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Dendrimer for targeted drug delivery and Vaccine and Immunostimulatory: applications and methods

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Research Article

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Abstract

Dendrimers are a new class of branched polymeric materials. They all are originated from a single nucleus and described as macromolecules with a three-dimensional branching structure. Dendrimers exist in the blossoming phase of drug delivery in micro and Nanosystems for local or systemic brain administration. Dendrimers are three-dimensional molecules containing structural symmetry. They include continuously branched molecules comprising a central unit called core along with branching points. In dendrimers, branching points are essential for functioning and deciding branching generations. The more the number of branching points, the more is the generation number. Synthesized dendrimers are classified as polyamidoamine (PAMAM) dendrimers, polylysine dendrimers, carbosilane dendrimers, and phosphorus-containing dendrimers. Some researchers classify dendrimers as polyatomic and polyionic dendrimers. However, polyanionic dendrimers are preferred because of their less toxicity. Polyamidoamine class of dendrimers is popular and most widely used as a result of their reproducibility, safety, biocompatibility, stability, small size, and precision. They contain tertiary amine branches and alkyl diamine core and are polyatomic. Dendrimer enters the cells like neurons and astrocytes through receptor-mediated endocytosis and micropinocytosis. The main advantage of dendrimers is their drug-loading ability within the cavities of dendrimers, which acts as the main site of the encapsulation process. They have wide applications in neurodegenerative disorders such as cerebral palsy, AD, PD, prions disease, and also in central nervous system imaging and diagnosis. Cationic phosphorous-containing dendrimers were found to interact with the aggregation of plaques and tangles. It was reported that sialic acid–conjugated dendrimers can inhibit the hyperphosphorylation of tau tangles at a micromolar concentration, which is lower than soluble sialic acid. PPI and G5 polyamidoamine dendrimers show anti-prion activity in neuroblastoma ScN_2 cells. It was recently revealed that conjugation of CY5-labeled free activable cell-penetrating peptides to PAMAM dendrimers can differentiate the tumor and adjacent tissues thus increasing tumor resects in a mouse xenograft model. Researchers suggested that the intravenous route of administration effectively penetrates the central nervous system with wide biodistribution for extended therapy. The toxicity of dendrimers markedly depends on factors such as the number of generations, core, and surface properties. Amino-terminated dendrimers were found to be toxic due to the shielding of internal cationic charge by surface modification. To overcome the toxicity of dendrimers, the generation and conjugation with biocompatible groups like Polyethylene glycol is increased. Biologically, dendrimers are highly biocompatible and have predictable biodistribution and cell membrane interacting characteristics determined by their size and surface charge. Dendrimers have optimal characteristics to fill the need for efficient immunostimulating compounds (adjuvants) to increase the efficiency of vaccines. The reason is that dendrimers can provide molecularly defined multivalent scaffolds to produce highly defined conjugates with small-molecule immunostimulators or antigens.

1. Introduction

Dendrimers are three-dimensional, monodisperse, globular macromolecules with a perfectly branched and tree-like structure. Dendrimers comprise a well-defined inner core surrounded by many branches. The branching in dendrimer signifies the “dendrimer generation,” where the “first-generation” dendrimer is comprised of only one layer of branching points while that of the fifth-generation dendrimer comprises five branching units. Higher generation dendrimers possess multiple functional groups on their surface, which provide coupling with biologically active moiety. Dendrimers have been widely explored as nanocarriers for antigen delivery as a result of their biocompatibility, biodegradability, and self-adjuvant properties. Dendrimers facilitate rapid uptake of an antigen across the intestinal epithelium and express strong immunogenicity. The immune response induced by dendrimers is mainly affected by the size, charge, and loading of antigen. Dendrimers with particle sizes of < 200 nm, spherical shape, and high antigen-loading facilitate stronger immune responses compared to the conventional oral vaccine. The commonly employed polymer for the fabrication of dendrimers are polyethyleneimine, polyamidoamine (PAMAM), poly-(N-isopropylacrylamide), and polypropyleneimine [1].

Dendrimers are monodispersing, unimolecular, micellar nanostructures, with the size of about 20 nm, regularly branched symmetrical structures and several functional end groups at their periphery [1–3]. They are known to be strong, covalently fixed, and three-dimensional structures possessing both a solvent-filled interior core (nanoscale container) as well as a homogeneous exterior surface functionality (nanoscaffold). Dendrimers act as an effective slow delivery agent since cavities serve as binding sites for the slow release of small guest molecules [4–7]. The surface activity of dendrimer branches arises from their hydrophobic edge parts and hydrophilic core. Cosmetic agent carriers are a large number of external groups suitable for multifunctionalization [8–11, 261–265]. The Newkome dendrimer was one of the first synthesized dendrimers in 1985. Many large companies, like L’Oréal, Dow Chemical Company, and Unilever, have several patents for the use of dendrimers in hair, skin, and nail care products. Due to their versatility, both hydrophilic and hydrophobic molecules can be incorporated into dendrimers [12–15, 266–271].

Dendrimers are a family of three-dimensional and nanoscale polymers that are characterized in solution by a compact spherical structure (Fig. 1). Research on dendrimers began in the 1990s. However, it was not until 1931 that the first family of high-branched polymers was discovered by Tomalia et al [1–4]. These highly branched molecules were called dendrimers, a Greek word derived from Dendron, meaning tree. At the same time, another group reported such macromolecules and called them Arbores, which means tree in Latin [16–19, 272–275]. The word cascading molecules was used instead of the dendrimer, but the best word is "dendrimer" [20–23, 276–280]. Although the origin of dendrimers can be linear polymers and then branched polymers, the amazing structural properties of dendrimers and high-branched macromolecules are quite different from those of traditional polymers [24–27, 281–285]. Despite the use of polymers in drug delivery systems, dendrimers have more benefits [28–31, 286–292]. They have limited polydispersity and nanometer dimensions that make them easier to cross biological barriers. Dendrimers can carry guest molecules through receptors on their surface or encapsulate them in cavities between branches [32–34, 293]. The development of molecular nanostructures with appropriate particle size and shape has been considered for biomedical applications such as the delivery of active

drugs, imaging materials, or gene transfer [35–37, 294]. For example, structures used as carriers in drug delivery generally need to be in the nanometer range and in the definite size to increase their ability to cross the membrane and reduce the risk of clearance from the body through the liver and spleen [38–41].

Dendrimeric polymers or dendrimers are the examples of structures for drug delivery [42–45]. The ability to adapt dendrimers to therapeutic needs makes them ideal carriers for small molecule drugs and biomolecules [46–48]. Dendrimeric carriers can deliver the drug through a variety of connections, including the skin, eyes, mouth, and lungs [49–51]. The present review provides a general outline of the structure and types of dendrimers, dendrimers synthesis, and their applications in Nanomedicine with an emphasis on drug delivery. Dendrimers have optimal characteristics to fill the need for efficient immunostimulating compounds (adjuvants) to increase the efficiency of vaccines. This is because dendrimers can provide molecularly defined multivalent scaffolds to produce highly defined conjugates with small-molecule immunostimulators and/or antigens.

2. Method Of Preparation Of Dendrimer

Dendrimers can be synthesized by two major approaches. In the divergent approach, used in early periods, the synthesis starts from the core of the dendrimer to which the arms are attached by adding building blocks in an exhaustive and step-wise manner [52–54]. In the convergent approach, synthesis initiates from the exterior, beginning with the molecular structure that ultimately becomes the outermost arm of the final dendrimer [55–57]. In this strategy, the final generation number is pre-determined, necessitating the synthesis of branches of a variety of requisite sizes beforehand for each generation [75–80].

Dendrimers are usually made in two divergent-convergent ways. In the divergent method, dendrimers grow from the nucleus of a multifactorial molecule. The nucleus of the molecule (G0) interacts with the monomer molecules and produces the first generation (G1) dendrimer. In the next step, this new surface is the molecule that is activated to react with more monomers [58–61]. Figure 2A) shows the steps for generating several generations, and a step-by-step dendrimer. The divergent method is suitable for producing large amounts of dendrites [62–64]. Though, it will lead to some side effects and incomplete reactions resulting in structural defects [65–67]. Large amounts of reagents are required to prevent side reactions and force the reaction to complete, which in turn create problems in the purification of the final products [68–71]. The convergent method was developed in response to the weaknesses of divergent synthesis. In this method, the dendrimer is made in stages from the end group’s inwards [72–76]. When the branches of the dendron are large enough, they attach to the nucleus of a multifactorial molecule (Fig. 2b). The convergent growth method has several advantages, including the desired product, which is relatively easy to purify and minimize the occurrence of defects in the final structure. However, the convergent method does not allow the formation of many generations because of the spatial barriers in the reaction between dendrons and nuclei. Once formed, dendrimers include the central nucleus, bifurcation, and internal cavities (Fig. 2).

3. Types Of Dendrimers

In recent years, various dendrimers with different functions have been synthesized for experimental and laboratory research, because of their branched structure, symmetrical shapes, and single scattering. Here are some dendrimers with different properties [77–80]. Dendrimers are distinguished based on their shape, terminal functional groups, and internal cavities (Table 1).

