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ADVANCED REVIEW

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# Carbosilane dendritic nanostructures, highly versatile platforms for pharmaceutical applications

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## Abstract

Dendrimers are multifunctional molecules with well-defined size and structure due to the step-by-step synthetic procedures required in their preparation. Dendritic constructs based on carbosilane scaffolds present carbon–carbon and carbon–silicon bonds, which results in stable, lipophilic, inert, and flexible structures. These properties are highly appreciated in different areas, including the pharmaceutical field, as they can increase the interaction with cell membranes and improve the therapeutic action. This article summarizes the most recent advances in the pharmaceutical applications of carbosilane dendritic molecules, from therapeutics to diagnostics and prevention tools. Dendrimers decorated with cationic, anionic, or other moieties, including metallodendrimers; supramolecular assemblies; dendronized nanoparticles and surfaces; as well as dendritic networks like hydrogels are described. The collected examples confirm the potential of carbosilane dendrimers and dendritic materials as antiviral or antibacterial agents; in therapy against cancer, neurodegenerative disease, or oxidative stress; or many other biomedical applications.

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**KEYWORDS**

anticancer activity, antimicrobial properties, biomedical applications, carbosilane dendrimers, nanodendritic systems

## 1 | INTRODUCTION

Dendrimers are globular, three-dimensional, highly hyperbranched, and monodisperse macromolecules, with a well-defined structure. The term dendrimer has its origin in the Greek word *dendron*, which means "tree" and the word *meros* which means "part." The main difference between dendrimers and other conventional polymers lies in their controlled synthesis, that is, their size, shape, and functional groups can be previously selected, unfolding a wide range of possibilities and applications. These characteristics endow the system with unique physicochemical properties: nanometric size, monodispersity, synthetic versatility, low viscosity, and multivalency. These systems have been synthesized with a very wide range of diverse elemental compositions (i.e., both organic and inorganic). Their structure encompasses a core, several branching chains emerging from this core and multiple peripheral groups at the surface. Each branching point is known as "generation" and its number defines the size of the dendrimer.

Different families of dendrimers have been developed, employing a wide variety of monomeric units. Among the most relevant systems described are poly(amidoamine) (PAMAM), poly(propylenamine) (PPI), and bis-MPA polyesters, broadly employed due to their commercial availability. However, other interesting families include polyether, triazine, poly(L-Lysine) (PLL), phosphorus, and carbosilane (CBS) dendrimers. The versatility of the dendritic scaffold as well as of the functional groups anchored to the dendrimer surface have entailed extensive research in the biomedical field (Tomalia et al., 2012).

The CBS dendritic macromolecules are a broad family of materials sharing a common scaffold, based on carbon–carbon and carbon–silicon bonds, which lead to highly hydrophobic frameworks, in contrast to other highly hydrophilic frameworks as those of PAMAM, PPI, or polyesters. Hence, the presence of silicon heteroatoms plays an important role in the scaffold properties such as solubility and polarity. Furthermore, the tetravalent Si atom offers different degree of branching (two or three) of the dendritic system. Accordingly, carbosilane dendrimers are highly stable, flexible, inert, and hydrophobic (P. Ortega, Sanchez-Nieves, et al., 2020).

The CBS dendritic family has evolved over time, continuously increasing the complexity of the materials (Figure 1). Traditional monodisperse dendrimers and dendrons have been employed to generate hybrid materials such as metallodendrimers, or dendronized surfaces and nanoparticles, which combine the properties of their components; additionally, they have been linked through self-assembly or induced-crosslinking to achieve higher size materials with new possibilities. The expansion of the variability of structures better assessed the needs of the potential applications, especially in the biomedical field.

Although CBS dendrimers have found uses in different areas, including catalysis and sensoring, it is due to the pharmaceutical applications that this field has grown faster. Their promising performance as antivirals (Sepulveda-Crespo, Gómez, et al., 2015; Sepulveda-Crespo, Sánchez-Rodríguez, et al., 2015) or antibacterial agents (Fuentes-Paniagua

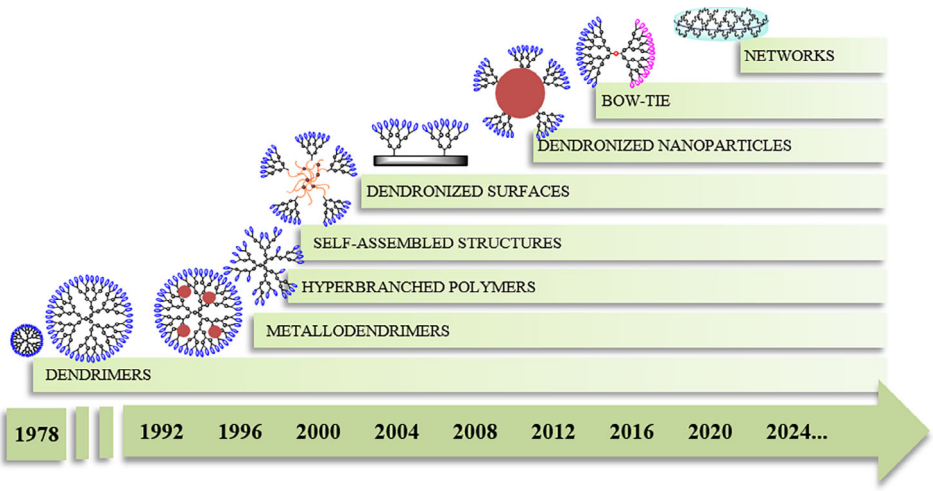


**FIGURE 1** Evolution of carbosilane dendritic structures over time. First examples of traditional dendrimers (Hadjichristidis et al., 1978; van der Made et al., 1993), metallodendrimers (van Koten & Jastrzebski, 1999), hyperbranched polymers (Drohmann et al., 1998), self-assembled structures (Chang et al., 2000), dendronized surfaces (Xiao et al., 2002) and nanoparticles (Gonzalez de Rivera et al., 2011), bow-tie dendrimers (Hatano et al., 2014), and dendritic networks (García-Gallego et al., 2021)

et al., 2014) encouraged the research into other fields such as anticancer therapy, neurodegenerative diseases, arthritis or even cosmetics.

This article will provide the reader with a practical overview of the latest advances in the pharmaceutical applications of CBS dendritic materials. We encourage the reader to check existent reviews for previous work in this field (Barbara Klajnert & Cena, 2013; del Olmo, Carloni, et al., 2020; P. Ortega, Sanchez-Nieves, et al., 2020; Pedziwiatr-Werbicka et al., 2019).

## 2 | PHARMACEUTICAL APPLICATIONS OF CARBOSILANE DENDRITIC MOLECULES

### 2.1 | Cationic dendritic systems

The presence of positive charges on the dendritic structures, such as ammonium or phosphonium terminal groups, enables their use in gene and drug delivery as well as in antibacterial and anti-amyloid therapy (Strasak et al., 2017). Besides their charge, the topology of the dendritic systems affects its potential activity, as it will be described in the following examples (Fuentes-Paniagua et al., 2016; Lozano-Cruz et al., 2020).

#### 2.1.1 | Gene carriers

CBS dendrimers protect small interfering RNA (siRNA) from protease degradation, being a promising tool for the treatment of genetically based disorders such as cancer, neurodegenerative diseases or HIV infection, among others (Krasheninina et al., 2019; Laurini et al., 2021; Rabiee et al., 2020). A comparative study between third-generation dendrimers with (trimethyl)ammonium ($-NMe_3^+$) or (trimethyl)phosphonium ($-PMe_3^+$) or peripheral groups was carried out by Maly and co-workers (Herma et al., 2019; Figure S1). They found no differences in transfection capacity using 10 mM of Silencer™ GAPDH siRNA. However, phosphonium-functional systems were slightly less toxic than their ammonium analogs. On the other hand, Bryszewska et al. evaluated the influence of the nature of ammonium group on the transfection capacity of CBS systems. The presence of ammonium groups with or without pH-dependent properties ($NHMe_2^+$ vs. $NMe_3^+$), Figure S2, did not affect the ability to form the nanocomplex or the transfection of pro-apoptotic siRNA (Mcl-1 and Bcl-2); however, pH-dependent ($NHMe_2^+$) systems did show increased toxicity (Bialkowska et al., 2021). Recently, and considering the importance of studying the therapeutic activity of new drugs in the three-dimensional (3D) in vitro tumor spheroids, cytotoxicity of CBS dendrimers, Figure S2, and their dendriplexes with pro-apoptotic siRNA (Mcl-1 and Bcl-2) were tested on MCF-7 cells cultured as spheroids (Bialkowska et al., 2022). The results obtained corroborated previous data from 2D experiments and indicate that the effect of dendriplexes on MCF-7 cells cultured as spheroids depends on a variety of factors including the structure of the dendrimer, the size of the complex and doses of dendriplexes added at specified time intervals.

