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Arkivoc **2022**, part vi, 0-0

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Synthetic strategies for the functionalization of upper or lower rim of supramolecular calix[4]arene platform[#]

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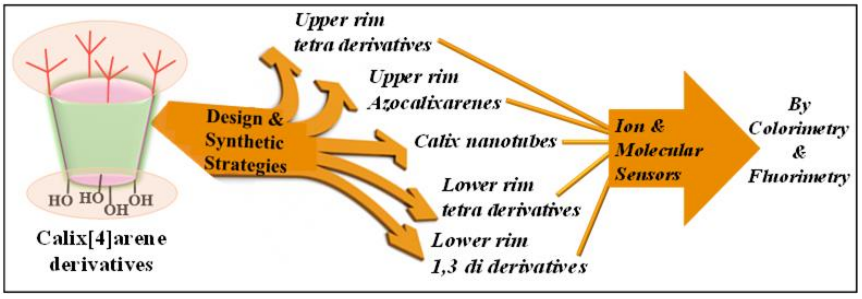
This paper is dedicated to Professor S.R. Kotha on his 65th birthday

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

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Abstract

In the broad area of supramolecular chemistry, the calix[n]arene provides a congenial platform for synthetic modifications, and further has been a highly studied system and thereby occupies a unique position among the supramolecular scaffolds. This is attributable to its pre-organised hydrophobic cavity, amenability to synthetic modifications to generate derivatives, presence of pre-organised ion binding cores along with reporter moieties both at its lower and upper rims. Such derivatizations lead to well defined conformations, and tunable functionalization at both these rims. Among various possible derivatizations, the synthetic strategies of those leading to cone conformation have been rationalized in this review article. In addition, some insights into the synthesis of calix[4]arene dimers and tubes, and a variety of different macrocyclic derivatives of the calixarene have also been taken into consideration. All the conjugated derivatives of calix[4]arene platform reported in this article have been provided with a relevance to highlight their application potential.



Keywords: Calix[4]arenes, cone conformation, synthetic strategy, lower rim derivatives, upper rim derivatives, calixtubes, ion and molecular sensors, cargo to transport genetic material

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1. Introduction

Calix[4]arene is a supramolecular macrocycle formed from the base catalyzed condensation of *tert*-butyl phenol with formaldehyde. The macrocycle has a lower rim with four phenolic-OH groups and an upper rim with four *p*-*tert*-butyl groups. All the four phenolic-OH groups are interconnected through circular hydrogen-bonds at the lower rim to result in a cone-like structure. As a result, the supramolecule possesses a hydrophobic cavity which is well known for its host guest interactions.[1-5] The macrocycle can be modified both at its lower rim as well at its upper rim by organic derivatization and such derivatizations are well reported. The literature witnessed that the macrocycle has derivatizations at both the rims of the calix[4]arene.[6-10] Thus the organic derivatization on the platform of such supramolecule results in multiple-functionalization of calix[4]arene either at its lower rim or at its upper rim or both and turns out to be a cause

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to generate plethora of conjugates. The idea behind such organic derivatization is to generate conjugates having specific function and or application.

All this has been possible because of the remarkable role played by various eminent scientists to introduce and explore the calix[n]arenes as supramolecules with important applications. Professor David Gutsche, who is known as the godfather of the calixarene chemistry, along with his co-workers reported various fundamental aspects of the synthesis of calixarenes and optimized the reaction conditions for one-pot synthesis of calix[4], [6] and [8]arenes on a large scale. They also explored the mechanism of calixarene formation along with isolation and characterization of larger members of this supramolecular family.[11-13] On the other hand, Shinkai and co-workers have explored novel strategies for the cavity design using calix[n]arene platforms and explained how the cavity shape has greater affinity and selectivity towards the guest molecules.[14-15] Ungaro's group made significant contribution to this area by obtaining the X-ray structure of some of these molecules at an early stage wherein the toluene trapped calix[4]arene has been the first example of a receptor under this class of supramolecules.[16-17] Reinhoudt and co-workers have developed different molecular structures/three dimensional networks based on non-covalent interactions exhibited by the self-assembly of more than two calixarene platforms. This group also reported the selective introduction of functional groups both at the upper and at the lower rim of the calix[4]arene and explored their enzyme mimetic activity, membrane transport and selective ion sensor property.[18-19] McKervey's group pioneered in the development of novel calixarene derivatives and demonstrated their ion complexing and sensing aspects.[20]

All these activities brought a sharp turning point resulting in a sudden surge in the research related to the calix[n]arenes. This also motivated chemists to tackle the synthetic challenges and several other scientists to use these supramolecules for demonstrating a property or an application or a purpose or a combination of more than one of these with a view to generate some viable technologies in the time to come.

Therefore, the primary focus of this review article is to address the emergence of different types of derivatizations on calix[4]arene which were well spread in the literature.[21-23] The outcome of such an exercise would help the designers to come out with propositions for novel derivatizations. All this pose challenges to the synthetic chemists and eventually to quench the thirst of application scientists in bringing useful properties of such supramolecular conjugates for the benefit of mankind. Thus, there is a huge potential for the translational research based on calixarene conjugates. The recent literature has started witnessing the modification of the property and or the purpose of such a supramolecular conjugate upon anchoring on to some surfaces in bringing out an added dimensionality for such molecules. The sensing and the recognition properties of lower rim 1, 3 di derivatized calix[4]arene are well documented and were reviewed in the literature,[24-28] however, there has not been enough efforts in bringing out the applications of the derivatives when anchored on to a surface.[29-34] In this article we attempted to bring a variety of the synthetic strategies used across various derivatizations on the calix[4]arene scaffold on to a common platform to provide a focus and impetus to the supramolecular designers and the synthetic chemists alike.

1.1 Conformations of calix[4]arene

Among the various calix[n]arene derivatives, calix[4]arene has been widely studied. Calix[4]arene mainly exists in four different conformations, viz., cone, partial cone, 1,2-alternate, and 1,3-alternate as represented in Figure 1. Depending upon the chemical modification, the calix[4]arene derivative can be frozen into one of these conformations.[35-38] The relative stability of various conformers of *p-tert*-butylcalix[4]arene follows the order: cone (most stable) > partial-cone > 1,2-alternate > 1,3-alternate. The calix[4]arene cone conformation is confirmed by the ^{1}H-NMR having a pair of doublets at delta 4.45 and 3.14 ppm due to bridging methylene

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groups.[39] Most widely explored conformation among these is the cone and the one next to that is the 1, 3 alternate conformation. In this article our main focus is to bring out the well proven strategies for the derivatization of the upper and lower rim of calix[4]arene primarily in their cone conformation on to a common platform so as to assist and encourage the chemists to design their derivatives and to execute their synthetic tasks with ease.

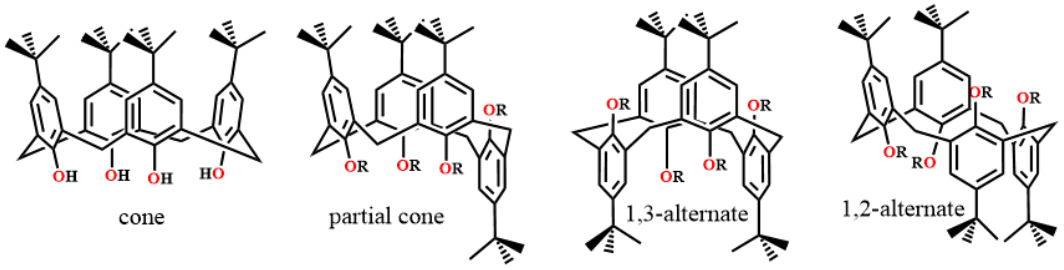


Figure 1. Four different conformations of *p-tert*-butyl-calix[4]arene.

1.2 Derivatizations on the platform

p-tert-Butylcalix[4]arene, shown in Figure 2, can be modified in different ways due to its reactive positions at the upper rim formed upon the removal of *p-tert*-butyl group, and at the lower rim by functionalizing the hydroxyl groups with identical or non-identical functional groups. With that, overall there are three possible centers of modifications of calix[4]arene derivatives, viz., (i) at the lower rim, (ii) at the upper rim and (iii) at both the rims simultaneously. Since there are four such positions at each of the rim, possible conjugates are several and all such combinations are not well explored in the literature. Here, in the present article, different kinds of commonly found multi-functional calix[4]arenes have been addressed as long as such derivatives are used in some application. The convenient way of making bifunctional building blocks has been presented in Scheme 1. All this will help the readers to design the calixarene as to meet their specific application.

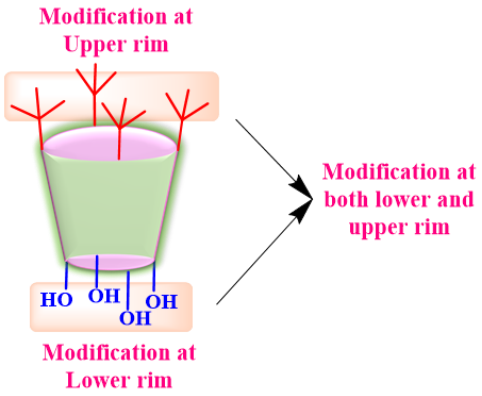


Figure2. The generalized modes of modification at calix[4]arene platform.