Table 1
Types of dendrimers

Type of dendrimer	Synthesis	Identification
Polypropylene imine (PPI) dendrimer	Divergent	[208–209]
Polyamidoamine (PAMAM) dendrimer	Divergent	[210–212]
Frechet-type dendrimer	Convergence	[213]
Core-shel to dendrimer	Divergent	[214]
Chiral dendrimer	Convergen	[215]
Liquid crystalline dendrimer	Convergen	[216]
Peptide dendrimer	Convergen	[217–218]
Multiple antigen peptide dendrimer	Divergent and convergent	[219]
Glycodendrimer	Divergent and convergent	[220]
Hybrid dendrimer	Divergent	[221]
Polyester dendrimer	Divergent	[222–223]

3.1. Liquid crystal dendrimers

Recently, there has been an increasing interest in the field of liquid crystalline dendrimers. Such a fast development is driven by the multiple possibilities offered by combining the mesomorphic properties of single mesogenic subunits with the supermolecular and versatile architectures of dendrimers to yield a new class of highly functional materials [81–85]. The induction and the control of the mesomorphic properties (phase-type and stability) in dendrimers can be achieved by a dedicated molecular design based on the chemical nature and structure of both the functional groups and the dendritic matrix [86–88]. In particular, the intrinsic connectivity of the dendrimer such as the multivalency of the focal core and the multiplicity of the branches, both controlling the geometrical rate of growth, or the dendritic generation, plays a crucial role. It affects the subtle relationships between the supermolecular structure and the mesophase structure and stability at various stages [89–92]. In this critical review paper, various types of dendritic systems will be discussed that form liquid-crystalline mesophases along with a description of the self-organization of representative case-study supermolecules into liquid crystalline mesophases along with a description of the self-organization of representative case-study

supermolecules into liquid crystalline mesophases will be discussed in the introduction[93–95]. Then, in the following sections, the selected examples will be described including side-chain, main-chain, fullerodendrimers, shape-persistent dendrimers, supramolecular dendromesogens, and metallodendrimers, as representative families of LC dendrimers. In the conclusion section, some further developments will be highlighted [96–100]. This review will not cover liquid crystalline hyperbranched and dendronized polymers that might be considered as being somehow less structurally “perfect”. Figure 3 shows a liquid crystal dendrimer [81–82].

3.2. Tecto-dendrimers

tecto-dendrimers. This class of polymer comprising a central dendrimer with multiple dendrimers attached to its periphery, holds promise for multidrug delivery and environmental remediation applications [101–105]. We find that (i) the maximum number of tecto-units that may be attached to the central core varies logarithmically with the ratio of the sizes of the component dendrimers; (ii) the total density profiles display a minimum near the junction of the tecto-units with the core; (iii) a simple expression captures the radius of gyration for a wide range of topologies; (iv) the intrinsic viscosity displays a maximum as a function of the number of tecto-units attached; (v) the sphericity increases with an increasing number of attached tecto-units. These results support the notion that the dendritic components can be viewed as independent building blocks for multifunctional devices [106–109].

Tecto-dendrimers consist of a central dendrimer enclosed by the surrounding dendrimers. Figure 4 shows a single-shell core polyamidoamine dendrimer. Tecto-dendrimers made for therapeutic and biological purposes by the Michigan Institute of Nanotechnology have the capabilities of patient cell detection, disease site diagnosis, drug delivery, status reporting, and treatment efficacy [83–87].

3.3. Chiral dendrimers

Chirality in dendrimers is caused by the presence of branches that are chemically the same but completely different structurally (chiral species) [110–112]. Due to the differences in these species, chiral dendrimers are also effective in targeted drug release and detection of chiral compounds in the body. Figure 5 displays the chiral dendrimer [1–4, 28–30].

3.4. poly(amidoamine-organosilicon) dendrimers

Radially arranged poly (amidoamine-organosilicon) dendrimers (PAMAMOS = poly (amidoamine-organosilicon)) become single-molecule micelles with nucleophilic polyamidoamine (PAMAM) inside as well as an organosilicon (OS) outside. A poly (amidoamine-organosilicon) dendrimer is shown in Fig. 6 [1–4, 113–116].

3.5. Hybrid dendrimers

Hybrid dendrimers are a combination of dendritic and linear polymers in hybrid components or bonded copolymer forms [117–121]. Figure 7 shows a hybrid dendrimer. [1–4].

3.6. Peptide dendrimers

Peptide-containing dendrimers on the body surface of traditional dendrimers and amino acid-containing dendrimers are defined as peptide dendrimers. These peptides can be located in branched units or nuclei [122–126]. Due to their biological and therapeutic properties, peptide dendrimers play an important role in various fields such as cancer, antibacterial, antiviral, central nervous system, anesthetic, asthma, allergy, and calcium metabolism [127–129]. Because they are absorbed into the cell, peptides are very useful for drug delivery [130–133]. A peptide dendrimer is displayed in Fig. 8.

3.7. Glycodendrimers

The term "glycodendrimer" is used to describe dendrimers with a structure containing carbohydrates [37, 134–140]. Figure 9 displays a Glycodendrimers dendrimer.

3.8. Polyamidoamine Dendrimers

Polyamidoamines are very popular in drug delivery. Figure 5 shows a polyamidoamine dendrimer with three generations [101–103]. Many polyamidoamine dendrimers with altered levels are not immune-stimulating. However, they are water-soluble and contain mutable end amines that can attach to different guest or target molecules [141–145]. The internal cavity of polyamidoamine dendrimers can host metal or guest molecules due to its unique structure containing triple amine and amide bonds [146–150]. Polyamidoamine Dendrimers are shown in Fig. 10.

3.9. Mechanisms of drug loading in dendrimeric carriers

3.9.1. Physical encapsulation of drug molecules

One of the most important properties of dendrimers is the possibility of encapsulating guest molecules in their internal cavities. Vogtle et al. demonstrated the first physical encapsulation of low-soluble drug molecules in the empty cavity of dendrimers (Fig. 11) [1–4, 111–114]. The polymer is simply mixed with the drug solution and the hydrophobic drug binds to the non-polar nucleus through hydrophobic interactions [42, 151–155]. After establishing physical contact between the host and dendrimeric carrier molecules, the release of encapsulated molecules in the aqueous medium is controlled by a set of non-covalent interactions such as hydrophobic forces, hydrogen bonds, spatial barriers, and electrostatic interactions [43, 156–161]. To maximize the loading capacity of the drug molecules by dendrimers, the structure of the polymer, especially the properties of the inner cavity, must be carefully considered [44, 162–165].

3.9.2. Chemical binding of drug molecules

Chemical attachment of antitumor drugs to surface groups of dendrimers is used to control and temporarily release bound drugs [166–170]. A large number of surface groups and the versatility of the chemical structure of dendrimers allow the binding of various anticancer drugs and imaging agents [45–47, 171–174]. While the compact and spherical geometry of the dendrimer is maintained in solution (Fig. 12).

3.9.3. Direct connection of the drug to the dendrimer

In this method, drug molecules are trapped by a variety of junctions by receptors on the dendrimer surface. Experiments show that in the case of some therapeutic molecules, such as some anticancer drugs, the dendrimer binding process mainly increases the solubility of the loaded drug. However, it limits the release of the drug, anticancer activity in clinical and laboratory conditions. An anti-cancer drug on the surface of the dendrimer is a vital parameter to prevent their onset [48, 175–180].

3.9.4. Sensitive binding to pH

Objectives such as accurate drug delivery to the cancer cell and release of the anticancer drug led to the development of a dendrimer-drug pair with hydrolyzable junctions [181–182]. To obtain desired therapeutic activity, these connections must remain intact in the extracorporeal cycle, enter the cancer cell once, and release the bound drug [183–185]. The formation of pH-sensitive binding in the dendrimer-drug pair seems to meet the desired criteria because they remain stable in the body cycle (pH 7.4). Though, in acidic environments such as endosomes/lysosomes (pH 5–6), rapid hydrolysis releases the attached drug into the target cell [186–189]. pH-sensitive binding senses only the acidity of the cell's endosomal chamber while it is unable to distinguish cancer cells from healthy cells. In this case, the attached drug is released only in response to the enzymes secreted only by cancer cells [190–192].

3.9.5. Light sensitive connection

Dendrimers are designed with light-receiving antennas. In such dendrimers, absorption pigments are located on the outer surface and transfer light energy to other pigments located in the nucleus [193–194]. By receiving light from the dendrimer optical receptors, the cavity can open or close. Therefore, the trapped drug is absorbed or released. An example of these optical antennas was reported by Archut et al. [193]. It was the dendrimer (polypropylene imine with the 32 end groups of azobenzene) with pores opened photochemically (Fig. 13). Azobenzene groups in this dendrimer are reversible by optical isomerization. Isomer E changes to Z form upon receiving 313 nm light and is converted back to the isomerous, E, at 254 nm or heat. Such dendrimers can act as a light-switching host for eosin, which is a red crystalline powder with the formula, $C_{20}H_8O_5Br_4$, used as a powder with sodium or potassium salts in biology to stain cells. These photochemical changes in the surface of the dendrimers cause the release of guest molecules [52–53, 195–200].

4. Dendrimer Drugs

The nanometer size of dendrimers allows them to cross biological barriers easily. This feature permits dendrimers to hold host molecules in or on their surface by bonding [201].

4.1. Dendrimers in dermal drug delivery

Recently, dendrimers are applied in dermal delivery systems. Bioactive drugs usually have hydrophobic groups in their structure that reduce water solubility and prevent effective drug delivery to cells. In contrast, dendrimers are highly water-soluble and biocompatible and can improve the properties of drugs such as solubility and deliver drugs effectively [202–204, 285–290]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective in treating acute and chronic rheumatism and osteoarthritis. Though, with an oral injection of NSAIDs, their clinical use is often limited due to the intestinal, gastrointestinal, and renal side effects. Dermal medication overcomes these side effects and maintains the healing level of the blood for a long time [205–206, 291–295]. One of the disadvantages of dermal delivery is the low delivery rate due to the skin barriers. Ketoprofen bound to polyamidoamine G5 dendrimers in laboratory studies on cut skin of rats showed that the secretion of ketoprofen from the ketoprofen-dendrimer complex was 1.5 times higher than that of ketoprofen suspended in normal saline [207–211, 296–301]. The analgesic effects of the drugs were evaluated in rats. The results show that the ketoprofen-dendrimer complex reduces pain within 2–3 hours after dermal injection, while the same dose of pure ketoprofen reduces pain symptoms between 2–5 after dermal administration [55–56, 212–215].

