J Incl Phenom Macrocycl Chem (2012) 73:1–15
DOI 10.1007/s10847-011-0062-z

REVIEW ARTICLE

Applications of calixarene nano-baskets in pharmacology

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Received: 29 July 2011 / Accepted: 11 October 2011 / Published online: 16 November 2011

Abstract Calixarene nano-baskets enable to encapsulate the guest drugs and show different biological activities. This review deals with the behavior of calixarene-based drugs and illustrates their potentials in the pharmacological sciences. The role of calixarene's scaffolds and substitutions in aspects of anti-cancer, anti-mycobacterial, anti-proliferativity, catalytic and inhibitory activities as well as solubility control, drug analysis, drug purification, drug supports and structural studies is reviewed.

Keywords Nano-baskets · Calixarene · Prodrug · Pharmacology

Introduction

Macrocyclic compounds of phenolic units linked by methylene groups at the 2,6-positions, named calixarenes or nanobasket. They present some of the requirements to serve as platforms for the nano-material [1], analytical [2], biological, [3–5] and industrial [6] investigations (using gas chromatograph, Teif Gostar Faraz Co.). Calixarenes have been subjected to extensive researches in development of extractants [7, 8], transporters [9–12], stationary phases [13], electrode ionophores, optical sensors and medical researches over the past decades. In the nineteenth century, Baeyer [14] synthesized them via the reaction of formaldehyde with *p*-substituted phenols in basic or acidic environment. In the 1940s, Zinke and Ziegler [15] discovered that the products possessed cyclic tetrameric structures. In 1975, Gutsche [16] introduced the presently accepted name of calixarene.

Calixarene nano-baskets have considered as the third applied host molecules after cyclodextrins and crown ethers [17, 18] and are used in various applications including chromatography, purification, enzyme mimics, ion channels, self-assembling monolayers, transport across membranes, catalysis, ion selective electrodes, and phase transfer [19]. The poor solubility of most calixarenes precludes their applications in the applications carry out in the aqueous media [20]. Calixarenes present well-defined conformational properties and cavities with molecular dimensions that enable to encapsulate guest drugs. They have antibacterial, antiviral, antifungal, and anticancer activities (including HIV as target). Cornforth et al. [21] in 1955 reported the first medical application of calixarene derivative (Macrocyclon). Rodik et al. [22] discussed antiviral, antithrombotic, bactericidal, antituberculosis, anticancer activity as well as toxicity, membranotropic properties and specific protein complexation of modified calixarenes in a review paper. Fatima et al. [23] provided an overview and discussed the importance of calixarenes for drugs development.

More discussions about the calixarene scaffolds and their derivatives have been reported as review papers, including calixcrowns [24–26], thiacalixarenes [27–29], lower-rim substituted calixarenes [30] and other literatures [31–33].

In this short review paper, the applications of calixarenes in pharmacological applications are reviewed. The paper focuses on the their role in aspects of anti-cancer, anti-mycobacterial, anti-proliferativity, catalytic and inhibitory activities as well as solubility control, drug analysis, drug purification, drug supports and structural studies. They followed by graphical representations about the scaffolds and interactions.

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Anti-cancer activity

Base upon the reports of Anthony et al. [34], cancers are one of the main causes of mortality and are responsible for more than 30% of deaths in France. One-third of cancers exhibit resistance to multiple drugs (multiple drug resistant) and this is a dramatic problem from not only the therapeutic point of view but also from a psychological point of view for patients. Moreover, some compounds used for treating cancers because secondary effects such as a certain degree of toxicity. Furthermore, cancer treatments using such compounds represent an economic problem. Therefore, the need for compounds has improved the properties for treating cancer. In this regards, specific calixarenes exhibit anticancer activity and make it possible to resolve, in part in or whole, the problems mentioned above. Anthony et al. [34] patented a novel calixarene derivative as anticancer agent and illustrated the anticancer effect of calix[4]arene dihydrophosphonic acid on different tumor cells in culture, in particular fibrosarcoma, melanoma and leukemic cells. Moreover, they compared the anticancer effect of calix[4]arene dihydrophosphonic acid (C4diP), *para*-octanoyl-calyx[4]arene dihydroxyphosphonic acid and *p-tert*-Butylcalix[4]arene dihydroxyphosphonic acid on cell cultures. Figure 1 shows the chemical structures of four calix[4]arene dihydrophosphonic derivatives were used by Anthony et al. [34]. They presented the effect of C4diP on a culture of chemosensitive human acute lymphoblastic leukemic cells and the results revealed a mortality of 50% for a mean concentration of 7.33 μM of C4diP with a standard deviation of 3.06.

The contribution of chloride channels to the pathology of several diseases as well as the physiology of various cell types is well known. Owing to unavailability of high affinity ligands, the chloride channels were studied by *para*-sulfonated calixarenes, which are potent blockers of outwardly rectifying chloride channel with long block times and subnanomolar inhibition constants. Singh et al. [35] used both ion channel kinetic analysis and computational chemical methods to investigate such channels. The kinetic analysis, which is determined from critical-closed-time plots, emphasizes on the estimation of the block-time constant. The computational chemical methods are used to deduce the features of the disulfonic stilbene molecule necessary for potent blockade of outwardly rectifying chloride channel (ORCC). Base upon those methods, they found that *para*-sulfonated calixarenes were potent blockers of ORCC with subnanomolar inhibition constants and exceptionally long block times. Other calixarene derivatives were also assessed to investigate those chloride channels [36, 37]. Figure 2 depicts some of the calixarenic structures, which were synthesized and studied by Atwood et al. [36].

Harris [38] described acylic phenyl-formaldehyde oligomers, calixarenes or oxacalixarenes, cyclotriveratrylene derivatives, cyclic tetrameric resorcinol-aldehyde derivatives known as Hogberg compounds, which have anti-HIV, anti-cancer and anti-viral activity. Krishnan and Lohrmann

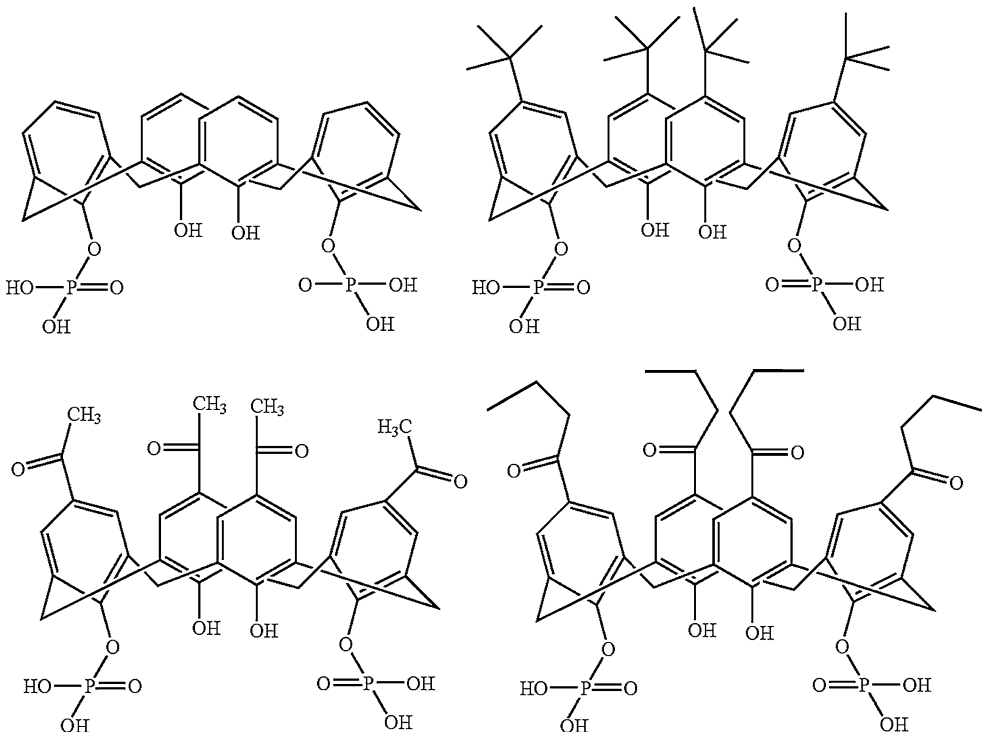


Fig. 1 The chemical structure of calix[4]arene dihydrophosphonic derivatives in the Anthony et al. [34] patent

