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Review article

Para-sulfonatocalix[n]arene-based biomaterials: Recent progress in pharmaceutical and biological applications

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ABSTRACT

The history, properties, and characteristics of para-sulfonato-calixarenes are described. On the one hand, the inherent antibacterial and antifungal properties against microorganisms, and on the other hand non-toxicity of these supramolecules toward human organs are analyzed. The resulting biocompatibility of para-sulfonato-calixarenes makes them potential candidates for diverse life sciences and pharmaceutical applications without significant side effects. The interactions with different drugs, the capability of drug encapsulation, delivery, and release, the formation of host-quest assemblies and inclusion complexation between para-sulfonato-calixarenes and drugs were also investigated in detail. Besides, their function in cancer treatment and their toxicity against different cancer cell lines were fully reviewed and summarized. Afterward, the capability of these macrocyclic compounds for biosensing of organic compounds, peptides and enzymes activity was highlighted. In this review, we also take a brief look at recent reports on the applications of para-sulfonato-calixarenes in fluorescence imaging and their usage as highly stable and bright probes for *in vivo* and *in vitro* imaging and sensing.

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1. Introduction

Calixarenes are macrocyclic supramolecules having different numbers of phenol ring linked by methylene bridges via ortho position [1,2]. The discovery of calixarenes happened during the investigations of Baeyer in 1872 when he studied the reaction of phenols and formaldehyde in the presence of strong acids [3]. The chemistry of calixarene further developed by Zinke and Ziegler about 70 years later [4]. Finally, Gutsche and co-workers introduced calixarenes thoroughly to the researchers by naming this supramolecule as "Calix[n]arene" where [n] refers to the number of aromatic rings [5]. The calixarenes can be functionalized on the upper rim or lower rim with different functional groups which can differ macrocycle properties such as solubility and degree of hydrophobicity [6]. The reactive hydroxyl groups on the lower rim are capable for the introduction of new functionality such as esters and ethers [7]. The upper rim, on the other hand, can be modified by halogenation [8], nitration [9], sulfonation [10] and others [11–14]. This versatility enables researchers to provide the different chemical and physical properties required onto a calixarene platform for the majority of intended applications. Because the synthesis of calixarenes requires toxic chemicals and organic solvents and their solubility in an aqueous media is very limited it dissuades researchers from exploring their biological potentials and properties of calixarene families. In order to diminish these limitations and restrictions, different functional groups such as carboxylates [15], phosphates [16–18] and ammonium [19] have been used to modify the water solubility of calixarene molecules.

The introduction of para-sulfonato-calixarene (p-SCX) derivatives by Shinkai has attracted the chemists' attention and changed the negative impression of the biological capabilities of the calixarene family [20]. According to this pioneering method, p-SCX was synthesized via electrophilic substitution in concentrated sulfuric acid leading to a pure crystalline product with high solubility in water [21]. Further investigations by other research groups demonstrated three general methods for the preparation of p-SCX including direct sulfonation, Ipso-sulfonation, and chlorosulfonation.

Up to now different biological functions and applications of p-SCX including drug delivery and drug inclusion capability [22,23], enzyme inhibition [24], cancer chemotherapy [25] and antimicrobial properties [26] have been investigated as well. There are some review papers that focused on the biological and biochemical properties of p-SCX in detail [27–30]. Herein, this review is dedicated to the bio-applications of p-SCX including drug-delivery systems, drug inclusion complexes, bio-sensing and bio-imaging properties of p-SCX-based products in the last decades (Fig. 1).

2. Physicochemical properties

The calix[n]arenes have the potential to be functionalized from both upper and lower rims with various types of compounds that have different functionality [31–34]. p-SCX has several properties such as easy synthesis with satisfactory yields, crystalline structure, and high stability under heat, light, and acidic conditions. The important aspect of the physicochemical properties of p-SCXs is their high solubility in aqueous media; hence, they attract scientists' attention in biological fields [35,36]. The p-SCXs including *p*-sulfonatocalix[4]arene (p-SCX4), *p*-sulfonatocalix[6]arene (p-SCX6), and *p*-sulfonatocalix[8]arene (p-SCX8) are three most studied water-soluble calixarenes. Their molecular weight and spectral data are summarized in Table 1. For instance, the chemical structure and configuration of p-SCX4 with hydrophobic cavity and hydrophilic sites are depicted in Fig. 2b. Due to the similarities in shape, the word "Calix" is taken from bowl-like"chalice" (Fig. 2c).

3. Antimicrobial and anticancer effects

The interior surface and sulfonate groups of p-SCX provide association sites for both hydrophobic and hydrophilic molecules, respectively. Due to the possessing of three-dimensional, flexible and π-electron-rich cavities, p-SCX are able to interact with numerous biomolecules via non-covalent interaction. Therefore, these materials can incorporate various active agents in their platforms for biomedical purposes [42,43].

p-SCXs have also shown interesting biological benefits by presenting substantial antiviral (such as HIV and Herpes), antibacterial (*Corynebacterium*), and antifungal activities (*Rosellinia necatrix* [R-8] and *Colletotrichum dematium* [C.d.8901]) [26,44–46]. The antitumoral effect of p-SCXs has been also studied on human K562 myelogenous leukemia cells in experimental photodynamic therapy [47]. The results revealed that the larger cavities would geometrically be more suited for a closer and stronger interaction with cells than the smaller ones. But the p-SCX8 had less effect than p-SCX6 due to the higher reactivity, larger size (more optimal for the cell), and higher aggregation capacity of p-SCX6. The post-irradiation of p-SCX6 treated cells induced over 60% mortality in the cell suspension, while p-SCX8 only approximately 30%. Therefore, p-SCX6 was more photoactive than p-SCX8. The mechanism of this cytotoxic effect was figured out via apoptotic activation via caspase system, membrane integrity disruption and mitochondrial damage.

