A MINIMALISTIC APPROACH FOR FUNCTIONAL SELF-ASSEMBLING PEPTIDE AND PSEUDOPEPTIDE SYSTEMS

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by

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Dedicated in the Lotus Feet of My Revered Master

‘H. H. SHRI ASHUTOSH MAHARAJ JI’

Founder & Head of DIVYA JYOTI JAGRATI SANSTHAN (DJJS)…

CERTIFICATE

This is to certify that the thesis entitled, **"A Minimalistic Approach for Functional Self-Assembling Peptide and Pseudopeptide Systems"**, being submitted by **Mr. Sameer Dhawan**, to the Indian Institute of Technology Delhi, for the award of degree of **Doctor of Philosophy in Chemistry**, is a record of bonafide research work carried out by him. **Mr. Sameer Dhawan** has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted in part or in full, to any other University or Institute for award of any degree or diploma.

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ABSTRACT

The thesis entitled **"A Minimalistic Approach for Functional Self-Assembling Peptide and Pseudopeptide Systems"** presents the modest designs of peptide and pseudopeptide molecules for the multifaceted applications in the diverse fields of nanotechnology and biotechnology. In addition, we have explored a hitherto unknown class of vesicles altogether different from the conventional bilayer vesicles. The work presented in the thesis has been divided into five chapters.

Chapter 1

Chapter 1 gives a panoramic view of designer peptide and pseudopeptide systems in a systematic manner encompassing all the preliminary designs as well as the recent advancements. A variety of self-assembling peptidic systems ranging from short peptides, amphiphilic peptides, cyclic peptides, linear peptides to polymeric peptides have been reviewed thoroughly. The mechanistic insight into the formation of nanotubes and vesicles using different strategies proposed in the literature, is also given. In addition, the diverse applications of designer peptides in the field of drug delivery, anion sensing and organic electronics is highlighted.

Chapter 2

Chapter 2 deals with the design, synthesis and self-assembling properties of a series of cystine-cored minimalistic dipeptides that exhibited the prominent redox-responsive behavior. Various experimental as well as the computational investigations were performed to reveal the self-assembling mechanism of dipeptides in water. Further, the encapsulation of drug molecules by the vesicle-forming dipeptide and their subsequent redox-triggered sustained release in an intracellular milieu is demonstrated.

Chapter 3

Chapter 3 presents the minimalistic design strategy for the development of amino acid appended supersensitive anion sensors that can detect anions in both aqueous as well as organic media. Various spectroscopic and electrochemical measurements were performed to demonstrate the ultratrace sensing of anions in water with the lowest limit of detection values reported so far. Further, the self-assembled morphologies of the host molecules were also investigated using different ultramicroscopic techniques.

Chapter 4

Chapter 4 outlines the fabrication of organic field effect transistors (OFETs) in a bottom-gate/bottom-contact configuration using the self-assembling peptidic polydiacetylenes. The peptide-based OFETs were found to exhibit a p-type FET behavior with an exceptionally high hole mobility of up to 9.29 $cm^2 V^{-1} s^{-1}$ at room temperature. The key role of aromatic amino acids in providing high mobility values to the OFET is highlighted.

Chapter 5

Chapter 5 describes the new class of vesicles named as “reverse micellar vesicles”, possessing dual features of classical micelles and conventional vesicles. The novel model of vesicles was established by using a series of self-assembling pseudopeptidic polymers that were synthesized by the ring opening metathesis polymerization (ROMP) of lipidated amino acids appended norbornene monomers. The comprehensive ultramicroscopic and spectroscopic analyses were performed to delineate the hierarchical mechanism of formation of reverse micellar vesicles.