2. Modifications at the Lower Rim of Calix[4]arene

The phenolic hydroxyl groups at the lower rim of the calix[4]arene provide excellent reactive centers for the introduction of various chemical groups which in turn are useful in tuning the functional properties of these

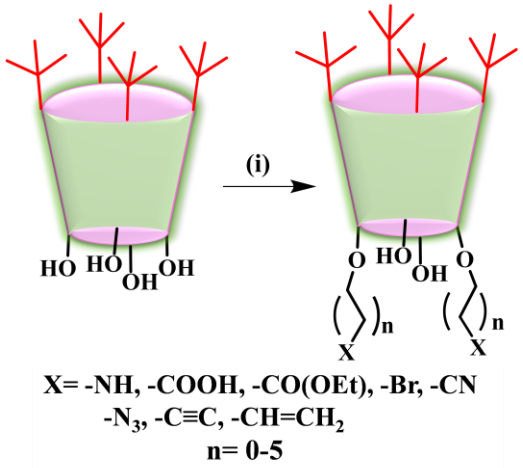
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supramolecules. The hydroxyl groups of calix[4]arene at the lower rim can derivatized to result in mono-, di-, tri- and tetra- substituted derivatives to provide different terminal functional groups. Among these the 1,3-diderivatives are the most commonly occurring ones owing to their cone conformation and these are dealt in detail in this article.

2.1 Substitution at two alternate (1,3-) –OH groups on the lower rim

There are simple ways to functionalize two alternate –OH groups of *tert*-butyl calix[4]arene platform selectively. The alkylation and the etherification at the lower rim are a few most commonly performed reactions which resulted in high yields of products.

2.1.1 Terminal linker groups as lead precursors: Different functional groups or moieties can be introduced at these two positions of calix[4]arene by a variety of terminal linkers, such as, amino, carboxylic, ester, azide, nitrile, bromo, alkyne, alkene, and several related ones, as can be noticed from Scheme 1. All this can be achieved by using a mild base, such as, K_2CO_3 in dry acetonitrile or acetone under argon atmosphere. For such O-alkylation reactions, Br-CH_2-$(CH_2)_n$-X, where X = -NH_2, -COOH, -CO(OEt), N_3, CN, Br, -C≡CH, -CH=CH_2 , acts as precursors, where the 'n' varied from one to five. The resultant derivatives act as lead precursors to further develop different calixarene conjugates possessing suitable binding groups and or flurophores. The resultant conjugates were explored for various applications including those of ion and molecular sensing. In almost all the reactions mentioned in Scheme 1, the precursors were obtained in 70-90% yield.[40-42]

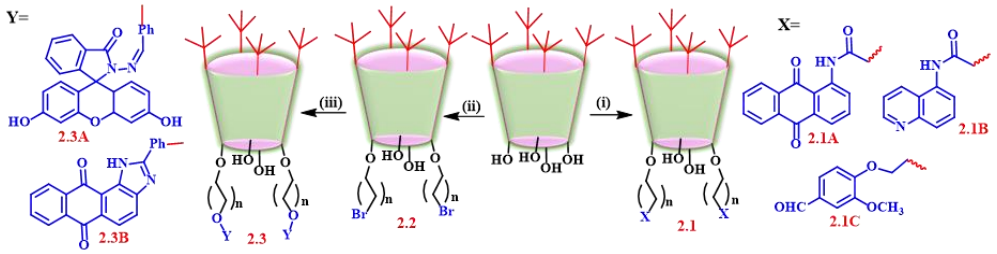


Scheme 1. General synthetic scheme for lower rim 1, 3-alternate calix[4]arene derivatives. The reagents and conditions for the reaction (i) are K_2CO_3, X-CH_2-$(CH_2)_n$-Br, dry CH_3CN, 24-48 h, reflux.

2.1.2. Synthetic strategies from the terminal halide group and the application potential of the derivatives: The lower rim hydroxyl groups can easily undergo reaction at its alternate –OH groups in a single step as given in Scheme 2 under **2.1**. Three different derivatives of the calix[4]arene have been discussed under the category of **2.1**, viz., **2.1A**, **2.1B** and **2.1C**. The synthetic strategy is rather simple and gave product yield of 70-80 % upon adding ether to the reaction mixture. In **2.1A**, two amido-anthraquionone groups present at the lower rim of calix[4]arene results in a selective F^- sensor.[43] Carboxamidoquinoline appended calix[4]arene (**2.1B**) derivative has also been synthesized in a single step reaction of *p*-tert-butyl-calix[4]arene with 2-chloro-N-(quinolin-8-yl) acetamide to result in 55% yield. This derivative has been demonstrated as a turn-on fluorescent sensor for Zn^{2+} ions.[44] Similarly, the 1,3 disubstituted aldehydes given under **2.1C** were also

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synthesized by a direct reaction in 65% yield as white solid, which further acts as a precursor for Schiff's base derivatizations.[45]

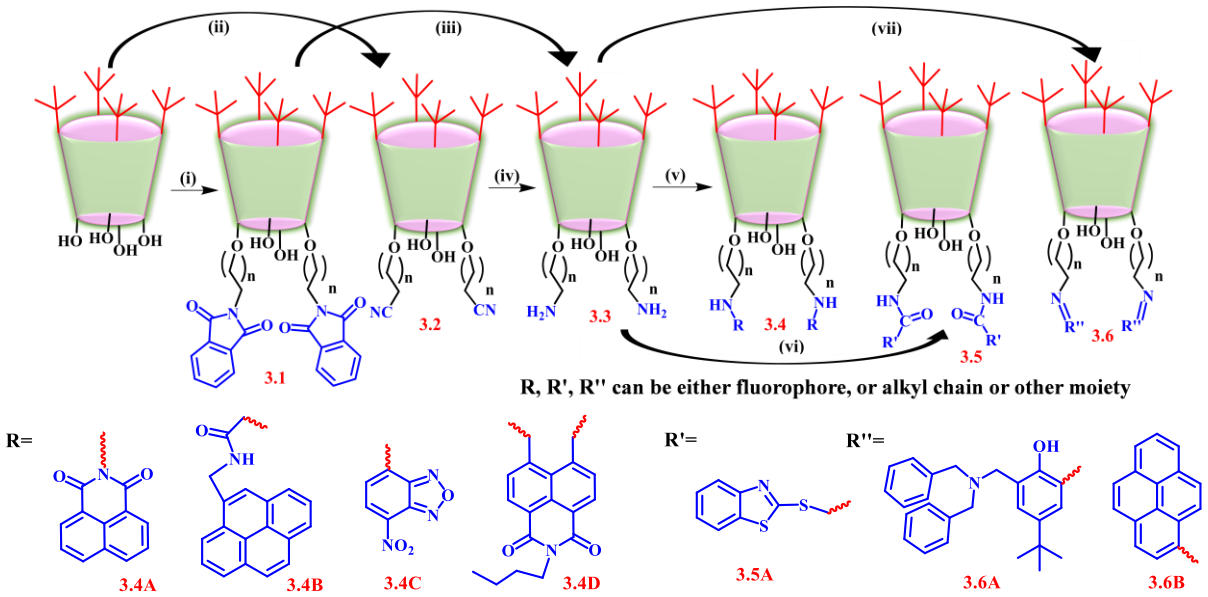


Scheme 2. Synthetic scheme for calix[4]arene derivatives either by direct reaction of two alternate –OH groups or by using terminal –Br group derivative as precursor. Reaction conditions where (i) K_2CO_3, NaI, X-CH_2-$(CH_2)_n$-Br, CH_3CN, N_2 atm, 2-4 days results in **2.1A/2.1B/2.1C**; (ii) K_2CO_3, CH_3CN, N_2 atm, 24h, 1,3 dibromopropane to result in **2.2**; (iii) p-hydroxy benzaldehyde, K_2CO_3, reflux results in **2.3**, further reaction in acetic acid, ethanol and reflux with fluorescein hydrazine results in **2.3A**/diaminoanthraquinone results in **2.3B**.

Similarly, the calix[4]arene derivatives having bromo- terminal group were generated from the reactions carried out using dibromoalkanes in the presence of mild base to result in the lead molecule with **2.2**. This structure further generates novel calixarene conjugates of importance to result in a variety of applications. Two such examples have been given here as **2.3A** and **2.3B**. The reaction of the **2.2** with p-hydroxy benzaldehyde resulted in the formation of aldehyde derivative at the terminal which upon further reaction with different hydrazine/amine resulted in Schiff base cores. The off-white solid product of the **2.3A** has been recrystallized from acetonitrile and obtained a pure product in 85% yield whereas **2.3B** obtained in ~80% yield. The **2.3A** has been demonstrated to be a suitable derivative for exhibiting preferential recognition of Cu^{2+} ions over several others[46] and the **2.3B** for Zn^{2+} ions[47] and hence these two derivatives are suitable as sensors because of their cone conformation and the congenial binding core selective for the corresponding ion over several other ions studied.