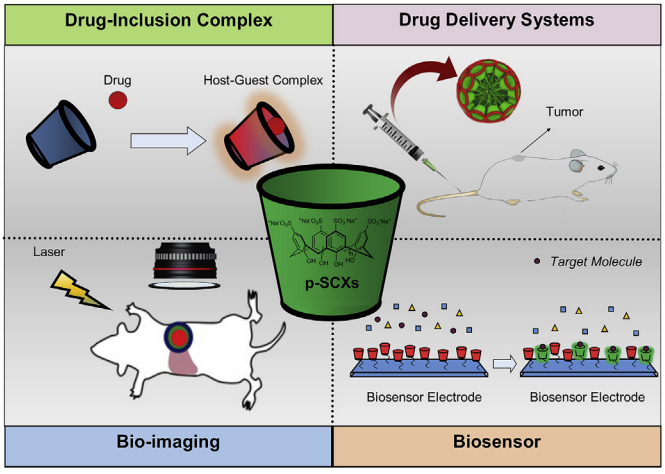


Fig. 1. Bio-applications of p-SCX in various fields (Drug-delivery systems - Drug inclusion complexes - Bio-sensor and Bio-imaging).

Table 1
Chemical formula, molecular weight, and spectral analysis (FTIR, ^{1}HNMR, and ^{13}CNMR) of p-SCX4, p-SCX6, and p-SCX8.

Compound	p-SCX4	p-SCX6	p-SCX8
Chemical Formula	$C_{28}H_{24}O_{16}S_4$	$C_{42}H_{36}O_{24}S_6$	$C_{52}H_{40}O_{32}S_8$
M_w (g mol^{-1})	744.72	1117.09	1433.34
FTIR (cm^{-1})	ν_{OH} 3440 ν_{SO3} 1180, 1040	ν_{OH} 3440 ν_{SO3} 1160, 1040	ν_{OH} 3460 ν_{SO3} 1190, 1050
^{1}H NMR (ppm)	($ArCH_2Ar$) 3.45, 4.25 (d, 8H) (ArH) 7.93 (s, 8H)	($ArCH_2Ar$) 4.32, (s, 12H) (ArH) 7.84 (s, 12H)	($ArCH_2Ar$) 4.11 (s, 16H) (ArH) 7.61 (s, 16H)
^{13}C NMR (ppm)	30.40, 126.44, 128.04, 135.80, 151.34	31.24, 126.39, 127.50, 138.14, 153.21	30.50 126.10, 128.00, 135.10, 153.30
References	[21,37]	[38,39]	[21,40]

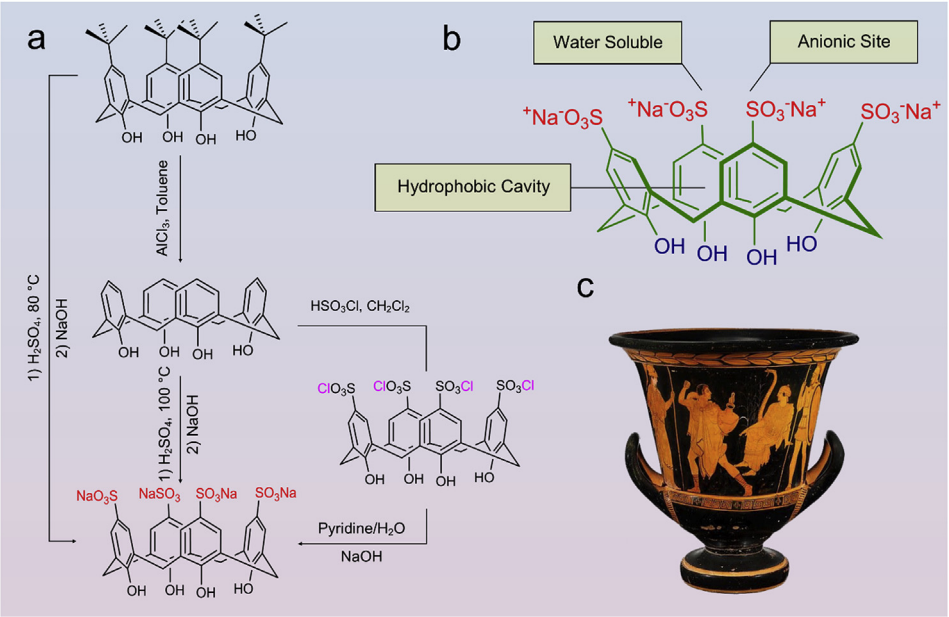


Fig. 2. (**a**) Synthetic routes to para-sulfunatocalix[4]arene (p-SCX4) – (**b**) Structure of p-SCX4 (This scheme structure has been inspired by Ref. [41]) – (**c**) The word calixarene is derived from Greek word "chalice" because this type of molecule resembles a vase.

4. Biocompatibility and cytotoxicity

p-SCX also shows significant biological properties such as bioavailability and oral absorption with excellent potential in biomedical applications and exhibits good biocompatibility and non-cytotoxicity [27,48]. *In-vitro* evaluation of p-SCXs revealed no hemolytic toxicity at concentrations up to 50 mM, which does not stimulate neutrophils and no nonspecific immune responses. In addition, the hemolysis assay results revealed that p-SCX4 and three of its lower rim mono-substituted derivatives (bearing ethoxy-carboxyl, ethoxy-amide, and ethoxy-amine functional groups) have effectively no hemolytic effects for concentrations up to 200 mM, however, p-SCX6 and p-SCX8 containing ethoxy-amine functional groups showed high hemolytic effects on human red blood cells with hemolysis of 12% and 29%, respectively [49].

