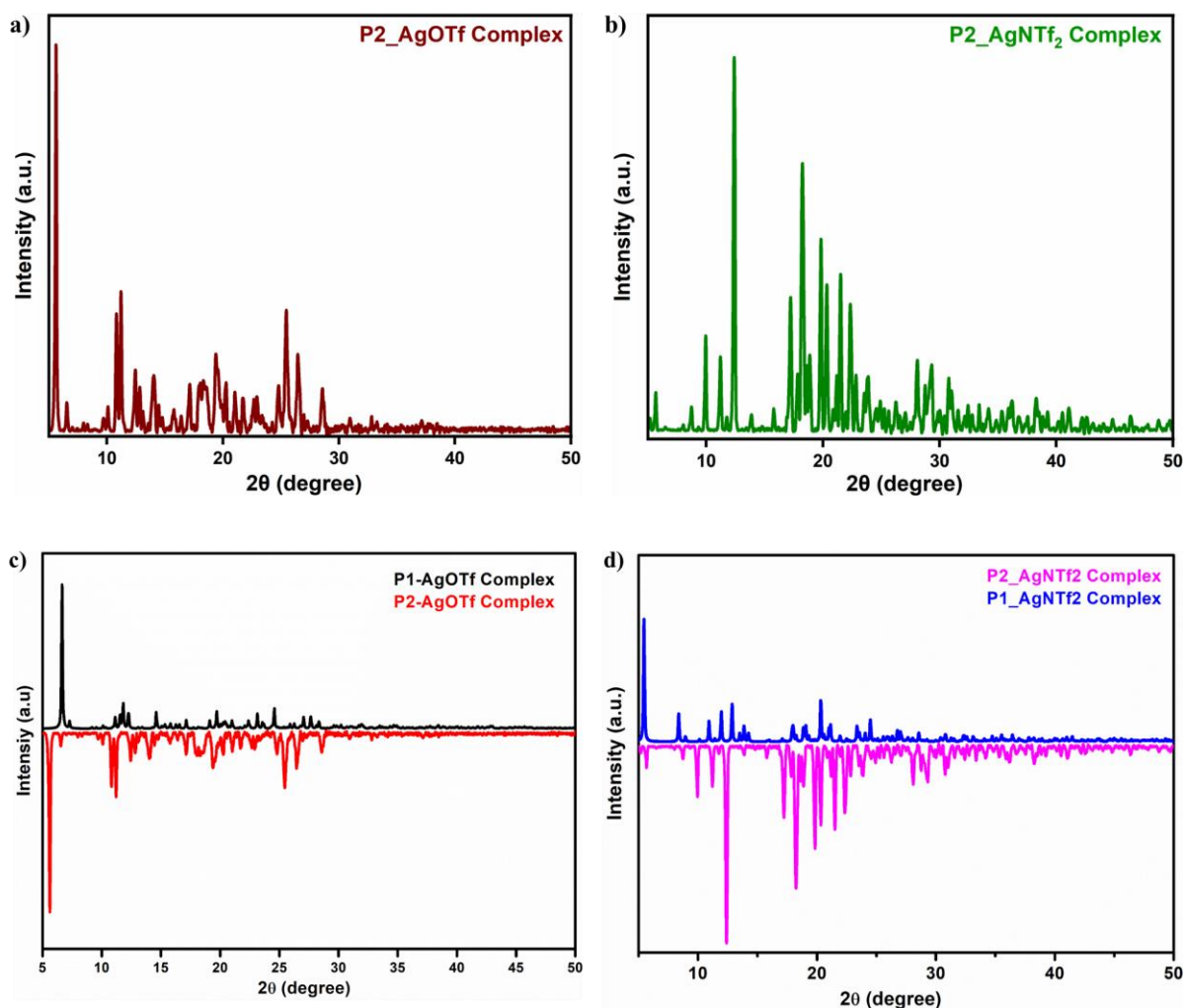


Figure 7: a), and b) PXRD data of **P2-AgOTf** and **P2-AgNTf₂** complexes at 150 K temperature. c) Comparing PXRD data of **P2-AgOTf** complex with simulated PXRD data of **P1-AgOTf** crystal. d) Comparing PXRD data of **P2-AgNTf₂** complex with simulated PXRD data of **P1-AgNTf₂** crystal.

The PXRD data of **P2-AgOTf** and **P2-AgNTf₂** at 150 K was analyzed using the Highscore Plus software suit. McMaille method was used to index the pattern and the cell parameters were refined for zero 2-theta shift.

Table 13: Indexed PXRD unit cell parameter for **P2-AgOTf** complex at 150 K.

Crystal System		Monoclinic
Space Group		P 2 ₁ /n
Cell Parameters		ESDs
a (Å)	24.10	0.01
b (Å)	3.651	0.003

c (Å)	15.715	0.007
α (°)	90	0
β (°)	94.326	0.007
γ (°)	90	0
V (Å ³)	1378.63	0

Table 14: Indexed PXRD unit cell parameter for **P2**-AgNTf₂ complex at 150 K.

Crystal System		Tetragonal
Space Group		P 4₂
Cell Parameters		ESDs
a (Å)	15.24	0.01
b (Å)	15.24	0.01
c (Å)	10.59	0.02
α (°)	90	0
β (°)	90	0
γ (°)	90	0
V (Å ³)	2460.72	0

3.2.8. Crystal Structures Analysis of Peptide **P3**:

Motivated by the structural diversity inherent in the backbone configurations of short α -tripeptides **P1** and **P2** in the presence of several silver salts, we shout to design another tripeptide, denoted as **P3**. In the design of **P3**, we replace sterically hindered α,α -dialkyl amino acids (Aib) from middle to terminal position as well as manipulated the coordinating site of the peptide, recognizing the pivotal role that such alterations play in influencing structural diversity. Specifically, in the construction of peptide **P3**, we replaced the C-terminal 4-pyridyl coordinating group with a bipyridine binder, but, we retained the 4-pyridyl binder at the N-terminal end in peptide **P1**, as shown in Figure 8b. Subsequently, our investigation involved attempts to crystallize peptide **P3**. Remarkably, through the controlled process of slow evaporation of methanol at ambient temperature, a single crystal of **P3** was successfully obtained.

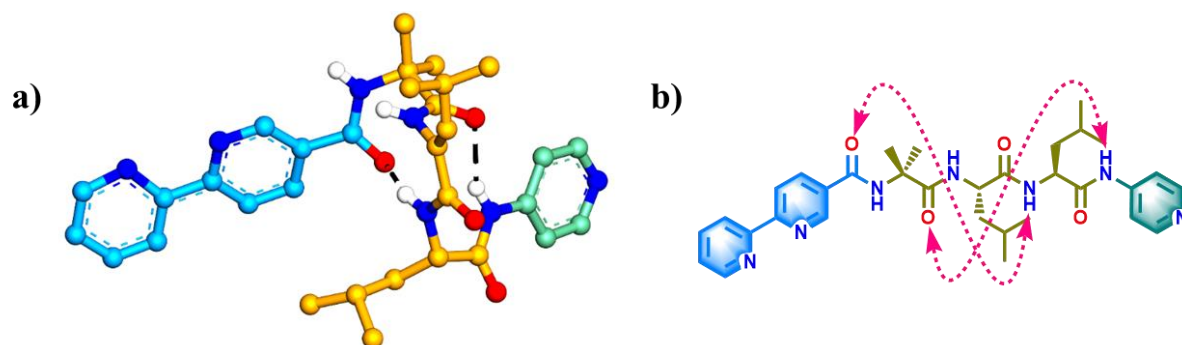


Figure 8: a) X-ray diffraction structures **P3**. b) H-bonding pattern of **P3** 3_{10} -helix is represented here.

The crystal structure revealed that peptide **P3** adopted a classical right-handed 3_{10} -helix conformation in single crystals. The short helix structure is stabilized by two successive intramolecular 10-membered hydrogen bonds between the residues of CO (*i*) to NH (*i*+3) shown in Figure 8a. The average ϕ and ψ torsion angles of Leu residues are $-80 \pm 5^\circ$ and $-15 \pm 2^\circ$ respectively, while Aib displayed -51° and -49° respectively.

The torsion angles and H-bond parameters of the **P3** are given in Table 15 -16.

Table 15: Torsion Angle Parameters of **P3**.

Peptide		Residue	ϕ	Ψ
P4		Aib	-51	-49
		Leu	-69	-13
		Leu	-89	-15

Table 16: H-bond Parameters of **P3**.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
			in angstroms		in degrees
Peptide P4	Molecule 1	Py CO $\leftarrow$ NH Leu	2.17	2.91	144
	Molecule 2	Aib CO $\leftarrow$ NH Py	2.16	2.95	152
Complex		Hydrogen Bond (intermolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
			in angstroms		in degrees
Peptide P4	Molecule 1	Leu CO(2) $\leftarrow$ NH Aib(1)	2.046	2.88	150
	Molecule 2	Leu CO(1) $\leftarrow$ NH Aib(3)	2.046	2.88	148

	Molecule 3	Leu NH(1) ← N Py(4)	2.06	2.903	165
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3.2.9. Crystal Structures Analysis of P3-AgBF₄ Complex:

In our previous study, Peptide **P3** was identified as forming a robust 3_{10} -helix in the absence of metal coordination. In order to elucidate the impact of metal coordination on its conformation, we conducted a comprehensive crystallization study involving diverse metal salts and solvent combinations. Notably, single crystals were exclusively obtained at the interface of a peptide solution in methanol and an aqueous solution containing various silver salts. Subsequent analysis of these single crystals through X-ray diffraction unveiled crucial structural insights. Peptide **P3** gave single crystals at the interface of methanol/water upon treatment of AgBF₄ at ambient temperature. The resulting **P3**-AgBF₄ complex crystallized in the P 2₁/n space group. Notably, the helical nature of **P3** persisted, adopting a classical right-handed 3_{10} -helix conformation within the confines of these single crystals. The stability of this abbreviated helical structure was ascribed to the formation of two emerging 10-membered intramolecular hydrogen bonds between CO (*i*) and NH (*i*+3) residues, as shown in Figure 9a. The average torsion angles (ϕ and ψ) of Leu residues were determined to be $-70\pm5^\circ$ and $-20\pm5^\circ$, respectively, while Aib exhibited torsion angles of -53° and -34° , respectively. Moreover, the terminal bipyridyl and 4-pyridyl moieties exhibit active involvement in silver ion coordination, effectively linking the two 3_{10} -helices through the silver ion in a head-to-tail orientation shown in Figure 9b. In addition to the ionic interaction with the silver ion, BF₄⁻ engages in intermolecular hydrogen bonding interactions with the Aib NH and Leu1 NH via NH...F interactions. The head-to-tail coordination of the silver ion with Peptide **P3** gives rise to the development of a right-handed infinite superhelical structure. The side view and the top view of this superhelix are shown in Figure 9c and 9d.

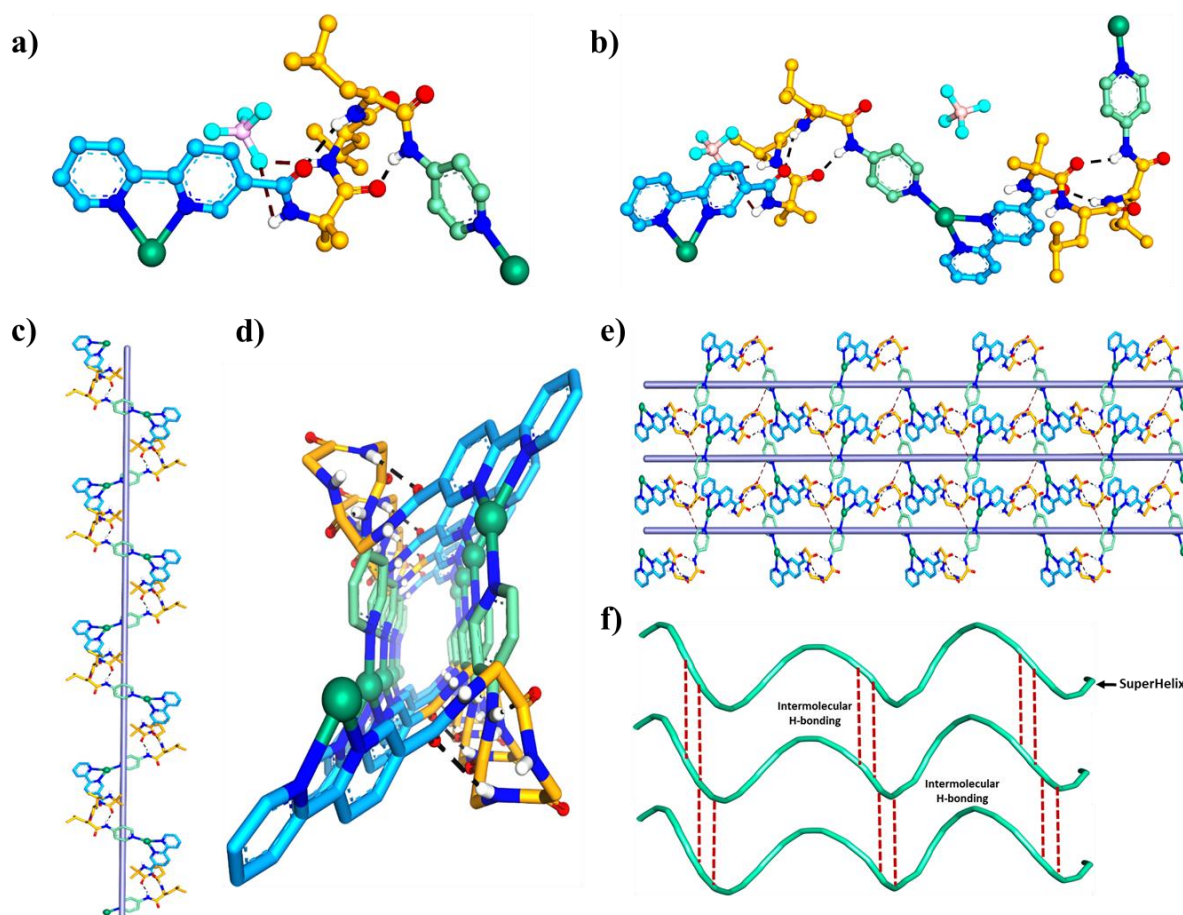


Figure 9: a) Crystal structure of silver coordinated **P3** in the presence of AgBF_4 derived from single crystal X-ray diffraction data. b) The ‘head-to-tail’ Silver ion-directed peptide assembly. c), and d) Side and upper view of superhelical structure along the vertical direction (for clarity side-chain residues have been omitted). e) Supramolecular assembly of the superhelical polymer by intermolecular H-bonds. f) A cartoon representation of a hierarchical assembly of superhelical Sheet.

Notably, each **P3**- AgBF_4 coordinated superhelix demonstrates interconnectivity through intermolecular "head-to-tail" hydrogen bonds with another **P3**- AgBF_4 coordinated superhelix. This intricate molecular arrangement culminates in the emergence of a remarkable hierarchical superhelical β -sheet structure, as illustrated in Figure 9e and 9f.

The torsion angles and H-bond parameters of the **P3**- AgBF_4 complex are given in Table 17 - Table 18.

Table 17: Torsion Angle Parameters of **P3-AgBF₄**.

Peptide	Residue	ϕ	Ψ
P4-AgBF₄	Aib	-53	-34
	Leu	-59	-25
	Leu	-78	-15

Table 18: H-bond Parameters of **P3-AgBF₄**.

Complex	Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
		in angstroms		in degrees
P4-AgBF ₄	Py CO $\leftarrow$ NH Leu	2.239	3.054	158
	Aib CO $\leftarrow$ NH Py	2.092	2.911	159

3.2.10. Crystal Structures Analysis of **P3-AgNO₃** Complex:

Inspired by the superhelical sheet architecture observed in Peptide **P3** upon interaction with AgBF₄, we conducted X-ray crystallography on singular crystals generated through the interaction of **P3** with AgNO₃. Peptide **P3** exhibited a propensity to form single crystals at the methanol/water interface following exposure to AgNO₃ at ambient temperature. The resultant **P3-AgNO₃** complex crystallized within the P 2₁/n space group. Analogous to the **P3-AgBF₄** complex, the **P3-AgNO₃** complex also form a classical right-handed 3₁₀-helix conformation within the confines of single crystals. The stability of the abbreviated helical structure was discerned through the formation of two incipient 10-membered intramolecular hydrogen bonds between CO (*i*) and NH (*i*+3) residues, as shown in Figure 10a. The average torsion angles (ϕ and ψ) of Leu residues were determined to be $-70 \pm 5^\circ$ and $-20 \pm 5^\circ$, respectively, while Aib exhibited torsion angles of -54° and -27° , respectively. Analogous to the **P3-AgBF₄** complex, the **P3-AgNO₃** complex demonstrates the engagement of the terminal bipyridyl and 4-pyridyl moieties in silver ion coordination, facilitating the connection between two 3₁₀-helices through the silver ion in a head-to-tail conformation, as depicted in Figure 10b. Beyond the ionic interaction with the silver ion, NO₃⁻ participates in intermolecular hydrogen bonding with the Aib NH and Leu1 NH via NH...F interactions. The head-to-tail coordination of the silver ion

with Peptide **P3** instigates the formation of a right-handed infinite superhelical structure, as shown in Figure 10c (Side View) and 10d (Top View).

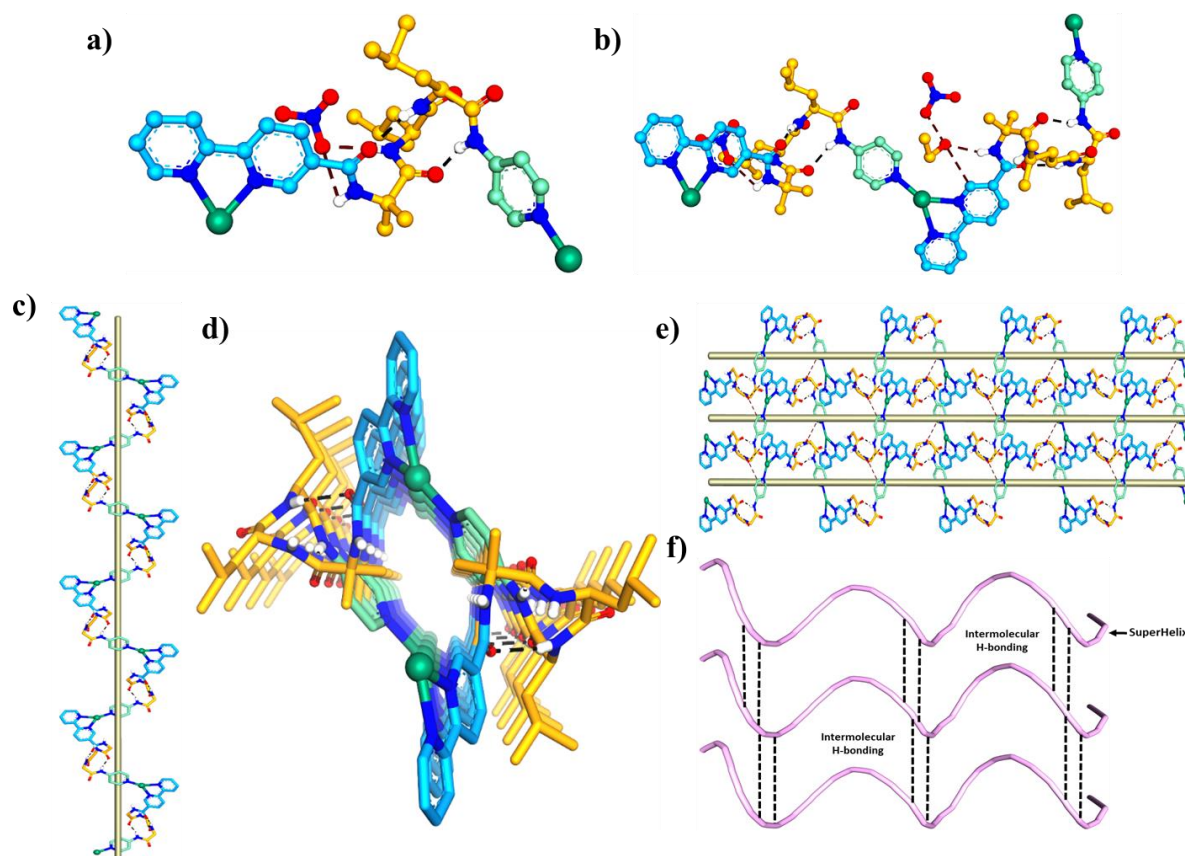


Figure 10: a) Crystal structure of silver coordinated **P3** in the presence of AgNO₃ derived from single crystal X-ray diffraction data. b) The 'head-to-tail' Silver ion-directed peptide assembly. c), and d) Side and upper view of superhelical structure along the vertical direction (for clarity side-chain residues have been omitted). e) Supramolecular assembly of the superhelical polymer by intermolecular H-bonds. f) Cartoon diagram of a hierarchical assembly of superhelical Sheet.

Instructively, each **P3**-AgNO₃ coordinated superhelix demonstrates interconnectivity through intermolecular "head-to-tail" hydrogen bonds with another **P3**-AgNO₃ coordinated superhelix. This intricate molecular assembly leads to the development of a remarkable hierarchical superhelical β -sheet structure, elucidated in Figures 10e and 10f. These findings contribute significantly to the nuanced understanding of the structural intricacies inherent in the interaction between Peptide **P3** and diverse metal ions, further advancing our comprehension of the conformational landscape of such molecular assemblies.

The torsion angles and H-bond parameters of the **P3**-AgNO₃ complex are given in Table 19-20.

Table 19: Torsion Angle Parameters of **P3-AgNO₃**.

Peptide	Residue	ϕ	Ψ
P3-AgNO₃	Aib	54	27
	Leu	60	24
	Leu	75	15

Table 20: H-bond Parameters of **P3-AgNO₃**.

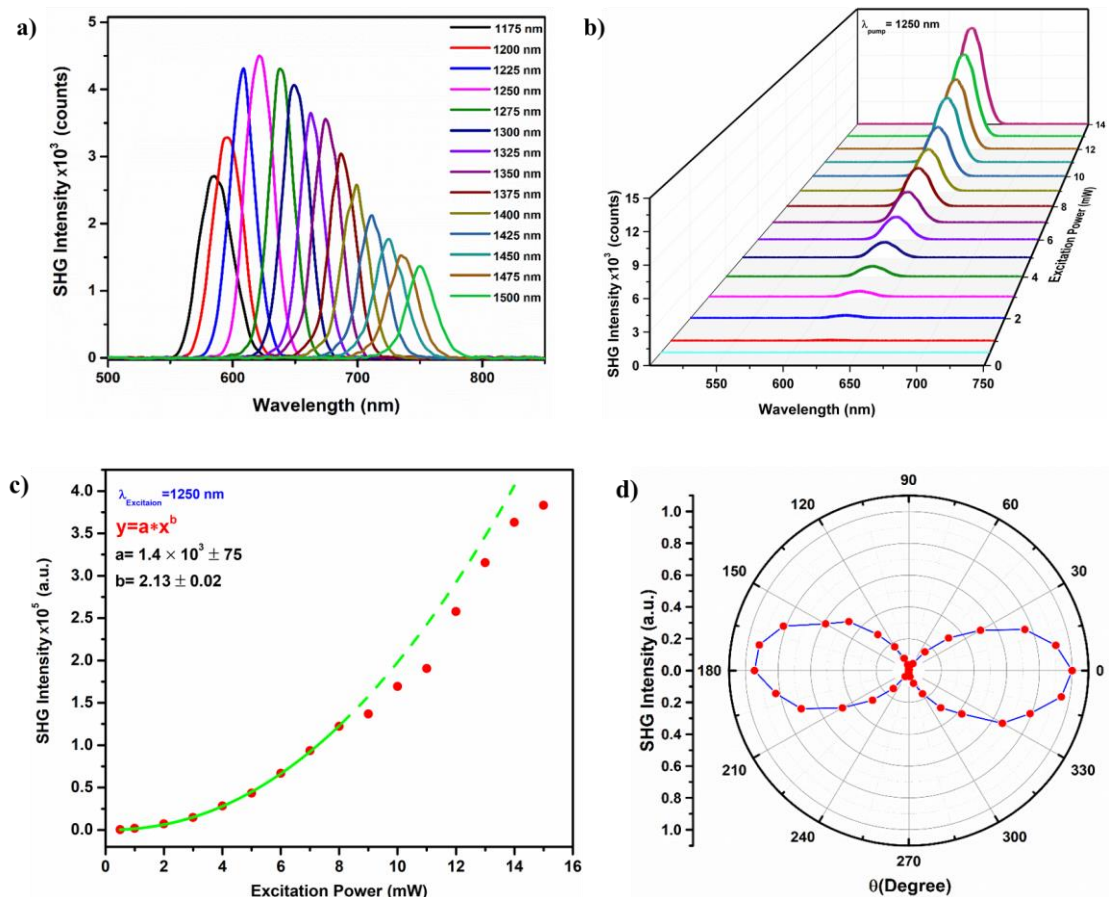
Complex	Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
		in angstroms		in degrees
P3-AgNO₃	Py CO $\leftarrow$ NH Leu	2.207	3.053	161
	Aib CO $\leftarrow$ NH Py	2.033	2.873	160

4. Nonlinear Optical Properties of Peptide-Metal Complex:

Due to the adoption of a non-centrosymmetric space group by these peptide-silver complexes and the inherent presence of a macro-dipole, an investigation into their second-order nonlinear optical properties through second harmonic generation (SHG) is warranted.²⁴ SHG, a nonlinear optical phenomenon, involves the combination of two incident photons of frequency ω within a non-centrosymmetric medium, resulting in a single photon with double the frequency (2ω).²⁵ The energy upconversion inherent in SHG has found applications in diverse fields such as imaging, healthcare, and data storage.²⁶ While inorganic crystals traditionally serve as common materials for SHG, recent attention has extended to hybrid metal-halide perovskites, organic dyes²⁷, chromophore-conjugated peptide crystals, and self-assembled peptides in exploring their SHG properties²⁸. Notably, the investigation of SHG properties in metalloptides remains relatively underexplored. In light of this, we embarked on a study to assess the applicability of metalloptides for SHG. Specifically, we examined silver ion-coordinated **P1** crystals, encompassing diverse structures and assemblies, as potential candidates for showcasing SHG phenomena within the realm of metalloptide systems.

4.1. Second Harmonic Generation (SHG) of **P1-AgOTf** Complex:

SHG measurements were conducted on crystals of the **P1**-AgOTf complex, where **P1** exhibited a right-handed helical structure within the crystal packing. Utilizing the output of an ultrafast optical parametric amplifier with a pulse width of approximately 50 fs as the excitation source for SHG experiments (details given below), the **P1**-AgOTf crystals demonstrated tunable SHG responses across a broad spectral range spanning from 550 to 800 nm. These responses were observed when subjecting the crystals to various infrared pump wavelengths while maintaining a constant power of 8 mW. Remarkably, the highest SHG intensity manifested at a pump wavelength of 1250 nm. The corresponding SHG intensity at different input wavelengths of light is depicted in Figure 11a. Furthermore, to assess the optical stability, the Laser-Induced Damage Threshold (LIDT) of the **P1**-AgOTf complex was calculated. Power-dependent SHG measurements of the **P1**-AgOTf complex at 1250 nm (Figures 11b and 11c) revealed a notably high LIDT value of 24 GW/cm², indicative of excellent optical stability (detailed calculation shown below). The two-lobed SHG response obtained by varying the plane of polarization of the incident light is illustrated in Figure 11d. Additionally, Figure 11f portrays the emission of red light from the crystals subsequent to irradiation at a wavelength of 1250 nm. These collective findings strongly support the assertion that **P1**-AgOTf crystals exhibit pronounced SHG activity.



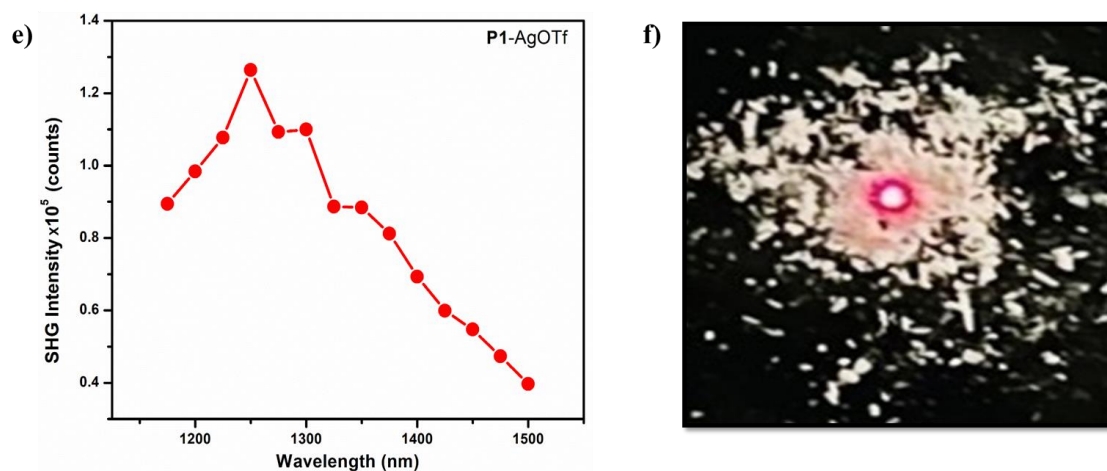


Figure 11: a) The SHG spectra of **P1-AgOTf** complex with different excitation wavelengths (1175 nm- 1500 nm). b) Excitation power-dependent SHG spectra of **P1-AgOTf** complex at 1250 nm. c) Quadratic fitting of the power-dependent SHG response at 1250 nm. An increase in SHG output was observed with an increase in excitation power having a quadratic dependence till 8 mW for **P1-AgOTf** complex. Deviation from the respective fits reflects the laser-induced damage threshold. For **P1-AgOTf** complex, crystal above 8 mW was the deviation of SHG output. d) Variation of SHG intensity with the change in direction of polarization of incident light of **P1-AgOTf** crystal using 1250 nm as excitation wavelength at 5mW power. e) Integrated intensity at different excitation wavelengths from 1175 nm to 1500 nm. f) Red light of 625 nm generated due to the 1250 nm pump wavelength.

4.1.1. Laser-Induced Damage Threshold (LIDT) Calculation of P1-AgOTf Complex:

The pump intensity, at which the SHG response deviates from a quadratic behaviour, determines the LIDT value.²⁹ Peak laser intensity corresponding to that pump intensity is the LIDT for the sample.

LIDT of Peptide-Metal complex = Peak intensity at which SHG response deviates from quadratic behavior called average power.

$$\text{Peak Intensity} = \frac{\text{Energy per pulse}}{(\text{Pulse width}) \times (\text{Effective spot area})}$$

$$\text{Energy per pulse} = \frac{\text{Average Power}}{\text{Repetition Rate}}$$

$$\text{LIDT} = \text{Peak Intensity} = \frac{\text{Average power}}{(\text{Repetition rate}) \times (\text{Pulse width}) \times (\text{Effective spot area})}$$

For our setup, $Repetition\ rate = 1000\ Hz$, $Pulse\ width = 50 \times 10^{-15}\ s$, $Beam\ radius = 460 \times 10^{-6}\ m$.

For **P1**-AgOTf complex, SHG response deviates from quadratic behavior after 8mW. $Average\ power = 8 \times 10^{-3}\ W$ for **P1**-AgOTf complex.

$$\begin{aligned}
 LIDT(\mathbf{P1} - AgOTf) &= \frac{8 \times 10^{-3}\ W}{(1000\ Hz) \times (50 \times 10^{-15}\ s) \times (\pi \times (460 \times 10^{-6}\ m)^2)} \\
 &= 24 \times 10^{13}\ W/m^2 \\
 &= 24\ GW/cm^2
 \end{aligned}$$

4.2. Second Harmonic Generation (SHG) of **P1**-AgPF₆ Complex:

Similar to the non-centrosymmetric structure observed in **P1**-AgOTf crystals, peptide **P1** also adopts a non-centrosymmetric structure in the presence of AgPF₆ salt. Further, we examined **P1**-AgPF₆ crystals for the SHG activity using pump pulses spanning wavelengths from 1175 nm to 1500 nm at a constant power of 7 mW. Remarkably, despite the non-centrosymmetric nature of the crystals, no discernible second harmonic generation (SHG) signals were detected shown in Figure 12. This absence of SHG activity can be attributed to the coexistence of both left-handed and right-handed ₃₁₀-helical conformations within the asymmetric unit.

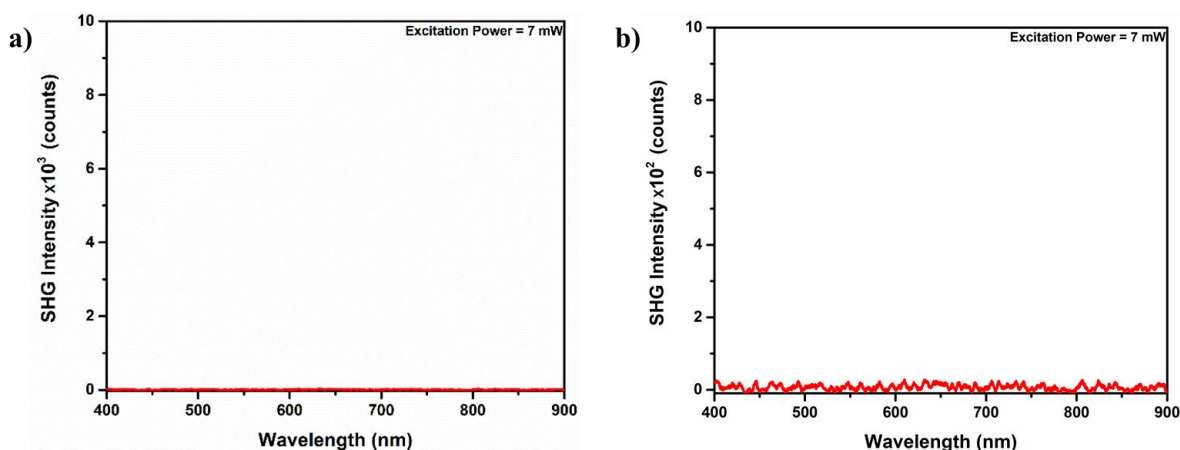
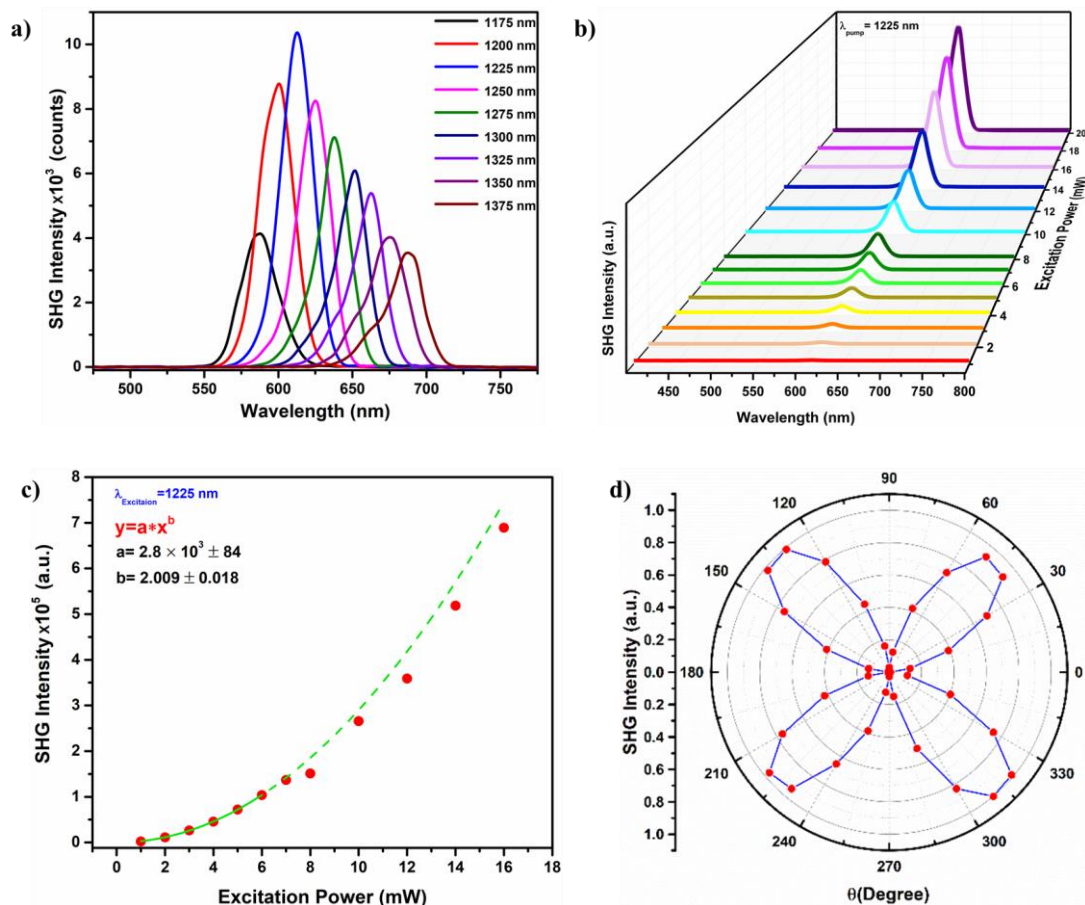


Figure 12: a), and b) The SHG spectra of **P1**-AgPF₆ complex with different excitation wavelengths 1150 nm to 1575 nm at 7mW excitation power. All other experimental conditions were kept the same as that of **P1**-AgOTf and **P1**-AgNTf₂.

4.3. Second Harmonic Generation (SHG) of P1-AgNTf₂ Complex:

Continuing our investigation, crystals of **P1-AgNTf₂**, featuring a silver ion-coordinated superhelix assembly derived from the 3₁₀^{EL}-helix, exhibited tunable second harmonic generation (SHG) responses across a broad spectral range spanning from 550 to 700 nm. These responses were observed when subjecting the crystals to various infrared pump wavelengths at a constant power of 7.5 mW. Analogous to the behavior observed in **P1-AgOTf** crystals, the maximum SHG intensity was recorded at a pump wavelength of 1225 nm. Furthermore, the **P1-AgNTf₂** complex demonstrated a high Laser-Induced Damage Threshold (LIDT) value of 22.5 GW/cm², underscoring the excellent optical stability of this complex. The intensity of the SHG response at different input wavelengths is delineated in Figure 13a. Additionally, polarization-dependent SHG measurements were conducted on **P1-AgNTf₂** crystals at a constant power of 5 mW, employing a pump wavelength of 1225 nm. The resultant four-lobed SHG response, as depicted in Figure 13d, suggests a relatively more isotropic polarization tensor within the **P1-AgNTf₂** complex. Finally, upon irradiation with near-infrared light at 1225 nm, the emission of orange light from the **P1-AgNTf₂** crystals is illustrated in Figure 13f, further corroborating the distinctive nonlinear optical behavior of this complex.



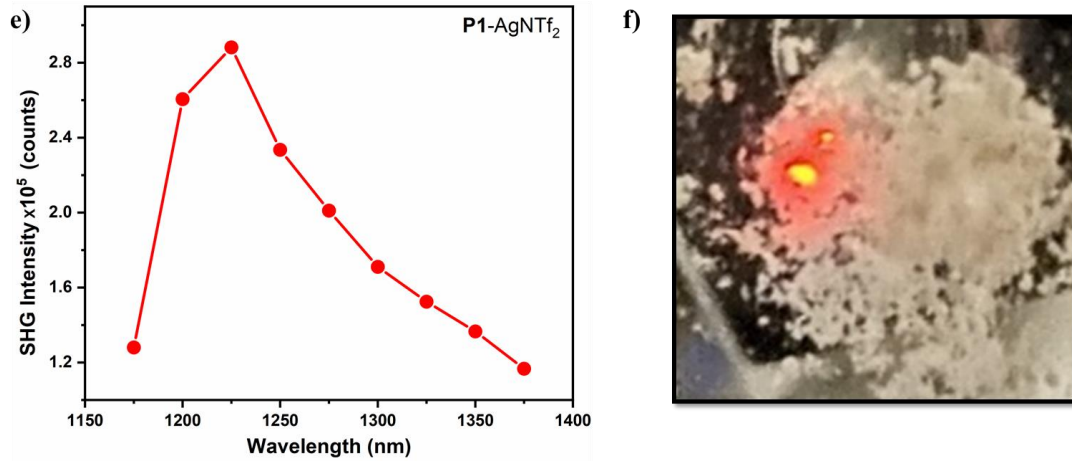


Figure 13: a) The SHG spectra of **P1-AgNTf₂** complex with different excitation wavelengths (1175 nm- 1375 nm). b) Excitation power-dependent SHG spectra of **P1-AgNTf₂** complex at 1225 nm. c) Quadratic fitting of the power-dependent SHG response at 1225 nm. An increase in SHG output was observed with an increase in excitation power having a quadratic dependence till 7.5mW for **P1-AgNTf₂** complex. Deviation from the respective fits reflects the laser-induced damage threshold. For **P1-AgNTf₂** complex, crystal above 7.5 mW was the deviation of SHG output. d) Variation of SHG intensity with the change in direction of polarization of incident light of **P1-AgNTf₂** crystal using 1225 nm as excitation wavelength at 5mW power. e) Integrated intensity at different excitation wavelengths from 1175 nm to 1375 nm. f) Orange light of 612 nm generated due to the 1225 nm pump wavelength.

4.3.1. Laser-Induced Damage Threshold (LIDT) Calculation of P1-AgNTf₂ Complex:

The pump intensity, at which the SHG response deviates from a quadratic behaviour, determines the LIDT value.²⁹ Peak laser intensity corresponding to that pump intensity is the LIDT for the sample.

For **P1-AgNTf₂** complex, SHG response deviates from quadratic behaviour after 7.5 mW.

$$\begin{aligned}
 LIDT(\mathbf{P1} - \mathbf{AgNTf2}) &= \frac{7.5 \times 10^{-3} \text{ W}}{(1000 \text{ Hz}) \times (50 \times 10^{-15} \text{ s}) \times (\pi \times (460 \times 10^{-6} \text{ m})^2)} \\
 &= 22.5 \times 10^{13} \text{ W/m}^2 \\
 &= 22.5 \text{ GW/cm}^2
 \end{aligned}$$

4.4. Details of the Second Harmonic Generation Experiments:

The second harmonic generation (SHG) experiments were performed using home-built setup.³⁰ We used near-infrared (NIR) to short-wave infrared (SWIR) output from an optical parametric amplifier (OPA, Light Conversion) as the excitation light for SHG experiments. The OPA was pumped by the output (800 nm, 35 fs, 1 kHz) from an ultrafast regenerative amplifier (Spitfire X-Pro, Spectra-Physics). The pump wavelengths from 1175 nm to 1550 nm with temporal width of ~50 femtosecond were used in the experiments. An 850 nm long-pass filter in the beam path made sure that only the desired NIR pump wavelengths reach the sample. A neutral density (ND) filter was used to vary the pump intensity. The pump beam was focused by a 200 mm plano-convex lens onto the sample. The sample was kept 135 mm away from the lens to avoid any damage to the sample and to get a large enough spot size for interaction. Sample crystals were sandwiched between two quartz microscopic slides and mounted on a cage rotation mount (Thorlabs CRM1/M). The output SHG signal, collimated by a 25 mm lens, was passed through a 750 nm short-pass filter that rejected any remaining pump wavelength, and was coupled to a 400 μm optical fibre connected to a miniature spectrometer (USB4000, Ocean Optics). A Glan polarizer and a half-wave plate assembly were used to change the polarization of the pump beam for polarization-dependent SHG measurements.

The beam diameter at the sample position was measured by the popular Knife-edge technique. The power measured (P) passing the edge of the knife was fitted to the following equation,

$$P = P_0 + \frac{P_{max}}{2} \left(1 - \operatorname{erf} \left(\frac{\sqrt{2}(x-x_0)}{w} \right) \right) \quad \dots\dots\dots (1)$$

where P_0 is the background power, P_{max} is the maximum power, x is the stage position, erf is the standard error function, and w is the beam radius where intensity dropped to $1/e^2$ times maximum value. The beam radius measured for the given setup was 460×10^{-6} m.

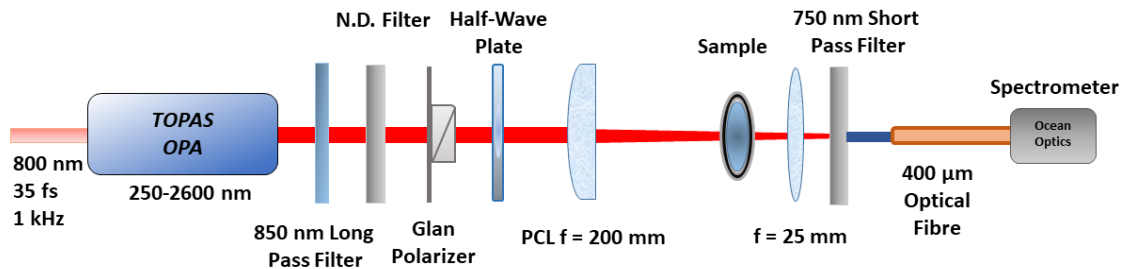


Figure 14: Schematic representation of the SHG setup.

4.5. UV-Visible Spectra of Peptide-Metal Complex:

Optical diffused reflectance spectra were acquired at room temperature employing an integration sphere within a Shimadzu UV3600 pulsed UV-Vis-NIR spectrophotometer. In these measurements, crystal powders of both the **P1**-AgOTf and **P1**-AgNTf₂ complexes were utilized, ensuring a 100% reflectance baseline. The diffused reflectance signals were subsequently transformed into absorbance spectra using the Kubelke-Munk function. It is noteworthy that the absorption spectra of all Metal-Peptide complexes were consistently observed to occur prior to the wavelength of 500 nm in the recorded data.

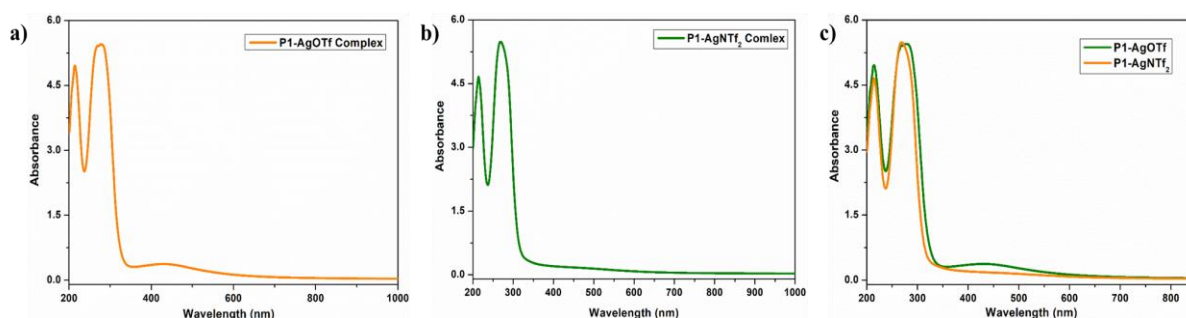


Figure 15: a) UV- Visible absorption spectra of **P1**-AgOTf complex. b) UV-Visible absorption spectra of **P1**-AgNTf₂ complex. c) Superimposition of one spectra with another.

5. Conclusion:

We have demonstrated the utilization of short helical peptides terminated by 3- and 4- pyridyl moieties in the construction of divergent metal-coordinated networks. The tripeptide adopted the classical right-handed 3_{10} -helix, left-handed 3_{10} -helix and 3_{10}^{EL} conformations in the presence of different silver salts. Interestingly, the conformations displayed by the tripeptides have also been seen in the protein structures. Both **P1** and **P2** adopted right-handed helical conformation in porous networks, in the presence of AgOTf and AgPF₆, respectively. In contrast, **P1** adopted both left- and right-handed helical conformations in the asymmetric unit of the single crystals in the presence of AgPF₆. Further, in the presence of bulky counter anion bis(trifluoromethanesulfonyl)imide, the **P1**-Ag (I) complex displayed superhelix conformation, where the helix supercoiled around the central axis, whereas **P2** adopted 2:2 bridged macrocyclic conformation in the presence of nitrate anion. In both the cases, peptides displayed 3_{10}^{EL} conformations. Interestingly, **P3** revealed a noteworthy hierarchical superhelical β -sheet structure in the presence of both AgBF₄ and AgNO₃ salts. The crystals of **P1** with porous network and superhelix showed the nonlinear optical effects, whereas the

crystals with left-and right-handed conformations showed no SHG properties. The structural networks and non-linear optical properties displayed by the metal-peptides networks may pave the way to design new functional materials.

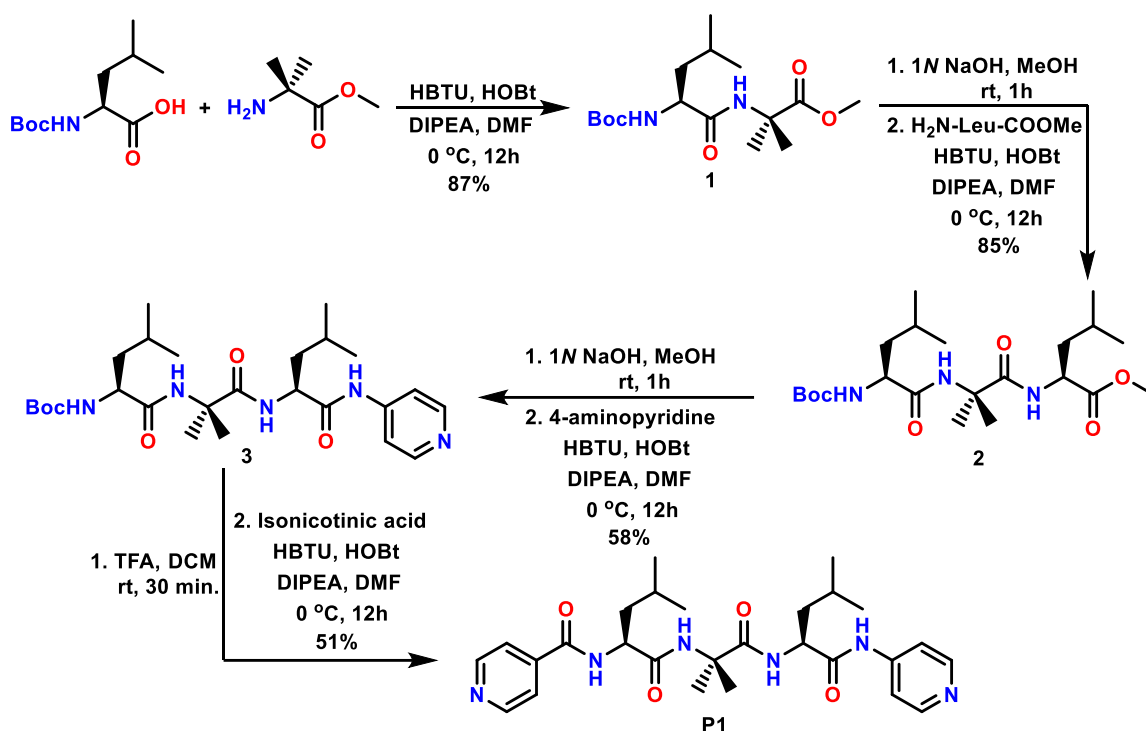
6. Experimental Section:

6.1. Materials and Methods:

All the coupling reactions were performed under N₂ conditions. All the amino acids, Boc anhydride, HBTU, HOBt, AgBF₄, AgPF₆, AgNO₃, AgOTf, AgNTf₂, 3-aminopyridine, 4-aminopyridine, nicotinic acid, isonicotinic acid, Trifluoroacetic acid (TFA), N, N-Diisopropylethylamine (DIPEA), DMF, EtOAc, Hexane, THF, were purchased from different commercial sources. Ethyl acetate and Hexane were distilled before use. Column chromatography was performed on silica gel (100-200 mesh). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and ninhydrin or Iodine staining. ¹H NMR and ¹³C NMR spectra were recorded in deuterated solvents on 400 MHz and 101 MHz NMR machines respectively using the residual solvent signal as the internal standard (CDCl₃). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad doublet (bd), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using MALDI-TOF Instrument. CD spectra were recorded on a CD spectrometer. The X-ray data were collected at low temperatures (150 K) on a Bruker APEX (II) DUO CCD diffractometer using Mo K α (λ = 0.71073 Å) and Cu K α radiation (λ = 1.54178 Å) graphite monochromated radiation.

6.2. General Procedure for the Synthesis of Peptides:

6.2.1. Synthesis of Peptide P1:



Scheme 3: Synthesis of short α - tripeptide **P1**.

N-Boc protected Leucine (10 mmol, 2.31 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (11 mmol, 4.18 g), HOBT (11 mmol, 1.49 g) and DIPEA (25 mmol, 4.38 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH protected Aib (H₂N-Aib-COOMe) (15 mmol, 2.30 g) in little amount of DMF and remaining DIPEA (25 mmol, 4.38). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (20% EtOAc/ Hexane) to get a white product Compound **1** having overall yield was 87%.

The purified product of compound **1** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product which was used for further reaction. Now Dipeptide acid (8 mmol, 2.52 g) was

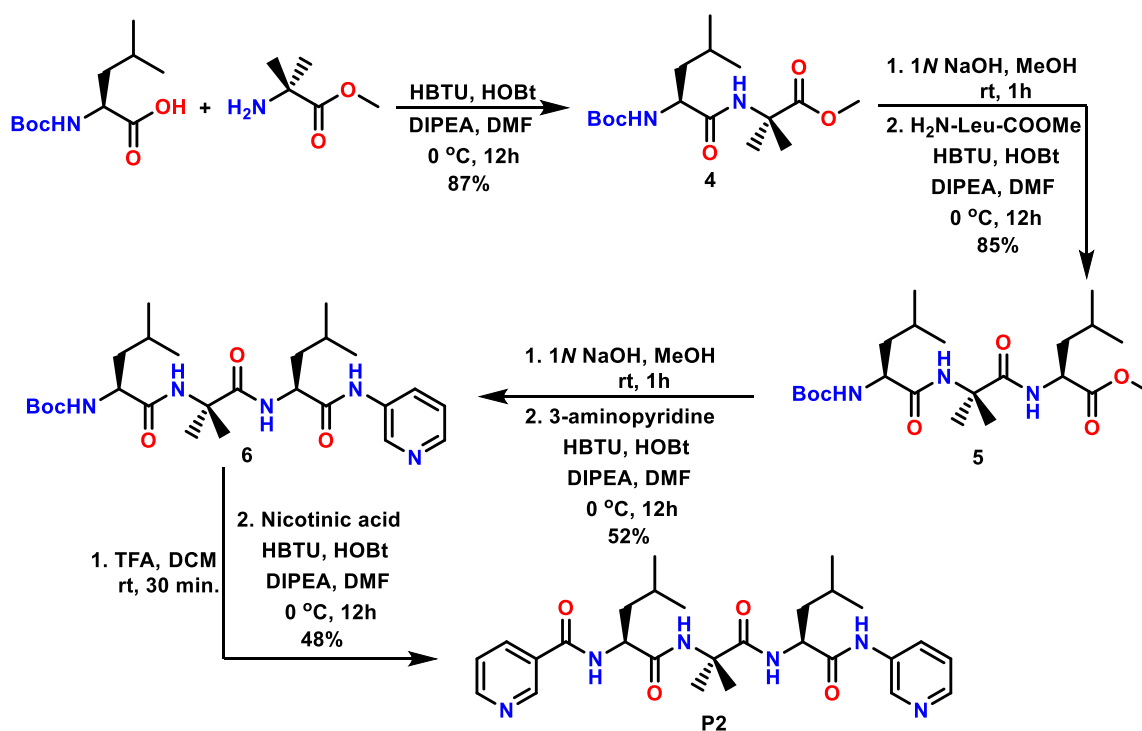
dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (8.8 mmol, 3.34 g), HOBT (8.8 mmol, 1.19 g) and DIPEA (20 mmol, 3.5 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH protected Leu (H₂N-Leu-COOMe) (12 mmol, 1.74 g) in little amount of DMF and remaining DIPEA (20 mmol, 3.5 mL). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (40% EtOAc/ Hexane) to get a white product Compound **2** having overall yield was 85%.

The purified product of compound **2** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product which was used for further reaction. Now Tripeptide acid (2.8 mmol, 1.2 g) was dissolved in 3 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (3.07 mmol, 1.17 g), HOBT (3.07 mmol, 417 mg) and DIPEA (8.37 mmol, 1.46 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of 4-aminopyridine (4.19 mmol, 395 mg). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (4% MeOH/ DCM) to get a white product Compound **3** having overall yield was 58%.

Compound **3** (0.99 mmol, 500 mg) was subjected to Boc deprotection using 50% TFA in DCM (2 mL TFA in 2 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (3 mmol, 0.6 mL) to get the free amine of compound **3**. Now Isonicotinic acid (1.18 mmol, 147 mg) was dissolved in 2 mL of DMF and

the solution was then cooled to 0 °C using an ice bath under N₂ atmosphere. To this, HBTU (1.09 mmol, 414 mg), HOBT (1.09 mmol, 149 mg) and DIPEA (3 mmol, 0.6 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound 3 and the reaction mixture was further stirred for overnight at room temperature. The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (6% MeOH/ DCM) to get a white product Peptide **P1** having overall yield was 51%.

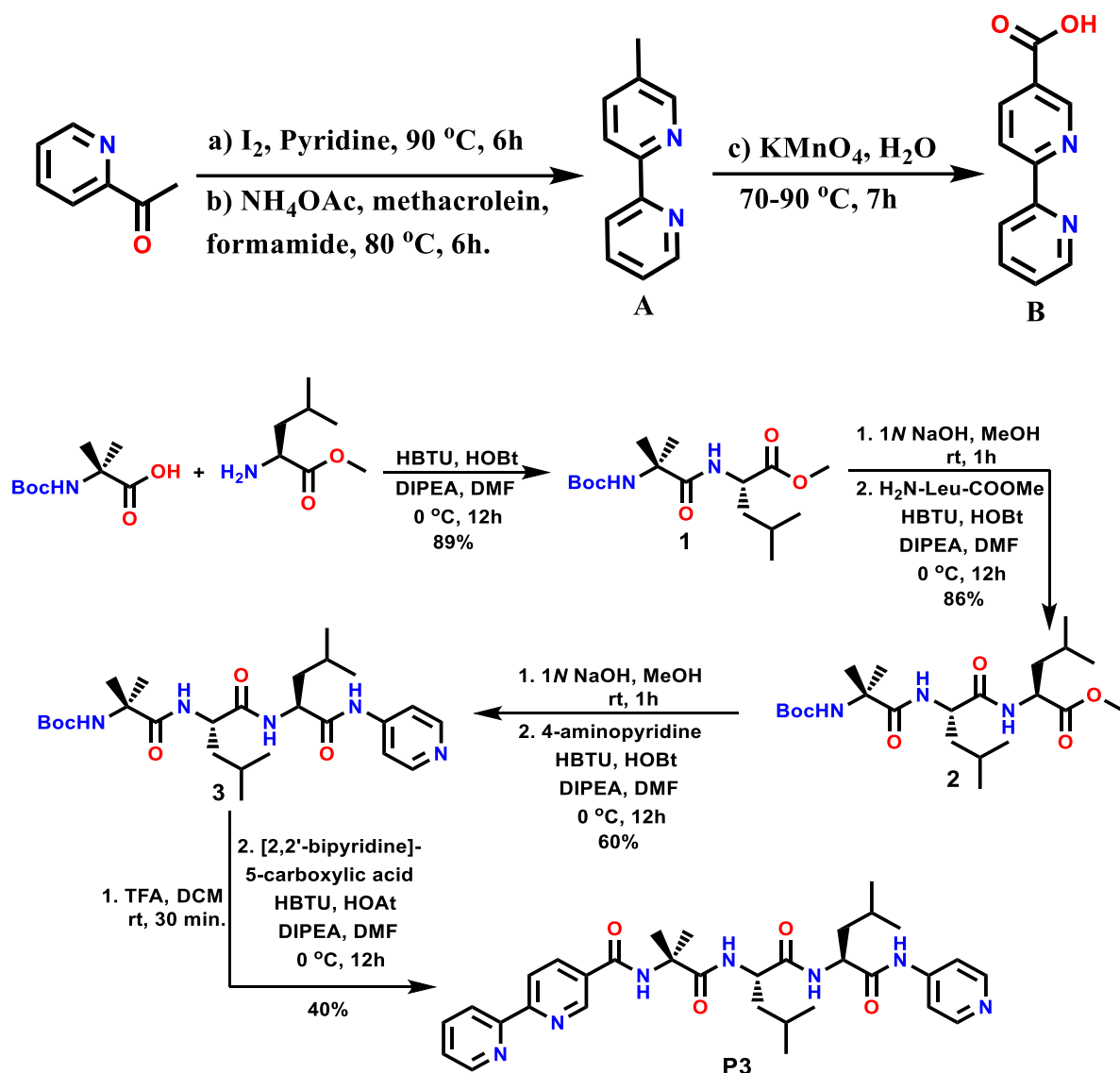
6.2.2. Synthesis of Peptide P2:



Scheme 4: Synthesis of short α- tripeptide **P2**.

The Synthesis of peptide **P2** was carried out as described in the above scheme, following similar protocols as of **P1** (overall yield was 48%).

6.2.3. Synthesis of Peptide P3:



Scheme 5: Synthesis of short α -tripeptide **P3**.

[2,2'-bipyridine]-5-carboxylic acid (**B**) was synthesized using the protocol reported by Prof. Joost N. H. Reek's group in 2019.³¹

Now *N*-Boc protected 2-Aminoisobutyric acid (10 mmol, 2.032 g) was dissolved in 5 mL of DMF and was cooled down to 0°C under N_2 atmosphere. To this, HBTU (11 mmol, 4.18 g), HOBT (11 mmol, 1.49 g), and DIPEA (25 mmol, 4.38 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected Leucine ($\text{H}_2\text{N-Leu-COOMe}$) (15 mmol, 2.17 g) in a small amount of DMF and the

remaining DIPEA (25 mmol, 4.38). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (20% EtOAc/ Hexane) to get a white product Compound **1** having an overall yield of 89%.

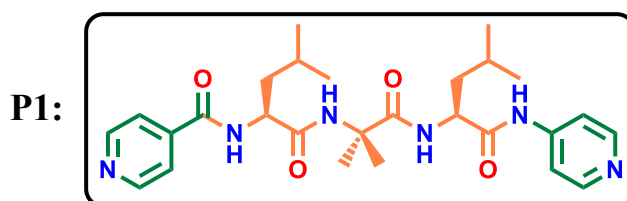
The purified product of compound **1** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of the reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product used for further reaction. Now Dipeptide acid (8 mmol, 2.52 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (8.8 mmol, 3.34 g), HOBt (8.8 mmol, 1.19 g), and DIPEA (20 mmol, 3.5 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected Leu (H₂N-Leu-COOMe) (12 mmol, 1.74 g) in a small amount of DMF and the remaining DIPEA (20 mmol, 3.5 mL). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (40% EtOAc/ Hexane) to get a white product Compound **2** having an overall yield of 86%.

The purified product of compound **2** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of the reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product which was used for further reaction. Now Tripeptide acid (2.8 mmol, 1.2 g) was dissolved in 3 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (3.07 mmol, 1.17 g), HOBt (3.07 mmol, 417 mg), and DIPEA (8.37 mmol, 1.46 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition

of 4-aminopyridine (4.19 mmol, 395 mg). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (4% MeOH/ DCM) to get a white product. Compound **3** had an overall yield was 60%.

Compound **3** (0.99 mmol, 500 mg) was subjected to Boc deprotection using 50% TFA in DCM (2 mL TFA in 2 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (3 mmol, 0.6 mL) to get the free amine of compound **3**. Now [2,2'-bipyridine]-5-carboxylic acid (1.18 mmol, 200.2 mg) was dissolved in 2 mL of DMF and the solution was then cooled to 0 °C using an ice bath under N₂ atmosphere. To this, HBTU (1.09 mmol, 414 mg), HOAt (1.09 mmol, 149 mg), and DIPEA (3 mmol, 0.6 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **3** and the reaction mixture was further stirred for overnight at room temperature. The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (7% MeOH/ DCM) to get a white product Peptide **P3** having overall yield was 40%.

6.3. Characterisation of Peptides (P1-P3):

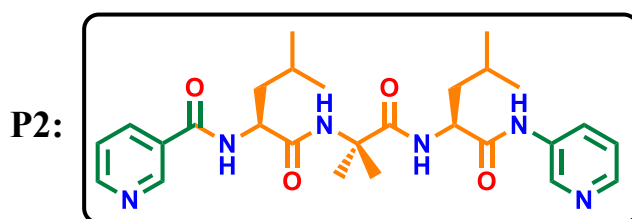


¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 8.96 (s, 1H), 8.55 (d, *J* = 6.1 Hz, 1H), 8.43 (d, *J* = 6.1 Hz, 1H), 8.29 (d, *J* = 6.5 Hz, 1H), 8.19 (d, *J* = 6.6 Hz, 1H), 7.73 (d, *J* = 43.9 Hz, 1H),

7.66 – 7.60 (m, 3H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.31 (d, $J = 6.1$ Hz, 1H), 4.59 – 4.18 (m, 2H), 2.20 (s, 1H), 2.00 – 1.80 (m, 4H), 1.68 (d, $J = 2.1$ Hz, 3H), 1.56 (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 2.6$ Hz, 1H), 1.07 – 0.90 (m, 12H).

^{13}C NMR (101 MHz, CDCl_3) δ 174.66, 173.91, 172.32, 168.01, 150.48, 150.21, 149.06, 146.08, 145.66, 139.35, 139.16, 120.87, 114.21, 113.98, 77.35, 77.03, 76.72, 57.76, 55.30, 52.73, 39.79, 39.13, 27.83, 27.15, 25.39, 24.91, 23.44, 23.22, 22.72, 21.89, 21.08.

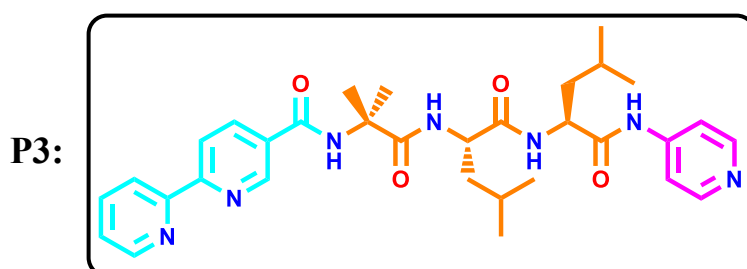
MALDI TOF/TOF m/z calculated for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ is 511.30 and observed value is 511.55. $[\text{M}+\text{Na}]^+$ is 533.30 and observed value is 533.59.



^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.77 (s, 1H), 9.24 (s, 1H), 9.11 – 9.06 (m, 1H), 9.01 (s, 1H), 8.88 – 8.81 (m, 1H), 8.75 – 8.68 (m, 1H), 8.52 (dd, $J = 4.8, 1.5$ Hz, 1H), 8.24 (dq, $J = 4.2, 2.2$ Hz, 1H), 8.14 – 8.08 (m, 1H), 8.01 – 7.91 (m, 1H), 7.73 – 7.57 (m, 1H), 7.19 (ddd, $J = 57.9, 8.2, 4.8$ Hz, 1H), 4.48 – 4.37 (m, 1H), 4.35 – 4.21 (m, 1H), 1.85 – 1.68 (m, 4H), 1.64 – 1.51 (m, 2H), 1.45 (s, 2H), 1.42 – 1.35 (m, 4H), 0.99 – 0.73 (m, 12H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 175.35, 174.64, 171.85, 167.15, 152.47, 148.84, 144.62, 141.10, 135.77, 135.42, 135.24, 129.65, 128.74, 126.22, 123.41, 56.89, 54.01, 52.43, 40.50, 40.29, 40.09, 39.88, 39.67, 39.46, 39.25, 27.30, 25.78, 25.17, 25.06, 24.77, 23.64, 23.51, 23.19, 22.29, 21.13.

MALDI TOF/TOF m/z calculated for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ is 511.30 and observed value is 511.55. $[\text{M}+\text{Na}]^+$ is 533.30 and observed value is 533.65. $[\text{M}+\text{K}]^+$ is 549.30 and observed value is 549.54.



¹H NMR (400 MHz, Acetone-*d*₆) δ 9.17 (dd, *J* = 11.9, 2.3 Hz, 1H), 8.72 – 8.69 (m, 1H), 8.61 (s, 1H), 8.50 (ddd, *J* = 8.9, 5.7, 3.4 Hz, 2H), 8.44 – 8.33 (m, 4H), 8.14 (d, *J* = 5.5 Hz, 1H), 8.05 (dd, *J* = 8.5, 3.8 Hz, 1H), 8.00 – 7.90 (m, 2H), 7.84 (d, *J* = 6.5 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 4.57 – 4.43 (m, 1H), 4.31 – 3.98 (m, 1H), 2.01 – 1.76 (m, 4H), 1.75 – 1.63 (m, 8H), 1.01 – 0.88 (m, 12H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 206.43, 177.68, 176.43, 173.07, 167.32, 159.25, 155.79, 151.01, 150.35, 149.68, 146.80, 138.02, 137.03, 130.18, 125.55, 122.12, 120.69, 114.39, 79.20, 58.37, 55.22, 53.46, 40.71, 38.85, 26.64, 25.77, 25.53, 24.98, 24.48, 23.68, 23.33, 21.28, 21.02.

MALDI TOF/TOF *m/z* calculated for C₃₂H₄₁N₇O₄ [M+Na]⁺ is 610.71 and observed value is 610.52. [M+K]⁺ is 626.82 and observed value is 626.49.

6.4. Crystal Structure Information:

6.4.1. Crystal Structure Analysis of P1-AgOTf Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P1** in ethanol and 25 mM of 500 μL of an aqueous solution of AgOTf in a capped microtube, formation of plate-shaped crystals were observed at the interface of ethanol and water layer after 15 days. A single crystal (0.16 × 0.14 × 0.06) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo Kα radiation (λ=0.71073 Å), ω-scans (2θ = 50.29), for a total of 62961 independent reflections. Space group P 2₁, a = 9.262(1), b = 15.876(19), c = 24.269(3), α = 90, β = 91.96(3), γ = 90, V = 3566.7(7) Å³, Monoclinic, Z = 2 for chemical formula C₅₈ H₇₆ Ag₂ F₆ N₁₂ O₁₄ S₂, with two molecules in asymmetric unit; ρ calcd = 1.452 g cm⁻³, μ = 0.690 mm⁻¹, F(000) = 1600, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0601 (wR2 = 0.1813) 12744 observed reflections (*F*₀ ≥ 4σ(|*F*₀|)) and 885 variables, S = 1.028.

There is some partially occupied solvent molecule also present in the asymmetric unit. A significant amount of time was invested in identifying and refining the disordered molecule. Option SQUEEZE of program PLATON³³ was used to correct the diffraction data for diffuse scattering effects and to identify the solvent molecule.

6.4.2. Crystal Structure Analysis of P1-AgPF₆ Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P1** in ethanol and 25 mM of 500 μL of an aqueous solution of AgPF₆ in a capped microtube, formation of plate-shaped

crystals were observed at the interface of ethanol and water layer after 30 days. A single crystal ($0.18 \times 0.16 \times 0.08$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 49.998$), for a total of 63109 independent reflections. Space group P 2₁, $a = 15.078(4)$, $b = 15.682(4)$, $c = 16.300(4)$, $\alpha = 90$, $\beta = 114.74(6)$, $\gamma = 90$, $V = 3500.3(16) \text{\AA}^3$, Monoclinic, $Z = 4$ for chemical formula C₂₉ H₄₄ Ag F₆ N₆ O₅ P, with two molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.536 \text{ g cm}^{-3}$, $\mu = 0.699 \text{ mm}^{-1}$, $F(000) = 1664$, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0505 ($wR_2 = 0.1214$) 12258 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 883 variables, $S = 0.697$.

6.4.3. Crystal Structure Analysis of P1-AgNTf₂ Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P1** in ethanol and 25 mM of 500 μL of an aqueous solution of AgNTf₂ in a capped microtube, formation of needle-shaped crystals were observed at the interface of ethanol and water layer after 10 days. A single crystal ($0.18 \times 0.06 \times 0.20$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 56.87$), for a total of 119184 independent reflections. Space group P 2₁2₁2₁, $a = 10.372(2)$, $b = 11.154(2)$, $c = 32.363(6)$, $\alpha, \beta, \gamma = 90$, $V = 3744.1(12) \text{\AA}^3$, Orthorhombic, $Z = 4$ for chemical formula C₂₉ H₃₈ Ag F₆ N₇ O₈ S₂, with one molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.594 \text{ g cm}^{-3}$, $\mu = 0.736 \text{ mm}^{-1}$, $F(000) = 1832$, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0618 ($wR_2 = 0.1447$) 9427 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 486 variables, $S = 1.176$.

6.4.4. Crystal Structure Analysis of P2-AgPF₆ Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P2** in methanol and 25 mM of 500 μL of an aqueous solution of AgPF₆ in a capped microtube, formation of plate-shaped crystals were observed at the interface of ethanol and water layer after 60 days. A single crystal ($0.14 \times 0.08 \times 0.04$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 50.052$), for a total of 141181 independent reflections. Space group C 2 2 2₁, $a = 19.097(10)$, $b = 26.507(14)$, $c = 28.562(15)$, $\alpha, \beta, \gamma = 90$, $V = 14458(13) \text{\AA}^3$, Orthorhombic, $Z = 16$ for chemical formula C₂₇ H₃₇ Ag F₆ N₆ O₄ P, with two molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.401 \text{ g cm}^{-3}$, $\mu = 0.671 \text{ mm}^{-1}$, $F(000) = 6224$, The

structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0994 (wR2 = 0.2983) 12719 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 824 variables, S = 1.025.

There is some partially occupied solvent molecule also present in the asymmetric unit. A significant amount of time was invested in identifying and refining the disordered molecule. Option SQUEEZE of program PLATON³³ was used to correct the diffraction data for diffuse scattering effects and to identify the solvent molecule.

6.4.5. Crystal Structure Analysis of P2-(AgPF₆+AgBF₄) Complex:

Crystals were grown by layering 25 mM of 500 μ L solution of **P2** in methanol and 25 mM of 500 μ L of an aqueous solution of AgPF₆ and AgBF₄ (1:1) mixture in a capped microtube, formation of plate-shaped crystals was observed at the interface of ethanol and water layer after 60 days. A single crystal (0.14 $\times$ 0.08 $\times$ 0.04) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 50.336$), for a total of 134967 independent reflections. Space group C 2 2 2₁, a = 19.236 (8), b = 23.976 (9), c = 29.951 (11), $\alpha, \beta, \gamma = 90$, V = 13814 (9) $\text{\AA}^3$, Orthorhombic, Z = 4 for chemical formula C₁₀₈ H₁₅₂ Ag₄ B₂ F₁₄ N₂₄ O₁₈ P, with two molecules in asymmetric unit; ρ calcd = 1.358 gcm⁻³, μ = 0.654 mm⁻¹, F (000) = 5804, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0956 (wR2 = 0.2811) 12409 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 804 variables, S = 1.023.

There is some partially occupied solvent molecule also present in the asymmetric unit. A significant amount of time was invested in identifying and refining the disordered molecule. Option SQUEEZE of program PLATON³³ was used to correct the diffraction data for diffuse scattering effects and to identify the solvent molecule.