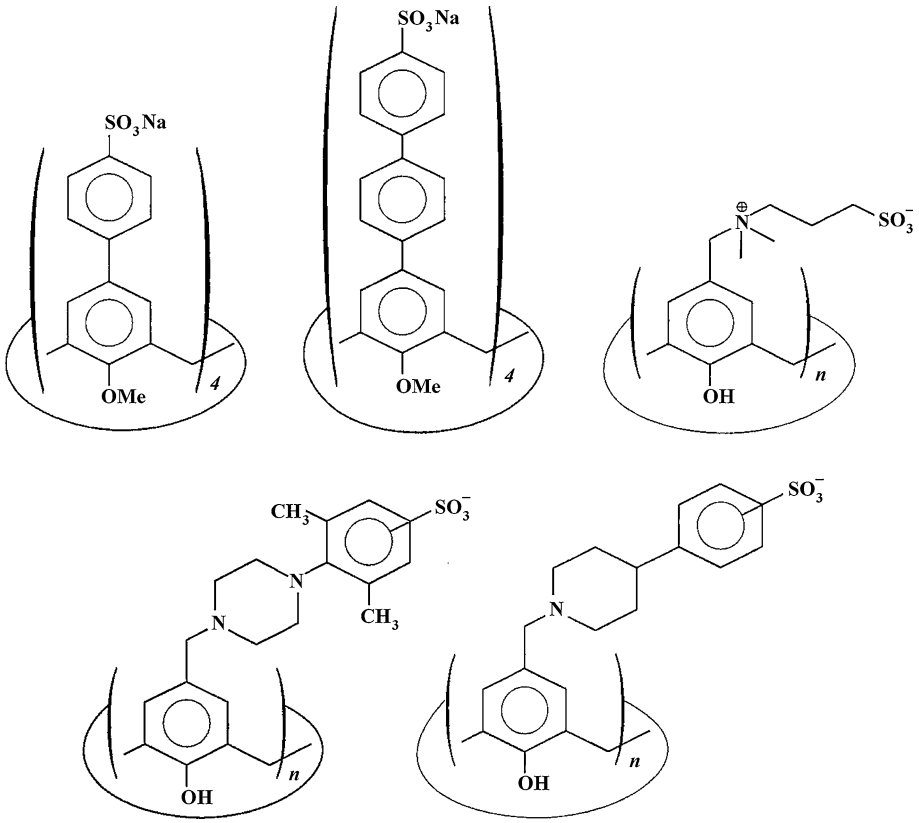


Fig. 2 The chemical structure of some synthesized calixarenes by Atwood et al. [36]

[39] described calixarene conjugates for diagnostic imaging agents and tomography.

Photodynamic therapy is a novel treatment for cancer and even for certain noncancerous diseases, which are generally characterized by overgrowth of abnormal or unwanted cells. This therapy is base upon the retention of photosensitizers in tumor cells and activation of them (within the tumor) through irradiation with light of appropriate wavelength. The destructive potential of photosensitizers depends mainly on the generation of reactive oxygen species produced by the light activated photosensitizers. Neagu et al. [40] studied the antitumoral effect of *p*-sulfonato-calixarenes [6, 8] human K562 myelogenous leukemia cell line in experimental photodynamic therapy. They expected that the larger cavities would geometrically be more suited for a closer and stronger interaction than the smaller ones. But the *p*-sulfonato-calix[8]arene had less effect than calix[6]arene due to the higher reactivity of calix[6], the size of *p*-sulfonato-calix[6]arene (more optimal for the cell), and a higher aggregation capacity. According to Fig. 3, the post-irradiation of calix[6]arene loaded cells induced over 60% mortality in the cell suspension, while calix[8]arene only approximately 30%. The cells were irradiated with Hg lamp for 30 min at fluence rate of 100 mW/cm^2. Therefore, they showed that *p*-sulfonato-calix[6]arene was more photoactive than *p*-sulfonato-calix[8]arene.

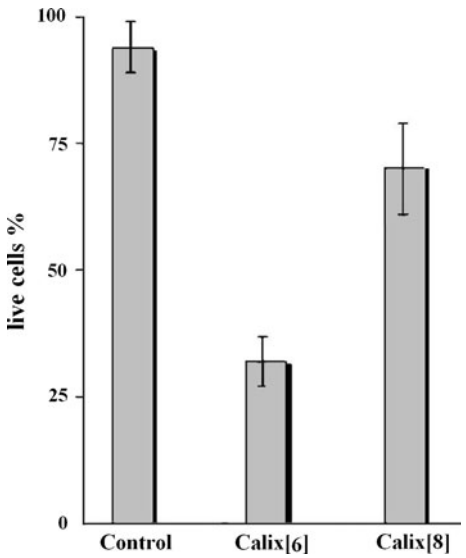


Fig. 3 Illustration of the mean ± SD of six individual experiments with triplicate sample for post-irradiation total cell counts and live cell percentage of 62 loaded with 1 and 20 μg mL^{-1} calix[6]- and calix[8]arenes, respectively [40]

Bezouska et al. [41] investigated the attractive role of thiacalix[4]arene and carboxylated calixarenes (Fig. 4) for protection of leukocyte killer cells in combined animal tumor therapies. They assessed three calixarene scaffold and revealed that thiacalix[4]arene had the highest affinity

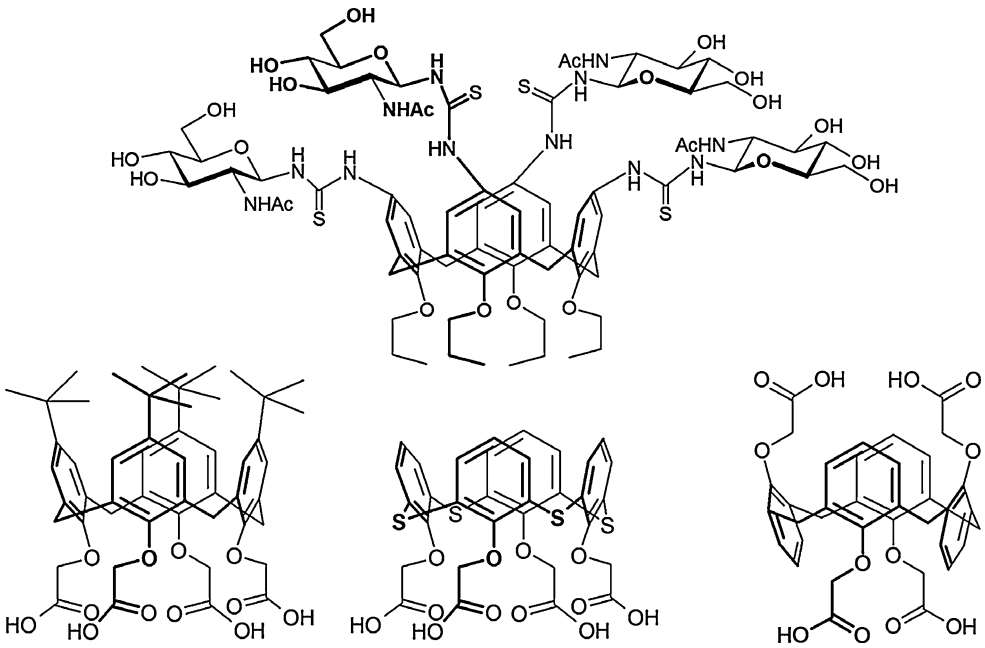


Fig. 4 The chemical structure of carboxylated thiacalix[4]arene derivative was used for protection of leukocyte [41]

for CD69 leukocyte membrane receptor. They proved that carboxylated calixarenes were effective at protection of CD69 lymphocytes from apoptosis triggered by a multivalent ligand or antibody.

One major problem in conventional anti-cancer therapy lies in the effectively close similarity between the anti-cancer compounds, which renders them susceptible to efflux by the ABC transporters (multi-drug resistance). The calixarenes are of variable size and functionality as well as three-dimensional and hence are not associated with the structures of typical anti-cancer drugs. They also are designed to extract membrane proteins (e.g., ABC transporters) specifically from cell membranes and thus are vectorised against chemotherapeutically resistant cancers. These drugs should be modified so that they can carry a toxic payload to the cancer cell. However, the calixarene molecule itself should not be toxic. Relevant studies, seek to confirm that the calixarenes are non-toxic, are discussed latter.

