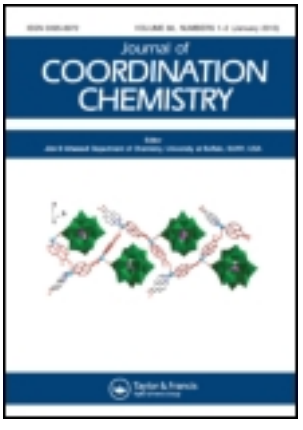

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Review: Medical applications of nano-baskets

Bahram Mokhtari [a] & Kobra Pourabdollah [a]
[a] Department of Chemical Engineering , Shahreza Branch, Islamic Azad University , Shahreza , Iran
Published online: 14 Sep 2011.

To cite this article: Bahram Mokhtari & Kobra Pourabdollah (2011) Review: Medical applications of nano-baskets, Journal of Coordination Chemistry, 64:18, 3189-3204, DOI: 10.1080/00958972.2011.616930

To link to this article: http://dx.doi.org/10.1080/00958972.2011.616930

Journal of Coordination Chemistry
Vol. 64, No. 18, 20 September 2011, 3189–3204

Review: Medical applications of nano-baskets

BAHRAM MOKHTARI and KOBRA POURABDOLLAH*

Department of Chemical Engineering, Shahreza Branch, Islamic Azad University, Shahreza, Iran

(*Received 8 September 2010; in final form 27 July 2011*)

Applications of nano-baskets of calixarenes are assessed and reviewed in six main divisions of medical sciences and technologies including hematology, pathology, pharmacy and pharmacology, infectious diseases, nuclear medicine, and chemotherapy. Although it is difficult to distinguish a boundary between medical and biological studies, the aim was to focus on medical research rather than biological using more than 50 references. Although recent reports have focused on the synthesis, optimization, and application of one kind or a unique group of calixarenes, this review deals with synthesis and behavior of a variety of calixarene-based medical platforms to illustrate potential in the medical sciences.

Keywords: Nano-basket; Calixarene; Medicine

1. Introduction

Nano-baskets of calixarenes, macrocyclic compounds of phenolic units linked by methylene groups at the 2,6-positions, present some requirements to serve as platforms for the analytical, medical, biological, and industrial investigations. Calixarenes have been subjected to extensive research in development of transporters, extractants, stationary phases (using gas chromatograph, Teif Gostar Faraz Co.), electrode ionophores, optical sensors, and medical research [1–8]. In the nineteenth century, Baeyer [9] synthesized them *via* reaction of formaldehyde with *p*-substituted phenols in basic or acidic environments. In the 1940s, Zinke and Ziegler [10] discovered that the products possessed cyclic tetrameric structures. In 1975, Gutsche [11] introduced the presently accepted name of calixarene.

Calixarenes are considered as host molecules after cyclodextrins and crown ethers [12] 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 [13]. The poor solubility of most calixarenes precludes applications in aqueous media [14]. Numerous calixarene

*Corresponding author. Email: pourabdollah@iaush.ac.ir

Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online
DOI: 10.1080/00958972.2011.616930

derivatives have been synthesized and various functionalizing methods have been developed for them during the past decades. They are easily functionalized to a variety of donor groups by comparatively straightforward reactions due to their phenolic hydroxyls in the lower rim and receive intensive investigations in host : guest phenomena, mainly those functionalized on the upper rim with *p-tert*-butyl groups or hydrogen on the lower rim. Although the identities of substituents in parapositions relative to the phenolic oxygens influence their ionophoric propensities, this feature has been much less explored owing to the lack of suitable functionalization on the upper rim. The lower rim functional moieties are mainly responsible for physical properties of calixarenes, while different complexing moieties at the upper rim attract desirable molecules with pre-defined selectivity [15].

Cornforth *et al.* [16] in 1955 reported the first medical application of a calixarene derivative (Macrocyclon). Rodik *et al.* [17] discussed antiviral, antithrombothic, bactericidal, antituberculosis and anticancer activities as well as toxicity, membranotropic properties, and specific protein complexation of modified calixarenes in a review.

In section 2 of this article, the application of calixarenes in hematology is briefly reviewed. Then, sections 3 and 4 focus on the role of calixarenes in pathology, pharmacy, and pharmacology. After that, application of calixarenes in the infectious diseases and nuclear medicine is reviewed in sections 5 and 6, followed by section 7 about chemotherapic applications.

2. Hematology

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 atherosclerosis or in response to some insults including implantation of medical devices or surgery. Blood clots break loose and become lodged as embolus in the cerebrovascular or pulmonary circulatory systems. Hwang *et al.* [18] patented a method of inhibiting thrombus formation in a mammalian subject using effective dose of calixarene derivatives. They compared the physical properties of synthesized macrocycles, which included tetrameric macrocyclic compounds or mixtures with predominantly tetrameric forms, using absorption spectroscopy, mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy. The 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 para-sulfonic acid subunits linked by methylene bridges.

Paclet *et al.* [19] investigated the cytotoxicity of three water-soluble para-sulfonato-calix[4,6,8]arenes, examining activation of NADPH oxidase in polymorphonuclear neutrophils (PMNs) by those calixarenes; they did not stimulate the neutrophils. The results revealed that the para-H-calix[4]arene and the para-sulfonato-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 1 shows the effect of 0.1 and 10 $\mu mol\,L^{-1}$ calixarene treatment on NADPH oxidase activity in PMNs.

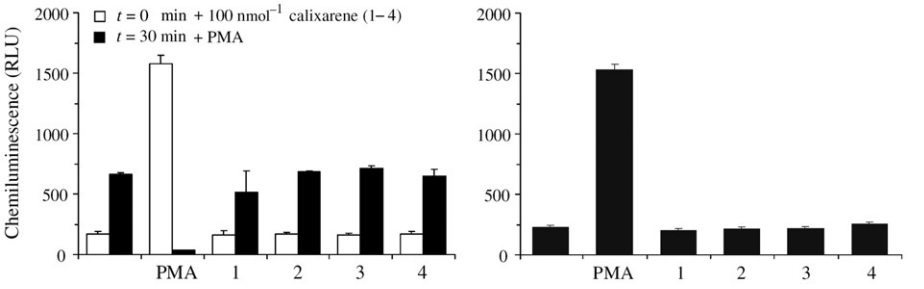

Figure 1. Effect of 0.1 μmol L^{-1} (left) and 10 μmol L^{-1} (right) calixarenes treatment on the activity of NADPH oxidase in PMNs.