6.4.6. Crystal Structure Analysis of P2-AgNO₃ Complex:

Crystals were grown by layering 25 mM of 500 μ L solution of **P2** in methanol and 25 mM of 500 μ L of an aqueous solution of AgNO₃ in a capped microtube, formation of plate-shaped crystals were observed at the interface of ethanol and water layer after 60 days. A single crystal (0.16 $\times$ 0.15 $\times$ 0.10) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 50.226$), for a total of 57253 independent reflections. Space group P 3, a = 22.737(3), b = 22.737(3), c = 10.828(19), $\alpha = 90, \beta = 90, \gamma =$

120, $V = 4847.9(15) \text{ \AA}^3$, Trigonal, $Z = 1$ for chemical formula $C_{162} H_{225} Ag_6 N_{40} O_{38}$, with two molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.366 \text{ g cm}^{-3}$, $\mu = 0.672 \text{ mm}^{-1}$, $F(000) = 2063$, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0965 ($wR_2 = 0.2784$) 11432 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 749 variables, $S = 2.064$.

There is some partially occupied solvent molecule also present in the asymmetric unit. A significant amount of time was invested in identifying and refining the disordered molecule. Option SQUEEZE of program PLATON³³ was used to correct the diffraction data for diffuse scattering effects and to identify the solvent molecule.

6.4.7. Crystal Structure Analysis of Peptide P3:

Crystals were grown by slow evaporation of MeOH in one drop of water solution. A single crystal ($0.12 \times 0.06 \times 0.08$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), ω -scans ($2\theta = 135.25$), for a total of 29311 independent reflections. Space group P -1, $a = 8.33(3)$, $b = 9.74(3)$, $c = 22.35(9)$, $\alpha = 88.94(11)$, $\beta = 82.47(8)$, $\gamma = 69.66(12)$, $V = 1685(11) \text{ \AA}^3$, Triclinic, $Z = 2$ for chemical formula $C_{32} H_{41} N_7 O_4$, with one molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.158 \text{ g cm}^{-3}$, $\mu = 0.633 \text{ mm}^{-1}$, $F(000) = 628$, the structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.1449 ($wR_2 = 0.4448$) 6000 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 395 variables, $S = 1.737$.

6.4.8. Crystal Structure Analysis of P3-AgBF₄ Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P3** in methanol and 25 mM of 500 μL of an aqueous solution of AgBF_4 in a capped microtube, formation of plate-shaped crystals was observed at the interface of methanol and water layer after 75 days. A single crystal ($0.17 \times 0.16 \times 0.05$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), ω -scans ($2\theta = 50.106$), for a total of 84149 independent reflections. Space group P $2_1/n$, $a = 8.880(3)$, $b = 24.866(9)$, $c = 17.213(6)$, $\alpha = 90$, $\beta = 99.325(9)$, $\gamma = 90$, $V = 3751(2) \text{ \AA}^3$, Monoclinic, $Z = 4$ for chemical formula $C_{32.75} H_{40} Ag B F_4 N_7 O_5$, with one molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.428 \text{ g cm}^{-3}$, $\mu = 0.605 \text{ mm}^{-1}$, $F(000) = 1654$, The structure was obtained by direct methods using SHELXS-97.³² The final R value was 0.0628 ($wR_2 = 0.1582$) 6656 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 476 variables, $S = 1.049$.

6.4.9. Crystal Structure Analysis of P3-AgNO₃ Complex:

Crystals were grown by layering 25 mM of 500 μ L solution of **P3** in methanol and 25 mM of 500 μ L of an aqueous solution of AgNO₃ in a capped microtube, formation of plate-shaped crystals was observed at the interface of methanol and water layer after 60 days. A single crystal (0.16 $\times$ 0.15 $\times$ 0.08) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation (λ =0.71073 $\text{\AA}$), ω -scans (2θ = 50.308), for a total of 68528 independent reflections. Space group P 2₁/n, a = 8.6536(9), b = 25.473(3), c = 17.166(2), α = 90, β = 99.867(4), γ = 90, V = 3728(7) $\text{\AA}^3$, Monoclinic, Z = 2 for chemical formula C₆₆ H₇₆ Ag₂ N₁₆ O₁₇, with one molecules in asymmetric unit; ρ calcd = 1.409 gcm⁻³, μ = 0.600 mm⁻¹, $F(000)$ = 1628, The structure was obtained by direct methods using SHELXS-97.³⁴ The final R value was 0.0712 (wR2 = 0.2010) 6690 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 488 variables, S = 1.071.

6.5. ORTEP Diagrams:

6.5.1. ORTEP Diagram of P1-AgOTf:

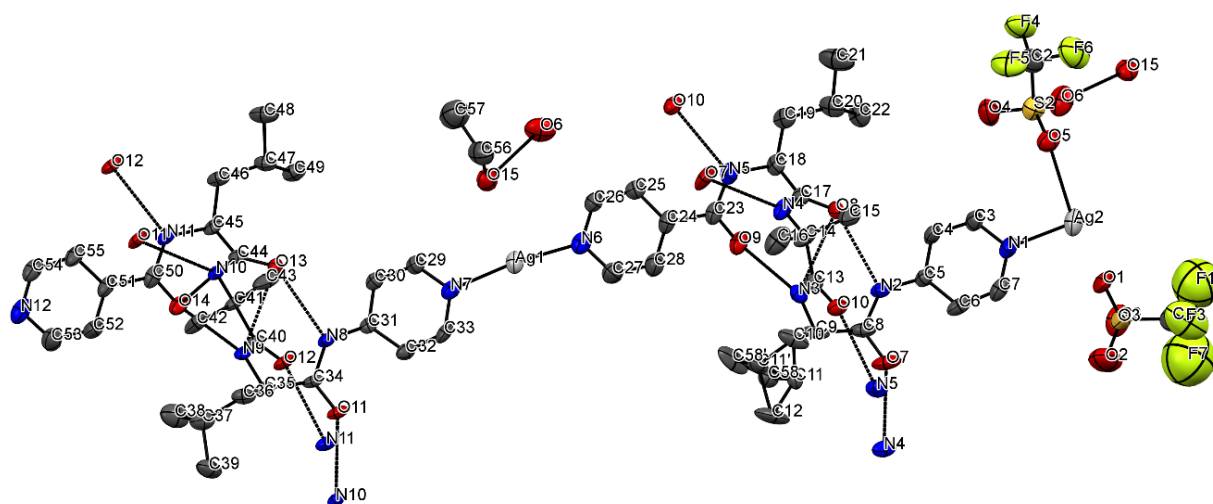


Figure 16: ORTEP diagram of **P1-AgOTf** (CCDC no. 2278582). H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.2. ORTEP Diagram of P1-AgPF₆:

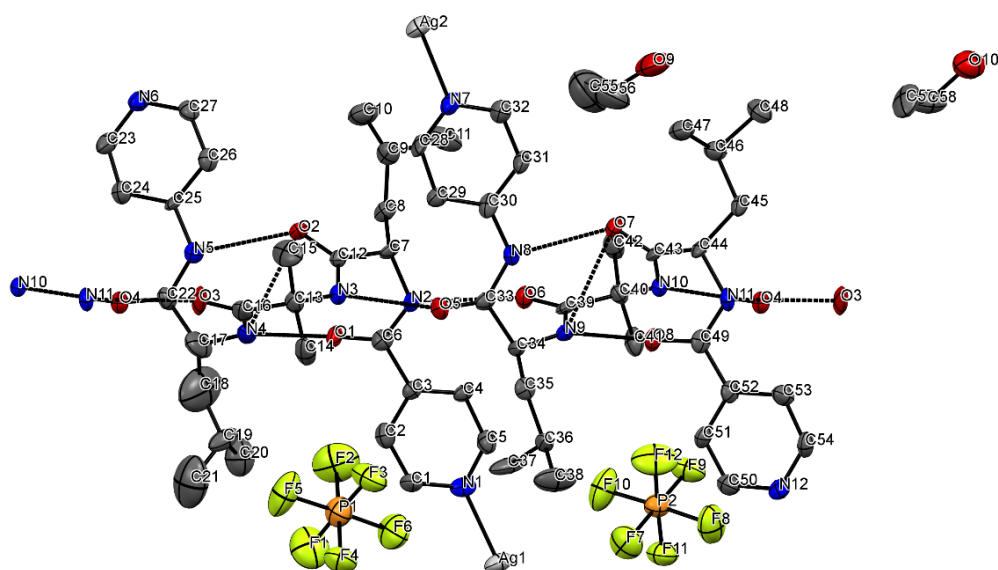


Figure 17: ORTEP diagram of **P1-AgPF₆** (CCDC no. 2278581). H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.3. ORTEP Diagram of P1-AgNTf₂:

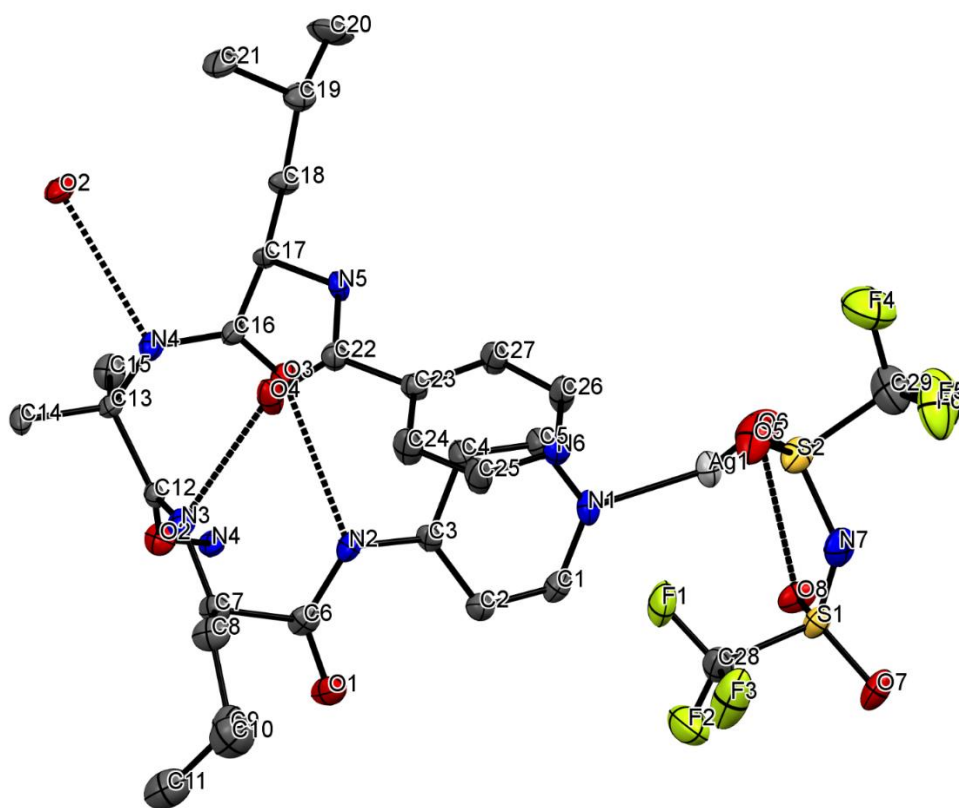


Figure 18: ORTEP diagram of **P1-AgNTf₂** (CCDC no. 2278588). H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.4. ORTEP Diagram of P2-AgPF₆:

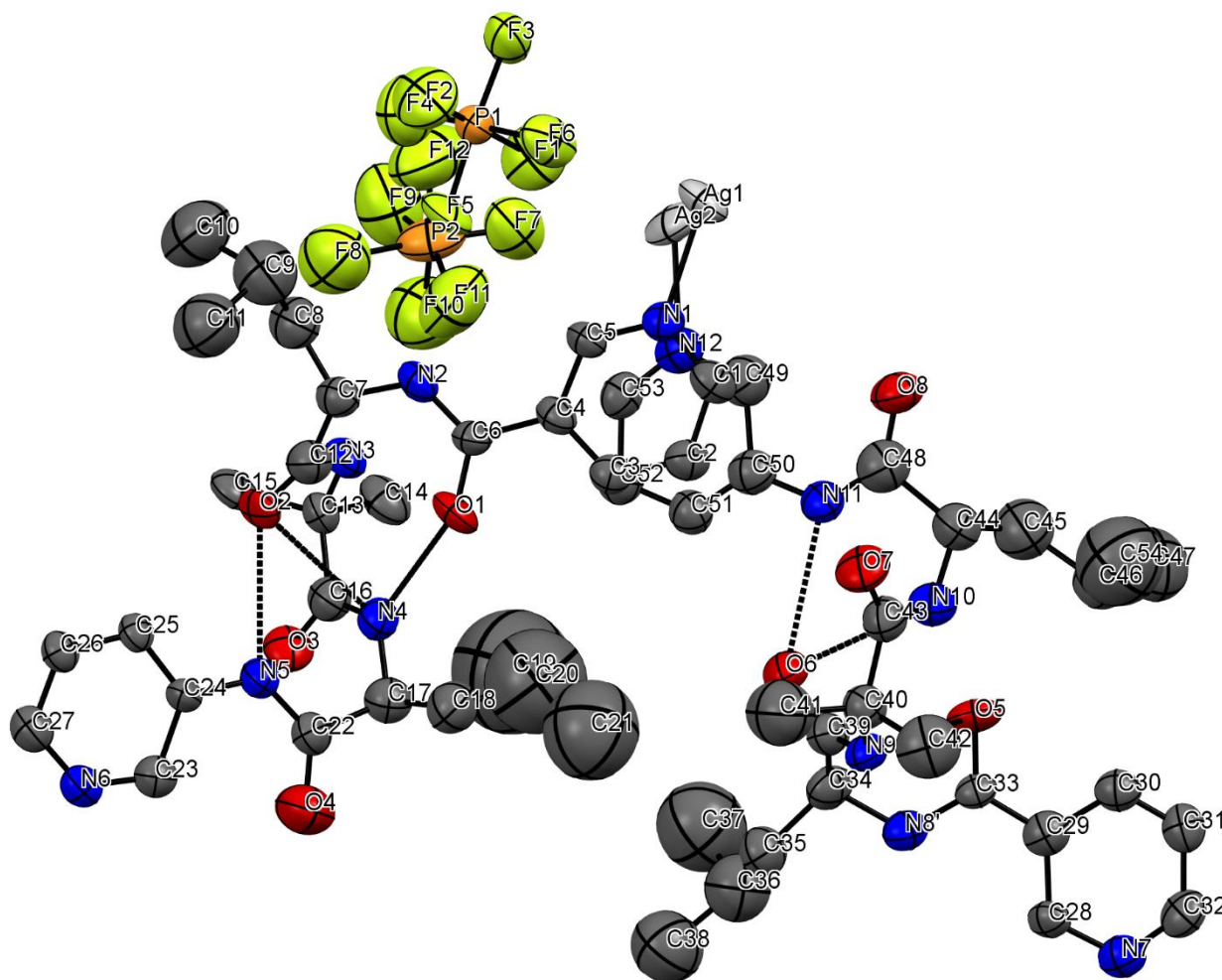


Figure 19: ORTEP diagram of **P2-AgPF₆** (CCDC no. 2278589). H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.5. ORTEP Diagram of P2-(AgPF₆+AgBF₄):

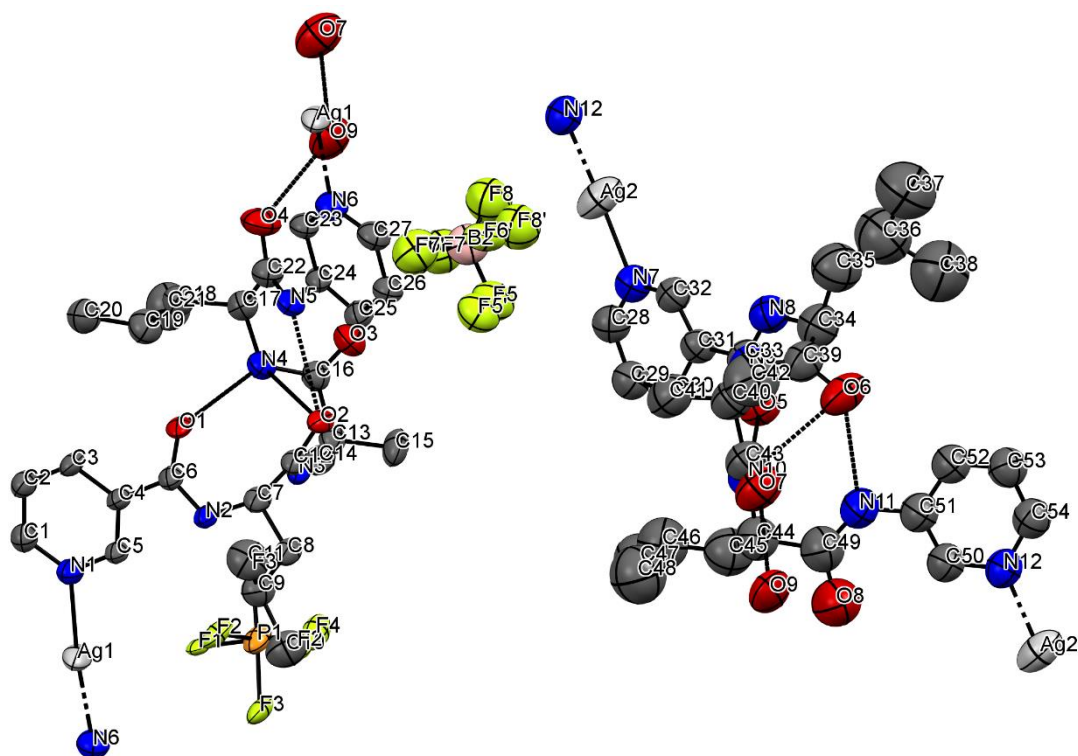


Figure 20: ORTEP diagram of P2-AgPF₆+AgBF₄. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.6. ORTEP Diagram of P2-AgNO₃:

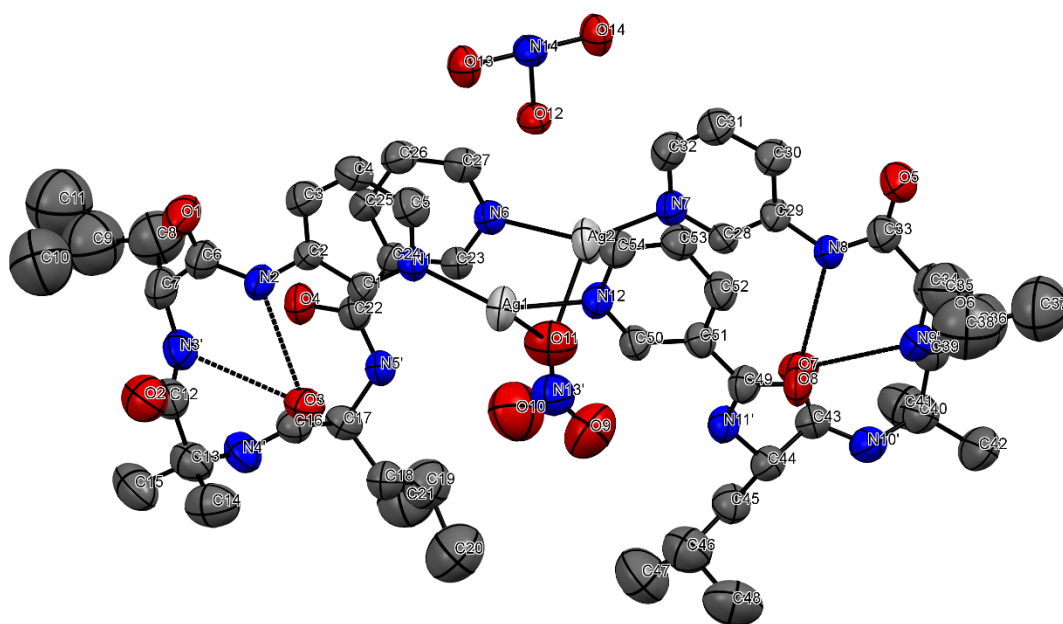


Figure 21: ORTEP diagram of **P2-AgNO₃** (CCDC no. 2278590). H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.7. ORTEP Diagram of P3:

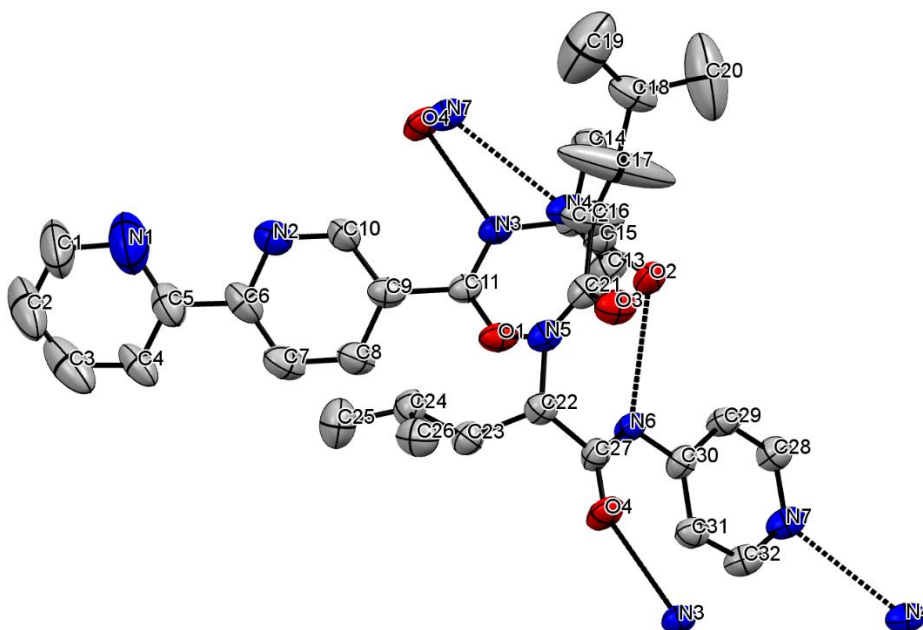


Figure 22: ORTEP diagram of **P3**. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.8. ORTEP Diagram of P3-AgBF₄:

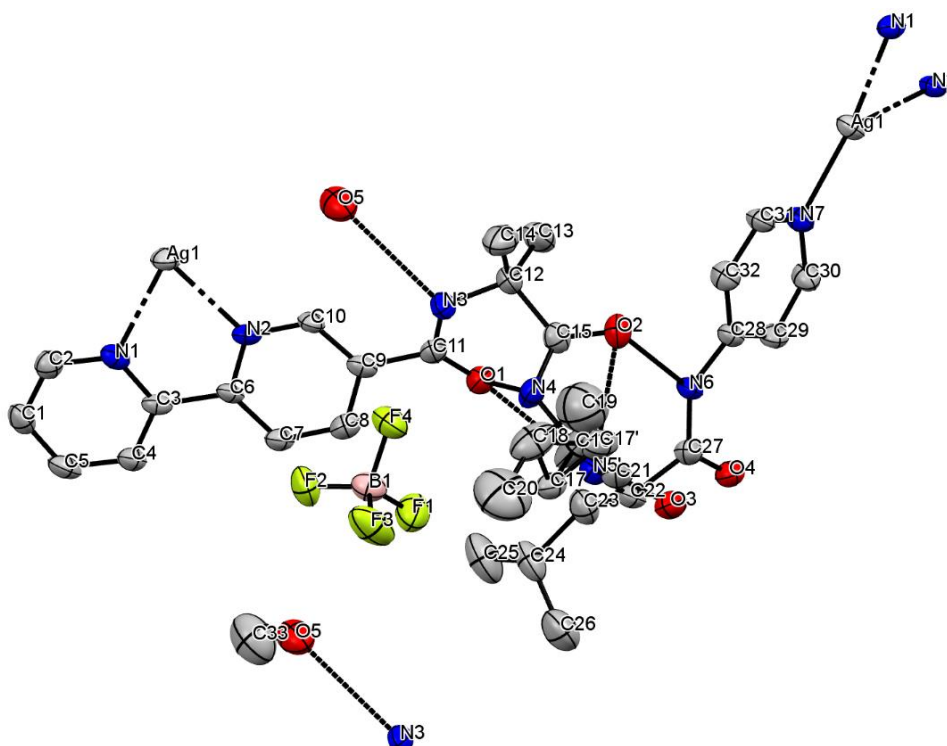


Figure 23: ORTEP diagram of **P3-AgBF₄**. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.9. ORTEP Diagram of P3-AgNO₃:

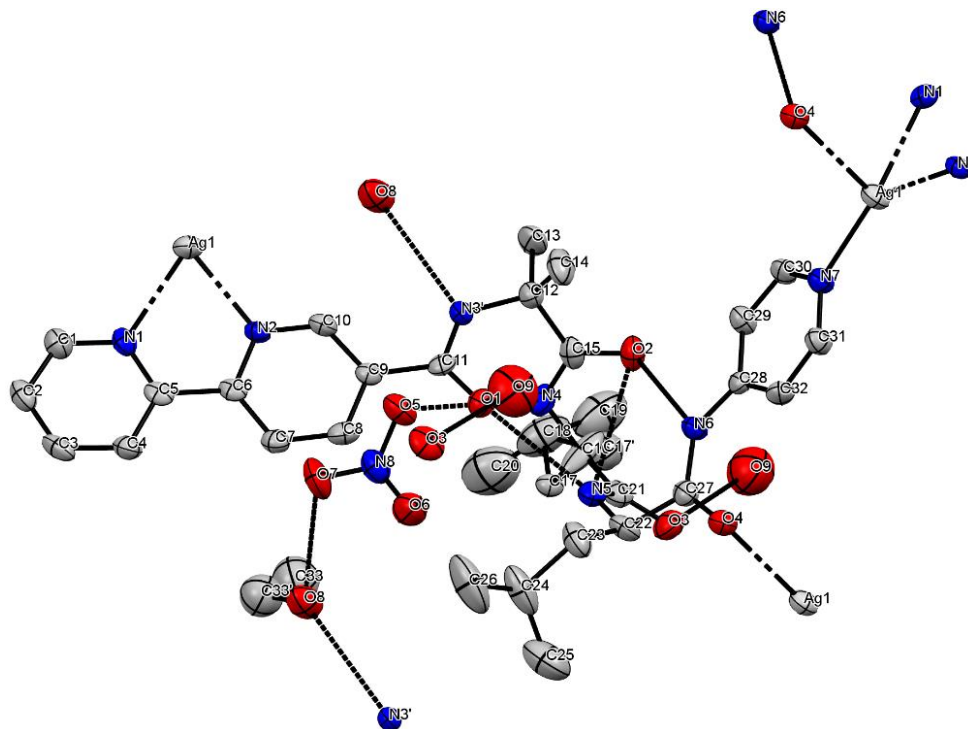


Figure 24: ORTEP diagram of **P3-AgNO₃**. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

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33. Spek, A. L. *Acta Crystallogr.* **1990**, A46, C34.

8. ^1H , ^{13}C NMR, and Mass Spectra of Peptides:

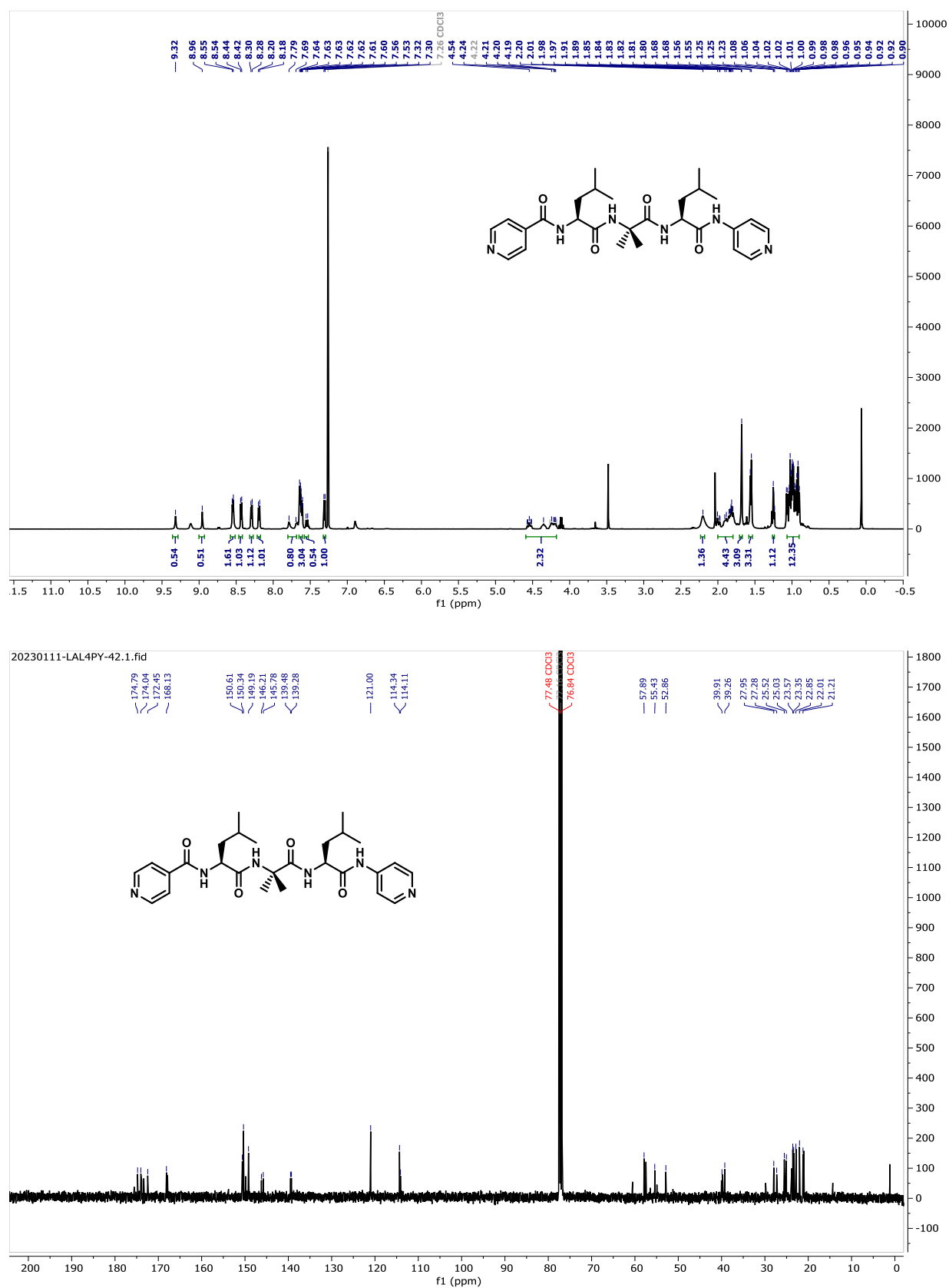


Figure 25: ^1H & ^{13}C NMR spectrum of **P1** in CDCl_3 .

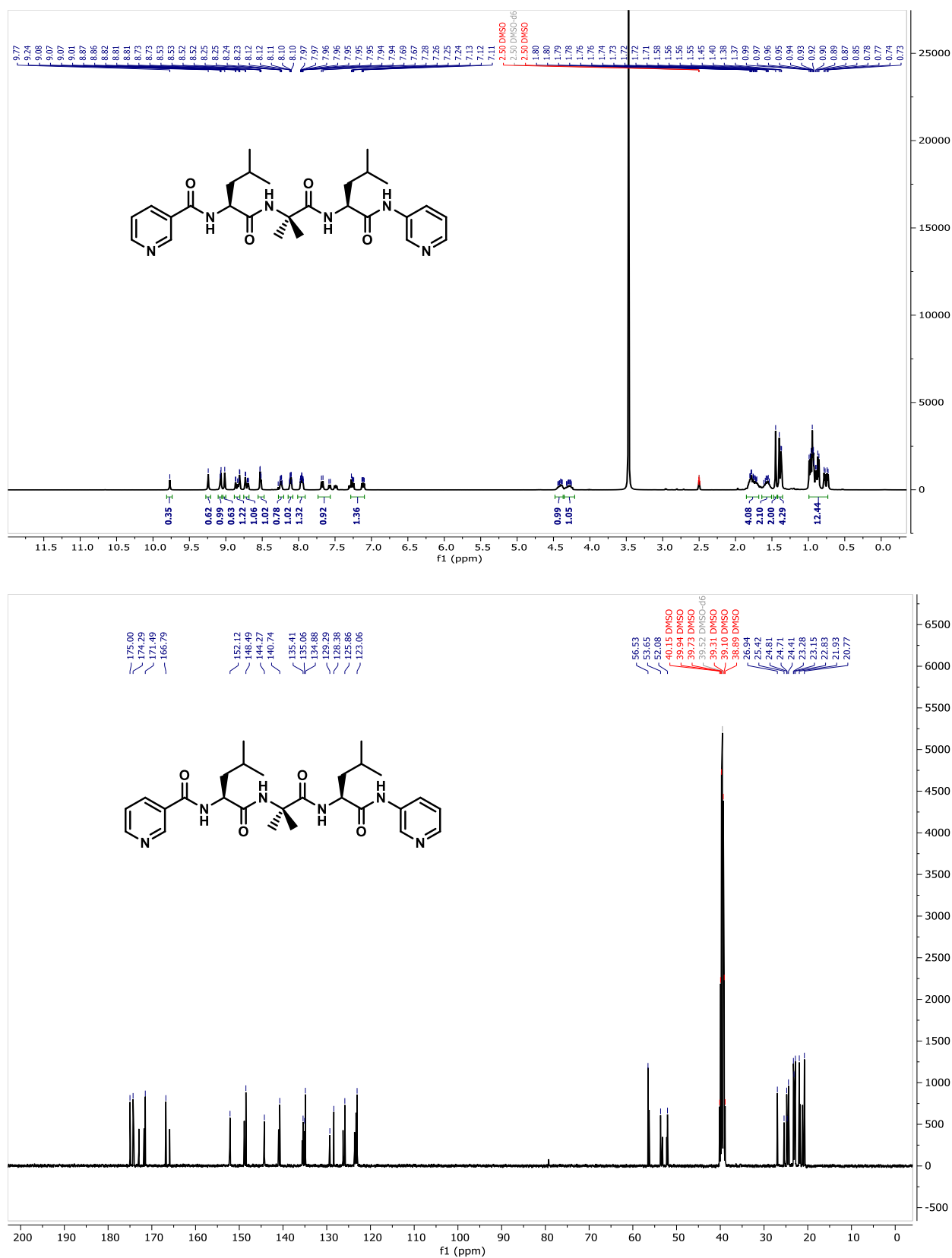


Figure 26: ¹H & ¹³C NMR spectrum of **P2** in DMSO-*d*₆.

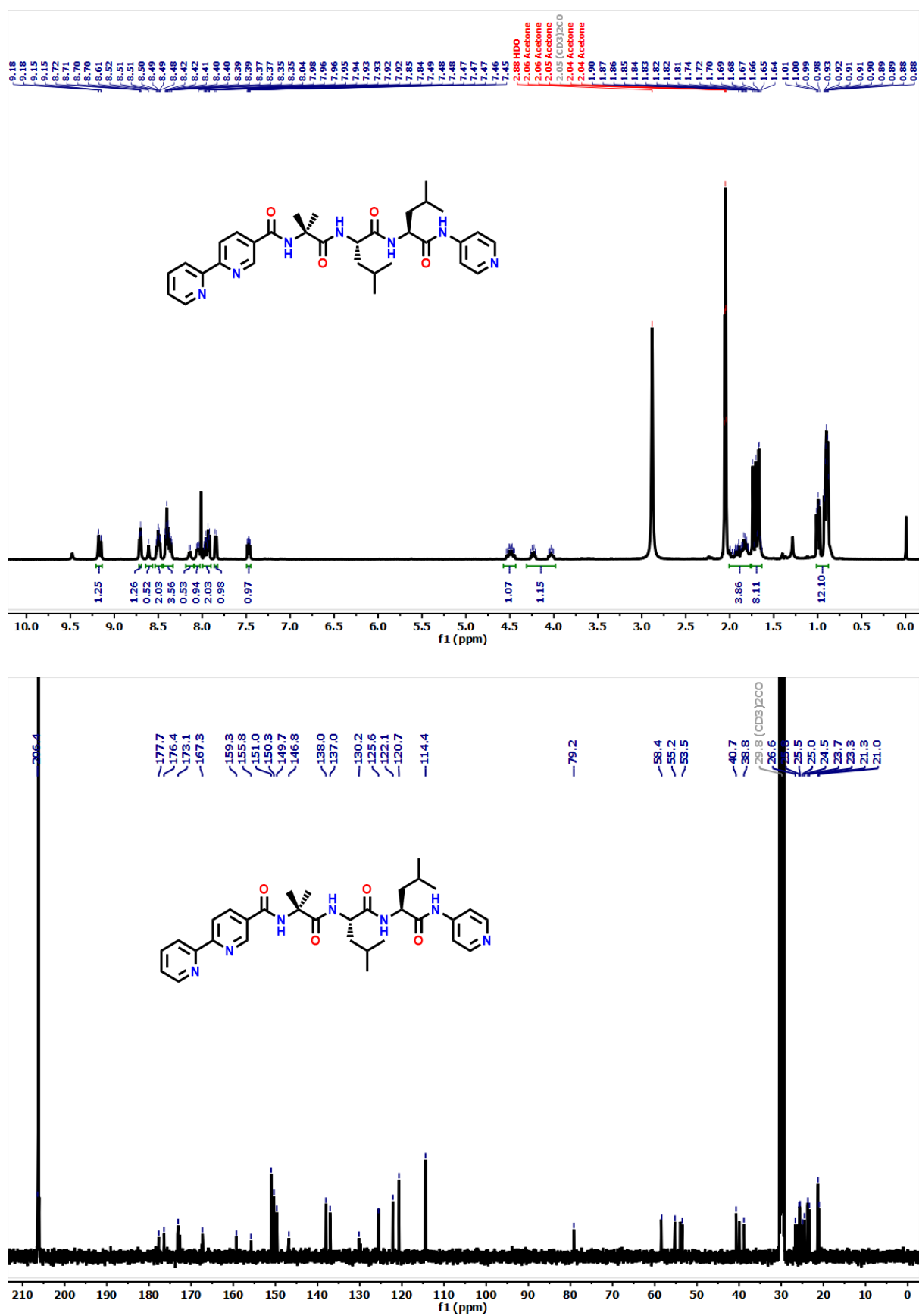


Figure 27: ¹H & ¹³C NMR spectrum of **P3** in Acetone-*d*₆.

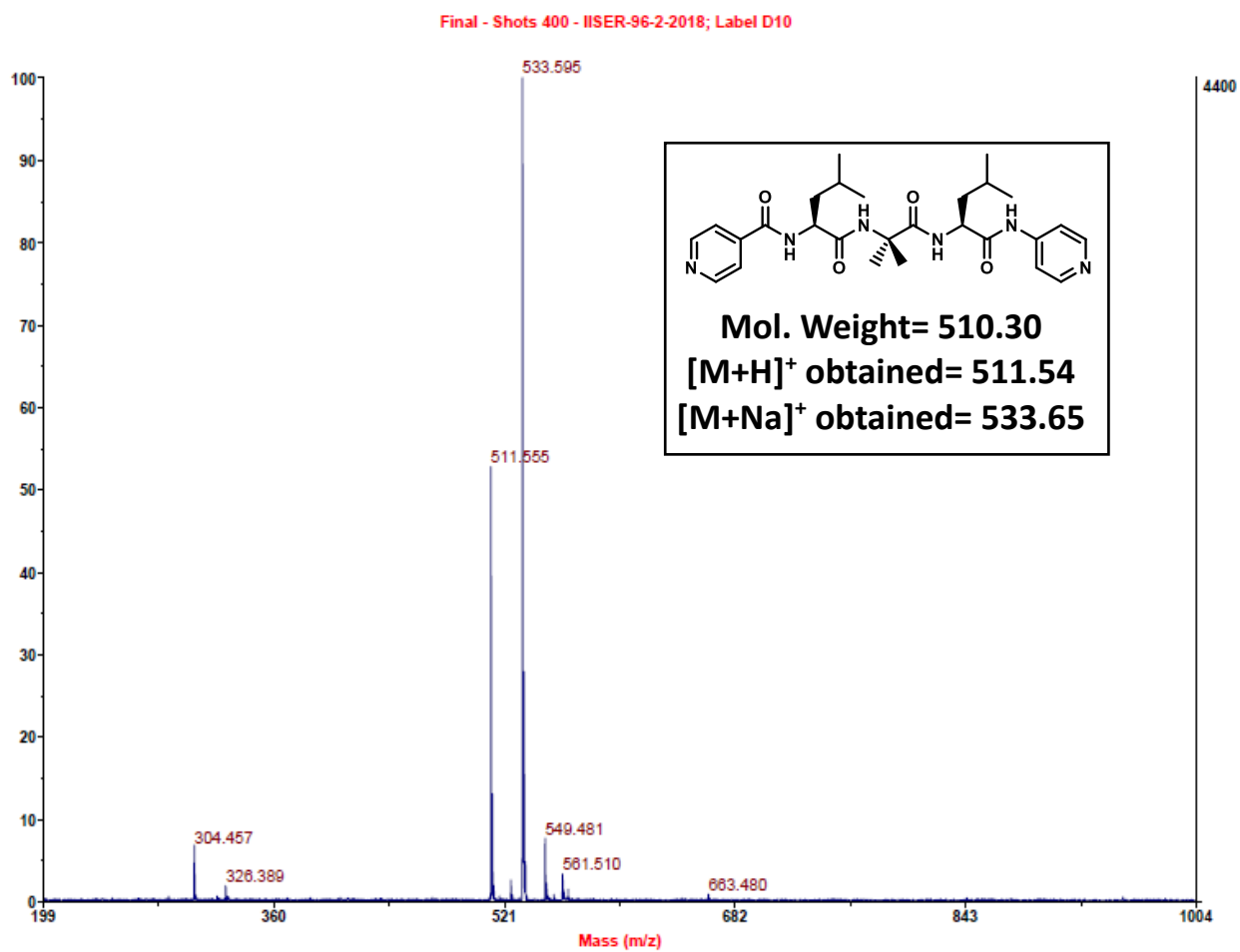


Figure 28: MALDI-TOF/TOF mass spectrum of **P1**.

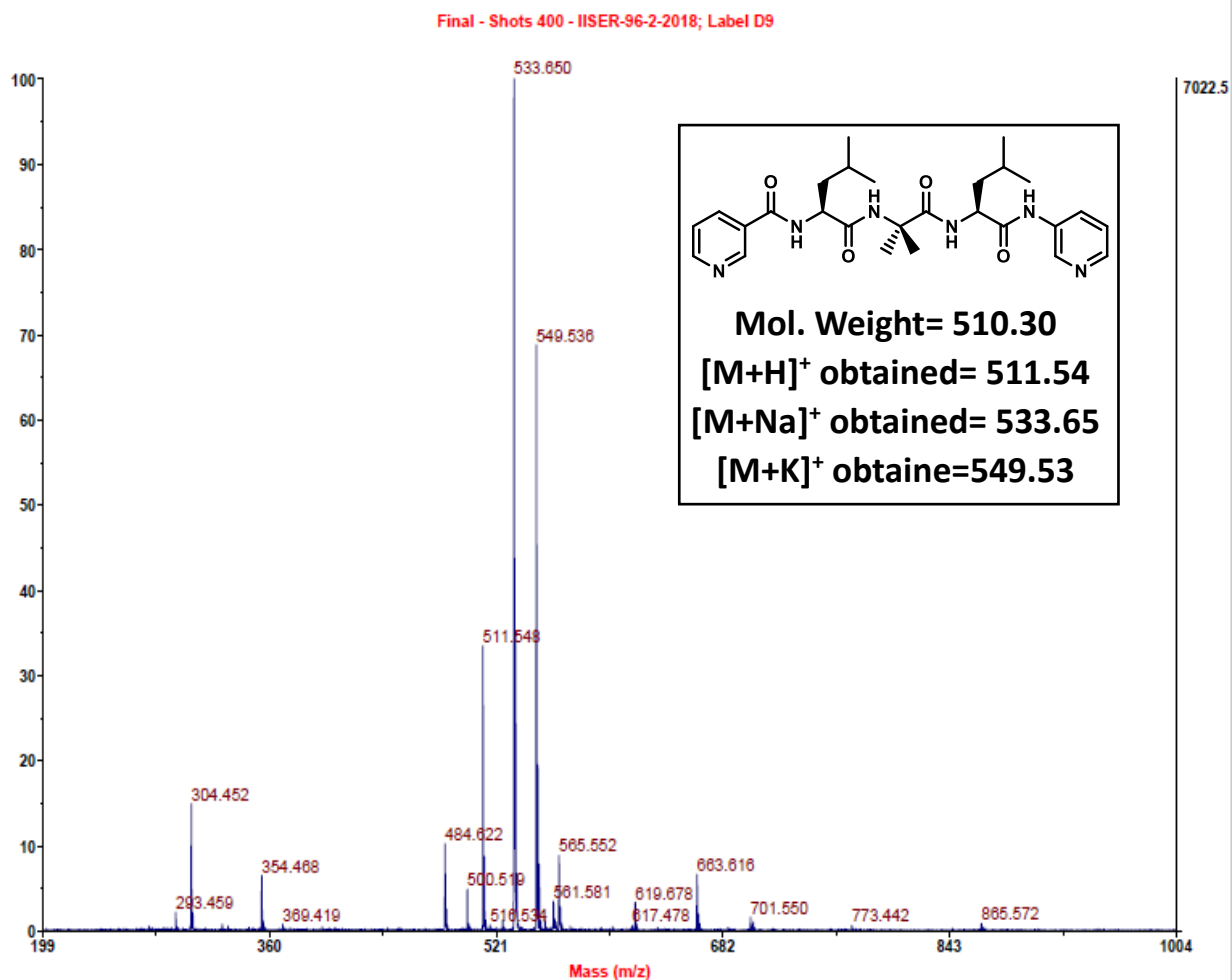


Figure 29: MALDI-TOF/TOF mass spectrum of **P2**.

Spectrum Report

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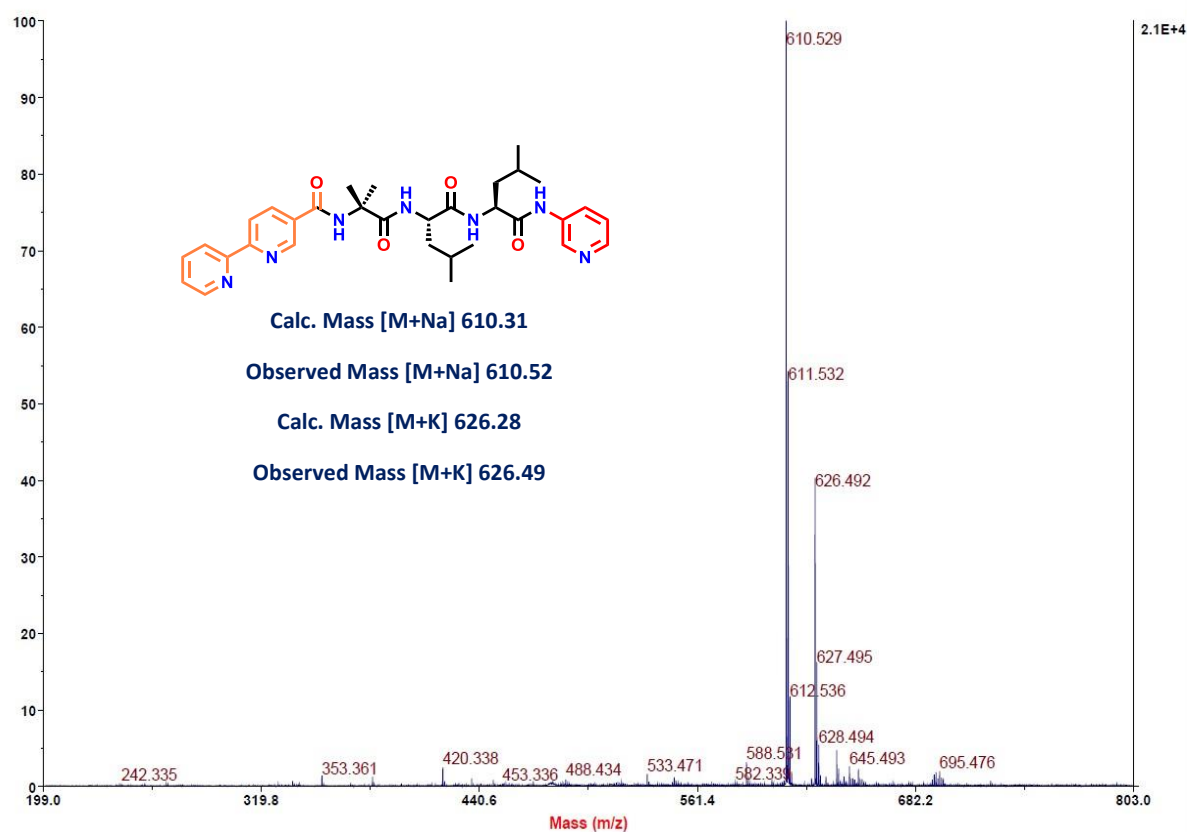
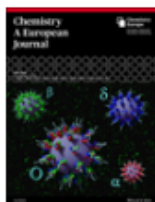


Figure 30: MALDI-TOF/TOF mass spectrum of **P3**.

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Chapter 3

Metal Induced β -turns in the short Tripeptides

1. Introduction:

Protein functionality is fundamentally intertwined with their distinctive three-dimensional configurations.¹ The theoretical deconstruction of the three-dimensional architecture of proteins delineates three discrete categories of secondary structural motifs, encompassing helices, β -sheets, and reverse turns, in conjunction with flexibly structured loops. The reverse turn motifs serve the pivotal function of altering the trajectory of polypeptide chains. Among the reverse turns, β -turns are predominant in protein. In contrast to β -sheets and α -helices, the intricate design of reverse turns poses a formidable challenge due to their non-periodic characteristics and structural heterogeneity.² In addition to the inherent β -turn-inducing motif, diverse research groups have systematically employed varied amino acids and organic templates to generate a spectrum of β -hairpin mimetics.³ The β -hairpin structural motif, comprised of binding epitopes within various proteins, assumes a pivotal role in molecular recognition processes. High-resolution structural analyses have elucidated the presence of turns within distinct antibody-peptide complexes,⁴ underscoring the significance of these structural elements in molecular interactions at the atomic level. The intricate architecture of these complex structures aligns seamlessly with the recognition motifs derived from the structure-activity relationships inherent in various peptide hormones, including bradykinin,^{5a, 5b} angiotensin II,^{5c, 5d} somatostatin,^{5e, 5f} and the RGD (Arg-Gly-Asp)^{5g, 5h} sequence. Furthermore, the β -hairpin structural motifs, characterized by diverse reverse turn motifs, are integral components of an extensive family of cationic antimicrobial peptides, exemplified by mammalian defensins, tachyplesins, protegrins, among others. Notably, these peptides exhibit a broad-spectrum antimicrobial efficacy against a diverse array of both Gram-positive and Gram-negative bacteria, thereby underscoring their potential therapeutic relevance.⁶ Apart from their antimicrobial properties, various β -hairpin scaffolds have been systematically investigated for their capacity to emulate the structural likeness of epitopes and cytokine receptors.⁷ Within this context, Robinson and co-authors documented the utilization of β -hairpin peptidomimetics, featuring $^D\text{Pro}-^L\text{Pro}$ as a reverse turn motif. These peptidomimetics demonstrated an affinity for the HDM2 protein, resulting in the inhibition of the p53-HDM2 interactions shown in Figure 1b.^{7f} This molecular interaction modulation underscores the potential therapeutic implications of β -hairpin structures in the realm of protein-protein interactions and their regulatory roles. In addition to their significant biological relevance, diverse β -hairpin structures serve as effective asymmetric catalysts in various organic transformation reactions, owing to their inherent tunable and modifiable properties.⁸ The

research conducted by Miller and colleagues exemplifies an extensive exploration of various β -turn mimetic catalysts. These catalysts have been employed to systematically elucidate mechanism-based phosphorylation, conjugate addition, asymmetric acylation, asymmetric C-C bond formation, and site-specific reactions shown in Figures 1c and 1d.^{8a-8e}

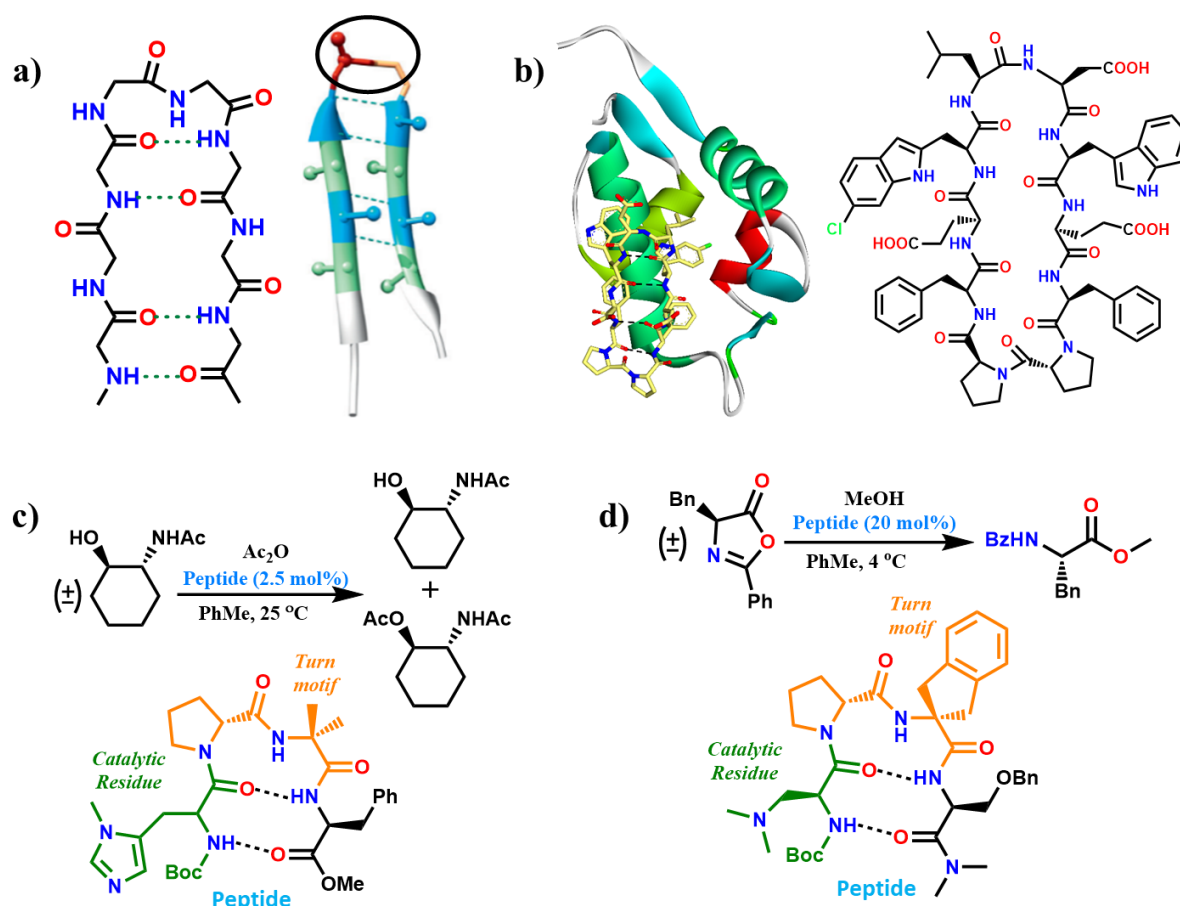


Figure 1: a) Schematic presentation of β -turn and β -hairpin motif. b) Interaction of designed β -hairpin with HMD2 protein (PDB Code: 2AXI). c) and d) Asymmetric catalysis using designed β -turn peptides.

Furthermore, various β -hairpin structures find application in the design of self-assembled materials, specifically in the context of hydrogels. These hydrogels, characterized by their three-dimensional network structure, hold substantial utility in diverse biotechnological applications. Notably, they have been employed for tissue culture purposes, serving as scaffolds that facilitate cellular growth and proliferation.⁹ Additionally, the inherent properties of these β -hairpin-based hydrogels make them promising candidates for drug delivery systems, where controlled release mechanisms can be finely tuned. In this investigation, we elucidate the anion-tuned silver ion-mediated, coordination site-dependent various β -turn motifs using short α -tripeptide sequences. These metal coordinated β -turns showed remarkable second

harmonic generation (SHG), an interesting non-linear optical property. Thus, the β -hairpin emerges as a pivotal structural motif with broad-ranging applications spanning biology, medicinal chemistry, as well as in material chemistry. The diverse utility of β -hairpins has attracted considerable attention from synthetic chemists and structural biologists to engineer stable β -turns and β -hairpins employing an array of both natural and non-natural amino acids.

2. Design of β -turn:

In the context of hairpin structures, the linkage between two antiparallel β -strands involves a segment of reverse turn residues. The categorization of these reverse turns is contingent upon the hydrogen bonding patterns, leading to distinct classes. Examination of various high-resolution protein structures has revealed that β -turns constitute the most prevalent form of reverse turns. A β -turn, comprising four residues denoted as i , $i+1$, $i+2$, and $i+3$, induces an approximate 180° alteration in the polypeptide chain direction. Notably, β -turn structures undergo further classification into distinct types, including type I, type II, type I', type II', etc., based on the torsion angles exhibited by residues $i+1$ and $i+2$. The specific torsion angles corresponding to different β -turn types are shown in Table 1.

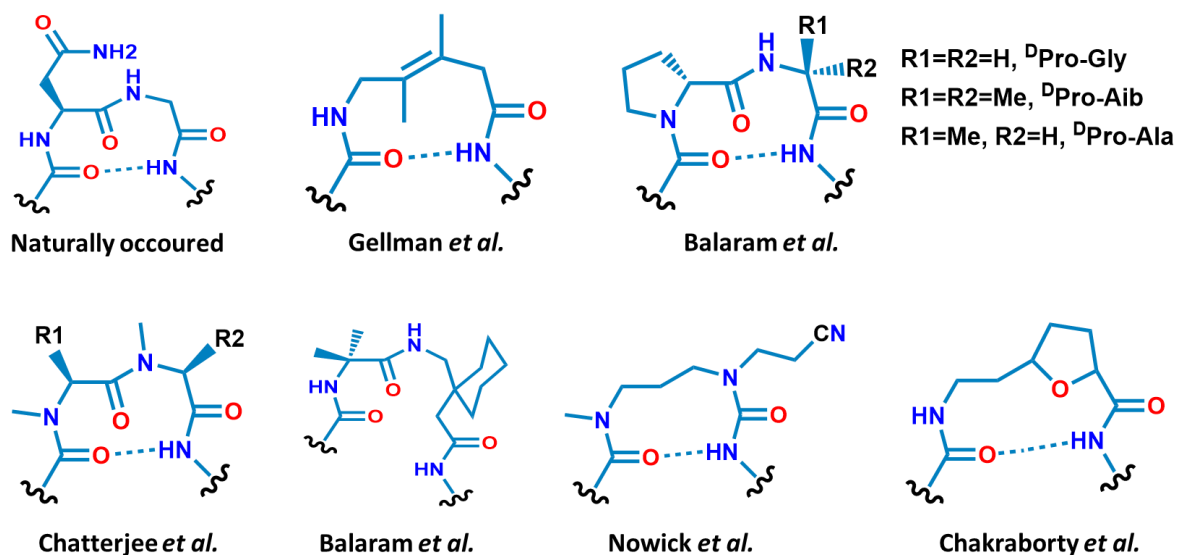
Table 1: List of different β -turns and their torsion angles:

Type	Φ_{i+1} (°)	Ψ_{i+1} (°)	Φ_{i+2} (°)	Ψ_{i+2} (°)
Type-I	-60	-30	-90	0
Type-II	-60	120	80	0
Type-I'	60	30	90	0
Type-II'	60	-120	-80	0

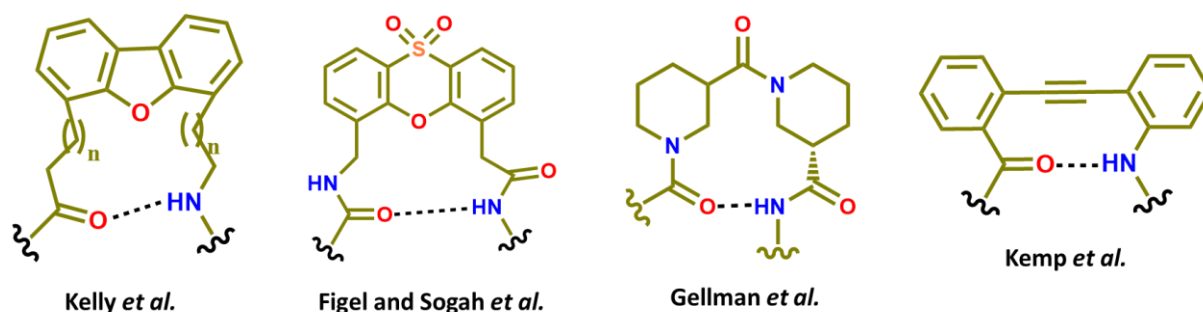
Type I β -turns emerge as prevalent structural motifs in protein configurations, playing a pivotal role in diverse biological processes encompassing protein-protein, protein-peptide, protein-DNA interactions, biomolecular recognition, phosphorylation, glycosylation, and hydroxylation.¹⁰ Substantial efforts spanning several decades have been directed towards the artificial design of β -turns. These engineered β -turns not only contribute to an enhanced understanding of higher-order biomolecular structures but also hold potential utility in the creation of drug-like functional epitopes. In this context, diverse forms of β -turns, such as $^D\text{Pro-Xxx}$ (where Xxx represents Gly, Pro, Aib), Aib- ^DAla , have been meticulously crafted to stabilize β -hairpin conformations.¹¹ Beyond the scope of $^D\text{Pro-Xxx}$ (Xxx= Gly, Aib, Pro, Ala,

etc.) as a β -turn segment, Balaram and collaborators have significantly expanded the repertoire of β -turn mimics by employing the D Pro-Xaa (Xaa= β -, γ -, and δ - amino acid) dipeptide template. Their investigations reveal that peptides incorporating α,β - and α,γ - residues at the turn can adopt β -hairpin structures in polar protic solvents.¹²

Amino acid based template as reverse turn:



Organic Template Based Reverse Turn:



Scheme 1: Amino acid and organic template based reverse turn.

In addition to peptide-based designs, various organic templates and building blocks have been recognized as effective β -turn mimetics. Kemp and colleagues have demonstrated the β -turn mimetic properties of 2,2'-substituted tolan.¹³ Figel and Sogah have explored the reverse turn-inducing capabilities of 4-phenoxathiin derivatives,¹⁴ while Kelly and co-workers have examined the potential of dibenzofuran-based amino acids as reverse turns.¹⁵ Gellman and collaborators have demonstrated the utility of tetrasubstituted alkenes in inducing β -turns.¹⁶ Borggraeve and co-workers have designed amino(oxo)piperidinecarboxylate scaffolds as

reverse turns,¹⁷ and Nowick and colleagues have highlighted the effectiveness of urea derivatives and 5-amino-2-methoxybenzoic acids as β -turns.¹⁸

3. Scope and Aim of the Current Work:

From the last few years, our research endeavors have been focused on exploring the application of diverse non-natural amino acids in the rational design of functionally distinct peptide foldamers.¹⁹ Recently, our investigations have elucidated the design principles, crystal conformations, and coordination site-dependent characteristics of distinct silver-coordinated frameworks derived from short α,γ -hybrid tripeptide 12-helices. These helices are distinguished by terminal pyridyl moieties, and our attention has been particularly drawn to understanding the efficacy of these metal-helix frameworks in the adsorption of carbon dioxide (CO_2). Upon silver ion coordination, we observed nuanced structural behaviors within the 12-helices, with noteworthy distinctions between those terminated by 3-pyridyl and 4-pyridyl derivatives. The 12-helix terminated by 3-pyridyl derivatives exhibited an intriguing 2:2 macrocyclic structure, while retaining its helical conformation after metal coordination shown in Figure 2a-2c. Conversely, the 12-helix terminated by 4-pyridyl derivatives manifested as extraordinary porous metal-helix frameworks, showcasing a remarkable capacity for CO_2 sequestration. Importantly, akin to its precursor peptide, the 4-pyridyl-terminated 12-helix retained its helical integrity upon metal coordination shown in Figure 2d-2g.²⁰ These findings contribute valuable insights into the structural stability of α,γ -hybrid tripeptide 12-helices under the influence of silver ion coordination.

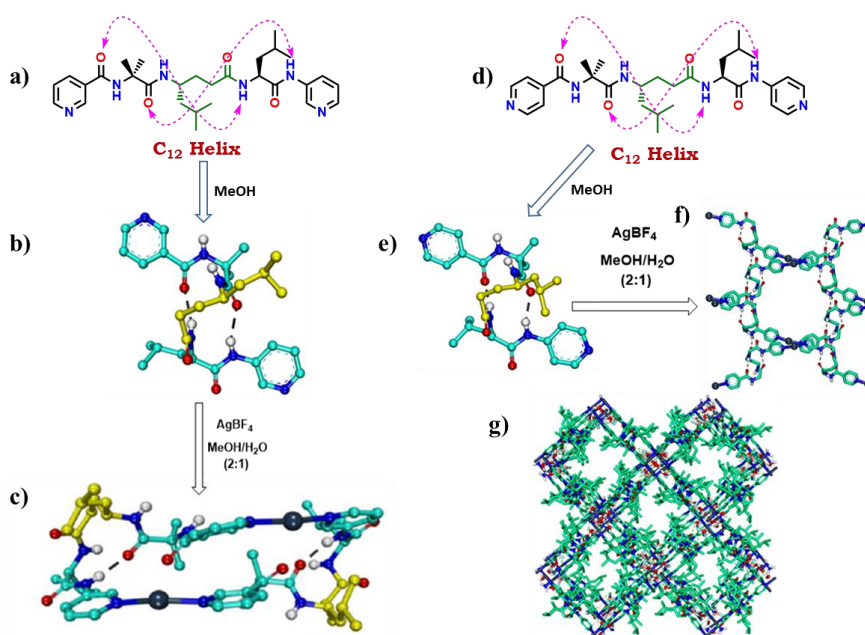


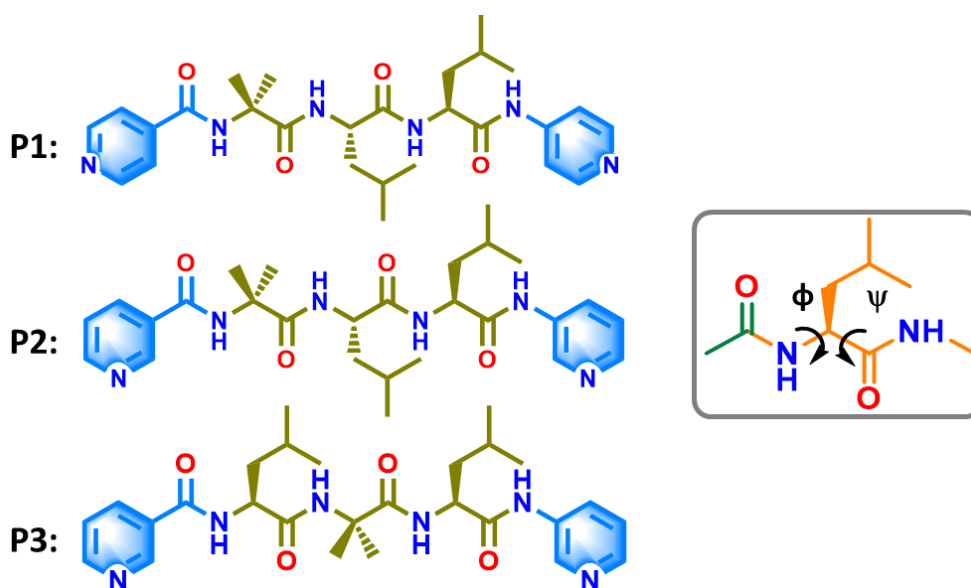
Figure 2: a), and d) Sequence of designed α,γ -hybrid tripeptide. b), and e) X-ray diffraction structure peptides which form 12-Helix. c) Upon silver ion coordination displayed 2:2 macrocyclic structure. f) Head-to-tail silver ion coordination and H-bonding between the helices observed in the crystal packing. c) The porous 12-helical metal peptide framework observed along the c-axis.

This peptide sequence, demonstrating a propensity for helical structure formation through intramolecular hydrogen bonding, stands out as a candidate for the shortest hybrid configuration with such characteristics. Motivated by this distinctive feature, our research endeavours have led us to contemplate the substitution of the γ -residue with its α -counterpart. Our objective is to systematically investigate the ensuing structural modifications both before and after metal coordination. Based on our earlier research, we observed that strategic modification of the metal coordinating site has demonstrated the capacity to finely tune structural properties. As such, our current research endeavors are directed towards systematically probing the variations in structural properties through the deliberate alteration of the binding site.

4. Results and Discussion:

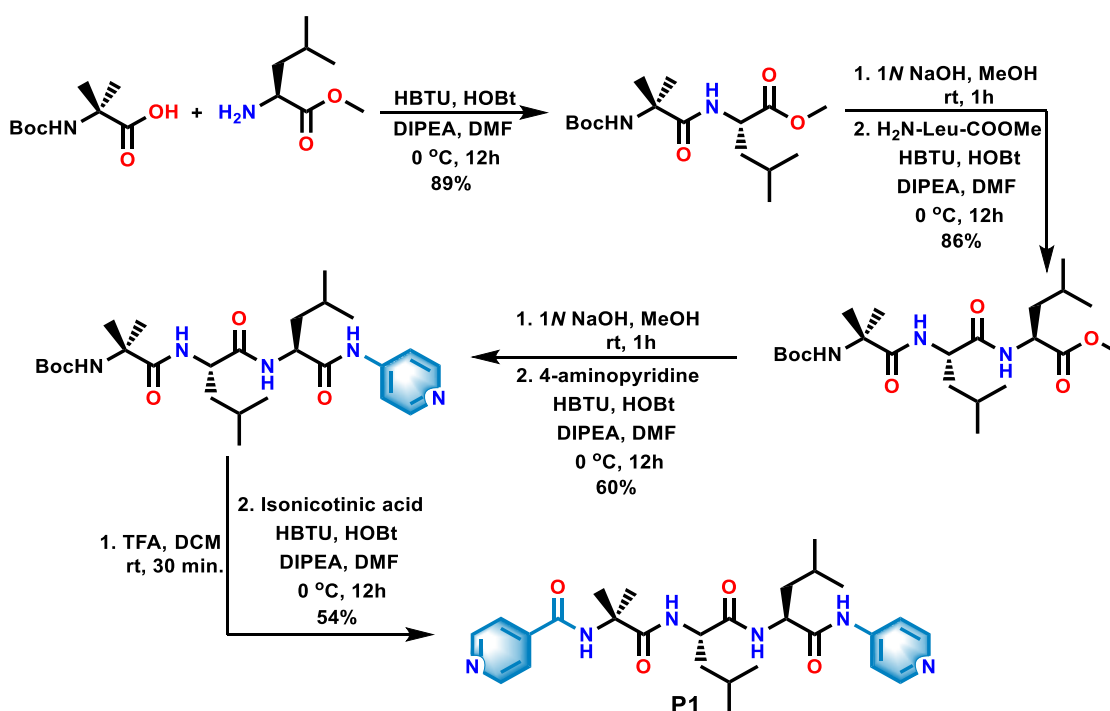
4.1. Design and Synthesis of Peptides:

To broaden the landscape of potential metal-coordination architectures derived from peptide β -turns and helical secondary structures, we conceived the design of three distinct tripeptides labelled as **P1**, **P2**, and **P3**, as shown in Scheme 1. Aib, strategically incorporated within the peptide sequences, assumes a pivotal role in imparting structural stability, particularly in the formation of resilient β -turns and helices. The terminals of these peptides are linked to either 3-pyridyl, or 4-pyridyl, strategically chosen as metal-coordinating entities. The introduction of pyridyl moieties serves the purpose of maintaining structural integrity by keeping these groups away from the metal-coordination site.



Scheme 2: Sequences of short tripeptides from **P1** – **P3**. Torsion angle variables of α -residue are also shown.

The synthesis of all tripeptides, namely **P1**, **P2**, and **P3** was accomplished through a conventional solution-phase strategy, involving sequential Boc-deprotection and coupling methods. The synthetic protocol is detailed in Scheme 2. Employing this methodology, each peptide was synthesized in solution phase and subsequently purified through column chromatography, yielding products with a range of 45% to 60%.



Scheme 3: Synthesis of short α - tripeptide **P1**.

4.2. Crystal Structures Analysis of Peptide P1, P2, and P3:

In our quest to unravel the potential metal-coordinated assemblies accessible to **P1**, **P2**, and **P3**, and to understand the influence of metal coordination on the peptide conformation, these peptides were subjected to crystallization experiments utilizing a variety of silver salts and solvent combinations. Remarkably, single crystals were exclusively obtained at the interface of a methanol-based peptide solution and an aqueous solution containing various silver salts. It is noteworthy that the formation of crystals did not occur when employing metal salts other than those of silver. Subsequent to their formation, the single crystals resulting from silver coordination were systematically subjected to X-ray diffraction analysis, yielding intricate structural details, which are described below.

4.2.1. Crystal Structures Analysis of P1-AgBF₄ Complex:

We started our investigation with peptide **P1** with the treatment of AgBF₄ salt. The resultant interaction led to the formation of single crystals at the methanol/water interface under ambient temperature conditions. The X-ray diffraction analysis of the **P1**-AgBF₄ complex is shown in Figure 3. Notably, the structural elucidation unveiled the crystallization of the **P1**-AgBF₄ complex within the centrosymmetric space group $P 2_1/n$. Within the crystalline lattice, peptide **P1** adopted a classical 3_{10} -Turn (β -Turn) conformation. The β -turn, formed in an $\alpha\alpha$ segment, exhibited structural stabilization through an incipient 10-membered intramolecular hydrogen bond linking CO (*i*) to NH (*i*+4) residues. Additionally, the structural integrity was further reinforced by π - π stacking interactions between the terminal pyridyl groups, as shown in Figure 3a. Detailed examination of the torsion angles revealed distinctive characteristics of the Aib and Leu residues. Specifically, the torsion angles ϕ and ψ for Aib residues were determined to be -49° and -46° , respectively. In contrast, the Leu residues exhibited torsion angles of -104° and 18° as well as 121° and -3° indicative of a type-I β -Turn configuration. This conformational arrangement underscores the intricacies of the structural motif adopted by the **P1**-AgBF₄ complex in its crystalline state. Moreover, the terminal 4-pyridyl groups exhibit engagement in silver ion coordination, establishing intermolecular connections between two β -Turn peptides in a head-to-tail arrangement. The connection between β -turn units is established through Ag (I) ion coordination, forming an intriguing 2:2 macrocycle, as shown in Figure 3b. The BF₄ anion engages in multifaceted interactions, forming intermolecular hydrogen bonds with the 4-pyridyl NH and establishing NH...F bonds with the NH protons of Aib and two Leu groups. Notably, Crystal structure analysis further reveals that these macrocyclic units are

interconnected through intermolecular hydrogen bonding, leading to the development of a continuous polymeric macrocycle along the horizontal direction (Figure 3c). This intricate network of interactions contributes to the establishment of a robust and interconnected polymeric architecture in the crystal lattice.