Anti-mycobacterial and anti-proliferativity

Tuberculosis is the leading cause of death among infectious diseases, accounting for more than two million deaths annually and its incidence is increasing owing to the resurgence of drug-resistant strains of mycobacterium tuberculosis. Calixarenes are able to modify its growth and macrocyclon is effective in controlling its infections. Colston et al. [42] revealed that macrocyclons (Fig. 5) were effective in athymic and they synthesized a number of structurally related calixarenes expressing significant anti-mycobacterial activity. They showed that macrocyclon significantly affected mycobacterial growth in murine macrophages by a mechanism involving L-arginine metabolism and inducible nitric oxide synthase (iNOS) activity. They also described the antimycobacterial activity of calixarenes bearing *t*-octyl group at the upper rim or polymeric polyethylene glycol (PEG) chain lengths at the lower rim. They demonstrated that the PEG chain of six repeat units was sufficient to produce calixarenes with high antimycobacterial activities, while a chain extension to PEG-12 offered no significant advantages. Finally, they suggested that ring cavity size may be important when there is no functionalization at the lower rim.

Other studies about synthesis of calixarenes with anti-mycobacterial activity have been reported [21, 43].

Rouge et al. [44] used calix[4]arenes bearing alkyl ester and alkyl acid moieties at the lower rim, Pires et al. [45] used calix[4]arenes bearing two hydrazide function or ornithine, glutamic/aspartic acid groups at the lower rim, and Latxague et al. [46] used calix[4]arenes bearing diamino-tetraesters, diamino-tetraalcohols, diamino-tetraacid and tetraaryloxypentoxy groups at the lower rim. They compared their calixarene derivatives with 4-3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl-benzoic acid as a new oral chelator. The antiproliferative effect of those compounds, which was inhibited by intracellular iron level, were studied and the results revealed that the antiproliferative effect was due to their cytotoxicity. They show that novel substituted calix[4]arenes open the way to novel valuable medicinal chemistry scaffolding. Krenek et al. [47] linked the calixarenes substituted with 2-acetamido-2-deoxy-beta-D-glucopyranose by a thiourea spacer and

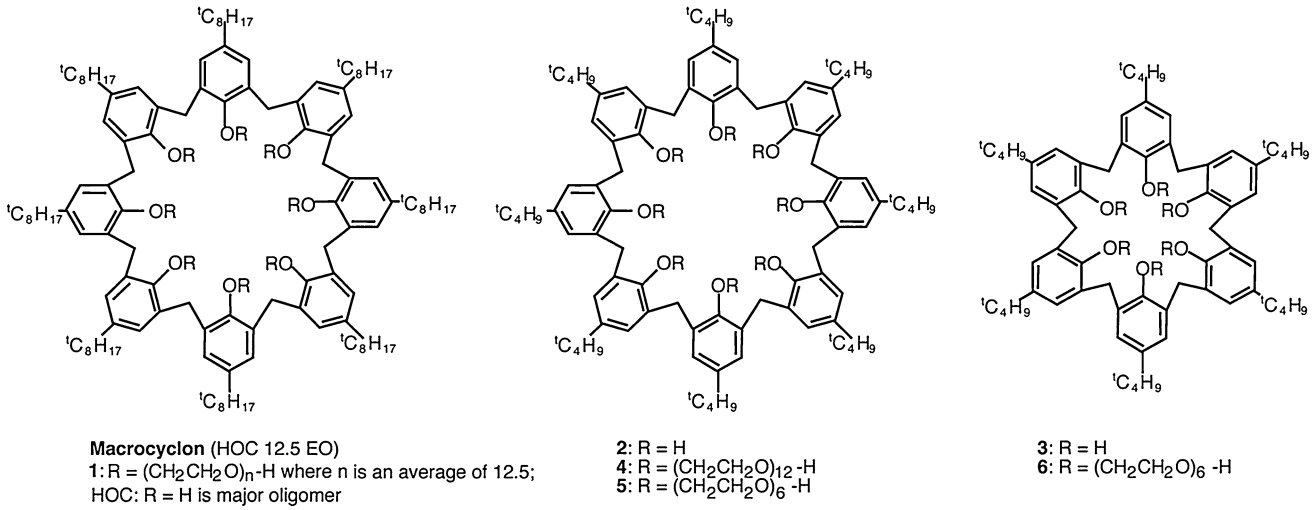


Fig. 5 The chemical structures of macrocyclons were used by Colston et al. [42]

tested it as activation receptors for the human macrophages and the rat natural killer cells. They showed that 5,11,17,23-tetrakis *N*-(2-acetamido-2-deoxy-beta-D-glucopyranosyl)-thioureido-25,26,27,28-tetrapropoxycalix4arene (top scheme in Fig. 4) has the best ligand abilities towards the human macrophages.

Catalytic and inhibitory activity

Kalchenko et al. [48] studied the inhibition of nonspecific alkaline phosphatases because these enzymes catalyze the hydrolysis of phosphate monoesters. They synthesized a series of calixarene based phosphatase inhibitors and Ca^{2+} exchange regulators and examined the high phosphatase inhibition activity and Ca^{2+} exchange regulation properties of those calixarenes. Table 1 shows the enantioselective inhibition of phosphatase. Among the phosphatase inhibitors, they reported that the calixarene-methylene-bis-phosphonic acid is one of the most efficient substances. The chemical structure of calixarene based phosphatase inhibitors and calcium exchange regulators are presented in Fig. 6.

The hemostasis and the associated process of blood coagulation prevent undue loss of blood from injured blood vessels. Thrombosis is inappropriate coagulation of blood, which may occur as atheroschlerosis or in response to some insults including implantation of medical devices or surgery. Such blood clot breaks loose and become lodged as embolus in the cerebrovascular or pulmonary circulatory systems. Hwang et al. [49] patented a method of inhibiting thrombus formation in a mammalian subject using effective dose of a calixarene derivatives. They prepared the physical properties of synthesized macrocycles, which were included tetrameric macrocyclic compounds or mixtures with predominantly tetrameric forms, using absorption spectroscopy, mass spectrometry and nuclear magnetic resonance spectroscopy (NMR). Their approach involved administering to the subject a therapeutically effective dose of a calix[n]arene, which was derivatized at its ring positions meta to the bridge attachments to the ring, with polar substituents having terminal sulfonate moieties, including amides and esters, which were cleavable in vivo. One exemplary compound of this type was a tetramer of phenol parasulfonic acid subunits linked by methylene bridges.

Table 1 Enantioselective inhibition for porcine kidney alkaline phosphatase by the chiral aminophosphonous acids [48]

Inhibitor	Inhibition constant (μM)	Selectivity
B-(R)	73	2.28
B-(S)	32	2.28
C-(RR)	1.7	50.5
C-(SS)	86	50.5

Tsou et al. [50] reported the dual inhibition effect of a tetrabutoxy-calix[4]arene derivative for both HCV and HIV. They studied the upper-rim interacting head groups and the lower-rim alkylation on the roles of calix[4]arene as dual antiviral activities. Hence, they used a range of lower and upper-rim modifications (such as aspartate, isophthalate and glutamate) on the activity of main scaffold. The substitutions of tetrabutoxy-calix[4]arene derivatives are presented in Fig. 7.

Maintaining the cone conformation of the calixarene scaffold is important for antiviral activity. Preorganization of the scaffold into a cone conformation for projection of the recognition groups appears to be important for both anti-HCV and anti-HIV activities. Calix[4]arene with four hydroxyl groups at the lower rim can stabilize the scaffold

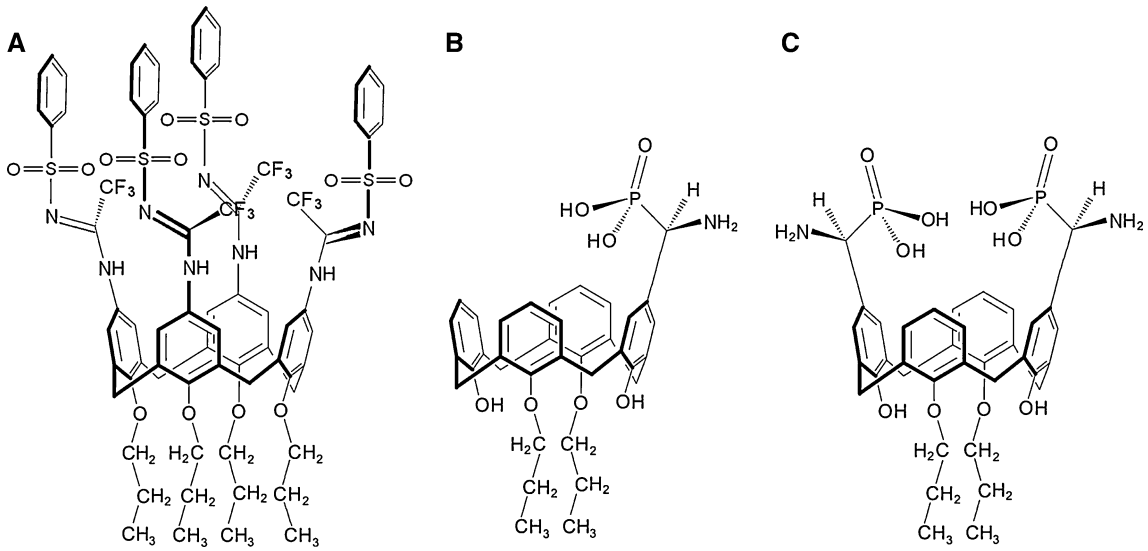


Fig. 6 The chemical structure of calcium exchange regulators. Structures **b** and **c** are the enantioselective inhibitors of porcine kidney alkaline phosphatase bearing the chiral aminophosphonous acids [48]