#### 2.1.2 | Treatment of neurodegenerative disorders

In the treatment of neurodegenerative diseases such as Parkinson's, Alzheimer's, or type 2 diabetes, dendritic systems with positive charges in the structure exhibited excellent anti-amyloid properties, preventing the folding of proteins involved in the neurodegenerative process. Several studies have shown that the topology of the dendritic system is a key factor in protein interaction to avoid aggregation. For example, in Parkinson's disease, bow-tie dendrimers (Figure S2) prevent the abnormal accumulation of α-synuclein in dopamine neurons at noncytotoxic concentrations (Figure 2, left), while the spherical and dendritic wedge topologies (Figure S3) did not show any effect (Ferrer-Lorente et al., 2021). However, in the prevention of β-amyloid aggregates in pancreatic islets isolated from Tg-hIAPP mice, the dendritic wedge was the most promising system (Figure 2, right; Lozano-Cruz et al., 2020). In this case, attaching the chemical chaperone 4-phenylbutyric acid, which prevents the misfolding and mislocalization of proteins (Jiang et al., 2018), at the focal point of the cationic dendron (Figure S4) did not affect the insulin secretion of the pancreatic islets and therefore this dendron is a promising anti-amyloid agent in the treatment of type 2 diabetes.

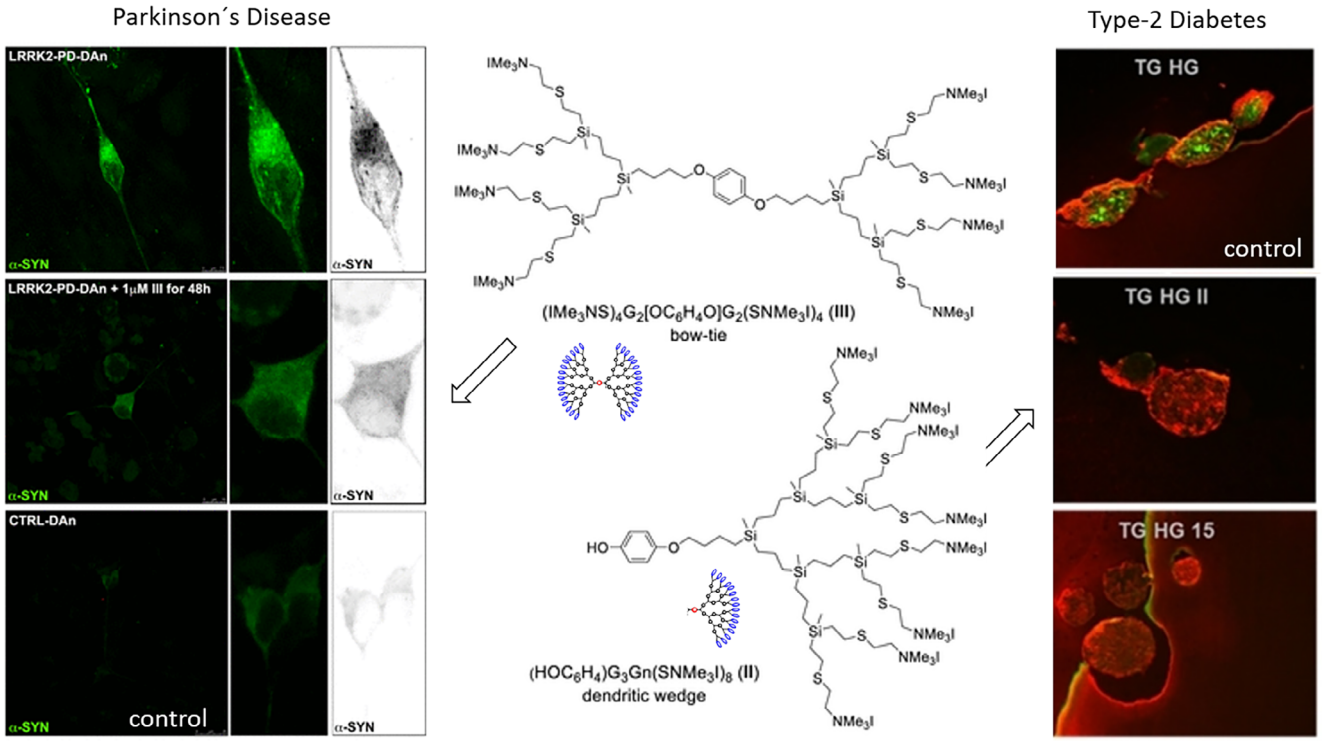


**FIGURE 2** Effect of cationic CBS dendrimers on the abnormal accumulation of α-synuclein in dopamine neurons from Parkinson's disease patients (left, Copyright ACS 2021; Ferrer-Lorente et al., 2021) and on the amyloid severity on type-2 diabetes (right, Copyright Wiley 2020; Lozano-Cruz et al., 2020).

### 2.1.3 | Antibacterial and antiparasitic activity

The resistance to conventional antibiotics generated by bacteria and other microorganisms has driven efforts to find new therapeutic agents to overcome this problem. Due to the proven antibacterial activity of quaternary ammonium groups and the multivalent nature of the dendritic systems, they exhibit a high potential as antibacterial and antifungal agents (Nadagouda et al., 2022; Rasines et al., 2009). One of the pathologies where CBS dendrimers have been evaluated as amoebicidal agents is acanthamoeba keratitis—a severe ocular disease in humans caused by *Acanthamoeba polyphaga*. CBS dendrimers (Figure S5) decorated with guanidine or biguanide moieties (Heredero-Bermejo et al., 2018; Martin-Perez et al., 2019) and cationic carbosilane dendrons derived from 4-phenylbutyric acid (Figure S4; López-Barona et al., 2022) caused a cytoplasmic damage in both trophozoites and cysts forms, including vacuolization, depletion of cytoplasmic contents, and reduced cell size. The multivalency of dendritic systems can play two different roles. On the one hand, it increases the number of therapeutically active functional groups on the same platform. On the other hand, it also allows heterofunctionalization to improve the properties of the system. One of the well-known procedures to optimize structures toward biomedical properties is the incorporation of polyethylene glycol (PEG) fragments. This transformation was also done in cationic CBS dendrimers (Figure S6), in order to test its impact on their antibacterial effect on planktonic cells and biofilms of *Pseudomonas aeruginosa*, alone and in combination with phage-derived endolysin (Quintana-Sanchez et al., 2022). These PEGylated dendrimers modified, in a negative manner, the hydrophilic/hydrophobic balance thus reducing the antibacterial activity with respect to the non-PEGylated system.

### 2.1.4 | Other applications

Cationic dendrimers have been recently explored in other applications. In the field of protein sample preparation, Garcia and co-workers demonstrated that fourth-generation dendrimers (Figure S7) are capable to interact and precipitate myoglobin, making them suitable candidates in protein separation as an alternative to the conventional methods (Gonzalez-Garcia et al., 2020). On the other hand, cationic dendrimers could be used as mucoadhesive polymers in

eyedrop formulations containing acetazolamide. Low doses of cationic CBS dendrimers (Figure S8) were well tolerated and able to improve the hypotensive effect of this active principle in glaucoma treatment (Bravo-Osuna et al., 2016). Recently, cationic dendrimers with PEG groups in their structure (Figure S9) have been found to be interesting antiviral agents against HSV-2 and HCMV infections (Royo-Rubio et al., 2022). The mechanism of action seems to indicate an affinity of these systems for cell receptors involved in the early stages of infection, which prevents virus attachment and inhibits these viral infections.