4.2. Oral delivery of dendrimers

The oral drug delivery system has been considered the dominant method for many years because of its major benefits well received by patients [216]. However, low water solubility and poor penetration of intestinal membranes are among the weaknesses of this system [217]. The penetration of the insoluble drug naproxen through the epithelium was examined [218–220]. The stability of the drug bound to Polyamidoamine G0 dendrimer in 50% of homogenized liver and 80% of human plasma was compared. The results showed that the lactate ester bonds retained the inactive drug with high plasma stability and slow hydrolysis in the homogenized liver [221–222]. The couple may have the potential for controlled release. Using diethylene glycol binders, the resulting pair will have high chemical stability but quickly release the drug into the homogenized plasma and liver. Therefore, these pairs as nanocarriers increase oral absorption [1–4, 56–58].

4.3. Dendrimers in ocular drug delivery

There is general agreement on the low bioavailability of intraocular drugs. This defect is caused by the drainage of excess fluid through the nasal mucosa and the removal of the solution by tears [223]. Ideal systems for ocular drug delivery need to be sterile, isotonic, biocompatible, and bioavailable and should not be overlooked. Dendrimers have a good solution for complex ocular drug delivery problems [224]. In recent research, the shelf life of pilocarpine in the eye has been increased using Polyamidoamine dendrimers with carboxyl or hydroxyl surface groups [59, 225–228].

4.4. Dendrimers in pulmonary drug delivery

Dendrimers have been also used in pulmonary medicine. In one study, the efficacy of polyamidoamine dendrimers in increasing the pulmonary absorption of enoxaparin was investigated. Generations G2 and G3 of positively charged polyamidoamine dendrimers increase enoxaparin uptake by 40%. While in G2.5 Polyamidoamine, which is a half-generation dendrimer and contains negatively charged carboxyl groups, this effect is not seen [59, 229–231].

5. Dendrimers In Targeted Drug Delivery

Today, general cancer chemotherapy is less effective in treating tumors due to the non-selective application of very potent drugs. Using drug delivery systems to target tumor cells is an alternative way to treat cancer while increasing therapeutic indicators and reducing drug resistance [59, 232–234]. Dendrimers have ideal properties that make them suitable for targeted drug delivery systems. One of the most effective targeting agents delivered by dendrimers is Folic Acid. Membrane folate receptors are proteins bound to folate that are abundant on the surfaces of various types of cancer cells. Polyamidoamine dendrimers attach to Folic Acid to target tumor cells and fluorescein is thiocyanate to image. The two molecules then attach to the complementary oligonucleotide [235–236]. This DNA-dendrimer aggregation allows different drugs to be combined with different targeting and imaging agents. In another study, dendrimer-bound Folic Acid was used as the targeting agent, and then methotrexate was attached to them. The kit was injected and evaluated into mice with defective immune systems carrying human KB (HeLa or cervical adenocarcinoma) [245] tumors. Bio-dispersion studies show that the percentage of injected dose, especially in tumor cells, using a targeted polymer complex (with Folic Acid, Tetrahydro Folic Acid, Folic Acid -(glutamic acid-13C5), Vitamin B12, Biotin), triples after one day compared to a non-target polymer complex (without Folic Acid, Tetrahydro Folic Acid, Folic Acid -(glutamic acid-13C5), Vitamin B12, Biotin). Besides, clear and rapid removal of the dendrimer complex is performed through the kidney on the first day after injection [59, 161–163].

6. Dendrimers For Controlled Drug Release

To increase the solubility in water, polyethylene glycol (PEG) units attached to the dendrimer surface were used. Polyethylene glycol was connected to the G3 polyamidoamine dendrimer. Methotrexate was encapsulated in the prepared kit and tested for drug release in a dialysis bag [164–165]. According to the results, the polyethylene glycol -dendrimer complex is conjugated with the encapsulated drug and prolongs the release of methotrexate compared to the unencapsulated drug. Controlled release of flurbiprofen is achieved with 4 G4 (Polyamidoamine) dendrimers with an amino end [166–167]. The prepared dendrimeric set shows that the loaded drug has a rapid initial release followed by a slow release [1–4, 237–239].

7. Dendrimers For Vaccine And Immunostimulatory

Dendrimers are well-defined (monodisperse) synthetic globular polymers with a range of interesting chemical and biological properties [224, 240–242]. Chemical properties include the presence of multiple accessible surface functional groups that can be used for coupling biologically relevant molecules and methods allowing precise heterofunctionalization of surface groups. Biologically, dendrimers are highly biocompatible and have predictable biodistribution and cell membrane interacting characteristics determined by their size and surface charge [300–302]. Dendrimers have optimal characteristics to fill the need for efficient immunostimulating compounds (adjuvants) that can increase the efficiency of vaccines. This is because dendrimers can provide molecularly defined multivalent scaffolds to produce highly defined conjugates with small-molecule immunostimulators and/or antigens [225, 243–246]. The present paper gives an overview of the use of dendrimers as molecularly defined carriers/presenters of small antigens, including constructs with built-in immunostimulatory (adjuvant) properties and stand-alone adjuvants that can be mixed with antigens to provide efficient vaccine formulations. These approaches allow the preparation of molecularly defined vaccines with highly predictable and specific properties and enable knowledge-based vaccine design substituting the traditional empirically based approaches for vaccine development and production [226, 247–248, 256–260].

Infectious diseases continue to pose problems to human and animal populations. However, they have been known for a long time, with the associated phenomenon of inflammation being among the earliest described medical symptoms. Moreover, the universal principle of preventive action, vaccination, has been presented for more than 300 years. Known as variolation, this covers the rather delicate practice of preventing infectious disease by injecting infectious material into an individual. A vaccine traditionally contains pathogens (microbial agents that can cause disease) modified to make the pathogen lose its disease-inducing capacity. While a sufficient similarity is maintained at the same time with the unmodified pathogen to provoke the vaccinated host to become immune to disease through the actions of the host's immune system. Vaccination has proven to be a very cost-effective way to control infectious diseases caused by microbial pathogens. It has been known in its modern form since the pioneering work in the late 18th century when Jenner introduced vaccinia (cowpox virus) as the first reliable vaccine. Subsequently, a range of other successful vaccines has been developed empirically, based on attenuated or killed microorganisms or their toxins [228]. Nevertheless, efficient vaccines are still lacking against HIV, tuberculosis, malaria, and a range of respiratory and intestinal infectious diseases. Vaccination has had great successes, for example, resulting in the eradication of smallpox (officially declared extinct in 1980) and the dramatic decrease in formerly widespread diseases like polio, measles, and rinderpest (cattle disease). Nonetheless, a wide range of infectious diseases are still abundantly present around the globe (malaria, tuberculosis, and bacterial and viral diarrhea being the most widespread). Such diseases are generally caused by complex pathogens where a more rational approach to vaccine design is needed. Some of these "difficult" pathogens attack the immune system itself or can change rapidly to avoid the immune system. There is therefore a growing need for new-generation vaccines to target these infectious diseases. With increased knowledge of the molecular actions of the immune system, there is now a unique possibility to exploit well-defined chemical methods to create such new vaccines with optimal qualities. Biocompatibility of dendrimers has attracted a huge deal of interest for biological or biomedical

purposes, therapy, diagnostic purposes, and vaccination. The biocompatibility includes cytotoxicity, immunogenicity, and the ability to penetrate various physiological and cellular barriers (including cell membranes), their biodistribution, and biological fate (half-life in circulation, excitability, etc.). As a rule, the dendrimer interior structure is to a large extent shielded from the surroundings by the outer shell and the surface, meaning that the biological properties of a dendrimer to a large extent are governed by the characteristics of the surface groups and of the dendrimer's size. Amino surface groups interact strongly with biological membranes as a result of their highly positive charge and the negative charge of most cell membranes resulting in a high cellular uptake of these molecules by endocytosis. However, with higher-generation (G > G3) amino-terminated dendrimers, the membrane affinity leads to a more destructive interaction with the membrane resulting in cell lysis and high cytotoxicity both in vitro and in vivo. The opposite behavior is observed with negatively charged surfaces dendrimers such as carboxylic acid surfaces [229]. These dendrimers do not interact with most cellular surfaces. Hence, they do not show significant generation-dependent cytotoxicity. Noncharged groups may be divided into polar and nonpolar groups, polar membrane noninvasive groups like polyethylene glycol chains resulting in a nontoxic behavior of the dendrimer. Nevertheless, nonpolar groups such as lipids interact with the cellular membrane by hydrophobic interactions, in some cases rendering the dendrimer cytotoxic. However, lipids, as an important part of for example bacterial surfaces and molecular targets of the immune system can endow dendrimers with immunostimulating properties (see below). Generally, dendrimers with higher molecular size show a lower permeability, regardless of the nature of their surface groups. In vivo, high-generation dendrimers have high clearance rates from the body via renal excretion, as their size and lack of flexibility result in limited permeability of these dendrimers into the tissues. This results in high levels of dendrimer deposited in the organs (e.g., liver and kidneys) before excretion. High-generation dendrimers with noncharged polyethylene glycol chains or negatively charged carboxylate groups on their surfaces show no toxicity. Carboxylate-surfaced dendrimers are cleared more rapidly from the bloodstream and deposited into the organs compared to polyethylene glycol-modified dendrimers. The longer blood circulation times of the polyethylene glycol-covered dendrimers are presumably due to the noninvasive character of polyethylene glycol, which reduces interaction with the vascular walls. High-generation cationic dendrimers (G > G6) may cause problems of toxicity in vivo. In addition to the tissue toxicity, high-generation amino surfaced dendrimers also result in inflammation and activation of the complement system. As with the membrane interacting, lipid-bearing dendrimers, there is a fine balance between cytotoxicity and stimulation of cellular components of the immune system [230, 249, 295].