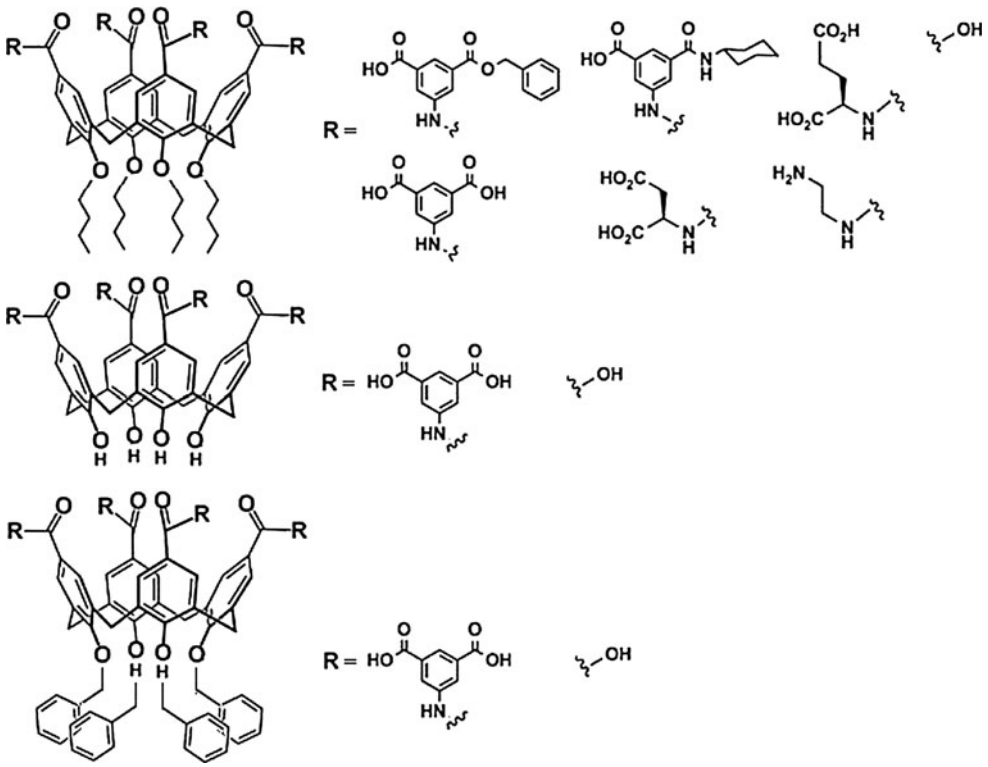


Fig. 7 The chemical structure of tetrabutoxy-calix[4]arene derivatives were used as inhibitors for HCV and HIV [50]

into a cone conformation through intramolecular hydrogen bonding. Introduction of *n*-butyl groups at the lower-rim locks the calix[4]arene scaffold into a cone conformation as the bulky substitutions are unable to invert through the ring. Moreover, as indicated by the pair of doublets from the bridging methylene protons in the ^{1}H NMR spectrum, benzylated calixarenes exist in a cone conformation. Tsou et al. [50] also studied the importance of projected diacid moieties and aromatic substitutions on the upper-rim. They suggested that aromatic substitutions were superior to aliphatic derivatives at the upper-rim for HIV inhibition, while anti-HCV activity was not as sensitive to that change.

Co-infection with both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is a public health challenge and afflict more than ten million people in the

world. With the advancement of highly active antiretroviral therapy (HAART), the liver disease has emerged as a leading cause of death among HIV infected patients. Moreover, such therapies result more liver toxicity and no specific anti-HCV drug is available yet. Therefore, the improvement of a dual drug candidate would be desirable to block HCV and HIV infection.

Solubility control

When the hydrophobic calixarene derivatives are designed, the lack of solubility in biological media made them unsuitable for in vitro standard evaluation as antimicrobial agents. Gaining hydro-solubility leads to access the biological activities. Thus, researchers are developing the synthetic strategies leading to a water-soluble analogue via introduction of hydrophilic groups at the upper and lower rims of the calixarene scaffold. Dibama et al. [51] synthesized a water-soluble calixarene bearing the nalidixic acid, a quinolone antibiotic, and examined its prodrug behavior in vitro by high performance liquid chromatography. Figure 8 presents the chemical structure of the synthetic prodrug. As the result, various Gram-negative and Gram-positive reference strains revealed dominant antibacterial activities.

Nifedipine, as a calcium-channel blocker, is practically insoluble in water. Yang et al. [52] investigated its complexes towards *para*-sulphonato-calix[8]arene to produce stable complexes in water and confirmed it using electrospray ionization mass spectroscopy and thermal analysis. They showed that the stability and the solubility of complexes were maximum for *para*-sulphonatocalix[8]arene, intermediate for *para*-sulphonato-calix[6]arene and minimum for para-sulphonato-calix[4]arene. They showed that the first complex was bioequivalent to a nifedipine PEG-solution and the oxidative degradation of the drug was greatest when combined with the calix[6]arene. Yang and Villiers [53] studied the aqueous solubility of niclosamide

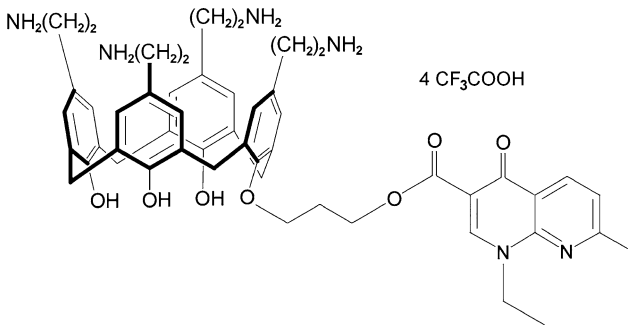


Fig. 8 Chemical structure of a calix[4]arene bearing nalidixic acid as a prodrug [51]

as a poorly water-soluble drug to produce stable complexes with six water-soluble 4-sulphonato-calix[n]arenes using phase solubility studies and thermal analysis. The selected calixarene derivatives were 4-sulphonato-calix [6]arene+hydroxypropyl-β-cyclodextrin, 4-sulphonato-calix[6]arene+β-cyclodextrin, 4-sulphonato-calix[6]arene+γ-cyclodextrin, 4-sulphonato-calix[6]arene, 4-sulphonato-calix[8]arene, and 4-sulphonato-calix[4]arene.

Yang and Villiers [54] studied the water solubility of furosemide drug by 4-sulphonic calix[n]arenes and showed that the concentration of the calix[n]arenes and the molecular size of the 4-sulphonic calix[n]arenes influenced the increase in the solubility of furosemide. Because of the incorporation of the non-polar portions of the furosemide molecule into the non-polar cavities of the calixarenes, when n was selected to be 4, 6 and 8, the solubility of furosemide was improved $\pm$73–81, $\pm$84–102, and $\pm$104%, respectively. They discussed the driving force of that interaction to be reduction of non-polar water interfacial surface after inserting the guest furosemide into the 4-sulphonic calix[n]arenes host.

Recently, the covalent functionalization of fullerene (C_{60}) is applied to widening their applicability in the pharmaceutical uses. Inclusion of C_{60} within cavity of water-soluble hosts is one of the most fruitful methods to overcome the water solubility of fullerene derivatives. Kunsagi-Mate et al. [55] used photoluminescence and quantum chemical methods to study the fullerene encapsulation with water-soluble calixarenes (thia calix[4]arene-tetrasulfonate and calix[6]arene-hexasulfonate) and revealed that functionalization of calixarenes and fullerenes induced significant changes in molecular encapsulation processes. Figure 9 illustrated the encapsulation of one of the fullerene derivatives by thiacalix[4]arene-tetrasulfonate.

