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Dendrimer Space Exploration: An Assessment of Dendrimers/Dendritic Scaffolding as Inhibitors of Protein−Protein Interactions, a Potential New Area of Pharmaceutical Development

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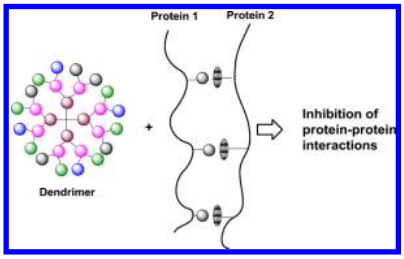

CONTENTS

1. INTRODUCTION

Nanotechnology represents a huge multidisciplinary field encompassing chemistry, biology, physics, engineering, etc., and has significantly changed the scientific research landscape. Two main approaches have been developed: miniaturization and the formation of nanostructures.[1−3] To date, the main therapeutic application of nanotechnology is in the development of new nanomaterials and nanodevices as "global killers'" in the fields of cancer, cardiovascular disease, and central nervous system disorders.[4−7] Within this new domain of medicine, different nanomaterial systems have been developed as innovative powerful strategies to deliver various therapeutic agents such as drugs, vaccines, recombinant proteins, siRNAs, nucleotides, genes, and aptamers.[8,9]

The main applications in nanomedicine are the following: (a) delivery of drugs, heat, and light to specific targets such as cancer cells; (b) therapeutic techniques, such as radiation therapy to treat cancerous tumors by use of carbon nanotubes or gold nanoparticles and absorption of harmful free radicals released after brain injury;[10] (c) diagnostic techniques/biomedical sensors, for example, (i) early detection of cancerous tumors by the release of biomarkers once the nanoparticle is attached to the tumor, (ii) use of gold nanorods to detect biomarkers in urine (for instance, in acute kidney injury), or (iii) use of silver nanorods to separate viruses, bacteria, and various other microscopic components from blood samples; and (d) imaging agents.[11]

Interestingly, the theranostic approach has been recently set up by linking therapeutic and diagnostic approaches. This personalized approach to therapy enables the right therapy for the right patient given at the right time. Most progress in the theranostic field has been made in oncology, reflecting the disease complexity and variability among individuals. In many cases, the target therapy works only if the right population segment is identified for the intended drug.[3,12] Altogether, these examples demonstrate the considerable impact that nanoparticles have had on therapeutics, and various nanoscaled systems have already been approved by the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency).[13]

Alongside magnetic, metal, and polymeric-based nanoparticles, polymeric micelles, and linear polymers, dendritic nanostructures represent useful nanocarriers for drug delivery.[14,15] Dendrimers (from the Greek words "dendri" and "meros") are a family of nanosized globular macromolecules characterized by a homostructural, highly branched 3D architecture and compact spherical geometry in solution. They display an exponential number of dendritic branches (hydrophobic and hydrophilic moieties) radiating from a central core, and their shape and size can be precisely controlled and manufactured. As shown in Figure 1, dendritic macromolecule structures can be divided into four main

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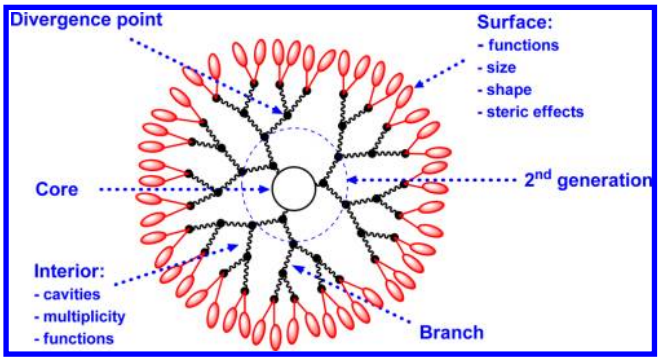

Figure 1. Schematic representation of a dendrimer.

components: (a) central core moiety, (b) interior layers (generations G*n*, where *n* is 0, 0.5, 1, 1.5, ...) made of regularly repeating branching units attached to the core, (c) terminal functionalities distributed in three-dimensional space, and (d) empty spaces to be filled by molecular cargo. Several representative examples of dendrimers useful in biology are shown in Figure 2. Importantly, multiple fine-tuning architectural variations (core, branches, and peripheral groups) by introduction of different chemical moieties (basic, acidic, hydrophobic, hydrogen-bonding capability, charges, etc.) allow their optimization for specific biomedical applications, either per se or as nanocarriers. Both drug-encapsulating dendrimers (drugs encapsulated within the empty spaces of the dendrimers) and drug-conjugating dendrimers [drug covalently linked to the surface of the dendrimer via covalent attachments subject to stimuli-responsive cleavage by pH, light, glutathione, reactive oxygen species (ROS), etc.] have been intensively developed.[16]

Various optimization achievements have been made, including solubility and bioavailability enhancements, pharmacokinetic (PK) and pharmacodynamic (PD) behavior improvements, controlled and sustained release achievements, and enzymatic degradation and stabilities of therapeutic agents carried by various dendrimers.[15,17]

Importantly, the introduction of PEGylated chains [where PEG = poly(ethylene glycol)] on the surface of dendrimers modified not only the size of the nanoparticle (typically less than 200 nm in the nanomedicine domain) but also improved the PK/PD behaviors of both dendrimers and drug cargo.[18] Dendrimers have been studied for the delivery of both nontargeted and targeted drugs. In the targeted approach, the attachment of specific groups on the surface of the dendrimers

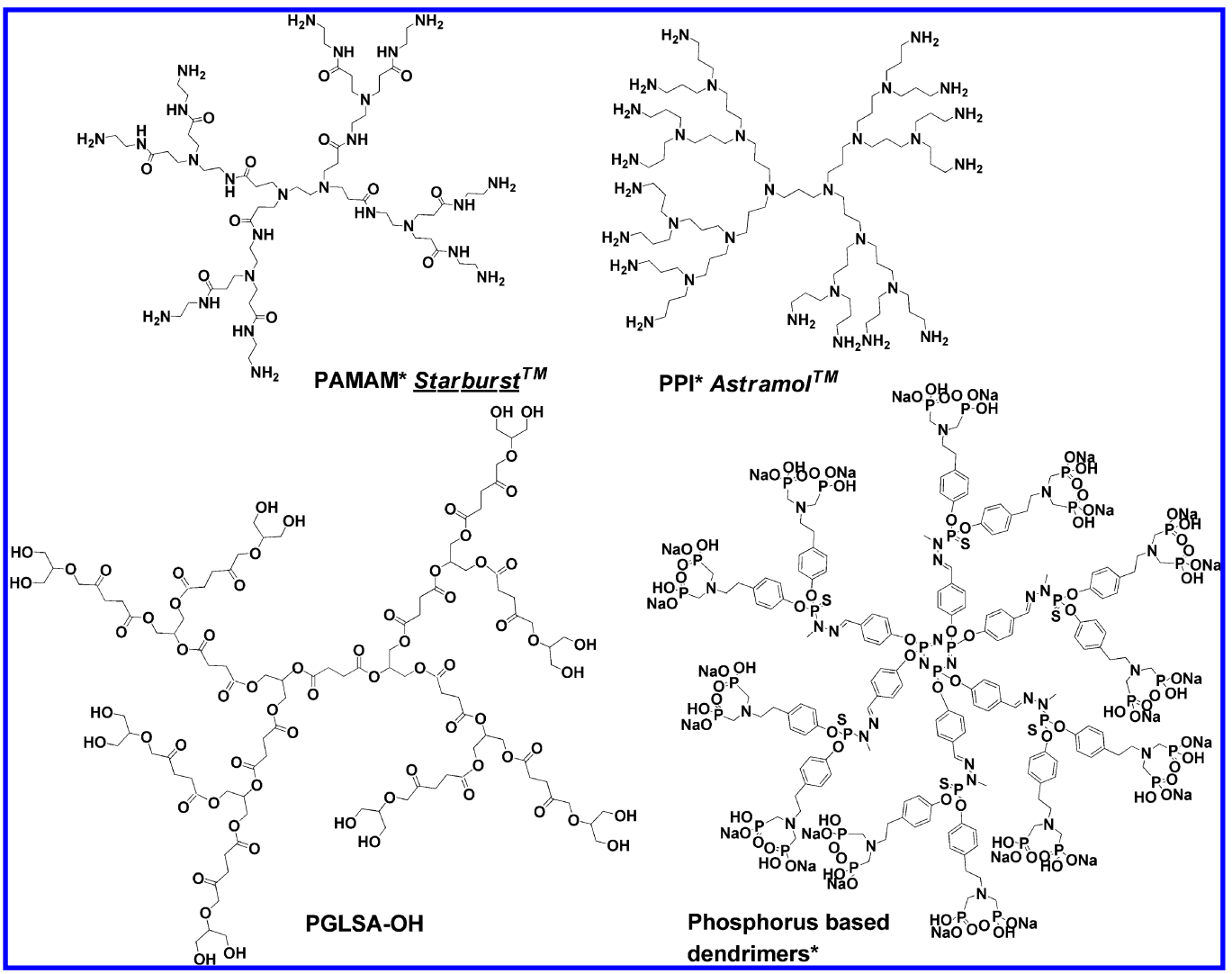

Figure 2. Chemical structures of several common dendrimers for biomedical applications (asterisk indicates commercially available).