2.1.3. Synthetic strategies from the terminal cyano group and the application potential of the derivatives: The calixarene 1,3 lower rim derivatives having $–NH_2$ or –NHR group can be synthesized by different routes as shown in Scheme 3. The **3.3** with –amino-terminal can be synthesized using deprotection of bromopropylpthalimide (**3.1**) or by the reduction of –CN derivative (**3.2**) using $LiAlH_4$. The off-white solid product of **3.3** obtained through the bromopropylpthalimide route was ~87% and that obtained by the reduction method was ~80%.[48] Different conjugates of **3.3** can be generated by a few basic reactions followed by amide coupling or Schiff's base reaction as can be noticed from Scheme 3 (**3.4**, **3.5**, **3.6**) and hence provides more general approach to obtain these derivatives in such high yields.

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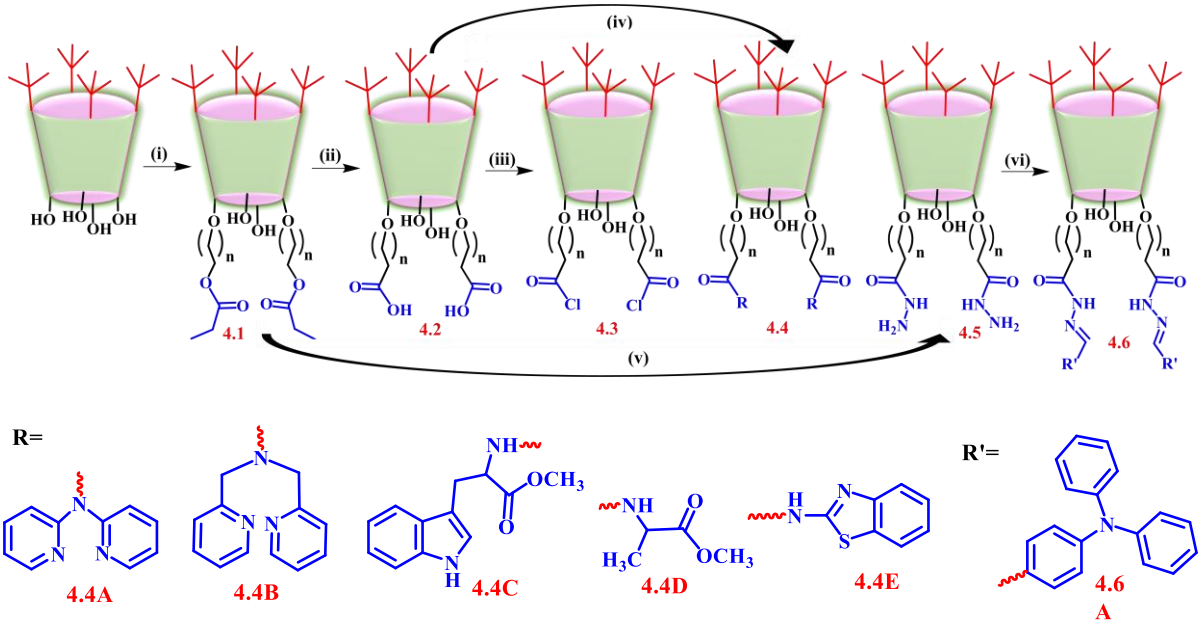
Scheme 3. Synthetic strategy for various amine and nitrile terminal lower rim 1, 3 alternate calix[4]arene derivatives: (i) 3-bromopropylnapthalimide, K_2CO_3, 24 h, acetonitrile, N_2 atm (**3.1**); (ii) K_2CO_3, $ClCH_2CN$, acetone, 7h reflux (**3.2**); (iii) hydrazinehydrate, reflux, ethanol, 24 h (**3.3**); (iv) $LiAlH_4$, $C_2H_5OC_2H_5$, 5h reflux (**3.3**); (v) naphthalic anhydride, C_2H_5OH, reflux, 12 h (**3.4A**), 2-pyrenemethyl isocyanate, dioxane, N_2 atm, 4h (**3.4B**); 7-chloro 4-nitrobenzofurazan, pyridine, ethanol, 24 h (**3.4C**); N-butyl-4-Bromo-5-nitro-1,8-napthalimide methoxyethanol, reflux, 10h (**3.4D**); (vi) 2-mercaptoheterocycle, $NaHCO_3$, CH_3CN, reflux (**3.5A**); (vii) 3-((dibenzylamino)methyl)-5-tert-butyl-2-hydroxybenzaldehyde, EtOH, RT, 12 h (**3.6A**); 1-pyrenecarbaldehyde, MeOH/THF, reflux, 6h (**3.6B**).

The nucleophilic reaction of **3.3**, the $–NH_2$ derivative of calix[4]arene, with different organic halides as given in Scheme 3 resulted in **3.4A**, **3.4B**, **3.4C**, **3.4D** in very high product yields of 70 to 90 %. The 1, 3-di-naphthalidiimide derivative of calix[4]arene with **3.4A** exhibited efficient receptor properties for various environmental pollutants of polyaromatic hydrocarbons.[49] The pyrene appended calix[4]arene derivative **3.4B** shows high selectivity towards HSO_4^- over other anions owing to its specific H-bonding interactions present between the anionic guest species and the urea protons and also between -OH of the guest with the ether oxygens, thus separating the π…π stacking interactions.[50] The **3.4C** has been demonstrated to be an excellent sensor for F^- having a limit of detection (LOD) of 10.1 nM owing to their selective X-H…F^- interactions where X = O, N or C emerging from the arms and bridging -CH_2 moiety.[51] A naphthalimide derivative with **3.4D** showed selective sensing for Cu^{2+} and F^- as supported by the fluorescence emission studies.[52] While the selectivity for Cu^{2+} was attributed to the binding core formed by the N_2O_2 arsing from the naphthalimide nitrogens and calixarene oxygens, that for F^- is attributable to the binding pocket extending H-bonding through four hydrogens of NH and OH groups. The **3.5A** bearing benzothiazole moiety at the lower rim of –amino-calix[4]arene was obtained in ~80% yield and has been demonstrated to be an iodide sensor.[53] In this the selectivity iodide ion is attributed to the orientation of both the arms such that the amide NH groups extend hydrogen bonding with the guest species. The salicylyl imine conjugate having dibenzyl moiety with **3.6A** has been obtained in 52% yield as yellow solid and has been demonstrated for sensing bio-essential transition elements, such as, iron, copper and zinc using colorimetric and fluorometric techniques.[54] The sensing of Cu^{2+} and Zn^{2+} has been attributed to the N_2O_2 coordination core formed by these ions with the arm moieties to result in distorted geometries of square planar and tetrahedral respectively. The pyrene appended calixarene

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3.6B has been obtained in 78 % yield as a light yellow solid and was further recrystallized from dichloromethane/methanol to yield pure product that is very well suited for fluorimetric sensing applications due to the presence of the fluorescent pyrene moiety since its fluorescence changes can be easily monitored.[55]

2.1.4 Synthetic strategies from the terminal ester / acid group and the application potential of the derivatives: The conjugates of the lower rim 1,3 di derivatives of the ester and acid groups are synthesized using the routes given in the Scheme 4. The calix[4]arene 1,3 diester, **4.1**, can be easily converted to the diacid (**4.2**), followed by di-acid chloride (**4.3**), wherein **4.3** acts as a reactive lead to generate amide derivatives through condensation reaction with the corresponding amine yielding the products in 60-80%.[56-57] Alternatively, even the diacid precursor can also be used directly to convert to amide using the standard amide coupling regents, such as, EDC and DCC to result in the product yields of ~50-60%. [58]



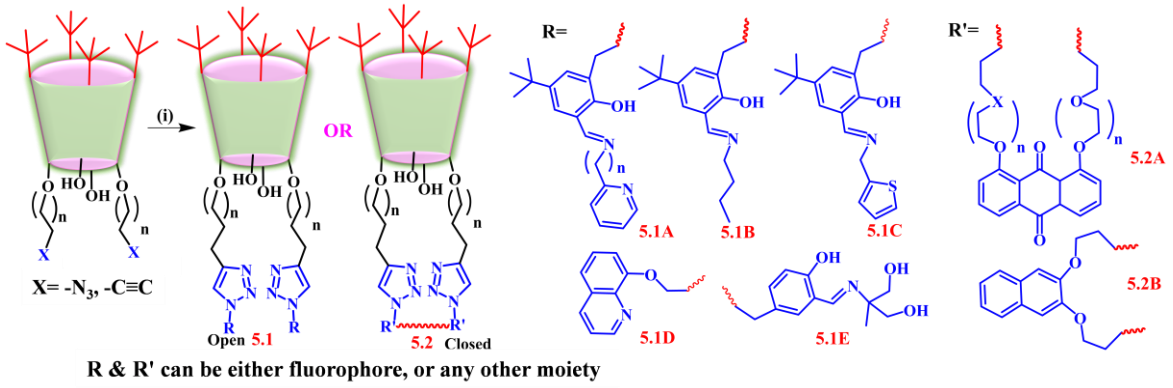
Scheme 4. Synthetic strategy for ester and acid terminal lower rim 1, 3 alternate calix[4]arene derivatives: (i) acetone, K_2CO_3, $BrCH_2COOEt$, reflux,15 h (**4.1**); (ii) EtOH, aq NaOH, reflux, 24 h (**4.2**); (iii) $SOCl_2$/benzene, reflux (**4.3**); (iv) 2,2'-dipyridyl amine, Et_3N, THF, 48h, RT (**4.4A**); bis(2-picolyl)amine, Et_3N, THF, 48h, RT (**4.4B**); DMAP, Et_3N, dry $CHCl_3$, (**4.4C**); ester of alanine, dry THF, Et_3N, HOBT, DCC (**4.4D**); 2-aminobenzothiazole, Et_3N, THF (**4.4E**); (v) $NH_2NH_2.H_2O$, $CHCl_3$:MeOH (1:3) (**4.5**); (vi) 4-formyltriphenylamine, triethylamine, EtOH (**4.6A**).

