

# **PROTEIN ENGINEERING: DESIGN, SYNTHESIS AND FUNCTIONAL PROPERTIES OF PEPTIDOMIMETIC FOLDAMERS**

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# **Protein Engineering: Design, Synthesis and Functional Properties of Peptidomimetic Foldamers**

by

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Submitted

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*Dedicated to my parents and family members*

## CERTIFICATE

This is to certify that the thesis entitled, "**Protein Engineering: Design, Synthesis and Functional Properties of Peptidomimetic Foldamers**", being submitted by **Mr. Hanuman Singh** to the Indian Institute of Technology, Delhi, for the award of the degree of **Doctor of Philosophy in Chemistry**, is a record of genuine research work carried out by him. **Mr. Hanuman Singh** has worked under my direction and supervision and has completed all of the prerequisites for the submission of this thesis, which, to the best of my knowledge, has attained the necessary level of quality. The findings presented in this thesis have not been presented, in whole or in part, to any other academic institution for the purpose of receiving a certificate, degree, or other academic honor.

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# ABSTRACT

The thesis entitled "**Protein Engineering: Design, Synthesis and Functional Properties of Peptidomimetic Foldamers**" describes the simple designs of peptidomimetic foldamers derived from pseudopeptide molecules, which have a wide range of applications in chemical biology and biophysical chemistry. In addition, we have also studied the rotational dynamics of these peptidomimetic foldamers. Further, we described the molecular-topology-based approaches for creating reproducible vesicular assemblies in different solvent environments and topologically intriguing structures showing ion channel transporters. The thesis work has been broken up into five chapters.

## Chapter 1

Chapter 1 gives a comprehensive overview of designer peptidomimetic foldamers in a systematic manner, encompassing all the preliminary designs as well as the recent advancements. A variety of well-defined protein secondary structure folding peptidic systems, ranging from amphiphilic peptides and cyclic peptides, have been reviewed thoroughly. Furthermore, the study of different topological arrangements of dynamic foldamers which are closely related to motor proteins and self-assembly of peptidomimetic foldamers to quaternary structures such as vesicles using different strategies proposed in the literature is also explored. In addition, foldamers having molecular knotted structures that could also be used for ion transport studies were also highlighted.

## Chapter 2

Chapter 2 deals with the development of synthetic bispidine based scaffolds that nucleate well-folded secondary and quaternary structures. These bispidine-scaffolded peptides were studied by CD, IR, NMR, single crystal XRD, and Molecular Dynamics (MD) simulations to investigate their conformational preferences. The solid state and solution studies also confirm that bispidine is a

versatile scaffold that could be placed either at the terminal or at the middle of the peptide strand for nucleating  $\beta$ -strand structure. Bispidine placed at the C-terminus of the peptide chain could nucleate  $\beta$ -strand conformation, while at the middle resulted in a  $\beta$ -arch conformation. This nucleation activity stems from the ability to restrict the  $C_{\alpha}$ -CO torsional angle ( $\psi$ ) through the intramolecular C5 hydrogen bonding between the equatorial hydrogens of bispidine and the carbonyl oxygen(s) of the amino acid close to the scaffold. Further, the bispidine peptidomimetic with a super secondary structure, namely  $\beta$ -arch assembled into single-hole nanocages and spherical vesicles were also showed.

### **Chapter 3**

Chapter 3 outlines the development of artificial molecular rotors is a challenging endeavor. Herein, we have synthesized a series of bispidine diamides that exhibit rotation reminiscent of a molecular rotor. Dynamic NMR, X-ray diffraction, and molecular dynamics provided the insights into the rotational dynamics. Studies showed a unidirectional rotation and rate of rotation depends on the nature of substitution. These engineered systems may aid in the development of biologically relevant synthetic molecular motors. Studies on homochiral and heterochiral bispidine peptides revealed the direction of rotation can be controlled by chirality and the nature of amino acid.