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allows preferential targeting to, for example, cancer cell lines versus normal cell lines. The small size of the dendrimers enables their crossing through the gastrointestinal epithelium, tumor vasculature, and endothelium of cancer and inflammatory sites. Notably, while they are able to access the spleen and liver via fenestration, nanoparticles 50−100 nm in size are far too large to cross the endothelial barrier in all other healthy tissue but can reach some cancer cells or inflamed tissues.[19] Finally, nanoparticles have been shown to accumulate preferentially at tumor and inflammatory sites, notably because of the enhanced permeability and retention (EPR) effect of the vasculature.[20]

Recently, for the first time, we introduced the concept of "dendrimer space" to provide medicinal chemists with a new visual approach of identifying original dendrimer-based drug delivery systems. This dendrimer space shapes the boundaries of a new druggable cluster that is included within the huge volume of chemical space.[21] Dendrimer space is interpreted as a druggable cluster based on the large number of biological applications of dendrimers. This concept is founded on druglikeness and druggability, both established concepts that remain fully and practically integrated into the drug discovery process.[22a] A druggable cluster is defined as a chemical area that contains specific biologically active derivatives with adequate physicochemical or topological properties, whereas druggability is determined as the capability of a protein to bind druglike compounds with high affinity. Druglikeness is defined as a balance of various molecular properties and structure features that determine whether a particular molecule is similar to known drugs.[22b−d]

Alongside standard drug targets such as enzymes, nuclear ion channels, and G-protein-coupled receptors, for which most of the marketed drugs are dedicated, the inhibition and stabilization of PPIs have emerged from both academic and pharmaceutical research as promising candidate targets to develop new therapeutic agents to satisfy otherwise unmet clinical needs.[23] The purpose of this review is to summarize the progress made in the inhibition of protein−protein interactions (PPIs) by use of dendrimers as drugs. We will present at first the various approaches used so far to tackle PPIs. Then the use of dendrimers as PPIs inhibitors will be positioned in this general context.

2. INHIBITION OF PROTEIN−PROTEIN INTERACTIONS: A CONCISE OVERVIEW

In a cell, the vast majority of proteins interact with others, inducing specific biological processes such as gene expression, nutrient uptake, morphological change, mobility, intercellular communication, etc. Specific protein−protein molecular recognition is critical for cellular function (e.g., cell proliferation, cell growth, and cell differentiation), programmed cell death, signal transduction, and viral self-assembly.[24] Protein−protein interactions are highly attractive, well-validated targets in terms of biological function and are involved in a large number of disease pathways.[25] Consequently, considerable efforts have been centered on determining the main principles governing PPIs, such as interface residue contacts, morphology, hydrophobic patches, conservation, residue propensities, and secondary structure.[26] It has now become clear that only a small subset of all interface residues (interacting "hot spots" with high-affinity binding) is essential for recognition.[27]

Noncontiguous hot-spot interaction analysis of targets has provided a unique strategy for identification of small-molecule inhibitors (binding epitopes) able to impede protein−protein interactions.[28] Protein surfaces are challenging targets in drug design approaches due to their relatively large interfacial solvated surfaces (approximately 750−1500 Å^2) and quite flat contact surfaces with a featureless topology comprising few and practically indistinguishable grooves and pockets.[29] Protein−protein interactions are often noncontiguous, meaning that simple mimicry of interfacial areas is difficult by simple synthetic peptides or peptidomimetics.[30] In addition, no endogenous small-molecule partners are involved in PPIs. For many PPIs, the apparent complementarity between the two surfaces involves a significant degree of protein flexibility and adaptivity.[31]

Weak transient interactions between proteins that expose their interfaces to a small molecular ligand are characterized by a dissociation constant (K_d) in the micromolar range (lifetime of seconds), and strong transient interactions are characterized by a lower K_d in the nanomolar range, whereas permanent interactions show strong binding energy yielding rare interfacial area expositions.[32,33]

These PPI signatures suggest that large ligands may be required to compete effectively with one of the two interfacial areas and suggest the inappropriateness of the druglike small-molecule approach (see below). In addition, the absence of well-defined binding pockets renders difficult the design of selective inhibitors. Nevertheless, despite these challenges, given the major importance of regulating certain biological processes, there remains tremendous interest in designing small-molecule inhibitors to disrupt the specific PPIs involved.

Orthosteric and allosteric inhibition strategies have been developed to tackle PPIs. For example, and very interestingly, Morelli and co-workers[34] designed a tool to calculate a series of biophysical and geometrical parameters (buried accessible surface area, hydrogen bonds, secondary structure contribution, etc.) that characterize orthosteric modulation of PPIs. Targeting several small pockets at the protein−protein interface dramatically increased the chances of success at identifying PPI inhibitors.[35] An allosteric ligand modulates the receptor's activation by its primary (orthosteric) ligand.

The identification of allosteric inhibition targets such as, for instance, allosteric cross-talk between sites of phosphorylation and protein−protein interactions have been outlined.[36] Accounting for the unsuitability of Lipinsky's "rule of five" (druglike properties that are consistent with good clinical performance[37]) to finding PPI inhibitors, Morelli et al.[38] proposed a "rule of four" based on a statistical analysis of 39 PPI inhibitors, describing the chemical space covered by the PPI inhibitors by use of the following criteria: molecular weight (>400 000), AlogP (>4), number of rings (>4), and number of hydrogen-bond acceptors (>4).

Several examples of PPI inhibitors, with low and high molecular weight, have been reported. Two main different strategies have been used for their identification: screening, including in silico screening, and drug design approaches, including nanoparticles for protein surface recognition. Figure 3 depicts the different PPI-inhibiting strategies.[39] We provide below some relevant representative examples classified as follows: small molecules and peptides, supramolecular multivalent scaffolds, and miniature proteins. Several reviews have outlined the different chemical series that inhibit PPIs and their

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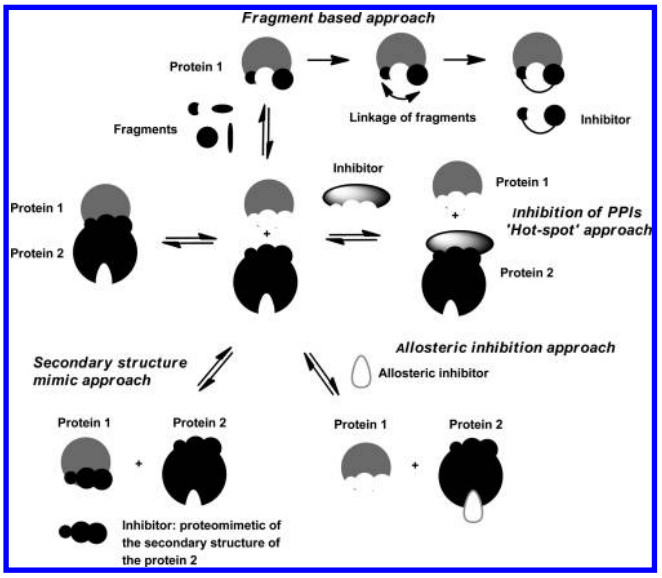

Figure 3. Main approaches developed to disrupt PPIs (adapted from ref 39).

approaches.[28,30,39−42] Table 1 shows the different chemical inhibitor types developed to disrupt PPIs.

2.1. Small Molecules and Peptides

To the best of our knowledge, only one PPI inhibitor is on the market. Maraviroc (Pfizer, Figure 4) is a chemokine CCR5 receptor antagonist and has been developed for the treatment of human immunodeficiency virus (HIV).[43] Maraviroc offers an alternative treatment strategy to the majority of current anti-HIV drugs targeting the viral reverse transcriptase or protease enzymes.

While even large libraries of compounds are unlikely to possess the complete functional and topological diversity displayed by PPI inhibitors, several successes have been described by use of either high-throughput screening (HTS) or fragment-based approaches yielding potent PPI inhibitors (Figure 4). Very interestingly, these inhibitors possess chemical architectures that differ from the pharmacophores in other known drug families.[44] One example is the series of *cis*-imidazolines (termed Nutlins) identified by Hoffman-La Roche as potent p53-hDM2 interaction inhibitors (antitumor agents). The most promising agent among them is Nutlin-3a that occupies the p53 transactivation domain (tumor-suppressor gene), and displays potent in vitro binding affinity (K_i ∼70 nM), excellent cell permeability and cell death, good pharmacokinetic profiles, and high effectiveness in vivo activity in several xenograft models.[45] Nutlin-3a is currently in a phase I clinical trial for the treatment of retinoblastoma.[46] Similarly, Johnson & Johnson identified a series of 1,4-benzodiazepine-2,5-diones via the ThermoFluor screening method.[47] The most interesting derivative, DIZ, displayed potent binding affinity with K_d = 80 nM against p53-hDM2 (Figure 4).[48]

Other small-molecule inhibitors of the p53-hDM2 protein−protein interaction have been reported including chalcones;[49] aryl sulfonamides, identified by a virtual screening approach (Cyclacel Pharmaceuticals, Inc.);[50] and dioxopyrazolines, identified by a molecular modeling approach.[51]

Using a fragment-based approach, Fesik and co-workers[52] (Abbott) identified ABT-737 as a potent inhibitor of Bcl-2 family PPIs. Overexpression of the anti-apoptotic Bcl-2 genes is observed in solid tumors and contributes highly toward cancer progression and resistance to the apoptosis induced by cytotoxic anticancer agents. ABT-737 displays potent binding affinity to the BH_3 domains (nanomolar range) of Bcl-2 genes and inhibits interaction with the pro-apoptotic proteins Bax and Bak. Currently, ABT-737 is in phase II clinical trials for use in human hematological malignancies.[53] Unfortunately, ABT-737 is not orally bioavailable, and consequently a second generation of PPI inhibitors within the same chemical series was developed to afford ABT-263 (Navitoclax, Abbott/Genentech), which is currently in phase II clinical trials for use against small-cell lung cancer and hematological malignancies.[54,55]

Interestingly, development of the structure-based design approach has afforded, among others, the spirooxindole derivative MI-219 (Figure 4), which binds to MDM2 and has shown higher levels of potency and selectivity than Nutlin-3. As shown in xenograft tumor tissues, the resulting rapid and transient stimulation of p53 activation yields the inhibition of cell proliferation and the induction of apoptosis.[56] MI-219 is currently in phase I clinical trials and has displayed anticancer activity against malignant B-cell lymphomas.[57a]

Very recently, Wang and co-workers[57b] published a new series of spirooxindole-containing compounds. The most potent derivative (MI-888) binds to MDM2 with K_i of 0.44 nM and displayed complete and long-lasting tumor regression against SJSA-1 osteosarcoma tumor xenograft model at a dose of 100 mg/kg (oral gavage for 14 days). Interestingly, the stereochemistry in this new class of spirooindoles (*cis*−*cis* configuration) is different from the previous reported spirooindoles.

