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Dendrimers: An Overview

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ABSTRACT:

It is observed that Nature uses dendritic structural motif where a particular function needs to be enhanced or exposed for e.g. structure of tree for photo synthesis, network of Nerves in human body. In synthetic organic chemistry, design and synthesis of dendritic architectures is relevantly new field. One of the primer synthetic targets for researcher for design of dendritic architecture is a "dendrimer". A dendrimer is new class of polymer first synthesized by vogtle et al. in 1979. Structure of dendrimer consists of three architecture components mainly a core, generations and outer functionality. In the initial development of dendrimer synthesis mainly divergent and convergent methodologies were used for dendrimer synthesis. but with recent developments new accelerated approaches have been introduced. Dendrimers poses several unique properties compared to lineal polymers such as monodisperse molecular weight distribution, nanoscale size, intrinsic viscosity behavior and polyvalency. Therefore, dendrimers have been successfully applied in various fields of application which includes both biomedical and non-biomedical fields of interest. This review covers structure of dendrimer, synthetic routes including their merits and limitations, unique properties of dendrimer and present status of dendrimers in various fields of applications such as drug delivery, drug solubilisation, catalysis, biomimics etc.

Keywords: Dendrimer, drug delivery, divergent approach, light harvesting, biomimmics

[I] INTRODUCTION

A dendritic structure is a widespread motif used in nature where a particular function is to be needs to be exposed or enhanced. For example tree uses dendritic structure above the ground to enhance exposure to their leaves to sunlight which is crucial for photosynthesis. Also dendritic structure of tree creates a microenvironment which maintains high humidity and more stable temperature throughout the day compared to surroundings. Trees also used dendritic structural motif beneath the ground i.e. dendritic network of roots which gives maximum surface area for collecting water.

There are also examples of dendritic networks in humans and animals which enhances certain properties. For example, lungs uses dendritic network of bronchioles and alveoli in order to give maximum surface for the transfer of oxygen into the bloodstream. There is also dendritic arterial network which transports oxidized blood

to various organs [1]. The central nervous system and brain also utilized cells with dendritic structure known as neurons which provides largest gain of materials and information surrounding the tissue. So nature has greatly applied dendritic structures throughout with great success.

In synthetic organic chemistry, design and synthesis of dendritic molecules is relatively new field. Vogtle and coworkers gave the first example of creation and design of dendritic structures by organic synthesis [2]. The relatively small molecules were then termed as "Cascade molecules". Vögtle and co-workers saw the perspectives in using these polymers as, e.g. molecular containers for smaller molecules. Several years later, Tomalia and co-workers developed well defined amide containing macromolecules [3, 4]. Tomalia categorized them as new class of macromolecules and termed them as "Dendrimer". The word dendrimer was derived from Greek words "Dendros" means "Trees" or "Branch" and "Meros" means "part". Later several researchers developed and refined synthetics tool to obtain dendritic macromolecules based originally on "Vogtle's Cascade Theme" [5, 6, 7].

Dendrimers are also termed as "Arborols" or "arborescent polymers" or more broadly "hyperbranched polymers". Dendrimer however due to their well-defined structures should be sub classified under hyperbranched polymers. After initial efforts on design and synthesis of dendrimers [8-13], large number of efforts are put into for application of dendrimers in various field of applications ranging from biomedical applications such as drug delivery [14], drug solubilisation [15], diagnostics [16], cancer therapy [17] to non-biomedical applications such as catalysis [18], water remediation [19], sensors [20] and many more. Present review covers dendrimer structure, synthetic routes, properties and present status in various fields of applications.