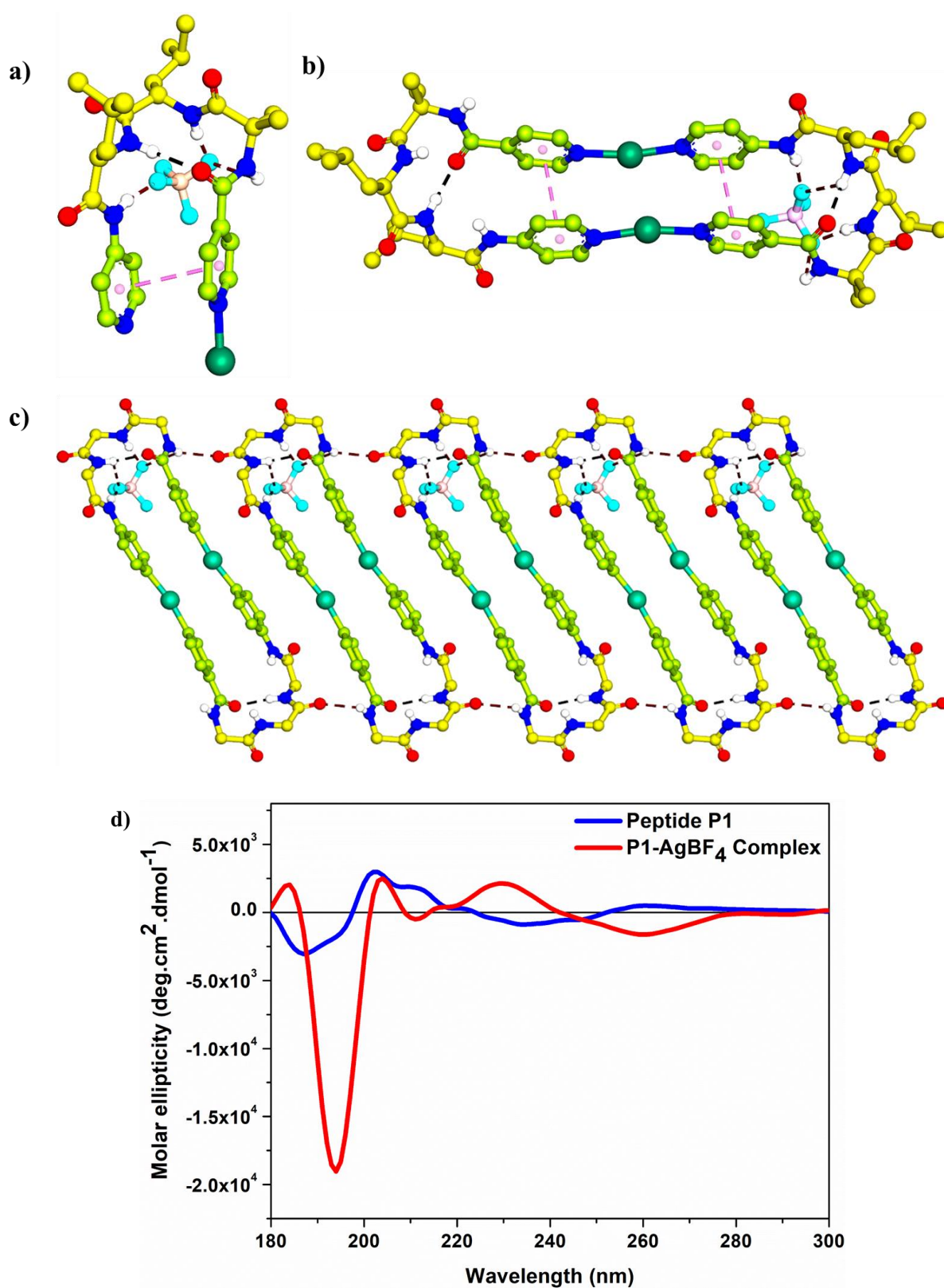


Figure 3: a) The X-ray diffraction structure of silver coordinated **P1** in the presence of AgBF₄. b) The ‘Head to Tail’ coordinated macrocyclic structure of **P1** in the presence of AgBF₄. c) Continuous polymeric structure along the horizontal direction (for clarity side-chain residues have been omitted). d) CD spectra of the peptide **P1** in the presence of AgBF₄ salt.

The torsion angles and H-bond parameters of the **P1**-AgBF₄ complex are given in Table 2 -3.

Table 2: Torsion Angle Parameters of **P1**-AgBF₄

Peptide		Residue	Φ (°)	Ψ (°)
P1-AgBF₄	Molecule 1	Aib	-49	-47
		Leu	-104	18
		Leu	121	-3
	Molecule 2	Aib	49	47
		Leu	104	18
		Leu	-121	3

Table 3: H-bond Parameters of **P1**-AgBF₄

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P1-AgBF₄	Molecule 1	Py CO ← NH Leu	2.155	2.97	154
	Molecule 2	Py CO ← NH Leu	2.155	2.97	154
Complex		Hydrogen bond (intermolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P1-AgBF₄	Molecule 1	Leu CO(2) ← NH Aib(1)	2.329	2.865	119
	Molecule 2	Leu CO(1) ← NH Aib(2)	2.329	2.865	119

4.2.2. Crystal Structures Analysis of **P1**-AgOTf Complex:

Inspired by the observed β-turn conformation exhibited by **P1** in the presence of AgBF₄, our investigation extended to an X-ray analysis of single crystals generated through the interaction

of **P1** with AgOTf. Peptide **P1** yielded singular crystals at the methanol/water interface upon exposure to AgOTf under ambient temperature conditions. The X-ray diffracted single crystal structure of the **P1**-AgOTf complex is shown in Figure 4. Structural examination unveiled that the **P1**-AgOTf complex crystallized within the centrosymmetric space group P-1. In the crystalline state, peptide **P1** assumed a classical 3_{10} -turn (β -turn) conformation. The abbreviated β -turn, occurring within an $\alpha\alpha$ segment, found stabilization through an incipient 10-membered intramolecular hydrogen bond connecting Aib CO (i) to NH ($i+4$) of 4-pyridyl residues. Additionally, β -turn structure also stabilized π - π stacking interactions involving the two terminal pyridyl groups, as shown in Figure 4a.

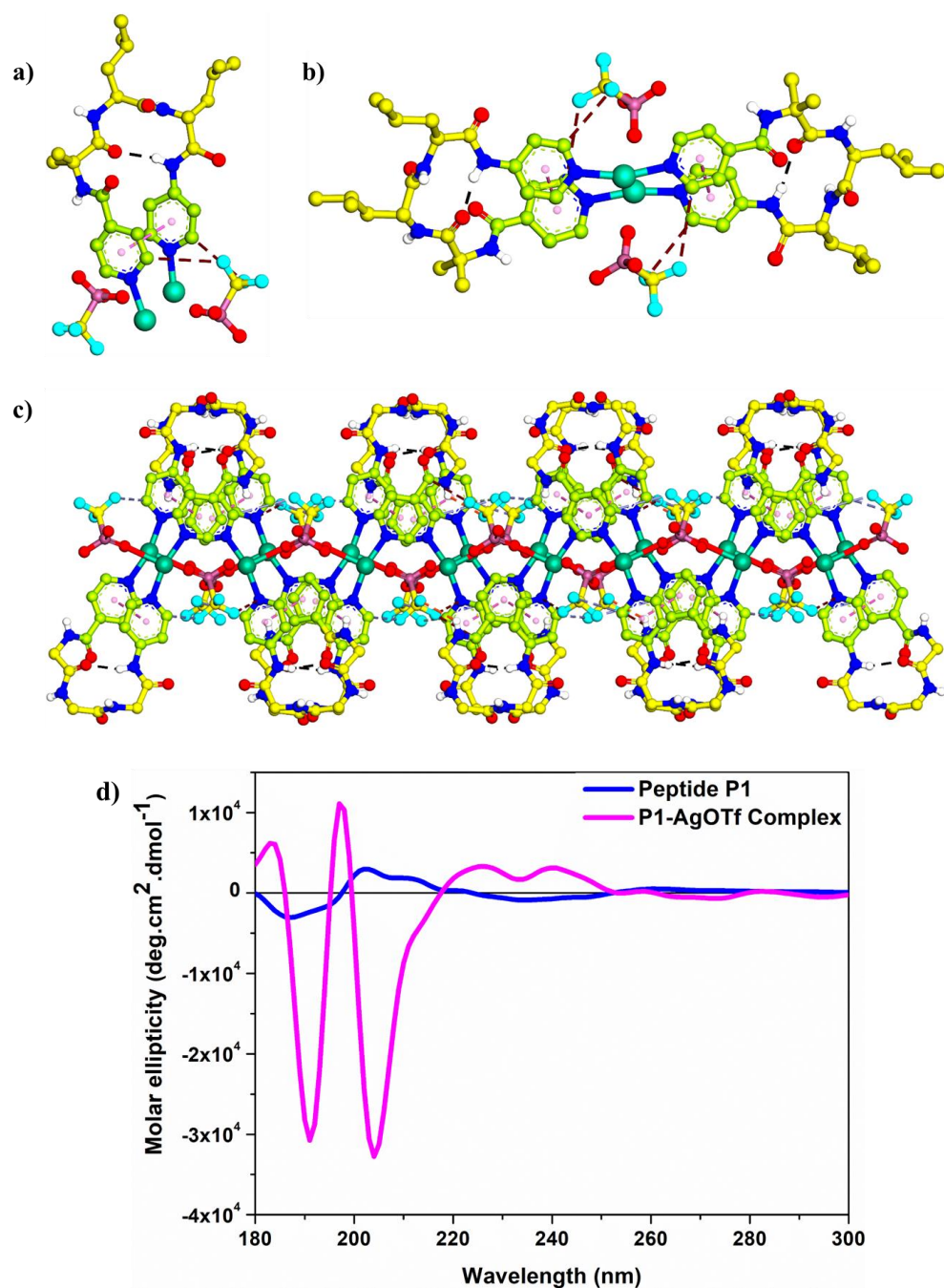


Figure 4: a) The X-ray diffraction structure of silver coordinated **P1** in the presence of AgOTf. b) The ‘Head to Tail’ coordinated macrocyclic structure of **P1** in the presence of AgOTf. c) Continuous Zig-Zag polymeric structure along the horizontal direction (for clarity side-chain residues have been omitted). d) CD spectra of the peptide **P1** in the presence of AgOTf salt.

Torsion angle analysis revealed that the ϕ and ψ of Aib residue is 59° and -153° respectively whereas Leu residues are -67° and 123° respectively, while another Leu displayed 99° and -8° respectively. These characteristic torsion angles signify the adoption of a type-II β -turn configuration. Moreover, the terminal 4-pyridyl groups intricately engage in silver ion coordination, establishing intermolecular connections between two β -turn peptides in a head-to-tail arrangement, as depicted in Figure 4b. The trifluoromethanesulfonate interacts with the Ag (I) coordinated to the 4-pyridyl group through a salt bridge and additionally forms CH---F bonds with the 4-pyridyl groups. Within this context, the coordination of one β -turn unit to another is facilitated through Ag (I) ion coordination, resulting in the formation of a remarkable 2:2 macrocycle, as shown in Figure 4b. Structural examination further reveals that these macrocyclic units intricately connect through intermolecular hydrogen bonding and the strong interaction between Ag (I) and the trifluoromethanesulfonate anion orchestrates to the development of a continuous Zig-Zag polymeric macrocycle along the horizontal direction, as portrayed in Figure-4c. The systematic exploration of these structural intricacies enhances our understanding of the conformational dynamics exhibited by the **P1**-AgOTf complex in its crystalline manifestation.

The torsion angles and H-bond parameters of the **P1**-AgOTf complex are given in Table 4 -5.

Table 4: Torsion Angle Parameters of **P1**-AgOTf

Peptide		Residue	ϕ	Ψ
	Molecule 1	Aib	62	-154
		Leu	-62	122
		Leu	96	-3
	Molecule 2	Aib	-62	154
		Leu	62	-122
		Leu	-96	3

P1-AgOTf	Molecule 3	Aib	59	-153
		Leu	-63	122
		Leu	97	-2
	Molecule 4	Aib	-59	153
		Leu (i)	63	-122
		Leu (i+1)	-97	2

Table 5: H-bond Parameters of **P1-AgOTf**

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O...H-N
			in angstroms		in degrees
P1-AgOTf	Molecule 1	Aib CO ← NH Py	2.025	2.847	159
	Molecule 2	Aib CO ← NH Py	2.025	2.847	159
	Molecule 3	Aib CO ← NH Py	2.036	2.856	159
	Molecule 4	Aib CO ← NH Py	2.036	2.856	159

4.2.3. Crystal Structures Analysis of P2-AgOTf Complex:

The backbone structural diversity of peptide **P1** in response to different counter anions of silver salt prompted an exploration into the backbone structures and assemblies of a related peptide, denoted as **P2**, possessing distinct coordination sites. Specifically, **P2** was designed with 3-pyridyl groups positioned at both the C- and N-termini, and subjected to crystallization in the presence of various silver salts. Notably, **P2** yielded single crystals at the methanol/water interface when exposed to AgOTf at ambient temperature. Analogous to the β -turn backbone structure observed in **P1** in the presence of AgOTf, the single crystal analysis of **P2** under the same conditions revealed the adoption of a classical 3_{10} -turn (β -turn), as shown in Figure 5a. The structural analysis also revealed that **P2-AgOTf** complex crystallized within the non-

centrosymmetric space group $P 2_1$. The structural stability of the β -turn in **P2** is upheld by an incipient 10-membered intramolecular hydrogen bond between the 4-pyridyl CO (*i*) residue and the NH (*i*+4) of the Leu residue. Additionally, π - π stacking interactions between two pyridyl groups further contribute to this stabilization, as illustrated in Figure 5a.

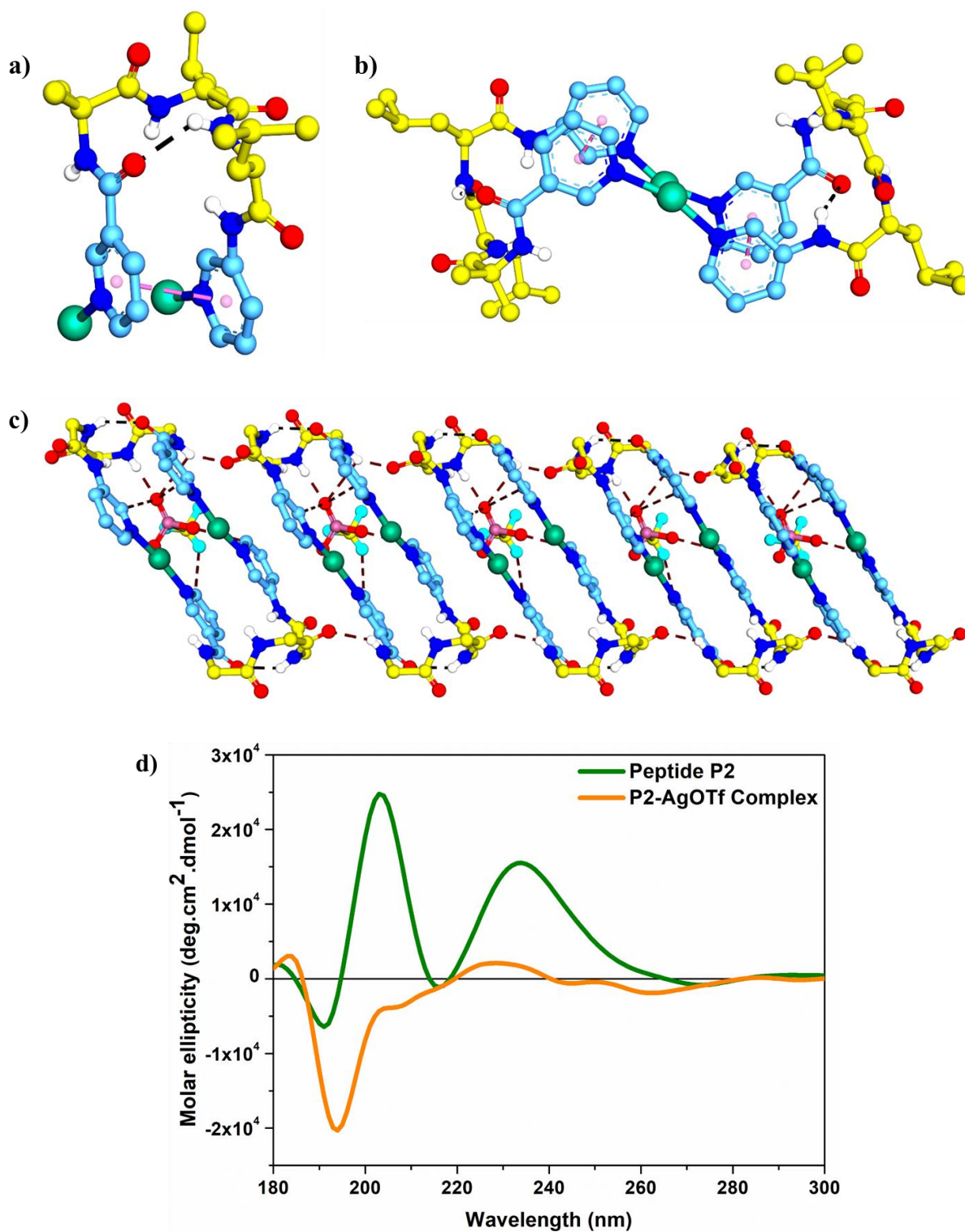


Figure 5: a) Crystal structure of silver coordinated **P2** in the presence of AgOTf salt derived from single crystal X-ray diffraction data b) The ‘Head to Tail’ coordinated metalloclip structure of **P2** in the presence of AgOTf. c) Continuous polymeric structure along the horizontal direction (for clarity side-chain residues have been omitted). d) CD spectra of the peptide **P2** in the presence of AgOTf salt.

Moreover, the terminal 3-pyridyl groups coordinate with silver ions, linking two β -turn peptides in a head-to-tail fashion (Figure 5b). Trifluoromethanesulfonate forms a salt bridge with 3-pyridyl-coordinated Ag (I) and engages in CH---O-H bonds with both terminal 3-pyridyl groups and Leu1 NH---O-H bonds. This results in the formation of a distinctive 2:2 metalloclip structure, where one β -turn unit connects with another through Ag (I) ion coordination (Figure 5b). Crystal structure analysis further reveals that these metalloclip units are interconnected through intermolecular hydrogen bonding, leading to the formation of a continuous polymeric macrocycle along the horizontal direction, as depicted in Figure 5c. This intricate network of interactions, involving metal coordination, hydrogen bonding, and anion binding, contributes to the creation of a robust and extended polymeric architecture within the crystal lattice.

The torsion angles and H-bond parameters of the **P2**-AgOTf complex are given in Table 6 -7.

Table 6: Torsion Angle Parameters of **P2**-AgOTf.

Peptide		Residue	ϕ	Ψ
P2-AgOTf	Molecule 1	Aib	-49	-49
		Leu	-80	25
		Leu	68	17
	Molecule 2	Aib	52	40
		Leu	90	-20
		Leu	-71	-17

Table 7: H-bond Parameters of **P2**-AgOTf.

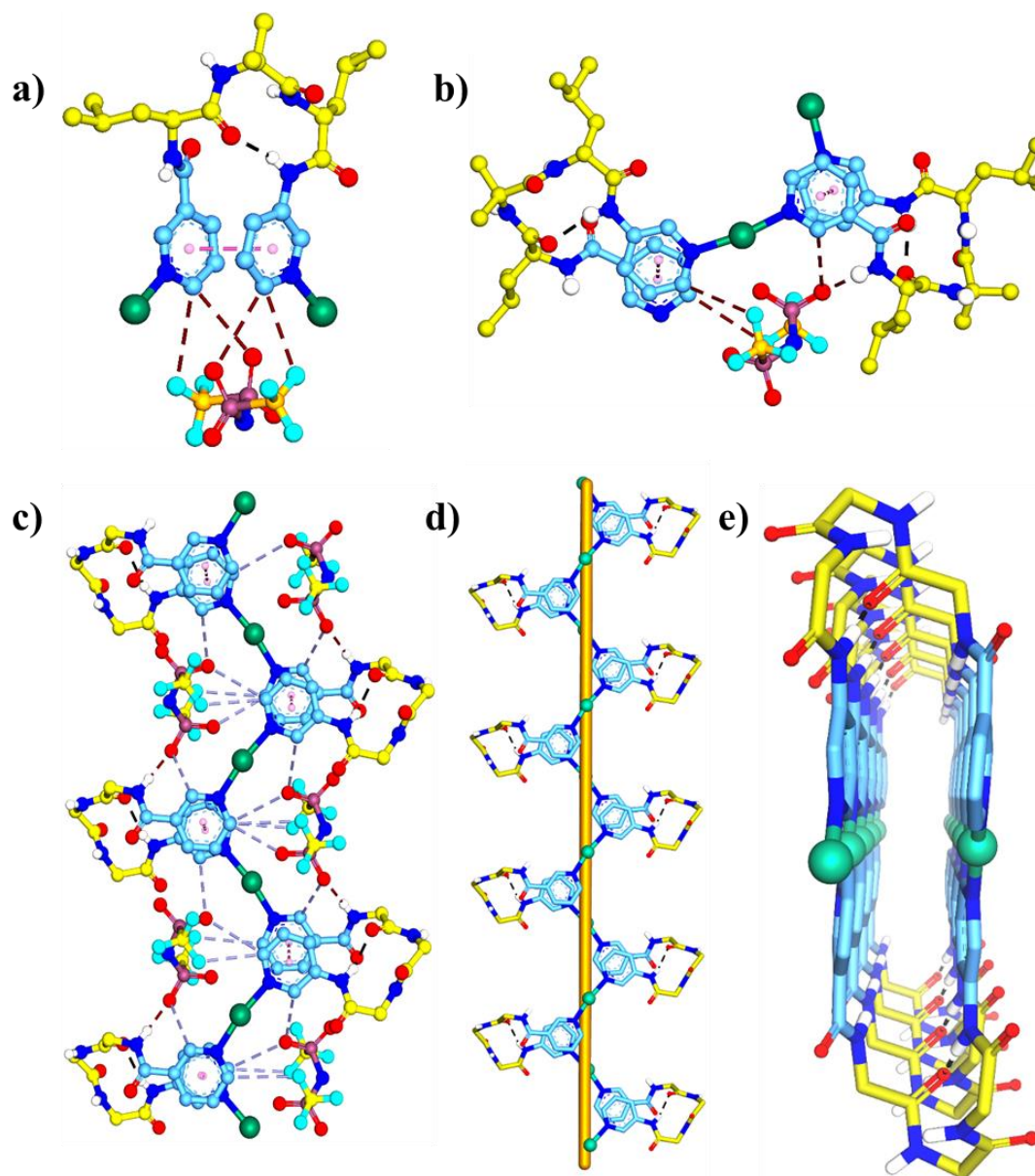
Complex	Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
		in angstroms		in degrees

P2-AgOTf	Molecule 1	Py CO $\leftarrow$ NH Leu	2.40	2.923	120
	Molecule 2	Py CO $\leftarrow$ NH Leu	2.187	2.833	132
Complex		Hydrogen Bond (intermolecular)	C=O...H-N	C=O...N-H	$\angle$O...H-N
			in angstroms		in degrees
P2-AgOTf	Molecule 1	Leu CO(2) $\leftarrow$ NH Aib(1)	1.923	2.702	150
	Molecule 2	Leu CO(1) $\leftarrow$ NH Aib(2)	2.209	2.975	148
		Leu CO(1) $\leftarrow$ N Py(2)		2.918	

4.2.4. Crystal Structure Analysis of P3-AgNTf₂ Complex:

The structural consistency observed between **P1** and **P2** in the presence of diverse counter anions of silver salt prompted an investigation into the backbone structural attributes of a short tripeptide denoted as **P3**. In this design, the peptide features 3-pyridyl groups as coordination sites at both the C- and N-terminal ends, with the strategically positioned sterically hindered Aib at the central position. Crystallization attempts were undertaken for peptide **P3** in the presence of various silver salts, specifically employing bulkier counter anions. Remarkably, **P3** yielded single crystals at the methanol/water interface in the presence of AgNTf₂ salt at ambient temperature. Analogous to the observed behavior in **P1** and **P2**, single crystal analysis in the presence of AgNTf₂ unveiled the adoption of a classical β -turn by Peptide **P3**, as shown in Figure 6a. The **P3**-AgNTf₂ crystallized in the space group of P 2₁2₁2₁. The compact β -turn, formed within an $\alpha\alpha$ segment, found stabilization through an incipient 10-membered intramolecular hydrogen bond between Leu1 CO (*i*) and NH (*i*+4) of 4-pyridyl residues. Additionally, π - π stacking interactions between two terminal pyridyl groups further contributed to this stabilization. The interconnection of two β -turn peptide units occurs through the mediation of a silver ion in a head-to-tail arrangement shown in Figure 6b. In addition to the ionic interaction with the silver ion, bis(trifluoromethanesulfonyl)imide is involved in intermolecular H-bonding with the Leu3 NH, concurrently bringing the two peptide units into closer proximity through intermolecular CH...O and CH...F interactions with the three 3-pyridyl groups present in the two β -turn peptides. The silver ion coordinates with **P3** in a head-to-tail fashion, contributing to the formation of a right-handed infinite superhelical coordinated polymer, as shown in Figure 6c. Notably, the central axis of the superhelix is occupied by the bis(trifluoromethanesulfonyl)imide anions, underscoring their pivotal role in the molecular

architecture and assembly of the peptide structure. The side-view and upper view of the superhelix without amino acid side-chains are shown in Figures 6d and 6e, respectively.



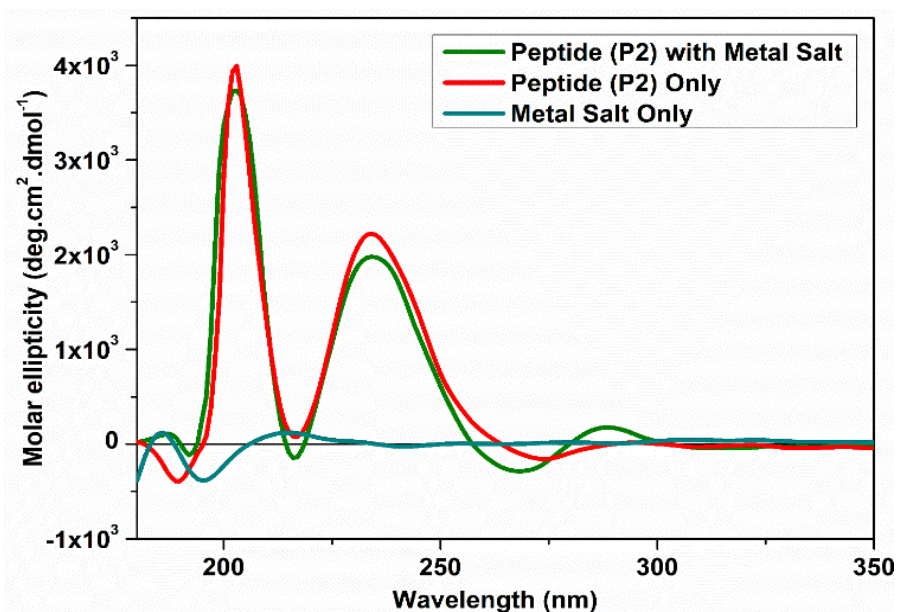


Figure 6: a) Crystal structure of silver coordinated **P3** in the presence of AgNTf₂ derived from single crystal X-ray diffraction data. b) The ‘head-to-tail’ Silver ion-directed peptide assembly and c) Interaction with NTf₂ anion in the crystal packing. d), and e) Side and top view of superhelical structure along the vertical direction (for clarity side-chain residues have been omitted). f) CD spectra of the peptide **P3** in the presence of AgNTf₂ salt.

The helical conformation demonstrated by the **P3**-AgNTf₂ complex was substantiated through a comparative examination of circular dichroism (CD) spectra alongside those of the native helical peptide **P3**, as shown in Figure 3f. The CD spectra of Peptide **P3** exhibit distinctive maxima at 203 nm and 234 nm. In parallel, the CD spectra of the **P3**-AgNTf₂ complex reveal analogous features, with maxima consistently observed at 203 nm and 234 nm. These spectral similarity provide the spectroscopic evidence for the helical nature of **P3**-AgNTf₂.

The torsion angles and H-bond parameters of the **P3**-AgNTf₂ complex are given in Table 8 -9.

Table 8: Torsion Angle Parameters of **P3**-AgNTf₂.

Peptide	Residue	ϕ	Ψ
P3 -AgNTf ₂	Leu	-89	155
	Aib	49	43
	Leu	88	3

Table 9: H-bond Parameters of **P3-AgNTf₂**.

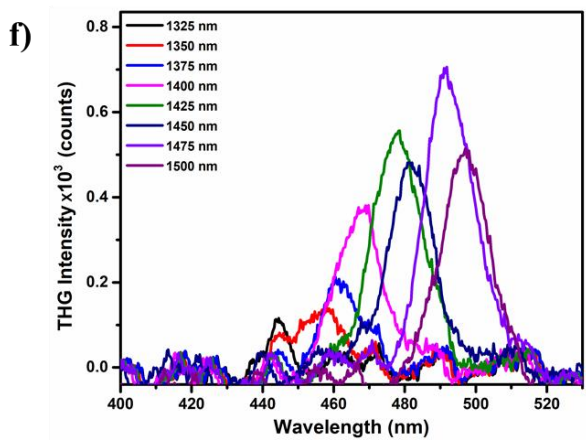
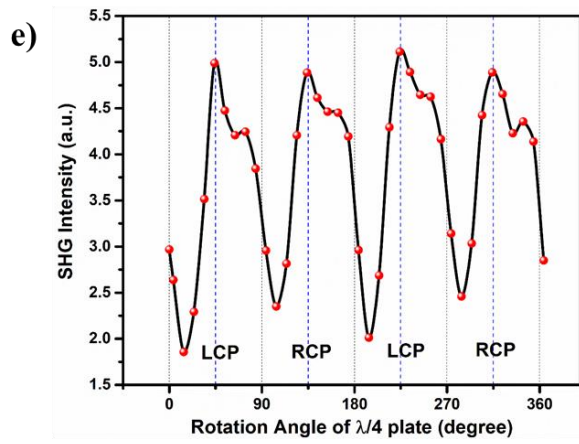
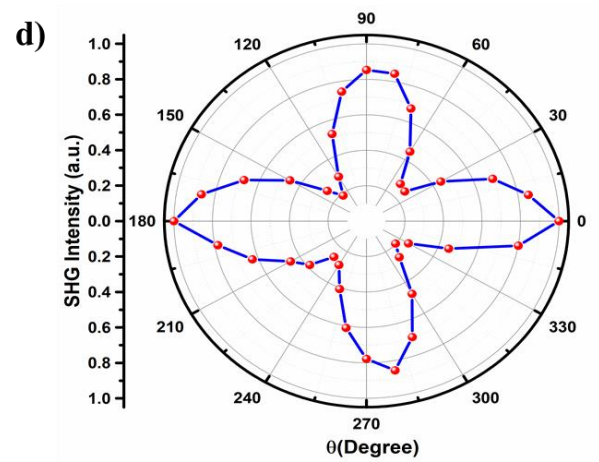
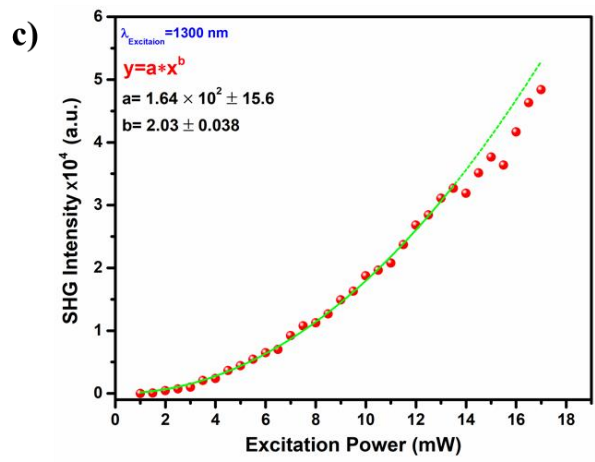
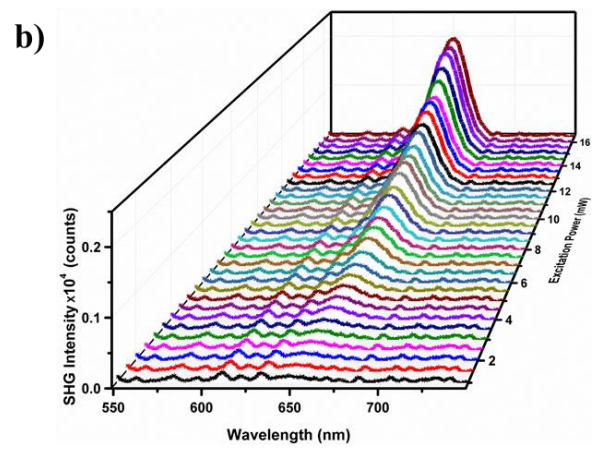
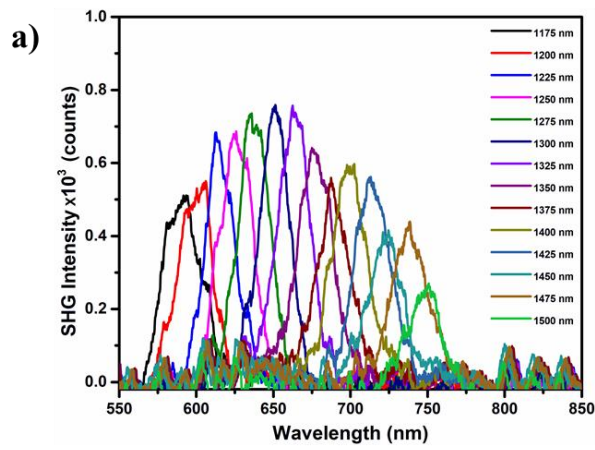
Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P3-AgNTf₂	Molecule 1	Leu CO ← NH Py	2.076	2.886	156
Complex		Hydrogen Bond (intermolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P3-AgNTf₂	Molecule 1	Aib CO(1) ← NH Aib(2)	2.175	2.895	141

5. Nonlinear Optical Properties of Peptide-Metal Complex:

Given the non-centrosymmetric space group adopted by these peptide-silver complexes and their inherent possession of a macro-dipole, we are motivated to investigate their second-order nonlinear optical properties, specifically through second harmonic generation (SHG).^{21, 22} SHG, a nonlinear optical phenomenon, involves the merging of two incident photons of frequency ω within a non-centrosymmetric medium, resulting in a single photon with double the frequency (2ω)²³. The energy upconversion inherent in SHG has diverse applications in imaging, healthcare, semiconductor fabrication, telecommunication, and data storage²⁴. While inorganic crystals have traditionally served as common materials for SHG, recent attention has extended to hybrid metal-halide perovskites, organic dyes²⁵, chromophore-conjugated peptide crystals, and self-assembled peptides in exploring their SHG properties.²⁶ Significantly, the exploration of SHG properties in metallopeptides remains relatively underexplored. In recent investigations, we systematically examined the nonlinear optical properties of a select group of metallohelical complexes, thereby introducing a novel dimension to this research trajectory.²⁷ Consequently, we initiated a study to evaluate the potential of silver ion-coordinated **P3** crystals, characterized by different diverse structures and assemblies compared to our previous study, emerge as promising candidates for manifesting SHG phenomena within the domain of metallopeptide systems. This endeavor aims to contribute novel insights into the utilization of metallopeptides in the context of SHG and broaden the understanding of their nonlinear optical properties.

5.1. Second Harmonic Generation (SHG) of P3-AgNTf₂ Complex:

Nonlinear optical property assessments were conducted on crystals of the **P3-AgNTf₂** complex, wherein **P3** assumed a classical 3₁₀-turn (β -turn) conformation within the crystalline packing. The measurements of nonlinear optical properties were performed utilizing an optical parametric amplifier (OPA) system, specifically the TOPAS-C, propelled by an ultrafast Ti: Sapphire-based regenerative amplifier laser system, yielding output at 800 nm with a pulse duration of 45 fs and a repetition rate of 1 kHz. The sample underwent excitation with pump pulses spanning from 1165 to 1580 nm, and the resulting wavelength-tunable nonlinear optical emissions were collected in transmission mode.^{27, 28} The **P3-AgNTf₂** crystals demonstrated tunable second-order (SHG) and third-order (THG) nonlinear responses across a wide spectral range spanning from 400 to 800 nm. These responses were observed by subjecting the crystals to various infrared pump wavelengths while maintaining a constant power of 20 mW. Notably, the highest SHG intensity manifested at a pump wavelength of 1300 nm, whereas the highest THG intensity was observed at 1475 nm. The corresponding SHG and THG intensity at different input wavelengths of light is shown in Figures 7a and 7f. Furthermore, to assess optical stability, the Laser-Induced Damage Threshold (LIDT) of the **P3-AgNTf₂** complex was calculated. Power-dependent SHG and THG measurements of the **P3-AgNTf₂** complex at 1300 nm and 1475 nm (Figures 7b and 7h) revealed a notably high LIDT value of 102-106 GW/cm², indicative of excellent optical stability (detailed calculation shown below). Also, polarization-dependent SHG and THG measurements were conducted on **P3-AgNTf₂** crystals at a constant power of 20 mW, employing a pump wavelength of 1300 nm and 1475 nm respectively. The four-lobed SHG and THG response obtained by varying the plane of polarization of the incident light is shown in Figures 7d and 7i. The four-lobed SHG response in **P3-AgNTf₂** indicates a relatively more isometric polarization tensor in this complex. From the polarization-dependent response, we measured the polarization ratio (ρ) of the **P3-AgNTf₂** complex, which was determined to be $(68.36 \pm 0.1) \%$, signifying a favorable degree of polarization. The polarization ratio defined as $\rho = (I_{\max} - I_{\min}) / (I_{\max} + I_{\min})$ was calculated using this formula.³⁰ Additionally, we recorded second harmonic generation circular dichroism (SHG-CD), defined as $\text{SHG-CD} = (I_{\text{RCP}} - I_{\text{LCP}}) / (I_{\text{RCP}} + I_{\text{LCP}})$, where I_{RCP} and I_{LCP} refer to the SHG intensity for the right- and left-circularly polarized pump, respectively, serving as a metric for the nonlinear optical chiroptical effect.³¹ The calculated SHG-CD for the **P3-AgNTf₂** complex was determined to be $(45 \pm 0.1) \%$. Collectively, these findings strongly support the assertion that **P3-AgNTf₂** crystals exhibit pronounced SHG and THG activity.



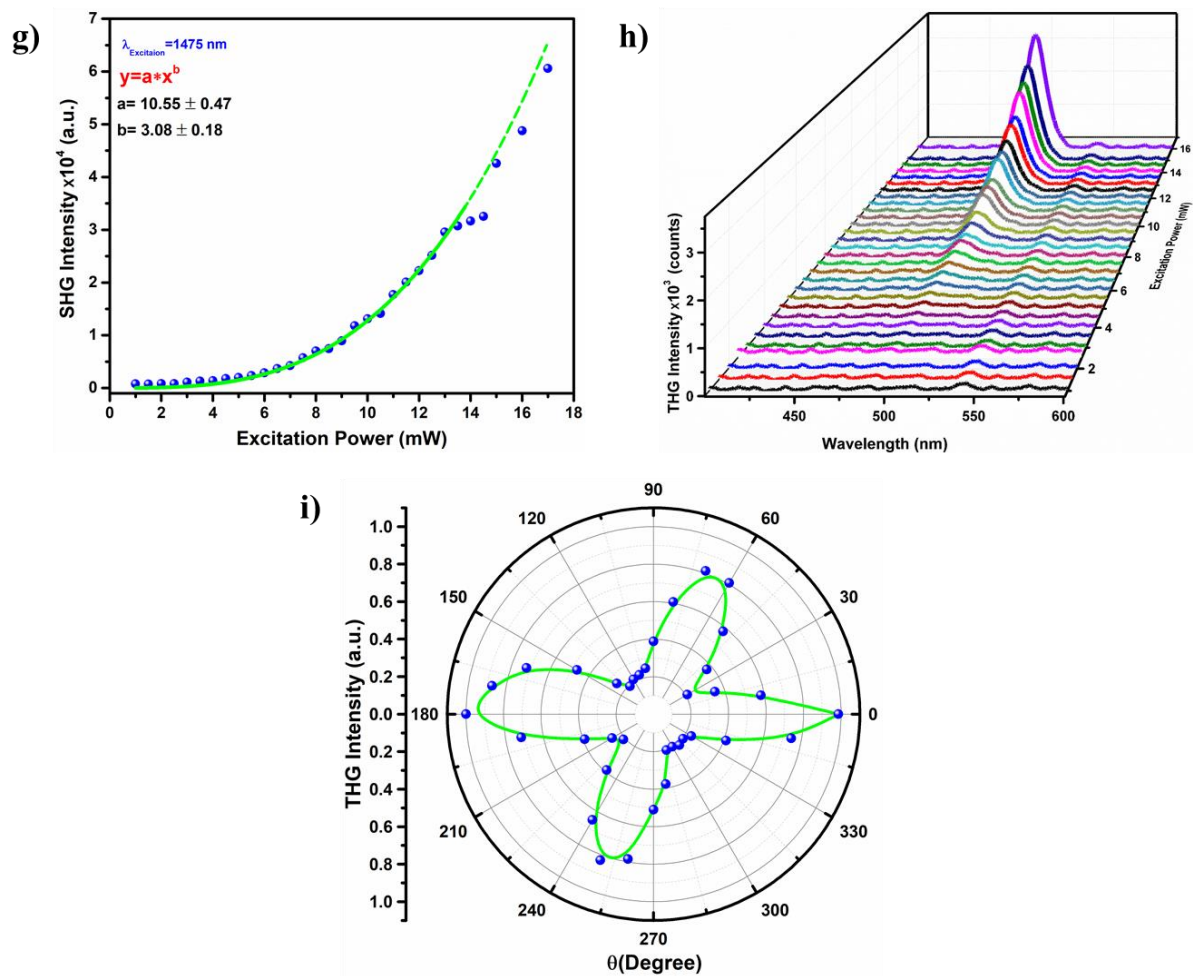


Figure 7: a) The SHG spectra of P3-AgNTf_2 complex with different excitation wavelengths (1175 nm- 1500 nm). b) Excitation power-dependent SHG spectra of P3-AgNTf_2 complex at 1300 nm. c) Quadratic fitting of the power-dependent SHG response at 1300 nm. An increase in SHG output was observed with an increase in excitation power having a quadratic dependence till 13.5 mW for P3-AgNTf_2 complex. Deviation from the respective fits reflects the laser-induced damage threshold. For P3-AgNTf_2 complex, crystal above 13.5 mW was the deviation of SHG output. d) Variation of SHG intensity with the change in direction of polarization of incident light of P3-AgNTf_2 crystal using 1300 nm as excitation wavelength at 20 mW power. e) SHG intensity from the P3-AgNTf_2 as a function of the rotation angle of the $\lambda/4$ plate. The pump was left-handed circularly polarized when the rotation angle was 45° and 225° , and was right-handed circularly polarized when the rotation angle was 135° and 315° . f) The THG spectra of P3-AgNTf_2 complex with different excitation wavelengths (1325 nm- 1500 nm). g) Quadratic fitting of the power-dependent THG response at 1475 nm. An increase in THG output was observed with an increase in excitation power having a quadratic dependence till 13 mW for P3-AgNTf_2 complex. Deviation from the respective fits reflects the

laser-induced damage threshold. For **P3**-AgNTf₂ complex, crystal above 13 mW was the deviation of THG output. h) Excitation power-dependent THG spectra of **P3**-AgNTf₂ complex at 1475 nm. i) Variation of THG intensity with the change in direction of polarization of incident light of **P3**-AgNTf₂ crystal using 1475 nm as excitation wavelength at 20 mW power.

5.1.1. Laser-Induced Damage Threshold (LIDT) Calculation of **P3**-AgNTf₂ Complex:

The Laser-Induced Damage Threshold (LIDT) value is established by identifying the pump intensity at which the second harmonic generation (SHG) and third harmonic generation (THG) response diverges from quadratic behavior.³² The LIDT is consequently determined by the peak laser intensity corresponding to that specific pump intensity for the sample.

LIDT of Peptide-Metal complex = Peak intensity at which SHG response deviates from quadratic behavior called average power.

$$\text{Peak Intensity} = \frac{\text{Energy per pulse}}{(\text{Pulse width}) \times (\text{Effective spot area})}$$

$$\text{Energy per pulse} = \frac{\text{Average Power}}{\text{Repetition Rate}}$$

$$\text{LIDT} = \text{Peak Intensity} = \frac{\text{Average power}}{(\text{Repetition rate}) \times (\text{Pulse width}) \times (\text{Effective spot area})}$$

For our setup, $\text{Repetition rate} = 1000 \text{ Hz}$, $\text{Pulse width} = 50 \times 10^{-15} \text{ s}$, $\text{Beam radius} = 460 \times 10^{-6} \text{ m}$.

For **P3**-AgNTf₂ complex, SHG response deviates from quadratic behavior after 13.5 mW. $\text{Average power} = 13.5 \times 10^{-3} \text{ W}$ for **P3**-AgNTf₂ complex.

$$\begin{aligned} \text{LIDT}(\text{P3} - \text{AgNTf}_2) &= \frac{13.5 \times 10^{-3} \text{ W}}{(1000 \text{ Hz}) \times (50 \times 10^{-15} \text{ s}) \times (\pi \times (460 \times 10^{-6} \text{ m})^2)} \\ &= 106.2 \times 10^{13} \text{ W/m}^2 \\ &= 106.2 \text{ GW/cm}^2 \end{aligned}$$

For **P3**-AgNTf₂ complex, THG response deviates from quadratic behavior after 13 mW. $\text{Average power} = 13 \times 10^{-3} \text{ W}$ for **P3**-AgNTf₂ complex.

$$\text{LIDT}(\text{P3} - \text{AgNTf}_2) = \frac{13 \times 10^{-3} \text{ W}}{(1000 \text{ Hz}) \times (50 \times 10^{-15} \text{ s}) \times (\pi \times (460 \times 10^{-6} \text{ m})^2)}$$

$$= 102.3 \times 10^{13} \text{ W/m}^2$$

$$= 102.3 \text{ GW/cm}^2$$

5.2. Details of the Second Harmonic Generation Experiments:

The second harmonic generation (SHG) experiments were performed using home-built setup.³³ We used near-infrared (NIR) to short-wave infrared (SWIR) output from an optical parametric amplifier (OPA, Light Conversion) as the excitation light for SHG experiments. The OPA was pumped by the output (800 nm, 35 fs, 1 kHz) from an ultrafast regenerative amplifier (Spitfire X-Pro, Spectra-Physics). The pump wavelengths from 1175 nm to 1550 nm with temporal width of ~45 femtosecond were used in the experiments. An 850 nm long-pass filter in the beam path made sure that only the desired NIR pump wavelengths reach the sample. A neutral density (ND) filter was used to vary the pump intensity. The pump beam was focused by a 200 mm plano-convex lens onto the sample. The sample was kept 135 mm away from the lens to avoid any damage to the sample and to get large enough spot size for interaction. Sample crystals were sandwiched between two quartz microscopic slides and mounted on a cage rotation mount (Thorlabs CRM1/M). The output SHG signal, collimated by a 25 mm lens, was passed through a 750 nm short-pass filter that rejected any remaining pump wavelength, and was coupled to a 400 μm optical fibre connected to a miniature spectrometer (USB4000, Ocean Optics). A Glan polarizer and a half-wave plate assembly were used to change the polarization of the pump beam for polarization-dependent SHG measurements.

The beam diameter at the sample position was measured by the popular Knife-edge technique. The power measured (P) passing the edge of the knife was fitted to the following equation,

$$P = P_0 + \frac{P_{max}}{2} \left(1 - \operatorname{erf} \left(\frac{\sqrt{2}(x-x_0)}{w} \right) \right) \quad \dots\dots\dots (1)$$

where P_0 is the background power, P_{max} is the maximum power, x is the stage position, erf is the standard error function, and w is the beam radius where intensity dropped to $1/e^2$ times maximum value. The beam radius measured for the given setup was $460 \times 10^{-6} \text{ m}$.

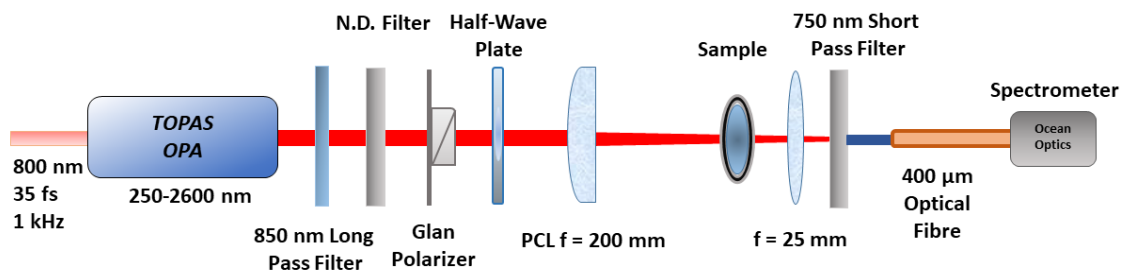


Figure 8: Schematic of the SHG setup.

6. Conclusion:

In conclusion, our investigation underscores the structural adaptability inherent in short peptides, featuring terminal 3-, 4-pyridyl, and Bipyridyl moieties, and highlights their utility in constructing diverse metal-coordinated networks. Specifically focusing on $\alpha\gamma$ -hybrid tripeptides, incorporating saturated γ -amino acids, we observe a consistent C_{12} helical structure in single crystals, evident both before and after metal coordination. Intriguingly, a subtle sequence alteration, involving the substitution of γ -amino acids with their α -counterparts, instigates a notable conformational shift from a helix to a beta-turn configuration upon metal coordination. This investigation focused on the **P3**-AgNTf₂ complex, unveils the creation of crystals characterized by an impressive superhelical arrangement, showcasing significant nonlinear optical phenomena. This study imparts meticulous insights into the structural plasticity exhibited by short peptides, thereby advancing our understanding of their dynamic behavior across diverse environmental conditions.

7. Experimental Section:

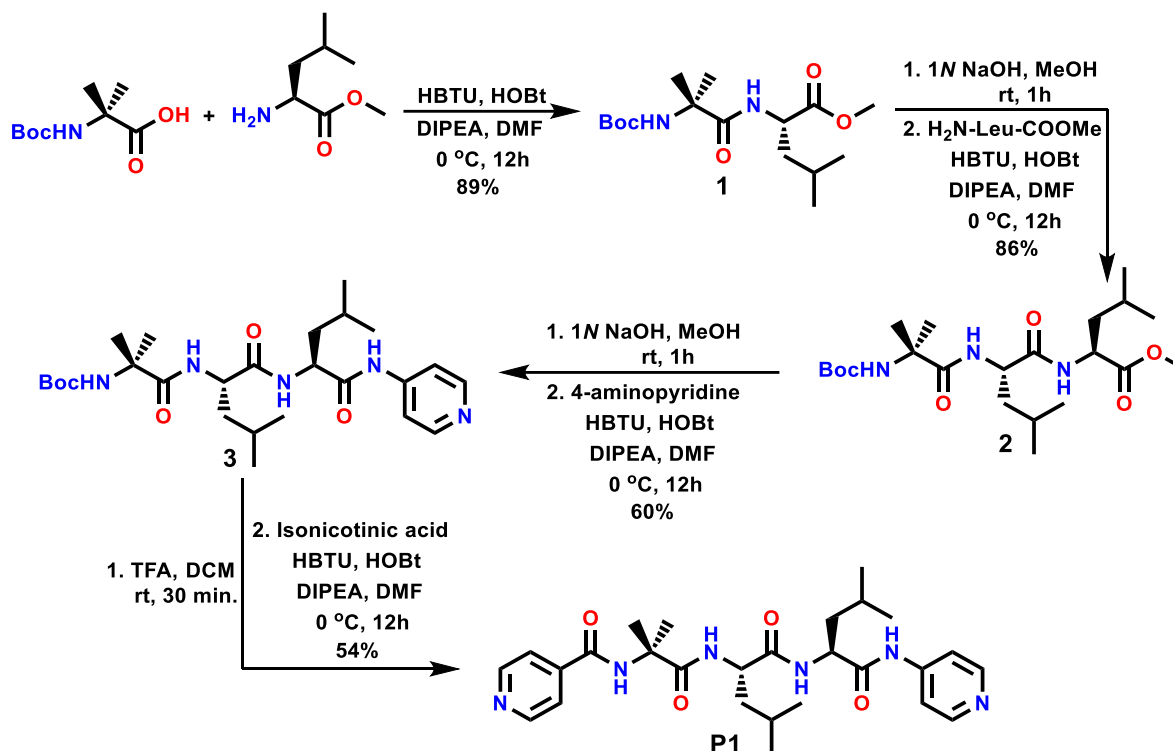
7.1. Materials and Methods:

All the coupling reactions were performed under N₂ conditions. All the amino acids, Boc anhydride, HBTU, HOBt, AgBF₄, AgNO₃, AgOTf, AgNTf₂, 3-aminopyridine, 4-aminopyridine, nicotinic acid, isonicotinic acid, Trifluoroacetic acid (TFA), N, N-Diisopropylethylamine (DIPEA), DMF, DCM, EtOAc, Hexane, THF, were purchased from different commercial sources. Ethyl acetate, DCM, Methanol, and Hexane were distilled before use. Column chromatography was performed on silica gel (100-200 mesh). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and ninhydrin or Iodine staining. ¹H NMR and ¹³C NMR spectra were recorded in deuterated solvents on 400 MHz and 600 MHz NMR machines respectively using the residual solvent signal as the internal standard. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad doublet (bd), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using MALDI-TOF Instrument. CD spectra were recorded on a CD spectrometer. The X-ray data were collected at low

temperatures (150 K) on a Bruker APEX (II) DUO CCD diffractometer using Mo K α (λ = 0.71073 Å) and Cu K α radiation (λ = 1.54178 Å) graphite monochromated radiation.

7.2. General Procedure for the Synthesis of Peptides:

7.2.1. Synthesis of Peptide P1:



Scheme 4: Synthesis of short α - tripeptide **P1**.

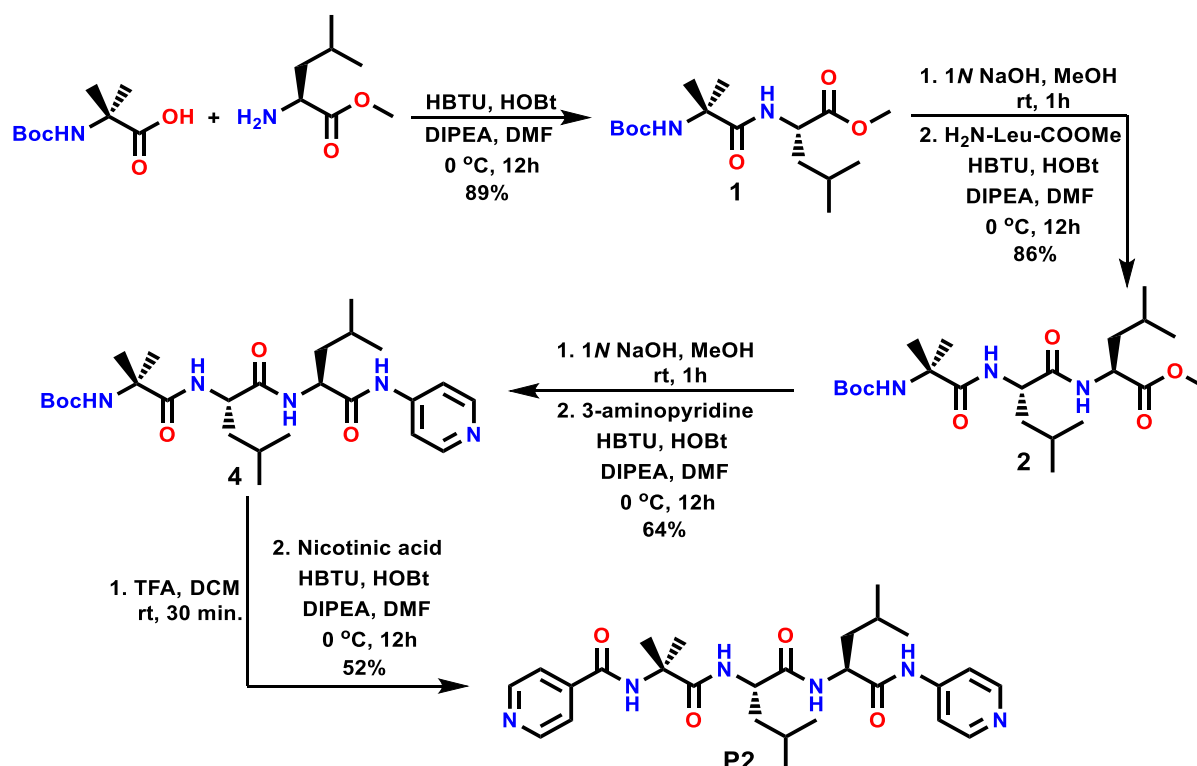
N-Boc protected 2-Aminoisobutyric acid (10 mmol, 2.032 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (11 mmol, 4.18 g), HOBt (11 mmol, 1.49 g), and DIPEA (25 mmol, 4.38 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected Leucine (H₂N-Leu-COOMe) (15 mmol, 2.17 g) in a small amount of DMF and the remaining DIPEA (25 mmol, 4.38). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (20% EtOAc/ Hexane) to get a white product Compound **1** having an overall yield of 89%.

The purified product of compound **1** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of the reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product used for further reaction. Now Dipeptide acid (8 mmol, 2.52 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (8.8 mmol, 3.34 g), HOBt (8.8 mmol, 1.19 g), and DIPEA (20 mmol, 3.5 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected Leu (H₂N-Leu-COOMe) (12 mmol, 1.74 g) in a small amount of DMF and the remaining DIPEA (20 mmol, 3.5 mL). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude-product which was then purified by column chromatography (40% EtOAc/ Hexane) to get a white product Compound **2** having an overall yield of 86%.

The purified product of compound **2** was dissolved in MeOH in 250 mL RB, 1N NaOH was added into it and the reaction was left for 1h. After completion of reaction, MeOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product which was used for further reaction. Now Tripeptide acid (2.8 mmol, 1.2 g) was dissolved in 3 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (3.07 mmol, 1.17 g), HOBt (3.07 mmol, 417 mg) and DIPEA (8.37 mmol, 1.46 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of 4-aminopyridine (4.19 mmol, 395 mg). The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (4% MeOH/ DCM) to get a white product Compound **3** had an overall yield was 60%.

Compound **3** (0.99 mmol, 500 mg) was subjected to Boc deprotection using 50% TFA in DCM (2 mL TFA in 2 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (3 mmol, 0.6 mL) to get the free amine of compound **3**. Now Isonicotinic acid (1.18 mmol, 147 mg) was dissolved in 2 mL of DMF and the solution was then cooled to 0 °C using an ice bath under N₂ atmosphere. To this, HBTU (1.09 mmol, 414 mg), HOBT (1.09 mmol, 149 mg), and DIPEA (3 mmol, 0.6 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **3** and the reaction mixture was further stirred for overnight at room temperature. The reaction mixture was stirred for overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3) and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (6% MeOH/ DCM) to get a white product Peptide **P1** having overall yield was 54%.

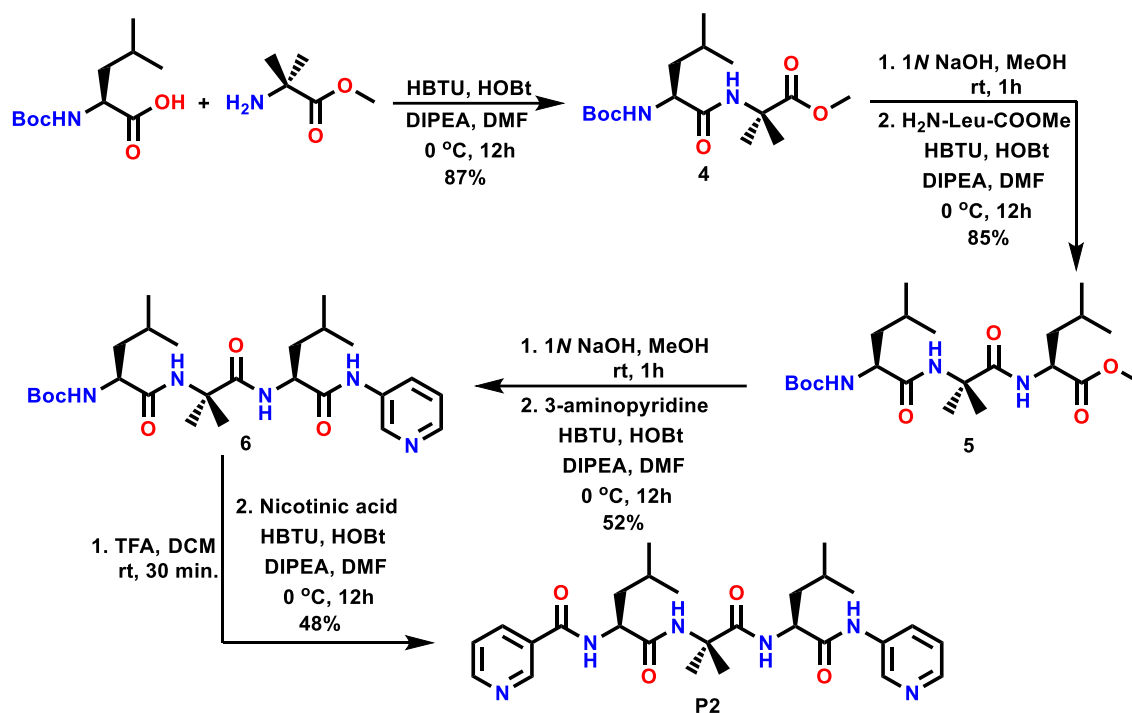
7.2.2. Synthesis of Peptide P2:



Scheme 5: Synthesis of short α - tripeptide **P2**.

The Synthesis of peptide **P2** was carried out as described in the above scheme, following similar protocols as of **P1** (overall yield was 52%).

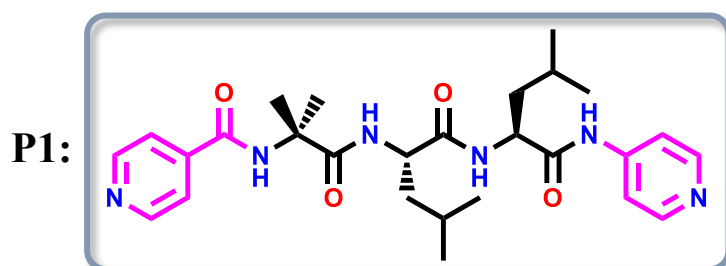
7.2.3. Synthesis of Peptide P3:



Scheme 6: Synthesis of short α - tripeptide **P3**.

The Synthesis of peptide **P3** was carried out as described in the above scheme, following similar protocols as of **P1** (overall yield was 48%).

7.3. Characterisation of Peptides (P1-P3):

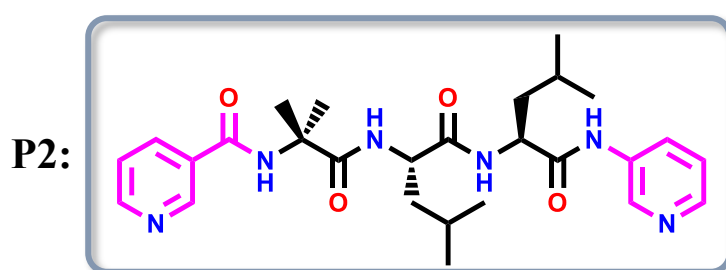


^1H NMR (400 MHz, Methanol- d_3) δ 9.09 (dd, $J = 2.3, 0.9$ Hz, 1H), 9.01 (dd, $J = 2.3, 0.9$ Hz, 1H), 8.66 (ddd, $J = 10.7, 5.0, 1.7$ Hz, 1H), 8.37 – 8.32 (m, 3H), 8.25 (ddd, $J = 7.4, 3.8, 1.8$ Hz, 1H), 8.20 (dd, $J = 7.9, 2.4$ Hz, 1H), 7.89 (s, 1H), 7.85 – 7.82 (m, 1H), 7.75 – 7.73 (m, 1H), 7.51 (dddd, $J = 17.0, 7.9, 5.0, 0.9$ Hz, 1H), 4.50 (dddd, $J = 17.4, 11.7, 7.8, 4.0$ Hz, 1H), 4.28 (ddd,

$J = 10.3, 7.4, 5.0$ Hz, 1H), 1.97 (dddd, $J = 20.4, 13.6, 11.2, 4.4$ Hz, 1H), 1.83 – 1.66 (m, 5H), 1.61 – 1.56 (m, 6H), 0.97 – 0.90 (m, 12H).

^{13}C NMR (151 MHz, Methanol- d_3) δ 178.48, 177.35, 175.44, 175.04, 174.03, 168.04, 152.55, 150.54, 149.66, 147.87, 137.41, 131.66, 124.79, 115.30, 58.60, 54.29, 53.69, 41.15, 39.84, 26.09, 26.04, 25.84, 24.87, 23.54, 21.28.

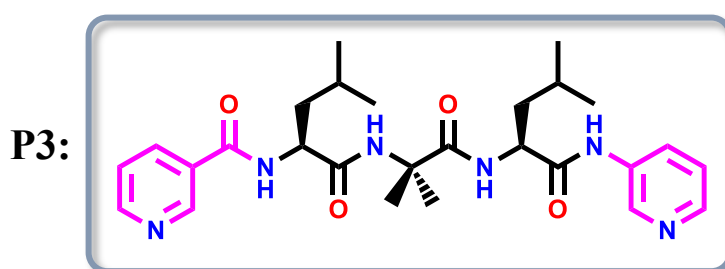
MALDI TOF/TOF m/z calculated for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ is 511.30 and observed value is 511.50. $[\text{M}+\text{Na}]^+$ is 533.28 and observed value is 533.49. $[\text{M}+\text{K}]^+$ is 549.25 and observed value is 549.45.



^1H NMR (600 MHz, Chloroform- d) δ 9.18 (s, 1H), 8.93 (d, $J = 2.5$ Hz, 1H), 8.88 – 8.79 (m, 1H), 8.70 (dd, $J = 8.1, 2.5$ Hz, 1H), 8.60 (ddd, $J = 26.7, 4.9, 1.6$ Hz, 1H), 8.18 (dd, $J = 14.9, 4.5$ Hz, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.94 – 7.75 (m, 1H), 7.63 (d, $J = 8.6$ Hz, 1H), 7.37 (s, 1H), 7.22 – 7.18 (m, 1H), 7.12 (ddt, $J = 17.6, 8.1, 3.6$ Hz, 1H), 4.70 – 4.53 (m, 1H), 4.28 (tq, $J = 10.9, 6.7, 5.7$ Hz, 1H), 1.97 – 1.80 (m, 5H), 1.69 – 1.62 (m, 6H), 1.59 – 1.51 (m, 1H), 0.97 (ddd, $J = 24.7, 19.3, 6.5$ Hz, 12H).

^{13}C NMR (151 MHz, Chloroform- d) δ 176.05, 174.95, 172.49, 171.84, 166.16, 152.63, 147.99, 144.24, 141.13, 135.47, 128.78, 128.20, 127.04, 123.55, 57.69, 54.63, 53.15, 50.87, 39.78, 38.45, 29.71, 25.46, 25.21, 24.94, 23.16, 21.39, 20.96.

MALDI TOF/TOF m/z calculated for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_4$ $[\text{M}+\text{H}]^+$ is 511.30 and observed value is 511.52. $[\text{M}+\text{Na}]^+$ is 533.28 and observed value is 533.54. $[\text{M}+\text{K}]^+$ is 549.25 and observed value is 549.47.



¹H NMR (400 MHz, DMSO-*d*₆) δ 9.77 (s, 1H), 9.24 (s, 1H), 9.11 – 9.06 (m, 1H), 9.01 (s, 1H), 8.88 – 8.81 (m, 1H), 8.75 – 8.68 (m, 1H), 8.52 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.24 (dq, *J* = 4.2, 2.2 Hz, 1H), 8.14 – 8.08 (m, 1H), 8.01 – 7.91 (m, 1H), 7.73 – 7.57 (m, 1H), 7.19 (ddd, *J* = 57.9, 8.2, 4.8 Hz, 1H), 4.48 – 4.37 (m, 1H), 4.35 – 4.21 (m, 1H), 1.85 – 1.68 (m, 4H), 1.64 – 1.51 (m, 2H), 1.45 (s, 2H), 1.42 – 1.35 (m, 4H), 0.99 – 0.73 (m, 12H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 175.35, 174.64, 171.85, 167.15, 152.47, 148.84, 144.62, 141.10, 135.77, 135.42, 135.24, 129.65, 128.74, 126.22, 123.41, 56.89, 54.01, 52.43, 40.50, 40.29, 40.09, 39.88, 39.67, 39.46, 39.25, 27.30, 25.78, 25.17, 25.06, 24.77, 23.64, 23.51, 23.19, 22.29, 21.13.

MALDI TOF/TOF *m/z* calculated for C₂₇H₃₈N₆O₄ [M+Na]⁺ is 533.30 and observed value is 533.48. [M+K]⁺ is 549.30 and observed value is 549.44.

7.4. Crystal Structure Information:

7.4.1. Crystal Structure Analysis of P1-AgBF₄ Complex:

Crystals were grown by layering 25 mM of 500 μ L solution of **P1** in methanol and 25 mM of 500 μ L of an aqueous solution of AgBF₄ in a capped microtube, formation of plate-shaped crystals was observed at the interface of methanol and water layer after 15 days. A single crystal (0.20 $\times$ 0.16 $\times$ 0.1) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation (λ =0.71073 $\text{\AA}$), ω -scans (2θ = 50.25), for a total of 115928 independent reflections. Space group P 2₁/n, *a* = 8.8182(13), *b* = 19.144(3), *c* = 19.103(3), α = 90, β = 99.047(4), γ = 90, *V* = 3184.8(8) $\text{\AA}^3$, Monoclinic, *Z* = 2 for chemical formula C₅₄ H₇₄ Ag₂ B₂ F₈ N₁₂ O₁₂, with two molecules in asymmetric unit; ρ calcd = 1.538 gcm⁻³, μ = 0.706 mm⁻¹, *F* (000) = 1512, The structure was obtained by direct methods using SHELXS-97.³⁴ The final *R* value was 0.031 (*wR*2 = 0.0784) 5689 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 412 variables, *S* = 1.052.

7.4.2. Crystal Structure Analysis of P1-AgOTf Complex:

Crystals were grown by layering 25 mM of 500 μ L solution of **P1** in methanol and 25 mM of 500 μ L of an aqueous solution of AgOTf in a capped microtube, formation of plate-shaped

crystals was observed at the interface of methanol and water layer after 60 days. A single crystal ($0.17 \times 0.14 \times 0.05$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 50.928$), for a total of 36269 independent reflections. Space group P-1, $a = 11.137(3)$, $b = 13.175(3)$, $c = 26.143(6)$, $\alpha = 84.157(7)$, $\beta = 84.046(7)$, $\gamma = 89.862(7)$, $V = 3795.3(16) \text{\AA}^3$, Triclinic, $Z = 2$ for chemical formula $\text{C}_{56} \text{H}_{76} \text{Ag}_2 \text{F}_6 \text{N}_{12} \text{O}_{20} \text{S}_2$, with four molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.427 \text{ g cm}^{-3}$, $\mu = 0.657 \text{ mm}^{-1}$, $F(000) = 1672$, The structure was obtained by direct methods using SHELXS-97.³⁴ The final R value was 0.0828 ($wR2 = 0.2601$) 13830 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 895 variables, $S = 1.04$.

7.4.3. Crystal Structure Analysis of P2-AgOTf Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P2** in methanol and 25 mM of 500 μL of an aqueous solution of AgOTf in a capped microtube, formation of plate-shaped crystals was observed at the interface of methanol and water layer after 60 days. A single crystal ($0.18 \times 0.16 \times 0.08$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 49.998$), for a total of 51434 independent reflections. Space group $P 2_1$, $a = 8.628(4)$, $b = 18.351(9)$, $c = 21.309(8)$, $\alpha = 90$, $\beta = 96.552(11)$, $\gamma = 90$, $V = 3352(3) \text{\AA}^3$, Monoclinic, $Z = 2$ for chemical formula $\text{C}_{56} \text{H}_{76} \text{Ag}_2 \text{F}_6 \text{N}_{12} \text{O}_{14} \text{S}_2$, with two molecules in asymmetric unit; $\rho_{\text{calcd}} = 1.521 \text{ g cm}^{-3}$, $\mu = 0.732 \text{ mm}^{-1}$, $F(000) = 1576$, The structure was obtained by direct methods using SHELXS-97.³⁴ The final R value was 0.1285 ($wR2 = 0.2946$) 11654 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 789 variables, $S = 1.059$.

7.4.4. Crystal Structure Analysis of P3-AgNTf₂ Complex:

Crystals were grown by layering 25 mM of 500 μL solution of **P3** in ethanol and 25 mM of 500 μL of an aqueous solution of AgNTf₂ in a capped microtube, formation of needle-shaped crystals was observed at the interface of ethanol and water layer after 20 days. A single crystal ($0.18 \times 0.16 \times 0.06$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda=0.71073\text{\AA}$), ω -scans ($2\theta = 130.73$), for a total of 116590 independent reflections. Space group $P 2_12_12_1$, $a = 10.8626(8)$, $b = 11.9138(8)$, $c = 31.722(2)$, $\alpha, \beta, \gamma = 90$, $V = 4105.3(5) \text{\AA}^3$, Orthorhombic, $Z = 4$ for chemical formula $\text{C}_{31} \text{H}_{44} \text{Ag} \text{F}_6 \text{N}_7 \text{O}_9 \text{S}_2$, with one

molecules in asymmetric unit; ρ calcd = 1.528 gcm⁻³, μ = 5.641 mm⁻¹, F (000) = 1936, the structure was obtained by direct methods using SHELXS-97.³⁴ The final R value was 0.0477 (wR2 = 0.1272) 6992 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 515 variables, S = 0.948.