3. Pathology

Based upon reports of Anthony *et al.* [20], cancers are one of the main causes of mortality and are responsible for more than 30% of deaths in France. One-third of cancers exhibits resistance to multiple drugs (Multiple Drug Resistant). The problem is dramatic not only from a therapeutic point of view but also from a psychological view for patients. Some compounds used for treating cancer cause secondary effects, such as certain degrees of toxicity. Cancer treatments using such compounds represent an economic problem. Therefore, compounds with improved properties for treating cancer are needed. Specific calixarenes exhibit anticancer activity and make it possible to resolve, in part or in whole, the problems mentioned above. Anthony and coworkers patented a 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 effects of calix[4]arene dihydrophosphonic acid (C4diP), para-octanoyl-calyx[4]arene dihydroxyphosphonic acid, and *p-tert*-butyl-calix[4]arene dihydroxyphosphonic acid on cell cultures. Figure 2 shows the chemical structures of four calix[4]arene dihydrophosphonic derivatives used by Anthony *et al.* The effect of C4diP on a culture of chemosensitive human acute lymphoblastic leukemic cells revealed a mortality of 50% for a mean concentration of 7.33 μmol L^{-1} 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, chloride channels were studied by para-sulfonated calixarenes, which are potent blockers of outwardly rectifying chloride channel (ORCC) with long block times and subnanomolar inhibition constants. Singh *et al.* [21] 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 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 ORCC. Based upon those methods, 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 [22, 23]. Figure 3 depicts some of the calixarenic structures, which were synthesized and studied by Atwood *et al.* [22].

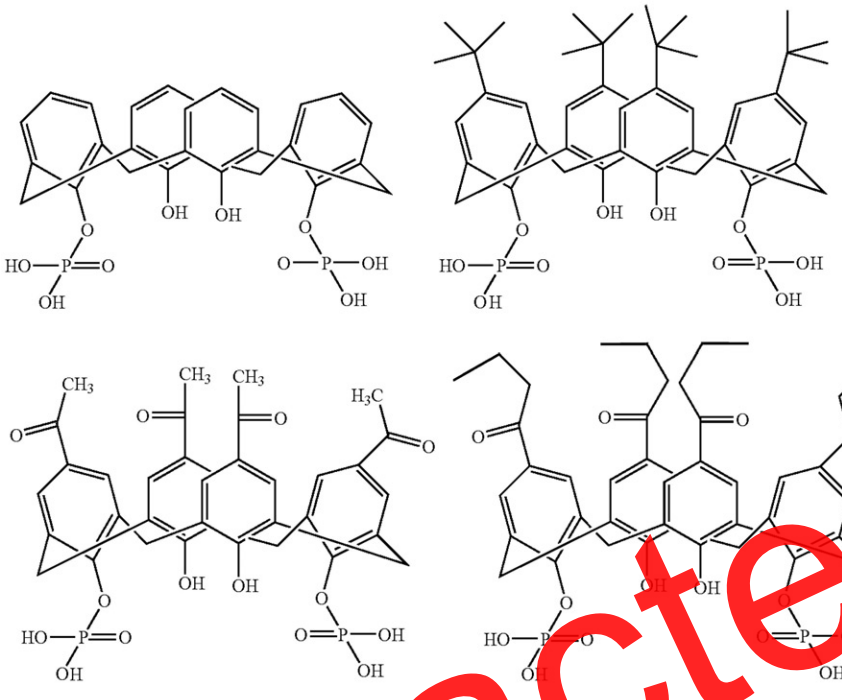

Figure 2. The chemical structure of calix[4]arene dihydrophosphonic derivatives in Anthony *et al.*'s [20] patent.

Rouge *et al.* [24] studied calix[4]arenes bearing alkyl ester and alkyl acid moieties at the lower rim. Pires *et al.* [25] calix[4]arenes bearing two hydrazide function or ornithine, glutamic/aspartic acid groups at the lower rim, and Latxague *et al.* [26] calix[4]arenes bearing diamino-tetraesters, diamino-tetraalcohols, diamino-tetraacid, and tetraaryloxypentoxy groups at the lower rim. Calixarene derivatives were compared with 4-3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl-benzoic acid as a new oral chelator. The antiproliferative effects of the compounds, which were inhibited by intracellular iron level, were studied and the results revealed that the antiproliferative effect was due to their cytotoxicity. Substituted calix[4]arenes open the way to valuable medicinal chemistry scaffolding. Krenek *et al.* [27] linked calixarenes substituted with 2-acetamido-2-deoxy-beta-D-glucopyranose by a thiourea spacer and tested it as activation receptors for the human macrophages and rat natural killer cells; 5,11,17,23-tetrakisN-(2-acetamido-2-deoxy-beta-D-glucopyranosyl)-thioureido-25,26,27,28-tetrapropoxycalix4arene (figure 4) has the best ligand abilities toward the human macrophages.

Harris [28] described acylic phenyl-formaldehyde oligomers, calixarenes or oxacalix-arenes, cyclotriveratrylene derivatives, cyclic tetrameric resorcinol-aldehyde derivatives known as Hogberg compounds, which have anti-human immunodeficiency virus (HIV), anticancer, and antiviral activity. Krishnan and Lohrmann [29] described calixarene conjugates for diagnostic imaging agents and tomography.

Photodynamic therapy is a treatment for cancer and even for certain non-cancerous diseases, which are generally characterized by overgrowth of abnormal or unwanted

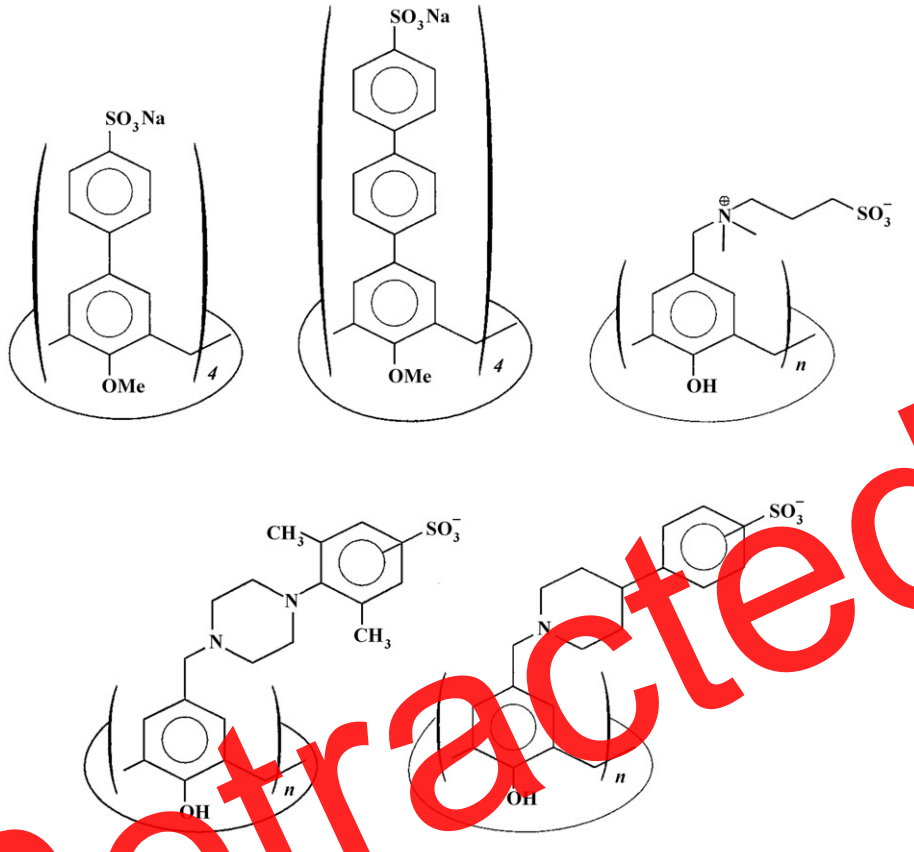

Figure 3. The chemical structure of some synthesized calixarenes by Atwood *et al.* [22].