[II] STRUCTURE OF DENDRIMER

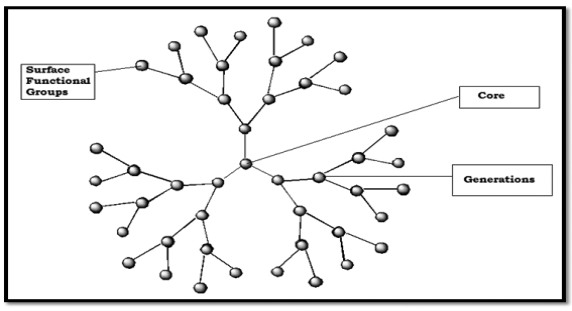

Figure 1. Structure of Dendrimer with its three architectural components.

A dendrimer consists of three architecturing components namely as shown in **[Figure 1.]**: I. Core, II. Generations and III. Terminal functionality [4].

I. Core:

Core is a multifunctional moeity present as a base or building block in dendritic architecture which can an atom or a big large molecule. Overall shape of dendrimer is affected by core. Core may homogeneous or heterogeneous with dendrimer. The shape, size, multiplicity and specific functional group of core clearly affects final dendritic architecture. Chelating units, molecular recognition tool, hydrophobic/ hydrophilic domains could be selected as core for dendrimer as per desired application. Therefore selection of core unit has vital importance for dendrimer synthesis.

II. Generations:

Generations are resulting homo-structural layers between focal points or branching point when travel from core to periphery. The no. of focal points exists when going from core to periphery of the dendrimer is known as generation number.

III. Surface functionality:

Surface groups are crucial with the point of view of final application of dendrimer. Efficacy of dendrimer in application depends upon the number and the types of functional group exposed at the periphery of dendrimer. The functional group can be transformed and amplified as per application by chemical method.

[III] ROUTES OF DENDRIMER SYNTHESIS

Dendrimers can be synthesized by either bottom-up or top-down approaches, which are known as divergent and convergent methods. In divergent method, dendrimers are prepared from core onto which branching units are attached in layer wise manner. In convergent procedure, several dendrons are prepared and attached to a core. In recent year, several accelerated approaches have been introduced. In whichever techniques used for dendrimer synthesis, reaction must be quick, quantitative and by-products must be removed easily. The techniques are described herein with merits and limitations.

3.1. Divergent route

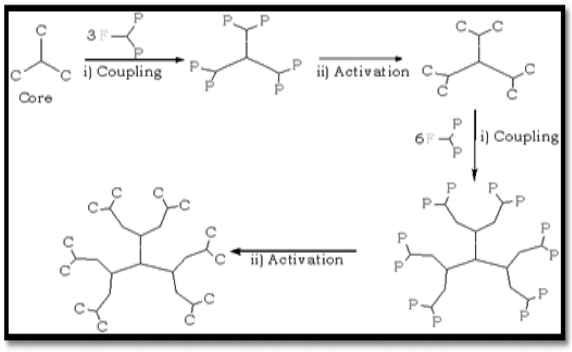

Figure 2. Shows "Divergent Approach" (Where F= Unprotected functional group, P= Protected functional group and C= Coupling point)

In divergent approach, construction of dendrimer starts from core and completes on periphery. It involves two basic set of reactions i) coupling of branching monomer to core unit followed by ii) deprotection/activation of end groups branching monomer to create reactive functionality **[Figure 2.]**. These two steps are iterated until the desired generation number in achieved.

Most studied classes of dendrimers i.e. Polyamidoamine and polypropylene-imine are synthesized by these method [2, 4]. This technique enables synthesis of high generation dendrimer. With increase in generation number, number of reaction also increases exponentially hence, time required for completion of reaction also increases. Also after certain limit, structural defects also increases with divergent procedure. In divergent procedure, reactive monomer and synthesized dendrimer have same functional groups therefore product is difficult to purify and separate, which leads to polydisperse final product [21, 22].