8. Other Applications Of Dendrimers

There are more than fifty families of dendrimers, each with unique properties, and their outer, inner, and core surfaces can be used in a variety of ways. Dendrimers are also used in diagnostic methods [168–170]. Dade International has defined a new method of heart testing where the proteins in the blood sample are attached to immunoglobulins fixed to glass by dendrimers. The damage to the heart muscle will be shown by the results. This method significantly reduces the waiting time for blood test results to about 2 min [171–173]. The same test takes more than 2 min when performed in a dendrimer-free

immunoglobulin solution. Moreover, pairing the dendrimers and antibodies improves the accuracy and sensitivity of the test. Dendrimers can be used as a coating agent to protect or deliver drugs to specific areas of the body or as a timed-release machine for biologically active agents [174–177]. Fluorouracil (5FU) has good antitumor activity but is highly toxic. PAMAM acetylated dendrimers slow the release of 5FU and reduce its toxicity. These dendrimers appear to be useful carriers for anticancer drugs. Dendrimers have been tested in preclinical studies as a distinguishing factor for nuclear magnetic resonance imaging (MRI). The addition of a distinguishing agent such as paramagnetic metal cations improves the sensitivity and specificity of the method [250–254].

9. Conclusion

- Since the first dendrimer was synthesized, there has been a growing interest in dendrimer chemistry. Advances in controlled polymerization and synthetic techniques have led to the development of well-controlled dendrimer structures with a large number of surface groups. This paper deals with dendrimers in a very specialized way and points out how to prepare them in two ways, divergent and convergent. In this paper, we will study the features and types of dendrimers. Some types of dendrimers are PAMAM dendrimers, glycodendrimers, peptide dendrimers, hybrid dendrimers, PAMAMOS dendrimers, chiral dendrimers, single to dendrimers, and liquid crystal dendrimers.
- In general, dendrimers can carry drugs or biomolecules on their surface or inside their cavities. Dendrimers have the property of releasing their host molecules into the target tissue in a controlled manner, which in turn can lead to a reduction in drug use and some of its destructive effects. They have characteristics making them very attractive. Controllable features in dendrimers such as size, shape, branch length, and surface properties allow dendrimers to be modified for any requirement, thus making them ideal carriers for many applications. The mechanisms of drug loading in dendrimer carriers are different, and drug delivery may take place through the skin, mouth, eyes, or lungs. Depending on the type of drug, the dendrimer can be also useful in the diagnostic process and carry anticancer drugs and imaging agents.
- Dendrimers are hyperbranched nanostructures with some noteworthy features such as low polydispersity index with surface functionality, versatile properties, uniformity in size, and molecular weight. They consist of a core molecule, branches, and peripheral groups, which can be synthesized by two techniques, the divergent growth method, and the convergent growth method. However, some recent techniques have also been employed for the synthesis of dendrimers such as lego chemistry, click chemistry, and the double exponential growth method. Depending on different types of core and peripheral groups, the dendrimer can be classified as polyamidoamine dendrimer, poly (propylene imine) dendrimer, glycodendrimer, liquid crystalline dendrimer, and peptide dendrimer. To attain more efficient results, dendrimers are developed by applying some modifications to their properties, namely, PEGylation, liposomes locked in dendrimers, and synthesis of targeted dendritic scaffolds. Dendrimers offer several applications in the field of photodynamic therapy, gene delivery, small interfering ribonucleic acid delivery, oligonucleotide delivery, vaccine delivery, and imaging. This section provides an insight into the dendrimer with its properties, synthesis scheme, different classes,

functional modification, and various applications along with some ideas about the commercially available dendrimer.

- Despite the molecular characteristics of dendrimers (multiplicity, definability, serializability, and molecular weights above 2 kD), they are presently used to a limited extent as carrier molecules to enhance the immunogenicity of antigens for vaccine purposes, with the exception being the lysine-based MAP carrier dendrons emerging from the peptide field. Although developed specifically for presenting small peptide antigens to the immune system, the accommodation of nonpeptidic haptens (e.g., carbohydrates and of several different types of peptides simultaneously (B and T cell epitopes) have also been demonstrated. Also, convergent strategies for MAP synthesis have been developed for the synthesis of self-adjuvating (lipid-containing) MAPs. After the first descriptions, further developments/improvements have been presented. The MAP dendrimer approach has been left for the benefit of a linear combination of T and B cell stimulatory peptides. The use of dendrimers as stand-alone adjuvants is even less well described and investigated. The application of dendrimers as molecular adjuvants should be further explored and developed, especially in the case of DNA vaccination where one of several critical steps is the delivery of DNA to the target cells step. This is known to be facilitated by the administration of certain dendrimer types, at least in vitro. DNA-dendrimer complex formation could be even imagined to help overcome two other pivotal steps in the DNA vaccination method, namely, protecting the DNA against breakdown and targeting the DNA to specific host cells, e.g., in the mucosa (by exploiting the heterofunctionalization potential of the dendrimer to include targeting ligands in the construct). It is also clear that the potential of dendrimers for other vaccine purposes, both as antigen carriers or adjuvants and as combinations of these, is far from fully explored. Being monodisperse polymers, dendrimers offer the possibility of producing molecularly defined adjuvants combining very specific immunomodulating activities with targeting relevant tissues such as mucosal surfaces, and antigen transportation. The resulting macromolecular constructs are expected to behave as highly immunoreactive and specific adjuvant/carrier compounds. Thus, dendrimers are useful generic platforms for developing defined and safe vaccines with new properties and application potentials. They will also be useful for basic investigations of the mechanisms behind the induction and control of immunity.

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-Ethics approval and consent to participate

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Figures

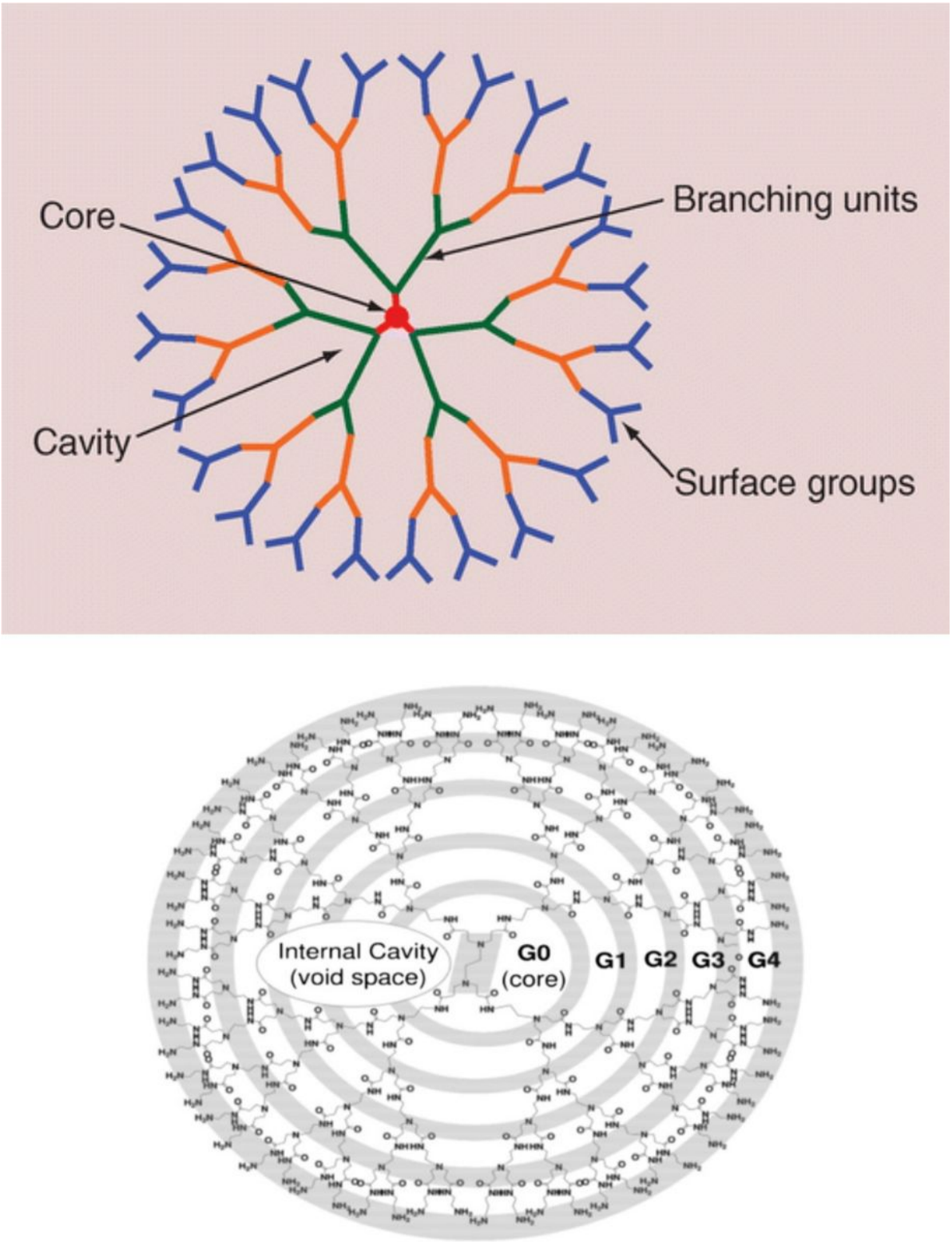


Figure 1

The general characteristics of dendrimer including core, generations (four-generation dendrimer, right), and terminal surface groups [1-3].