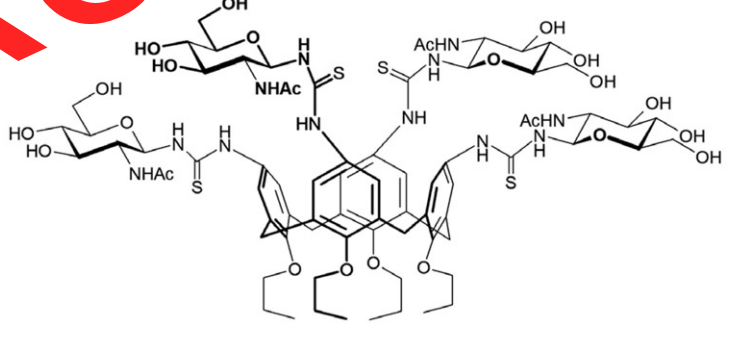

Figure 4. The chemical structure of calixarene derivative was studied by Krenek *et al.* [27].

cells. The therapy is based upon 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 generation of reactive oxygen species produced by the light activated photosensitizers. Neagu *et al.* [30] studied the antitumoral effect of *p*-sulfonato-calix[6,8]arenes on human K562

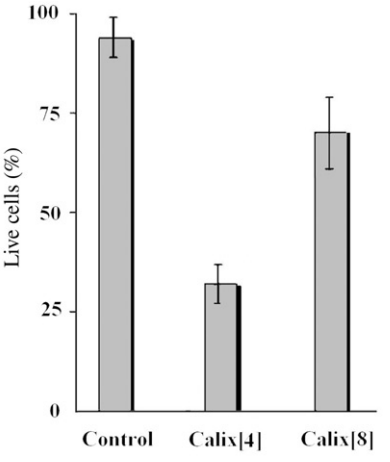

Figure 5. Illustration of the mean ± SD of six individual experiments with triplicate sample for post-irradiation total cell counts and live cell percentage of K562 loaded with 1 μg mL^{-1} calix[6]- or 20 μg mL^{-1} calix[8]arenes.

myelogenous leukemia cell line in experimental photodynamic therapy. It was expected that the larger cavities would geometrically be more suited for a closer and stronger interaction than the smaller ones, but *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. Post-irradiation of calix[6]arene loaded cells induced over 60% mortality in the cell suspension, while calix[8]arene only 30% (figure 5). The cells were irradiated with Hg lamp for 30 min at a fluence rate of 100 mW cm^{-2}. Thus *p*-sulfonato-calix[6]arene was more photoactive than *p*-sulfonato-calix[8]arene.

^{211}At is α-emitting without β or γ emissions and has a reasonable half-life of 7.2 h. Its X-ray emission is detectable by γ-counters. Therefore, there is increasing interest to use it as a radio immunotherapeutic agent. Yordanov *et al.* [31] synthesized and characterized a tetramer-captocalix[4]arene and its ^{211}At complex. The group evaluated complex stability in nude mice for the purpose of α-radioimmunotherapy of cancer. The result of their experiments was contrary to what they predicted; they revealed that this complex lacked adequate stability. Bezouska *et al.* [32] investigated the role of thiacalix[4]arene and carboxylated calixarenes (figure 6) for protection of leukocyte killer cells in combined animal tumor therapies. Three calixarene scaffolds were assessed, revealing that thiacalix[4]arene had the highest affinity for CD69 leukocyte membrane receptor. Carboxylated calixarenes were effective in protection of CD69 lymphocytes from apoptosis triggered by a multivalent ligand or antibody.

4. Pharmacy and pharmacology

Calixarenes have well-defined conformational properties and cavities with molecular dimensions that encapsulate guest drugs. They have antibacterial, antiviral, antifungal,

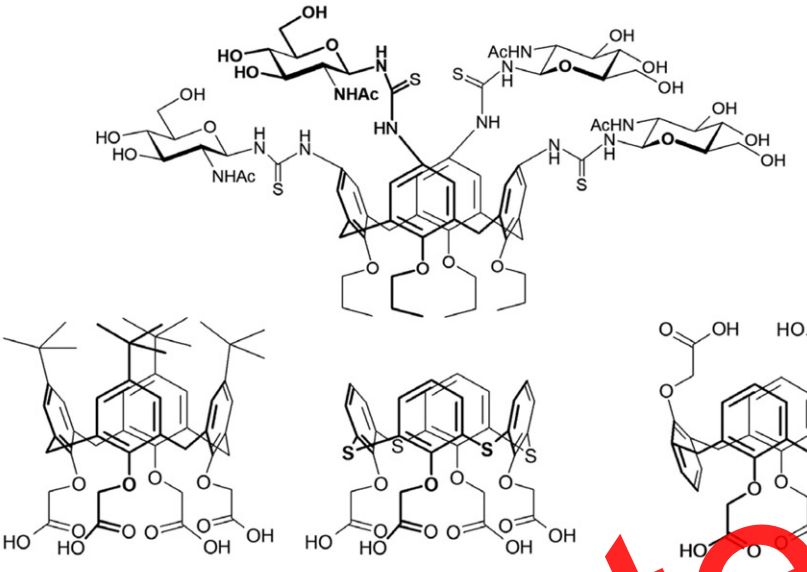

Figure 6. The chemical structure of carboxylated thiacalix[4]arene derivative used for protection of leukocyte.

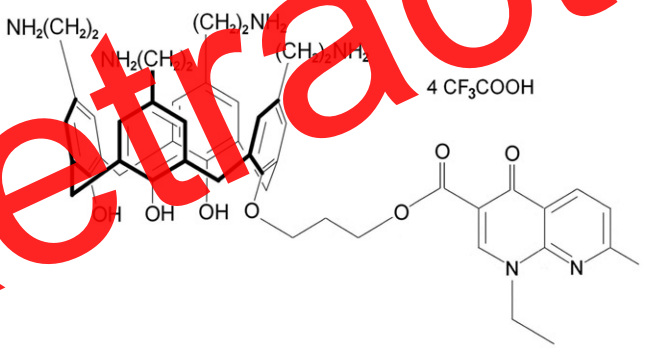

Figure 7. Chemical structure of a calix[4]arene bearing nalidixic acid as a prodrug.

and anticancer activities (including HIV as target). Fatima *et al.* [33] provide an overview and discussed the importance of calixarenes for drug development.