## 2.2 | Anionic dendritic systems

### 2.2.1 | Antiviral activity

Anionic CBS dendrimers have been thoroughly studied as compounds with antiviral activity. Like other polyanionic systems, their activity is mainly related to the ability to block specific proteins of viral capsids used to anchor to host cells or receptors in the host cells (Bianculli et al., 2020; Lüscher-Mattli, 2005). However, an important drawback of traditional polyanionic systems was that their complex structures hindered the establishment of structure–activity relationships. These previous studies were an impulse to develop anionic dendrimers, with precisely controlled structures. A milestone in this research field was the design of polylysine dendrimers with sulfonate groups as SPL7013, the active principle in VivaGel® (Starpharma; Tyssen et al., 2010). This family of dendrimers showed promising in vitro behavior against HIV and HSV. Nevertheless, as with other microbicides, these results did not match with the in vivo experiments and clinical trials. Problems such as vaginal inflammation and lack of activity in the presence of semen were hurdles that these dendrimers did not surpass (McGowan et al., 2011). Amyloid fibrils, which are present in semen, are considered the cause of ineffectiveness of topical vaginal gel in vivo after microbicides failed as HIV-1 prophylaxis (Notario-Pérez et al., 2017; Zirafi et al., 2014).

Like their polylysine counterparts, polyanionic CBS dendrimers have also shown attractive antiviral properties against HIV and HSV (Figure S10). In the embryonic work, a CBS dendrimer with 16 sulfonate moieties (G2-S16 or AB216) were rather active against several HIV strains. Furthermore, this dendrimer did not show a pro-inflammatory profile and did not cause vaginal irritation in female rabbits (Chonco et al., 2012; Rasines et al., 2012). As expected, this dendrimer was able to bind to both the gp120 protein from the virus envelope and the CD4 receptor in macrophages, showing higher affinity for gp120. An important step toward the application of this dendrimer as microbicide was the demonstration that G2-S16 kept the activity against HIV-1 in the presence of mock and semen (Ceña-Díez et al., 2016). Several preclinical studies were performed to confirm the potential of this technology. In particular, it is worth highlighting the study on humanized mice, which represented the first demonstration that transmission of HIV-1 can be efficiently blocked by vaginally applied G2-S16 in h-BLT mice (Sepúlveda-Crespo et al., 2015). The hydrophobic CBS framework seems very relevant in the activity of these anionic dendrimers, since polylysine dendrimers with the same type of groups lose their activity in the presence of semen. Studies carried out by Caminade et al. described the pivotal importance of dendritic framework in dendrimers activity (Caminade et al., 2015).

Syncytia are aggregates formed by fusions of uninuclear cells (e.g., muscle cells). However, they can be also formed by virus-induced membrane fusion, favoring the direct infection between neighboring cells (Leroy et al., 2020). Muñoz-Fernández et al. demonstrated that anionic dendrimers like G2-S16 reduced infectivity through syncytia due to its ability to disrupt gp120-CD4 preformed complexes (Guerrero-Beltrán et al., 2018). This dendrimer also kept the antiviral activity in the presence of spermicides as Platycodin D and did not modify the functionality of this contraceptive (Cena-Díez et al., 2019). On the other hand, the use of the labeled sulfonate dendrimer G2-S16-FITC (Figure S11; Gutiérrez-Ulloa et al., 2020) enabled the analysis of the internalization of this type of anionic dendrimer in macrophages and justify the inhibition of infection observed from infected macrophages to healthy lymphocytes. Thus, G2-S16 prevents the formation of HIV reservoirs (Relano-Rodríguez et al., 2021). The application of G2-S16-FITC to the epithelial vaginal tissue of BALB/c mice confirmed that this family of dendrimers crosses this barrier reaching the circulatory system. The study of organs and other biochemical data confirmed that this anionic dendrimer, alone or combined with antiretroviral drugs (tenofovir and emtricitabine), is a promising system to develop an effective microbicide against HIV-1 infection (Martin-Moreno et al., 2022; I. Rodríguez-Izquierdo, Sepúlveda-Crespo, et al., 2022).

In order to optimize the synthetic procedure or the antiviral activity of CBS dendrimers, small structural changes were performed. For example, dendrimers with sulfonate or carboxylate peripheral moieties and a polyphenoxo group at the core—unlike the traditional silicon atom—were designed. With this core, the flexibility of the dendrimer

increases and the number of functional groups is different (Sepúlveda-Crespo et al., 2018). It is worth highlighting that the combination of G2-P24 (Figure S10), with the polyphenoxo core, with an antiretroviral drug increased synergistically the antiviral efficacy and enhanced the anti-HIV-1 spectrum of the mixture with respect to a single-drug (D. Sepúlveda-Crespo et al., 2015). Amyloid fibrils of semen block the activity of drugs such as tenofovir or maraviroc, enhancing viral infection. However, when anionic dendrimers are combined with these drugs, they kept high protection against HIV-1 infection (García-Broncano et al., 2017).

Anionic CBS dendrons—with heterofunctional properties—have been also explored (Figures S12 and S13) (Moreno et al., 2017). Comparing the topology between sulfonate dendrimers and dendrons, the assays showed that all of them interact with gp120 and CD4 (Gutierrez-Ulloa et al., 2019). The main differences were related to the interaction site of CD4, where more flexible or smaller systems displayed better adaptation to this region. Regarding toxicity and activity, these parameters were more favorable for spherical G2-S16 dendrimer. Clearly, correlation between theoretical complex formation data and experimental antiviral data is not so immediate, since probably other interactions with surrounding biomolecules in physiological environment will affect biological behavior.

It is important to note that, on some occasions, small changes in dendrimer structure can lead to important changes in the biological behavior. The use of sulfonate-decorated dendrimers with a vicinal sulfur atom to the sulfonate moiety (G2-STE16, Figure S10) instead of a nitrogen atom (G2-S16) produced vaginal damage and irritation in BALB/c mice. Hence, this type of dendrimers would not be useful as vaginal microbicide (Ceña-Díez et al., 2017).

Anionic CBS dendrimers as G2-S16 (Figure S10) are also efficient agents to prevent hepatitis C virus infection (Sepulveda-Crespo et al., 2017), vaginal and human cytomegalovirus (Relano-Rodríez et al., 2021), and herpes virus (Figure 3). These viruses are related to HIV, finding important coinfections rate with HIV in several countries.

### 2.2.2 | Theranostic activity in inflammatory diseases

Anionic CBS dendrimers could be also promising drug carriers. A fluorescein-labeled carboxylate G4 dendrimer (Figure S14) was conjugated to infliximab, a broad-spectrum antibody used in rheumatology or inflammatory diseases

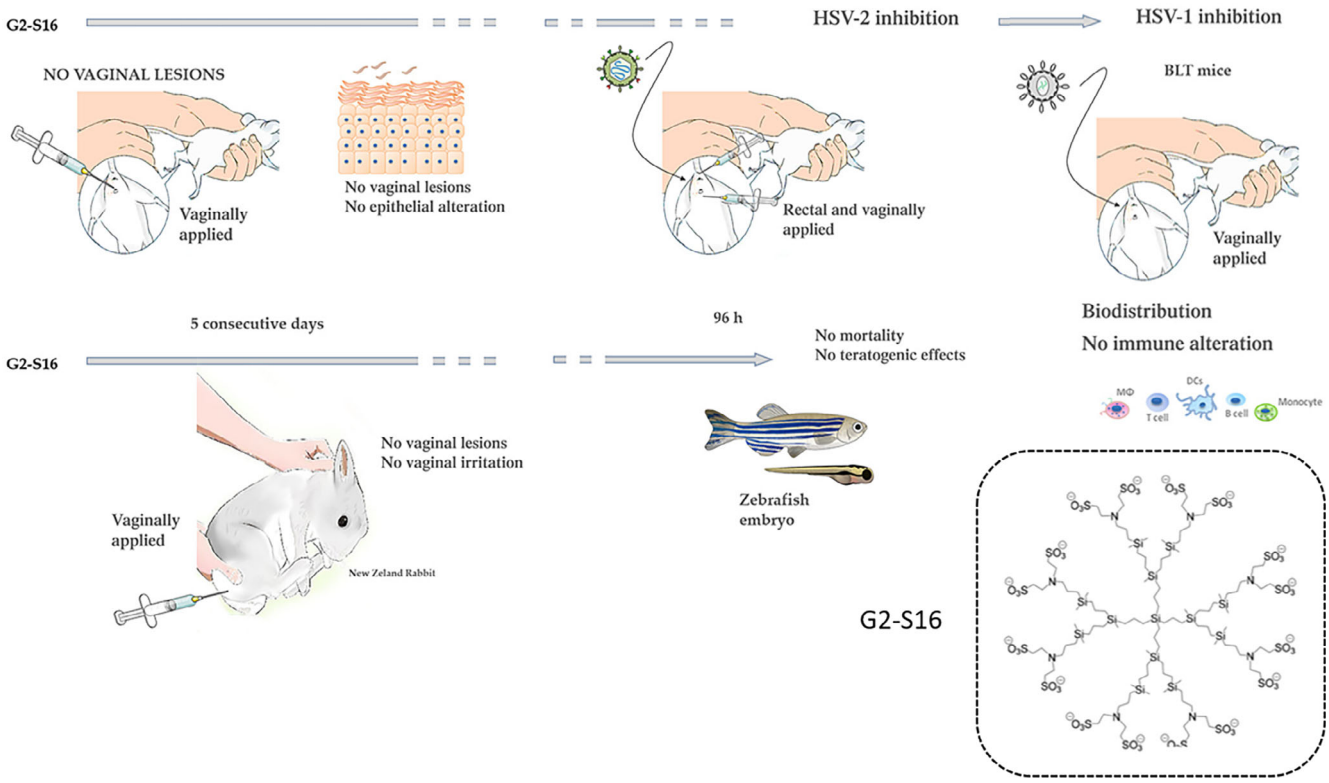


**FIGURE 3** Summary of main in vivo assays performed with polyanionic carbosilane dendrimer G2-S16 as vaginal microbicides against HSV. Reprinted with permission from Rodríguez-Izquierdo, Serramía, et al. (2022). Copyright© 2022, Wiley