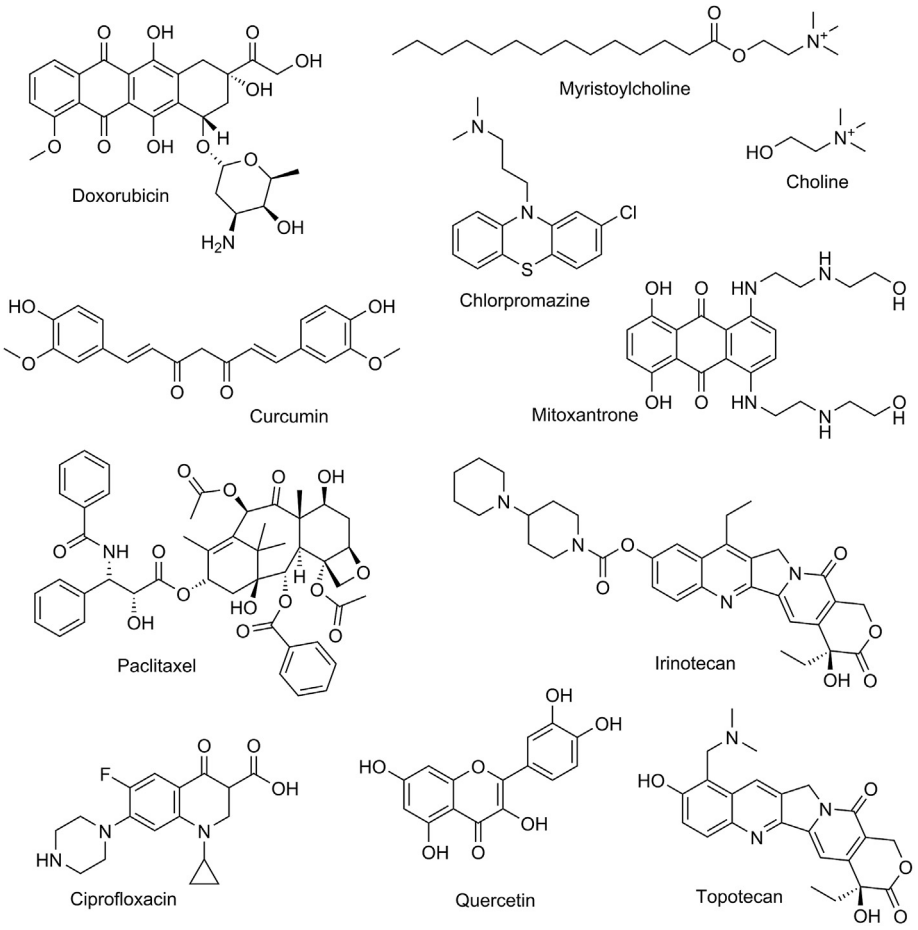
Also, all cytotoxicity results demonstrate that the three common water-soluble p-SCXs are not toxic [50]. However, after the *in-vivo* experiment in a mice model, p-SCX4 shows no significant acute toxicity with doses equivalent to 2–5 g in humans [51]. Finally, this derivative is immediately cleared via elimination in urine without gathering in the liver, spleen and is not observed in the brain therefore it is unlikely that p-SCX4 is metabolized [51].

5. Preparation and mechanism of p-SCX nanostructures

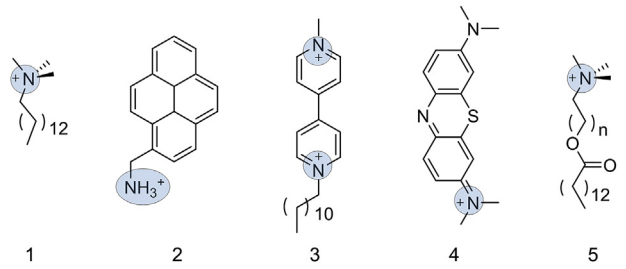
One of the main features of p-SCX derivatives is their ability to form host-guest complexes with cationic and neutral compounds due to the inherent anionic character of p-SCX. This quality enables them to emerge as one of the most important host receptors in supramolecular chemistry [52]. Broad diversity of chemical species is able to be hosted by p-SCXs, depending on the cavity size, shape and functional groups. Some cationic and neutral guests (drugs) used for the assembly of supramolecular amphiphiles are shown in Scheme 1.

Self-assembled nanostructures based on noncovalent interactions with p-SCX were also used and employed more frequently in the last few years. The micelles based on p-SCXs was reported by Basilio et al. for the first time [53]. Alternatively, some compounds can form vesicles in aqueous solution in the presence of a smaller and pre-organized calixarene and the surfactant (Scheme 2) [54]. For example, the complex of p-SCX4 and quaternized ammonium with an alkyl side chain (compound 1) formed nanoparticles with a diameter of around 120 nm after sonication. Such a system was characterized by many analytical techniques, including NMR, surface tension or dynamic light scattering. However, there are several host-guest complexes made from p-SCX and cationic species that display a bilayer-type arrangement in the solid-state, and their structure and composition remain unknown [55].

Overall, the introducing of polar and unipolar moieties on the calixarenes' upper or lower rims makes them suitable for self-assembling amphiphilic macrocycles including micelles, vesicles, liposomes, and other aggregates useful in the drug transportation.



Scheme 1. Cationic and neutral drug guests used for the assembly of supramolecular amphiphiles with p-SCX.



Scheme 2. Structures of some cationic surfactant used for the assembly of supramolecular amphiphiles.

The development of self-organizing synthetic amphiphilic calixarenes with the ability of inclusion and encapsulation allows complex hydrophobic molecules to be transported in a hydrophilic environment; this is crucial in biomedical applications [48].

6. Pharmaceutical and biomedical applications

The strong binding affinity of p-SCX towards drug molecules is driven by the synergistic effect of sulfonate groups besides the intrinsic cavities. The binding affinities depend on the size of the calixarene cavity, guest substituents, as well as pH. The host-quest complexes derived from p-SCXs and drugs are stabilized by hydrophobic effects and/or ion-dipole interactions, hydrogen bonding, and π-π stacking. Different factors including the degree of substitution of the calixarene platform, the size of the functional groups, and the charge on the molecules (calixarene and drug) have been affected on the formation of host-guest complexes [56]. Benefits of p-SCX over other classes of macrocycles include their ease of chemical functionalization when compared with cucurbit[n]urils, their high binding affinity to guest drugs compared with β-cyclodextrin, and their unique bowl shape which is distinct from the barrel shape of cucurbit[n]urils, the cone shape of β-cyclodextrin, and the tube shape of pillar[n] arenes (Table 2).

6.1. Nanoparticulate drug delivery

Some other macrocyclic receptors, including cyclodextrin and cucurbiturils, are widely used in drug delivery systems the same as calixarene. The presence of an internal cavity could maintain the guest molecules (anticancer drugs or antibiotics) and could prevent them from self-aggregation. These three macrocyclic species exhibit specific advantages in building water-soluble supramolecular architectures; more notably, they are all friendly to organisms. However, p-SCXs have unique self-assembly with high aggregate stability and compactness.

Among other forms of nanoparticulate formulations (micelles and liposomes), calixarene vesicles show remarkable advantages that can entrap and capture more drugs in their cavities [30]. The encapsulated drugs can be released in the responses to external stimuli such as temperature and enzyme by weakening interaction and cleaving bonds the drug-calixarenes, respectively [22].