The derivatives given in the Scheme 4 have been obtained in moderate to good yield and were explored for some ion sensing applications. A calix[4]arene derivative possessing bis-{N-(2,2'-dipyridylamide)} pendants forms two distinct binding cores, viz., one with N_4 and the other with O_6 and exhibit Zn^{2+} sensing by *switch-on* and Ni^{2+} by *switch-off* fluorescence. The sensing is due to the formation of a complex with N_4 binding core in case of Zn^{2+} with tetrahedral geometry and an N_4O core with a vacant site exhibiting an octahedral geometry in case of Ni^{2+}, thus showing that the binding cores and their geometric orientation of the arms provides tuning to the selectivity to a particular ion over the other.[59] On the other hand, the 1,3-di{bis(2-picolyl)}amide derivative of calix[4]arene with **4.4B** obtained in 35% yield and showed high selectivity toward Ag^+ by forming a 1:1 complex, among several other biologically important metal ions studied.[57] Chiral recognition of asymmetric compounds is important in the field of supramolecular and biomedical chemistry. The tryptophan appended calixarene derivative with **4.4C** obtained as a white powder in 60% yield and it showed

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enantioselective fluorescent sensing towards enantiomers of mandelate.[60] Amido-calix conjugate with **4.4D** exhibited potential receptor property towards carboxylic rich amino acids, viz., Asp/Glu residues owing to the specific H-bonded interaction extended between the arms on the derivative and that of the guest molecule.[61-62] The compound with **4.4.E**, obtained in 50% yield upon re-crystallization from EtOH/$CHCl_3$ as white solid showed excellent sensing property for Cu^{2+} with LOD of 403 ppb.[56] The selectivity for this sensing comes from the 1:1 complex formed between **4.4E** and Cu^{2+} through N_3S_2 coordination core, wherein one of the N-comes from the solvent acetonitrile, leading to trigonal pyramidal geometry about the metal centre. The **4.6A** bearing triphenylamine unit at the lower rim of the calix[4]arene has been recrystallized using 1:5 vol/vol mixture of $CHCl_3$/EtOH and obtained as white solid in 57% yield. This pure product of conjugate of calixarene is an effective naked eye sensor for Hg^{2+} owing to its visual colour changes in acetonitrile and further the Hg^{2+} bound system shows fluorescence quenching in presence of F^- ion and thus calix[4] derivative **4.6A** acts as a dual sensor.[63]

2.1.5 Synthetic strategies from the terminal azide and alkyne groups and the application potential of the derivatives: Lower rim 1, 3 di-derivative of calix[4]arene having $–N_3$ and alkyne group at the terminal leads to the development of various molecules *via* click reaction in the presence of $CuSO_4$ and sodium ascorbate in a suitable solvent medium as given in the Scheme 5. 1,3 Di-derivative of calix[4]arene appended with alkyne group has been recrystallized from $CHCl_3$/MeOH as white solid in 86% yield. Click chemistry has also been used to synthesize calixarene conjugates possessing chromophores and bioactive molecules having open and closed structures as can be noticed from Scheme 5.[64-65] Click reaction has been further used as a general method to functionalize the calix[4]arene lower rim due to the highly selective nature of the alkyne–azide cycloaddition reaction. Thus, the click chemistry-derived triazoles play important role in sensing ions and molecules and are important in exhibiting biological activities.



Scheme 5. Synthetic strategy for the azide and alkyne based 1,3 di-derivatives of calix[4]arene to result in the products of open (using the reagent based on R, **5.1**) and closed (using the reagent based on R', **5.2**) structures *via* click reaction: (i) $CuSO_4.5H_2O$ and sodium ascorbate in DCM : water (1:1), rt, 12 h.

Our research group synthesized a series of triazole based calix[4]arene derivatives with **5.1A**, **5.1B**, **5.1C**, **5.1D** and **5.1E** in excellent yields of ~80-95% and demonstrated their efficiency and selectivity towards Zn^{2+} sensing by turn-on fluorescence due to the formation of a square pyramidal complex with N_3O_2 core where the coordination extends from both the arms. The receptor **5.1A** is robust enough to sense Zn^{2+} ions even in the presence of proteins and or even in serum where the N_3O_2 coordination core is not exposed to the

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medium or the proteins present in the serum to interact.[66] This aspect is very clear when one looks at the crystal structure. The **5.1B** has been obtained as an yellow crude product and upon recrystallization from MeOH yielded pure product in excellent yield of ~95%.[67] The Zn^{2+} complex of the conjugates of **5.1B** and **5.1C** act as secondary sensors for anionic species of cysteine and phosphates by removing the Zn^{2+} from its parental complex.[68] The hydroxy quinolone appended di- derivative of calix[4]arene with **5.1D** obtained as pale white solid in 93% yield and the product has been demonstrated as a potential sensor for Hg^{2+} ion in acetonitrile–water (3:1, v/v) due to the formation of complex with N_4 core arising from both the arms of the derivative **5.1D**. [69]

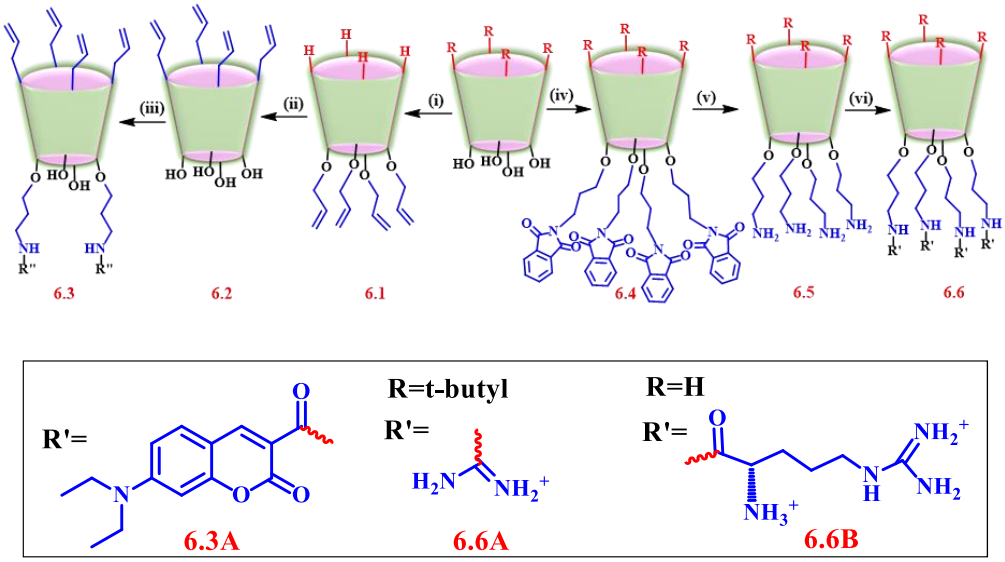
Calix[4]arene with **5.2A** having an anthraquinone moiety linked through triazole results in a closed structure by click reaction and resulted the product in 35% yield and this product has been demonstrated to be a selective chemosensor for Ca^{2+} owing to the 1:1 complex formed with **5.2A** using the phenolic and ether oxygens in addition to the triazole nitrogens with the cyclic core formed on the platform. The corresponding Ca^{2+} complex as a sensor for F^- ions by fluorescence quenching due to the removal of the Ca^{2+} ion from this complex.[70] A similar conjugate with naphthyl-calix[4]arene derivative, **5.2B**, in the closed form has been obtained by click reaction in 50% yield upon purification by column chromatography using ethyl acetate and pet-ether in 2:1 ratio as eluant. This conjugate of closed form at the lower rim of calix[4]arene exhibited high affinity towards *p*-nitroaniline due to the formation of 1:1 complex through some specific hydrogen bonding and hydrophobic interactions and is not selective the other related derivatives. [71]

2.2 Substitution at all the four lower rim –OH groups (tetra-derivative)

Derivatization at all the four –OH groups of the lower rim can be achieved by using a strong base, such as, sodium hydride. The dealkylated calix[4]arene in the presence of allyl bromide by using NaH as a base results in **6.1** as off white solid in 71% yield.[72] The **6.1** undergo Claisen rearrangement to result in **6.2** and the recrystallization of the crude product from methanol resulted in white crystals in 91% yield.