### **Chapter 4**

Chapter 4 presents a novel molecular-topology-based approach for creating reproducible vesicular assemblies in different solvent environments, including aqueous, using specifically designed pseudopeptides. Deviating from the classical “polar head group and hydrophobic tail” model of amphiphiles, we show (reversible) self-assembly of the synthesized pseudopeptides into vesicles. Naming these new type/class of vesicles as “pseudopetosomes”, we characterize them by high resolution scanning electron-, transmission electron-, atomic force-, epifluorescence- and

confocal- microscopy along with dynamic light scattering. While accounting for hydrophobicity of constituent amino-acids (side chains) of the pseudopeptides, we probe molecular interactions resulting in assembly of pseudopeptosomes by fourier-transform infrared- and fluorescence- spectroscopies. Molecular characterization by X-ray crystallography and Circular dichroism reveal “Trp-Zip” arrangements and/or hydrogen-bonded one-dimensional assembly depending on specific pseudopeptides and the solvent environments. Our data indicate that pseudopeptosomes are formed in solutions by self-assembly of bispidine pseudopeptides (of Trp, Leu and Ala amino-acid constituents) into sheets that transform into vesicular structures. Thus, we show that assembly of pseudopeptosomes utilizes the full spectrum of all four weak interactions essential in biological systems. Our findings not only have direct implications in chemical and synthetic biology but also may provide a new avenue of investigations on origins of life via pseudopeptosome-like assemblies. We also showed that these designer peptides can act as carrier for cellular transport.

## **Chapter 5**

Chapter 5 describes the synthesis of topologically intriguing structures is highly challenging. We herein present bispidine as a platform for the design of molecules with various topologies and functions. Bispidine-based acyclic molecule, showing intriguing S-shape topology was discussed. Single crystal X-ray revealed that this molecule exists in solid state as two conformational enantiomers. In addition to that, bispidine-based designer macrocycles were synthesized and investigated for ionophoric properties. Patch clamp experiments revealed that these macrocycles transport  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  by channel mechanism. The results indicated that the self-assembling macrocycle form tubular assembly as evident from ultramicroscopic techniques and single crystal X-ray crystallographic studies. Our design highlights the utilization of non-conventional dihydrogen interactions in nanotube fabrication.

## सारांश

"प्रोटीन इंजीनियरिंग: पेप्टिडोमिमेटिक फोल्डेमर्स के डिजाइन, सिंथीस और कार्यात्मक गुणों का शोधपत्र" शीर्षक वाली थीसिस में, प्यूडोपेप्टाइड मोलेक्यूल से प्राप्त पेप्टिडोमिमेटिक फोल्डेमर्स के सरल डिजाइन का वर्णन किया गया है, जो रासायनिक जीवविज्ञान और भौतिकीय रासायनिकता में विभिन्न अनुप्रयोगों के लिए उपयोगी हैं। इसके अलावा, हमने इन पेप्टिडोमिमेटिक फोल्डेमर्स के घूमने की गतिकी का भी अध्ययन किया है। इसके अतिरिक्त, हमने विभिन्न द्रावक पर्यावरणों में दोहरने योग्य वेसिक्युलर असेंबलीज़ और आयन चैनल ट्रांसपोर्टर को दिखाने वाली आणविक-टोपोलॉजी आधारित दृष्टिकोण तकनीकों का वर्णन भी किया है। इस थीसिस का कार्य पांच अध्यायों में विभाजित किया गया है।

### अध्याय 1

अध्याय 1 में डिजाइनर पेप्टिडोमिमेटिक फोल्डेमर्स के विस्तृत अवलोकन को एक समन्वित तरीके से प्रस्तुत किया गया है, जिसमें प्रारंभिक डिजाइन्स सहित सभी महत्वपूर्ण डिजाइन्स और हाल के प्रगतियां सम्मिलित हैं। एम्फिलिक पेप्टाइड और साइक्लिक पेप्टाइड सहित विभिन्न प्रकार के स्पष्ट प्रोटीन सेकेंडरी संरचना फोल्डिंग पेप्टिडिक प्रणालियों का विस्तृत समीक्षण किया गया है। इसके अलावा, गतिशील फोल्डेमर्स के विभिन्न टोपोलॉजिकल व्यवस्थाओं का अध्ययन भी किया गया है, जो मोटर प्रोटीनों से सम्बंधित हैं और पेप्टिडोमिमेटिक फोल्डेमर्स की स्व-संघटना से संबंधित होती हैं, जैसे कि विभिन्न रचनात्मक रणनितियों के माध्यम से वेसिकल्स के रूप में क्वार्टररी संरचनाओं तक। इसके अतिरिक्त, आयन परिवहन अध्ययन के लिए उपयोग किए जा सकने वाले मोलेक्युलर नोटेड संरचनाओं वाले फोल्डेमर्स को भी प्रमुखता दी गई है।