Carbamazepine as one of the anticonvulsant drugs is widely used in the treatment of simple and complex trigeminal neuralgia, seizures, and bipolar affective disorders. The problem is it's practically insolubility in water (less than 0.2 mgmL^{-1}). The best way to enhance its aqueous solubility is to use complexing agents to form host:guest structures. *p*-sulfonated calix[4, 6]arenes are widely used as complexing agents. Panchal et al. [56] studied the effect of *p*-sulfonated calix[4, 6]arenes on aqueous solubility of carbamazepine by HPLC, DSC, PXRD, FT-IR, UV–Vis, and FT-Raman spectroscopy and proposed the inclusion structures as illustrated in Fig. 10. The dissolution of *p*-sulfonated calix[4]arene inclusion complex was slightly slower compared to *p*-sulfonated calix[6]arene inclusion complex, which was evaluated by the stability constant of complexes.

Topotecan (TPT) a derivative of camptothecin, is a chemotherapy agent, a topoisomerase I inhibitor, and is

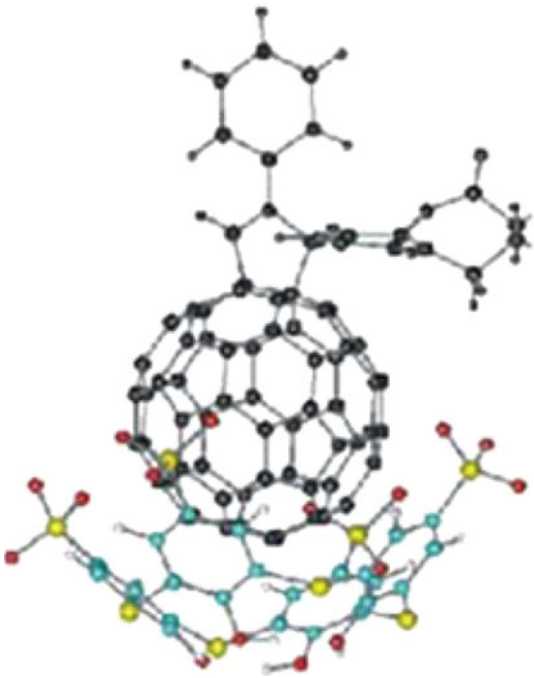


Fig. 9 Encapsulation of a fullerene derivative by thiacalix[4]arene-tetrasulfonate [55]

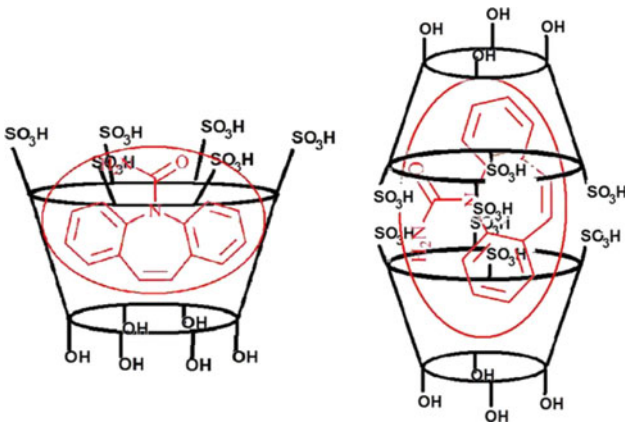


Fig. 10 Schematically presentation of inclusion complexes of *p*-sulfonated calix[4, 6]arenes and carbamazepine [56]

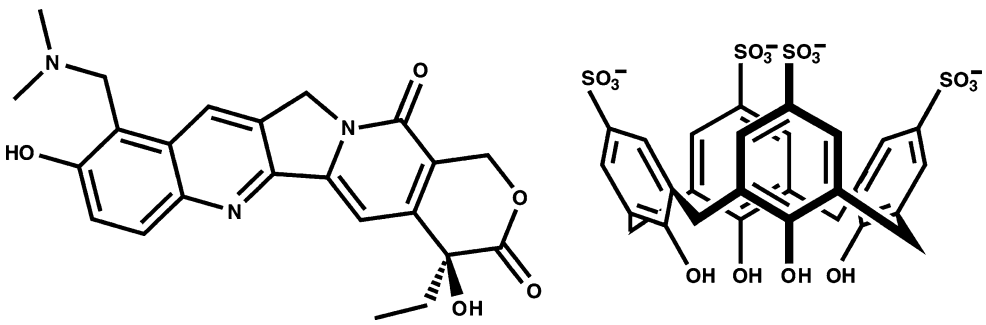
used in the treatment of many diseases including small cell lung, ovarian and cervical cancer. The problem is its low solubility, which have to be prepared as TPT-hydrochloride for improving the solubility. Wang et al. [57] prepared the inclusion complexes of TPT (Fig. 11) with a sulfonatocalixarene derivative (Fig. 11) and elucidated that the dimethylaminomethyl group of topotecan and the quinoline ring were encapsulated in sulfonatocalixarene and the complex was more soluble than free topotecan. The encapsulated schematic of topotecan is presented in Fig. 12. They confirmed the formation of inclusion complex by DSC and 1H NMR and they proposed that complex can be regarded as an important choice in the design of novel formulation of TPT for medicine.

It is obvious that little systematic research had been conducted to date on the toxicity of the calixarenes and the drug encapsulated ones. Either at the cellular level or in vivo, the calixarenes have showed no activity in the Ames test. For instance, *p*-sulphonato-calixarenes are innocuous with regard to hemolytic effects at doses less than 50 mmol/L, but the hemolytic effects increase with increased ring size. Moreover, no acute toxicity for the *p*-sulphonato-calix[4, 6, 8]arenes is reported when injected in mice. These results revealed the extremely low levels of toxicity of calixarene complexes at the cellular level, but many behaviors in animals are remains to be determined.

Paclet et al. [58] investigated the cytotoxicity of three water-soluble *para*-sulphonato-calix[4, 6, 8]arenes They examined activation of NADPH oxidase in polymorphonuclear neutrophils (PMNs) by those calixarenes and they did not stimulate the neutrophils, Their results revealed that the *para*-H-calix [4]arene and the *para*-sulphonato-calix[4,6 or 8]arenes were not cytotoxic. Even by further in vitro evaluation, those calixarenes proved to be appropriate candidates for bio-pharmaceutical applications. Figure 13 shows the effect of 0.1 and 10 μM calixarenes treatment on NADPH oxidase activity in PMNs.

Mourer et al. [59] synthesized nine anionic water-soluble calix[4]arene derivatives as anti-HIV agents and

Fig. 11 The chemical structure of topotecan (*left*) and encapsulating sulfonatocalixarene derivative (*right*) [57]



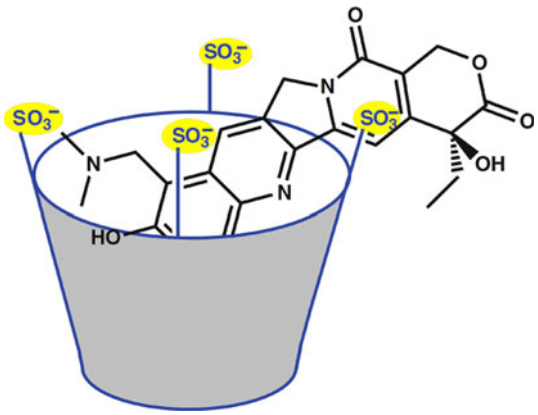


Fig. 12 Schematically illustration of encapsulated topotecan in sulfonatocalixarene [57]

detected their toxicities. According to Fig. 14, the synthesized scaffolds incorporated carboxylate, sulfonate, phosphonate moieties on the upper rim and 2,2′-bithiazole groups on the lower rim. Although most of them showed an antiviral activity in the concentration range of 10–50 μM, the sulfonylated calix[4]arene displayed an activity at a micro-molar concentration. They evaluated nine anionic water-soluble calix[4]arene derivatives on the two cell lines MT4 and CEM-SS and displayed a very weak or not toxicity as the CC_{50} was not reached at 100 μM.