2.2.1 Synthetic strategies for lower rim tetra-amino derivatives and their cargo-application to deliver plasmid DNA: The upper rim allyl derivative of the calix[4]arene, viz., **6.2** upon reaction with N-bromopropyl phthalimide resulted in lower rim intermediate derivative which upon reaction in presence of hydrazine hydrate resulted in an upper rim tetraallyl and lower rim di-amino derivative of calix[4]arene in ~75% yield.[73] The upper rim tetraallyl and lower rim di-amino calix[4]arene derivative on reaction with 2,5-dioxocyclopent-3-en-1-yl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate resulted in **6.3A** in 70% yield as yellow powder and this acts as a selective sensor for Fe^{3+} through binding in acetonitrile in nanomolar range. However, the detection goes to picomolar when **6.3A** was anchored on to SiO_2 nanospheres.[74] The *p*-*t*-butyl calix[4]arene/DC4A can be derivatized at all its –OH groups of the lower rim with –propyl phthalimide group to result in **6.4** in ~77% yield. The **6.5** has been obtained by the reduction of **6.4** in presence of hydrazine hydrate. The lower rim tetra guanidinium derivative of calixarene, i.e., **6.6A** has been synthesized by using the reaction conditions given in Scheme 6 in quantitative yield as white crystalline material.[75] The **6.6B** (Figure 5, Scheme 6) having four single arginine units has been synthesized by covalently attaching to the lower rim of a calix[4]arene and this resulted in white powder product in 65% yield.[76] The derivatives, **6.6A** and **6.6B**, possessing cationic guanidine and arginine moieties on the calix[4]-platform have been used as cargo to deliver DNA in cell transfection studies.

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Scheme 6. Synthetic strategy for lower rim di- and tetra-derivatives: (i) NaH/THF, allylbromide, N_2 atmosphere, reflux, 24 h (**6.1**); (ii) N,N-dimethyl-aniline, N_2 atmosphere, 210 °C, 6 h (Claisen rearrangement, **6.2**); (iii) 3-bromopropyl phthalimide, K_2CO_3, in acetonitrile, at 48 h reflux followed by deprotection using $NH_2NH_2.H_2O$ and 2,5-dioxocyclopent-3-en-1-yl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate, N,N-Diisopropylethylamine (DIPEA), and dry DMF, 24 h, stir in dark (**6.3A**); (iv) N-(3-bromopropyl)phthalimide, NaH, dry DMF, N_2, rt (**6.4**); (v) $NH_2NH_2{\cdot}H_2O$, EtOH, N_2, reflux (**6.5**); (vi) N,N′-di-Boc-N″-triflylguanidine, CH_2Cl_2, N_2, rt followed by HCl 37%, 1,4-dioxane, rt (**6.6A**) / Carbobenzyloxy-L-Arg-OH, N,N' –dicyclohexylcarbodiimide (DCC), HOBt, dry DMF, rt followed by H_2/Pd(C), HCl, ethanol, rt (**6.6B**).

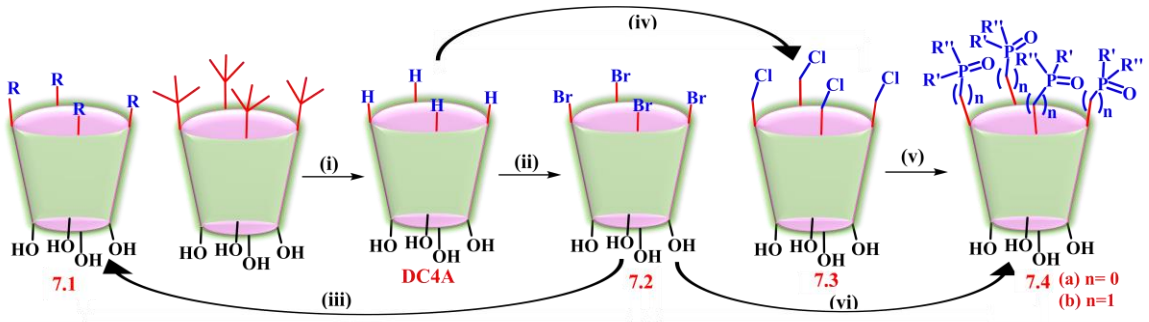
3. Upper Rim Derivatizations

The calix[4]arene has been modified at the upper rim by introducing various functional groups. The upper rim modification can be done either by dealkylating the tertiary butyl group or by carrying out the ipso-reaction. The sulfonation, nitration, phosphorylation, alkylation and acylation are some common reactions used for the modification of the upper rim of calix[4]arene.[77-78] The direct upper rim modification reactions have resulted in products with excellent yields of ~70-90% and this gives a synthetic leverage to derivatize at the upper rim.

3.1. Upper rim tetra-halo and tetra-phosphonato derivatives

Removal of *p-t*-butyl groups by the catalysis of $AlCl_3$ (Friedal Crafts' reaction) resulted in the formation of dealkylated calix[4]arene (DC4A). The DC4A on reaction with bromine resulted in the formation of an upper rim tetrabromo calix[4]arene derivative given in **7.2**. The **7.2** is converted to **7.1**. by palladium catalysed Sonogashira-Hagihara cross-coupling reaction with different acetylene linkers.[79] The **7.4** can be synthesized from tetra-*p*-chloromethyl-calix[4]arene, i.e., **7.3**. in the presence of $POEt_3$/Ph_2POEt, to form tetra-phosphonatoester as white gummy powder in ~78% yield.[80-81]

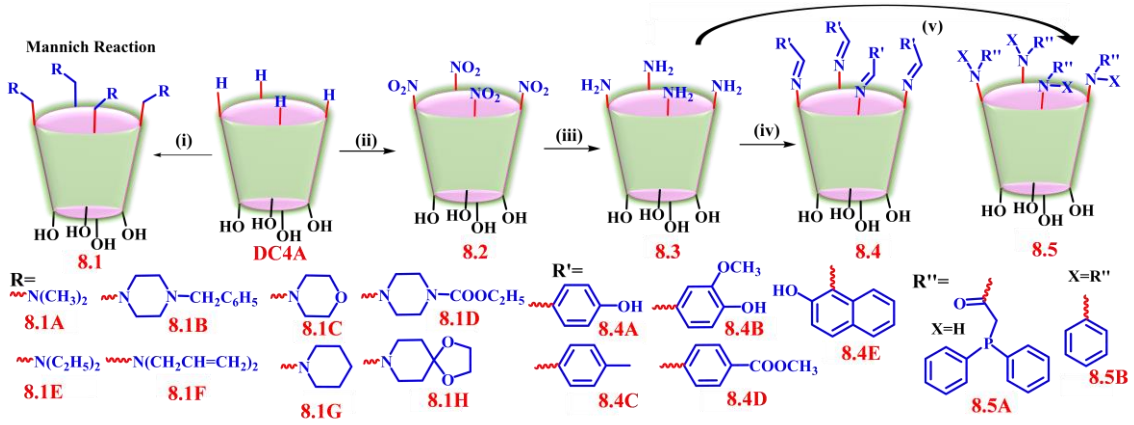
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Scheme 7. Synthetic route for the upper rim tetra-derivatives: (i) $AlCl_3$, phenol, toulene, rt, 24h (**DC4A**); (ii) Br_2, DMF, rt, 4 hrs (**7.2**, R is an acetylene linker); (iii) $Pd(PPh_3)_2$, CuI, DIPEA, THF, 65^{0}C, 60 h (**7.1**); (iv) $POEt_3$, CH_2Cl_2, reflux (**7.3**); (v) $P(OEt)Ph_2$/ $P(OEt)_3$, toluene, reflux, 6 h (**7.4**); (vi) $P(OR')_3$, $NiCl_2$, diphenyl ether, 210˚C (R=R'=OCH_3) (**7.4**).

3.2. Upper rim tetra-amino / -Schiff base / -Mannich base derivatives and their application potential

The upper rim calix[4]arene derivatives incorporated with $–NO_2$ and $–NH_2$ groups have been explored in the literature.[82-84] The DC4A reacts readily with secondary amine and formaldehyde, and this resulted in the formation of Mannich bases. This reaction has been demonstrated using a broad range of secondary amine derivatives (**8.1A** to **8.1H**) as shown in Scheme 8. All the upper rim calix[4]arene derivatives which are Mannich bases (**8.1 A-H**) were obtained in excellent yields in the range 72 to 86% as white crystalline solid. In this Scheme, the synthetic strategy for the formation of tertaaminocalix[4]arene (**8.3**) has been shown starting from DC4A followed by nitration using HNO_3 and then the reduction using Pd/C in the presence of hydrazine hydrate. The tetra-aminocalixarene has been explored for the formation of various imino-calix[4]arene derivatives *via* Schiff base formation (**8.4A-H**). [82-84] The yield of yellow precipitate of imino-calix[4]arene derivatives obtained by performing the reaction in anhydrous ethanol, i.e., in case of **8.4A, 8.4B, 8.4E** yielded the products in ~83-85% whereas by changing the solvent to anhydrous acetonitrile as in case of **8.4C** and **8.4D** the yields increased to 93-96%. The tetraamine derivative of the calix[4]arene, i.e., **8.3** undergoes amide coupling reaction to result in **8.5A** as white solid in ~70% yield.[85] Similarly, the **8.5B** is obtained in 80-82% yield via nucleophilic substitution reaction of tetraamine calix[4]arene derivative.[86]