(T. Rodríguez-Prieto, Hernández-Breijo, et al., 2020). This immunocomplex kept the activity of both the antibody and the fluorescent label and could be employed in combination therapy to further carry other inflammatory drugs.

## 2.3 | Carbosilane metallodendrimers

Metallodendrimers arise from the attachment of metal ions to dendritic scaffolds, frequently in a controlled manner. This strategy generates multivalent metallodrugs with improved activity, compared to their mononuclear counterparts (Sanz del Olmo, Carloni, et al., 2020). CBS dendrimers are versatile precursors of different metallodendrimers, mainly oriented toward the fields of catalysis or nanomedicine. Examples of their use in the field of cancer and infectious diseases are described in this section.

### 2.3.1 | Carbosilane metallodendrimers in cancer treatment

Cancer is a deadly disease, with 19.3 million new cases and 10.0 million deaths worldwide in 2020 (Ferlay et al., 2021). Breast, lung, and prostate cancer are the three most diagnosed cancers worldwide. The design of CBS metallodendrimers as antitumor agents has mainly focused on two relevant metal ions: ruthenium (II) and copper (II). Ru(II) is a highly versatile metal while Cu(II) is also biocompatible and cheap (Figure S15). CBS dendrimers bearing iminopyridine moieties on the periphery exhibited an outstanding versatility for the design of metallodrugs (Maroto-Diaz et al., 2019; Sanz del Olmo et al., 2019; Sanz del Olmo, Carloni, et al., 2020). Due to their structural perfection, it is easy to correlate the influence of parameters on the biological response. Indeed, the impact of parameters such as the dendrimer generation, the metal ion, and counter-ion, or the ligands in the aromatic ring is outstanding.

For example, Cu(II) metallodendrimers with chloride counterion exhibit a higher membrane stabilization than the nitrate analogs, which ultimately influences the metallodrug uptake and intracellular fate (Canonico et al., 2020). On the other hand, the presence of substituents on the iminopyridine ring produced an increased cytotoxicity in tumor cells, through two different routes depending on the substituent and the counterion employed (Carloni et al., 2021). First-generation dendrimer G1-$Cu(ONO_2)_2$ produced a significant tumor size reduction in vivo toward resistant prostate cancer, with no signs of toxicity during the experiment, confirming their promising potential as anticancer metallodrugs.

Regarding Ru(II) metallodendrimers, advanced studies have also been accomplished with iminopyridine-decorated systems. For example, in an advanced prostate cancer mice model, the administration of a first-generation Ru(II) dendrimer bearing *p*-cymene ligands inhibited tumor growth up to 36% using 5 mg/kg/3 days (Figure 4a; Maroto-Diaz et al., 2019). Changing the ligands to cyclopentadienyl and 1,3,5-triaza-7-phosphaadamantane (Cp/PTA), however, led to 45% tumor growth inhibition with a dosing 7.5 mg/kg/4–5 days (del Olmo, Bajo, et al., 2020). The authors demonstrated that such promising antitumor activity can be further improved through combination therapy with conventional antitumor drugs such as 5-flurouracyl, methotrexate, and doxorubicin, substantially decreasing the drug dose required (Michlewska et al., 2021). On the other hand, *N*-heterocyclic carbenes are also interesting ligands for the attachment of Ru(II) ions (Figure S16). The cytotoxic activity in a panel of tumor cell lines (PC3, HCC1806, HeLa, HepG2) revealed $IC_{50}$ values in the micromolar range but higher than cisplatin, with a relevant selectivity toward cancer cells for the second-generation metallodendrimer (Rodríguez-Prieto et al., 2021).

Besides the antitumor activity per se of the Ru(II) and Cu(II) metallodendrimers, they can be also employed as non-viral vectors of anticancer siRNA (Figures 4b and S15; Michlewska et al., 2018; Rodríguez-Prieto et al., 2021; Sanz del Olmo, Holota, et al., 2020). They protect siRNA against nuclease degradation and assist them in the internalization into cells. For example, breast cancer cells MCF-7 treated with a sub-toxic concentration of first-generation Cu(II) dendrimer G1-$[CuCl_2]_4$ exhibited viability of 95%, whereas its complexation with pro-apoptotic siRNA Mcl-1 reduced cell viability to 32% (Sanz del Olmo, Holota, et al., 2020). On the other hand, metallodendrimers G2-$[CuCl_2]_8$ and G2-$[Cu(ONO_2)_2]_8$, which generate around 60% cytotoxicity of MCF-7 cells, can reach 90% cell death when complexed with Mcl-1. Beyond the intrinsic anticancer activity of the metallodendrimers, it is their ability to carry and protect the siRNA that makes a difference: while the naked siRNA cannot enter MCF-7 cells, almost 50% cell uptake can be achieved with siRNA-metallodendrimer complexes.

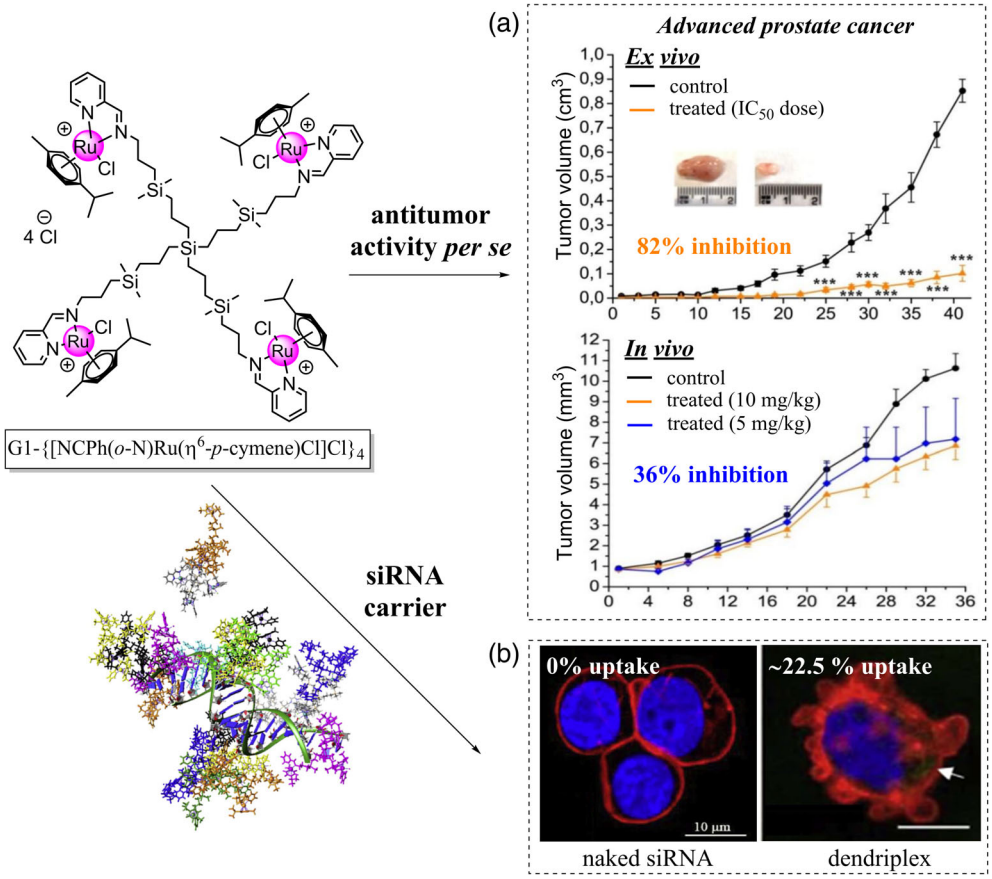


**FIGURE 4** Ru(II) CBS metallodendrimers are promising candidates against cancer, with antitumor activity per se and as siRNA carriers. For example, metallodendrimer G1-{[NCPh(*o*-N)Ru($\eta^6$-*p*-cymene)Cl]Cl}$_4$ produced up to 82% and 36% inhibition of tumor volume in ex vivo and in vivo experiments in mice with prostate cancer (a). The same dendrimer generated also 22.5% uptake of pro-apoptotic siRNA Mcl-1 into breast cancer cells and reduced their viability to 32% (b). Reprinted with permission from del Olmo, Carloni, et al. (2020), Copyright© 2020, Elsevier