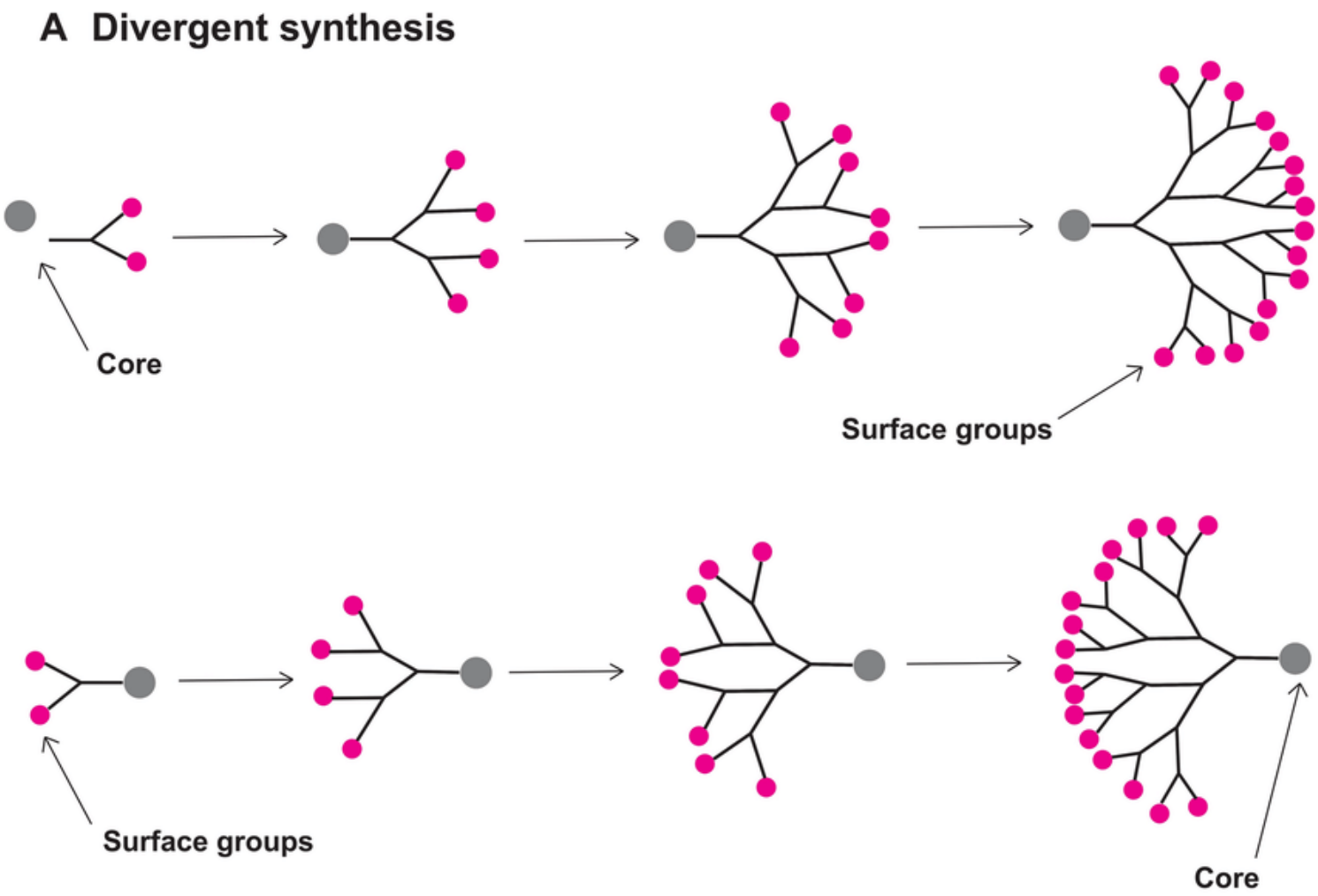


Figure 2

The synthesis of dendrimers by (a) divergent methods; (b) convergent methods [1-4].

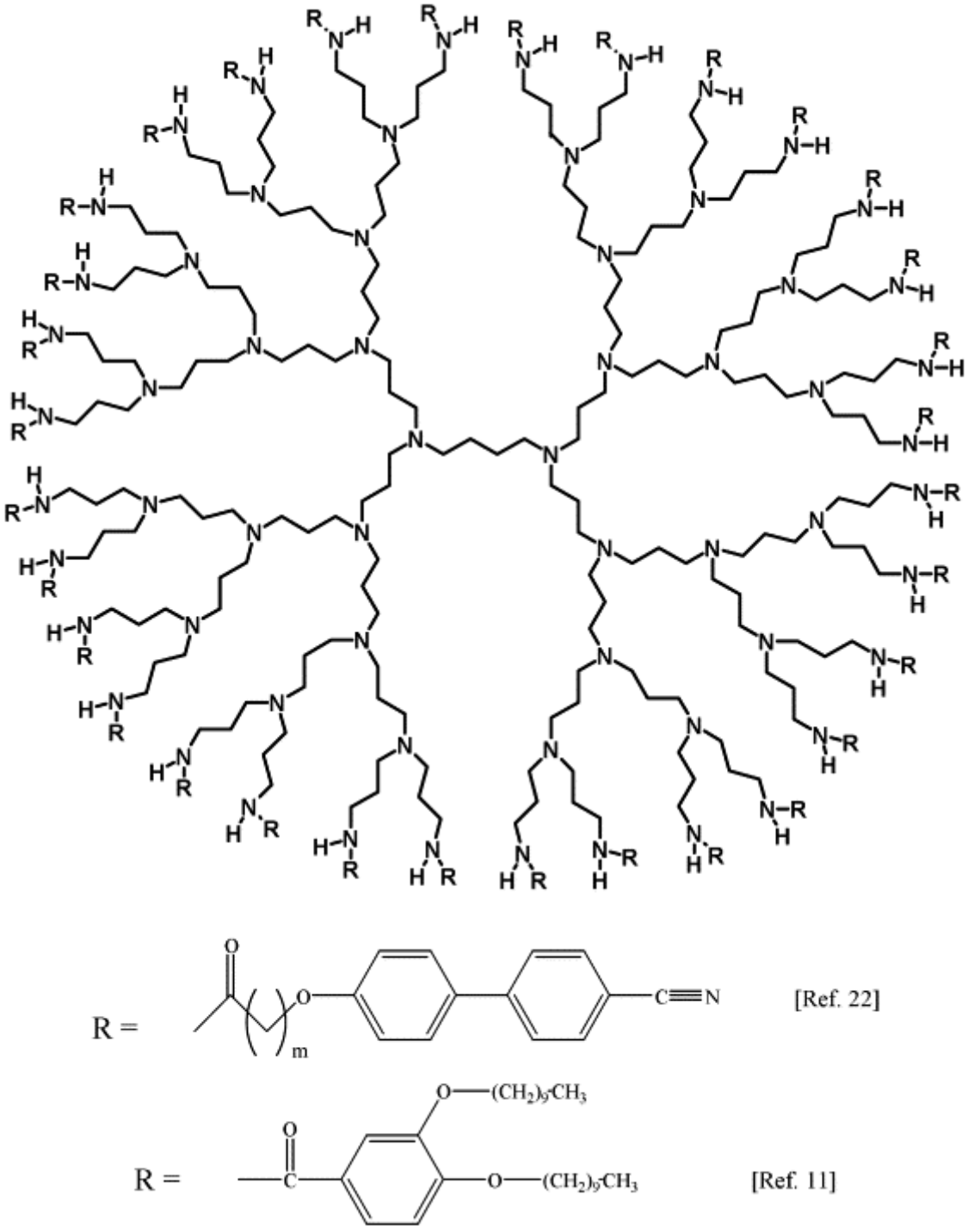


Figure 3

The liquid crystal dendrimer [4].