Importantly, as depicted in Figure 5, several other PPI inhibitors are under clinical development such as Tevas's Obatoclax (GX 15-070, inhibitor of Bcl-2, phase II); Roche's RG-7112 (RO5045337) in patients with hematologic neoplasms (inhibiting p53-hDM2 interaction, phase I), which is a backup compound of RO 5503781, the structure of which has not been disclosed (MDM2-p53 inhibitor against advanced malignancies, oral route); and Sunesis's SAR 1118-23 (dry eye/keratoconjunctivitis sicca, ICAM-1/LFA-1 inhibitor, phase III).[58]

Another approach to disrupting PPIs has been developed by the preparation of stable (conformationally robust) peptides with specific secondary structures. More than ∼15 amino acid residues are necessary to obtain adequate conformation stability. Stable β-turns, α-helices constrained by such as a hydrogen-bond surrogate[59] and β-sheet systems for diverse therapeutic indications (cancer, HIV etc.) have been described and recently reviewed.[39,60] Figure 6 shows several β-strand and β-sheet conformational templates.[44]

In addition, Korsmeyer and co-workers[61] constrained a peptide corresponding to the BH_3 domain of the BID (BH_3 interacting domain death agonist) protein by substitution of two nonnatural amino acids and olefin metathesis. This stapled peptide displayed higher affinity to Bcl-2 than the corresponding unmodified peptide, protease resistance, and high cellular potency (leukemia cells) and in vivo activity in human leukemia xenograft models (Figure 7).

This approach represents an interesting means to render druggable an otherwise undruggable target, such as in cancer,[62] and is currently being developed by several pharmaceutical industries such as Aileron Therapeutics.[63] In this way, ALRN-5281 is currently in phase I clinical trials as an anticancer agent. The performance of stapled peptides has recently been addressed.[64] In addition, azobenzene photoaddressable[65] and

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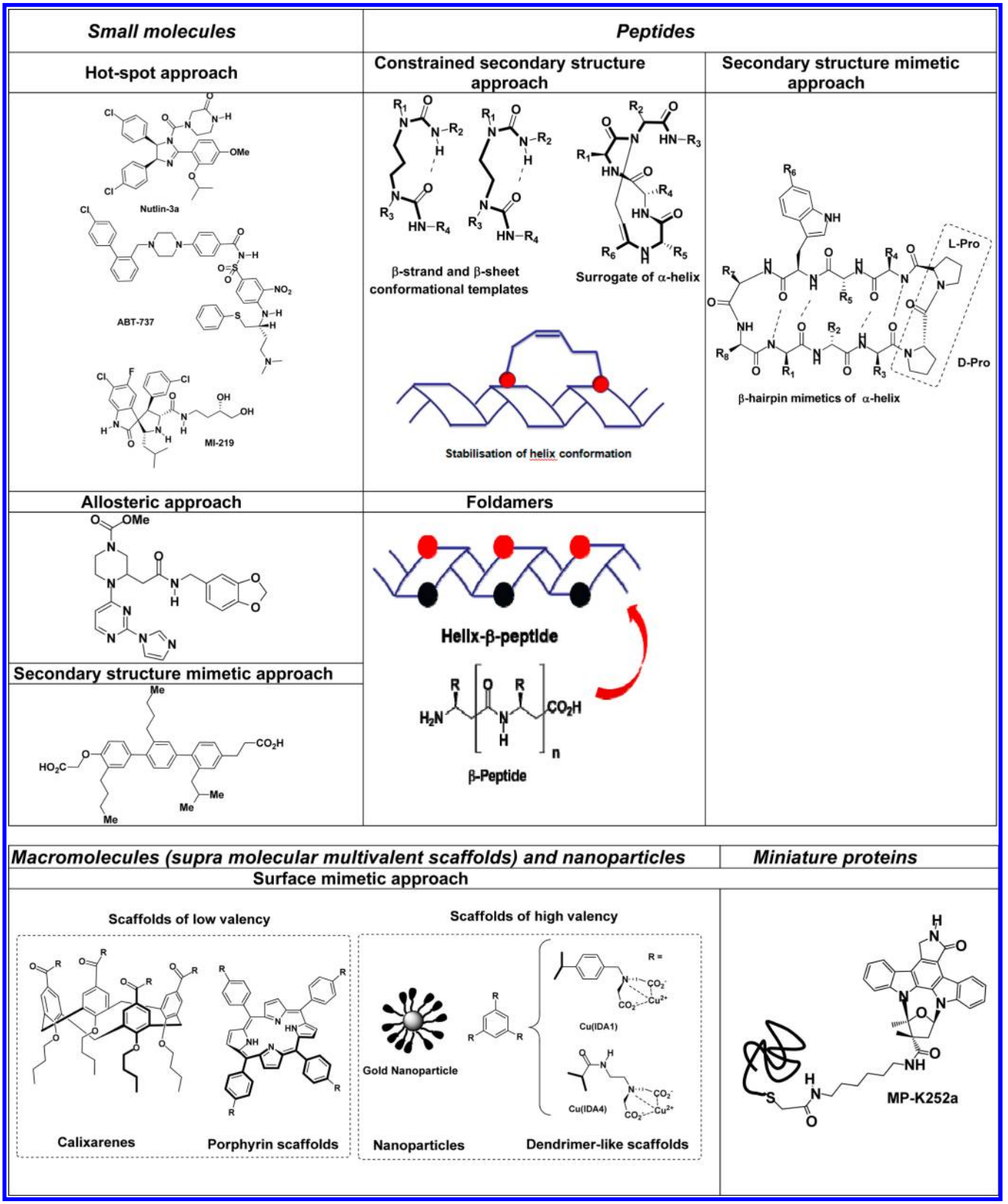
Table 1. Examples of PPI Inhibitor Types[a]



[a]See text for details and other examples.

dipicolylamine−bipyridine[66] cross-linking units have also been used to stabilize peptides (Figure 8).

Interestingly, in an analogous manner to the α-helix system, foldamers represent another approach to inhibit PPIs. Several β-peptides have been shown to potently inhibit p53-hDM2/p53-hDMX protein−protein interactions and display high cell permeability.[67] These β-peptides are capable of presenting side chains along one face, similarly to α-helices but with a different

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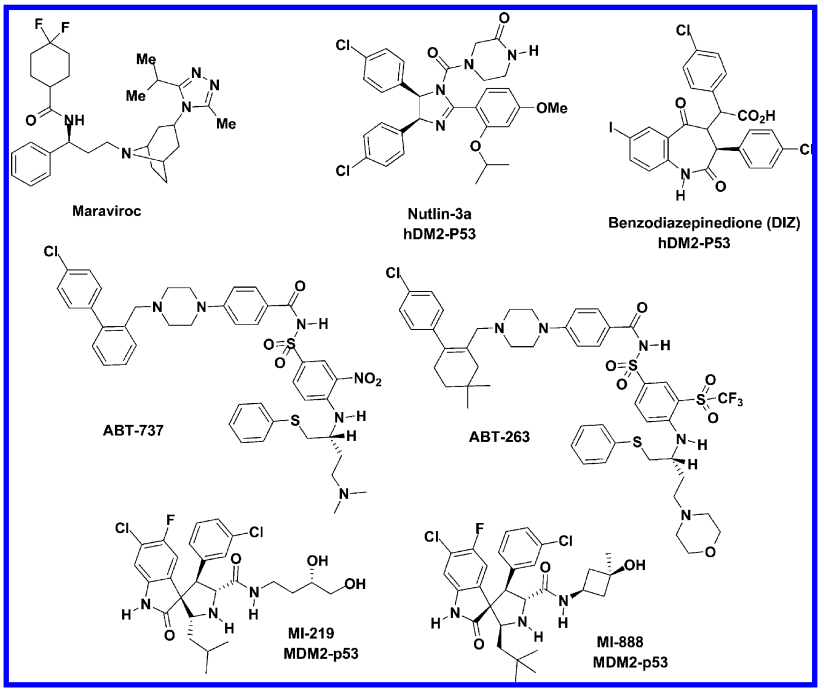

Figure 4. Chemical structures of Maraviroc, Nutlin-3a, DIZ, ABT-737, ABT-263, MI-219, and MI-888.