When hydrophobic calixarene derivatives are designed, the lack of solubility in biological media makes them unsuitable for *in vitro* standard evaluation as antimicrobial agents. Gaining hydro-solubility allows assessing the biological activities. Thus, researchers are developing synthetic strategies leading to water-soluble analogs *via* introduction of hydrophilic groups at the upper and lower rims of the calixarene scaffold. Dibama *et al.* [34] synthesized a water-soluble calixarene bearing nalidixic acid, a quinolone antibiotic, and examined its prodrug behavior *in vitro* by high performance liquid chromatography. Figure 7 presents the chemical structure of the

synthetic prodrug. As the result, various Gram-negative and Gram-positive strains reveal antibacterial activities.

Nifedipine is a calcium-channel blocker that is practically insoluble in water. Yang *et al*. [35] investigated its complexes toward para-sulfonato calix[8]arene to produce stable complexes in water and confirmed it using electrospray ionization mass spectroscopy and thermal analysis. Stability and solubility of complexes were maximum for para-sulfonato calix[8]arene, intermediate for para-sulfonato calix[6]arene and minimum for para-sulfonato calix[4]arene. The first complex was bioequivalent to a nifedipine polymeric polyethylene glycol (PEG)-solution and oxidative degradation of the drug was greatest when combined with the calix[6]arene. Yang and Villiers [36] studied aqueous solubility of niclosamide as a poorly water-soluble drug to produce stable complexes with six water-soluble 4-sulfonato-calx[*n*]arenes using phase solubility studies and thermal analysis. The selected calixarene derivatives were 4-sulfonato-calix[6]arene + hydroxypropyl-β-cyclodextrin, 4-sulfonato-calix[6]arene + β-cyclodextrin, 4-sulfonato-calix[6]arene + γ-cyclodextrin, 4-sulfonato-calix[6]arene, 4-sulfonato-calix[8]arene, and 4-sulfonato-calix[4]arene.

Yang and Villiers [37] studied the water solubility of furosemide drug by 4-sulfonic calix[*n*]arenes and showed that the concentration of the calix[*n*]arenes and the molecular size of the 4-sulfonic calix[*n*]arenes increased 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 ±73–81%, ±84–102%, and ±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-sulfonic calix[*n*]arenes host.

Kalchenko *et al*. [38] studied inhibition of non-specific alkaline phosphatases because these enzymes catalyze the hydrolysis of phosphate monoesters, synthesizing a series of calixarene-based phosphatase inhibitors and Ca^{2+} exchange regulators and examining 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, calixarene-methylene-bis-phosphonic acid is one of the most efficient substances (figure 8).

Other research focused on the pharmaceutical and pharmacological aspects of calixarenes, summarized in table 2.

Table 1. Enantioselective inhibition for porcine kidney alkaline phosphatase by chiral aminophosphonous acids.

Inhibitor	Inhibition constant (μmol L^{-1})	Selectivity
B-(R)	73	2.28
B-(S)	32	2.28
C-(RR)	1.7	50.5
C-(SS)	86	50.5

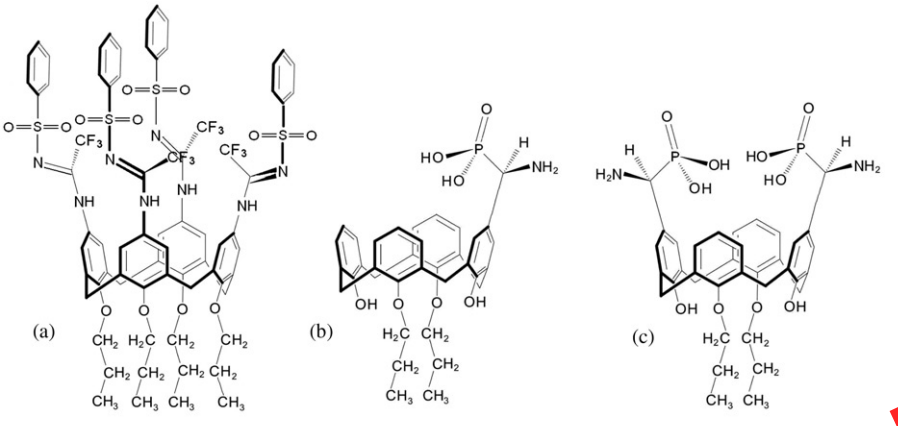

Figure 8. The chemical structure of calcium exchange regulators. Structures (b) and (c) are the enantioselective inhibitors of porcine kidney alkaline phosphatase bearing the chiral aminophosphonous acids.

Table 2. Tabulated pharmaceutical and pharmacological studies using calixarenes.

Drug	Calixarene	Reference
Atropine	Diethoxy-thiophosphoryl-oxy-dimethylethyl-calix[6]arene-tetrol Diethoxy-thiophosphoryl-oxy-dimethylethyl-calix[6]arene-42-ol Diethoxy-thiophosphoryl-oxy-dimethylethyl-calix[6]arene-pentol	[39]
Pyrrolizidine	*p*-Sulfonic acid calix[6]arene	[40]
Drug carriers	Thiacalix[4]arene-tetrasulfonate Calix[6]arene-hexasulfonate	[41]
Carbamazepine	*p*-Sulfonated calix[4,6]arenes	[42]
Phenothiazine	*p*-Sulfonatocalix[6]arene	[43]
Phenothiazine	*p*-Sulfonatocalix[8]arene	[44]
Methylene blue	Octaethyl-*p*-tert-butylcalix[8]arene octaacetate	[45]
Anesthetic tetracaine	*p*-Sulfonic acid calix[6]arene	[46]
Tricyclic neuroleptics	Calix[8]arenes	[47]
Celecoxib	*p*-Sulfonatocalix[8]arene	[48]

5. Infectious diseases

Co-infection with both hepatitis C virus (HCV) and HIV is a public health challenge, afflicting more than 10 million people. With the advancement of highly active antiretroviral therapy (HAART), liver disease has emerged as a leading cause of death among HIV infected patients. Such therapies result in more liver toxicity and no specific anti-HCV drug is available yet. Therefore, a dual drug candidate would be desirable to block HCV and HIV infection. Tsou *et al.* [49] reported dual inhibition of a tetrabutoxy-calix[4]arene derivative for both HCV and HIV, studying the upper rim interacting head groups and lower rim alkylation on the roles of calix[4]arene in dual antiviral activities. Hence, they used a range of lower and upper rim modifications (such as aspartate, isophthalate, and glutamate) on the activity of the main scaffold. The substitutions of tetrabutoxy-calix[4]arene derivatives are presented in figure 9.