Wang et al. [22], constructed self-assembled nano-

Table 2
Different types of drugs (anticancer and antibiotics) carried by diverse p-SCXs.

Type of p-SCX	Drug	Target cell line	*In-vivo*	Ref.
p-SCX4/self-assembled vesicles	Doxorubicin	NIH3T3 (Fibroblasts cells) HepG-2 (Human liver cancer cell line)	-	[22]
p-SCX4/hyperbranched polyglycerol and citric acid	Curcumin	–	–	[57]
p-SCX/binary vesicles	Myristoylcholine	LO2 (Normal human liver cell)	–	[58]
p-SCX/MSN	Choline	–	–	[59]
p-SCX5/1-pyrenemethylaminium	Doxorubicin	–	–	[62]
p-SCX4/multilamellar spherical micelles	Chlorpromazine	–	–	[63]
p-SCX4/tetrahexyloxy nanocapsules	Paclitaxel	HeLa (Human cervical cancer cell)	–	[65]
p-SCX4/tetrahexyl self-assembled micelles	Mitoxantrone Irinotecan	MCF-7 (Human breast cancer cells)	–	[66]
p-SCX8/trimethylammonium chloride diassembly	Ciprofloxacin	–	–	[67]
p-SCX4/MNPs-polyionic liquid	Doxorubicin Methotrexate	MCF-7 (Human breast cancer cells)	–	[69]
p-SCX4/MNPs-amine functionalized	Doxorubicin Methotrexate	MCF-7 (Human breast cancer cells)	–	[70]
p-SCX4/Gold NPs	Quercetin	SW-620 (Human colon cancer cell) DLD1 (Colorectal adenocarcinoma cell) 4T1 (Murine breast cancer cells)	*In-vivo*	[71]
p-SCX4/inclusion complex	Phenanthriplatin	–	–	[80]
p-SCX8/inclusion complex	Ciprofloxacin	–		[81]
p-SCX6 & p-SCX8/inclusion complex	3-phenyl-1H-[1]benzofuro[3,2-c]pyrazole	–	–	[82]
p-SCX4/inclusion complex	Topotecan	HT-29 (Human colon carcinoma cells)	–	[72]
p-SCX4 & p-SCX5/inclusion complex	Metformin Phenformin	–	–	[73]
p-SCX4/inclusion complex	Dinuclear platinum complex	A2780 (Human ovarian carcinoma cells)	–	[76]
p-SCX4/inclusion complex	Nedaplatin	–	–	[77]
p-SCX6/inclusion complex	Doxorubicin	HepG2 (Liver cancer cell line)	–	[78]

supramolecular vesicles using p-SCX4 and viologen as host and quest, respectively. The preparation of these vesicles was confirmed by different techniques and revealed that they are capable of responding to external stimuli such as temperature, host-guest inclusion, and redox condition. The loading and the release potential capability of these vesicles were investigated by using DOX as an anticancer drug model molecule. Considering the responsiveness of these carriers to temperature, the further drug release was successfully observed upon warming. It is quite interesting and meaningful that the viability of normal cells in the DOX-loaded vesicle group is much more than that in the DOX group. Whereas, the loaded vesicle group had more cytotoxic effects on HepG-2 human liver cancer cells.

Rafiee et al. [57], synthesized hyperbranched polymers (HPCs) consisting of polyglycerol and citric acid with p-SCX4 at the core (p-SCX4/HPCs). The fluorescence inspections revealed that these supramolecular tubes could encapsulate anticancer drugs, e.g. curcumin. Drug release investigation showed that the rate of release of encapsulated curcumin increases by changing the pH from 7.4 to 5, which is related to lower stabilities of supramolecular tubes in acidic conditions. Considering this feature, these self-assembled tubes could be promising candidates as smart drug carriers with the capability to release their load in the target tissues at the physiological condition.

One of the powerful strategies to controlled manner drug release is creating a stimuli-responsive property to the drug carrier. In this regard, enzyme-responsive drug carrier has several advantages in comparison with other responsive properties such as reducing the side effects of the therapeutic agents. Thus, nanocarriers can be modified with enzyme-labile linkages to provide on-demand enzyme-responsive drug release. Guo et al. [58], have constructed an enzyme responsive supramolecular binary vesicle based on the host-guest complexation between p-SCX4 (SC4A, Cmacrocyclic host) and myristoylcholine (enzyme-cleavable quest) with highly specific and efficient responsiveness to cholinesterase enzyme (Fig. 3). The sensitivity of myristoylcholine to cholinesterase enzyme leads to dissipation and disassembly of the binary vesicle and further controlled release of entrapped drug at a specific site where the target enzyme is located. Sun et al. [59], also reported a mesoporous silica nanoparticle (MSNs) surface-functionalized with choline moieties encircled by p-SCX4 with enzyme-labile bonds. The MSNs protect the drug molecules and transport them to target cells with good therapeutic efficacy and low adverse side effects. The MSNs were modified with cholines (the class of quaternary ammonium salts) and rhodamine B as a model drug was loaded. The host–guest complexation strategy was performed and the negatively charged p-SCX4 introduced to encircle the choline stalks on the surfaces of MSN nanoparticles. Two enzyme and pH cleavable sites on the cholines stalks regulate the release of the loaded model drug from MSNs. These sites also respond to the different types of external stimuli, i.e. adding a competitive binding agent.

Design and preparation of vesicles is an interesting topic for research in the fields of chemistry, biology, and materials science for their various applications in nanomedicine, *in vivo* imaging and drug delivery [60,61]. Regarding this issue, Wang et al. [62], reported the successful construction of nanoscale supramolecular binary vesicles based on host-guest complex formation between p-SCX5 and 1-pyrenemethylaminium (PMA). The resulting vesicle has thermal reversibility and can disintegrate as the temperature increases up to 35–40 °C. This temperature-responsive property makes the DOX-loaded vesicle as a potential drug cargo model for special substrates.