### अध्याय 2

अध्याय 2 में, सिंथेटिक बिस्पीडाइन पर आधारित स्कैफोल्ड्स के विकास के साथ मुख्यतः बायोजैमिक

प्रणालियों में उभरते द्वितीयक और क्वाटर्नरी संरचनाओं का अध्ययन किया गया है। इन बिस्पीडाइन-स्कैफोल्डेड पेप्टाइडों का अध्ययन CD, IR, NMR, एकल क्रिस्टल XRD और मॉलेक्युलर डायनेमिक्स (MD) सिमुलेशन के माध्यम से उनके आकारिकी रूचियों का अध्ययन करने के लिए किया गया है। ठोस अवस्था और द्रव्यमान अध्ययन ने यह साबित किया है कि बिस्पीडाइन एक विविधतापूर्ण स्कैफोल्ड है जिसे बीटा-स्ट्रैंड संरचना को न्यूक्लियेट करने के लिए पेप्टाइड स्ट्रैंड के अंत या मध्य में रखा जा सकता है। पेप्टाइड श्रृंखला के सी-टर्मिनस पर रखे गए बिस्पीडाइन द्वारा बीटा-स्ट्रैंड रूप न्यूक्लियेट होता है, जबकि मध्य में रखने से एक बीटा-आर्च संरचना प्राप्त होती है। यह न्यूक्लियेशन गतिविधि बिस्पीडाइन के द्वारा अक्षगुर्थ C $\alpha$ -CO टोर्सनियल एंगल ( $\psi$ ) को रोकने की क्षमता से होती है, जो स्कैफोल्ड के पास के एमिनो एसिड के कार्बोनिल ऑक्सीजन के बीच के इकट्टा हाइड्रोजन बॉन्डिंग के माध्यम से होती है। इसके अलावा, बिस्पीडाइन पेप्टिडोमिमेटिक के साथ एक सुपर द्वितीयक संरचना, यानी बीटा-आर्च, एकल-छेद नैनोकेजेज़ और गोलाकार वेसिकल्स में भी संगठित हो जाती है।

### अध्याय 3

अध्याय 3 में, कृत्रिम मोलेक्युलर रोटर्स के विकास पर चर्चा की गई है। यहाँ, हमने बिस्पीडाइन डायमाइडों की एक श्रृंखला का संश्लेषण किया है जो मोलेक्युलर रोटर की याद दिलाने वाली घूर्णन को प्रदर्शित करती है। गतिशील NMR, एकल क्रिस्टल X-रे विकिरण और मोलेक्युलर डायनेमिक्स ने घूर्णन गतिविधि की पहचान करने के लिए संदेह पैदा की। अध्ययनों ने एकदिशीय घूर्णन और घूर्णन की दर को परिवर्तित होने का निर्धारण किया है, जो संवर्धन की प्रकृति पर निर्भर करता है। इन इंजीनियर्ड प्रणालियों से जीववैज्ञानिक रूप से महत्वपूर्ण कृत्रिम मोलेक्युलर मोटर के विकास में मदद मिल सकती है। होमोकिरल और हेटरोकिरल बिस्पीडाइन पेप्टाइडों पर अध्ययन ने दिखाया है कि चिरता और एमिनो एसिड की प्रकृति द्वारा घूर्णन की दिशा को नियंत्रित किया जा सकता है।