Maintaining the cone conformation of the calixarene scaffold is important for antiviral activity. Preorganization of the scaffold into a cone conformation for

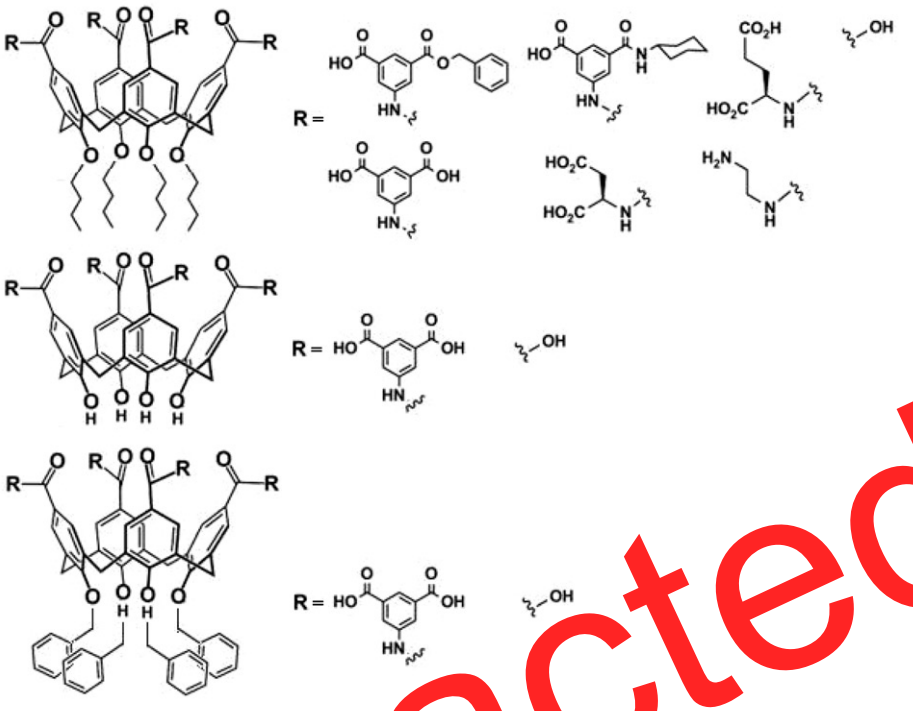

Figure 9. Tetrabutoxy-calix[4]arene derivatives used as inhibitors for HCV and HIV.

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 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*. also studied the importance of projected diacid moieties and aromatic substitutions on the upper rim, suggesting 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.

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*. [50] revealed that macrocyclons (figure 10) were effective in athymic and synthesized a number of structurally related calixarenes expressing significant antimycobacterial activity. 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 PEG chain lengths at the lower rim. It was demonstrated that the PEG chain of six repeat units was sufficient to produce calixarenes with high antimycobacterial activities, while a chain extension to

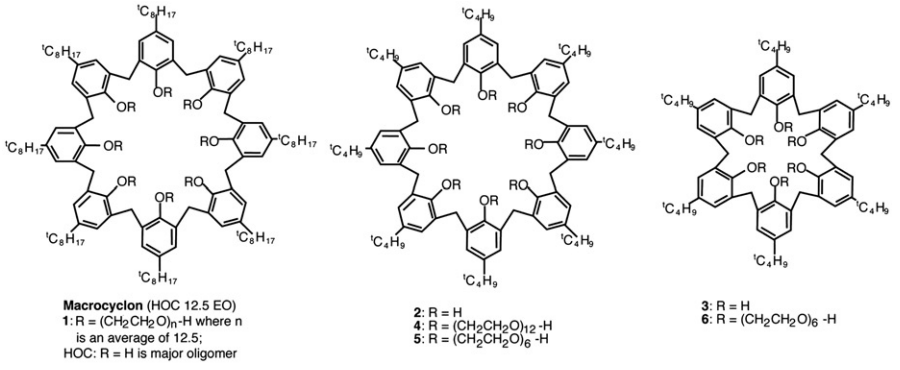

Figure 10. The chemical structures of macrocyclons used by Colston *et al.* [50].

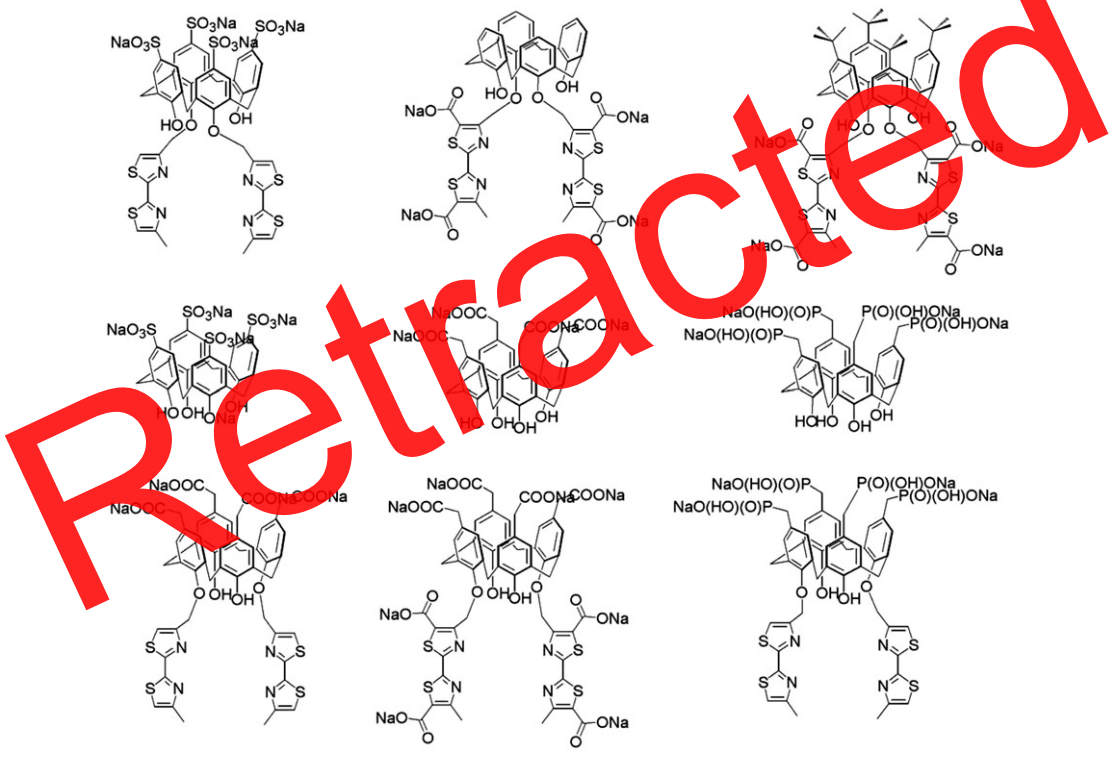

Figure 11. The synthesized scaffolds bearing carboxylate, sulfonate, and phosphonate moieties on the upper rim and 2,2′-bithiazole and hydroxyl groups on the lower rim.