The small molecular antipsychotic drug chlorpromazine (CPZ) can self-assemble at a critical concentration, forming micelle-like structures. This character makes temperature- and concentration-dependent phase transitions. Therefore, CPZ utilized as an ideal model drug molecule for co-assembly. Qin and colleagues [63], directly assembled CPZ into nanostructures based on the non-covalent interactions, induced by p-SCX and its tetraheptyl ether functionalized form with high drug loading efficiencies via two different assembling models. The binary host-guest assemblies characterized and showed solid multilamellar spherical micelles. Additionally, trimethylated chitosan (TMC) as a cationic ligand can

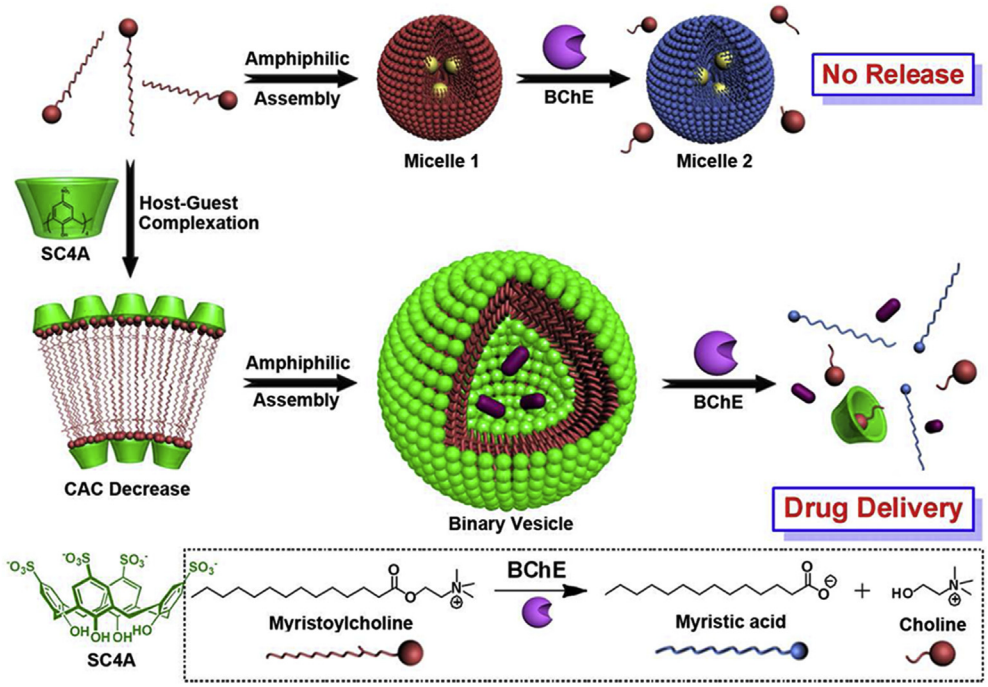


Fig. 3. Amphiphilic assemblies of myristoylcholine in the absence and presence of p-SCX4 (SC4A, enzyme-responsive drug delivery) (Reprint license number: Adapted with permission from Ref. [58] Copyright 2012 American Chemical Society).

facilitate the active transport of carrier transcytosis [64]. So, TMC-modified binary assemblies could be used as a drug carrier for delivery to the brain.

An amphiphilic tetrahexyloxy-p-SCX4 was successfully prepared by Chen and co-workers [65], and then self-assembled into supramolecular nanocapsules as a carrier for paclitaxel (PTX). The resulting formulation was optimized with high drug encapsulation efficacy and size of the carrier. These nano-capsules based on amphiphilic p-SCX described herein pave the way for the development of tumor-targeted drug delivery systems in the future. Wang et al. [66], proposed a novel supramolecular strategy "drug chaperone", in which mitoxantrone (MTZ) and Irinotecan (IRC) as the cationic drugs were directly encapsulated into a multifunctional and amphiphilic p-SCX4 with dual roles (fabricating self-containing nano-vehicle by co-assembling with cationic drug and of anchoring a targeting ligands in its cavity with host-guest recognition). The biotin−pyridinium (BtPy) and hyaluronic acid−pyridinium (HAPy) were used as the targeting ligands (Fig. 4). It is expected that modification with other functional moieties will provide the co-assembly with new functions, like imaging probes for diagnostics and PEGs for extending circulation time in blood. Additionally, the present supramolecular strategy of "drug chaperone" based on macrocyclic amphiphiles would open novel paths to build versatile drug delivery platforms with desired performance and further search for the optimum combination of anticancer drug or imaging probe and targeting ligand for diagnosis and therapeutics.

Amphoteric calix[8]arene with negatively charged upper rim (sulfonic acid) and positively charged lower rim (quaternized amine) was synthesized based on water-soluble p-SCX8 by Xue et al. [67]. Only the *in vitro* drug loading and release were studied. Ciprofloxacin (CIP), a well-known antimicrobial drug with an extensive antibacterial activity against both Gram-positive and Gram-negative strains was chosen as the model drug to study the loading and releasing behavior of the amphoteric p-SCX8. The pH-sensitive amphoteric p-SCX8 exhibited not only a good hydrophobic drug loading capacity but also a pH-triggered drug-releasing behavior.

Magnetic drug delivery system is one of the essential strategies for cancer diagnosis and treatment. Thus, Fe_3O_4 as the magnetic nanoparticle is commonly decorated by various compounds and polymers [68]. Rahimi et al. [69,70], developed two magnetic carriers with branched architecture based on p-SCX4, to act as the dual-drug carriers for the co-delivery of doxorubicin and methotrexate to MCF7 breast cancer cells. Regarding the biological studies, these carriers had good biocompatibility on human red blood cells and functional efficacy in killing cancer cells (in the drug-formulated form) with significant cellular internalization.

Yilmaz and his co-workers [71], developed a nanohybrid delivery platform with a non-covalently tunable surface. Firstly, quercetin as a model drug was encapsulated in the cavity of p-SCX4 to form inclusion complexes (p-SCX4-quercetin hosts-guest) and showed very high aqueous solubility property (62 000-fold) and excellent enhancement in the cytotoxicity effects on SW-620 colon cancer cells. A pH-stimuli responsive behavior was observed for quercetin from the platform in an acidic environment. Then, gold nanoparticles (GNPs) were decorated with p-SCX4-quercetin hosts-guest to accommodate noncovalent nanoparticles. The drug-loaded platform dramatically enhanced the cytotoxicity with more than 50-fold of the parent NPs in colon cancer and altered its cell membrane transport mode. An animal model was also performed on a mouse bearing 4T1 tumor and showed a reduction of tumor volume in mice treated with SCX4-quercetin/GNPs without apparent toxic effects. Further analysis of the tumor-derived RNA highlighted that treatment with quercetin-loaded nanoparticles altered the expression of 27 genes related to apoptosis (Fig. 5).