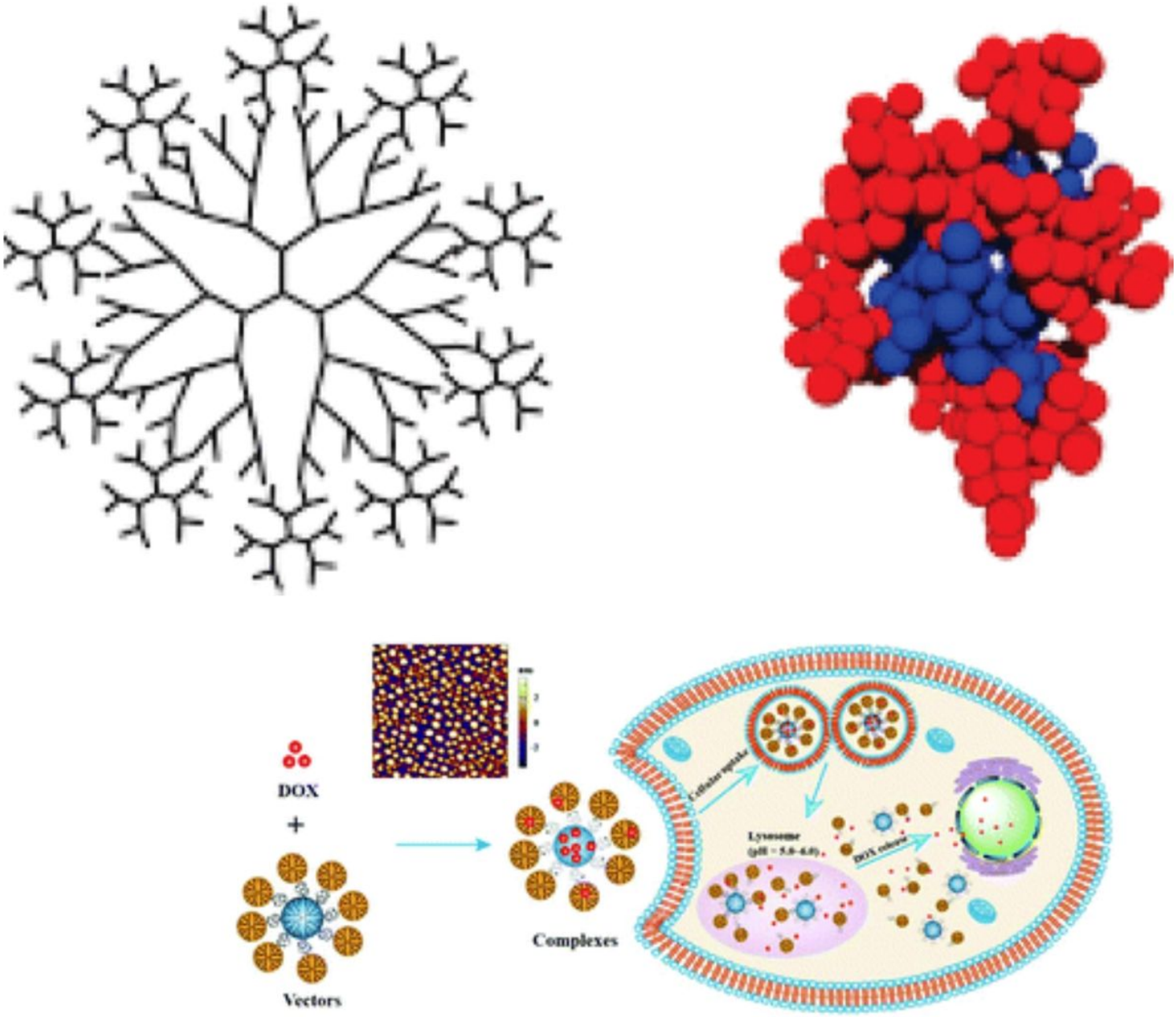
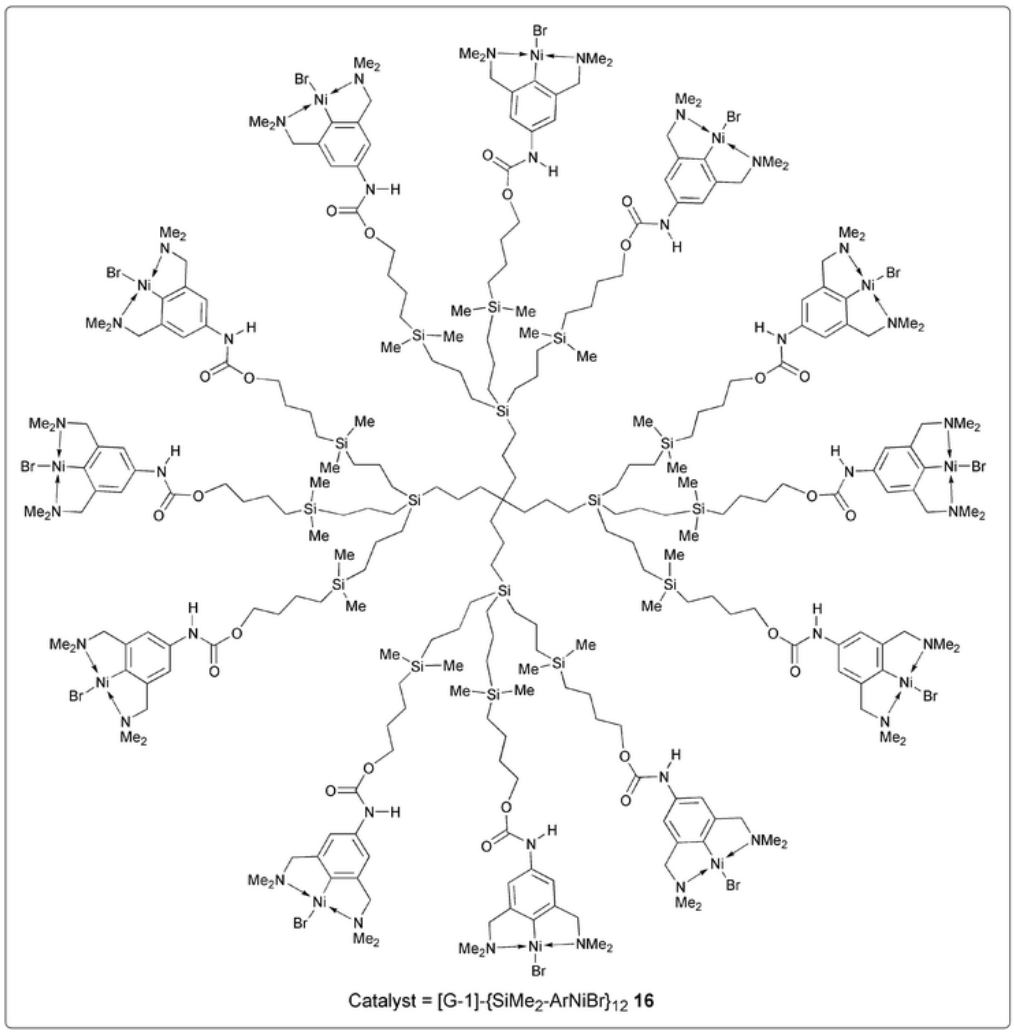


Figure 4

The core-shell Polyamidoamine Tecto- dendrimer [83].



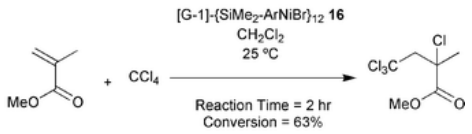


Figure 5

The Chiral dendrimer [4].

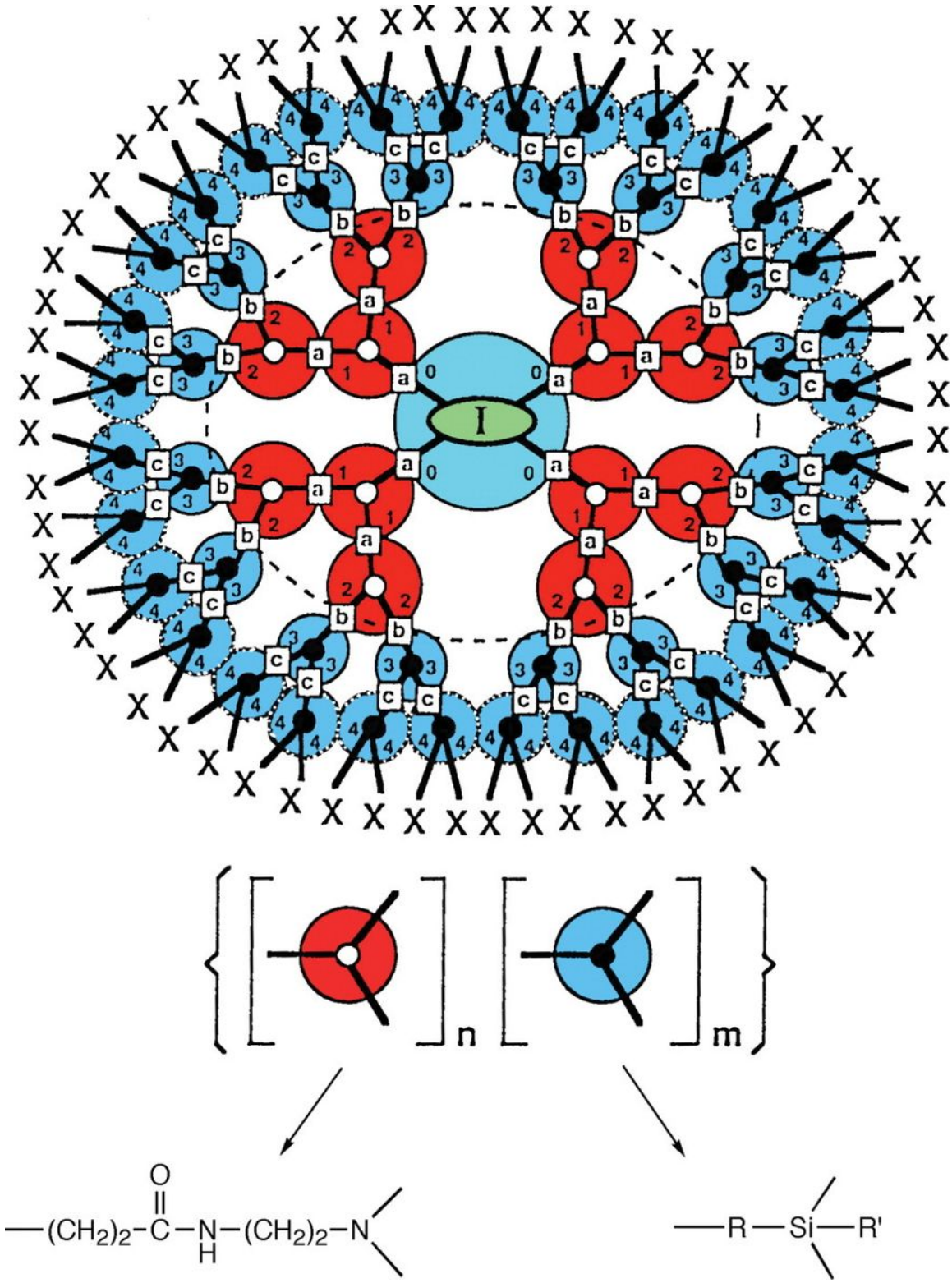


Figure 6

The poly(amidoamine-organosilicon) dendrimer [3].