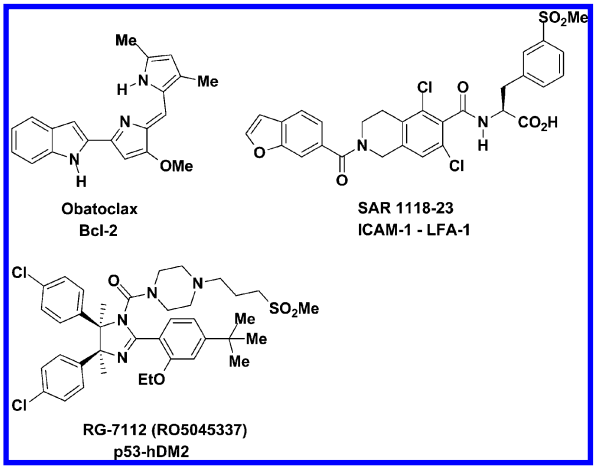

Figure 5. Chemical structures of Obatoclax, RG-7112, and SAR 1118-23.

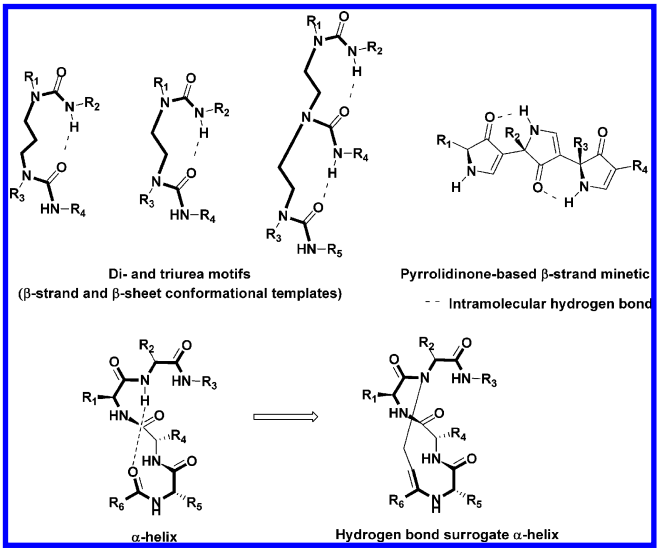

Figure 6. *β*-Strand and *β*-sheet mimetics.

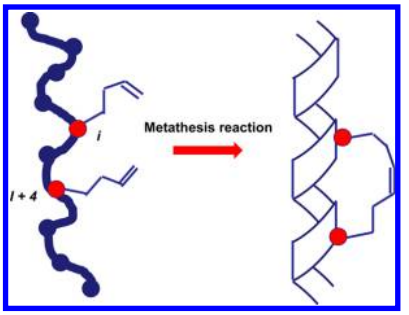

Figure 7. Stabilization of helix conformation by hydrocarbon stapling approach via metathesis reaction.

3D orientation (Figure 9). The main advantages offered by this system are the strong conformational stability (well-defined protein secondary structures) and proteolytic stability.[68] In addition, foldamer-based recognition is the mechanism used by potent inhibitors of HIV viral fusion by blocking gp41 assembly[69] and by inhibitors of Bcl2−BAK interactions.[70]

Another example of conformationally constrained peptides is *β*-hairpin peptidomimetics. *β*-Hairpin (secondary structure motif of proteins) peptidomimetics of the *β*-turns (also called *β*-bends or tight turns) are a type of secondary structure motif of proteins, including cyclic peptides bearing an L-Pro-D-Pro dipeptide unit; they have been prepared as mimetics of *α*-helical p53 peptides with an IC_{50} of 140 nM and showed modest to good inhibitory activities (Figure 10).[71]

Secondary structure mimetics of peptide fragments have been also designed, such as the D-glucose-based scaffold mimetic for the cyclic peptide somatostatin[72] and pyrrolidinone-based mimetics as HIV-1 protease inhibitors.[73] In a similar direction, Saraogi and Hamilton[74] elegantly designed a terphenyl scaffold as a structural and functional mimetic of the *α*-helix. As depicted in Figure 11, the 3,2′,2″-substituents of the

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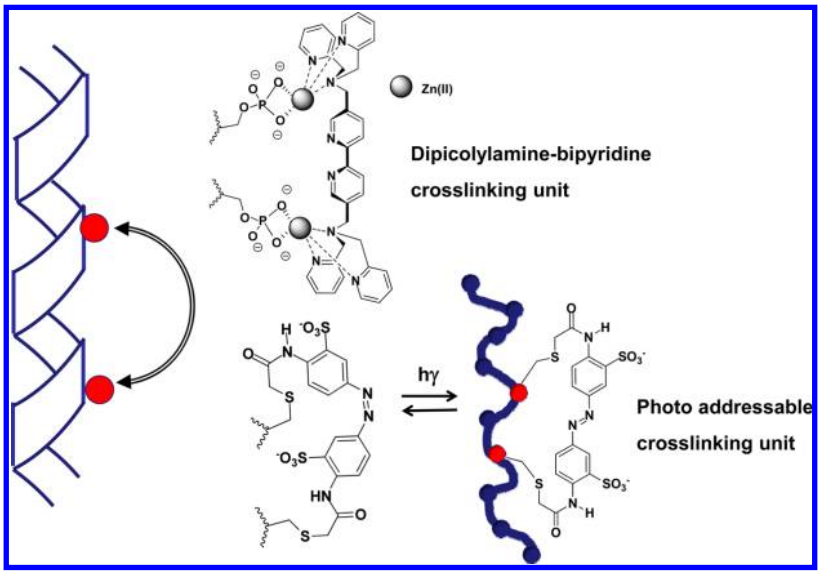

Figure 8. Helix conformation stabilization approach: azobenzene and dipicolylamine−bipyridine cross-linking units.

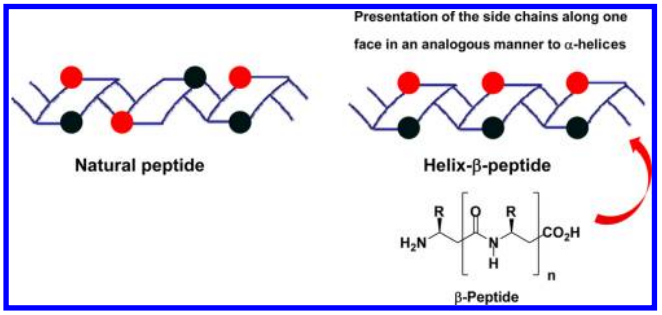

Figure 9. Constrained secondary structures: natural peptides versus β-peptides.

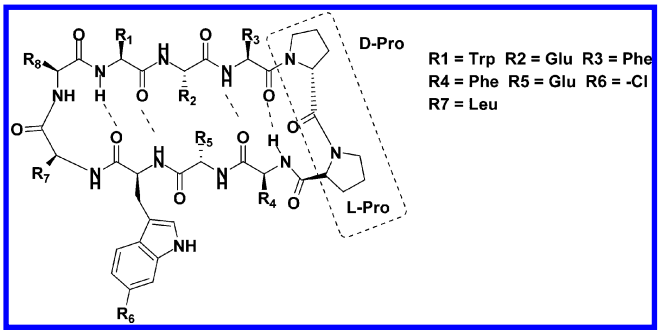

Figure 10. Example of β-hairpin mimetics of α-helical p53 peptides.

terphenyls project their functionality in a special orientation that mimics the i, (i + 3 or i + 4), and (i + 7) residues, all of which are located on the same face of an α-helix. Several potent PPI inhibitors have been developed by this approach to target the p53−hDM2 interaction, BclX−BAK BH_3 domain, and HIV gp41 assembly and viral fusion.[74] Other examples of terphenyl scaffolds acting to inhibit different PPIs, such as calmodulin and hexameric gp41 self-assembly, have been described in several reviews.[30,39,40]

Hamilton and co-workers[75,76] and other groups (e.g., Moreau and co-workers)[77] have also described the preparation of other scaffold-type α-helix mimetics including, for instance, terephthalamides, oligoamides, oligobenzamides, polyquinolines, and biphenyldicarboxamides. Allenes, alkylidene cycloalkanes, and

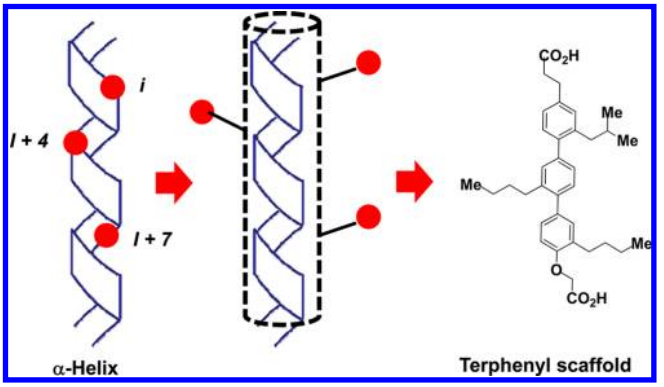

Figure 11. Similarity between α-helix and one example of terphenyl scaffold (adapted from ref 30).

spiranes have also been proposed as potential α-helical mimetics.[78] Commercial helical mimetic libraries are now available for purchase through companies like BioFocus DPI.[79]

Interestingly, Reymond and co-workers[80] reported the design and preparation of peptide dendrimers adopting a α-helical conformation. Among the different peptide dendrimers synthesized, the second-generation dendrimer $(AcA\text{-}MEA)_4(KKLME)_2KMKLA$ showed a higher α-helix content and a lower β-sheet fraction than the corresponding linear peptide (Figure 12).