6.2. Drug-inclusion complexes

Recently, Wang et al. [72], reported the inclusion complex of p-SCX4 with antitumor drug topotecan (TPT) and their binding behaviors. Incorporation of TPT with p-SCX4 enhanced its water

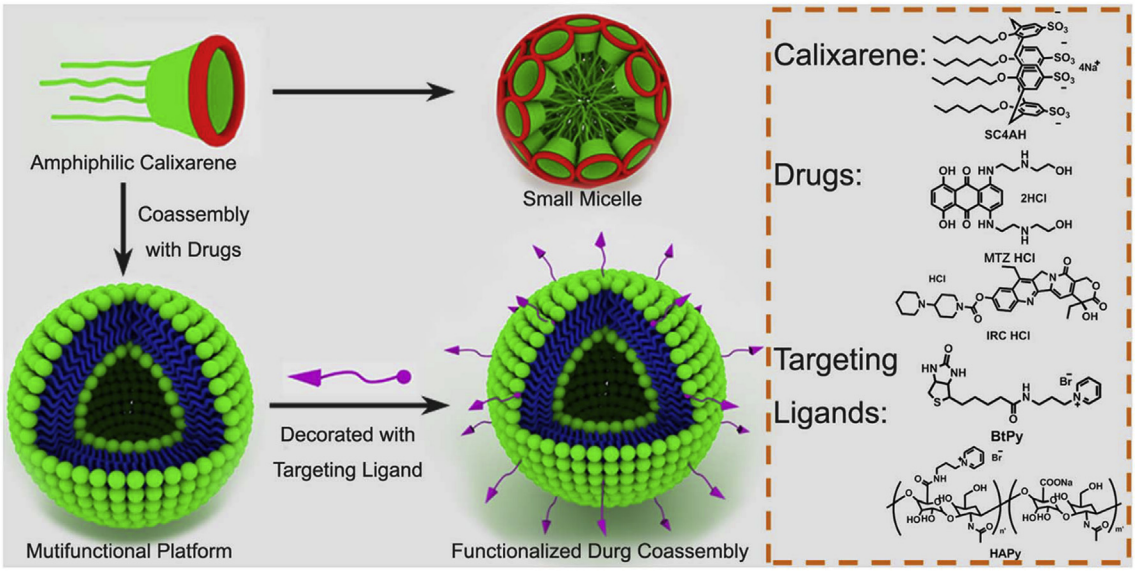


Fig. 4. Route for the Functionalization of "drug chaperone" strategy and chemical structures of anticancer drugs (IRC and MTZ), p-SCX4, and targeting ligands (HAPy and BtPy). (Reprint license number: Adapted with permission from Ref. [66] Copyright © 2015, Springer Nature).

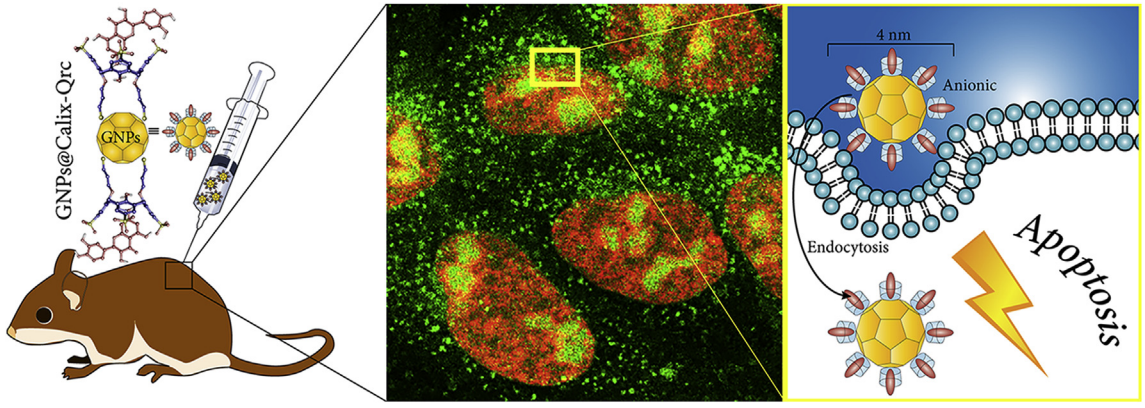


Fig. 5. Gold nanoparticles (GNPs) decorated with p-SCX4-quercetin hosts-guest to induce apoptotic effects on SW-620 (Reprint license number: Adapted with permission from Ref. [71] Copyright 2019 American Chemical Society). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

solubility. Regarding this complex stability and solubility in physiological conditions and its anti-proliferative activity against human colon carcinoma HT-29 cell lines, it could be used as a novel complex for further investigations. Moreover, the binding behaviors of p-SCX4 and p-SCX5 with metformin (MFM) and phenformin (PFM), two important biguanidiniums molecules for the treatment of hyperglycemia in patients with noninsulin-dependent diabetes mellitus, were also studied to understand the inclusion phenomena, recognition mechanism, and thermodynamic origins of SCX more systematically and comprehensively [73].

Platinum-based anticancer drugs formed host-guest complexes and provided no barrier to drug degradation [74,75]. Brown et al. [76], used three dinuclear platinum for the formation of complexes (transplatin) with the bowl-shaped macrocycle p-SCX4 with host-guest interaction. Binding of the macrocycle to the metal complexes slightly changes their cytotoxicity in the human ovarian carcinoma cell line A2780, while significantly affects in the cisplatin-resistant cell line A2780cp70. The results of this work provide important knowledge on the nature of the host-guest complex formation of flexible dinuclear platinum complexes and can now be used to develop more advanced drug delivery vehicles where p-SCX4 can be conjugated with tumor-targeting groups to deliver multinuclear platinum drugs in chemotherapy better. In another study, Fahmy and colleagues [77], presented a complexation between nedaplatin (a second-generation antineoplastic drug) and p-SCX4 with good biocompatibility and relatively low hemolytic toxicity for potential cancer therapy.