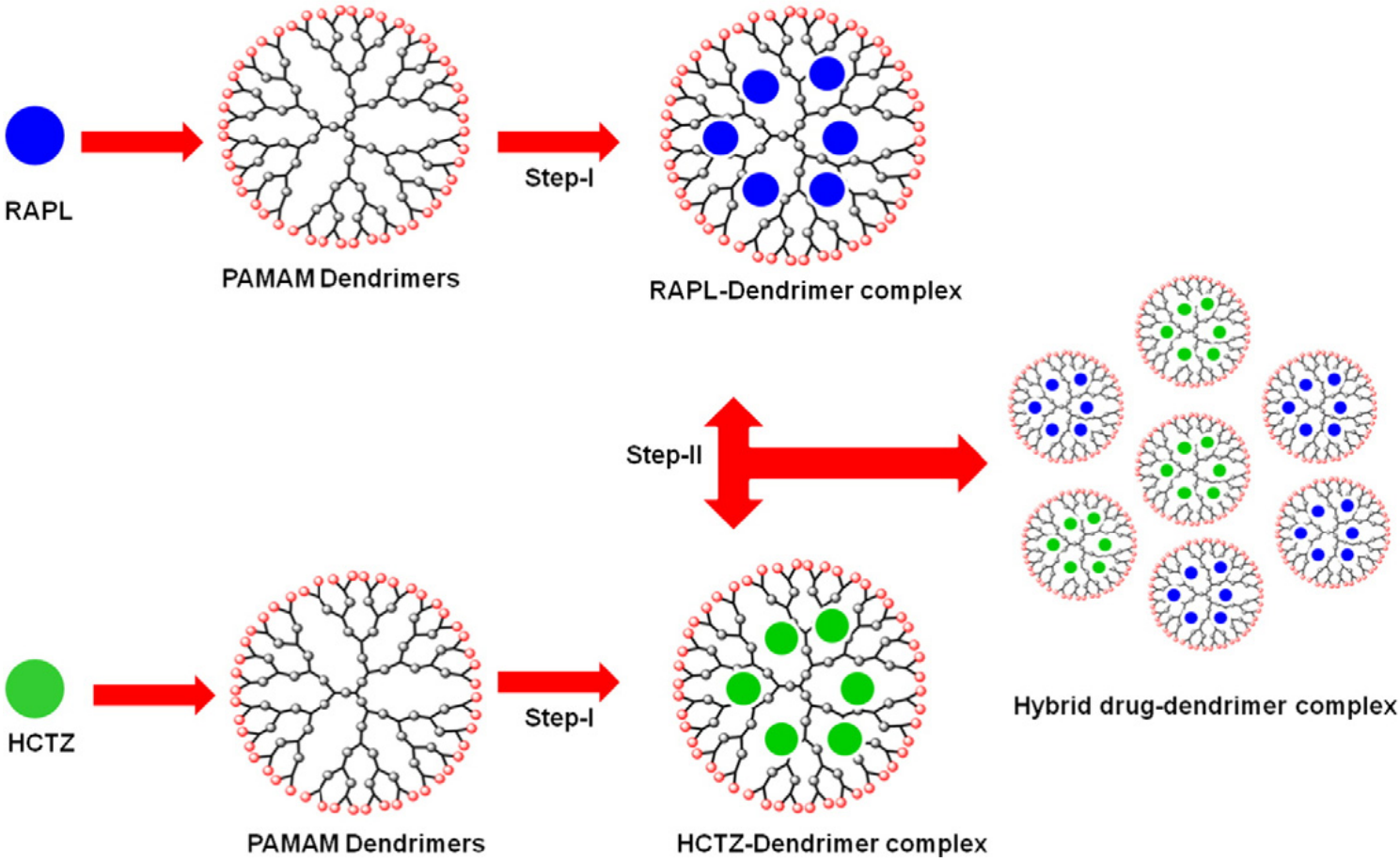


Figure 7

A hybrid dendrimer [4].

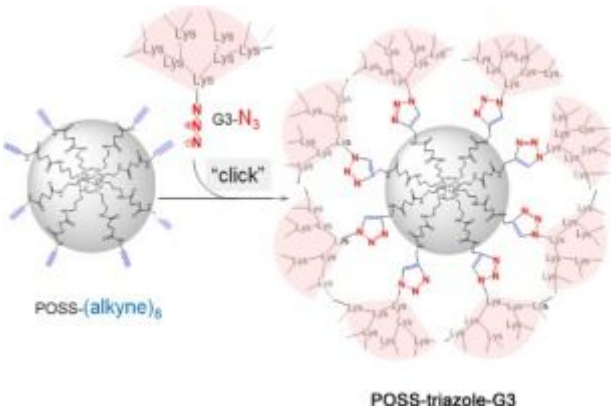
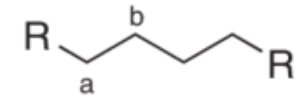
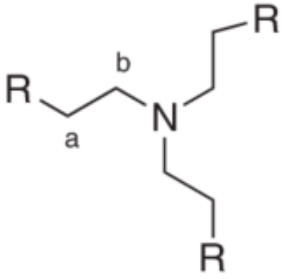


Figure 8

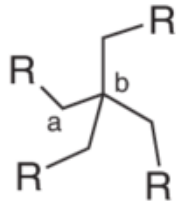
A peptide dendrimer [1-4].



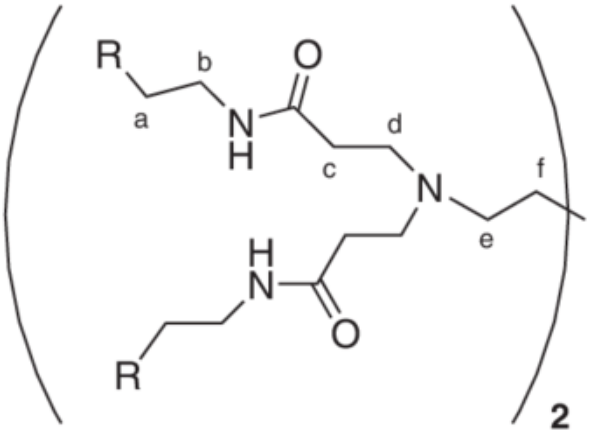
Glycodendrimer **1**



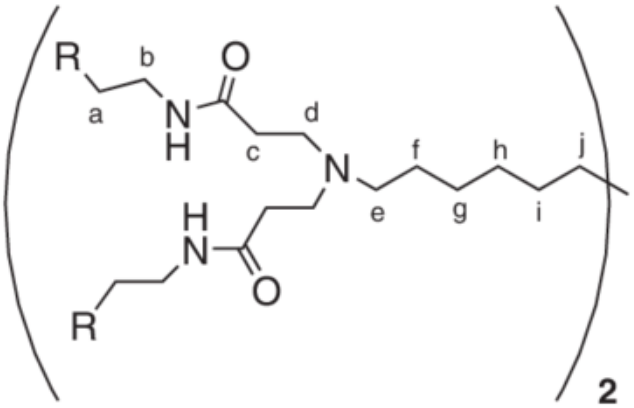
Glycodendrimer **2**



Glycodendrimer **3**



Glycodendrimer **4**



Glycodendrimer **5**

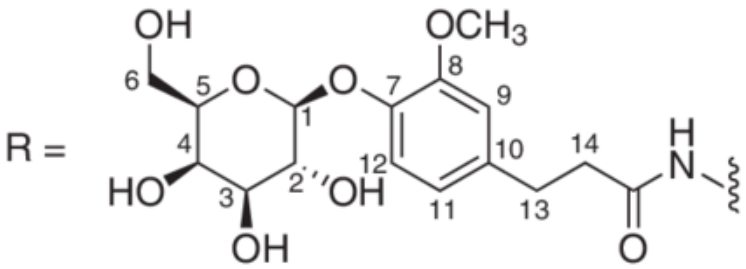


Figure 9

A carbohydrate-coated glycodendrimer[1-4].