One way to improve the solubility of poorly water-soluble drugs is to prepare soluble host-guest complexes with macromolecules such as cyclodextrins and calixarenes. The inner cavity diameters of α-, β-, γ-cyclodextrins are 5.7, 7.8, and 9.5 Å, respectively. In contrast, calix[4, 6, 8]arenes have inner cavity diameters of 3.0, 7.6, and 11.7 Å, respectively. Thus, calix[6]arene has comparable inner cavity diameter to that of -cyclodextrin. In comparison, there is another difference between the phenols of calixarenes and the oligosaccharide units of cyclodextrins. Subsequently, during the last 20 years, water-soluble calixarenes and especially *p*-sulfonated calix[n]arene, have been the subject of growing interest in the pharmacological sciences. There are many advantages to using calixarenes as host molecules, one being the weak forces, π-π interactions, hydrogen bonding and dipole–dipole moments, which play a major role in complexation. For instance, the *p*-sulfonated calix[n]arenes provide not only hydrophilic heads (SO_3^-), but also a hydrophobic environment (alkyl chains or benzene rings). In other words, these calixarenes possess properties of both micelles and cyclodextrins.

Drug analysis and purification

Atropine inhibits nerve responses and is administered in oral form or via eye drops and injection to relax muscles. It also is used as an antispasmodic and to dilate the pupils. Zareh and Malinowska [60] determined the atropine concentration using a selective membrane electrode (SME). They synthesized three calixarene derivatives and used the electrode successfully for analyzing atropine sulfate in eye drops and injection solution. The calixarene derivatives in this work are listed in Table 2.

The practical linear ranges for derivatives listed above were 1.9×10^{-6} to 7.9×10^{-3}, 7.9×10^{-6} to 7.9×10^{-3}, and 6.3×10^{-6} to 7.9×10^{-3} $molL^{-1}$, respectively. The recovery percentage and the relative standard deviation (n=5) were determined for them to be 97.5–99.1% and 0.39–0.72%, respectively.

Hashem and Jira [61] studied the effects of different chromatographic conditions on the separation of nine tricyclic neuroleptics and the effect of structural differences of analytes by a new HPLC stationary phase with calixarenes. They showed that chemical structure and pKa of neuroleptics influenced their separation on the calix[8]arene stationary phase.

Celecoxib as a diaryl pyrazol belongs to the class of non-steroidal anti-inflammatory drugs and diaryl heterocyclic inhibitors, and exhibits anti-inflammatory, analgesic and antipyretic activities. It relieves the symptoms and signs of osteoarthritis and rheumatoid arthritis. Hashem et al. [62] used another method for extraction and quantification of celecoxib in tablets with a detection limit of 0.122 $mgmL^{-1}$. With their proposed method, a satisfactory separation of celecoxib in tablets, extended linear range and rapid analysis time was obtained. No interference

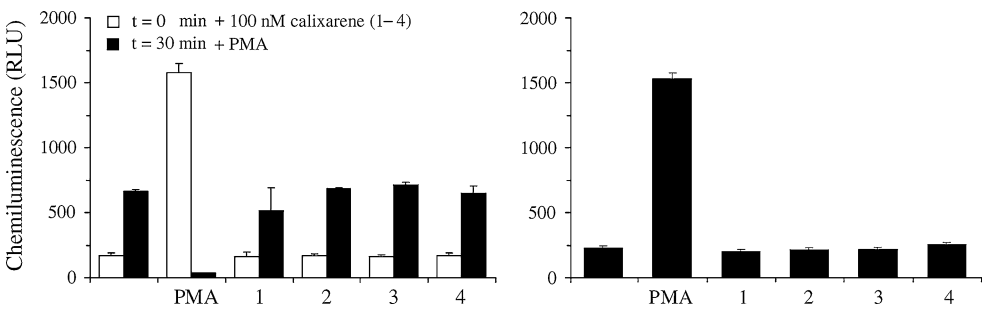


Fig. 13 Effect of 0.1 μM (*left*) and 10 μM (*right*) calixarenes treatment on the activity of NADPH oxidase in PMNs [58]

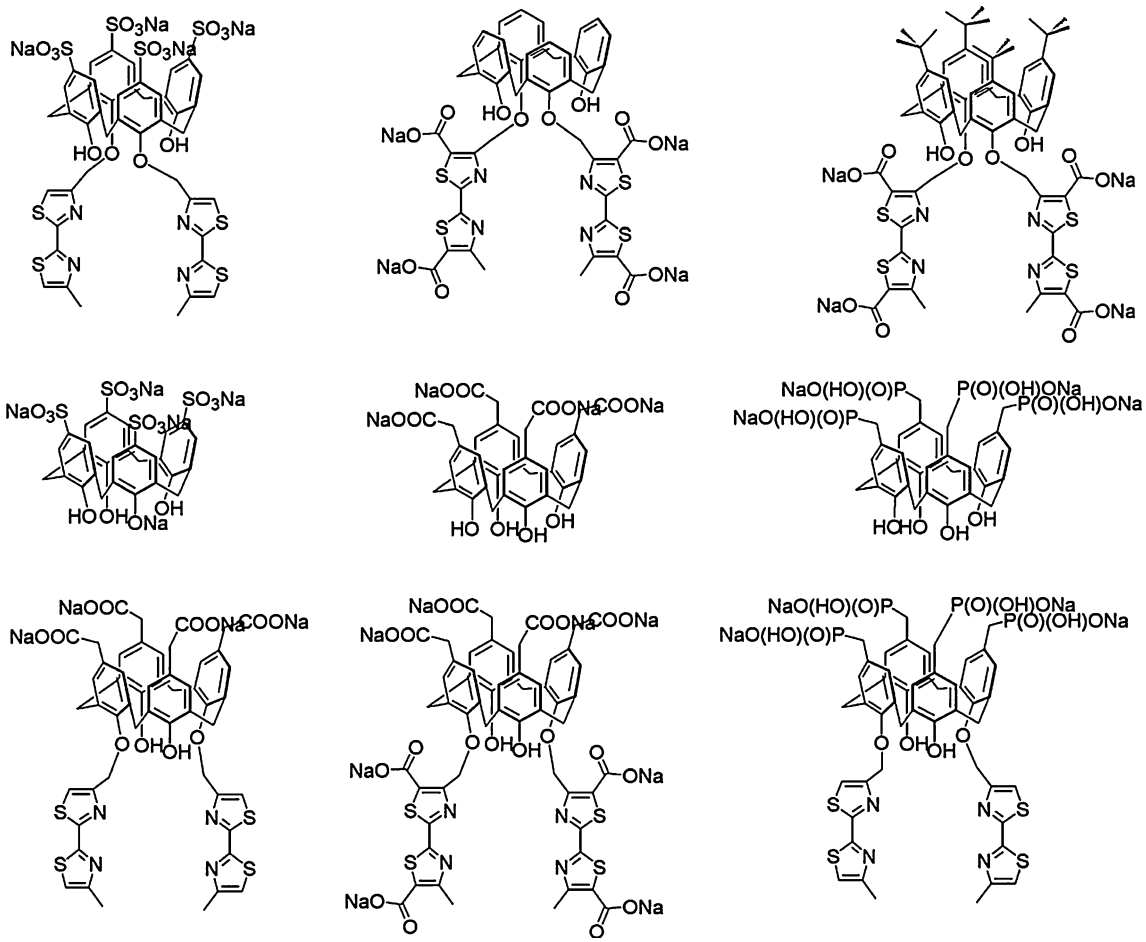


Fig. 14 The synthesized scaffolds bearing carboxylate, sulfonate and phosphonate moieties on the upper-rim and 2,2′-bithiazole and hydroxyl groups on the lower-rim [59]

Table 2 The list of calixarene derivatives were used by Zareh and Malinowska [60]

No.	Calixarene derivative
1	37,40-Bis-[(diethoxy-thiophosphoryl)oxy]-5,11,17,23, 29,35-hexakis(1,1-dimethyl-ethyl)-calix[6]arene-8,39,41,42-tetrol
2	37,38,39,40,41-Pentakis-(diethoxythiophosphoryl)-oxy]-5,11,17,23,29,35-hexakis(1,1-dimethylethyl)-calix[6]arene-42-ol
3	37-[(Diethoxythiophosphoryl)oxy]-5,11,17,23,29,35-hexakis-(1,1-dimethylethyl)-calix[6]arene-38,39,40,41,42-pentol

between the celecoxib's peaks and those of degradation products was observed.

Al-Jammaz et al. [63] synthesized *p-tert*-Butylcalix[4]arene tetra-di-isopropylacetamide and studied the extraction of radioactive Tl^{+} and Tl^{3+}, which are used in the production of ^{201}Tl of pharmaceutical quality.