Ostos and co-workers [78], demonstrated that p-SCX6 could act as a good host to encapsulate DOX as an inclusion complex and transport of the antibiotic towards the polynucleotide. The cytotoxicity results revealed that the presence of p-SCX6 in the solution partially reduces the side effects that DOX provokes in the human organism. Only in the case of the liver cancer cell line (HepG2), the concentration of the complex used must be low to decrease such side effects.

Molecular modeling and density functional theory (DFT) calculations are used to inspect molecular interactions and evaluation of bond properties such as type, strength, length, and angle between host and guest molecules [79]. Kahwajy et al. [80], examined the binding of phenanthriplatin (PHT) anticancer drug to p-SCX by ^{1}H NMR spectrophotometry and molecular modeling. The binding of anticancer drugs to this macrocycle lead to the formation of a 2:1

host-guest inclusion complex of the calixarene platform with PHT through each arm of the PHT ligand and calixarene cavity. According to this investigation, the resultant capsule-like structure could be used as a drug carrier for phenanthriplatin and reach it to the target tissue. Moreover, Moussa et al. [81], investigated the formation of host-guest inclusion complexes of p-SCX8 with the antibiotic drugs isoniazid and CIP which are stabilized by hydrophobic effects, hydrogen bonding, electrostatics, and π-π stacking. The interaction of drug molecules with p-SCX8 and the formation of 1:1 host-guest complexes of p-SCX8 with isoniazid and CIP was inspected by ^{1}H NMR spectrometry and fluorescence spectrophotometry which was further simulated by molecular modeling for ease of interpretation of these spectra (Fig. 6). The special configuration of the p-SCX8 skeleton with two pseudo-cavities enables it to encapsulate two different types of drugs in its cavities simultaneously and deliver it to target tissues. Besides, Galindo-Murillo and coworkers [82] examined the suitability of p-SCXs as a drug delivery agent for 3-phenyl-1H-[1]benzofuro[3,2-c]pyrazole (a promising new tyrosine kinase inhibitor drug). DFT theoretical calculations and results showed that p-SCXs with coordinating $-SO_3H$, hydrogen bond donor, substituents at the upper rim yield the most stable complexes over the less coordinating ethoxy groups. p-SCX6 and 8 are the most promising drug carriers due to their capacity for wrapping around the guest drug and enhance the weak interactions between aromatic groups in both molecules. Additionally, the large calixarenes allow drugs to interact with lower rim substituents ($-SO_3^-$) as well as the ones located at the upper rim, increasing the number of coordinating sites.

6.3. Biosensor

Development of applicable sensor devices for the early detection of diseases and continuous population screening is needed for healthcare. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are the actual techniques for diagnostic fields which are costly and not suitable for constant monitoring [83]. Synthetic supramolecular receptors offer new candidates for the development of specific, selective and cheap sensor devices for biological sensing of specific target molecules in complex mixtures. The essential challenges toward developing such devices are the precise transfer of the molecular recognition events at the solid-liquid interface and its transduction into a readable signal.

Colorimetric investigation of aromatic amines was explored by Han et al. [84], on diamine aromatic compounds (including o-diaminobenzene, o-nitroaniline, m-nitroaniline, p-nitroaniline, o-chloroaniline, p-chloroaniline, o-toluidine, m toluidine, p-toluidine, and aniline). In this regard, the surface of gold nanoparticles (AuNPs) was decorated with p-SCX (p-SCX/AuNPs) to employ as colorimetric probes. In the probing process, some bridges were formed between NPs and diamine compounds via electrostatic interaction and host-guest interaction to induce aggregation of the nanoparticles and the broadening with red-shifts of bands on the surface plasmon absorption was observed. Overall, this kind of probes can detect drugs in aqueous solutions.

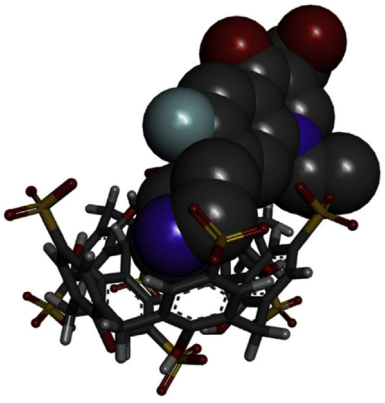


Fig. 6. (a) A molecular model generated by Autodock 4.2 showing the proposed structure of p-SCX with CIP (1:1 host-guest inclusion complex) [81]. (Reprint license number: 4710040545061).

A thionine mediated p-SCX4 capped AuNPs was prepared and used for sensitive detection of acetylcholinesterase (AChE) activity by signal amplification occurring on the electrode interface. This electrode has the capability of taking the assay of a neurological disease marker [85]. The designed gold chip has several advantages in comparison to the conventional colorimetric and electrochemical assays (Fig. 7). The performance of this strategy is greatly improved and the detection limit can be lowered to 2.4 pU mL^{-1} making it possible to detect the target marker with high sensitivity and excellent capability for the development of disease diagnosis and therapy in the future.

Guo and co-workers [86], produced host-guest complexes between p-SCX and the cationic aromatic fluorescent dye lucigenin (LCG) and characterized them by optical spectroscopic techniques, NMR, cyclic voltammetry, isothermal titration calorimetry, and X-ray crystallography to sense acetylcholine and choline with low micromolar sensitivity in combination with the enzymes acetylcholinesterase and/or choline oxidase. Additionally, the activity of both mentioned enzymes can be followed by these highly sensitive reporter pairs, as well as other enzymes such as amino acid decarboxylases. This enables inhibitor and activator screening by the supramolecular tandem assay methodology, the usefulness of which we have augmented herein by an enzyme -coupled variant, and verified by the observed inhibition exhibited by Alzheimer's drugs.

Dye displacement assays which can be carried out in physiological solution attracts considerable attention especially the water-soluble calixarene derivatives such as p-SCX. Hof and co-workers [87], presented a dye-displacement sensor for *in-vitro* detection of cationic peptides. In this regard, they mixed and matched the toolkit of readily available dyes and calixarene host molecules. Also, the developed toolkit can be used for the detection of different types of anionic peptides or proteins. The authors claimed that even though this approach is limited to *in-vitro* analysis with the higher analytic concentration requirements (in comparison to antibodies), it is cheaper than other biological assays with a promising application for host-guest recognition.

