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Recent Development of Macrocyclic Compounds as Potential Tool for Cancer Therapy and Diagnosis: A Mini-Review

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Abstract: Macrocyclic compounds can be easily sustained into varied functionality, which has recently famed them as an individual supramolecular entity. Owing to their tenable non-covalent interactions or dynamic covalent bonding, these macrocyclic formulations have contemporaneously inhibited and controlled the progression of infectious diseases and cancers. Macrocyclic supramolecular assemblies have been fabricated for staging the medicinal accuracy of different therapies as well as diagnostic pathways. This mini-review, therefore, focuses on the design of a hierarchical assembly process at the molecular level of chemical composition and presents interesting illustrations of supramolecular assembled structural motifs as new cancer diagnostic and therapeutic options.

Keywords: cancer diagnostic; nanoparticles; nanomedicine; supramolecules; therapeutic.

1. Introduction

In recent years, macrocyclic compounds have attracted considerable attention for cancer treatment while being nanofabricated in many cases [1-3]. An important advantage of such descending in size not only miniaturizes the experimental study of treatment but also improves their availability for site-specific targeting applications [4, 5]. In particular, some of the attractive properties of macrocyclic platforms include the propensity to generate inclusion compounds, [6] thermally activated delayed fluorescence property credited to their unique structure [7], and regulated ability to self-assemble for selective interaction with substrates [8]. Therefore, macrocyclic systems have addressed unmet objectives in therapeutic and diagnostic technologies apart from conventional platforms. For instance, porphyrins' therapeutic and diagnostic properties, which were encapsulated into self-assembling nanostructures for creating a new and stable platform for drug delivery and cancer theragnostic, have been reported [9, 10]. Furthermore, the concept and relevance of a scalable, nanofabricated macrocyclic platform provide crucial insight to ease the chemical complexity and automate

many processes at the cellular level. A clear demonstration of the development of science and technology by coupling nanotechnology with supramolecular chemistry was given by *Ariga et al.* for designing 'nano architectonics' [11]. Based on self-assembly, this concept combines non-nanotechnology fields such as supramolecular chemistry with functional materials of nanoscale units for applications in drug delivery, cell culture, supramolecular differentiation, molecular recognition, and molecular tuning, and many more [3, 12-14].

In this review, the ability of several macrocyclic structures to get arranged in a geometrically confined space to render excellent cytotoxic selectivity and encapsulate selected drugs for particular medicinal therapies has been discussed. A deep understanding of progression in cancer therapy and diagnosis under the shelter of supramolecular chemistry and nanomedicine is further enlightened for exploring newer medicinal strategies.

2. Controlled Drug Delivery in Cancer Therapy

Amongst the various diseases and pathogens responsible for mortality, cancer is considered the second largest contributor. Cancer progression initiates from tumor- an abnormal cell mass growth due to an unregulated cell proliferation which originates from alterations and mutations in signaling and metabolic pathways [15]. An estimated 1.9 million new cancer cases are predicted to be diagnosed in 2021 by the American Cancer Society (ACS) [16] Figure 1.

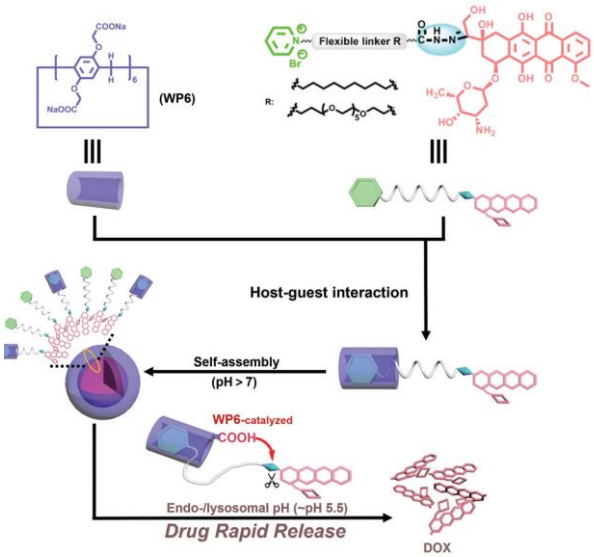

Figure 1. Formation of pH-responsive supramolecular prodrug nanoparticles based on carboxylate pillar[6]arene and doxorubicin-based prodrugs. Figure reproduced from ref. [17] with permission from American Chemical Society, copyright 2015.