The plants containing the Pyrrolizidines alkaloid are widely distributed in many geographic regions of the world. Pyrrolizidines occur naturally in a variety of plant species (*Leguminosae*, *Asteraceae*, and *Boraginaceae*). Although it was found that Pyrrolizidines exhibit antitumor activity, they were never used in clinical trials owing to their hepatotoxicity associated with the presence of a necine in the basic state. Retronecine as a toxic pyrrolizidine is synthesized by plants from the genus Senecio. da Silva et al. [64] isolated the retronecine from Senecio braziliensis shoots with an overall yield of 4% in relation to the total alkaloid content and studied the inclusion complexation of *p*-sulfonic acid calix[6]arene towards retronecine by NMR techniques, which obtained the detailed information about the interactions in aqueous solution. They suggested that one moiety of retronecine was inside the *p*-sulfonic acid calix[6]arene. The proposed complex topology is shown in Fig. 15.

Analytical role of calixarenes in determination and recognition of drugs and metabolites is not summarized in the above-mentioned methods and are used in both stationary phases and mobile phases of liquid chromatography. Calixarene–bonded stationary phases are preferable to the use as mobile-phase additives, because the UV

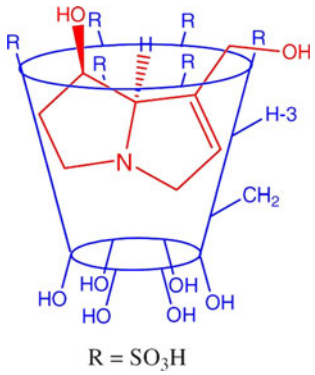


Fig. 15 The proposed complex topology for inclusion of *p*-sulfonic acid calix[6]arene towards retronecine [64]

detection of analytes is prevented by strong absorbance of calixarenes. Additionally, poor solubility of most calixarenes precludes their applications as additives in aqueous eluents. With various methods for functionalizing calixarenes have been developed, more and more applications of different calixarene bonded stationary phases have been reported for drug analysis. The resulting interactions of different calixarenes stationary phase influence the retention factors and improve the selectivity of the solutes. The modification of the calixarenes, for instance, by varying the conformations, ring size, and substituents, enable a more enhanced interaction spectrum and can improve the specificity for guest drugs.

Supports and structural studies

A lot of implantable medical devices are used for the repair of hard and soft tissue, initiate acute inflammation and resulting in device failure. α-Melanocyte-stimulating hormone (MSH) bearing a short peptide sequences is produced in the body. It is a potent and natural anti-inflammatory hormone, which is amenable for easy laboratory synthesis. Charnley et al. [65] used α-melanocyte-stimulating hormone-calixarene molecules (Fig. 16) to dip and dry treat medical devices with an anti-inflammatory coating. Base upon their results, GKP(D)V peptide had been immobilized onto the glass surface using calixarene chemistry and retained anti-inflammatory properties. This strategy supported the future research into its application as an anti-inflammatory coating for biomaterials.

^{211}At is an α-emitting without β or γ emissions and has a reasonable half life of 7.2 h. Its X-ray emission leads to be detectable by γ-counters. Therefore, there is an increasing interest to use it as a radio immunotherapeutic agent. Yordanov et al. [66] synthesized and characterized a tetramer-captocalix[4]arene and its ^{211}At complex. They evaluated the complex stability in nude mice for the purpose of α-radioimmunotherapy of cancer. The result of their experiments was against what they had predicted. They revealed that this complex lacked adequate stability.

The chemistry of rhenium has developed rapidly owing to the recent introduction of β-emitting isotopes ^{186}Re and ^{188}Re in radiotherapy. The most commonly used chelates for rhenium are the N_2S_2 or ligands. Bommel et al. [67] synthesized the N_2O_2 and N_2S_2 tetradentate calix[4]arene rhenium complex both in organic and water solvents, and demonstrated its stability in a phosphorus-buffered saline solution. According to Fig. 17, they reacted the $ReO(PPh_3)_2Cl_3$ substrate with tetradentate N_2O_2-calix[4]-arene and produced a novel mixed-ligand rhenium complex with the structure $ReO(N_2O_2$-calix)OEt. Attempts to crystallize that complex resulted in the formation of a dimeric structure, which is presented in Fig. 18.

Synthesis and characterization of the N_2S_2-calix[4]arene rhenium complex is shown in Fig. 19. They determined the crystal structures of mono- and bimetallic complexes, which have potential applications as radiopharmaceuticals. Base upon the results, calix[4]arenes are good platforms for the syntheses of novel potential radiopharmaceuticals. Both N_2O_2- and N_2S_2-calix[4]arene rhenium complexes were compared and the latter showed more stability in PBS solutions.

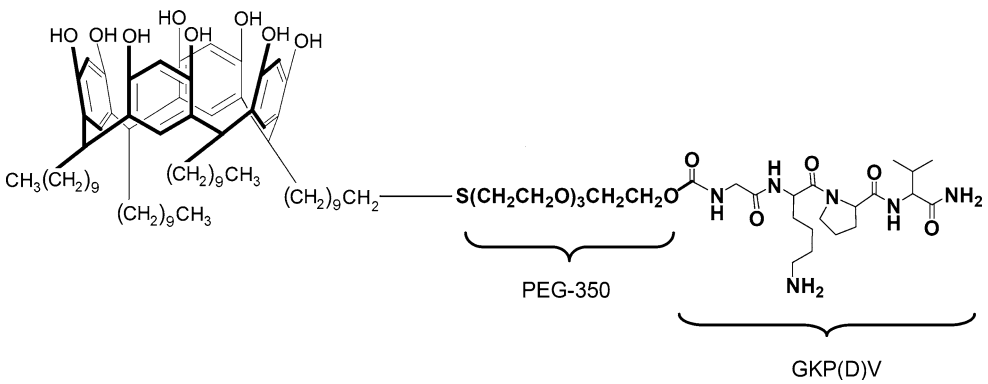


Fig. 16 Illustration of the GKP(D)V peptide attached to the calix[4]arene compound via a PEG-350 tether link, which was then coated onto glass [65]

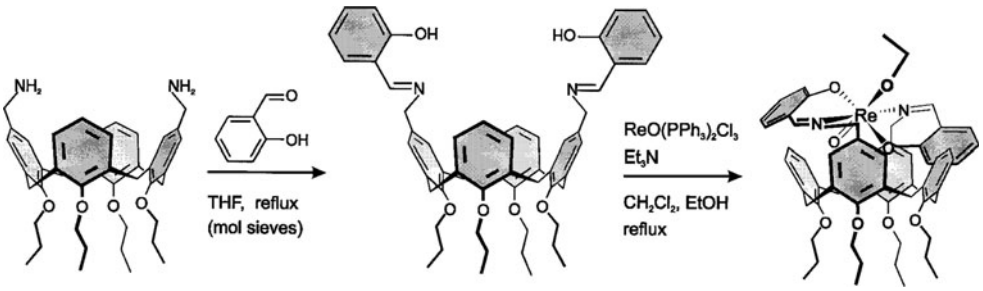


Fig. 17 The synthesis steps for N_2O_2-calix rhenium complex [67]

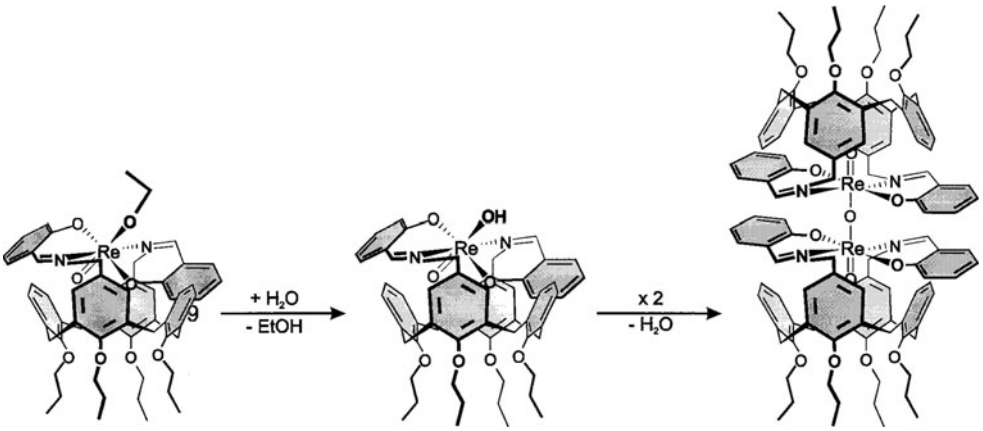


Fig. 18 Formation of calix-dimer during the crystallization process [67]