7.5. ORTEP Diagrams:

7.5.1. ORTEP Diagram of P1-AgBF₄:

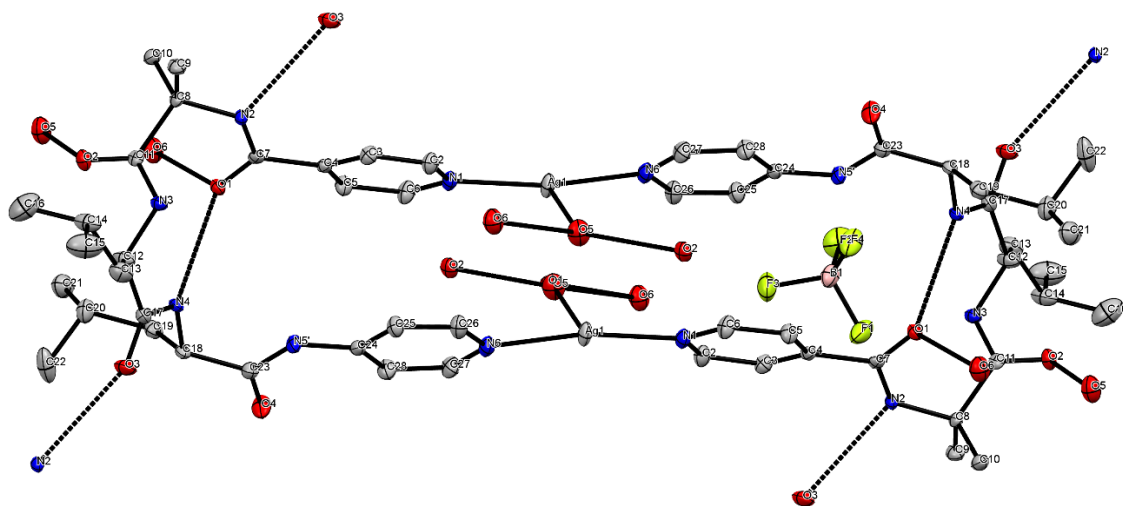
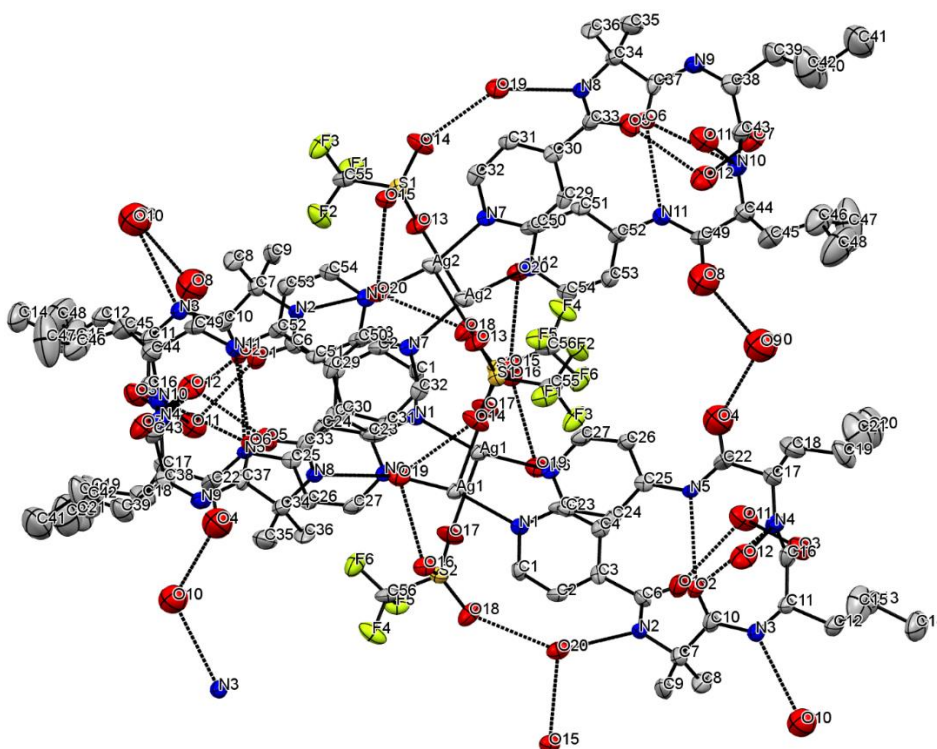
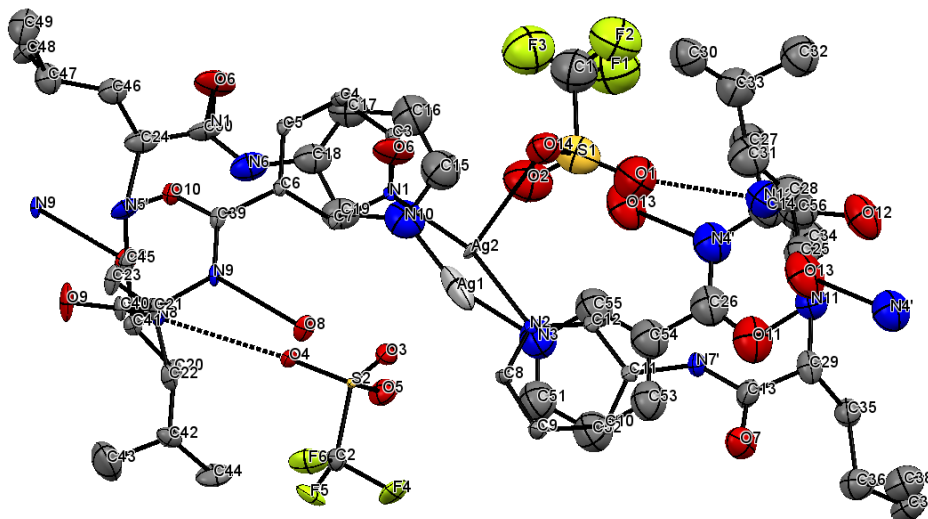


Figure 9: ORTEP diagram of P1-AgBF₄. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

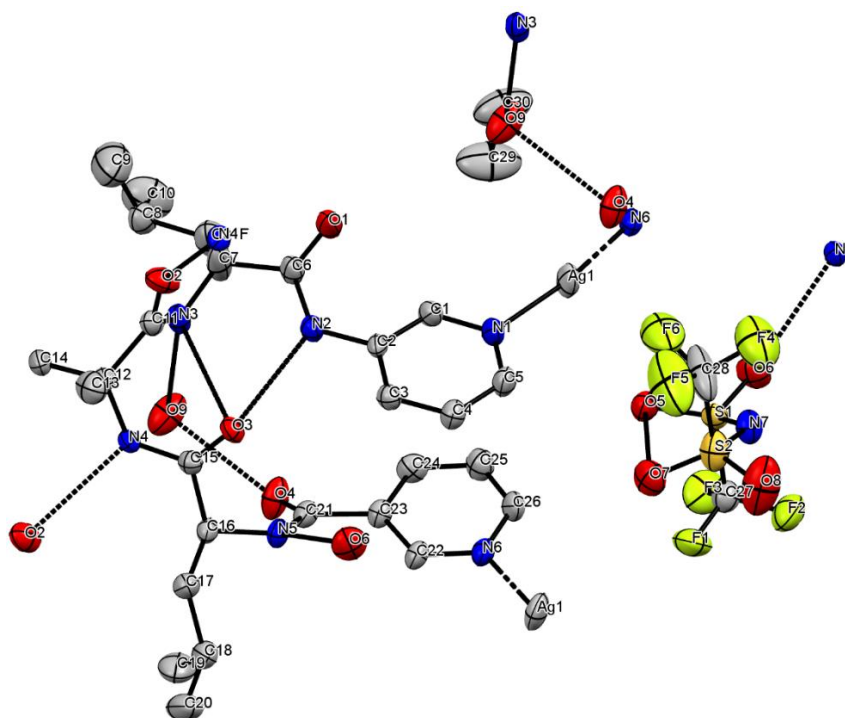
7.5.2. ORTEP Diagram of P1-AgOTf:



7.5.3. ORTEP Diagram of P2-AgOTf:



7.5.4. ORTEP Diagram of P3-AgNTf₂:



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8. References:

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9. ^1H , ^{13}C NMR, and Mass Spectra of Peptides:

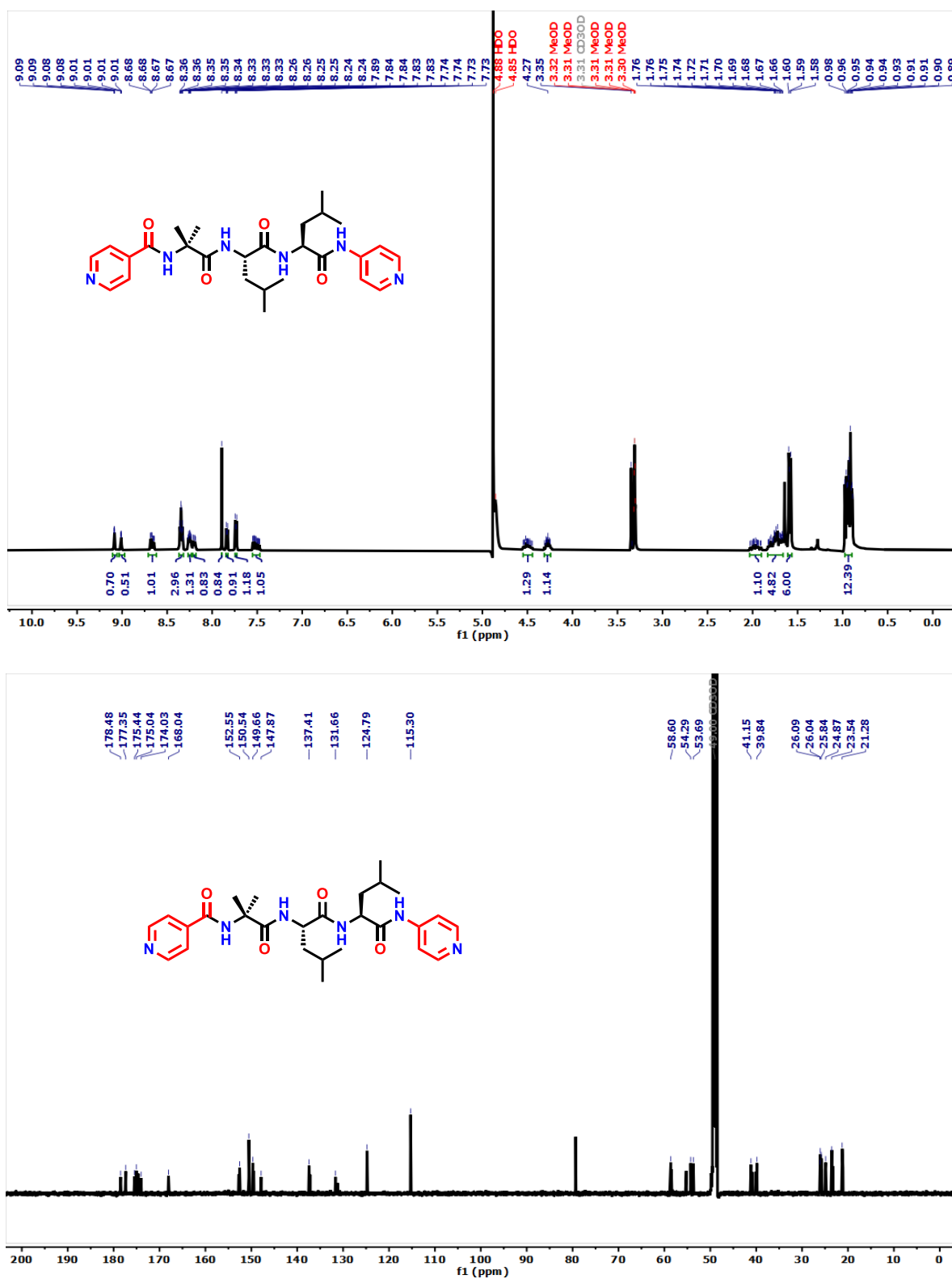


Figure 13: ^1H & ^{13}C NMR spectrum of **P1** in Methanol- d_3 .

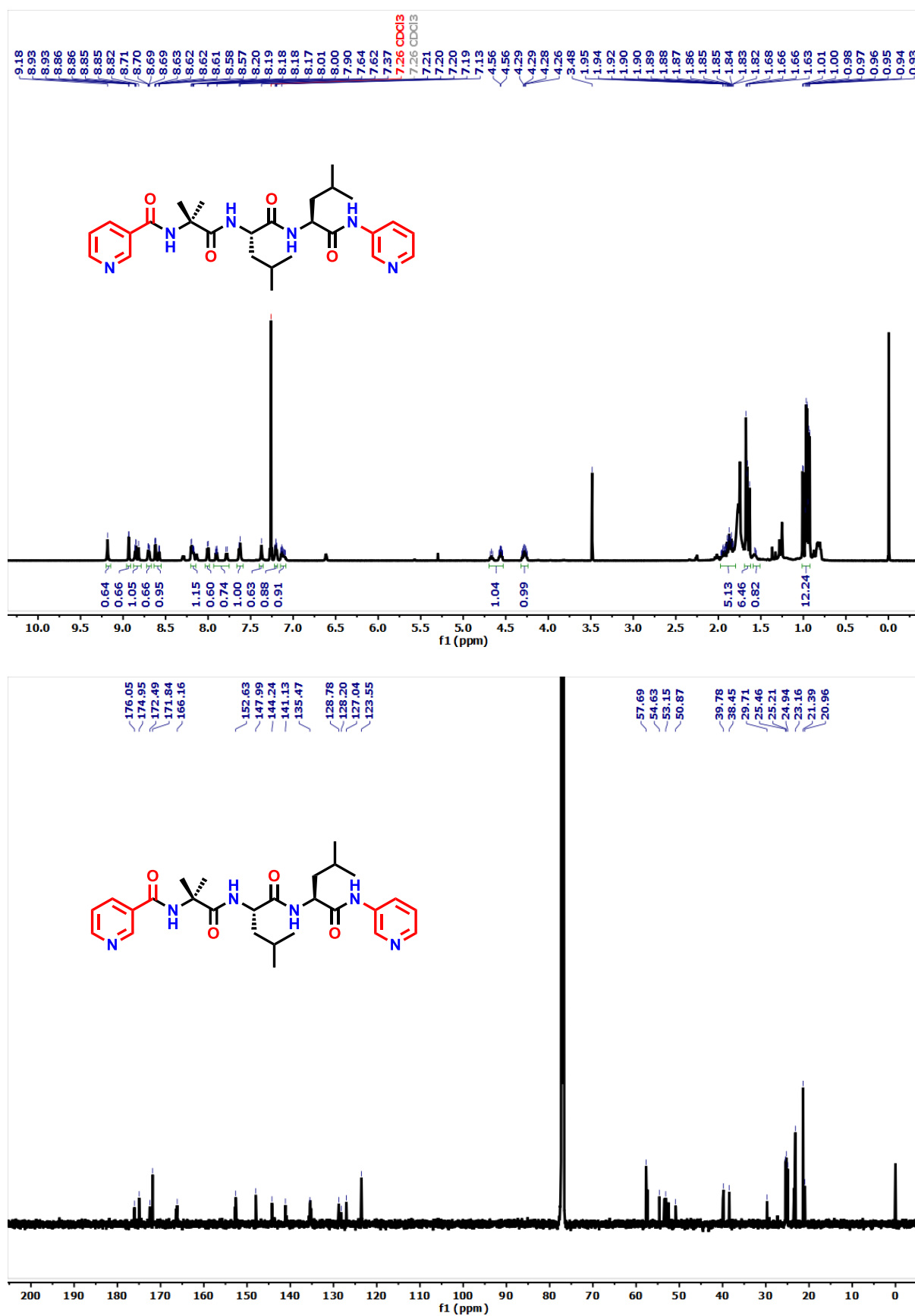


Figure 14: ¹H & ¹³C NMR spectrum of **P2** in CDCl₃.

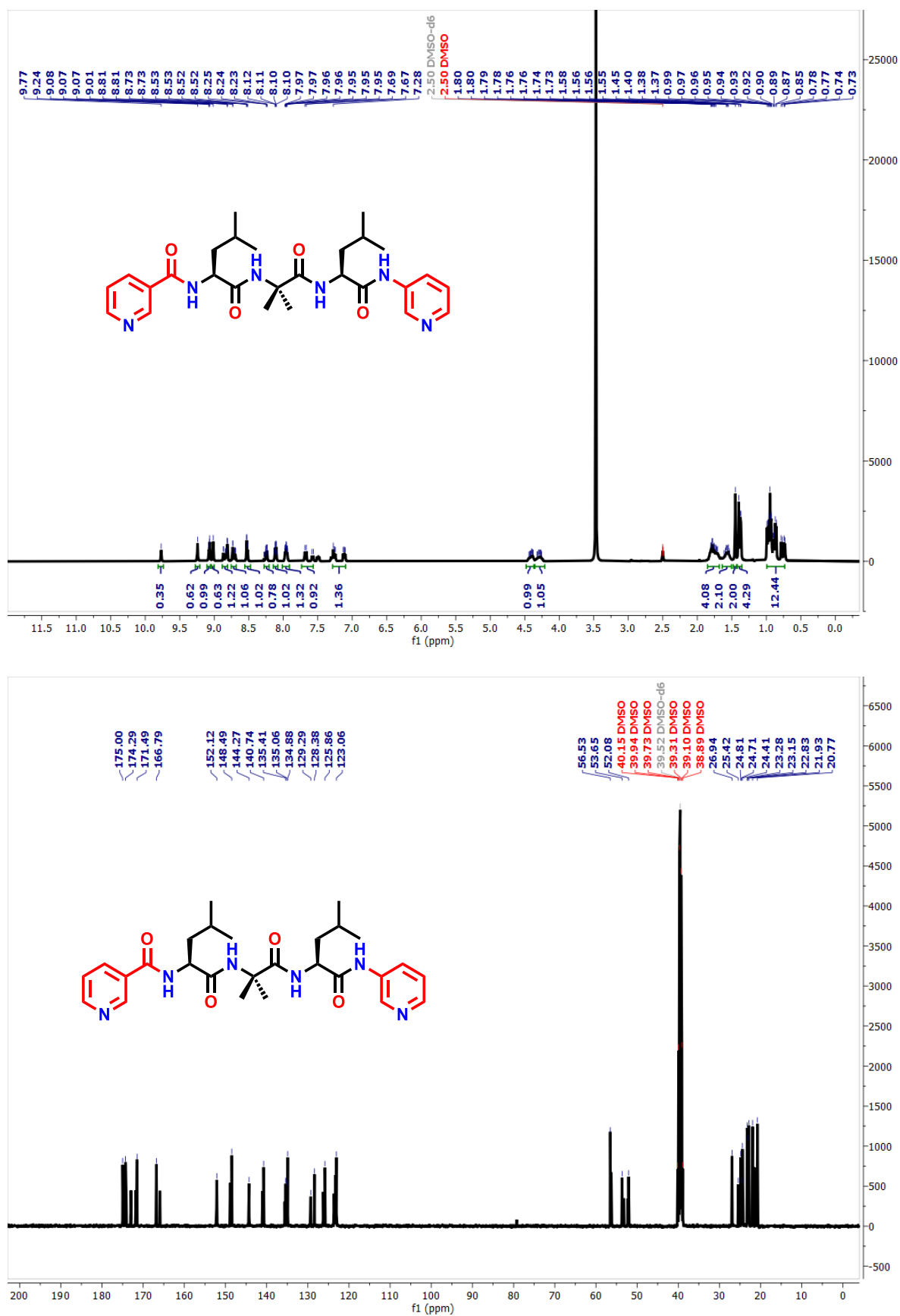


Figure 15: ^1H & ^{13}C NMR spectrum of **P3** in $\text{DMSO-}d_6$.

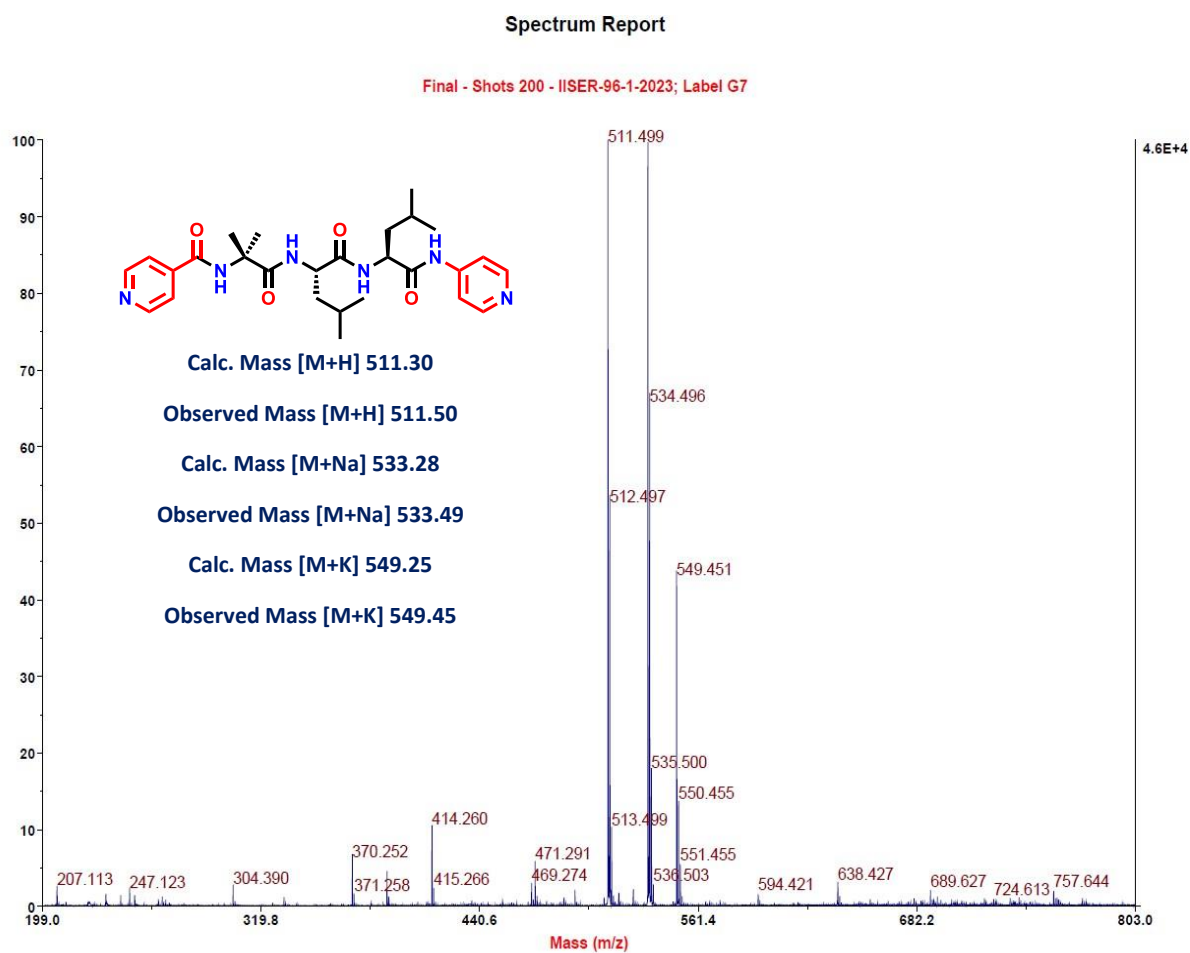


Figure 16: MALDI-TOF/TOF mass spectrum of **P1**.

Spectrum Report

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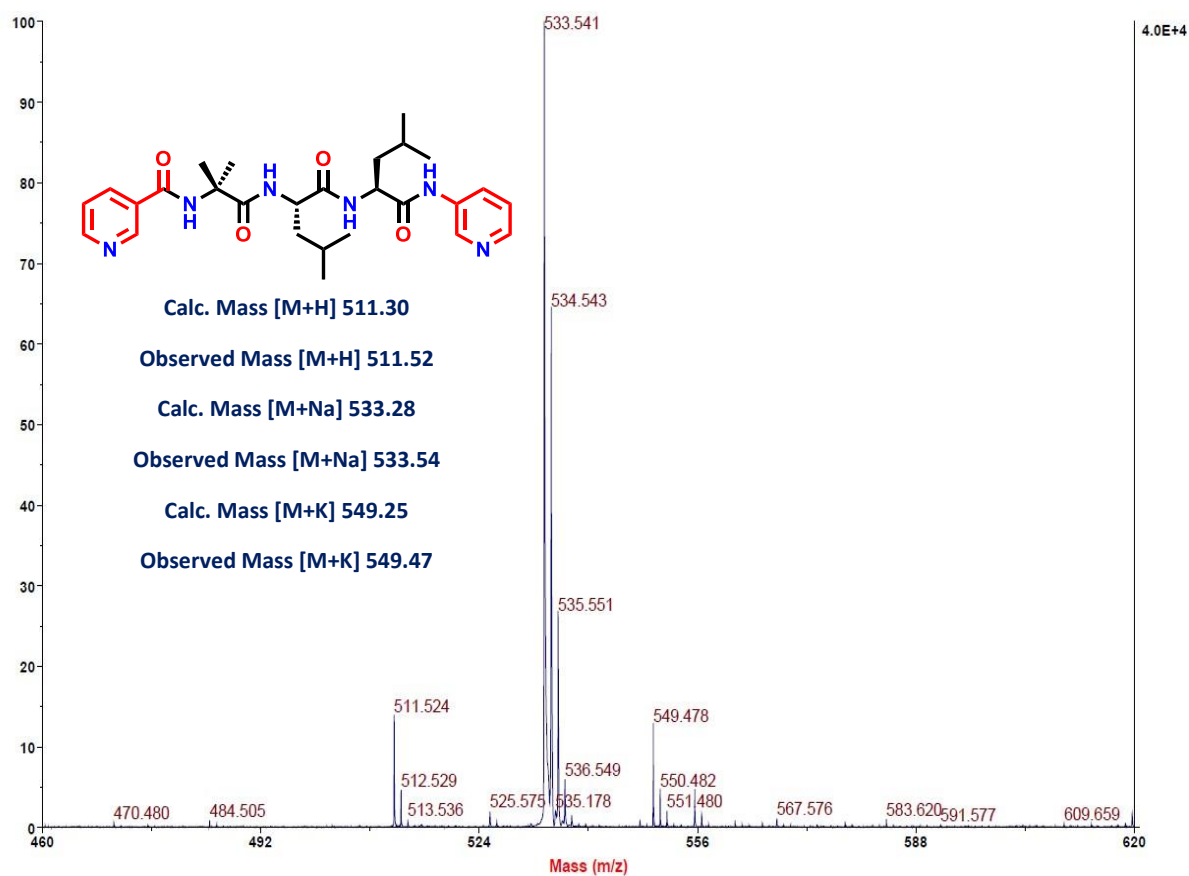


Figure 17: MALDI-TOF/TOF mass spectrum of P2.

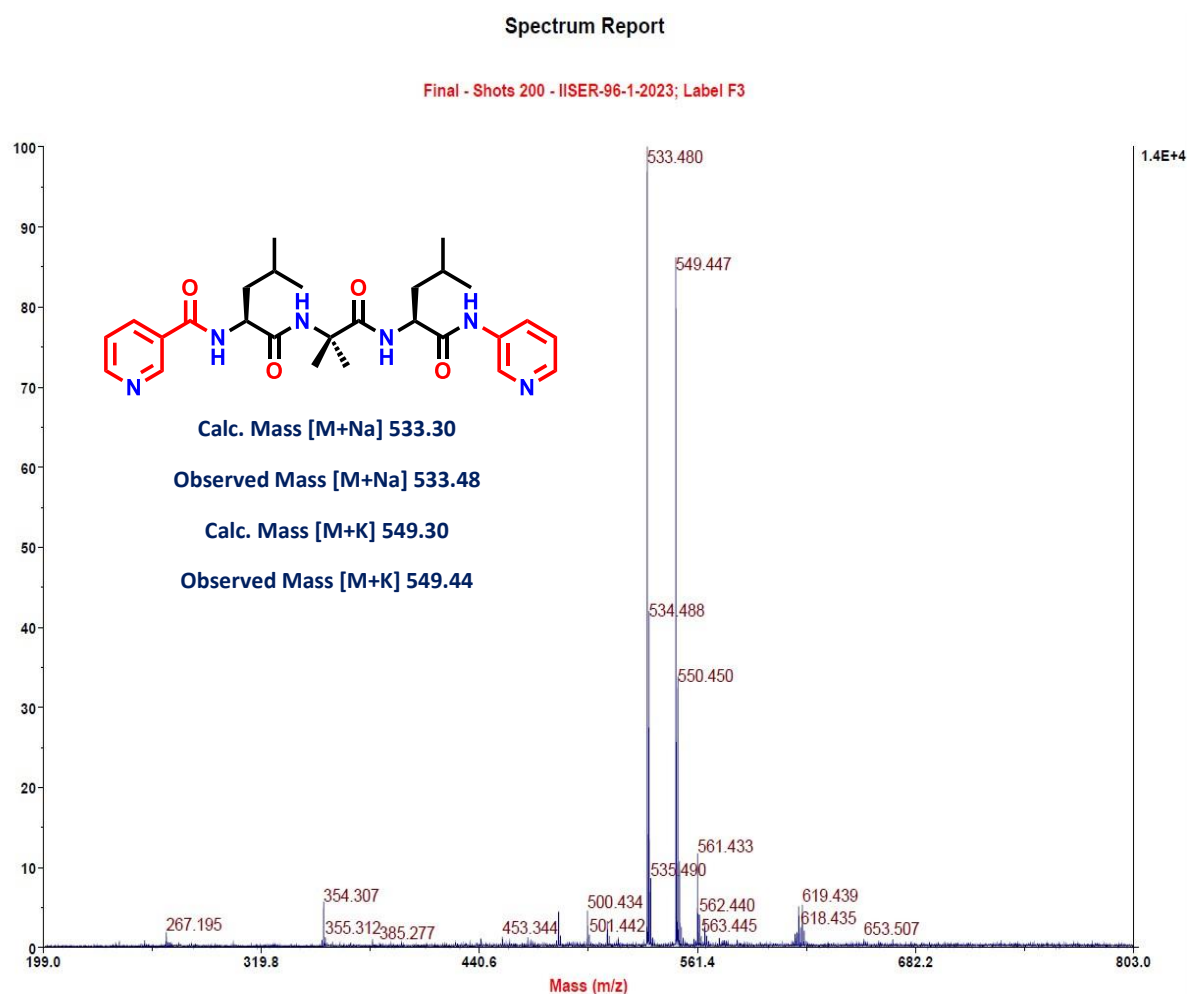


Figure 18: MALDI-TOF/TOF mass spectrum of **P3**.

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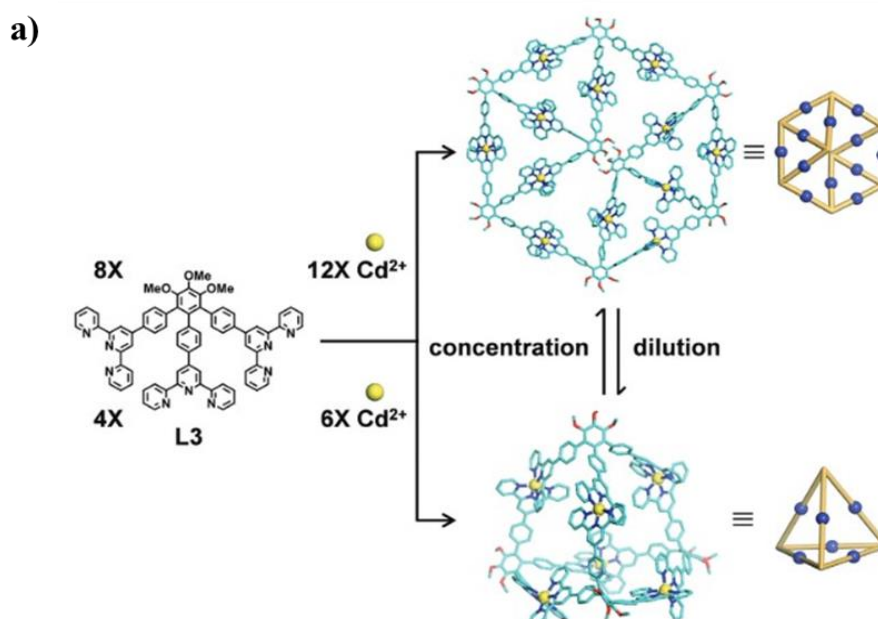
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Chapter 4

Structural Elucidation of Pi-Stacked Short Hybrid Peptide Foldamers within a Helical Framework

1. Introduction:

Because of the controlled and reversible tendencies observed in metal-ligand interactions, the utilization of coordination-driven self-assembly has been extensive in crafting numerous metallo-supramolecules characterized by well-defined structures and desired functionalities in recent years.¹⁻³ Utilizing a variety of N-heteroaromatic ligands, including pyridine,⁴ 2,2'-bipyridine,⁵ 1,10-phenanthroline,⁶ tetrazole,⁷ and 2,2':6',2''-terpyridine (tpy),⁸ has been a common practice for the construction of metallo-supramolecules. This is achieved through the coordination of these ligands with metal ions, resulting in the formation of intricate molecular assemblies. The diverse nature of these ligands contributes to the creation of a wide array of metallo-supramolecules, each characterized by specific structural features and tailored functionalities. This methodology has become a prominent strategy in the construction of functional materials and compounds with applications across various scientific and technological domains. Specifically, ligands derived from terpyridine (tpy) emerge as adaptable foundational units for constructing supramolecular assemblies due to their robust chelate effect. The versatility of tpy ligands is manifested in their capacity to form coordination bonds with a diverse spectrum of transition metal ions. This includes but is not limited to Cr (II), Mn (II), Fe (II), Co (II), Ni (II), Zn (II), Cu (II), Cd (II), and Ru (II). Through this coordination, a distinctive pseudo-octahedral connectivity is established, characterized by the formation of tpy–M(II)–tpy linkages as shown in Figure 1. This complex arrangement not only underscores the structural diversity achievable with tpy-based ligands but also highlights their potential to facilitate a wide range of tailored supramolecular architectures.



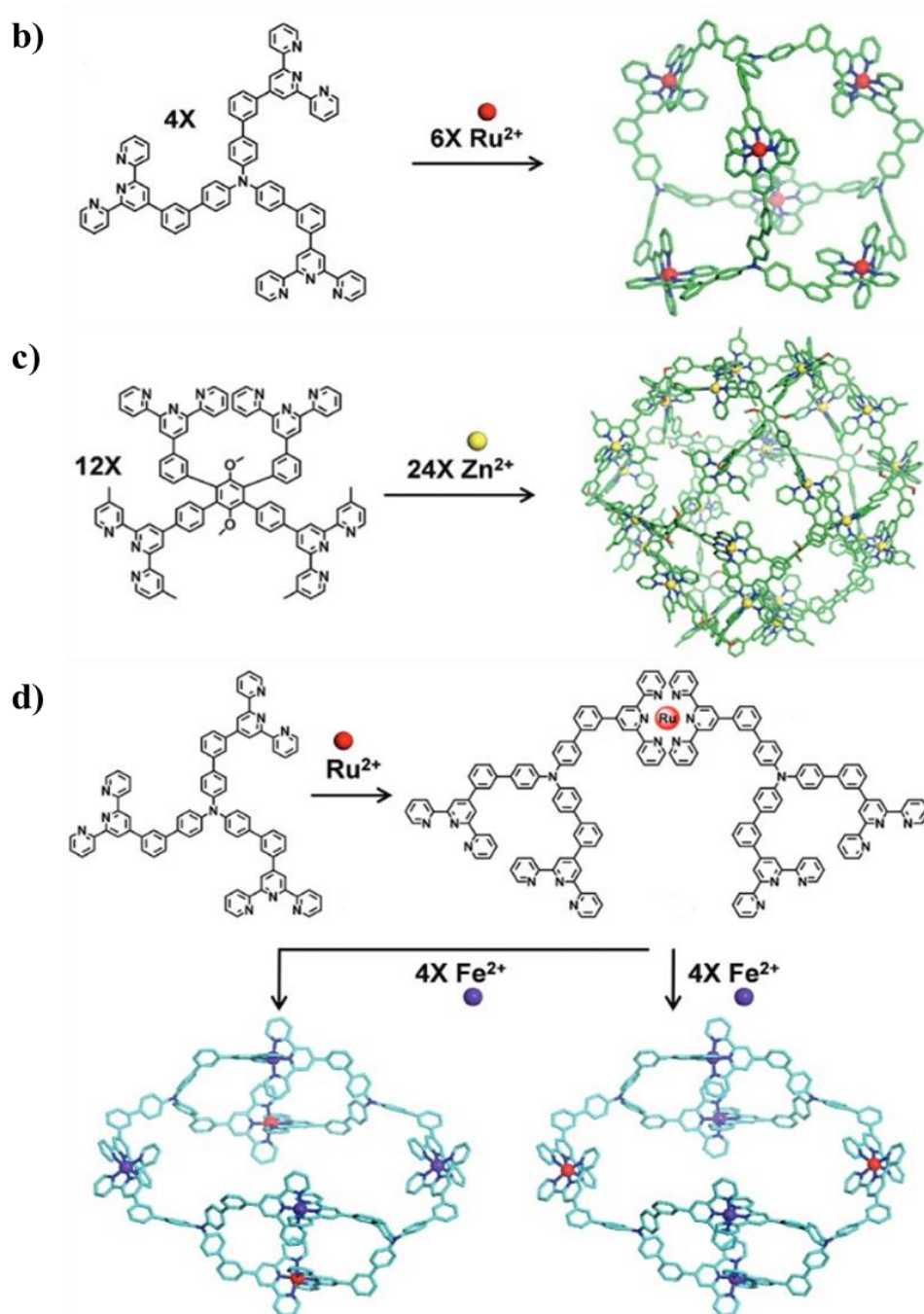


Figure 1: a) Simulated self-assembly of a tritopic tpy ligand yields bis-rhombus and tetrahedral structures, with concentration-dependent structural interconversion. b) Crystal structures of stable Ru (II) truncated tetrahedrons from direct self-assembly of tritopic tpy ligands. c) Crystal structure of triangular orthobicupola from direct self-assembly of a tetratopic tpy ligand. d) Stepwise self-assembly of a metallo-organic tpy ligand produces simulated structures of two non-reversible isomeric nanocages.

Significant progress has been achieved in the development of peptide-metal frameworks derived from short peptides containing three or fewer amino acids, have witnessed remarkable

progress, showcasing sophisticated pore architectures.⁹ These advanced frameworks stand out for their intricate design, yielding complex pores that not only showcase remarkable structural intricacy but also impart a discriminative ability for chiral substrates.¹⁰ Moreover, the dynamic behavior inherent in these frameworks underscores their adaptability and responsiveness to environmental cues, enhancing their potential for varied applications. Remarkably, these systems extend their functionality to catalytic processes, showcasing their capacity to facilitate and participate in chemical transformations, thereby contributing to the expanding landscape of versatile and multifunctional materials in catalysis.¹¹⁻¹³ However, the existence of noncovalent porous peptide lattices remains infrequent, with the design principles and supramolecular reactivity governing them less firmly established. Consequently, there arises a compelling requirement for the systematic and strategic design of noncovalent peptide frameworks.¹⁴⁻¹⁸ This necessity arises from the potential inherent in such frameworks, where sequence variations could serve as a catalyst for the swift evolution of highly sophisticated porous materials. This pursuit is underlined by the aim to comprehensively understand and harness the versatile nature of noncovalent interactions in peptide-based architectures, opening avenues for the creation of tailored and adaptable porous structures with enhanced functional capabilities.

2. Scope and Aim of the Current Work:

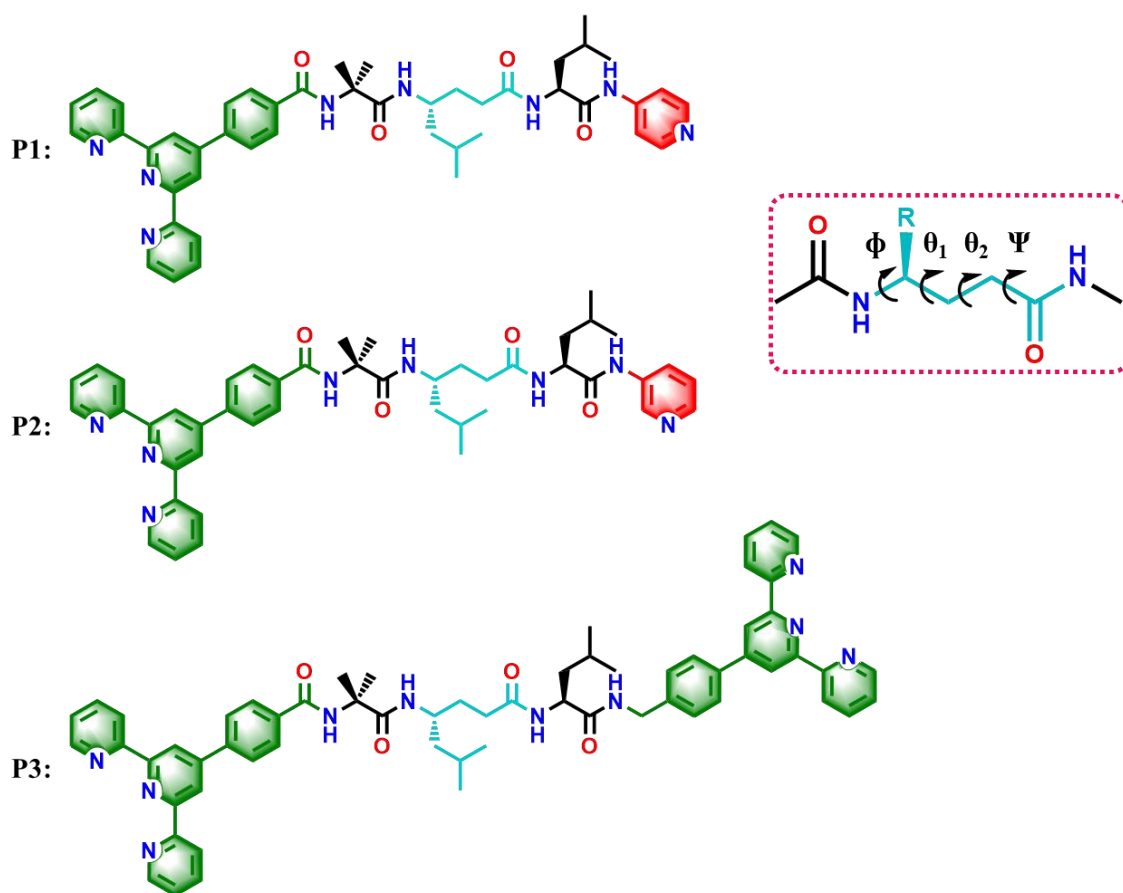
The progression from uncomplicated, self-assembled peptides to the formation of proteins serves as a robust guide in shaping intricate synthetic materials. Earlier investigations have highlighted the exploration of peptide–metal frameworks employing concise sequences containing three or fewer residues has unveiled substantial potential. These materials have emerged as promising proteomimetic entities, not only exhibit advanced capabilities but also manifest intricate functionalities, marking a significant stride in the quest for sophisticated biomimetic materials. Yet, progress in their advancement has been impeded by limited variability in residues and constrained options for side-chains compatible with metal ions. To create versatile and functionally intricate porous peptide frameworks resilient across diverse environments, Nguyen and co-workers¹⁹ integrated multiple design components. These include a resilient secondary structure building blocks, hydrophobic π -stacking residues for lattice formation, and strategically positioned variable sites directing into the pore space. Their objective involved achieving an α -helical secondary structure, capitalizing on its numerous tunable positions facilitated by the regular heptad arrangement of side chains.²⁰ To ensure the consistent imposition of helicity, they utilized the conformational rigidity inherent in the

noncanonical amino acid 2-aminoisobutyric acid (Aib), a well-known inducer of folding, particularly into a 3_{10} or α -helix within the peptide sequence.²¹ In this study, we devised a noncovalent strategy, incorporating π -stacking Terpyridyl residues, to assemble short hybrid helical peptides into crystalline frameworks in the absence of metal ions. The subsequent coordination with Tb^{3+} and Eu^{3+} ions enhances the photoluminescence of Tb, suggesting potential applications in optoelectronic materials.

3. Results and Discussion:

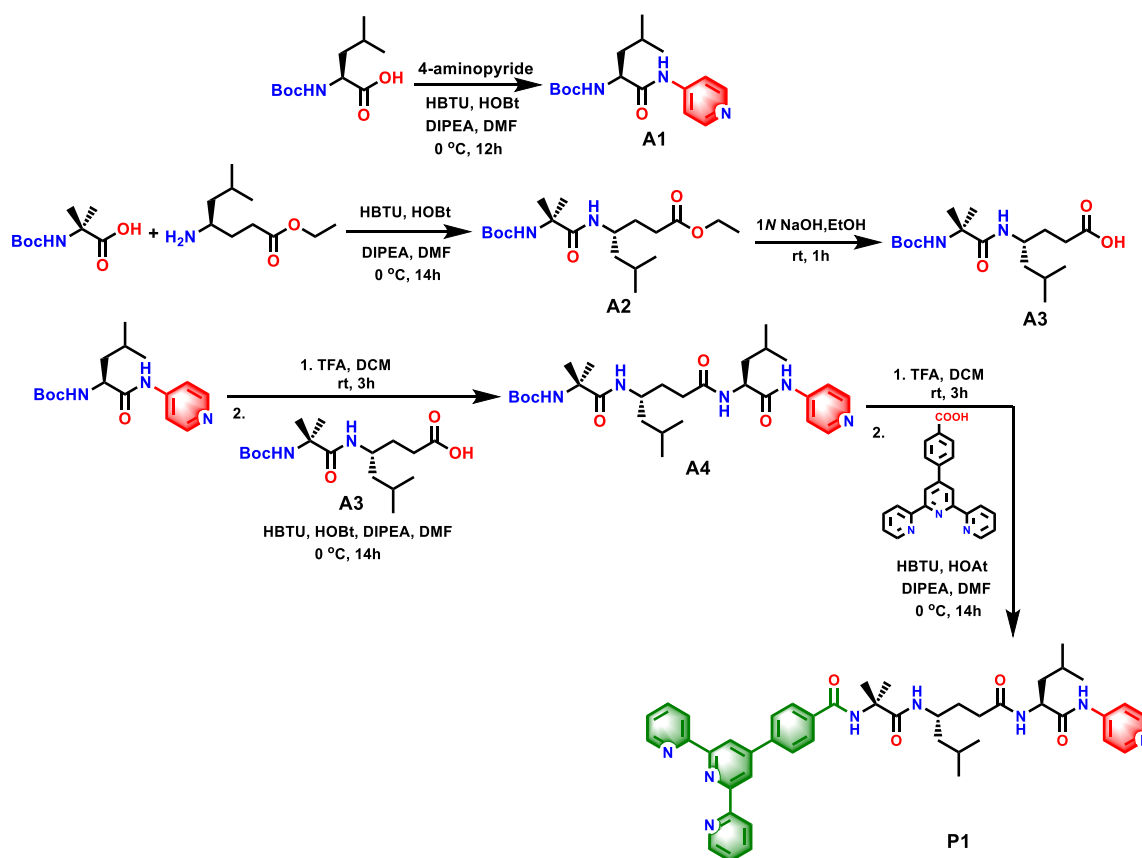
3.1. Design and Synthesis of Peptides:

To create porous peptide frameworks devoid of metal, we designed three concise hybrid tripeptides denoted as **P1**, **P2**, and **P3** as shown in Scheme 1. In the structural configuration of **P1** and **P2**, the terpyridin group was affixed at the N-terminal, while at the C-terminal, 3-pyridyl and 4-pyridyl groups were respectively attached. In contrast, peptide **P3** featured terpyridyl groups at both the C- and N-terminal ends.



Scheme 1: Sequence of short α,γ -hybrid tripeptides **P1**, **P2**, and **P3**. The torsion angle variable of γ -residue was also given.

The synthesis of each tripeptide followed a conventional solution-phase strategy, involving Boc-deprotection and coupling methodologies as elucidated in Scheme 2. Employing these procedures, tripeptides (**P1-P3**) were successfully synthesized, and subsequent purification through column chromatography yielded the desired products with overall yields ranging from 40% to 45%.



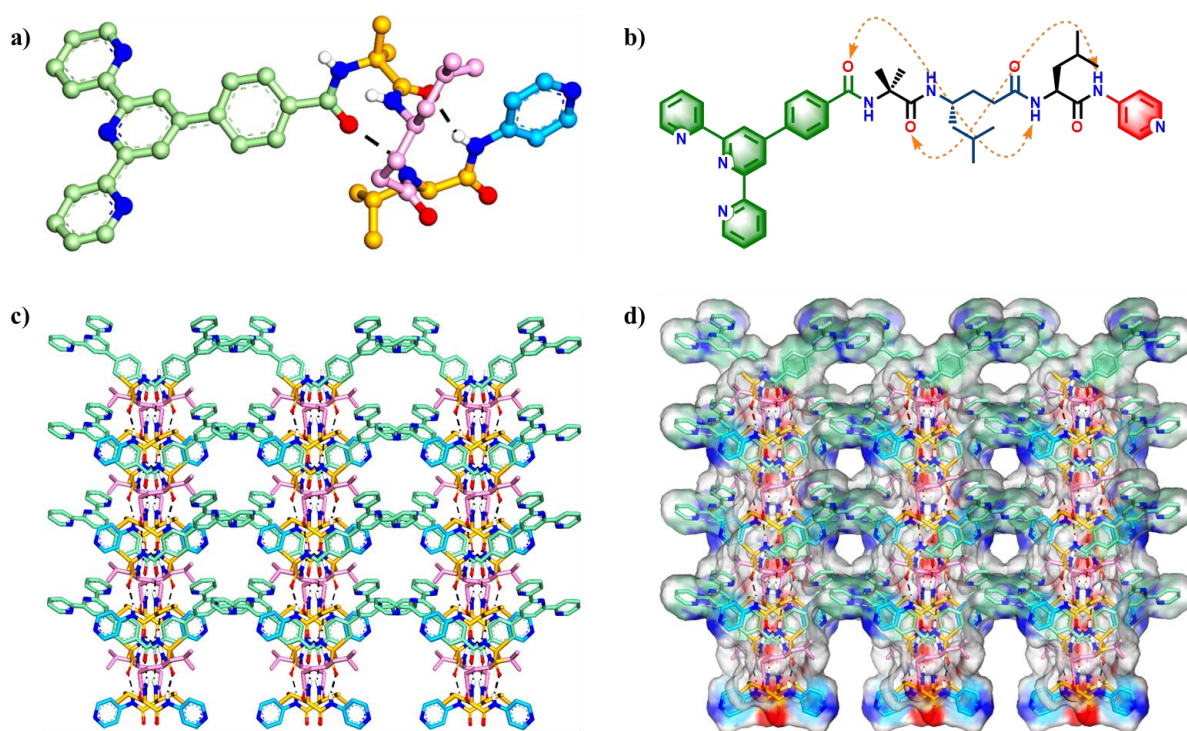
Scheme 2: Synthesis of terpyridine containing short α,γ - hybrid tripeptide **P1**.

3.2. Crystal Structures Analysis of Peptides:

Utilizing single crystal X-ray diffraction as a definitive tool for revealing peptide structures, we initiated crystallization experiments with the terpyridine-containing short hybrid peptides in diverse solvent combinations. Peptides **P1** and **P2** yielded single crystals of X-ray diffraction quality when dissolved in the specified solvents, unveiling unambiguous structural insights. Conversely, peptide **P3**, despite exhaustive attempts, did not produce any discernible crystal structure under the applied conditions. Subsequent sections provide an in-depth discussion of the detailed structural information derived from the successfully crystallized peptides **P1** and **P2**.

3.2.1. Crystal Structures Analysis of Peptide **P1**:

Initiating our investigation with peptide **P1**, we induced the formation of single crystals through the controlled evaporation of a MeOH/H₂O solvent mixture at ambient temperature. The resultant X-ray diffraction analysis, depicted in Figure 2a, elucidated the crystal structure of **P1** within the space group C2. Notably, **P1** adopted a C₁₂-helix configuration within the single crystals, where the stability of the 12-helix structures was maintained through successive intramolecular 12-membered hydrogen bonds between CO (*i*) and NH (*i*+3) residues. Critical to the structural integrity, the two amide NH protons at the N-terminus and two carbonyl groups at the C-terminus engaged in head-to-tail intermolecular hydrogen bonding with adjacent helices within the crystal lattice. The backbone conformation of γ -residues, discerned through torsion angles (ϕ , θ_1 , θ_2 , and ψ) as outlined in Scheme 1, exhibited a helix-favoring *gauche*+ (*g*+) and *gauche*+ (*g*+) conformation along C γ -C β (θ_1) and C β -C α (θ_2) bonds. Specifically, the Aib residue displayed torsion angles ϕ and ψ at -61° and -45° , while Leu exhibited -88° and -21° , respectively. Furthermore, the γ Leu torsion angles were found to be -123° , 50° , 68° , and -114° for ϕ , θ_1 , θ_2 , and ψ , respectively. Backbone torsion angle calculations substantiated the adoption of a classical right-handed helix by peptide **P1**. The CD spectrum of **P1** is shown in Figure 2e. It is surprising to notice that the peptide displayed CD minima at 234 nm.



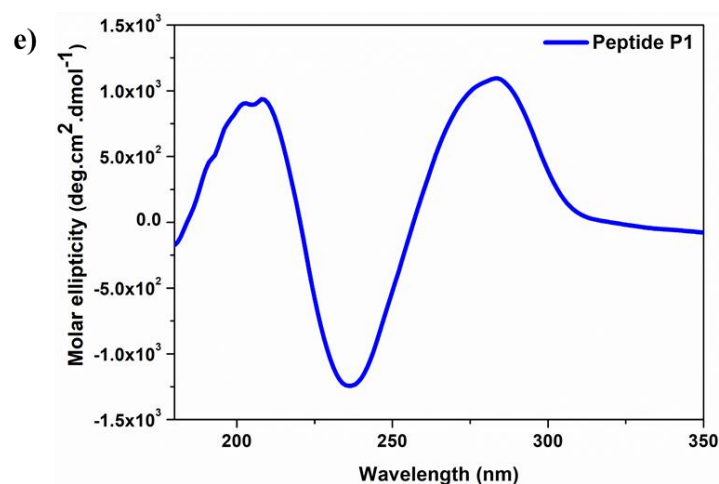


Figure 2: a) The X-ray diffracted structure of **P1**. b) The H-bonding pattern of peptide **P1** is shown here. c), and d) Pi stacked porous framework along a-axis. e) CD spectrum of peptide **P1**.

The formation of a three-dimensional porous network along the a-axis resulted from continuous intermolecular hydrogen bonds between the C₁₂-helices and π - π interactions between terpyridyl and 4-pyridyl groups, as shown in Figures 2c and 2d. This intricate assembly showcased a pore size measuring 6.6 x 6.9 Å², emphasizing the development of a sophisticated and porous structural network.

The torsion angles and H-bond parameters of peptide **P1** are given in Table 1 and Table 2.

Table 1: Torsion Angle Parameters of Peptide **P1**.

Peptide	Residue	ϕ	θ_1	θ_2	Ψ
Peptide P1	Aib	-61	-	-	-45
	γ Leu	-123	50	68	-114
	Leu	-88	-	-	-21

Table 2: H-bond Parameters of **P1**.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
			in angstroms		in degrees
P1	Molecule 1	TPy CO $\leftarrow$ NH Leu	2.12	2.95	160
	Molecule 2	Aib CO $\leftarrow$ NH Py	2.06	2.86	156

Complex		Hydrogen bond (intermolecular)	C=O...H-N	C=O...N-H	∠O....H-N
			in angstroms		in degrees
P1	Molecule 1	Leu CO ← NH γLeu(2)	2.098	2.89	153
	Molecule 2	γLeu CO ← NH Aib(2)	2.16	3.01	168
	Molecule 3	Leu CO(3) ← NH γLeu	2.09	2.89	153
	Molecule 4	γLeu CO(3) ← NH Aib	2.16	3.01	168

3.2.2. Crystal Structures Analysis of Peptide P2:

Inspired by the porous network observed in **P1**, our investigation extended to X-ray analysis of single crystals generated from peptide **P2**. Single crystals of **P2** were obtained through the gradual evaporation of ethyl acetate/hexane at ambient temperature. The structural analysis revealed that peptide **P2** crystallized in the space group of C 2. Figure 3a illustrates the X-ray diffracted single crystal structure of **P2**, revealing the adoption of a classical C₁₂-helix structure within these single crystals. The structural stability of the 12-helix configurations was facilitated by two successive intramolecular 12-membered hydrogen bonds between CO (*i*) and NH (*i*+3) residues. Integral to the structural integrity, the N-terminus's two amide NH protons and the C-terminus's two carbonyl groups engaged in head-to-tail intermolecular hydrogen bonding with adjacent helices in the crystal packing. The backbone conformation of γ-residues, discerned through torsion angles (ϕ , θ_1 , θ_2 , and ψ) as outlined in Scheme 1, favored a helix-inducing *gauche*⁺ (*g*⁺) and *gauche*⁺ (*g*⁺) conformation along Cγ-Cβ (θ_1) and Cβ-Cα (θ_2) bonds. Specifically, the torsion angles for Aib residue were 60° (ϕ) and 45° (ψ), while Leu exhibited 85° (ϕ) and 23° (ψ). Additionally, γLeu torsion angles were observed at 126°, -51°, -67°, and 115° for ϕ , θ_1 , θ_2 , and ψ , respectively. Intriguingly, the torsion angle parameters of peptide **P2** displayed an exact opposite trend to **P1**, suggesting the adoption of a left-handed helix. The CD spectrum of **P2** is shown in Figure 3e, interesting the peptide displayed different CD spectrum than P1. The overlay of CD spectra of P1 and P2 is shown in Figure 3f.

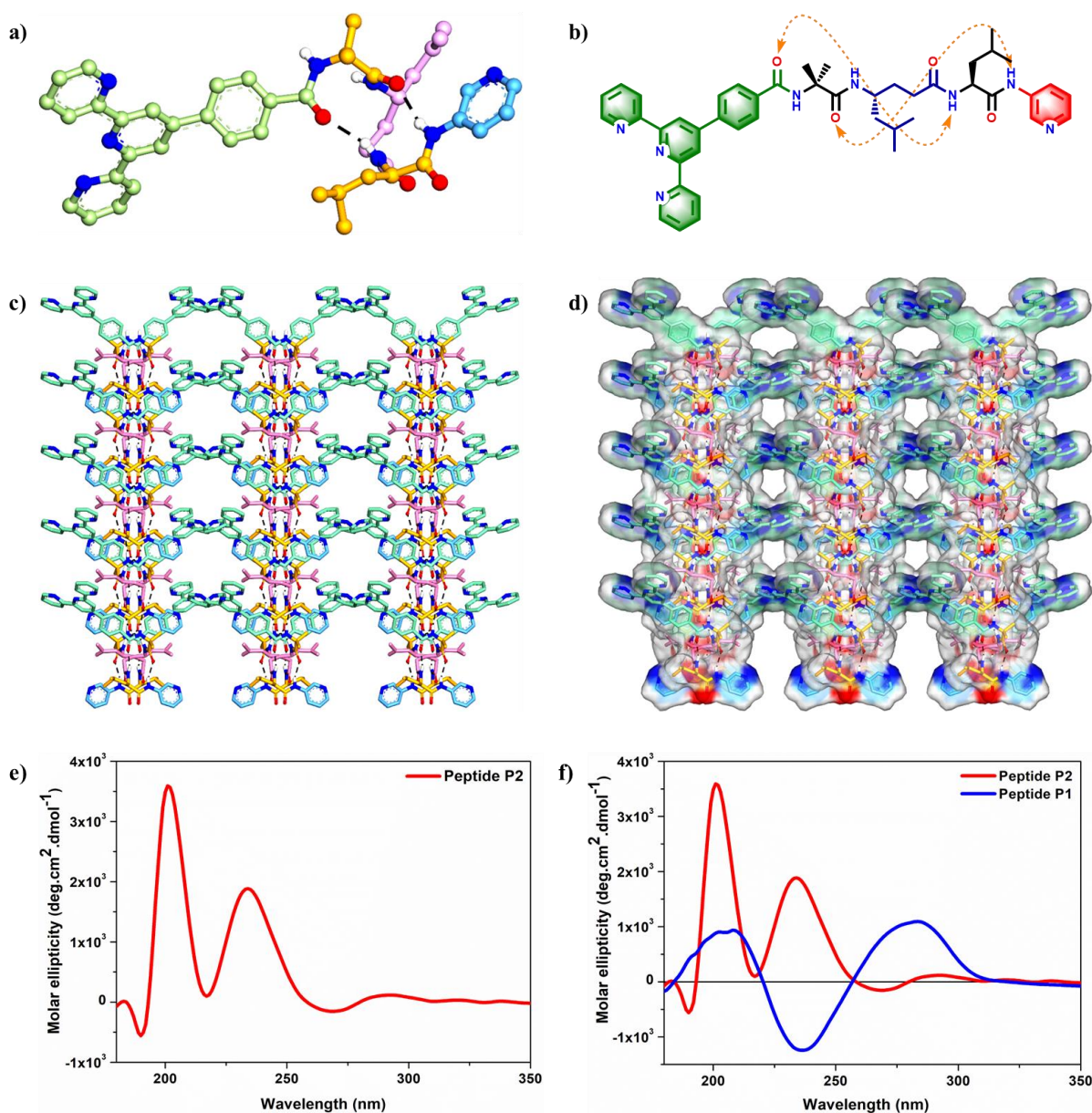


Figure 3: a) The X-ray diffracted structure of **P2**. b) The H-bonding pattern of peptide **P2** is shown here. c), and d) Pi stacked porous framework along a-axis. e) CD spectrum of peptide **P2**. f) Comparison of CD spectra between peptides **P1** and **P2**.

Continued intermolecular hydrogen bonding between the C_{12} -helices and π - π interactions between terpyridyl and 3-pyridyl groups culminated in the formation of a three-dimensional porous network shown in Figures 3c and 3d. This intricate assembly showcased a discernible pore size measuring $6.6 \times 7.5 \text{ \AA}^2$, underscoring the development of a sophisticated and porous structural network in peptide **P2**.

The torsion angles and H-bond parameters of peptide **P2** are given in Table 3 and Table 4.

Table 3: Torsion Angle Parameters of Peptide **P2**.

Peptide	Residue	ϕ	θ_1	θ_2	Ψ
Peptide P2	Aib	60	-	-	45
	γ Leu	126	-51	-67	115
	Leu	85	-	-	23

Table 4: H-bond Parameters of **P2**.

Complex		Hydrogen Bond (intramolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
			in angstroms		in degrees
P2	Molecule 1	TPy CO $\leftarrow$ NH Leu	2.12	2.93	158
	Molecule 2	Aib CO $\leftarrow$ NH Py	2.06	2.86	155
Complex		Hydrogen bond (intermolecular)	C=O...H-N	C=O...N-H	$\angle$ O...H-N
			in angstroms		in degrees
P2	Molecule 1	Leu CO $\leftarrow$ NH γ Leu(2)	2.19	2.95	148
	Molecule 2	γ Leu CO $\leftarrow$ NH Aib(2)	2.11	2.96	168
	Molecule 3	Leu CO(3) $\leftarrow$ NH γ Leu	2.19	2.95	148
	Molecule 4	γ Leu CO(3) $\leftarrow$ NH Aib	2.11	2.96	168

3.3. Hierarchical Self-assembly of peptide and Metal-peptide Complexes:

3.3.1. Hierarchical Self-assembly of peptide P1, P2, and P3:

Motivated by the multitude of interactions, including CH- π , π - π , and hydrogen bonds, between the stable helical structures, our investigation delved into their hierarchical self-assemblies through scanning electron microscopy (SEM). SEM samples were prepared by dissolving peptides in a methanol/water combination, followed by drop-casting onto a SiO₂/Si substrate and subsequent drying at room temperature. The SEM analysis unveiled strikingly monodispersed vesicles formed by the peptides, as illustrated in Figure 4. All peptides **P1**, **P2**, and **P3**, exhibited the formation of hollow spheres with a diameter ranging from 100 to 300 nm. This uniformity across the peptides, despite variations in binding sites, signifies the

spontaneous self-assembly into monodispersed vesicles, emphasizing the robustness and consistency of the self-assembly process across different peptide sequences.

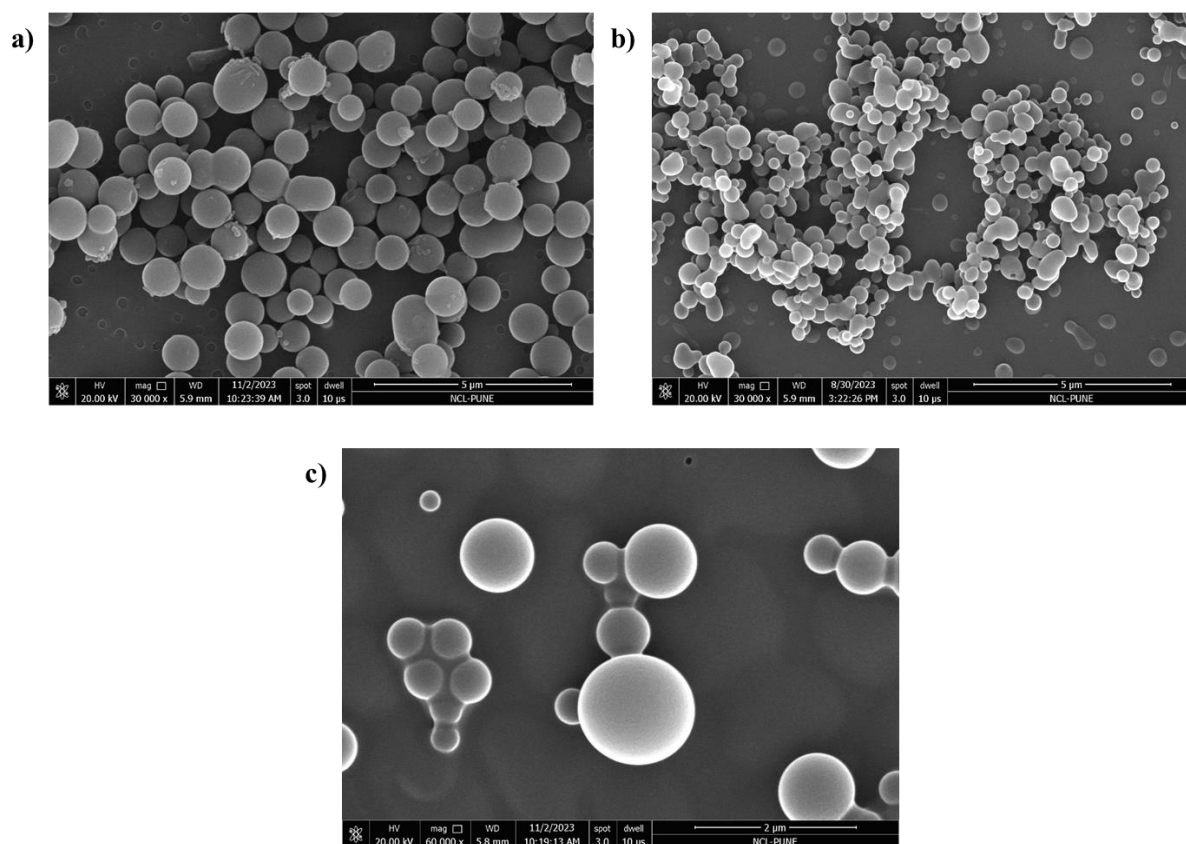


Figure 4: a) SEM images of hybrid peptide **P1**. b) SEM images of hybrid peptide **P2**. c) SEM images of Hybrid peptide **P3**.

3.3.2. Hierarchical Self-assembly of **P1-TbCl₃** and **P1-EuCl₃** Complex:

Incorporating a terpyridine binder in our design was motivated by its affinity for higher-coordinated metal ions, particularly lanthanides. The initiation of our investigation with peptide **P1** involved treatment with TbCl_3 and EuCl_3 salts, aiming to elucidate the potential coordination complexes. Unfortunately, despite exhaustive efforts involving various solvent combinations and temperature variations, we are unable to obtain the single-crystal structure of these complexes. Inspired by the observed vesicle self-assembly of peptides itself, we shifted our focus towards investigating the hierarchical self-assembly of **P1-TbCl₃** and **P1-EuCl₃** complexes using scanning electron microscopy (SEM). Sample preparation involved dissolving peptides in a methanol/water combination, drop-casting onto a SiO_2/Si substrate, and subsequent drying at room temperature. SEM analysis revealed the formation of monodispersed vesicles which was almost similar to what we observed in the case of peptides

as shown in Figures 5a and 5c. This remarkable self-assembly pattern was further validated through high-resolution transmission electron microscopy (HR-TEM) analysis (Figure 5b and 5d).

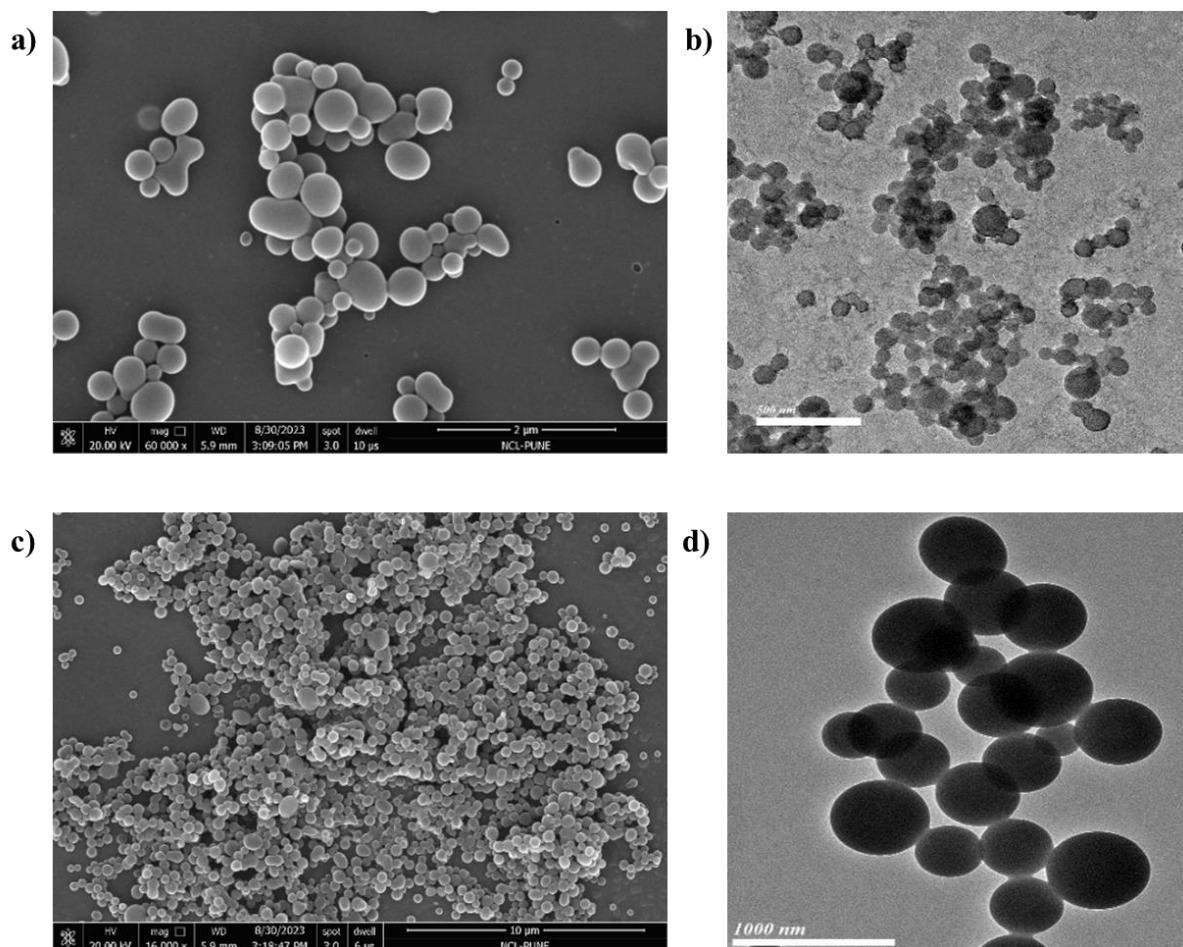


Figure 5: a) and b) SEM and TEM images of **P1-TbCl₃** complex. c) and d) SEM and TEM images of **P1-EuCl₃** complex.

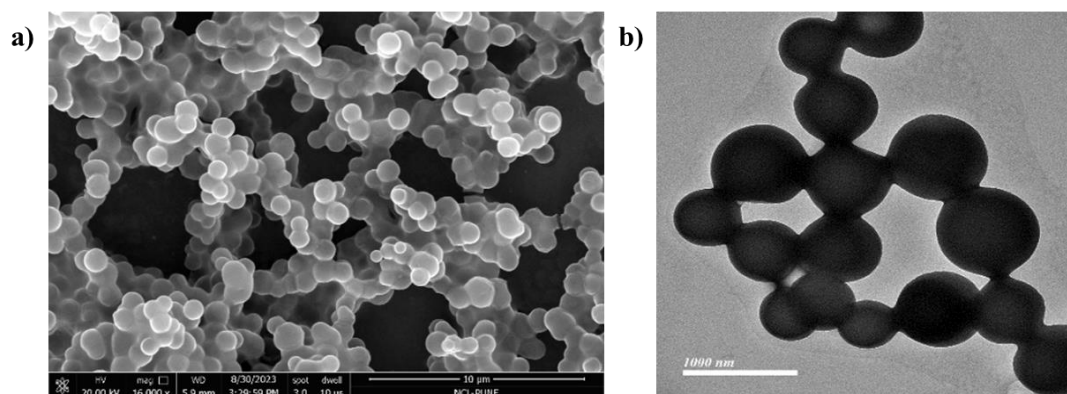
Remarkably, the **P1-TbCl₃** and **P1-EuCl₃** complexes exhibited spherical spheres with diameters ranging from 300 to 700 nm, surpassing the dimensions of the peptide-derived hollow spheres. To gain further insight into the elemental composition of these vesicles, energy dispersive X-ray spectroscopy (EDAX) was performed shown in Figure 6. Elemental analysis confirmed the presence of carbon, nitrogen, oxygen, chlorine, terbium, and europium in the vesicles, providing compelling evidence that nanostructures were indeed formed in the context of metal-peptide complexes. This outcome underscores the potential for tailored nanostructure formation through the strategic integration of metal ions in conjunction with peptides.



Figure 6: a) EDAX and elemental analysis of **P1-TbCl₃** complex. b) EDAX and elemental analysis of **P1-EuCl₃** complex.

3.3.3. Hierarchical Self-Assembly of **P2-TbCl₃** and **P2-EuCl₃** Complex:

Inspired by the vesicle self-assembly observed in the **P1-TbCl₃** and **P1-EuCl₃** complexes, we extended our investigation to analyse the hierarchical self-assembly properties of **P2-TbCl₃** and **P2-EuCl₃** complexes through SEM analysis. The SEM samples were meticulously prepared by dissolving peptides in a methanol/water combination, followed by drop-casting onto a SiO₂/Si substrate and subsequent drying at room temperature. Similar to the **P1-metal** complexes, the SEM analysis of **P2-metal** complexes also revealed the formation of monodispersed vesicles, as evidenced by SEM images shown in Figure 7a and 7c. This finding was further substantiated through high-resolution transmission electron microscopy (HR-TEM) analysis (Figure 7b and 7d).



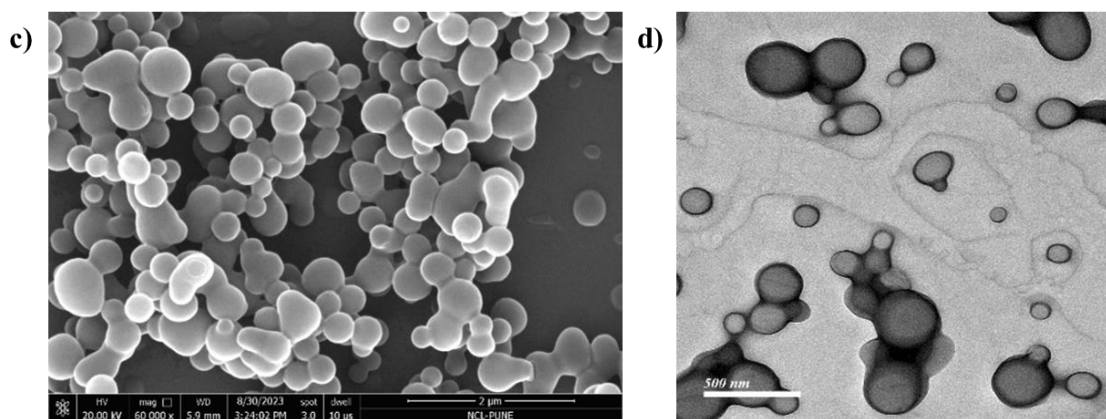


Figure 7: a) and b) SEM and TEM images of **P2-TbCl₃** complex. c) and d) SEM and TEM images of **P2-EuCl₃** complex.

Remarkably, both **P2-TbCl₃** and **P2-EuCl₃** complexes exhibited the formation of spherical spheres with a diameter ranging from 300 to 700 nm, closely resembling the characteristics observed in **P1-metal** complexes. To deepen our understanding of the elemental composition of these vesicles, energy-dispersive X-ray spectroscopy (EDAX) was employed, as illustrated in Figure 8. Elemental analysis affirmed the presence of carbon, nitrogen, oxygen, chlorine, terbium, and europium in the vesicles, providing robust evidence that nanostructures were indeed generated within the context of metal-peptide complexes. This consistent observation underscores the reproducibility and versatility of the nanostructure formation across different peptide sequences and metal ions.