Our scientific understanding of cancer diagnosis and treatment/therapy has significantly been an advent; however, the mortality rate is still high. Some widely known attributed reasons are i) Late detection due to poor selectivity and sensitivity of diagnosis; ii) Safety, efficacy, and toxicity issues with current anticancer therapeutics either due to broad mechanism of action or poor pharmacokinetics; iii) Problems of treatment regime monitoring drug release/delivery, distribution and treatment response; iv) Poor bioavailability of anticancer bioactive in the body; and v) multidrug resistance [18]. The advent of nanotechnology has remarkably improved cancer therapy, which is possible due to diverse nanoplatforms categories and anticancer drug delivery to the cancerous tissues. The unique attributes of nanocarriers/nanoplatforms include size, high surface-to-volume ratio, enhanced

solubility and stability, protection of anticancer bioactive from excretion or biodegradation, and enhanced physicochemical characteristics, and favorable pharmacokinetic and pharmacodynamics profiles of drugs [19-25]. An additional imaging modality of these nanoplatforms allows real-time and accurate therapeutic monitoring, early detection, and prediction of the treatment response outcomes [26, 27]. Currently studied nanoplatforms or nanomedicine for cancer therapy include i) Organic nanomedicine including polymeric nanoparticles (NPs), micelles, liposomes, nanoemulsions, and dendrimers; and ii) Inorganic-based nanomedicines such as silica nanoparticles (silica, gold, silver, iron oxide, etc.), carbon nanotubes, quantum dots, etc. [28-31]. The bridge between the nanomedicines mentioned above and its chemical foundation, known as supramolecular chemistry, has augmented a new arena now famously known as supramolecular nanomedicine, which has recently demonstrated promising prospects for diagnosis and treatment, and prevention of cancers and many other diseases [25]. The aim of supramolecular nanomedicine is to synthesize dynamics and adaptive supramolecular nanomedicine using readily available and cost-effective raw materials as carriers/building blocks within minimum organic modification work. Below, we discuss some supramolecular nanomedicine examples that have shown promising prospects as an alternative therapy.

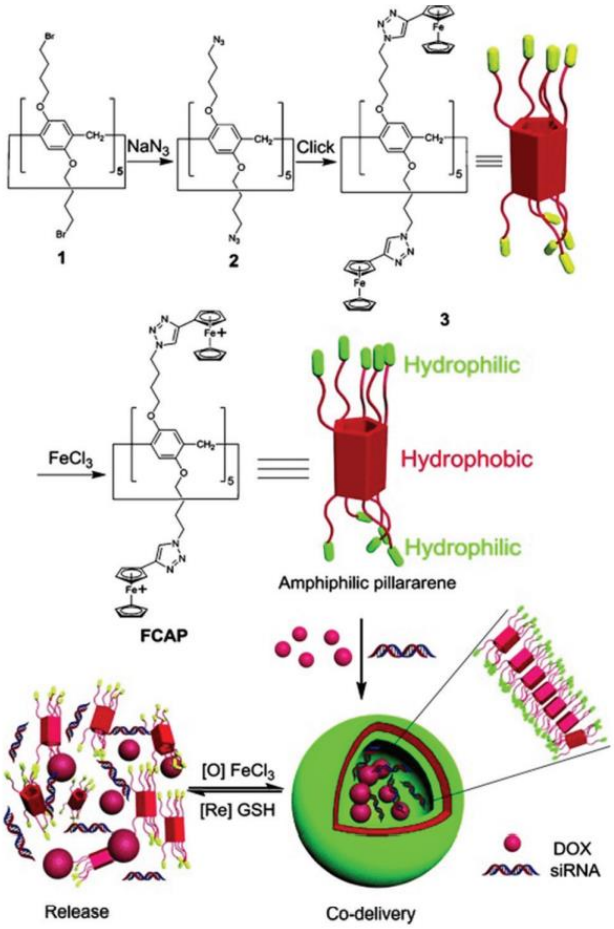

Figure 2. Synthesis of a ferrocenium-capped amphiphilic pillar[5]arene and redox responsive drug/siRNA cationic vesicles. Figure reproduced from (40) with permission, copyright 2014.