3.2. Convergent Route

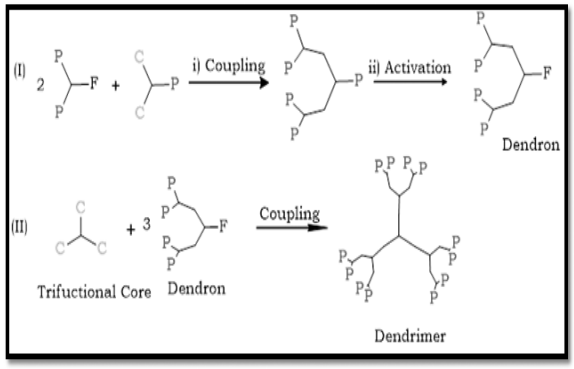

Figure 3. Shows "Convergent Approach" (Where C= Coupling point, P= Protected focal point and F= Unprotected or activated focal point)

In convergent method, dendrimer is constructed from surface to core **[Figure 3.]**. In first step, a branched monomer with activated functional group is coupled with branched monomer with activated focal point to give a dendron. In next step dendron undergoes activation step in which focal point functional group become deprotected for further reaction. In the final step, several dendrons with activated focal point is reacted with a multifunctional core to give a dendrimer. This technique was first developed by Hawker and Frechet [23].

Compared to divergent technique, this technique has an advantage that it doesnot produce dendrimers with structural defects. As synthesized products and excess reactants have different functional groups and properties therefore products are easier to isolate and purify. Hence, dendrimers produced are monodisperse. Frechet's polyarylether type of dendrimers can be prepared by this method. However, this technique is limited to low generation dendrimer.

3.3. Double Exponential growth

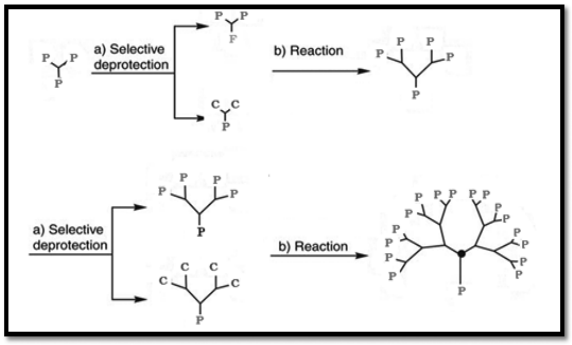

Figure 4. Shows Double Exponential Technique Where, C=coupling group, F=functional group; P=protected group)

Double exponential growth is an accelerated technique for dendrimer growth. In this technique branched monomer with protected groups undergoes two different reactions simultaneously

1. Focal point activation: focal point functional group is activated for coupling.
2. Surface group activation: surface end groups are activated for coupling.

In next step, the products i.e. monomer with activated focal point and monomer activated surface groups undergoes coupling reaction to give a dendron **[Figure 4.]**. The obtained dendron have protected or deactivated functional groups at focal point and surface groups. Again the above two steps are repeated to give fourth generation dendron [24].

3.4. Double Stage Convergent Method

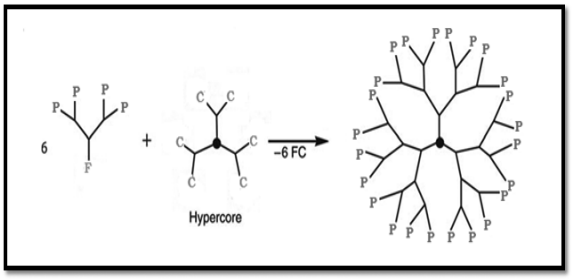

Figure 5. Double stage convergent method (where C= Functional group, F= activated focal point and P= protected focal point)

Double stage convergent method is a combination of convergent and divergent method **[Figure 5.]**. A dendron is synthesized by convergent route in first step. In the second step, synthesized dendron is reacted with a multifunctional Hypercore or a dendrimer with activated surface group to a dendrimer [25, 26]. Compared to traditional convergent technique this technique gives faster access to high terminal functionalized dendrimer. It also have an advantage that Hypercore is subjected to less steric hindrance compared to non-core building blocks of conventional convergent synthesis. Layered block dendrimer with different inner and outer branching units can be synthesized by this method [27, 28].