Other examples of CBS metallodendrimers with potential anticancer activity include those decorated with boron clusters, in particular cobaltabisdicarbollides (Juárez-Pérez et al., 2009; Viñas et al., 2014), which may be employed as delivery agents for the Boron Neutron Capture Therapy (BNCT) of tumors.

### 2.3.2 | Carbosilane metallodendrimers as antimicrobial agents

As discussed above, dendrimers and dendritic materials are promising tools in the clinical management of infectious diseases caused by microbes such as viruses, bacteria, fungi, parasites, and amoebas (M. Ortega, Guzmán Merino, & Fraile-Martínez, 2020). They offer innovative tools for the prevention, treatment, and diagnosis of these diseases.

As described in Section 2.2, CBS dendrimers decorated with anionic moieties have been extensively evaluated as antiviral agents against HIV, as well as Hepatitis C virus and cytomegalovirus. The attachment of metal complexes in the dendritic structure can further enhance the antiviral activity by interfering in other steps of the viral cycle. For example, Cu(II) CBS metallodendrimers with pendant carboxylate and sulfonate groups exhibited preventive and therapeutic activity against HIV infection (Galán et al., 2012).

In the field of antibacterial agents, Cu(II) and Ru(II) iminopyridine-decorated dendrimers were tested against planktonic and biofilm-forming bacteria (Figure S15; Llamazares et al., 2019; Llamazares et al., 2021). These metallodendrimers are potential broad-spectrum antibiotics, probably due to the generation of Reactive Oxygen Species (ROS). In particular, first-generation dendrimer G1-Cu$(ONO_2)_2$ is a promising candidate, exhibiting MIC values of

4 mg/L toward *Staphylococcus. aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) in both planktonic and biofilm-forming bacteria.

The design of heterofunctional scaffolds with two types of antimicrobial moieties can further improve the antibacterial action. A CBS metallodendron bearing a ferrocene complex at the focal point and several ammonium groups in the periphery (Figure S17) exhibited one of the lowest MIC (2 mg/L for *E. coli* and *S. aureus*) of the whole metallodendrimer field (Lozano-Cruz et al., 2015). Silver (I) *N*-heterocyclic carbene complexes anchored to CBS dendrimers (Figure S18) or dendrons exert a significant antibacterial action against *E. coli* (MIC 2–8 mg/L), *S. aureus* (1–4 mg/L), and *Bacillus subtilis* (1–4 mg/L; Rodríguez-Prieto, Popp, et al., 2020), mainly due to membrane depolarization not observed with the dendritic or metal precursors alone. Cell membrane depolarization and pore formation studies showed that cationic imidazolium dendritic systems strongly depolarize the cell membrane producing its disruption, while silver (I) N-heterocyclic carbene complexes induced two biosensors of cell envelope modifying the lipid distribution and protein delocalization with subsequent internalization, which is not observed with the imidazolium dendritic system or with $AgNO_3$ alone.

## 2.4 | Sugar, peptide, or polyphenol-decorated dendritic systems

Despite most CBS systems tested for different biomedical applications are decorated with cationic or anionic groups, several examples have recently appeared which are functionalized with other moieties such as polysaccharides, peptides, or polyphenolic groups, among others.

### 2.4.1 | Carbosilane dendrimers decorated with polysaccharides

Carbohydrates play an important role in glycobiology, where they are involved in numerous physiological (growth, differentiation, recognition, and cell embryogenesis) as well as pathological processes (infectious, inflammatory, and tumor processes) (Kim et al., 2021). Again, in a study focused on how glucose-modified CBS dendrimers interact with biological membranes and serum proteins, the topology and dendritic generation play a key role (Wrobel et al., 2020). While the second-generation dendrimer (Figure S19) showed a higher level of interaction with human serum albumin (HSA) than with lipid membranes, the opposite was observed for the third-generation dendrimer. This indicated that the flexibility of the skeleton and the availability of its hydrophobic interior, as well as the formation of larger assemblies in buffer solution, are key factors for the interaction. In subsequent research, the same authors determined the cytotoxicity toward breast and ovarian cancer cell lines and noncancer BJ cell line (human fibroblast cell type) of several dendrimers bearing glucose, galactose, or oligo(ethyleneglycol)-modified galactose peripheral units and prepared glycodendrimer–doxorubicin complexes (Figure 5; Mullerova et al., 2022). The results obtained indicated that these

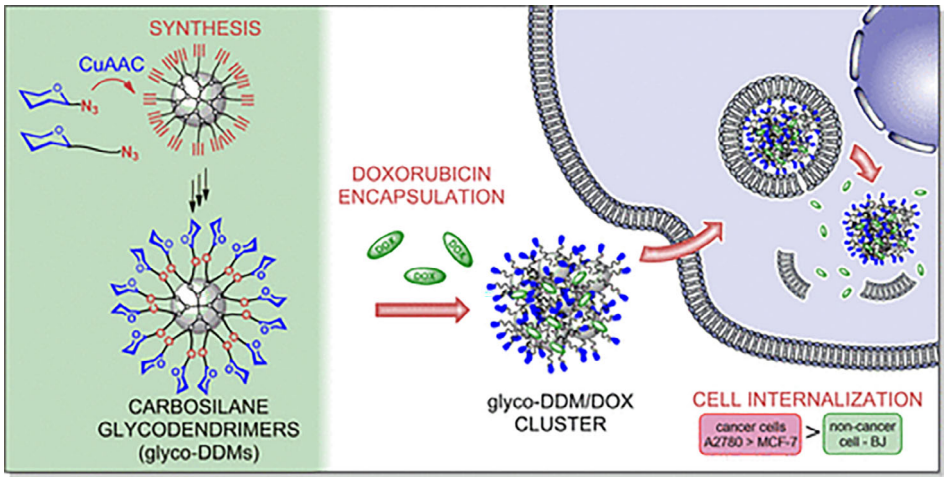


**FIGURE 5** Example of CBS glycodendrimer as drug carrier in antitumor therapy. Reprinted with permission from Mullerova et al. (2022). Copyright 2022, American Chemical Society

systems are suitable candidates for the encapsulation and subsequent release of doxorubicin, which is more efficiently released in acidic environments (tumor conditions) than under physiological conditions (pH 7.4).

### 2.4.2 | Carbosilane dendrimers as peptide carriers

The current spread of antibiotic resistance has encouraged the research on antibacterial peptides as alternatives for the treatment of infectious diseases. However, due to their unstable nature, controlled release systems are needed to ensure their therapeutic effect. These peptides can be linked to dendritic systems through covalent or electrostatic interactions. In this sense, nanoconjugates formed by covalently anchored antimicrobial peptides to the focal point of CBS dendrons with ammonium groups on the surface (Figure S20) (Fernandez et al., 2019) were studied against planktonic Gram-positive and Gram-negative bacteria. The results confirmed the cooperative effect between both antimicrobial fragments, exhibiting a more potent inhibitory and bactericidal activity while employing a smaller amount of dendron and peptide, compared to the individual treatment. The nanoconjugate efficiently permeabilized the bacterial membrane, causing significant morphological alterations and cellular integrity damages. The same authors also explored the antimicrobial capacity of the nanoconjugate dendron-cell-penetrating peptide, called gH625, in the prevention and eradication of *S. aureus* biofilms-related infections (Fernandez et al., 2021). Here again, the nanoconjugate activity was superior to the dendron alone, and the amount of dendron needed to inhibit or eradicate biofilm formation decreased. In addition, the combination of the nanoconjugate with levofloxacin further increased the ability to prevent the formation of biofilm. Peptide dendrimers can also be used in antiviral therapy. A dumbbell-type CBS dendrimer functionalized with hemagglutinin binding peptide exhibited particularly strong inhibitory activity against two human influenza viruses ($IC_{50} = 0.60$ μM for H1N1 and H3N2 strains; Hatano et al., 2014).