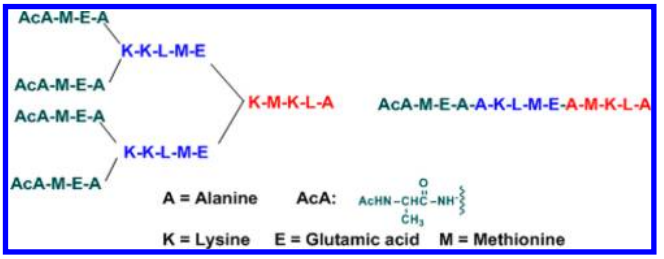

Figure 12. Secondary structure of peptide dendrimer versus linear peptides for α-helix stabilization.

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2.2. Allosteric Inhibitors

As shown in Figure 3, in allosteric inhibition a ligand binds at one site (allosteric site) and induces a conformational change at a distant location, leading to a change in the overall shape/conformation at the active site.[23] Similarly to allosteric enzyme inhibition, the disruption of a PPI occurs upon the binding of a ligand to a PPI allosteric site that is distantly located from the protein−protein interface and thus, importantly, not competing with the binding protein partner. The main advantages of this approach are high level of control over the PPI modulation and easier identification of the suitable allosteric site or "hot spot".

One earlier study by McMillan and co-workers[81] at Pharmacopeia and Berlex, using libraries of compounds, reported the development of original compounds inhibiting inducible nitric oxide synthase (iNOS) in either its dimeric or monomeric form (Figure 13). iNOS represents an attractive

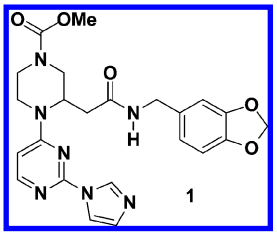

Figure 13. Chemical structure of allosteric inhibitor **1**.

enzyme target in both inflammation and autoimmune diseases. Of these compounds, **1** inhibited NO-production by cytokine-stimulated human glioblastoma A-172 cells with an IC_{50} of 0.6 nM. In addition, it inhibited iNOS (IC_{50} = 28 nM) more selectively compared to neuronal NOS (IC_{50} = 140 nM) and endothelial NOS dimerization (IC_{50} = 32 μM). Remarkably, it could also suppress NO production in vivo following intraperitoneal injection in a rat model of endotoxin-induced systemic iNOS induction, with an ED_{50} of 1.2 mg/kg.

Crystallographic studies revealed that the free imidazole nitrogen of **1** coordinates to the hem (sixth axial position) of iNOS, leading to its allosteric inhibition via the disruption of helix 7 and partial disruption of helix 8. They also showed that the imidazole, pyridine, and part of the piperidine ring are nearly coplanar. Other examples include the identification of inhibitors (4-phenylthiazol-2-amine derivatives) of the runx1−CBFb interaction (anticancer agents), which have been shown to inhibit the proliferation of the human leukemia ME-1 cell line (IC_{50} in the micromolar range).[82]

2.3. Supramolecular Multivalent Scaffolds

As outlined above, since the traditional small-molecule approach does not represent the best way of disrupting PPIs,[83] other strategies have been developed that mimic selective protein−protein binding mechanisms. These strategies are based on disrupting the large interacting surfaces and their highly charged overall interactions (charge−charge electrostatic interactions). Note that other interactions such as hydrophobic, aromatic, and hydrogen-bonding interactions are also important with regard to interaction selectivity.[84]

2.3.1. Scaffolds of Low Valency. Selective disruption of PPIs has been elaborated by several teams using macromolecules. Earlier work by Hamilton and co-workers[85] included the design of 4-fold symmetric calix[4]arene derivatives that could bind to the surface of platelet-derived growth factor (PDGF; cytokines, hormones etc.) and thereby inhibit its interaction with its receptor (PDGFR), thus inducing antitumor and antiangiogenesis activities. Of particular interest, the calix[4]arene derivative GFB-111 targets loops I and III of PDGF, the regions of the protein that bind its receptor (PDGFR, Figure 14). Four hexacyclic peptide loops are attached to the central calix[4]arene core, giving it a surface area of ~500 Å^2 and allowing a potent antagonist activity with an IC_{50} of 250 nM on PDGFR. Other cyclic peptides have been introduced on the upper rim of the calix[4]arene scaffold bearing either peripheral carboxylic acid (Calix1) groups or amino groups (Calix2), which also bind PDGF but with lower potency (IC_{50} = 2.5 and 40 μM). Interestingly, Calix2 displayed another protein−protein interaction allowing it to disrupt the cytochrome *c* (cyt *c*)−Apaf-1 complex with a K_d ~ 30 nM.[86]

As shown in Figure 15, 4-fold symmetric, essentially flat porphyrin scaffolds have also been designed that are able to disrupt several PPIs. These include the recognition of the surface of cyt *c* with anionic porphyrins **P1**−**P4** (pK_d = 0.67−860 nM),[87] the human Kv1.3 potassium channel with cationic porphyrin **P5** (K_i = 20 nM),[88] and bFGF−FGFR (basic heparin-binding human fibroblast growth factors−fibroblast growth factor receptor) with cationic porphyrin P1016 (IC_{50} = 20 nM).[89] Unfortunately, in the Lewis lung carcinoma tumor model, P1016 displayed limited suppression of tumor metastasis in mice versus its analogue P1020. Interestingly, the water-soluble cationic porphyrin P1021 exhibited good potency both in vitro and in vivo and inhibited lung metastasis formation at a concentration of 5 mg/kg in mice.

Large flat aromatic scaffolds substituted with naphthalenes and anthracenes have been prepared and are respectively able to disrupt HIV viral fusion by blocking gp41 assembly (micromolar range)[90] and to block cyt *c*−lysozyme-selective receptors (nanomolar to micromolar range).[91]

Breslow and co-workers[92] have demonstrated the selective disruption of protein aggregation using various β-cyclodextrin dimers (β-CD, Figure 16). Only β-CD compounds that had their cavities facing each other and correctly separated by a

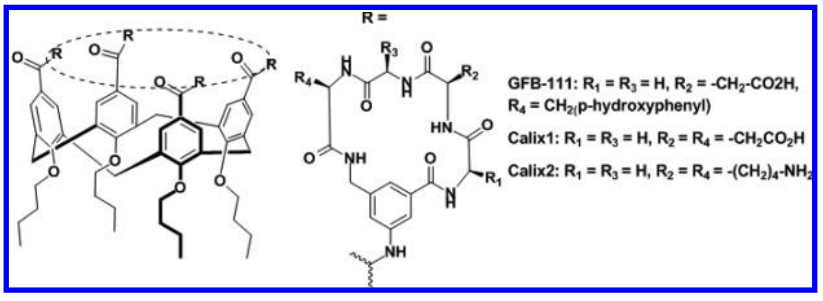

Figure 14. Chemical structures of GFB-111, Calix1, and Calix2.

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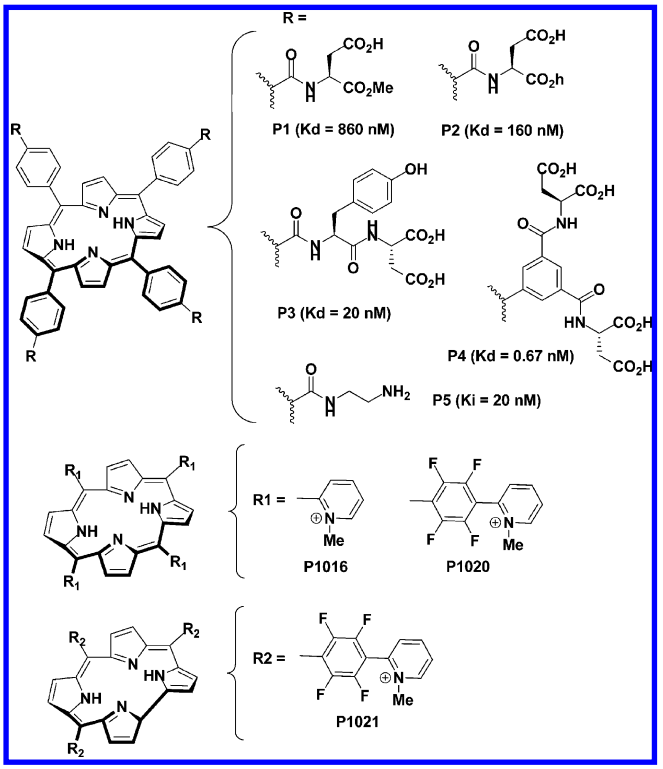

Figure 15. Chemical structures of cationic porphyrins used as PPI inhibitors.

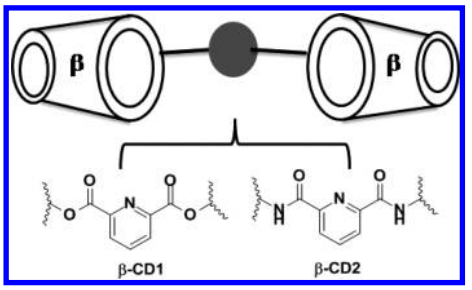

Figure 16. β-Cyclodextrin dimers disrupting self-assembly of CS and LDH.

linker displayed protein aggregation disruption. Thus, the dimeric citrate synthase (CS) and the tetrameric lactate dehydrogenase (LDH) were inhibited by β-CD1 and β-CD2 with IC_{50} values of 140 μM and 30 μM, respectively. The nature of the linker is crucial for the inhibition, as no inhibition was observed with an isophthalic acid linker toward either CS or LDH. No disruption was exhibited against monomeric adenoside deaminase, dimeric glucose-6-phosphate dehydrogenase, dimeric D-galactose dehydrogenase, dimeric phosphohexose isomerase, tetrameric fumarase, or tetrameric sorbitol dehydrogenase.