3.5. Hypermonomer or Hypercore Approach

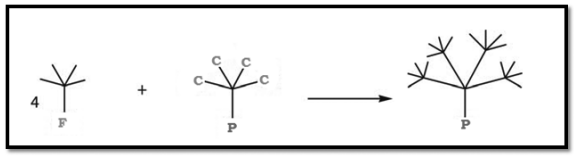

Figure 6. The hypermonomer method (C=coupling unit, F=functional group, P=protective group)

As shown in **[Figure 6]**, A branching monomer with four or more active functional groups is reacted with a branching unit with activated focal point to give a high terminally functionalized dendron. [29, 30]

3.6. Orthogonal synthesis

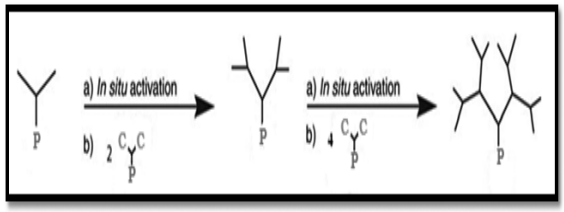

Figure 7. "Orthogonal Coupling Strategy" (Where P= Protecting group which on in situ activation is converted into C= Functional group which spontaneously undergoes Reaction)

Two different branching units with complementary coupling functions are used in orthogonal coupling method. An advantage of

this method is functional group activation or protection is avoided. As shown in **[Figure 7.]**, deactivated functional groups of branching monomer are transformed to activated functional group *in situ.* The activated functional groups undergoes coupling and dendrimer can be constructed by either convergent or divergent method. However this technique is popularized for dendrimer synthesis as the monomer should meet stringent structural requirements [31]. Zeng and Zimmerman reported the first application of orthogonal coupling to the synthesis of higher generation dendrimer [31]. Spindler and Fréchet were the first to prepare a third-generation polyethercarbamate dendron in a one-pot synthesis [32]. Freeman and Frechet [33] reported convergent synthesis of poly (benzyl ester) dendrimer and Shimanek et al. [34] reported synthesis of melamine based dendrimer by using orthogonal coupling strategy.

3.7. Click Chemistry

Click chemistry was first reported by Sharpless et al. in 2001 [35], which provides fast track route for compounds via joining smaller units by a way of heteroatom bonds. Characteristic reactions utilised in click chemistry are 1,3-dipolar cycloadditions, nucleophilic substitutions for ring opening of strained electrophilic heterocycles, as well as additions to carbon-carbon multiple bonds e.g. epoxidation. Azide functionalized PAMAM dendrons were synthesized by Lee et al. by "Convergent method" using click chemistry [36]. Wooley et al. [37] reported second and third-generation dendrimers with a "divergent click strategy". A first generation azido dendrimer terminated was converted into a triazole dendrimer with hydroxyl groups via Cu(I)-catalysed reaction with an alkynylated monomer. Hydroxyl groups of triazole dendrimers were in turn converted into azido groups in order to undergo further reaction with an alkynylated monomer [38]. Unprotected glycol-dendrimers, peptido- and redox-dendrimers and dendronized polymer organogels can also be prepared by click chemistry [39].

3.8. Lego Chemistry

Phosphorus containing dendrimers can be synthesized by lego chemistry via coupling of highly functionalized cores and branched monomers. The end groups are generally phosphines and hydrazines. Generation dendron 4 was synthesized in only 4 Steps and no. surface group increases from 48 to 250. This synthesis requires minimum volume of solvent, allow facile purification and produce environmentally benign by products such as water and nitrogen [40].