Scheme 8. Synthetic strategy using nitro and amine functionalized upper rim calix[4]arene derivatives for further modifications: (i) THF, acetic acid, formaldehyde (37%), 24h, rt, {**8.1A** dimethylamine (40%); **8.1B** N-benzyl piperazine; **8.1C** morpholine; **8.1D** 1-piperazine carboxylate; **8.1E** diethylamine; **8.1F** Diallylamine;

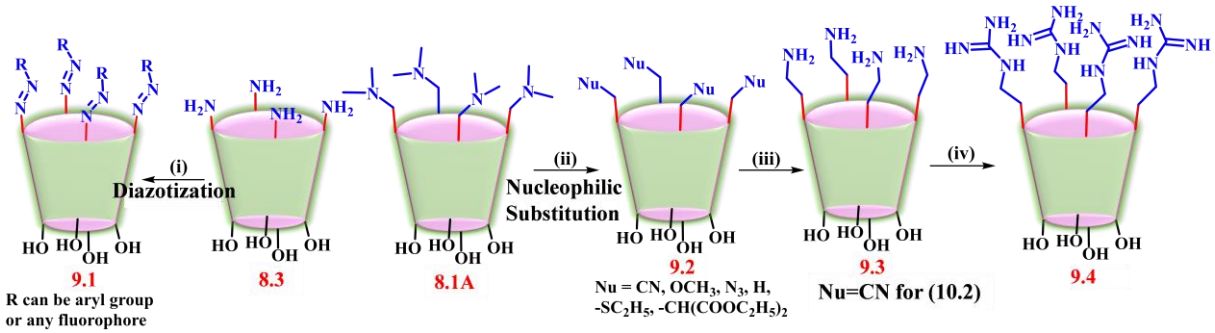
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8.1G Piperidine; **8.1H** 1, 4 dioxo-8-azaspiro [4, 5]decane}; (ii) benzene, HOAc, HNO_3, 0^0C; (iii) Pd/C, $NH_2NH_2.H_2O$, methanol, reflux; (iv) anhydrous ethanol/ anhydrous acetonitrile, N_2, 2 h, rt {**8.4A** 4-Hydroxy benzaldehyde; **8.4B** vanillin; **8.4C** 4-Methyl benzaldehyde; **8.4D** methyl 4-formylbenzoate; **8.4E** 2-Hydroxy1-napthaldehyde}; (v) **8.5A** (Et_3N, dry $CHCl_3$, N_2 atm, p-nitrophenyl (diphenylphosphoryl)acetate, 24h, rt; **8.5B** $PhCH_2Br$, pyridine, dry acetonitrile; 24h, rt}.

The novel Schiff bases (**8.4A** and **8.4B**) which upon further substitution with alkyl chains at the lower rim yield liquid crystalline properties existing in three mesophases, *viz*., sematic phase C, sematic phase A and nematic phase.[83] The imino-calixarene derivative appended with 4-methyl benzene (**8.4C**) and methyl benzoate (**8.4D**) have been used as precursors for the formation of water soluble calixarene derivatives upon further modifications.[83] The carbomylmethyl phosphine oxide calix[4]arene derivative (**8.5A**) anchored on to the silica showed high affinity for Eu^{III} over Am^{III}.[85] The tertra-diaminobenzyl calix[4]arene derivative (**8.5B**) has been explored for the selective recognition of neutral aromatic substrates wherein the arms provide aromatic regions to extend π…π interactions with the guest species.[86]

3.3. Upper rim tetra-cationic (guanidinium type) derivatives and their DNA cargo-application potential

The Mannich bases (such as, **8.1A**) can be converted easily to their quaternary ammonium salts in presence of methyl iodide, which reacts *in situ* with different nucleophiles, *via* calix[4]arene *p*-quinone methide intermediate. The **8.1A** resulted in a variety of functionalized calixarenes as shown in **9.2** carrying -CN, $-OCH_3$, $-N_3$,-H, -SEt, $-CH(COOEt)_2$ groups with 88% (pale yellow solid), 62% (colourless solid), 62% (pale yellow solid), 34% (white solid), 53% (colourless crystals) and 92% (colourless solid) product yields respectively.[87] The *p*-cyanomethylcalix[4]arene derivative, i.e., **9.2** where the nucleophile is CN, and this results in **9.3** (*p*-2-aminoethyl calix[4]arene) upon reduction carried out using the reaction conditions mentioned in Scheme 10 (iii) followed by recrystallization from $CHCl_3$-CH_3OH which resulted in colourless crystals with 83% yield. The reaction of **9.3**, i.e., tetraethyl amino derivative of calix[4]arene upon reaction in presence of Boc-triflyl-guanidine followed by the treatment of octa-Boc derivative with trifluoroacetic acid resulted in **9.4**, the tetra-guanidinium salt of the calix[4]arene possessing four positively charged arms in 52% yield and therefore is of use in DNA plasmid delivery.[88]



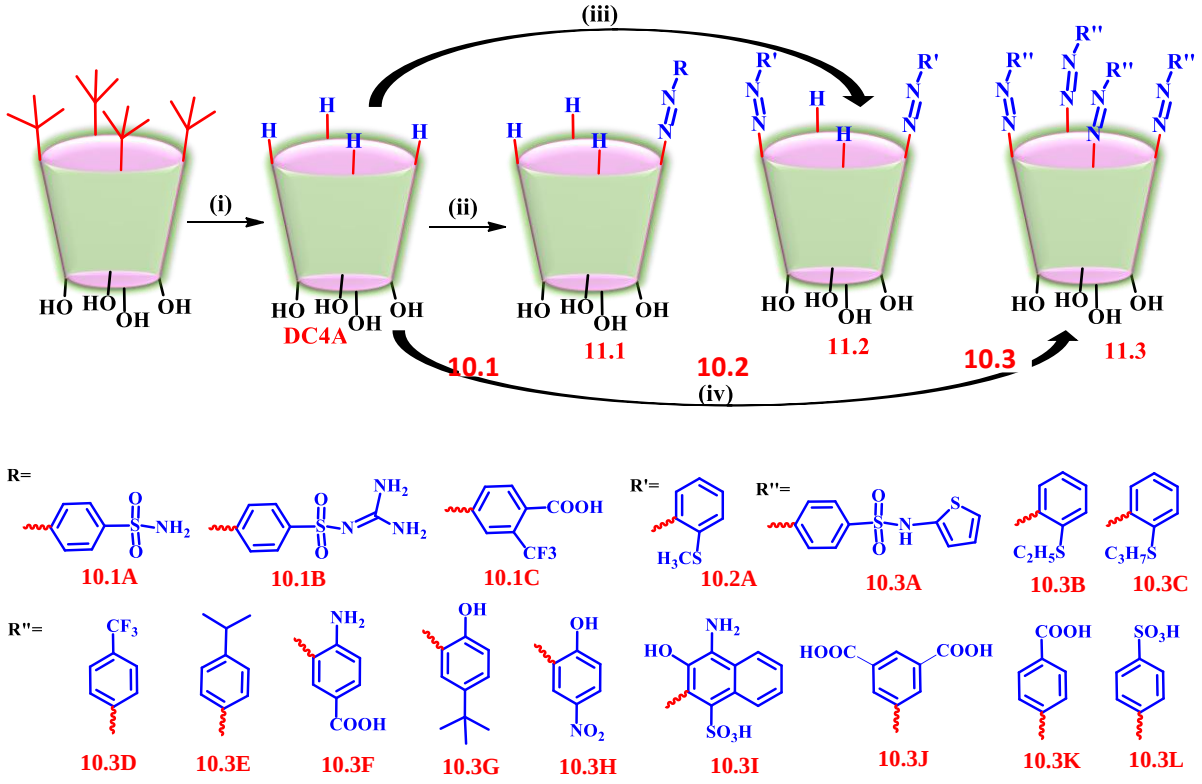
Scheme 9. Synthetic strategy for the tetra-derivatives at the upper rim: (i) AcOH, H_2SO_4, $NaNO_2$, DMF, R = phenol derivatives; (ii) DMSO, CH_3I, N_2 atm. 2h, 80^0C, followed by acidification with 2N HCl, Nu = CN (NaCN), OCH_3 ($NaOCH_3$), N_3 (NaN_3), H ($NaBH_4$), $-SC_2H_5$ (ethyl mercaptan), $-CH(COOC_2H_5)_2$ (sodium diethylmalonate); (iii) B_2H_6 (1.0 M), THF, N_2, 80^0C, reflux, 24h; (iv) Boc-triflyl-guanidine, NaOH, dioxane, rt followed by trifluoroacetic acid, CH_2Cl_2, rt.

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Our own research group recently published the synthesis of a bimodal fluorescent cationic calix[4]arene conjugate wherein the guanidinium groups are attached to the upper rim at 1,3-positions through a triazole linker and the coumarin moieties were attached to the lower rim at 2,4-positions through amide links.[89] This conjugate has been demonstrated to bind to DNA and to condense plasmid pBR322, and to transfect the MCF-7 cells by carrying the red fluorescent protein (RFP) encoded plasmid pCMV-tdTomato-N1 to emit both the intrinsic fluorescence of the conjugate as well as that from RFP. The transfection efficiency of this bimodal conjugate has been compared with the commercially available lipofectamine (LTX) in two cancer cell lines, viz., MCF 7 and SHSY5Y, and found that this conjugate is as efficient as that of LTX. Hence, our bimodal conjugate of calix[4]arene is an efficient and effective cargo to transport genetic material into the cells.