Dendrimers are radially symmetric 3D globular platforms with a high degree of multivalence and mono-dispersity. Dendrimers, as polymeric nanostructures, have the potential to transform conventional cancer diagnosis and treatment by overcoming the drawbacks of the conventional drug carriers [32]. The unique structural features enable dendrimers for

programmed chemical modification to conjugate, complex, or encapsulate therapeutic anticancer drugs or imaging moieties with desired bio-distribution and pharmacokinetics [32]. The dendrimer's radial core and branching structural arrangement creates a "void space" to accommodate/encapsulate anticancer drugs/agents by either hydrophobic/electrostatic interactions or covalent conjugation to the surface groups. Such void spaces also protect the drug's environment from enzymatic or cellular degradation, along with an added feature of programmable payload release [33, 34]. The multivalence feature of the dendrimer enables flexible functionalization with arrays of diverse ligands for multiple functions. Such unique and programmable features of dendrimers have been demonstrated to solve the problem of poor solubility of the current regime of anticancer drugs such as doxorubicin (DOX), methotrexate (MTX), paclitaxel (PTX), docetaxel (DTX), tamoxifen, camptothecin, and dimethoxycurcumin [16]. The most used dendrimers for cancer therapy include poly-L-lysine (PLL), poly(amidoamine) (PAMAM), carbosilane dendrimers, phosphorous dendrimers, and glycodendrimers [35-39].

Bismuth-based complexes have been explored to reduce the resistance and side effects of the most potent and widely used chemotherapy drug, cisplatin. Recent studies have demonstrated that bismuth compounds exhibit anticancer activity and antimicrobial activity [41]. The first one was a bismuth compound complex with 6-mercaptopurine. Some of the interesting ligands for bismuth ions currently under research are thiosemicarbazones, hydrazones, and dithiocarbamate compounds. More information about the bismuth-based nanoparticles possessing anticancer properties has been described by Kowalik *et al*. [41].

The supramolecular chemistry of calixarenes, pillararenes, cyclodextrins (CyDs), and several macrocyclic peptides and metallo-supramolecular compounds has been widely explored for applications including drug formulation and delivery, programmed drug release, and sensing/bioimaging for diagnostic and monitoring purposes.

Supramolecular prodrug nanoparticles were synthesized from pillar[6]arene and prodrug of doxorubicin (DOX) by flexible ethylene glycol chain through hydrazone bond cleavage. The carboxylate group of each pillar[6]arene chain was protonated to form acids that alter the hydrophilic/hydrophobic ratio and thereby catalyze hydrazone bond cleavage of the prodrug (Fig 2). This gives the site to the pH-sensitive response of the hydrazone bond based on the pillar[6]arene system and can be utilized for the controlled release of the prodrug [17].

Ferrocenyl-modified pillar[5]arene was synthesized by a click reaction between acetylenic ferrocene and azide capped pillar[5]arene, which on oxidation gives rise to ferrocenium capped amphiphilic pillar[5]arene (FCAP) [40], as shown in Figure 2. Later, the system self-assembled in an aqueous solution into cationic vesicles whereby negative-charged multidrug-resistant protein siRNA (MRP1siRNA) was loaded via electrostatic interactions. The system was found to be biocompatible and possessed high drug loading efficiency.