PEG-12 offered no significant advantages. Finally, it was suggested that ring cavity size may be important when there is no functionalization at the lower rim.

Other studies of calixarenes with antimycobacterial activity have been reported [51, 52]. Mourer *et al.* [53] synthesized nine anionic water-soluble calix[4]arene derivatives as anti-HIV agents and detected their toxicities. The scaffolds incorporated carboxylate, sulfonate and phosphonate moieties on the upper rim and 2,2′-bithiazole groups on the lower rim (figure 11). Although most showed antiviral activity in the

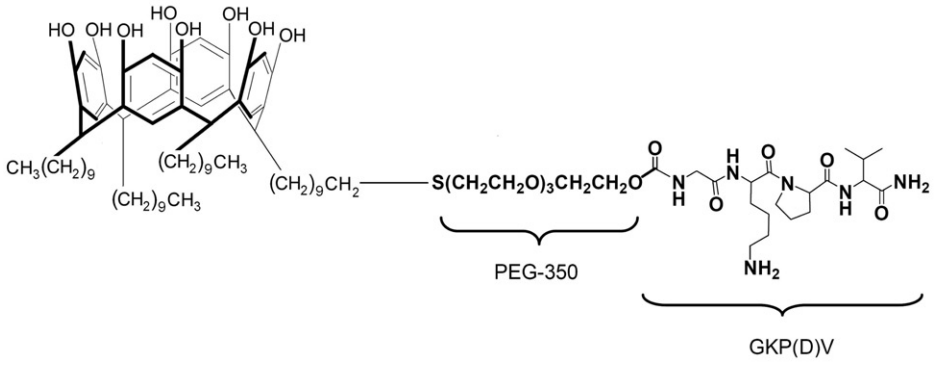

Figure 12. Illustration of the GKP(D)V peptide attached to the calix[4]arene compound *via* a PEG-350 tether link, which was then coated onto glass.

concentration range 10–50 μmol L^{-1}, the sulfonylated calix[4]arene displayed activity at a micromolar concentration. They evaluated nine anionic water-soluble calix[4]arene derivatives on the two cell lines MT4 and CEM-SS and displayed very weak or no toxicity as the CC_{50} was not reached at 100 μmol L^{-1}.

Implantable medical devices used for repair of hard and soft tissue initiate acute inflammation resulting in device failure. α-Melanocyte-stimulating hormone (MSH) bearing a short peptide sequence is produced in the body. It is a potent and natural anti-inflammatory hormone, which is easily synthesized. Charnley *et al.* [54] used α-MSH-calixarenes (figure 12) to dip and dry treat medical devices with an anti-inflammatory coating. Based 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 future research into its application as an anti-inflammatory coating for biomaterials.

6. Nuclear medicine

Al-Jammaz *et al.* [55] 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 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 N_2S_2 ligands. Bommel *et al.* [56] synthesized N_2O_2 and N_2S_2 tetradentate calix[4]arene rhenium complexes both in organic and water solvents, and demonstrated stability in a phosphorus-buffered saline solution. The $ReO(PPh_3)_2Cl_3$ substrate was reacted with tetradentate N_2O_2-calix[4]arene and produced a mixed-ligand rhenium complex with the structure $ReO(N_2O_2$-calix)OEt (figure 13). Attempts to crystallize that complex resulted in formation of a dimeric structure (figure 14). Synthesis and characterization of the N_2S_2-calix[4]arene rhenium complex is shown in figure 15. They determined crystal structures of mono- and bimetallic complexes, which have potential applications as radiopharmaceuticals.

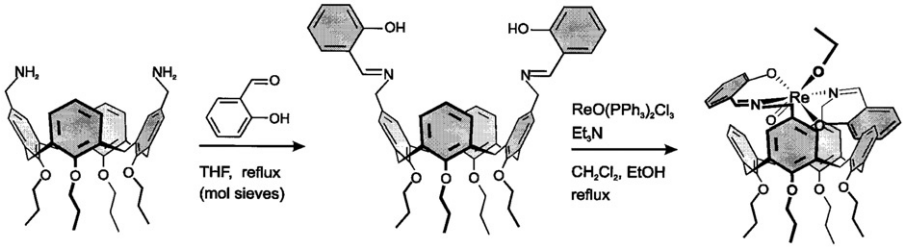

Figure 13. The synthesis for N_2O_2-calix rhenium complex.

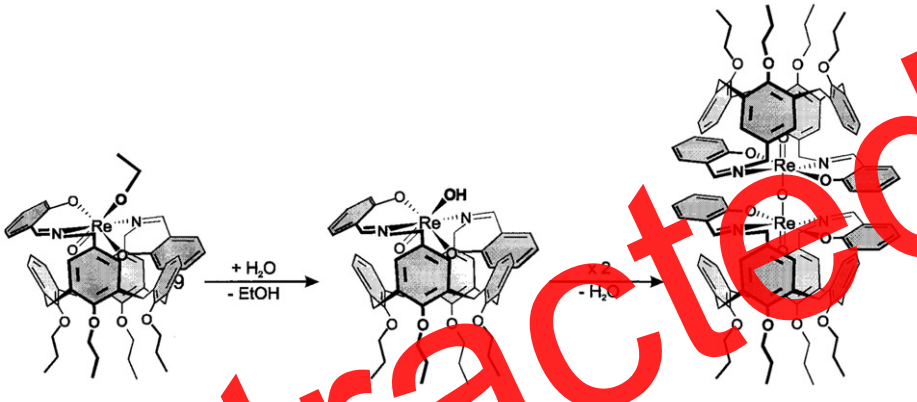

Figure 14. Formation of calix-dimer during crystallization.