### अध्याय 4

अध्याय 4 में, विभिन्न द्रव्यमान पर्यावरणों, समावेशी जलीय, के लिए पुनरावर्तनशील वेसिकुलर संरचनाओं की निर्माण के लिए एक नवीनतम आणविक-टोपोलॉजी आधारित तकनीक प्रस्तुत की गई है, जिसमें विशेष रूप से डिजाइन किए गए प्यूडोपेप्टाइडों का उपयोग किया गया है। अम्फिफिल्स के क्लासिक "धार्मिक सिर समूह और हाइड्रोफोबिक पूंछ" मॉडल से अलग होकर, हम प्रदर्शित करते हैं कि सिंथेटिक प्यूडोपेप्टाइडों का (पुनर्प्राप्तिशील) स्व-संघटन वेसिकल्स में हो सकता है। इन नई प्रकार/क्लास के वेसिकल्स को "प्यूडोपेटोसोम्स" के नाम से पुकारा जाता है, हम इन्हें उच्च रिज़ोल्यूशन वाले स्कैनिंग इलेक्ट्रॉन-, पाठ्यक्रम विक्षोभ-, परमाणु क्षेत्र-, ईपिफ्लोरेसेंस- और कॉन्फोकल- माइक्रोस्कोपी के साथ डायनामिक लाइट स्कैटरिंग के माध्यम से वर्णन करते हैं। प्यूडोपेप्टाइडों के घटक एमिनो-एसिड (साइड चेन्स) की हाइड्रोपैथी-सूचियों का ध्यान देते हुए, हम फुरियर-परिवर्तन इन्फ्रारेड- और फ्लोरेसेंस-स्पेक्ट्रोस्कोपी द्वारा प्यूडोपेटोसोम्स के अभिप्रेरणात्मक संरचना में होने वाली आणविक अंतराक्रियाओं का पता लगाते हैं। एक्स-रे क्रिस्टलोग्राफी और सर्कुलर डाइक्रोइज़म द्वारा आणविक विश्लेषण से पता चलता है कि विशेष प्यूडोपेप्टाइडों और रोषण वातावरण के आधार पर "ट्राप-ज़िप" व्यवस्थाओं और/या हाइड्रोजन-बॉन्डेड एक-आयामी संरचना प्रकट होती है। हमारे आंकड़े इस बात की संकेत करते हैं कि प्यूडोपेटोसोम्स समाधानों में बाइस्पिडाइन प्यूडोपेप्टाइडों (ट्राप, लेव और अला एमिनो-एसिड घटकों के) के स्व-संघटन द्वारा तालिकात्मक संरचनाओं में परिवर्तित शीटों में बनाए जाते हैं जो वेसिकुलर संरचनाओं में परिवर्तित हो जाते हैं। इस प्रकार, हम दिखाते हैं कि प्यूडोपेटोसोम्स के संगठन बायोलॉजिकल प्रणालियों में महत्वपूर्ण सभी चार कसंकर्षणीय संपर्क तत्वों का व्याप्त स्पेक्ट्रम उपयोग करता है। हमारी खोज के अनुसार, ये प्यूडोपेटोसोम्स जीवविज्ञानिक प्रणालियों में महत्वपूर्ण निर्धारित चार कमजोर इंटरैक्शनों का पूरा स्पेक्ट्रम उपयोग करके तैयार होते हैं। हमारे अनुसंधान के नतीजे न केवल रासायनिक और संश्लेषण जीवविज्ञान में सीधे प्रभाव रखते हैं, बल्कि प्यूडोपेटोसोम जैसे संघटनों के माध्यम से जीवन की मूल स्रोतों पर अध्ययन की एक नई संभावना भी प्रदान कर सकते हैं। हमने इसके अलावा यह भी दिखाया है कि ये डिज़ाइनर

पेटाइड्स सेलुलर परिवहन के लिए एक कैरियर के रूप में कार्य कर सकते हैं।

## अध्याय 5

अध्याय 5 में, टोपोलॉजिकली रोचक संरचनाओं की संश्लेषण का संश्लेषण करना बहुत चुनौतीपूर्ण होता है। हम यहां बिस्पिडीन को एक मंच के रूप में प्रस्तुत करते हैं, जिसका उपयोग विभिन्न टोपोलॉजी और कार्यों वाले अणुओं के डिज़ाइन के लिए किया जा सकता है। एस-आकार टोपोलॉजी वाले रोचक अणुज और इसकी विचारशील रूप विश्लेषण किया गया है। एकल प्रतिमा एक्स-रे द्वारा प्रकट करती है कि यह अणु ठोस अवस्था में दो प्रकार के संरेखाग्रही अणुरूपी होता है। इसके अलावा, बिस्पिडीन पर आधारित डिज़ाइनर मैक्रोसाइकलेस उत्पन्न किए गए और आयनोफोरिक गुणों के लिए जांचे गए। पैच क्लैंप प्रयोगों ने दिखाया कि ये मैक्रोसाइकलेस नात्रियम ( $\text{Na}^+$ ), पोटैशियम ( $\text{K}^+$ ) और कैल्शियम ( $\text{Ca}^{2+}$ ) को चैनल प्रणाली के माध्यम से परिवहन करते हैं। परिणाम इसे स्पष्ट करते हैं कि स्व-संघटित मैक्रोसाइकल अणुलिपि अल्ट्राइक्रोस्कोपिक तकनीकों और एकल प्रतिमा एक्स-रे क्रिस्टलोग्राफीय अध्ययनों के द्वारा साबित होती है। हमारा डिज़ाइन उपनिर्माण में गैर-पारंपरिक डायड्रोजन अंतरक्रियाओं का उपयोग करने को प्रमुखता देता है।