The cucurbit[n]urils (CBn) act as supramolecular hosts with their hydrophobic cavity to form inclusion bodies in the water. Amongst various cucurbiturils, CB[8] is one of the largest CBS, with the potential to accommodate two guest molecules in its cavity. A recent study by *Sherman et al*. demonstrated the CB[8] to act as an on/off system when fluorescent moieties are included. Briefly, they functionalized pyrene with an imidazolium group and further complexed it with viologen lipid, resulting in the formation of a ternary pyrene-viologen-CB[8] complex in aqueous solution, which undergoes self-assembly into vesicles. In *in vitro* studies using HeLa cells, these vesicles didn't show any cytotoxicity and enhanced fluorescence emission with a release of fluorescent pyrene, enabling an excellent system for *in vivo*

bioimaging of cancer cells and therapy progress [42, 43]. Huang *et al.* reported macrocyclic compounds based on pillararenes to synthesize cancer therapy's smart stimulus-responsive and low-toxicity structures. A thermoresponsive pillar[10]arene was synthesized which had two conformations in solution, each one responsive to a specific temperature and thus enabling the controlled release of small molecules [44]. They also designed a nanocontainer based on pillar[5]arene and its conjugation with hollow mesoporous silica nanoparticles. Pillar[5]arene was pH-sensitive macrocyclic compound, enabling storage and release of the drug and reducing toxicity [45]. Another macrocyclic compound, cyclodextrins, consists of a hydrophobic cavity formed by a cyclic arrangement of oligosaccharides comprising six to eight α-D-glucopyranoside units linked by α-1,4-glycosidic bonds. This structure of CyDs enables it to bind hydrophobically to various guest moieties, including resiquimod [46], gefitinib [47], docetaxel [48], MC11 peptide [49], miRNA-34a [50], and pDNA.

Another classical intervention of supramolecular nanomedicine in the classical anticancer drug is Bortezomib (BTZ). BTZ is a boronate proteasome inhibitor widely used for cancer therapy with an issue of efficacy due to its inhibition by dietary polyphenols because of the boronate-catechol complexation [51]. Changping *et al.* demonstrated the conjugation of BTZ with catechol-containing natural phenols via boronate ester bonds to allow the formation of dynamic drug amphiphiles with pH-dependent assembly/disassembly behaviors under different physiological conditions. They also incorporated iron (III) into the supramolecular BTZ-polyphenol complex via metal-phenolic coordination, which resulted in enhanced stability and bioimaging. The designed supramolecular consisted of BTZ, polyphenol, and ferric ion-induced apoptosis of cancerous cells and suppressed tumor growth in subcutaneous and bone tumor models [52]. Recently, a supramolecular nanomedicine designed by self-assembly of D-peptides was reported as a potential candidate for cancer therapy [53]. A D-peptide NMTP-5 with good stability and bioavailability was identified, which targeted NRP1 and MDM2 by displaying strong anticancer activity against SK-Hep-1 cells in vitro and in vivo without any toxicity. In comparison with small molecules, self-assembly of D-peptides has excellent advantages such as high selectivity, sensitivity, and safety with a striking application as anticancer therapeutics [54, 55].

3. Nanodevices for Imaging, Diagnosis, and Therapy

Nanodevices can sense a chemical or physical phenomenon in response to the internal or external stimulus and signal processing capabilities [56, 57]. Nanodevices platforms can execute various processes ranging from highly sensitive diagnosis to therapeutic implications. Presently, nanodevices are mostly applied in cancer diagnosis and cancer treatment due to their selectivity profile. Multifunctional nanodevices with this dual diagnostic and therapeutic function are called theranostic nanodevices. In addition, nanodevices deployment in cancer is sufficiently inspired by the enhanced permeability and retention effect (EPR) that leads to effective accumulation in cancerous tissues [53]. They have been successfully tested for facilitating the transport of the targeting agent to cancerous tissues [58], supporting the easy recovery of analyzed samples [59], and miniaturing the drug dosage form [60].

The topology and scientific basis of any nanomedicine depend on biobuilding functionalities involved in its structure. Likewise, the field of nanomedicine has been extended for the design and development of nanodevices for diagnostic and therapeutic applications. Some important parameters, as well as challenges for general nanodevice and its safety working, include (a) successful transport of the targeting agent to cancerous tissues [58] (b)

easy recovery of the analyzed samples out of the device for further analysis [59] (c) Reduced drug dosage [40].