6.4. Bio-imaging

Nanocomposites including magnetic and luminescent functionalities were synthesized and reported for biological applications, such as MRI contrast, drug delivery agents, and cell labeling. Fang et al. [88], reported a novel protocol to use magnetite (Fe_3O_4) nanoparticles stabilized with p-SCX6, to self-assemble doped $LaPO_4$ nanorods into three-dimensional "koosh nano-balls" as a bifunctional luminescent ferro-fluidic system.

The only approved material used as a near-infrared (NIR) fluorescent dye in biomedical applications is Indocyanine green (ICG) [89]. It has several drawbacks such as low aqueous stability and fluorescence quantum yield, photo-degradation with diminishing fluorescence property. Therefore, these drawbacks lead to the limitation of ICG for using *in-vitro* and *in-vivo* bio-imaging. Jin and co-workers [90], provided nano-sized micelles based on p-SCX4-6 incorporated ICG with significant stability and fluorescent

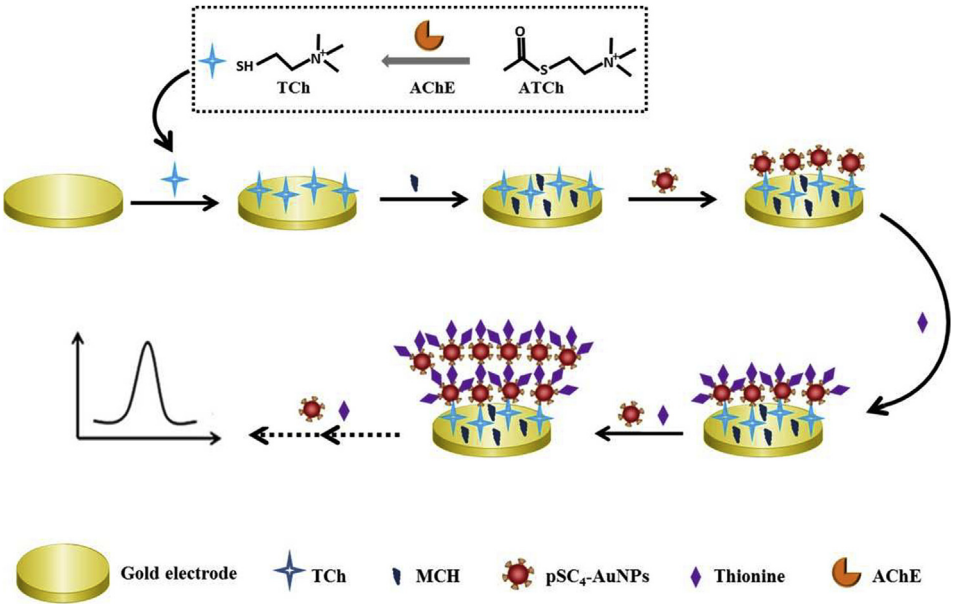


Fig. 7. Schematic of thionine mediated p-SCX4 capped AuNPs multilayers signal amplification on the electrode surface [85]. (Reprint license number: 4710030777146).

brightness in aqueous solution for NIR fluorescence imaging. The results showed non-invasive NIR fluorescence imaging of the liver and lymph system in mice and nude mice bearing human breast tumors. The ICG/p-SCX4 micelle system acts as a highly stable and bright probe for NIR fluorescence imaging *in-vitro* and *in-vivo*.

Oguz et al. [46], synthesized a water-soluble fluorescent calix[4] arenes and inspected its application in living cell imaging for Hg^{2+} detection at a low concentration. The fluorescent study showed that both water-soluble ligands were Hg^{2+} selective and follow the photo-induced electron transfer (PET) process. The interactions between ligands and Hg^{2+} were also demonstrated in living cells, SW-620, using Fluorescent Cell Imager. While ligands alone show fluorescent properties, they lost their action with the presence of Hg^{2+} in SW-620 cells.

7. Pre-clinical and clinical evaluation

So far, there have been reported many studies on p-SCX *in vitro* evaluation, however, only a chemotherapeutic alkylating agent was done *in vivo* for glioblastoma (GBM) which named Temozolomide (TMZ). It is a common and aggressive primary brain tumor in adults and has poor stability with unfavorable pharmacokinetic profile limitations in clinical applications [91]. There is an unmet need to tailor the therapeutic window of TMZ, either through complex derivatization or by utilizing pharmaceutical excipients. Renziehause et al. [92], encapsulated TMZ in a p-SCX4 nanocapsule for enhancing stability and aqueous solubility and evaluated this novel complex according to FDA (Food and Drug Administration) and EMA (European Medicines Agency) guidelines. Further exploration for the stability profile of complex was conducted in mice model via LC-MS/MS plasma stability assays. The inclusion complex (TMZ/p-SCX) was compared to that of unbound TMZ in GBM cell lines and patient-derived primary cells with known O6-methylguanine-DNA methyltransferase (MGMT) expression status and *in-vivo* in an intracranial U87 xenograft mouse model. All conditions tested showed significantly stability enhancement of TMZ in encapsulation form. The results of *in-vivo* study were also revealed that the native TMZ was rapidly degraded in mouse plasma, whereas the stability of the inclusion complex was enhanced 3-fold with increased therapeutic efficacy in an orthotropic model. This novel formulation based on p-SCX has clinical advantages serving as a cost-effective and highly efficient treatment. It could be useful for GBM patients with further “pre-clinical” and “clinical” capability.

Summary and outlook

Although it is a long time since calixarenes have been discovered, their applications in biomedicine are in the initial steps. Their exceptional biological features such as biocompatibility and non-toxicity make them ideal candidates for biomedical applications. Modification of calixarenes with various functional groups in the upper rim and lower rim gives them distinct characteristics for different purposes. Due to their geometric structure, various drugs including anticancer agents and antimicrobial compounds can be incorporated into the cavity of these macrocycles and enhance their therapeutic significance. Furthermore, pH-triggered drug release can be achieved by special modifications on their structure that release the chemotherapeutic agents in the tumor microenvironment with acidic pH. In addition to drug delivery systems, they have also used in other biomedical applications such as biosensors and bio-imaging with ideal characteristics. As mentioned above, the utilization of p-sulfonato-calixarenes in biomedical purposes is in its early stages and more efforts and investigations are needed to enter clinical applications.

Declaration of competing interest

The authors report no conflicts of interest.

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