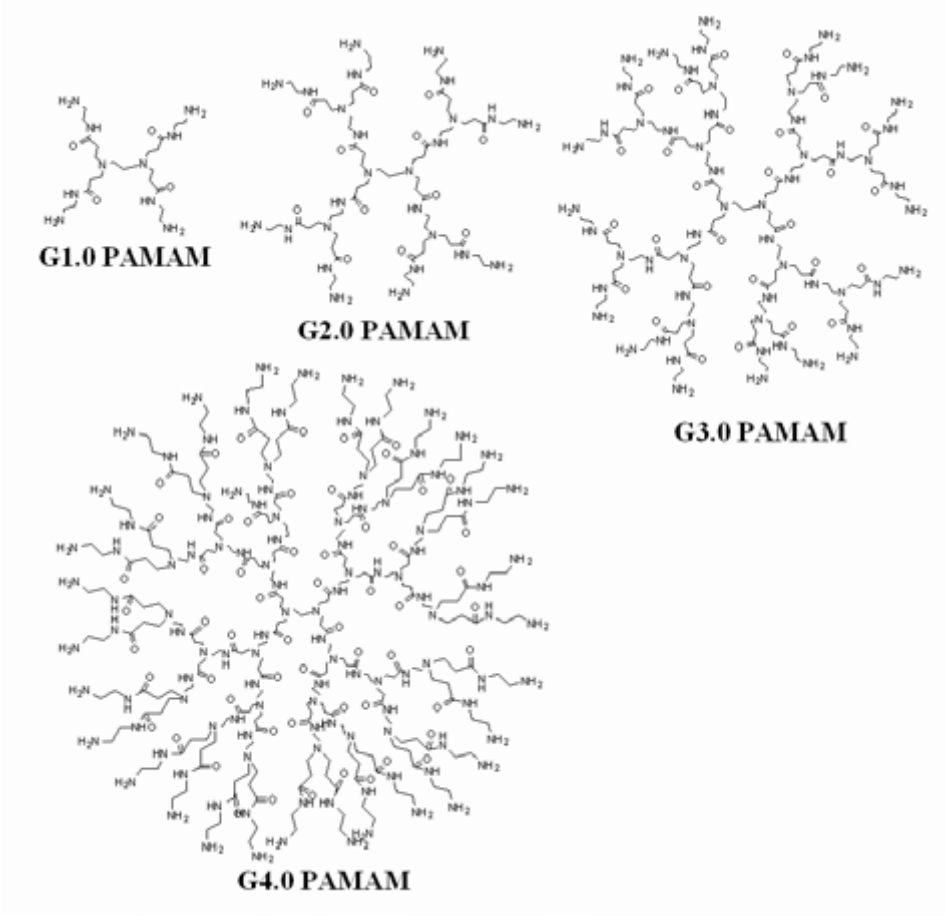


Figure 10

Polyamidoamine dendrimers (G1-G4) [38].

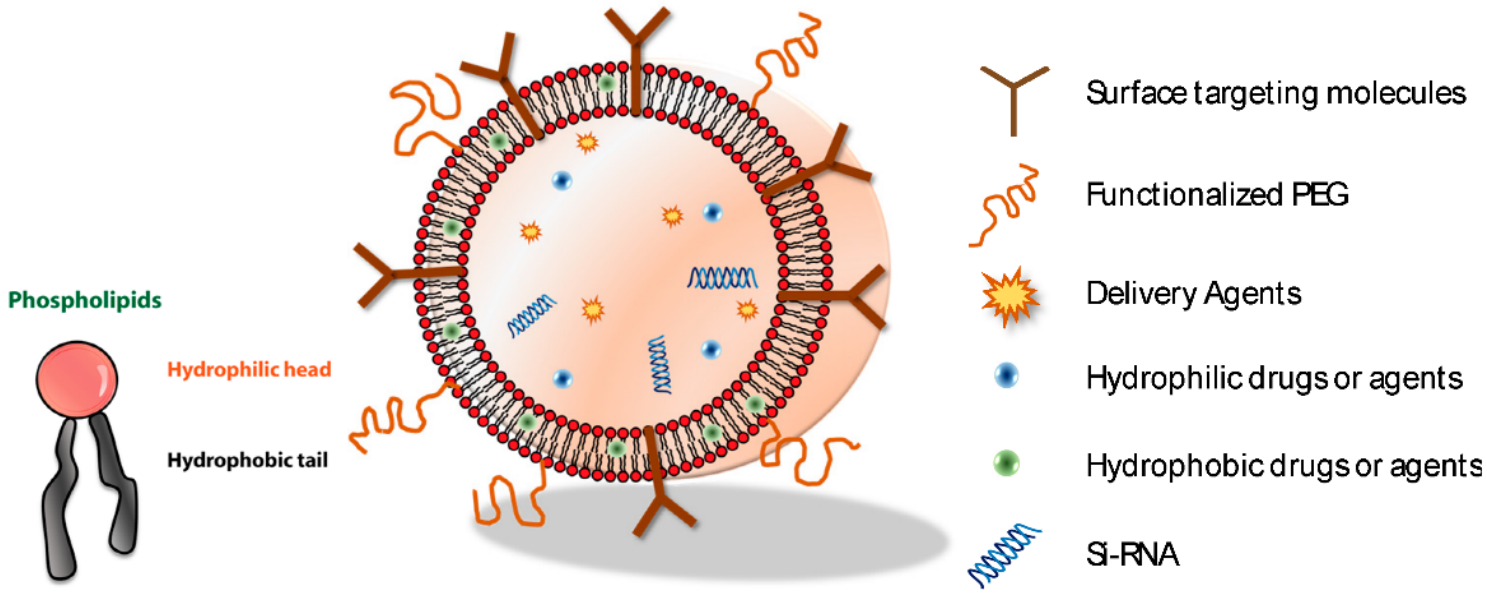


Figure 11

The hydrophobic drug molecules inside cavities [43].

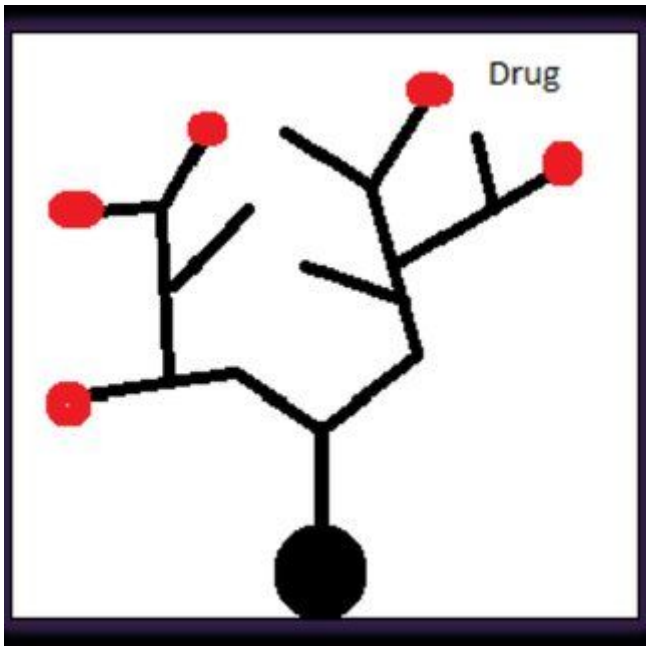
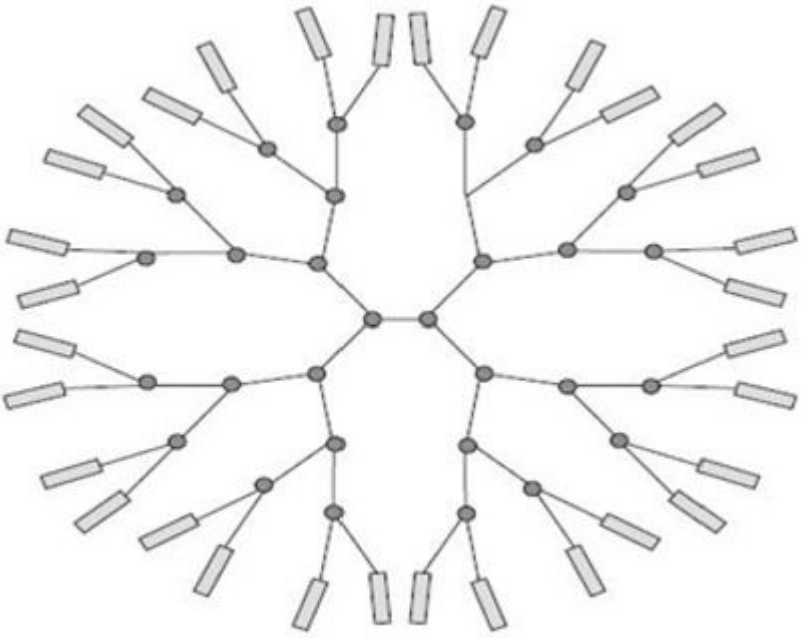


Figure 12

Drug molecules (red) on the dendrimer surface [45].



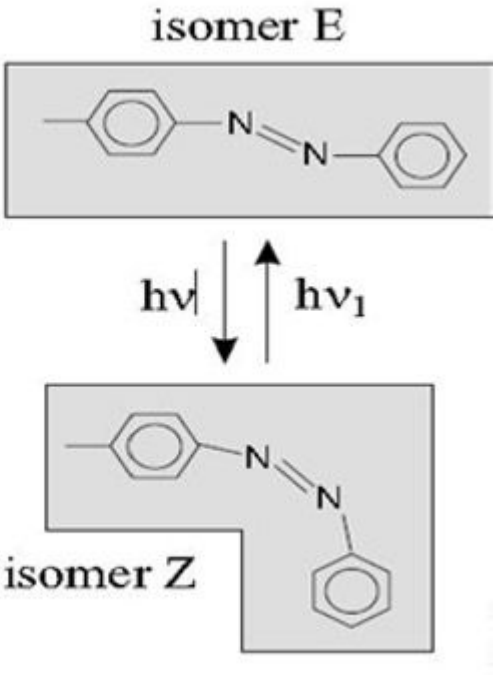


Figure 13

Dendrimer with terminal azobenzene groups and a sample of azobenzene E, Z isomers [4].