Hamilton and co-workers[93] also designed functionalized G-quartets (short DNA sequence) able to disrupt the cyt *c* protein surface (micromolar range). The DNA sequence was functionalized at the 5′ terminal group with peptide-binding groups interacting with cyt *c*.

2.3.2. Scaffolds of High Valency. In an earlier study, Rotello and co-workers[94] showed that surface recognition is possible by use of self-assembled systems such as amphiphilic gold clusters (anionic nanoparticles). Mixed-monolayer protected gold clusters (MMPCs) functionalized with terminal anionic groups (mercaptoundecanoic acid, MUA) interact with the positively charged surface of α-chymotrypsin (ChT) (Figure 17). The activity inhibition occurs through a two-step

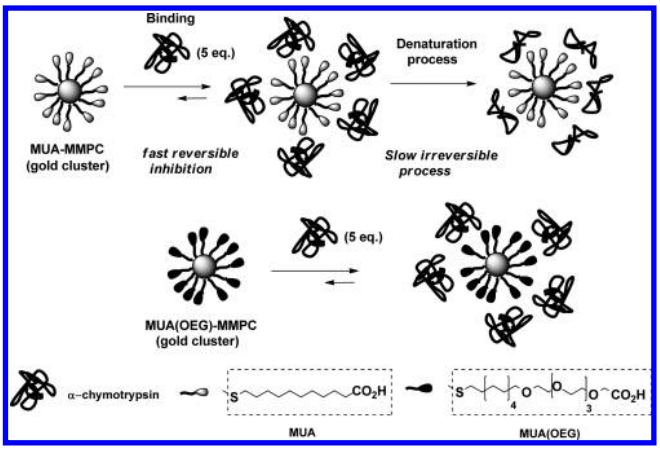

Figure 17. Surface recognition of α-chymotrypsin by use of gold clusters (adapted from refs 30 and 39).

mechanism: (1) a fast reversible step of inhibition, followed by (2) a slow irreversible step in which the enzyme is slowly denatured. Based on circular dichroism spectroscopy, the interaction of the gold nanoparticle and ChT was found to be very efficient with K_i(app) of 10 nM, involving a stoichiometry of five protein molecules to one MMPC. The inhibition process was found to be highly selective toward ChT by comparison with β-galactosidase, serine protease elastase, and cellular retinoic binding protein. In addition, no activity toward ChT was observed with cationic MMPCs or when the hydrophobicity of the gold nanoparticle was decreased by replacing MUA by the corresponding PEGylated MUA [MUA(OEG)].[95]

Rotello and co-workers[96] also showed that in situ modification of the nanoparticle surface by addition of cationic surfactants [carboxylate-functionalized nanoparticles, $AuCO_2H$ (MUA ~85% and -S-*n*-octyl ~15%)] reversed the inhibition of ChT.

Rotello and co-workers[97] also developed UV light-induced inhibition of ChT by using photocleavable monolayer units on gold nanoparticles. One of the main advantages of this strategy is the possibility to activate or deactivate a desired binding interaction at any particular time and to a particular level. Under external UV−visible light (l > 300 nm), the photocleavable phenacyl ester linkages on the surface of the gold nanoparticles induced a change in the surface environment by presenting newly formed carboxyl groups. Two different gold monolayer clusters were prepared: cationic MMPC 1 and anionic MMPC 2 (Figure 18). The newly exposed surface of MMPC 1 allowed potent de novo inhibition of ChT and enhanced the pre-existing inhibitory capability of the anionic gold particles MMPC 2. The activity of ChT was assayed by use of benzoyl tyrosine *p*-nitroanilide as a substrate, and no aggregation was observed before the inhibitory effect.

2.3.3. Miniature Proteins. Another interesting methodology, termed "protein grafting", was developed by Schepartz and co-workers[98,99] to disrupt PPIs. In an earlier study, they reported a strategy for both DNA and protein surface recognitions.[98] The designed miniature protein (MP) recognized the α-helix in the small and well-folded protein aPP (avian pancreatic polypeptide), which displays recognition

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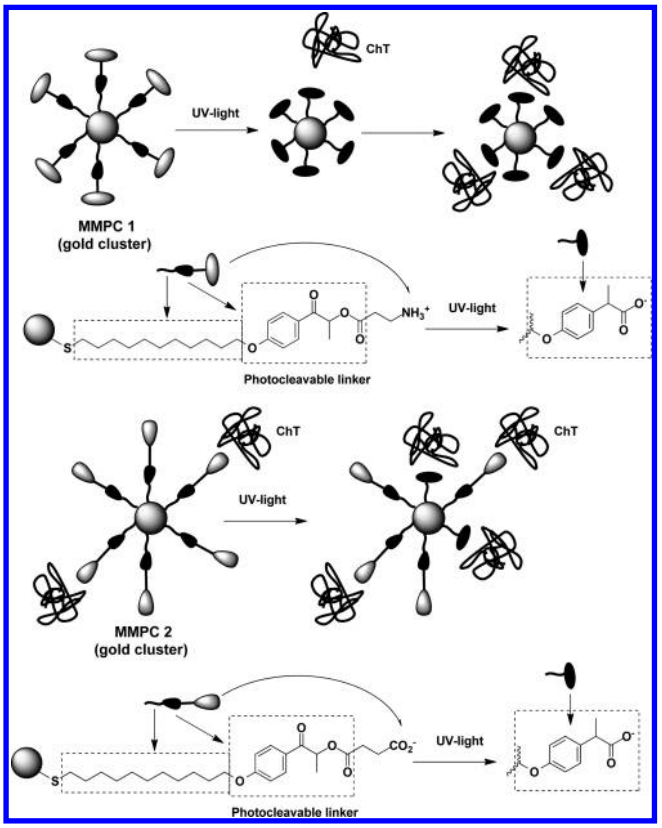

Figure 18. Structures of gold nanoparticles MMPC 1 and MMPC 2 (adapted from ref 97).

epitopes found in several large proteins. On the basis of these studies, and due to the large number of kinases encoded by the human genome, the authors grafted K252aΔ with MP (Figure 19).[99] The objective was to increase the selectivity of K252a (a

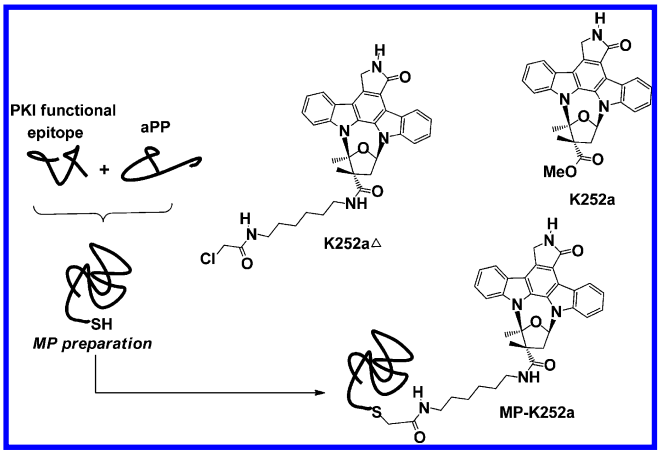

Figure 19. Miniature protein strategy to disrupt PPIs: case of staurosporin (adapted from ref 99).

staurosporine analogue), which has a potent kinase inhibitory effect (direct interaction with the ATP pocket in the kinase) but also has very low selectivity against many tyrosine and serine threonine kinases. The MP, built from protein kinase inhibitor (PKI) protein functional epitopes and aPP, specifically recognized protein kinase A (PKA; c-AMP-dependent protein kinase) and enabled high selectivity of MP-K252a relative to the nongrafted K252a. K252a and MP displayed an inhibitory activity (streptavidin-matrix capture of biotinylated [^{32}P]-phosphorylated substrates assay) with IC_{50} values of 0.140 and 117 nM, respectively. MP-K252a was 30 times more active (IC_{50} = 0.13 nM) than nongrafted MP and 26-fold less active than nongrafted K252a.

As shown above, dendrimers and dendrons[15] are gaining enormous interest as nanodevices in medicine. This is illustrated by the development of different types of dendritic macromolecules: (1) as carriers for the delivery of drugs and genes, (2) for targeting, (3) for solubilization, (4) for diagnostic purposes, (5) bearing multivalent ligands for various biological applications, etc.

Importantly, dendrimers have been described as therapeutic agents in different diseases[100] including prion disease,[17c,101] HIV,[102] Alzheimer's disease, Parkinson's disease,[103] inflammatory diseases,[104] cancer,[105] and also toxin-related diseases. Interestingly, the use of dendrimers as artificial enzymes has been investigated by Kofoed and Reymond,[106] and the use of dendrons as therapeutic agents was recently nicely reviewed by Haag and co-workers[15] Below we present several (nonexhaustive) examples of dendrimers and dendrons as therapeutic agents.

Fassina and co-workers[107] highlighted the elegant design and synthesis of dendrimeric peptide mimics that interact with human immunoglobulins of the G class (IgG). Two different dendrimeric peptide mimics were prepared, based on four copies of the tripeptide Arg-Thr-Tyr (L-amino acids) or a partial-retro-inverso (Arg-Thr-Tyr, D-amino acids) linked to an asymmetric polysine core. The best potency was obtained with a natural amino acid series. Structural evidence that a *Staphylococcus aureus* protein A dendrimeric peptide mimic binds close to the fragment (Fc) of human IgG has also been shown.