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## LIST OF ABBREVIATIONS

%	Percent
$\delta$	Chemical shift
$^{\circ}\text{C}$	Degree centigrade
$\lambda$	Wavelength
$\Phi$	Barrier height
$\mu\text{M}$	Micro molar
$\mu\text{m}$	Micro meter
$\mu\text{L}$	Micro litre
ACN	Acetonitrile
ADP	Adenosine diphosphate
AFM	Atomic force microscopy
AIE	Aggregation-induced emission
aq.	Aqueous
ATR-IR	Attenuated total reflectance infrared
Boc	<i>tert</i> -butyloxycarbonyl
br	Broad
CAC	Critical aggregation concentration
CD	Circular dichroism
$\text{CHCl}_3$	Chloroform
Conc.	Concentration
d	Doublet
DCC	N, N'-dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet doublet
DFT	Density functional theory
DIC	Differential interference contrast
DMSO	Dimethylsulfoxide
DIPEA	N,N'-Diisopropylethylamine
DLS	Dynamic light scattering
DMF	N,N-dimethylformamide

E <sub>A</sub>	Activation energy
EDC.HCl	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
Hz	Hertz
LC-MS	Liquid chromatography –mass spectrometry
m	Multiplet
MD	Molecular dynamics
MeOH	Methanol
mg	Milli gram
min	Minutes
mL	Milli litre
mmol	Milli moles
mol	Mole
MP	Melting point
MTT	3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide
m/z	Mass/charge
NHS	N-hydroxysuccinimide
NMR	Nuclear magnetic resonance
NR	Nile red
ppm	Parts per million
PXRD	Power X-ray diffraction
q	Quartet
RB	Rhodamine B
RT	Room temperature
s	Singlet
SD	Standard Deviation
SEM	Scanning electron microscopy
t	Triplet
T	Temperature
TBA	Terabutylammonium
TBABF <sub>4</sub>	Terabutylammonium tetrafluoroborate
TBAF	Terabutylammonium fluoride
TBAH <sub>2</sub> PO <sub>4</sub>	Terabutylammonium dihydrogen phosphate

TBAP	Terabutylammonium perchlorate
TEA	Triethylamine
TEG	Tri (ethylene glycol)

## NOTES

1. All of the L-configuration amino acids that were utilized in the synthesis were procured from SRL India and used exclusively for that purpose. Unless otherwise mentioned, the single-letter and triple-letter codes that are typical for representing amino acids will be used.
2. All of the commercial chemicals and reagents that were used in the chemical synthesis were purchased from Sigma-Aldrich or Alfa Aesar, unless it was specifically indicated otherwise, and they were used exactly as they were received without undergoing any additional purification.
3. Prior to their use, each of the solvents for the reactions were distilled and dried as described in the standard protocols.
4. All reactions that were sensitive to air were conducted in oven-dried glassware within an inert atmosphere of argon.
5. The feasibility of each reaction was checked using silica gel thin layer chromatography (TLC) whenever it was feasible to do so.
6. A silica gel column chromatography with a mesh range of 100–200 was used to purify all the synthesized compounds. In most cases, chloroform, DCM, and/or methanol were used to make the slurry.
7. The  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, and High Resolution Mass Spectrometry (HRMS) techniques were deployed in order to characterize the synthetic compounds.
8. A Bruker-DPX-300/400/500 MHz spectrometer was used to record  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, and the chemical shifts are given downfield in relative to tetramethylsilane (TMS).  $^1\text{H}$  NMR data are reported as br (broad), s (singlet), d (doublet), q (quartet), t (triplet) and m (multiplet). The unit of measurement for  $^1\text{H}$  NMR coupling constants is the Hz.

9. Using the Electrospray Ionization (ESI) technique, high resolution mass spectra (HRMS) were recorded in the Bruker MicrO-TOF-QII model.
10. Infrared spectra were recorded on a Perkin Elmer spectrum IR, version 10.6.0 using KBr pellets.
11. Circular Dichroism (CD) spectra were recorded on AVIV model 410 spectropolarimeter equipped with a temperature controller.
12. Melting points were recorded on a Fisher-Scientific melting point apparatus.
13. X-ray diffraction analysis was carried out on a Rigaku Oxford and BRUKER AXS SMARTAPEX Diffraction with (Mo) X-ray Source diffraction source.
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