सारांश

थीसिस शीर्षक "**उपादेय स्व-संयोजित पेप्टाइड और स्यूडोपेप्टाइड सिस्टम्स के लिए एक सरलतम कार्यनीति**" नैनो प्रौद्योगिकी और जैव प्रौद्योगिकी के विविध क्षेत्रों में बहुआयामी अनुप्रयोगों के लिए पेप्टाइड और स्यूडोपेप्टाइड यौगिकों के सरलतम डिजाइन प्रस्तुत करता है। इसके अलावा, हमने पुटिकाओं के एक नवीनतम वर्ग का पता लगाया है जो पारंपरिक बाइलेयर पुटिकाओं से बिल्कुल अलग है। थीसिस में प्रस्तुत कार्य को पाँच अध्यायों में विभाजित किया गया है।

अध्याय 1

अध्याय 1 सभी प्रारंभिक डिजाइनों के साथ-साथ हालिया प्रगति को शामिल करते हुए एक व्यवस्थित तरीके से डिजाइनर पेप्टाइड और स्यूडोपेप्टाइड सिस्टम्स का एक विहंगम दृश्य प्रस्तुत करता है। लघु पेप्टाइड्स, एम्फीफिलिक पेप्टाइड्स, चक्रीय पेप्टाइड्स, रैखिक पेप्टाइड्स से लेकर बहुलक पेप्टाइड्स तक के विभिन्न प्रकार के स्व-संयोजित पेप्टिडिक प्रणालियों की अच्छी तरह से समीक्षा की गई है। साहित्य द्वारा प्रस्तावित विभिन्न रणनीतियों का उपयोग करके नैनोट्यूब और पुटिकाओं के निर्माण में निहित पद्धतियों की अंतर्विवेचना भी प्रस्तुत की गयी है। इसके अलावा, दवा वितरण, आयन सेंसिंग और ऑर्गेनिक इलेक्ट्रॉनिक्स के क्षेत्र में डिजाइनर पेप्टाइड्स के विविध अनुप्रयोगों पर प्रकाश डाला गया है।

अध्याय 2

अध्याय 2 सिस्टीन-कोर डाइपेप्टाइड्स की सरलतर श्रृंखला के डिजाइन, संश्लेषण और स्व-संयोजन गुणों से संबंधित है, जो प्रमुखतः रेडॉक्स-संवेदनशील व्यवहार का प्रदर्शन करते हैं। पानी में डाइपेप्टाइड्स के स्व-संयोजन तंत्र को प्रकट करने के लिए विभिन्न प्रयोगात्मक और कम्प्यूटेशनल जांच की गई है। इसके

अतिरिक्त, पुटिका बनाने वाले डाइपेप्टाइड द्वारा दवा के अणुओं के एनकैप्सुलेशन और इंट्रासेल्युलर परिवेश में उनके रेडॉक्स-ट्रिगर निरंतर रिलीज को प्रदर्शित किया गया है।

अध्याय 3

अध्याय 3 अमीनो एसिड्स युक्त सुपरसेंसिटिव आयन सेंसर्स के विकास के लिए सरलतम डिजाइन पद्धति प्रस्तुत करता है, जो जलीय और कार्बनिक मीडिया दोनों में आयनों का पता लगा सकते हैं । पानी में आयनों की अल्ट्राट्रेस सेंसिंग को प्रदर्शित करने के लिए विभिन्न स्पेक्ट्रोस्कोपिक और इलेक्ट्रोकेमिकल माप किए गए हैं, जो अब तक के साहित्य में वर्णित डिटेक्शन वैल्यू की न्यनतम सीमा दर्शाते हैं । इसके अलावा, विभिन्न अल्ट्रामाइक्रोस्कोपिक तकनीकों का उपयोग करके मेजबान अणुओं की स्व-संयोजित आकारिकी की भी जांच की गई।

अध्याय 4

अध्याय 4 स्व-संयोजित पेप्टिडिक पॉलीडायसेटिलीनों द्वारा बॉटम-गेट/बॉटम-कॉन्टैक्ट कॉन्फ़िगरेशन में ऑर्गैनिक फील्ड इफेक्ट ट्रांजिस्टर (OFETs) के निर्माण की रूपरेखा प्रदर्शित करता है। पेप्टाइड-आधारित OFETs को कमरे के तापमान पर 9.29 $cm^2\ V^{-1}\ s^{-1}$ तक की असाधारण उच्च होल मोबिलिटी (Hole Mobility) के साथ p-प्रकार का FET व्यवहार प्रदर्शित करते दर्शाया गया है । OFET को उच्च मोबिलिटी मूल्य प्रदान करने में एरोमेटिक अमीनो एसिड्स की महत्वपूर्ण भूमिका पर प्रकाश डाला गया है।

