DESIGN, SYNTHESIS AND SELF-ASSEMBLING PROPERTIES OF PEPTIDE-BASED DENDRIMERS

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DESIGN, SYNTHESIS AND SELF-ASSEMBLING PROPERTIES OF PEPTIDE-BASED DENDRIMERS

by

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Dedicated to my dear parents

(Shri R.J. Verma and Smt. Sampti devi)

CERTIFICATE

This is to certify that the thesis entitled, **"Design, Synthesis and Self-Assembling Properties of Peptide-Based Dendrimers"**, being submitted by **Mr. Ram Prakash Verma**, 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. Ram Prakash Verma** 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

This thesis, **"Design, Synthesis and Self-Assembling Properties of Peptide-Based Dendrimers,"** is concerned with dendrimers crafted from natural amino acids. Dendrimers are molecules that have attracted immense interest in chemistry, biology and material sciences, because of the challenges involved in their synthesis and their functional properties. Peptide dendrimers, with large size and surface area, are similar in many ways to globular proteins and hence can be considered as protein models. The *de novo* design of protein is a challenge, because of the lack of predictability of 3D structure from primary structure. Dendritic architectures using peptide systems may provide an efficient strategy to circumvent protein folding problem, as dendritic peptides are topologically forced to adopt globular shapes, thus mimicking certain features of globular proteins.

Chapter 1 gives a detailed introduction to the history, dendrimer synthesis, recent developments and applications in the area of peptide dendrimers.

Chapter 2 This chapter deals with the design and synthesis of a variety of peptide dendrimers. A series of novel designer dendrimers was synthesized by employing a Huisgen 1,3-dipolar cycloaddition reaction, commonly called a click reaction. The dendritic structures reported here include symmetrical and unsymmetrical dendrimers with a variety of cores such as triazole, aliphatic, aromatic and Lys-Asp dipeptide. The clean synthesis with high yield along with several possibilities for design is salient features of this chapter. This chapter also discusses the self-assembly behavior of these dendrimers.

Chapter 3 In this chapter, we have synthesized urea cored and urea-triazole cored dendrimers with intrinsic tendency for self-assembling. The self-assembling properties of all the dendrimers were investigated by different electron microscopic techniques, scanning electron microscopy

(SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). The studies revealed urea-cored dendrimers self-assemble to fibrous while urea-triazole cored dendrimers vesicular morphology.

Chapter 4 This chapter deals with the synthesis and spectroscopic characterization of a variety of amphiphilic lysine based peptide dendrimers. The self-assembling properties of these peptide dendrimers were examined by electron microscopic methods, like SEM, TEM and AFM. The lipidated dendrimers showed strong tendency self-assembled to vesicular structures as demonstrated by microscopic studies.

Chapter 5 addresses the synthesis of multi-tier designer dendritic molecules incorporating an aromatic core and heterocyclic and peptide units. The aromatic cored peptide dendrimers showed self-assembly to spherical vesicles with diameter in the range of 2.0-2.4 μm. The self-assembled vesicles are useful for encapsulation of guest molecules.

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NOTES

1. All amino acids used were of L-configuration. Unless otherwise stated, all reagents were used without further purification.
2. All solvents employed in the reaction were distilled or dried from appropriate drying agent prior to use.
3. Melting points were recorded in a Fisher-Johns melting point apparatus and were uncorrected.
4. Optical rotations were measured with a Rudolph Research Analytical Autopol® V Polarimeter; concentrations are given in grams/100 ml.
5. IR spectra were recorded on a Nicolet, Protégé 460 spectrometer as KBr pellets.
6. ^{1}H NMR spectra were recorded on Brucker-DPX-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer using tetramethylsilane (^{1}H) as an internal standard. Coupling constants are in Hz and the ^{1}H NMR data are reported as s (singlet), d (doublet), br (broad), br d (broad doublet), t (triplet), q (quartet), m (multiplet).
7. HRMS were recorded with AB Sciex, 1011273/A model and Bruker MicrO-TOF-QII using ESI-technique.
8. Reactions were monitored wherever possible by thin layer chromatography (TLC). Silica gel G (Merck) was used for TLC and column chromatography was done on silica gel (100-200 mesh) columns, which were generally made from slurry in hexane, hexane/ethyl acetate or chloroform.
9. Analytical reverse-phase HPLC (RP-HPLC) was performed on a Perkin Elmer 200 Series instrument, using C-18 (Merck, Lichro CART®, 5 μm, 4 mm × 125 mm) column.

10. X-ray diffraction study was carried out on a BRUKER AXS SMART-APEX diffractometer with a CCD area detector (Mo Kα = 0.71073Å, monochromator: graphite). Frames were collected at T = 298 by ω,ϕ and 2θ-rotation at 10 s per frame with SMART. The measured intensities were reduced to F^2 and corrected for absorption with SADABS. Structure solution, refinement, and data output were carried out with the SHELXTL program. Non-hydrogen atoms were refined anisotropically. C-H hydrogen atoms were placed in geometrically calculated positions by using a riding model. Image was created with the Diamond program.
11. MD simulations were performed on 320 processors SUN Microsystems clusters at Supercomputing Facility (SCFBio) at IIT Delhi.

LIST OF ABBREVIATIONS

%	percent
δ	chemical shift
^{o}C	degree centigrade
aq.	aqueous
Ar	Aryl
AFM	Atomic force microscope
Ac	Acyl
Boc	t-butyloxycarbonyl
BOP	benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate
br	broad
CD	Circular dichroism
Conc.	Concentrated
d	doublet
DCC	N,N'-dicyclohexylcarbodiimide
DIEA	N,N'-Diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ESI	Electrospray ionization
Fmoc	9-fluorenylmethoxycarbonyl
g	gram

h	hour
Hz	Hertz
HBTU	1-[bis(dimethylamino) methylene]-1H-benzotriazolium hexafluorophosphate 3-oxide
HOBt	1-hydroxybenzotriazole
HRMS	High resolution mass spectrum
IR	infrared
J	coupling constant
m	multiplet
min	minutes
mmol	milli moles
mol	mole
MSA	Methanesulfonic acid
mp	melting point
m/z	mass/charge
NMR	nuclear magnetic resonance
ppm	parts per million
PyAOP	7-azabenzotriazol-1-yloxytris (pyrrolidino)phosphonium hexafluorophosphate
q	quartet
RT	Room temperature
s	singlet
SEM	Scanning electron microscope

TEM	Transmission electron microscope
t	triplet
UV	Ultraviolet
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
Z	Benzyloxycarbonyl