The design of nanodevices for therapeutic applications is relied on the integration of three main components and their respective functions, i.e., sensing, processing, and operation. The sensing unit detects the targets inside the body; the processing unit modulates the properties and functions responding to internal or external stimuli. The operating components conduct the intended task in the body in a regulated manner [61].

In nanodevice fabrication, cyclodextrin [CyD] has been widely investigated for enzyme immobilization that uses supramolecular interactions. This immobilization can be done on the metallic surface with the help of cyclodextrin by modifying the metal surfaces and nanoparticles with sulfur-containing cyclodextrin derivatives [62]. Subsequently, the protein can then be immobilized on the modified surface when one or more of its bulky hydrophobic moieties are introduced into the CyD cavity. This immobilization can be stronger upon protein functionalization with cyclodextrin guests such as adamantane, which facilitates protein-cyclodextrin binding. This enzyme immobilization on metallic surfaces is essential for designing and fabricating biosensors and nanodevices. Examples are a biosensor based on monolayers of adamantane-modified cytochrome c [63] and a bienzymatic nanodevice comprising gold nanoparticles stabilized with CyD associated with catalase and superoxide dismutase modified with complementary host-guest residues [64].

Host-guest interaction between N,N-dimethylethylenediamine-functionalized β-CyD host, and the adamantane-modified dimethylamino-azobenzene [DMA-Azo-AD] guest gives rise to an amphiphilic supramolecular structure. The resulting structures show pH- as well as photoinduced emission due to the morphological transition. This complex has the ability to condense pDNA and is thereby used in *in vivo* bioimaging [65].

Stimuli-responsive or "smart" nanomaterials (nanodevices) have been intensively studied in the past 20 years to control matter at a smaller scale. In this pursuit, various kinds of DNA nanodevices with diverse sensing capabilities have been designed in recent decades. One such example is DNA biosensors, where the sensitive component is normally composed of a single ssDNA that facilitates the hybridization of complementary single-stranded molecules. Such nanodevices have the unique ability to detect and respond to a wide range of stimuli or signals [66].

In another study, the macrocyclic compound sulfonatocalix[4]arene with modifiable lower and upper rims and its metal coordinated state, i.e., Tb^{3+} ions, was proposed as a strategy for the facile fabrication of a multifunctional nanodevice. Intriguingly, this nanodevice can perform functions of fluorescent ratiometric molecular recognition as well as nanologic gate with two output channels [67].

The nano system's photophysical properties aid in imaging applications, which can be combined with its sensing capability for the design of biosensors. Light-triggered nanodevices can spatially and temporally control the therapeutic effects. The imaging capability is embedded into nanoscale drug carriers, which give anatomic, pharmacokinetic, and pharmacodynamic information. Nanomaterials such as "quantum dots," PEBBLESS (probes encapsulated by biologically localized embedding), and perfluorocarbon particles are used to improve fluorescent markers for diagnostic and screening purposes, largely replacing traditional methods color-based markers. Researchers have demonstrated that noble metal nanoparticles can be useful imaging tools due to their outstanding luminescence characteristics. One synthetic method was given by Li *et al.* to produce hydrophilic Upconversion

Nanophosphors (UCNPs) with high upconversion luminescence emission [68], by coating nano phosphors $NaYF_4$ with adamantane acetic acid that undergoes self-assembly with β-CyD. Chen, Kang *et al.* used a similar approach to functionalize a fluorene-based polymer with β-CyD to yield an amphiphilic PFC6CD capable of self-assembling into fluorescent nanoparticles [69]. Other examples of fluorescence-based theranostic nanodevices are Cyanine 5.5/doxorubicin(DOX) micelles and Cy 5.5/Paclitaxel-loaded micelles which offer good resolution and labeling ease [70].