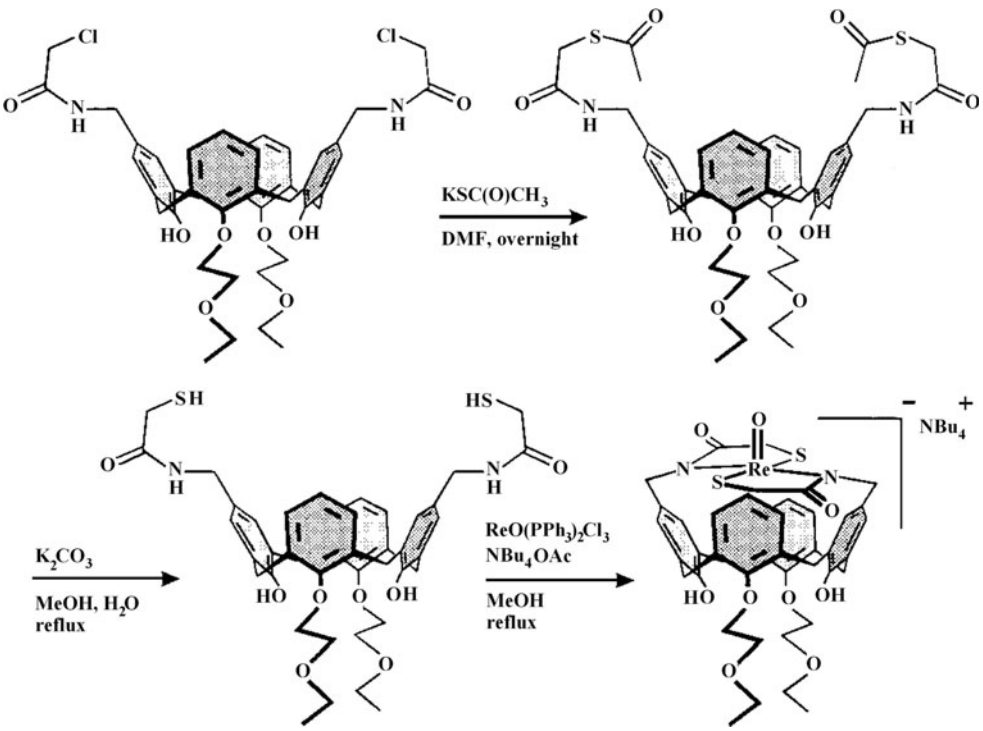


Fig. 19 The synthesis procedure of N_2S_2-calix rhenium complex [67]

Phenothiazines occur in various antipsychotic and antihistaminic drugs and are used as inodilators in congestive heart failure, acting upon the type I calcium/calmodulin dependent phosphodiesterase. Inazumi et al. [68] studied the inclusion complexation of *p*-sulfonato calix[6]arene with three kinds of phenothiazines, determined their association constants and revealed that with increasing external pressure, the inclusion equilibrium was shifted to the

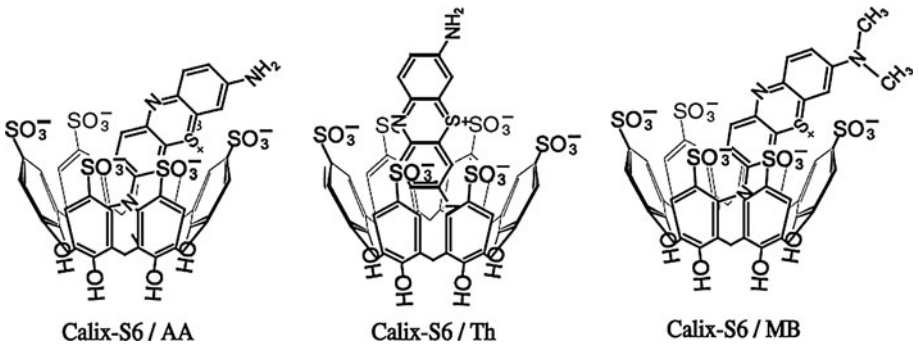


Fig. 20 The plausible structures of phenothiazine's inclusion complexes with *p*-sulfonatocalix[6]arene [68]

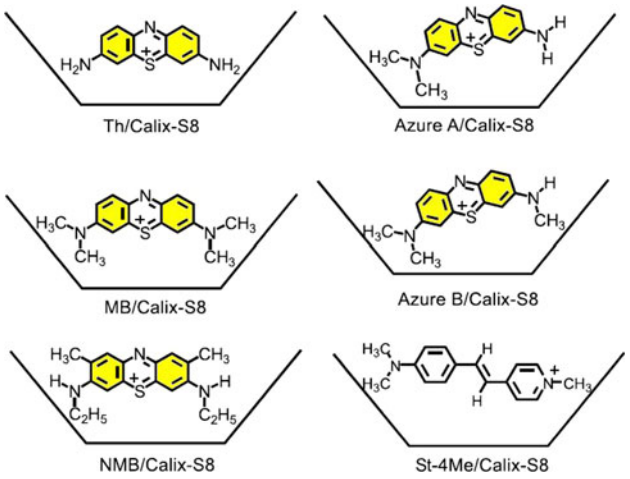


Fig. 21 The plausible structures of phenothiazine's inclusion complexes with *p*-sulfonatocalix[8]arene [69]

dissociation side. According to their results, the plausible structures of inclusion complexes with phenothiazine are schematically illustrated in Fig. 20.

Likewise, Sueishi and Asano [69] examined the effects of solvent polarity and pressure on the inclusion complexation of *p*-sulfonatocalix[8]arene with phenothiazines and methylene blue [70] The plausible structures of inclusion complexes with phenothiazine are schematically illustrated in Fig. 21. They revealed that the inclusion equilibria of phenothiazines with *p*-sulfonatocalix[8]arene are dependent on the bulkiness of the guest molecules.

Tetracaine is from aminoester family of local anesthetics, an important class of nonciceptive agents, whose action involves blockage of nervous impulse transmission. Both the uncharged and the cationic species of local anesthetics bind to the Na^+ channels of the nerve membranes, stabilizing its inactivated state, blocking the initiation and propagation of nervous impulses. Local anesthetics depict a short duration of action in the range of 1–4 h. Fernandes et al. [71] studied the complexation of *p*-sulphonic acid calix[6]arene towards local anesthetic tetracaine using H-NMR experiments and optimized their performance. Figure 22 presents the proposed topology for the complexes of *p*-sulphonic acid calix[6]arene with tetracaine.

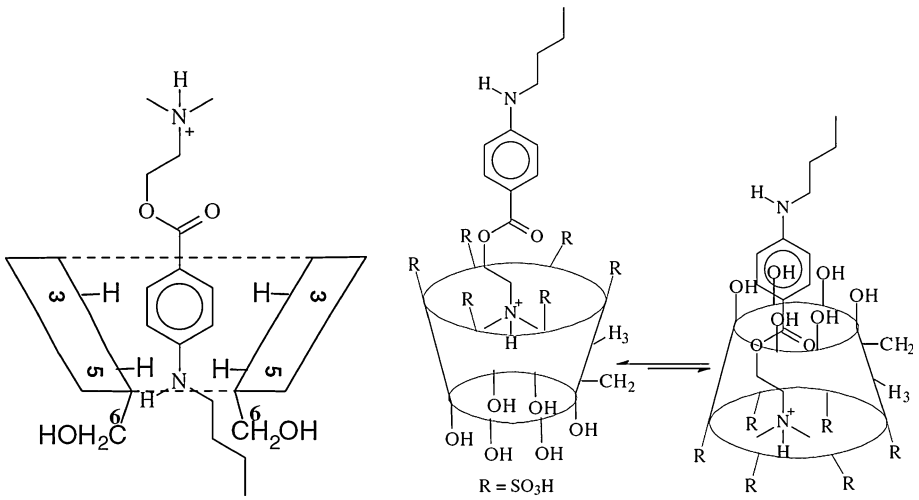


Fig. 22 The proposed topology for the complexes of *p*-sulphonic acid calix[6]arene with tetracaine [71]

Acknowledgments This work was supported by Islamic Azad University (Shahreza branch) and Iran Nanotechnology Initiative Council.

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