[IV] PROPERTIES OF DENDRIMER

4.1. Monodisperse molecular weight distribution

Traditional linear polymers are synthesized by either conventional free radical polymerization or polycondensations. This reactions are random in nature, therefore it yields products with different size and molecular weight. Therefore, traditional polymers have polydisperse molecular weight distribution. As discussed earlier, dendrimers are synthesized by stepwise set of reactions and products are purified and separated at each step. Therefore dendrimers have monodisperse molecular weight distribution. Monodispersity of dendrimers were first verified by using mass spectrometry, size exclusion chromatography, gel electrophoresis and electron microscopy [41]. Generally divergent method yields dendrimers with high Polydispersity index compared to convergent method because of difficulty in purification and isolation of products as discussed earlier [42].

4.2. Intrinsic Viscosity

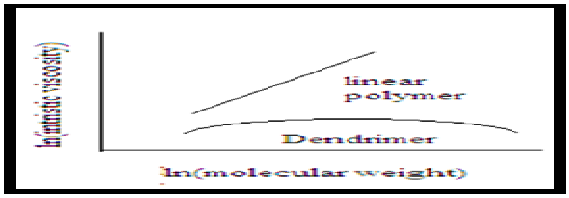

Figure 8. Intrinsic viscosity behavior of dendrimers and linear polymers with increase in molecular weight.

In solution, traditional polymers exists as flexible coils whereas dendrimers exists as tightly packed ball. This has greater impact on their rheological properties. Dendrimers have significantly lower intrinsic viscosity that linear polymers [43]. In case of linear polymers, intrinsic viscosity increase with increase in molecular weight, in case of dendrimer, intrinsic viscosity increases with increase in molecular weight up to certain molecular weight than decreases [44].

4.3. Nanoscale size

In relevance to linear polymers, dendrimers have nanoscale size and shape. It was observed in case of Polyamidoamine dendrimer that G1-G10 dendrimers have diameter in the range of 1.1-12.4 nm [45]. The shape of dendrimer is also important as not it defines surface functionality, but also defined void spaces inside dendritic architecture for applications. It was revealed that G1-G4 polyamidoamine dendrimers have ellipsoidal shape where as higher generation dendrimers G5-G10 have roughly spherical shapes [45]. Thus, nanoscale size and shape of dendrimers which resemble to biomolecule like protein led to variety of applications such gene therapy, photodynamic therapy etc. [46].

4.4. Polyvalency

Polyvalency indicates outward presentation of peripheral functional groups of dendrimer. The surface groups have important role during applications of dendrimer as these are exposed to outlayer of dendrimer. As generation of dendrimer increases the surface groups will obviously increase which is known as amplification of surface groups. As amplification of dendrimer increases, surface groups becomes dense and rigid. The amplification of surface group is used as gating properties for development of dendrimer as unimolecular container. Moreover, surface groups of dendrimers can be modified as per application. This leads to application of dendrimer in wide range of application. [47-49].

[V]PRESENT STATUS OF DENDRIMERS IN FIELDS OF APPLICATIONS

Initial efforts in the field of dendrimer were focused on synthesis and characterization. As a result several new types of dendrimer were synthesized which could be tailor-made for desired application. Due to its unique properties discussed earlier they are used in variety of application. An overview of application of dendrimer is provided below.

5. 1. Dendrimer in Drug Delivery

In drug delivery, active pharmaceutical agent is delivered to specific site of the body at specific rate to achieve desired therapeutic effect. Dendrimers delivery drugs in the body by either forming inclusion complex of drug with dendrimer or by chemical binding of drug with dendrimer. Dendrimers have successfully delivered many drugs such as in *oral drug delivery*, dendrimers have delivered drugs like Doxorubicin [50], Naproxen [51] and quercetin, a versatile flavonoid [52]. In *ocular drug delivery*, dendrimer have been used to deliver drugs like pilocarpine [53], carteolol [54], puerarin [55] etc. There are also examples of dendrimer based drug delivery systems for *transdermal drug delivery* for drugs like Indomethacin [56], Non-steroidal anti-inflammatory agents [57], Diclofenac Sodium [58] etc. There are also examples of *pulmonary delivery* of drugs like Enoxaparin [59], beclometasone dipropionate [60] and *controlled release of drugs* such as Flurbiprofen [61], paclitaxel [62] by dendrimer.