Zairov and co-workers reported nanoparticles made of calix[4]arene tetra-diketone complexes with terbium and gadolinium coated with polystyrene sulfonate to obtain stable colloidal nanoparticles with tunable luminescence and magnetic relaxation properties [71]. In particular, the low toxicity of these systems paves the way for biomarker application.

In addition, supramolecular-derived nanoplatforms are also being tested for the controlled release of the drug. Polymeric micelles incorporating the anticancer drug oxaliplatin are formed by complexation between oxaliplatin and poly-(ethylene glycol)-β-poly(glutamic acid) [PEG-β-P(Glu)]. Release of oxaliplatin drug from the polymeric micelles occurs via ligand substitution of Pt(II) from carboxylate to Cl^- in a pH and [Cl^-] ion-dependent manner. Depending on pH and [Cl^-], drug-loaded micelles accelerate oxaliplatin release into the endosomal environment [72, 73]. It was found that oxaliplatin-loaded micelles overcome the drug resistance by bypassing the cytoplasmic detoxification mechanism activated in the drug-resistant cancer cells [61, 73]. There are now designed nanodevices that can release active drugs in acidic organelles, such as endosomes and lysosomes, avoiding P-glycoprotein-mediated drug efflux. This strategy helps in overcoming multidrug resistance in cancer cells by bypassing drug-inactivation pathways [74].

4. Other Implications

Some of the other supramolecular deployments in nanomedicine are for the application of self-healing. It uses poly(vinyl alcohol) chains containing viologen functionalities and rod-like cellulose nanocrystals, which lead to parallel hydrogen-bonded cellulose chains with excellent mechanical properties, bearing a naphthyl functionality, and cucurbit[*n*]urils to create supramolecular hydrogels [75].

Recently, using similar materials, nano-Saturn systems with a spherical molecule and a macrocyclic ring have been designed by researchers. Nano-Saturn systems comprise spherical molecules (fullerene, C60) and a macrocyclic ring (Anthracene Ring) and are proved to be a fascinating structural motif for researchers [76].

Scientists were able to manipulate the rotational direction of the flexible motor using a supramolecule. These surface-supported nanomechanical devices are made up of platinum-porphyrin-based supramolecular assembled dimers supported on Au (111) surfaces. Upon connecting the electric current to this molecular motor, the constructed motor spins in one direction. Intriguingly, the rotational direction of the motor can be reversed upon rearranging the motor parts and altering the operating conditions [77].

Macrocyclic and their nanocomposites have been largely considered alternatives for Pt-based oxygen reduction reaction (ORR) catalysts in fuel cell applications [78]. The nanocomposites of CoII (hexamethyltetraaza [14] and [16] annulenes)]HMTAA-14/16 macrocycles are successfully tested for oxygen reduction electrocatalysis. Researchers found that aromaticity/π-electron conjugation and macrocycle cavity strongly correlate with ORR activity in hexamethyltetraaza [14] and [16] annulenes. In another comparative study,

nanocomposite Co^{II}HMTAA-16@C showed good ORR activity compared to Co^{II}HMTAA-14@C in O_2-saturated KOH electrolyte [79].

5. Conclusions

The coupling of stimuli-sensitive macrocycles/supramolecules with diverse nanomaterial properties surely opens the door to a plethora of applications. Using these systems' non-covalent and covalent chemistry, many parameters have been disclosed for their appropriate implication in therapeutic and diagnostic results. Soon, we will surely witness many pioneering nanomedicines with macrocyclic compounds by controlling and manipulating their chemistry for critical healthcare applications. Nanofabrication of macrocyclic compounds has improved cancer therapy selectivity with remarkable checkpoints. Drug delivery, materials science, molecular imaging, molecular and cellular biology, and clinical oncology are among the sectors where medical nanodevices have already been applied. Beyond their present use, nanodevices can be deployed to organs and tissues with additional equipment to overcome biological barriers such as extravasation, tissue penetration, and cellular internalization at the target region. Thus, this mini-review hopefully tries to provide a plausible pool of appropriate information on nanofabricated macrocyclic systems and augments significant diagnostic and therapeutic applications.

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Conflicts of Interest

The authors declare no conflict of interest.

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