A cationic CBS dendrimer (Figure S21) combined with neuropeptides, vasoactive intestinal peptide (VIP), and growth hormone-releasing hormone (GHRH), produced dendriplexes with antitumor behavior in advanced prostate cancer cells PC3 (Sánchez-Milla et al., 2019). These systems showed an important change with respect to the behavior of the free peptides. They improved cell adhesion while avoiding cell migration. Also, the expression of vascular endothelial growth factor (VEGF) and cyclic adenosine monophosphate (cAMP) was reduced. This is important due to the protumoral activity of VIP and GHRH peptides, which increased expression of VEGF and cAMP. Finally, at the active nanosystem concentrations, they were not toxic against fibroblasts or against nontumor prostate cells (RPWE-1).

### 2.4.3 | Polyphenolic carbosilane dendrimers

Recently, there is a growing interest in the development of new materials with antioxidant properties considering that oxidative stress is closely related to the progress of numerous pathophysiological diseases where the levels of free radicals and other ROS play an essential role (Khalil et al., 2019). Dendritic systems can be decorated with multiple antioxidant moieties such as polyphenols and then be used, alone or in combination therapy, to inhibit the ROS generated by oxidative stress in the body responsible of damaging cells, proteins, and DNA. The transport of polyphenolic systems through dendritic structures can be achieved by encapsulation, through noncovalent interactions, or covalent anchoring. Up to now, only homofunctional spherical systems with ferulic, caffeic, and gallic acid and cationic dendrons with vanillin, protocatechuic aldehyde, or caffeic acid at the focal point have been described in the literature (Sanz del Olmo et al., 2022; Sanz del Olmo, Pena Gonzalez, et al., 2020). In these dendrimers (Figure S22), the presence of four polyphenolic units on the surface of the first-generation system seems to be enough to achieve efficient antioxidant activity, maintaining similar activity values with the second-generation derivative. In addition, these dendrimers were water-soluble and, at 16 mg/L, showed a bacteriostatic effect against Gram-positive and Gram-negative bacteria. Among the different dendrimers, gallic acid derivatives showed the most promising antioxidant activity in spherical systems, meanwhile, in the case of dendrons, the compound functionalized with caffeic acid units was the most efficient.

## 2.5 | Supramolecular dendritic assemblies

Micelles are monolayers of amphiphilic molecules with a nonpolar tail and a polar head, leading to a spherical system formed spontaneously by self-assembly. By introducing two nonpolar tails in the amphiphilic system, liposomes can be

formed, which are also spherical structures but formed by a bilayer, whose structure is very similar to biological membranes. A great advantage of such self-assembled structures is their ability to encapsulate both hydrophilic and lipophilic substances, acting as promising drug or gene carriers. These carriers enable insoluble cargo circulates through the bloodstream until they reach the therapeutic target and, additionally, they protect sensitive cargo from degradation through a physiological change or by the attack of another biomolecule.

The versatile and precise synthesis of dendritic systems enable their use as amphiphilic molecules to form dendritic micelles or liposome-like structures, also called dendrimersomes (Apartsin & Caminade, 2021). The lipophilic nature of the CBS skeleton together with a proper functionalization enabled to fine-tune the balance between hydrophilic/lipophilic domains necessary to afford supramolecular structures.

CBS dendritic micelles based on dendrons containing palmitic or hexanoic acid at the focal point and sulfonate and ammonium groups in the periphery were described (Figure S23; Gutierrez-Ulloa et al., 2017), Figure 6. The self-assembly process was affected by the length of the aliphatic chain as well as by the size of the CBS scaffold (generation of dendron). The cationic micelles efficiently bounded nucleic acids, while the anionic derivatives showed a high loading capacity for cationic drugs (e.g., procaine), suggesting their potential as nanocarriers.

pH-dependent micelles were designed by attaching carboxylate (propionate or succinate, Figure S24) groups to the periphery of amphiphilic CBS dendrons (Mencía, Lozano-Cruz, Valiente, Jiménez, et al., 2020). These aggregates acted as nanocarriers of hydrophilic (ibuprofen sodium salt and procaine hydrochloride) and hydrophobic (diclofenac and celecoxib) molecules. The micelles were stable at neutral and basic pH, but in acidic conditions, due to the protonation of the carboxylate groups, the supramolecular system degraded. Moreover, the negatively charged amphiphilic CBS dendrons were tested as anti-HIV agents due to their negative charge. For these systems, the best activity was achieved with the G3 dendrons at concentrations below micelle formation.

Fluorine-containing amphiphilic CBS dendrons were synthetized with perfluorinated alkyl chains as the hydrophobic part and ammonium groups in the hydrophilic side (Mencía, Lozano-Cruz, Valiente, de la Mata, et al., 2020). Fluorine atoms increase hydrophobicity in the molecules favoring the interaction with biological membranes and increasing biocompatibility. Moreover, due to its low abundance in biological systems and its high sensibility in magnetic resonance is a great candidate as an imaging agent for $^{19}F$ magnetic resonance imaging. Preliminary supramolecular studies by surface tension measurements were carried out, but CMC values observed were above 1 mM.

Vesicle-like supramolecular assemblies (dendrimersomes, Figure S25) are constituted by dendrons with two fatty acids and ammonium groups on both sides, respectively, of the amphiphilic dendron. A pH-sensitive linker constituted by a piperazine-triazine unit was used, prompting a reorganization and disruption of the dendrimersomes at pH lower than 6.5 (Apartsin et al., 2020). The supramolecular systems encapsulated anticancer drugs such as doxorubicin, methotrexate, and 5-fluorouracil and were efficiently released in two different leukemia cell lines generating apoptosis. This type of dendrimersome enhances cellular uptake. Thus, encapsulation of Bengal Rose increased intracellular ROS production and therefore its phototoxicity in murine basal cell carcinoma lines (AsZ, BsZ, and CsZ; Sztandera et al., 2022).

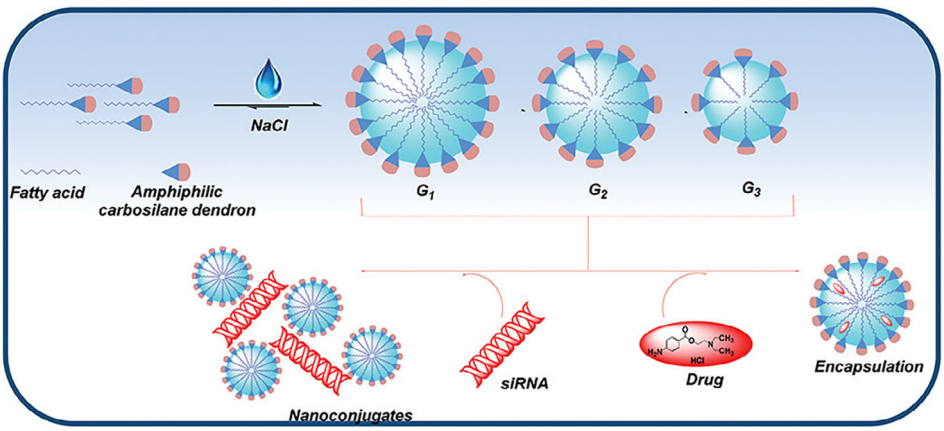


**FIGURE 6** Self-assembly of CBS dendrons into micelles and potential uses as gene and drug carriers. Reprinted with permission from Gutierrez-Ulloa et al. (2017)

## 2.6 | Carbosilane dendritic materials

Dendrimers and dendrons can further be employed to modify the surface properties of existing materials, or even generate new ones. Surface dendronization affords materials able to carry out specific functions that cannot be fulfilled by the original material. The appropriate functionalization of the material provides properties from the dendrimers, or the dendritic moiety can be used as a linker between other compounds and the surface to be functionalized. In this way, different nanoparticles such as metallic nanoparticles, silica, and carbon nanotubes have been functionalized with CBS dendritic systems. On the other hand, the multivalent and monodisperse properties of CBS dendrimers are attractive properties to generate 3D networks for different applications, as herein described.