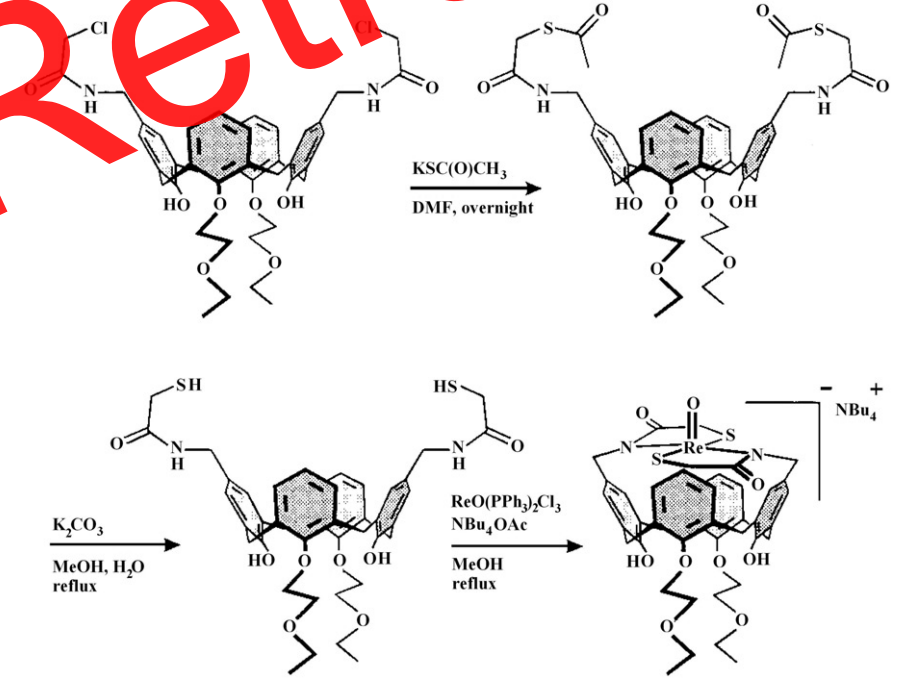

Figure 15. The synthesis of N_2S_2-calix rhenium complex.

Based upon the results, calix[4]arenes are good platforms for syntheses of 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.

7. Chemotherapy

Topotecan (TPT), a derivative of camptothecin, is a chemotherapy agent, a topoisomerase I inhibitor, used in the treatment of many diseases including small cell lung, ovarian, and cervical cancers. A problem is low solubility, which means that the agents need to be prepared as a TPT-hydrochloride to improve solubility. Wang *et al*. [57] prepared inclusion complexes of TPT (figure 16) with a sulfonatocalixarene derivative (figure 16); the dimethylaminomethyl group of TPT and the quinoline ring were encapsulated in sulfonatocalixarene and the complex was more soluble than free TPT. The encapsulated schematic of TPT is presented in figure 17. Formation of an inclusion complex was confirmed by DSC and ^{1}H NMR spectroscopy. The complex can be regarded as an important choice in the design of novel formulations of TPT for medicine.

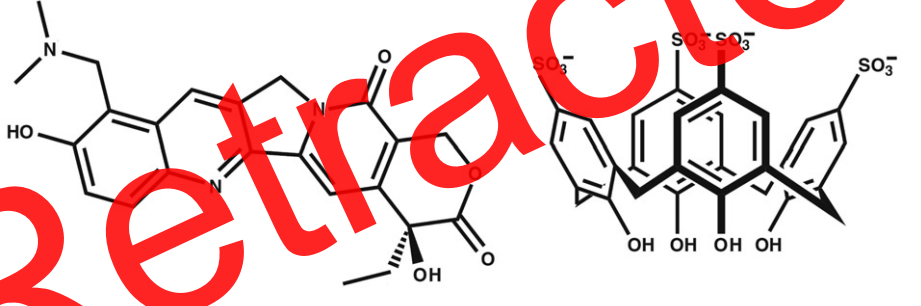

Figure 16. The chemical structure of TPT (left) and encapsulating sulfonatocalixarene. derivative (right).

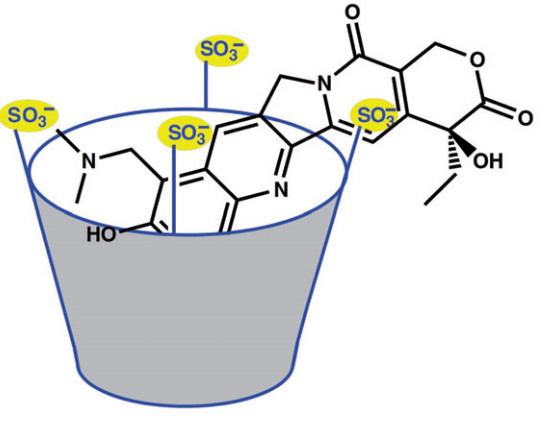

Figure 17. Schematic illustration of encapsulated TPT in sulfonatocalixarene.