अध्याय 5

अध्याय 5 पुटिकाओं के नवीनतम वर्ग का वर्णन करता है जिसे "रिवर्स माइसलर वेसिकल्स" नाम दिया गया है, जिसमें क्लासिकल माइसल्स और पारंपरिक पुटिकाओं की दोहरी विशेषताएं हैं। पुटिकाओं का नया मॉडल स्व-संयोजित स्यूडोपेप्टिडिक पॉलीमर्स की एक श्रृंखला का उपयोग करके स्थापित किया गया है, जो

लिपिडेटेड अमीनो एसिड्स युक्त नॉरबोर्निन मोनोमर्स के रिंग ओपनिंग मेटाथिसिस पोलीमराइजेशन (ROMP) द्वारा संश्लेषित होते हैं। रिवर्स माइसलर वेसिकल्स के गठन में निहित पदानुक्रमित तंत्र को चित्रित करने के लिए व्यापक अल्ट्रामाइक्रोस्कोपिक और स्पेक्ट्रोस्कोपिक विश्लेषण किए गए हैं।

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LIST OF ABBREVIATIONS

%	Percent
δ	Chemical shift
^{o}C	Degree centigrade
μ	Mobility
ν_d	Drift velocity
λ	Wavelength
Φ	Barrier height
κ	Curvature
ΔF	Dehydrophenylalanine
μM	Micro molar
μm	Micro meter
μL	Micro litre
5-Fu	5-fluorouracil
ACN	Acetonitrile
ADP	Adenosine diphosphate
AFM	Atomic force microscopy
AIE	Aggregation-induced emission
Amoc	Anthracenemethoxycarbonyl
AMP	Adenosine monophosphate
aq.	Aqueous
Ar	Aryl
ArH	Aromatic proton
ATP	Adenosine triphosphate
ATR-IR	Attenuated total reflectance infrared
Boc	*tert*-butyloxycarbonyl
br	Broad
C	Oxide capacitance
CA	Chronoamperometry
CAC	Critical aggregation concentration

CD	Circular dichroism
$CHCl_3$	Chloroform
CLSM	Confocal laser scanning microscopy
Conc.	Concentrated
CPT	Camptothecin
CuCl	Copper(I) Chloride
CV	Cyclic voltammetry
d	Doublet
Da	Dalton
DAPI	4’,6-diamidino-2-phenylindole
DCC	N,N’-dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Double doublet
DFT	Density functional theory
DIC	Differential interference contrast
DIPEA	N,N'-Diisopropylethylamine
DLS	Dynamic light scattering
DMEM	Dulbecco’s modified Eagle’s medium
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DNP	Double numerical plus polarization
DOPA	3,4-dihydroxy-L-phenylalanine
DOX	Doxorubicin
DPBS	Dulbecco’s phosphate buffered saline
DPV	Differential pulse voltammetry
DTNB	5,5’-dithio-bis(2-nitrobenzoic acid)
DTT	1,4 Dithiothreitol
E	Peak potential
E_A	Activation energy
ECM	Extracellular matrix
EDC·HCl	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride

EDOT-OH	Hydroxymethyl-(3,4-ethylenedioxythiophene)
EE	Encapsulation efficiency
E_{rel}	Relative energy
ESI	Electrospray ionization
EtOAc	Ethyl acetate
FBS	Fetal bovine serum
FET	Field effect transistor
FIB	Focused ion beam
Fmoc	9-fluorenylmethoxycarbonyl
FTIR	Fourier-transform infrared
g	Gram
G2	Grubbs second generation catalyst
GCE	Glassy carbon electrode
GGA	Generalized gradient approximation
GPC	Gel permeation chromatography
GSH	Glutathione
GTP	Guanosine triphosphate
h	Hour
HBS	Hank's buffered saline
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HRTEM	High resolution transmission electron microscope
Hz	Hertz
I	Peak current
I_{DS}	Drain to source current
IR	Infrared
ITC	Isotheral calorimetry
J	Coupling constant
k	Boltzmann constant
L	Channel length
LC	Loading capacity