### 2.6.1 | Dendronized nanoparticles

*Treatment and diagnosis of viral infections*

Gold nanoparticles (AuNP) were decorated with sulfonate dendrons containing a thiol moiety at the focal point (Figure S26; Peña-González et al., 2016). The presence of the anionic groups led to attractive anti-HIV properties, achieving a higher inhibition of HIV-1 infection with dendronized AuNP than with precursor dendrons. This effect was clearly more relevant for the first-generation dendron, which showed rather low activity by itself. Electron-Paramagnetic Resonance (EPR) analysis revealed that the availability of sulfonate functions to interact with the environment was generation-dependent, being particularly unfavorable for the second-generation dendron and the corresponding AuNP.

In the field of diagnosis, magnetic nanoparticles (MNP) functionalized with anionic CBS dendrons were used to separate HIV from infected samples to improve detection. The higher accessibility and positive density of gp120 in X4 than in R5 virus particles led to increase capture of X4 virions. However, in the presence of semen, virus capture was importantly reduced, probably due to interactions with cationic charges of the amyloids fibrils (Barrios-Gumiel, Sánchez-Nieves, et al., 2019).

*Gene carriers*

AuNP decorated with cationic CBS dendrons (Figure S27) showed better toxicity profiles for smaller dendrons (Peña-González, Pedziwiatr-Werbicka, Shcharbin, et al., 2017). Furthermore, dendronization of AuNP reduced interaction with serum proteins, as alpha-1-microglobulin, with respect to dendrons. Hence, the modified AuNP are better candidates for drug delivery than dendrons (Shcharbin et al., 2018). In this way, studies of interaction of these AuNP with anticancer siRNAs (anti-Bcl-xl siRNAs, siBcl-xl) showed that these AuNP stabilized the nanoplexes (Abashkin et al., 2021). In particular, the AuNP decorated with third-generation dendrons formed dendriplexes even in the presence of heparin. Experiments carried out using labeled siRNA confirmed that these complexes were transported inside cancer cells (Pedziwiatr-Werbicka, Gorzkiewicz, Michlewska, et al., 2021).

Aiming to reduce the toxicity of AuNP with bigger dendrons, AuNP decorated with both dendrons and PEG ligands were prepared in a one-step synthesis (Barrios-Gumiel et al., 2020). As expected, the biocompatibility was enhanced after PEGylation of the AuNP, being the effect dependent on dendron/PEG ratio and dendron generation. The dendron size affected the exposure of PEG and the interaction of this ligand with AuNP environment. Regarding dendron/PEG ratio, a higher PEG concentration diminished toxicity, but can also increase immunogenic response. Further analysis of these AuNP related with interaction with proteins and dendriplex formation with siBcl-xl concluded that AuNP with second-generation dendron and dendron:PEG ratios 3:1 or 1:1 were the most promising for siRNA delivery (Pedziwiatr-Werbicka, Gorzkiewicz, Horodecka, et al., 2021).

Dendronized silver nanoparticles (AgNP) were also explored as siRNA carriers (anticancer siBcl-xl) (Pedziwiatr-Werbicka et al., 2020). First, toxicity assays showed that AgNP with bigger dendrons were more toxic, although this phenomenon was minimized after complexation with siRNA. Confocal microscopy proved the uptake in HeLa cells of these dendronized AgNP/siRNA complexes. However, the cell uptake was low and further studies are required to validate them as efficient carriers.

Carbon nanotubes (multi-wall MWCNT and single-wall SWCNT) decorated with cationic CBS dendrons were also explored as nanocarriers. Dendronized MWCNT required higher charge ratios to bind siRNA than dendronized SWCNT, probably by worse dispersion of the MWCNT. Regarding the influence of dendron generation, CNT decorated with smaller dendrons were clearly less efficient than CNT with dendrons of higher generations (second and third; Gutierrez-Ulloa et al., 2018).

*Treatment and diagnosis of bacterial infections*

Silver compounds and nanoparticles (AgNP) have been used as antibacterial agents for centuries before any knowledge about their nature was obtained. In the last decades, combination of AgNP with other antibacterial systems seems to be a powerful strategy looking for new microbicides. For this goal, AgNP covered with cationic CBS dendrons (Figure S27; Peña-González, Pedziwiatr-Werbicka, Martín-Pérez, et al., 2017) or dendrons and PEG were prepared (A. Barrios-Gumiel, Sepúlveda-Crespo, et al., 2019). These AgNP showed relevant antibacterial and antifungal properties, highlighting the results for AgNP with first-generation dendrons, which were barely active by themselves. Furthermore, both types of AgNP did not generate resistance in planktonic cells. The presence of PEG ligands had important effects on the behavior of dendronized AgNP with respect to AgNP modified only with CBS dendrons. First, although activity was slightly lower for PEGylated systems, their biocompatibility was clearly enhanced with PEG ligands. Second, regarding biofilm growth, only AgNP with PEG and CBS dendrons reduced its formation at concentrations below MIC (A. Barrios-Gumiel, Sepúlveda-Crespo, et al., 2019).

Combination of AgNP modified with the CBS dendrons and PEG favored the action of lysozyme, which is a peptidoglycan-degrading enzyme. The complex formed between these systems was hidden better from serum proteins, becoming more active against *E. coli* than the complex formed between AgNP covered only with CBS dendrons and lysozyme (Ciepluch et al., 2020). That is, the presence of PEG in these AgNP reduces the formation of protein corona (Terehova et al., 2021).

With the idea to use MNP to separate microorganisms, MNP functionalized with cationic CBS dendritic systems were prepared, due to the ability of these moieties to interact with bacteria membrane (Heredero-Bermejo et al., 2018). These cationic MNP were tested for bacteria capture and the activity was dependent on the type of dendritic system (size, topology) and of the bacteria (Gram-negative *E. coli* or Gram-positive *S. aureus*), Figure 7 (Quintana-Sánchez et al., 2022). For *E. coli*, the best result was performed with MNP covered with higher density of cationic groups, that is covered with dendrons, as a consequence of the lesser cationic charge of Gram-negative bacteria membrane. For *S. aureus*, the most efficient systems were MNP grafted with the biggest groups, third-generation dendron (with eight cationic groups), or first-generation dendrimer (with seven cationic groups), which were able to capture bacteria at lower concentrations.

*Other applications*

The ability of CBS dendritic systems to interact with proteins enabled the design of a library of modified materials looking for a greener approach to extract proteins from waste products of food industry. SWCNT (González-García et al., 2017), AuNP (Vasquez-Villanueva et al., 2019), and MNP (Prados et al., 2022) covered with anionic CBS systems (carboxylate and sulfonate, Figure S27) were explored and successfully recovered different proteins using water as solvent, even from complex mixtures coming from plum and olive seeds and cheese whey.

### 2.6.2 | Dendronized surfaces

In order to provide antibacterial properties to certain surfaces, cationic CBS dendritic systems were grafted to silica. As expected, the best systems were those with higher density charge (ammonium better than amine groups)

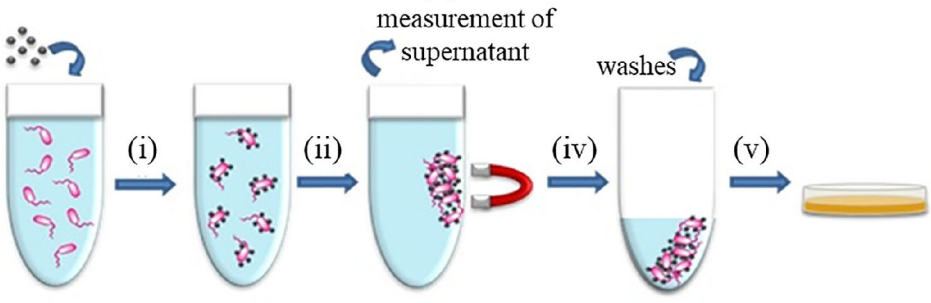


**FIGURE 7** Approach to capture different bacteria with cationic dendronized MNP. Reprinted with permission from Quintana-Sánchez et al. (2022)

**BOX 1 Main pharmaceutical applications of carbosilane dendritic systems**

**ANTIVIRAL (HIV, HERPES VIRUS, HEPATITIES VIRUS, CYTOMEGALOVIRUS, AND INFLUENZA)**

- *Dendrimers*: homofunctional systems decorated with —$COO^-$ or —$SO_3^-$ with intrinsic antiviral activity or in combination with conventional drugs.
- *Dendrons*: heterofunctional systems decorated with —$COO^-$ or —$SO_3^-$ with intrinsic antiviral activity.
- *Metallodendrimers*: Cu(II)-bound dendrimers with —$COO^-$ or —$SO_3^-$ terminal groups.
- *Dendronized nanoparticles*: AuNPs decorated with —$COO^-$ or —$SO_3^-$ and PEG with intrinsic antiviral activity.
- *Micelles*: propionate or succinate-decorated assemblies.