3.4. Upper rim mono-, di- and tetra-azo derivatives and their bactericidal activity

Azo-calix[4]arene is one of the important class of calix[4]arene derivatives owing to their versatile applications in the field of dyeing of textile fibres and in colouring of different materials.[90] Calix[4]arene derivatives having azo moiety at the upper rim of calix[4]arene are generally synthesized by the insertion of nitrogen at the para-position of the DC4A as can be noticed from Scheme 11. All the four para-positions of calix[4]arene are equally available for the insertion of the nitrogen to result in tetrakis-azo product. Therefore, it is always challenging to introduce such group in a selective fashion among the four para positions due to the symmetry of calix[4]arene. The synthetic strategy for the development of such mono-, di- and terta-azocalix[4]arene derivatives has been shown in the Scheme 10.



Scheme10. Synthetic strategy for mono, di and tetraazacalix[4]arene derivatives: (i) $AlCl_3$, phenol, dry toluene, 24 h, RT (**DC4A**); (ii) $NaNO_2$, conc. HCl, sodium acetate, {(4-aminobenzenesulfonamide, (1 equiv.), **10.1A**); (sulfaguanidine (1 equiv.), **10.1B**); (4-amino-2-trifluoromethylbenzoic acid, (1 equiv.), **10.1C**)}; (iii) $NaNO_2$, conc. HCl, 2-methylthio benzene, THF/pyridine, stirring at 0-5°C followed by stirring for 20 min at 10-15°C

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(**10.2**); (iv) $NaNO_2$, conc. HCl, pyridine, stirring at 0-5℃, {(N-(thiophen-2-yl)benzenesulfonamide **10.3A**), (2 ethyl thioaniline **10.3B**), (2 propyl thioaniline **10.3C**)}, $NaNO_2$, conc. HCl, sodium acetate, DMF/water {(3(trifluoro)methylaniline, 4 equiv., **10.3D**); (isopropylaniline, 4 equiv., **10.3E**); (4-aminobenzoic acid, **10.3F**); (4-*tert*-butylphenol, **10.3G**); (4-Nitrophenol, **10.3H**); (4-amino-3-hydroxynapthalene-1-sulfonic acid, **10.3I**); (3,5-dicarboxy aniline, **10.3J**); (4-benzenecarboxylic acid, **10.3K**); (4-amino benzene sulphonic acid, **10.3L**)}. Lower panel: The structures of the R, R' and R" as per the Scheme 11.

Three mono azocalix[4]arene derivatives having different functional moieties, such as, sulphanilamide (**10.1A**), sulfa-guanidine (**10.1B**) and 2-methyl-4 benzoic acid (**10.1C**) have been synthesized using the route given in Scheme 11 starting from dealkylated calix[4]arene, i.e., DC4A. All the mono-azo derivatives of calixarene have been obtained as orange solid and purified by column chromatography using $CHCl_3$/MeOH in 7:1 ratio in 67% yield in case of **10.1A**, and using Hexane/Ethyl acetate in 2:3 ratio in case of **10.1B** and **10.1C** wherein the yields were 55 and 48% respectively. These mono-azo derivatives of calixarene were screened against five gram-positive bacterial strains and proven their bactericidal activity against *B. subtilis*, Methicillin-resistant Staphylococcus aureus (MRSA), *S. aureus*, *S. epidermidis* and *E. faecalis* with minimum inhibition concentration (MIC) values ranging from 0.97 to 62.5 μg/mL suggesting that the azo derivatives of calix[4]arene are better therapeutic agents.[91] The di-azocalixarene derivative, i.e., **10.2A** has been synthesized as per the reaction conditions given in Scheme 10 (iii) as red crystalline solid by crystallizing from $CHCl_3$/Hexane mixture to yield the product in 49%. The tetra-derivatives of azocalix[4]arene appended with 2-alkylthiobenzenediazonium groups, **10.3A** (60%), **10.3B** (21%), **10.3C** (51%) have been obtained with lesser yields as red solid when crystallized from THF/MeOH mixture.[92] Terta-azocalix[4]arene derivative having **10.3D** and **10.3E** are obtained in good yields of ~72-75% and these derivatives showed limited inhibitory activities against bacterial strains of *S. epidermidis* and *E. faecalis* bacteria.[91] However, the structure activity correlations among this category of azo-derivatives has been least understood.

3.5. Upper rim tetra-azo derivatives and their application in dyeing fabrics

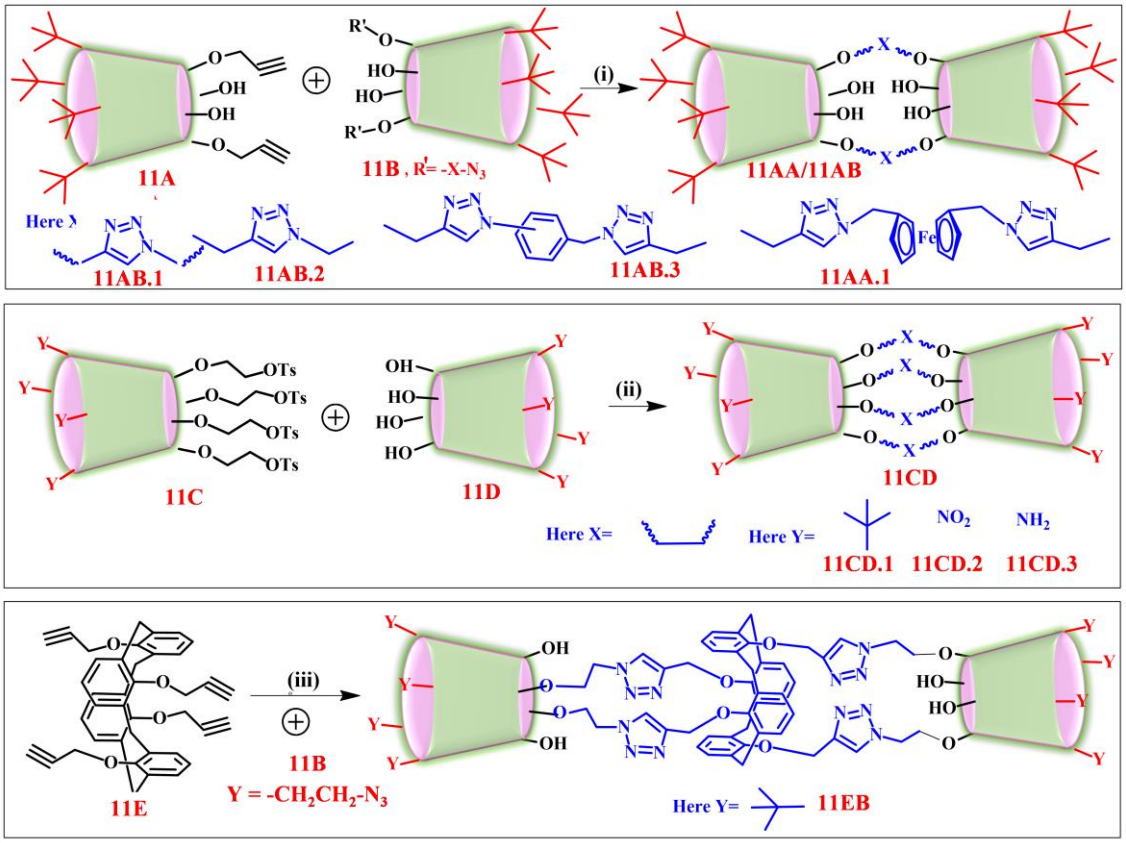
The tetra azocalix[4]arene derivatives, i.e., **10.3F**, **10.3G**, **10.3H** and **10.3I** have been synthesized in 67–90% yield and were purified by crystallization carried out using aqueous DMF as solvent mixture. These calixarene conjugates have been studied for their resistance to heat. The thermal analysis data of all these four molecules suggested that the stability of the azocalix[4]arene depends on the substituted groups and their position in the calix[4]arene. Such molecules can be used as potential systems and were explored for their applications, such as, ink-jet printing, photocopying, lasers etc.[93] Water soluble tetraazo-calix[4]arene derivatives with **10.3J**, **10.3K**, **10.3L** having di -COOH, mono -COOH and $–SO_3H$ groups have been synthesized. These three products were obtained as pale brown solids upon recrystallization from acetonitrile-MeOH, DMF/H_2O and acetonitrile-MeOH respectively, where the corresponding product yields were 77, 87 and 64 %. These calixarene conjugates act as excellent candidates for dyeing silk, cotton and wool due to their binding and colouring properties.[94]

4. Calix[4]arene based Nanotubes

Nanotubes are one of the most interesting molecular architectures resulting from calix[4]arene. Depending upon the chemical modifications performed at the lower and the upper rim, the resulting derivatives form a variety of calix[4]arene nanotubes when two such platforms having complimentary and reactive groups comes together to form a