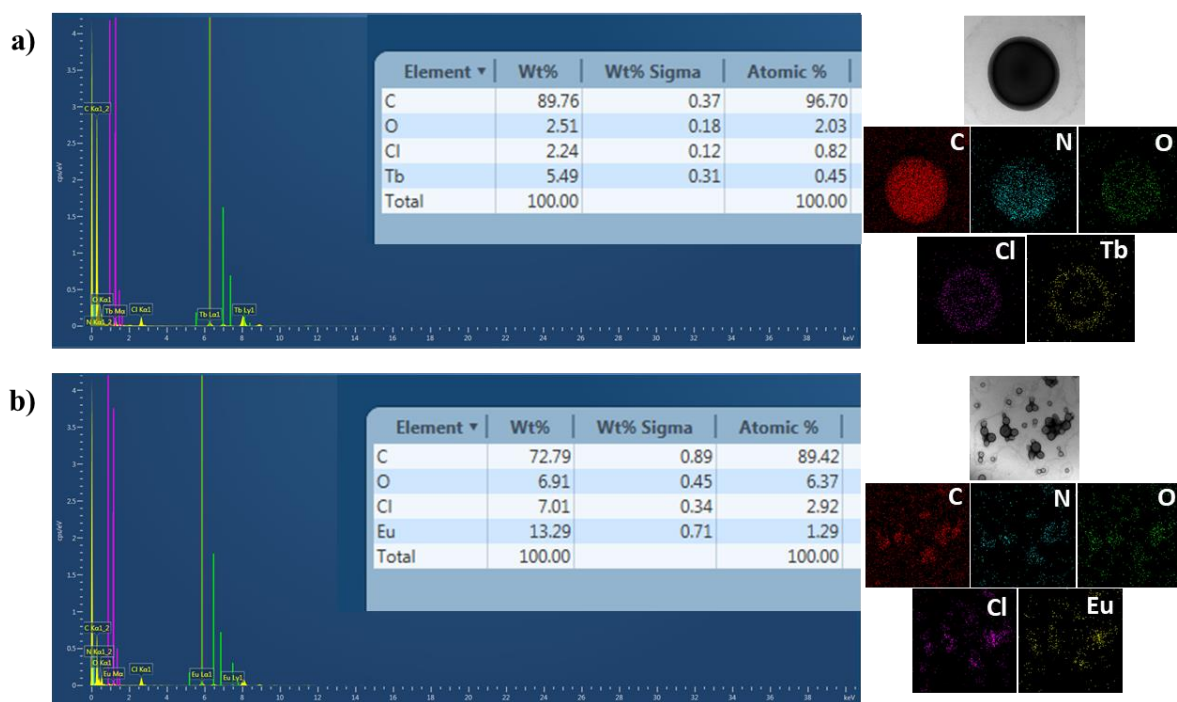


Figure 8: a) EDAX and elemental analysis of **P2**-TbCl₃ complex. b) EDAX and elemental analysis of **P2**-EuCl₃ complex.

3.3.4. Hierarchical Self-Assembly of **P3**-TbCl₃ and **P3**-EuCl₃ Complex:

Inspired by the morphological resemblances observed between **P1** and **P2** in the presence of TbCl₃ and EuCl₃, we expanded our investigation to explore the impact of peptide **P3**. In **P3**, the terpyridine binder was strategically attached at both the C- and N-terminal ends of the peptide sequence, and its interaction with TbCl₃ and EuCl₃ was examined through SEM analysis. Similar to the **P1** and **P2** metal complexes, SEM analysis showcased the formation of monodispersed vesicles for **P3**-metal complexes, as shown in Figure 9a and 9c. This consistent observation was further confirmed through high-resolution transmission electron microscopy (HR-TEM) analysis, as depicted in Figure 9b and 9d.

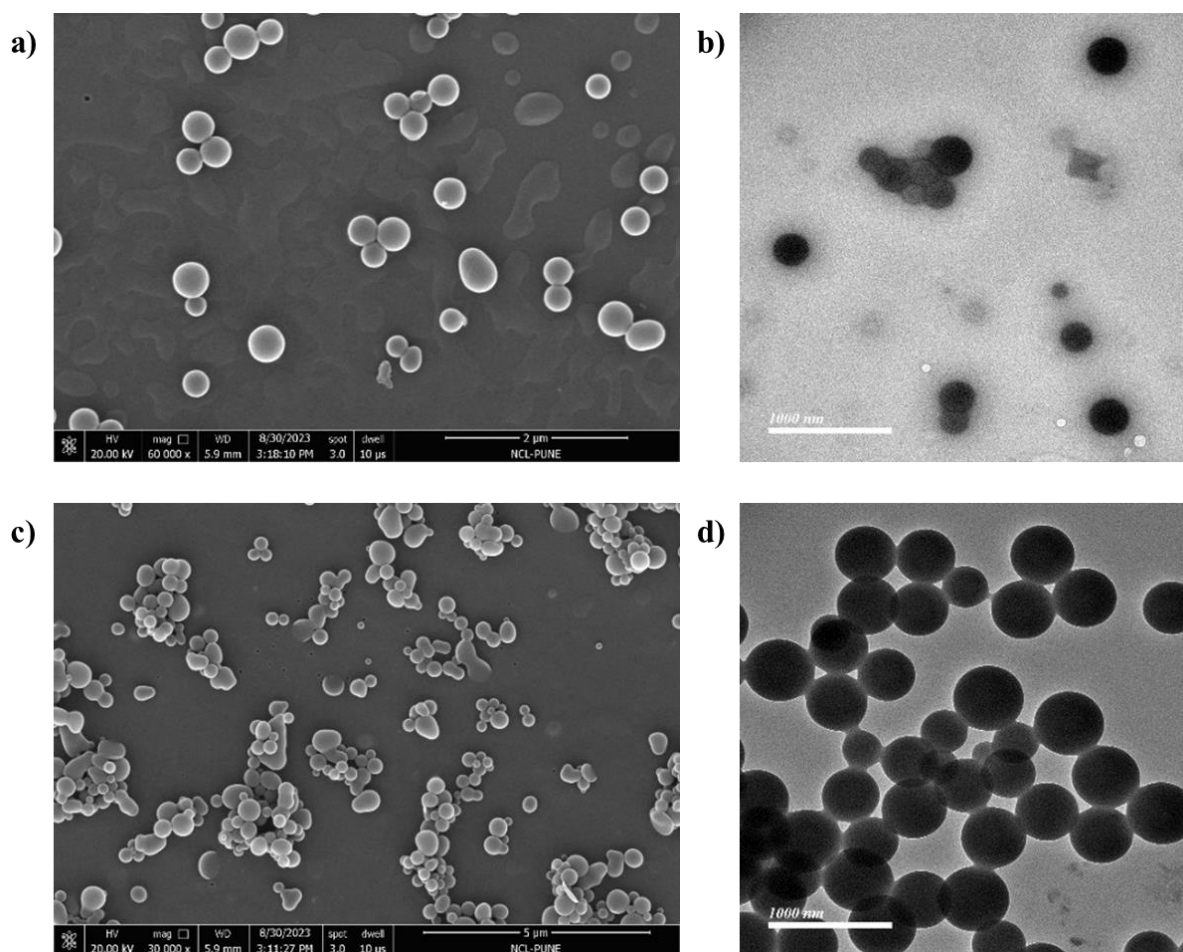


Figure 9: a) and b) SEM and TEM images of **P3**-TbCl₃ complex. c) and d) SEM and TEM images of **P3**-EuCl₃ complex.

The **P3**-TbCl₃ and **P3**-EuCl₃ complexes exhibited the formation of spherical spheres with a diameter ranging from 300 to 700 nm, aligning closely with the characteristics observed in **P1** and **P2** metal complexes. Elemental analysis of **P3**-TbCl₃ and **P3**-EuCl₃ further affirmed the presence of carbon, nitrogen, oxygen, chlorine, terbium, and europium in these monodispersed vesicles, as shown in Figure 10. This robust consistency across different peptide sequences and metal ions underscores the reproducibility and versatility of nanostructure formation within the context of metal-peptide complexes.



Figure 10: a) EDAX and elemental analysis of **P3**-TbCl₃ complex. b) EDAX and elemental analysis of **P3**-EuCl₃ complex.

4. Photoluminescence Properties of Peptide-Metal Complex:

In recent times, there has been a growing focus on the bioinspired fabrication of nanomaterials, emerging as a viable alternative to traditional nanofabrication techniques like photolithography. The utilization of peptides for nanofabrication has gained prominence due to their molecular recognition capabilities, functional flexibility, and environmentally friendly processes that eschew harsh chemical substances.²² Within the realm of nanostructure-forming peptides and their derivatives, diphenylalanine (Phe-Phe, FF) stands out as a straightforward building block capable of effortlessly yielding nanotubes characterized by remarkable chemical stability and mechanical robustness.²³ Notably, the investigation of photoluminescence properties in metallopeptides remains relatively underexplored. This report unveils a

groundbreaking development in the creation of a novel photoluminescent metallopeptide complex. The complex is seamlessly crafted through the in situ incorporation of lanthanide ions, specifically terbium (Tb) and europium (Eu), into peptides containing a terpyridine binder. This binder exhibits a notable affinity for metal ions through metal coordination, contributing to the distinctive photoluminescence properties of the resulting metallopeptide complex.

4.1. Absorbance and Fluorescence Properties of Hybrid Peptides (P1-P3):

We delved into the fundamental optical characteristics of peptides **P1-P3**, specifically examining absorbance and fluorescence spectra before the introduction of lanthanide ions. The absorbance spectrum of hybrid peptides unveiled their almost transparency to visible (380–750 nm) and near-UV light (330–380 nm) while exhibiting significant light absorption in the mid-UV spectral range (200–330 nm). The peptides demonstrated two prominent absorption peaks at 230 and 275 nm, attributed to the π - π^* electronic transition of the terpyridyl and pyridyl groups within the peptides. Additionally, a subtle absorption peak around ~330 nm was associated with the n - π^* electronic transition of the carbonyl group in hybrid peptides as shown in figure 11.

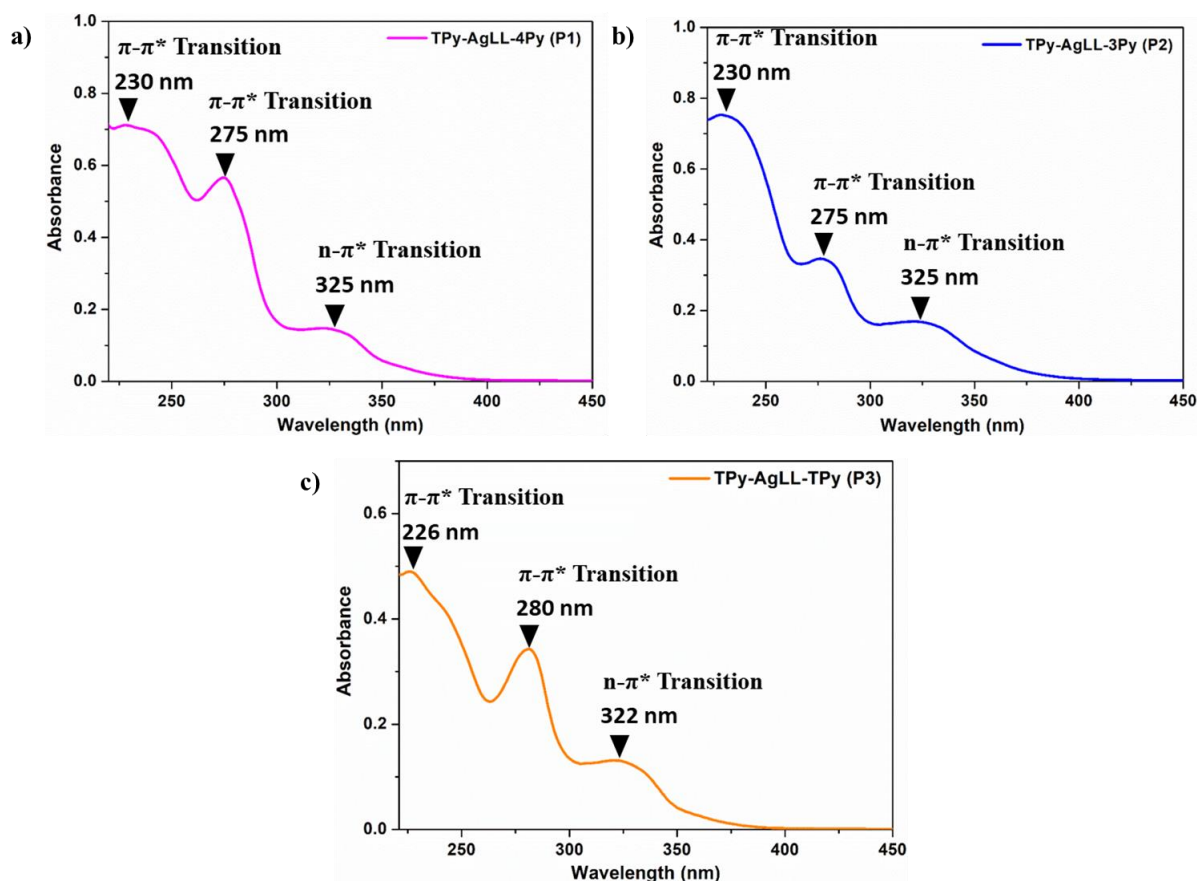


Figure 11: a), b), and c) absorbance spectra of hybrid peptides (**P1-P3**) showing two strong absorption peaks at around 230 nm and 275 nm, and a weak peak at 325 nm.

Upon further exploration of fluorescence properties, hybrid peptides (**P1-P3**) exhibited a blue emission in the 400-450 nm range under 330 nm excitation shown in Figure 12. Both the absorbance and fluorescence excitation spectra of hybrid peptides showcased a peak at approximately 330 nm, indicating the involvement of the $n-\pi^*$ electronic transition of the carbonyl group in generating fluorescence within the hybrid peptides (**P1-P3**).

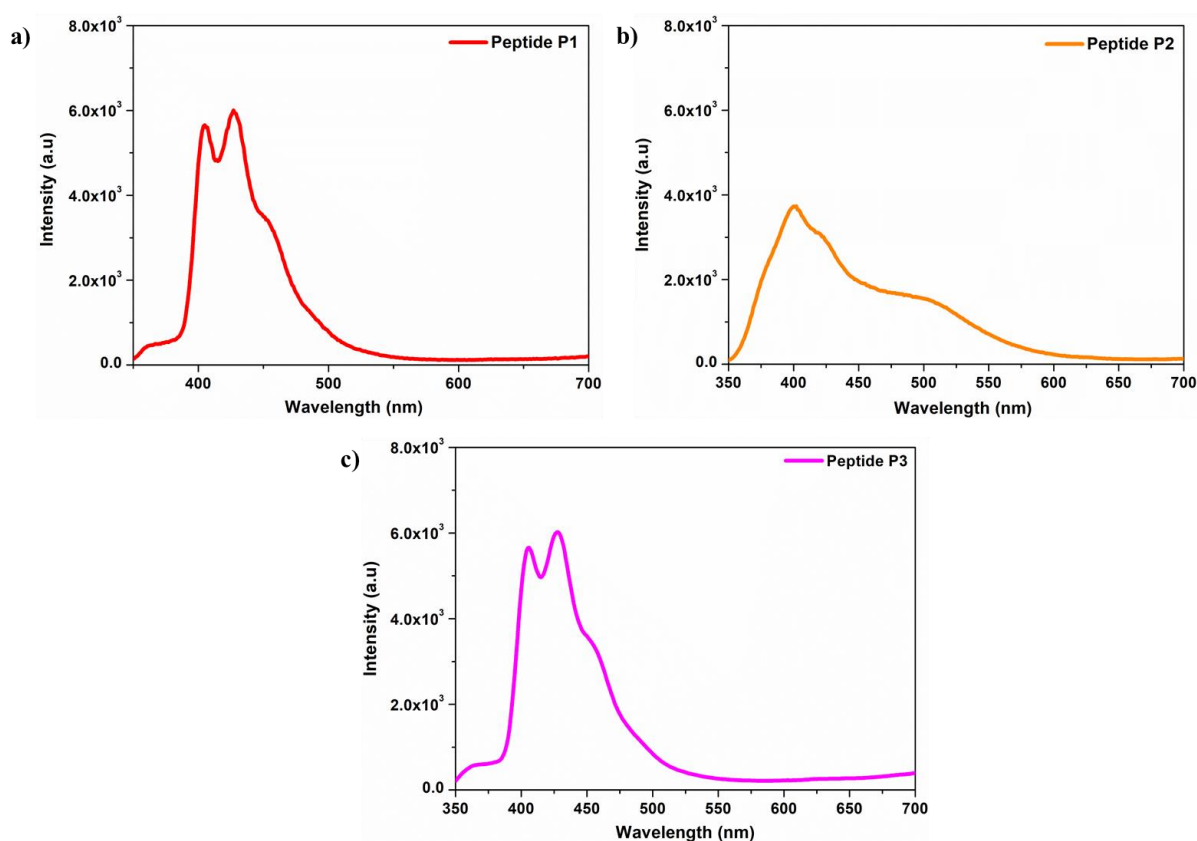


Figure 12: a), b), and c) Emission spectrum of hybrid peptides (**P1-P3**) when excited at 330 nm. The emission peak was located at around 400-450 nm.

4.2. Enhance Photoluminescence of Lanthanides by Helical Peptides:

To unravel the amplified photoluminescence mechanism of lanthanide ions facilitated by hybrid helical peptides, we studied the photoluminescent spectra of the peptide-lanthanides complex in detail. Our attention was specifically directed towards the photoluminescence of Tb, given its more pronounced emission compared to Eu. Excitation wavelengths spanning from 250 to 340 nm at 10 nm intervals were employed for each sample. Notably, At 330 nm excitation wavelength, we found the highest enhanced photoluminescence. Before

investigating the photoluminescence spectra of lanthanide ion–peptide complex, an assessment was undertaken to elucidate the impact of individual components, namely peptide (P1-P3) itself and TbCl₃ salt alone, on lanthanide photoluminescence. Experimental observation revealed that Tb salts show very negligible characteristic emission peak at 330 nm excitation wavelength because of their low absorbance. However, the introduction of helical peptides (**P1-P3**) into the Tb salt solution in methanol yielded a substantial enhancement in the photoluminescence of Tb, suggesting a synergistic effect. These fascinating outcomes emerged when the helical peptides were utilized as a host matrix for lanthanide ions. The incorporation of helical peptides (**P1-P3**) into the Tb-containing solution resulted in the simultaneous quenching of peptides' fluorescence and a remarkable enhancement in the photoluminescence of Tb ions. This dual effect serves as compelling evidence for the integration of Tb into peptides and the direct transfer of energy from peptides to Tb ions as shown in Figure 14.

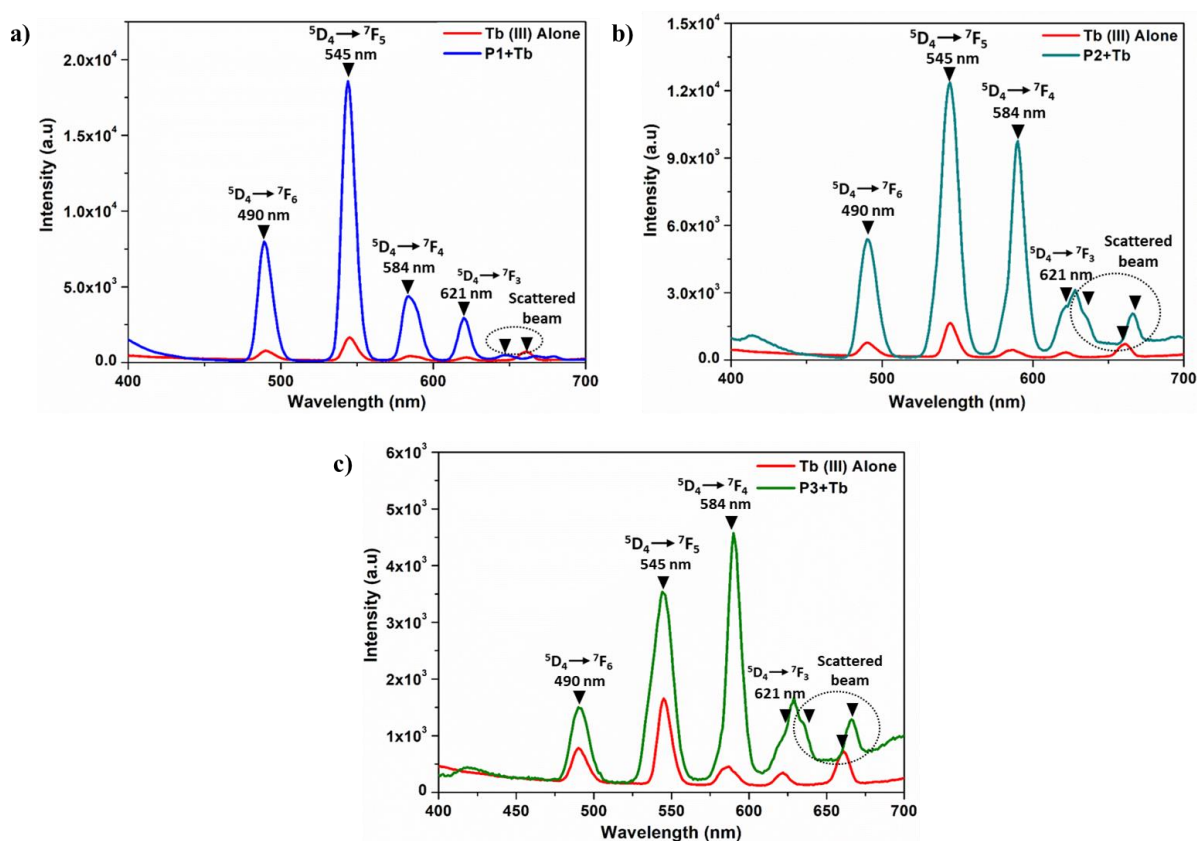


Figure 13: a) Enhanced photoluminescence of Tb (1 mM) by helical peptide **P1** (10 mM). b) Enhanced photoluminescence of Tb (1 mM) by helical peptide **P2** (10 mM). c) Enhanced photoluminescence of Tb (1 mM) by helical peptide **P3** (10 mM).

Figure 13 provides a detailed depiction of the significantly enhanced photoluminescence of Tb achieved through the integration of Tb ions into peptides (**P1-P3**). Notably, the positions of the

characteristic emission peaks of Tb remained almost unchanged across all samples. The discerned emission peaks at 490, 545, 584, and 621 nm for Tb ions with peptides correspond to transitions from the 5D_4 state of Tb to 7F_J ($J=6, 5, 4, 3$) states, respectively. It is essential to note that the additional peaks at 640, 660, and 670 nm are attributed to the scattering and diffraction effects of the excitation beam with a wavelength of 330 nm. These findings contribute to a comprehensive understanding of the intricate photoluminescent behaviour observed in the Tb-peptide complexes.

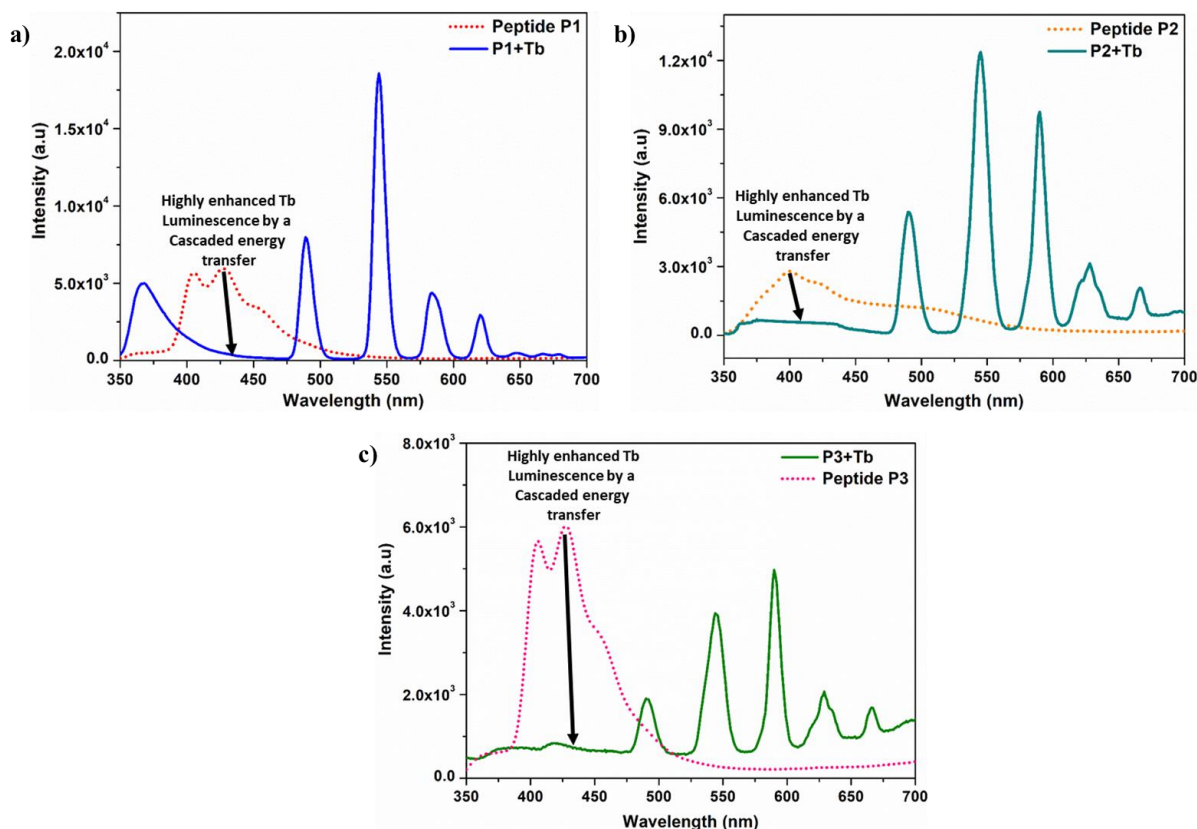


Figure 14: a), b), and c) Emission spectra showing the cascade energy transfer from Peptides (P1-P3) (10 mM) to Tb (1 mM) for highly enhanced photoluminescence.

4.3. Control Experiment for Enhance Photoluminescence of Lanthanides:

To assess the influence of terpyridine-containing peptides on the enhancement of lanthanide photoluminescence, two control experiments were conducted, isolating the peptide backbone without any binder and examining only the terpyridine binder. Initial examination of absorption spectra revealed a singular characteristic peak at 202 nm for the peptide, attributed to $\pi-\pi^*$ transition. Conversely, the terpyridine binder exhibited three distinctive peaks at 233 nm, 276 nm, and 317 nm, corresponding to $\pi-\pi^*$ and $n-\pi^*$ transitions. Subsequent investigation of photoluminescence spectra in the presence of Tb salts at a 330 nm excitation wavelength

disclosed noteworthy findings. The photoluminescence spectra of the peptide in the presence of Tb indicated an unaltered spectral pattern post-incorporation of Tb salts, suggesting that the peptide itself does not exhibit binding affinity with the metal in the absence of any binder. While terpyridine binds with Tb, the absence of characteristic peaks following binding implies that the binder alone does not contribute to the enhancement of Tb photoluminescence, as illustrated in Figure 15.

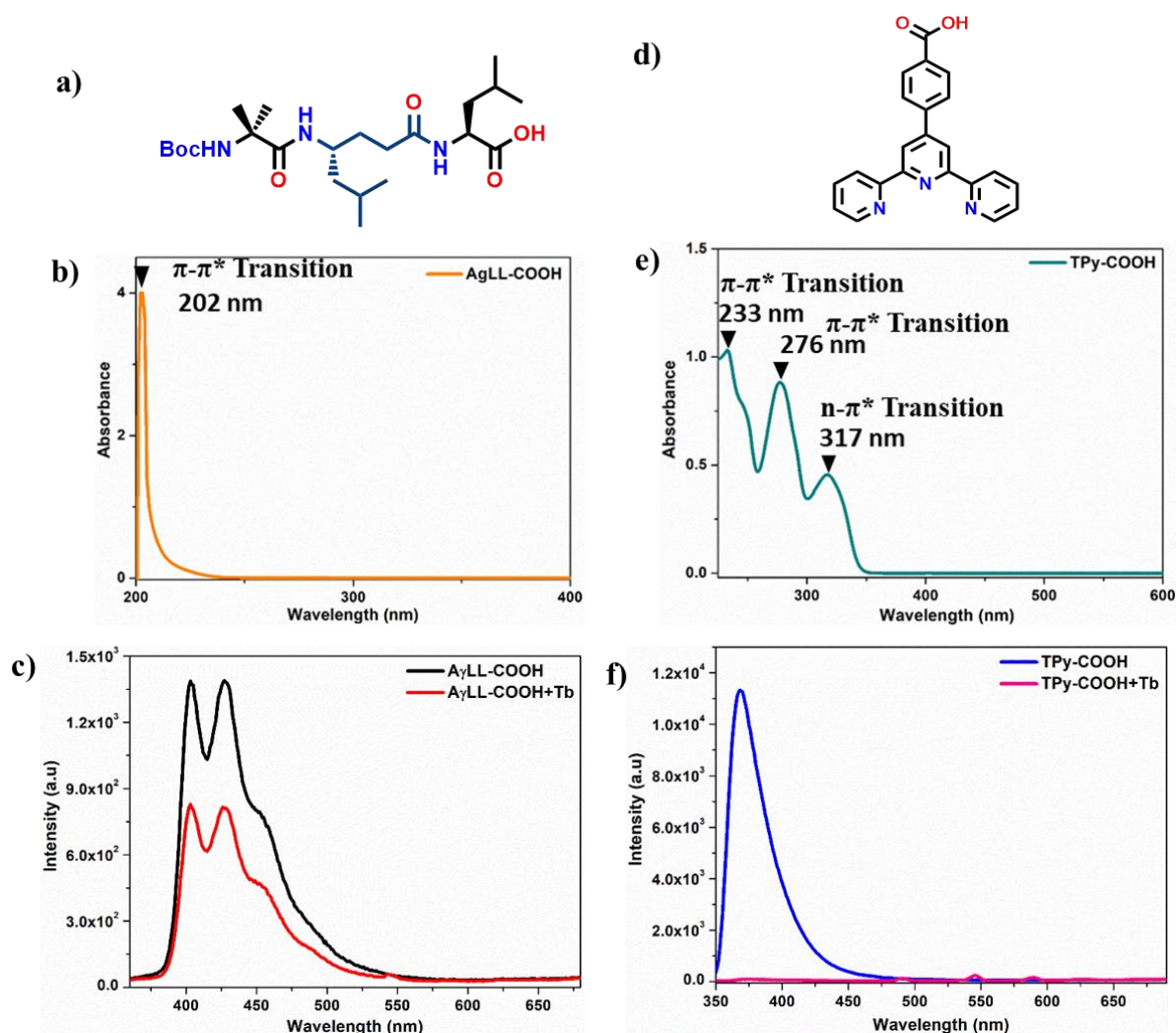


Figure 15: a) Sequence of the peptide backbone. b) Absorbance spectra of peptide. c) Photoluminescence spectra of peptide (10 mM) presence and absence of metal salts (10 mM:1 mM). d) Representation of terpyridine binder. e) and f) Absorption and Photoluminescence spectra of the binder itself (concentration of peptide and metal salts is 10 mM: 1 mM).

4.4. Proposed Mechanism for Enhance Photoluminescence of Lanthanides:

Drawing insights from these findings, we propose that an increased absorption cross-section and a cascaded energy transfer from peptides to lanthanide ions (Tb) may lead to significant

enhancement of Tb photoluminescence, as illustrated in Figure 16. According to the literature,^{24, 25} the efficacy of energy transfer between lanthanide ions and proximate molecules is intricately linked to the magnitude of the energy gap between the lowest triplet state of the ligand and the resonance energy level of lanthanide ions. In essence, a larger energy gap correlates with a diminished energy-transfer efficiency. In light of this understanding, we propose that the introduction of an excited triplet state with an intermediate energy level between helical peptides and lanthanide ions into the metal-peptide complex could markedly enhance the photoluminescent characteristics of lanthanide ions. This enhancement would be achieved through a cascaded energy transfer mechanism operating between the excited triplet state and the lanthanide ions, thereby amplifying their photoluminescent properties.

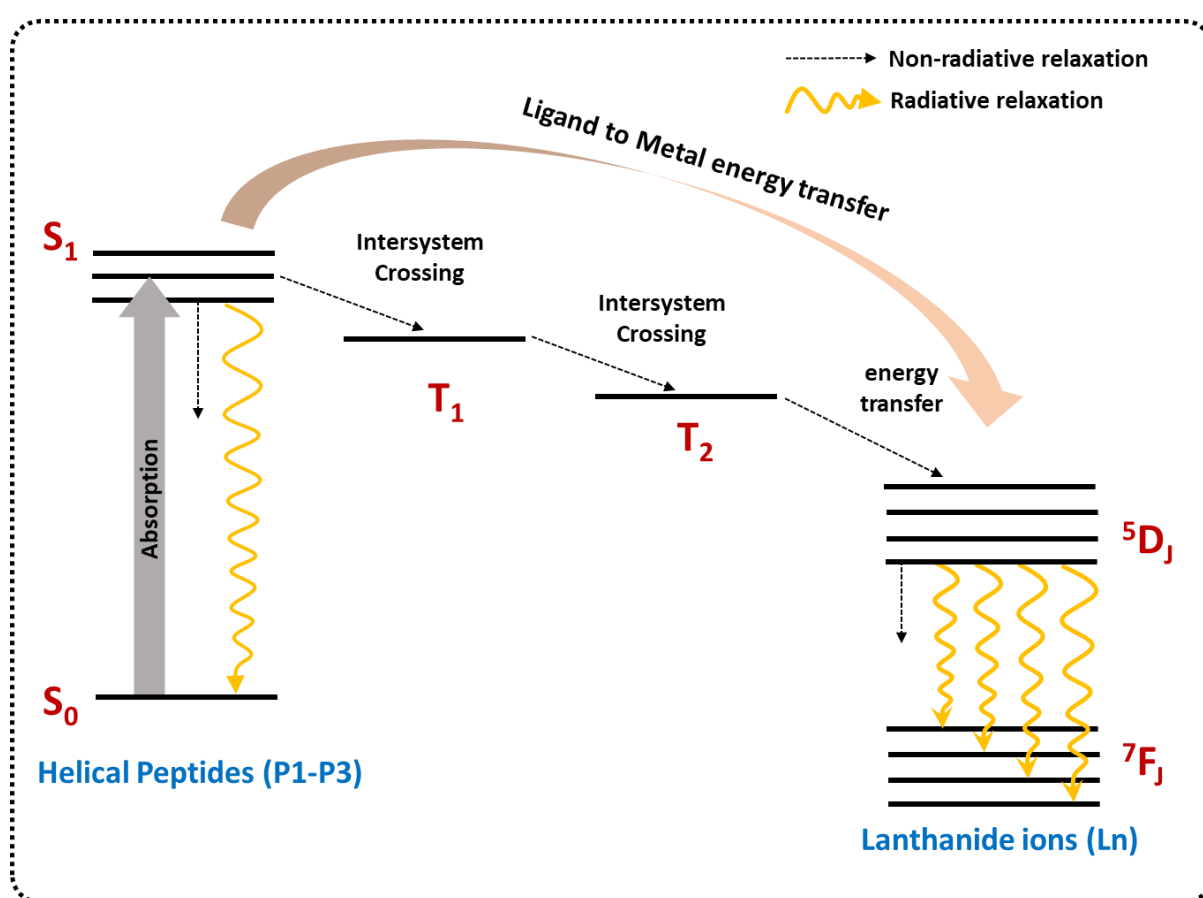


Figure 16: Possible mechanism for the enhanced photoluminescence of lanthanide ions upon incorporation into helical peptides without photosensitizers.

5. Conclusion:

In conclusion, we introduced a noncovalent strategy by incorporating π -stacking Terpyridyl residues, facilitating the assembly of short hybrid helical peptides into crystalline porous

frameworks even in the absence of metal ions. Subsequent coordination with Tb³⁺ and Eu³⁺ ions amplifies the photoluminescence of Tb, showcasing the potential for applications in optoelectronic materials. This innovative approach not only advances our understanding of peptidomimetic materials but also opens avenues for the development of tailored synthetic structures with enhanced functionalities, highlighting the versatility and adaptability of peptide-based frameworks in material science.

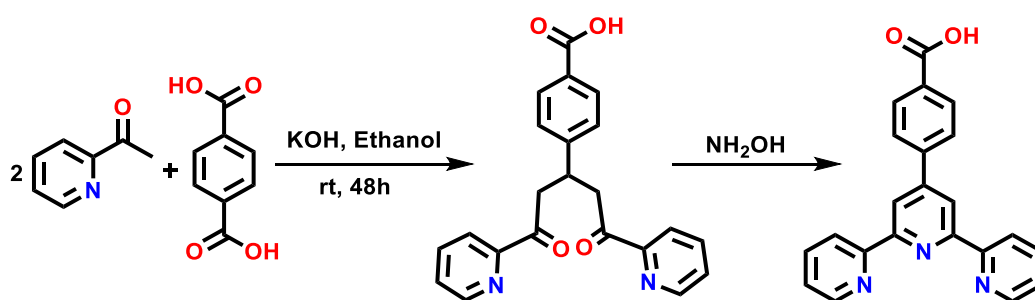
6. Experimental Section:

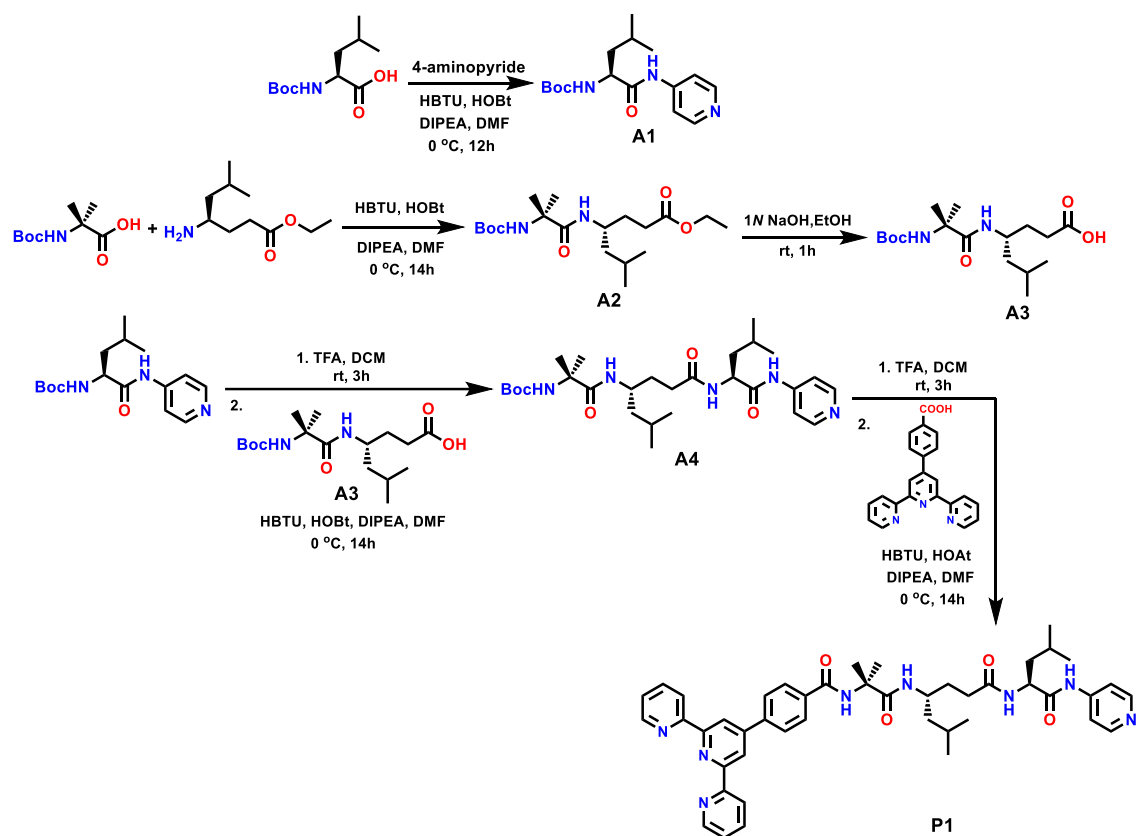
6.1. Materials and Methods:

All the coupling reactions were performed under N₂ conditions. All the amino acids, Boc anhydride, HBTU, HOBt, TbCl₃, EuCl₃, 3-aminopyridine, 4-aminopyridine, Trifluoroacetic acid (TFA), N, N-Diisopropylethylamine (DIPEA), DMF, EtOAc, Hexane, THF, were purchased from different commercial sources. Ethyl acetate and Hexane were distilled before use. Column chromatography was performed on silica gel (100-200 mesh). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and ninhydrin or Iodine staining. ¹H NMR and ¹³C NMR spectra were recorded in deuterated solvents on 400 MHz and 101 MHz NMR machines respectively using the residual solvent signal as the internal standard (CDCl₃). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad doublet (bd), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using MALDI-TOF Instrument. CD spectra were recorded on a CD spectrometer. The X-ray data were collected at low temperatures (150 K) on a Bruker APEX (II) DUO CCD diffractometer using Mo K α (λ = 0.71073 Å) and Cu K α radiation (λ = 1.54178 Å) graphite monochromated radiation.

6.2. General Procedure for the Synthesis of Peptides:

6.2.1. Synthesis of Peptide P1:





Scheme 3: Synthesis of terpyridine acid and short α,γ - hybrid tripeptide **P1**.

2-acetyl pyridine was added to the stirring solution of 4-carboxy benzaldehyde, KOH and NH₄OH in 150 mL ethanol. The reaction mixture was stirred at room temperature whilst open to the air for 48h until the colloid suspension is formed, indicated by the change of brown to yellow color. After that, the solution was adjusted to slightly acidic (pH=5) with the addition of conc. HCl. The light yellow precipitate product was filtered, recrystallized with a mixture of ethanol and methanol, and dried in vacuum to collect the colorless crystal.²⁶

N-Boc protected Aib (15 mmol, 3.26 g) was dissolved in 10 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (16.5 mmol, 6.27 g), HOBT (16.5 mmol, 2.24 g), and DIPEA (45 mmol, 7.88 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of 4-aminopyridine (21 mmol, 1.98 g). The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography to get a white crystalline product **A1** had an overall yield was 87%.

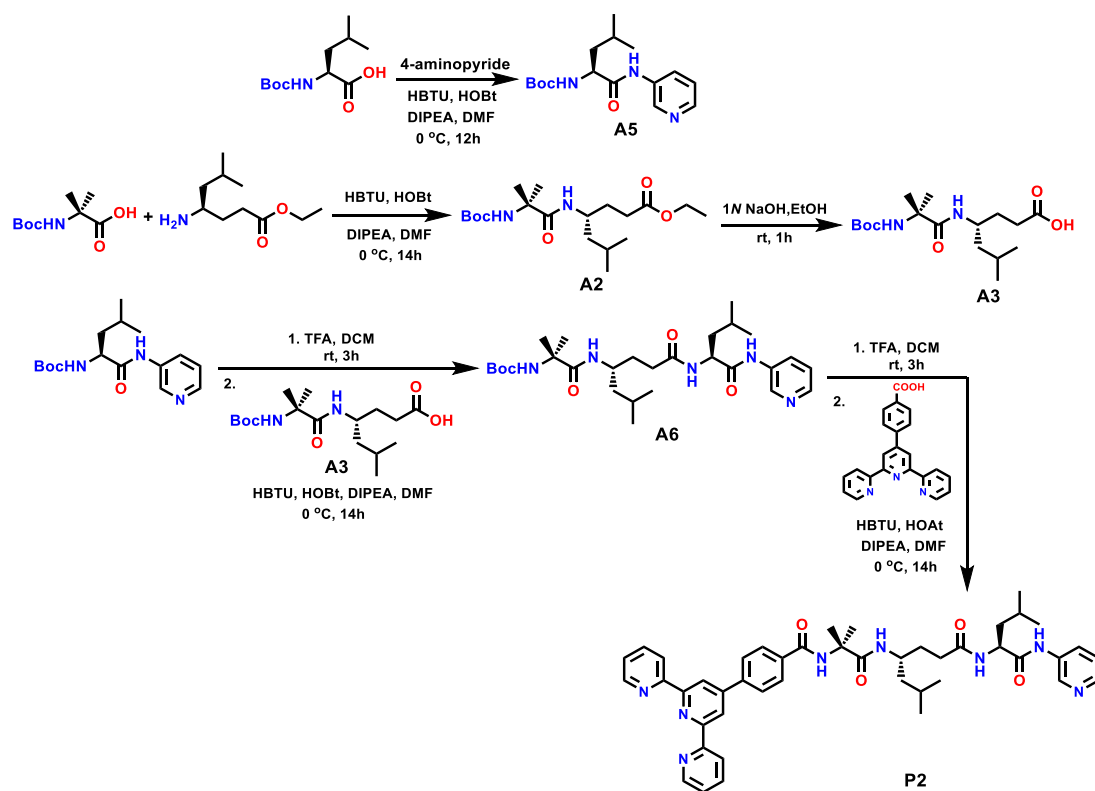
Now, N-Boc protected Aib (14 mmol, 3.04 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (11 mmol, 4.18 g), HOBT (11 mmol, 1.49 g), and DIPEA (30 mmol, 5.25 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected γ -Leu (H₂N- γ -Leu-COOEt) (10 mmol, 2.87 g) in a little amount of DMF and remaining DIPEA (30 mmol, 5.25 mL). The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography to get a white product **A2** had an overall yield was 88%.

The purified product of compound **A2** was dissolved in EtOH in 250 mL RB, 1N NaOH was added to it and the reaction was left for 1h. After completion of the reaction, EtOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product **A3** which was used for further reaction.

Compound **A1** (3.94 mmol, 1.15 g) was subjected to Boc deprotection using 50% TFA in DCM (4 mL TFA in 4 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (8.45 mmol, 1.48 mL) to get the free amine of compound **A1**. Now hybrid dipeptide acid (compound **A3**) (2.8 mmol, 1.01 g) was dissolved in 3 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (3.09 mmol, 1.17 g), HOBT (3.09 mmol, 422 mg), and DIPEA (8.45 mmol, 1.48 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **A1** and the reaction mixture was further stirred overnight at room temperature. The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 2), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography (4% MeOH/DCM) to get a white product **A4** had an overall yield was 82%.

Compound **A4** (0.94 mmol, 500 mg) was subjected to Boc deprotection using 50% TFA in DCM (2 mL TFA in 2 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (3 mmol, 0.5 mL) to get the free amine of compound **A4**. Now Terpyridine acid (1.02 mmol, 360 mg) was dissolved in 2 mL of DMF and the solution was then cooled to 0 °C using an ice bath under N₂ atmosphere. To this, HBTU (1.04 mmol, 393 mg), HOAt (1.04 mmol, 141 mg), and DIPEA (3 mmol, 0.5 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **A4** and the reaction mixture was further stirred overnight at room temperature. The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (6% MeOH/ DCM) to get a white product Peptide **P1** having an overall yield was 45%.

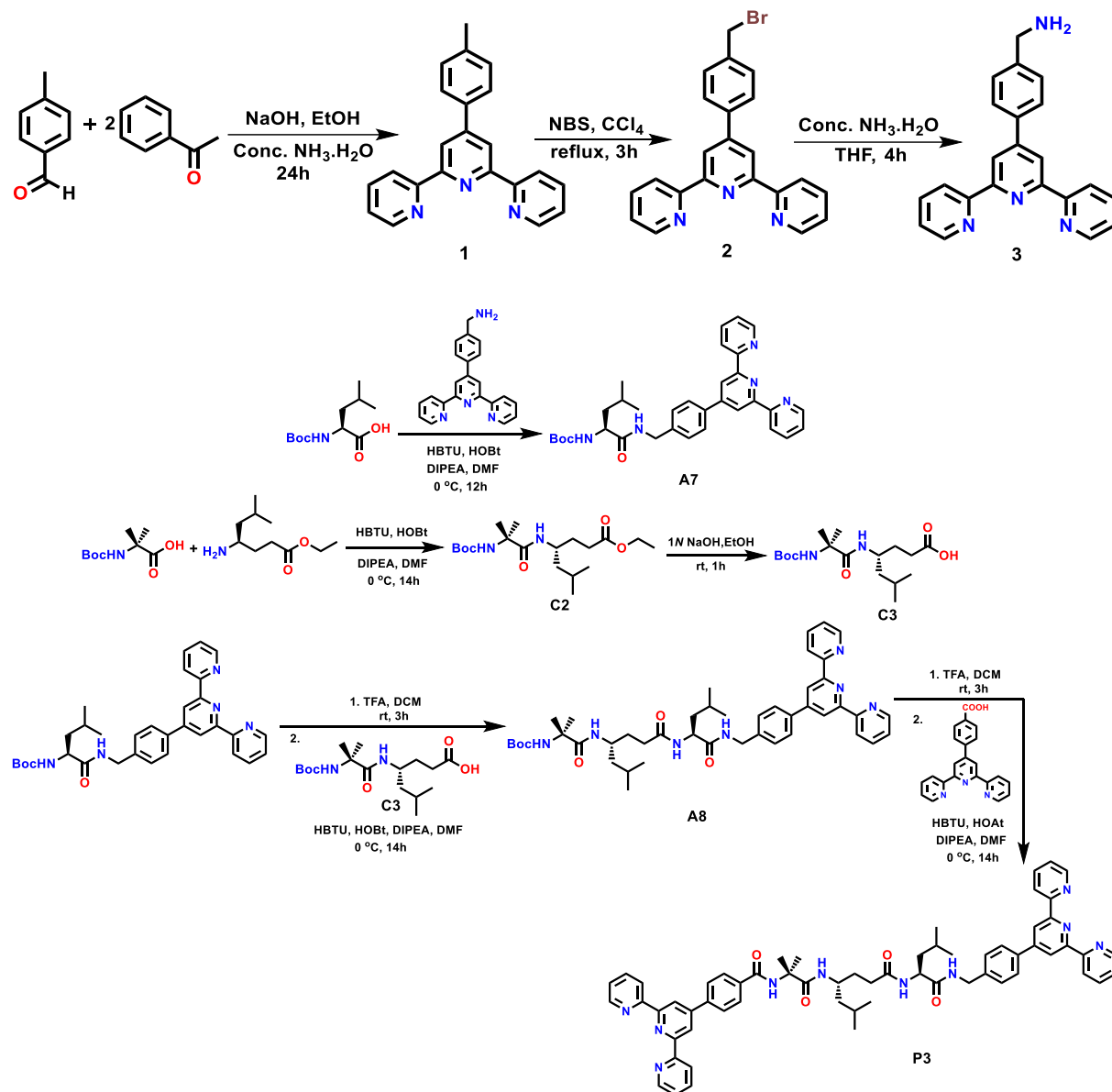
6.2.2. Synthesis of Peptide **P2**:



Scheme 4: Synthesis of short α,γ - hybrid tripeptide **P2**.

The synthesis of **P2** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 42%).

6.2.3. Synthesis of Peptide **P3**:



Scheme 5: Synthesis of terpyridine amine and short α,γ - hybrid tripeptide **P3**.

The synthesis of Terpyridine amine was synthesized using the following protocol²⁷:

2-acetyl pyridine (4.48 mL, 40 mmol) was added into a solution of 4-methyl benzaldehyde (2.35 mL, 20 mmol) in ethanol (100 mL). KOH pellets (3.08 g, 40 mmol) and aq. NH_3 (60 mL, 29.3%) was then added to the solution. The solution was stirred at 34 °C for 24h. The mixture

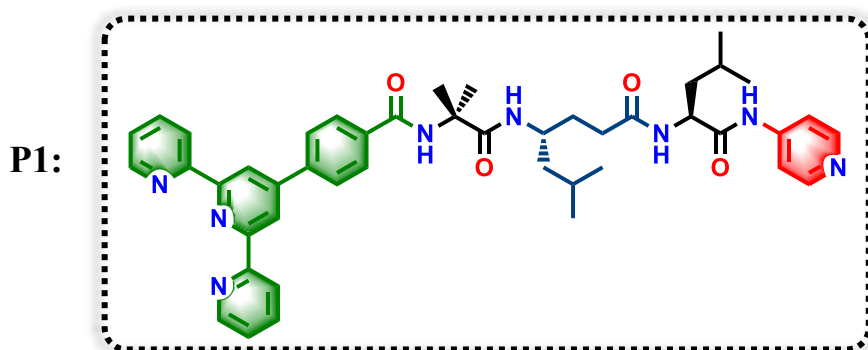
was cooled to 20 °C and then the off-white solid was collected by filtration and washed with ice-cold ethanol (10 mL). Recrystallization from ethanol forms a white crystalline solid **1**.

A mixture of **1** (5.0 g, 15.5 mmol), NBS (3.3 g, 18.5 mmol) and AIBN (0.2 g, 1.2 mmol) in dry CCl₄ (50 mL) was refluxed for 2h. The warm reaction mixture was filtered to remove the succinimide and the solvent was evaporated. The crude product was recrystallized from ethanol to give **2** as a pale yellow solid.

THF (40 mL) and NH₃ (80 mL) were added to a 250 mL round bottom flask. Then the mixture was stirred at 25 °C. **2** (1g, 2.5 mmol) was dissolved in 80 mL of THF and was added in the flask drop by drop within 4h by constant pressure funnel, then the reaction was continued for another 4h. The organic phase was dried over Na₂SO₄. The solvent was evaporated and product **3** was given as a light yellow solid and the crude product need not further purification.

The synthesis of **P3** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 38%).

6.3. Characterisation of Peptides (P1-P3):

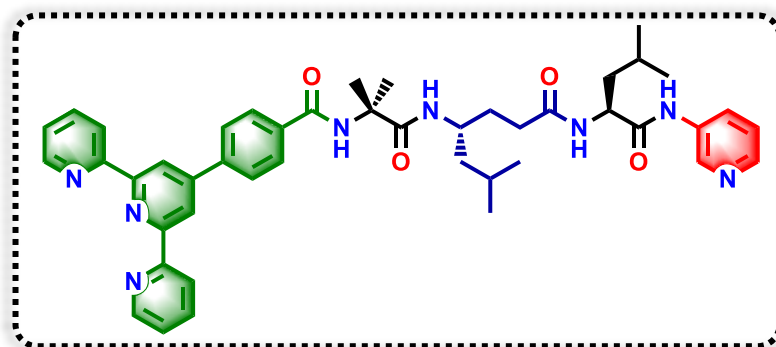


¹H NMR (400 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 8.78 – 8.64 (m, 6H), 8.40 (d, *J* = 6.0 Hz, 2H), 8.00 – 7.84 (m, 6H), 7.79 – 7.70 (m, 2H), 7.43 – 7.34 (m, 2H), 7.19 (d, *J* = 6.0 Hz, 1H), 6.75 (s, 1H), 5.84 (d, *J* = 10.2 Hz, 1H), 4.34 (dt, *J* = 10.7, 5.6 Hz, 1H), 4.04 (dt, *J* = 10.3, 6.0 Hz, 1H), 2.68 – 2.55 (m, 1H), 2.31 – 2.17 (m, 2H), 1.74 (d, *J* = 7.2 Hz, 6H), 1.58 (ddd, *J* = 17.4, 10.5, 4.8 Hz, 2H), 1.44 – 1.35 (m, 2H), 1.34 – 1.27 (m, 3H), 0.88 – 0.73 (m, 12H).

¹³C NMR (101 MHz, CDCl₃) δ 173.80, 173.45, 172.55, 167.19, 164.46, 156.08, 155.73, 153.76, 149.87, 149.01, 148.52, 146.00, 136.83, 127.66, 127.44, 123.91, 121.28, 118.66, 114.32, 77.16, 57.19, 54.63, 50.58, 46.26, 45.51, 40.71, 35.07, 32.13, 31.53, 25.63, 25.07, 24.63, 22.65, 22.10, 21.43.

MALDI TOF/TOF m/z calculated for $C_{45}H_{52}N_8O_4$ $[M+H]^+$ is 769.51 and observed value is 769.73. $[M+Na]^+$ is 791.51 and observed value is 791.72. $[M+K]^+$ is 807.51 and observed value is 807.69.

P2:

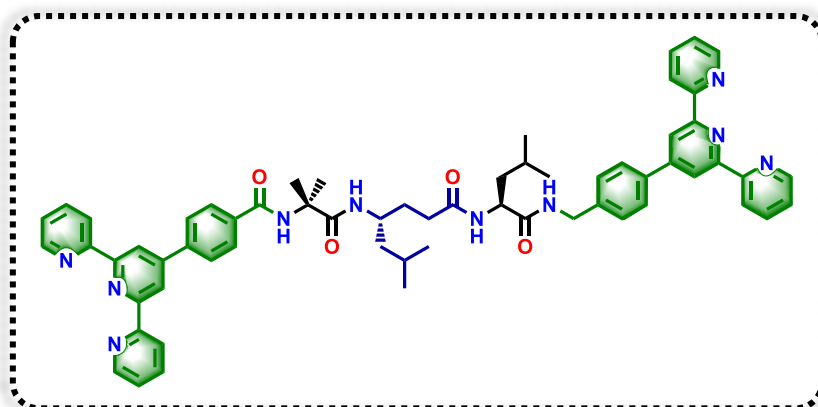


1H NMR (400 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 8.82 (d, J = 2.6 Hz, 1H), 8.76 – 8.63 (m, 6H), 8.33 – 8.20 (m, 2H), 7.96 – 7.81 (m, 6H), 7.37 (ddd, J = 7.6, 4.8, 1.2 Hz, 2H), 7.22 – 7.13 (m, 2H), 6.99 – 6.90 (m, 1H), 5.90 (d, J = 9.9 Hz, 1H), 4.46 – 4.35 (m, 1H), 4.13 – 3.99 (m, 1H), 2.64 (td, J = 13.9, 2.7 Hz, 1H), 2.32 – 2.16 (m, 2H), 1.73 (s, 6H), 1.65 – 1.60 (m, 1H), 1.52 (dt, J = 13.2, 6.8 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.36 (t, J = 7.7 Hz, 1H), 1.30 – 1.24 (m, 3H), 0.85 (dd, J = 15.7, 6.5 Hz, 6H), 0.70 (dd, J = 17.8, 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.21, 173.77, 172.66, 167.49, 156.34, 156.06, 149.32, 148.90, 144.48, 142.59, 142.37, 137.13, 136.00, 133.76, 127.89, 124.20, 123.28, 121.58, 119.00, 57.52, 54.62, 46.48, 45.80, 41.25, 32.36, 31.91, 25.97, 25.81, 25.29, 25.01, 23.09, 22.89, 22.21, 21.68.

MALDI TOF/TOF m/z calculated for $C_{45}H_{52}N_8O_4$ $[M+H]^+$ is 769.51 and observed value is 769.59. $[M+Na]^+$ is 791.51 and observed value is 791.70. $[M+K]^+$ is 807.51 and observed value is 807.65.

P3:



¹H NMR (400 MHz, Chloroform-*d*) δ 8.77 – 8.60 (m, 10H), 8.59 – 8.51 (m, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.99 (s, 3H), 7.86 (tt, J = 7.7, 1.8 Hz, 3H), 7.78 (dt, J = 15.0, 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 1H), 7.43 (dd, J = 7.9, 2.4 Hz, 1H), 7.39 – 7.29 (m, 5H), 7.19 (s, 1H), 7.16 – 7.03 (m, 2H), 5.84 (d, J = 9.3 Hz, 1H), 4.61 (dd, J = 15.0, 6.7 Hz, 1H), 4.54 – 4.43 (m, 1H), 4.27 (dd, J = 14.7, 5.2 Hz, 1H), 3.99 – 3.89 (m, 1H), 2.63 (s, 1H), 2.38 – 2.24 (m, 4H), 2.02 (d, J = 15.2 Hz, 3H), 1.27 (d, J = 12.5 Hz, 6H), 1.18 (t, J = 7.1 Hz, 2H), 0.94 – 0.77 (m, 12H).

MALDI TOF/TOF m/z calculated for C₆₂H₆₄N₁₀O₄ [M+H]⁺ is 1014.51 and observed value is 1014.90 [M+Na]⁺ is 1035.51 and observed value is 1035.88. [M+K]⁺ is 1051.51 and observed value is 1051.85.

6.4. Crystal Structure Information:

6.4.1. Crystal Structure Analysis of Peptide P1:

Crystals were grown by slow evaporation of MeOH in one drop of water solution. A single crystal (0.20 × 0.10 × 0.08) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation (λ =0.71073 Å), ω -scans (2θ = 131.026), for a total of 35768 independent reflections. Space group C 2, a = 17.293(3), b = 16.524(3), c = 18.635(3), α = γ = 90, β = 112.818(9), V = 4908.2(15) Å³, Monoclinic, Z = 4 for chemical formula C₄₅ H₅₂ N₈ O₄, with one molecules in asymmetric unit; ρ calcd = 1.041 gcm⁻³, μ = 0.544 mm⁻¹, $F(000)$ = 1640, the structure was obtained by direct methods using SHELXS-97²⁸. The final R value was 0.1353 (wR_2 = 0.3695) 8476 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 509 variables, S = 1.308.

6.4.2. Crystal Structure Analysis of Peptide P2:

Crystals were grown by slow evaporation of MeOH in one drop of water solution. A single crystal (0.16 × 0.07 × 0.08) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation (λ =0.71073 Å), ω -scans (2θ = 57.244), for a total of 45161 independent reflections. Space group C 2, a = 17.196(5), b = 16.511(5), c = 18.989(6), α = γ = 90, β = 113.738(7), V = 4935(3) Å³, Monoclinic, Z = 4 for chemical formula C₄₅ H₅₂ N₈ O₄, with one molecules in asymmetric unit; ρ calcd = 1.035 gcm⁻³, μ = 0.68 mm⁻¹, $F(000)$ = 1636, the structure was obtained by direct methods using SHELXS-97²⁸. The final R value was 0.2292 (wR_2 = 0.4518) 12086 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 520 variables, S = 1.22.

6.5. ORTEP Diagrams:

6.5.1. ORTEP Diagram of Peptide P1:

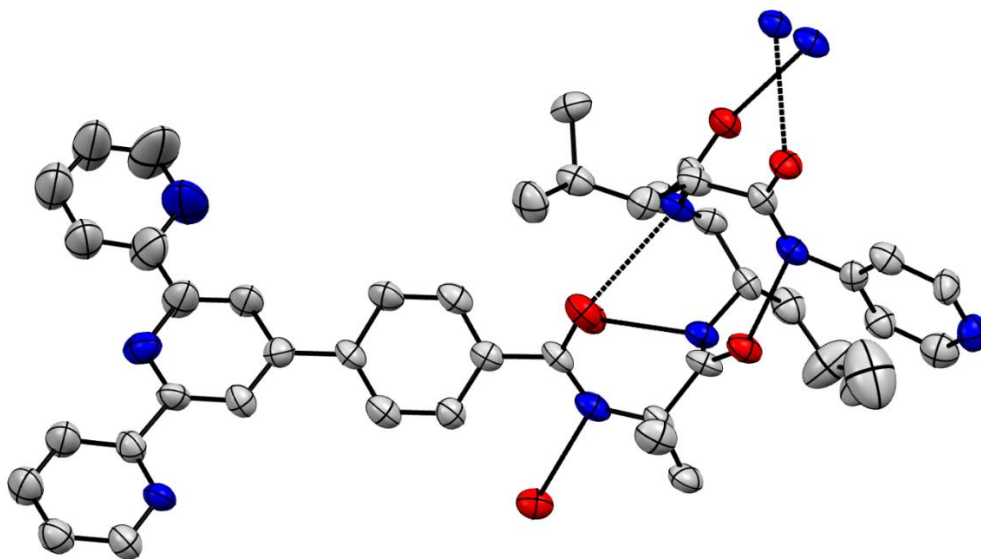


Figure 17: ORTEP diagram of Peptide **P1**. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

6.5.2. ORTEP Diagram of Peptide P2:

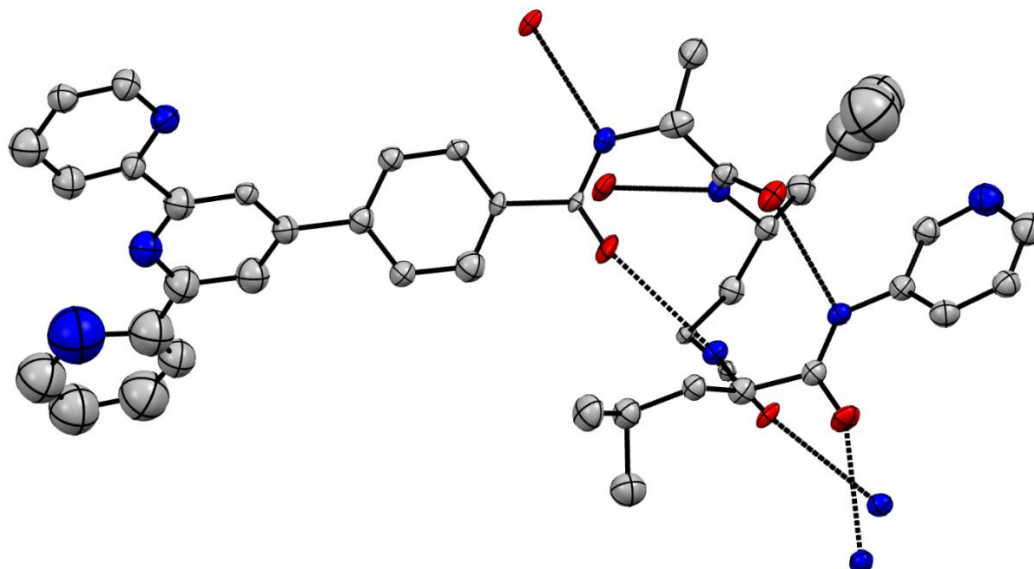


Figure 18: ORTEP diagram of Peptide **P2**. H-bonds are shown in dotted lines. H-atoms are omitted for clarity. Ellipsoids are drawn at 50% probability.

7. References:

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8. ^1H , ^{13}C NMR, and Mass Spectra of Peptides:

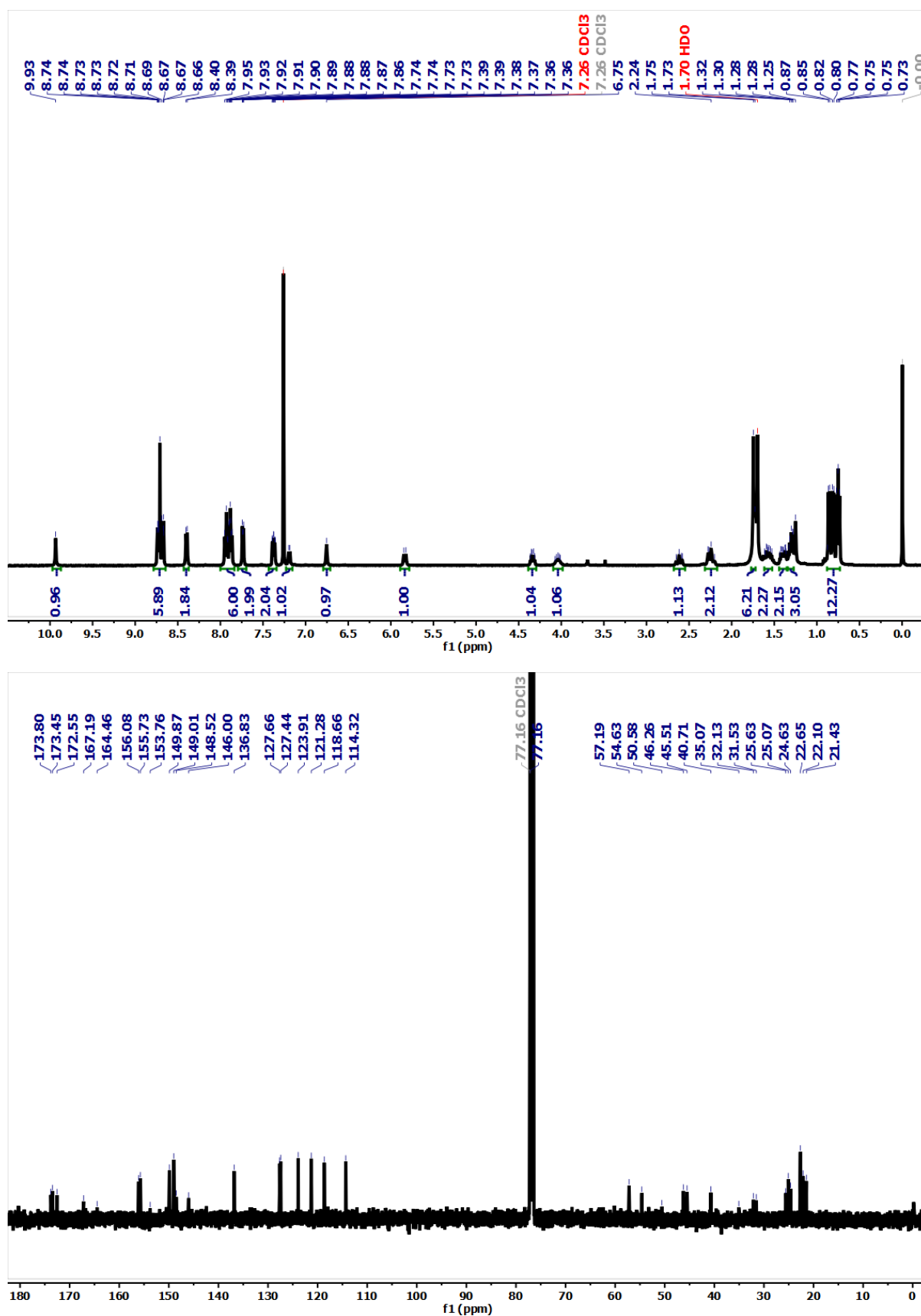


Figure 19: ^1H & ^{13}C NMR spectrum of **P1** in CDCl_3 .

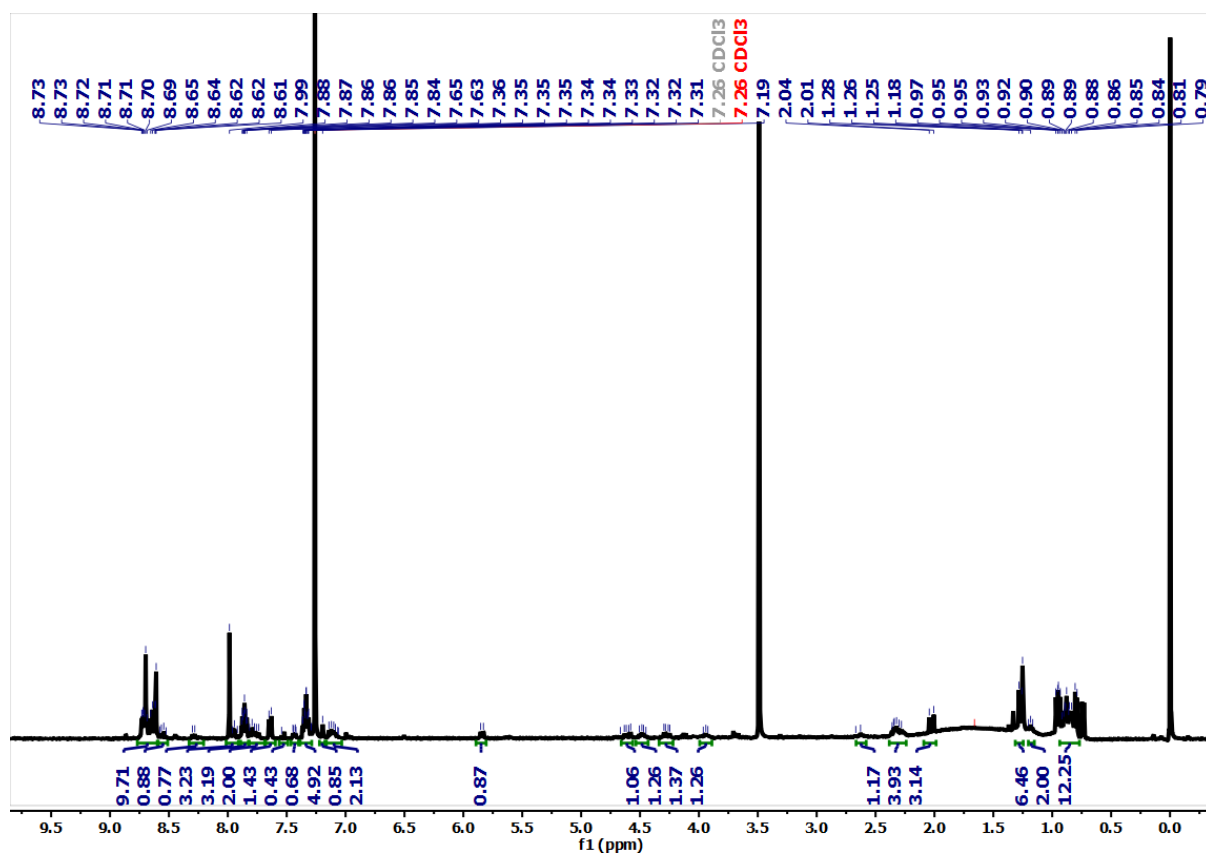


Figure 21: ^1H spectrum of **P3** in CDCl_3 .

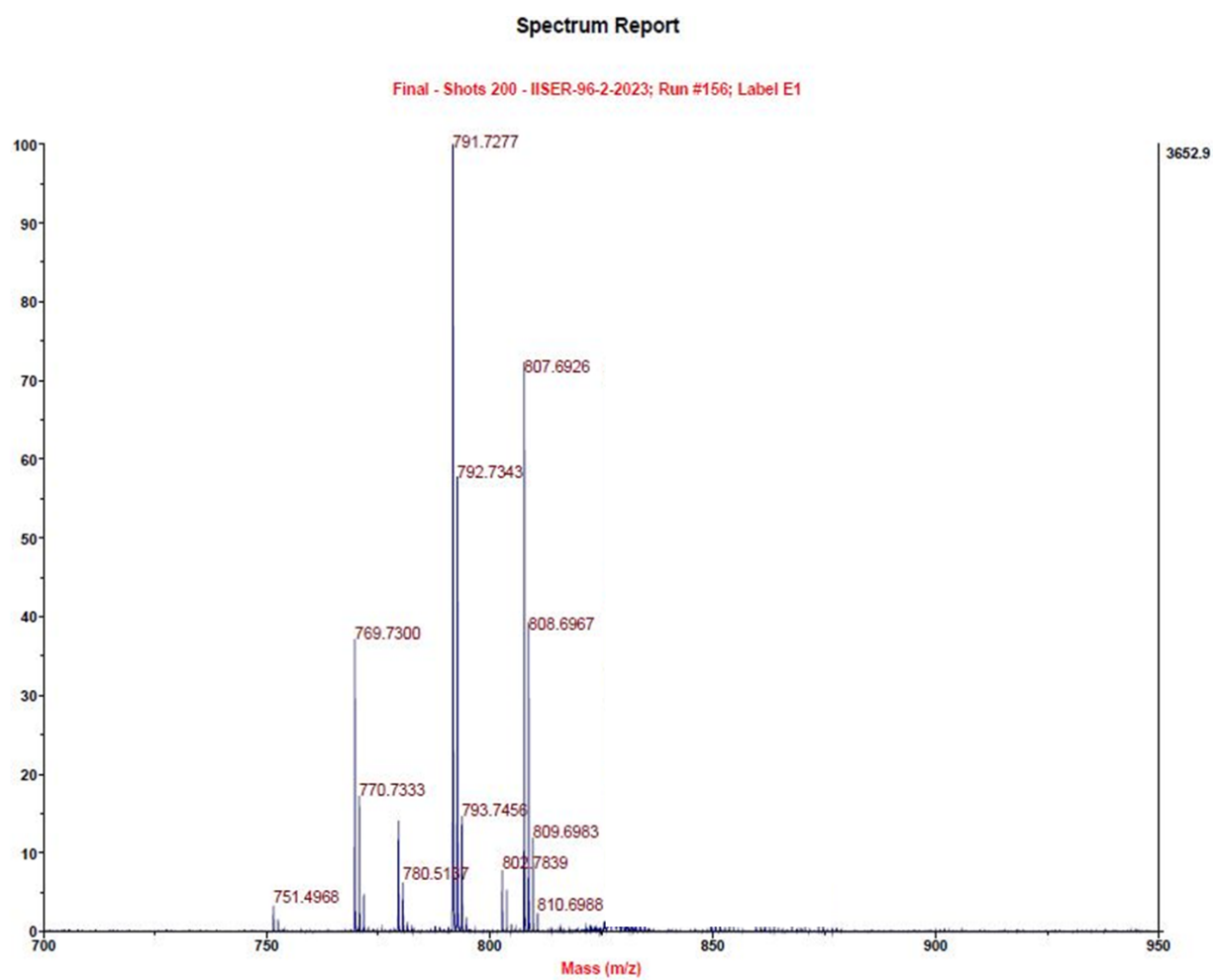


Figure 22: MALDI-TOF/TOF mass spectrum of **P1**.