**ANIBACTERIAL AND ANTIPARASTITIC**

- *Dendrimers*: homofunctional systems decorated with —$NMe_3^+$, —$PMe_3^+$, and so forth.
- *Dendrons*: heterofunctional systems decorated with —$NMe_3^+$ and isobutyric acid.
- *Dendronized nanoparticles*: AgNPs decorated with —$NMe_3^+$ and PEG.
- *Dendritic networks*: hydrogels with cationic charges capable of encapsulating antibiotics.

**GENE OR DRUG CARRIERS**

- *Dendrimers*: homofunctional systems decorated with —$NMe_3^+$, —$PMe_3^+$, and so forth for gene delivery.
- *Dendrimers*: homofunctional systems decorated anionic groups (e.g., —$COO^-$ or —$SO_3^-$) for cationic drug delivery.
- *Micelles*: cationic or anionic dendritic micelles.
- *Dendrimersomes*: Ammonium-decorated vesicles.

**ANTITUMOR**

- *Metallodendrimers*: Iminopyridine-decorated dendrimers with Ru(II) or Cu(II); N-heterocyclic carbene-decorated dendrimers with Ru(II). Antitumor activity per se or as siRNA carriers.
- *Glycodendrimers*: sugar-decorated dendrimers with antitumor activity per se.
- *Dendrimers*: cationic dendrimers as antitumor peptide carriers.

**NEURODEGENEERATIVE DISEASES**

- *Dendrimers*: homofunctional systems decorated with —$NMe_3^+$, —$PMe_3^+$, and so forth.
- *Dendrons*: heterofunctional systems decorated with —$NMe_3^+$ and isobutyric acid.

**DIAGNOSTICS AND THERANOSTICS**

- *Micelles*: Ammonium-decorated micelles with perfluorinated alkyl chains ($^{19}F$ MRI).

**ANTIOXIDANT**

- *Dendrimers*: homofunctional systems decorated with ferulic, caffeic, and gallic acid.
- *Dendrons*: heterofunctional systems with cationic groups and vanillin, protocatechuic aldehyde, or caffeic acid.

**PPOTEIN SEPARATION**

- *Dendrimers*: homofunctional systems decorated with —$NMe_3^+$ or —$NMe_2$.

and better exposure of the active groups. For these reasons, silicas with high-generation cationic dendrons (Figure S23) were the most active materials as bacteria growth inhibition surfaces (Sánchez-Milla et al., 2020).

The multifunctionality of dendrimers can be very useful to control the immobilization of enzymes to surfaces and drive away enzyme from material support to avoid undesired interactions (Sheldon & Pelt, 2013). Silica modified with amine-functional CBS dendrimers were used for grafting thermolysin and the hydrolysis ability of the new system was explored (Hernandez-Corroto et al., 2020). Although thermolysin hydrolyzed BSA, due to the hydrophobic character of CBS framework, peptides released in this process were retained by the modified material making difficult the applicability of this immobilized enzyme.

### 2.6.3 | Dendritic networks and hydrogels

Hydrogels are polymeric networks with high biocompatibility, porosity, and water-content. Most hydrogels are hydrophilic with poor ability to load hydrophobic drugs. However, the use of CBS dendrimers as crosslinking points in the preparation of hydrogels can improve the compatibility with hydrophobic cargo, as well as the control of the structure-to-activity of the network (García-Gallego et al., 2021; Recio-Ruiz et al., 2022). The use of highly efficient tools for the crosslinking, such as the click thiol-ene reaction, further improves the control of the network properties. The CBS dendritic precursor, bearing alkene groups on the periphery (Figure S28), reacts with a dithiol polymer [such as poly(ethyleneglycol) or Pluronic] in the presence of a photoinitiator and UV light irradiation. The wise selection of the number of alkene groups used for crosslinking and those left unreacted for subsequent functionalization generates a broad library of dendritic hydrogels as multipurpose materials.

These dendritic hydrogels are versatile materials for the loading and delivery of bioactive molecules, being particularly attractive toward low polarity compounds such as ibuprofen or caffeic acid. Furthermore, the bioactive molecules can be also covalently attached to the network for higher loading and control on the release, using the available functional groups of the dendritic molecules. Degradable (e.g., ester bonds) and nondegradable (e.g., triazol bonds) can be easily generated in the network. Furthermore, these hydrogels can exhibit thermo-responsive behavior, which can modulate the swelling and the drug delivery.

The precise control of the crosslinking/functionalization of CBS dendritic hydrogels can also deliver functional networks with antibacterial properties. Cationic moieties, with inherent antimicrobial activity, can be easily attached through covalent bonds and generate active hydrogels, which can further encapsulate traditional antibiotics for enhanced activity (Box 1).

## 3 | CONCLUSION

Nanotechnology has emerged as a strategy with enormous potential in the development of systems that allow the implementation of new formulas for seeking solutions to current health problems. The generation of nanoscopic-sized structures that act in biomedical processes is based on the multivalent nature of these presentations. In this context, dendrimers have been used as novel synthetic platforms where this multivalent effect has been highly developed, given the versatility of the existing typologies and topologies and their ideally monodisperse character, contrary to what is evidenced in conventional polydisperse polymers. Thus, dendrimers have been used in different biomedical applications, such as transport of biomolecules and drugs, diagnosis, sensors or as therapeutic agents per se (antiviral, antibacterial, anti-neurodegenerative, or anticancer, among others).

Within the different types of dendrimers, dendrimers with a CBS structure are characterized by having a skeleton with great chemical stability, flexibility, and hydrophobicity. These properties endow these systems with biomedical behaviors that are sometimes different from the rest of the typologies. In this sense, CBS dendrimers with cationic groups on the surface have behaved as excellent nucleic acid carriers, where the processes of transfection and release of the material are subject to subtle changes in the peripheral ammonium groups, in the core and branches or in the used generation. Also, they have been used as broad-spectrum antibacterial agents, with no resistance observed as consequence of their nonspecific mechanism of action. Another important application of these systems has been their use as anti-amyloid agents where the topology has proven to be an important factor to consider. Regarding anionic systems, these have been shown to act as important antiviral systems against viruses such as HIV, HSV, or influenza with an eye on the search for microbicides in the prevention of viral infections. Finally, the inclusion of metals on the surface has opened up a field of research focused on the multivalent action of metal fragments as new metallodrugs, mainly in cancer. Other types of applications such as the use of dendritic micelles or vesicles as carrier of drugs and

biomolecules, in protein separation, as antioxidants through polyphenols groups, or the generation of dendritic networks and hydrogels, should be developed in the near future, diversifying both the synthetic tools and biomedical applications.

A very powerful synthetic weapon that is beginning to be developed is dendronization, where the information acquired in dendritic systems of different topologies is transferred to new nanostructured platforms (nanoparticles, polymers, and carbon nanotubes) or even surfaces, toward the search for new or different presentations and/or interactions with biomolecules, viruses, or bacteria. Undoubtedly, these dendronization processes should be developed in order to provide cooperation between the function provided by the dendritic system and that of the material to be dendronized.

Future research should focus on finding higher levels of control of the dendritic structure, as well as on the development of biodegradable materials, thus attempting to reduce their toxicity. With these premises, the chemistry of dendrimers in general and that of CBS dendrimers, in particular, must present a bright future in the short term for the different biomedical applications here discussed, and summarized in two main axes, (i) greater efficacy in the administration of drugs and (ii) the search for nanomedicines.

## AUTHOR CONTRIBUTIONS

**Francisco Javier de la Mata:** Conceptualization (lead); funding acquisition (equal); resources (equal); supervision (lead). **Rafael Gómez:** Conceptualization (supporting); funding acquisition (equal); supervision (equal); writing – review and editing (supporting). **Jesús Cano:** Formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Javier Sánchez-Nieves:** Formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Paula Ortega:** Formal analysis (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Sandra García-Gallego:** Conceptualization (equal); resources (lead); supervision (lead); writing – original draft (equal); writing – review and editing (lead).

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## CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## SUPPORTING INFORMATION

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