Other interesting examples for different medicinal applications[108] are the use of multivalent glycomimetics such as glycodendrons as anti-inflammatory agents,[109] antibacterial compounds,[110] and antibiotics,[111] and the design of dendrons specifically mimicking the endogenous interleukin 1 receptor antagonist (IL-1ra) and interleukin 8 (IL-8).[112] In the next section, we will describe in more detail several examples of dendrimers showing per se PPI-disruptive activity.

3. INHIBITION OF PROTEIN−PROTEIN INTERACTIONS: DENDRIMER-LIKE SCAFFOLDS

Mallik and co-workers[113] described the design and synthesis of metallodendritic-like species with copper(II) metal ions on their periphery that selectively target a particular pattern of histidine residues found on the surface of carbonic anhydrase (CA) enzymes bearing six histidine residues. As shown in Figure 20, various metallodendritic-like species with three Cu(II)-iminodiacetate arms separated by different spacers were prepared.

Interestingly, no interaction against lysozyme (one histidine residue), myoglobin (Mb, seven histidine residues), and chicken egg albumin (CEA, six histidine residues) was observed. The multivalent Cu(II)−ligand complex Cu−IDA1 bound to CA with $K_a \sim 3 \times 10^5$ M^{-1} and showed good selectivity versus that toward CEA, ~300 [K_a(CA)/K_a(CEA)], and Mb, ~15 ([K_a(CA)/K_a(Mb)]. The dendritic complex Cu−IDA2 displayed lower potency against CA with K_a of 7.5×10^4 M^{-1}. A shorter spacing between the three Cu-iminodiacetate groups induced a less favorable enthalpic contribution (based on isothermal titration microcalorimetry assay, ITC), and the

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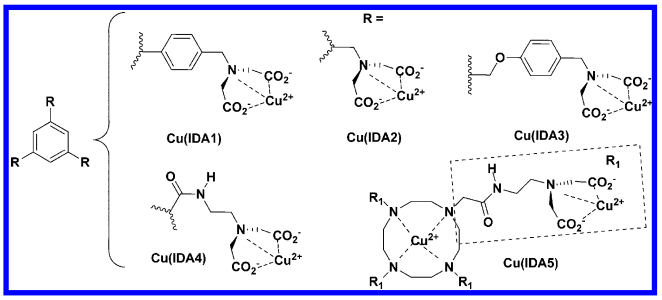

Figure 20. Structures of dendritic Cu(II) complexes.

more flexible dendritic complex (Cu–IDA3) demonstrated weak potency with K_a of 3.3 × 10^4 M^{-1} due to the loss of entropy contribution (ITC assay). Cu–IDA4 and Cu–IDA5 exhibited K_a values of ∼34 × 10^3 M^{-1}. The complexes Cu–IDA3 and Cu–IDA4 were designed to probe the role of rigidity versus flexibility during the recognition process. In addition, no disruption was observed with plain dendrimers whatever the nature of the scaffold. Importantly, Cu–IDA2 and Cu–IDA3 displayed low to moderate selectivity compared to CEA and Mb (∼1–10).

Tsukube and co-workers[114,115] designed and synthesized proteodendrimers **1a–4a** as synthetic receptors that included a polyanionic heptaglutamic acid unit (providing four pairs of CO_2^- per dendrimer), hydrophobic dendrons (benzyl ether groups), a hydrophilic polyether surface (providing water solubility), and a fluorescent zinc porphyrinate as core (signaling device) (Figure 21).

Interestingly, **1a–4a** displayed anti-apoptotic activity against human epithelial carcinoma HeLa and reversed the mitochondrial apoptotic effect of the ceramide analogue C2-ketoCer (*N*-[(2*S*,4*E*)-1-hydroxy-3-oxo-4-octadecen-2-yl]acetamide). C2-ketoCer induced mitochondrial apoptosis against HeLa cells as well as human leukemia HL-60 cells, presumably via the competitive inhibition (disruption) of Apaf1–cytochrome *c* protein interaction. The cell viability decreased in a time-dependent manner until death of ∼90% of the HeLa cells was reached in 6 h. C2-ketoCer activated caspase 3 within 2 h.

Treatment with **1a–4a** (10 μM) induced the recovery of cell viability following C2-ketoCer-induced apoptosis (5 μM). In this assay, the most potent proteodendrimer was **2a**, which showed the lowest cytotoxicity and the highest solubility and suppressed caspase 3 activation after cytochrome *c* release. The polyanionic patch of the proteodendrimer interacted with the polycationic patch of cytochrome *c* (four protonated lysines) with an interfacial area of ∼1000 Å^2.

Recently, Twyman and co-workers[116] described the interactions of polyanionic G1.5–G4.5 PAMAM dendrimers, possessing 8–64 CO_2H terminal groups, with cytochrome *c* protein and chymotrypsin (Figure 22).

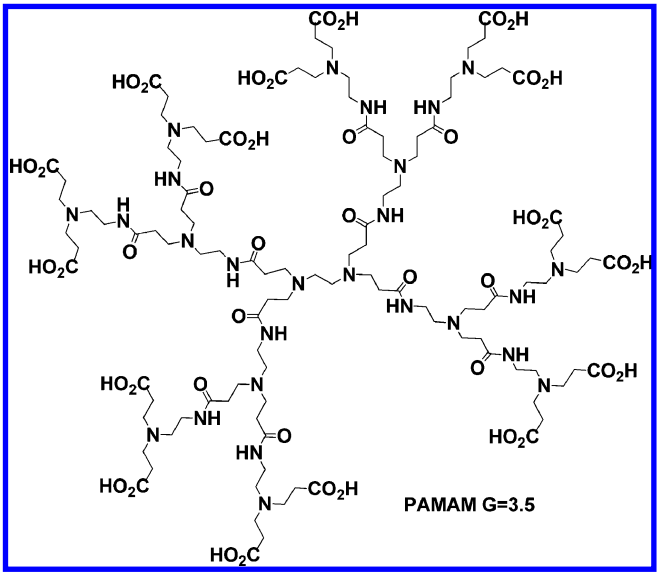

Figure 22. Chemical structure of PAMAM G3.5.

Interestingly, as shown in Scheme 1, the dendrimer displaying the best binding capacity has a maximum addressable surface area of similar dimensions to the interfacial surface area of the protein. The interfacial surface areas of cytochrome *c* and chymotrypsin are ∼1100 and ∼2400 Å^2, respectively, whereas

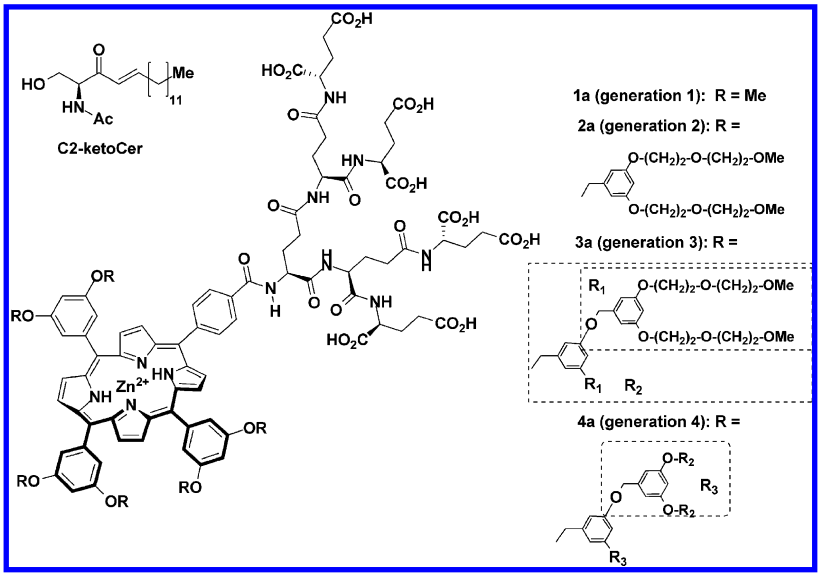

Figure 21. Chemical structures of C2-ketoCer and **1a–4a**.

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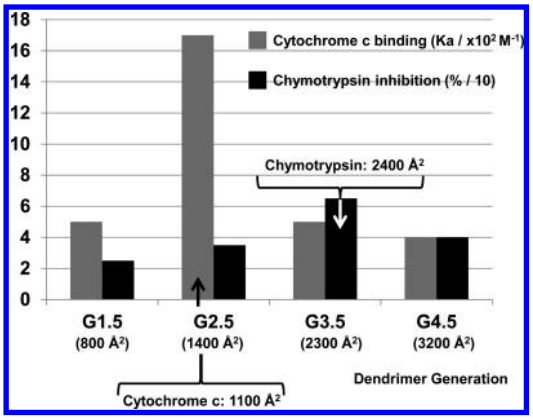
Scheme 1. Binding and Inhibition of PAMAM G1.5−G4.5[a,b]



[a]Binding was measured against cytochrome *c*; inhibition was measured against chymotrypsin. [b]Adapted from ref 116.

the maximum addressable surface areas of G1.5, G2.5, G3.5, and G4.5 are 800, 1400, 2300, and 3200 Å^2, respectively.

The G2.5 PAMAM dendrimer (~1400 Å^2) showed the strongest binding toward cytochrome *c* (~1100 Å^2), while G3.5 PAMAM dendrimer (~2300 Å^2) fitted best against chymotrypsin (~2400 Å^2).

Taken together, as highlighted by the authors, the best specific interaction between the dendrimer and the protein surface is the result of maximized thermodynamic contributions such as enthalpic factors (charge to charge, site to site interactions) as well as entropic factors (solvation/desolvation and hydrophobic binding). Dendrimer flexibility is also an important factor to be considered for the best surface interactions, and larger dendrimers may bind to their protein targets more weakly than the optimum-sized dendrimers.