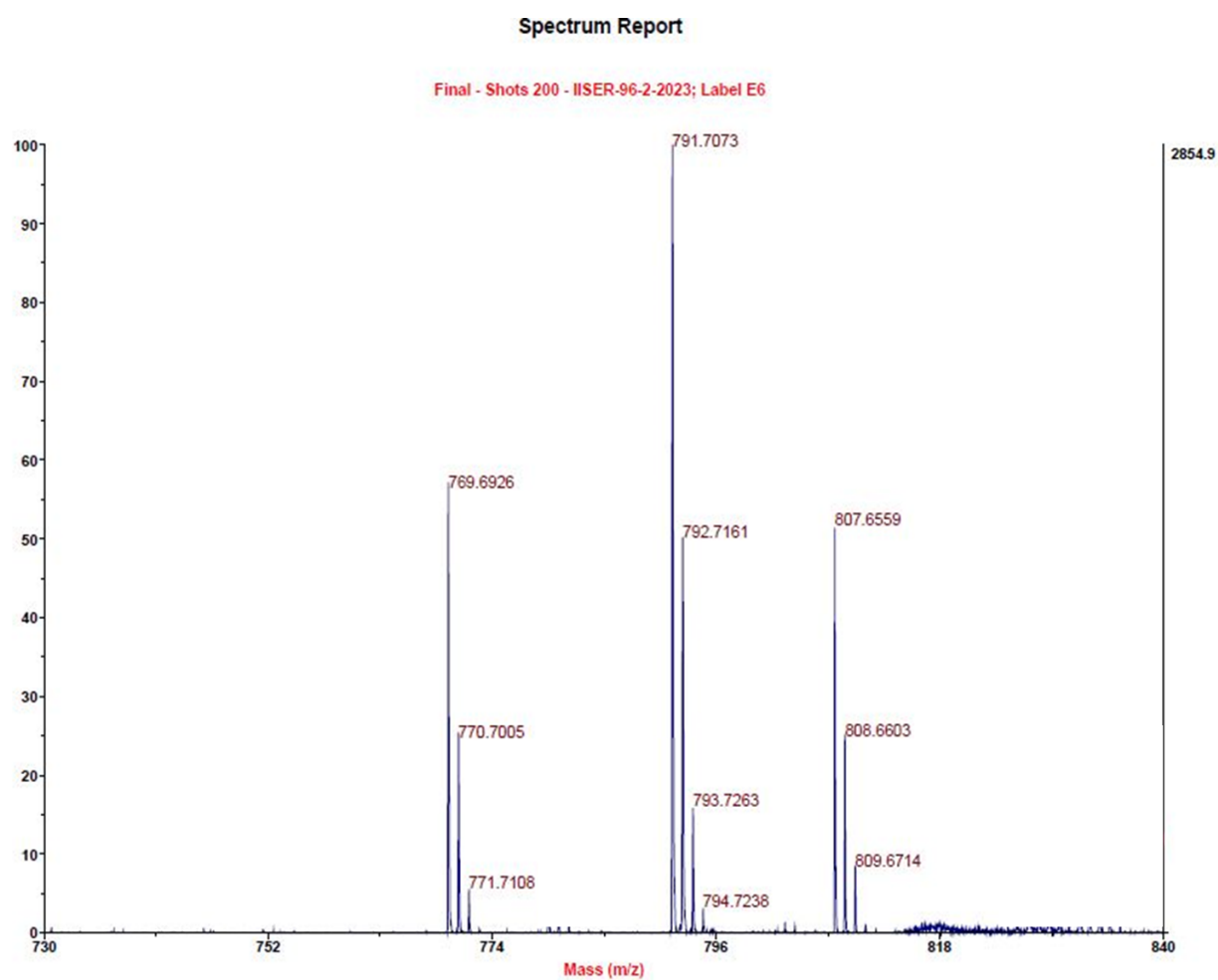


Figure 23: MALDI-TOF/TOF mass spectrum of **P2**.

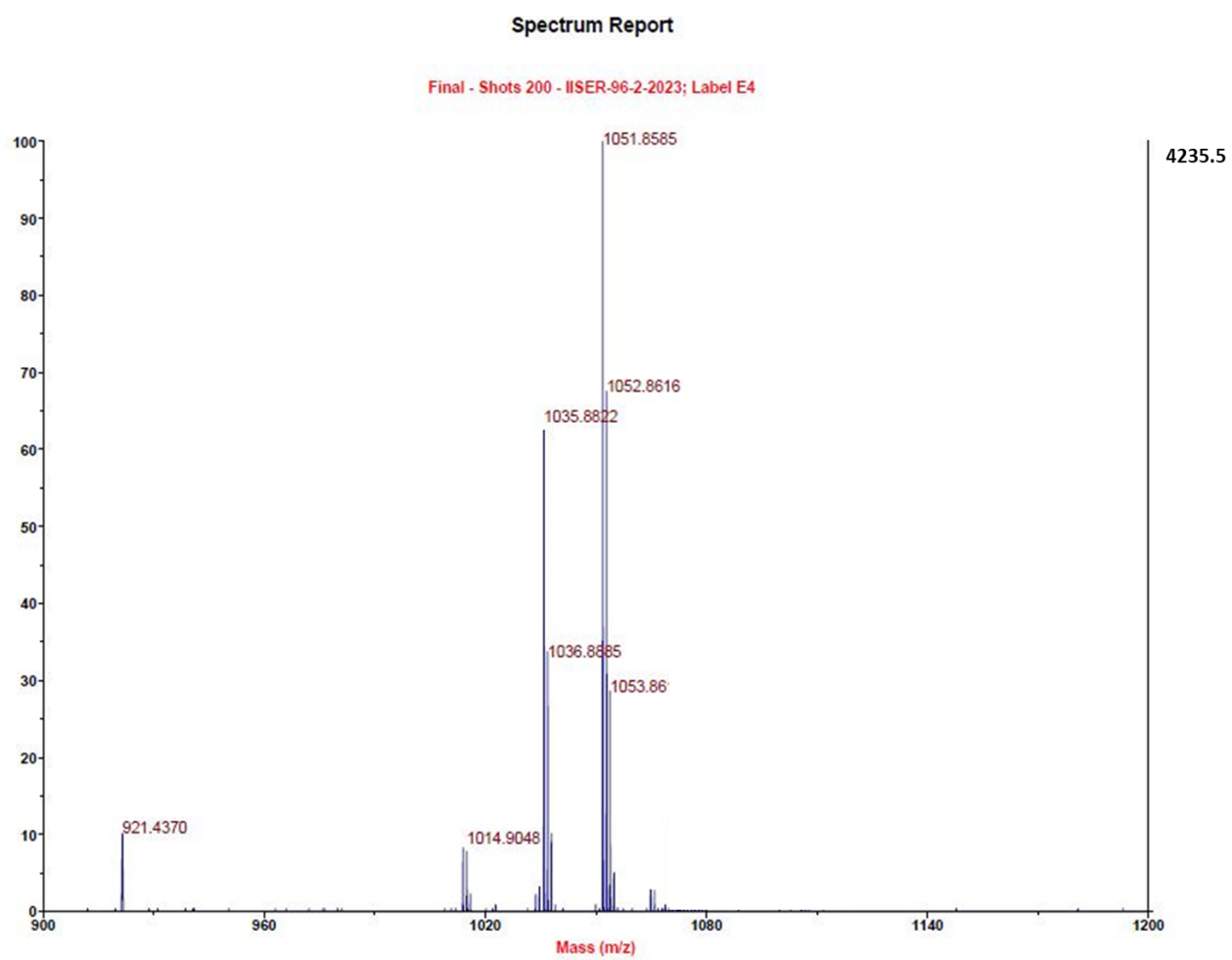


Figure 24: MALDI-TOF/TOF mass spectrum of **P3**.

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Chapter 5

Hybrid Peptides Driven Gelation of Active Methylene Compounds

1. Introduction:

The predominant focal point within the domains of nanoscience and nanotechnology revolves around the deliberate creation of intricately organized self-assembled materials at the nanoscale.¹ The captivating properties exhibited by these nanostructures have garnered significant scientific interest in recent times, primarily attributable to their multifaceted applications across diverse domains, encompassing but not limited to energy technologies, catalytic processes, biomedical advancements, and chemical biology.² Beyond the numerous varieties of nano-assemblies originating from small organic molecules, biopolymers, including lipids, proteins, carbohydrates, and nucleic acids, frequently undergo self-assembly to form intricately organized supramolecular architectures.³ The hierarchical supramolecular structures of these biomacromolecules are stabilized through diverse non-covalent interactions, encompassing hydrogen bonding, salt bridge interactions, van der Waals forces, and aromatic pi-stacking.⁴ This sophisticated interplay of molecular forces contributes to the stability and functionality of the resulting supramolecular assemblies, highlighting the complex and highly regulated nature of these biological nanostructures. In conjunction with biomacromolecules, short peptides have demonstrated a diverse spectrum of supramolecular intricacies, serving as formidable tools for the rational design of various self-assembled biomaterials.⁵ Notably, the identification of a self-assembled peptide nanotube derived from a Phe-Phe dipeptide by Gazit and colleagues has significantly expanded the horizons in the fabrication of soft materials using short peptides.⁶ These dipeptide nanotubes have been systematically investigated as templates for various applications, including the templating of silver nanowires, serving as agents for drug delivery, constituting components in light-harvesting systems, functioning as materials for energy storage, and presenting potential as antimicrobial agents.⁷ Moreover, the intrinsic self-assembling characteristics of peptides have found applicability in disparate domains, spanning from tissue engineering to the intricate realm of nanoelectronics.⁸ Therefore, short peptide-based self-assembled materials represent a growing and dynamically evolving field within contemporary scientific research.

2. Short Peptide-Based Self-Assembly:

The emergence of supramolecular gels, comprising low molecular weight gelators (LMWGs), constitutes a growing area of scientific investigation, driven by the manifold applications of these gels in domains such as drug delivery, tissue engineering, wound healing, oil spill recovery, and waste management.⁹⁻¹⁵ Short peptide-based gels, a noteworthy subset of self-

assembling materials, represent a pivotal focus within this research paradigm. These gels manifest through self-assembly in the presence of diverse organic solvents, including but not limited to dimethyl sulfoxide (DMSO), acetonitrile, acetone, N, N-dimethylformamide, toluene, chlorobenzene, nitrobenzene, methanol, and ethanol as well as several aqueous solvents like different buffers.^{12b, 16} The versatility of peptide-based gels across this spectrum of solvents underscores their potential utility in a broad array of applications and positions them as a significant area of exploration in contemporary scientific inquiry.

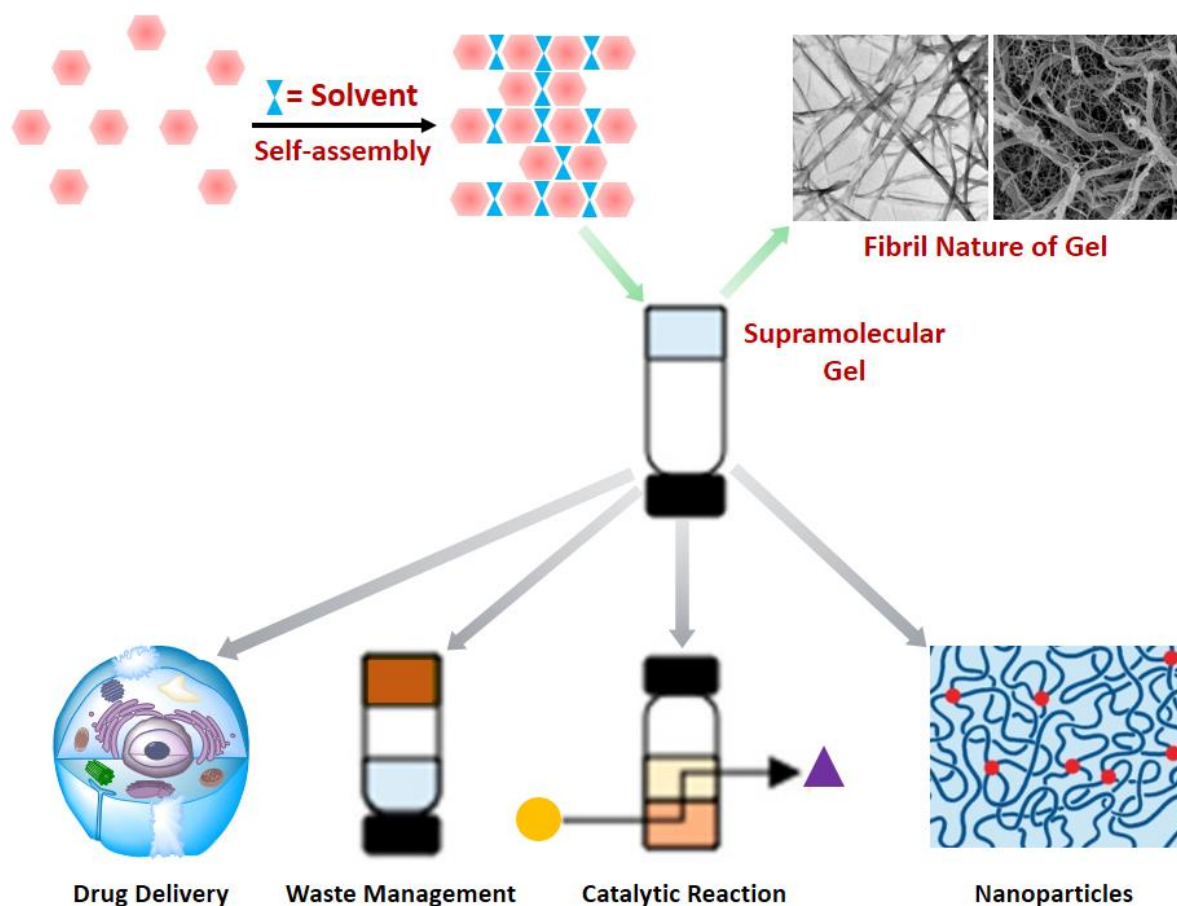


Figure 1: Representation of supramolecular gel formation and its variety of applications.¹⁷

The operational mechanism of peptide-based low molecular weight gelators (LMWGs) relies on a hierarchical self-assembly process, characterized by the following sequential steps: (i) initiation through multiple non-covalent interactions, such as hydrogen bonds, π - π interactions, and van der Waals forces, among molecular-scale building blocks, facilitating their self-assembly into supramolecular polymers known as fibrils; (ii) subsequent assembly of fibrils into nanoscale bundles, denoted as fibres; (iii) further interplay between these fibres results in the establishment of a self-supporting, sample-spanning 'solid-like' network. This intricate and ordered series of events underscores the fundamental principles governing the formation of

peptide-based LMWGs and their transition from molecular-scale interactions to the development of macroscopic gel structures.

3. Various Non-Canonical Amino acids in a Short Peptide Based Assembly:

In conjunction with α -peptides, efforts have been directed towards comprehending the molecular self-assemblies arising from non-canonical amino acids. Notably, investigations into β - and γ -peptides have garnered substantial attention within the literature, with a particular focus on elucidating their propensity for generating diverse self-assembled structures.¹⁸ β - and γ -peptides offer distinct advantages over α -peptides, primarily owing to their enhanced proteolytic stability and the ability to achieve folded structures with shorter sequences.¹⁹ This attribute not only confers greater resilience but also streamlines the design and synthesis process. The supramolecular assemblies of β - and γ -peptides exhibit a broad array of architectural diversity, giving rise to structures such as tapes, fibers, ribbons, polyhedrons, nanotubes, and vesicles.²⁰ Bing Xu and collaborators demonstrated the creation of stable hydrogels through the coupling of β -dipeptides with a naphthyl group at the N-terminal.²¹ Hamley and colleagues investigated the impact of self-assembling properties inherent in the core sequences of amyloid beta A β (16–20), specifically the KLVFF peptide, through the incorporation of γ -amino acids at the N-terminal of the peptide sequences.²² Their findings revealed that the inclusion of two γ -amino acids, in conjunction with the D-amino acid version of the KLVFF peptide, resulted in a noteworthy reduction in cytotoxicity towards A β within a physiologically relevant concentration range. Malhotra and colleagues recently presented a study elucidating the antimicrobial attributes of self-assembled α,γ -hybrid peptides.²³ Beyond the self-assembly dynamics of backbone homologated peptides, investigations have been conducted into Δ Phe– Δ Phe peptides by Chauhan and colleagues,²⁴ as well as side-chain homologated Phe–Phe dipeptides by Gazit and co-workers.²⁵ Moreover, studies have delved into the exploration of β -Cyclobutane-based amino acids by certain researchers²⁶ and Oxatene-based amino acids by others²⁷ for the examination of diverse self-assembled materials.

4. Scope and Aim of the Current Work:

Extensive efforts in the literature have been dedicated to enhancing the biocompatibility of organogels and expanding their applications. Beatriu Escuder and co-workers have documented the incorporation of pyridine and proline moieties at both the N- and C-terminals of peptide-based organogels.²⁸ This strategic modification introduces a novel dimension to organogel functionality, as the basic nature of pyridine nitrogen affords distinctive properties

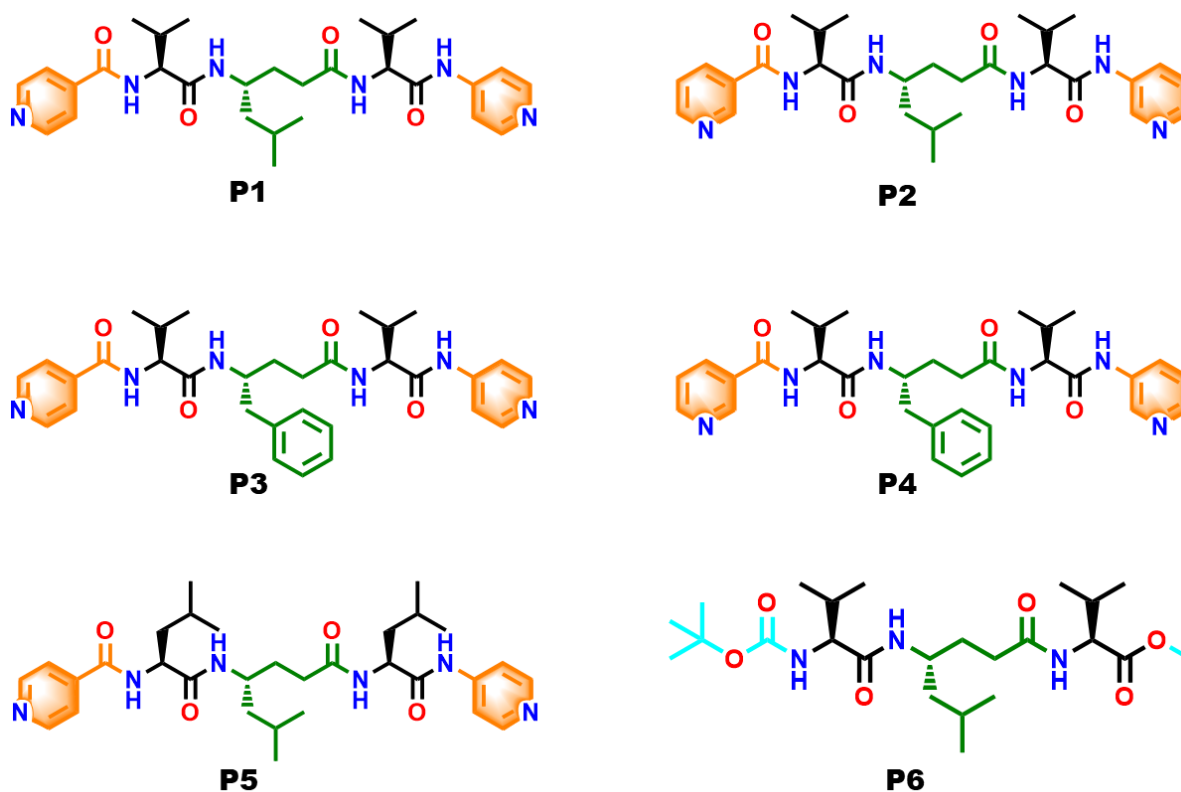
to the resultant materials. Peptides incorporating pyridine functionalities exhibit the capacity to form gels in conjunction with compounds possessing hydroxyl groups and iodide atoms, facilitated by non-covalent hydrogen bonding interactions. On the other hand, a proline-based peptide gelator shows organocatalysis reactions.²⁹ The research endeavors led by Shinkai, Das, and Kato have extensively investigated the gelation properties within organic and aqueous solvents utilizing gelators containing pyridine and N-(4-Pyridyl)isonicotinamide moieties.³⁰ The pyridine unit is inherently compelling in this context for several reasons. Firstly, its acid-base behavior offers potential for the development of pH-responsive hydrogels.³¹ Secondly, the donor properties of the pyridine nitrogen atom may be leveraged for multipoint molecular recognition involving hydrogen-bond donors or for the coordination of transition metals, presenting opportunities in catalytic applications.³²⁻³³ In a recent investigation, our research group disclosed the formation of peptide-based metallogels in the presence of metal salts, specifically AgBF₄, AgPF₆, and CuCl₂, within ethanol under varying concentrations of the respective metal salts. Characterization through FE-SEM and HR-TEM unveiled a distinctive twisted helical morphology within these peptide-metallogels. This observed morphology was further substantiated through single-crystal analysis conducted under gel-state conditions.³⁴ Presently, our research endeavors focus on the design and synthesis of peptide-based functional organogelators incorporating pyridyl moieties at both the C- and N- terminal ends. These entities are designed to facilitate the formation of a supramolecular gel when exposed to active methylene solvents, leveraging donor-acceptor hydrogen bonding interactions for the establishment of the gel matrix.

5. Results and Discussion:

5.1. Design and Synthesis of Peptides:

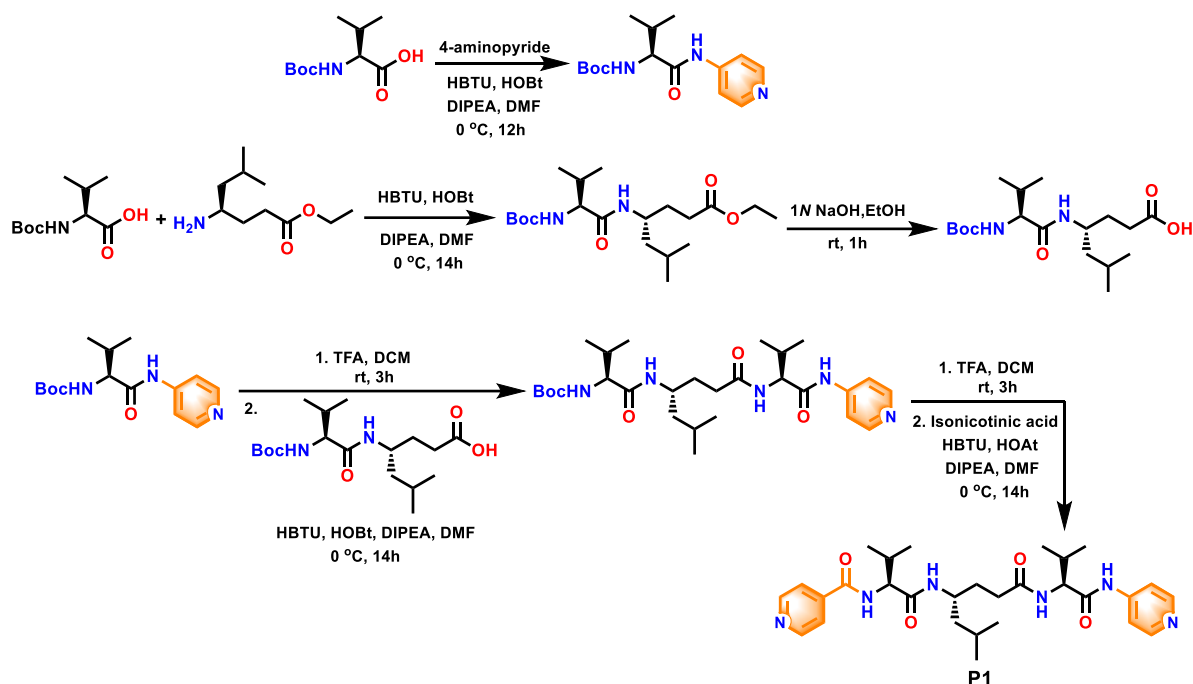
In the course of our investigative efforts towards the development of innovative peptide-based Gelators, and with the aim of comprehending the influence of amino acid residues within short tripeptide sequences, we have strategically designed six hybrid tripeptides. These peptides incorporate 4-pyridyl and 3-pyridyl groups at the C- and N- termini, respectively, as outlined in Scheme 1. The initial four peptides in our design (**P1-P4**) feature β -sheet-promoting, beta-branched amino acid Val at the terminal positions, with a helix-promoting γ -amino acid positioned in the middle of the peptide sequence. In the case of peptide **P5**, an arrangement of exclusively helix-promoting amino acids is introduced throughout the sequence. Conversely,

in the design of peptide **P6**, the 4-pyridyl groups at both C- and N- termini are replaced with Boc- and methyl ester-protecting groups, respectively.



Scheme 1: Sequence of short α,γ -hybrid tripeptides **P1-P6**.

The synthesis of each tripeptide was conducted using a conventional solution-phase strategy, involving Boc-deprotection and coupling methodologies. The synthetic procedure is detailed in Scheme 2. Tripeptides, **P1-P6**, were synthesized through solution-phase techniques and purified via column chromatography. The outlined procedures in Scheme 2 yielded the desired products with an overall yield ranging from 75% to 85%.



Scheme 2: Synthesis of short α,γ -hybrid tripeptide **P1**.

5.2. Crystal Structures Analysis of Peptide **P1**, **P2**, **P3**, **P5**, and **P6**:

In order to gain unambiguous structural insights into the peptides, we opted for single-crystal X-ray diffraction studies. The short hybrid peptides, namely **P1**, **P2**, **P3**, **P5**, and **P6**, were subjected to crystallization using diverse solvent combinations. Single crystals were successfully obtained through the gradual evaporation of peptide solutions in various solvent systems, including MeOH/H₂O, CHCl₃/n-heptane, and nitromethane. The crystal structures of these peptides are shown in Figure 2.³⁴ The examination of X-ray crystal structures elucidated that peptides **P1**, **P2**, **P3**, and **P5** adopted a right-handed 12-helix conformation within the single crystals. Notably, these tripeptides manifested helical conformations despite the absence of steric constraints posed by helix-favoring residues. It is noteworthy that, although β -branched Val residues are recognized for their propensity to favour β -sheet formation in proteins, tripeptides **P1** and **P2**, each containing two Val residues, exhibited a preference for helical conformations. Significantly, the incorporation of a γ -residue, characterized by a flexible -CH₂-CH₂- backbone, at the central position of a tripeptide dictates the conformational preference towards a helical arrangement, even in the concurrent presence of two β -sheet promoting residues.³⁵ The helical structures are stabilized by two consecutive 12-membered intramolecular H-bonds between CO (*i*) and NH (*i*+3) residues. The torsion angle calculation also revealed the formation of a stable C₁₂-helix in the crystal structure.

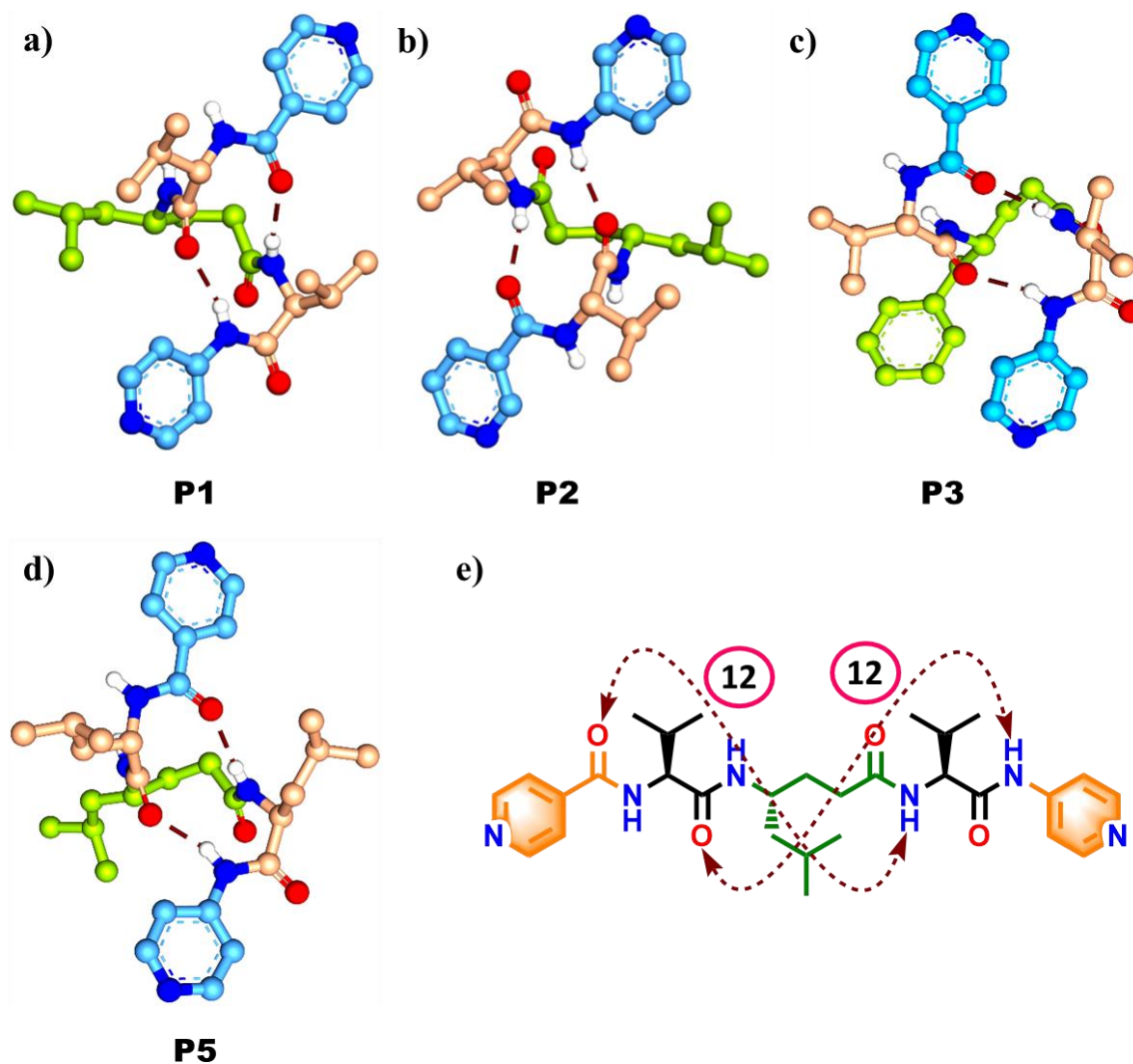


Figure 2: Crystal structure of a) **P1**, b) **P2**, c) **P3**, and d) **P5**. e) Hydrogen-bonding patterns of 12-helix are shown here.

Again crystal structure analysis unveiled the adoption of a sheet structure by peptide **P6** within single crystals in nitromethane. The examination of crystal packing further elucidated that peptide **P6** engages in the formation of a parallel β -sheet through intermolecular hydrogen bonding between two distinct stands, as shown in Figure 3.

Table 1: Formation of gel in active methylene solvents.

Peptide	Nitromethane	Acetyl Acetone	DEM	Acetonitrile	EAA	Diisopropyl malonate	DCM	MAA
P1	Gel	Sol	Gel	Sol	Sol	Gel	Sol	Sol
P2	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
P3	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
P4	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
P5	Sol	Sol	Sol	Sol	Sol	Sol	Sol	Sol
P6	Sol	Sol	Sol	Sol	Sol	Sol	Sol	Sol

5.3.1. Active Methylene Organogel Formation with Peptide P1:

To elucidate the response of peptide **P1** to organic solvents, a comprehensive investigation into its gelation behavior was undertaken across a spectrum of active methylene solvents, as previously mentioned. Subsequently, 10 mg of peptide **P1** was individually introduced into discrete glass vials, each containing 1 mL of the respective solvent. The ensuing mixture underwent controlled heating to induce solubility, followed by a sonication period lasting 4-5 minutes. Remarkably, the prompt formation of a robust gel was discerned, which was confirmed by the vial inversion method, as shown in Figure 4.

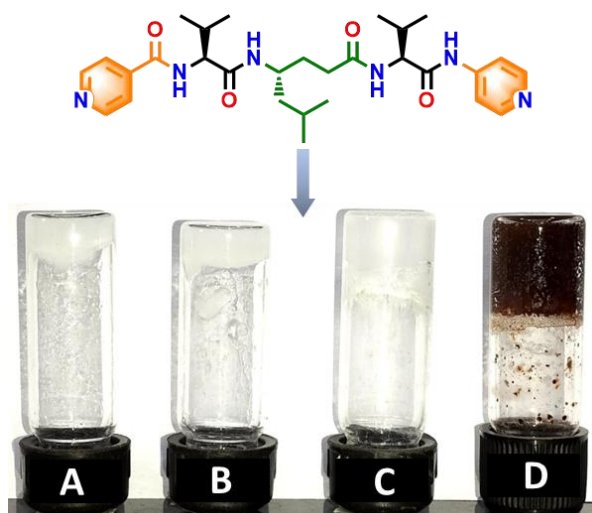


Figure 4: Formation of organogel from peptide **P1** in the presence of different active methylene solvents (A) nitromethane, (B) dethyl malonate, (C) diisopropyl Malonate, (D) dicyanomalonate.

5.3.2. Active Methylene Organogel formation with Peptide P2:

The gelation investigation involving peptide **P2** within an active methylene solvent was executed following the previously outlined procedure employed for peptide **P1**, as illustrated in Figure 5.

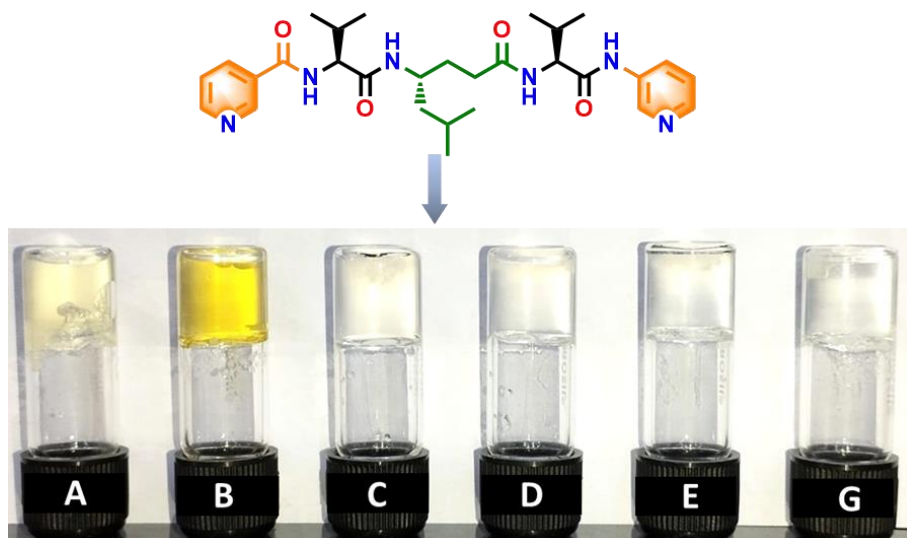


Figure 5: Formation of organogel from peptide **P2** in the presence of different active methylene solvents (A) nitromethane, (B) acetyl acetone, (C) ethyl acetoacetate, (D) diethyl malonate, (E) methyl acetoacetate, (F) acetonitrile.

5.3.3. Active Methylene Organogel formation with Peptide P3:

The gelation examination for peptide **P3** in an active methylene solvent adhered to the established protocol employed for peptide **P1**, as depicted in Figure 6.

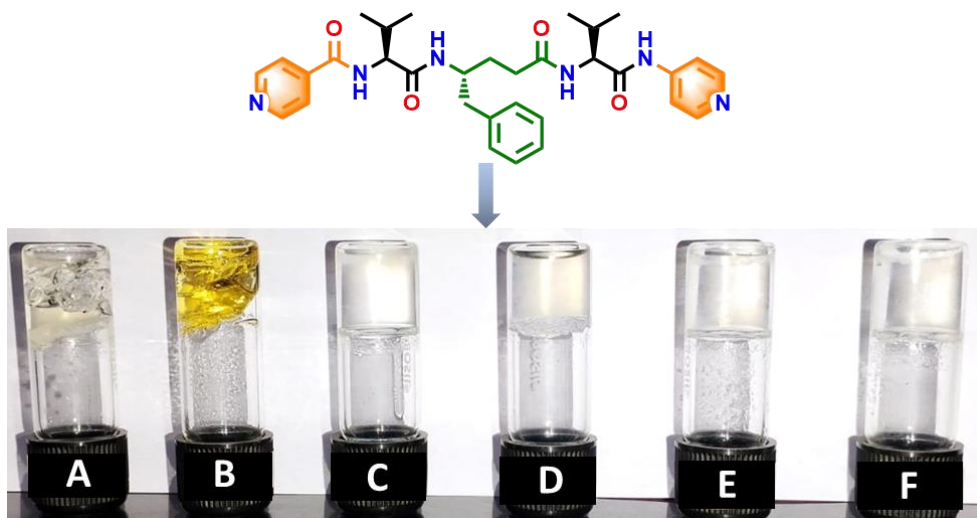


Figure 6: Formation of organogel from peptide **P3** in the presence of different active methylene solvents (A) nitromethane, (B) acetyl acetone, (C) ethyl acetoacetate, (D) diethyl malonate, (E) diisopropyl malonate, (F) acetonitrile.

5.3.4. Active Methylene Organogel formation with Peptide P4:

The gelation investigation for peptide **P4** in an active methylene solvent was conducted in accordance with the established protocol previously employed for peptide **P1**, as shown in Figure 7.

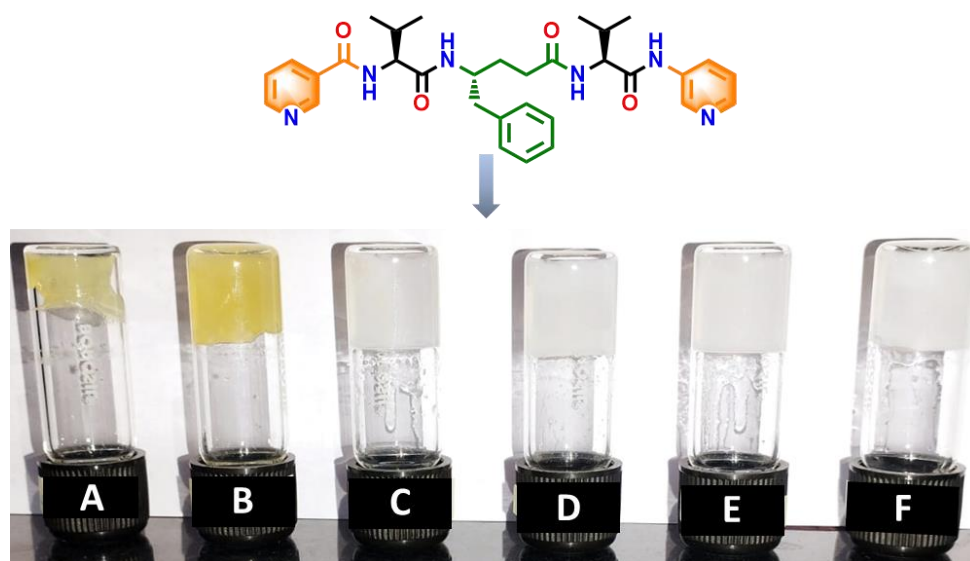


Figure 7: Formation of organogel from peptide **P4** in the presence of different active methylene solvents (A) nitromethane, (B) acetyl acetone, (C) diethyl malonate, (D) acetonitrile, (E) ethyl acetoacetate, (F) diisopropyl malonate.

5.3.5. Active Methylene Organogel formation with Peptide P5:

Subsequent to the substitution of the β -sheet promoting valine with helix-promoting leucine within our peptide sequence **P5**, an investigation into its gelation behavior in the presence of active methylene solvents was undertaken. In this study, 10 mg of peptide **P5** was introduced into separate glass vials, each containing 1 mL of the respective solvent. The resulting mixture underwent controlled heating for solubility and subsequent sonication for 4-5 minutes. Remarkably, no gel formation was observed even after an extended period of time, which was confirmed by the vial inversion method, as shown in Figure 8.

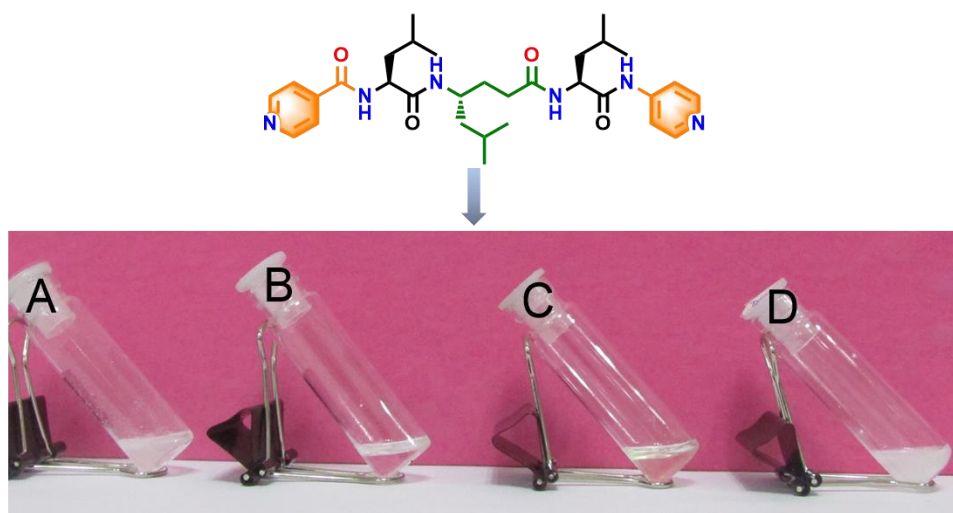


Figure 8: Examine gelation studies of peptide **P5** in the presence of different active methylene solvents (A) nitromethane, (B) acetonitrile, (C) acetyl acetone, (D) diethyl malonate.

5.3.6. Active Methylene Organogel formation with Peptide **P6**:

An analogous investigation was conducted with peptide **P6**, wherein the C- and N-terminal pyridyl groups were replaced with Boc- and methyl ester-protecting groups, respectively, in the presence of active methylene solvent. In this experimental paradigm, 10 mg of peptide **P6** was introduced into distinct glass vials, each containing 1 mL of the respective solvent. The resulting mixture underwent controlled heating for solubility, followed by sonication for 4-5 minutes. Intriguingly, no discernible organogel formation was observed even after an extended duration, as verified through the vial inversion method, as shown in Figure 9.

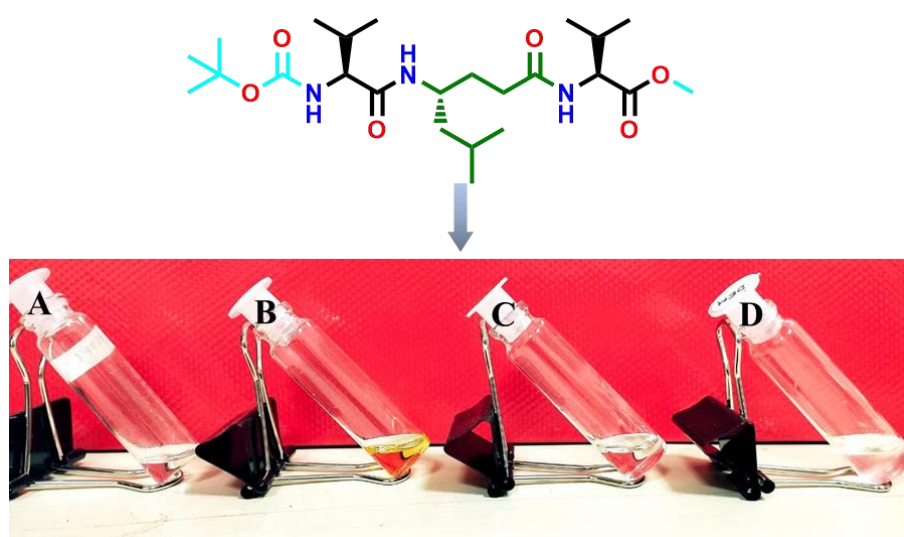


Figure 9: Examine gelation studies of peptide **P6** in different active methylene solvents (A) nitromethane, (B) acetyl acetone, (C) ethyl acetoacetate, (D) diethyl malonate.

5.4. Morphology analysis of Peptide Organogel:

To elucidate the supramolecular assembly of peptide organogels formed by peptides **P1** to **P4** in the presence of active methylene solvent, a comprehensive analysis employing FE-SEM, HR-TEM, and AFM was conducted. Peptides **P5** and **P6**, being non-gelators in the presence of active methylene solvent, were excluded from the morphological investigation. FE-SEM analysis revealed a distinctive fibrillar sheet morphology for the **P1** organogel. This observation was corroborated by HR-TEM, as shown in Figures 10 and 11. Furthermore, AFM images of the **P1** organogel showcased the elongated morphology of the fibrils, as shown in Figure 12. The **P2** organogel exhibited a remarkable fibrillar network, as evidenced by FE-SEM and HR-TEM analyses, further confirmed by the elongated morphology of fibrils observed in AFM images shown in Figures 13-15. Peptides **P3** and **P4** organogels exhibited a densely packed fibril network compared to **P1** and **P2** organogels, as confirmed by FE-SEM and HR-TEM analyses depicted in Figure 16-20. This consistent observation was reinforced by AFM images illustrating an extended fibril morphology shown in Figures 18 and 21.

5.4.1. Morphology analysis of P1 Organogel:

5.4.1.1. FE-SEM images of P1 Organogel:

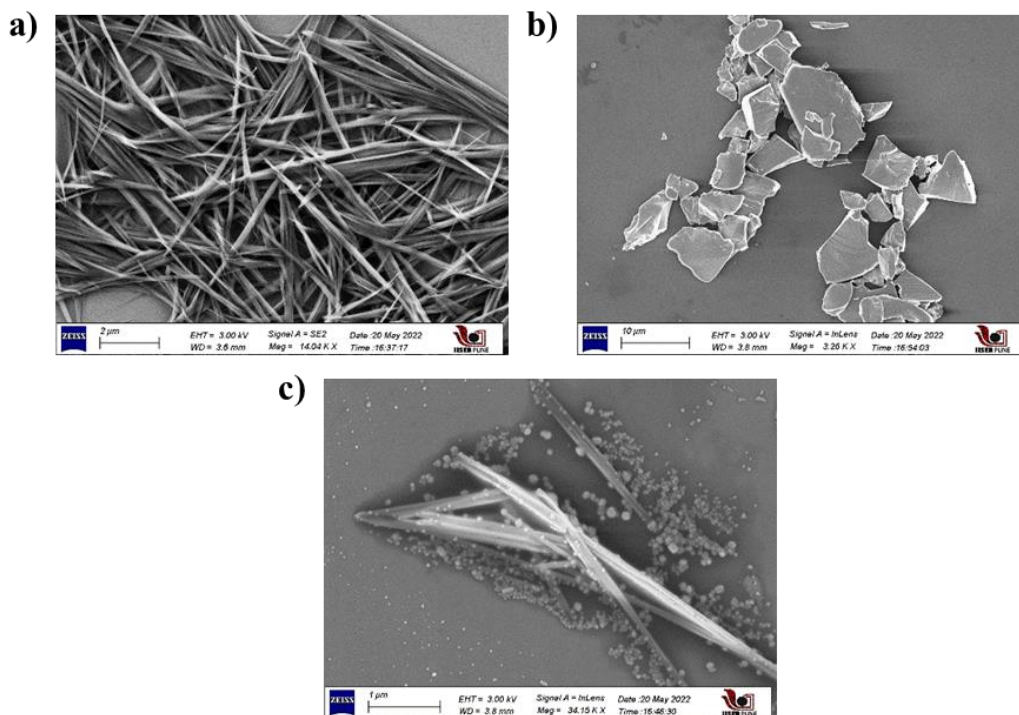


Figure 10: FE-SEM images of peptide **P1** organogel in the presence of different active methylene solvents a) diethyl malonate, b) dicyano malonate, c) diisopropyl malonate.

5.4.1.2. HR-TEM images of P1 organogel:

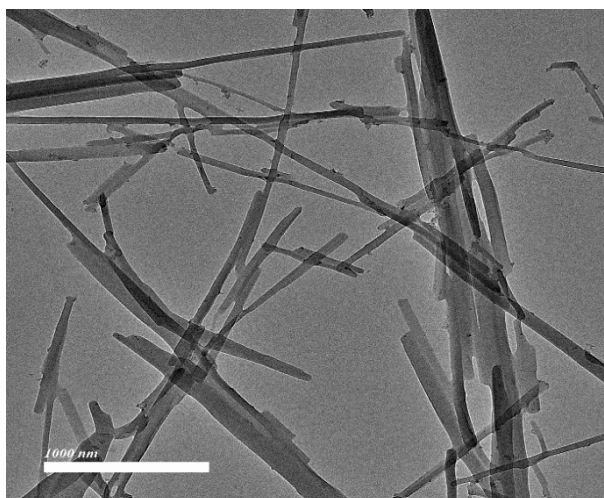


Figure 11: HR-TEM images of peptide **P1** organogel.

5.4.1.3. AFM analysis of P1 organogel:

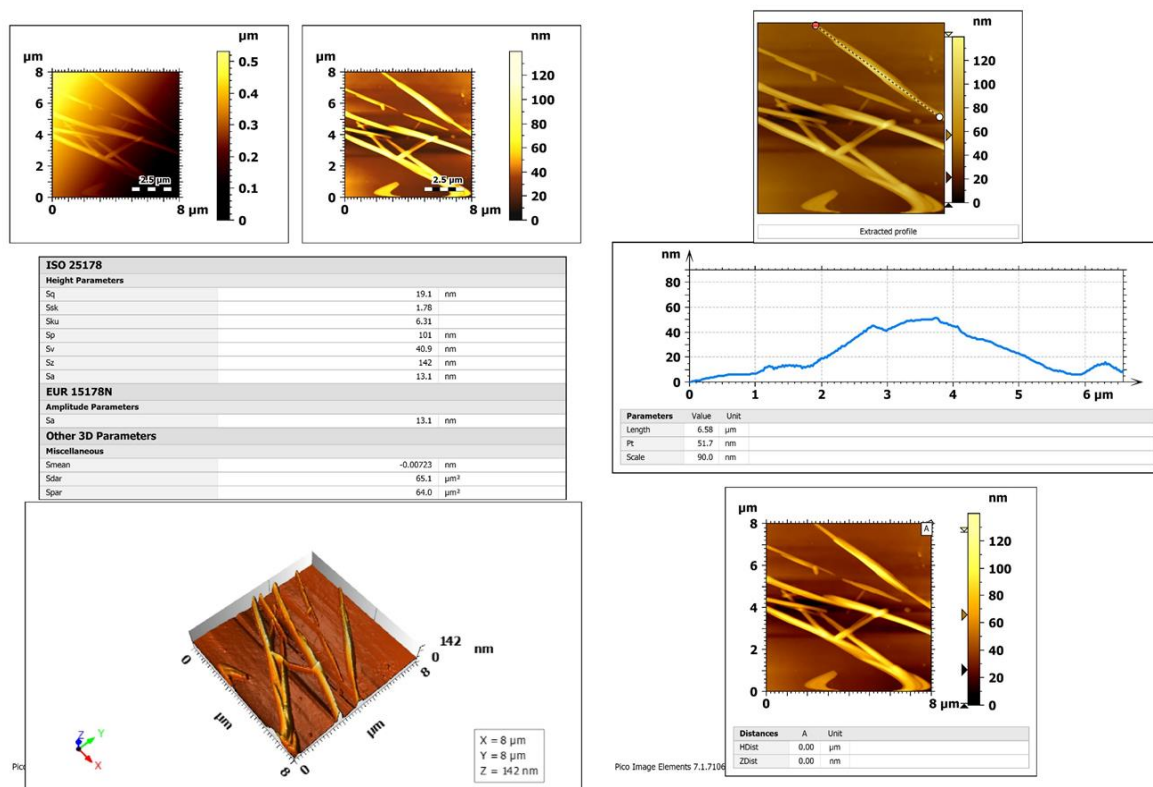


Figure 12: AFM images of peptide **P1** organogel in diethyl malonate showed the fibrils.

5.4.2. Morphology analysis of P2 organogel:

5.4.2.1. FE-SEM images of P2 organogel:

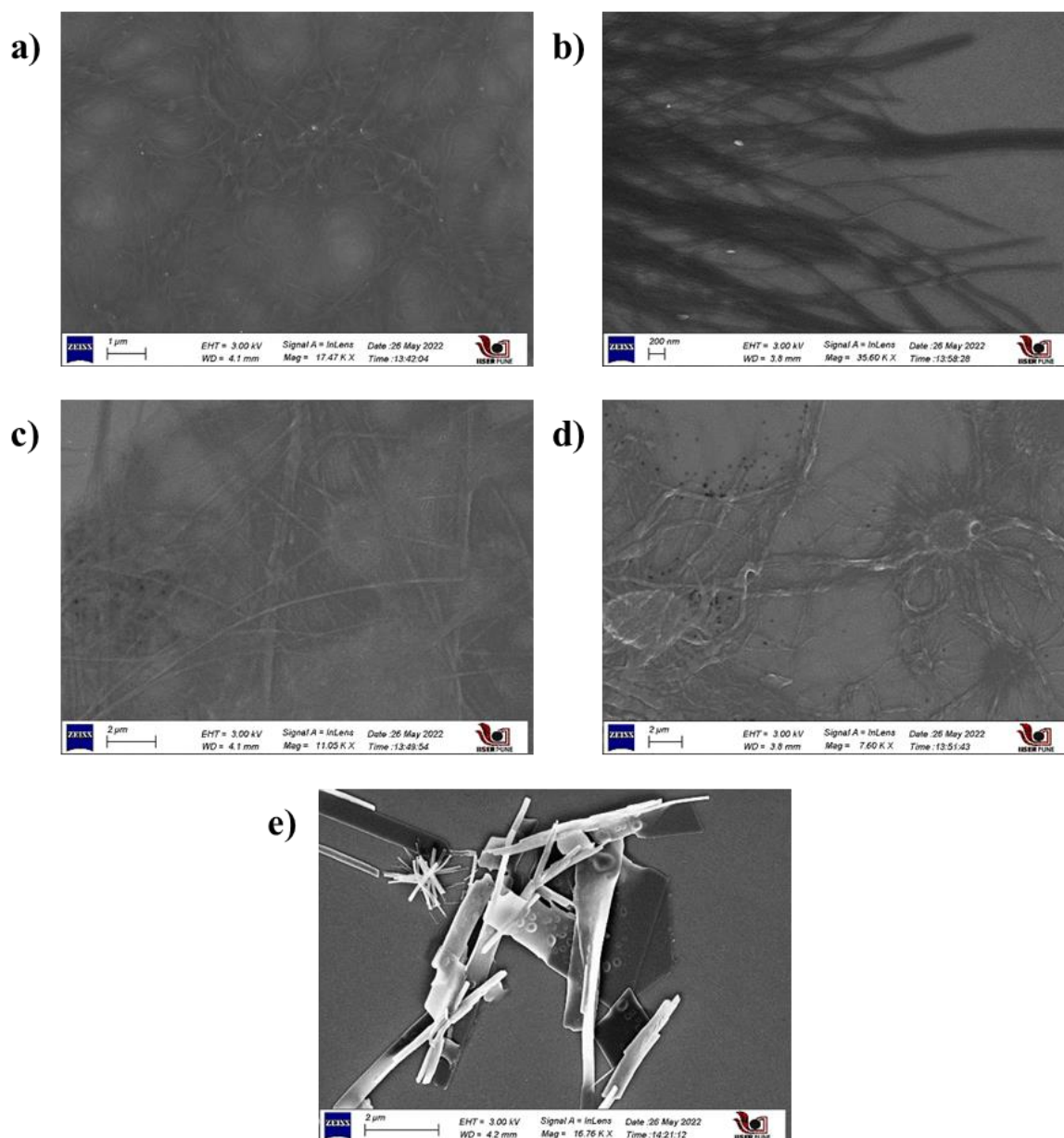


Figure 13: FE-SEM images of peptide **P2** organogel in different active methylene solvents a) nitromethane, b) ethyl acetoacetate, c) diethyl malonate, d) acetonitrile, e) methyl acetoacetate.

5.4.2.2. HR-TEM images of P2 organogel:

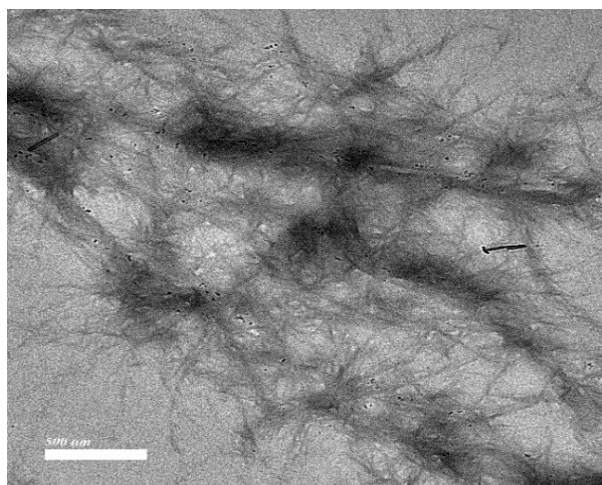


Figure 14: HR-TEM images of peptide **P2** organogel.

5.4.2.3. AFM analysis of peptide P2 organogel:

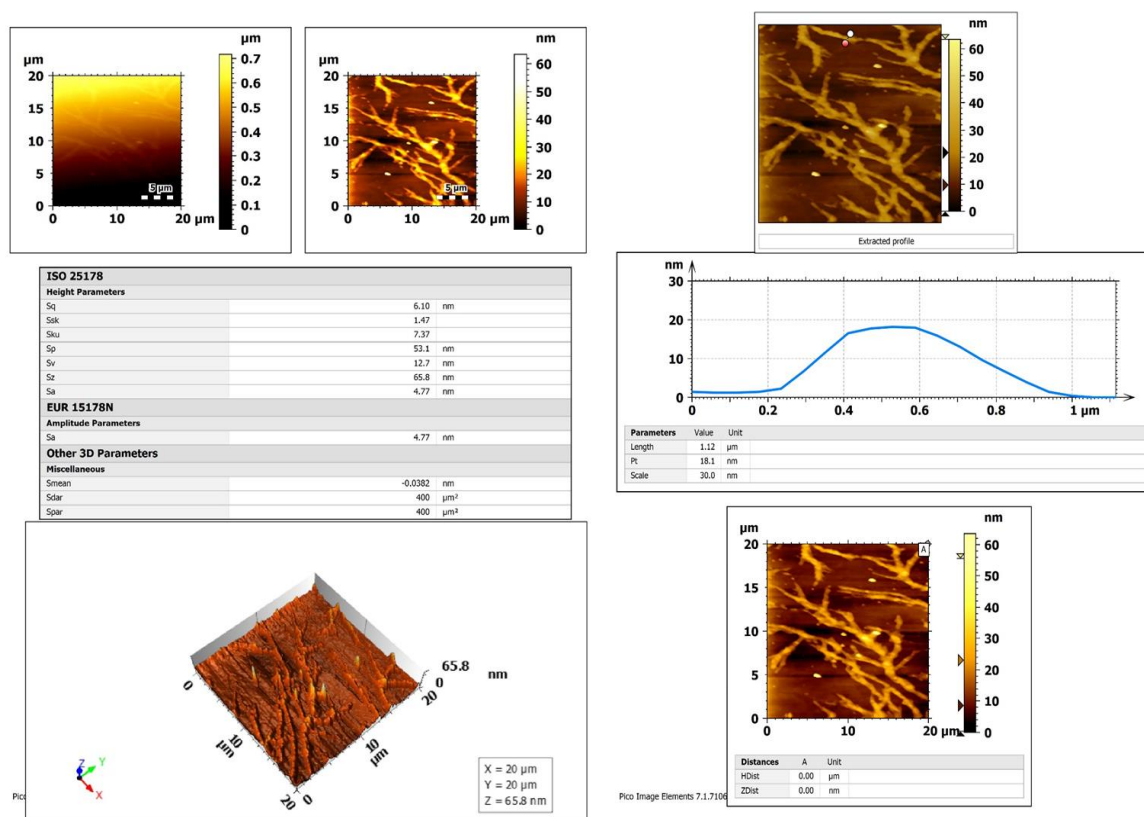


Figure 15: AFM images of peptide **P2** organogel in diethyl malonate showed the fibrils.

5.4.3. Morphology analysis of P3 organogel:

5.4.3.1. FE-SEM images of P3 organogel:

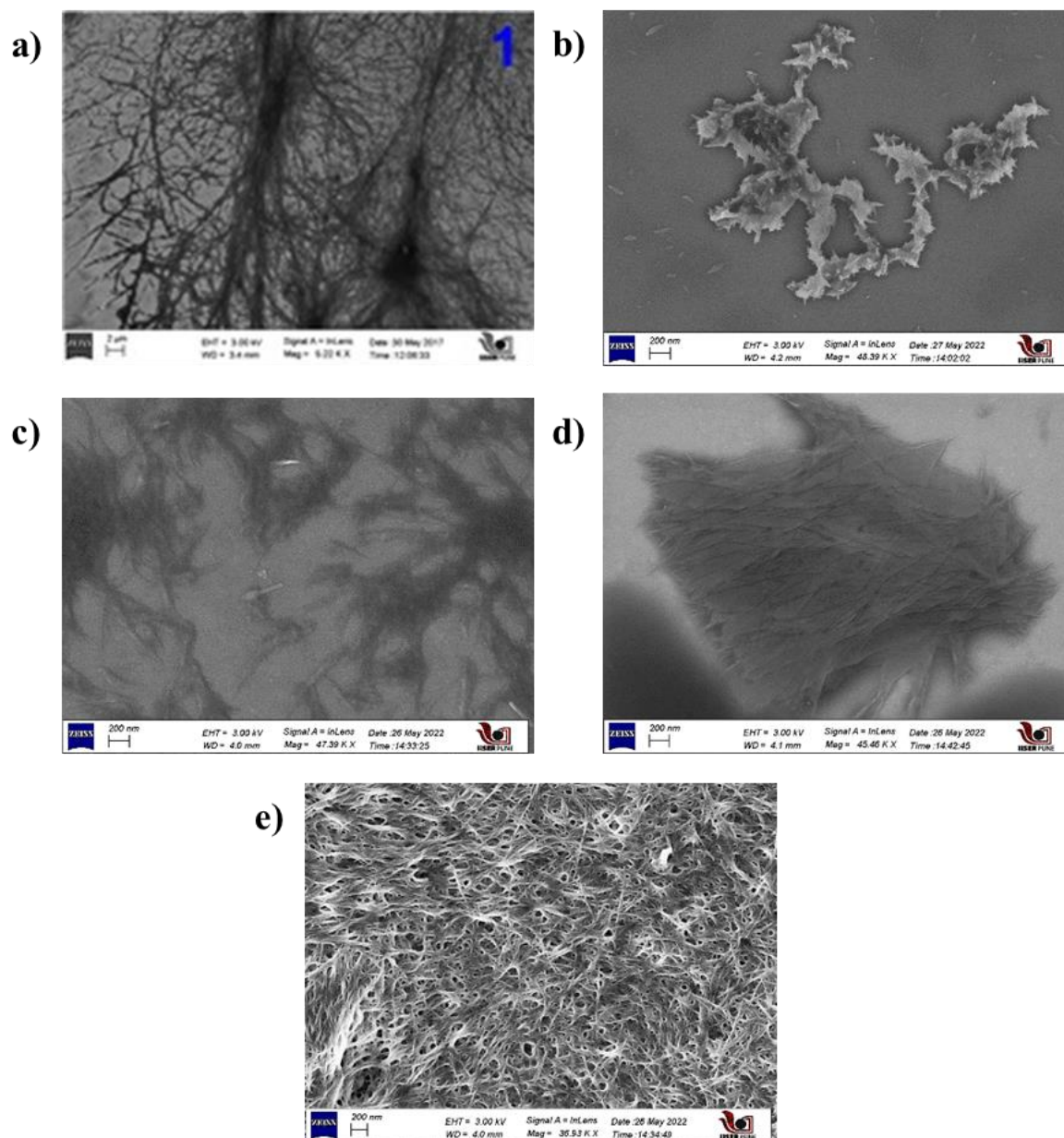


Figure 16: FE-SEM images of peptide **P3** organogel in different active methylene solvents a) nitromethane, b) ethyl acetoacetate, c) diethyl malonate, d) diisopropyl malonate, e) acetonitrile.

5.4.3.2. HR-TEM images of P3 organogel:

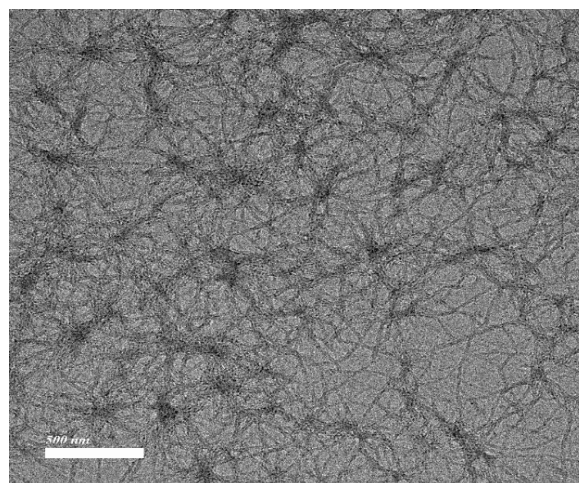


Figure 17: HR-TEM images of peptide **P3** organogel.

5.4.3.3. AFM analysis of peptide P3 organogel:

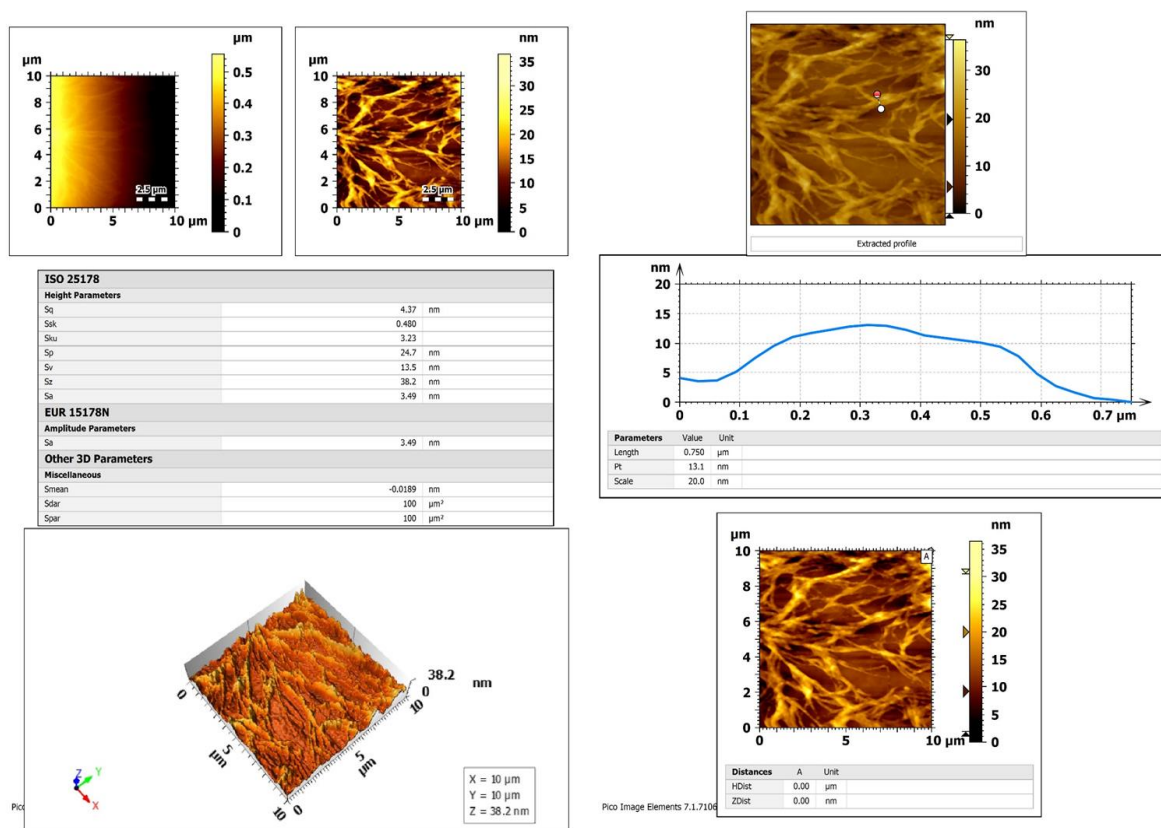


Figure 18: AFM images of peptide **P3** organogel in diethyl malonate showed the fibrils.

5.4.4. Morphology analysis of P4 organogel:

5.4.4.1. FE-SEM images of P4 organogel:

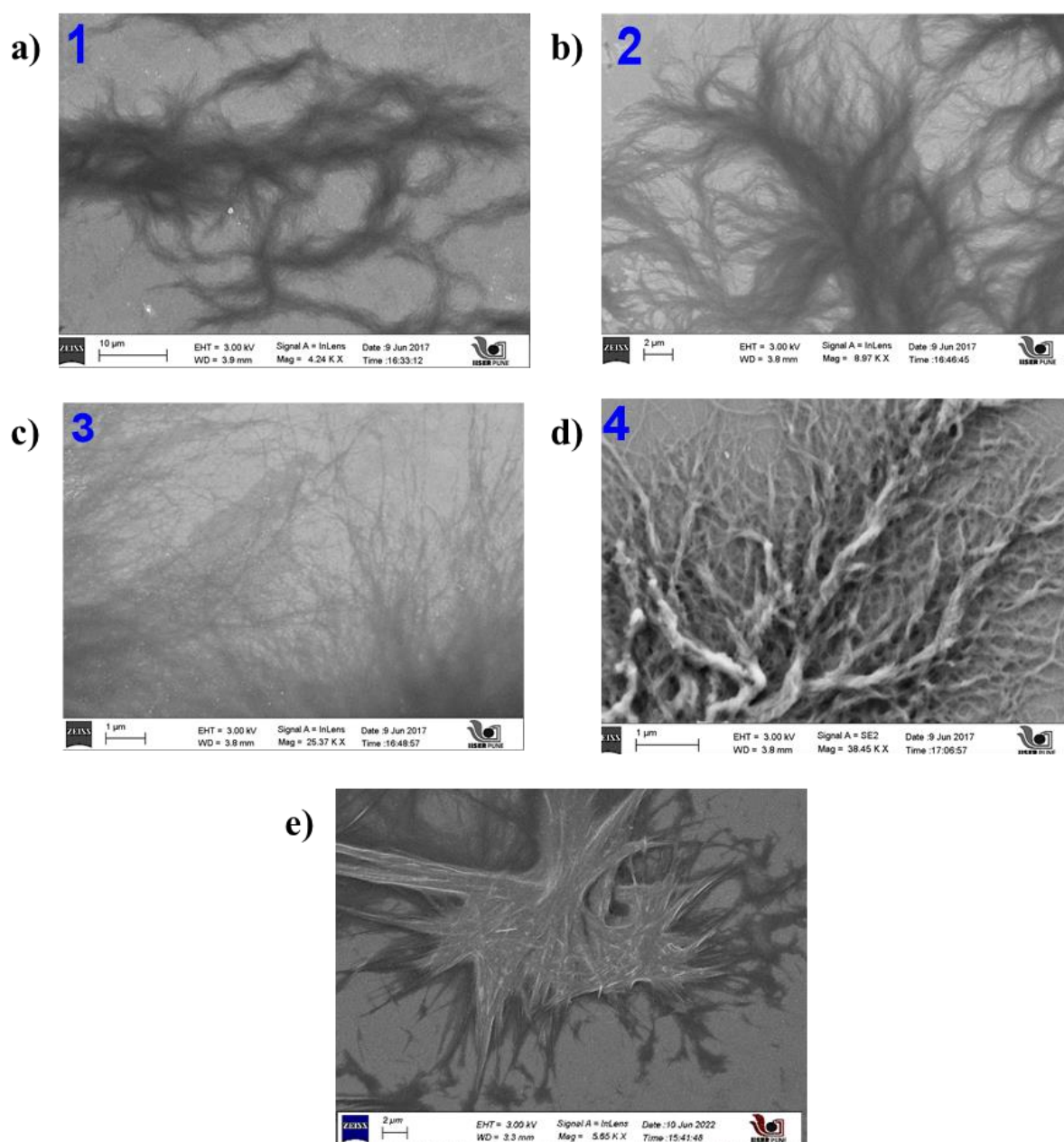


Figure 19: FE-SEM images of peptide **P4** organogel in different active methylene solvents a) diethyl malonate, b) ethyl acetoacetate, c) nitromethane, d) acetonitrile, e) diisopropyl malonate.

5.4.4.2. HR-TEM images of P4 organogel:

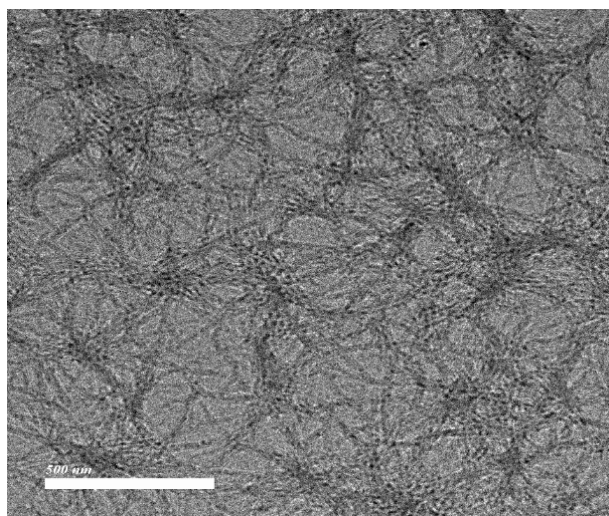


Figure 20: HR-TEM images of peptide **P4** organogel.