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covalent dimer. That means, an easy approach for the formation of nanotubes is to bridge a pair of calixarenes or more via intramolecular bridges or intermolecular covalent attachment. Such synthetic strategy has been used in the literature to generate nanotubes using the precursors of different size and functionality. The click chemistry has been thoroughly explored for the synthesis of various bis-calix[4]arene derivatives while one of them carries alkyne functionality the other (the complimentary one) possesses azide functionality to couple together and provide a covalent triazole linker through a simple click reaction. For example, a dipropargylated calixarene derivative (**11A**), on reaction with diazide calix[4]arene derivative (**11B**), results in the formation of **11AB.1**, **11AB.2** and **11AB.3** depending upon the connecting linker used. **11AA.1** has been synthesized by taking two molecule of **11A** on reaction with 1,4-bis-azidomethyl benzene by click chemistry that resulted in ~83% yield.[95] Novel calix[4]arene tube, **11CD.1**, has been obtained in ~51% yield by the template-driven condensation of **11C** with **11D** in acetonitrile.[96] Water soluble octa-cationic and octa-neutral calix[4]arene tubes, i.e., **11CD.2** and **11CD.3** have been synthesised by the methodology given in Scheme 12 starting from **11CD.1**.[97] The reaction between **11B** and tetrakis-alkyne, **11E** in a mole ratio of 2:1 in the presence of reaction condition given in Scheme 12 resulted in tris-calixarene semitubes, i.e., **11EB** in ~38 % yield.[98]

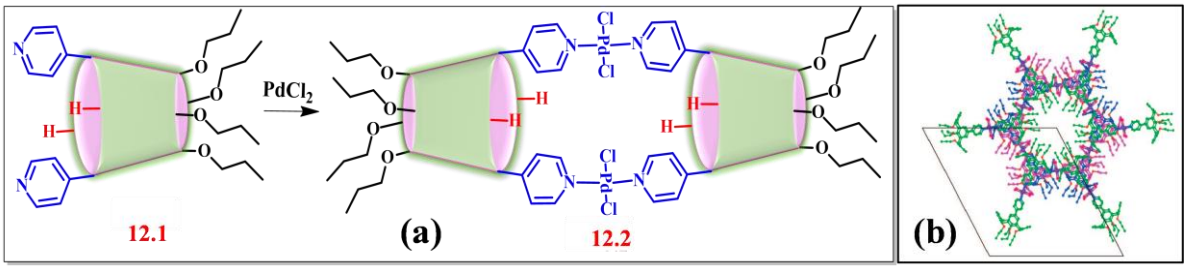


Scheme 11. Synthetic strategy for generating calix-tube structures from two appropriately derivatized calix-platforms: (i) $(OEt)_3P.CuI$, DIPEA, toluene, reflux (**11AB.1** to **11AB.3**, **11AA.1**); (ii) CH_3CN, K_2CO_3 (**11CD.1** to **11CD.3**); (iii) CuI (0.3 equiv.), Et_3N, toluene, rt, 48 h, **11EB**.

A metallocyclic calix[4]arene wheel (**12.2**) has been synthesized as per the strategy given in Scheme 13 as a palladium coordinated system.[99] Dipyridyl-substituted tetrapropoxy-calix[4]arene (**12.1**) has been synthesized by the literature known procedure[100] and when this was subjected to the reaction with $PdCl_2$, it resulted in the formation of a metallocyclic calixarene wheel having double pyridyl N-$PdCl_2$-N pyridyl coordination, i.e. **12.2**. The macrocyclic tubular

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derivatives of the calixarene have been well explored for the encapsulation of various organic guest molecules, such as, pyridinium ions, viologens, toluene.[101-102]



Scheme 12. (a) Synthetic scheme for the upper rim pyridyl calix[4] derivative to form a metallocyclic calix[4]arene tube, **12.2**. (b) Formation of calix-wheel in the crystal structure of **12.2**.

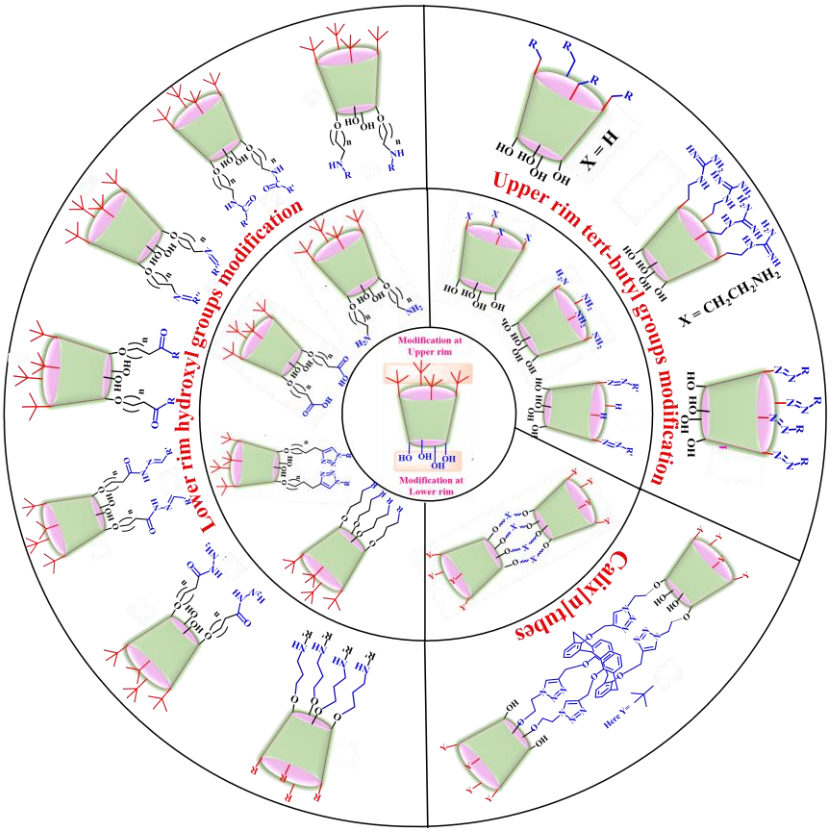
5. Conclusions and comparisons

The present article provides some perspectives based on the recent developments of the synthetic strategies reported in the literature for the derivatization on the calix[4]arene platform.

5.1 Based on the lower rim

The article highlights the synthetic methods for the lower rim derivatization of the calix[4]arene with appropriate discussions. The synthetic routes for introducing different functional groups at the two alternate –OH groups of calix[4]arene by a variety of terminal linkers, such as, amino, carboxylic, ester, azide, nitrile, bromo, alkyne, and alkene, have resulted to give the breadth of the derivatization. The synthesis routes concerned with various lower rim conjugates of calixarenes at alternate two –OH groups with terminal $–NH_2$ or –NHR group *via* nucleophilic reaction, amide coupling and the schiff's base reactions have been introduced. Similarly, the synthetic directions for the conjugates of the lower rim 1,3 di derivatives of the ester and acid groups have been given in this article. Lower rim 1, 3 di-derivatives of calix[4]arene having $–N_3$ and alkyne group at the terminal leads to the development of various molecules *via* click reaction in the presence of $CuSO_4$ and sodium ascorbate in a suitable solvent medium, a reaction that revolutionized during past couple of decades and even brought the laurel of Nobel prize in chemistry this year. Such derivatives are further functionalized with different groups, and these were a part of this article.

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Scheme 13. Pictorial illustration showing diversity of calix[4]arene conjugates

The derivatizations at all the four –OH groups of the calix[4]arene have been achieved by using the sodium hydride as a base (Scheme 6) and the synthetic strategies of a few such derivatives of calixarene have been a part of this article. All such details were associated by providing the application domain of these important supramolecular systems based on the calix[4]arene platform. The derivatization diversity emerging from the synthetic modifications brought at the lower and the upper rim of calix[4]arene platform can be appreciated from Scheme 13.

5.2. Based on the upper rim

The present article also focuses on the upper rim derivatization of the *p-tert* butyl calix[4]arene. The upper rim modification can be achieved either by dealkylation (DC4A) of the tertiary butyl group or by carrying out the ipso-reaction. The sulfonation, nitration, phosphorylation, alkylation and acylation are a few common reactions carried out at the upper rim of calix[4]arene. The DC4A readily reacts with secondary amine and formaldehyde and results in the formation of Mannich bases used for various applications (Scheme 8). Introduction of azo moiety at upper rim of the calix[4]arene has been generally affected by the insertion of nitrogen at the para position of the DC4A. The synthetic strategies for the selective derivatization at one, two and all four positions have also been a part of this article (Schemes 9, 10). Chemical strategies for the derivatization at lower and the upper rims of the calix[4]arene to form a variety of calix[4]arene nanotube structures and their strategies were also an integral part of this article (Schemes 11, 12) to bring the application domain of these supramolecular systems into light. All these were schematically shown in Scheme 13 for the purpose of comparison.

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Acknowledgements

CPR acknowledges Department of Science and Technology for JC Bose National Fellowship (SB/S2/JCB/066/2015) and IIT Tirupati for providing an MHRD Professorship. CPR expresses his gratitude to IIT Bombay for fostering his academic and research activities for over three decades. BU acknowledges J.C. Bose University of Science and Technology, Faridabad for her faculty position.

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