Collectively, the best interactions appear to be the result of the right balance between structure (size, shape, functionality of the dendrimer/protein) and thermodynamic contributions (enthalpic and entropic factors).

Recently, on the basis of circular dichroism spectroscopy assays, Twyman and co-workers[117] demonstrated that dendrimer−protein binding (G2.5/G3.5 PAMAM dendrimers−chymotrypsin) is not accompanied by changes in the protein's structure and that binding takes places on the interfacial area/active-site entrance and inhibits activity through the mechanism displayed in Figure 23.

Recently, interactions of a homologous series of 19 PAMAM dendrimers with human serum albumin (HSA) have been described by Giri et al.[118] It is well-known that interactions of nanoparticles with plasma proteins have a strong implication on their in vivo transport, clearance, and toxicity of drug delivery systems.[119] The HSA binding constant (K_b) was measured by use of protein-coated silica particles in aqueous solutions at physiological pH (7.4) as a function of the generation of dendrimers and the nature of terminal groups and the core. In this study, the generation used are G0−G8 and the dendrimer core and dendrimer terminal groups are the following: ethylenediamine, diaminobutane, diaminohexane, cystamine, and diaminododecane for the core; and amine, amidoethanol, succinamic acid, sodium carboxylate, tris(hydroxymethyl)-amidomethane, carbomethoxypyrrolidinone, amidoethylethanolamine, and poly(ethylene glycol) as terminal groups, respectively.

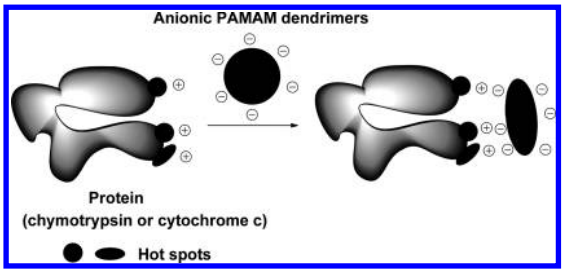


Figure 23. Schematic representation of binding mechanism between dendrimer and protein through PPIs (adapted from ref 117).

Analysis of the K_b values suggests several mechanisms of interaction between HSA and PAMAM dendrimers: electrostatic interactions, hydrogen bonding, hydrophobic interactions, and specific interactions between dendrimer carboxylic groups and protein aliphatic binding sites. These interactions are relatively weak, and on the basis of ^{1}H NMR saturation transfer difference experiments and atomistic molecular dynamics simulation, the inner-shell protons of the dendrimer groups interact more strongly with HSA proteins. The K_b values depend on dendrimer size and the chemical nature of the terminal groups. The strongest interactions were observed for different dendrimer generations (G0-NH_2 and G4-NH_2) and terminal groups [G4-NH_2 and G4-OH (amidoethanol groups)]. Collectively, the data suggest that PAMAM dendrimers adopt backfolded conformations as they form weak complexes with HSA (aqueous solution at pH 7.4).

4. CONCLUDING REMARKS AND PERSPECTIVES

Allthough the modulation of PPIs remains one of the most difficult fields in chemical biology and drug development, it is also one of the most exciting, offering a vast potential source of novel targets. In general, the topology of PP interfaces differs greatly from the active site of enzymes and receptors. Consequently, low hit rates have been obtained with typical corporate libraries/collections. Although several small PPI inhibitors are already under clinical trial (see above), numerous PPI stabilizers belong to several chemical families: (1) constrained secondary structure peptides or foldamers, (2) secondary structure mimetics, and (3) surface mimetics. Crucial PPIs are largely driven by hydrophobic interactions, hydrogen bonds, and electrostatic interactions, and the interfacial surface for specific recognition is typically large. Consequently, PPIs are difficult to mimic with small molecules and the ligand efficiency index (LE), which is a measurement of the binding energy per atom of a ligand, is consistently lower (mean LE ~ 0.24) for PPIs[111] than for classical protein interactions with small molecules (for aminergic GPCRs, ion channels, and metalloprotease, mean LE ~ 0.4; for nuclear hormone receptors, serine protease, phosphodiesterases, and protein kinases, LE ~ 0.3; for peptide GPCRs, LE ~ 0.2).[120]

As already proposed by Lipinski and Hopkins,[121] one of the foremost challenges facing drug discovery is the identification and development of specific chemical areas. As depicted in Figure 24, within the vast continuum of chemical space, the overlapping of several well-parametrized subareas, for instance, druglike space (rule of 5) and target classes, the boundaries of which are delimited by molecular descriptors of active compounds, define the druggable target space, whereas the nonoverlapping area corresponds to poorly druggable target space. On the basis of the huge therapeutic applications of biocompatible dendrimers, active either per se or as nano-

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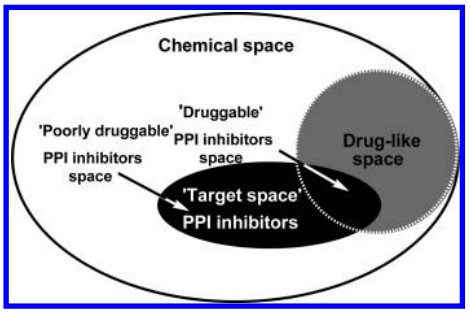

Figure 24. Druglike space and target space PPI inhibitors.

carriers, we have defined the dendrimer space concept[21] as a new druggable subarea that should enhance the druggability of a specific target space such as PPIs. Taken together, the focus of the dendrimer approach should switch from poorly druggable compounds to efficiently druggable biocompatible drug–dendrimers. Importantly, Morelli et al.[38] recently proposed a "rule of four" to describe the chemical space covered by small PPI inhibitors. Future analyses of the relevant molecular descriptors that should define the boundaries of the dendrimer space toward expanding the druggable PPI inhibitors are required.

The PPI allosteric inhibitor approach undeniably represents a very interesting strategy that would permit the use of classical small PPI inhibitors. The main challenges remain to localize the allosteric site(s) of PPIs and to develop useful techniques (high-throughput screening, crystallography, algorithms, etc.) to identify the allosteric inhibitors.

As highlighted by Esfand and Tomalia,[122] dendritic polymers are often referred to as artificial globular proteins, based on their closely matched size and contours of important proteins (e.g., cytochrome *c*, hemoglobin, immunoglobulin prealbumin, and hemerythrin) and bioassemblies (e.g., DNA–histone complex) and their electrophoretic properties and other biomimetic properties. They will play a significant role in the development of new strategies such as inhibition of protein–protein interactions for the treatment of human disease.

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Notes

The authors declare no competing financial interest.

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Saïd El Kazzouli was born in Beni Mellal (Morocco) in 1975. He obtained his M.Sc. (DEA degree) in 2000 from the University of Orleans (France). In 2004, he received his Ph.D. in organic chemistry from the University of Orleans under the guidance of Professors G. Guillaumet and A. Mouaddib, and then he worked at the same University as a postdoctoral fellow with Professor L. Agrofoglio. In 2005 he was involved in an industrial project with Professor S. Berteina-Raboin and the firm Syngenta. In 2006, he joined the National Cancer Institute at the National Institutes of Health (U.S.) to work as a postdoctoral fellow with Dr. V. E. Marquez. In 2009, he became a scientist researcher and then project leader at INANO-TECH, MAScIR Foundation in Rabat (Morocco). In 2013, he was promoted to Permanent Professor at the Euro-Mediterranean University of Fez, Morocco. His main research interests are the design and synthesis of bioactive molecules, drug delivery, and catalysis.

Mosto Bousmina is presently the President of the Euro-Mediterranean University of Fez, Morocco, and the Chancellor of the Hassan II Academy of Science and Technology, Morocco. He was full professor and Senior Canada Research Chair at Laval University-Canada (1994–2008), President of the Quebec Society of Polymers, Vice-president of the Canadian Society of Rheology, Director of the Society of Plastic Engineers (Quebec Section), member of the Canada Team for

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Aerospace Research, and President of the Canada National Research Council Committee for Chemical and Metallurgical Engineering. He is a member of the African Academy of Sciences (AAS) and the World Academy of Sciences (TWAS) and vice-president of the Network of the African Science Academies (NASAC). He is the Editor-in-Chief of *World Research Journal of Chemistry*, Co-Editor of *Journal of Polymer Engineering*, Associate Editor of *Journal of Nanoscience and Nanotechnology*, and Regional Editor of *Recent Patents in Nanotechnology*. He is the author of more than 180 scientific publications and six patents. He has received various awards: Louis-Pasteur Award in 1993, Innovation Award from the Quebec Ministry of Commerce and Technology in 1988, Canada Top-20 Explorer Award in 2002 from CIAR (Canadian Institute for Advanced Research); International Morand Lamba Award from the Polymer Processing Society in 2000, the prestigious Steacie Award from NSERC-Canada in 2004, and the Grand Prize of Innovation, Morocco, in 2009.

Jean-Pierre Majoral is Emeritus Director of Research at the CNRS in Toulouse. His research interest is focused on the design and properties of macromolecules such as phosphorus dendrimers and hyperbranched polymers. Main efforts are directed to the use of dendrimers in medicinal chemistry and material sciences. Emphasis is also laid on immobilization of molecular and macromolecular organocatalysts and metal catalysts and their use for fine chemical synthesis. He has received various prestigious awards from Germany, Poland, Spain, the United Kingdom, and France. He is a member of several Academies of Sciences worldwide and an author of 525 publications and 45 patents.

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