5.4.4.3. AFM analysis of peptide P4 organogel:

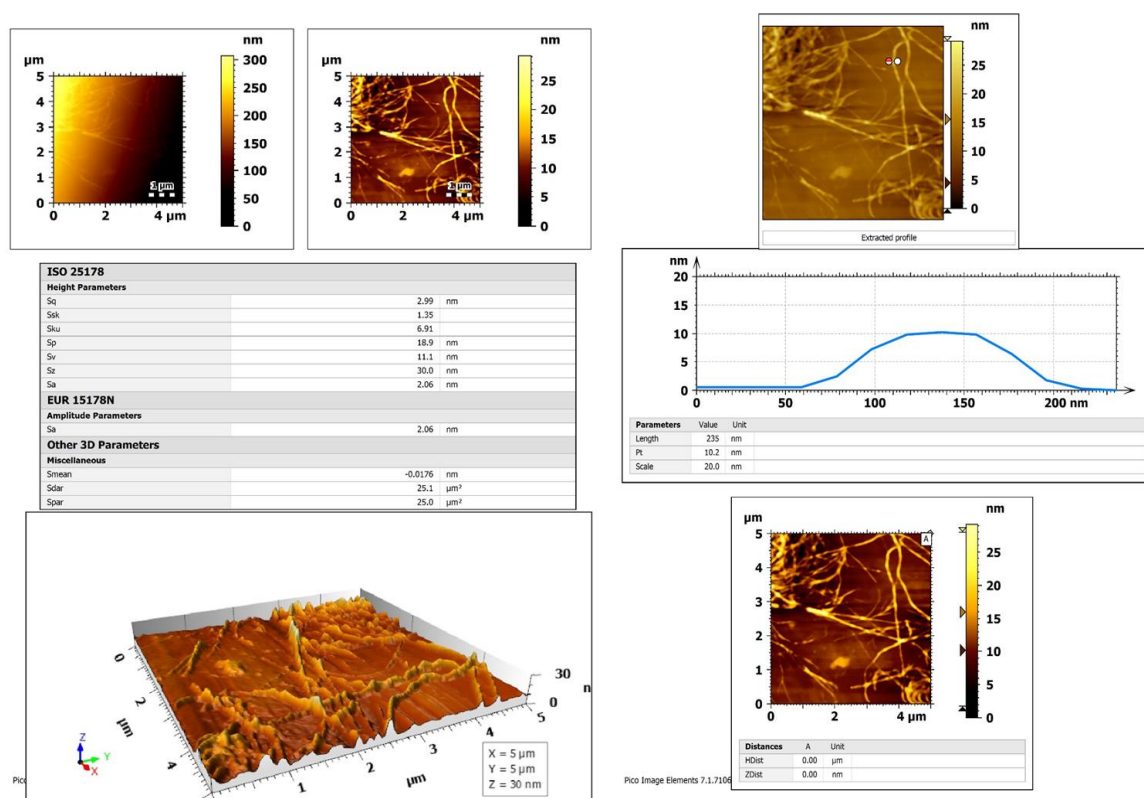


Figure 21: AFM images of peptide **P4** organogel in diethyl malonate showed the fibrils.

5.5. FT-IR Study of Peptide Organogel:

In the investigation of protein secondary structure, IR spectroscopy serves as a prominent technique, particularly through the analysis of the amide I and amide II bands. The amide I band, primarily associated with C=O stretching modes, manifests in the range of 1695-1630 cm^{-1} , offering valuable insights into protein secondary structure determination. Meanwhile, the amide II band, arising from NH deformation, is observed in the 1560-1510 cm^{-1} range.³⁷ Within the amide I region, an α -helix conformation typically presents a characteristic band between 1640 cm^{-1} and 1660 cm^{-1} , while a β -sheet conformation exhibits a distinctive band within 1620 cm^{-1} to 1640 cm^{-1} range. In the amide II region, the characteristic band for α -helix occurs between 1530 cm^{-1} and 1550 cm^{-1} , whereas for β -sheet conformation, it lies between 1510 cm^{-1} and 1530 cm^{-1} .³⁸ In the case of peptide **P1**, known for its stable C_{12} -helix according to crystal structure analysis in methanol, the IR frequencies were observed at 1652 cm^{-1} for the amide I region and 1538 cm^{-1} for the amide II region. However, in the **P1** organogel, these frequencies shifted to 1635 cm^{-1} for amide I and 1521 cm^{-1} for amide II, aligning with the characteristic bands of β -sheet conformation, as depicted in Figure 22a. Similarly, Peptides **P2**, **P3**, and **P4** exhibited characteristic IR bands at 1648, 1649, and 1650 cm^{-1} for the amide I region and 1545, 1535, and 1548 cm^{-1} for the amide II region, indicative of α -helix conformation. In contrast, the organogels formed by Peptides **P2**, **P3**, and **P4** displayed characteristic IR bands at 1634, 1635, and 1635 cm^{-1} for amide I and 1519, 1514, and 1525 cm^{-1} for amide II, consistent with characteristic signals for β -sheet conformation, as illustrated in Figure 22b-22d.

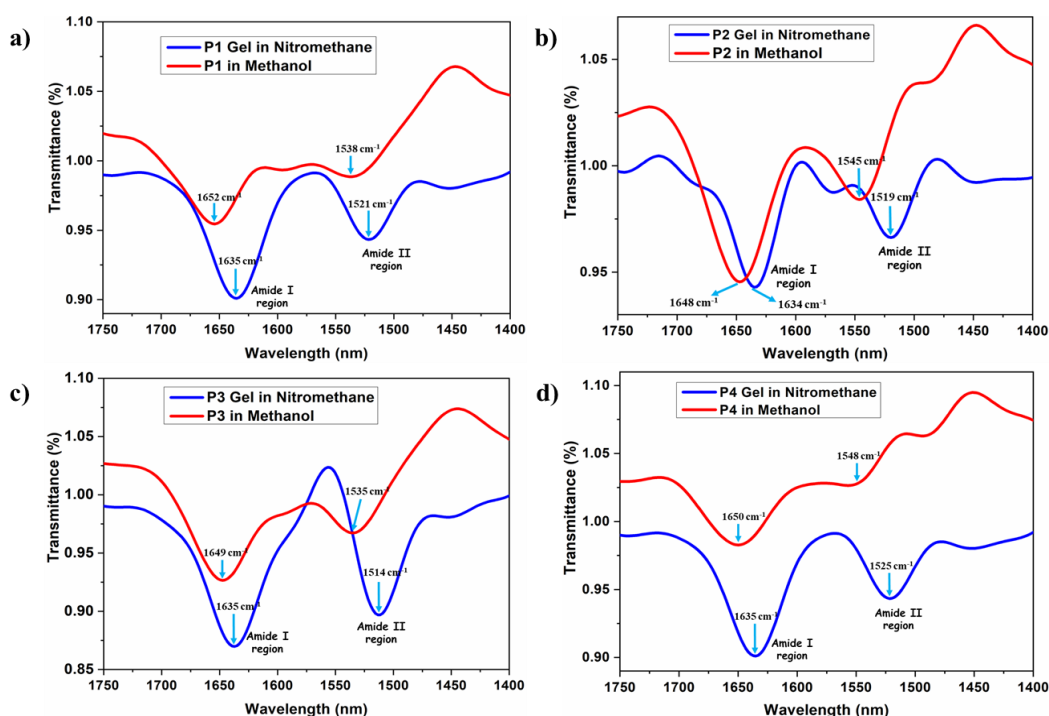


Figure 22: a) FT-IR spectra of **P1** in MeOH and Gel state, b) FT-IR spectra of **P2** in MeOH and Gel state, c) FT-IR spectra of **P3** in MeOH and Gel state, d) FT-IR spectra of **P4** in MeOH and Gel state.

A comparative analysis between the infrared (IR) spectra of peptide organogels and the IR spectra of the **P6** crystal, which forms a parallel β -sheet in single crystal analysis, was undertaken. The examination disclosed a notable alignment in the amide I region, with the peptide organogels exhibiting a peak at 1645 cm^{-1} , precisely matching the IR spectra of the **P6** crystal. Similarly, examination of the amide II region indicated a close resemblance was observed between the peptide organogels and the **P6** crystal, as shown in Figure 23, which indicates the polymeric sheet character within the peptide organogels.

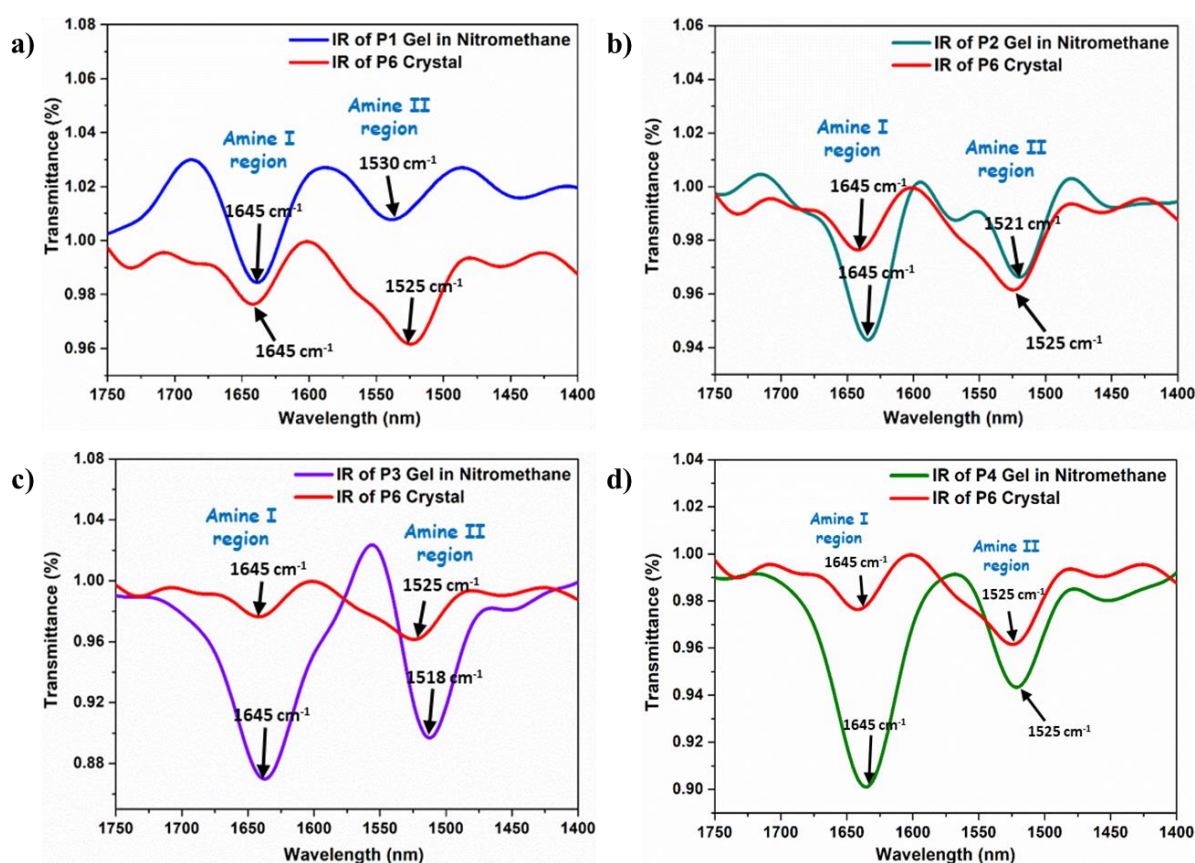


Figure 23: Comparative analysis of IR spectra between a) **P1** Gel and **P6** crystal, b) **P2** Gel and **P6** crystal, c) **P3** Gel and **P6** crystal, d) **P4** Gel and **P6** crystal.

5.6. CD Spectra Analysis of Peptide Organogel:

Circular Dichroism (CD) emerges as a prominent technique in the exploration of protein secondary structures. Our investigation focused on comparing CD spectra between peptides dissolved in methanol, exhibiting a stable helical structure, and peptides forming organogels in

a gel state. Interestingly, distinctive CD spectra were observed for the two conditions. In the case of peptides in methanol, a minima was evident at ~ 249 nm, accompanied by a maxima at ~ 219 nm. In contrast, peptide organogels exhibited a singular minimum at 285 nm, as illustrated in Figure 24. This comparative analysis provides clear insights into the structural disparities between peptide organogels and peptides in methanol.

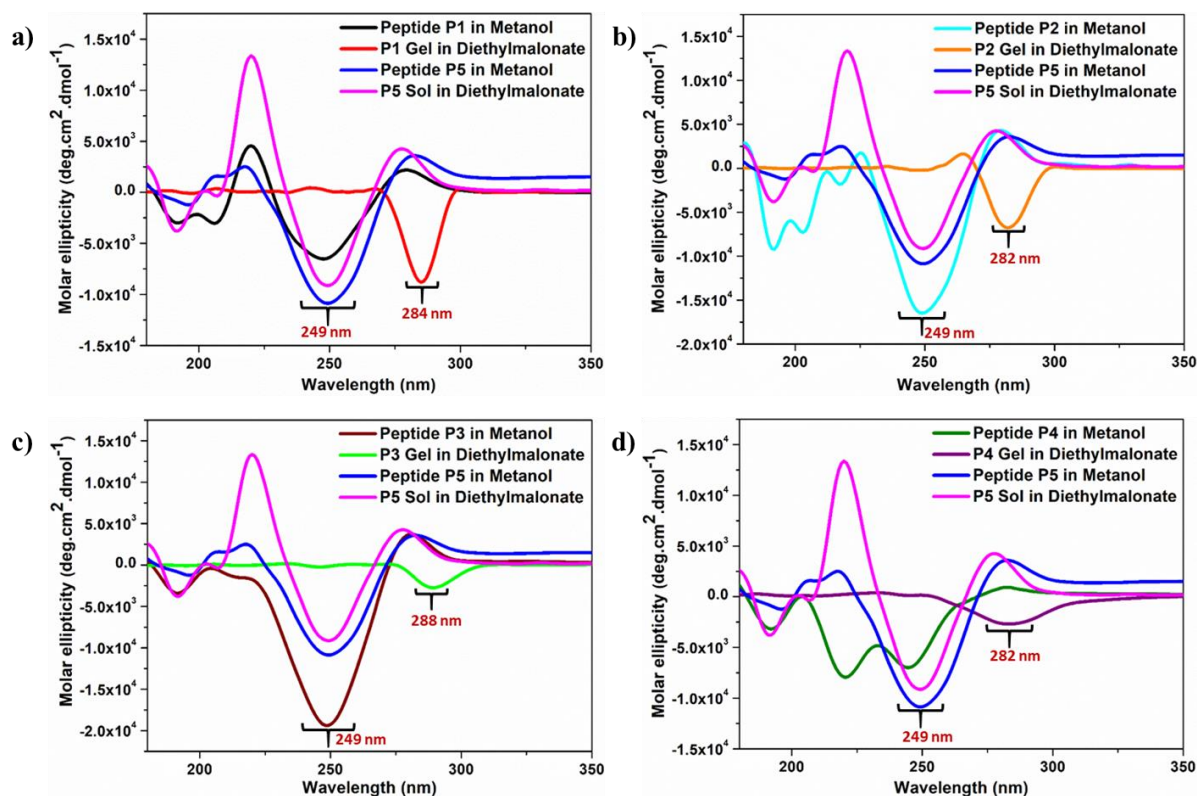
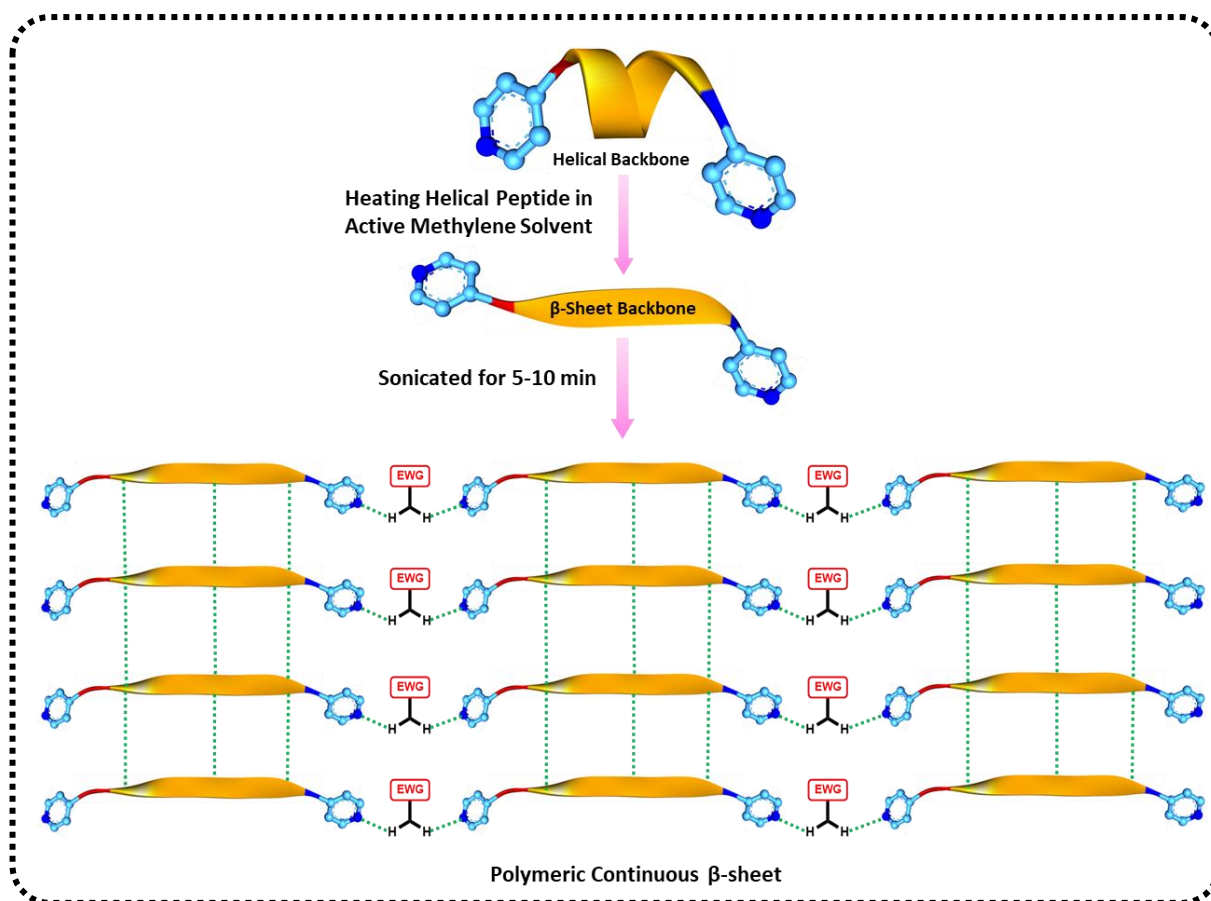


Figure 24: Comparative analysis of CD spectra of a) **P1** Gel with **P1** and **P5** in MeOH, b) **P2** Gel with **P2** and **P5** in MeOH, c) **P3** Gel with **P3** and **P5** in MeOH, d) **P4** Gel with **P4** and **P5** in MeOH.

5.7. Proposed Mechanism for Peptide Gelation:

The generation of peptide organogel within active methylene solvents suggests a fibrillar morphology in the gel state, a confirmation established through imaging techniques such as FE-SEM, HR-TEM, and AFM. Our analysis of secondary structures using IR and CD spectra indicates that the fibrillar morphology is attributed to an interconnected β -sheet crosslinked peptide network. This crosslinked network is a result of intermolecular hydrogen bonding between the peptide linker and the acidic proton of active methylene solvent, where the pyridyl nitrogen acts as a donor and the active methylene solvent's acidic proton serves as an acceptor, as shown in Scheme 3.



Scheme 3: Proposed mechanism of gelation in active methylene solvents.

According to our proposed mechanism, the stable helical peptide undergoes a helicity breakdown in the presence of active methylene solvents upon heating, forming a β -sheet backbone. Subsequent sonication of this mixture leads to the formation of a continuous polymeric β -sheet through intermolecular hydrogen bonding, as illustrated in Scheme 3. Additionally, the β -branch valine residue plays a pivotal role in inducing the β -sheet nature in the peptide backbone. This fibrillar morphology is consistently observed across various active methylene solvents in our study.

5.8. Viscoelastic Property:

To delve into the viscoelastic properties of **P1-P4** organogels, we conducted comprehensive rheological assessments. The examination of these organogels' viscoelastic nature involved both strain-sweep and frequency-sweep experiments, maintaining a constant angular frequency of 1 rad/s. Here we found in strain sweep experiment that, storage modulus (G') is larger than loss modulus (G'') suggesting the viscoelastic nature of the gels. Again, there is no crossover of G' and G'' was observed in the frequency sweep experiment. The constant separation of G'

and G'' suggests the good stability of these peptide organogels (Figure 25). These studies also suggest the strong interaction between peptides and active methylene solvents.

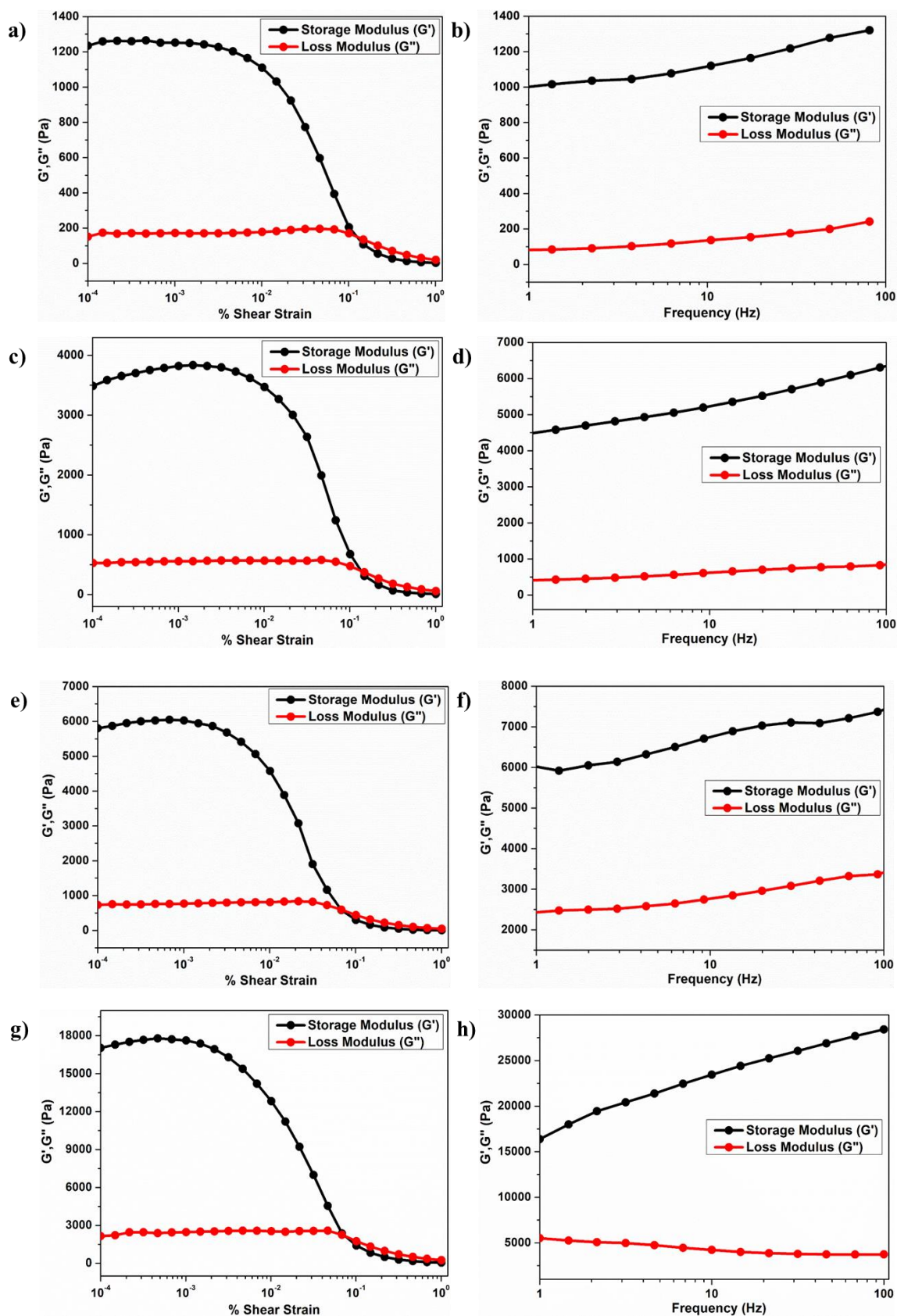


Figure 25: a) Linear Viscoelastic range rheological analysis of **P1**-Gel in DEM (CGC=18 mM) at a fixed angular frequency of 1 rad/s. b) Frequency sweep rheological analysis of **P1**-Gel in DEM (CGC=18 mM) at a constant strain of 0.1%. c) Linear Viscoelastic range rheological analysis of **P2**-Gel in DEM (CGC=18 mM) at a fixed angular frequency of 1 rad/s. d) Frequency sweep rheological analysis of **P2**-Gel in DEM (CGC=18 mM) at a constant strain of 0.1%. e) Linear Viscoelastic range rheological analysis of **P3**-Gel in Nitromethane (CGC=17 mM) at a fixed angular frequency of 1 rad/s. f) Frequency sweep rheological analysis of **P3**-Gel in Nitromethane (CGC=17 mM) at a constant strain of 0.1%. g) a) Linear Viscoelastic range rheological analysis of **P4**-Gel in Nitromethane (CGC=17 mM) at a fixed angular frequency of 1 rad/s. h) Frequency sweep rheological analysis of **P4**-Gel in Nitromethane (CGC=17 mM) at a constant strain of 0.1%.

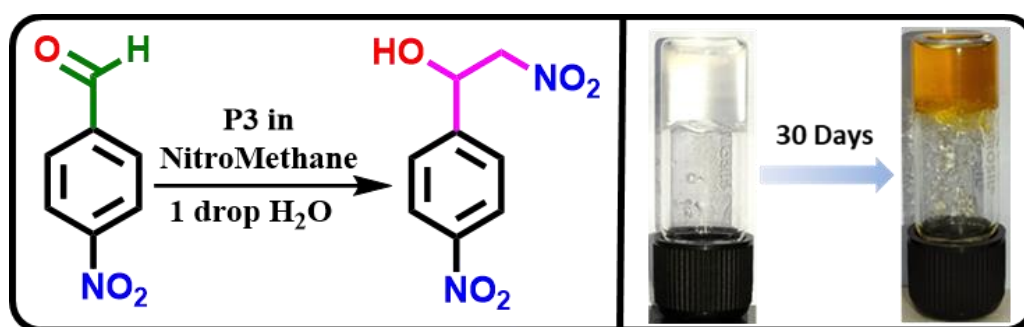
5.9. Catalytic Reaction using Peptide Organogels:

We conducted the Henry reaction, also known as the nitroaldol reaction, within the gel state, utilizing our peptide organogels in active methylene solvents. The specific peptide employed in this context featured 3-pyridyl and 4-pyridyl groups at the C- and N-terminal ends of the peptide backbone, respectively. In this reaction, the active methylene solvent played a dual role, serving not only as the reaction medium but also as an essential reactant for the Henry reaction. The active methylene solvent's participation in the reaction was particularly crucial, as it not only contributed to the chemical transformation but also played a pivotal role in the gel formation process itself. This intricate interplay between the peptide organogel, active methylene solvent, and the Henry reaction adds a layer of complexity and significance to the study of these gel-state reactions.

5.9.1. Catalytic Reaction of P3 Organogel in Nitromethane and Acetyl acetone:

Our exploration commenced with peptide **P3** organogel which forms a densely packed gel in nitromethane and was confirmed through viscoelastic properties as well as FE-SEM images. In a 5 mL vial, we combined peptide **P3** (0.035 mmol, 20 mg) and 4-nitrobenzaldehyde (0.07 mmol, 10.6 mg). Given the critical gelation concentration of our peptides as 10 mg/mL, we introduced 2 mL of nitromethane into the gelation vial, subsequently followed by the addition of a single drop of water to the reaction mixture. This blend was then heated to achieve solubility, with sonication carried out for 4-5 minutes. Over the course of a few hours, the emergence of a stable gel was observed and confirmed through the vial inversion method. The

next phase involved allowing the reaction mixture to undergo a gel-state catalytic reaction, left undisturbed for 25-30 days. After this duration, the initially colorless gel underwent a transformation, assuming an orange hue within the reaction vial as shown in Scheme 4. Upon completion, the reaction mixture was diluted with 15 mL EtOAc and washed with brine (20 mL x 2), 10% HCl solution (20 mL x 1), 10% Na₂CO₃ solution (20 mL x 1), and finally with brine (20 mL x 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by preparative TLC (20% EA/Hexane) to get a purified product having an overall yield was ~70%. The final product was confirmed through ¹H and ¹³C NMR as well as HRMS spectra.



Scheme 4: Representation of catalytic reaction of **P3** organogel in Nitromethane.

¹H, ¹³C NMR, and Mass Spectra:

¹H NMR (400 MHz, Chloroform-*d*) δ 8.32 – 8.26 (m, 2H), 7.66 – 7.60 (m, 2H), 5.61 (dd, *J* = 8.3, 4.0 Hz, 1H), 4.68 – 4.55 (m, 2H), 3.17 (s, 1H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 185.44, 144.86, 126.94, 124.24, 80.60, 69.97.

HRMS Spectra *m/z* calculated for C₈H₈N₂O₅ [M-H]⁺ is 211.0355 and the observed value is 211.0353.

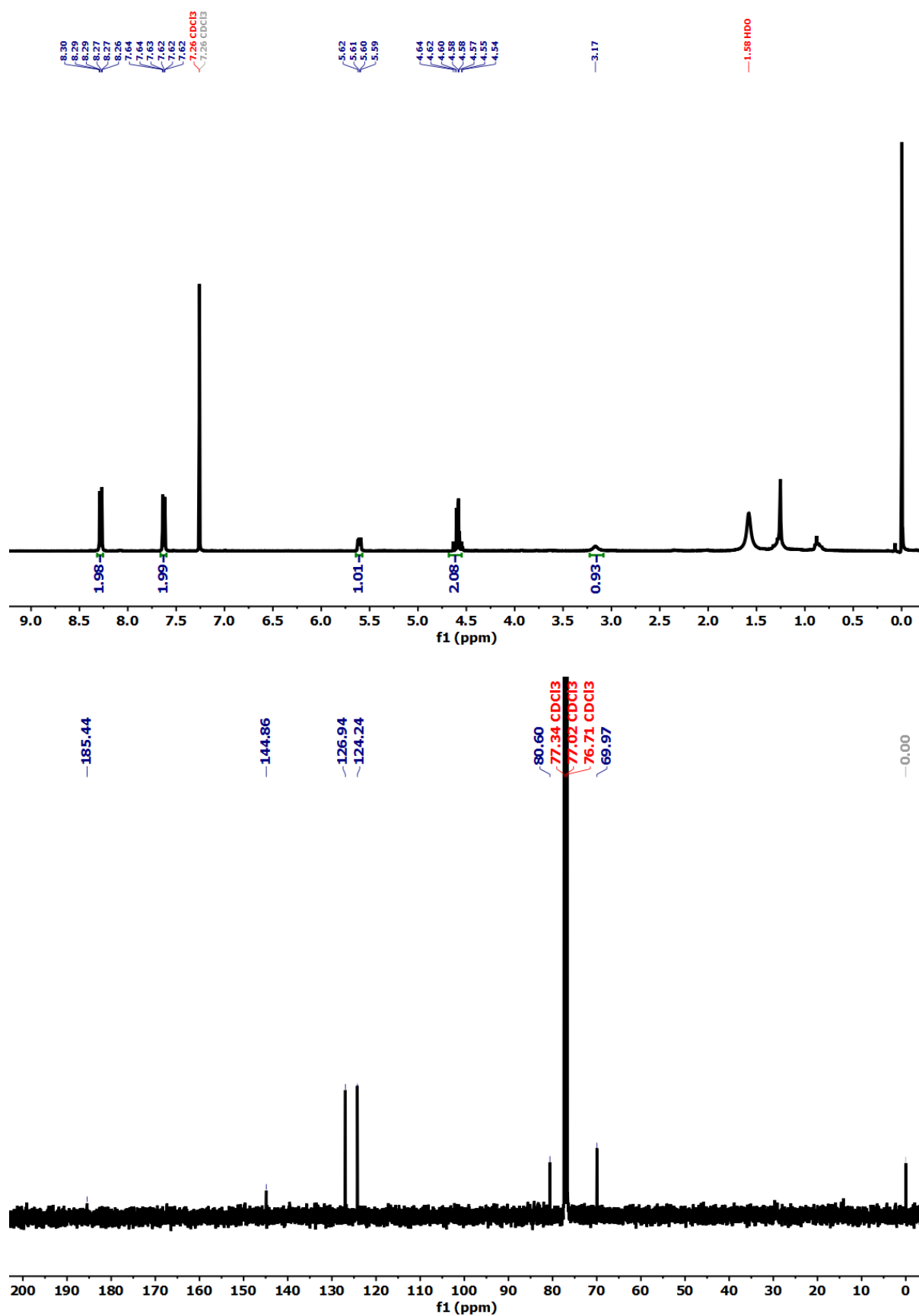


Figure 26: ^1H & ^{13}C NMR spectrum in CDCl_3 .

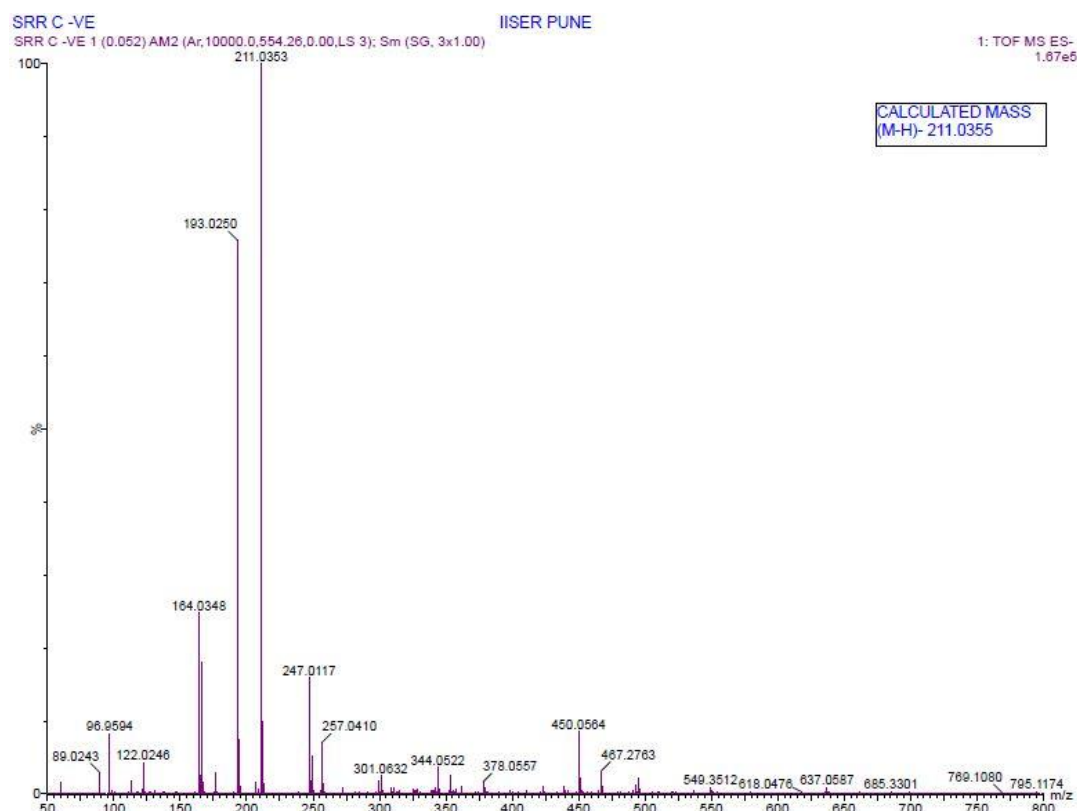
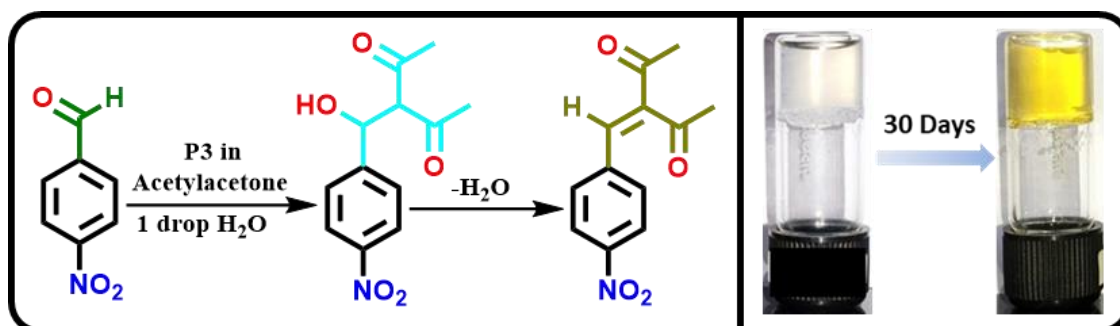


Figure 27: HRMS spectra of product with **P3** organogel in Nitromethane.

Furthermore, we extended our investigations to encompass a catalytic reaction in the presence of acetyl acetone shown in Scheme 5. The experimental setup involved combining Peptide **P3** (0.035 mmol, 20 mg) and 4-Nitrobenzaldehyde (0.07 mmol, 10.6 mg) within a 5 mL vial. The reaction unfolded following the established protocol mentioned earlier. Verification of the final product formation was confirmed through ^1H and ^{13}C NMR as well as mass spectra.



Scheme 5: Representation of catalytic reaction of **P3** organogel in Acetyl acetone.

^1H , ^{13}C NMR, and Mass Spectra:

^1H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.99 (m, 2H), 7.35 – 7.31 (m, 2H), 7.03 (s, 1H), 2.23 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.26, 195.95, 148.50, 145.64, 139.26, 136.46, 130.24, 124.15, 31.75, 26.70.

HRMS Spectra m/z calculated for $\text{C}_{12}\text{H}_{11}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ is 256.0585 and the observed value is 256.0584.

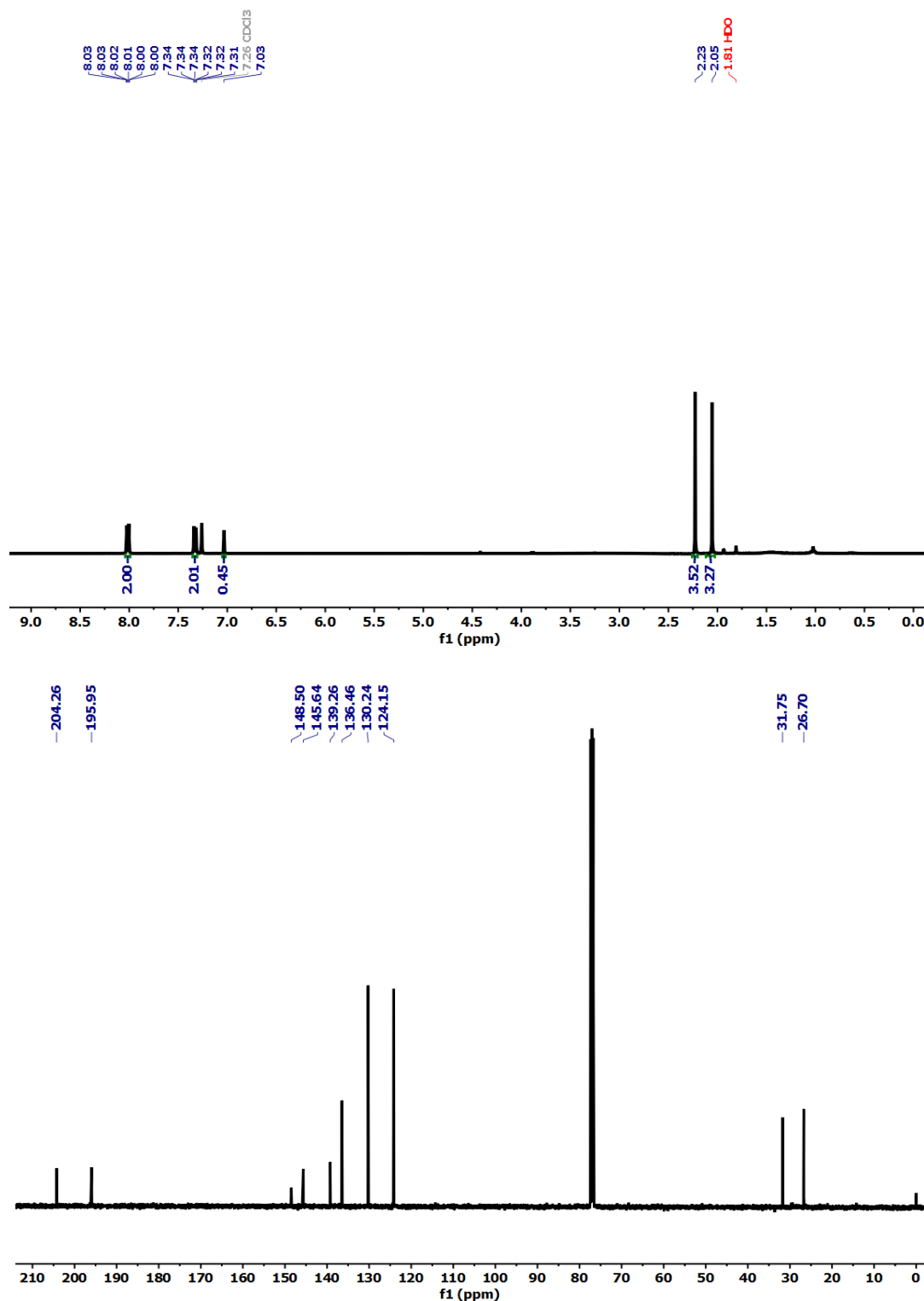


Figure 28: ^1H and ^{13}C NMR spectrum in CDCl_3 .

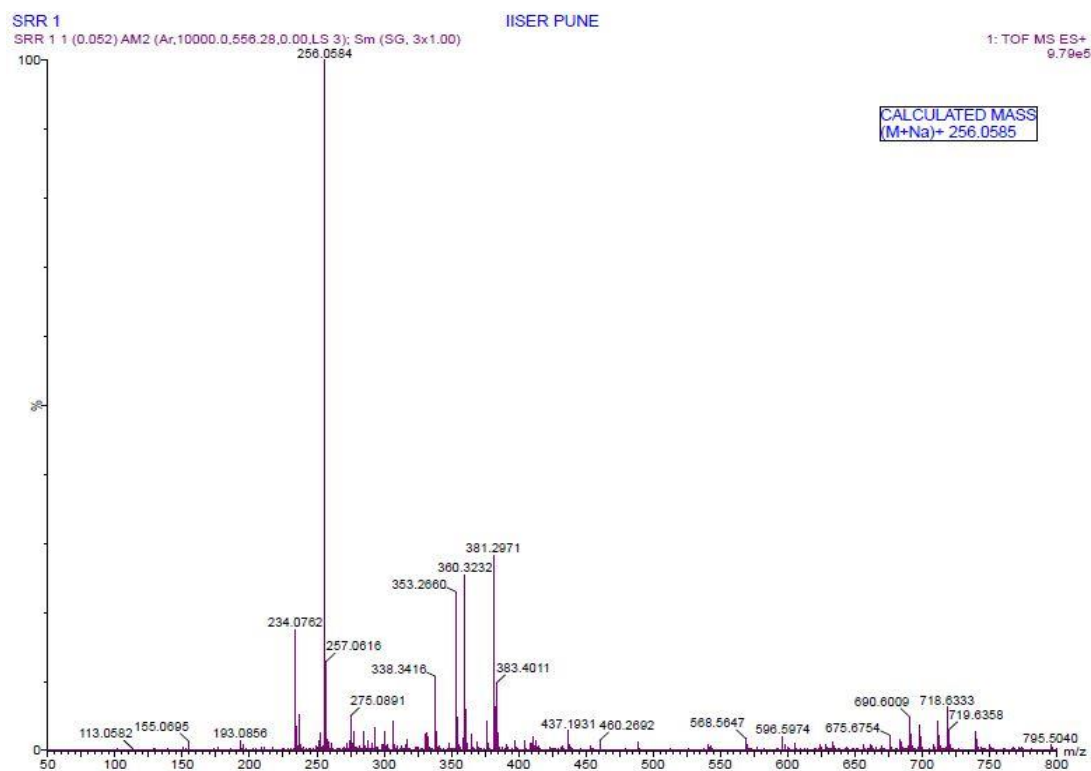
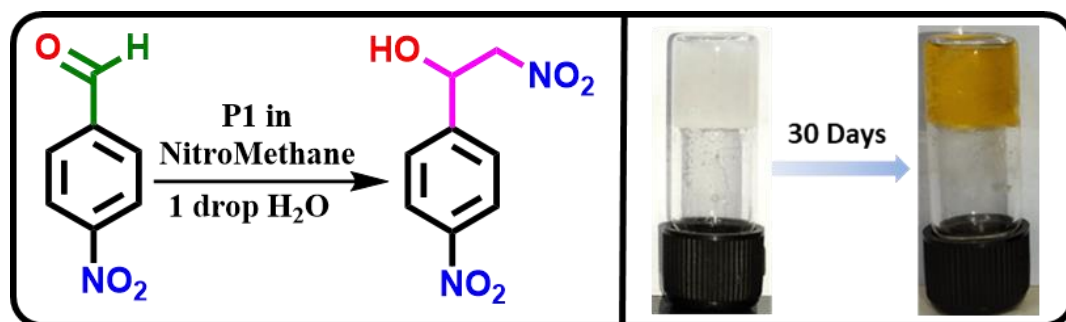


Figure 29: HRMS spectra of product with **P3** organogel in Acetylacetone.

5.9.2. Catalytic Reaction of **P1** Organogel in Nitromethane:

Similar to the catalytic reaction performed with **P3** organogel, we conducted an analogous reaction utilizing **P1** organogel in the presence of nitromethane. In a 5 mL vial, we combined Peptide **P1** (0.037 mmol, 20 mg) with 4-Nitrobenzaldehyde (0.074 mmol, 11.2 mg) and introduced 2 mL of nitromethane. The reaction was carried out using the previously mentioned protocol. Post-reaction, the crude product underwent purification via Preparative TLC (20% EA/Hexane), yielding a purified product with an approximate overall yield of 65%. Final product was confirmed through ^1H and ^{13}C NMR as well as HRMS spectra.



Scheme 6: Representation of catalytic reaction of **P1** organogel in Nitromethane.

^1H , ^{13}C NMR, and Mass Spectra:

^1H NMR (400 MHz, Chloroform-*d*) δ 8.35 – 8.18 (m, 2H), 7.71 – 7.57 (m, 2H), 5.60 (dd, J = 8.4, 4.0 Hz, 1H), 4.69 – 4.51 (m, 2H), 4.12 (q, J = 7.1 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 148.21, 144.90, 126.94, 124.23, 80.62, 69.96.

HRMS Spectra m/z calculated for $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$ $[\text{M}-\text{H}]^-$ is 211.0355 and the observed value is 211.0360.

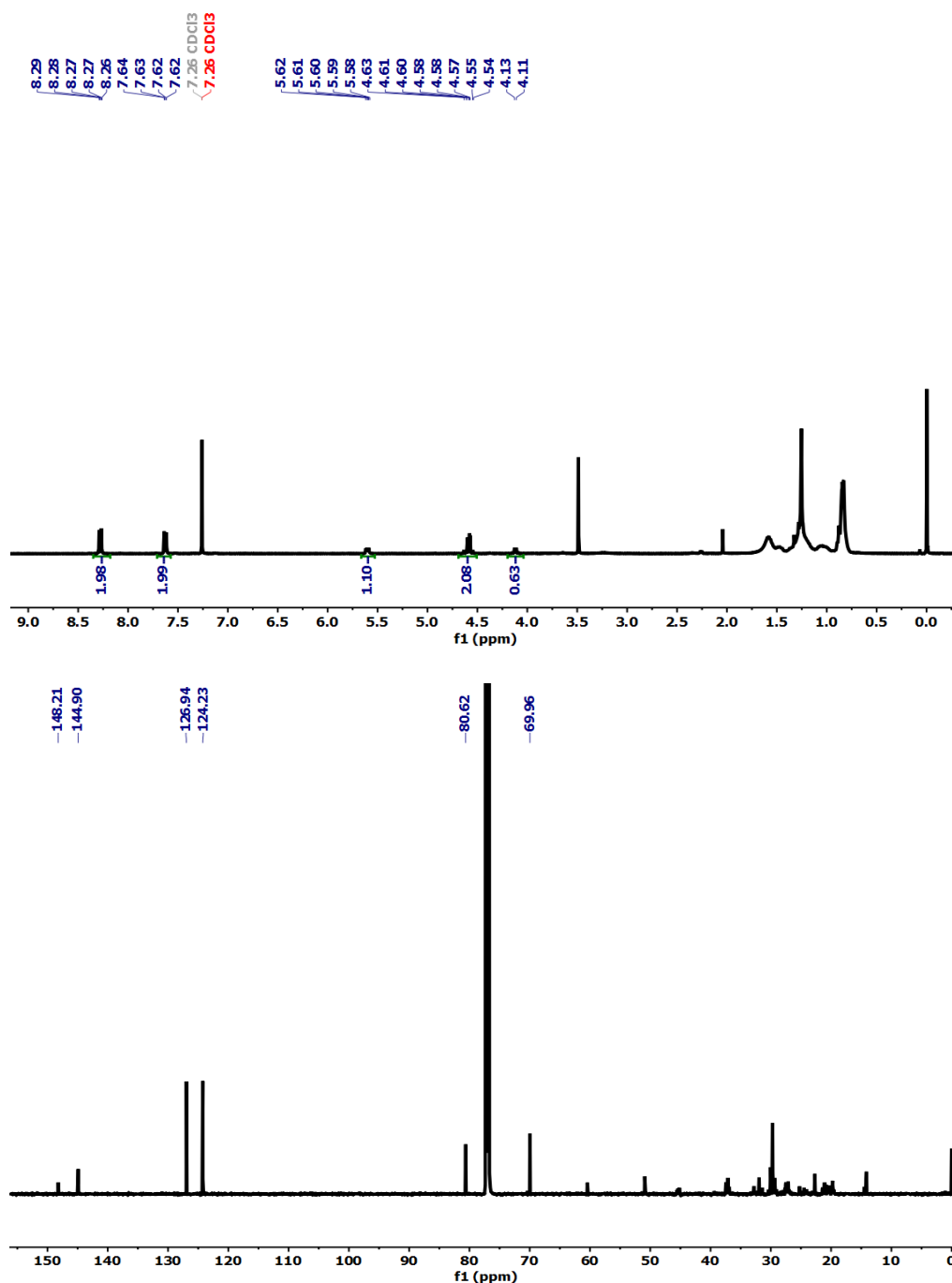


Figure 30: ^1H and ^{13}C NMR spectrum in CDCl_3 .

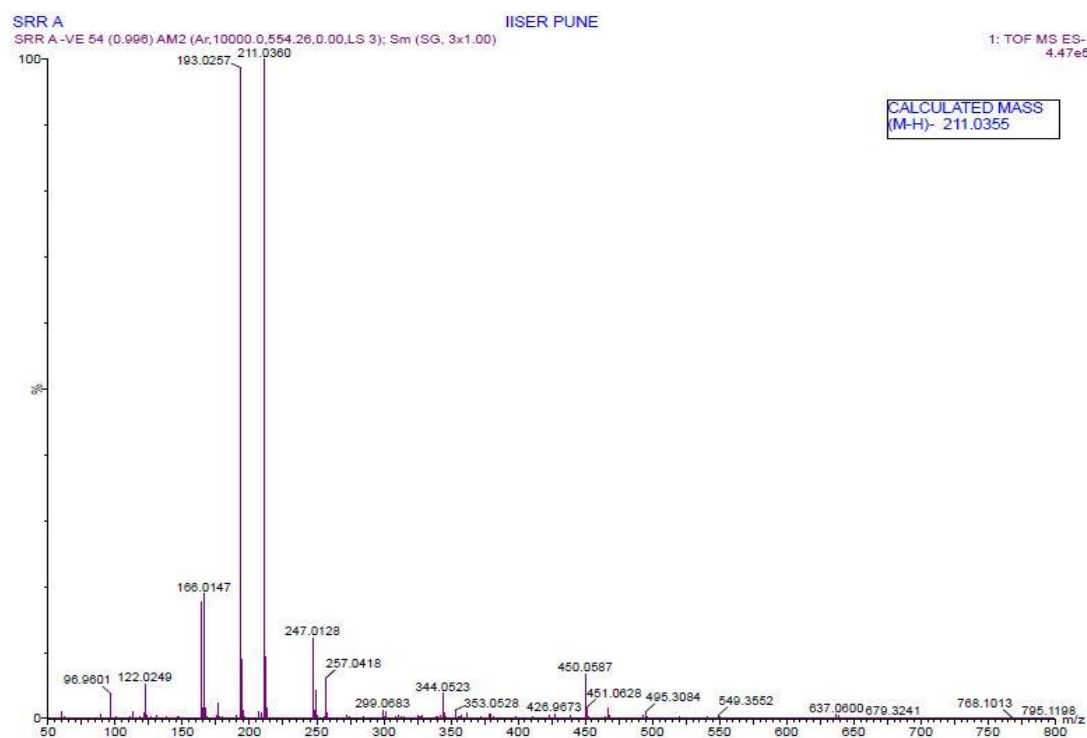
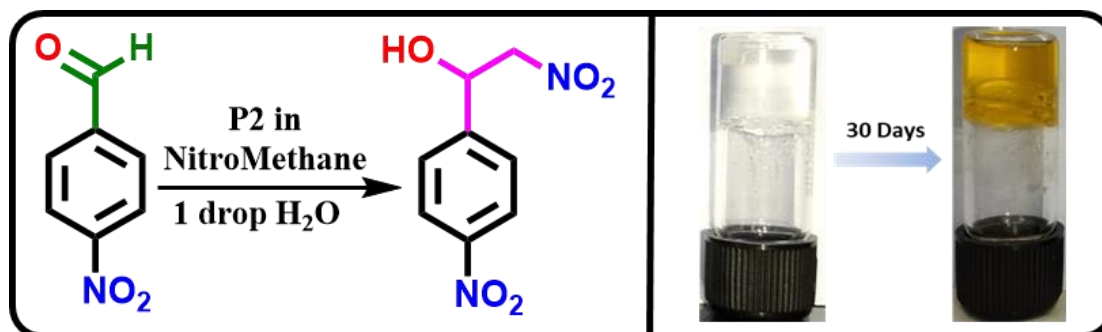


Figure 31: HRMS spectra of product with **P1** organogel in Nitromethane.

5.9.3. Catalytic Reaction of **P2** Organogel in Nitromethane:

In alignment with our previous endeavors with **P3** and **P1** organogels, we replicated a similar catalytic reaction with **P2** organogel in the presence of nitromethane. Within a 5 mL vial, Peptide **P2** (0.037 mmol, 20 mg) and 4-Nitrobenzaldehyde (0.074 mmol, 11.2 mg) were combined, followed by the addition of 2 mL of nitromethane. Employing the established protocol, the reaction unfolded, and the resultant crude product underwent purification through Preparative TLC (20% EA/Hexane), yielding a purified product with an overall yield of ~60%. Final product was confirmed through ^1H and ^{13}C NMR as well as HRMS spectra.



Scheme 7: Representation of catalytic reaction of **P2** organogel in Nitromethane.

^1H , ^{13}C NMR, and Mass Spectra:

^1H NMR (400 MHz, Chloroform-*d*) δ 8.35 – 8.20 (m, 2H), 7.69 – 7.57 (m, 2H), 5.60 (dd, J = 8.4, 4.0 Hz, 1H), 4.66 – 4.51 (m, 2H), 3.23 (s, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 148.20, 144.91, 126.95, 124.23, 80.62, 70.15.

HRMS Spectra m/z calculated for $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$ $[\text{M}-\text{H}]^-$ is 211.0355 and the observed value is 211.0354.

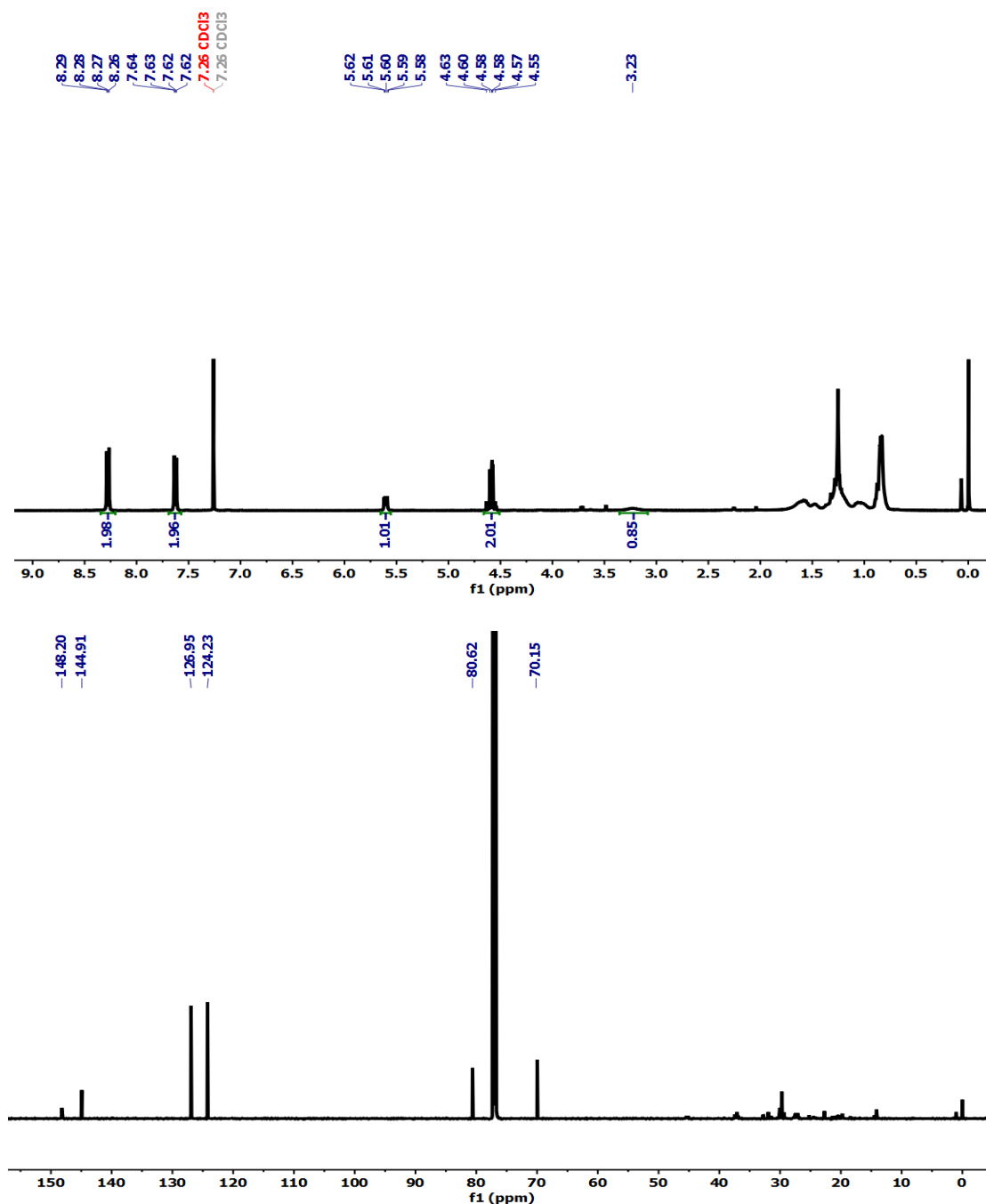


Figure 32: ^1H and ^{13}C NMR spectrum in CDCl_3 .

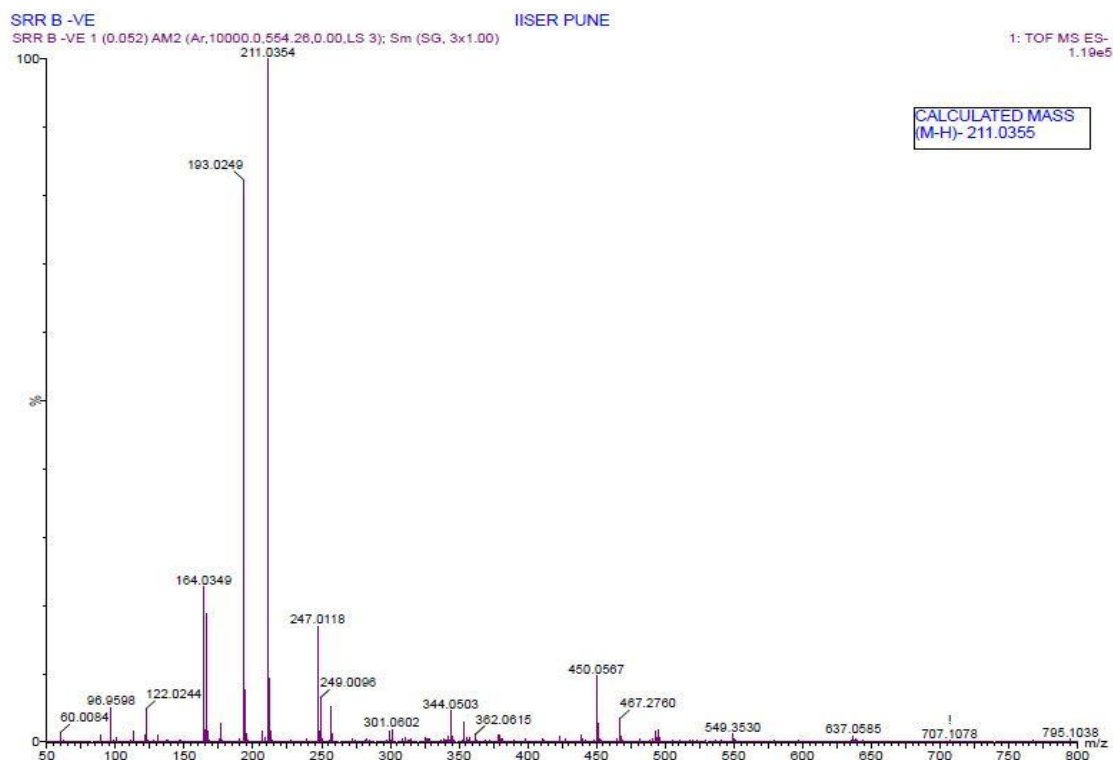
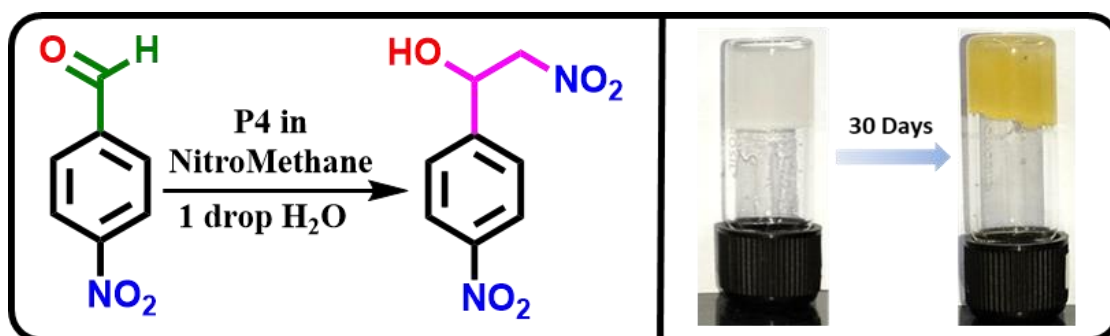


Figure 33: HRMS spectra of product with **P2** organogel in Nitromethane.

5.9.4. Catalytic Reaction of **P4** Organogel in Nitromethane:

In continuation of our exploration involving **P3**, **P1**, and **P2** organogels, we conducted a parallel catalytic reaction utilizing **P4** organogel in the presence of nitromethane. In a 5 mL vial, we combined Peptide **P1** (0.037 mmol, 20 mg) with 4-Nitrobenzaldehyde (0.074 mmol, 11.2 mg) and introduced 2 mL of nitromethane. The reaction was carried out using the previously mentioned protocol. Post-reaction, the crude product underwent purification via Preparative TLC (20% EA/Hexane), yielding a purified product with an approximate overall yield of 65%. Final product was confirmed through ^1H and ^{13}C NMR as well as HRMS spectra.



Scheme 8: Representation of catalytic reaction of **P4** organogel in Nitromethane.

^1H , ^{13}C NMR, and Mass Spectra:

^1H NMR (400 MHz, Chloroform-*d*) δ 8.30 – 8.24 (m, 2H), 7.66 – 7.59 (m, 2H), 5.60 (dd, J = 8.3, 4.0 Hz, 1H), 4.64 – 4.53 (m, 2H), 3.27 (s, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 148.18, 144.96, 126.95, 123.85, 80.63, 69.97.

HRMS Spectra m/z calculated for $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$ $[\text{M}-\text{H}]^-$ is 211.0355 and the observed value is 211.0353.

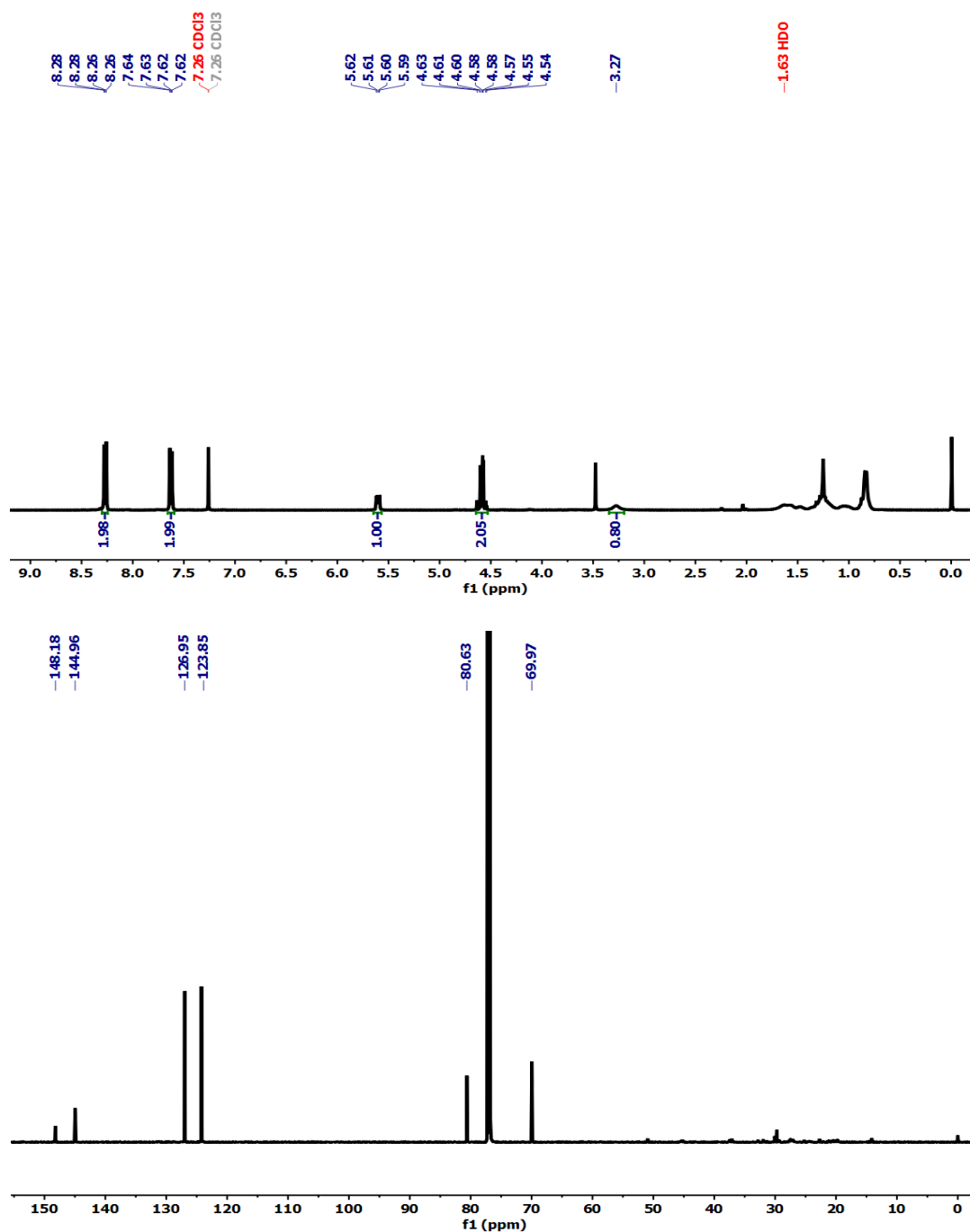


Figure 34: ^1H and ^{13}C NMR spectrum in CDCl_3 .

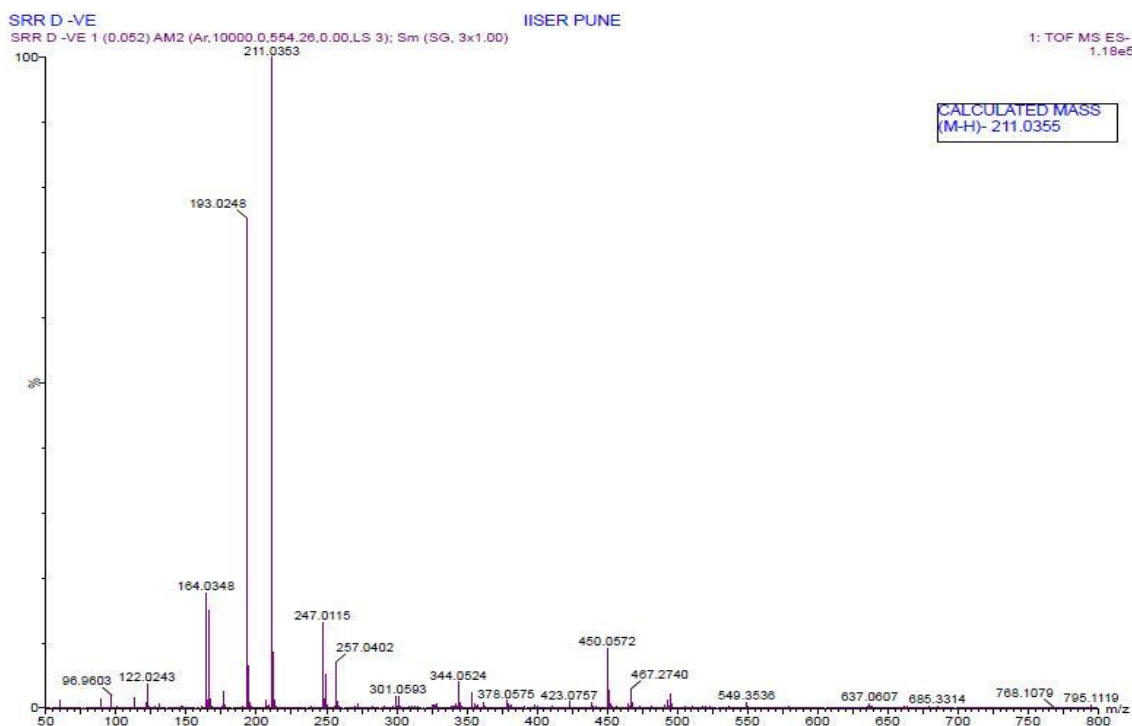


Figure 35: HRMS spectra of product with **P4** organogel in Nitromethane.

6. Conclusion:

In summary, our investigation has successfully demonstrated the formation of self-assembled organogels driven by short tripeptides. These peptides, strategically designed with β -branch valines at both ends and γ -Leu and γ -Phe in the middle, facilitated the gelation process in the presence of active methylene solvents. The terminal pyridine groups played a crucial role by establishing intermolecular hydrogen bonding with the acidic proton of the active methylene solvents. Notably, Peptides **P5** and **P6**, incorporating α -Leu, did not exhibit organogel formation with active methylene solvents, emphasizing the significance of the helix-inducing amino acid in the designed sequence. Furthermore, our study revealed that Peptides **P3** and **P4**, featuring γ -Phe in the middle, formed a densely packed fibrillar network, distinguishing them from **P1** and **P2** organogels with γ -Leu at the central position. Beyond the structural insights, we showcased the practical utility of these peptide organogels by employing them in catalyzing the Henry reaction in a gel state. This novel approach of designing functional peptide organogels for participation in catalytic reactions adds a new dimension to the potential applications of gelation studies in active methylene solvents.

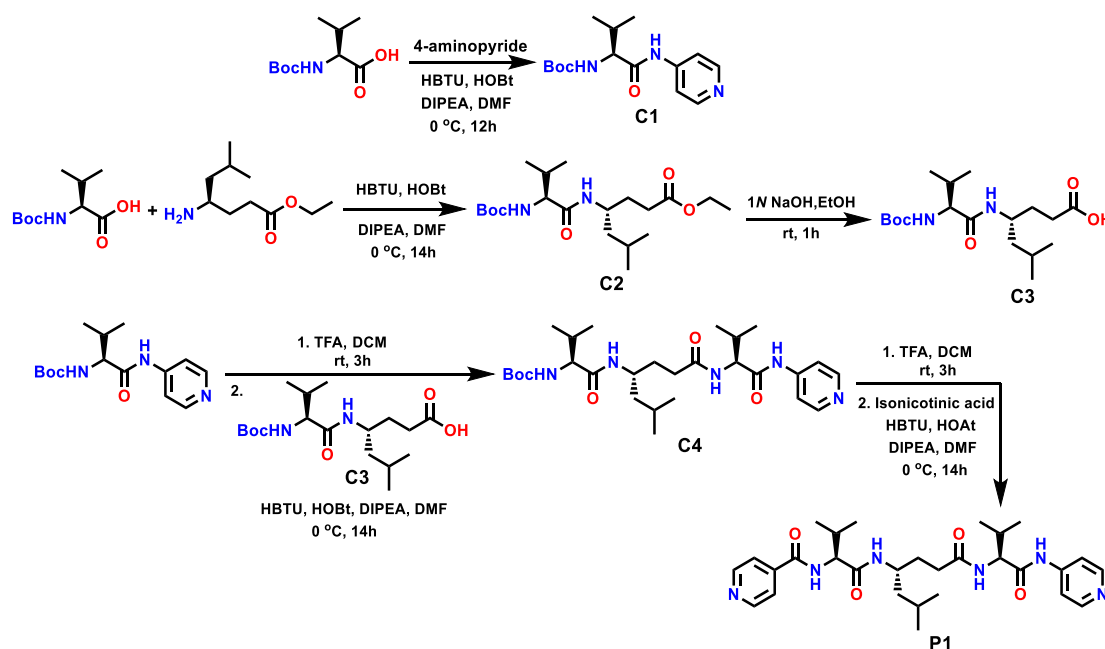
7. Experimental Section:

7.1. Materials and Methods:

All the coupling reactions were performed under N₂ conditions. All the amino acids, Boc anhydride, HBTU, HOBt, HOAt, 3-aminopyridine, 4-aminopyridine, nicotinic acid, isonicotinic acid, Trifluoroacetic acid (TFA), N, N-Diisopropylethylamine (DIPEA), DMF, EtOAc, Hexane, THF, Dichloromethane (DCM), and Methanol were purchased from different commercial sources. Ethyl acetate, Hexane, DCM, and Methanol were distilled before use. Column chromatography was performed on silica gel (100-200 mesh). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and ninhydrin or Iodine staining. The ¹H spectra were recorded on Bruker 600 MHz (or 150 MHz for ¹³C) / Bruker 400 MHz (or 100 MHz for ¹³C) spectrometers using residual solvent signals as an internal reference (CDCl₃ ¹H-7.26 ppm, ¹³C- 77.23 ppm, DMSO-*d*₆ ¹H-2.5 ppm, ¹³C-39.5 ppm and CD₃OH ¹H-3.31 ppm). The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad doublet (bd), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using MALDI-TOF Instrument.