LC-MS	Liquid chromatography-mass spectrometry
LED	Light emitting diode
LOD	Limit of detection
LOQ	Limit of quantification
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
MD	Molecular dynamics
MeOH	Methanol
mg	Milli gram
min	Minutes
mL	Milli litre
mmol	Milli moles
MMP	Matrix metalloproteinase
mol	Mole
MP	Melting point
MTT	3-(4,5- dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide
MWCO	Molecular weight cut-off
m/z	Mass/charge
NCCS	National Centre for Cell Science
NDI	1,4,5,8-naphthalenetetracarboxylic diimide
NHE	Normal hydrogen electrode
NHS	*N*-hydroxysuccinimide
NMR	Nuclear magnetic resonance
NPT	Isothermal isobaric
NR	Nile red
OFET	Organic field effect transistor
PAG	Photoacid generator
PARP	Poly(ADP-ribose) polymerase
PB	Polybutadiene
PBS	Phosphate buffered saline
PDA	Polydiacetylene

PDF	Pair distribution function
PDI	Polydispersity Index
PEG	Polyethylene glycol
PGA	Poly(L-glutamic acid)
ppm	Parts per million
PXRD	Powder X-ray diffraction
Py	Pyrene
q	Quartet
QC	Quantum confinement
QCM-D	Quartz crystal microbalance
RAFT	Regioselectively addressable functional template
RB	Rhodamine B
ROMP	Ring opening metathesis polymerization
RT	Room temperature
s	Singlet
SAM	Self-assembled monolayer
SANS	Small-angle neutron scattering
SAXS	Small-angle x-ray scattering
SCE	Saturated calomel electrode
SD	Standard deviation
SEM	Scanning electron microscopy
SS	Subthreshold slope
t	Triplet
T	Temperature
TBA	Tetrabutylammonium
$TBABF_4$	Tetrabutylammonium tetrafluoroborate
TBAF	Tetrabutylammonium fluoride
$TBAH_2PO_4$	Tetrabutylammonium dihydrogen phosphate
TBAP	Tetrabutylammonium perchlorate
TEA	Triethylamine
TEG	Tri(ethylene glycol)

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Tetramethylsilane
TPE	Tetraphenylethylene
TTF	Tetrathiafulvalene
UV	Ultraviolet
V_{DS}	Drain to source voltage
V_{GS}	Gate to source voltage
Vis	Visible
W	Channel width
WAXS	Wide-angle X-ray scattering
WCA	Water contact angle

NOTES

1. All amino acids used in syntheses were of L-configuration and were purchased from SRL India. Unless, otherwise stated, the standard single/triple letter codes are used to represent amino acids.
2. All commercial chemicals and reagents used in chemical syntheses were purchased from Sigma-Aldrich or Alfa Aesar unless, otherwise stated and used as received without any further purification.
3. All the solvents employed in the reactions were distilled/dried by standard protocols prior to use.
4. All air sensitive reactions were carried out in oven dried glassware under an inert atmosphere of argon.
5. All the reactions were monitored by silica gel thin layer chromatography (TLC), wherever possible.
6. All the synthesized compounds were purified by silica gel (100-200 mesh) column chromatography. The slurry was generally made in chloroform, DCM and/or MeOH.
7. The characterization of synthesized compounds was done by ^{1}H NMR, ^{13}C NMR, IR and High Resolution Mass Spectrometry (HRMS).
8. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-DPX-300/400/500 MHz spectrometer and the chemical shifts are reported downfield relative to tetramethylsilane (TMS). ^{1}H NMR data are reported as br (broad), s (singlet), d (doublet), q (quartet), t (triplet) and m (multiplet). ^{1}H NMR coupling constants are reported in Hz.
9. High resolution mass spectra (HRMS) were recorded in Bruker MicrO-TOF-QII model using Electrospray Ionization (ESI) technique.

10. IR spectra were recorded on Agilent-Cary 660 Series FTIR spectrometer/Nicolet, Protégé 460 spectrometer as KBr Pellets.
11. Attenuated Total Reflectance Infrared (ATR-IR) spectra were recorded on an Agilent-Cary 660 Series FTIR spectrometer. For ATR-IR, the samples were placed on the diamond sample holder and 32 scans were performed on each sample.
12. Melting points were recorded on a Fisher-Scientific melting point apparatus.