5.2. Dendrimers as solubility enhancers of drug

Most of the newly invented pharmaceutical agents are rejected due to low bioavailability due to poor water solubility [63]. Solubility enhancement of poorly water soluble drugs is one of critical problems in pharmaceutical research and development. Dendrimers with hydrophobic interior and hydrophilic exterior shows micelle like behavior and poses “Container” like properties in solution [64]. It has been revealed

that dendrimer enhances solubility of many drugs ranging from non-steroidal anti-inflammatory drugs (NSAIDS) like Ibuprofen[65], Ketoprofen[66], Naproxen, Diflunisal [67], Indomethacin [68] to anti-cancer drugs such as Methotrexate [69], Paclitaxel [70] etc. It is revealed that dendrimers can enhance aqueous solubility of drugs by hydrophobic interactions, hydrogen bonding and electrostatic interaction between dendrimers and drugs [71, 72].

5.3. Dendrimers in Catalysis

Homogenous catalysts are effective due to a good accessibility of active sites but they are often difficult to separate from the reaction stream. Heterogeneous catalysts are easy to separate from the reaction mixture but the kinetics of the reaction is limited mass transport. The combination of high surface area and high solubility makes dendrimer useful as nanoscale catalysts [73]. Thus it combines advantages of both homogeneous and heterogeneous catalysis. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra-filtration methods [74].

5.4. Dendrimer in Gene Transfection

Gene transfection is a technique in which DNA is coupled to a nanoparticle of inert solid, which is then directly targeted to the cell nucleus. As transfection, if eukaryotic cells is a methodology for effective changes in the genetic material of cells [7]. The ideal vector for transfection should be apart from high efficiency, non-immunogenic, non-toxic, either bio-degradable or excretable and has long blood circulation time. The use of dendrimers for transfection was first reported by the group of Szoka [75] and Baker [76]. PAMAM dendrimers were the first found to be useful for transfection. PAMAM dendrimers were the first found to be useful for transfection. The company named Quiagen developed a commercial transfection system based on PAMAM dendrimers followed by the work of Szoda et al and Baker et al. [77] A series of amphiphilic dendrimers based on the rigid diphenylethyne core was synthesized and their activities as transfection agent were described [78]. These dendrimers show high transfection activity, variety of substitution patterns, but the hydrophobic parameters influenced the DNA binding and transport more strongly than predicted, exhibits lower toxicity and an unusual serum effect. These dendrimers do not show a minimum size limitation for transfection. However, an optimum molecular weight greater than

116kDa was found for PAMAM dendrimers which gave an optimum activity. Recently, Cheng et al. synthesized fluorinated dendrimers for gene transfection which showed excellent gene transfection efficacy in several cell lines and superior biocompatibility compared with several commercial transfection reagents such as Lipofectamine 2000 [79].

5.5. Dendrimers as MRI contrast agents

Magnetic Imaging resonance technique enables to visualize organs, tissues and blood vessels in human body by generating inhomogenous, well defined magnetic fields which enables nuclear magnetic resonance signal of water in human body, ultimately producing image [80]. Introduction of contrast agent i.e. paramagnetic metal ions significantly shortens the relaxation time of the water protons in the organ under investigation [81]. Schering et al. developed the dendritic contrast agent “Gadomer-24”, a dendrimer with trimesic acid core and branched second generation polylysine dendron with 24 Gd(III)-cyclen complex at periphery. Gadomer-24 has unique advantage of low toxicity as it is completely excreted by renal excretion. Gadomer-24 have a longer residence time in body therefore it has high *in vivo* stability and improve visualization [82]. Recently, Shen et al. prepared targeted biodegradable dendritic MRI contrast agent from a polyester dendrimer conjugated with gadolinium (Gd) chelates and PEG chains with

distal folic acid. Synthesized dendritic contrast agents have high longitudinal relaxivity, high contrast enhancement and longer time than commercial contrast agent Magnevist [83].