7.2. General Procedure for the Synthesis of Peptides:

7.2.1. Synthesis of Peptide P1:



Scheme 9: Synthesis of short α,γ - hybrid tripeptide **P1**.

N-Boc protected valine (15 mmol, 3.26 g) was dissolved in 10 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (16.5 mmol, 6.27 g), HOBT (16.5 mmol, 2.24 g), and DIPEA (45 mmol, 7.88 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of 4-aminopyridine (21 mmol, 1.98 g). The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography to get a white crystalline product **C1** had an overall yield was 87%.

Now, N-Boc protected valine (14 mmol, 3.04 g) was dissolved in 5 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (11 mmol, 4.18 g), HOBT (11 mmol, 1.49 g), and DIPEA (30 mmol, 5.25 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of COOH-protected γ -Leu (H₂N- γ Leu-COOEt) (10 mmol, 2.87 g) in a little amount of DMF and remaining DIPEA (30 mmol, 5.25 mL). The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 1), 10% HCl solution (100 mL X 3), 10% Na₂CO₃ solution (100 mL X 3), and finally with brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography to get a white product **C2** had an overall yield was 88%.

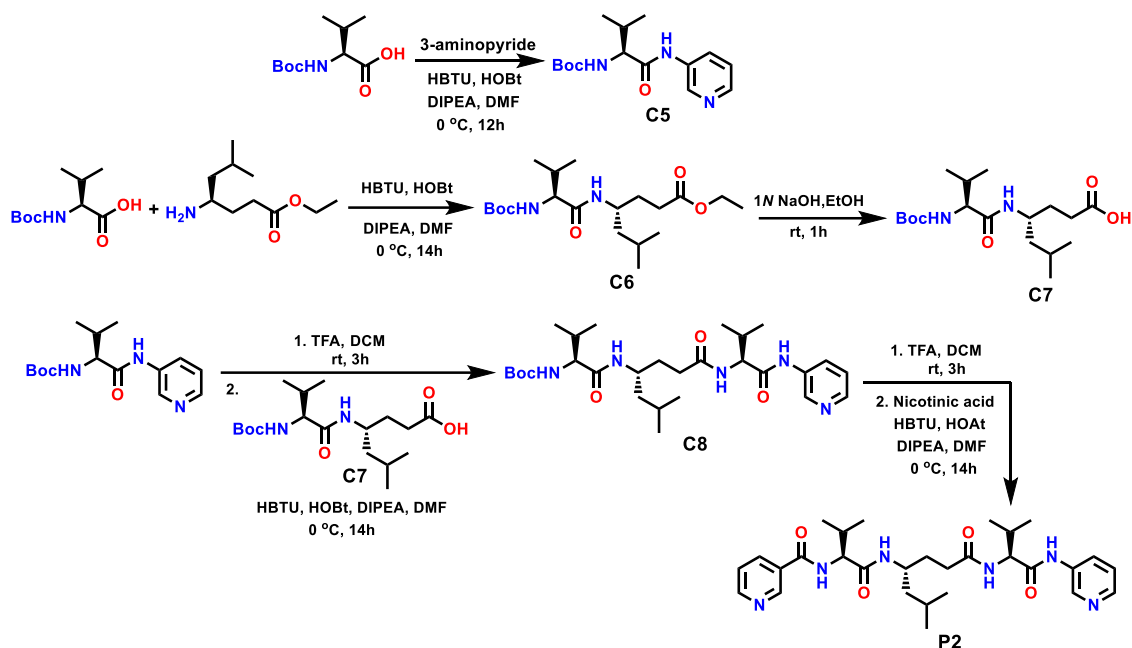
The purified product of compound **C2** was dissolved in EtOH in 250 mL RB, 1N NaOH was added to it and the reaction was left for 1h. After completion of the reaction, EtOH was evaporated off and the product was acidified with 10% HCl, and then was extracted using EtOAc (100 mL X 3) and finally with brine (100 mL X 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a viscous crude product **C3** which was used for further reaction.

Compound **C1** (3.94 mmol, 1.15 g) was subjected to Boc deprotection using 50% TFA in DCM (4 mL TFA in 4 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (8.45 mmol, 1.48 mL) to get the free amine of

compound **C1**. Now hybrid dipeptide acid (compound **C3**) (2.8 mmol, 1.01 g) was dissolved in 3 mL of DMF and was cooled down to 0 °C under N₂ atmosphere. To this, HBTU (3.09 mmol, 1.17 g), HOBT (3.09 mmol, 422 mg), and DIPEA (8.45 mmol, 1.48 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **C1** and the reaction mixture was further stirred overnight at room temperature. The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 200 mL EtOAc and was washed with brine (100 mL X 2), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 1). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude powder which was then purified by column chromatography (4% MeOH/DCM) to get a white product **C4** had an overall yield was 82%.

Compound **C4** (0.94 mmol, 500 mg) was subjected to Boc deprotection using 50% TFA in DCM (2 mL TFA in 2 mL DCM). Upon completion, the reaction mixture was evaporated several times with DCM to remove the residual TFA. The resulting TFA salt of amine was dissolved in 2 mL DMF and was quenched with DIPEA (3 mmol, 0.5 mL) to get the free amine of compound **C4**. Now Isonicotinic acid (1.32 mmol, 161.4 mg) was dissolved in 2 mL of DMF and the solution was then cooled to 0 °C using an ice bath under N₂ atmosphere. To this, HBTU (1.04 mmol, 393 mg), HOAt (1.04 mmol, 141 mg), and DIPEA (3 mmol, 0.5 mL) were added and the reaction mixture was stirred for 10 minutes. This was followed by the addition of amine cocktail of compound **C4** and the reaction mixture was further stirred overnight at room temperature. The reaction mixture was stirred overnight and the progress was monitored by TLC. Upon completion, the reaction mixture was diluted with 150 mL of EtOAc and was washed with brine (100 mL X 1), 10% Na₂CO₃ solution (100 mL X 3), and finally brine (100 mL X 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product which was then purified by column chromatography (6% MeOH/DCM) to get a white product Peptide **P1** having an overall yield was 80%.

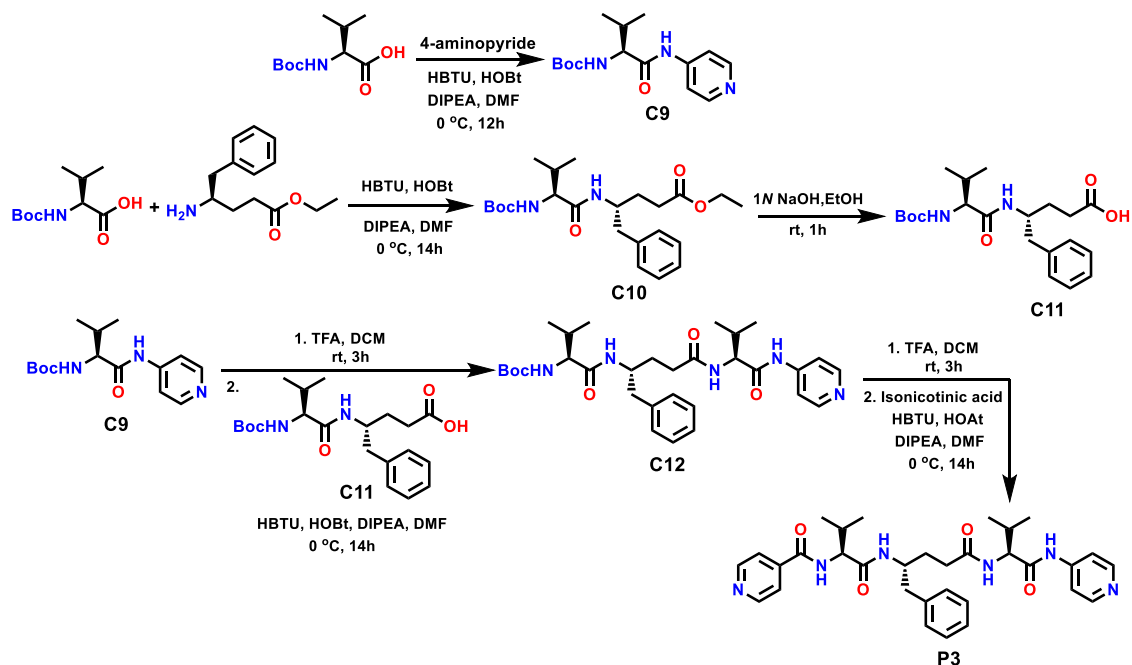
7.2.2. Synthesis of Peptide **P2**:



Scheme 10: Synthesis of short α,γ - hybrid tripeptide **P2**.

The synthesis of **P2** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 82%).

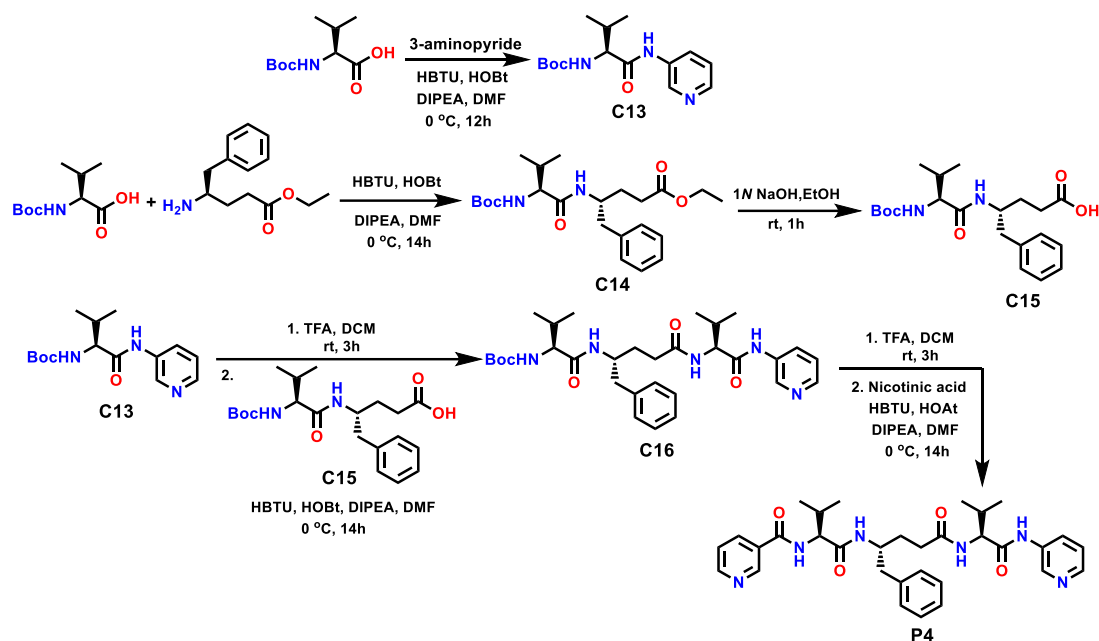
7.2.3. Synthesis of Peptide **P3**:



Scheme 11: Synthesis of short α,γ - hybrid tripeptide **P3**.

The synthesis of **P3** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 84%).

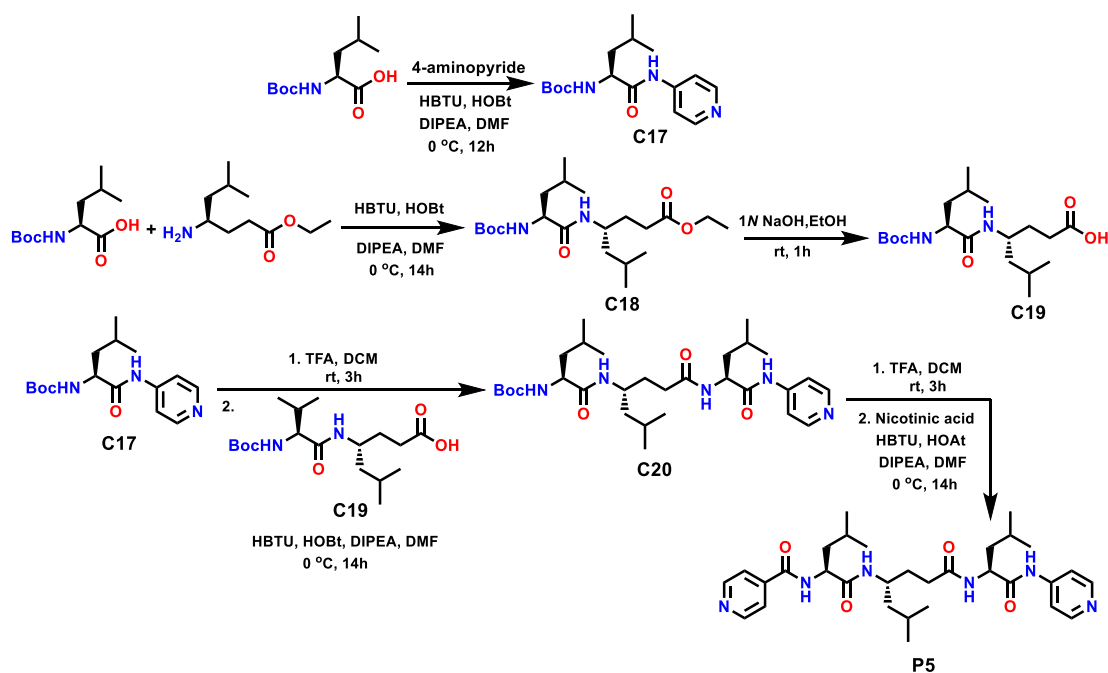
7.2.4. Synthesis of Peptide P4:



Scheme 12: Synthesis of short α,γ - hybrid tripeptide **P4**.

The synthesis of **P4** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 75%).

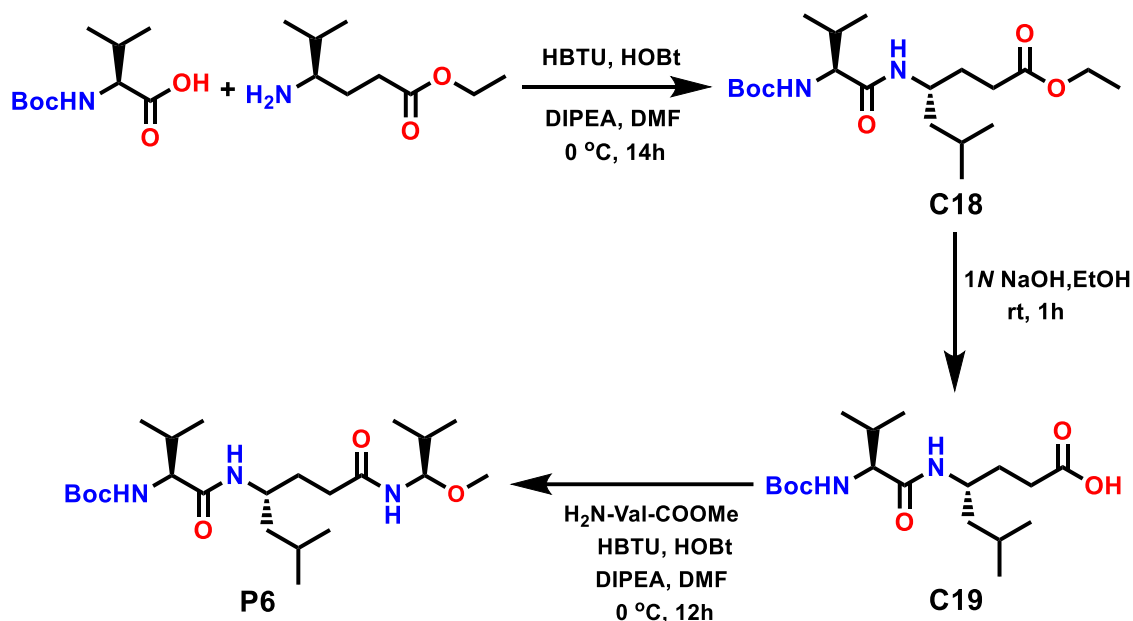
7.2.5. Synthesis of Peptide P5:



Scheme 13: Synthesis of short α,γ - hybrid tripeptide **P5**.

The synthesis of **P5** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 85%).

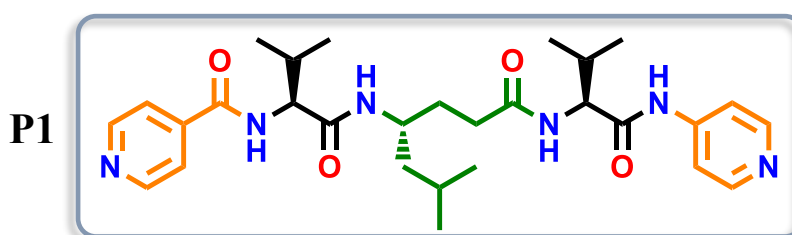
7.2.6. Synthesis of Peptide P6:



Scheme 14: Synthesis of short α,γ - hybrid tripeptide **P6**.

The synthesis of **P6** was carried out as described in the above scheme, following similar protocols as of **P1** (Yield- 92%).

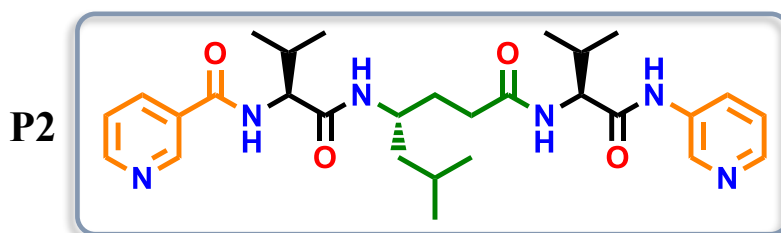
7.3. Characterisation of Peptides (P1-P6):



¹H NMR (600 MHz, DMSO-*d*₆) δ 10.44 (s, 1H), 8.71 – 8.68 (m, 2H), 8.58 (d, *J* = 8.6 Hz, 1H), 8.41 – 8.37 (m, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.74 (td, *J* = 5.5, 5.0, 1.7 Hz, 2H), 7.59 – 7.55 (m, 2H), 4.25 – 4.16 (m, 3H), 2.15 (t, *J* = 7.8 Hz, 2H), 2.13 – 2.07 (m, 1H), 1.65 – 1.58 (m, 1H), 1.58 – 1.50 (m, 2H), 1.31 (ddd, *J* = 14.5, 9.9, 4.9 Hz, 1H), 1.16 (ddd, *J* = 13.5, 9.1, 4.5 Hz, 1H), 0.92 (d, *J* = 2.3 Hz, 3H), 0.91 (d, *J* = 2.3 Hz, 3H), 0.89 (d, *J* = 4.0 Hz, 4H), 0.88 (d, *J* = 3.9 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, DMSO- d_6) δ 173.02, 172.07, 170.67, 165.51, 150.50, 150.34, 145.65, 141.58, 121.80, 113.64, 79.30, 60.08, 59.46, 46.64, 43.53, 32.04, 31.54, 30.41, 29.98, 24.51, 23.38, 21.97, 19.60, 19.35, 19.08, 18.54.

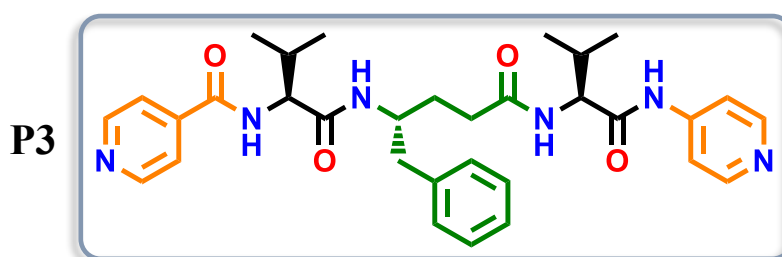
MALDI TOF/TOF m/z calculated for $\text{C}_{29}\text{H}_{42}\text{N}_6\text{O}_4$ $[\text{M}+\text{Na}]^+$ is 561.68 and the observed value is 561.601. $[\text{M}+\text{K}]^+$ is 577.79 and the observed value is 577.54.



^1H NMR (600 MHz, DMSO- d_6) δ 10.26 (s, 1H), 8.99 (dd, J = 2.2, 0.9 Hz, 1H), 8.75 (d, J = 2.5 Hz, 1H), 8.69 (dd, J = 4.8, 1.7 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.24 (dd, J = 4.7, 1.5 Hz, 1H), 8.19 (dt, J = 8.0, 2.0 Hz, 1H), 8.03 (ddd, J = 8.4, 2.6, 1.6 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.50 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.32 (dd, J = 8.3, 4.7 Hz, 1H), 4.24 – 4.18 (m, 2H), 3.79 (dp, J = 14.0, 4.8 Hz, 1H), 2.16 (t, J = 7.6 Hz, 2H), 2.14 – 2.08 (m, 1H), 2.03 (hept, J = 6.8 Hz, 1H), 1.63 (td, J = 13.2, 7.9 Hz, 1H), 1.54 (tt, J = 15.4, 7.5 Hz, 2H), 1.32 (ddd, J = 14.7, 9.9, 5.0 Hz, 1H), 1.16 (td, J = 9.1, 4.5 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H), 0.90 (d, J = 2.7 Hz, 3H), 0.89 (d, J = 2.6 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, DMSO) δ 173.10, 171.53, 171.01, 165.80, 152.32, 149.00, 144.78, 141.39, 135.88, 135.79, 130.36, 126.86, 124.12, 123.88, 60.24, 59.44, 46.78, 43.83, 32.28, 31.76, 30.73, 30.21, 24.72, 23.60, 22.18, 19.85, 19.61, 19.31, 18.79.

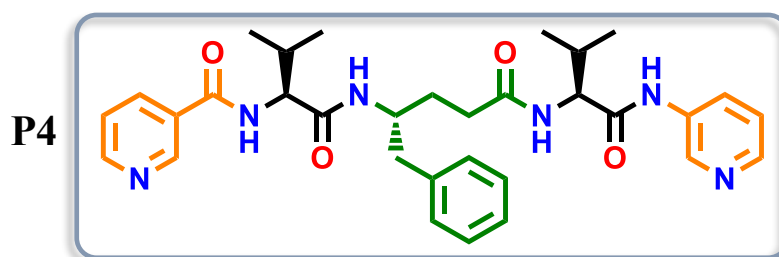
MALDI TOF/TOF m/z calculated for $\text{C}_{29}\text{H}_{42}\text{N}_6\text{O}_4$ $[\text{M}+\text{Na}]^+$ is 561.68 and the observed value is 561.61. $[\text{M}+\text{K}]^+$ is 577.79 and the observed value is 577.64.



¹H NMR (600 MHz, CD₃OH) δ 10.39 (s, 1H), 8.72 – 8.68 (m, 2H), 8.47 (d, *J* = 7.8 Hz, 1H), 8.37 – 8.34 (m, 2H), 8.15 (d, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.70 – 7.66 (m, 2H), 7.14 – 7.01 (m, 5H), 4.23 (t, *J* = 7.0 Hz, 1H), 4.21 – 4.16 (m, 1H), 4.09 (ddt, *J* = 14.1, 9.2, 4.4 Hz, 1H), 2.83 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.71 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.17 (h, *J* = 6.8 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.96 (dtd, *J* = 16.6, 8.3, 3.9 Hz, 1H), 1.74 – 1.64 (m, 1H), 1.03 (d, *J* = 3.3 Hz, 3H), 1.02 (d, *J* = 3.2 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 4H).

¹³C NMR (151 MHz, CD₃OH) δ 174.70, 172.29, 171.96, 166.57, 149.52, 149.20, 146.61, 142.10, 138.25, 128.96, 127.87, 125.89, 121.80, 114.15, 61.20, 60.64, 50.49, 40.64, 31.94, 30.58, 30.40, 30.02, 18.46, 18.27, 18.09, 17.33.

MALDI TOF/TOF *m/z* calculated for C₃₂H₄₀N₆O₄ [M+Na]⁺ is 595.70 and the observed value is 595.607. [M+K]⁺ is 611.81 and the observed value is 611.55.

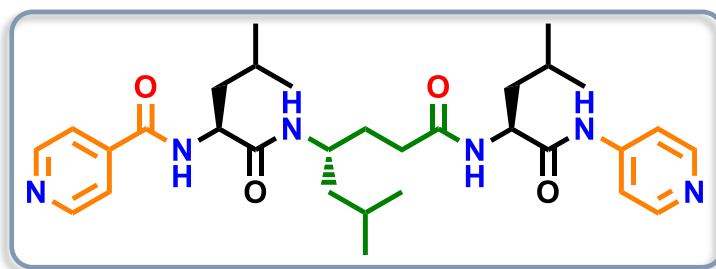


¹H NMR (400 MHz, DMSO-*d*₆) δ 10.27 (s, 1H), 8.99 (d, *J* = 1.6 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 8.26 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.19 (dt, *J* = 8.1, 1.9 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H), 7.34 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.19 – 7.04 (m, 5H), 4.26 – 4.10 (m, 2H), 3.93 (s, 1H), 2.69 (qd, *J* = 13.7, 6.7 Hz, 2H), 2.26 – 2.13 (m, 2H), 2.02 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.69 (d, *J* = 7.8 Hz, 1H), 1.62 – 1.53 (m, 1H), 0.90 – 0.82 (m, 13H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 172.95, 171.52, 171.03, 165.65, 152.33, 149.06, 144.81, 141.37, 139.11, 135.88, 135.83, 130.26, 129.64, 128.42, 126.84, 126.35, 124.16, 123.86, 60.26, 59.41, 50.27, 32.33, 30.76, 30.48, 30.23, 29.43, 19.77, 19.60, 19.37, 18.80.

MALDI TOF/TOF *m/z* calculated for C₃₂H₄₀N₆O₄ [M+Na]⁺ is 595.70 and the observed value is 595.62. [M+K]⁺ is 611.81 and the observed value is 611.54.

P5

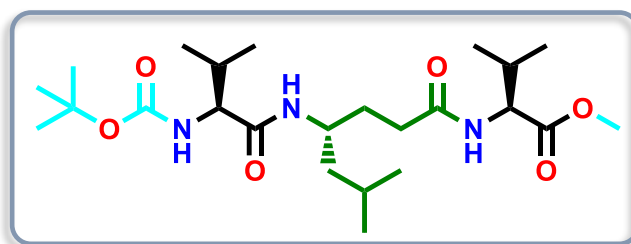


^1H NMR (600 MHz, $\text{DMSO-}d_6$) δ 10.38 (s, 1H), 8.73 (s, 1H), 8.72 – 8.70 (m, 2H), 8.39 – 8.35 (m, 2H), 8.10 (d, J = 7.4 Hz, 1H), 7.81 – 7.77 (m, 2H), 7.74 (d, J = 9.0 Hz, 1H), 7.61 – 7.56 (m, 2H), 4.47 (ddd, J = 10.4, 8.0, 5.0 Hz, 1H), 4.37 (ddd, J = 10.1, 7.4, 5.1 Hz, 1H), 3.77 (qt, J = 9.3, 4.7 Hz, 1H), 2.11 (t, J = 7.7 Hz, 2H), 1.72 (ddd, J = 13.0, 10.3, 5.1 Hz, 1H), 1.64 (dq, J = 18.5, 6.1, 5.1 Hz, 3H), 1.59 – 1.43 (m, 5H), 1.34 (ddd, J = 14.9, 9.9, 5.0 Hz, 1H), 1.16 (ddt, J = 13.7, 9.1, 4.5 Hz, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.88 – 0.85 (m, 6H), 0.82 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $\text{DMSO-}d_6$) δ 172.85, 172.53, 171.55, 164.90, 150.23, 150.17, 145.68, 141.17, 121.58, 113.45, 64.98, 52.34, 48.65, 46.22, 43.55, 40.40, 31.83, 31.40, 24.52, 24.39, 24.30, 23.22, 23.05, 22.99, 21.81, 21.52, 21.50, 15.22.

MALDI TOF/TOF m/z calculated for $\text{C}_{31}\text{H}_{46}\text{N}_6\text{O}_4$ $[\text{M}+\text{Na}]^+$ is 589.74 and the observed value is 589.669. $[\text{M}+\text{K}]^+$ is 605.85 and the observed value is 605.58.

P6



^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 6.62 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 5.06 (d, J = 8.7 Hz, 1H), 4.48 (ddd, J = 11.0, 8.5, 5.3 Hz, 2H), 3.89 (dd, J = 8.7, 6.4 Hz, 1H), 3.73 (s, 3H), 2.15 (dtd, J = 13.8, 6.9, 5.1 Hz, 2H), 1.74 (s, 3H), 1.69 – 1.62 (m, 2H), 1.61 – 1.52 (m, 1H), 1.47 – 1.40 (m, 9H), 1.32 – 1.19 (m, 1H), 0.97 – 0.84 (m, 18H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.54, 172.33, 172.08, 156.33, 80.51, 60.53, 57.64, 52.60, 52.26, 41.29, 31.62, 31.05, 28.73, 25.07, 23.31, 22.47, 19.77, 19.36, 18.22.

MALDI TOF/TOF m/z calculated for $\text{C}_{24}\text{H}_{45}\text{N}_3\text{O}_6$ $[\text{M}+\text{Na}]^+$ is 471.33 and the observed value is 471.44. $[\text{M}+\text{K}]^+$ is 510.33 and the observed value is 510.40.

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8. ^1H , ^{13}C NMR, and Mass Spectra of Peptides:

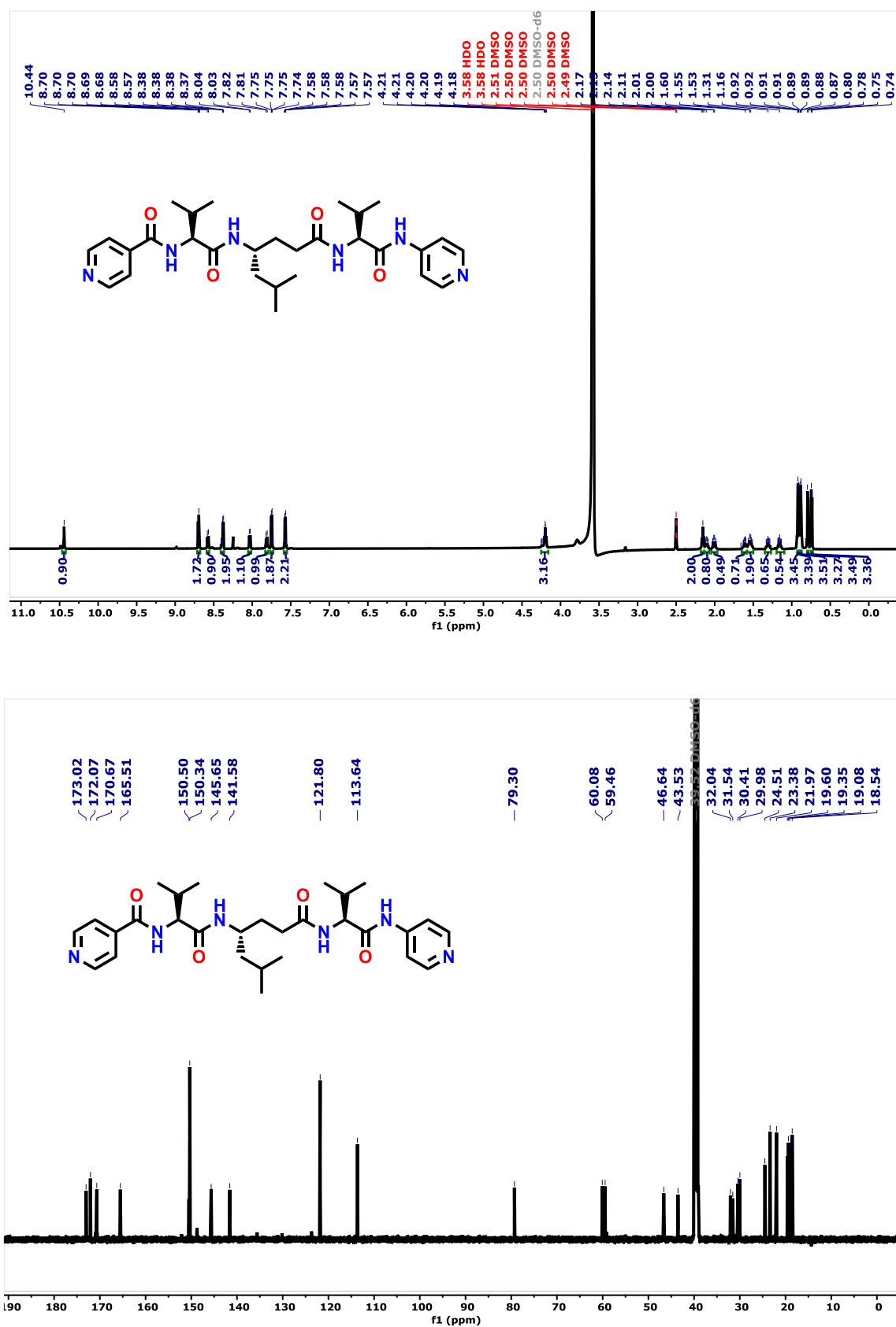


Figure 36: ^1H & ^{13}C NMR spectrum of **P1** in $\text{DMSO}-d_6$.

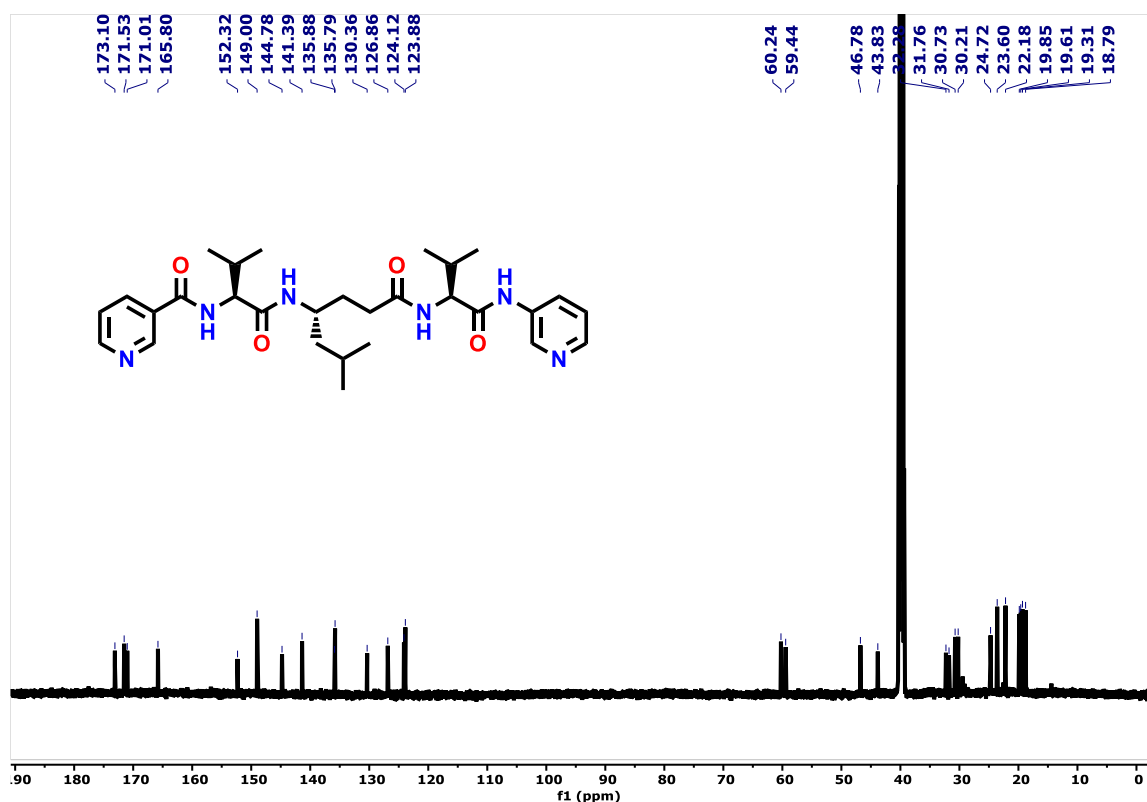
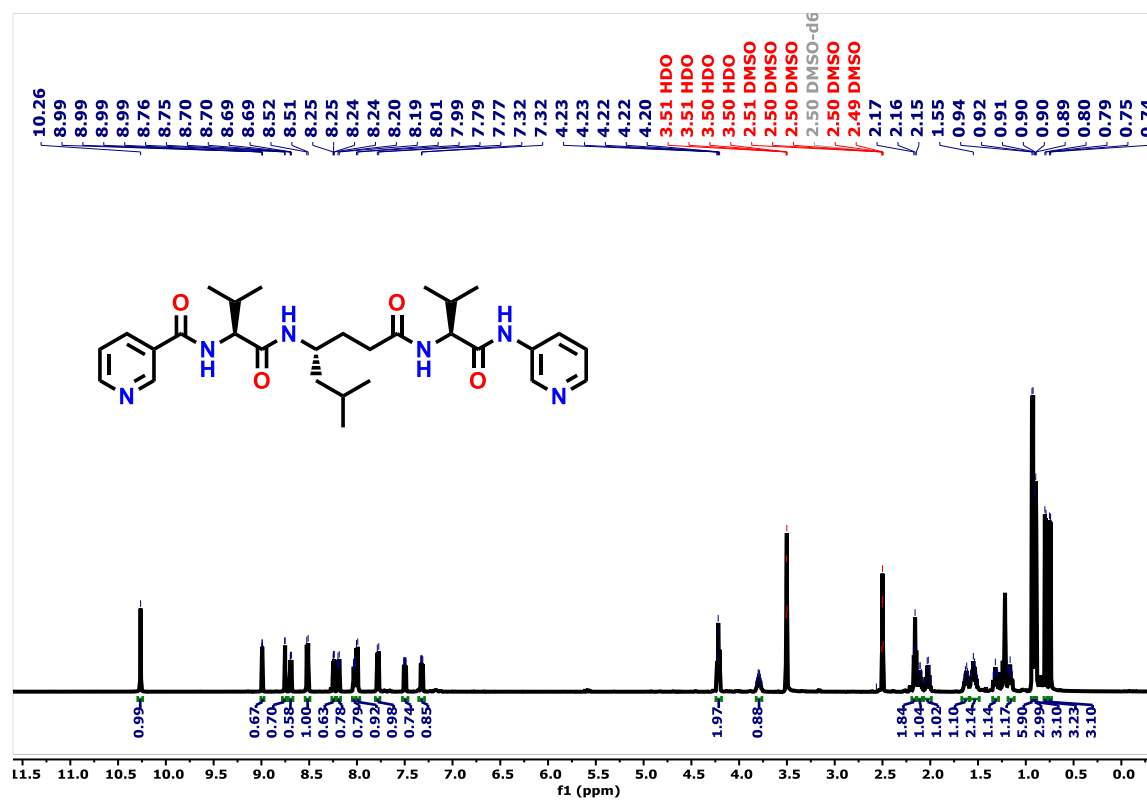


Figure 37: ^1H & ^{13}C NMR spectrum of **P2** in DMSO- d_6 .

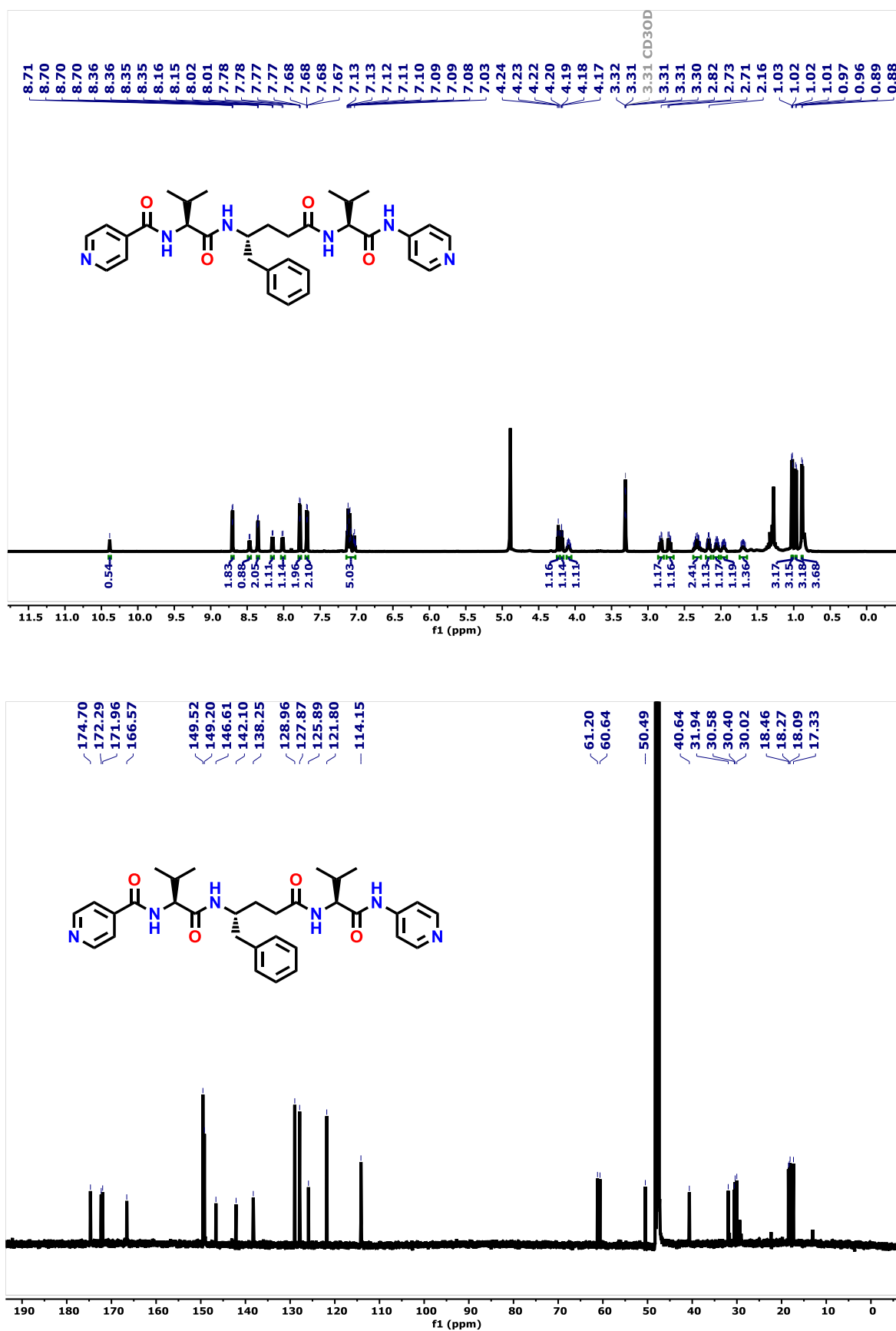


Figure 38: ¹H & ¹³C NMR spectrum of **P3** in CD₃OH.

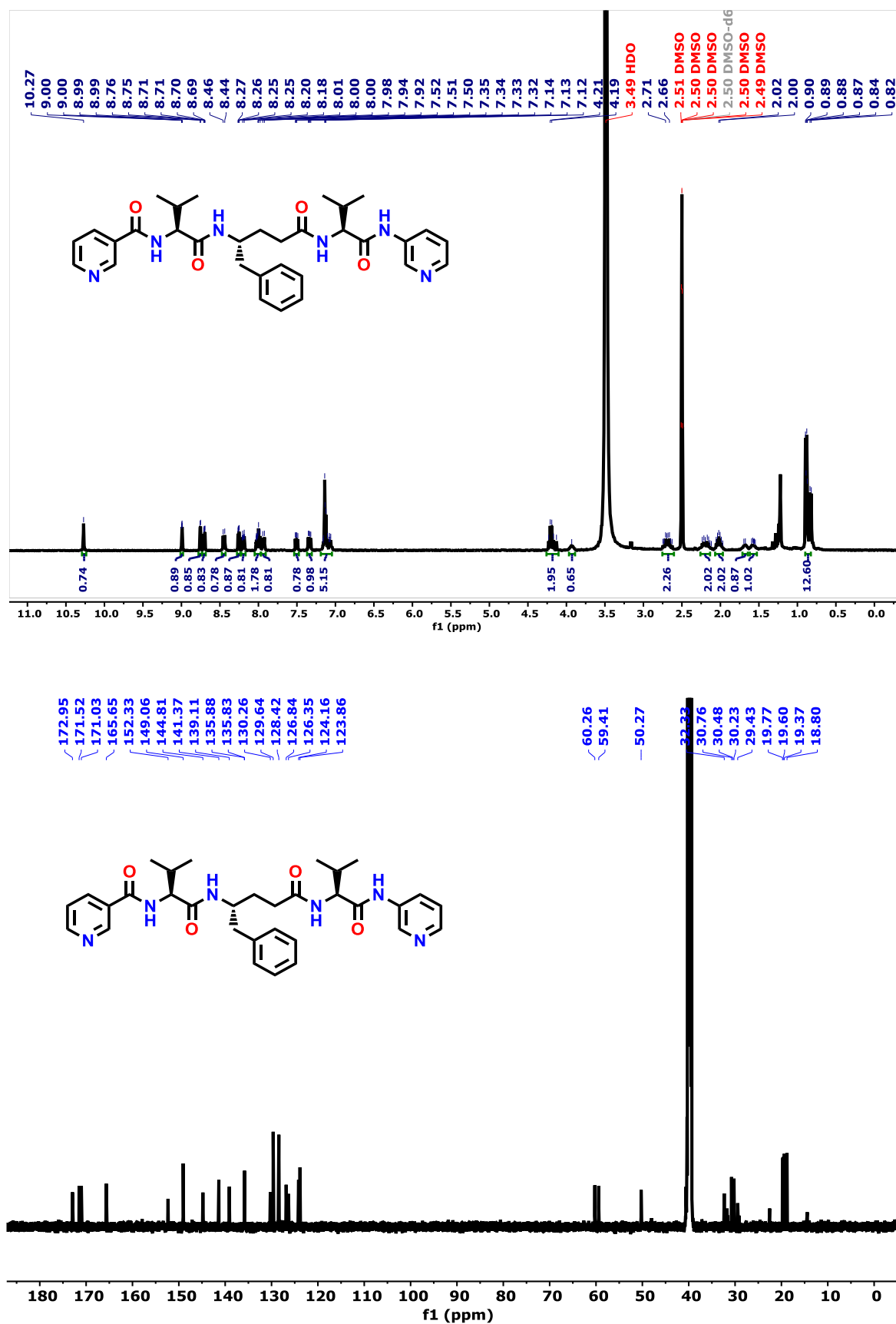


Figure 39: ¹H & ¹³C NMR spectrum of **P4** in DMSO-*d*₆.

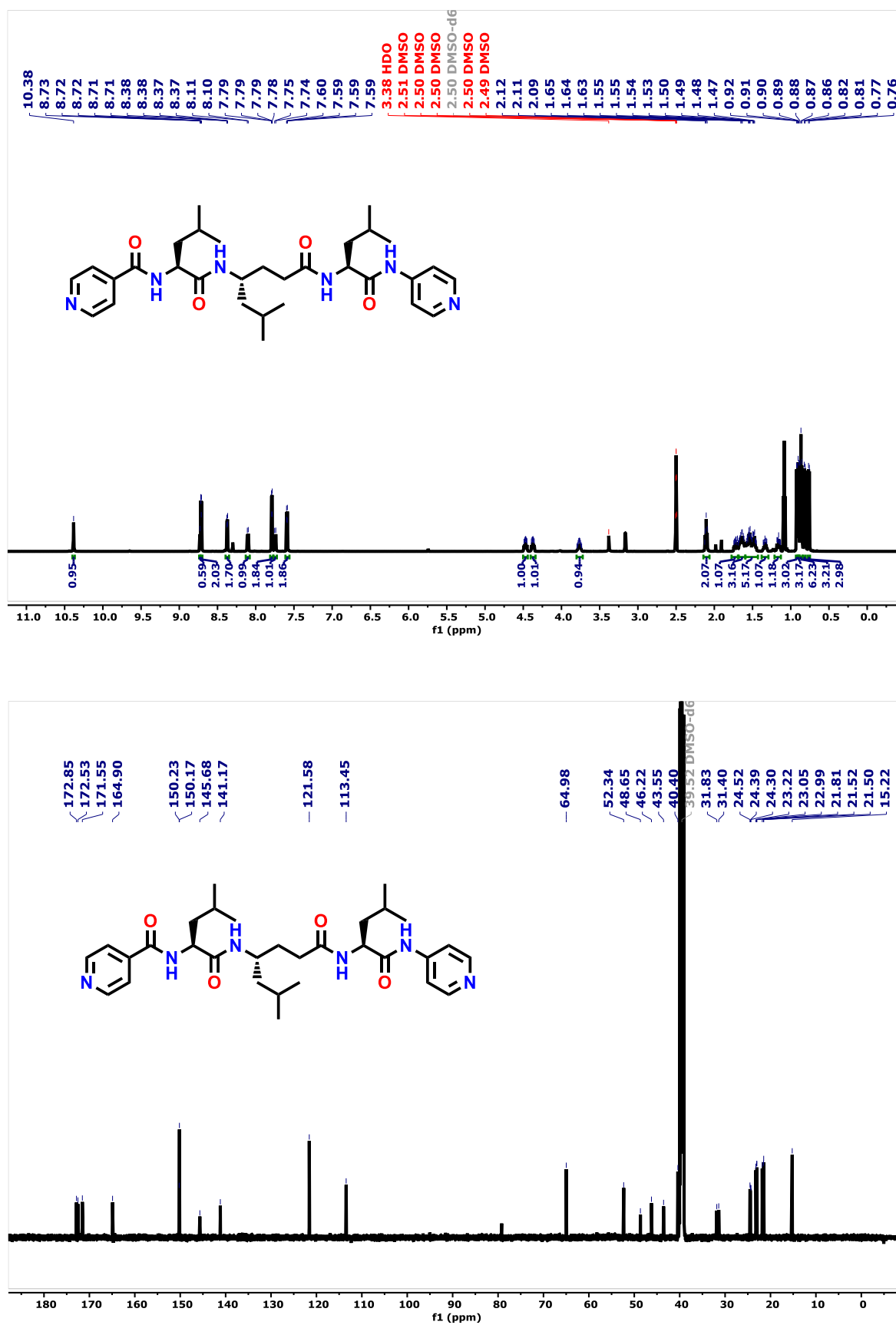


Figure 40: ¹H & ¹³C NMR spectrum of P5 in DMSO-*d*₆.

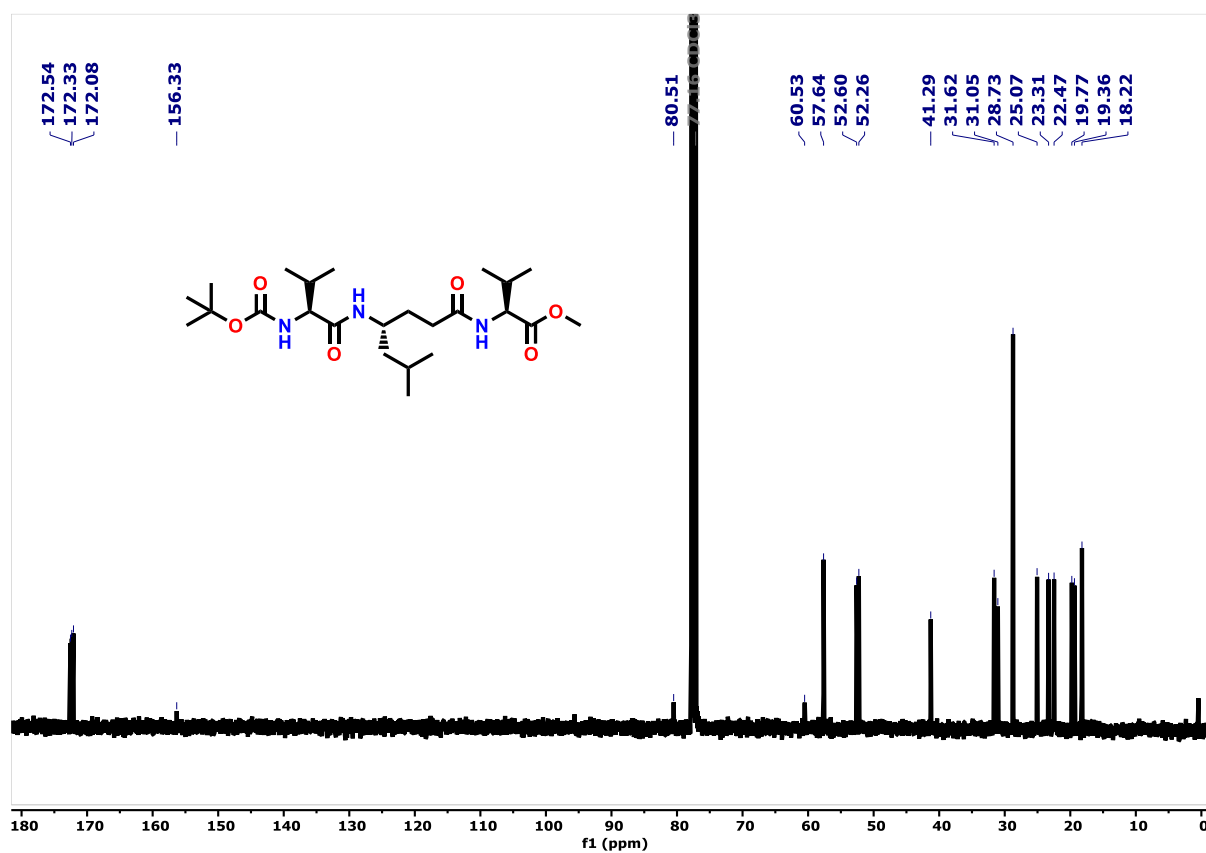
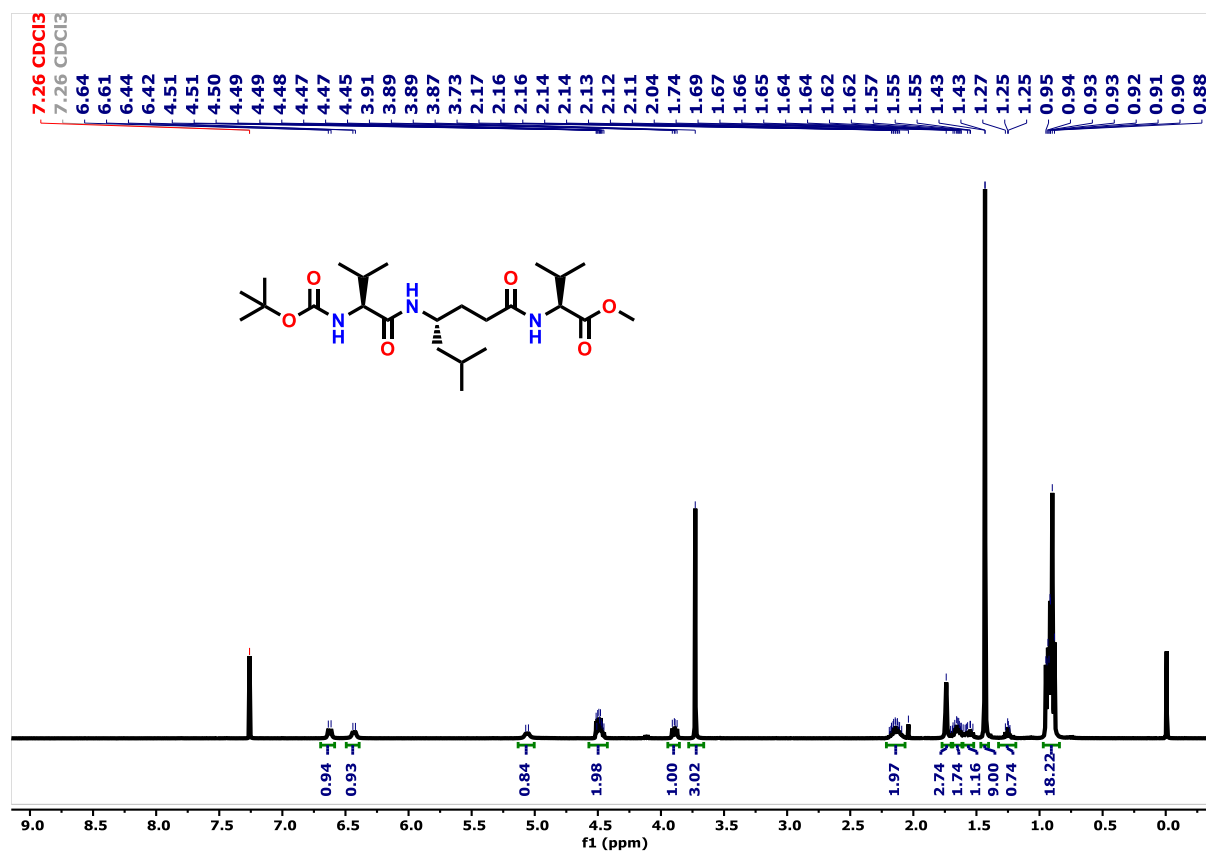


Figure 41: ¹H & ¹³C NMR spectrum of **P6** in CDCl₃.

Spectrum Report

Final - Shots 500 - IISER-96-2-2018; Label E9

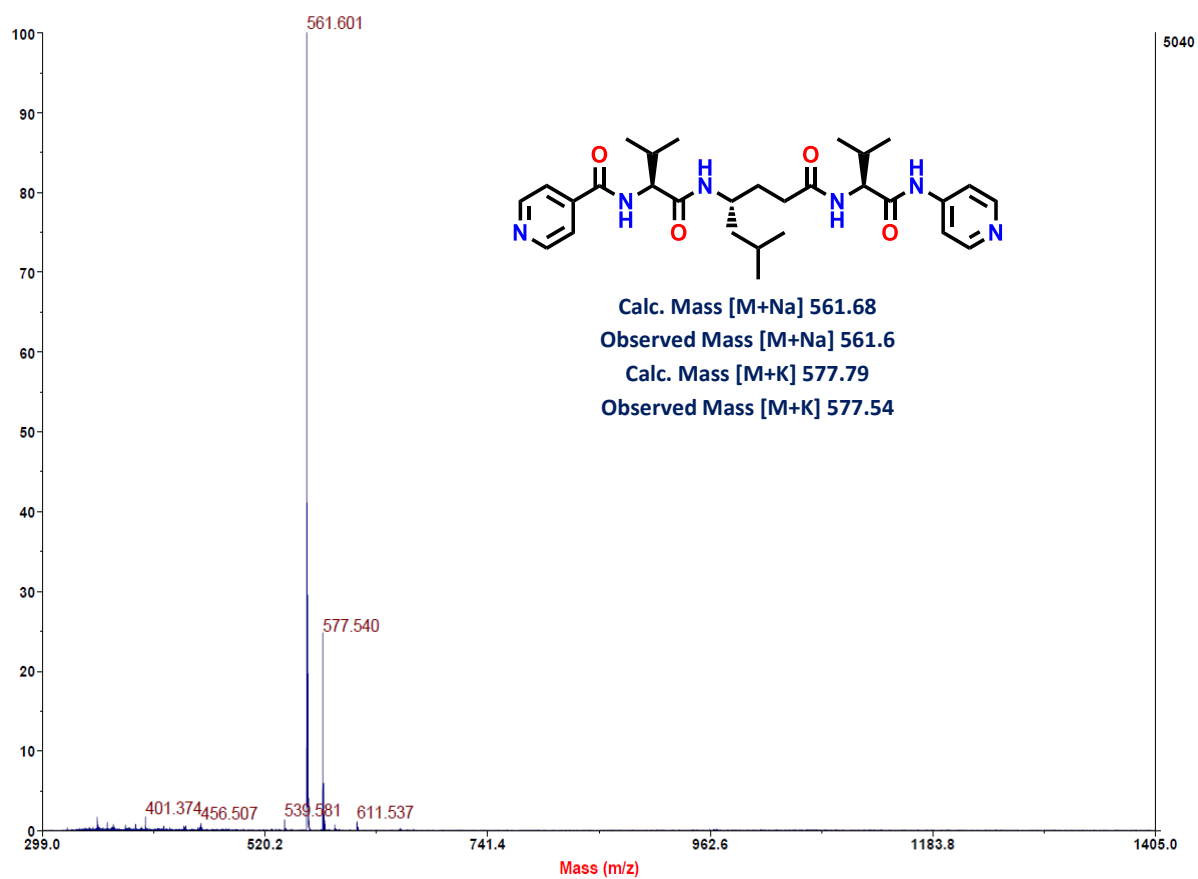


Figure 42: MALDI-TOF/TOF mass spectrum of **P1**.

Spectrum Report

Final - Shots 500 - IISER-96-2-2018; Label E8

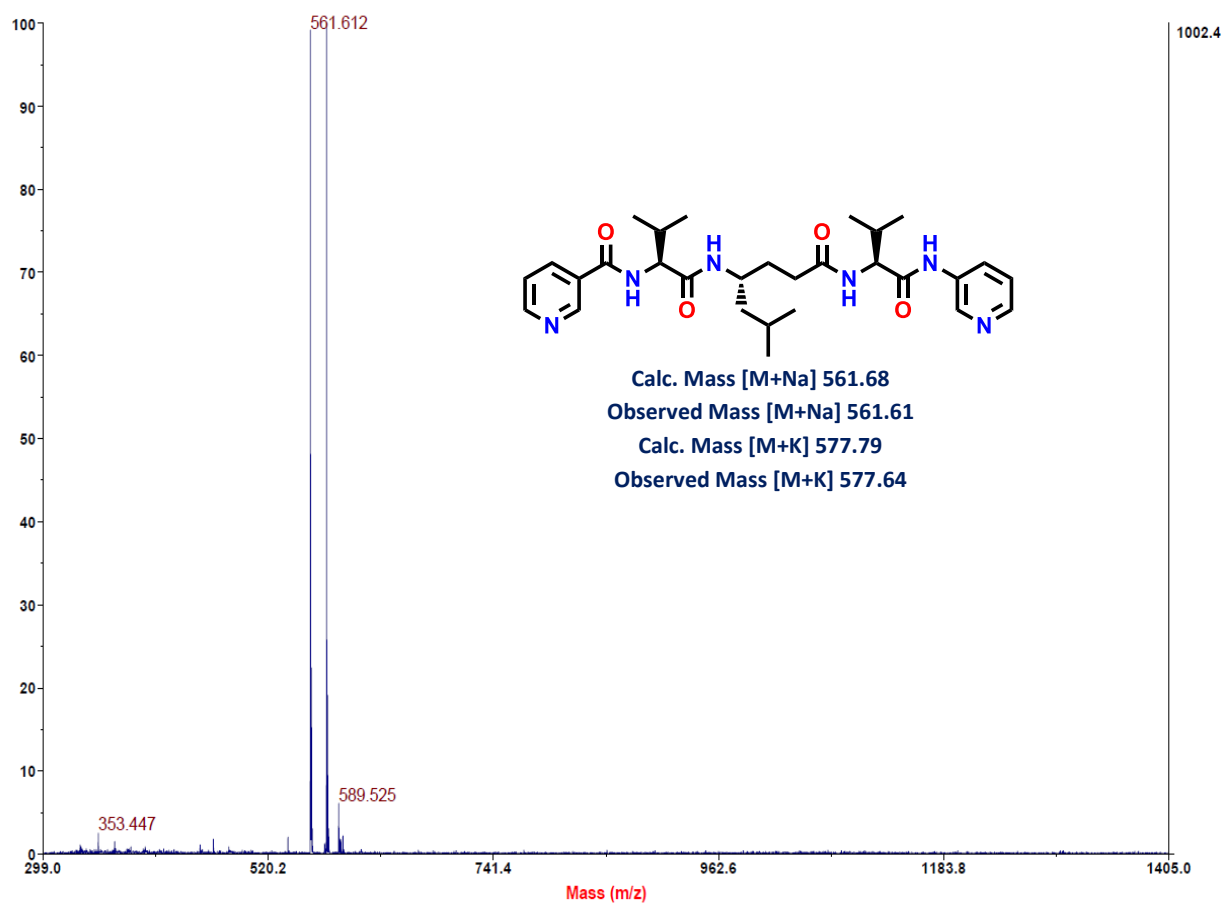


Figure 43: MALDI-TOF/TOF mass spectrum of **P2**.

Spectrum Report

Final - Shots 500 - IISER-96-2-2018; Label F5

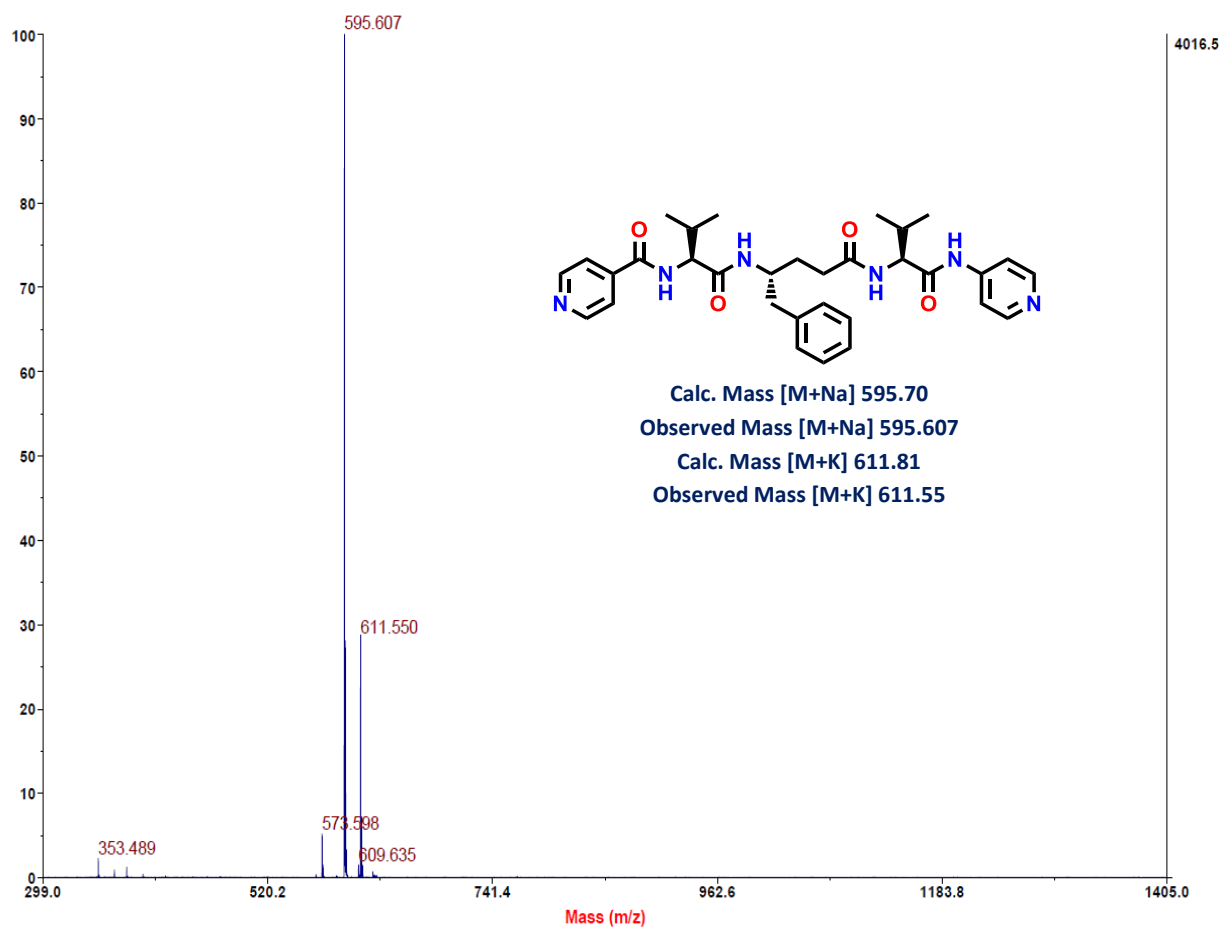


Figure 44: MALDI-TOF/TOF mass spectrum of **P3**.

Spectrum Report

Final - Shots 500 - IISER-96-2-2018; Label E6

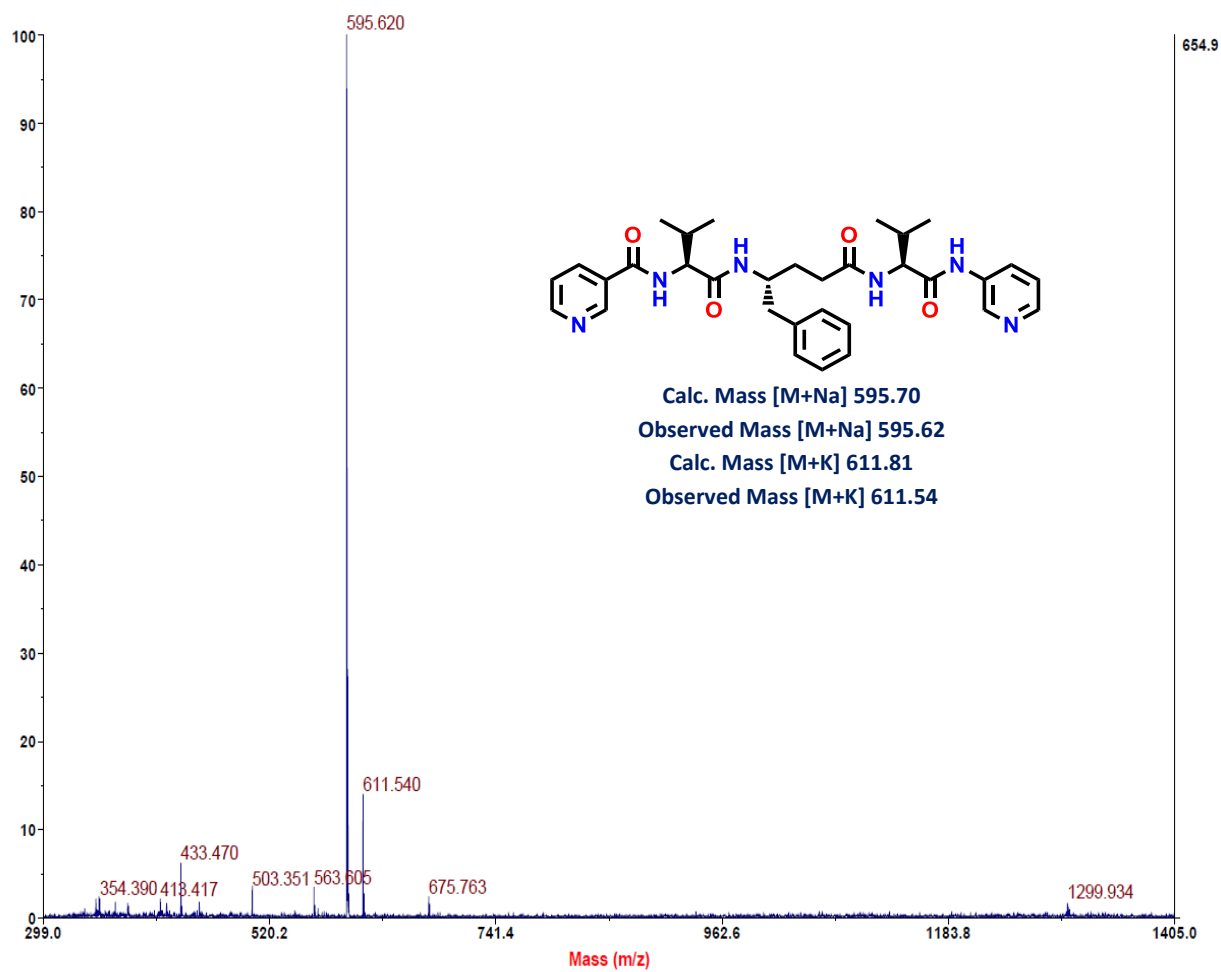


Figure 45: MALDI-TOF/TOF mass spectrum of **P4**.

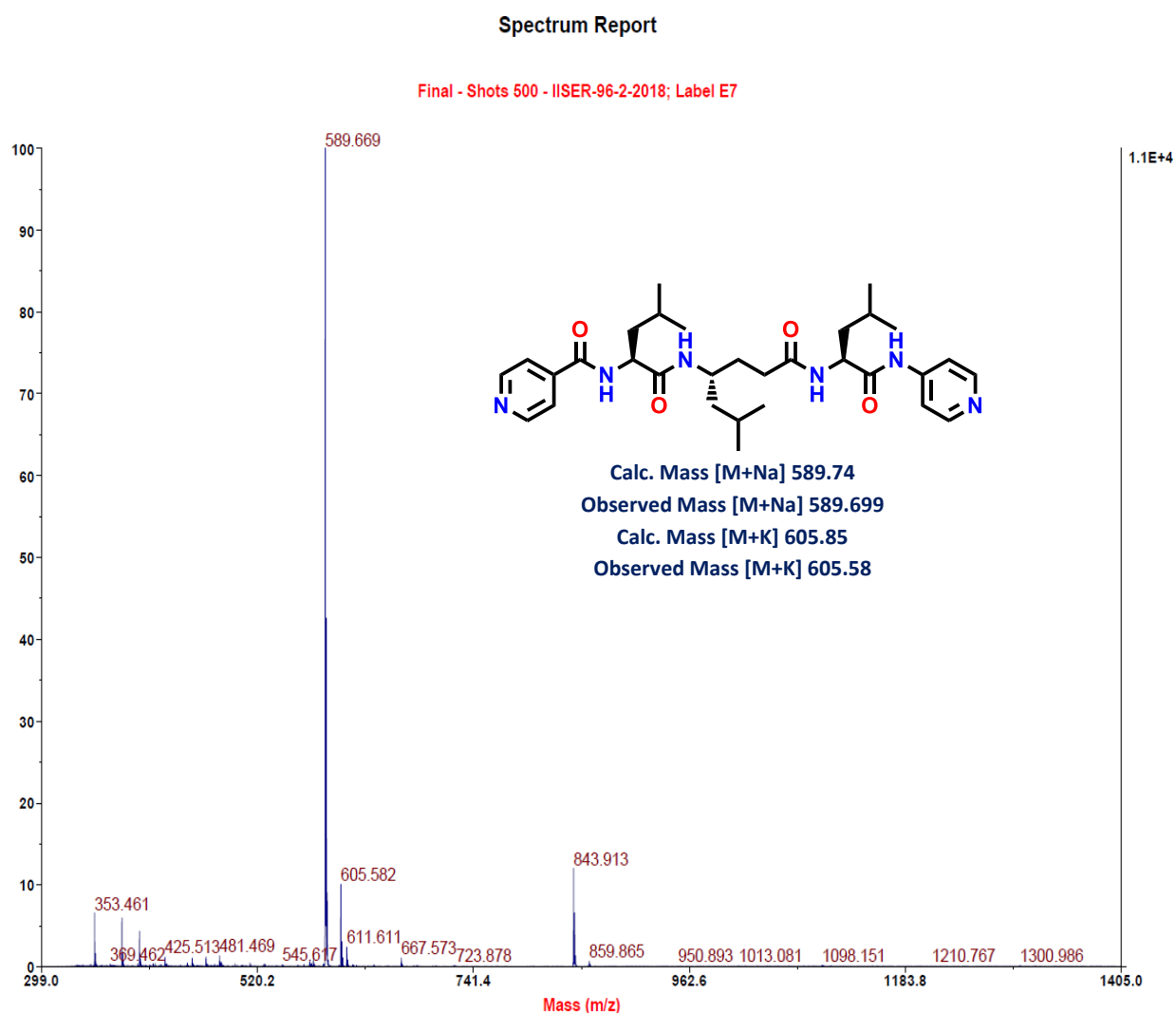
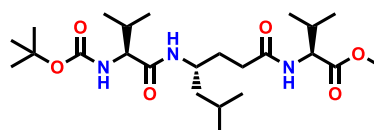


Figure 46: MALDI-TOF/TOF mass spectrum of **P5**.

Final - Shots 200 - IISER-96-1-2023; Label B5



Calc. Mass [M+Na] 494.33
Observed Mass [M+Na] 494.44
Calc. Mass [M+K] 510.33
Observed Mass [M+K] 510.40

255