Acknowledgments

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

References

[1] B. Mokhtari, K. Pourabdollah, N. Dalali. *J. Incl. Phenom. Macrocycl. Chem.*, **69**, 1 (2011).
[2] B. Mokhtari, K. Pourabdollah, N. Dallali. *J. Radioanal. Nucl. Chem.*, **287**, 921 (2011).
[3] B. Mokhtari, K. Pourabdollah, N. Dalali. *J. Coord. Chem.*, **64**, 743 (2011).
[4] B. Mokhtari, K. Pourabdollah, N. Dalali. *Chromatographia*, **73**, 829 (2011).
[5] B. Mokhtari, K. Pourabdollah. *Asian J. Chem.*, **23**, 4717 (2011).
[6] B. Mokhtari, K. Pourabdollah. *Supramol. Chem.*, (2011), DOI: 10.1080/10610278.2011.605452.
[7] B. Mokhtari, K. Pourabdollah. *J. Coord. Chem.*, (2011), DOI: 10.1080/00958972.2011.613462.
[8] B. Mokhtari, K. Pourabdollah. *J. Incl. Phenom. Macrocycl. Chem.*, in press (2011).
[9] A. Baeyer. *Chem. Ber.*, **5**, 280 (1872).
[10] A. Zinke, E. Ziegler. *Chem. Ber.*, **77**, 264 (1944).
[11] C.D. Gutsche, R. Muthukrishnan. *J. Org. Chem.*, **43**, 4905 (1978).
[12] H. Li, Y. Zhang, X. Wang, D. Xiong, Y. Bai. *Mater. Lett.*, **61**, 1474 (2007).
[13] M. Ersoz. *Adv. Colloid Interface Sci.*, **134–135**, 96 (2007).
[14] C. Ding, K. Qu, Y. Li, K. Hu, H. Liu, B. Ye, Y. Wu, S. Zhang. *J. Chromatogr. A*, **1170**, 73 (2007).
[15] D. Filenko, T. Gotszalk, Z. Kazantseva, O. Rabinovych, I. Koshets, Y. Shirshov, V. Kalchenko, I.W. Rangelow. *Sensors Actuators B*, **111–112**, 264 (2005).
[16] J.W. Cornforth, P. Darcy-Hart, G.A. Nicholls, R.J.W. Rees, J.A. Stock. *Br. J. Pharmacol.*, **10**, 73 (1955).
[17] R.V. Rodik, V.I. Boyko, V.I. Kalchenko. *Curr. Med. Chem.*, **16**, 1630 (2009).
[18] K.M. Hwang, Y.M. Qi, S.Y. Liu, W.C. Lee, W. Choy, J. Chen. *US Patent 5409959*, 1995.
[19] M.H. Paclet, C.F. Rousseau, C. Yannick, F. Morel, A.W. Coleman. *J. Incl. Phenom. Macrocycl. Chem.*, **55**, 353 (2006).
[20] W. Anthony, C. Loris, G. Baggetto, A. Nicoleta, L. Mickael, H. Michaud, S. Magnard. *US Patent 20100056482*, 2010.
[21] A.K. Singh, C.J. Venglarik, R.J. Bridges. *Kidney Int.*, **48**, 985 (1995).
[22] J.L. Atwood, R.J. Bridges, R.K. Juneja, A.K. Singh. *US Patent 5489612*, 2010.
[23] H. Li, I.A. Findlay, D.N. Sheppard. *Kidney Int.*, **66**, 1926 (2004).
[24] P. Rouge, V.S. Pires, F. Gaboriau, A. Dassonville-Klimpt, J. Guillon, S.D. Nascimento, J.M. Leger, G. Lescoat, P. Sonnet. *J. Enzyme Inhib. Med. Chem.*, **25**, 216 (2010).
[25] V.S. Pires, F. Gaboriau, J. Guillon, S. Nascimento, A. Dassonville, G. Lescoat, V. Desplat, J. Rochette, C. Jarry, P. Sonnet. *J. Enzyme Inhib. Med. Chem.*, **21**, 261 (2006).
[26] L. Latxague, F. Gaboriau, O. Chassande, J.M. Leger, V. Pires, P. Rouge, A. Dassonville-Klimpt, S. Fardeau, C. Jarry, G. Lescoat, J. Guillon, P. Sonnet. *J. Enzyme Inhib. Med. Chem.*, **26**, 204 (2011).
[27] K. Krenek, M. Kuldova, K. Hulíkova, I. Stibor, P. Lhotak, M. Dudic, J. Budka, H. Pelantova, K. Bezouska, A. Fiserova, V. Kren. *Carbohydr. Res.*, **342**, 1781 (2007).
[28] S.J. Harris. *WIPO Patent 019974*, 1995.
[29] A.M. Krishnan, R. Lohrmann. *US Patent 5846515*, 1998.
[30] M. Neagu, R.M. Ion, G. Manda, C. Constantin, E. Radu, Z. Cristu. *Rom. J. Biochem.*, **47**, 17 (2010).
[31] A.T. Yordanov, K. Deal, K. Garmestani, H. Kobayashi, B. Herring, T.A. Waldmann, M.W. Brechbiel. *J. Labelled Compd. Radiopharm.*, **43**, 1219 (2000).
[32] K. Bezouska, R. Snajdrova, K. Krenek, M. Vancurova, A. Kadek, D. Adamek, P. Lhotak, D. Kavan, K. Hofbauerova, P. Man, P. Bojarova, V. Kren. *Bioorg. Med. Chem.*, **18**, 1434 (2010).
[33] A. Fatima, S.A. Fernandes, A.A. Sabino. *Curr. Drug Discov. Technol.*, **6**, 151 (2009).
[34] H.M. Dibama, I. Clarot, S. Fontanay, A.B. Salem, M. Mourer, C. Finance, R.E. Duval, J.B. Regnouf-de-Vains. *Bioorg. Med. Chem. Lett.*, **19**, 2679 (2009).
[35] W. Yang, D.P. Otto, W. Liebenberg, M.M. Villiers. *Curr. Drug Discov. Technol.*, **5**, 129 (2008).
[36] W. Yang, M.M. Villiers. *AAPS J.*, **7**, 241 (2005).
[37] W. Yang, M.M. Villiers. *J. Pharm. Pharmacol.*, **56**, 703 (2004).
[38] V. Kalchenko, V. Kukhar, S. Kosterin. *Science and Innovation*, **Special Issue**, 22 (2007).
[39] M.M. Zareh, E. Malinowska. *J. AOAC Int.*, **90**, 147 (2007).
[40] D.L. Silva, E.C. Tavares, L.S. Conegero, A. Fatima, R.A. Pilli, S.A. Fernandes. *J. Incl. Phenom. Macrocycl. Chem.*, **69**, 149 (2010).

[41] S. Kunsagi-Mate, G. Vasapollo, K. Szabo, I. Bitter, G. Mele, L. Longo, L. Kollar. *J. Incl. Phenom. Macrocycl. Chem.*, **60**, 71 (2008).
[42] J.G. Panchal, R.V. Patel, S.K. Menon. *J. Incl. Phenom. Macrocycl. Chem.*, **67**, 201 (2010).
[43] N. Inazumi, S. Yamamoto, Y. Sueishi. *J. Incl. Phenom. Macrocycl. Chem.*, **59**, 33 (2007).
[44] Y. Sueishi, K. Asano. *J. Incl. Phenom. Macrocycl. Chem.*, **63**, 37 (2009).
[45] N. Inazumi, Y. Sueishi. *J. Incl. Phenom. Macrocycl. Chem.*, **68**, 93 (2010).
[46] S.A. Fernandes, L.F. Cabeca, A.J. Marsaioli, E. Paula. *J. Incl. Phenom. Macrocycl. Chem.*, **57**, 395 (2007).
[47] H. Hashem, T. Jira. *Pharmazie*, **60**, 186 (2005).
[48] H. Hashem, C. Trundelberg, T. Jira. *Chromatographia*, **71**, 91 (2010).
[49] L.K. Tsou, G.E. Dutschman, E.A. Gullen, M. Telpoukhovskaia, Y.C. Cheng, A.D. Hamilton. *Bioorg. Med. Chem. Lett.*, **20**, 2137 (2010).
[50] M.J. Colston, H.C. Hailes, E. Stavropoulos, A.C. Herve, G. Herve, K.J. Goodworth, A.M. Hill, P. Jenner, P.D. Hart, R.E. Tascon. *Infect. Immun.*, **72**, 6318 (2004).
[51] J.W. Cornforth, P.D. Hart, G.A. Nicholls, R.J. Rees, J.A. Stock. *Br. J. Pharmacol. Chemother.*, **10**, 73 (1955).
[52] P.D. Hart. *Science*, **162**, 686 (1968).
[53] M. Mourer, N. Psychogios, G. Laumond, A.M. Aubertin, J.B. Regnouf-de-Vains. *Bioorg. Med. Chem.*, **18**, 36 (2010).
[54] M. Charnley, K. Fairfull-Smith, N.H. Williams, J.W. Haycock. *Eur. Cells Mater.*, **11**, 26 (2006).
[55] I. Al-Jammaz, J.K. Amartey, A.F. Namor, M.M. Vora, R.M. Lambrecht. *Radiochim. Acta*, **88**, 179 (2000).
[56] K.J.C. Bommel, W. Verboom, R. Hulst, H. Kooijman, A.L. Spek, D.N. Reinhoudt. *Inorg. Chem.*, **39**, 4099 (2000).
[57] G.S. Wang, H.Y. Zhang, F. Ding, Y. Liu. *J. Incl. Phenom. Macrocycl. Chem.*, **69**, 85 (2011).