5.6. Dendrimers in Wound Healing

For the said purpose, PAMAM dendrimers were functionalized with glucosamine groups and glucosamine-6-sulphate groups. Dendrimers functionalized with glucosamine acts as immunomodulators and those functionalized with glucosamine-6-sulfate acts as antiangiogenic substances. Applications of both dendrimers for rabbit which undergone operation for glaucoma shown better healing and scar-tissue formation [84]. S.I. Stupp reported for gel formation in bone fissures which may have application in treatment of bone fractures [85]. Recently Park et al. [86] combined gene therapy with wound healing for diabetic patients. Minicircle plasmid DNA encoding vascular endothelial growth factor (VEGF) was combined with an arginine-grafted cationic dendrimer, PAM-RG4. The formed complexes were injected subcutaneously into the skin wounds of diabetic mice. Minicircle plasmid DNA encoding vascular endothelial growth factor (VEGF) was combined with an arginine-grafted cationic dendrimer, PAM-RG4. The formed complexes were injected subcutaneously into the skin wounds of diabetic mice.

5.7. Dendrimers for Additives in Printing Inks and Paints

Dendrimers can be used in toners material with additives which require less material than their liquid counterparts. Xerox Corp. Patented a dry toner compound dendrimers as charge enhancing species in the form of an additive [87]. Using additives in printing inks, dendritic polymers ensure uniform adhesion of ink to polar and non-polar foils. Here, first the hyper branched compounds attach themselves to the pigment particles and there are still large numbers of functional groups remaining to give adhesion to the surface of the foils. Verdonk et al. utilized PAMAM dendrimers as an additive for ultraviolet curable ink composition [88].

5.8. Dendrimers as Light harvesting materials

A light-harvesting complex is a complex of subunit proteins that may be part of a larger supercomplex of a photosystem, the functional unit in photosynthesis. It is used by plants and photosynthetic bacteria to collect more of the incoming light than would be captured by the photosynthetic reaction center alone. Dendrimers with Tree-like Structure and decreasing number of chromophores from periphery to core is an attractive candidate for light-harvesting applications. Dendritic designs with different kinds of light collecting chromophores at periphery and an energy sink at the core have demonstrated high energy transfer efficiency [89]. Dendrimer can play a role as scaffold for light harvesting system and can also be dendritic backbone itself which can act as chromophores. Non-conjugated dendrons such as the widely used poly(aryl ester) dendron function as just a scaffold linking together light-harvesting chromophores at the rim and the energy acceptor chromophore at the core for e.g. Frechet and Co-workers synthesized poly(aryl)ether dendrimers containing amino functionalized coumarin-2 as a donor and acid functionalized Coumarin343 as acceptor [90]. Efficient, unidirectional energy transfer from a dendritic framework to a single core chromophore was reported by Xu and Moore [91].

5.9. Dendrimers as Biomimics

Dendritic architectures can be used to mimic protein folding [80]. As discussed earlier, synthesis of dendrimer permits incorporation of both natural and unnatural amino acids within dendritic architecture i.e. peptide dendrimers which may be attractive for biomedicine. Synthetic peptide dendrimers can also exhibit enzyme like activities [92]. Wedge-shaped dendritic peptide components were formed by solid-phase synthesis starting from lysine units. The multiple antigen proteins (MAP) obtained in

this way contained between two and eight peptide chains and displayed significantly better immunogenicity than individual proteins [93].

[VI] CONCLUSION

Dendrimers have attracted interest of many researchers since last three decades. Several new synthetic approaches have made task of a synthetic organic chemist to synthesize a dendrimer significantly easier. Due to several unique properties of dendrimers such as monodispersity, nanoscale size, container like behavior, amplifiable and modifiable functionality, Dendrimers have unlocked all the possibilities regarding the field of applications.

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